Evidence-based treatment strategies in Acute Kidney injury:
Special cases of Cardiorenal and Hepatorenal syndromes

Frederic Rahbari-Oskoui MD, MS
Associate Professor of Medicine
Emory University School of Medicine
Renal Division
# AKI: Definition and diagnostic criteria

**Definition:** Sudden decrease in renal function

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>RIFLE criteria</th>
<th>AKIN criteria</th>
<th>KDIGO criteria</th>
<th>Conventional criteria for diagnosis of AKI in cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase in SCr to ≥1.5 times baseline, within 7 days; or GFR decrease &gt;25%; or</td>
<td>Increase in sCr by ≥0.3 mg/dl (26.5 μmol/L) within 48 h; or Increase in sCr ≥1.5 times baseline within 48 h; or</td>
<td>Increase in sCr by ≥0.3 mg/dl (26.5 μmol/L) within 48 h; or Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume &lt;0.5 ml/kg/h for 6 h</td>
<td>A percentage increase in sCr of 50% or more to a final value of sCr &gt;1.5 mg/dl (133 μmol/L)</td>
</tr>
<tr>
<td>Staging</td>
<td>Urine volume &lt;0.5 ml/kg/h for 6 h</td>
<td>Urine volume &lt;0.5 ml/kg/h for 6 h</td>
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<tr>
<td>Risk:</td>
<td>sCr increase 1.5-1.9 times baseline; or GFR decrease 25-50%; or Urine output</td>
<td>Stage 1: sCr increase 1.5-1.9 times baseline; or sCr increase ≥0.3 mg/dl (26.5 μmol/L); or Urine output &lt;0.5 ml/kg/h for 6 h</td>
<td>Stage 1: sCr increase 1.5-1.9 times baseline; or Cr increase ≥0.3 mg/dl (26.5 μmol/L); or Urine output &lt;0.5 ml/kg/h for 6-12 h</td>
<td>Not provided</td>
</tr>
<tr>
<td>Injury:</td>
<td>&lt;0.5 ml/kg/h for 12 h</td>
<td>Stage 2: sCr increase 2.0-2.9 times baseline; or Urine output &lt;0.5 ml/kg/h for</td>
<td>Stage 2: sCr increase 2.0-2.9 times baseline; or Urine output &lt;0.5 ml/kg/h for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sCr increase ≥3.0 times baseline; or GFR decrease 50-75%; or Urine output &lt;0.5</td>
<td>12 h</td>
<td>≥12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ml/kg/h for 12 h</td>
<td>Stage 3: sCr increase 3.0 times baseline; or sCr increase ≥4.0 mg/dl (353.6 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L); or Urine output &lt;0.3 ml/kg/h for 24 h; or Anuria for ≥12 h</td>
<td>Stage 3: sCr increase 3.0 times baseline; or sCr increase to ≥4.0 mg/dl (353.6 μmol/L); or Initiation of renal replacement therapy; or Urine output &lt;0.3 ml/kg/h for ≥24 h; or Anuria for ≥12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or GFR decrease 50-75%; or sCr increase ≥4.0 mg/dl (353.6 μmol/L) with an acute</td>
<td>increase of at least 0.5 mg/dl (44 μmol/L); or Urine output &lt;0.3 ml/kg/h for 24 h; or Anuria for ≥12 h</td>
<td></td>
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</table>
AKI in the Hospital

- Renal 60%
  - Acute tubular necrosis 50%
  - Tubulointerstitial nephritis 3-5%
  - Glomerulonephritis 3-5%
  - Vascular disease
    - (RAS, BCN, RVT, AERD) 2-3%
- Prerenal (↓ Blood flow) 30%
- Post renal (obstructive) 10%
Prerenal Azotemia

- Volume depletion:
  - Diuretics
  - GI losses (nausea, vomiting, diarrhea)
  - Skin losses: (fever, burns)
  - Bleeding (external, internal)
- Third-spacing
  - Pancreatitis, post surgical, sepsis
- Drugs: NSAIDs (early on), ACE-I, etc
- Heart failure
- Hepatic failure
Cardiorenal Syndrome

• Definition: Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.

• 2008 Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) in Italy

• Five subgroups identified:
Classification

- CRS-Type 1: Acute Cardio-Renal Syndrome
- CRS-Type 2: Chronic Cardio-Renal Syndrome
- CRS-Type 3: Acute Reno-Cardiac Syndrome
- CRS-Type 4: Chronic Reno-Cardiac Syndrome
- CRS type 5: Secondary Cardio-Renal Syndromes
Pathophysiology of Cardiorenal syndromes

Arterial underfilling
- Decreased cardiac output
- Decreased effective circulating volume
- Decreased RBF, RPF
- Activation of RAAS, SNS
- Inflammatory pathways

HEART
- Decreased GFR
- Na and H₂O retention
- Increased edema, preload
- Increased afterload

Venous congestion and venous hypertension, raised IAP
- Decreased AV perfusion gradient
- Kidney interstitial edema
- Activation of RAAS, SNS
- Inflammatory pathways

Venous congestion

KIDNEY
Pathophysiology of Cardiorenal syndromes
Pre-Test. Based on results of RCTs, which statement reflects the most accurate strategy (ies) to reduce mortality in cardiorenal syndromes?

0%  1. Renal dose dopamine
0%  2. Milrinone
0%  3. Vasopressin receptor antagonists
0%  4. Slow Ultrafiltration
0%  5. Cardiac resynchronization
0%  6. All of the above
0%  7. None of the above
Interventions

- Most of the studies were conducted in CRS-1
  - Salt restriction
  - Diuretics
  - Ultrafiltration
  - Dopamine
  - Milrinone
  - ACE-Inhibitors
  - Nesiritide
  - Cardiac resynchronization therapy
Salt Restriction

• 1- 410-patients, RCT comparing 1.8 g/d of sodium vs 2.8 g/d of sodium and 1-L fluid restriction vs 2-L fluid restriction
  - Decreased readmissions at 6 mo in the group with liberal sodium intake
• 2- 123-patient prospective, nonrandomized observational study in the ambulatory setting
  - Higher mortality and increased hospitalizations in the higher-sodium group

No specific guidelines at this point. Larger trials needs.  

All have sulfa moiety except for ethacrynic acid which is the only drug that can be safely used in true sulfa allergic patients.
Diuretics

• **DOSE-HF trial:** Felker et al, *NEJM* 2011

  308 patients with acute DHF, randomized in a 2x2 design to BID IV regimen vs continuous infusion, either at previous dose or x2.5 previous dose.

  Continuous group showed
  - More fluid loss (4.5 vs 3.6 liters over 72h)
  - Improved dyspnea score
  - No difference in mortality, length of stay, Hosp readmission rate
  - No difference in long term renal function
  - But higher AKI (23 vs 14%).
Torsemide vs Furosemide

Open label RCT of 234 hospitalized patients with ADHF, for one year.
Torsemide group had lower ADHF readmission rates (17% vs 32%)
Shorter duration of hospital stay (106 vs 296 d).
Less fatigued.
But no effect on dyspnea

TORIC trial: 1977 patients in open label, surveillance trial, outpatient oral use.
Mortality benefit for Torsemide (2.2 vs 4.5%)
Improved NYHA class: (46 vs 37%)
Better electrolyte AEs: (3 vs 30%)

Torsemide vs Furosemide

Prospective RCT, 237 primary care office patients with NYHA II-IV CHF,
Torsemide group had improved symptoms (40% vs 30%)
No difference in mortality or hospital admission rates

High dose vs low dose diuretics

- Some studies (but not all) showed higher episodes of AKI associated with higher doses of diuretics.
- Using diuretics is still part of mainstream treatment of acute and chronic CHF, but increased BUN/Creatinine ratio, AKI, hypotension and contraction metabolic alkalosis, may indicate overdiuresis.
- Aldosterone agonist have mortality benefit in CHF.
Thiazide diuretics

• Rational is to block distal reabsorption of sodium
• Very few well done trials available.
• Most commonly used agents are metolazone (PO) or chlorothiazide (IV).
• Electrolytes need to be monitored very closely.
# Aldosterone Antagonist

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Mechanism of action    | Nonselective aldosterone receptor antagonist; structurally similar to progesterone | Selective aldosterone receptor antagonist with limited affinity for progesterone and androgen receptors | ● 1999—RALES<sup>28</sup>  
- 1663 patients with NYHA III/IV class heart failure  
- Excluded creatinine >2.5 mg/dL; potassium >5 mmol/L  
- Spironolactone associated with 11% absolute reduction in mortality and 35% reduction in hospitalization |
| Indication             | NYHA class II-IV CHF with EF ≤35%  
- Essential hypertension | NYHA class II-IV CHF with EF ≤35%  
- Essential hypertension | ● 2003—EPHESUS<sup>27</sup>  
- 3313 patients after AMI with EF <40% and CHF  
- Eplerenone associated with reduced mortality (HR = 0.85), SCD, and hospitalization |
| Typical doses           | 25-100 mg/d (higher doses in patients with liver failure)                     | 25-50 mg/d                                                                 | ● 2011—EMPHASIS-HF<sup>29</sup>  
- 2737 patients with NYHA class II with EF <30% or EF <35% and widened QRS.  
- Eplerenone associated with lower mortality (HR = 0.76) and hospitalizations |
| Adverse effects         | Antiandrogenic effects (dose-dependent incidence of gynecomastia, with 6.9%-10% experiencing this at doses >50 mg/d)  
- Dysmenorrhea, amenorrhea  
- Hyperkalemia | Selective binding to mineralocorticoid receptors results in minimal antiandrogenic effects  
- Hyperkalemia | |
| Cost ($/mo)<sup>d</sup> | 45                                                                            | 125                                                                         | |

<sup>d</sup> Cost may vary based on pharmacy and location.
Vasopressin Receptor Antagonists

- **ACTIV in CHF trial**
  - 319 hospitalized patients with persistent ADHF
  - Randomized to Tolvaptan or placebo (plus STD Rx)
  - Positive trend for increased diuresis and weight loss.

- **EVEREST trial**
  - 4133 hospitalized patients with persistent ADHF
  - FU 10 months
  - Tolvaptan caused significant weight reduction and dyspnea score improvement at 24h, and decreased edema by day 7
  - No mortality or hospitalization benefit in the main paper.
  - If hemoconcentration occurred then mortality decreased.
Vasodilators

- Nitroglycerin: historically used in acute CHF but adequately powered randomized trials are completely lacking.

- Nitroprusside: effect on cGMP, causing arterial and venous vasodilatation, indicated in CHF with severe hypertension. Concerns about cyanide toxicity in CKD population.
## Dopamine

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanisms of action</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Dopamine | • Increased cardiac inotropy and chronotropy through stimulation of β-receptors  
  • At lower doses, increase in renal blood flow via renal arterial vasodilation mediated by stimulation of DA$_1$ and DA$_2$ receptors$^{38}$  
  • In patients with ADHF and renal failure, may have no effect or actually be deleterious to renal blood flow$^{49,50}$ | • 2001-2002—Two systematic reviews$^{10,40}$  
  - No difference in mortality or renal function  
  • 2010—DAD-HF$^{45}$  
  - 60 patients with ADHF  
  - Dopamine at 5 µg/kg per minute for 8 h vs placebo  
  - No differences in diuresis, dyspnea scores, inpatient hospital days, mortality, renal function, or rehospitalization rates  
  • 2013—ROSE-AHF$^{46,47}$  
  - 360 patients with ADHF and renal failure  
  - Dopamine at 2 µg/kg per minute or nesiritide for 72 h vs placebo  
  - For dopamine vs placebo: no difference in renal function, urine output, 60-d mortality, or heart failure events |
Milrinone

• PDE3-Inhibitor: Increases cardiac contractility and decreases pulmonary vascular resistance

• OPTIME-CHF trial
  -951 patients with acute decompensation of chronic systolic HF.
  Randomized to 48h of milrinone (5 mic/min) or saline
  -No difference in the number of hospital admission days within 60 days.
  -↑Hyoptension and Afib on milrinone.
ACE-I

• Enalapril has been used in CONSENSUS and SOLVD trials.
• Survival benefit in CHF patients in CONSENSUS inspite of the acute hemodynamic effect.
• Worsening renal function in SOLVD in spite of benefit on hospitalization and symptoms.
• CATS trial: no beneficial role of captopril in post-MI
ACE-I: benazepril

Endpoints: doubling of Creat, ESRD, death

Creatinine 1.5-3
Creatinine >3.0

Graph showing percentage not reaching the primary end point over months.

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1, benazepril</td>
<td>102</td>
<td>96</td>
<td>84</td>
<td>40</td>
</tr>
<tr>
<td>Group 2, benazepril</td>
<td>107</td>
<td>96</td>
<td>73</td>
<td>32</td>
</tr>
<tr>
<td>Group 2, placebo</td>
<td>108</td>
<td>88</td>
<td>59</td>
<td>22</td>
</tr>
</tbody>
</table>
Nesiritide (Recombinant BNP)

Nesiritide
- Recombinant human brain natriuretic peptide
- Augmented natriuresis, sympatholysis, antiproliferative effects, and RAAS inhibition

- 2000 (VMAC study) and 2002\textsuperscript{51,52}
  - Nesiritide for 3 h vs placebo
  - Reduction in PCWP and dyspnea scores in the nesiritide group

- 2002—PRECEDE\textsuperscript{53}
  - 255 patients randomized to receive nesiritide or dobutamine
  - Less ventricular tachyarrhythmias with nesiritide

- 2005—Two meta-analyses\textsuperscript{54,55}
  - Increased renal failure, hypotension, and mortality rates with nesiritide

- 2008—FUSION II\textsuperscript{56}
  - No clinical benefit to outpatient nesiritide infusion

- 2011—ASCEND-HF\textsuperscript{57,58}
  - 7141 patients randomized to receive nesiritide or placebo
  - No difference in dyspnea, death, or heart failure hospitalization
  - More hypotension in the nesiritide arm

- 2013—ROSE-AHF\textsuperscript{46,47}
  - 360 patients with ADHF and renal failure
  - Dopamine or nesiritide (0.005 μg/kg per minute) for 72 h vs placebo
  - For nesiritide vs placebo: no difference in urine output, renal function, symptoms, 60-d mortality, or rehospitalizations
Ultrafiltration

- Venovenous removal of isotonic fluid
- Greater net loss of sodium; less neurohormonal activation
- Adjustable rate of volume removal, leading to greater control

- **2005—RAPID-CHF**
  - 40 patients with ADHF and renal failure to single UF session vs usual care
  - UF group with significantly more volume removal and improved dyspnea score; no difference in 24-h weight loss and renal function

- **2007—UNLOAD**
  - 200 patients with ADHF to UF and intravenous diuretics
  - UF group with greater weight loss, better dyspnea score, and lower rehospitalizations and 90-d unscheduled visits
  - UF compared with continuous diuretic infusion showed similar fluid loss; however, associated with fewer rehospitalizations

- **2012—CARRESS-HF**
  - 188 patients with ADHF and worsened renal failure
  - UF compared with stepped pharmacologic therapy shows no significant weight loss but worse renal function and higher serious adverse event rates

Bart et al NEJM 2012
Invasive Heart Monitoring

IHM

- 2008—COMPASS-HF\(^92\)
  - Chronic device: implantable hemodynamic monitor in the RV outflow tract
  - No significant clinical benefit
- 2011
  DOT-HF\(^95\)
  - Randomized 335 patients to receive management based on intrathoracic impedance via OptiVol device or usual therapy
  - No mortality benefit; increased visits and hospitalizations in intervention arm
  REDUCE-HF\(^93\)
  - Hemodynamic sensor implanted in the RV outflow tract along with ICD
  - Study stopped early due to high incidence of device failure

CHAMPION-HF\(^96\)  In NYHA class III

- Randomized 550 patients to receive implantable CardioMEMS-guided therapy or standard therapy
- A 28% reduction in HF hospitalizations at 6 mo and shorter hospital stays in the intervention arm

CardioMEMS was FDA approved in 2014
Multiple trials are ongoing evaluating other IHM devices

No systematic assessment of renal function in these trials.
Lowering increased intra-abdominal pressure

- IAP measured by transvesical monitor
- 9 patients with IAP >8 mmHg and worsening renal function on diuretics underwent paracenthesis or UF.
- IAP dropped from 13 to 7.1.
- Creatinine went from 3.4 to 2.4.
Cardiac resynchronization therapy in CKD-IV

• Simultaneous pacing of the right ventricle (RV) and the left ventricle (LV).

• 71 consecutive patients who underwent CRT. (Comparison group ICD)

• Long term renal and CV outcomes improved (50% reduction of risk for events) with CRT vs ICD).

Hoke et al, CJASN sept 2015
Prognostic value of Urine Osm for CV outcomes in ADHF

- 134 patients in Japan
- Low urine median urine Osm 369, high Uosm 391

$P = 0.0003; \text{HR}, 2.47; 95\% \text{CI}, 1.50-4.14.$
Is there any role for lowering uric acid in CRS?

- Several small size studies have shown a benefit in renal function preservation in CKD patients. Both allopurinol and Rasburicase have shown the same results. (Siu et al 2006, Goicoechea et al 2010)

- Larger studies are needed.
Summary

• Diuretics:
  – No difference between continuous vs intermittent use of loop diuretics
  – Torsemide is more effective in inpatient setting
  – Consider Bumex when severe hypoalbuminemia
  – Aldosterone or eplerenone should be used in CHF patients.

• Vaptans:
  – Short term benefits (increased urine output, weight loss), but no long term mortality benefit.
  – Conivaptan → higher injection site phlebitis (34%)
Summary

• ACE-Is: One of the few strategies to protect both the kidneys and the heart in CRS type 2 and 4. Renal protection is even more pronounced in advanced CKD.

• Dopamine (and fenoldepam):
  - No benefit even at “renal dose”

• Milrinone:
  – No benefit

• Nesiritide:
  – No benefit on either of the outcomes (renal, mortality, rehospitalization).
Summary

• Decreasing IAP:
  – May have a role in renal function protection I HRS-I

• Ultrafiltration:
  - Either no effect or worsened renal function.
  - May have a mild impact on rehospitalization rates.
  - Overall, no benefit

• Cardiac resynchronization:
  – Encouraging results from a relatively small trial in CKD-IV. Larger trials are needed.
Hepatorenal Syndrome
Definitions

• HRS is a functional renal failure caused by intrarenal vasoconstriction which occurs in patients with end stage liver disease as well as in patients with acute liver failure or alcoholic hepatitis.

• HRS is characterized by impaired renal function, marked alterations in cardiovascular function, and overactivity in the endogenous vasoactive systems.

1. Diagnosis of Cirrhosis and Ascites

2. Presence of AKI per ICA-AKI criteria

3. No sustained improvement of serum creatinine (decrease to a level of 133 µmol/l (1.5 mg/dl) or less) after >48h of diuretic withdrawal and volume expansion with albumin (25%) at 1 g/kg of body weight per day to a maximum of 100 g/day.

4. Absence of shock

5. No current or recent treatment with nephrotoxic drugs (NSAIDs, iodinated contrast, aminoglycosides, etc)

6. No macroscopic signs of structural kidney injury as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography. (ATN should also be ruled out).

AKI classification in liver cirrhosis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline sCr</td>
<td>A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.</td>
</tr>
</tbody>
</table>
| Definition of AKI| • Increase in sCr $\geq 0.3$ mg/dl ($\geq 26.5$ $\mu$mol/L) within 48 hours; or,  
• A percentage increase sCr $\geq 50\%$ from baseline which is known, or presumed, to have occurred within the prior 7 days |
| Staging of AKI   | • **Stage 1**: increase in sCr $\geq 0.3$ mg/dl (26.5 $\mu$mol/L) or an increase in sCr $\geq 1.5$-fold to 2-fold from baseline  
• **Stage 2**: increase in sCr $>2$-fold to 3-fold from baseline  
• **Stage 3**: increase of sCr $>3$-fold from baseline or sCr $\geq 4.0$ mg/dl (353.6 $\mu$mol/L) with an acute increase $\geq 0.3$ mg/dl (26.5 $\mu$mol/L) or initiation of renal replacement therapy |
| Progression of AKI | **Progression**  
Progression of AKI to a higher stage and/or need for RRT  
**Regression**  
Regression of AKI to a lower stage |
| Response to treatment | **No response**  
No regression of AKI  
**Partial response**  
Regression of AKI stage with a reduction of sCr to $\geq 0.3$ mg/dl (26.5 $\mu$mol/L) above the baseline value  
**Full response**  
Return of sCr to a value within 0.3 mg/dl (26.5 $\mu$mol/L) of the baseline value |
Hepatorenal Syndrome: Clinical types

- HRS type 1: Rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to a level > 226 µmol/l or 2.5 mg/dl in less than two weeks. It may occur spontaneously, but it can also follow a precipitating event.

  Clinical pattern: Acute renal failure

- HRS Type 2: is characterized by moderate renal failure (serum creatinine from 133 to 226 µmol/l or 1.5 to 2.5 mg/dl) with a steady or slowly progressive course.

  Clinical pattern: Refractory ascites

Mortality in Hepato-renal syndrome

Probability of survival

P < 0.001

Type 2 HRS

Type 1 HRS

Etiologies of Acute renal failure in patients with cirrhosis and ascites

1. Prerenal and Hepatorenal: (58%)
   1. Prerenal failure (38%)
   2. Hepatorenal syndrome (20%)

2. Intrinseque renal disease (41.7%)
   1. Acute tubular necrosis
   2. AIN

3. Postrenal failure (0.3%)

GI bleed
Large volume paracenthesis
Sepsis (SBP and others)
NSAIDs
Ionated Contrast
ACE-I and ARBs
Aminoglycosides
Diuretics

Systemic Arterial Vasodilation Hypothesis

- **Compensated Cirrhosis (No Ascites)**
  - Systemic Arterial Vasodilation: ↑
  - Plasma Hormones (AVP, Renin, Aldosterone, NE): Normal
  - Plasma Volume: ↑

- ** Decompensated Cirrhosis (Ascites)**
  - Systemic Arterial Vasodilation: ↑
  - Plasma Hormones (AVP, Renin, Aldosterone, NE): ↑
  - Plasma Volume: ↑

- **Hepatorenal Syndrome**
  - Systemic Arterial Vasodilation: ↑
  - Plasma Hormones (AVP, Renin, Aldosterone, NE): ↑
  - Plasma Volume: ↑

Circulatory dysfunction in HRS

Changes

Cirrhosis  Ascites  Type 1 HRS

Time

EFFECTIVE CIRCULATING VOLUME

Cardiac output

Splanchnic arterial vasodilation

Prognostic predictors: Hyponatremia

New Biomarkers: NGAL, KIM-1, IL-18, FeNa

HRS is a state of extreme avidity for sodium. FeNa is often <0.1%

New biomarkers ok kidney injury: NGAL, KIM, IL-18 all differentiate HRS from ATN (higher levels in ATN).

Plasma Renin Activity is higher (17 vs 7 mcg/ml/min) in SBP with HRS compared to SBP without HRS

Except for FeNa, the use of these biomarkers is still limited to research.
Quiz

• What is the single most useful test to help with establishing the cause of AKI in a patient with liver cirrhosis?

  – A. Urine dipstick
  – B. Urine microscopy
  – C. Serum sodium level
  – D. Urinary sodium excretion and FeNa
  – E. Ultrasound of the bladder and the kidneys
  – F. Urine output.
Pre-lecture Quiz

• Second to liver transplantation, which strategy has proven to be most effective in reducing mortality and improving recovery of renal function in hepatorenal syndrome?
  – A. Normal saline infusions
  – B. Albumin infusion
  – C. Dopamine
  – D. Midodrine + Octreotide + Albumin
  – E. Terlipressin and albumin
  – F. Transjugular Intrahepatic Portosystemic Shunt
Therapeutic approaches to HRS

- Aldosterone antagonists
- Albumin and Midodrin+Octreotide
- Vasoconstrictors
- Terlipressin
- TIPS
- Extracorporeal liver/renal support
Aldosterone antagonism promotes weight loss and disappearance of ascites in decompensated cirrhosis.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CIRRHOTIC PATIENTS</th>
<th></th>
<th>SPIRONOLACTONE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROL (n=22)</td>
<td></td>
<td>SPIRONOLACTONE (n=21)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Weight loss (lb)</td>
<td>6 ± 2</td>
<td></td>
<td>24 ± 4</td>
<td></td>
</tr>
<tr>
<td>Disappearance of ascites</td>
<td>4</td>
<td></td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Gregory et al., 1977
## Effects of albumin on morbidity and mortality due to SBP

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Cefotaxime (n° = 63)</th>
<th>Cefotaxime plus albumin (n° = 63)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure n° (%)</td>
<td>21 (33%)</td>
<td>6 (11%)</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Death in hospital n° (%)</td>
<td>18 (29%)</td>
<td>6 (10%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Death at 3 months n° (%)</td>
<td>26 (41%)</td>
<td>14 (22%)</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

Vasoconstrictors in HRS-1

- **Groupe A:**
  Low dose Dopamine

- **Groupe B:**
  Albumin (20-40 g/day, intravenously)
  Midodrine (7.5-12.5 mg *t.i.d.*, orally)
  Octreotide (100-200 µg *t.i.d.*, /SC)

## Terlipressin and albumin vs albumin
Results of two RCTs

<table>
<thead>
<tr>
<th></th>
<th>Spanish Trial (n° = 45)</th>
<th>USA Trial (n° = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (%)</td>
<td>Terlipressin and albumin</td>
<td>Albumin</td>
</tr>
<tr>
<td>Response (%)</td>
<td>43.5*</td>
<td>8.7</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>At 3 months 27</td>
<td>At 3 months 19</td>
</tr>
</tbody>
</table>

- * p < 0.025
- # p < 0.01

Survival in HRS-1 on Terlipressin and albumin according to improvement of renal function (n=46)

Terlipressin vs Midodrine+Octreotide
RCT (n=49)

Terli: 3-12 mg /d IV, Midodrine 7.5-12.5 PO TID, Octreotide 100-200 mcg SC-TID
Response: Either creatinine <1.5 or 50% decrease from baseline

Cavallin et al. Hepatology 2015
Terlipressin vs Midodrine+Octreotide RCT (n=49)

Group TERLI
- Responders
- Non responders

Group MID/OCT
- Responders
- Non responders

Cavallin et al. Hepatology 2015
Renal function after TIPS procedure

Table 2  Changes in renal parameters in patients with hepatorenal syndrome treated with a transjugular intrahepatic portosystemic shunt

<table>
<thead>
<tr>
<th>Study</th>
<th>Serum creatinine (mg/dl) before TIPS</th>
<th>Serum creatinine (mg/dl) 1 month after TIPS</th>
<th>Creatinine clearance (ml/min) before TIPS</th>
<th>Creatinine clearance (ml/min) 1 month after TIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guevara et al. [8], prospective (N=7)</td>
<td>5±0.8</td>
<td>1.8±0.8</td>
<td>9±4</td>
<td>27±7</td>
</tr>
<tr>
<td>Brensing et al. [9], prospective (N=31)</td>
<td>2.3 (1.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 (1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 (15)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44 (28)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alessandria et al. [10], prospective (N=9)</td>
<td>2.1±0.6</td>
<td>1.38±0.3</td>
<td>28.1±8.7</td>
<td>39.4±9.1</td>
</tr>
<tr>
<td>Wong et al. [7], prospective (N=5)</td>
<td>--</td>
<td>--</td>
<td>Significant change, no exact values stated</td>
<td>Significant change, no exact values stated</td>
</tr>
</tbody>
</table>

TIPS, transjugular intrahepatic portosystemic shunt.

<sup>a</sup>Mean (SD).

From Busk et al: European Journal of Gastroenterology 2013
HRS impacts post-transplant survival, length of stay and dialysis-dependence

<table>
<thead>
<tr>
<th>Events</th>
<th>HRS</th>
<th>NO-HRS</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year survival</td>
<td>60 %</td>
<td>65 %</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Days in ICU post-LT</td>
<td>18 ± 23</td>
<td>6 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days in Hospital post-LT</td>
<td>42 ± 34</td>
<td>27 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyalisis post-LT</td>
<td>35 %</td>
<td>5 %</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Post transplant outcomes in HRS-1

Wong et al 2015 Liver transplantation
Algorithm for treatment of AKI in cirrhotic patients

Post Test. Second to liver transplantation, which strategy has proven to be most effective in reducing mortality and improving recovery of renal function in hepatorenal syndrome?

A. Normal saline infusions
B. Albumin infusion
C. Dopamine
D. Midodrine + Octreotide + Albumin
E. Terlipressin and albumin
F. Transjugular Intrahepatic Portosystemic Shunt
Post Test. Second to liver transplantation, which strategy has proven to be most effective in reducing mortality and improving recovery of renal function in hepatorenal syndrome?
Summary

- Type 1 HRS is often precipitated by bacterial (particularly subdiaphramatic) infections or reduced cardiac output from any other causes. It can be effectively prevented by using albumin together with the antibiotic treatment.
- Urine microscopy is critically important in the workup for HRS-I. Patients with Na< 133 and FeNa <0.1% are at greater risk of HSR-I.
- Vasoconstrictors and albumin are effective in the treatment of HRS-1 but Terlipressin (not yet available in the US) is superior to Midodrin+Octreotide (RCT 2015).
- TIPS procedure may have a positive impact on recovery of renal function in HRS.
- Even after liver transplantation only 75% of patients with HRS recover their kidney function. Duration of dialysis is the only significant predictor of recovery.
Evaluation

- Please take < 90 seconds to evaluate this session.
- Time permitting, speaker will take questions following evaluation.
- Responses are not displayed and are important in maintaining high quality education.
The overall performance of the speaker:

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
How well were the learning objectives met?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
Did speaker present a balanced view of therapeutic options?

1. Yes
2. No
3. N/A
How useful will this session be in your practice?

1. Poor
2. Fair
3. Average
4. Good
5. Excellent
As a result of this program, do you intend to change your patient care?

1. Yes
2. No
Thank you!