Hepatorenal Syndrome Type 1 (HRS-1): A Diagnostic and Therapeutic Challenge

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September 6th, 2014
3rd Southeastern Kidney Disease Consortium Conference
Charleston, SC
Outline

- Historical Perspective
- Diagnosis: Current definition and pitfalls
- Treatment Options
  - Albumin + Vasoconstrictors
    - *Does it matter what vasoconstrictor we choose or how we use it?*
  - Paracentesis / Decompression
    - *“To tap or not to tap”?*
## Renal Failure in Laennec's Cirrhosis of the Liver. I. Description of Clinical and Laboratory Features

By Solomon Papper, M.D., Joseph L. Belsky, M.D., and Kenneth H. Bleifer, Captain, USAF (MC), Boston, Massachusetts

<table>
<thead>
<tr>
<th>ETOH Cirrhosis Ascites</th>
<th>Preceding Event</th>
<th>Serum Sodium (mEq/L)</th>
<th>SBP DBP</th>
<th>Bilirubin (mg/dL)</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n = 8)</td>
<td>GI bleeding</td>
<td>116 - 143</td>
<td>90-110</td>
<td>2 - 16</td>
<td>“frequently but not always hyaline &amp; granular casts, albumin, RBCs”</td>
</tr>
<tr>
<td>Group II (n = 3)</td>
<td>Paracentesis</td>
<td>117 - 125</td>
<td>100</td>
<td>2.6 - 17</td>
<td>“trace albumin, occasional RBCs”</td>
</tr>
<tr>
<td>Group III (n = 5)</td>
<td>Progressive Jaundice</td>
<td>120 - 128</td>
<td>90</td>
<td>4 - 34</td>
<td>“albumin, RBCs”</td>
</tr>
<tr>
<td>Group IV (n = 5)</td>
<td>None</td>
<td>130 - 140</td>
<td>90</td>
<td>1.6 - 15</td>
<td>“bland”</td>
</tr>
</tbody>
</table>

Am J Med, 1964
All died in kidney failure and hepatic coma.

Kidney biopsy of 18/22 patients revealed occasional minimal tubular cell flattening and bile staining, but were essentially normal.

“…we propose that the present observations, both clinical and laboratory, are most consistent with the presence of reduced glomerular filtration rate and renal blood flow, rather than renal parenchymal disease.”
HRS: A Functional Disorder

7 kidneys from patients with liver cirrhosis (1 per pt., and 2 from 1 pt.) were transplanted into 7 ESRD recipients.

Duration of HRS: 5 - 104 days

Urine: all Na<10mEq/l; 2 had granular casts

Allograft function by day 14: 6/7 (86%)!
RECOVERY FROM “HEPATOrenal SYNDrome” AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Shunzaburo Iwatsuki, M.D., Mordecai M. Popovtzer, M.D., Jacques L. Corman, M.D., Makoto Ishikawa, M.D., Charles W. Putnam, M.D., Fred H. Katz, M.D., and Thomas E. Starzl, M.D., Ph.D.

- 3 pts. With ESLD and HRS developed 6-14 days prior, underwent OLT.
- All 3 gained adequate kidney function within 2 weeks.
HRS-1: 2007 Definition by IAC

Box 1 | New diagnostic hepatorenal syndrome criteria in cirrhosis*

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l (1.5 mg/dl)
- No improvement of serum creatinine (decrease to a level of ≤133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

*Criteria have been developed by the International Ascites Club. Reproduced from [Gut, Salerno, F. et al. 56, 1310–1314. Copyright 2006, with permission from BMJ Publishing Group Ltd.]

- CVP ≥ 8 mmHg ?
- What if Cr ↑ from 0.6 to 1.3 mg/dl?
- What if Cr ↓ from 4.0 to 2.5 mg/dl after fluids?
- > 10 rbc / hpf w/o Foley ?
- Granular casts?
- IAP < 25 mmHg ?
- UNa < 20 mEq/L ?

Arroyo V, Nat Nephrol Rev 2011
HRS-1: A Diagnostic Challenge

- No test for definite diagnosis
- Clinical picture often cloudier than desired
- HRS-1 and ATN may coexist (so-called “HRS physiology”)
- 2 initiatives to redefine acute kidney dysfunction in ESLD:
  - Acute Dialysis Quality Initiative (ADQI)\(^1\)
  - Working Party Statement (WPS)\(^2\)
    *Merely transferred the AKIN/RIFLE criteria without addressing the distinction between HRS and ATN or other causes of AKI*
- HRS is the cause of AKI in only 10-15% of ESLD subjects\(^3\)

1. Nadim M et al, Critical Care 2012
2. Wong F et al, Gut 2011
Summary (1)

- Diagnosis of HRS is challenging and requires careful clinical evaluation.
- In the absence of a gold-standard for HRS diagnosis, an effort to integrate a revised version of the traditional pathophysiology-based definition of HRS with the current AKI terminology is necessary to guide physicians to the correct diagnosis.
HRS Treatment

- What do we accomplish if HRS is successfully treated?

R: HR 0.5 (0.3-0.7)

NR (n=5): 0.4 m
R (n=16): 5 m

1. Restuccia et al. J Hepatol 2004
2. Rice et al. Transplantation 2011

NR (n=16): 81%
R (n=11): 90%

no HRS: 95%
NR: 60%
R: 95%

1-year
3-year
What do we accomplish if HRS is successfully treated?


180 day survival

- R: 41% (7/17)
- NR: 4% (2/47)
- 57% (20/35)
HRS Treatment: Vasoconstrictors

- Dopamine
- Midodrine / Octreotide
- Ornipressin
- Terlipressin
- Vasopressin
- Norepinephrine
HRS Treatment: Vasoconstrictors

- Dopamine
- Midodrine / Octreotide
- Ornipressin
- Terlipressin
- Vasopressin
- Norepinephrine
Treatment of Hepatorenal Syndrome: Midodrine + Octreotide vs. Dopamine
Prospective Non-Parallel Trial

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th>Midodrine + Octreotide (n = 5)</th>
<th>Dopamine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 3</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>HRS type 1/2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>4.3 ± 1</td>
<td>6.1 ± 1</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>5.0 ± 0.4</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Urine Output</td>
<td>680 ± 92</td>
<td>479 ± 104</td>
</tr>
<tr>
<td>Serum Na</td>
<td>130 ± 3</td>
<td>128 ± 3</td>
</tr>
<tr>
<td>MAP</td>
<td>76 ± 3</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>0/1/4</td>
<td>0/1/7</td>
</tr>
</tbody>
</table>

Angeli et al. Italy. Hepatology 1999
# Treatment of Hepatorenal Syndrome: Midodrine + Octreotide vs. Dopamine

## Prospective Non-Parallel Trial

Angeli et al. Italy. Hepatology 1999

| STUDY DESIGN |  
|--------------|--------------------------------------------------|
| **Midodrine + Octreotide** *(n = 5)* | **Dopamine** *(n = 8)*  
| **Albumin** | All patients: 20 – 40 g/d IV day 1 + 20 – 40 g if CVP < 12 mmHg or if PRA not ↓ 50% by day 3  
| **Drug Dose** | Midodrine: 7.5-12.5 mg po tid  
Octreotide: 100-200 µg sc tid  
2-4 µg/kg/min  
| **Titration** | Rise in MAP ≥ 15 mmHg  
sCr or Uv  
| **Paracentesis** | 3-L as needed  
| **Enrollment** | Worsening renal fxn 5 days prior  
| **Exclusion** | Recent GI bleed; hepatic encephalopathy, infection |
Treatment of Hepatorenal Syndrome: Midodrine + Octreotide vs. Dopamine
Prospective Non-Parallel Trial

% improved Cr by day 5

- Midodrine/Octreotide
- Dopamine

Survival by d 30

- Midodrine/Octreotide: 80%
- Dopamine: 12.5%

RRT

- Midodrine/Octreotide: 20%
- Dopamine: 37.5%

Angeli et al. Italy. Hepatology 1999
# Treatment of Hepatorenal Syndrome: Midodrine + Octreotide vs. Dopamine Prospective Non-Parallel Trial

Angeli P. Hepatology 1999

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Baseline</th>
<th>Day 5</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Midodrine + Octreotide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Cr</td>
<td>5.0 ± 0.8</td>
<td>4.6 ± 1.3</td>
<td>3.3 ± 0.7</td>
</tr>
<tr>
<td>Urine Output</td>
<td>680 ± 92</td>
<td>1040 ± 112</td>
<td>1320 ± 97</td>
</tr>
<tr>
<td>MAP</td>
<td>76 ± 3</td>
<td>91 ± 5</td>
<td>97 ± 7</td>
</tr>
<tr>
<td>PRA</td>
<td>16.8 ± 2</td>
<td>7.7 ± 1</td>
<td>5.1 ± 1</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Cr</td>
<td>3.6 ± 0.6</td>
<td>5.5 ± 0.8</td>
<td>5.1 ± 1.5</td>
</tr>
<tr>
<td>Urine Output</td>
<td>698 ± 117</td>
<td>1578 ± 314</td>
<td>1578 ± 314</td>
</tr>
<tr>
<td>MAP</td>
<td>79 ± 4</td>
<td>75 ± 2</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>PRA</td>
<td>13.6 ± 1</td>
<td>13.3 ± 1</td>
<td>16.8 ± 4</td>
</tr>
</tbody>
</table>
Treatment of Hepatorenal Syndrome: Midodrine + Octreotide

Retrospective Trial

Skagen et al. Univ. Wisconsin J Clin Gastroenterol 2009

Survival 3-month For HRS 1

- Midodrine + Octreotide: 44%
- Untreated: 18%

p = 0.0004
HRS Treatment:
Vasoconstrictors

- Dopamine
- Midodrine / Octreotide
- Ornipressin
- Terlipressin
- Vasopressin
- Norepinephrine
HRS-1 Treatment
Terlipressin

~ 50-60 % response rate
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin (n = 56)</th>
<th>Placebo (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>51 ± 10</td>
<td>53 ± 11</td>
</tr>
<tr>
<td><strong>HRS type 1</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>15.0 ± 13</td>
<td>15.8 ± 15</td>
</tr>
<tr>
<td><strong>Serum Cr</strong></td>
<td>3.9 ± 2.1</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>2.6 ± 0.8</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td><strong>Serum Na</strong></td>
<td>131 ± 7</td>
<td>132 ± 7</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td>76 ± 11</td>
<td>77 ± 13</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td>33 ± 6</td>
<td>33 ± 6</td>
</tr>
</tbody>
</table>
Treatment of Hepatorenal Syndrome: Terlipressin vs. Placebo

Largest Randomized Controlled Trial

- Terlipressin
- Placebo

HR = HRS reversal
TS = treatment success

Sanyal et al. USA. Gastroenterol 2008
Treatment of HRS: Terlipressin (REVERSE Trial)

A Placebo-Controlled, Double-Blind Study to Confirm the Reversal of Hepatorenal Syndrome Type 1 With Terlipressin

This study has been completed.

Sponsor: Ikaria

Information provided by (Responsible Party): Ikaria

ClinicalTrials.gov Identifier: NCT01143248

First received: June 11, 2010
Last updated: March 12, 2014
Last verified: March 2014
History of Changes
HRS Treatment:
Vasoconstrictors

- Dopamine
- Midodrine / Octreotide
- Ornipressin
- Vasopressin
- Terlipressin
- Norepinephrine
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine (n = 10)</th>
<th>Terlipressin (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>56 ± 3</td>
<td>55 ± 2</td>
</tr>
<tr>
<td><strong>HRS type 1/2</strong></td>
<td>4/6</td>
<td>5/7</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>4.4 ± 1</td>
<td>5.1 ± 1</td>
</tr>
<tr>
<td><strong>Serum Cr</strong></td>
<td>2.3 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td><strong>Urine Output</strong></td>
<td>788 ± 84</td>
<td>698 ± 117</td>
</tr>
<tr>
<td><strong>Serum Na</strong></td>
<td>126 ± 2</td>
<td>124 ± 2</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td>71 ± 2</td>
<td>74 ± 3</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td>26 ± 1</td>
<td>26 ± 2</td>
</tr>
</tbody>
</table>
Treatment of Hepatorenal Syndrome: Norepinephrine vs. Terlipressin
Randomized Controlled Trial

Alessandria et al. Italy. J Hepatol 2007

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine</th>
<th>Terlipressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HRS Reversal</td>
<td>70 %</td>
<td>83 %</td>
</tr>
<tr>
<td>Recurrence</td>
<td>29 %</td>
<td>60 %</td>
</tr>
<tr>
<td>OLT</td>
<td>70 %</td>
<td>67 %</td>
</tr>
<tr>
<td>RRT</td>
<td>0 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>
## Treatment of Hepatorenal Syndrome: Norepinephrine vs. Terlipressin Randomized Controlled Trial

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Baseline</th>
<th>End of therapy (d15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norepinephrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Cr</td>
<td>2.3 ± 0.2</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Urine Output</td>
<td>788 ± 84</td>
<td>1583 ± 243</td>
</tr>
<tr>
<td>MAP</td>
<td>71 ± 2</td>
<td>84 ± 2</td>
</tr>
<tr>
<td>PRA</td>
<td>15 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td><strong>Terlipressin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Cr</td>
<td>2.5 ± 0.4</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Urine Output</td>
<td>698 ± 117</td>
<td>1578 ± 314</td>
</tr>
<tr>
<td>MAP</td>
<td>74 ± 3</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>PRA</td>
<td>21 ± 5</td>
<td>7 ± 3</td>
</tr>
</tbody>
</table>

Alessandria et al. Italy. J Hepatol 2007
An Open Label, Pilot, Randomized Controlled Trial of Noradrenaline *Versus* Terlipressin in the Treatment of Type 1 Hepatorenal Syndrome and Predictors of Response

(*Am J Gastroenterol* 2008;103:1689–1697)  
Department of Gastroenterology, G. B. Pant Hospital, New Delhi, India

<table>
<thead>
<tr>
<th>BASELINE CHARACTERISTICS</th>
<th><strong>Norepinephrine (n = 20)</strong></th>
<th><strong>Terlipressin (n = 20)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>48 ± 13</td>
<td>48 ± 9</td>
</tr>
<tr>
<td><strong>HRS type 1</strong></td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>5.2 ± 1</td>
<td>7.6 ± 1</td>
</tr>
<tr>
<td><strong>Serum Cr</strong></td>
<td>3.3 ± 0.4</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td><strong>Urine Output</strong></td>
<td>479 ± 184</td>
<td>449 ± 215</td>
</tr>
<tr>
<td><strong>Serum Na</strong></td>
<td>125 ± 2</td>
<td>125 ± 2</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td>78 ± 5</td>
<td>81 ± 11</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td>31 ± 6</td>
<td>29 ± 6</td>
</tr>
</tbody>
</table>
Treatment of Hepatorenal Syndrome: Norepinephrine vs. Terlipressin
Randomized Controlled Trial

Median duration of treatment: 7 days

Survival
- Norepinephrine: 55%
- Terlipressin: 55%

Sharma et al. India. Am J Gastroenterol 2008

% HRS Reversal

- Norepinephrine: 50%
- Terlipressin: 50%

Sharma et al. India. Am J Gastroenterol 2008
Treatment of Hepatorenal Syndrome: Norepinephrine vs. Terlipressin
Randomized Controlled Trial

Singh et al. India. J Hepatol 2012
HRS Treatment:
Raising the Mean Arterial Pressure

Table 4. Variables with Independent Predictive Value of Response to Treatment with Terlipressin and Albumin in Patients with Type 1 HRS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum bilirubin</td>
<td>0.901</td>
<td>0.834-0.974</td>
<td>0.009</td>
</tr>
<tr>
<td>Δ MAP at day 3 ≥5 mm Hg</td>
<td>9.482</td>
<td>1.007-89.316</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Table 5. Response Rate According to Variables with Independent Predictive Value of Response to Treatment with Terlipressin and Albumin in Patients with Type 1 HRS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum bilirubin &lt;10 mg/dL</th>
<th>Serum bilirubin ≥10 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ MAP at day 3 ≥5 mm Hg</td>
<td>7/7 (100)</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>Δ MAP at day 3 &lt;5 mm Hg</td>
<td>9/17 (53)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>16/24 (67)</td>
<td>2/15 (13)</td>
</tr>
</tbody>
</table>

Nazar et al. Hepatology 2010

Terlipressin

Boyer et al. J Hepatol 2011

Placebo
Therapeutic Response to Vasoconstrictors in Hepatorenal Syndrome Parallels Increase in Mean Arterial Pressure: A Pooled Analysis of Clinical Trials

Juan Carlos Q. Velez, MD,¹ and Paul J. Nietert, PhD²

Electronic database search for treatment of HRS in adults: 453 references examined

421 references excluded due to publication type (i.e., case report, review) or absence of HRS or vasoconstrictor therapy

32 eligible studies involving vasoconstrictor therapy in HRS identified and reviewed

11 studies excluded due to unavailable relevant data

MAP: Not reported at all in 8 studies; baseline but not serial values reported in 3 studies.

Serum Creatinine: Not reported at all in 2 studies; baseline but not serial values reported in 8 studies.

21 manuscripts selected for analysis

10 dual-arm studies → 20 cohorts

11 single-arm studies

5 studies: 1 group reported → 5 cohorts

6 studies: 2 subgroups reported → 12 cohorts

37 cohorts entered into the analysis
HRS Treatment: Raising the Mean Arterial Pressure

Velez & Nietert. MUSC, USA. Am J Kidney Dis 2011
## HRS Treatment:
**Raising the Mean Arterial Pressure**

<table>
<thead>
<tr>
<th>Study (year, country)</th>
<th>HRS Type</th>
<th>Study Design</th>
<th>Age (y); Sex*</th>
<th>Drug Tested</th>
<th>Colloid Used (dose)</th>
<th>Cohort as Reported and Entered in the Analysis</th>
<th>No. per Arm</th>
<th>Baseline MAP (mm Hg)b</th>
<th>Baseline SCR (mg/dL)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong43 (2004, CA)</td>
<td>1</td>
<td>Prospective, uncontrolled</td>
<td>55 ± 3 y; 79% M</td>
<td>Midodrine + octreotide</td>
<td></td>
<td>Responders vs nonresponders</td>
<td>10 vs 4</td>
<td>81 ± 5 vs 79 ± 4</td>
<td>2.6 ± 0.3 vs 3.9 ± 1.3</td>
</tr>
<tr>
<td>Saner29 (2004, DE)</td>
<td>1, 2</td>
<td>Prospective, uncontrolled</td>
<td>NA</td>
<td>NA</td>
<td>Tertlipressin</td>
<td>Tertlipressin-treated</td>
<td>7</td>
<td>58 ± 4</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Alessandra29 (2007, IT)</td>
<td>1, 2</td>
<td>Prospective, randomized, controlled</td>
<td>55 ± 2 y; 73% M</td>
<td>Norepinephrine; tertipressin</td>
<td>GPS</td>
<td>Norepinephrine-vs tertipressin-treated</td>
<td>10 vs 12</td>
<td>71 ± 2 vs 74 ± 3</td>
<td>2.3 ± 0.2 vs 2.5 ± 0.3</td>
</tr>
<tr>
<td>Sharma32 (2008, IN)</td>
<td>1</td>
<td>Prospective, randomized, controlled</td>
<td>48 ± 2 y; 85% M</td>
<td>Norepinephrine; tertipressin</td>
<td></td>
<td>Norepinephrine-vs tertipressin-treated</td>
<td>20 vs 20</td>
<td>81 ± 2 vs 78 ± 1</td>
<td>3.0 ± 0.5 vs 3.3 ± 1.3</td>
</tr>
<tr>
<td>Sanyal7 (2008, US &amp; RU)</td>
<td>1</td>
<td>Prospective, randomized, controlled</td>
<td>52 ± 1 y; 71% M</td>
<td>Tertlipressin; placebo</td>
<td>Alb (100 g; 25 g/d)</td>
<td>Tertlipressin-vs placebo-treated</td>
<td>56 vs 56</td>
<td>76 ± 1 vs 77 ± 2</td>
<td>3.9 ± 2.1 vs 3.8 ± 1.1</td>
</tr>
<tr>
<td>Martin-Lallah30 (2008, ES)</td>
<td>1, 2</td>
<td>Prospective, randomized, controlled</td>
<td>57 ± 2 y; 62% M</td>
<td>Tertlipressin + Alb; Alb</td>
<td>Alb (1 g/kg; 40 g/d)</td>
<td>Responders vs nonresponders</td>
<td>107 vs 131</td>
<td>75 ± 4 vs 68 ± 3</td>
<td>2.9 ± 0.8 vs 4.0 ± 2.1</td>
</tr>
<tr>
<td>Neri31 (2008, IT)</td>
<td>1</td>
<td>Prospective, randomized, controlled</td>
<td>60 ± 4 y; 40% M</td>
<td>Tertlipressin + Alb; Alb</td>
<td>Alb (1 g/kg; 20-40 g/d)</td>
<td>Tertlipressin + Alb-vs Alb-treated</td>
<td>26 vs 26</td>
<td>68 ± 3 vs 72 ± 2</td>
<td>2.9 ± 1.2 vs 2.8 ± 1.1</td>
</tr>
<tr>
<td>Munoz44 (2009, MX)</td>
<td>1</td>
<td>Prospective, uncontrolled</td>
<td>55 ± 6 y; 92% M</td>
<td>Tertlipressin</td>
<td>Alb (30-80 g/d)</td>
<td>Responders vs nonresponders</td>
<td>8 vs 5</td>
<td>70 ± 3 vs 69 ± 3</td>
<td>3.0 ± 1.7 vs 3.9 ± 1.5</td>
</tr>
<tr>
<td>Nazar6 (2010, ES)</td>
<td>1</td>
<td>Retrospective, uncontrolled</td>
<td>56 ± 1 y; 74% M</td>
<td>Tertlipressin</td>
<td>Alb (1 g/kg; 40 g/d)</td>
<td>Responders vs nonresponders</td>
<td>18 vs 21</td>
<td>75 ± 3 vs 79 ± 2</td>
<td>3.5 ± 1.4 vs 3.9 ± 1.4</td>
</tr>
</tbody>
</table>

*Velez & Nietert. MUSC, USA. Am J Kidney Dis 2011*
HRS-1 Treatment: Raising MAP
Renal Blood Flow Autoregulation Curve is Shifted in ESLD
Role of Sympathetic Nervous System Activation

Stadlbauer V et al. UK. Gastroenterology 2008

~ 62 mmHg
~ 91 mmHg

HRS-2
Hepatorenal Syndrome Type 1: Hemodynamic Features

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 1 HRS ($n=8$)</th>
<th>No type 1 HRS ($n=15$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At SBP diagnosis</td>
<td>At SBP resolution</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>83 ± 7</td>
<td>73 ± 8*</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml·h⁻¹)</td>
<td>18.4 ± 11.2†</td>
<td>28.3 ± 12.4*</td>
</tr>
<tr>
<td>Norepinephrine (pmol/l)</td>
<td>4,711 ± 1,336‡</td>
<td>7,625 ± 2,453*</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn·s/cm⁻⁵)</td>
<td>1,137 ± 220‡</td>
<td>1,268 ± 320</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.7 ± 0.9‡</td>
<td>4.6 ± 0.7*</td>
</tr>
</tbody>
</table>

Ruiz del Arbol et al, Spain. Hepatology 2005
Efficacy of Midodrine/Octreotide in HRS and Its Dependency of MAP rise

Correlation between the highest achieved MAP and the subsequent change in sCr (from baseline to the day after the day of the peak MAP)

- Quartile 1 (-14.1 to +1.8 mmHg)
- Quartile 2 (+1.9 to +7.5 mmHg)
- Quartile 3 (+7.8 to +15.8 mmHg)
- Quartile 4 (+15.9 to +29.4 mmHg)

n = 79
p = 0.0008

Kadian et al, MUSC. To be submitted
Efficacy of Norepinephrine in HRS and Its Dependency of MAP rise

Kadian et al, MUSC. To be submitted

- n = 13
  - 10 failed Midod/Octreot
  - 3 de novo

4/13 (30.8%) had ≥ 25% ↓ in sCr in 48 hrs

3 got OLT within 1 wk
Efficacy of Norepinephrine in HRS and Its Dependency of MAP rise

Kadian et al, MUSC. To be submitted

by Day 3

% fall in sCr

delta MAP

R=0.65
p<0.005
HRS-MAP Study Limitations

- Not a randomized controlled trial
- Magnitude of effect on kidney function observed in Midod/Octreot cohort was modest
- Rate of recurrence after successful vasoconstrictor therapy is ~ 50%. No definite therapy once norepinephrine is stopped
- Increase in ICU cost
Targeting a 10 mmHg-increase in MAP in HRS-1

Maddukuri et al, St Louis University. Di Dis Sci 2013

% RRT-requirement

- MAP responders (n=27)
- MAP non-responders (n=32)

p<0.034
Summary (2)

- Vasoconstrictor therapy (w/albumin) for ≥ 3 days may improve kidney function in 40 - 60 % of HRS cases.
- Standard practice in USA of using midodrine/octreotide is not supported by solid evidence. Norepinephrine seems a valid, perhaps better alternative.
- Reversal of HRS with vasoconstrictor therapy without a substantial rise in MAP has not been reported.
- Targeting a rise in MAP (10-15 mmHg) appears reasonable as HRS-1 treatment.
HRS-1 Treatment: Role of Large-Volume Paracentesis (LVP)

- LVP has traditionally been considered a precipitating factor for HRS, but actual data supporting this notion is sparse.
- Post-paracentesis-induced circulatory dysfunction (PICD) is defined by change in PRA post-LVP, not in GFR\(^1\)
- Incidence of PICD is significantly reduced with IV albumin\(^2\)
- Most studies showing transient fall in GFR post-LVP were done in patients with normal renal function\(^3-5\), not with HRS
- Most studies using vasoconstrictors allowed LVP: none showed a negative effect of LVP on outcomes

Renal Failure in Cirrhosis

Pere Ginès, M.D., and Robert W. Schrier, M.D.

TO THE EDITOR: Ginès and Schrier (Sept. 24 issue) offer a succinct and thoughtful review of various causes of renal failure in cirrhosis, including the hepatorenal syndrome, hypovolemia due to hemorrhage or fluid losses, parenchymal disease, and drug-induced renal failure.

In addition, intraabdominal hypertension secondary to significant ascites should be included.

THE AUTHORS REPLY: We appreciate Lott’s comment on the possible effect of increased abdominal pressure caused by ascites on the pathogenesis of renal failure in cirrhosis. Unfortunately, however, studies involving patients with large-volume ascites and renal failure have shown that renal function does not improve after large-volume paracentesis. Therefore, increased intraabdominal pressure caused by ascites seems to play little, if any, in the pathogenesis of renal failure in cirrhosis.

Comparison of Paracentesis and Diuretics in the Treatment of Cirrhotics With Tense Ascites
Results of a Randomized Study
HRS Management: Role of Abdominal Compartment Syndrome

- Paracentesis did not improve kidney fxn. (1.9 to 2.1 mg/dl) in 13 pts with cirrhosis & ascites. They had CKD, not AKI.¹

- Paracentesis performed in 25 cirrhotics with IAP > 25 cm H₂O (bladder press.): IAP ↓ (33.5 to 19 cm H₂O). At 2 hrs: Uv ↑ (47 to 55 ml/h), CrCl ↑ (46 to 63 ml/min).²

- 11 pts. w/HRS. 2-L paracent. ↓ IAP (30 to 17 cm H₂O) and ↑ Uv (8 to 90 ml/h) but ↓ again as ascites reaccumulated. Uv remained high if IAP was kept low.³

HRS Management: Role of Abdominal Compartment Syndrome

Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial

Andreas Umgelter¹, Wolfgang Reindl¹, Katrin S Wagner², Michael Franzen¹, Konrad Stock¹, Roland M Schmid¹ and Wolfgang Huber¹

<table>
<thead>
<tr>
<th>n = 19</th>
<th>Baseline</th>
<th>Post LVP</th>
<th>48 h post LVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAP (mmHg)</td>
<td>22 (18 – 24)</td>
<td>9 (18 – 24)</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>81 (74 – 100)</td>
<td>80 (71 – 89)</td>
<td>84 (75 – 96)</td>
</tr>
<tr>
<td>RPP (mmHg)</td>
<td>61 (53 - 79)</td>
<td>67 (60 – 81)</td>
<td></td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>23 (12 – 49)</td>
<td>33 (16 – 50)</td>
<td>44 (18 – 72)</td>
</tr>
<tr>
<td>CI (L/min)</td>
<td>4.1 (3.2 – 4.3)</td>
<td>4.2 (3.8 – 4.4)</td>
<td>3.9 (3.5 – 4.4)</td>
</tr>
</tbody>
</table>

Germany. Critical Care 2008
The role of LVP in HRS treatment remains undefined. However, the assumption that LVP may worsen HRS-1 lacks supporting evidence.

LVP may be reasonable in selected cases of HRS-1, such as those refractory to vasoconstrictor therapy and/or severe IAH (bladder pressure ≥ 25 mmHg).
Conclusions

- HRS represents a diagnostic challenge because of the lack of gold-standard, the complexity of the clinical scenarios and the severity of the disease.
- Better distinction of HRS from other causes of AKI may facilitate medical decisions in this very sick patient population.
- Treatment of HRS may require a multi-step approach aimed to improve renal perfusion pressure by optimizing MAP and APP. However, prospective studies are needed before this strategy can be advocated.