Minimizing Complications in Cirrhosis

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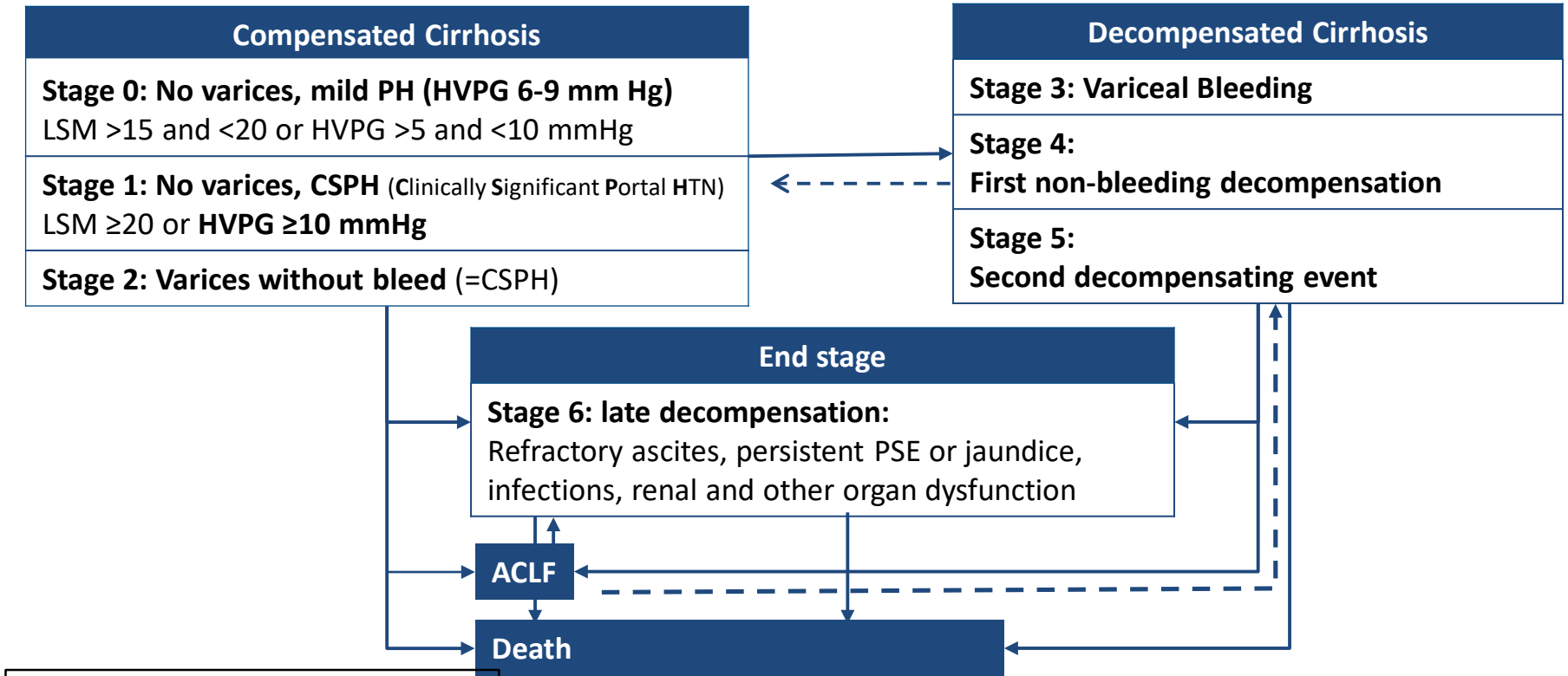
Multi-stage model for the clinical course of cirrhosis (Compensated to Decompensated)

- 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



LSM = Liver Stiffness Measurement
HVPG = Hepatic Vein to Portal pressure Gradient

Normal HVPG = 1-5 mmHg

D'Amico G, et al. J Hepatol 2018;68:563–76;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

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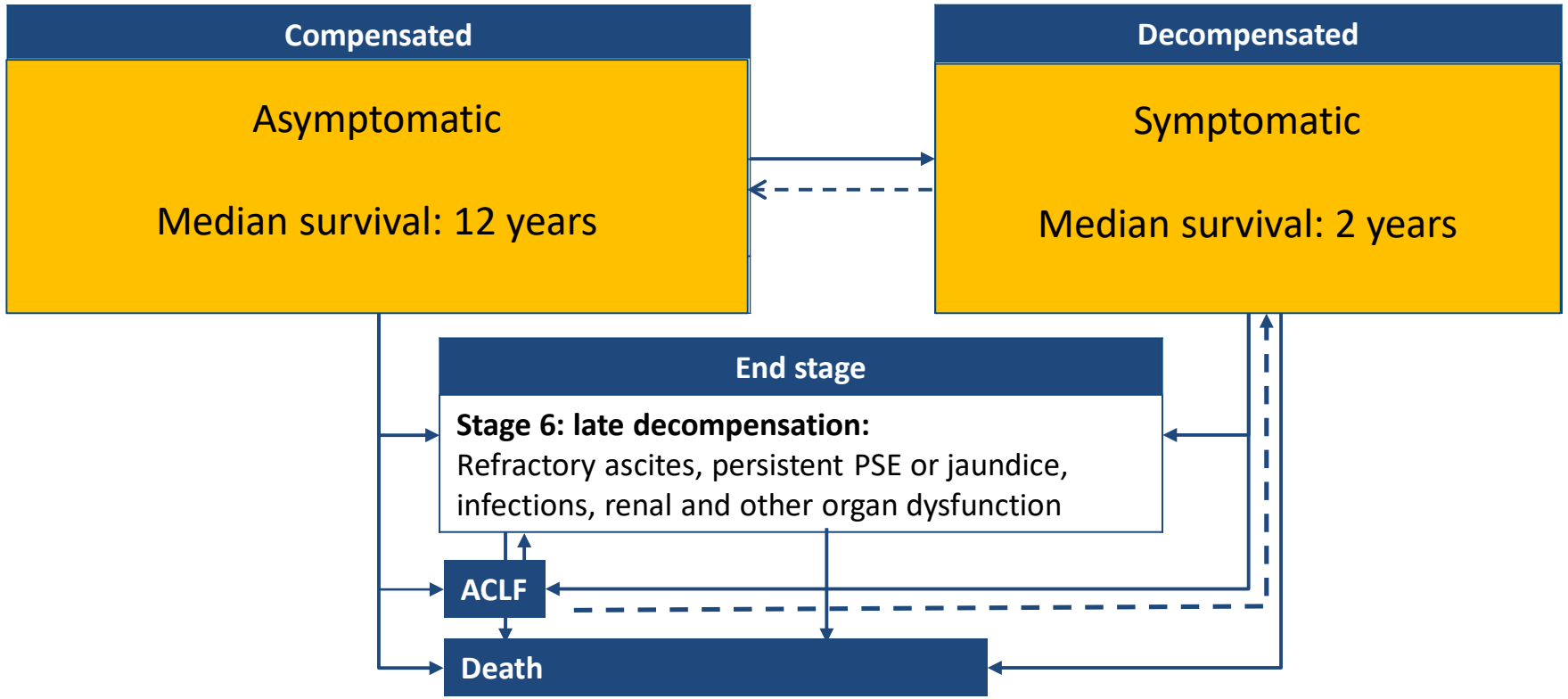

D'Amico G, et al. J Hepatol 2018;68:563–76;
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Nutrition in Cirrhosis
What we Know

- 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).

Frailty is associated with waitlist mortality independent of ascites and hepatic encephalopathy

Objective:

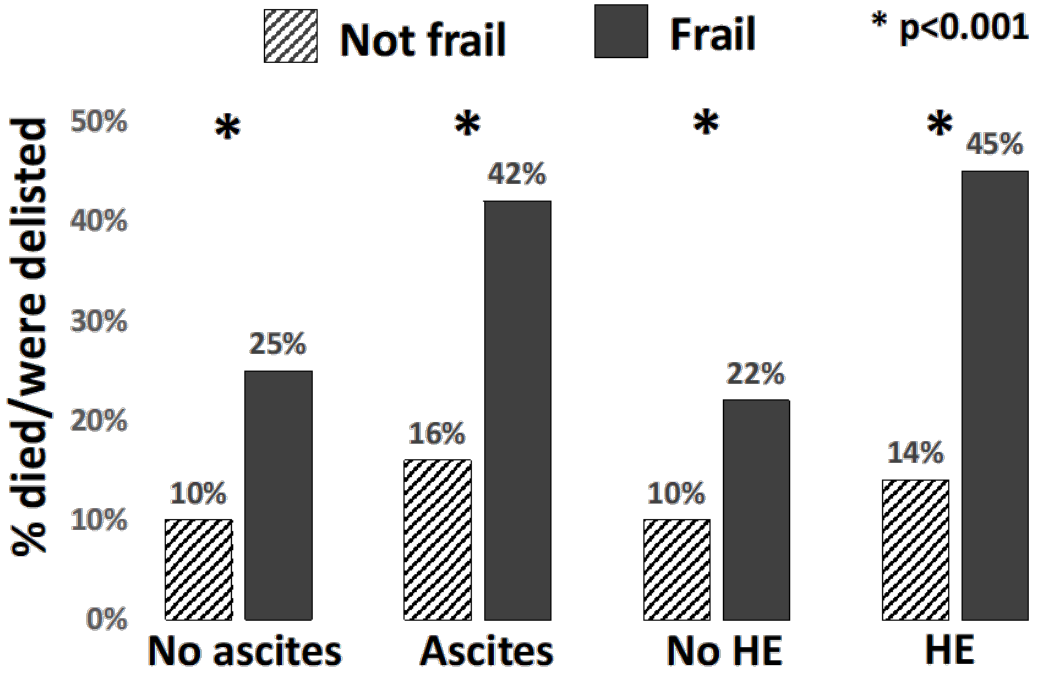
To investigate the relationship between physical frailty and ascites/hepatic encephalopathy (HE)

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

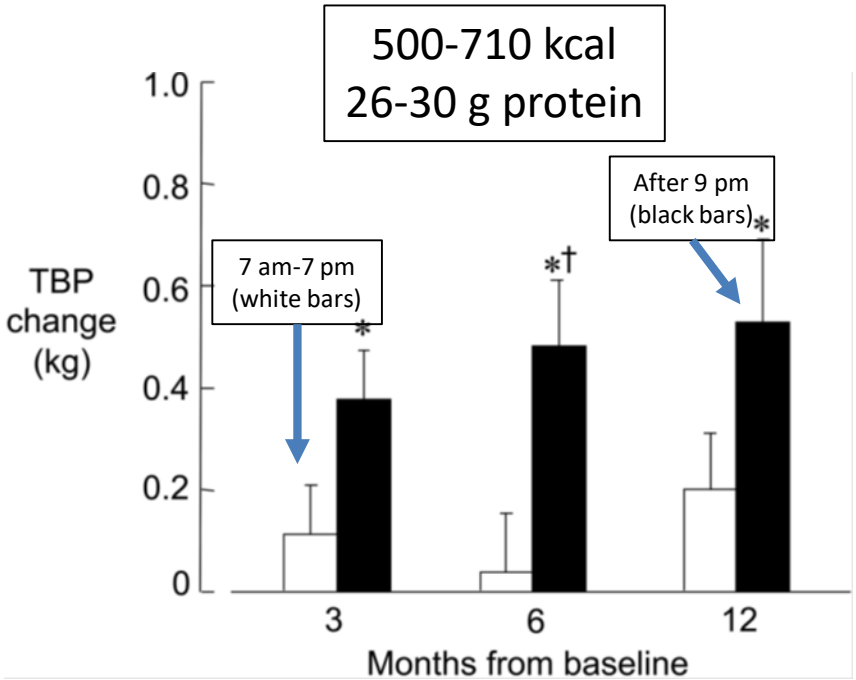
Frail = LFI >/= 4.5

https://liverfrailtyindex.ucsf.edu/

LFI = (–0.330 x gender adjusted grip strength) + (-2.529 x number of chair stands per second + (–0.040 x balance time) + 6

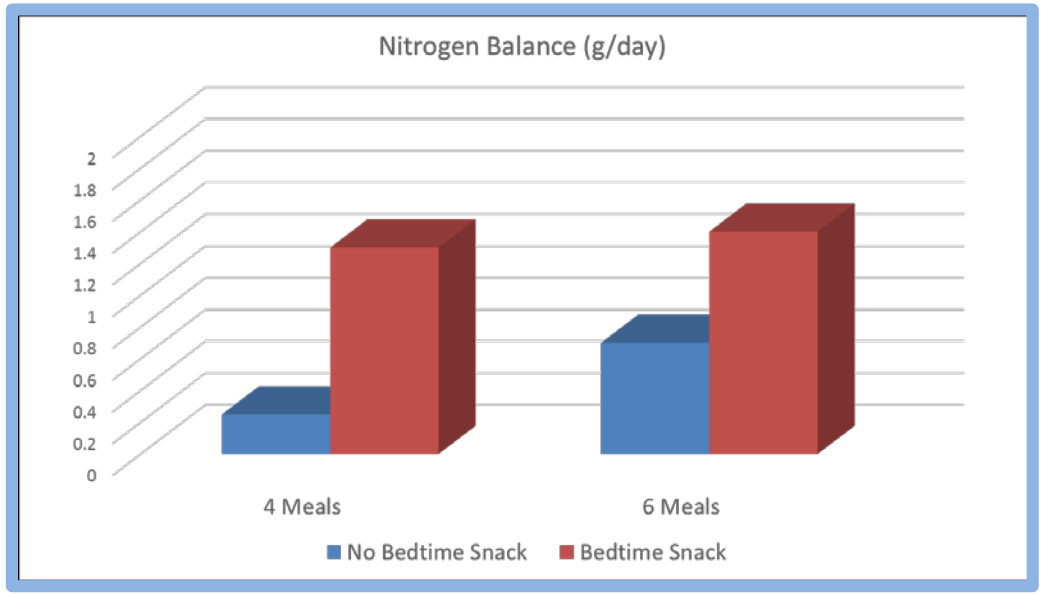
Nutrition in Cirrhosis

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



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

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

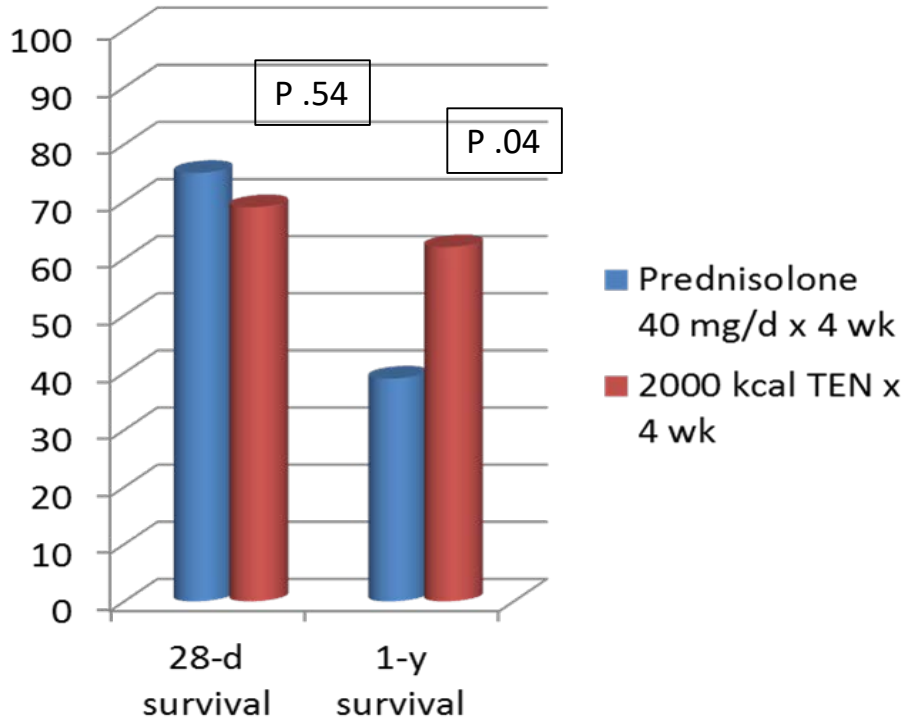


Bedtime Supplement is more important than Frequent meals

Nutrition in Alcoholic Hepatitis

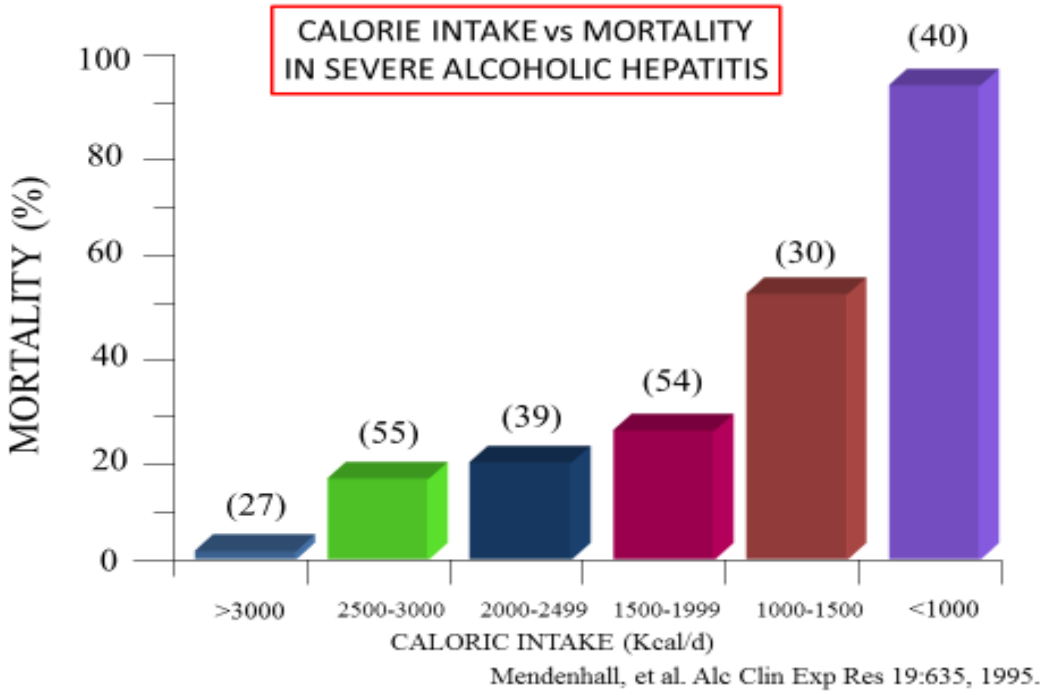
Enteral Nutrition in Alcoholic Hepatitis

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

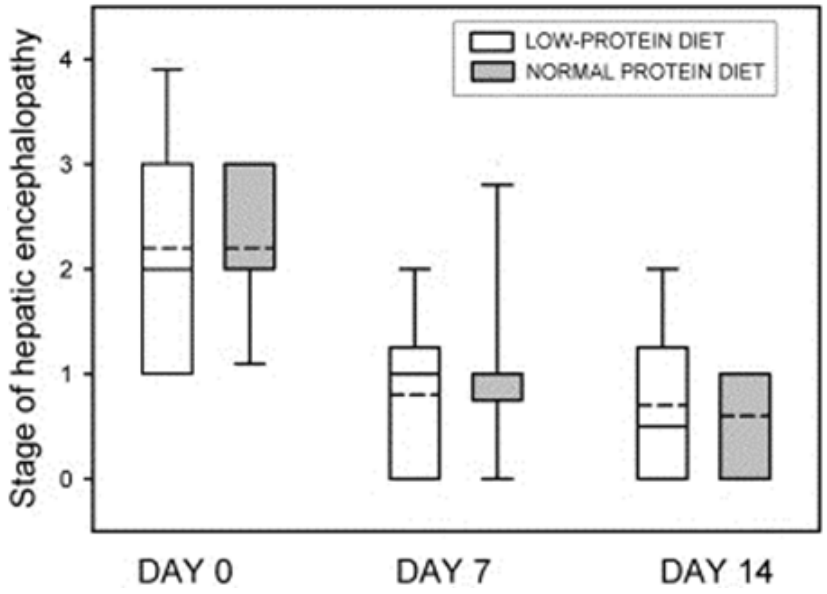


In Severe AH, the mortality is lower in patients with high calorie intake

Nutrition in Hepatic Encephalopathy

Low- vs Normal-Protein Diet in HE

Cordoba J; J Hepatol 2004;41:38–43

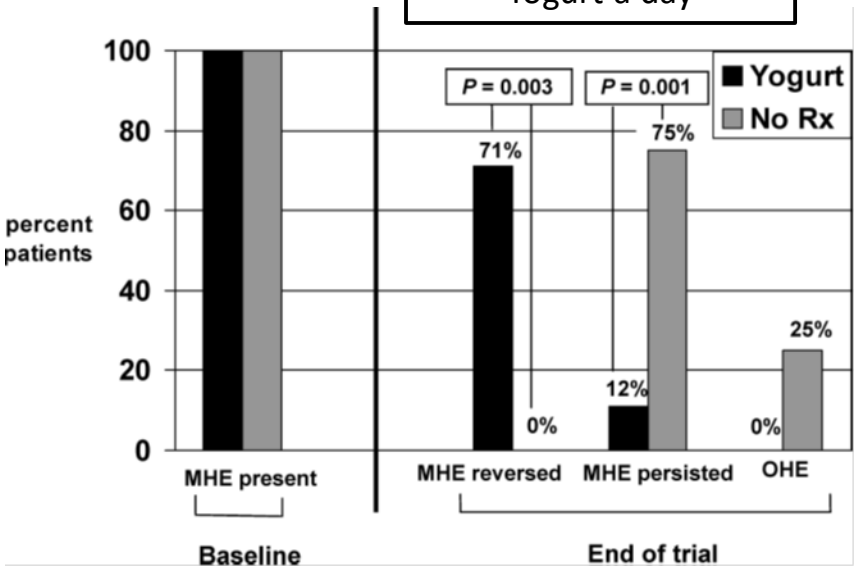


Diet with "normal protein intake" improves HE equally as "low protein" diet

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

Improving Nutrition in Cirrhosis

Recommendation

- **Calories:** 35-40 kcal/kg of ideal body weight/day (ESPEN; Clinical Nutrition 2006;25: 285–294) (Bemeur AP et al; Hepatology. 2013 Jul;58(1):325-36).
  - 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

Grade	Symptoms
0 (Minimal)	No detectable changes in behavior or personality[1]
1	Euphoria or anxiety[2] Impaired performance of addition[2] Shortened attention span[2] Trivial lack of awareness[2]
2	Minimal disorientation to time or place[2] Inappropriate behavior[2] Impaired performance of subtraction[2] Lethargy or apathy[2] Subtle personality change[2]
3	Confusion[2] Gross disorientation[2] Somnolence to semistupor (may respond to verbal stimuli)[2]
4	Coma (no response to verbal or noxious stimuli)[2]

HE = hepatic encephalopathy.

1. Mullen et al. *Semin Liver Dis*. 2007;27(suppl 2):32-48. **2.** Ferenci et al. *Hepatology*. 2002;35:716-721.

Types (by Cause)

- **Type A: A**cute Liver Failure
- **Type B:** Large Spontaneous or Post-traumatic Portal-Systemic **B**y-pass (normal liver)
  - Uretero-Sigmoid anastomosis.
- **Type C: C**irrhosis; 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.

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)

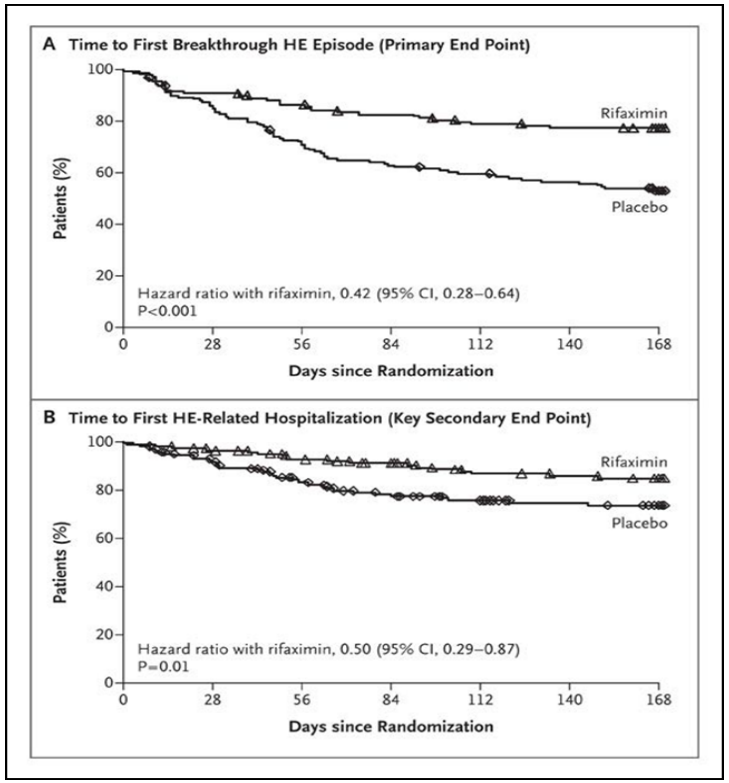
Mechanism of Action of Therapies for HE

- **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 NH_4^+ to NH_3 and the passage of 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.

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.

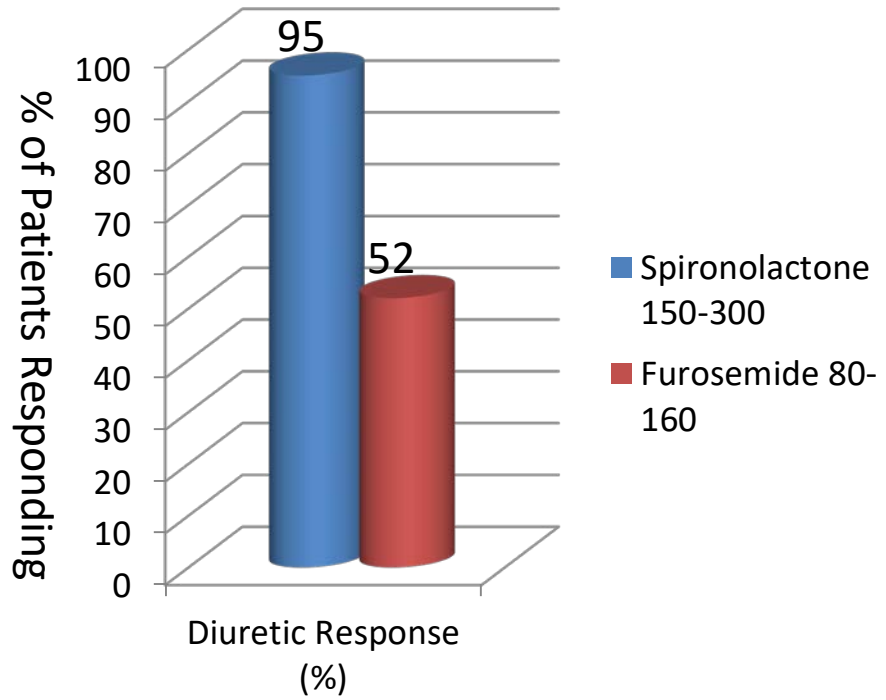
Ascites Management

- 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

Spironolactone vs furosemide in Cirrhotic Ascites

Perez-Ayuso RM; Gastroenterology 1983;84:961-968



Spironolactone is superior to Furosemide in controlling ascites

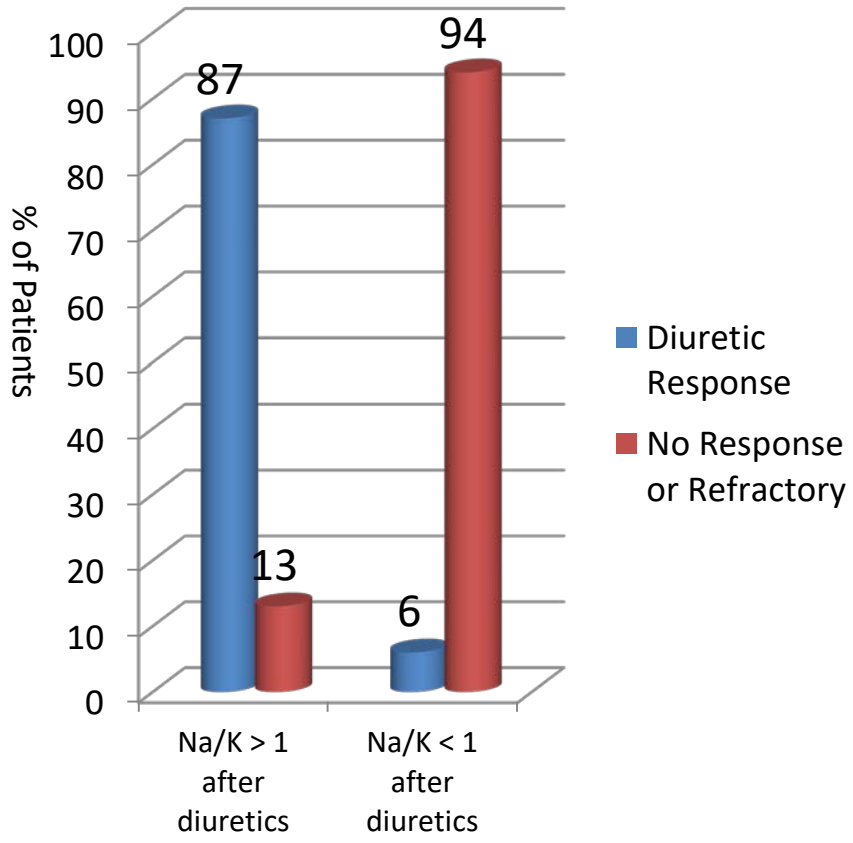
Diuretic Titration

- 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.

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.

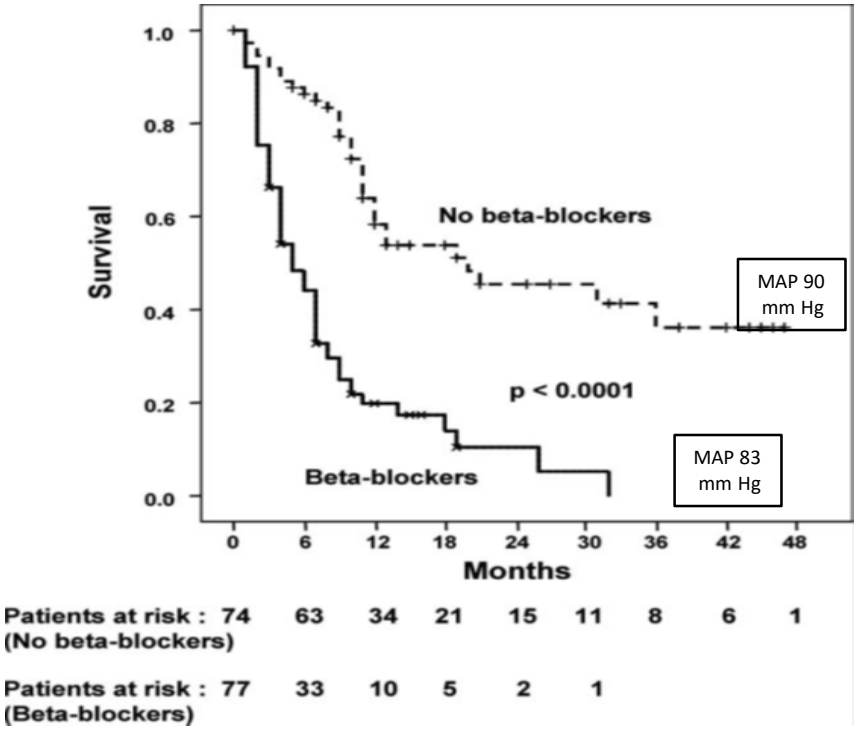
Refractory Ascites
What We Know

- 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:
  - **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.
  - Preliminary data: Rifaximin increases SVR, GFR, and Natriuresis; also decreases portal HTN (Kalambokis GN; Clin Gastroenterol Hepatol. 2012 Jul;10(7):815-8; Vlachogiannakos J; J Gastroenterol Hepatol. 2013 Mar;28(3):450-5).

Ascites & Refractory Ascites

Effect of Beta-blockers in Refractory Ascites

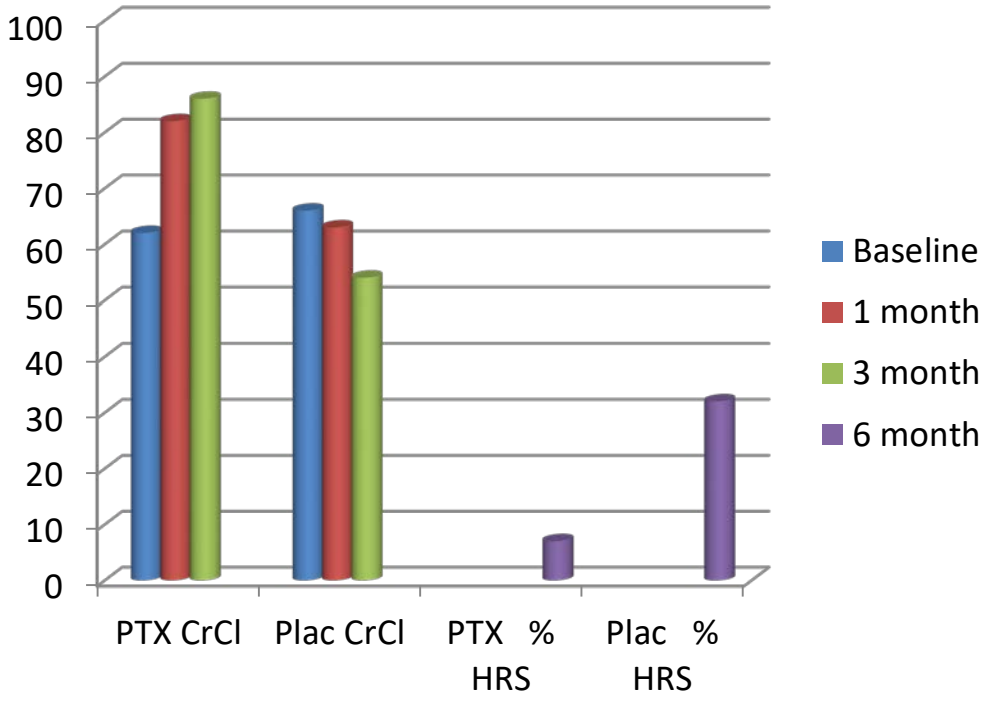
Serste T; Hepatology 2010;52(3):1017-1022



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

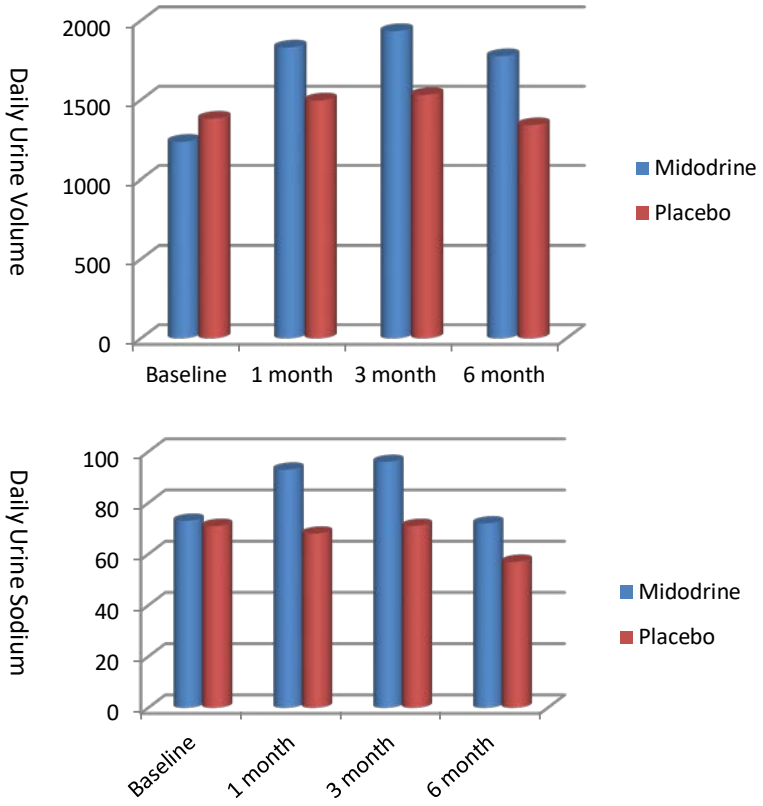


In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS

Ascites & Refractory Ascites

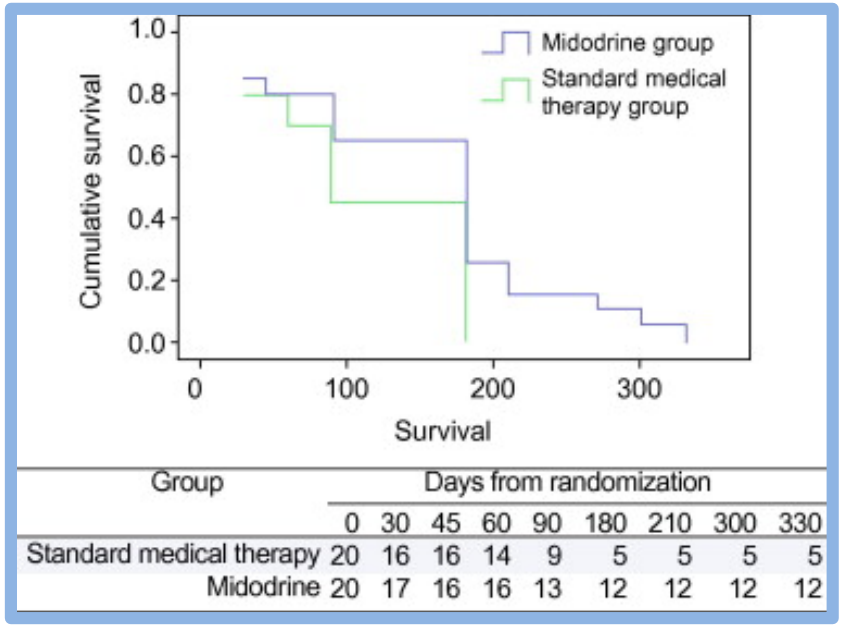
Midodrine in Refractory/Recurrent Ascites

Singh V; Journal of Hepatology 2012; 56:348–354



Midodrine in Refractory/Recurrent Ascites

Singh V; Journal of Hepatology 2012; 56:348–354



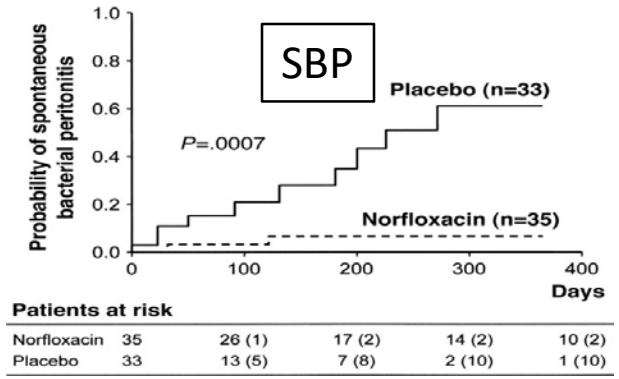
Group	Days from randomization								
	0	30	45	60	90	180	210	300	330
Standard medical therapy	20	16	16	14	9	5	5	5	5
Midodrine	20	17	16	16	13	12	12	12	12

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

Ascites & Refractory Ascites

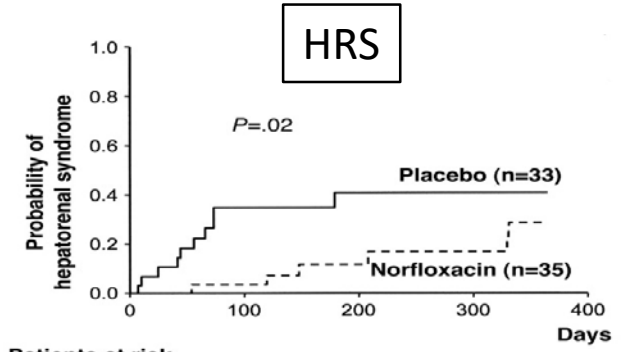
Norfloxacin SBP prophylaxis in ascites with either bili > 3, or creat > 1.2, or Na < 130

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



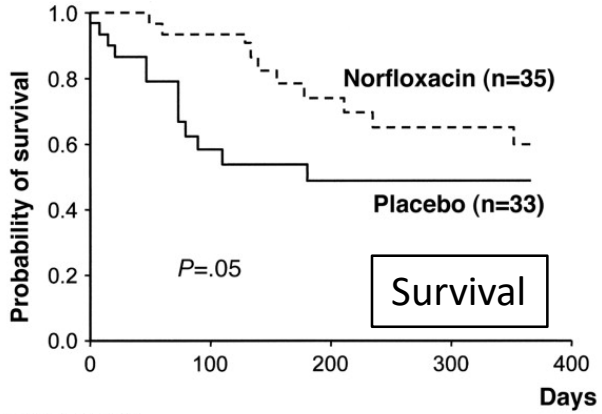
Patients at risk

Norfloxacin	35	26 (1)	17 (2)	14 (2)	10 (2)
Placebo	33	13 (5)	7 (8)	2 (10)	1 (10)



Patients at risk

Norfloxacin	35	26 (1)	17 (3)	14 (4)	10 (6)
Placebo	33	13 (9)	7 (10)	2 (10)	1 (10)



Patients at risk

Norfloxacin	35	26 (2)	17 (7)	14 (9)	10 (10)
Placebo	33	13 (11)	7 (13)	2 (13)	1 (13)

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

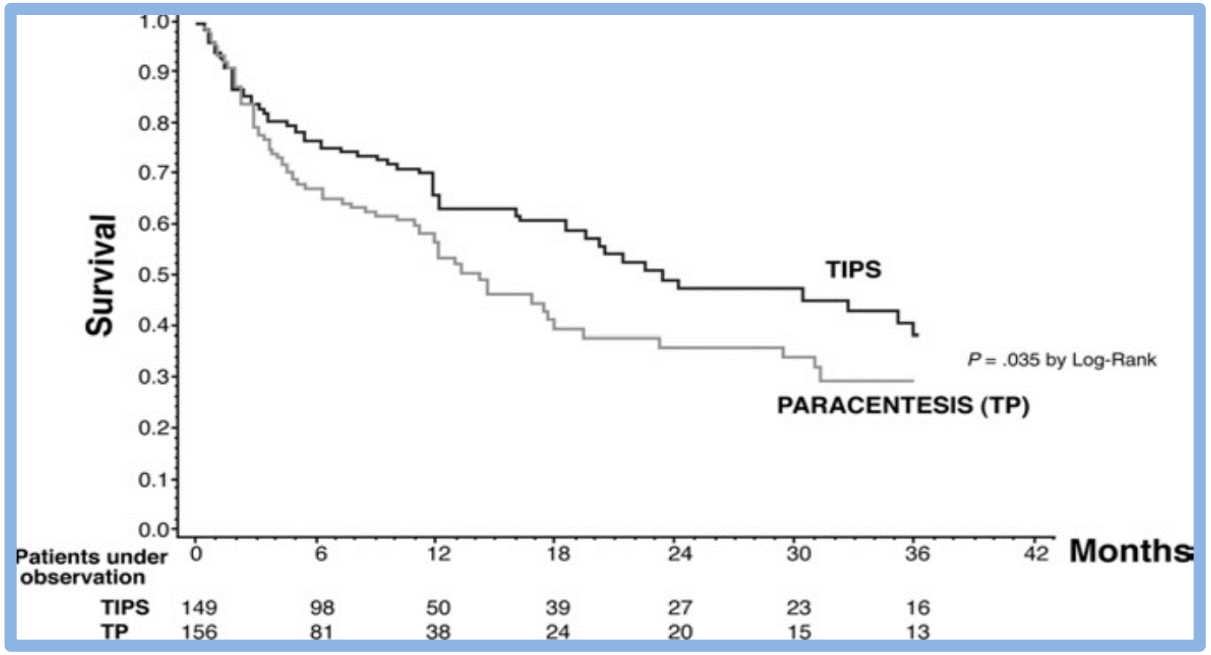
Refractory Ascites

- 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

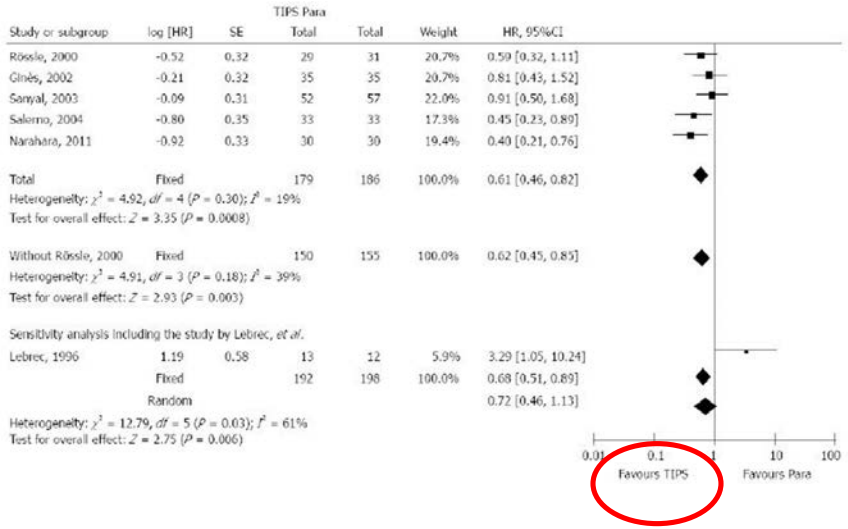


Survival was higher with TIPS than with LVP up to a MELD of 20

Bili >/= 3, Age > 60 and Na </= 130 increases the risk of complications

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

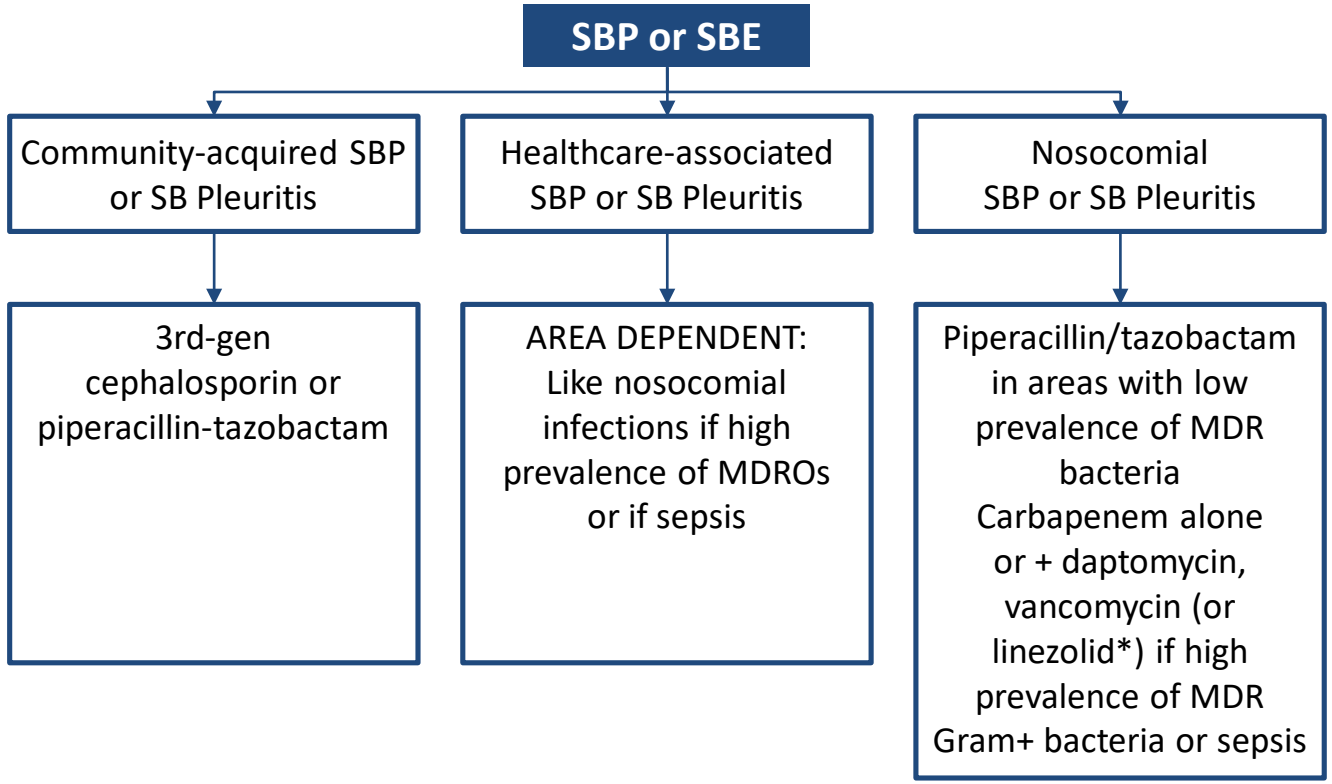


TIPS improves Transplant-free Survival in Refractory Ascites

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; 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)



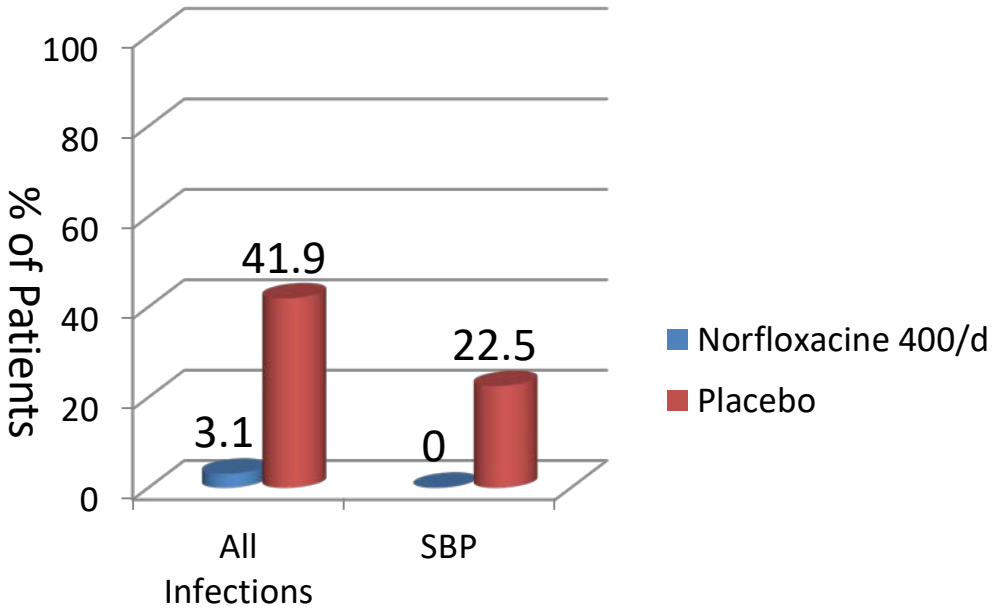
*In areas with a high prevalence of vancomycin-resistant enterococci

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

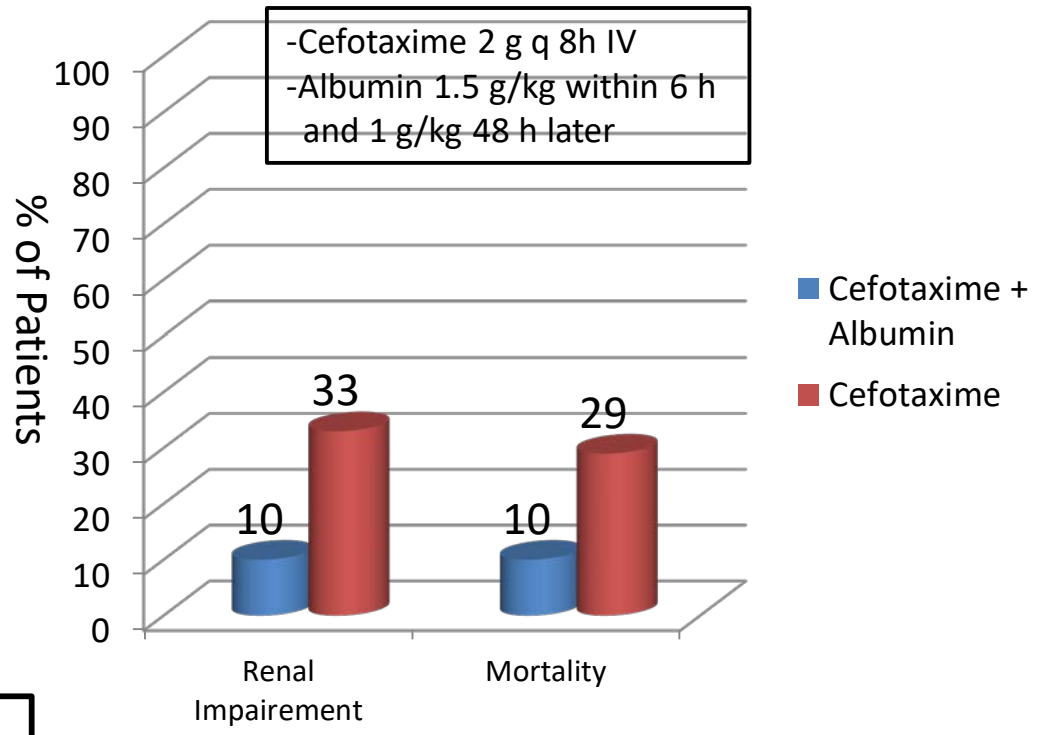
Spontaneous Bacterial Peritonitis (SBP)

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



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

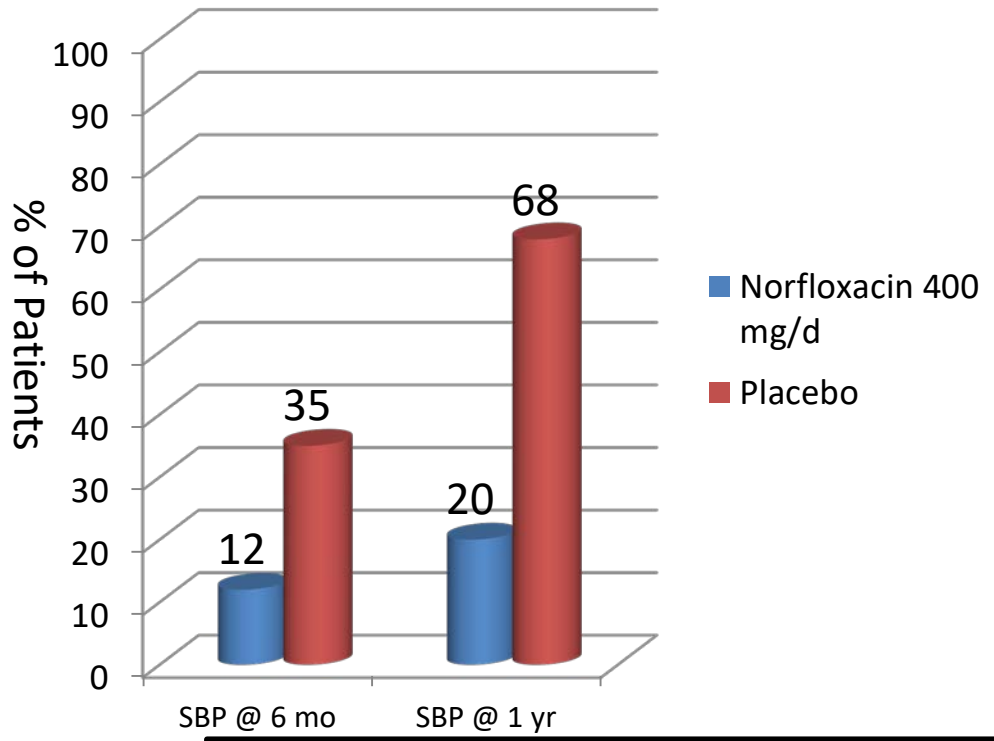
Effect of albumin in azotemia and mortality in SBP
Sort P; N Engl J Med 1999; 341:403-409



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

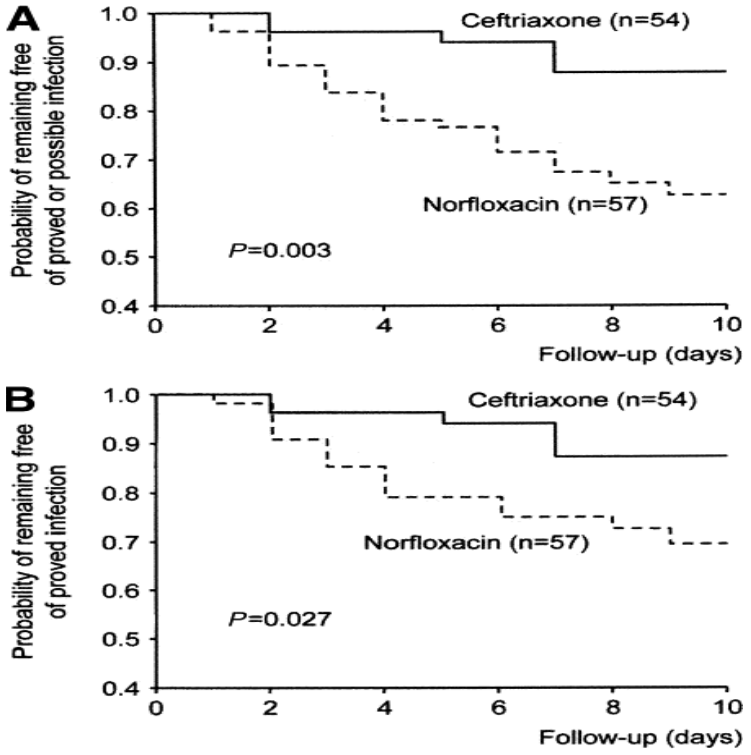
Complications of Cirrhosis

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



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

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.

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 </= 1.5 g/dL, Norfloxacin 400 mg/d is indicated during the hospital stay.

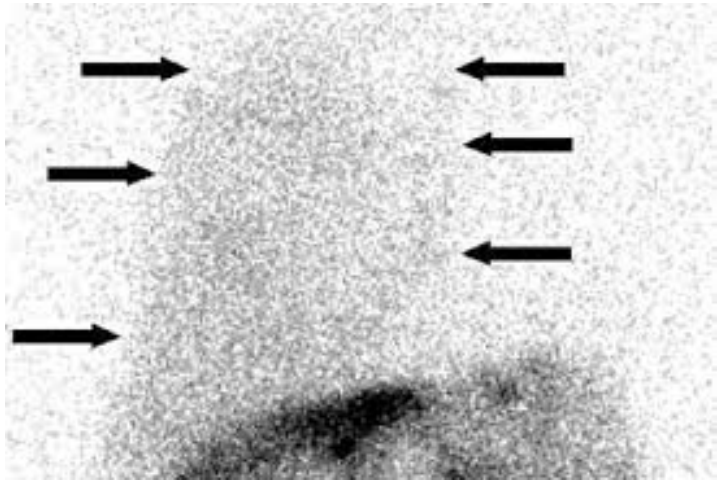
SBP
Prophylaxis and Management

- 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.

Chest scan after partial thoracentesis and injection of the radionucleide in abdomen

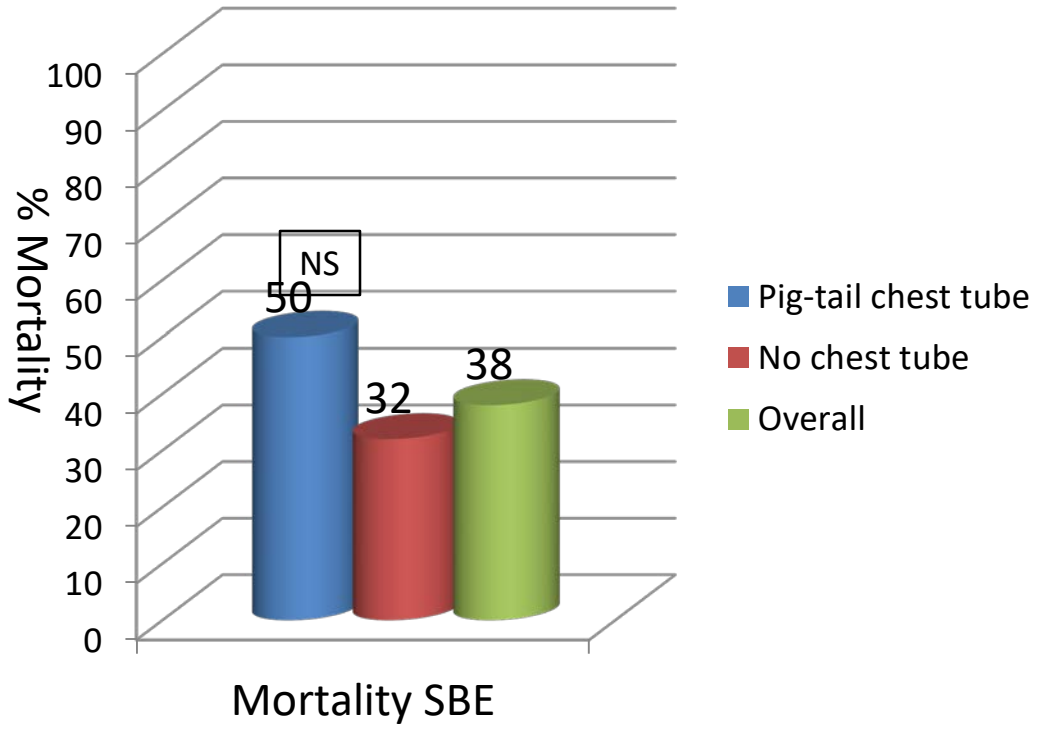


Spontaneous Bacterial Pleuritis

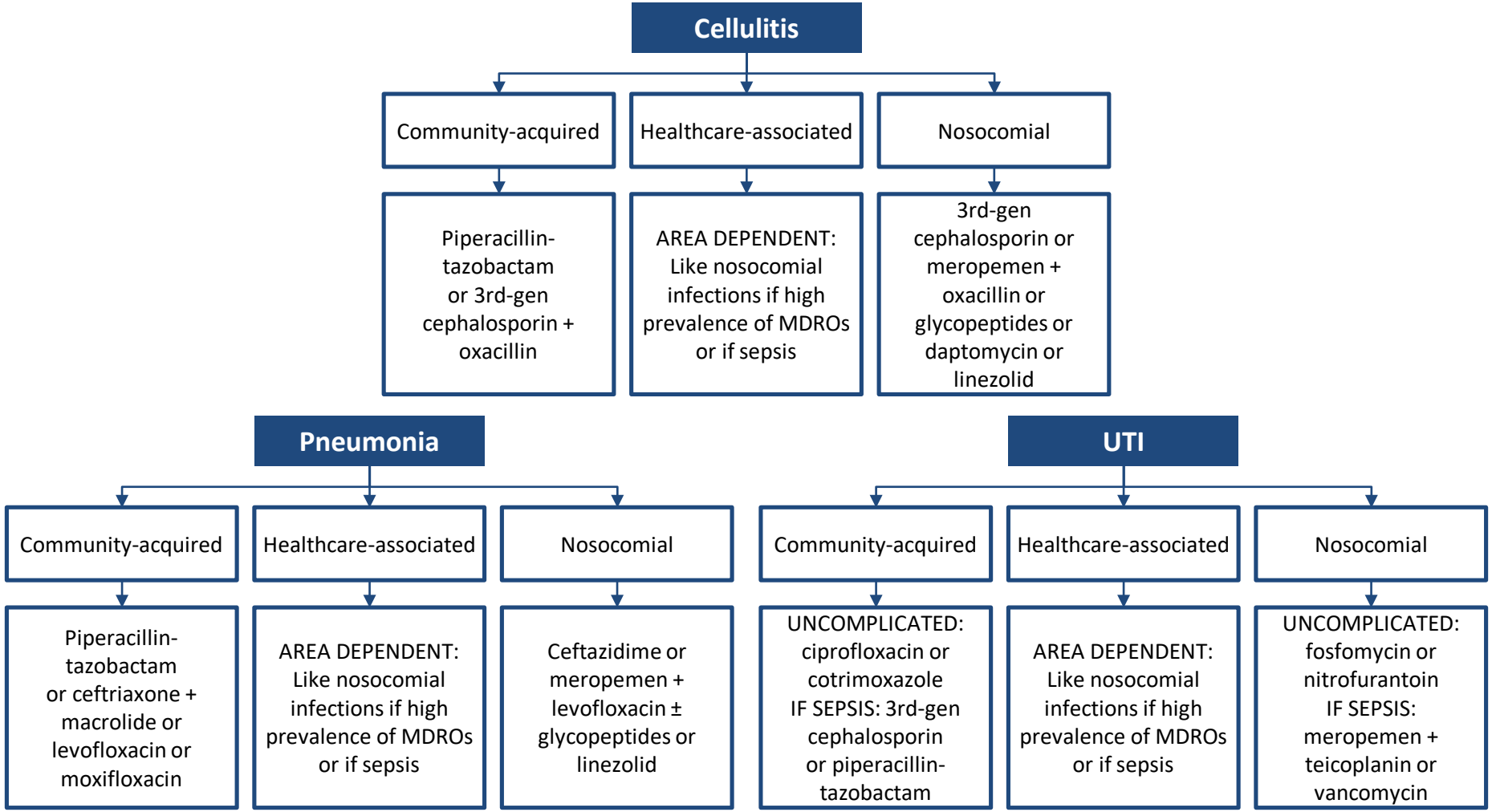
SB Empyema – What we know

- 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/mm^3 plus a (+) culture, or
  - PMN count > 500/mm^3, 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



Other infections: recommended empirical antibiotic treatment



Adapted from Jalan R, et al. J Hepatol 2013;60:1310–24;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

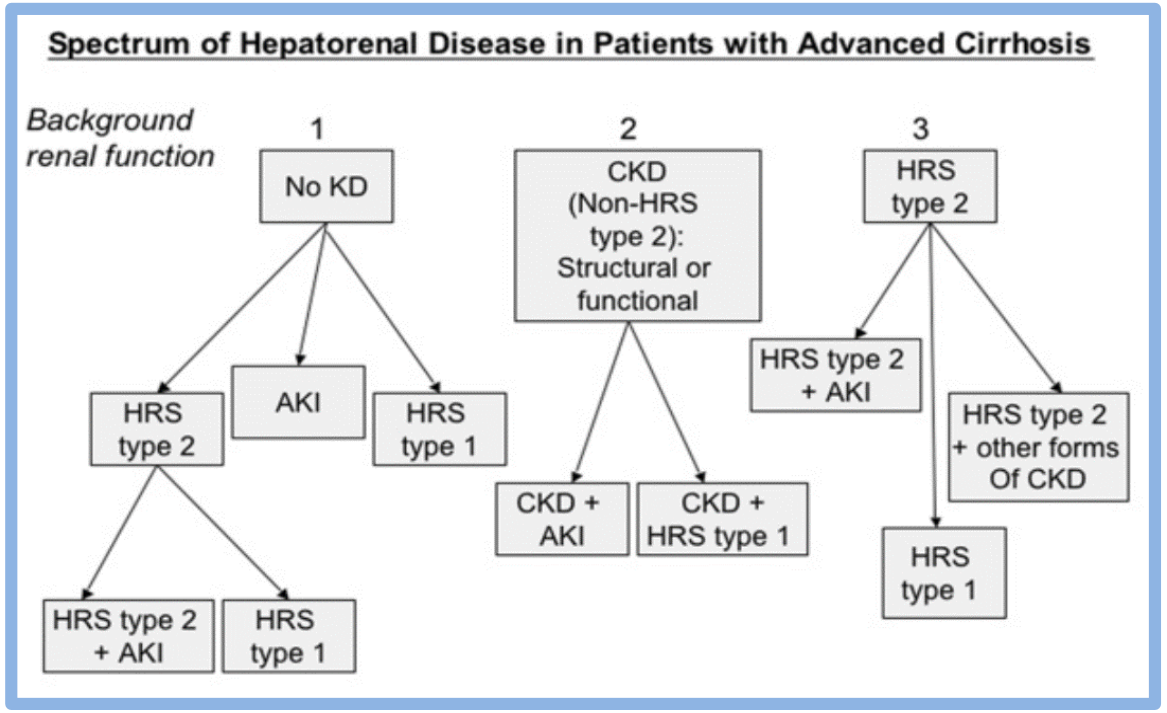
AKI in Cirrhosis

Staging System for AKI According to AKIN

AKI Stage	Serum Creatinine criteria	Urine output criteria
1	-Increase in serum creatinine >/= 0.3 mg/dL, or -Increase to >/= 150% to 200% from baseline	-Urine output 0.5 mL/kg/h for > 6 h (-No HRS)
2	-Increase of serum creatinine to more than 200% to 300% from baseline	-Urine output < 0.5 mL/kg/h for > 12 h (-Many have HRS-2)
3	-Increase of serum creatinine to > 300% from baseline, or -Serum creatinine >/= 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)

Spectrum of Hepatorenal Disorder in Cirrhosis.

Critical Care 2012, 16:R23



HRS is one type of AKI in Cirrhosis

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

Diagnostic Criteria for HRS type AKI

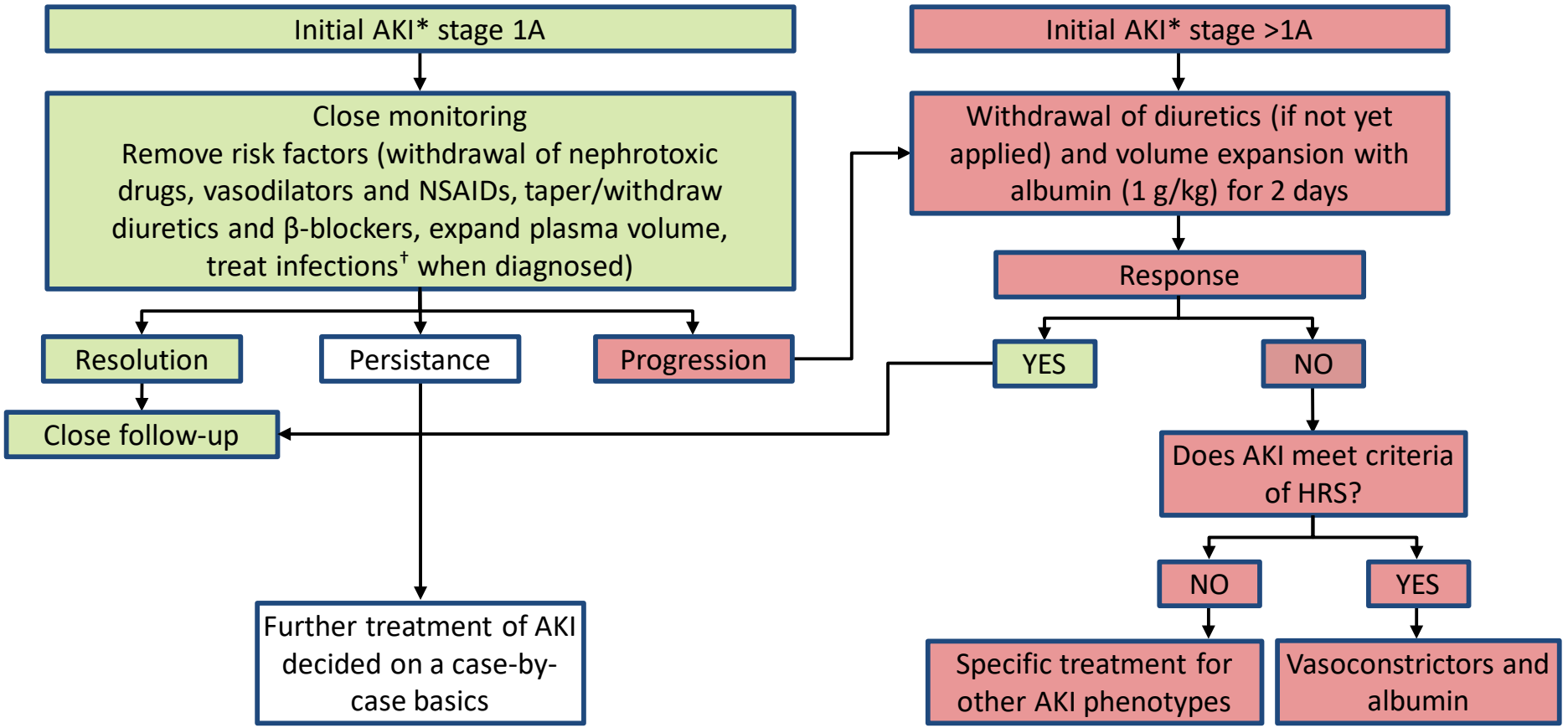
Journal of Hepatology Volume 62, Issue 4, April 2015, Pages 968–974

- Diagnosis of cirrhosis and ascites.
- Diagnosis of AKI by International Club of Ascites (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

ICA management algorithm for AKI in cirrhosis

- Investigation and management should begin immediately

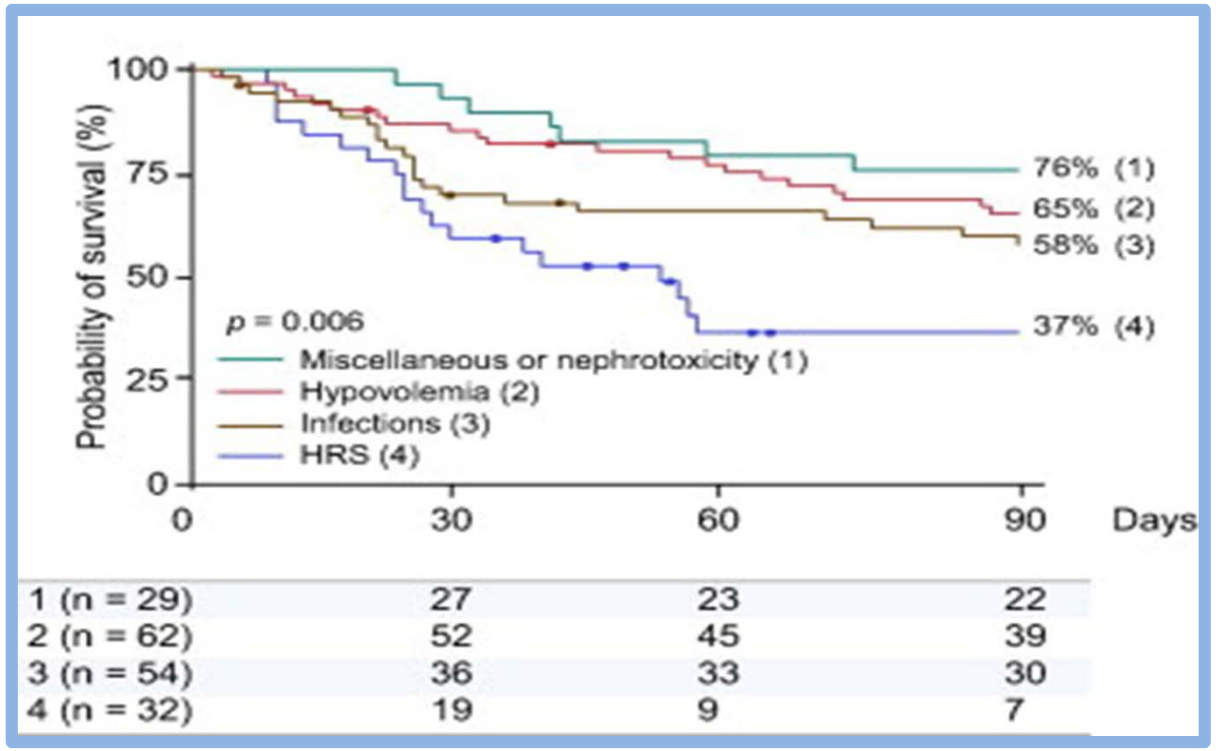


*Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria;
†Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines
Adapted from Angeli P, et al. J Hepatol 2015;62:968–74;
EASL CPG decompensated cirrhosis. J Hepatol 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



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

Association of AKI with in-hospital mortality in Hospitalized Cirrhotics

Belcher JM et al. Hepatology 2013; 57:753-762

Initial Stage	Evolution (%)		Mortality (%)
AKI-1 (no HRS)	*No Progression*	*(53%)*	*2*
	Progression to AKI-2	(19%)	**29**
	Progression to AKI-3	(11%)	**50**
	Progression needing Dialysis	(17%)	**56**
AKI-2 (many HRS-2; few HRS-1)	*No Progression*	*(54%)*	*7*
	Progression to AKI-3	(19%)	**18**
	Progression Needing Dialysis	(27%)	**60**
AKI-3 (many HRS-1)	**No Progression**	(67%)	**21**
	Progression needing Dialysis	(33%)	**71**

Progression of AKI worsens Mortality; Early Intervention is Critical

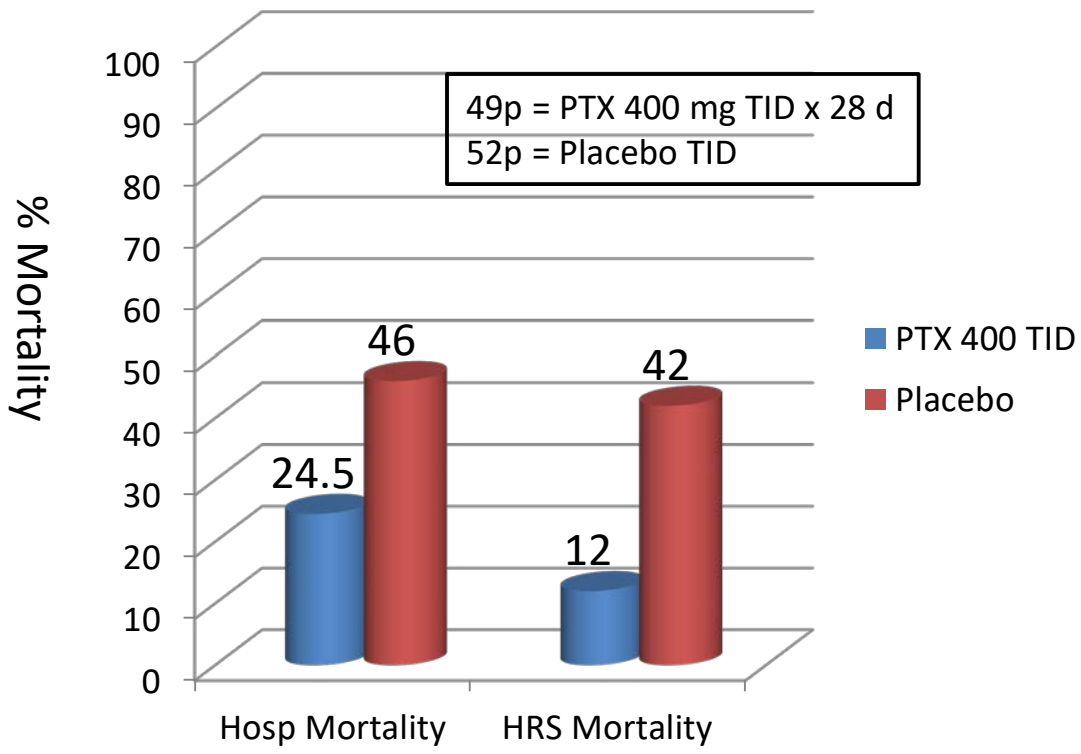
Hepatorenal Syndrome
What we know

- **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).
- **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

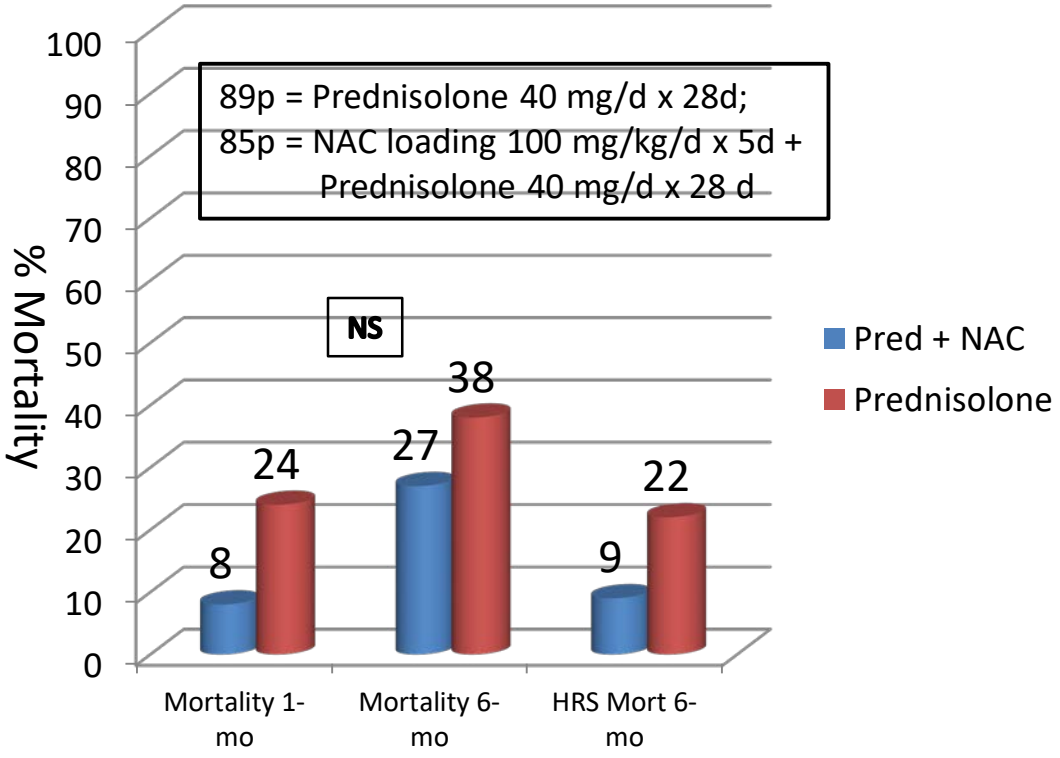
Akriviadis E; Gastroenterology 2000 Dec;119(6):1637-48



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

Prednisolone + NAC in Severe Alcoholic Hepatitis

Nguyen-Khac E; N Engl J Med 2011; 365:1781-1789



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

Hepatorenal Syndrome
What we know

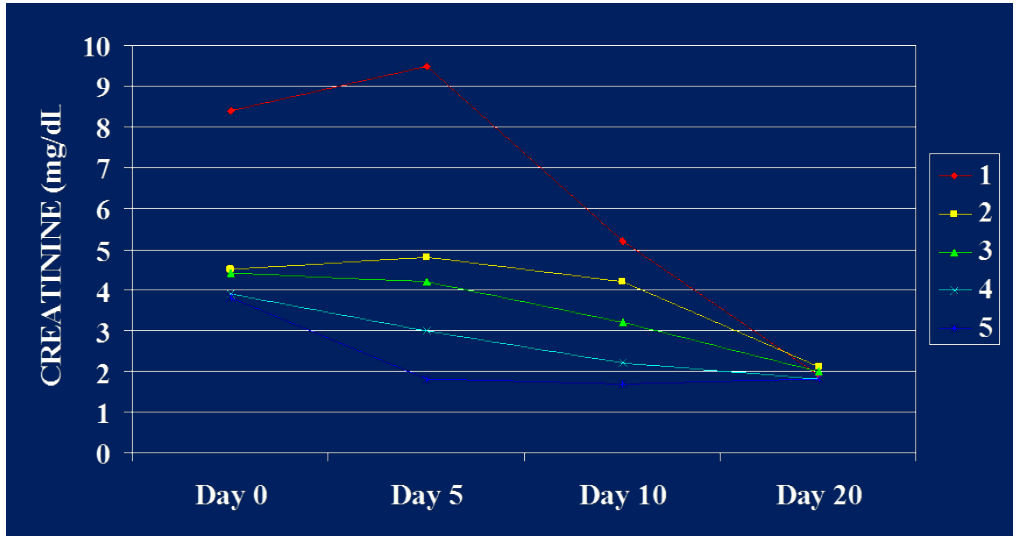
- HRS type I and II can be treated with volume expansion plus vasopressors;
  - high dose IV NAC also has been reported to be effective.
- Successful treatments have been published with:
  - Ornipressin + Albumin (Guevara M; HEPATOLOGY 1998;27:35-41).
  - N-Acetylcysteine intravenous (Holt S; Lancet 1999;353(9149):294-295).
  - Midodrine + Octreotide + Albumin (Angeli P; HEPATOLOGY 1999;29:1690-1697) and (Esrailian E; Dig Dis Sci 2007;52:742-748).
  - Noradrenaline + Albumin (Duvoux C; Hepatology 2002;36:374-380).
  - Terlipressin + Albumin (Martín-Llahí M; GASTROENTEROLOGY 2008;134:1352–1359) (Sanyal AJ; Gastroenterology 2008;134(5):1360-8).
- 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 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

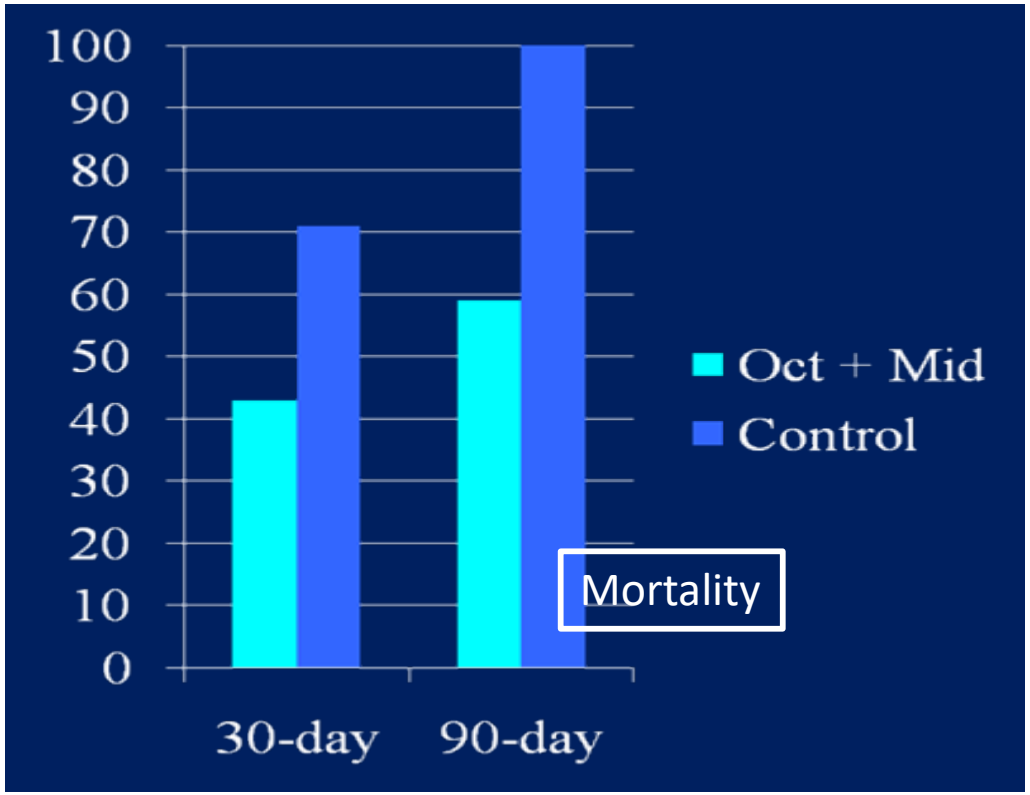
Midodrine 7.5-15 mg po TID +
Octreotide 100-200 mcg SQ TID
5 patients with HRS-1
Responders reached MAP = 95



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

Octreotide + Midodrine + Albumin in HRS-I

Esrailian E; Dig Dis Sci 2007;52:742-748



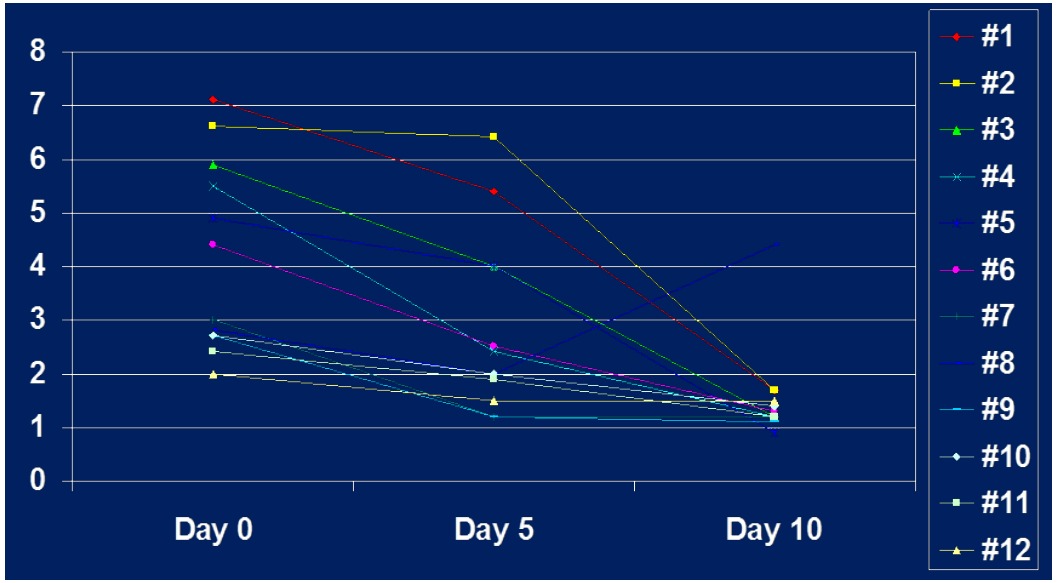
Octreotide + Midodrine decrease 1 & 3-month mortality in HRS-1

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

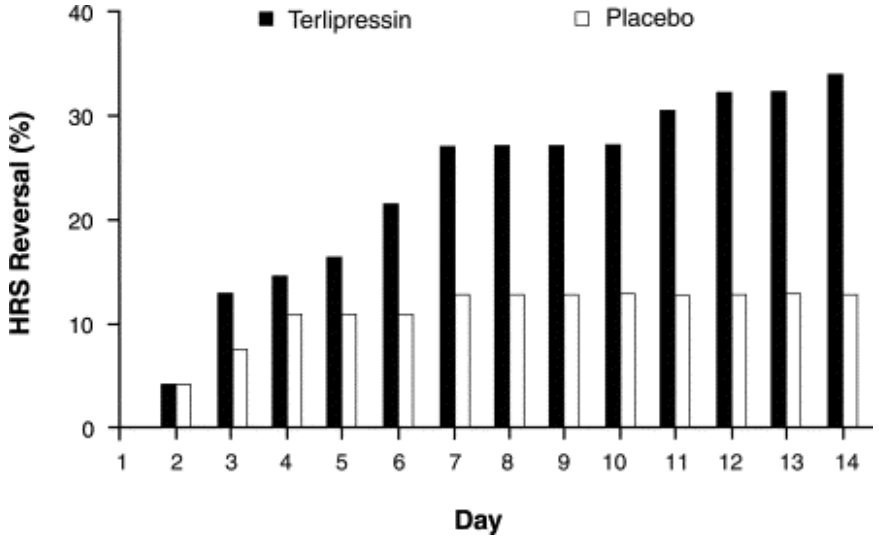


Noradrenaline + Albumin takes up to 10 days to work

Terlipressin + Albumin 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

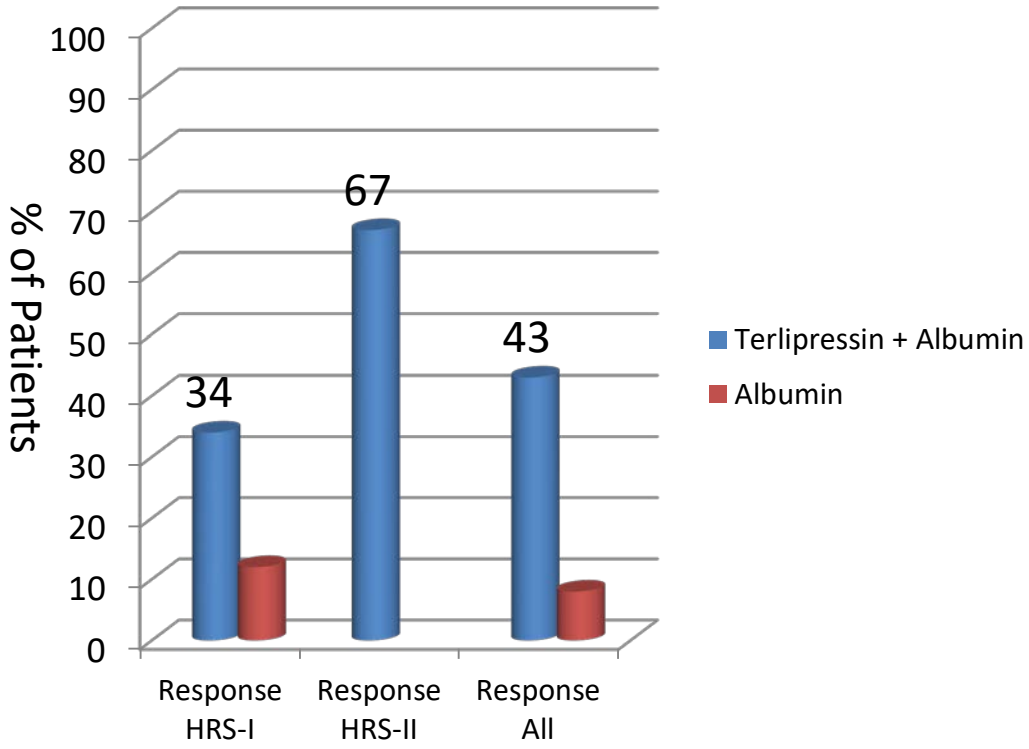


Terlipressin + Albumin takes up to 2 weeks to work

Treatment of Hepatorenal Syndrome

Terlipressin + Albumin vs Albumin in HRS

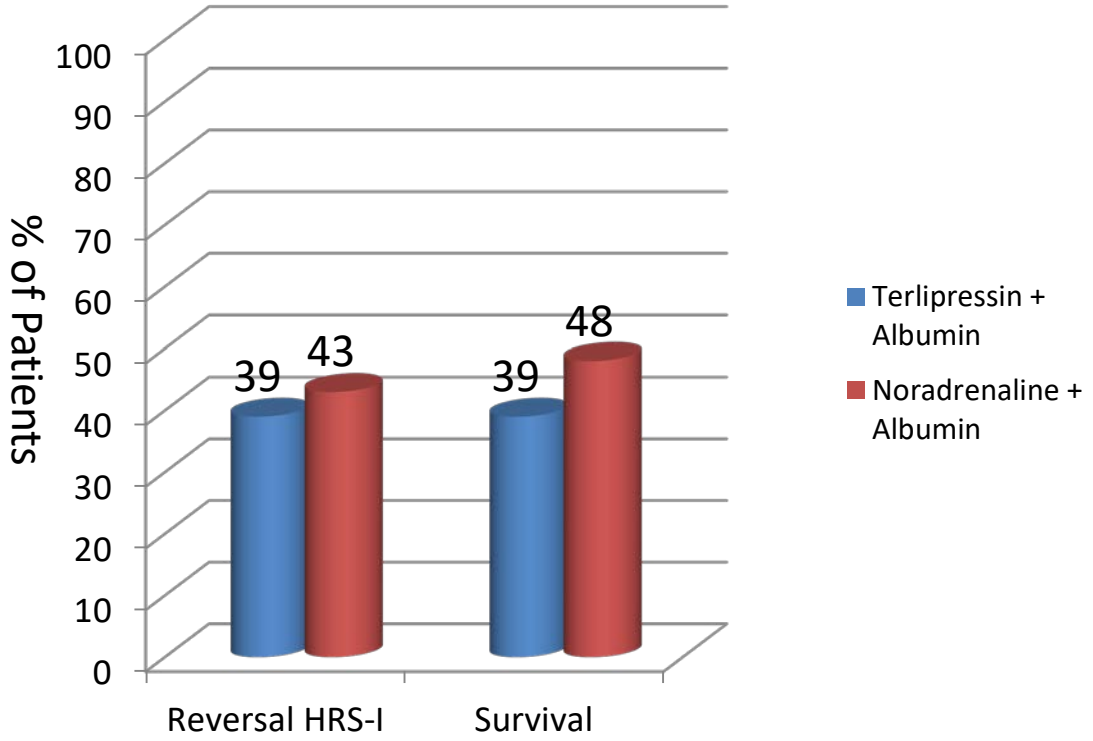
Sanyal AJ; Gastroenterology 2008;134(5):1360-8



HRS-II responds better than HRS-I

Terlipressin vs Noradrenaline in HRS-I

Singh V; J of Hepatology 2012;56;1293–1298



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.
- Doing a TIPS after drug-reversal of HRS maintains the response (Wong F; Hepatology 2004;40(1):55-64).
  - 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

- 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 a MAP of 85 mmHg.
  - Continue until creatinine is </= 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 Somatostanine IV for 5 days decrease rebleeding rate after variceal bleed (Corley DA; GASTROENTEROLOGY 2001;120:946-954).

Acute Esophageal Variceal Bleed Recommendations

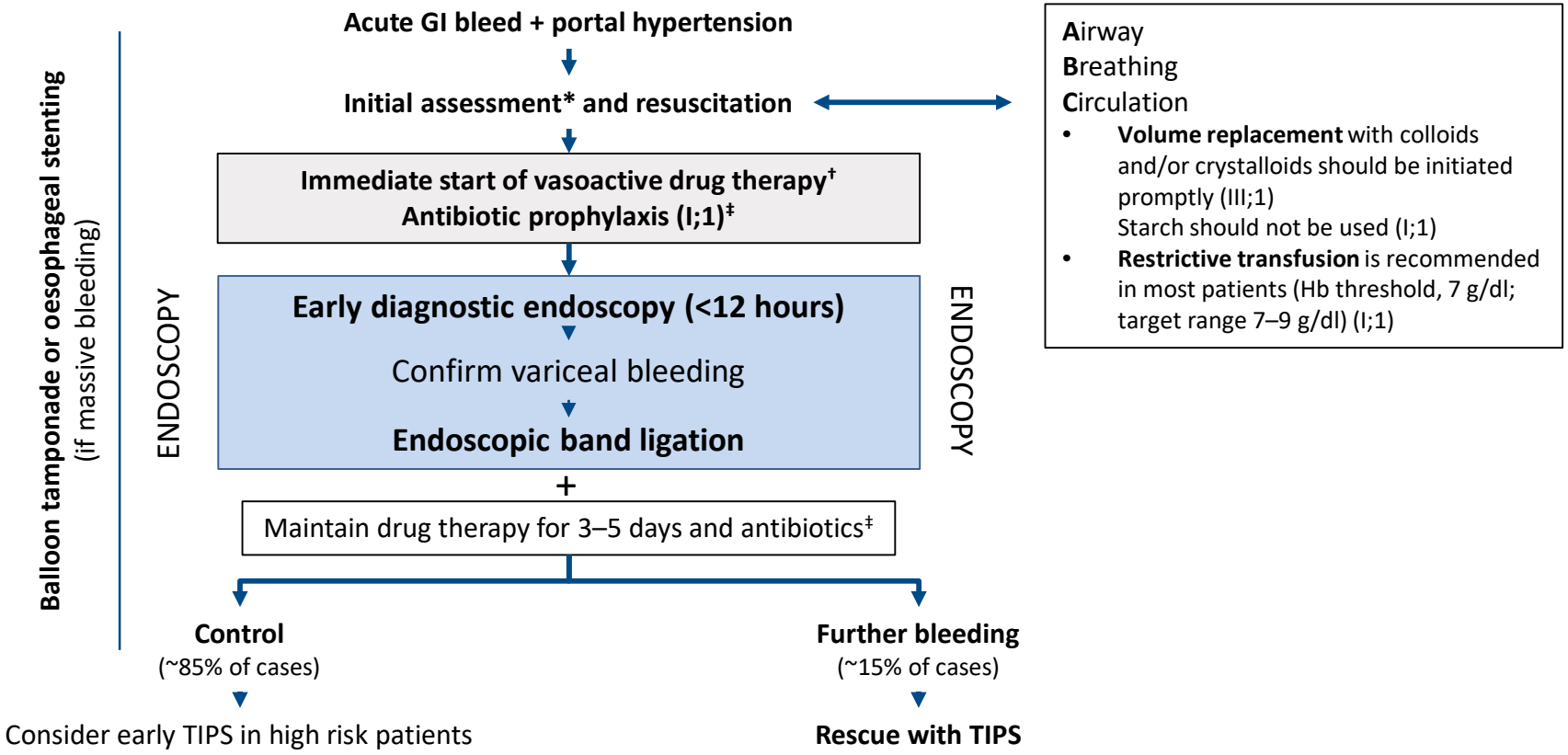
- Correct hypovolemia with IV crystalloids and albumin.
- Start immediately Ceftriaxone 1 g/day for 7 days.
- Start immediately Octreotide 50 mcg bolus + 50 mcg/h x 5 days (can be D/C early after TIPS or adequate beta-blockade).
- Do early EGD to treat in all, and also to detect active bleeding in Child-Pugh 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



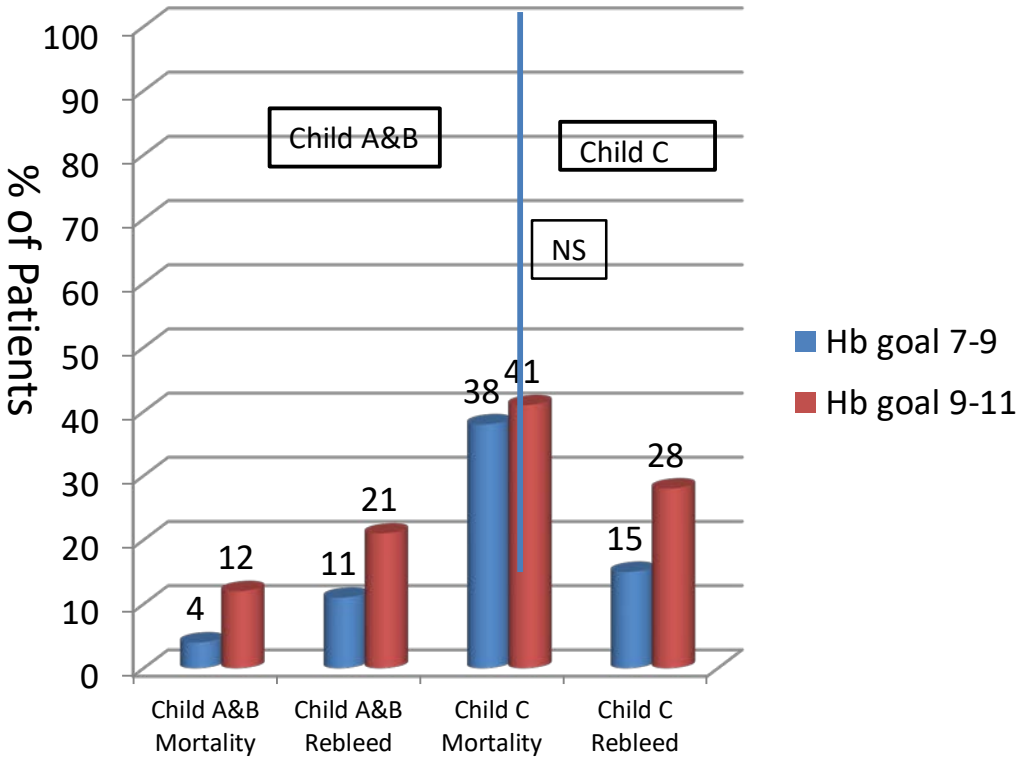
*History, physical and blood exam, cultures; †Somatostatin/terlipressin; ‡Ceftriaxone (1 g/24 hours) is the first choice in patients with DC, those already on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections. Oral quinolones (norfloxacin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

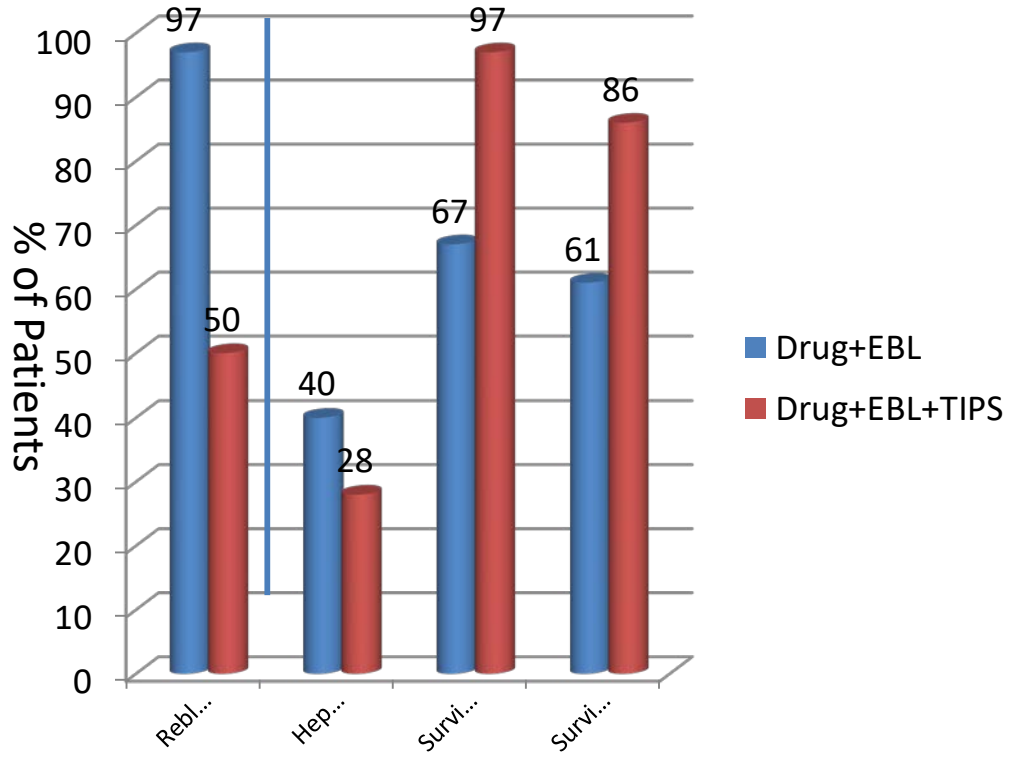
Villanueva C; N Engl J Med 2013; 368:11-21



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

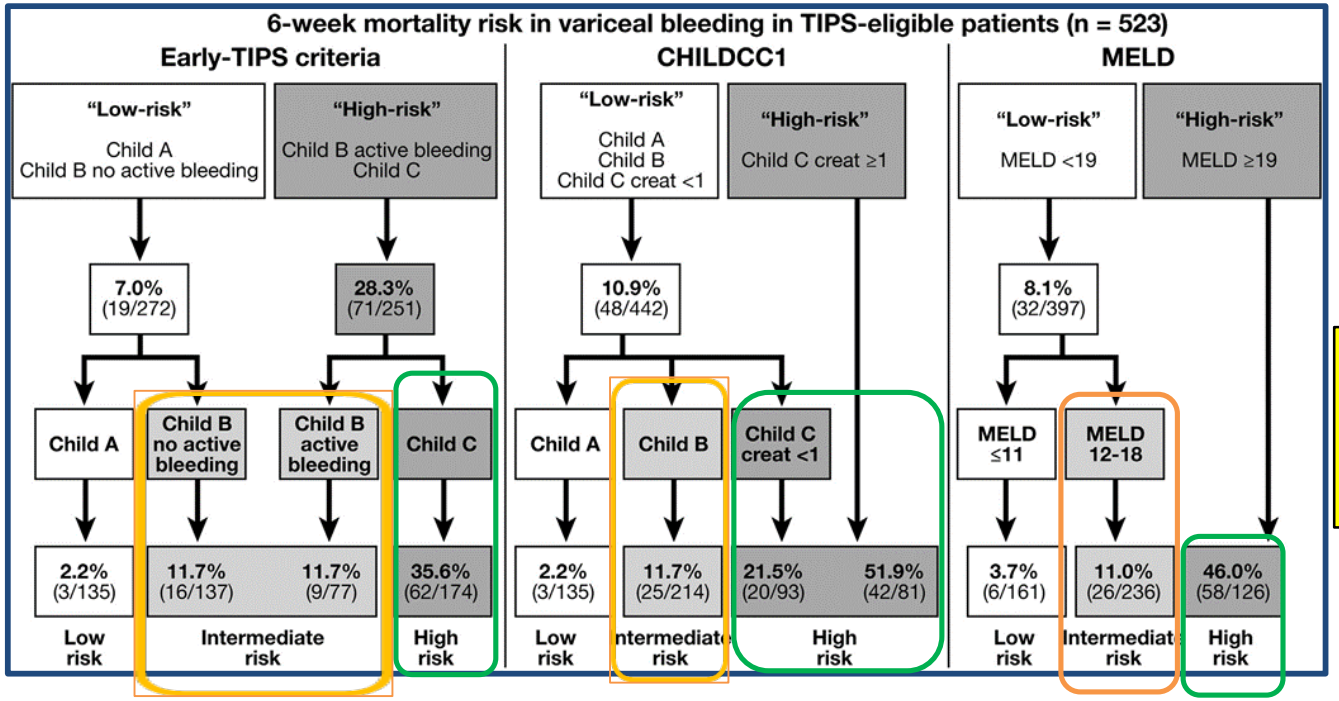
Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379



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

Mortality (6-weeks) in Acute Variceal Bleeding without Early TIPS

Clinical Gastroenterology and Hepatology 2018;16:132–139



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 Clínic Liver Cancer staging system stages C or D, and no portal thrombosis.

No TIPS if:
Creat >/= 3 mg/dL,
or
Child-Pugh >/= 14

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

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
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 studied well for secondary prophylaxis.

Thank you for your attention

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

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

*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

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

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

Recommendation	Grade of evidence	Grade of recommendation
ECG in patients with cirrhosis should be performed with dynamic stress testing* (systolic dysfunction may be masked by hyperdynamic circulation and reduced afterload) • Lack of increased CO after physiological/pharmacological stress† indicates systolic dysfunction	II-1	1
Myocardial strain imaging and assessment of GLS may be useful in the assessment of left ventricular systolic function in patients with DC	II-2	2
Cardiac MRI may identify structural changes	III	2
Diastolic dysfunction may occur as an early sign of CCM in the setting of normal systolic function, and should be diagnosed using ASE criteria: • Average E/e'>14 • Tricuspid velocity >2.8 m/s • LAVI >34 ml/m^2	II-1	1

*Either pharmacologically, or through exercise; †And in the absence of influence of β-blockade

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Cirrhotic cardiomyopathy

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

Recommendation	Grade of evidence	Grade of recommendation
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	II-1	1
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

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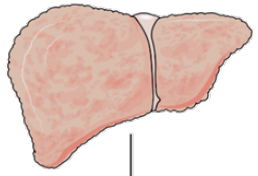
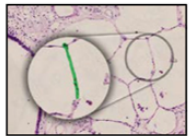
Pathogenesis of HPS

- Hepatic injury/failure
- Portal hypertension



- Portosystemic shunt
- Hyperdynamic circulation
- Bacterial translocation



Pulmonary capillary

Increased ET-1 release

Systemic inflammation

ET_B receptor

Endothelial cell

Endothelial activation of CX3CL1

CX3CL1

Endothelial cell

Increased adherence of macrophages/ monocytes to endothelial cells

Macrophage recruitment in the lungs

Macrophage

Increased eNOS expression and activity

Genetic factors

Endothelial cell

VFG-A release

Increased release of NO

Endothelial cell proliferation

Increased iNOS and HO expression and activity

ANGIOGENESIS

Increased NO and CO release

VASODILATION

HEPATOPULMONARY SYNDROME

VASODILATION

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

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

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Diagnosis of HPS

- In patients with portal hypertension and the clinical suspicion of HPS partial pressure of oxygen (PaO_2) in ABG should be assessed

Recommendation	Grade of evidence	Grade of recommendation
In patients with chronic liver disease, HPS should be suspected and investigated in presence of tachypnoea and polypnoea, digital clubbing and/or cyanosis	II-2	1
Screening in adults: • If pulse oximetry SpO_2 <96% – ABG analysis should be performed • If ABG PaO_2 <80mmHg and/or P[A-a]O_2 ≥15 mmHg* (in ambient air) – further investigations should be performed	II-2	1
The use of contrast (microbubble) echocardiography to characterize HPS is recommended	II-2	1

*For adults ≥65 years a P[A-a]O2 ≥20 mmHg cut-off should be used

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Diagnosis of HPS

- When PaO_2 suggests HPS, further investigations are needed to determine the underlying mechanism

Recommendation	Grade of evidence	Grade of recommendation
MAA scan should be performed to quantify the **degree of shunting** in patients with severe hypoxaemia and coexistent intrinsic lung disease, or to assess the prognosis in patients with HPS and very severe hypoxaemia (PaO_2 <50 mmHg)	II-2	1
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 (PaO_2 <60 mmHg), poorly responsive to administration of 100% oxygen, and in whom there is a strong suspicion of arteriovenous communications that are amenable to embolization	II-2	1
Trans-oesophageal contrast-enhanced echocardiography (although associated with risks) can definitively exclude intra-cardiac shunts	II-2	2

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Management of HPS

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

Recommendations for medical treatment	Grade of evidence	Grade of recommendation
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	II-2	1
No recommendation can be proposed regarding the use of drugs or the placement of TIPS for the treatment of HPS	I	1
Recommendations for liver transplantation		
Patients with **HPS and PaO_2 <60 mmHg should be evaluated for LT** since it is the only treatment for HPS that has been proven to be effective to date	II-2	1
Severe hypoxaemia (PaO_2 <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

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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

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Monitoring and medical management of PPHT

- The evidence base for pharmacological therapies in PPHT is limited

Recommendation	Grade of evidence	Grade of recommendation
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

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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

Recommendation	Grade of evidence	Grade of recommendation
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 III	1 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

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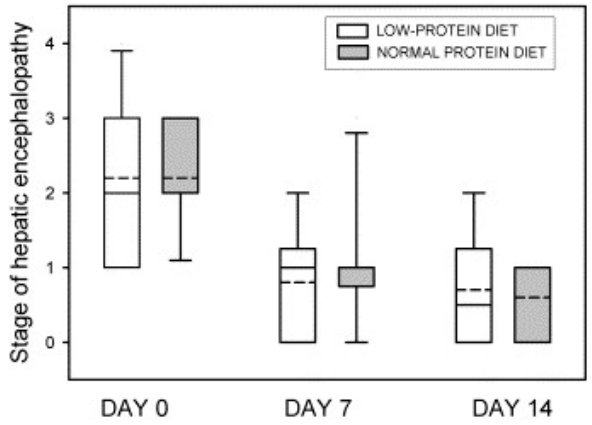
Nutrition in Cirrhosis

Low- vs Normal-Protein Diet in HE

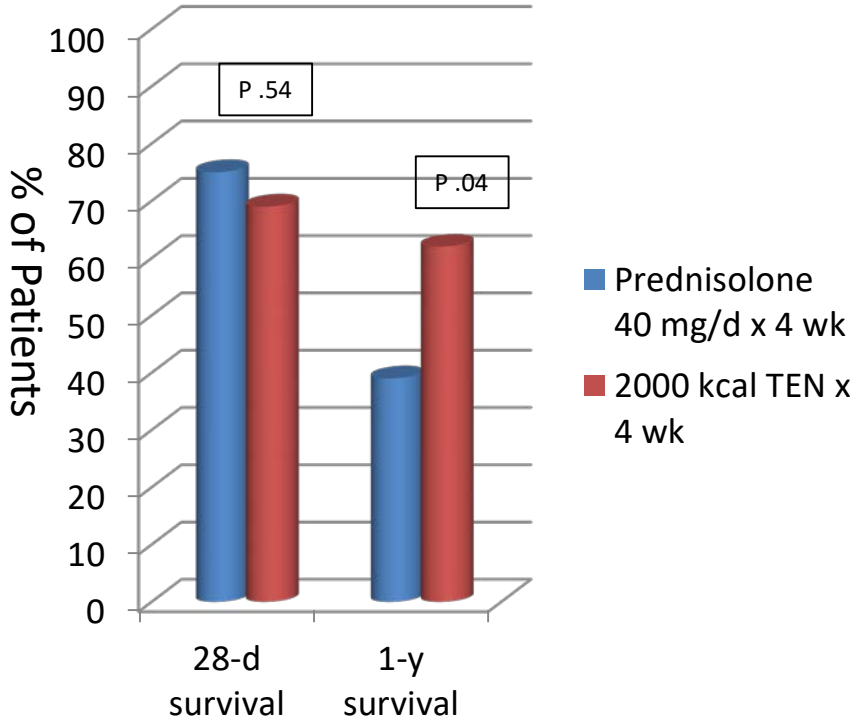
Cordoba J; J Hepatol 2004;41:38–43



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

Enteral Nutrition in Alcoholic Hepatitis

Cabre E; Hepatology 2000;32:36–42

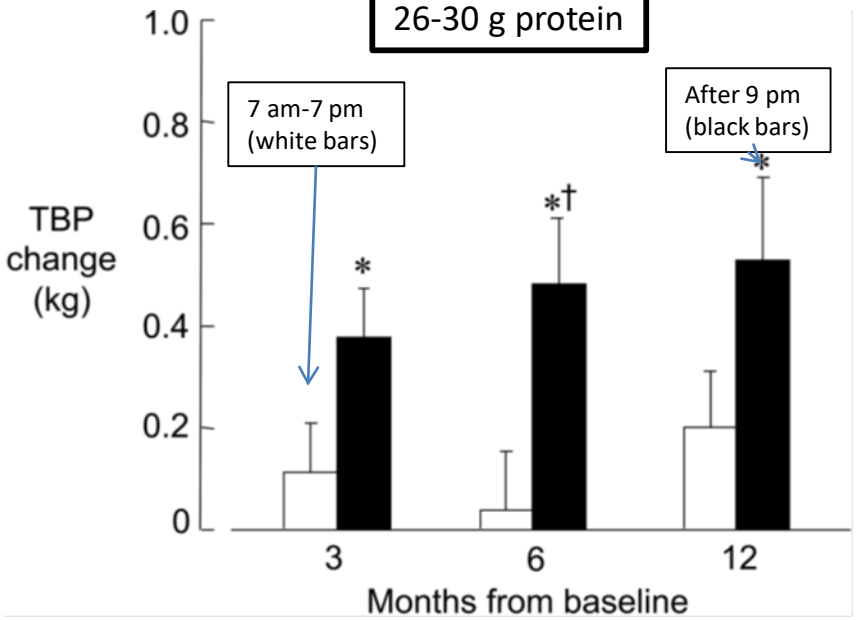


In Severe AH, Total Enteral Nutrition is as good as steroids at 4 weeks, but superior after 1 year

Nutrition in Cirrhosis

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

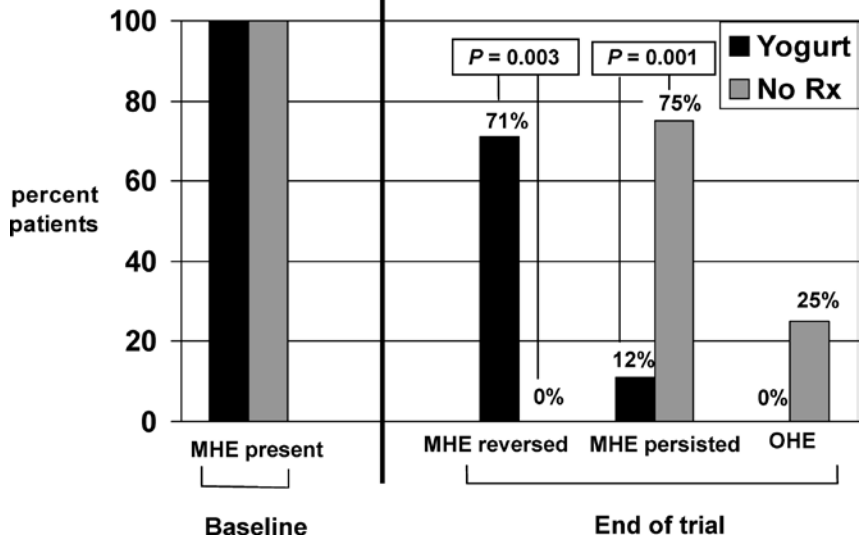
500-710 kcal
26-30 g protein



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

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

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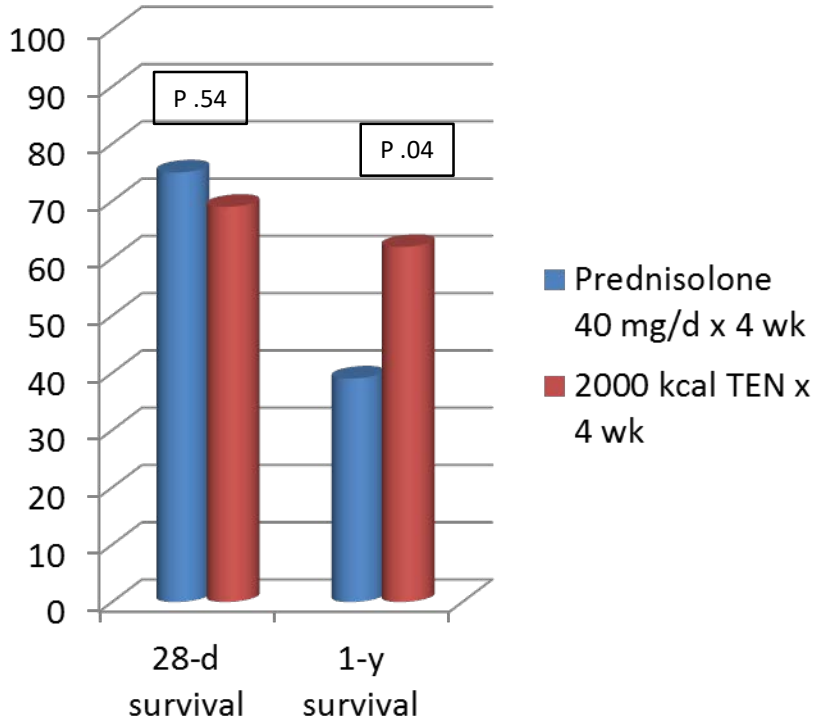

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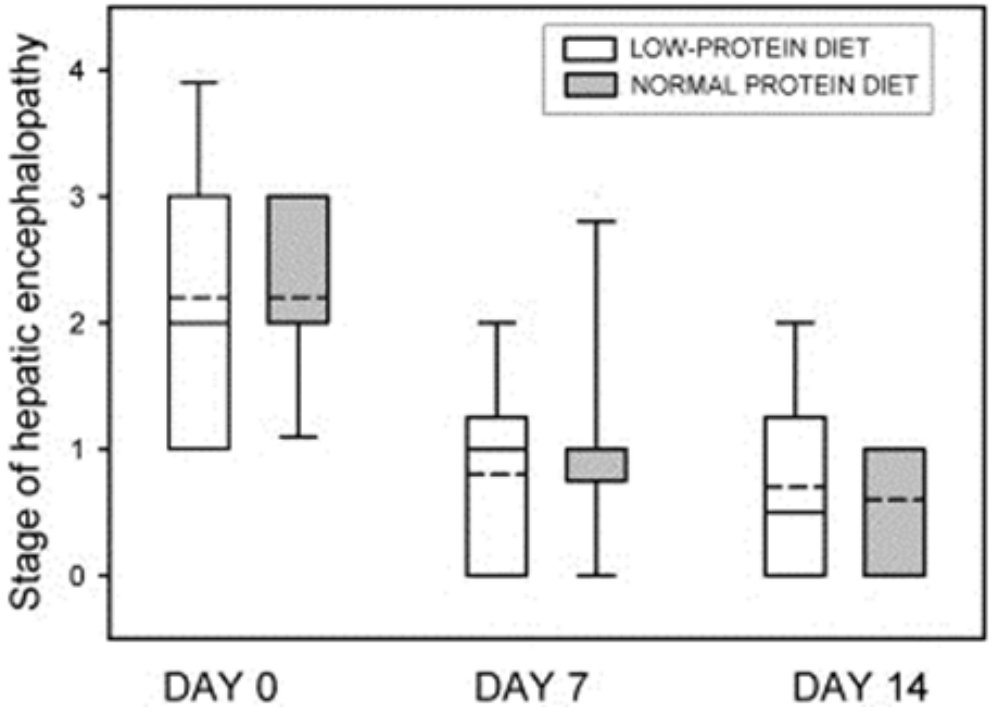

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