Portal HTN:

Variceal Bleed,
Portal Gastropathy,
Hepatopulmonary Syndrome,
Porto-Pulmonary Hypertension,
Cardiomyopathy, and
Acute on Chronic Liver Failure

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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% will develop varices each year.
- Grade F1: small (</= 5 mm) straight EV;
  - Progression to large 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:**
  - Size > 5 mm
  - Red signs
  - Child-Pugh B or C
- **Surveillance:**
  - 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 (30% do not respond)
- ***Variceal ligation***
- Octreotide/lanreotide (?)
- Losartan: No
- Nitrates (ISMN,ISDN):No
- Sclerotherapy: No
- TIPS: No
- Shunt surgery: No

Esophageal Varices

Ligation as Primary Prophylaxis

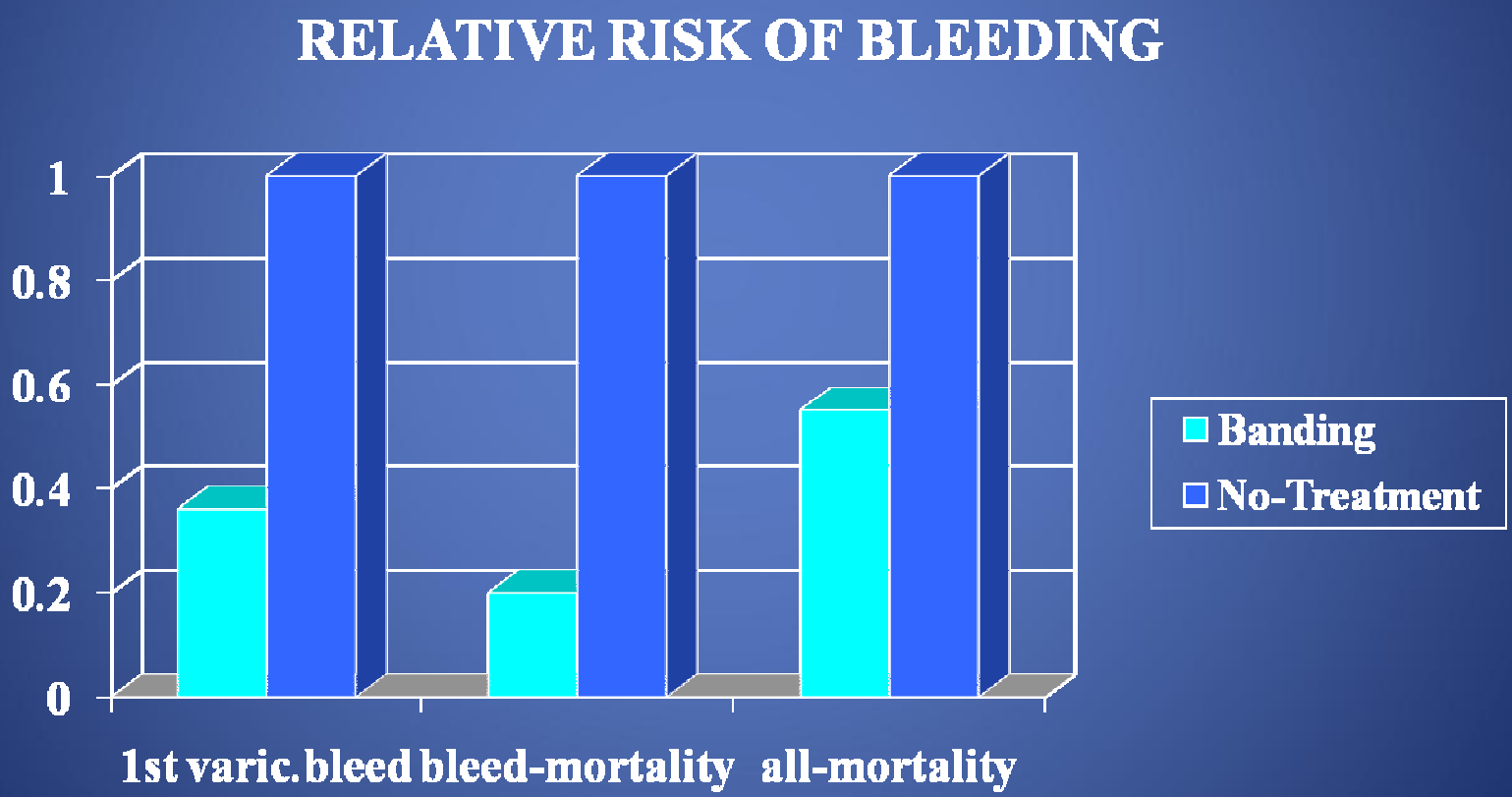
Meta-Analysis *(Hepatology 2001;33:802-807)*

- 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**

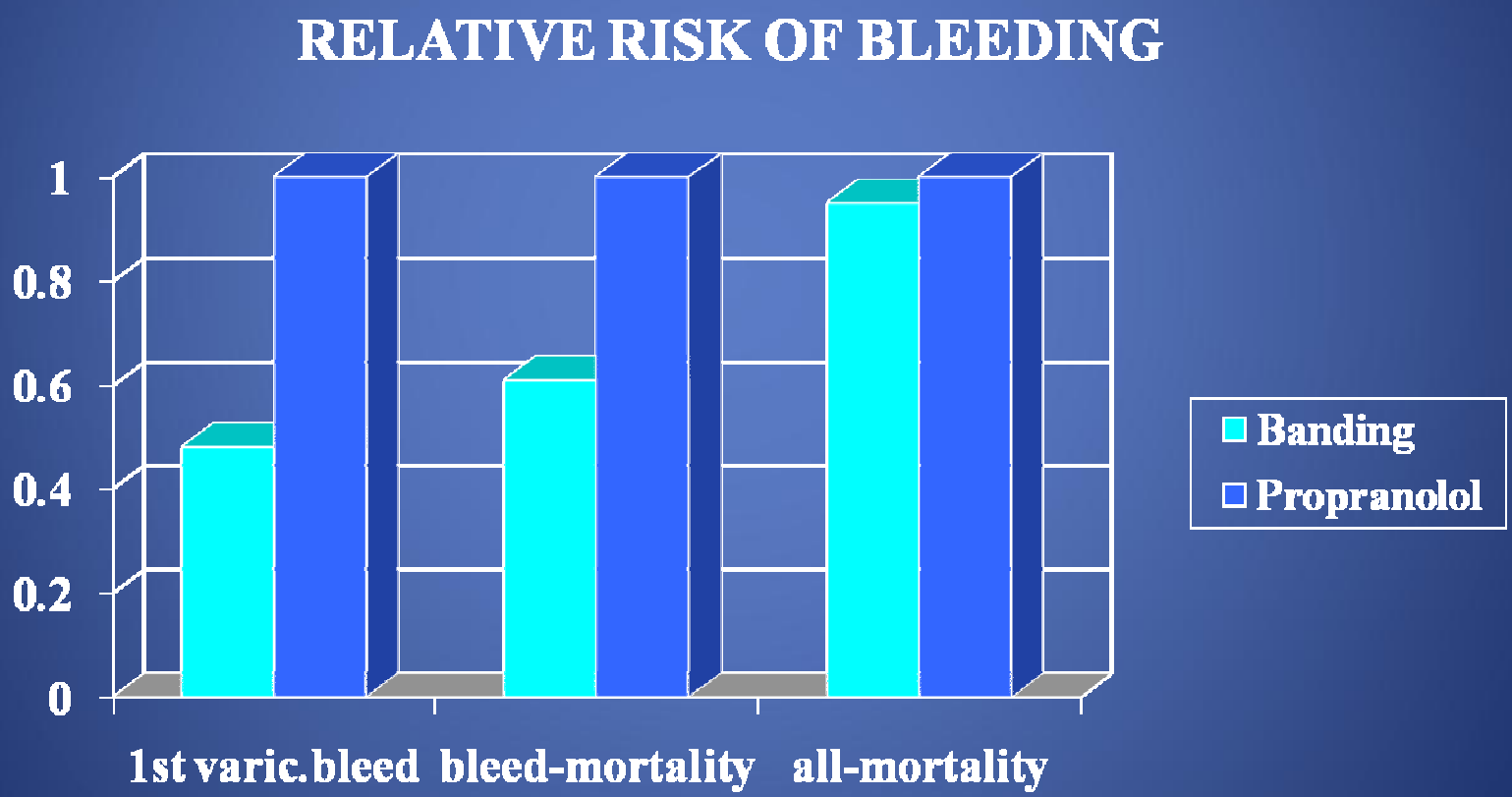
Primary Prophylaxis Meta-Analysis Banding vs No-Treatment

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.***

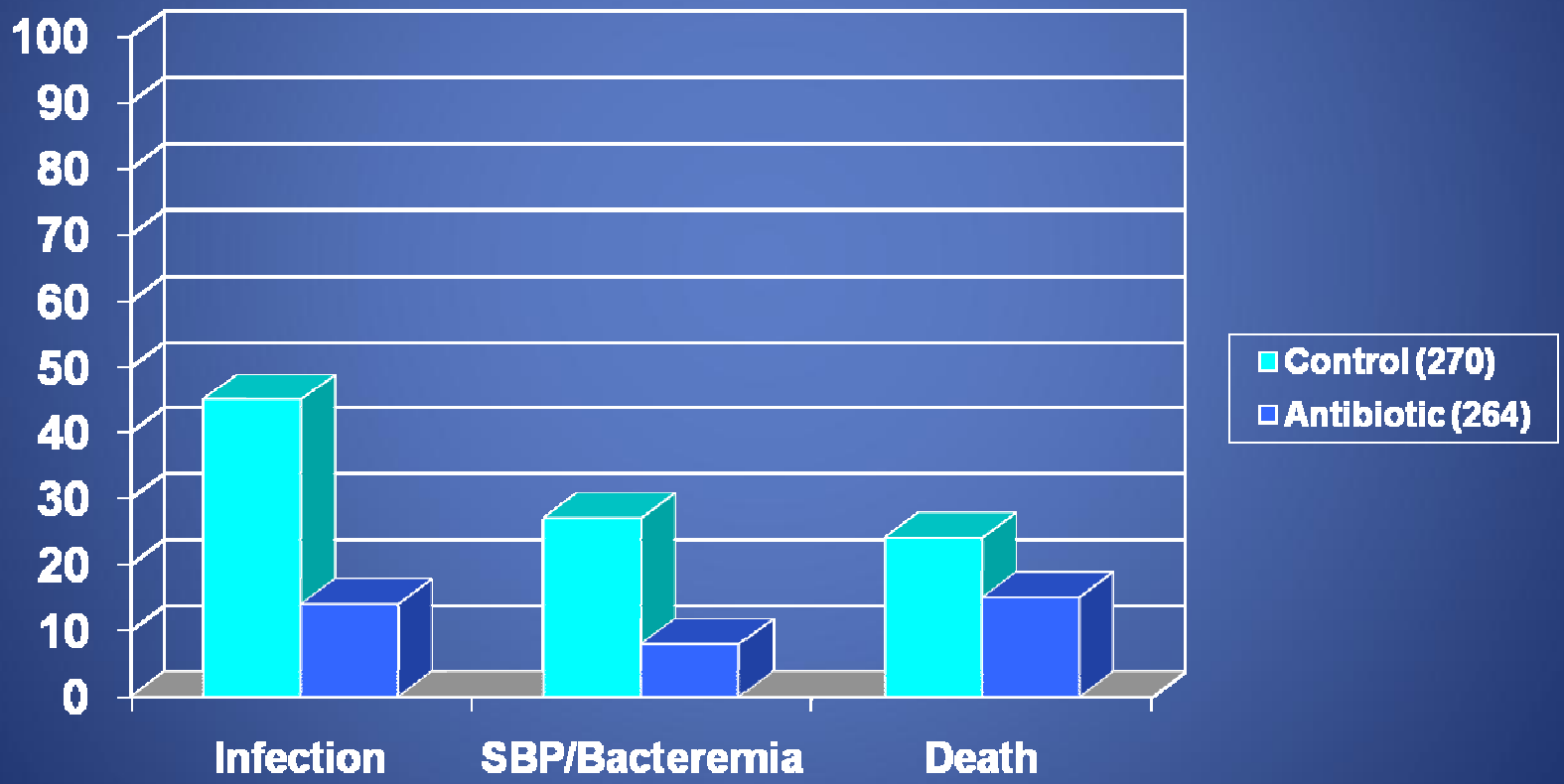
Acute Variceal Bleed

Acute Variceal Hemorrhage

- Spontaneous hemostasis = 40%
- Rebleeding and failure to control bleeding = 40 %
  - 83 % if HVPG > 20 mm Hg
  - 29% if HVPG < 20 mm Hg
- High mortality in: continuous bleed, rebleed & advanced disease
- Mortality = 40 % (20% with antibiotic prophylaxis)
- 1-year mortality depends on HVPG:
  - > 20 mm Hg = 64%
  - < 20 mm Hg = 20%

Prophylactic Antibiotic & Outcome in Cirrhotics with GI Hemorrhage

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



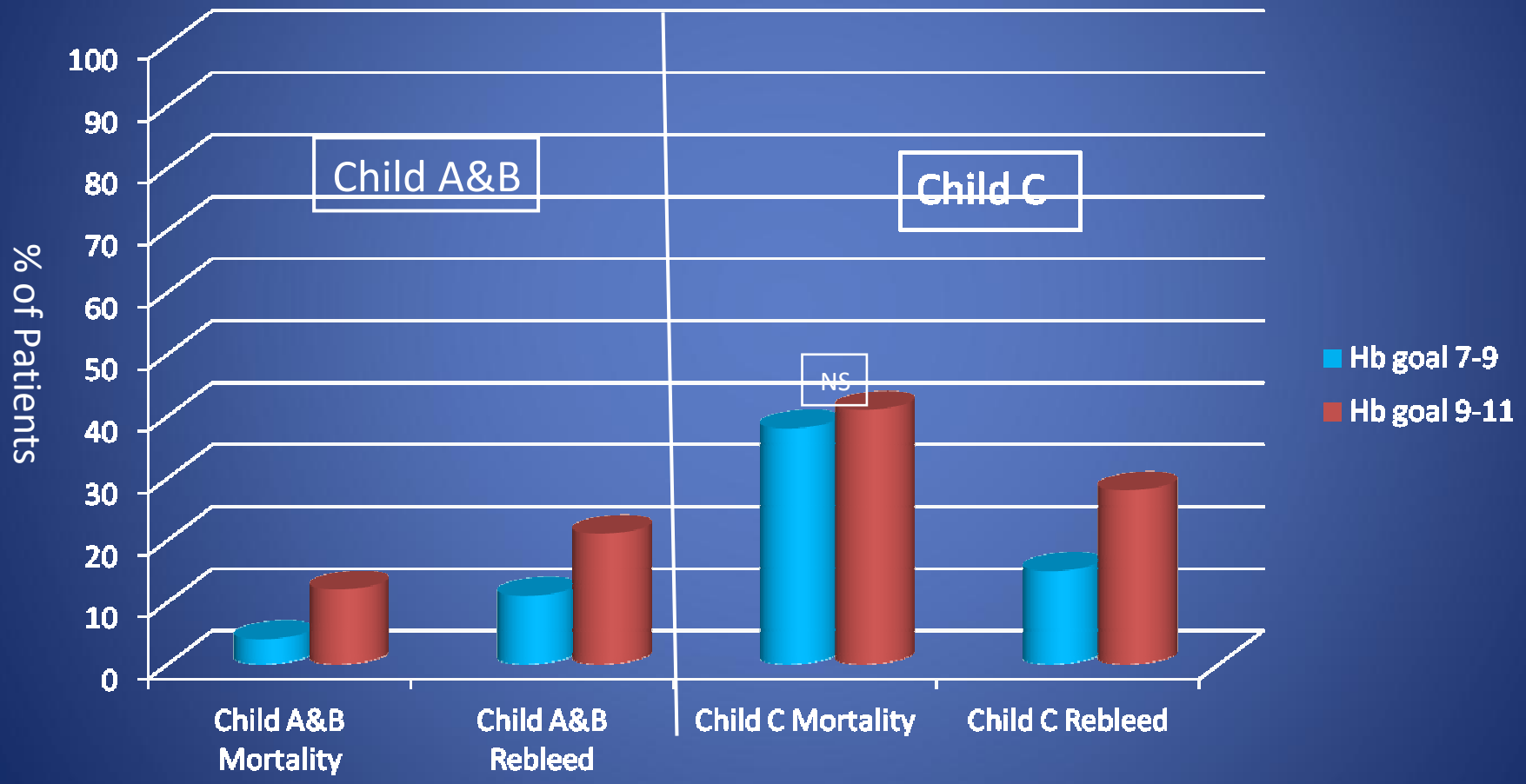
Transfusion Strategies in Cirrhotics

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.

Acute GI Bleed in Cirrhosis

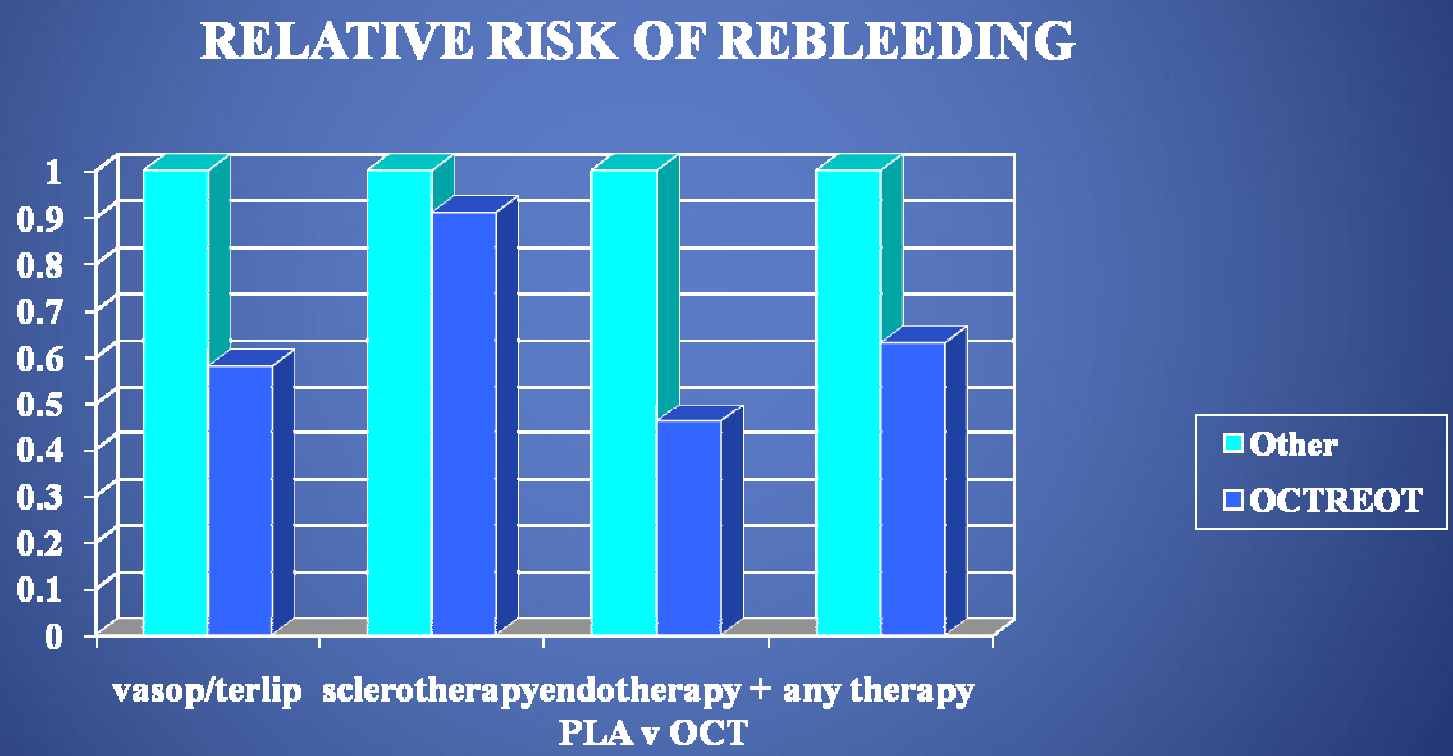
Restrictive vs Liberal Transfusion in GI Bleed
Villanueva C; N Engl J Med 2013; 368:11-21



Rebleed from Acute Variceal-bleed

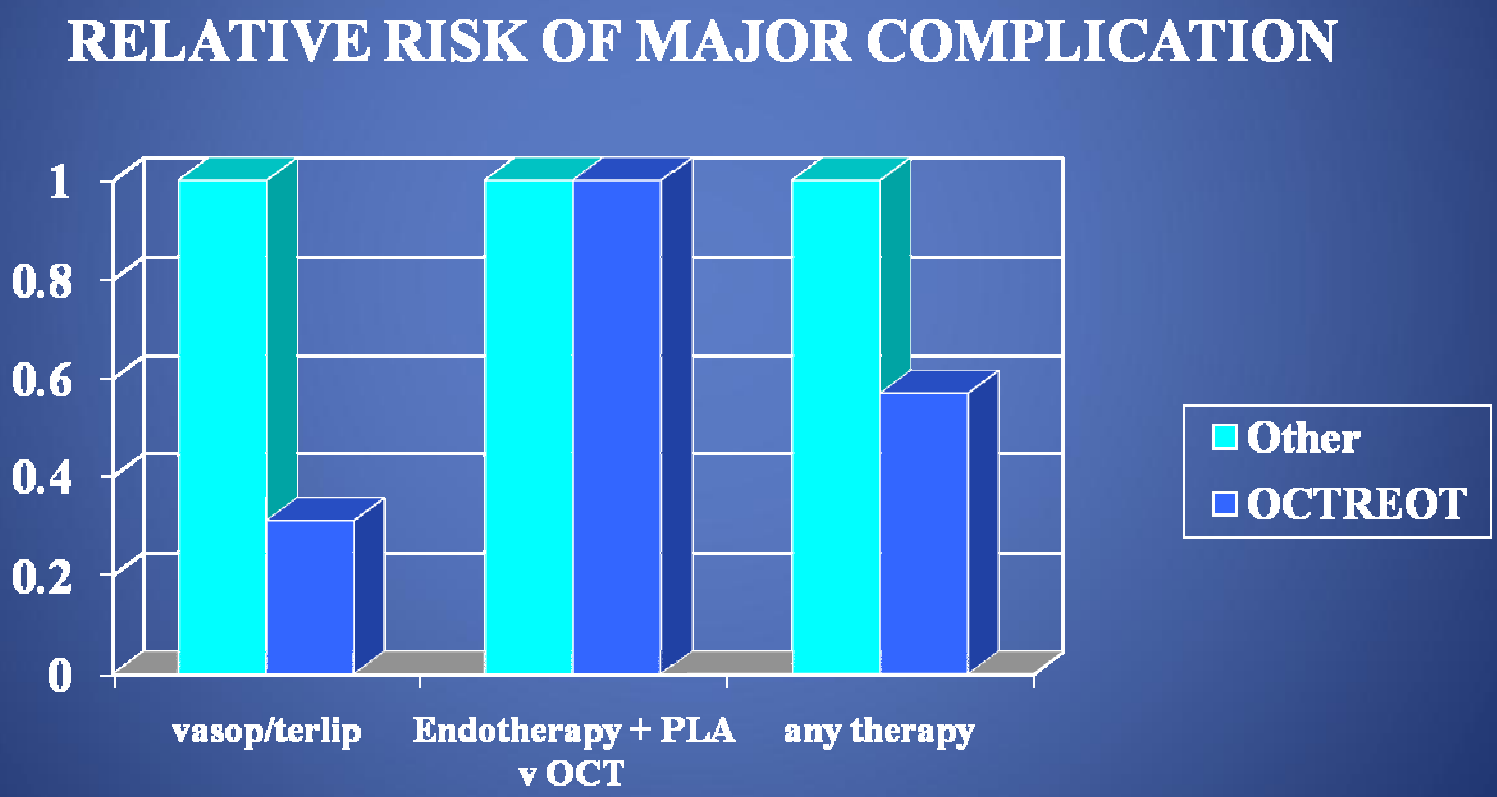
Octreotide Meta-Analysis

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***.

Acute Variceal Bleed Treatment

- ***GOAL***
- *Control Hemorrhage*:
  -Local control
  -Decrease Portal Pressure
- *Prevent Rebleeding*
- *No over-expand*:
  - Transfuse when < /= Hct 21/Hb 7 (keep Hb 7-9, unless higher needed for CAD)
- *Prevent Infection*

- ***INTERVENTIONS***
- ***Banding***
- Somatostatine
- ***Octreotide x 5 days***
- ***Ceftriaxone 1 g IV x 7d, or Norfloxacin 400 BID x7 days***
- Sclerotherapy (+/-)
- TIPS (rescue), or
- Early TIPS in Child C, or Child B bleeding @ EGD, if MELD < 15 (MELD 15-18?)
- Shunt surgery (+/-) rescue (DSRS in Child A/B)

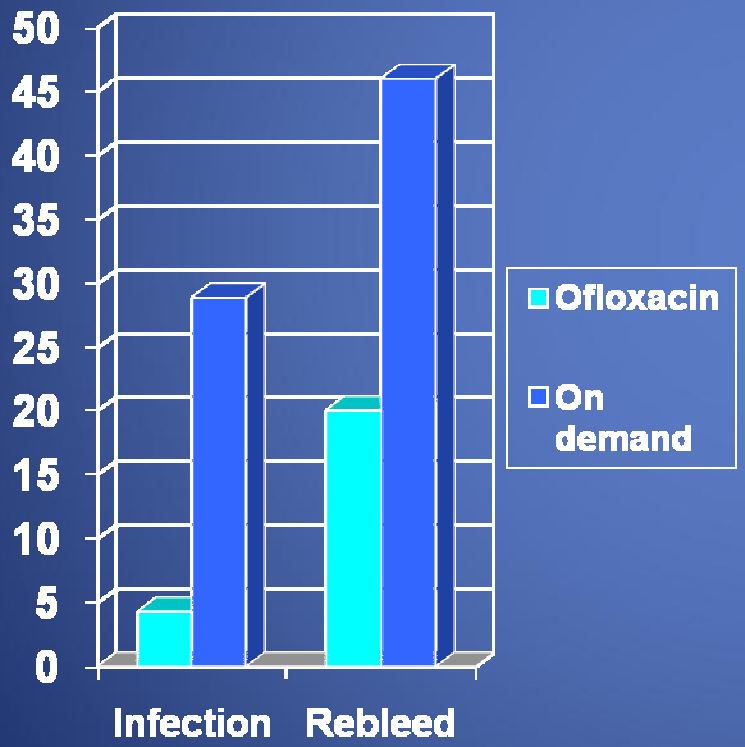
Variceal Rebleed

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 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 < 15 (MELD 15-18?) **and** Child-Pugh B actively bleeding at EGD, or Child-Pugh 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

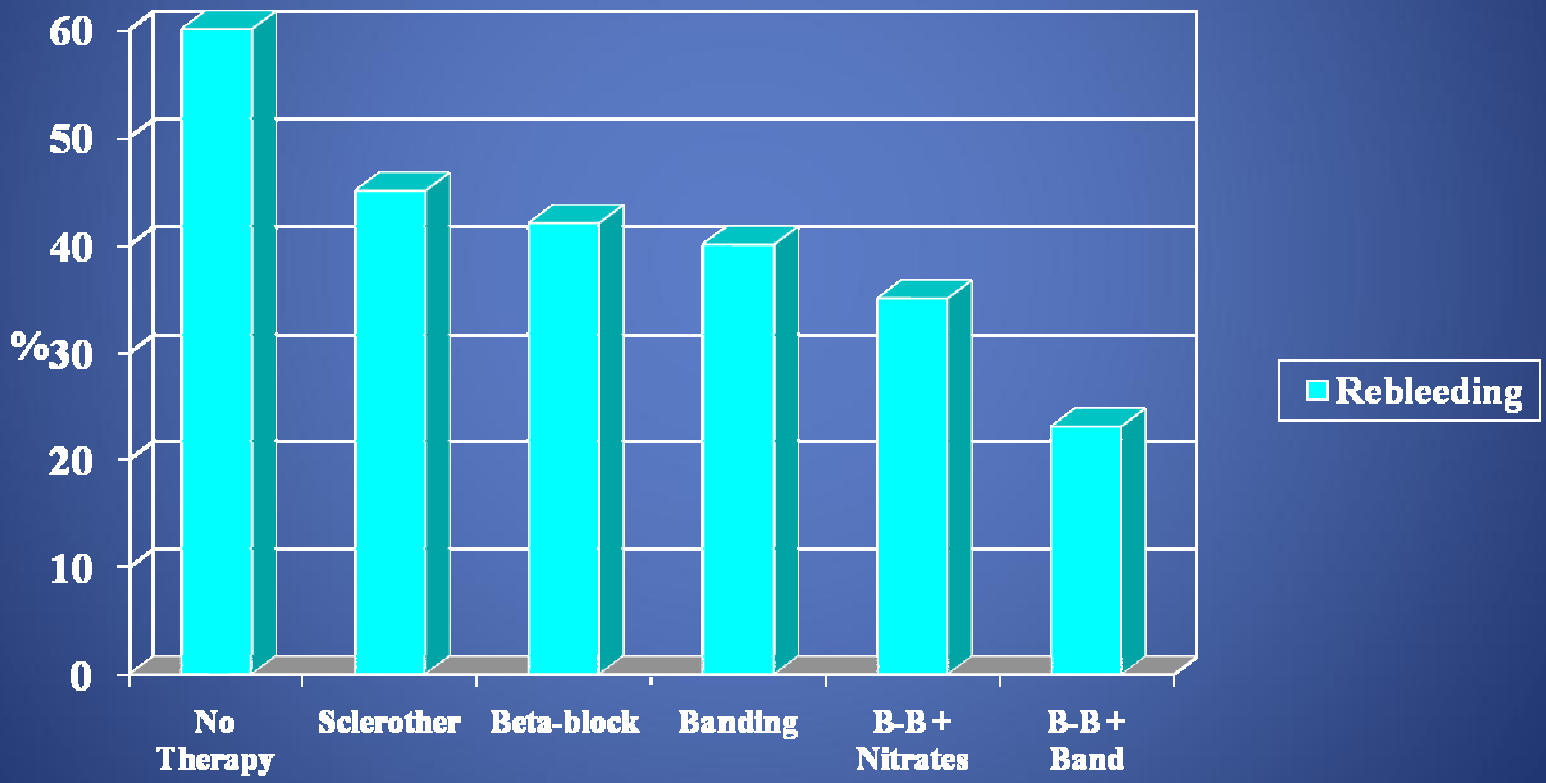
- Nadolol is given orally at an initial dose of 40 mg/day; keep MAP > 83 mm Hg*.
- The dose is then increased by 20 mg daily for a period of 5-7 days until:
  - intolerance appears, or
  - the heart rate decreases to 55 beats per minute, or
  - a maximal dose of 160 mg/day is reached , or
  - MAP is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

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

Variceal Rebleed

LONG TERM PROPHYLAXIS

LONG TERM Rebleeding Risk
Different Prophylaxis



Esophageal Variceal Rebleed
TIPS vs EBL+BB

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

- 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)

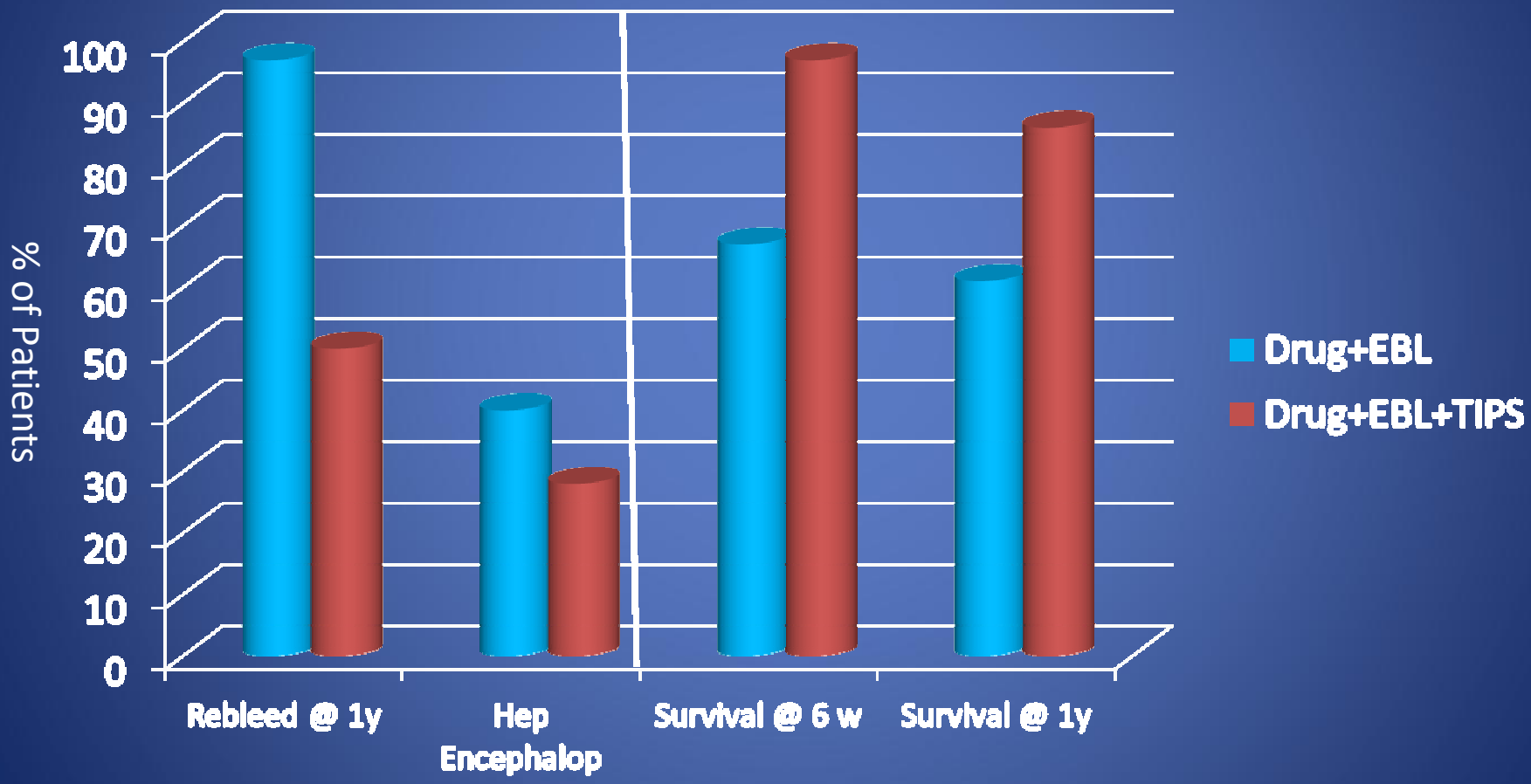
Esophageal Variceal Rebleed
TIPS vs EBL+BB

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

- 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 GI Bleed in Cirrhosis

Early TIPS in Variceal Bleed: Actively bleeding Child B, or any Child C
Garcia-Pagan JC; N Engl J Med 2010; 362:2370-2379



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.*
- TIPS if MELD < 19 & Child B bleeding or Child C
- 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

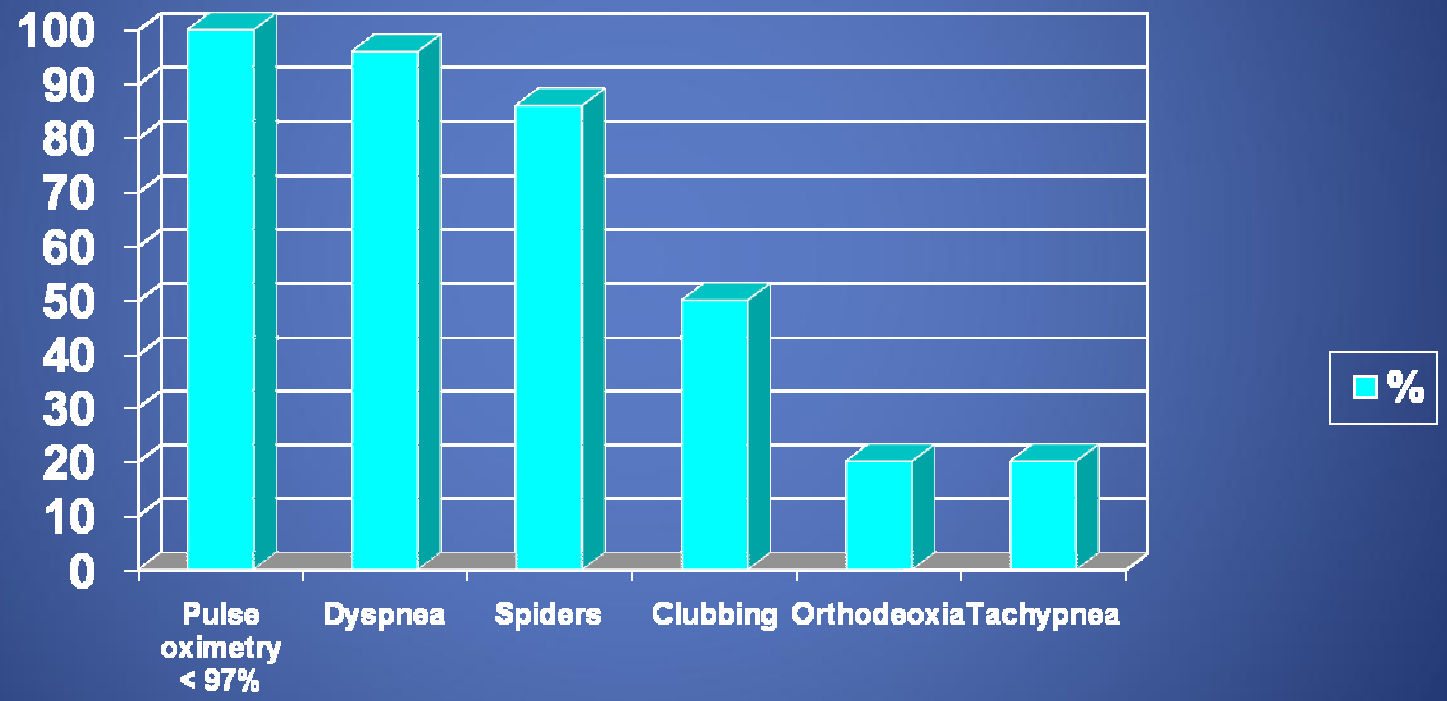
Hepatopulmonary Syndrome

- Occurs in 4-25% of LTx candidates.
- **Clinical features**: cirrhosis, spider nevi, absence of lung disease, cyanosis, clubbing, dyspnea on exertion and/or at rest, platypnea, orthodeoxia, and intrapulmonary vascular dilation.
- **Screening**: ABG (RA) if pulse oximetry < 97%
- **Diagnostic Criteria**: no pulmonary cause, and
  - PaO_2 < 80 (70 if age > 65) mmHg **or** A-a O_2 gradient > 15 (20 if > age 65) mmHg at Room Air, **plus**
  - ECHO bubble (+) in Lt heart, 3-6 beats after seen in Rt heart, **or** Tc MAA (20 micron) 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

- Severity (at Room Air):
  - Mild: $PaO_2 > 80$;
  - Moderate PaO_2 60-80;
  - Severe: PaO_2 50-60;
  - Very Severe: $PaO_2 < 50$ (or < 300 breathing @ 100% O_2)
- Natural Hx: Increase mortality from that expected from MELD.
  - Median survival 24 months (vs 87 months);
  - 5-y survival 23% (vs 63%)
- Extra MELD points may be given (24 points) if $PaO_2 < 60$mmHg
- Worsens 5 mmHg PaO_2 per year.
- LTx mortality increases to 34% with $PaO_2 < 50$ mmHg or MAA shunt > 20%
- Treatment:
  - Oxygen supplementation;
  - Liver Transplantation;
  - Coil embolization of discrete A-V fistulas may help (but is uncommon);
  - Octreotide, methylene blue, allium sativum (garlic), N(G)-nitro-L-arginine methyl ester (L-NAME), nitric oxide synthase inhibitors, inhaled nitric oxide, TIPS

Portopulmonary Hypertension

- Pulmonary hypertension in patient with portal hypertension, with or without liver disease.
  - Occurs in 0.7% of cirrhotics.
- **Screening**:
  - ECHOCARD with PAS pressure > 30 mmHg (assumes RA pressure=5 mmHg);
  - PPV = 59%; NPV = 100%.
- **Cause**: postulated mediators are:
  - serotonin, interleukin-1, endothelin-1, glucagon,secretin, thromboxane B2, and vasoactive intestinal peptide.
- **Histology**: remodeling of the muscular pulmonary artery walls, and in situ thrombosis.

Portopulmonary Hypertension

- **Symptoms**: dyspnea on exertion, syncope, chest pain, fatigue, hemoptysis, and orthopnea.
- **Signs**: accentuated pulmonic component of the second heart sound, a systolic murmur of TR, and edema.
  - CXR: prominent PA and cardiomegaly.
  - EKG: RVH, Rt axis deviation, RBBB.
- **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

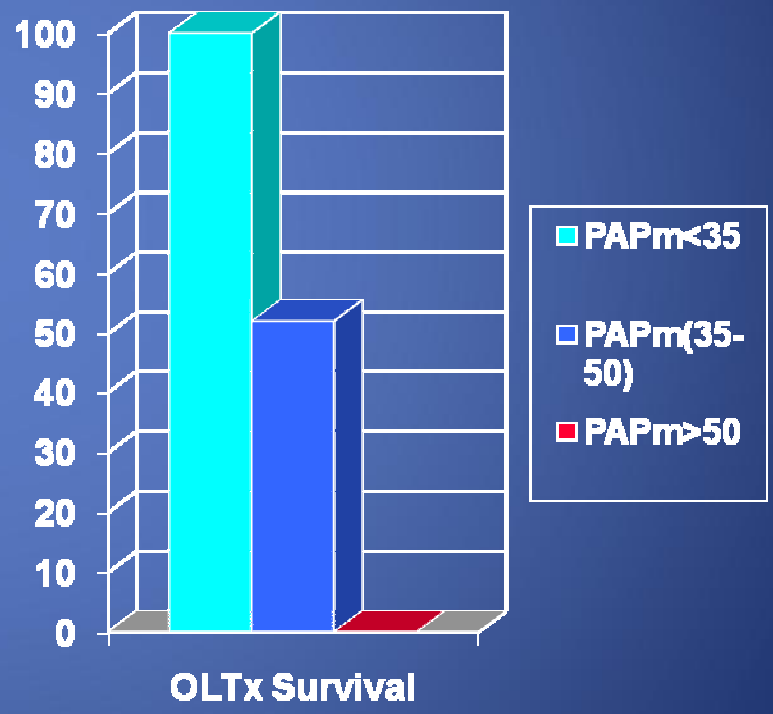
- **General management**:
  - Has risk of pulmonary vascular thrombosis and thromboembolic disease due to venous stasis, slowed pulmonary blood flow, right heart failure, anasarca and ascites:
    - Anticoagulation (in Right heart failure) +
    - Diuretics.
  - Betablockers and TIPSS may be harmful;
    - use only after careful assessment of risk & benefit.
- **Specific Therapy**:
  - Epoprostenol, Bosentan, Ambrisentan, Sildenafil, and/or Iloprost.
  - Asses response every 6 months
- **Prognosis without OLTx**: even with low MELD:
  - 2-y survival is 67%, and
  - 5-y survival is 40%.

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 > 250 dynes/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 unless has Right heart failure



Acute on Chronic Liver Failure

- **Definition:** acute deterioration of cirrhosis that represents the main cause of hospitalization
- **Group at risk:** Usually in patients with compensated cirrhosis or recently decompensated cirrhosis in the last 3 months.
- **Triggers:**
  - Bacterial infections or active alcoholism.
  - Less frequently hepatitis, TIPSS, paracentesis without albumin, or surgery.
  - Uncommon after GI bleed. In 20% no precipitating factor is found.
- Infected and non-infected patients have elevated WBC and CRP.

Definitions in ACLF

ORGAN FAILURE

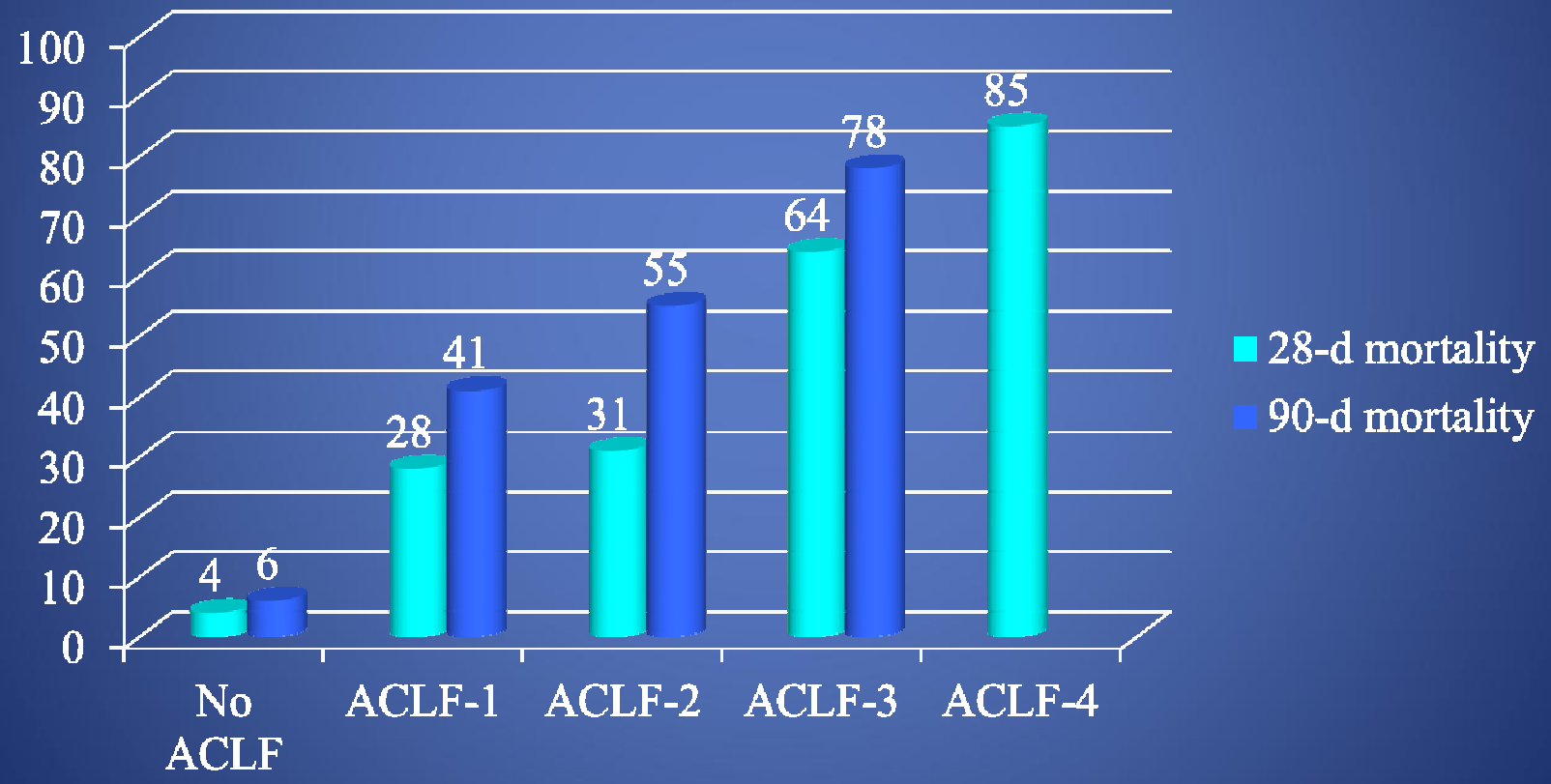
- **Coagulation:** INR > 2.5
  (mortality OR 6.8)
- **Kidney:** Creat > 2 mg/dL
  (mortality OR 6.3)
- **Liver:** Bili > 12 mg/dL
  (mortality OR 3.9)
- **Brain:** HE III or IV
  (mortality OR 3.9)
- **Lung:** SpO_2/FiO_2 </= 214
  (mortality OR 2.8)
- **Circulation:** need of inotropes
  (mortality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

Mortality of ACLF

28 and 90 days



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:
  - Useful: Rest, Na restriction, diuretics, oxygen supplementation, beta-blockers, potassium canreonate.
  - Not helpful: Digoxin, dobutamine, and angiotensin-converting enzyme inhibitors.