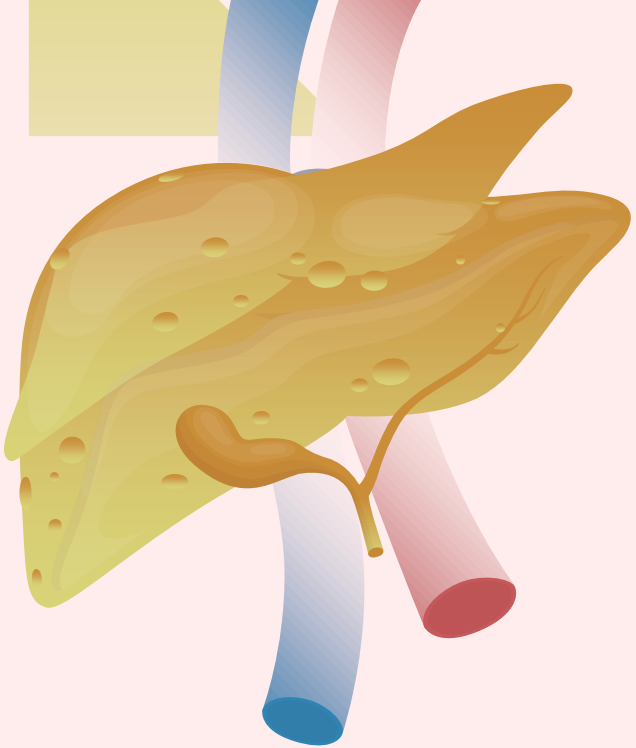


# Complications of Liver Cirrhosis

Dr Pascal Werimo Kuka
MMed, MRCP(UK)
Gastroenterology Fellow
Charlotte Maxeke/ Wits Donald Gordon Hospitals - Johannesburg

WITS UNIVERSITY

Project ECHO

AASLD

EASL

bsg BRITISH SOCIETY OF GASTROENTEROLOGY

APAGE

THE LANCET
Gastroenterology & Hepatology

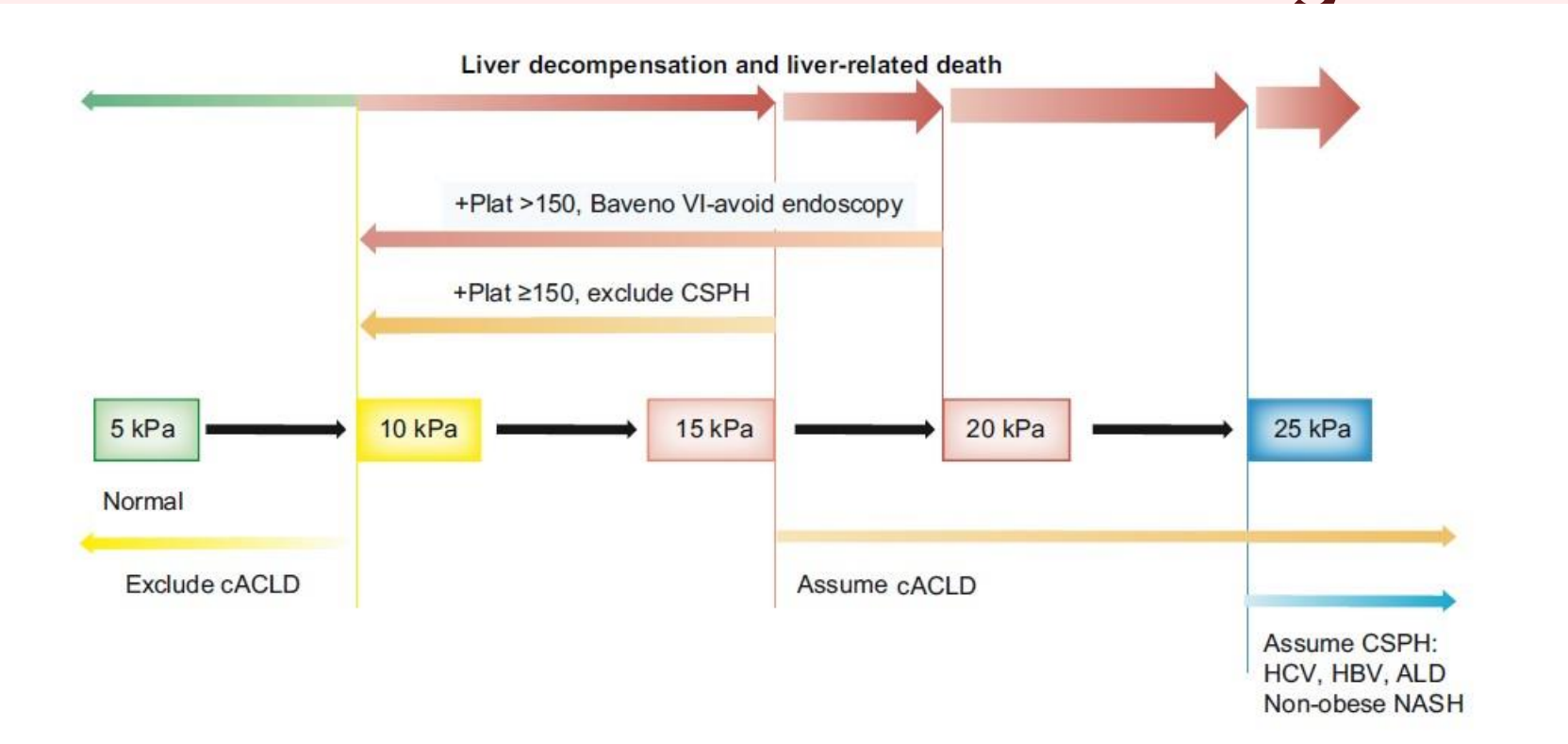
# Managing cirrhosis with limited resources: perspectives from sub-Saharan Africa

Mark W Sonderup, MMed [a] · Prof Patrick S Kamath, MD [b] · Yaw A Awuku, FWACP [c] · Prof Hailemichael Desalegn, PhD [d] · Neliswa Gogela, MPhil [a] · Leolin Katsidzira, DPhil [e] · Prof Christian Tzeuton, MD [f] · Bilal Bobat, FCP [g] · Chris Kassianides, FCP [h] · Prof C Wendy Spearman, PhD [a] on behalf of the Gastroenterology and Hepatology Association of sub-Saharan Africa Show less

# Baveno VII Consensus : Definitions

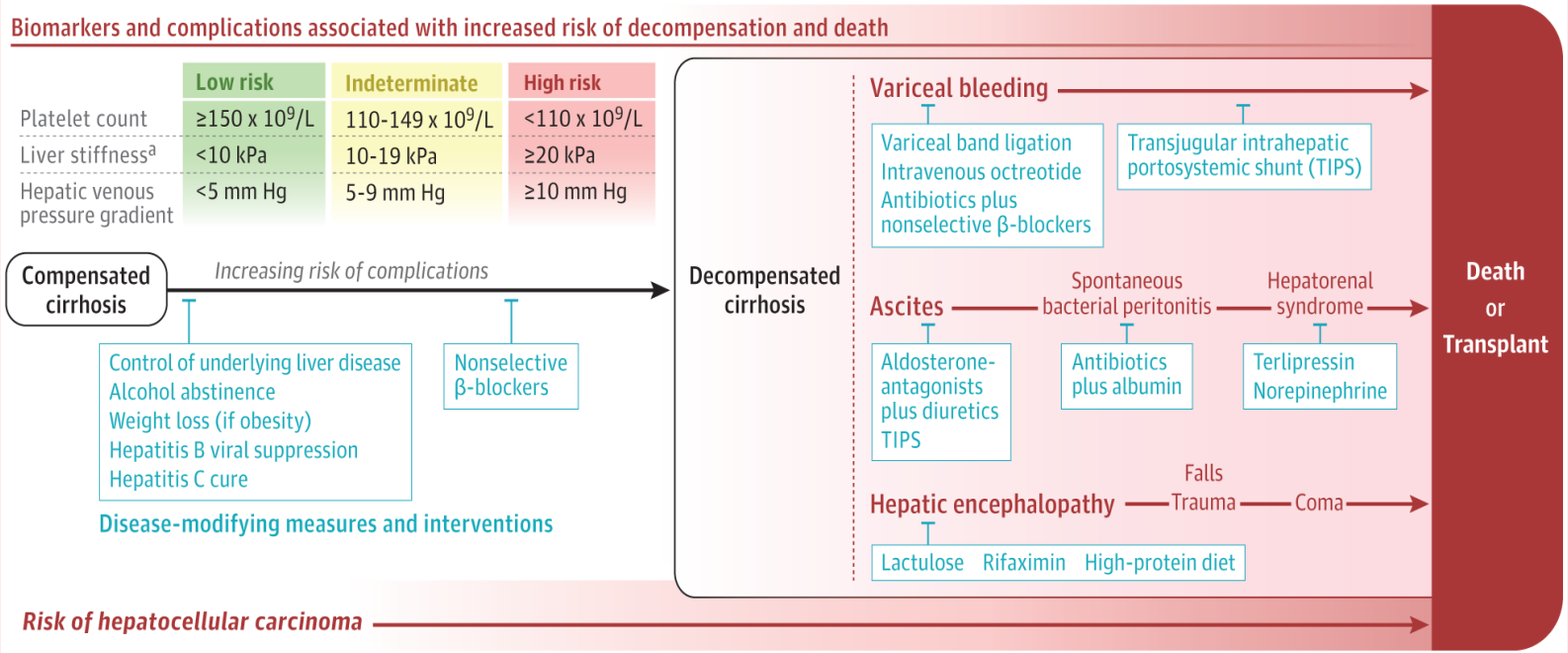
- Cirrhosis : Fibrotic changes and nodular regeneration of liver due to chronic insults
- Compensated advanced chronic liver disease : > 15 kPa liver stiffness. Divided into 2 depending of CSPH
    - Clinical significant portal hypertension : HVWP > 10 mmHG and Liver stiffness >25 kPA. Ruled out if T.E <15 kPA and Platelets > 150
- Decompensated cirrhosis : events – ascites, hepatic encephalopathy, GIT bleed
- Acute liver failure : jaundice (liver damage)  to encephalopathy (impaired function) in less than 28 weeks
    - Hyperacute : 7 days
    - Acute : 8 – 28 days
    - Subacute : 4 weeks to 28 weeks

# Liver stiffness and Cirrhosis Stage

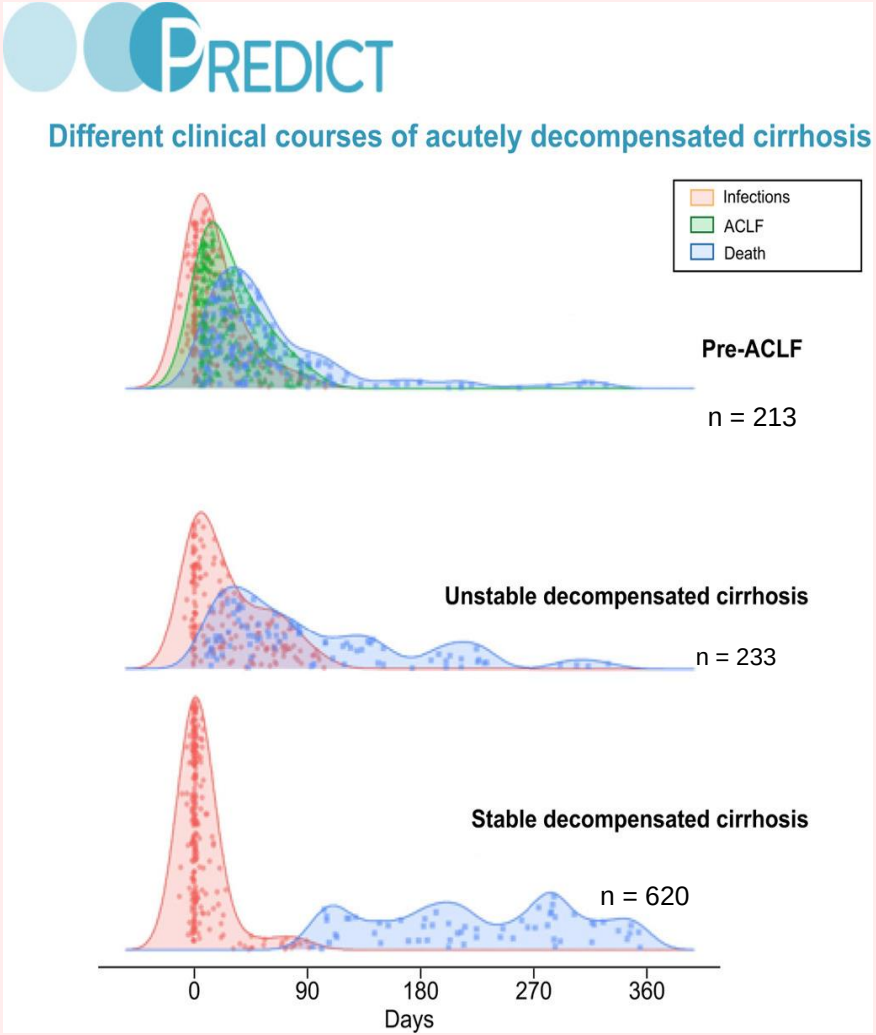



Baveno VII, 2021

# Course of Cirrhosis




Tapper. JAMA. 2023




3 groups of acute decompensation without ACLF

- PreACLF : CLIF C ACLF criteria within 90 days
- Unstable Decompensated cirrhosis : recurrent events
- Stable Decompensated Cirrhosis

2 major pathophysiology

- Systemic inflammation
- Portal hypertension

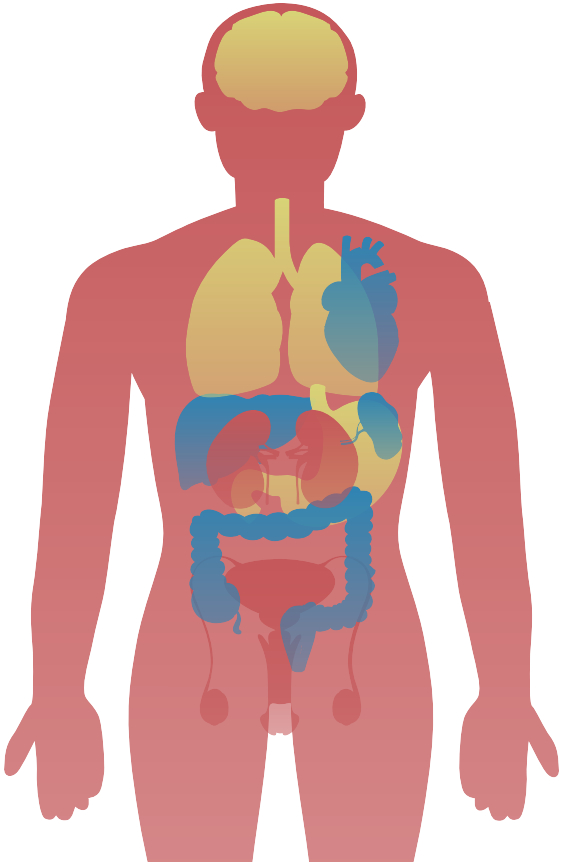
- Patient tailored approach in managing acute decompensation

Trebicka. JHepatology. 2020

# Complications of Cirrhosis

## Related to Portal Hypertension

- Ascites
- Varices
- Hepatic encephalopathy
- Cirrhotic cardiomyopathy
- Portopulmonary syndrome
- Hepatopulmonary syndrome
- Hepatorenal syndrome
- Portal hypertensive gastropathy
- Relative adrenal insufficiency



## Non - Portal Hypertension

- Altered drug metabolism
- Sarcopenia
- Frailty
- Hypogonadism
- Hyponatremia
- Coagulopathy
- Hepatocellular carcinoma

# Ascites

Mild : only detected by imaging

Moderate: symmetrical distension of the abdomen

Severe : marked distension

# Ascites

## Uncomplicated

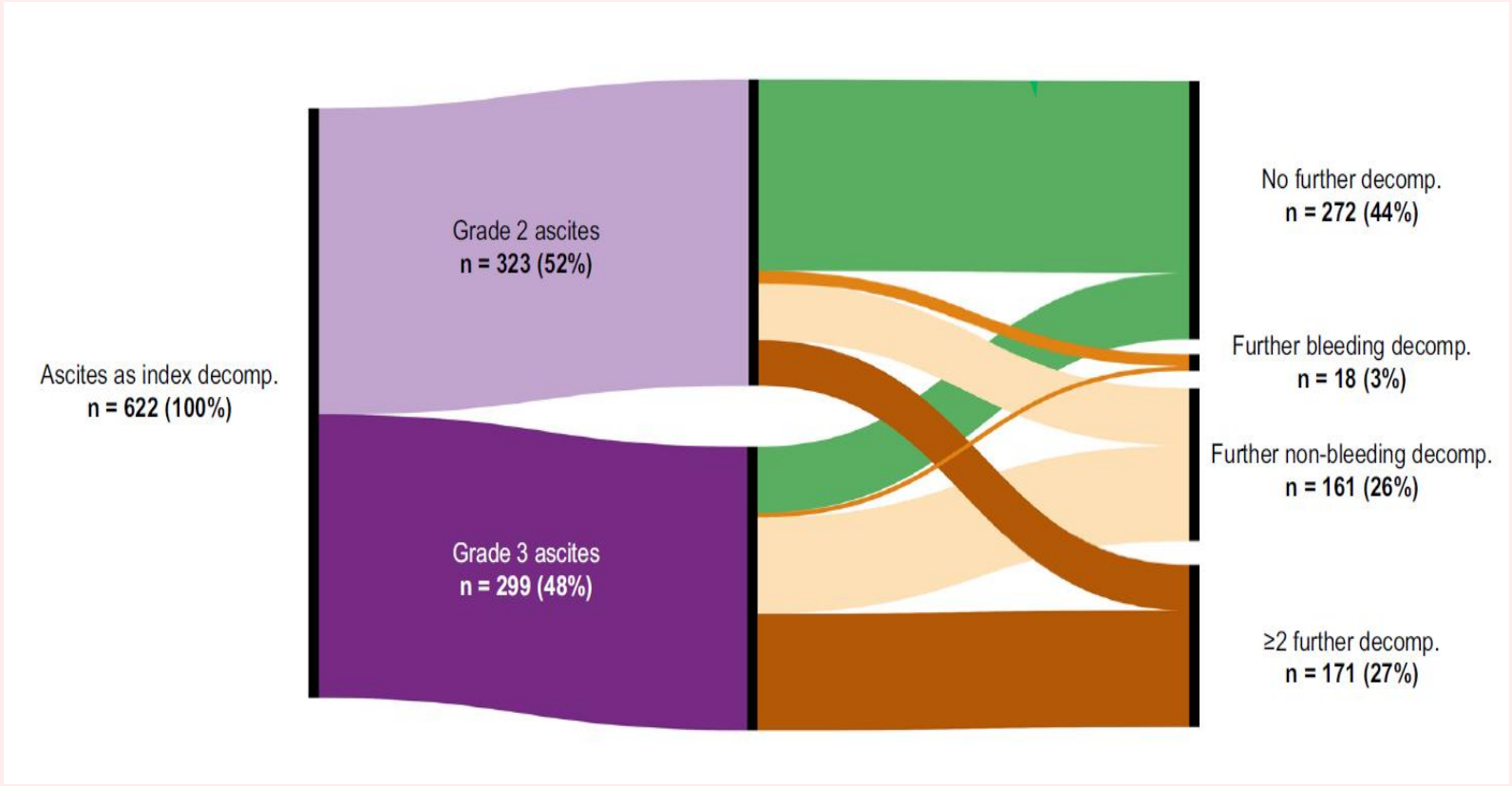
Not infected
Not associated with renal dysfunction

## Refractory - no mobilization or early recurrence (grade 2/3 within 4 weeks)

Diuretic resistant : refractory to dietary sodium restriction and intensive treatment

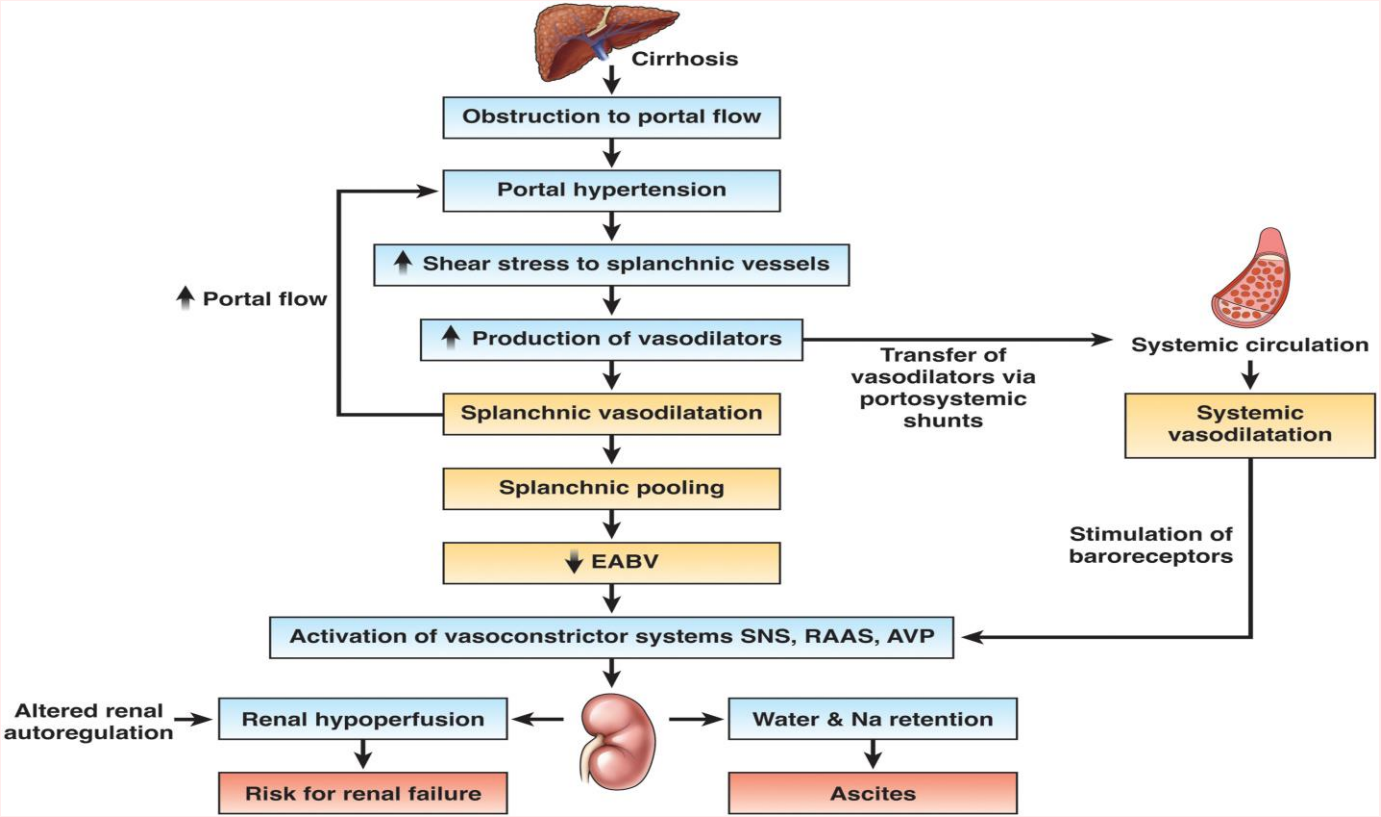
Diuretic intractable : treatment induced complications

BSG. Gut. 2021




Balcar. JHep.2022

# Pathophysiology of Ascites




EASL Guidelines …..decompensated cirrhosis. Jhepatol (2018)

# Evaluation of ascites

## Clinical evaluation

Features / risks of chronic liver disease

Shifting dullness

## Imaging

Ultrasound or CT scan : for mild ascites and other complications

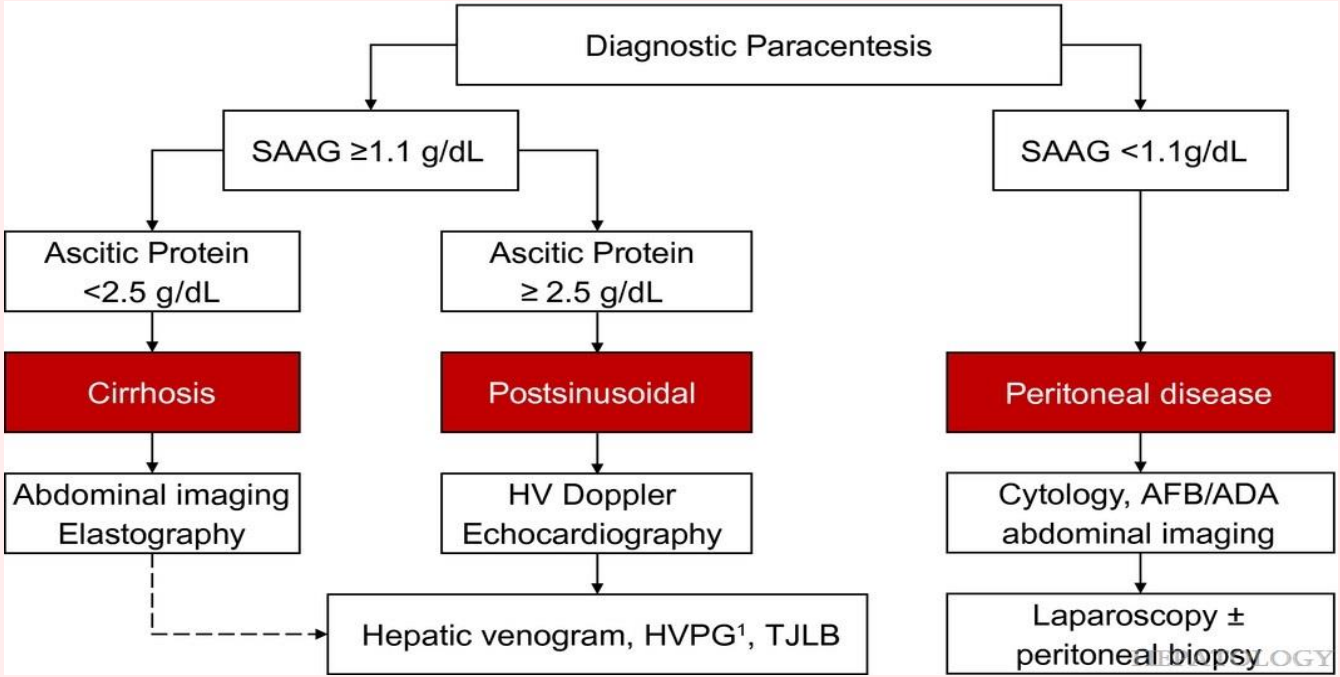
## Diagnostic paracentesis

- Cell count : PMN > 250 cells (SBP) . > 500 PMN (greater specificity)

  High levels ? Secondary infection

- Culture, Bacterial DNA detection
- Protein, albumin levels
- Cytology
- Triglycerides, amylase, lipase, BNP, ADA

# SAAG




Biggins, Hepatology. August 2021.

# Treatment of ascites

- Dietary salt restriction : no added salt or no precooked/ packaged meals

- Diuretics : symptomatic benefit. No modified natural history of ascites
  - Spironolactone : start dose 100 mg (max 400mg) titrated every 3 – 4 days
  - Amiloride : not recommended
  - Eplerenone : intolerance or gynecomastia
  - Furosemide : start 40 mg OD (max 160 mg OD)

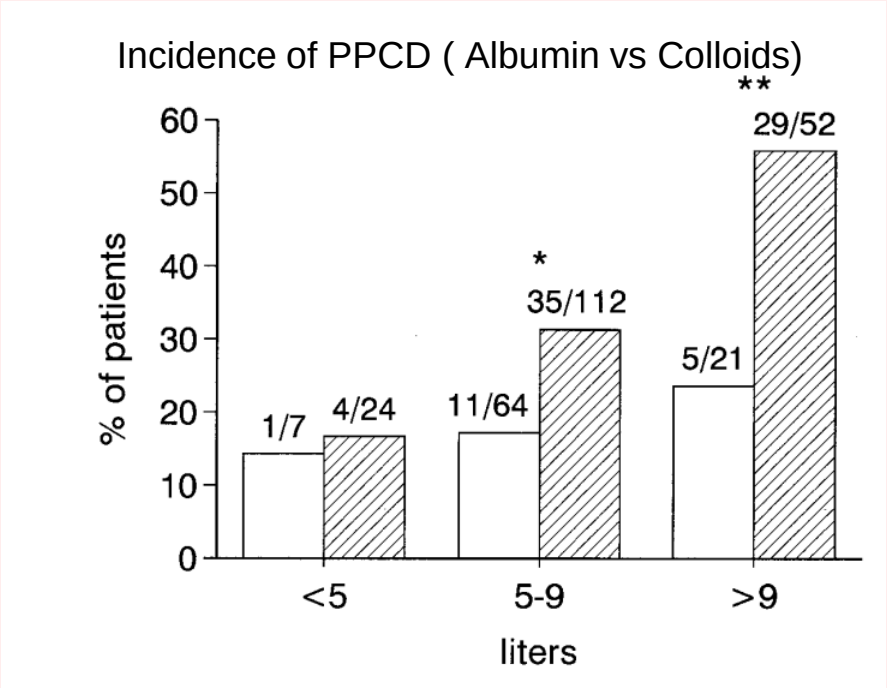
- Sequential vs Combination :  Rapid mobilization vs complications of therapy
  - Moderate ascites : Spironolactone monotherapy

  - Persistent or severe ascites : combination

- Targets : <0.5 kg/day – no edema ; <1 kg/day - edema

# Therapeutic paracentesis

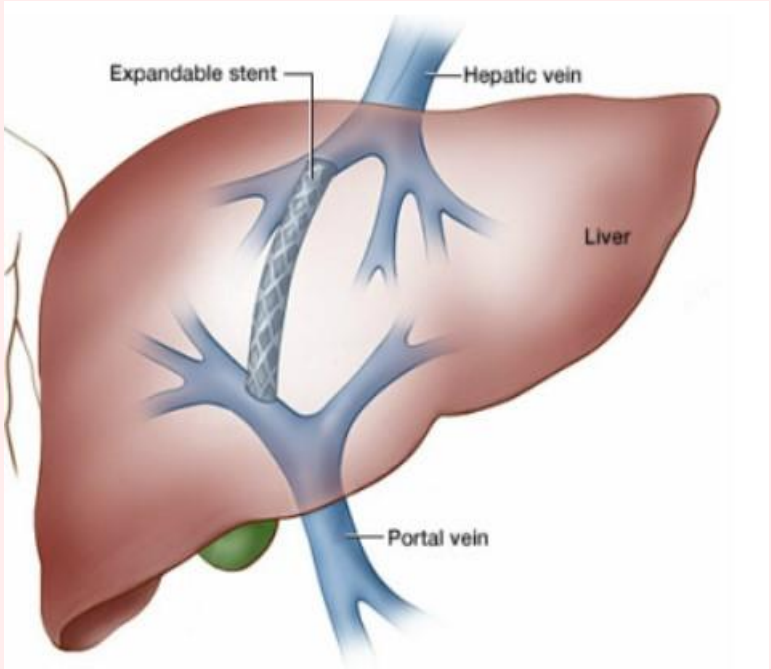
- Rapid mobilization.
- Large volume : 5 litres + Human albumin 6 – 8 g/litre
- Human albumin : if less than 5 liters
  - SBP
  - Renal impairment
  - Acute on chronic liver failure




Gines et al. Gastroenterology 1996

# TIPSS in Ascites

- Benefits : better control, improved QOL, improved nutrition status
- Complications : Hepatic encephalopathy, stent thrombosis, stenosis, availability
- Patient selection: caution in age >70, Platelets < 75, MELD > 18, Current H.E, infection, HRS
- Contraindication : heart failure, pulmonary hypertension




Aithal GP. Gut. 2021

# Spontaneous Bacterial Peritonitis

## Early diagnosis + treatment

Risk of mortality with delay

## Empiric antibiotics

Setting , Severity, Local resistance

## Albumin

## Diagnostic paracentesis

Neutrophils > 250 cells /mm
Risk factor : total protein < 15g/L

## Repeat diagnostic tap

48 hours (> 25% of neutrophil count reduction

Aithal GP. Gut. 2021

# SBP : primary vs secondary prophylaxis

- High risk : acute GI bleed, low ascitic protein, prior SBP

- Primary : Norfloxacin 400 mg OD
  - EASL : in CTP >9 , Bilirubin > 3 , Protein < 15g/L , Renal dysfunction
  - AASLD : Fluid protein < 15g/l + renal dysfunction
  - SSA : Ciprofloxacin use. Concern of long term antibiotics

  - Rifaximin : no role
- Secondary
  - Recurrence in 1 year – 70%, Survival decreased 25 – 30% at 2 year
  - Norfloxacin 400 mg OD or Ciprofloxacin

# Hepatic Hydrothorax

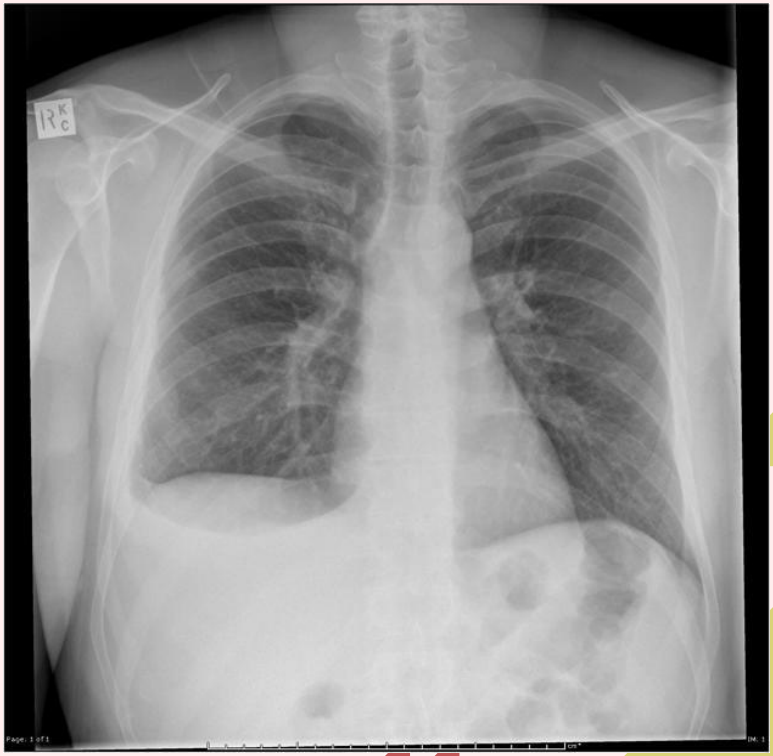
Transudate pleural fluid + raised Serum Pleural fluid Albumin gradient

Micro leaks in diaphragm defects

Poor prognosis : median survival 8 -12 months

Treatment : diuretics + paracentesis

Refractory : thoracocentesis / TIPSS / Liver transplant

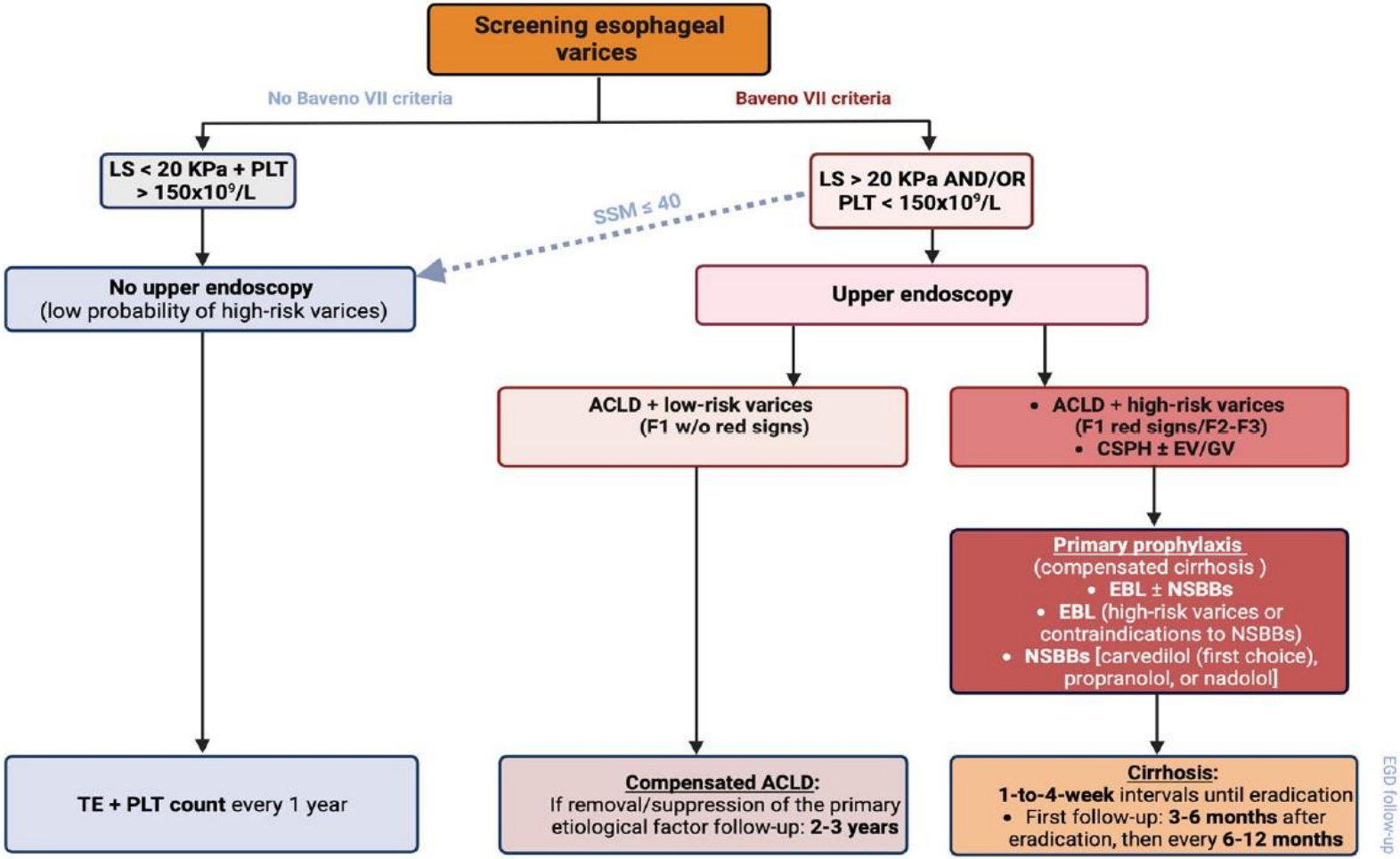


# GI Bleed in Cirrhosis

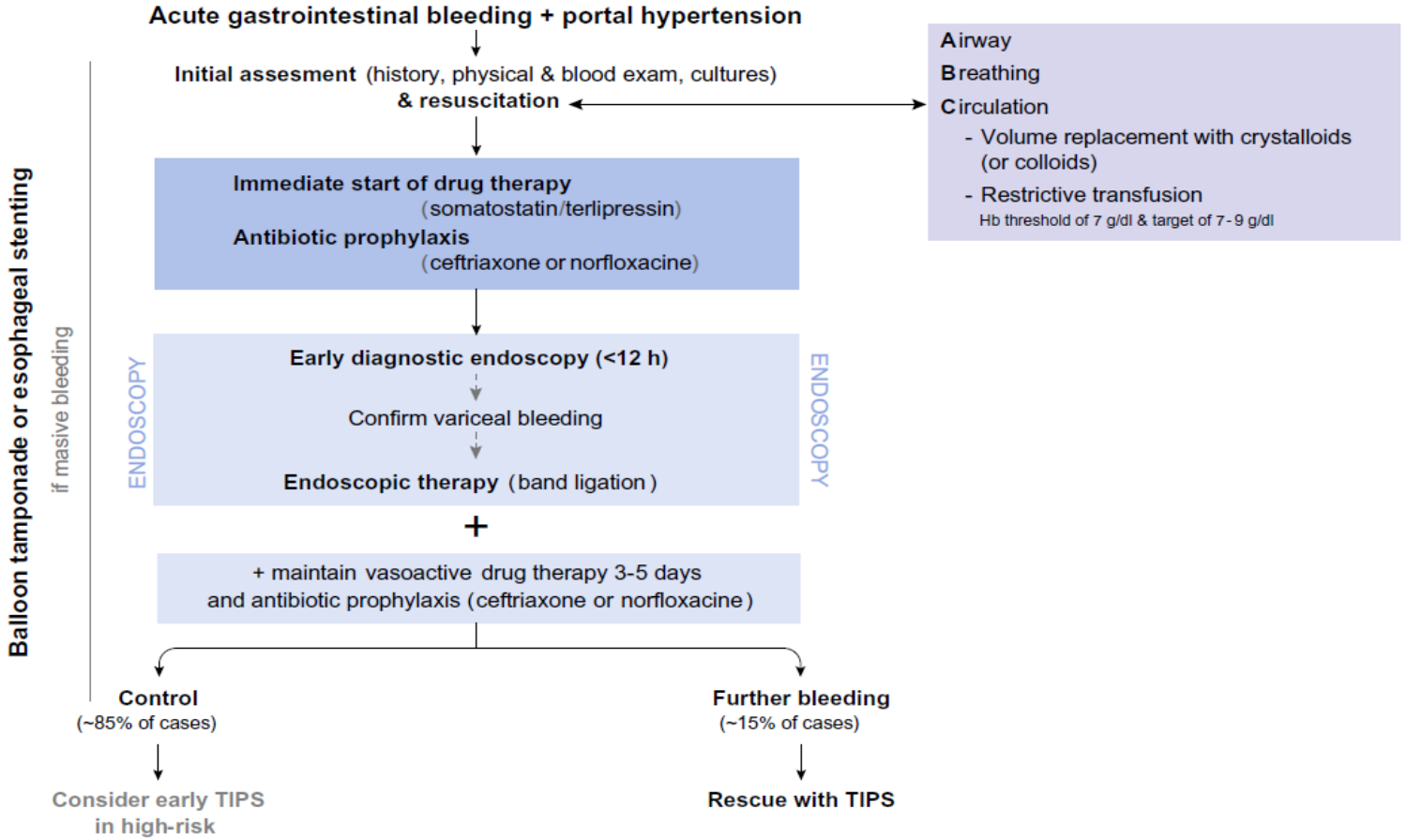
70 % of bleed in portal HTN : variceal

Risk of variceal bleed
CTP A : 42% , CTP B/C : 72%
Size of varices
Red wale signs

Progression from small to large varices: higher in CTP B/C, alcohol cirrhosis and in decompensation




Pallio, S.;Diagnostics.2023




EASL Guidelines …..decompensated cirrhosis. Jhepatol. 2018

# Secondary Prophylaxis GI Bleed : Baveno 7 consensus

- NSBB (Carvedilol, preferred) + Endoscopic band ligation

- TIPSS : if rebleed despite NSBB
  - Early preemptive : High risk  CP C or B>7 with active bleed at endoscopy (or HVWP > 20)
  - Salvage : if other methods don't control bleed

  - Ineffective without planned transplant in : CP > 14, MELD > 30, Lactate >12

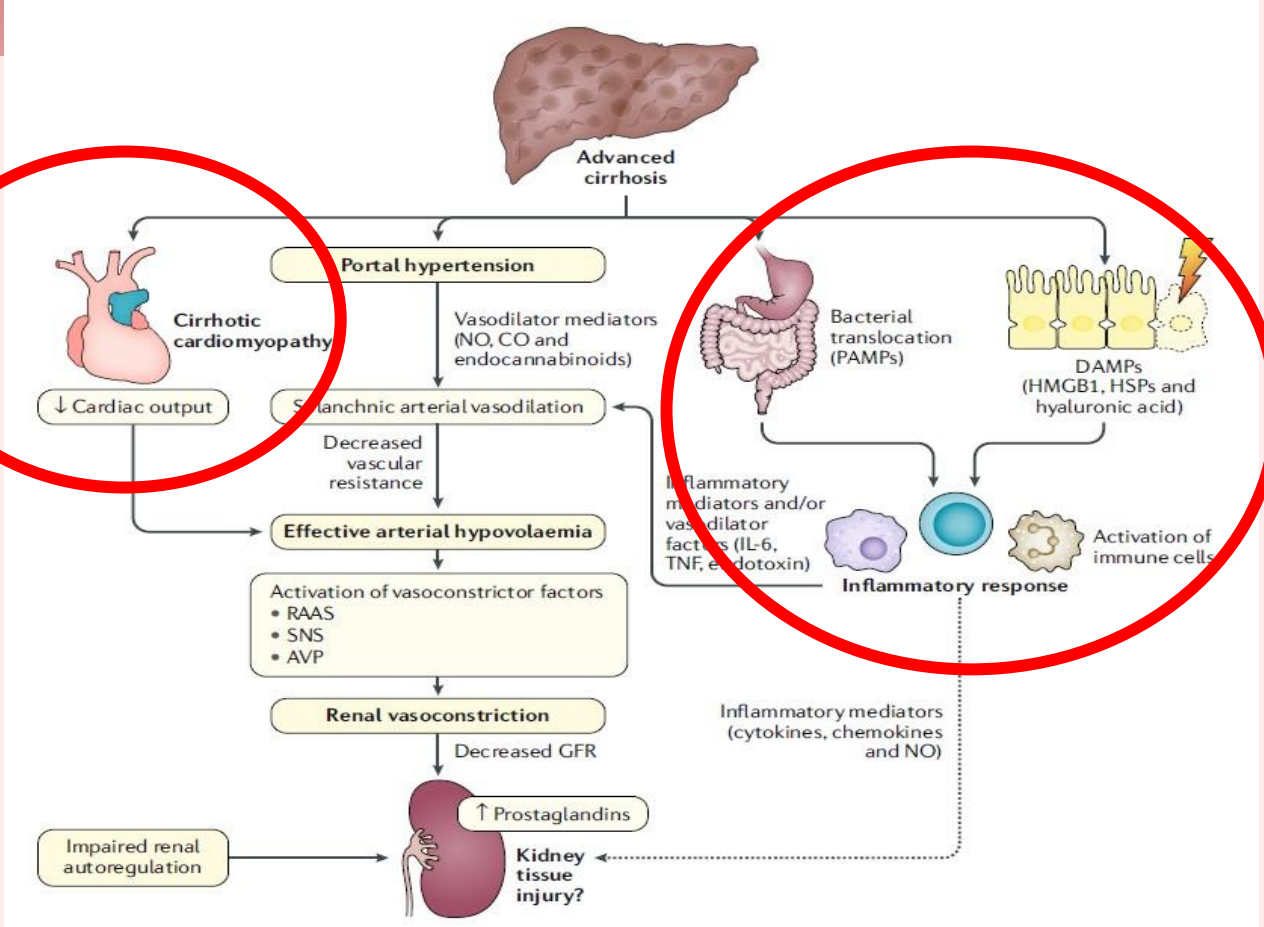
- Gastric varices : EUS guided coiling vs cyanoacrylate injection

- HVPG guided therapy :
  - Invasive and limited availability
  - 50% reduction or to less than 12 mmHG

# Renal Impairment in Cirrhosis

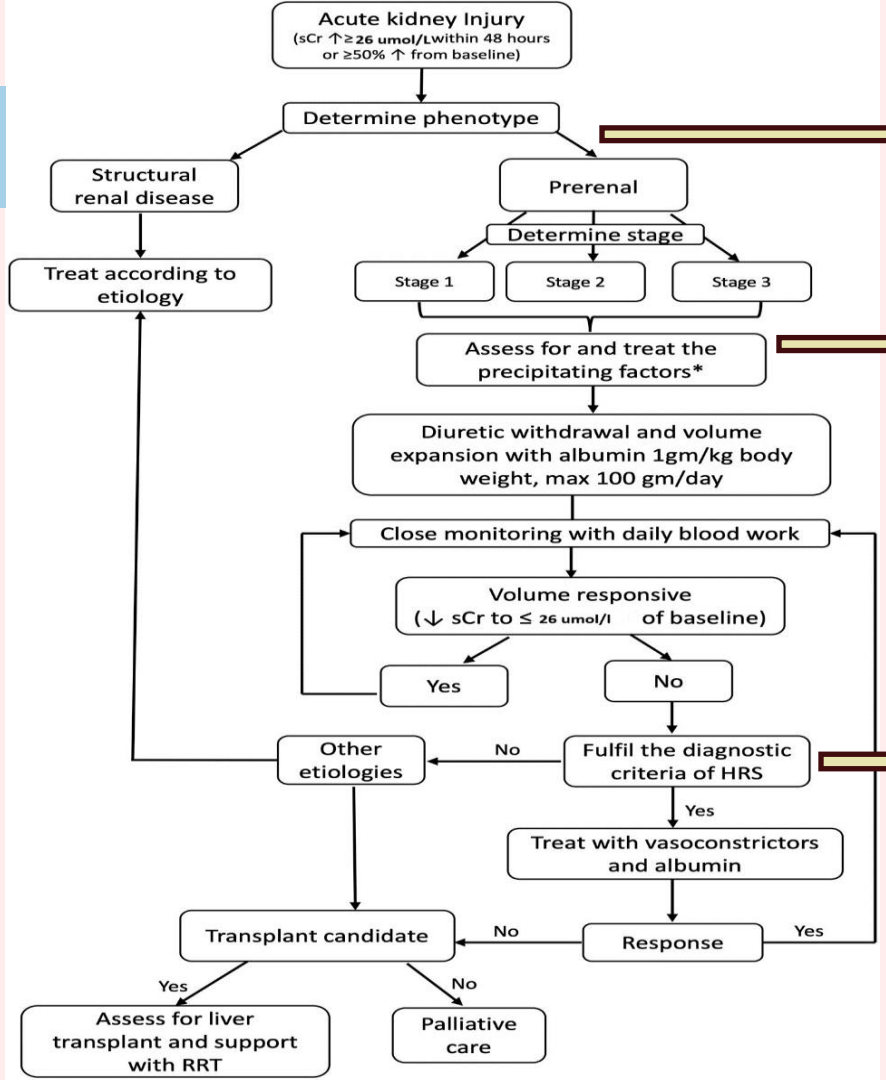
## Triggers

- Infections
- Diuretic-induced
- GI bleeding
- Paracentesis without adequate volume expansion
- Nephrotoxic drugs
- NSAIDs




EASL Guidelines …..decompensated cirrhosis. Jhepatol (2018)

Proteinuria >500mg /day
Micro hematuria >50 RBC/HPF
Renal ultrasound




Urine sediment
Urine biomarkers : NGAL, IL 18

Infections
Volume loss
Nephrotoxic drugs

HRS AKI
HRS NAKI : HRS-AKD vs HRS- CKD

Simultaneous kidney, liver transplant in :

- CKD : Stage 3b >90 days or biopsy 30% fibrosis
- AKI on dialysis for 8 – 12 weeks

# HRS- AKI

## Criteria

- Serum Creatinine ≥26.5 umol/L within 48 hours
- Increase in serum Cr ≥50%
- Urinary output ≤ 0.5 ml/kg B.W. ≥6 hours
- No/ poor response to diuretic withdrawal , volume expansion and albumin : 48 hours
- Absence of shock, nephrotoxic drugs , renal parenchymal disease

## Treatment

| | |
|---|---|
| **Vasoconstrictors** | Terlipressin (most studied) + albumin |
| | Norepinephrine + albumin (target MAP > 10 mmHG from baseline) |
| | Midodrine + octreotide : less effective |
| **Renal Replacement** | General indications |
| **TIPSS** | Consider if safe (MELD 18 , Tbil <80) |
| **Liver transplant** | |

# Terlipressin

- Vasoconstrictor activity in the splanchnic (V1) and systemic vasculature (V2 – renal tubules)
- Dose titration : increase if no Creatinine decrease by 25% in 48 hours
- Poor response (less than within 26.5 umol of baseline): continue for 14 days
- Side effects : diarrhea, abdominal cramps, ischemia (cardiac, intestinal), skin discoloration, respiratory failure

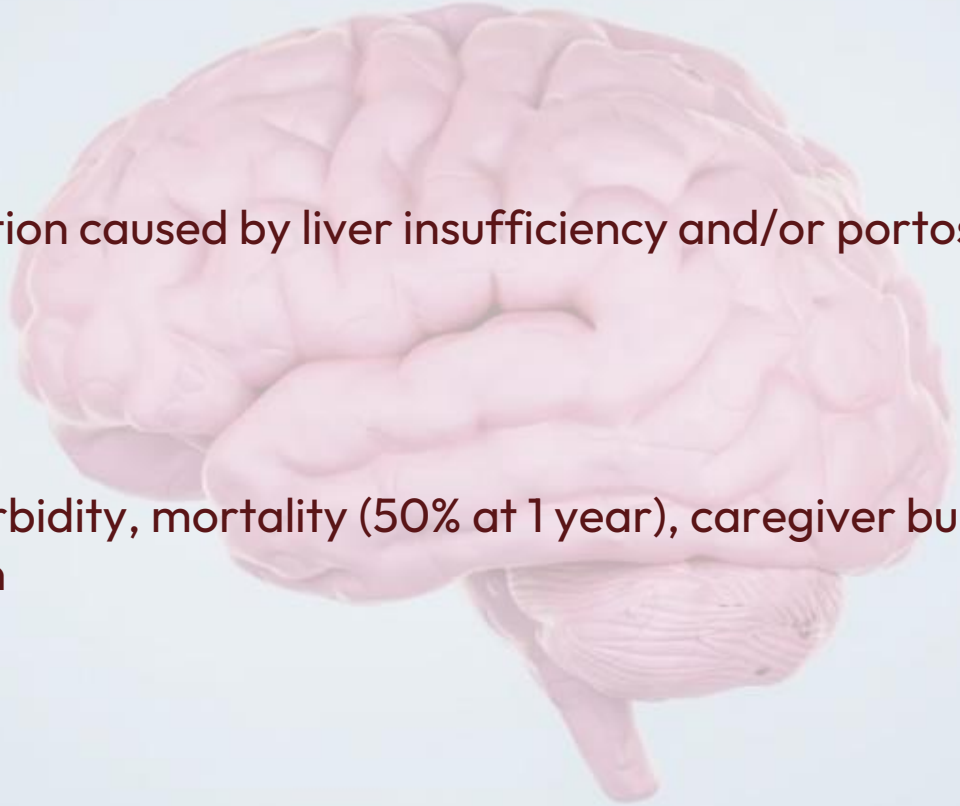
# Hyponatremia

- Hypovolemic vs Hypervolemic
- MELD-Na : better prognostic score than MELD
- Evaluation : urine osmolality, volume status

## Treatment

| | |
|---|---|
| Fluid Restriction | Less than 1 litre/day |
| Volume expansion | Crystalloids<br>Albumin |
| Hypertonic saline | Severe Hyponatremia<br>Symptomatic |
| Not recommended : vaptans | |

# Hepatic Encephalopathy

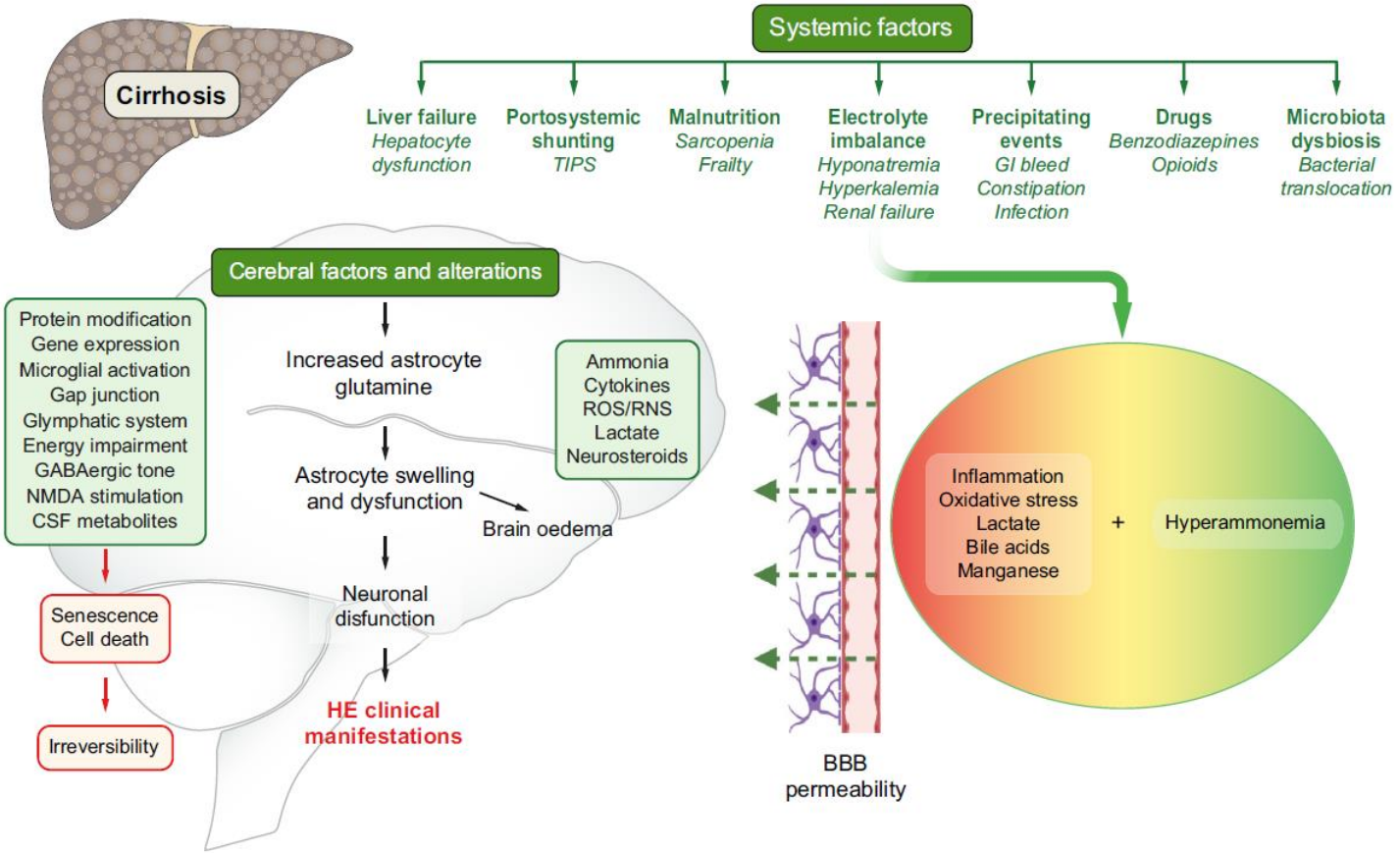


- Brain dysfunction caused by liver insufficiency and/or portosystemic shunting

- Impact on morbidity, mortality (50% at 1 year), caregiver burden and hospitalization

# Four Axes of Classifiying Hepatic Encephalopathy

| Type | Grade | | Time course | Presence of precipitants |
|---|---|---|---|---|
| **A : A**cute Liver failure | Covert | Minimal<br>1 | Episodic (no further in > 6 months) | Precipitated |
| **B :** Portosystemic **B**ypass or shunt (without cirrhosis) | Overt | 2<br>3<br>4 | Recurrent (within 6 months) | Spontaneous |
| **C : C**irrhosis | | | Persistent (Never resolved) | |




Rose. J Hepatology. 2020

# Management : Diagnosis

- Covert : Psychometric or neurophysiological tests
- Grade 1 : inattention, anxiety, dysphoria, trivial lack of awareness, sleep wake reversal
- Overt – exclude other causes
- Role of ammonia measurement
    - High negative predictive value
    - Careful sampling, handling and measurement
    - Level in cirrhosis: unclear correlation with severity / prognosis of H.E
    - High levels in cirrhosis : target for treatment - controversial

# Treatment

## Airway protection

H.E Grade 3 -4
GCS < 8

## Rule out other causes/ Precipitants

## Osmotic laxatives

Lactulose: primary prevention in CP B,C

Polyethylene glycol

## Rifaximin

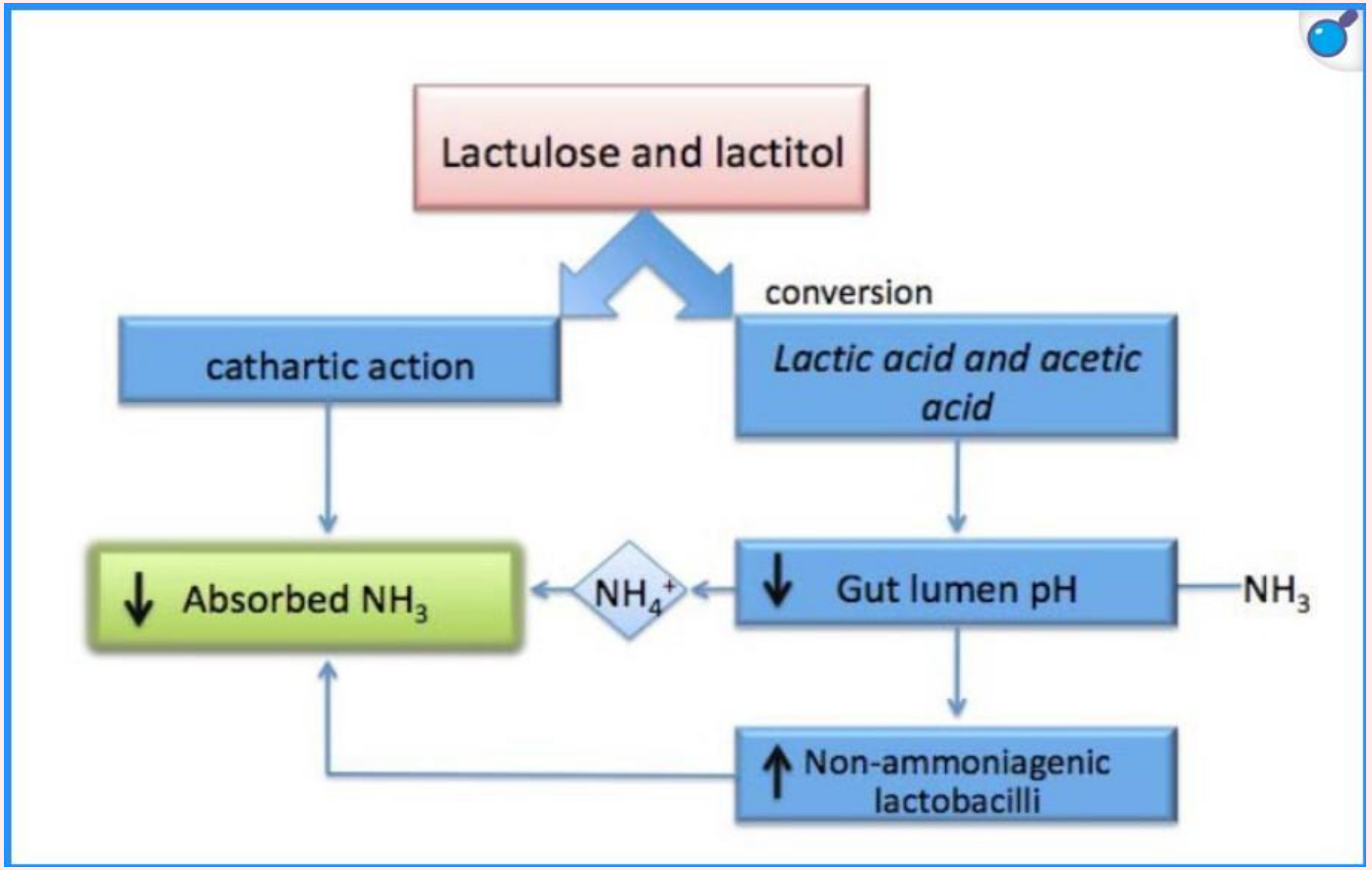
Add on to lactulose for secondary prevention

## L-ornithine-L-aspartate

Stimulation of hepatic urea synthesis and muscle glutamine synthesis

In refractory to 1st line

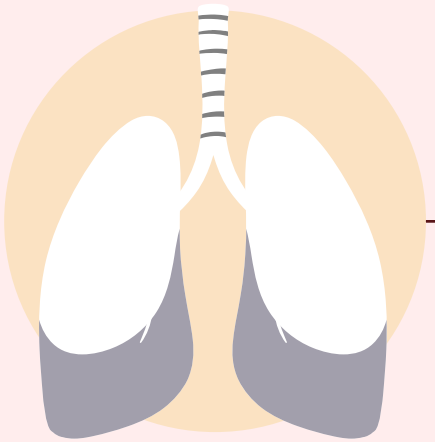
# Mechanism of Action



# Management of Persistent / Refractory H. E

- Embolization of shunts : MELD < 11
- Albumin and albumin dialysis : anti-inflammatory effect and toxin binder
- Nutrition : high energy, high protein diet prevent sarcopenia and promote muscle glutamine synthesis.
- Liver transplantation : Ultimate treatment. Persistent neurological complications in some recipients ( 8 – 47%)
- Fecal microbiota transplant : stimulation of hepatic urea synthesis. Trials ongoing

# CardioPulmonary complications in Cirrhosis



- **Cirrhotic cardiomyopathy**
- **Portopulmonary Hypertension**
- **Hepatopulmonary syndrome**
- **Ascites, Hydrothorax**
- **Muscle wasting**
- **Lung damage in liver disease : AATD, CF**

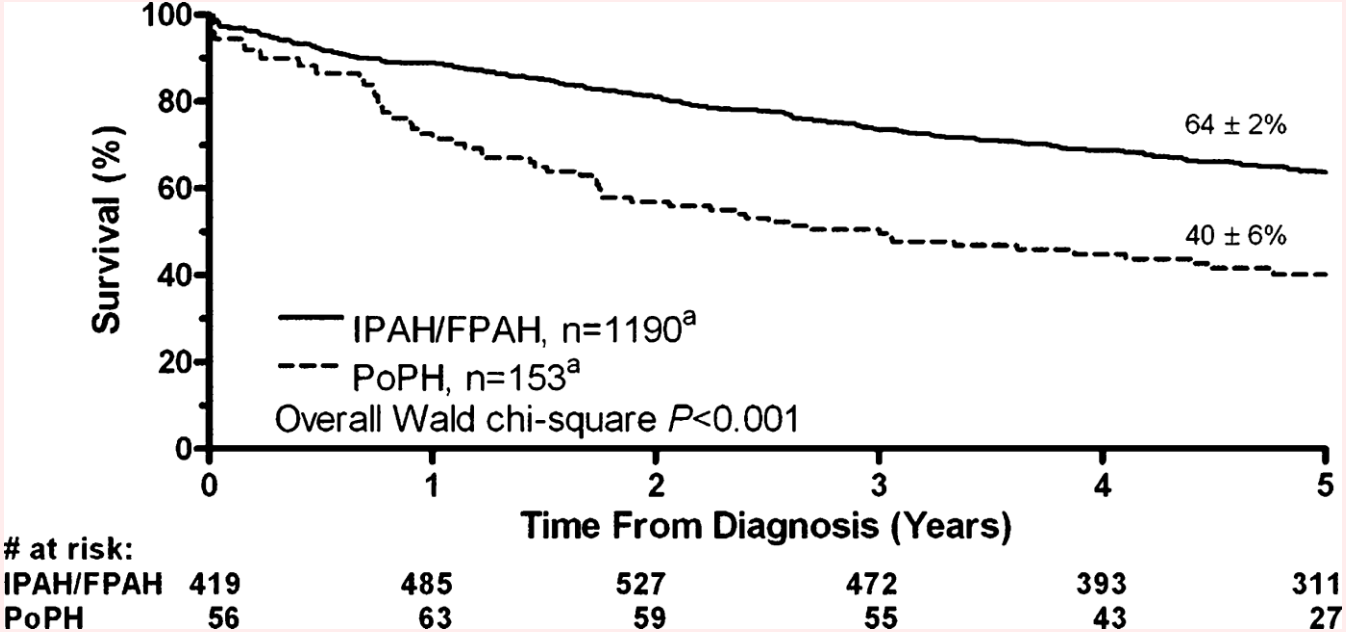
## Portopulmonary Hypertension

- PH in patient with portal HTN in absence of other causes

- Elevated mean Pulmonary arterial pressure (mPAP), elevated pulmonary vascular resistance and normal Pulmonary capillary wedge pressure (< 15mmHg)

- Classification based on mean Pulmonary pressure
  - Mild : mPAP 25 – 35 mmHg
  - Moderate : mPAP 35 – 45 mmHG
  - Severe : mPAP > 45 mmHg

# PPHT 5 Year Survival

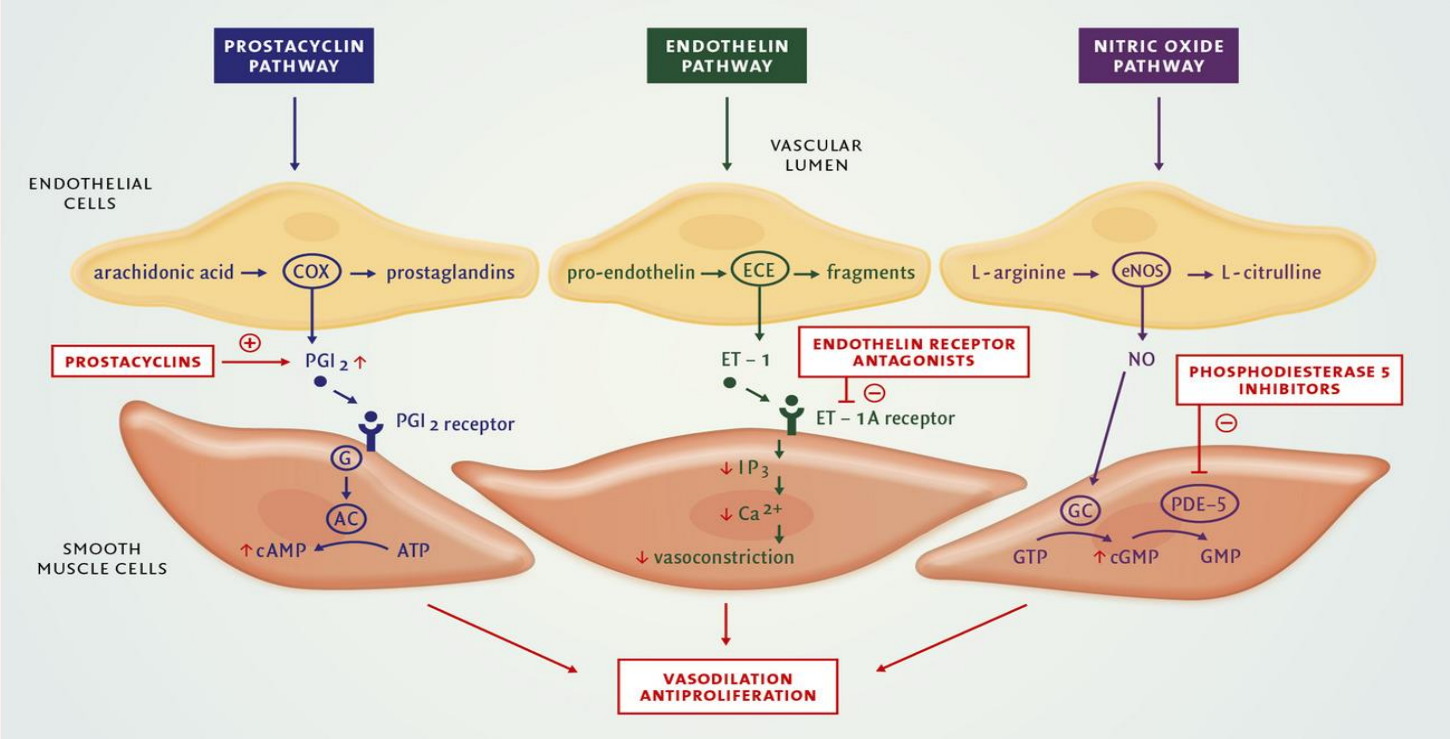



*Krowka CHEST.* 2012

# PPHT Clinical features and evaluation

| | |
|---|---|
| **Presentation spectrum** | Asymptomatic, exertional dyspnea, Features of RH failure |
| **Risk factors** | Female, autoimmune liver diseases, Spontaneous portosystemic shunts |
| **Screening** | Echo for high risk patients : symptomatic + asymptomatic (pre liver transplant , pre TIPSS) |
| **Right heart catheterisation candidates** | Echo findings of RVSP > 50 mmHg / PASP > 40 mmHg |

# Pathogenesis and treatment




Liver International, Volume: 35, Issue: 6, Pages: 1646-1660, First published: 27 January 2015, DOI: (10.1111/liv.12791)

# PPHT outcomes in liver transplant

- Liver transplantation : relative contraindication
- Severe mPAP – absolute
- Moderate mPAP 35 – 45% high risk of prolonged hospital stay and ventilator dependence.
- Aggressive optimization of patients pre Liver transplant

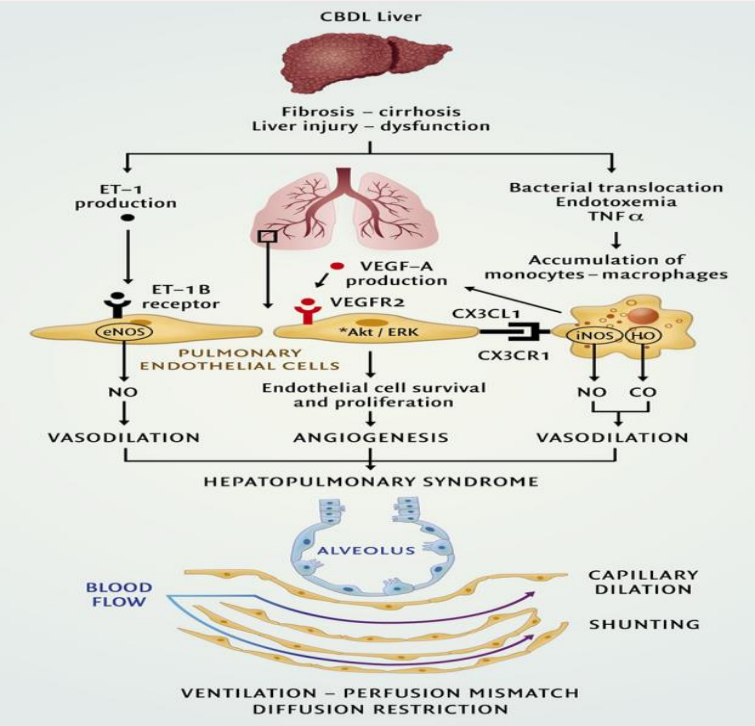
# Hepatopulmonary syndrome

- Disorder in pulmonary oxygenation caused by intrapulmonary vasodilatation (or pleural + pulmonary AV communication) in setting of portal hypertension

- Diagnostic criteria
  - Hypoxia (pAO2 < 70 or Alveolar-arterial (AA) gradient > 15)
  - Pulmonary vascular defect (on contrast echo or lung perfusion scan)

- Setting : Cirrhosis, Prehepatic PH without cirrhosis, Acute liver failure

# Hepatopulmonary syndrome




Dyspnea

Platypnea

Orthodeoxia

Finger clubbing

# Hepatopulmonary syndrome

## Prognosis

23%  Five-year survival

## MELD Points

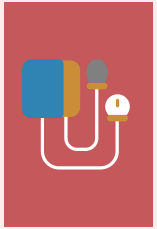
22 , and additional  every three months

## Outcomes post liver transplant

85% correction of hypoxemia

# Cirrhotic Cardiomyopathy

**Cardiac dysfunction in patients with cirrhosis in the absence of known cardiac disease**



## Diagnosis : Echo, MRI

Systolic dysfunction : blunted repsonse to stress

Diastolic dysfunction : altered relaxation

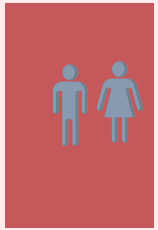
## Course

Asymptomatic
Manifest as heart failure post TIPSS or LT
Complicate AKI

## Treatment

No standard therapy

# Sarcopenia and Frailty



**Impaired muscle mass ; function**

## Diagnosis

Sarcopenia – MRI or CT skeletal muscle index
Frailty : liver frailty index , Perfomance status, 6 minute walk test

## Pathophysiology

Cytokines, DAMPS, PAMPS, hyperammonemia, underlying etiology

## Treatment

Liver etiology optimisation; Nutrition; Exercise program; Testesterone

# Summary

- Cirrhosis is associated with a multitude of complications
- Management requires multi displinary approach
- Early recognition and targeted treatment improves outcomes and quality of life
- Guideline guided therapy and adaptation to local resources and expertise
- Liver transplantation is the definite treatment for many advanced complications

WITS UNIVERSITY

Project ECHO