COMPLICATIONS OF CIRRHOSIS

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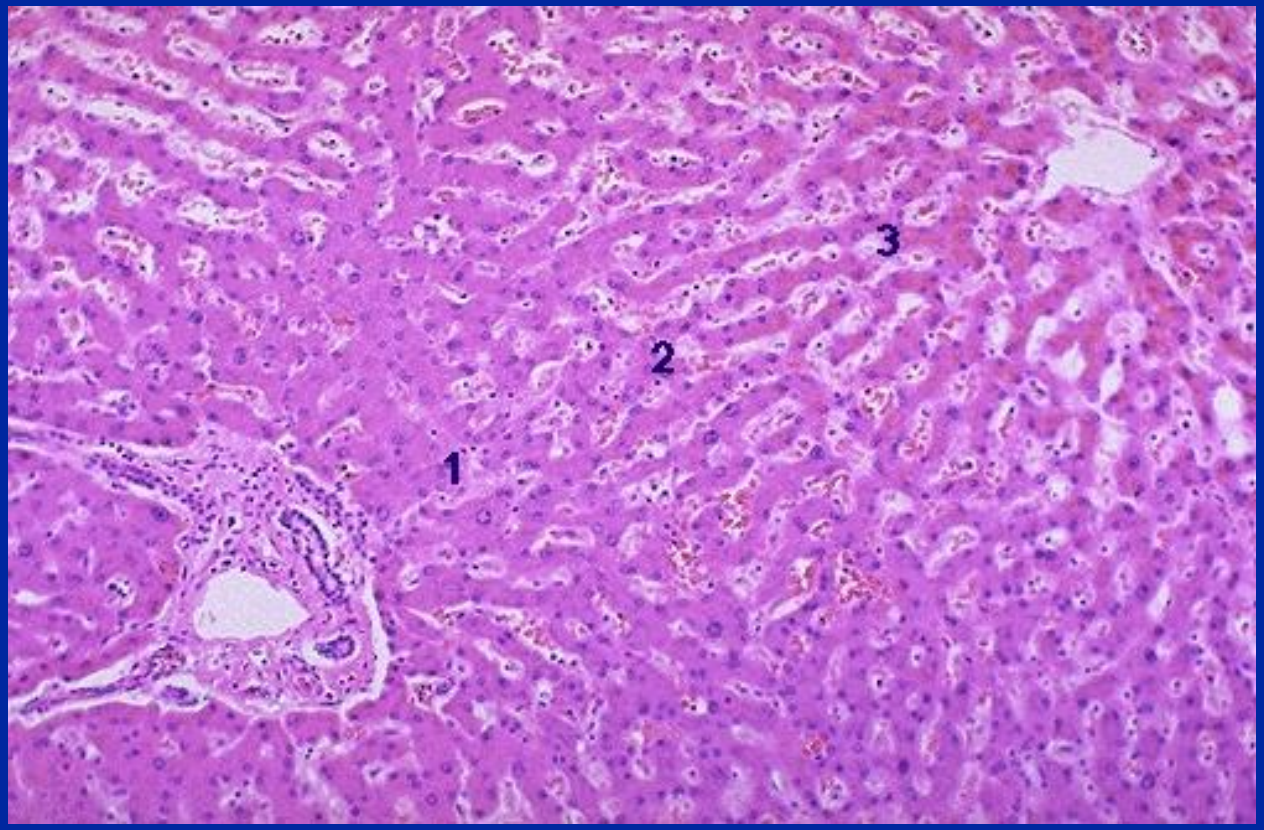
OBJECTIVES

Conceptual Framework

Pathophysiology, clinical features and therapies:

- **Varices**
- **Ascites**
- **Hepatic encephalopathy**
- **Acute Kidney injury**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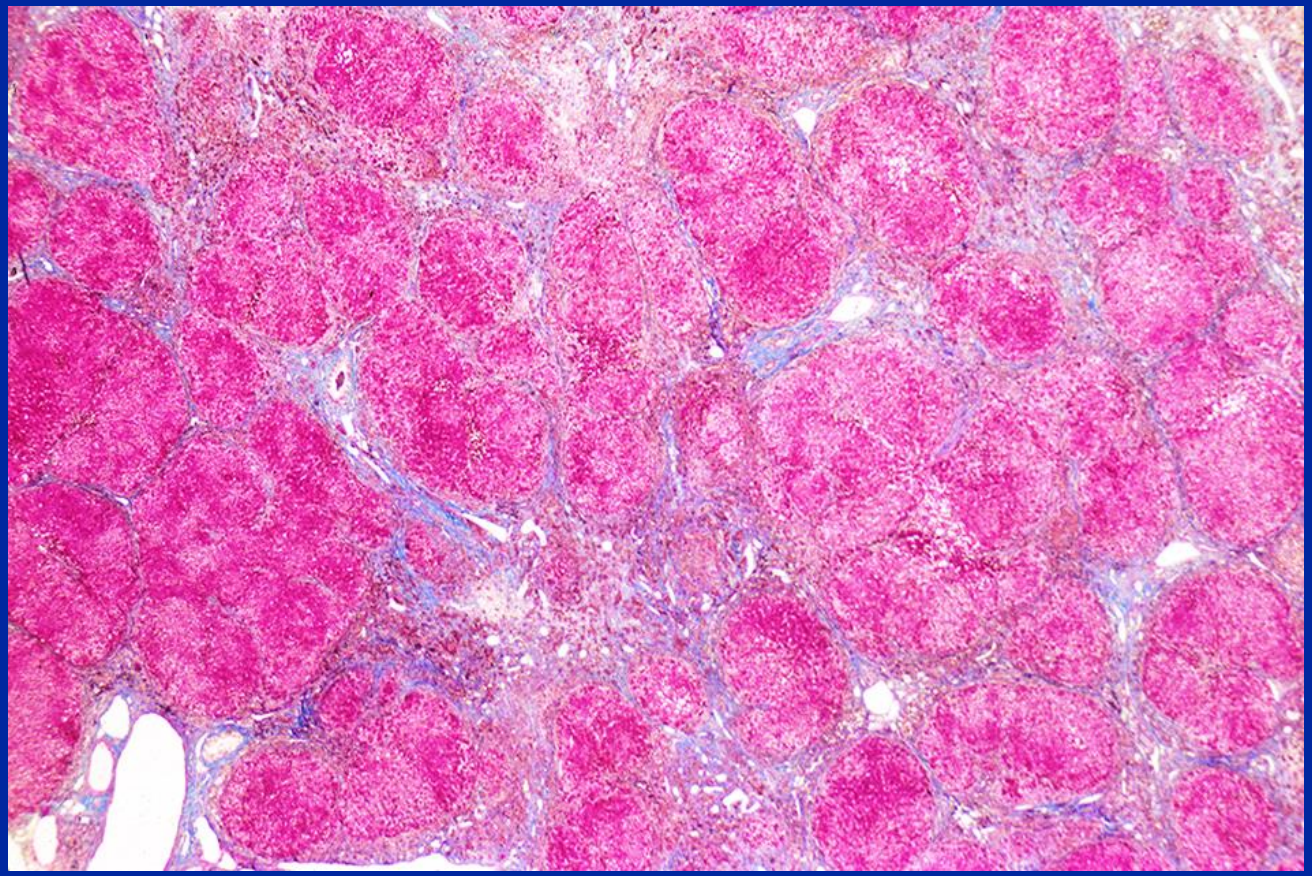


Complications of Cirrhosis

(1) Portal hypertension	“plumbing”
(2) hepatic dysfunction	“metabolism”
(3) altered vessel tone	“vasculature”

Complications of Cirrhosis

Portal Hypertension

↓

porto-systemic shunting
increased hepatic lymph

↓

varices
ascites
encephalopathy
splenomegaly

Hepatic dysfunction

↓

defective synthesis and degradation

↓

low serum albumin
high prothrombin time
elevated total bilirubin
encephalopathy

Altered vessel tone

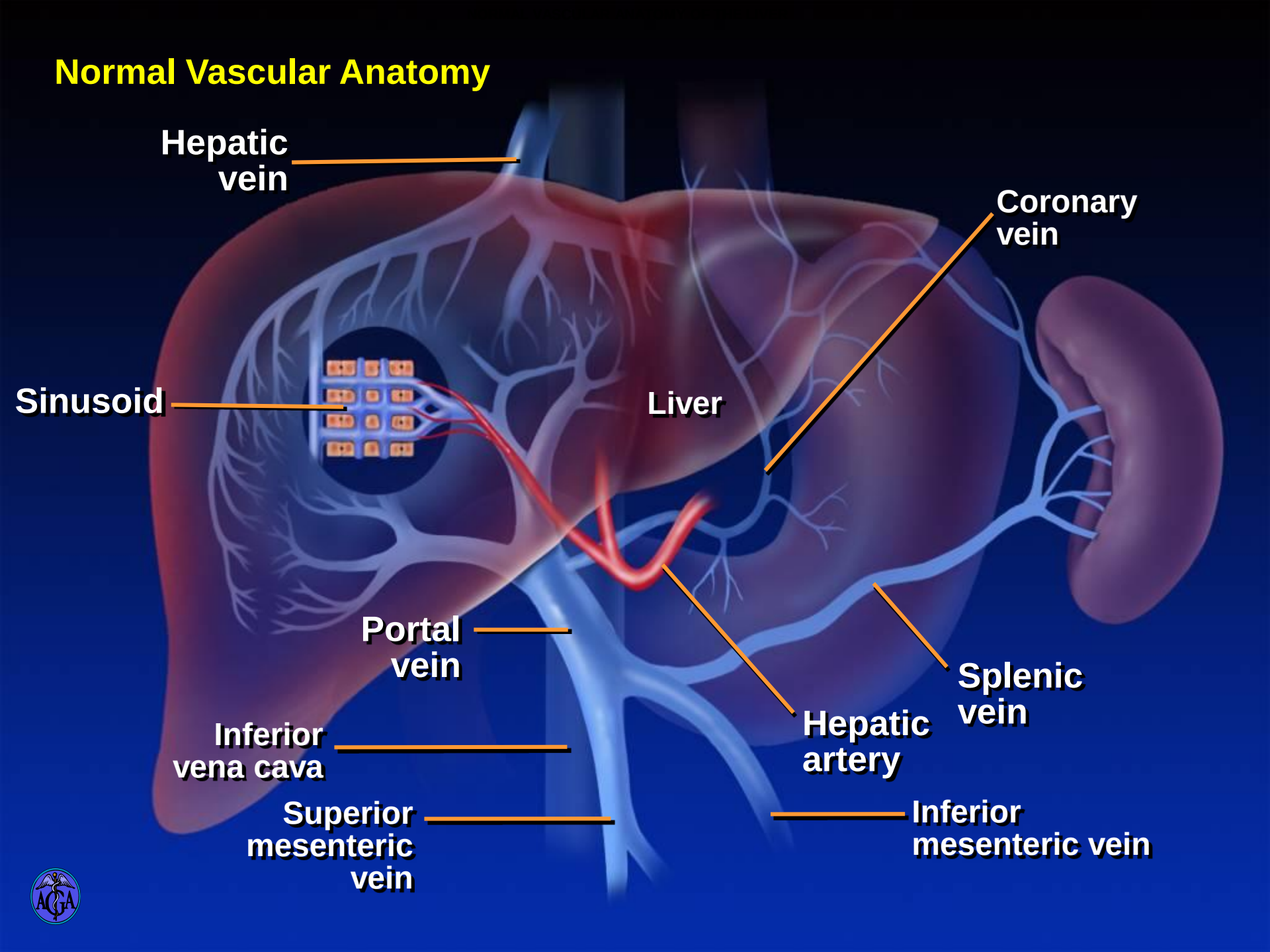
↓

vasoactive mediators

↓

hyperdynamic circulation
hepatorenal syndrome
hepatopulmonary syndrome
portal hypertensive gastropathy

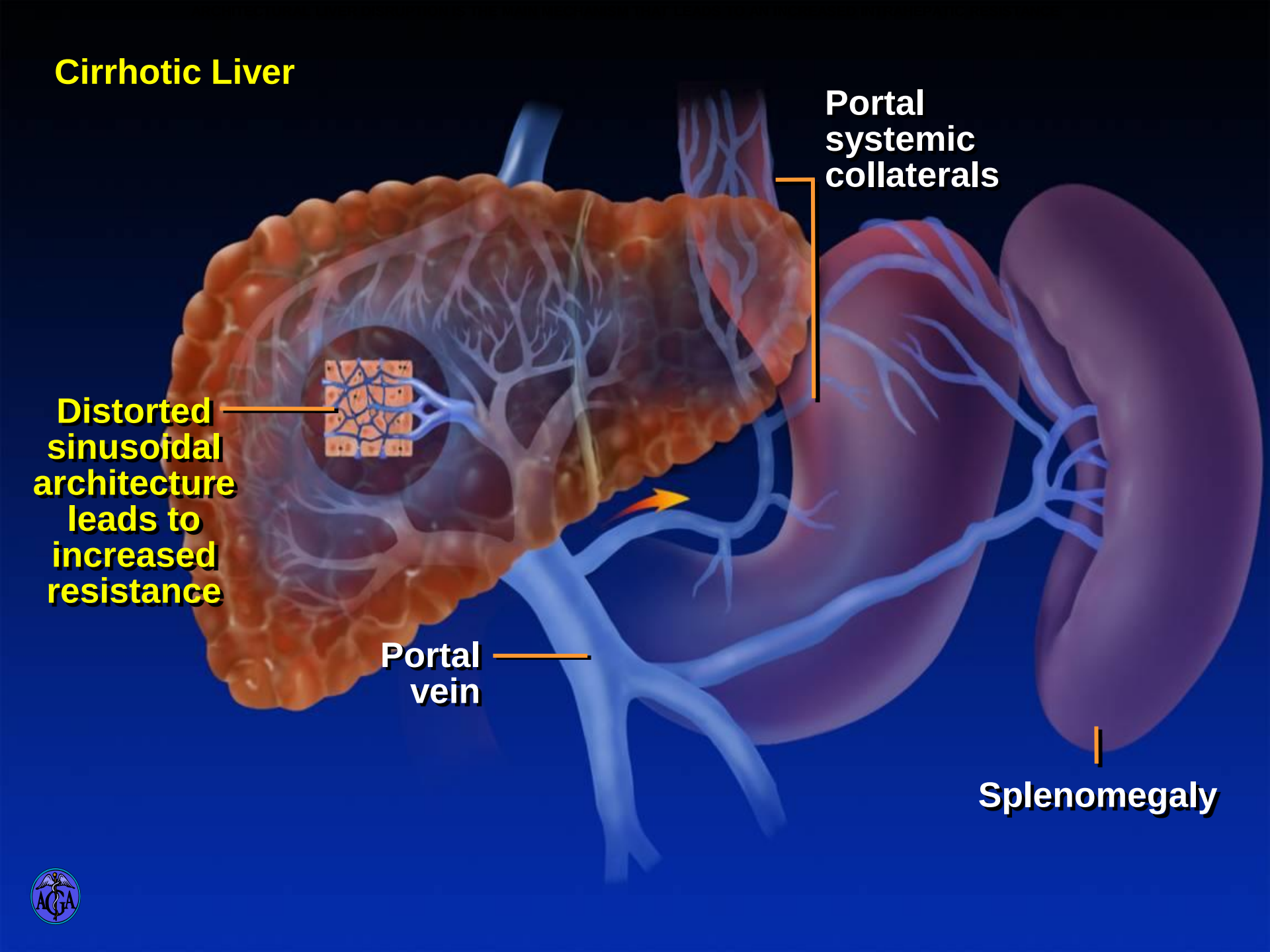
Normal Vascular Anatomy



Portal Hypertension Is Classified According to the Site of Increased Resistance

Type	Example
Pre-hepatic vein	Portal or splenic thrombosis
Pre-sinusoidal	Schistosomiasis
Sinusoidal	**Cirrhosis**
Post-sinusoidal disease	Veno-occlusive
Post-hepatic syndrome	Budd-Chiari

Varices


Cirrhotic Liver
Portal systemic collaterals
Distorted sinusoidal architecture leads to increased resistance
Portal vein
Splenomegaly

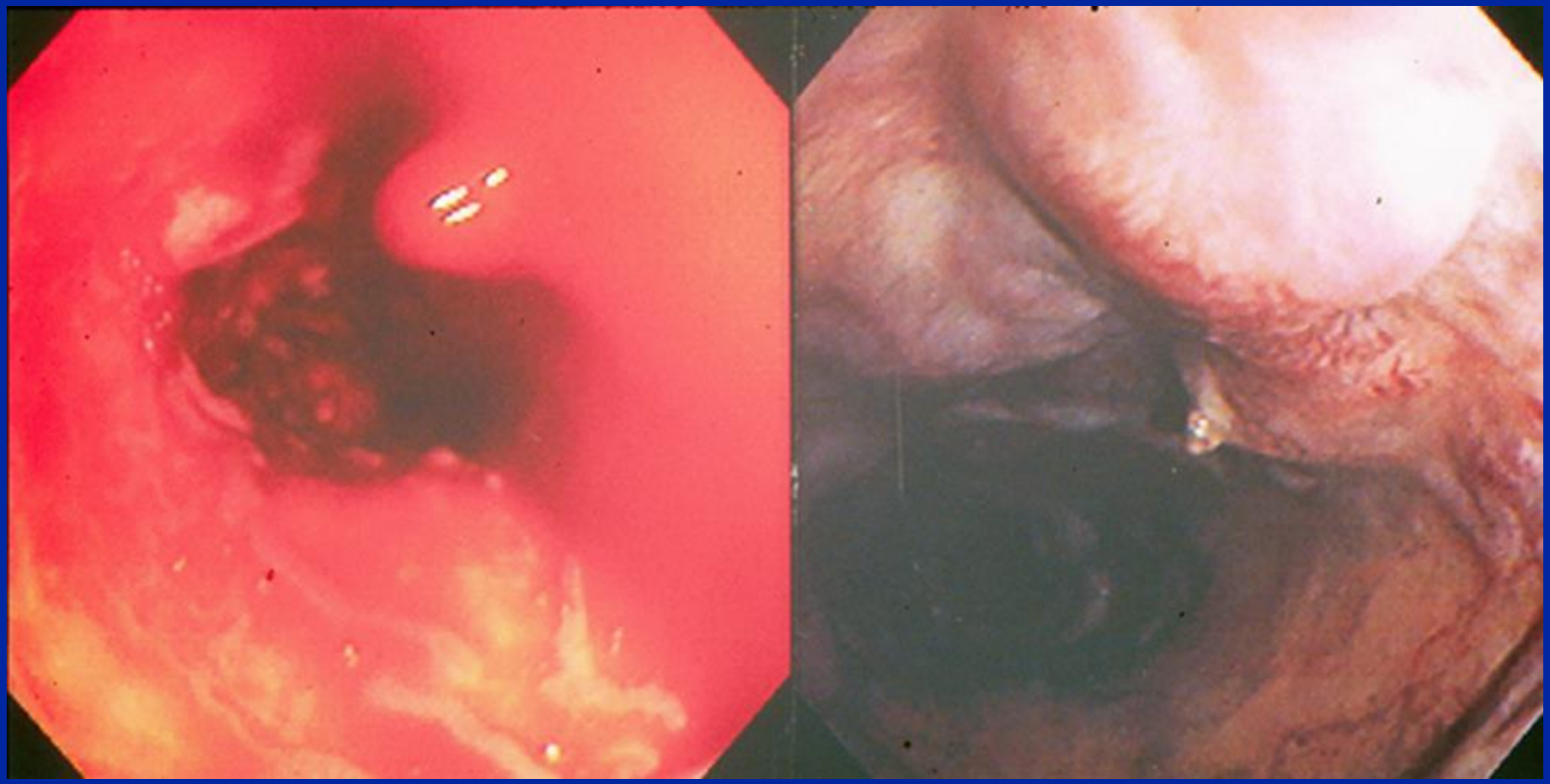
Varices Increase in Diameter Progressively

No varices → Small varices → Large varices

7-8%/year

7-8%/year

Merli et al. J Hepatol 2003;38:266



Variceal hemorrhage

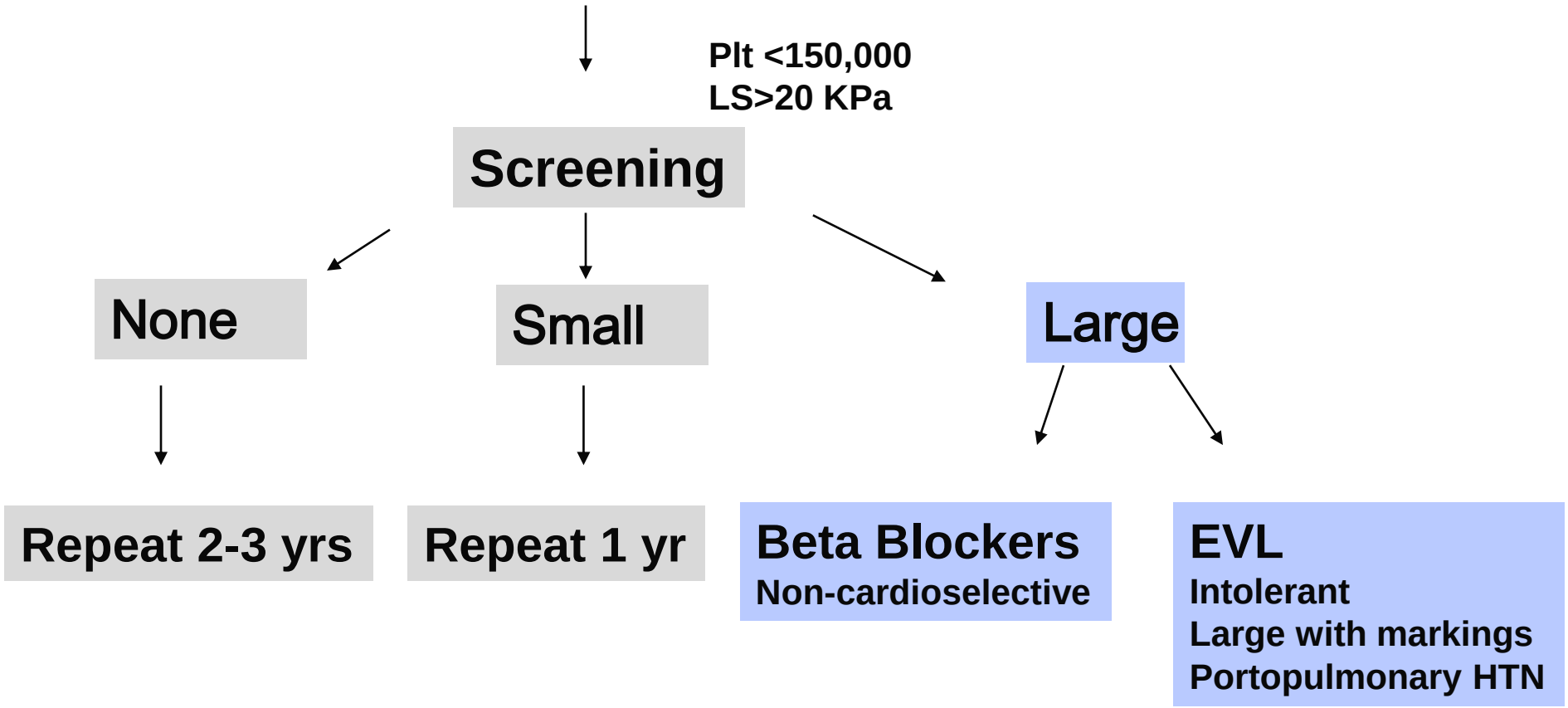
Varix with red signs

Predictors of hemorrhage:

- Variceal size
- Red signs
- Child B/C

NIEC. N Engl J Med 1988; 319:983

Cirrhosis: primary prevention



Acute Variceal Bleeding

Resuscitate/risk stratify (US, Child Pugh score, cardiac echo)

Restrictive transfusion: threshold 7g/dl maintain 7-9 g/dl
Antibiotics: ceftriaxone 1gm q 24hrs (maximum 7 days)
Octreotide 50ug bolus then 50ug/hr
EGD within 6-12 hrs (band ligation)

Continue therapy for 3-5 days

controlled

Beta Blocker
Serial band ligation (q 2-4 weeks)

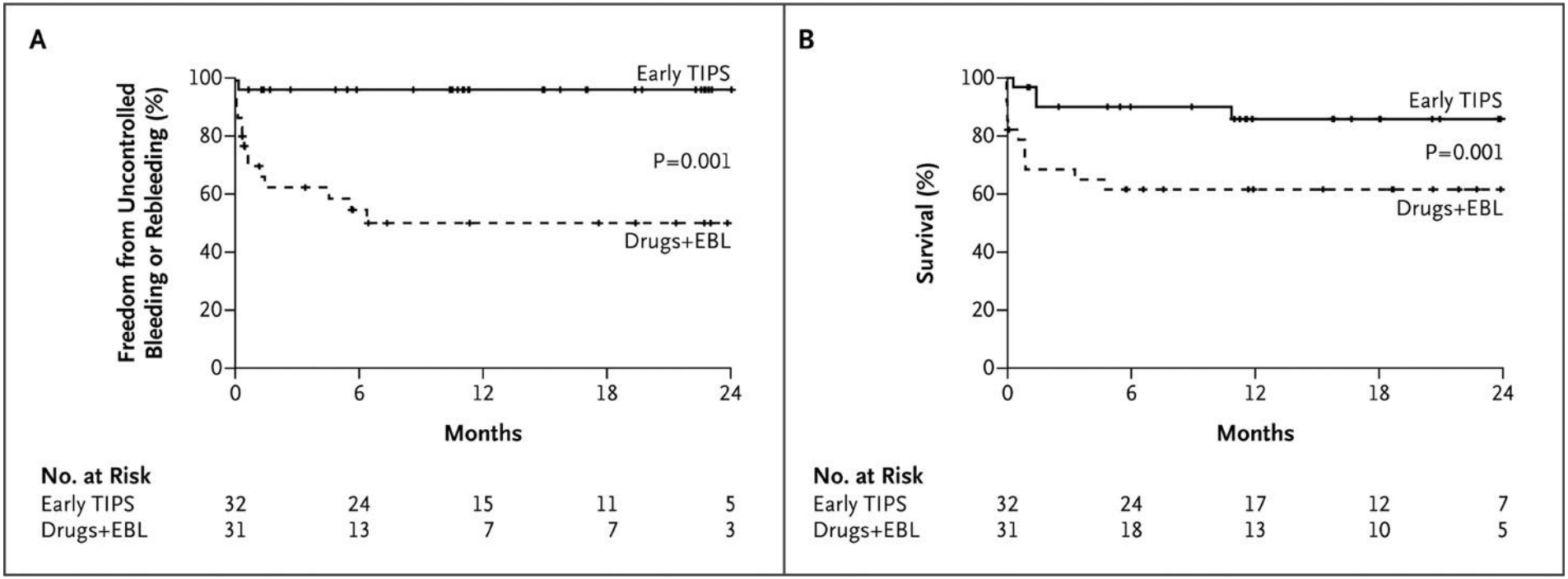
Rebleed or gastric varices
(TIPS, BRTO, glue, OLT)

Re-bleed

Salvage TIPS

Child Pugh C 10-14 (no contraindication)
Early TIPS (72hrs)

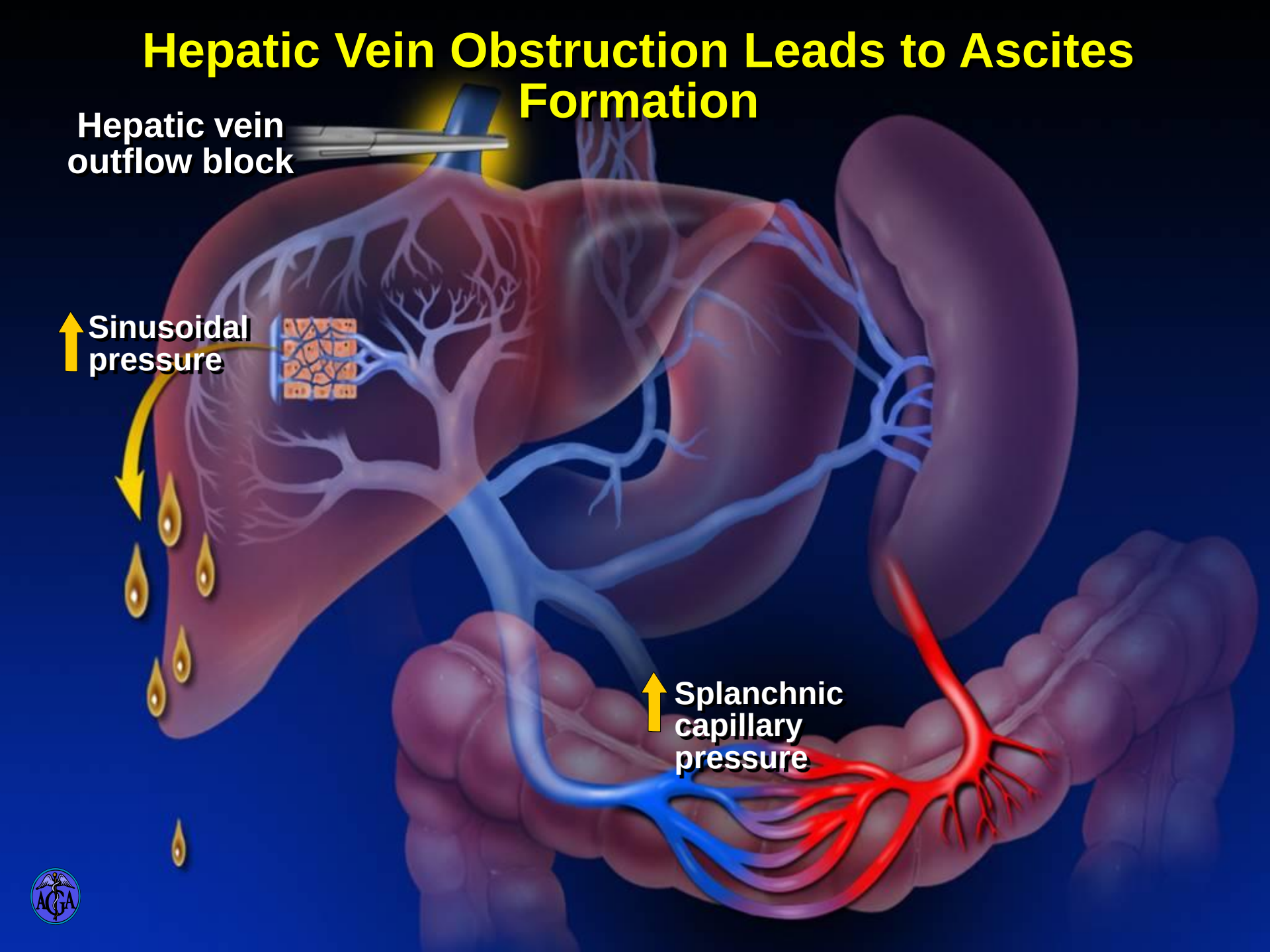
Bleeding/rebleeding and survival in TIPS vs Medical therapy



Garcia-Pagan et al NEJM 2010

Ascites

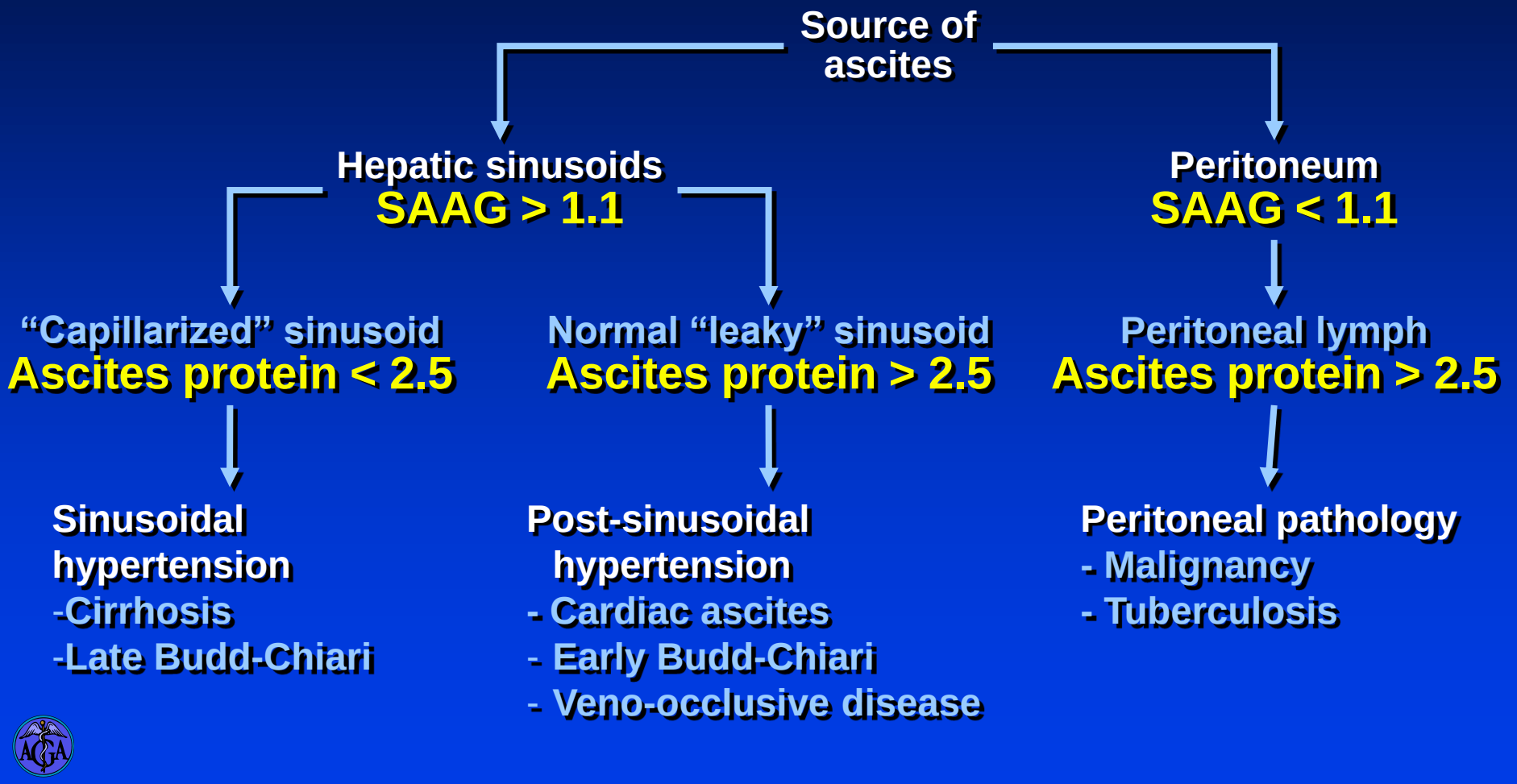
Hepatic Vein Obstruction Leads to Ascites Formation



Serum-to-ascites albumin gradient (SAAG)

- SAAG = $[Albumin]_{serum} - [Albumin]_{ascites}$
  - portal hypertension ≥ 1.1
  - no portal hypertension < 1.1
- 97 % accuracy

Ascites Can Be Characterized by Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein



Type ascites according to SAAG

High Gradient (≥ 1.1g/dL) "Transudate"	Low gradient (<1.1 g/dL) "Exudate"
Cirrhosis (80%)	Carcinomatosis
CHF	Tuberculosis
Hepatic vein thrombosis	Pancreatic ascites
Alcoholic hepatitis	Nephrotic Syndrome

Ascites
Cell Count

- **Single most helpful test: defines infection**
- **PMNs ≥ 250 = SBP**
- **Traumatic tap (250 RBC = 1 PMN)**

Ascites

Diagnostic paracentesis (at diagnosis, ? Infection, any change of concern)

No data that FFP or plts decrease bleeding risk (spinal needle)

Inoculate blood cultures at bedside

Cardiac echo

Sodium restriction (pickles, pickle juice, canned soup)

No salt substitute

Avoid NSAIDs, ACEI, ARBs

Diuretics aldactone +/- furosemide (~2:1)

LVP vs TIPS

SBP

Diagnostic paracentesis (? Infection, any change of concern)

Inoculate blood cultures at bedside

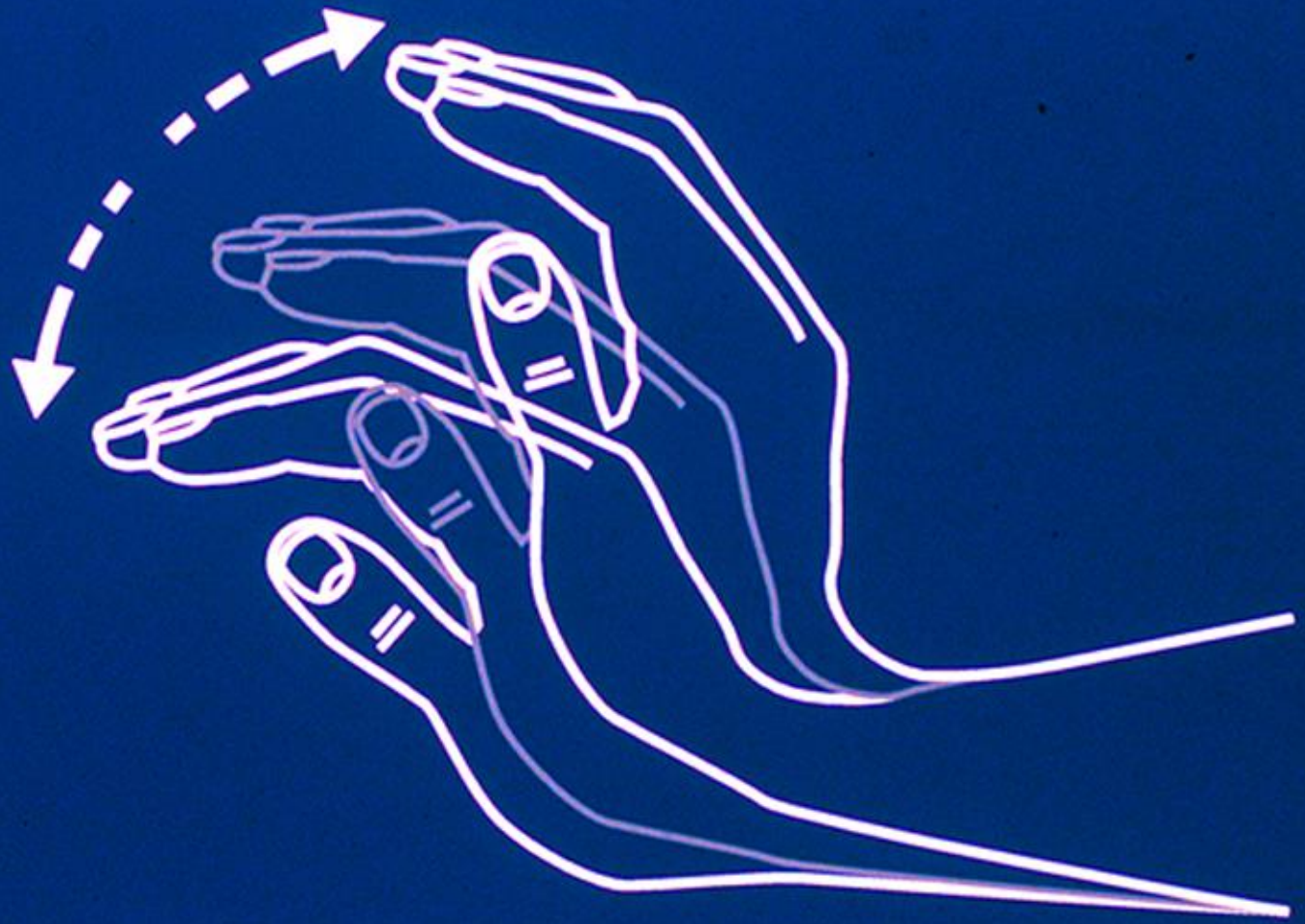
Early SBP does NOT present as peritonitis

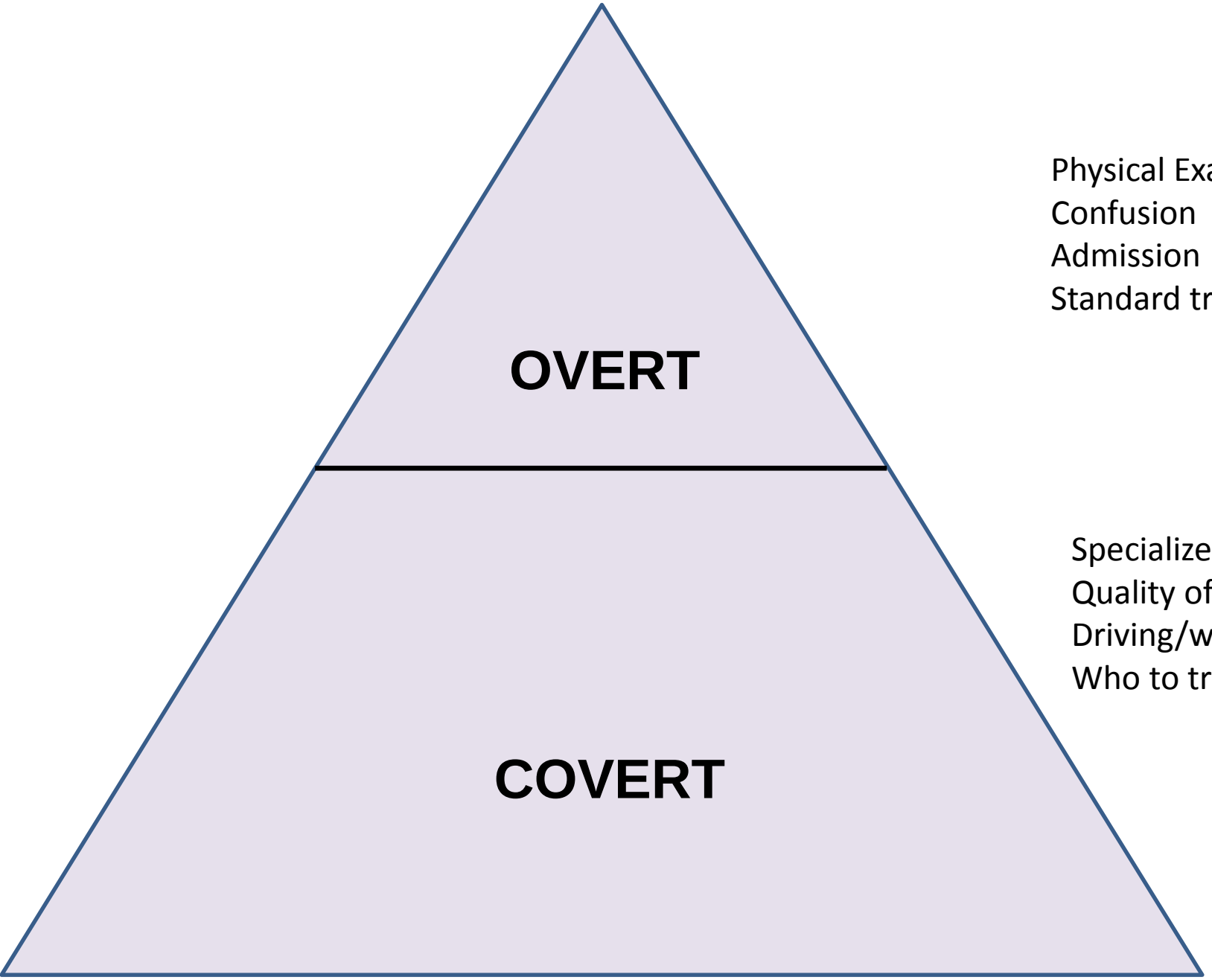
Third generation cephalosporin (cefotaxime 2grams q8hrs)

Albumin 1.5g/Kg BW and 1.0g/Kg on day 3

Repeat paracentesis if atypical response or nosocomial situation

HEPATIC ENCEPHALOPATHY



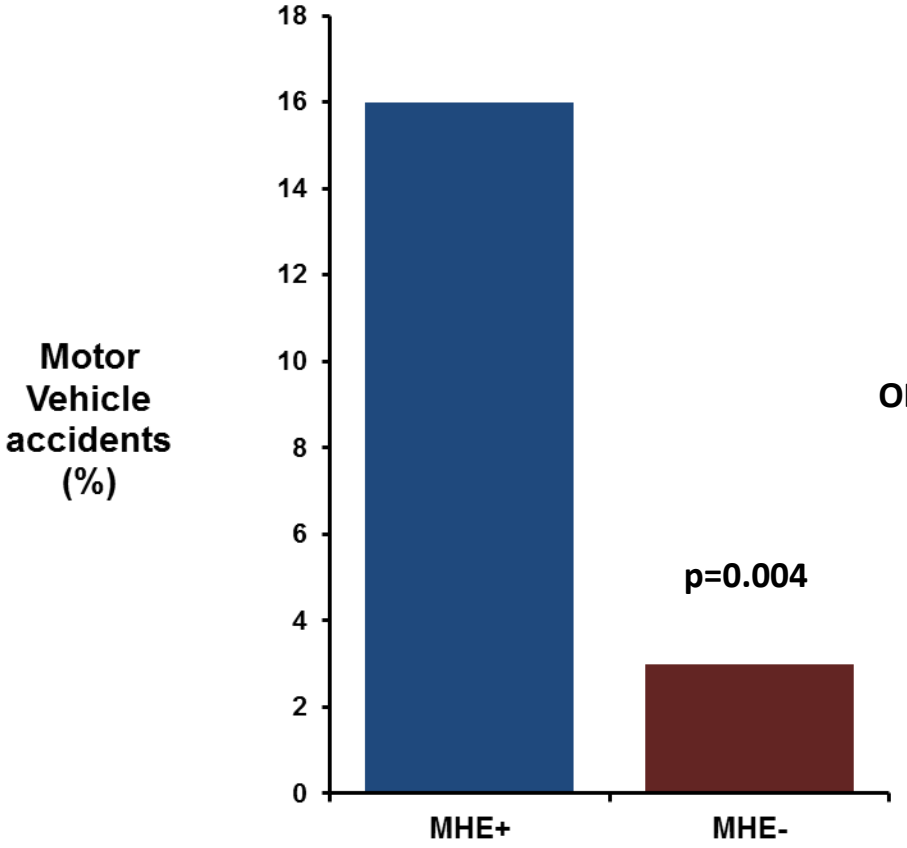


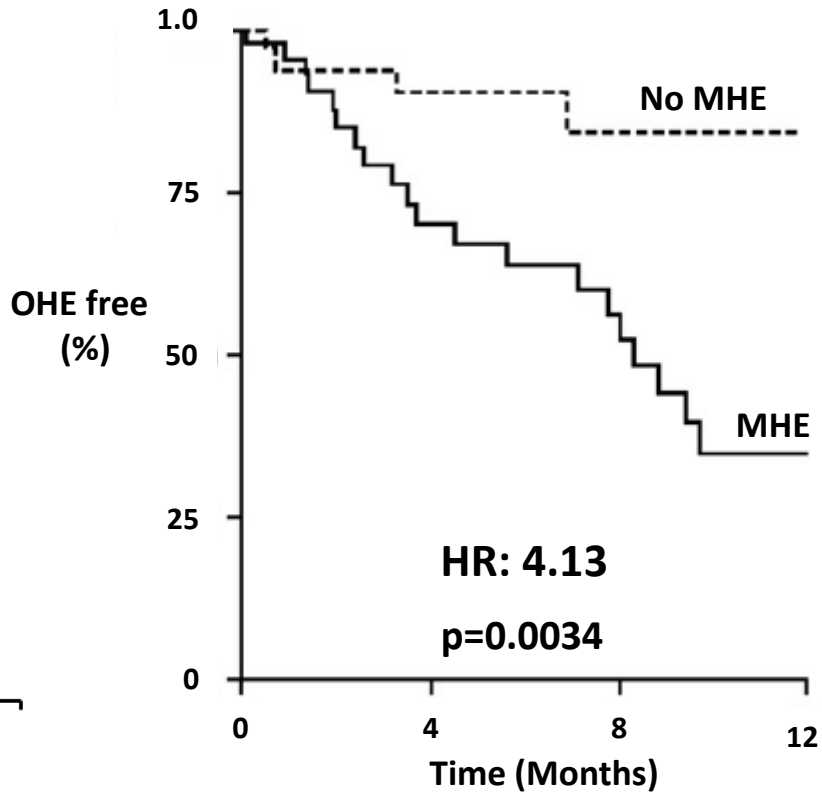
Physical Exam
Confusion
Admission
Standard treatments

Specialized tests
Quality of life
Driving/work
Who to treat?

West Haven Criteria		SONIC			
GRADE	INTELLECTUAL	STAGE	MENTAL STATUS	SPECIAL TESTS	ASTERIXIS
0	Normal	Unimpaired	Not impaired	Normal	Absent
Minimal	Normal exam Work, driving problems	Covert HE	Not impaired	Abnormal	Absent
1	Personality changes attention Irritability				
2	Altered sleep-wake cycle lethargy behavior cognition	Overt HE	Impaired	Abnormal	Present (unless coma)
3	Altered consciousness confusion				
4	Stupor and coma				

CHE: Risks

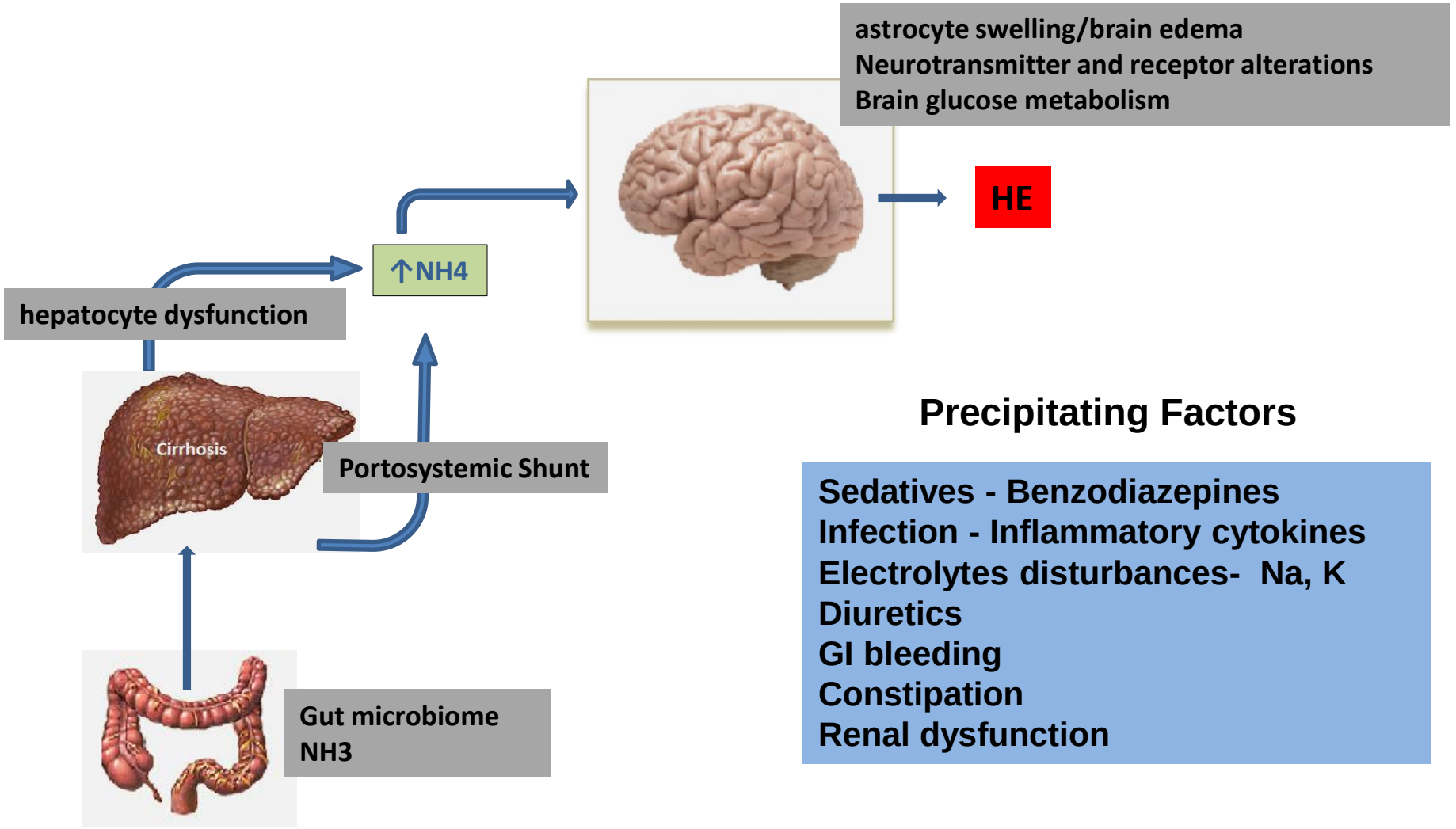




Bajaj et al, Hepatology 2009

Riggo et al, CGH 2011

Prevention of HE



Precipitating Factors

Sedatives - Benzodiazepines
Infection - Inflammatory cytokines
Electrolytes disturbances- Na, K
Diuretics
GI bleeding
Constipation
Renal dysfunction

HE: Diagnosis

- **Clinical**

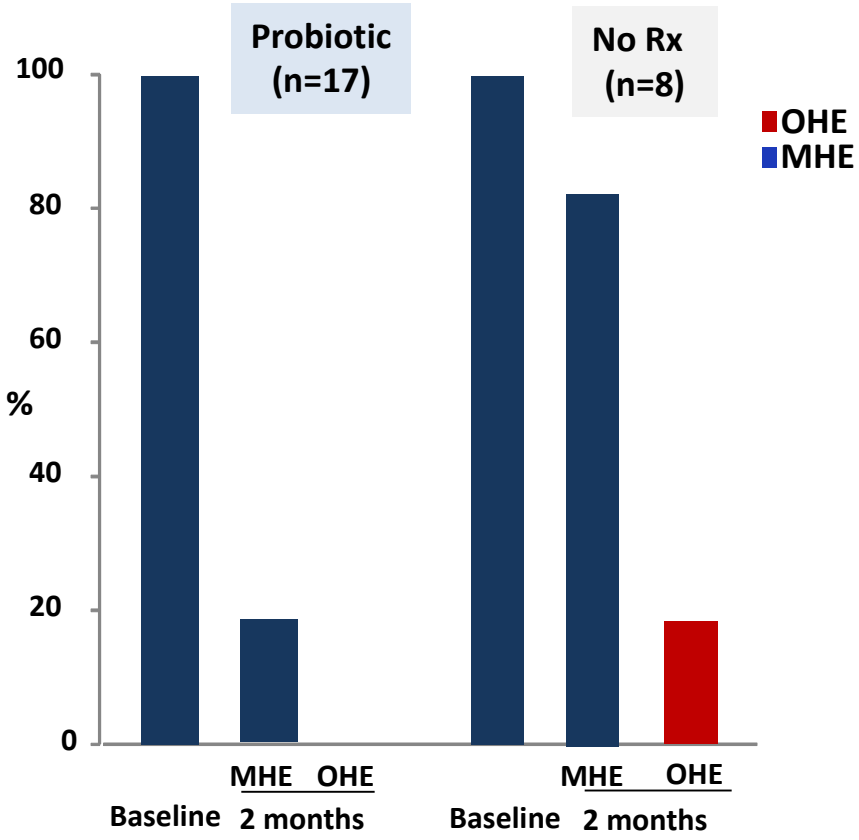
- **Neurocognitive tests for covert**
- **(PHES, STROOP, CNS-VS)**

- **Ammonia**
- **low sensitivity and specificity**
- **no diagnostic level**

OTC deficiency

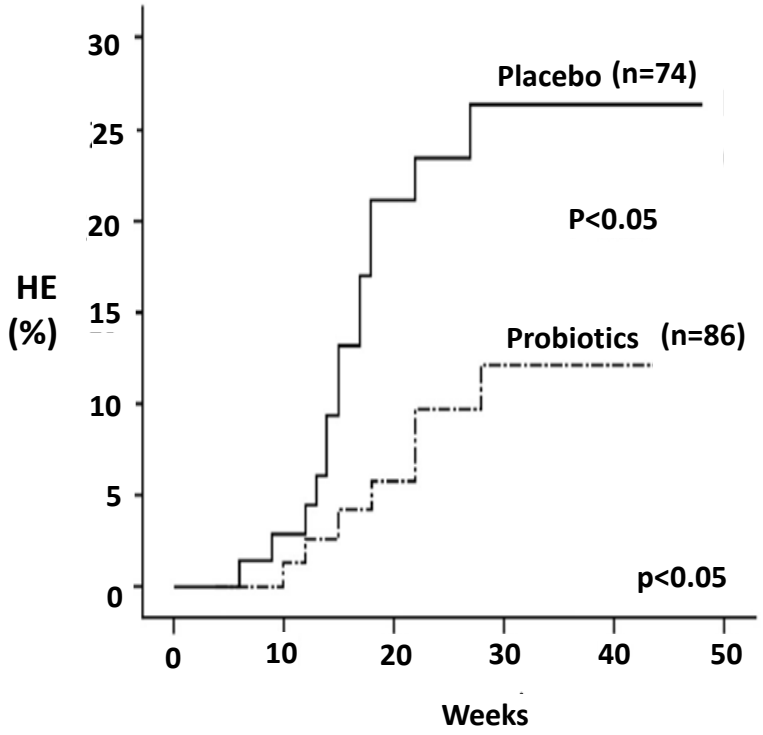
GI bleeding
Muscular exertion
Tourniquet use
Delayed processing/cooling of blood
Drugs: alcohol, barbiturates, diuretics, narcotics
Smoking

Probiotics and HE



Yogurt 12 oz q day for 2 months

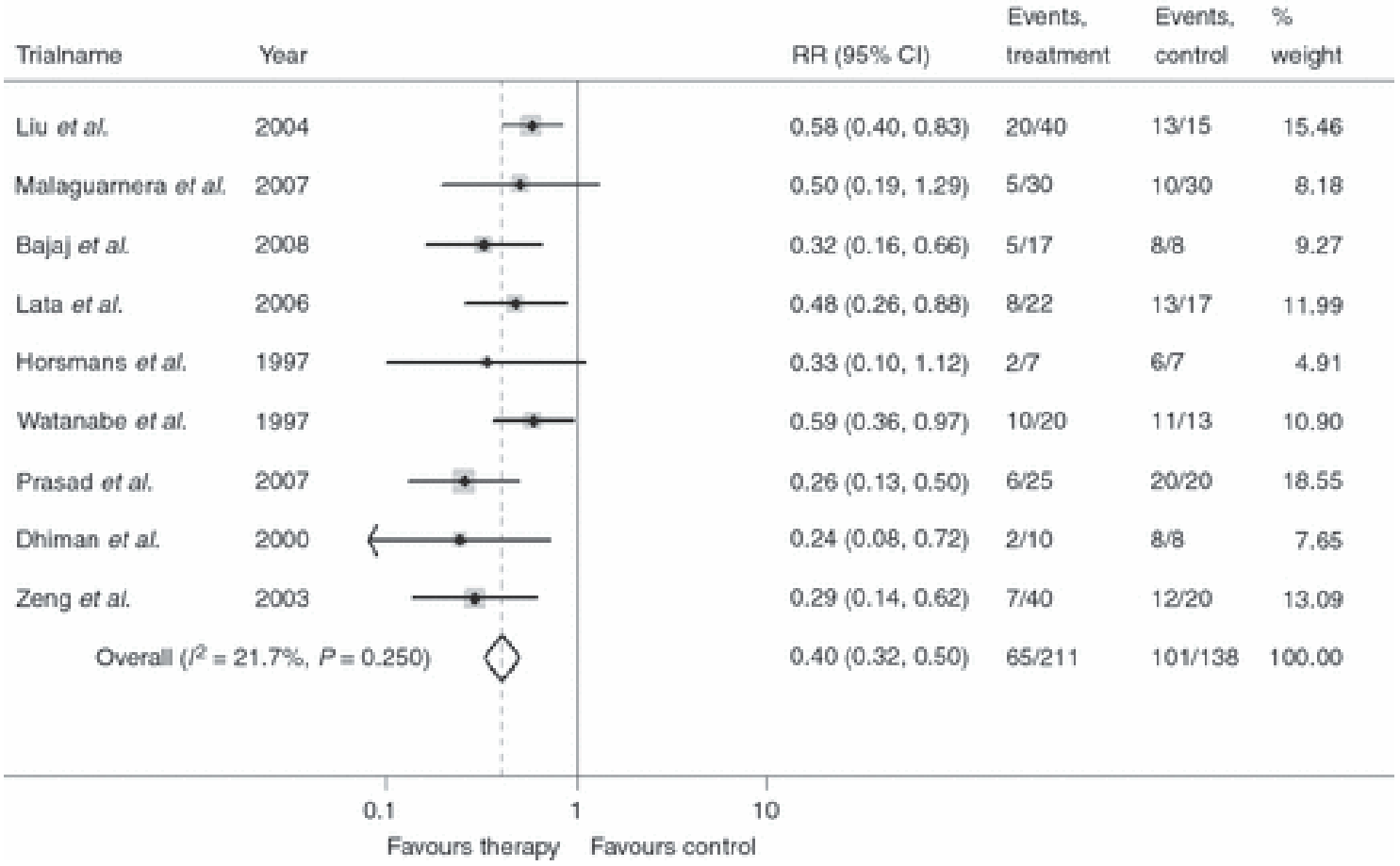
Bajaj, Am J Gastro, 2008



VSL#3 one TID for at least 6 months

Lunia et al, Clin Gastroenterol Hepatol. 2014

Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy



Alimentary Pharmacology & Therapeutics
Volume 33, Issue 6, pages 662-671, 20 JAN 2011 DOI: 10.1111/j.1365-2036.2010.04574.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2010.04574.x/full#f2

HE

Alternate causes and contributors (infection, bleeding, medications)

? Head CT imaging

UDS

Probiotics

Lactulose 10grams/15mls (titrate to 2-3 BMS qd) route?

Rifaxamin 550mg PO BID

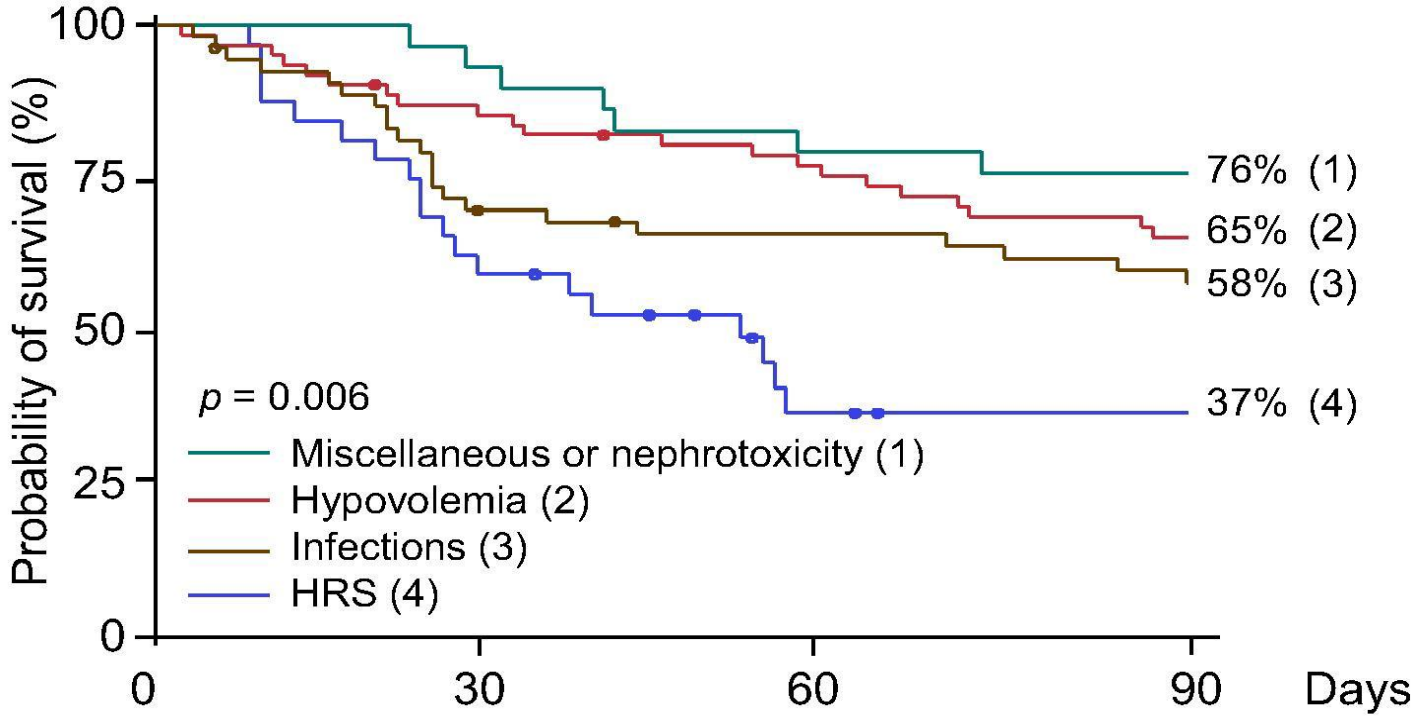
Zinc, neomycin, polyethylene glycol, BCAAs

No protein restriction

Acute Kidney Injury

HRS: *Classification*

- Type 1 HRS
  - Rapid and progressive
  - Doubling of initial Cr > 2.5 or 50% reduction in GFR (<20ml/min) over 2 weeks
- Type 2 HRS
  - Diuretic resistant ascites, intense sodium retention, Cr > 1.5, prolonged survival



1 (n = 29)	27	23	22
2 (n = 62)	52	45	39
3 (n = 54)	36	33	30
4 (n = 32)	19	9	7

Fagundes et al. J Hepatol. 59, 2013:477-481

Summary of the effects of baseline characteristics on HRS reversal (multivariate analysis, ITT population).

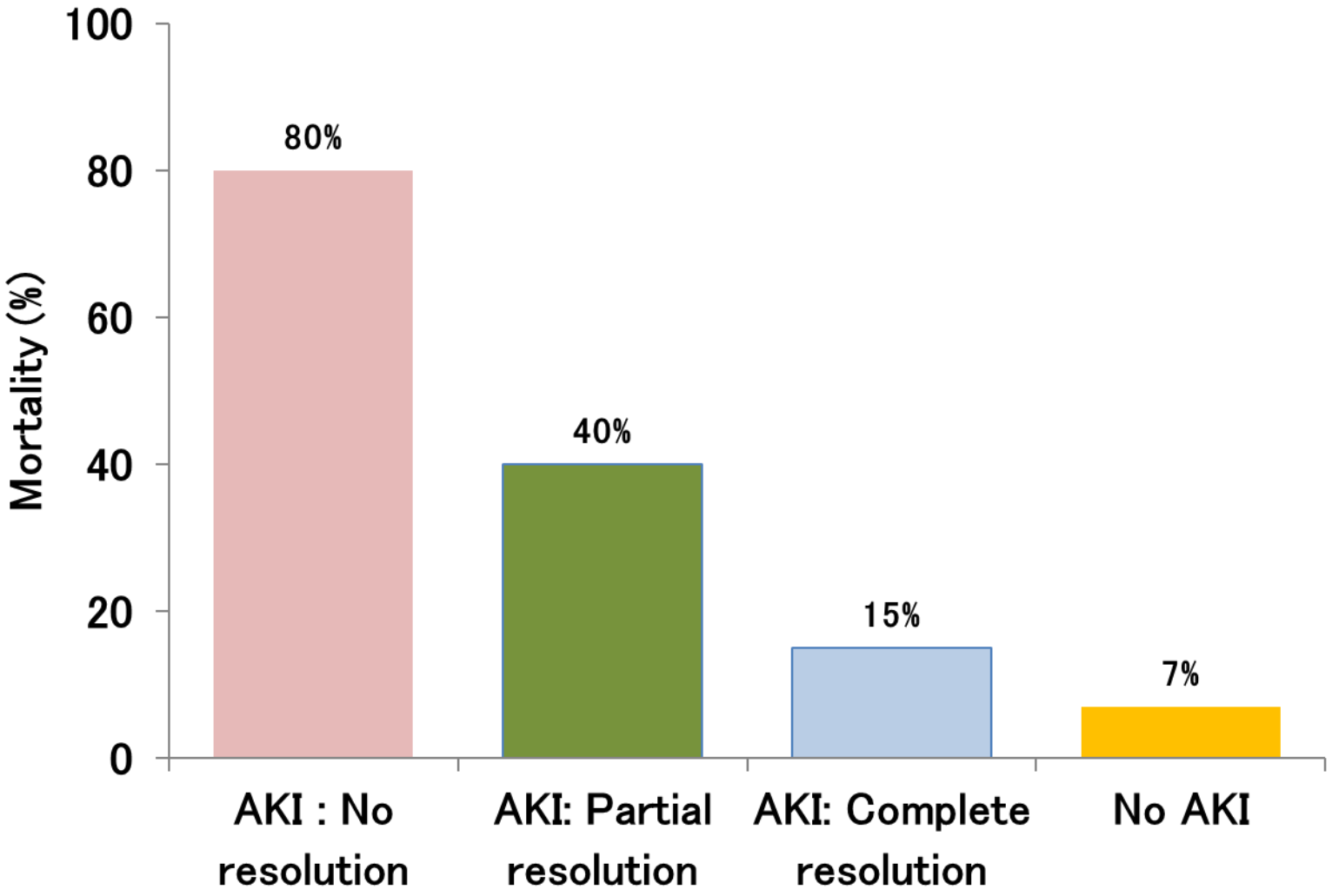
Baseline parameter	**RR**	**95% CI**	***p* value**
Alcoholic Hepatitis	0.98	0.32–2.94	0.965
Gender	0.68	0.23–1.96	0.472
MELD Score	0.92	0.80–1.05	0.223
Child-Pugh Score	0.89	0.62–1.27	0.513
Serum Creatinine	0.51	0.28–0.93	0.029
Bilirubin	1.02	0.97–1.08	0.374
Mean Arterial Pressure	0.98	0.94–1.02	0.348

RR: relative risk; 95% CI: 95% confidence intervals

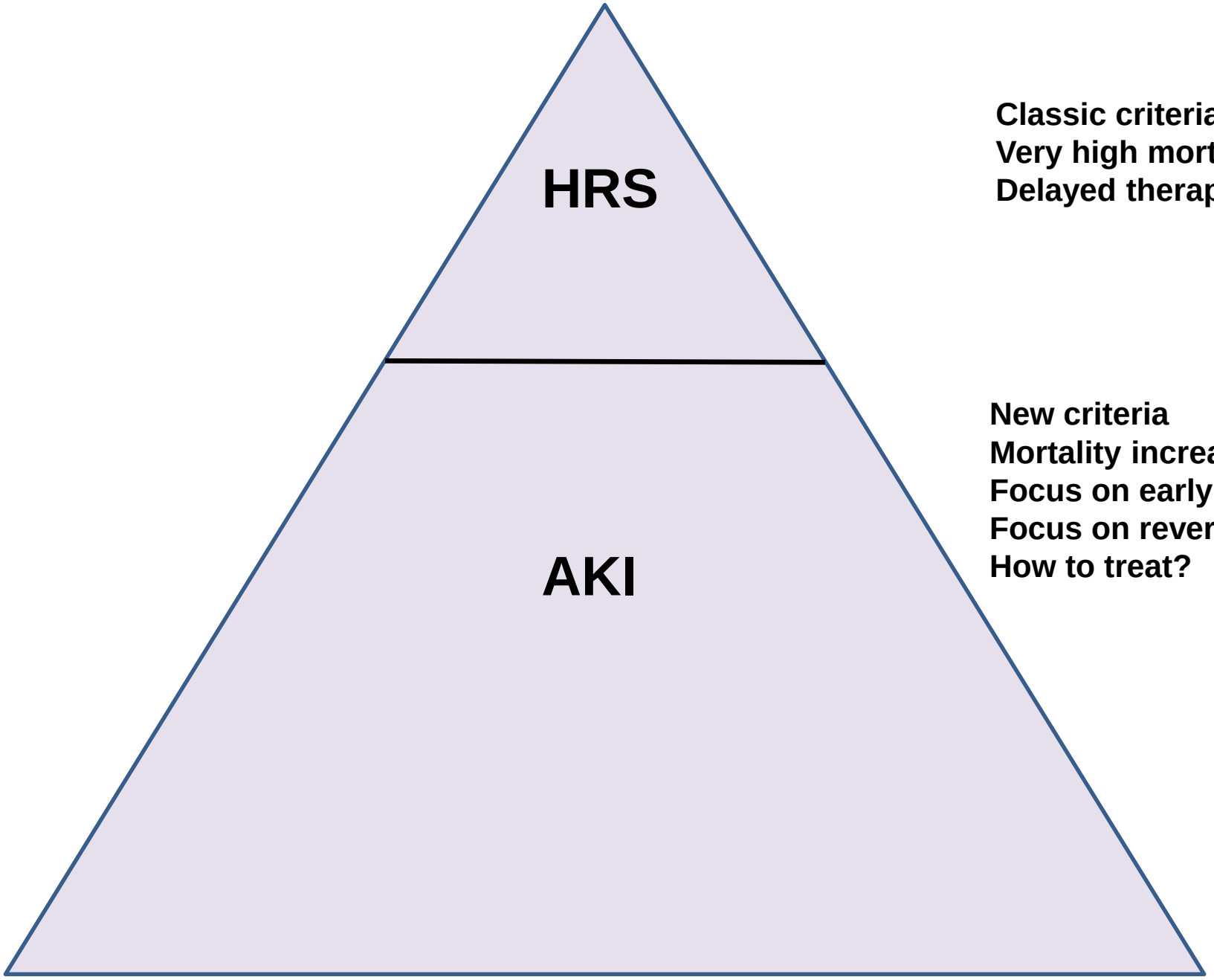
Boyer et al. J Hepatol 2011

Acute Kidney Injury in cirrhosis

- **20% of hospitalized cirrhotics**
- **Mortality 15 - 65% based on progression**
- **Often functional and linked to infection**



Adapted from Wong *et al.* *Gatroentrology* 2013



Classic criteria
Very high mortality
Delayed therapy

New criteria
Mortality increased
Focus on early detection
Focus on reversible causes
How to treat?

Diagnosis and Prevention

Cr poor measure of renal function in cirrhosis

- **muscle mass**
- **creatine conversion to creatinine**
- **volume of distribution**

Consensus AKI criteria in cirrhosis

- **Increase in Cr >0.3 mg/dl in 48 hrs**
- **Increase in Cr 1.5 fold above baseline within 3 months**

Table 1.

The diagnostic criteria of acute kidney injury in cirrhosis

Parameter	Definition
Baseline SCr	Stable SCr ≤3 months
	If not available, a stable SCr closest to the current one
	If no previous SCr at all, use admission SCr
Definition of AKI	↑ in SCr ≥26.5 µmoL/L (0.3 mg/dL) ≤ 48 hours, or ↑ 50% from baseline
Staging	Stage 1 : ↑ SCr ≥26.4 µmoL/L (0.3 mg/dL) or ↑ SCr ≥1.5–2.0 × from baseline
	Stage 2 : ↑ SCr >2.0–3.0 × from baseline
	Stage 3 : ↑ SCr >3.0 × from baseline, or
	SCr ≥352 µmoL/L (4.0 mg/dL) with an acute ↑ of ≥26.4 µmoL/L (0.3 mg/dL), or
	Initiation of renal replacement therapy

With standard exclusions fulfills criteria for HRS

SCr, Serum creatinine; AKI, acute kidney injury.

IAC definition *Wong, F Clin Mol hepatol 2016*

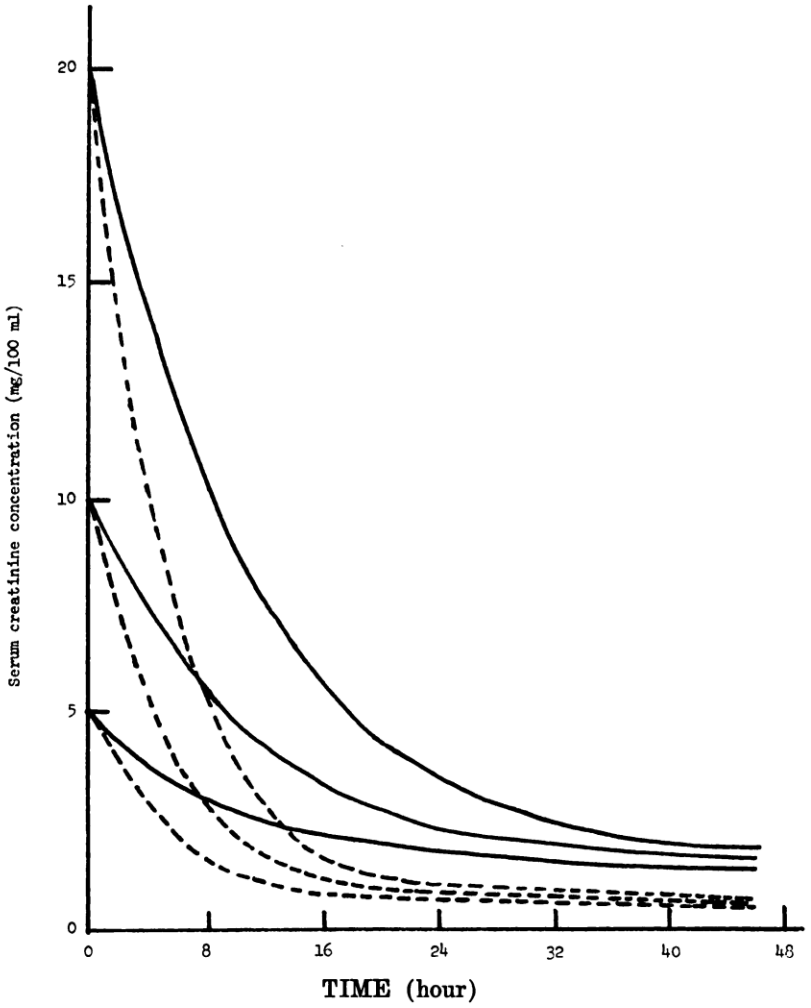
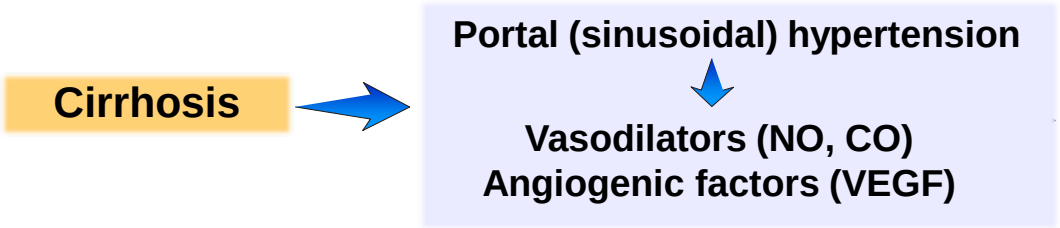


Fig. 2. Decay patterns of serum creatinine levels after improvement of renal function: solid lines, patients with 50 per cent of normal function; broken lines, patients with normal renal function.

Chiou, W and Hsu, F J Clin Pharm 1975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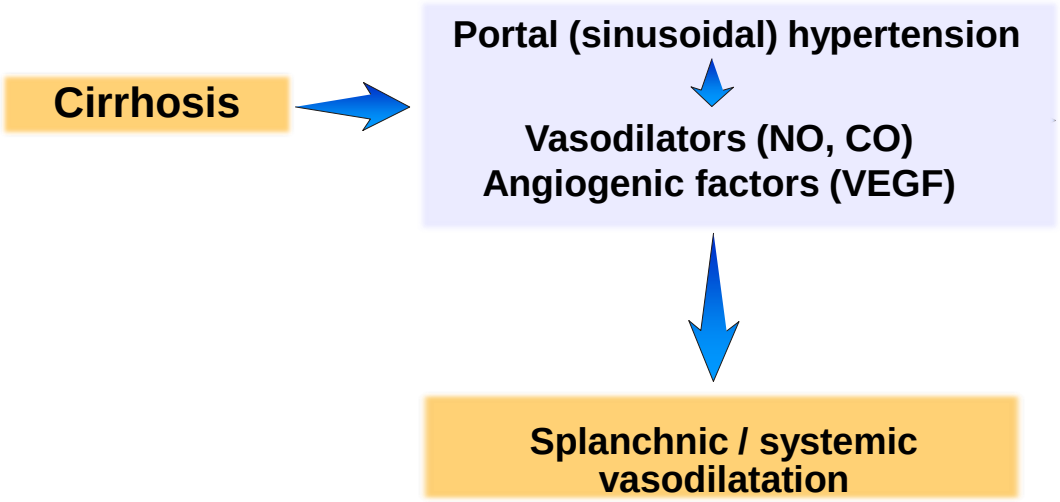
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)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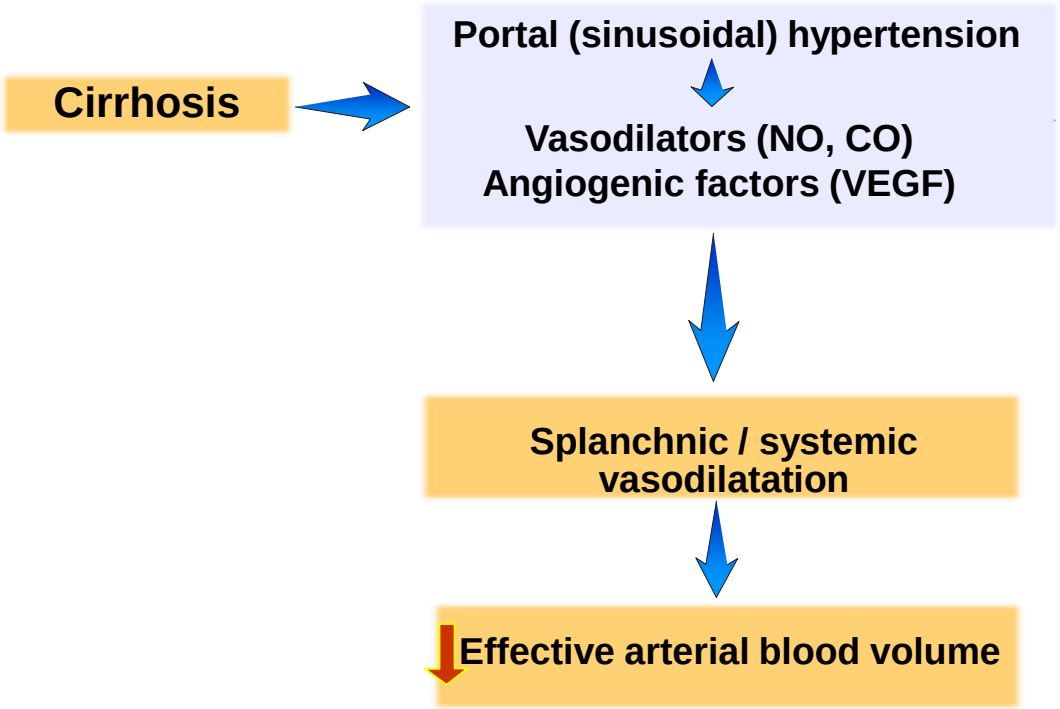
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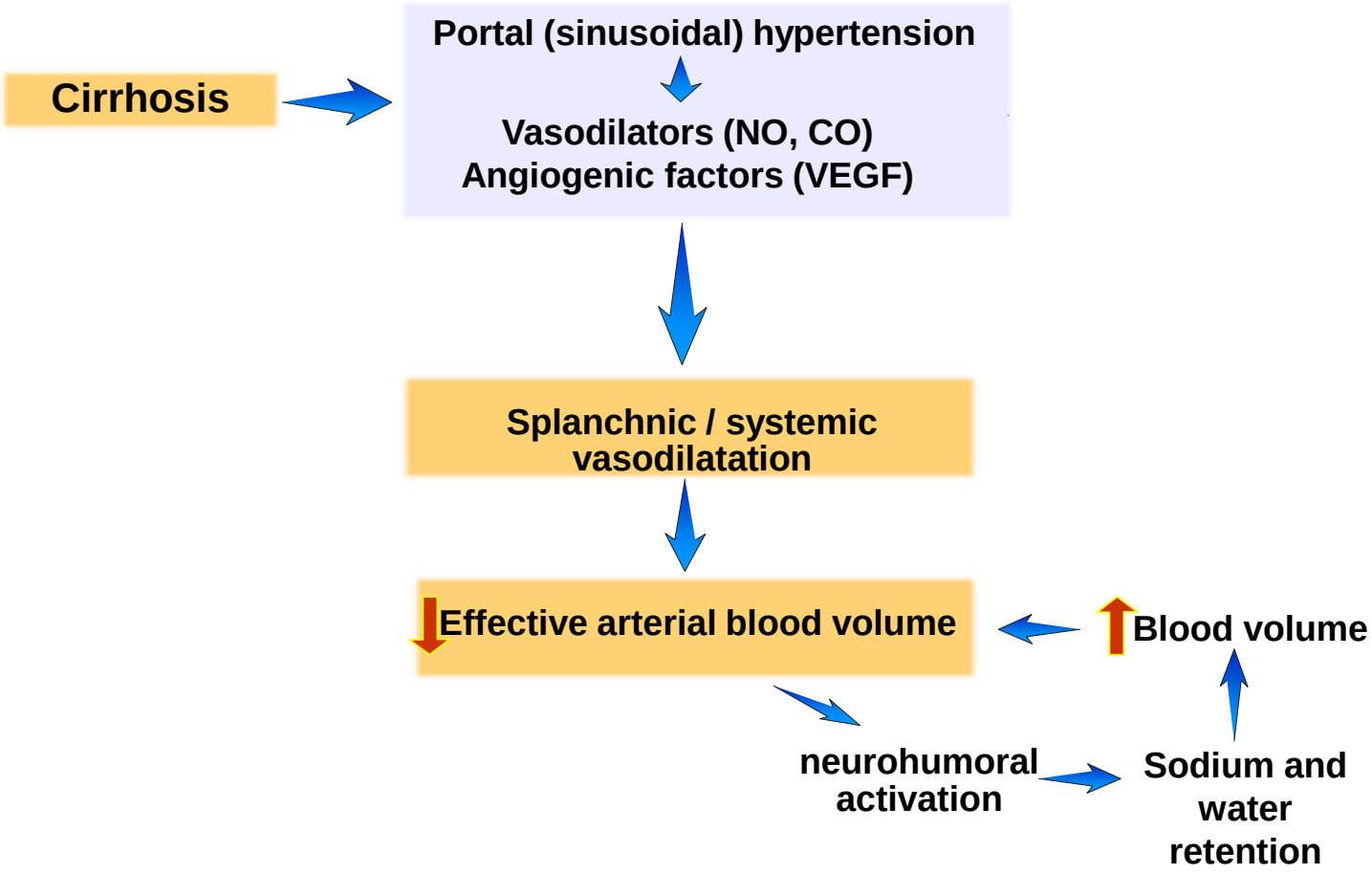
Effective arterial blood volume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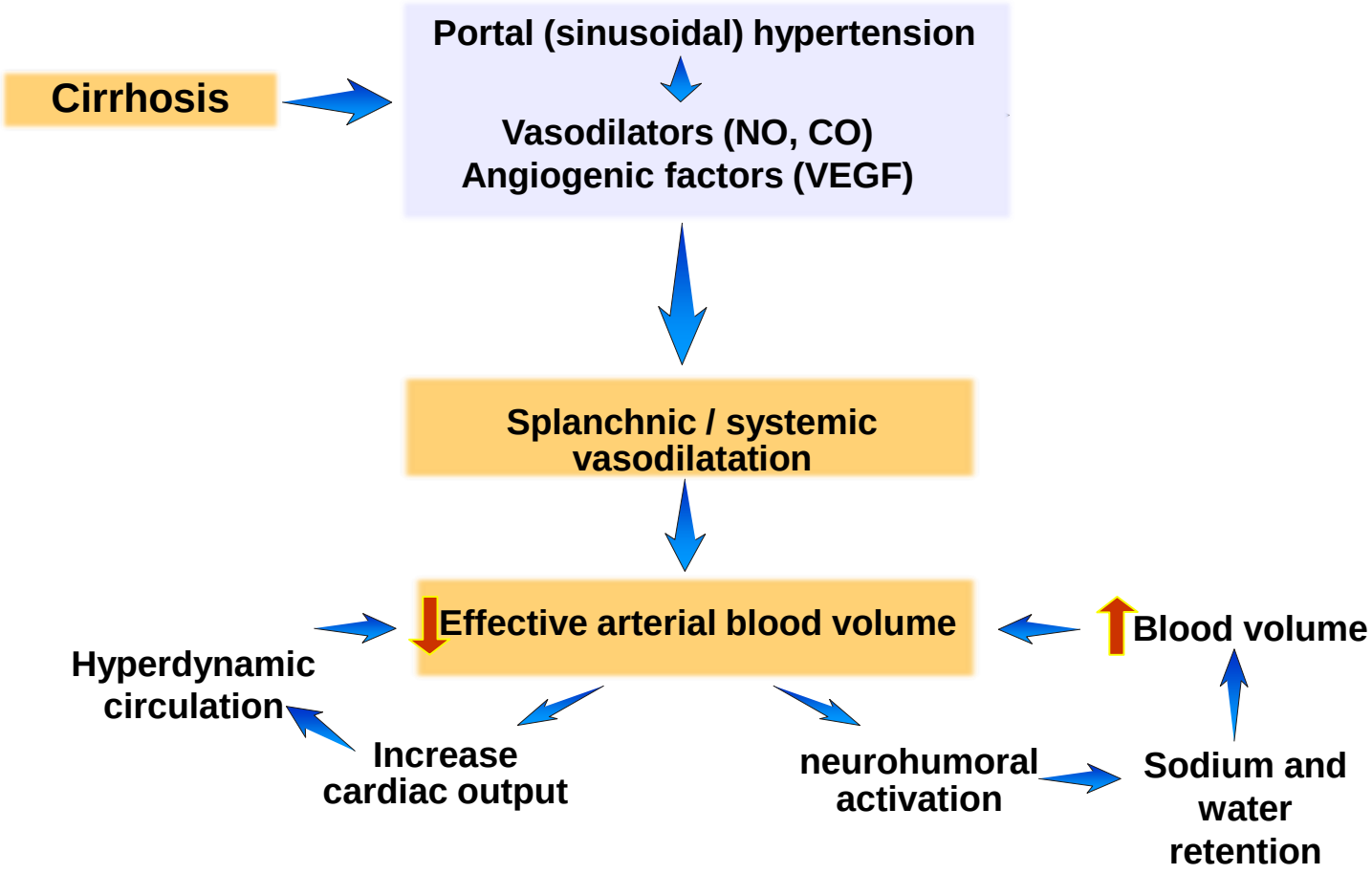
Blood volume
neurohumoral activation
Sodium and water retention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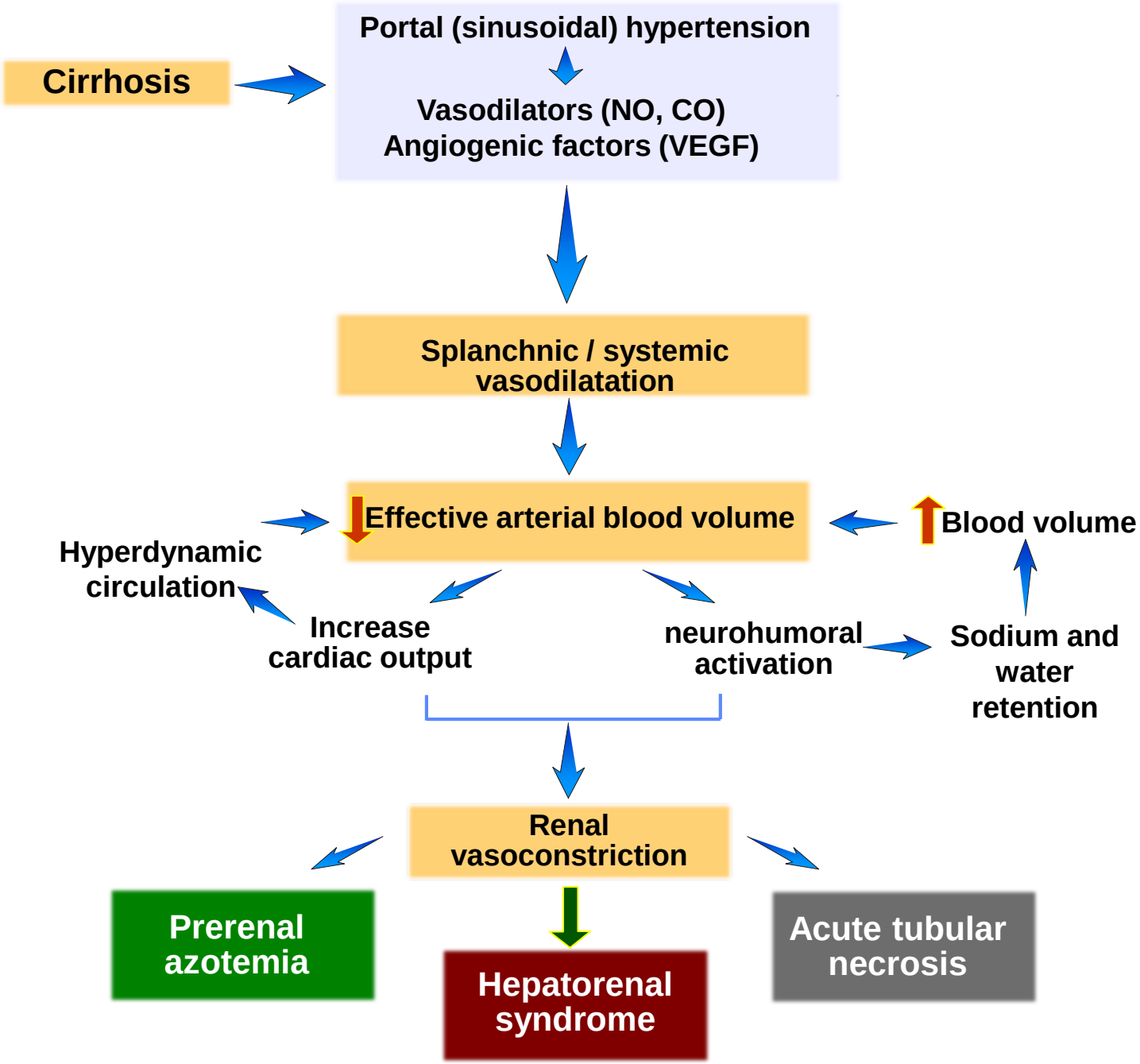
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention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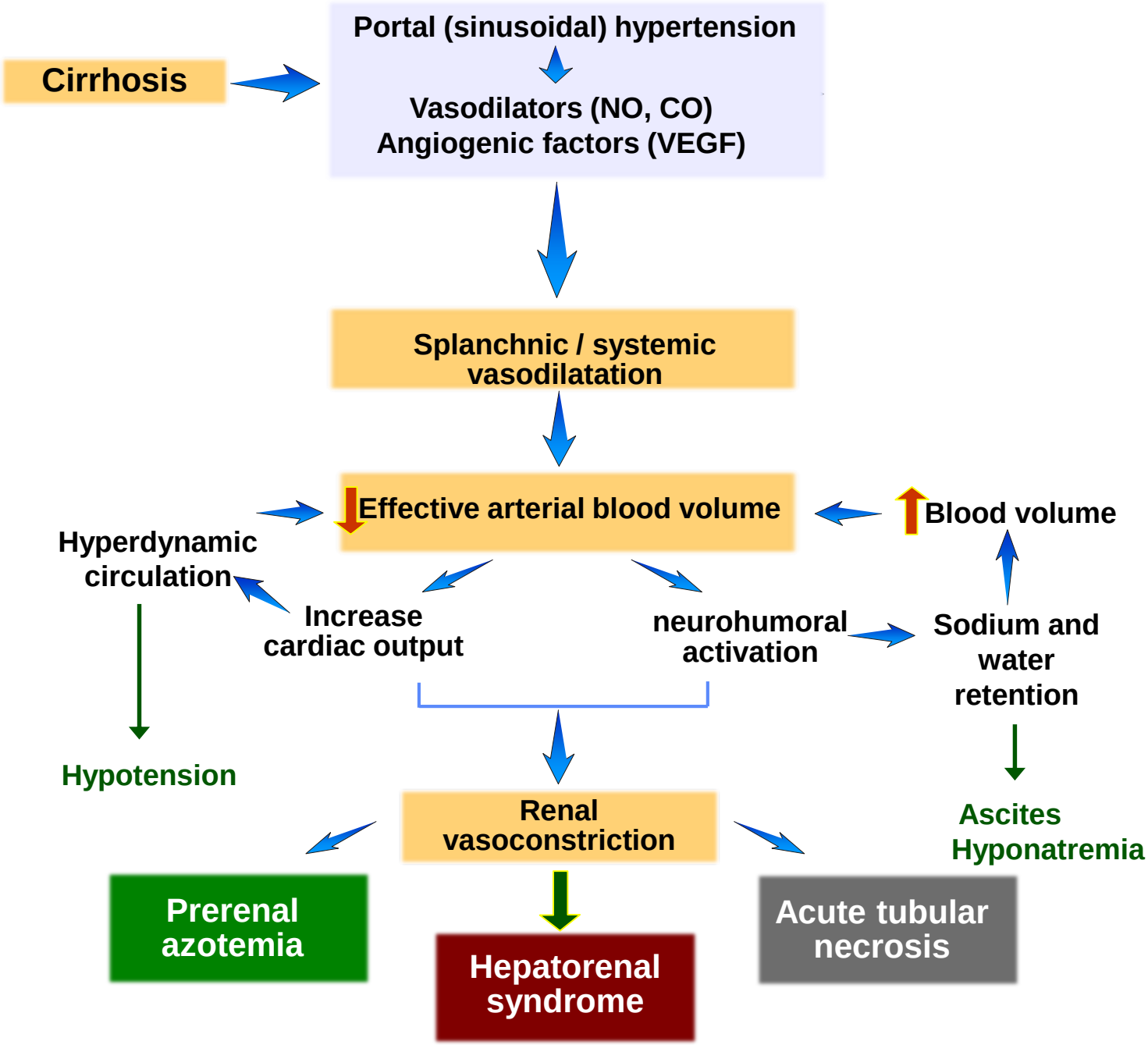
Sodium and water retention
Renal vasoconstriction
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis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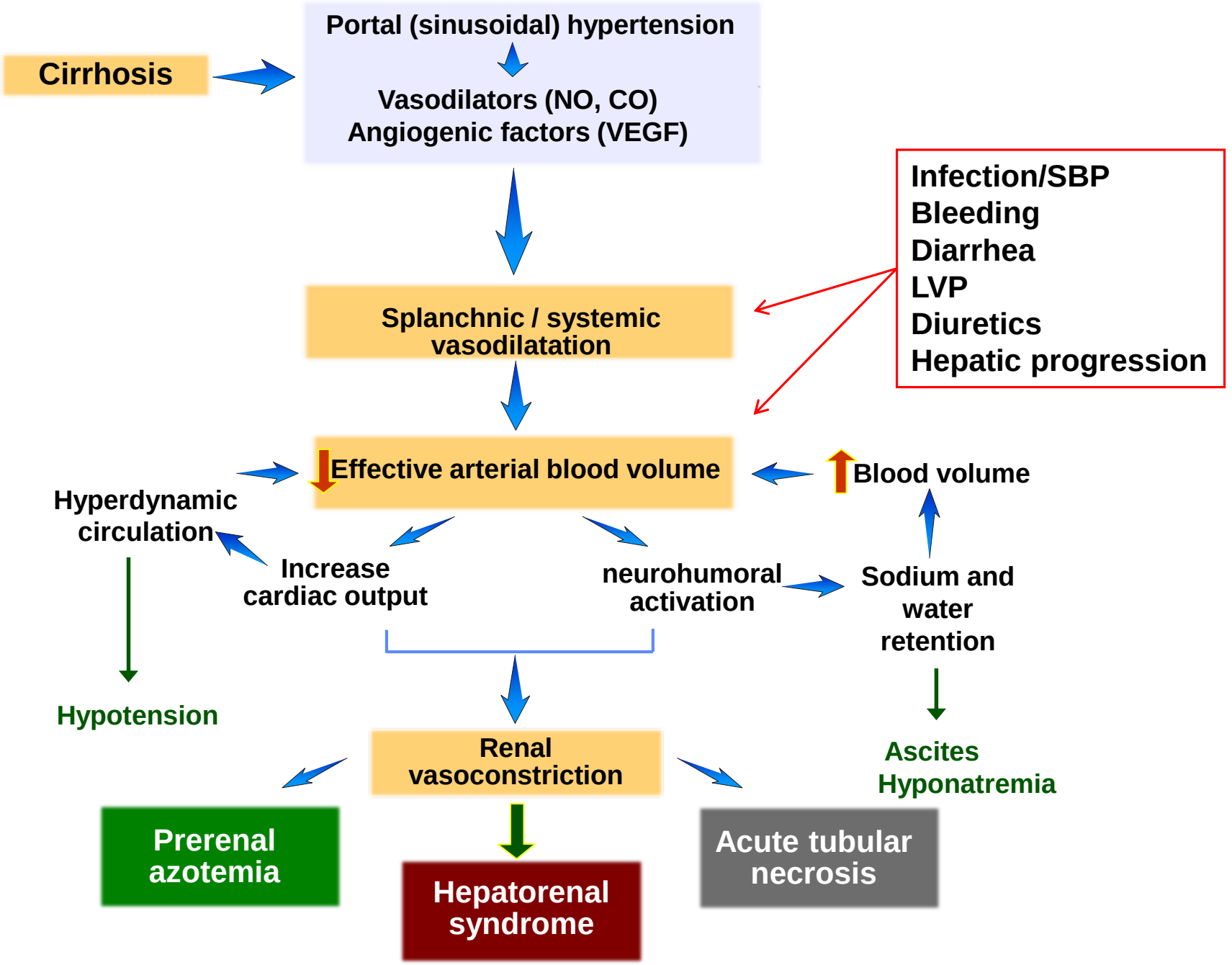
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Infection/SBP
Bleeding
Diarrhea
LVP
Diuretics
Hepatic progression
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Blood volume
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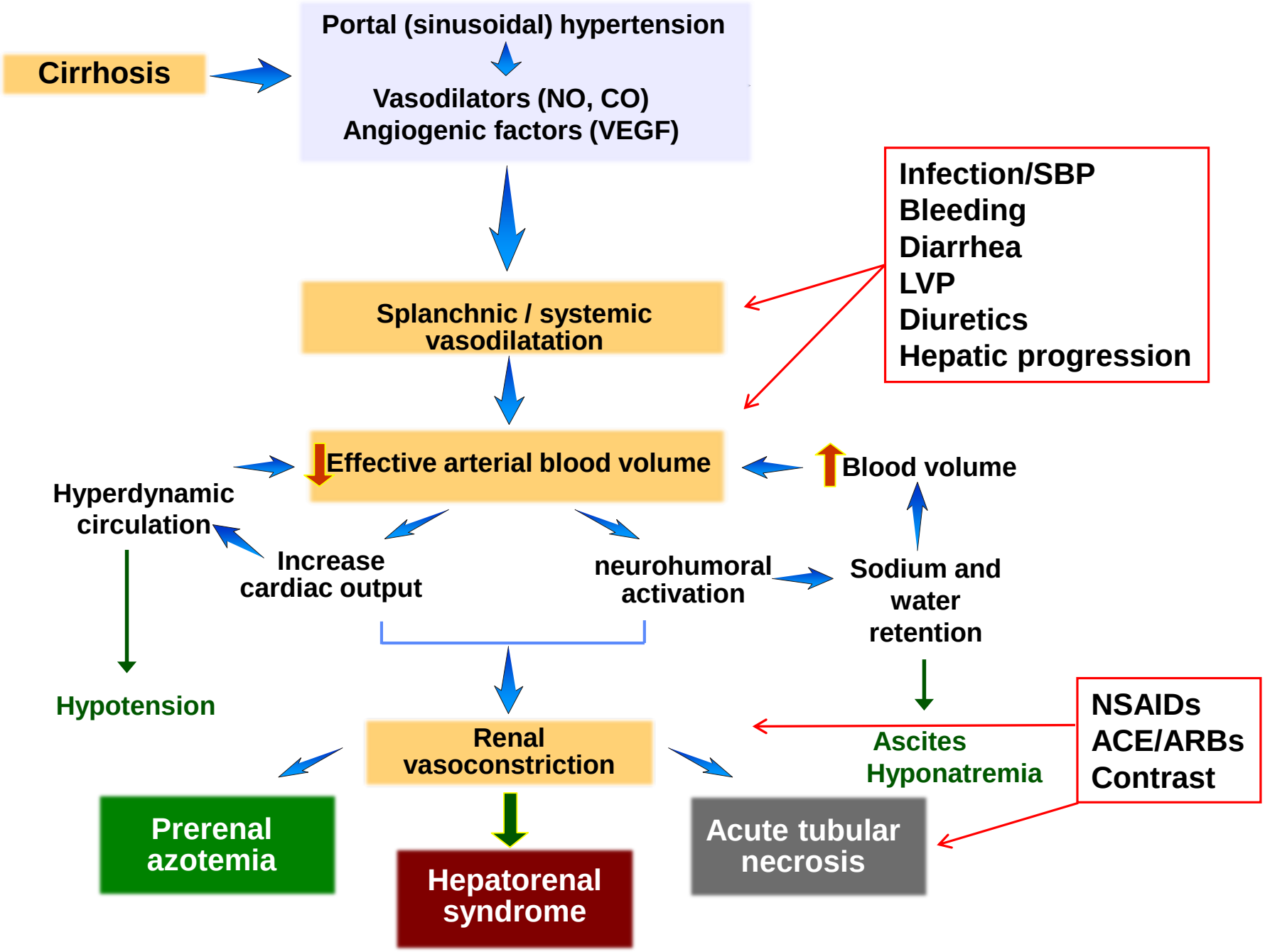
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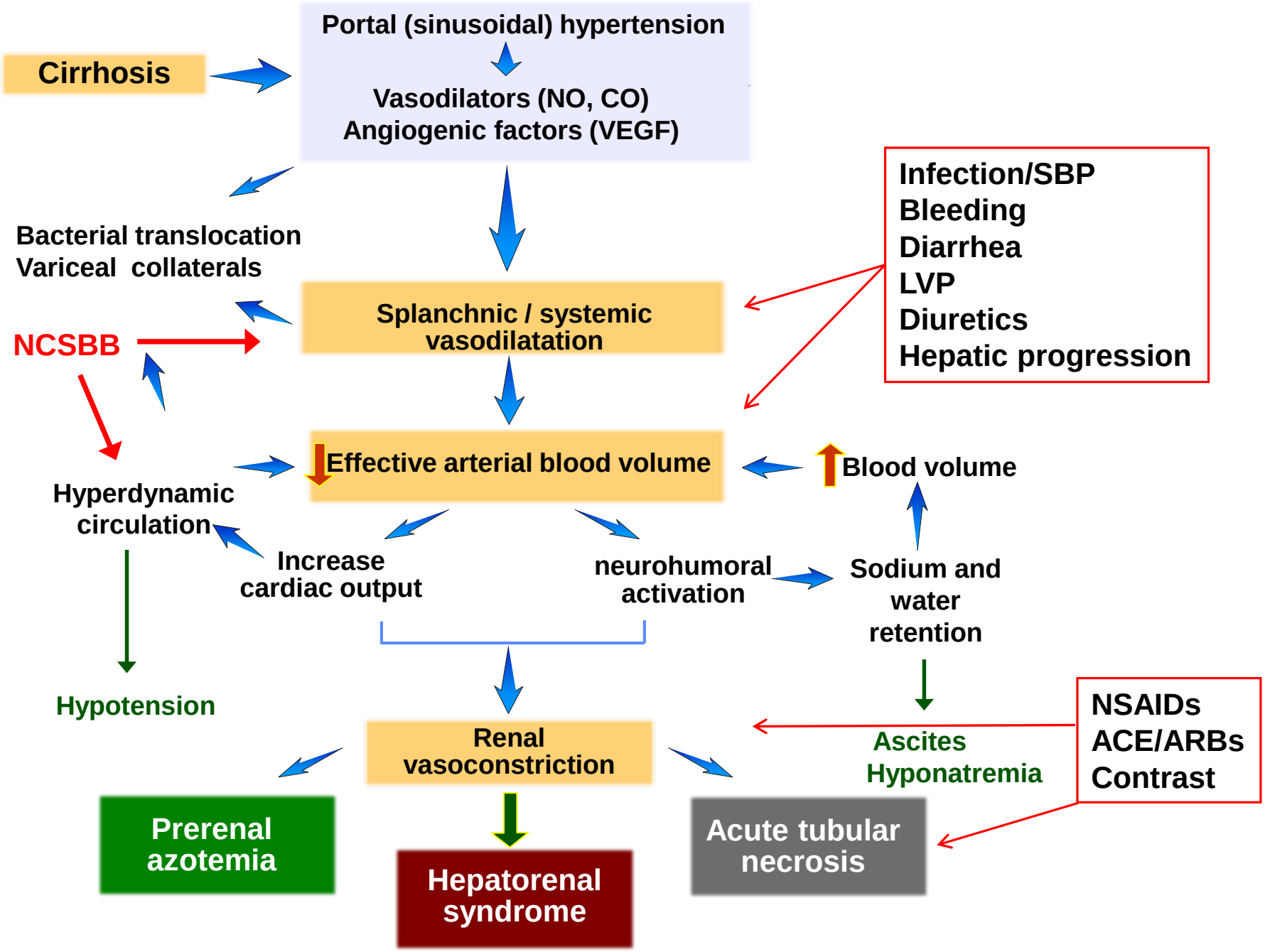
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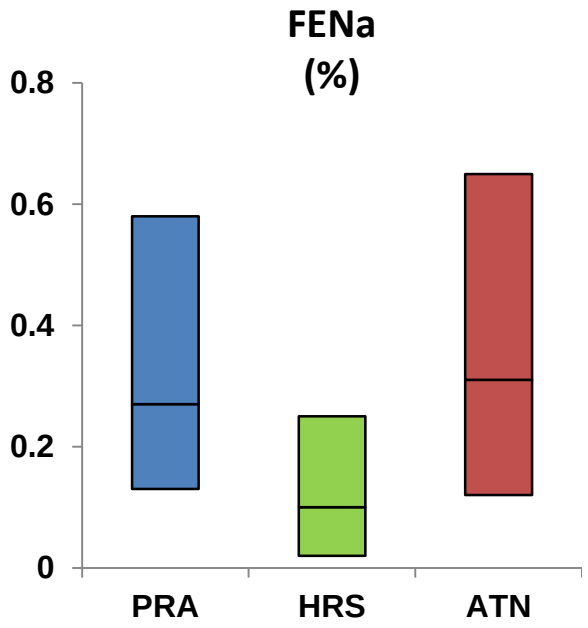
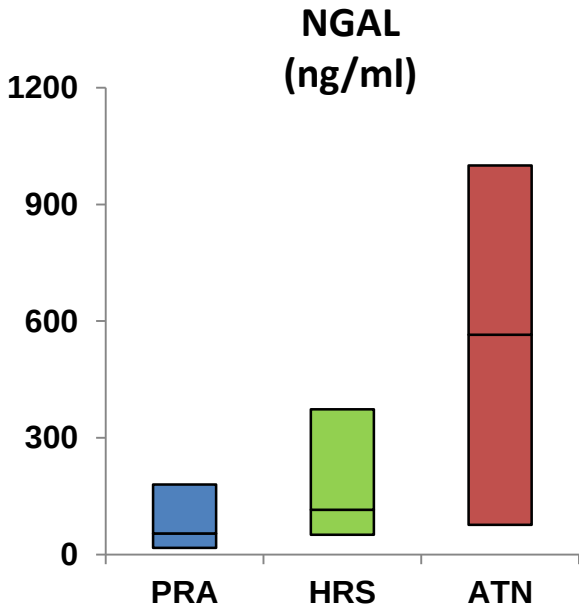
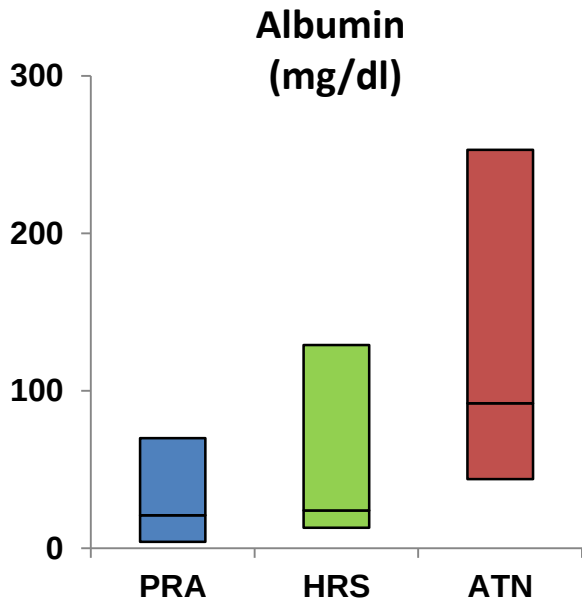
Urinary Biomarkers in AKI







n=79 progressive AKI

PRA=19 + 36 non-progressive
ATN=39
HRS=16

Belcher et al, Hepatology 2014

AKI: Management

- **Prophylaxis of complications (varices, SBP, PSE)**
- **Avoid NSAIDs, COX2 , ACE, ARBs, contrast**
- **Avoid nephrotoxins (antibiotics, contrast)**
- **Consider and prepare for OLT**

AKI: Hospital

- **Stop diuretics**
- **Stratify by likely mechanism**
- **Albumin (25%) ~1gm/Kg (12-24hrs)**
- **If ?, treatment for infection**
- **SBP – IV albumin (1.5g/kg) at diagnosis**
  (1gm/kg) at 48 hrs **(Sort NEJM 1999;5:403)**

Progressive AKI

Midodrine, octreotide and albumin

- 4 retrospective studies (n=154)
  - 7.5mg-12.5 PO TID
  - 100ug SQ Octreotide or IV 25ug/hr
  - albumin 20 – 50gm daily
- ↑MAP 15mm Hg or >90mmHg*
- Results
  - 35-60% Cr< 1.5 mg/dL
  - Survival improved (LT included)

Progressive AKI

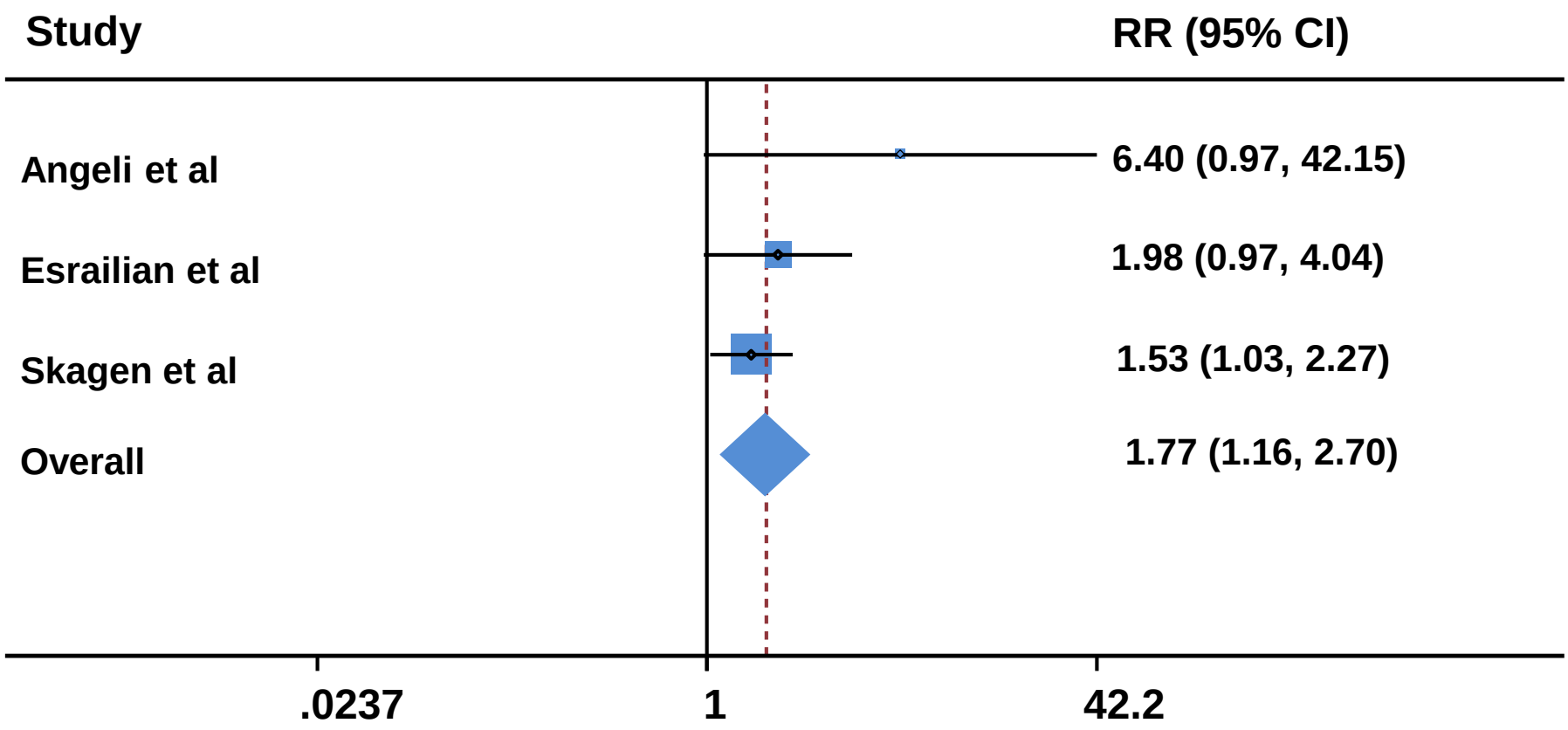
Norepinephrine and albumin

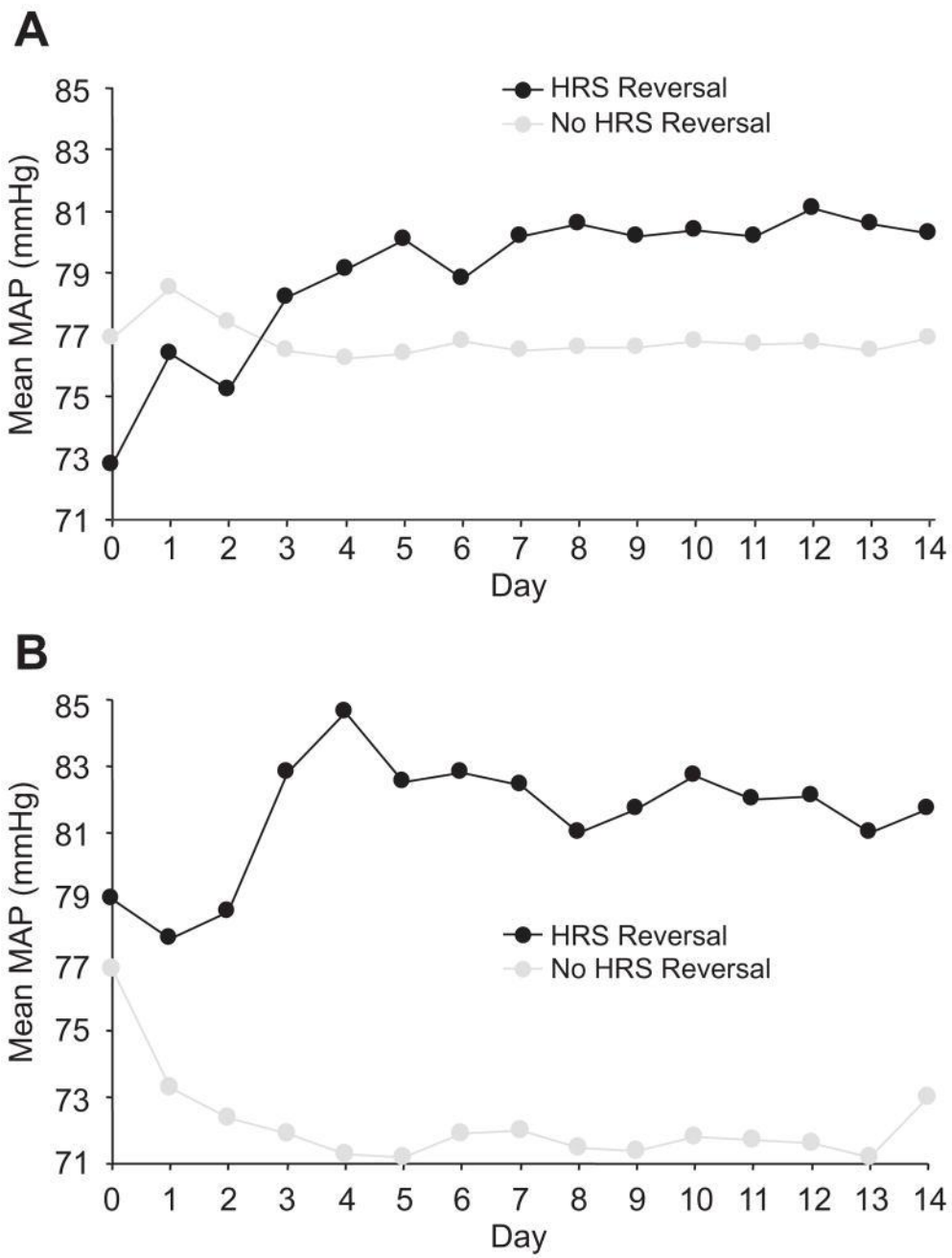
0.5 -3.0 mg/hr infusion ICU

albumin 20 – 50gm daily

↑ MAP 10mm Hg or increase in urine output

Midodrine and Octreotide: 30 day Survival





Boyer et al. J Hepatol 2011

-Variceal Bleeding

Prophylaxis works (risk groups, tx choice)
Early TIPS (subgroup 5-15%)

-Ascites

Early intervention, prevention
Diagnostic paracentesis
Beta blockers

-HE

Focus on covert and precipitants (QOL, driving, probiotics, apps)

-Acute Kidney Injury

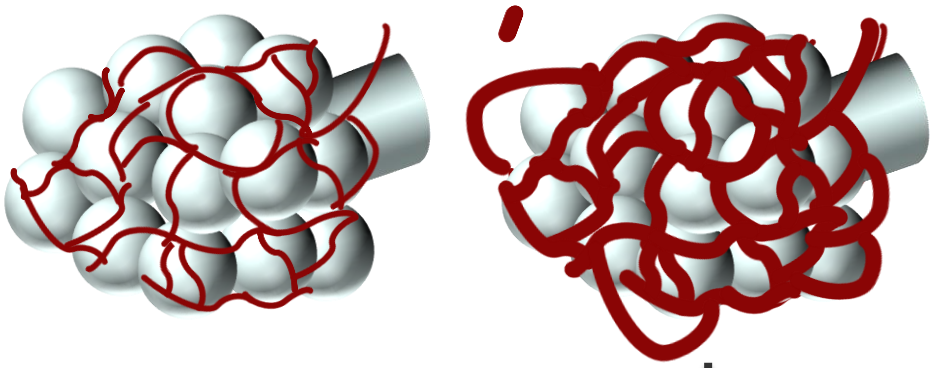
New definitions
Prevention
Early recognition and treatment (“cause” less important)

- ❖Portal Hypertension
- ❖Cirrhosis
- ❖Portosystemic shunting

40-50%

40-60%

Normal Pulmonary Microvasculature



Pulmonary vasodilatation

? Angiogenesis

50%

Abnormal ABGs

HPS

Rodriguez-Roisin et al , Thorax 1992, Eur Respir J 2004