Minimizing Complications in Cirrhosis

Luis S. Marsano, MD, FACG, FAASLD
Professor of Medicine
Director of Clinical Hepatology
University of Louisville & Louisville VAMC
2016
Nutrition in Cirrhosis
What we Know

• Most cirrhotics have malnutrition.
  – even cirrhotics with overweight and NASH often have protein malnutrition.

• Cirrhotics are hypermetabolic, and go to a catabolic state after a few hours of fasting.
  – Catabolic state causes gluconeogenesis and muscular wasting.
  – Frequent meals and bedtime supplement prevent catabolic state.

• After a meal, attention and executive function improves temporarily in cirrhotics, decreasing “covert” Hepatic Encephalopathy (HE) (Vaisman N; Am J Clin Nutr 2010;92:137–40).
Nutrition in Cirrhosis

Day-time vs Night-time Nutrition Supplementation
Plank LD; Hepatology 2008; 48(2):557-66

Effect of Bedtime Snack and Meal Frequency in Nitrogen Balance
McCullough AJ AASLD Postgraduate Course 2013; 142-150

500-710 kcal
26-30 g protein

Bed-time Nutrition Increases Nitrogen Retention & Muscular Mass
(equivalent to 2 kg of muscle, after 12 months)

Bedtime Supplement is more important than Frequent meals

Nitrogen Balance (g/day)

4 Meals
6 Meals
No Bedtime Snack
Bedtime Snack
In Severe AH, Intense Nutrition is as good as Steroids at 4-weeks but is superior at 1-year

In Severe AH, the mortality is lower in patients with high calorie intake
Improving Nutrition in Cirrhosis

Recommendation

  - Consider Metabolic cart study to assess resting energy expenditure.
  - If patient is obese with BMI 30-40, give 25-35 kcal/kg IBW/d; if BMI > 40, give 20-25 kcal/kg IBW/d; Decrease carbohydrates and fat but increase fiber to 25-45g/d.
  - Should include a bedtime supplement with 50 g of complex carbohydrates (plus protein).

- **Protein:** 1.2-1.5 g/kg/day (ideal body weight) of whole protein;
  - If Encephalopathy develops while on whole protein, give BCAA-enriched formulas to satisfy nitrogen needs.

- **Fiber:** 25-45 g a day

- **Sodium:** if patient has edema or ascites, restrict sodium to 2 g/d

- **Fluids:** Restrict only if Na < 125 mEq/L

- **Frequency:** 3 meals + 3 small snack + bed-time supplement with 26-30 g protein and at least 50 g of complex carbohydrates, giving 500-710 kcal nightly.
  - Two of the snacks could be “probiotic yogurt”, to improve covert HE.
  - Naso-enteric feeding tube if not eating enough. PEG contraindicated in cirrhotic ascites.

- **Precautions:**
  - All animal products should be well cooked: risk of vibrio or listeria infections.
  - All fruits and vegetables should be washed.
Hepatic Encephalopathy
What we know

- Many episodes of overt HE have a trigger.
- Frequent meals (Vaisman N; Am J Clin Nutr 2010;92:137–140) and improved nutrition are useful in controlling hepatic encephalopathy.
- Normal protein intake does not delay recovery from overt HE (Cordoba J; J Hepatol 2004;41:38–43).
- Zinc deficiency worsens hepatic encephalopathy;
  - Zn supplements can improve it (Marchesini G; Hepatology 1996;23(5):1084-1092).
- Probiotic yogurt helps in covert HE (Bajaj JS; Am J Gastroenterol 2008;103:1707-1715).
- Lactulose is still considered the initial step in therapy;
  - titrate to 3 or 4 BM/d.
- Other drugs that can help to control episodic overt HE.
  - Rifaximin, added to Lactulose, decreases recurrence and re-hospitalizations.
  - Zinc 50 mg/d; L-Carnitine 990-1320 mg TID; neomycin; metronidazole; sodium phenylbutyrate; sodium benzoate; ornithine aspartate; acarbose; sorbitol; L-ornithine and L-aspartate (LOLA).
Nutrition in Hepatic Encephalopathy

Low- vs Normal-Protein Diet in HE
Cordoba J; J Hepatol 2004;41:38–43

Probiotic Yogurt in Covert Hepatic Encephalopathy
Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

Diet with “normal protein intake” improves HE equally as “low protein” diet

Probiotic Yogurt Improves Covert HE & Protects against Overt HE

12 ounces of Probiotic Yogurt a day
Hepatic Encephalopathy

Rifaximin + Lactulose in Hepatic Encephalopathy
Bass NM; N Engl J Med 2010; 362:1071-1081

HE Long Term Management

- Evaluate for Liver Transplant, if potential candidate.
- Look for, and treat triggering factors.
- Initially treat with Lactulose +/- Rifaximin.
- Give diet with normal protein content;
  - divide the protein through the day;
  - 3 meals + 3 snacks + bedtime supplement is ideal.
  - Consider 2 servings of probiotic yogurt a day, as part of the 3 snacks, to treat “covert” Hepatic Encephalopathy.
- In chronic stable HE, BCAA-enriched formulas can be helpful.
- Once patient has the 1st episode of HE:
  - Keep him/her on Lactulose + Rifaximin, long term.
  - Currently, up to 64% of patients are not receiving therapy after discharge.

Rifaximin 550 mg BID decreases:
recurrence of overt HE by 58%, and
HE related hospitalizations by 50%
Ascites Management

- Cirrhotic ascites develops only in the presence of Na intake.
  - You need 3 g of Na to form 1 liter of ascites.
  - Maximal absorption of ascites is 930 mL per day (Shear L et al. N Engl J Med 1970;282:1391-1396); Maximal Wt loss = 2 lb a day.
- Diet: 2 g Na restriction is critical for success.
- Improve nutritional status (frequent meals + hs supplement)
- Drugs to avoid due to increased risk of renal impairment:
  - NSAIDs: can cause AKI and increase Na retention.
  - ACE-inhibitors,
  - Angiotensin II antagonists,
  - Alfa 1-adrenergic receptor blockers,
  - Aminoglycosides
- Spironolactone is the most effective diuretic, and dose can be titrated by “spot urine Na to K ratio”
Ascites Management

Diuretic Titration

- Usually give spironolactone 100 mg + furosemide 40 mg in a single morning dose.
- Adjust dose daily by:
  - Weight loss,
  - Random spot-urine Na/K ratio.
    - Random Na/K > 1, has a PPV of 84-87% and NPV of 90-94% for negative Na balance and if Na/K ≥ 3.5 has a PPV of 100% (HEPATOLOGY 2002;36:222A); (Liver Int. 2012;32(1):172-3), and
  - Elevation of serum creatinine.
- Goal:
  - Weight loss of: 1 lb/day if without edema; 2 lb/day if with edema
  - Spot urine Na/K ratio > 1
  - Creatinine elevation: ideally none, < 0.3 mg/dL.

Spironolactone vs furosemide in Cirrhotic Ascites
Perez-Ayuso RM; Gastroenterology 1983;84:961-968

Diuretic Response (%)

- Spironolactone 150-300: 95%
- Furosemide 80-160: 52%

Spironolactone is superior to Furosemide in controlling ascites
Assessment of Ascites Diuretic Response by spot urine Na/K ratio

Hepatology 2002; 36(4):222A

- Cirrhosis + Ascites
- 2 g Na diet
- Single a.m. dose of Spironolactone + Furosemide.
- 24 h urine Na/K
- Spot urine Na/K @
  - 0-3 h
  - 3-6h
  - 6-9h
  - 24h

- RESULTS:
  - Both, “24 h urine with Na/K > 1”, and “random spot-urine with Na/K > 1” predicted diuretic response.
  - If random spot-urine Na/K < 1 while in spironolactone 400 + furosemide 160, the patient has “Refractory Ascites”
Refractory Ascites

• **Definition:** in a patient who is in a 2 g (88 mEq) Na diet a day,
  – ascites that does not respond with a weight loss of > 0.8 kg over 4 days, after at least 7 d of maximal diuretics (Spironolactone 400 mg/d + Furosemide 160 mg/d), or
  – diuretic therapy that causes:
    • azotemia (doubling of creatinine to >/= 2 mg/dL),
    • overt HE in the absence of other cause,
    • drop of serum Na > 10 mEq/L to serum Na < 125 mEq/L, or
    • hyper-kalemia (> 6 mEq/L) or hypo-kalemia (< 3 mEq/L) despite proper measures.

• **Significance:** Median survival of 6 months.
Refractory Ascites
What We Know

• Refractory ascites (RA) and hyponatremia are predictive of development of Hepatorenal Syndrome (HRS) and of short survival.
• In Refractory Ascites, Beta-blockers decrease patient’s survival.
• In Cirrhosis with renal dysfunction or refractory ascites, long term:
  – **Pentoxifylline** improves diuresis and natriuresis; increases, MAP, SVR and serum sodium; and decreases risk of HRS.
  – **Midodrine** increases mean arterial pressure (MAP), Systemic Vascular Resistance (SVR), response to diuretics with higher natriuresis and urine output, and decreases mortality.
  – **Norfloxacin** improves hemodynamics by increasing MAP and SVR, and decreases risk for spontaneous bacterial peritonitis (SBP), HRS and death.
Ascites & Refractory Ascites

Effect of Beta-blockers in Refractory Ascites
Serste T; Hepatology 2010;52(3):1017-1022

In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS

Pentoxifylline in ascites with CrCl 41-80
Tyagi P; Eur J Gastroenterol Hepatol 2011;23(3):210-7

Beta-blockers decrease survival in patients with refractory ascites
In Refractory ascites, Midodrine 7.5 mg TID increases Natriuresis and improves Survival
Ascites & Refractory Ascites

Norfloxacin SBP prophylaxis in ascites with either bili > 3, or creat > 1.2, or Na < 130

Fernandez J; Gastroenterology 2007;133(3):818-24

In ascites with Child >/= 9 or renal dysfunction, Norfloxacin decreases risk of SBP, HRS, and improves survival.
TIPS in Refractory Ascites

Cumulative Probability of Survival without Transplant in Refractory Ascites; Meta-Analysis TIPS vs LVP
Salerno F et al. Gastroenterology 2007;133:825-834

TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: An updated meta-analysis
Ming B et al. World J Gastroenterol. 2014 March 14; 20(10): 2704–2714

Survival was higher with TIPS than with LVP up to a MELD of 20
Bili $\geq 3$, Age $> 60$ and Na $\leq 130$ increases the risk of complications

TIPS improves Transplant-free Survival in Refractory Ascites
Spontaneous Bacterial Peritonitis (SBP)

What we know

• 10-27% of hospitalized patients with cirrhotic ascites have or develop SBP.
  – SBP symptoms may be minimal or absent.
• Hospitalized cirrhotic patients with low protein ascites (< 1.5 g/dL) are at high risk of SBP;
  – Norfloxacin 400 mg/d decreases their risk of SBP.
• Patients with SBP are at high risk of developing HRS.
  – Treatment of SBP with Cefotaxime PLUS IV Albumin, decreases mortality and risk of HRS;
  – the albumin benefit is mostly in patients with creat > 1 mg/dL, BUN > 30 mg/dL, or Bili > 4 mg/dL (Sigal SH; Gut 2007;56:597-599).
• After first episode of SBP, long-term Norfloxacin decreases SBP recurrences.
• In cirrhosis with GI bleed, Ceftriaxone decreases the risk of infections, and SBP.
Spontaneous Bacterial Peritonitis (SBP)

Norfloxacin in Hospitalized patients with low protein (< 1.5g/dL) ascites
Soriano G; Gastroenterology 1991;100:477–481

![Graph showing infections](image)

- Norfloxacin 400/d
- Placebo

3.1% All Infections
41.9% SBP
22.5% Placebo
0% Norfloxacin

Effect of albumin in azotemia and mortality in SBP
Sort P; N Engl J Med 1999; 341:403-409

![Graph showing albumin effect](image)

- Cefotaxime 2 g q 8h IV
- Albumin 1.5 g/kg within 6 h and 1 g/kg 48 h later

Volume expansion with IV albumin decreases risk of HRS & Mortality, in SBP treated with Cefotaxime

Daily, in-hospital, Norfloxacin decreases risk of all infections, and of SBP in patients with ascites-protein < 1.5 g/dL
Complications of Cirrhosis

Long Term Norfloxacin prevents SBP recurrence
Gines P; Hepatology 1990;12:716-724

Ceftriaxone 1 g/d is superior to Norfloxacin 400 BID x 7d in preventing infections in cirrhosis with GI bleed
Fernandez J; Gastroenterology 2006;131:1049–1056

In cirrhosis with GI bleed, Ceftriaxone:
- decreases hospital infections & SBP,
- has no effect in hospital mortality.

Long term Norfloxacin decreases rate of SBP Recurrence but not the mortality
SBP
Prophylaxis and Management

- Evaluate for Liver Transplant, if potential candidate.
- CRP > 24.7 ng/mL and Procalcitonin > 0.49, predict sepsis with ROC curve of 0.81 and 0.89 respectively.
- If patient has SBP, treat with:
  - Cefotaxime 2 g q 8h or ceftriaxone 2 g/d for 5 days;
  - Nosocomial SBP is often due to MDR gram (+) and (-) bacteria; use albumin + piperacillin/tazobactam, or meropenem + daptomycin (Hepatology 2016; 63:1299-1309)
  - if creat > 1, BUN > 30, or T Bili > 4, add IV albumin, 1.5 g/kg at time of diagnosis, and 1 g/kg on day 3.
- Once a patient has had SBP, continuous outpatient prophylaxis with Norfloxacin 400 mg/d is indicated.
- Outpatients with ascites and severe decompensation (Child-Pugh >/= 9), should receive Norfloxacin 400 mg/d to decrease the risk of SBP, HRS, and mortality, if they have:
  - renal dysfunction (creat >/= 1.2 mg/dL),
  - hypo-Natremia (Na </= 130), or
  - T Bili >/= 3 mg/dL.
Hepatic Hydrothorax and Spontaneous Bacterial Empyema (SBE) / Spontaneous Bacterial Pleuritis

- Hepatic hydrothorax occurs in 10% of patients with ascites;
  - is more frequent in the right side.
- The diagnosis is established by Nuclear Medicine scan, with injection of Tc-99m labeled albumin or Tc-99m pertechnetate into the abdomen, after partial thoracentesis to facilitate migration of the tracer from the abdomen into the chest, demonstrating the abdomen-chest communication.
Spontaneous Bacterial Pleuritis

SB Empyema – What we know

• Spontaneous Bacterial Empyema occurs in 16% of hepatic hydrothorax.
• SBE is diagnosed in a patient without lung infection, by either:
  – PMN count > 250/mm³ plus a (+) culture, or
  – PMN count > 500/mm³, with a negative culture.
• SBP co-exist in 50% of SBE (Xiol X; Hepatology 1996;23:719–723).
• The treatment of SBE is Cefotaxime 2 g q 8h plus IV albumin like in SBP.
• **Chest tube is contraindicated in SB Empyema, unless the patient has obvious pus in the pleural space** (Tu CY; Curr Opin Pulm Med 2012, 18:355–358)

Mortality in Spontaneous Bacterial Empyema
Chen CH; Liver Int. 2011 Mar;31(3):417-24

- Pig-tail chest tube
- No chest tube
- Overall

% Mortality

Mortality SBE

Chen CH; Liver Int. 2011 Mar;31(3):417-24
Recommended empirical antibiotic treatment for community-acquired and nosocomial bacterial infections in cirrhosis
J Hepatol 2014; 60: 1310-24

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Community Acquired</th>
<th>Nosocomial</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, SBP, or Spontaneous Bacteremia</td>
<td>Cefotaxime&lt;br&gt;or ceftriaxone&lt;br&gt;or amoxicillin/clavulanic acid</td>
<td>Piperacillin/tazobactam&lt;br&gt;or meropenem ± vancomycin&lt;br&gt;or meropenem + daptomycin</td>
</tr>
<tr>
<td>Urinary Infection</td>
<td><strong>Uncomplicated:</strong>&lt;br&gt;or co-trimoxazole&lt;br&gt;or ciprofloxacin&lt;br&gt;&lt;strong&gt;If sepsis:**&lt;br&gt;cefotaxime&lt;br&gt;or ceftriaxone&lt;br&gt;or amoxicillin/clavulanic acid</td>
<td><strong>Uncomplicated:</strong>&lt;br&gt;nitrofurantoin&lt;br&gt;or fosfomycin&lt;br&gt;&lt;strong&gt;If sepsis:**&lt;br&gt;piperacillin/tazobactam&lt;br&gt;or meropenem ± vancomycin</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Amoxicillin/clavulanic acid&lt;br&gt;or ceftriaxone + macrolide&lt;br&gt;or levofloxacin, or moxifloxacin</td>
<td>Piperacillin/tazobactam&lt;br&gt;or meropenem/ceftazidime + ciprofloxacin +/- vancomycin&lt;br&gt;vancomycin should be added in patients with risk factors for MRSA</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Amoxicillin/clavulanic acid&lt;br&gt;or ceftriaxone + oxacillin</td>
<td>Meropenem/ceftazidime + oxacillin&lt;br&gt;or vancomycin</td>
</tr>
</tbody>
</table>

Vancomycin should be added in patients with risk factors for MRSA.
AKI in Cirrhosis

### Staging System for AKI According to AKIN

<table>
<thead>
<tr>
<th>AKI Stage</th>
<th>Serum Creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- Increase in serum creatinine (\geq 0.3) mg/dL, or - Increase to (\geq 150%) to 200% from baseline</td>
<td>- Urine output 0.5 mL/kg/h for &gt; 6 h (-No HRS)</td>
</tr>
<tr>
<td>2</td>
<td>- Increase of serum creatinine to more than 200% to 300% from baseline</td>
<td>- Urine output &lt; 0.5 mL/kg/h for &gt; 12 h (-Many have HRS-2)</td>
</tr>
</tbody>
</table>
| 3         | - Increase of serum creatinine to > 300\% from baseline, or - Serum creatinine \(\geq 4.0\) mg/dL  
**After:** - An increase of at least 0.5 mg/dL, or - Treatment with renal replacement therapy | - Urine output < 0.3 mL/kg/h for 24 h, or - Anuria for 12 h (-Many have HRS-1) |

**HRS is one type of AKI in Cirrhosis**

### Spectrum of Hepatorenal Disorder in Cirrhosis

Urinary neutrophil gelatinase-associated lipocalin Nl: 20; Pre-rerenal: 20; CKD: 50; HRS: 105; ATN 325 ng/mL

**Critical Care 2012, 16:R23**
Box 1. Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury*, defined as:
  - absence of proteinuria (>500 mg/day)
  - absence of microhaematuria (>50 RBCs per high power field),
  - normal findings on renal ultrasonography

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.

ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
<table>
<thead>
<tr>
<th>Definitions of Response to Treatment AKI in Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No response</strong></td>
</tr>
<tr>
<td>No regression of AKI</td>
</tr>
</tbody>
</table>
Algorithm for Treatment of AKI in Cirrhosis

Journal of Hepatology Volume 62, Issue 4, April 2015, Pages 968–974

Use of Vasopressors when creatinine is < 1.5 mg/dL is not well defined
Prognosis of AKI in Cirrhosis

Survival in AKI in Cirrhosis, by Type
Fagundes C et al. J Hepatol. 2013 May 10

Association of AKI with in-hospital mortality in Hospitalized Cirrhotics
Belcher JM et al. Hepatology 2013; 57:753-762

<table>
<thead>
<tr>
<th>Initial Stage</th>
<th>Evolution (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI-1 (no HRS)</td>
<td>No Progression (53%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Progression to AKI-2 (19%)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Progression to AKI-3 (11%)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Progression needing Dialysis (17%)</td>
<td>56</td>
</tr>
<tr>
<td>AKI-2 (many HRS-2; few HRS-1)</td>
<td>No Progression (54%)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Progression to AKI-3 (19%)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Progression Needing Dialysis (27%)</td>
<td>60</td>
</tr>
<tr>
<td>AKI-3 (many HRS-1)</td>
<td>No Progression (67%)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Progression needing Dialysis (33%)</td>
<td>71</td>
</tr>
</tbody>
</table>

Cirrhotic with HRS has worse prognosis than those with other causes of AKI

Progression of AKI worsens Mortality; Early Intervention is Critical
Hepatorenal Syndrome

What we know

• Main risk-factors for HRS are:
  – diuretic resistant or intolerant ascites,
  – hyponatremia,
  – SBP or other infection infection,
  – alcoholic hepatitis, and
  – acute on chronic liver injury.

• In patients with severe alcoholic hepatitis:
  – Treatment with Pentoxifylline decreases the risk of HRS and mortality.
  – Adding NAC to Prednisolone decreases the risk of HRS, and 1 month mortality, but the not the 6 months mortality (negative study).
  – Pentoxifylline therapy is not inferior to Prednisolone therapy.

• In patients with SBP, adding IV albumin to Cefotaxime treatment decreases the risk of HRS and mortality.

• In patients with ascites:
  – if creat clearance is 41-80 mm Hg but creatinine < 1.5 mg/dL, long term Pentoxifylline 400 mg TID decreases the risk of hyponatremia and HRS,
  – if Child-Pugh >/= 9 with Creatinine > 1.2 mg/dL, or Na < 130 mmol/L, or T Bili > 3 mg/dL, long term Norfloxacin 400 mg/d decreases the risk of HRS, SBP, and mortality.
Prevention of HRS & Mortality

**Pentoxifylline in Severe Alcoholic Hepatitis**
Akriviadis E; Gastroenterology 2000 Dec;119(6):1637-48

**Prednisolone + NAC in Severe Alcoholic Hepatitis**

In Severe AH, PTX decreases risk of HRS, and 1 & 5 month mortality

In Severe AH, adding NAC to Prednisolone, decreased risk of HRS, 1 month mortality, and 6 month HRS-related mortality.
Prevention of HRS & Mortality

**Prednisolone vs PTX in Severe AH**
*De BK et al, World J Gastroenterol 2009 April 7; 15(13): 1613-1619*

- 34p = PTX 400 TID x 4-12 wks (I)
- 34p = Pred 40/d x 4 wks + taper (II)

**MELD**

- PTX (I)
- Prednisolone (II)

**SURVIVAL**

PTX is at least as effective as Prednisolone in Severe Alcoholic Hepatitis, and decreases frequency of Hepatorenal Syndrome.
Hepatorenal Syndrome

What we know

• HRS type I and II can be treated with volume expansion plus vasopressors;
  – high dose IV NAC also has been reported to be effective.
• Successful treatments have been published with:
  – Ornipressin + Albumin (Guevara M; HEPATOLOGY 1998;27:35-41).
  – Midodrine + Octreotide + Albumin (Angeli P; HEPATOLOGY 1999;29:1690-1697) and
    (Esrailian E; Dig Dis Sci 2007;52:742-748).
  – Terlipressin + Albumin (Martín-Llahí M; GASTROENTEROLOGY 2008;134:1352–1359) (Sanyal
• Noradrenaline has been found to be as effective as Terlipressin in
  reversing HRS Type-1 (Singh V; J of Hepatology 2012;56;1293–1298).
  – Phenylephrine + Albumin are also effective in reversing HRS Type-1 (personal
    observation)
• In most studies, the response is more likely if a MAP of 85-90 mm Hg is
Treatment of Hepatorenal Syndrome

Octreotide + Midodrine + Albumin in HRS-I
Angeli P; HEPATOLOGY 1999;29:1690-1697

Midodrine 7.5-15 mg po TID + Octreotide 100-200 mcg SQ TID
5 patients with HRS-1
Responders reached MAP = 95

Octreotide + Midodrine + Albumin in HRS-I
Esrailian E; Dig Dis Sci 2007;52:742-748

Midodrine + Octreotide + Albumin takes up to 3 weeks to work

Octreotide + Midodrine decrease 1 & 3-month mortality in HRS-1

Mortality
Treatment of Hepatorenal Syndrome

Noradrenaline + Albumin in HRS-I
Duvoux C; Hepatology 2002;36:374-380
Noradrenaline 0.5-3 mg/h + Albumin
12 patients with HRS-1

Terlipressin + Albumin vs Albumin in HRS
Sanyal AJ; Gastroenterology 2008;134(5):1360-8
Terlipressin 1 mg q 4-6 h IV + Albumin
56 patients with HRS-1
Responders reached MAP = 84

Noradrenaline + Albumin takes up to 10 days to work
Terlipressin + Albumin takes up to 2 weeks to work
Treatment of Hepatorenal Syndrome

Terlipressin + Albumin vs Albumin in HRS
Sanyal AJ; Gastroenterology 2008;134(5):1360-8

Terlipressin vs Noradrenaline in HRS-I
Singh V; J of Hepatology 2012;56;1293–1298

HRS-II responds better than HRS-I

Noradrenaline + Albumin is equally effective as Terlipressin + Albumin
Hepatorenal Syndrome
What we know

- To obtain desired response with drug therapy often takes up to 7-20 days.
- Response rate for HRS Type-1 with Midodrine + Octretide + Albumin is 40% (Esrailian E; Dig Dis Sci 2007;52:742-748).
- Response rate of HRS with Terlipressin or Noradrenaline is:
  - for HRS Type-1 is 35-40%, and
  - for HRS-2 is 65-70%.
- Once response is achieved, 70% maintain response for >/= 3 months (Esrailian E; Dig Dis Sci 2007;52:742-748).
  - Patients not responding to pharmacologic therapy should be tested for adrenal and thyroid dysfunction (personal observation); treatment of endocrinopathy frequently reverses the lack of response.
  - TIPS can reverse HRS types I and II but study of too few patients prevent a strong recommendation (Brensing KA; Gut. 2000;47:288-95; Testino G; Hepatogastroenterology 2003;50:1753-5).
  - Improvement after TIPS is slow, and takes up to 6 months, but improves serum creatinine, natriuresis, and lean body-mass (Rossle M; Gut 2010;59:988-1000).
Acute GI Bleed in Cirrhosis
What we know

• Antibiotic Prophylaxis during GI bleed in cirrhotic patients decreases the rate of infections, re-bleeding rate, transfusion needs and improves survival.
  – Odds of being free of infection increase by 32%,
  – Odds of being free of bacteremia or SBP increase by 19%, and
  – Mean survival rate increase by 9% (Bernard B; HEPATOLOGY 1999;29:1655-1661).

• Ceftriaxone is superior to Norfloxacin in preventing the complication of GI bleeding in cirrhotics (Fernandez J; GASTROENTEROLOGY 2006;131:1049–1056).

• Octreotide or Somatostanin IV for 5 days decrease rebleeding rate after variceal bleed (Corley DA; GASTROENTEROLOGY 2001;120:946-954).
Acute GI Bleed in Cirrhosis
What we know

• Restrictive blood transfusion (only when Hb < 7, with target of 7-9) is better than liberal blood transfusion (when Hb < 9, with target of 9-11). (Villanueva C; N Engl J Med 2013; 368:11-21).
  – Decreases re-bleeding rate in all patients, and
  – Decreases mortality in Child A & B.
  – Liberal transfusion increases portal pressure .

• In esophageal variceal bleed, the use of early TIPS (within 24-72 hours) using a PTFE covered stent decreases rebleeding rate (NNT: 2.1) and mortality at 6 months (NNT: 3.3) and 1-year (NNT: 4), when compared to EBL + Beta-blockers, (Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379) in:
  – Child-Pugh B (score 7-9) with active bleeding, and
  – Child-Pugh C (score 10-13) with or without active bleeding.
Acute GI Bleed in Cirrhosis

Restrictive vs Liberal Transfusion in GI Bleed
Villanueva C; N Engl J Med 2013; 368:11-21

Early TIPS in Variceal Bleed:
Actively bleeding Child B, or any Child C

Restrictive Transfusion in cirrhosis with GI bleed has lower re-bleeding and mortality rates

Early TIPS improved survival in variceal bleed with actively bleeding Child B, and all Child C
Acute GI Bleed in Cirrhosis

Restrictive vs Liberal Transfusion in GI Bleed
Villanueva C; N Engl J Med 2013; 368:11-21

- Child A&B
- Child C

NS

Hb goal 7-9
Hb goal 9-11

Child A&B Mortality
Child A&B Rebleed
Child C Mortality
Child C Rebleed

Early TIPS in Variceal Bleed:
Actively bleeding Child B, or any Child C

- Drug+EBL
- Drug+EBL+TIPS

Rebleed @ 1y
Hep Encephalop
Survival @ 6w
Survival @ 2y

Restrictive Transfusion in cirrhosis with GI bleed has lower re-bleeding and mortality rates
Early TIPS improved survival in variceal bleed with actively bleeding Child B, and all Child C
Thank you for your attention
Prevention of Variceal Rebleeding

Beta-blocker +/- ISMO Protocol

- Nadolol is given orally at an initial dose of 40 mg/day; keep MAP > 83 mm Hg*.
- The dose is then increased by 20 mg daily for a period of 5-7 days until:
  - intolerance appears, or
  - the heart rate decreases to 55 beats per minute, or
  - a maximal dose of 160 mg/day is reached, or
  - MAP is 84 mmHg (MAP <= 83 has high mortality in refractory ascites).
- Oral isosorbide mononitrate is started after beta blockade is reached, at 20 mg once at bedtime,
  - then followed by 20 mg twice a day for 1 day, and
  - finally increased to 40 mg BID if tolerated.

LONG TERM Rebleeding Risk
Different Prophylaxis

- *Betablockers increase mortality in refractory ascites, especially if MAP is =/< 83;
- D/C betablockers and band varices if needed.
Acute Esophageal Variceal Bleed Recommendations

• Start immediately Ceftriaxone 1 g/day for 7 days.
• Start immediately Octreotide 50 mcg bolus + 50 mcg/h x 5 days (can be D/C early after TIPS or adequate beta-blockade).
• Do early EGD to treat in all, and also to detect active bleeding in Child-Pugh B.
• Use “restrictive blood transfusions” when Hb <= 7 (unless higher needed for CAD). Avoid to elevate Hb to more than 9 g/dL.
• If patient is Child-Pugh C, or if Child-Pugh B with active bleed, do early TIPS if MELD score is < 15; consider TIPS if MELD 15-18.
• Start early aggressive Beta-blockade if TIPS is not done (avoid drop of MAP to <= 83 mm Hg), and plan for sequential banding for eradication of varices.
Nutrition in Cirrhosis

Low- vs Normal-Protein Diet in HE
Cordoba J; J Hepatol 2004;41:38–43

Diet with “normal protein intake” improves HE equally as “low protein” diet

Enteral Nutrition in Alcoholic Hepatitis
Cabre E; Hepatology 2000;32:36–42

In Severe AH, Total Enteral Nutrition is as good as steroids at 4 weeks, but superior after 1 year
Nutrition in Cirrhosis

Day-time vs Night-time Nutrition Supplementation; Plank LD; Hepatology 2008; 48(2):557-66

Probiotic Yogurt in Covert Hepatic Encephalopathy; Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

Bed-time Nutrition Increases Nitrogen Retention & Muscular Mass
(equivalent to 2 kg of muscle, after 12 months)

12 ounces of Probiotic Yogurt a day

Probiotic Yogurt Improves Covert HE & Protects against Overt HE
Enteral Nutrition in Alcoholic Hepatitis

Cabre E; Hepatology 2000;32:36–42

In Severe AH, Total Enteral Nutrition is as good as steroids at 4 weeks, but superior after 1 year.
Diet with “normal protein intake” improves HE equally as “low protein” diet