European School of Internal Medicine

Winter School in Riga 2016

Liver cirrhosis: a systemic disease

Armando Carvalho

Internal Medicine A

Liver Unit

FMUC FACULDADE DE MEDICINA UNIVERSIDADE DE COIMBRA

CHUC HOSPITAIS DA UNIVERSIDADE DE COIMBRA

Summary

- **Chronic Liver Disease**
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - Hepatopulmonary syndrome
  - Hepatorenal syndrome
  - Coagulopathy
  - Bacterial infections

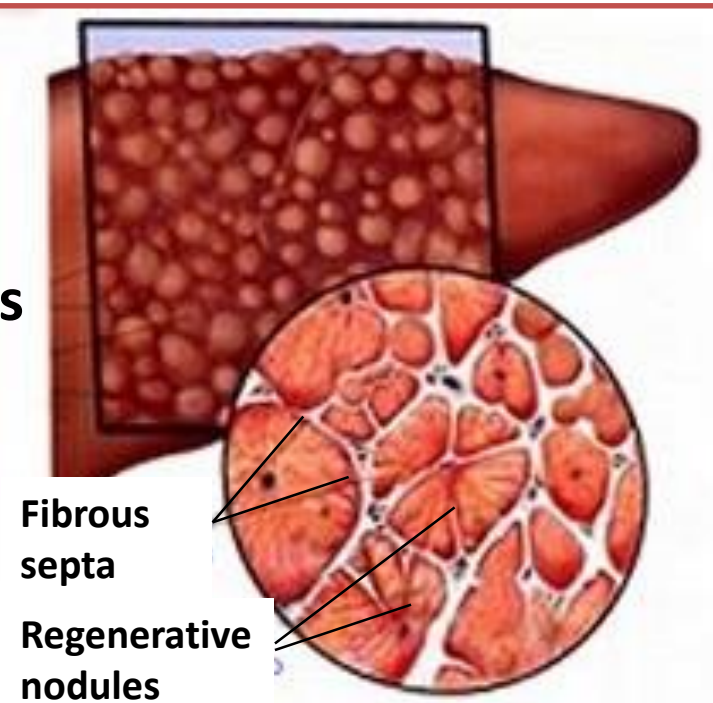
Summary

- **Chronic Liver Disease**
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - Hepatopulmonary syndrome
  - Hepatorenal syndrome
  - Coagulopathy
  - Bacterial infections

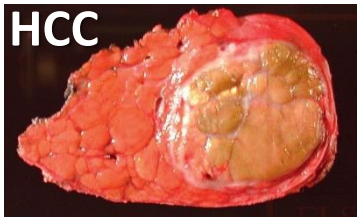
Aggression
Response

Chronic hepatitis
Necro-inflammation
Fibrosis

Cirrhosis



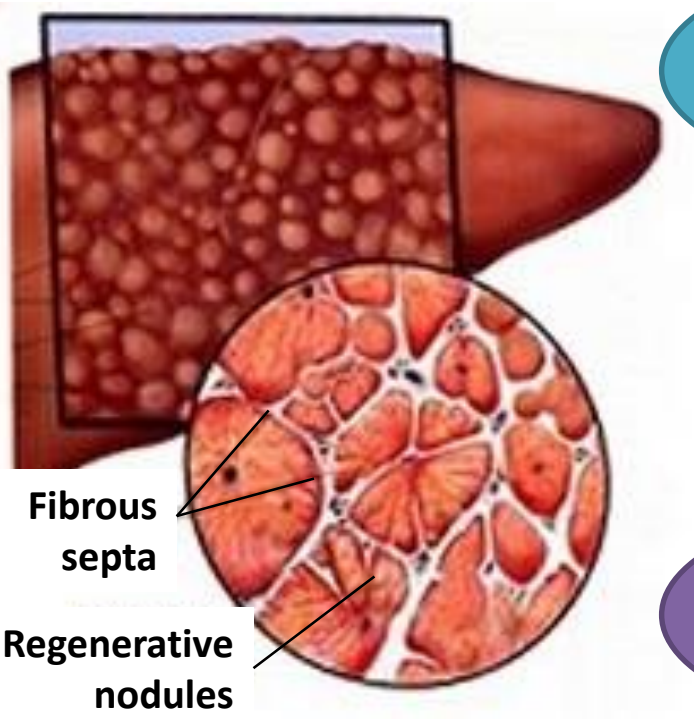
Complications
Portal hypertension
Liver failure



Functional compromise of the liver

Metabolic

Synthetic

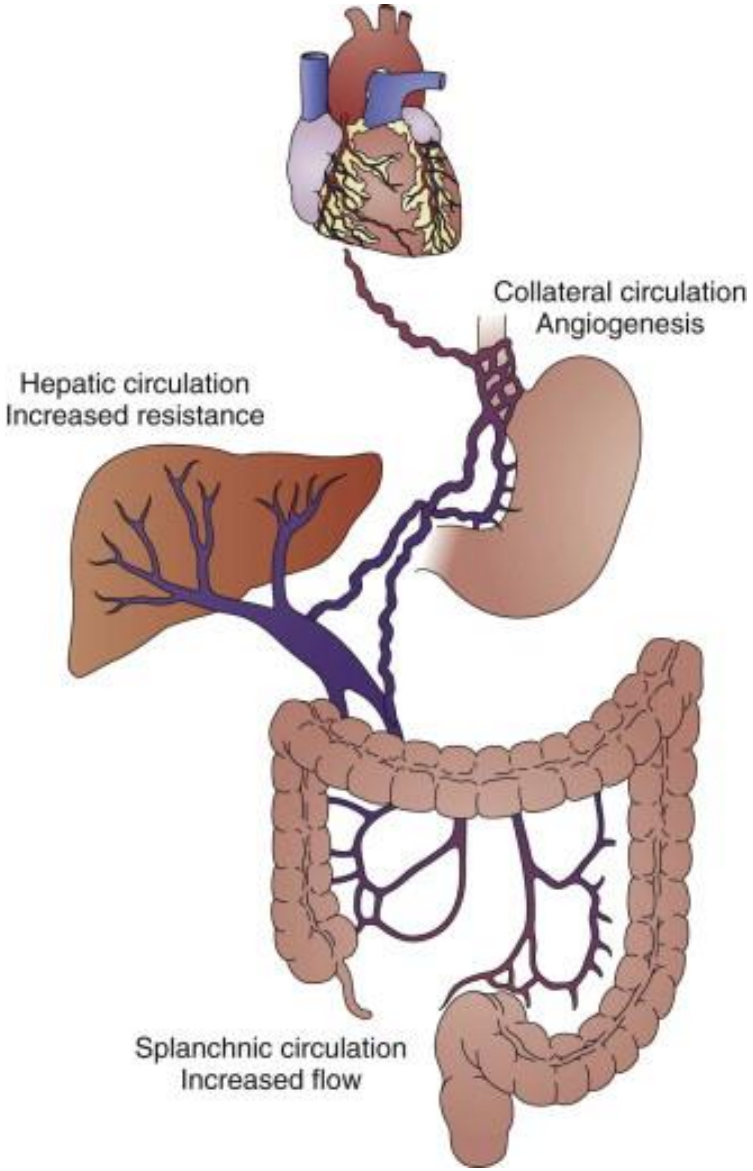


Excretory

Detoxifying

Immunologic

Portal hypertension (PHT)



Clinical syndrome defined by hepatic vein pressure gradient (HVPG) > 5 mmHg

HVPG = WHVP - FHVP

WHVP – Wedged Hepatic Vein Pressure

FHVP – Free Hepatic Vein Pressure

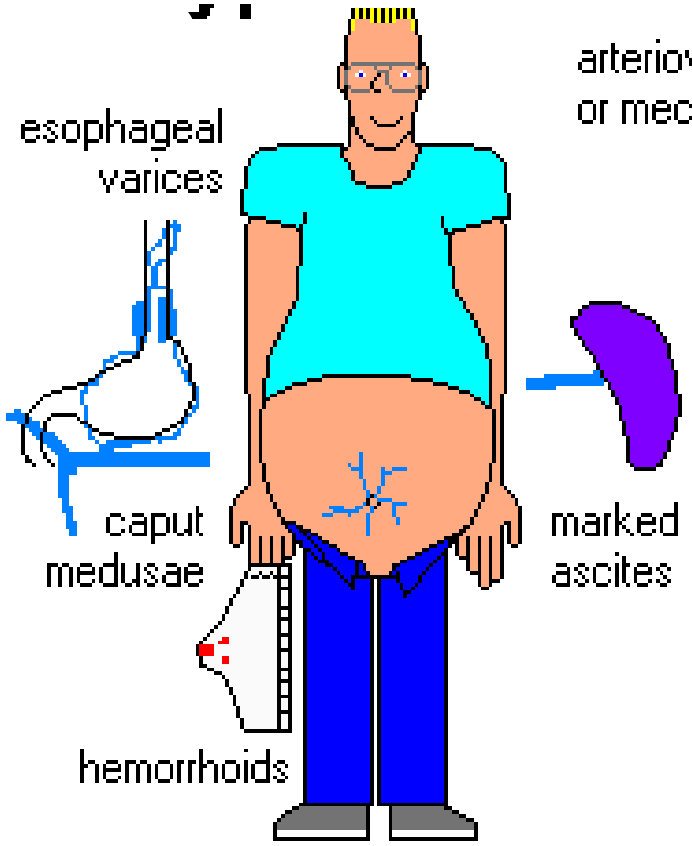
Decreased intrahepatic NO production

↓

Increased intrahepatic vascular tone, responsible for 30% of the magnitude of PHT

Consequences of PTH

Overproduction of NO in the splanchnic circulation → Systemic vasodilatation, hyperdynamic circulation



arteriovenous shunting and/ or mechanical obstruction

hypersplenism:
-- moderate anemia
-- neutropenia
-- thrombocytopenia

Of course, liver failure and its signs are often present as well.

Workup of the patient with cirrhosis

- Diagnosis
- Etiology
- General evaluation
- Staging
- Prognosis
- Associate conditions
- Treatment

- History and physical examination
- Past history
- Signs of liver disease
- Mental status
- Nutritional status
- Diuresis

- Complete blood count
- Coagulation tests
- Glycaemia, creatinine, BUN
- Electrolytes, blood gases
- ALT, AST, GGT, AP, bilirubin
- Total proteins, albumin
- Urinalysis
- Viral hepatitis markers
- Immunology, autoantibodies
- Serum iron and ferritin,
- Coper, ceruloplasmine, alfa-1-AT
- US, CT, MR, Nuclear Medicine
- Digestive endoscopy
- Histopathology, elastography

Etiology of cirrhosis

- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Viral hepatitis (HCV, HBV, HDV)
- Autoimmune liver disease
  - Autoimmune Hepatitis (AIH)
  - Primary Biliary Cholangitis (PBC)
  - Primary Sclerosing Cholangitis (PSC)
- Genetic diseases
  - Hemochromatosis
  - Wilson disease
  - Others (alpha-1-antitrypsine deficiency, glycogenosis, cystic fibrosis)

Child-Turcotte-Pugh

	1 point	2 points	3 points
Total Bilirubin (mg/dl)	≤ 2	2-3	>3
Albuminemia (g/l)	> 35	28-35	<28
INR / PT(s)	< 1.7 / 1-3	1.71-2.30 / 4-6	>2.30 / >6
Ascites	No	mild	mod/severe
Encephalopathy	No	Grade I-II	Grade III-IV

Points	Class	Survival – 1 year	Survival – 2 years
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Child CG, Turcotte JG. The liver and portal hypertension. Saunders 1964: 50-64
Pugh RN, et al. Br J Surgery 1973; 60: 646–9

MELD score

Model of End-stage Liver Disease

3.78[Ln bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln creatininemia (mg/dL)] + 6.43

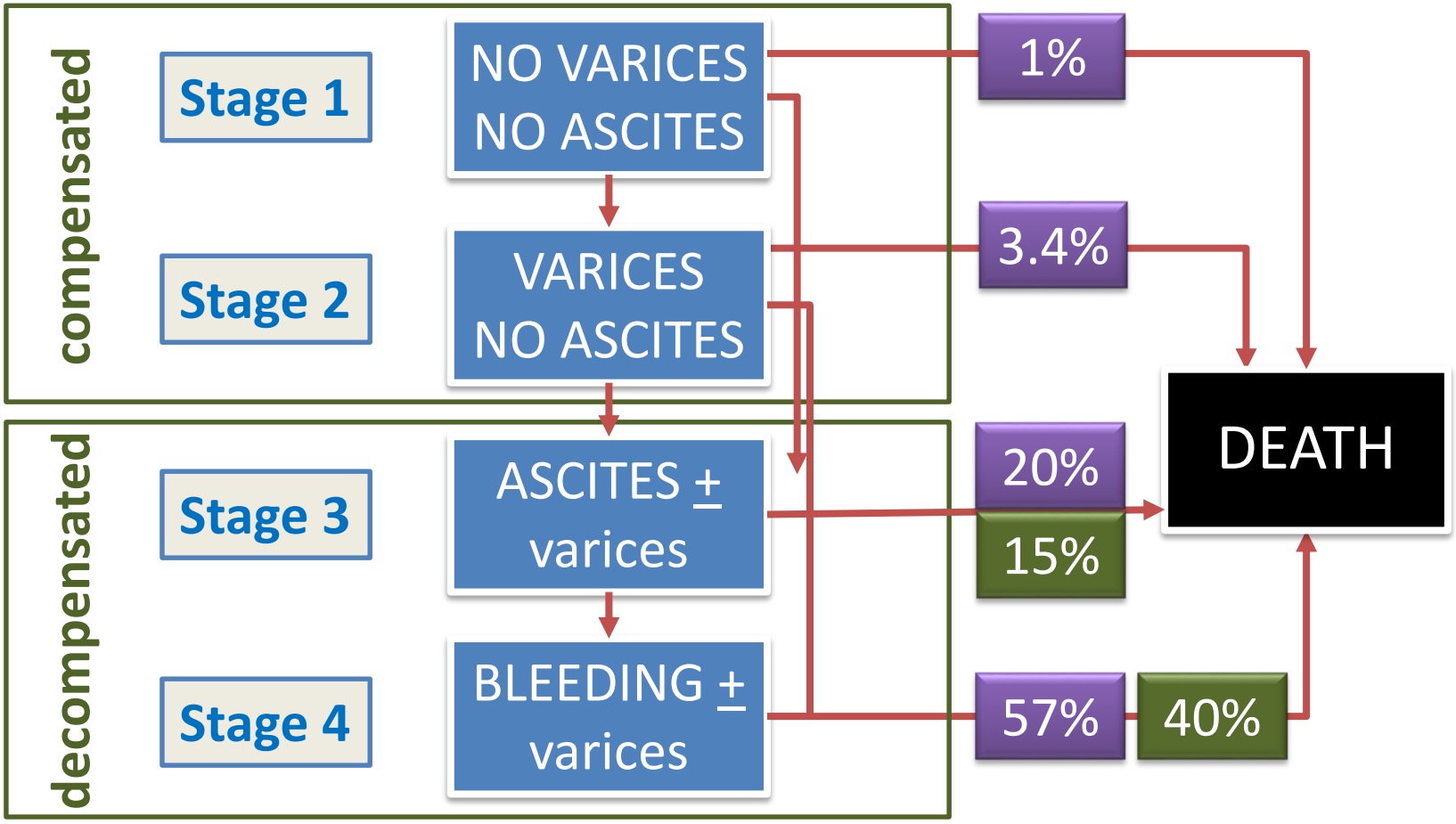
http://www.mayoclinic.org/meld/mayomodel6.html

Mortality at 3 months (inpatients)	
≥ 40	71.3%
30–39	52.6%
20–29	19.6%
10–19	6.0%
<9	1.9%

Wiesner *et al.* Gastroenterology 2003; 124: 91-6

Clinical stages of cirrhosis

One year outcome probability from cohort studies

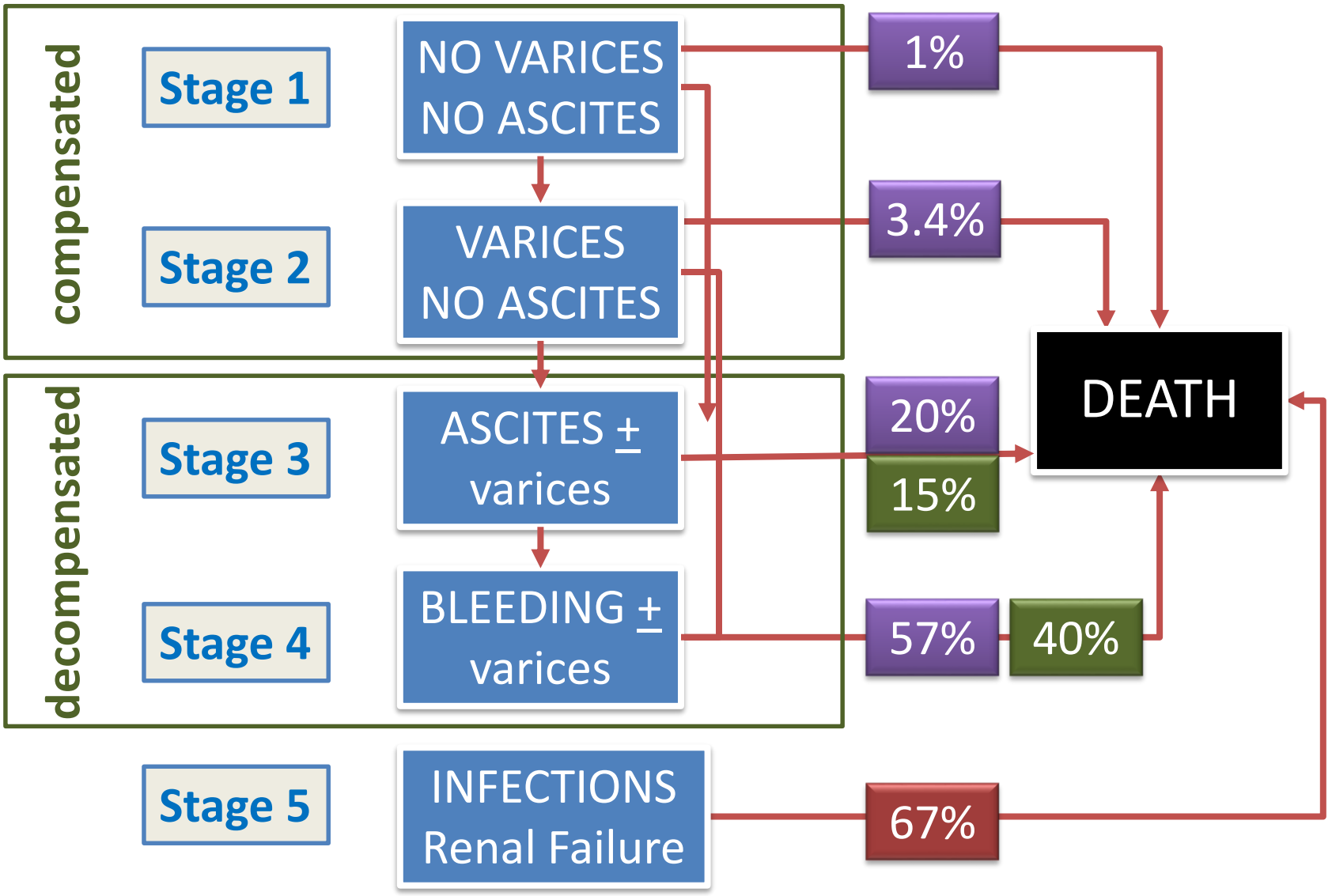


D'Amico G. Dig Dis Sci 1986; 31: 468-75
D'Amico G. Gastroenterology 2001; 120: A2

Planas R. Clin Gastro Hepa 2006; 4: 1385-94
Stokkeland K. Hepatology 2006; 43: 500-5
El-Serag. Am J Gastro 2000; 95: 3566-73

Clinical stages of cirrhosis

One year outcome probability from cohort studies



Arvaniti V, et al. Gastroenterology 2010;139:1246-56; Fede G, et al. J Hepatol 2012;56:810-8

Liver cirrhosis as a systemic disease

Respiratory
Hepatopulmonary syndrome
Portopulmonary syndrome

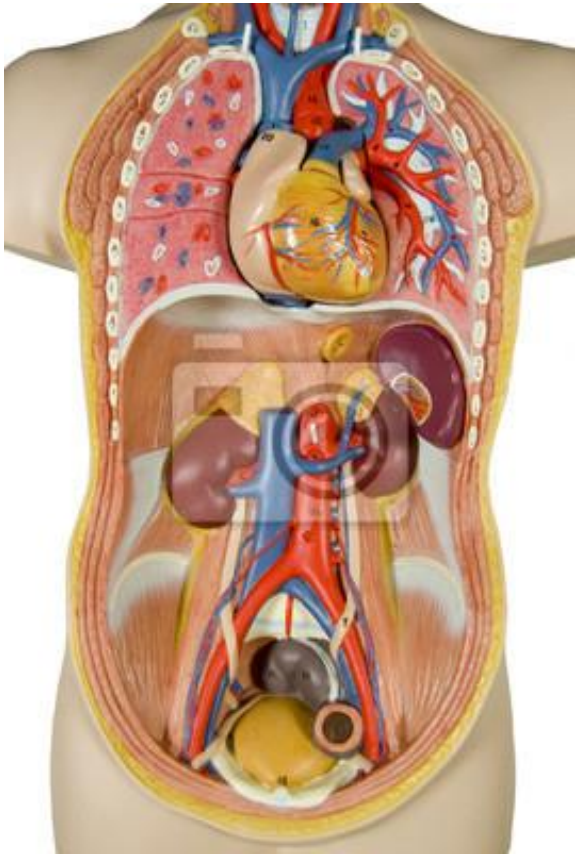
Renal
Fluid retention
Hepatorenal syndrome

Gastrointestinal
Anorexia, dyspepsia
Nausea, vomiting
Change in bowel habits
Dull abdominal pain
Esophageal, gastric varices
Hemorrhoids
Hematemesis, melena
Hypertensive gastritis

Reproductive
Amenorrhea
Testicular atrophy
Gynecomastia (male)
Erectile dysfunction

Infection
Bacterial and fungal; Sepsis

Neurologic
Hepatic encephalopathy
Peripheral neuropathy
Asterixis



Integumentary
Jaundice
Spider angioma
Palmar erythema
Purpura, petechiae

Hematologic
Cytopenia
Coagulopathy
Splenomegaly

Metabolic
Potassium deficiency
Hyponatremia
Hypoalbuminemia

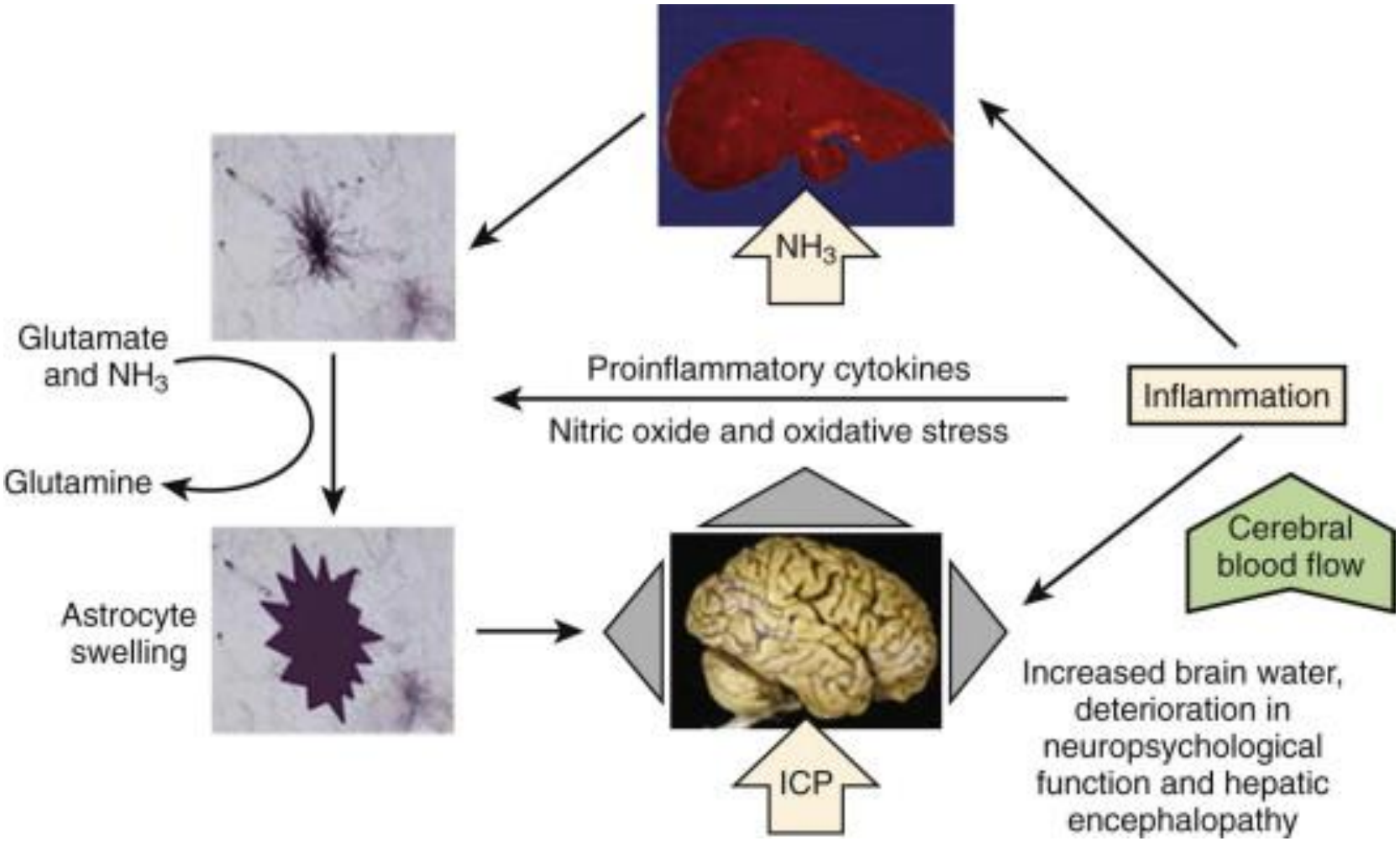
Cardiovascular
Fluid retention
Peripheral edema

Endocrine
Glucose intolerance
Hyperinsulinism
Insulin resistance
Hyperglucagonemia

Summary

- Chronic Liver Disease
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - **Encephalopathy**
  - Hepatopulmonary syndrome
  - Hepatorenal syndrome
  - Coagulopathy
  - Bacterial infections

Pathophysiology of Hepatic Encephalopathy (HE)



Amonia, and other gut toxins (benzodiazepine-like, neurotoxic short- and medium-chain fatty acids, phenols, and mercaptans)

Classification of HE

Type	Grade		Time Course	Spontaneous or Precipitated
A	MHE	Covert	Episodic	Spontaneous
	1			
B	2	Overt	Recurrent	Precipitated (specify)
	3			
C			Persistent	
	4			

Type – underlying disease
- A – resulting from acute liver failure
- B – resulting predominantly from portosystemic shunting
- C – resulting from cirrhosis

Grade – severity of manifestations
- Covert (minimal and grade 1), Overt (grades 2, 3, and 4)

Time course
- Episodic
- Recurrent (bouts that occur with a time interval $\leq$ 6 months)
- Persistent (behavioral alterations that are always present)

Spontaneous or precipitated
- Spontaneous (non precipitated)
- Precipitated (precipitating factors should be specified)

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Precipitating factors for HE

(by decreasing frequency)

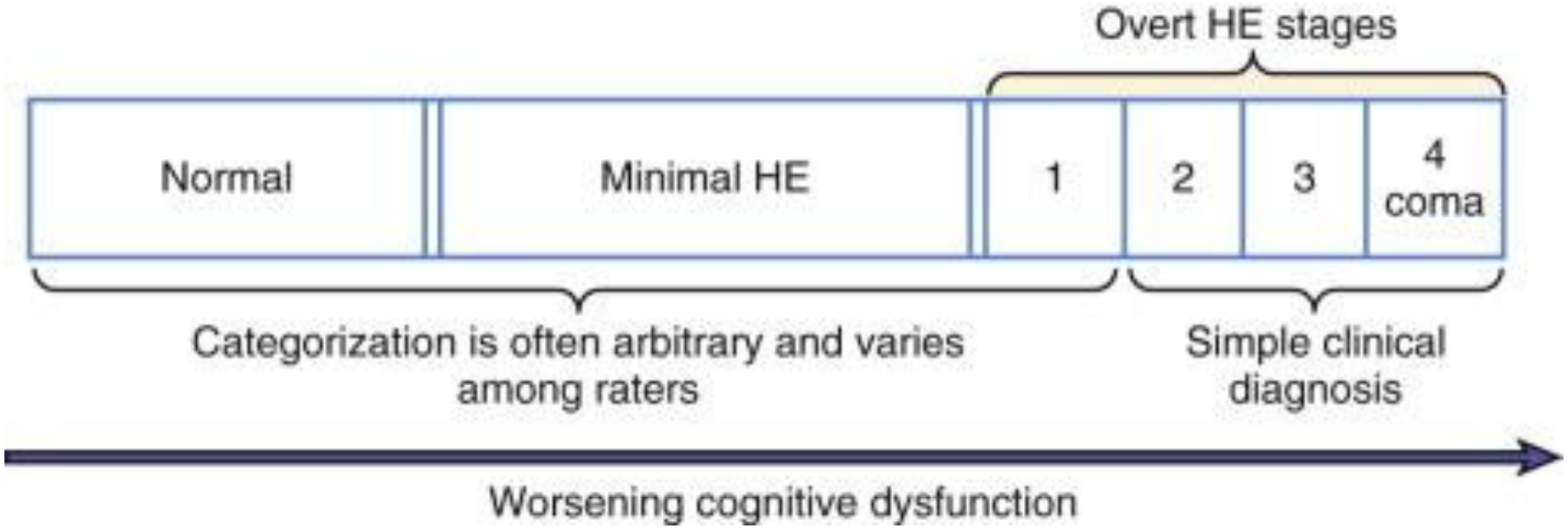
EPISODIC	RECURRENT
Infections	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Severity of manifestations of HE

At the time of diagnosis of cirrhosis

- 10-14% in general
- 6-21% in decompensated
- 10-50% in patients with TIPS



Minimal and OHE occurs in 20%-80% of patients with cirrhosis

Diagnosis of HE

- Overt hepatic encephalopathy (OHE)
  - diagnosed by clinical criteria, graded by West Haven Criteria and Glasgow Coma Scale
- Minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy (CHE)
  - Diagnosis and grading can be made using several neurophysiological and psychometric tests, that could be used in patients who would most benefit from testing, such as those with impaired quality of life or implication on employment or public safety
- Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease, but a normal value calls for diagnostic reevaluation

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Differential diagnosis of HE

Overt HE or acute confusional state
Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea
Hyponatremia and sepsis can both produce encephalopathy per se and precipitate HE by interactions with the pathophysiological mechanisms. In end-stage liver disease, uremic encephalopathy and HE may overlap.

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

West-Haven criteria

Unimpaired	No encephalopathy at all, no history of HE
Minimal	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • *Asterixis*
Grade III	• Somnolence to semi stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior
Grade IV	Coma

Treatment of HE

- Treatment of minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy (CHE) is not routinely recommended apart from a case-by-case basis
- Support therapy
- Identification and removal of precipitant factors
  - Gastrointestinal hemorrhage
  - Infections
  - Renal and electrolytic abnormalities
  - Psychoactive drugs
  - Constipation
  - Excess of protein intake
  - Acute on chronic liver disease
- Reduction of intestinal absorption of nitrogenous products
- Evaluation of long-term therapy

Treatment of HE

- Lactulose is the first choice for treatment of episodic OHE
- Rifaximin is an effective add-on therapy to lactulose for prevention of OHE recurrence
- Oral branched-chain amino acids (BCAAs), or i.v. L-ornithine L-aspartate (LOLA) can be used as an alternative or additional agent for patients nonresponsive to conventional therapy
- Neomycin and metronidazole are alternative choices for treatment of OHE

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Nutrition in patients with HE

- Daily energy intakes should be 35-40 kcal/kg ideal body weight
- Daily protein intake should be 1.2-1.5 g/kg/day
- Small meals or liquid nutritional supplements, evenly distributed throughout the day, and a late-night snack
- Oral BCAA supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Prevention of HE

- Lactulose is recommended for prevention of recurrent episodes of HE
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding), or liver function or nutritional status improved, prophylactic therapy may be discontinued

H Vilstrup, et al. HE in CLD: 2014 Practice Guideline by AASLD and EASL. Hepatology; DOI: 10.1002/hep.27210

Summary

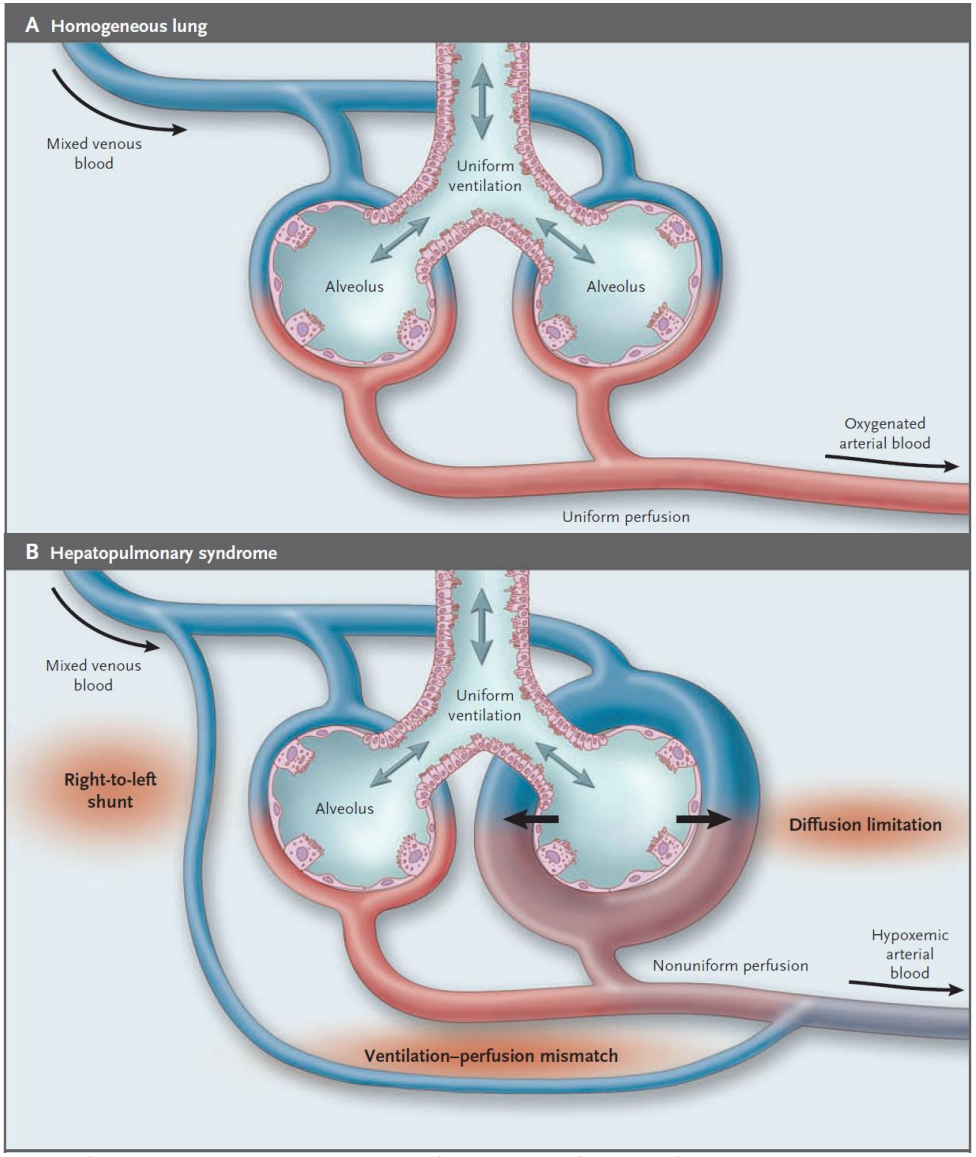
- Chronic Liver Disease
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - **Hepatopulmonary syndrome**
  - Hepatorenal syndrome
  - Coagulopathy
  - Bacterial infections

Pulmonary involvement in liver cirrhosis

- **Hepatopulmonary syndrome** (HPS)
  - The primary pathological process is abnormal pulmonary vasodilation
  - It is a manifestation of generalized circulatory dysfunction in portal hypertension (vascular dilatation and hyperdynamic circulation)
- **Portopulmonary hypertension** (PPHT)
  - Vasoconstriction is the pulmonary circulatory abnormality
  - There is fibro-obliteration of the vascular bed (opposite from the changes that occur in HPS)
- Rarely, patients can have features of both disorders

JA Grace, PW Angus. J Gastroenterol Hepatol 2013; 28: 213–219

Hepatopulmonary Syndrome (HPS)
Mechanisms of arterial hypoxemia

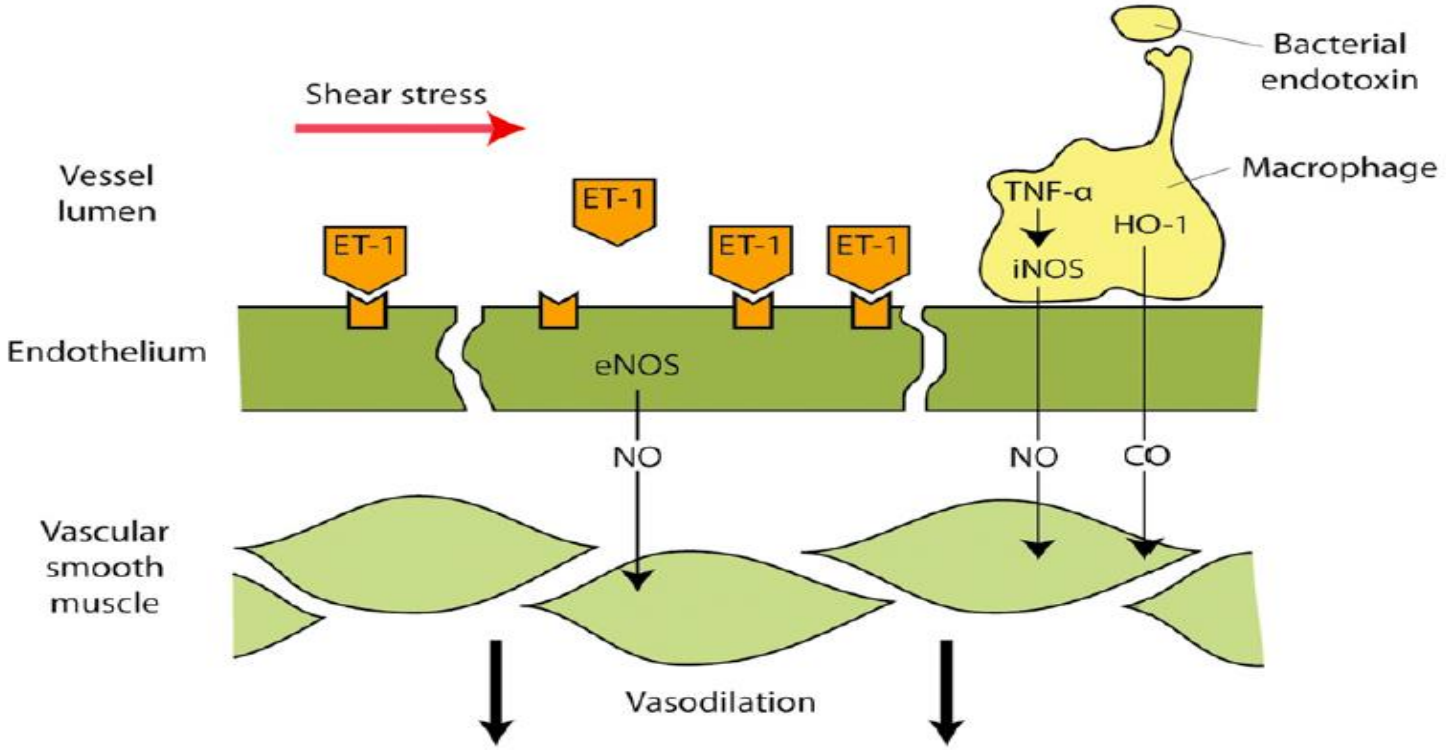


- **Healthy person (A)**
  - Capillary diameter is 8-15 µm,
  - O_2 diffuses properly into the vessel
  - Ventilation-perfusion well balanced

- **Hepatopulmonary syndrome (B)**
  - Many capillaries are dilated and blood flow is not uniform
  - Ventilation-perfusion mismatch is the predominant mechanism, with or without intrapulmonary shunts
  - Restricted oxygen diffusion into the center of the dilated capillaries in the most advanced stages

R Rodriguez-Roisin, MJ Krowka. N Engl J Med 2008; 358:2378-87

Possible mediators of pulmonary vasodilation

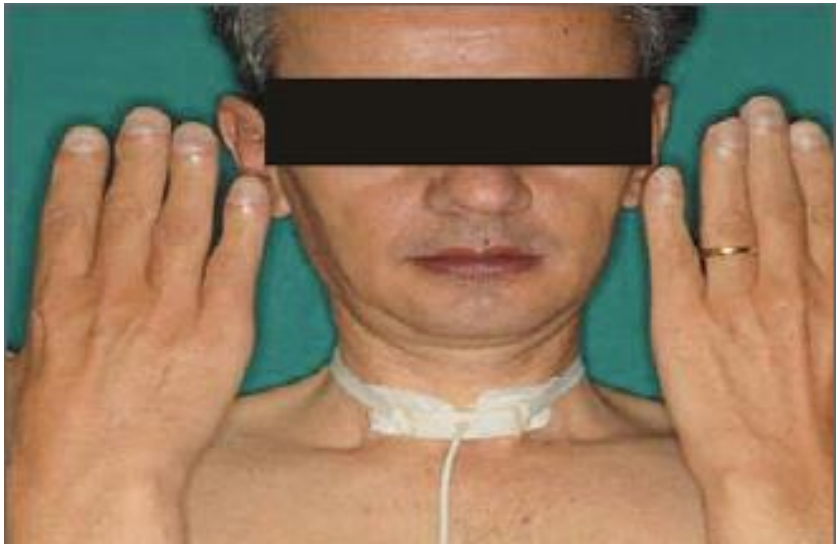


- **Nitric oxide (NO)** appears to be a **key mediator** of pulmonary vasodilation in HPS
- **Pulmonary endothelin-B receptors are increased**, at least partly due to shear stress secondary to PHT. **Circulating endothelin-1** (ET-1) produced by the injured liver binds to endothelin-B receptors, **stimulating endothelial NO synthase** (eNOS)
- Phagocytosis of **bacterial endotoxin** by pulmonary intravascular macrophages releases TNF-alfa, which activates inducible NO synthase (iNOS)
- Carbon monoxide (CO) may also play a role in vasodilation

JA Grace, PW Angus. J Gastroenterol Hepatol 2013; 28: 213–219

Clinical manifestations of HPS

- **Dyspnea**, common in cirrhosis, present in 50% of pts with HPS
- **Platypnea** (dyspnea that increases from the supine to the erect position), is a more specific symptom, which may be associated with **orthodoxia** (hypoxia that is worse when erect)



- **Finger clubbing** is present in almost 50% of HPS patients (2% in others)
- Cyanosis and clubbing in a cirrhotic patient is highly suggestive of severe HPS

R Rodriguez-Roisin, MJ Krowka. N Engl J Med 2008;358:2378-87
JA Grace, PW Angus. J Gastroenterol Hepatol 2013; 28: 213–219

Diagnostic criteria – HPS *vs.* PPHT

Hepatopulmonary syndrome

1. Liver disease that meets listing criteria for OLT, *and*
2. PaO_2<70 mmHg or alveolo-arterial O_2 gradient >20 mmHg, *and*
3. Pulmonary vascular dilatation documented by either
   a) "positive" contrasted enhanced transthoracic echocardiogram, *or*
   b) brain uptake > 6% following lung perfusion scanning (99mTc macroaggregated albumin)

In most cases, the results of arterial blood gases and a study to detect intrapulmonary shunting are sufficiently specific, once other intrinsic cardiorespiratory diseases are excluded.

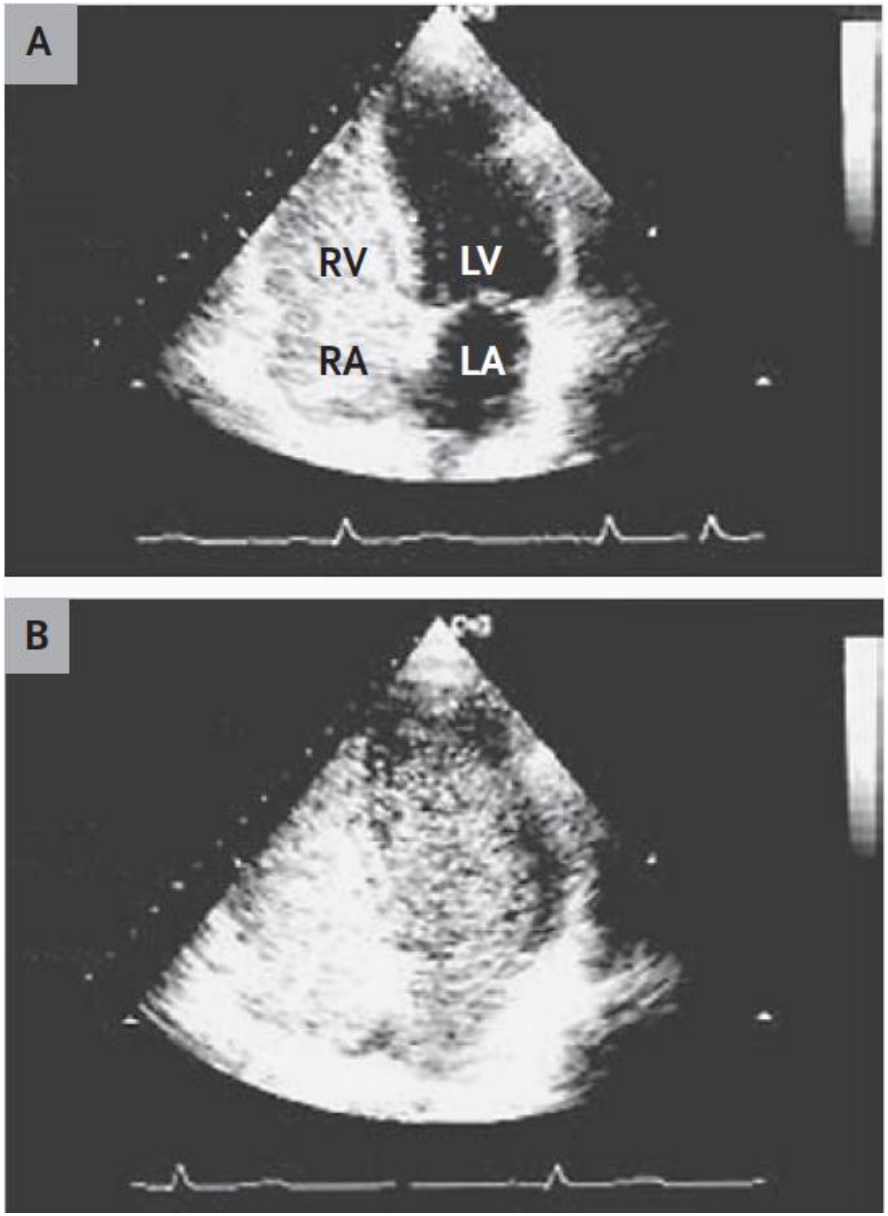
Portoportal hypertension

1. Liver disease that meets listing criteria for OLT, *and*
2. MPAP $\geq$ 25 mmHg, *and*
3. PVR $\geq$ 120 dynes/s/cm^{-5}, *and*
4. PCWP $\leq$ 15 mmHg

MPAP – mean pulmonary artery pressure
PVR – pulmonary vascular resistance
PCWP – pulmonary capillary wedge pressure

MJ Krowka, et al. Liver Transplantation 2004; 10: 174-182

Contrasted-enhanced transthoracic echocardiogram



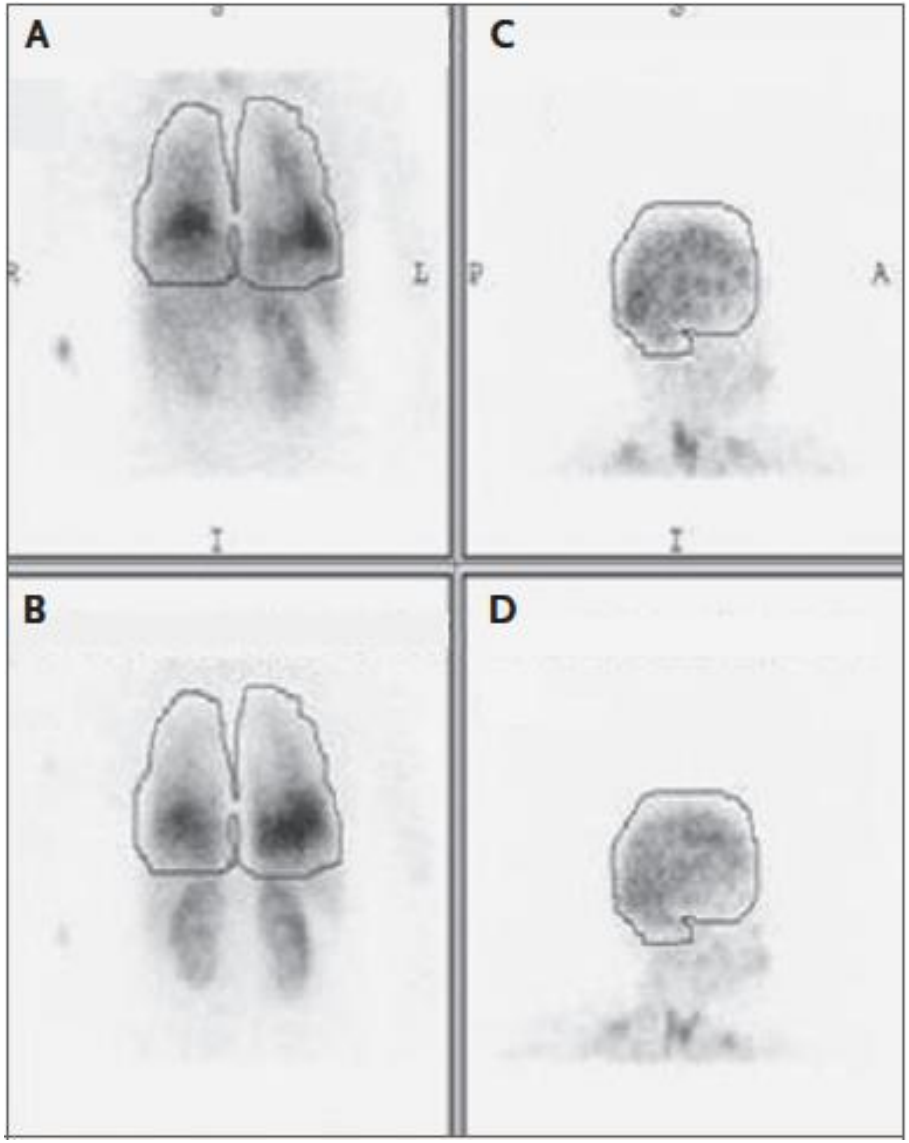
- Opacification of the right atrium (RA) and right ventricle (RV)
- Delayed opacification of the left atrium (LA) and left ventricle (LV)

These findings are the standard for the diagnosis of the HPS

R Rodriguez-Roisin, MJ Krowka. N Engl J Med 2008;358:2378-87

Lung and Brain Scans in HPS

Technetium-99m–labeled macroaggregated albumin



Radioactivity present in:

- anterior lungs (A)
- posterior lungs, kidneys (B)
- right side of the cerebrum (C)
- left side of the cerebrum (D)

uptake in the brain: 62%
normal uptake: < 6%

R Rodriguez-Roisin, MJ Krowka. N Engl J Med 2008;358:2378-87

Degree of severity of HPS

Degree	Alveolar-arterial O_2 gradient ($PA\text{-}aO_2$)	PaO_2
Mild	$\geq$ 15 mmHg	$\geq$ 80 mmHg
Moderate	$\geq$ 15 mmHg	$\geq$ 60 mmHg to < 80 mmHg
Severe	$\geq$ 15 mmHg	$\geq$ 50 mmHg to < 60 mmHg
Very Severe	$\geq$ 15 mmHg	< 50 mmHg (< 300 mmHg, while pt is breathing 100% O_2)

- All criteria were determined by contrast-enhanced echocardiography
- Cut-off values of PaO2 $\leq$ 70 mmHg or $PA\text{-}aO_2$ $\geq$ 20 mmHg are suggested for patients older than 64 years

R Rodriguez-Roisin, MJ Krowka. N Engl J Med 2008;358:2378-87

Treatment of HPS

- Liver transplant remains the only effective treatment of HPS
  (post-transplant survival is often reduced compared with patients without HPS)
- The role of TIPS in the management of HPS remains unproven
- Intra-arterial coil embolization of discrete pulmonary arteriovenous shunts has been used successfully
- An effective medical therapy for HPS has yet to be established
- Oxygen is used for symptomatic relief in HPS and helps prevent hypoxic end-organ damage

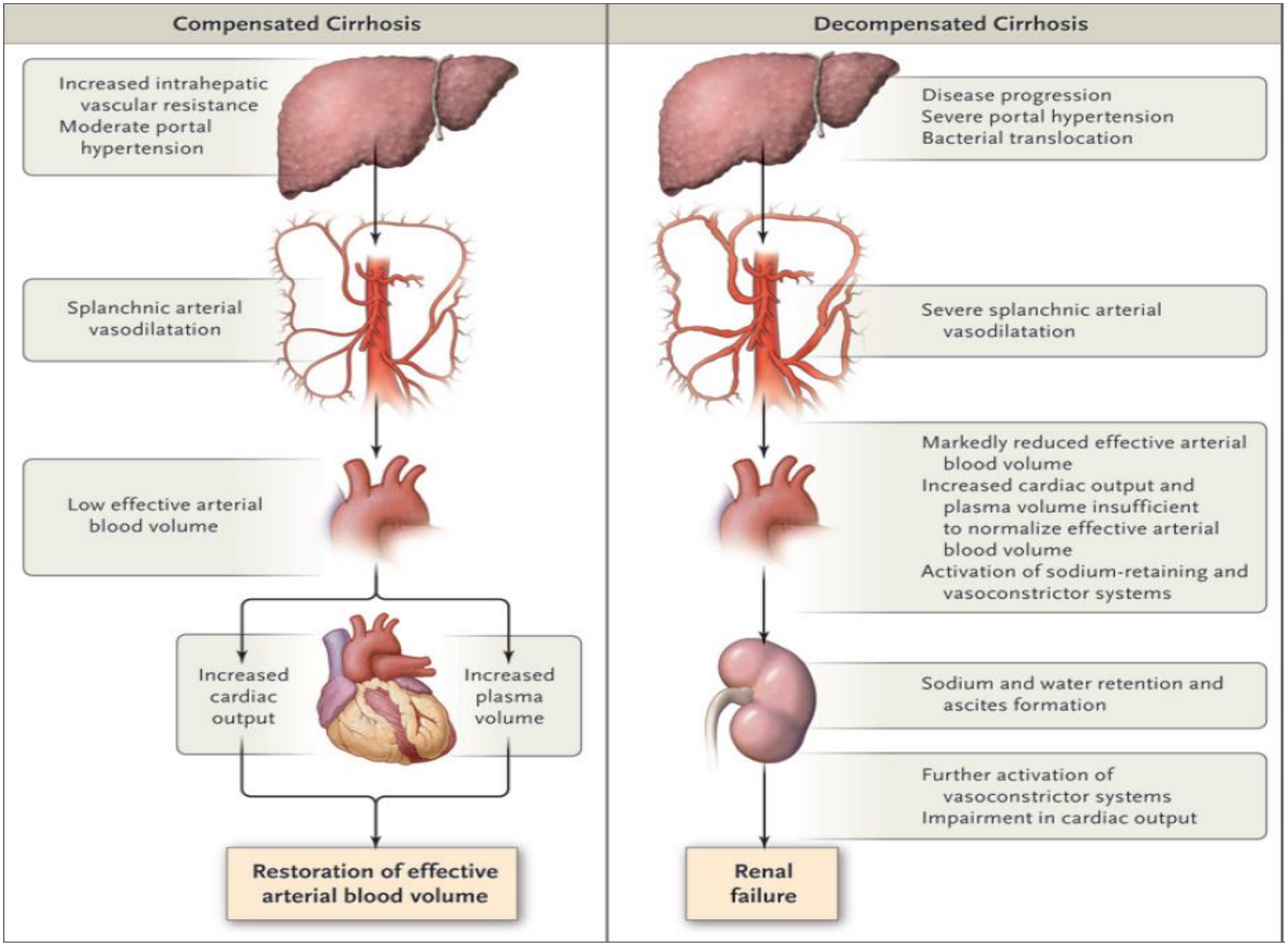
Prognosis of HPS

- Patients with HPS have an increased mortality compared with cirrhotic patients without HPS and a similar liver dysfunction
- Without liver transplantation, they have a 23% 5-year survival from diagnosis of HPS, compared with a 63% 5-year survival in matched cirrhotic controls
- Prognosis is worst in patients with severe hypoxia
  - Most patients with $PaO_2 < 60$ mmHg dying within 6 months
  - Allocating MELD points to HPS patients with $PaO_2 < 60$ mmHg who are listed for transplant

Summary

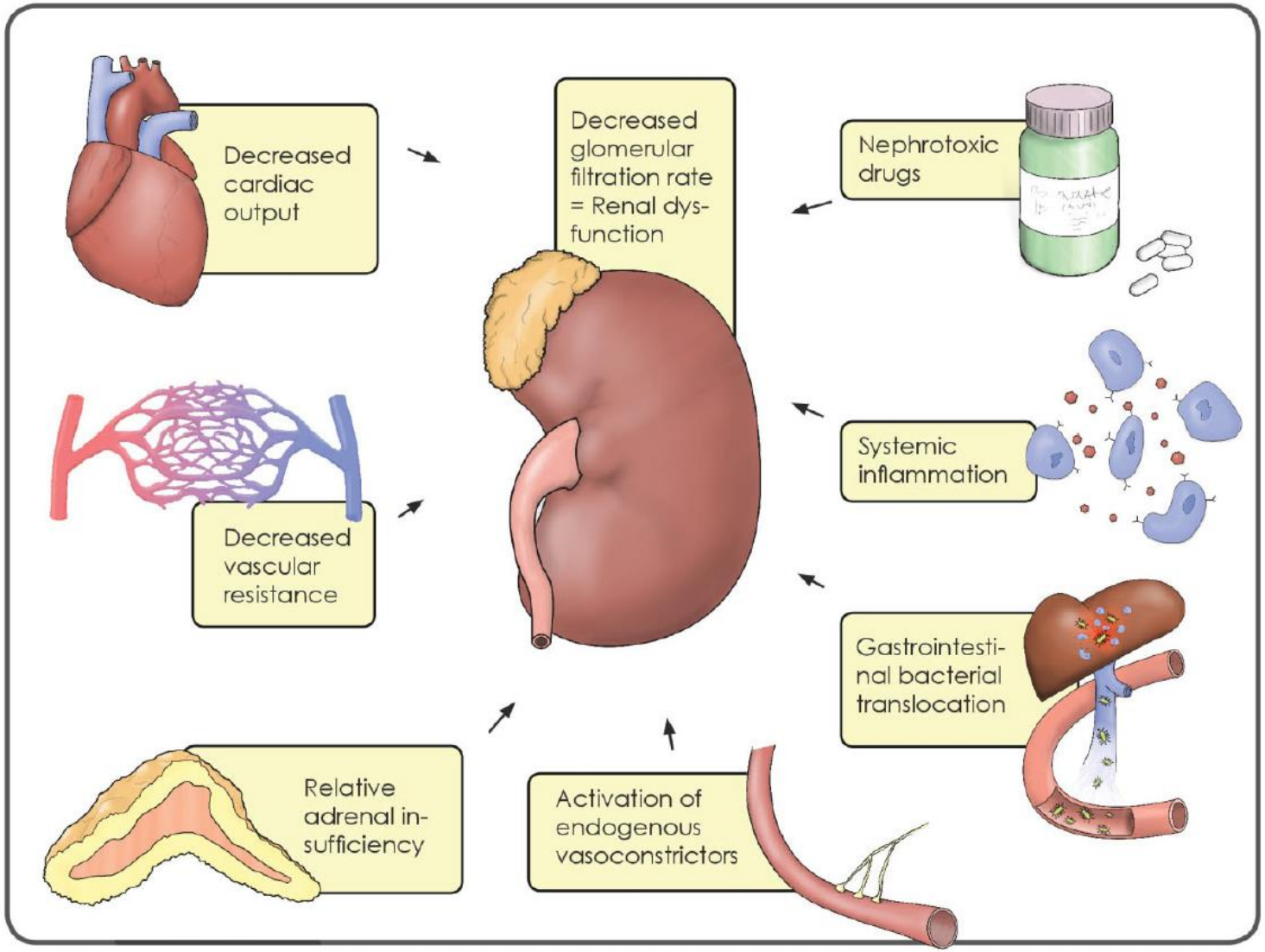
- Chronic Liver Disease
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - Hepatopulmonary syndrome
  - **Hepatorenal syndrome**
  - Coagulopathy
  - Bacterial infections

Circulatory abnormalities and renal failure in cirrhosis



Gines P, Schrier RW. N Engl J Med 2009; 361: 1279-90

Factors associated with renal dysfunction in cirrhotic patients



Journal of Gastroenterology and Hepatology **30** (2015) 236–243

Hepatorenal Syndrome (HRS)
Diagnostic criteria

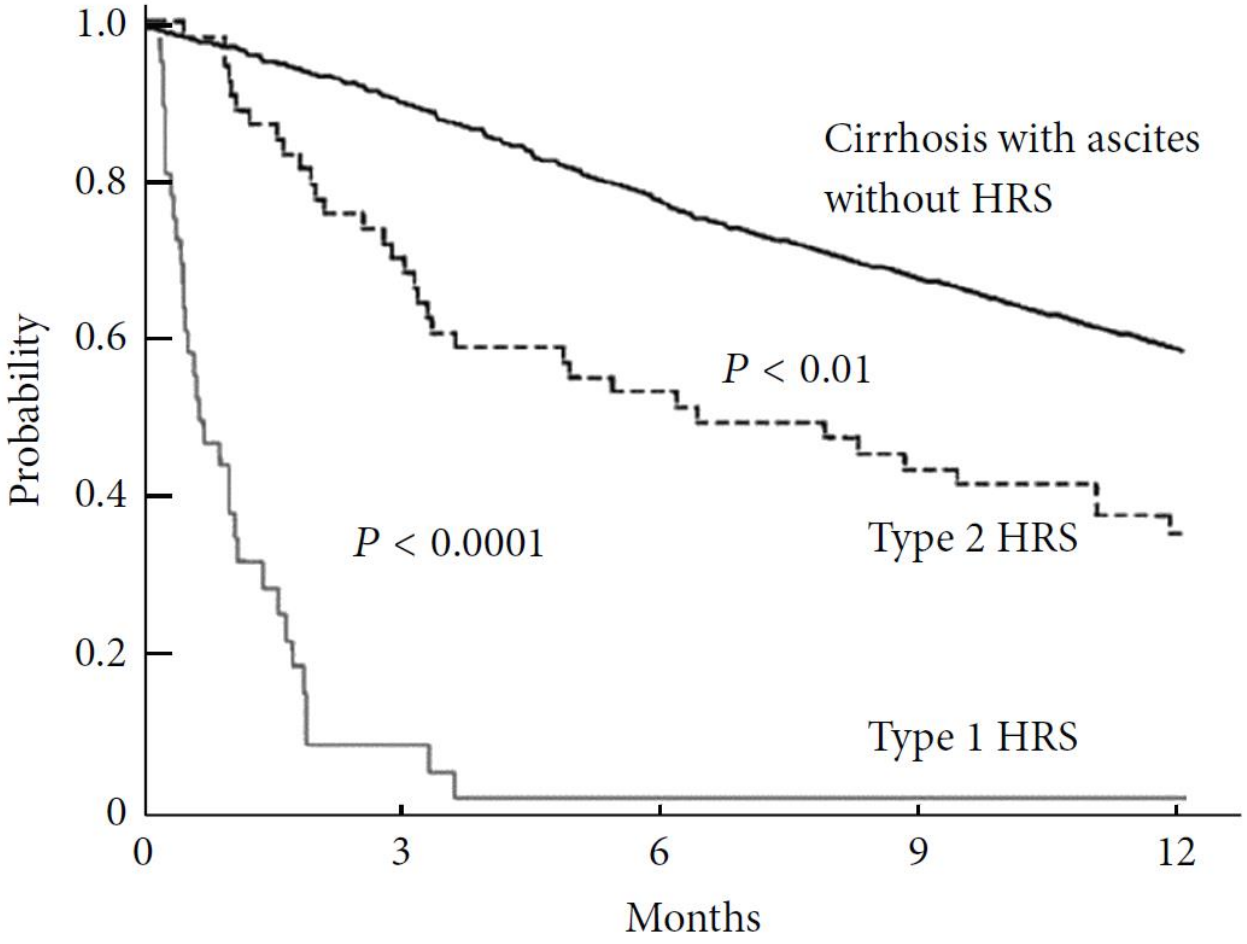
Cirrhosis with ascites
Serum creatinine > 1.5 mg/dL (133 mmol/L)
No shock
No hypovolemia (no improvement in renal function after 2 days without diuretics and with i.v. albumin (1g/kg/d up to 100 g/d)
No recent or current treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microscopic hematuria (> 50 red blood cells per high power field), and/or abnormal renal US

Salerno et al. Gut 2007; 56: 1310–8

Types of HRS

- **Type 1**
  - Rapid and progressive renal impairment
  - Doubling serum creatinine above baseline value, to a level > 2.5 mg/dl (> 226 μmol/L) in less than 2 weeks
- **Type 2**
  - Moderate renal impairment (serum creatinine > 1.5 and up to 2.5 mg/dL (133 – 226 μmol/L), with a steady progressive curse (over weeks to months)
- **Epidemiology**
  - Annual incidence: 7,6%; Prevalence: 13 to 45,3%

Probability of survival in cirrhotic patients



G. Low, et al. Gastroenterol Res Pract 2015; http://dx.doi.org/10.1155/2015/207012

Evidence-based treatment of HRS

Liver transplantation should be considered in all patients with HRS and advanced liver disease

HRS type 1

Terlipressin: The recommended dose is 1 mg × 4–6/day. The dose may be increased by lack of effect to a maximum of 2 mg × 6/day. Treatment continues to the S-creatinine level is < 1.5 mg/dL (< 133 μmol/L)

Albumin: The recommended dose is 1 g/kg human albumin on the first day of treatment followed by 20–40 g daily

HRS type 2

Therapeutic paracentesis: Should be offered to cirrhotic patients with refractory ascites who do not qualify for treatment with TIPS

TIPS: Should be considered in all patients with HRS type 2 and refractory ascites

Journal of Gastroenterology and Hepatology **30** (2015) 236–243

Drugs that should be avoided or used with caution in cirrhotic patients with ascites

NSAIDs	Should be avoided
ACE inhibitors, AT-II receptor antagonists and α_1-adrenergic receptor blockers	Use with caution and avoid completely at elevated creatinine
Diuretics	Caution should be taken by monitoring of creatinine, electrolytes and hydration
Laxatives	Pay attention to diarrhoea and dehydration
Aminoglycosides	Should be avoided
Contrast media	Use with caution and avoid completely at elevated creatinine
Beta-blockers	Careful titration and caution at elevated creatinine and low blood pressure

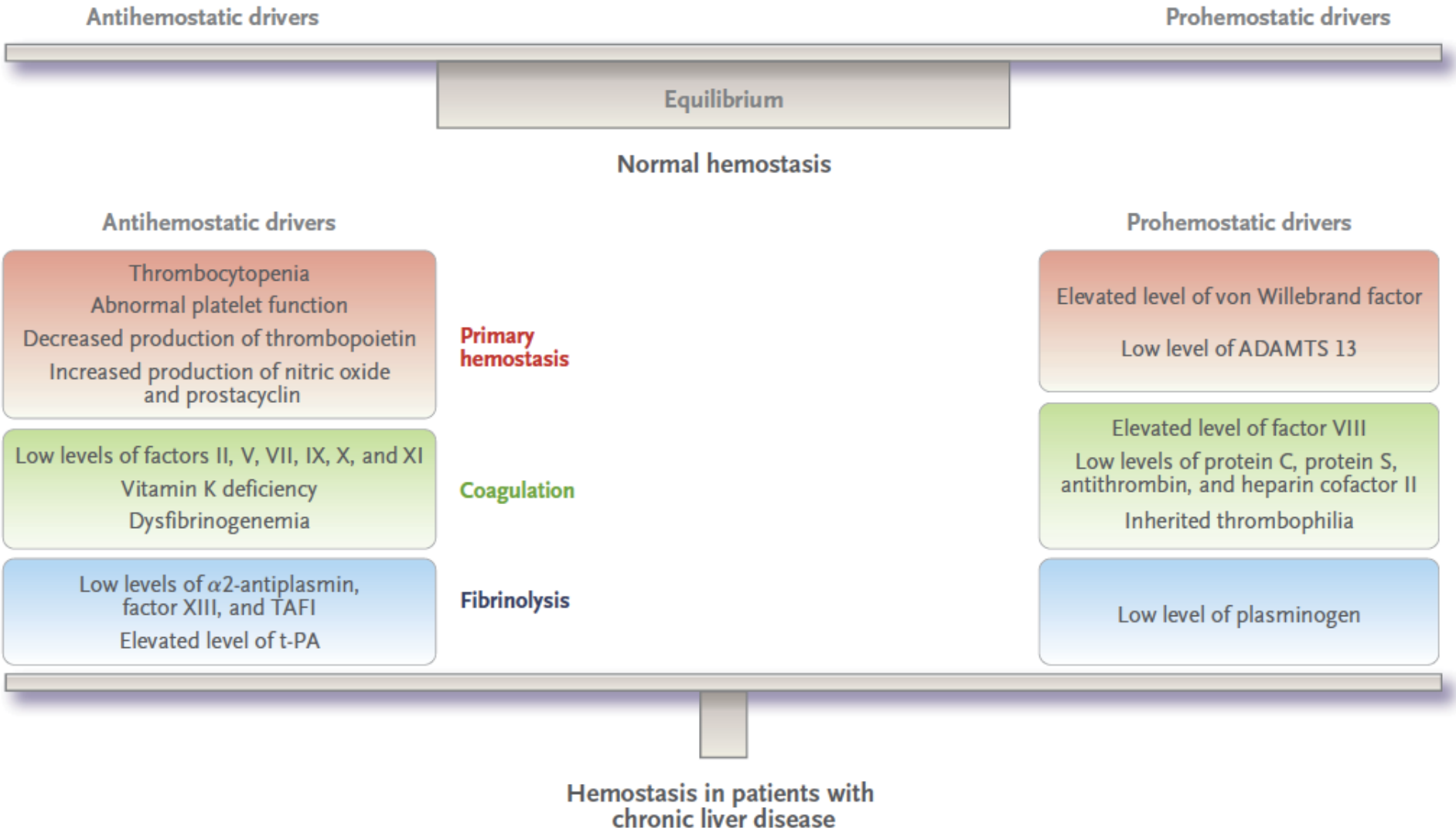
ACE, angiotensin converting enzyme; AT, angiotensin; NSAID, non-steroid anti-inflammatory drug.

Journal of Gastroenterology and Hepatology **30** (2015) 236–243

Summary

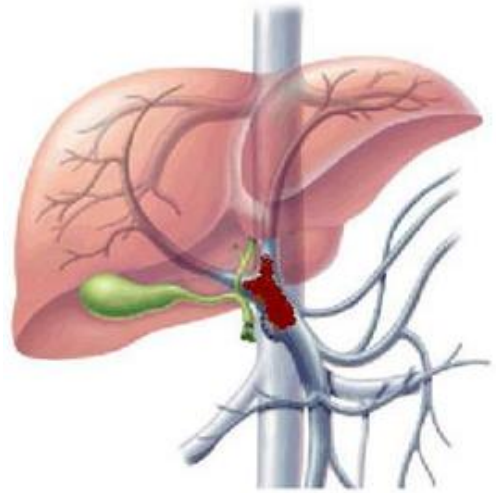
- Chronic Liver Disease
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - Hepatopulmonary syndrome
  - Hepatorenal syndrome
  - **Coagulopathy**
  - Bacterial infections

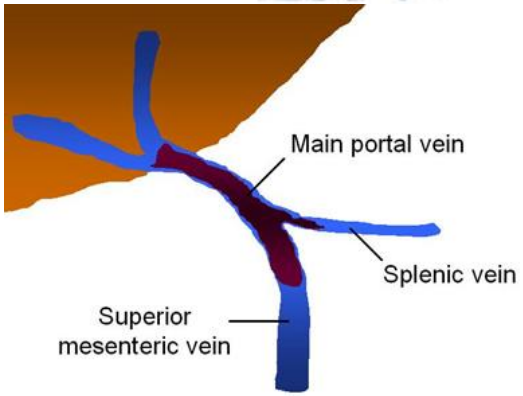
Balance of antihemostatic and prohemostatic drivers in patients with liver cirrhosis



A Tripodi, PM Mannucci. N Engl J Med 2011;365:147-56.

Portal vein thrombosis (PVT)





- Acute PVT is defined as a recent formation of a thrombus within the portal vein and/or right or left branches
  - The thrombus may extend into the mesenteric or splenic veins
  - Occlusion may be complete or partial
- PVT consists of two different entities, acute and chronic, which represent successive stages of the same disease and share similar causes, but differ in management
- PVT is caused by a combination of local and general risk factors (a local risk factor can be identified in about 30% of patients, and a general risk factor in 70%)

EASL CPG: Vascular diseases of the liver. J Hepatol 2015
AASLD Practice Guidelines, HEPATOLOGY 2009

Etiological factors in Budd-Chiari syndrome and PVT

	BCS	PVT
Risk factor	Frequency (%)	Frequency (%)
Thrombophilia		
Inherited	21	35
Acquired	44	19
Myeloproliferative neoplasm	49	21
JAK2 pos	29	16
Hormonal factors	38	44
Oral contraceptives	33	44
Pregnancy	6	0
PNH	19	0
Other systemic factors	23	n.d.
Local factors	0	21

BCS, Budd-Chiari syndrome; PVT, portal vein thrombosis; PNH, paroxysmal nocturnal haemoglobinuria; n.d, no date.

EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Workup of cirrhotic patients with thrombotic diseases

- Investigate underlying local and systemic prothrombotic factors
- Diagnosis for inherited and acquired thrombophilia factors
  (myeloproliferative neoplasms, PNH, and autoimmune disorders)
- Investigate patients for local risk factors
  (intra-abdominal inflammatory conditions and abdominal malignancies)
- Thrombophilia screening
  (protein S, protein C, antithrombin, FVL mutation, prothrombin G20210A gene variant, antiphospholipid antibodies)
- Test for JAK2V617F mutation
  (if negative, calreticulin mutation screening should be performed;
  if both negative, bone marrow histology)
- Treat the underlying condition appropriately
  (in case of MPN, anticoagulant treatment should be given indefinitely)

EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Diagnosis of acute PVT

- Consider the diagnosis of acute portal vein obstruction in any cirrhotic patient with abdominal pain
- Doppler ultrasound as the first line for acute PVT, and CT for diagnostic confirmation and assessment of extension
- Establish or rule out underlying cirrhosis or obliterative portal venopathy
- Consider intestinal infarction in patients with persisting severe abdominal pain, rectal bleeding, moderate or massive ascites, or multi-organ dysfunction

EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Treatment of acute PVT

- Aim of therapy for acute PVT
  - to prevent the extension of thrombosis to mesenteric veins and, thereby, mesenteric venous infarction
  - to achieve portal vein recanalization
- Thrombus extension was prevented in all patients who had early initiation of anticoagulant therapy
- With proper anticoagulation, recanalization of the portal vein was obtained in 39%, of the splenic vein in 80% and of the superior mesenteric veins in 73%
- Bleeding while on anticoagulation occurred in 9% of patients (Mortality rate was 2% and was not related to bleeding or PVT)

EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Treatment of acute PVT

- Initiate immediate anticoagulation with LMWH, in the absence of major contraindications
  - Anti-Xa activity should be monitored in overweight patients, pregnancy, and poor kidney function (level between 0.5 and 0.8 IU/ml)
- Oral vitamin K antagonists for long-term anticoagulation, given for at least 6 months, targeting an INR between 2 and 3
- Perform a CT scan to assess recanalization of the portal venous system at 6-12 months follow-up
- Screen for gastroesophageal varices in unrecanalized patients
- MR cholangiography in patients with persisting cholestasis or biliary tract abnormalities suggestive of portal biliopathy

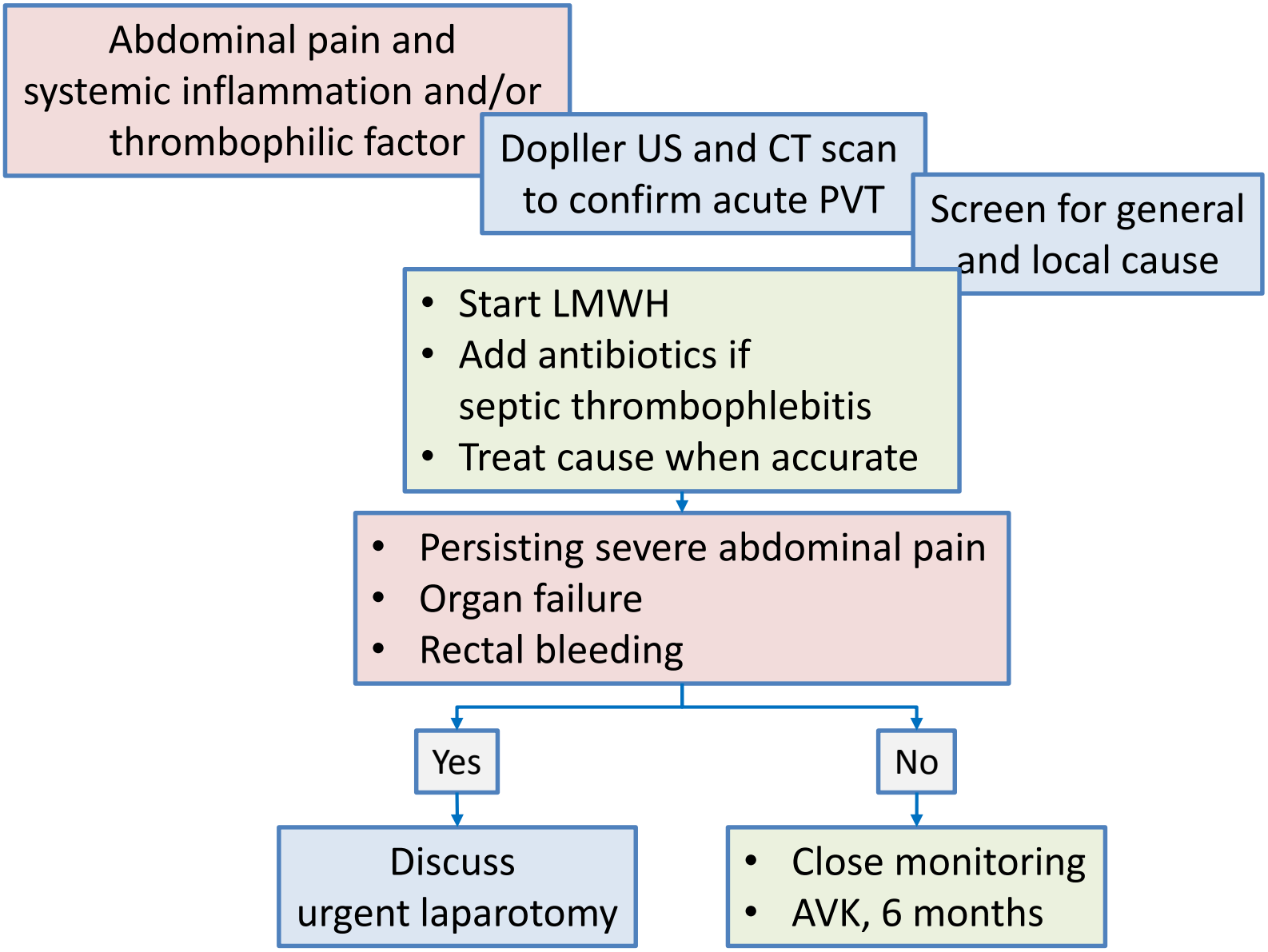
EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Treatment of PVT

- Local thrombolysis (venous or arterial)
  - Experience in no more than 100 patients, mainly as case reports
  - Recanalization rates similar to those achieved with anticoagulation
  - 50% of treated patients developed major procedure-related bleeding, with a fatal outcome in some
- Balloon angioplasty and/or stent placement without thrombolysis or thrombectomy
  - May be a safe and effective treatment modality for post-operative main portal vein and superior mesenteric vein thrombosis
- **Long-term outcome of patients with chronic PVT is good (5-year survival > 70%) and mostly related to the associated conditions – the risk/benefit balance of such invasive procedures have to be considered**

EASL CPG: Vascular diseases of the liver. J Hepatol 2015

Algorithm for the management of acute PVT



EASL CPG: Vascular diseases of the liver. J Hepatol 2015

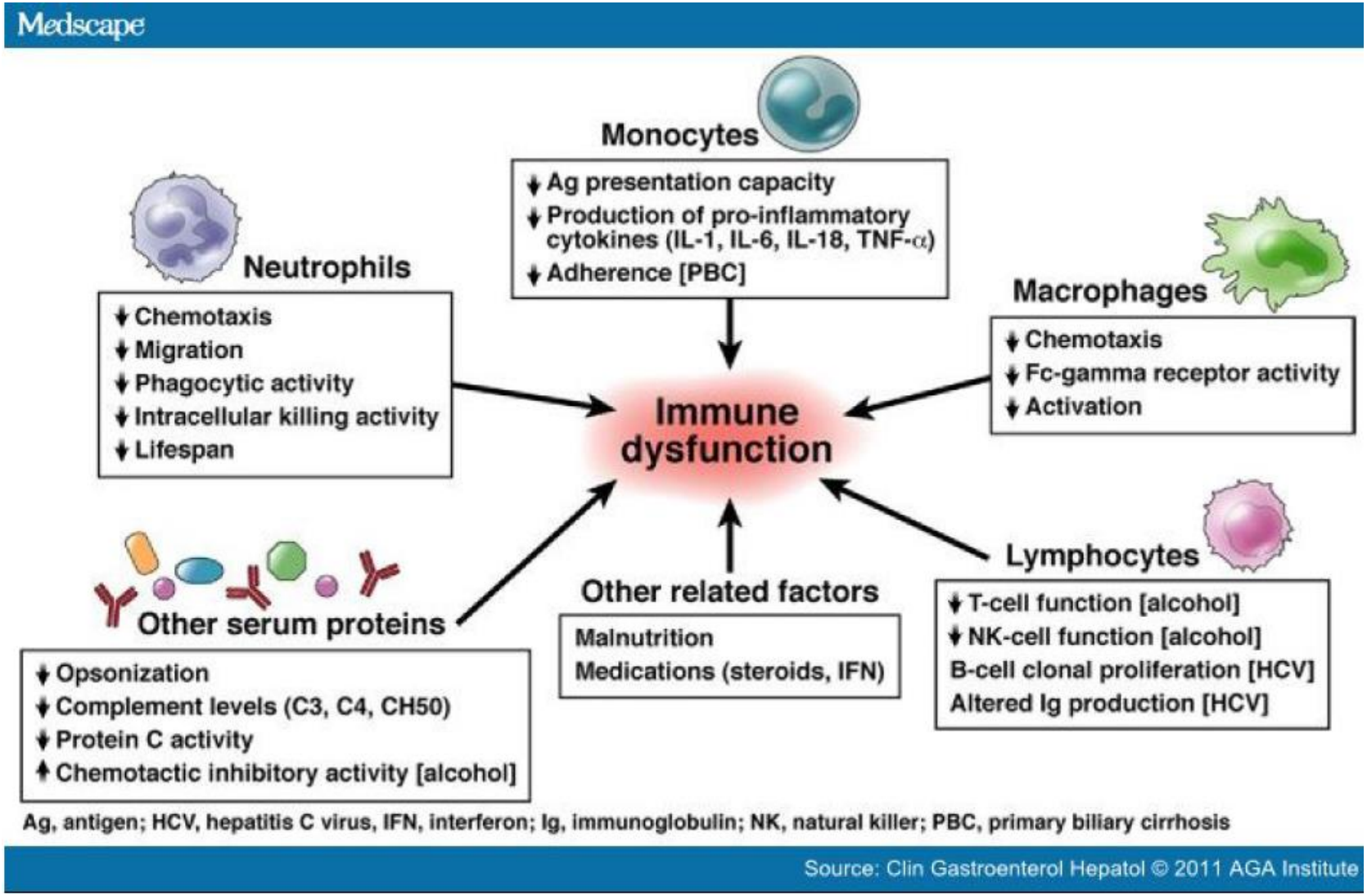
Summary

- Chronic Liver Disease
  - Natural History (chronic hepatitis, cirrhosis, HCC)
  - Pathophysiology
  - Evaluation
- **Systemic complications of liver cirrhosis**
  - Encephalopathy
  - Hepatopulmonary syndrome
  - Coagulopathy
  - Hepatorenal syndrome
  - **Bacterial infections**

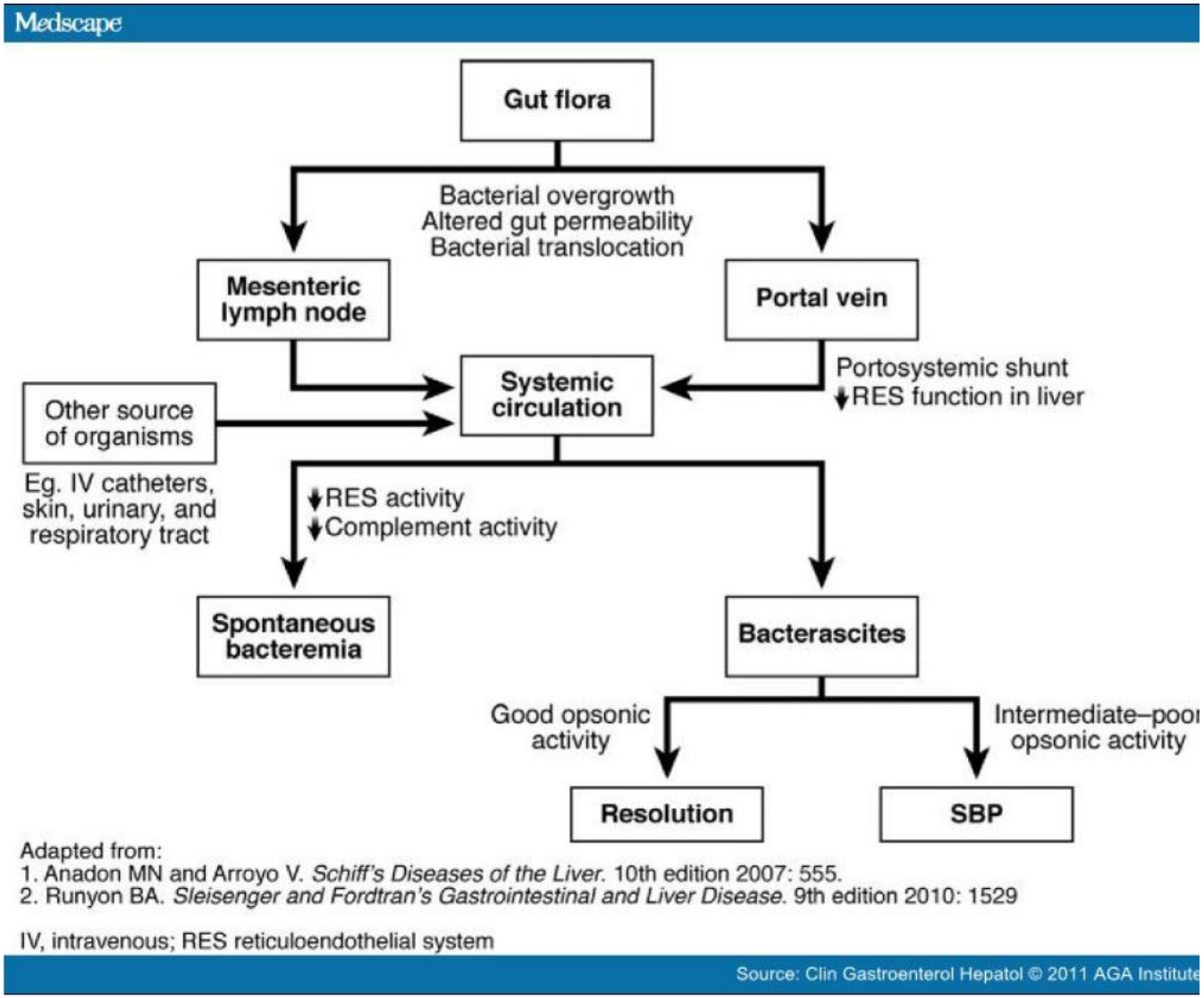
Bacterial infections in cirrhosis

- Patients with cirrhosis have an increased risk of developing bacterial infections, sepsis, and death
- Infection is present at admission or develops during hospitalization in about 25% to 35% of patients
- Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent, followed by pneumonia, cellulitis, and bacteremia
- Concerning acquisition of infection, approximately
  - 30% are community-acquired
  - 30% are health care–associated
  - 35% to 40% are nosocomial

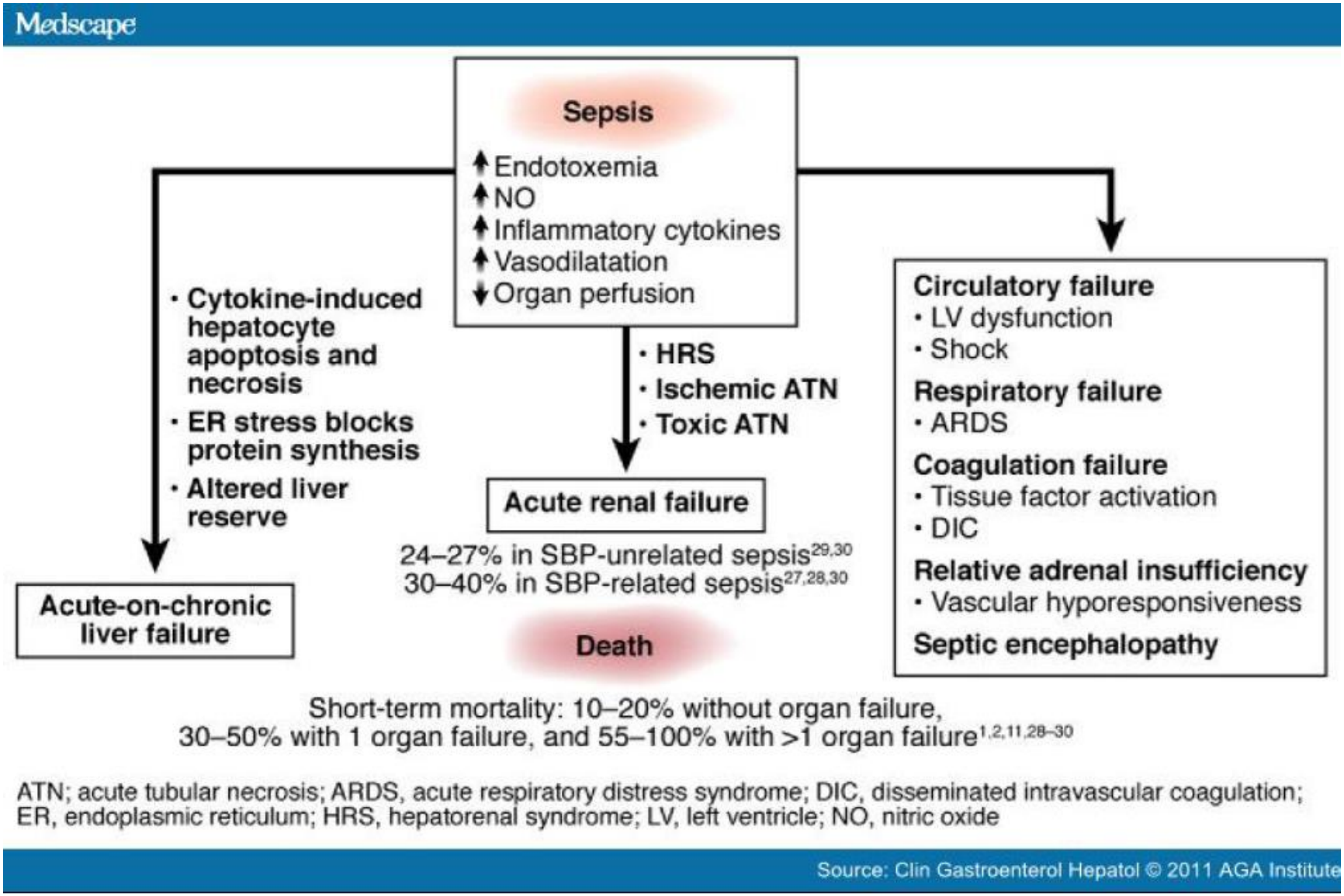
Immune dysfunction in liver cirrhosis



Source of infection in liver cirrhosis



Sepsis in liver cirrhosis



MULTIRESISTANT BACTERIA IN CIRRHOTIC PATIENTS

RECOGNIZE THE LOCAL PATERN

Cochicho J., Madaleno J., Louro E., Silva N., Simão A., Carvalho A.

CHUC
HOSPITAIS DA UNIVERSIDADE DE COIMBRA

Serviço de Medicina Interna A
Director: Prof. Doutor Armando de Carvalho

U C

FMUC FACULDADE DE MEDICINA UNIVERSIDADE DE COIMBRA

Material and Methods

- Retrospective study of clinical and microbiological data from cirrhotic patients admitted in Internal Medicine wards between January 2010 and December 2013

- European Center for the Disease Prevention and Control criteria for multiresistance: bacteria resistant to 3 or more of the main antibiotic families, including β-lactam

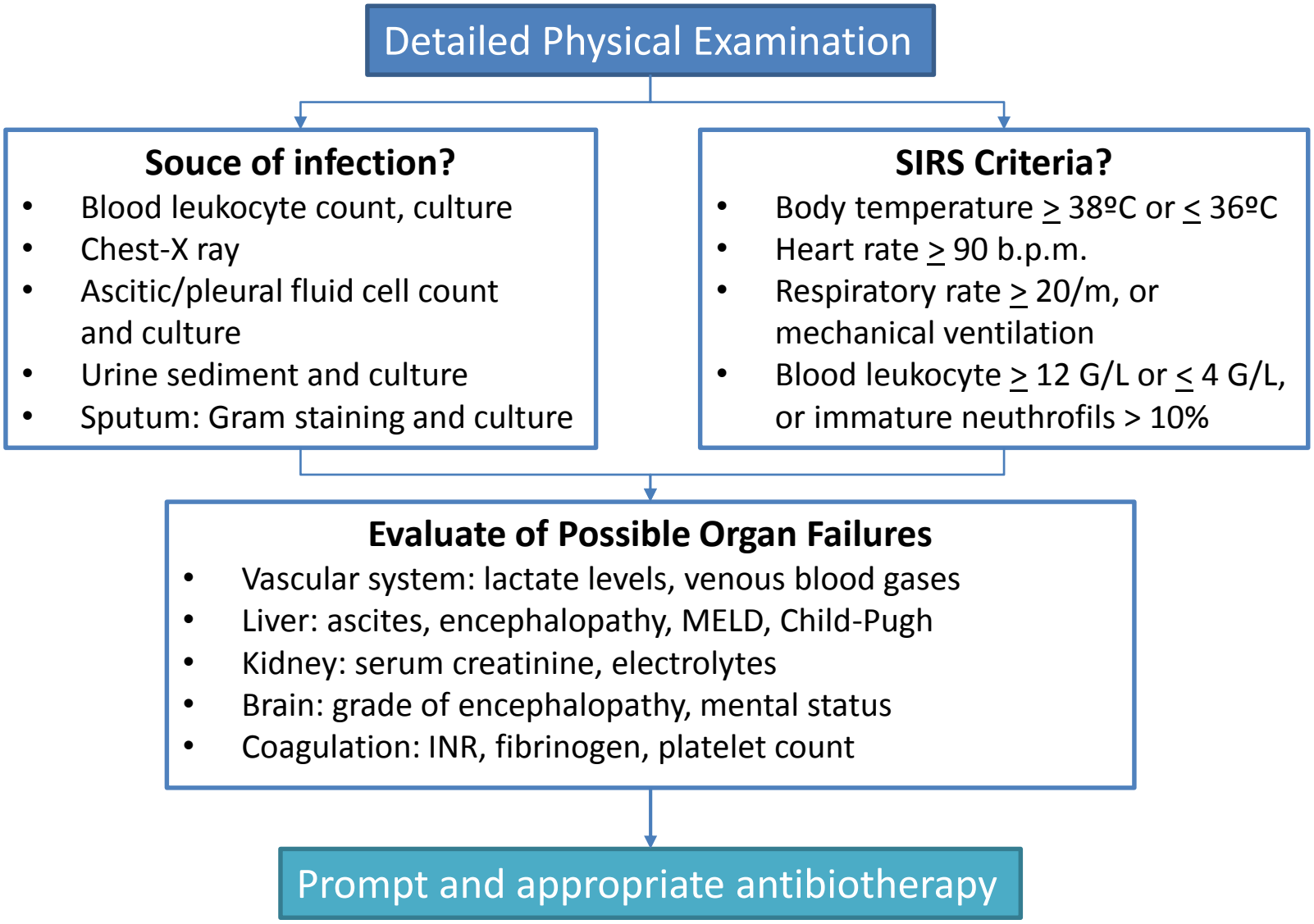
Results

- 307 admission of 163 patients (71.5% male; mean age 63.5 ± 11.4 years)
- Alcoholic cirrhosis in 77.3%; Child-Pugh class: 28,8% B, 68,6% C
- Infection confirmed in 154/307 admissions (50.2%)
  - Community acquired in 12%
  - Nosocomial in 40%
  - Health-care associated in 48%
  - **Positive cultures in 126 admissions**
  - **Multi-resistant bacteria in 26%**

	%
E. coli	38
MRSA	26
K.pneumoniae	18
A. baumannii	9
Enterobacteriaceae β-lactamase-producting	22

In vitro resistance to, at least, one EASL recommended antibiotics for empiric therapy was found in 52% of our cases

Diagnosis of bacterial infections in cirrhosis



J Fernandez, V Arroyo. Clin Liver Dis 2013; 2:102-5

Antibiotic prophylaxis in cirrhosis

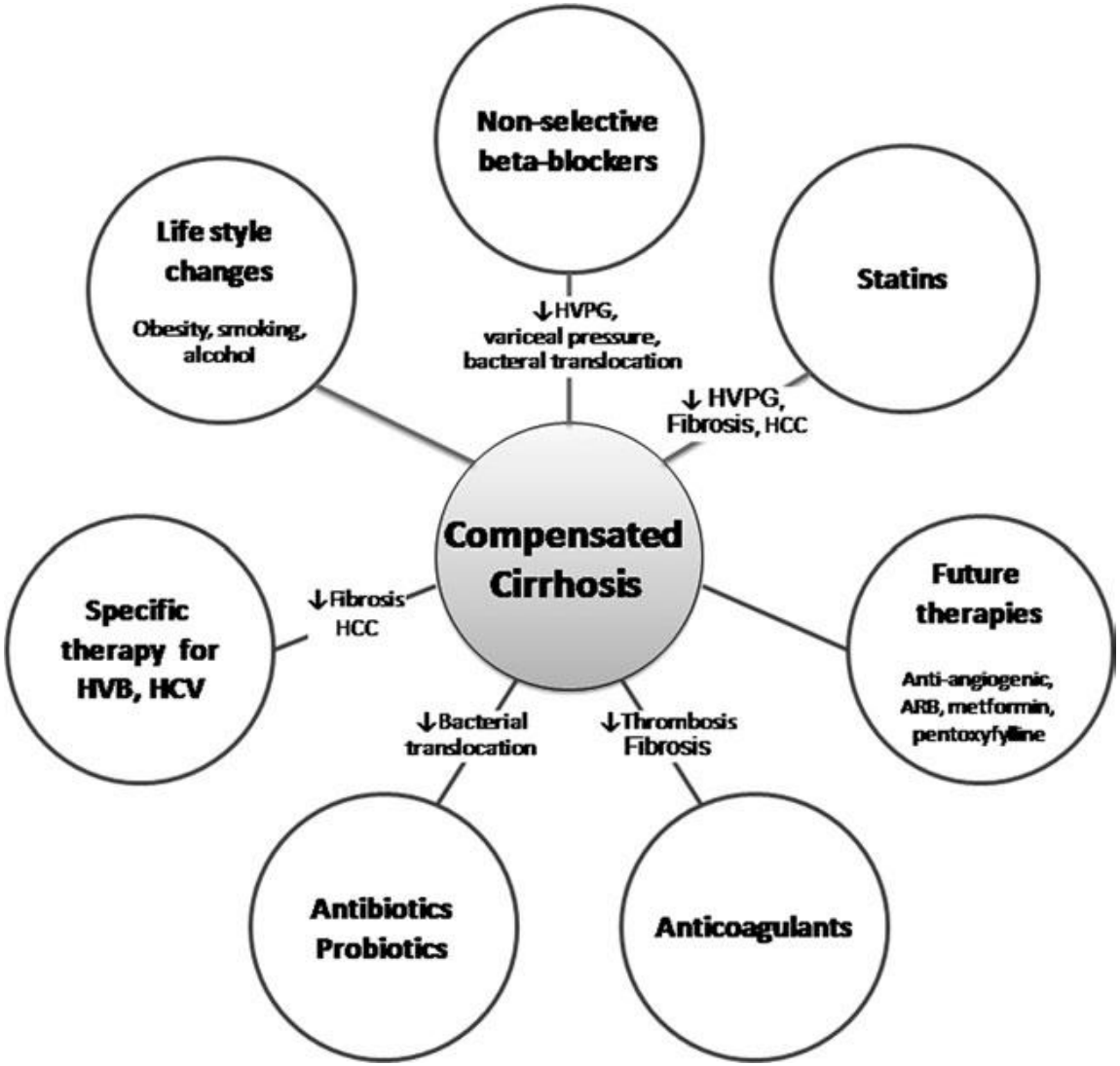
- Antibiotic prophylaxis must be restricted to selected patients at a very high risk for the development of bacterial infections
- This restriction is essential to prevent the development of antibiotic resistance in cirrhosis and to make prophylactic strategies cost-effective
- Current indications of antibiotic prophylaxis are gastrointestinal bleeding, low protein ascites in advanced cirrhosis, and previous episode of SBP

Indication	Antibiotic Regimen	Duration
Gastrointestinal bleeding	Norfloxacin 400 mg/12 hours by mouth Intravenous ceftriaxone 1 g/day in patients with advanced cirrhosis (at least two of the following: ascites, jaundice, hepatic encephalopathy, malnutrition)	Seven days
Low protein ascites (<15 g/L) and advanced cirrhosis	Norfloxacin 400 mg/day PO in patients with renal dysfunction (serum creatinine ≥1.2 mg/dL, blood urea nitrogen ≥25 mg/dL, or serum sodium ≤130 mEq/L) and/or poor liver function (Child-Pugh score ≥9 with serum bilirubin ≥3 mg/dL)	Until liver transplantation, disappearance of ascites, or death
Secondary prophylaxis for SBP	Norfloxacin 400 mg/day by mouth	Until liver transplantation or death

J Fernandez, V Arroyo. Clin Liver Dis 2013; 2:102-5

New paradigm in the treatment of cirrhosis

Preventing rather than treating its complications



EA Tsochatzis, et al.. HEPATOLOGY 2012; 56: 1983-1992