Minimizing Complications in Cirrhosis

Luis S. Marsano, MD, FACG, FAASLD
Professor of Medicine
Director of Clinical Hepatology
University of Louisville & Louisville VAMC
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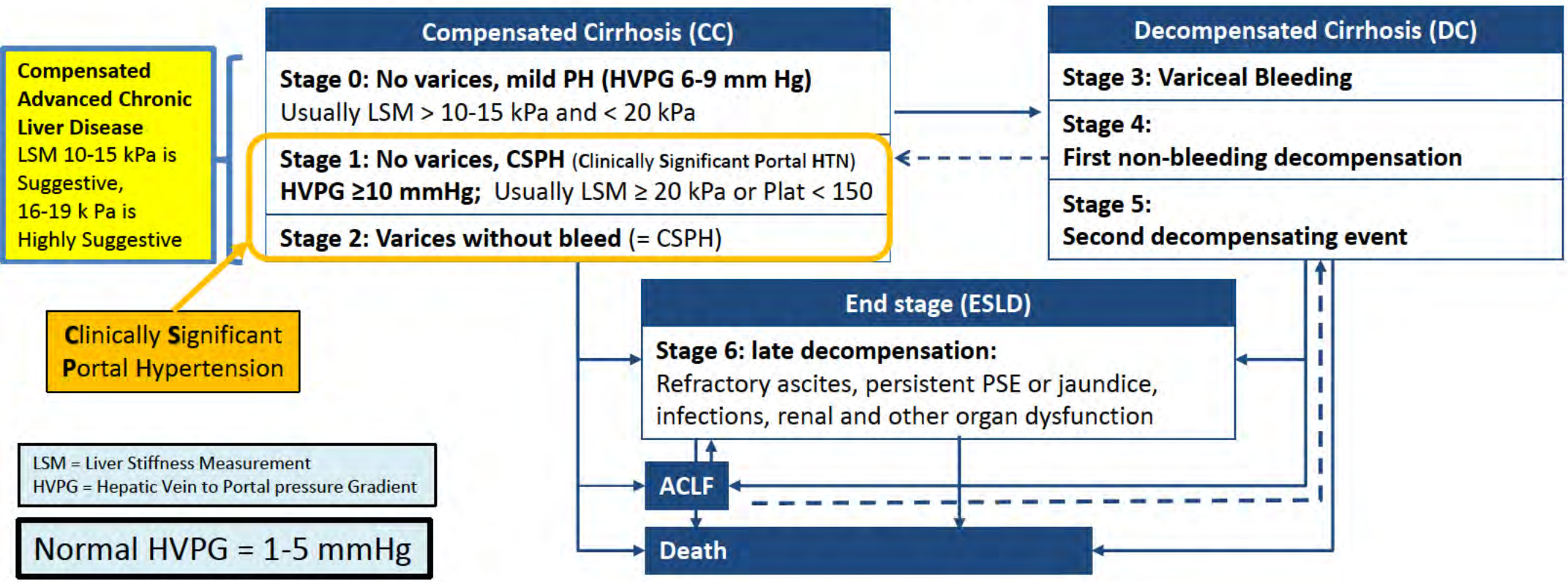
Multi-stage model for the clinical course of cirrhosis (Compensated to Decompensated Cirrhosis)

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



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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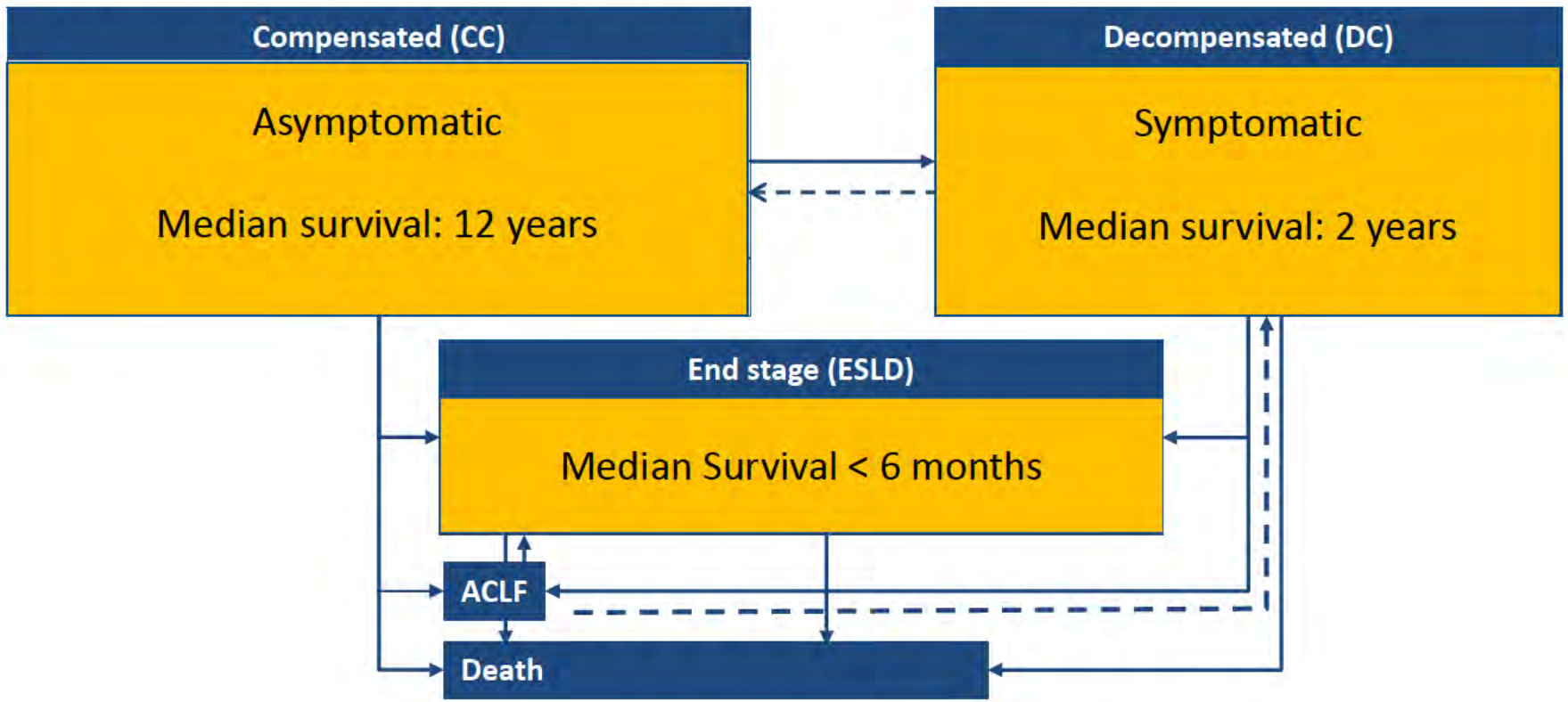

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Pharmacologic Prevention of Decompensation

Clinically Significant Portal Hypertension (CSPH)

Clinically Significant Portal Hypertension (CSPH) by TE & Platelet Count

- Compensated Advanced Chronic Liver Disease (Baveno VI)(**cACLD**):
  - LSM 10-15 kPa is suggestive of cACLD and **16-19 kPa is suggestive of cACLD**
- **CSPH Ruled in** (except in NASH with BMI >/= 30) **by**:
  - Liver Stiffness Measurement (LSM) >/= 25 kPa (PPV > 90%)
  - LSM 20-25 kPa and Platelet Count < 150,000, or LSM 15-20 kPa & Plat < 110,000
  - EGD, CT Scan or MRI showing Esophageal varices or Porto-Systemic collaterals
- **CSPH Ruled Out by:**
  - LSM < 15 kPa AND Platelet count >/= 150,000 (NPV > 90%)

PREDESCI trial + Meta-Analysis of Carvedilol in compensated cirrhosis: patients with compensated cirrhosis and CSPH but without High-Risk Varices treated with **Carvedilol** (6.25 mg/d and titrated up to 25 mg/d or maximum dose tolerated, keeping BPs >/= 90 mm Hg & MAP >/= 65 mm Hg) had an increased decompensation-free survival, especially a delayed development of ascites (Lancet 2019; 393: 1597–608; Gastroenterology 2021; 161:770-773)

Statins decrease risk of decompensation and death in cirrhosis (Mohanty, A et al. Gastroenterology 2016;150:430–440). To be safe use Simvastatin 20 mg/day only if Bili < 5 mg/dL and not in Child-Pugh C.

Probability of CSPH in NASH

Pons M et al. Am J Gastroenterol 2021;116:723–732

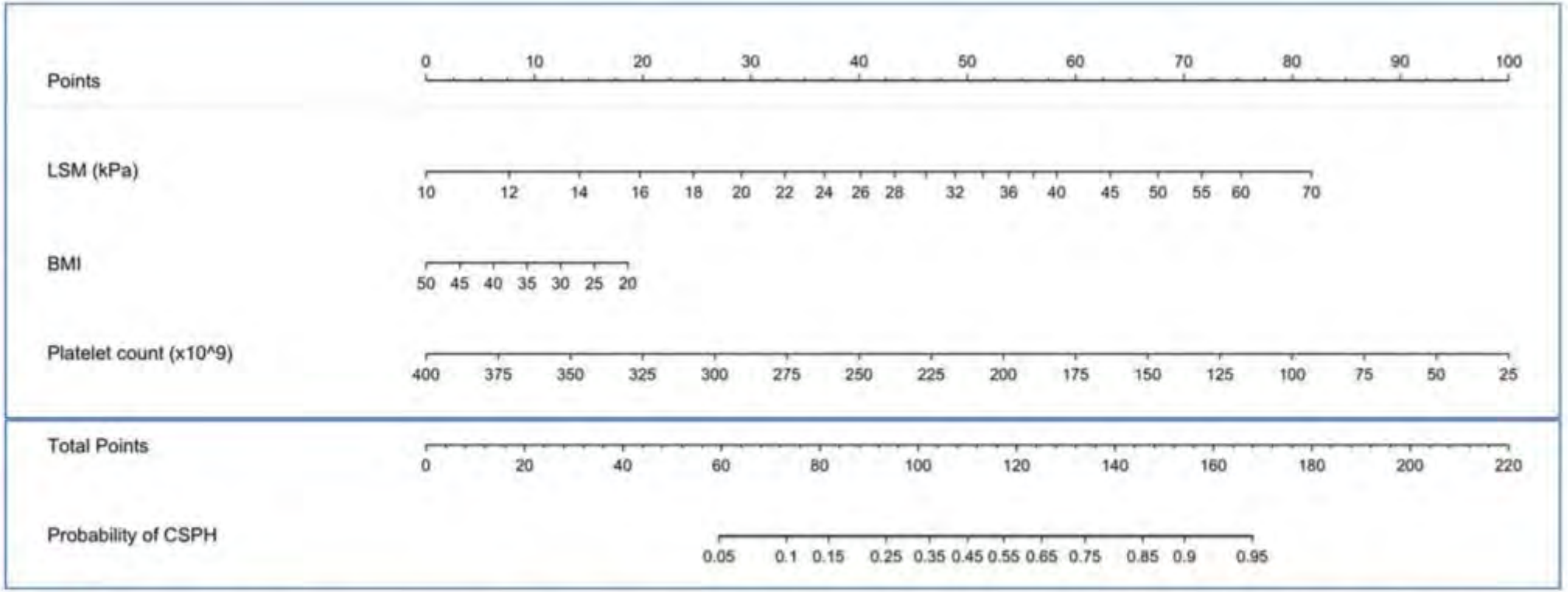
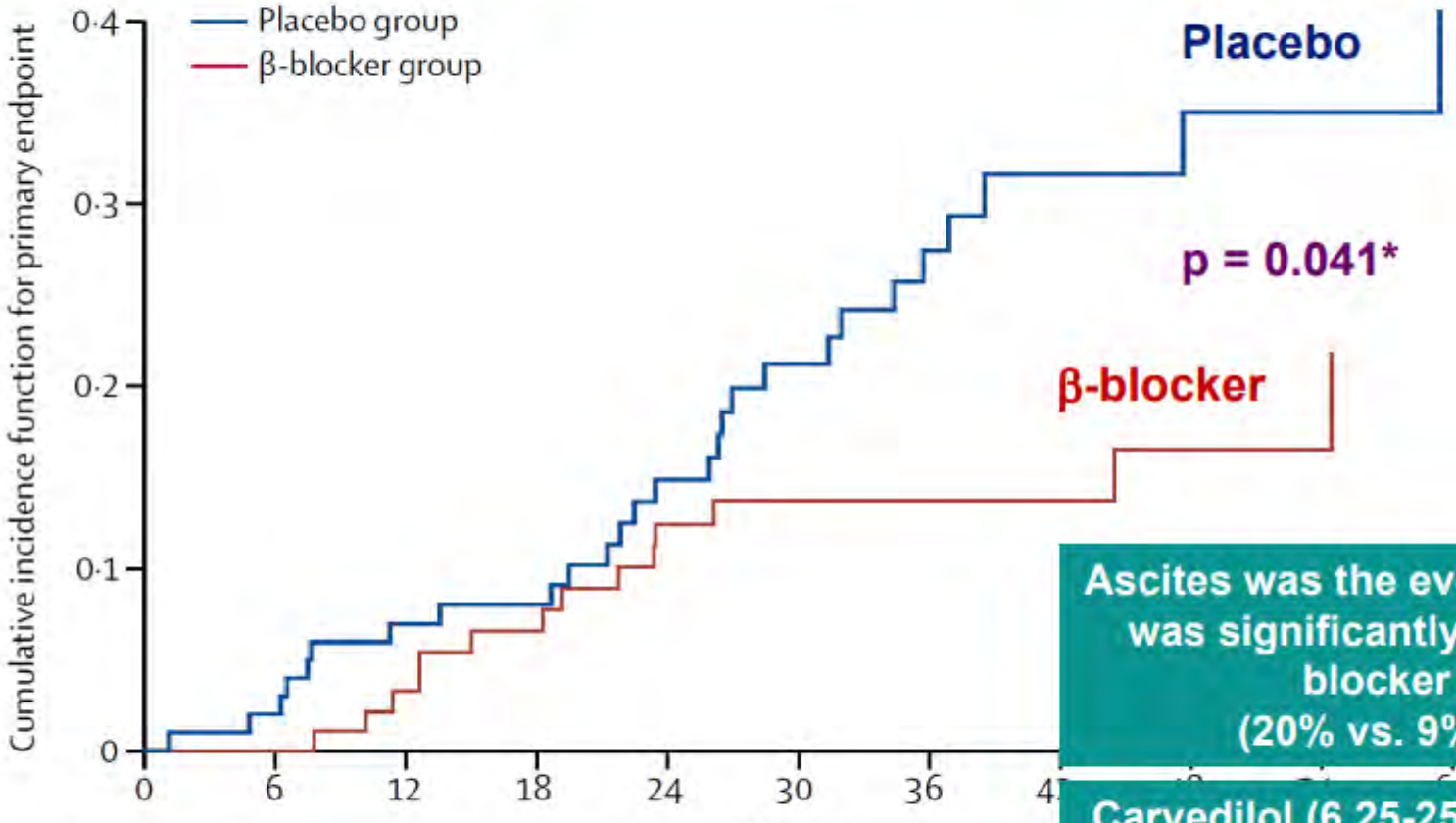


Figure 3. Nomogram to predict the presence of clinically significant portal hypertension (CSPH) in patients with nonalcoholic steatohepatitis (NASH) using the variables liver stiffness measurement (LSM), body mass index (BMI), and platelet count. To obtain the risk of CSPH trace a vertical line from each of the 3 predictors' axis to the first line ("points"). Add the total points and trace a vertical line from the "total points" axis to the probability axis to calculate the risk of CSPH. As shown, a patient with a LSM value of 20 kPa (29 points), a BMI of 35 (9 points), and a platelet count of 150×10^9 (67 points) would have a predictive probability of CSPH of 40% (for a total of 105 points).

In a RCT, β-blockers prevented decompensation and/or death in patients with compensated cirrhosis (mostly HCV) and CSPH (no or small varices)

Probability of developing any decompensating event / death



Ascites was the event that, by itself, was significantly lower in the β-blocker group (20% vs. 9%, p=0.03)

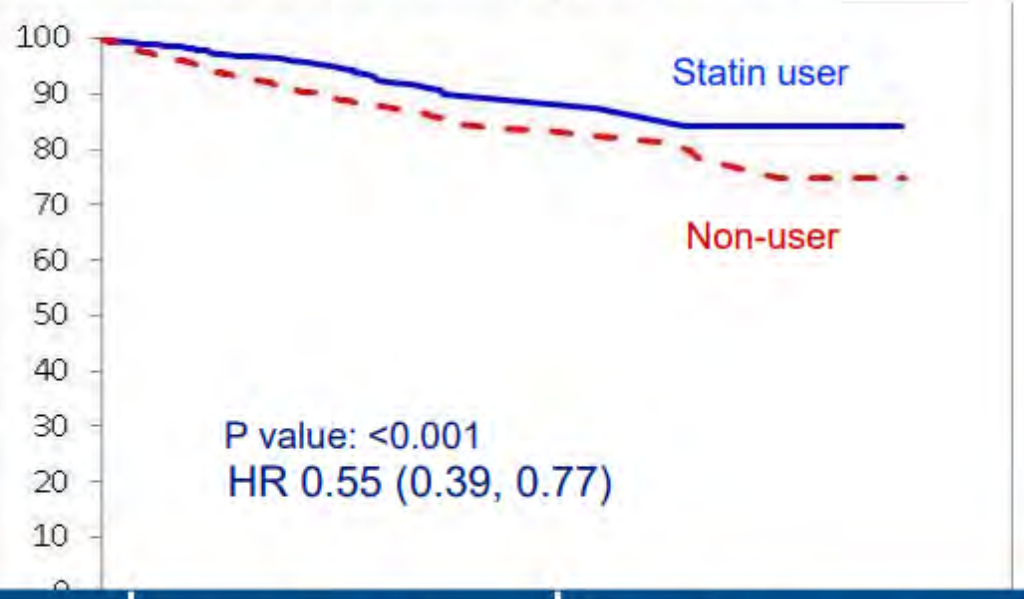
Carvedilol (6.25-25 mg QD) seemed to be more effective than propranolol (40-160 mg BID), titrated to a heart rate >55 bpm and systolic blood pressure >90 mmHg

Villanueva et al (PREDESCI trial). Lancet 2019 20;393:1597-1608

CSPH= clinically significant portal hypertension defined as an HVPG ≥ 10 mmHg

Statins are associated with a decreased risk of decompensation and death in HCV compensated cirrhosis*

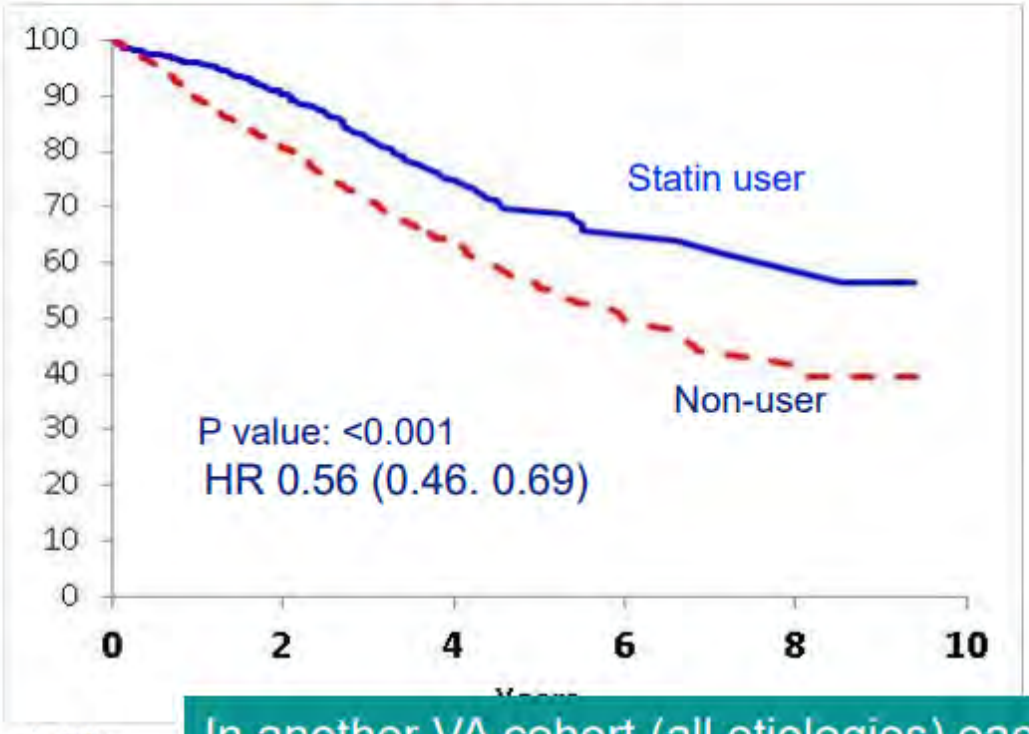
Free of decompensation



	Ascites		Variceal Hemorrhage	
	Events	Rate	Events	Rate
Non-user	112	2.4	58	1.3
Statin user	26	1.4	9	0.5
	0.59 (0.39,0.91) p=0.02		0.39 (0.19,0.78) p=0.01	

Mohanty, Tate and Garcia-Tsao. Gastroenterology. 2016;151:374

Free of death



No. at risk	
User	685
Nonusr	2062

In another VA cohort (all etiologies) each cumulative year of statin exposure was associated with an 8%-9% decrease of mortality in Child A/B patients

Kaplan et al. Gastroenterology 2019;156:1693-1706

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:

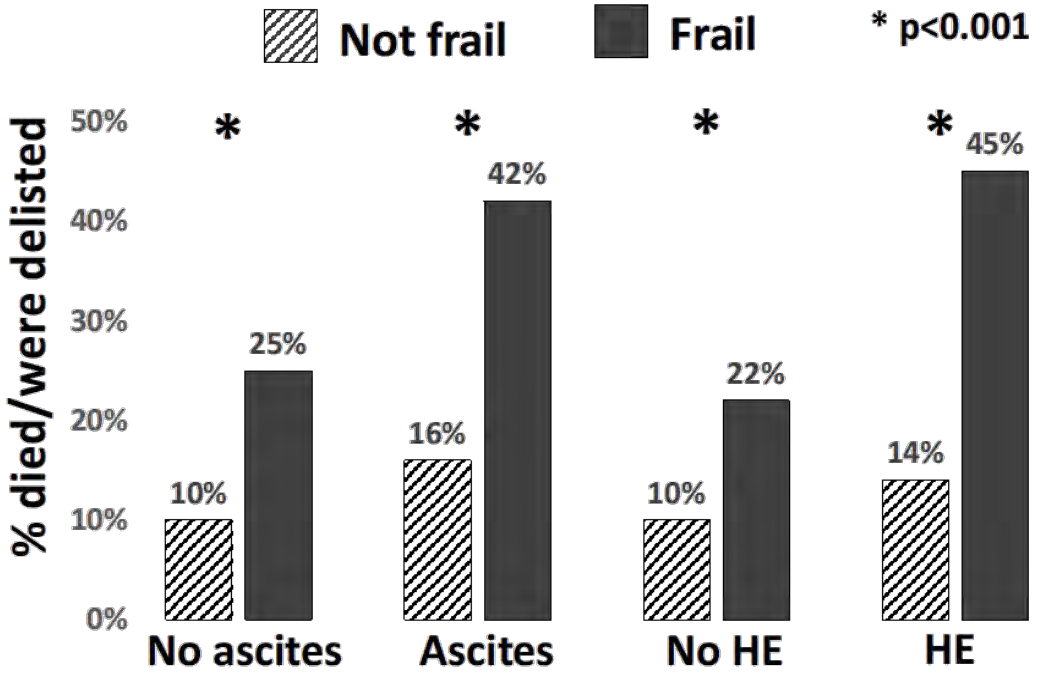
To investigate the relationship between physical frailty and ascites/hepatic encephalopathy (HE)

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

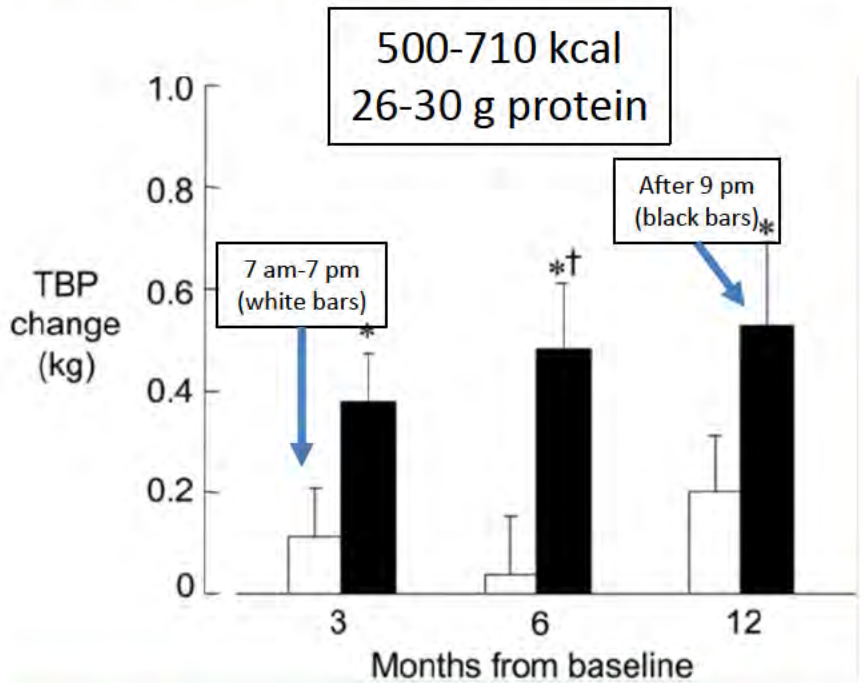
https://liverfrailtyindex.ucsf.edu/

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

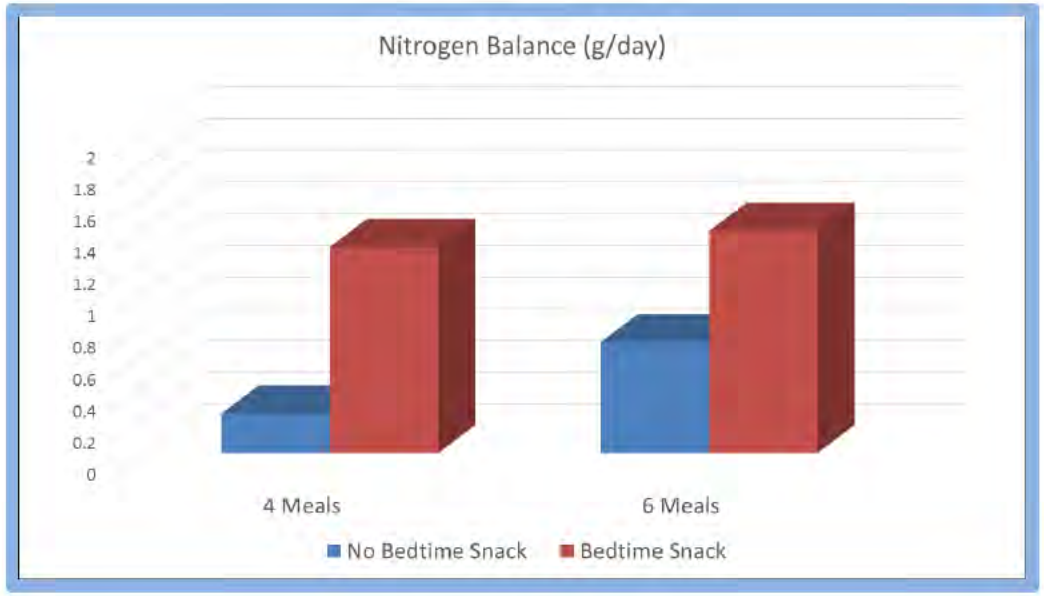


Bed-time Nutrition Increases Nitrogen Retention & Muscular Mass

(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

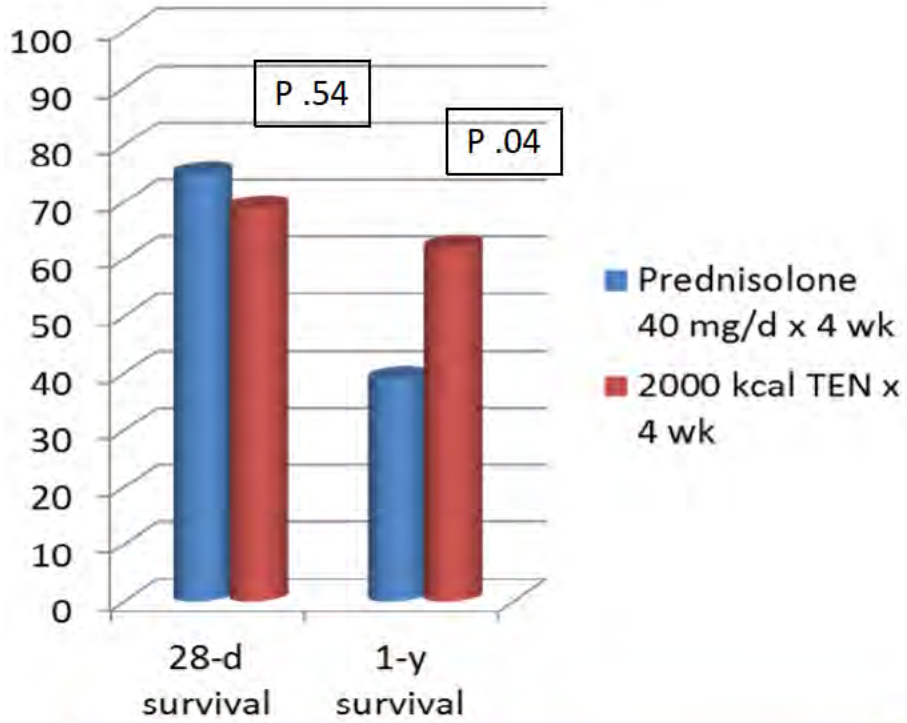


Bedtime Supplement is more important than Frequent meals

Nutrition in Alcoholic Hepatitis

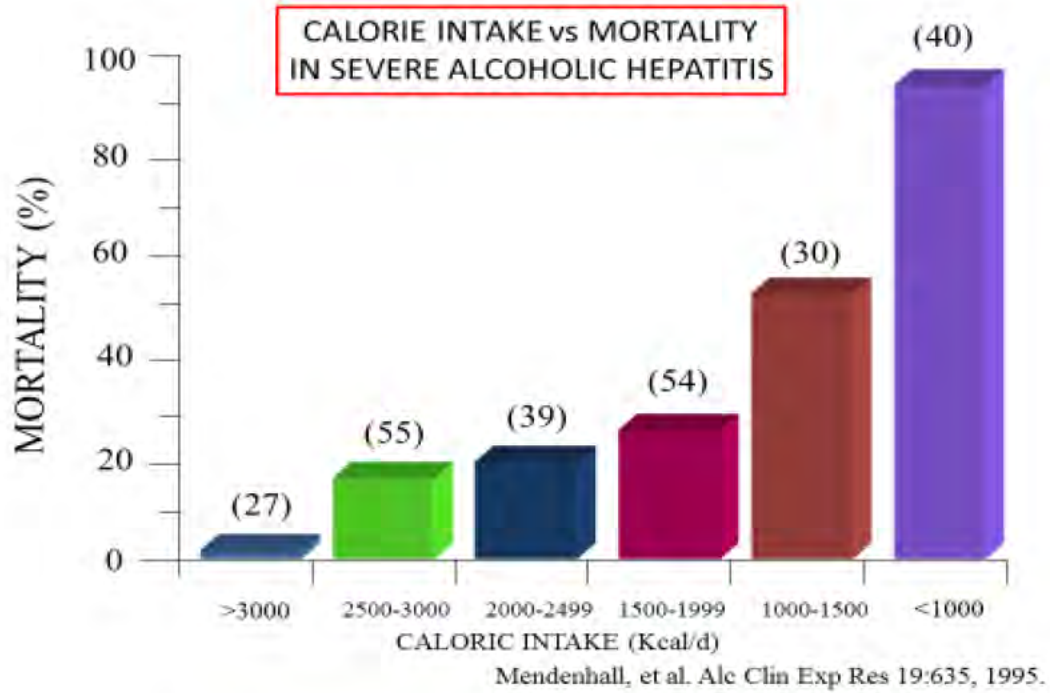
Enteral Nutrition in Alcoholic Hepatitis

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



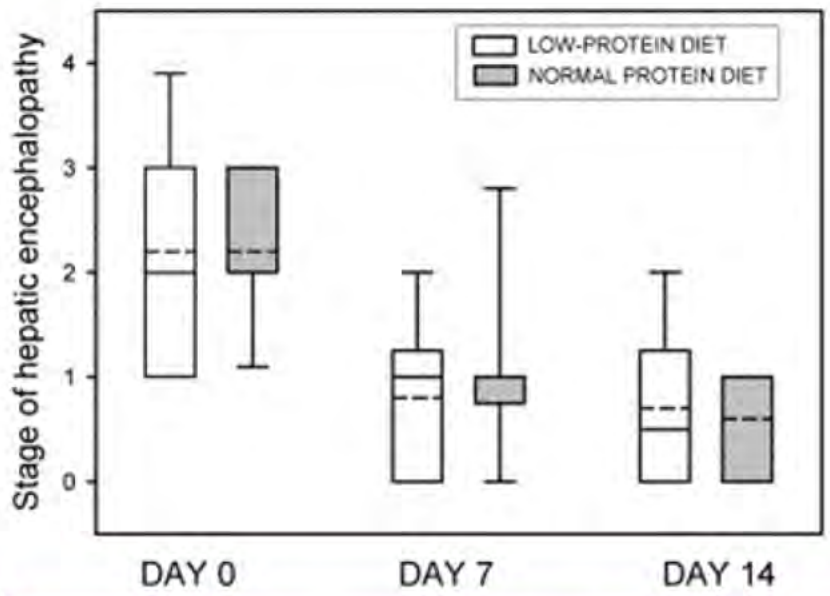
Mendenhall, et al. Alc Clin Exp Res 19:635, 1995.

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

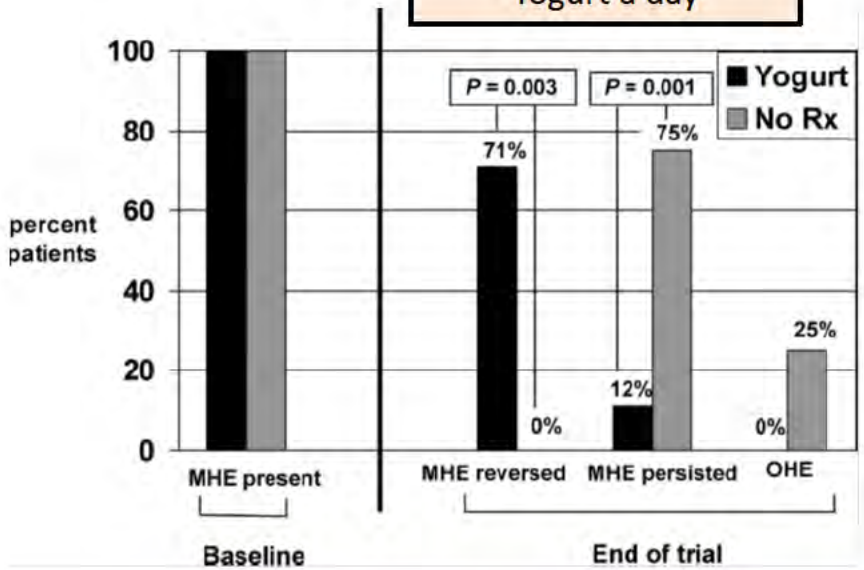


Diet with "normal protein intake" improves HE equally as "low protein" diet

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

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.

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)

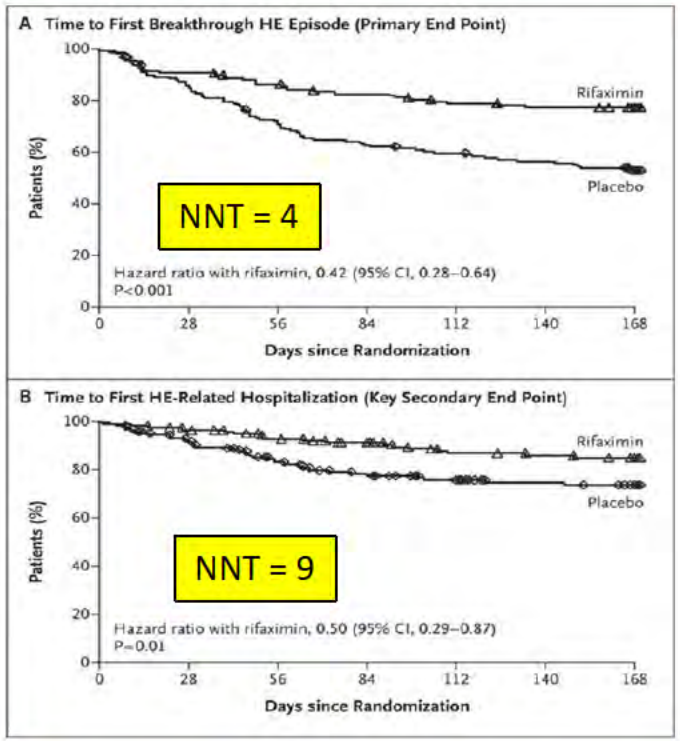
Mechanism of Action of Therapies for HE

- **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.

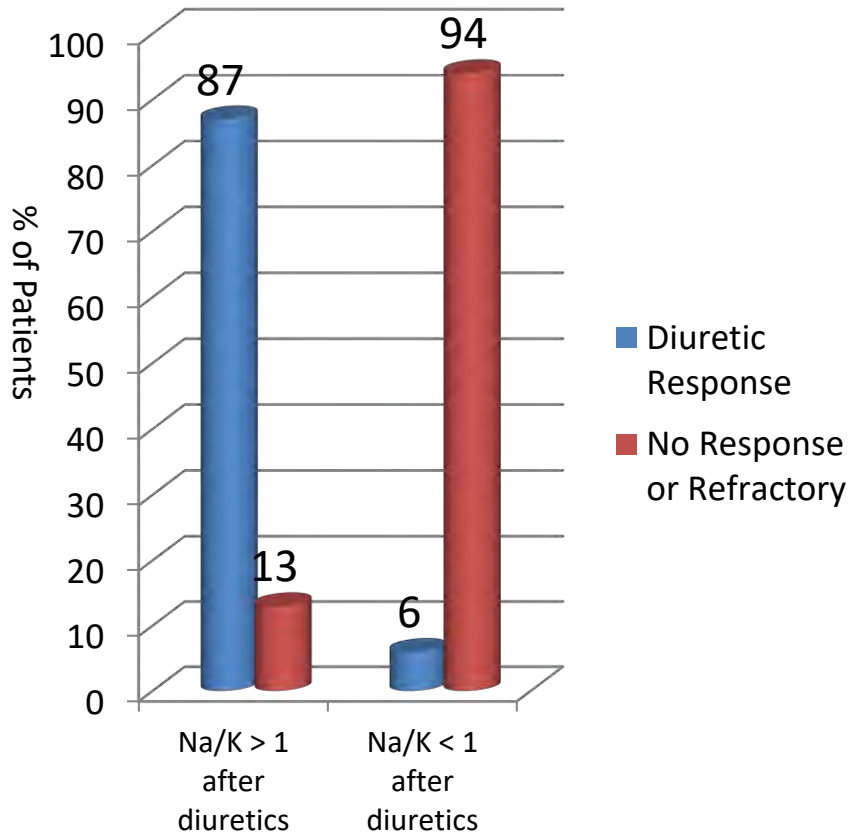
Ascites Management

- 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”

Assessment of Ascites Diuretic- Response by spot urine Na/K ratio

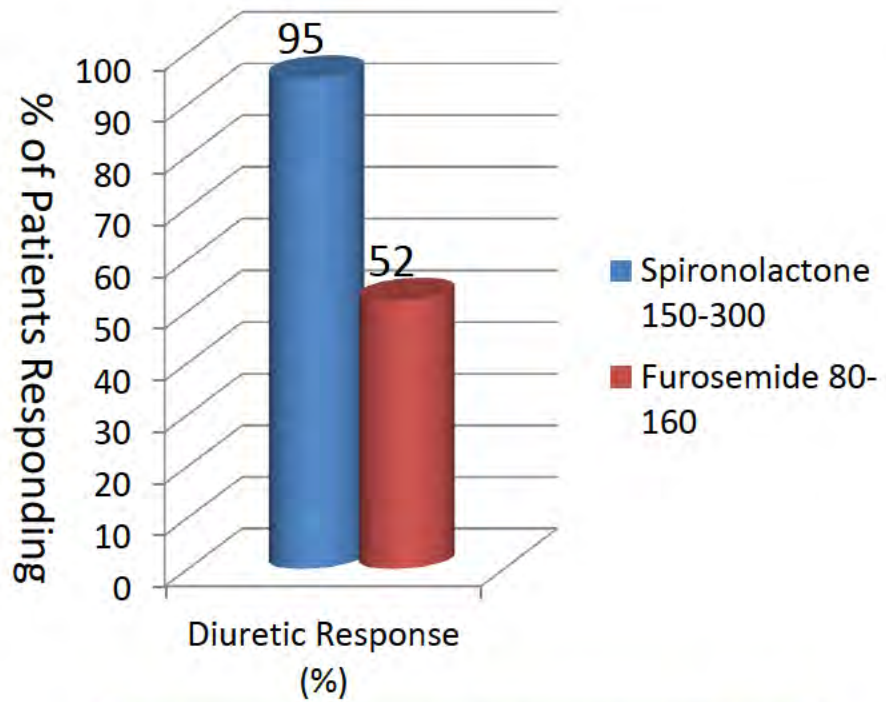
Runyon B et al. Hepatology 2002; 36(4):222A

- 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”



Ascites Management

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



Spironolactone is superior to Furosemide in controlling ascites

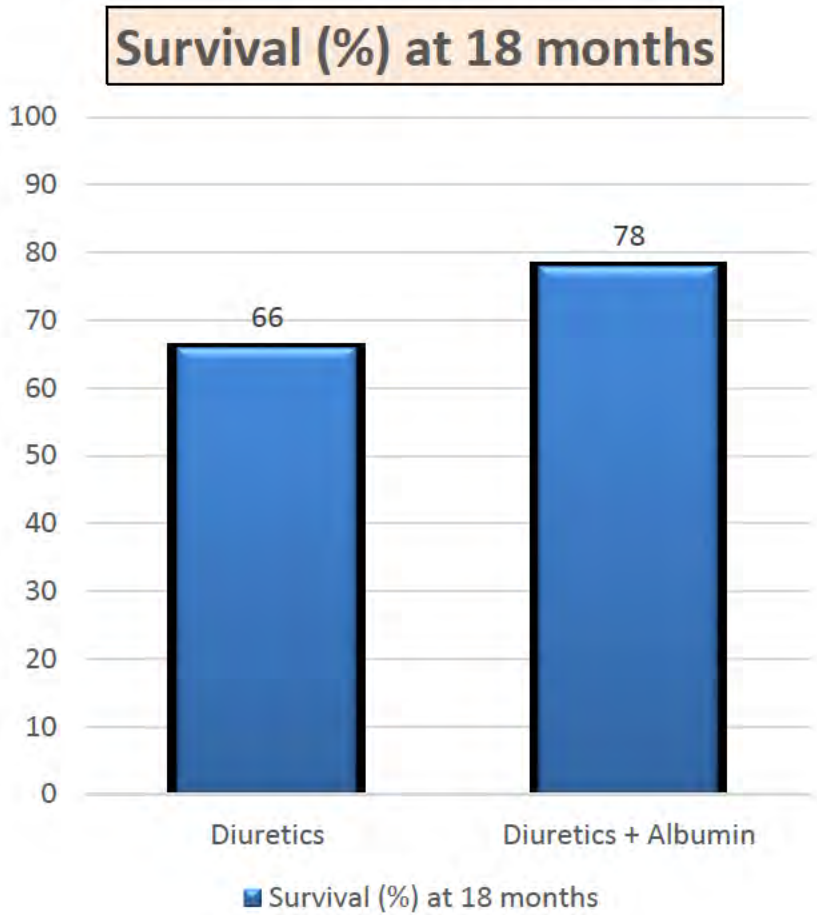
Diuretic Titration

- 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.

IV Albumin in Cirrhosis with Ascites

ANSWER STUDY: Caraceni P , Riggio O , Angeli P , et al . Long-Term albumin administration in decompensated cirrhosis (answer): an open-label randomised trial. Lancet 2018;391:2417–29

- 440 cirrhotics with non-refractory ascites.
- Mean: Age 60, Child-Pugh 8.1, MELD 13.
- Exclusion: refractory ascites, HCC.
- All on spironolactone + furosemide.
- F/U 18 months.
- Randomized Groups:
  - A) Diuretics + diet.
  - B) Diuretics + diet + **IV Albumin 40 grams BIW x 2 weeks and then once a week**.
- **Primary end point:** Survival
- **Secondary end points:** Paracentesis > 3 per month, Hospital admission, Other complications, QofLife.
- Other Results:
  - Decrease in PSE, HRS, Infections, any paracentesis (38% vs 66%) and 25% less days in Hospital.
  - Tendency to better QofL.



Refractory Ascites

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

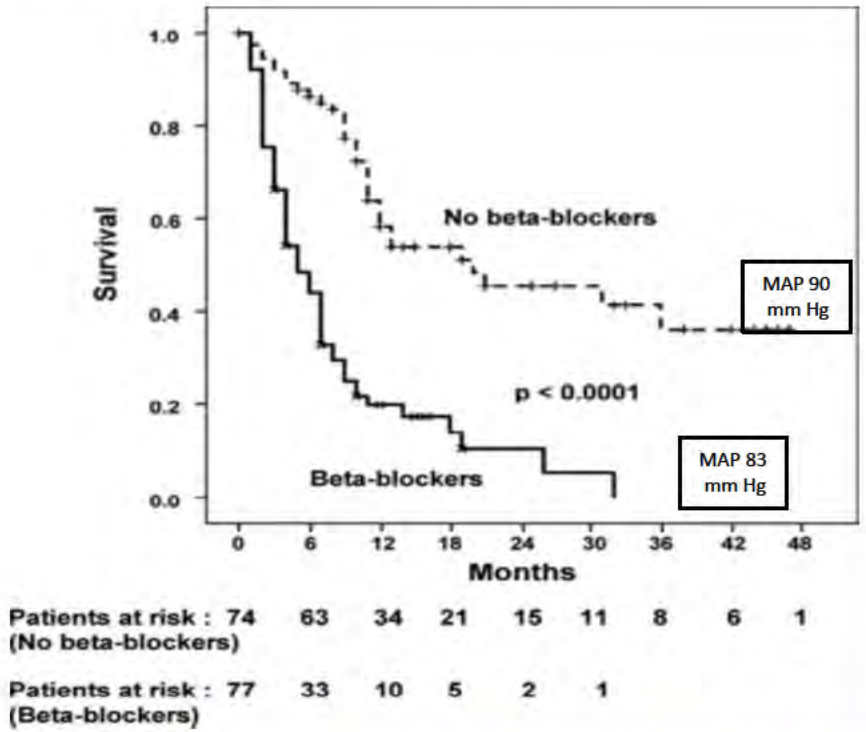
Refractory Ascites
What We Know

- Refractory ascites (RA) and hyponatremia are predictive of development of Hepatorenal Syndrome (HRS) and of short survival.
- In Refractory Ascites, Beta-blockers decrease patient's survival (if MAP < 65 mm Hg).
- 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

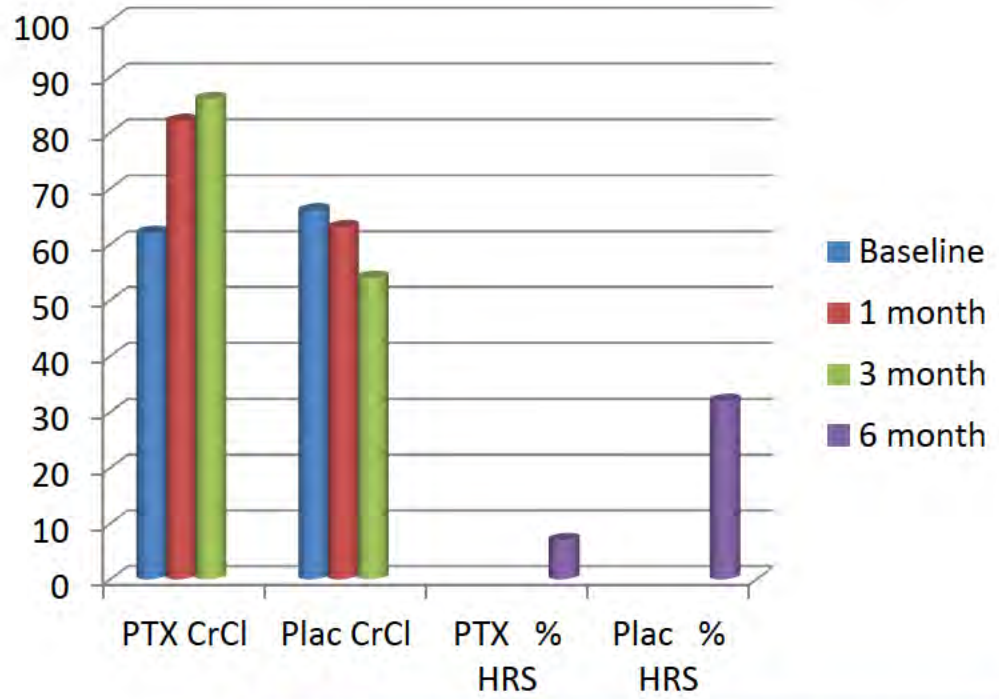
Serste T; Hepatology 2010;52(3):1017-1022



Beta-blockers decrease survival in patients with refractory ascites

Pentoxifylline in ascites with CrCl 41-80

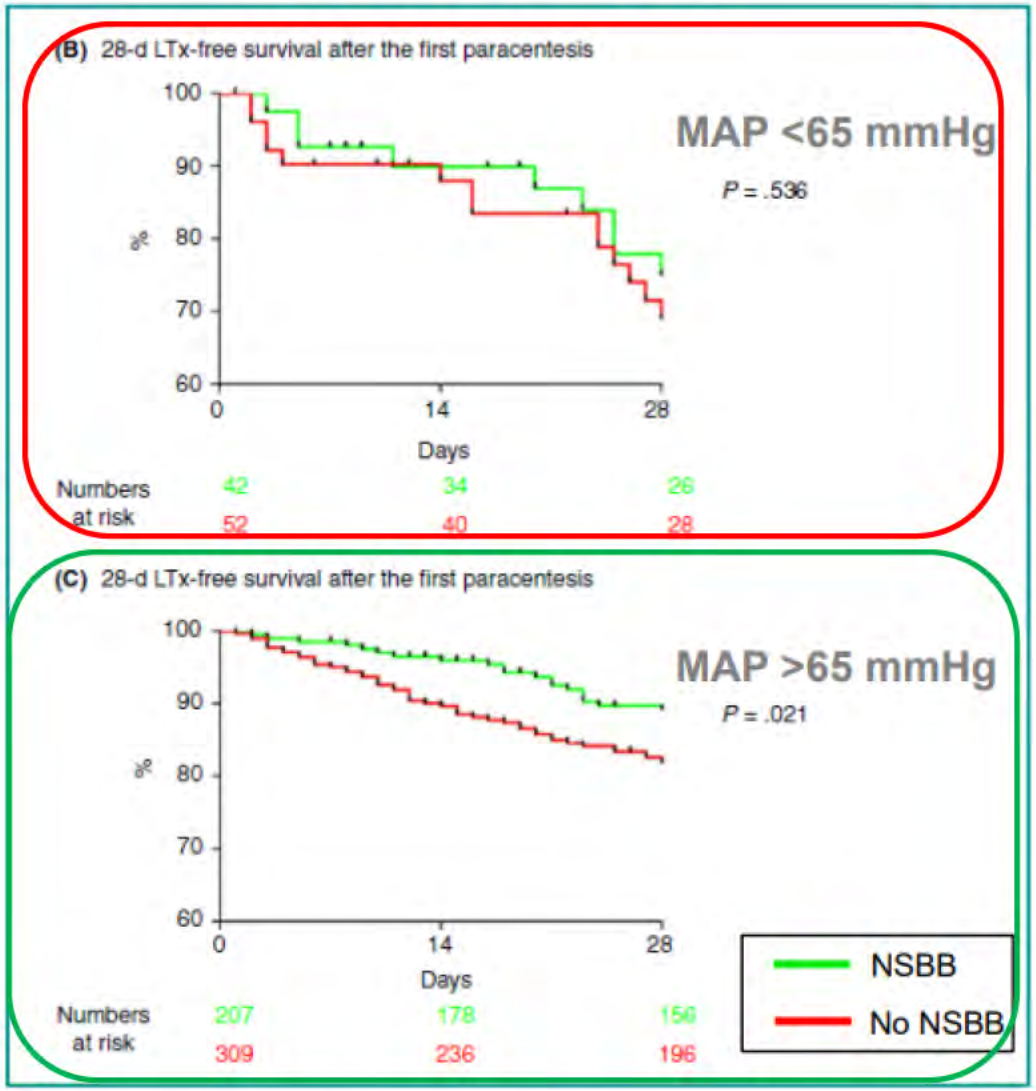
Tyagi P; Eur J Gastroenterol Hepatol 2011;23(3):210-7



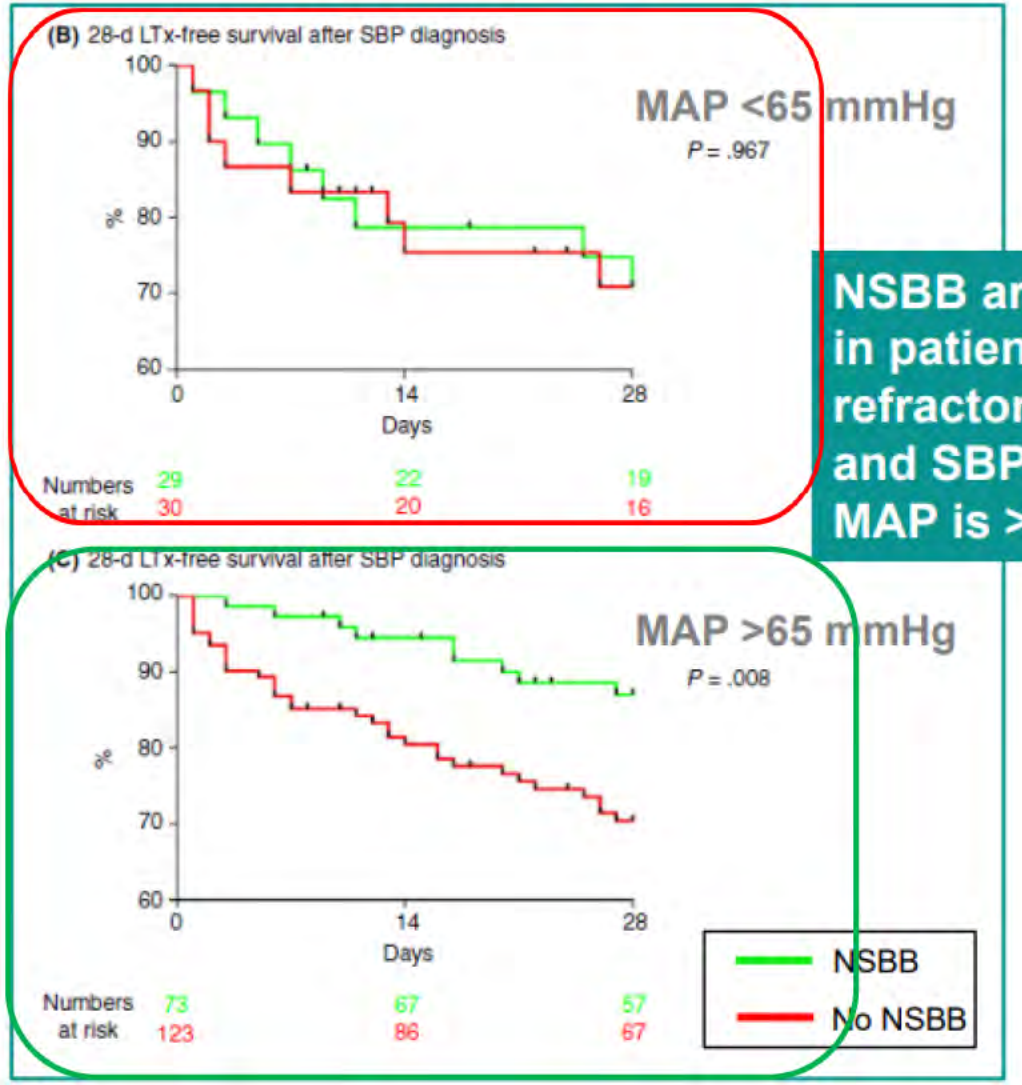
In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS

Systemic arterial blood pressure determines the therapeutic window of non-selective beta-blockers (NSBB) in decompensated cirrhosis

Ascites requiring LVP



Ascites with SBP



NSBB are beneficial in patients with refractory ascites and SBP as long as MAP is >65 mmHg

Tergast et al. APT 2019;50:696–706

Determination of MAP

Calculated = MAP = (SBP + 2 x DBP)/3

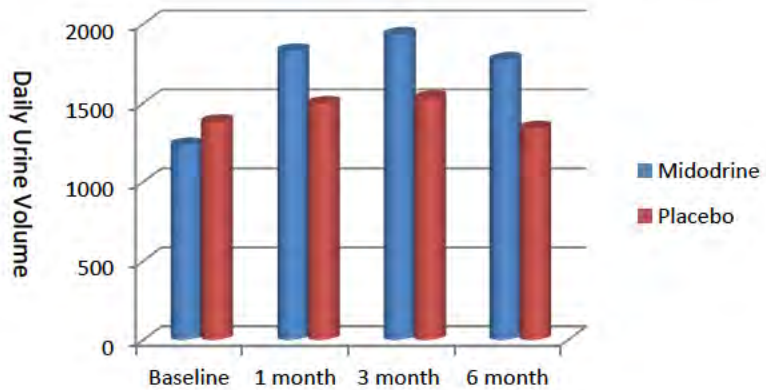
Measured by the Equipment

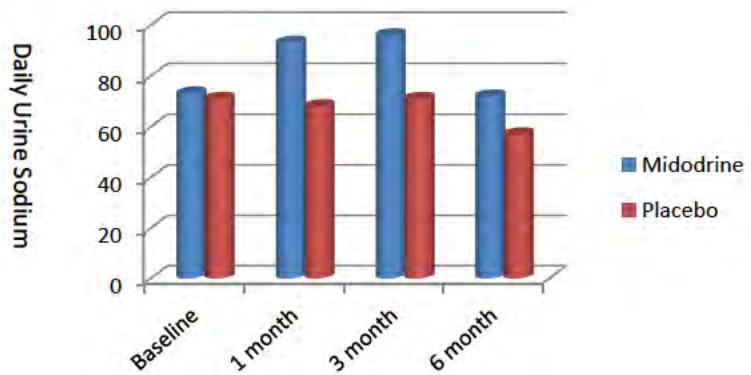
The maximal oscillation during cuff inflation or deflation corresponds to the mean arterial pressure (MAP).
This measured value (the MAP) is used to estimate systolic and diastolic BP with mathematical algorithms.

Ascites & Refractory Ascites

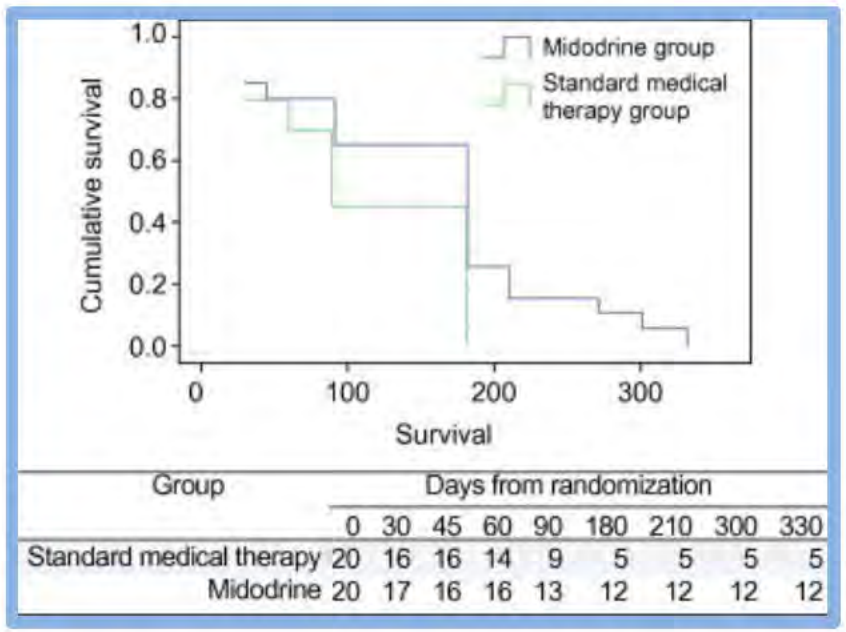
Midodrine in Refractory/Recurrent Ascites

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





Midodrine 7.5 mg PO, TID

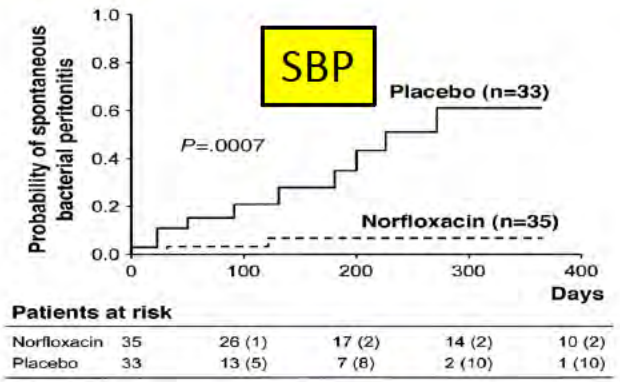


Group	Days from randomization								
	0	30	45	60	90	180	210	300	330
Standard medical therapy	20	16	16	14	9	5	5	5	5
Midodrine	20	17	16	16	13	12	12	12	12

In Refractory ascites, Midodrine increases Natriuresis and improves Survival

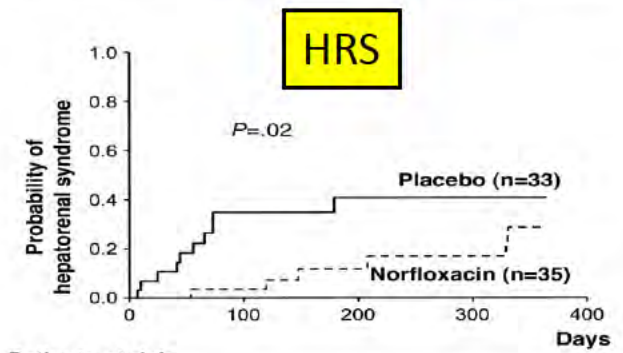
Ascites & Refractory Ascites

- Norfloxacin prophylaxis in Child-Pugh >/= 9 with ascites with either bili > 3, or creat > 1.2, or Na < 130



Patients at risk

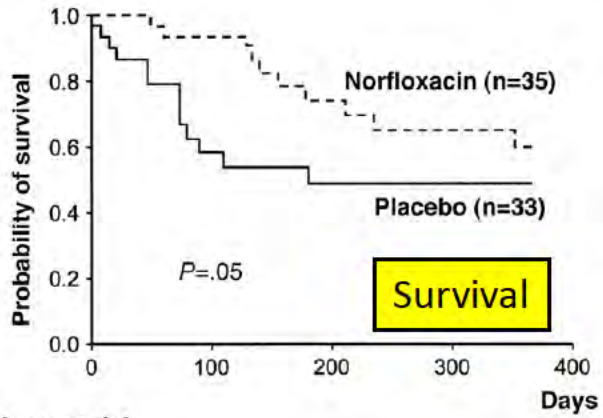
Norfloxacin	35	26 (1)	17 (2)	14 (2)	10 (2)
Placebo	33	13 (5)	7 (8)	2 (10)	1 (10)



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.

Prevention of Mortality with Primary SBP Prophylaxis

Meta-analysis: prevention of mortality in pure primary prophylactic RCT's

Study or subgroup	Fluroquinolones Events	Total	No prophylaxis Events	Total	Weight	RR M-H, Fixed, 95% CI
Fernandez 2007[145]	10	35	13	35	35.1%	0.77 (0.39 to 1.52)
Grange 1998[146]	8	53	10	53	27.0%	0.80 (0.34 to 1.87)
Terg 2008[140]	6	50	14	50	37.8%	0.43 (0.18 to 1.03)
Total (95% CI)		**138**		**138**	**100.0%**	**0.65 (0.41 to 1.02)**
Total events	24		37			

Heterogeneity: χ^2=1.34, df=2 (p=0.51); I^2=0%
Test for overall effect: Z=1.88 (p=0.06)

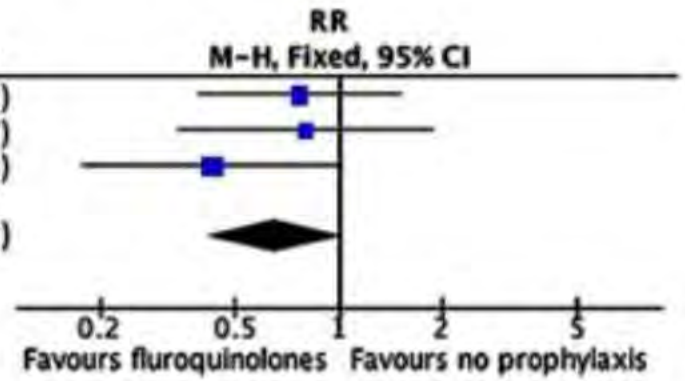


Figure 4 Meta-analysis of randomised controlled trials of primary prophylaxis for spontanous bacterial peritonitis (12 months follow-up).

Gut 2012;**61**:297–310. doi:10.1136/gutjnl-2011-300779

Primary prophylaxis with norfloxacin 400 mg/day (or Cipro 500 mg/day) in patients with Child-Pugh score ≥ 9 and serum bilirubin ≥ 3 mg/dl, with either impaired renal function (Cr >/=1.2) or hyponatremia (Na </=130), and ascitic fluid protein lower than 1.5 g/dL is recommended (I;1) (EASL 2018)

SBP Incidence is 27-41% when Ascites Protein is </= 1 g/dL; Primary prophylaxis is also indicated

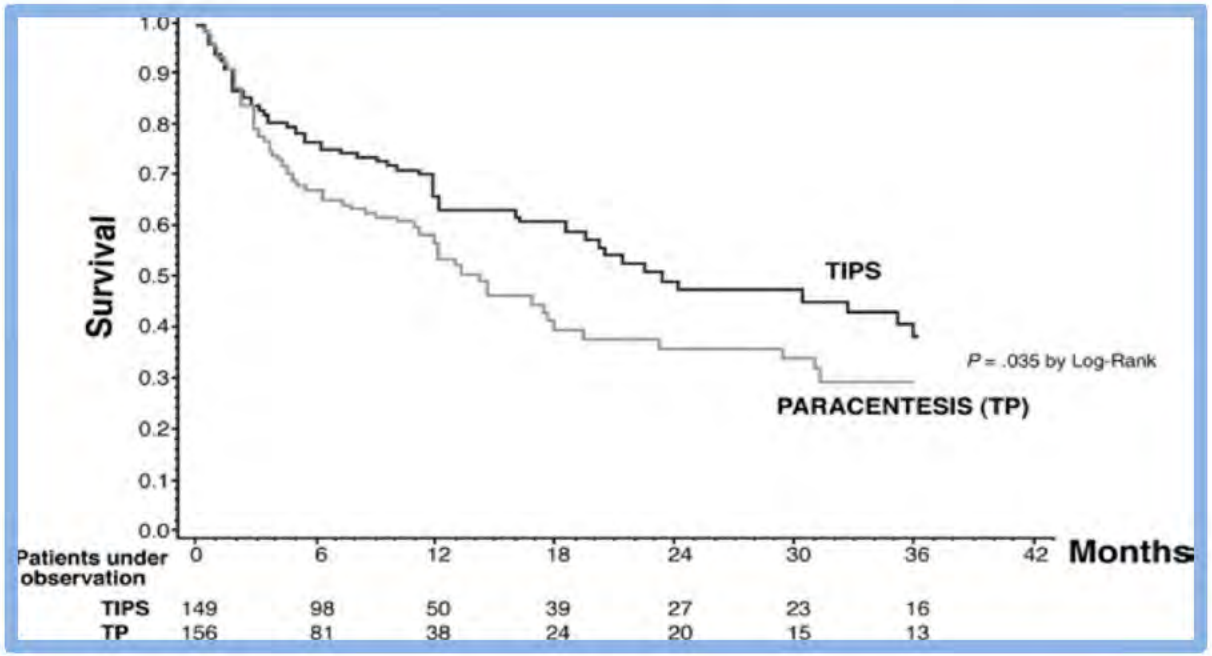
Refractory Ascites

- Management:
  - Evaluate for Liver Transplant, if potential candidate.
  - Treat esophageal varices with banding and D/C beta-blockers if MAP < 65 mm Hg.
  - 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:** TIPS with 8 mm PTFE-covered stent, if MELD < 15, or 16-20 with Bilirubin < 3 mg/dL. TIPS specially preferred if:
      - Loculated Ascites
      - LVP needed too frequently
      - TIPS indicated for additional indication (like variceal bleed)
    - **Second Line:** Large volume paracentesis with albumin replacement to control ascites.
  - 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

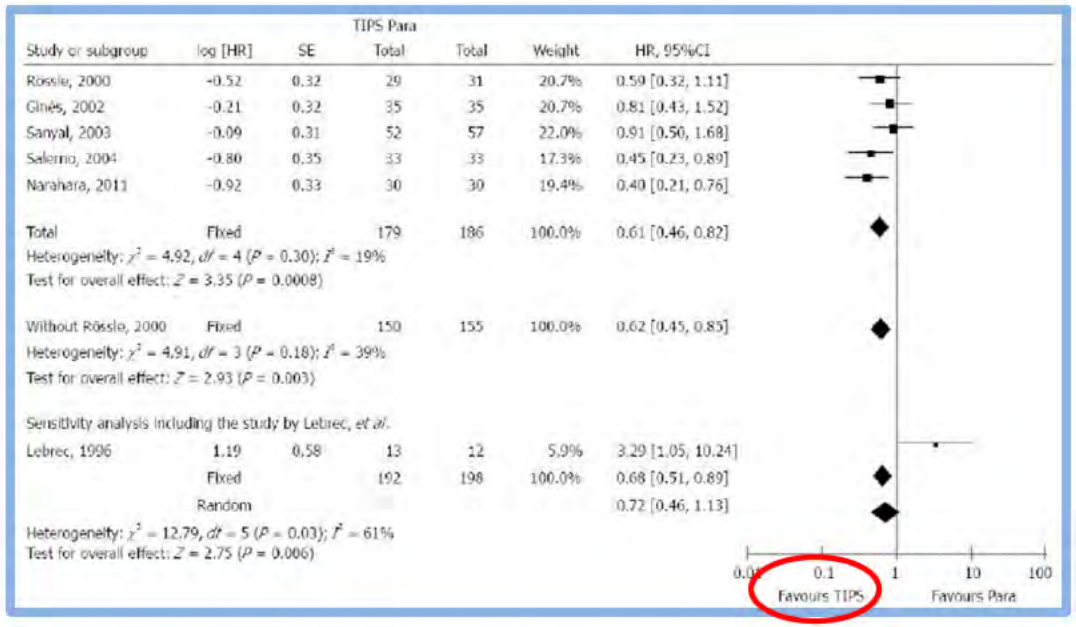


Survival was higher with TIPS than with LVP up to a MELD of 20

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

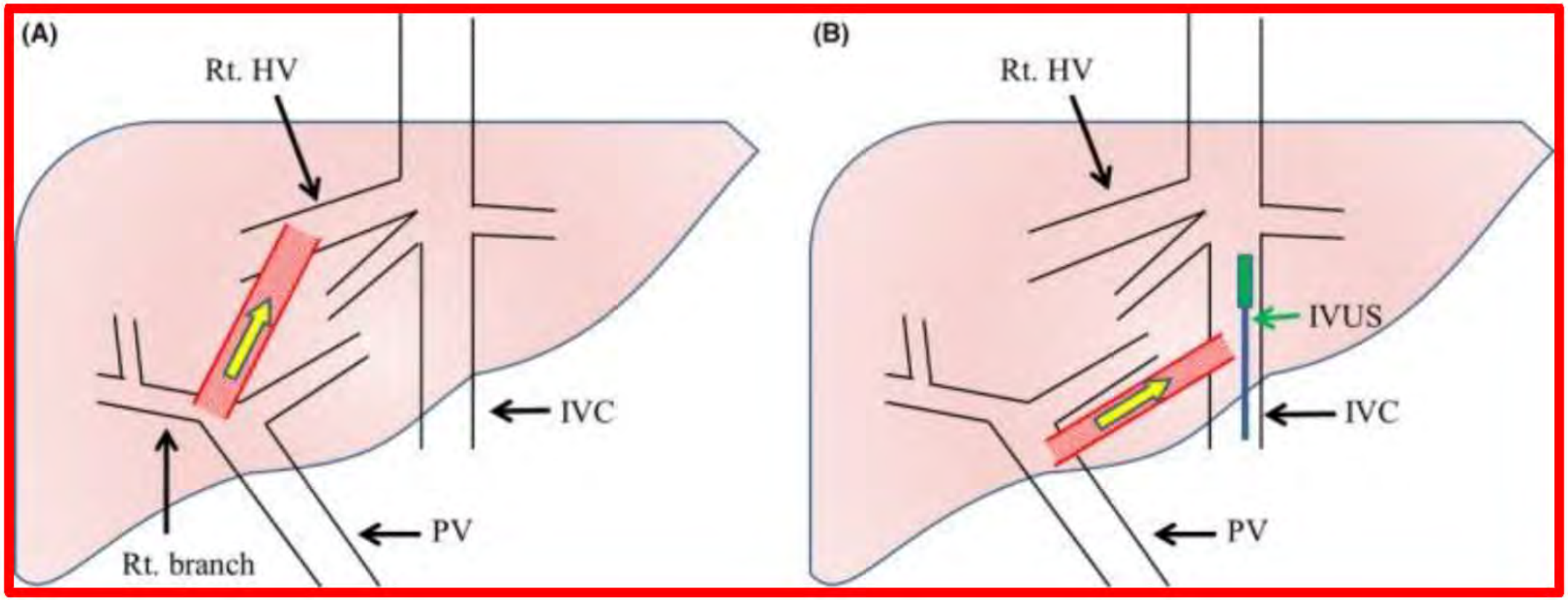
TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: An updated meta-analysis

Ming B et al. World J Gastroenterol. 2014 March 14; 20(10): 2704–2714



TIPS improves Transplant-free Survival in Refractory Ascites

TIPS and DIPS

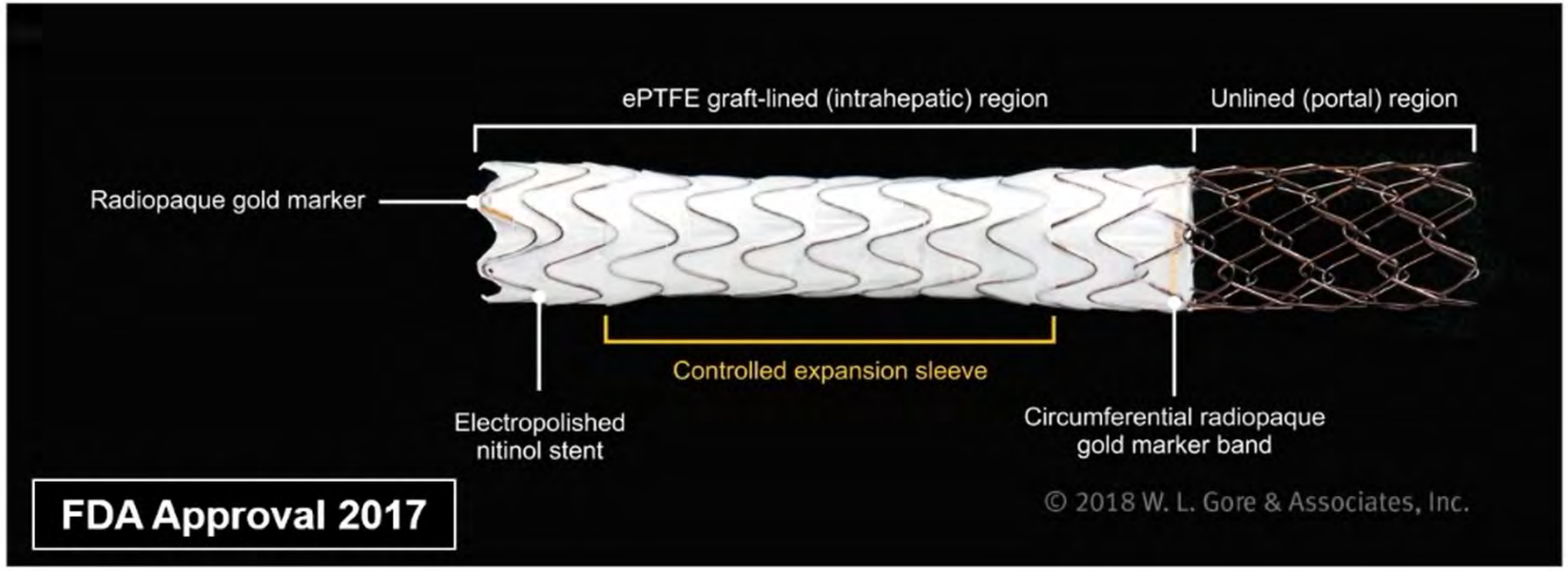


In Esophageal Variceal bleed: Goal PSG of < 12 mm Hg or 50%–60% decrease from initial

TIPS v3.0: Controlling TIPS Diameter

Viatorr CX (Controlled Expansion) PTFE "covered" endoprosthesis

- Controlled Expansion = self expands to 8mm; can be dilated up to 10mm



AASLD The Liver Meeting®

KPK

TIPS v3.0: TIPS Diameter as Our Lever

	Desired PS Shunting
Variceal hemorrhage	↑
Ascites	↑
Hepatic Function	↓
Hepatic Encephalopathy	↓
Right Heart Function	↓

$$Q = \frac{\pi D^4 \Delta P}{128 \mu \Delta x}$$

Poiseuille Equation

8 mm → 10 mm:
2.4x more flow through TIPS*!

AASLD The Liver Meeting®

KPK

Contraindications for Elective TIPS

ALTA (Advanced Liver Therapeutic Approaches) 2021

Clinical Gastroenterology and Hepatology; August, 2021

ABSOLUTE

- Severe hepatic failure (does not apply in variceal bleed)
- Severe Congestive Heart Failure (ACC/AHA **stage C or D** HF)
- Severe Valvular Heart Disease (AHA/ACC **stage C or D** VHD)
- Severe tricuspid regurgitation
- Severe pulmonary HTN with **PAPm >/= 45 mm Hg** despite medical optimization
- Uncontrolled systemic infection
- Refractory overt HE
- Unrelieved biliary obstruction
- Lesions (eg, cysts) or tumors in the liver parenchyma that preclude TIPS creation

Stage C HF: Structural heart disease with symptoms of heart failure
Stage D HF: Refractory heart failure requiring specialized interventions
Stage C VHD: Asymptomatic patients who have the criteria for severe VHD
Stage D VHD: Symptomatic VHD

RELATIVE

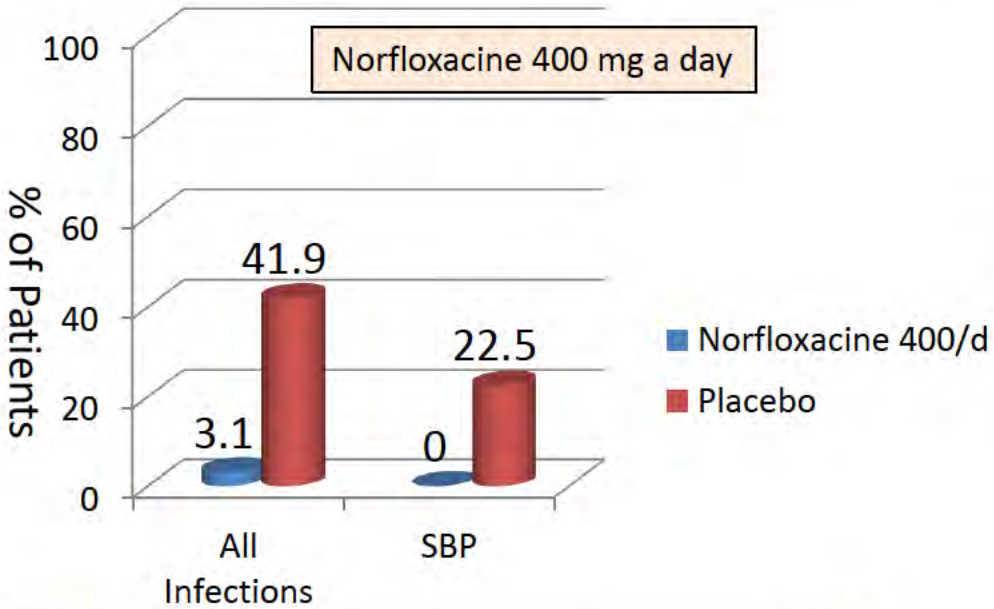
- Active infection - Controlled
- Poorly controlled PSE
- Portal V thrombosis with or without cavernoma
- Moderate or severe POPH on treatment PAPm > 35 mm Hg, pulmonary vascular resistance > 3 wood units) has risk of RV failure.
- Avoid elective TIPS in LVEF < 50% or grade III diastolic dysfunction.
- Obtain Right Heart Catheterization and Cardiology Consult If:
  - RVSP > 45 mm Hg or TAPSE < 1.6 cm, to evaluate for RV dysfunction and pulmonary hypertension before TIPS creation.
  - If pre-TIPS RA pressure > 14 mm Hg, to R/O and measure Pulmonary HTN. (Pre-TIPS RAP > 14.5 and post-TIPS RAP > 21.5 increases mortality)

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 with low protein ascites (< 1.5 g/dL) are at risk of SBP **(specially if C-P B >/= 9, Bili >/= 3, Creat >/= 1.2, Na </= 130)**; SBP Incidence is 27-41% when Ascites Protein is </= 1 g/dL.
  - 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 use Piperacillin/tazobactam or Carbapenem PLUS Albumin.
  - 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.

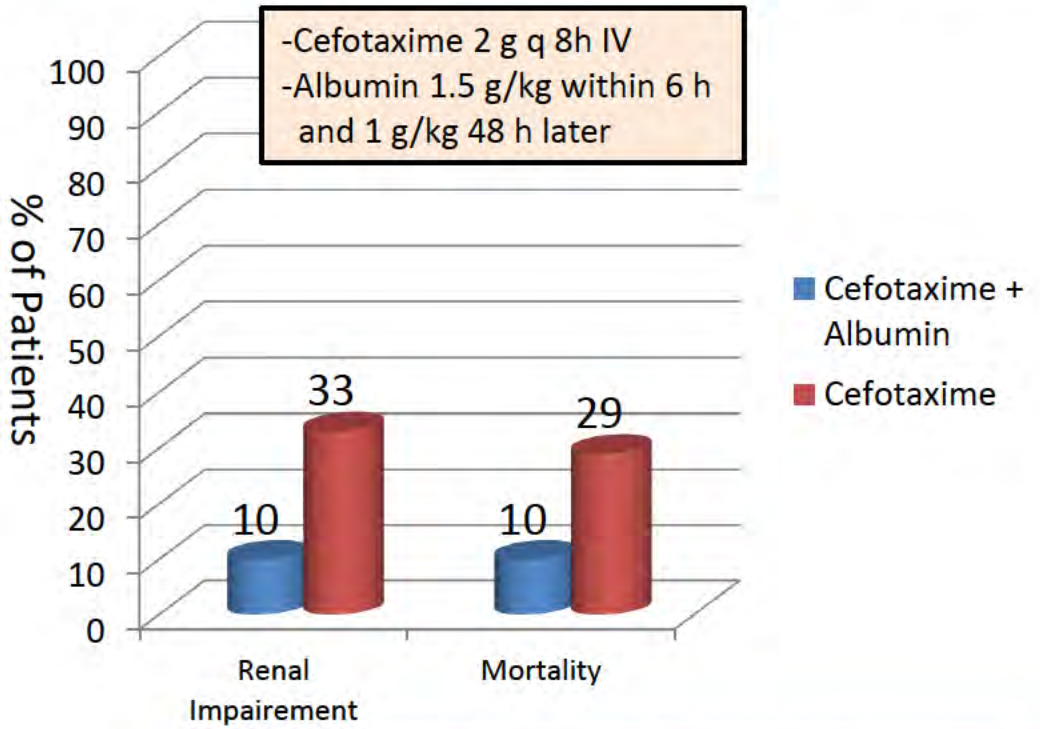
Spontaneous Bacterial Peritonitis (SBP)

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



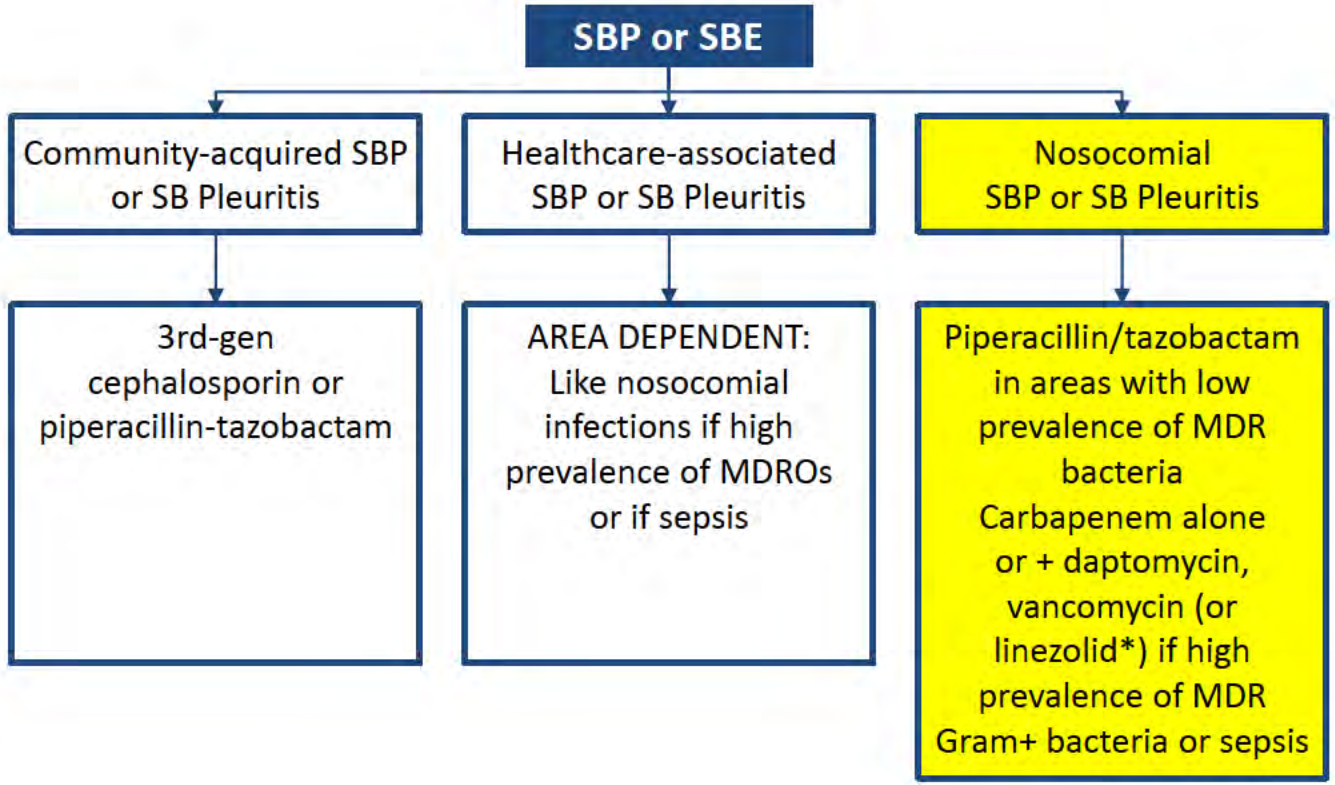
Daily, in-hospital, Norfloxacin decreases risk of all infections, and of SBP in patients with ascites-protein < 1.5 g/dL and C-P >/=9, Bili >/= 3, Cr >/= 1.2, or Na </=130) or if ascites Protein </= 1 g/dL

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

Empirical antibiotic treatment of SB Peritonitis or SB Empyema (Pleuritis)



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

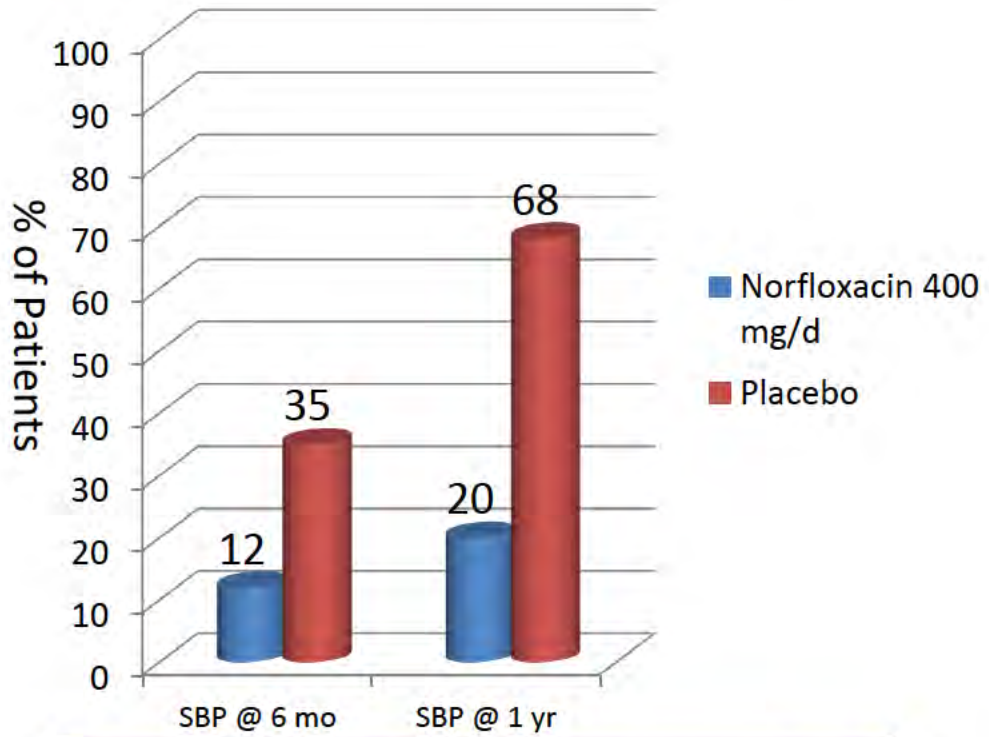
Adapted from Jalan R, et al. J Hepatol 2014;60:1310–24;

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

Complications of Cirrhosis

Long Term Norfloxacin prevents SBP Recurrence

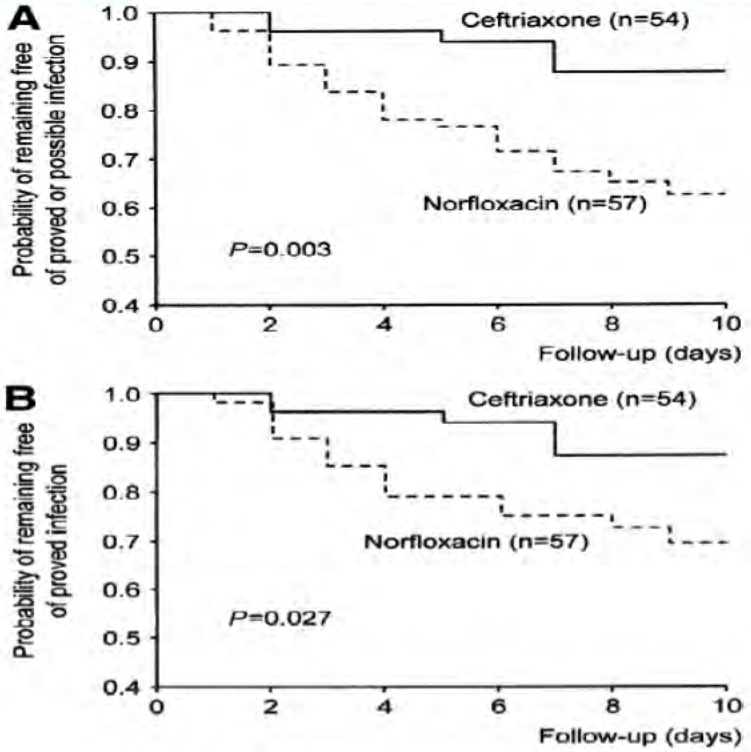
Gines P; Hepatology 1990;12:716-724



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 g/dL or </= 1.5 g/dL + Bili>/= 3, creat >/= 1.2, Na </= 13, or C-P >/=9, CXiprofloxacin 500 mg/d is indicated during the hospital stay.

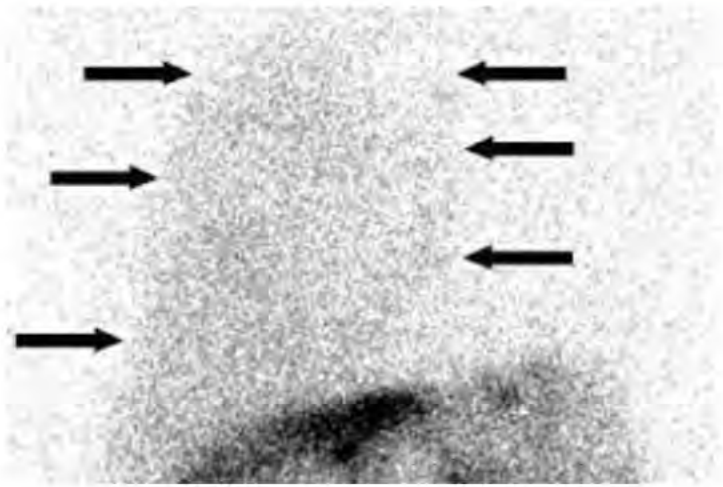
SBP
Prophylaxis and Management

- 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 or Pip/Tazo 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 Ciprofloxacin 500 mg/d is indicated and also avoid PPIs if possible.
- Outpatients with ascites and severe decompensation (Child-Pugh >/= 9), should receive Ciprofloxacin 500 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 radionuclide in abdomen

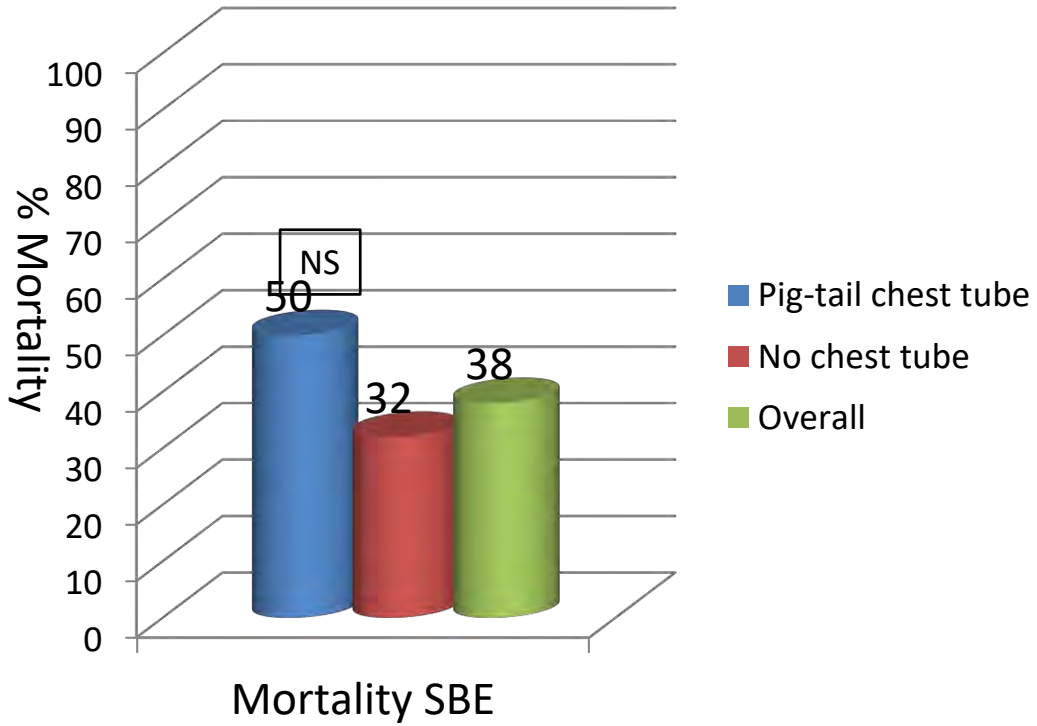


Spontaneous Bacterial Pleuritis

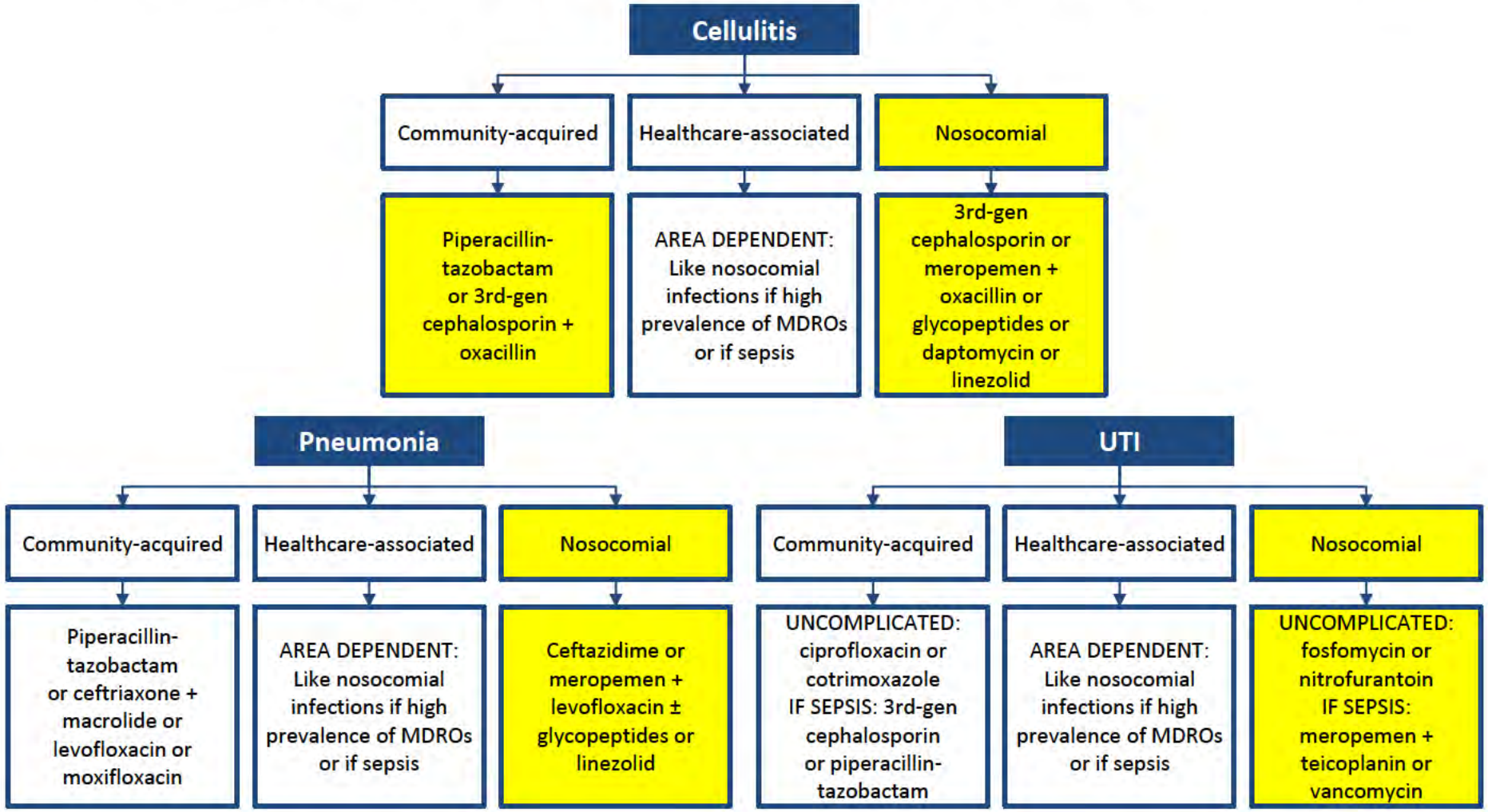
SB Empyema – What we know

- Is NOT an Empyema, is a **Pleuritis**.
- Spontaneous Bacterial Pleuritis 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 Pleuritis
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

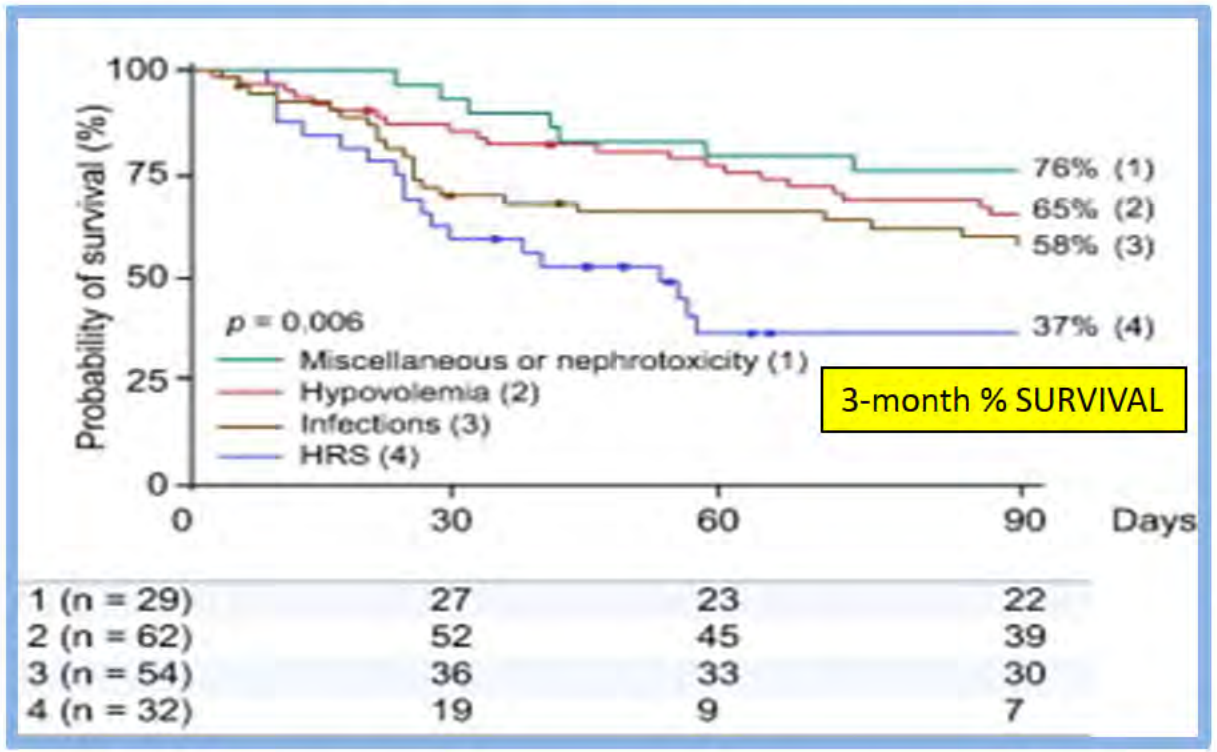
Definition of AKI in Cirrhosis

- **Baseline serum creatinine:** value of serum creatinine obtained in the ***previous 3 months***.
  - In patients with more than one value obtained within the previous 3 months, the ***value closest to the admission time*** to hospital should be used.
  - In patients without a previous serum creatinine value, the serum creatinine on admission should be used as baseline.
- **STAGES OF AKI (KDIGO):**
  - **Stage 1A**: an increase in serum creatinine **≥0.3 mg/dl to a value lower than 1.5 mg/dl** from baseline at diagnosis of AKI.
  - **Stage 1B**: an increase in serum creatinine **≥0.3 mg/dl to a value ≥1.5 mg/d** from baseline at diagnosis of AKI.
  - **Stage 2**: an increase in serum creatinine **greater than twofold** to threefold from baseline.
  - **Stage 3**: an increase of serum creatinine **greater than threefold** from baseline or serum **creatinine ≥4.0 mg/dl** with an acute **increase ≥0.3 mg/dl** or initiation of renal replacement therapy.

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 if 1a) (many HRS if 1b)	*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-CKD; few HRS-AKI)	*No Progression*	*(54%)*	*7*
	Progression to AKI-3	(19%)	**18**
	Progression Needing Dialysis	(27%)	**60**
AKI-3 (many HRS-AKI)	No Progression	(67%)	**21**
	Progression needing Dialysis	(33%)	**71**

Progression of AKI worsens Mortality; Early Intervention is Critical

New Classification of HRS

- **AKI-Hepatorenal Syndrome (HRS-AKI)**
  - Increase of Serum creatinine **> 0.3 mg/dL within 48 hours, or > 50% from baseline** within 3 months and **presumed to have occurred in the last 7 days.**
- **HRS Non-AKI (HRS-NAKI)**
  - **GFR < 60 mL/min/1.73 m^2 for < 3 months**
  - Increase of serum creatinine **< 50% but > 0.3 mg/dL from baseline** within 3 months**, but longer than 48 hours**.
- **HRS-CKD**
  - A specific type of CKD that only occurs in cirrhosis characterized by chronic impairment of kidney function defined as **GFR** (estimated from the serum creatinine) **< 60 ml/min/1.73 m^2 for > 3 months**, and **lack** of signs suggestive **of intrinsic kidney disease** (for example, hematuria, proteinuria and abnormal kidney ultrasonography) or other potential causes of kidney disease.

Diagnostic Criteria for HRS type AKI (HRS-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

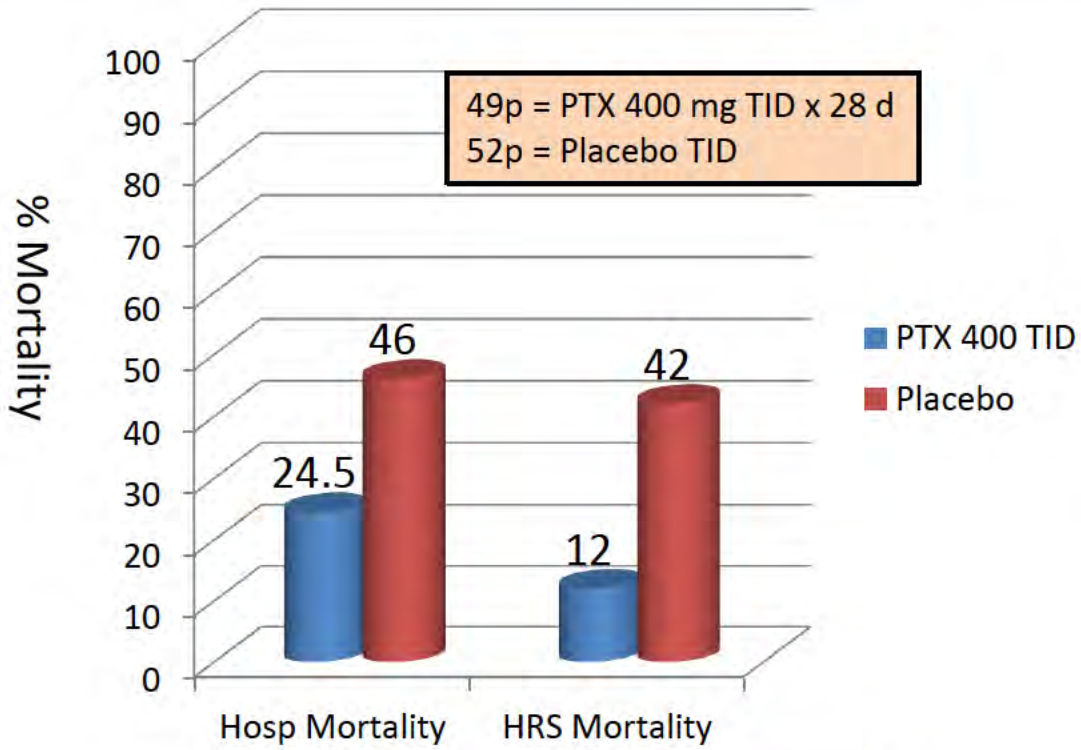
Hepatorenal Syndrome
What we know

- **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

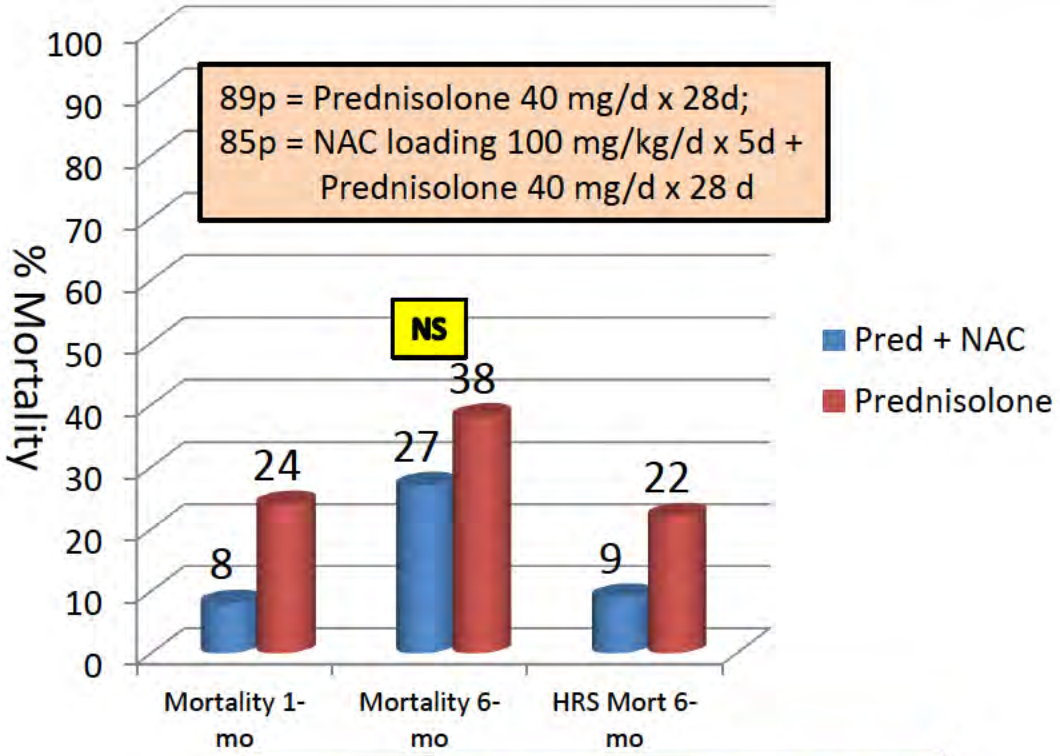
Akriviadis E; Gastroenterology 2000 Dec;119(6):1637-48



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.

Pharmacologic Therapy in Alcoholic Hepatitis

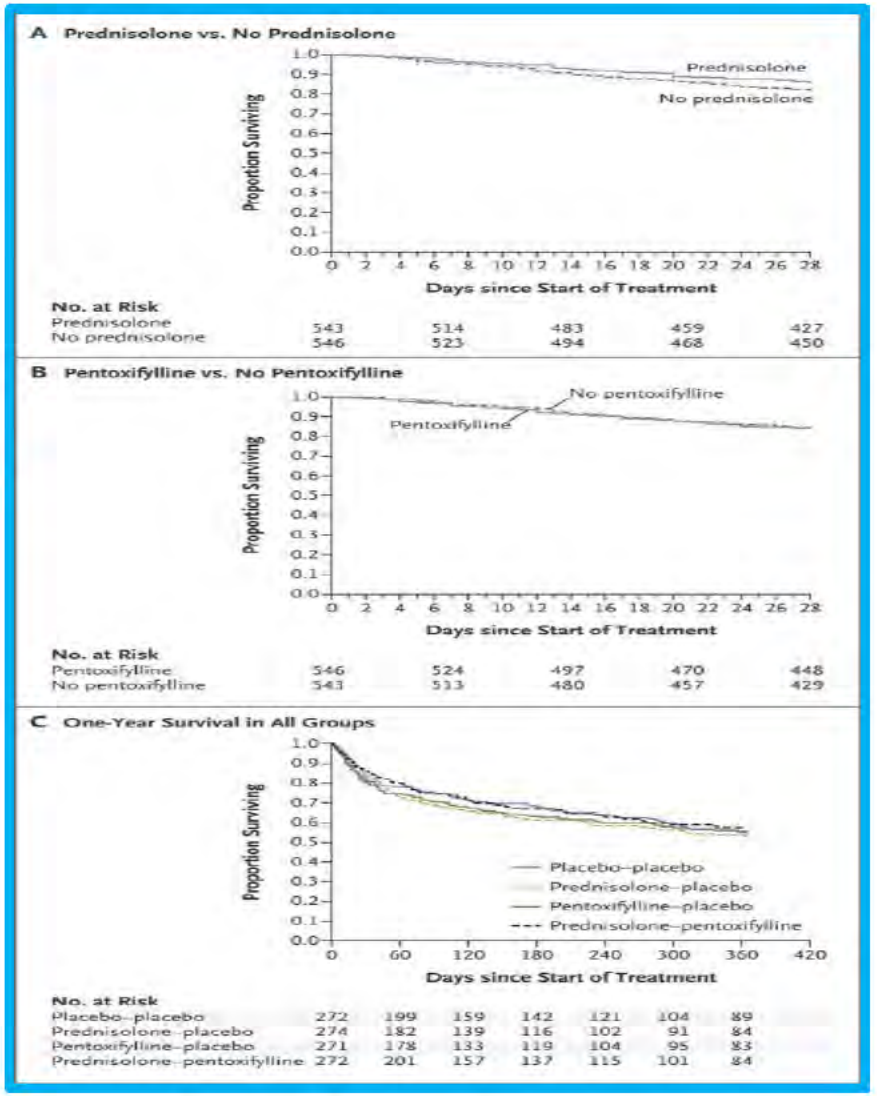
The STOPAH Trial

N Engl J Med 2015; 372:1619-1628

Table 2. Mortality at 28 Days, 90 Days, and 1 Year.*

End Point	Prednisolone	No Prednisolone	Pentoxifylline	No Pentoxifylline	Prednisolone		Pentoxifylline	
					Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
28-Day mortality — no./total no. (%)	73/526 (14)	95/527 (18)	85/518 (16)	83/535 (16)	0.72 (0.52–1.01)	0.06	1.07 (0.77–1.49)	0.69
90-Day mortality or liver transplantation — no./total no. (%)	144/484 (30)	141/484 (29)	139/478 (29)	146/490 (30)	1.02 (0.77–1.35)	0.87	0.97 (0.73–1.28)	0.81
1-Year mortality or liver transplantation — no./total no. (%)	210/371 (57)	211/376 (56)	205/365 (56)	216/382 (57)	1.01 (0.76–1.35)	0.94	0.99 (0.74–1.33)	0.97

* The interaction between interventions was investigated as a secondary analysis.



Pentoxifylline did not improve survival in patients with alcoholic hepatitis.

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

During this times, patients received intense nutrition and HRS was treated with Albumin/ Terlipressin

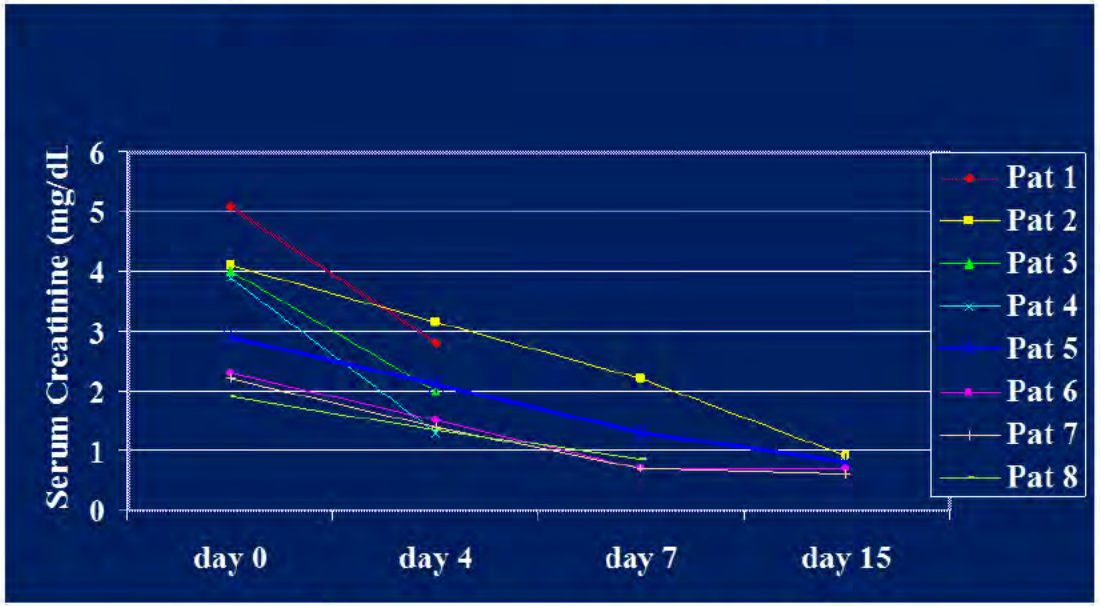
Hepatorenal Syndrome
What we know

- HRS type AKI and CKD 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 (HRS-AKI) (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

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

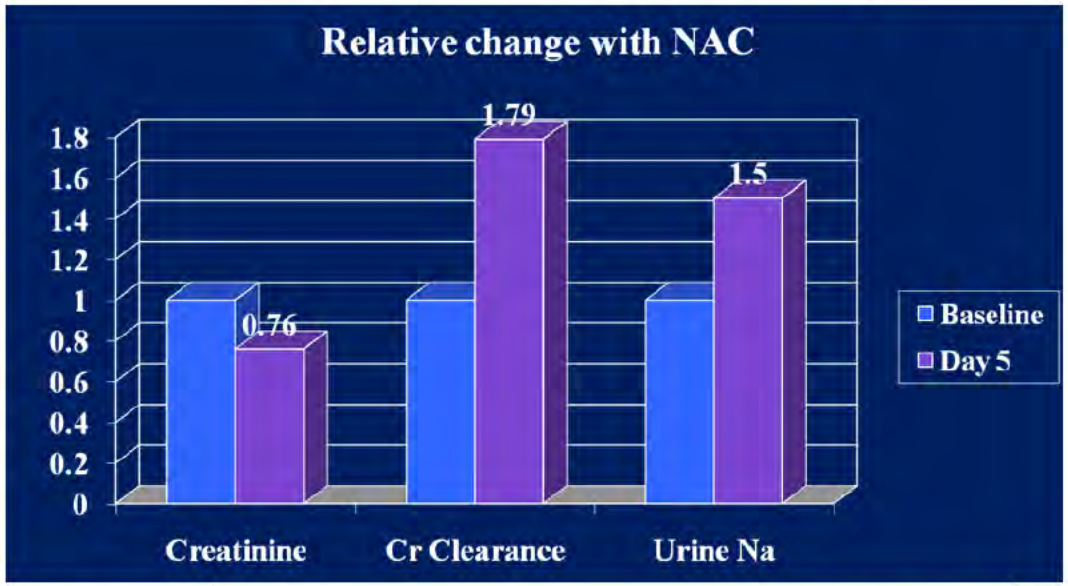
Ornipressin 2 IU/h x 15 d + Albumin
8 patients with HRS-1
Responders reached MAP = 84



Ornipressin + Albumin takes up to 2 weeks to work

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

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

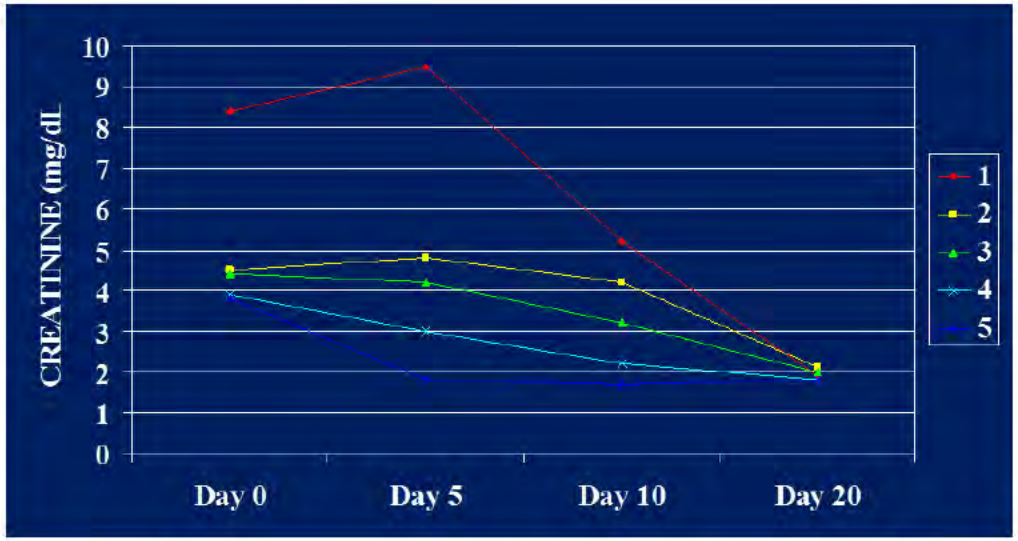


NAC can improve creatinine clearance and natriuresis in HRS-1

Treatment of Hepatorenal Syndrome

Octreotide + Midodrine + Albumin in HRS-I (HRS-AKI)
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

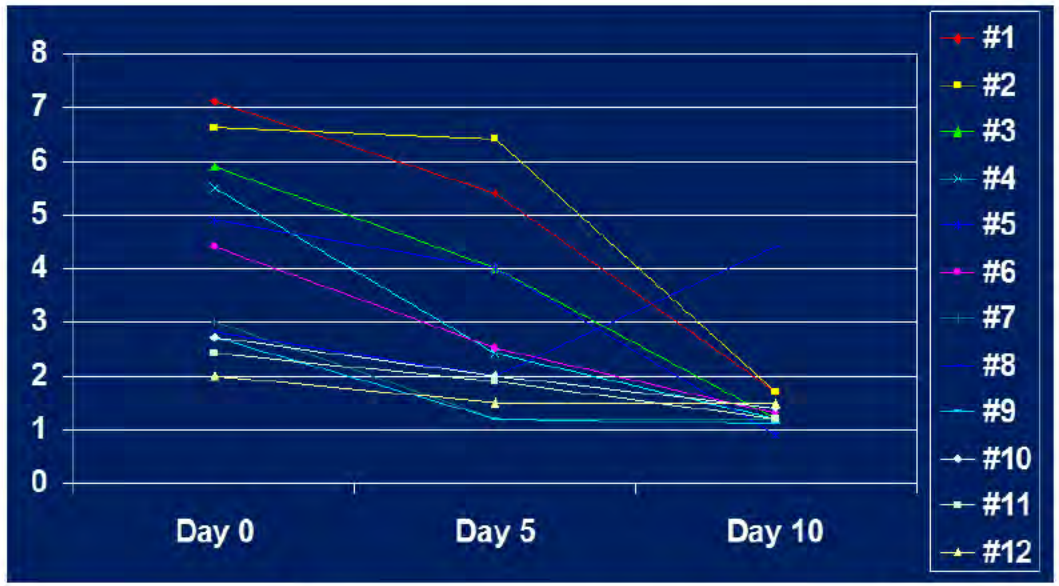
Octreotide + Midodrine + Albumin in HRS-I (HRS-AKI)
Esrailian E; Dig Dis Sci 2007;52:742-748

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

Treatment of Hepatorenal Syndrome

Noradrenaline + Albumin in HRS-I (HRS-AKI)
Duvoux C; Hepatology 2002;36:374-380

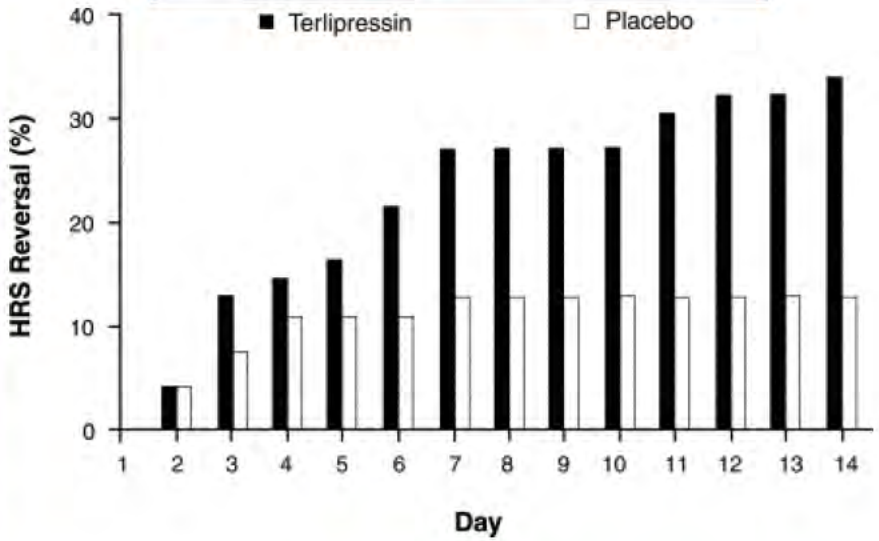
Noradrenaline 0.5-3 mg/h + Albumin
12 patients with HRS-1



Noradrenaline + Albumin takes up to 10 days to work

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

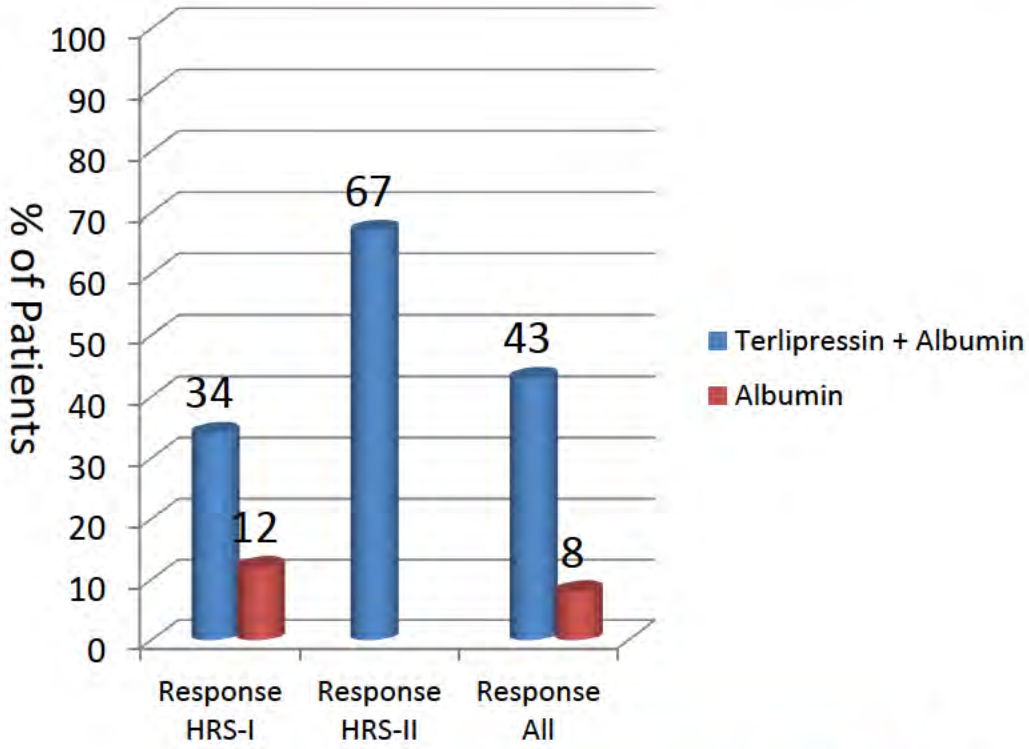
Terlipressin 1 mg q 4-6 h IV + Albumin
56 patients with HRS-1
Responders reached MAP = 84



Terlipressin + Albumin takes up to 2 weeks to work

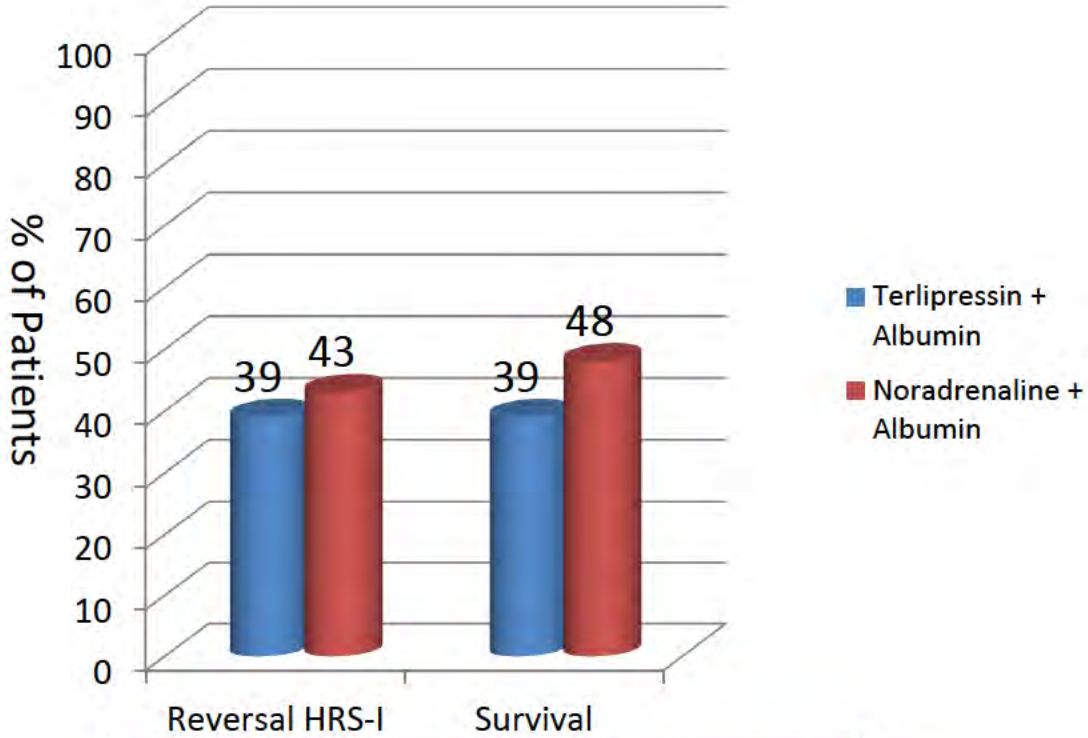
Treatment of Hepatorenal Syndrome

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



HRS-II (HRS-CKD) responds better than HRS-I (HRS-AKI)

Terlipressin vs Noradrenaline in HRS-I (HRS-AKI)
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-AKI 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-AKI is 35-40%, and
  - for HRS-CKD 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 AKI and CKD 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).

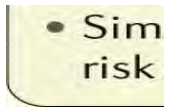
HRS Prevention & Management

- Patients suspected to have HRS type-AKI or HRS type-CKD 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.

Algorithm for liver transplant alone versus simultaneous liver and kidney transplant in HRS



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 decompensated 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).

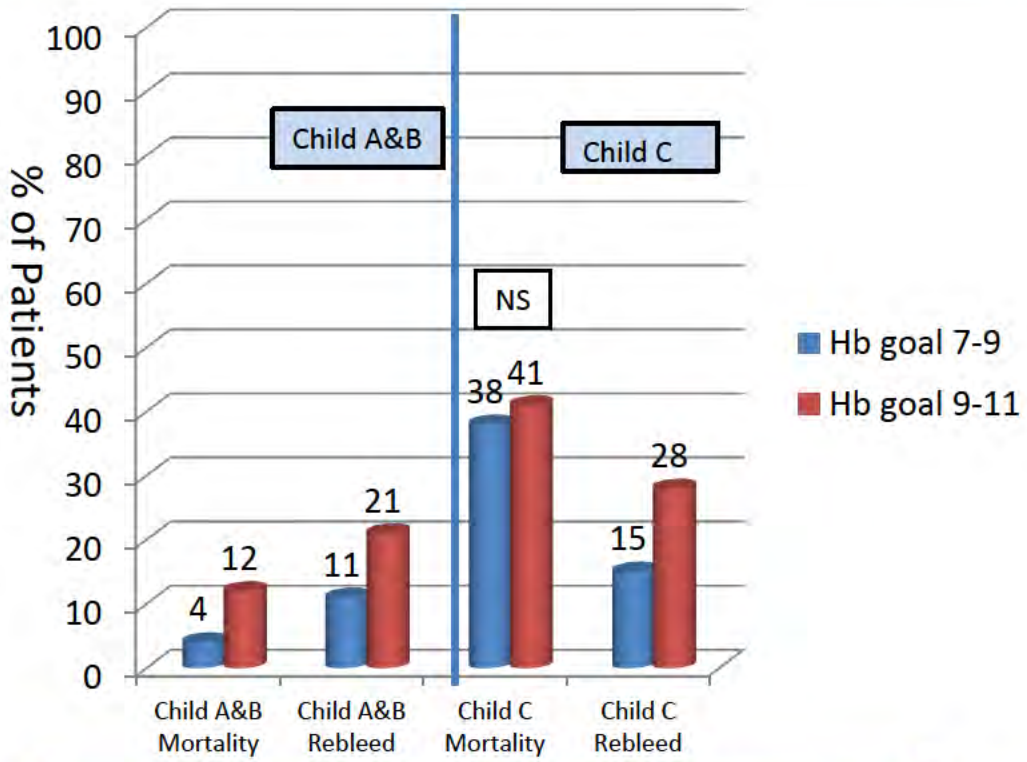
Acute GI Bleed in Cirrhosis
What we know

- **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 8-9) **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

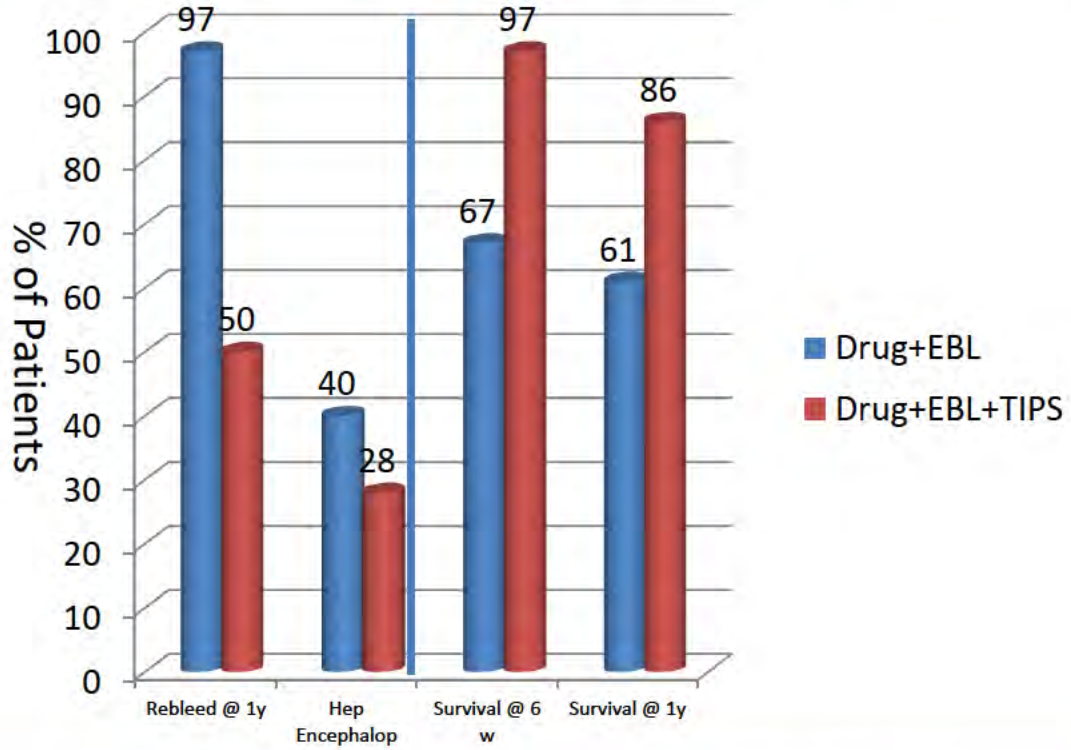
Villanueva C; N Engl J Med 2013; 368:11-21



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

Early TIPS in Variceal Bleed:
Actively bleeding Child B *>/= 8*, or Child C up to 13

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



Early TIPS improved survival in variceal bleed with actively bleeding Child B *>/=8-points*, and Child C up to 13

Early (</= 72 hours) TIPS after Esophageal Variceal Bleed
Meta-Analysis of Individual Patient Data

Nicoara-Farcau, O et al. Gastroenterology 2021;160:193–205

Early TIPS Survival in Active bleed + Child-Pugh B 7 vs Active Bleed + Child-Pugh B >/= 8 points

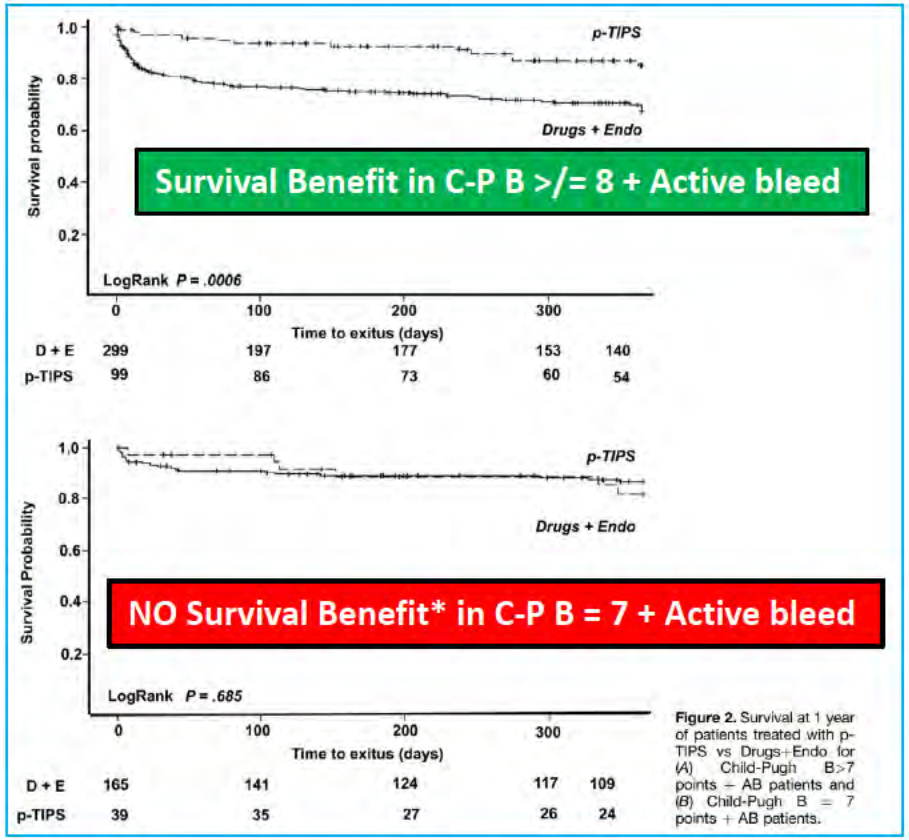
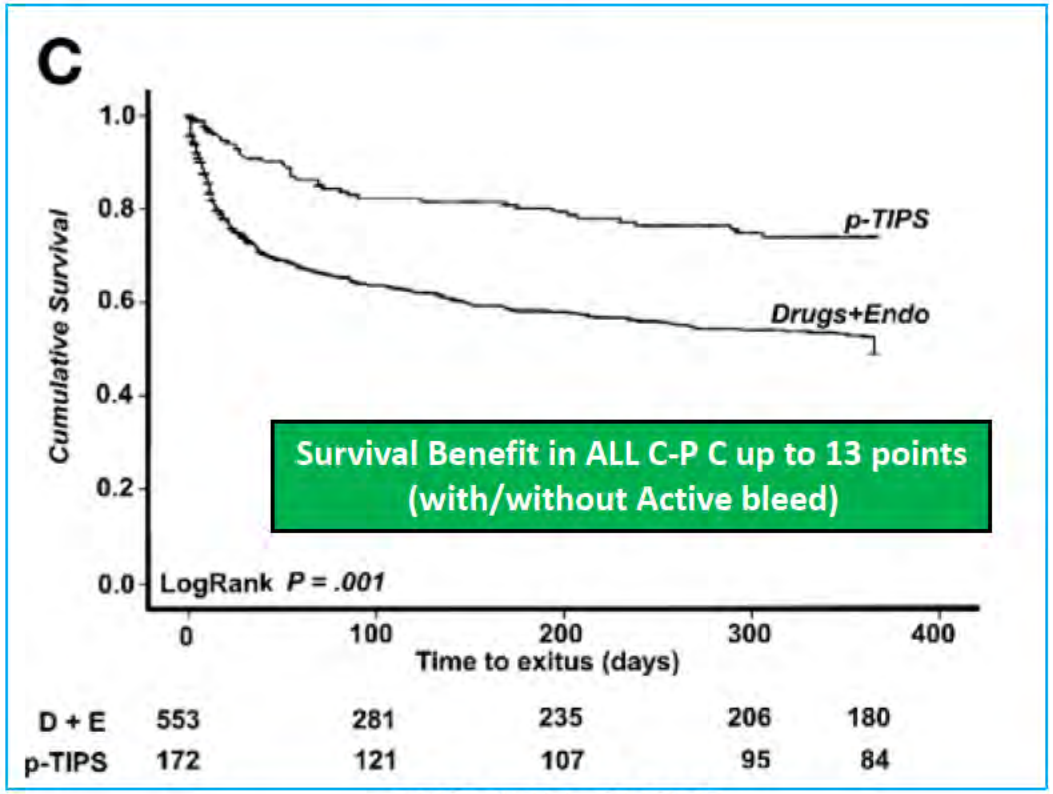


Figure 2. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo for (*A*) Child-Pugh B>7 points + AB patients and (*B*) Child-Pugh B = 7 points + AB patients.

* But decreases Risk of Developing Ascites

Early TIPS in Child-Pugh C up to 13 points Survival

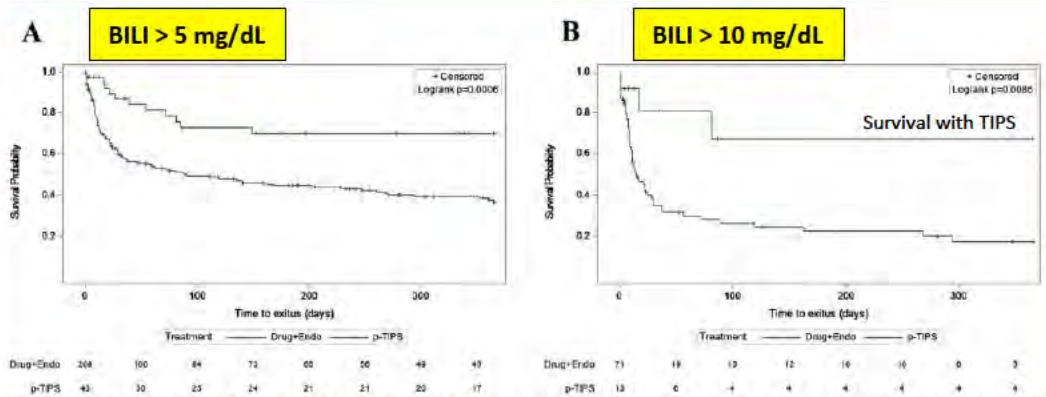


SURVIVAL CURVE

Meta-Analysis of Individual Patient Data

Nicoara-Farcau, O et al. Gastroenterology 2021;160:193–205

Early TIPS improves Survival even if Bili > 10 mg/dL



Supplementary Figure 7. Survival at 1 year of patients treated with p-TIPS vs Drugs + Endo in A. patients with Bilirubin > 5 mg/dL and B. patients with Bilirubin > 10 mg/dL.

SURVIVAL CURVE

Early TIPS is Beneficial even with Multiple Risk Factors

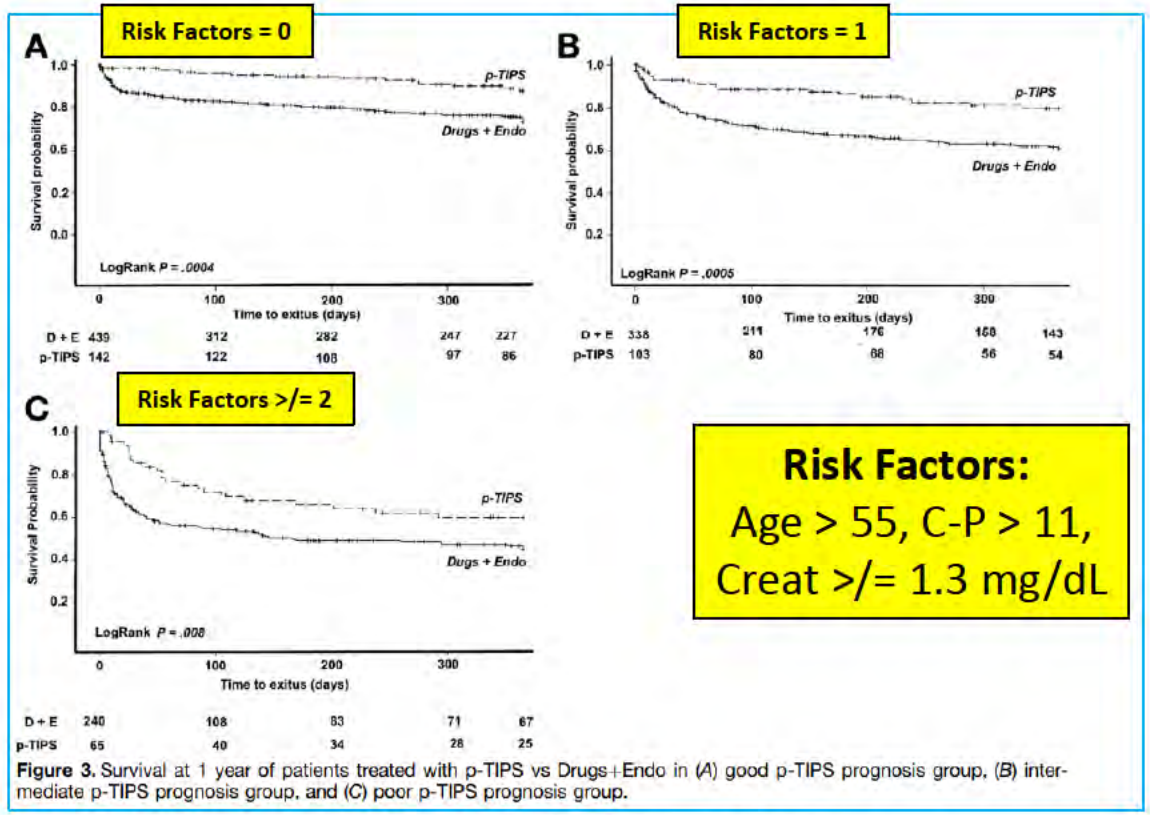


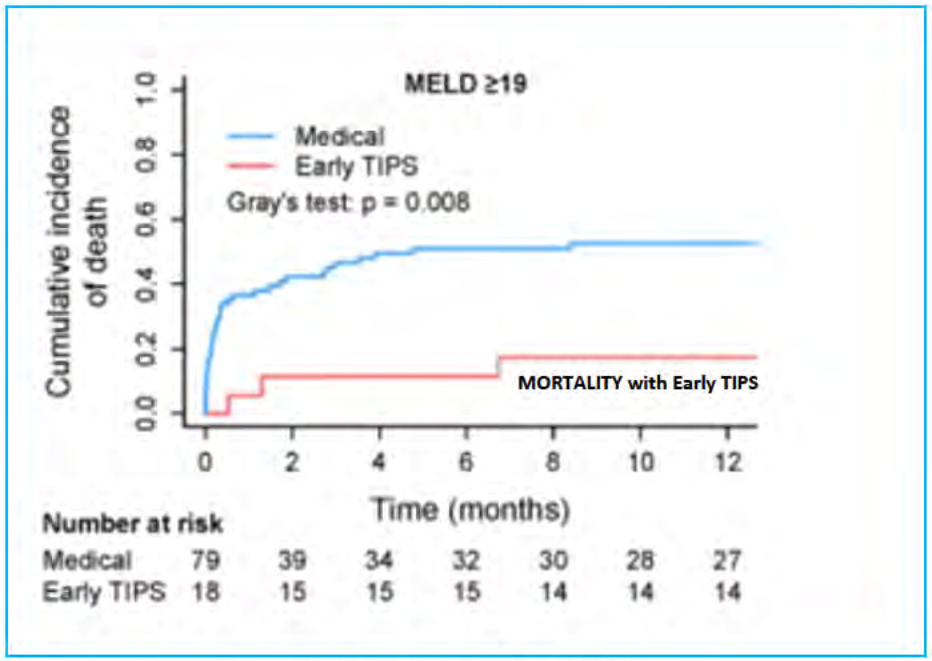
Figure 3. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo in (*A*) good p-TIPS prognosis group, (*B*) intermediate p-TIPS prognosis group, and (*C*) poor p-TIPS prognosis group.

SURVIVAL CURVE

Early TIPS in High MELD and in ACLF

Early TIPS in High MELD

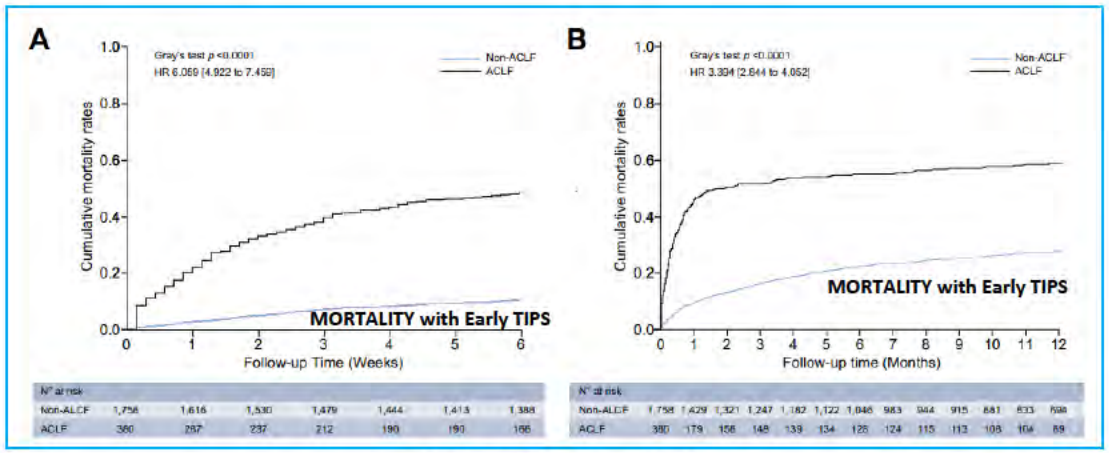
Lv Y, et al. Gut 2019;68:1297–1310



MORTALITY CURVE

Early TIPS in ACLF

Trebicka J et al. Journal of Hepatology 2020 vol. 73: 1082–1091



MORTALITY CURVE

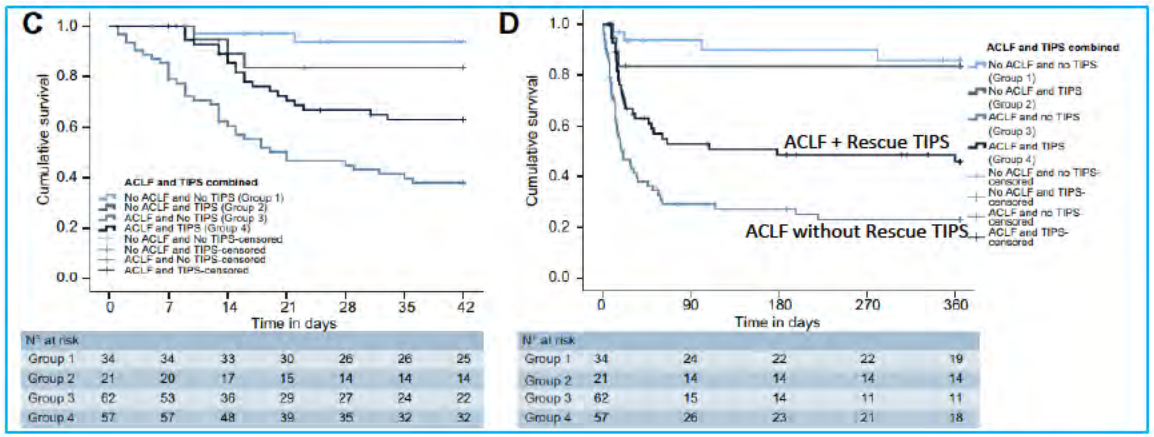
Early TIPS Decreases Mortality even in High MELD and in ACLF Child-Pugh B >/= 8 with bleeding and Child-Pugh up to 13

Is there a Limit to Rescue and Salvage TIPS?

Rescue TIPS Improves Survival in ACLF

1-Year Survival with Rescue TIPS in ACLF

Kumar R et al. Journal of Hepatology 2021 vol. 74: 66–79



6-week Survival with Rescue TIPS by ACLF Grade

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

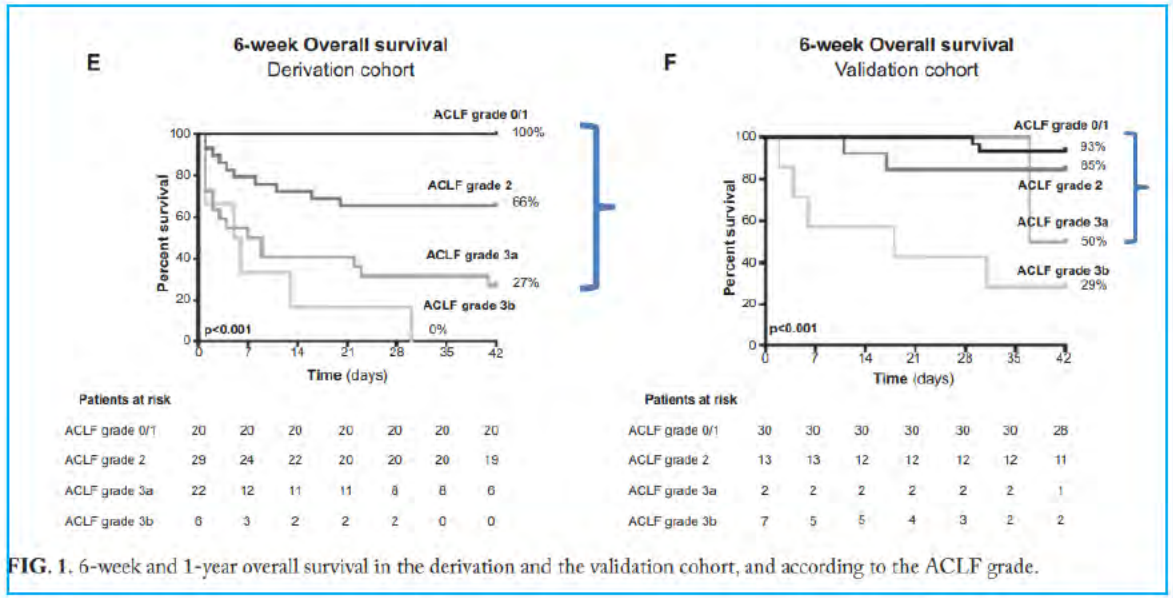


FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

Rescue TIPS Improves Survival in ACLF with up to 3 organ failures

Point of Futility for Rescue / Salvage TIPS

Walter A et al. Hepatology, VOL. 74, NO. 4: 2085-2101, 2021

TIPS is Futile in ACLF with >/= 4 Organ Failures (3b)

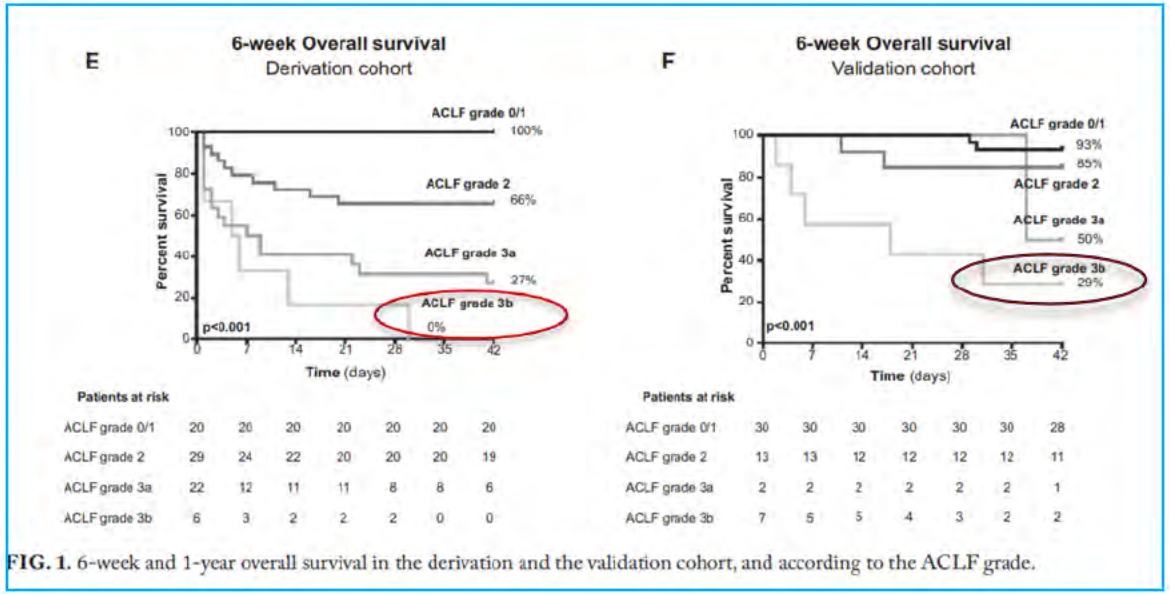


FIG. 1. 6-week and 1-year overall survival in the derivation and the validation cohort, and according to the ACLF grade.

TIPS is Futile if Lactate is >/= 12 mmol/L or MELD >/= 30

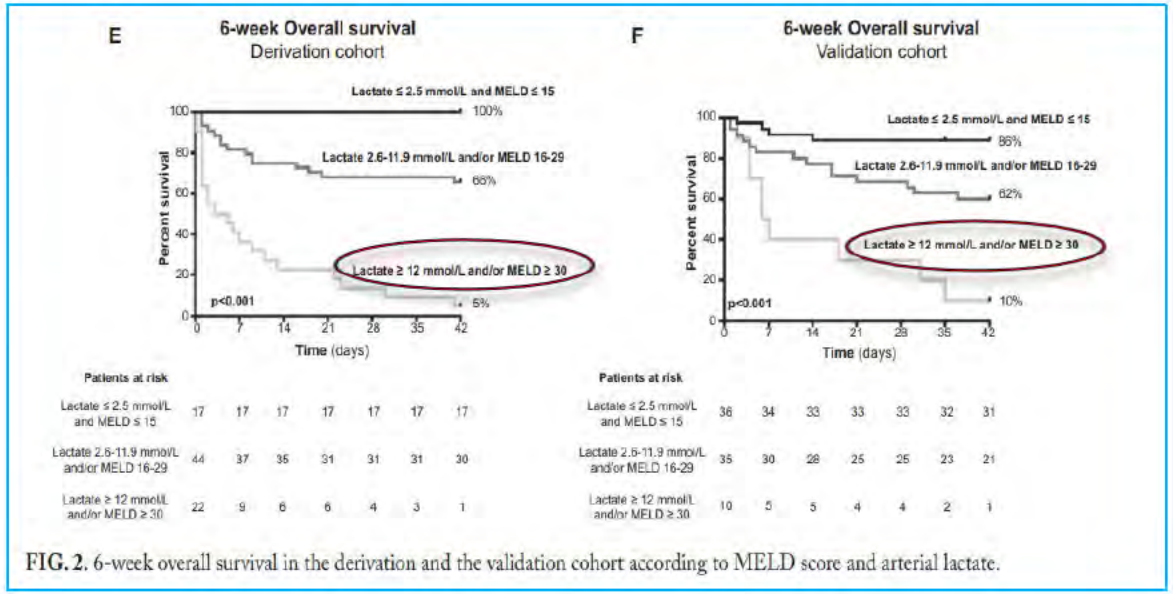


FIG. 2. 6-week overall survival in the derivation and the validation cohort according to MELD score and arterial lactate.

ACLF 3b = Failure of 4 or more organs

Do all patients have the same benefit?: CP-C

- Child C patients <14 points: Survival benefit in all studies
- Child C 14-15 : always futile?

Transplant International ISSN 0934-0874

LETTER TO THE EDITORS

Salvage transjugular intrahepatic portosystemic shunt followed by early transplantation in patients with Child C14-15 cirrhosis and refractory variceal bleeding: a strategy improving survival

Rudler, Rousseau & Thabut. Transplant International 2013

Salvage TIPS followed by rapid LT in patients with CP-C 14-15
MELD score at the time of listing for LT ranged from 29 to 40.
The median delay between TIPS and LT was 8 days (range 3–17 d)
The 6-month survival was 100% (TIPS+LT) vs 0% (TIPS) ($P < 10^{-4}$).

Secondary Prophylaxis for Esophageal Variceal Hemorrhage

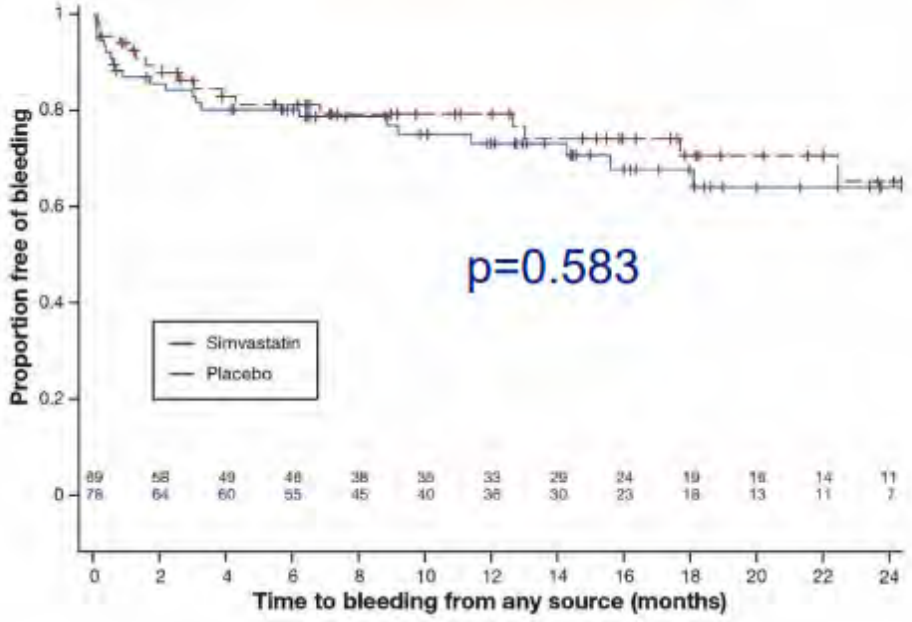
EVL + NSBB

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 nor MAP < 65	•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 nor MAP < 65	•At every outpatient visit make sure that heart rate is on target •Continue indefinitely
Carvedilol	•**With EVL.** •Start with 6.25 mg *once* a day •After 3 days increase to 6.25 mg twice-daily •Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension)	•Systolic arterial blood pressure should not decrease <90 mm Hg	•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.

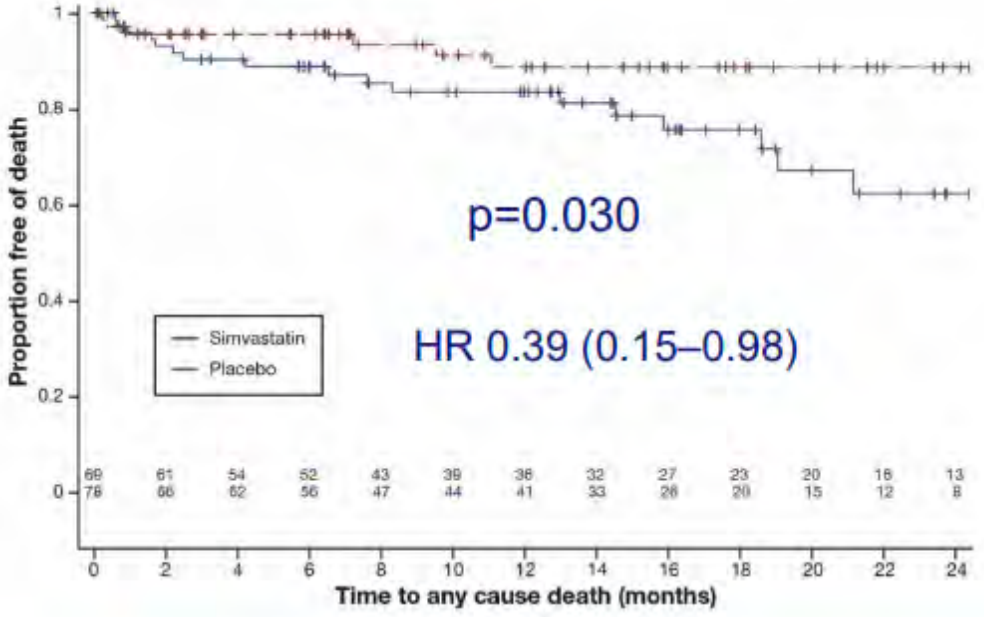
In patients who had bled from varices, the addition of simvastatin to NSBB + ligation reduced mortality but not rebleeding

Rebleeding



p=0.583

Mortality



p=0.030

HR 0.39 (0.15–0.98)

Symptomatic rhabdomyolysis occurred in two (3%) patients (bilirubin >5 mg/dL) in the simvastatin group

Abraldes, Villanueva et al. Gastroenterology 2016;150(5):1160-1170

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 da**ys (can be D/C early after TIPS or adequate beta-blockade).
- Do **early EGD** (</= 12 hours) 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 10-13 points**, or if **Child-Pugh B >/= 8 points with active bleed**, do **early TIPS** unless Serum Lactate > 12 mmol/L or MELD >/= 30.
- Start **early aggressive Beta-blockade if TIPS is not done** (avoid drop of MAP to </= 65 mm Hg), and plan for sequential banding for eradication of varices.
- Consider Simvastatin if Bili < 5 mg/dL and Child-Pugh A or B (not C).

Relative Adrenal Insufficiency in Cirrhosis

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	Grade of evidence	Grade of 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

CBG, corticosteroid-binding globulin; RAI, relative adrenal insufficiency

*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

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

Definition of Cirrhotic Cardiomyopathy (2020)

Izzy M et al. Hepatology 2020;71:334-345

Systolic Dysfunction + One of the Following	Diastolic Dysfunction and 2 or 3* of the Following
Ejection/Fraction </= 50%	Average E/e' ** > 14 (>9.2 increases atrial arrhythmia risk)
Global Longitudinal Strain (Absolute Value < 18%)	Peak Tricuspid Regurgitation Velocity > 2.8 m/sec
	Septal e' < 7 cm/sec
	Left Atrial Volume Index > 34 mL/m^2 (Increases first year mortality)

- * Two criteria: "Diastolic Dysfunction of Indeterminate Grade";
  Three criteria: "Gradable Diastolic Dysfunction" with additional testing
- ** e' = early diastolic mitral annular velocity

Global Longitudinal Strain < 20.6 predicts 6-times increase in post-OLTx CHF
< 20.5 predicts 6-times increase in post-OLTx CAD

Evaluation of Diastolic Dysfunction in ESLD

Izzy M et al. Hepatology 2020;71:334-345

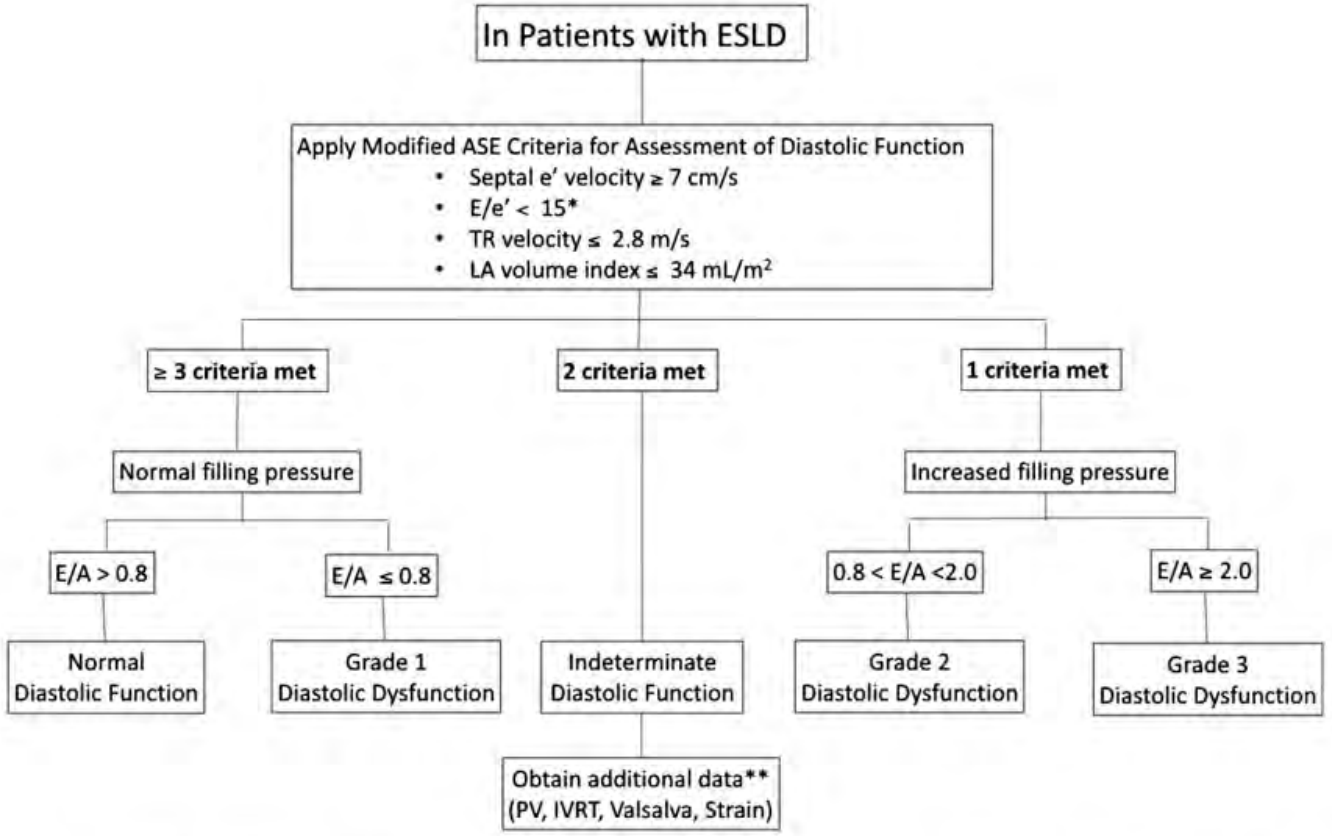


FIG. 3. Evaluation of diastolic function in patients with end-stage liver disease (A simplified algorithm, revised from the 2016 ASE guideline. [Adapted from Oh JK et al.[33] Submitted to JACC Imaging]). *In this algorithm, only medial annulus velocity is recommended. After applying the modified criteria, filling pressure is first assessed, then diastolic function is graded based on E/A ratio. **For values of PV, IVRT, and strain assessment in patients with indeterminate diastolic function, refer to Fig. 4. Advanced diastolic dysfunction (grade 2 or 3) in patients with ESLD in the absence of known heart disease is diagnostic of cirrhotic cardiomyopathy. Abbreviations: LA, left atrium; PV, pulmonary vein; IVRT, isovolumetric relaxation time.

E/F as Predictor of 90-day Mortality in OLTx

	90-day post-LT Mortality (%)	Multivariate Adjusted HR
MELD >/= 20 & E/F </= 60%	13	1.93 (1.11-3.35)
MELD >/= 20 & E/F > 60%	7.4	
MELD > 35 & E/F </= 60%	26.7	2.63 (1.11-6.23)
MELD > 35 & E/F > 60%	11.5	

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; Absolute value < 18% is abnormal.	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
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

CO, cardiac output; DC, decompensated cirrhosis; ECG, electrocardiogram; GLS, global longitudinal systolic strain; LAVI, left atrial volume index; MRI, magnetic resonance imaging; ASE, American Society of Echocardiography

Cirrhotic cardiomyopathy

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

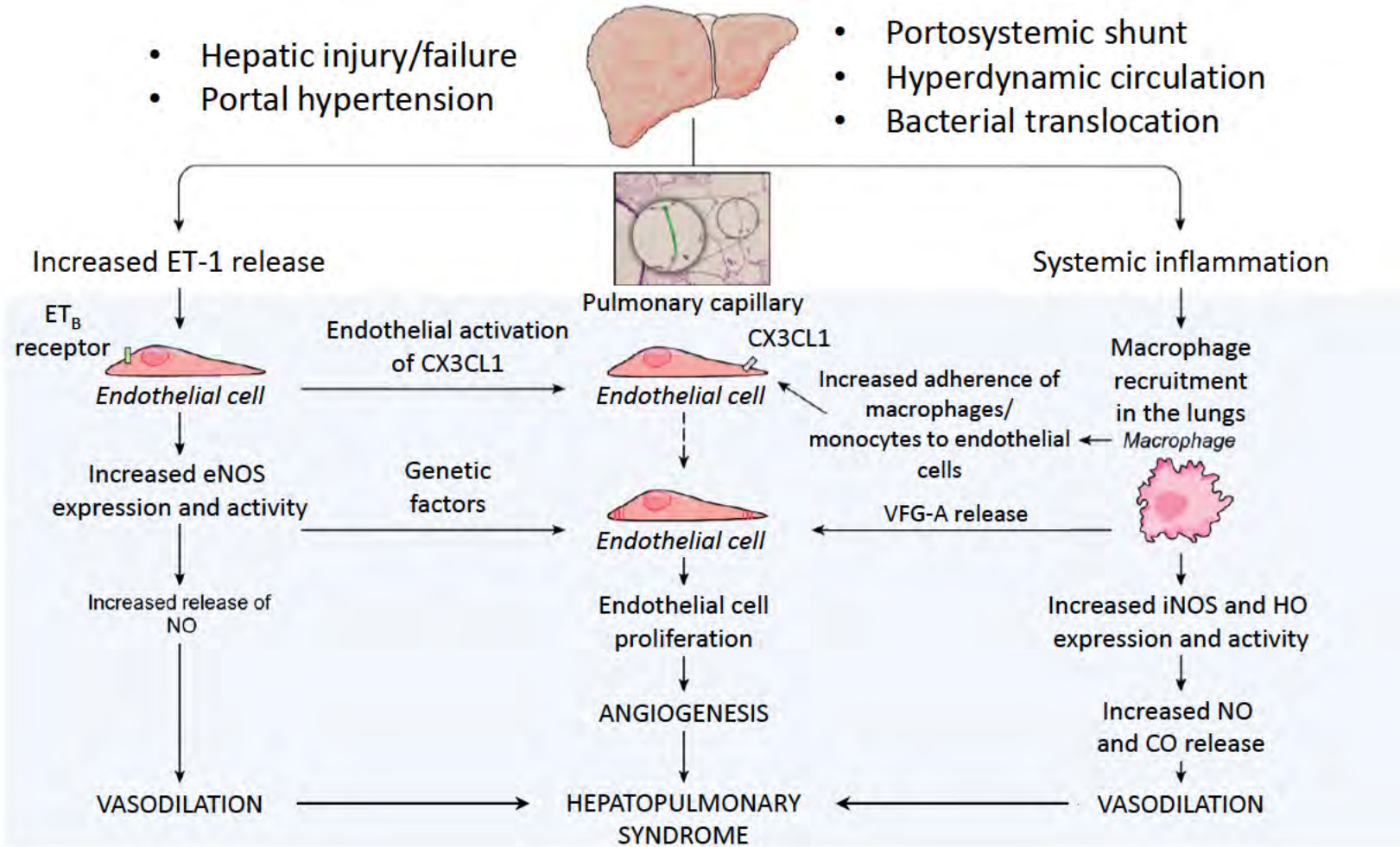
Recommendation	Grade of evidence	Grade of recommendation
In patients with AD, reduced CO (as a manifestation of CCM) is associated with the development of AKI (specifically hepatorenal dysfunction) after infections such as SBP	II-1	1
QTc interval prolongation is common in cirrhosis and may indicate a 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

AD, acute decompensation; AKI, acute kidney injury; CCM, cirrhotic cardiomyopathy; CO, cardiac output; LT, liver transplantation; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt

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

Hepato-Pulmonary Syndrome

Pathogenesis of HPS



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 $P[A\text{-}a]O_2$ ≥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

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

ABG, arterial blood gas; HPS, hepatopulmonary syndrome; PaO2, arterial partial pressure of oxygen; P[A-a]O2, alveolar-arterial oxygen gradient; SpO2, pulse oximetric saturation

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

HPS, hepatopulmonary syndrome; MAA, technetium-99 m–labelled macro-aggregated albumin; PaO2, arterial partial pressure of oxygen

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

Management of HPS

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

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

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

ABG, arterial blood gas; HPS, hepatopulmonary syndrome; LT, liver transplantation; PaO2 arterial partial pressure of oxygen; TIPS, transjugular intrahepatic portosystemic shunt

Porto-Pulmonary Hypertension

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

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

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

LT, liver transplantation; PPHT, portopulmonary hypertension; TDE, transthoracic doppler echocardiography; TIPS, transjugular intrahepatic portosystemic shunt

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

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

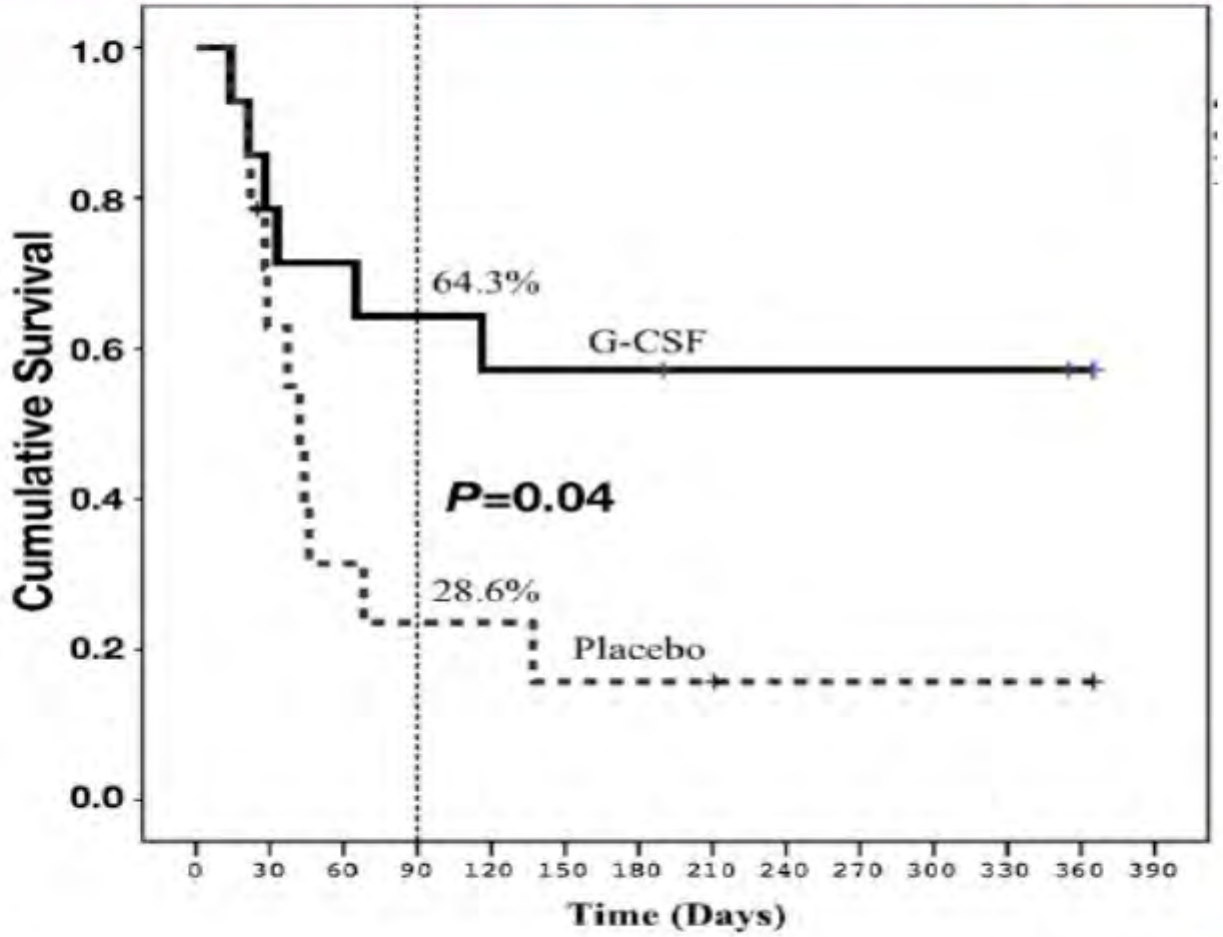
Recommendation	Grade of evidence	Grade of recommendation
If mPAP <35 mmHg and right ventricular function is preserved, **LT** should be **considered** • mPAP of ≥45 mmHg should be considered an absolute contraindication to LT irrespective of therapy applied	II-2 III	1 1
Therapy to lower mPAP and improve 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

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

IV, intravenous; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; mPAP, mean pulmonary arterial pressure; PPHT, portopulmonary hypertension; PVR, pulmonary vascular resistance

Thank you for your attention

GCSF improved survival in steroid non-responders with severe alcohol-associated hepatitis

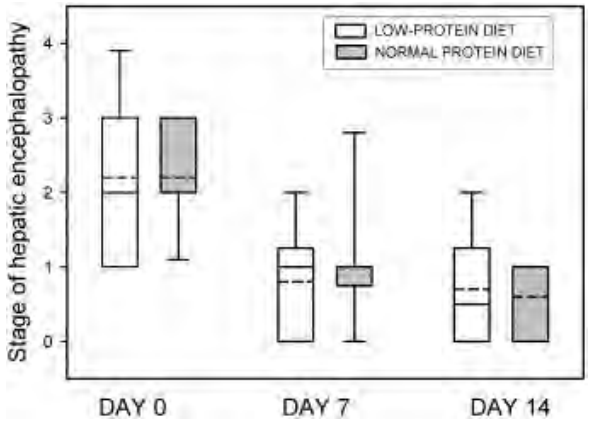


Shasthry S, et al. Hepatology 2019; 70:802-811

Nutrition in Cirrhosis

Low- vs Normal-Protein Diet in HE

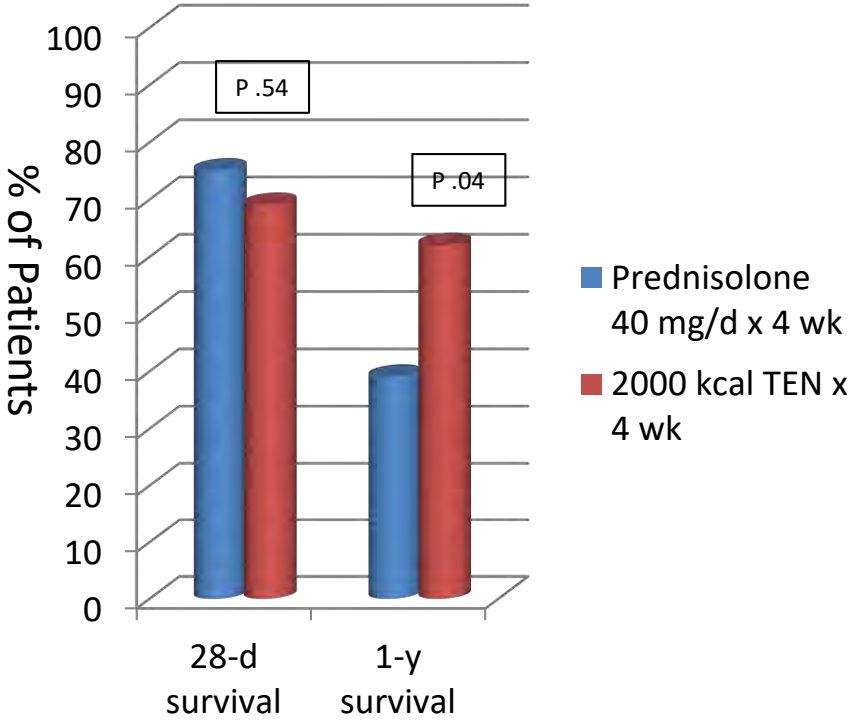
Cordoba J; J Hepatol 2004;41:38–43



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

Enteral Nutrition in Alcoholic Hepatitis

Cabre E; Hepatology 2000;32:36–42

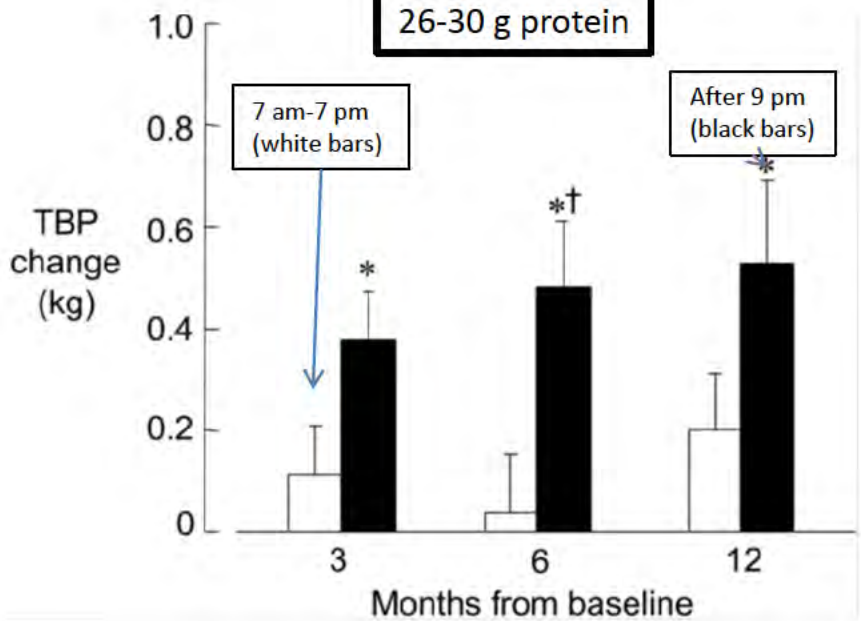


In Severe AH, Total Enteral Nutrition is as good as steroids at 4 weeks, but superior after 1 year

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)

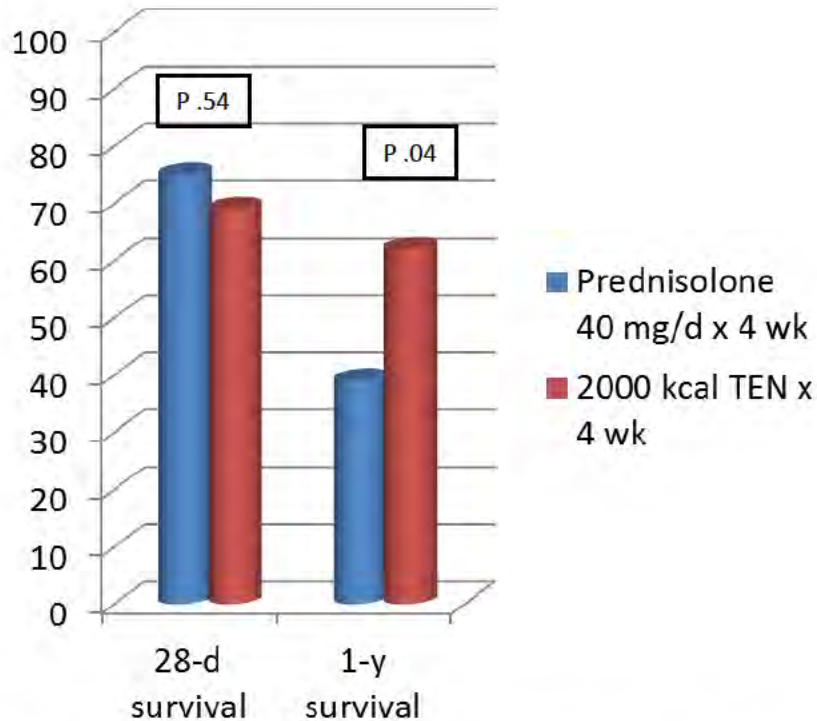
Probiotic Yogurt in Covert Hepatic Encephalopathy
Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

12 ounces of Probiotic Yogurt a day

Probiotic Yogurt Improves Covert HE & Protects against Overt HE

Enteral Nutrition in Alcoholic Hepatitis

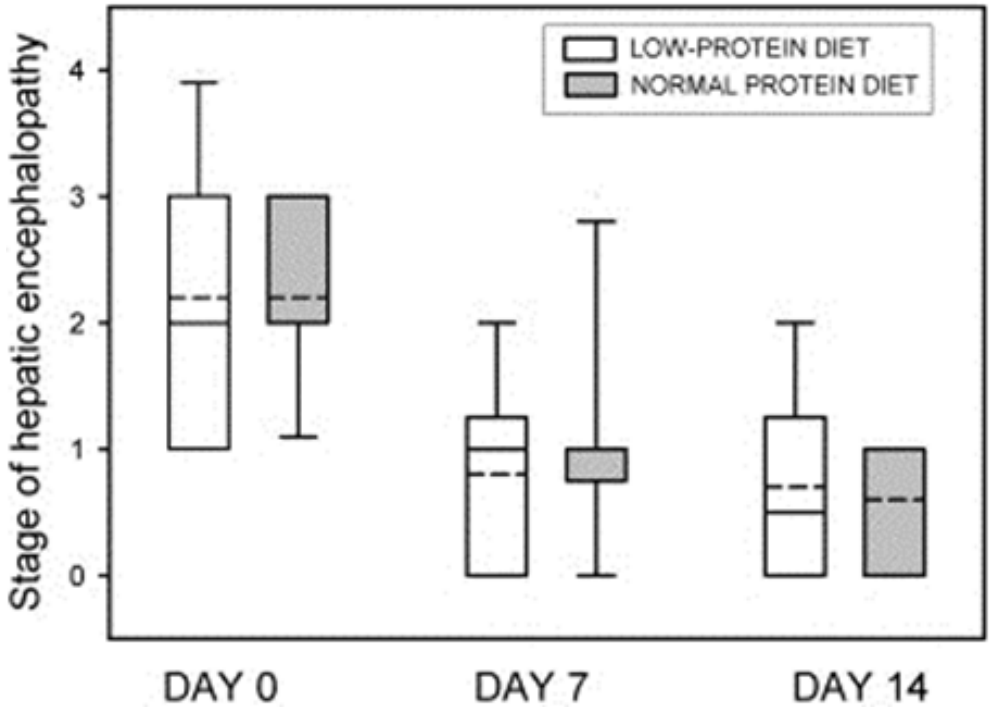
Cabre E; Hepatology 2000;32:36–42



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

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

Early (</= 72 hours) TIPS after Esophageal Variceal Bleed
Meta-Analysis of Individual Patient Data

Nicoara-Farcau, O et al. Gastroenterology 2021;160:193–205

Early TIPS in Active bleed + Child-Pugh B 7 vs >/= 8
Survival

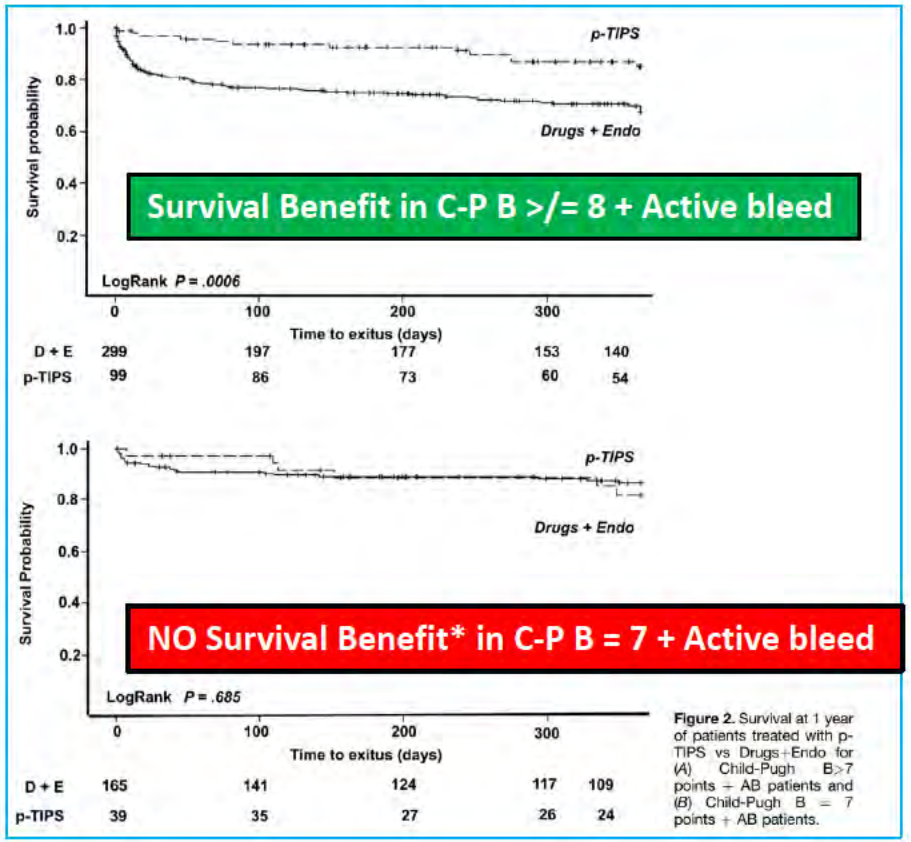
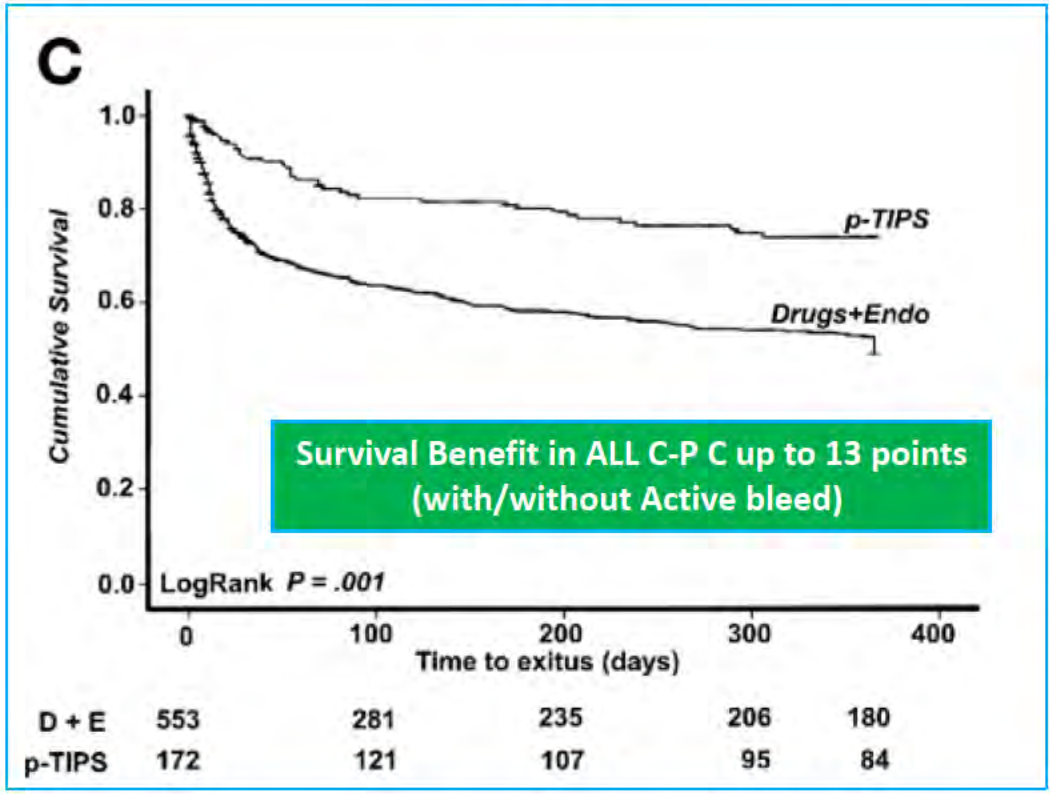


Figure 2. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo for (A) Child-Pugh B>7 points + AB patients and (B) Child-Pugh B = 7 points + AB patients.

* But decreases Risk of Developing Ascites

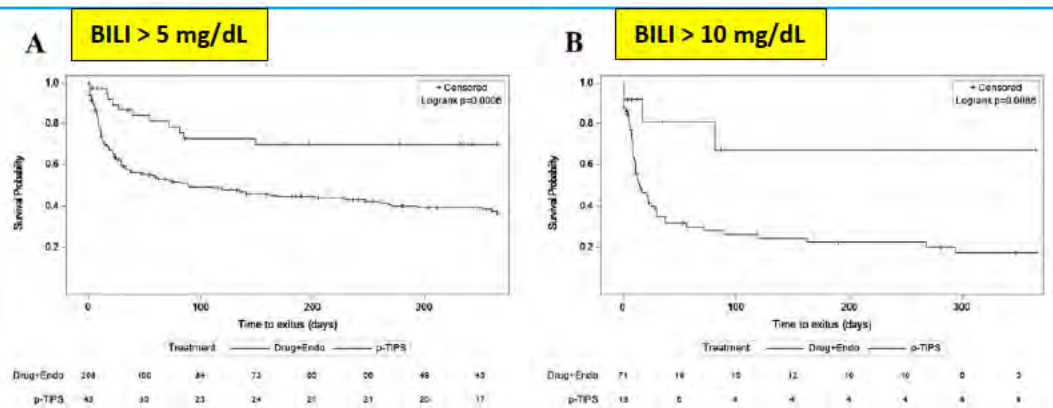
Early TIPS in Child-Pugh C up to 13
Survival



Meta-Analysis of Individual Patient Data

Nicoara-Farcau, O et al. Gastroenterology 2021;160:193–205

Early TIPS improves Survival even if Bili > 10 mg/dL



Supplementary Figure 7. Survival at 1 year of patients treated with p-TIPS vs Drugs + Endo in A. patients with Bilirubin > 5 mg/dL and B. patients with Bilirubin > 10 mg/dL.

Early TIPS is Beneficial even with Multiple Risk Factors

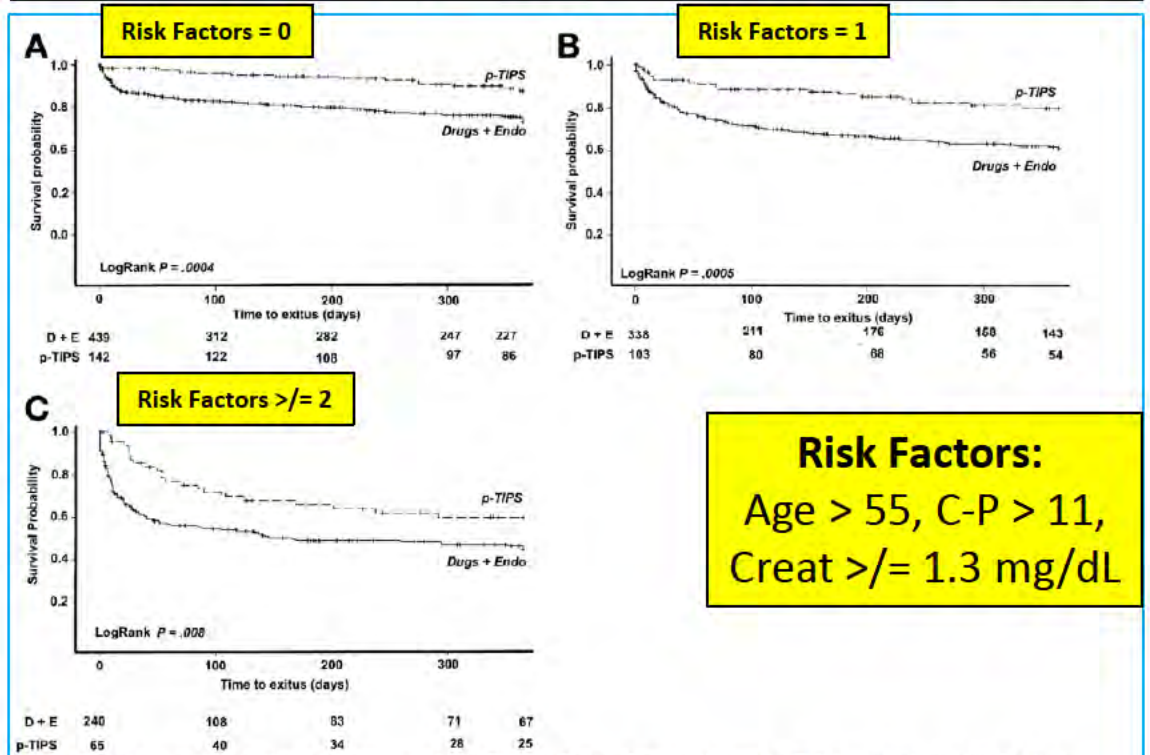


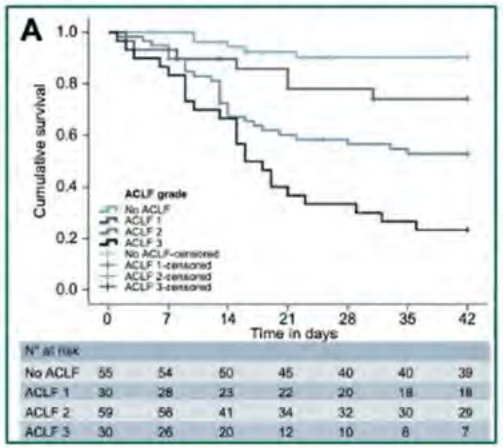
Figure 3. Survival at 1 year of patients treated with p-TIPS vs Drugs+Endo in (*A*) good p-TIPS prognosis group, (*B*) intermediate p-TIPS prognosis group, and (*C*) poor p-TIPS prognosis group.

Risk Factors:
Age > 55, C-P > 11,
Creat >/= 1.3 mg/dL

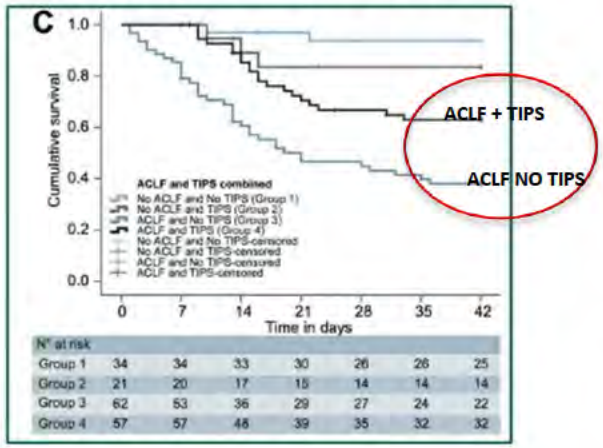
Are all patients candidates to Recue TIPS?

6 week mortality

According to ACLF grade



According to ACLF &TIPS status

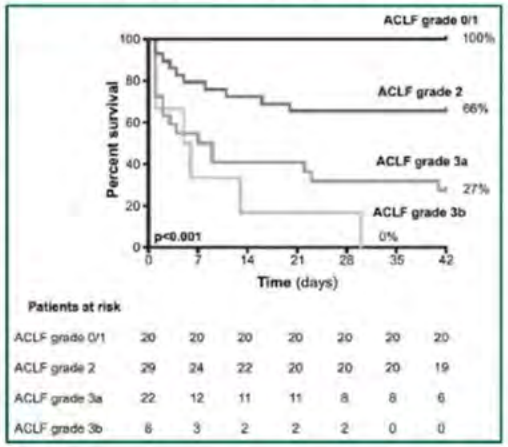


*Age, CLIF-C OF score and TIPS status were independent predictors of mortality

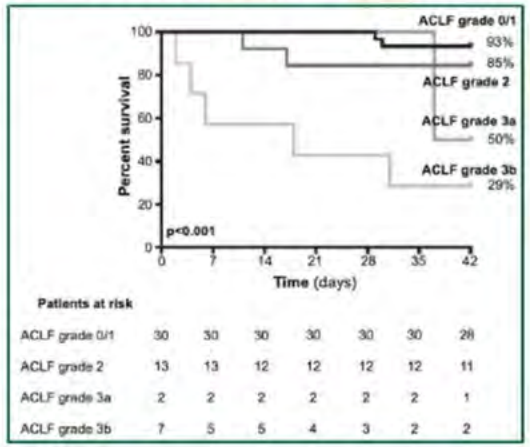
Kumar R et al. J Hepatol 2020

6 week mortality

Study cohort (France)



Validation cohort (Spain)



ACLF-3b grade may appear as indicative of futile prognosis for salvage TIPS

Walter A et al. Hepatology 2021

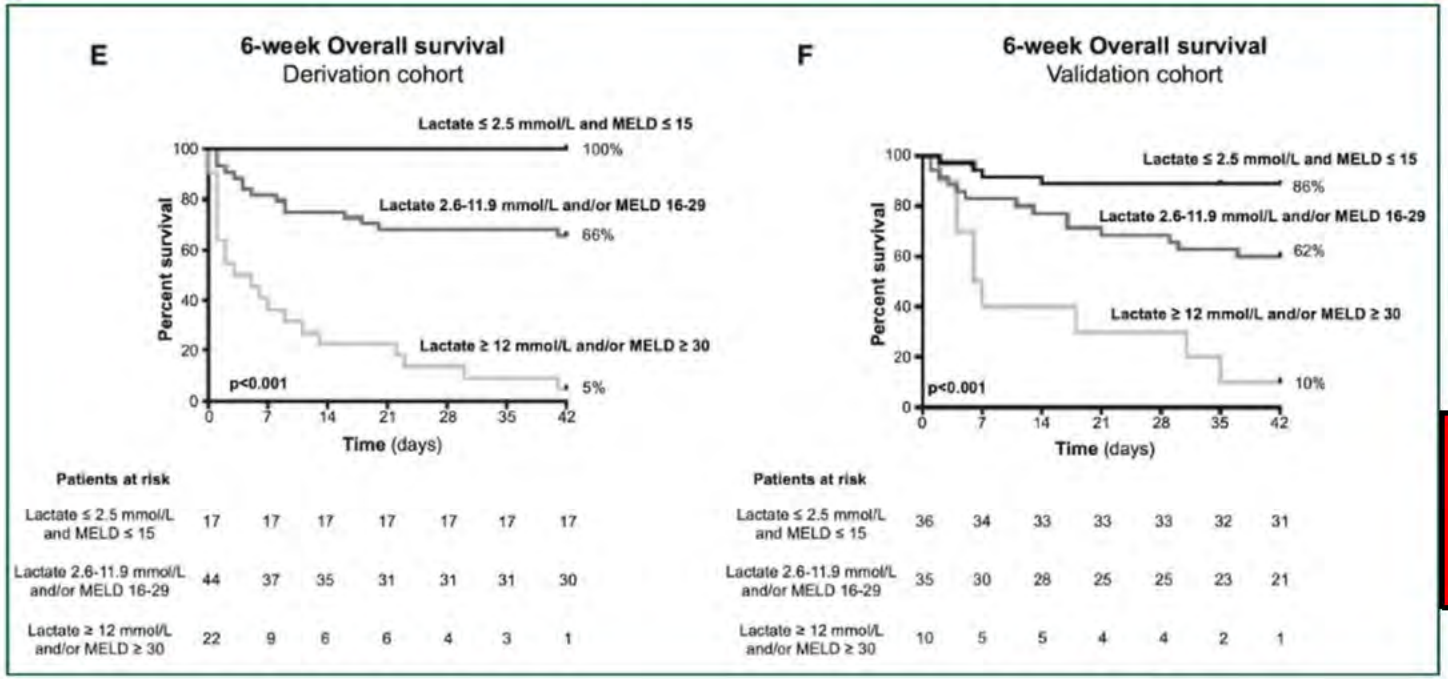
Rescue TIPS Improves Survival even in ACLF

ACLF-3b: >/= 4 Organ Failures
TIPS Futile as "Rescue"

AASLD The Liver Meeting®

Are all patients candidates to Recue TIPS?

Low risk of death (**lactate ≤ 2.5mmol/L and MELD ≤ 15**)
6-week OS: 100.0% - 86.0%
High risk of death (lactate ≥ 12mmol/L and/or a MELD ≥ 30)
6-week OS: 5.0% - 10.0%



Six-week survival rate after salvage TIPS for refractory bleeding was 58%

Rescue TIPS has very Poor Survival if Lactate >/= 12 mmol/L, or MELD >/= 30

Walter A et al. Hepatology 2021

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