Hepatorenal Syndrome: A Hospitalist’s Perspective

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Learning Objectives

1. **Define** Hepatorenal Syndrome
2. Familiarize yourself with the **pathophysiology**
3. Understand the **clinical assessment** needed to make this diagnosis
4. Familiarize yourself with basic **therapeutic considerations**
5. Discuss how this syndrome may be **prevented**
Case

HPI: 46 y/o female presented to Express Med clinic with complaints of “inability to urinate” over the last few days. Urine was described as dark. No fevers or abdominal pain. No other complaints. The patient had recently been treated at another hospital for SBP 2 weeks ago and completed five days of ceftriaxone. She denied NSAID use or other recent changes in medications.
Case Continued

PMH: Cryptogenic Cirrhosis with full w/u for underlying causes, including liver biopsy, at an outside facility 3 years prior.

Meds: None other than daily norfloxacin for secondary sbp prophylaxis, aldactone 200mg daily and lasix 40mg twice daily for volume control

Social: No etoh use

Labs: Cr is 3.4 up from Cr 1.0 2 weeks ago
What is this patient’s diagnosis?

1. AKI- related to HRS-1
2. AKI- related to HRS-2
3. AKI- related to interstitial nephritis from antibiotics
4. AKI- related to volume overload
5. AKI- need more information
HRS as Defined Today

Definition:
1. **Cirrhosis with ascites**

2. **Serum Cr greater than 1.5mg/dl**

3. No improvement of serum Cr (decrease to a level of less than 1.5mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin defined as 1g/kg body weight per day up to a max of 100g/day.

4. **Absence of shock**

5. No current or recent treatment with nephrotoxic drugs

6. Absence of parenchymal kidney disease as indicated by proteinuria (greater >500mg/day), microhematuria (>50 RBC/HPF), and/or abnormal renal ultrasonography.

Arroyo V, et al. Journal of Hepatology
Types of HRS

Type 1: Rapidly progressive. Defined as a **doubling of the initial serum creatinine** concentration to a level greater than **2.5 in less than 2 weeks**. It can appear spontaneously, but often after a precipitating event such as **SBP**

Type 2: **Moderate renal failure with a steady progressive course** *(Ser Cr >1.5)* that does not meet the definition of HRS 1. Typically associated with **refractory ascites**.

### HRS 1 and 2: Probably Different Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>HRS-1</th>
<th>HRS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Failure</td>
<td>Acute, Rapid Decline</td>
<td>Slow, steady decline</td>
</tr>
<tr>
<td>Circulatory Function</td>
<td>Rapidly Impaired</td>
<td>Stable</td>
</tr>
<tr>
<td>Inciting Event</td>
<td>Usually present (SBP)</td>
<td>Spontaneous in most cases</td>
</tr>
<tr>
<td>Clinical Course</td>
<td>Rapid Hepatorenal Failure and Death</td>
<td>Refractory Ascites ultimately culminating in death over months time</td>
</tr>
<tr>
<td></td>
<td>(Avg survival 2 weeks without tx)</td>
<td></td>
</tr>
<tr>
<td>Organs Effected</td>
<td>Kidneys, Liver, Heart, Brain, Adrenals</td>
<td>Kidneys</td>
</tr>
<tr>
<td></td>
<td>(Mimics Severe Septic Shock)</td>
<td></td>
</tr>
</tbody>
</table>
Mortality

Which of the following ultimately leads to the development of HRS?

1. Ineffective Cardiac Output
2. Hepatic Vasoconstriction
3. Decreased Effective Arterial Blood Volume
4. Splanchnic Arterial Vasodilation
Effective Arterial Blood Volume

- Intravascular Volume
- Cardiac Output
- Systemic Vascular Resistance
Pathophysiology of HRS

HEPATOrenal syndrome

Cirrhosis

- Elevated splanchnic nitric oxide
- Portal hypertension

Splanchnic Arterial Vasodilation

- Arterial underfilling
- Decreased total systemic vascular resistance
- Decreased effective arterial blood volume

- Sodium and water retention
  - Increase in plasma volume
- Stimulation of vasoconstrictors: RAAS, SNS, AVP

- Central hypovolemia & impaired cardiac function
  - Fall in cardiac output

- Development of severe renal vasoconstriction

Hepatorenal Syndrome
Pathophysiology of HRS

CIRRHOSIS

Elevated splanchnic nitric oxide

Portal hypertension

SBP, bacterial infections, LVP, Alcoholic hepatitis

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Arterial underfilling

Decreased total systemic vascular resistance

Decreased effective arterial blood volume

Sodium and water retention

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Central hypovolemia & impaired cardiac function

Fall in cardiac output

Development of severe renal vasoconstriction

Hepatorenal Syndrome
Causes of Splanchnic Vasodilation

1. Abnormal response of portal vasculature to neurohormonal stimulation.
2. NO
3. Classic and Alternate RAS pathways
4. Carbon Monoxide (Bolognesi, J Pharm Exp Ther 2007)
5. Glucagon (Sieber, Am J Phys 1992)
6. Prostacyclin (Fernandez, Gastroenterology 1998)
7. Adrenomedullin (Guerva, Gastroenterology 1998)
Abnormal Response to Neurohormonal Stimulation

-33 cirrhotic pts undergoing liver transplant and 30 organ donors
-blocked beta and alpha-2 receptors and measured response to alpha-1 agonist (methoxamine)

Increased Shear-Stress

Increased Portal HTN

Over time, Decreased Effective Arterial Volume Leading to HRS

Fig. 5. Splanchnic overproduction and intrahepatic deficit of endothelial NO. ? = unknown. A stimulus originated from increased intrahepatic resistance is likely.

New Understandings of the Role of RAS in HRS

Expression of AngII and Ang-(1-7) in Cirrhotic Patients v Control

Pathophysiology of HRS

HEPATORENAL SYNDROME

CIRRHOSIS

Elevated splanchnic nitric oxide

Portal hypertension

SBP, bacterial infections, LVP, Alcoholic hepatitis

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Stimulation of vasoconstrictors: RAAS, SNS, AVP

Central hypovolemia & impaired cardiac function

Development of severe renal vasoconstriction

Hepatorenal Syndrome

Fall in cardiac output
Ineffective Cardiac Output: Clinical Observations

Changes in left ventricular function during exercise in alcoholic and non-alcoholic cirrhosis (mean±standard error)

<table>
<thead>
<tr>
<th></th>
<th>Resting ejection fraction (%)</th>
<th>Peak exercise ejection fraction (%)</th>
<th>Change in end systolic volume (%)</th>
<th>Change in end diastolic volume (%)</th>
<th>Change in stroke volume (%)</th>
<th>Change in cardiac output (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic cirrhosis</td>
<td>55±3</td>
<td>56±4</td>
<td>+20±11</td>
<td>+22±6</td>
<td>+24±5</td>
<td>+96±14</td>
</tr>
<tr>
<td>Non-alcoholic cirrhosis</td>
<td>52±3</td>
<td>53±4</td>
<td>+20±7</td>
<td>+24±4</td>
<td>+26±5</td>
<td>+97±11</td>
</tr>
</tbody>
</table>

Under maximal exercise, cardiac output increased by only 97% in cirrhotic patients (1) compared to 300% in their clinically matched healthy subjects (2)

(1) Grose, J Hepatology, 1995;22.
(2) Poliner, Circulation, 1980;62.
Cardiac Output related to Development of Hepatorenal Syndrome

N=66 patients with cirrhosis and tense ascites
Followed Prospectively in same Hepatology Clinic
27 patient developed HRS

24 patients with cirrhosis and ascites were followed for 12 months

- Measured Cardiac Index at baseline

- 43% of patients with CI < 1.5 developed HRS-1 within 3 vs 5% of patients with a CI > 1.5 (p = 0.04)

- MELD score failed to predict mortality in these same patients

Moller Heart, 2002;87.

Decreased Pre-load

Cardiodepressant substances (NO, TNF-α, CO, bile acids, endotoxins)

Conductance abnormalities

Fibrosis, oedema

β receptor/post-receptor defects

Abnormal plasma membrane fluidity

Hyperdynamic circulation

Vagal dysfunction

Sympathetic dysfunction

CNS

SNS

K⁺

QTc
Pathophysiology of HRS

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Central hypovolemia & impaired cardiac function

Fall in cardiac output

Development of severe renal vasoconstriction

Hepatorenal Syndrome
Hepatorenal Reflex

Role of RAA

Table 4. Hormonal Levels During the Medical Treatment Phase (Midodrine, Octreotide, and Albumin) in Both Responders and Nonresponders

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 10)</th>
<th>Nonresponders (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Rx</td>
<td>End of Rx</td>
</tr>
<tr>
<td>Renin (N: 6.4-23.8 ng/L)</td>
<td>201 ± 78</td>
<td>39 ± 12*</td>
</tr>
<tr>
<td>Aldosterone (N: 27-444 pmol/L)</td>
<td>2574 ± 375</td>
<td>930 ± 341**</td>
</tr>
<tr>
<td>Norepinephrine (N: 0.8-2.4 nmol/L)</td>
<td>3.93 ± 0.54</td>
<td>4.03 ± 0.90</td>
</tr>
</tbody>
</table>

Abbreviations: Rx, medical treatment consisting of midodrine, octreotide, and albumin; N, normal.
*P < .05 versus pretreatment; **P < .01 versus pretreatment; \#P < .05 versus responders; \#\#P < .01 versus responders.

Wong, Hepatology 2004;40: 55-64.
Pathophysiology of HRS

CIRRHOSIS

- Elevated splanchnic nitric oxide
- Portal hypertension
- SBP, bacterial infections, LVP, Alcoholic hepatitis

Splanchnic Arterial Vasodilation

- Arterial underfilling
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Development of severe renal vasoconstriction

Hepatorenal Syndrome
Renal Vasoconstriction

The RI of Cortical Vessels correlated positively with PRA and Ser Cr levels and inversely with Cr Cl and Ur Na excretion

56 Cirrhotic Patients:
- 10 w/ refractory ascites
- 28 w/ medical responsive ascites
- 19 w/out ascites

Case Continued

PE: BP 88/50 (baseline according to patient and records), pulse 99, Temp 98.4, RR 14, 98% RA sats
A&O x 3, icteric sclera
JVP flat
Spider angiomata present over the chest
Heart without murmurs
Lungs clear
Abdomen with tense ascites
1+ bilateral LEE to the knees
Given the current history and exam, HRS-1 is on you differential diagnosis. Which of the following are the best next steps to determine the true etiology of this patient’s AKI?

1. Stop diuretics
2. Initiate albumin 1g/kg
3. Obtain a urinalysis
4. Obtain a renal sono
5. 2,3, and 4 only
6. 1, 3, and 4 only
7. 1, 2, 3, and 4
Algorithmic Approach to HRS

Figure 3: Diagnostic flow chart of HRS in patients with cirrhosis

In some cases, renal failure may not be due to a single cause but to a combination. In these cases, the identification of the causative factors may be difficult with the current diagnostic tools.

Labs

Creatinine 3.4 (1.0 upon leaving previous institution)
Urinalysis: Bland, no casts or red cells, no indication of infection, no protein
Total Bilirubin 4.0 (baseline)
INR 1.8 (baseline)
Ur Na 20 (on lasix)
Renal Sono: no obstruction, normal size kidneys
Urine eosinophils: negative
Paracentesis not consistent with SBP
Cr 4.0 after two days of cessation of diuretics and albumin infusion at 1g/kg body weight
You are now confident in your diagnosis of HRS-1. Which of the following is the best treatment for HRS?

1. Terlipressin and albumin
2. Midodrine, octreotide, and albumin
3. Liver transplant
4. TIPS
5. Albumin alone
Treatment of HRS

Figure 1: Proposed pathogenesis of HRS in cirrhosis, according to the arterial vasodilatation theory, and effective therapeutic interventions.
Survival of HRS-1 Patients treated for HRS with terlipressin: Transplant vs nontransplant

Cohort of 99 patients followed for 180 days:

-97% survival for transplant patients

-47% for terlipressin responders who were not transplanted

-4% for terlipressin non-responders who were not transplanted

Survival post transplant between HRS patients and non-HRS patients

Retrospective Review of 300 patients:

- Non HRS survival 1 and 2 year (87% v 82%)

- HRS survival 1 and 2 year (76%)

- No statistical difference in survival between the two groups

**FIGURE 1.** Actuarial patient survival rates in patients with and without HRS following orthotopic liver transplantation.

Comparative Outcomes of Transplanted Patients with and without HRS

Cohort of 569 pts (56 HRS and 516 non-HRS) from Baylor Dallas
All Recovered Renal Function

<table>
<thead>
<tr>
<th>Patients</th>
<th>HRS</th>
<th>Non-HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Stay</td>
<td>42 days</td>
<td>27 days</td>
</tr>
<tr>
<td>Occurrence of ESRD</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Transplant Outcomes in Patients with HRS who responded to Treatment vs Patients without HRS

<table>
<thead>
<tr>
<th>Patients</th>
<th>HRS (N=9)</th>
<th>Non-HRS (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Child’s Score</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>BUN (P=.001)</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>Ser Cr</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Etiology of Liver Dz</td>
<td>Mix of Viral, ETOH, and other</td>
<td>Mix of Viral, ETOH, and other</td>
</tr>
</tbody>
</table>

Transplant Outcomes in Patients with HRS who responded to Treatment vs Patients without HRS

<table>
<thead>
<tr>
<th>Patients</th>
<th>HRS (Not Significant)</th>
<th>Non-HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year survival</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>Development of Renal Failure at 6 mo</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Infections Requiring Ab</td>
<td>22%</td>
<td>33%</td>
</tr>
<tr>
<td>Acute Rejection based on Histology</td>
<td>33%</td>
<td>41%</td>
</tr>
<tr>
<td>ICU days</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hospital days</td>
<td>27</td>
<td>31</td>
</tr>
</tbody>
</table>

Clinical Parameters Before and After OLT in Patients with HRS

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before OLT (HRS) N=11</th>
<th>After OLT (HRS) (P&lt;0.001 for all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr Cl (mL/min)</td>
<td>46 (22)</td>
<td>77 (64)</td>
</tr>
<tr>
<td>Ser Na (mEq/L)</td>
<td>130 (127)</td>
<td>138 (138)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>81 (71)</td>
<td>101 (96)</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>901 (1273)</td>
<td>204 (222)</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>26.5 (45)</td>
<td>3.85 (3.98)</td>
</tr>
<tr>
<td>ALD (ng/dl)</td>
<td>78 (97)</td>
<td>19 (20.6)</td>
</tr>
</tbody>
</table>

Liver transplantation is the best treatment for both type 1 and type 2 HRS. HRS should be treated before liver transplantation, since this may improve post-liver transplant outcomes.

Level of Evidence: A1
Treatment of HRS

Figure 1: Proposed pathogenesis of HRS in cirrhosis, according to the arterial vasodilation theory, and effective therapeutic interventions.
Transjugular Intrahepatic Portosystemic Shunt

Effects of TIPS on RAS

TIPS for HRS 1 and 2

Prospective Study of 41 non-transplant patients:
-20 HRS-1
-21 HRS-2
-Exclusion: TB>15, Child >12

-Natural Progression of Type 1 is 0% at 1 year

-Natural Progression of Type 2 is 35% at 1 year

Limitations for TIPS

Absolute Contraindications:
1. Pulmonary HTN
2. Congestive Heart Failure

Relative, but Observed, contraindications:
1. severe pre-tips encephalopathy
2. TB >5
3. Age >60
4. INR >2
5. Child’s score >12. (Class A=5-6, B=7-9, C=10-15)
6. MELD >18
7. Portal Vein Thrombosis
8. Hepatoma
Although the insertion of TIPS may improve renal function in some patients, there are insufficient data to support the use of TIPS as a treatment of patients with type 1 HRS.

Level of Evidence: B1
Treatment of HRS

Gines, Lancet
2003;362:1819-1827.

Figure 1: Proposed pathogenesis of HRS in cirrhosis, according to the arterial vasodilatation theory, and effective therapeutic interventions.
Physiology Behind the Use of Vasopressin

Vascular Bed Sensitivity to Vasopressin
Muscle > Mesentery > Kidney

Schmid, American Journal of Physiology
1974;227:998-1004.
Terlipressin for Treatment of HRS-1

RCT, placebo, double-blind

-56 patients terlipressin and albumin

-56 patients albumin alone

-Success: Cr less than or equal to 1.5 for 48 hours or more

-HRS reversal 34% vs 13% (p=0.008)
Terlipressin for Treatment of HRS-1

Sanyal A. A RCT of Terlipressin for Type 1 HRS. Gastroenterology, 2008; 134: 1360-1368.
Limitations of Terlipressin

- Failure to reverse HRS in nearly 50% or more of patients
- Cannot be used in patients with vascular disorders (CAD, Cardiomyopathies, Arterial HTN, CVA, PAD, Asthma)
- SE include Abd pain, cutaneous ischemia, arrhythmias
- Not available in the US
Can you predict who will respond to Terlipressin?

Prospective Study:

39 patients treated with terlipressin and albumin

-Independent predictors of response included the following:

Serum Bilirubin <10
Initial Cr< 5
Increase in MAP>5 after three days of tx

Can you predict who will not Respond to Terlipressin?

Table 2. Summary of the effects of baseline characteristics on HRS reversal (multivariate analysis, ITT population).

<table>
<thead>
<tr>
<th>Baseline parameter</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic Hepatitis</td>
<td>0.98</td>
<td>0.32-2.94</td>
<td>0.965</td>
</tr>
<tr>
<td>Gender</td>
<td>0.68</td>
<td>0.23-1.96</td>
<td>0.472</td>
</tr>
<tr>
<td>MELD Score</td>
<td>0.92</td>
<td>0.80-1.05</td>
<td>0.223</td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td>0.89</td>
<td>0.62-1.27</td>
<td>0.513</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.51</td>
<td>0.28-0.93</td>
<td>0.029</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.02</td>
<td>0.97-1.08</td>
<td>0.374</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>0.98</td>
<td>0.94-1.02</td>
<td>0.348</td>
</tr>
</tbody>
</table>

RR: relative risk; 95% CI: 95% confidence intervals.

Low Urine Na

Prospective Study of 68 patients unable to have a transplant:

- All received vasoconstrictors
- Ur Na less than 5 was associated with survival

![Survival graph](image)

**Fig. 2** Survival by urine Na 5 mEq/l or less versus greater than 5 mEq/l

Guidelines

• Drug therapy of type 1 hepatorenal syndrome Terlipressin (1 mg/4–6 h intravenous bolus) in combination with albumin should be considered the **first line therapeutic agent for type 1 HRS**.

• The aim of therapy is to improve Cr to less than or equal to 1.5

• If Cr does not decrease by 25% after 3 days of tx, terlipressin can be increased stepwise to a max dose of 2mg/4h.

• For patients with partial or no response, tx should be discontinued after 14 days

• Level of Evidence: A1

### Terlipressin vs Noradrenalin

Randomized, non-blinded trial of 22 patients, 9 with HRS-1 and 13 with HRS-2

<table>
<thead>
<tr>
<th>Patients</th>
<th>Terlipressin</th>
<th>Noradrenalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Child’s Score</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Terlipressin</th>
<th>Noradrenalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of HRS</td>
<td>83%</td>
<td>70%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>60%</td>
<td>29%</td>
</tr>
<tr>
<td>Transplanted</td>
<td>67%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Limitations of NE

- Similar to Terlipressin (ischemia, arrhythmias)
Midodrine/Octreotide/Albumin  
Retrospective Trial of 81 patients, 60 with octreotide/midodrine and 21 controls

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>28.3</td>
<td>25.8</td>
</tr>
<tr>
<td>Child’s Score</td>
<td>11.4</td>
<td>10.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day Mortality (P&lt;0.05)</td>
<td>43%</td>
<td>71%</td>
</tr>
<tr>
<td>3 month Mortality of Survivors at 30 Days (P&lt;0.03)</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>60% f/u</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained Reduction in Cr (P&lt;0.05)</td>
<td>40%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Limitations of Midodrine

- Overall, fairly well tolerated
- Can cause urinary retention (10%)
- Use caution in patients with severe heart dz

- Dosing may make a difference: In the previously mentioned trial, those HRS-1 patients who got 15mg tid responded 88% of the time vs 33% response in patients getting <12.5mg tid.
Guidelines

• Potential alternative therapies to terlipressin include norepinephrine or midodrine plus octreotide, both in association with albumin, but there is very limited information with respect to the use of these drugs in patients with type 1 HRS

• Level of Evidence: B1
You have a patient with HRS whose Serum Cr is 3 when you start therapy and you want to decrease the Ser Cr to 1.5. How should you titrate your vasopressor?

1. Titrate Vasopressor to goal increase in MAP of **3mmHg**.
2. Titrate Vasopressor to goal increase in MAP of **6mmHg**.
3. Titrate Vasopressor to goal increase in MAP of **8mmHg**.
4. Titrate Vasopressor to goal increase in MAP of **10mmHg**.
5. Titrate Vasopressor to goal increase in MAP of **13mmHg**.

Guidance on medication titration

Pooled Analysis of 501 patients across 21 studies:

- Increase in MAP was associated with a decrease in serum Cr regardless of vasoconstrictor used (terlipressin v NE v midodrine)

- Increase in MAP was associated with a decrease in serum Cr regardless of HRS type (1 vs 2)

- For every 1mm Hg increase in MAP there is a 0.12 mg/dL decrease in Serum Cr

<table>
<thead>
<tr>
<th>Baseline SCr</th>
<th>SCr Reduction Required to Achieve Goal</th>
<th>Predicted Increase in MAP to Achieve Desired SCr Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 mg/dL</td>
<td>25.0%</td>
<td>3.7 (2.5-4.9)</td>
</tr>
<tr>
<td>2.5 mg/dL</td>
<td>40.0%</td>
<td>6.1 (4.7-7.5)</td>
</tr>
<tr>
<td>3.0 mg/dL</td>
<td>50.0%</td>
<td>8.5 (6.7-10.3)</td>
</tr>
<tr>
<td>3.5 mg/dL</td>
<td>57.1%</td>
<td>10.9 (8.5-13.3)</td>
</tr>
<tr>
<td>4.0 mg/dL</td>
<td>62.5%</td>
<td>13.3 (10.3-16.3)</td>
</tr>
</tbody>
</table>

Abbreviations: HRS, hepatorenal syndrome, MAP, mean arterial pressure; SCr, serum creatinine.

*aSCr goal is 1.5 mg/dL.

*bValues given as mean (95% confidence interval).

Initial Drug Dosages

Albumin: -1g/kg (no more than 100g) on Day 1
- 20-60g/day (we use 40g) after

Terlipressin: 1mg every 4-6 hours

NE: 0.5mg/h

Midodrine: 7.5mg tid with Octreotide 100mcg tid
Combination Therapy with Midodrine and TIPS

Wong, Hepatology 2004:40;55-64.
Clinical Case

- Pt started on Midodrine and Octreotide titrated up to raise MAP by 15mmHg and Albumin 20g daily was administered
- Cr declined to 1.0 after 7 days of treatment
- TB declined to 2.0, INR 1.5, Child Score 10
- TIPS placed on day 14
- Renal function remained stable over next 3 months at which time she was transplanted
Prevention of HRS

1. Treatment of SBP

2. Primary and Secondary Prevention of SBP

3. Treatment of Acute ETOH Hepatitis

4. Albumin infusion with Large Volume Paracentesis
## Treatment of SBP using Albumin

Randomized Trial of 126 pts given albumin 1.5g/kg day 1 and 1 g/kg day 3

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin and Cefotaxime</th>
<th>Cefotaxime Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Failure Developed (P=0.002)</td>
<td>10%</td>
<td>33%</td>
</tr>
<tr>
<td>Hospital Mortality (P=0.01)</td>
<td>10%</td>
<td>29%</td>
</tr>
<tr>
<td>Three Month Mortality (P=0.03)</td>
<td>22%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Sort, NEJM 1999;341:403-409.
Primary Prophylaxis of SBP
74 patients randomized to daily norfloxacin or placebo

Ascitic fluid protein level of less than 1.5g/dL and one or both of the following:

1. Ser Cr greater than or equal to 1.2, BUN greater than or equal to 25, or Ser Na less than or equal to 130mEq/L.
2. Child’s Score of greater than or equal to 9 with Ser bilirubin level of greater than or equal to 3 mg/dL.

Fernandez, Gastroenterology, 2007;133:818-824.
## Primary Prophylaxis of SBP

<table>
<thead>
<tr>
<th>Patients</th>
<th>Norfloxacin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year probability of SBP (P&lt;0.001)</td>
<td>7%</td>
<td>61%</td>
</tr>
<tr>
<td>1 year probability of developing HRS (P=0.02)</td>
<td>28%</td>
<td>41%</td>
</tr>
<tr>
<td>3 months probability of survival (P=0.003)</td>
<td>94%</td>
<td>62%</td>
</tr>
<tr>
<td>1 year probability of survival (P&lt;0.05)</td>
<td>60%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Fernandez, Gastroenterology, 2007;133:818-824.
Diagnosis and Secondary Prophylaxis for SBP

1. Patients with ascites should have a surveillance tap at the time of admission to the hospital for detection of unsuspected SBP given its high prevalence and non-specific clinical findings. (Borzio, Dig Liver Dis 2001;33:41-48.)

2. Patients with cirrhosis and gastrointestinal hemorrhage should be treated with ceftriaxone daily or bid norfloxacin for 7 days. (Soriano, Gastro 1991;100:477-481. and Fernandez, Gastro 2006;131:1049-1056.)


Runyon, Hepatology 2009;49.
Prevention of HRS in pts with ETOH Hepatitis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pentoxifylline (n=49)</th>
<th>Untreated (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Term Survival (P=0.037))</td>
<td>24.5% Died during index hospitalization</td>
<td>46.1% Died during the index hospitalization</td>
</tr>
<tr>
<td>Development of HRS in patients who died RR of 0.29 (P=0.009)</td>
<td>50%</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

Thought secondary to the decrease in TNF synthesis prevented by pentoxifylline.

Evangelos, Gastroenterology, 2000;119:1637-1648.
N-Acetylcysteine

Randomly assigned 174 patients:

-NAC + Prednisolone v Prednisolone

-Lower 30 day mortality 8% v 24%

-Mortality difference disappeared at 6 months

-Death due to HRS was statistically different at six months: 9% v 22%

Prevention of Paracentesis-Induced Circulatory Dysfunction (Measured by PRA and PAC levels)
73 pts (35 saline, 37 albumin)

Sola-Vera, Hepatology 2003;37:1147-1153.
Clinical Take Home Points

1. Clinical Assessment of HRS:
   A. **History and Physical** (looking for other signs of AKI such as contrast or nsaid)
   B. **UA** looking for hematuria/proteinuria
   C. **Renal Sono** looking for intrinsic/obstructive causes of AKI
   D. **Stop all diuretics**
   E. Volume Challenge with **1g/kg/day albumin (up to 100g) for two consecutive days**

2. Treatment:
   A. **Transplant is the best option** for all HRS patients
   B. Terlipressin is the drug of choice for HRS (In the US, **midodrine and Octreotide v NE. All regimens should use albumin**
   C. TIPS is not first line treatment for HRS; however, it may be used in select patients

3. Treatment Guidance:
   A. Elevated Bilirubin (>10) and Cr (>5) portend poor response
   B. **Increase in MAP parallels decrease in Cr (try to get MAP increased by 5mmHG by day 3 and use prognostic table to determine goal MAP based on initial Cr**
Clinical Take Home Points

The best way to address HRS is through prevention

A. Treatment of SBP with albumin and 3\textsuperscript{rd} Gen Ceph
B. Primary and Secondary Prophylaxis of SBP
C. Treatment of ETOH Hepatitis
D. Use of albumin 8g/liter of ascites removed, in all Large Volume Taps
Thank You

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Greg Bowling, MD

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