Hepatorenal Syndrome 2018

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Case Presentation

60 year male with Diabetes
Cirrhosis : NASH
Stable : well compensated

Portal HTN

10 yrs
(58% of all cases)

Ascites
Stable : well compensated

1 -5 yrs
(20 – 40% of all cases)

Hepatorenal Syndrome

U.S. Prevalence
3.9 million with liver disease
633,000 cases of Cirrhosis
New cases of Cirrhosis / yr
30,000
Deaths / yr
20-40,000
Outline of Discussion Topics

- What are the diagnostic criteria for Hepatorenal Syndrome (HRS)?
- Does a patient with HRS have Acute Kidney Injury or Chronic Kidney Disease or Both?
  - Or is it Fake News and there is no “True” kidney disease?
- What is the pathophysiology behind the development of HRS?
- What therapeutic options are available for HRS?
- Does a patient with Cirrhosis and HRS need a Liver Transplant only or a combined Liver and Kidney Transplant?
- Will we finish this topic before noon?
Importance of Accurate Assessment of Renal Function in Liver Disease

Determine the need for combined liver / kidney Transplantation

Determine the MELD score

Determine drug dosing

Diagnosis / Treatment response of HRS
Serum Creatinine

- Creatine
  - Synthesized in the liver and stored in muscle
  - Also ingested orally and localized to muscle
- Creatinine
  - Cyclic anhydride of creatine (nonenzymatic)
  - End product of muscle metabolism
- Renal excretion of creatinine
  - GFR - filtration
  - Tubular secretion
Origin of Creatinine

Oral Ingestion - Meat (creatine)

Muscle (Energy source - Metabolized)

Hepatic Synthesis (creatine)

Creatinine
The normal creatinine level is relative to muscle mass. 
Women < 1.2 mg/dl
Men < 1.5 mg/dl (represents 2 SD above the mean)
Creatine Production in Patients with Cirrhosis


50% decrease in creatine production in liver disease
Lower Baseline Creatinine Levels than the Normal Population

- Cirrhosis
  - Minimal protein intake with severe malnutrition
  - Impaired liver synthesis of creatine
- Pregnancy
  - Volume expansion and an increase in GFR
- Extremes of age/nutrition – pediatric / elderly

- Baseline or “normal” creatinine in these conditions may be 0.4 - 0.6 mg/dl
- Patients can be in AKI or CKD in all these circumstances with serum creatinines of 1.1 mg/dl
Bilirubin Interference and Creatinine Measurement

**Jaffe Reaction**

Creatinine + picric acid $\rightarrow$ Creatinine – picric acid complex

Reaction is read at a specific wavelength (570)

Bilirubin absorbs light at 570 which leads to a spuriously low serum creatinine

Usually noted with a bilirubin level > 25 mg/dl
Assessment of Renal Function in Cirrhosis: Inaccuracy of the Serum Creatinine

- Decreased Protein Intake
- Decreased Muscle Mass
- Decreased Hepatic Creatine Synthesis
- Spuriously Low Creatinine Measurement with Hyperbilirubinemia
GFR and Cirrhosis

At serum Creatinine levels < 1.5 mg/dl: a significant proportion of patients with cirrhosis will have GFRs < 60 cc/min: much greater than the general population.
Kidney Function in Cirrhosis

**Creatinine**
- Real and Spurious decrease in serum concentration
- Renal Function “appears” better than it really is

**GFR**
- True decline in GFR compared to the general population
- Majority of these patients will have serum creatinine levels < 1.5 mg/dl
- The CKD-EPI formula is not an accurate predictor of GFR and alternative formulas using cystatin C may be considered
Assessment of Renal Function in Cirrhosis: Inaccuracy of the BUN

- Decreased Protein Intake
- Decreased hepatic synthesis
- Reduced efficacy of the BUN/Cr ratio to detect pre-renal azotemia
- Possible disproportionate increase in BUN in the setting of GI bleed
Hepatorenal Syndrome: Diagnostic Criteria – International Ascites Club 2015

- Cirrhosis or Acute Hepatic disease and Portal Hypertension
- Cr Increase of 0.3 mg/dl in 48 hrs or a 50% increase over 7 days
- Absence of nephrotoxic agents
- Absence of shock
- Absence of renal parenchymal disease
  - Proteinuria < 500 mg/d
  - No Hematuria
  - Normal renal ultrasound (size/echogenicity)
- No improvement after 48 hours following
  - Diuretic withdrawal
  - Volume expansion with
    - Albumin 1 g/kg/day (maximum 100 g)
Definition of AKI in the General Population

- Increase of the serum creatinine by 0.3 mg/dl within 48 hours
- Increase in serum creatinine by > 50% (over 7 days)
- Urine output < 0.5 ml/kg/hr for more than 6 hours
International Ascites Club 2015
Revised Definition of AKI in Patients with Cirrhosis

• Increase of the serum creatinine by 0.3 mg/dl within 48 hours

OR

• Increase in serum creatinine by > 50% (over 7 days)

OR

• Urine output < 0.5 ml/kg/hr for more than 6 hours
Conditions Causing Simultaneous Renal and Liver Failure

- Hepatorenal syndrome
- Acute tubular necrosis
- Volume depletion
- Circulatory
  - CHF
  - Shock
- Genetic: ADPKD
- Collagen vascular disease

- Infections
  - Sepsis
  - Leptospirosis
  - Reye’s syndrome
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
Conditions Causing Simultaneous Renal and Liver Failure

- **Toxins and Medication**
  - Methoxyflourane
  - Carbon tetrachloride
  - Tetracycline
  - Acetaminophen
  - Elemental phosphorous
  - Toluene
  - Immunosuppressive drugs

- **Miscellaneous**
  - Amyloidosis
  - Sarcoidosis
  - Wilsons disease
  - Hemochromatosis
  - Venooclusive disease
  - Cryoglobulininemia
Hepatorenal syndrome does not include every disease that affects the liver and kidney simultaneously.

Hepatorenal syndrome is a distinct syndrome that first requires the sequential initial development of liver dysfunction accompanied by portal hypertension and ascites culminating in the development of acute kidney injury.
Hepatorenal Syndrome: “Non Essential” Diagnostic Criteria

- Additional supportive criteria but not required for diagnosis
  - Urine volume < 500 ml/day (65%)
  - Urine sodium < 10 mEq/l
  - Urine osm > plasma osm
  - Serum sodium < 130 mEq/l
Clinical Types of Hepatorenal Syndrome

- **Type I HRS**
  - Rapid deterioration in renal function
  - < 2 weeks
  - Doubling of initial Serum Creatinine > 2.5 mg/dl

- **Type II HRS**
  - Serum creatinine > 1.5 mg/dl
  - Slow progressive course
Probability of Hepatorenal Syndrome


N = 236 pts. nonazotemic + cirrhosis

Precipitating Factor – 50%

Years Followup

%
AKI Classification of Hepatorenal Syndrome

Pre-Renal Azotemia

No improvement with Fluid

Obstruction

No Hydronephrosis

Urine Na low FENA < 1%

HRS-AKI
Portal HTN

Compression, Distortion, Obliteration of Hepatic Architecture

Decreased Hepatic production of vasodilatory substances

Activated Hypercontractile Intrahepatic stellate cells
Intrahepatic Pressure and Early Portal HTN

Hepatofugal
NFPF (Non Forward Portal Flow) Blood flow
Away from the liver versus
Hepatopetal: normal flow into the liver
Backward Theory of Ascites Formation

Portal Hypertension / Hypoalbuminemia

Reversal of Starling’s Equilibrium in the Splanchnic Microcirculation

Increased Splanchnic Lymph Formation

Ascites Formation

Decreased Effective Circulatory Volume
<table>
<thead>
<tr>
<th>Feature</th>
<th>Backward Theory</th>
<th>Hepatorenal Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low urine sodium</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Systemic resistance</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
Splanchnic Arterial Vasodilation

- Increased vasodilatory substances (nitric oxide)
- Intestinal Bacterial translocation
- Mesenteric Vascular Hyporesponsiveness

Portal HTN
Nitric Oxide in Cirrhosis

Liver
Decreased

Splanchnic
Increased
Role of bacterial translocation through permeable capillaries in the intestines

Migration to lymph nodes with increased cytokine release and local inflammatory response (PAMPs: pathogen-associated molecular patterns)

Vasodilation

Increase in ascites
Glucagon

- Elevated levels in cirrhosis
  - Desensitizes mesenteric circulation to catecholamines and AII
  - Direct vasodilation
  - Increases cAMP leading to increased NO synthesis
Blood Volume Distribution

Normal

Cirrhosis
(Splanchnic pooling)
Blood Volume Distribution in Cirrhosis

<table>
<thead>
<tr>
<th>Organ</th>
<th>Normal</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splanchnic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>2.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Liver</td>
<td>11.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td>24.7</td>
</tr>
<tr>
<td>Thorax</td>
<td></td>
<td>27.3</td>
</tr>
<tr>
<td>Thorax</td>
<td>25</td>
<td>37.7</td>
</tr>
</tbody>
</table>

% Blood Volume Distribution
Systemic Blood Flow and HRS

- Splanchnic arteriolar vasodilation **IS NOT** accompanied by peripheral vasodilation in all vascular beds
  - Cerebral / Femoral / Brachial / Hepatic beds all experience progressive vasoconstriction which is directly related to the GFR
Organ Perfusion in Cirrhosis and HRS

- Splanchnic bed: Increased
- Renal blood flow: Decreased
- Cerebral blood flow: Decreased
- Coronary blood flow: Decreased
- Peripheral blood flow: Decreased

Total peripheral vascular resistance DECREASES
RAAS Activation in Cirrhosis ± HRS

Progressive increase in RAAS activation with ascites formation indicating decreasing effective circulating volume.

In HRS there is maximal RAAS activation.
Hepatorenal Syndrome: Pathophysiology

Cirrhosis → Splanchnic Arterial Vasodilation

Decreased Effective Circulating Volume

Adaptive Response:
- Increased Renal Vascular Resistance
- Sodium and water Retention

Renin-Angiotensin-Aldosterone
- Sympathetic Nervous System
- Vasopressin / Increase water channels
- Leukotriene E2
- Endothelin-1
- F2-isoprostanes

Nitric Oxide
- Glucagon
- Endocannabinoids
- Cytokines
- Carbon Monoxide

Counteradaptive Response:
- Intrarenal vasodilation
- Natriuresis

Prostaglandins
- Kallikreins
- ANP
Hepatorenal Syndrome

Severe vasoconstriction of the cortical vessels in the kidney in HRS, which is completely reversible with therapy. Confirms that the injury is one of vascular tone.
The resistive index is high throughout the renal vasculature in HRS to the same degree – (no RI gap !)
In Cirrhosis alone the resistance is high in the larger vessels and not as pronounced in the smaller vessels that have a lower resistive index (RI gap)
Precipitating Event
SBP, GI bleed, Large Volume Paracentesis

Splanchnic Vasodilation
Inadequate Cardiac Output

Increased AII, NE, ADH

Increased Hepatic Resistance
Aggravation of Portal HTN

Regional Vasoconstriction

Kidneys – HRS
Brain – Encephalopathy
Liver – Liver Failure
Adrenal – Adrenal Insufficiency
Circulatory Function and the Hepatorenal Syndrome

Cardiac Output

Renin

Aldosterone

Circulatory Function and the Hepatorenal Syndrome
Differences Between Type I and Type II HRS

Hepato-Cardio-Renal Syndrome

- Cirrhotic Cardiomyopathy
  - Clinical Features
    - Blunted systolic and diastolic contractile response to stress
    - Ventricular hypertrophy / Dilation
    - Prolonged Q-T interval
Cirrhosis

- Increased Intrahepatic Resistance
- Increased Splanchnic Vasodilators

Portal HTN
Splanchnic Vasodilation

- Decreased Blood Volume Distribution
- Impaired Effective Circulating Volume
- Activation of Renal Vasoconstriction
- Hepatorenal Syndrome

- Decreased Cardiac Preload
- Cirrhotic Cardiomyopathy
  - Impaired Contractility
  - Impaired Relaxation

Hepatorenal Syndrome
Type II HRS
HRS-CKD
Pathogenesis of Type I HRS (HRS-AKI)
Hepato – Cardio – Renal Syndrome

Peripheral Vasodilation Theory

Peripheral Vasodilation + Cardiomyopathy Theory + acute decrease in volume

Arroyo V, J Hepatol 46:935, 2007
Risk for Developing Type I HRS
The “Second Hit “ Hypothesis

SBP risk: 30% in patients with ascites
20% mortality rate

- UGI Bleed
- Large Volume Paracentesis
- SBP (30%)
- Acute Alcoholic Hepatitis (25%)
- Hospital admission for Ascites (17%

(> 5 L)
Circulatory Function and the Hepatorenal Syndrome

• Conclusions
  – Patients who develop HRS have
    • Lower baseline CO
    • Higher baseline levels of renin / Aldosterone / Catecholamines
  – Cardiac output decreases dramatically in Type I HRS resulting in a greater severity of renal hypoperfusion
• Etiology of “Cirrhotic cardiomyopathy”
  – Chronic high catecholamine levels
    • Left ventricular remodeling / fibrosis
    • Diastolic dysfunction
Bile Cast Nephropathy

- Reported in patients with **Direct** bilirubin levels > 6 mg/dl and **Total** bilirubin of 15 mg/dl
- Casts form primarily in the distal tubule but may be seen in the proximal tubule
- Direct tubular toxicity secondary to mitochondrial dysfunction from bile salts
- Confirmed by two stains (Fouchet’s stain and Perl’s stain). Bile casts were considered positive according to green color on Fouchet’s staining (Halls stain) and negative Perl’s stain (Prussian blue)
AKI Classification of Hepatorenal Syndrome

Pre-Renal Azotemia

Obstruction

HRS

ATN

Obstruction

Intratubular obstruction with casts

Direct tubular toxicity of bilirubin

No improvement with fluid but will improve with albumin and splanchnic vasoconstriction

HRS is a combination of all 3!

Pre Renal >>>>>>>>>>>>>>>>>> ATN >>>>> Obstruction
Prevalence of HRS as a Cause of AKI in Cirrhosis

Salerno 2011: 30%
Martin-Llahi 2010: 43%
Thabut 2007: 27%
Montoliu 2010: 15%
Types of Kidney Disease seen in Cirrhosis

- CKD: 36%
- ATN: 24%
- Pre renal Azotemia: 20%
- HRS: 11%
- AGN: 6%
- AKI on CKD: 3%
Kidney Diseases other than HRS in Patients with Cirrhosis

- **Hepatitis C**
  - Membranoproliferative glomerulonephritis
  - Membranous GN
  - Vasculitis

- **Diabetes**
  - Diabetic Nephropathy

- **Hepatitis B**
  - Membranous GN
  - IgA nephropathy
  - Vasculitis

In patients with AKI and cirrhosis it is essential to know the cause of liver failure as it may contribute to the differential diagnosis.
Do not forget !!!

Abdominal Compartment Syndrome and Cirrhosis: AKI

Normal Intra-abdominal pressure (IAP) 4 – 7 mmHG

Intra-abdominal hypertension (IAH) 12 – 20 mmHG

Intra-abdominal Compartment Syndrome (ICS) 12 – 20 mmHG
Abdominal Compartment Syndrome and Cirrhosis: AKI

- Increased Renal Venous HTN
- Increased sub-capsular pressure
- Decreased Renal Blood Flow
- Decreased GFR
Hyponatremia in Cirrhosis and Ascites
Risk of Complications at 1 Month Followup

Angeli P. Hepatology 44:1535, 2006
**Hepatorenal Syndrome:**

**Targets for Therapy**

- **Reduce Splanchnic Blood Flow**
  - TIPS

- **Increase Splanchnic Vasoconstriction**
  - α-1 agonists
    - Midodrine
    - Noradrenaline
  - Glucagon antagonism
    - Somatostatin
    - Octreotide
  - V-1 agonists
    - Vasopressin
    - Terlipressin

- **Antagonize Inflammation / Bile Acids**
  - Albumin infusion
  - Ursodeoxycholic acid
Albumin

- **Non-Oncotic Properties**
  - Transport
  - Free radical scavenging
    - Sulfhydryl groups (thiols)
      - Bind reactive oxygen species
        - Superoxide hydroxyl
        - Peroxynitrite
    - Decreased Capillary permeability
    - Decrease neutrophil adhesion and activation
    - Anti-thrombotic and Anticoagulant effect
Hepatorenal Syndrome: Management
Increase Splanchnic Vasoconstriction

- **Terlipressin** (non FDA approved)
  - Vasopressin analogue
  - **Always combined with albumin infusion**
  - Bolus infusion
  - Preferential vasoconstriction of the splanchnic vasculature (?)

- Increases blood pressure and renal perfusion pressure
- Decreases plasma renin, aldosterone, norepinephrine levels
- Increases ANP levels
Terlipressin in HRS: Meta Analysis of Randomized Trials

- Sagi S. J of Gastroenterol Hepatol 25:880, 2010

<table>
<thead>
<tr>
<th>Resolution of hepatorenal syndrome</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Llahi, 2008</td>
<td>9.0 (1.24, 65.41)</td>
</tr>
<tr>
<td>Neri, 2008</td>
<td>4.20 (1.87, 9.44)</td>
</tr>
<tr>
<td>Sanyal, 2008</td>
<td>2.71 (1.24, 9.54)</td>
</tr>
<tr>
<td>Solanki, 2003</td>
<td>11.0 (0.67, 179.29)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.76 (2.21, 6.29)</td>
</tr>
</tbody>
</table>

Reversal of Type I HRS – 46%
**Terlipressin in HRS:**  
*Meta Analysis of Randomized Trials*

- Sagi S. J of Gastroenterol Hepatol 25:880, 2010

### Table 2: Side effects with Terlipressin requiring discontinuation of therapy

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal ischemia</td>
<td>3</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>1</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

One patient had both myocardial infarction and intestinal ischemia.

- 7% serious Ischemic complications
Hepatorenal Syndrome: Octreotide and Midodrine

- **Therapy**
  - Target of treatment aimed at increasing mean arterial blood pressure by a minimum of 15 mmHg
    - **Midodrine (α-1 agonist)**
      - Oral administration
      - 7.5 mg T.I.D. with maximum of 12.5 mg T.I.D.
    - **Octreotide (antagonist of glucagon)**
      - 100 μg T.I.D. subcutaneously with maximum 200 μg T.I.D.
  - Albumin infused at 20 g/day and increased to a maximum of 40 g/day based on achieving a CVP > 12
Terlipressin vs Midodrine

Terlipressin Wins the Battle! But ………

Grey = Terlipressin
White = Midodrine + Octreotide

Because Midodrine did not achieve a rise in BP the failure of therapy may be related not to the drug combination but the lack of titration to the proper blood pressure endpoint.
**Vasoconstrictor Therapy in HRS**

*Kiser T, et al. Neph Dial Transpl 20;1813, 2005*

<table>
<thead>
<tr>
<th></th>
<th>Change MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>10 mmHg</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>6 mmHg</td>
</tr>
</tbody>
</table>
Increase in MAP > 10 resulted in improved survival for HRS.
Noradrenaline Versus Terlipressin in the Treatment of Type 1 Hepatorenal Syndrome

Terlipressin vs Norepinephrine
It’s a Tie !!!

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandria et al. 2007</td>
<td></td>
<td>0.84 (0.52, 1.36)</td>
<td>7/10</td>
<td>10/12</td>
<td>24.91</td>
</tr>
<tr>
<td>Sharma et al. 2008</td>
<td></td>
<td>1.00 (0.54, 1.86)</td>
<td>10/20</td>
<td>10/20</td>
<td>14.83</td>
</tr>
<tr>
<td>Singh et al. 2012</td>
<td></td>
<td>1.11 (0.56, 2.22)</td>
<td>10/23</td>
<td>9/23</td>
<td>11.94</td>
</tr>
<tr>
<td>Ghosh et al. 2013</td>
<td></td>
<td>1.00 (0.71, 1.41)</td>
<td>17/23</td>
<td>17/23</td>
<td>48.32</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.904)</td>
<td></td>
<td>0.97 (0.76, 1.23)</td>
<td>44/76</td>
<td>46/76</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with other vasoactive drugs</td>
<td>Risk with terlipressin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (All-cause)</td>
<td>Study population</td>
<td>RR 0.94 (0.88 to 1.05)</td>
<td>474</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(681 to 1000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>577 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(529 to 637)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome (Number of participants who did not achieve reversal of hepatorenal syndrome)</td>
<td>Study population</td>
<td>RR 0.76 (0.63 to 0.99)</td>
<td>304</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(560 per 1000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>442 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(353 to 554)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Study population</td>
<td>RR 0.96 (0.88 to 1.06)</td>
<td>474</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(474 to 574)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No benefit of terlipressin compared to other vasoconstrictors.
Reversal of HRS Syndrome and Lack of Improvement of Mortality

No improvement in mortality compared to other vasoconstricting therapy
Terlipressin and the FDA

• Approved in 40 countries for the treatment of HRS
  – Not approved in Canada or the U.S.

• U.S. Trials ongoing
  – Mallinckrodt: Type 1 HRS currently in Phase 3 trials
  – BioVie Inc: Ascites
    • No current drugs have been approved for the treatment of ascites
    • Phase 2 Trials: Orphan Drug Designation
    • Fast Track Application
HRS: Current Treatment Recommendations

- Administer one of the following vasoconsticting regimens
  - Norepinephrine (0.5 – 3.0 mg/hr IV)
  - Midodrine (7.5 – 12.5 mg p.o. T.I.D.) + Octreotide (100 – 200 μg SQ T.I.D.)
  - Terlipressin (0.5 – 2.0 mg IV q 4 – 12 hours)
- Concomitant administration of
  - Albumin (1 g/kg IV on day 1 followed by 20 – 40 g/day)
- Duration of therapy – maximum 2 weeks
- Target increase in MAP by 10 mmHg
- CVP > 10 cmH2O
- Endpoint = reduction of creatinine < 1.5 mg/dl
Contraindications to Vasoconstrictor Use in HRS

- Active CAD
- Cardiomyopathy
- Cardiac Arrhythmias
- Cerebrovascular disease
- PVOD
- Severe HTN
Treatment of Refractory Ascites

No response to 400 mg/day Spironolactone. 160 mg/day of Furosemide

- Large Volume Paracentesis

- TIPS – Transjugular Portosystemic Shunt

- Alfa Pump
Transjugular Intrahepatic Portosystemic Shunt (TIPS) Placement

Reduces Portal Pressure
Prevention of HRS by Placement of TIPS

Castells A, Hepatology. 1994;20(3):584
Alfa Pump for Refractory Ascites

(Automated Low-Flow Ascites Pump)

Efficacy currently limited by risk of infection

fully implantable, programmable, and rechargeable pump system that automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by micturition

Mean duration of implant procedure was 65.0 ± 20.6 min (min. 30, max. 130), all were performed under general anesthesia (12 laparoscopically [44.4%], 15 open [55.6%]).
Liver Transplantation in HRS

Liver TP Alone

Liver / Kidney TP
HRS Diagnosis

- **From a Nephrologic Perspective**
  - Prolonged ischemic and vasoconstriction will lead to upregulation of cytokines that lead to progressive sclerosis
  - The duration of time required for these irreversible events is not measurable or defined

- Decreased renal blood flow
- Mesangial contraction
- Hepatic Glomerulosclerosis
MELD Score

- Point criteria for determining the allocation of liver TP
- MELD = **Medical Evaluation of Liver Disease**
  - Major factors
    - INR
    - Bilirubin
    - Creatinine
Marked Increase in the Number of Simultaneous Liver/Kidney Transplants since the Inception of the MELD Score

150% increase since 2002
What We Want to Avoid!
Risk of CKD is Dependent on Pre-TP Renal Function in Non-Renal TP Patients

It is absolutely essential to maximize the GFR in liver TP candidates to minimize the risk of post-TP CKD.
Transplantation in HRS: Liver or Combined Liver-Kidney

Key concepts
- HRS is not an indication for combined liver–kidney transplant
  - HRS will recover in 80% of patients posttransplant
- Kidney TP should be given only to patients with
  - ESRD: Dialysis > 3 months
  - CKD (3 months) with a GFR < 30 cc/min
    - These patients will likely require dialysis within 3 years after transplantation with CNI exposure
- AKI
  - Dialysis > 6 weeks
  - GFR < 25 cc/min > 6 weeks
- Pre-transplant renal function directly affects liver TP survival
  - All efforts to treat HRS and improve renal function before transplantation are important
Hepatorenal Syndrome: Transplantation
One or Two Organs?

• By definition –
  – Hepatorenal syndrome is a reversible phenomena of functional nature rather than structural damage
  – Patients meeting the strict criteria for this syndrome should be transplanted with a liver TP only
  – Kidney TP if Stage 4 CKD or dialysis dependent for > 6 weeks

• Management concern
  – Risk of calcineurin nephrotoxicity in a kidney that has been under prolonged ischemia
  – Difficulty of obtaining a renal biopsy due to the coagulopathy of liver failure
Hepato(cardio)renal Syndrome

- A unique constellation of hemodynamic events associated with advanced liver failure resulting in a form of vasomotor nephropathy
  - Must be distinguished from ATN, pre-renal azotemia and coincident involvement of the kidneys and the liver by specific disease states
- Primary splanchnic arteriolar vasodilation appears to be the main pathogenesis
Hepatorenal Syndrome

- HRS rarely develops spontaneously but often accompanies acute iatrogenic changes in intravascular volume
- Treatment with TIPS, Octreotide + Midodrine, Noradrenaline, Vasopressin analogues (with albumin-when approved!) and/or liver transplantation has been successfully employed in HRS
- HRS has a major adverse long term impact on patient survival and precautions must be initiated to avoid this syndrome
Thank you!
University of Miami #1

2017 Transplant Program in the U.S. Volume / Outcomes