Inpatient Management of Patients with Liver Cirrhosis

Nizar N. Zein, M.D.
Endowed Chair in Liver Diseases
Medical Director of Liver Transplantation
The Cleveland Clinic
Inpatient Care in Patients with Cirrhosis (Data from 2004)

- Estimated annual number of hospital admissions in patients with cirrhosis is 1.2 million of which 150,000 directly due to complications of cirrhosis.

- The annual cost of inpatient care for cirrhosis complication (encephalopathy, ascites, GI bleeding, etc.) is nearly $4 billion.

- Complications of cirrhosis account for > 40,000 death annually (similar to DM and greater than annual death due to kidney failure).
Adding Fuel to the Fire

Increasing Incidence of Cirrhosis Complications

High Readmission Rate
HCV-Related Cirrhosis Is Projected to Peak by 2020

In 2010, 25% of patients were estimated to have cirrhosis.

37% of patients with HCV projected to develop cirrhosis by 2020, peaking at 1 million.

Complications Cirrhosis Expected to Rise Over the Next 10 Years

Cases

Year

Decompensated cirrhosis

HCC

30-Day Readmission Rate Among Patients
Advanced Cirrhosis: A Quality Measure

Berman K, et al. 2010

- 20%


- 37%
1-Year Readmission rate Among Patients Advanced Cirrhosis (encephalopathy)

Planas R, et al. 2004

76%
YET, ¼ OF READMISSIONS IN PATIENTS WITH ADVANCED CIRRHOSIS ARE POTENTIALLY PREVENTABLE WITH APPROPRIATE INPATIENT AND POST-DISCHARGE CARE
Complications

• Variceal hemorrhage
• Ascites
  — SBP
  — HRS
• Hepatic encephalopathy
• Liver Cancer

• Liver – Lung
  — HPS
  — PPHT
  — HHT
• Adrenal insufficiency
• Cytopenias
Ascites

• Recognized since ancient times

• Celsus (20 B.C.) is credited with the first description of paracentesis
Pathophysiology-The Under fill Theory

Splanchnic vasodilatation

Activation of renin-angiotensin system

Decrease in effective arterial volume

Retention of renal salt and water

Increased intravascular hydrostatic pressure

Decreased intravascular oncotic pressure
Ascites

• The most common of the 3 major complications of cirrhosis (50% at 10 years)

- Diuretic-Responsive: 20% 1-year mortality
- Diuretic-Resistant: 50% 1-year mortality
- SBP: 70% 1-year mortality
Management

- **Urine Na⁺**
  - > 30
  - 10-30
  - < 10

- **Na⁺ Intake**
  - Dietary Intake

- **Na⁺ Excretion**

- **Paracentesis**

- **TIPS**

- **Furosemide + Spironolactone**

- **Refractory Ascites**
Paracentesis should be performed:
Every patient with new-onset ascites
Every patient with ascites admitted to hospital
Therapeutic measure in refractory ascites (serial therapeutic paracentesis)
Spontaneous Bacterial Peritonitis

SBP

PMNs > 250
or
Positive Culture
TIPS
(Transjugular Intrahepatic Porto-Systemic Shunt)
Indications for TIPS

• Refractory ascites
• Control of variceal hemorrhage
Effects of TIPS on Sodium Homeostasis

Urinary Sodium Excretion

Plasma Renin Activity

Re-absorption of Sodium

Aldosteron

TIPS and Ascites

- Effective in ~75% within 3 months
- Most still need low-dose diuretics
- 10%-15% restenosis within 2 years with the newer covered stents
Refractory Ascites: TIPS vs. LVP

Table 6. TIPS Versus Large Volume Paracentesis in Treatment-Refactory Cirrhotic Ascites

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Ascites Improved</th>
<th>Survival</th>
<th>New or Severe Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIPS</td>
<td>LVP</td>
<td>TIPS</td>
</tr>
<tr>
<td>TIPS</td>
<td>LVP</td>
<td></td>
<td>TIPS</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>29</td>
<td>31</td>
<td></td>
<td>84%*</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td></td>
<td>51%*</td>
</tr>
<tr>
<td>52</td>
<td>57</td>
<td></td>
<td>58%*</td>
</tr>
<tr>
<td>33</td>
<td>33</td>
<td></td>
<td>79%*#</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to LVP
# p < 0.01 compared to LVP
Refractory Ascites: TIPS Have Survival Advantage

Gastroenterology. 2007;133(3):825-34.
Spontaneous Bacterial Peritonitis (SBP)

- **Streptococcal Pneumoniae**
- **Klebsiella Pneumoniae**
- **Escherichia Coli**

A bacterial translocation syndrome
Spontaneous Bacterial Peritonitis

• Have a Low threshold to look for SBP
  – Abdominal pain
  – Worsening ascites
  – Worsening encephalopathy
  – General malaise, nausea/vomiting
  – Rise in creatinine
  – Any hospitalization

Rarely that patients with SBP have the “classic” signs of infection (fever and chills)
Spontaneous Bacterial Peritonitis

Neutrocytic

PMNs > 250 or WBC > 500

Non-neutrocytic Bacterascites

PMNs < 250 but Positive culture
Treatment of SBP

• **Antibiotics:**
  - Cefotaxime (2 gm IV Q8 hours) or a similar 3rd generation cephalosporin.
  - Effective in 95% of cases of SBP
  - Duration of therapy 5 days (10 days NOT better than 5 days)

• **Albumin:**
  - 1.5 gm per KG body weight on day 1 and 1.0 gm per KG on day 3
  - Decreased mortality from 29% to 10%
Oral Antibiotics for SBP

• One randomized controlled trial:
  ✓ Ofloxacin 400mg BID for average of 8 days
  ✓ cefotaxime 2 gm IV Q 8 hours

• Exclusion: shock, vomiting, or advanced PSE, or creatinine > 3mg/dl

• All treated in hospital

Both treatments were equally as effective

Patients who survived one SBP should receive long-term antibiotic prophylaxis with daily Norfloxacin (or trimethoprim/sulfamethoxazole)

**Graph:**
- **Y-axis:** Probability of spontaneous bacterial peritonitis
- **X-axis:** Days
- **Legend:**
  - Norfloxacin (n=35)
  - Placebo (n=33)

**Table: Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Norfloxacin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (1)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>100</td>
<td>17 (2)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>200</td>
<td>14 (2)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>300</td>
<td>10 (2)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

*Fernandez et al Gastro 2007*
Summary Slide

• If a patient has ascites, it should be tapped.

• **Refractory ascites** should trigger an immediate referral for liver transplantation evaluation and a consideration for TIPS placement.

• Should have a low threshold to exclude SBP.

• Treatment of SBP includes both antibiotics and albumin.

• Anyone who survive an episode of SBP should be on long-term prophylactic dose antibiotics.
Hepatorenal Syndrome (HRS)

- Renal vasoconstriction
- Arterial hypotension
- Low systemic resistance
- Low GFR

- Cirrhosis
- Low Urinary Na+
- No Proteinuria
HRS

Type 1

- Rapidly progressive renal failure
- Doubling of serum creatinine to > 2.5 / less than 2 weeks
- Clinically acute renal failure

Type 2

- Stable renal failure
- Clinically Refractory Ascites

International Ascites Club, Hepatology 1996;23:164-76
Diagnosis is Clinical

• Cirrhosis

• Serum creatinine > 1.5 mg/dL

• No improvement of creatinine after 2 days of
  — Diuretic withdrawal
  — Volume expansion with albumin (1 gm/KG of body weight daily)

• Absence of shock/hypotension

• Normal renal US
Treatment of HRS

• Advances in treatment have been focused on type 1 HRS for its poor outcome

• Most effective pharmaceutical agents are vasoconstrictors:
  — Terlipressin (vasopressin analog)
  — Octreotide (somatostatin analog).
  — Midodrine (selective alpha-1 adrenergic agonist)
  — Norepinephrine (in intensive care unite)

• Recent meta-analysis suggested that vasoconstricor therapy have been shown to reduce mortality in HRS

Terlipressin + albumin (best choice when available)
Terlipressin + albumin

Alternative regimen

Midodrine (12.5 mg PO TID) + Octeotide (200 mcg SQ TID) + Albumin

Patients at risk:

23  22  19  17  14  12  12  11  10

23  21  18  18  17  16  16  15  15

Variceal Hemorrhage
Natural History of Varices

• Varices develop at a rate of ~8% per year
  — WHVP gradient > 10 mm Hg

• Small varices become large ~8% per year

• Bleeding most likely
  — Large
    — Child B or C cirrhosis
    — Red wale marks
Development of varices in cirrhosis

Groszman RJ et al NEJM 2005; 353: 2254-61

No. at Risk
HVPG ≥10 mm Hg  134  120  96  78  48  36  14
HVPG <10 mm Hg  79  74  67  58  41  32  24

Baseline HVPG <10 mm Hg
Baseline HVPG ≥10 mm Hg
Management of Acute Variceal bleeding

Mortality from a single bleeding episode

1980s: 30%-50%

Now: 10%-20%
Management of Acute Variceal bleeding

Step 1
- Volume resuscitation
- Vasoactive therapy
- Antibiotics

Step 2
- Admit to controlled environment (ICU)

Step 3
- Protect airway
- Endoscopy

Step 4
- Emergency TIPS
- Balloon tapenade
Vasoactive Therapy

- When compared to vasoactive medications (Octreotide, Vasopressin/NTG, Terlipressin), emergency endoscopic therapy had similar efficacy with a higher rate of complications. Accordingly, pharmacologic therapy is considered a first-line treatment.

- Octreotide: 50ug bolus then 50ug/hr x 5 days

Antibiotics Regimens With Established Benefit (decrease infections and improved survival) in Acute Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>400mg BID</td>
<td>PO or NG tube</td>
<td>7 days</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400mg BID</td>
<td>IV then PO</td>
<td>10 days</td>
</tr>
<tr>
<td>Ciprofloxacin+ Amoxiclav</td>
<td>200mg BID 1gm/200mg BID</td>
<td>IV then PO (1 day after bleeding stopped)</td>
<td>3 days after bleeding stopped</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500mg BID</td>
<td>PO</td>
<td>7 days</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400mg BID</td>
<td>PO</td>
<td>7 days</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200mg BID</td>
<td>IV then PO (at the 3rd day)</td>
<td>7 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1gm OD</td>
<td>IV</td>
<td>7 days</td>
</tr>
</tbody>
</table>
Emergency TIPS: A Rescue Therapy in Acute Variceal Bleeding
## Emergency TIPS for Acute Variceal Bleeding

<table>
<thead>
<tr>
<th>Author</th>
<th>N pts</th>
<th>% Pugh’s C</th>
<th>Immediate control (%)</th>
<th>Previous endoscopic therapy</th>
<th>% rebleeding</th>
<th>Interval of rebleeding (days)</th>
<th>Site of rebleeding</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LaBerge et al. [3]</td>
<td>32</td>
<td>NG</td>
<td>97</td>
<td>Sclerotherapy</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Haag et al. [4]</td>
<td>19</td>
<td>68</td>
<td>100</td>
<td>Sclerotherapy</td>
<td>11</td>
<td>10</td>
<td>SU</td>
<td>26 (30 days)</td>
</tr>
<tr>
<td>Helton et al. [5]</td>
<td>23</td>
<td>78</td>
<td>NG</td>
<td>Sclerotherapy</td>
<td>NG</td>
<td>11</td>
<td>NG</td>
<td>56 (in hospital)</td>
</tr>
<tr>
<td>Le Moine et al. [6]</td>
<td>4</td>
<td>84</td>
<td>91</td>
<td>Sclerotherapy</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>75 (30 days)</td>
</tr>
<tr>
<td>Rubin et al. [7]</td>
<td>3</td>
<td>84</td>
<td>90</td>
<td>SGVT</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Jalan et al. [8]</td>
<td>30</td>
<td>41</td>
<td>95</td>
<td>Sclerotherapy</td>
<td>14</td>
<td>30</td>
<td>V</td>
<td>13 (50 days)</td>
</tr>
<tr>
<td>Jabbour et al. [9]</td>
<td>11</td>
<td>64</td>
<td>91</td>
<td>Sclerotherapy</td>
<td>27</td>
<td>14</td>
<td>NG</td>
<td>27 (30 days)</td>
</tr>
<tr>
<td>Sanyal et al. [10]</td>
<td>48</td>
<td>56</td>
<td>85</td>
<td>Sclerotherapy</td>
<td>8.5</td>
<td>NG</td>
<td>NG</td>
<td>26 (30 days)</td>
</tr>
<tr>
<td>Peramai [11]</td>
<td>56</td>
<td>41</td>
<td>95</td>
<td>Sclerotherapy</td>
<td>15.6</td>
<td>30</td>
<td>NG</td>
<td>75 (30 days)</td>
</tr>
<tr>
<td>Banares et al. [12]</td>
<td>11</td>
<td>64</td>
<td>91</td>
<td>Sclerotherapy</td>
<td>14</td>
<td>30</td>
<td>NG</td>
<td>75 (30 days)</td>
</tr>
<tr>
<td>Gerbes et al. [13]</td>
<td>8</td>
<td>81</td>
<td>90</td>
<td>Sclerotherapy</td>
<td>27</td>
<td>14</td>
<td>NG</td>
<td>75 (30 days)</td>
</tr>
<tr>
<td>Chau et al. [2]</td>
<td>112</td>
<td>71</td>
<td>96</td>
<td>Sclerotherapy</td>
<td>13 EV</td>
<td>7</td>
<td>EV-GV-SU</td>
<td>37 (30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 GV</td>
<td></td>
<td>EV-GV-SU</td>
<td></td>
</tr>
<tr>
<td>Barange et al. [14]</td>
<td>32</td>
<td>47</td>
<td>90</td>
<td>Sclerotherapy</td>
<td>14</td>
<td>14</td>
<td>NG</td>
<td>25 (30 days)</td>
</tr>
<tr>
<td>Bizollon et al. [15]</td>
<td>28</td>
<td>61</td>
<td>96</td>
<td>Sclerotherapy, Band ligation</td>
<td>8</td>
<td>14</td>
<td>V-SU</td>
<td>25 (40 days)</td>
</tr>
<tr>
<td>Azoulay et al. [1]</td>
<td>58</td>
<td>81</td>
<td>90</td>
<td>Sclerotherapy</td>
<td>6</td>
<td>14</td>
<td>V-GU</td>
<td>29 (30 days)</td>
</tr>
</tbody>
</table>

- **75-100% Control of Bleeding**
- **15-40% 30 Day Mortality**

However, Early Use of TIPS in Patients With Variceal Hemorrhage may be Beneficial
Risk of bleeding and survival in patients who had early (not emergency) TIPS after acute variceal haemorrhage compared to standard therapy (Drugs + Endoscopic Therpy)

**Diagram A**
- Freedom from Uncontrolled Bleeding or Rebleeding (%)
- Months
- No. at Risk
  - Early TIPS: 32, 24, 15, 11, 5
  - Drugs+EBL: 17, 13, 7, 7, 3

**Diagram B**
- Survival (%)
- Months
- No. at Risk
  - Early TIPS: 32, 24, 17, 12, 7
  - Drugs+EBL: 31, 18, 13, 10, 5

P = 0.001
Management of variceal hemorrhage requires vasoactive medications (octreotide or terlipressin) and antibiotics followed by endoscopic therapy.

Risk Reduction for re-bleed is feasible (to do before discharge):
- Beta blocker (+)
- Endoscopic band ligation (++)
- Early TIPS (emerging concept)
Hepatic encephalopathy (HE)
A Diagnostic Workup is Required in Cirrhotic Patients with Mental Status Changes

- ETOH
- Drugs
- Electrolyte Imbalance
- Psychiatric Disorders
- Intracranial Bleeding
- Infections
- Dementia
Diagnostic Value of Serum Ammonia?

• High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients with cirrhosis.

• However, a normal value of ammonia calls for diagnostic reevaluation.
Treatment

• Nonabsorbable Disaccharides-Lactulose:
  — Acts like a probiotic by enhancing growth of certain bacterial strains
  — Low cost making it the preferred agent

• Rifaximin
  — Nonabsorbable antibiotic
  — Equivalent or slightly superior to Lactulose or Neomycin

Often, these agents are combined
Other Therapies with Limited Data

• Branched Chain Amino Acides (BCAAs)
• Metronidazole
• Neomycin
• Probiotics
• Flumazenil
• Zinc

Liver transplantation is curative
Overall Conclusions

• Appropriate inpatient care for patients with liver cirrhosis will likely:
  — Decrease mortality
  — Lower the rate of readmissions
  — Lower cost of care