Minimizing Complications in Cirrhosis

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Potential Conflict of Interest

• Speaker: Salix (Xifaxan/Rifaximin)
Nutrition in Cirrhosis

What we Know

• Most cirrhotic patients suffer from malnutrition.
  – even cirrhotic patients with overweight and NASH often have protein malnutrition.
• Cirrhotic patients are hypermetabolic, and go to a catabolic state after a few hours of fasting.
  – This catabolic state causes gluconeogenesis and muscular wasting.
  – Frequent meals and bedtime supplements prevent the catabolic state and increase muscular mass.
• After a meal, attention and executive function improves temporarily in cirrhosis, decreasing “covert” Hepatic Encephalopathy (HE stages 0-1) (Vaisman N; Am J Clin Nutr 2010;92:137–40).

Nutrition in Cirrhosis and Alcoholic Hepatitis

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

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

500-710 kcal
26-30 g protein

P .54
P .04

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

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

Recommendation

  - 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.
- **Protein:** 1.2-1.5 g/kg of ideal body weight/day 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
- **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

- Most episodes of overt HE (stages 2-4) do not 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).
- Probiotic yogurt helps in covert HE (Bajaj J; Am J Gastroenterol 2008;103:1707-1715).
- Lactulose is still the initial step in therapy of overt HE;
  - titrate to 3 or 4 BM/d.
- Other drugs that can help to control episodic overt HE.
  - Rifaximin, added to Lactulose, decreases recurrence of HE and re-hospitalizations related to HE.
  - 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

Diet with “normal protein intake” does not delay recovery from Overt HE when compared to “low protein” diet.

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

12 ounces of Probiotic Yogurt a day

**Probiotic Yogurt Improves Covert HE & Protects against Overt HE**

Hepatic Encephalopathy

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

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

**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.
Ascites Management

• Diet: 2 g Na restriction is critical for success.
  – You need 3 g of Na to form 1 liter of ascites.
• Improve nutritional status.
• Avoid drugs that increase risk of renal impairment:
  – NSAIDs: can cause AKI and increase Na retention.
  – ACE-inhibitors,
  – Angiotensin II antagonists,
  – Alfa 1-adrenergic receptor blockers,
  – Aminoglycosides
• Spironolactone as main diuretic: is the most effective
  – dose can be titrated by “spot urine Na to K ratio”
• Avoid drop of MAP:
  – If MAP is >/= 83, then 1 y survival is 70%;
  – If MAP is < 83, then 1 year survival is 40% [Llach J et al. Gastroenterology 1988;94:482-87]

Diuretic Titration

• Usually start with spironolactone 100 mg + furosemide 40 mg in a single morning dose.
• Adjust dose daily by:
  – Weight loss,
    • 1 lb/d if without edema
    • 2 lb/d if with edema
  – 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
    • Na/K >/= 3.5 has a PPV of 100% (HEPATOLOGY 2002;36:222A); [Liver Int. 1993;13(1):173-3], and
  – Avoiding elevation of serum creatinine;
    • Ideally none
    • < 0.3 mg/dL

Spironolactone is superior to Furosemide in controlling ascites
Assessment of Ascites Diuretic-Response by spot urine Na/K ratio  
Runyon B et al; 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:
  - **Midodrine** increases mean arterial pressure (MAP), Systemic Vascular Resistance (SVR), and response to diuretics with higher natriuresis and urine output, as well as decreases mortality.
  - **Norfloxacin** improves hemodynamics by increasing MAP and SVR, and decreases risk for spontaneous bacterial peritonitis (SBP), HRS and death.
  - **Pentoxifylline** improves diuresis and natriuresis; increases, MAP, SVR and serum sodium; and also decreases risk of HRS.

Ascites & Refractory Ascites

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

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

- Beta-blockers decrease survival in patients with refractory ascites.
- In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS.
Ascites & Refractory Ascites

Midodrine in Refractory/Recurrent Ascites

In Refractory ascites, Midodrine 7.5 mg TID increases Natriuresis and improves Survival.

Midodrine in Refractory/Recurrent Ascites

Ascites & Refractory Ascites

Norfloxacin in advanced cirrhosis + ascites with either bilirubin > 3, or creatinine > 1.2, or Na < 130

In ascites with Child > 9 or renal dysfunction, Norfloxacin decreases risk of SBP, HRS, and improves survival.

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

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Spontaneous Bacterial Peritonitis (SBP)
What we know

- 10-27% of hospitalized patients with cirrhotic ascites have or develop SBP.
- 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 HRS risk;
    - 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 the first episode of SBP, long-term Norfloxacin decreases SBP recurrences.
- In cirrhosis with GI bleed, Ceftriaxone decreases the risk of infections, and of SBP better than Norfloxacin.

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

40 50 60 70 80 90 100
% of Patients

0 10 20 30 40 50 60 70 80 90 100
SBP @ 6 mo SBP @ 1 yr

Norfloxacin 400 mg/d
Placebo

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

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

Hepatic Hydrothorax and Spontaneous Bacterial Empyema (pleuritis) (SBE)

- 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.

Chest scan after partial thoracentesis and injection of the radionucleide in abdomen
**Spontaneous Bacterial Empyema (pleuritis)**

**SBE – What we know**

- Spontaneous Bacterial Pleuritis occurs in 16% of hepatic hydrothorax.
- SBE is diagnosed in a patient without lung infection, by either:
  - PMN count > 250/mm³ plus a (+) fluid culture, or
  - PMN count > 500/mm³, with a negative fluid 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).

**Hepatorenal Syndrome**

**What else we know?**

- Main risk-factors for HRS are:
  - diuretic resistant or intolerant ascites,
  - hyponatremia,
  - SBP or other 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.
    - Pentoxifylline therapy is not inferior to Prednisolone therapy.
  - Adding NAC to Prednisolone decreases the risk of HRS, and 1 month mortality, but not the 6 months mortality (negative study).
**Prevention of HRS & Mortality**

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

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

% Mortality

- Hosp Mortality
- HRS Mortality

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

**Prednisolone + NAC in Severe Alcoholic Hepatitis**

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

% Mortality

- Mortality 1-mo
- Mortality 6-mo
- HRS Mort 1-mo
- HRS Mort 6-mo

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 mg 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 Treatment

What we know

- HRS type I and II can be treated with volume expansion plus vasopressors.
- 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).
- Noradrenaline has been found to be as effective as Terlipressin in reversing HRS Type-1 and 2 (Singh V; J of Hepatology 2012;56:1293–1298).
- In most studies, the response is more likely if a MAP of 85-90 mm Hg is sustained (Velez JC; Am J Kidney Dis. 2011;58:928-38).

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

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

Mortality

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

Control

30-day 90-day
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

Noradrenaline + Albumin takes up to 10 days to work

**Terlipressin + 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

Terlipressin + Albumin takes up to 2 weeks to work

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

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

Terlipressin + Albumin vs Albumin in HRS

Noradrenaline + Albumin is equally effective as Terlipressin + Albumin

HRS-II responds better than HRS-I
Hepatorenal Syndrome Treatment

What we know

• To obtain desired response with drug therapy often takes up to 10-20 days.
• Response rate for HRS Type-1 with Midoctrine + Octreotide + 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.
• Doing a TIPS after drug-reversal of HRS maintains the response (Wong F; Hepatology 2004;40(1):55-64).

Acute GI Bleed in Cirrhosis

What else 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).
  – Liberal blood transfusion increases portal pressure.
  – Restrictive transfusion decreases re-bleeding rate in all patients, and
  – Restrictive transfusion decreases mortality in Child A & B.
• In 2 specific groups of patients with esophageal variceal bleed, the use of early TIPS (within 24-72 hours) using a PTFE covered stent (when compared with EBL + Beta-blockers), decreases rebleeding rate (NNT: 2.1) and decreases mortality at 6 months (NNT: 3.3) and 1-year (NNT: 4) (Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379) in 2 groups:
  – 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

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

Take Home Points

- Intensive nutrition with normal protein and frequent meals (7 meals a day), including complex carbohydrate + protein at bedtime, improves HE and muscular mass.
- Probiotic Yogurt can improve covert HE.
- Rifaximin + Lactulose decrease HE recurrence and HE related re-hospitalizations.
- To control ascites, Na restriction and Spironolactone are the best tools.
- Spot Urine Na/K ratio > 1 can guide diuretic therapy.
- Beta-blockers should be avoided in “refractory ascites”.
- MAP < 83 increases mortality.
Take Home Points

- **Norfloxacin, 400 mg/d**, can:
  - Prevent SBE in Hospitalized patients.
  - Decrease SBP recurrence after 1st SBP episode.
  - Decrease risk of mortality, SBP, and HRS in very decompensated Child-Pugh B patients.
- **Midodrine 7.5-20 mg TID**:
  - Improves diuretic responsiveness and decreases mortality.
- **Pentoxifylline 400 mg TID**:
  - Improves creatinine clearance and decreases risk of HRS in cirrhotics with CrCl of 40-80.
  - Decreases risk of HRS in Alcoholic Hepatitis (AH).
  - In AH is at least as effective improving survival as Prednisolone.
- **Albumin + Cefotaxime** improves outcome in SBP.
- Ceftriaxone is more effective than Norfloxacin in decreasing infections in patients with cirrhosis complicated with GI bleed.

Take Home Points

- Chest tube is contraindicated in Hepatic Hydrothorax and in Spontaneous Bacterial Empyema or Pleuritis.
- Treatment of HRS can take 10-21 days.
- Volume expansion + vasopressors are needed to treat HRS.
- Type-2 HRS responds better than Type-1 HRS.
- To reverse HRS usually is needed adequate volume expansion with albumin and a sustained MAP of 85-90 mm Hg with vasopressors.
- In GI bleeding in patients with cirrhosis:
  - Ceftriaxone IV decreases infections and rebleeding.
  - Restrictive blood transfusions decrease re-bleeding and improve survival.
  - Early TIPS improves survival in Child B with active variceal bleed, and decreases rebleeding in all Child C patients with variceal bleed.