Minimizing Complications in Cirrhosis

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Multi-stage model for the clinical course of cirrhosis (Compensated to Decompensated)

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction

### Compensated Cirrhosis

| Stage 0: No varices, mild PH (HVPG 6-9 mm Hg) |
| LSM >15 and <20 or HVPG >5 and <10 mmHg |
| Stage 1: No varices, CSPH (Clinically Significant Portal HTN) |
| LSM ≥20 or HVPG ≥10 mmHg |
| Stage 2: Varices without bleed (=CSPH) |

### Decompensated Cirrhosis

| Stage 3: Variceal Bleeding |
| Stage 4: First non-bleeding decompensation |
| Stage 5: Second decompensating event |

### End stage

- Stage 6: late decompensation: Refractory ascites, persistent PSE or jaundice, infections, renal and other organ dysfunction

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**Normal HVPG = 1-5 mmHg**

**LSM = Liver Stiffness Measurement**

**HVPG = Hepatic Vein to Portal pressure Gradient**

Multi-stage model for the clinical course of cirrhosis (Compensated to Decompensated)

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction

Nutrition in Cirrhosis
What we Know

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

• Malnutrition worsens patient Frailty
  – Frailty increases mortality (independently of ascites or HE)

• 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
What we Know

• Enteral Nutrition improves nutritional status and liver function, reduces complications and prolongs survival in patients with cirrhosis and/or with alcoholic hepatitis (Kearns PJ; Gastroenterology 1992;102:200–5; Cabre E; Gastroenterology 1990;98:715–720)

• Use of BCCC-enriched formulas:
  – Supplementation with BCAA-enriched formula slows progression of hepatic failure (Marchesini G; Gastroenterology 2003;124:1792–1801) but is more expensive than whole protein formulas.
  – If Encephalopathy develops while on whole protein, BCAA-enriched formulas can be used to satisfy nitrogen needs (Horst D; Hepatology 1984;4:279–87).

• Enteral Access:
  – Use of naso-enteric feeding tubes is safe in cirrhosis, even with esophageal varices (De Ledinghen V; Dig Dis Sci 1997;42:536–541).
Frailty is associated with waitlist mortality independent of ascites and hepatic encephalopathy

**Objective:**
To investigate the relationship between physical frailty and ascites/hepatic encephalopathy (HE)

**Methods:**
- Data collected prospectively from 9 U.S. liver transplant centers in the Multi-Center Functional Assessment in Liver Transplantation (FrAILT) Study.
- 1044 adults listed for liver transplantation without exception points underwent testing of physical frailty using Liver Frailty Index (grip strength, chair stands, balance).

**Conclusions:**
Frailty is associated with significantly higher rates of waitlist mortality independently of ascites/HE and should be considered an independent complication of cirrhosis.

Lai JC, et al., Abstract 217

Frail = LFI \( \geq 4.5 \)

https://liverfrailtyindex.ucsf.edu/

\[
LFI = (-0.330 \times \text{gender adjusted grip strength}) + (-2.529 \times \text{number of chair stands per second}) + (-0.040 \times \text{balance time}) + 6
\]
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

<table>
<thead>
<tr>
<th>Months from baseline</th>
<th>7 am-7 pm (white bars)</th>
<th>After 9 pm (black bars)</th>
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<tr>
<td>3</td>
<td>*</td>
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<tr>
<td>6</td>
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<td>12</td>
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</table>

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
Nutrition in Alcoholic Hepatitis

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

In Severe AH, Intense Nutrition is as good as Steroids at 4-weeks but is superior at 1-year

**Calorie Intake vs Mortality in Severe Alcoholic Hepatitis**

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

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Mortality data from:
Pentoxifylline did not improve survival in patients with alcoholic hepatitis.

Prednisolone was associated with a reduction in 28-day mortality that did not reach significance and with no improvement in outcomes at 90 days or 1 year.
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

12 ounces of Probiotic Yogurt a day

Probiotic Yogurt Improves Covert HE & Protects against Overt HE
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 (HE)  
Definition & Pathogenesis

• Reversible neuro-psychiatric manifestation of severe liver dysfunction.
  – One-year survival 40%.

• Decreased hepatic clearance of ammonia derived from:
  – 1) kidney,
  – 2) urease activity of gastro-intestinal bacteria, and
  – 3) deamination of glutamine in small bowel.

• Increased Gut-derived neuro-mediators:
  – 1) benzodiazepine-like substances,
  – 2) neurotoxic short- and medium-chain fatty acids,
  – 3) phenols and,
  – 4) mercaptans.
### Manifestations and Grading of HE

**West Haven Criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>0 (Minimal)</td>
<td>No detectable changes in behavior or personality&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Euphoria or anxiety&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Impaired performance of addition&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>Shortened attention span&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Trivial lack of awareness&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Minimal disorientation to time or place&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Inappropriate behavior&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>2</td>
<td>Impaired performance of subtraction&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Lethargy or apathy&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Subtle personality change&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>3</td>
<td>Confusion&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Coma (no response to verbal or noxious stimuli)&lt;sup&gt;2&lt;/sup&gt;</td>
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HE = hepatic encephalopathy.

Types (by Cause)

- **Type A:** Acute Liver Failure
- **Type B:** Large Spontaneous or Post-traumatic Portal-Systemic By-pass (normal liver)
  - Uretero-Sigmoid anastomosis.
- **Type C:** Cirrhosis; Portal HTN or Shunt

- **Hepatic Myelopathy:** Symmetrical demyelination of lateral corticospinal tracts
Sub-Categories of Cirrhotic Hepatic Encephalopathy

• **Covert:**
  – Detected only by psycho-metric testing (*Minimal HE*) or subjective findings (*Grade 1*).
  – Impairs concentration and ability to drive.

• **Overt Episodic:**
  – Clinically apparent (*Grades 2 to 4*)
  – Usually precipitated after a triggering event.
  – May be precipitated, spontaneous, or recurrent

• **Chronic Persistent:**
  – H.E. fluctuating from “mild” to “severe”
  – Usually without apparent trigger;
  – May be treatment dependent.
  – Very rare.
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Subcategory</th>
<th>Subdivision</th>
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<tbody>
<tr>
<td>A</td>
<td>Encephalopathy associated with acute liver failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Encephalopathy associated with cirrhosis or portal hypertension/portosystemic shunts</td>
<td>Episodic HE</td>
<td>Precipitated, Spontaneous, Recurrent</td>
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<tr>
<td></td>
<td></td>
<td>Persistent HE</td>
<td>Mild, Severe, Treatment dependent</td>
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<td></td>
<td>Minimal</td>
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Precipitating Factors

- Constipation
- Gastrointestinal bleed
- Infection
- Overdiuresis
- Azotemia & dehydration
- Hypokalemia
- Hypo- or hyper-natremia
- Sedative or opiate
- Hepatic injury (toxic, viral, HCC)
- Portal vein thrombosis
- Excessive protein intake.
- TIPSS
- Non-compliance with H.E. therapy
Differential Diagnosis

- **Intracranial lesion**
  - bleed,
  - tumor,
  - infarct,
  - abscess
- **CNS infection**
- **Metabolic**
  - Hyper- or hypo-glycemia,
  - uremia,
  - acidosis,
  - electrolyte disorder
- **Neuro-psych disorder**
- **Alcohol-related**
  - Intoxication,
  - withdrawal,
  - Wernicke, Korsakoff
- **Drug**
  - sedative,
  - psychoactive,
  - heavy metal
- **Post-ictal**
Treatment of Hepatic Encephalopathy

• Reduction of Ammonia load:
  – Lactulose p.o. to give 3-4 BM/day or 30 minutes retention enema (300 ml + 700 ml water) TID
  – Rifaximin 550 mg BID, p.o.
  – Neomycin 4-6 grams/day p.o.
  – Metronidazole 250 mg TID, p.o.
  – Others: L-carnitine 990 mg TID, arginine benzoate, sodium benzoate (Ammonul), ornithine aspartate, sodium phenylbutyrate (Buphenyl), Acarbose, fiber, sorbitol, LOLA (L-ornithine and L-aspartate)
Mechanism of Action of Therapies for HE

• **Lactulose:** (also sorbitol, fiber, and acarbose) inhibit intestinal ammonia production by a number of mechanisms:
  – Conversion of unabsorbed sugar to lactic acid results in acidification of the gut lumen. This favors conversion of $\text{NH}_4^+$ to $\text{NH}_3$ and the passage of $\text{NH}_3$ from tissues into the lumen.
  – Gut acidification inhibits ammoniagenic coliform bacteria, leading to increased levels of nonammoniagenic lactobacilli.
  – Unabsorbed carbohydrates works as a cathartic, reducing colonic bacterial load.

• **Antibiotics:** such as rifaximin, neomycin, metronidazole, oral vancomycin, paromomycin, and oral quinolones,
  – decrease the colonic concentration of ammoniagenic bacteria.

• **Zinc:**
  – improves hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.
Mechanism of Action of Therapies for HE

- **L carnitine:**
  - Unclear if improves blood ammonia levels or if works centrally by decreasing brain ammonia uptake.

- **Sodium benzoate:**
  - Interacts with glycine to form hippurate. The renal excretion of hippurate results in the loss of ammonia ions.

- **Sodium phenylbutyrate** is converted to phenylacetate.
  - **Phenylacetate**, reacts with glutamine to form phenylacetylglutamine, which is subsequently excreted in the urine, with loss of ammonia ions.

- **LOLA** is a stable salt of l-ornithine and l-aspartate:
  - L-ornithine stimulates the urea cycle, with resulting loss of ammonia.
  - Both l-ornithine and l-aspartate are substrates for glutamate transaminase. Their administration increases glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase.
Treatment of Hepatic Encephalopathy

• Drugs affecting Neurotransmission:
  – Flumazenil: used more often in Acute Liver Failure in person without chronic benzodiazepine use.
  – Bromocryptine: may improve extra-pyramidal signs.
Treatment of Hepatic Encephalopathy

• Nutritional Management:
  – Early nutrition to cover calorie needs and 1.2-1.5 g protein/kg/day.
  – In Chronic Persistent PSE: branched-chain aminoacids enriched formula (Nutra-Hep)
  – Zn 50 mg QD or BID.

• Manipulation of Splanchnic Circulation:
  – Radiology-guided occlusion of shunts.
  – Reduction of TIPS with hourglass-shaped expanded polytetrafluoroethylene (ePTFE) stent-graft.
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

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”
IV Albumin in Cirrhosis with Ascites

ANSWER STUDY: Mauro Bernardi et al. EASL 2017

- 440 cirrhotics with non-refractory ascites.
- Mean: Age 60, Child-Pugh 8.1, MELD 13.
- Exclusion: refractory ascites, HCC.
- All on spironolactone + furosemide.
- F/U 18 months.
- Randomized Groups:
  - A) Diuretics + diet.
  - B) Diuretics + diet + IV Albumin 40 grams BIW x 2 weeks and then once a week.

- **Primary end point:** Survival
- **Secondary end points:** Paracentesis > 3 per month, Hospital admission, Other complications, QofLife.
- Other Results:
  - Decrease in PSE, HRS, Infections, any paracentesis (38% vs 66%) and 25% less days in Hospital.
  - Tendency to better QofL.
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.
  – **Norfloxacain** 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

Beta-blockers decrease survival in patients with refractory ascites

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

In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS
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.
Refractory Ascites

• Management:
  – Evaluate for Liver Transplant, if potential candidate.
  – Treat esophageal varices with banding and D/C beta-blockers.
  – D/C diuretics if 24h urine Na elimination is < 30 mm/day.
  – Evaluate for and treat thyroid and/or adrenal dysfunction.

• Standard Therapy:
  – **First Line:** Large volume paracentesis with albumin replacement to control ascites.
  – **Second Line:** TIPS with 8 mm PTFE-covered stent, if MELD < 15, or 16-20 with Bilirubin < 3 mg/dL. TIPS preferred if:
    – Loculated Ascites
    – LVP needed too frequently
    – TIPS indicated for additional indication (like variceal bleed)

• Other therapeutic options:
  – Midodrine 7.5-20 mg TID (+/- Clonidine 0.1 mg BID; alpha-2 agonist to suppress RAAS activity). Once MAP is >/= 85 mm Hg, and re-try diuretics
  – Treat as HRS.
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
Refractory Ascites & HRS

- Preventive Management of HRS:
  - Evaluate for Liver Transplant, if potential candidate.
  - Norfloxacin 400 mg/d in Child-Pugh >/= 9 and:
    - if Creatinine is > 1.2 mg/dL, or
    - Na < 130 mmol/L, or
    - T Bili > 3 mg/dL
  - Pentoxifylline 400 mg TID in cirrhotics with ascites, if creat clearance is 41-80 mm Hg but creatinine < 1.5 mg/dL.
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; Avoid PPIs.
  – Norfloxacin 400 mg/d decreases their risk of SBP.
• Patients with SBP are at high risk of developing HRS.
  – Treatment of community acquired SBP with Cefotaxime PLUS IV Albumin, decreases mortality and risk of HRS; In nosocomial SBP Piperacillin/tazobactam or Carbapenem.
  – 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 Norfloxacine decreases SBP recurrences. Avoid PPIs.
• In cirrhosis with GI bleed, Ceftriaxone decreases the risk of infections, and SBP.
Empirical antibiotic treatment of SB Peritonitis or SB Empyema (Pleuritis)

**SBP or SBE**

- **Community-acquired SBP or SB Pleuritis**
  - 3rd-gen cephalosporin or piperacillin-tazobactam

- **Healthcare-associated SBP or SB Pleuritis**
  - AREA DEPENDENT: Like nosocomial infections if high prevalence of MDROs or if sepsis

- **Nosocomial SBP or SB Pleuritis**
  - Piperacillin/tazobactam in areas with low prevalence of MDR bacteria
  - Carbapenem alone or + daptomycin, vancomycin (or linezolid*) if high prevalence of MDR Gram+ bacteria or sepsis

*In areas with a high prevalence of vancomycin-resistant enterococci
Adapted from Jalan R, et al. J Hepatol 2014;60:1310–24;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Spontaneous Bacterial Peritonitis (SBP)

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

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

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

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

- Patients with new-onset ascites should have a diagnostic paracentesis.
- Any cirrhotic with ascites who has a non-elective hospital admission, should have a diagnostic paracentesis at admission.
- Any hospitalized cirrhotic who has ascites or pleural effusion and has clinical deterioration, should have a diagnostic centesis.
- The fluid should be tested for cell count + differential, total protein, and albumin concentration (to subtract from serum albumin concentration for calculation of SAAG)
- The fluid should be inoculated in blood culture medium at the bedside, if infection is suspected.
  - If there is no SBP but ascites protein is $\leq 1.5$ g/dL, Norfloxacin 400 mg/d is indicated during the hospital stay.
SBP
Prophylaxis and Management

• Evaluate for Liver Transplant, if potential candidate.
• If patient has community acquired SBP, treat with:
  – Cefotaxime 2 g q 8h or ceftriaxone 2 g/d for 5 days;
  – 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 and avoid PPIs.
• 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.
  - Median survival 8-10 months
- 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

• Is NOT an Empyema, is a Pleuritis.
• 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

<table>
<thead>
<tr>
<th>Mortality SBE</th>
<th>Pig-tail chest tube</th>
<th>No chest tube</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>32</td>
<td>38</td>
</tr>
</tbody>
</table>

% Mortality
Other infections: recommended empirical antibiotic treatment

Cellulitis
- Community-acquired: Piperacillin-tazobactam or 3rd-gen cephalosporin + oxacillin
- Healthcare-associated: AREA DEPENDENT: Like nosocomial infections if high prevalence of MDROs or if sepsis
- Nosocomial: 3rd-gen cephalosporin or meropenem + oxacillin or glycopeptides or daptomycin or linezolid

Pneumonia
- Community-acquired: Piperacillin-tazobactam or ceftriaxone + macrolide or levofloxacin or moxifloxacin
- Healthcare-associated: AREA DEPENDENT: Like nosocomial infections if high prevalence of MDROs or if sepsis
- Nosocomial: Ceftazidime or meropenem + levofloxacin ± glycopeptides or linezolid

UTI
- Community-acquired: UNCOMPPLICATED: fosfomycin or nitrofurantoin IF SEPSIS: meropenem + teicoplanin or vancomycin
- Healthcare-associated: UNCOMPPLICATED: fosfomycin or nitrofurantoin
- Nosocomial: UNCOMPPLICATED: fosfomycin or nitrofurantoin

### 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>
<tr>
<td>3</td>
<td>-Increase of serum creatinine to $&gt; 300%$ from baseline, or -Serum creatinine $\geq 4.0$ mg/dL <strong>After:</strong> -An increase of at least 0.5 mg/dL, or -Treatment with renal replacement therapy</td>
<td>-Urine output $&lt; 0.3$ mL/kg/h for $24$ h, or -Anuria for $12$ h (-Many have HRS -1)</td>
</tr>
</tbody>
</table>

HRS is one type of AKI in Cirrhosis

Spectrum of Hepatorenal Disorder in Cirrhosis. *Critical Care* 2012, 16:R23

Urinary neutrophil gelatinase-associated lipocalin Ni: 20; Pre-renal: 20; CKD: 50; HRS: 105; ATN 325 ng/mL
Diagnostic Criteria for HRS type AKI

• Diagnosis of cirrhosis and ascites.
• Diagnosis of AKI by ICA criteria.
  – Increase of serum creatinine ≥ 0.3 mg/dL within 48 hours.
  – Increase in creatinine ≥ 50% from the closest baseline within the previous 3 months, known or presumed to have occurred over the prior 7 days.
• No response after 2 days of diuretic withdrawal + volume expansion with IV albumin 1 gram/ kg of weight each day.
• Absence of shock.
• No current nor recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast, etc.)
• No macroscopic signs of structural kidney injury:
  – No proteinuria > 500 mg/day.
  – No microhematuria > 50 RBCs per high power field.
  – Normal renal ultrasound.

These patients may still have tubular damage; Urine biomarkers may help differentiation.
# Definitions of Response to Treatment

**AKI in Cirrhosis**

<table>
<thead>
<tr>
<th>No response</th>
<th>Partial Response</th>
<th>Full Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regression of AKI</td>
<td>Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 μmol/L) above the baseline value</td>
<td>Return of sCr to a value within 0.3 mg/dl (26.5 μmol/L) of the baseline value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase to a higher stage of AKI and/or need for RRT.</td>
<td>Decrease to a lower stage of AKI.</td>
</tr>
</tbody>
</table>
ICA management algorithm for AKI in cirrhosis

- Investigation and management should begin immediately

**Initial AKI* stage 1A**

- Close monitoring
- Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, taper/withdraw diuretics and β-blockers, expand plasma volume, treat infections† when diagnosed)

- Resolution
- Persistance
- Progression

- Close follow-up

**Initial AKI* stage >1A**

- Withdrawal of diuretics (if not yet applied) and volume expansion with albumin (1 g/kg) for 2 days

- Response

  - YES
  - NO

- Does AKI meet criteria of HRS?

  - NO
  - YES

- Specific treatment for other AKI phenotypes
- Vasoconstrictors and albumin

---

*Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria;
†Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines
Adapted from Angeli P, et al. J Hepatol 2015;62:968–74;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
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</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(53%)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Progression to AKI-2</td>
<td>(19%)</td>
</tr>
<tr>
<td></td>
<td>(11%)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Progression needing Dialysis</td>
<td>(17%)</td>
</tr>
<tr>
<td></td>
<td>(56%)</td>
<td>56</td>
</tr>
<tr>
<td>AKI-2 (many HRS-2; few HRS-1)</td>
<td>No Progression</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(54%)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Progression to AKI-3</td>
<td>(19%)</td>
</tr>
<tr>
<td></td>
<td>(27%)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Progression Needing Dialysis</td>
<td>(33%)</td>
</tr>
<tr>
<td></td>
<td>(71%)</td>
<td></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

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosp Mortality</td>
<td>24.5%</td>
</tr>
<tr>
<td>HRS Mortality</td>
<td>46%</td>
</tr>
</tbody>
</table>

- 49p = PTX 400 mg TID x 28 d
- 52p = Placebo TID

**Prednisolone + NAC in Severe Alcoholic Hepatitis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality 1-mo</td>
<td>8%</td>
</tr>
<tr>
<td>Mortality 6-mo</td>
<td>24%</td>
</tr>
<tr>
<td>Prednisolone 6-mo</td>
<td>27%</td>
</tr>
<tr>
<td>NAC 6-mo</td>
<td>38%</td>
</tr>
<tr>
<td>PTX 6-mo</td>
<td>22%</td>
</tr>
</tbody>
</table>

- 89p = Prednisolone 40 mg/d x 28d;
- 85p = NAC loading 100 mg/kg/d x 5d + Prednisolone 40 mg/d x 28 d

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

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

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

Ornipressin + Albumin in HRS-I
Guevara M; HEPATOLOGY 1998;27:35-41

Ornipressin 2 IU/h x 15 d + Albumin
8 patients with HRS-1
Responders reached MAP = 84

Intravenous NAC x 5 d in HRS-I
Holt S; Lancet 1999;353(9149):294-295

NAC IV load + 100 mg/kg/d x 5 d
12 patients with HRS-1

Ornipressin + Albumin takes up to 2 weeks to work

NAC can improve creatinine clearance and natriuresis in HRS-1
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

![Graph showing treatment efficacy over time]
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).
HRS Prevention & Management

- Evaluate for Liver Transplant, if potential candidate.
- Prevent HRS:
  - When treating alcoholic hepatitis, consider Pentoxifylline, or the combination of steroids + NAC.
    - Aggressive nutrition therapy is also imperative.
  - In SBP, give IV albumin,
    - Specially if creatinine is > 1, BUN > 30, or T Bili > 4.
  - In cirrhosis with GI bleed, give Ceftriaxone 1 g IV a day x 7 days.
  - In outpatients with cirrhotic ascites and renal dysfunction, consider long term Pentoxifylline.
  - In cirrhotics with ascites and jaundice, hyponatremia, or renal dysfunction, consider long term daily Norfloxacine.
  - In refractory ascites, consider Midodrine.
HRS Prevention & Management

• Patients suspected to have type-1 or type-2 HRS should have:
  – Discontinuation of diuretics + expansion of intravascular volume with 5% albumin 1.5-2 L/day (1 g/kg up to 100 g) x 2 days;
    • consider evaluation of CVP to assure proper volume expansion.
  – Renal U/S + urine analysis to assess for parenchymal or obstructive renal disease
  – Complete evaluation for infection, with proper therapy if infection is present.
  – Norfloxacine 400 mg/d if they have ascites with protein < 1.5 g/dL and no SBP.
• If there is no clear evidence of CKD, and after proper intravascular expansion, treat as HRS.
  – In the medical ward start oral Midodrine 10 mg q 8h + Octreotide 100 mcg SQ q 8h, and see MAP response.
  – If MAP is < 85 mm Hg, increase Midodrine to 20 mg q 8h and Octreotide to 200 mcg q 8h SQ.
  – If MAP is still < 85 mm Hg and patient is not improving, test adrenal and thyroid function and move patient to ICU.
  – Treat endocrinopathy, if found.
HRS Prevention & Management

• In ICU evaluate CVP, and give extra IV albumin if needed. CVP goal is 12-14.
  – If CVP > 18, hold fluids and give IV furosemide until CVP is < 18 but > 12.
• Start Terlipressin (if available), or Noradrenaline (norepinephrine).
  – Titrate to sustain an MAP of 85 mmHg.
  – Continue until creatinine is \(\leq 1.3\) mg/dL.
  – If noradrenaline causes arrhythmia, consider change to phenylephrine.
• Discontinue therapy if there is no response after 14 days.
  – If patient does not respond to vasopressors and MELD is < 15, consider to proceed to TIPS.
  – If not a good TIPS candidate, consider NAC IV 150 mg/Kg over 2 h + 100 mg/Kg/d x 5 days
  – If MELD > 15-20, or bili > 3 mg/dL patients should be informed of higher 30 d TIPS mortality and TIPS performed only in the absence of other options.
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 Somatostaninie IV for 5 days decrease rebleeding rate after variceal bleed (Corley DA; GASTROENTEROLOGY 2001;120:946-954).
Acute Esophageal Variceal Bleed
Recommendations

• Correct hypovolemia with IV crystalloids and albumin.
• 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.
• Do NOT give FFP nor factor rVIIa to correct INR due to cirrhosis.
• Unclear if Platelets transfusion helps (likely not) (No recommendation).
• 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.
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.
Variceal haemorrhage: management of acute GI bleeding

**Medical emergency**: high rate of complications and mortality in DC

- Requires immediate treatment and close monitoring

### Initial assessment* and resuscitation

- Acute GI bleed + portal hypertension
- Immediate start of vasoactive drug therapy†
  - Antibiotic prophylaxis (I;1)‡

### Early diagnostic endoscopy (<12 hours)

- Confirm variceal bleeding
- Endoscopic band ligation

### Control

- (~85% of cases)
- Maintain drug therapy for 3–5 days and antibiotics‡

### Further bleeding

- (~15% of cases)
- Consider early TIPS in high risk patients

### Endoscopy

- **Balloon tamponade or oesophageal stenting**
  - (if massive bleeding)

### Airway
- **Breathing**
- **Circulation**
  - **Volume replacement** with colloids and/or crystalloids should be initiated promptly (III;1)
  - Starch should not be used (I;1)
  - **Restrictive transfusion** is recommended in most patients (Hb threshold, 7 g/dl; target range 7–9 g/dl) (I;1)

*History, physical and blood exam, cultures; †Somatostatin/terlipressin; ‡Ceftriaxone (1 g/24 hours) is the first choice in patients with DC, those already on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. Oral quinolones (norfloxacin 400 mg BID) should be used in the remaining patients (I;1)

Figure adapted from de Franchis R, et al. J Hepatol 2015;63:743–52; EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Acute GI Bleed in Cirrhosis

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

- Hb goal 7-9
- Hb goal 9-11

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

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

Early TIPS improved survival in variceal bleed with actively bleeding Child B, and all Child C
Eligible criteria for early TIPS included the following: age younger than 75 years, creatinine level less than 3 mg/dL, Child-Pugh score lower than 14, hepatocellular carcinoma within Milano criteria or Barcelona Clinic Liver Cancer staging system stages C or D, and no portal thrombosis.

6-week mortality with early TIPS is 3%; Child-Pugh B with or without active bleeding at Endoscopy and MELD >/= 12, Child-Pugh C up to 13 points with or without bleeding at Endoscopy (6% and 19% 1-y mortality with early-TIPS, respectively), and patients with MELD 12-18 benefit from early-TIPS.
## Secondary Prophylaxis for Esophageal Variceal Hemorrhage

### EVL + NSBB

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Recommended Dose</th>
<th>Therapy Goals</th>
<th>Maintenance/Follow-up</th>
</tr>
</thead>
</table>
| Propranolol | • With EVL.  
• 20-40 mg orally *twice* a day  
• Adjust every 2-3 days until treatment goal is achieved  
• Maximal daily dose:  
  • 320 mg/day in patients without ascites  
  • 160 mg/day in patients with ascites | • Resting heart rate of 55-60 beats per minute  
• Systolic blood pressure should not decrease <90 mm Hg | • At every outpatient visit make sure that heart rate is on target  
• Continue indefinitely |
| Nadolol | • With EVL.  
• 20-40 mg orally *once* a day  
• Adjust every 2-3 days until treatment goal is achieved  
• Maximal daily dose:  
  • 160 mg/day in patients without ascites  
  • 80 mg/day in patients with ascites | • Resting heart rate of 55-60 beats per minute  
• Systolic blood pressure should not decrease <90 mm Hg | • At every outpatient visit make sure that heart rate is on target  
• Continue indefinitely |
| EVL | • With NSBB.  
• Every 1-4 weeks until the eradication of varices | • Variceal eradication (no further ligation possible) | • First EGD performed 3-6 months after eradication and every 6-12 months thereafter |

NSBB is the main component of the therapy. If intolerant to NSBB, consider TIPS. Carvedilol has not been study well for secondary prophylaxis.
Thank you for your attention
Prevention of Variceal Rebleeding

**Beta-blocker Protocol**

- Nadolol is given orally at an initial dose of 40 mg/day; keep MAP > 83 mm Hg*.
  - In refractory ascites limit Propranolol or Nadolol to ≤ 80 mg/d
- 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).

**LONG TERM Rebleeding Risk**

- Different Prophylaxis
  - *Refractory Ascites*: Betablockers increase mortality, if MAP is =/≤ 83;
    - Limit nadolol or propranolol to ≤ 80 mg/d.
    - D/C betablockers and band varices if needed.
Relative adrenal insufficiency

- Inadequate cortisol response to stress in the setting of critical illness*
  - Pathophysiology in cirrhosis is not well defined
- Diagnosis is influenced by the method used to measure cortisol
- It is not known whether cortisol supplementation in clinically stable cirrhosis with RAI is of any value

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis of RAI</strong></td>
<td></td>
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</tr>
<tr>
<td>• &lt;248 nmol/L (9 mcg/dl) change in total serum cortisol after 250 mcg corticotropin injection, or</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>• Random total cortisol of &lt;276 nmol/L (&lt;10 mcg/dl)</td>
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<tr>
<td><strong>Salivary cortisol determination can be preferred</strong></td>
<td></td>
<td></td>
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<tr>
<td>• Serum free cortisol concentration can be influenced by reduced serum levels of CBG and albumin, frequently seen in patients with cirrhosis</td>
<td>II-2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hydrocortisone treatment</strong> (at a dose of 50 mg/6 hours) of RAI cannot be recommended</td>
<td>I</td>
<td>2</td>
</tr>
</tbody>
</table>

*Also known as critical illness-related corticosteroid insufficiency (CIRCI)
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Cirrhotic cardiomyopathy

• CCM occurs in patients with established cirrhosis characterized by:
  – Blunted contractile response to stress (pharmacological/surgery or inflammatory)
  – Altered diastolic left ventricular relaxation or/and increased left atrial volume
  – Electrophysiological abnormalities e.g. prolonged QTc
  – Cardiac output tending to decrease with decompensation
  – Systolic dysfunction: LVEF <55%

• CCM is largely subclinical but its presence influences prognosis in advanced disease
Cirrhotic cardiomyopathy

• Numerous electrocardiographic criteria, along with transmitral Doppler assessment, are used for the evaluation and diagnosis of diastolic dysfunction
  — However, there is the need for more controlled studies and correlation with clinical endpoints

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<tr>
<td><strong>ECG in patients with cirrhosis should be performed with dynamic stress testing</strong> (systolic dysfunction may be masked by hyperdynamic circulation and reduced afterload)</td>
<td>II-1</td>
<td>1</td>
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<tr>
<td>• Lack of increased CO after physiological/pharmacological stress† indicates systolic dysfunction</td>
<td></td>
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<tr>
<td><strong>Myocardial strain imaging and assessment of GLS may be useful in the assessment of left ventricular systolic function in patients with DC</strong></td>
<td>II-2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cardiac MRI may identify structural changes</strong></td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td><strong>Diastolic dysfunction may occur as an early sign of CCM in the setting of normal systolic function, and should be diagnosed using ASE criteria:</strong></td>
<td>II-1</td>
<td>1</td>
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<tr>
<td>• Average E/e’&gt;14</td>
<td></td>
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<tr>
<td>• Tricuspid velocity &gt;2.8 m/s</td>
<td></td>
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<tr>
<td>• LAVI &gt;34 ml/m²</td>
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*Either pharmacologically, or through exercise; †And in the absence of influence of β-blockade
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Cirrhotic cardiomyopathy

- Cardiac evaluation in patients with cirrhosis is important since CCM can influence prognosis

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<tr>
<td>In patients with AD, reduced CO (as a manifestation of CCM) is associated with the development of AKI (specifically hepatorenal dysfunction) after infections such as SBP</td>
<td>II-1</td>
<td>1</td>
</tr>
</tbody>
</table>
| QTc interval prolongation is common in cirrhosis and may indicate a poor outcome  
  • Agents that can prolong the QT interval should be used cautiously | II-2 | 2 |
| Detailed functional cardiac characterization should be part of the assessment for  
  • TIPS insertion  
  • LT | II-2  
  II-1 | 2  
  1 |
| Standardized criteria and protocols for the assessment of systolic and diastolic function in cirrhosis are needed | II-2 | 2 |
Pathogenesis of HPS

- Hepatic injury/failure
- Portal hypertension

- Portosystemic shunt
- Hyperdynamic circulation
- Bacterial translocation

Increased ET-1 release

- Increased ETB receptor
- Increased eNOS expression and activity
- Increased release of NO

Endothelial cell

- VASODILATION

Endothelial activation of CX3CL1

- Genetic factors

Endothelial cell

- Increased adherence of macrophages/monocytes to endothelial cells

Endothelial cell

- VFG-A release

CX3CL1

- Increased iNOS and HO expression and activity

Macrophage recruitment in the lungs

- Macrophage

Pulmonary capillary

- ANGIogenesis

Endothelial cell proliferation

HEPATOPULMONARY SYNDROME

Endothelial cell

- Increased NO and CO release

VASODILATION
Diagnostic criteria for HPS

- Hypoxia with partial pressure of oxygen <80 mmHg or alveolar–arterial oxygen gradient ≥15 mmHg in ambient air (≥20 mmHg in patients older than 65 years)
- Pulmonary vascular defect with positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
- Commonly in presence of portal hypertension, and in particular:
  - Hepatic portal hypertension with underlying cirrhosis
  - Pre-hepatic or hepatic portal hypertension in patients without underlying cirrhosis
- Less commonly in presence of:
  - Acute liver failure, chronic hepatitis
Diagnosis of HPS

- In patients with portal hypertension and the clinical suspicion of HPS partial pressure of oxygen (PaO₂) in ABG should be assessed

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<tr>
<td>In patients with chronic liver disease, HPS should be suspected and investigated in presence of tachypnoea and polypnoea, digital clubbing and/or cyanosis</td>
<td>II-2</td>
<td>1</td>
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<tr>
<td>Screening in adults:</td>
<td></td>
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<tr>
<td>• If pulse oximetry SpO₂ &lt;96% – ABG analysis should be performed</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>• If ABG PaO₂ &lt;80 mmHg and/or P[A-a]O₂ ≥15 mmHg* (in ambient air) – further investigations should be performed</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>The use of contrast (microbubble) echocardiography to characterize HPS is recommended</td>
<td>II-2</td>
<td>1</td>
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</table>

*For adults ≥65 years a P[A-a]O₂ ≥20 mmHg cut-off should be used
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Diagnosis of HPS

- When $\text{PaO}_2$ suggests HPS, further investigations are needed to determine the underlying mechanism

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<tr>
<td><strong>MAA scan</strong> should be performed to quantify the <strong>degree of shunting</strong> in patients with severe hypoxaemia and coexistent intrinsic lung disease, or to assess the prognosis in patients with HPS and very severe hypoxaemia ($\text{PaO}_2 &lt; 50 \text{ mmHg}$)</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Neither contrast echocardiography nor MAA scan can definitively differentiate discrete arteriovenous communications from diffuse precapillary and capillary dilatations or cardiac shunts • Pulmonary angiography should be performed only in patients with the severe hypoxaemia ($\text{PaO}_2 &lt; 60 \text{ mmHg}$), poorly responsive to administration of 100% oxygen, and in whom there is a strong suspicion of arteriovenous communications that are amenable to embolization</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Trans-oesophageal contrast-enhanced echocardiography (although associated with risks) can definitively exclude intra-cardiac shunts</td>
<td>II-2</td>
<td>2</td>
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EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024
Management of HPS

• There is no established medical therapy currently available for HPS, the only successful treatment for HPS is LT

<table>
<thead>
<tr>
<th>Recommendations for medical treatment</th>
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<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>Long-term oxygen therapy is recommended in patients with HPS and severe hypoxaemia despite the lack of available data concerning effectiveness, tolerance, cost effectiveness, compliance and effects on survival rates of this therapy</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>No recommendation can be proposed regarding the use of drugs or the placement of TIPS for the treatment of HPS</td>
<td>I</td>
<td>1</td>
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<thead>
<tr>
<th>Recommendations for liver transplantation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>Patients with HPS and PaO₂ &lt;60 mmHg should be evaluated for LT since it is the only treatment for HPS that has been proven to be effective to date</td>
<td>II-2</td>
<td>1</td>
</tr>
</tbody>
</table>
| Severe hypoxaemia (PaO₂ <45–50 mmHg) is associated with increased post-LT mortality  
  • ABG analysis should be carried out every 6 months to facilitate prioritization to LT | II-2 | 1 |
Portopulmonary hypertension

- PPHT occurs in patients with portal hypertension in the absence of other causes of arterial or venous hypertension
- Classification is based on mean pulmonary arterial pressure (mPAP), and assumes high pulmonary vascular resistance (PVR) and normal pulmonary occlusion pressures
  - Mild: mPAP ≥25 and <35 mmHg
  - Moderate: mPAP ≥35 and <45 mmHg
  - Severe: mPAP ≥45 mmHg
- Incidence between 3–10% cirrhosis patients based on haemodynamic criteria; women are at 3x greater risk and it is more common in autoimmune liver disease
- There is no clear association between the severity of liver disease or portal hypertension and the development of severe PPHT
Monitoring and medical management of PPHT

- The evidence base for pharmacological therapies in PPHT is limited

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</table>
| **Screening for PPHT** should be via TDE in patients deemed potential recipients for TIPS or LT  
  - In those with a positive screening test, right heart catheterization should be performed | II-1              | 1                       |
| In patients with PPHT who are listed for LT, **echocardiography should be repeated** on the waitlist (the specific interval is unclear) | III               | 1                       |
| **β-blockers should be stopped and varices managed by endoscopic therapy** in cases of proven PPHT | II-3              | 1                       |
| Therapies approved for primary pulmonary arterial hypertension may improve exercise tolerance and haemodynamics in PPHT  
  - However, **endothelin antagonists should be used with caution** because of concerns over hepatic impairment | II-2              | 1                       |
| **TIPS should not be used in patients with PPHT**                              | II-3              | 1                       |
Liver transplantation in PPHT

• Although severe PPHT has, historically, been a contraindication for LT, the advent of improved haemodynamic control (with agents such as IV prostacyclin) allows LT to be considered

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| If mPAP <35 mmHg and right ventricular function is preserved, LT should be **considered**  
  • mPAP of ≥45 mmHg should be considered an absolute contraindication to LT irrespective of therapy applied | II-2              | 1                       |
| **Therapy to lower mPAP** and improve right ventricular function should be commenced in patients with mPAP ≥35 mmHg  
  • Right ventricular function should be periodically evaluated | II-2              | 1                       |
| **MELD exception** can be considered in patients with **proven PPHT** in whom targeted therapy fails to decrease mPAP <35 mmHg but does facilitate normalization of PVR to <240 dyn.s/cm⁻5 and right ventricular function | II-3              | 2                       |
| **MELD exception should be advocated** in patients with **proven PPHT** of moderate severity (mPAP ≥35 mmHg) in whom targeted treatment lowers mPAP <35 mmHg and PVR <400 dyn.s/cm⁻5 | II-2              | 1                       |
Nutrition in Cirrhosis

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

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

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

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

- 500-710 kcal
- 26-30 g protein

<table>
<thead>
<tr>
<th>Months from baseline</th>
<th>TBP change (kg)</th>
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<tbody>
<tr>
<td>3</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>**</td>
</tr>
<tr>
<td>12</td>
<td>**</td>
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- 7 am-7 pm (white bars)
- After 9 pm (black bars)

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

- 12 ounces of Probiotic Yogurt a day

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

**Probiotic Yogurt Improves Covert HE & Protects against Overt HE**
In Severe AH, Total Enteral Nutrition is as good as steroids at 4 weeks, but superior after 1 year.
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.