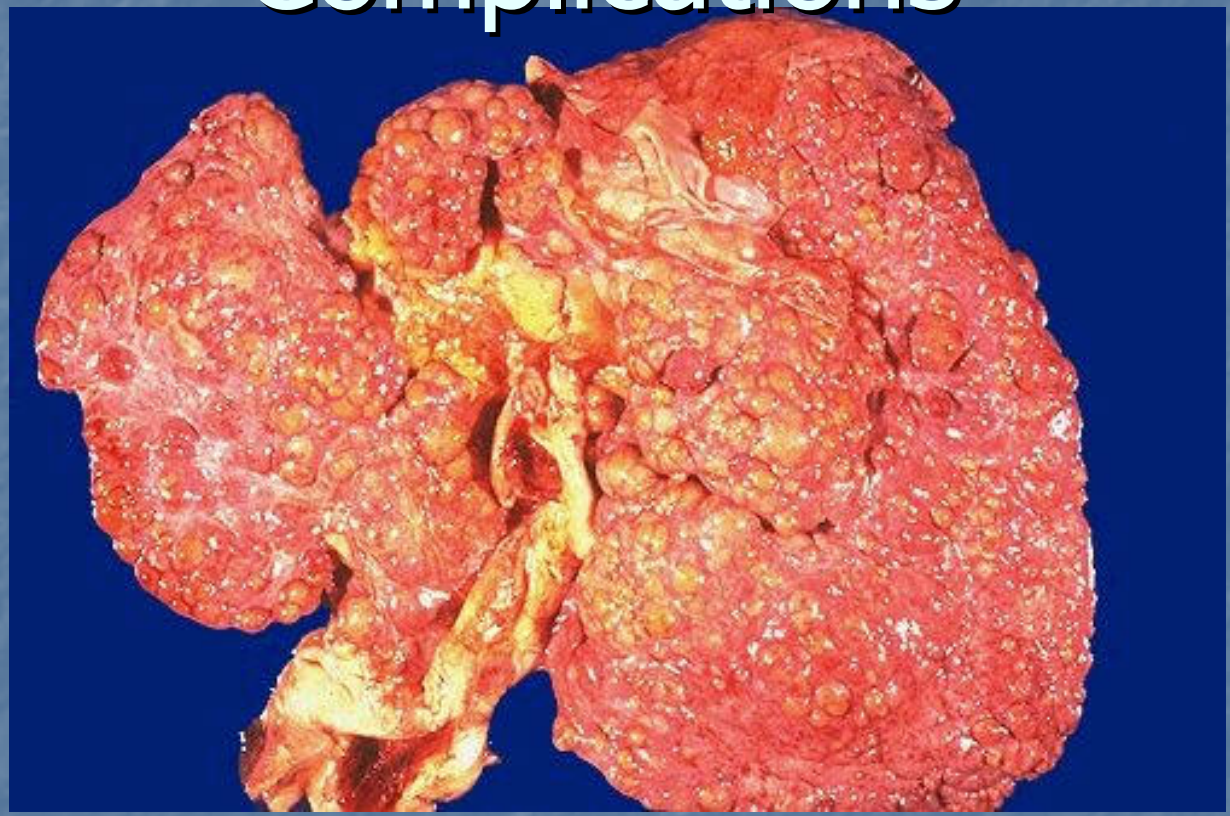
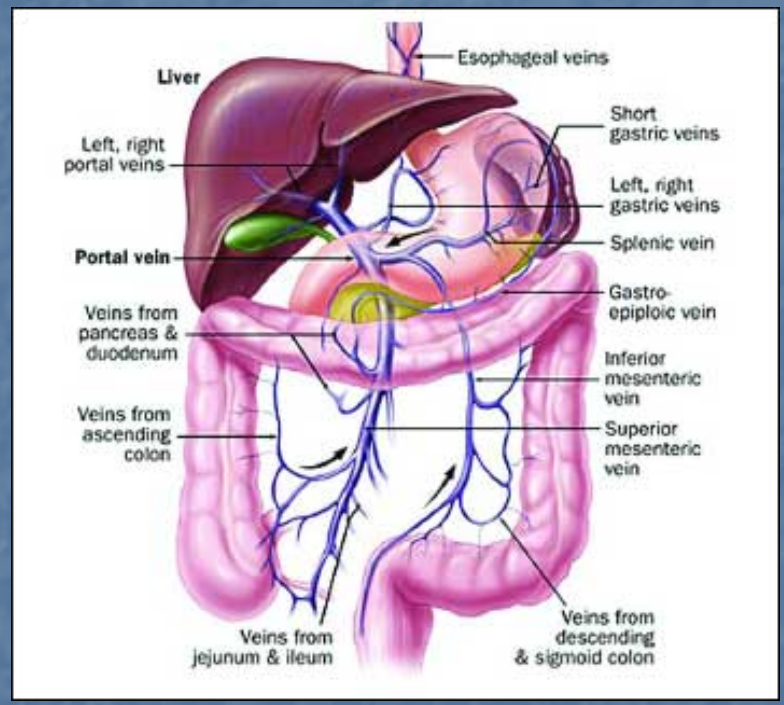
Portal Hypertension and its Complications



Tom Frazier

What I'm Gonna Tell You

- Pathophysiology of Portal HTN and its Complications
- Review diagnostic concerns and management of…
  - Ascites
  - Gastric and esophageal varices
  - HRS
  - HPS
  - Hepatic encephalopathy



J Physiol Pharmacol. 2008 Aug;59 Suppl 2:231-8

What I expect you to remember

- General Pathophys of portal htn, he, varices, hrs
- Where to find answers when they come up
- HE treatment and problems with our curent assumptions

Pathogenesis of Portal Hypertension: Hemodynamic Factors

- Cirrhosis most common etiology
- portal pressure gradient > 5 mm Hg
- Hallmark is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG)
- HVPG = WHVP – FHVP
- Ohm's law: P= Q (blood flow) x R
- Two steps
  - Decreased outflow
  - Increased inflow

Classification of portal hypertension

1.Prehepatic	
	Portal vein thrombosis – independent of cause, splenic vein thrombosis, cavernous transformation of the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly
2.Intrahepatic	
a) presinusoidal	
	Schistosomiasis, chronic viral hepatitis HBV, HCV, cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson's disease, hemochromatosis, amyloidosis, remaining storing diseases, polycystic liver disease, infiltration of liver hilus - independent of cause, benign and malignant neoplasms
b) sinusoidal	
	Liver cirrhosis - independent of etiology, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy
c) postsinusoidal	
	Venous-occlusion disease, alcoholic hyaline sclerosis of central veins
3.Extrahepatic	
	Hepatic veins thrombosis (Budd- Chiari disease), inflammatory/neoplastic infiltration cavering hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency

Step 1: Increased outflow resistance

- This results from 2 factors:
  - (1) mechanical obstruction to flow because of fibrotic disruption of architecture
  - (2) a dynamic component produced by active contraction of vascular smooth muscle cells and activated stellate cells
- The dynamic component accounts for approximately 30% of the intrahepatic resistance in cirrhosis

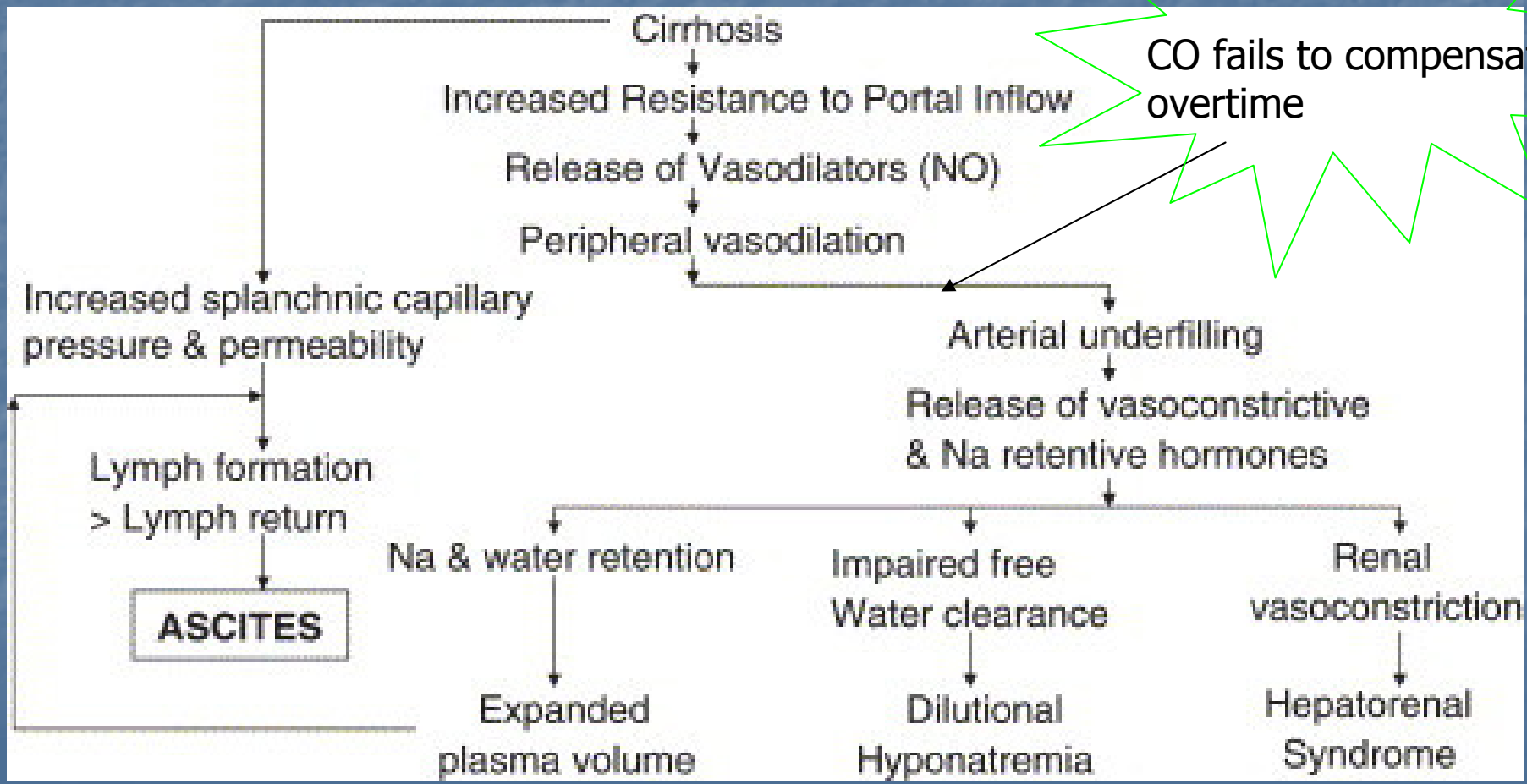
Step 1: The DYNAMIC component

- Intrahepatic ↓(eNOS) activity and NO production.
  - impaired Akt-mediated eNOS phosphorylation (which is partially reversible by statins)
  - increased caveolin expression (particularly if folate deficiency exists).
  - nitrosylation reactions secondary to oxidative stress (↓NO) and vasoconstriction mediated by endothelin, angiotensinogen, and eicosanoids.
- other vasoactive mediators such as carbon monoxide, adrenergic tone, endotoxemia, and inflammatory cytokines

Step 2: Increased Portal Venous Inflow

- Mesenteric arterial vasodilation
  - ↑ portal venous inflow
  - systemic hyperdynamic circulatory state (↓ svr and map with ↑ CO).
- Caused by ↑ NO
  - Shear stress, ↑ VEGF, and TNF-α are causes of ↑ splanchnic NO production in cirrhosis
  - ↑ heme oxygenase activity and CO production may also contribute
  - Bacteremia can ↑ vasodilation by stimulating TNF-α production and activation of endocannabinoids, which are potent vasodilators.
  - Blockade of VEGF signaling attenuates the increase in portal venous inflow seen in cirrhosis

Portal HTN and its Complications



Clinics in Liver Disease - Volume 9, Issue 4 (November 2005)

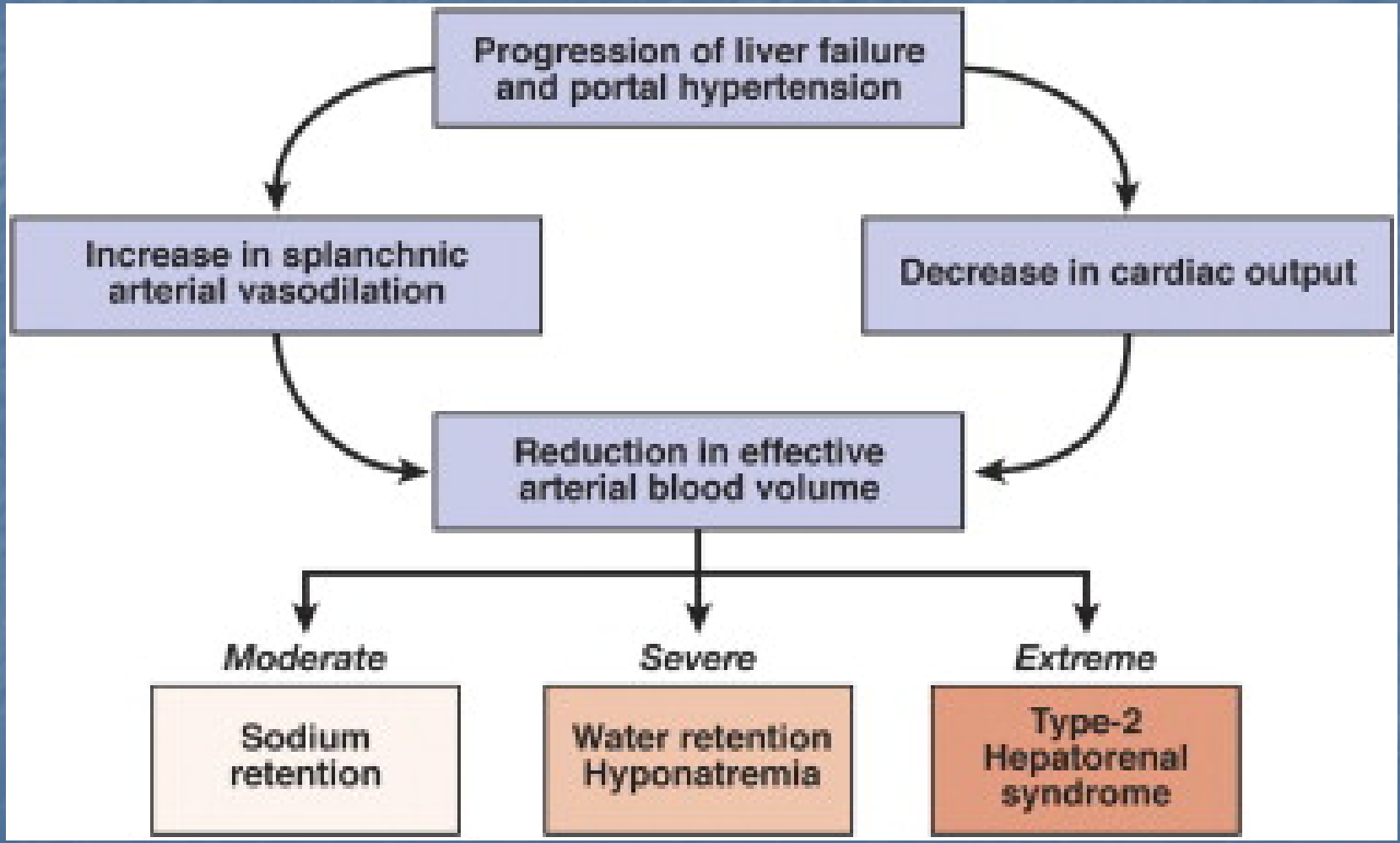
Acites Formation

- Increased hepatic sinusoidal pressure
- Three interrelated pathophysiologic processes contribute to the development of ascites.
  - systemic arteriolar vasodilation,
  - activation of Na and H2O retention,
  - sinusoidal portal hypertension.

Acites Formation

- *splanchnic arterial vasodilation -> effective hypovolemia -> increased CO (hyperdynamic circulation).
- Over time splanchnic arterial vasodilation ↑ and CO ↓ (effectively), leading to circulatory dysfunction
  - renin-angiotensin-aldosterone system,
  - sympathetic nervous system, and
  - antidiuretic hormone.
- moderate circulatory dysfunction = sodium retention.
- Severe= impairment in free water excretion and dilutional hyponatremia.
- Extreme=HRS.

Pathophysiology of ascites and hepatorenal syndrome.



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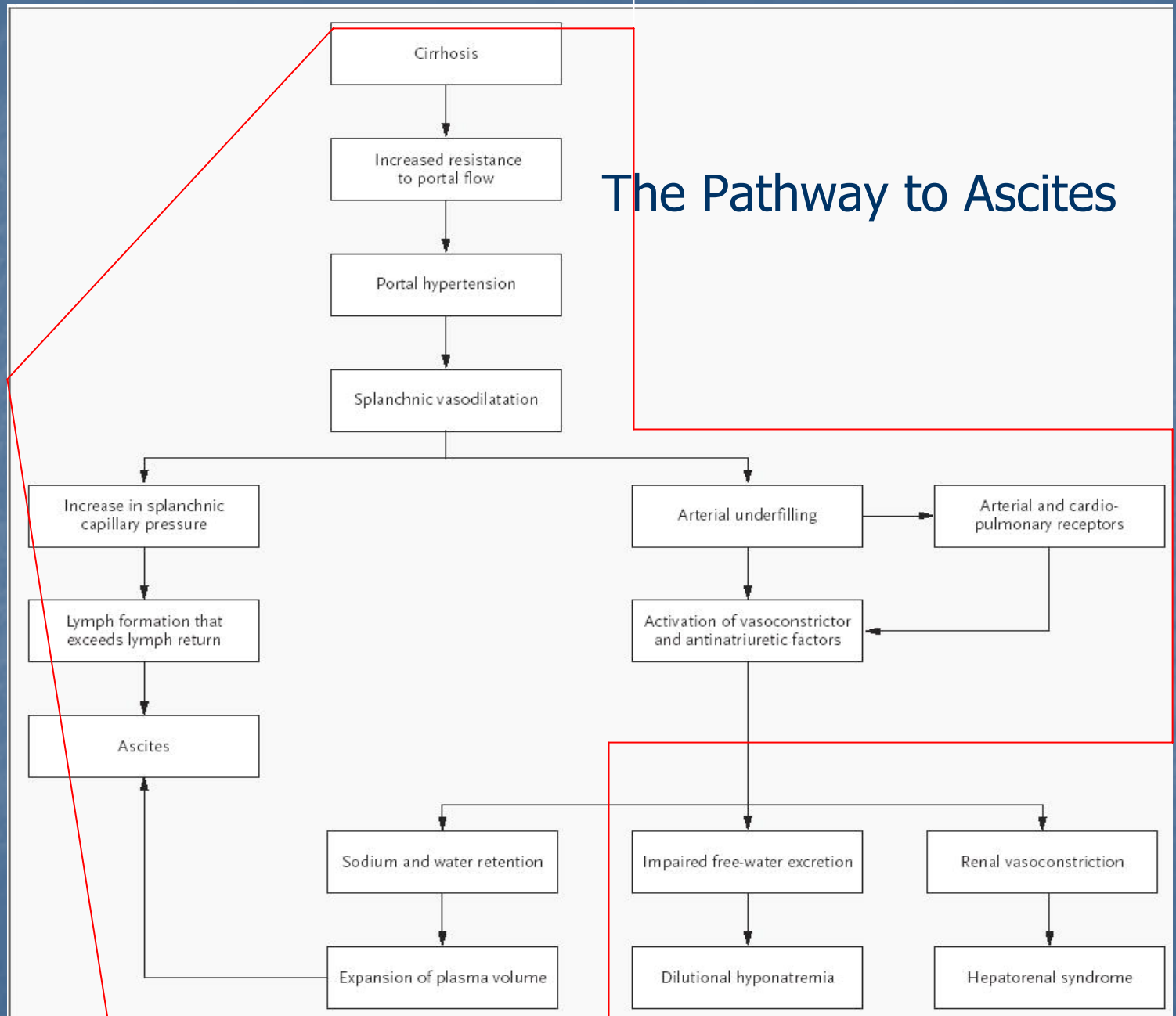
The Pathway to Ascites



NEJM. Volume 350(16), 15 April 2004, pp 1646-1654

Grading Ascites

- Grade 1—mild and detectable only on imaging studies
- Grade 2—moderate, manifested by symmetrical distension of abdomen
- Grade 3—large or gross with massive abdominal distension

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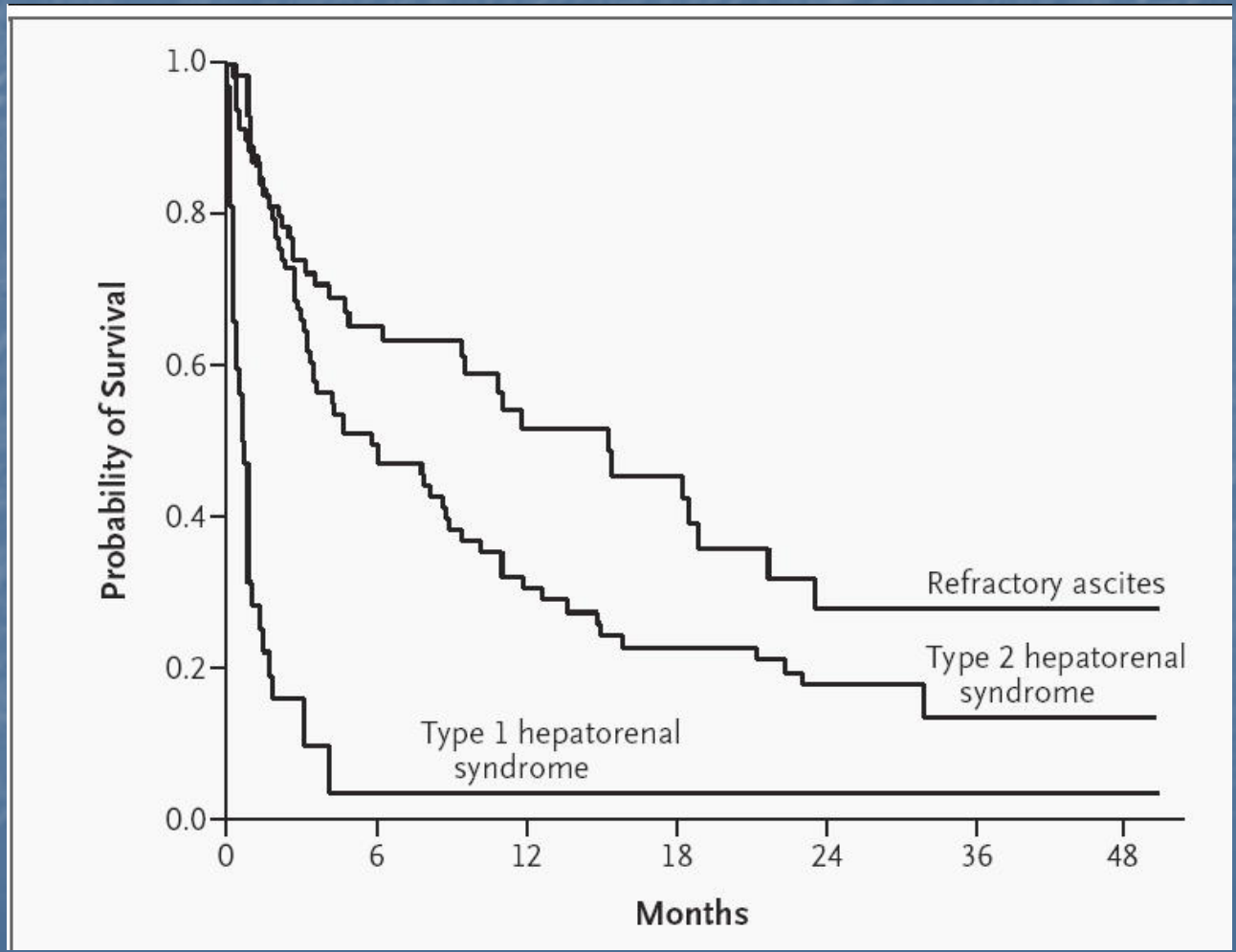
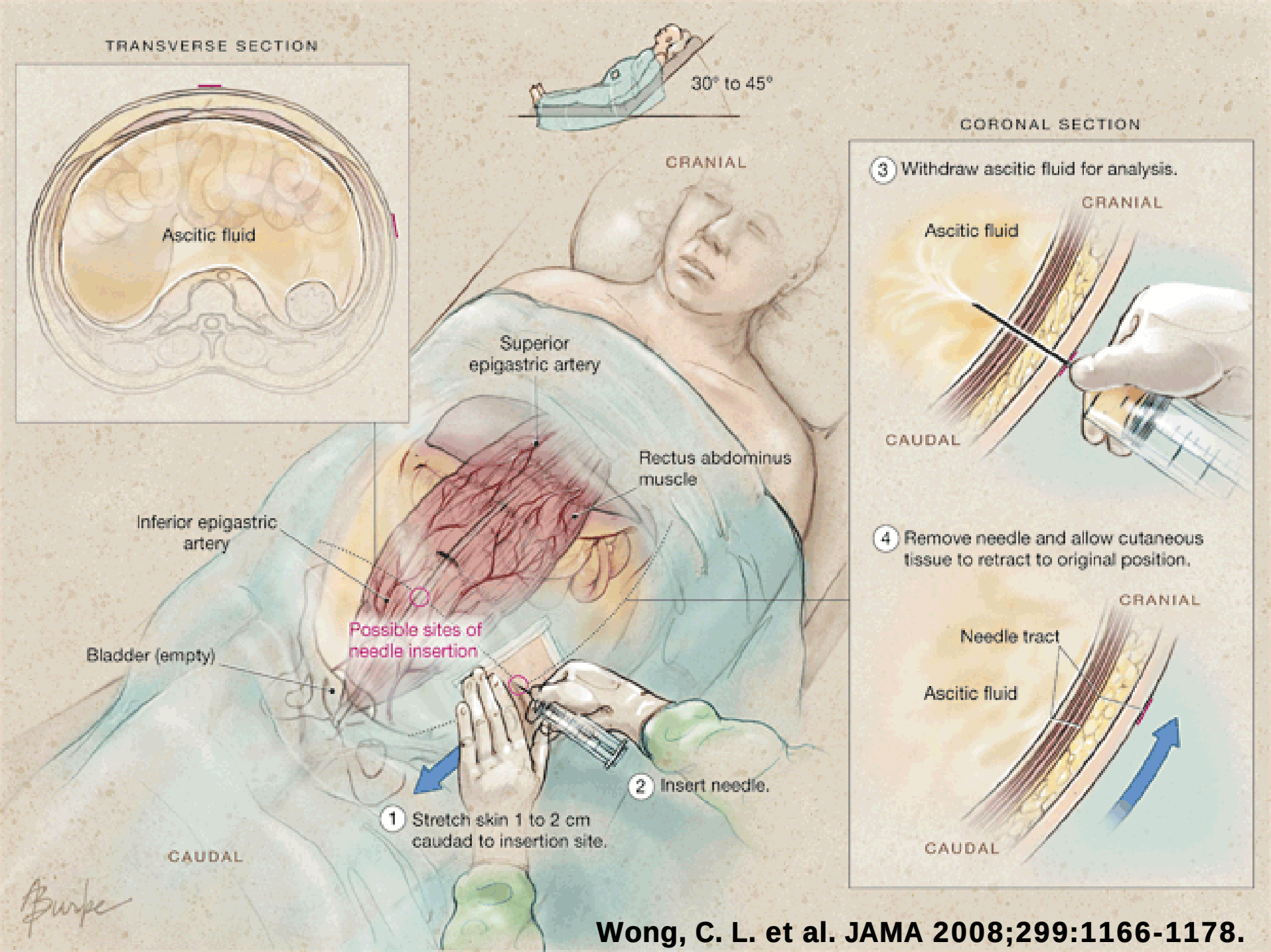
Survival of Cirrhotics with Survival of Cirrhotics with Ascites



Gines: N Engl J Med, Volume 350(16).April 15, 2004.1646-1654



Wong, C. L. et al. JAMA 2008;299:1166-1178.

Classification of Ascites

- Serum-ascites albumin gradient (SAAG)
- SAAG (g/dl) = $albumin_s$–$albumin_a$
- Gradient >1.1 g/dl = portal hypertension
- Serum globulin > 5 g/dl:
  - SAAG correction = (SAAG mean)(0.21+0.208 serum globulin g/dl)

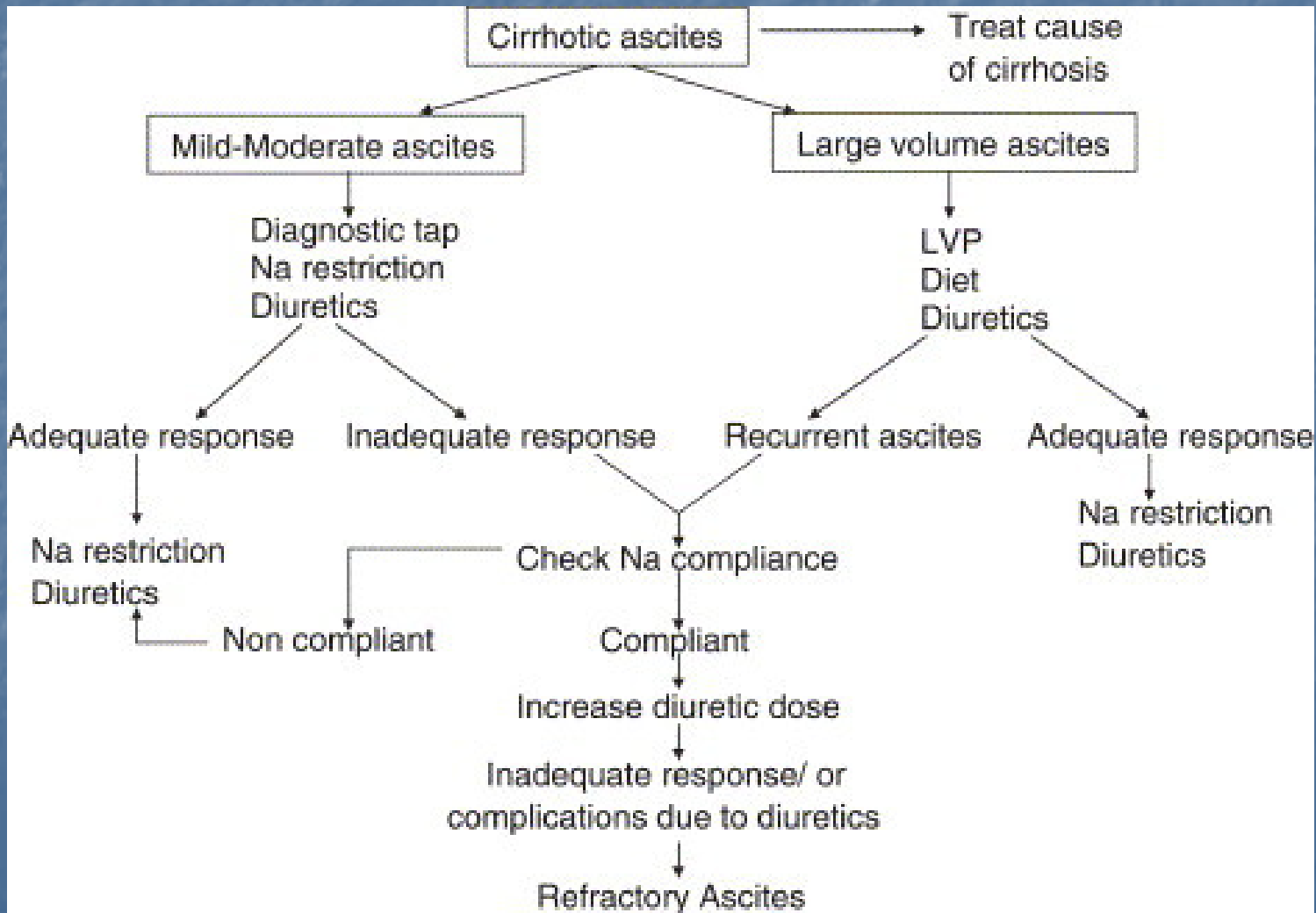
Ascites with High SAAG
> 1.1 g/dl = portal hypertension

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

Low SAAG
<1.1 g/dl

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

Management of Uncomplicated Ascites



Management of Uncomplicated Ascites

- Ideal wt loss w/o peripheral edema: 500g/day
- Ideal wt loss w peripheral edema: 1000g/d
- Checking urine Na:
  - urine Na ~ Na intake
  - ↑ Na: counsel on compliance with diet
  - ↓ Na: increase diuretic
  - Only check if patient has poor diuretic response
- Starting dose for diuretics is Furosemide 40mg and spironolactone 100mg. (max 160mg/d and 400mg)

Refractory Ascites

- **Diuretic resistant ascites**= failure to lose at least 1.5 kg/week of fluid weight, despite diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day)
- **Diuretic intractable ascites**: failure to mobilize 2/2 diuretic-induced side effects

Treatment of Refractory Acites

- Repeated LVP (most common)
- TIPS (better for control/less cost effective/no improvement in mortality)
  - ↑ Bili, coagulopathic, and RF are all predictors of poor outcomes with TIPS

SBP and CNNA

- ***SBP***= PMN >250/mm3with (+) culture (> 90% monobacterial)
- ***CNNA***= PMN >250/mm3with (-) culture (without previous antibiotics nor other causes of increased PMN [bleeding, cancer, TB, pancreatitis])

Symptoms and signs	SBP (%)	Bacterascites (%)	CNNA (%)	Secondary peritonitis (%)
Fever	68	57	50	33
Abdominal pain	49	32	72	67
Abdominal tenderness	39	32	44	59
Rebound	10	5	0	17
Encephalopathy	54	50	61	33

CNNA, culture negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.
Reproduced from *Sleisenger's & Fordtran's gastrointestinal and liver disease*, 7th ed, with permission from Elsevier.

Koulaouzidis: Postgrad Med J, Volume 83(980).June 2007.379-383

Microorganisms	SBP (%)	Bacterascites (%)	Secondary peritonitis (%)
Monomicrobial			
Escherichia coli	37	27	20
Klebsiella pneumoniae	17	11	7
Pneumococcus	12	9	0
Streptococcus viridans	9	2	0
Staphylococcus aureus	0	7	11
Miscellaneous Gram-negative	10	14	7
Miscellaneous Gram-positive	14	10	0
Polymicrobial	1	0	53

SBP, spontaneous bacterial peritonitis.
Reproduced from *Sleisenger's & Fordtran's gastrointestinal and liver disease*, 7th ed, with permission from Elsevier.

Koulaouzidis: Postgrad Med J, Volume 83(980).June 2007.379-383

SBP and CNNA

- **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)**

Table 2. Effective Interventions for Preventing Complications in Patients with Cirrhosis and Ascites.

Complication and Setting	Intervention	Comments	Reference
Gastrointestinal bleeding due to gastroesophageal varices	Propranolol or nadolol (stepwise increase in dose until the heart rate decreases by 25% or to 55–60 beats/min)	Reduces the risk of variceal bleeding and improves survival	Bosch et al.[16]
Spontaneous bacterial peritonitis			
In patients with acute variceal bleeding	Oral norfloxacin (400 mg twice daily for7 days), intravenous ofloxacin (400 mg daily for 7 days), or intravenous ciprofloxacin (200 mg daily) plus oral amoxicillin–clavulanic acid (1 g and 200 mg, respectively, three times daily) for 7 days	Reduces the risk of spontaneous bacterial peritonitis and improves survival	Rimola et al.[17]
In patients with ascitic-fluid protein concentration <15 g/liter	Oral norfloxacin (400 mg daily, indefinitely); oral ciprofloxacin (750 mg weekly, indefinitely); or oral trimethoprim–sulfamethoxazole (160 mg and 800 mg, respectively, five days per week, indefinitely)	Reduces the risk of a first episode of spontaneous bacterial peritonitis; use of antibiotics is controversial because a beneficial effect on survival has not been demonstrated and because there is an increased risk of infections with resistant organisms	Rimola et al.[17]
Hepatorenal syndrome in patients with spontaneous bacterial peritonitis	Intravenous albumin (1.5 g/kg of body weight on diagnosis of the infection and 1 g/kg after 2 days)	Reduces the risk of the hepatorenal syndrome and improves survival	Sort et al.[18]

Gines: N Engl J Med, Volume 350(16).April 15, 2004.1646-1654

Formation of Varices and Mechanism of Variceal Hemorrhage

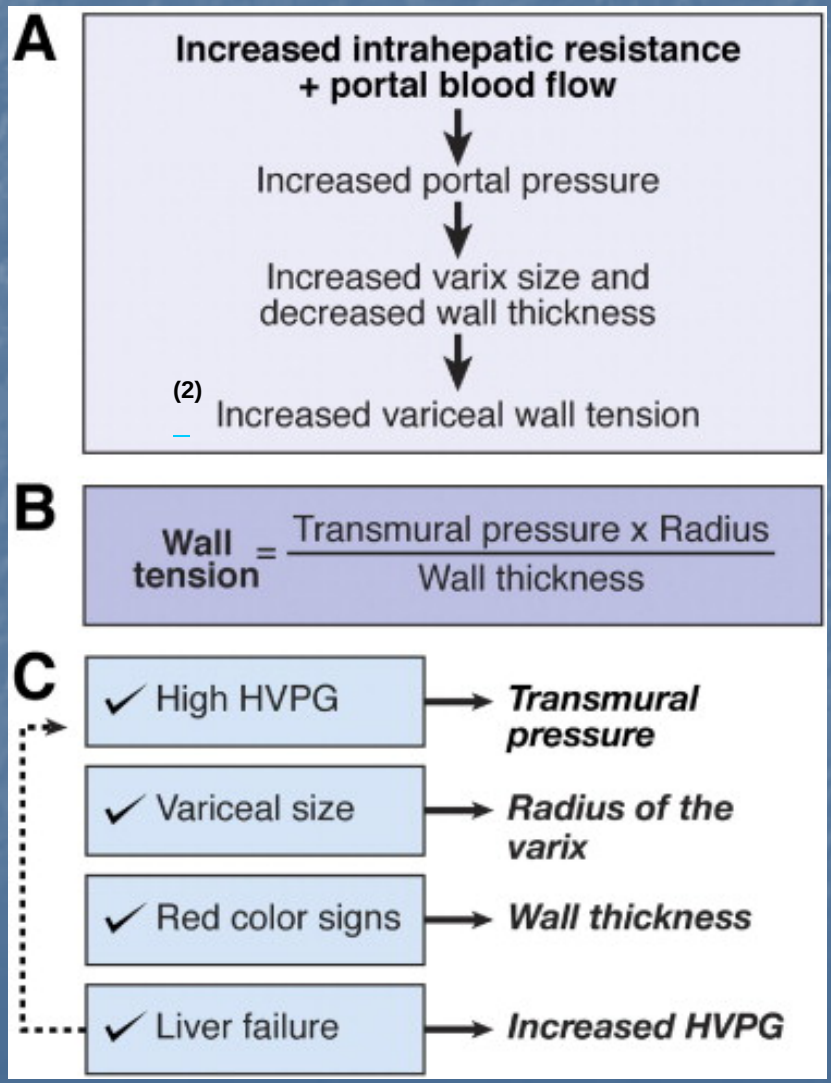
- ↑ portal vein pressures = diverting up to 90% of the portal flow through porta-systemic collaterals
  - flow-mediated remodeling and
  - enlargement of these vessels.
  - VEGF, NO-driven VEGF type II receptor expression, and platelet-derived growth factor drive this process.

Formation of Varices

- do not form until the HVPG >10 mm Hg and
- usually do not bleed unless the HVPG >12 mm Hg.
- Variceal rupture occurs when the wall tension exceeds the elastic limits of the variceal wall
- The wall tension is defined by Frank's modification of Laplace's law
- The wall is thinnest at the GE junction

$T = (P_{varices} - P_{esophageal\ lumen}) \times (\text{radius of varix})/\text{wall thickness}$

Pathophysiology of Variceal Bleeding



Ohm's law

P= Q (blood flow) x R

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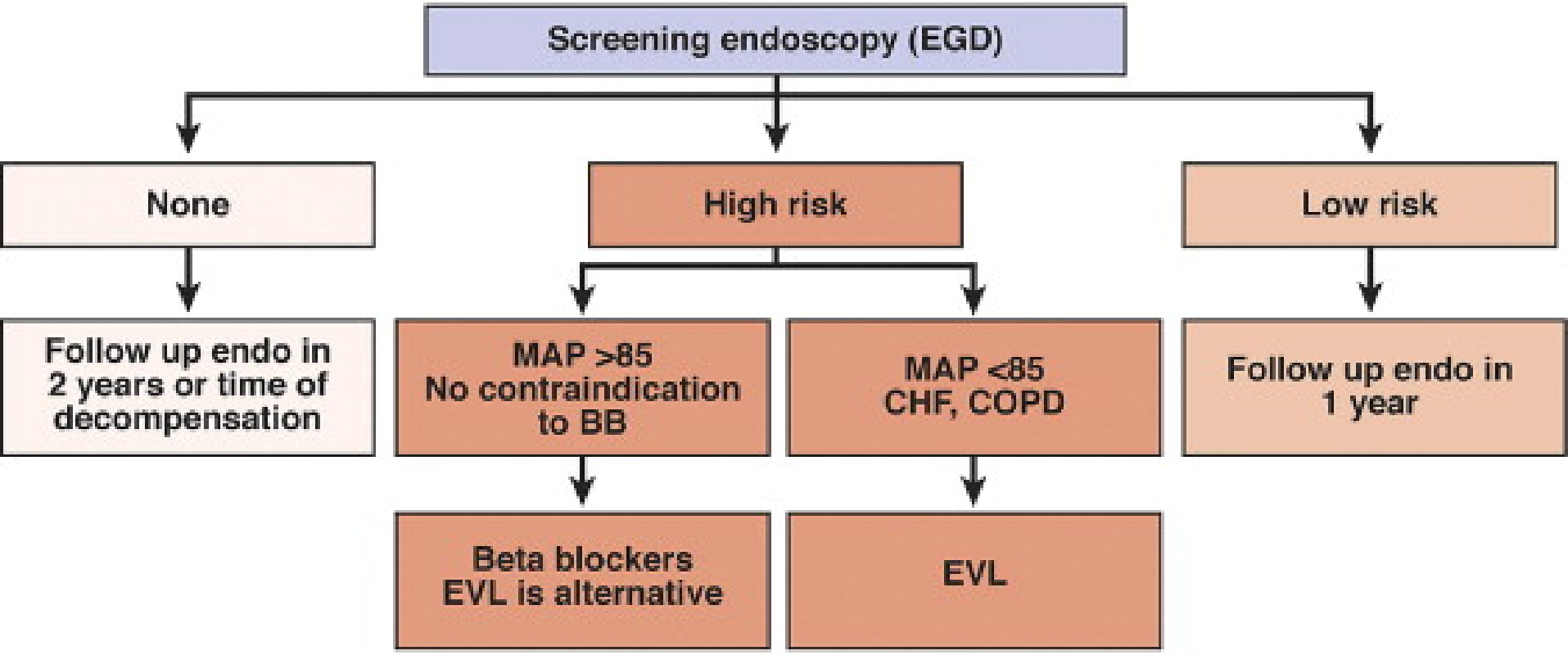
Prevention of Variceal Bleeding



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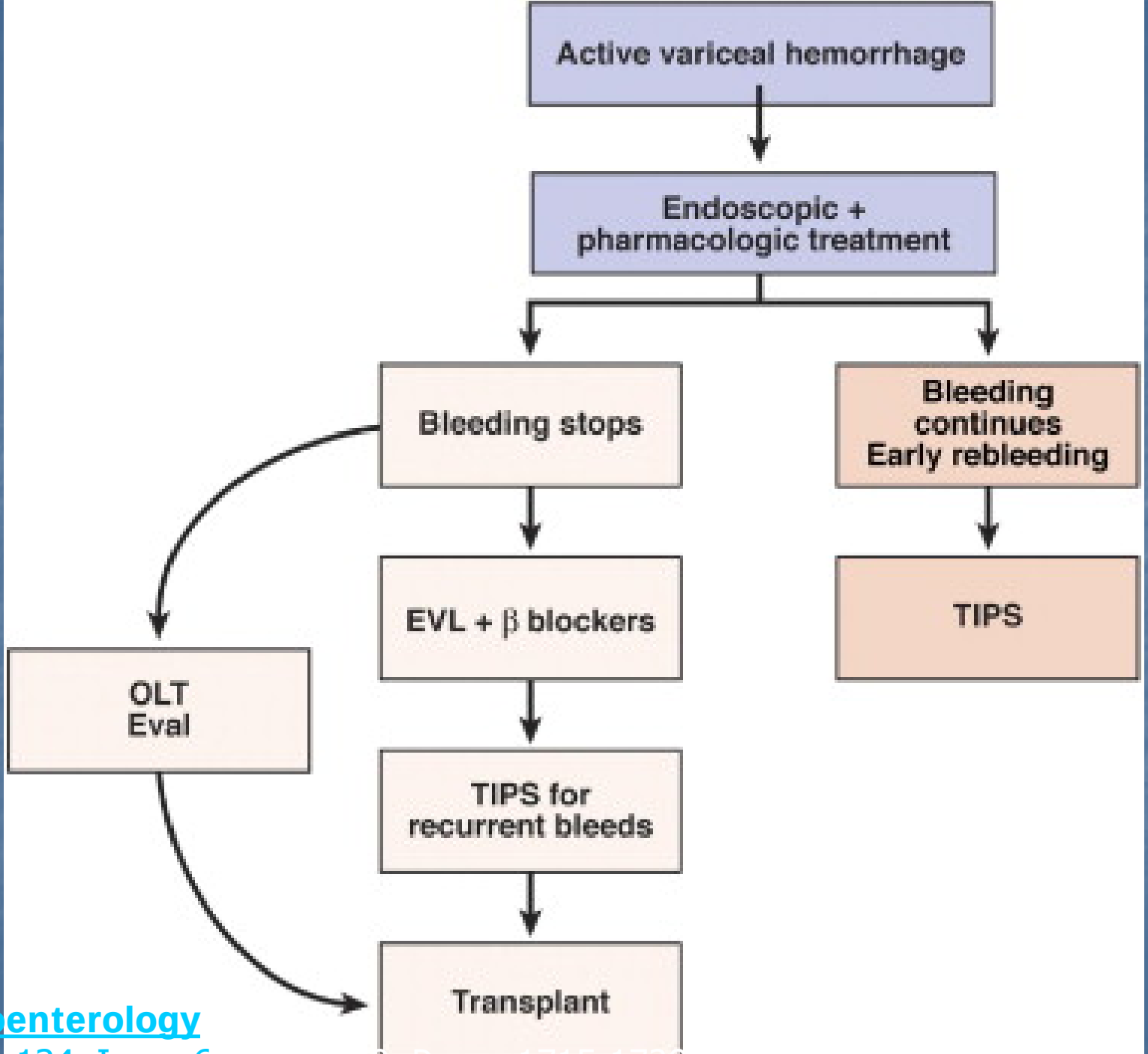

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AASLD GUIDELINES FOR GE Varices

- Recommendations for Diagnosis

1. **Screening EGD for the diagnosis of esophageal and gastric varices is recommended when the diagnosis of cirrhosis is made (Class IIa, Level C).**
2. **On EGD, esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted (Class IIa, Level C).**

Hepatology. 2007 Sep;46(3):922-38.

AASLD GUIDELINES FOR GE Varices

- Compensated cirrhosis w/o varices

1. nonselective -blockers cannot be recommended to prevent their development (Class III, Level B).
2. no varices on the initial EGD, it should be repeated in 3 years (Class I, Level C).
3. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C).

AASLD GUIDELINES FOR GE Varices

- ***Small Varices that have not bled***

1. ↑ risk of hemorrhage (Child B/C or presence of red wale marks on varices), nonselective -blockers should be used for the prevention of first variceal hemorrhage (Class IIa, Level C).
2. ↓ risk of bleeding, betablockers can be used, although their long-term benefit has not been established (Class III, Level B).

AASLD GUIDELINES FOR GE Varices

- ***Small Varices that have not bled***

1. In patients with small varices that have not bled and who are not receiving -blockers, EGD should be repeated in 2 years (Class I, Level C).
2. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C).
3. In patients with small varices who receive -blockers, a follow-up EGD is not necessary.

AASLD GUIDELINES FOR GE Varices

- Large Varices that have not bled

1. ↑ risk of hemorrhage (Child B/C or variceal red wale markings on endoscopy), nonselective -blockers (propranolol or nadolol) or EVL may be recommended for the prevention of first variceal hemorrhage (Class I, Level A).
2. ↓ of hemorrhage (Child A patients and no red signs), nonselective -blockers (propranolol, nadolol) are preferred and EVL should be considered in patients with contraindications or intolerance or non-compliance to -blockers (Class I, Level A).

AASLD GUIDELINES FOR GE Varices

- Large Varices that have not bled

1. If a patient is placed on a nonselective -blocker, it should be adjusted to the maximal tolerated dose; follow-up surveillance EGD is unnecessary.
2. If a patient is treated with EVL, it should be repeated every 1-2 weeks until obliteration with the first surveillance EGD performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence (Class I, Level C).
3. Nitrates (either alone or in combination with -blockers), shunt therapy, or sclerotherapy should not be used in the primary prophylaxis of variceal hemorrhage (Class III, Level A).

AASLD GUIDELINES FOR GE Varices

- **Acute Hemorrhage**

1. intravascular volume support, being careful to maintain a hemoglobin of 8 g/dL (Class I, Level B).
2. Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage (Class I, Level A).
   - Oral norfloxacin (400 mg BID) or intravenous ciprofloxacin (in patients in whom oral administration is not possible) is the recommended antibiotic (Class I, Level A).
   - In patients with advanced cirrhosis intravenous ceftriaxone (1 g/day) may be preferable particularly in centers with a high prevalence of quinolone-resistant organisms (Class I, Level B).

AASLD GUIDELINES FOR GE Varices

- **Acute Hemorrhage**

1. Pharmacological therapy (somatostatin or its analogues octreotide and vapreotide; terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 3-5 days after diagnosis is confirmed (Class I, Level A).
2. EGD, performed within 12 hours, should be used to make the diagnosis and to treat variceal hemorrhage, either with EVL or sclerotherapy (Class I, Level A).
3. TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level C).
4. Balloon tamponade should be used as a temporizing measure (maximum 24 hours) in patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS or endoscopic therapy) is planned (Class I, Level B).

AASLD GUIDELINES FOR GE Varices

- **Gastric Varices**

1. In patients who bleed from gastric fundal varices, endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available. Otherwise, EVL is an option (Class I, Level B).
2. A TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level B).

AASLD GUIDELINES FOR GE Varices

- **Post bleed recs.**

1. Patients with cirrhosis who survive an episode of active variceal hemorrhage should secondary prophylaxis (Class I, Level A).
2. Combination of NS bblker plus EVL is the best option for secondary prophylaxis of variceal hemorrhage (Class I, Level A).
3. The NS bblker should be adjusted to the maximal tolerated dose.
4. EVL should be repeated every 1-2 weeks until obliteration with the first surveillance EGD performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence (Class I, Level C).

AASLD GUIDELINES FOR GE Varices

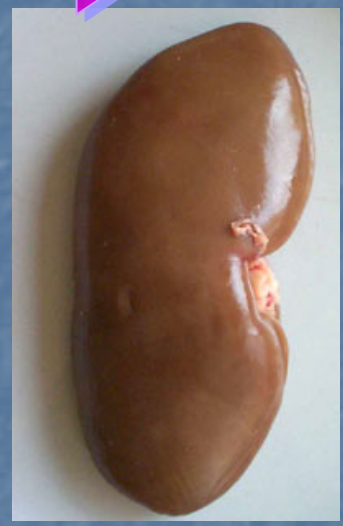
- Post bleed recs.

1. TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy. (Class I, Level A).
2. Patients who are otherwise transplant candidates should be referred to a transplant center for evaluation (Class I, Level C).

Beauty

And the...

Beast



Hepatorenal Syndrome

Diagnostic criteria of HRS

- ***MAJOR CRITERIA***
  - **Low GFR as indicated by serum Cr > 1.5 mg/dL or 24-hour creatinine clearance < 40 mL/min**
  - **Absence of shock, ongoing bacterial infection, and fluid losses, and current treatment with nephrotoxic agents**
  - **Lack of sustained improvement in renal function on discontinuation of diuretics and volume expansion by 1.5 L of a plasma expander**
  - **Proteinuria less than 500mg/d and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.**

Diagnostic criteria of HRS

- *MINOR CRITERIA*
  - Urine volume less than 500 mL/d
  - Urine sodium less than 10mEq/L
  - Urine osmolality greater than plasma osmolality
  - Urine RBCs less than 50 per high power field
  - Serum sodium concentration less than 130 mEq/L

	Type 1 HRS	Acute tubular necrosis
History of recent shock	No	Frequent
History of recent use of nephrotoxic drugs	No	Frequent
Urine findings		
Sodium concentrations (mmol/L)	<20	>40
Fractional excretion of sodium (%)	<1	>1
Urine osmolality (mOsm/kg)	<500	>350
Beta2-microglobulin (mg/L)	<1	>1.5
Renal pathology	No cellular lesion	Necrotic renal tubules

Hepatology. 2006 Mar;43(3):385-94

Table 3. Criteria for Diagnosis of the Hepatorenal Syndrome.*

Presence of the hepatorenal syndrome
Serum creatinine concentration >1.5 mg/dl or 24-hr creatinine clearance <40 ml/min
Absence of shock, ongoing bacterial infection, and fluid loss, and no current treatment with nephrotoxic drugs
Absence of sustained improvement in renal function (decrease in serum creatinine to ≤1.5 mg/dl) after discontinuation of diuretics and a trial of plasma expansion
Absence of proteinuria (<500 mg/day) or hematuria (<50 red cells per high-power field)
Absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Urinary sodium concentration <10 mmol/liter†
Type of hepatorenal syndrome
Type 1: progressive impairment in renal function as defined by a doubling of initial serum creatinine above 2.5 mg/dl in less than two weeks
Type 2: stable or slowly progressive impairment in renal function not meeting the above criteria

* To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† Although the urinary sodium concentration is less than 10 mmol per liter in most patients with the hepatorenal syndrome, this finding is not considered a major diagnostic criterion because some patients with this syndrome may not have markedly low sodium excretion.[6]

NEJM. Volume 350(16), 15 April 2004, pp 1646-1654

Table 4. Recommendations for Treatment with Vasoconstrictors in Patients with the Hepatorenal Syndrome.

Recommendation	Reference
Administration of one of the following drugs or drug combinations	
Norepinephrine (0.5–3.0 mg/hr intravenously)	Duvoux et al.[48]
Midodrine (7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed) in combination with octreotide (100 μg subcutaneously three times daily, increased to 200 μg three times daily if needed)	Angeli et al.[49]
Terlipressin (0.5–2.0 mg intravenously every 4–12 hr)*	Uriz et al.,[50] Moreau et al.,[51] Mulkay et al.,[52] Ortega et al.[53]
Concomitant administration of albumin (1 g/kg intravenously on day 1, followed by 20–40 g daily)	Duvoux et al.,[48] Angeli et al.,[49] Uriz et al.,[50] Ortega et al.[53]
Duration of therapy: 5–15 days	
End point: reduction of serum creatinine concentration to <1.5 mg/dl†	

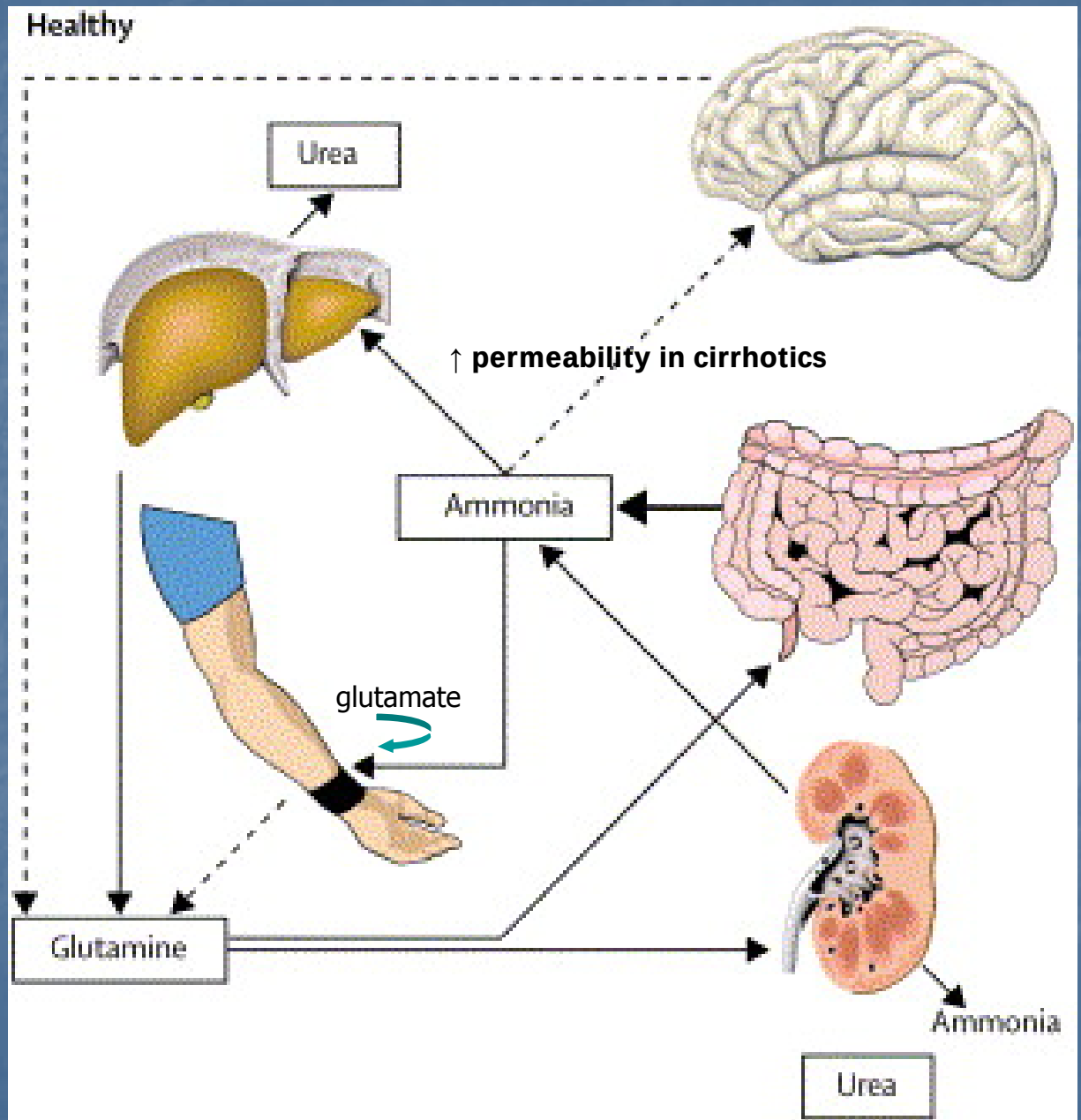
* Terlipressin is not available in some countries, including the United States.
† To convert the value for creatinine to micromoles per liter, multiply by 88.4.

NEJM. Volume 350(16), 15 April 2004, pp 1646-1654

ENCEPHALOPATHY 101

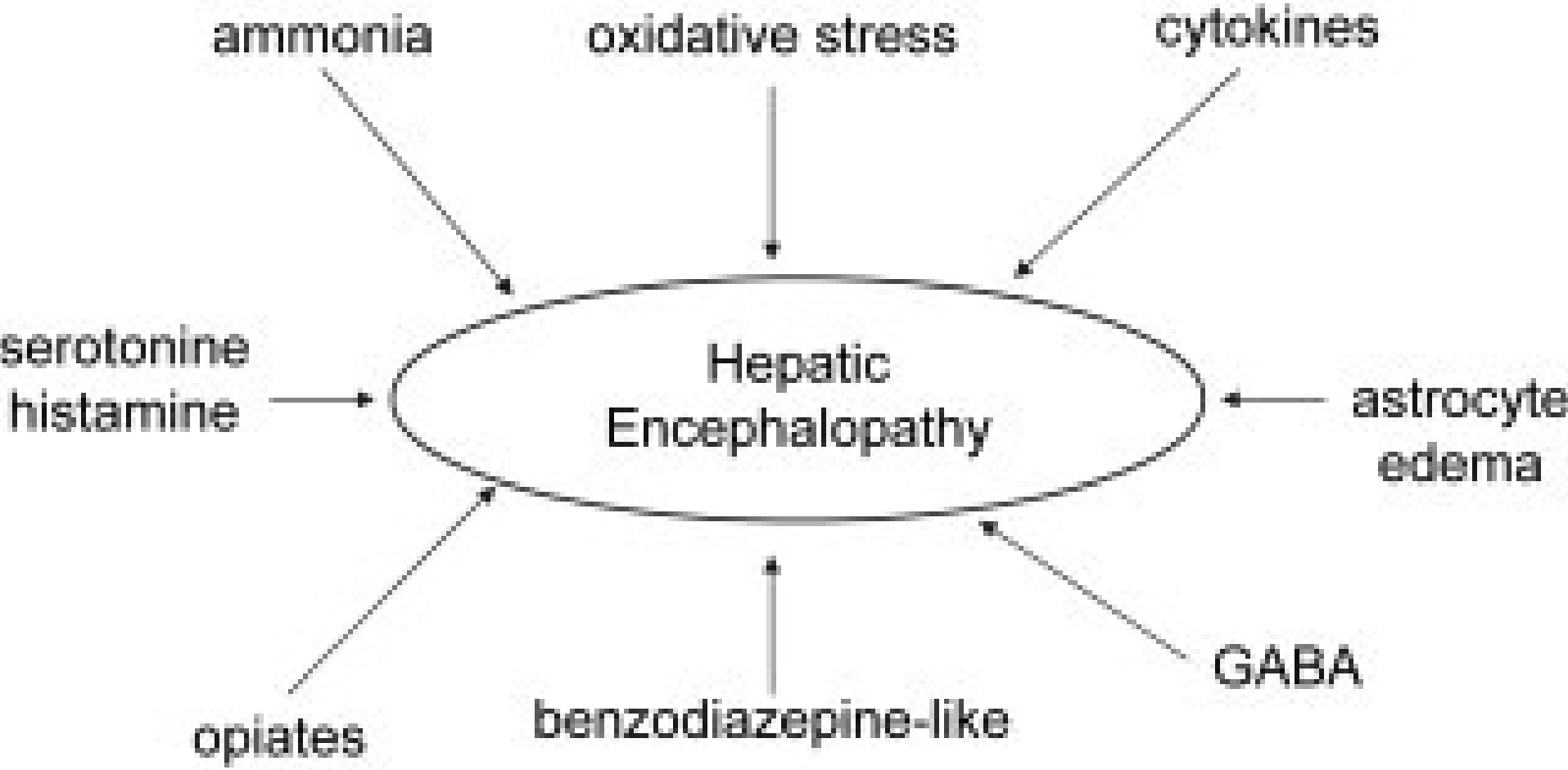
- Reversible neuro-psychiatric manifestation of portosystemic shunting.
- One-year survival 40%.
- 1/3rd to ½ of all hospitalizations for cirrhotics.
- Decreased hepatic clearance of ammonia derived from: 1) kidney, 2) urease activity of colonic bacteria, and 3) glutamine uptakein small bowel.

Whats ammonia got to do with it?



Shawcross D, Jalan R. Lancet. 2005 Jan 29-Feb 4;365(9457):431-3.

Neurologic impairment factors in HE



Munoz S. Medical Clinics of North America - Volume 92, Issue 4 (July 2008)

The Trojan Horse Glutamine

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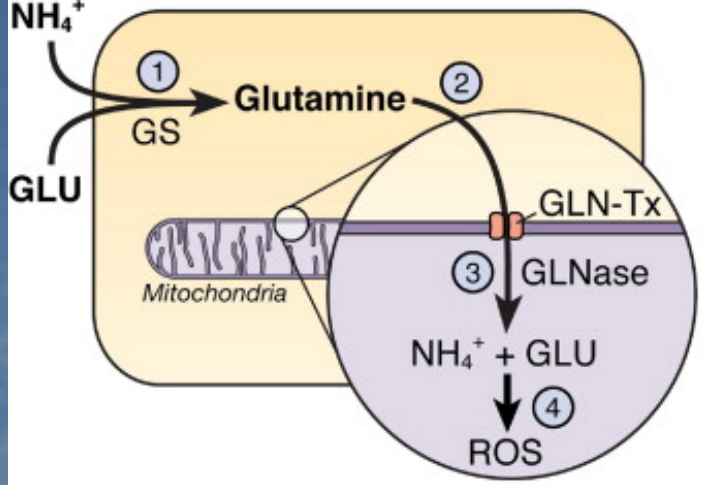
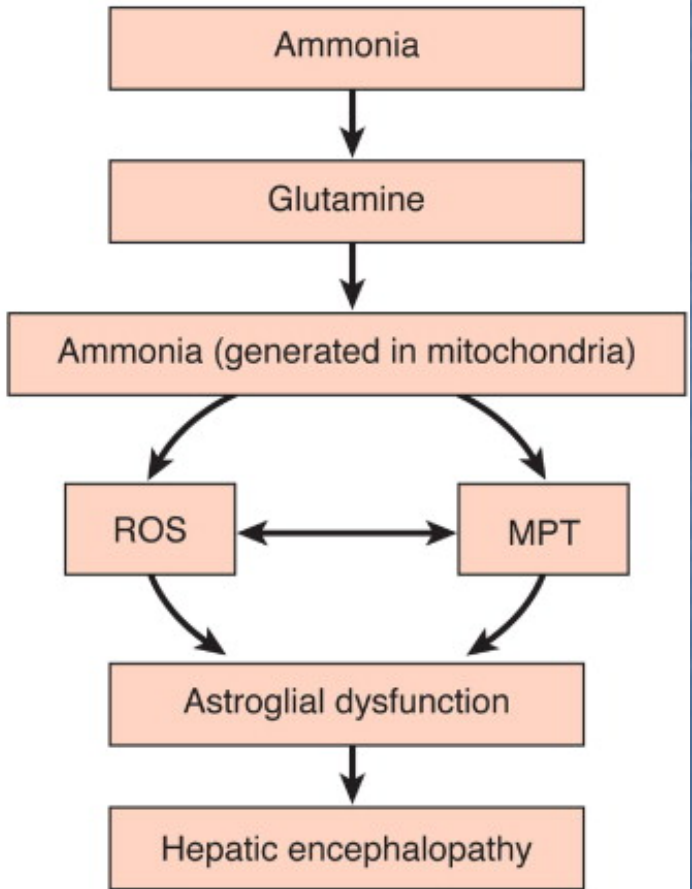




Precipitating factors for hepatic encephalopathy

- Dehydration
- GIB
- Infections
- Constipation
- Excessive dietary protein
- Central nervous system acting drugs
- Hypokalemia
- Renal failure
- Hyponatremia
- Surgery
- TIPS
- Superimposed liver injury (acute hepatitis, drug-induced liver injury)
- Hepatocellular carcinoma
- Terminal liver disease
- Urinary obstruction
- ? H.Pylori

Major differential diagnoses in hepatic encephalopathy

- Metabolic encephalopathies (uremia, sepsis, hypoxia, hypoglycemia, ketoacidosis, hypercapnea, thyroid dysfunction, or cerebral edema)
- Intracranial bleeding: subdural hematoma, intracranial hemorrhage
- Ischemic brain disease: transient ischemic attack, ischemic stroke
- Central nervous system abscess, encephalitis, meningitis (bacterial, viral, fungal)
- Central nervous system neoplasm
- Delirium tremens
- Alcoholism
- Postictal state

a)

The West Haven Criteria for Grading Mental State in Patients with Cirrhosis

Grade 0	No abnormality detected
Grade 1	Trivial lack of awareness Euphoria Anxiety Shortened attention span Impairment of addition and subtraction
Grade 2	Lethargy or Apathy Disorientation of time Obvious personality change Inappropriate behavior
Grade 3	Somnolence to semistupor Responsive to stimuli Confused Gross Disorientation Bizarre behavior
Grade 4	Coma, unable to test mental state

b)

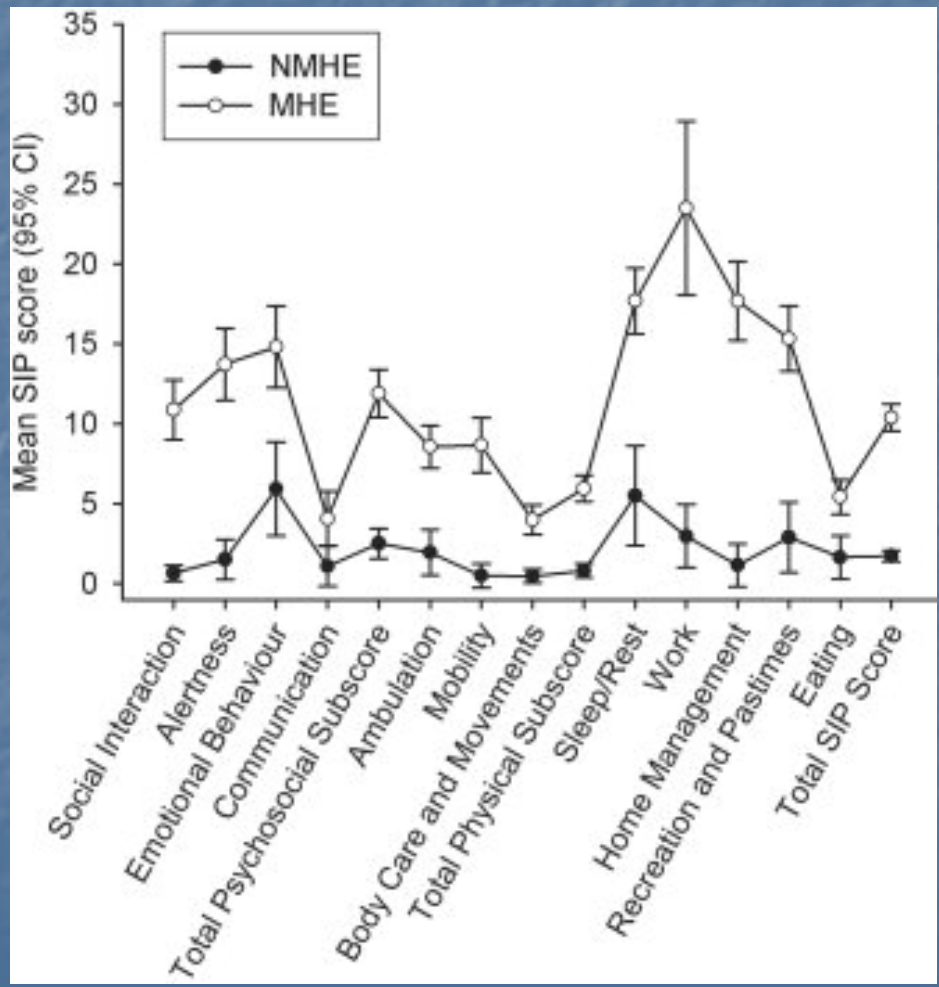
Portosystemic Encephalopathy Index

PSE = (grade of mental state)x3 + (grade of number connection test) + (grade of flapping tremor) + (grade of blood ammonia)

Shores NJ, Keeffe EB. Dig Dis Sci. 2008 Sep;53(9):2330-3.

Minimal Hepatic Encephalopathy

- Prevalence 30% and 84%
- memory reduction, personality changes ↓concentration and reaction times = ↓QOL
- ? marker for future episodes of clinical HE



Hepatology. Volume 45, Issue 3, Pages 549-559

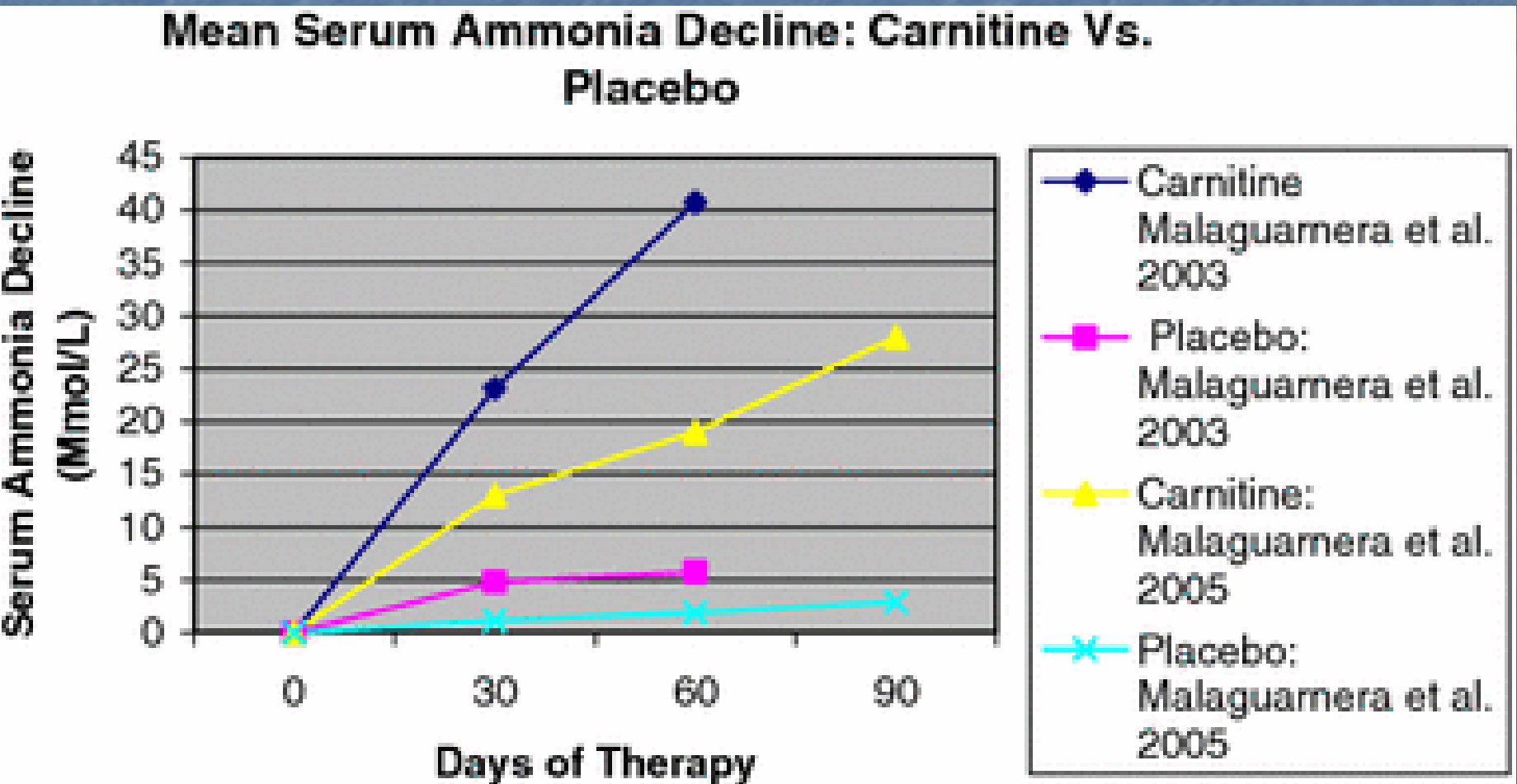
l-acyl-carnitine

- co-factor required for transport of long-chain fatty acids through the mitochondrial membrane (important for metabolism and energy production)
- maintains the intramitochondrial salvage pathways
- re-activates coenzyme A
- reduce peroxidation and intracellular malonyl-aldehyde levels
- act as a scavenger and to contribute to neurotransmitter synthesis due to the structural affinity to acetyl-choline.

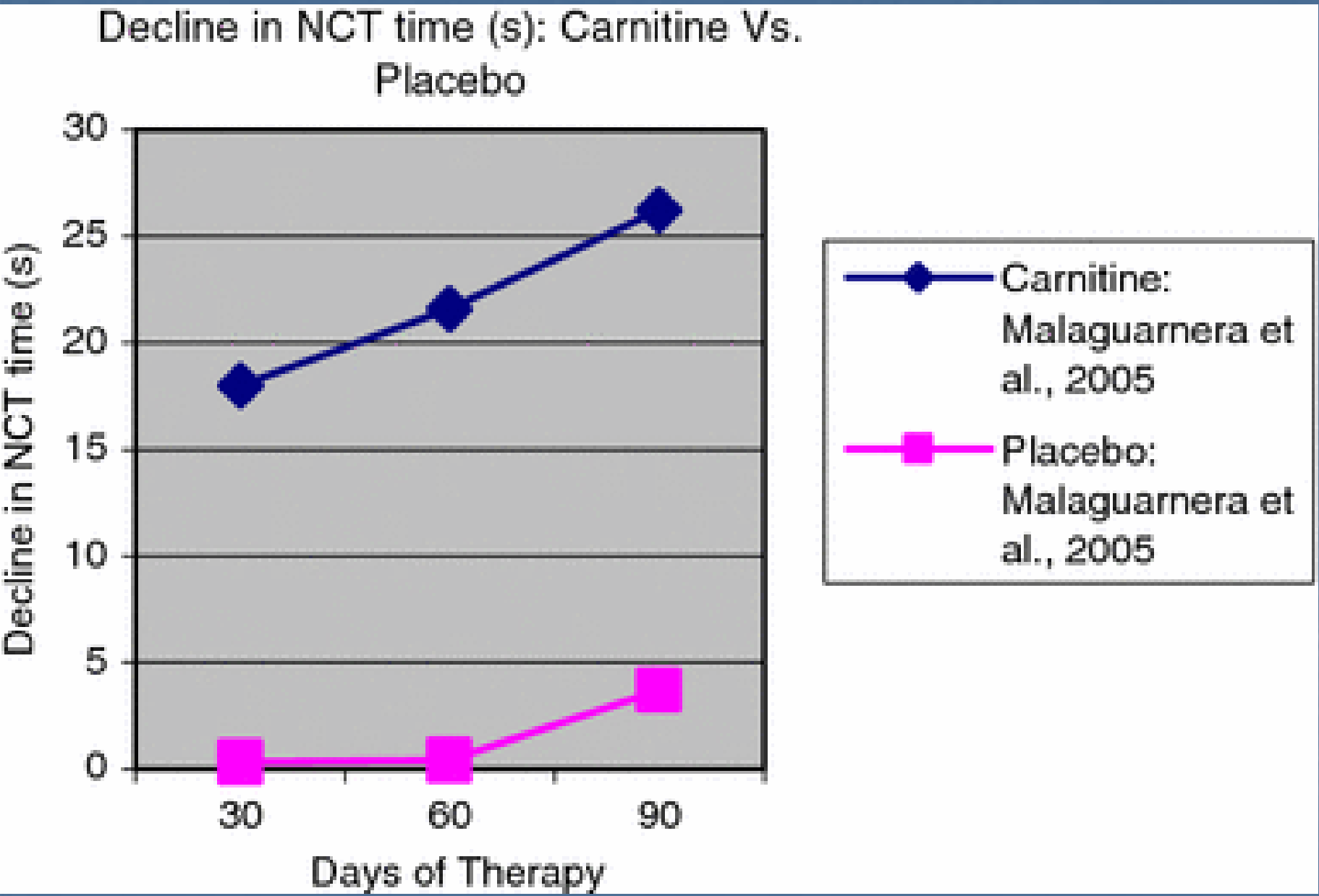
l-acyl-carnitine

- Malaguarnera et al. (3 rct's) oral carnitine
  - ↓ serum ammonia levels
  - ↑ patient performance on a variety of psychometric tests (ONLY grade 0, 1, or 2)
- In critically ill patients with hepatic coma
  - ↓ serum ammonia levels
  - ↑ Glasgow coma score appears to have worsened compared to placebo.
- All 4gm oral cartinine
- IMPORTANT LIMITATION: single center by one investigator

Mean decline in serum ammonia with carnitine versus placebo in two randomized controlled series

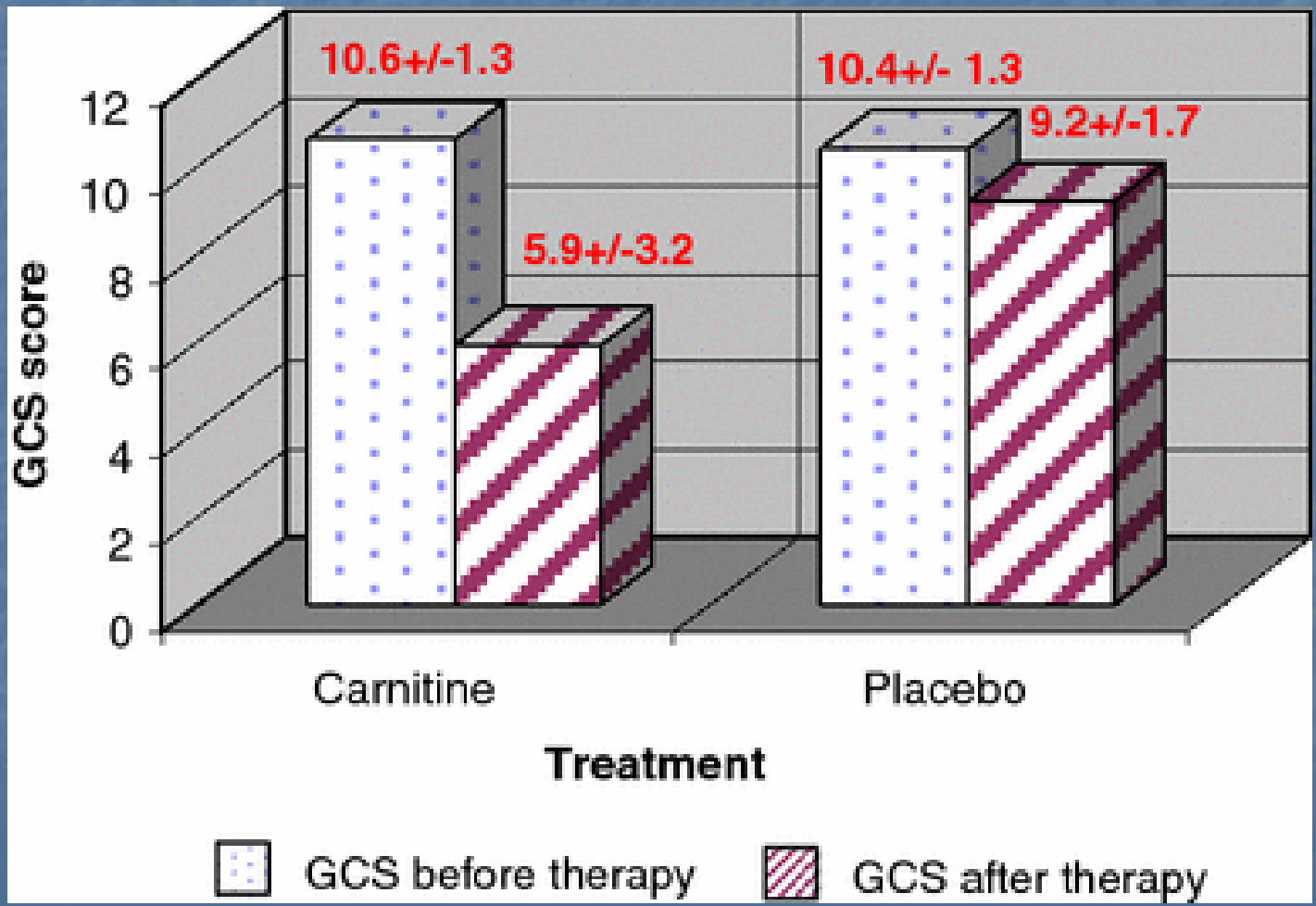


Shores NJ, Keeffe EB. Dig Dis Sci. 2008 Sep;53(9):2330-3.



Shores NJ, Keeffe EB. Dig Dis Sci. 2008 Sep;53(9):2330-3.

Mean change in the Glasgow coma scale of critically ill cirrhotic patients treated with l-carnitine versus placebo



Shores NJ, Keeffe EB. Dig Dis Sci. 2008 Sep;53(9):2330-3.

To Lactulose or not to Lactulose

- Lactulose has been used as the standard treatment for hepatic encephalopathy, and its efficacy has been considered to be beyond
- It was implemented in clinical practice because two trials found it "equally effective" to neomycin, which had been the standard treatment for hepatic encephalopathy since 1957.

Als-Nielsen et al. BMJ. 2004 May 1;328(7447):1046.

Treating HE

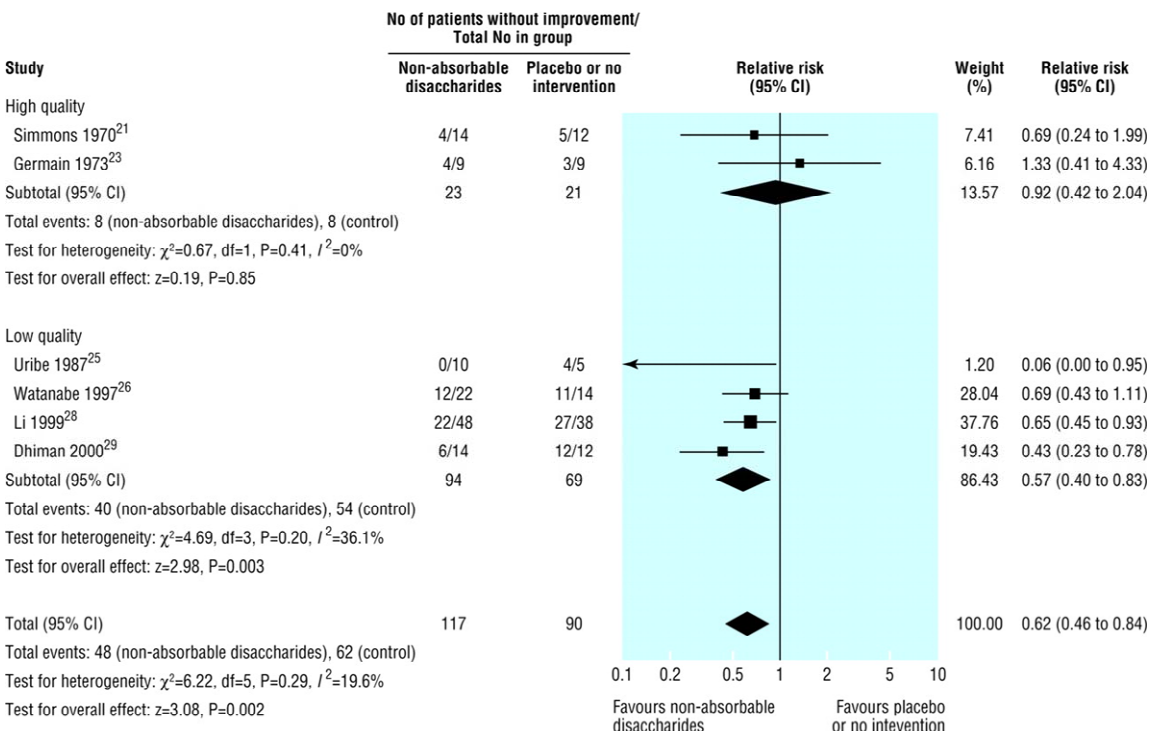
- Non-absorbable disaccharides for hepatic encephalopathy.
  - "There is insufficient evidence to support or refute the use of non-absorbable disaccharides for hepatic encephalopathy. Antibiotics were superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important."
  - BMJ 2004;328:1046 (1 May)

Treating HE

- Non-absorbable disaccharides for hepatic encephalopathy.
  - minimal hepatic encephalopathy appears to be the exception

Treating HE

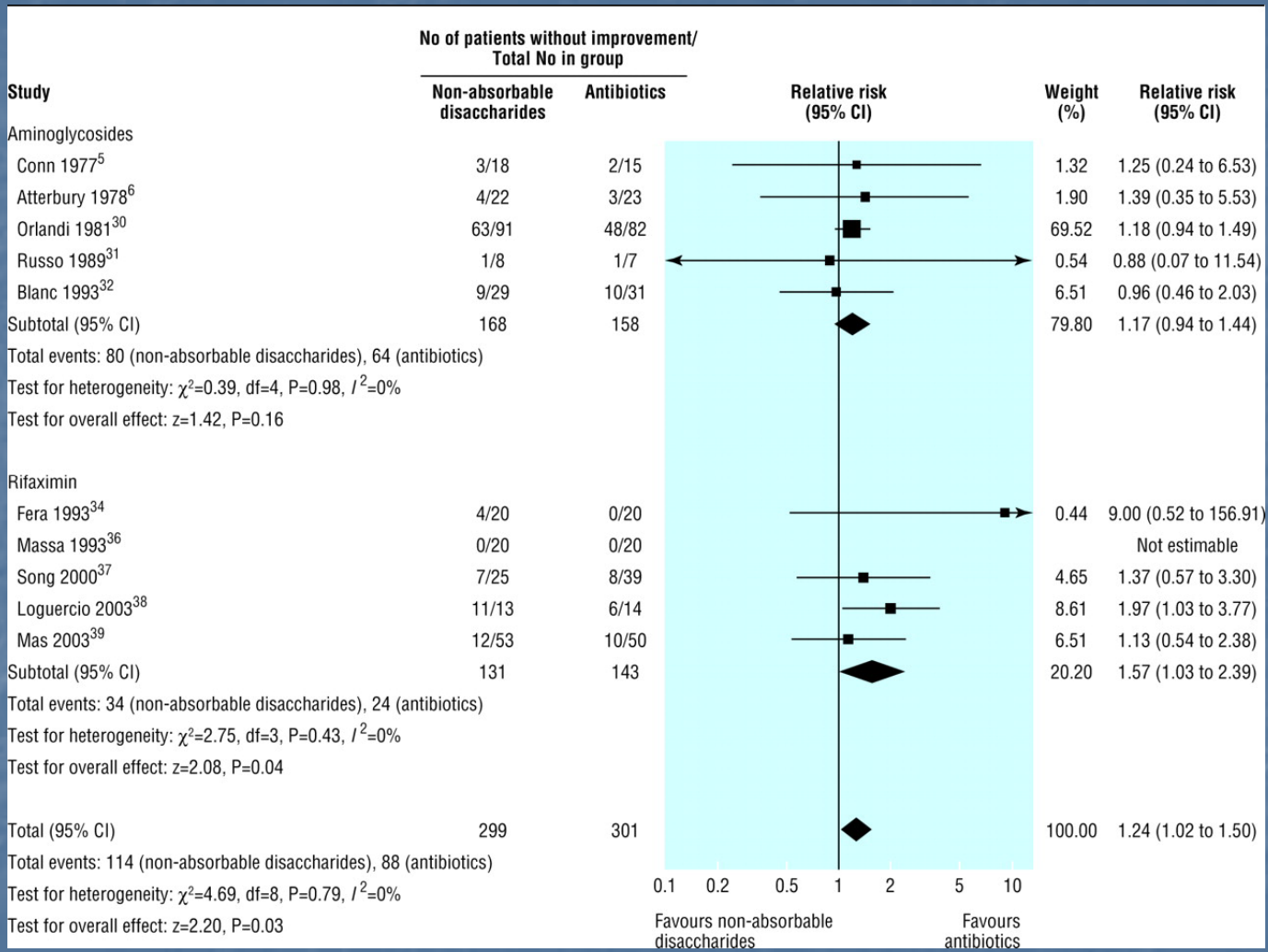
Fig 2 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods



Als-Nielsen, B. et al. BMJ 2004;328:1046

BMJ

Fig 3 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic



Als-Nielsen, B. et al. BMJ 2004;328:1046

To Lactulose or not to Lactulose

- Als-Nielsen B, Gluud LL, Gluud C. BMJ 2004;328:1046 (1 May)
- 22 trials were included.
- reduce the risk of no improvement in patients with HE
- High quality trials found no significant effect (0.92, 0.42 to 2.04, two trials).
- no significant effect on mortality
- inferior to antibiotics in reducing the risk of no improvement and lowering blood ammonia concentration

Treating HE

- Branched-chain amino acids for hepatic encephalopathy.
  - "We did not find convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy". Cochrane Database Syst Rev. 2003;(2):CD001939

Treating HE

- Benzodiazepine receptor antagonists for hepatic encephalopathy.
  - "Flumazenil had a significant beneficial effect on short-term improvement of hepatic encephalopathy in patients with cirrhosis and a highly favourable prognosis. Flumazenil had no significant effect on recovery or survival."
  - Cochrane Database Syst Rev. 2004

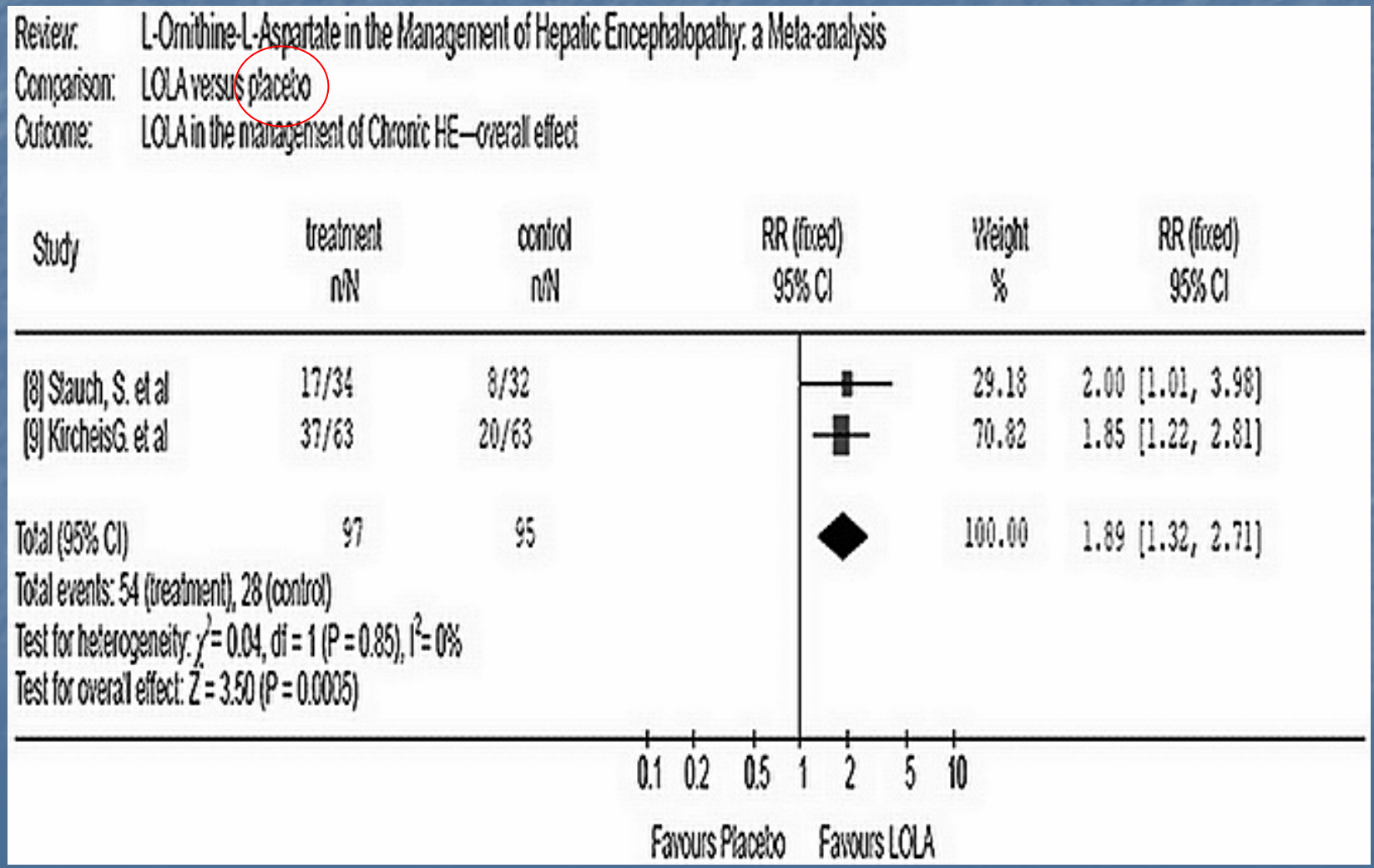
Treating HE

- Dopaminergic agonists for hepatic encephalopathy.
  - "This review does not provide evidence that dopaminergic agonists are of benefit to patients with acute or chronic hepatic encephalopathy, or fulminant hepatic failure…there is also insufficient evidence to exclude a potential beneficial effect."
  - Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003047.

l-ornithine-l-aspartate (LOLA)

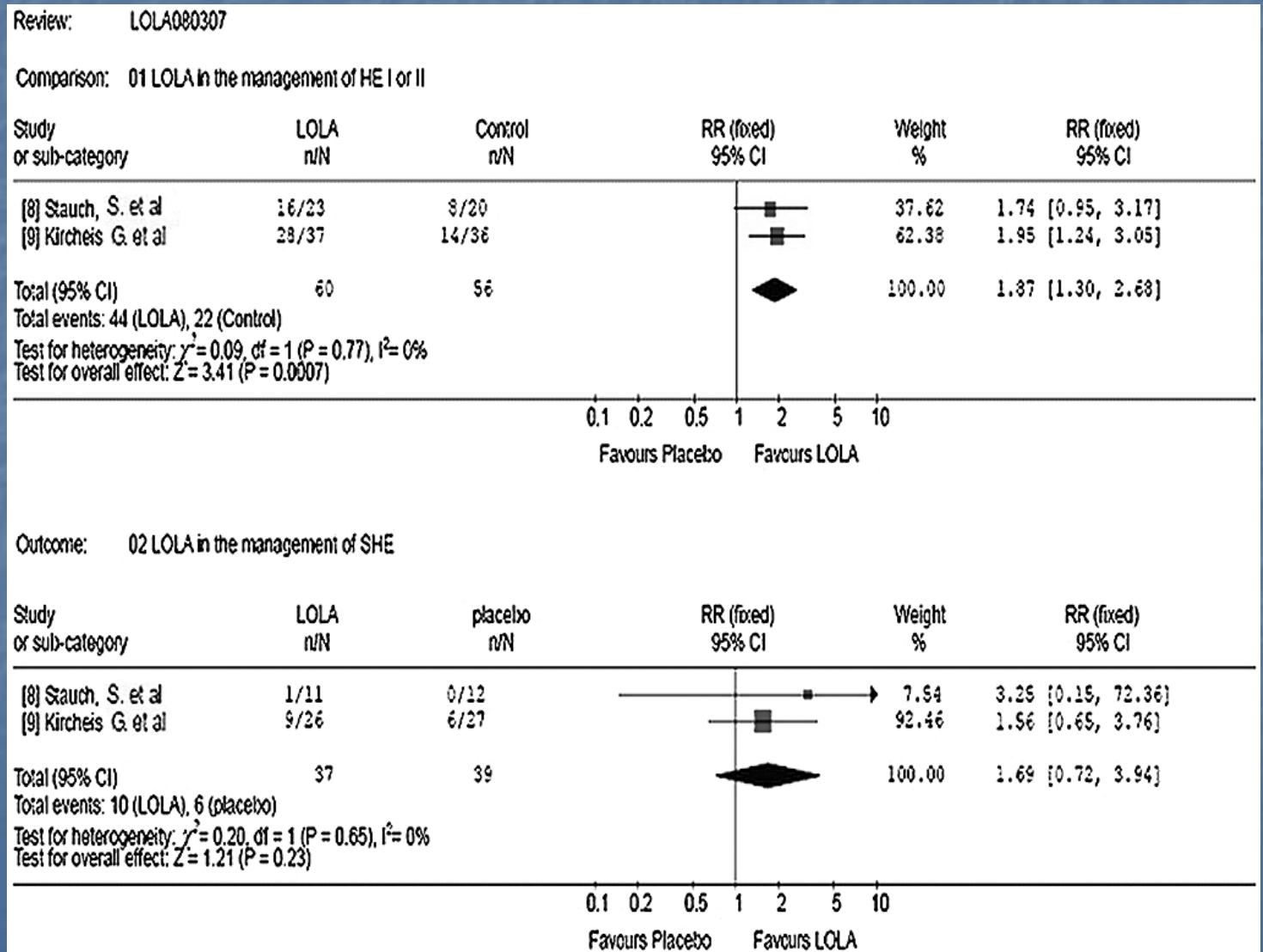
- Ornithine + ammonia -> urea
- aspartate + ammonia -> glutamine
- LOLA thus provides for both of these ammonia detoxification pathways.
- Several randomized controlled trials with LOLA have been carried out in Germany over the last 10 years.
- All these studies showed a beneficial effect of this compound on HE

LOLA



J Gastroenterol Hepatol. 2008 Sep 24.

LOLA



J Gastroenterol Hepatol. 2008 Sep 24.

Zinc and HE

- **long-term oral zinc speeds up the kinetics of urea formation from amino acids and ammonia.**
- **Cirrhotics have reduced Zinc levels**
- **Zinc levels inversely correlate with ammonia levels in cirrhotics with HE**
- **Diuretics reduce zinc levels**
- **Short term vs Long term: data suggests long term therapy is needed.**
- **Dose: 220 mg po qday or bid**

- Reding P, Duchateau J, Bataille C. Lancet. 1984 Sep 1;2(8401):493-5.
- Bresci G, Parisi G, Banti S. Eur J Med. 1993 Aug-Sep;2(7):414-6.

HE 101

- Nutritional Management:
  - –Early nutrition to cover calorie needs and 1-1.5 g protein/kg/day.
  - –In Chronic Stable PSE: ? branched-chain aminoacidsenriched formula (Nutra-Hep)
- Manipulation of Splanchnic Circulation:
  - Radiology-guided occlusion of shunts.

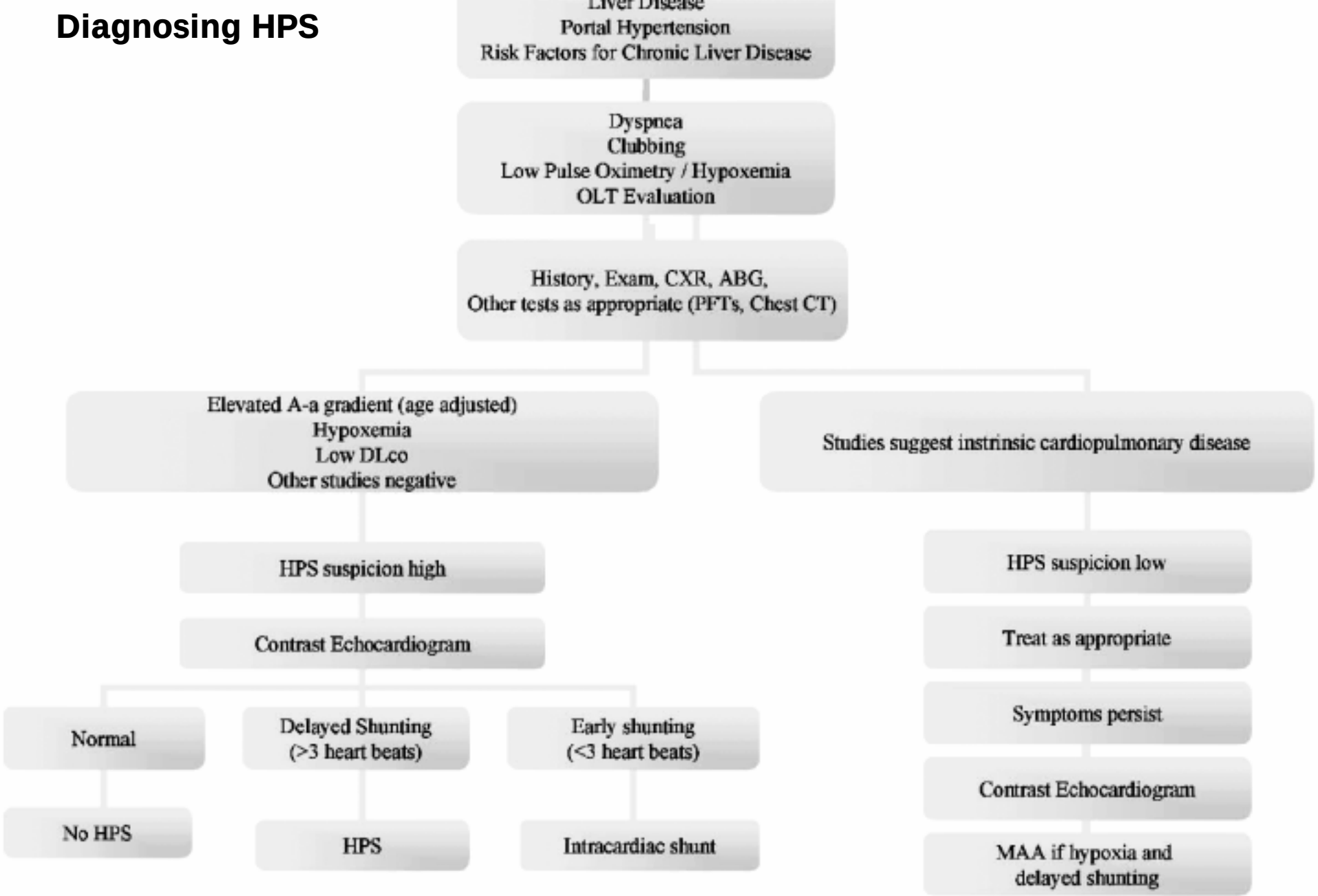
Hepatopulmonary Syndrome

- Does not require portal htn
- triad of liver disease, hypoxemia, and intrapulmonary vascular dilations (IPVDs)
- s/s: cyanosis, dyspnea, platypnea, orthodeoxia (fall in PaO2 5% or 4 mm Hg while standing), and clubbing.
- Diagnosis of HPS is based on arterial deoxygenation and CEE+ in the absence of intrinsic cardiopulmonary disease.
- 15–20% of patients with chronic liver diseases

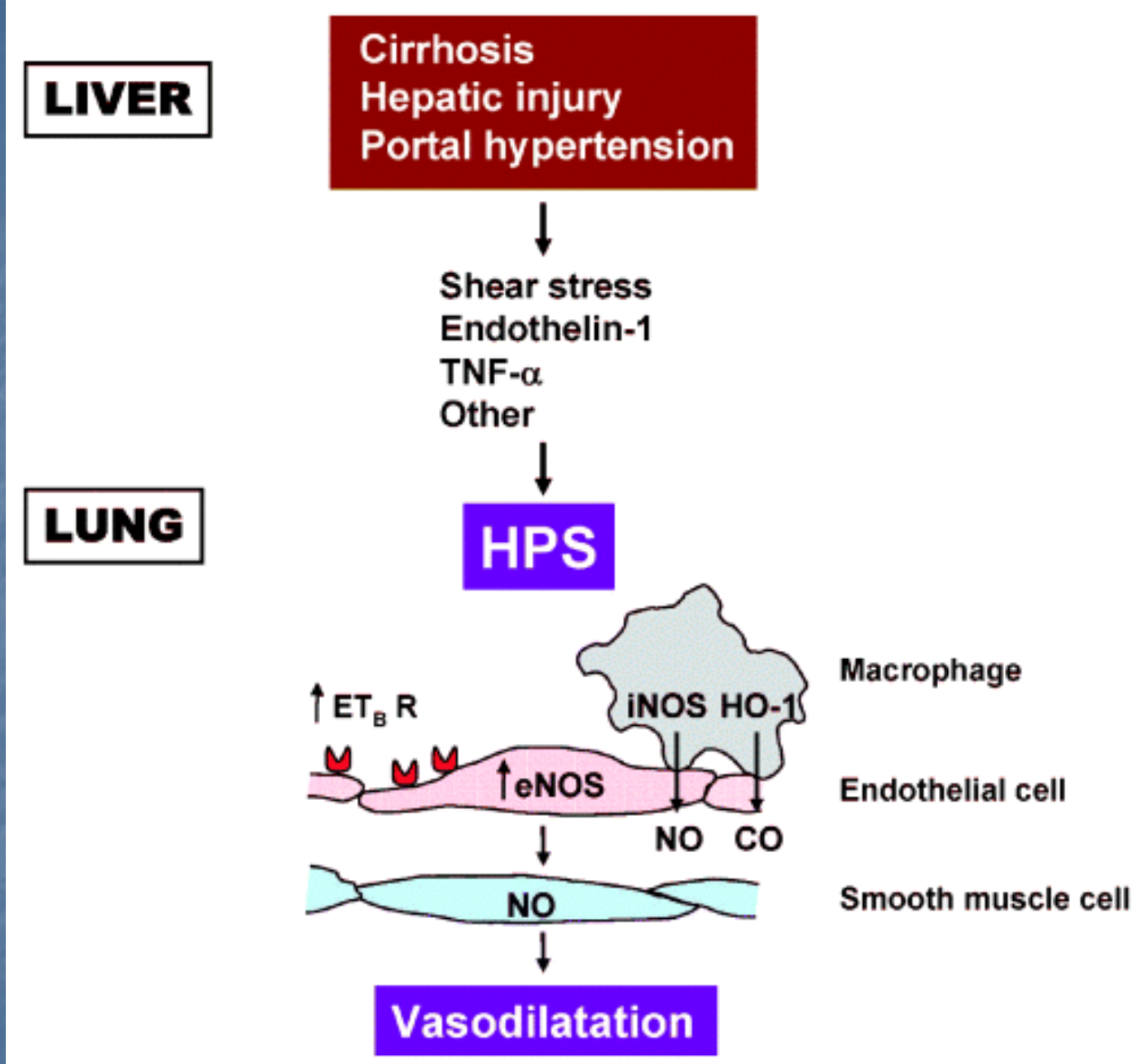
Hepatopulmonary Syndrome

- Pathophysiology
  - intrapulmonary vasodilatation
  - Cytokine-mediated injury
  - induction of inducible nitric oxide synthase
- Treatment
  - Liver transplant (not always successful)
  - Pentoxifylline 400mg PO tid

Diagnosing HPS

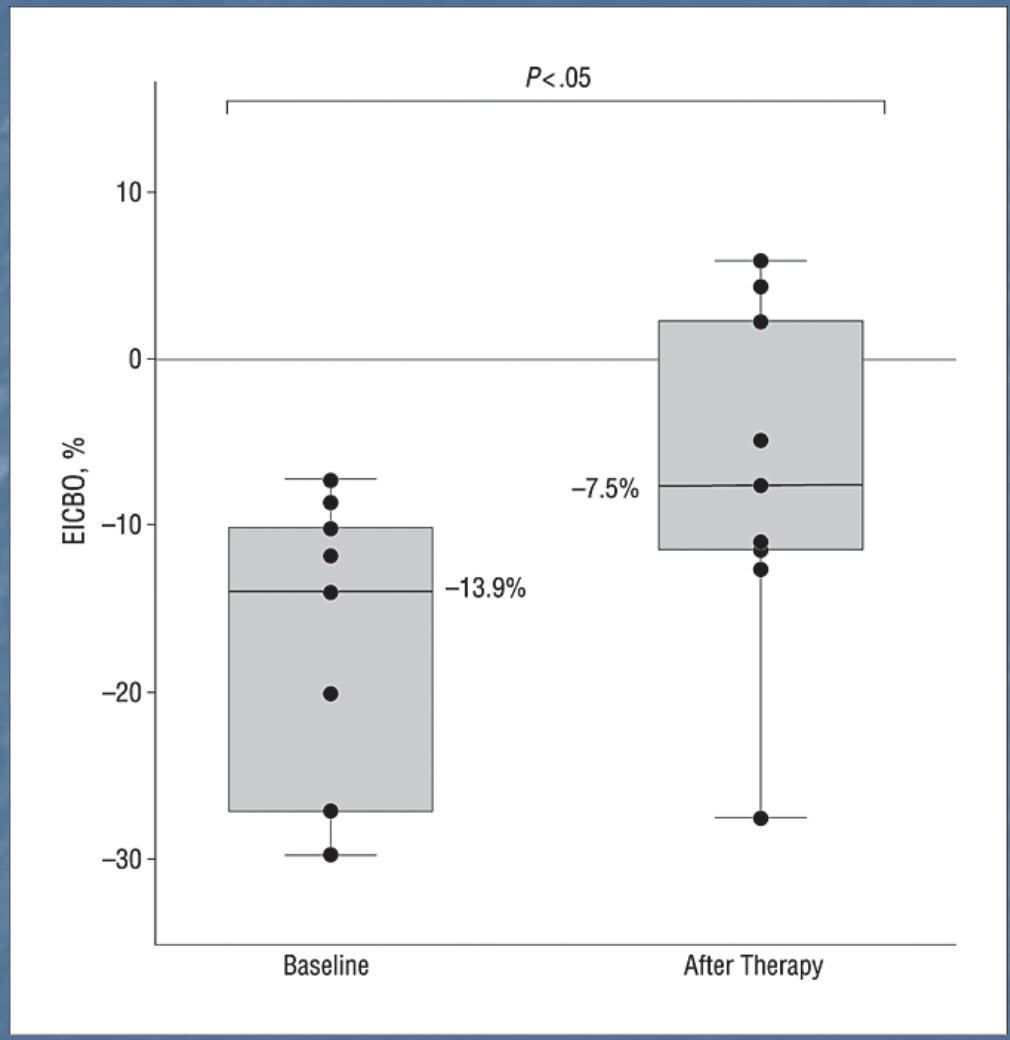


Gaines and Fallon. Liver International Vol. 24, 5 Pages: 397-401



Gaines and Fallon. Liver International Vol. 24, 5 Pages: 397-401

Baseline and posttherapy median (range) values of exercise-induced change in blood oxygen (EICBO)



Gupta, L. B. et al. Arch Intern Med 2008;168:1820-1823.

"pentoxifylline can be considered a safe and effective therapy for HPS"