Minimizing Complications in Cirrhosis

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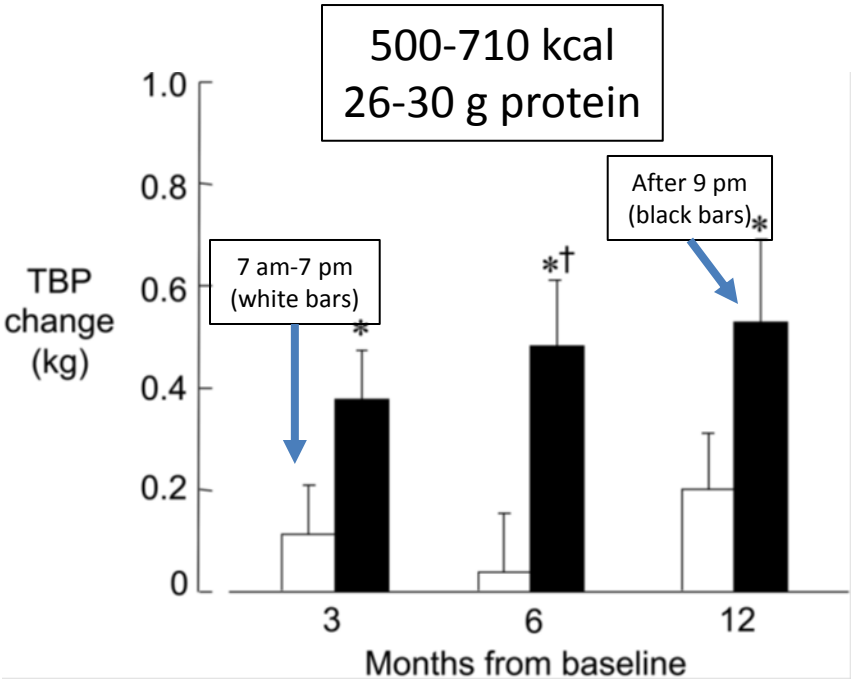
Nutrition in Cirrhosis
What we Know

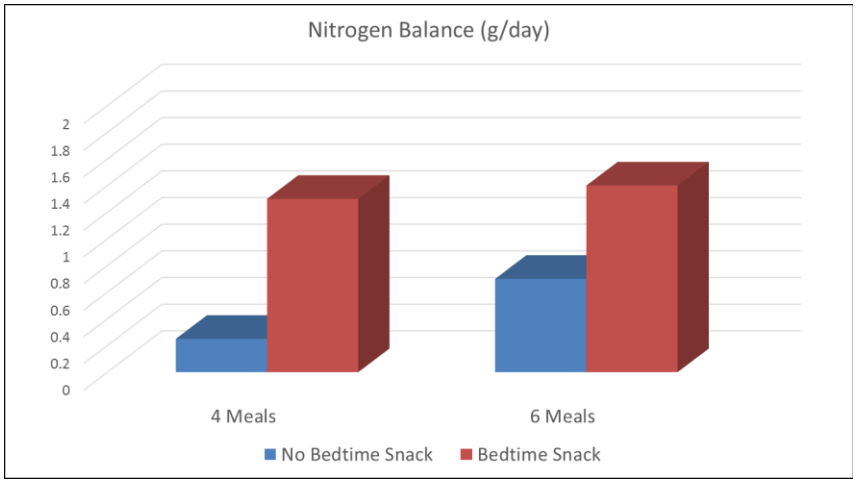
- Most cirrhotics have malnutrition.
  - even cirrhotics with overweight and NASH often have protein malnutrition.
- Cirrhotics are hypermetabolic, and go to a catabolic state after a few hours of fasting.
  - Catabolic state causes gluconeogenesis and muscular wasting.
  - Frequent meals and bedtime supplement prevent catabolic state.
- After a meal, attention and executive function improves temporarily in cirrhotics, decreasing “covert” Hepatic Encephalopathy (HE) (Vaisman N; Am J Clin Nutr 2010;92:137–40).

Nutrition in Cirrhosis

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



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



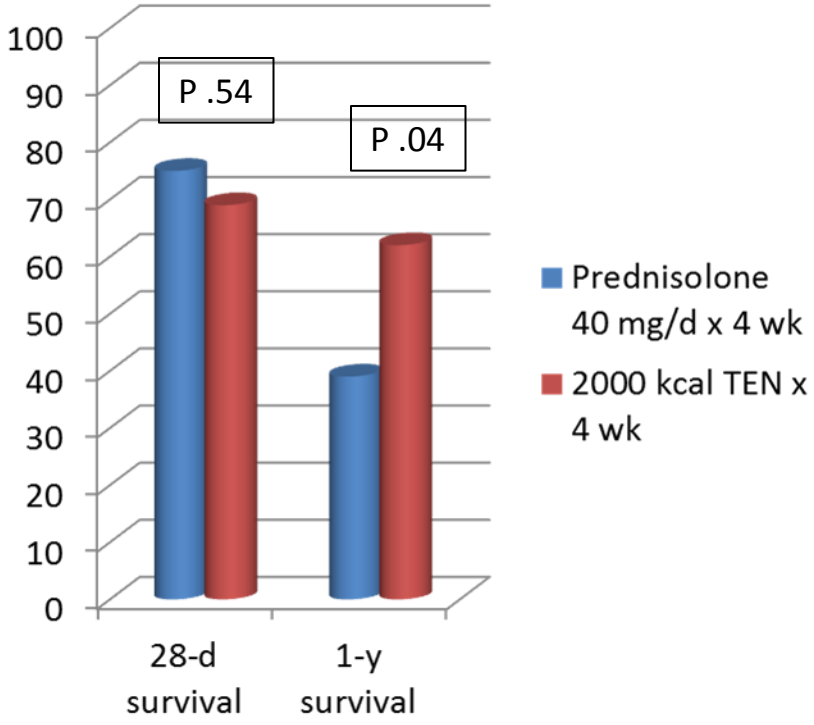
Bed-time Nutrition Increases Nitrogen Retention & Muscular Mass
(equivalent to 2 kg of muscle, after 12 months)

Bedtime Supplement is more important than Frequent meals

Nutrition in Alcoholic Hepatitis

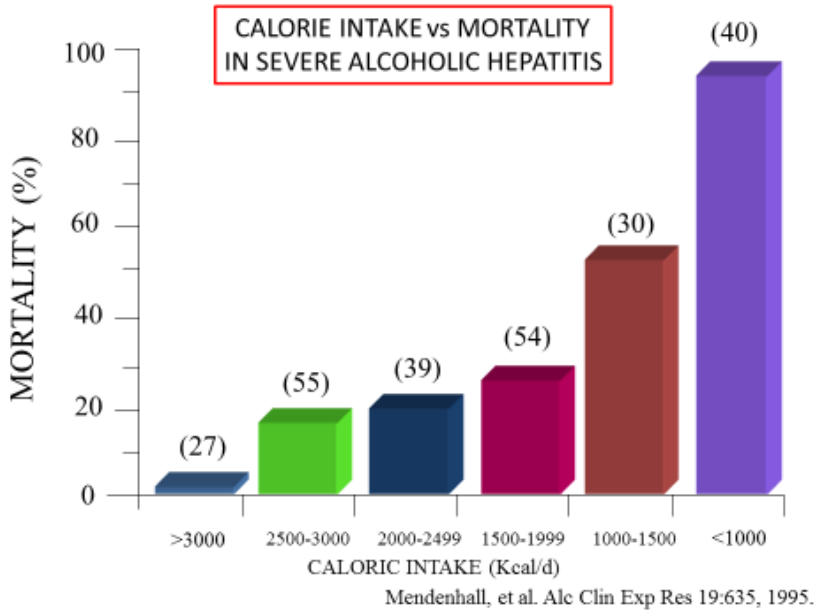
Enteral Nutrition in Alcoholic Hepatitis

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

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 asses resting energy expenditure.
  - If patient is obese with BMI 30-40, give 25-35 kcal/kg IBW/d; if BMI > 40, give 20-25 kcal/kg IBW/d; Decrease carbohydrates and fat but increase fiber to 25-45g/d.
  - Should include a bedtime supplement with 50 g of complex carbohydrates (plus protein).
- **Protein:** 1.2-1.5 g/kg/day (ideal body weight) of whole protein;
  - If Encephalopathy develops while on whole protein, give BCAA-enriched formulas to satisfy nitrogen needs.
- **Fiber:** 25-45 g a day
- **Sodium:** if patient has edema or ascites, restrict sodium to 2 g/d
- **Fluids:** Restrict only if Na < 125 mEq/L
- **Frequency:** 3 meals + 3 small snack + bed-time supplement with 26-30 g protein and at least 50 g of complex carbohydrates, giving 500-710 kcal nightly.
  - Two of the snacks could be “probiotic yogurt”, to improve covert HE.
  - Naso-enteric feeding tube if not eating enough. PEG contraindicated in cirrhotic ascites.
- **Precautions:**
  - All animal products should be well cooked: risk of vibrio or listeria infections.
  - All fruits and vegetables should be washed.

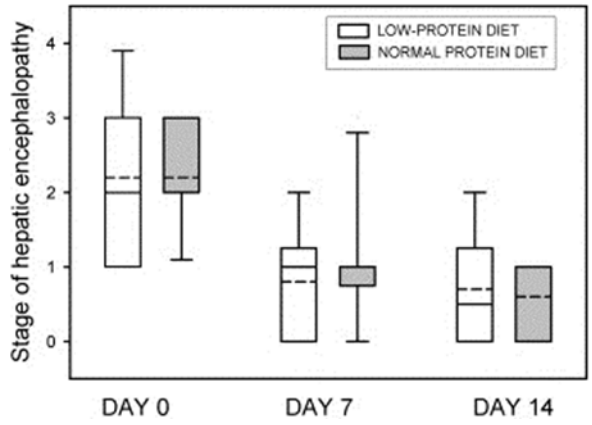
Hepatic Encephalopathy
What we know

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

Nutrition in Hepatic Encephalopathy

Low- vs Normal-Protein Diet in HE

Cordoba J; J Hepatol 2004;41:38–43

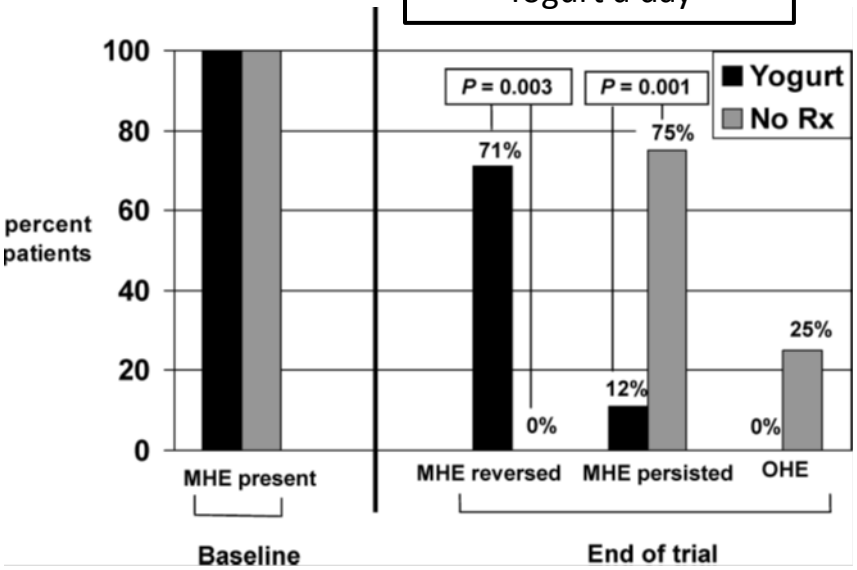


Diet with "normal protein intake" improves HE equally as "low protein" diet

Probiotic Yogurt in Covert Hepatic Encephalopathy

Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

12 ounces of Probiotic Yogurt a day

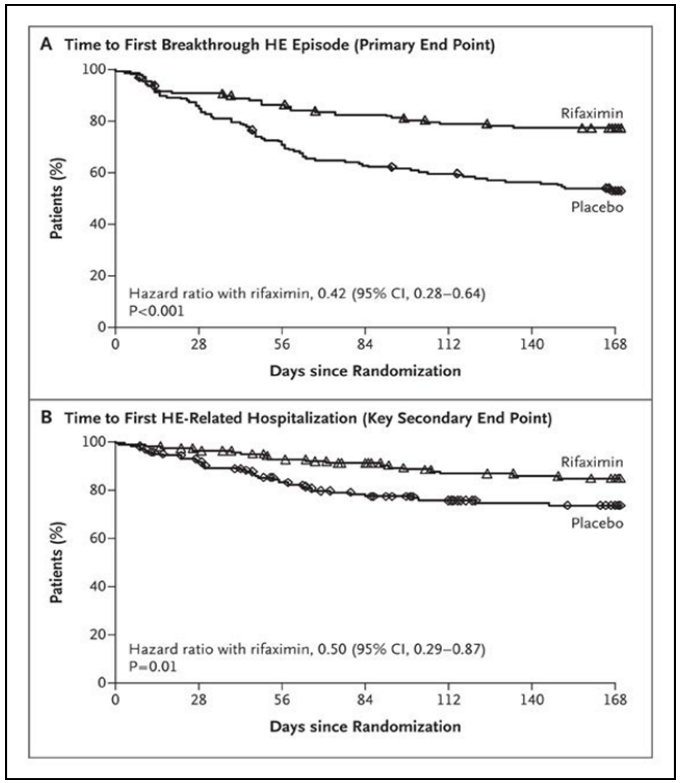


Probiotic Yogurt Improves Covert HE & Protects against Overt HE

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.

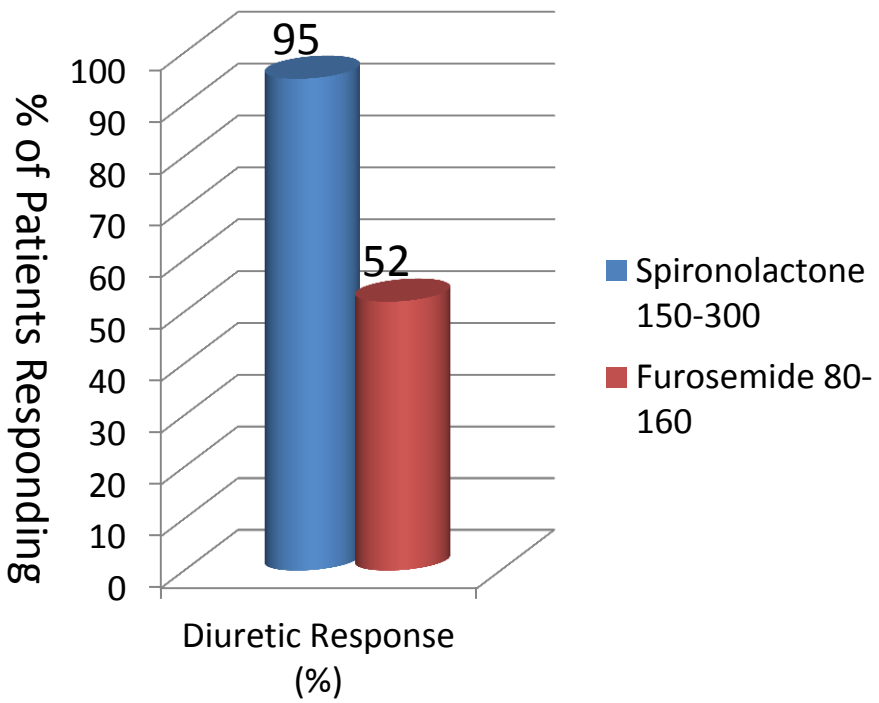
Ascites Management

- 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

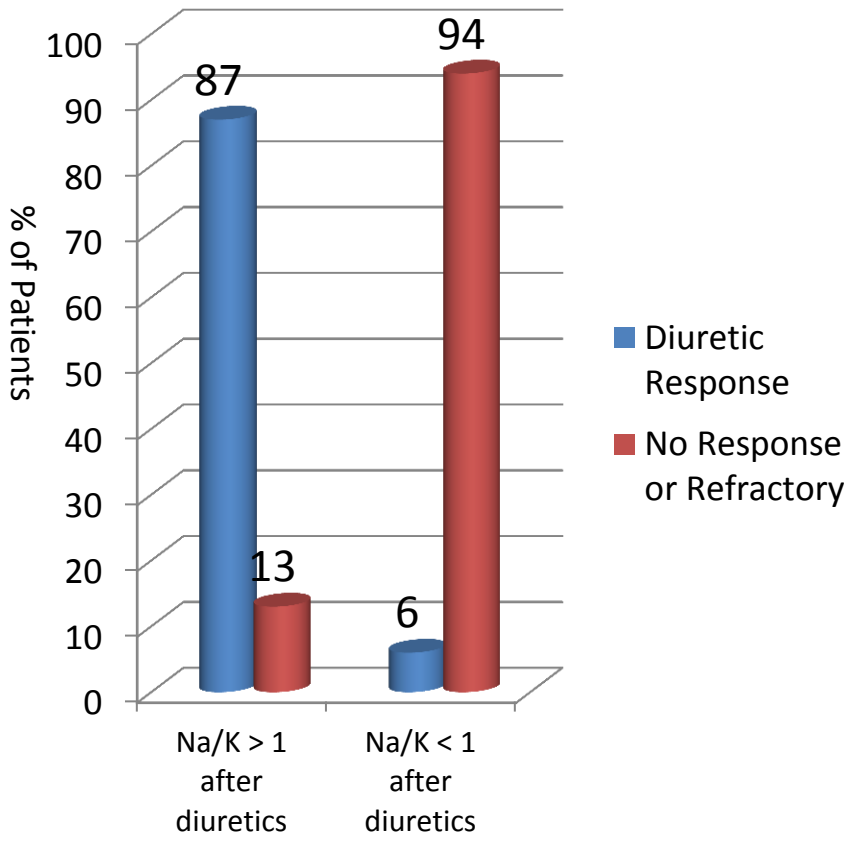
Diuretic Titration

- 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

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.

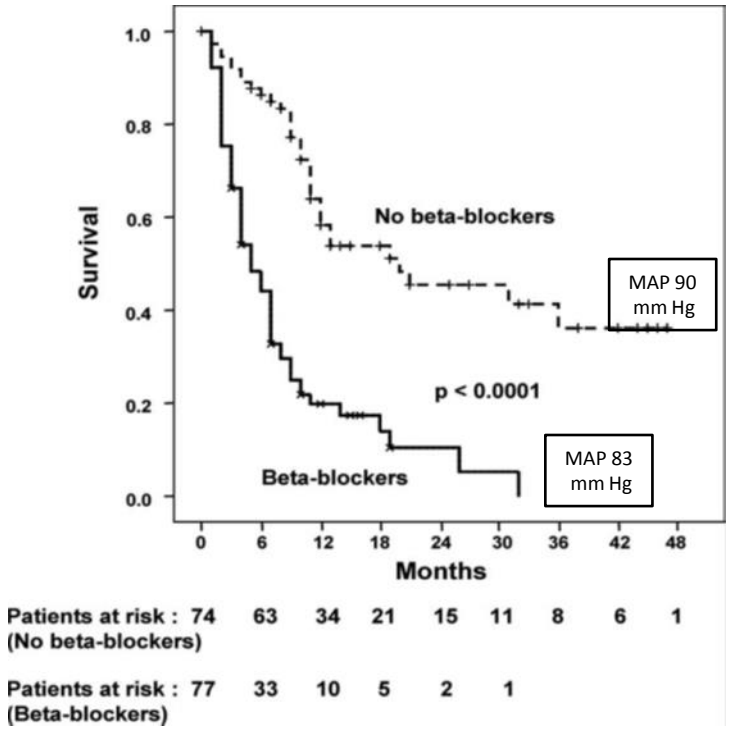
Refractory Ascites
What We Know

- 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

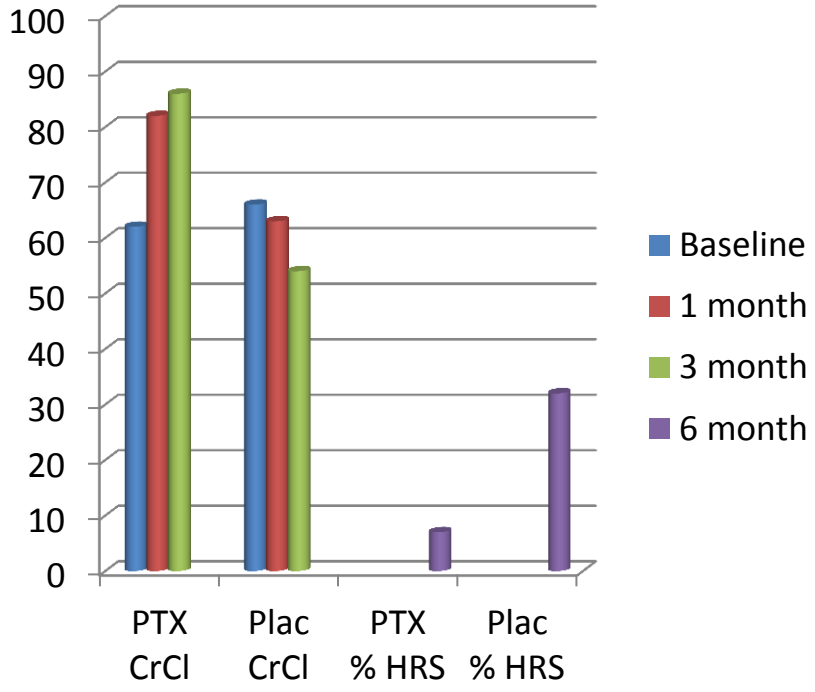
Serste T; Hepatology 2010;52(3):1017-1022



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

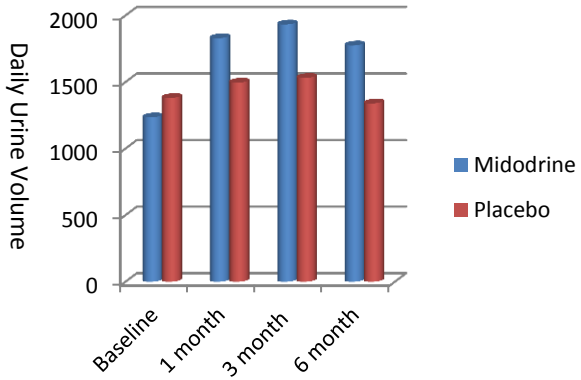


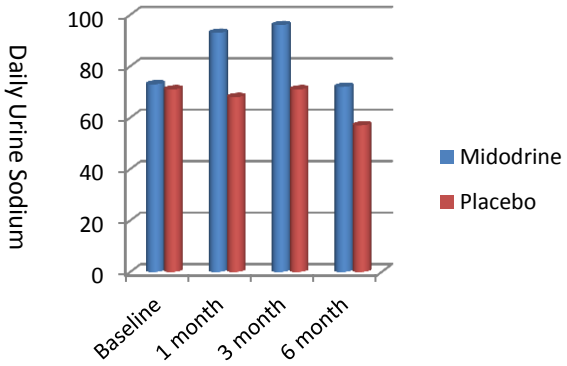
In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS

Ascites & Refractory Ascites

Midodrine in Refractory/Recurrent Ascites

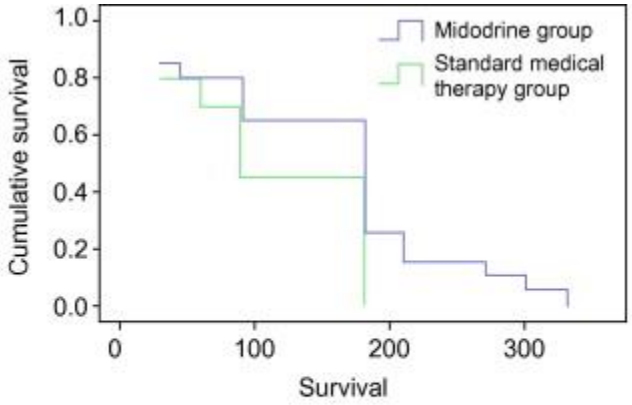
Singh V; Journal of Hepatology 2012; 56:348–354





Midodrine in Refractory/Recurrent Ascites

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

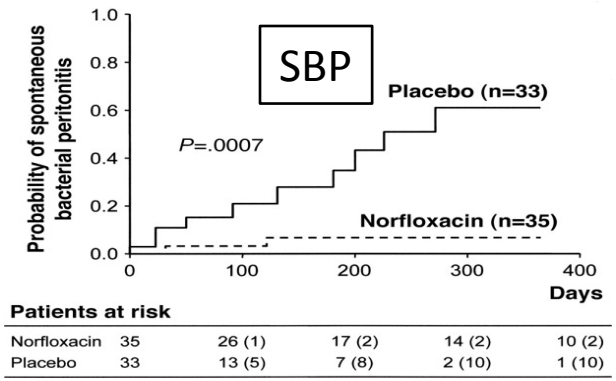


Group	Days from randomization								
	0	30	45	60	90	180	210	300	330
Standard medical therapy	20	16	16	14	9	5	5	5	5
Midodrine	20	17	16	16	13	12	12	12	12

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

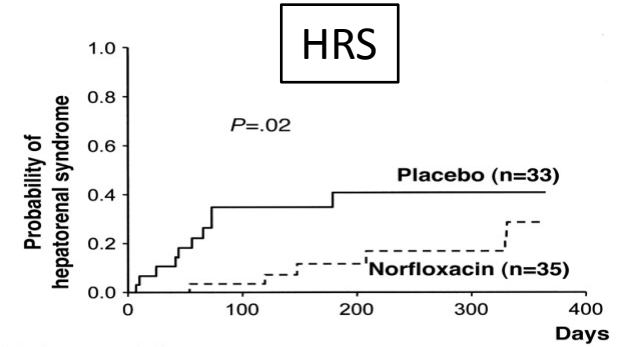
Ascites & Refractory Ascites

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



Patients at risk

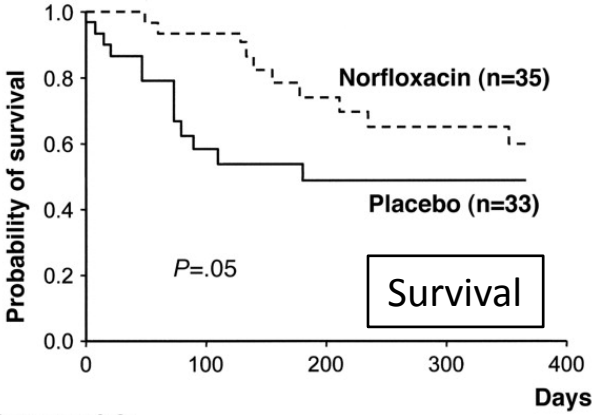
Norfloxacin	35	26 (1)	17 (2)	14 (2)	10 (2)
Placebo	33	13 (5)	7 (8)	2 (10)	1 (10)



Patients at risk

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

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



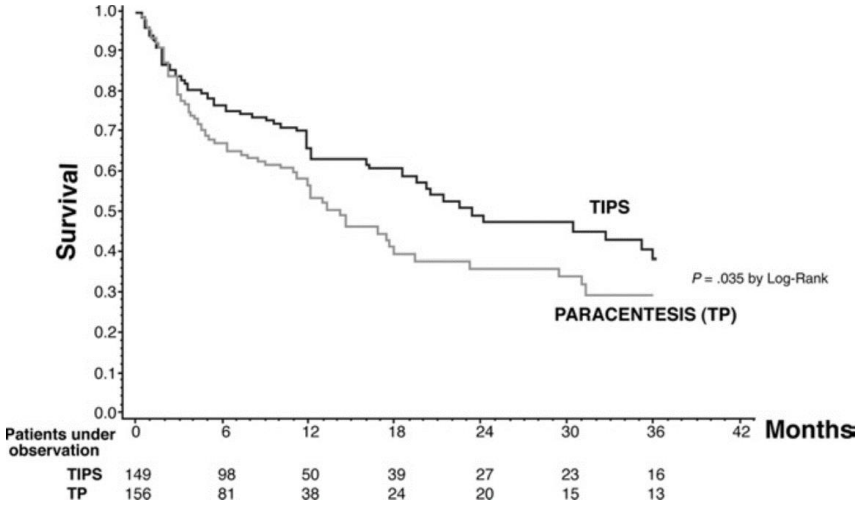
Patients at risk

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

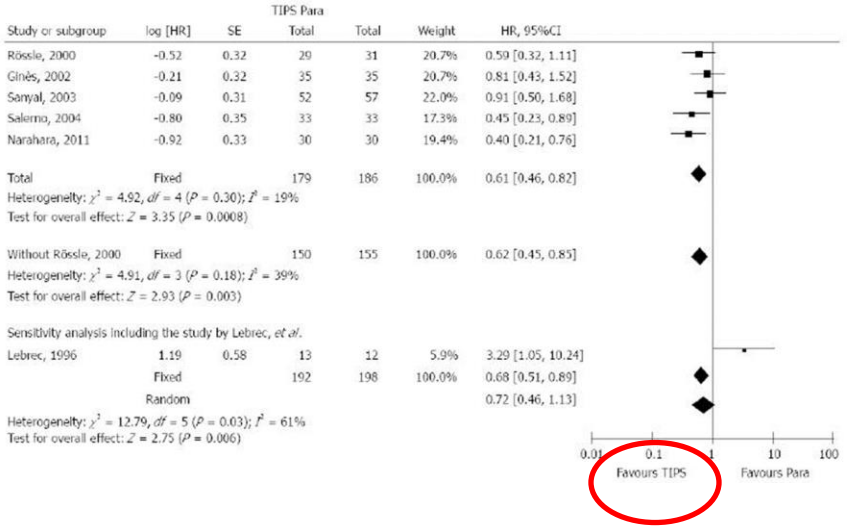
In ascites with Child >/= 9 or renal dysfunction, Norfloxacin decreases risk of SBP, HRS, and improves survival.

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

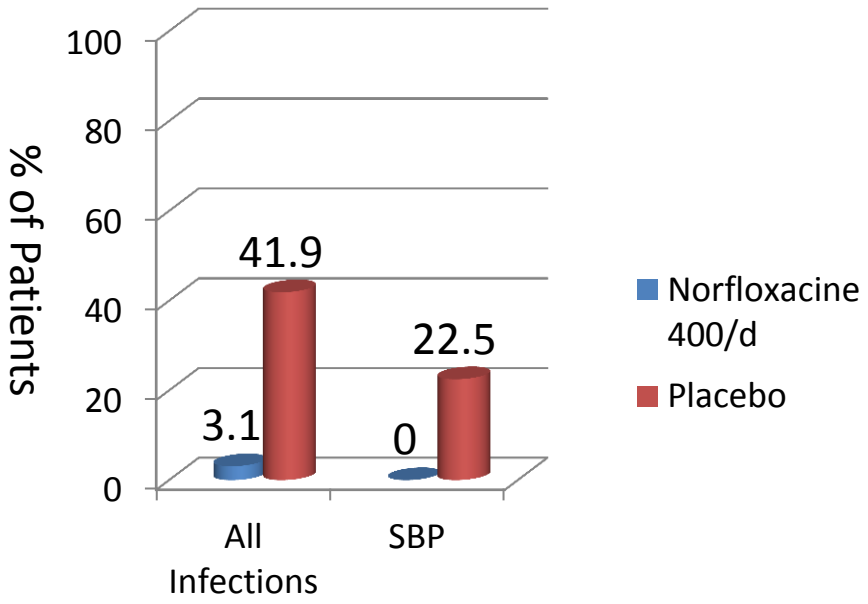
TIPS improves Transplant-free Survival in Refractory Ascites

Spontaneous Bacterial Peritonitis (SBP) What we know

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

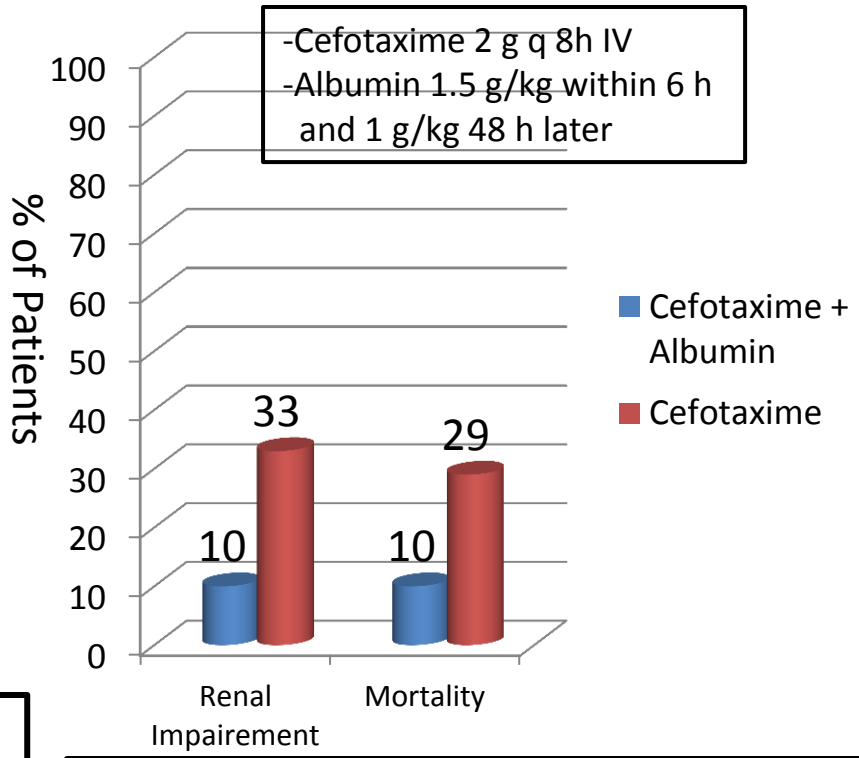
Spontaneous Bacterial Peritonitis (SBP)

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



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

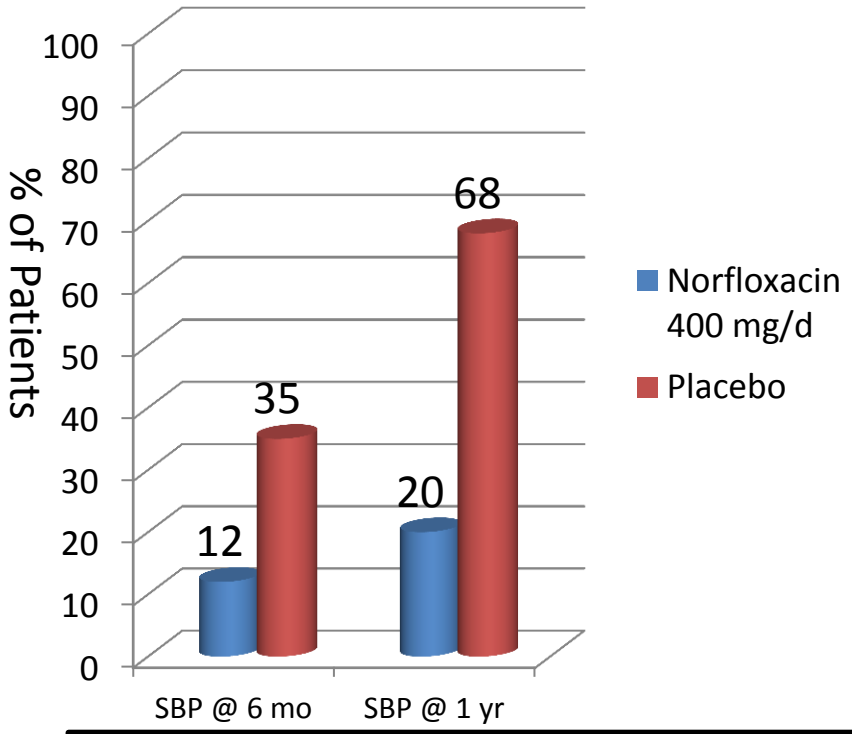


Volume expansion with IV albumin decreases risk of HRS & Mortality, in SBP treated with Cefotaxime

Complications of Cirrhosis

Long Term Norfloxacin prevents SBP recurrence

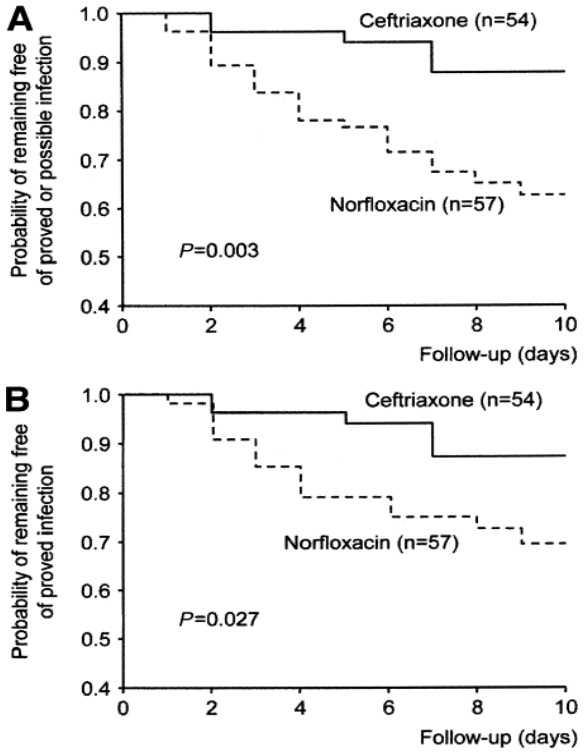
Gines P; Hepatology 1990;12:716-724



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.

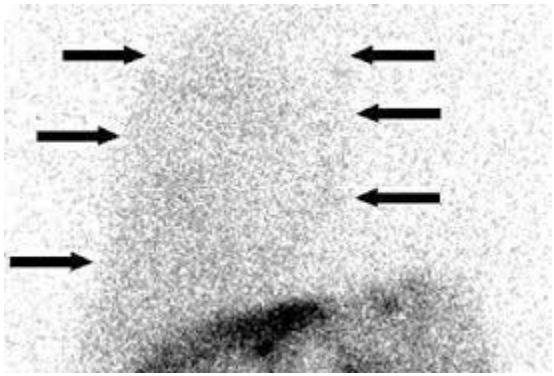
SBP
Prophylaxis and Management

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

Hepatic Hydrothorax and Spontaneous Bacterial Empyema (SBE) / Spontaneous Bacterial Pleuritis

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

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

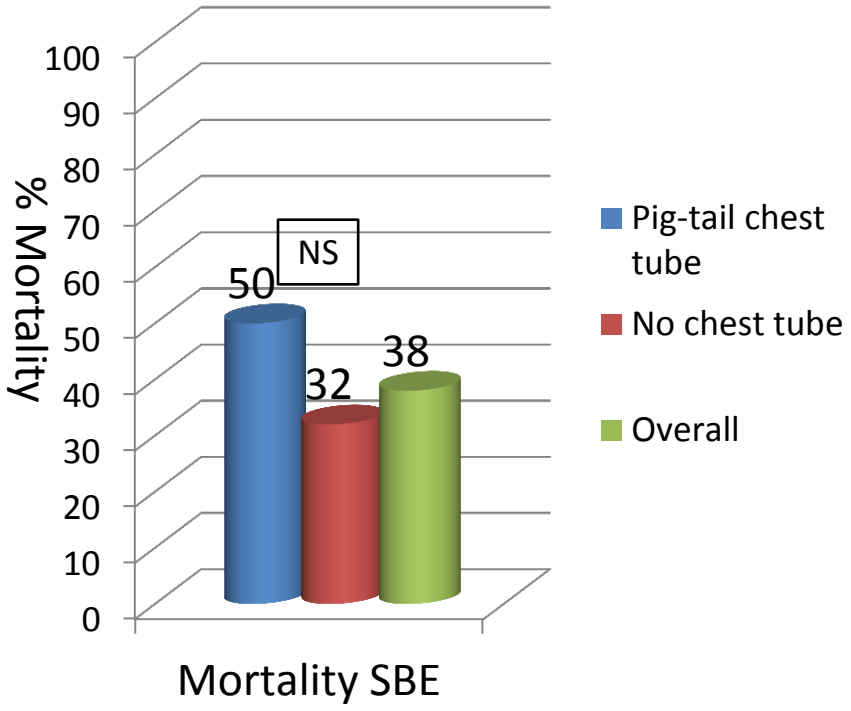


Spontaneous Bacterial Pleuritis

SB Empyema – What we know

- Spontaneous Bacterial Empyema occurs in 16% of hepatic hydrothorax.
- SBE is diagnosed in a patient without lung infection, by either:
  - PMN count > 250/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



Recommended empirical antibiotic treatment for community-acquired and nosocomial bacterial infections in cirrhosis

J Hepatol 2014; 60: 1310-24

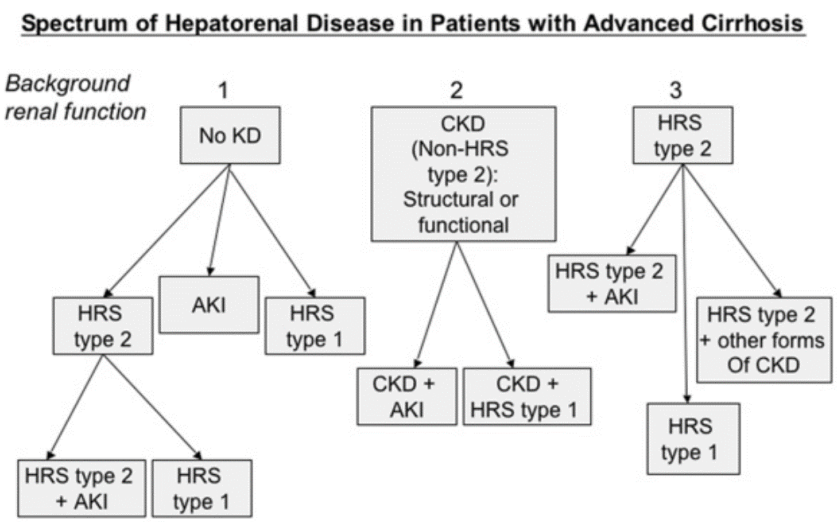
Type of Infection	Community Acquired	Nosocomial
SBP, SBP, or Spontaneous Bacteremia	Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	Piperacillin/tazobactam **or** meropenem ± vancomycin **or** meropenem + daptomycin
Urinary Infection	**Uncomplicated:** **or** co-trimoxazole **or** ciprofloxacin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

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

Box 1. Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

HRS-AKI

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

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.
ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.

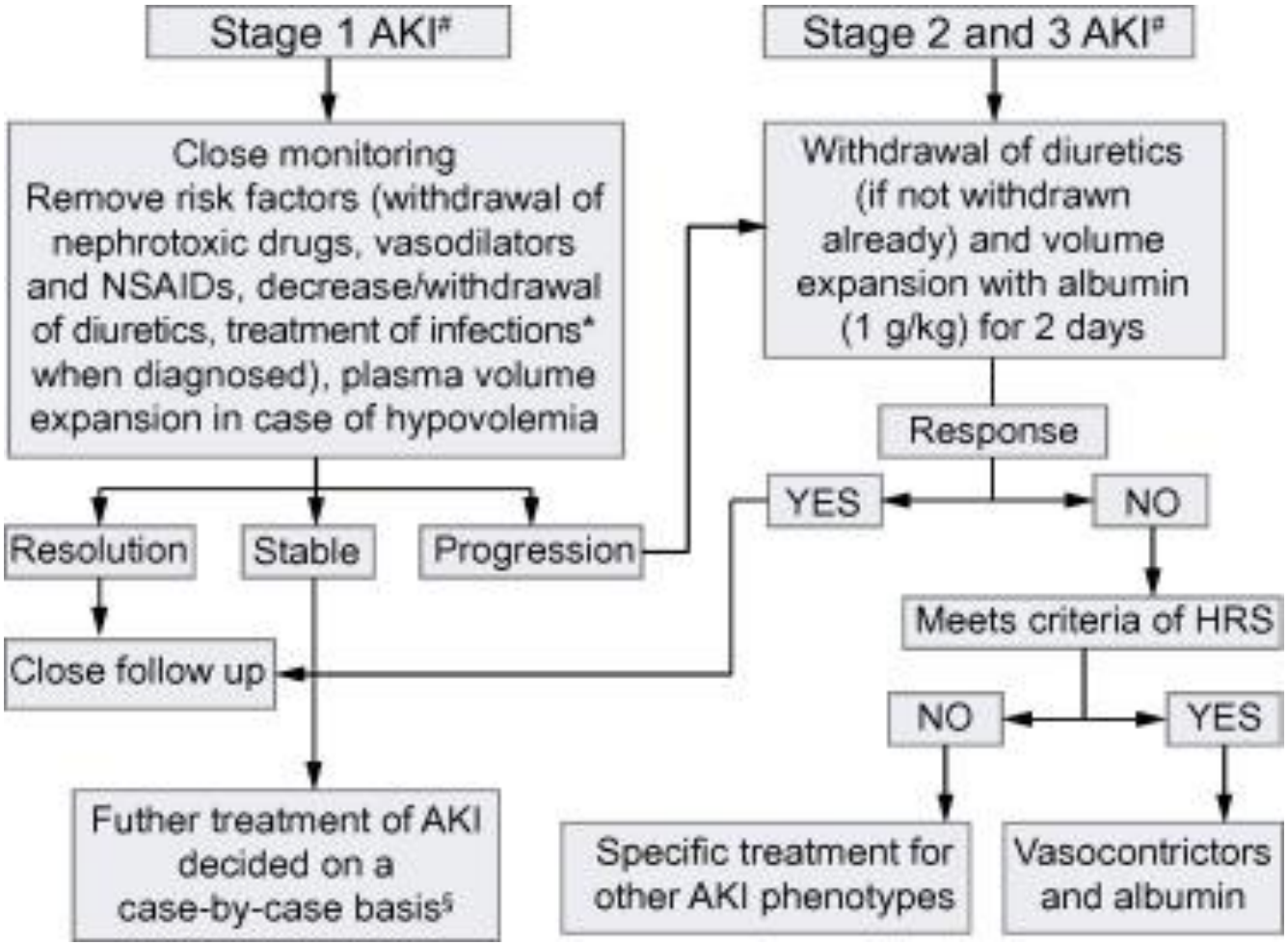
Journal of Hepatology Volume 62, Issue 4, April 2015, Pages 968–974

Definitions of Response to Treatment AKI in Cirrhosis

No response	Partial Response	Full Response
No regression of AKI	Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value	Return of sCr to a value within 0.3 mg/ dl (26.5 µmol/L) of the baseline value

Algorithm for Treatment of AKI in Cirrhosis

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

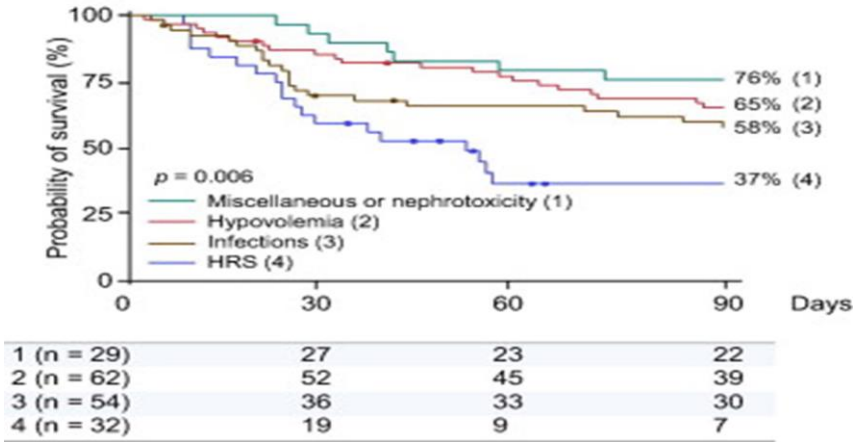


Use of Vasopressors when creatinine is < 1.5 mg/dL is not well defined

Prognosis of AKI in Cirrhosis

Survival in AKI in Cirrhosis, by Type

Fagundes C et al. J Hepatol. 2013 May 10



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

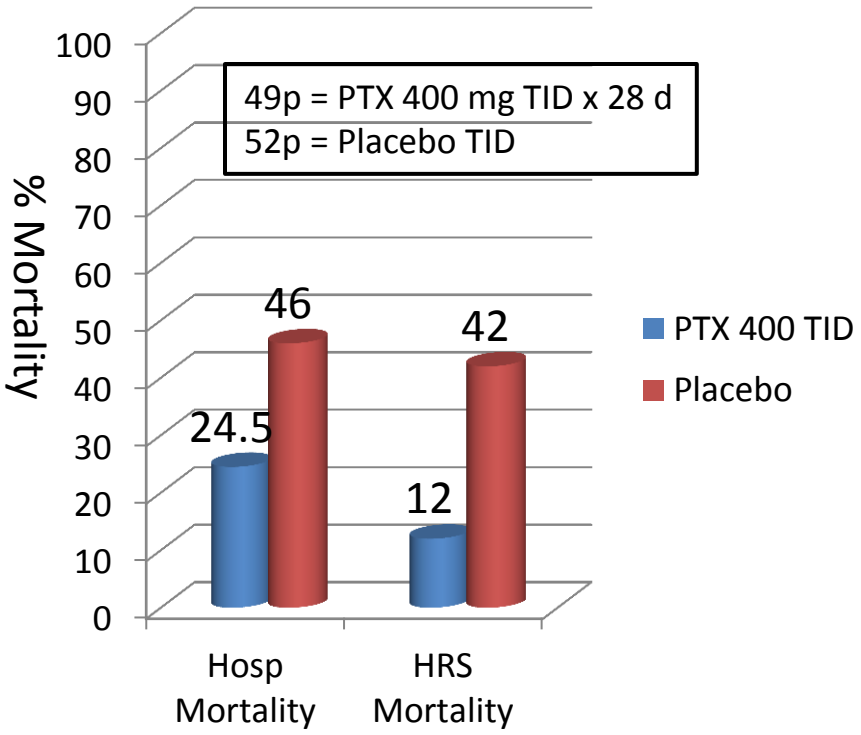
Hepatorenal Syndrome
What we know

- 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).
  - 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

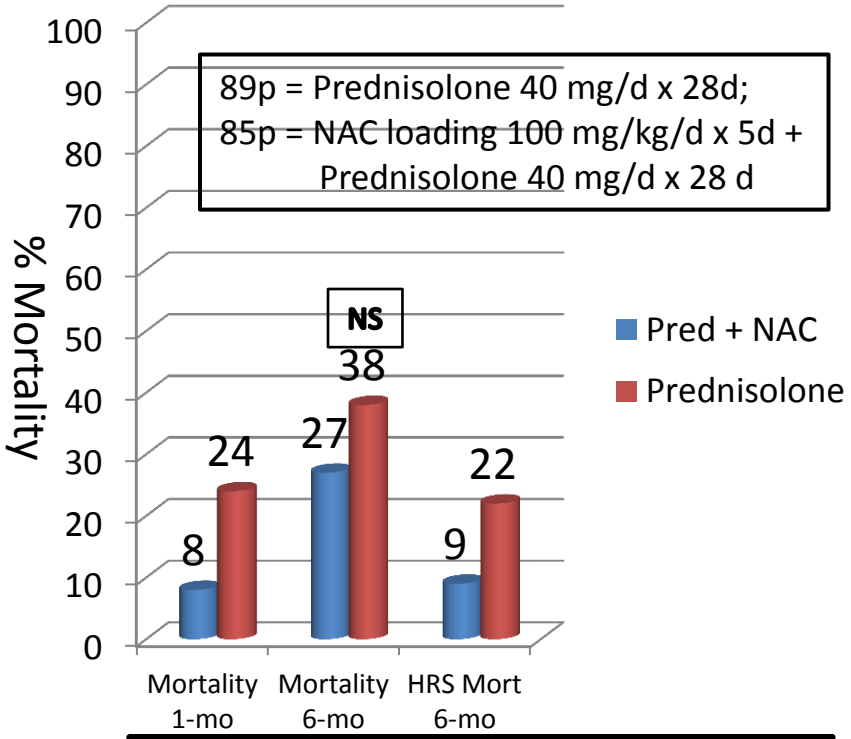
Akriviadis E; Gastroenterology 2000 Dec;119(6):1637-48



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

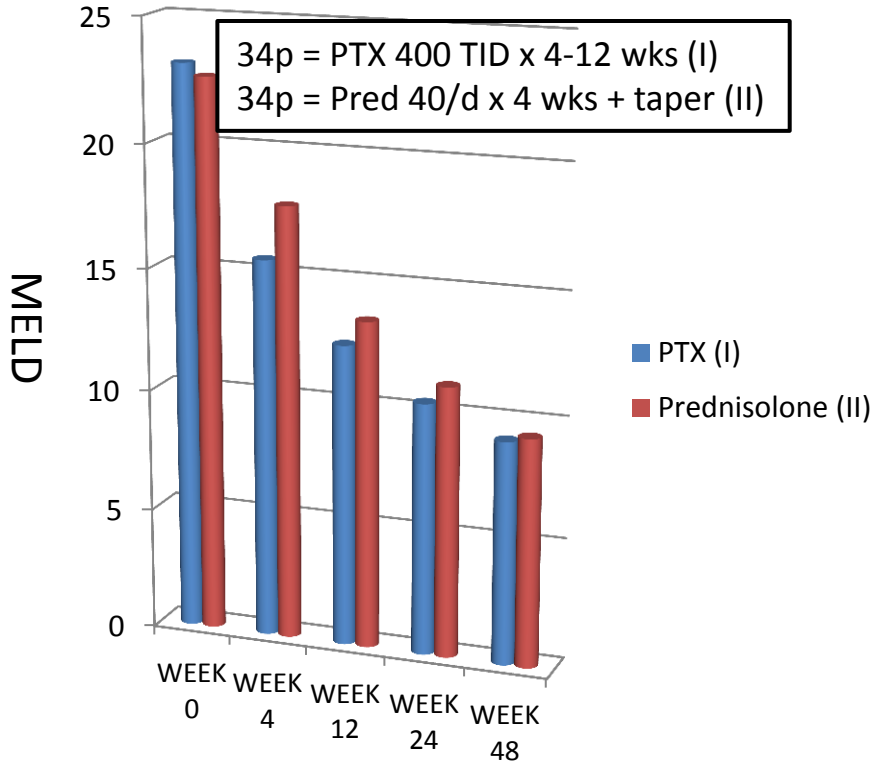


In Severe AH, adding NAC to Prednisolone, decreased risk of HRS, 1 month mortality, and 6 month HRS-related mortality.

Prevention of HRS & Mortality

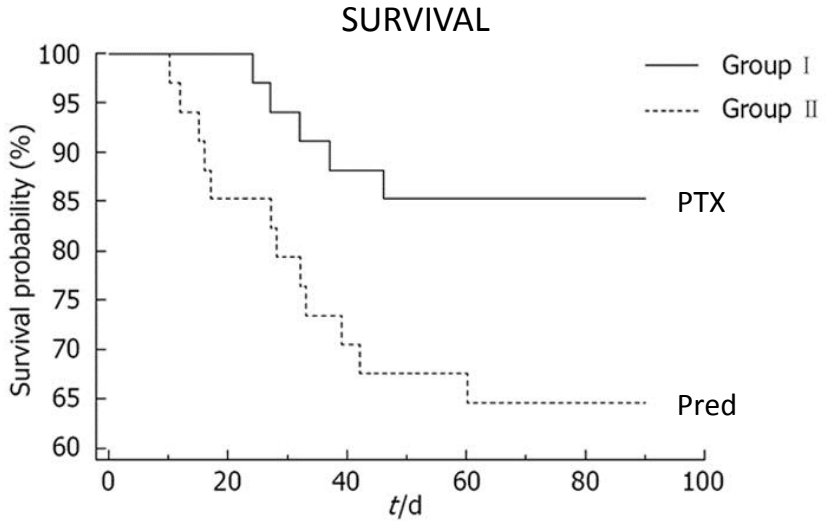
Prednisolone vs PTX in Severe AH

De BK et al, World J Gastroenterol 2009 April 7; 15(13): 1613-1619



Prednisolone vs PTX in Severe AH

De BK et al World J Gastroenterol 2009 April 7; 15(13): 1613-1619



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

Hepatorenal Syndrome
What we know

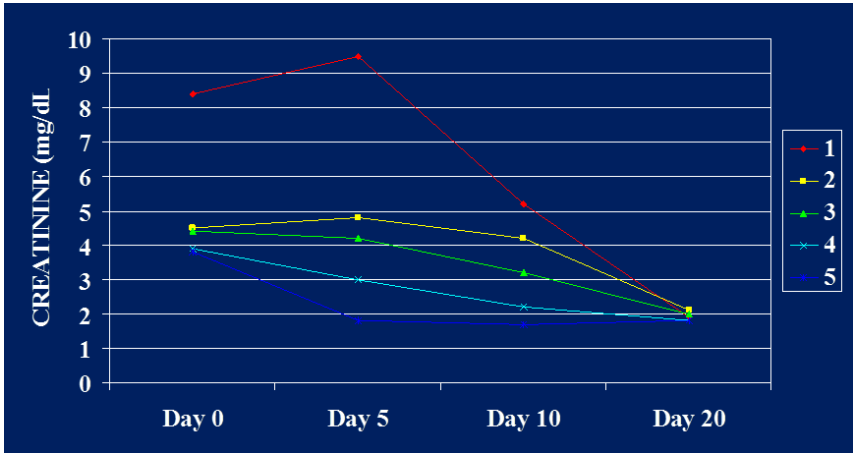
- HRS type I and II can be treated with volume expansion plus vasopressors;
  - high dose IV NAC also has been reported to be effective.
- Successful treatments have been published with:
  - Ornipressin + Albumin (Guevara M; HEPATOLOGY 1998;27:35-41).
  - N-Acetylcysteine intravenous (Holt S; Lancet 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

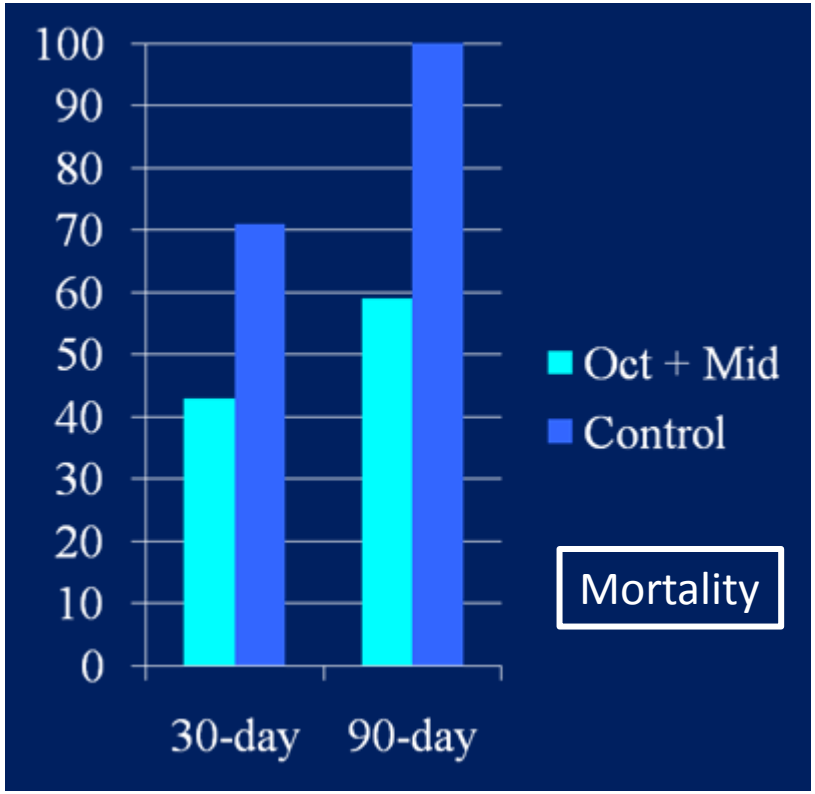
Midodrine 7.5-15 mg po TID +
Octreotide 100-200 mcg SQ TID
5 patients with HRS-1
Responders reached MAP = 95



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



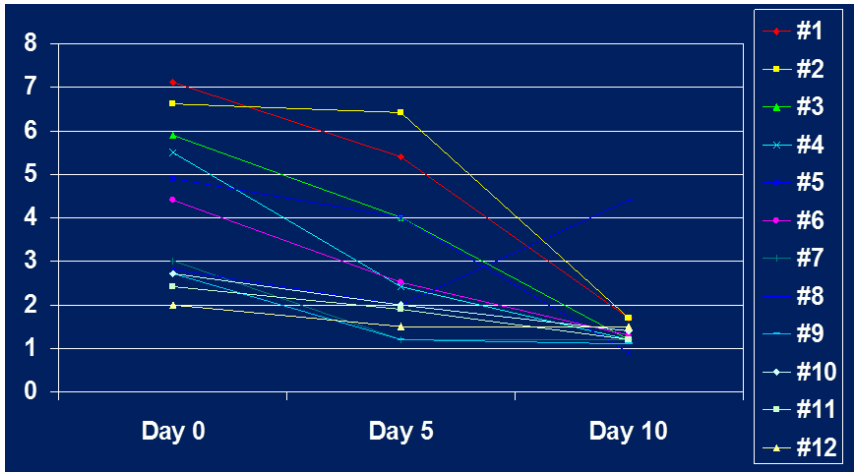
Octreotide + Midodrine decrease 1 & 3-month mortality in HRS-1

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

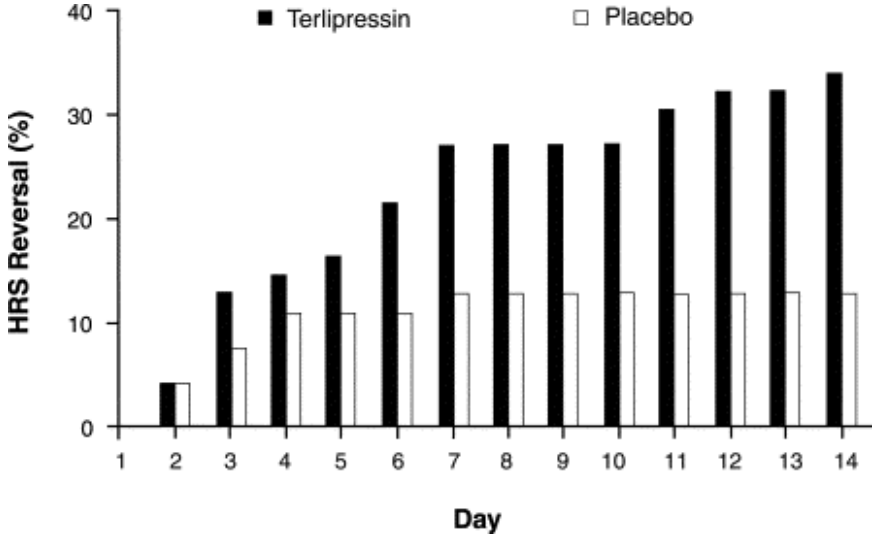


Noradrenaline + Albumin takes up to 10 days to work

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

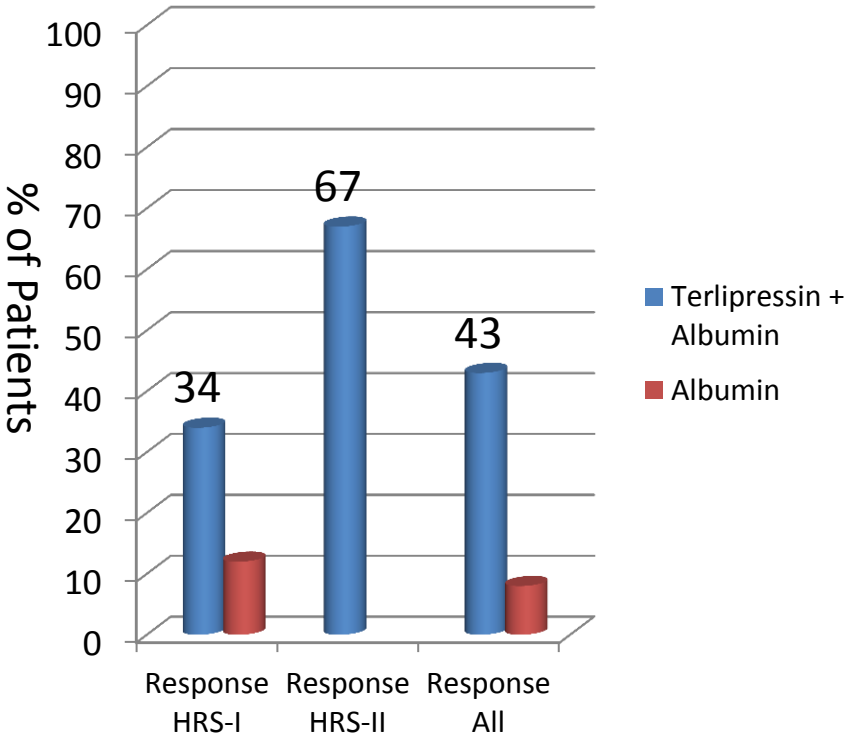


Terlipressin + Albumin takes up to 2 weeks to work

Treatment of Hepatorenal Syndrome

Terlipressin + Albumin vs Albumin in HRS

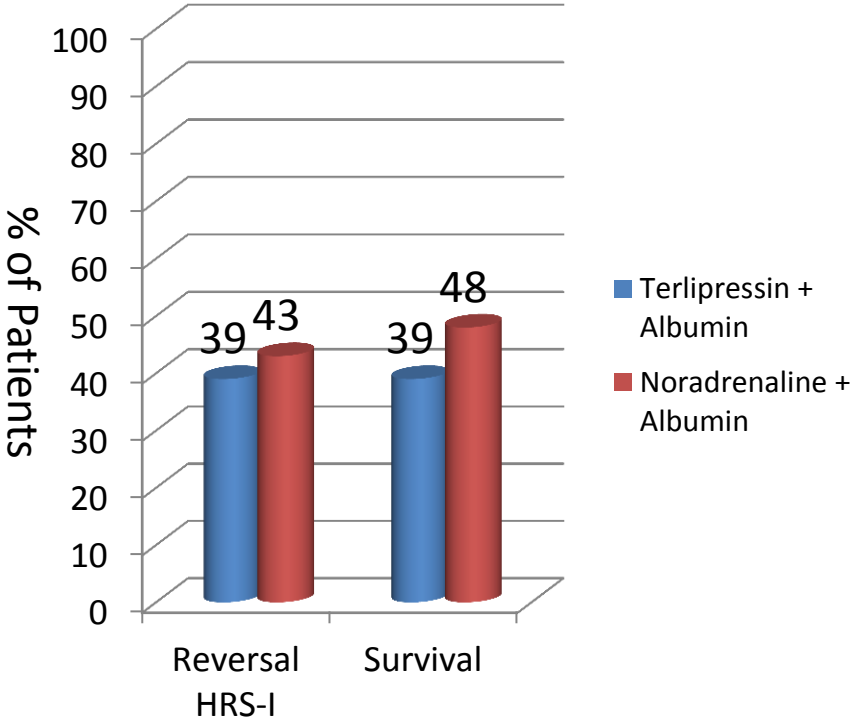
Sanyal AJ; Gastroenterology 2008;134(5):1360-8



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).

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).

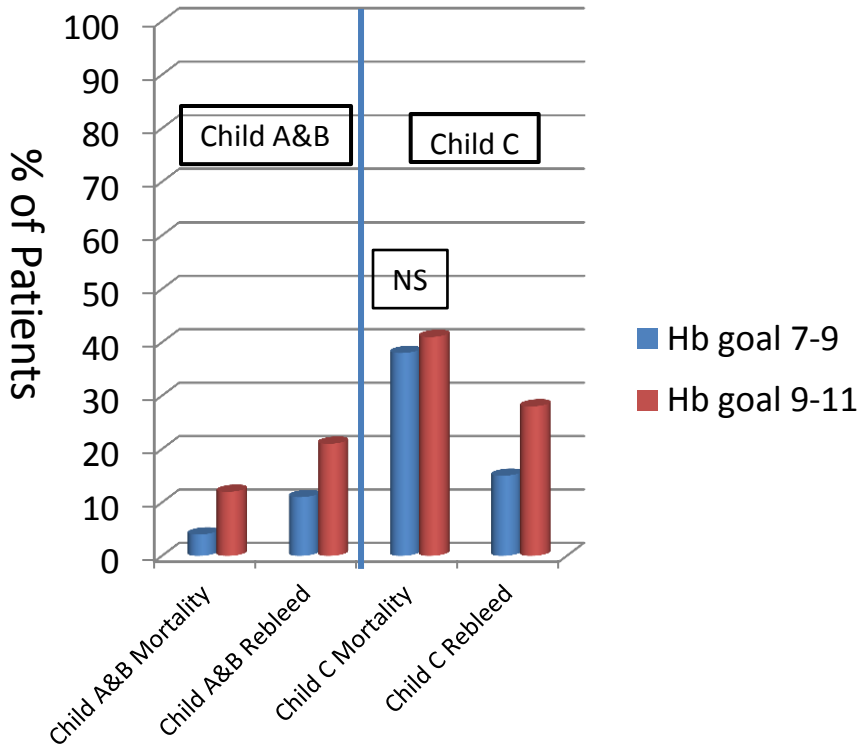
Acute GI Bleed in Cirrhosis
What we know

- Restrictive blood transfusion (only when Hb < 7, with target of 7-9) is better than liberal blood transfusion (when Hb < 9, with target of 9-11). (Villanueva C; N Engl J Med 2013; 368:11-21).
  - Decreases re-bleeding rate in all patients, and
  - Decreases mortality in Child A & B.
  - Liberal transfusion increases portal pressure .
- In esophageal variceal bleed, the use of early TIPS (within 24-72 hours) using a PTFE covered stent decreases rebleeding rate (NNT: 2.1) and mortality at 6 months (NNT: 3.3) and 1-year (NNT: 4), when compared to EBL + Beta-blockers, (Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379) in:
  - Child-Pugh B (score 7-9) **with active bleeding**, and
  - Child-Pugh C (score 10-13) **with or without active bleeding**.

Acute GI Bleed in Cirrhosis

Restrictive vs Liberal Transfusion in GI Bleed

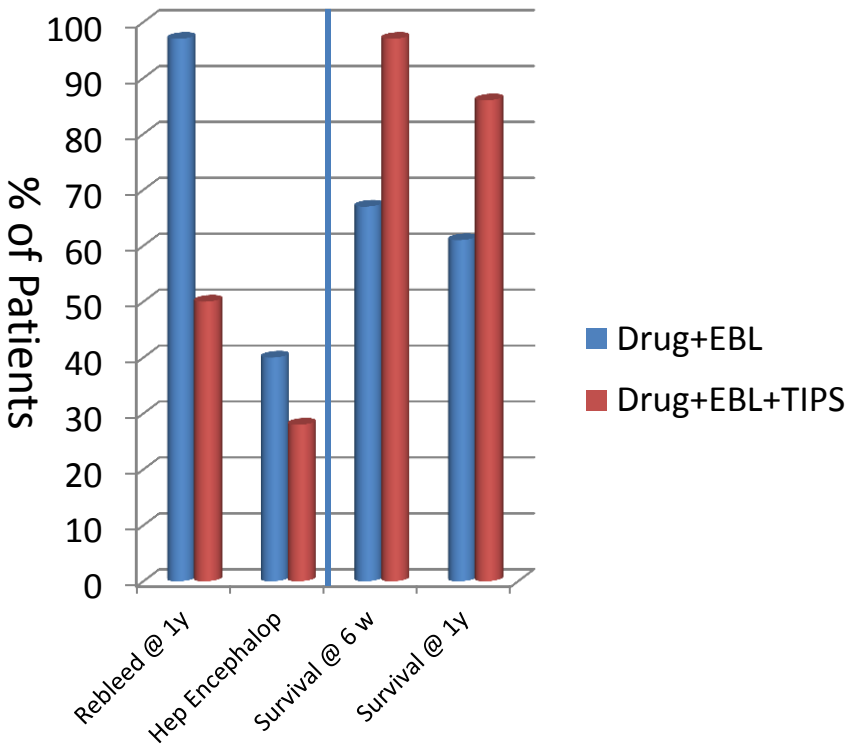
Villanueva C; N Engl J Med 2013; 368:11-21



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

Acute GI Bleed in Cirrhosis

Restrictive vs Liberal Transfusion in GI Bleed

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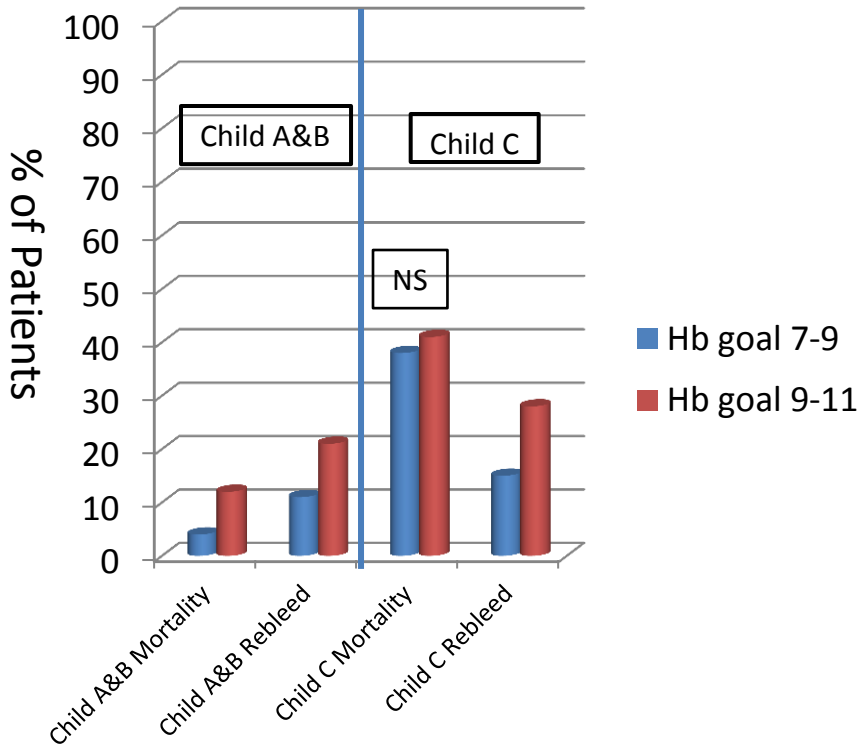

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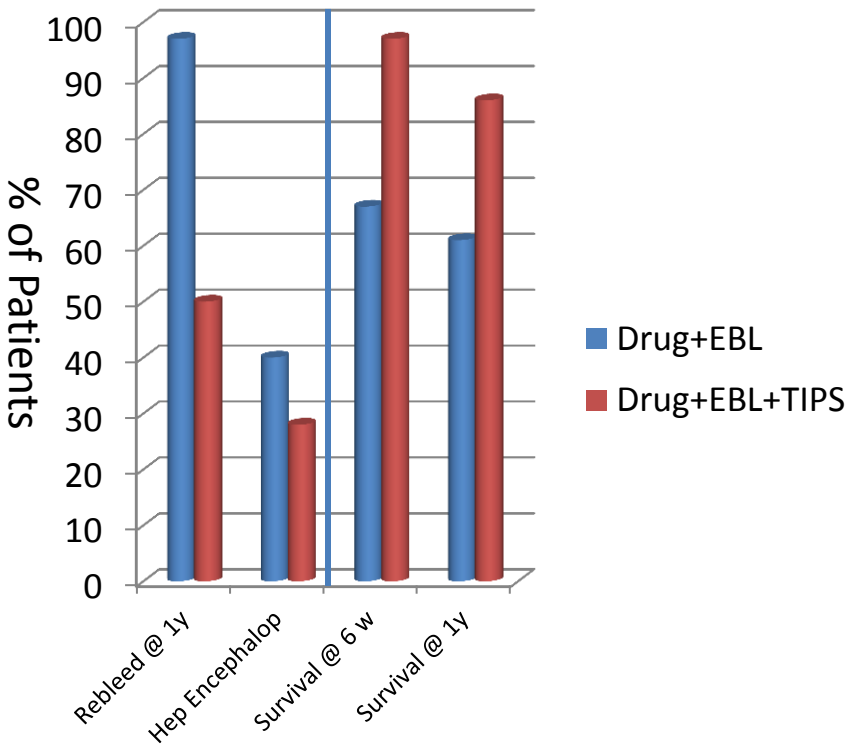


Early TIPS improved survival in variceal bleed with actively bleeding Child B, and all Child C

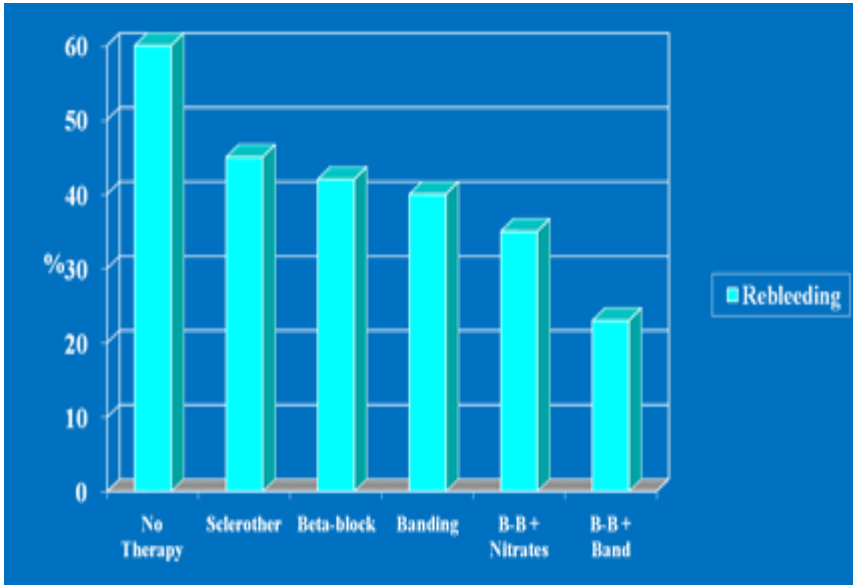
Thank you for your attention

Prevention of Variceal Rebleeding

Beta-blocker +/- ISMO Protocol

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

LONG TERM Rebleeding Risk
Different Prophylaxis



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

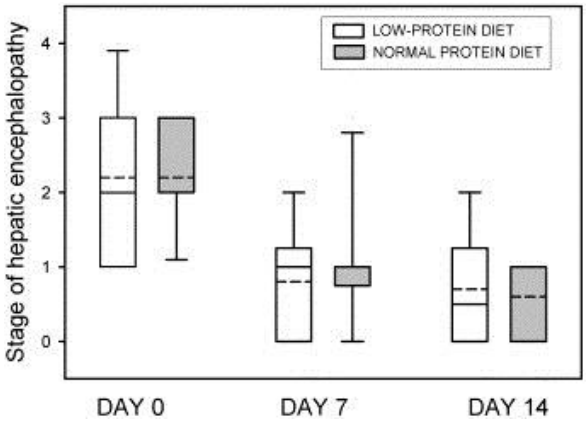
Acute Esophageal Variceal Bleed Recommendations

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

Nutrition in Cirrhosis

Low- vs Normal-Protein Diet in HE

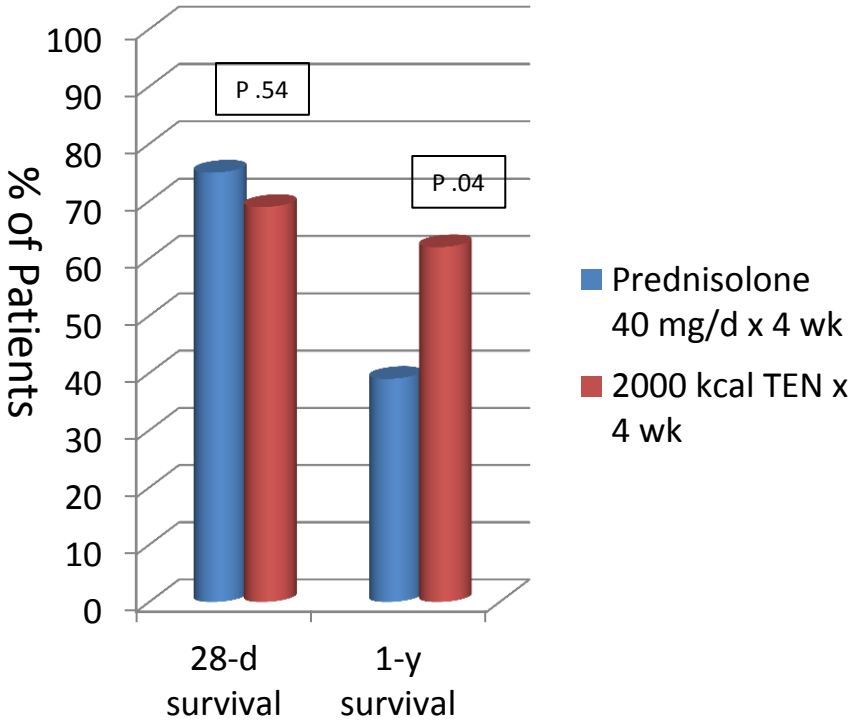
Cordoba J; J Hepatol 2004;41:38–43



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

Enteral Nutrition in Alcoholic Hepatitis

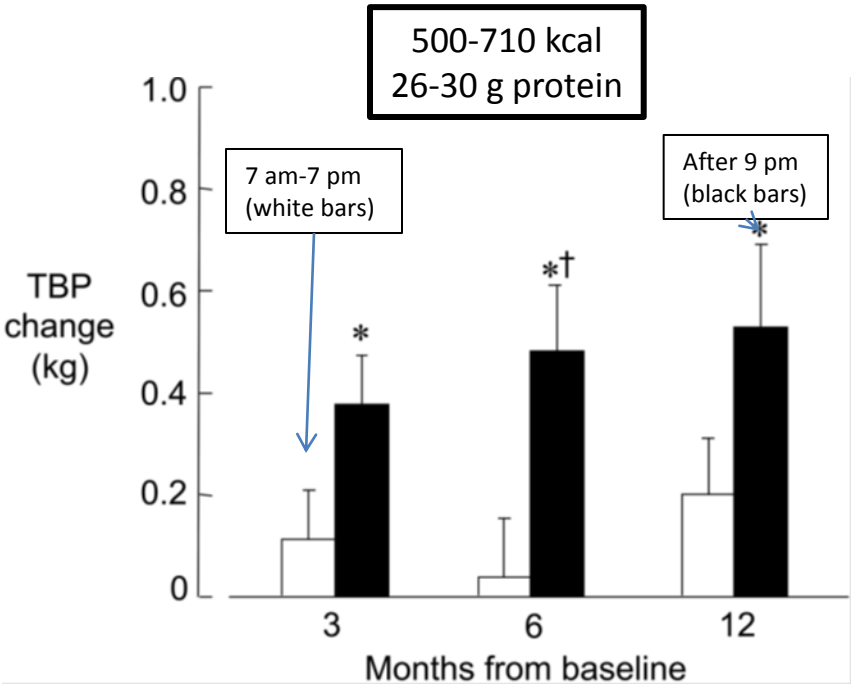
Cabre E; Hepatology 2000;32:36–42



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

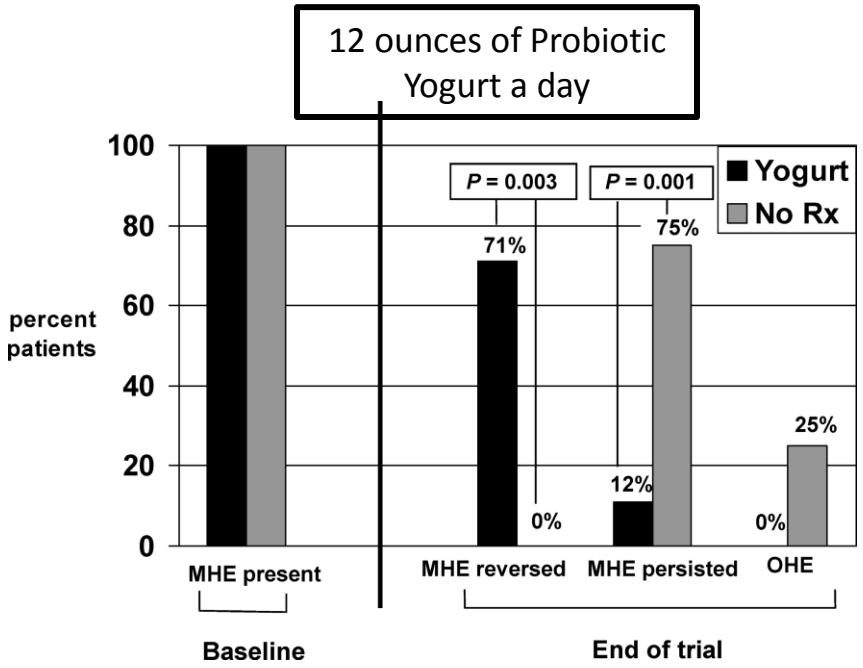
Nutrition in Cirrhosis

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



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

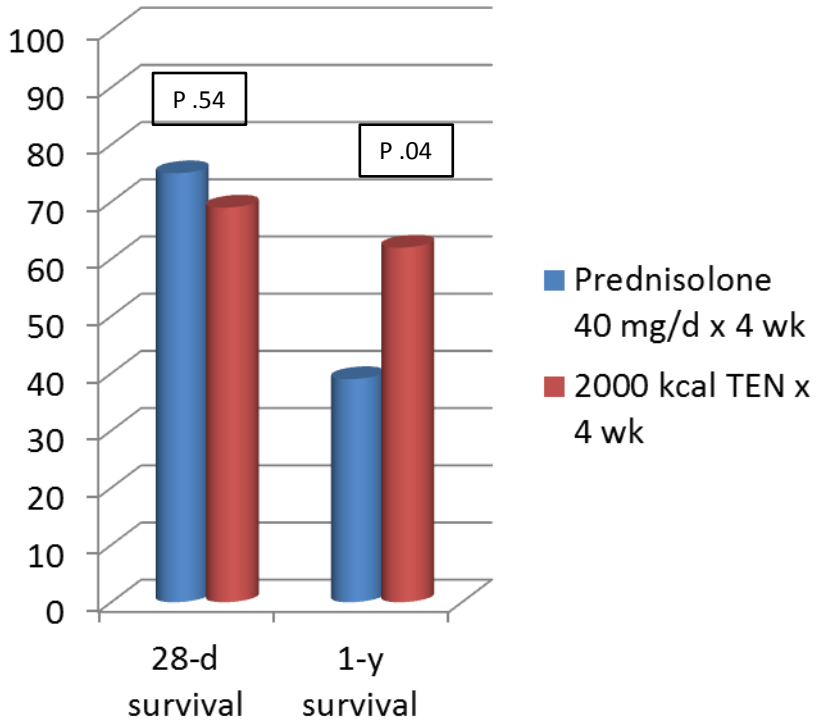
Probiotic Yogurt in Covert Hepatic Encephalopathy
Bajaj JS; Am J Gastroenterol 2008;103:1707-1715



Probiotic Yogurt Improves Covert HE & Protects against Overt HE

Enteral Nutrition in Alcoholic Hepatitis

Cabre E; Hepatology 2000;32:36–42



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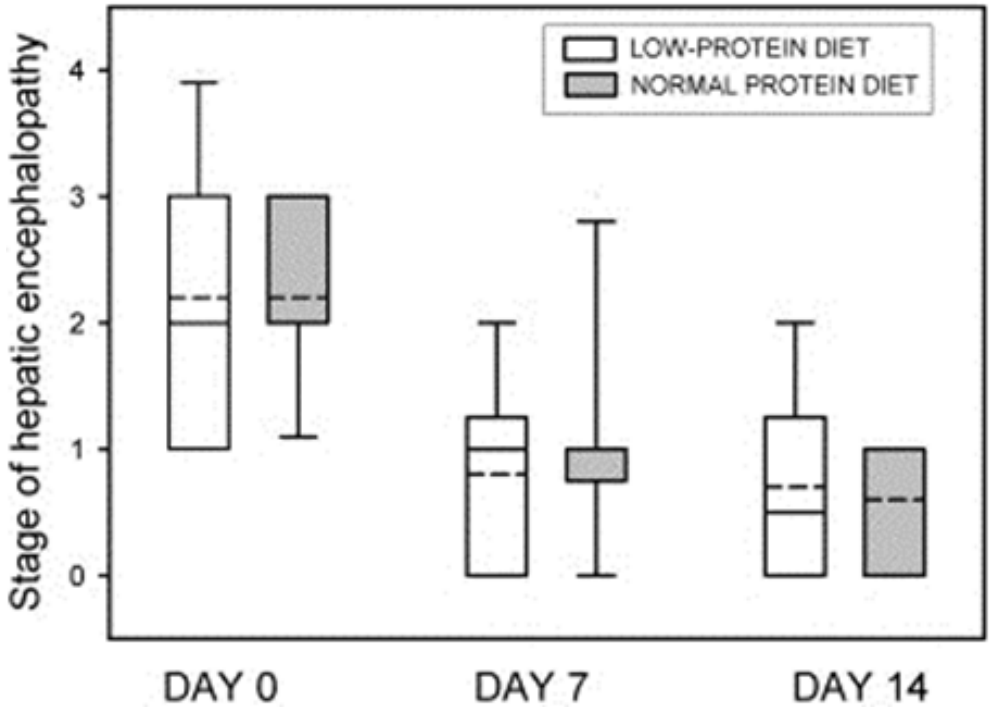
Low- vs Normal-Protein Diet in HE

Cordoba J; J Hepatol 2004;41:38–43



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