LA CIRROSI E LE SUE COMPLICANZE

Lezione Gastroenterologia

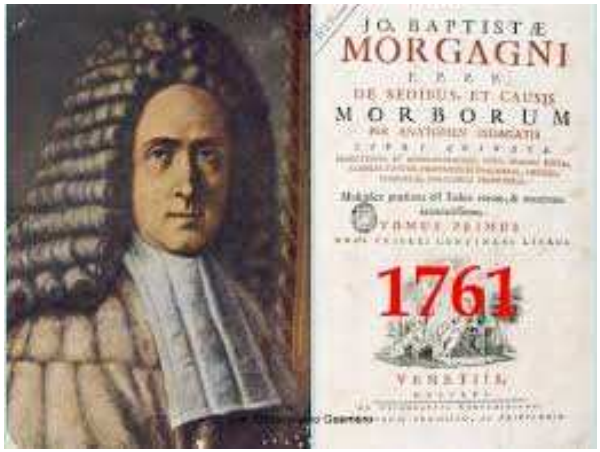
14/04/18

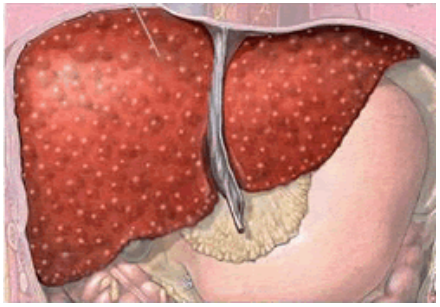
V anno Medicina e Chirurgia

LA CIRROSI

"Fegato duro"

Libro III, Delle malattie del ventre, Lettera XXXVIII,
Dell'Idropisia ascite, della Timpanite, dell'Idropisia del peritoneo
e di altre idropisie dette saccate)



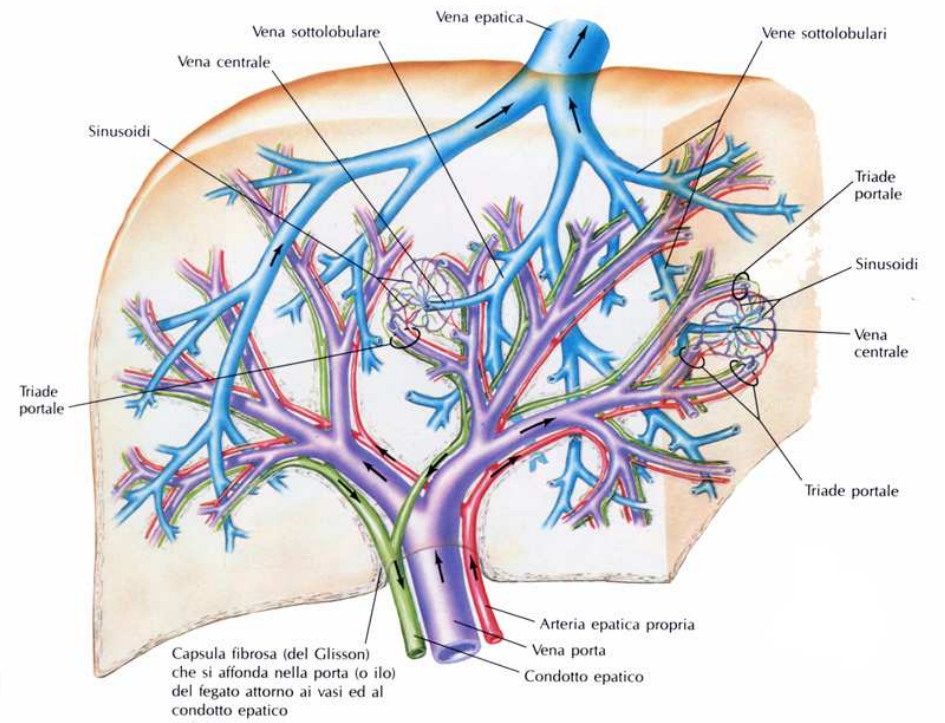


Definizione <u>ISTOLOGICA</u>
ALTERAZIONE DIFFUSA DEL FEGATO **FIBROSI**+**NODULI RIGENERATIVI**

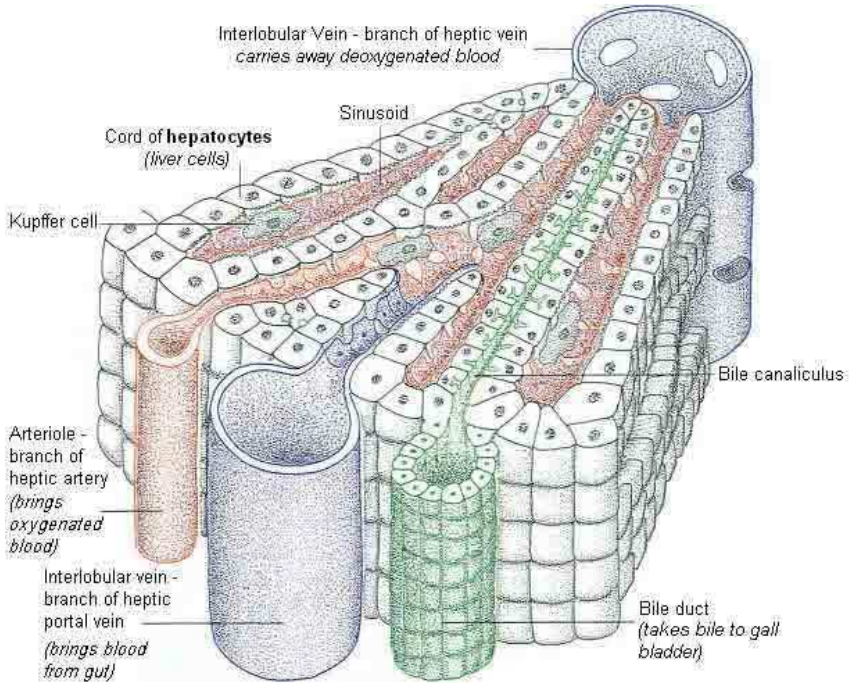
EPIDEMIOLOGIA

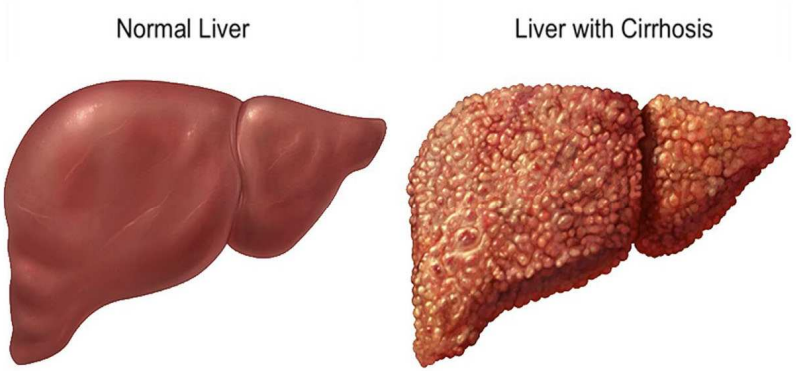
- 1,6% epatopatia cronica (3,9 milioni, USA 2015)
- 49500 morti anno cirrosi (USA, 2010)
- 19500 morti anni carcinoma epatico (USA)
- 8° causa di morte (USA)
- 2 Bilioni dollari costi+10 bilioni costi indiretti

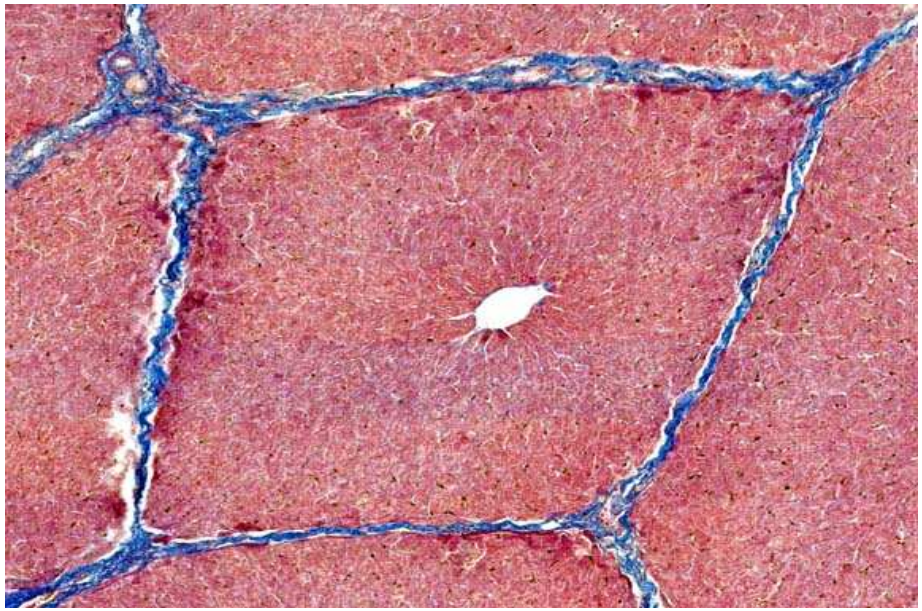
Architettura Macroscopica

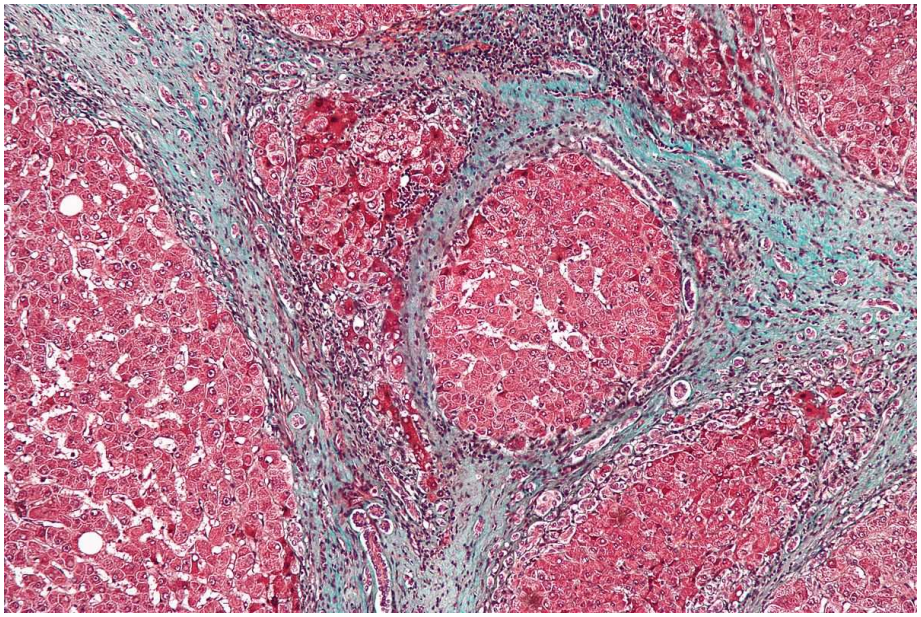


Architettura Microscopica







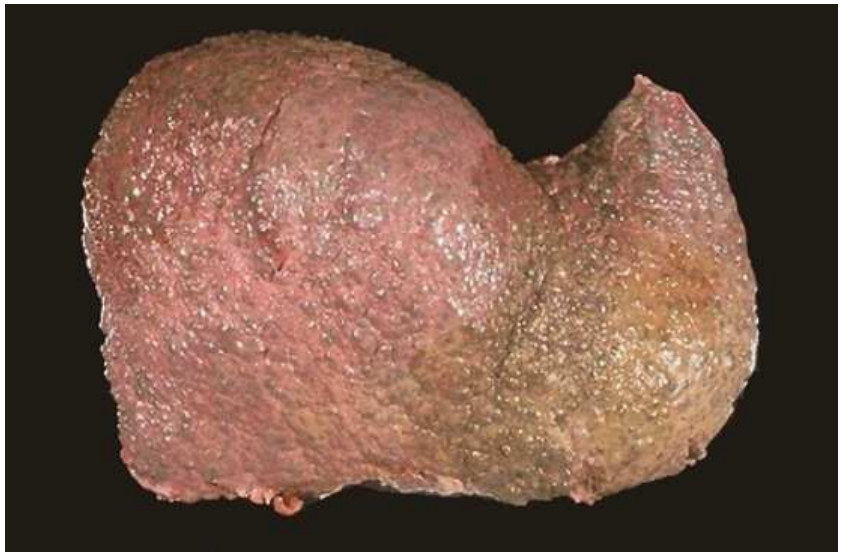


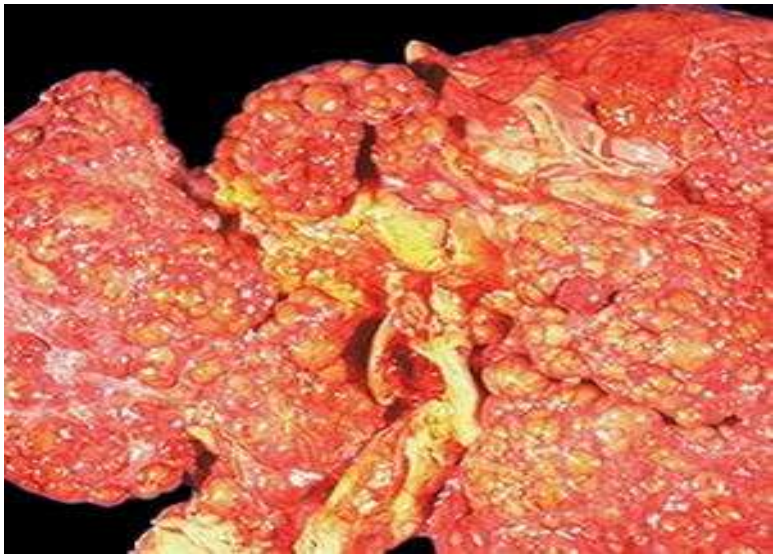
NORMAL LIVER

CIRRHOTIC LIVER

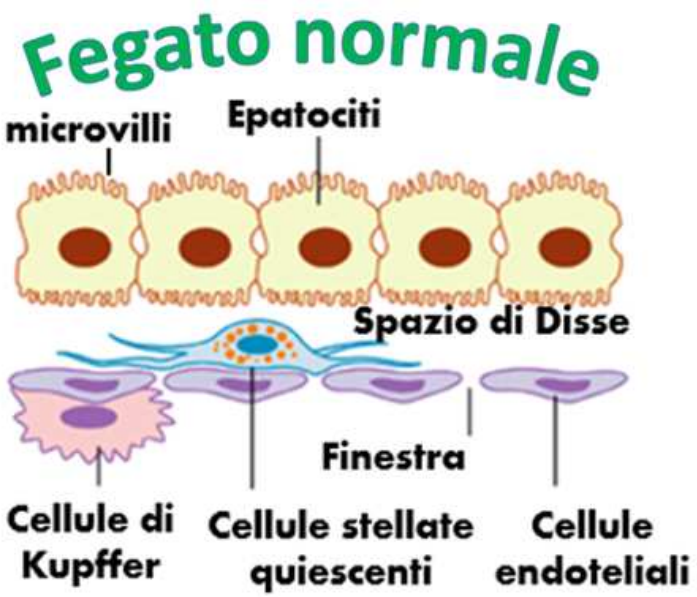
Cirrosi Micronudulare (es etilica)

Cirrosi Macronudulare (es epatiti)

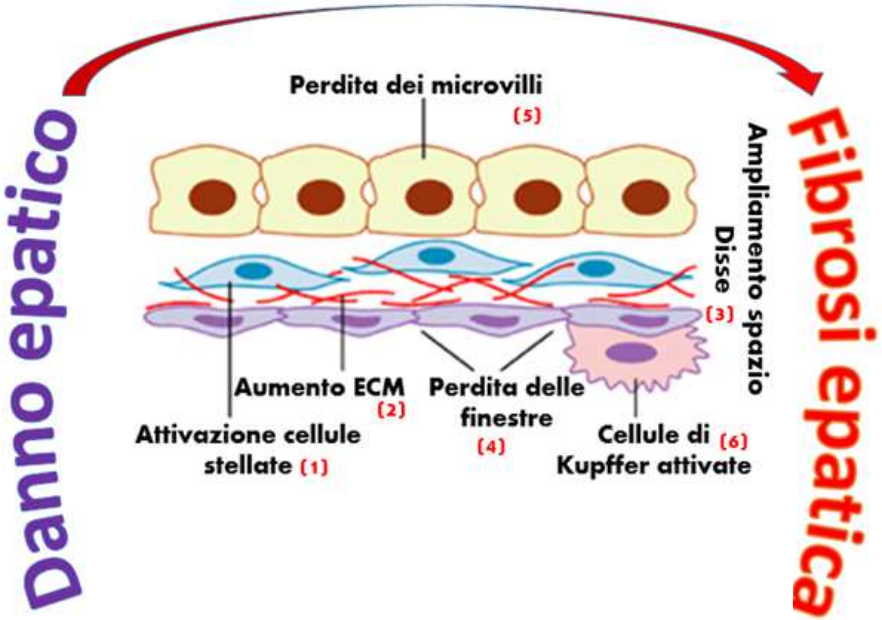




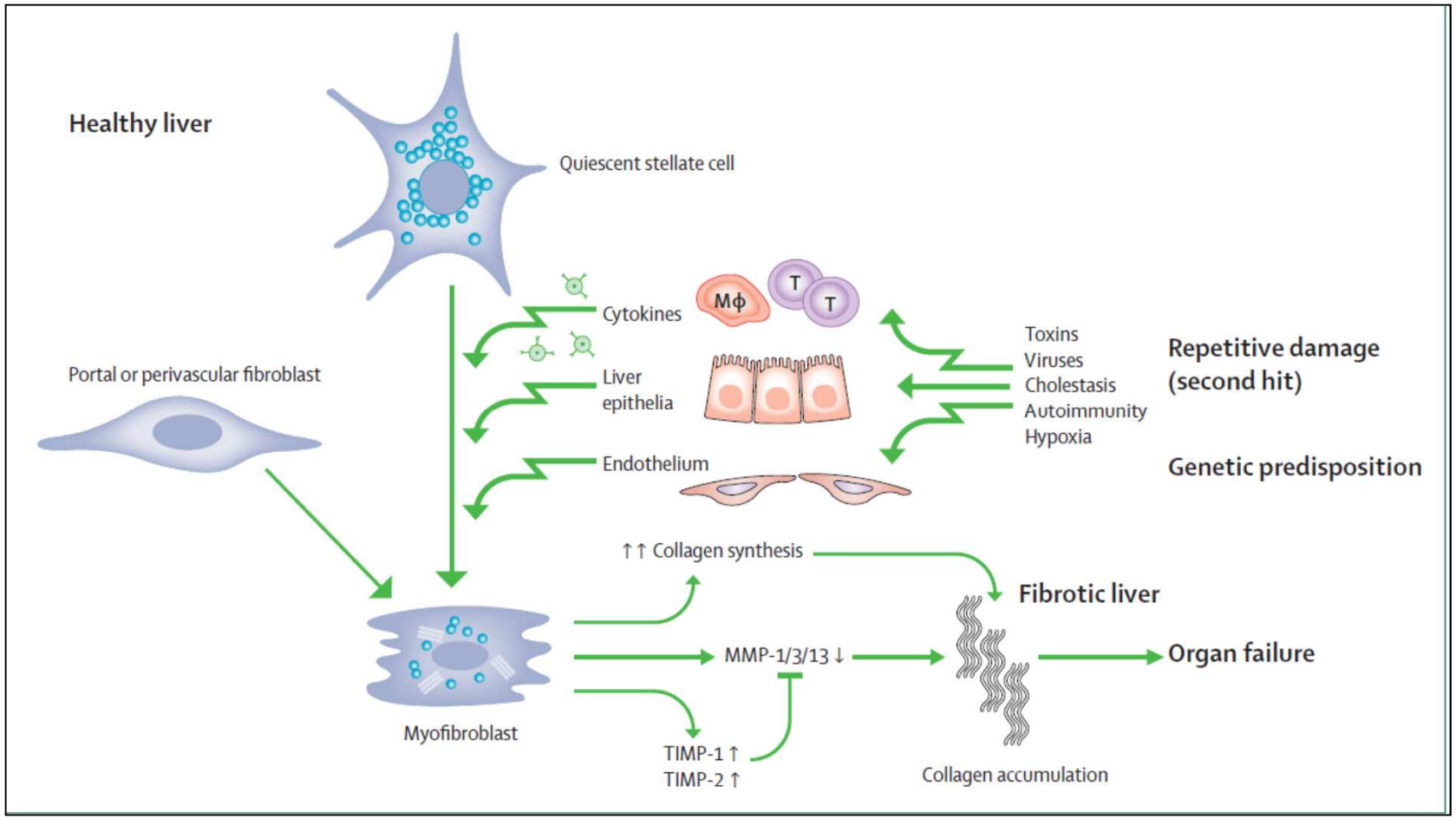
Macronoduli >3 mm

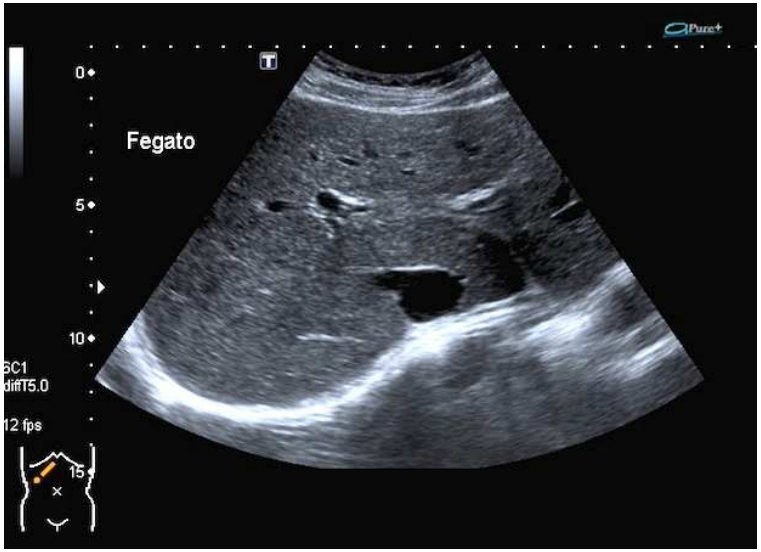


Noxa patogena



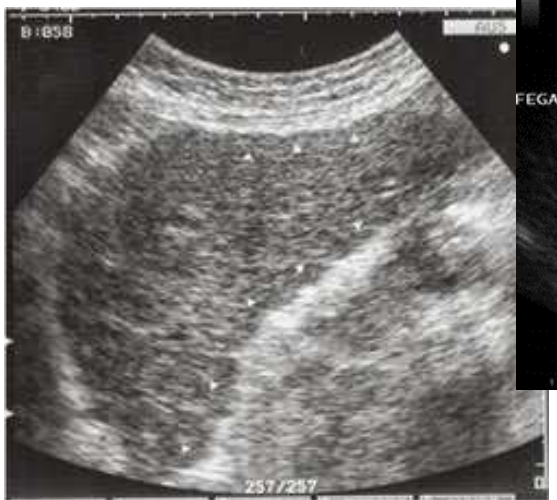
Initiation and maintenance of fibrogenesis

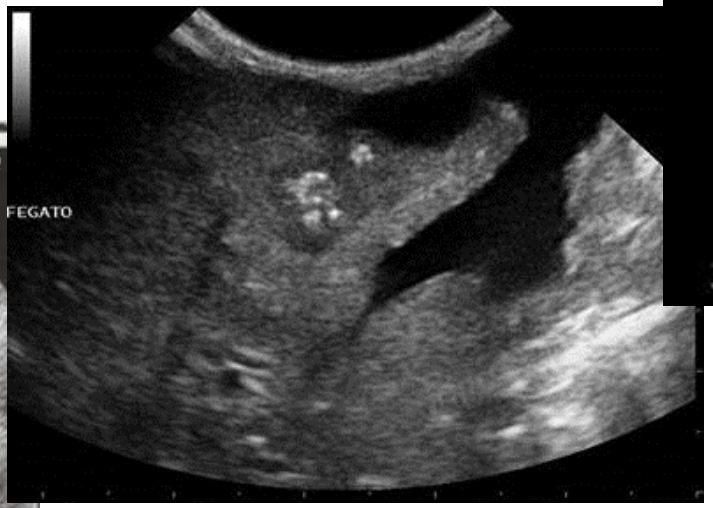


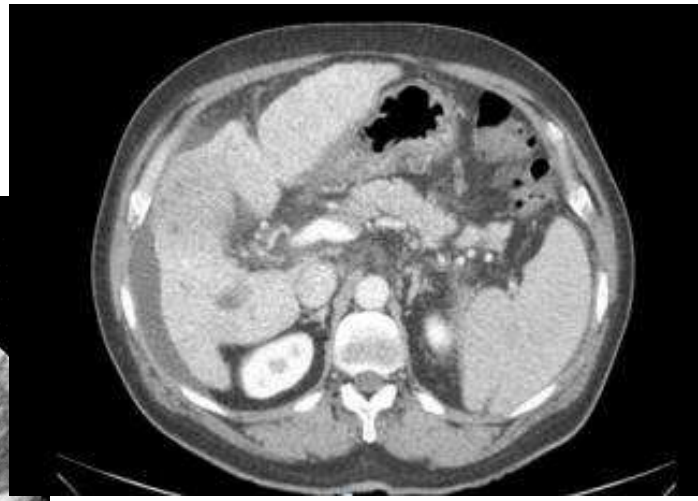


Fegato normale

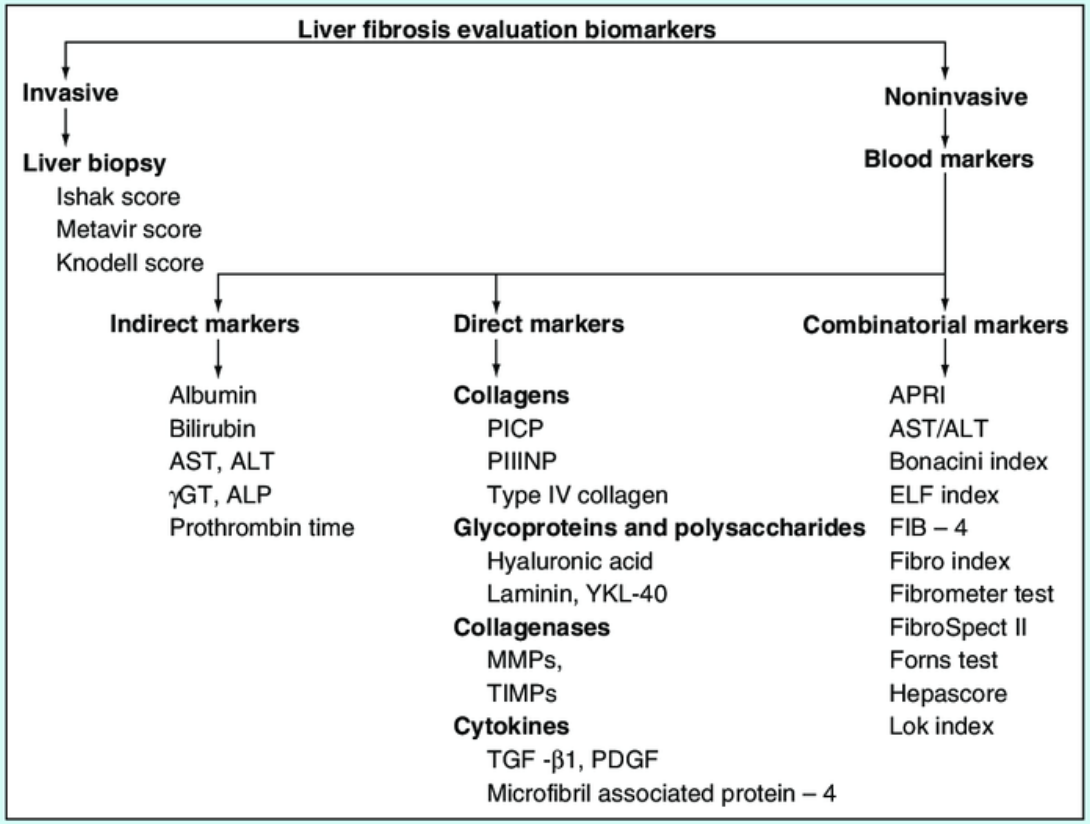
Fegato cirrotico



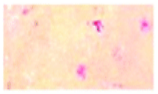
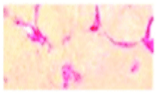
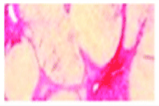
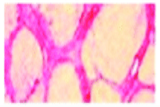


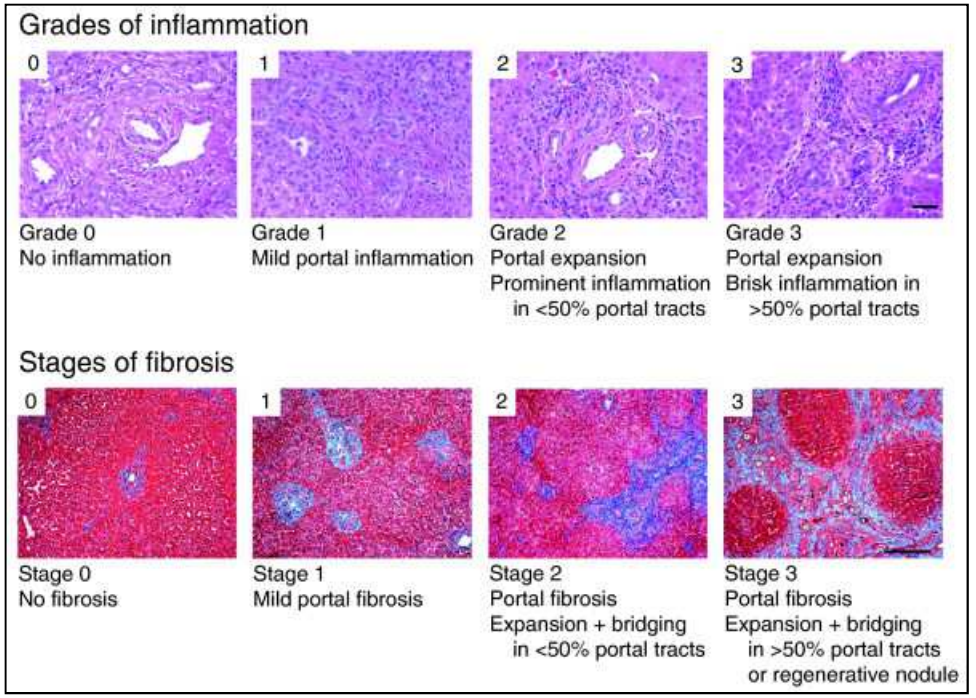


METODICHE QUANTIFICAZIONE FIBROSI



LIVER BIOPSY

Appearance	Ishak stage: categorical description	Ishak	Metavir
	No fibrosis (normal)	0	F0
	Fibrosis expansion of some portal areas ± short fibrous septa	1	F1
	Fibrosis expansion of portal areas ± short fibrous septa	2	F2
	Fibrosis expansion of most portal areas with occasional portal to portal (P-P) bridging	3	
	Fibrosis expansion of portal areas with marked portal to portal (P-P) bridging as well as portal to central (P-C)	4	F3
	Marked bridging (P-P and / or P-C) with occasional nodules (incomplete cirrhosis)	5	
	Cirrhosis, probable or definite	6	F4



FIBROSCAN

- Onde elastiche→rigidità strutture epatiche (fibrosi (kPa, normale 5,3 kPa).
- Cilindro epatico (4,0 cm lung. Ed 1 cm spessore)
- Velocità onda elastica proporzionale fibrosi
- kPa >7,6 fibrosi significativa.

EZIOLOGIA

VIRALE
Epatite B-C (10%)

METABOLICHE Acquisite
Epatosteatite (10%)

METABOLICHE Congenite
Emacromatosi (5-10%)
Tyrosinemia
Galattosemia
Glicogenosi
Wilson
Porfiria
Deficit akfa1antitripsina

CARDIOGENA

TOSSINE
Alcol (60-70%)
Farmaci (alfa-metildopa, amiodarone, isoniazide, methotrexate, triglitazone, vitamina A….)
Erbe

AUTOIMMUNI
Epatiti autoimmune tipo 1,2 e 3

COLESTASI
Colangite primitiva
Colangite scelrosante
Colagiopatie congenite

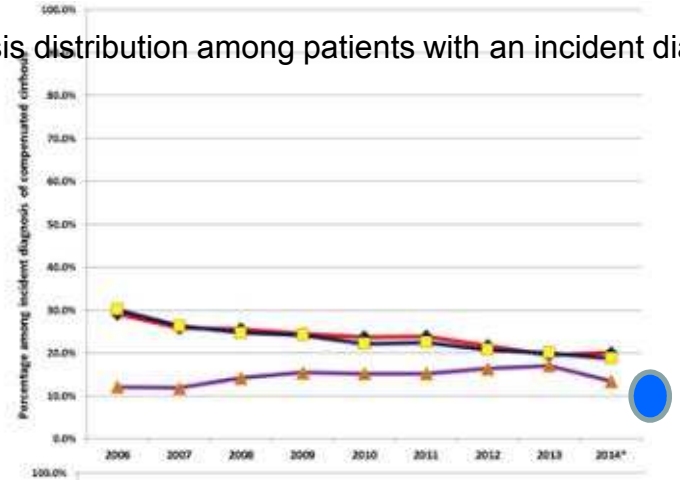
30 grammi die uomo
20 grammi die donna

Il

12 grammi di alcol

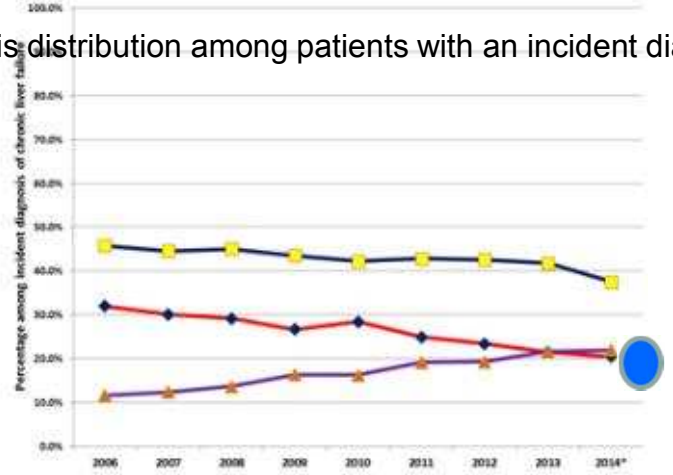
Diagnosis distribution among patients with an incident diagnosis of compensated cirrhosis in HealthCore, 2006-2014

a



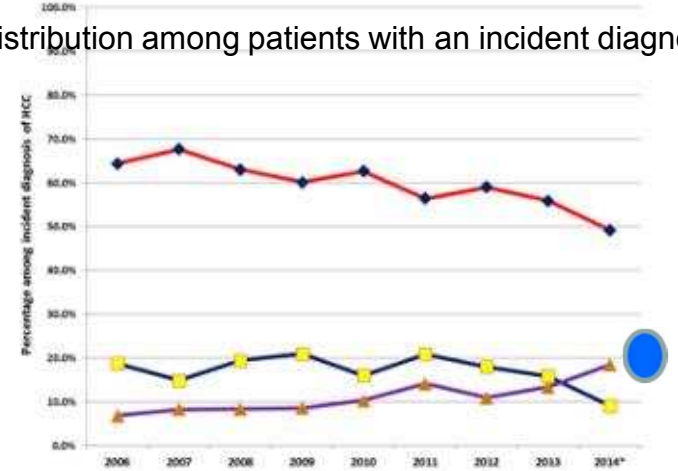
Diagnosis distribution among patients with an incident diagnosis of chronic liver failure in HealthCore, 2006-2014

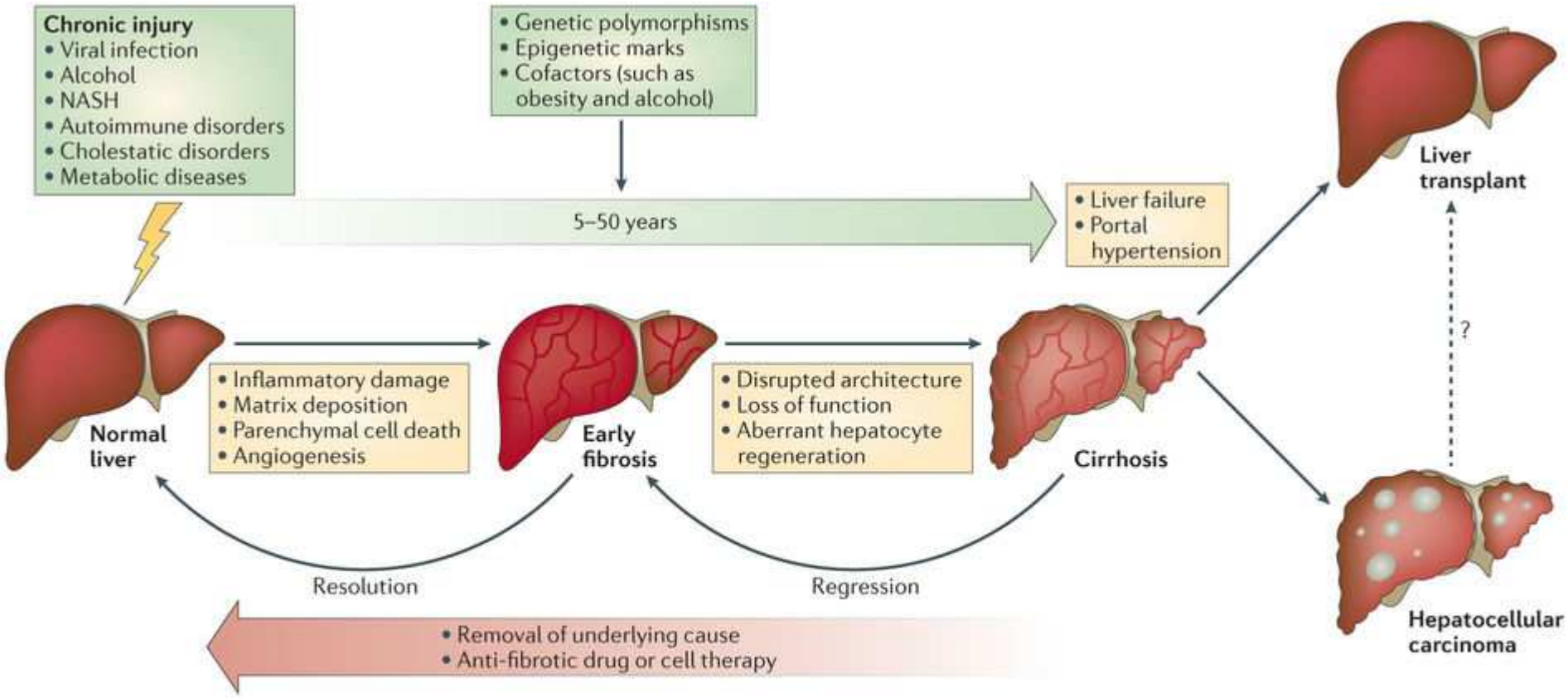
b



Diagnosis distribution among patients with an incident diagnosis of hepatocellular carcinoma in HealthCore, 2006-2014

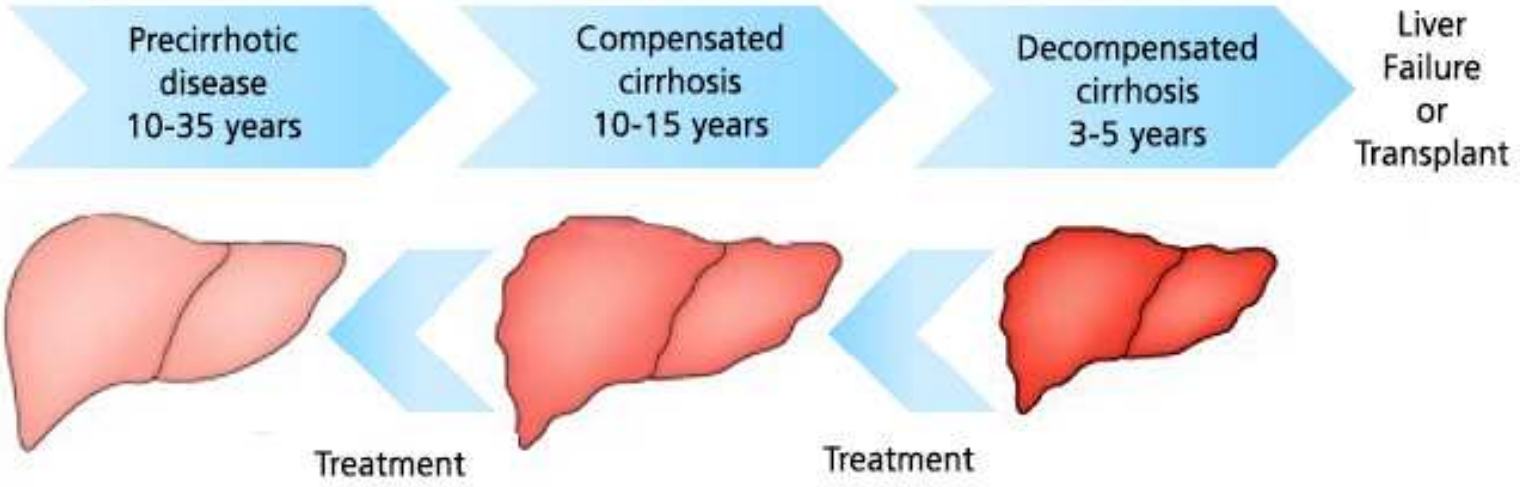
c

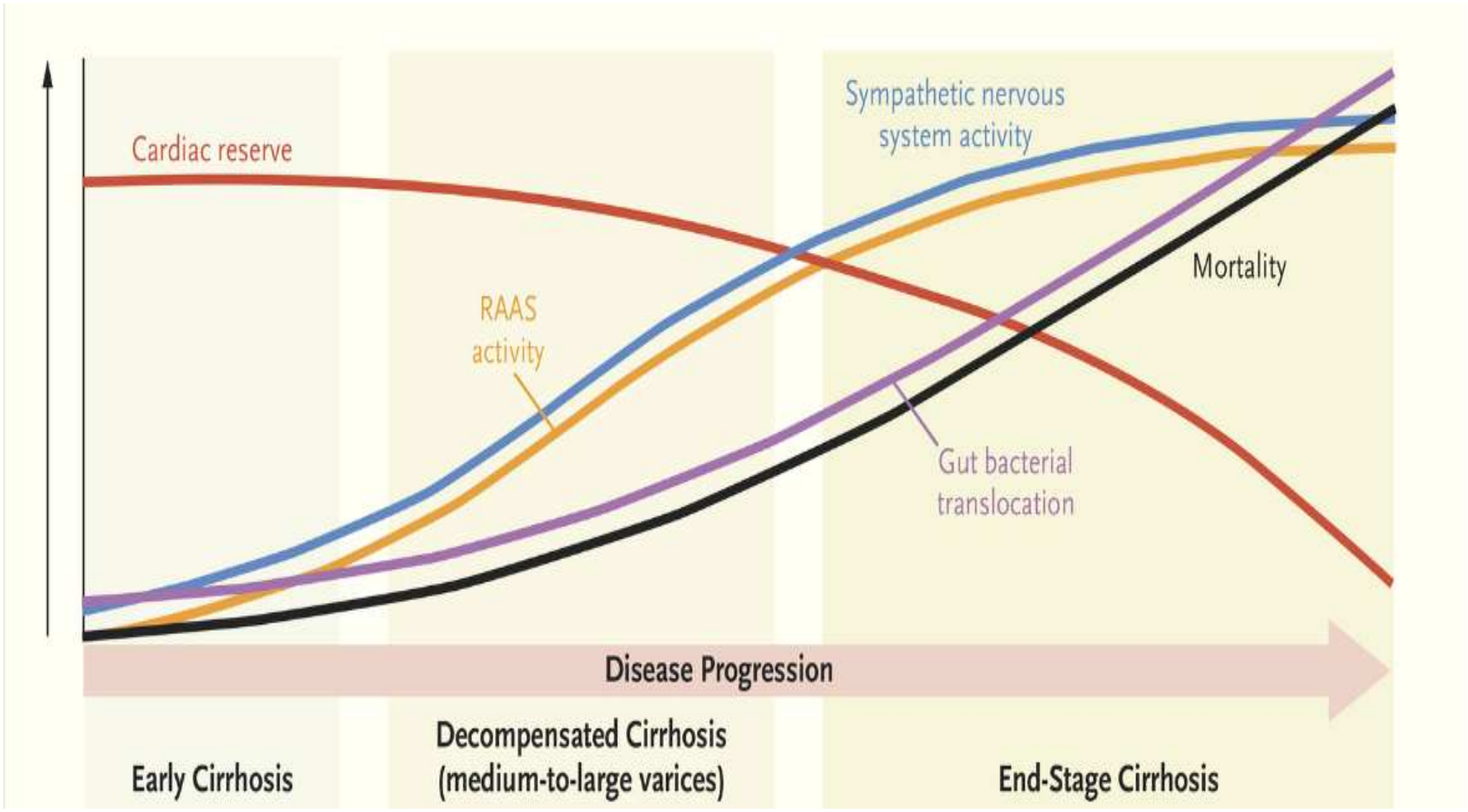


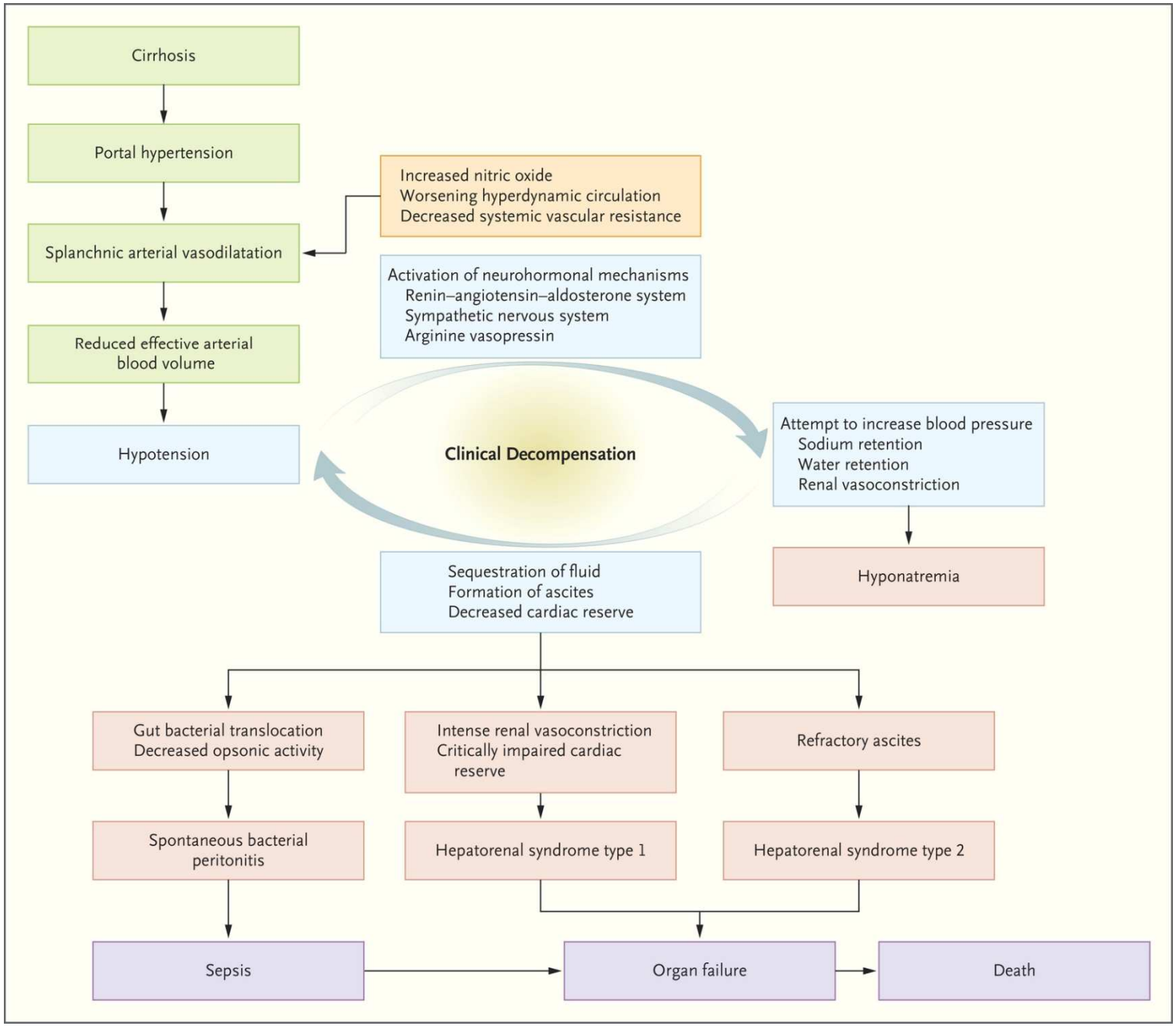


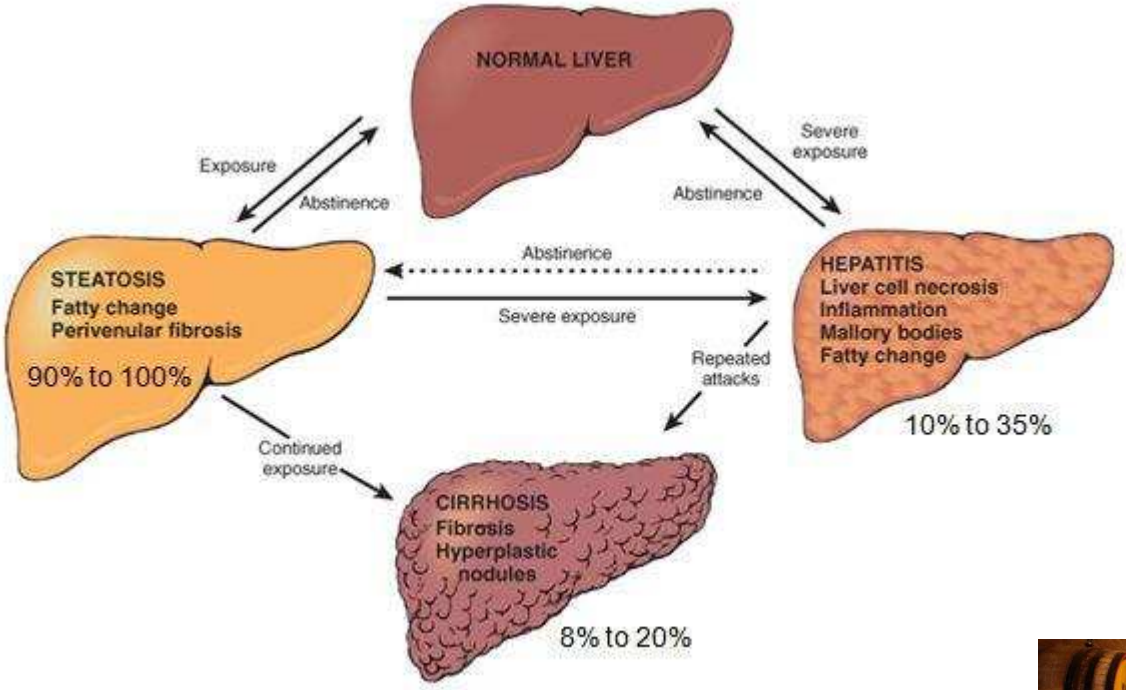
Nature Reviews | Immunology

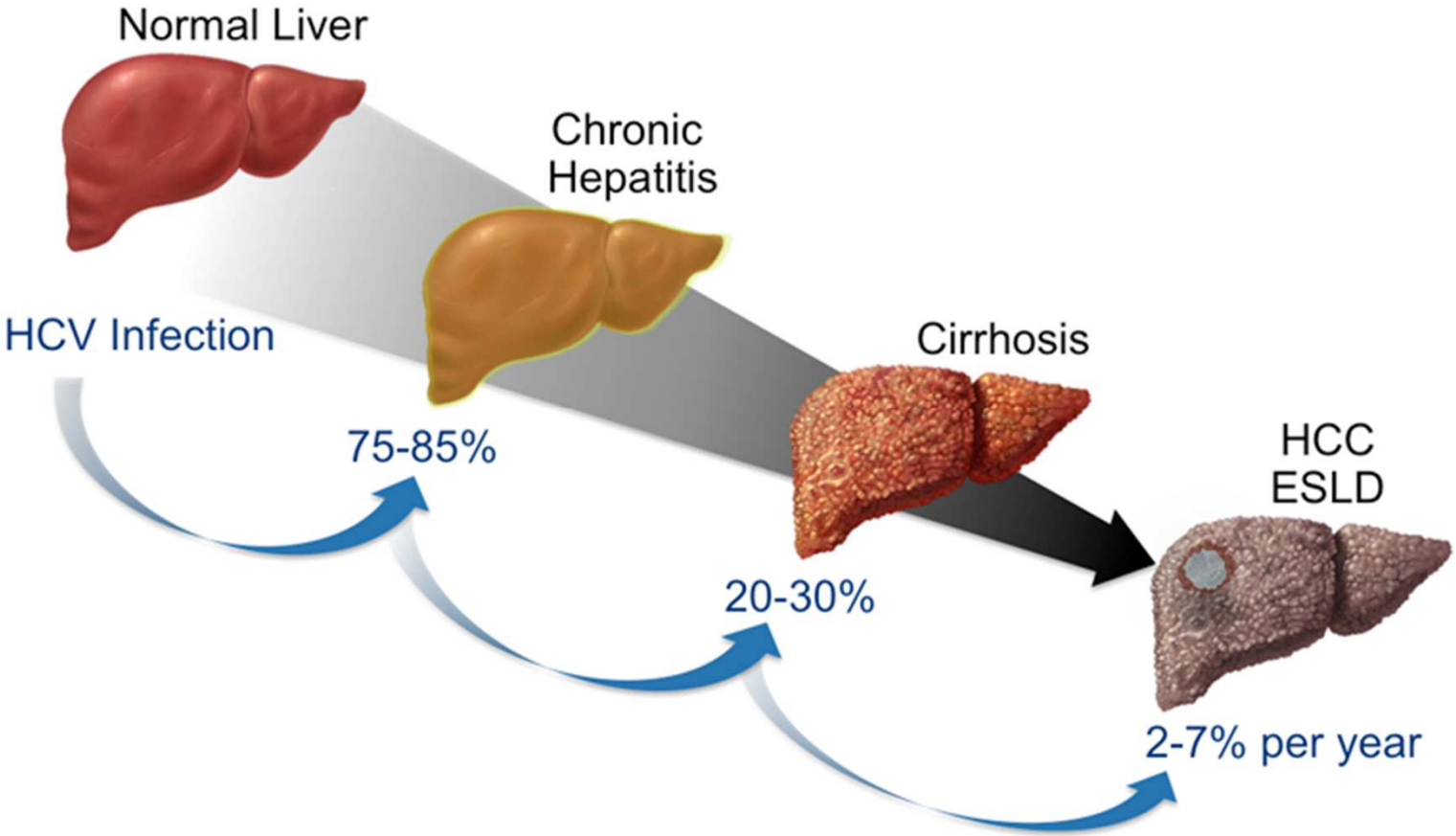
Cirrhosis - landscape and treatment progression

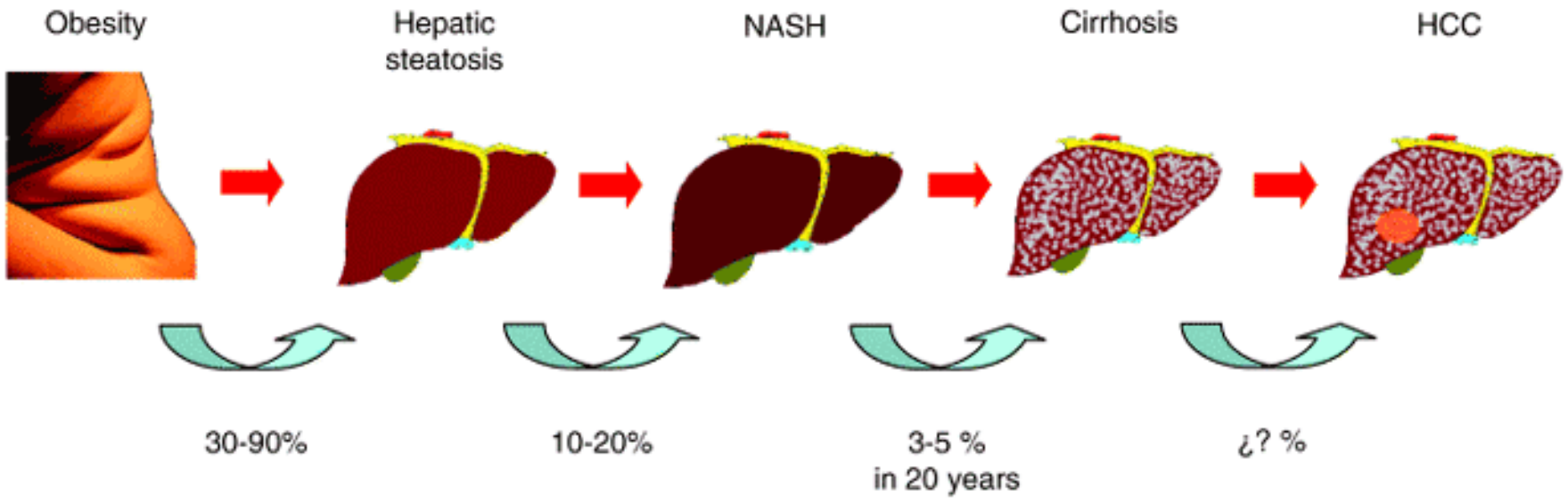



Cardiac reserve
Sympathetic nervous system activity
RAAS activity
Mortality
Gut bacterial translocation
Disease Progression
Early Cirrhosis
Decompensated Cirrhosis (medium-to-large varices)
End-Stage Cirrhosis


Cirrhosis
Portal hypertension
Splanchnic arterial vasodilatation
Reduced effective arterial blood volume
Hypotension
Increased nitric oxide
Worsening hyperdynamic circulation
Decreased systemic vascular resistance
Activation of neurohormonal mechanisms
Renin–angiotensin–aldosterone system
Sympathetic nervous system
Arginine vasopressin
Clinical Decompensation
Attempt to increase blood pressure
Sodium retention
Water retention
Renal vasoconstriction
Hyponatremia
Sequestration of fluid
Formation of ascites
Decreased cardiac reserve
Gut bacterial translocation
Decreased opsonic activity
Intense renal vasoconstriction
Critically impaired cardiac reserve
Refractory ascites
Spontaneous bacterial peritonitis
Hepatorenal syndrome type 1
Hepatorenal syndrome type 2
Sepsis
Organ failure
Death


NORMAL LIVER
Exposure
Abstinence
Severe exposure
Abstinence
Abstinence
Severe exposure
STEATOSIS
Fatty change
Perivenular fibrosis
90% to 100%
HEPATITIS
Liver cell necrosis
Inflammation
Mallory bodies
Fatty change
10% to 35%
Repeated attacks
Continued exposure
CIRRHOSIS
Fibrosis
Hyperplastic nodules
8% to 20%

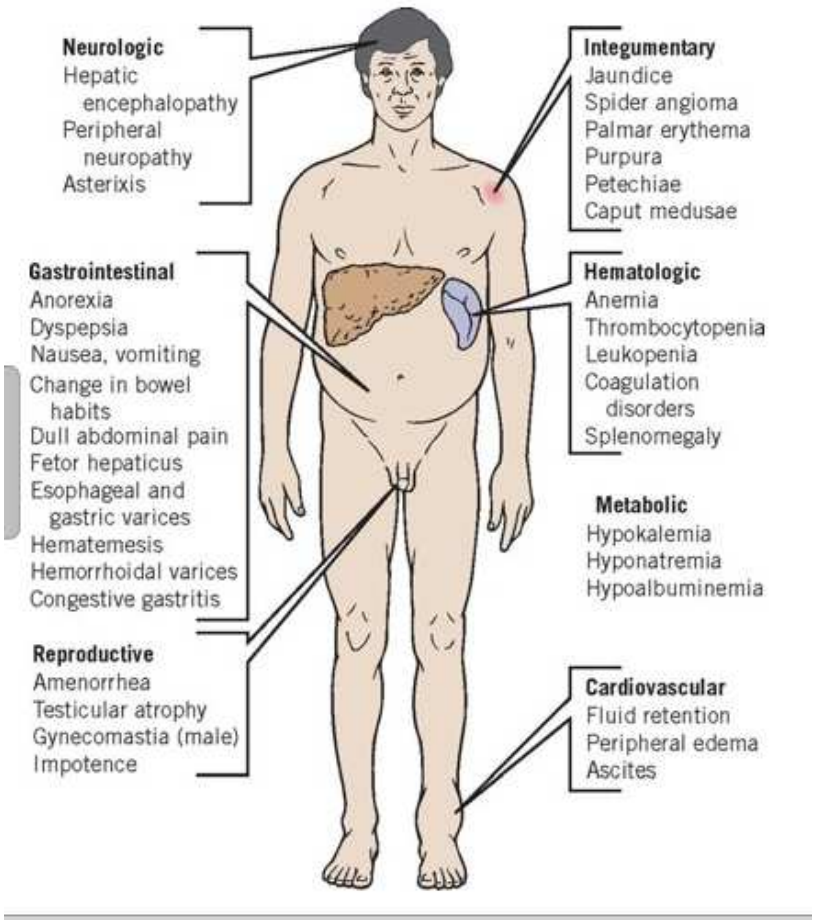

Normal Liver
Chronic Hepatitis
HCV Infection
Cirrhosis
HCC ESLD
75-85%
20-30%
2-7% per year



SOSPETTO CIRROSI

- Soggetti a rischio (etilisti, epatite virale)
- Stigmate cliniche (ittero, ascite…)
- Reperti laboratorio alterati casuali
- Reperti strumentali alterati casuali

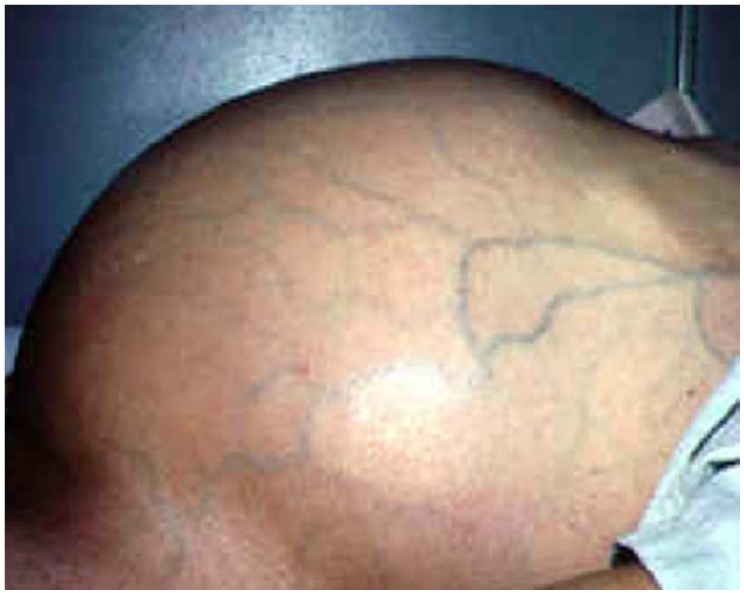
Fig. 45-5 Systemic clinical manifestations of liver cirrhosis.

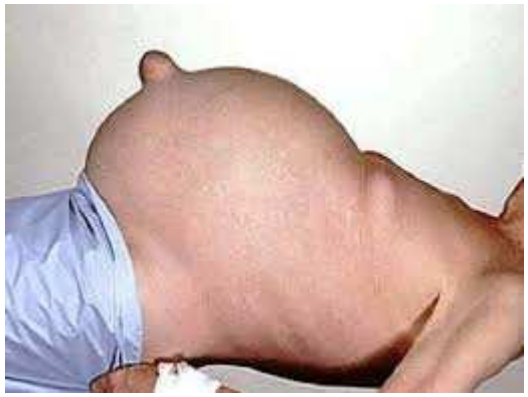


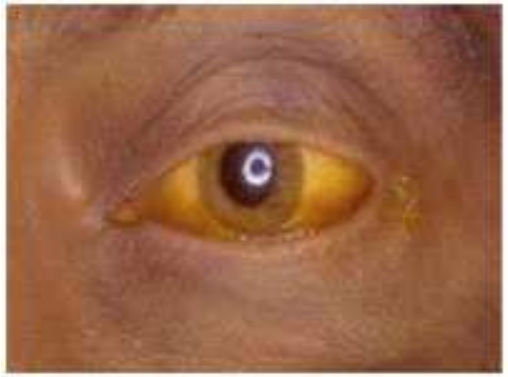
	Description	Cause
Jaundice[1-3]	Yellow discoloration of skin, cornea, and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >20 mg/L
Spider angiomata[9,10]	Central arteriole with tiny radiating vessels, mainly on trunk and face	Raised oestradiol, decreased oestradiol degradation in liver
Nodular liver[2]	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly[2]	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites[1-3,11]	Proteinaceous fluid in abdominal cavity, clinically detected when ≥1·5 L	Portal hypertension
Caput medusae[2]	Prominent veins radiating from umbilicus	Portal hypertension, reopening of umbilical vein that shunts blood from portal vein
Cruveilhier-Baumgarten syndrome[12]	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusae
Palmar erythema[1-3]	Erythema sparing central portion of the palm	Increased oestradiol, decreased oestradiol degradation in liver
White nails[13]	Horizontal white bands or proximal white nail plate	Hypoalbuminaemia
Hypertrophic osteoarthropathy/ finger clubbing[14]	Painful proliferative osteoarthropathy of long bones	Hypoxaemia due to right-to-left shunting, portopulmonary hypertension
Dupuytren's contracture[15]	Fibrosis and contraction of palmar fascia	Enhanced oxidative stress, increased inosine (alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern[16]	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to oestrone and oestradiol, reduced oestradiol degradation in liver
Hypogonadism[1-3]	Mainly in alcoholic cirrhosis and haemochromatosis	Direct toxic effect of alcohol or iron
Flapping tremor (asterixis)[1-3]	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus[17]	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting[1-3]	Occurs in >50% of patients with cirrhosis	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes[1-3]	Occurs in 15–30% of patients with cirrhosis	Disturbed glucose use or decreased insulin removal by the liver

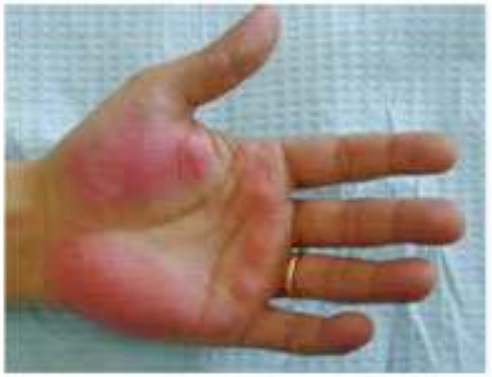
Data from references 1–3, and 15 if not specified otherwise. *Usually absent in compensated cirrhosis; some findings only occur in a few cases.

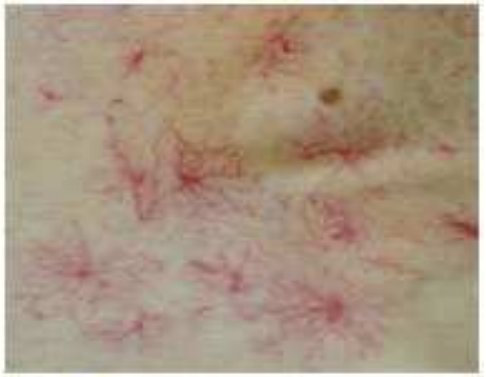
Table 1: Clinical features of cirrhosis*



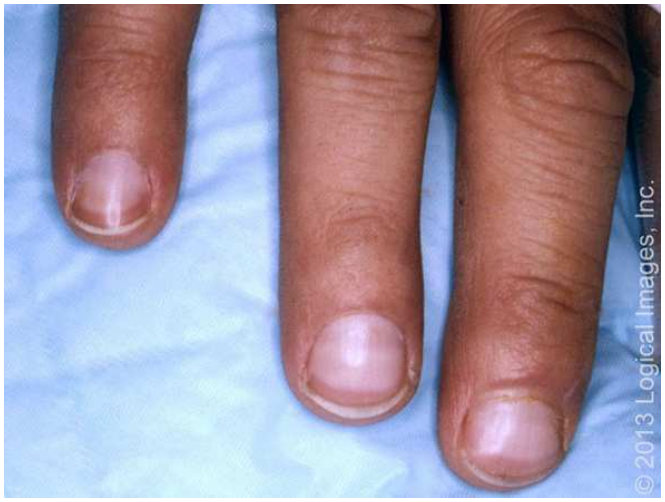




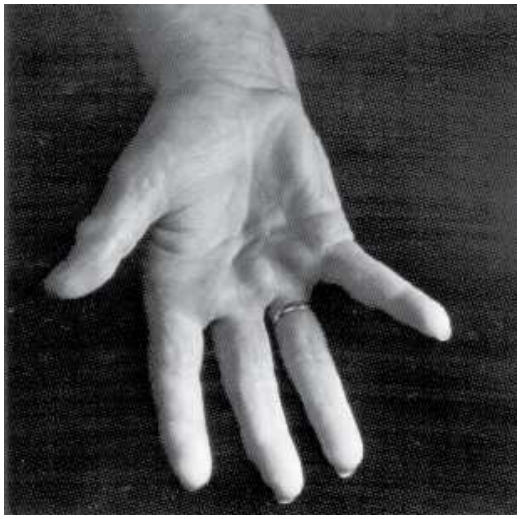




Terry nails



Dupuytren's contracture



Diagnostic tests in chronic liver disease, according to cause

	Specific physical associations	Diagnostic (laboratory) variables	Value of liver biopsy (identifiable features)
HBV	Arthritis	HBsAg, HBeAg, HBc-antibodies, HBV DNA	+
HCV	Cryoglobulinaemia	HCV antibodies, HBV RNA	+
Viral hepatitis D	..	HBsAg, HDV antibodies, HDV RNA	++ (HDAg)
Alcoholic	..	AST:ALT ratio ≥2, increased CDT and γ–GT	++ (Mallory bodies, steatosis, granulocytes >hepatocyte ballooning)
Non-alcoholic steatohepatitis	Overweight/obesity, metabolic syndrome, type 2 diabetes	Uric acid, fasting glucose/insulin/triglycerides	++ (Mallory bodies, steatosis, hepatocyte ballooning>granulocytes)
Autoimmune	..	Autoantibodies (ANA, LKM antibodies, SLA antibodies), increased γ-globulins	+++ (bridging necrosis)
Primary biliary cirrhosis	Sicca syndrome, xanthelasma	AMA; increased ALP, γGT, and cholesterol	++ (cholangitis, paucity of bile ducts, granuloma, ductopenia)
Primary sclerosing cholangitis	Ulcerative colitis (90%)	pANCA antibodies (70%), increased ALP and γGT, imaging: beaded intra-hepatic and extra-hepatic bile ducts	+++ (concentric peribile ductular fibrosis, ductopenia)
Haemochromatosis	Arthritis, myocarditis, diabetes	Fasting transferrin saturation >60% (men), >50% (women); increased ferritin, HFE mutation	++ (periportal iron-loaded hepatocytes, quantification of liver iron)
Wilson's disease	Neurological	Increased oeruloplasmin, and copper in 24 h urine; slit-lamp: corneal copper deposits	+++ (quantification of liver copper)
α1-antitrypsin	Pulmonary fibrosis	Reduced α1-antitrypsin; α1-antitrypsin subtyping	+++ (α1-antitrypsin-loaded hepatocytes)
Congenital disease	..	..	+++ (eg, bile ductular plate malformations)

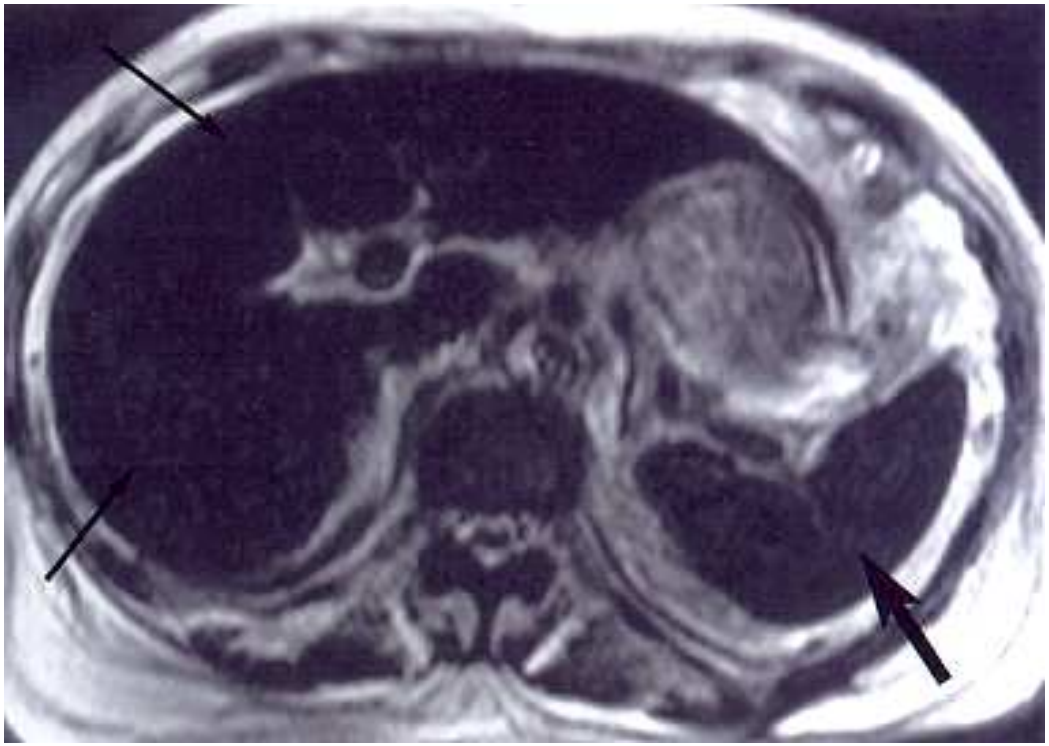
HBcAg=hepatitis B core antigen. HBe=hepatitis B envelope antigen. HBsAg=hepatitis B surface antigen. HBV=viral hepatitis B. HCV=viral hepatitis C. HDAg=hepatitis D antigen. HDV=viral hepatitis D. AST=aspartate aminotransferase. ALT=alanine aminotransferase. AMA=antimitochondrial antibodies. ANA=anti-nuclear antibodies. CDT=carbohydrate-deficient transferrin. γ-GT=γ-glutamyl transpeptidase. HFE=haemochromatosis C282Y mutation. LKM=liver kidney membrane. SLA=soluble liver antigen. pANCA=perinuclear neutrophil cytoplasmic antigen.

Laboratory tests and findings in cirrhosis

	Description	Cause
AST, ALT	Often normal or moderately raised	Leakage from damaged hepatocytes; AST-to-ALT ratio often >1, especially in alcoholic cirrhosis (relative vitamin B6 deficiency)
ALP	Increased by less than three-fold, apart from PBC and PSC	Cholestasis
γ-GT	More specific for liver than ALP, high concentrations in active alcoholics	Cholestasis
Bilirubin	Raised later than γ-GT and ALP, important predictor of mortality	Cholestasis, decreased hepatocyte and renal excretory function (exacerbated by systemic inflammation)
Albumin	Decreased in advanced cirrhosis	Decreased hepatic production, sequestration into ascites and interstitium (exacerbated in systemic inflammation); DD: malnutrition, protein losing enteropathy
Prothrombin time	Decreased in advanced cirrhosis	Decreased hepatic production of factor V/VII (while thrombin production is maintained); DD: vitamin K deficiency (eg, due to mechanical biliary obstruction)
Immunoglobulins	Increased (mainly IgG)	Shunting of portal venous blood carrying (intestinal) antigens to lymph tissues with resultant stimulation of plasma cells[26]
Sodium imbalance	Hyponatraemia	Inability to excrete free water via kidneys due to increased activity of antidiuretic hormone (vasopressin 2 receptor effect)[27]
Anaemia	Macrocytic, normocytic, or microcytic anaemia	Folate deficiency, hypersplenism, direct toxicity (alcohol), gastrointestinal blood loss (eg, via oesophageal varices)
Thrombocytes and leucocytes	Thrombocytopenia (leucopenia)	Hypersplenism, dysfibronogenemia, reduced hepatic thrombopoietin production[28]

Data from references 1–3, and 25 if not specified otherwise. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ALP=alkaline phosphatase. DD=differential diagnosis. γ-GT=γ-glutamyl transpeptidase. PBC=primary biliary cirrhosis. PSC=primary sclerosing cholangitis.

Hemochromatosis on magnetic resonance imaging



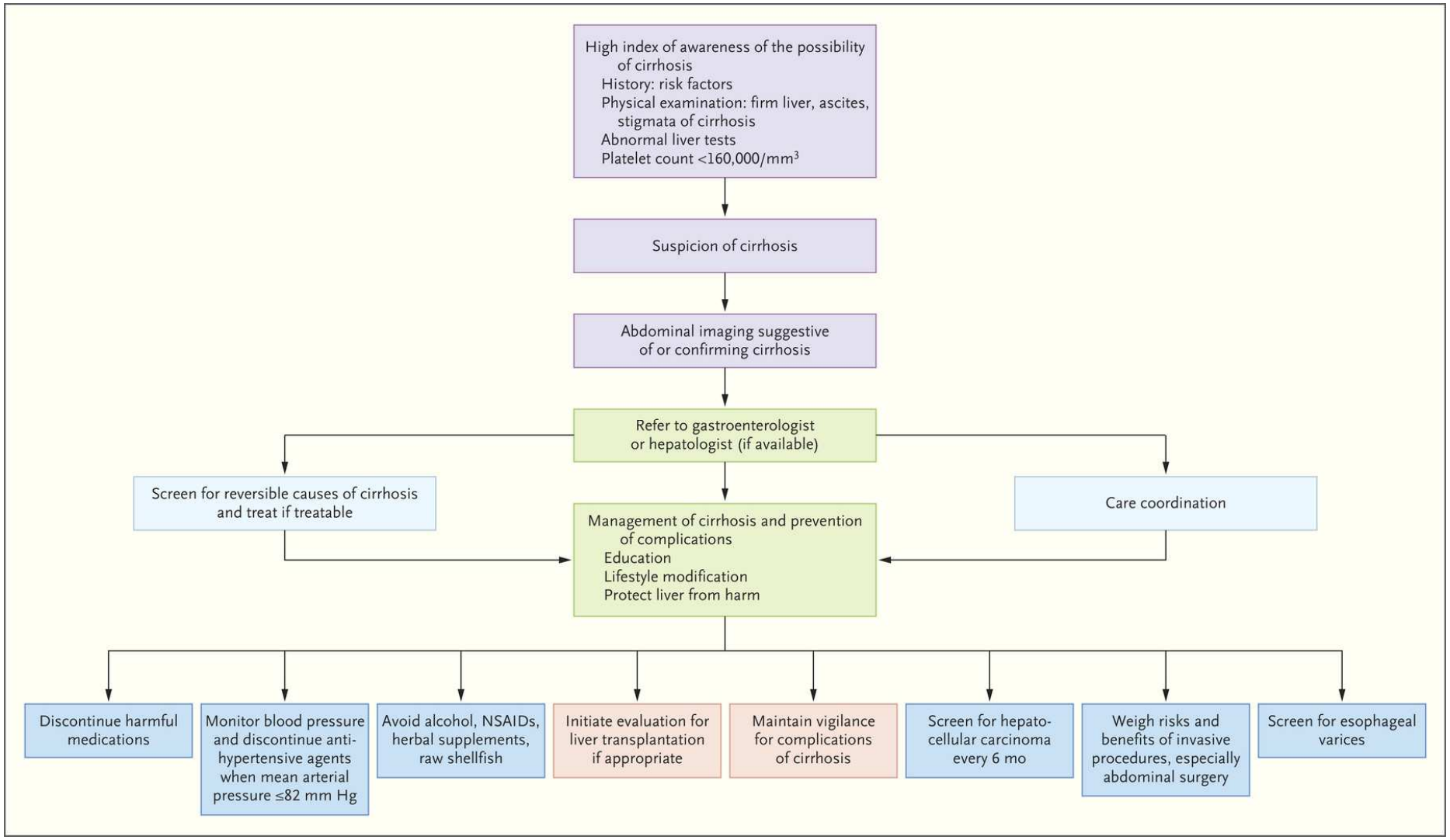

High index of awareness of the possibility of cirrhosis
History: risk factors
Physical examination: firm liver, ascites, stigmata of cirrhosis
Abnormal liver tests
Platelet count <160,000/mm3
Suspicion of cirrhosis
Abdominal imaging suggestive of or confirming cirrhosis
Refer to gastroenterologist or hepatologist (if available)
Screen for reversible causes of cirrhosis and treat if treatable
Care coordination
Management of cirrhosis and prevention of complications
Education
Lifestyle modification
Protect liver from harm
Discontinue harmful medications
Monitor blood pressure and discontinue anti-hypertensive agents when mean arterial pressure ≤82 mm Hg
Avoid alcohol, NSAIDs, herbal supplements, raw shellfish
Initiate evaluation for liver transplantation if appropriate
Maintain vigilance for complications of cirrhosis
Screen for hepato-cellular carcinoma every 6 mo
Weigh risks and benefits of invasive procedures, especially abdominal surgery
Screen for esophageal varices

Table S2: Commonly used medications and cirrhosis

Medication	Safety	Comments
Disulfiram	Contraindicated	Reports of fulminant hepatotoxicity, and subject to numerous drug-drug interactions.
NSAIDs	Contraindicated	Increased risk for gastrointestinal bleeding including variceal hemorrhage, renal failure, development of diuretic-resistant ascites, and hepatotoxicity
Acetaminophen	Caution	Well tolerated at doses of 4 grams or less per day. Avoid in patients actively consuming alcohol.
ACE inhibitors	Caution	Discontinue in patients with refractory ascites or sepsis/SBP, as may cause drop in mean arterial pressure resulting in hemodynamic compromise and development of hepatorenal syndrome.
Benzodiazepines	Caution	Avoid usage in patients with hepatic encephalopathy. Short-acting benzodiazepines such as lorazepam and oxazepam may be used for management of alcoholic hepatitis.
Beta-blockers	Caution	Discontinue in patients with refractory ascites or sepsis/SBP, as may cause drop in mean arterial pressure resulting in hemodynamic compromise and development of hepatorenal syndrome.
Herbal supplements	Caution	Many herbal supplements contain substitutes, fillers, and contaminants that are undisclosed and may be hepatotoxic.
Metformin	Caution	Generally safe, however avoid in patients with renal insufficiency, advanced cirrhosis, or active alcoholism due to risk for potentially fatal lactic acidosis.
Proton-pump inhibitors	Caution	Risk factor for development of bacterial infections, particularly SBP and *Clostridium difficile*. Acid suppression should only be prescribed in settings where there is a clear indication.
Vaptans	Caution	May improve hyponatremia however studies have indicated hepatotoxicity and increased mortality in patients with ascites receiving diuretics.
Baclofen	Safe	Indicated for suppression of alcohol cravings. Start at 5mg three times daily and up-titrate to effect. Doses up to 90 mg/day have been successfully used in patients with cirrhosis.
Furosemide	Safe	Combined with spironolactone for the treatment of ascites. Should be given orally rather than intravenously as vigorous diuresis may result in hepatic encephalopathy or diuretic-induced azotemia. Typical ratio of furosemide 40 mg to spironolactone 100 mg to maintain normal serum potassium.
Spironolactone	Safe	Combined with furosemide for the treatment of ascites. Typical ratio of furosemide 40 mg to spironolactone 100 mg to maintain normal serum potassium.
Statins	Safe	Well tolerated in patients with compensated cirrhosis, statins have established cardiovascular benefits.

FATTORI PROGNOSTICI

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

Class A = 5 to 6 points (least severe liver disease)

Class B = 7 to 9 points (moderately severe liver disease)

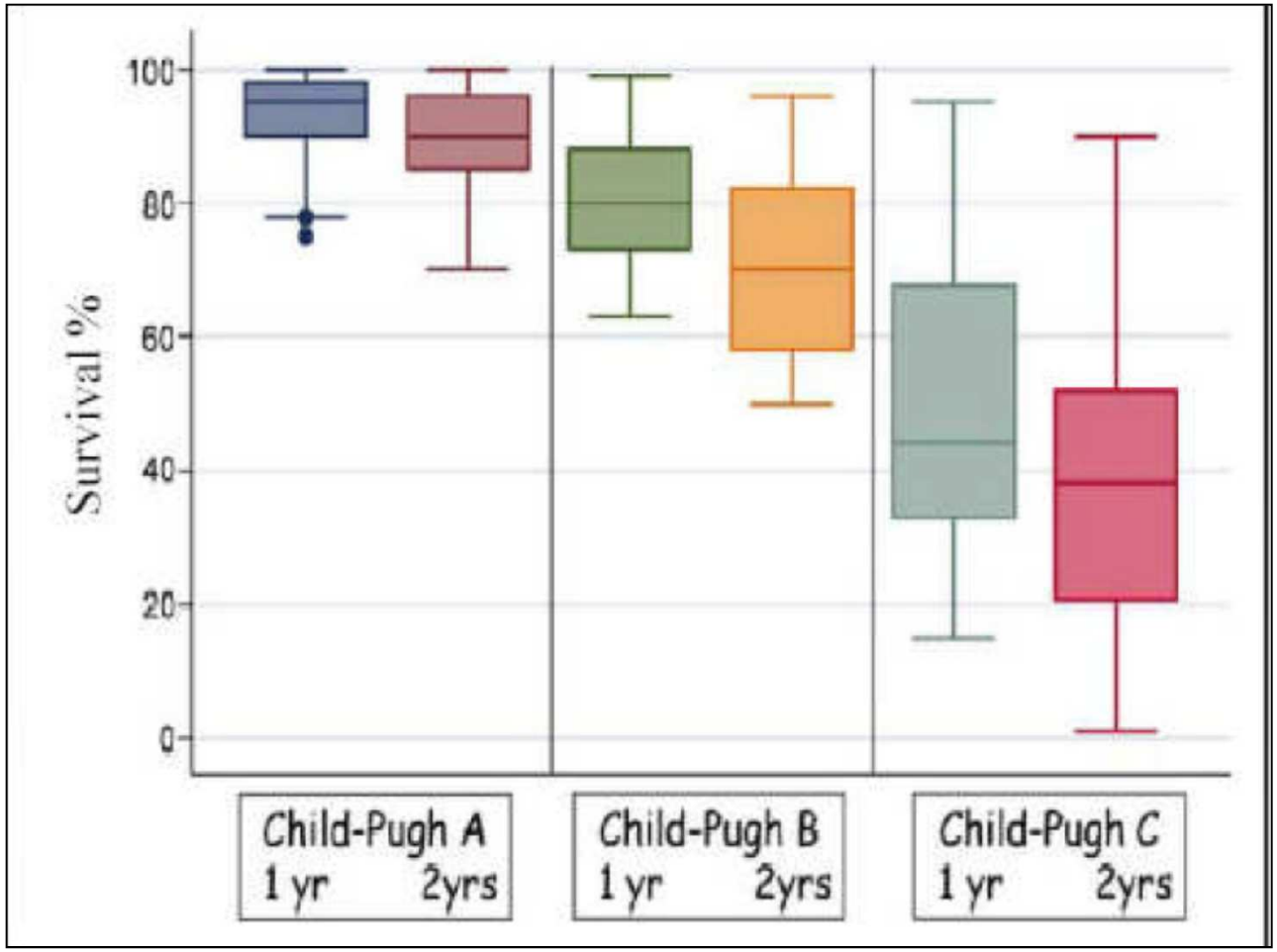
Class C = 10 to 15 points (most severe liver disease)

Medscape® www.medscape.com

Score	Components
MELD score*	9.6 * $\log_e$ (creatinine mg/dL) + 3.8 * $\log_e$ (bilirubin mg/dL) + 11.2 * $\log_e$ (INR) + 6.4
MELD-sodium†	MELD + 1.59 * (135-Na [mEq/L])
MELD-XI	5.11 * $\log_e$ (bilirubin mg/dL) + 11.76 * $\log_e$ (creatinine mg/dL) + 9.44
Delta MELD	Difference between current MELD and the lowest MELD measure within 30 days prior to current MELD

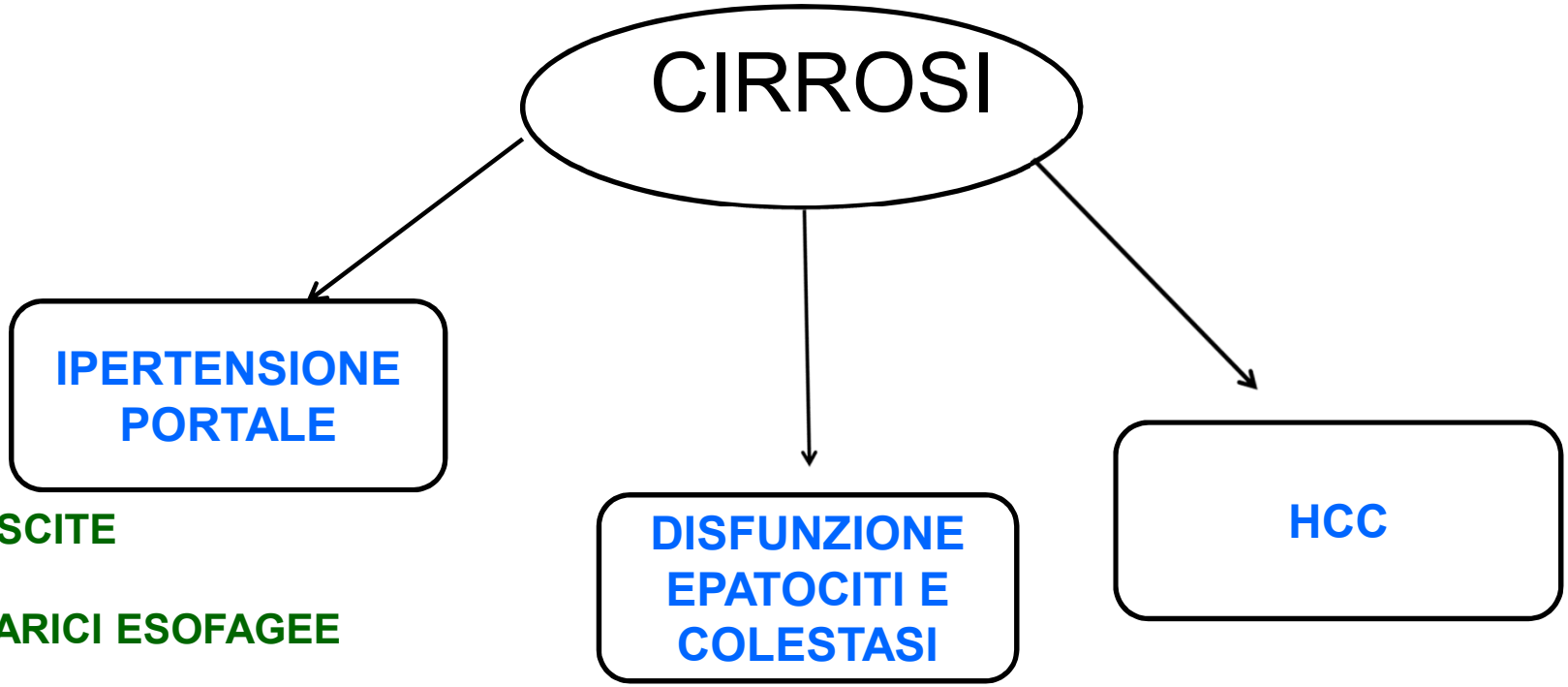
*Values of creatinine, bilirubin, and INR below 1 are rounded to 1. Serum creatinine values above 4 mg/dL are rounded to 4. Patients on hemodialysis are given a creatinine value of 4 mg/dL. MELD score ranges from 6 to 40 points.
†Values of serum sodium below 120 mEq/L are rounded to 120. Values over 135 mEq/L are rounded to 135.
MELD, model for end-stage liver disease; INR, international normalized ratio.

Source: Semin Liver Dis © 2008 Thieme Medical Publishers



D'Amico et al. J Hepatol, 2006

COMPLICANZE CIRROSI



ASCITE

VARICI ESOFAGEE

PBS

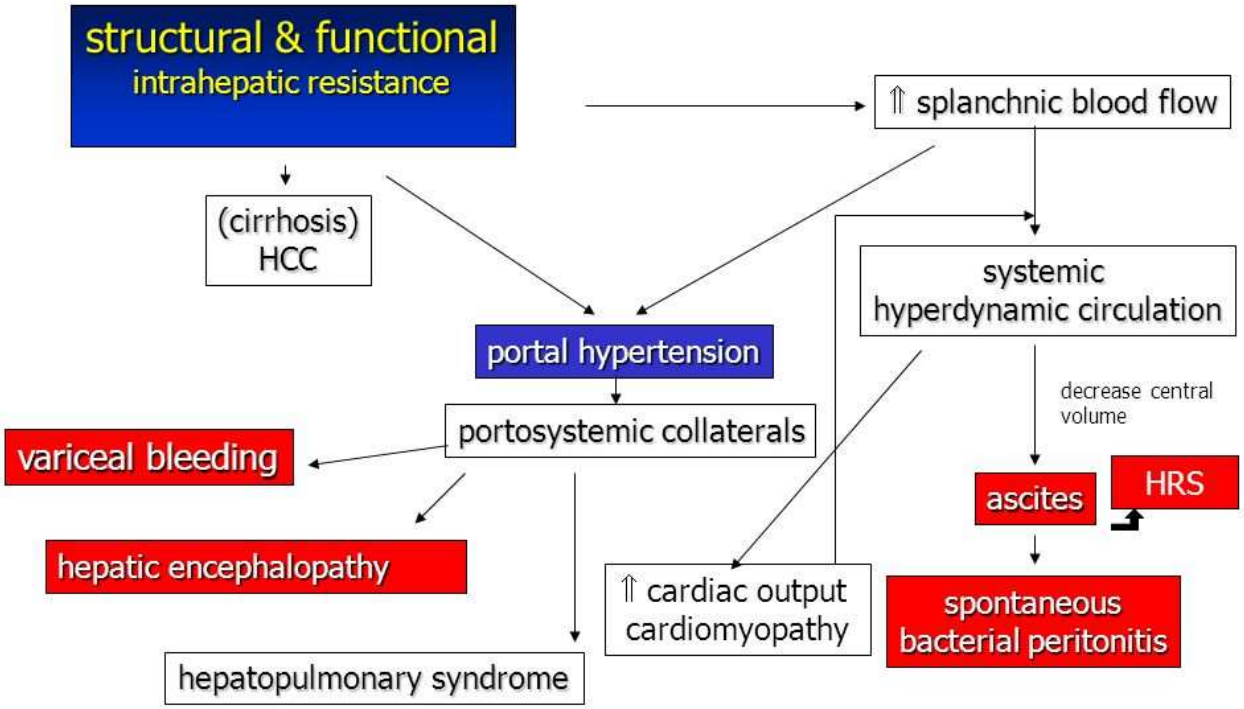
SER

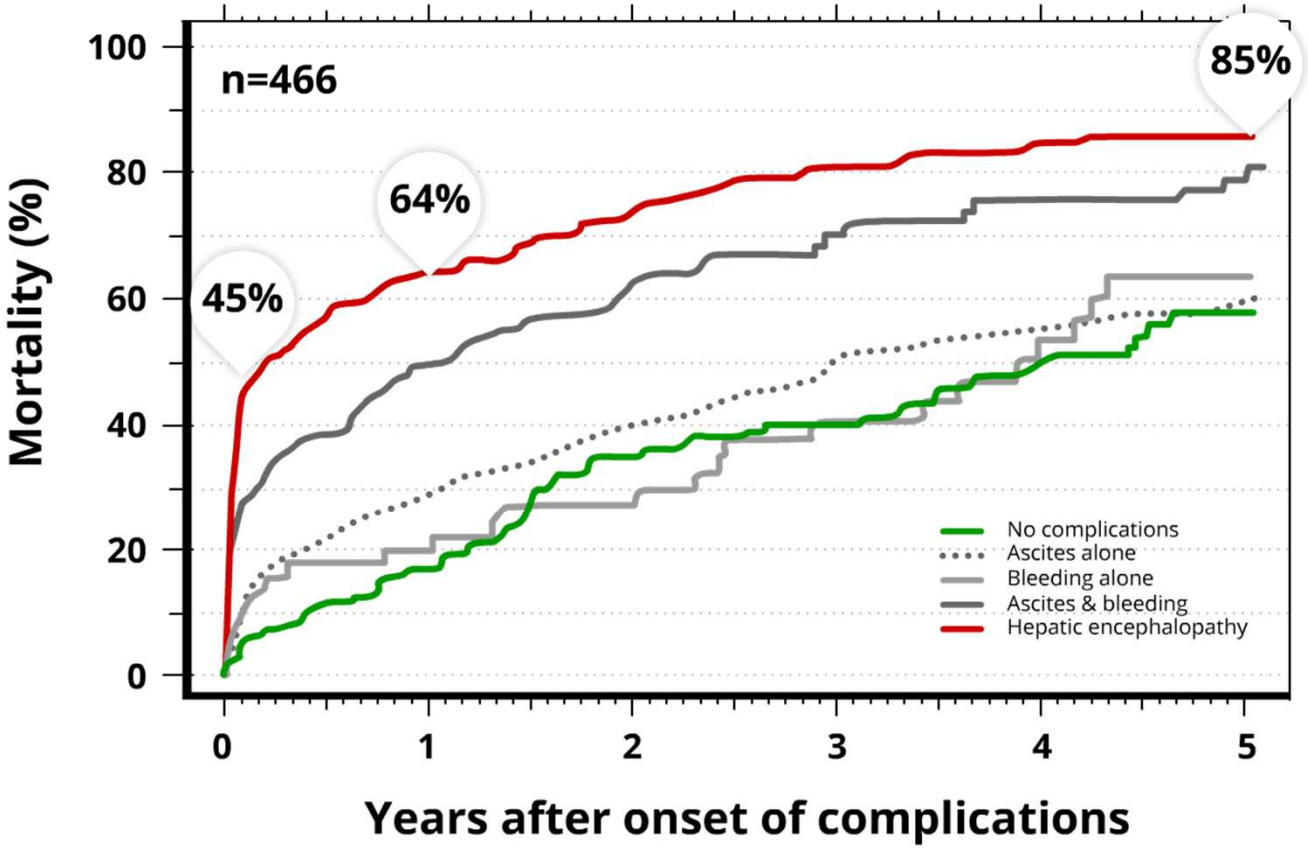
ENCEFALOPATIA

CARDIOPATIA

SDR EPATOPOLMONARE

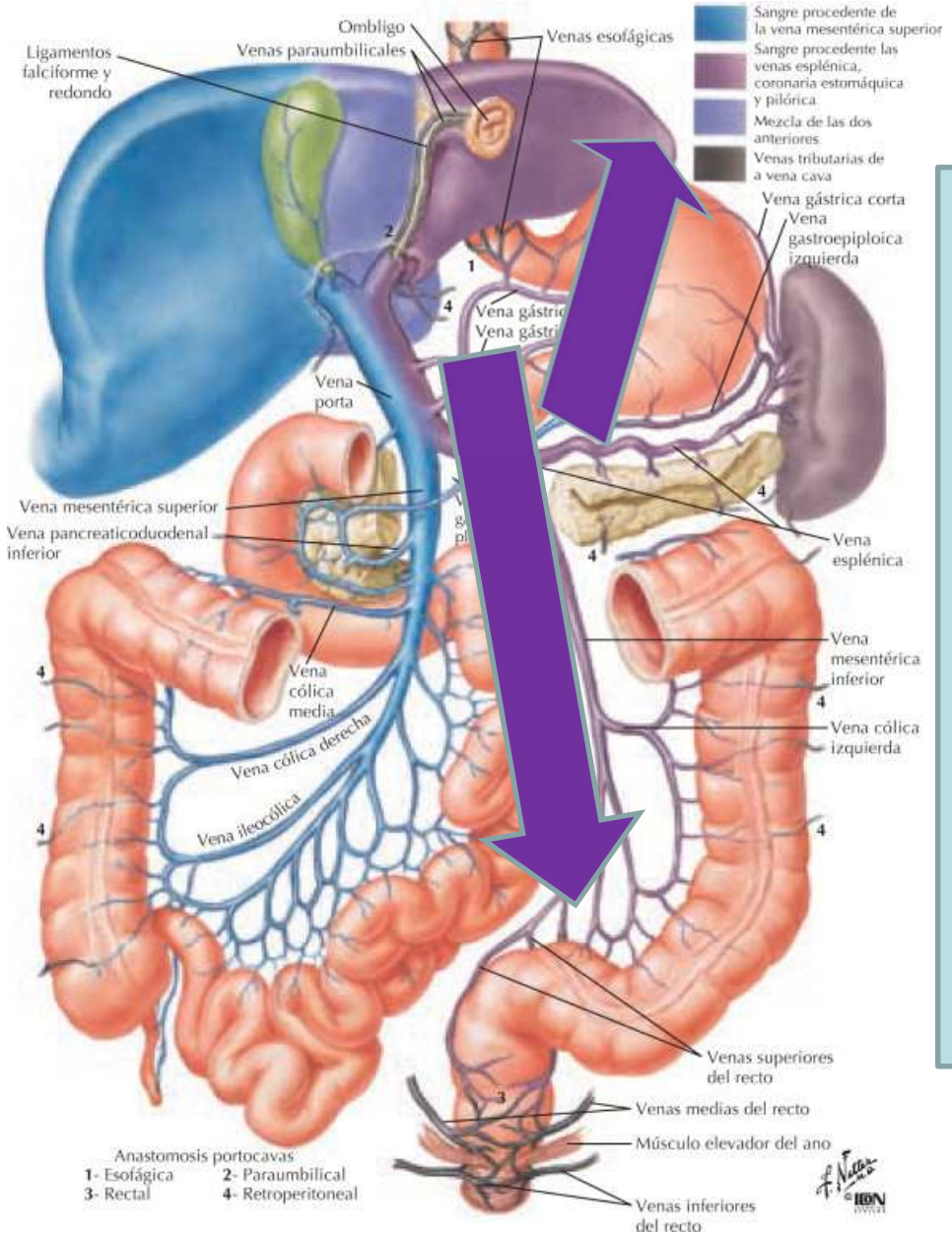
CONSEQUENCES OF DEVELOPING PROGRESSIVE HEPATIC FIBROSIS





Jepsen, P., Ott, P., Andersen, P. K., Sørensen, H. T. and Vilstrup, H. (2010), Clinical course of alcoholic liver cirrhosis: A Danish population-based cohort study. Hepatology, 51: 1675–1682. doi:10.1002/hep.23500.

IPERTENSIONE PORTALE



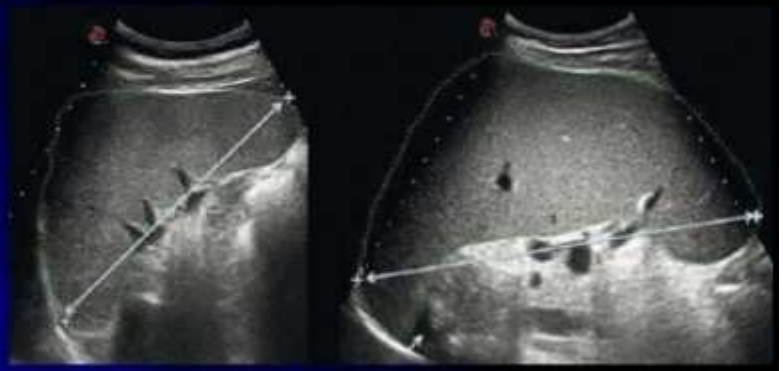
1. VARICI ESOFAGEE
2. VARICI GASTRICHE
3. EMORROIDI
4. CIROLI PARIETALI (TORACO-EPIGASTRICI
5. SPLENOMEGALIA

ECOGRAFIA IPERTENSIONE PORTALE

Splenomegalia

- Limite superiore normale del diam. bipolare: 12 cm (donne),13 cm (uomini)
- Limite superiore normale dell'area di sezione: 45 cm^2
- Diametro bipolare > 12 cm: sensibilità 52% -63% nella diagnosi di ipert. portale
- Splenomegalia severa: diam.bipolare > 16 cm e/o area sezione > 90 cm^2
- Corr. tra splenomegalia e dimensioni varici esofagee e tra splenomegalia > 14,5 cm e mortalità

Vilgrain V 1990; Macias-Rodrigues MA 1999; Piscaglia F 2002;



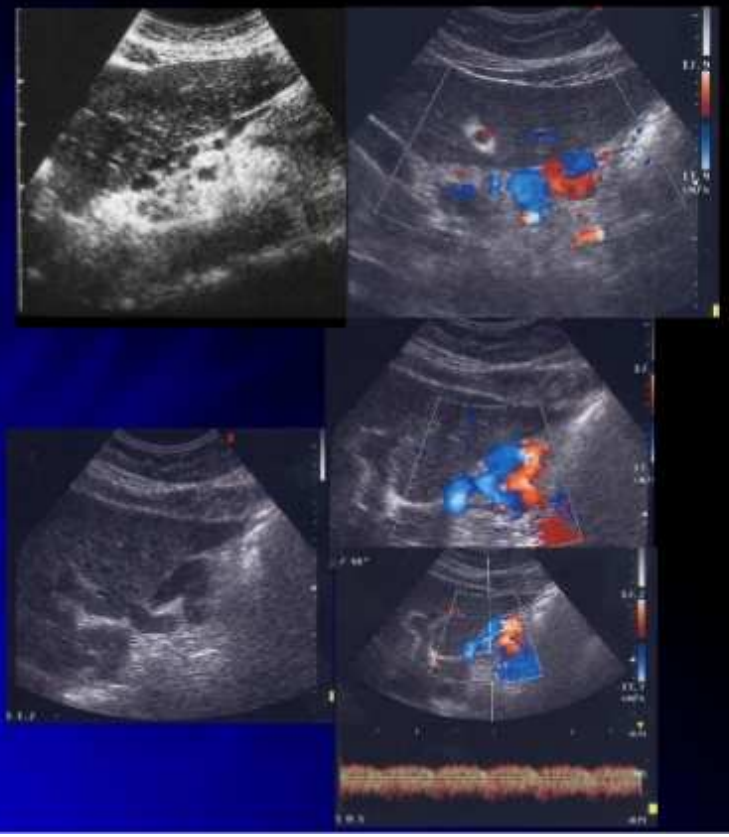
Thomopoulos Kc, Dig Liver Dis 2003

Shunt spleno-renale spontaneo

- Vasi venosi tortuosi tra il polo inferiore della milza e l'ilo renale sinistro
- Flusso epatofugo nella vena splenica
- Vena renale sinistra di calibro aumentato

Vene gastroesofagee

- Ectasie vascolari tortuose visibili in epigastrio in prossimità della giunzione gastro-esofagea caratterizzate da spettri flussimetrici di tipo venoso



Vene paraombelicali

- Ectasia delle vene paraombelicali e non ricanalizzazione della vena ombelicale
- Struttura canalare con flusso epatofugo originante dal ramo portale sinistro visualizzabile nel legamento rotondo
- Circolo protettivo riguardo la formazione di varici esofagee a rischio di sanguinamento in pazienti con cirrosi compensata

Caturelli E, 1994
Gupta D, 2000

Ridotta elasticità dei vasi del sistema portale

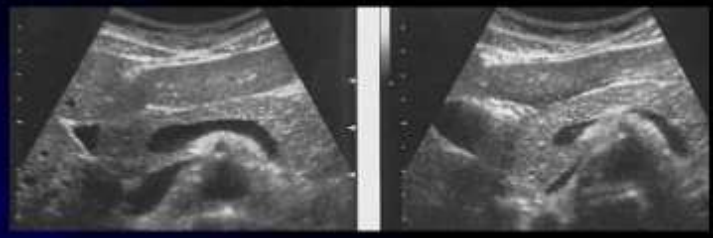
- L'ipertensione portale impedisce il fisiologico aumento di calibro dei vasi del sistema portale in inspirazione profonda

  Bolondi L,1982

- Incremento calibro vena splenica e vena mesenterica superiore < 40% in inspirazione profonda: sensibilità 42% nella diagnosi di ipertensione portale

  Vilgrain V, 1990

V.SPLENICA (normale)



inspirazione espirazione

V.MES.SUP (iper.port.)

VARICI ESOFAGEE

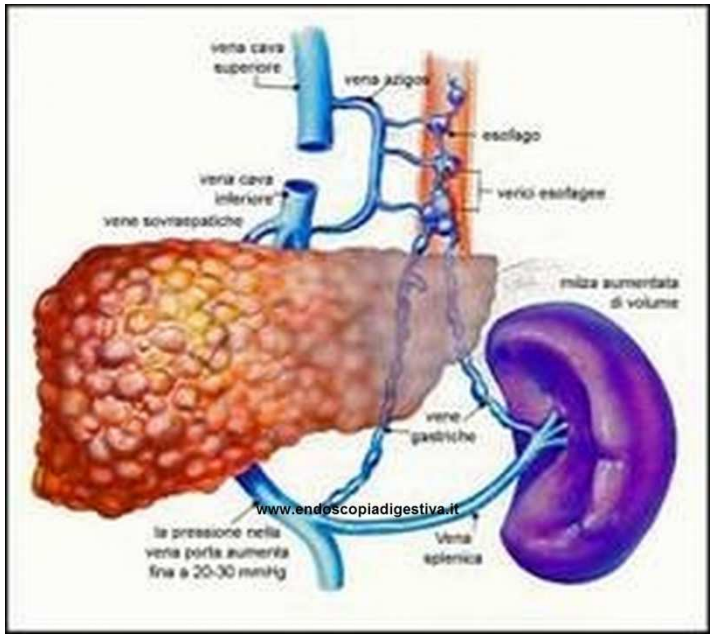
-Circa 50% pz con cirrosi hanno varici (prevale Child B-C).

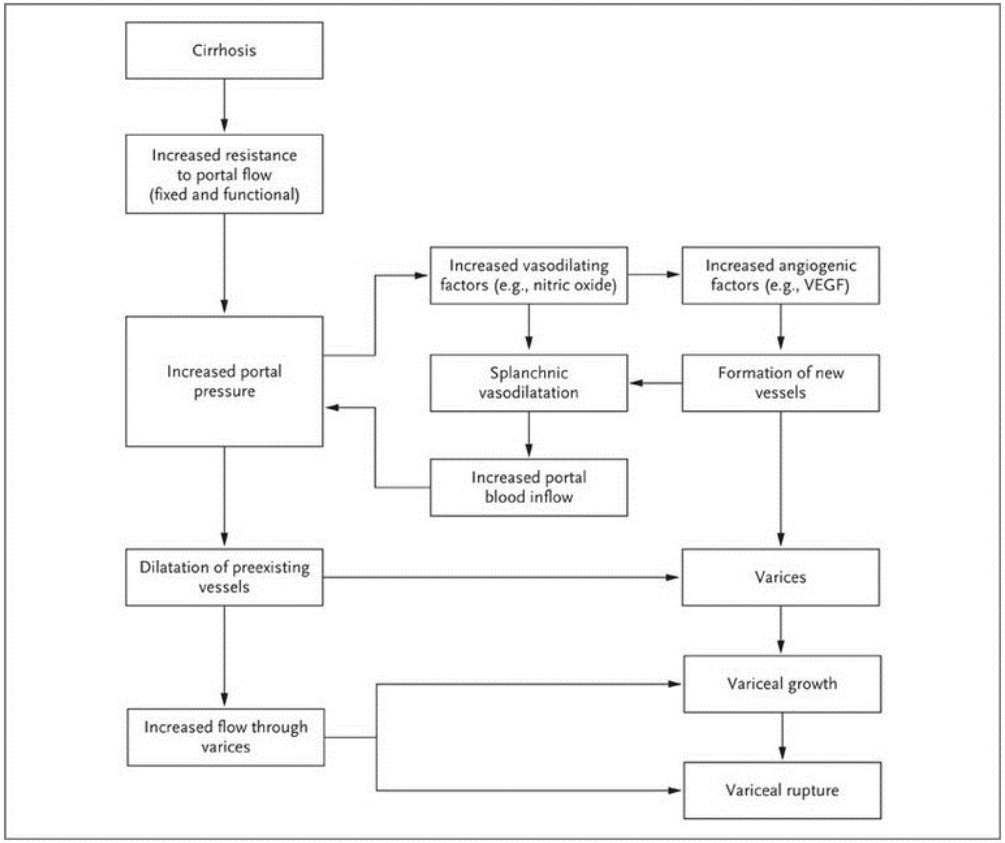
- In 1 anno quota di sviluppo 7% e sanguinamento 12%.

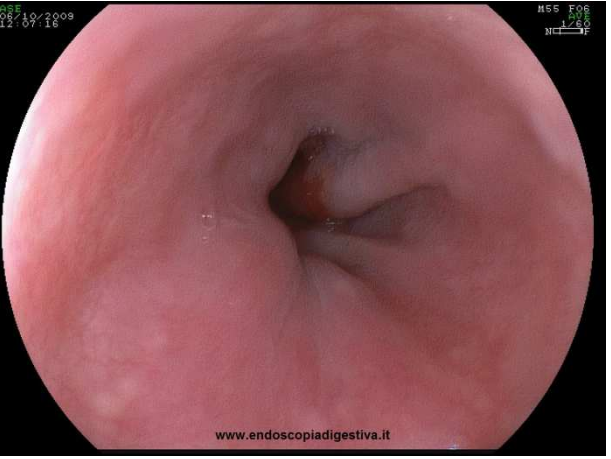
- Rischio maggiore di sanguinamento (grandezza, segni rossi, Child B-C, HVGP>10 mmHg).

- Tasso di risanguinamento nel 1° anno 60%.

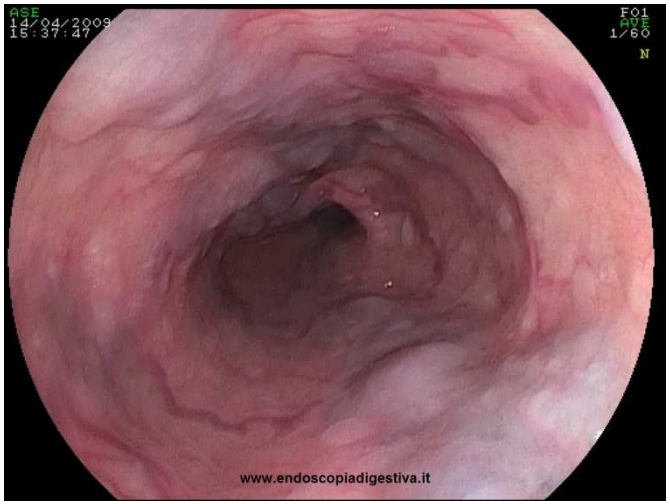
-Tasso mortalità dopo sanguinamento nelle 6 sett 15-20%.





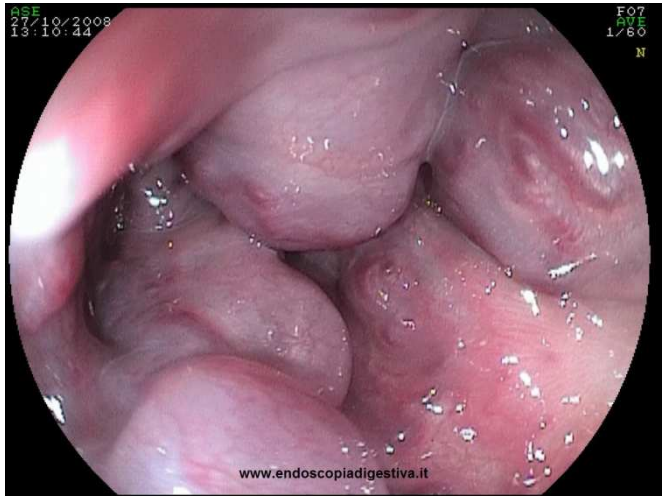


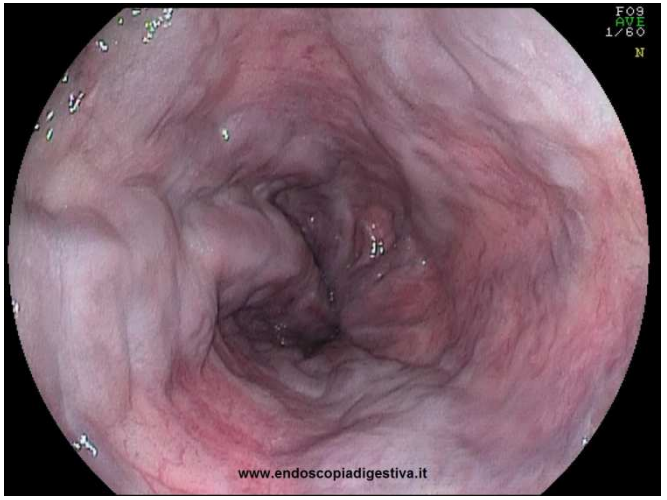
Esofago normale



VARICE F1 (<1/3 lume, lineare)

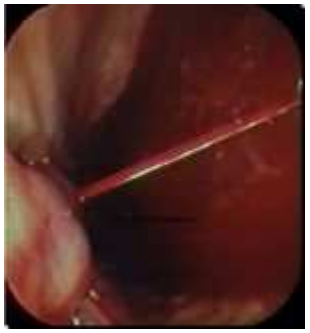
VARICE F3 (centro lume)



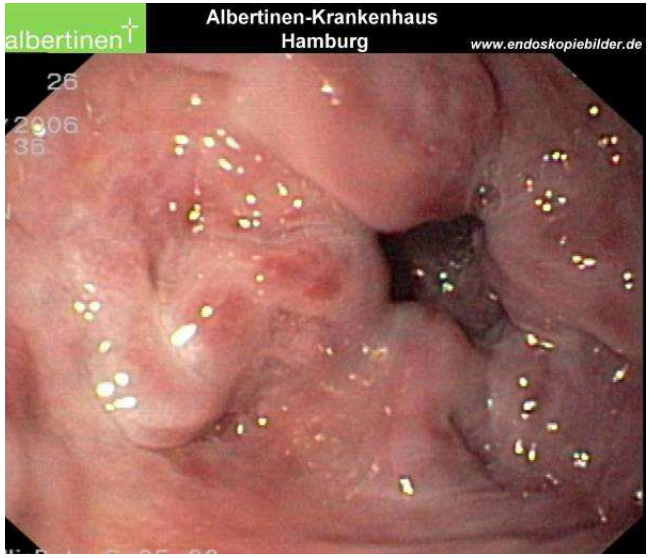


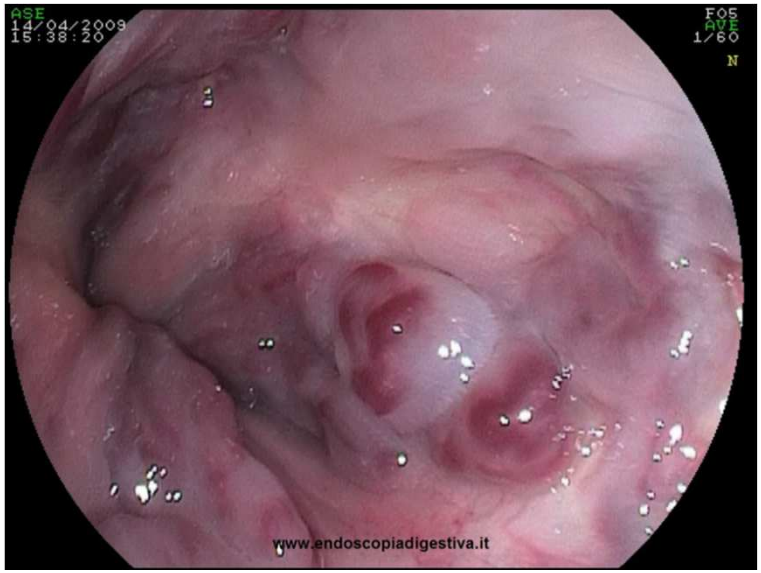
VARICE F2 (<2/3 lume, tortuose

Sanguinamento

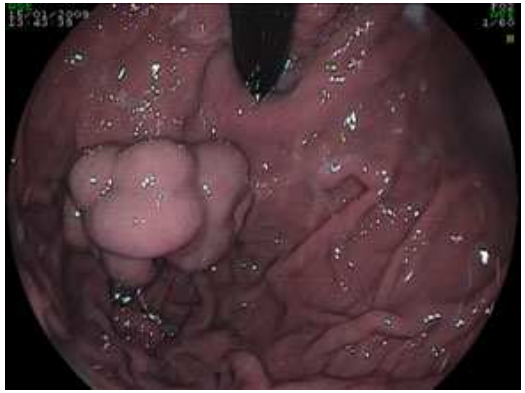


Segni rischio sanguinamento (segni rossi, ectasia venosa ed ematocisti)





VARICI GASTRICHE



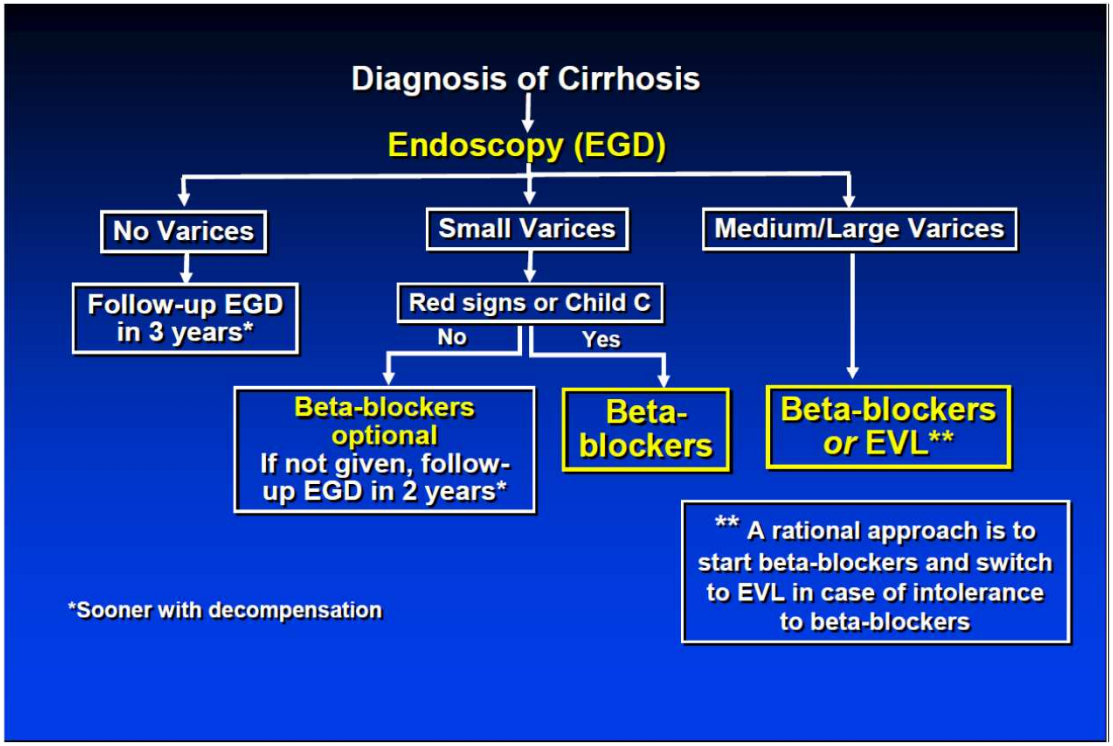
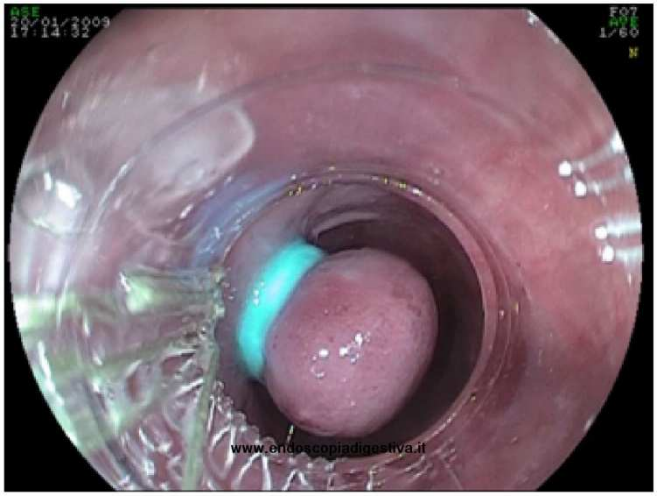


Table 2. Primary Prophylaxis against Variceal Hemorrhage.*

Regimen†	Dose	Goal	Duration	Follow-up
Propranolol	Starting dose of 20 mg given orally twice a day	Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min	Indefinite	Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy
Nadolol	Starting dose of 40 mg given orally once a day	Increase to maximally tolerated dose or until heart rate is approximately 55 beats/min	Indefinite	Ensure heart-rate goals met at each clinic visit; no need for follow-up endoscopy
Endoscopic variceal ligation	Every 2–4 weeks	Obliterate varices	Until variceal obliteration achieved (usually 2–4 sessions)	Perform first surveillance endoscopy 1–3 mo after obliteration, then every 6–12 mo indefinitely

* Therapies that should not be used as prophylaxis include nitrates alone, endoscopic variceal sclerotherapy, shunt therapy (either transjugular intrahepatic portosystemic shunt or surgical shunt), nonselective beta-blockers plus endoscopic variceal ligation, and nonselective beta-blockers plus nitrates.
† Only one of the three regimens should be used.



Emorragia Acuta

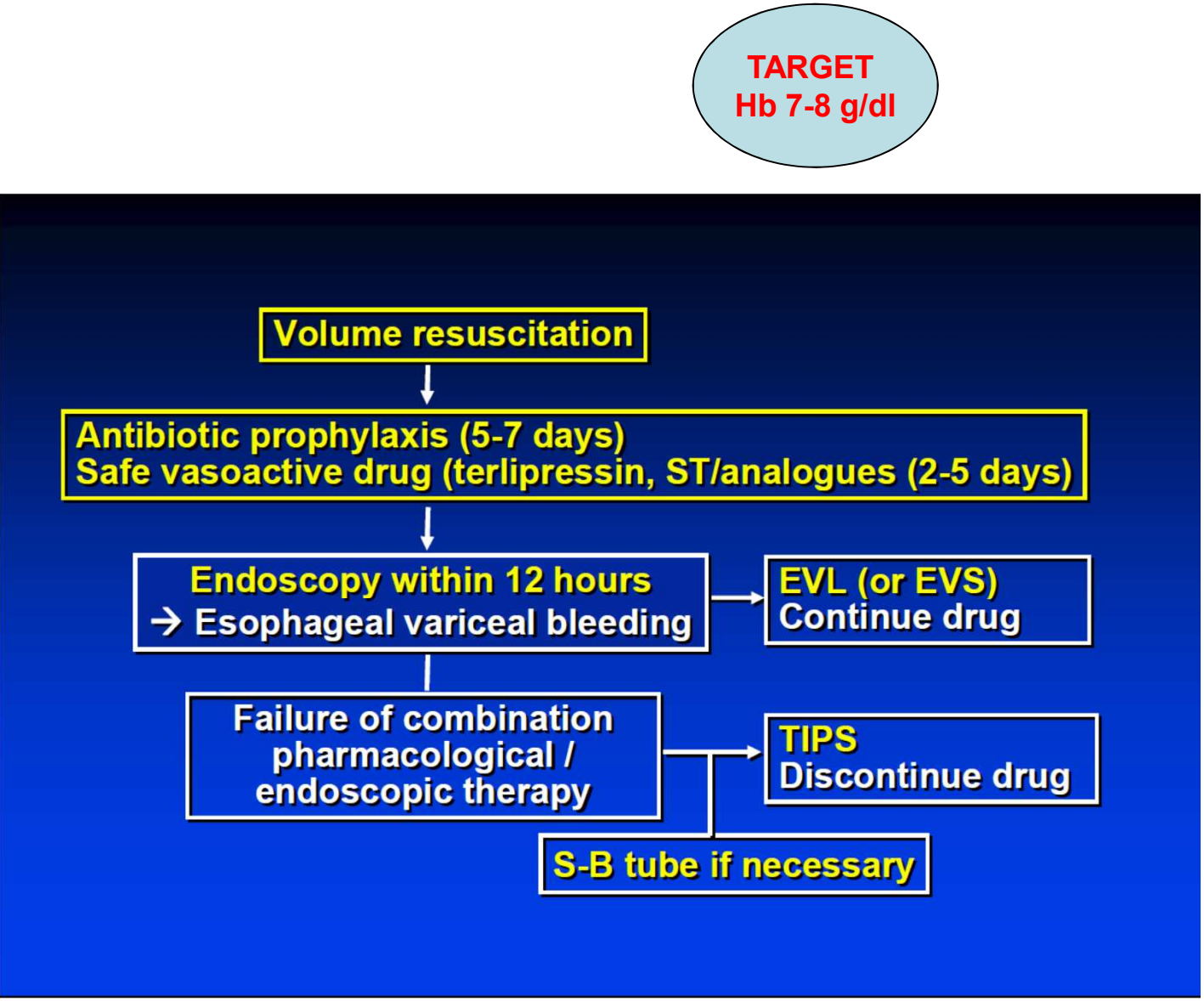
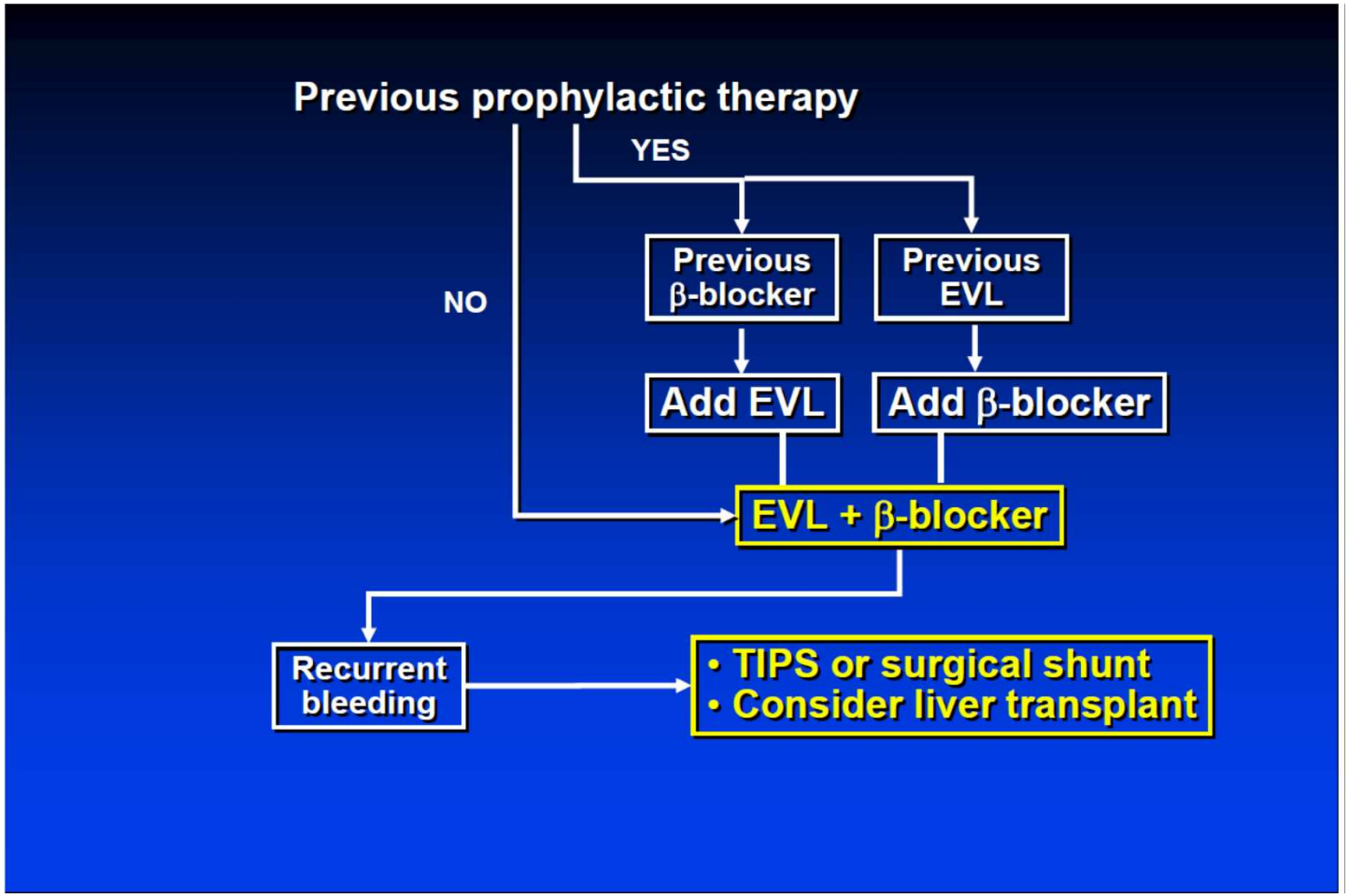


Table 3. First-Line Management of Acute Esophageal Variceal Hemorrhage.*

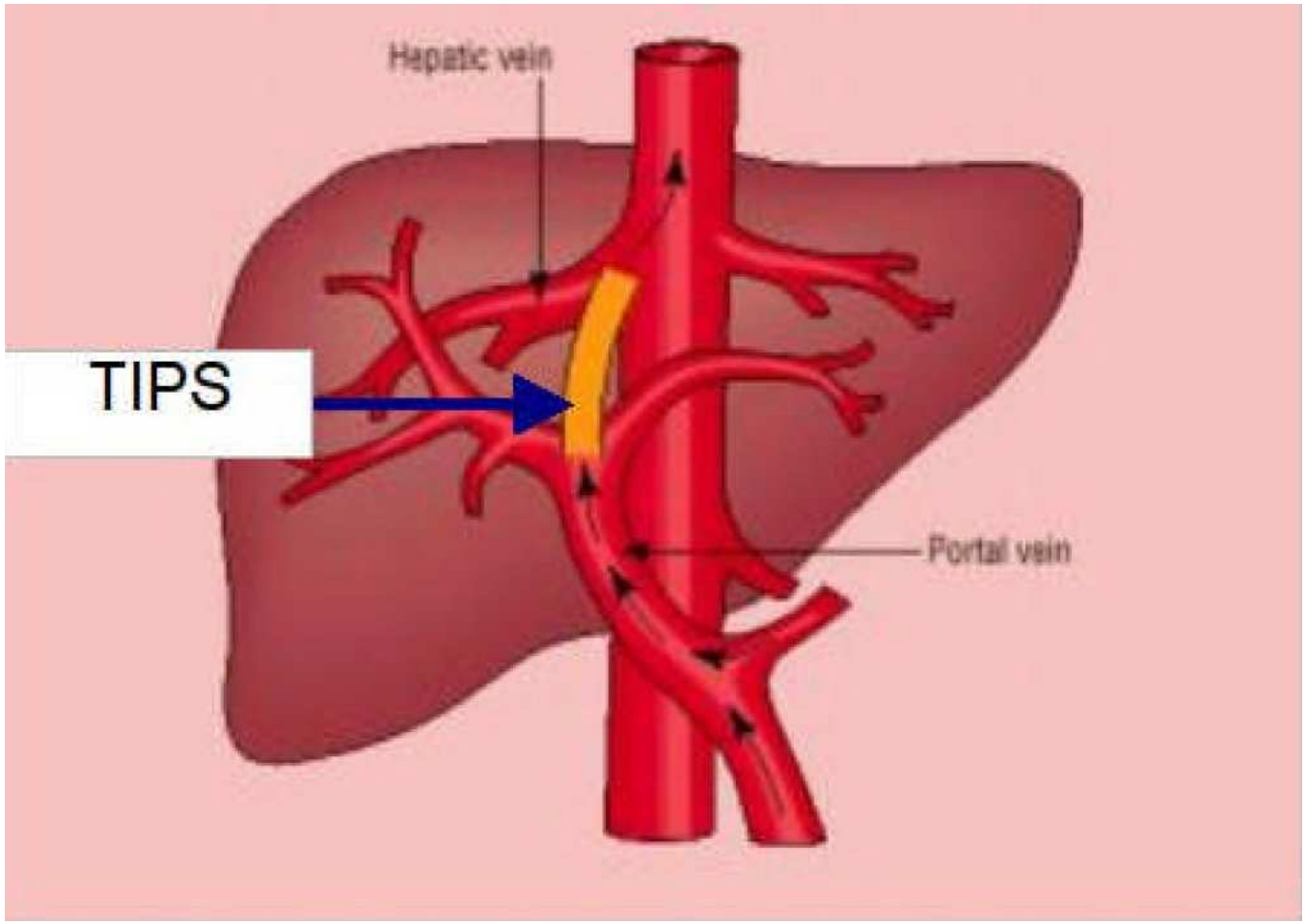
Regimen	Dose	Duration	Follow-up	Comments
Vasoconstrictor				
Octreotide	Intravenous 50-μg bolus, followed by infusion of 50 μg/hr	2–5 days	Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS	Available in the United States
Terlipressin	2 mg given intravenously every 4 hr for first 48 hr, followed by 1 mg given intravenously every 4 hr	2–5 days	If rebleeding occurs during therapy, consider TIPS	Not available in the United States
Somatostatin	Intravenous 250-μg bolus, followed by infusion of 250–500 μg/hr	2–5 days	Bolus can be repeated in first hr if variceal hemorrhage uncontrolled; if rebleeding occurs during therapy, consider TIPS	Not available in the United States
Vapreotide†	Intravenous 50-μg bolus, followed by infusion of 50 μg/hr	2–5 days	If rebleeding occurs during therapy, consider TIPS	Not available in the United States
Antibiotic				
Ceftriaxone	Intravenous ceftriaxone at a dose of 1 g once a day	5–7 days or until discharge	No long-term antibiotics unless spontaneous bacterial peritonitis develops	Used in patients with advanced liver disease, high probability of quinolone resistance, or both
Norfloxacin	400 mg given orally twice a day	5–7 days or until discharge	No long-term antibiotics unless spontaneous bacterial peritonitis develops	Used in patients with low probability of quinolone-resistant organisms
Endoscopic therapy				
Endoscopic variceal ligation	Once, at time of diagnostic esophagogastroduodenoscopy	Until variceal obliteration achieved	If rebleeding occurs during therapy, consider TIPS	Requires endoscopist with special expertise
Endoscopic variceal sclerotherapy	Once, at time of diagnostic esophagogastroduodenoscopy	Only at diagnostic endoscopy	Continue with endoscopic variceal ligation until obliteration achieved	Used when endoscopic variceal ligation not possible; requires endoscopist with special expertise

* Only one vasoconstrictor plus one antibiotic plus endoscopic therapy should be used. Therapies that should not be used for first-line management of acute esophageal variceal hemorrhage are endoscopic variceal obturation (which is indicated in fundal gastric hemorrhage but not in esophageal variceal hemorrhage) and recombinant factor VIIa. NA denotes not applicable, and TIPS transjugular intrahepatic portosystemic shunt.

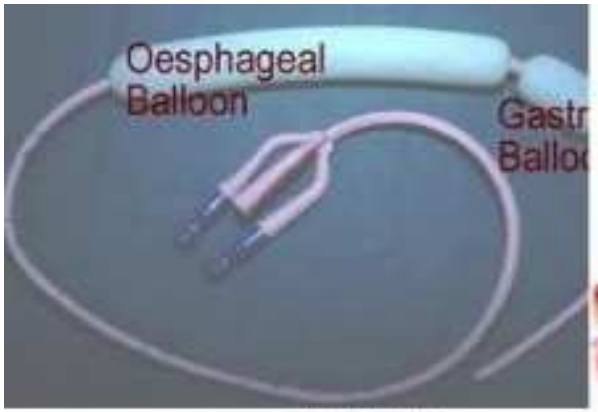
† Recommendations for vapreotide are based on findings from a single study.[47]

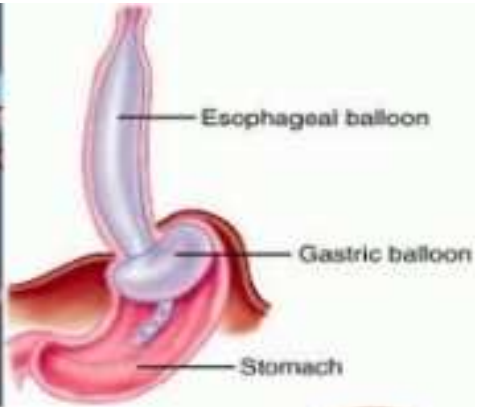

Previous prophylactic therapy
YES
NO
Previous β-blocker
Previous EVL
Add EVL
Add β-blocker
EVL + β-blocker
Recurrent bleeding
• TIPS or surgical shunt
• Consider liver transplant

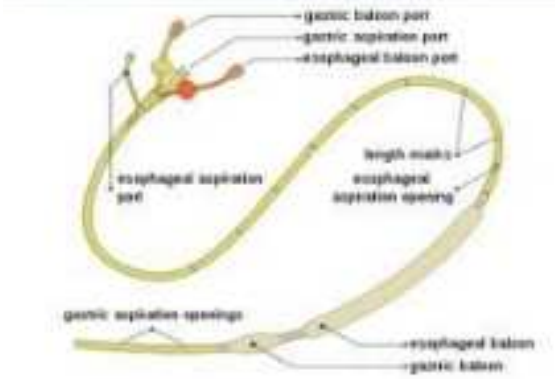
Transjugular intrahepatic portosystemic shunt



Sonda Sengstaken-Blakemore







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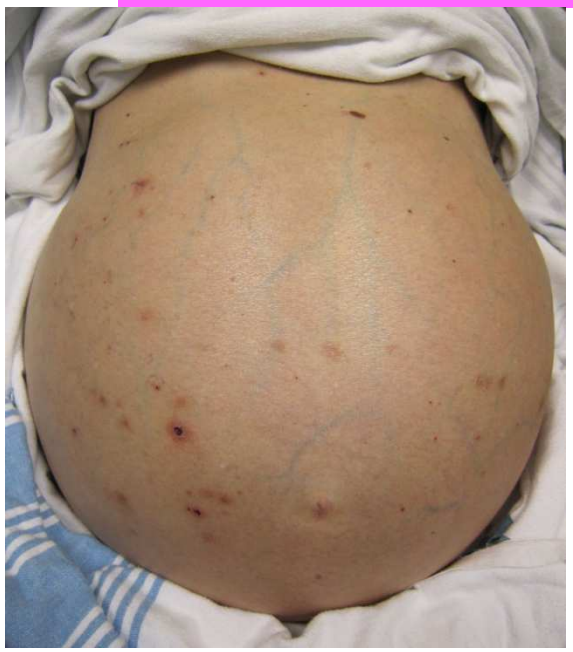
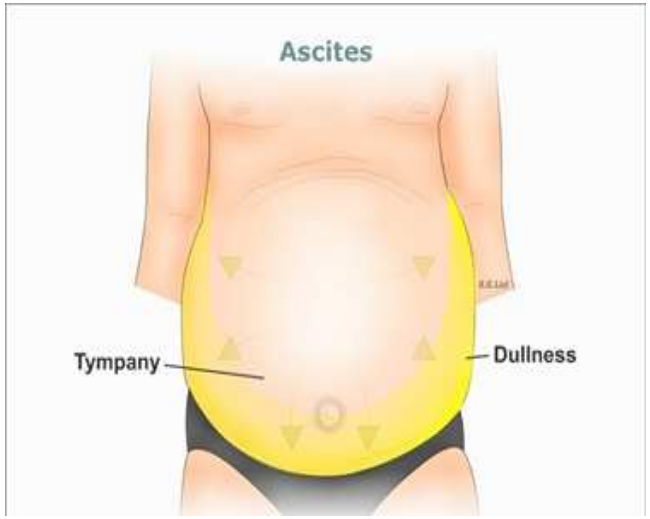
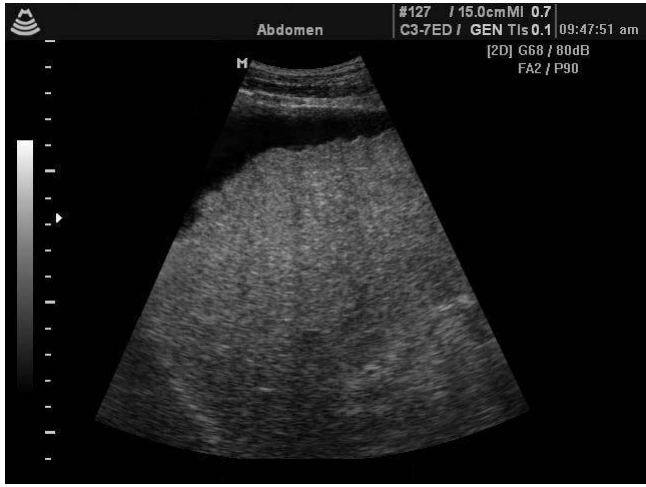
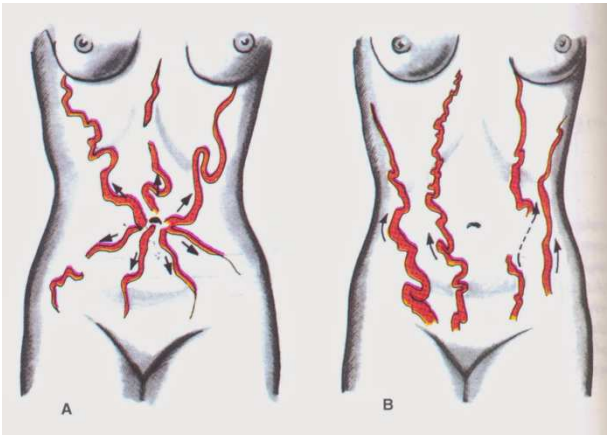


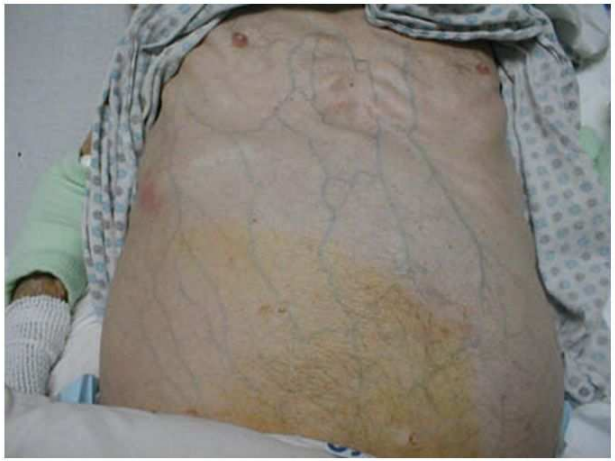




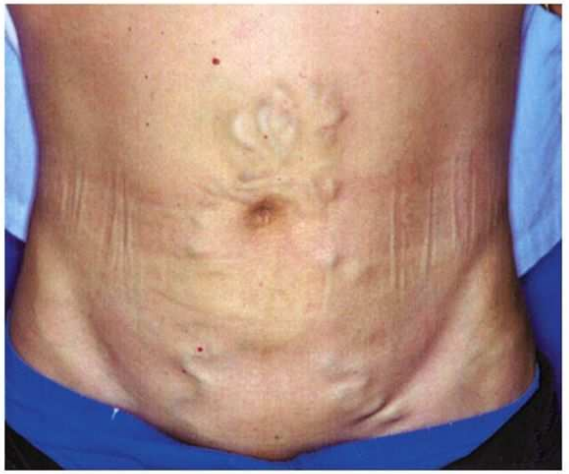
- La mortalità ad 1 anno è circa 40% e 50% a 2 anni.
- Paracentesi diagnostica (esordio ascite grado 2-3, peggioramento ascite o altre complicanze cirrosi).
- Fattori predittori di cattiva prognosi (iponatremia, ipotensione,incremento creatinina, bassa sodiuria)



Circoli collaterali addominali



Circoli collaterali
a “Caput Medusae”

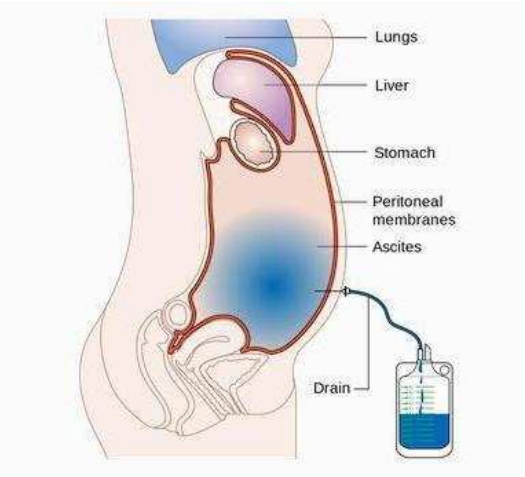


TRATTAMENTO ASCITE

Grade	Definition	Treatment
1	Mild ascites only detectable by ultrasound	No treatment
2	Moderate ascites evident by moderate symmetrical distension of abdomen	Restriction of sodium intake and diuretics
3	Large or gross ascites with marked abdominal distension	Large-volume paracentesis followed by restriction of sodium intake and diuretics (unless patients have refractory ascites)

- Restrizione moderata sodio (sodio 80–120 mmol/die, 4.6– 6.9 g di sale/die).
- Restrizione idrica quando presente. Iponatremia.
- Spironolattone inizia 100 mg/die fino massimo 400 mg/die. Non risposta (riduzione peso di meno di 2 Kg/settimana o sviluppo iperkaliemia, si aggiunge furosemide inizia 40 mg/die al massimo 160 mg/die.

8 g albumina/1 lit. liquido estratto



ESAMI SUL LIQUIDO ASCITICO:

- **proteine totali** (< 15 g/L → rischio elevato di PBS)
- **albumina ***
- **conta neutrofili**
- **colturale mediante inoculazione in flaconi da emocoltura al letto del paziente**
- *** Calcolo del gradiente albuminemico siero/ascite:**
  ≥ 1,1 → ascite da ipertensione portale (<u>solo casi dubbi</u>)
- **citologico, almeno alla prima PARAC.** (Non previsto dalle L.G. EASL 2010)

IN CASO DI DUBBIO O DI SOSPETTO:

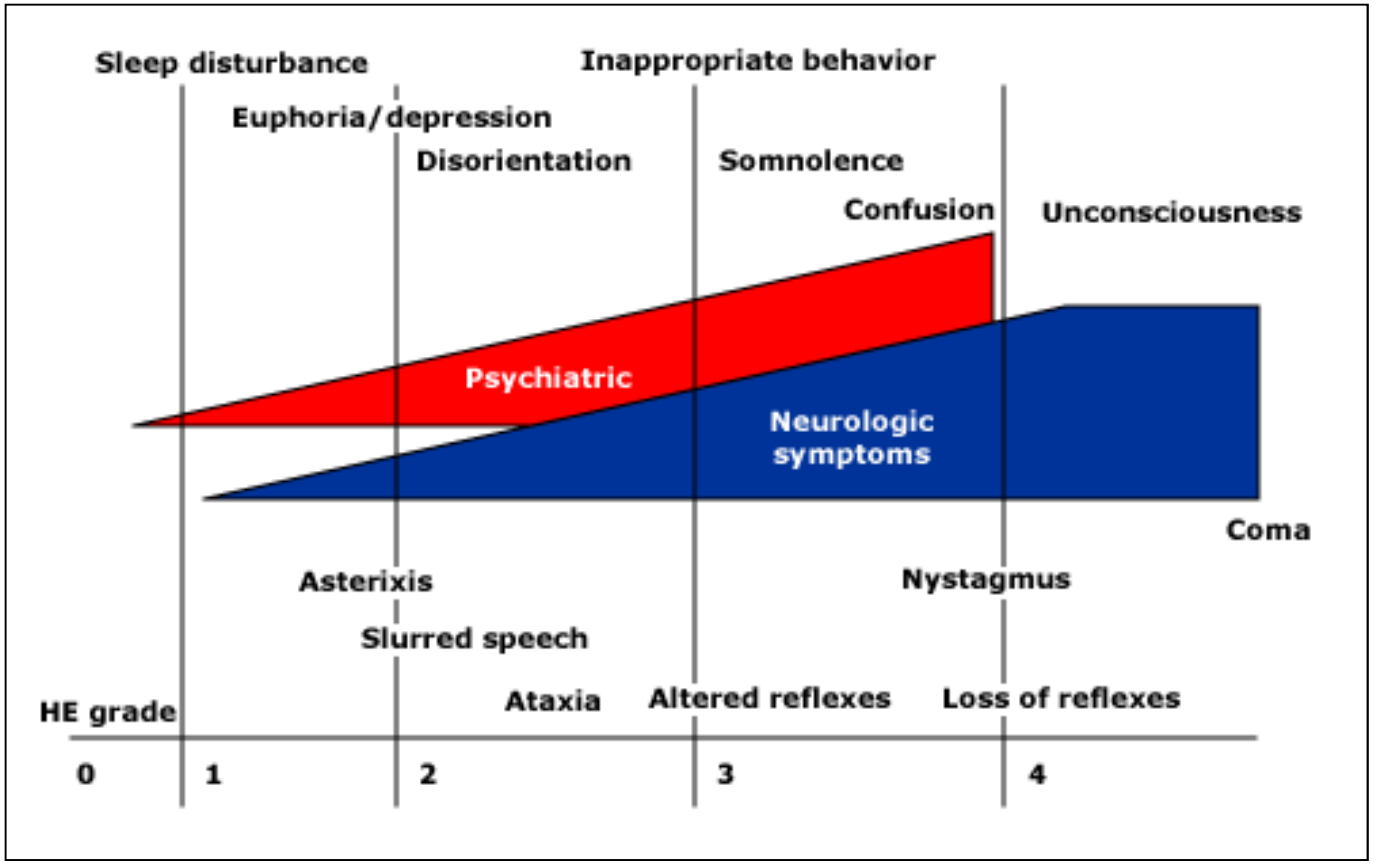
- **citologico; es. x mycobatteri diretto, PCR e colturale; amilasi**

- **Diuretic-resistant ascites Ascites** that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment

- **Diuretic-intractable ascites** Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diureticinduced complications that preclude the use of an effective diuretic dosage

TIPS o TRAPIANTO

ENCEFALOPATIA EPATICA



Type A: hepatic encephalopathy occurring in the setting of acute liver failure

- Type B: hepatic encephalopathy occurring in the setting of portal-systemic bypass with no intrinsic hepatocellular disease
- Type C: hepatic encephalopathy occurring in the setting of cirrhosis with portal hypertension or systemic shunting

HE Precipitating Factors

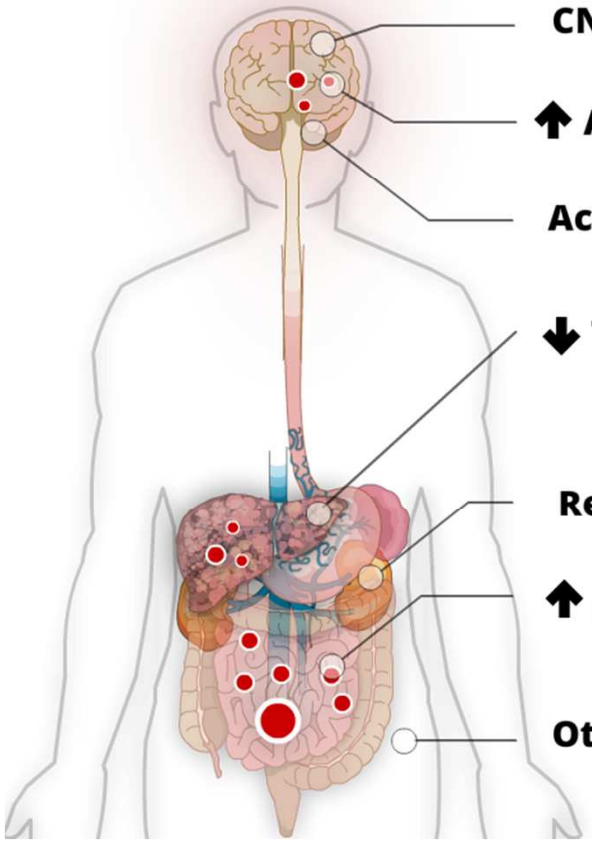
Episodic

- Infection
- GI Bleeding
- Diuretic Overdose
- Electrolyte Disorder
- Constipation
- Unidentified

Frequency

Recurrent

- Electrolyte Disorder
- Infection
- Unidentified
- Constipation
- Diuretic Overdose
- GI Bleeding



CNS Depression • Psychoactive drugs

Ammonia Diffusion across the BBB • Systemic alkalosis

Activation of GABA-BDZ receptors • Benzodiazepines

Toxin Metabolism
- Hepatoma
- Shunts
- Arterial hypotension
- Arterial hypoxemia
- Dehydration
- Anemia

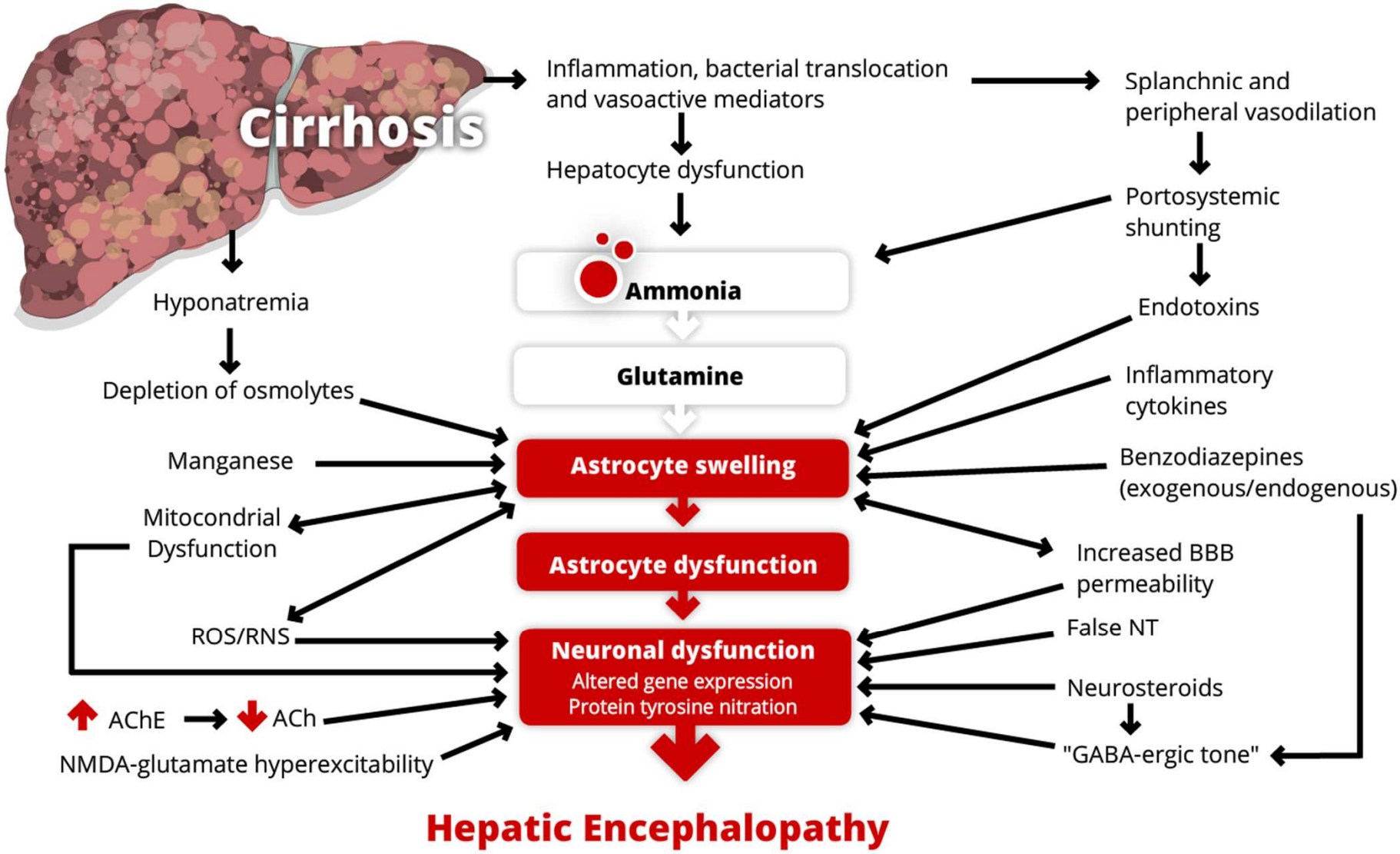
Renal Failure • Azotemia

Ammonia Production
- GI hemorrhage
- Hypokalemia
- Constipation
- Excess dietary protein
- Infection

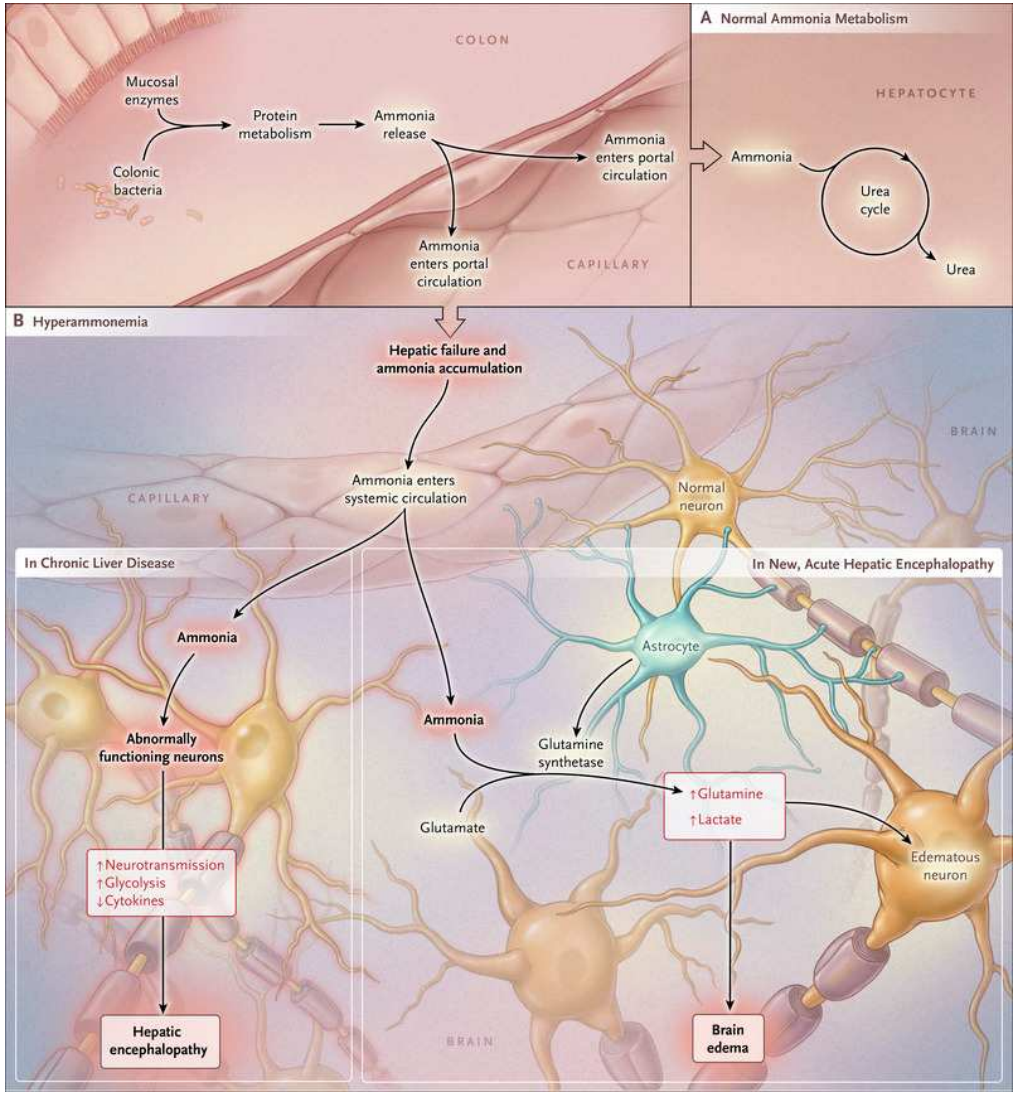
Other
- Sepsis
- Hyponatremia

Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K. and Wong, P. (2014), Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 60: 715–735. doi:10.1002/hep.27210

Multifactorial



Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema.



TRATTAMENTO ENCEFALOPATIA EPATICA

- The goal of initial management of hepatic encephalopathy is to reduce ammonia absorption from the intestinal lumen with the use of lactulose or lactilol. These **nonabsorbable disaccharides** have laxative effects and change the gut microbiome to non–urase-producing bacteria, reducing intestinal ammonia production (25 ml twice daily)

- **Intravenous l-ornithine–l-aspartate** lowers ammonia levels by providing an alternative substrate for the urea cycle; its use is considered in patients who do not have a response to lactulose.

- **Probiotics** (e.g., yogurts with lactobacillus or saccharomyces) have been shown to prevent or ameliorate hepatic encephalopathy in patients with cirrhosis.

- **Infection**, which could precipitate **gastrointestinal hemorrhage** and **dehydration**, should be treated, and correction of hyponatremia and hypovolemia is warranted

- For recurrent hepatic encephalopathy in patients with cirrhosis, **rifaximin** (550 mg twice a day), which alters gut microbiota, is added to lactulose.

- For patients with hepatic encephalopathy and cirrhosis who do not have a response to standard treatments, large portosystemic shunts are considered. End-stage liver disease can be an indication for liver transplantation.

SBP- Definition

- Ascitic fluid infection without evident intra-abdominal surgically treatable source
- Usually occurs in patients with cirrhosis and ascites

SBP – Risk Factors

- Advanced cirrhosis
- Ascitic fluid total protein <1g/dL
- Prior SBP
- Serum total bilirubin >2.5 mg/dL
- Variceal hemorrhage
- Malnutrition
- PPI use
- Ascitic fluid total protein <1.5 g/dL +
  - Child-Pugh score ≥9 points + serum bilirubin ≥3 gm/dL *OR*
  - Plasma creatinine ≥1.2 mg/dL, BUN ≥25 mg/dL or plasma Na ≤130 mEq/L

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SBP - Diagnosis

- Clinical presentation
- Ascitic fluid positive for bacteria
- Ascitic fluid absolute polymorphonuclear leukocyte (PMN) count ≥250 cells/mm^3
- Exclusion of secondary causes

SBP – Signs and Symptoms

- **Fever** (most common)
- **Abdominal pain/tenderness**
- **Altered mental status**
- Diarrhea
- Paralytic ileus*
- Hypotension*
- Hypothermia*
- Abnormal laboratory values (e.g. leukocytosis, metabolic acidosis, azotemia)

*Advanced infection

SBP - Treatment

Ascitic PMN <250 cells/mm^3 +

- Signs/symptoms of infection:
  - Empiric antibiotic therapy, e.g. **ceftotaxime 2 g IV q8h**, while awaiting cultures

American Association for the Study of Liver Disease

SBP - Treatment

Ascitic PMN <250 cells/mm^3 +

- Signs/symptoms of infection:
  - Empiric antibiotic therapy, e.g. **ceftotaxime 2 g IV q8h**, while awaiting cultures

American Association for the Study of Liver Disease (2012)

SBP - Treatment

Ascitic PMN ≥250 cells/mm^3 +

- Community-acquired setting + absence of β-lactam antibiotic exposure:
  - Empiric antibiotic therapy, e.g. IV third generation cephalosporin, preferably **cefotaxime 2 g IV q8h**
- Nosocomial setting ± in the presence of recent β-lactam antibiotic exposure:
  - Empiric antibiotic therapy based on *local susceptibility testing of bacteria in patients with cirrhosis*
- Can substitute with **ofloxacin 400 mg PO BID** in inpatients without prior exposure to quinolones, vomiting, shock, grade ≥II hepatic encephalopathy, or SCr >3 mg/dL

American Association for the Study of Liver Disease (2012)

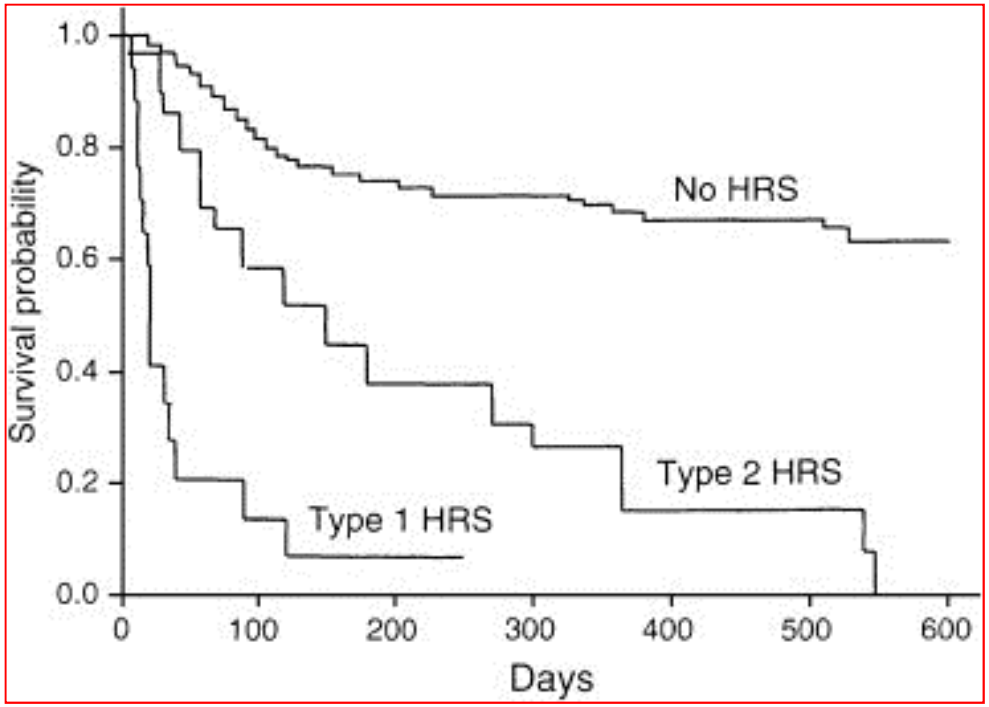
Major diagnostic criteria for hepatorenal syndrome

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement in serum creatinine (decrease to a level of <1.5 mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (<50 RBC/high power field) and/or abnormal renal ultrasonography

Minor diagnostic criteria for hepatorenal syndrome

- Urine volume < 500 mL/24 h
- Urine sodium <10 mEq/L
- Urine osmolality greater than plasma osmolality
- Urine red blood cells < 50 per high power field
- Serum sodium <130 mEq/L

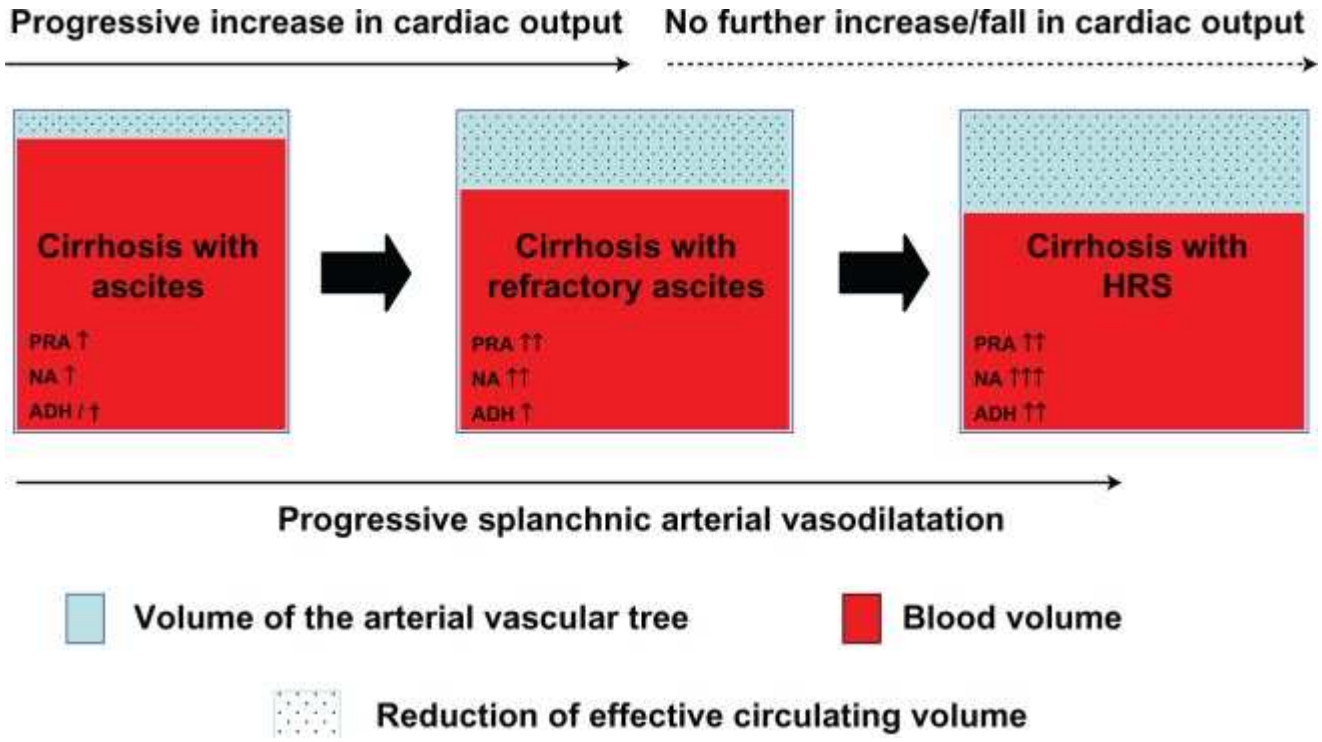
PROGNOSI HRS



Munoz S. Medical Clinics of North America July 2008

Causes of AKI in pts with cirrhosis

- Acute tubular necrosis (41.7%)
- Pre-renal failure (38%)
- **Hepatorenal syndrome (20%)**
- Post-renal failure (0.3%)


Progressive increase in cardiac output
No further increase/fall in cardiac output
Cirrhosis with ascites
PRA ↑
NA ↑
ADH / ↑
Cirrhosis with refractory ascites
PRA ↑↑
NA ↑↑
ADH ↑
Cirrhosis with HRS
PRA ↑↑
NA ↑↑↑
ADH ↑↑
Progressive splanchnic arterial vasodilatation
Volume of the arterial vascular tree
Blood volume
Reduction of effective circulating volume

Type 1 HRS: rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to a level > 226 μmol/L or 2.5 mg/dL in less than 2 weeks. It may occurs spontaneously, but it can also follow a precipitating event.

Clinical pattern: acute renal failure

Type 2: is characterized by moderate renal failure (serum creatinine from 133 to 226 μmo1/L or 1.5 to 2.5 mg/dL) with a steady or slowly progressive course.

Clinical pattern: refractory ascites

The management of type 1 hepatorenal syndrome

- Be sure of the diagncsis by excluding the other forms of renal failure
- Look carefully for a precipitating event especially bacterial infections
- Remember that the clinical picture is an acute renal failure and, thus adopt all the general measures for this clinical condition
- Start treatment with vasoconstrictors plus albumin monitoring closely its efficacy and safety
- Set up high priority for liver transplant in suitable patients
- Take into account TIPS in patients without severe liver failure who failed to respond to vasoconstrictors and albumin
- Take into account techniques of renal replacement when indicated

The management of type 2 hepatorenal syndrome

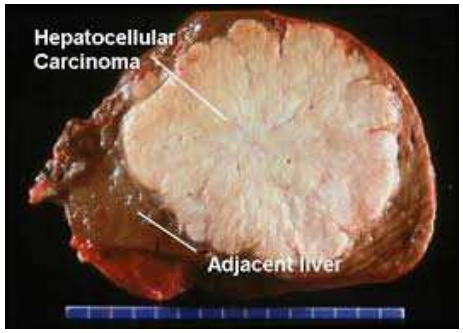
- Be sure of the diagnosis by excluding the other forms of renal failure
- Look carefully for a precipitating event especially bacterial infections
- Remember that the main clinical problem is refractory ascites
- Adopt therapeutic paracentesis with plasma volume expansion by means of albumin infusion as first choice treatment of ascites
- Use diuretics in order to reduce the frequency of repeated paracentesis only if they are tolerated
- Consider TIPS, when not contraindicated, if paracentesis becomes too frequent or ineffective
- Refer suitable patients to a liver transplant center

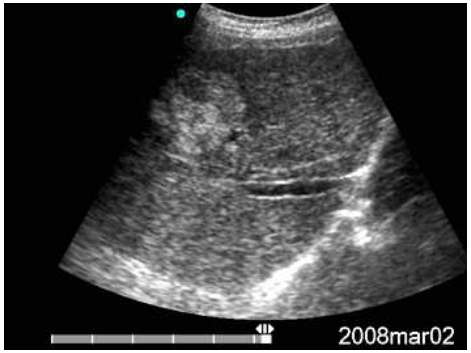
HCC

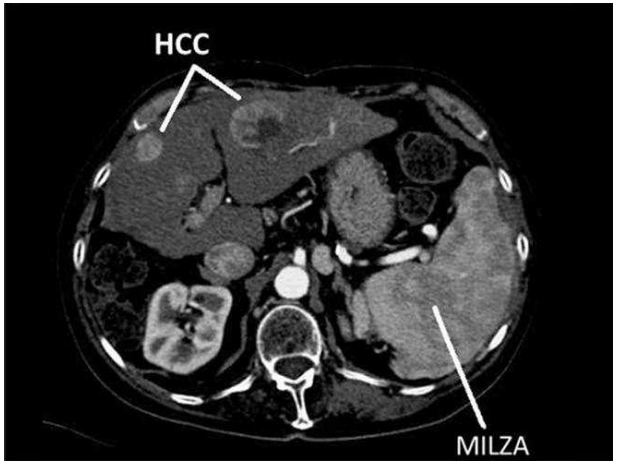
- **Incidenza in aumento (1,5 milioni nuovi casi anno**
- **5 causa tumore uomo. 7 donne.**
- **3 causa mortalità per tumore**
- **Principale causa HBV-HCV.**
- **Cofattori: obesità, diabete, NALFD, alcol.**

PREVENZIONE

- **Ecografia 6 mesi**
- **alfaFP**





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THE END