

Cirrhotic Ascites and its Complications

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Pathophysiology of Cirrhotic Ascites

↑ Hepatic sinusoidal pressure



Activation of hepatic baroreceptors



Peripheral arterial vasodilation with hypervolemia,
(normal renin, aldosterone, vasopressin, or
norepinephrine)



↑ Peripheral arterial vasodilation (“underfilling”)



Neurally mediated Na⁺ retention, (with
elevated renin, aldosterone, vasopressin, or
norepinephrine)

Compensated

Decompensated

Classification of Ascites

- Serum-ascites albumin gradient (SAAG)
- $\text{SAAG (g/dl)} = \text{albumin}_s - \text{albumin}_a$
- Gradient ≥ 1.1 g/dl = portal hypertension
- Serum globulin > 5 g/dl:
 - SAAG correction = (SAAG mean)(0.21+0.208 serum globulin g/dl)

Ascites with High SAAG

≥ 1.1 g/dl = portal hypertension

- Cirrhosis
- Alcoholic Hepatitis
- Cardiac ascites
- Massive hepatic metastasis
- Fulminant hepatic failure
- Budd-Chiari syndrome
- Portal vein thrombosis
- Veno-occlusive disease
- Acute fatty liver of pregnancy
- Myxedema
- Mixed ascites

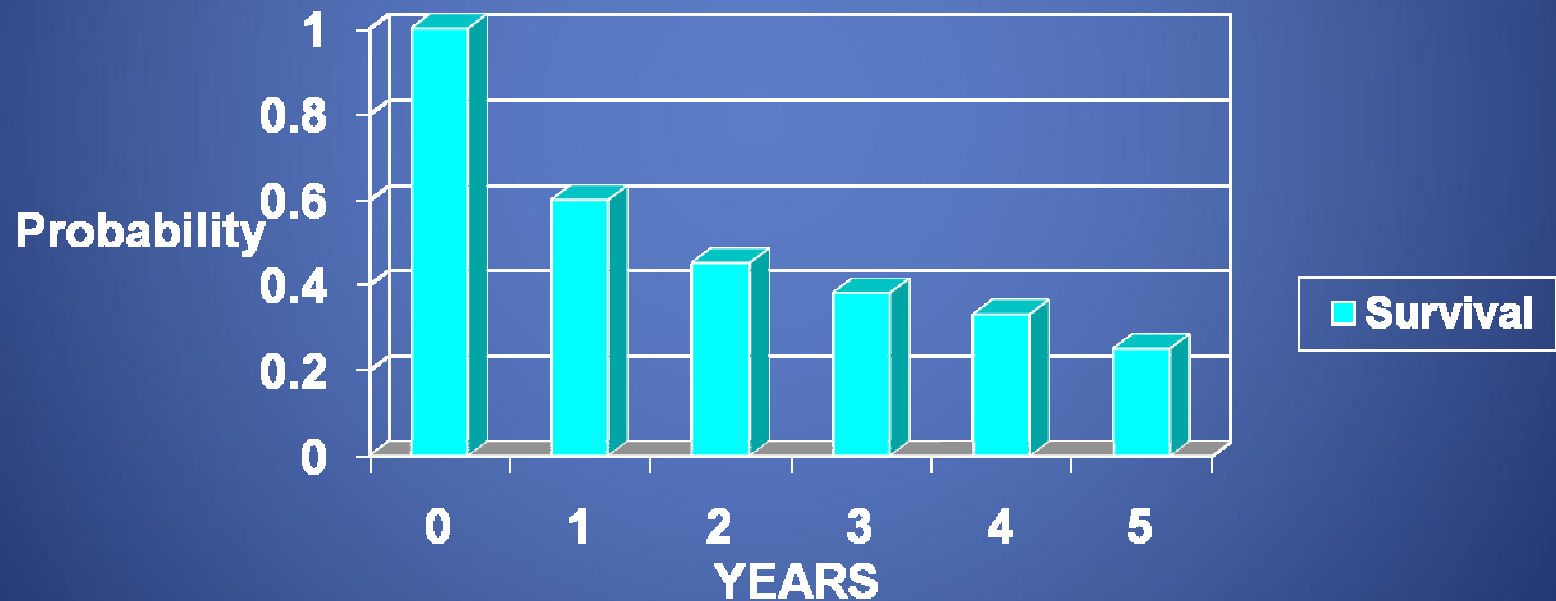
Low SAAG

<1.1 g/dl

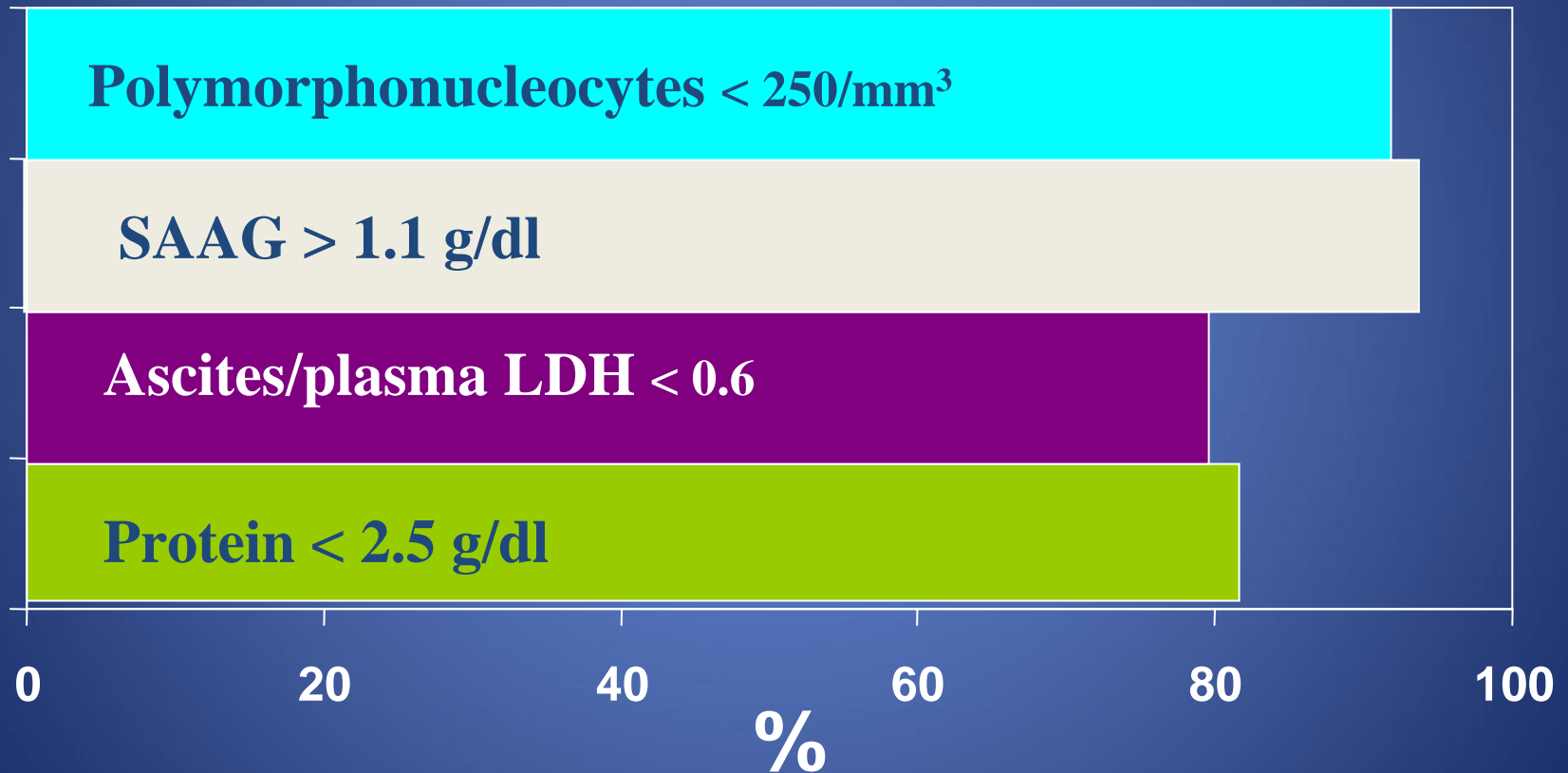
- Peritoneal carcinomatosis
- Tuberculous peritonitis (without cirrhosis)
- Biliary ascites (without cirrhosis)
- Pancreatic ascites (without cirrhosis)
- Nephrotic ascites
- Connective tissue disease
- Intestinal obstruction/infarction
- Eosinophilic Ascites (eosinophilic gastroenteritis)
- Ovarian Hyperstimulation Syndrome
- POEMS Syndrome
- Chylous Ascites
- Urinary ascites

Survival of Cirrhotics with Ascites

Survival in cirrhotic ascites



Characteristics of Uncomplicated Cirrhotic Ascites



Ascites/plasma amylase ~0.5

Leucocytes < 300/mm³; intense diuresis 1100/mm³

Treatment of Ascites with High SAAG (≥ 1.1 mg/dl)

- ***Treat primary disease***
 - alcoholism, Wilson's, autoimmune hepatitis, cardiac insufficiency, ...
- ***Na⁺ restriction:***
 - Inpatient: 250-1000 mg (11-44 mEq) depending on urinary loss
 - Outpatient: 1-2 g (44-88 mEq) of Na/day with diuretics for 0 or slightly negative balance

Treatment of Ascites

- **Diuretics**

- **General therapeutic goal**

- Without edema : 1 lb/d weight loss
 - With edema : 1-2 lb/d weight loss
 - If urine Na/K ratio 24 h after diuretics is >1 , then 87% of patients will lose at least 88 mEq Na/day (Hepatology 2002; 36(4):222A);
 - any Random spot urine Na/K > 0.97 has similar value (PPV 84%; NPV 90%) and if Na/K ≥ 3.5 , PPV is 100% (Liver Int. 2012;32(1):172-3).

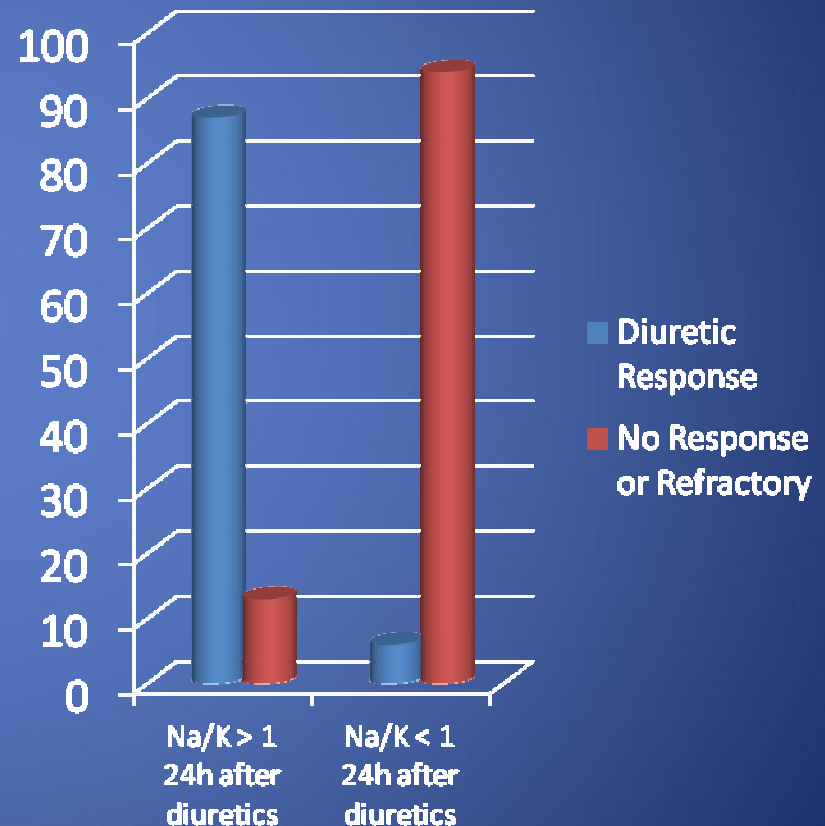
- **Spironolactone**: more effective than loop diuretics. Can produce hyperK and acidosis

- Dose: 100, 200, or 400 mg QD

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:
 - Only “24 h urine Na/K > 1”, and “spot-urine 24 h post diuretic Na/K > 1” predicted diuretic response.
 - If 24 h spot-urine Na/K < 1 while in spironolactone 400 + furosemide 160, the patient has “Refractory Ascites”



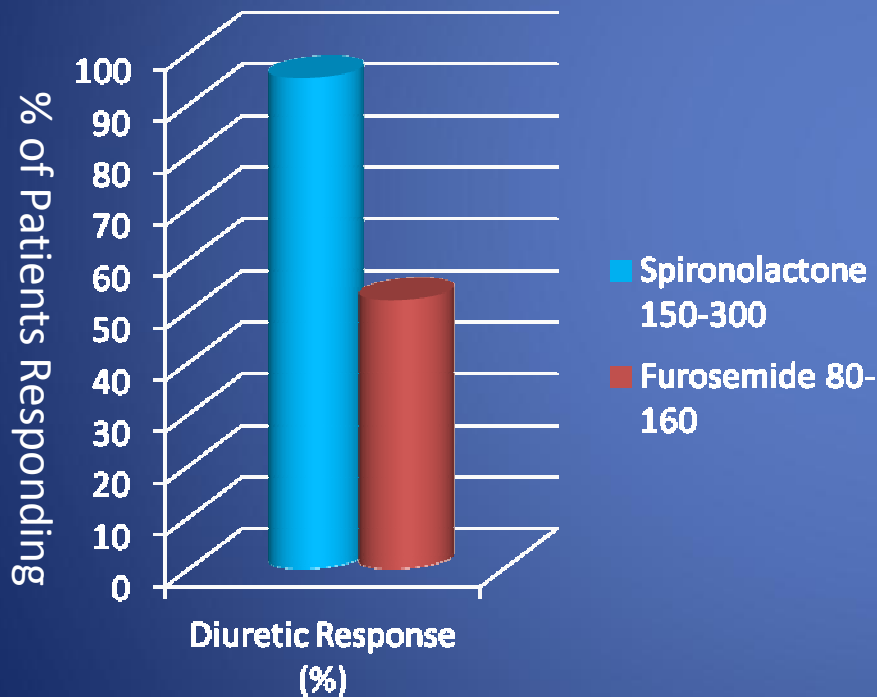
Treatment of Ascites

- **Furosemide:** produces hypok and alkalosis
 - Dose: 40, 80, or 160 mg QD
- **Metolazone:** added when maximal spironolactone 400 + Furosemide 160 is not controlling ascites and MAP > 83 mm Hg. Causes severe hypok
 - Dose 2.5-10 mg QD

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

- 2 g Na diet (3 meals + 3 snack + hs supplement) .
- Usually start spironolactone 100 mg + furosemide 40 mg in a single morning dose.
 - Double dose daily until goal is reached.
- Adjust dose by:
 - weight loss,
 - Na/K spot urine ratio before next morning diuretics (HEPATOLOGY 2002;36:222A), 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 after > 24 h post diuretics (before AM diuretics) > 1
 - Creatinine elevation: ideally none, < 0.3 mg/dL.

Treatment of Ascites with High SAAG

- **Water restriction**
 - If serum Na < 126-130 mEq/L
 - Restrict to 0.8-1.5 liters/day
- **Aggressively correct malnutrition**
 - Meal divided in 3 meal, 3 snacks and bedtime “supplement” (Boost-plus, or Ensure-Plus 2 cans @ hs)
 - Protein 1-1.5 g/kg
 - Calories: 25 k-cal/kg/d (in overweight, decrease caloric need by 500 k-cal/d)

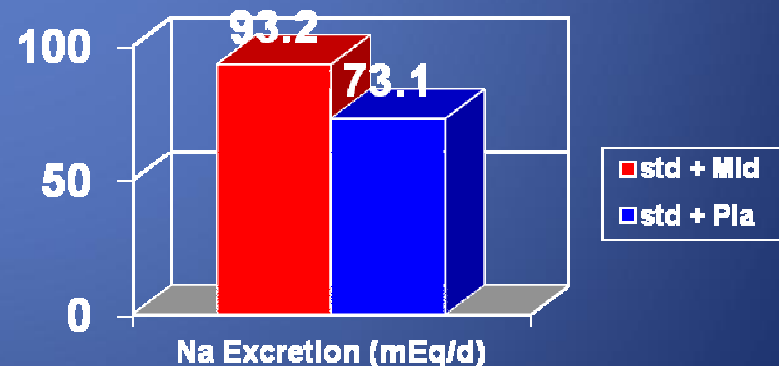
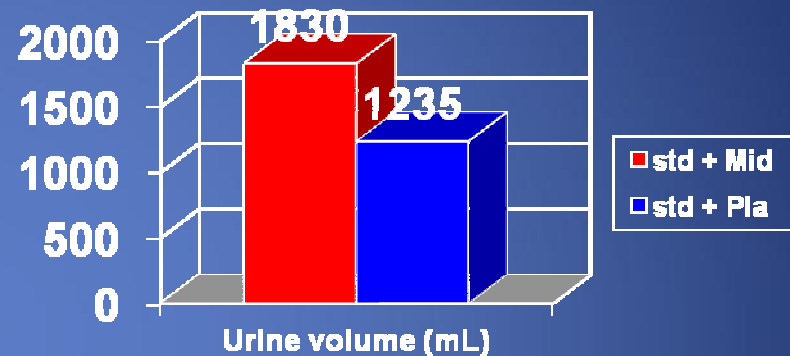
Treatment of Ascites

- ***Therapeutic paracentesis:*** done in patients with stable cirrhosis with or without edema
 - Single large volume paracentesis (4-6 L): with or without colloid infusion
 - Serial LVP (4-6 L/Day): Colloid infusion (40 g albumin) need is controversial
 - Total paracentesis (6-22 L over 1 hr) with
 - IV albumin (6-8 g/L removed) or
 - Dextran 70 (8 g/L removed), or
 - Midodrine 5-10 mg p.o. TID with goal to increase baseline MAP by 10 mmHg x 72 hours (Am J Gastroenterol 2008;103:1399-1405)

Pilot Study of Midodrine for cirrhosis with refractory/recurrent ascites

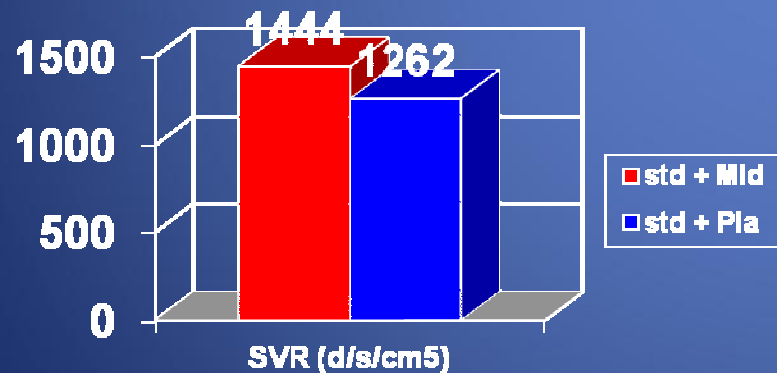
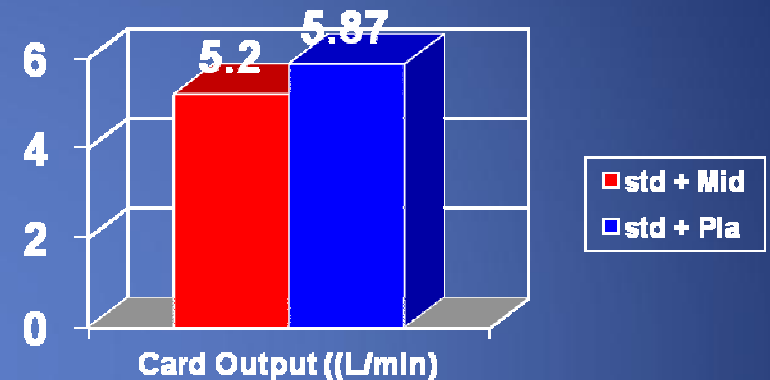
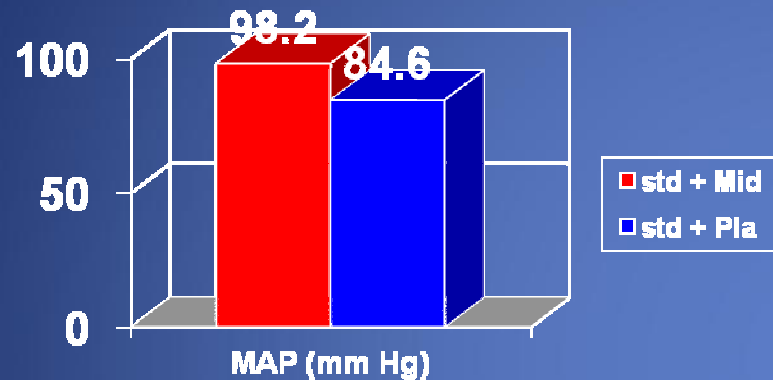
Singh V, et al. AASLD Abstr 314, 2009

- Study:
 - Prospective, randomized, controlled in cirrhotic patients with refractory ascites.
- Intervention:
 - a) std medical therapy + Midodrine 7.5 mg TID (N:20),
 - b) std medical therapy (N:20)
- Mean duration of therapy
 - 63+/-27 d,
- Mean F/U
 - 137+/-78 d.



Pilot Study of Midodrine for cirrhosis with refractory/recurrent ascites

Singh V, et al. AASLD Abstr 314, 2009



- Midodrine was superior for ascites control at 3 mo.
- Midodrine improved survival after more than 3 months but not at 3 months.

Treatment of Refractory Ascites

- **Definition:**

- Ascites that can not be controlled on a 2 g Na diet with Spironolactone 400 mg + Furosemide 160 mg, without causing azotemia.

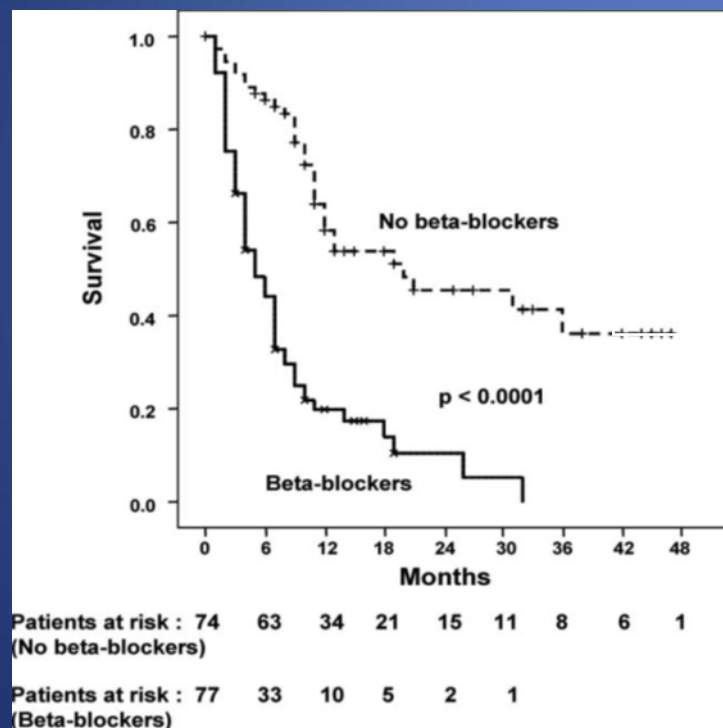
- **Treatment:**

- LVP + Albumin
- Midodrine 7.5 mg TID
- Albumin + Midodrine + Octreotide
- **TIPSS** (higher mortality if MELD > 15-18, or bili > 4 mg/dL)
- **Non-selective surgical Shunt**
- **Betablockers increase mortality in refractory ascites, especially if MAP is \leq 83; D/C betablockers and band varices if needed (Hepatology 2010 Sep;52(3):1017-22).**
- **Pentoxifylline and Norfloxacin decrease risk of HRS in refractory ascites.**

Ascites & Refractory Ascites

Effect of Beta-blockers in Refractory Ascites

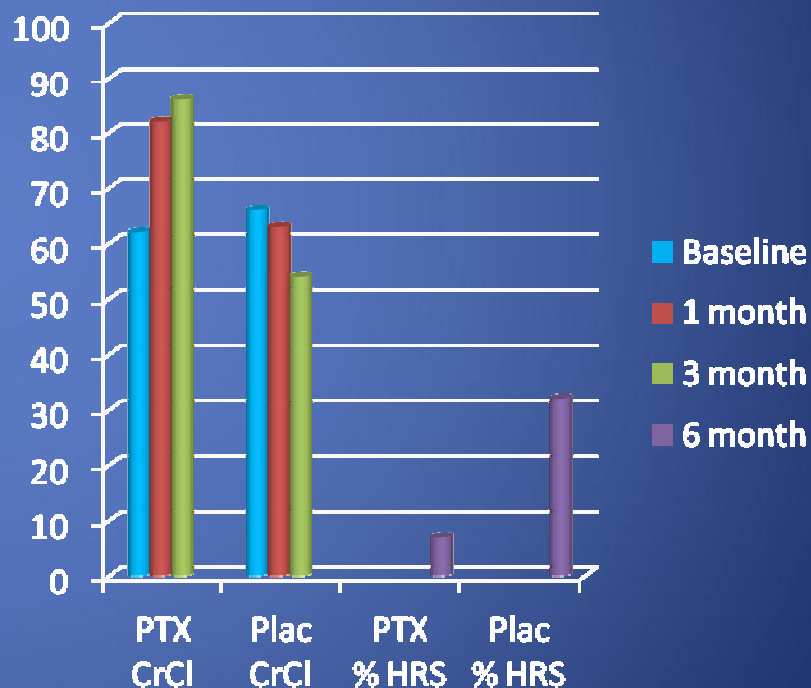
Serste T; Hepatology 2010;52(3):1017-1022



Beta-blockers increase mortality in patients with refractory ascites

Pentoxifylline in ascites with CrCl 41-80

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

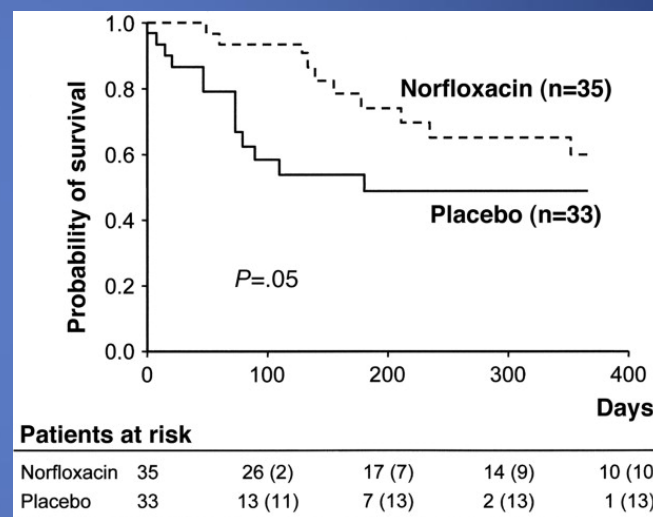
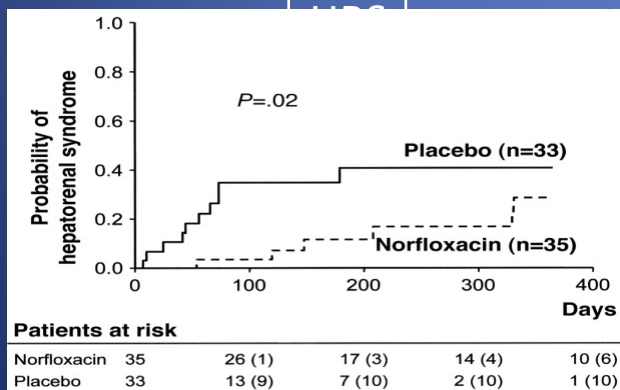
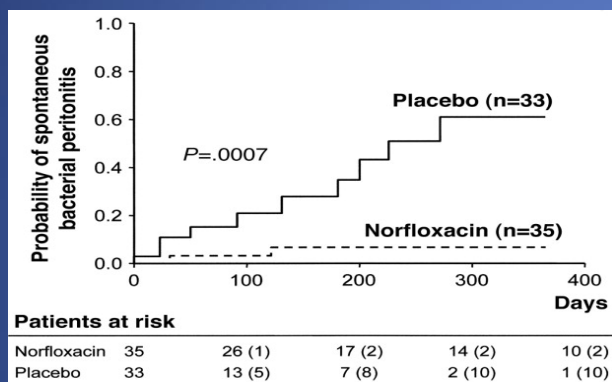


In ascites with renal dysfunction, Pentoxifylline decreases risk of HRS

Ascites & Refractory Ascites

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

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



In ascites with Child ≥ 9 or renal dysfunction, Norfloxacin decreases risk of SBP, HRS, and mortality.

Multicenter RCT on TIPS vs LVP in Refractory and Recidivant Ascites

	Ascites Refrac/ Residiv	# TIPS	# LVP	% Ascites improve TIPS	% Ascites improve LVP	% PSE TIPS	% PSE LVP	% Survival TIPS	% Survival LVP
Lebrec	100/0	13	12	38	0	15	6	29	60
Rossle	55/45	29	31	84	43	23	13	58	32
Gines	100/0	35	35	51	17	60	34	26	30
Sanyal	100/0	52	57	58	16	38	21	35	33
Salerno	68/32	33	33	79	42	61	39	59	29

EASL Guidelines for Refractory Ascites

J. of Hepatology 2010

- **First line treatment of refractory ascites:**
 - Repeated LVP plus albumin (8 g/L of ascites removed (Level A1).
- **Diuretics Management in refractory ascites:**
 - discontinue in patients who do not excrete >30 mmol/day of sodium under diuretic treatment.
- **Value of TIPS:** effective in the management of refractory ascites but,
 - is associated with a high risk of hepatic encephalopathy, and
 - studies have not been shown to convincingly improve survival compared to repeated large-volume paracentesis (Level A1).
- **Consider TIPS in patients with:**
 - very frequent requirement of large-volume paracentesis, or
 - in those in whom paracentesis is ineffective (e.g. due to the presence of loculated ascites) (Level B1).

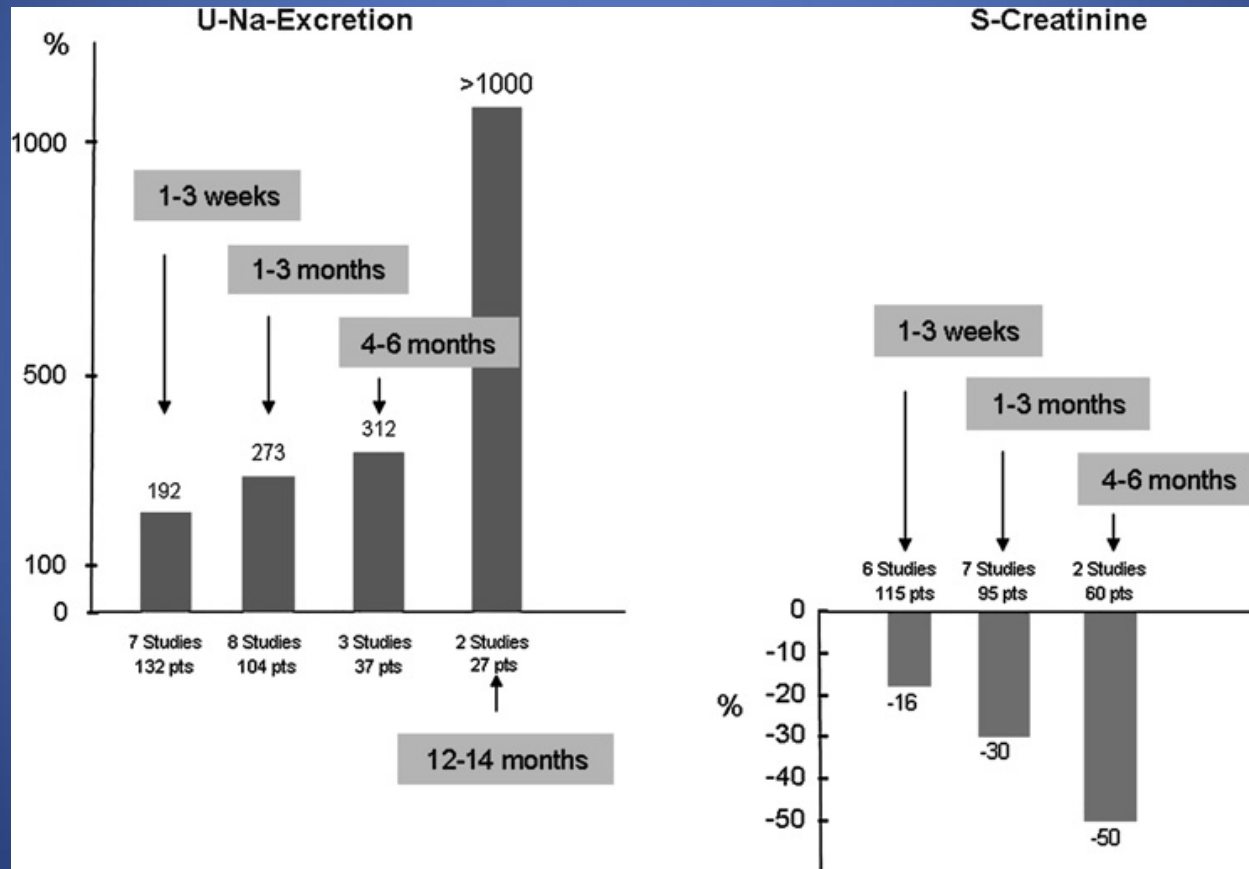
EASL Guidelines for Refractory Ascites

J. of Hepatology 2010

- Course after TIPS:
 - Resolution of ascites is slow and
 - most patients require continued administration of diuretics and salt restriction (Level B1).
- Caution for TIPS:
 - If MELD > 15-18, or bili > 4 mg/dL patients should be informed of higher 30 d TIPS mortality and
 - TIPS can be performed only in the absence of other options.
- Contraindications for TIPS: cannot be recommended in patients with:
 - severe liver failure (serum bilirubin >5 mg/dl, INR >2 or Child-Pugh score >11,
 - current hepatic encephalopathy grade 2 or chronic hepatic encephalopathy,
 - concomitant active infection,
 - progressive renal failure (but may be “rescue” for HRS), or
 - severe cardiopulmonary diseases (Level B1).

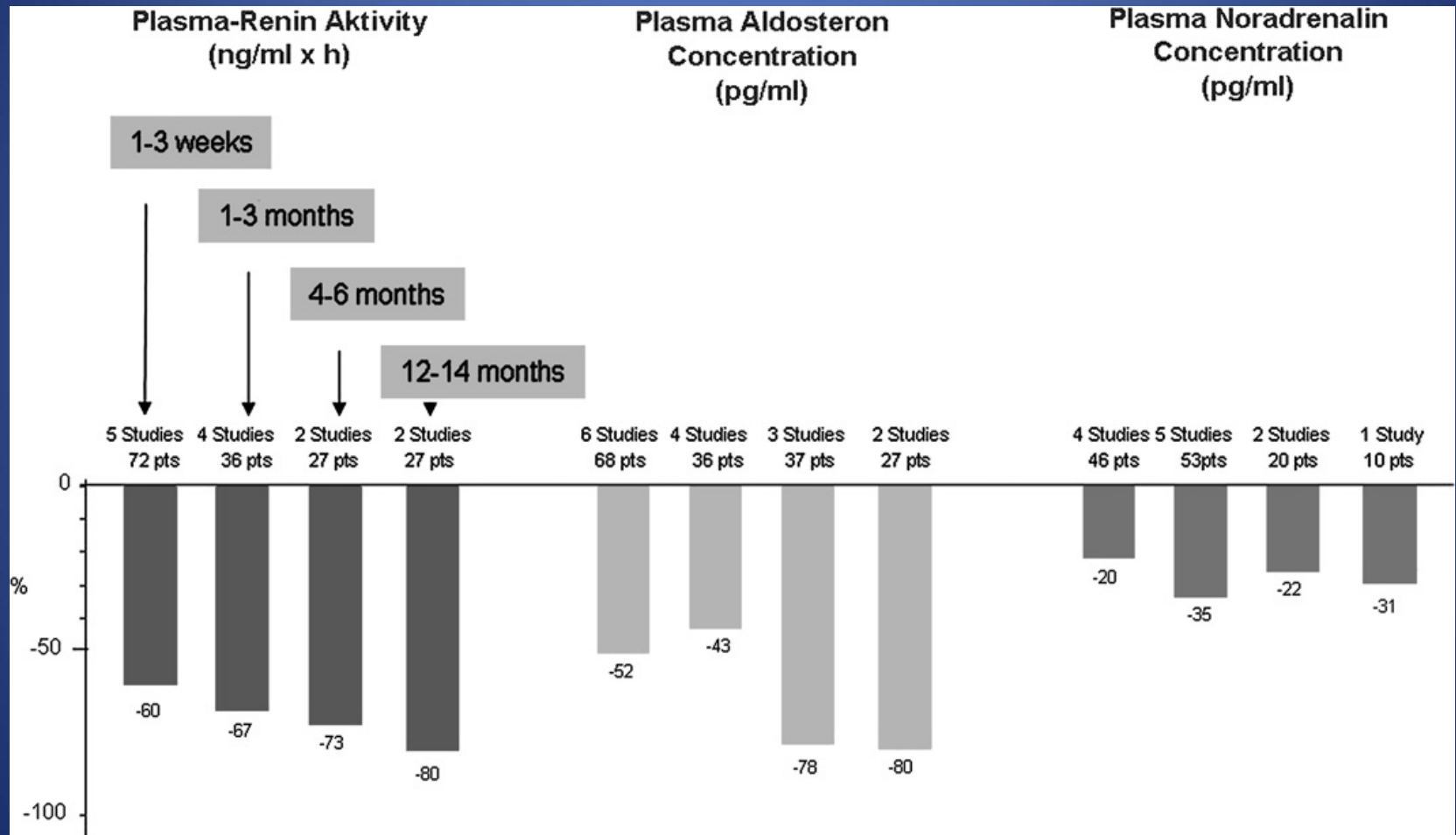
Effects of TIPS on Natriuresis and Azotemia

Rossle M et al. Gut 2010;59:988-1000.



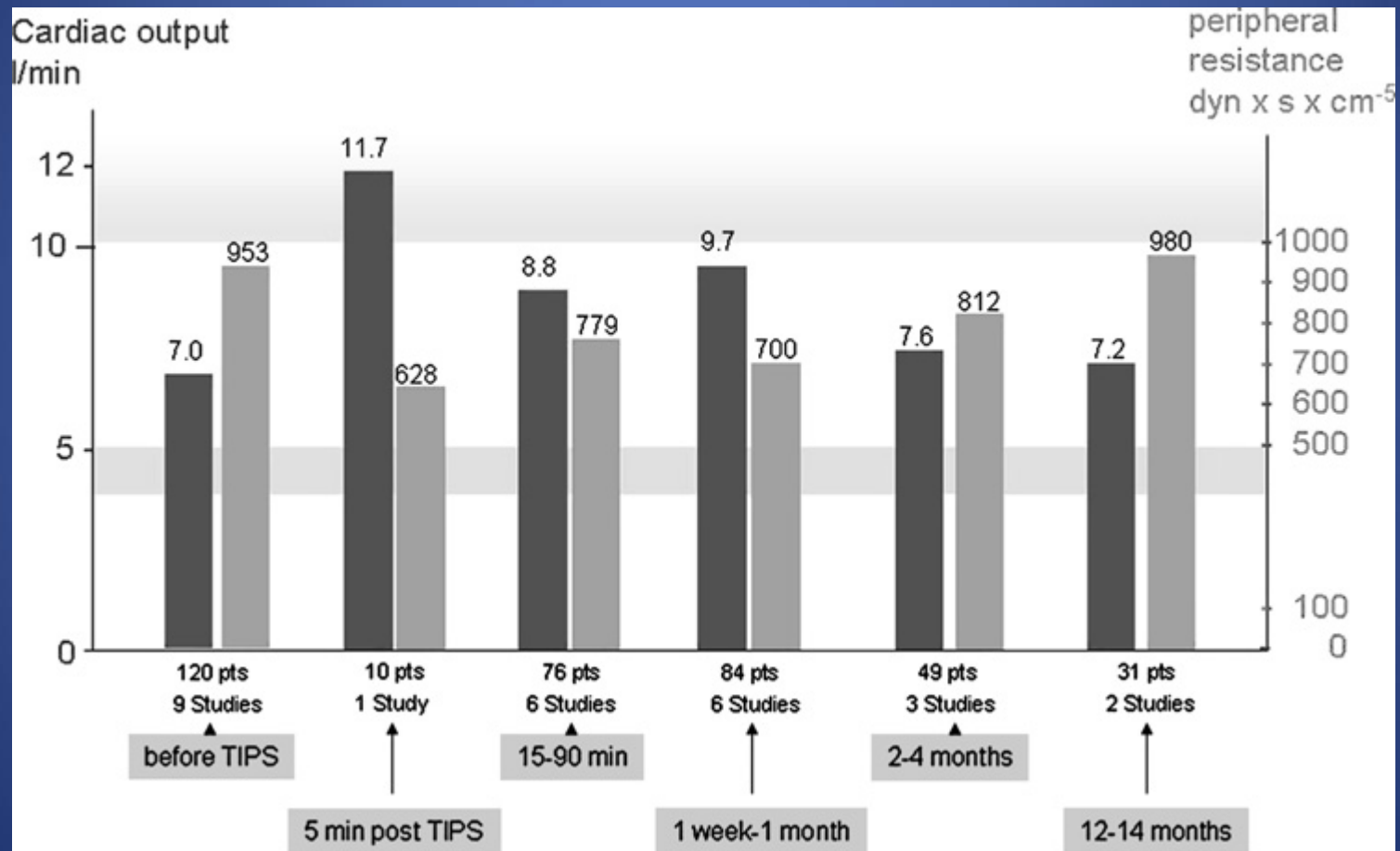
Effect of TIPS on Plasma Renin, Aldosterone & Noradrenaline levels

Rossle M et al. Gut 2010;59:988-1000.



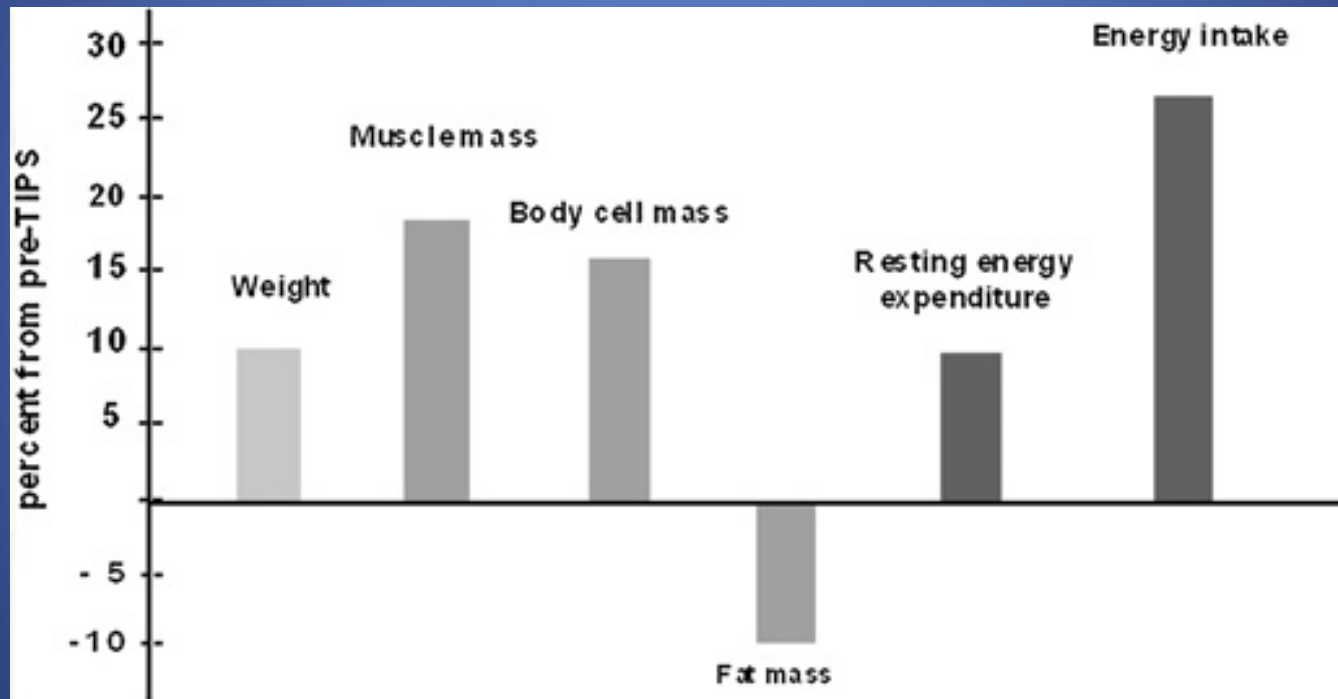
Effect of TIPS on Cardiac Output & Peripheral Vascular Resistance

Rossle M et al. Gut 2010;59:988-1000.



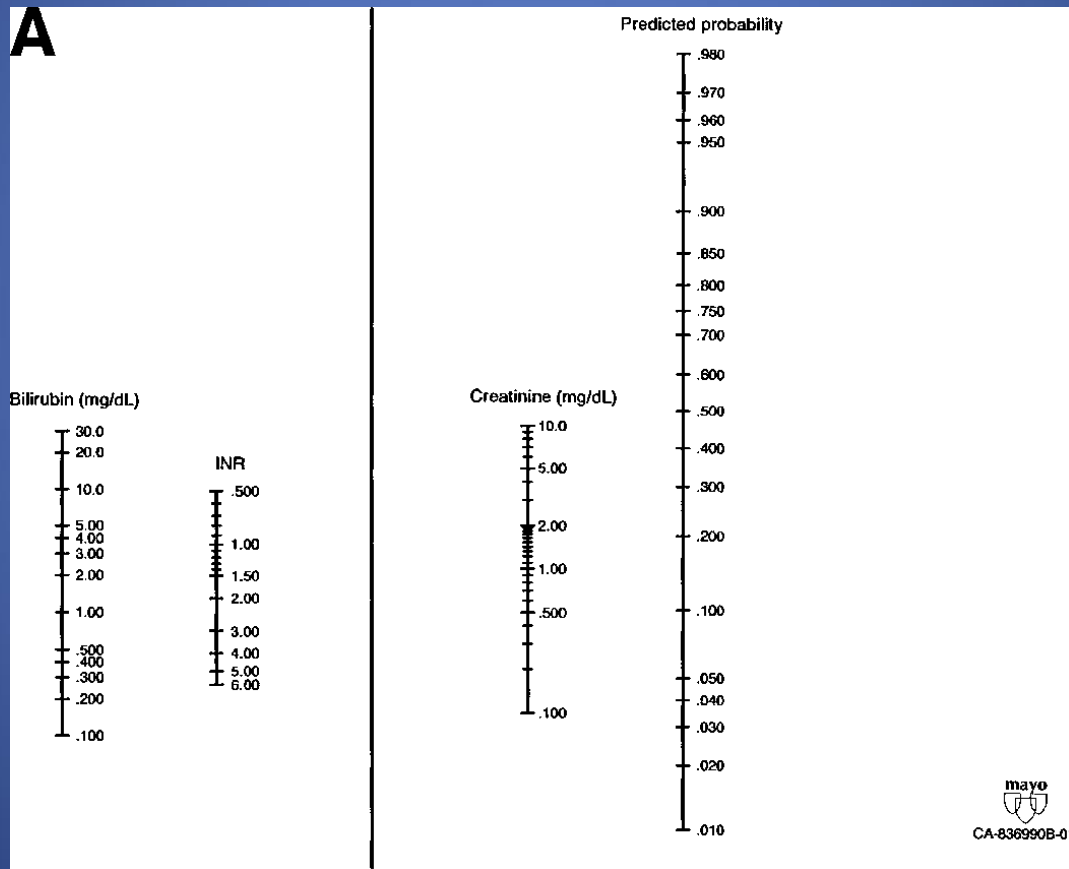
Effect of TIPS in Nutrition after 6 month Follow-up

Rossle M et al. Gut 2010;59:988-1000.



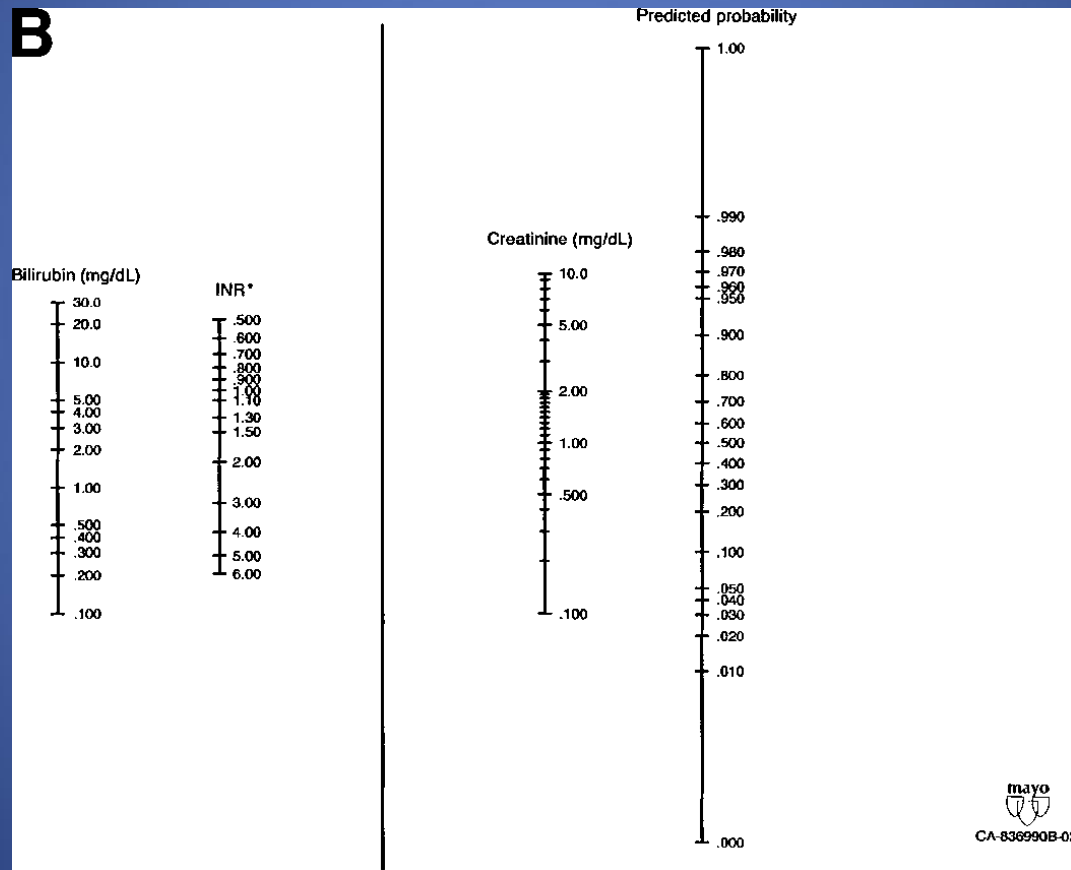
Nomogram to predict 3-month TIPS mortality in Alcoholic and Cholestatic Liver Disease

Malinchoc M et al. HEPATOLOGY 2000;31:864-871



Nomogram to predict 3-month TIPS mortality in Viral, NASH, Cryptogenic, A1AT, Wilson, MTX, etc

Malinchoc M et al. HEPATOLOGY 2000;31:864-871



Mortality (%) at 3 months after Elective TIPS

Malinchoc et al. Hepatology 2000;31:864-871

- Table of 3 month mortality after TIPS, compared with hospitalized cirrhotics not receiving TIPS (<http://www.soapnote.org/digestive-system/meld/>)
- MELD is “UNOS MELD”
 - Creat ≥ 1 and ≤ 4 mg/dL;
 - Bili is ≥ 1 mg/dL
- Tabulated from Malinchoc et al. Hepatology 2000;31:864-871)
- Group A: Alcoholic or Cholestatic Liver Disease.
- Group B: Viral, NASH, Cryptogenic, A₁AT defic, Wilson, MTX, etc.
- MELD 3-month Mortality from Weisner R
 $S3mo = 0.98465 \exp(\text{MELD score} - 10) * 0.1635$
 Gastroenterology 2003;124:91-96

MELD	Alcohol/ Cholestasis	Viral/NASH/MTX/ Wilson/A1AT/Crypto	Hospitalized without TIPS
10	15	27	1.6
12	17	30	2.2
14	22	37	3
15	23	39	3.5
16	25	42	4
17	28	46	5
18	30	49	6
19	32	52	7
20	35	57	8
21	38	60	9
22	43	64	11
23	43	71	12
24	47	73	14
25	50	78	17

Contraindications for TIPSS

ABSOLUTE

- Severe CHF
- Severe Pulmonary HTN (45 mm Hg)
- Polycystic liver disease
- Severe hepatic failure
- Portal V thrombosis with cavernoma

RELATIVE

- Active infection
- Poorly controlled PSE
- Hypervascular liver tumor
- Portal V thrombosis without cavernoma
- Biliary obstruction

Complications of Ascites

Spontaneous Bacterial Peritonitis (SBP) and Culture Negative Neutrocytic Ascites (CNNA)

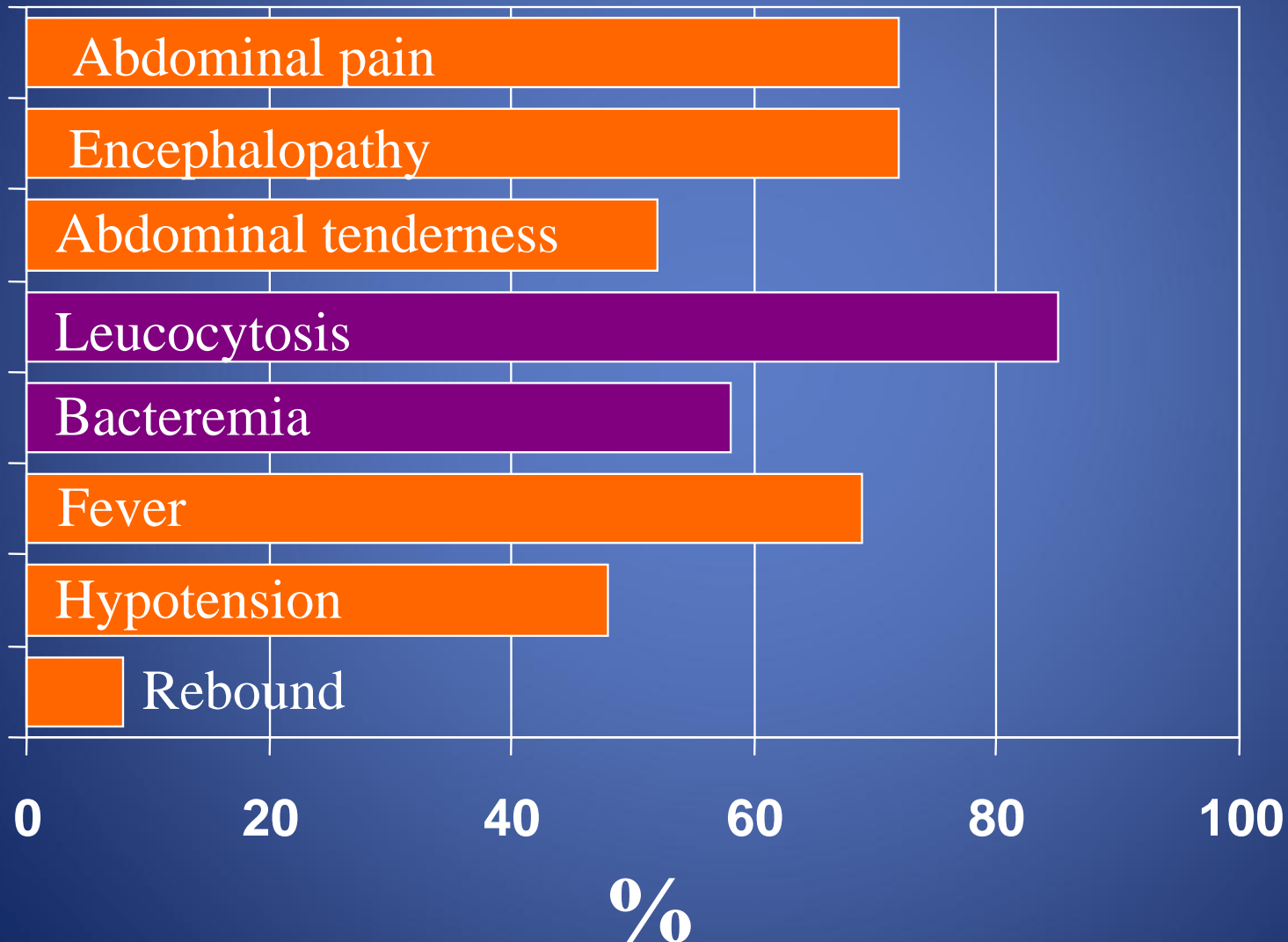
- ***Prevalence:***

- 10-27% in hospitalized patients with cirrhotic ascites

- ***Pathogenesis:***

- distant bacteremia (UTI, URI, etc.) or
- translocation of bacteria from intestinal lumen

Signs and Symptoms of SBP



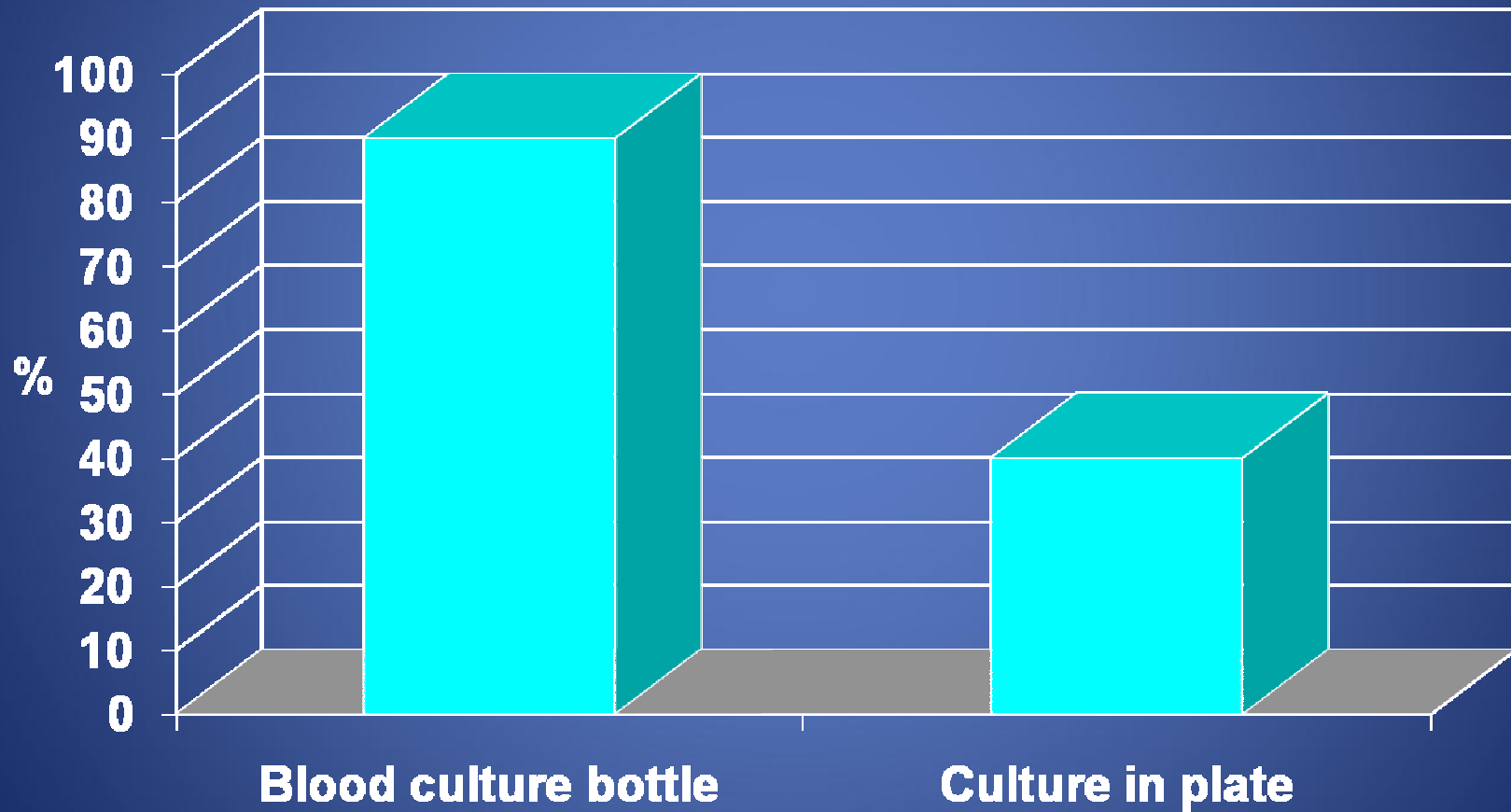
Diagnosis of SBP and CNNA

- **SBP** = PMN $>250/\text{mm}^3$ with (+) culture ($> 90\%$ monobacterial)
 - Other predictors:
 - Ascites WBC $> 1000/\text{uL}$
 - Ascites pH < 7.35
 - Blood-ascites pH gradient ≥ 0.1
- **CNNA** = PMN $>250/\text{mm}^3$ with (-) culture
 - without previous antibiotics, nor
 - other causes of increased PMN [bleeding, cancer, TB, pancreatitis]

Bacteriology of SBP

- ***Gram-Negative Bacilli*** **70%**
 - Escherichia coli
 - Klebsiella spp.
- ***Gram-Positive Cocci*** **20%**
 - Streptococcus pneumonia
 - Enterococcus spp
 - Staphylococcus spp
- ***Anaerobes, Microaerophils & others*** **10%**

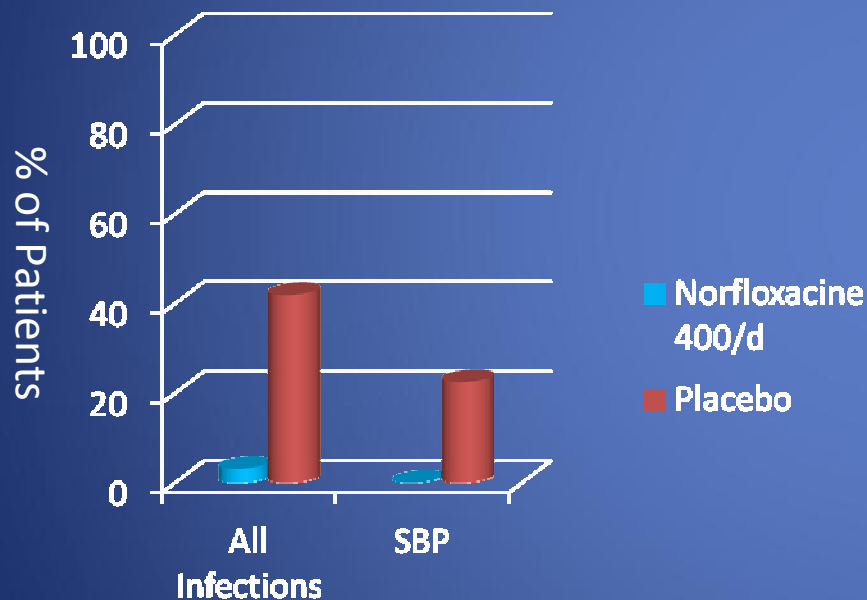
Ascites Culture



Spontaneous Bacterial Peritonitis (SBP)

Norfloxacin in Hospitalized patients with low protein (< 1.5g/dL) ascites

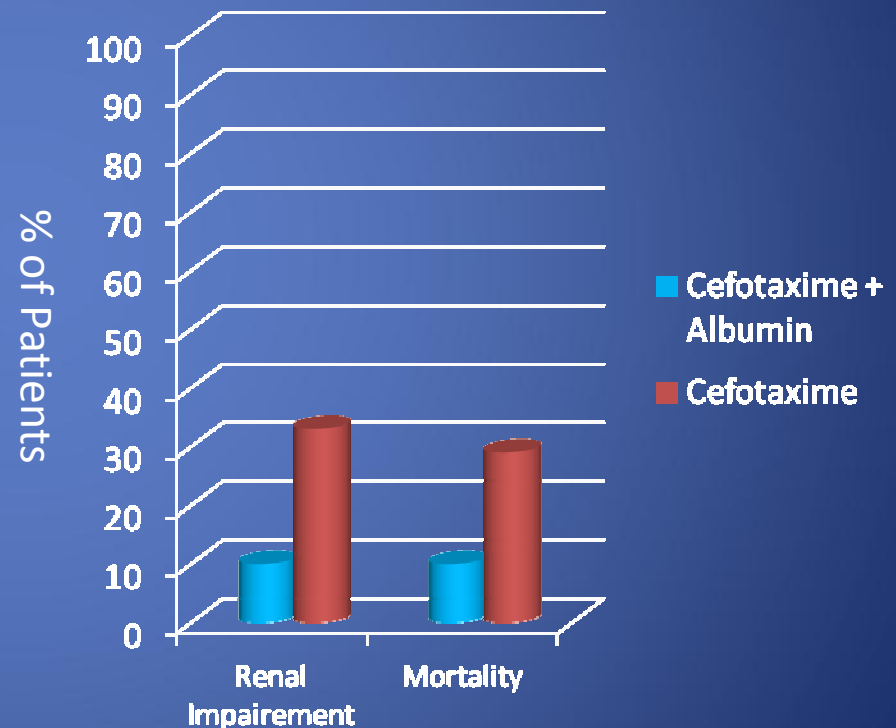
Soriano G; Gastroenterology 1991;100:477-481



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

Effect of albumin in azotemia and mortality in SBP

Sort P; N Engl J Med 1999; 341:403-409

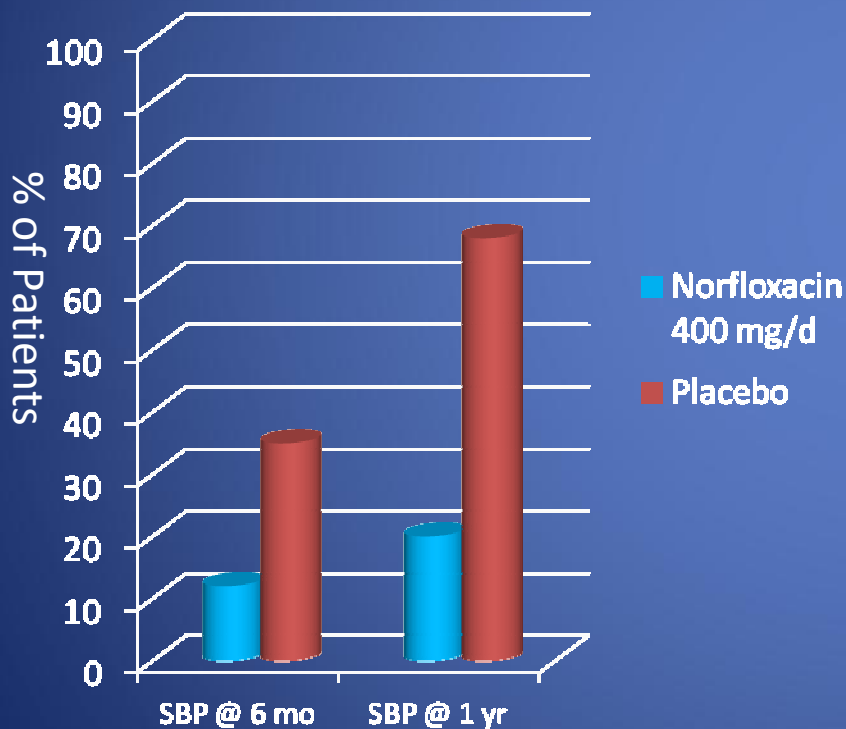


Volume expansion with IV albumin 1.5 g/kg day 1, and 1 g/kg 72 h later, decreases risk of HRS & Mortality, in SBP treated with Cefotaxime

Complications of Cirrhosis

Long Term Norfloxacin prevents SBP recurrence

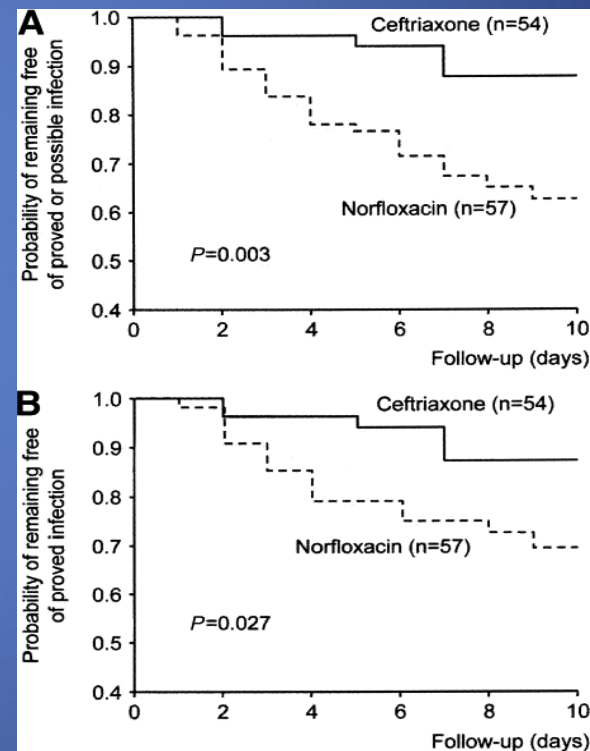
Gines P; Hepatology 1990;12:716-724



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 & CNNA

- ***In Hospital Prophylaxis***
 - **Cirrhotic with total protein < 1.5 g/dl;**
 - Norfloxacin 400 mg/d po or Bactrim DS 5 days/week during hospitalization
 - **Cirrhotic with GI bleed (SBP & other infections)**
 - Norfloxacin 400 mg po BID x 7 days, or
 - Cefotaxime 2 gm q 8h IV x 7 days (1st line)

SBP and CNNA

- ***Morbidity and Mortality***
 - Mortality without treatment: 78-100%
 - Mortality w. Cefotaxime: 30% (HRS= 33%)
 - Mortality w. Cefotaxim+albumin: 10% (HRS=10%)
 - Recurrent SBP in 69%
- ***Treatment***
 - Cefotaxime 2g TID x 5 days + Albumin 1.5 gm/Kg @ day 1 & 1 gm/Kg @ day 4
 - Re-paracentesis at 48hrs (50% reduction in WBCs)
- ***Post SBP (Secondary) Prophylaxis***
 - *Norfloxacin 400 mg PO daily decreases recurrence from 35% to 12%; no effect on mortality (from 25% to 18%)*

Primary Prophylaxis of SBP

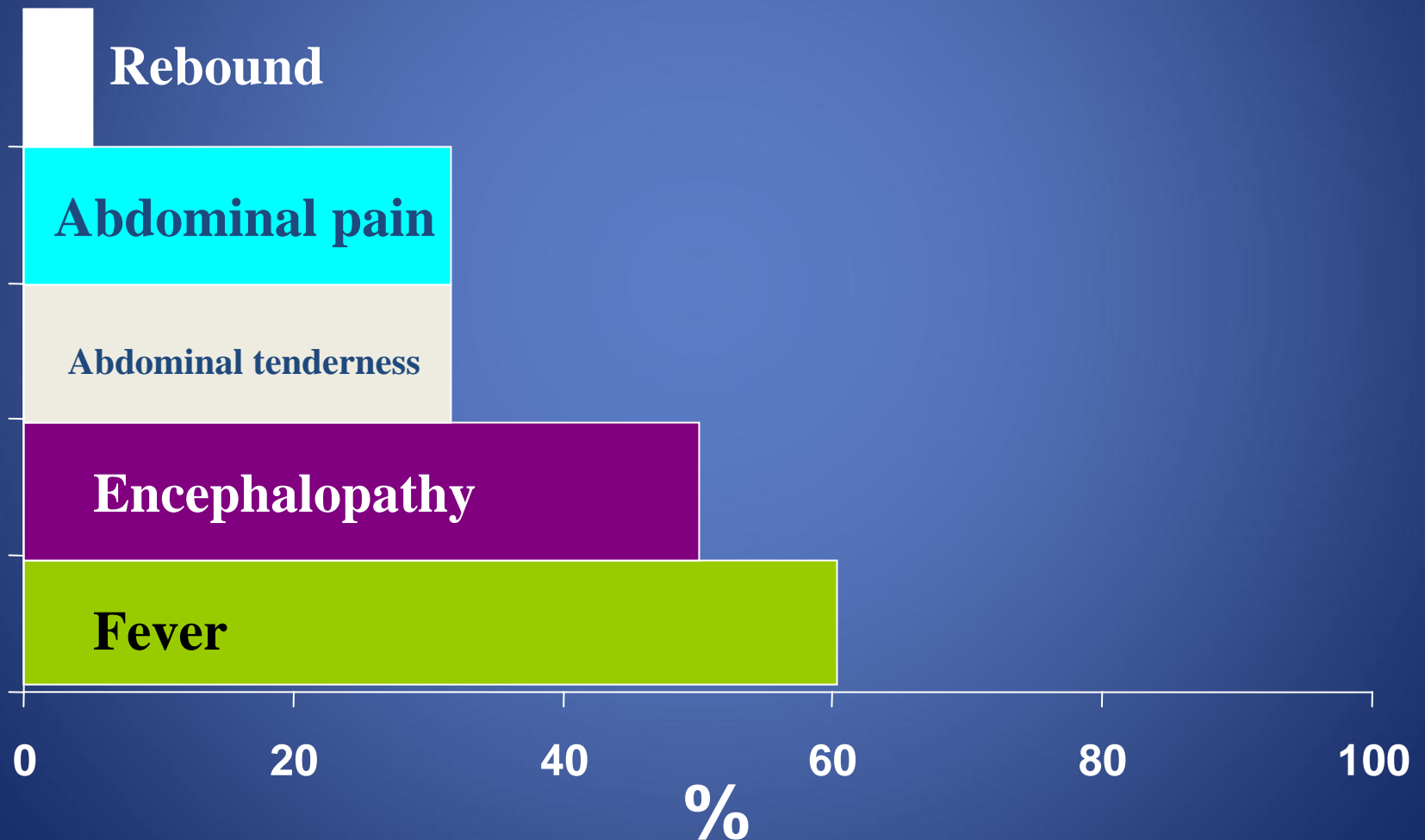
- **Severe liver disease** (Child-Pugh score ≥ 9 **with** serum bilirubin ≥ 3 mg/dl, or impaired renal function (serum creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl), or serum Na ≤ 130 mEq/L) with ascitic fluid protein < 1.5 g/dL and no prior SBP:
 - Norfloxacin (400 mg/day) reduced the risk of SBP, HRS, and improved survival.
 - In these patients should be considered for long-term prophylaxis with norfloxacin (Level A1).
- **Moderate liver disease**, ascites protein concentration < 1.5 g/dL, and no prior history of SBP:
 - The efficacy of quinolones in preventing SBP or improving survival is not clearly established.
 - Studies are needed in this field.

Monomicrobial Bacterascites

- Diagnosis

- (+) ascites culture with PMN $< 250/\text{mm}^3$ and without surgically treatable intra-abdominal source of infection

Signs and Symptoms of Monomicrobial Bacterascites



Monomicrobial Bacterascites

- Mortality: 40%
- Treatment
 - Cefotaxime 2 g TID as per antibiotic susceptibility
 - Repeat paracentesis in 48 hr

Ascites Management

- **EVALUATE:**

- Paracentesis post-adm, PSE, Azotemia, Fever
- Check: Prot, Alb, WBC, Glu, LDH in serum & ascites
- Bedside Culture in Blood Culture bottle

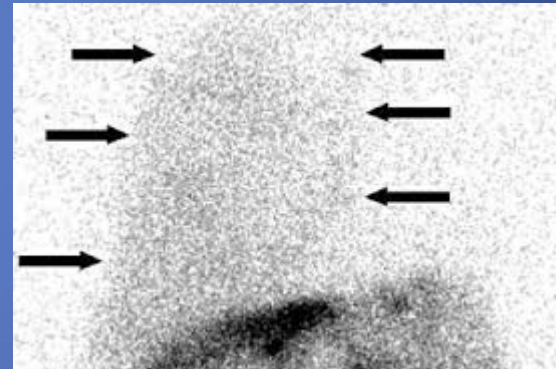
- **TREAT:**

- Na restrict + LVP + diuretics
- PMN>250: Cefotaxim + Albumin
- Prot < 1.5g: Norfloxacin
- GI Bleed: Norfloxacin

Hepatic Hydrothorax and Spontaneous Bacterial Empyema (SBE)

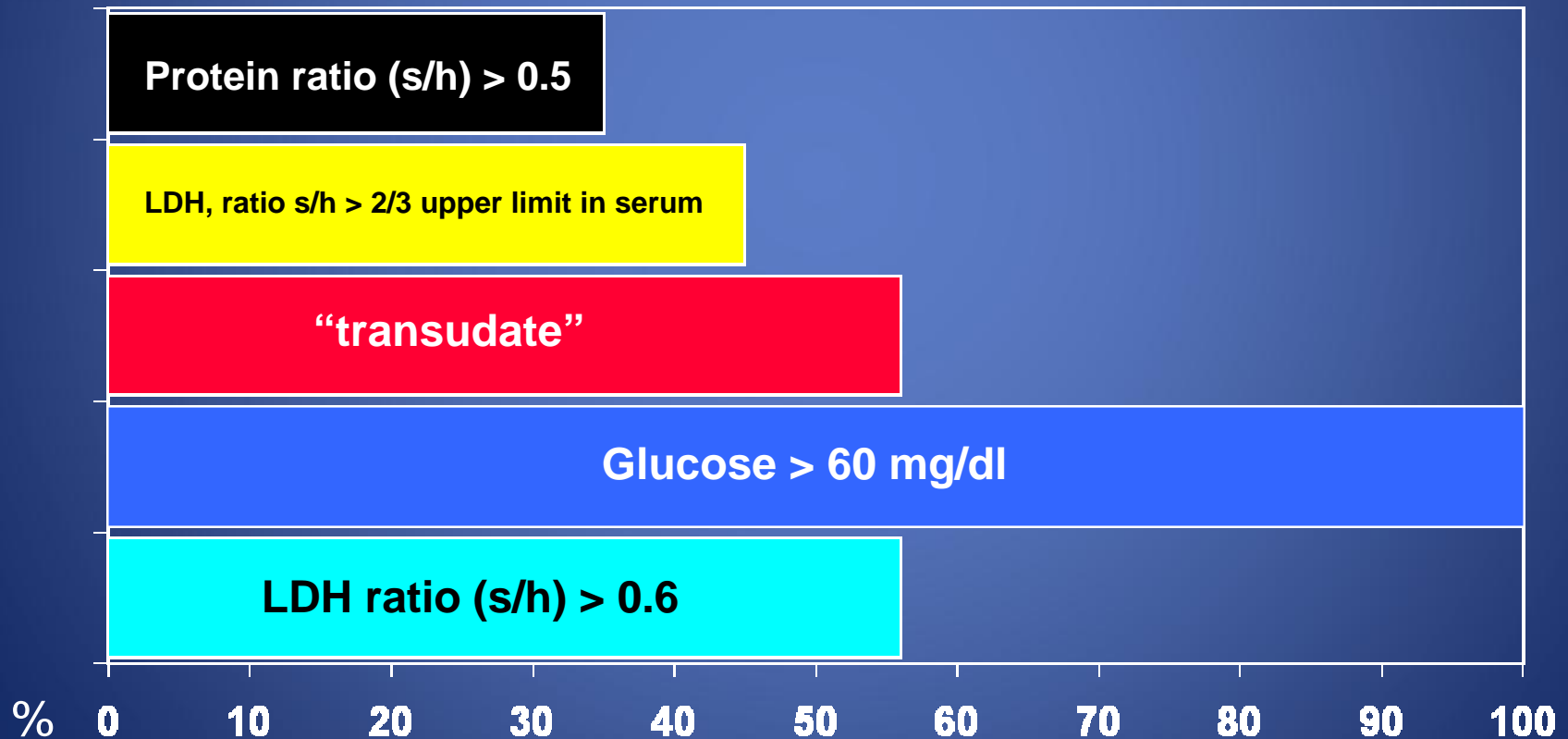
- Hepatic hydrothorax occurs in 10% of patients with ascites;
 - is more frequent in the right side.
- The diagnosis is established by Nuclear Medicine scan, with injection of Tc-99m labeled albumin or Tc-99m pertechnetate into the abdomen, after partial thoracentesis to facilitate migration of the tracer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

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

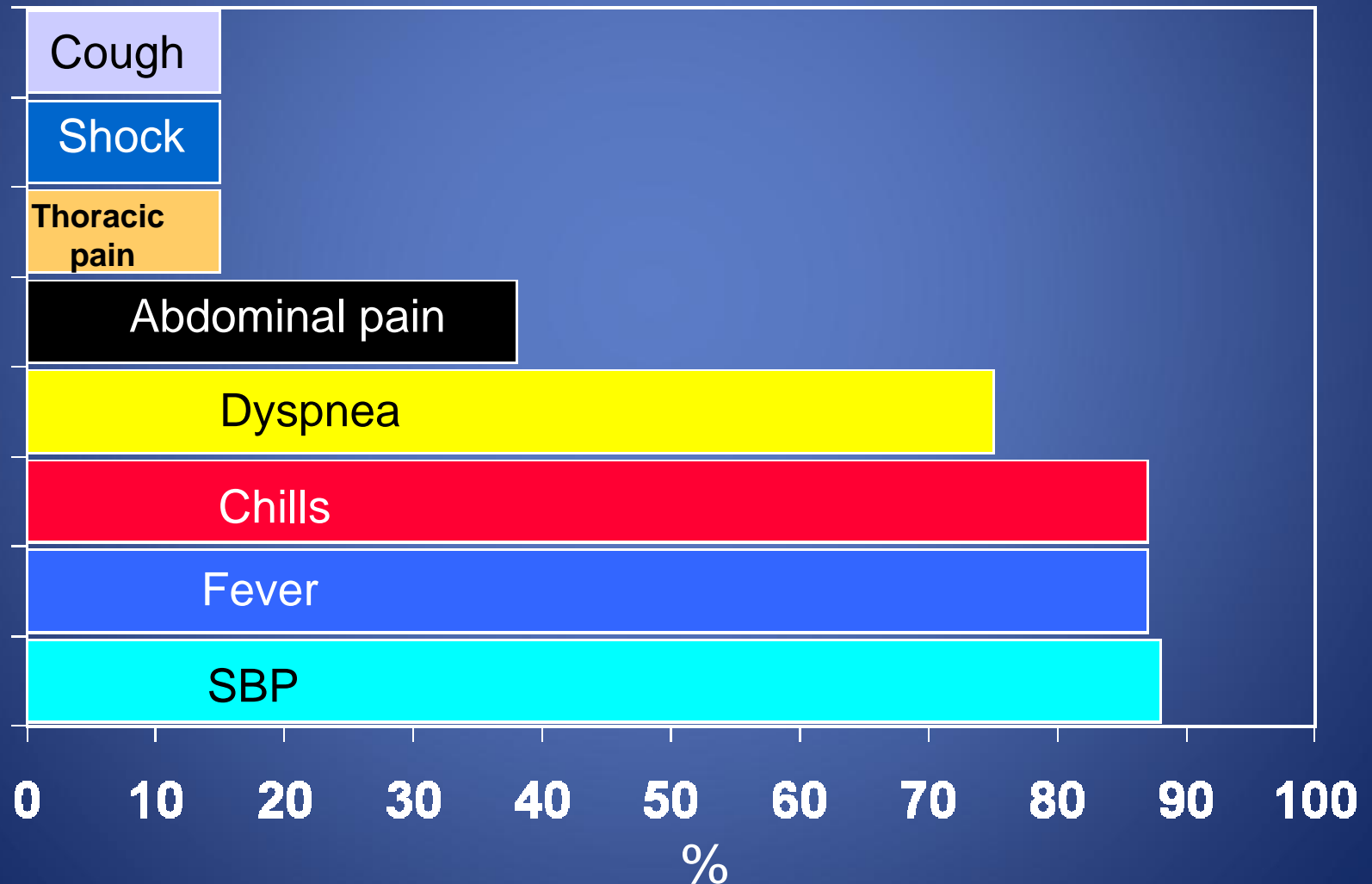


Hepatic Hydrothorax

- T. protein in hydrothorax > ascites by 0.75-1 g/dl
- DX: (+) Tc colloid “Shunt Study” from abdomen to chest (thoracentesis pre-study, to facilitate “flow”).



Signs and Symptoms: Spontaneous Bacterial Empyema



Spontaneous bacterial empyema

- **Diagnosis:** Hepatic Hydrothorax + no lung infection +
 - A) culture (+) (in blood culture bottle) + PMN $> 250/\text{mm}^3$,
or
 - B) PMN $> 500/\text{mm}^3$ in pleural fluid + negative culture
- **Bacteriology:**
 - single bacteria (E.coli, K. pneumonia, C. perfringes)
 - bacteremia in 36%

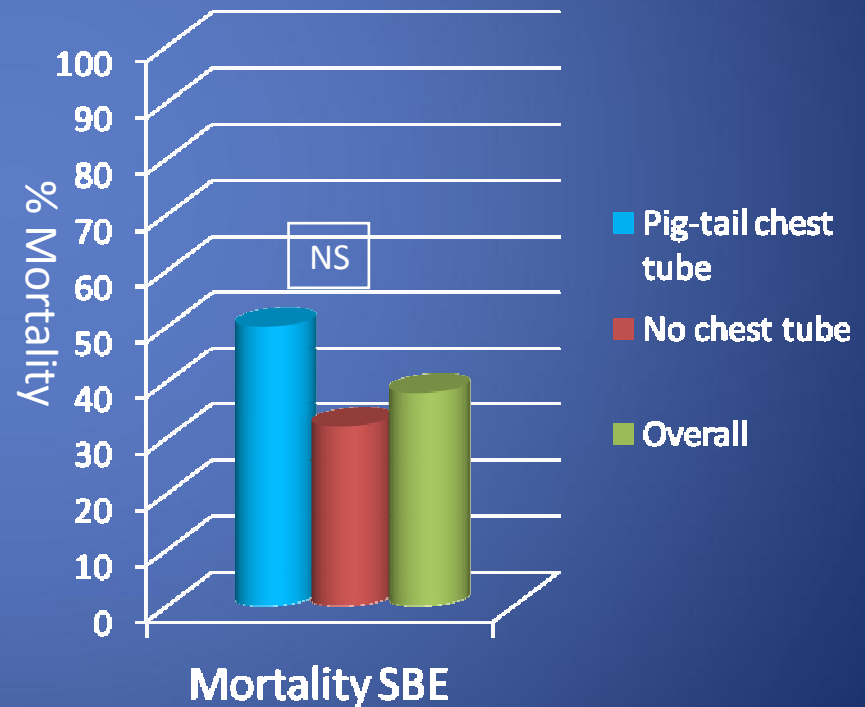
Spontaneous Bacterial Empyema

SBE – What we know

- Spontaneous Bacterial Empyema occurs in 16% of hepatic hydrothorax.
- 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



Spontaneous bacterial empyema

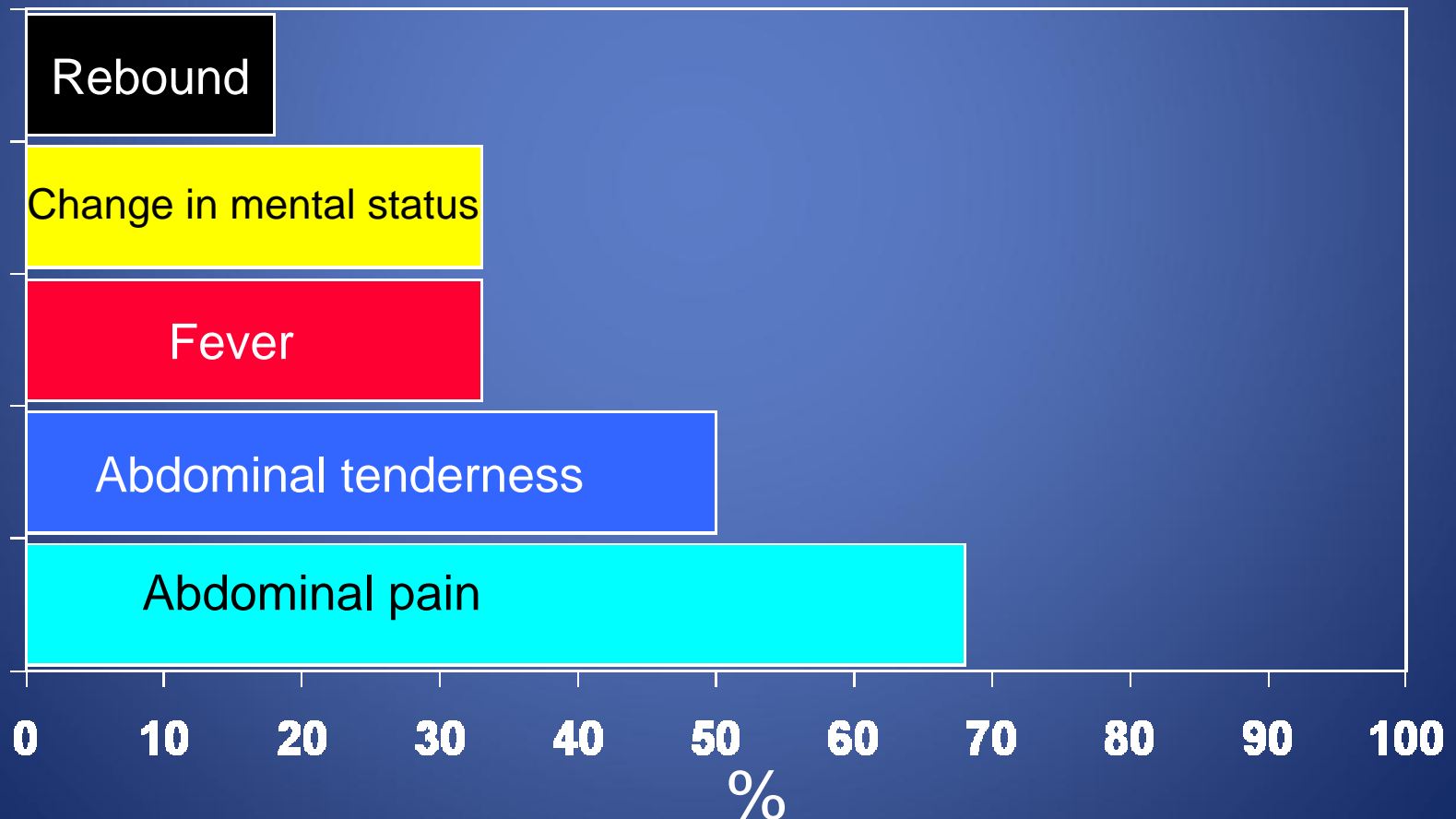
- **Mortality:**
 - in culture (+) = 50%;
 - in general = 27%
- **Relapse rate:**
 - 38% at 1 year;
 - mortality at 1 year = 50%
- **Treatment:**
 - Cefotaxime (or as per antibiotic susceptibility) + albumin expansion.
- **Response to therapy = 72%**

Suspect Secondary Peritonitis in:

- Multiple organisms or fungi in culture
- Ascitic infection in peritoneal carcinomatosis or cardiac ascites
- Increased PMN count after 48 hr therapy of SBP
- Two of the following:
 - Ascites glucose < 50 mg/dl (67%)
 - Ascites protein > 1 g/dl (83%)
 - Ascites LDH $>$ upper normal in serum (100%)

Secondary peritonitis

Pathogenesis: perforation/microperforation on hollow viscus or contamination from intraabdominal abscess



Secondary peritonitis

- **Evaluation:** look for perforation (extravasation of contrast) or loculated pus.
- **Treatment:**
 - Surgery (if perforation or abscess found)
 - Antibiotics (Cefotaxime + metronidazol) + albumin expansion