Managing Complications of Cirrhosis

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Major Complications of Cirrhosis
Advances in Management

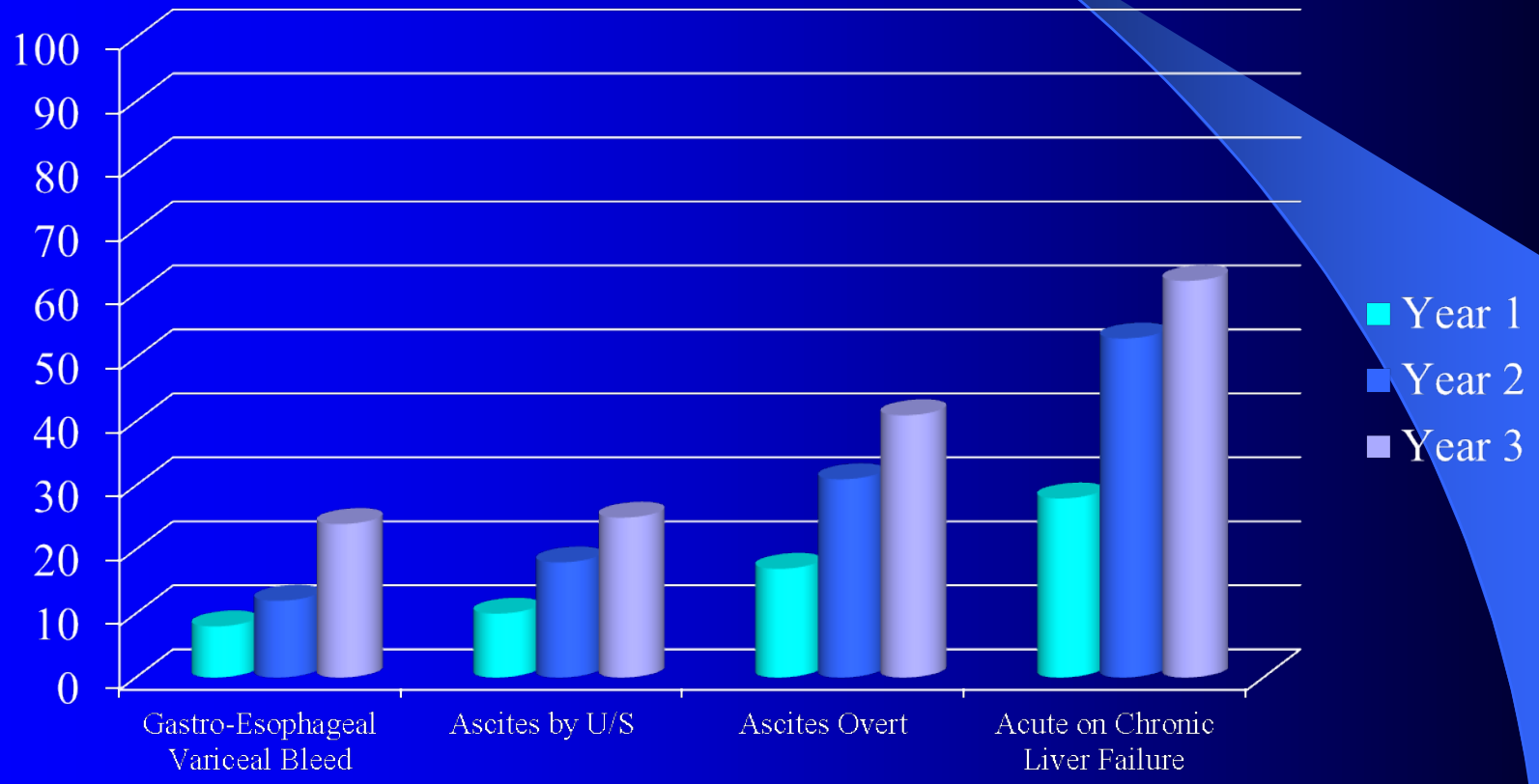
- **Hepatic Encephalopathy, Myelopathy, & AHCD.**
- **Ascites and Spontaneous Bacterial Peritonitis**
- **Hepatorenal Syndrome**
- **Variceal Hemorrhage**
- **Hepatopulmonary Syndrome**
- **Portopulmonary Hypertension**
- **Acute on Chronic Liver Failure**
- **Cirrhotic Cardiomyopathy**

Hu JQ et al. Deaths: final data for 2007. National vital statistics reports; Vol 58; 19. Hyattsville, MD: National Center for Health Statistics; 2010
Asrani S et al. Liver related mortality in the US is underestimated. Hepatology 2010; 52:408; A169.

- CLD and cirrhosis were estimated by the Centers for Disease Control and Prevention (CDC) to be the 12th leading cause of mortality in the USA in 2007 accounting for 29 165 deaths which is 3.4% higher than 2006, resulting in the 2nd largest percentage increase of all-cause mortality.
- Data suggest that liver related mortality is in fact substantially higher than estimated; Asrani reported it to be 121% higher than CDC estimates, making CLD the 8th leading cause of death in the US.

Mortality of Cirrhosis after First Decompensation

Bruno S et al. Am J Gastroenterol 2013; 108: 1112-1122



Hepatic Encephalopathy

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.

Types (by Cause)

- **Type A:** Acute Liver Failure
- **Type B:** Large Spontaneous or Post-traumatic Portal-Systemic By-pass (normal liver)
  - Uretero-Sigmoid anastomosis.
- **Type C:** Cirrhosis; Portal HTN or Shunt

- Hepatic Myelopathy: Symmetrical demyelination of lateral corticospinal tracts

Sub-Categories of Cirrhotic Hepatic Encephalopathy

- **Covert:**
  - Detected only by psycho-metric testing (Minimal HE) or subjective findings (stage 1).
  - Impairs concentration and ability to drive.
- **Overt Episodic:**
  - Clinically apparent (stages 2 to 4)
  - Usually precipitated after a triggering event.
  - May be spontaneous and recurrent
- **Chronic Persistent:**
  - H.E. fluctuating from “mild” to “severe”
  - Usually without apparent trigger;
  - May be treatment dependent.
  - Very rare.

Current Terminology for the Classification of HE

Type	Description	Subcategory	Subdivision
A	Encephalopathy associated with **a**cute liver failure	---	---
B	Encephalopathy with portosystemic **b**ypass and no intrinsic hepatocellular disease	---	---
C	Encephalopathy associated with **c**irrhosis or portal hypertension/portosystemic shunts	• Episodic HE	• Precipitated • Spontaneous • Recurrent
		• Persistent HE	• Mild • Severe • Treatment dependent
		• Minimal	---

Ferenci P et al. *Hepatology* 2002;35:716-721.

Neurologic Manifestations of OHE

Common

- Confusion or coma
- Asterixis
- Loss of fine motor skills
- Hyper-reflexia
- Cognitive deficits detected by special testing
- Slow speech

Less Common

- Babinski sign
- Slow, monotonous speech
- Extrapyramidal-type movement disorders
- Clonus
- Decerebrate posturing
- Decorticate posturing
- Hyperventilation
- Seizures[a]

[a]Seizures seen primarily in type A HE.

Mullen KD. *Semin Liver Dis*. 2007;27(suppl 2):3-9.

West Haven Criteria

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

HE = hepatic encephalopathy.

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

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

Multiple Factors Can Lead to HE Breakthrough

GI hemorrhage
Hypokalemia
Azotemia
Constipation
Excess dietary protein
Infection

Systemic alkalosis

Progressive parenchymal damage
Dehydration
Anemia
Arterial hypotension
Arterial hypoxemia
Hepatoma
Shunts

Benzodiazepines

Psychoactive drugs

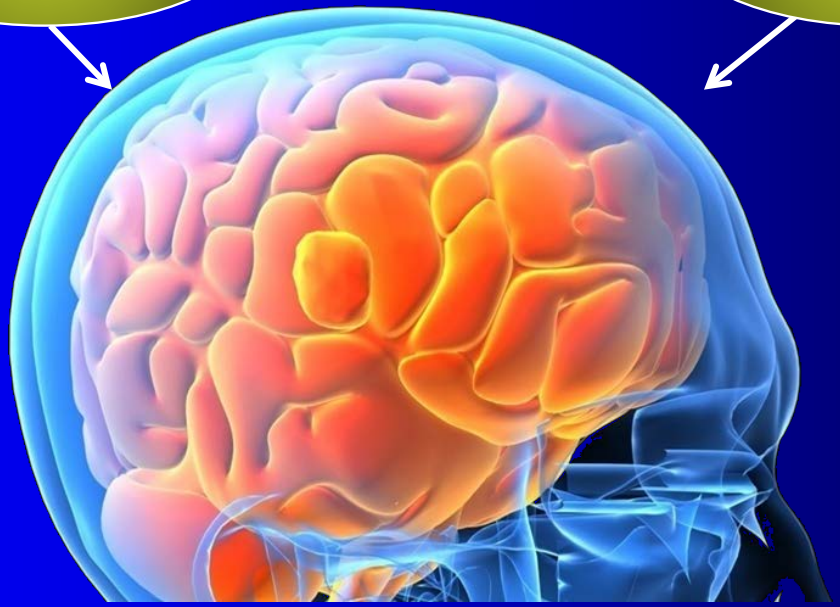
↑ Ammonia production

↑ Diffusion of ammonia across BBB

↓ Toxin metabolism

Activation of central GABA-benzodiazepine receptors

CNS depression



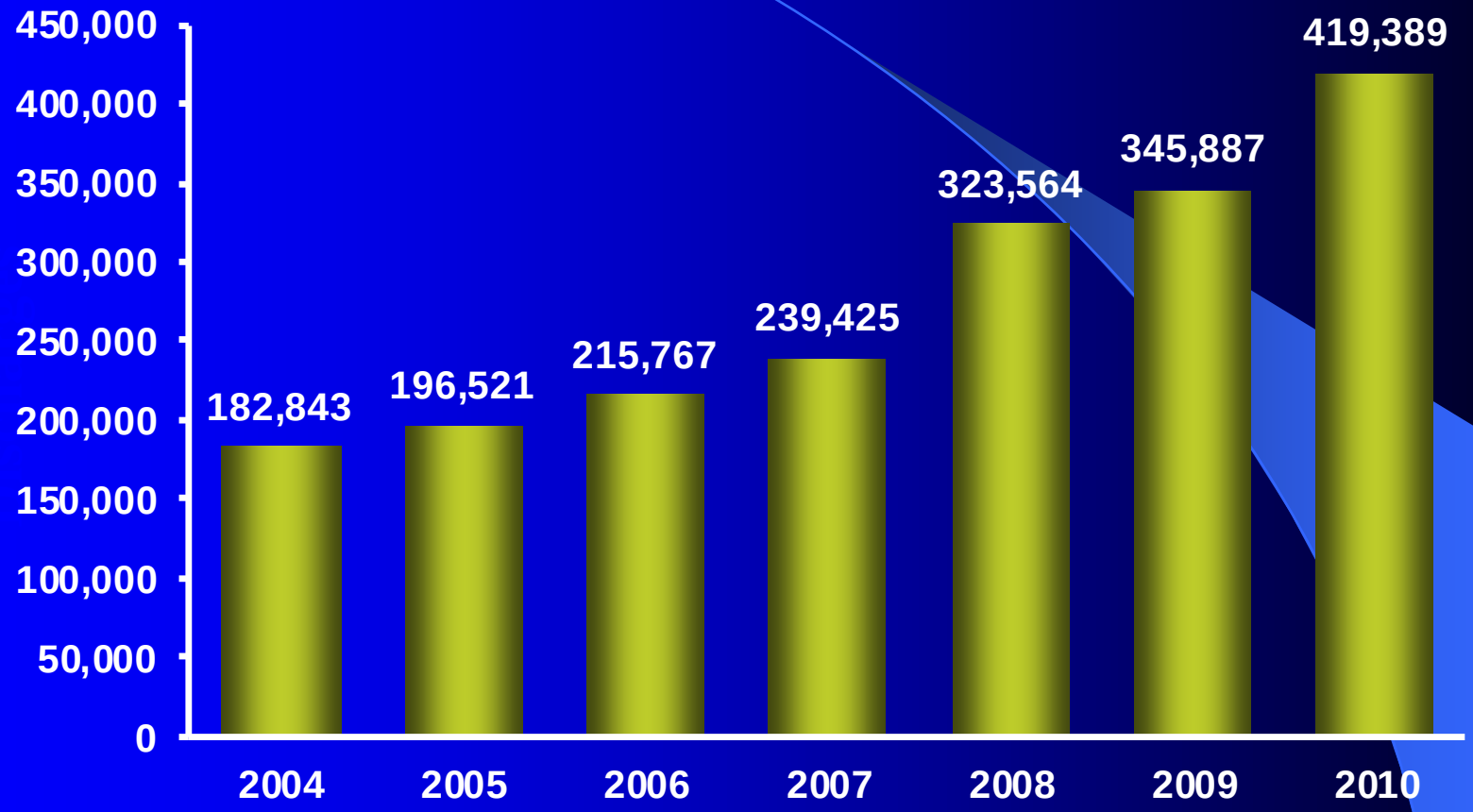
BBB = blood brain barrier;
CNS = central nervous system;
GABA = γ-aminobutyric acid;
GI = gastrointestinal;
HE = hepatic encephalopathy.

Riordan and Williams. *N Engl J Med.* 1997;337:473-479.

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

Hospital Discharges Associated with HE Increased by 21% in 2010

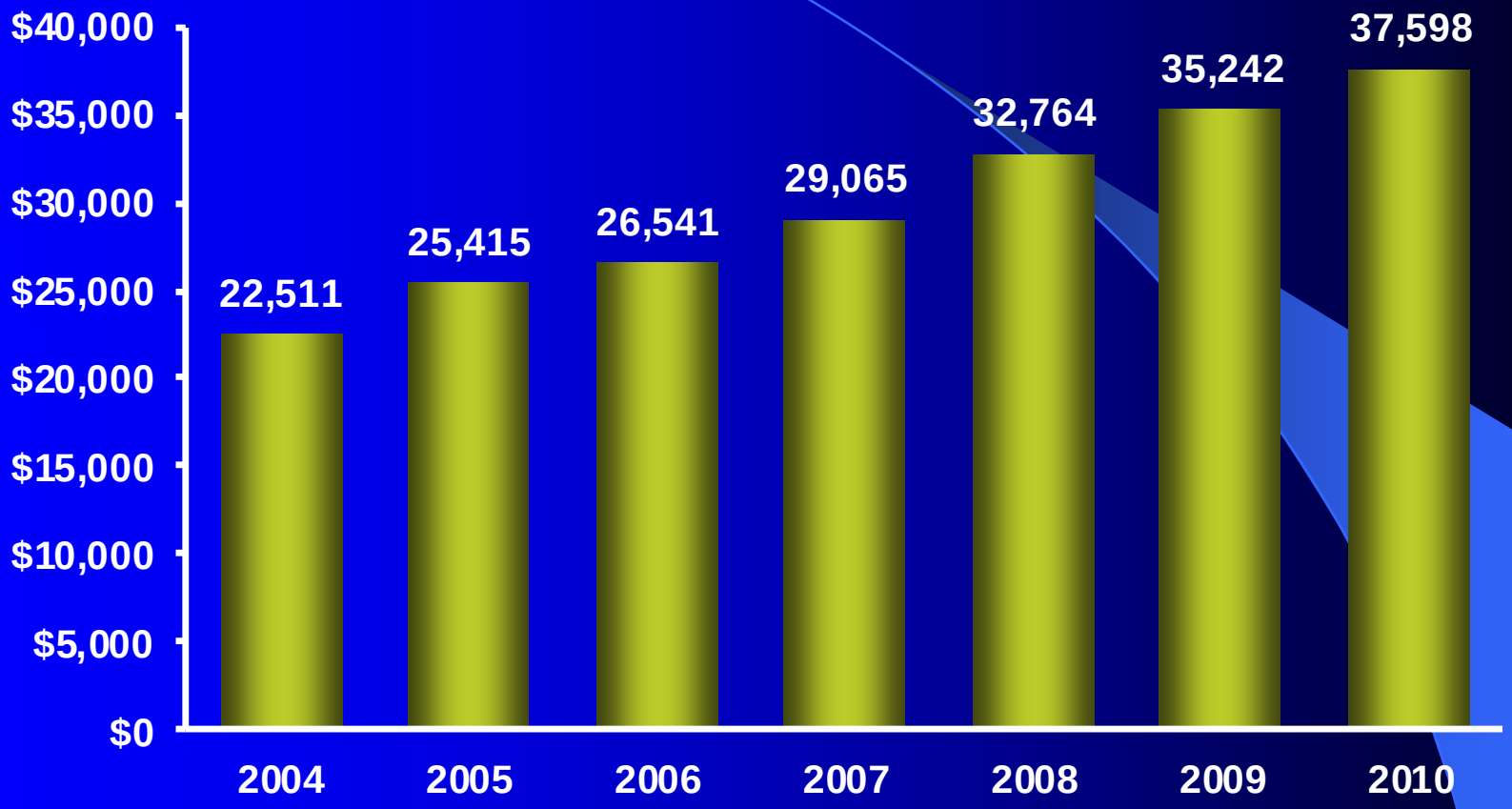


HE = hepatic encephalopathy; ICD = International Classification of Diseases.

*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. http://hcupnet.ahrq.gov. Accessed May 28th, 2012

Greater Than 50% Increase in Cost Per HE Discharge Since 2004



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Poor QoL and Prognosis in Patients With HE

- HE significantly diminishes physical and mental QoL[1]
  - Patient may be disabled from driving, employment, and independent care[2]
- <50% survival at 1 year after diagnosis of HE and <25% survival at 3 years[3]

  - For patients with severe HE who are hospitalized in intensive care, 1-year survival rate is <50%[4]

HE = hepatic encephalopathy; QoL = quality of life.

1. Arguedas et al. *Dig Dis Sci.* 2003;48:1622-1626. **2.** Munoz. *Med Clin N Am.* 2008;92:795-812. **3.** Bustamante et al. *J Hepatol.* 1999;30:890-895. **4.** Fichet et al. *J Crit Care.* 2009;24:364-370. Reprinted from *Journal of Hepatology*, volume 30, Bustamante et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis, Pages 890-895, Copyright 1999, with permission from Elsevier.

Cognitive Deficits in Patients With a History of Overt HE

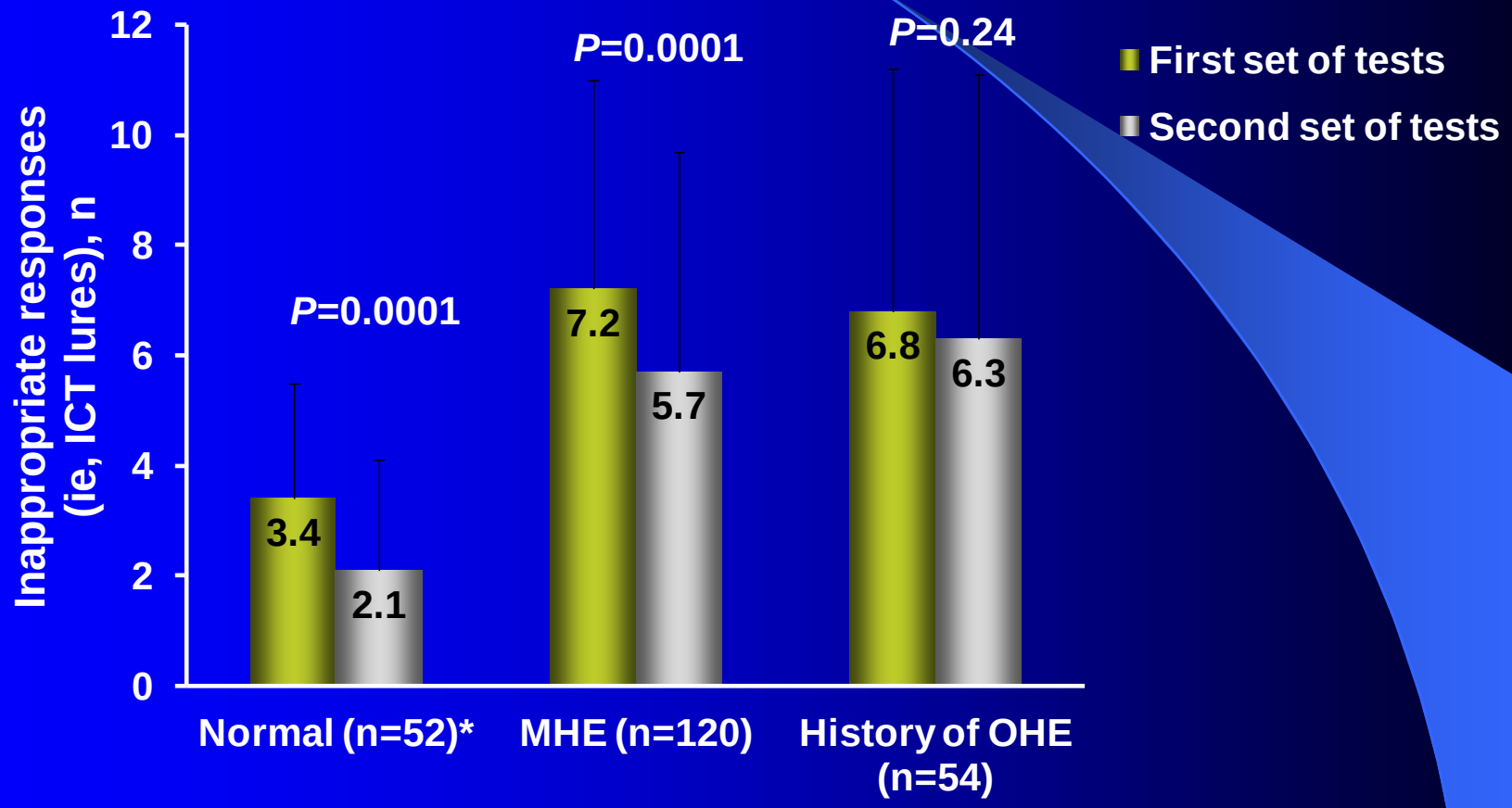
- 226 patients with cirrhosis and a history of overt HE, MHE,* or no HE underwent psychometric evaluation
  - 54 had prior overt HE†
  - 120 had MHE
  - 52 had normal psychometric test results
- Patients with a history of overt HE performed significantly worse than normal patients with cirrhosis ($P \leq 0.001$) and had impaired learning on the ICT

ICT = inhibitory control test; HE = hepatic encephalopathy; MHE = minimal HE.

*Patients had an impairment of 2 standard deviations from normal on 2 of the 4 following: number connection tests A or B, block design test, or digit symbol test. †Patients adherent on lactulose therapy.

Bajaj et al. *Gastroenterology*. 2010;138:2332-2340.

History of Overt HE May Cause Learning Deficit



HE = hepatic encephalopathy; ICT = inhibitory control test; MHE = minimal HE; OHE = overt HE.

*Patients with cirrhosis with normal cognitive function.

Bajaj et al. *Gastroenterology*. 2010;138:2332-2340.

Treatment Goals for Patients with HE

- Investigate precipitating factors that may have led to an HE event[1]
  - Precipitating factors may include GI bleed, sepsis, and dehydration[1]
  - In a large clinical trial, 80% of HE events at baseline were considered spontaneous[2]
- After ruling out precipitating factors, chronic management of HE should be initiated
  - The prevention of further episodes of HE is an important goal in the treatment of patients with liver disease[3]
  - After an episode of OHE, prophylactic therapy with lactulose or rifaximin is recommended for an indefinite period of time or until liver transplantation[4]

1. *The Modern Management of Hepatic Encephalopathy*, http://www.medscape.com/viewarticle/718706_6 Accessed May 15th, 2012. **2.** Data on file **3.** Bass et al. *N Engl J Med*. 2010;362:1071-1081. 4. Khungar, V ., Poordad, F. *Clinics in Liver Disease*. 2012;16 301-320.

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 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.
- **Zn:** improves hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.

Mechanism of Action of Therapies for HE

- **Sodium benzoate**: interacts with glycine to form hippurate. The renal excretion of hippurate results in the loss of ammonia ions.
- **Sodium phenylbutyrate** is converted to phenylacetate. **Phenylacetate**, reacts with glutamine to form phenylacetylglutamine, which is subsequently excreted in the urine, with loss of ammonia ions.
- **L carnitine:** is unclear if improves blood ammonia levels or if works centrally by decreasing brain ammonia uptake.
- **LOLA** is a stable salt of l-ornithine and l-aspartate:
  - L-ornithine stimulates the urea cycle, with resulting loss of ammonia.
  - Both l-ornithine and l-aspartate are substrates for glutamate transaminase. Their administration increases glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase.

Treatment of Hepatic Encephalopathy

- Reduction of Ammonia load:
  - Lactulose p.o. to give 3-4 BM/day or 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: arginine benzoate, sodium benzoate (Ammonul), ornithine aspartate, L-carnitine 990 mg TID, sodium phenylbutyrate (Buphenyl), Acarbose, fiber, sorbitol, LOLA (l-ornithine and l-aspartate)

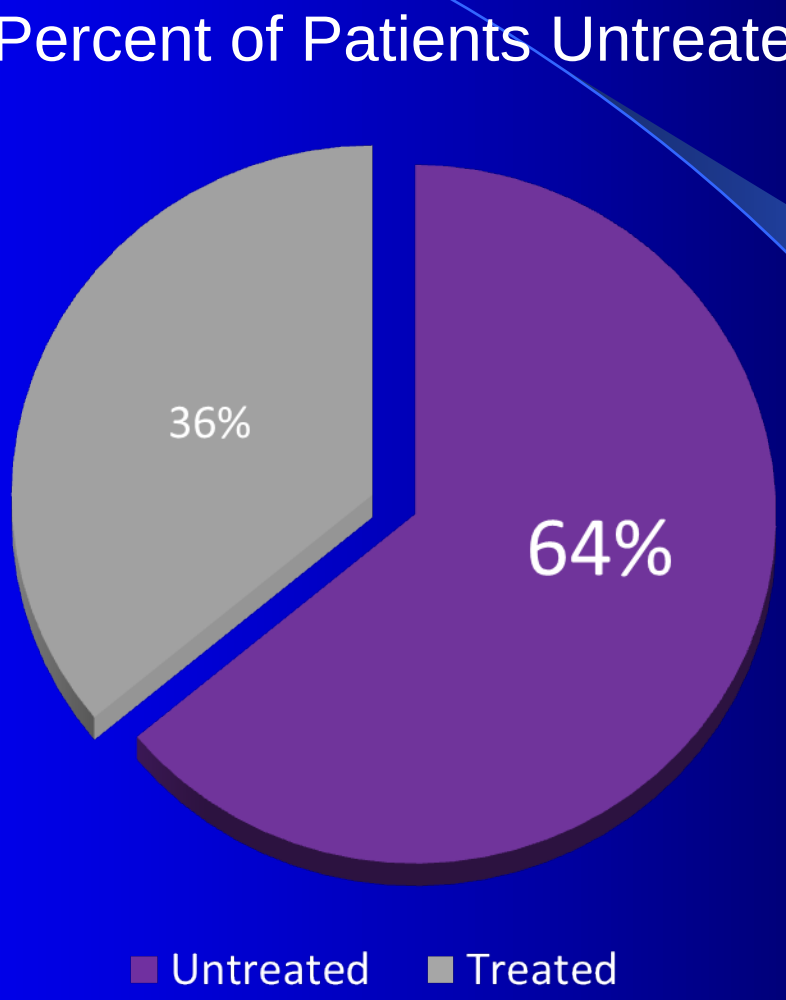
Treatment of Hepatic Encephalopathy

- Nutritional Management:
  - Early nutrition to cover calorie needs and 1-1.5 g protein/kg/day.
  - Frequent meals (3 meals + 3 snacks) + bedtime nutrition supplementation (Am J Clin Nutr 2010;92:137–40; Hepatology. 2008 Aug; 48(2):557-66).
  - In Chronic Persistent PSE: branched-chain aminoacids enriched formula (Nutra-Hep)
  - Zn 50 mg QD or BID.
- Manipulation of Splanchnic Circulation:
  - Radiology-guided occlusion of shunts.
  - Reduction of TIPS with hourglass-shaped expanded polytetrafluoroethylene (ePTFE) stent-graft.

Treatment of Hepatic Encephalopathy

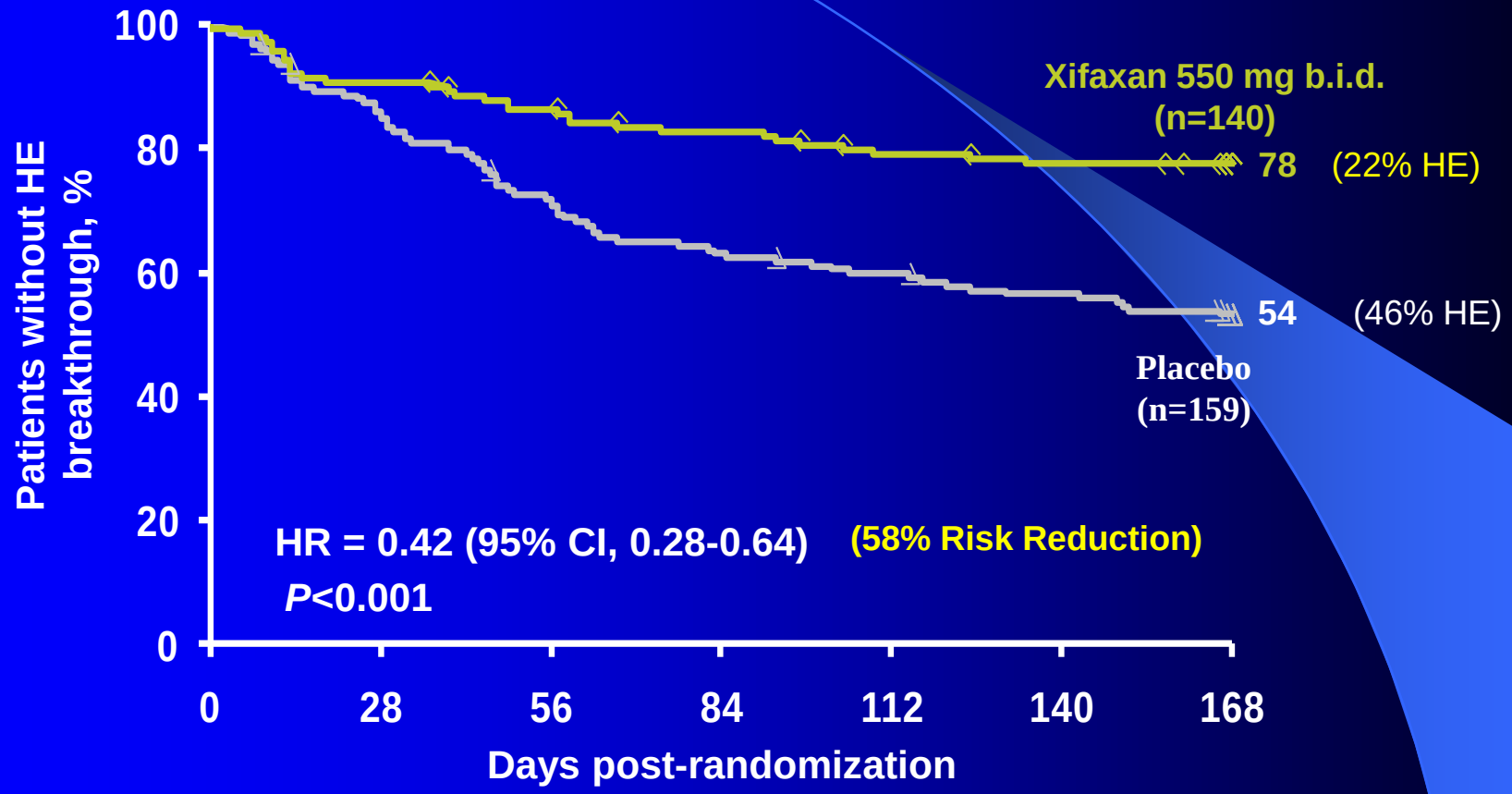
- Drugs affecting Neurotransmission:
  - Flumazenil: used more often in Acute Liver Failure in person without chronic benzodiazepine use.
  - Bromocryptine: may improve extra-pyramidal signs.

64% of Patients Did Not Receive Treatment for their HE Outside the Hospital in 2011



Walters Kluwer 2012
ICD-9 Code: 572.2 Hepatic Encephalopathy

Xifaxan550 Reduced the Risk of Breakthrough HE Episode* by 58% vs Placebo

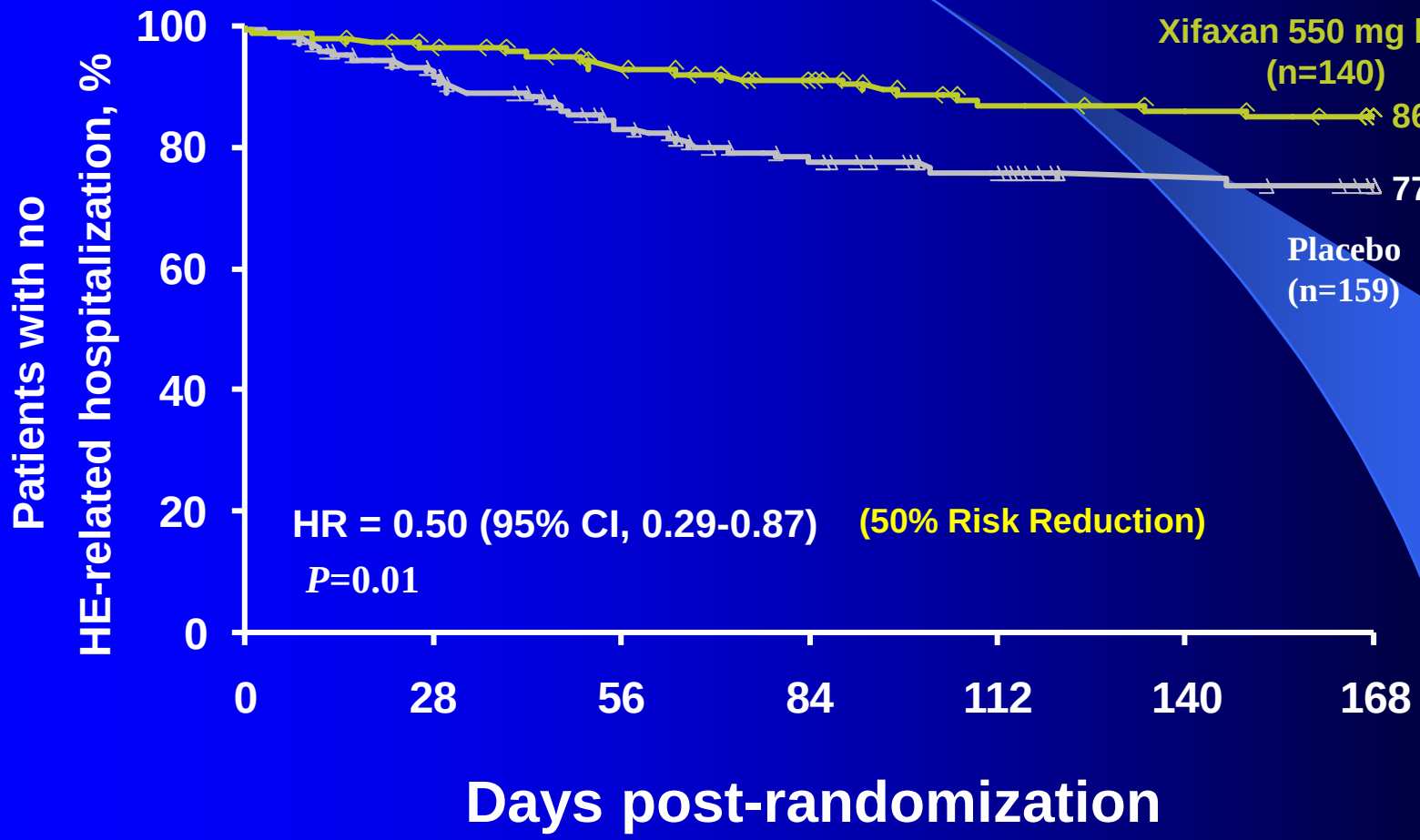


b.i.d. = twice daily; CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.

*HE breakthrough defined as increase in Conn score to ≥2 or, if baseline Conn = 0, an increase of 1 each in Conn score and asterixis grade.

From Bass et al. *N Engl J Med.* 2010;362:1071-1081. With permission. Copyright © 2010 Massachusetts Medical Society. All rights reserved.

Xifaxan550 Reduced the Risk of HE-Related Hospitalization by 50% vs Placebo



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From Bass et al. *N Engl J Med.* 2010;362:1071-1081. With permission. Copyright © 2010 Massachusetts Medical Society. All rights reserved.

Minimal Covert Hepatic Encephalopathy

Minimal Hepatic Encephalopathy

- **Cirrhotic patients**
  - Without clinical signs of encephalopathy
  - Perform worse in psychometric tests when compared with healthy controls
- **Affects an estimated 60% (50% to 80%)* of patients with cirrhosis**
- **Cerebral dysfunction has a major impact on patients' daily living**
- **No consensus on diagnostic criteria or diagnostic tests has been established**

*depends on mode of diagnosis

Mullen KD. *Aliment Pharmacol Ther.* 2006;25(suppl 1):11-16.

Diagnostic Methods for Detecting Minimal HE

Methods	Advantages	Limitations
Formal neuropsychologic assessment	Established and well-recognized clinical significance	• Expensive • Time consuming
Short neuropsychologic batteries	• Easy to administer in office setting • Inexpensive • Rapid results • High sensitivity for discerning minimal HE from other encephalopathies	• Test often copyrighted • Limited access
Computerized tests (CFF, ICT, reaction times, etc)	• Easy to apply	• Limited data on diagnostic significance • Require standardization
Neurophysiologic tests (EEG, spectral EEG, P300)	• Allows for objective repeat testing	• Equipment • Limited data on diagnostic significance

CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electroencephalography; P300, auditory event-related evoked potential.

Adapted from Mullen KD et al. *Semin Liver Dis*. 2007;27(suppl 2):32-47.

Standard "Pencil-and-Paper" Psychometric Tests for the Detection of HE

- Number connection test A (NCT-A)
- Number connection test B (NCT-B)
- Digit symbol test (DST)
- Serial-dotting test (SDOT)
- Line-tracing test (LTT)
- Figure connection test
- Block design test

} The Porto-systemic Encephalopathy (PSE) Syndrome Test [a]

[a]PSE psychometric test is not currently available in the United States.

Ferenci P et al. *Hepatology* 2002;35:716-721.

Recommendations for MHE Testing

- **Alternatives to psychometric hepatic encephalopathy score (PHES) in the United States**
  - Impairment in 2 of 4 tests below
    - Number connection test-A
    - Number connection test-B
    - Digit Symbol
    - Block Design tests of the Wechsler's Adult Intelligence Scale-III (Psychological Corp, San Antonio, TX)
  - Above tests need psychological expertise to order, administer, and interpret

Ferenci P et al. *Hepatology*. 2002;35(3):716-721.
Bajaj JS et al Gastroenterol 2008 135(5):1591-1600
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.
Romero-Gomez M et al. *Hepatology*. 2007;45(4):879-885.

Test Studied in the U.S. for MHE

Inhibitory Control Test

- A computerized test of attention and response inhibition which consists of lures and targets.
- Does not need a psychologist for administering or interpretation
- Can be administered by a medical assistant within 15 minutes.
- ICT has a high sensitivity and specificity for MHE diagnosis and predicting overt HE.

Bajaj JS et al *Gastroenterol* 2008;135(5):1591-1600
Garavan et al *Proc Natl Sci Usa* 1999; 96(14):8301-6.
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.

Inhibitory Control Test

- ICT has good reliability between 2 administrations
- ICT also has external validity, i.e. gets worse after TIPS and gets better after therapy
- ICT performance has been correlated with driving simulator performance.
- Available on the Chronic Liver Disease Foundation website (www.hecme.tv) for download with detailed instructions.

Bajaj JS et al *Gastroenterol* 2008;135(5):1591-1600
Garavan et al *Proc Natl Sci Usa* 1999; 96(14):8301-6.
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.
Bajaj JS et al *Hepatol* 2008;47(2):596-604.

Probiotic Yogurt in the treatment of MHE

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

- Subjects: 25 nonalcoholic MHE cirrhotics (defined by a standard psychometric battery); 84% were Child A
- **Groups:** randomized with unblinded allocation to receive for 60 days in 2:1 ratio
  - **A:** probiotic yogurt (N: 18) (CC's Jersey Crème Yogurt 6 oz BID; with proven culture stability)
  - **B:** no treatment (no Rx) (N: 7).
- **Measurements:** Quality of life (short form [SF]-36), adherence, venous ammonia, model of end-stage liver disease (MELD) scores, and inflammatory markers (tumor necrosis factor [TNF]-α, interleukin [IL]-6).
- **Outcomes**:
  - MHE reversal using blinded scoring,
  - OHE development, and
  - Adherence.

Probiotic Yogurt in the treatment of MHE

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

- RESULTS:
  - A significantly higher percentage of yogurt patients reversed MHE compared to no Rx patients (71% *vs* 0%, *P* = 0.003, intention-to-treat).
  - Yogurt patients demonstrated a significant improvement in number connection test-A (NCT-A), block design test (BDT), and digit symbol test (DST) compared to baseline/no Rx group.
  - Overt HE: developed in 25% of no Rx *versus* 0% of yogurt patients.
  - Adherence: Eighty-eight percent of yogurt patients.
  - No adverse effects or change in covariates were observed.
  - All patients who completed the yogurt arm were agreeable to continue yogurt for 6 months if needed.

CC's Jersey Crème Yogurt
6 oz BID

Treatment of MHE

(Mittal VV et al. Eur J Gastroenterol Hepatol 2011; 23:725–732).

- 160 cirrhotics with MHE were randomized in 4 groups of 40 patients to receive for 3 months:
  - Group A: no therapy,
  - Group B: lactulose 30–60 ml b.i.d.,
  - Group C: probiotics of 110 billion colony-forming units b.i.d. or
  - Group D: L-ornithine-L-aspartate 6 g t.i.d. (LOLA).
- Parameters:
  - health-related quality of life (HRQoL) improvement, and
  - progression to overt hepatic encephalopathy.
- **RESULTS:**
  - A) Using neuropsychological assessment, recovery of MHE was seen in groups: A = 10%, B = 48%, C =35% and D = 35% (P = 0.006).
  - There was no significant difference in recovery from MHE or changes in ammonia levels when comparing lactulose to either probiotics or LOLA.
  - B) Nine (6%) developed overt PSE.

Culturelle has only 10 billion cells/capsule

Treatment of MHE

(Bajaj JS et al. Gastroenterology 2011; 140:478–487; e1).

- 42 cirrhotics with MHE at baseline were randomized to 8 weeks of rifaximin (n = 21) or placebo (n = 21) and tested in a driving simulator.
- RESULTS:
  - A) Rifaximin group showed improvement in avoiding total driving errors (76 vs. 31%; P = 0.013), speeding (81 vs. 33%; P = 0.005), and illegal turns (62 vs. 19%; P = 0.01) compared to those given placebo; however,
  - B) The number of collisions were not significantly different between groups.
  - C) In rifaximin group, the cognitive performance improved (91 vs. 61%; P = 0.01) compared to placebo group.

Hepatic Myelopathy

- **Symptoms:**
  - Subacute bilateral lower extremity weakness,
  - Puppet-like walk or inability to walk in setting of cirrhosis or porto-caval shunt.
  - Upper extremity involvement is very rare.
  - Disorder is progressive and irreversible.
- **Signs:** Spastic paraparesis, hyperreflexia, extensor plantar response, and no sensory level (Zieve 1960).
- **Pathogenesis:** Symmetrical demyelination of lateral corticospinal tracts, occasionally with axonal loss.

Hepatic Myelopathy

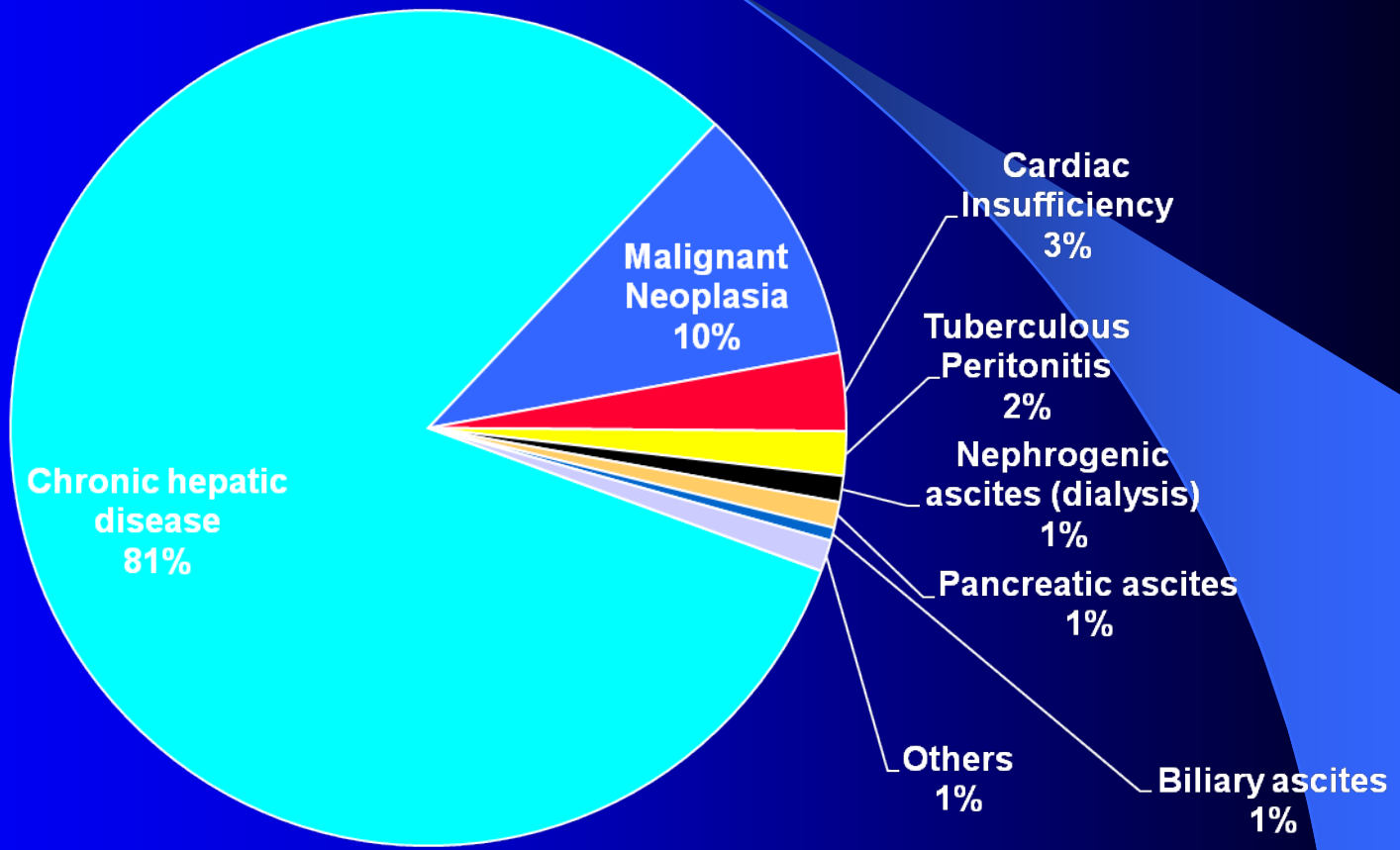
- Imagen:
  - a) Brain MRI: may show FLAIR in subcortical white matter,
  - b) MRI of spine with contrast, or CT myelogram: No evidence of compression. MRI may show FLAIR in subcortical spinal tracts.
- Central motor conduction time (CMCT): abnormal in lower lumbar spine, and normal in upper cervical spine.
- Treatment: Closure of shunt or liver transplantation.

Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD)

- Clinico-pathological syndrome of brain dysfunction associated with a variety of liver diseases. (Victor *et al.* in 1965).
- Clinical features: dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis.
- Evolution: chronic and largely irreversible syndrome.
- Pathogenesis: poorly understood; may be damage accumulated from multiple episodes of hepatic encephalopathy
- Neuropathological findings: diffuse but patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and uneven neuronal loss in the cerebral cortex, basal ganglia and cerebellum.
- MRI: T1-weighted images hyperintensities in the globus pallidus, and 75% have extrapallidal involvement.

Ascites and SBP

Causes of Ascites



Pathophysiology of Cirrhotic Ascites

↑ Hepatic sinusoidal pressure

↓

Activation of hepatic baroreceptors

↓

Compensated

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

↓

↑ Peripheral arterial vasodilation (“underfilling”)

↓

Decompensated

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

Classification of Ascites

- Serum-ascites albumin gradient (SAAG)
- SAAG (g/dl) = $albumin_s$ – $albumin_a$
- Gradient $\geq$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

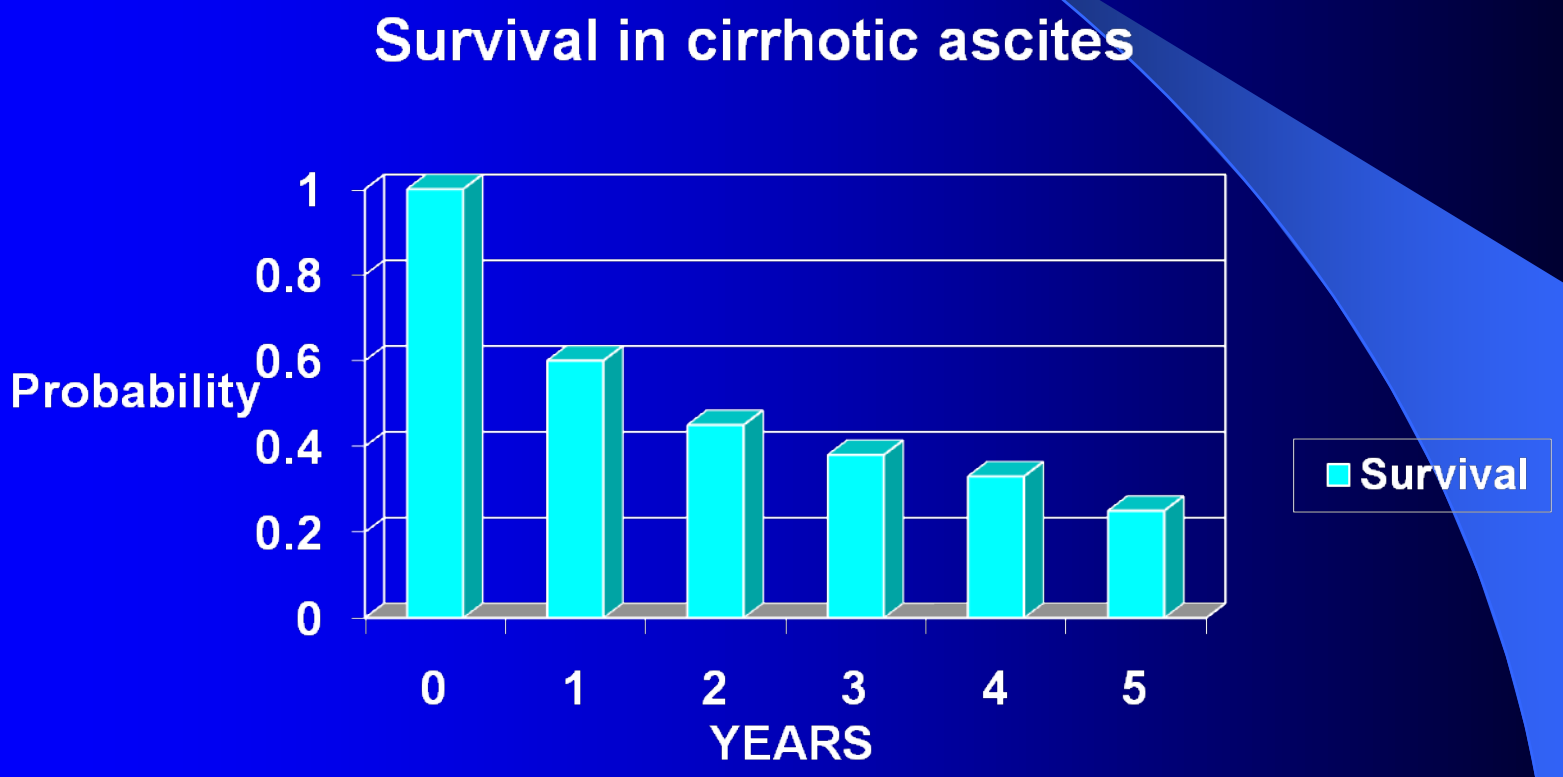
≥1.1 g/dl = portal hypertension

- 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

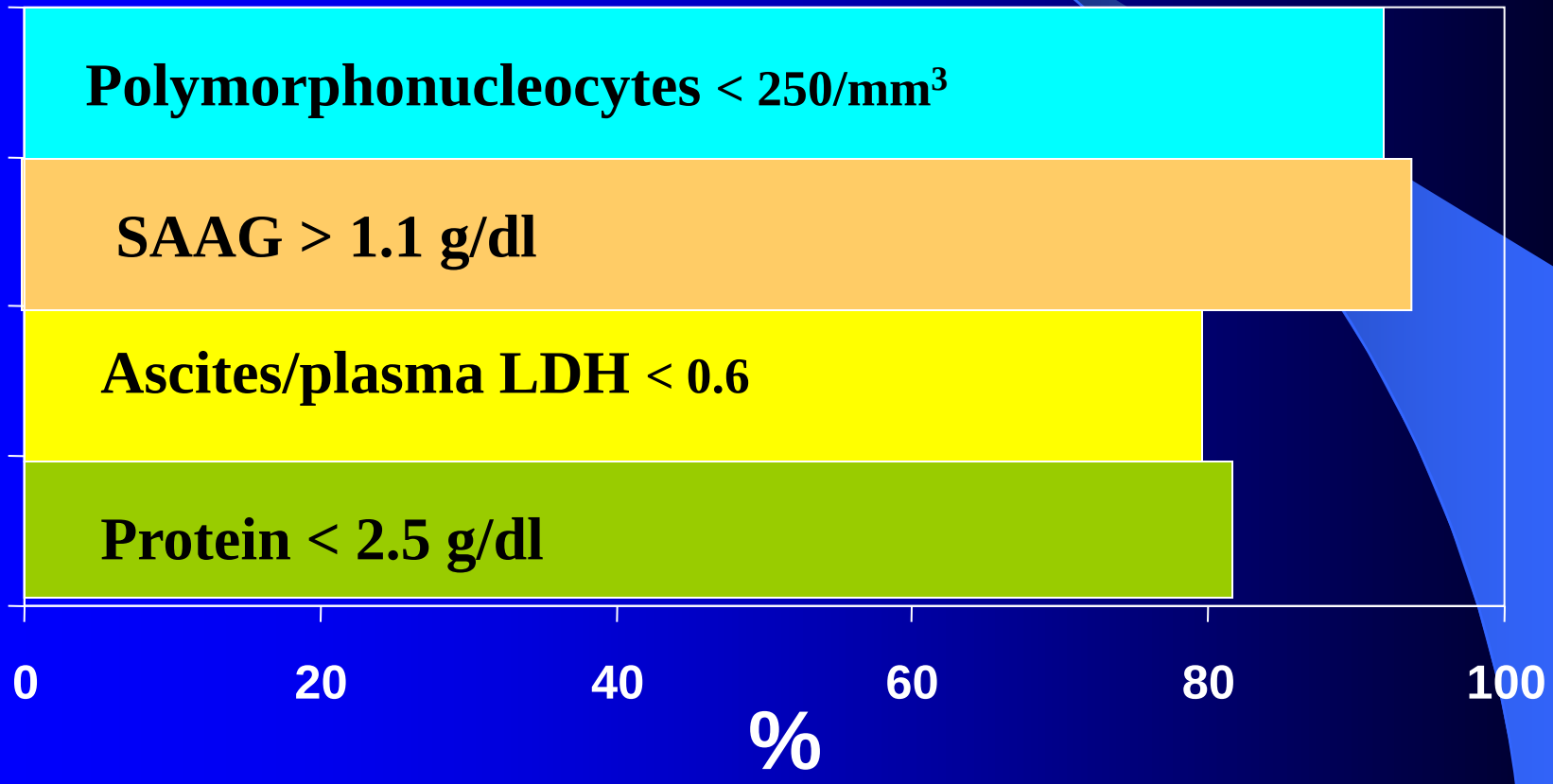
Low SAAG
<1.1 g/dl

- Peritoneal carcinomatosis
- Tuberculous peritonitis (without cirrhosis)
- Biliary ascites (without cirrhosis)
- Pancreatic ascites (without cirrhosis)
- Nephrotic ascites
- Connective tissue disease
- Intestinal obstruction/infarction

Survival of Cirrhotics with Ascites



Characteristics of Uncomplicated Cirrhotic Ascites



Ascites/plasma amylase ~0.5

Leucocytes < 300/mm^3; intense diuresis 1100/mm^3

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 90% of patients will loose at least 88 mEq Na/day.
  - **Spironolactone**: more effective than loop diuretics. Can produce hyperK and acidosis
    - Dose: 100, 200, or 400 mg QD

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 but MAP > 83 mm Hg. Causes severe hypoK
  - Dose 2.5-10 mg QD

Diuretic Adjustment Protocol

- Place patient in 2 gm Na diet (3 meals + 3 snacks + 20 g protein/500 kcal @ hs).
- Start with: Spironolactone 100 mg + Furosemide 40 mg q am.
- Check Na/K ratio in spot urine just before next morning diuretics.
- If spot urine Na/K > 1 keep dose and adjust to loose 1 lb/d if without edema, or 2 lb/d if with edema
- If Na/K < 1, double diuretics and repeat next a.m. spot Na/K. Keep doubling dose until:
  - Na/K > 1 with spironolactone </= 400 & furosemide </= 100, or
  - Spironolactone 400 & Furosemide 160 with urine Na/K < 1, or
  - Creatinine raises >/= 0.3 mg/dL

Refractory Ascites

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)

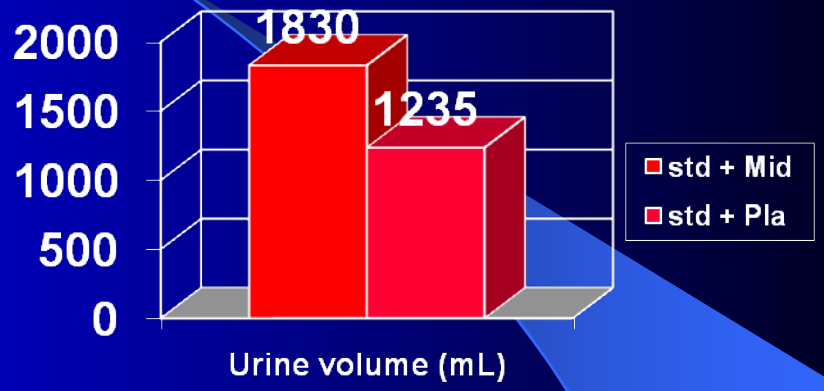
Treatment of Ascites

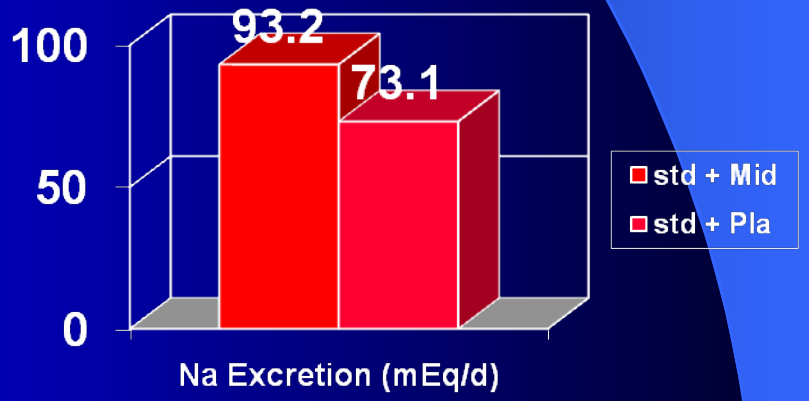
- ***Therapeutic paracentesis:*** done in patients with stable cirrhosis with or without edema
  - Single large volume paracentesis (4-6 L): with or without colloid infusion
  - Serial LVP (4-6 L/Day): Colloid infusion (40 g albumin) need is controversial
  - Total paracentesis (6-22 L over 1 hr) with
    - 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.





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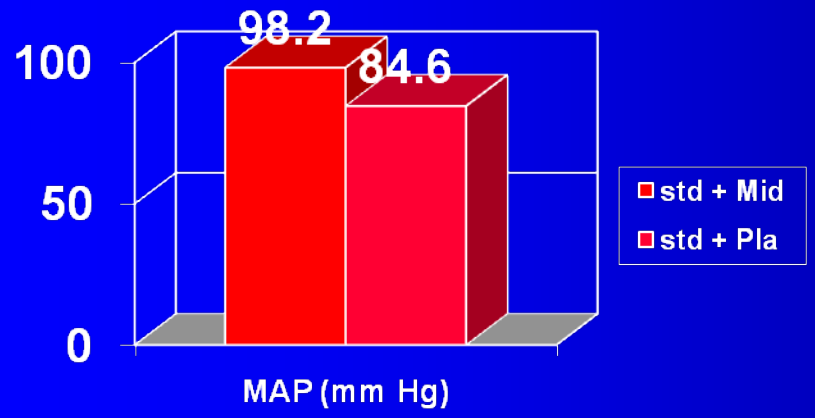
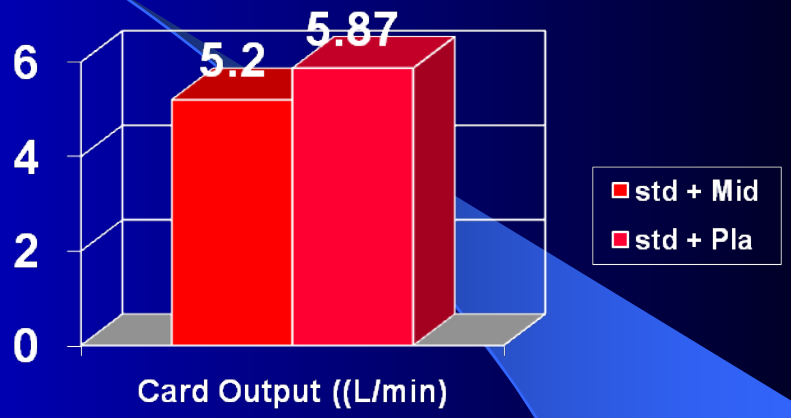
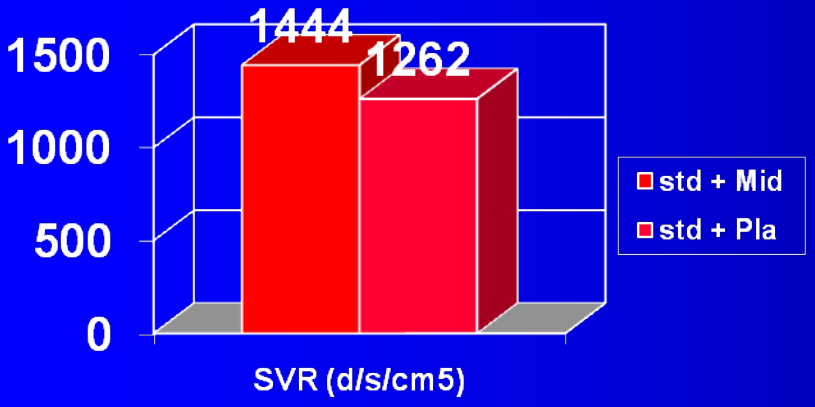






- Midodrine was superior for ascites control at 3 mo.
- Midodrine improved survival after more than 3 months but not at 3 months.

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 =/< 83; D/C betablockers and band varices if needed (**Hepatology 2010 Sep;52(3):1017-22**).**

Multicenter RCT on TIPS vs LVP in Refractory and Recidivant Ascites

	Ascites Refrac/ Residiv	# TIPS	# LVP	% Ascites inprove TIPS	% Ascites inprove 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).

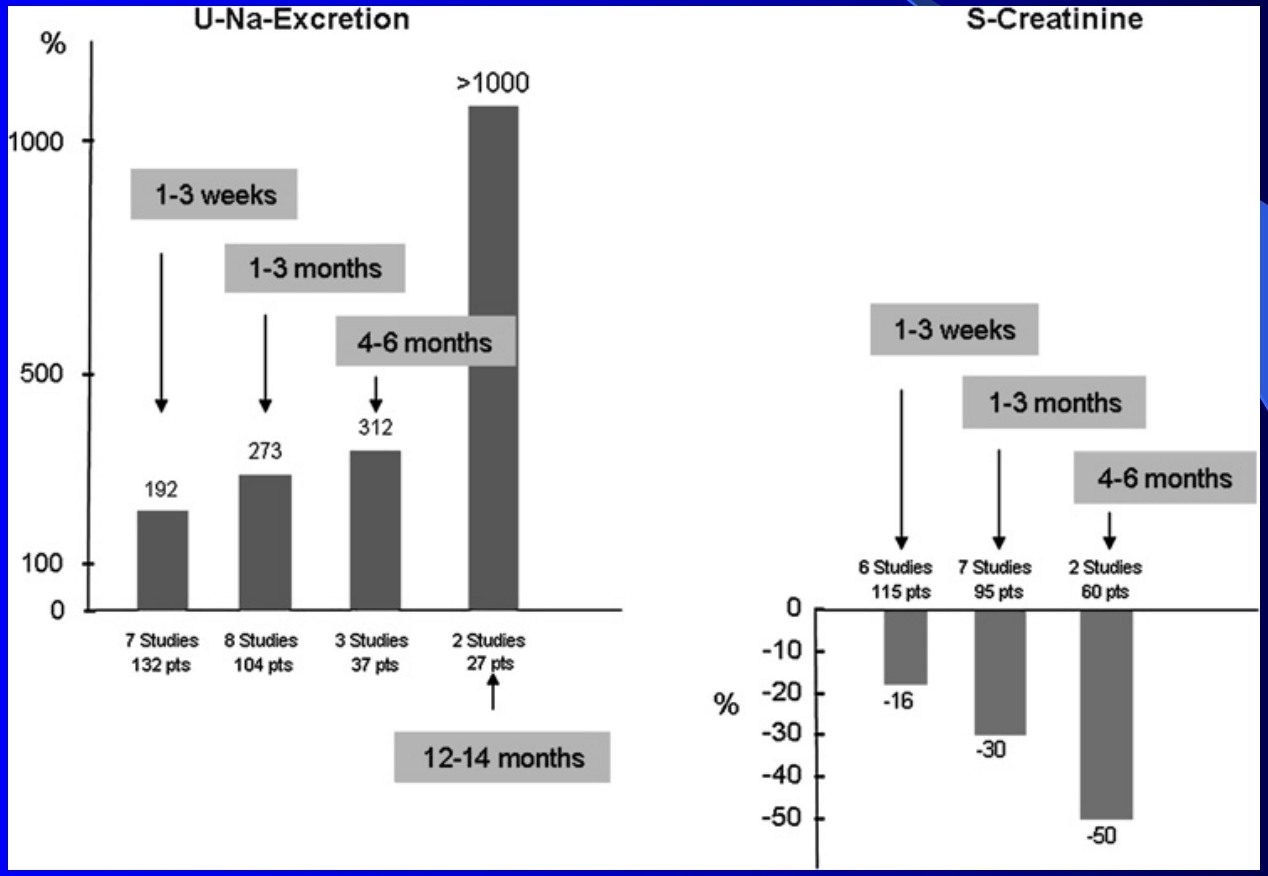
EASL Guidelines for Refractory Ascites

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).

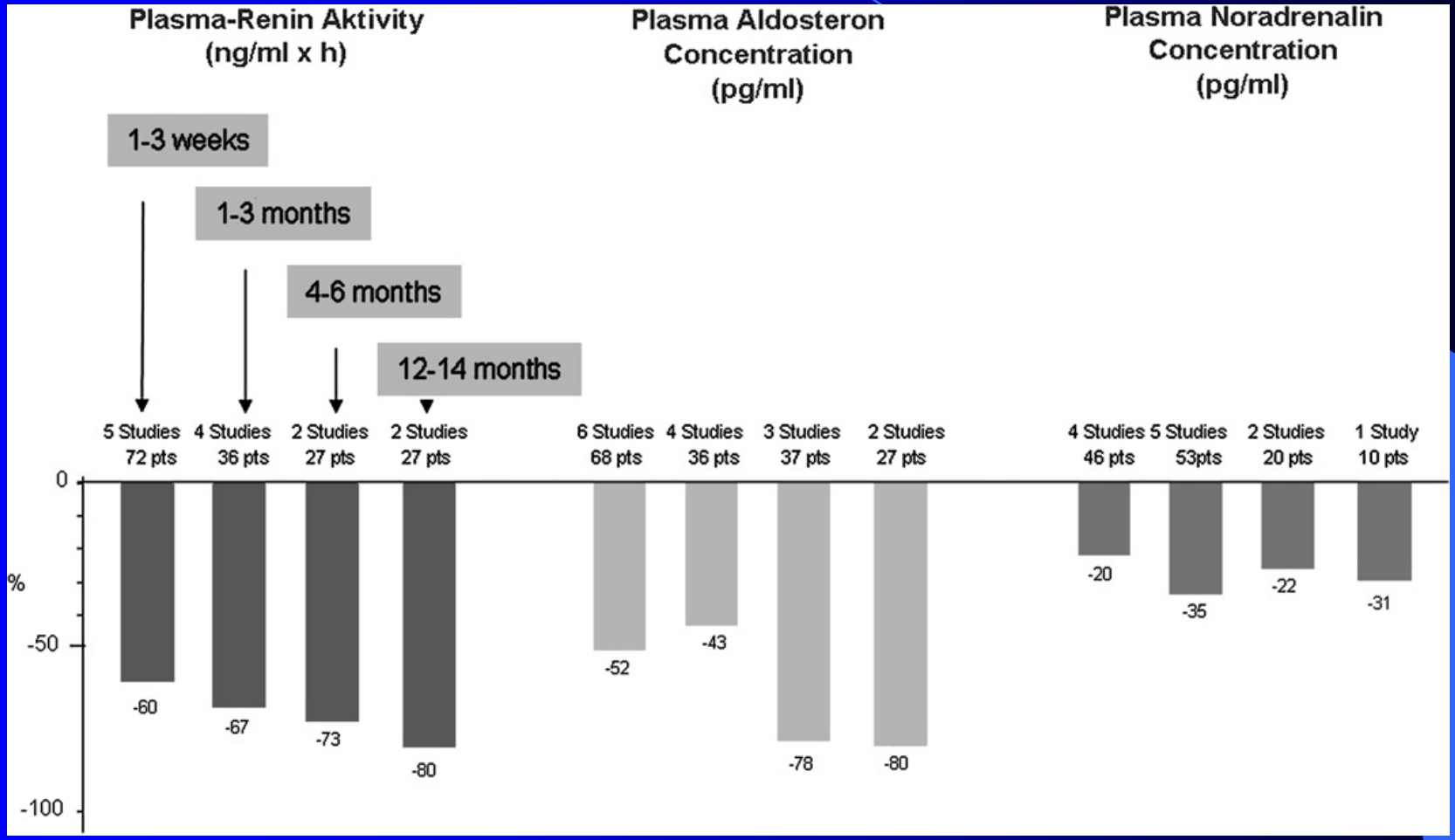
Effects of TIPS on Natriuresis and Azotemia

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



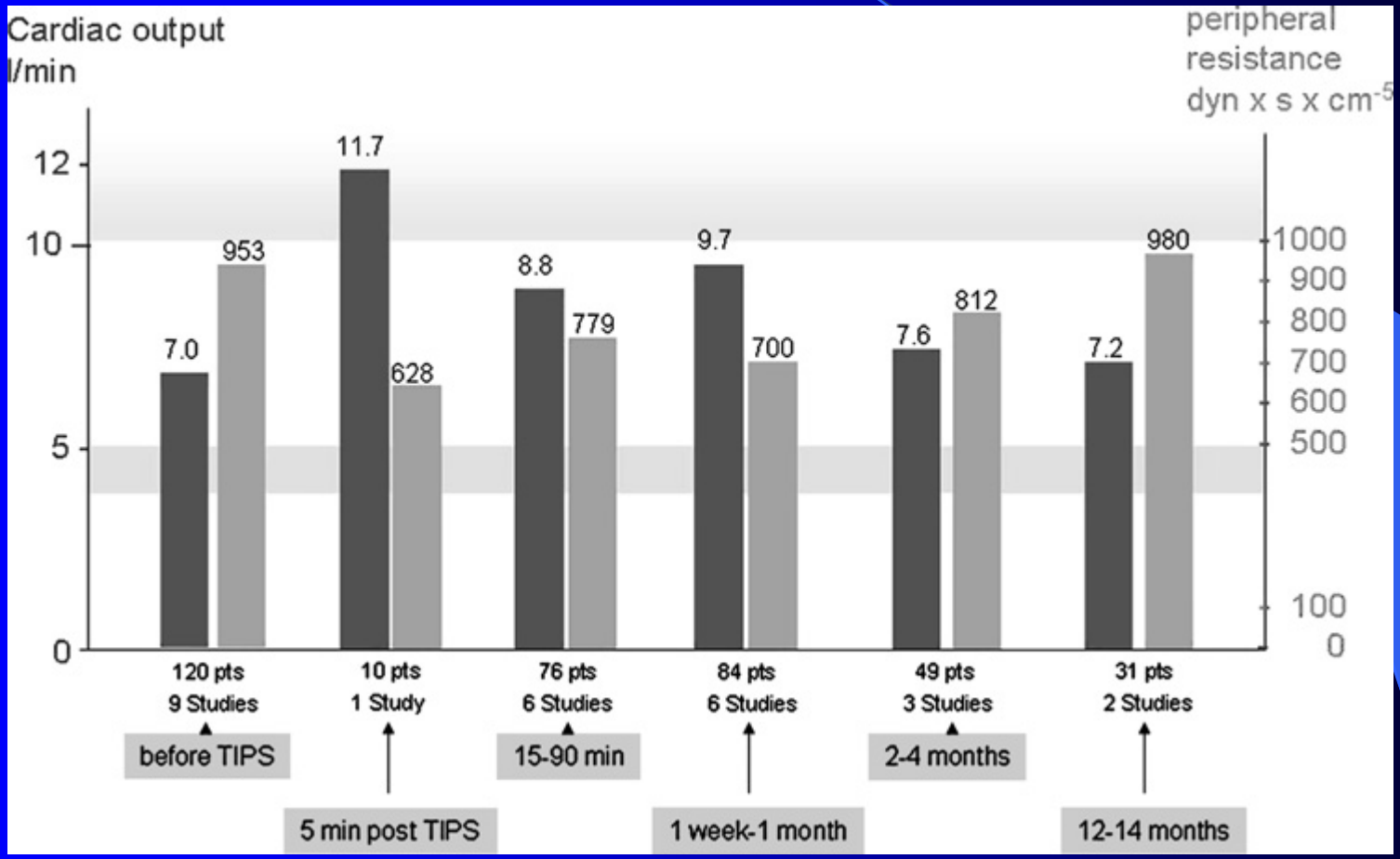
Effect of TIPS on Plasma Renin, Aldosterone & Noradrenaline levels

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



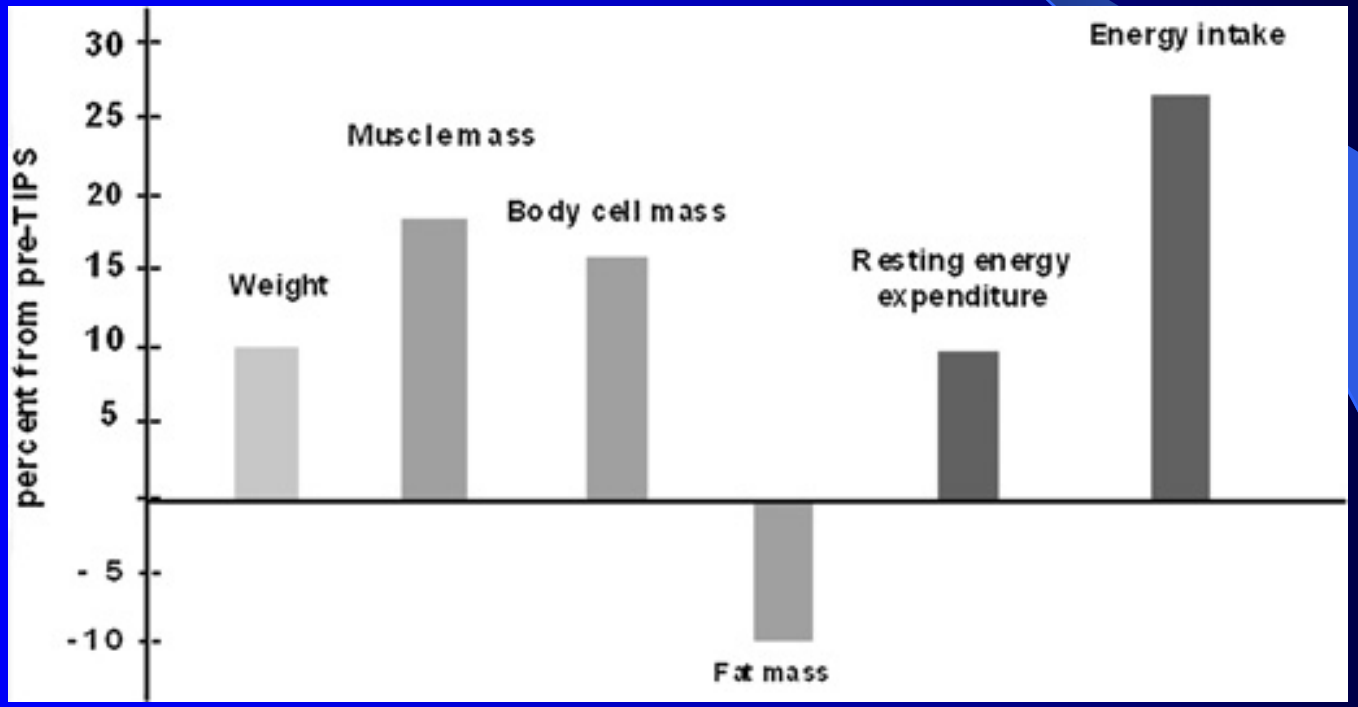
Effect of TIPS on Cardiac Output & Peripheral Vascular Resistance

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



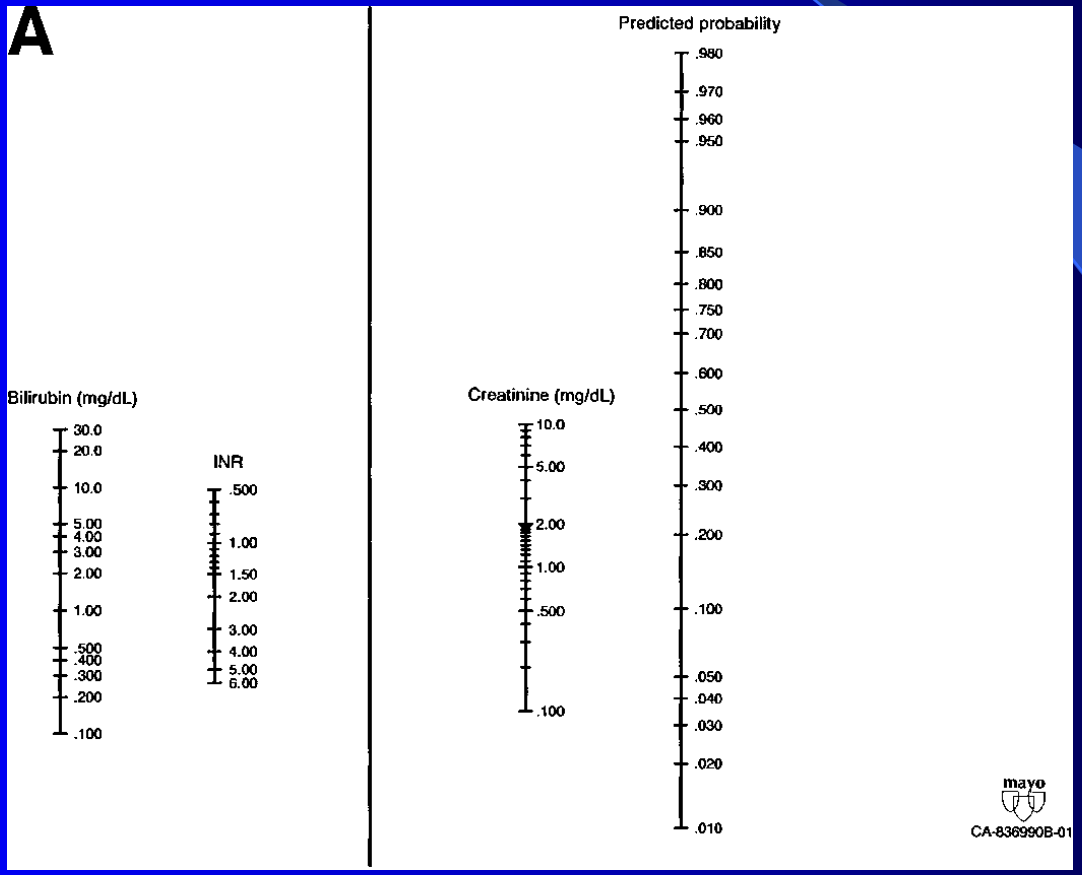
Effect of TIPS in Nutrition after 6 month Follow-up

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



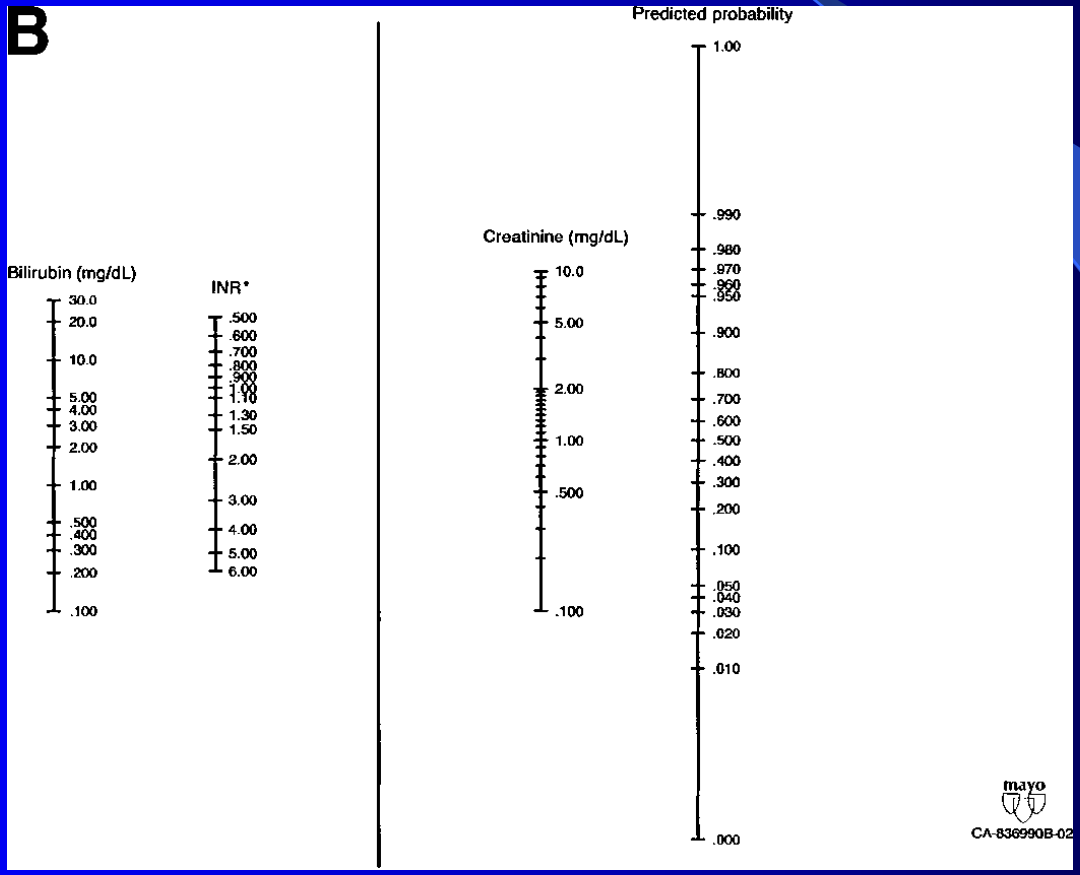
Nomogram to predict 3-month TIPS mortality in Alcoholic and Cholestatic Liver Disease

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, A_1AT defic, Wilson, MTX, etc.
- MELD 3-month Mortality from Weisner R S3mo=0.98465exp(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

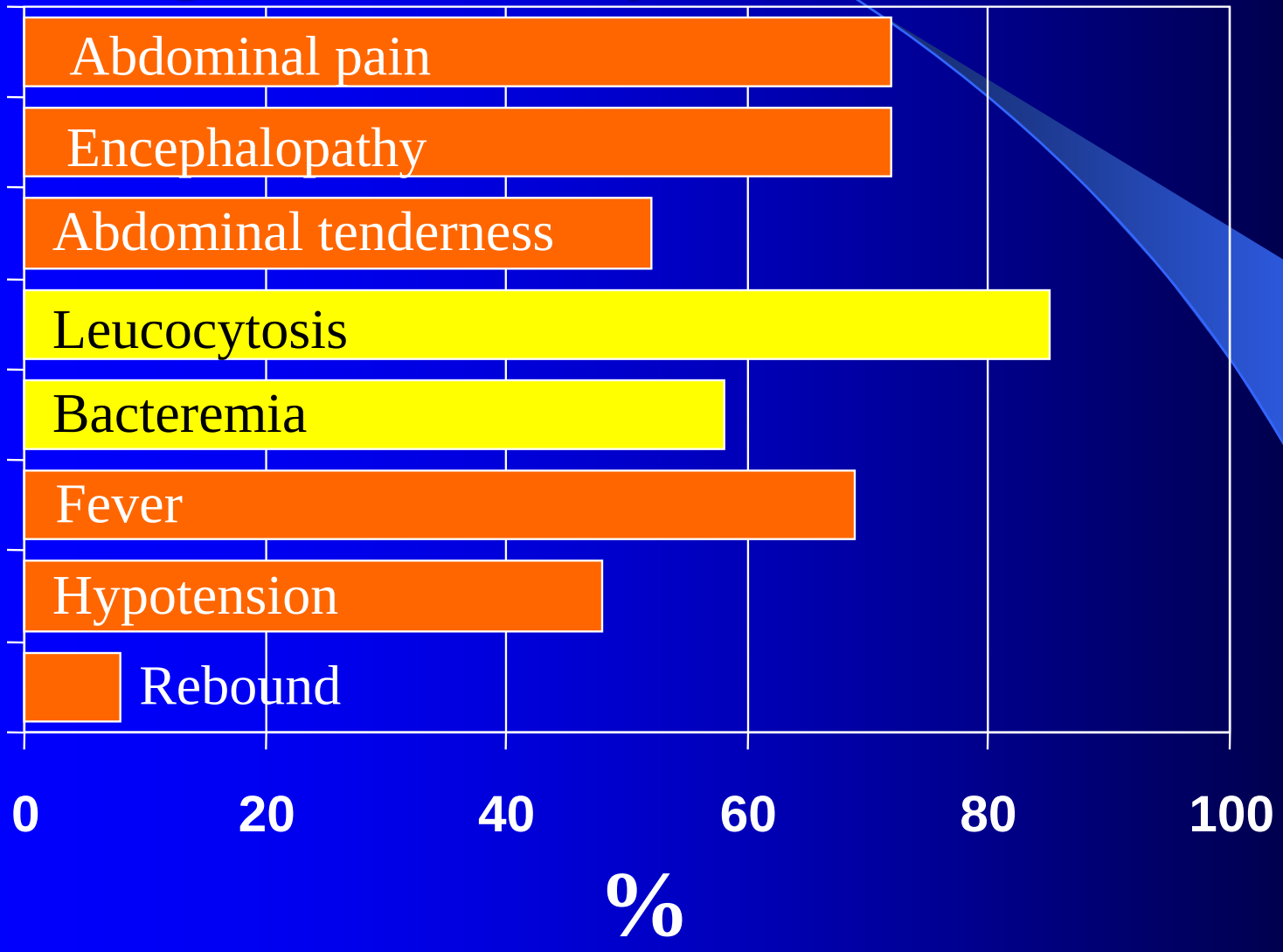
- Active infection
- Poorly controlled PSE
- Hypervascular liver tumor
- Portal V thrombosis without cavernoma
- Biliary obstruction

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



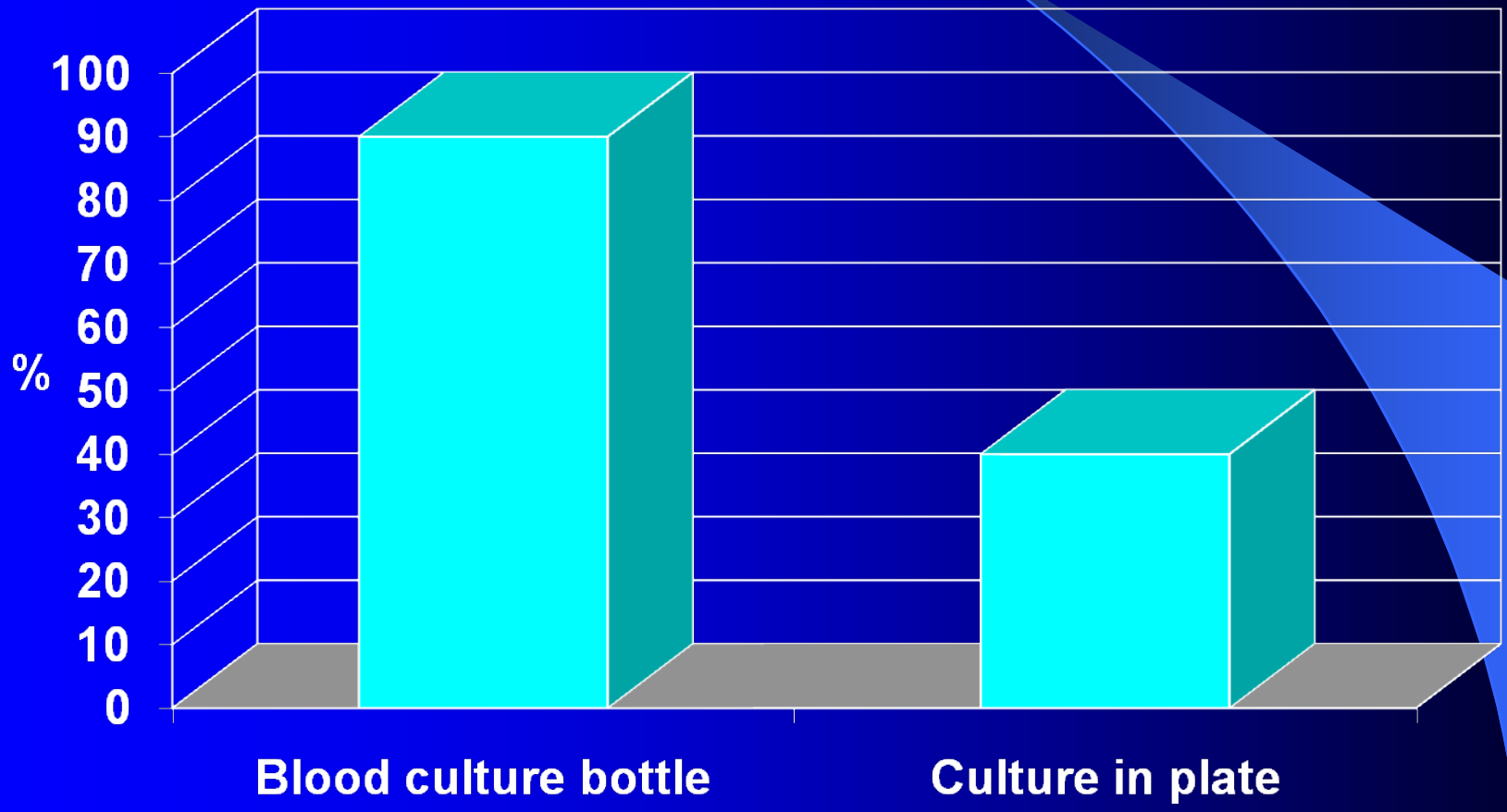
Diagnosis of SBP and CNNA

- ***SBP*** = PMN >250/mm^3 with (+) culture (> 90% monobacterial)
  - Other predictors:
    - Ascites WBC > 1000/uL
    - Ascites pH < 7.35
    - Blood-ascites pH gradient =/>0.1
- ***CNNA*** = PMN >250/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

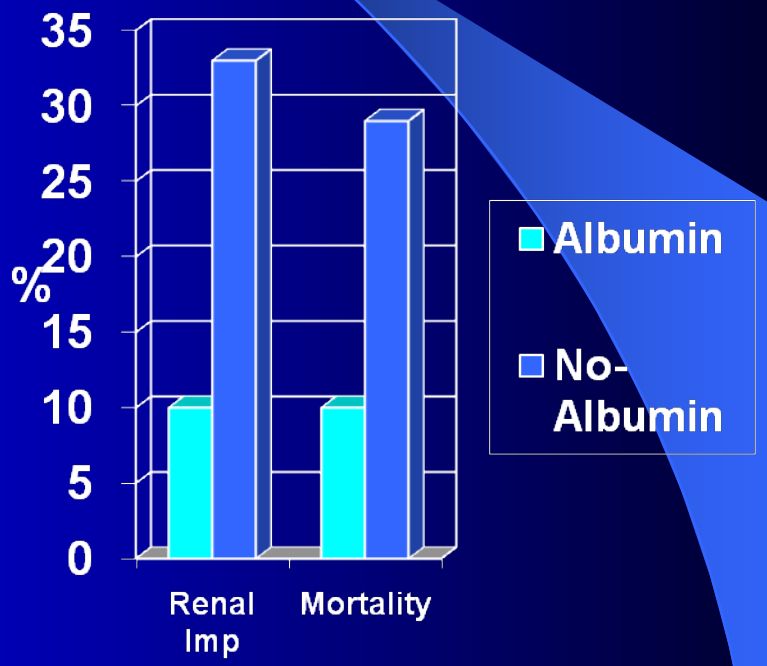


SBP & HRS

(Sort et al. NEJM 1999;341:404-409)

- Intervention: Cefotaxime 2 g q 8h +/- Albumin 1.5gm/kg & 1 gm/kg 3 days later
- Definition of Renal impairment:
  a) >50% incr. BUN or Cr if base Cr >1.5
  b) >50% incr. to Cr>1.5 or BUN>30 if base Cr <1.5

RESULTS



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%)***

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)

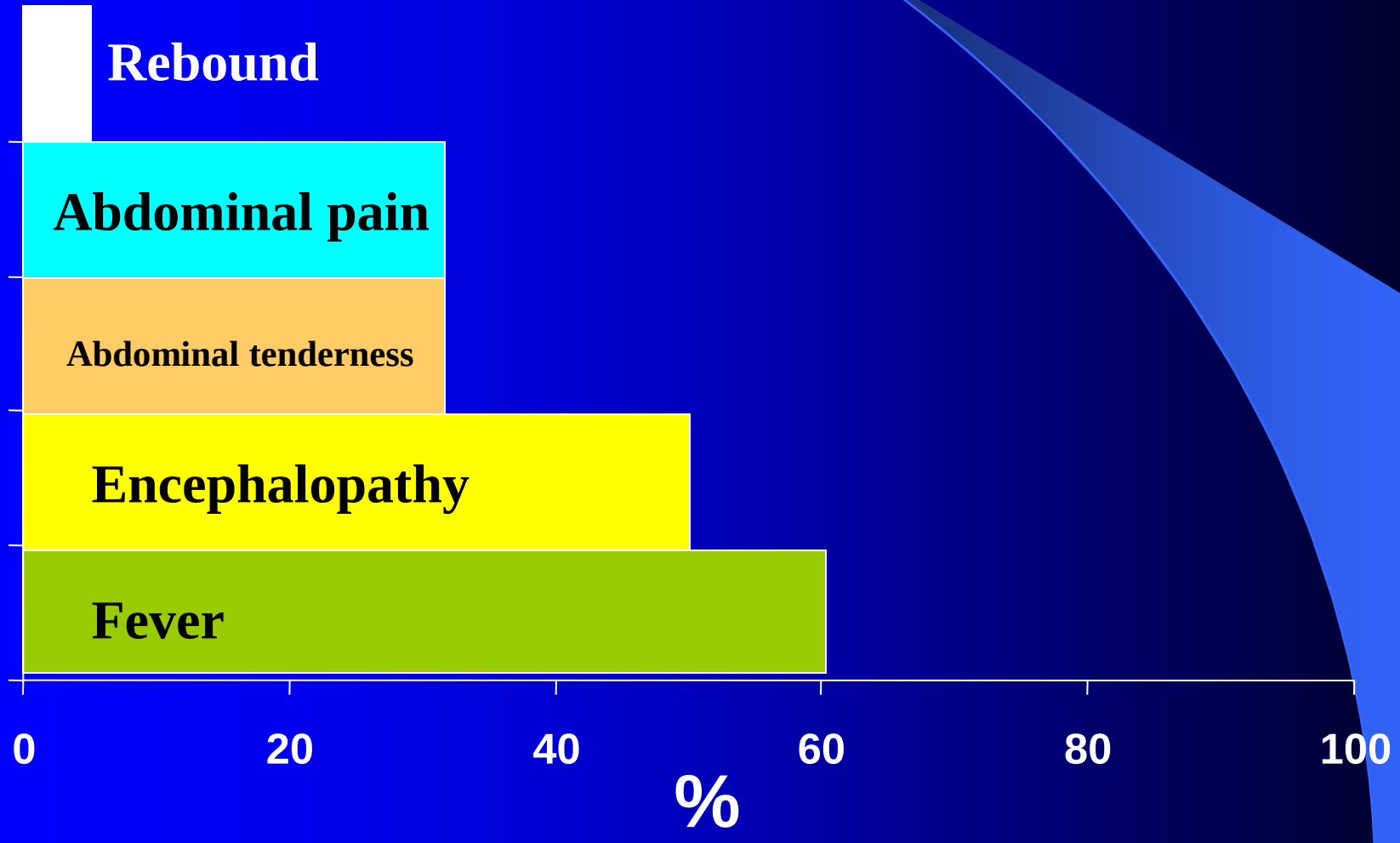
Primary Prophylaxis of SBP

- **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/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

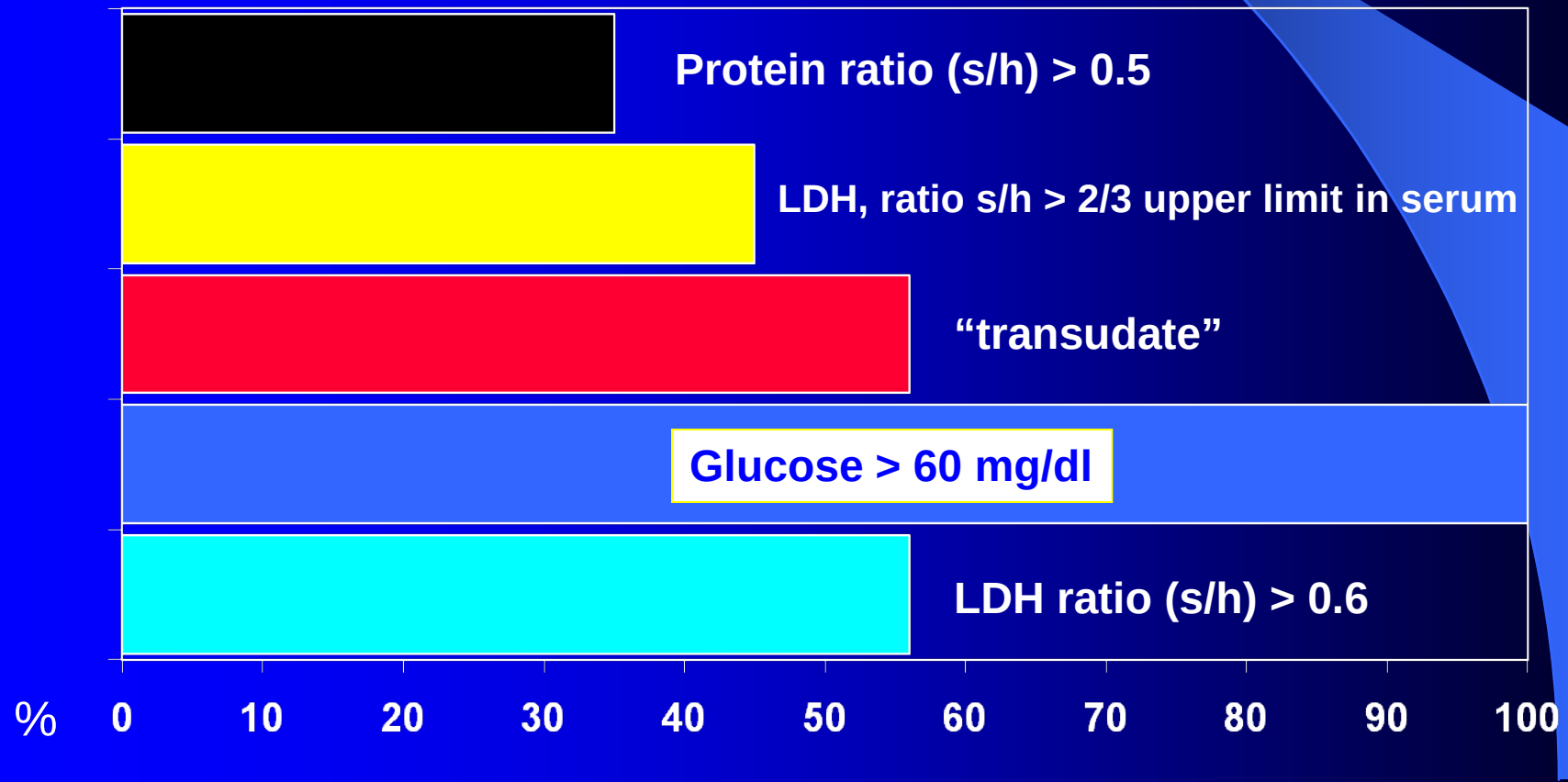
Ascites Management

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

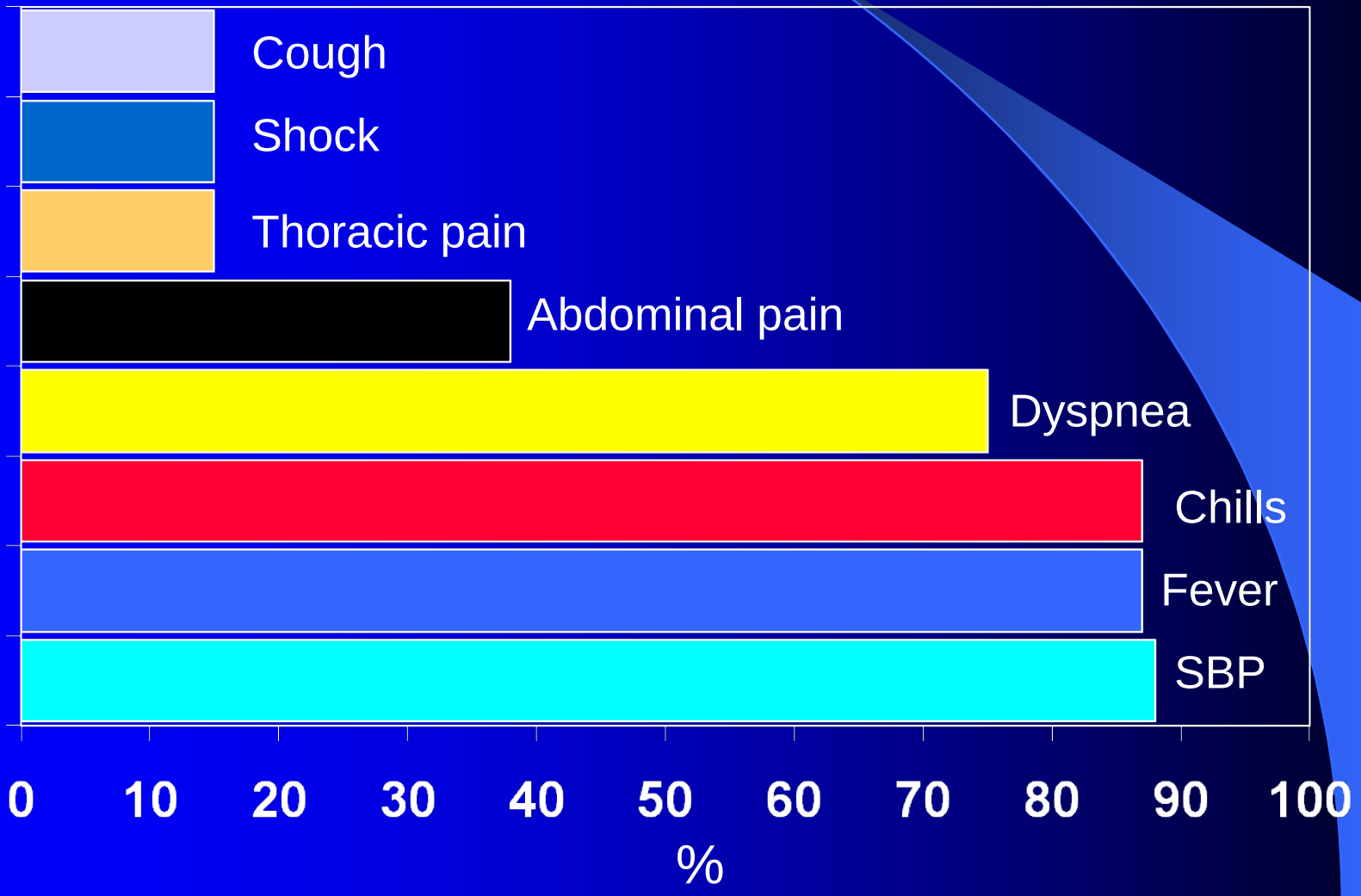
- **TREAT:**
- Na restrict + LVP + diuretics
- PMN>250: Cefotaxim + Albumin
- Prot < 1.5g: Norfloxac
- GI Bleed: Norfloxacin

Hepatic Hydrothorax

- In 10% of patients with ascites
- Usually right sided
- T. protein in hydrothorax > ascites by 0.75-1 g/dl
- DX: (+) Tc colloid “Shunt Study” from abdomen to chest.



Signs and Symptoms: Spontaneous Bacterial Empyema



Spontaneous bacterial empyema

- **Diagnosis**:
  - **A)** culture (+) (in blood culture bottle) + PMN > 250/mm^3 , or
  - **B)** PMN > 500/mm^3 in patients with known hepatic hydrothorax and CXR without pneumonia
- **Bacteriology**:
  - single bacteria (E.coli, K. pneumonia, C. perfringes)
  - bacteremia in 36%

Spontaneous bacterial empyema

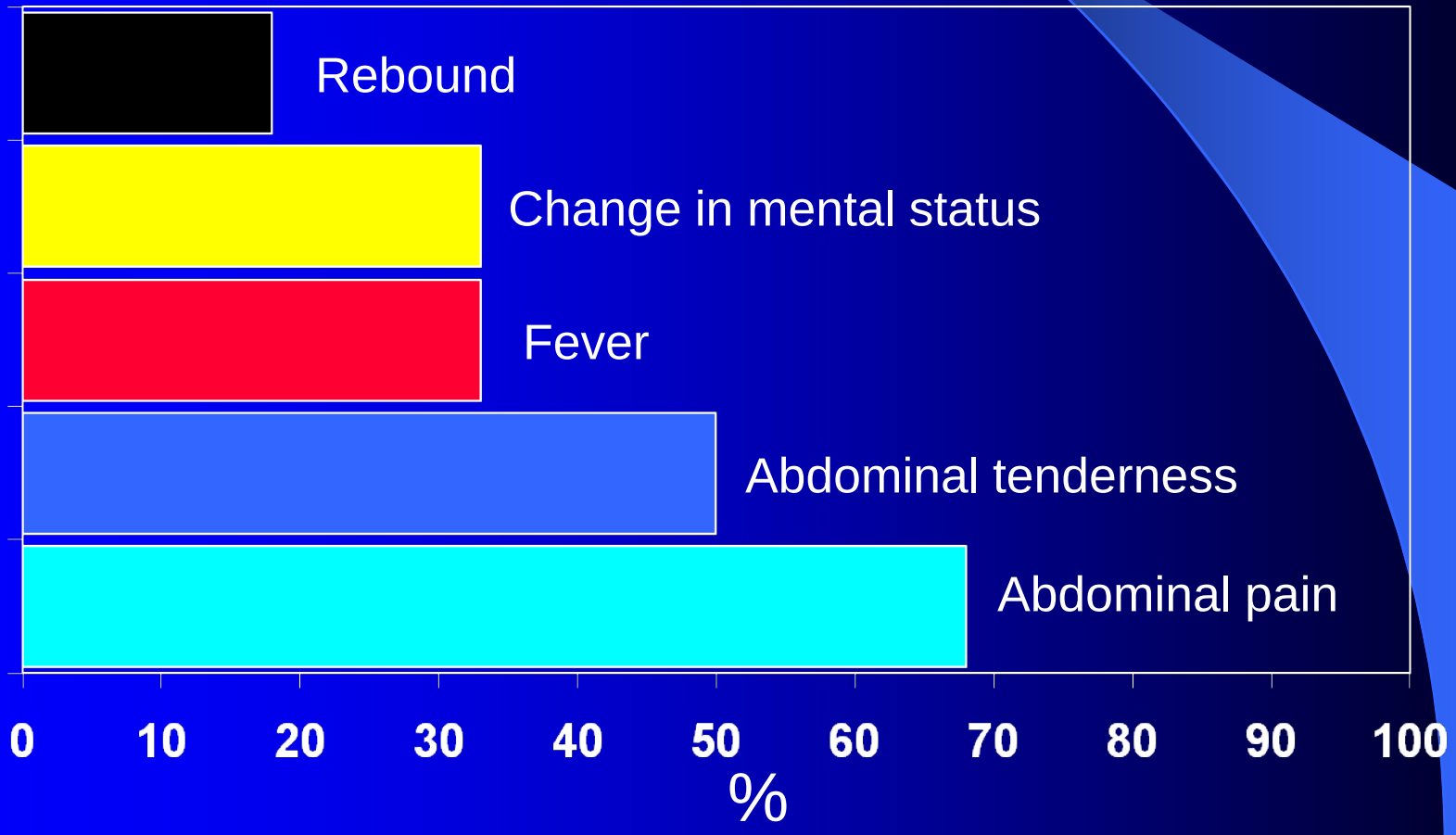
- **Mortality**:
  - in culture (+) = 50%;
  - in general = 27%
- **Relapse rate**:
  - 38% at 1 year;
  - mortality at 1 year =50%
- **Treatment**:
  - Cefotaxime (or as per antibiotic susceptibility) + albumin expansion.
  - Chest tube is contraindicated, unless the patient has obvious pus in the pleural space (Curr Opin Pulm Med 2012, 18:355–358; Liver Int. 2011 Mar;31(3):417-24)
- **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%)
- Other markers: Alkaline phosphatase > 240 U/L, or CEA > 5 ng/mL

Secondary peritonitis

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



Secondary peritonitis

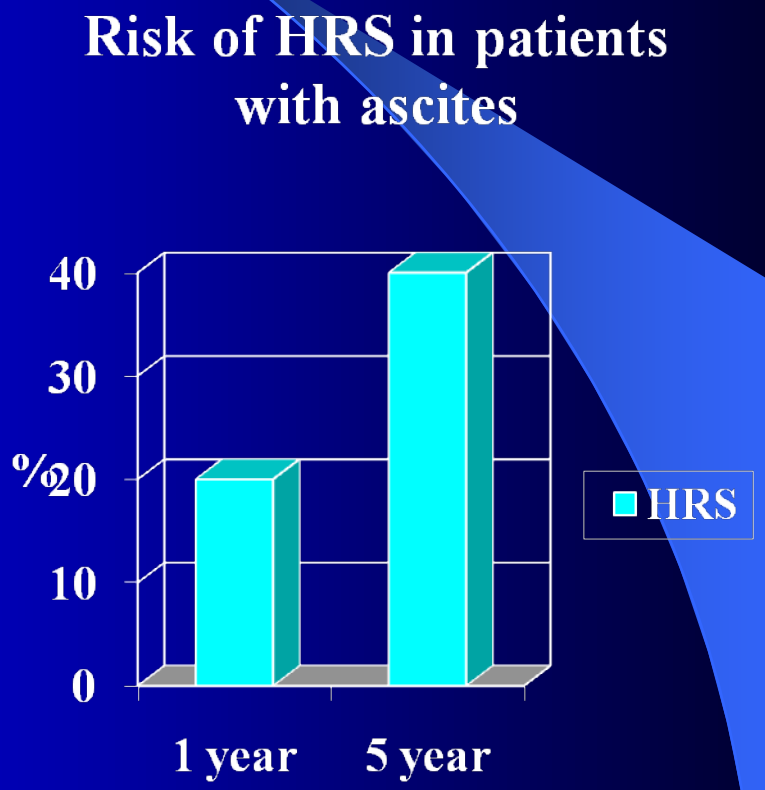
- **Evaluation**: look for perforation (extravasation of contrast) or loculated pus.
- **Treatment**:
  - Surgery (if perforation or abscess found)
  - Antibiotics (Cefotaxime + metronidazol) + albumin expansion

Hepatorenal Syndrome

New Medical Interventions

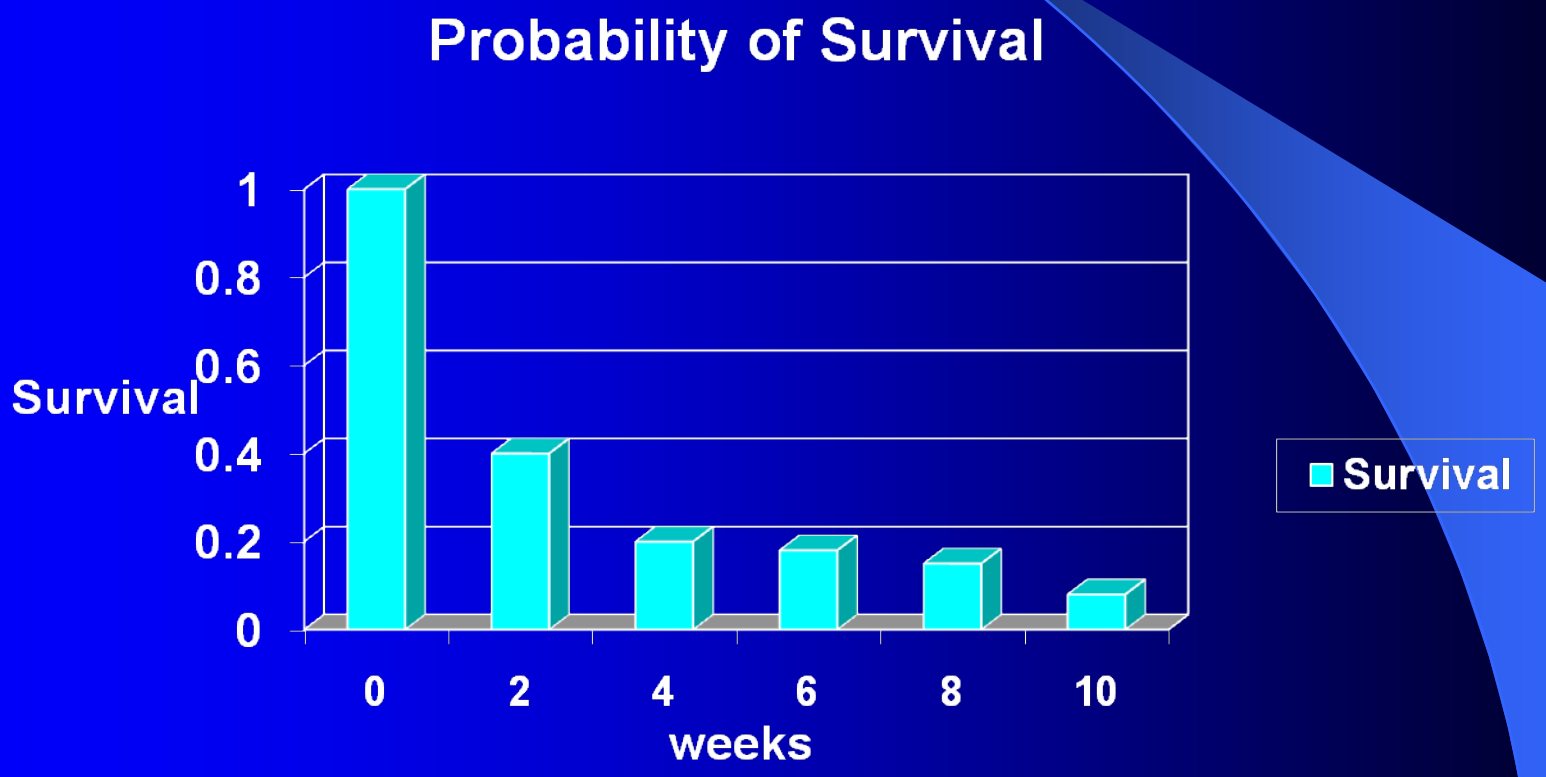
Hepatorenal Syndrome

- PREDISPOSING FACTORS
- Ascites
- Diuretic resistant or intolerant
- Extreme activity of renin-angiotensin & sympathetic system



Mortality of HRS

Gastroenterol 1993;105:229



Hepatorenal Syndrome 2007 Criteria

GUT 2007;56:1310-1318

- Cirrhosis with ascites
- Cr > 1.5 mg/dL (Classic but suboptimal criteria)
- **Best Criteria:** an increase of serum creatinine >/= 0.3 mg/dL, or 1.5 times from baseline (Stage 1 AKI)
- Absence of shock.
- No Response to a creat < 1.5 mg/dL after 2 days of :
  - Diuretic withdrawal +
  - Volume expansion with albumin 1 g/kg per day (up to 100 g/day).
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease:
  - Proteinuria < 500 mg/dL,
  - Urine sediment with < 50 RBC/hpf &
  - U/S without obstruction or parenchymal renal disease.

Hepatorenal Syndrome Subtypes

- ***TYPE I***

- Rapidly progressive decrease in GFR
- Doubling Cr to >2.5 *(or 50% drop of Cr Cl to < 20 ml/min)* in < 2 weeks
- Pattern: AKI

- ***TYPE II***

- Slowly progressive renal failure
- Cr = 1.25-2.5 mg/dL or *(Cr Cl < 40 mL/min).*
- Pattern: refractory ascites

HRS
Medical Therapy

- N-Acetylcysteine
- Ornipressin + Albumin
- Midodrine + Octreotide + Albumin
- Norepinephrine + Albumin
- Terlipressin + Albumin

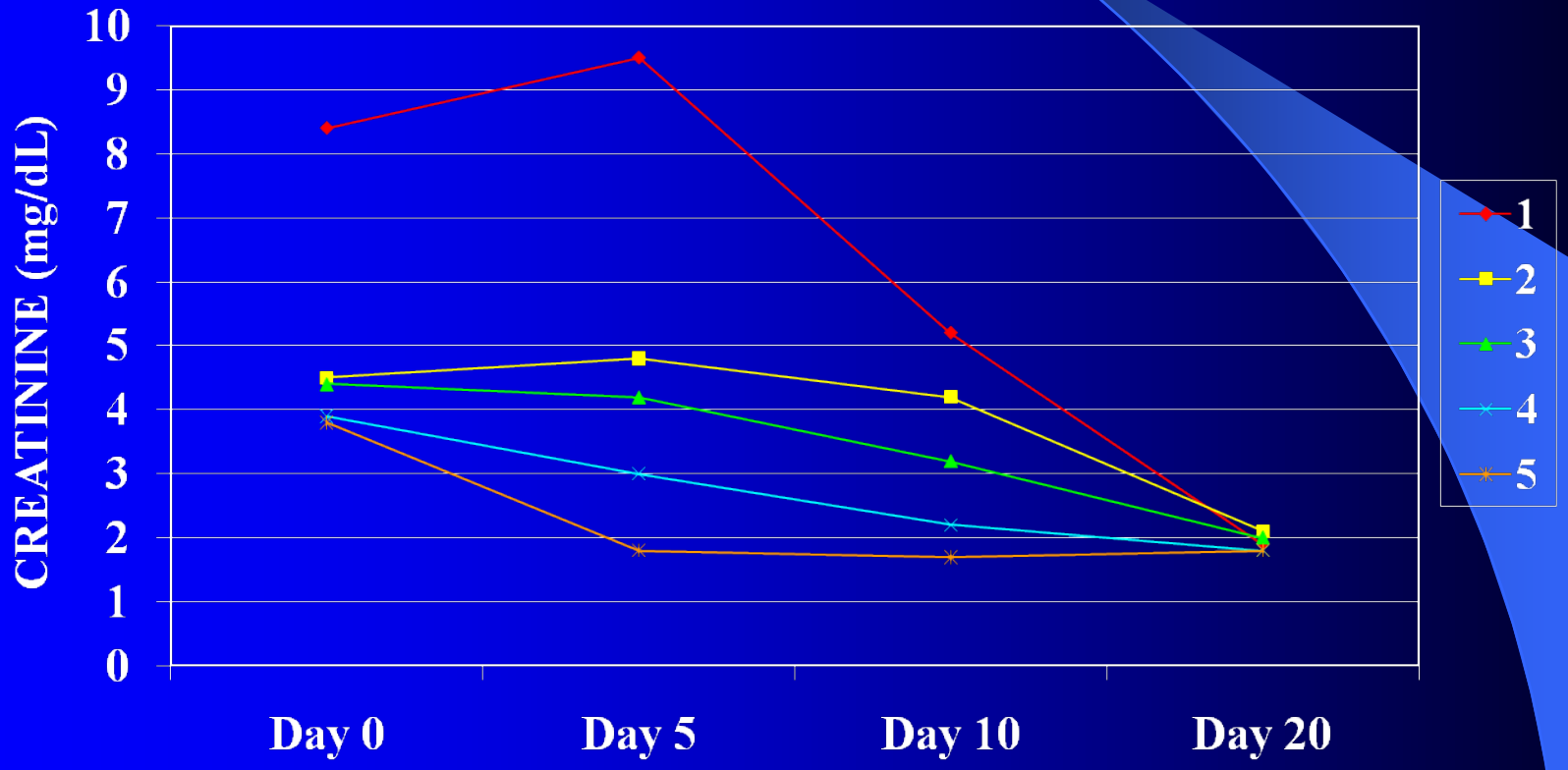
General Principles of Treatment

- Expand intravascular volume with IV albumin (1 g/kg/day up to 100 g, or 2L of 5% albumin), guided by CVP.
- Raise CVP to 10-15
- Use vasopressor to keep MAP of 85-90 mmHg (Velez JC, Am J Kidney Dis. 2011 Dec;58(6):928-38).
  - Midodrine 10-20 mg po q8h + Octreotide 100-200 mcg SQ q8h, or
  - Norepinephrine IV drip, or
  - Ornipressin IV drip, or
  - Terlipressin IV drip)
- Continue therapy until creatinine is </= 1.3 mg/dL (up to 14 days)

HRS + Midodrine & Octreotide

Serum Creatinine (mg/dL)

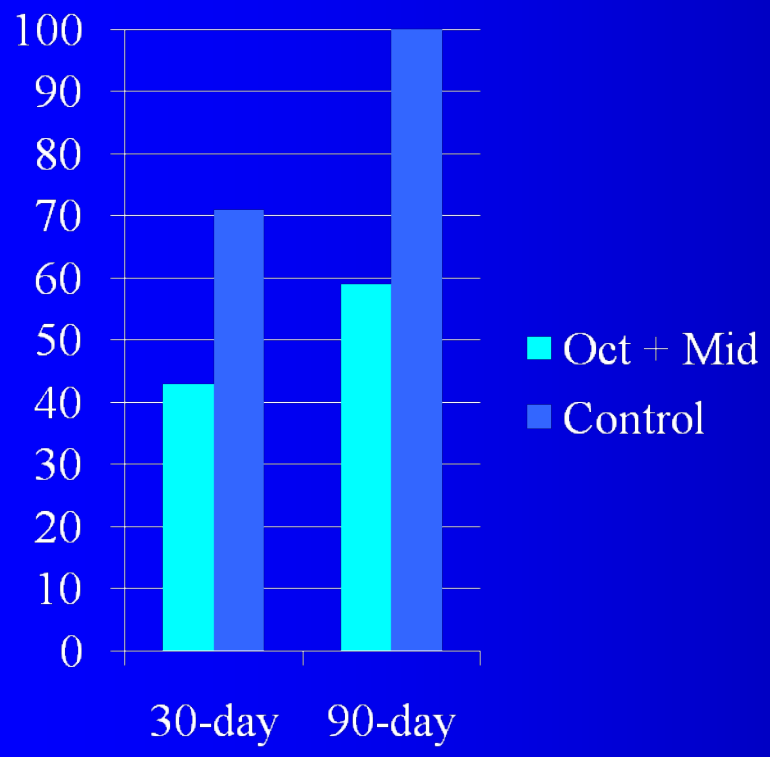
Hepatology 1999;29:1690-1697



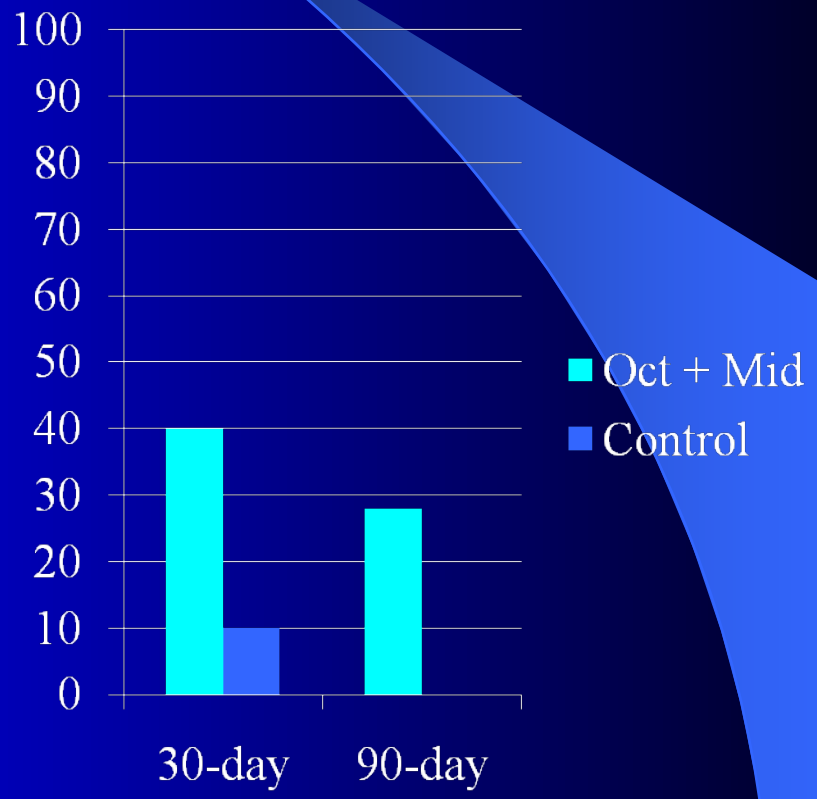
Mortality & Sustained Response
Octreotide + Midodrine in HRS

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

Mortality



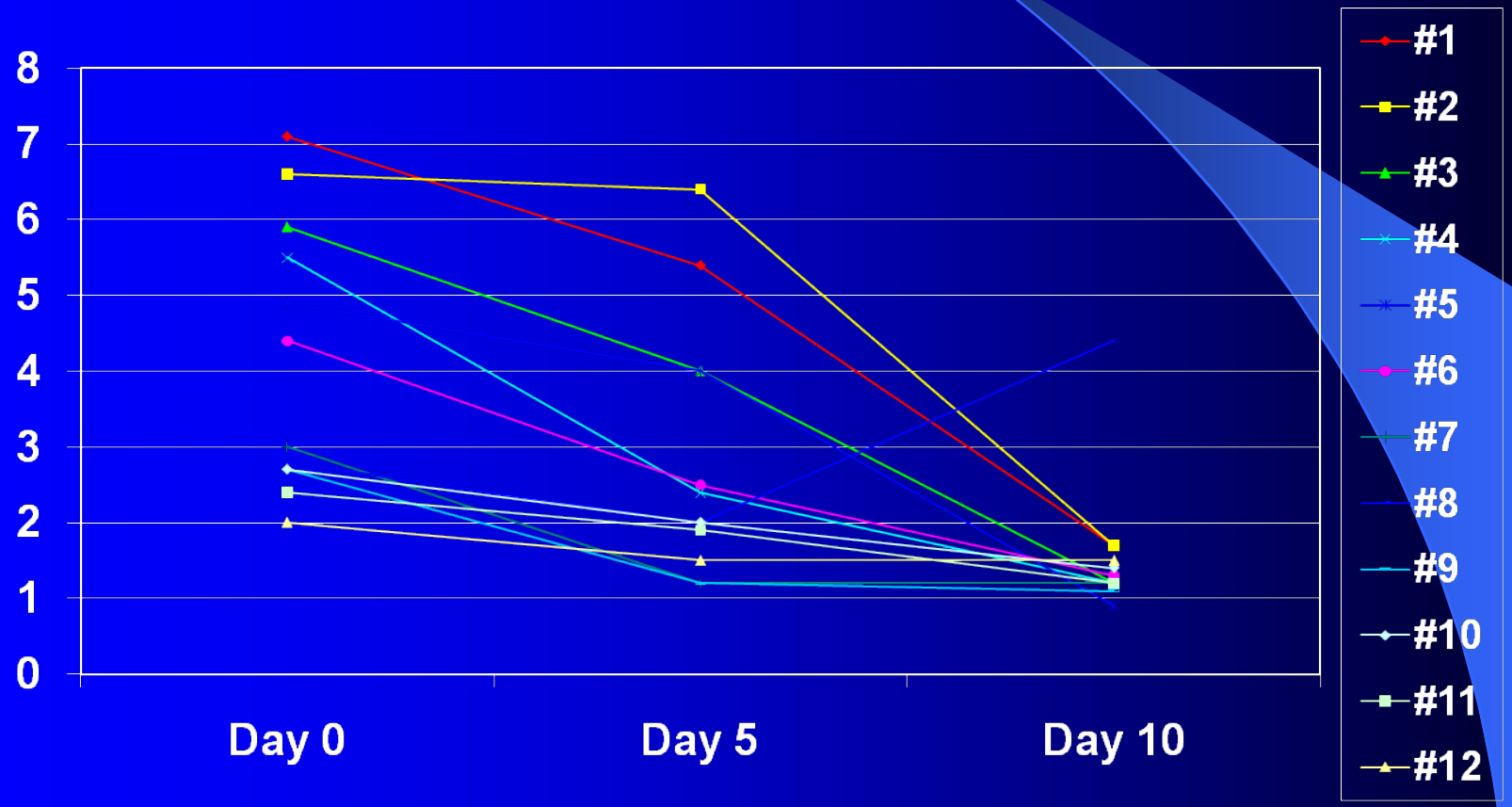
Sustained improved GFR



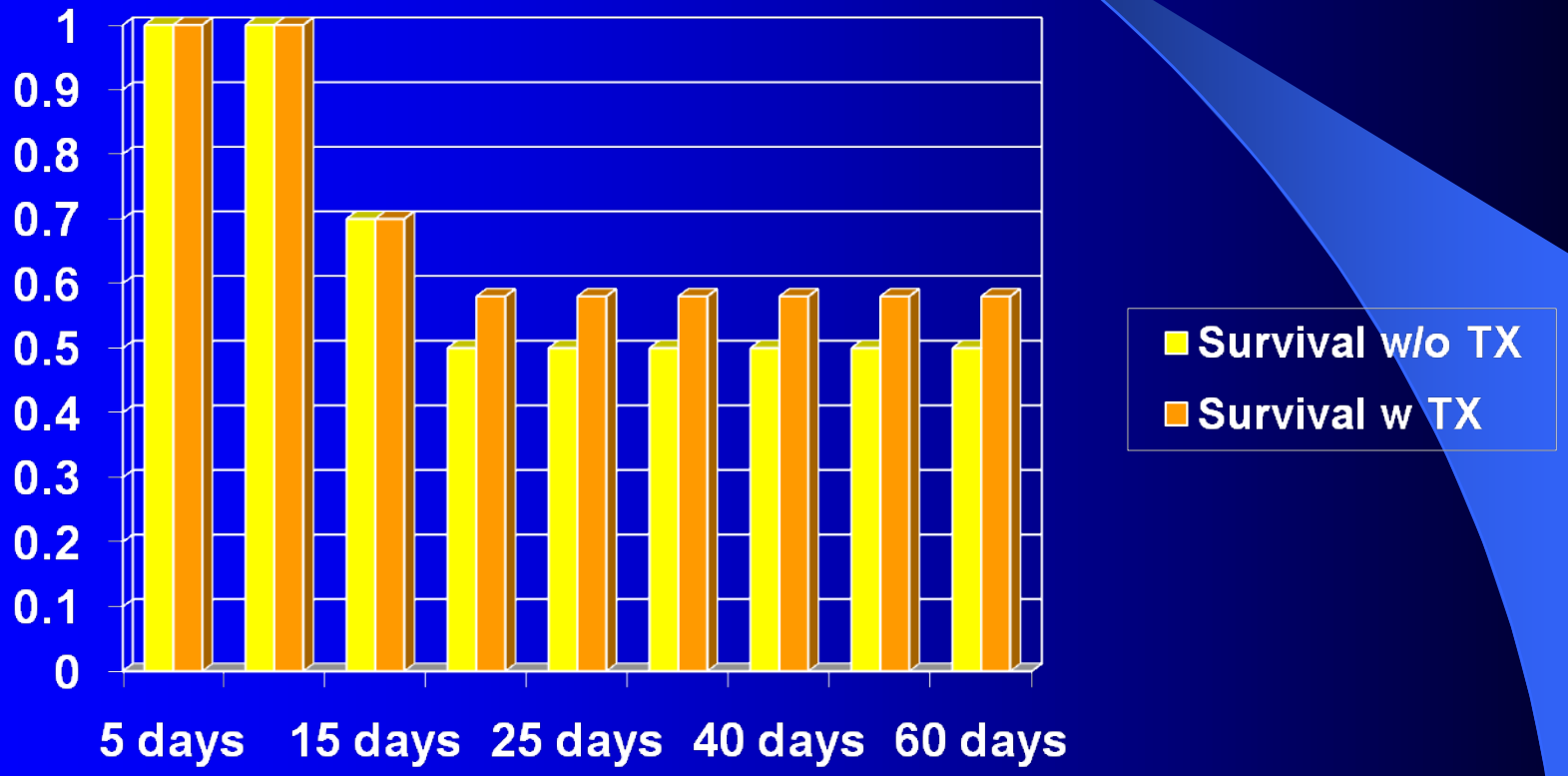
HRS-I & Noradrenaline + Albumin

Serum Creatinine (mg/dl)

(Duvoux et al. Hepatology 2002;36:374-380)

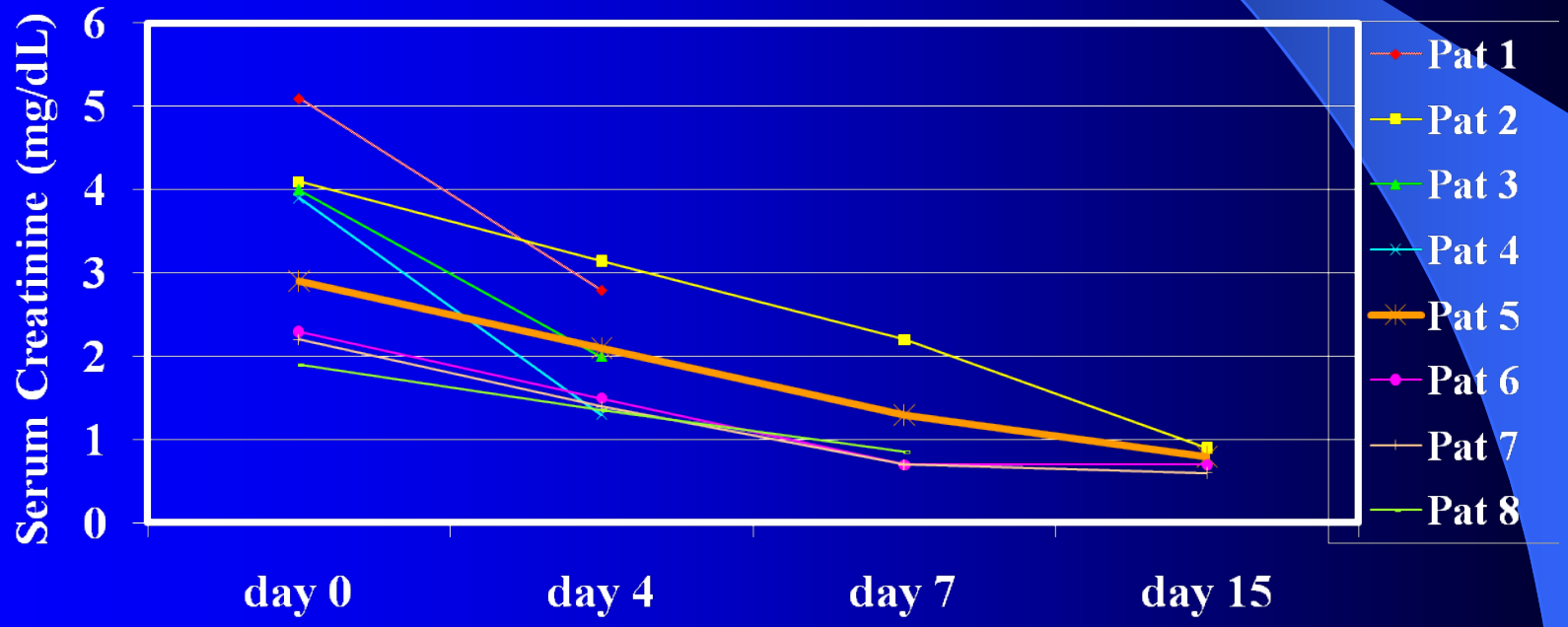


HRS-I & Noradrenaline + Albumin
Two-month Survival



Hepatorenal Syndrome & Ornipressin + Albumin

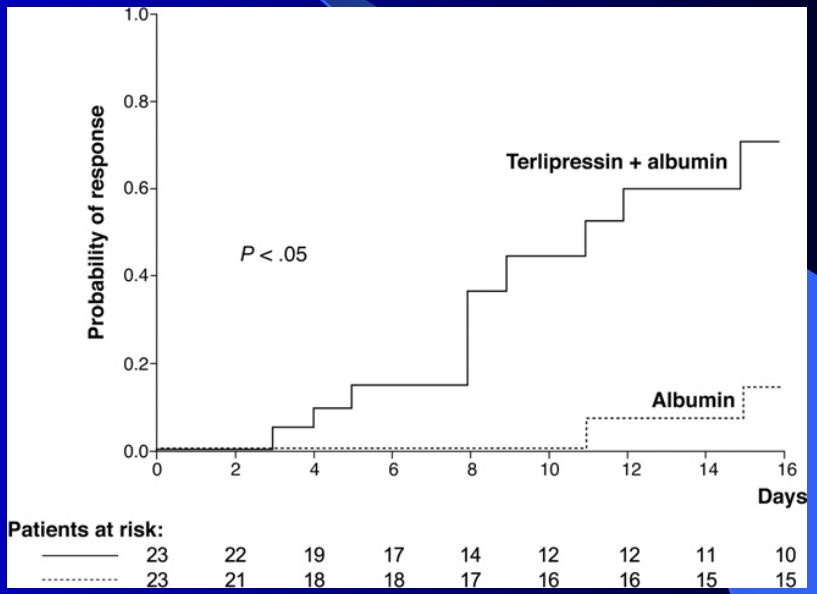
HEPATOLOGY 1998;27:35-41



Terlipressin + Albumin in HRS
RESULTS

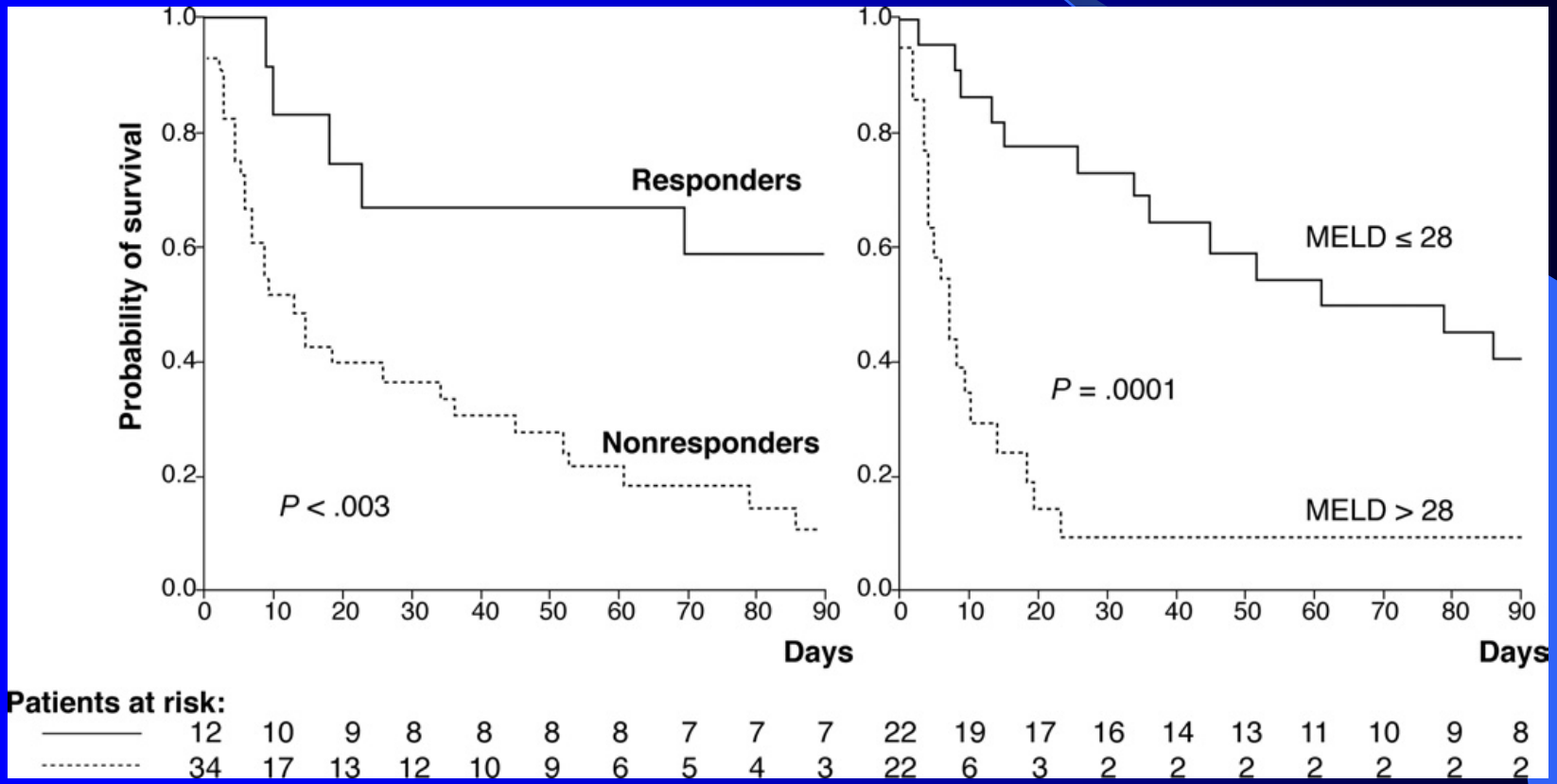
GASTROENTEROLOGY 2008;134:1352–1359

- Complete response: Creatinine </= 1.5 mg/dL
- Partial response: creatinine drop > 50%, but with final creat > 1.5 mg/dL.
- Response rate:
  - HRS-I: 35%
  - HRS-II: 67%
  - Overall: 43.5%
- MAP effect: in responders increased from 75+/-13 to 84+/-18



Inverse Kaplan–Meier: cumulative incidence of improvement of renal function.
Median time to improvement of renal function with terlipressin andalbumin was 11 days

Probability of survival at 3 months
By improvement of renal function *(left)*, and
By base-line MELD score (*right graph*).
(MELD score could not be calculated in 2 patients).



Side Effects and Conclusion

GASTROENTEROLOGY 2008;134:1352–1359

	Terlip + Alb (23)	Alb (23)	P value
Encephalopathy	70	70	.538
Bact. Infection	39	55	.23
GI Bleed	17	26	.722
Myocardial Infarct	4	0	1
Intest. Ischemia	13	0	.233
Arrhytmia	9	0	.489
Volume overload	30	17	.187
Arterial HTN	4	0	1
Other	30	9	.135

- **CONCLUSION:**
- Terlipressin + Albumin is effective in reversing HRS
- There was no effect on overall survival
- Responders had improved survival at 3 months: 58% vs 15%.

TIPS in HRS

TIPS in HRS Type I and II

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

- Guevara et al treated seven patients with Type-I HRS showing:
  - Significant improvement in serum creatinine, blood urea nitrogen, glomerular filtration rate and renal plasma flow by TIPS.
  - Three patients survived by more than 3 months.
- Brensing et al treated 31 nontransplantable patients (14 Type-I and 17 Type-II) and found that:
  - Renal function improved following TIPS.
  - One- and 2-year survival rates were 20% for Type-I and 70% and 45%, respectively, for Type-II HRS.
  - Due to a bilirubin cut-off of 10 mg/dl, nine patients had to be excluded from TIPS.
  - Liver failure was one of the most frequent causes of death following TIPS.
- Testino et al treated 18 patients with Type-II HRS and a Child-Pugh score of 10-12 awaiting transplantation:
  - All patients improved with respect to ascites and renal function.

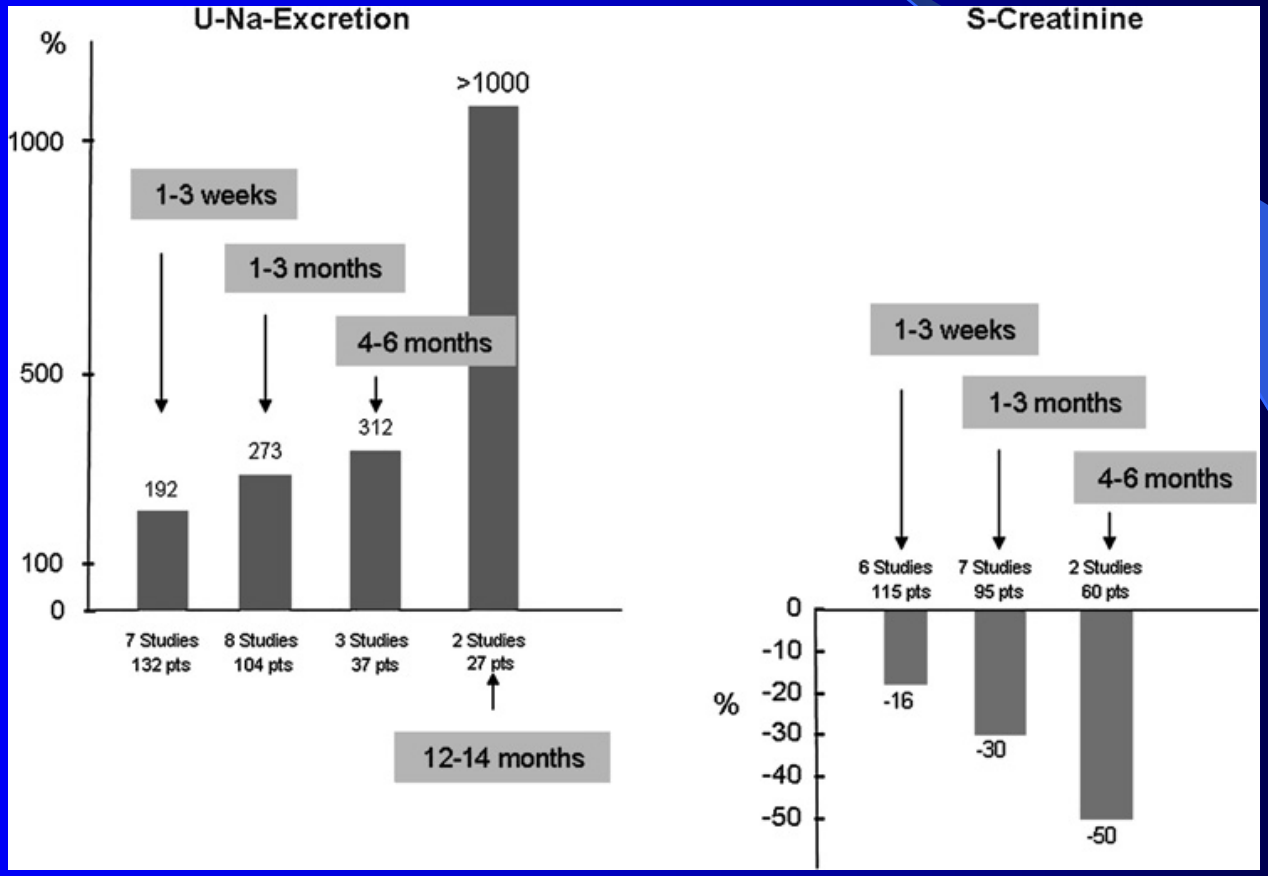
TIPS after Reversal of HRS

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

- Wong et al showed that TIPS may also have a role in maintaining patients who initially respond to vasoconstrictor treatment.
  - Fourteen patients with type 1 HRS were treated using a combination of midodrine, octreotide and albumin. Medical therapy for 14 days improved renal function in 10/14 patients with mean serum creatinine significantly decreasing from 233 mmol/l to 112 mmol/l.
  - Five responders were then treated with TIPS and showed further improvement in renal function (mean glomerular filtration rate: 96+/-20 ml/min at 12 months).

Effects of TIPS on Natriuresis and Azotemia

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

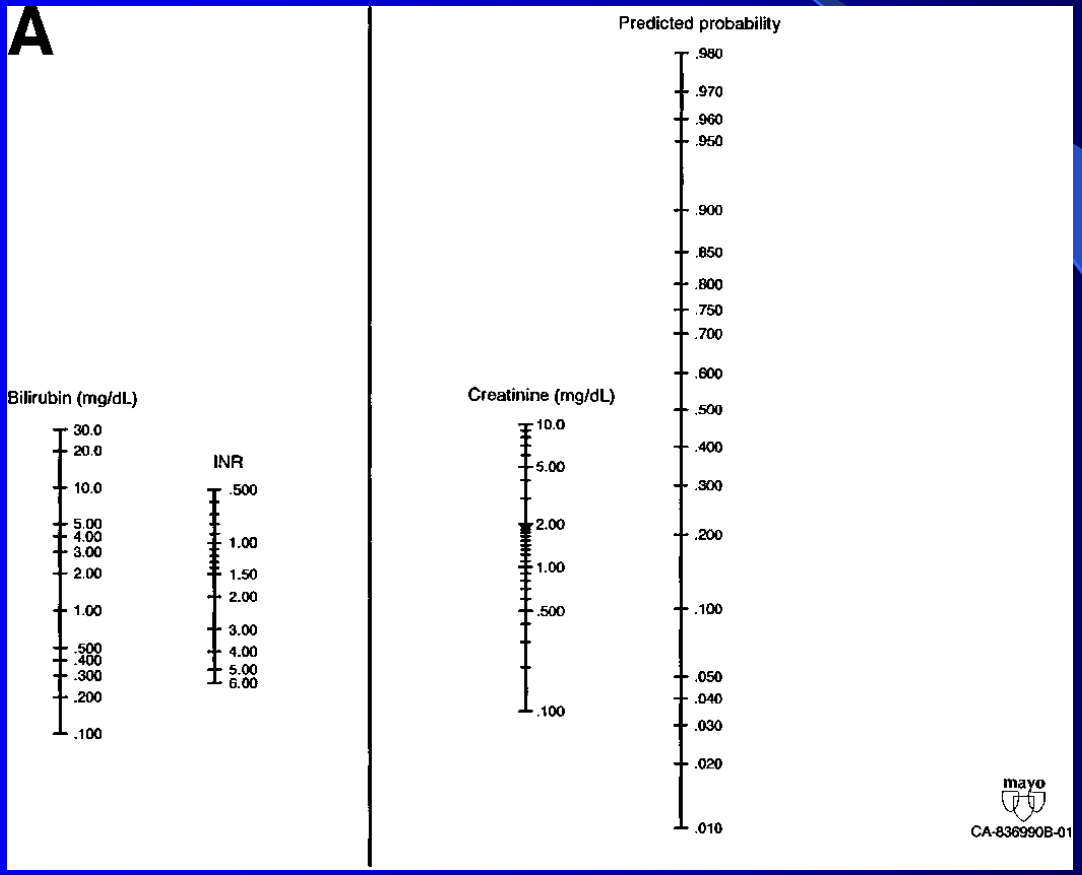


TIPS in HRS

- TIPS can improve renal function in type 1 and 2 HRS and eliminate ascites.
- Data are limited and survival may not be improved in patients with poor liver function.
- TIPS is indicated in selected patients with HRS and/or in candidates for liver transplantation.
- 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, or
  - severe cardiopulmonary diseases
- If MELD > 15-18, or bili > 4 mg/dL patients should be informed of higher 30 day TIPS mortality and TIPS performed only in the absence of other options.

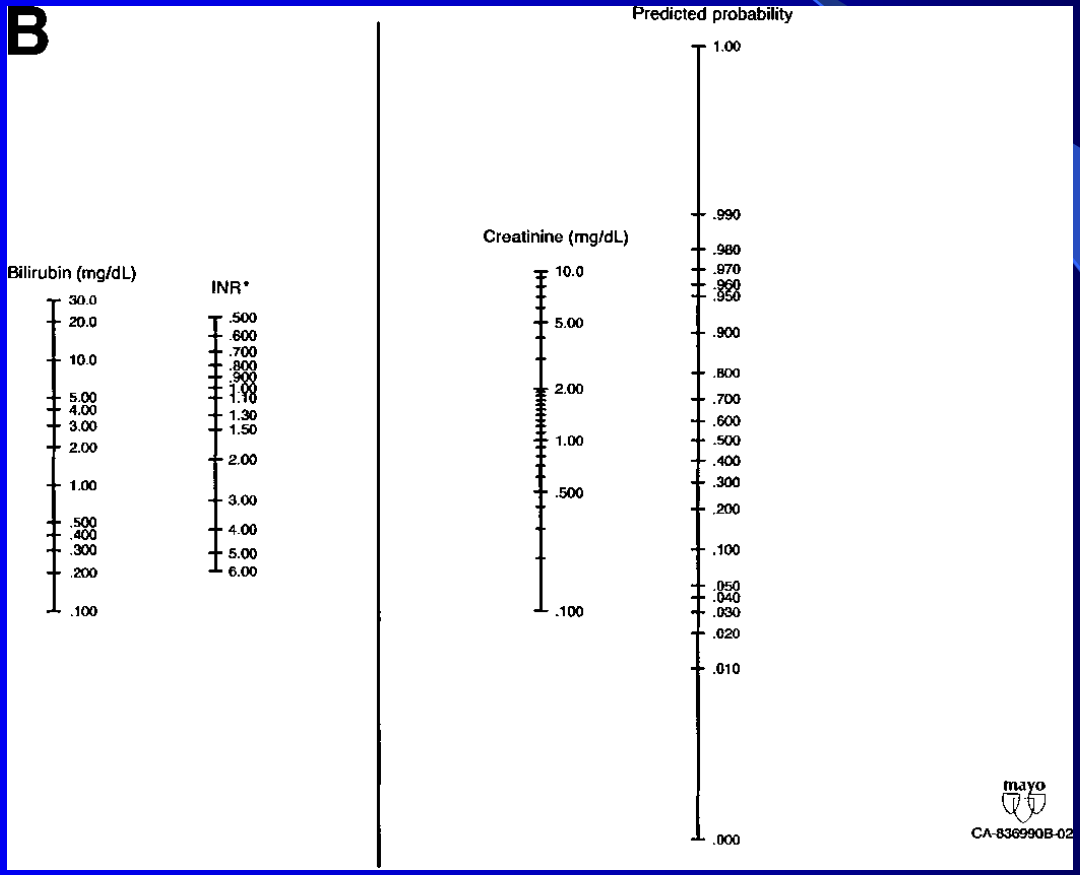
Nomogram to predict 3-month TIPS mortality in Alcoholic and Cholestatic Liver Disease

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

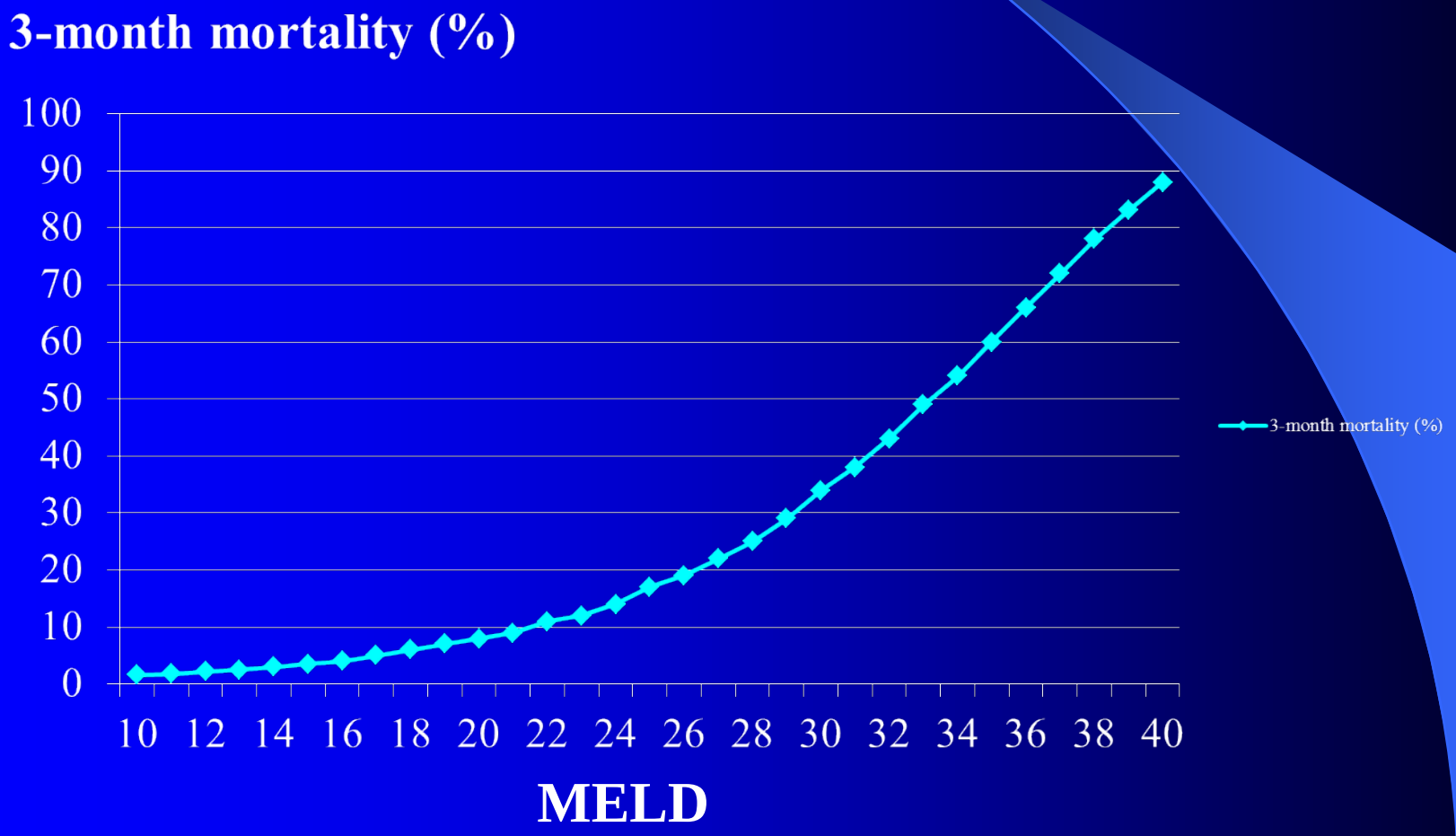
Malinchoc et al. Hepatology 2000;31:864-871

- 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 manually by L. Marsano from Malinchoc et al. Hepatology 2000;31:864-871)
- Group A: Alcoholic or Cholestatic Liver Disease.
- Group B: Viral, NASH, Cryptogenic, A_1AT defic, Wilson, MTX, etc.

MELD	Alcohol/ Cholestasis	Viral/NASH/MTX/ Wilson/A1AT/Crypto	*Hospitalized without TIPS*
10	10	18	*2*
12	12	24	*6*
14	18	35	*6*
15	19	46	*6*
16	19	48	*6*
17	24	58	*6*
18	27	62	*6*
19	32	75	*6*
20	35	82	*20*
21	40	85	*20*
22	44	90	*20*
23	48	92	*20*
24	50	94	*20*

3-month Mortality in 3437 patients by MELD score

Wiesner R et al. Gastroenterology 2003;124:91-96



Prevention of hepatorenal syndrome in patients with cirrhosis and ascites: a pilot randomized control trial between pentoxifylline and placebo.

Eur J Gastroenterol Hepatol. 2011 Mar;23(3):210-7

- 176 consecutive patients with cirrhosis and ascites were screened.
- Patients with creatinine clearance (Ccl) between 41 and 80 ml/min and serum creatinine of less than 1.5 mg/dl in absence of renal disease were randomized to receive either:
  - Treatment Arms:
    - pentoxifylline (group A, 1200 mg/day) or
    - placebo (group B) for 6 months.
  - Patients were followed monthly for 6 months, and kidney function tests were carried out at baseline, 1, 3, and 6 months.
  - Primary endpoint was the development of HRS within 6-month follow-up.

Prevention of hepatorenal syndrome in patients with cirrhosis and ascites: a pilot randomized control trial between pentoxifylline and placebo.

Eur J Gastroenterol Hepatol. 2011 Mar;23(3):210-7

- In Group A:
  - Improvement occurred in Ccl at 1 month (61.7±16.0 vs. 82.0±30.0 ml/min, P = 0.001) and at 3 months (61.7±16.0 vs. 86.2±30.7 ml/min, P = 0.001)
- In group B:
  - Ccl at 1 month (63.1±14.5 vs. 66.8±28.2 ml/min, P = 0.37) decreased at 3 months (63.1±14.5 vs. 54.4±18.3 ml/min, P = 0.008)
- Of the 12 patients who developed HRS:
  - 10 patients were in group B (type 1 HRS, n = 9 and type 2 HRS, n = 1) and
  - two patients (type-1 HRS, n = 2) were in group A (P = 0.01)
- **CONCLUSION:** Pentoxifylline is effective in preventing HRS in patients with cirrhosis and ascites at risk of HRS.

Practical Approach to HRS-I

- **AVOID HRS:**
- Strict Na restriction
- Minimize Diuretics
- Avoid intravascular depletion: albumin/LVP.
- Check for and treat hypothyroidism and adrenal dysfunction.
- No NSAIDs or aminoglicosides
- NAC + Na Bicarbonate for IV contrast
- Albumin in SBP (and other infections)
- Norfloxacine for cirrhosis + ascites & creat >/= 1.2 or Na </=130
- Pentoxifylline for AH.
- Add NAC to Prednisolone in AH.
- Pentoxifylline for cirrhosis + ascites & CrCl 41-80 mL/min

- **EARLY THERAPY:**
- Hold diuretics & give IV albumin/0.9%NaCl until CVP 10-15, then
- Raise MAP by 15, or to 85 mmHg with either Octreotide /Midodrine, or Noradrenaline, or Terlipressin (Phenylephrine also works well), until Cr is < 1.3 mg/dL.
- Check for and treat hypothyroidism and adrenal dysfunction when MAP is difficult to elevate or HRS recurs.
- Consider TIPS if MELD falls to </= 15
- NAC + TIPS
- Liver Transplant
- Pentoxifylline or Misoprostol (?)

Variceal Hemorrhage

Primary Prophylaxis

VARICEAL HEMORRHAGE

- Gastro-esophageal varices = 50% cirrhotics
  - 30% at time of diagnosis of cirrhosis; 90% after 10 y
  - Child A = 40%
  - Child C = 85%
- Bleeding only if Portal Pressure >12mm Hg
- Risk of bleeding:
  - a) small varices (up to 5 mm) < 10% /y
  - b) medium/large = 30% /year
- Mortality from variceal bleed = 40% (20% with antibiotic prophylaxis)
  - < 10% in Child-Pugh A;
  - > 70% in Child-Pugh C

Predictors of Presence of Varices in Cirrhosis

- Predictors of varices:
  - INR > 1.5
  - Portal V diameter > 13 mm
  - Thrombocytopenia
- Risk factor number and odds for varices:
  - 0 factors: < 10 %
  - 1 factor: 20-50 %
  - 2 factors: 40-60 %
  - 3 factors: > 90 %

Morphologic Classification of Esophageal Varices

- Grade F0: no EV detected;
  - 5-8% develop varices each year
- Grade F1: small (</= 5 mm) straight EV;
  - Progression to F2 or F3 varices: 8 % per year
- Grade F2: slightly enlarged tortuous EV occupying less than one-third of the esophageal lumen; and
- Grade F3: large coil-shaped EV that occupied more than one-third of the esophageal lumen

Predictors of Variceal Bleed & Surveillance Schedule

- **Predictors of variceal bleed:**
  - Size > 5 mm
  - Red signs
  - Child-Pugh B or C
- **Surveillance schedule:**
  - Cirrhosis without varices: q 2-3 y (q 1y if decompensated)
  - Cirrhosis with small varices: q 1-2 y (q 1y if decompensated); consider Nadolol to decrease growth (Mekel et al. Gastroenterol 2004; 127:476)

Preventing 1st Variceal Bleed

- **GOAL:**
- Decrease Portal P by >20%
- Decrease Portal P to < 12 mm Hg
- Decrease varices size and/or thicken the wall

- **MODALITIES:**
- Non-selective B-blocker
- ***Variceal ligation***
- Octreotide/lanreotide (?)
- Losartan: No
- Nitrates (ISMN,ISDN):No
- Sclerotherapy: No
- TIPS: No
- Shunt surgery: No

Esophageal Varices

Ligation as Primary Prophylaxis

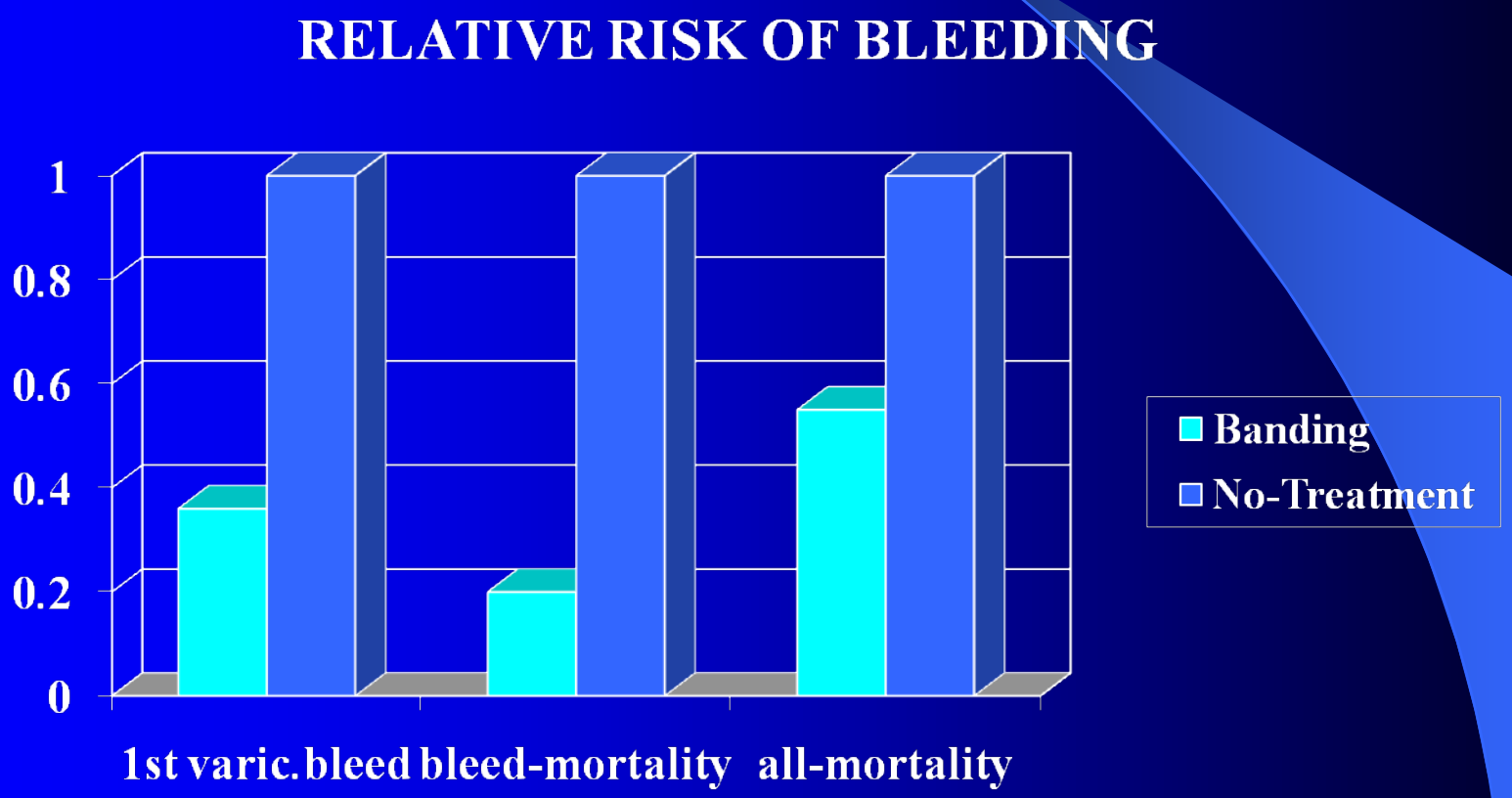
Meta-Analysis *(Hepatology 2001;33:802-807)*

- Grade III-IV esophageal varices
- Banding q 1-3 weeks
- Distal 5 cm esophagus
- A/B/C=27/45/28 %
- Mean F/U 19 mo (12-32)
- Mean sessions = 3.3

- Banding vs No-Treatment = **5 trials**
- Banding vs Propranolol to decrease HR by 25 %= **4 trials**

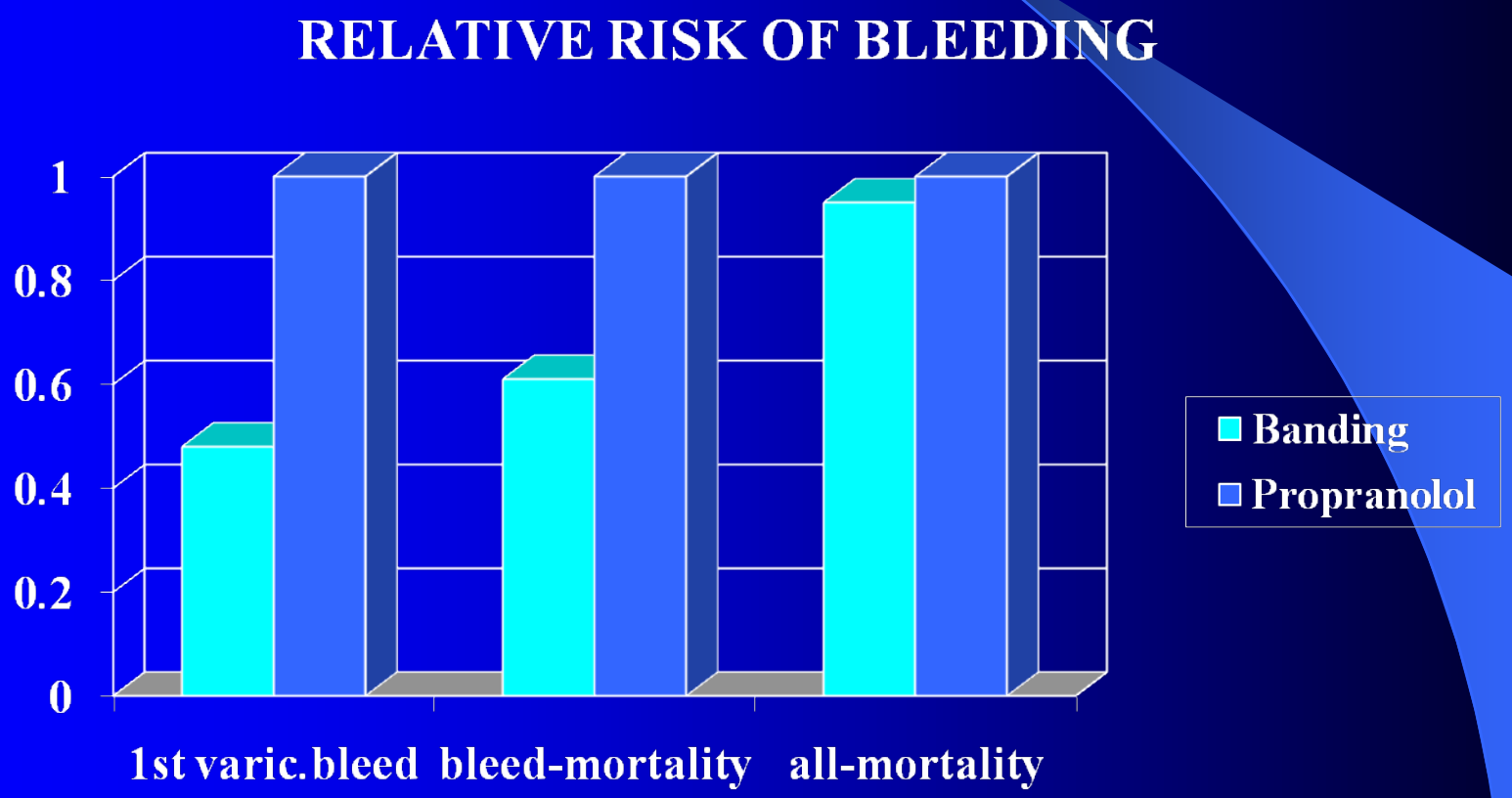
Primary Prophylaxis Meta-Analysis
Banding vs No-Treatment

Hepatology 2001;33:802-807



Primary Prophylaxis Meta-Analysis
Banding vs Propranolol

Hepatology 2001;33:802-807



Banding as Primary Prophylaxis **Meta-Analysis Conclusions**

- **Banding** of large varices **vs No-treatment**:
  - Reduces 1st bleed and total mortality.
- **Banding** of large varices **vs Propranolol**:
  - Reduces 1st bleed but no total mortality.
- ***Prophylactic banding should be considered for large esophageal varices when beta-blockers are not well tolerated.***

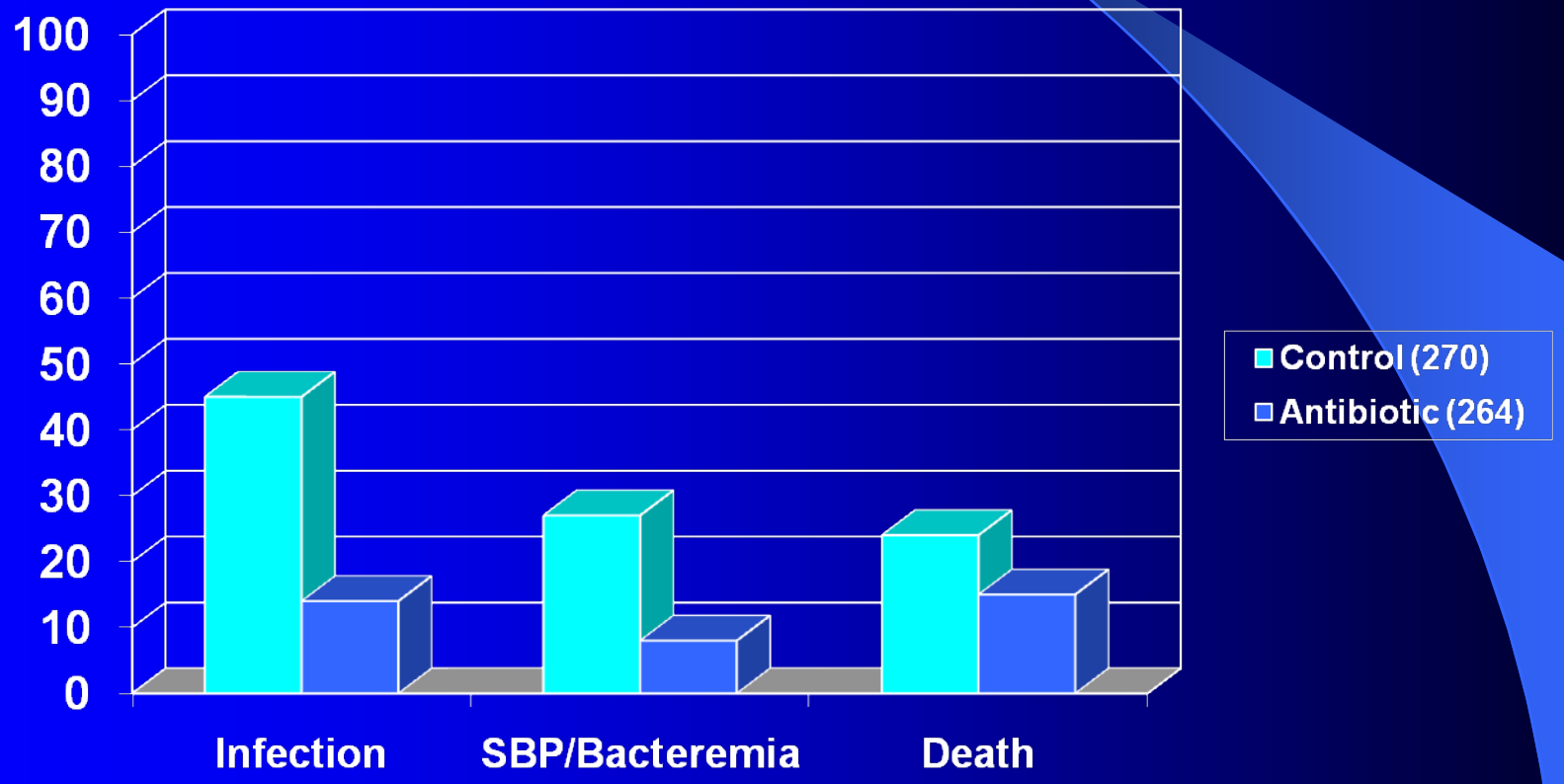
Acute Variceal Bleed

Acute Variceal Hemorrhage

- Spontaneous hemostasis = 40%
- Rebleeding = 40 %
- High mortality in: continuous bleed, rebleed & advanced disease
- Mortality = 40 % (20% with antibiotic prophylaxis)

Prophylactic Antibiotic & Outcome in Cirrhotics with GI Hemorrhage

(Barnard et al. Hepatology 1999; 29:1655)



Transfusion Strategies in Cirrhotics

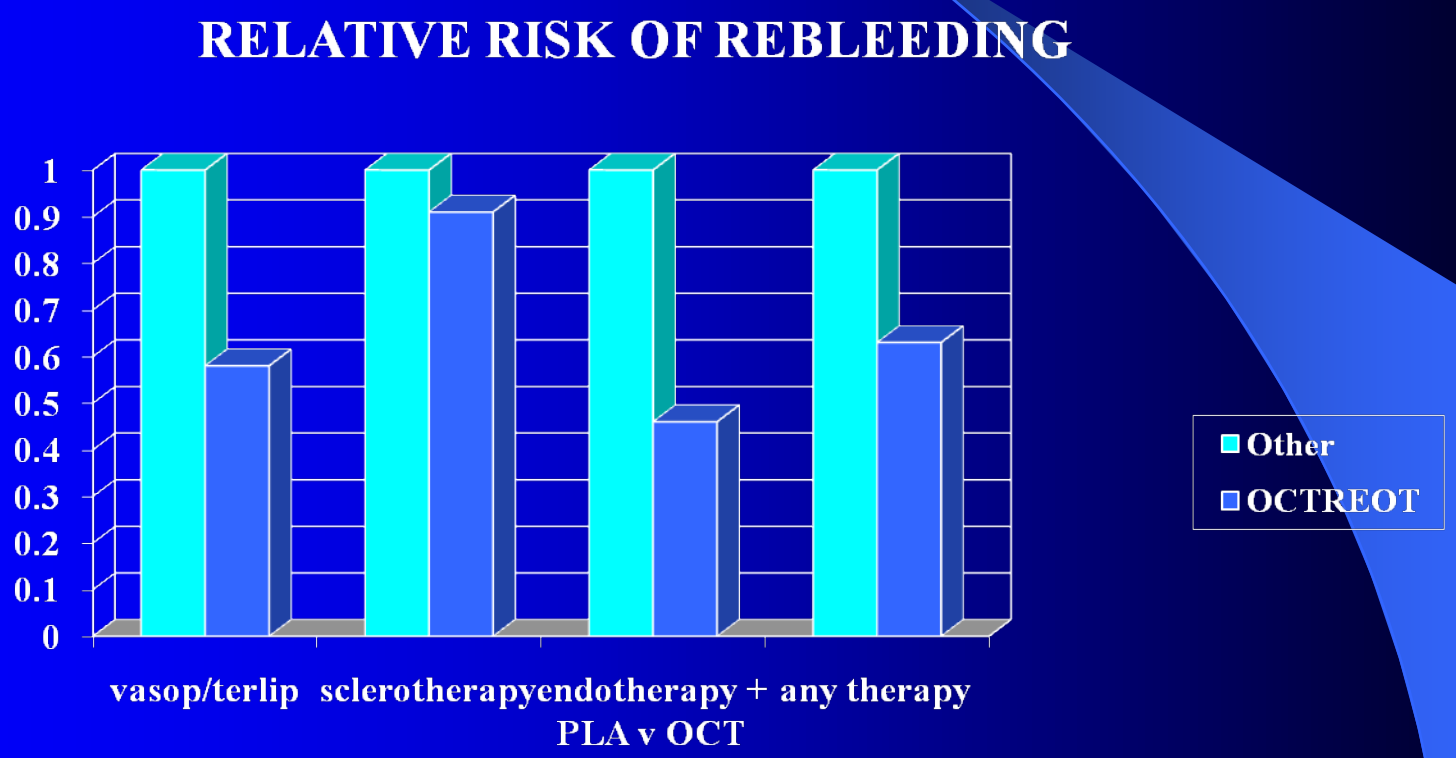
Villanueva C; N Engl J Med 2013; 368:11-21

- 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)
- Child A & B:
  - Decrease in 6 month mortality (4 vs 12%; 66% less)
  - Decrease in rebleeding rate (11 vs 21%; 10% less), and
- Child-Pugh C:
  - No difference in mortality in Child-Pugh C patients (38 vs 41%),
  - Rebleeding rate was decreased from 28% to 15% (13% less).
- Decrease in adverse events was seen in all patients.
- Liberal transfusion increases portal pressure.

Rebleed from Acute Variceal-bleed

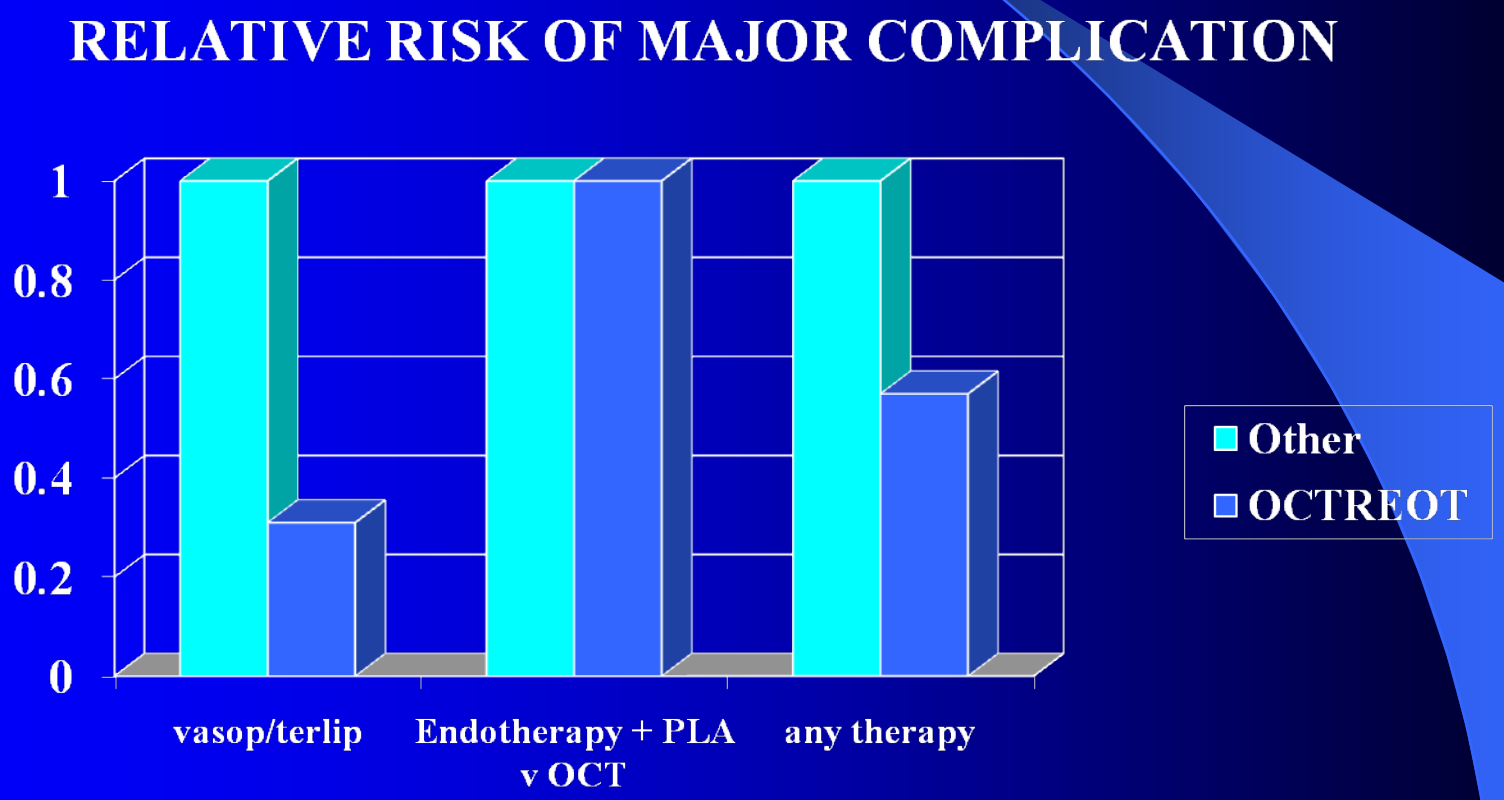
Octreotide Meta-Analysis

Gastroenterol 2001;120:946-954



Major Complications Octreotide Meta-Analysis

Gastroenterol 2001;120:946-954



Octreotide in Variceal Hemorrhage: ***Conclusions***

- ***Octreotide IV x 5 days decreases in-hospital rebleeding after endoscopic hemostasis.***
- ***When endoscopic hemostasis is not available, IV Octreotide is safer and more effective than vasopressin and as effective as endoscopic therapy.***

Esophageal Variceal Rebleed TIPS vs EBL+BB

Garcia-Pagan JC; N Engl J Med. 2010 Jun 24;362(25):2370-9

- Prospective, randomized study.
- Patients:
  - Cirrhotic Child B (score 7-9) with active bleeding at EGD, or Child C (only scores 10-13) with/without active bleeding at EGD, who had esophageal variceal bleed, and no previous endoscopic therapy nor beta-blockers.
  - All patients received antibiotics, early banding (< 12h) and octreotide, somatostatin, or terlipressin
- Treatment arms:
  - a) TIPS within 24-72h with PTFE-covered stent (N=32);
  - b) EBL q 10-14d + B-blocker + PPI +/- ISMO (N=31)

Esophageal Variceal Rebleed
TIPS vs EBL+BB

Garcia-Pagan JC; N Engl J Med. 2010 Jun 24;362(25):2370-9

- Outcomes:
  - a) Failure to control bleed or rebleed;
  - b) Mortality at 6 wks & 1 y
- Results:
  - a) Rebleeding-free at 1 y TIPS = 97%, EBL+BB = 50%; NNT:2.1
  - b) Survival @ 6 weeks: TIPS = 97%, EBL+BB = 67%; NNT 3.3.
  - c) Survival @ 1 y: TIPS = 86%, EBL+BB = 61%; NNT:4
  - d) Actuarial risk of Hepatic Encephalopathy and ascites was not increased by TIPS (both risks were decreased by TIPS)

Acute Variceal Bleed Treatment

- ***GOAL***
- *Control Hemorrhage*:
  -Local control
  -Decrease Portal Pressure
- *Prevent Rebleeding*
- *No over-expand*:
  transfuse Hct 24/Hb 8
- *Prevent Infection*

- ***INTERVENTIONS***
- ***Banding***
- Somatostatine
- ***Octreotide x 5 days***
- ***Ceftriaxone 1 g/d IV x7 days***
- Sclerotherapy (+/-)
- TIPS (rescue), or
- Early TIPS in Child C, or Child B bleeding @ EGD, if MELD < 15 (? 15-18)
- Shunt surgery (+/-) rescue (DSRS in Child A/B)

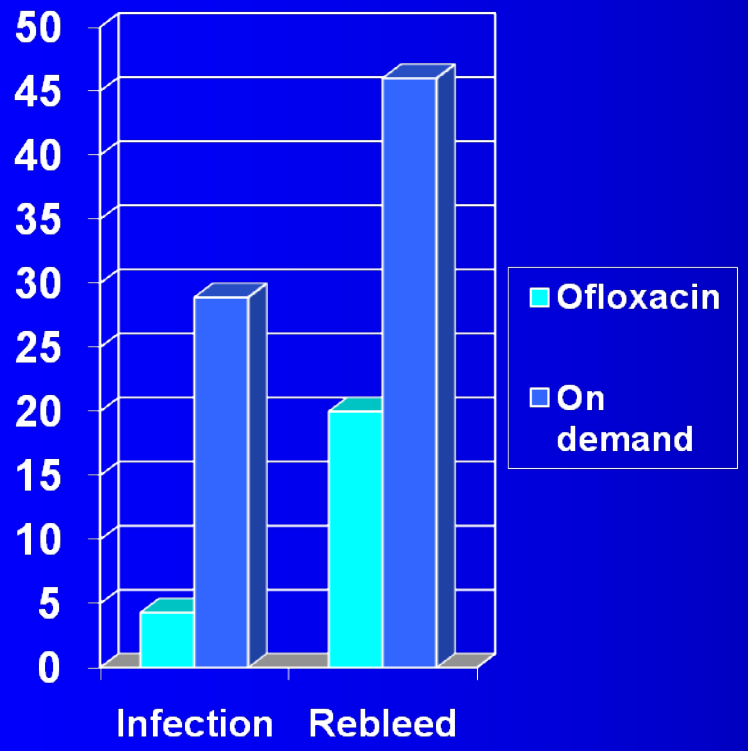
Variceal Rebleed

Immediate Prophylaxis

Effect of Antibiotic Prophylaxis on Rebleeding rate after Endoscopic treatment of Variceal bleed (283)

- Prospective, randomized.
- 91 cirrhotic patients with variceal bleed receiving endoscopic treatment
- Outcome: rate of rebleeding and infection
- Intervention: Ofloxacin 200mg BIDx 7d vs antibiotic for infection (46 vs 45)
- No difference on: age, sex, etiology, endoscopic finding, time to EGD, hepatoma, severity of bleed.

Results (%)



- ***CONCLUSION***
- Prophylactic antibiotics in variceal bleed decrease rebleeding rate and transfusion needs (0.7 vs 2.7 Units)

Practical Approach
Suspected or Proven Variceal Bleed

- Start empirical Octreotide 50 mcg bolus + 50 mcg/hour, at arrival, x 5 days.
- Selective intestinal decontamination with ceftriaxone 1 g IV/day x 7 days; start at arrival.
- Esophageal variceal bleed: Banding at arrival, then
  - Banding q 2-3 weeks until obliteration if Child A, Child B without active bleeding at EGD, or MELD score 19 or higher.
  - Early TIPS with PTFE stent if MELD score </= 18 and Child B actively bleeding at EGD, or Child C.
- Gastric variceal bleed: acute sclerotherapy or banding, followed by urgent TIPSS or shunt
  - splenectomy in splenic vein thrombosis with isolated gastric varices
- Nadolol or Propranolol or Carvedilol long term.
- Liver Transplant evaluation.

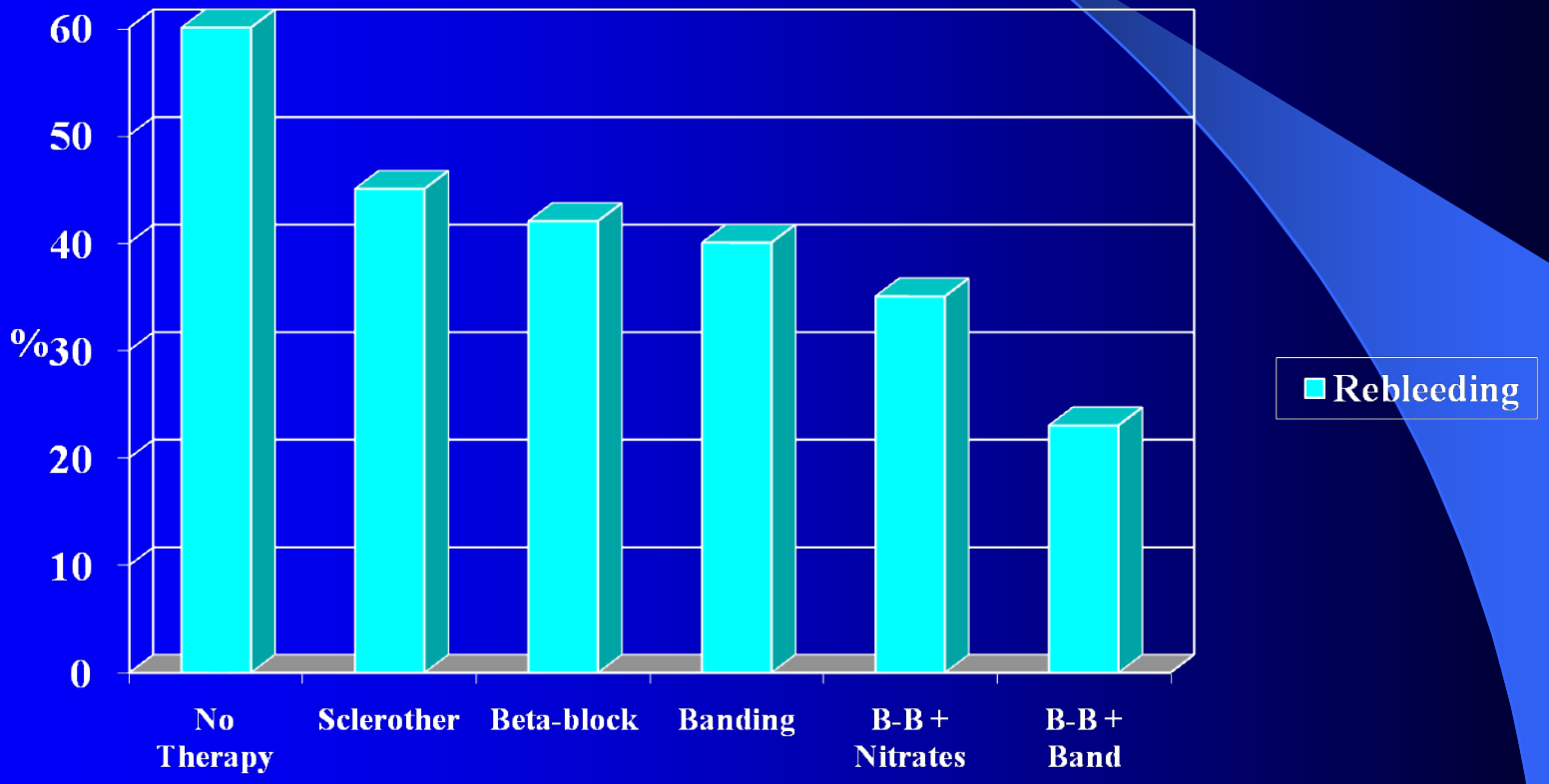
Beta Blockade +/- ISMO Protocol

- Nadolol is given orally at an initial dose of 40 mg/day; keep MAP > 82 mm Hg.
- Betablockers increase mortality in refractory ascites, especially if MAP is =/< 82; D/C betablockers and band varices if needed.
- The dose is then increased by 20 mg daily for a period of 5-7 days until:
  - intolerance appears, or
  - the heart rate decreases to 55 beats per minute, or
  - a maximal dose of 160 mg/day is reached , or
  - MAP is 84 mmHg (MAP </= 83 has high mortality in refractory ascites).
- Oral isosorbide mononitrate is started after beta blockade is reached, at 20 mg once at bedtime,
  - then followed by 20 mg twice a day for 1 day, and
  - finally increased to 40 mg BID if tolerated.

Variceal Rebleed

LONG TERM PROPHYLAXIS

LONG TERM Rebleeding Risk
Different Prophylaxis



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Practical Approach to Prevent Variceal Bleed

PREVENT 1st BLEED

- Cirrhotic: EGD q1-3 y
- No varices: re-scope
  - 1 y (decompensated) or
  - 3 y (compensated)
- F-1 (</= 5 mm) + Child B/C or red-wale = B-blocker
- F-2 varices Child A, no red-wale: Beta-blocker
- F-2 + Child B/C or red-wale: Beta-blocker and/or banding
- F-3 varices : Beta-blocker and/or banding

PREVENT RE-BLEED

- *Liver Transplant eval.*
- Early TIPS if MELD < 15 & Child B bleeding or Child C (MELD 15-18 ?)
- Banding + Beta-blocker
- Banding
- Shunt (+/-)
- Sclerotherapy (-)

Gastric Varices Classification

- GOV1: continuous with esophageal varices in lesser curvature; treat as esophageal.
- GOV2: extend from esophagus to fundus; cyanoacrylate +/- TIPSS
- IGV1: isolated fundic varices; likely splenic vein thrombosis = splenectomy.
- IGV2: isolated in antrum; rarely bleed; band or sclerose.

Gastric Variceal Bleed (GOV2)

- Causes 10-15% of variceal bleeds.
- Independent Predictors of Bleeding:
  - Varix size > 20 mm,
  - MELD >/= 17,
  - Portal HTN gastropathy.
- Vasoactive drugs + antibiotics used but not well studied.
- Cyanoacrylate injection (Dermabond) achieves hemostasis in 90%
- Balloon (Linton-Nacklas or modified Minnesota)
- TIPSS controls 90% of bleeds (goal HVPG pressure =/< 8 mmHg)

Primary prophylaxis for gastric variceal hemorrhage comparing cyanoacrylate injection to NSBB or no treatment.

Mishra SR et al. J Hepatol 2011; 54:1161–1167.

- Eighty-nine patients without any esophageal varices [GOV type 2 or isolated gastric varices (IGV) type 1] with no history of gastric variceal hemorrhage were randomized to:
  - cyanoacrylate injection (group I, $n = 30$),
  - beta-blocker (group II, $n = 29$) or
  - no treatment (group III, $n = 30$).
- RESULTS:
  - A decrease in the size of gastric varices was seen in group I, from 20 to 5mm ($P<0.01$) compared to an increase in size in groups II and III (20 to 25mm; 20 to 30mm; $P<0.01$).
  - HVPG remained elevated (>12mmHg) in groups I and III, whereas it decreased in about half of group II patients.
  - After median follow-up of 26 months, patients in groups I, II and III had an actuarial probability of overall gastric variceal hemorrhage of 13, 28 and 45% ($P = 0.003$);
  - Overall survival was not significant between groups I and II and II and III.

Portal HTN Gastropathy (PHG) vs GAVE

	PHG	GAVE
Mosaic Pattern	Present	Absent
Distribution	Proxim > Distal	Distal > Proxim
Red signs/spots	If severe	Always
Thrombi (Bx)	-	+++
Fibrohyalinosis (Bx)	+	+++
Spindle cell prolif (Bx)	+	++
Treatment	Beta-blocker, Fe, TIPSS	APC

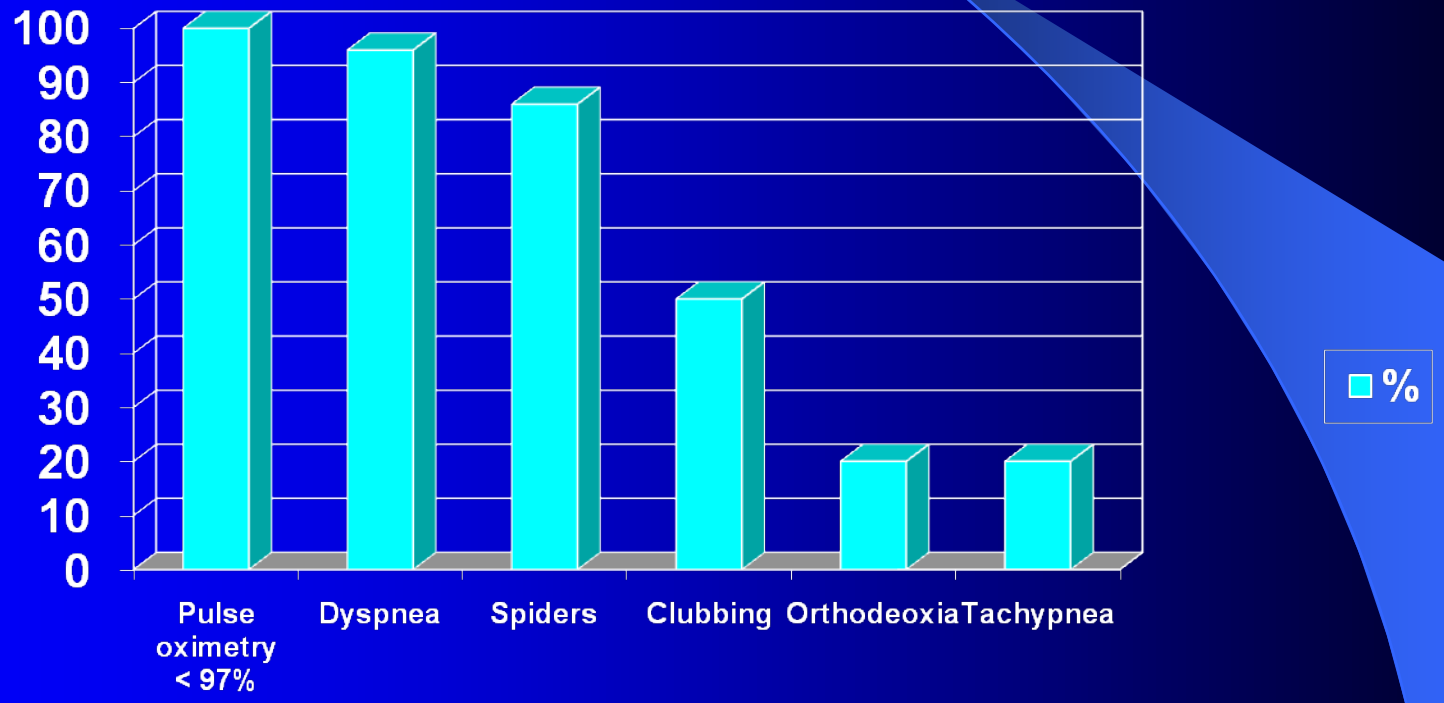
Hepatopulmonary Syndrome

- Occurs in 4-25% of LTx candidates.
- **Clinical features**: cirrhosis, absence of lung disease, cyanosis, clubbing, dyspnea, platypnea, orthodeoxia, and intrapulmonary vascular dilation.
- **Screening**: ABG (RA) if pulse oximetry < 97%
- **Criteria**: PaO_2 <70 mmHg **or** A-a O_2 gradient > 20mmHg, **plus** ECHO bubble (+) 3-6 beats after seen in Rt heart **or** Tc MAA shunt > 6% in brain.

Other Causes of HPS

- Portal vein thrombosis
- Inferior Vena Cava Obstruction
- Acute Hepatitis
- Chronic Hepatitis
- Ischemic Hepatitis

Clinical Features of HPS



Hepatopulmonary Syndrome

- Extra MELD points may be given (24 points) if PaO_2 < 60mmHg
- Worsens 5 mmHg PaO_2 per year.
- LTx mortality increases to 34% with PaO_2 < 50 mmHg or MAA shunt > 20%
- TIPS is controversial; Coil embolization of discrete A-V fistulas may help (but is uncommon)

Portopulmonary Hypertension

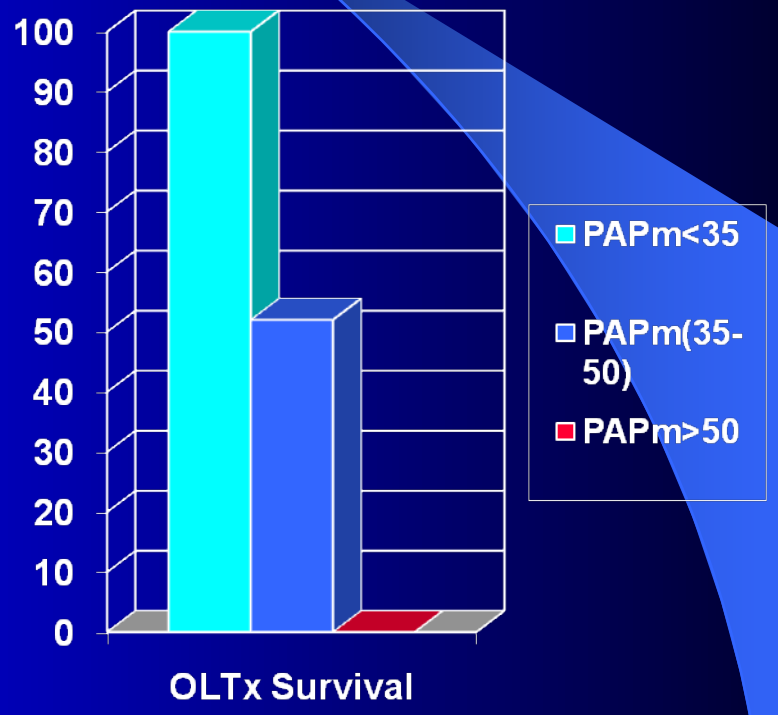
- Pulmonary hypertension in patient with portal hypertension, with or without liver disease.
- **Screening**: ECHOCARD with PAS pressure > 30 mmHg (assumes RA pressure=5 mmHg); PPV = 59%; NPV = 100%)
- **Diagnosis**: PAPm > 25 mmHg + PCWP < 15 mmHg* + Pulm. Vasc. Resist. (PVR) > 120 dynes/second/cm^{-5} .
  *(If PCWP > 15 mmHg: PAPm-PCWP > 15 mmHg)

Portopulmonary Hypertension

- **<u>Mortality with OLTx</u>:**
  - **PAPm 25-34= good LTx candidate (0% added)**
  - 100% mortality if PAPm >/= 50 mmHg,
  - 50% mortality if PAPm is 35-49 mmHg or PVR > 250dynes/sec/cm^{-5} .
    - They can be converted to LTx candidates if they responde to Epoprostenol 10-28 ng/kg/min continuous infusion;
    - 30-45% drop PAPm to values below 35 mmHg; transplantable.
    - Treatment response is re-asses at 6 month intervals.
    - Treatment has been given up to for 30 months.

Caution in PPHTN

- Avoid Beta-blockers
- Avoid Ca channel blockers
- Avoid Anticoagulation



Acute on Chronic Liver Failure

- **Definition:** acute hepatic insult in patient with chronic liver disease (without or with cirrhosis) causing bilirubin >/= 5 mg/dL and INR >/= 1.5 complicated within 4 weeks with ascites and/or PSE and associated with a high 28-day mortality (>/= 33%).

- **Group at highest risk:** Usually in patients with compensated cirrhosis or recently decompensated cirrhosis in the last 3 months.

Triggers of ACLF

- Alcohol
- Bacterial infection
- Drug or Herbal therapy/CAM.
- AIH flare-up
- Wilson disease flare-up
- HBV flare-up (HBV-DNA > $2x10^4$ IU/mL)
- HEV
- HAV/HCV/HDV
- Non-bacterial Infection
- Sepsis
- TIPS
- Paracentesis without albumin
- Surgery
- GI bleed (if causes jaundice & coagulopathy)
- Other
- 20-35 % have no precipitating factor

Sub-Types of ACLF

- By underlying Liver Disease Severity:
  - Type A: over Chronic liver disease without cirrhosis.
  - Type B: over Compensated Cirrhosis.
  - Type C: over Decompensated Cirrhosis
- By Trigger:
  - Infection related.
  - Non-infection related.

ACLF Evolving Concepts

- Infection-associated ACLF is that with evidence of infection before or within 48 h of admission.
- 2 of 3 of ACLF are not associated with infection.
  - 62% have not recognized cause.
- Mortality is slightly lower in non-infection cases.
- Infected and Non-infected patients have high WBC and CRP (both even higher in infected ones)
- 81% of ACLF develop SIRS within 7 days (1 week window)
  - 24% by day 4 + 57% more by day 7.

ACLF Evolving Concepts

- Mortality worsens with acquisition of any nosocomial infection (> 48 h after admission)
- Windows for therapy:
  - a) Best is before SIRS;
  - b) Before sepsis.
- In HRS, noradrenaline is better tolerated than terlipressin
- If AKI does nor improve, CRRT is better than SLED.
- Brain edema may occur in PSE of ACLF; need to follow ammonia level to guide therapy.
- In MELD > 30 or refractory HRS-1, MARS or Helios may help as bridge to OLTx.

Definitions in ACLF

ORGAN FAILURE

- **Coagulation:** INR > 2.5 (mortality OR 6.8)
- **Kidney:** Creat > 2 mg/dL (mortality OR 6.3)
- **Liver:** Bili > 12 mg/dL (mortality OR 3.9)
- **Brain:** HE III or IV (mortality OR 3.9)
- **Lung:** SpO_2/FiO_2 </= 214 (mortality OR 2.8)
- **Circulation:** need of inotropes (mortality OR 2.2)

GRADES OF ACLF

- **ACLF-1:**
  - renal failure (creat > 2 mg/dL), or
  - nonrenal organ failure associated with:
    - creatinine 1.5-2 mg/dL and/or
    - grade I-II encephalopathy
- **ACLF-2:** 2 organ failures
- **ACLF-3:** 3 organ failures, (78% 90-d mort for 3 or more OF)
- **ACLF-4:** 4-6 organ failures

CLIF Organ Failure Score

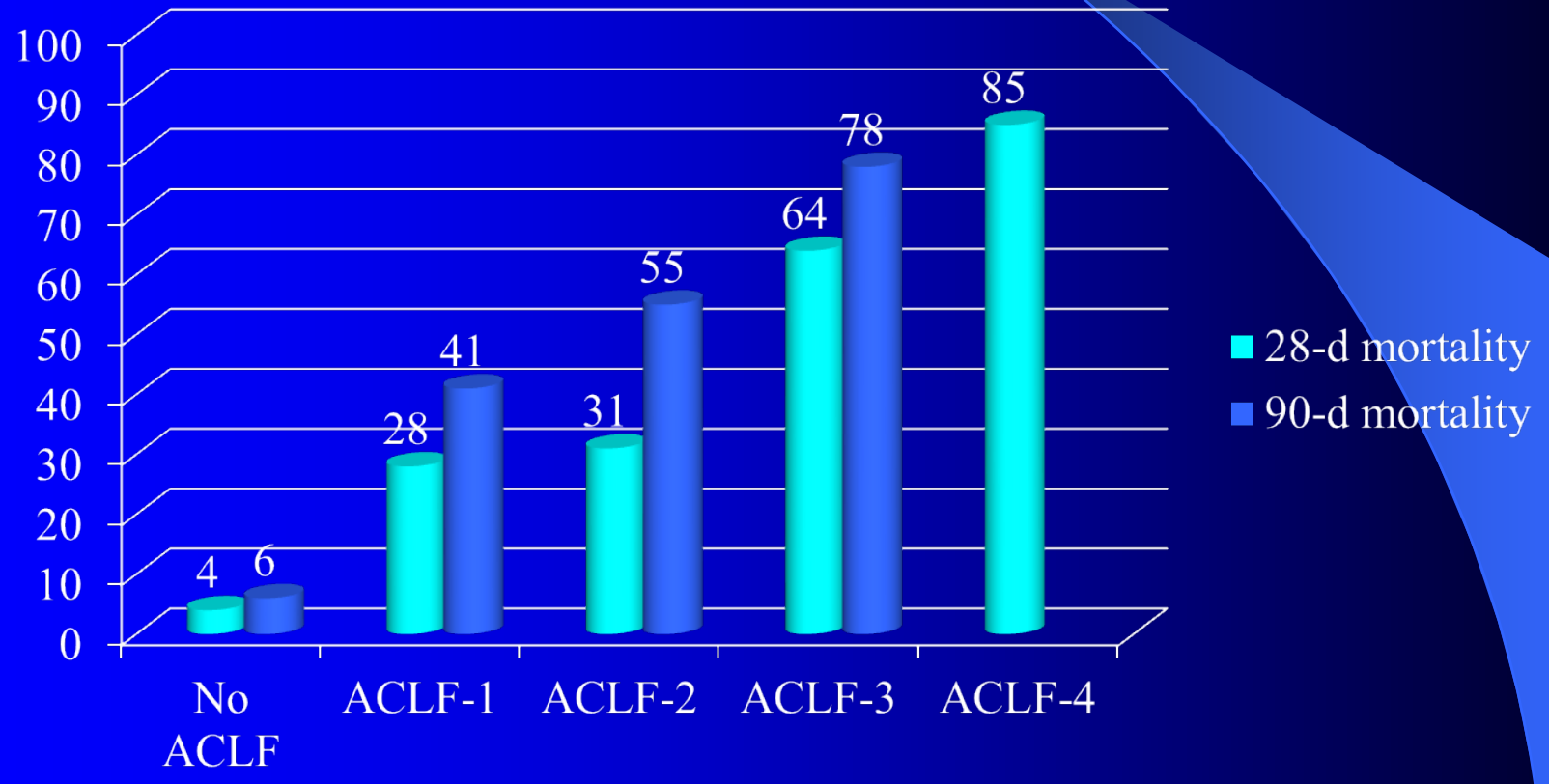
Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin <6 mg/dl	Bilirubin ≥6 mg/dl and <12 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <2 mg/dl	Creatinine ≥2 mg/dl and <3.5 mg/dl	Creatinine ≥3.5 mg/dl or renal replacement
Brain (West-Haven grade for HE*)	Grade 0	Grade 1-2	Grade 3-4**
Coagulation	INR <2.0	INR ≥2.0 and <2.5	INR ≥2.5
Circulatory	MAP ≥70 mmHg	MAP <70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	 >300 or >357	 ≤300 and >200 or >214 and ≤357	 ≤200# or ≤214#

**Patients submitted to Mechanical Ventilation (MV) due to HE and not due to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore = 3).
#Other patients enrolled in the study with MV were considered as presenting a respiratory failure (respiratory subscore = 3).

ADD ALL POINTS (Minimum 6; Maximum 18)

Mortality of ACLF

28 and 90 days



The CLIF Consortium ACLF Score (CLIF-C ACLF)

- CLIF-C ACLF = 10 x [0.33 x CLIF-OFs + 0.04 x Age + 0.63 x ln (WBC count) – 2]
- The probability of death (P) at time “t” is:
  - $P = 1-e[-CI(t)\times\exp(\beta(t)\times\text{CLIF-C ACLFs})]$
- http://www.clifresearch.com/ToolsCalculators.aspx

Prevention of ACLF

- Avoid infections, especially nosocomial infections:
  - PPI avoidance
  - Foley catheter avoidance
  - Minimization of duration and optimization of IV line management
  - Oral care (chlorhexidine)
- Avoid other known triggers of ACLF
  - Proper use of Albumin in LVP
  - Judicious use of antibiotic prophylaxis (d/c in past quinolone resistance)
  - Avoid hepatotoxins
  - Drug minimization
  - PPI avoidance
  - Good compliance with drug therapy (AIH, HBV, Wilson)
  - Recognition & management of HBc(+) and HBsAg before immunosuppression

Therapy of ACLF

- ICU management
- Treat HRS early
- Guided antibiotic use with narrowing of spectrum once sensitivity is known
- G-CSF
- Selective use of MARS/Prometheus (as bridge to Liver Tx)
- Liver Tx

G-CSF Use

(Shiv Kumar Sarin)

- Contraindications for g-CSF
  - Sepsis, severe sarcopenia, severe anemia, AKI
  - Macrophage activation syndrome
  - Ferritin > 1000 ng/mL, high LDH, skin with “slate gray color”
  - Plasmapheresis
- Predicting good response to g-CSG
  - BM Bx with:
    - high osteoblasts,
    - high CD34,
    - low vascularity,
    - low perivascular fibrosis,
    - high Hematopoietic Stem Cells (HSC), Multi Potential Progenitors (MPP), and Common Myeloid Progenitors (CMP).

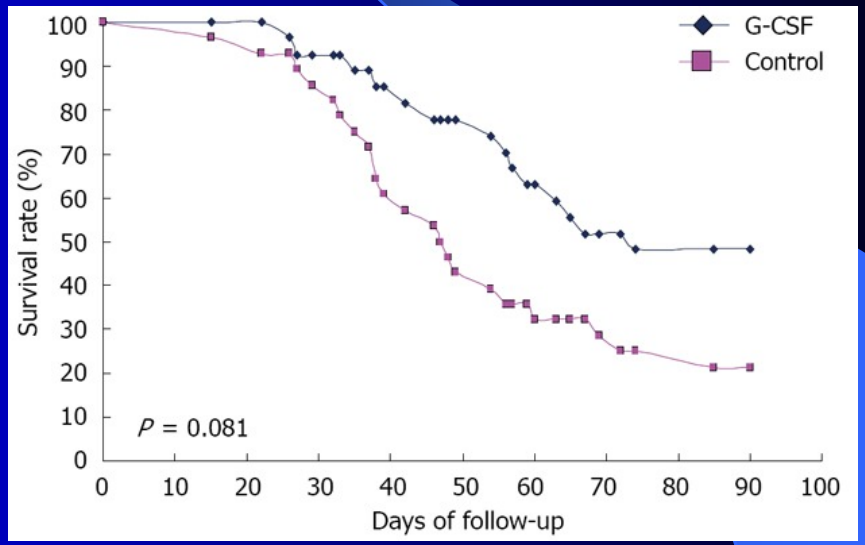
Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure

Duan XZ et al. World J Gastroenterol 2013 Feb 21;19(7):1104-10

g-csf 5 mcg/kg/d SQ x 6 days vs
Placebo (+ Entecavir in all)

Parameters	G-CSF group (27)	Control group (28)	*P* value
Gender (male %)	22 (81.5)	22 (78.6)	0.755
Age (yr)	43.5 (29-63)	45.9 (22-65)	0.332
WBC (10^9/L)	5.79 ± 1.81	6.61 ± 1.71	0.443
Neutrophil (10^9/L)	3.53 ± 1.46	3.82 ± 1.17	0.114
Platelets (10^9/L)	182 (147-215)	174 (149-175)	0.680
ALT (U/L)	276 (197-801)	252 (189-1239)	0.430
AST (U/L)	246 (195-788)	251 (187-980)	0.544
Total bilirubin (μmol/L)	336 (181-519)	320.0 (174.5-519.8)	0.605
Cr (μmol/L)	83.8 ± 16.9	85.4 ± 53.87	0.475
INR	2.11 ± 0.28	2.34 ± 0.34	0.606
ALB (g/L)	29.11 ± 4.05	28.75 ± 4.63	0.596
HBV DNA (log_{10})	5.11 ± 1.37	5.55 ± 1.59	0.280
CTP score	12.17 ± 1.47	12.25 ± 1.29	0.349
MELD score	25.11 ± 3.30	26.30 ± 4.12	0.588

SURVIVAL



G-CSF therapy promoted CD34(+) cell mobilization in patients with HBV-associated ACLF, and improved the liver function and the survival rate of these patients.

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

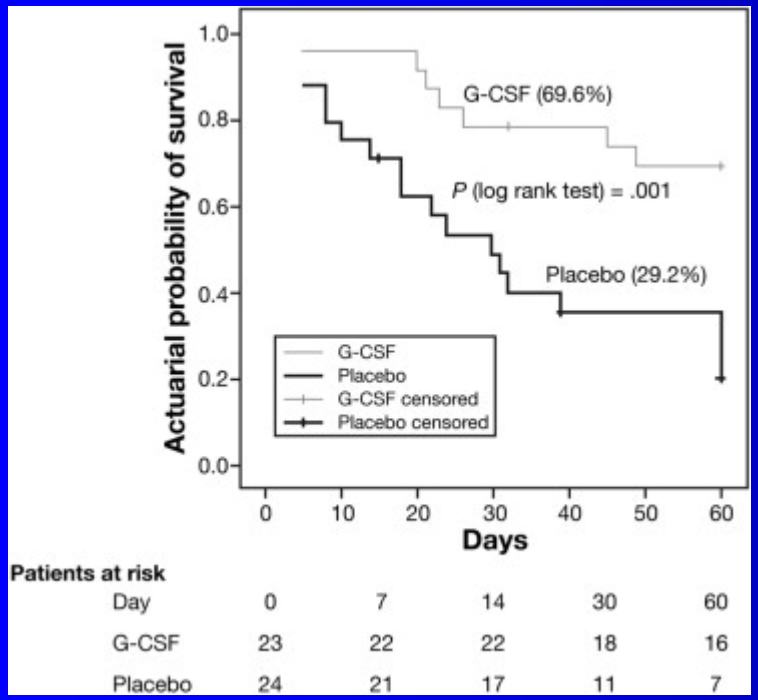
Parameters	Group A (n = 23)	Group B (n = 24)	*P* value
Male/female	20/3	21/3	.71
Age (*y*)	40 (30–65)	40 (19–55)	.70
Ascites	23 (100)	24 (100)	1
Total leukocyte count ($\times 10^3/mm^3$)	10.7 (3.9–22.1)	11.8 (3.8–28.7)	.34
Absolute neutrophil count ($\times 10^3/mm^3$)	8.3 (2.4–19.1)	8.7 (3.1–26.6)	.43
Platelets ($\times 10^3/mm^3$)	128 (50–265)	143 (75–186)	.90
Sodium (*mEq/dL*)	131 (124–138)	130 (115–146)	.19
Creatinine (*mg/dL*)	0.8 (0.5–3.7)	1.0 (0.3–4.9)	.06
Bilirubin (*mg/dL*)	25.6 (9.0–43.5)	23.9 (6.2–36.1)	.53
INR	2.20 (1.66–3.92)	2.71 (1.70–4.53)	.12
ALT (*IU/L*)	65 (21–250)	86 (34–247)	.11
Albumin (*g/dL*)	2.6 (1.8–3.5)	2.5 (2.0–3.8)	.27
Encephalopathy	5 (10.6)	8 (17)	.51
Grade of encephalopathy	2 (1–2)	2 (1–2)	.28
Grade of varix (n = 42)	2 (0–3) (n = 22)	2 (0–4) (n = 20)	.32
Grade of varices ≥2	15 (65.2)	17 (70.8)	.76
Hepatorenal syndrome	4 (8.5)	5 (10.6)	1
HBV DNA $\log_{10}$ (*IU/mL*) (n = 11)	5.34 (5.04–6.60) (n = 4)	5.50 (4.76–7.93) (n = 7)	.91
HVPG (*mm Hg*) (n = 21)	16 (13–28) (n = 11)	19.25 (11–30) (n = 10)	.32
Fibrosis score (modified Ishak) (n = 18)	4 (0–5) (n = 10)	4 (0–4) (n = 8)	.237
CTP score	12 (11–14)	12 (10–14)	.91
MELD score	29 (21–40)	31.5 (20–40)	.069
SOFA score	5 (4–9)	6 (4–10)	.40

Acute event	Group A	Group B
Alcoholic hepatitis	15 (65)	12 (50)
Reactivation of hepatitis B virus	4 (17)	6 (25)
Antitubercular therapy	2 (9)	1 (4)
Hepatitis E virus infection	1 (4)	2 (8)
Cryptogenic	1 (4)	3 (12)
Underlying chronic liver disease		
Alcoholic liver disease	17 (74)	12 (50)
Hepatitis B	4 (17)	7 (30)
Cryptogenic	2 (9)	4 (16)

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

Survival: [g-csf 5 mcg/kg/d x 5 d; then q 3rd d x 7 more doses] vs [Placebo]



Considerations + Conclusion

- Patients with HCC or sepsis were excluded.
- The percentages of patients who developed hepatorenal syndrome, hepatic encephalopathy, or sepsis were lower in the g-csf group than in the placebo group (19% vs 71% [*P* = .0002], 19% vs 66% [*P* = .001], and 14% vs 41% [*P* = .04], respectively
- Survival was higher in the g-csf group (69.6 %) than in the placebo group (29.2%)

Granulocyte Colony-Stimulating Factor in Severe Alcoholic Hepatitis: A Randomized Pilot Study

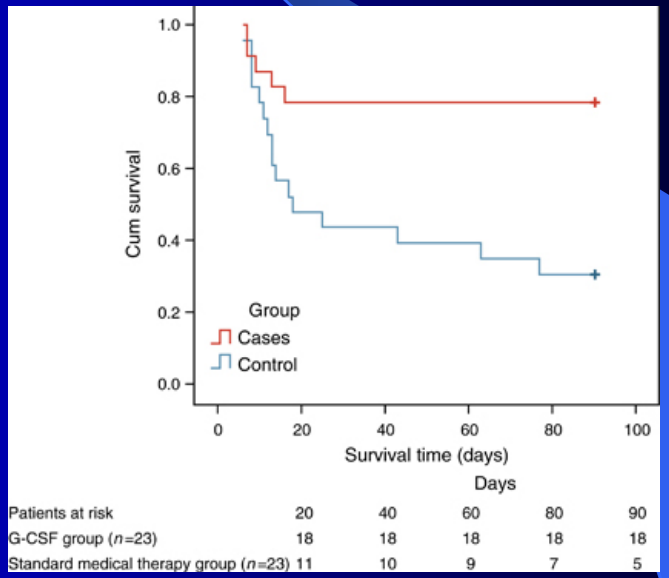
Singh V et al. Am J Gastroenterol 2014 Sep;109(9):1417-23

g-csf 5 mcg/kg BID SQ x 5 d vs Placebo (All had PTX 400 TID + Nutrition)

Variables	Group A (G-CSF; *n*=23)	Group B (SMT; *n*=23)	*P* value
Age (years)	41.7±7.5	44.3±13	0.417
Sex (M/F)	23:0	23:0	
Duration of symptoms before admission (days)	13.6±5.3	16.1±8.4	0.395
Total leukocyte count (/mm^3)	13,735±8,680	17,830±9,770	0.140
Platelets (/mm^3)	143,050±74,500	171,430±77,280	0.211
Bilirubin (mg/dl)	20.1±11.5	20.0±11.4	0.994
Alanine aminotransferase (IU/l)	101±41	136±95	0.118
Alkaline phosphatase (IU/l)	124±50	137±73	0.484
Albumin (g/dl)	3.0±0.7	2.8±0.5	0.437
Prothrombin time (s)	31.1±14	27.9±7.2	0.33
International normalized ratio	2.5±1.2	2.3±0.9	0.523
Sodium (mEq/dl)	135±8	135±9	0.762
Serum creatinine (mg/dl)	1.04±0.50	1.25±0.41	0.138
CTP score*	12	12	0.403
mDF score*	85.5	79.2	0.398
MELD score*	27	30	0.538
CD34+ cells	0.31±0.45	0.15±0.2	0.51

Excluded HCC, uncontrolled infection, Portal V. thrombosis, previous corticosteroid use.

Survival + Conclusion



G-CSF is safe and effective in the mobilization of hematopoietic stem cells and improves liver function as well as survival in patients with severe alcoholic hepatitis

Cirrhotic Cardiomyopathy

- May occur in cirrhosis of any etiology.
- Abnormal cardiac contractility in cirrhotic, with blunted response to cardiac stimulation test.
- Pathogenesis:
  - a) Abnormality in membrane fluidity, due to changes in lipid content, causing attenuation of beta-adrenergic receptor signaling.
  - b) Increased inducible NO Synthase (iNOS), causing increased activity of cGMP inhibitory pathways.
  - c) Increased cardiac production of endo-cannabinoid (anandamine), depressing ventricular contractibility.
  - d) Alteration in K and Ca channels, causing QT prolongation

Cirrhotic Cardiomyopathy

- Diagnosis:
  - 1) Abnormal inotropic & chronotropic response to exercise or drug stress-test.
  - 2) Echocardiogram showing diastolic dysfunction, with decreased E wave velocity and increased A wave velocity, causing a low E/A ratio.
  - 3) Dynamic cardiac MRI showing diastolic dysfunction.
  - 4) QT prolongation > 440 ms
- Potential consequences:
  - a) Higher risk of HRS,
  - b) Post-TIPSS CHF,
  - c) Post-LTX CHF.

Cirrhotic Cardiomyopathy

- Cirrhotic cardiomyopathy is reversible after LTX; reversal takes a mean of 9 months.
- Treatment:
  - Rest, Na restriction, diuretics, oxygen supplementation, beta-blockers, potassium canreonate.
  - Digoxin, dobutamine, and angiotensin-converting enzyme inhibitors are not helpful.

QUESTIONS ?

3-month Mortality in Cirrhosis by MELD Score

Wiesner R et al. Gastroenterology 2003;124:91-96

MELD	3-month mortality (%)	MELD	3-month mortality (%)
10	1.6	**26**	19
11	1.8	**27**	22
12	2.2	**28**	25
13	2.5	**29**	29
14	*3*	**30**	34
15	*3.5*	**31**	38
16	*4*	**32**	43
17	*5*	**33**	49
18	*6*	**34**	54
19	*7*	**35**	60
20	*8*	**36**	66
21	*9*	**37**	72
22	*11*	**38**	78
23	*12*	**39**	83
24	*14*	**40**	88
25	*17*		

Treatment of ascites

- **Peritoneal venous “shunt”**
  - Indication
    - Refractory ascites
    - Hepatorenal syndrome (?)
  - Effects
    - ⇧ transiently cardiac output
    - ⇧ glomerular filtration
    - ⇩ aldosterone, renin & catecholamines near normal
    - Improves cell mediated immunity

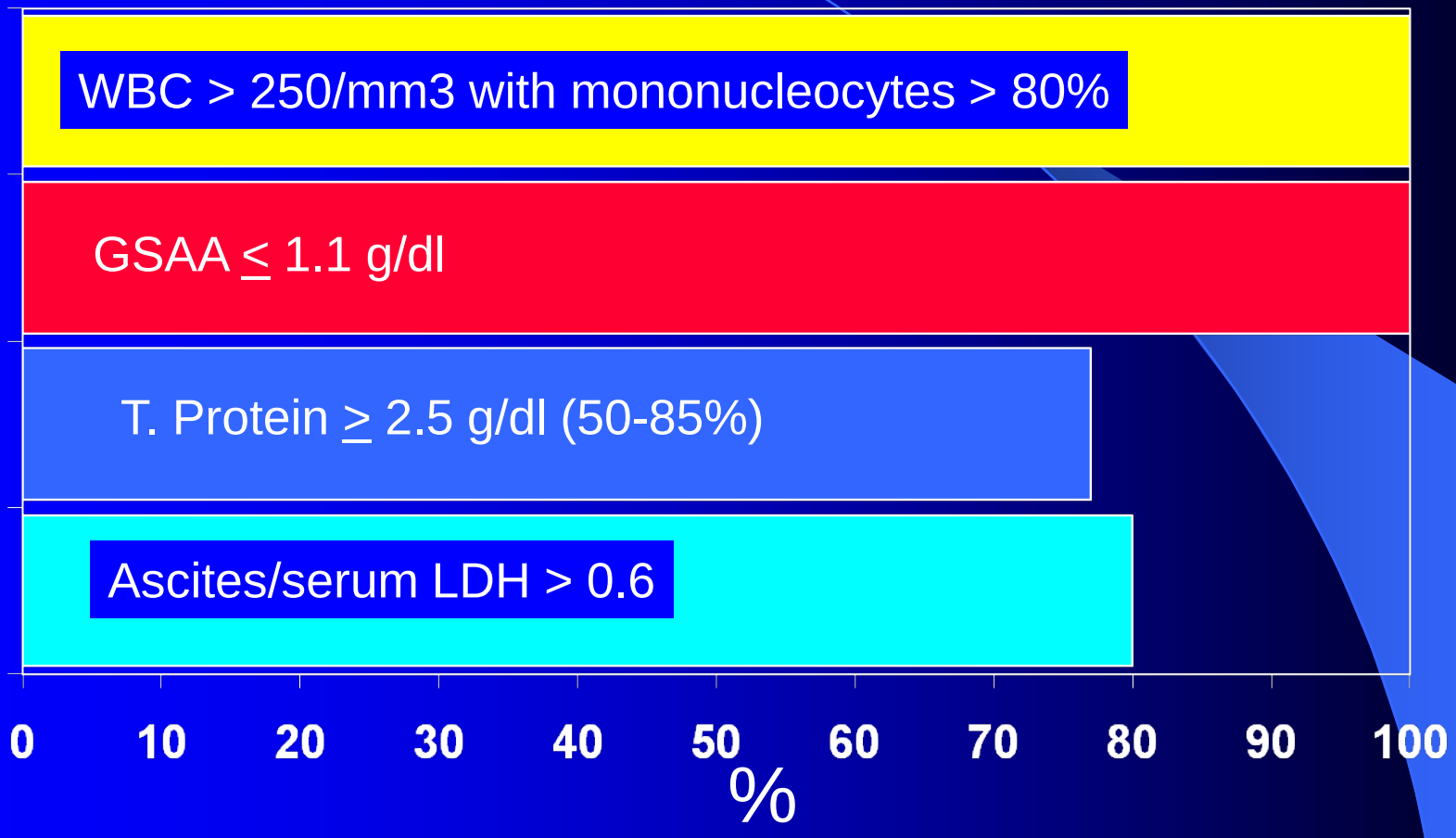
Treatment of Ascites

- Complications
  - Coagulopathy – 70%
  - Infection – 25%
  - Variceal bleed
  - Central venous thrombosis – 22%
- Effectiveness
  - 50% free of ascites at 1 year
  - No effect on mortality at 1 year
  - Mortality at 1 year is 75% in patients with bilirubin $\geq$ 3 mg/dl

Tuberculous Peritonitis

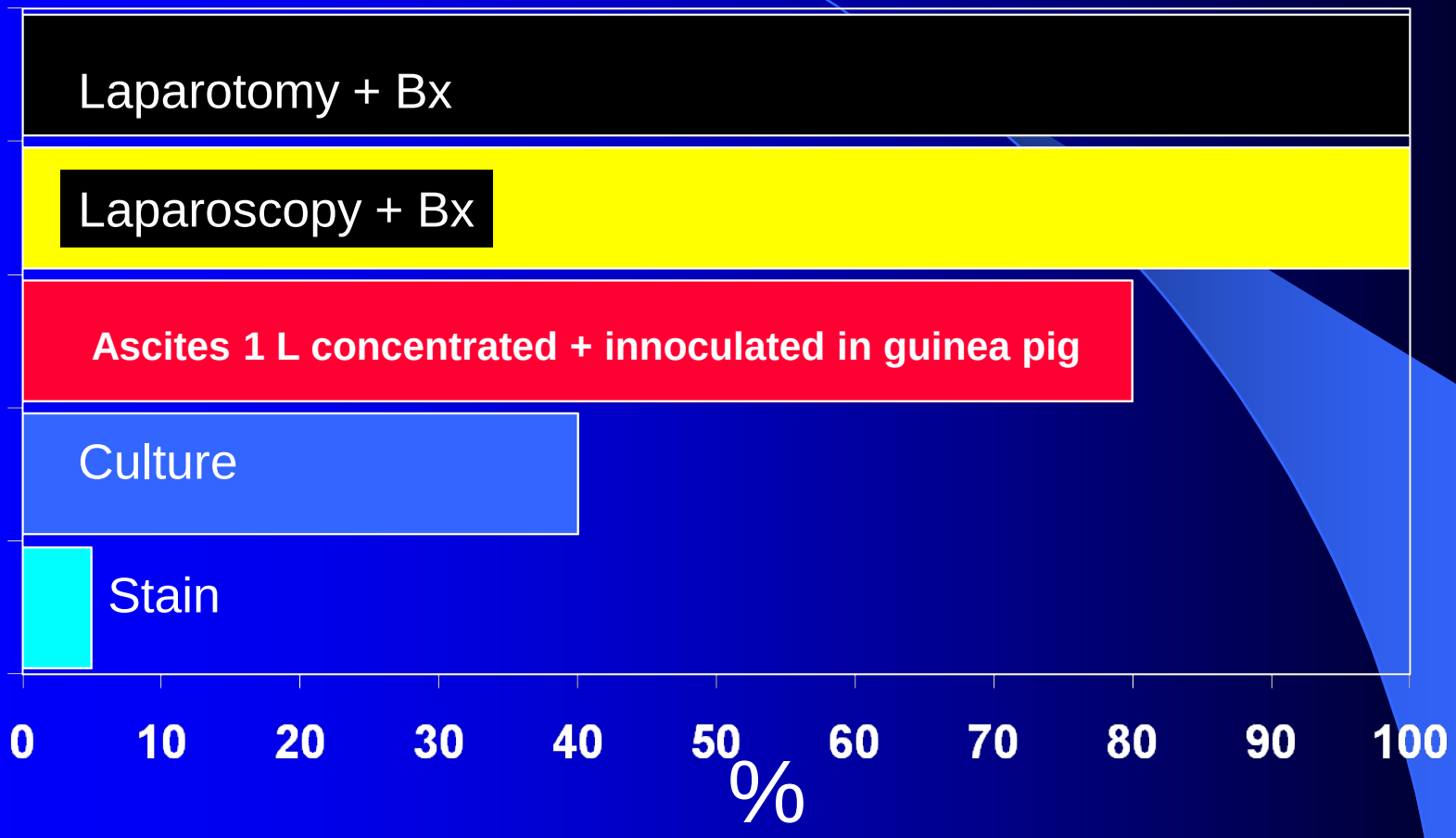
- **Pathophysiology**: infection of peritoneum causes exudate of protein which "pulls" fluid for oncotic balance;
- Classically SAAG is < 1.1 g/dl, and many patients have underlying cirrhosis → mixed ascites (SAAG $\geq$ 1.1 g/dl)

Characteristics of Tuberculous Peritonitis



- 78% serum glucose < 100 mg/dl
- 5-10% bloody

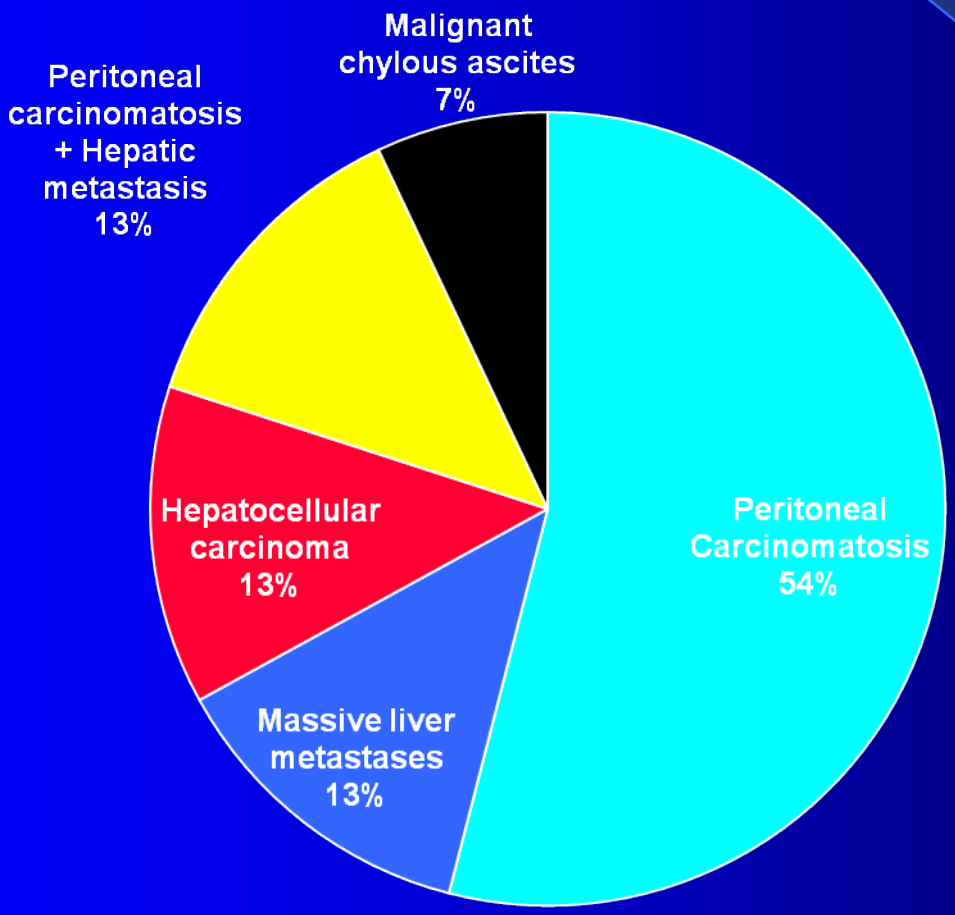
Diagnosis of Tuberculous Peritonitis



Tuberculous Peritonitis

- Mortality without therapy: 60%
- Treatment:
  - Anti-tuberculous agent
  - Anti-fungal agent

Causes of Malignant Ascites



Peritoneal Carcinomatosis (54%)

- Peritoneal protein exudate pulls fluid : SAAG < 1.1
- Other characteristics:
  - WBC >500
  - T. protein > 2.5 g (usually – 4.0)
  - LDH > 225 (usually – 1000 IU/L)
  - Glucose < 100 in 71%
- Cytology (+)

Massive hepatic metastases (13%)

- **Portal hypertension : SAAG > 1.1g/dl**
- **Bloody in 10%**
- **Cytology negative**

Peritoneal Carcinomatosis + liver metastases (13%)

- Mixed ascites : SAAG >1.1g/dl
- Bloody in 10%
- Cytology (+)
- WBC > 500 with dominant lymphocytes

Hepatocellular carcinoma (13%)

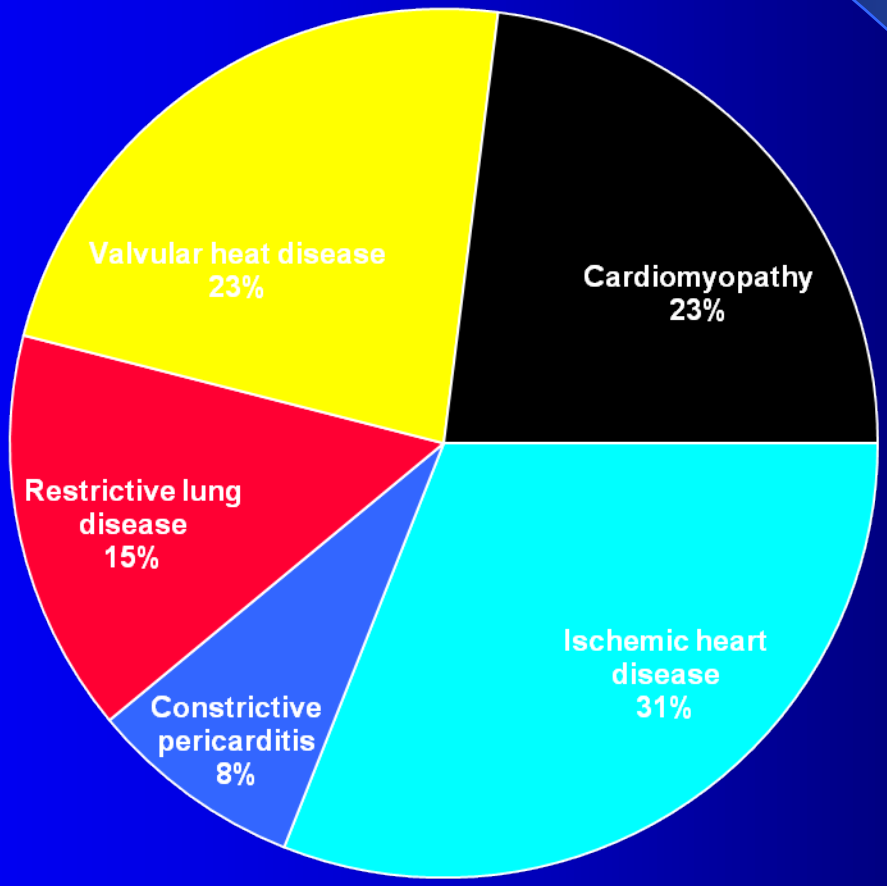
- Portal hypertension (cirrhosis +/- portal vein thrombosis)
- SAAG > 1.1g/dl
- Bloody in 50%
- Alpha-fetoprotein high (serum > ascites)
- Cytology negative

Malignant chylous ascites (7%)

- Lymph leak due to invasion of lymph nodes with rupture of lymphatic vessels
- Characteristics: SAAG < 1.1g/dl, triglycerides > 81 mg/dl or > plasma triglycerides (usually > 1000 mg/dl)
- Bloody in 10%
- Cytology is variable

Cardiac Ascites

Passive congestion causes portal hypertension : SAAG ≥1.1g/dl (100%)



Cardiac ascites

- Characteristics:
  - SAAG > 1.1 g/dl (100%)
  - T. protein > 2.5 g/dl (100%)
  - LDH < upper limit of normal (100%)
  - WBC is variable 480 $\pm$ 490/mm^3
  - PMN < 250/mm^3
- Treatment: underlying disease

Pancreatic Ascites

- Pancreatic duct or pseudocyst rupture in chronic alcoholics
- Up to 50% with cirrhosis (SAAG $\geq$1.1 mg/dl)
- Characteristics
  - Amylase > 1000
  - SAAG < 1.1 mg/dl
  - T. protein > 2.5 g/dl (100%)
  - High LDH (~2000 IU/L)
  - High WBC (~4000/mm^3)
  - High PMN (~3000/mm^3)
  - Glucose variable
- Secondary infection occurs in 25%
- Treatment: stenting, surgery, octreotide, bowel rest

Nephrotic ascites

- Hypoalbuminemia ➡ decreased effective arterial blood volume ➡ activation of renin/aldosterone/vasopressin/norepinephrine ➡ renal Na and water retention ➡ edema + ascites
- Characteristics
  - SAAG < 1.1g/dl
  - T. protein – 0.6 g/dl
  - Glucose - 100 mg/dl
  - LDH ascites/serum < 0.5
  - WBC < 250/mm^3
  - PMN few
- Treatment: Na restriction and diuretics

Nephrogenous ascites

- Unknown etiology
  - Patients on hemodialysis
  - 50% have cirrhosis
- Characteristics
  - SAAG < 1.1 g/dl in 50%
  - Protein > 2.5 g/dl (100%)
  - LDH < upper limit of normal 100%
  - Glucose > 100 mg/dl
  - WBC < 500/mm^3 in 75% (350$\pm$225), mostly lymphocytes
  - PMN < 250/mm^3
- Laparoscopy + bx to rule out cirrhosis + TB
- Treatment: vigorous dialysis

Biliary ascites

- Perforation of gall bladder, bile duct or proximal gut produces bile leak
- Characteristics
  - Bilirubin in ascites > 3 mg/dl and ascites/serum bili > 1
  - SAAG < 1.1 g/dl but variable (1.2±0.5)
  - LDH – 2500 IU/L
  - T. protein > 2.5 g/dl (2.6±0.2)
  - Glucose variable (90±85 g/dl)
  - WBC – 3400
  - PMN – 3000
  - Amylase usually not elevated (except in intestinal perforation)
- Usually monomicrobial
- Treatment: stenting, surgery

Hepatorenal Syndrome Major Criteria

HEPATOLOGY 1996;23:164-176

- Chronic or Acute Liver Disease + Hepatic Failure + Portal Hypertension.
- Low GFR (Cr>1.5 mg/dL or CrCl<40 ml/min)
- Absence of: shock, infection, nephrotoxin, volume depletion.
- No Response to: diuretic withdrawal + 1.5 L 0.9% NaCl infusion.
- Proteinuria <500 mg/dL & U/S without obstruction or parenchymal renal disease.

Hepatorenal Syndrome Minor Criteria

HEPATOLOGY 1996;23:164-176

- Urine Volume < 500 mL/d.
- Urine Na < 10 mEq/L.
- Urine Osm > Plasma Osm
- Urine RBC < 50/hpf
- Serum Na < 130 mEq/L

Midodrine & Octreotide

- ***MIDODRINE***
- Alpha-1-adrenergic agonist (arteriolar and venous constriction)
- Increases renal perfusion
- Increases blood pressure

- ***OCTREOTIDE***
- Decreases glucagon (vasodilator)
- Splachnic arterial vasoconstriction
- Increases GFR

Midodrine + Octreotide vs. Dopamine *Hepatology 1999;29:1690-1697*

- Patients: 15 consecutive, Type 1 HRS by 5 major criteria
- Two excluded: Heart disease & DM
- First 8: Dopamine + Albumin
- Next 5: Midodrine + Octreotide + Albumin

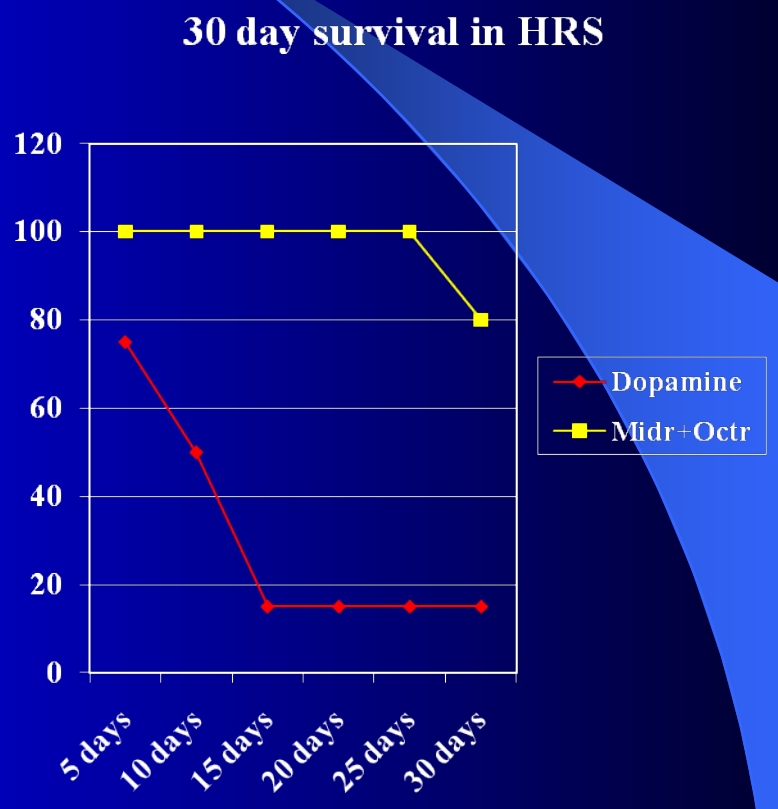
Hepatorenal Syndrome Midodrine + Octreotide

Hepatology 1999;29:1690-1697

- IV albumin to CVP of 12 mm Hg to all pat.
- Dopamine 2-4 mcg/kg/h IV infusion
- Midodrine 7.5-12.5 mg p.o. TID
- Octreotide 100-200 mcg SQ TID
- Goal: Plasma Renin Activity reduced > 50% after 3 days of therapy, and/or raise MAP > 15 mmHg

Hepatorenal Syndrome
Midodrine + Octreotide
Hepatology 1999;29:1690-1697

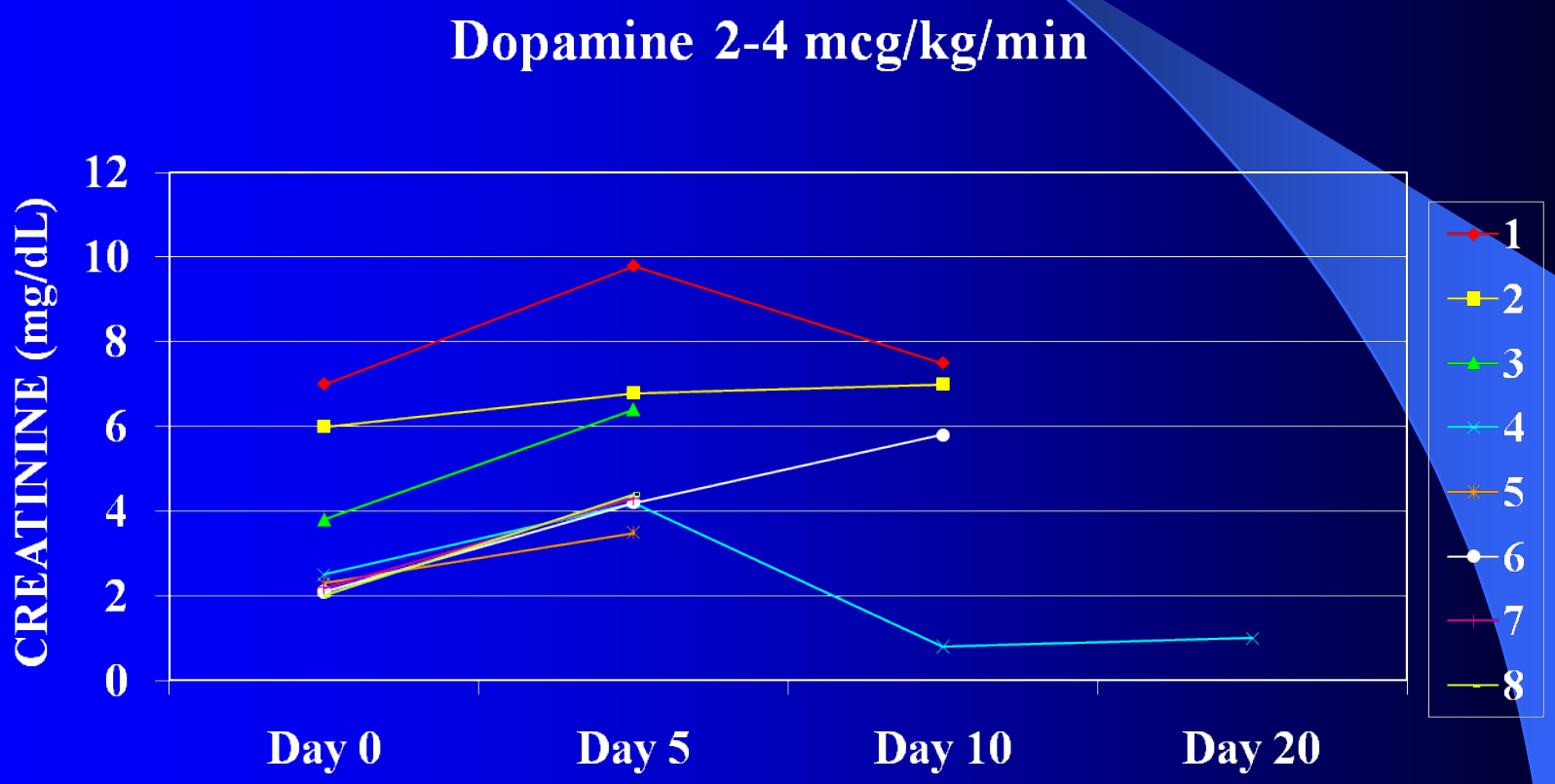
- Ascites + Cr >2mg/dl
- Off diuretics 5 days
- IV albumin .8-1.5 L/d x4
- Urine Na <10 mEq/L
- Normal sediment & Renal U/S
- No infection or shock
- MAP effect: active group increased from 75.9+/-3 to 90.9+/-5.2 @ 5d, and 96.9+/-6.5 @ day 10



HRS + Low Dose Dopamine

Serum Creatinine (mg/dL)

Hepatology 1999;29:1690-1697



HRS-I & Noradrenaline + Albumin
(Duvoux et al. Hepatology 2002;36:374-380)

- Type I HRS
- Consecutive 12 cirrhotic patients
- Prospective
- Exclusion: Child-Pugh > 13, CAD, obstructive cardiomyopathy, ventricular arrhytmia, obliterative arterial disease of lower limbs, infection within last week.

HRS-I & Noradrenaline + Albumin
(Duvoux et al. Hepatology 2002;36:374-380)

- Age 54+/-11
- Child-Pugh 11.3+/-1.7
- Bili 16.6+/-10.3
- Creatinine 2.7+/-1.1
- Cr Clearance 16.1+/-14
- Serum Na 123+/-6
- Urine Na 10+/-16
- Urine volume 697+/-555

HRS-I & Noradrenaline + Albumin
(Duvoux et al. Hepatology 2002;36:374-380)

- **Volume Expansion x 48 h** :
  -20% albumin infusion to goal CVP > 4
  -Lasix 120mg IV Q4 to goal U/O 25cc/h
- **If creatinine not improved and U/O <600cc/d**:
  -Noradrenaline 0.5 mg/h and increased by 0.5mg/h q4h (max 3 mg/h) until MAP increases by > 10 mmHg, and U/O to > 50cc/h
- **End point**: resolution of HRS (Cr<1.5 or CrCl >40cc/min) or 15 days.
- **MAP effect**: raised from 65+/-7, to 74+/-7 mmHg

N-Acetylcysteine

- Antioxidant
- Improves Renal Function in Experimental Cholestasis/Renal Failure
- Acetaminophen Induced Liver/Renal Failure: trend to improved renal function

Hepatorenal Syndrome & NAC

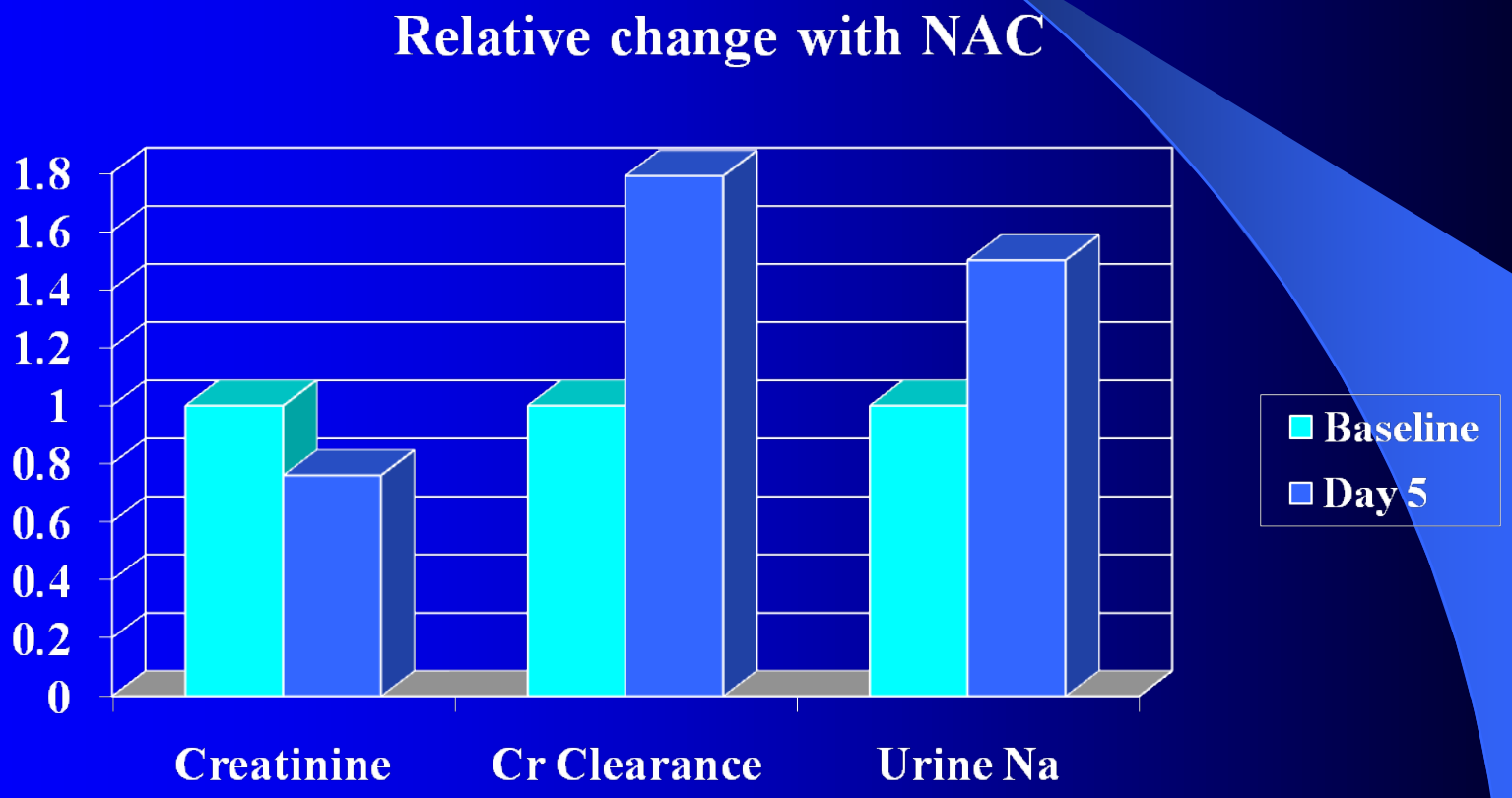
LANCET 1999;353:294-295

- Twelve pat. with all 5 major HRS criteria
- ALD=9, HCV=2, AIH=1
- NAC IV 150 mg/Kg in 2 h + 100 mg/Kg/d x 5 days

Base Cr= 2.5mg/dL & CrCl= 24 mL/min
EOT Cr=1.9mg/dL & Cr Cl= 43 mL/min

- Survival: 1 month= 67%; 3 months= 58%

Hepatorenal Syndrome & NAC



Ornipressin & Albumin

- ***ORNIPRESSIN***

- Splanchnic vasoconst.
- Systemic vasoconstrict
- Increase SVR
- Increase Blood Pressu
- Coronary vasoconstrict
- Decrease Card. output

- ***ALBUMIN***

- Expands intravascular volume
- Decreases Plasma Renin Activity

Hepatorenal Syndrome & Ornipressin + Albumin

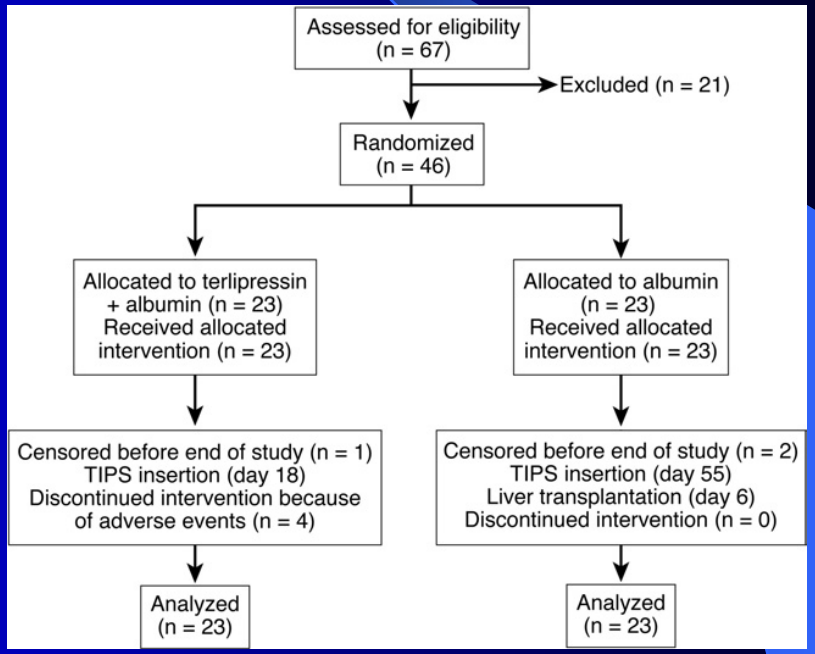
HEPATOLOGY 1998;27:35-41

- Patients: 8 with all 5 major criteria.
- Median age=53; M/F=6/2; ascites= 75%
- Median Cr= 3.2 mg/dL; Inulin Cl= 10mL/m
- Ornipressin 2 IU/h x 15 d + Albumin (20%) 1g/Kg to keep Plasma Renin Activ. Normal
- MAP effect: raised from 69+/-3, to 84+/-4 mmHg
- Four d/c therapy (day 4-9) due to ischemia

Terlipressin + Albumin vs Albumin in HRS

GASTROENTEROLOGY 2008;134:1352–1359

- Patient with Type I or II HRS (74 & 78% were type I)
- Randomized, prospective.
- All patients: D/C diuretics and received 1 g/kg albumin (20%) day 1; then 40 g/d. Lasix IV if CVP > 18
- Goal CVP 10-15
- Terlipressin 1 mg IV bolus q4h x 3 days; if creat has not decrease by 25%, increased to 2 mg q4h



Terlipressin in Type-I HRS: Effect on MAP in Responders vs Non-Responders

Sanyal et al. AASLD 2008

- Population: 111 pts with T-I HRS;
  - Terlipressin = 56; Placebo = 55.
- Intervention:
  - Albumin 100 g on day 1, then 25 g/day + Terlipressin 1 mg q 6h iv, vs
  - Albumin 100 g on day 1, then 25 g/day + Placebo q 6h iv;
  - Terlipressin or placebo were increased to double-dose if creat has not decreased 30% by day 3.
- Result:
  - Responders: MAP changed from 72.8 +/- 11.6 to 80.7 +/- 7.9
  - Non-Respon: MAP changed from 76.9 +/- 11.3 to 76.5 +/- 12.4

Hepatorenal Syndrome

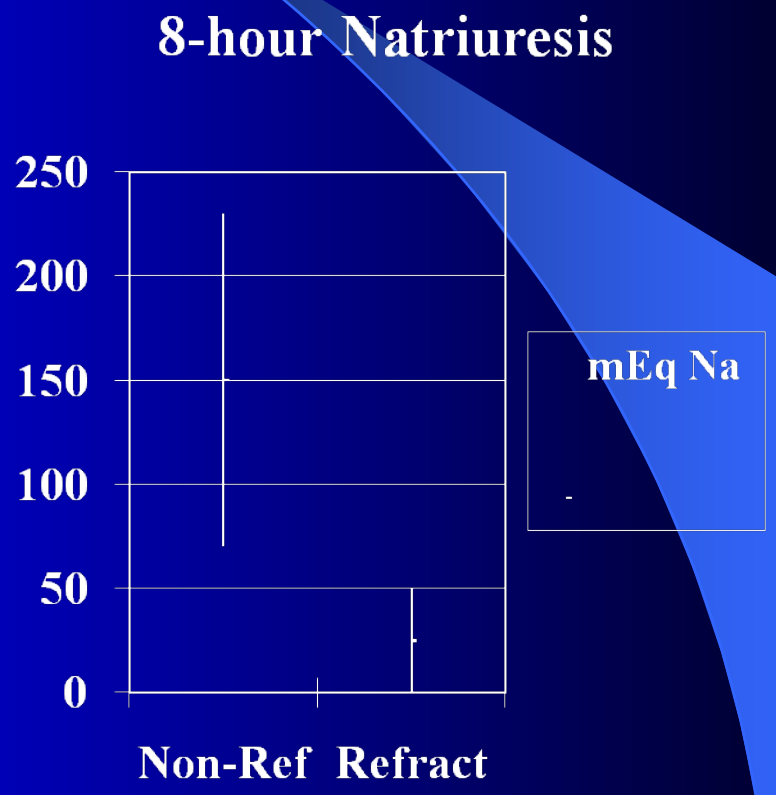
- Can it be predicted ?

Diuretic-Refractory Ascites

Furosemide-Natriuresis Test

Hepatology 2001;33:28-31

- Definition: Will not respond to s200 + f80 + m2.5 in the future
- Protocol:
  - No diuretics x 3 days
  - 80 mEq Na diet
  - Furosemide 80 mg IV
  - Eight hour urine study post furosemide
- Result: Na < 50 mEq/8 hours identified future refractory ascites



SBP & HRS

(Sort et al NEJM 1999;341:403-409)

- ***BACKGROUND***
- *POOR PROGNOSIS IN SBP:*
  - ***Creatinine > 2.1 mg/dl***
  - ***HRS***
  - Albumin < 2.5 mg/dl
  - Bilirubin > 8 mg/dl
  - PSE
  - UGI bleed

- ***STUDY: ALBUMIN in SBP***
- Prosp.& Random
- SBP: >250 PMN/mm3
- Creatinine < 3 mg/dl
- 63 Pts.: Cefotaxime
- 63 Pts.: Cefotaxime + Albumin 1.5gm/kg & 1 gm/kg 3 days later

Diagnosis of Small HCC

Sherman M, & Bolondi L. Hepatology 2005;42:14-16 & 27-34

- **Lesions < 1 cm**: watch q 3 months for enlargement;
  - if no change for 24 months, return to standard surveillance.
- **AFP > 500ng/ml** = likely HCC with lesion of any size (no need to biopsy); considered T2 lesion
- **Lesions 1-2 cm**, with arterial hyperenhancement and venous hypoattenuation by CT & MRI = HCC (no need to Bx)
- **Lesions > 2 cm** + [arterial hyperenhancement and venous hypoattenuation by either CT or MRI] OR [AFP>200 ng/mL] = HCC (no need to Bx)
- Lesions >/= 1 cm without classic features for HCC or hemangioma, in a cirrhotic liver or other "high risk for HCC" = Biopsy
  - **Biopsy**: False (-) 30% if 1-2 cm; 10% if > 2 cm. Tract seeding 2%.