Cirrhosis and Hepatorenal Syndrome

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The author has no conflicts of interests to disclose on this topic.

Presentation Objectives
- Define pathophysiology, causes, and complications of liver cirrhosis
- List hepatorenal syndrome (HRS) diagnostic criteria
- Discuss potential HRS prevention mechanisms
- Identify HRS treatment goals and strategies
- Evaluate literature describing therapeutic alternatives used to treat HRS
Liver Anatomy and Function

- Blood flows from portal branch into sinusoidal space
- Hepatocytes remove toxins from blood
- Detoxified blood flows out of sinusoid via hepatic venule
- Hepatic vein empties blood into vena cava

Liver Anatomy and Function

Cirrhosis – Pathophysiology

- Cascade beginning with hepatocellular injury
- Wound healing response
  - Inflammatory response
  - Chronic and abnormal collagen secretion
- Hepatic fibrosis and nodule formation
- Decreased metabolic and synthetic function


http://www.arizonatransplant.com/healthtopics/liver.html

Hepatocellular Injury and Resistance

- Stellate cells transform to resemble fibroblasts
- Fibrin deposition into sinusoids
- Blood flow resistance in hepatic lobules
- Changes in vasodilation and vasoconstriction mediation within liver
- Permanent hepatic scarring

Cirrhosis – Etiologies

- Alcohol abuse
- Chronic viral hepatitis
- Metabolic liver disease
  - Non-alcoholic steatohepatitis
  - Wilson’s disease
- Cholestatic liver disease
  - Primary sclerosing cholangitis
  - Primary biliary cirrhosis
- Exogenous toxins

Cirrhosis – Complications

Spontaneous bacterial peritonitis

- Translocation of enteric aerobic bacteria from gastrointestinal tract to the peritoneal cavity
- Potential pathogens
  - Enterobacteriaceae
    - Escherichia coli, Klebsiella pneumoniae
    - Streptococcus spp.
    - Anaerobes
  - Prophylactic and empiric therapy with third generation cephalosporins, fluoroquinolones, or sulfas
Cirrhosis – Complications

Hepatic encephalopathy
- Neurologic symptoms and altered mental status
- Accumulation of nitrogenous substances from gut flora cause alterations in neurotransmission
- Treat by lowering ammonia levels
  - Lactulose
  - Rifaximin
  - Metronidazole

Cirrhosis – Complications

Coagulopathy
- Hepatocyte dysfunction leads to decreased clotting factor and fibrinogen synthesis
- Fibrinolysis
- Disseminated intravascular coagulation
- Platelet dysfunction

Cirrhosis - Complications

Portal hypertension
- Build up of fibrous tissue in liver causes increased resistance to perfusion
- Loss of regulation of vasoregulatory substances
- Leads to other complications
  - Esophageal and gastric varices
  - Ascites
  - Hepatopulmonary syndrome
  - Hepatorenal syndrome
Hepatorenal Syndrome

- Incidence
  - Nearly one in every five patients with cirrhosis and ascites develop HRS within one year
  - 39% develop HRS within five years
  - As high as 48% in patients awaiting transplant
- Poor prognosis
- Complex pathophysiology

Historical Perspective

- GFR decreases in parallel with decreased renal perfusion. Suggestion that splanchnic bed is dilated
- Kidneys from HRS patients regain normal function when transplanted
- Circulatory dysfunction due to arterial vasodilation, not hypovolemia
-未来 targets identified 2013-7

Pathophysiology

- Intense renal vasoconstriction
  - Displays progression with worsening liver disease
- Four interrelated pathways
  - Peripheral vasodilation
  - Hyperdynamic circulation; subsequent renal vasoconstriction
  - Stimulation of renal sympathetic nervous system (SNS)
  - Cardiac dysfunction
  - Circulatory derangements and inflammatory cytokines acting upon renal circulation and other vascular beds
Peripheral Vasodilation

- Decrease in effective circulating volume
- Increased splanchnic blood pooling
- Profound vasodilator upregulation
- Unloads high-pressure baroreceptors
- SNS activation; renin-angiotensin-aldosterone system (RAAS) activation; nonsomotic vasopressin release
- Hyperdynamic circulation
- Compensatory vasoconstrictor mechanisms stimulation
- Extravasplanchnic vascular bed vasoconstriction

SNS and RAAS Stimulation

- Juxtaglomerular cells
- Renin
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- ACE
- Aldosterone
- ADH release

Cardiac Dysfunction

- Impaired myocardial activity at rest and with exercise in cirrhosis
- Correlative with degree; reverses with transplant
- Three defined mechanisms
  - Neurohormonal hyperactivity
    - Myocardial growth; fibrosis w/ disturbed diastole
    - Diminished myocardial β adrenergic receptor signal transduction
    - Ventricular function inhibition by circulating cytokines (i.e., TNF-α) and nitric oxide (NO)
Cytokines and Vasoactive Mediators

- Agents studies in HRS include NO, TNF-α, endothelin, endotoxin, glucagon, and intrarenal vasodilating prostaglandins
- Endothelial NO synthase activity upregulated
  - Sheer stress in splanchnic and systemic circulation
  - Endotoxin mediation
- Acute NO inhibition shown to decrease plasma renin activity and prostaglandin E2 excretion

Renal Compensation

- Renal vasoconstriction normally counterbalanced by mediators
  - Prostaglandins
  - Kallikreins, bradykinin
### Hemodynamics in Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Compensated Cirrhosis</th>
<th>Cirrhosis With Ascites</th>
<th>HRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splanchic vasoconstriction</td>
<td>Normal</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Circulating volume</td>
<td>Normal</td>
<td>-</td>
<td>---</td>
</tr>
<tr>
<td>Renin, aldosterone, vasopressin</td>
<td>Normal</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>+</td>
<td>++</td>
<td>+++++</td>
</tr>
<tr>
<td>Renal vasoconstriction</td>
<td>Normal/+</td>
<td>Normal/+</td>
<td>++++</td>
</tr>
</tbody>
</table>

HRS: hepatorenal syndrome; +, mild increase; ++, moderate increase; ++++, severe increase; +++++, very severe increase; --, mild decrease; ---, moderate decrease; ---, severe decrease


### Categorization

**International Ascites Club – 1996**

<table>
<thead>
<tr>
<th>HRS Type 1</th>
<th>Serum creatinine: Double to &gt; 2.5 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine: Less than 2.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance: &gt; 50% of predicted normal</td>
<td></td>
</tr>
<tr>
<td>Concomitant cardiac dysfunction may play role in progression</td>
<td></td>
</tr>
</tbody>
</table>

Gastroenterology 2002;122:1658-76.
Gut 2007 Sep;56(9):1310-8.

### Diagnosis

**International Ascites Club – 2007**

- Presence of cirrhosis or ascites
- Serum creatinine > 1.5 mg/dL
- No improvement in serum creatinine after
  - 48 hours of diuretic withdrawal
  - Volume expansion with albumin (1 g/kg/day)
- Absence of shock
- No current or recent nephrotoxic drug treatment
- Absence of parenchymal kidney disease

Gut 2007 Sep;56(9):1310-8.
Diagnosis – Evolution
International Ascites Club – 2007

Four major changes
- Creatinine clearance no longer incorporated
- Ongoing bacterial infection does not exclude diagnosis
- Albumin is preferred to saline for plasma volume expansion
- Nonessential minor diagnostic criteria including low sodium levels have been omitted

Mortality – “Grim Prognosis”

- Type 1 HRS
  - 80% mortality at two weeks; 10% at three months
- Type 2 HRS
  - Median survival of six months
- Model of end-stage liver disease (MELD) score
  - Independent predictor of mortality in type 2 HRS
  - Score ≥ 20: one month survival; score < 20: eight months
  - Not predictive in type 1 HRS
- Survival much worse when compared to cirrhosis with other forms of acute kidney injury

MELD Score

- Mortality predictor in liver disease
- Three factors comprise MELD score
  - International normalized ratio
  - Serum creatinine
  - Total bilirubin

<table>
<thead>
<tr>
<th>MELD</th>
<th>≤9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Month Mortality</td>
<td>4%</td>
<td>27%</td>
<td>76%</td>
<td>83%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Hepatology 2001;33(2):454-70
Hepatology 1996 Jan;23(1):164-76
Hepatology 2005 Jun;41(6):1282-8
Characterization Take Home Points

<table>
<thead>
<tr>
<th>Course</th>
<th>Precipitating Event</th>
<th>Diuretic-Resistant Ascites History</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 HRS</td>
<td>Precipitous doubling of serum creatinine in &lt; 2 weeks</td>
<td>Present in &gt; 50% of cases</td>
<td>May or may not be present</td>
</tr>
<tr>
<td>Type 2 HRS</td>
<td>Gradually progressive</td>
<td>Absent</td>
<td>Always present</td>
</tr>
</tbody>
</table>

Precipitating Factors

- Detectable in 70 to 100% of type 1 HRS cases
  - More than one event can occur in a single patient
- Bacterial infection
- Large-volume paracentesis without albumin infusion
- Gastrointestinal bleeding
- Acute alcoholic hepatitis
**Predictive Factors**

- Factors surrounding severe hemodynamic derangements and neurohormonal activation
  - Dilutional hyponatremia, low urinary sodium, reduced plasma osmolality, and low arterial BP
- One study showed three independent predictors via multivariate analysis
  - Hyponatremia, high plasma renin activity, absence of hepatomegaly

**Preventative Measures**

- Three studied mechanisms
  - Prophylactic antibiotic therapy for those at high SBP risk
  - Pentoxifylline (PTX) administration
  - Albumin use post-large-volume paracentesis
- Avoiding non-steroidal anti-inflammatory agents, aminoglycoside antibiotics, and diuretic overuse

**SBP Prophylactic Antibiotics**

- Daily norfloxacin shown to reduce one-year probability of developing SBP from 61% to 7%
- One-year probability of HRS: 41% to 28% ($p = 0.02$)
- Beneficial effect believed to be bacterial translocation prevention, proinflammatory cytokine prevention, and improved circulatory function
Pentoxifylline Administration

- TNF-α synthesis inhibitor
- 101 severe alcoholic hepatitis patients
- Four week comparison of PTX 400 milligrams orally three times daily versus placebo
- Short-term survival: 24.5%, PTX; 46.1%, placebo
- HRS cause of death: 50%, PTX; 91.7%, placebo
- Age, creatinine level at randomization, and PTX associated with survival

Volume Expansion – Albumin

- 289 patients randomized to treatment by total paracentesis plus albumin, dextran 70, or polygeline
- Monitored for postparacentesis circulatory dysfunction on sixth day after performed
  - Dextran 70: 34.4%, \( p = 0.018 \); polygeline: 37.8%, \( p = 0.004 \); albumin: 18.5%
- Albumin is preferred plasma expander

Volume Expansion - Albumin

<table>
<thead>
<tr>
<th>Patient's Category</th>
<th>Albumin</th>
<th>Dextran 70 or Polygeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.4 Liters</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5-9.1 Liters</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>&gt;9.1 Liters</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \); ** \( p < 0.02 \)
**HRS Treatment Goals**

- Improve circulating volume status
- Vasoconstrictor use to target splanchnic vasculature
- Decrease portal hypertension
- Bridge patient to liver transplant
- Four therapeutic options
  - Pharmacologic, transjugular intrahepatic portosystemic shunt (TIPS), renal replacement therapy (RRT), and liver transplantation

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**Albumin – Treatment**

- Plasma volume expansion
  - May aid in increasing effective circulating volume
  - Should definitively be used after large-volume paracentesis (8 g/L of ascitic fluid removed)
- Dose without paracentesis: 1 g/kg per day
- Frequently combined with other therapies
- Debate between use of albumin versus crystalloid
- Few trials that compare albumin use to controls

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**Terlipressin**

![Terlipressin](image1)

![Vasopressin](image2)
**Terlipressin in HRS**

- V1 vasopressin agonist
- Promotes increased circulating plasma volume
- Proposed selective vasoconstriction activity on splanchnic vasculature
- Theoretical suppression of endogenous vasoactive systems to improve renal perfusion

**Terlipressin – Adverse Events**

- Myocardial ischemia
- Arrhythmias
- Hypertension
- Intestinal ischemia
- Dyspnea
- Necrosis at injection site

**Terlipressin + Albumin vs. Albumin**

- 46 patients enrolled, treated for 15 days
  - Terlipressin 1-2 mg IV q4h
  - Albumin 1 g/kg followed by 20-40 g/day
- Outcomes
  - Improvement in renal function
  - Three-month survival
**Terlipressin + Albumin vs. Albumin**

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin + Albumin</th>
<th>Albumin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved Renal Function</td>
<td>10/23 (43.5%)</td>
<td>2/23 (8.7%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Survival</td>
<td>27%</td>
<td>19%</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Adverse events included:
- Myocardial ischemia
- Intestinal ischemia
- Arterial hypertension

*Gastroenterology 2008;134:1352-9.*

**Terlipressin + Albumin vs. Albumin**

![Graph showing probability of response over time]

*Gastroenterology 2008;134:1352-9.*

**Terlipressin vs. Norepinephrine**

- No significant differences between treatment groups
- NE group follow-up much shorter
- Very small study groups

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin</th>
<th>Norepinephrine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>10/12 (83%)</td>
<td>7/10 (70%)</td>
<td>ns</td>
</tr>
<tr>
<td>Therapy Duration*</td>
<td>6</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>HRS Recurrence</td>
<td>6/10 (60%)</td>
<td>2/7 (29%)</td>
<td>ns</td>
</tr>
<tr>
<td>Follow-up*</td>
<td>39 ± 9</td>
<td>19 ± 7</td>
<td>ns</td>
</tr>
</tbody>
</table>

* - Represented duration by days on therapy

**Midodrine + Octreotide**

- **Midodrine**
  - α-adrenergic agonist
  - Dose: 7.5-15 milligrams every eight hours
- **Octreotide**
  - Nonspecific vasodilatory inhibition, glucagon inhibition
  - Dose: 100 mcg subcutaneous every eight hours
- **Goal**: increase MAP and improve renal perfusion

**Midodrine + Octreotide**

- Combination versus placebo in type 1 HRS
- Retrospective, single-center study
- 81 patients identified
  - 60 in midodrine/octreotide group
  - 21 in placebo group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of SCr</td>
<td>24/60 (40%)</td>
<td>2/21 (10%)</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>26/60 (43%)</td>
<td>15/21 (71%)</td>
</tr>
</tbody>
</table>

**TIPS**

- Shunt insertion between hepatic and portal vein systems
- Alleviates portal hypertension
- Improvement in neurohormonal factors, hemodynamics, and renal function
- Study in 31 type 1 and 2 HRS patients showed three, six, 12-, and 18-month survival post-TIPS at 81%, 71%, 48%, and 35% respectively
- Ten week survival of type 1 HRS improved to 53%

Combination Therapy

- Midodrine, octreotide, albumin, and TIPS in type 1 HRS
  - Fourteen patients enrolled for pharmacologic therapy
  - Five received TIPS insertion
- All five TIPS patients were alive six to 30 months after placement (only one required transplant)
- Patients not eligible for TIPS either required liver transplant or died (two weeks-27 month survival)

References:
[Hepatology 2004;40:55-64.]

Renal Replacement Therapy

- Provides supportive therapy for patients with HRS who are waiting for transplant
- May help treat complications
  - Volume overload, metabolic acidosis, electrolyte abnormalities and uremia
- May improve short-term survival
- No evidence for long-term mortality
- Optimal RRT modality unclear

References:
**RRT – Challenges in HRS**

- Hemodynamic instability
- Coagulopathy in liver disease
- Encephalopathic patients
- No evidence for optimal modality and timing
- Justifiable in patients who are not transplant candidates?

**Liver Transplantation**

- Only definitive cure for HRS
- Barriers
  - Short survival expectancy
  - Long wait times for organs
  - Model for End-Stage Liver Disease (MELD) scores may be limiting
  - May require simultaneous kidney transplantation

**Liver Transplantation**

- Predictors of renal recovery
  - Younger age of recipient
  - Nonalcoholic liver disease
  - Low bilirubin at seven days post-transplant
  - Younger donor age
  - Terlipressin plus albumin use prior to transplant associated with improved survival
Ongoing Research

- REVERSE Trial – terlipressin in type 1 HRS
- Safety and pharmacokinetics of ifetroban
- Role of angiogenic factors
- LJPC-501: new investigative vasoconstrictor

Conclusions

- HRS is a complication of cirrhosis that is marked by acute kidney injury
- Transplantation is the only definitive cure for HRS
- Little evidence to direct bridging therapy for liver transplantation
- Ongoing research may provide new therapeutic targets and strategies for HRS management

Cirrhosis and Hepatorenal Syndrome

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Potential complications from portal hypertension include...
1) Ascites
2) Hepatorenal syndrome
3) Esophageal varices
4) Hepatopulmonary syndrome
5) All of the above

The following was a change in diagnostic criteria for HRS by the International Ascites Club in 2007:
1) The diagnostic creatinine clearance threshold was lowered to 50 mL/min
2) Albumin is preferred to saline for plasma volume expansion
3) Ongoing bacterial infections exclude diagnosis
4) Hyponatremia is a positive diagnostic for both types 1 and 2 HRS

The following preventative mechanisms have been associated with positive outcomes in HRS:
1) Albumin and dextran 70 infusions post large-volume paracentesis
2) TNF-α synthesis inhibition
3) Third generation cephalosporins as agents of choice in SBP prophylaxis
4) Early transjugular intrahepatic portosystemic shunt insertion
Review Question #4

<table>
<thead>
<tr>
<th>HRS treatment goals include...</th>
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</thead>
<tbody>
<tr>
<td>1) Selective vasoconstrictor use to target splanchnic vasculature</td>
</tr>
<tr>
<td>2) Reduction in hepatic venous portal gradient</td>
</tr>
<tr>
<td>3) Incorporate necessary therapeutic options to bridge to liver transplantation</td>
</tr>
<tr>
<td>4) Improve circulating volume status</td>
</tr>
<tr>
<td>5) All of the above</td>
</tr>
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</table>

Review Question #5

<table>
<thead>
<tr>
<th>The following is true regarding therapeutic alternatives for HRS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Nonalcoholic liver disease is associated with a higher likelihood of renal recovery post-liver transplantation</td>
</tr>
<tr>
<td>2) CRRT is the preferred RRT modality</td>
</tr>
<tr>
<td>3) Large, prospective studies have shown the octreotide and midodrine combination to improve mortality</td>
</tr>
<tr>
<td>4) Terlipressin plus albumin has superior mortality outcomes compared to albumin alone</td>
</tr>
</tbody>
</table>