Fluid Distension, Infection, Oh My: Approach to the Patient with Ascites

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Chief Division of Hepatology
Medical Director of Liver Transplantation
Carolinas Medical Center

Ascites Outline

- Diuretics
- Large volume paracentesis (albumin)
- TIPS (discussed by Dr Zaman)
- Role of beta blockers
- Hepatic hydrothorax
- Role of anticoagulation in portal vein thrombosis
Case

54 year-old male referred to you after presenting with lower extremity edema and abdominal distension to his PCP.

Past medical history of diabetes, hypertension and elevated cholesterol
Soc hx- married, working, 3 daughters, no alcohol or tobacco use

PE: abdominal distension c/w ascites, 2+ LE edema

Labs- t bili 1.0, alk phos 180, AST 42, ALT 54, INR 1.1
Creatinine 1.1, Na 141, K 4.2
Hgb 13, plt 150k
ANA 1:80, ASMA 32 (positive)

Abd US- moderate ascites, cirrhotic appearing liver, patent portal vein, no focal liver masses

Case

What is the most likely etiology of his liver disease?

What additional testing would you order?

Would you order a liver biopsy?

What would you prescribe for his ascites?

NAFLD
Hepatitis C antibody, hepatitis B surface antigen, iron, TIBC, alpha-1 antitrypsin
Possibly- autoantibodies, would not order ceruloplasmin
Would not order liver biopsy
Spironolactone 50 mg daily then increase 100 mg, furosemide 40 mg
Ascites: Epidemiology

- #1 complication of cirrhosis
- 50% cumulative probability of developing ascites in 10-years after cirrhosis
- 50% mortality 2 years after developing ascites
- 85% of patients with cirrhosis have ascites

Risk of decompensation over time

Fig. 2. Cumulative proportion of patients transitioning from a compensated to a decompensated stage. Individual patient data from two prospective studies of the natural history of cirrhosis [8,10].

Ascites
Epidemiology
Risk of death over time with compensated and
decompensated cirrhosis J Hepatol 2006;44:217-31

Mortality with ascites and variceal
bleeding or both

J Hepatol 2006;44:217-31
Causes of Ascites

<table>
<thead>
<tr>
<th>Portal Hypertensive</th>
<th>Nonportal Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal Carcinomastosis</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Biliary ascites</td>
</tr>
<tr>
<td>Cancer (nonperitoneal)</td>
<td>Pancreatic Ascites</td>
</tr>
<tr>
<td>Budd-Chiari,</td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td>Portal Vein thrombosis</td>
<td>Chylous</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Serositis (CVD)</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>TB</td>
</tr>
<tr>
<td>Sinusoidal obstructive syndrome (VOD)</td>
<td>Myxedema</td>
</tr>
</tbody>
</table>

Ascites Diagnosis
What Tests Should I order on Ascitic Fluid?

**Routine**
- Cell Count
- Total Protein
- Albumin

**Optional**
- Culture
- Glucose
- LDH
- Amylase
- Gram stain

Other only under specific circumstances (cytology, triglycerides, bilirubin, pH, lactate, cholesterol)
Ascites Treatment

- Low sodium diet (<2000 mg/d)
  - check urine sodium, if >50 mEq/d more likely to respond
- Potassium Sparing: spironolactone, amiloride
- Furosemide (not as monotherapy)
- No additional benefit from metolazone, zaroxylyn, torsemide, Bumetanide, HCTZ
- Clonidine, V2 receptor antagonists (tolvaptan) - fallen out due to hepatotoxicity
- Midodrine

Ascites - Treatment - back to our case

- Start with spironolactone 50 mg/d
- Increase to 100 - 150 mg/d
- Add lasix if no effect (40 mg/d)
- Goal diuresis 500 cc - 1 L/d
- Decrease or stop diuretics if creatinine >1.5 mg/dl
- Do not fluid restrict unless sodium <130
Ascites Treatment

Check urine sodium and potassium
If weight gain and
24 hr urine sodium (>78 mmol/d)
Or
Spot urine sodium/potassium ratio >1 and weight gain
Then may be noncompliant

If no weight loss and excrete <78 mmol sodium/d
then increase diuretics

Case

Over the next 18 months
- Spironolactone 200 mg and furosemide 80 mg/d
- Creatinine 1.5-1.8, serum sodium 131, t bili 1.2, INR 1.2
- He has been for large volume paracentesis monthly for past 3 months

In addition to referral for liver transplant-
what else would you order?

Doppler ultrasound- check portal vein
Urine sodium, potassium of suspect noncompliance
**Ascites Treatment**

Should I give FFP for LVP? - No

- Series of 1100 LVP’s with no transfusions or complications
- INR up to 8.7 and PLT = 19K
- 1% abdominal wall hematomas,
  Arch Intern Med 1986;146:2259.

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**Ascites Treatment**

Should I give albumin? : YES (8 g/L) (25-50 g)

- 61% reduction in post-paracentesis circulatory dysfunction
- 42% reduction in hyponatremia
- 36% reduction in mortality

If albumin is limited/restricted then:
- >5 liters
- or creatinine>1.5
- or no peripheral edema
Our case has developed refractory ascites

Diuretic refractory ascites:
- Rise in creatinine
- Hyponatremia
- Hyperkalemia
- Maximum doses of diuretics

TIPS for refractory ascites

- Patent portal vein (partial thrombosis may be TIPS may be feasible and resolve thrombosis)
- MELD<18, t bili< 3, (creatinine<1.9)
- No pulmonary HTN, (Echo)
- No history significant encephalopathy
- No specific age cut off but increased risk of encephalopathy age<70
What do you discuss with your patient about TIPS for ascites?

- 75% chance will reduce or eliminate need for LVP
- May still need to take diuretics
- May take 3-6 months to notice clinical response
- 30% rate of symptomatic encephalopathy
- 10% stenosis rate
- 1% liver failure


The week before his TIPS develops
Spontaneous Bacterial Peritonitis

Total white cells > 500 (his was 700)
Or
Neutrophil count > 250 (90% neutrophils)

*for bloody taps subtract 1 PMN for every 250 red cells
Ascites
Spontaneous bacterial peritonitis

- Occurs in 20% cirrhotics with ascites
- 15% mortality
- 50% patients with SBP are bacteremic

Treatment of SBP

- IV cefotaxime, amoxicillin/clavulanic acid, or quinolone with gram + coverage
- IV albumin
- Avoid therapeutic paracentesis/IV contrast or aggressive diuresis
Repeat diagnostic paracentesis in 48-72 hrs if no clear clinical response

If clinically responding or decrease in PMN’s by 25% on followup paracentesis can switch to oral therapy

Can treat outpatient if no nausea, vomiting, fever, renal dysfunction or encephalopathy

**Cefotaxime vs. ofloxacin**

<table>
<thead>
<tr>
<th></th>
<th>Cefotaxime</th>
<th>Ofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td>84%</td>
<td>85%</td>
</tr>
<tr>
<td>Mortality</td>
<td>19%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Gastroenterology 1996;111:1011-1017

Randomized clinical trial of 126 cirrhotic patients with SBP:
IV cefotaxime (median 5 – 6 days)
vs
IV cefotaxime + IV albumin- 1.5 g/kg day 1 then 1 g/kg day 3

### Ascites

**Treatment of SBP with IV cefotaxime plus albumin**

<table>
<thead>
<tr>
<th></th>
<th>Cefotaxime</th>
<th>Cefotaxime + albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>33%</td>
<td>10%, p=0.002</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In hospital</td>
<td>29%</td>
<td>6%, p=0.01</td>
</tr>
<tr>
<td>3 month</td>
<td>41%</td>
<td>22%, p=0.03</td>
</tr>
</tbody>
</table>

*NEJM 1999;341:403-9*

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### Ascites

**Treatment of SBP with IV cefotaxime plus albumin**

<table>
<thead>
<tr>
<th></th>
<th>Cefotaxime</th>
<th>Cefotaxime + albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN&lt;30, T bili&lt;4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>BUN&gt;30, T bili&lt;4</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>BUN&lt;30, T bili&gt;4</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>BUN&gt;30, T bili&gt;4</td>
<td>78%</td>
<td>43%</td>
</tr>
</tbody>
</table>

*NEJM 1999;341:403-9*
Ascites
Spontaneous bacterial peritonitis

Primary prophylaxis vs. Secondary prophylaxis

- Secondary prophylaxis is standard of care
  - cipro or norflox or bactrim daily, rifaximin
- Primary usually not done because of resistance, unless advanced cirrhosis

Low protein ascites <1.5
Ascites - Primary Prophylaxis for SBP

CPT > 9
Tbili > 3
Serum cr > 1.2
BUN > 25
Na < 130
### Ascites

#### Primary Prophylaxis for SBP

**Change in ascitic fluid WBC**

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-40</td>
<td>+13</td>
</tr>
</tbody>
</table>

**Neutrophils**

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-15</td>
<td>+1</td>
</tr>
</tbody>
</table>

**Plasma endotoxin EU/ml**

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>-1.7</td>
<td>+1</td>
</tr>
</tbody>
</table>


4.5% rifaximin group vs 46% control group developed SBP over 5 years, p=0.027

*J Gastroenterol Hepatol 2013:28:450-3.*
Ascites
Spontaneous bacterial peritonitis
Most common isolates of SBP
-E coli
-Klebsiella pneumoniae
-Pneumococci
Also consider enterococcus (VRE), candida
-Carbopenem resistant E coli, klebsiella

Carbopenem resistant E coli and Klebsiella

- 2.6% prevalence- feces colonized
- Cirrhosis associated with 12-fold increase risk
- Other risk factors: prolonged hospitalization (28 days), prior exposure to meropenem (OR=9) or clindamycin (OR=8)

Addition of probiotics to norfloxacin does not improve efficacy in the prevention of spontaneous bacterial peritonitis: a double-blind placebo-controlled randomized-controlled trial.

*Eur J Gastroenterol Hepatol* 2012;24:831-9

<table>
<thead>
<tr>
<th></th>
<th>Norflox+ Probiot n=55</th>
<th>Norflox + Placebo n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>Mortality 6 months</td>
<td>29%</td>
<td>32%</td>
</tr>
</tbody>
</table>

(Enterococcus faecalis JPC 30 million, Clostridium butyricum 2 million, Bacillus mesentericus JPC 1 million, Bacillus coagulans 50 million spores)

Primary prophylaxis against SBP for high risk patients

- Low protein ascites<1.5
- CPT>9
- Tbill>3
- Serum cr>1.2
- BUN>25
- Na<130
Back to our case

- Hospitalized for SBP the week before his TIPS
- Blood cultures, ascitic fluid culture negative
- Clinically responded, no repeat paracentesis
- Discharged the day before his scheduled TIPS
- Keep him a day or reschedule TIPS?

Reschedule the TIPS- elective procedure and seeding of the TIPS probably fatal-

TIPS failure

- Patient has TIPS but reaccumulates ascites
- TIPS is revised x 2
- Radiologists state they can attempt parallel TIPS but patient has problems with encephalopathy and has developed a partial portal vein thrombosis
- Options other than serial paracentesis
Peritoneal venous shunts

LeVeen and Denver Shunts

Ascites Treatment
LeVeen and Denver Shunts

J Hepatol 1986 212-8, randomized n=57
Ann Surg 1985 488-93, prospective n=140
Abdominal catheters for refractory ascites

- Patient is not a candidate for TIPS or transplant
- Patient does not want serial paracentesis
- Terminal, and will accept hospice/palliative care
- Remove 3-5 liters 2-3 times per week
- 6 month mortality ~100% - J Vasc Interv Radiol 2013;24:1303-8.
- Continuous peritoneal drainage over 72 hours can increase the interval between LVP - Dig Dis Sci 2011;2723-7.

Hepatic Hydrothorax

- Portosystemic gradient reduced from 26 to 10
- 82% hydrothorax improved, 71% resolved
- 64% 1 year survival
- 100% nonresponders died within 7 months
- Mean followup 16 months (1-54 month)
- 6 patients required pleurodesis or chest tube
- Better survival MELD<15

**Hepatic hydrothorax**

- Chest tube insertion
- 17 patients, MELD 14
- 16 had complications: AKI, pneumothorax, empyema
- Most common complications
- 35% 3 month mortality

**Hepatorenal syndrome**

- Renal failure in patients with liver failure associated with low urine sodium in the absence of renal pathology
- **Type I HRS** - rapidly progressive renal failure with the doubling of serum creatinine to a level of greater than 2.5 mg/dl or halving of the creatinine clearance to less than 20 ml/min within 2 weeks (after volume repletion)
- **Type II HRS** - chronic form with progressive increase in serum creatinine >1.5 mg/dl or creatinine clearance <40 ml/min
- Type I HRS median survival 2 weeks
- Type II HRS median survival 6 months
Ascites and hepatorenal syndrome
Treatment

- Octreotide + midodrine + albumin
- Terlipressin: vasopressin agonist
- Norepinephrine
- MARS (not widely available in U.S.)
- TIPS (special cases)
- Liver Transplantation
- Dopamine - no role

NO BP = NO PP - stop beta blockers

ACG 2014 Annual Scientific Meeting • October 20-2, 2014
Ascites and beta blockers

Among 607 cirrhotic patients who had a large volume paracentesis beta blockers were associated with:

- Reduced transplant free survival (HR=1.58, p=0.01)
- Increased HRS (24% vs 11% not on NSBBs, p=0.027)
- Increased grade C kidney injury (20% vs 8%, p=0.021)

Conclusion: Consider discontinuing beta blockers in patients with low-normal blood pressure who has paracentesis

Gastroenterology 2014;146:1680-90.

Ascites and portal vein thrombosis

MRI showing partial portal vein thrombosis
Ascites from portal vein thrombosis- role of anticoagulation

31 patients with acute or subacute thrombosis and 24 patients with progression of PVT were anticoagulated with LWH

- 60% partial or complete recanalization
- 38.5% recurred when anticoagulation was stopped
- 5 bleeding episodes
- Platelet count<50k associated with bleeding

Recommendation: Anticoagulate when symptomatic or thrombus propagating to SMV as long as plt>50k and no history of bleeding


Ascites Hyponatremia

- Fluid restriction <1.0 – 1.5 L/d
- Stop diuretics
- RECOGNIZE HYPOVOLEMIC HYПONATREMIA
- Avoid hypertonic saline (normal saline may be adequate)
- V2 receptor antagonists- principal receptor of vasopressin in renal collecting tubule (satavaptan, tolvaptan) not used due to hepatotoxicity.
Summary
Diagnosis and Treatment
Take home points

- Ascites is the most common complication of cirrhosis
- Serum albumin ascitic fluid gradient, cell count, culture are initial diagnostic tests
- Treatment- start with spironolactone then add lasix
- Spot urine Na:K useful for compliance

Summary
Diagnosis and Treatment
Take home points

- LVP- no need for FFP, platelets
- LVP-avoid in setting active infection, give albumin if incr. creatinine, no edema
- Stop diuretics if suspect SBP
- Reserve TIPS for diuretic refractory cases and t bili<3, MELD<20
- Peritoneal-venous shunts limited to no role
- Abdominal catheters for palliation
Summary
SBP
Take home points

• Primary prophylaxis Child C cirrhotic with hyponatremia, azotemia

Balanced against

• Resistance (carbopenem)

• Secondary prophylaxis is standard of care - same criteria for cell count for ascites apply to hydrothorax
Water, Water Everywhere: Approach to the Cirrhotic Patient with Acute Kidney Injury

Jasmohan S Bajaj, MD, MS, AGAF, FACG

Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center
Richmond, Virginia

Key Questions

• Why is it important?
• What are the sub-types?
• How can we differentiate between the types of AKI?
• What are the treatment options?
• Can we prevent this?
AKI and Renal dysfunction in Cirrhosis

- Renal dysfunction is common in patients with liver cirrhosis
- Occurs in ~20% of cirrhotic patients admitted to hospital
- Most cases of renal dysfunction are due to acute deterioration of renal function, collectively known as acute kidney injury (AKI)
- Most AKI episodes are related to hemodynamic changes in cirrhosis
- Most common precipitant is bacterial infection, especially SBP
- AKI is associated with poor survival of ~30% at 3 month
## Kidney dysfunction in cirrhosis

<table>
<thead>
<tr>
<th>AKI</th>
<th>Increase in serum creatinine ≥ 50% compared to baseline or ≥ 26.4 μmol/l within 48 hours. HRS type 1 is a specific form of AKI.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>GFR of &lt; 60 ml/min for &gt; 3 months calculated using MDRD6 formula. HRS type 2 is a specific form of CDK.</td>
</tr>
<tr>
<td>ACKD</td>
<td>Increase in serum creatinine ≥ 50% compared to baseline or ≥ 26.4 μmol/l within 48 hours in a patient with CKD</td>
</tr>
</tbody>
</table>

Source: Israelsen 2014 JGH
Survival Is Decreased With Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction

Survival Among Patients With Cirrhosis and Hepatorenal Syndrome

Definitions and sub-types

### Acute Kidney Injury Networks classification of acute kidney injury:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Increase in serum creatinine $\geq 50$ - $100%$ from baseline or $\geq 26.4 , \mu\text{mol/l}$ within 48 hours.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Increase in serum creatinine $&gt; 100$-$200%$ from baseline</td>
</tr>
<tr>
<td>Grade III</td>
<td>Increase in serum creatinine to $&gt; 200%$ from baseline or acute increase of $\geq 44 , \mu\text{mol/l}$ to $\geq 354 , \mu\text{mol/l}$</td>
</tr>
</tbody>
</table>

[![Acute Kidney Injury Networks classification of acute kidney injury:](image)](image)
Renal Injury in Cirrhosis

Hospitalized patients with cirrhosis

- Chronic renal failure: 1%
- AKI: 19%

Pre-renal: 68%

Intra-renal (ATN, GMN): 32%

Post-renal (obstructive): <1%

Volume-responsive: 66%
  - Infection
  - Hypovolemia
  - Vasodilators
  - Other

Not volume-responsive

HRS type 1: 25%

HRS type 2: 9%

AKI: Acute kidney injury
GMN: Glomerulonephritis
ATN: Acute tubular necrosis
HRS: Hepatorenal syndrome

Differential Diagnosis and Work-up

History of:
- Dehydration
- Excessive diuretics
- Bacterial infections

Presence of:
- Normal urinary sediment
- Proteinuria < 500 mg/day
- Normal renal ultrasound

Withdrawal of diuretics
Plasma volume expansion with albumin

Response

No response

PRERENAL/ARF

HRS/ARF

ATN/ARF

History of current or recent use of nephrotoxic drugs or contrast media

Presence of:
- Shock
- Granular casts or debris in urinary sediment
- Proteinuria > 500 mg/day


Angeli et al 2013 Liver International
Differentiation between AKI, Acute Tubular Necrosis and HRS

Belcher et al Hepatol 2014

Proposed Diagnostic Criteria for AKI in Cirrhosis

- Meeting of International Ascites Club and Acute Dialysis Quality Initiatives

- Proposed using smaller increase of serum creatinine to diagnose AKI

  - Rise in serum creatinine of ≥50% from baseline, or a increase of ≥0.3mg/dl (26.4µmol/l) in ≤48 hours

- Type 1 HRS is a specific form of AKI

- This may help to identify patients at an earlier stage of renal dysfunction for treatment

Wong et al, Gut 2011

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Problems with serum creatinine

- Serum creatinine is a poor marker of renal function in cirrhosis
- Muscle wasting and poor production of creatinine from creatinine
- Significant renal dysfunction may occur despite a normal serum creatinine
- Other formulae that calculate GFR are also inaccurate because they employ serum creatinine

A little increase in creatinine goes a long way

*Patient Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>ICU admission</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>AKI+</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>AKI-</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

* p<0.0001

Wong et al NACSELD Gastro 2013
A little increase in creatinine goes a long way

**Survival**

Wong et al NACSELD Gastro 2013

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**The AKI Patients - Outcomes**

Wong et al NACSELD Gastro 2013

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37
**A little increase in creatinine goes a long way**

*The AKI patients - Survival*

Wong et al NACSELD Gastro 2013

**AKIN criteria predict outcomes in hospitalized patients with cirrhosis**

Angeli et al Gut 2014
Hepatorenal Syndrome

A potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure, consisting of impaired renal function, marked abnormalities in cardiovascular function, and intense over-activity of the endogenous vasoactive systems

International Ascites Club, Gut 2007
Hepatorenal Syndrome – Type 1

1. Cirrhosis and ascites;
2. Serum creatinine > 1.5 mg/dl;
3. No improvement of serum creatinine (decrease of creatinine equal to or less than 1.5 mg/dl) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg b.w./day for 2 days);
4. Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure;
5. No current or recent treatment with nephrotoxic drugs;
6. Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml).

International Ascites Club, Liver Int 2010

Hepatorenal Syndrome: Risk Factors

- Development of bacterial infections, particularly SBP, is the most important risk factor
  - Hepatorenal syndrome develops in ~30% of patients with spontaneous bacterial peritonitis
  - Treatment with albumin infusion/antibiotics reduces the risk of developing hepatorenal syndrome and improves survival

Hepatorenal Syndrome: Prognosis

• The prognosis of hepatorenal syndrome is poor
  – Average median survival ~ 3 months
  – High MELD score and type 1 hepatorenal syndrome are associated with very poor prognosis
    • Median survival of patients with untreated type 1 hepatorenal syndrome is ~ 1 month


Pharmacological treatment of HRS 1

Vasoconstrictors
Terlipressin: 1 mg/4–6 hours intravenously. The dose is increased up to a maximum of 2 mg/4–6 hours after 3 days if there is no response to therapy (defined as a 25% or greater reduction in serum creatinine compared to pretreatment levels). A response to therapy is defined as a decrease in serum creatinine levels below 1.5 mg/dL (133 μmol/L). The treatment is usually applied for 5 to 15 days.
Midodrine and octreotide: 7.5 mg of midodrine orally 3 times daily (increased to 12.5 mg 3 times daily if needed) and 100 μg of octreotide subcutaneously 3 times daily (increased to 200 μg 3 times daily if needed). The duration of treatment depends on the effects on serum creatinine.
Norepinephrine: 0.5–3 mg/hour as a continuous intravenous infusion aimed at increasing the mean arterial pressure by 10 mm Hg. The treatment is continued until the serum creatinine level decreases below 1.5 mg/dL.

Albumin Administration
Concomitant administration of albumin and vasoconstrictor drugs (1 g/kg of body weight on day 1 followed by 20–40 g/day). Sola et al CLD 2013
Pharmacological treatment of HRS 1

Vasoconstrictors

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Sola et al CLD 2013
Meta-analysis of Vasoconstrictor Treatment for HRS 1

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Uehle, 2000</td>
<td>0.99 (0.69, 1.39)</td>
</tr>
<tr>
<td>Neri, 2008</td>
<td>0.71 (0.49, 1.04)</td>
</tr>
<tr>
<td>Pomier, 2003</td>
<td>0.86 (0.55, 1.39)</td>
</tr>
<tr>
<td>Sanyal, 2008</td>
<td>0.91 (0.67, 1.24)</td>
</tr>
<tr>
<td>Solanki, 2003</td>
<td>0.60 (0.37, 0.97)</td>
</tr>
<tr>
<td>Yang, 2001</td>
<td>0.13 (0.01, 2.10)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.82 (0.70, 0.90)</td>
</tr>
</tbody>
</table>

(Gluud LL. et al, Hepatology 2010)

TYPE 1 HRS

Candidate for transplant

- Evaluation for liver transplant

- Prioritize patients on transplant list

- Treatment with terlipressin (or other vasoconstrictors) plus albumin

- Improvement
  - Stop therapy after obtaining complete response* or maximum 15 days
  - Keep pre-treatment MELD score while awaiting transplant in responder patients**

- No improvement
  - Therapy with vasoconstrictors should be individualized
  - Consider RRT

Not candidate for transplant

Sola et al CLD 2013
Prevention is better than cure!

Prevention of Acute Kidney Injury

- Prevent/treat volume depletion or vasodilatation
  - Careful use of diuretics
  - Avoidance of diarrhea with use of lactulose
  - Use of albumin after large-volume paracentesis
- Prompt use of antibiotics during GI bleeding episodes and adequate SBP prophylaxis
- Avoid use of aminoglycosides and NSAIDs
- Aggressively treat hypovolemia/hypotension occurrence

Summary

• AKI is a multi-factorial disease process in cirrhosis
• Most AKI is not hepato-renal syndrome
• Minor increases in creatinine can go a long way in determining prognosis
• Treatment of AKI is not ideal therefore prevention strategies are critical

Acknowledgements

• Florence Wong, Toronto, Canada
• Arun J Sanyal, VCU, Richmond
• Members of NACSELD
A Rational Guide to the Use of TIPS

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Clinical Vice Chair of Medicine
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Learning Objectives

Upon completion of this activity, participants should be able to:

- List the primary and secondary indications for portal decompression via TIPS
- Identify the patients for whom early TIPS intervention may optimize outcomes when developing strategies to treat patients with esophageal varices
- List and discuss the relative contraindications to TIPS
Cirrhosis is the most common cause of portal hypertension. The site of increased resistance in cirrhosis is sinusoidal. Other causes of portal hypertension are classified according to the site of increased resistance.

### Portal Hypertension Is Classified According to the Site of Increased Resistance

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hepatic vein</td>
<td>Portal or splenic thrombosis</td>
</tr>
<tr>
<td>Pre-sinusoidal</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Sinusoidal</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Post-sinusoidal disease</td>
<td>Veno-occlusive</td>
</tr>
<tr>
<td>Post-hepatic syndrome</td>
<td>Budd-Chiari</td>
</tr>
</tbody>
</table>
**TIPS:**
Transjugular Intrahepatic Portosystemic Shunt

Pre TIPS

Post TIPS

**Polytetrafluoroethylene-covered TIPS stents**
Covered Stents Are More Likely to Remain Functional Than Uncovered Stents

Bureau, et al. Gastroenterology 2004;126:469

Covered TIPS Stents Lead to Less Encephalopathy with Equivalent Survival

Bureau, et al. Gastroenterology 2004; 126:469
**TIPS: Most Common Indications**

- **Variceal hemorrhage**
  - Acute bleeding refractory to endoscopic Rx
  - Unsuitable for endoscopic Rx
  - Gastric varices, lives far away from endoscopist

- **Refractory ascites, hepatic hydrothorax**
  - Inability to control with taps and diuretics
  - Complications of ascites (SBP) or secondary to Rx of the ascites (renal failure, electrolyte imbalance)

**Natural History of Esophageal Varices**

- Cirrhosis
- Development of varices (Form when HVPG >10mm Hg)
- Index variceal bleed (33% of all with varices)
- Recurrent bleeds (~70%)

TIPS in the Treatment of Variceal Hemorrhage

- TIPS is rescue therapy for recurrent variceal hemorrhage
  (at second rebleed for esophageal varices, at first rebleed for gastric varices)

- TIPS is indicated in patients who rebleed on combination endoscopic plus pharmacologic therapy

- In patients with Child A/B cirrhosis, the distal spleno-renal shunt is as effective as TIPS
  (dependent on local expertise)

Early TIPS In Patients With Acute Variceal Hemorrhage and HVPG >20 mmHg (High Risk) May Improve Survival

Early TIPS for Variceal Bleeding

- 63 patients with cirrhosis
  - Child’s C (score 10-13) or B with acute variceal bleeding

- In first 24 hrs pts were randomized
  - TIPS vs Med Rx (vaso-active drugs + EBL)
  - TIPS done with covered stent within 72 hrs post randomization

<table>
<thead>
<tr>
<th></th>
<th>Med Rx</th>
<th>TIPS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Pts</td>
<td>31</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Failure to Control Bleeding</td>
<td>14 (45.2%)</td>
<td>1 (3.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Free of bleeding @ 1 yr</td>
<td>50%</td>
<td>97%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 yr Survival</td>
<td>61%</td>
<td>86%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 yr rate of encephalopathy</td>
<td>40%</td>
<td>28%</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Garcia-Pagan. NEJM 2010;362:2370

Management of Acute Variceal Hemorrhage

Variceal Hemorrhage Suspected

Initial Management

- Transfuse to hemoglobin ~ 8 g/dL
- Early pharmacotherapy
- Antibiotic prophylaxis
Management of Acute Variceal Hemorrhage

Variceal Hemorrhage Suspected

Initial Management

- Transfuse to hemoglobin ~ 8 g/dL
- Early pharmacotherapy
- Antibiotic prophylaxis

Endoscopic Intervention

Endoscopic variceal band ligation (EVL) is preferred to sclerotherapy

Management of Acute Variceal Hemorrhage

Variceal Hemorrhage Suspected

Initial Management

Acute Hemorrhage Controlled?

NO

Balloon Tamponade (bridging therapy)

Rescue TIPS/Shunt surgery
Management of Acute Variceal Hemorrhage

Variceal Hemorrhage Suspected

Initial Management

Acute Hemorrhage Controlled?

- NO
  - Balloon Tamponade
  - Rescue TIPS/Shunt surgery

- YES
  - Consider Early TIPS

Acute Hemorrhage Controlled?

- NO
  - Rescue TIPS/Shunt surgery

- YES
  - 2nd Endoscopy

If not an Early TIPS Candidate and has Early Rebleed?

- YES
  - 2nd Endoscopy

Further bleeding
Gastric Varices

- 10-15% of variceal bleeding episodes
- Limited data from controlled trials
- Optimal therapy not known
- Vasoactive drugs used, but not studied
- Endoscopic cyanoacrylate injection: 90% control of bleeding
- Balloon tamponade with Linton-Nachlas tube
- TIPS: 90% control of bleeding

Management of Gastric Varices

- Gastric varices that are continuous with esophageal varices and extend along the lesser curve (GOV1) should be treated in the same way as esophageal varices
- In patients with isolated fundal varices (IGV1), splenic vein thrombosis should be investigated. If present, treatment consists of splenectomy
- Cirrhotic patients bleeding from gastric fundal varices require specific treatment
Management of Acute Gastric (Fundal) Variceal Bleeding

Variceal Hemorrhage Suspected

Initial Management

- Transfuse to hemoglobin ~8 g/dL
- Early pharmacotherapy
- Antibiotic prophylaxis

Variceal obturation possible?

NO

TIPS*

*Surgical shunt may be considered for Child’s Class A
Management of Acute Gastric (Fundal) Variceal Bleeding

Variceal Hemorrhage Suspected

Initial Management

Variceal obturation possible?

NO

YES

Bleeding controlled?

NO

TIPS*

YES

Variceal obliteration + beta-blockers

*Not possible or rebleed

*Surgical shunt may be considered for Child's Class A
Definition and Types of Refractory Ascites

Occurs in ~10% of cirrhotic patients

- **Diuretic-intractable ascites** 80%
  Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

- **Diuretic-resistant ascites** 20%
  No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

Arroyo et al. Hepatology 1996; 23:164

Meta-Analysis of TIPS vs. LVP + Albumin for Refractory Ascites

<table>
<thead>
<tr>
<th>Metric</th>
<th>More with LVP</th>
<th>More with TIPS</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites control (month 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites control (month 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival (month 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIPS v. Paracentesis for Ascites
Meta-Analysis of Individual Patient Data

<table>
<thead>
<tr>
<th></th>
<th>TIPS</th>
<th>Paracent.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>149</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Ascites recurrence</td>
<td>42%</td>
<td>89%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Avg number enceph. events</td>
<td>1.1</td>
<td>0.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Survival benefit for the TIPS group

Salerno. Gastroenterology 2007;133:825

TIPS: Less Common Indications

- Budd-Chiari syndrome
- Portal Gastropathy
- Portal vein occlusion
- Malignant compression of HV or PV
- Recurrent portal HTN post Tx
- Lower GI and stomal varices
- Pre-operative decompression
Portal Hypertensive Gastropathy

- Endoscopic changes seen in most patients with portal hypertension
- May be mild or severe
- Characterized by a cobblestone appearance of the mucosa and red signs on endoscopy
- Distribution is more proximal than distal
- Usually responds to measures aimed at reducing portal pressure

ENDOSCOPIC IMAGES OF MILD AND SEVERE PORTAL HYPERTENSIVE GASTROPATHY

Mild
Mosaic pattern

Severe
Mosaic pattern + red spots
Management of Chronic Bleeding from Portal Hypertensive Gastropathy

Initial medical management
(Beta-blockers and iron supplement)

Bleeding controlled?

YES

Continue medical therapy
Management of Chronic Bleeding from Portal Hypertensive Gastropathy

Initial medical management (Beta-blockers and iron supplement)

Bleeding controlled?

- Yes
  - Transfusion dependent?
    - No
      - Continue medical therapy
    - Yes
      - Blood transfusion as needed

- No
  - Transfusion dependent?
    - No
      - Continue medical therapy
    - Yes
      - TIPS

Bleeding controlled?

- Yes
  - Transfusion dependent?
    - No
      - Continue medical therapy
    - Yes
      - Blood transfusion as needed

- No
  - Transfusion dependent?
    - No
      - Continue medical therapy
    - Yes
      - TIPS
Bleeding Stomal Varices

- 8 patients
- Sclero-Rx temporarily effective
  - Led to stomal strictures in some patients
- Decompression of PV needed in all cases
- Literature review – TIPS controlled bleeding effectively in 40 patients in 19 different reports
  - Embolization rarely successful without decompression of the portal system


TIPS: Contraindications

- Severe hepatic insufficiency:
- Right heart failure
- Cavernous portal vein occlusion
- Relative:
  - Active infection
  - Hypervascular hepatic tumor
  - Polycystic liver disease – probably ok to do
Predictors of Post TIPS Mortality: Degree of Hepatic Insufficiency

- Ferral H. Radiology 2004
  - MELD >18, Child’s C, ascites as an indication

- Harrod-Kim P. JVIR 2006
  - MELD >25, Child’s C, PSG <8 mm Hg post TIPS

- Pan . JVIR 2008
  - MELD >15, bili >2.5, INR >1.4, creat >1.2, age >70

TIPS: Complications

- **Procedural 10-15%**
  - Intra-abdominal bleeding
  - Hemolysis
  - Hemobilia
  - Sepsis
  - Right heart failure
  - Transient renal insufficiency

- **30 Day Mortality**
  - Average 15% (3-25%)
TIPS: Long Term Complications

- **Deterioration of liver function**
  - Transient: 10-20%
  - Progressive liver failure: 3-8%

- **Hepatic encephalopathy**
  - 23-50%
  - Refractory to medical therapy: 3-5%

Summary

- TIPS now plays an integral role in the management of portal hypertension related complications
- Primary and secondary indications for portal decompression via TIPS
- Identifying patients for whom early TIPS intervention may optimize outcomes
- To maximize success must keep in mind the relative contraindications to TIPS