COMPLICATIONS OF CIRRHOSIS

Michael B. Fallon, MD

THE UNIVERSITY OF ARIZONA
College of Medicine
Phoenix

OBJECTIVES

Conceptual Framework

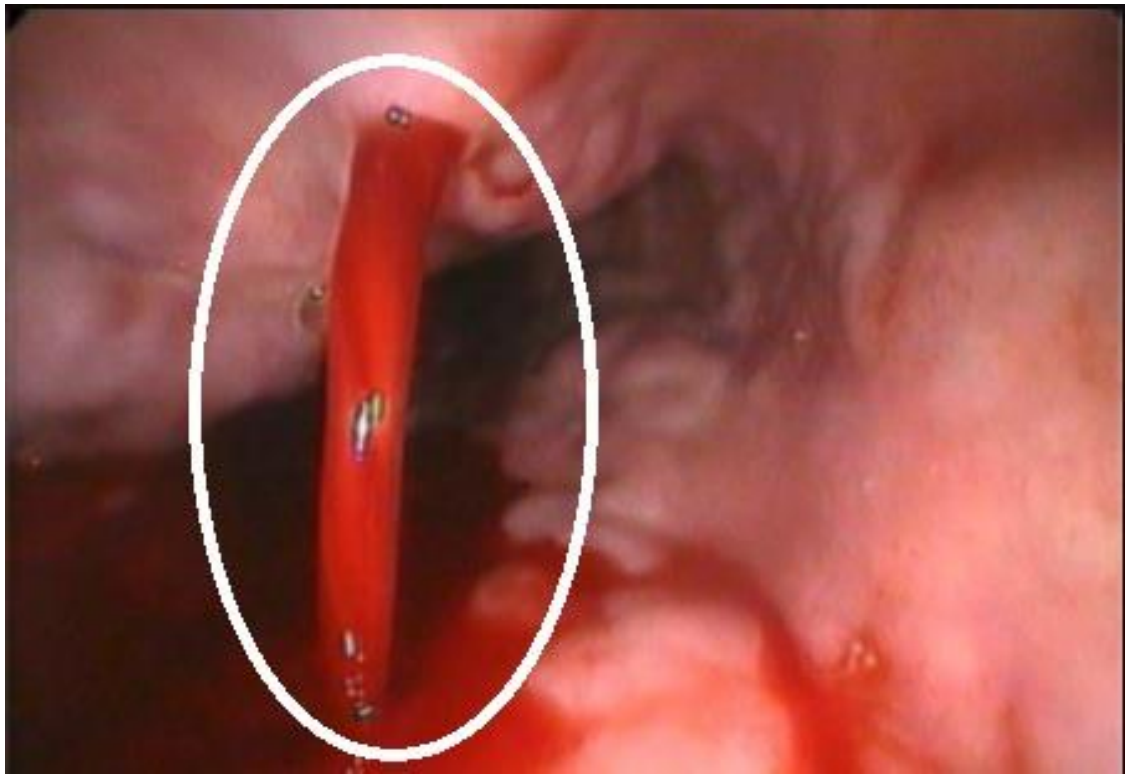
Pathophysiology, clinical features and therapies:

- **CSPH**
- **Varices**
- **Ascites/SBP**
- **Acute Kidney injury**
- **hepatic encephalopathy**
- **Hepatopulmonary Syndrome**
- **Portopulmonary Hypertension**
- **Hepatic Hydrothorax**

56 year old male ETOH cirrhosis (abstinent)

MELD Na 14

acute hematemesis



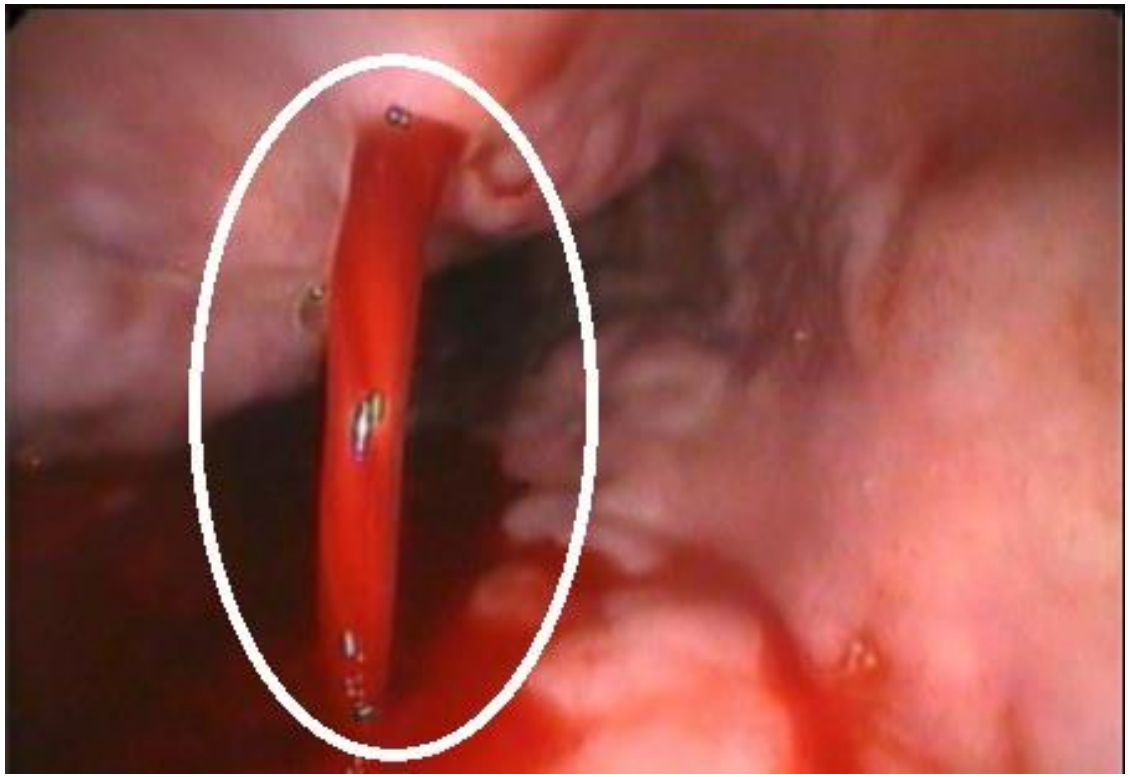
Which of these factors are the major treatable drivers of bleeding?

A) Hepatic sinusoidal constriction
B) Hyperdynamic circulation
C) Bacterial translocation
D) Low platelets and coagulation abns
E) Hepatic fibrosis

56 year old male ETOH cirrhosis (abstinent)

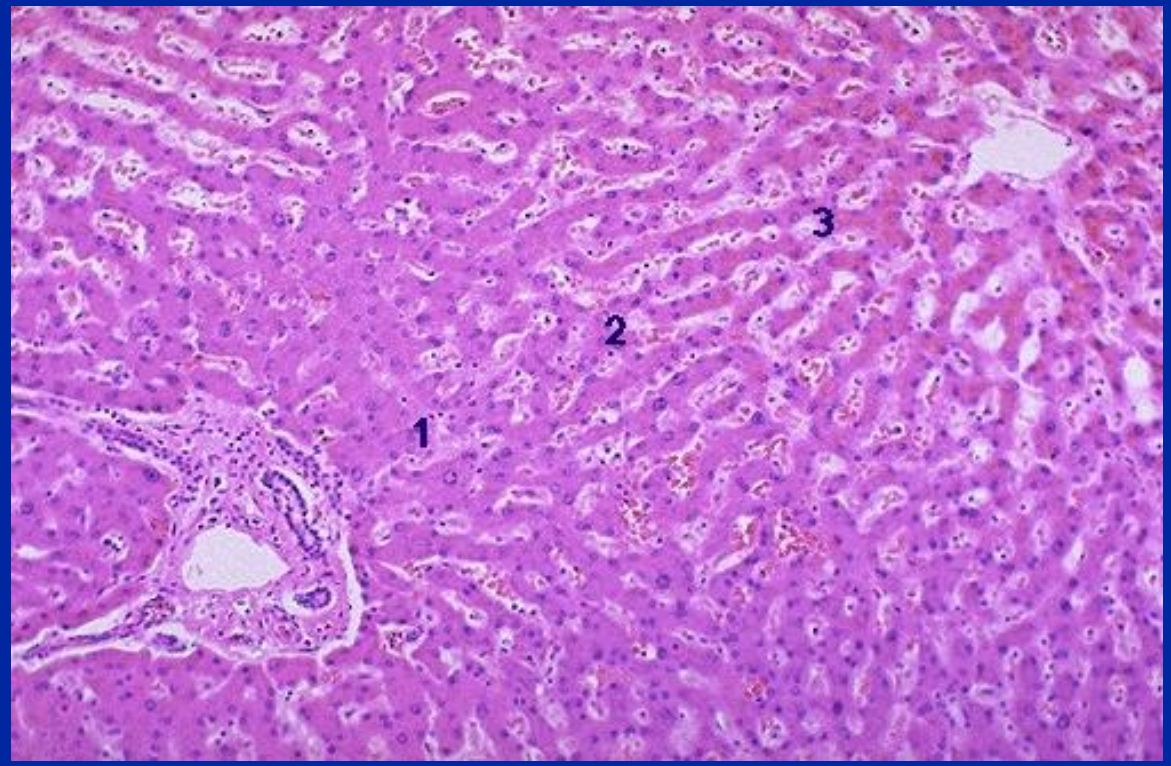
MELD Na 14

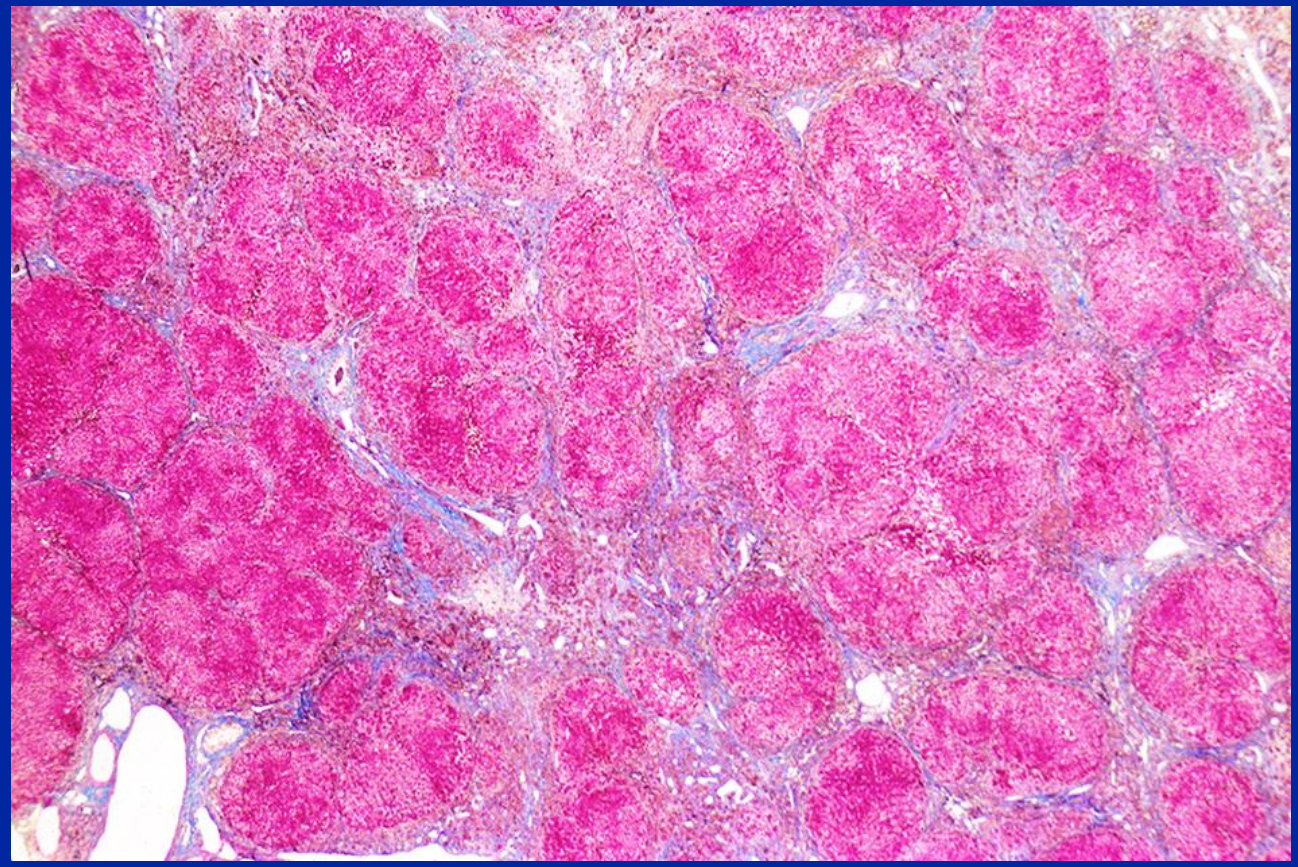
acute hematemesis



Which of these factors are the major treatable drivers of bleeding?

A) Hepatic sinusoidal constriction
B) Hyperdynamic circulation
C) Bacterial translocation
D) Low platelets and coagulation abns
E) Hepatic scarring


3
2
1



Complications of Cirrhosis

Portal Hypertension

Plumbing

porto-systemic shunting
increased hepatic lymph

varices
ascites
encephalopathy
splenomegaly

Hepatic dysfunction

Metabolism

defective synthesis
and degradation

low serum albumin
high prothrombin time
elevated total bilirubin
encephalopathy

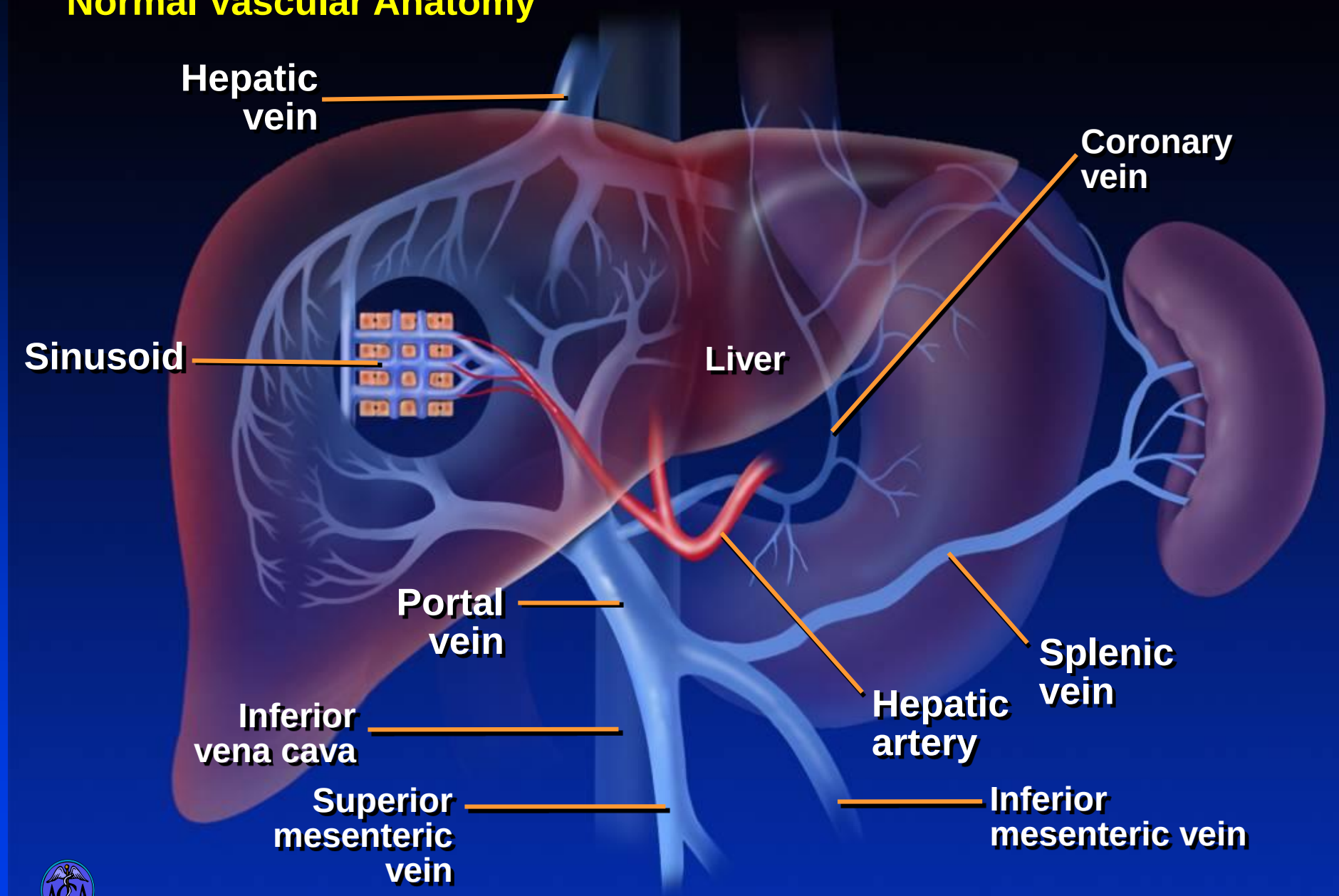
Altered vasculature/immune function

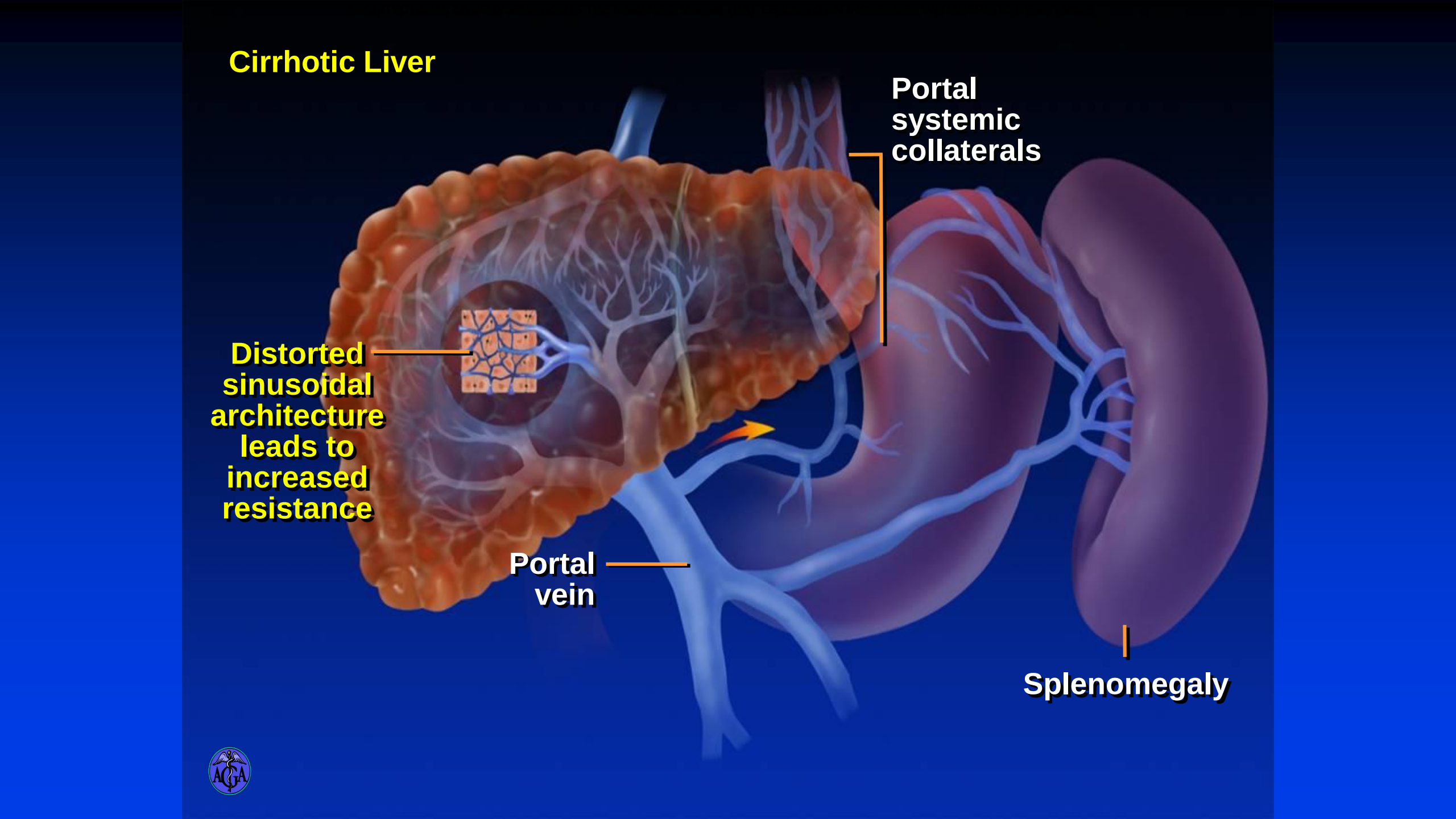
Vessels/immunity

vasoactive and inflammatory
mediators

hyperdynamic circulation
hepatorenal syndrome
hepatopulmonary syndrome
Portopulmonary hypertension
portal hypertensive gastropathy
Susceptibility to infection

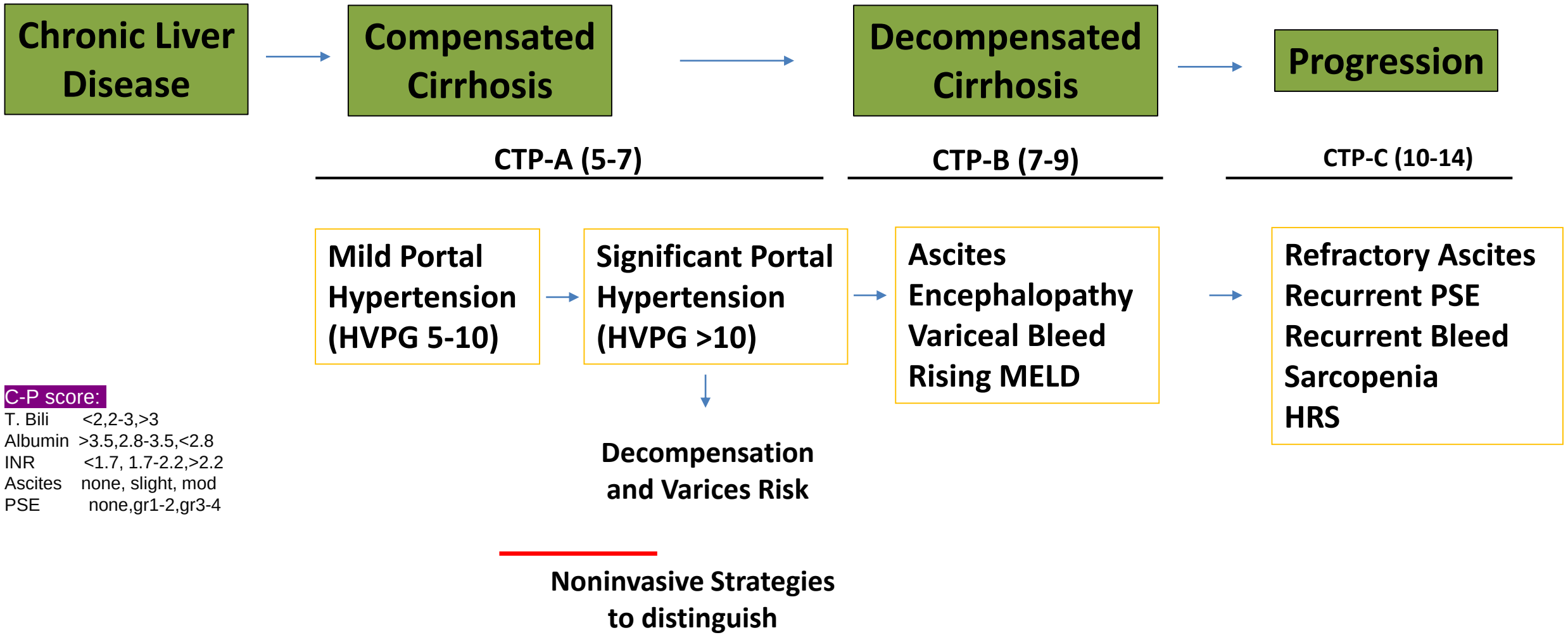
Normal Vascular Anatomy




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

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



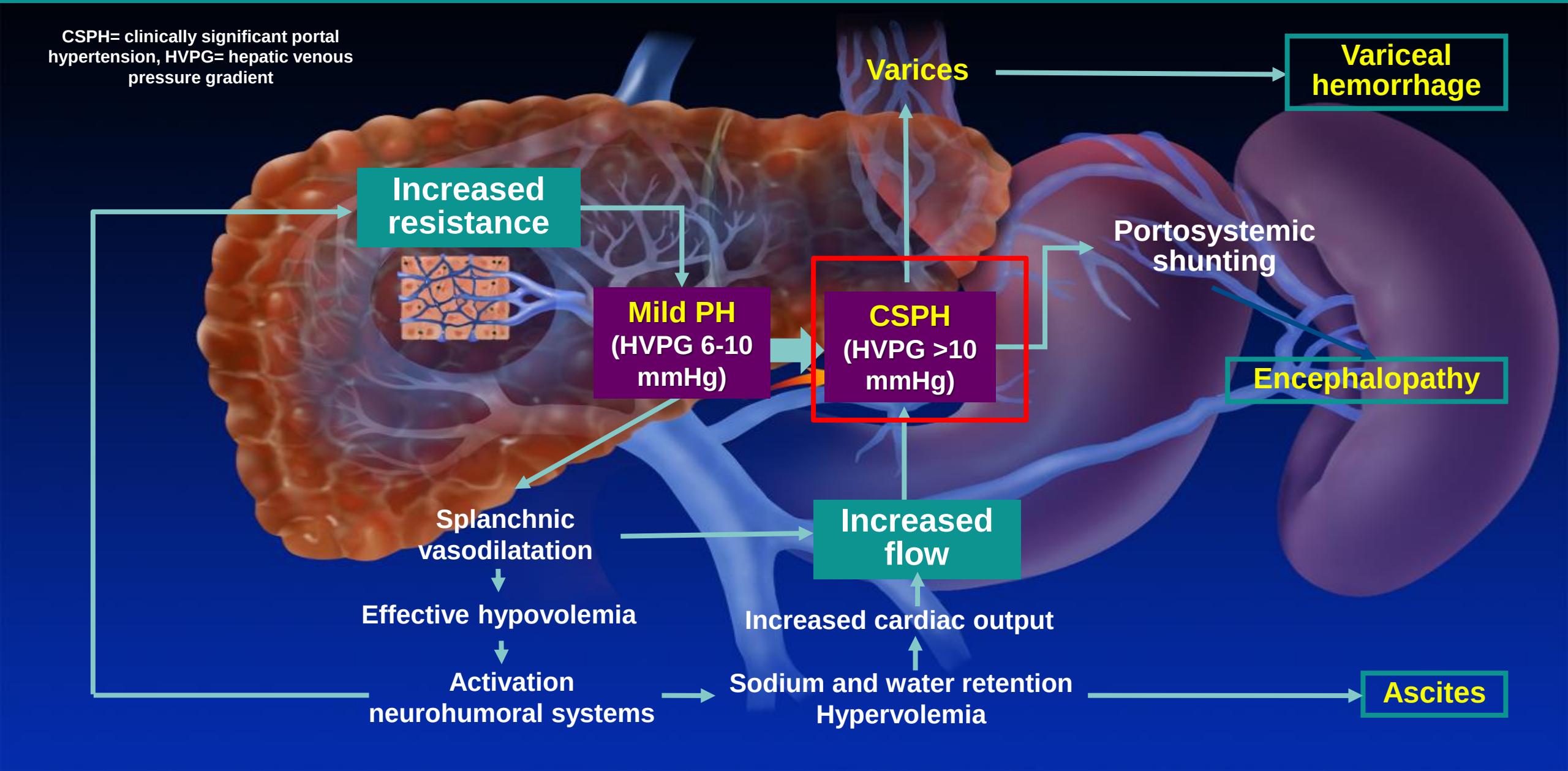
C-P score:

T. Bili	<2,2-3,>3
Albumin	>3.5,2.8-3.5,<2.8
INR	<1.7, 1.7-2.2,>2.2
Ascites	none, slight, mod
PSE	none,gr1-2,gr3-4

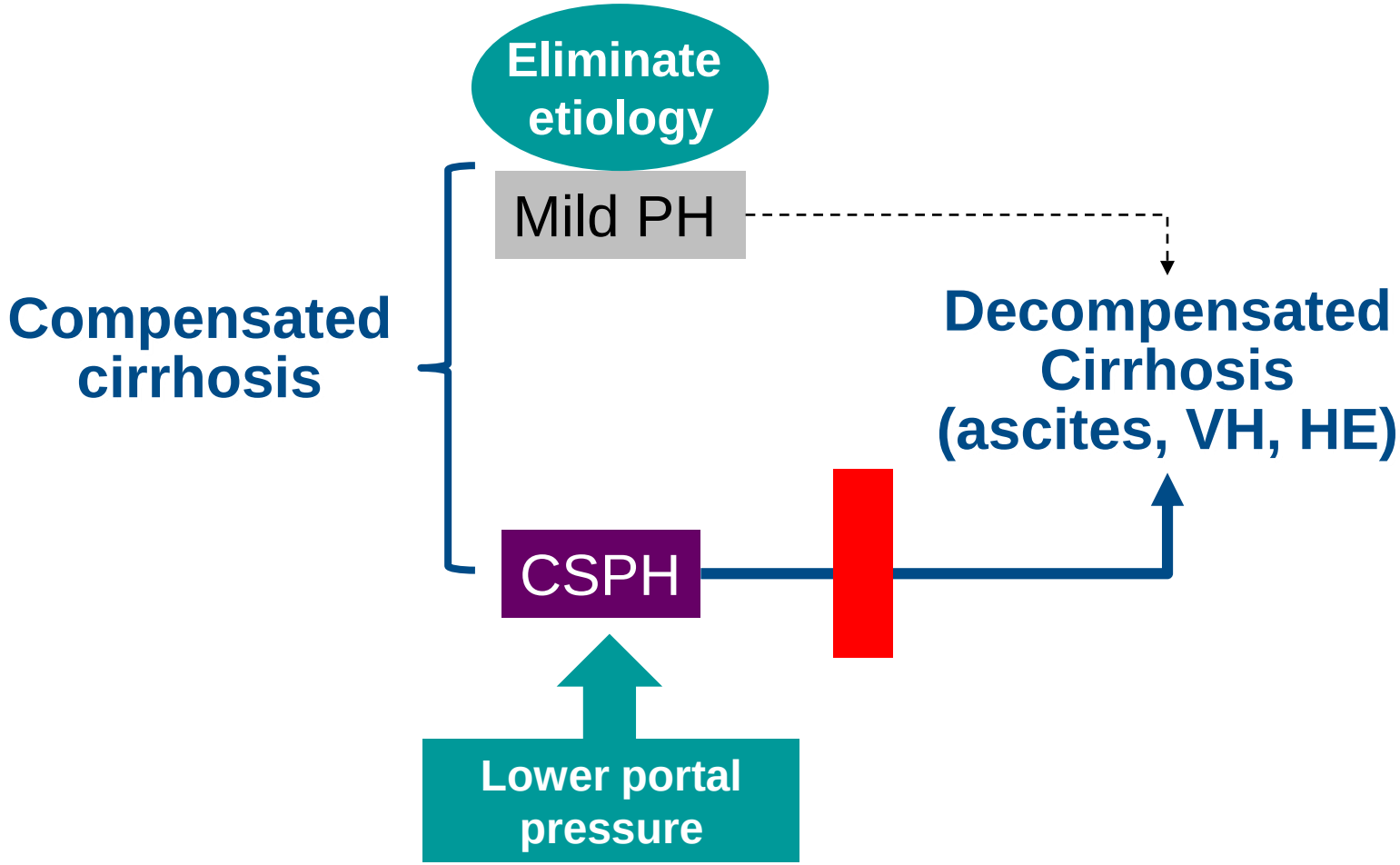
Adapted from: Garcia-Tsao et al. Hepatology 2017

CSPH is the main driver of decompensation and results from increased intrahepatic resistance and increased portal venous inflow

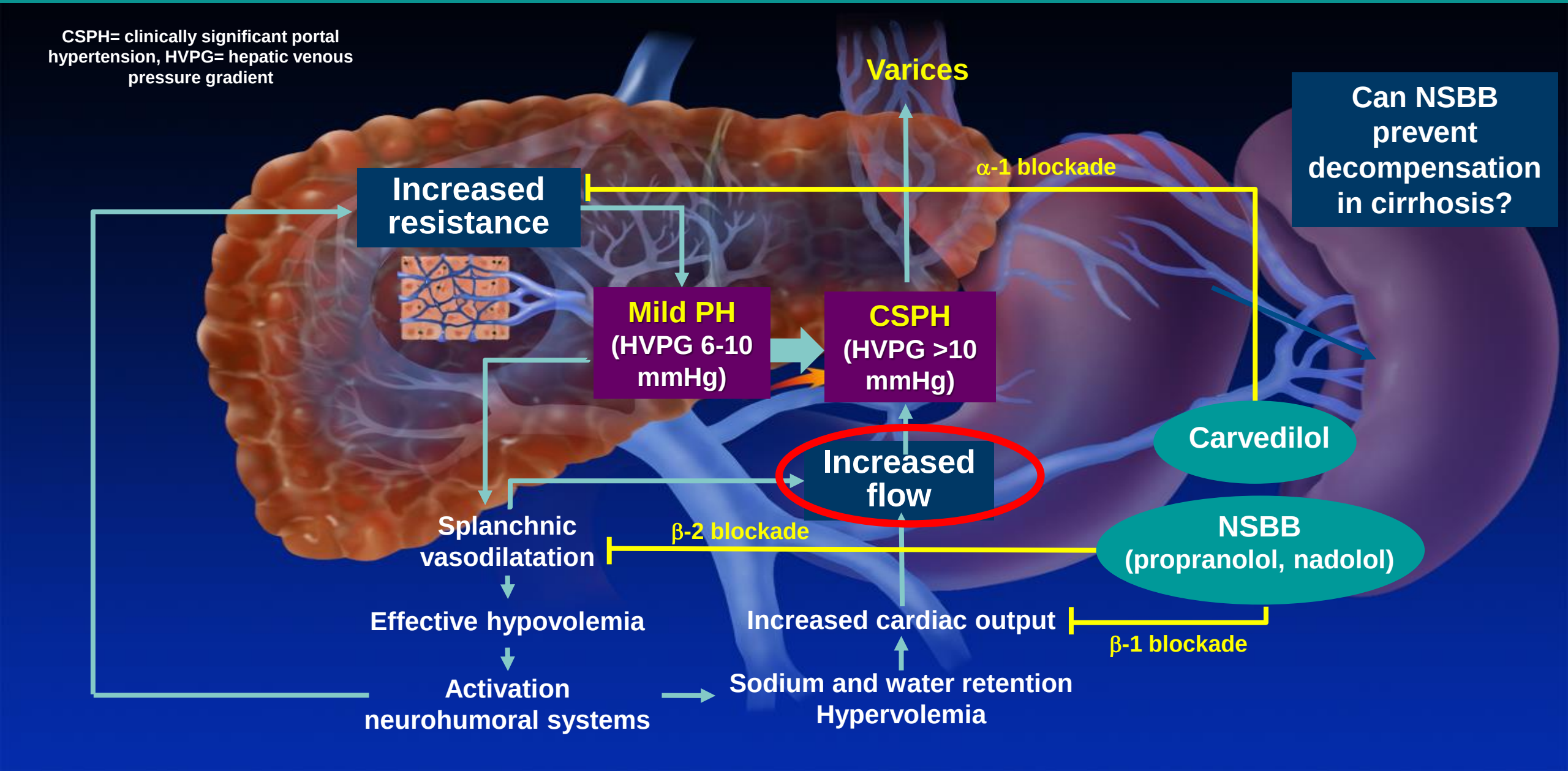
CSPH= clinically significant portal hypertension, HVPG= hepatic venous pressure gradient



The main objective of treatment in compensated cirrhosis is to prevent decompensation, not only variceal hemorrhage

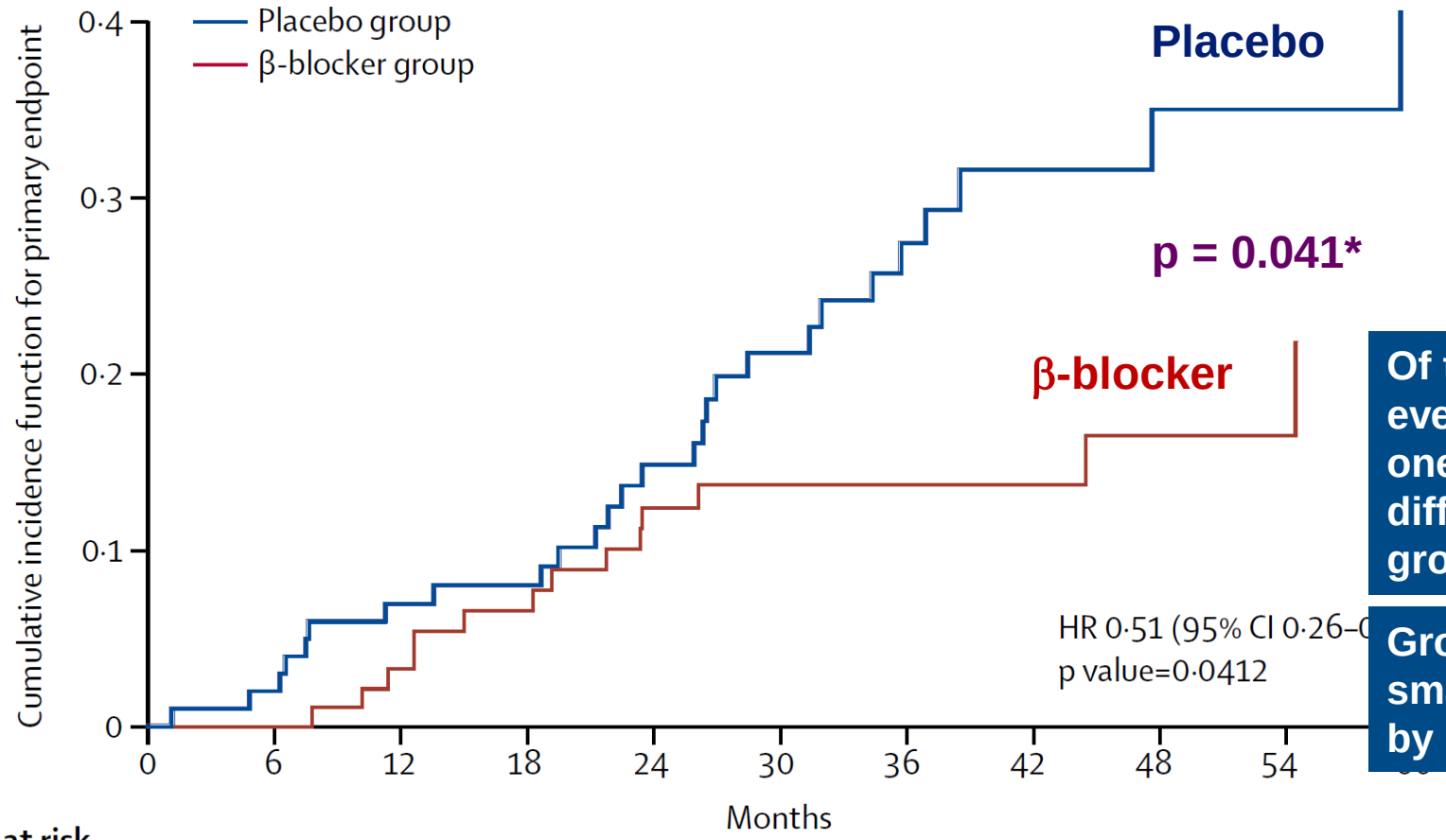


Non-selective beta-blockers (NSBB) are the mainstay in the treatment of portal hypertension and they act by decreasing portal venous inflow



In a RCT, β-blockers prevented decompensation and/or death in patients with compensated cirrhosis and CSPH (no or small varices)

Probability of developing any decompensating event / death



Of the 3 decompensating events, ascites was the only one that was significantly different between study groups (9% vs. 20%)

Growth of varices (from small to large) was reduced by 50%

*competing risk analysis (non-liver related deaths were competing events)

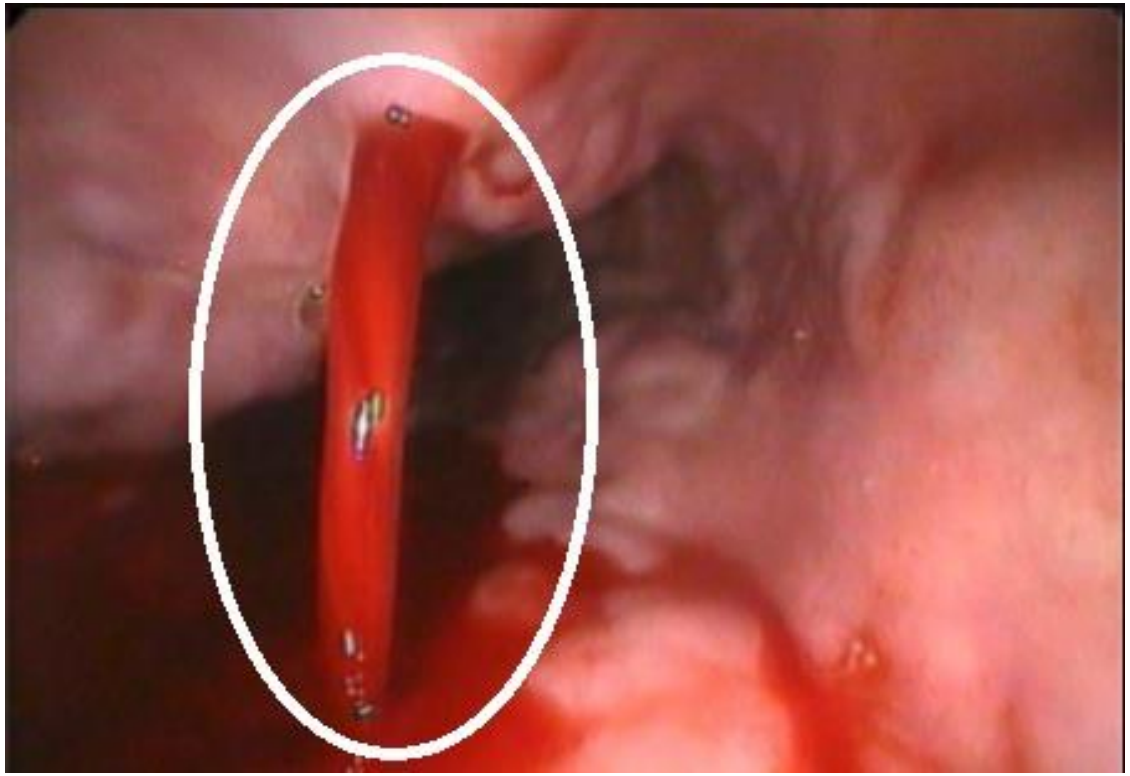
Villanueva et al (PREDESCI trial). Lancet 2019 20;393:1597-1608

Varices

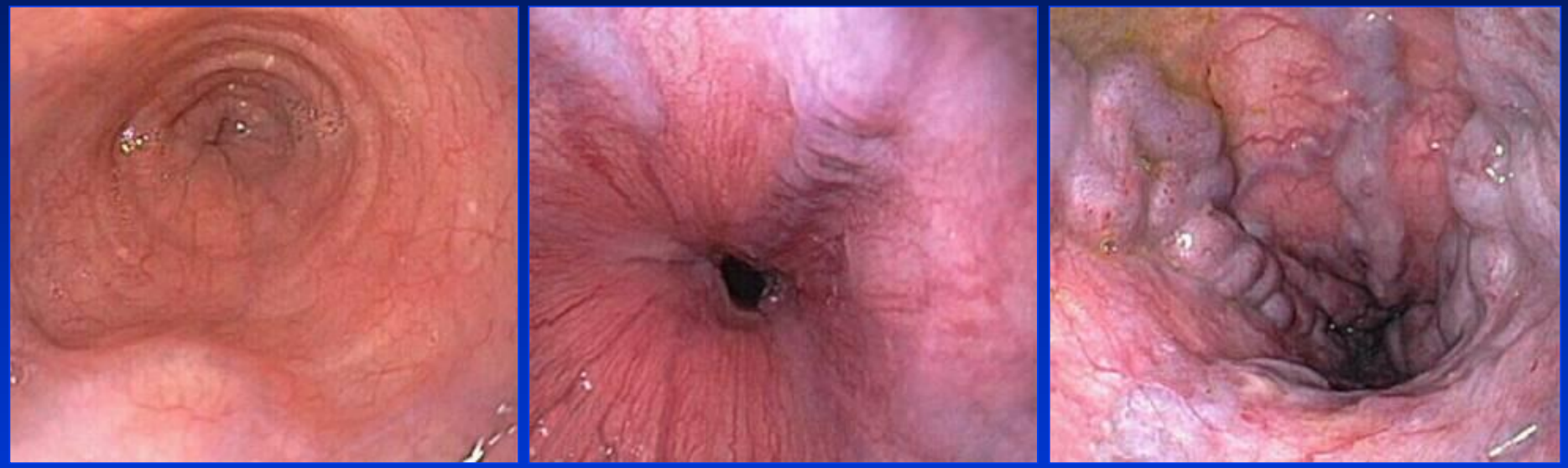
56 year old male ETOH cirrhosis (abstinent)

MELD Na 14

acute hematemesis



Varices Increase in Diameter Progressively

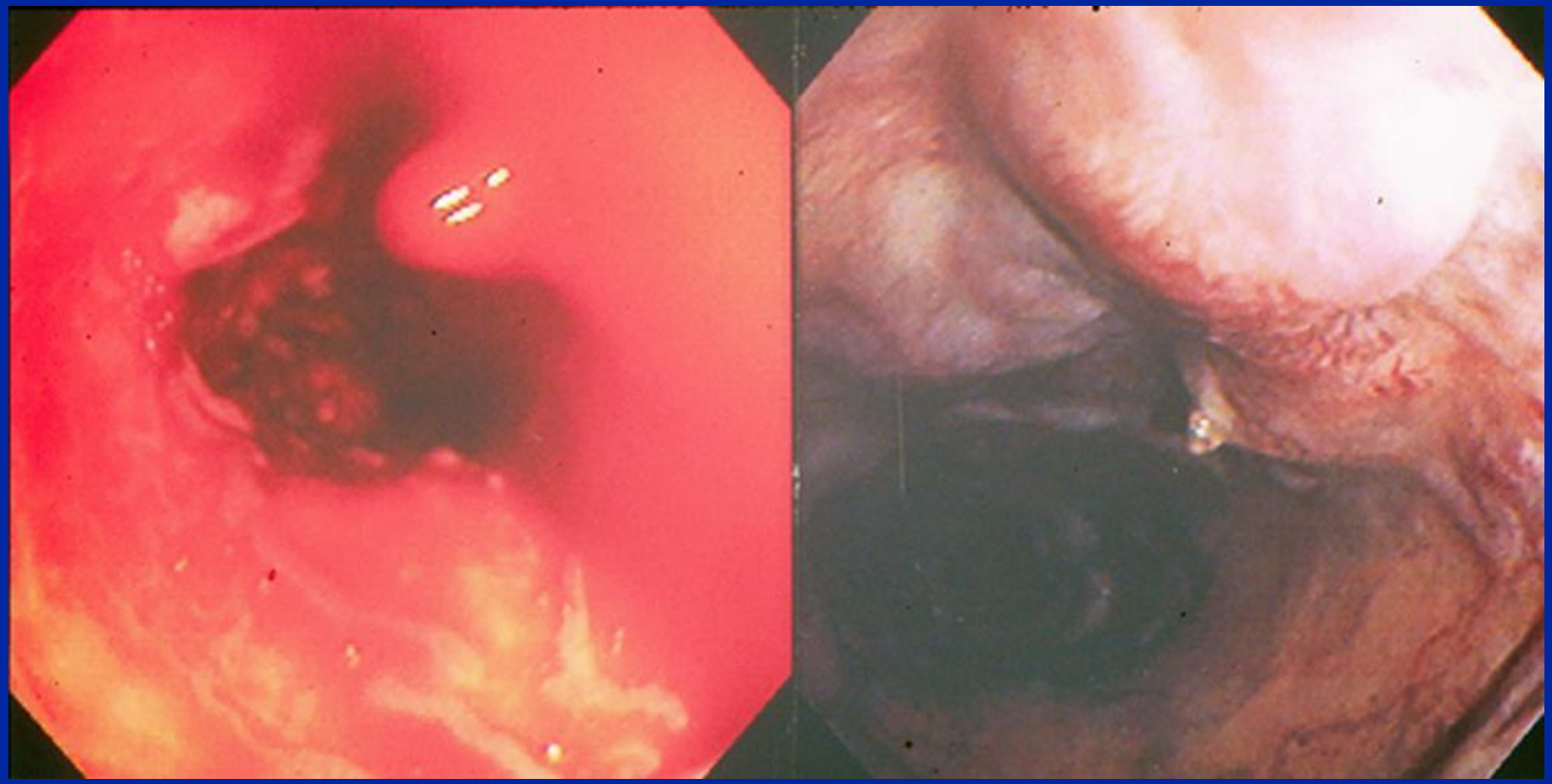


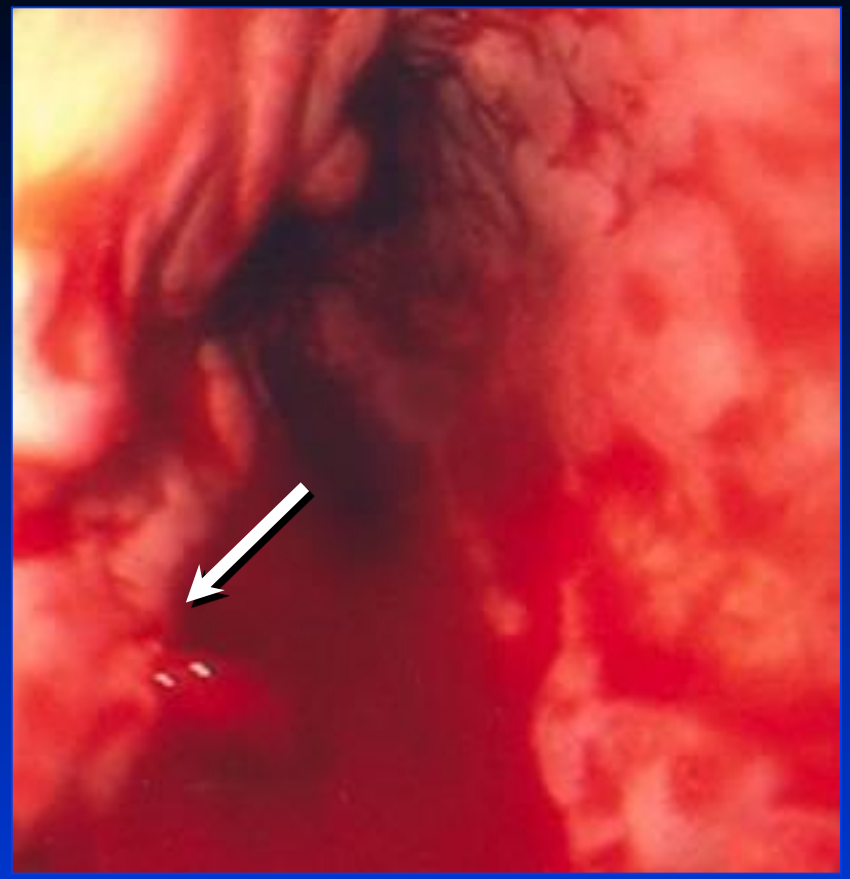
No varices → Small varices → Large varices

7-8%/year

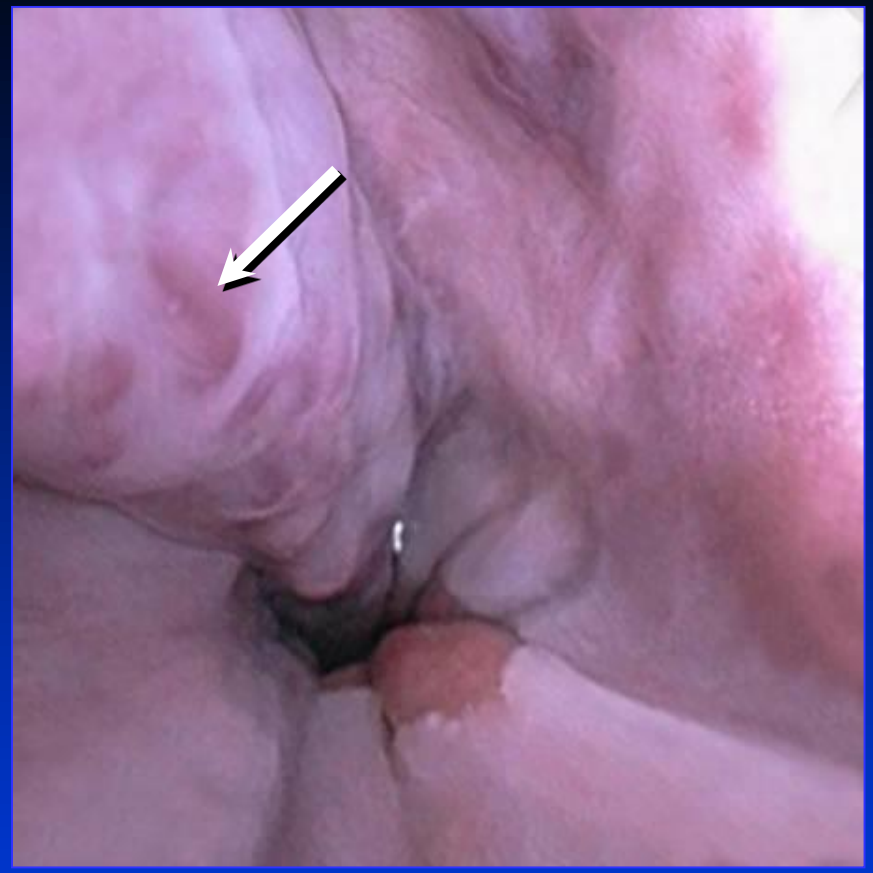
7-8%/year

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: Variceal Screening

Follow and repeat

LS <20 kPa
Platelets >150,000

Compensated

Decompensated

CSPH

When found

- Porto-systemic collaterals on cross-sectional imaging
- Liver stiffness measurement (LSM) >25 kPa

EGD

No varices

Small

Large

High risk markings
Decompensated

EGD q 1-2 years

EGD q 2-3 years

NSBBs

NSBBs or EVL

Garcia-Tsao et al. Hepatology 2017
de Franchis et al. J Hepatol 2015
Pons et al. Am J Gastro 2020

Acute Variceal Bleeding

C-P score:

T. Bili	<2,2-3,>3
Albumin	>3.5,2.8-3.5,<2.8
INR	<1.7, 1.7-2.2,>2.2
Ascites	none, slight, mod
PSE	none,gr1-2,gr3-4

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

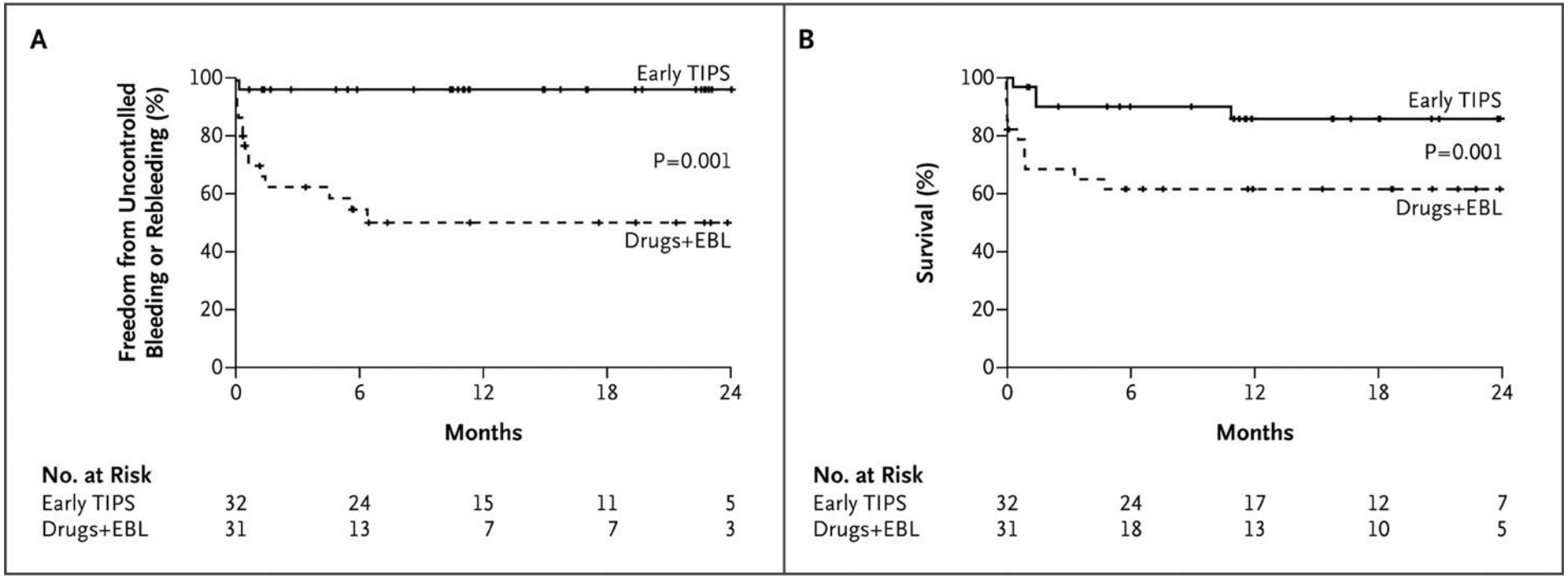
Salvage TIPS

Child Pugh C 10-13 (no contraindication)
Early TIPS (72hrs)

Exclusions:

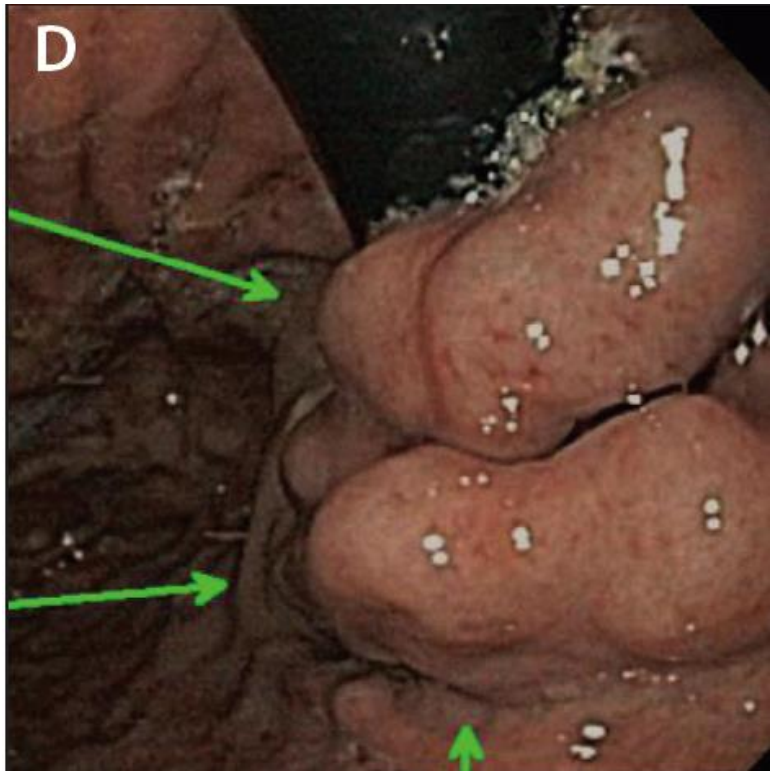
CHF	Age>75
Cr >3	HCC outside Milan
CP>13	Ectopic varices
Complete PVT	

Bleeding/rebleeding and survival in TIPS vs Medical therapy



Garcia-Pagan et al NEJM 2010

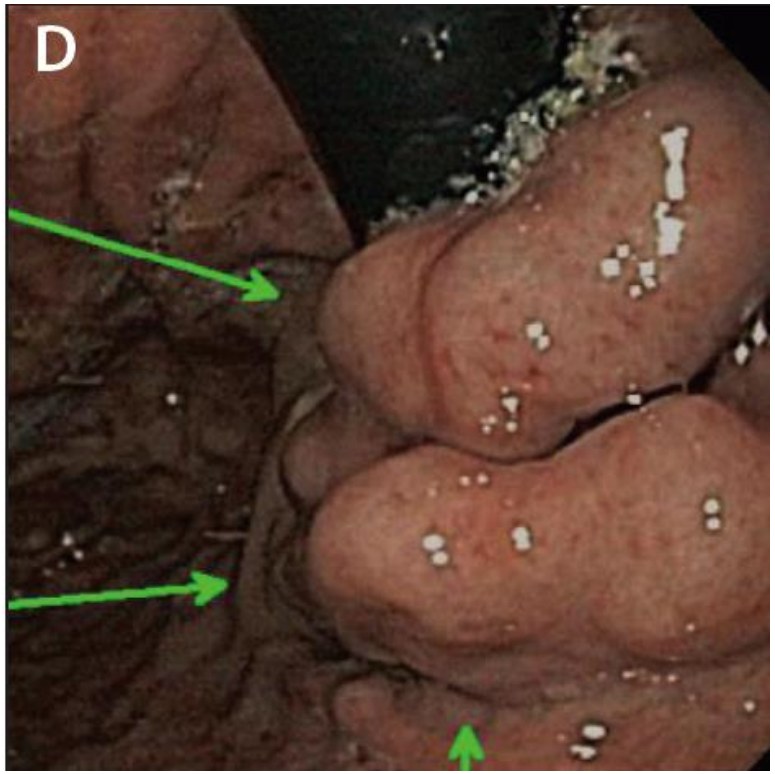
20 year old female
Regular ETOH and NSAID use
Pancreatitis 3 months ago (family history)
LFTs normal, plts 99, splenomegaly
acute hematemesis



What is the major underlying driver of bleeding?

A) Inherited cirrhosis
B) ETOH hepatitis
C) Severe gastritis
D) Splenic vein thrombosis
E) Hemosuccus pancreaticus

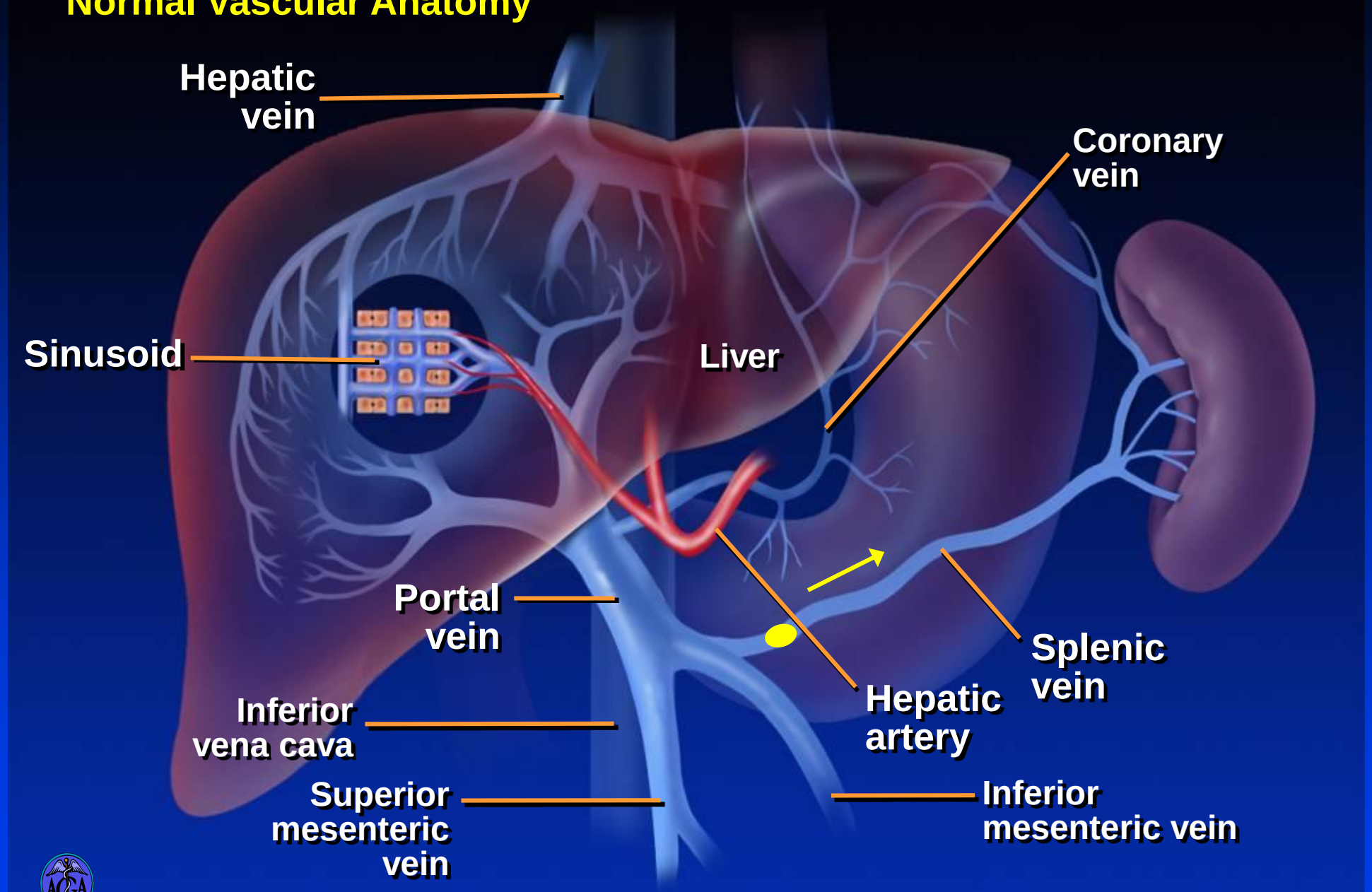
20 year old female
Regular ETOH and NSAID use
Pancreatitis 3 months ago (family history)
LFTs normal, plts 99, splenomegaly
acute hematemesis

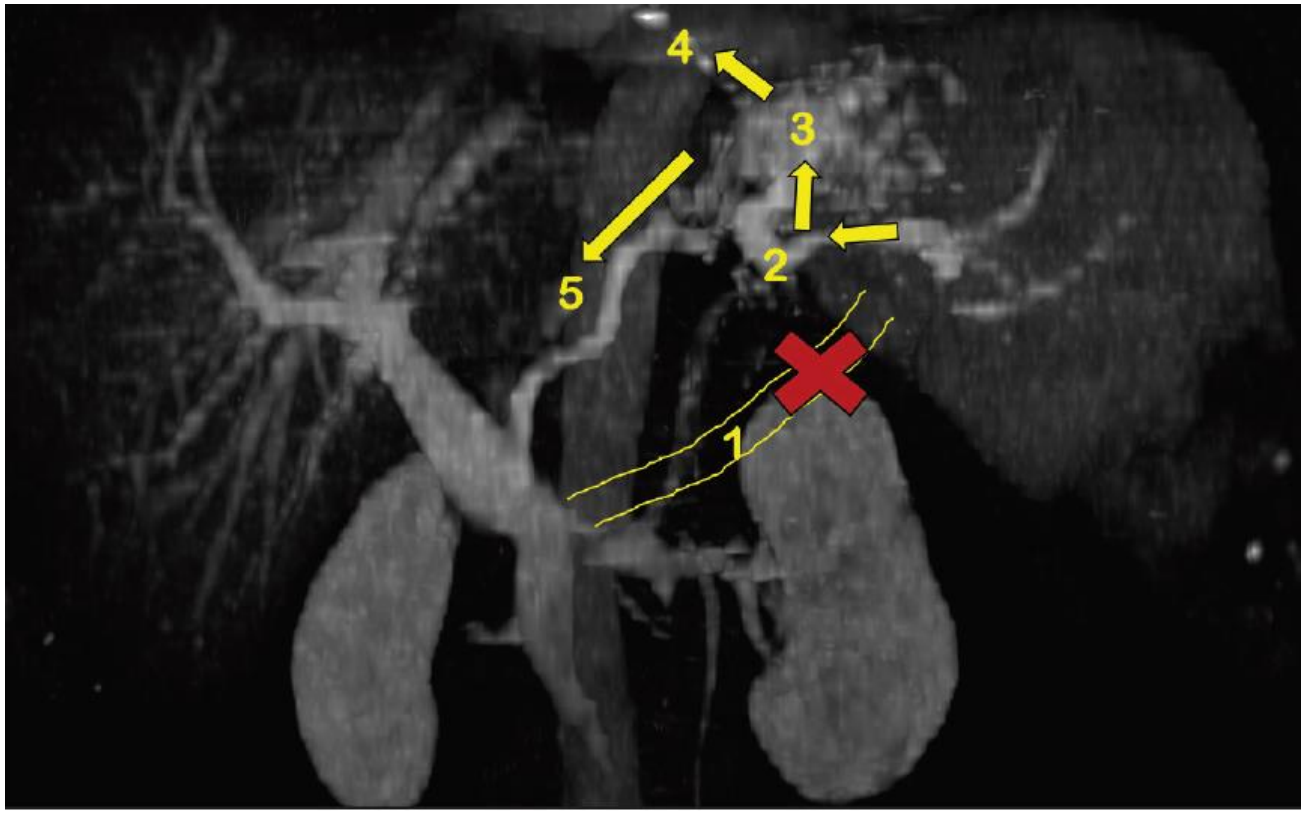


What is the major underlying driver of bleeding?

A) Inherited cirrhosis
B) ETOH hepatitis
C) Severe gastritis
D) Splenic vein thrombosis
E) Hemosuccus pancreaticus

Normal Vascular Anatomy





Therapy:
Cyanoacrylate glue
Splenectomy
Splenic embolization

Varices: Summary

- Location of portal blockage influences presentation and therapy
- Bleeding risk determined by endoscopic features (prevention) ?clinical
- Medical and endoscopic therapy for acute unless early TIPS candidate
- Restrictive transfusion strategy and limited use of FFP important

57yo: Compensated HCV cirrhosis (SVR)
3 weeks abdominal distention, “slowness”

Heart murmur
Knee osteoarthritis (NSAIDs)

Exam: BP 98/70
systolic murmur, Clear lungs
Ascites

Labs: MELD 13
BUN/Cr 19/0.9
INR 1.3

What is next step?

A) Abd US with doppler
B) Cardiac echo
C) Diagnostic paracentesis
D) Low Na diet
E) Stop NSAIDs

57yo: Compensated HCV cirrhosis (SVR)
3 weeks abdominal distention, “slowness”

Heart murmur
Knee osteoarthritis (NSAIDs)

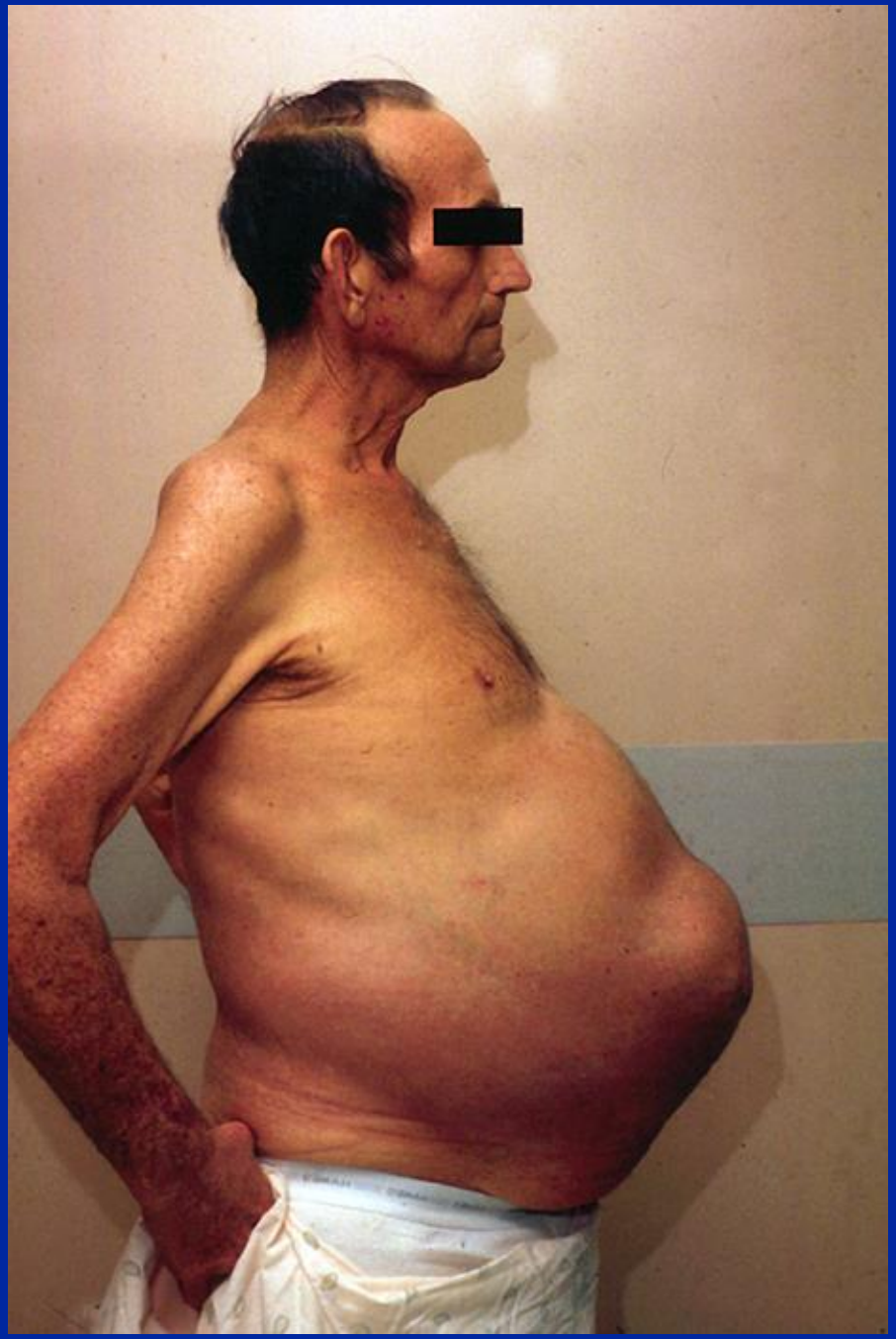
Exam: BP 98/70
systolic murmur, Clear lungs
Ascites

Labs: MELD 13
BUN/Cr 19/0.9
INR 1.3

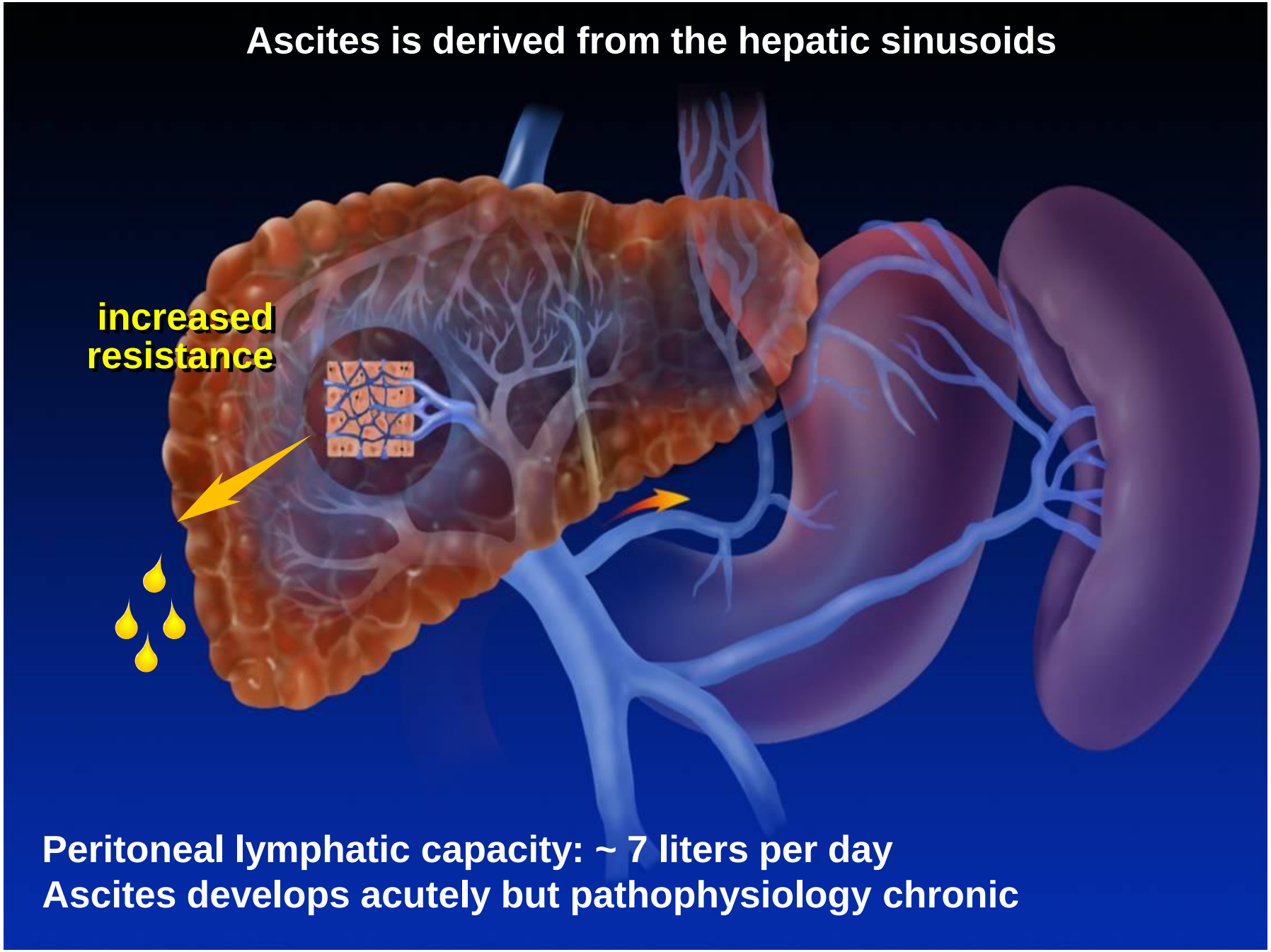
What is next step?

A) Abd US with doppler
B) Cardiac echo
C) Diagnostic paracentesis
D) Low Na diet
E) Stop NSAIDs

Ascites



Ascites is derived from the hepatic sinusoids



Peritoneal lymphatic capacity: ~ 7 liters per day
Ascites develops acutely but pathophysiology chronic

Serum-to-ascites albumin gradient (SAAG)

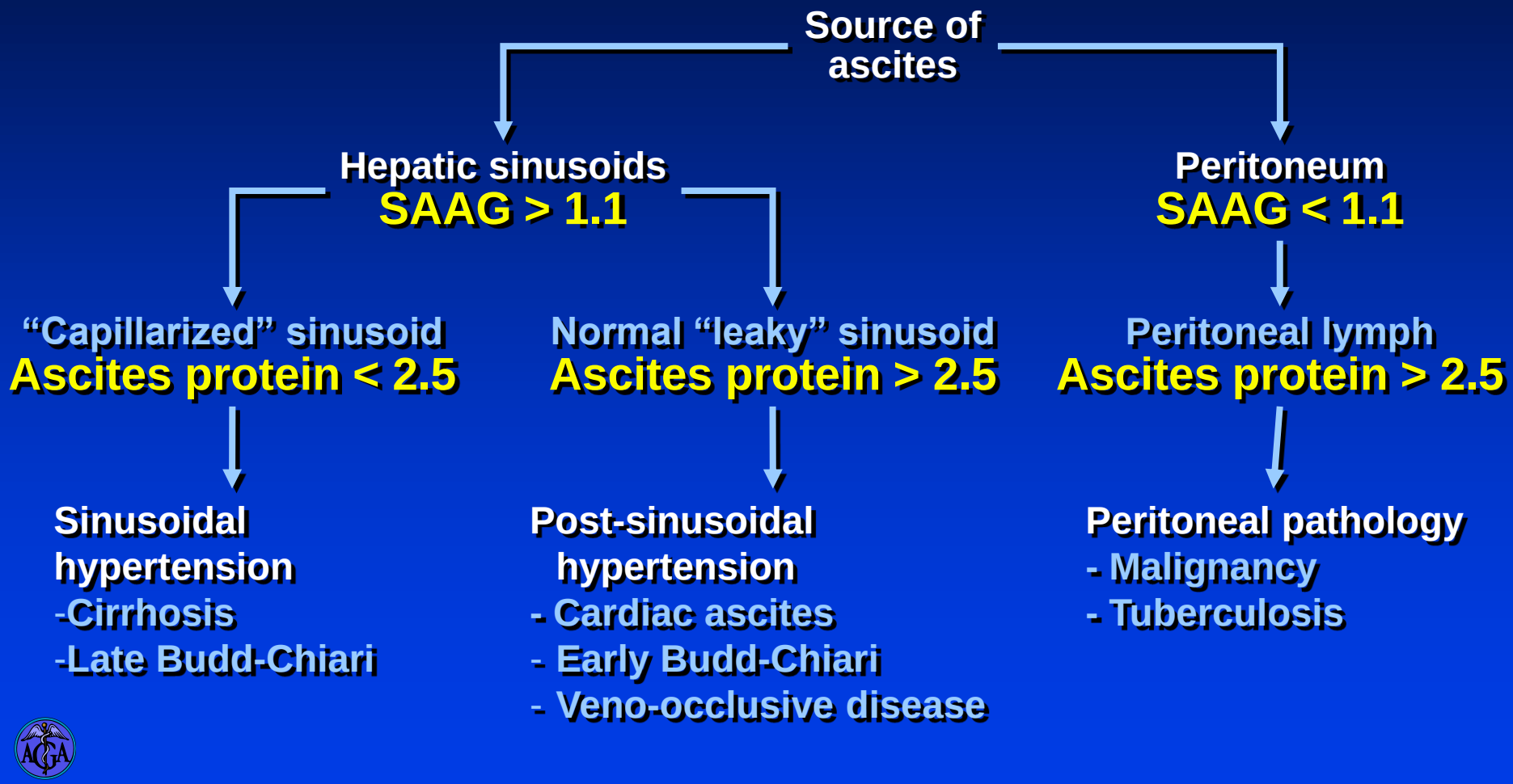
- SAAG = $[Albumin]_{serum} - [Albumin]_{ascites}$
  - portal hypertension ≥ 1.1 (85% of ascites)
  - no portal hypertension < 1.1
  - 97% accuracy

Sinusoidal perf. P + peritoneal onc. P = sinusoidal onc P + peritoneal P

Sinusoidal perf. P = sinusoidal onc P – peritoneal onc. P

Sinusoidal perf. P = serum albumin – ascites albumin

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



Initial Ascites Tests

Serum: albumin

Ascites: albumin, Total Protein, cell count and differential
culture (blood culture bottles at bedside)

Uncommon additions:

- **Lipase-pancreatic ascites**
- **bilirubin-bile leak**
- **Fungal/AFB culture, adenosine deaminase**

Not regularly useful or useless:

pH, glucose, LDH, CA-125, CA-19-9, cytology

Paracentesis Results

SAAG	1.5
TP	1.1
PMNs	806
RBCs	2012

- Cirrhosis
- SBP PMNs ≥ 250 = SBP
- Traumatic tap (250 RBC = 1 PMN)

Secondary BP?

Glucose	< 50mg/dl
LDH	> 225 mu/ml
Protein	>1mg/dl
PMNs	>10,000

Sens 90-97%

Spec 41-57%

SBP Therapy and Prophylaxis

New ascites or change in status (HE, AKI, subtle BP changes)

US guided Diagnostic Paracentesis

FFP/plts no effect on bleeding risk (spinal needle)
Inoculate blood cultures at bedside

Presumed SBP

Early SBP does not present with peritonitis

1º Prophylaxis
Ascites TP <1.0mg/dl
T. Bili >3mg/dl
Child Pugh >9
LT list

Third generation cephalosporin (ceftriaxone unless nosocomial, ?SIRS, prior prophylaxis)
Albumin 1.5g/Kg BW and 1.0g/Kg on day 3
Repeat paracentesis 48 hrs
2º Prophylaxis on discharge (70% recurrence untreated, daily cipro for now)

Instability, free air
Peritoneal signs
WBC >10,000
Multiple organisms

Poor response (clinical/cell count)

Perforation

Contrast CT
Antibiotics
Abscess
Resistance

Ascites Treatment

Sodium restriction key (canned soups, pickles/juice, chips)

Avoid salt substitutes

Stop NSAIDs, ACE/ARBs

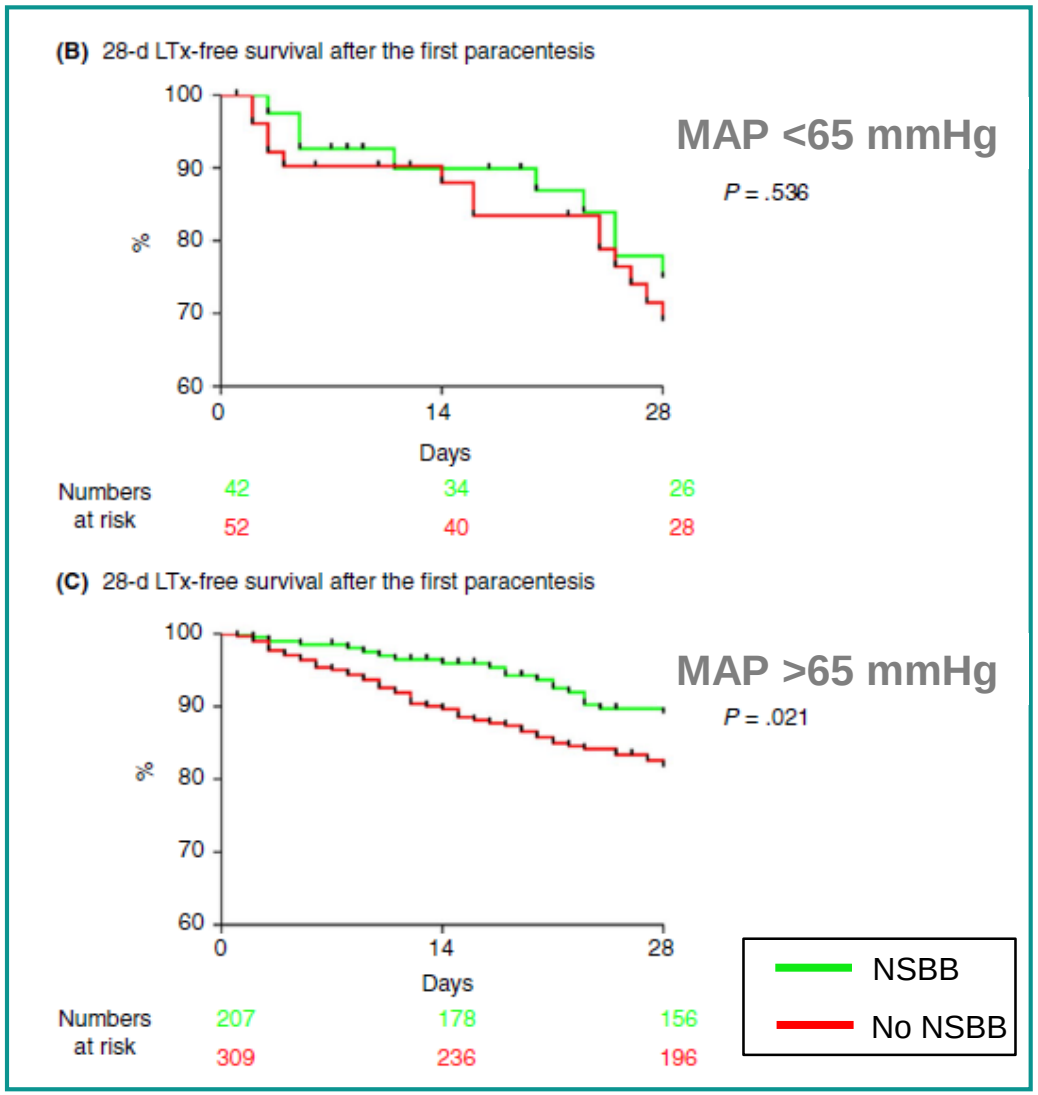
Diuretics: spironolactone/furosemide 2:1 ratio once daily

Follow weights, regular labs, clear directions

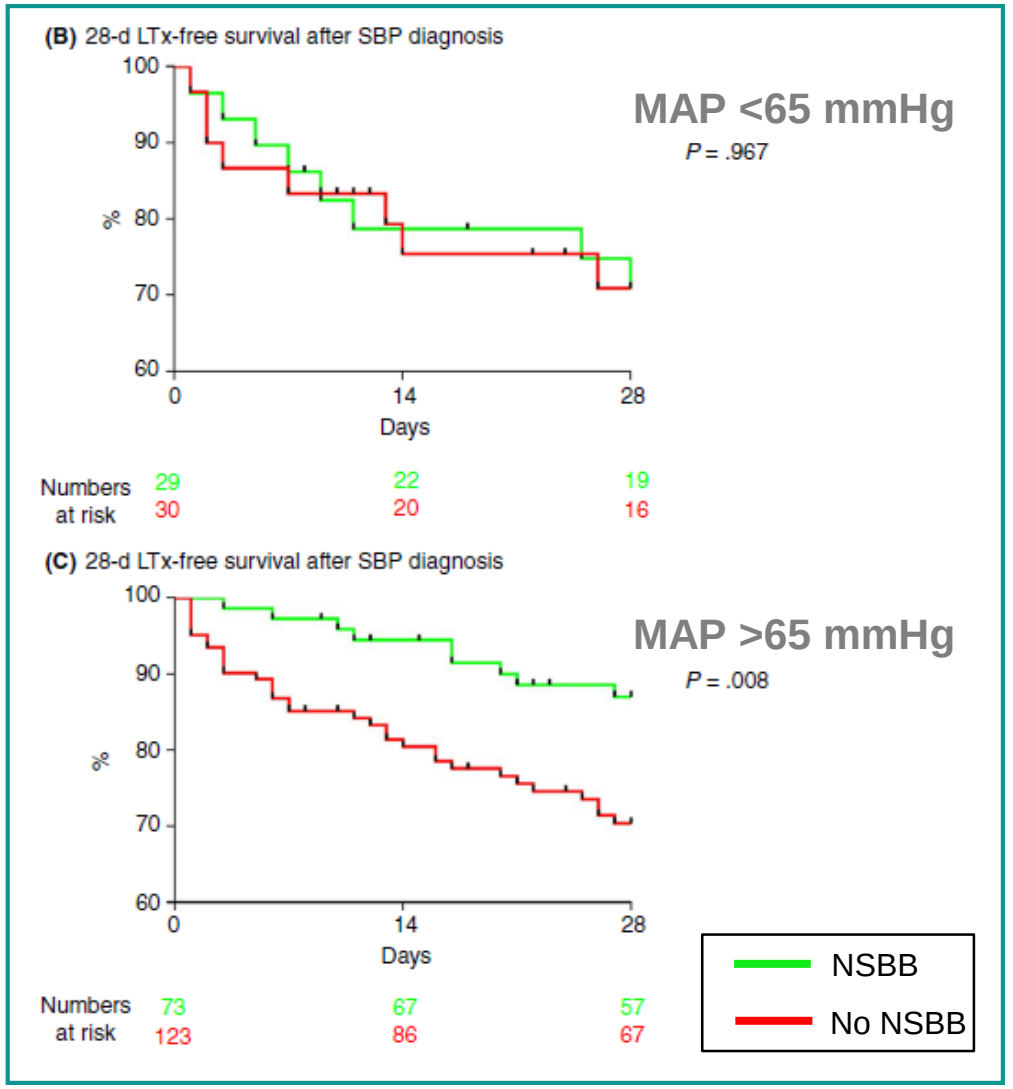
TIPS consideration for refractory

In patients with ascites requiring LVP and in those with SBP, NSBB use is associated with an improvement in survival in those with MAP>65 mmHg

Ascites requiring LVP



Ascites with SBP



Tergast et al. APT 2019;50:696–706

NSBB= nonselective beta-blockers; MAP= mean arterial pressure; SBP= spontaneous bacterial peritonitis

73yo: Prior healthy 3 month hx
abdominal distention, RUQ pain
15 lb Weight loss

Drinks one glass wine per day

Exam: VS normal
mild-mod ascites, hepatomegaly

Labs: Plt 174 Cr 0.4
T. bili 1.8 INR 1.3
Alk phos 395 MELD 12
Alb 3.6

Imaging: US inhomogenous liver, ascites, NL spleen

What is next step?

A) 3 phase CT
B) AFP
C) Diagnostic paracentesis
D) Low Na diet
E) Stop NSAIDs

73yo: Prior healthy 3 month hx
abdominal distention, RUQ pain
15 lb Weight loss

Drinks one glass wine per day

Exam: VS normal
mild-mod ascites, hepatomegaly

Labs: Plt 174 Cr 0.4
T. bili 1.8 INR 1.3
Alk phos 395 MELD 12
Alb 3.6

Imaging: US inhomogenous liver, ascites, NL spleen

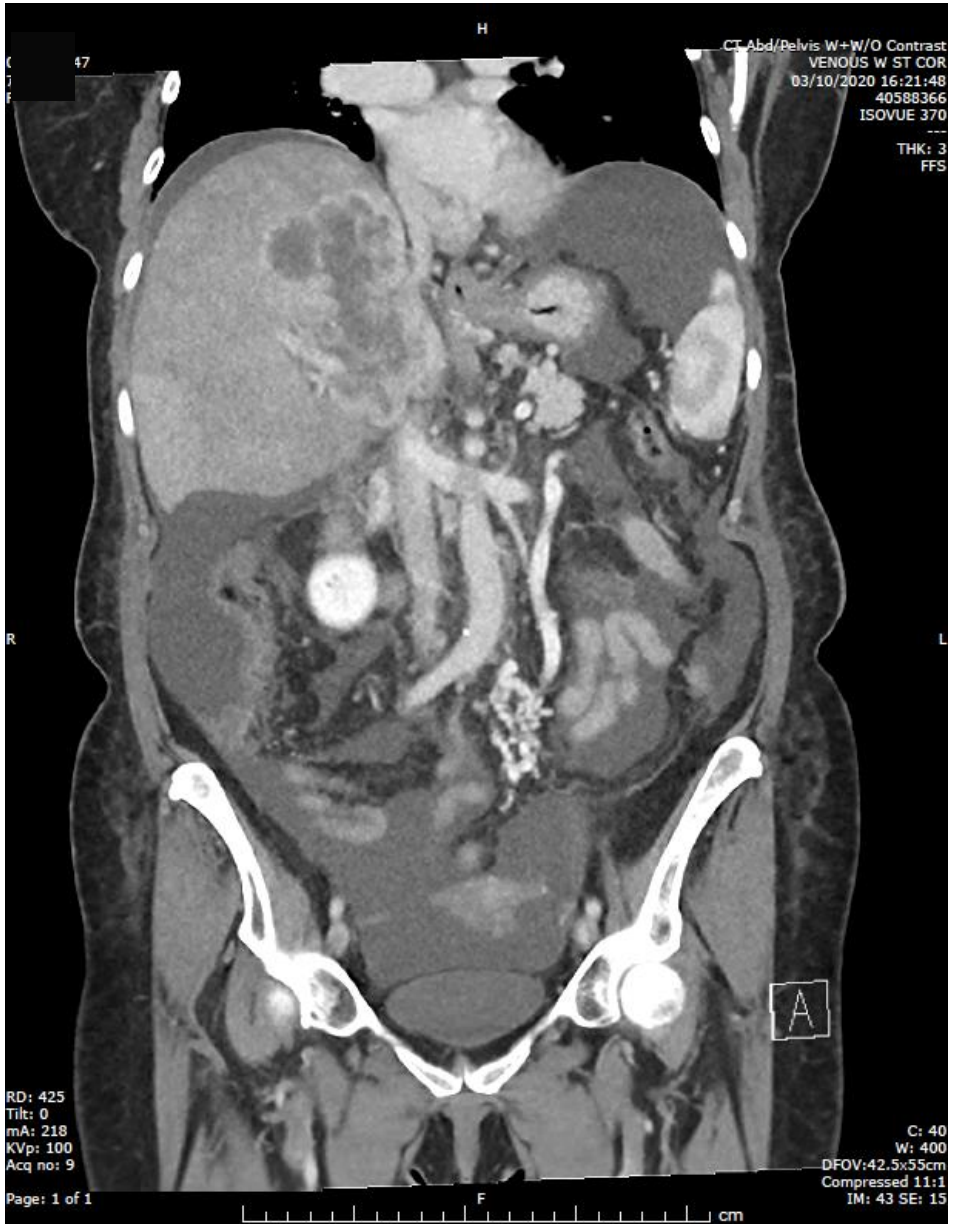
What is next step?

A) 3 phase CT
B) AFP
C) Diagnostic paracentesis
D) Low Na diet
E) Stop NSAIDs

Paracentesis Results

SAAG	1.0
TP	3.4
PMNs	29
RBCs	452

- ?Portal hypertensive (on the cusp)
- High protein: CHF or diffuse hepatic malignancy


H
CT Abd/Pelvis W+W/O Contrast
VENOUS W ST COR
03/10/2020 16:21:48
40588366
ISOVUE 370

THK: 3
FFS
R
L
A
RD: 425
Tilt: 0
mA: 218
KVp: 100
Acq no: 9
Page: 1 of 1
F
cm
C: 40
W: 400
DFOV:42.5x55cm
Compressed 11:1
IM: 43 SE: 15

Ascites: Summary

- Presentation often subacute but pathophysiology chronic
- Paracentesis key for diagnosis (SAAG/TP/cell count) 85% cirrhosis
- Sodium education and restriction early
- Treatment: medical management
- Transjugular intrahepatic portosystemic shunt (TIPS) for refractory

SBP: Summary

- Presentation is subtle, not peritonitis unless late or secondary
- Paracentesis key for diagnosis (cell counts, bedside inoculation)
- Early therapy, include albumin
- Prophylaxis after episode or decompensated

61yo: Admitted for abnormal outpatient labs

ETOH cirrhosis abstinent

Ascites (prior SBP, on cipro, controlled on diuretics)

HE on lactulose, rifaximin (loose stools)

back pain (intermittent NSAIDs)

Exam: afebrile, BP 98/70

Ascites, nontender

Alert, minimal asterixis

Labs: T. bili 2.0

INR 1.4

MELD 16

BUN/Cr 24/1.4 (3 months ago Cr 0.7)

urinalysis: trace protein, no RBCs, casts

What is the best next step?

A) hold NSAIDs and follow labs
B) initiate IV diuresis
C) hold NSAIDs, give albumin and re-assess in 12 hours
D) start midodrine and octreotide
E) diagnostic paracentesis

What is the best next step?

A) hold NSAIDs and follow labs
B) initiate IV diuresis
C) hold NSAIDs, give albumin and re-assess in 12 hours
D) start midodrine and octreotide
E) diagnostic paracentesis

What is the best next step?

A) hold NSAIDs and follow labs
B) initiate IV diuresis
C) hold NSAIDs, give albumin and re-assess in 12 hours
D) start midodrine and octreotide
E) diagnostic paracentesis

HRS: *Classification*

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

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

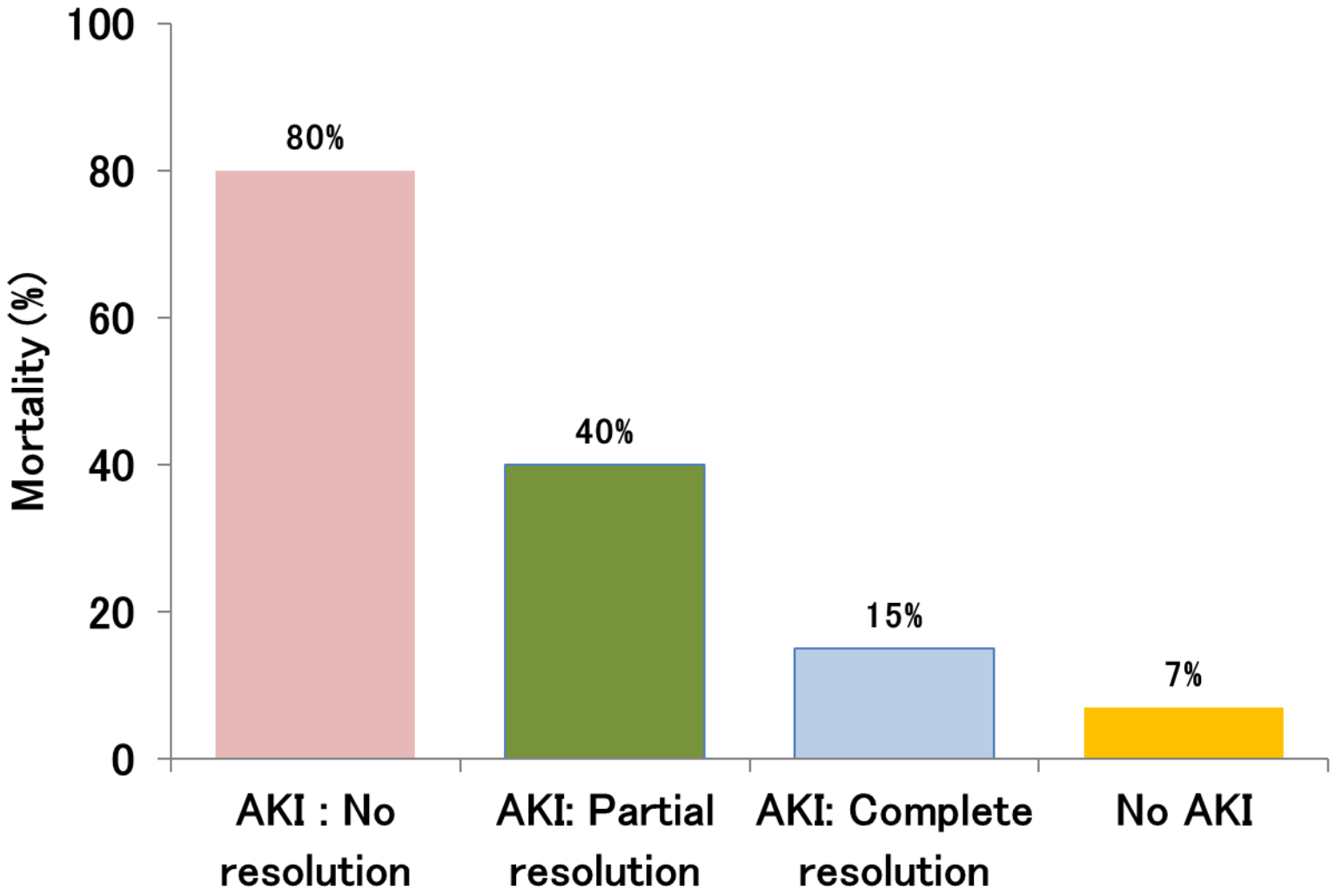
Baseline parameter	**RR**	**95% CI**	***p* value**
Alcoholic Hepatitis	0.98	0.32–2.94	0.965
Gender	0.68	0.23–1.96	0.472
MELD Score	0.92	0.80–1.05	0.223
Child-Pugh Score	0.89	0.62–1.27	0.513
Serum Creatinine	0.51	0.28–0.93	0.029
Bilirubin	1.02	0.97–1.08	0.374
Mean Arterial Pressure	0.98	0.94–1.02	0.348

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

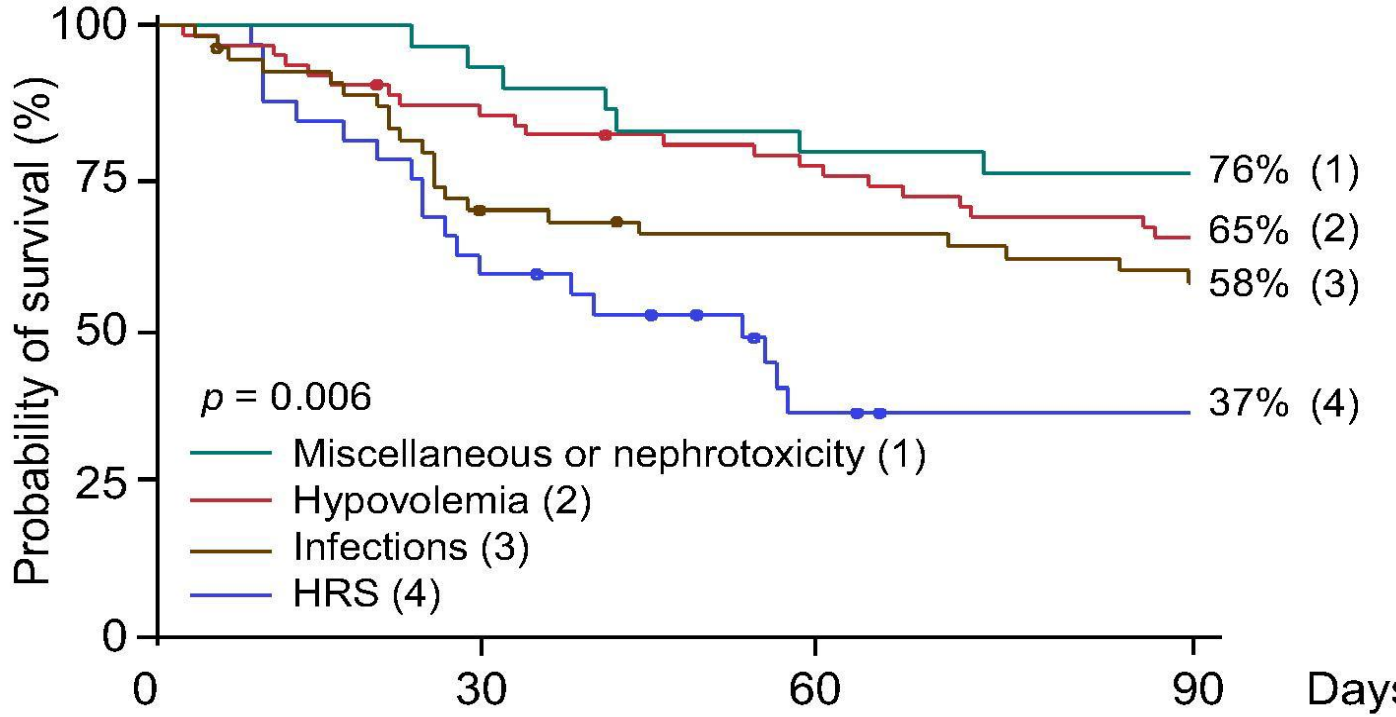
Boyer et al. J Hepatol 2011

Acute Kidney Injury in cirrhosis

- 20% of hospitalized cirrhotics
- Mortality 15 - 65% based on progression
- Often functional and linked to infection
- Hypovolemia, ATN, HRS



Adapted from Wong *et al. Gatroentrology* 2013



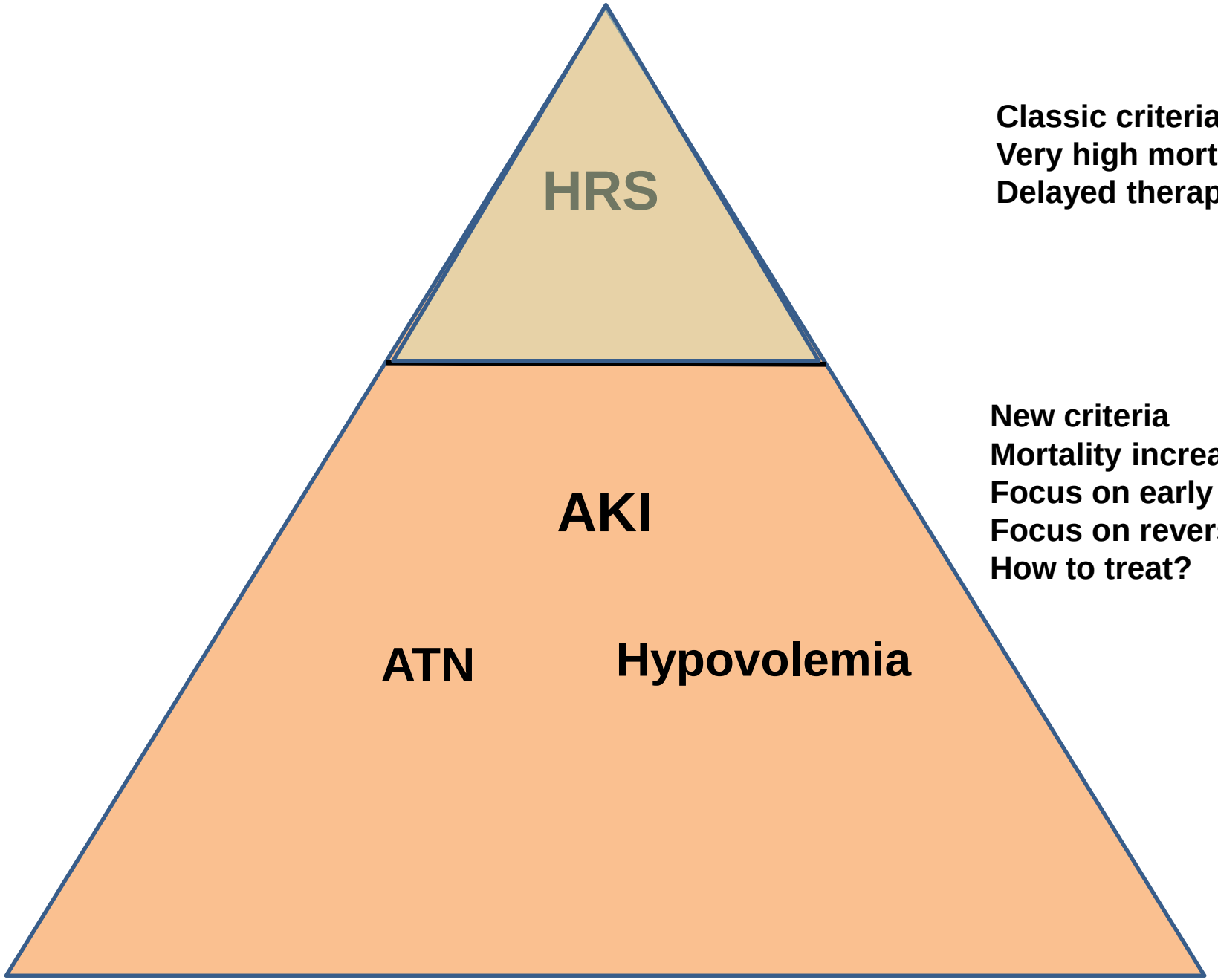
1 (n = 29)	27	23	22
2 (n = 62)	52	45	39
3 (n = 54)	36	33	30
4 (n = 32)	19	9	7

30% ATN, drugs, CKD

45% Hypovolemia

25% HRS

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



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*

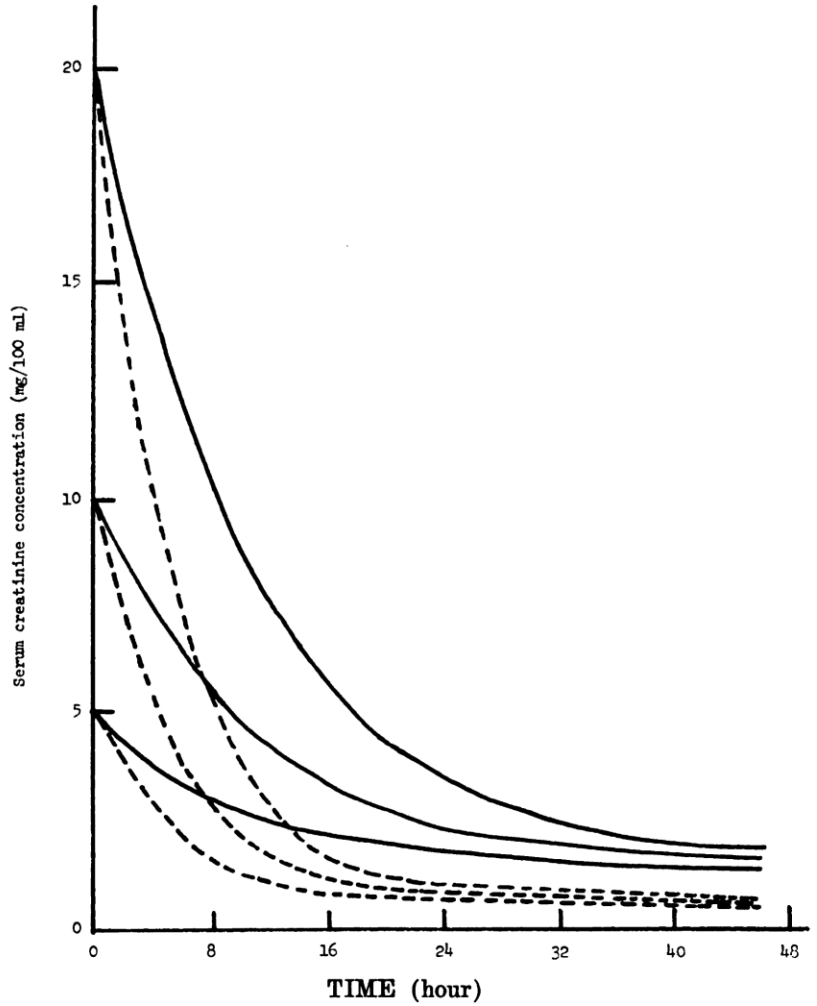
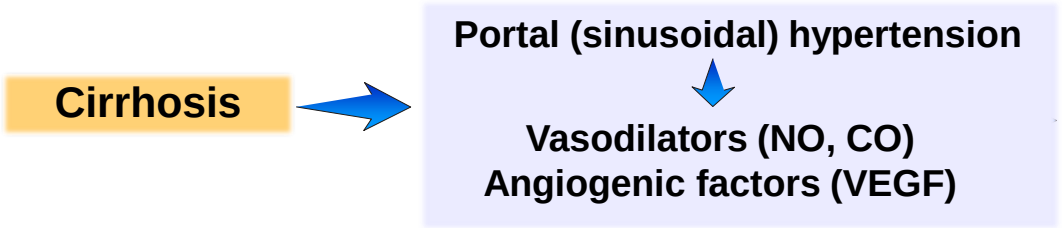
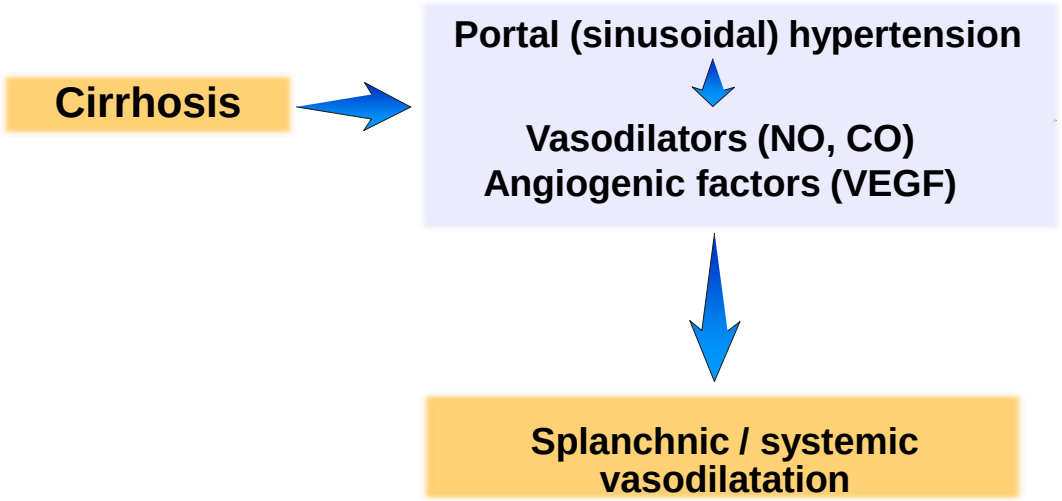
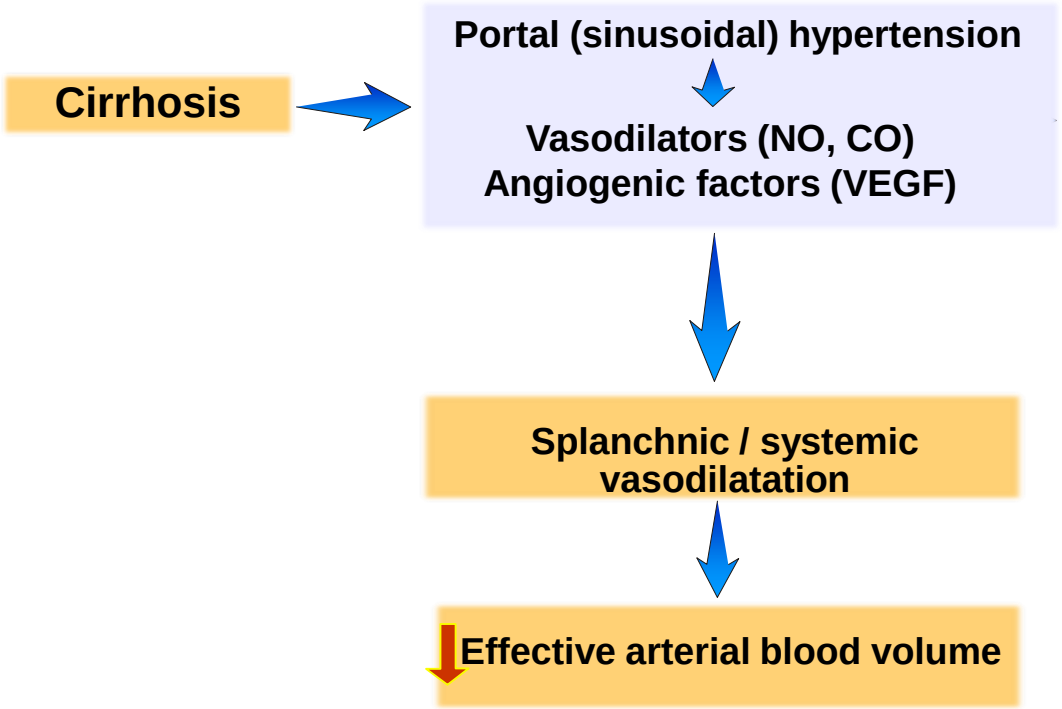


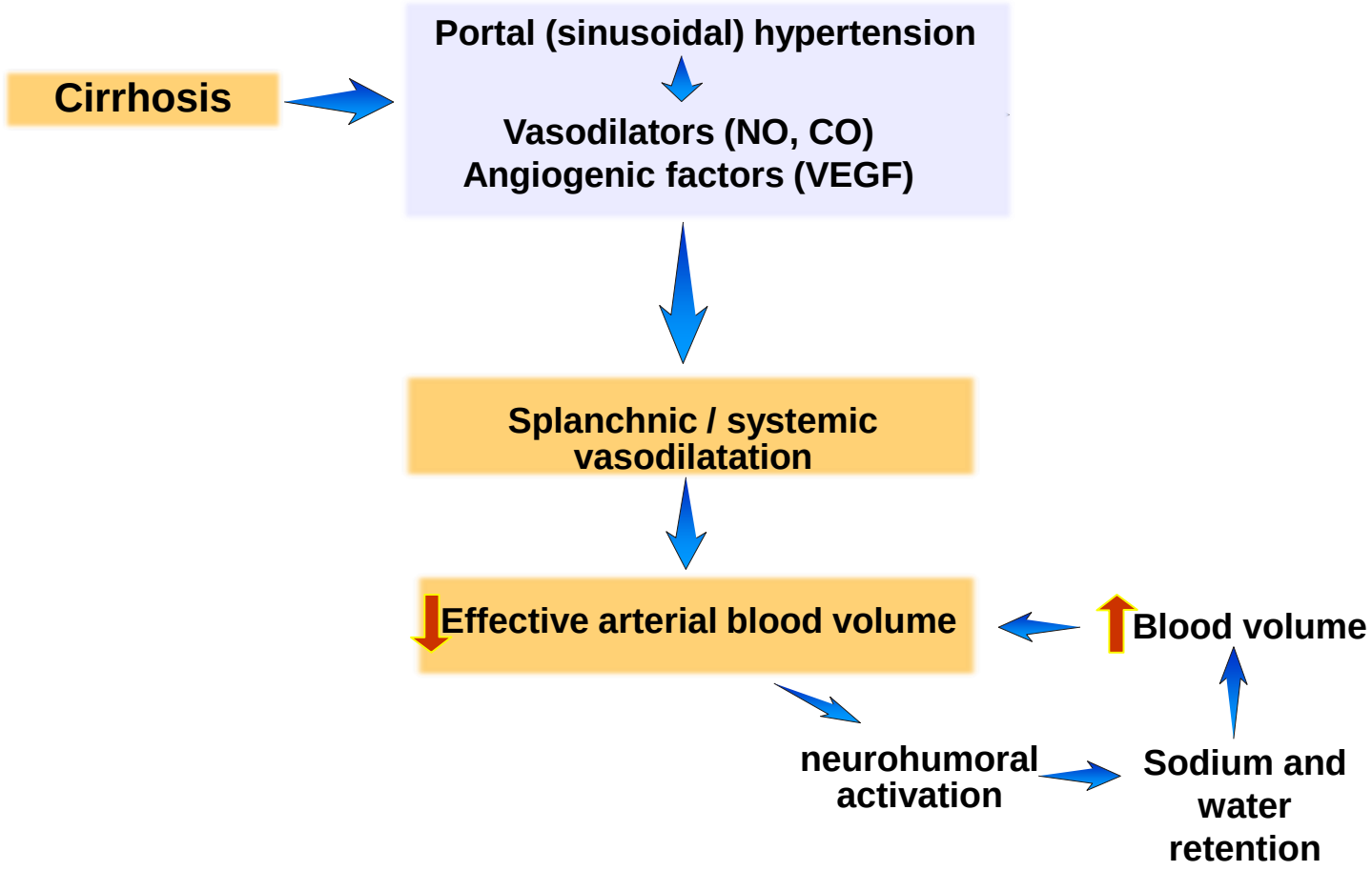
Fig. 2. Decay patterns of serum creatinine levels after improvement of renal function: solid lines, patients with 50 per cent of normal function; broken lines, patients with normal renal function.

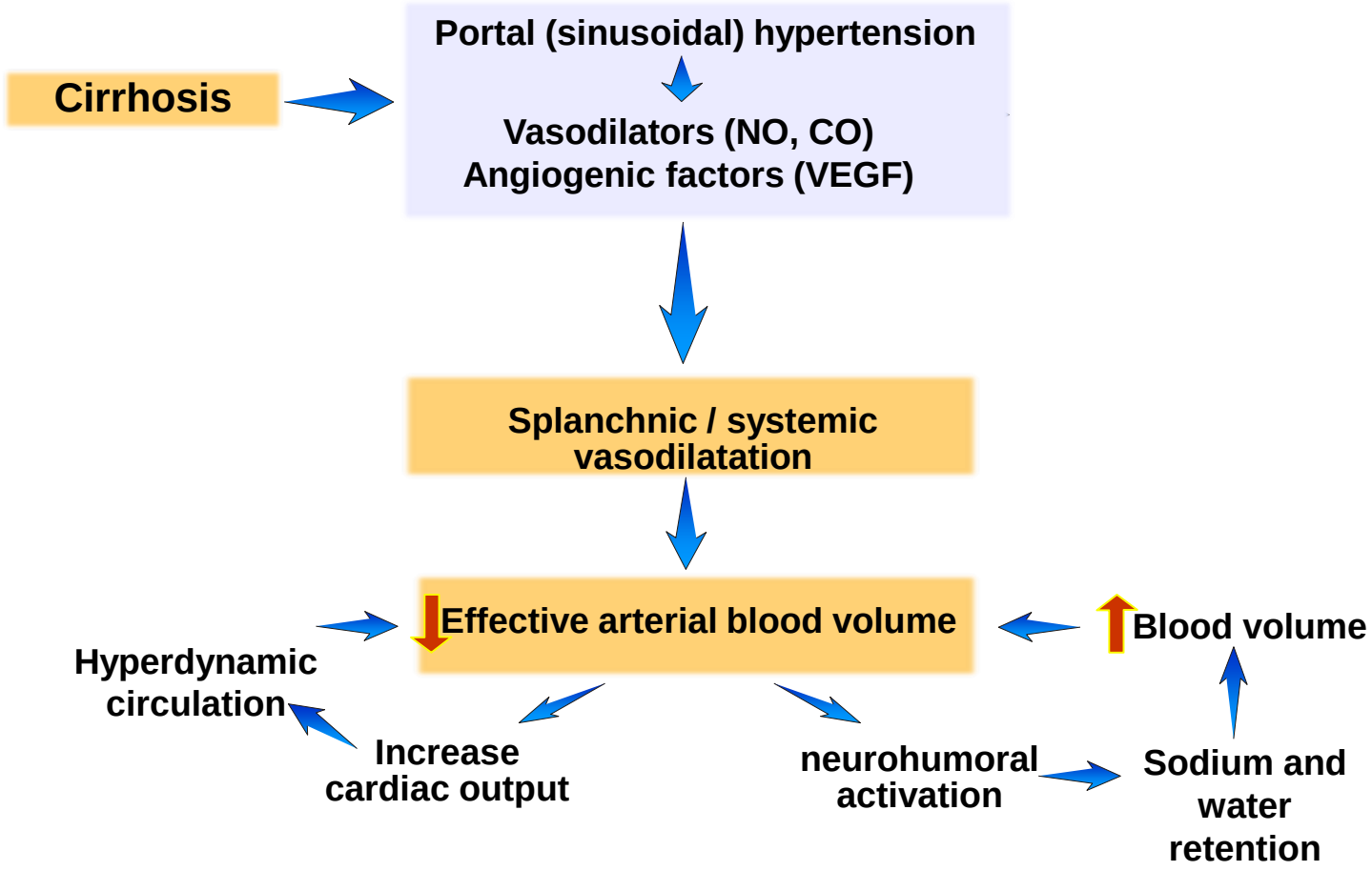
Chiou, W and Hsu, F J Clin Pharm 1975

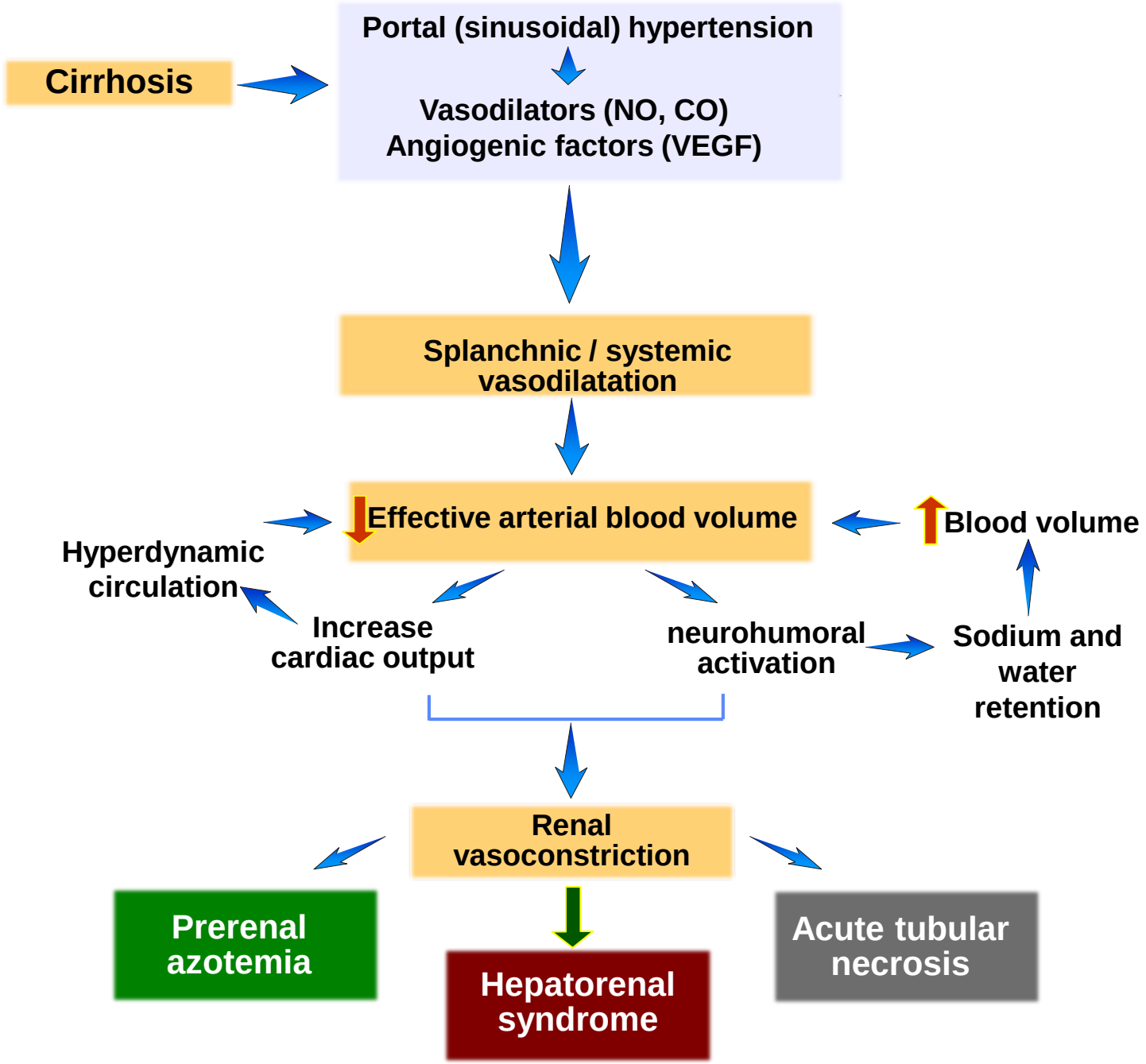

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)

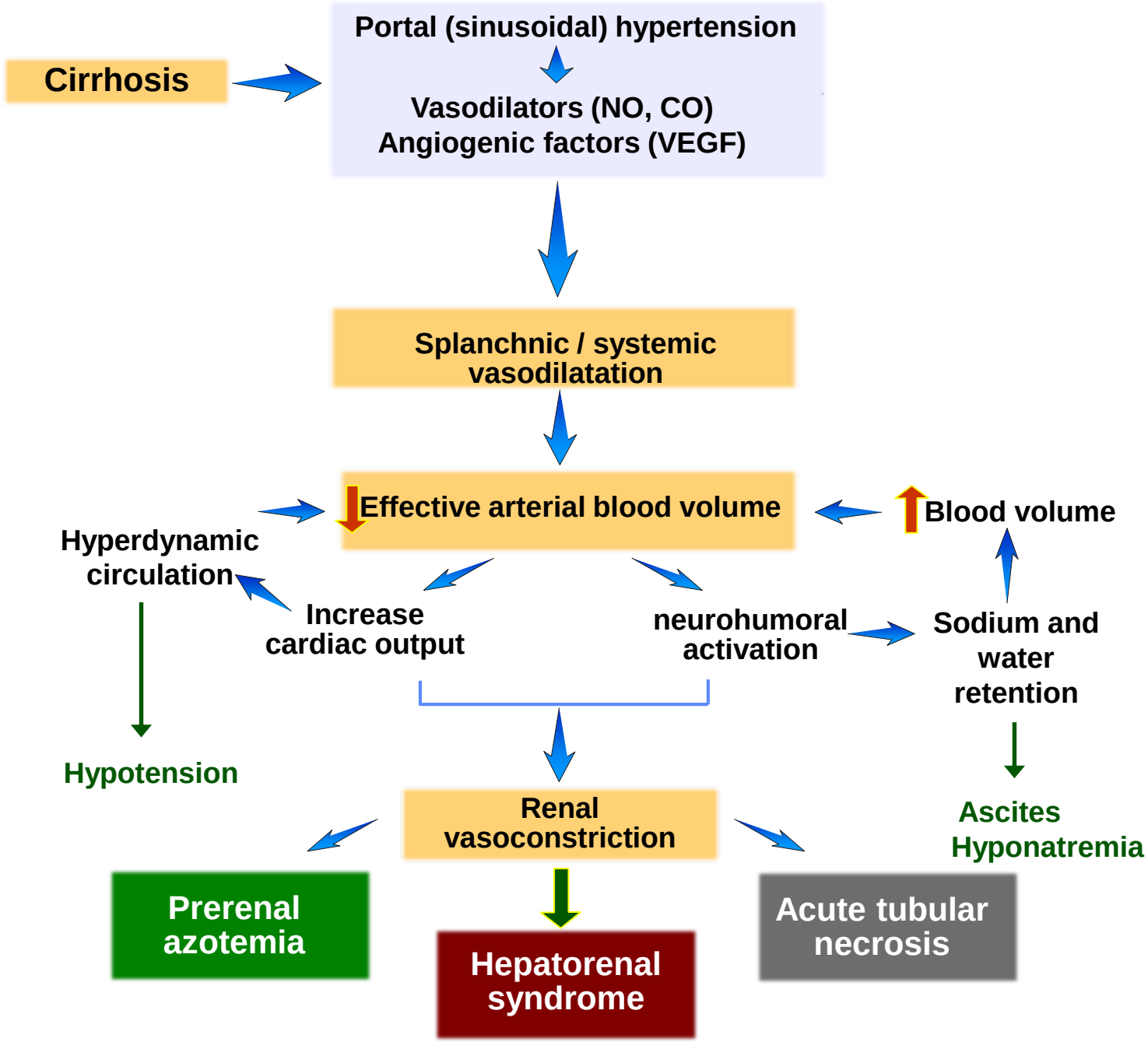

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation

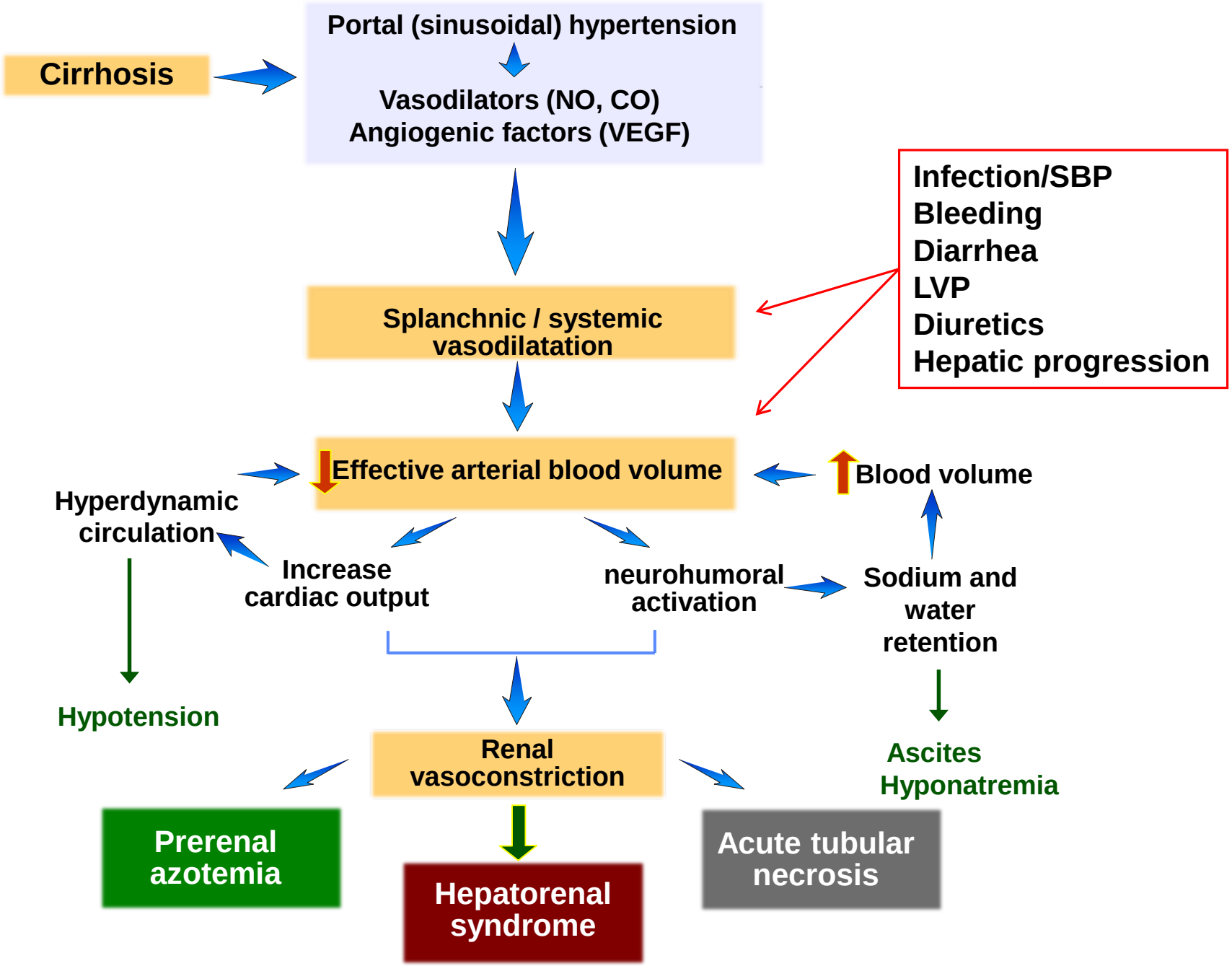

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Effective arterial blood volume

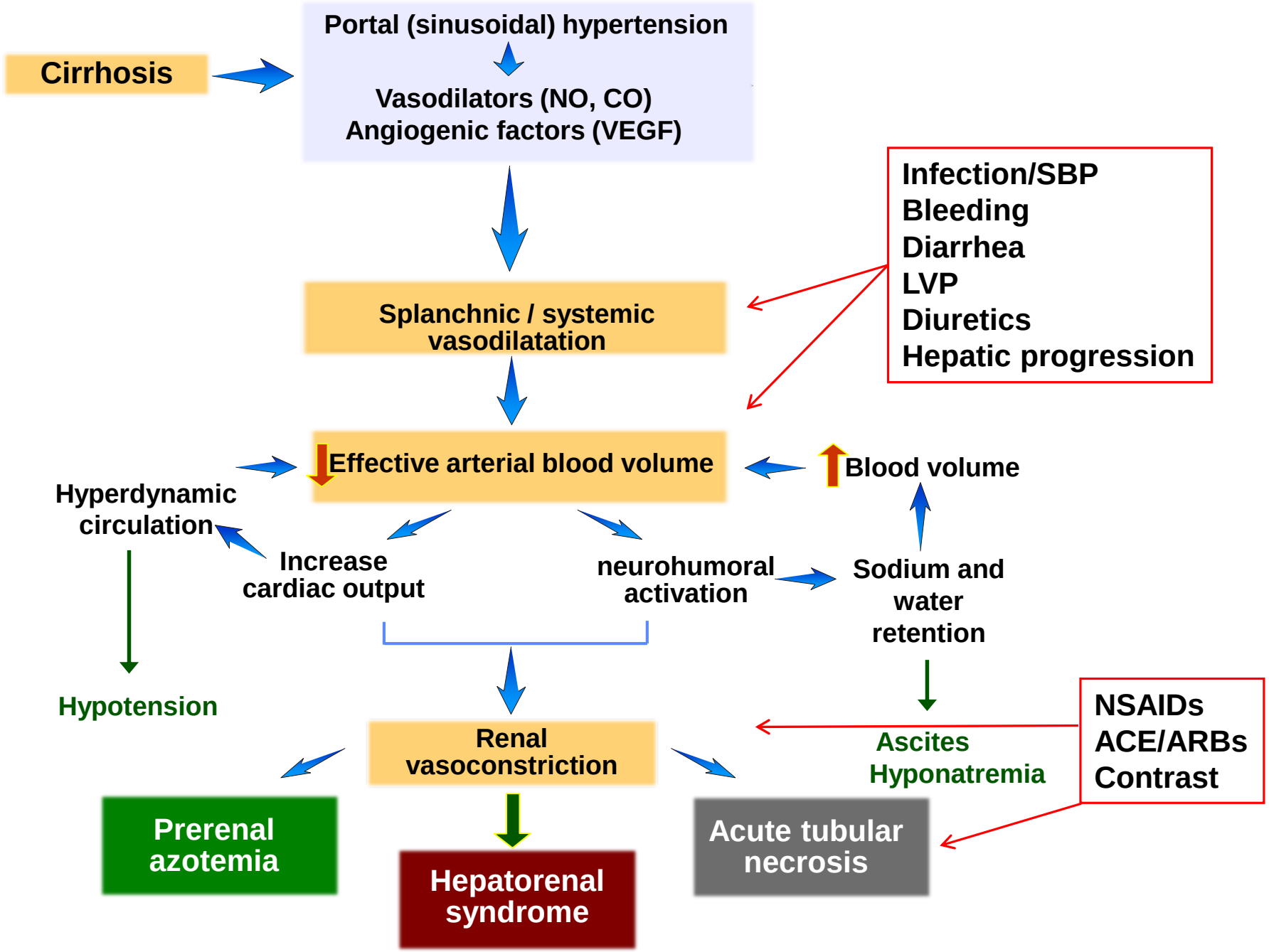

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Blood volume
neurohumoral activation
Sodium and water retention

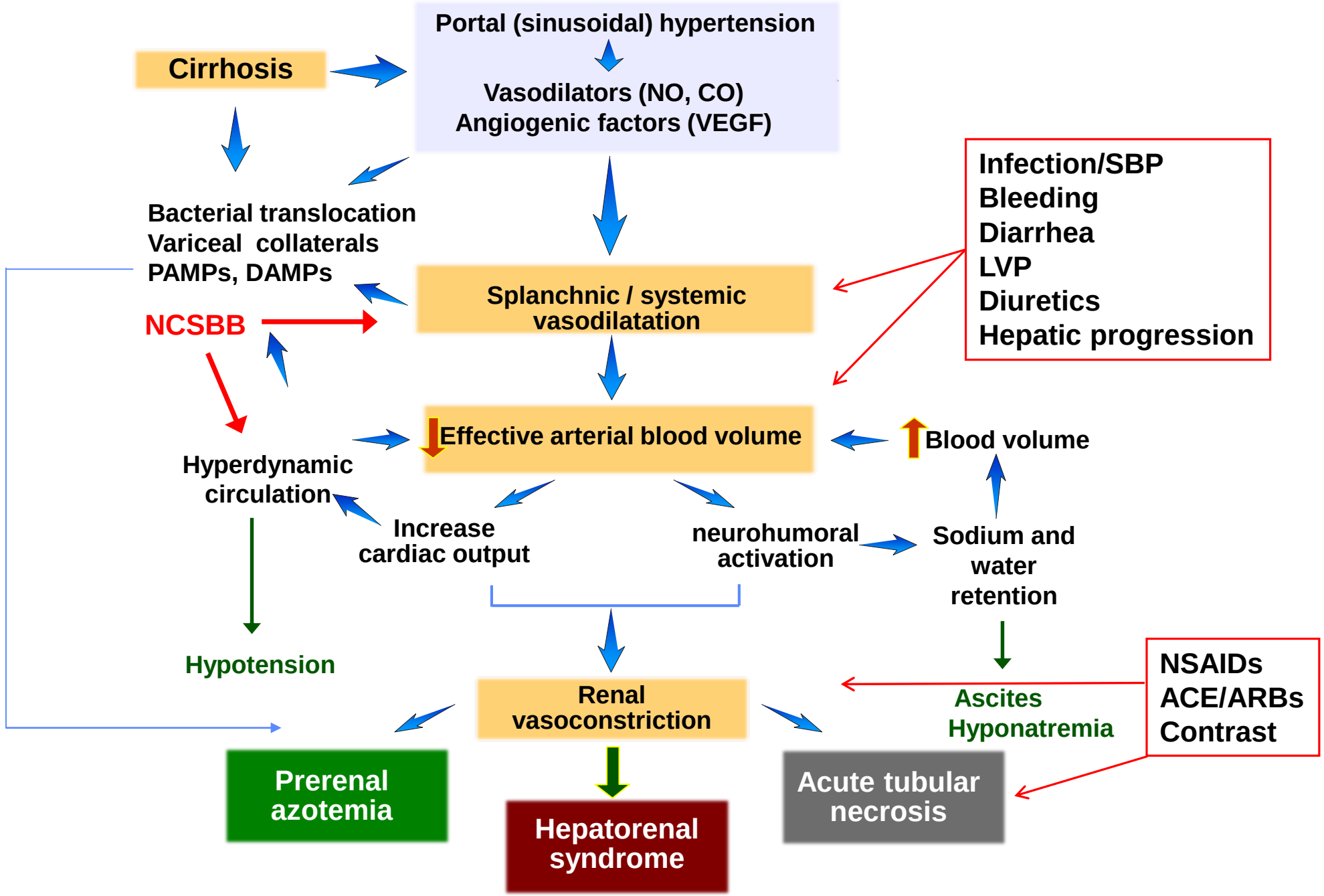

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Blood volume
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention

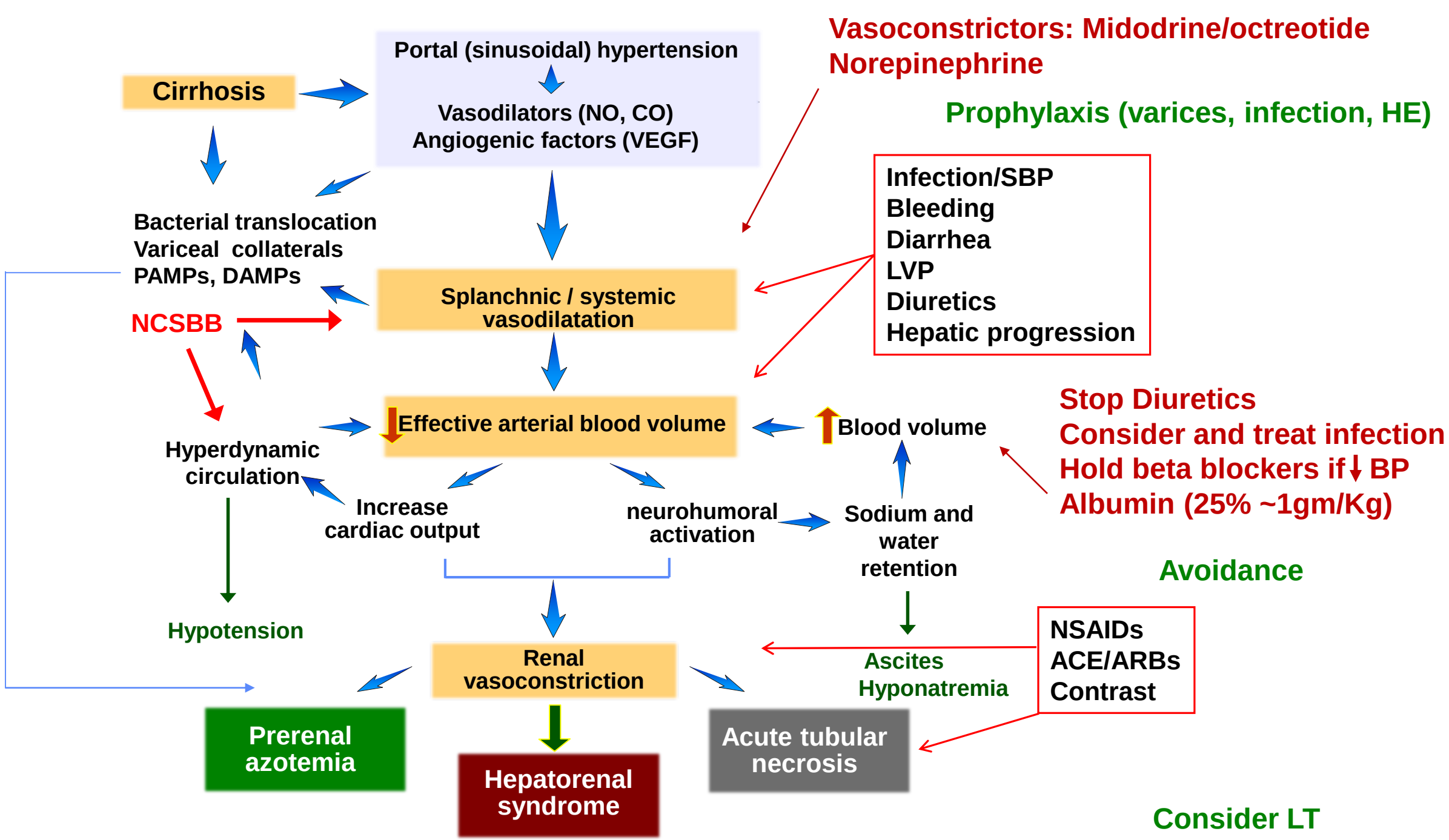

Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Hyperdynamic circulation
Blood volume
Increase cardiac output
neurohumoral activation
Sodium and water retention
Renal vasoconstriction
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis


Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Blood volume
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention
Hypotension
Renal vasoconstriction
Ascites
Hyponatremia
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis


Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Infection/SBP
Bleeding
Diarrhea
LVP
Diuretics
Hepatic progression
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Blood volume
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention
Hypotension
Renal vasoconstriction
Ascites
Hyponatremia
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis


Cirrhosis
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Splanchnic / systemic vasodilatation
Infection/SBP
Bleeding
Diarrhea
LVP
Diuretics
Hepatic progression
Effective arterial blood volume
Blood volume
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention
Hypotension
Renal vasoconstriction
Ascites
Hyponatremia
NSAIDs
ACE/ARBs
Contrast
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis


Portal (sinusoidal) hypertension
Cirrhosis
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Bacterial translocation
Variceal collaterals
PAMPs, DAMPs
Infection/SBP
Bleeding
Diarrhea
LVP
Diuretics
Hepatic progression
NCSBB
Splanchnic / systemic vasodilatation
Effective arterial blood volume
Blood volume
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention
Hypotension
Renal vasoconstriction
Ascites
Hyponatremia
NSAIDs
ACE/ARBs
Contrast
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis


Vasoconstrictors: Midodrine/octreotide
Norepinephrine
Prophylaxis (varices, infection, HE)
Portal (sinusoidal) hypertension
Vasodilators (NO, CO)
Angiogenic factors (VEGF)
Cirrhosis
Bacterial translocation
Variceal collaterals
PAMPs, DAMPs
NCSBB
Splanchnic / systemic vasodilatation
Infection/SBP
Bleeding
Diarrhea
LVP
Diuretics
Hepatic progression
Effective arterial blood volume
Blood volume
Stop Diuretics
Consider and treat infection
Hold beta blockers if ↓ BP
Albumin (25% ~1gm/Kg)
Hyperdynamic circulation
Increase cardiac output
neurohumoral activation
Sodium and water retention
Avoidance
Hypotension
Renal vasoconstriction
Ascites
Hyponatremia
NSAIDs
ACE/ARBs
Contrast
Prerenal azotemia
Hepatorenal syndrome
Acute tubular necrosis
Consider LT

Vasoconstrictor Therapy

Complete response rate (Cr<1.5gm/dl)

Midodrine, octreotide and albumin

7.5mg-12.5 PO TID
100ug SQ Octreotide or IV 25ug/hr
albumin 20 – 50gm daily
MAP 15mm Hg or >90mmHg*

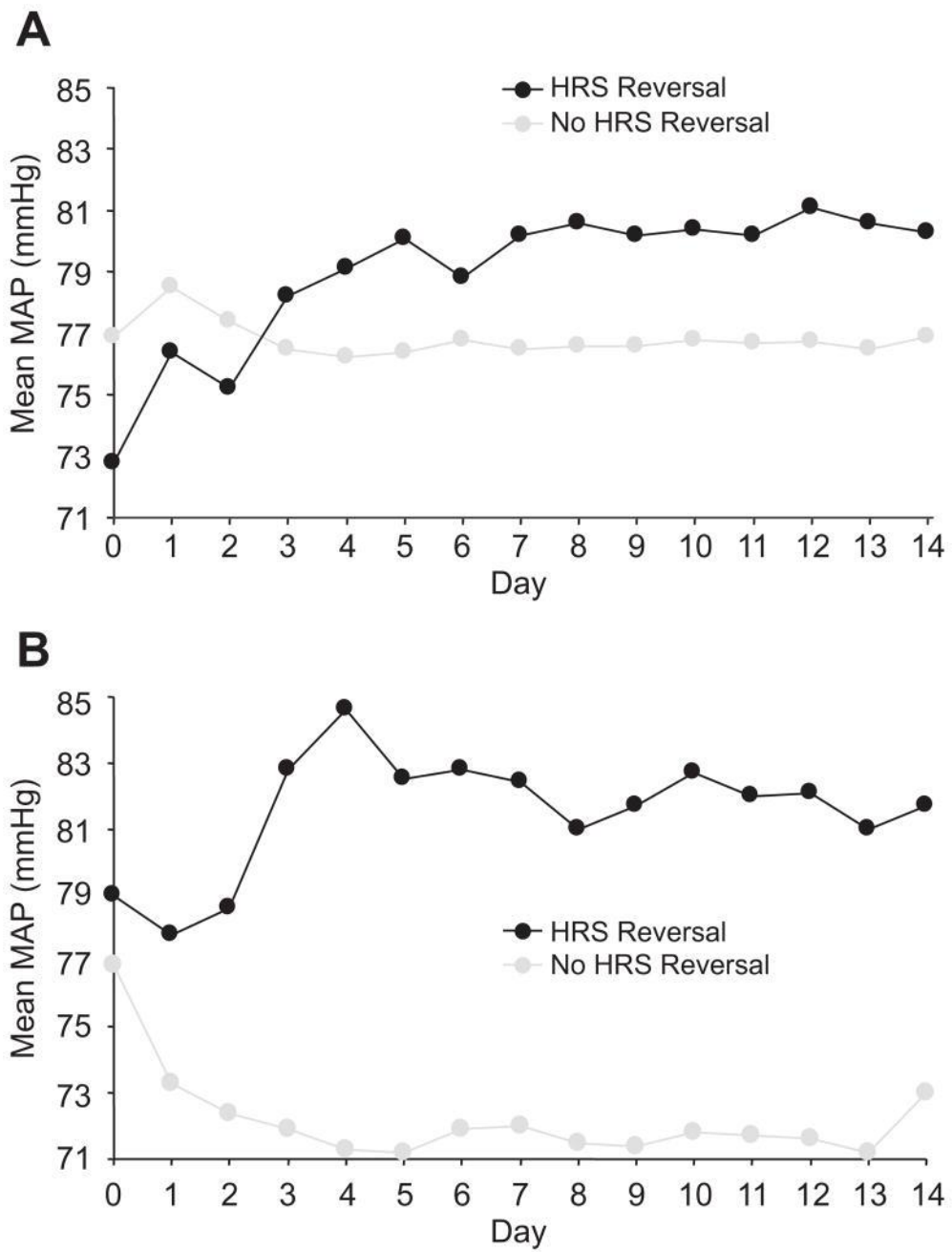
5-20%

Norepinephrine and albumin

0.5 -3.0 mg/hr infusion ICU
albumin 20 – 50gm daily
MAP 10mm Hg or increase in urine output

25-40%

Mattos et al. Ann Hepatol 2019
Practice Guidelines EASL J Hepatol. 2018



Boyer et al. J Hepatol 2011

Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome
Wong et al. NEJM 2021

Most ETOH disease

Mean cr >3 (late)

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
Secondary end points included in multiplicity adjustment			
HRS reversal§			<0.001
Clinical success	78/199 (39)	18/101 (18)	
Clinical failure	105/199 (53)	79/101 (78)	
Competing event‡			
Liver transplantation	11/199 (6)	4/101 (4)	
Death	5/199 (3)	0/101	
HRS reversal with no renal-replacement therapy through 30 days			0.001
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
Competing event‡			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	
HRS reversal in patients with systemic inflammatory response syndrome			<0.001
Clinical success	31/84 (37)	3/48 (6)	
Clinical failure	45/84 (54)	43/48 (90)	
Competing event‡			
Liver transplantation	4/84 (5)	1/48 (2)	
Death	5/84 (6)	0/48	
Verified reversal of HRS with no recurrence through 30 days			0.08
Clinical success	52/199 (26)	17/101 (17)	
Clinical failure	131/199 (66)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	

- **Increased respiratory failure (edema)**
- **No improvement in survival**
- **Not approved by FDA**
- **Lung has V2 receptors which may dilate arteries and constrict veins**
- **Norepinephrine constricts arteries and has mild inotropic effects and could be better**

Table 4. Adverse Events in the Safety Population.*

Event	Terlipressin (N=200)	Placebo (N=99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	8 (4)	6 (6)
Atrial fibrillation	1 (<1)	3 (3)
Gastrointestinal disorders	30 (15)	6 (6)
Abdominal pain	10 (5)	1 (1)
Gastrointestinal hemorrhage	8 (4)	0
General disorders and administration-site conditions	11 (6)	6 (6)
Multiple organ dysfunction syndrome	9 (4)	3 (3)
Hepatobiliary disorders	37 (18)	29 (29)
Chronic hepatic failure	9 (4)	8 (8)
Alcoholic cirrhosis	4 (2)	3 (3)
Hepatic cirrhosis	6 (3)	2 (2)
Hepatic failure	9 (4)	10 (10)
Worsening of HRS	3 (2)	3 (3)
Infections and infestations	19 (10)	5 (5)
Pneumonia	4 (2)	3 (3)
Sepsis	9 (4)	0
Nervous system disorders	13 (6)	3 (3)
Hepatic encephalopathy	9 (4)	3 (3)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)
Vascular disorders	10 (5)	4 (4)
Shock	5 (2)	3 (3)

A randomized trial of albumin infusions in hospitalized patients with cirrhosis

China et al. NEJM 2021

Most ETOH disease

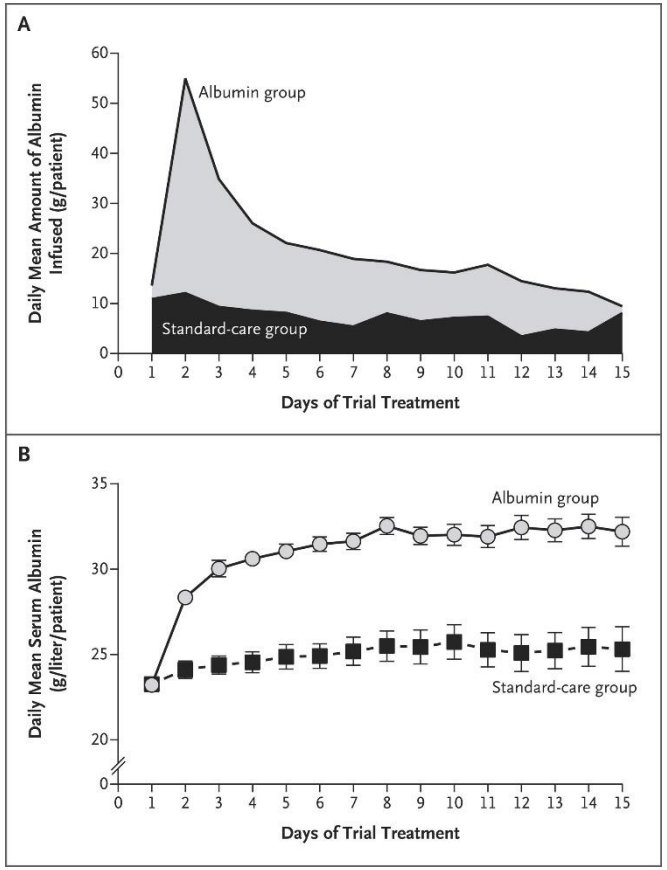


Table 2. End Points.*

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)†	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)‡				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158)§	

* Unless stated, the time of the end point is during the trial treatment period (15 days after randomization).
† Odds ratios are adjusted for stratification variables, with sites as random intercept terms.
‡ The end points are defined in the original trial protocol.[26]
§ This is the adjusted mean difference between the groups.

- **Increased pulmonary edema in albumin group (10-fold greater amount)**
- **No improvement in survival**

AKI: Summary

- Occurs in 20% of cirrhotic patients
- Multiple overlapping causes and contributors
- Early medical therapy critical for reversal
- Significant contributor to mortality

57yo: Compensated HCV cirrhosis (SVR)
3 weeks abdominal distention, “slowness”

Heart murmur
Knee osteoarthritis (NSAIDs)

Exam: BP 98/70
systolic murmur, Clear lungs
Non-focal neuro exam, asterixis
Ascites

Labs: MELD 13
BUN/Cr 19/0.9
INR 1.3

What is next step for slowness?

A) **Non-contrast head CT**
B) **Ammonia level**
C) **Evaluate precipitating factors**
D) **Protein restricted diet**
E) **Neurology consult**

57yo: Compensated HCV cirrhosis (SVR)
3 weeks abdominal distention, “slowness”

Heart murmur
Knee osteoarthritis (NSAIDs)

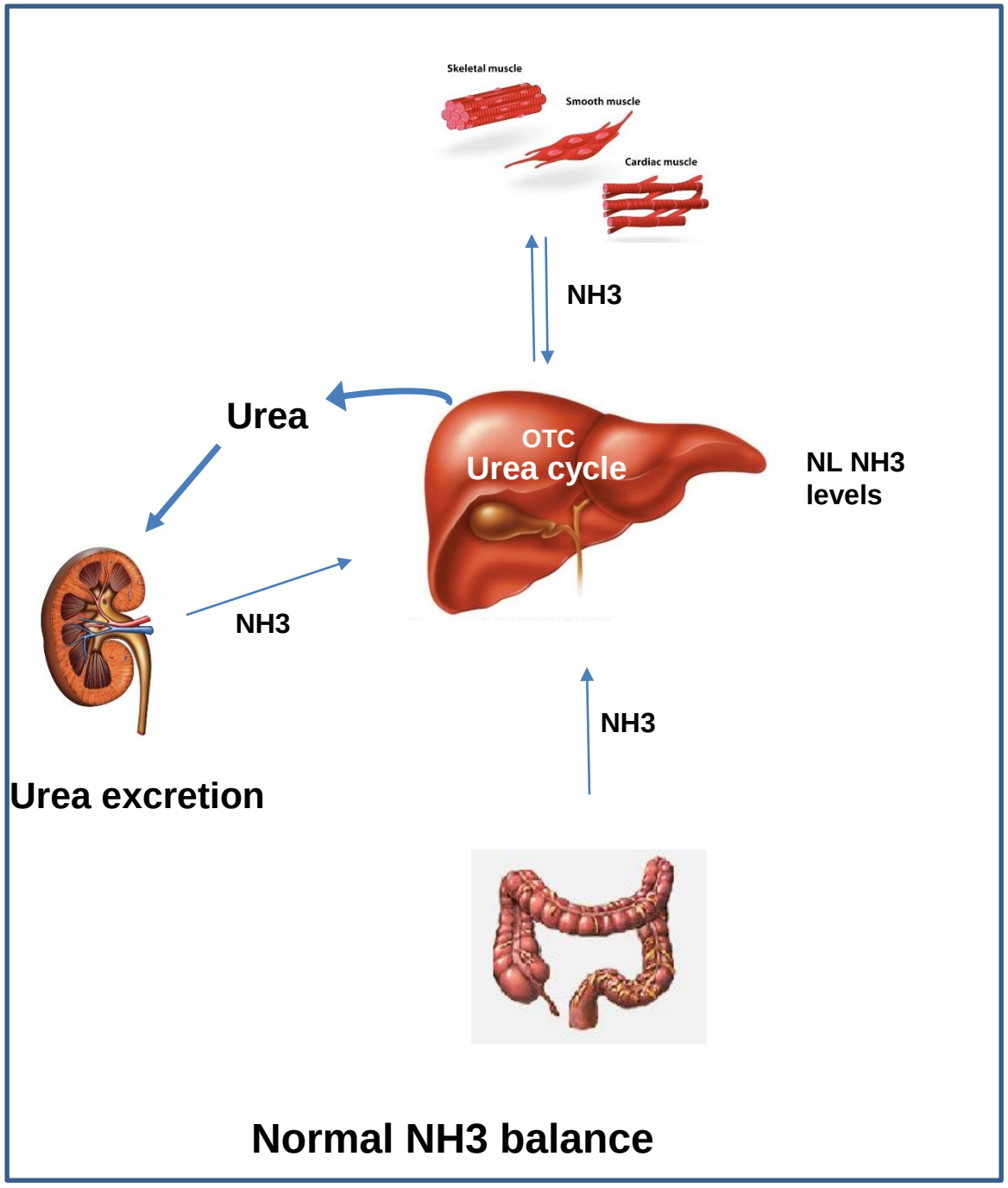
Exam: BP 98/70
systolic murmur, Clear lungs
Non-focal neuro exam, asterixis
Ascites

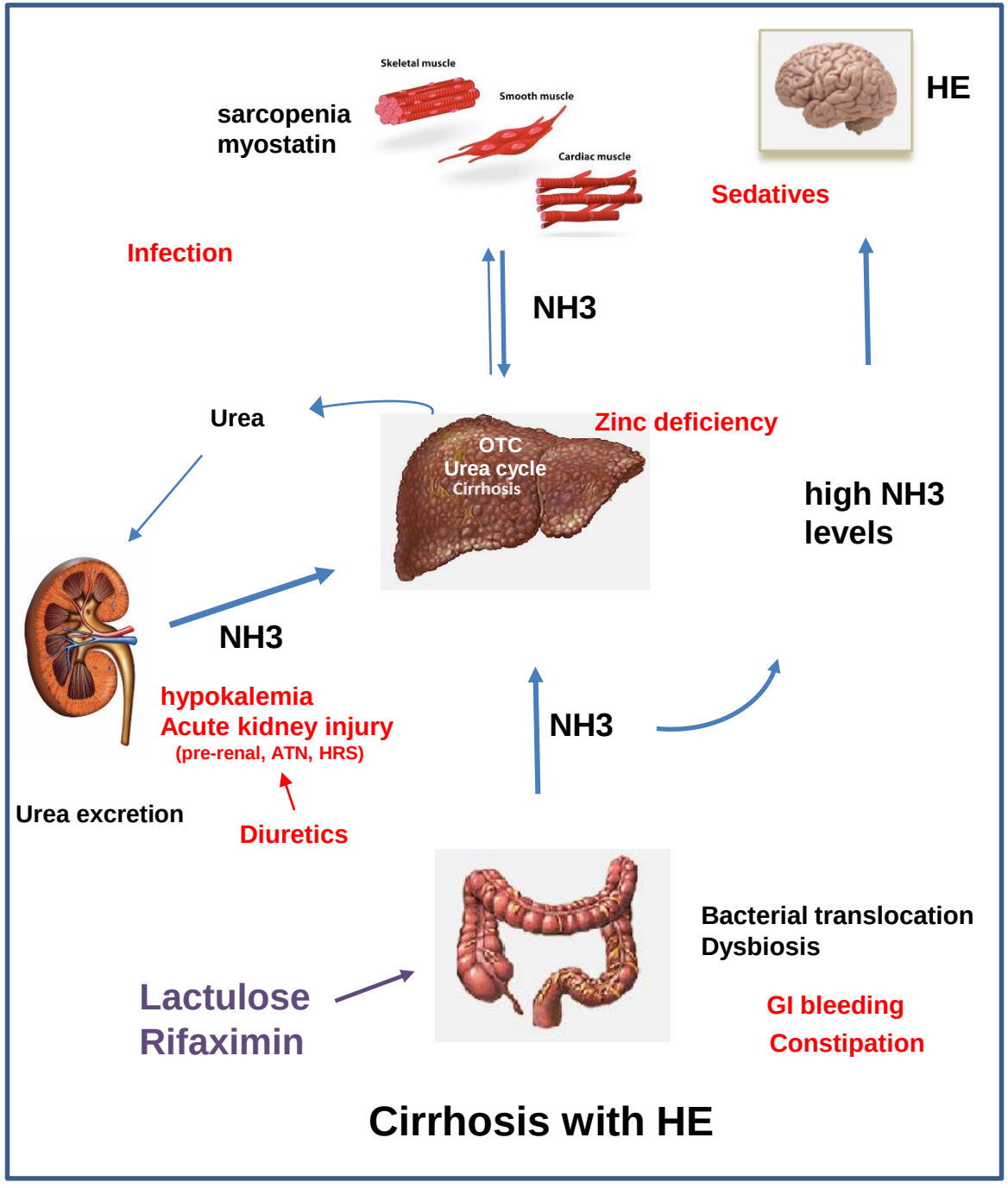
Labs: MELD 13
BUN/Cr 19/0.9
INR 1.3

What is next step for slowness?

A) Non-contrast head CT
B) Ammonia level
C) Evaluate precipitating factors
D) Protein restricted diet
E) Neurology consult

Hepatic encephalopathy

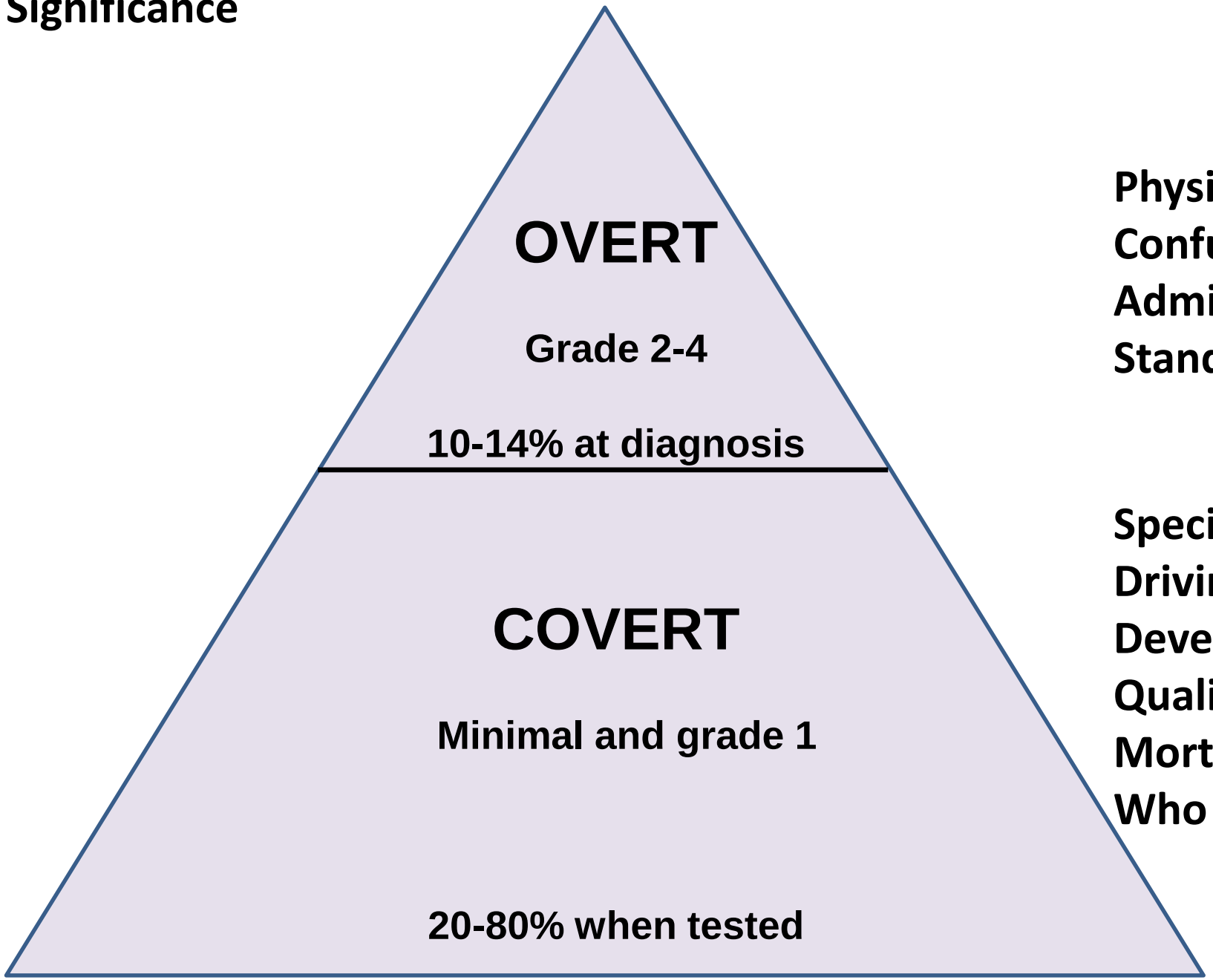

Skeletal muscle
Smooth muscle
Cardiac muscle
NH3
Urea
OTC
Urea cycle
NL NH3
levels
NH3
NH3
Urea excretion
Normal NH3 balance


Skeletal muscle
Smooth muscle
Cardiac muscle
sarcopenia
myostatin
HE
Sedatives
Infection
NH3
Urea
Zinc deficiency
OTC
Urea cycle
Cirrhosis
high NH3
levels
NH3
hypokalemia
Acute kidney injury
(pre-renal, ATN, HRS)
NH3
Urea excretion
Diuretics
Bacterial translocation
Dysbiosis
Lactulose
Rifaximin
GI bleeding
Constipation
Cirrhosis with HE

Minimal/Covert Hepatic Encephalopathy (~15 years)

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				

Clinical Significance



Physical Exam
Confusion
Admission
Standard treatments

Specialized tests
Driving
Development of overt
Quality of life
Mortality
Who to test and treat?

HE: Diagnosis

- Clinical

- Neurocognitive tests for covert
- (PHES, STROOP others)

- 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

HE

Diagnosis:

Alternate causes and contributors (infection, bleeding, medications)
? Head CT imaging
UDS

Treatment:

Probiotics
Lactulose 10grams/15mls (titrate to 2-3 BMS qd) route?
Rifaxamin 550mg PO BID
Zinc, neomycin, polyethylene glycol, BCAAs
No protein restriction

HE: Summary

- Ammonia plays a central role but levels hard to use
- Evaluate and treat precipitating factors
- Current therapies target the gut
- The spectrum of clinical findings now includes minimal HE

Questions?

65 yo female PBC (cirrhosis) slowly progressive shortness of breath
15 pack year smoker, stopped 5 years ago

Exam: BMI 25, dullness right lung base, digital clubbing

CXR: small right pleural effusion

PFTs: mild restrictive disease

ABG: pH 7.46 PCO2 34 PaO2 66

Cardiac Echo: LVEF 62%
RVSP 37 mmHg
Shunt: Delayed (left side after 3 cardiac cycles)

QUESTIONS

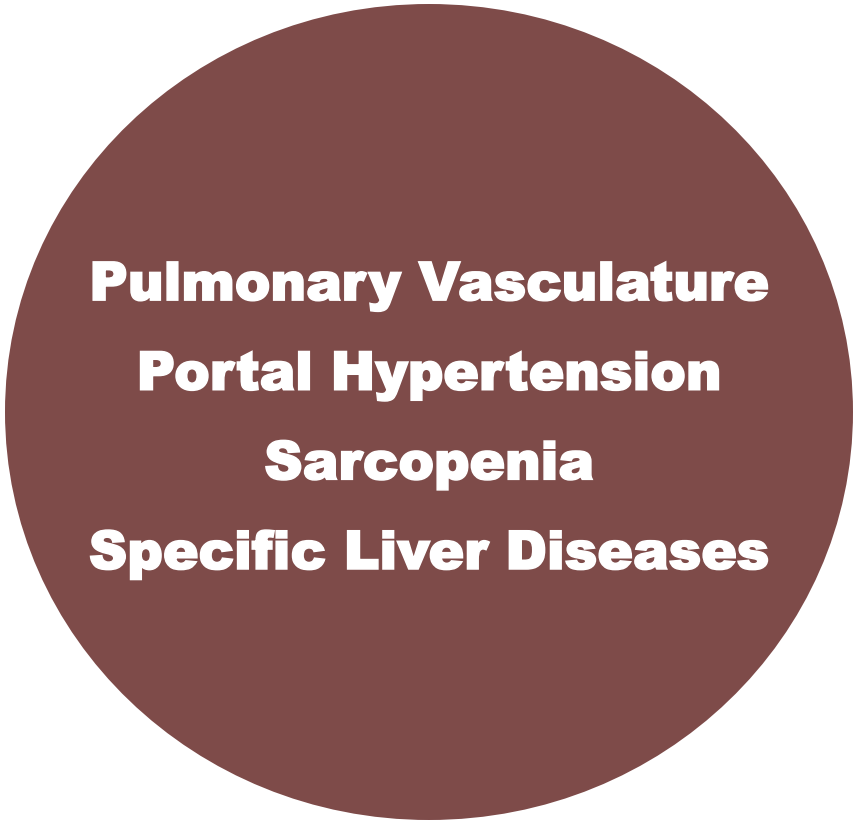
What are the causes of Hypoxemia in cirrhosis?

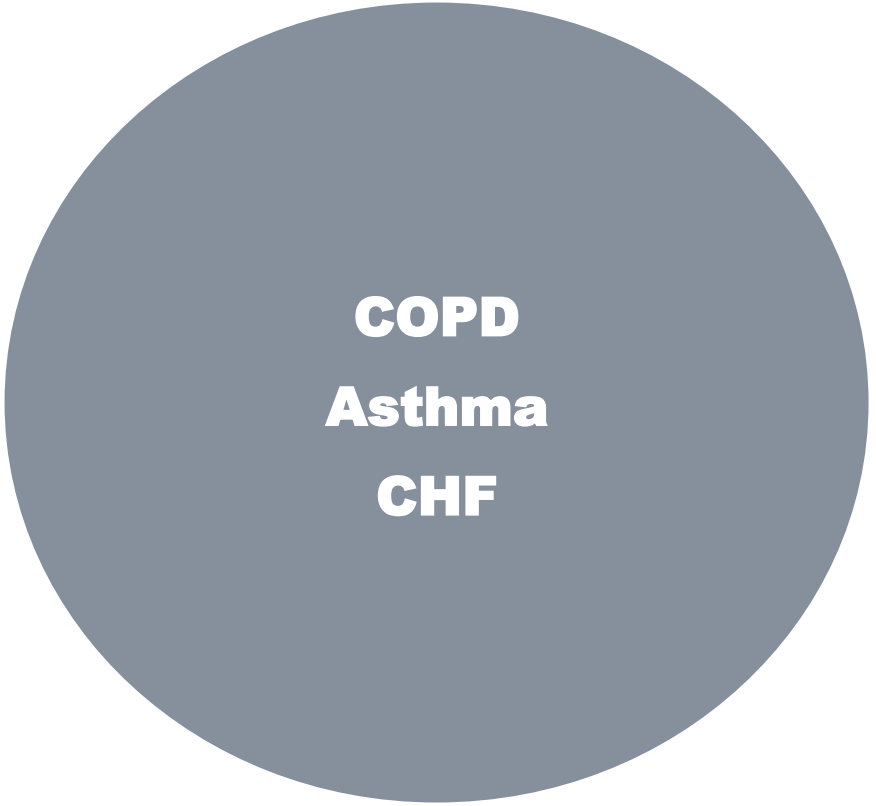
How do we evaluate them?

What can be done about them?

DYSPNEA AND HYPOXEMIA IN CIRRHOSIS

RELATED TO CHRONIC LIVER DISEASE





INTRINSIC LUNG DISEASE

Pulmonary vascular disorders	**20-30%**
COPD or restrictive disease	**20%**
Ascites, hepatic hydrothorax	**5%**
Congestive heart failure	**5%**
Specific liver diseases	**3%**
Deconditioning	**2%**
Asthma	**1%**

***Fallon et al*, Gastro 2008;135:1168-1175**
***DuBrock et al,* Liver Transpl 2020 submitted**

65 yo female PBC (cirrhosis) slowly progressive shortness of breath
15 pack year smoker, stopped 5 years ago

Exam: BMI 25, dullness right lung base, digital clubbing

CXR: small right pleural effusion

PFTs: mild restrictive disease

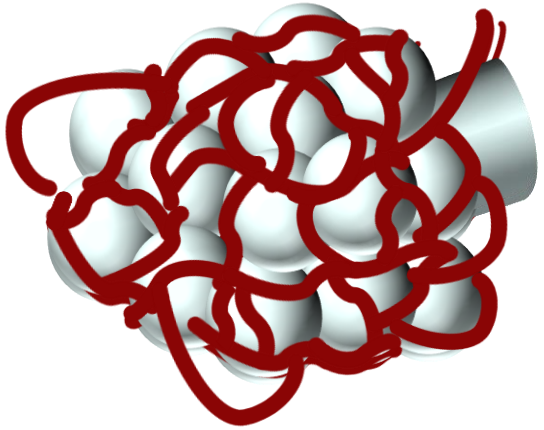
ABG: pH 7.46 PCO2 34 PaO2 66

Cardiac Echo: LVEF 62%
RVSP 37 mmHg
Shunt: Delayed (left side after 3 cardiac cycles)

Cirrhosis
Hepatic injury
Portal hypertension

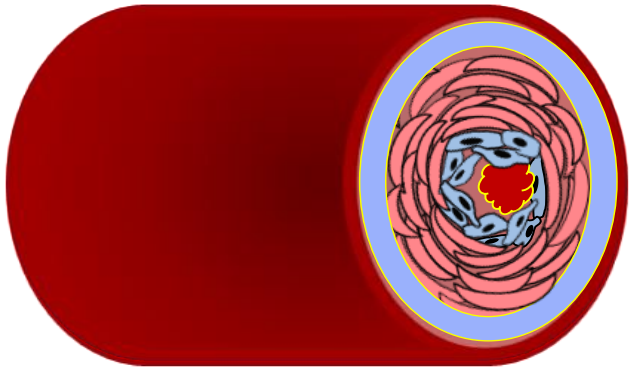
LUNG

HPS



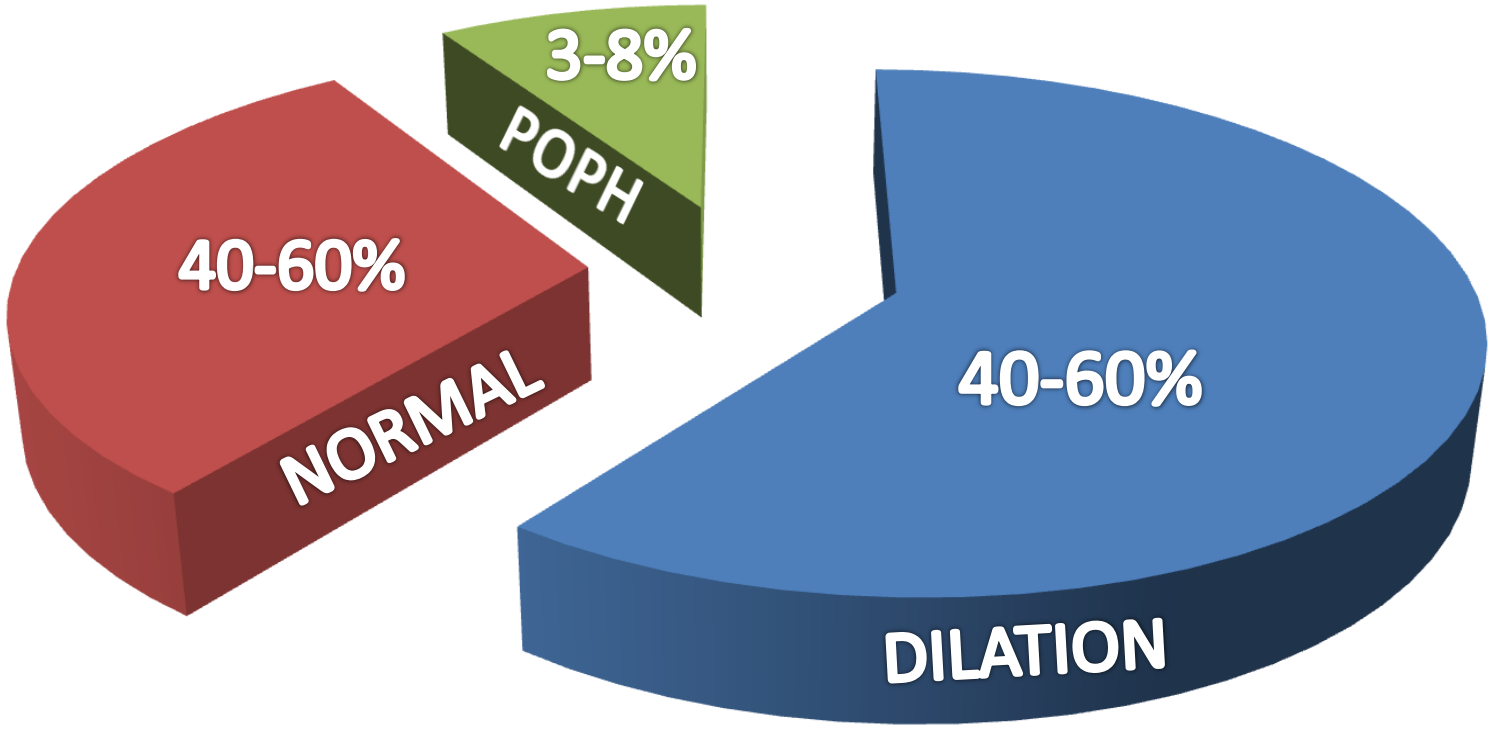
Vasodilatation and
Angiogenesis
in microvasculature

POPH

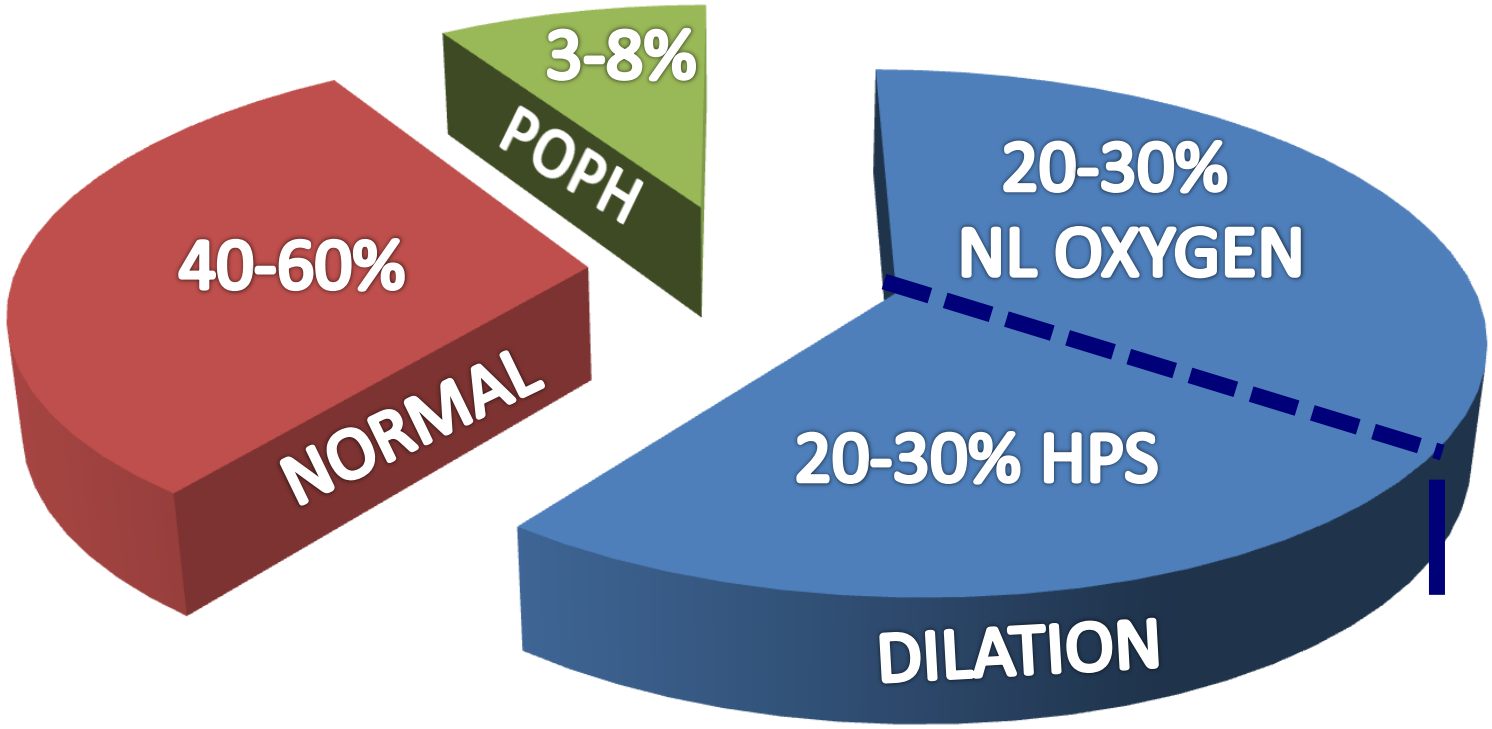


Vasoconstriction and
remodeling in resistance
vessels

PULMONARY VASCULATURE IN CIRRHOSIS



PULMONARY VASCULATURE IN CIRRHOSIS



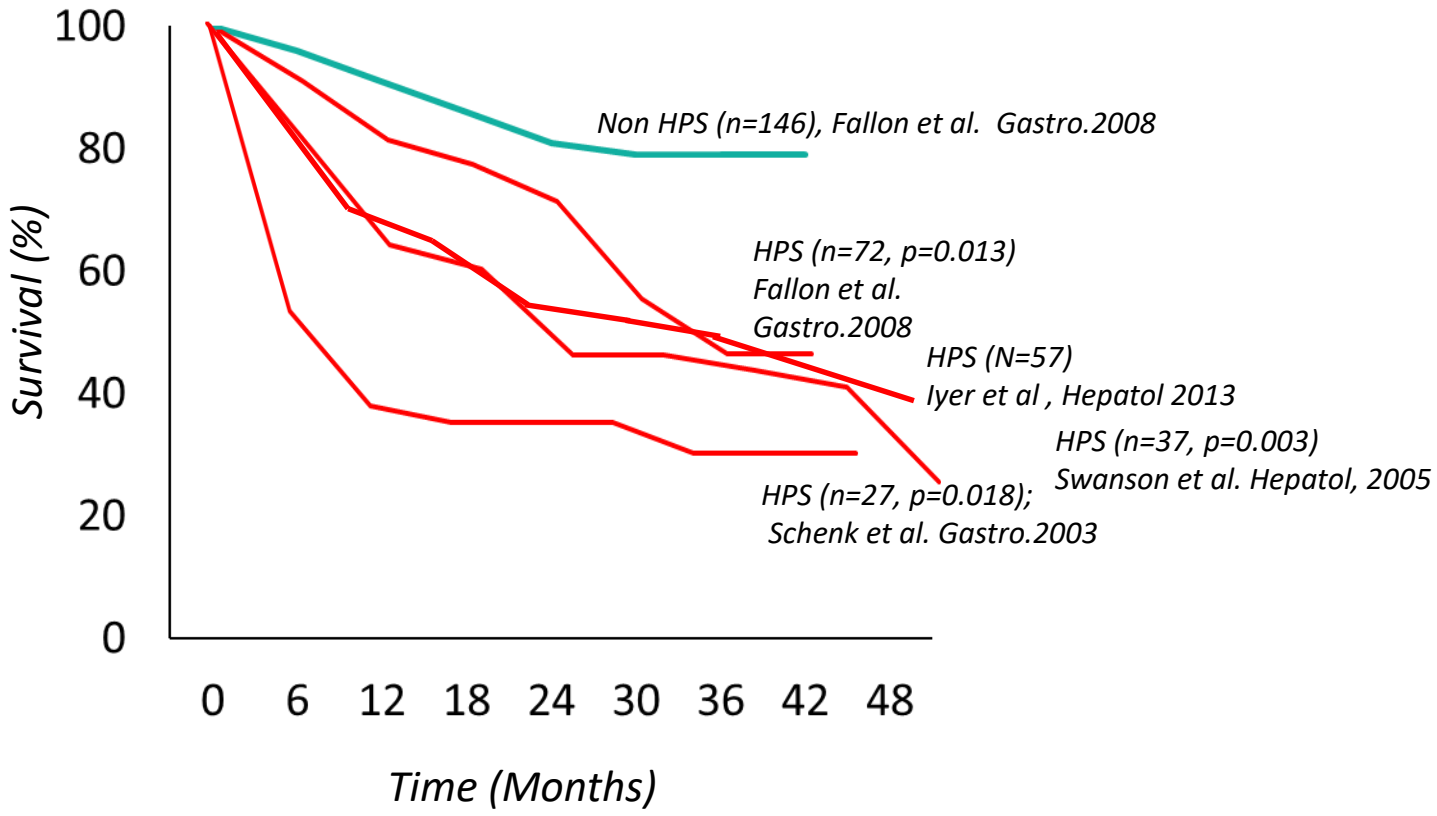
HEPATOPULMONARY SYNDROME (HPS)

HPS: DEFINITION

- **Cirrhosis and/or portal hypertension**
- **Arterial pO_2 < 70mmHg or A-aPO_2 > 15 mmHg**
- **Intrapulmonary vasodilatation**
- **No marked cardiopulmonary pathology**

Rodriguez-Roisin, Thorax 1992, Eur Respir J 2004

HPS: SURVIVAL



HPS: Clinical Features

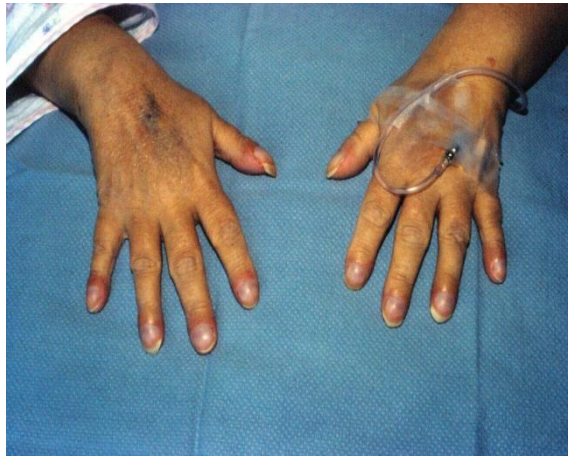
History: - Cirrhosis, dyspnea,

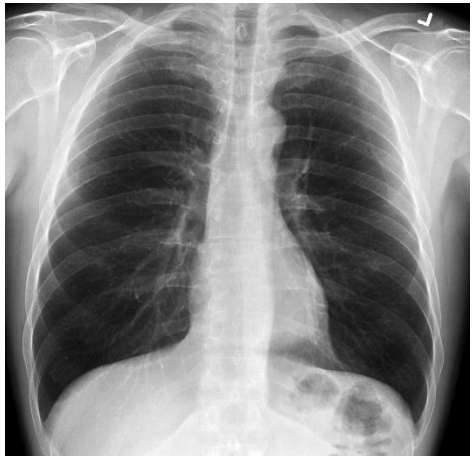
platypnea (dyspnea improved when recumbent)

Exam: - Low pulse oximetry, clubbing

Tests: - Normal chest X-ray

- Normal pulmonary function tests

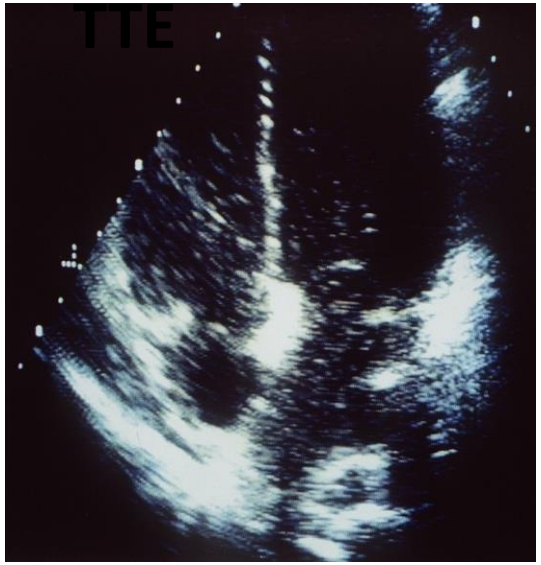




HPS= Hepatopulmonary syndrome

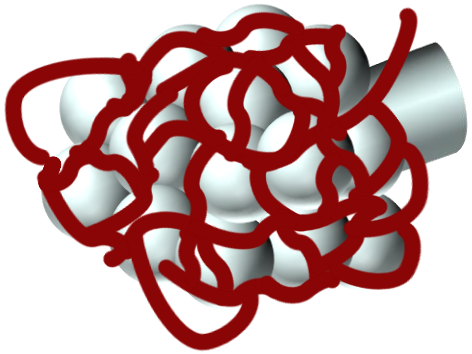
- Portal Hypertension
- Cirrhosis
- Portosystemic shunting

Contrast



Sensitive
Specific
Other cardiac data

40-60%

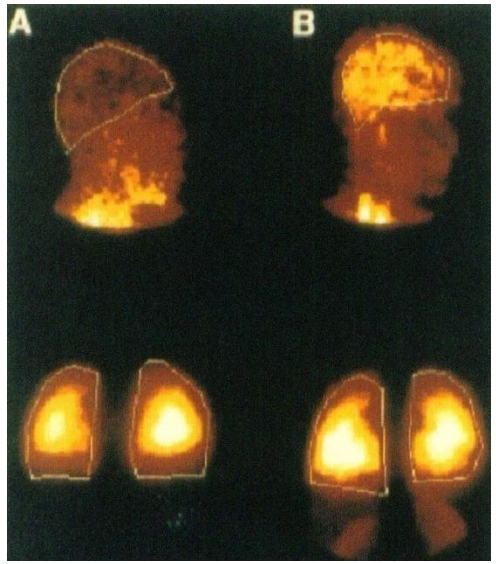


50%

Abnormal ABGs

HPS

MAA scan



Quantitative
Standardization

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

HPS: Diagnosis

Presence of intrapulmonary shunt

Bubble contrast transthoracic echocardiography	– Delayed shunting of bubbles from right to left (after 3rd cardiac cycle)

Abnormal oxygenation

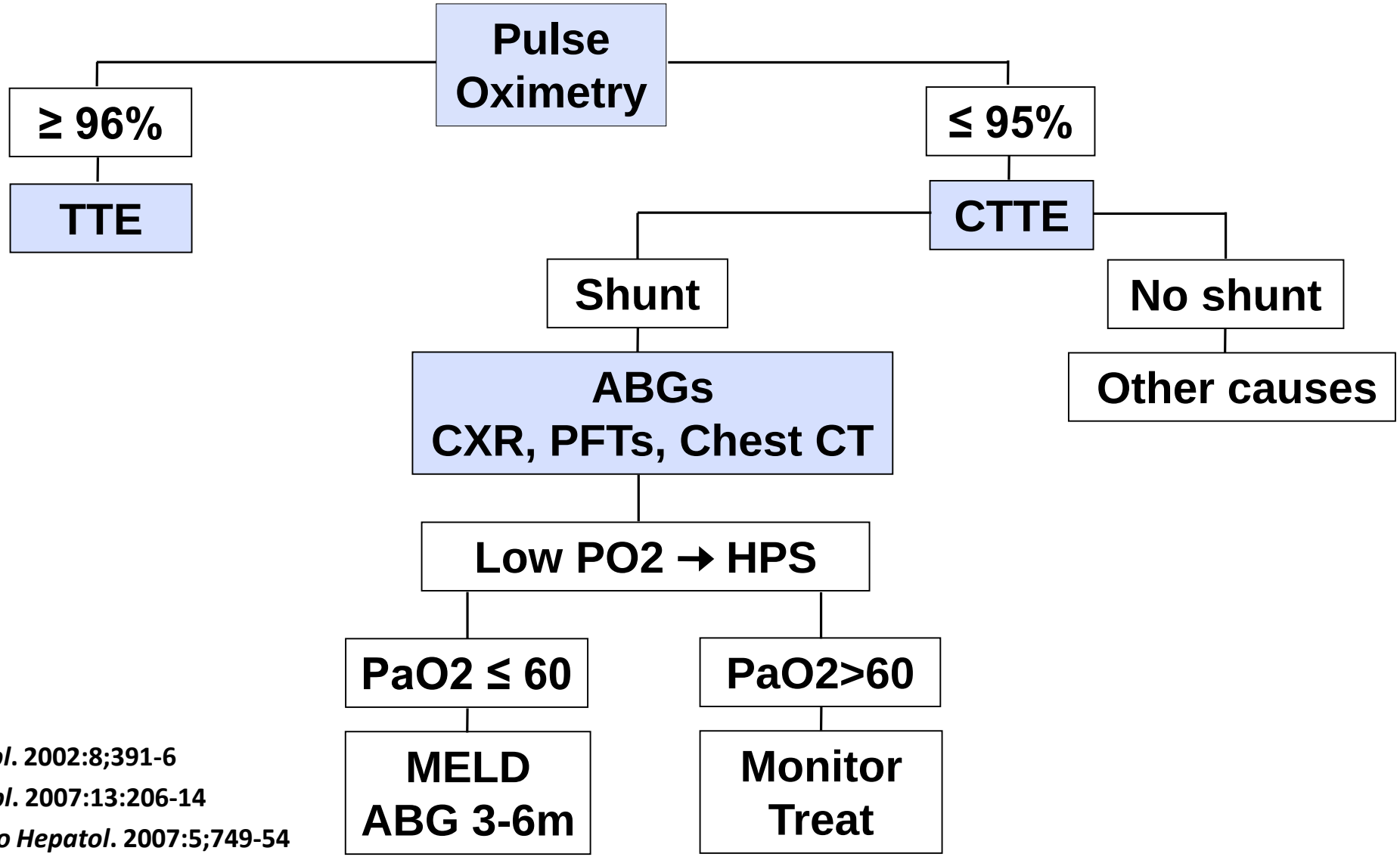
Arterial Blood Gas	– PaO2 <70mmHg or (A-a) gradient >15

No intrinsic lung disease

Pulmonary Function Tests	– Normal
Chest Radiography	– Normal

Rodriguez-Roisin, *Thorax* 1992, *Eur Respir J* 2004.

HPS: Screening



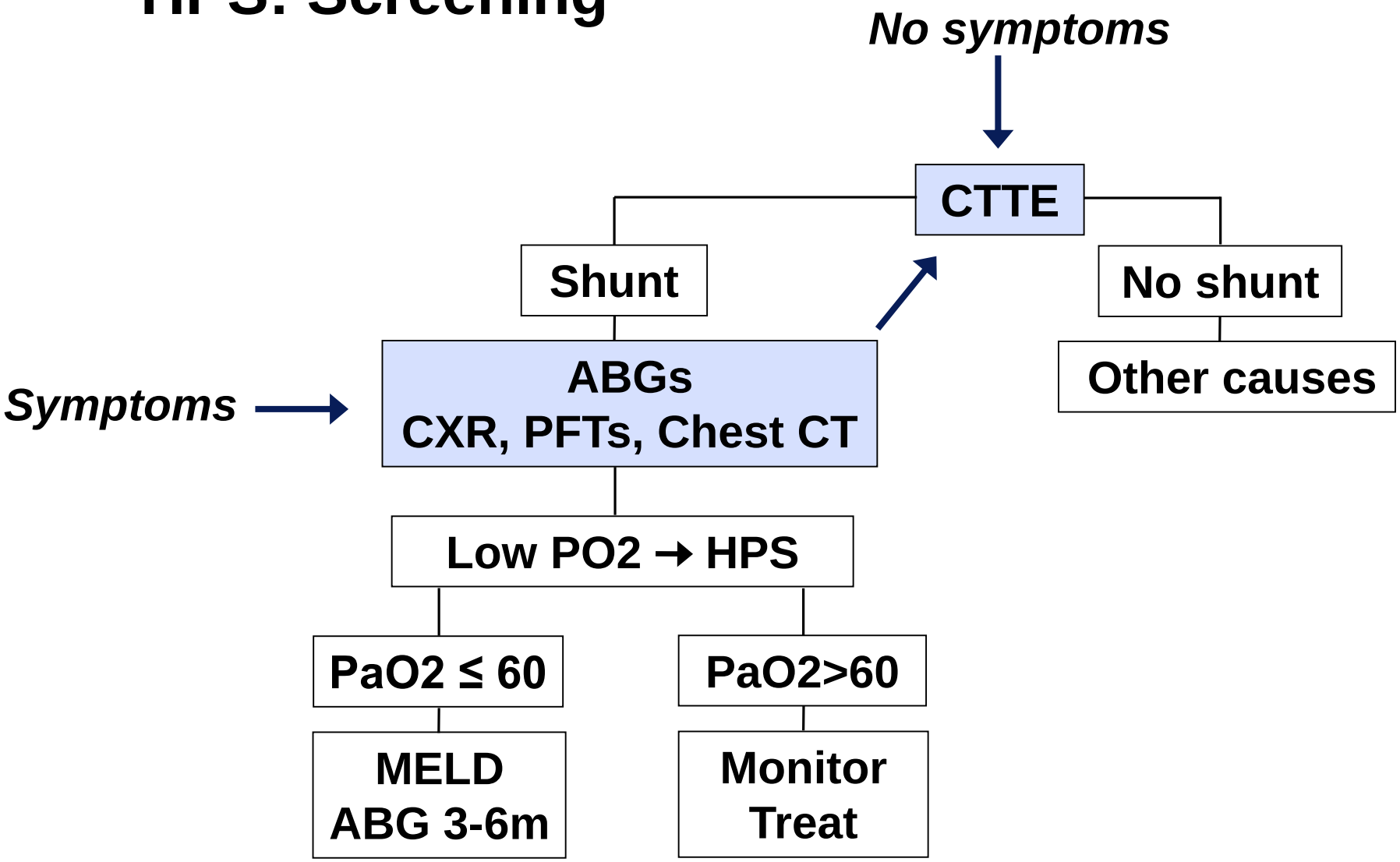
Abrams, *Liver Transpl*. 2002:8;391-6

Roberts, *Liver Transpl*. 2007:13:206-14

Arguedas, *Clin Gastro Hepatol*. 2007:5;749-54

Kochar, *Dig Dis Sci*. 2011:56;1862-8

HPS: Screening



Forde et al Hepatol 2019:69;270-281

HPS: Therapy

- Oxygen

- Liver transplantation (>90% resolution)
  - Priority increased when HPS severe (MELD exception)

- Medical (may improve oxygenation)
  - Garlic tablets (40-60% 10mmHg PaO2 increase)
    (Abrams et al, *J of Clinical Gastro*, 2005, De et al, *Can J Gastro*, 2010.)
  - Pentoxifylline (conflicting case series, efficacy unclear)
    (Tanikella et al, *Liver transplantation* 2008; Sarin et al, *Arch Intern Med* 2008.)
  - Sorafenib (phase II trial, negative)
    (Kawut et al, *Liver Transpl*, 2019)

HPS: Summary

- **Common cause of hypoxemia in cirrhosis (20-30%)**
- **Mortality increased 2.4-fold relative to non-HPS patients**
- **No proven medical therapies**
- **Liver transplantation effective and reserved for severe hypoxemia where MELD exception available**

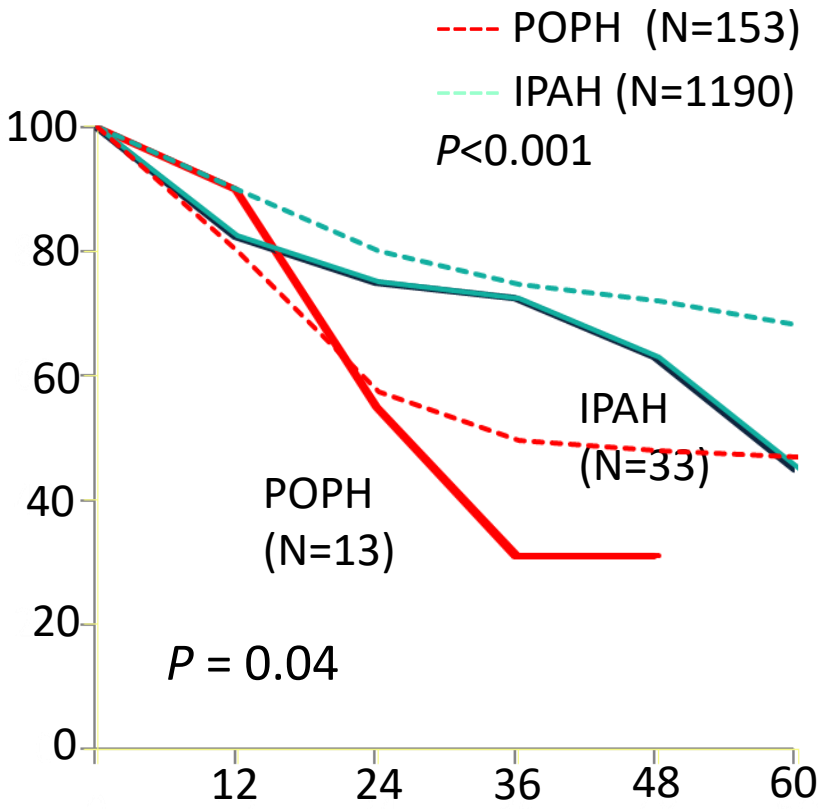
PORTOPULMONARY HYPERTENSION (POPH)

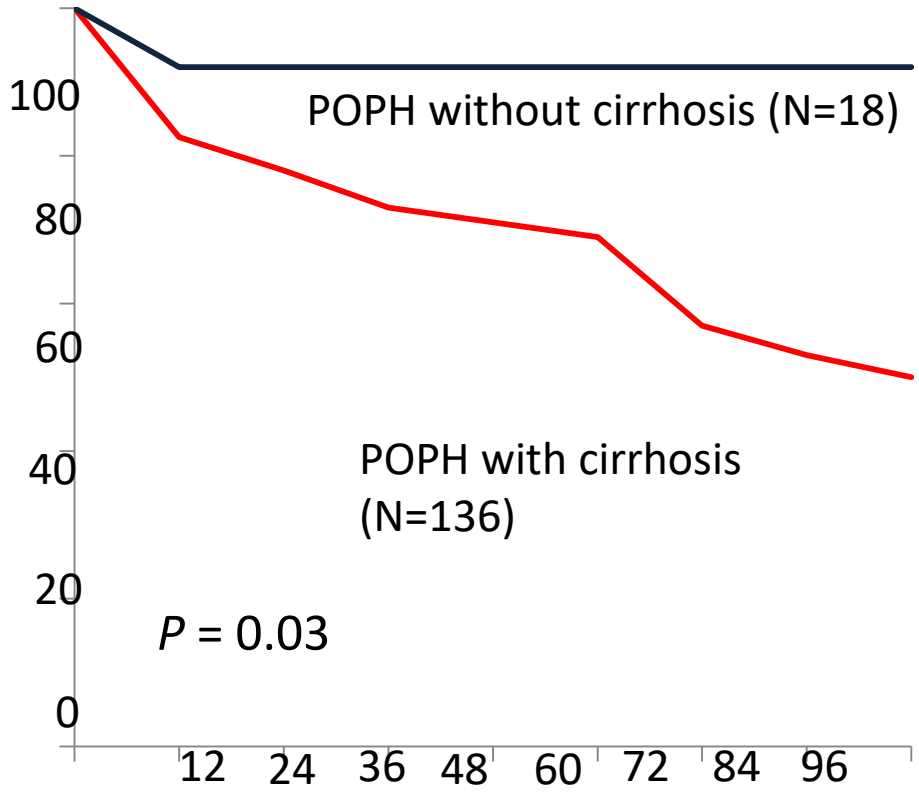
POPH: Definition

Portal hypertension plus all of the following

- ↑ Mean pulmonary artery pressure (>25 mmHg)
- ↑ Pulmonary vascular resistance (>240 dyn·sec/cm^5, 3WU)
- Normal pulmonary capillary wedge pressure

POPH: Natural History





Follow up time in months

Kawut, Liver Transplantation, 2005
Krowka, Chest, 2012

Le Pavec, Am J Res Crit Care Med, 2008

POPH: Clinical Features

History:
- Exertional dyspnea (81%)
- Syncope (17%)
- Chest pain

Risks:
- Females, autoimmune liver disease

Exam:
- Loud P2, tricuspid murmur (moderate-severe grade)

Tests:
- Echocardiography (↑right ventricular systolic pressure)
- CXR and pulmonary function tests: Normal
- ABGs: hypoxemia uncommon

POPH: Diagnosis

Pre TIPS

LT evaluation

Pulm sxs, edema

Transthoracic Echocardiograpy
Pulmonary artery systolic pressure >40mmHg

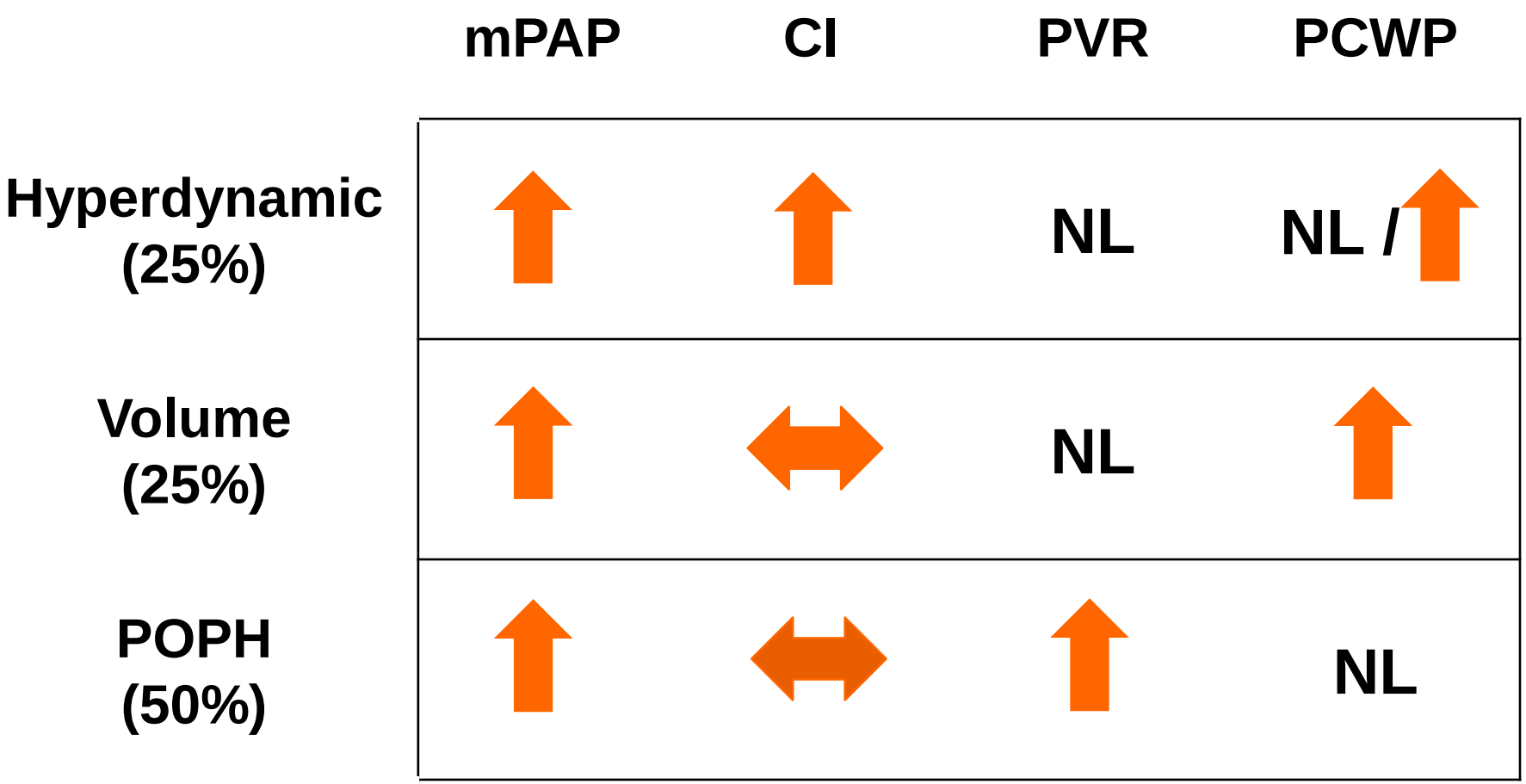
Systolic estimate

Right Heart Catheterization (RHC)

Mean measured

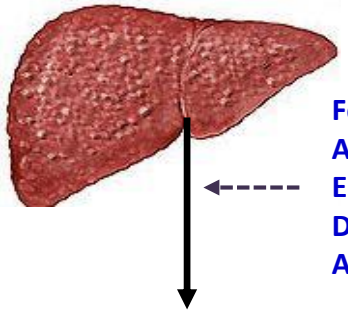
- Increased mean pulmonary arterial pressure
- Increased pulmonary vascular resistance
- Normal pulmonary capillary wedge pressure

RHC in Cirrhosis



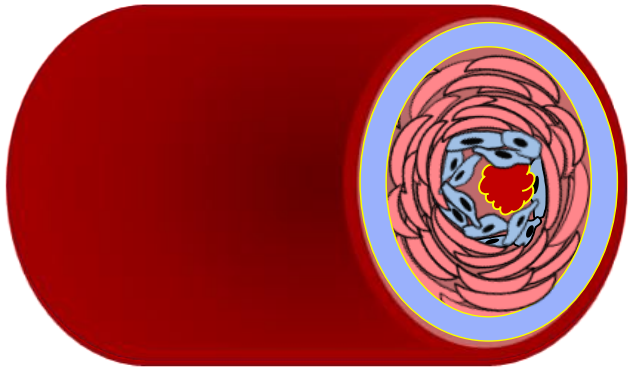
POPH: Pathophysiology

Cirrhosis
Portal Hypertension



Female gender
Autoimmune hepatitis
Estrogen
Degree of portosystemic shunting
Altered vasoactive mediator levels

Lung Resistance vessel →



Endothelial cell dysfunction

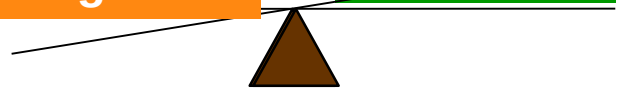
↓

↑Endothelin-1
↓Nitric oxide
↓Prostacyclin

Smooth muscle constriction and remodeling

Vasoconstriction
Remodeling

Vasorelaxation
~~Vasorelaxation~~

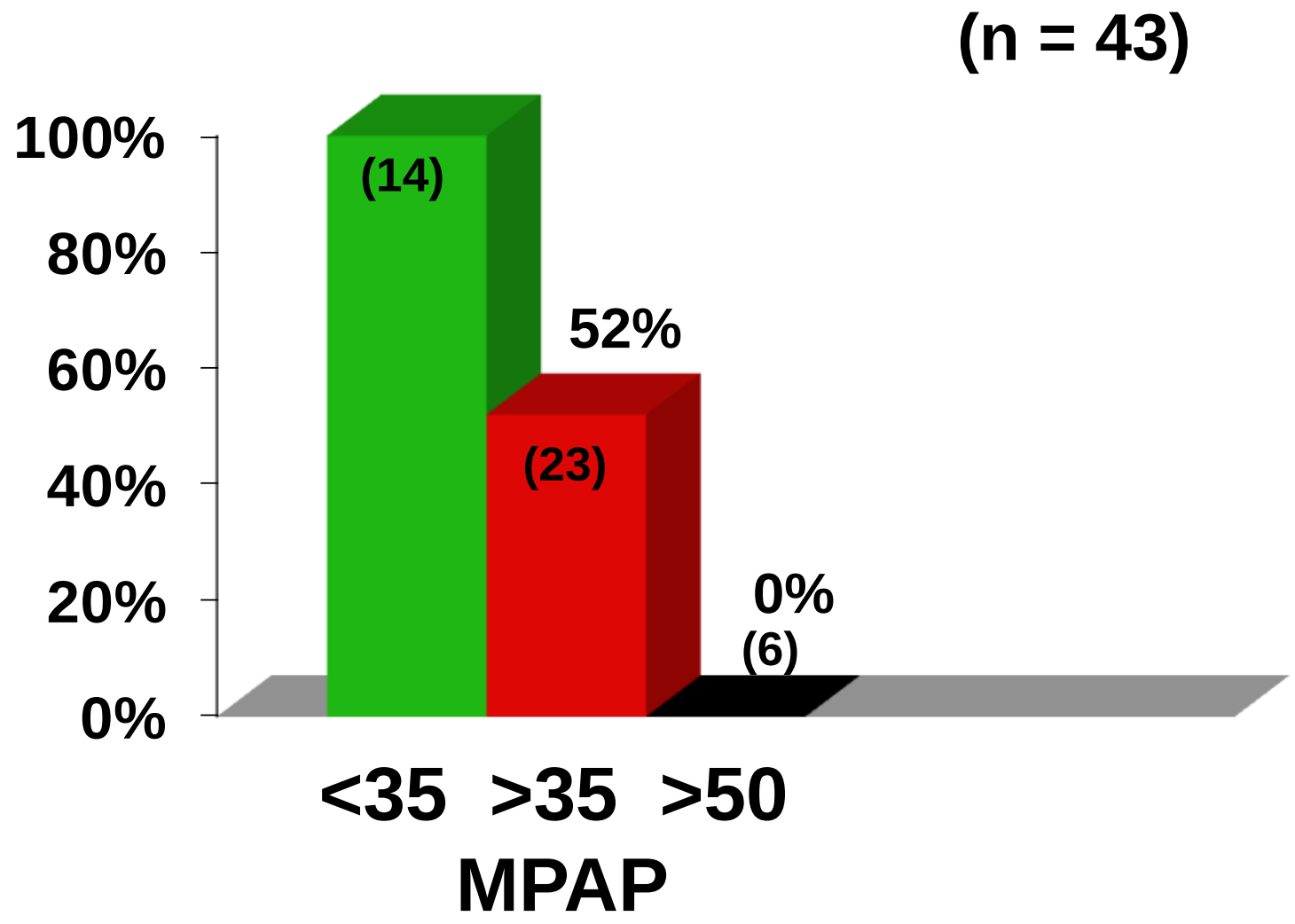


POPH: Therapy

- Medical therapies
  (lowers pressures, improves symptoms, not curative)
  - Endothelin receptor antagonists (Ambrisentan, macitentan)
  - Phosphodiesterase inhibitors (Sildenafil)
  - cGMP analogues (Riociquat)
  - Prostacyclin analogs (Treprostinil, iloprost)
  - IP prostacyclin receptor agonist (selexipag)

- Liver transplantation
  - Individuals with high mean pulmonary artery pressure and therapy response
  - Increased priority for liver transplantation (MELD exception)
  - May be curative in a subset of patients

POPH: Liver Transplantation Survival



POPH: Summary

- 3-8% of liver transplant evaluations
- Increased pre- and post-liver transplant mortality
- Medical therapies effective but not curative
- Liver transplant may reverse a subset

Hepatic Hydrothorax (HH)

Hepatic Hydrothorax (HH): Definition

- Transudative pleural effusion in cirrhotics due to passage of ascitic fluid into pleural space

- Clinical features
  - Cough
  - Dyspnea
  - Hypoxia
  - Chest discomfort
  - Ascites (detectable in 80%)

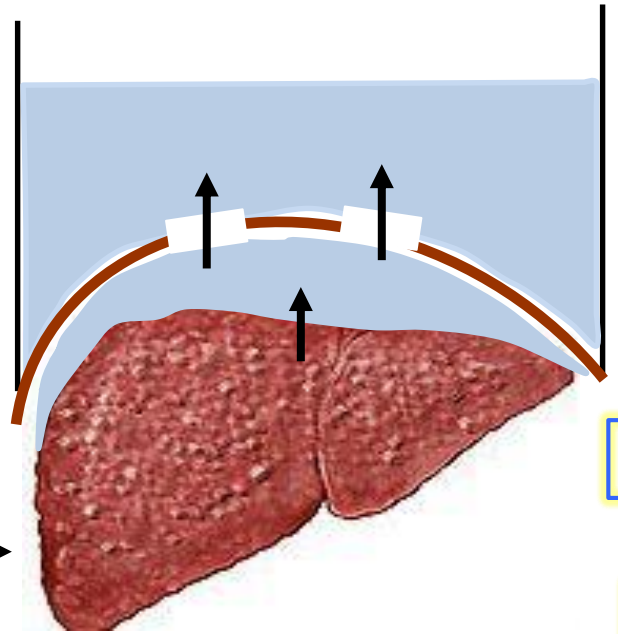
HH: Diagnosis

- Thoracentesis (Pleural Fluid Analysis)

  All of the following:
  - Serum-to-pleural fluid albumin gradient (SPAG) >1.1
  - Pleural fluid total protein <2.5 g/dL
  - Pleural fluid/serum lactate dehydrogenase ratio <0.6
  - PMN cell count <250 cells/mm^3

HH: Pathophysiology

Negative intra-pleural pressure



Diaphragmatic defects

Ascitic Fluid migration

Ascites development

Cirrhosis
Portal
Hypertension

HH: Therapy

- Medical Therapy
  - Sodium restriction, diuretics
  - Paracentesis: if large volume ascites present as well
  - Thoracentesis: short term symptomatic therapy
  - Avoid chest tube placement

- TIPS (transjugular intrahepatic portosystemic shunt)
  - Response rate 70-80%
  - Avoid in severe hepatic and/or cardiac failure

Hepatic Hydrothorax: Summary

- 5-10% of cirrhotic patients
- Right-sided effusion (90%) with or without ascites
- Diagnosis requires thoracentesis
- Treatment: medical management or transjugular intrahepatic portosystemic shunt (TIPS)