Inpatient Evaluation and Management of Patients with Cirrhosis

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I have no disclosures to make relative to my presentation

Honoring Women's Leadership in Gastroenterology and Hepatology

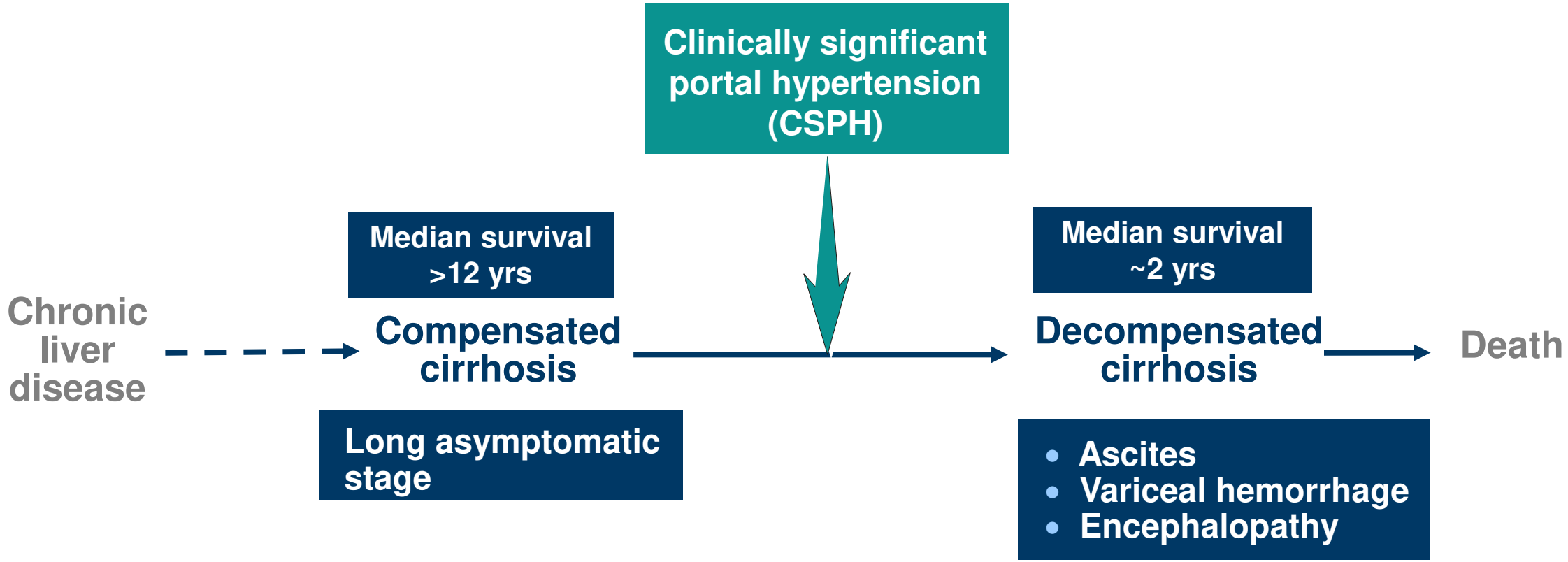
In 2017, the presidents of all 4 American GI Societies were female

Karen Woods	Sheila Crowe	Carol Burke	Anna Lok
ASGE	AGA	ACG	AASLD

In 2017, four females had been AASLD presidents

Terry Wright (2005)
Guadalupe Garcia-Tsao (2012)
Gyongyi Szabo (2015)
Anna Lok (2017)
Laurie DeLeve (2022)
Norah Terrault (2023)
Grace Su (2026)

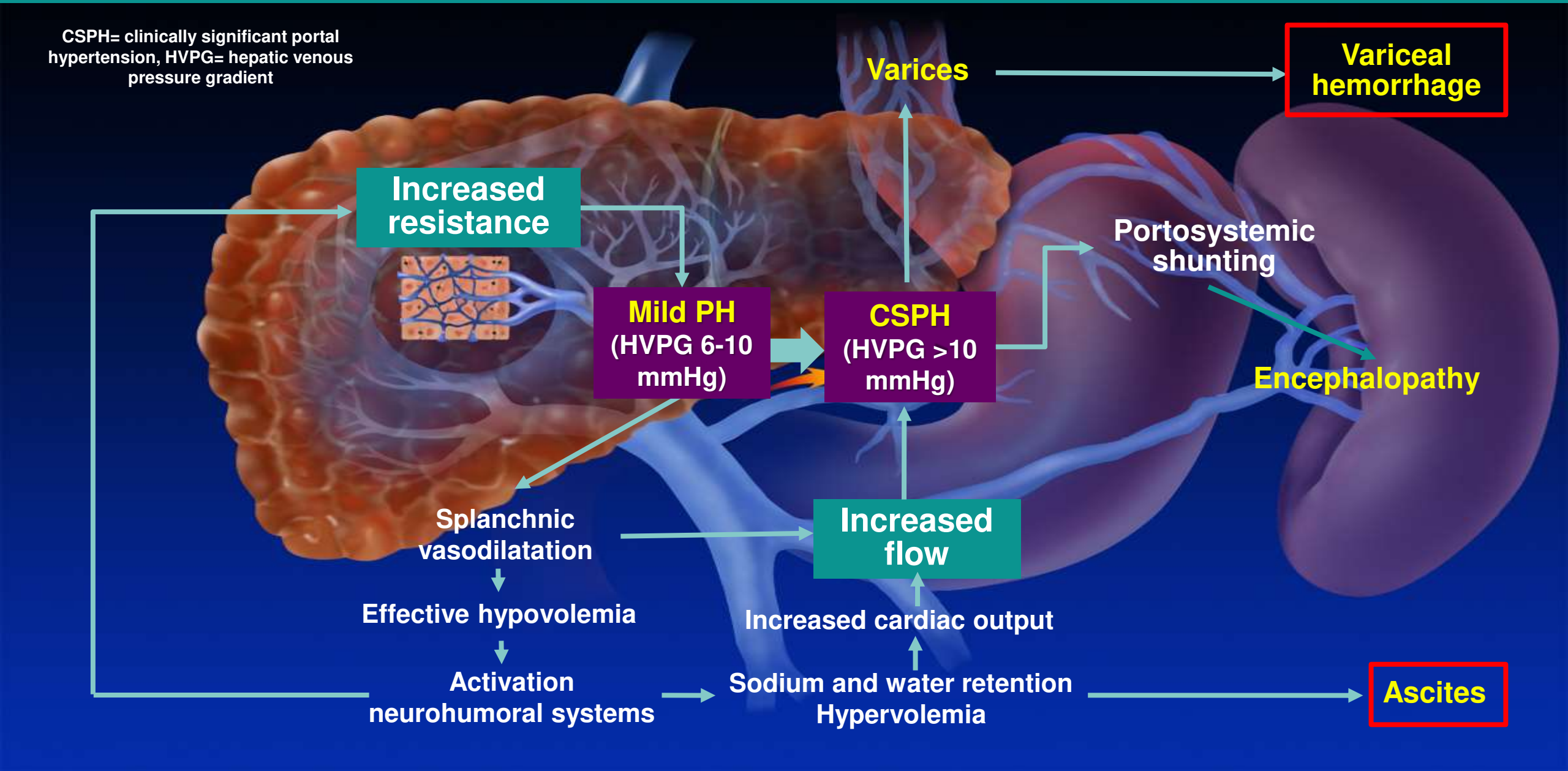
Decompensation is the main determinant of death in cirrhosis and the main driver of decompensation is CSPH



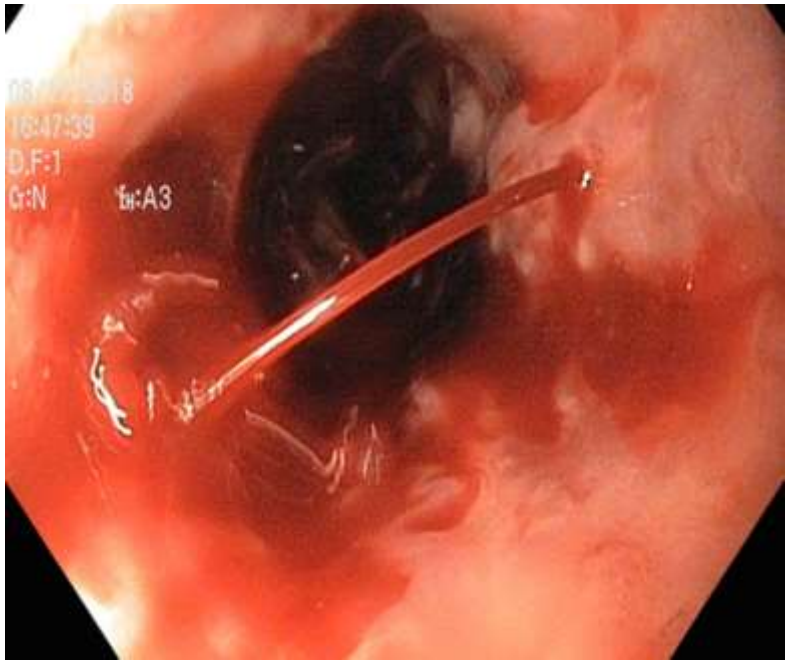
Defined as a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg

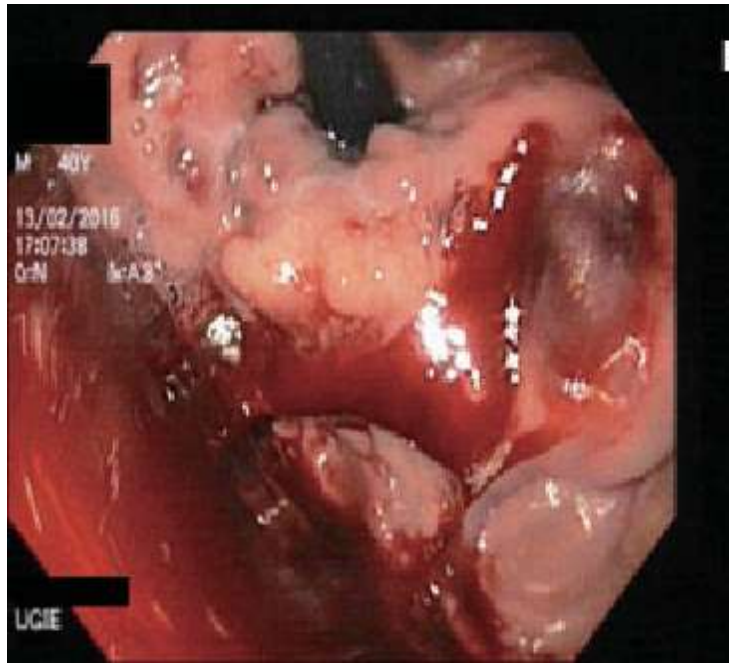
Ripoll et al. Gastroenterology 2007; 133:481.

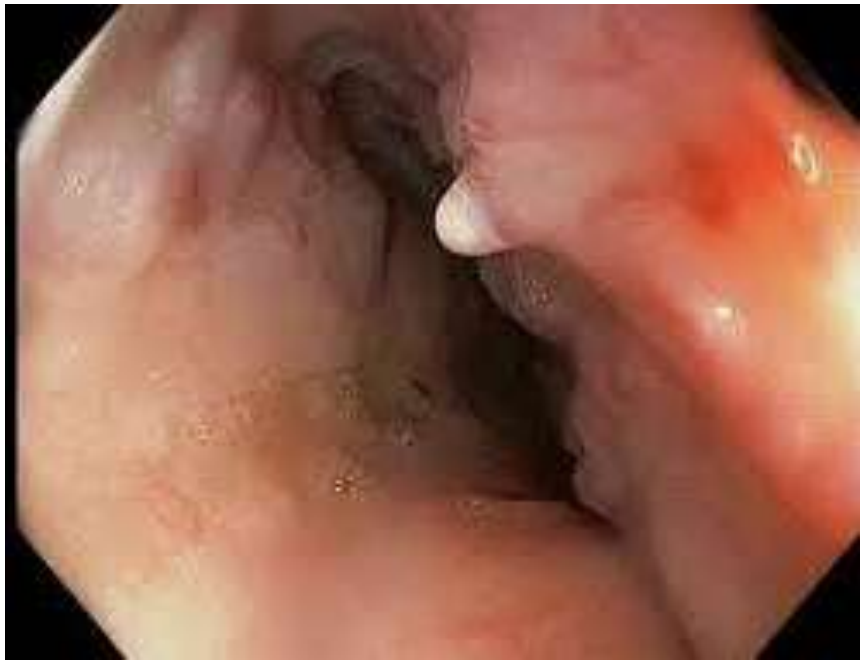
CSPH results from increased intrahepatic resistance and increased portal venous inflow



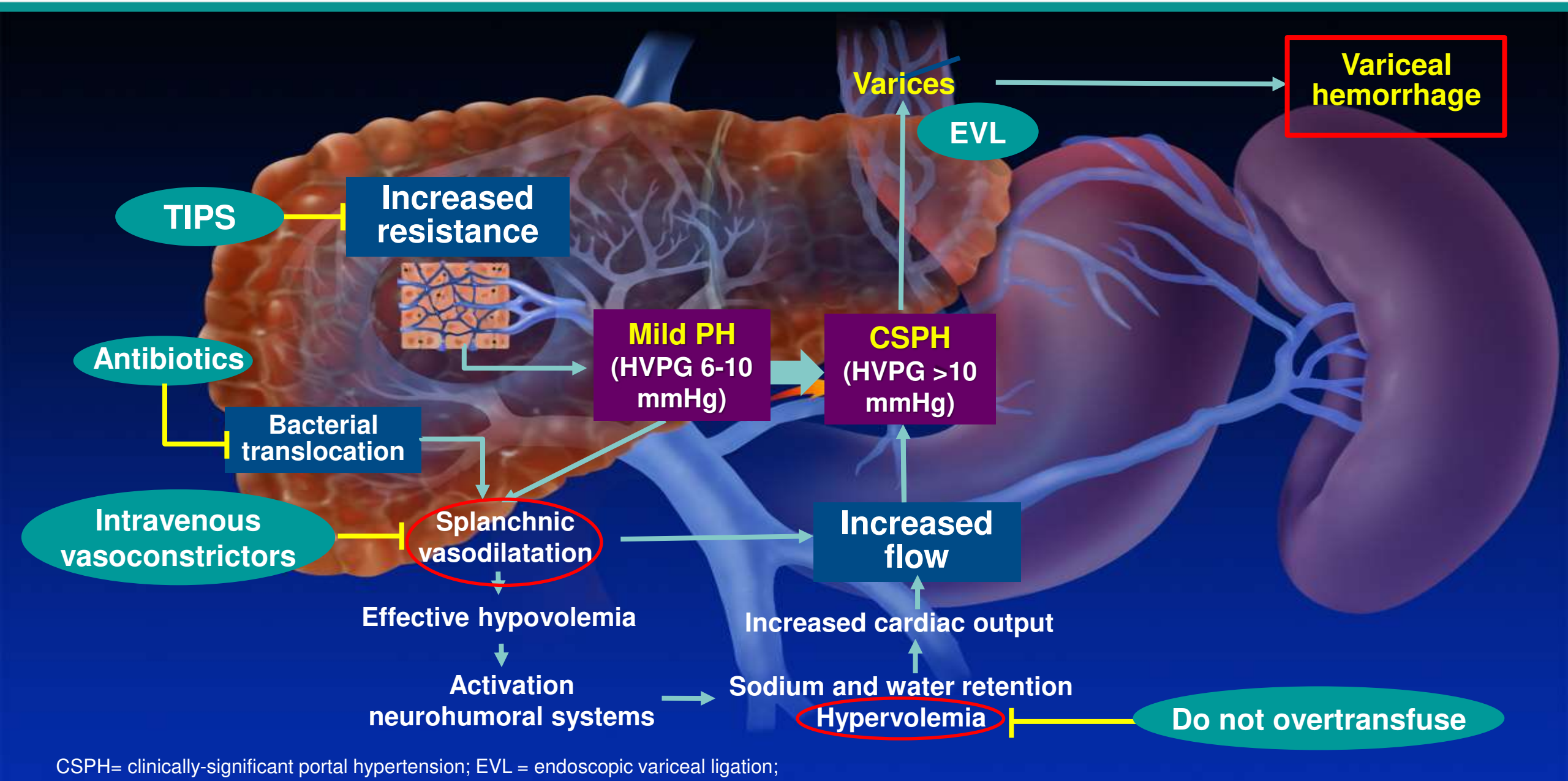
Variceal hemorrhage is an episodic but deadly complication of cirrhosis







Mechanism of action of different strategies used to treat variceal hemorrhage



CSPH= clinically-significant portal hypertension; EVL = endoscopic variceal ligation;

Management of variceal hemorrhage – Standard of Care (SOC)

- **Cautious PRBC transfusion: start at 7 g/dL, maintain at 7-9 g/dL**
- **Short term (maximum 7 days) antibiotic prophylaxis (ceftriaxone 1 g/d)**
- **Safe IV vasoactive drug (octreotide, somatostatin or terlipressin)**

Start PPI

- Variceal bleeding is due to portal hypertension, and the aim of the treatment should be focused on lowering portal pressure rather than correcting coagulation abnormalities
- FFP transfusion is not recommended as it will not correct coagulopathy and may lead to volume overload and worsening of portal hypertension

Baveno VII, 2021

Garcia-Tsao et al. AASLD guidance. Hepatology 2017;65:310-335

Management of variceal hemorrhage – Standard of Care (SOC)

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↓

Endoscopy (within 12 hours): VH confirmed

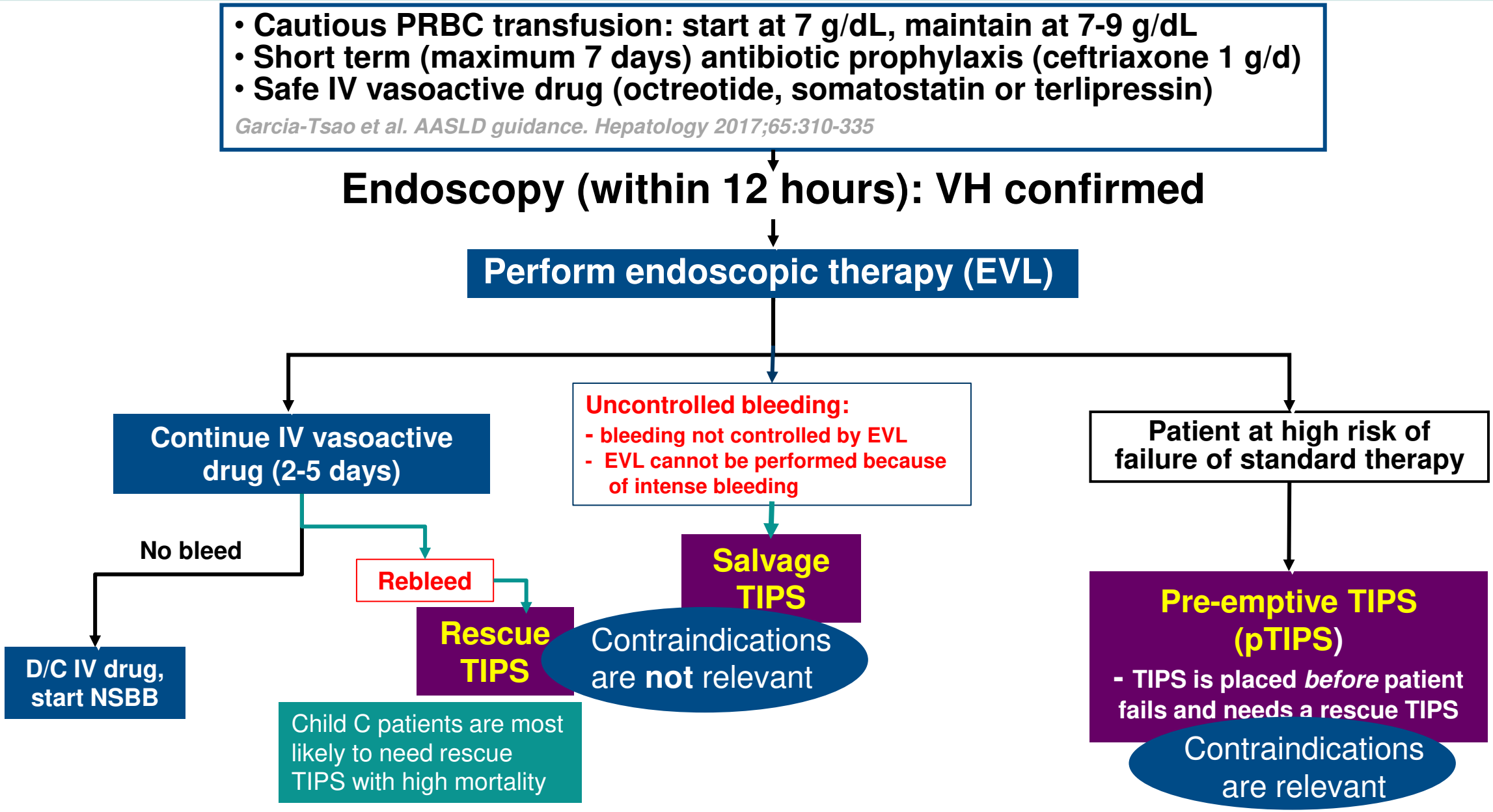
Stop PPI

PPIs, when started before endoscopy, should be stopped immediately after endoscopy confirms variceal hemorrhage unless there is a strict indication to continue them

Baveno VII, 2021

Garcia-Tsao et al. AASLD guidance. Hepatology 2017;65:310-335

TIPS in acute variceal hemorrhage



Patients excluded from pTIPS studies

- Child-Pugh score 14 and 15
- Age >70–75 years
- Recurrent overt encephalopathy without precipitating factors
- Serum creatinine above 2.5-3 g/dl
- Sepsis/active infection
- Heart failure
- Pulmonary hypertension

Cardiac echo

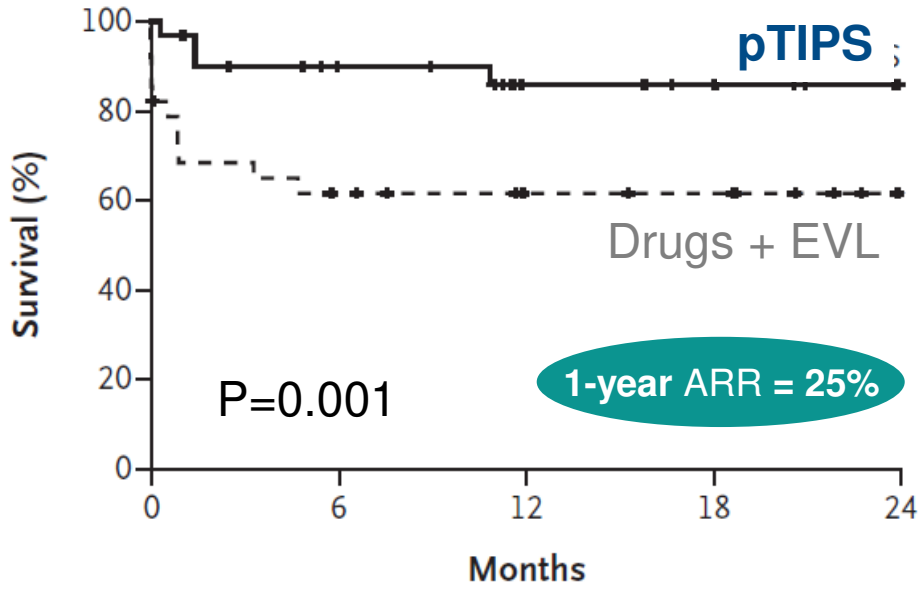
- HCC beyond Milan
- Complete PV thrombosis

Doppler US or cross-sectional imaging

Pre-emptive TIPS (pTIPS) placed within 72 hours of admission improves survival in Child C (10-13 points) and in selected Child B patients

50% 50%

Child C 10-13 + Child B with active bleeding at endoscopy

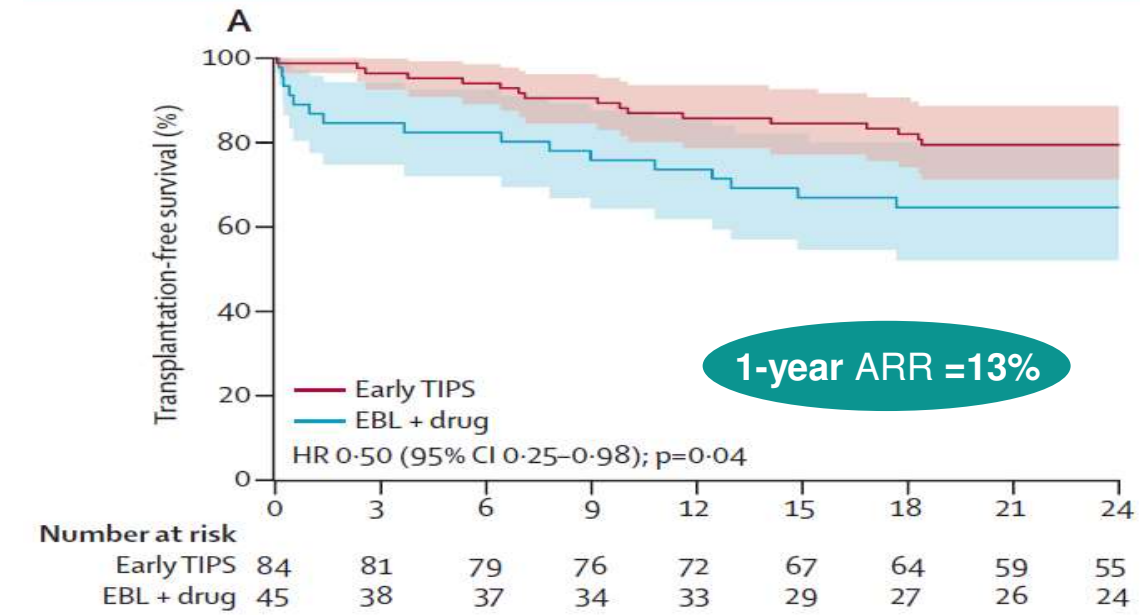


1-year ARR = 25%

No. at Risk		
Early TIPS	32	24
Drugs+EBL	31	18

22% 21% 57%

Child C (10-13) + Child B with or without active bleeding at endoscopy



1-year ARR =13%

Mostly Etoh

Mostly HBV cirrhosis

A recent additional RCT including 58 patients (29/group) did not find differences in survival and encountered problems regarding feasibility of pTIPS within the timeframe

Dunne et al. Aliment Pharmacol Ther. 2020;52:98–106

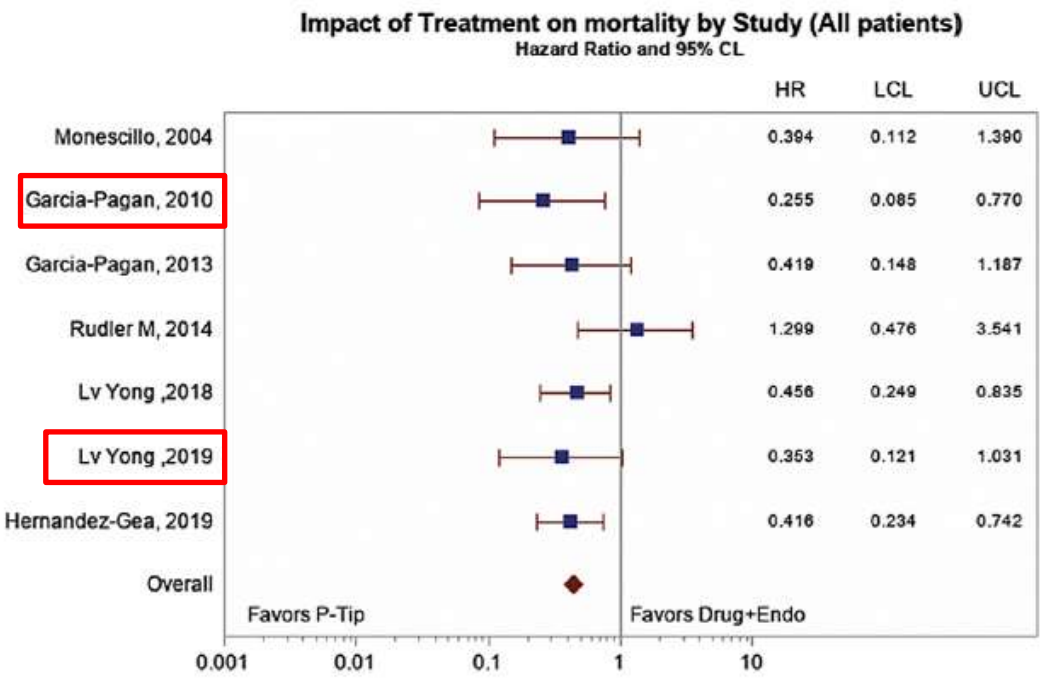
García-Pagán et al. N Engl J Med 201

ancet Gastroenterol Hepatol 2019:587-598

ARR = absolute risk reduction

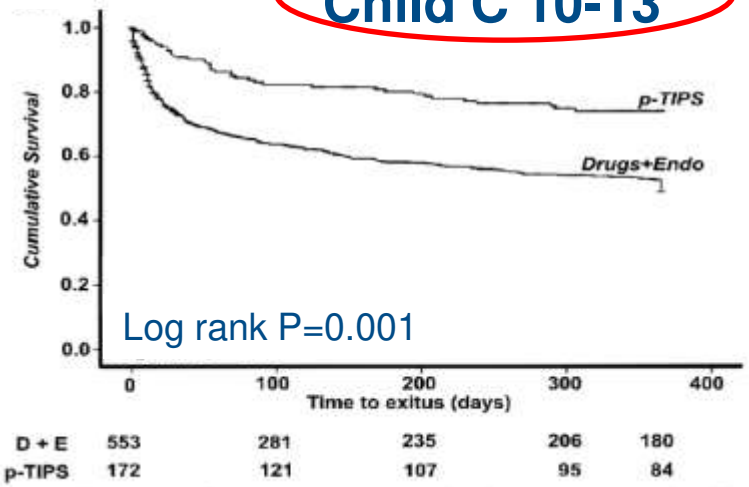
In an individual data meta-analysis, the groups that seem to benefit from preemptive TIPS (pTIPS) are Child C (10-13 pts) and Child B (8-9 pts)

All patients

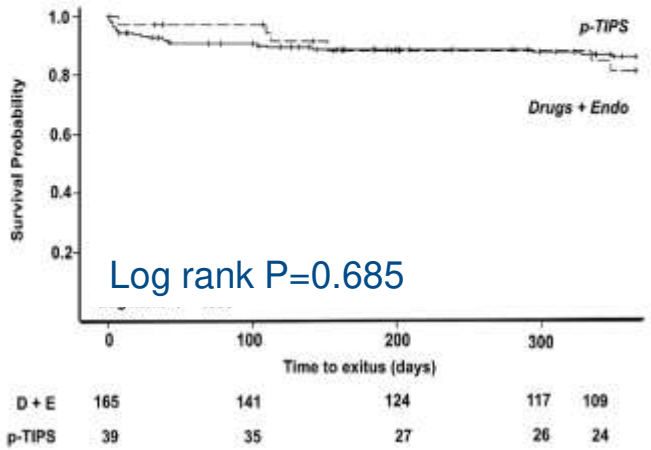


RCTs

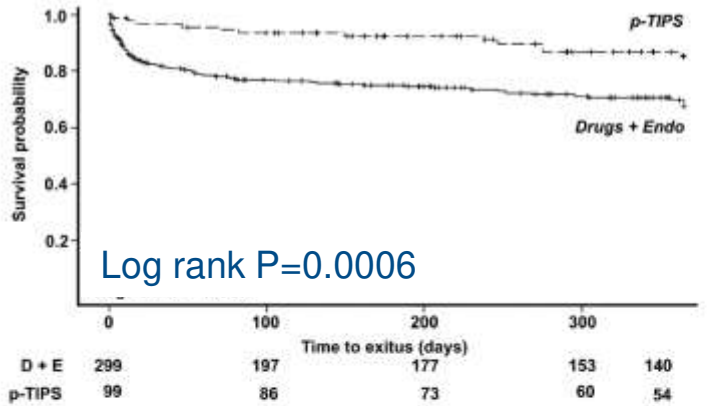
Child C 10-13



Child B=7 + active bleed

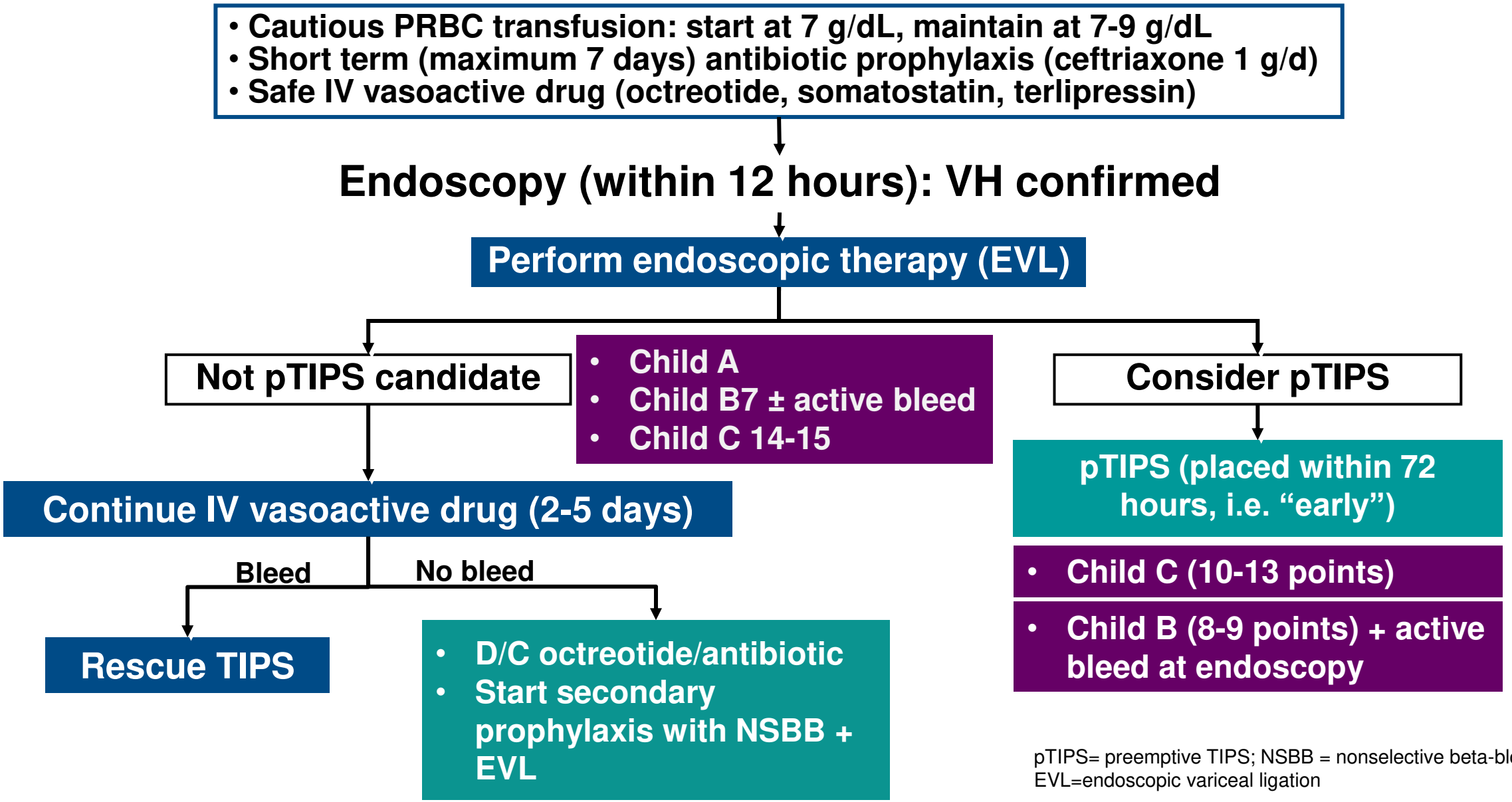


Child B>7 + active bleed



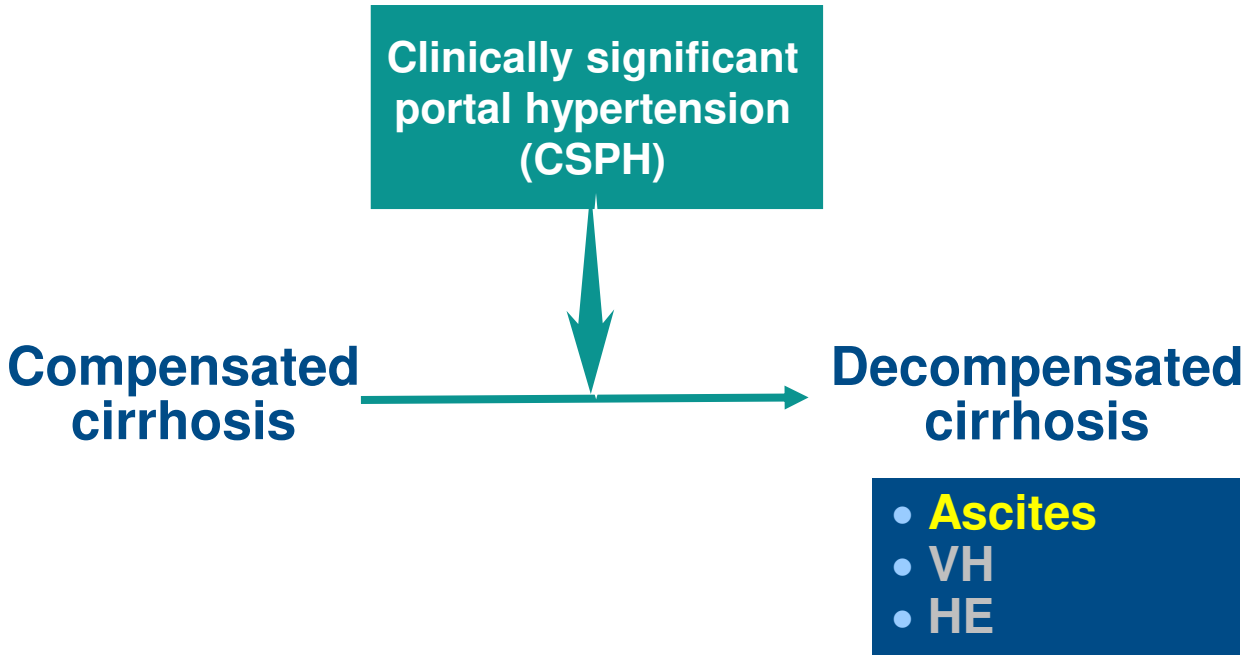
Nicoara Farcau et al. Gastroenterology 2021;160:193–205

Management of variceal hemorrhage



pTIPS= preemptive TIPS; NSBB = nonselective beta-blockers; EVL=endoscopic variceal ligation

Ascites is the most common complication of ascites but it is a chronic event that, unless complicated, does not require hospitalization

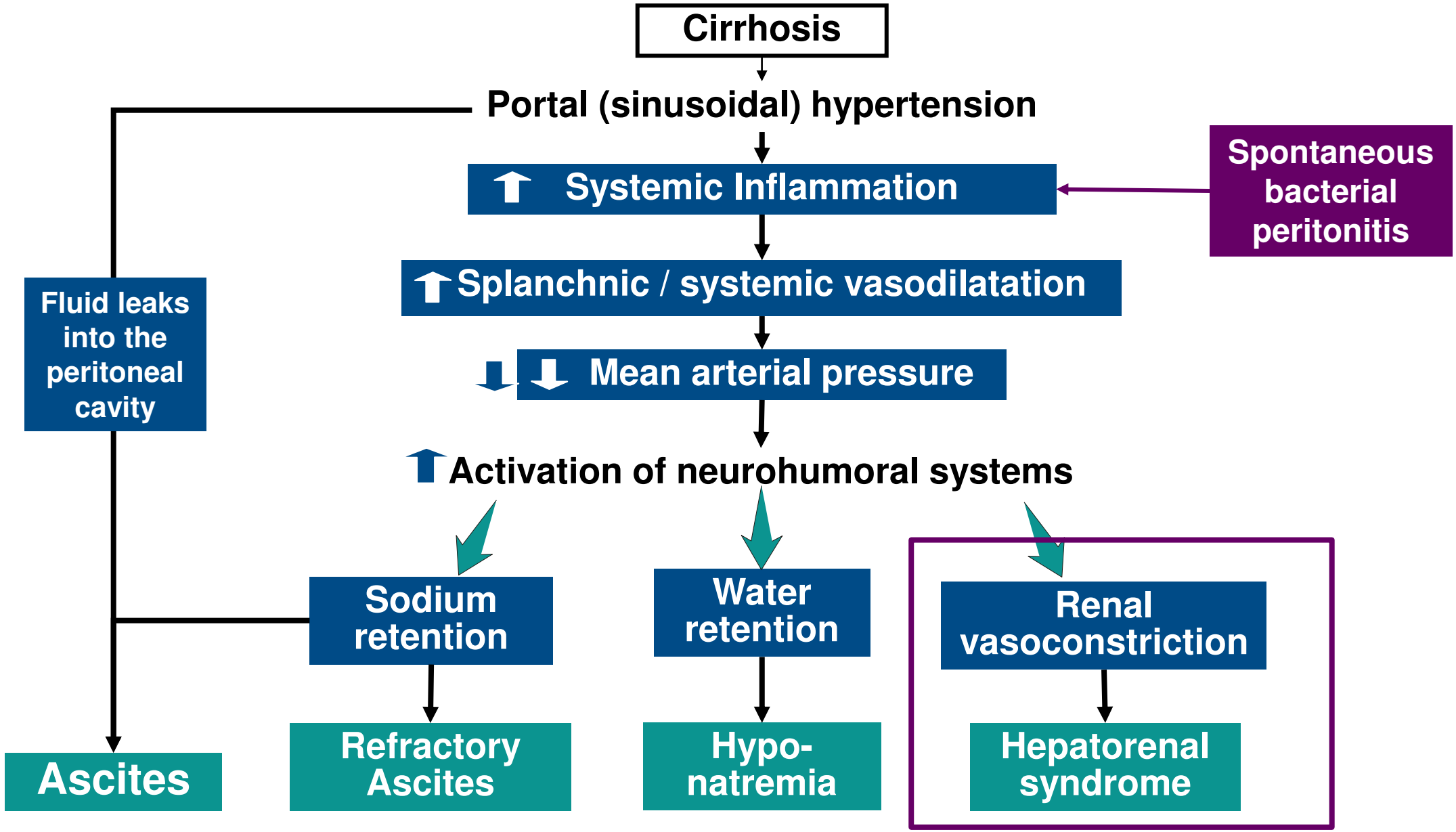


- Ascites is not an emergency
- Start diuretics once other complications (GI bleed, infection, acute kidney injury, encephalopathy) are absent or have resolved
- If patient uncomfortable because of tense ascites → large-volume paracentesis
- Main goal in a hospitalized patient is to rule out spontaneous bacterial peritonitis
- In a non-elective admission → hold diuretics

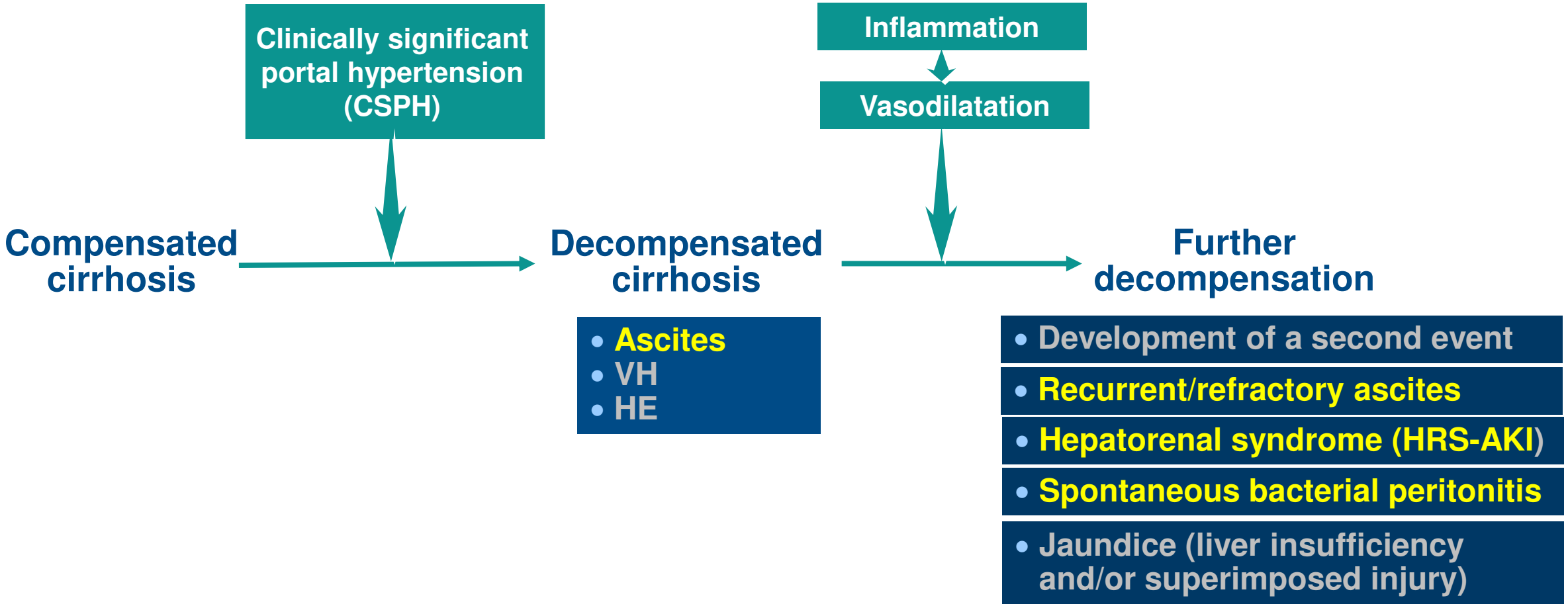
Baveno VII consensus conference, 2021.

CSPH= clinically significant portal hypertension; VH=variceal hemorrhage; HE= hepatic encephalopathy

Ascites, refractory ascites, hyponatremia and HRS represent a continuum in decompensated cirrhosis with progressive hemodynamic alterations



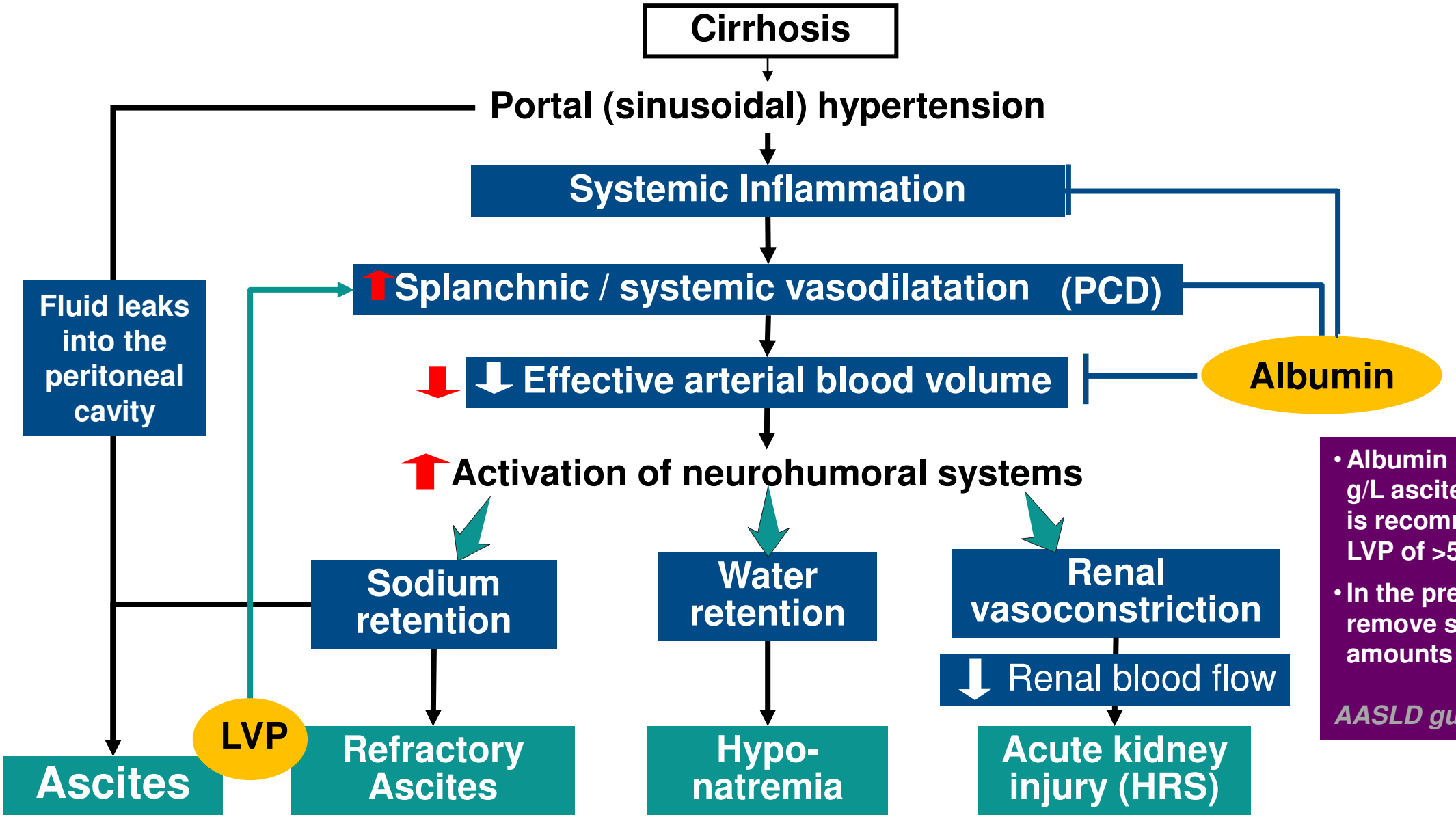
Recurrent/refractory ascites, spontaneous bacterial peritonitis and hepatorenal syndrome define a stage of “further” decompensation



Baveno VII consensus conference, 2021.

CSPH= clinically significant portal hypertension;
VH=variceal hemorrhage; HE= hepatic encephalopathy

Large-volume paracentesis (LVP) + albumin is the mainstay of therapy for recurrent / tense ascites



Is albumin alone useful??

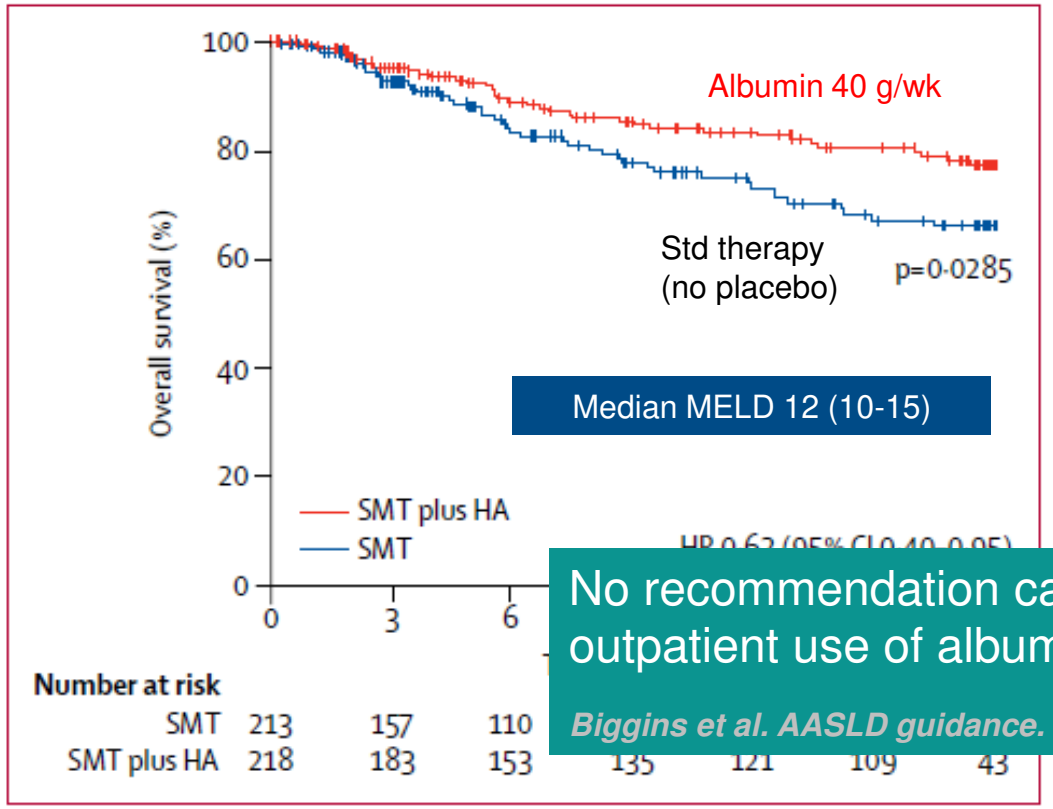
- Albumin infusion (6-8 g/L ascites removed) is recommended with LVP of >5L
- In the presence of AKI, remove smaller amounts + albumin

AASLD guidance 2021

PCD=post-paracentesis circulatory dysfunction

Chronic intravenous albumin administration in outpatients with cirrhosis and ascites have yielded contradictory results

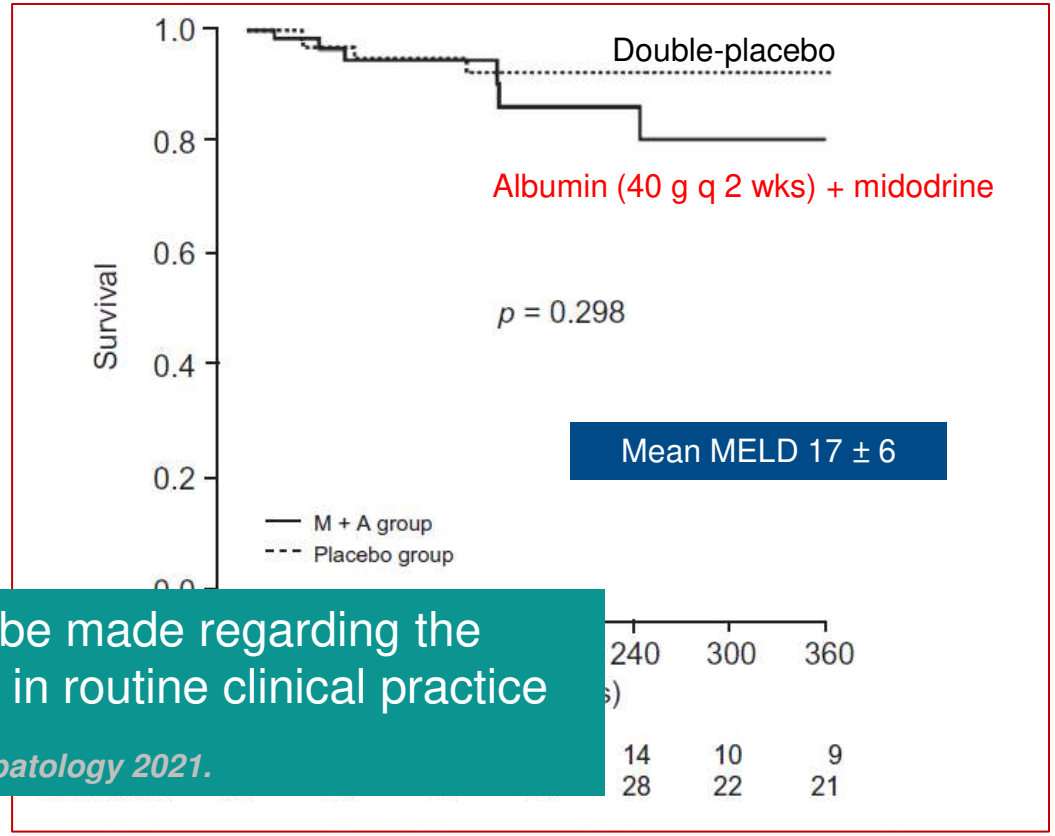
Overall survival



Also associated with lower rates of need for LVP, hyponatremia, SBP and hepatorenal syndrome

Caraceni et al (ANSWER trial). Lancet 2018;391:2417-2429

Survival



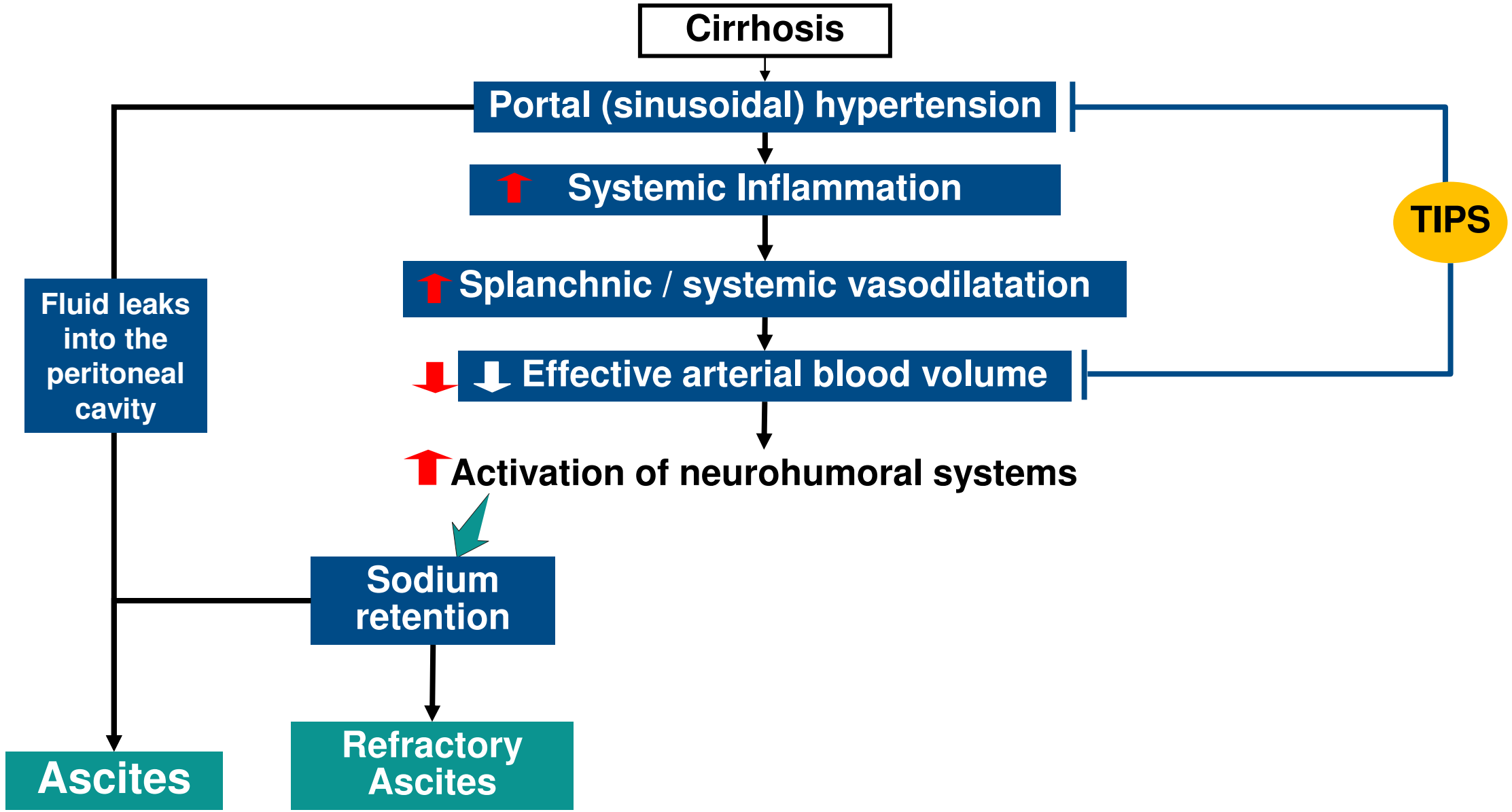
No differences in need for LVP, renal failure, hyponatremia, bacterial infections, encephalopathy or GI bleeding

Solà et al (MACHT trial) . J Hepatol. 2018;69:1250-1259

No recommendation can be made regarding the outpatient use of albumin in routine clinical practice

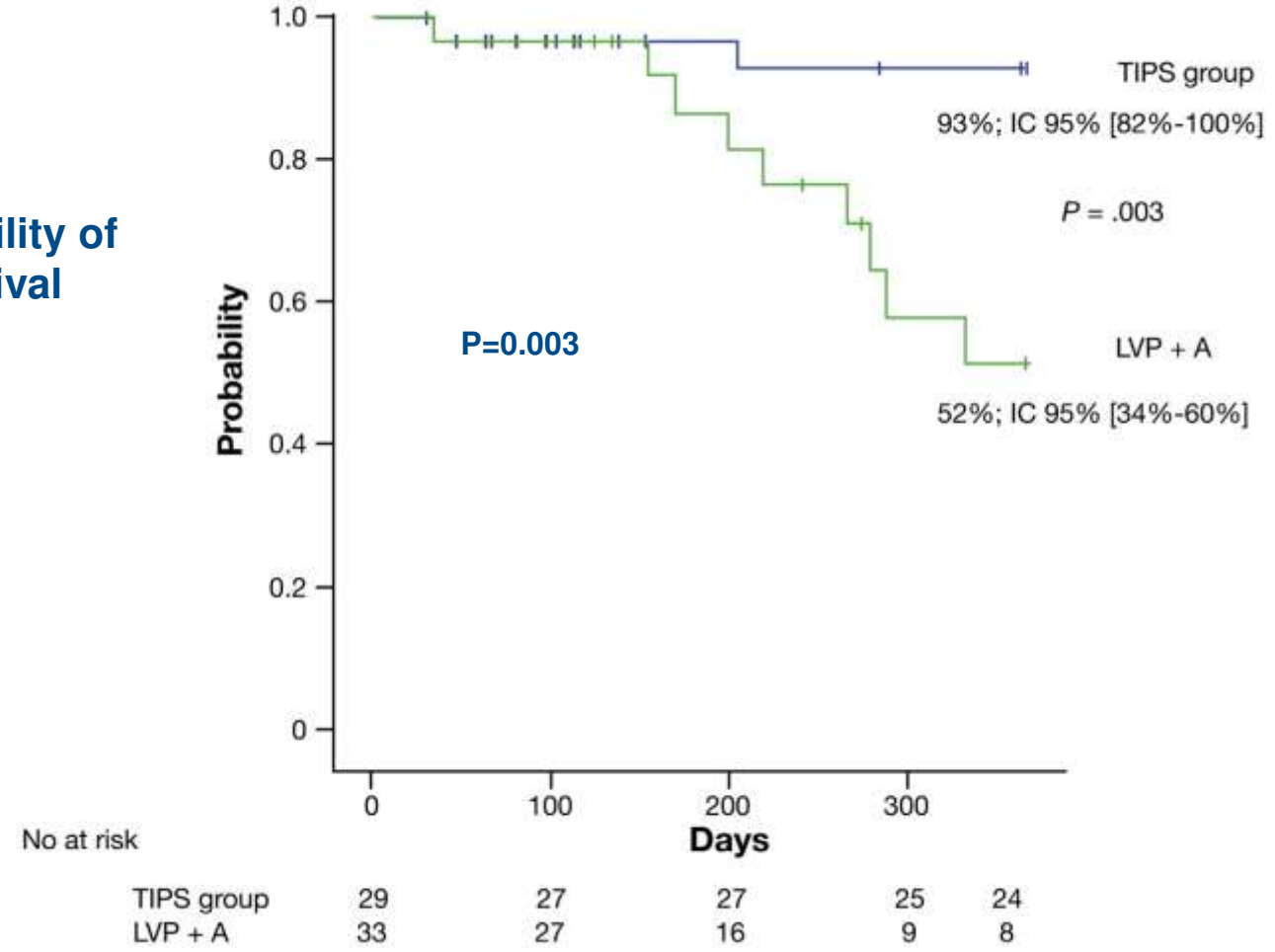
Biggins et al. AASLD guidance. Hepatology 2021.

The transjugular intrahepatic portosystemic shunt (TIPS) acts upstream of the ascites pathogenic cascade



TIPS with PTFE-covered stent improves survival in patients with cirrhosis and **recurrent** ascites

Probability of survival



All pts had "recurrent" tense ascites defined as requiring 2 LVP in a minimum period of 3 weeks

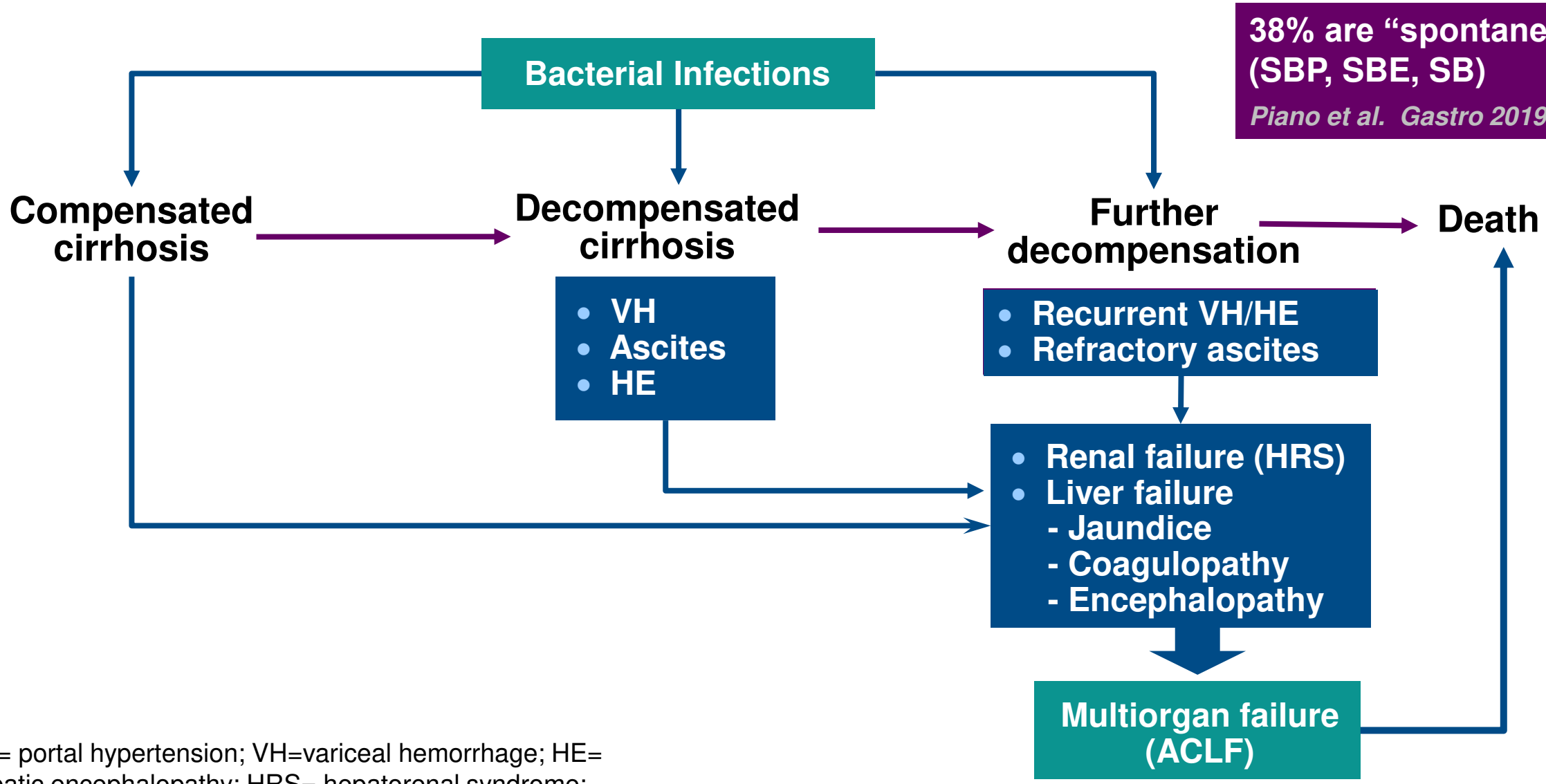
TIPS should be considered in selected patients who require at least three LVPs in a year despite optimal medical therapy

ALTA consensus, 2020; Baveno consensus, 20221

Bureau C et al. Gastroenterology 2017;152:157-163

TIPS= transjugular intrahepatic portosystemic shunt; LVP + A = large-volume paracentesis + albumin

Bacterial infections can lead to liver and extrahepatic organ failures in patients at any stage of cirrhosis



PH= portal hypertension; VH=variceal hemorrhage; HE= hepatic encephalopathy; HRS= hepatorenal syndrome; ACLF= acute on chronic liver failure

Diagnosis of SBP (or SBE) is based on fluid (ascites, pleural) PMN

- Although patient may present with abdominal pain, tenderness, ileus, the patient with SBP is often asymptomatic and may present only with encephalopathy or AKI
- In a prospective study, 6/17 (35%) patients with SBP were deemed not to have SBP based on clinical evaluation in the emergency department

Chinnock et al. Emerg Med. 2008;52:268-273

- Diagnosis is based on ascites (or hydrothorax fluid) PMNs, independent of culture results

PMN >250/mm^3 = SBP (or SBE)

In grossly hemorrhagic ascites: subtract 1 PMN per 250 RBC

Biggins et al. AASLD guidelines. Hepatology 2021;74:1014-1048

SBP= spontaneous bacterial peritonitis;
SBE= spontaneous bacterial empyema
PMN=polymorphonuclear count

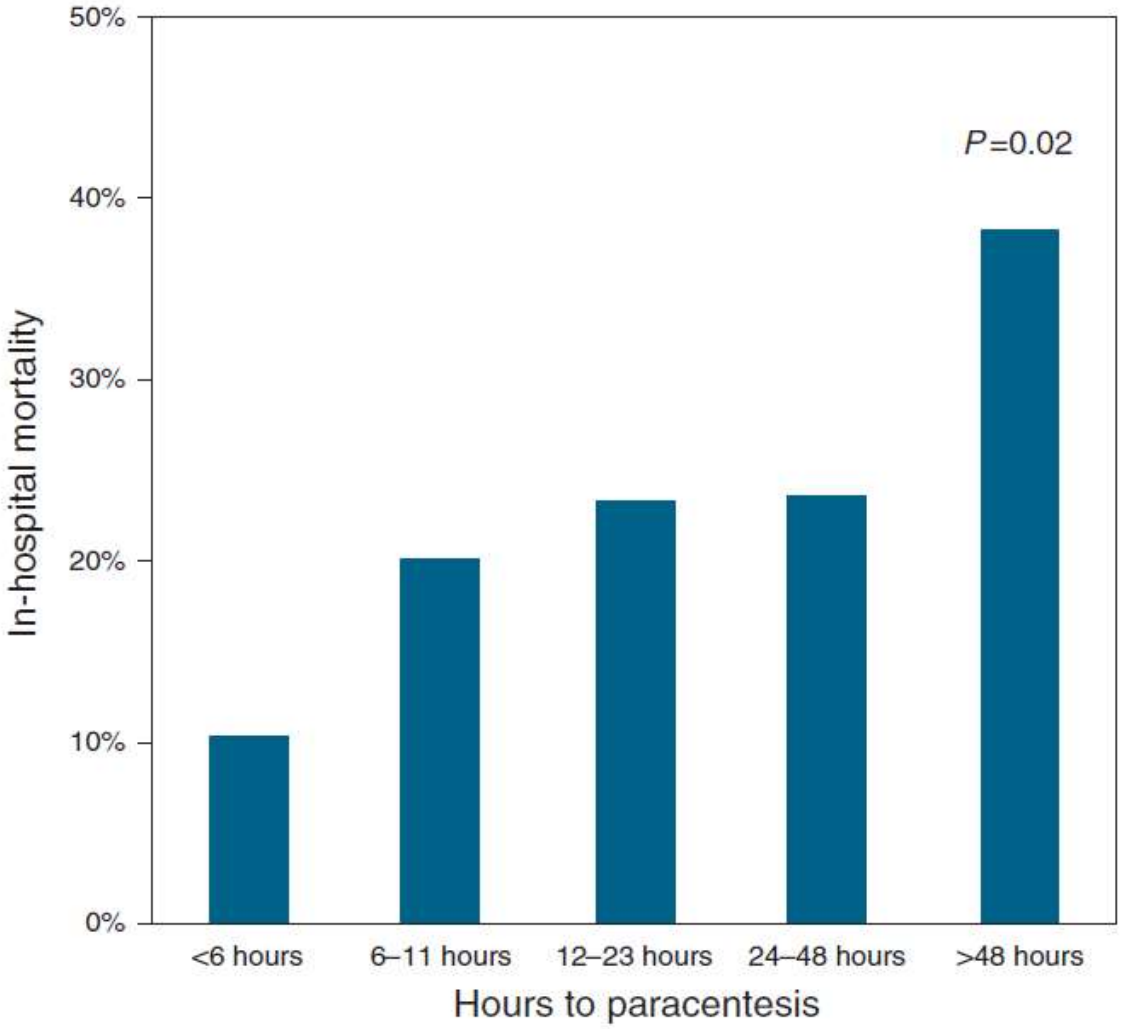
Workup and management of patients with cirrhosis and ascites admitted to the hospital

On admission (independent of symptoms)

↓

Dx paracentesis

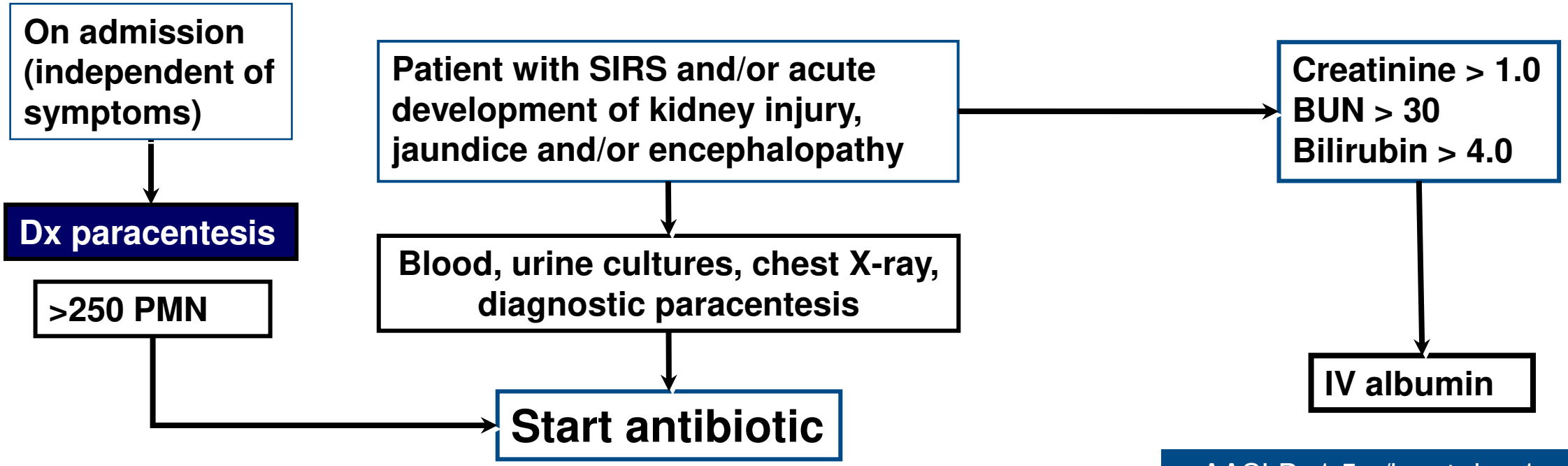
Delays in the performance of diagnostic paracentesis in SBP result in a higher mortality



Biggins et al. AASLD guidelines. Hepatology 2021 Aug;74:1014-1048

SBP = spontaneous bacterial peritonitis

Workup and management of patients with cirrhosis and ascites admitted to the hospital



Community acquired SBP	Nosocomial SBP
Third-generation cephalosporin	• Piperacillin/tazobactam AND • Daptomycin (if VRE in past or GI colonization) OR • Meropenem if known to harbor MDR gram-negative organisms

- AASLD: 1.5 g/kg at day 1and 1 g/kg at day 3; pts with AKI and/or jaundice are more likely to benefit from albumin

Biggins et al. Hepatology 2021

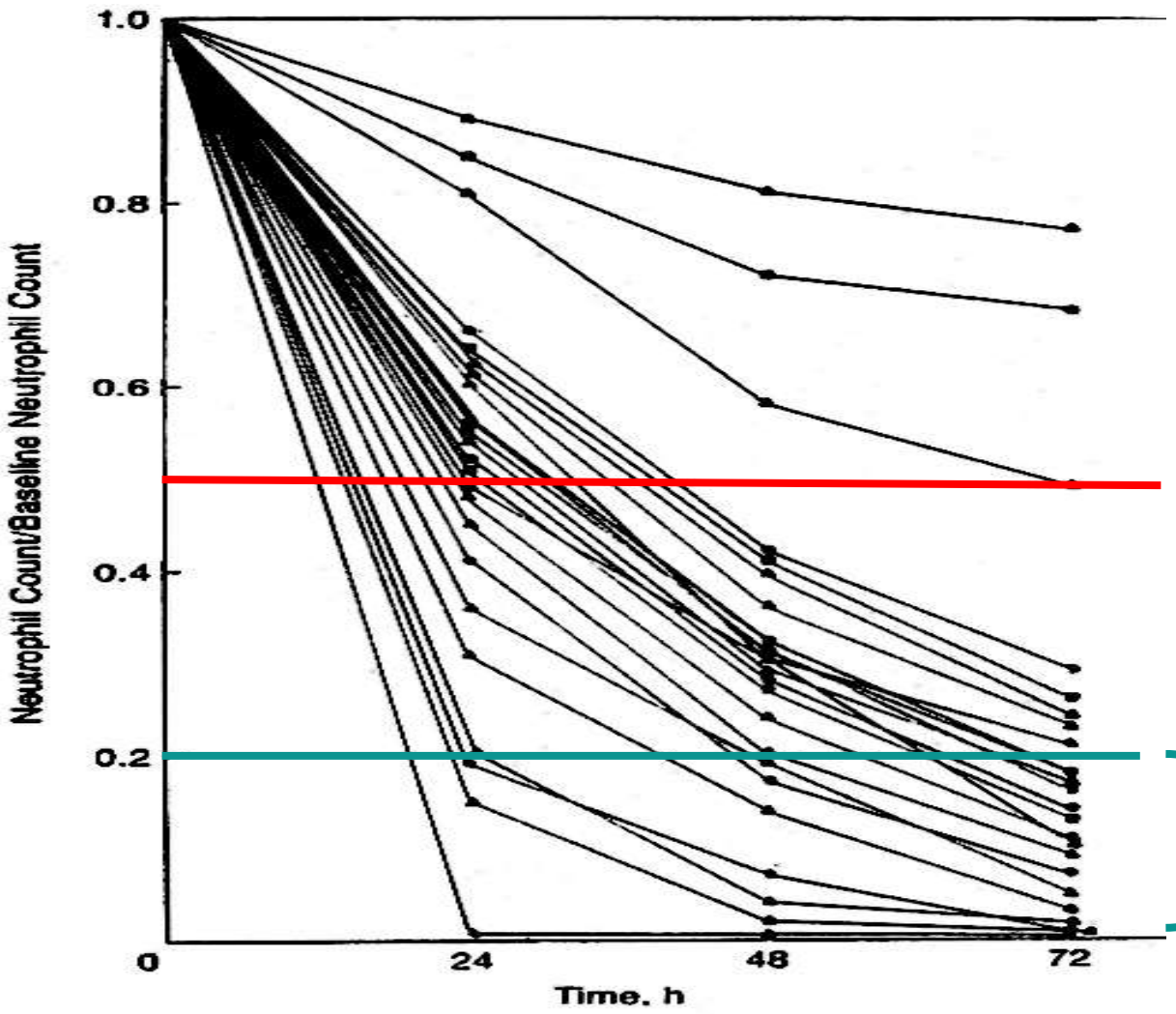
- BSG: In patients with SBP and an increased/rising serum creatinine

Aithal et al. Gut 2021;70:9–29

Biggins et al. AASLD guidance. Hepatology 2021:74:1014-1048

SBP = spontaneous bacterial peritonitis

A repeat ascites PMN count 48 hours after antibiotic initiation is of therapeutic and prognostic significance



Failure of therapy is defined as decrease in PMN <25% from baseline

Biggins, AASLD guidance 2021

- Check on culture results
- Investigate secondary peritonitis (abdominal film, CT scan)
- Broaden antibiotic spectrum

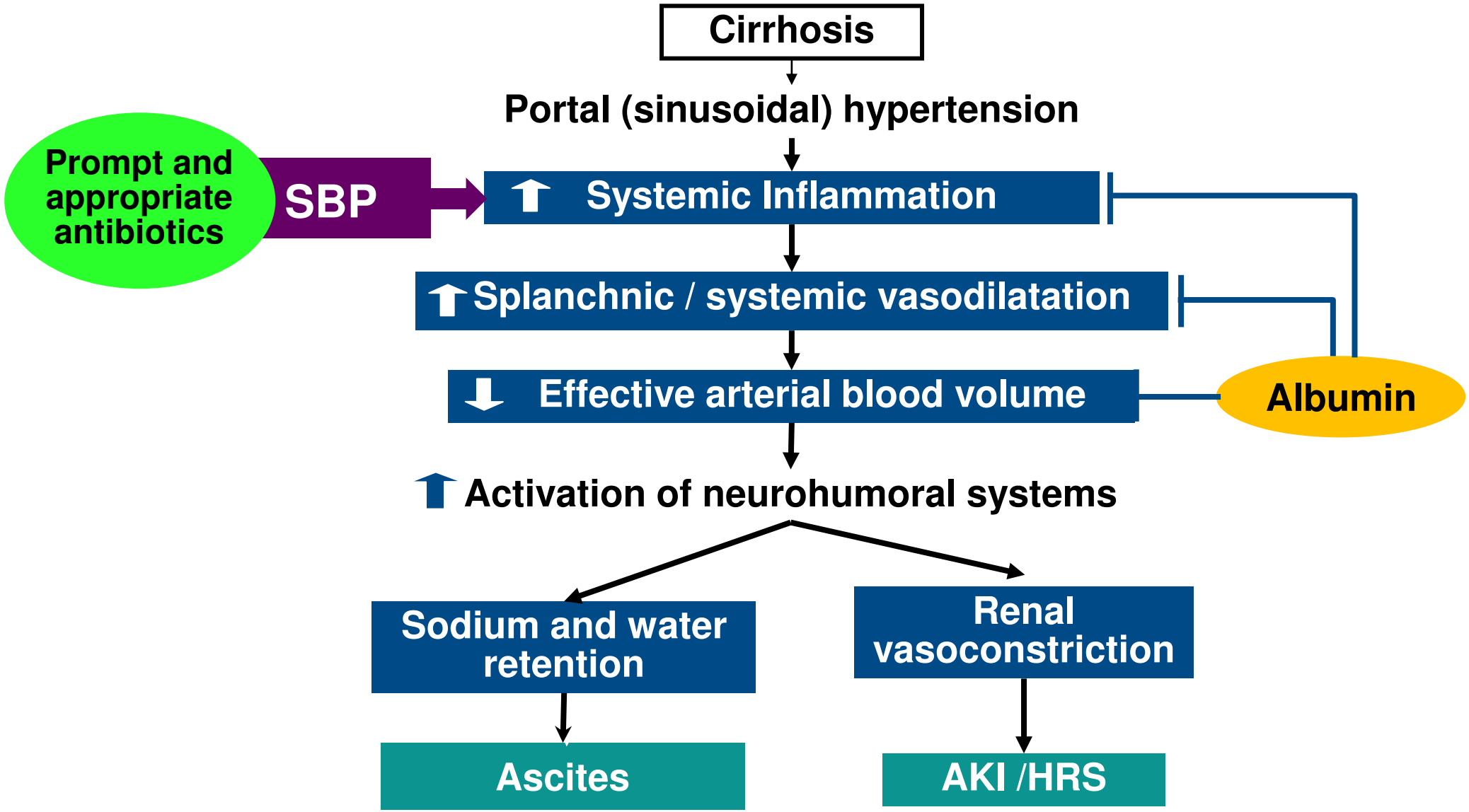
Ascites PMN decreases by at least 50% at day 2 after starting antibiotics.

A decline in PMN cell count > 80% predicted improved in-hospital survival (aOR 0.32, 95% CI 0.17-0.59) independent of cirrhosis severity.

Saffo et al. CGH 2021 [ePub ahead of print]

Runyon and Hoefs. Arch Intern Med 1986.

SBP is a frequent precipitant of acute kidney injury (AKI) and hepatorenal syndrome (HRS)



How should albumin be administered in patients with SBP/non-SBP infections?

- Dose of albumin used in patients with SBP (*Sort et al. NEJM 1999*) was empirical (1.5 g/Kg day at day 1 → 1 g/Kg day at day 3) and this dose is recommended in recent AASLD guidelines (2021)
- Albumin did not improve renal function or survival in non-SBP infections and led to pulmonary edema (*Thevenot et al. J Hep 2015*)
- Main predictor of death in SBP and non-SBP infections is the presence of AKI
- It would appear sensible to guide administration of albumin based on the presence/course of AKI (per Ascites Club criteria)

Serum creatinine (sCr) is used in the diagnosis of acute kidney injury (AKI) in cirrhosis but criteria have changed

The Old	**An increase in sCr ≥ 1.5 mg/dl (133 mmol/L)**

Arroyo et al (International Ascites Club). Hepatology 1996;23:164-76

The New **(based on KDIGO criteria)**	**a) An absolute increase in sCr ≥ 0.3 mg/dl (26.5 mmol/L) within 48 hours** ***and/or*** **b) Urinary output ≤ 0.5ml/Kg BW ≥ 6 hours (urinary catheterization)** ***or*** **b) Percent increase in sCr ≥ 50% within 3 months using the last available value of sCr**

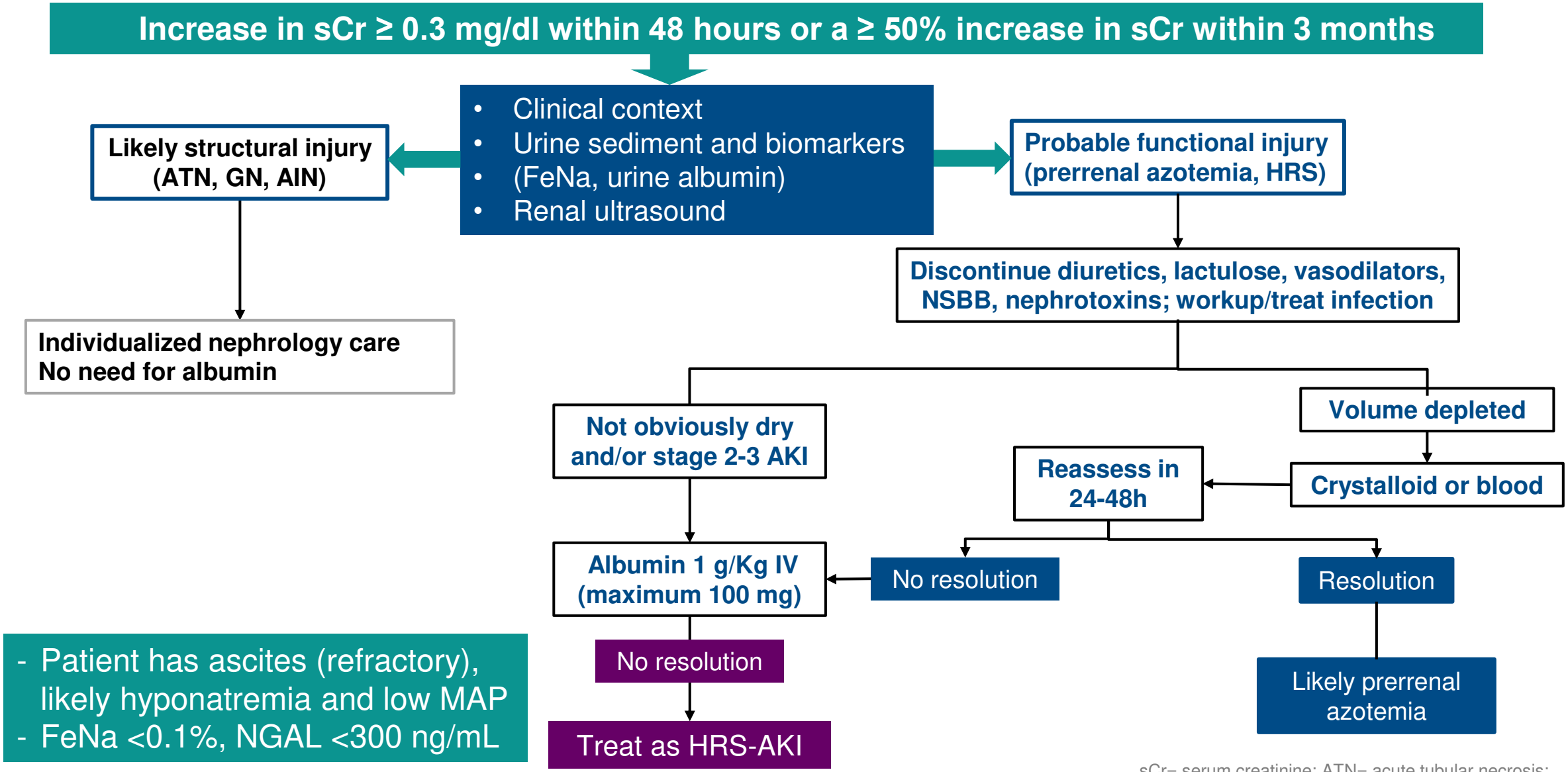
Angeli, Garcia-Tsao, Nadim, Parikh. J Hepatol 2019;71:811-822

Main differential among causes of AKI in cirrhosis

- **Pre-renal**: renal hypoperfusion without glomerular or tubular damage
  - **Prerrenal azotemia (most common)**
  - **Hepatorenal syndrome (HRS-AKI*)** is a type of pre-renal AKI that is unique to patients with cirrhosis and has the worst prognosis
- **Intra-renal**: acute tubular necrosis, interstitial nephritis or glomerulo-nephritis
- **Post-renal**: urinary tract obstruction (least common)

**Renamed from HRS-1 per Angeli, Garcia-Tsao, Nadim, Parikh. J Hepatol 2019;71:811-822*

Once AKI is diagnosed, it should be worked-up and treated as soon as possible

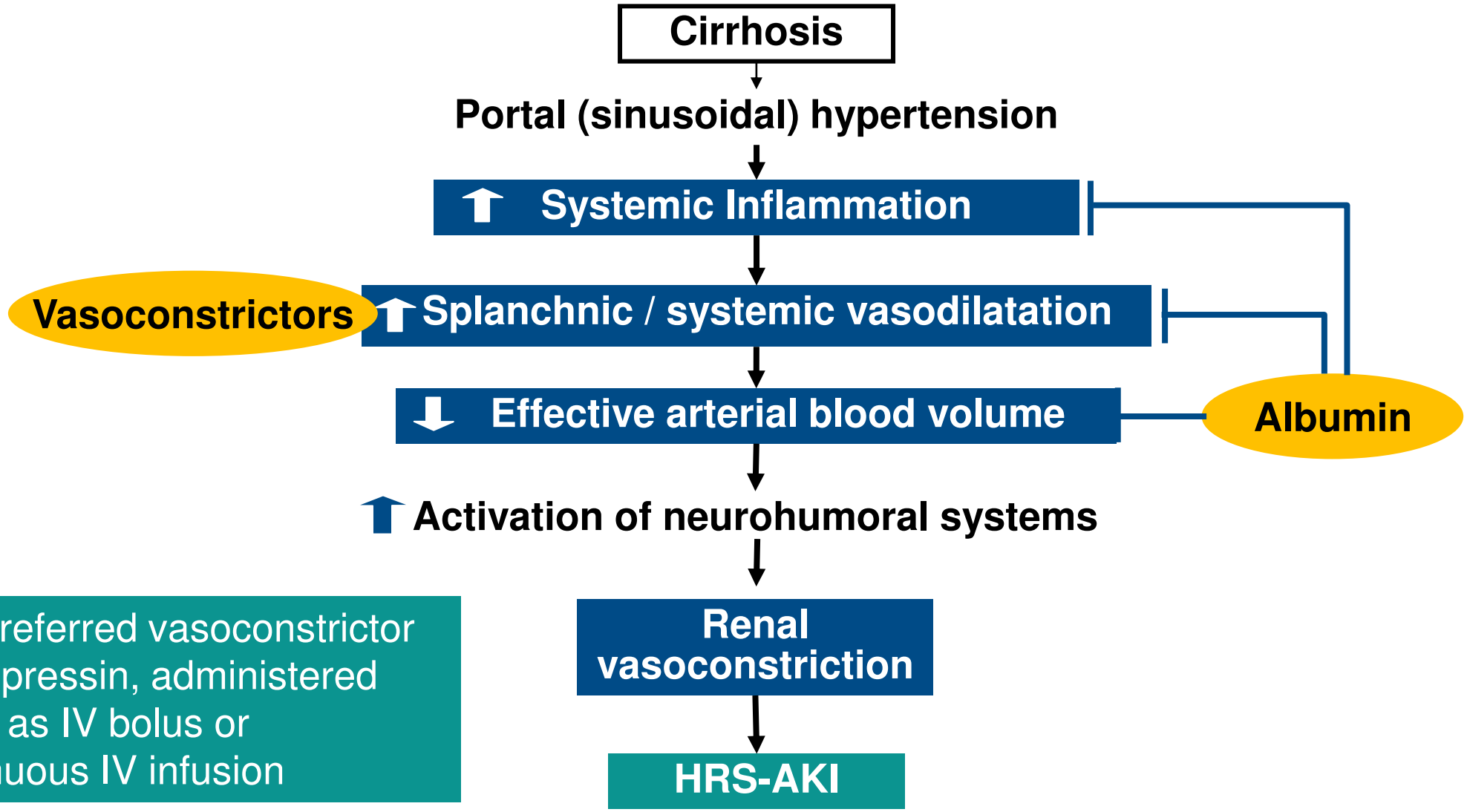


- Patient has ascites (refractory), likely hyponatremia and low MAP
- FeNa <0.1%, NGAL <300 ng/mL

Angeli, Garcia-Tsao et al. J Hepatol 2019;71:811-822; Biggins et al. AASLD guidance.Hepatology 2021;74:1014

sCr= serum creatinine; ATN= acute tubular necrosis; GN=glomerulonephritis; AIN=acute interstitial nephritis

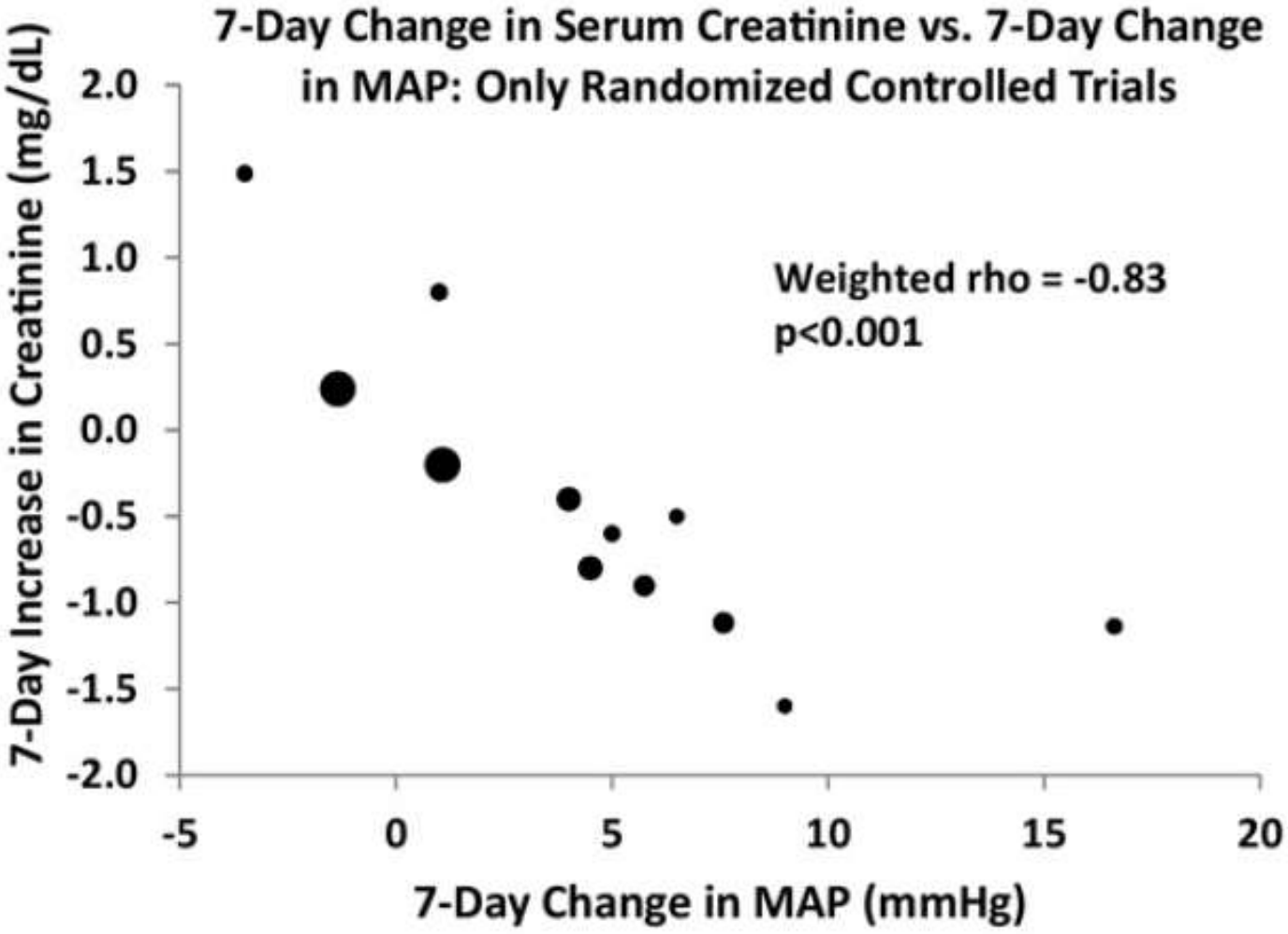
The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin



The preferred vasoconstrictor is terlipressin, administered either as IV bolus or continuous IV infusion

Biggins et al. AASLD guidelines. Hepatology 2021;74:1014-1048

In a pooled analysis of trials*, an increase in MAP was strongly associated with a decrease in creatinine



Velez and Nietert . Am J Kidney Dis. 2011 ;58:928-38

*using terlipressin as vasoconstrictor

In patients with HRS*, terlipressin was more effective than placebo in improving renal function but had more severe adverse events

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	

Verified HRS reversal= two consecutive creatinine values ≤1.5 mg/dl at least 2 hours apart, and surviving without dialysis for at least 10 days

- Death within 90 days due to respiratory disorders occurred in 11% on terlipressin vs. 2% on placebo
- At baseline, serum albumin levels were high (3.7 g/dL terli; 4.0 g/dL placebo). While on therapy, patients received more IV albumin (199 g in terli group; 240 g in placebo group)

Wong et al. CONFIRM study. NEJM 2021;384:818-828

*Defined as a creatinine >2.25 mg/dL

In a RCT, hospitalized patients with cirrhosis randomized to targeting serum albumin to a level >=3.0 mg/dL was not more beneficial than standard-of-care

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)	

China et al. ATTIRE study. NEJM 2021;384:808-817

Intravenous albumin targeted at a serum level >= 30 g was associated with 10X the amount of albumin infused and more pulmonary edema/fluid overload

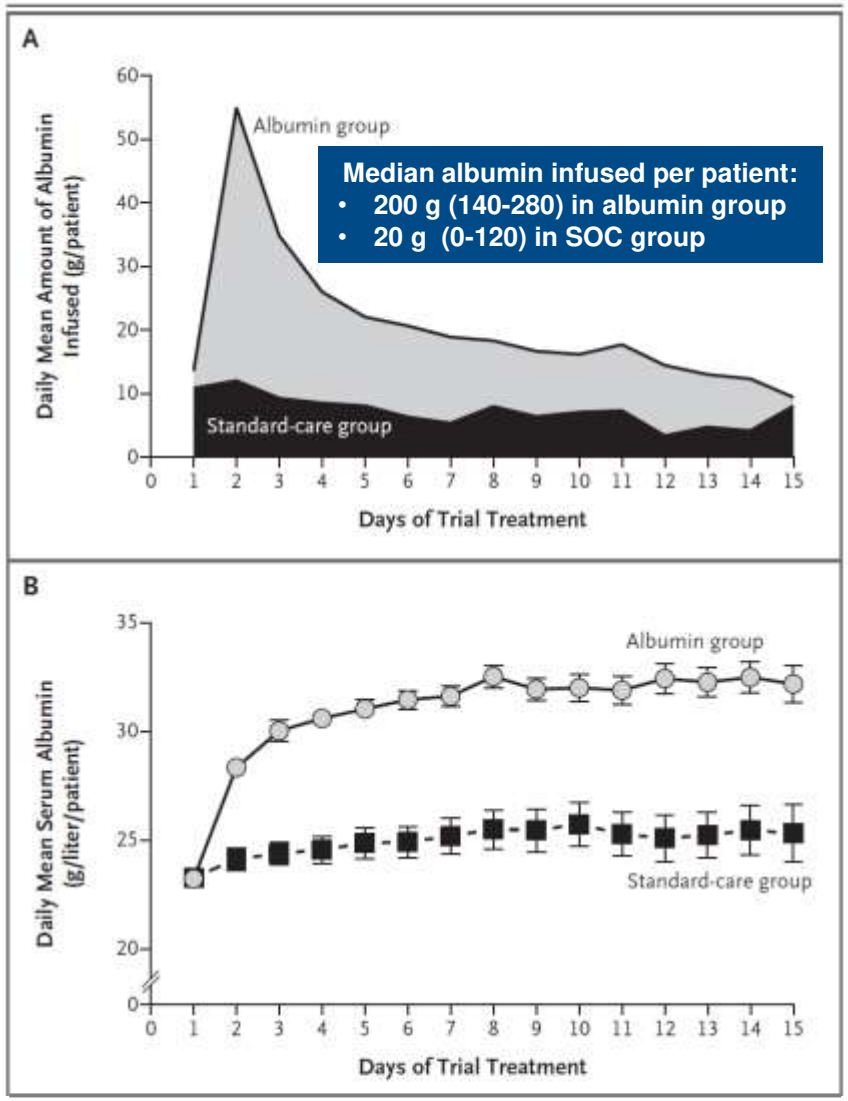


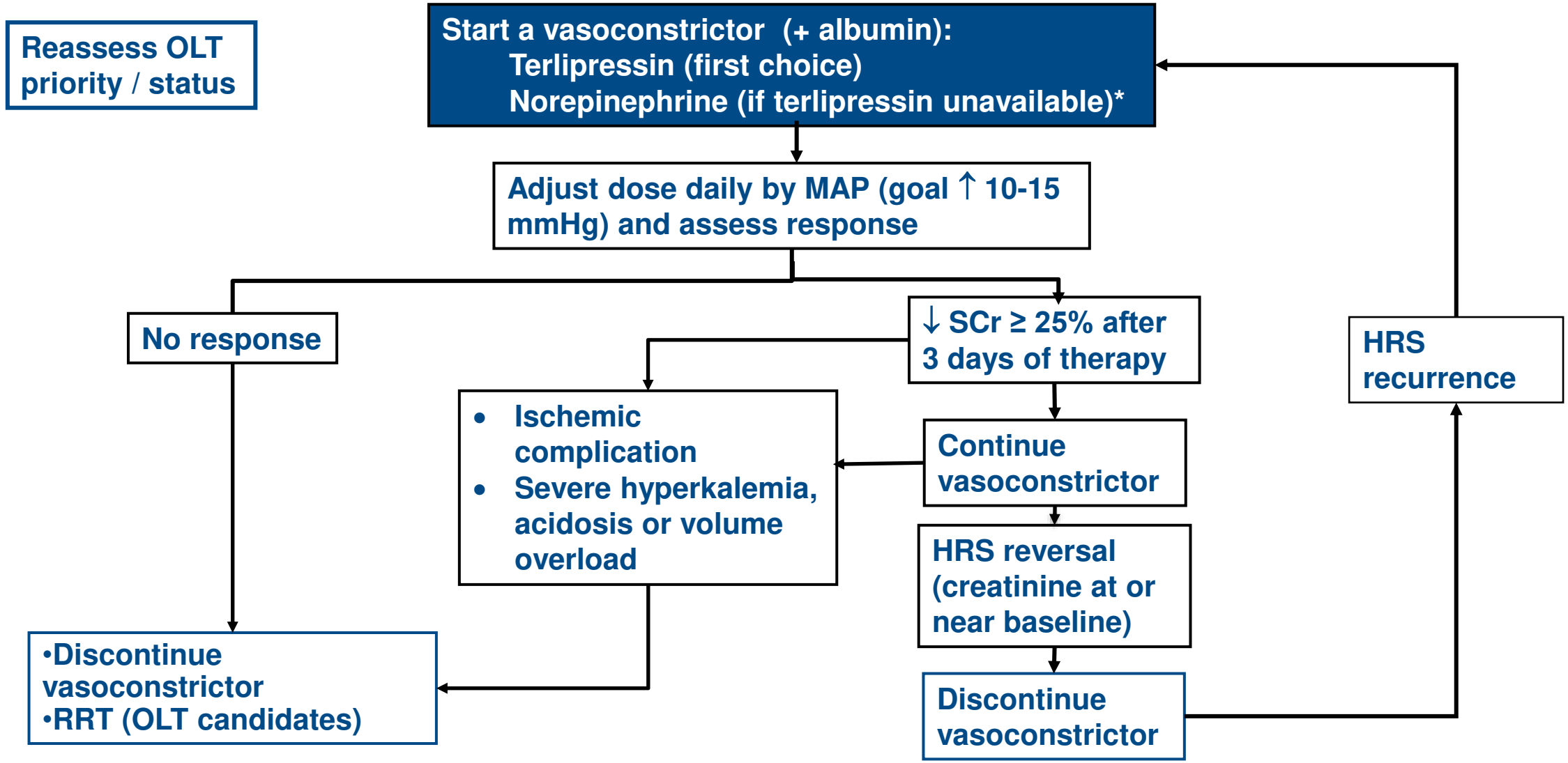
Table 3. Serious Adverse Events.*

Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
	number of events		
Serious adverse event			
Grade 3: severe event	28	11	39
Grade 4: life-threatening event	17	13	30
Grade 5: death	42	48	90
All events	87	72	159
Individual serious adverse events occurring in >1 patient†			
Anemia	1	1	2
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Multiorgan f			54
Other infecti			5
Lung infecti			23
Sepsis			7
Encephalopa			5
Acute kidney			2
Adult respiratory distress syndrome	0	2	2
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
All serious adverse events that included pulmonary edema or gastrointestinal bleeding†			
Any pulmonary edema or fluid overload	23	8	31
Any gastrointestinal bleeding	11	13	24

Validation of noninvasive methods to assess blood volume will be important in the management of patients with decompensated cirrhosis receiving albumin, particularly when combined with terlipressin

China et al. ATTIRE study. NEJM 2021 [ePub ahead of print]

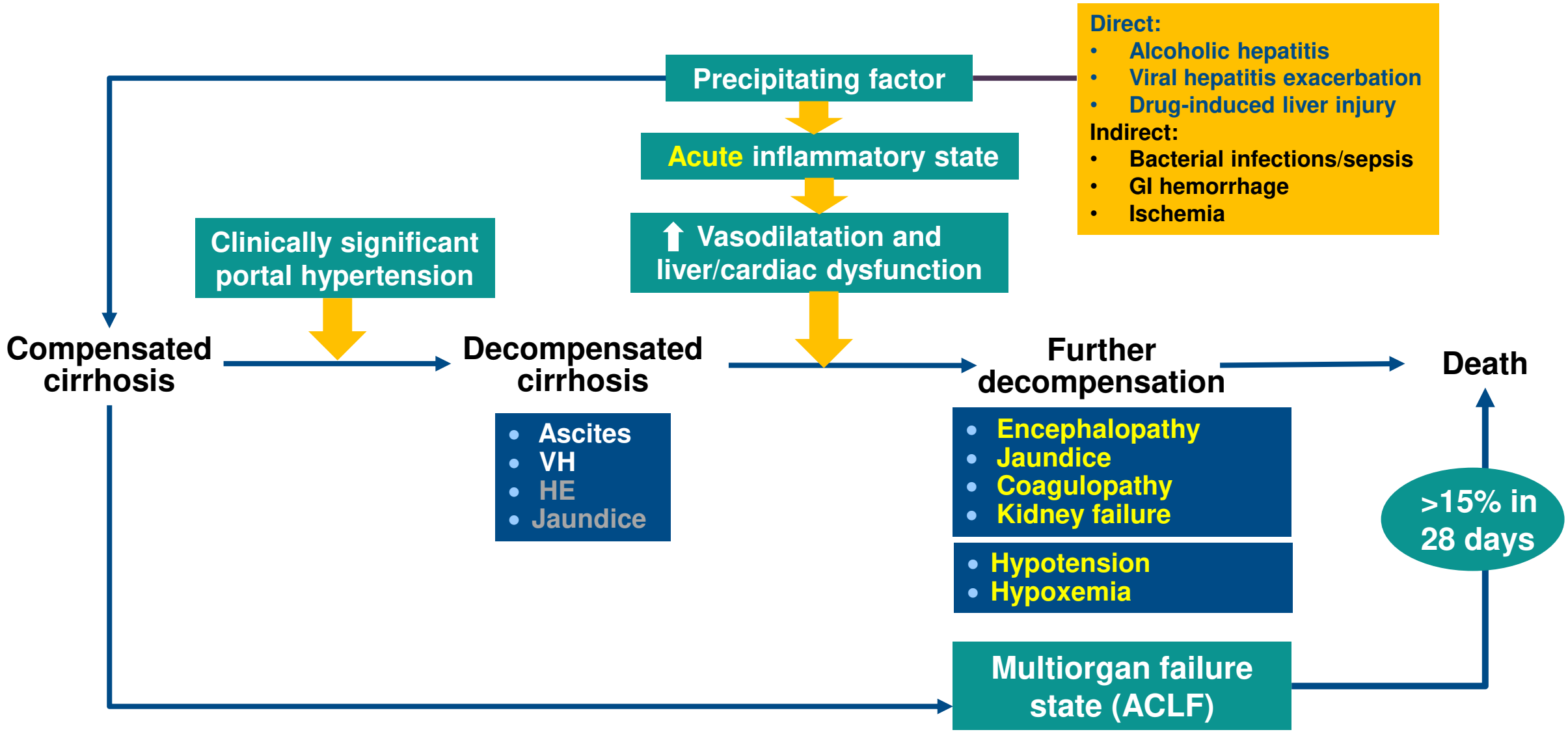
Management algorithm in patient with suspected HRS



*If neither terlipressin or norenephrine can be administered, a trial of oral midodrine in combination with octreotide may be considered

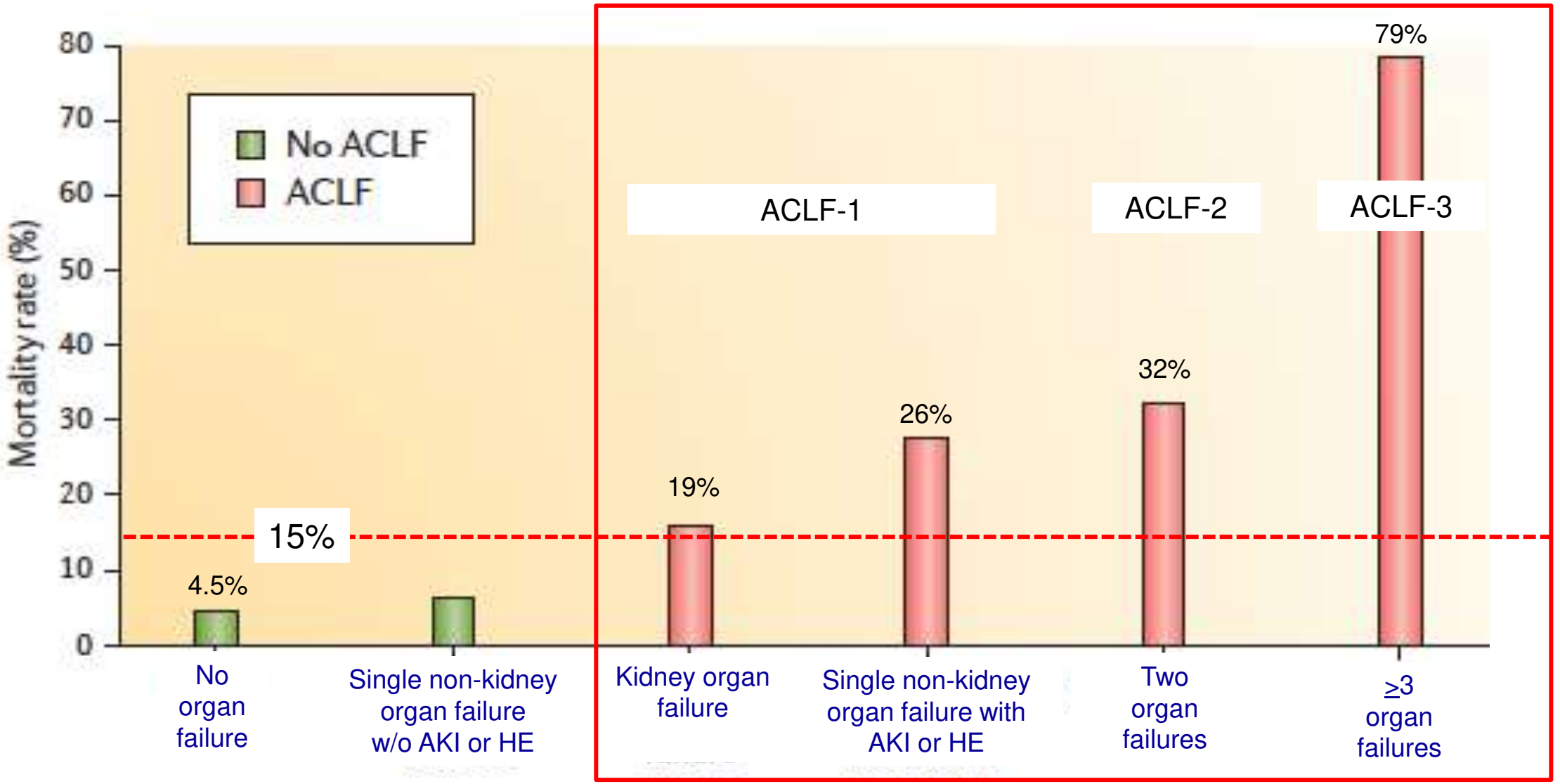
Biggins et al. AASLD guidance 2021

ACLF is an entity that occurs in hospitalized patients with cirrhosis and that is associated with a poor 30-day survival



ACLF= acute-on-chronic liver failure; VH = variceal hemorrhage; HE = hepatic encephalopathy; HRS=hepatorenal syndrome

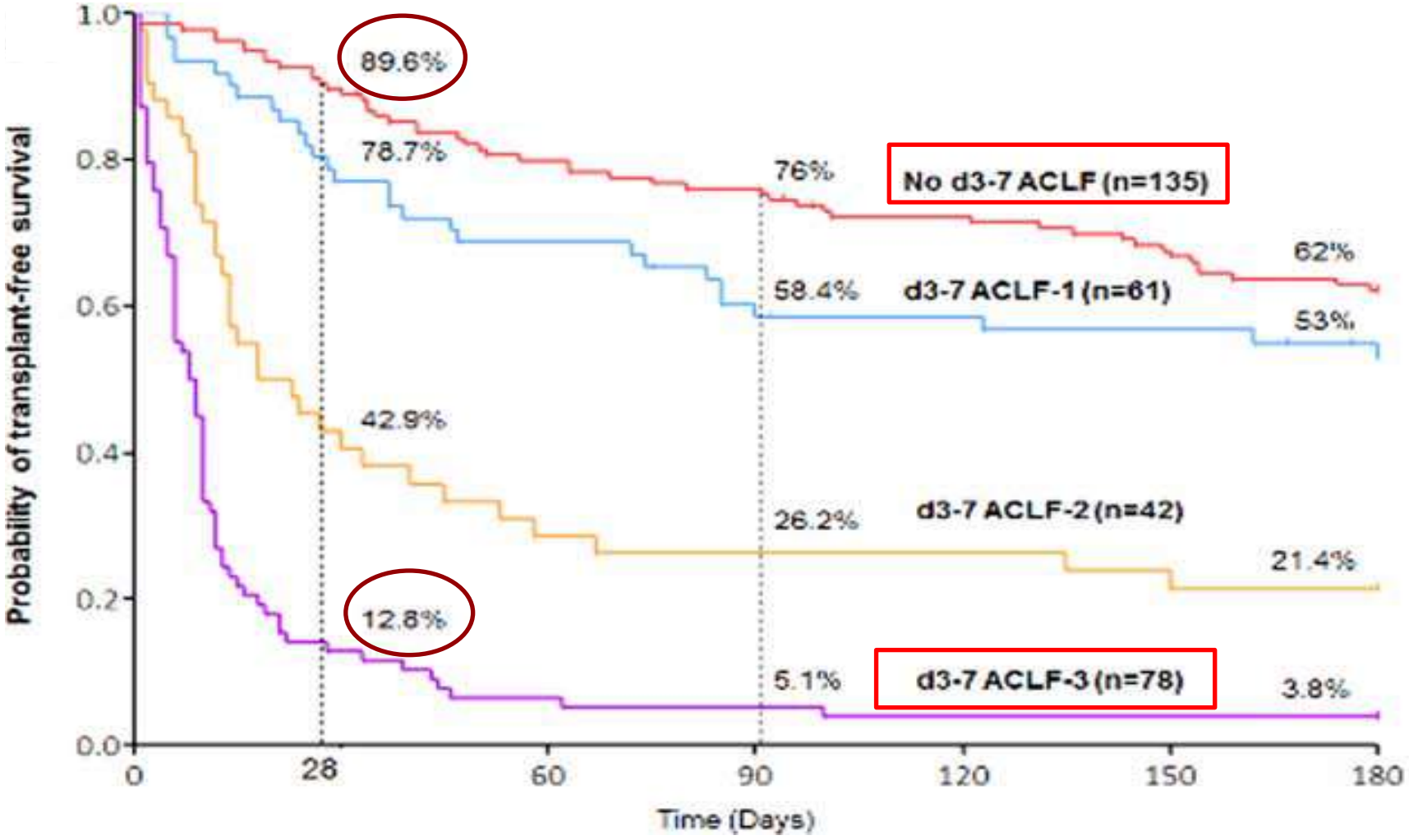
Not unexpectedly, the number of organ failures correlate directly with an increasingly higher 28-day mortality (EASL-CLIF)



n = 1,343

Moreau et al. Gastroenterology 2013;144:1426–1437

Short-term mortality in ACLF is more accurately predicted by its clinical course in the first 3 – 7 days

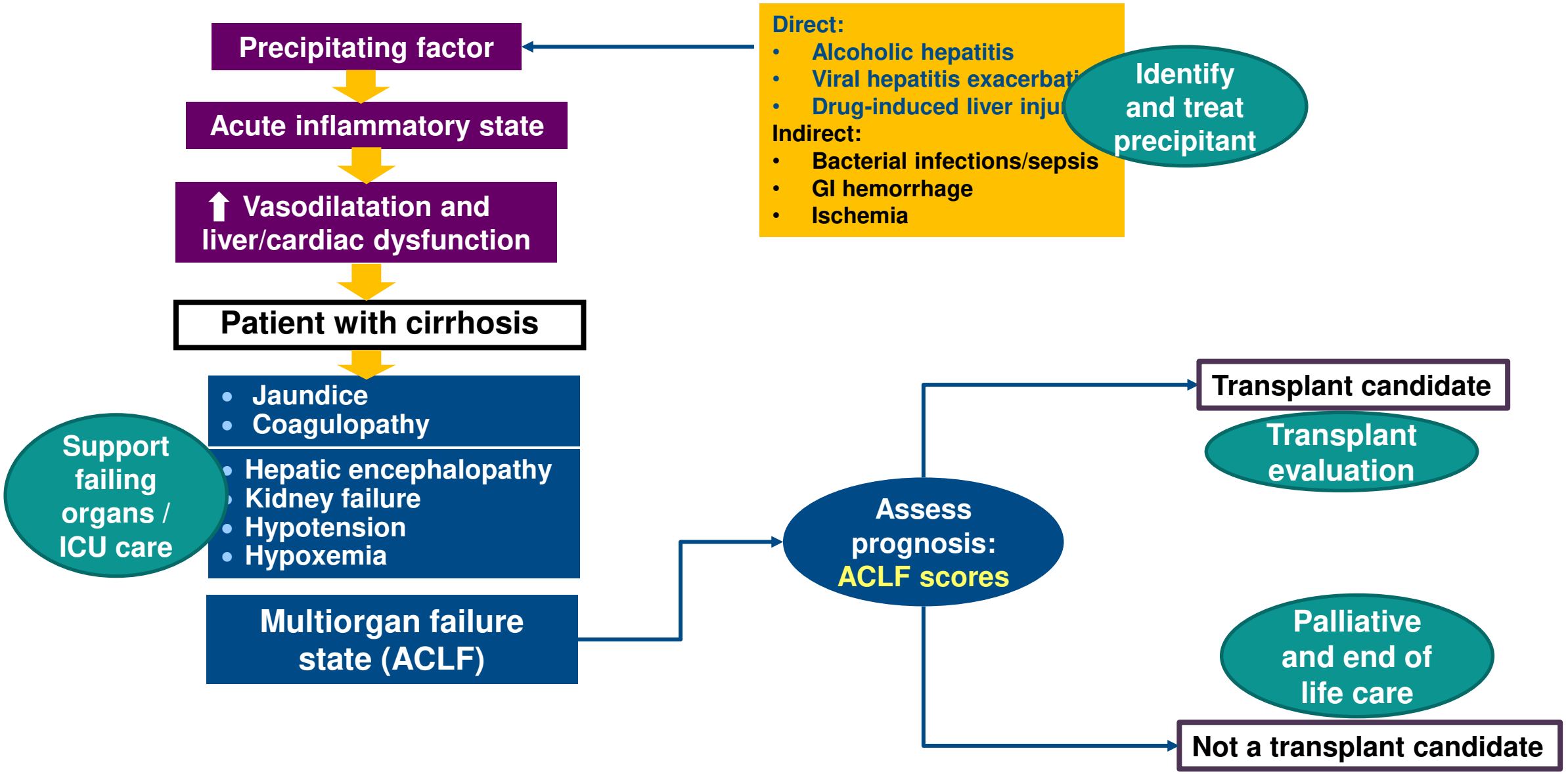


Among patients with ≥4 organ failures, or CLIF-C ACLFs score >64 at days 3-7, mortality was 100%

N=388

Gustot et al. Hepatology 2015;62:243-252

Management of ACLF is non-specific and based on support of organ failures



ACLF= acute-on-chronic liver failure; ICU=intensive care unit

Inpatient Management of Decompensated Cirrhosis

- The main decompensating events are ascites and variceal hemorrhage
- In patients with acute variceal hemorrhage, think of pTIPS candidacy at time of admission (mainly Child C patients 10-13 points)
- A diagnostic paracentesis (to rule out SBP) should be performed with each non-elective admission and with the development of symptoms (abdominal pain, fever) or any complication (AKI, encephalopathy)
- Be cautious about excessive albumin infusion in hospitalized patients
- ACLF is a multiorgan failure state in cirrhosis and its staging is of prognostic value and can inform future management