Management of Ascites

David Koch, MD
Associate Professor of Medicine
Medical University of South Carolina

Objectives

• Evaluation of the patient with ascites
• Natural history and Pathophysiology of Ascites
• Management of Uncomplicated Ascites
• Management of Refractory Ascites
  • LVP + Albumin, PVS, TIPS
  • Prognostic indicators to decide on appropriate TIPS placement
• TIPS for Hepatic Hydrothorax
  • Case Series
  • Effectiveness
Cirrhosis is the Most Common Cause of Ascites

- Cirrhosis
- Peritoneal malignancy
- Heart failure
- Peritoneal tuberculosis
- Others
  - Pancreatic
  - Budd-Chiari syndrome
  - Nephrogenic ascites

New-onset Ascites

- **History**
  - Risk factors for liver disease
  - Past history of cancer
  - Presence of renal disease or CHF

- **Physical Exam**
  - Evaluate for evidence of heart failure
    - JVD
    - S3
    - Displaced PMI
    - RV Heave
New-onset Ascites

- Physical Findings
  - Evidence of Chronic Liver Disease
    - Jaundice
    - Muscle Wasting
    - Gynecomastia
  - Dermatologic Abnormalities
    - Spider Angiomata
    - Palmar Erythema
    - Terry’s Nails
    - Muehrcke’s nails
  - Hepatomegaly or Splenomegaly
- Abdominal Exam
  - Flank Dullness- 1.5L ascites required
  - Shifting Dullness- 83% Sensitivity and 56% Specificity
  - Fluid Wave- Cumbersome and unnecessary.

Clinical Case

- A 65 yo man is seen in clinic for increasing abdominal distension for 2 months. He has no history of liver disease but admits to consuming 6 – 8 beers/d for 20 yrs.
- PE:
  - No jaundice. +palmar erythema & spider nevi.
  - CV exam is normal (i.e. no extra heart sounds, RV heave, or JVD).
  - Ab exam: Bulging flanks/shifting dullness & splenomegaly.
- Lab data: Platelet count 90,000/µL, bilirubin 1.5 mg/dL, AST 150 U/L, ALT 80 U/L, total protein 5.9 g/dL, albumin 3.0 g/dL, creatinine 0.9 mg/dL, and a normal urinalysis.
- Ab U/S: Moderate amount of ascites, enlarged liver and spleen.
Question #1
Which of the following will best help to determine the etiology of the ascites?

A) Measuring ascites total protein and same day serum total protein
B) Analyzing the ascites for malignancy with cytology
C) Measuring ascites total protein, albumin, cell count/differential, & culture along with same day serum albumin
D) 24-Hour Urine protein quantification

Ascites Fluid Analysis

<table>
<thead>
<tr>
<th>Routine</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Glucose</td>
</tr>
<tr>
<td>Protein</td>
<td>LDH</td>
</tr>
<tr>
<td>PMN cell count</td>
<td>Amylase</td>
</tr>
<tr>
<td>Cultures</td>
<td>Red blood cell count</td>
</tr>
<tr>
<td></td>
<td>TB smear and culture</td>
</tr>
<tr>
<td></td>
<td>Cytology</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
</tr>
</tbody>
</table>
Ascites Can Be Characterized by Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein

Source of ascites

Hepatic sinusoids
- SAAG > 1.1
  - "Capillarized" sinusoid
    - Ascites protein < 2.5
    - Sinusoidal hypertension
      - Cirrhosis
      - Late Budd-Chiari

Peritoneum
- SAAG < 1.1
  - Normal "leaky" sinusoid
    - Ascites protein > 2.5
    - Post-sinusoidal hypertension
      - Cardiac ascites
      - Early Budd-Chiari
      - Veno-occlusive disease
  - Peritoneal lymph
    - Ascites protein > 2.5
    - Peritoneal pathology
      - Malignancy
      - Tuberculosis

Clinical Stages of Cirrhosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Clinical</th>
<th>Symptoms</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>F1-F3</td>
<td>Non-cirrhotic</td>
<td>Compensated</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>Compensated</td>
<td>No Varices</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decompensated</td>
<td>(Varices)</td>
<td>Variceal Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>Ascites</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 6mmHg</td>
<td>&gt; 10mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 12mmHg</td>
<td>Stage 3,4</td>
</tr>
</tbody>
</table>
Ascites

- Most common complication of cirrhosis.
- 50% with compensated cirrhosis develop ascites over 10 years
- Most common complication requiring hospitalization
- 1-year mortality - 15%
- 5-year mortality - 44%

An Increase in Portal Venous Inflow Sustains Portal Hypertension
Cirrhosis

- Hepatic venous outflow block
- Ascites
- Sodium and water retention
- Activation of neurohumoral systems (renin, angiotensin, aldosterone)
- Effective arterial blood volume
- Arteriolar resistance (vasodilation)

Sinusoidal pressure (HVPG ≥ 10-12 mmHg)

Natural History of Ascites

- Portal Hypertension No Ascites
  - HVPG < 10 mmHg
  - Mild Vasodilation
- Uncomplicated Ascites
  - HVPG > 10 mmHg
  - Moderate Vasodilation
- Refractory Ascites
  - HVPG > 10 mmHg
  - Severe Vasodilation
- Hepatorenal Syndrome
  - HVPG > 10 mmHg
  - Extreme Vasodilation
Question # 2

- What would be your initial management plan for the ascites?
  A) Lasix 40mg qd.
  B) Large Volume Paracentesis as needed.
  C) Restrict Free Water intake to 800cc/day.
  D) Aldactone 100mg qd, lasix 40mg qd, and restrict sodium intake to 2000mg/day

Management of Uncomplicated Ascites

**Definition:** Ascites responsive to diuretics in the absence of infection and renal dysfunction

- Sodium restriction
- Diuretics

- Measures are identical for uncomplicated Hepatic Hydrothorax
Management of Uncomplicated Ascites

Sodium Restriction

- 2 g (or 5.2 g of dietary salt) a day
- Fluid restriction is not necessary unless there is hyponatremia (<125 mmol/L)
- Side effect: unpalatability may compromise nutritional status

Diuretic Therapy

Dosage
- Spironolactone 100-400 mg/day
- Furosemide (40-160 mg/d)

Spironolactone is the cornerstone of diuretic therapy for ascites.
- Once daily dosing (long half-life)

Lasix can be added:
- Sequentially (Aldactone to 400mg qd or hyperkalemia)
- Combination
- Ineffective as monotherapy

Dose of diuretics titrated every 3-4 days until desired weight loss.

Side effects
- Renal dysfunction, hyponatremia, hyperkalemia, encephalopathy, gynecomastia
Loop diuretics in Cirrhosis

Loop Diuretics inhibit Na Resorption

Revisiting the Case

- The patient is requiring LVP every 6 – 7 days with up to 10 liters removed each session.
- Aldactone 200mg daily and Lasix 80mg twice daily.
- There is no history of hepatic encephalopathy.
- Pertinent laboratory tests: sodium 134 meq/L, potassium 4.8 meq/L, creatinine 1.1 mg/dL, bilirubin 1.8 mg/dL, albumin 2.8 g/dL, and INR 1.5.
- A 24-hour urine for sodium quantification is 4 grams.
- The patient is tired of getting paracentesis weekly and is inquiring about TIPS placement.
Question #3

What is the best advice with regards to TIPS placement in managing his ascites?

A) TIPS placement is indicated since he is requiring regular LVP to control the ascites.
B) A TIPS should not be placed since he may develop hepatic encephalopathy.
C) A TIPS is high risk based on his Model of End Stage Liver Disease (MELD) score.
D) TIPS placement is not yet indicated since he does not yet meet criteria for Refractory Ascites.

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)
  Should prove adequate compliance with Sodium restriction- 24hr Urine
Patients with Refractory Ascites Have a Worse Survival than Patients with Diuretic-Responsive Ascites

- Survival probability over time for Non refractory ascites and Refractory ascites.
- 1 yr. survival ~ 40%
- p<0.001 for difference between groups.
- Data from Salerno et al., Am J Gastroenterol 1993; 88:514.

Cirrhosis
- Intrahepatic resistance
- Sinusoidal pressure
- Refractory ascites
- Hepatorenal syndrome
- Systemic arteriolar resistance
- Effective arterial blood volume
- Sodium and water retention
- Activation of neurohumoral systems
- Worsening liver disease
- Refractory ascites
- Non refractory ascites

Patients with Refractory Ascites Have A Worse Survival than Patients with Diuretic-Responsive Ascites

Salerno et al., Am J Gastroenterol 1993; 88:514

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**Treatment of Ascites**

- **Portal Hypertension No Ascites**
- **Uncomplicated Ascites**
- **Refractory Ascites**
  - 1) LVP + albumin
  - 2) TIPS
  - 3) PVS (in non-TIPS, non-transplant candidates)
- **Hepatorenal Syndrome**

**Large Volume Paracentesis**

- Safe and effective
- Minor complications (Ab. wall hematoma): 1% cases
- Severe complications (hemoperitoneum & bowel perforation): < 1/1000 cases
- Albumin (8g/L) if > 5L removed
- **No data to support use of FFP or platelets**
  - Series of 1100 LVP, no hemorrhagic complications despite:
    - No prophylactic transfusions
    - Platelet counts as low as 19,000 cells/mm³
    - INR as high as 8.7 (75% > 1.5 and 27% > 2.0)

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LVP = large volume paracentesis
TIPS = transjugular intrahepatic portosystemic shunt

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Post-Paracentesis Circulatory Dysfunction (PCD) Depends on the Type of Plasma Volume Expander and the Amount of Ascites Removed

Development of PCD

<table>
<thead>
<tr>
<th>Ascites removed</th>
<th>&lt;5-6 L</th>
<th>&gt;5-6 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>No expander</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Saline</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Synthetic expander</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Albumin</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Gines et al., Gastroenterology 1988; 94:1493
Gines et al., Gastroenterology 1996; 111:1002
Sola-Vera et al., Hepatology 2003; 37:1127

Peritoneo-Venous Shunt (PVS) is Useful in the Treatment of Refractory Ascites

Effectiveness equivalent to LVP + Albumin

High rate of obstruction (50% in 1st year)

Indicated only in patients requiring frequent LVP and not TIPS candidate.

Intraabdominal adhesions may complicate liver transplant surgery
Transjugular Intrahepatic Portosystemic Shunt (TIPS)

**Hepatic vein**

**Portal vein**

**Splenic vein**

**Superior mesenteric vein**

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**Cirrhosis**

- **↑ Intrahepatic resistance**
- **↓ Sinusoidal pressure**
- **Ascites**
- **Sodium and water retention**
- **↓ Arteriolar resistance (vasodilation)**
- **↑ Effective arterial blood volume**
- **↑ Activation of neurohumoral systems**

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Covered Stents Are More Likely to Remain Functional Than Uncovered Stents

- Covered: % free of shunt dysfunction decreases more slowly over time.
- Uncovered: % free of shunt dysfunction decreases more rapidly over time.

*p = 0.0005

Contraindications for TIPS

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>Hepatoma (esp. Centrally located)</td>
</tr>
<tr>
<td>Uncontrolled Systemic Infection/Sepsis</td>
<td>Portal Vein Thrombosis</td>
</tr>
<tr>
<td>Unrelieved Biliary Obstruction</td>
<td>Multiple Hepatic Cysts</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (Plt &lt; 20,000/cm³)</td>
</tr>
<tr>
<td></td>
<td>Moderate Pulmonary Hypertension</td>
</tr>
</tbody>
</table>
Predictors of Poor Outcome with TIPS

**Clinical Variables**
- Age
- Bilirubin
- Creatinine
- INR
- Sodium
- Albumin
- Pre-TIPS Encephalopathy
- Urgent TIPS placement

**Prognostic Scores**
- Child-Turcotte-Pugh
- MELD
- MELD-Na

Statistical model for Elective TIPS
- Predict patient survival
- Identify patients with post-TIPS liver-related mortality of 3 months or less.

Derived: 231 patients from 4 Medical Centers
- 58 (25%) Refractory Ascites

\[ R = 0.957 \times \text{log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{log}_e(\text{INR}) + 0.643 \times \text{cause of cirrhosis}. \]

MELD > 18 predicts increased mortality with TIPS.

**A Model to Predict Poor Survival in Patients Undergoing Transjugular Intrahepatic Portosystemic Shunts**

Michael Malinchoc,1 Patrick S. Kamath,1 Frederic D. Gordon,1 Craig J. Pines,2 Jeffrey Rank,4 and Peter C. J. ten Bokkel Huinink3

*HEPATOLOGY 2000;31:864-871*
MELD-Na

- More effective in predicting risk with low MELD scores.
- Reclassified 25% of subjects using cutoff of MELD 18.
  - 6mo mortality 38%
- For every 1mmol/L decrease in Na, 6% increased risk of death at 6mo post-TIPS

Studies Evaluating Post-TIPS Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>TIPS Placed for RA (%)</th>
<th>Mortality (%)</th>
<th>Multivariable Regression Analysis Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chalasani</td>
<td>73 (56%)</td>
<td>24 (19%)</td>
<td>Emergent Placement Serum Bilirubin &amp; ALT Pre-TIPS Encephalopathy</td>
</tr>
<tr>
<td>Malinchoc</td>
<td>58 (25%)</td>
<td>110 (48%)</td>
<td>Creatinine, Bilirubin, INR Etiology of Cirrhosis</td>
</tr>
<tr>
<td>Russo</td>
<td>36 (40%)</td>
<td>30 (33%)</td>
<td>Creatinine Emergent Placement</td>
</tr>
<tr>
<td>Angermayr</td>
<td>102 (21%)</td>
<td>230 (48%)</td>
<td>Creatinine, Bilirubin Age Refractory Ascites</td>
</tr>
<tr>
<td>Alessandria</td>
<td>48 (71%)</td>
<td>15 (22%)</td>
<td>Age</td>
</tr>
<tr>
<td>ter Borg</td>
<td>21 (26%)</td>
<td>45 (60%)</td>
<td>Age Albumin, Creatinine</td>
</tr>
<tr>
<td>Membreno</td>
<td>62 (38%)</td>
<td>93 (57%)</td>
<td>MELD, CTP Ethnicity Creatinine, Albumin</td>
</tr>
<tr>
<td>Thuluvath</td>
<td>65 (100%)</td>
<td>40 (61%)</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>D’Amico</td>
<td>162 (100%)</td>
<td>78 (48%)</td>
<td>Bilirubin</td>
</tr>
</tbody>
</table>
Prospective Trials of TIPS vs. LVP for Refractory Ascites

- 5 Prospective, Randomized Clinical Trials
  - Uncovered Stents
  - 330 patients
  - Only 1 showed higher mortality in the TIPS cohort
    - Highest rate of technical failures
    - Lowest reduction in HVPG
  - Recidivant Ascites included in 2 trials
    - Recurrent ascites ≥ 3x in 12 months

Randomized Clinical Trials of TIPS for Refractory Ascites

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>RA (%)</th>
<th>TIPS Success (%)</th>
<th>Δ HVPG (mmHg)</th>
<th>Variables Predictive of Post-TIPS Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebrec¹</td>
<td>25</td>
<td>100%</td>
<td>77%</td>
<td>20 → 13</td>
<td>Allocation to LVP, Age ≥ 60yrs</td>
</tr>
<tr>
<td>Rössle²</td>
<td>60</td>
<td>55%*</td>
<td>100%</td>
<td>24 → 10</td>
<td>Male Gender, <strong>Bilirubin ≥ 3mg/dL</strong>, Serum Sodium ≤ 125mmol/L</td>
</tr>
<tr>
<td>Ginès³</td>
<td>70</td>
<td>100%</td>
<td>97%</td>
<td>19.1 → 8.7</td>
<td>Increasing pre-TIPS CTP score, Increasing BUN levels</td>
</tr>
<tr>
<td>Sanyal⁴</td>
<td>109</td>
<td>100%</td>
<td>94%</td>
<td>19.8 → 8.3</td>
<td>No predictors of 6 month mortality</td>
</tr>
<tr>
<td>Salerno⁵</td>
<td>66</td>
<td>68%*</td>
<td>89%</td>
<td>22.5 → 8.7</td>
<td>Allocation to LVP, Baseline MELD</td>
</tr>
</tbody>
</table>

*Recidivant Ascites: 45% and 32%
Mortality with TIPS for Refractory Ascites

- D’Amico\(^1\) Meta-Regression Analysis
  - No difference in overall mortality
  - Mortality Predictors:
    - Bilirubin and Successful TIPS placement
    - Unable to assess best threshold for Bilirubin

- Salerno\(^2\) Meta-Analysis of Individual Pt Data
  - Included 4 of the 5 trials
  - TIPS increased Transplant-Free Survival
  - Age, Bilirubin, Sodium, TIPS

---

Transplant-Free Survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>TIPS</th>
<th>Paracentesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>24</td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>38</td>
<td>29</td>
</tr>
</tbody>
</table>

\(^1\)D’Amico G et al. (2005). Gastroenterology 129: 1282–1293
TIPS for Refractory Ascites: Summary

- TIPS is effective for Refractory Ascites
- Trend to improved overall mortality & transplant-free survival.
- Severity of liver disease can help estimate post-TIPS mortality
  - MELD > 18
  - MELD-Na may be a better predictor than MELD.
  - Bilirubin appears to be the strongest clinical predictor of poor outcome.
    - Threshold Bilirubin > 3g/dL.
- Effectiveness of Covered TIPS in RA needs further investigation.

Hepatic Hydrothorax

- Recurrent pleural effusion
  - Prevalence of 5 - 12%
  - Right-sided (85%)
- Passage of transudative fluid through diaphragmatic defects.
- Initial management identical to ascites
  - Sodium restriction and diuretics
- Chest tubes have high rate of morbidity and mortality
  - Renal Failure
  - Pneumothorax
  - Empyema
- TIPS experience for Refractory Hepatic Hydrothorax:
  - Case Series
# TIPS for Hepatic Hydrothorax

Published Case Series

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Time</th>
<th>n</th>
<th>Age</th>
<th>F/U Time (mo)</th>
<th>CTP</th>
<th>Bilirubin</th>
<th>Cr.</th>
<th>(\Delta) HVPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegerstetter⁸</td>
<td>2001</td>
<td>1994 - 1998</td>
<td>38</td>
<td>54</td>
<td>16.00</td>
<td>9</td>
<td>2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Spencer⁹</td>
<td>2002</td>
<td>1995 - 2000</td>
<td>21</td>
<td>56</td>
<td>7.20</td>
<td>10.2</td>
<td></td>
<td></td>
<td>19.9 → 7.4</td>
</tr>
<tr>
<td>Wilputte¹⁰</td>
<td>2007</td>
<td>1992 - 2001</td>
<td>28</td>
<td>53.6</td>
<td>11.90</td>
<td>9.7</td>
<td>3.4</td>
<td>1.27</td>
<td>17.4 → 7.1</td>
</tr>
<tr>
<td>Dhanasekaran¹¹</td>
<td>2010</td>
<td>1992 - 2008</td>
<td>73</td>
<td>55.6</td>
<td>25.30</td>
<td></td>
<td></td>
<td></td>
<td>18.9 → 5.7</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Statistics</strong></td>
<td></td>
<td></td>
<td>196</td>
<td>55.2</td>
<td>12.2</td>
<td>11.4</td>
<td>3.2</td>
<td>1.3</td>
<td>19.0 → 7.6</td>
</tr>
</tbody>
</table>

## Combined Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>TIPS Response (%) Complete</th>
<th>Partial</th>
<th>Failure</th>
<th>Enceph (%)</th>
<th>30-d Mortality</th>
<th>Overall Mortality</th>
<th>Predictors of Mortality</th>
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<tbody>
<tr>
<td>Gordon⁶</td>
<td>58.3</td>
<td>20.8</td>
<td>20.8</td>
<td>37.50</td>
<td>21.0</td>
<td>54</td>
<td>None</td>
</tr>
<tr>
<td>Jeffries⁷</td>
<td>42</td>
<td>16</td>
<td>42</td>
<td>33.00</td>
<td>25.0</td>
<td>58</td>
<td>None</td>
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<tr>
<td>Siegerstetter⁸</td>
<td>71</td>
<td>11</td>
<td>18</td>
<td>5.00</td>
<td>45.0</td>
<td>45</td>
<td>Age &gt; 60yrs</td>
</tr>
<tr>
<td>Spencer⁹</td>
<td>63</td>
<td>11</td>
<td>26</td>
<td>50.00</td>
<td>29.0</td>
<td>57</td>
<td>N/D</td>
</tr>
<tr>
<td>Wilputte¹⁰</td>
<td>57</td>
<td>11</td>
<td>32</td>
<td>14.3</td>
<td>61</td>
<td></td>
<td>CTP &gt; MELD</td>
</tr>
<tr>
<td>Dhanasekaran¹¹</td>
<td>58.9</td>
<td>20.5</td>
<td>20.5</td>
<td>15.10</td>
<td>19.0</td>
<td>85</td>
<td>MELD Clinical Response</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td><strong>58.3</strong></td>
<td>15.1</td>
<td>26.6</td>
<td>28.12</td>
<td>27.6</td>
<td>60</td>
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</tbody>
</table>

**Overall Response** 73.4%
Conclusion

- Ascites is a common complication of cirrhosis
- Treatment
  - Uncomplicated ascites:
    • Sodium restriction
    • Diuretics
  - Refractory Ascites
    • LVP + Albumin, PVS, or TIPS
- LVP is safe with low risk of bleeding complications
  - Transfusion of blood products not necessary
- TIPS may increase transplant-free survival if properly allocated.
- Patients with ascites (either uncomplicated or refractory) should be referred for liver transplant evaluation.

References