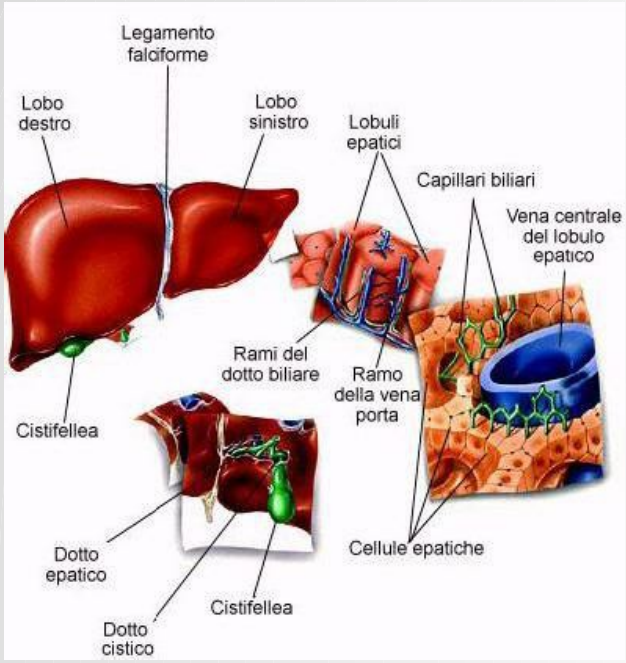
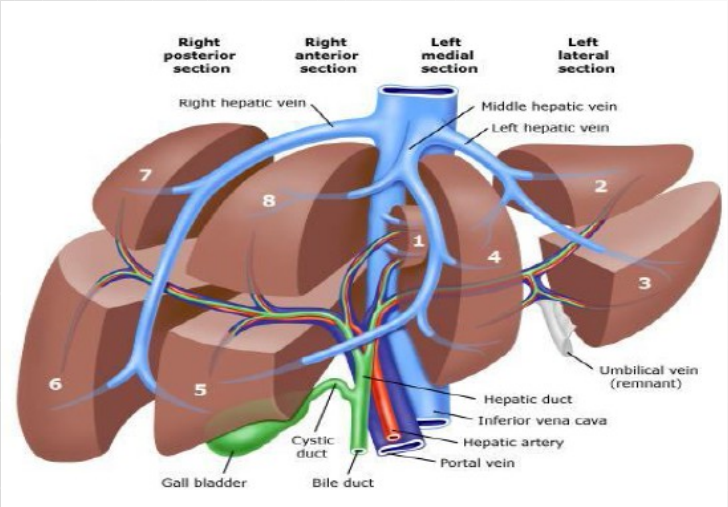
INSUFFICIENZA EPATICA IN ICU

Mercoledì 22 ottobre ore 14.30
(auletta 2° CR)

Dott.ssa Laura Lamberti
Scuola di Specializzazione in Anestesia e Terapia Intensiva





Il più grande organo dell'organismo (1-1,5 Kg)

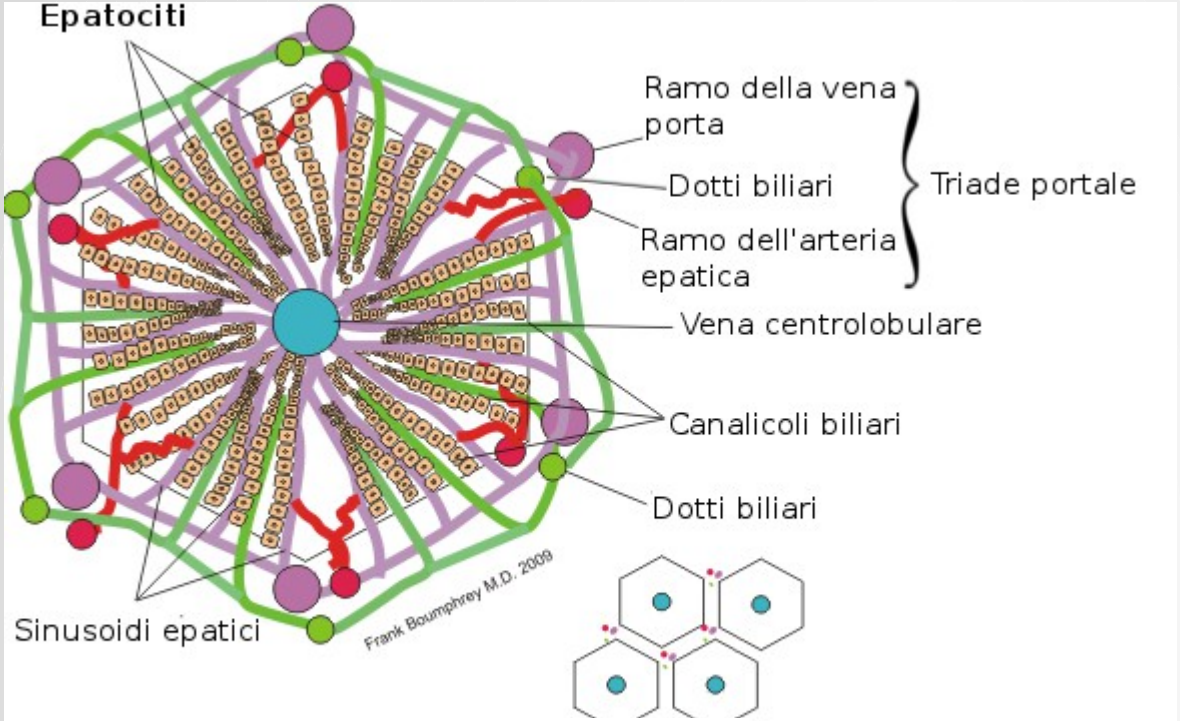
-LOBO DESTRO
(lobo caudato e lobo quadrato)
-LOBO SINISTRO

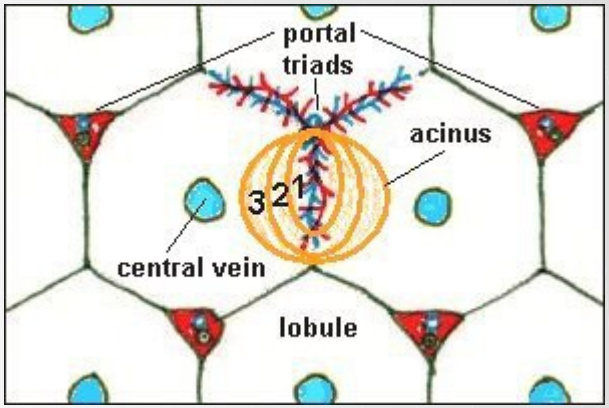
8 segmenti (ramificazioni biliari e vasi)

IN: Arteria epatica (dal tronco celiaco)
Vena porta (da mesenterica superiore e splenica)

OUT: 3 vv. epatiche (+ vv. epatiche minori) in VCI

Dotto epatico dx e sx in epatico comune che si unisce al cistico per formare coledoco (corre con il dotto pancreatico per andare nel duodeno)





Istologico: **LOBULO**

Funzionale: **ACINO**
(3 zone a seconda di gradienti funzionali, concentrazioni ematiche di ossigeno, nutrienti e ormoni)

1.periportale
2.mediana
3.centrolobulare

Funzioni epatiche

- Esocrine: sintesi ed escrezione bile
- Metabolismo glucidico: glucuneogenesi (glicogeno)
- Metabolismo lipidico: sintesi, immagazzinamento, eliminazione.
- Metabolismo proteico (es. albumina)
- Fattori della coagulazione (fibrinogeno, protrombina, fatt V, VII, VIII, IX, X, XI, XII)
- Metabolismo vitaminico (deposito ed utilizzo)
- Funzione detossificante
- Funzione immunitaria (cellule di Kuppfer)
- Emodinamica: 1/4 GC

VALUTAZIONE FUNZIONALE DEL FEGATO

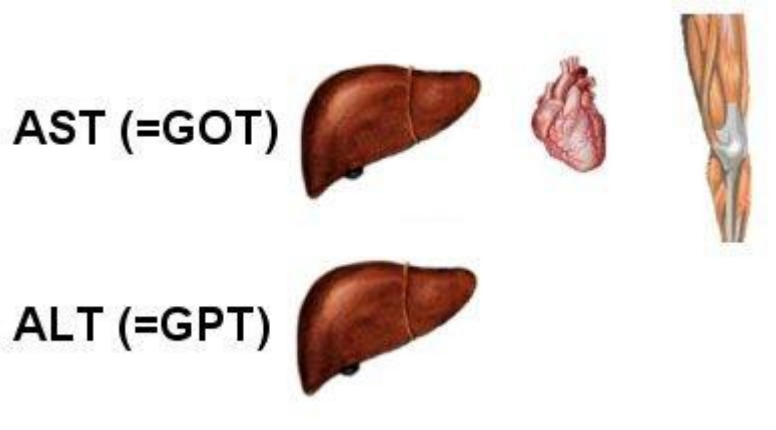
1) INDICI DI NECROSI:

TRANSAMINASI (AST E ALT) **enzimi citoplasmatici diffusi in molti tessuti che hanno quindi una bassa specificità.**

Costituiscono un indice di danno cellulare. Possono essere maggiormente indicativi di danno epatico quando:

– i valori sono molto elevati (500-1000 U/l) e permangono tali per più di 24-48 ore;

– l'aumento maggiore è a carico delle ALT (> specificità);



Rapporto AST/ALT

- **>2 forme alcool correlate,**
- **<2 forme non alcool correlate,(<1 epatiti virali)**

LATTICO DEIDROGENASI (LDH) 5 forme isoenzimatiche distribuite in diversi tessuti.

2) INDICI DI COLESTASI:

FOSFATASI ALCALINA (ALP)

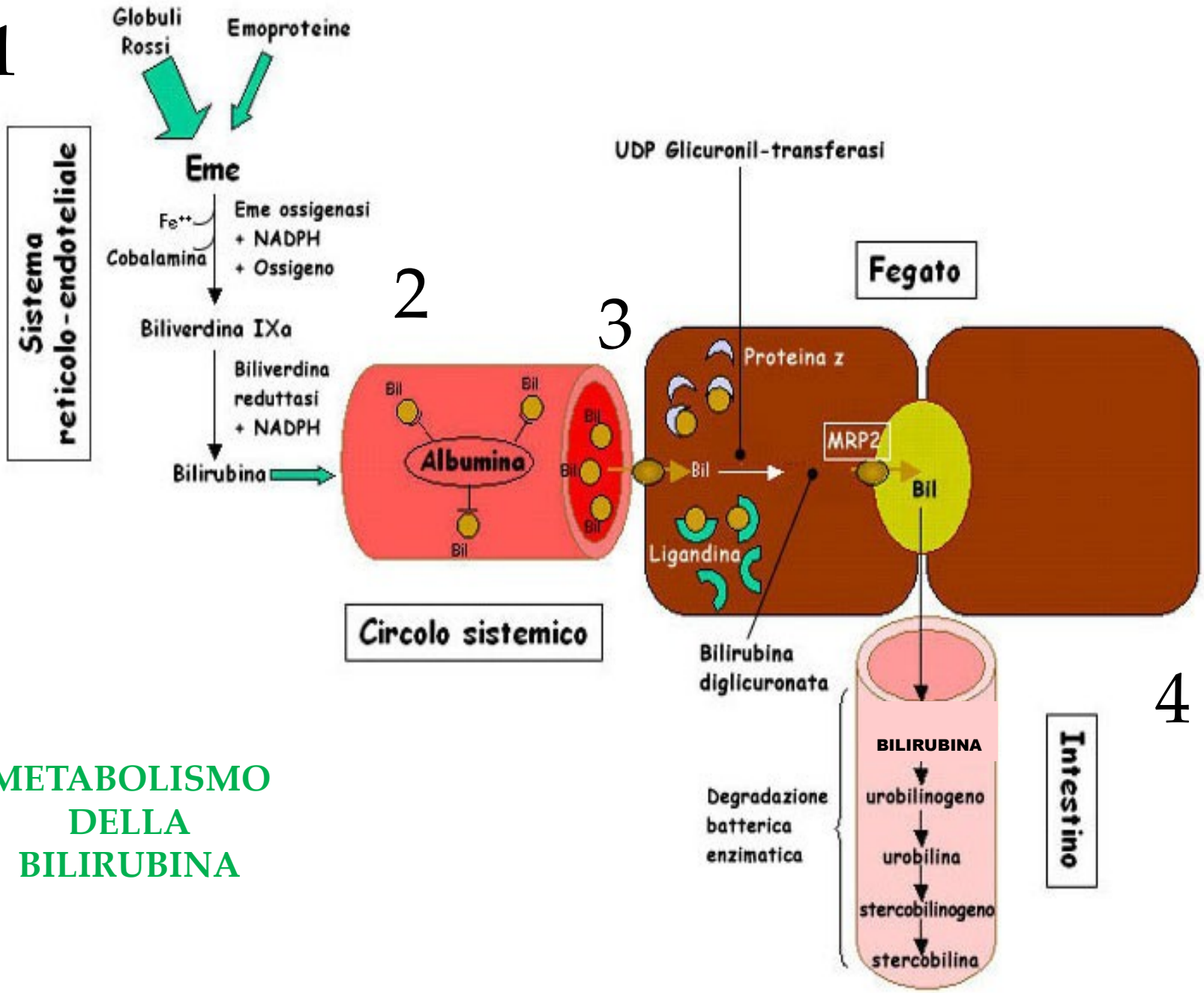
è un enzima sintetizzato dal tessuto osseo, dall'intestino, dal rene e, in minor grado, dagli epatociti. L'elevazione della sua concentrazione sierica è indice di colestasi

GAMMA GLUTAMIL-TRANSPEPTIDASI (GGT)

è una glicoproteina legata alla membrana plasmatica coinvolta nel metabolismo del glutatione. Parametro di stasi biliare influenzato soprattutto dall'assunzione di alcool e farmaci

BILIRUBINA TOTALE E FRAZIONATA

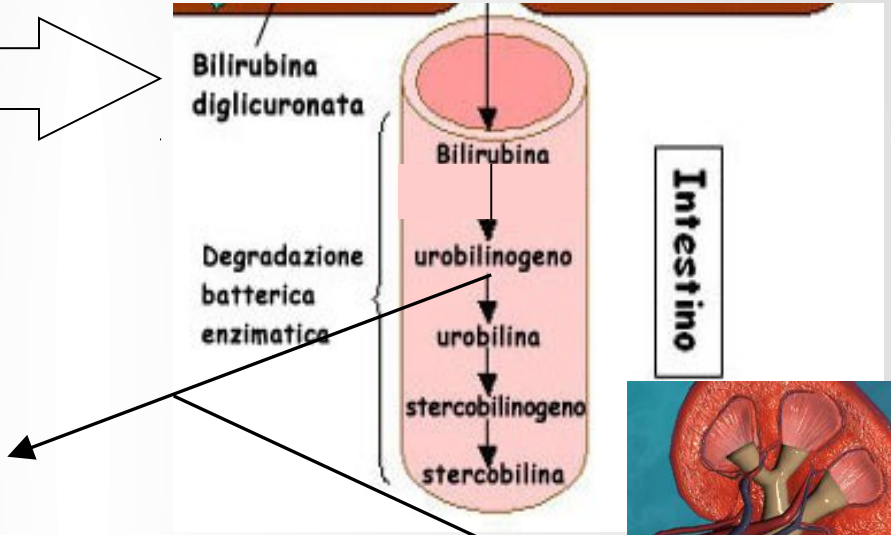
utilizzata per la valutazione della capacità escretoria dell'epatocita.

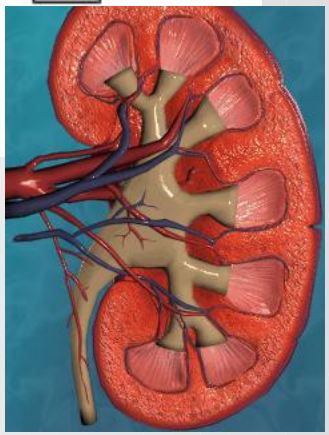


METABOLISMO DELLA BILIRUBINA

CIRCOLO ENTERO-EPATICO

BILE





URINE

ITTERO

«Colorazione giallastra della cute e delle mucose visibili, conseguente all'aumento della bilirubina plasmatica oltre i 2 – 2,5 mg/dl».

- ✓ **Ittero pre-epatico o emolitico**
- ✓ **Ittero epatocellulare**
- ✓ **Ittero ostruttivo**

Subittero

Ittero

Box 1. Etiologies of jaundice in the ICU

Obstructive jaundice

Choledocholithiasis
Cholangitis
Cholangiocarcinoma
Pancreatic duct stricture
Pancreatic head mass

Nonobstructive jaundice

Hemolysis
Massive transfusion
Hypotension/"shock liver"
Disseminated intravascular coagulation
Soft tissue trauma and hematoma resorption
Sepsis
Liver trauma/biloma
Liver failure/MSOF
Medications/hepatotoxins
Viral hepatitis

Surg Clin N Am 86 (2006) 1495–1502

3) INDICI DI INSUFFICIENZA EPATICA:

COAGULAZIONE E PIASTRINOPENIA con allungamento del PT

La PROTEINEMIA TOTALE E FRAZIONATA e l'elettroforesi sierica forniscono preziose informazioni sulla capacità sintetica dell'epatocita. I valori sierici delle proteine totali, dell'albumina sono ridotti in situazioni di grave scompenso epatico.

Le COLINESTERASI diminuiscono nel 30-50% nei casi di epatite acuta, e del 50-70% in casi di cirrosi e Ca con metastasi diffuse al fegato.

AMMONIEMIA. Deriva in parte dal metabolismo proteico, ma soprattutto, attraverso il circolo portale, dall'intestino, ove è elaborata dalla flora batterica durante la digestione delle proteine alimentari. Normalmente essa è trasformata nel fegato in urea, prodotto idrosolubile non tossico. Ogni qualvolta però vi sia un deficit a carico del metabolismo epatico la concentrazione di ammonio plasmatico aumenta. Si suppone abbia un ruolo preminente nella encefalopatia epatica.

MALATTIE EPATICHE

- **Malattie epatocellulari** – danno epatico, infiammazione, necrosi…

ALF: Acute Liver Failure

ACLF: Acute on Chronic Liver Failure

- **Malattie colestatiche (ostruttive) –** riduzione/blocco flusso biliare

EXTRAHEPATIC FORM

mechanical obstruction (decreased bile flow)

INTRAHEPATIC FORM

functional alterations at the hepatocellular level

- **Miste**

ALF VS ACLF: definition

Acute Liver Failure: Summary of a Workshop

William M. Lee,[1] Robert H. Squires Jr, [2] Scott L. Nyberg,[3] Edward Doo,[4] and Jay H. Hoofnagle[4]

The sudden loss of hepatic function in a person without preexisting liver disease defines ALF.[1,2] The most reliable signs of severe acute liver injury are the presence of coagulopathy (international normalized ratio [INR] ≥ 1.5) and any degree of hepatic encephalopathy, the length of illness being considered anything ≤ 24 weeks.

(HEPATOLOGY 2008;47:1401-1415.)

Table 2. West-Haven criteria for hepatic encephalopathy.

Stage	Level of consciousness	Intellect and behaviour	Neurological findings	Electroencephalographic abnormalities
0	Normal	Normal	Normal examination If impaired psychometric testing, then minimal hepatic encephalopathy	None
1	Mild lack of awareness Personality changes	Impaired concentration, mild confusion	Apraxia, mild asterixis or tremor	Triphasic waves with slow wave activity (5-6 cycles/s)
2	Lethargy	Disorientation, inappropriate behaviour	Obvious asterixis, dysarthria (slurred speech)	Triphasic waves with slow wave activity (5 cycles/s)
3	Somnolence	Gross disorientation, agressivity	Muscular rigidity and clonus, hyperreflexia, Babinski sign	Triphasic waves with slow wave activity (5 cycles/s)
4	Coma (awakening impossible)	Coma	Decerebrate posturing, rigidity	Delta activity, very slow wave activity (2-3 cycles/s)

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Management of critically-ill cirrhotic patients

Pere Ginès[1,2,*], Javier Fernández[1], François Durand[2], Faouzi Saliba[3]

[1]Liver Unit, IMDiM, Hospital Clinic Barcelona, University of Barcelona and IDIBAPS and Ciberehd, Barcelona, Spain; [2]Instituto Reina Sofía de Investigación Nefrológica (IRSIN), Spain; [3]Hepatology and Liver Intensive Care, Hospital Beaujon, INSERM, U773, Centre de Recherche Biomédicale Bichat Beaujon CRB3. Hospital Beaujon, Clichy, France; [4]Centre hépato-biliaire; Hôpital Paul Brousse, Villejuif, France; Université Paris-Sud, UMR-S 785 and Unité INSERM 785, Villejuif, France

Hepatic failure:
EPIDEMIOLOGY in ITALY

Non esiste un sistema di monitoraggio ALF!!!

SEIEVA (Sistema di sorveglianza delle epatiti acute; solo dati di mortalità)

CNT (Registro Centro Nazionale trapianti; no dati sui decessi né sulle guarigioni spontanee)

ISTAT (non attendibili per problemi di codifica)

ALF: prognostic definition

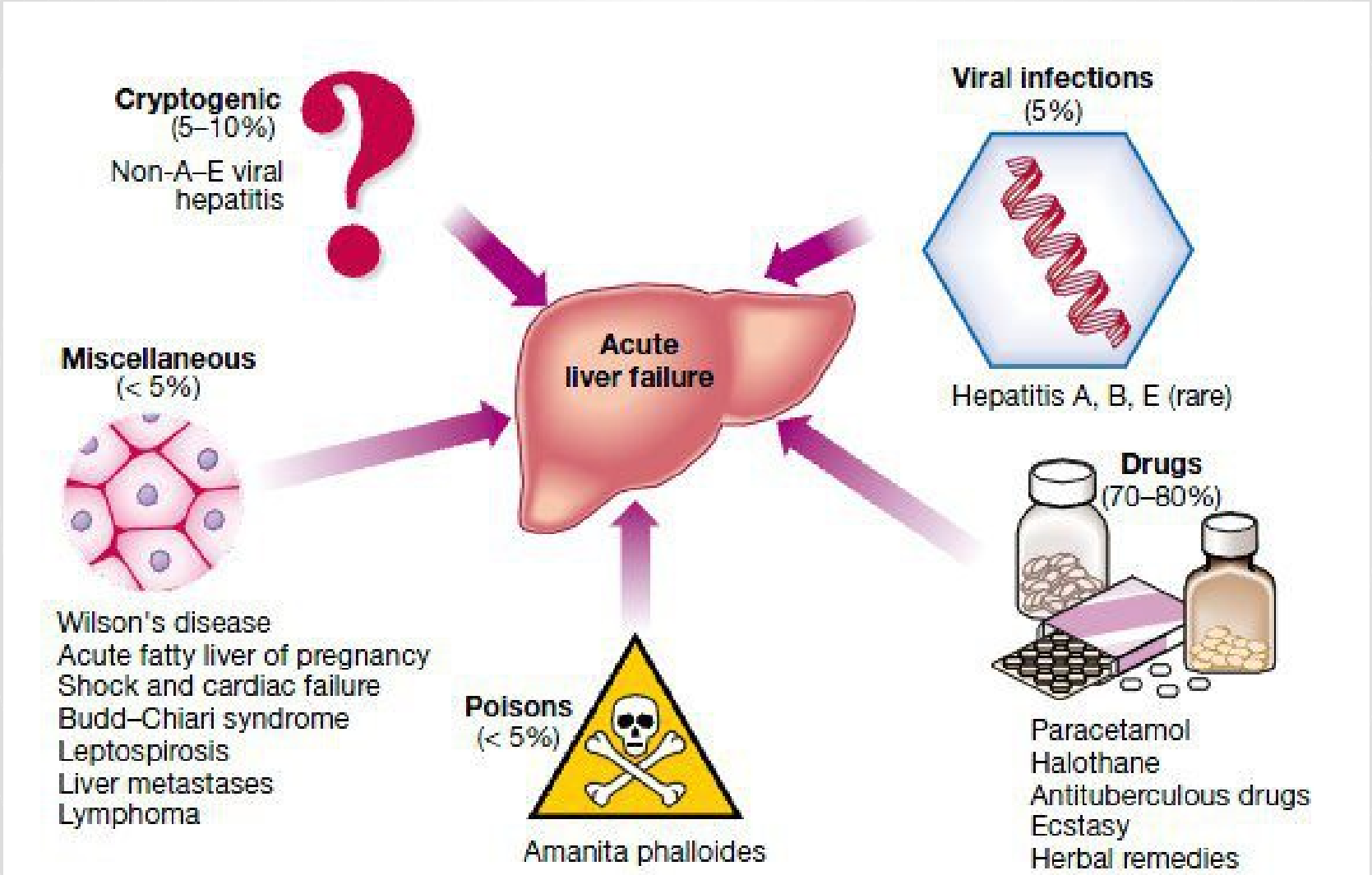
TIMING

Feature	Hyperacute	Acute	Subacute
Jaundice to encephalophaty	0-7	8-28	29-84
Cerebral oedema	Common	Common	Rare
Renal failure	Early	Late	Late
Ascites	Rare	Rare	Common
Coagulation disorder	Marked	Marked	Modest
Prognosis	Moderate	Poor	Poor

Schmidt, Hepatology- 2005

•Progress in Liver Diseases. Nex York: Grune & Stratton 1970, Patton,2012

Causes of ALF



Acquired Liver Injury in the Intensive Care Unit

Thomas Lescot, M.D., Ph.D.,* Constantine Karvellas, M.D., F.R.C.P.C.,†
Marc Beaussier, M.D., Ph.D.,‡ Sheldon Magder, M.D., F.R.C.P.C.§

 Anesthesiology 2012; 117:898–904

Causes of Liver Injury in the ICU

-Hypoxic hepatitis

-Sepsis

-Drugs

-Parenteral Nutrition

Hypoxic Hepatitis

Hypoxic hepatitis (*i.e.*, ischemic hepatitis, hypoxic hepatopathy, shock liver, or hypoxic liver injury) can be defined as liver injury as a consequence of a cardiovascular insult followed by a sudden transient elevation of aminotransferases greater than 10-fold above baseline with no other identified cause of liver damage. Hypoxic hepatitis often is characterized by the triad of acute elevation in serum aminotransferases, rapid elevation in INR, and altered renal function. Hypoxic hepatitis results from inadequate oxygen delivery to the liver. This can be caused by inadequate oxygen in blood (hypoxemic hypoxia), inadequate blood flow (ischemic hypoxia), or lack of carrying capacity (anemic hypoxia)

Sepsis

- **Hypoxic Hepatitis** → impairment of hepatic perfusion

↓

hepatocellular injury

- **Sepsis associated cholestasis** → increased intenstinal permeability (loss of tight gap junction) → endotoxin traslocation from intestinal lumen into portal circulation → pro inflammatory cytokines

↓

uptake bile acids, intracellular architecture, transporter systems, cellular junctions, reduce secretion of bile

Drugs

Two primary mechanisms are responsible for drug-induced hepatotoxicity: direct drug toxicity (dose-dependent) and idiosyncratic drug reactions. Direct or indirect drug toxicity is dose dependent and reproducible, whereas idiosyncratic reactions, caused by hypersensitivity reactions from allergic or toxic factors, are dose independent, unpredictable, and not reproducible.

Table 1. Medications Frequently Prescribed in the Intensive Care Unit that Potentially May Cause Liver Injury*

Drugs	Pattern	Mechanism
Antiinfectious agents		
Ketoconazole	Hepatocellular	Idiosyncratic reaction
Tetracyclines	Hepatocellular	Microvesicular steatosis
Isoniazid	Hepatocellular	Idiosyncratic reaction (CYP3A4?)
Rifampicin	Hepatocellular	Idiosyncratic reaction (CYP3A4?)
Amoxicillin or clavulanate	Cholestasis	Toxic-allergic reaction
Macrolides (*e.g.* erythromycin)	Cholestasis	—
Trimethoprim-sulfamethoxazole	Mixed	Idiosyncratic reaction, role of CYP450?
Nitrofurantoin	Mixed	Idiosyncratic reaction
Clindamycin	Mixed	Idiosyncratic reaction
Antiepileptics		
Phenytoin	Mixed	Idiosyncratic reaction
Valproic acid	Hepatocellular	Anticonvulsant hypersensitivity syndrome
Carbamazepine	Mixed	Idiosyncratic
Phenobarbital	Mixed	Anticonvulsant hypersensitivity syndrome
Acetaminophen		
Acetaminophen	Hepatocellular	Direct toxicity
Others		
Amiodarone	Hepatocellular	Alcoholic hepatitis-like reactions
Statins	Hepatocellular	Unknown
Propofol	Hepatocellular	

* Adapted from Lat *et al.*,[20] Navarro and Senior,[21] and Mindikoglu *et al.*[24]

CYP3A4 = cytochrome P450 3A4; CYP450 = cytochrome P450.

Although incompletely identified, the etiology of PN-induced hepatotoxicity may be related to hepatic bile acid transporter alterations, modifications of gene expression involved in apoptotic pathways, and/or alterations in detoxification processes.[25]

(Grau et al study, 3000 pt)

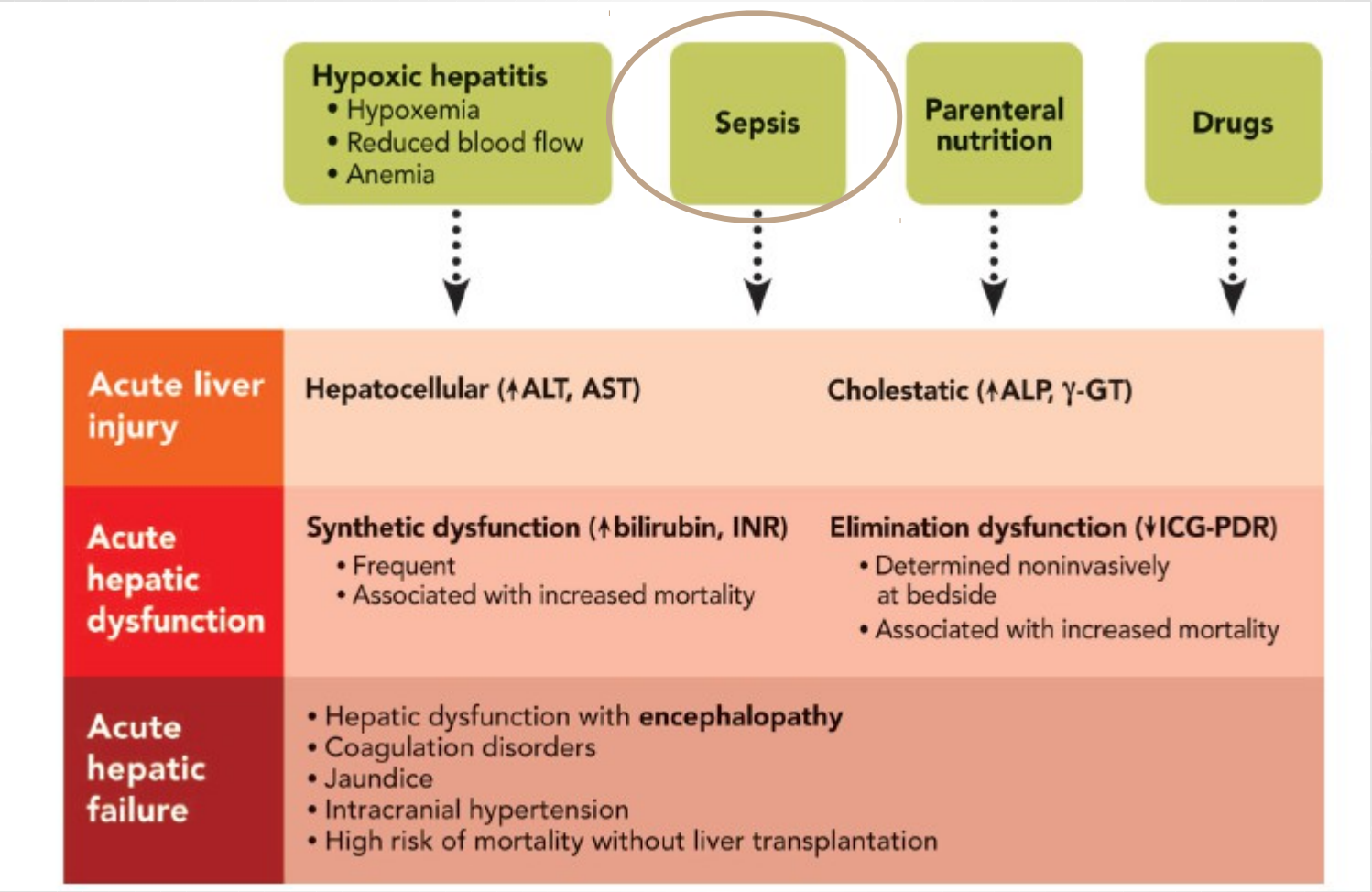


Fig. 1. Causes of liver insults, definitions, and key points of intensive care unit (ICU) acquired acute liver injury, hepatic dysfunction, and acute liver failure. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; γ-GT = γ-glutamyl transpeptidase; ICG-PDR = indocyanine green plasma disappearance rate; INR = international normalized ratio.

Table 1 – Sepsis, SIRS, and MODS: Defining the terms[12]

Term	Definition
Systemic inflammatory response syndrome (SIRS)	Response is manifested by 2 or more of the following conditions: • Temperature > 38°C (100.4°F) or < 36°C (96.8°F) • Heart rate > 90 beats per minute • Respiration rate > 20 breaths per minute or $Paco_2$ < 32 mm Hg • White blood cell count > 12,000/μL, < 4000/μL, or > 10% immature (band) forms
Sepsis	Systemic response to an infection defined by 2 or more SIRS criteria as a result of an infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities
Multiple organ dysfunction syndrome (MODS)	Presence of altered organ dysfunction in an acutely ill patient

Key Points

1. Acute liver failure is a paradigm for multiple system organ failure that develops as a consequence of sepsis.

MOF

Table 4 Similarity between sepsis and liver failure

	SIRS sepsis septic shock	Liver failure
Precipitant	± Infection	± Infection
Neurologic	Encephalopathy	Encephalopathy
	Critical illness neuropathy/myopathy	Critical illness neuropathy/myopathy
	Severity α acuity	Severity α acuity
	Reversible	Reversible
Hemodynamics	Vasodilated; hyperdynamic	Vasodilated; hyperdynamic
Pulmonary	Lung injury/acute respiratory distress syndrome	Lung injury/acute respiratory distress syndrome
Renal	Acute kidney injury (acute tubular necrosis)	Acute kidney injury (hepatorenal syndrome ± acute tubular necrosis)
Liver	Subclinical dysfunction common	Dysfunction amplified by infection
Infection	Identified in a third of patients	Suspected but identified organism and site in around a third
Nutrition	Catabolic; immune therapy	Branched-chain amino acid-enriched formulae

…infection is the most common cause of mortality

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- **Miste**

Hepatol Int (2009) 3:269–282
DOI 10.1007/s12072-008-9106-x

Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL)

Shiv Kumar Sarin · Ashish Kumar · John A. Almeida · Yogesh Kumar Chawla · Sheung Tat Fan · Hitendra Garg · H. Janaka de Silva · Saeed Sadiq Hamid · Rajiv Jalan · Piyawat Komolmit ·

AASLD POSITION PAPER

AASLD Position Paper: The Management of Acute Liver Failure

Julie Polson and William M. Lee

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Management of critically-ill cirrhotic patients

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Definizione **APASL**:

"Insulto epatico acuto che si manifesta con ittero e coagulopatia, complicato entro 4 settimane da ascite e/o encefalopatia in un paziente con malattia epatica cronica **nota o non nota".*

*Insulto epatico acuto:

a) Causa infettiva: - virus epatotropi/non epatotropi;
- riattivazioni virali ;
- altri agenti infettivi sul fegato .

b) Causa non infettiva: - alcol;
- farmaci/erbe;
- flare autoimmune/Wilson;
- chirurgia ;
- *rottura di varici*

c) Causa tossica non nota

** Malattia epatica cronica: - cirrosi compensata;
- epatite cronica;
- NASH (non alcoholic steatohepatitis);
- epatopatia colestatica;
- epatopatia metabolica.

Definizione **AASLD/EASL**:

*"Peggioramento acuto di una malattia epatica cronica preesistente**, di solito correlato ad un evento precipitante* ed associato ad un aumento della mortalità a 3 mesi a causa di insufficienza multiorgano".*

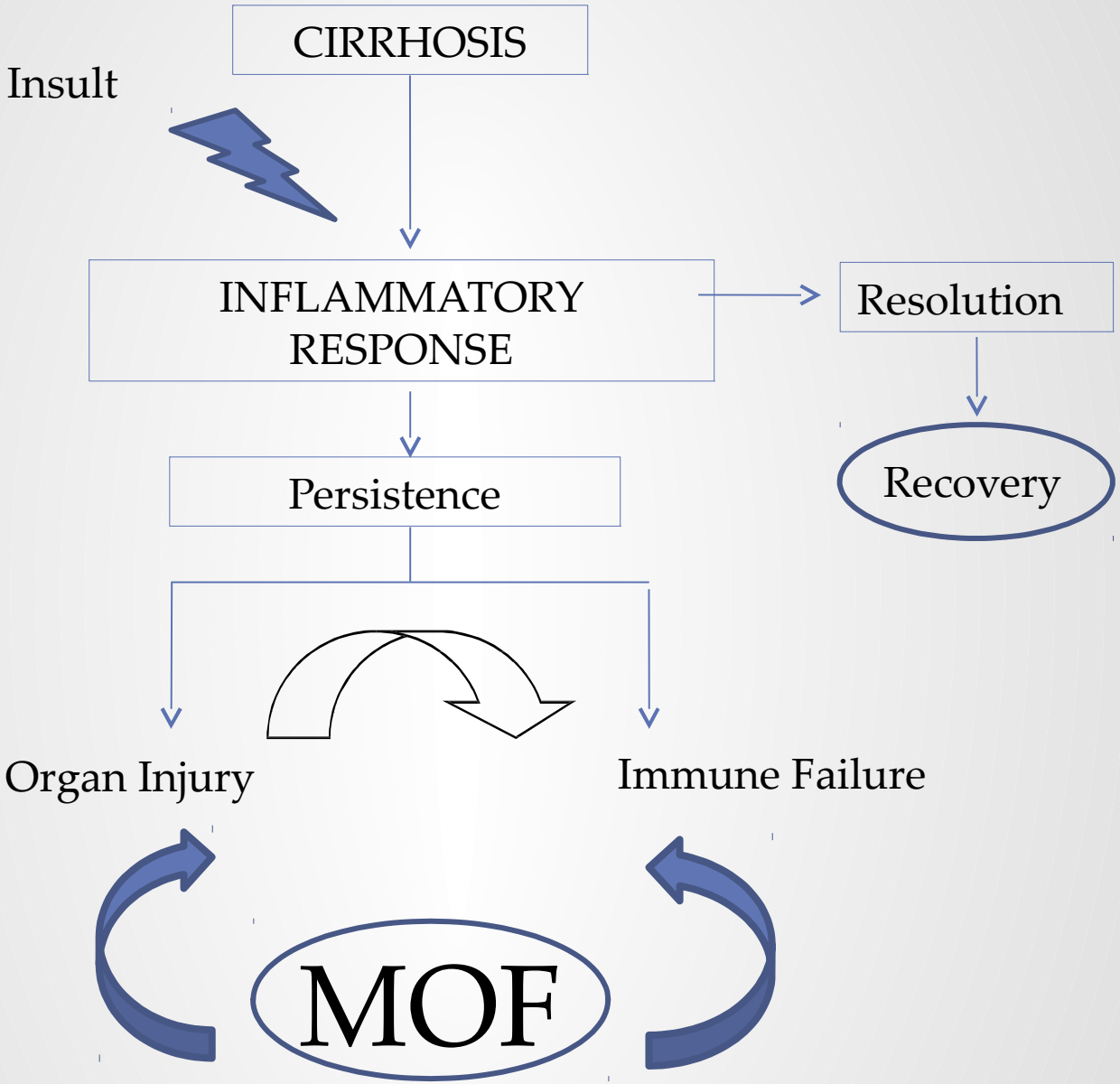
*Insulto epatico acuto:

a) Causa infettiva: - virus epatotropi/non epatotropi;
- riattivazioni virali ;
- altri agenti infettivi sul fegato .

b) Causa non infettiva: - alcol;
- farmaci/erbe;
- flare autoimmune/Wilson;
- chirurgia ;
- *rottura di varici*

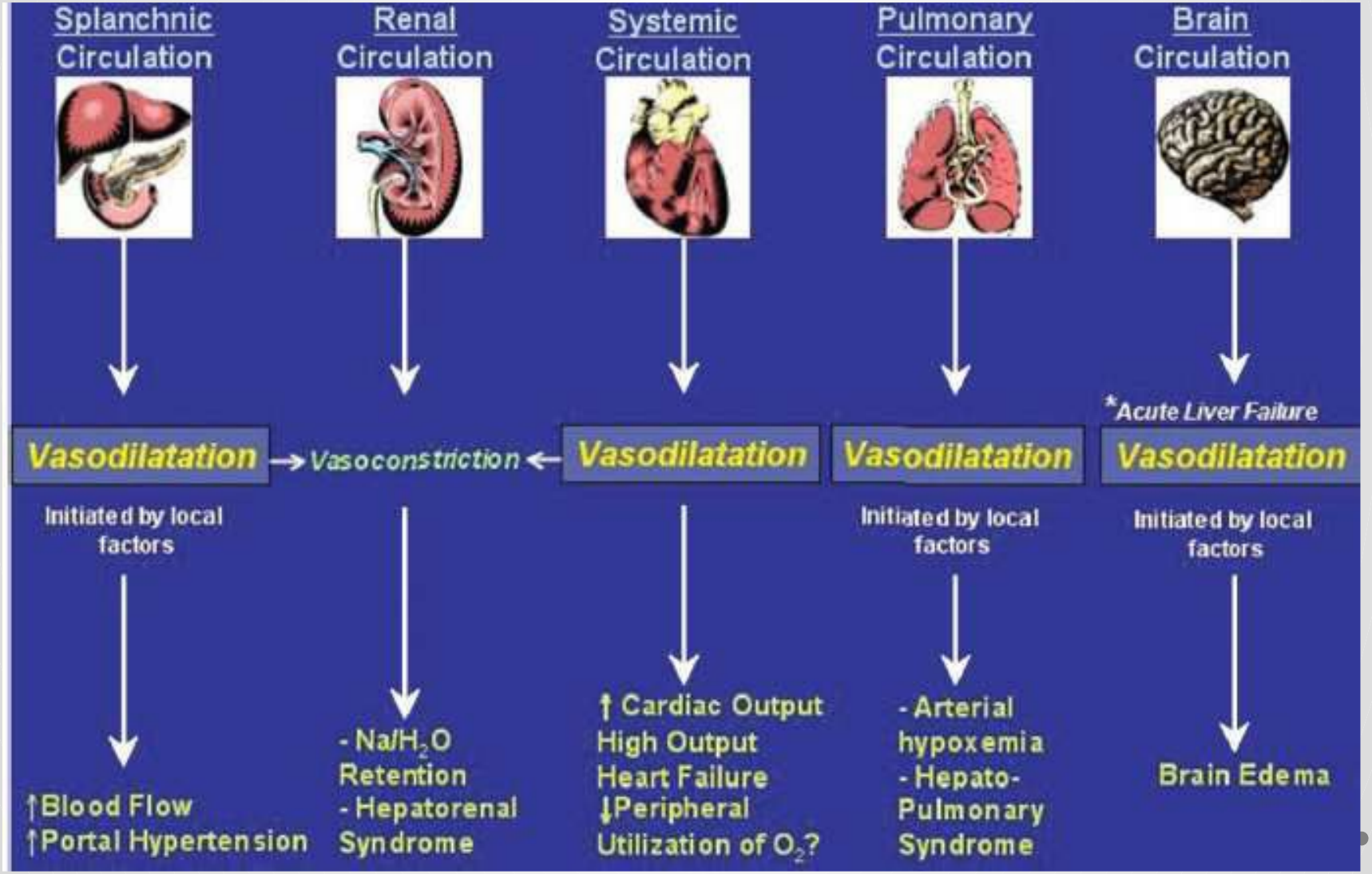
c) Causa tossica non nota

** Malattia epatica cronica: - cirrosi (qualsiasi stadio)



Malik J. Hepatol.2009;51:426-429

ACLF: worsening of Multiorgan circulatory disfunction in cirrhosis



ALF/ACLF: elementi comuni

- **vie fisiopatologiche** (SIRS/SEPSI come evento primario o secondario).
  SIRS first described in ALF
- esito in disfunzione multiorgano **(MOF)**
- necessità di approccio **SISTEMATICO MULTIORGANO** dal punto di vista diagnostico (diagnosi dell'insulto acuto e delle disfunzioni multiorgano) e terapeutico
- frequente necessità di **monitoraggio e terapia intensiva**
- opportunità di considerare (o controindicare) precocemente il **TRAPIANTO DI FEGATO** come parte integrante della terapia
- **prognosi legata alla MOF**, assenza tuttora di scores prognostici soddisfacenti in ottica epatologica

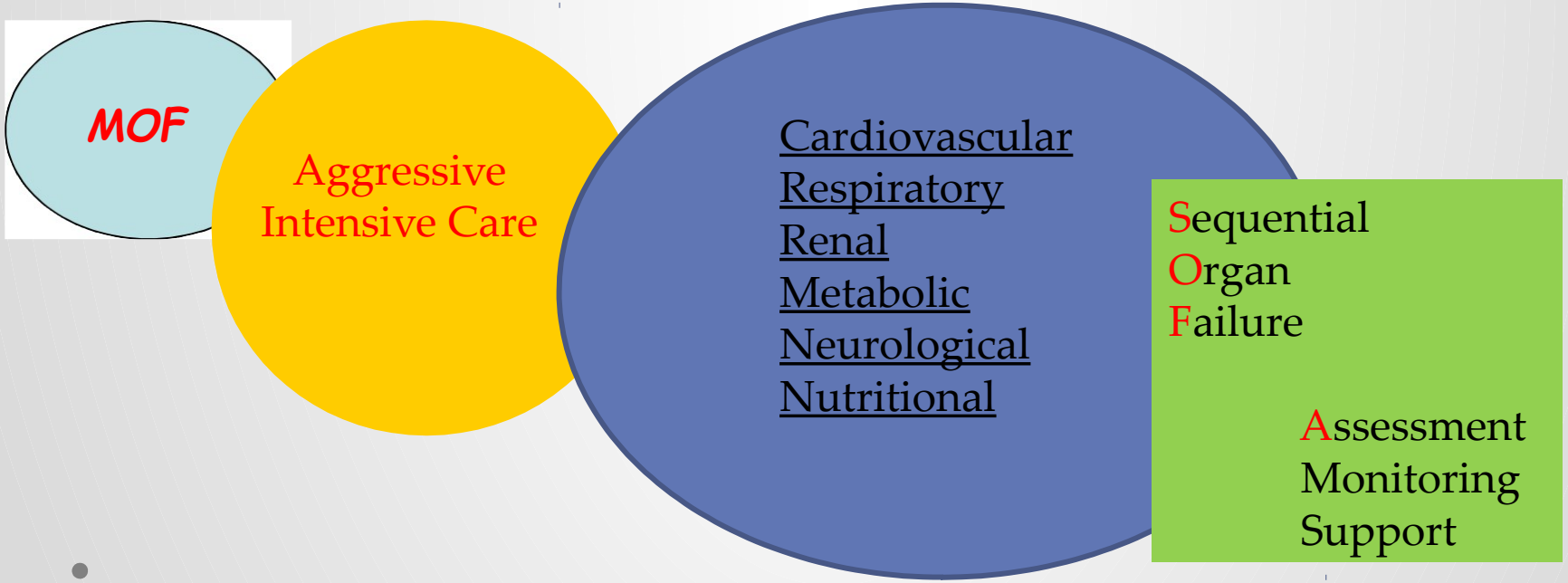
Nel caso dell'ACLF, l'esito in MOF rappresenta ***l'esasperazione della disfunzione macro e microcircolatoria multiorgano che caratterizza la cirrosi***

LIVER TRANSPLANTATION 14:S85-S89, 2008

AASLD/ILTS SYLLABUS

Application of Intensive Care Medicine Principles in the Management of the Acute Liver Failure Patient

David J. Kramer, Juan M. Canabal, and Lisa C. Arasi
Transplant Critical Care Service, Department of Transplantation, Mayo Clinic, Jacksonville, FL



Prognostic criteria of ALF in ICU

SAPS: Simplified Acute Phisiology Score

Table 1-9 Simplified Acute Physiology Score (SAPS II) and Expanded Version

SAPS II	0 points	Abnormal value points				
Age, years	<40	40-59 *7 points*	60-69 *12 points*	70-74 *15 points*	75-79 *16 points*	≥ 80 *18 points*
Heart rate, beats/min	70-119	40-69 *2 points*	120-159 *4 points*	≥ 160 *7 points*	< 40 *11 points*	
Systolic Blood Pressure, mmHg	100-199	>200 *2 points*	70 -99 *5 points*	≤ 70 *13 points*		
Body Temperature, °C	<39	≥ 39 *3 points*				
Only if on Mechanical Ventilation* Pao_2 mmHg/ Fio_2		≥ 200 *6 points*	100-199 *9 points*	<100 *11 points*		
Urinary Output, L/day	≥ 1	0.5-0.9 *4 points*	< 05 *11 points*			
Blood Urea Nitrogen, mg/dL	<28	28-83 *6 points*	≥ 84 *10 points*			
White Blood Cell Count, mm^3	1-19.9	≥ 20 *3 points*	< 1.0 *12 points*			
Potassium, mEq/L	3-4.9	< 3 or ≥ 5 *3 points*				
Sodium, mEq/L	125-144	≥145 *1 point*	< 125 *5 points*			
Bicarbonate, mEq/L	≥20	15-19 *3 points*	< 15 *6 points*			
Bilirubin, mg/dl	<4	4-5.9 *4 points*	≥ 6 *9 points*			
Glasgow Coma Score	14-15	11-13 *5 points*	9 - 10 *7 points*	6 - 8 *13 points*	<6 *26 points*	

SAPS II	0 points	Abnormal value points	
Chronic Disease		Metastatic cancer *9 points* Hematological malignancy *10 points* AIDS *17 points*	**SAPS II SCORE: add worst value for last 24 hours**
Type of Admission	Scheduled surgical	Medical *6 points* Unscheduled surgical *8 points*	

APACHE: Acute Phisiology and Chronic Health Evaluation SCORE

	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE- rectal(°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
MEAN ARTERIAL PRESSURE-mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
HEART RATE (ventricular response)	≥ 180	140-179	110-139		70-109		50-69	40-54	≤ 39
RESPIRATORY RATE-(non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. FiO_2 ≥ 0.5 record A-aDO_2	≥ 500	350-499	200-349		<200				
b. FiO_2 ≥ 0.5 record only PaO_2					OPO_2>70	$OPO_2$60-70		$OPO_2$55-60	OPO_2<55
ARTERIAL pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	≤ 7.15
SERUM SODIUM (mMOL/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	11-119	<7.15
SERUM POTASSIUM (mMOL/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	36-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-14		<0.6		
HEMATOCRIT (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/mm^3) (in 1,000,)	≥ 40		50-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score=15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS):Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) [Not preferred, use if no ABG.]	≥52	41-51.9		32-40.9	22-32.9		18-21.9	15-17.9	<15

SOFA: sepsis-related organ failure

SOFA score	0	1	2	3	4
Respirationa PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine </=5 or dobutamine (any)	Dopamine >5 or norepinephrine </=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

Combination ICU mortality calculator

Table 1-9 Simplified Acute Physiology Score (SAPS II) and Expanded Version

SAPS II	0 points	Abnormal value points				
Age, years	<40	40–59 *7 points*	60–69 *12 points*	70–74 *15 points*	75–79 *16 points*	≥ 80 *18 points*
Heart rate, beats/min	70–119	40–69 *2 points*	120–159 *4 points*	≥ 160 *7 points*	< 40 *11 points*	
Systolic Blood Pressure, mmHg	100–199	>200 *2 points*	70 -99 *5 points*	≤ 70 *13 points*		
Body Temperature, °C	<39	≥ 39 *3 points*				
Only if on Mechanical Ventilation* Pao_2 mmHg/ FIO_2		≥ 200 *6 points*	100–199 *9 points*	<100 *11 points*		
Urinary Output, L/day	≥ 1	0.5–0.9 *4 points*	< 05 *11 points*			
Blood Urea Nitrogen, mg/dL	<28	28–83 *6 points*	≥ 84 *10 points*			
White Blood Cell Count, mm^3	1–19.9	≥ 20 *3 points*	< 1.0 *12 points*			
Potassium, mEq/L	3–4.9	< 3 or ≥ 5 *3 points*				
Sodium, mEq/L	125–144	≥145 *1 point*	< 125 *5 points*			
Bicarbonate, mEq/L	≥20	15–19 *3 points*	< 15 *6 points*			
Bilirubin, mg/dl	<4	4–5.9 *4 points*	≥ 6 *9 points*			
Glasgow Coma Score	14–15	11–13 *5 points*	9 – 10 *7 points*	6 – 8 *13 points*	<6 *26 points*	

SAPS II	0 points	Abnormal value points	
Chronic Disease		Metastatic cancer *9 points* Hematological malignancy *10 points* AIDS *17 points*	**SAPS II SCORE: add worst value for last 24 hours**
Type of Admission	Scheduled surgical	Medical *6 points* Unscheduled surgical *8 points*	

	HIGH ABNORMAL RANGE				LOW ABNORMAL RANGE				
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE- rectal(°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
MEAN ARTERIAL PRESSURE-mm Hg	≥ 160	130-159	110-129		70-109		50-69		≤ 49
HEART RATE (ventricular response)	≥ 180	140-179	110-139		70-109		50-69	40-54	≤ 39
RESPIRATORY RATE-(non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. FiO_2 ≥ 0.5 record A-aDO_2	≥ 500	350-499	200-349		<200				
b. FiO_2 ≥ 0.5 record only PaO_2					OPO_2>70	$OPO_2$60-70		$OPO_2$55-60	OPO_2<55
ARTERIAL pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	≤ 7.15
SERUM SODIUM (mMOL/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	11-119	<7.15
SERUM POTASSIUM (mMOL/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	36-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-14		<0.6		
HEMATOCRIT (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/mm^3) (in 1,000,)	≥ 40		50-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score=15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS):Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) [Not preferred, use if no ABG.]	≥52	41-51.9		32-40.9	22-32.9		18-21.9	15-17.9	<15

SOFA score	0	1	2	3	4
Respirationa PaO_2/FIO_2 (mm Hg) SaO_2/FIO_2	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
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Cardiovascular[b] Hypotension	No hypotension	MAP <70	Dopamine </=5 or dobutamine (any)	Dopamine >5 or norepinephrine </=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

King's College criteria for liver transplantation in ALF

ACETAMINOPHEN-INDUCED ALF

Arterial pH <7.3 (regardless of HE)

OR all 3 of the following

- INR >6.5
- Creatinine >300 μmol/l
- HE grade 3–4

NON-ACETAMINOPHEN-INDUCED ALF

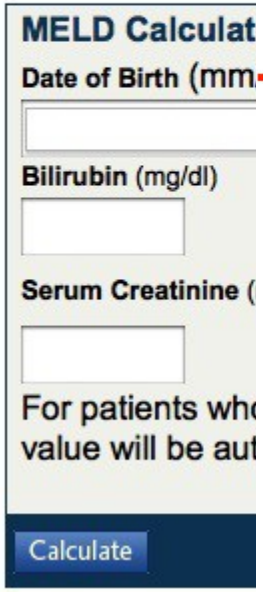
INR >6.5 (regardless of HE)

OR 3 of 5 of the following (regardless of HE)

- Age <10 or >40 years
- Etiology: indeterminate, drug-induced
- Time interval icterus to encephalopathy > 7 days
- INR >3.5
- Bilirubin >300 μmol/l

Prognostic criteria of ACLF in ICU

MELD



Child Pugh

Child-Turcotte-Pugh Classification

	1 point	2 points	3 points
Encephalopathy	0	1-2	3-4
Ascites	none	slight	moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT prolonged (s)	1-4	5-6	>6
(INR)	<1.7	1.8-2.3	>2.3

Child's A = 5-6 points Child's B = 7-9 points Child's C = 10-15 points

ALT BILIRUBINA INR

ENCEFALOPATIA EPATICA

- Relazione ittero/inizio encefalopatia (timing)

NON PERDERE TEMPO!!!!!

CONTATTARE CENTRO TRAPIANTO

Nel frattempo….

- ❖ Orientamento diagnostico e prognostico
- ❖ Profilassi atb empirica ad ampio spettro dopo invio screening es colturali
- ❖ Lattulosio
- ❖ Monitoraggio neurologico

Iter diagnostico dell'ALF in ICU

- Esclusione di **epatopatia preeesistente**:
  presupposto per la definizione di ALF ed inserimento in LAT
- Eventuale necessità di più metodiche strumentali e/o istologia
- Indagini eziologiche: per valutare terapia specifiche ove possibili per escludere controindicazioni a OLT (mediche o psicosociali)
- Assetto delle fx vitali multiorgano con attenzione alle principali cause di morte nell'ALF:
  - **Edema cerebrale** → aumento dell'ICP con possibilità di danni irreversibili da erniazione cerebrale o ischemia da ridotta PPC
  - **Sepsi** alla presentazione o durante il decorso

Table 2. Initial Laboratory Analysis

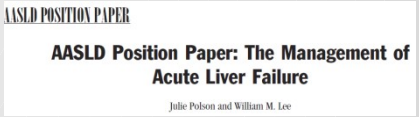
Prothrombin time/INR
Chemistries
sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate
glucose
AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin
creatinine, blood urea nitrogen
Arterial blood gas
Arterial lactate
Complete blood count
Blood type and screen
Acetaminophen level
Toxicology screen
Viral hepatitis serologies
anti-HAV IgM, HBSAg, anti-HBc IgM, anti-HEV§, anti-HCV*
Ceruloplasmin Level#
Pregnancy test (females)
Ammonia (arterial if possible)
Autoimmune markers
ANA, ASMA, Immunoglobulin levels
HIV status‡
Amylase and lipase

*Done to recognize potential underlying infection.

#Done only if Wilson disease is a consideration (*e.g.*, in patients less than 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.

‡Implications for potential liver transplantation.

§If clinically indicated.



MANAGEMENT

Table 4. Intensive Care of Acute Liver Failure

Cerebral Edema/Intracranial Hypertension

Grade I/II Encephalopathy

- Consider transfer to liver transplant facility and listing for transplantation
- Brain CT: rule out other causes of decreased mental status; little utility to identify cerebral edema
- Avoid stimulation, avoid sedation if possible
- Antibiotics: surveillance and treatment of infection required; prophylaxis possibly helpful
- Lactulose: possibly helpful

Grade III/IV Encephalopathy

- Continue management strategies listed above
- Intubate trachea (may require sedation)
- Elevate head of bed
- Consider placement of ICP monitoring device
- Immediate treatment of seizures required; prophylaxis
- Mannitol: use for severe elevation of ICP or first clinic
- Hyperventilation: effects short-lived; may use for impe

Infection

- Surveillance for and prompt antimicrobial treatment o
- Antibiotic prophylaxis possibly helpful but not proven

Coagulopathy

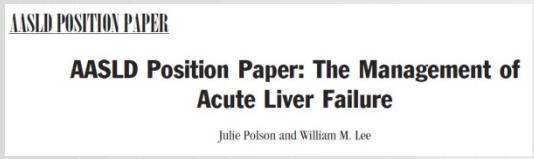
- Vitamin K: give at least one dose
- FFP: give only for invasive procedures or active bleeding
- Platelets: give for platelet counts $<10{,}000/mm^3$ or invasive procedures
- Recombinant activated factor VII: possibly effective for invasive procedures
- Prophylaxis for stress ulceration: give H2 blocker or PPI

Hemodynamics/Renal Failure

- Pulmonary artery catheterization
- Volume replacement
- Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure
- Avoid nephrotoxic agents
- Continuous modes of hemodialysis if needed
- NAC, prostacyclin: effectiveness unknown
- Vasopressin: not helpful in ALF; potentially harmful.

Metabolic Concerns

- Follow closely: glucose, potassium, magnesium, phosphate
- Consider nutrition: enteral feedings if possible or total parenteral nutrition



- ✓ *Acetaminophen hepatotoxicity:*

  N-acetylcysteine (NAC), (within 72 hours of ingestion)

  150 mg/Kg in 5% dextrose over 15'; 50 mg/Kg over 4 hours; 100 mg/Kg over 16 hours iv

- ✓ *Mushroom poisoning:* activated charcoal; Penicillin G 300000-1 mln U/Kg/die iv and NAC

- ✓ *HBV*: lamivudine, entecavir

- ✓ *Acute ischemic injury*: cardiovascular support

- ✓ *Autoimmune hepatitis*: methylprednisone 40-60 mg/die iv

- ✓ *Pregnancy-related disease* (HELLP): expeditious delivery

- ✓ *Budd-Chiari syndrome*: liver transplant

ALF: TRAPIANTO URGENTE

pz con ALF fulminante (aspettativa di vita <7 gg in assenza di Tx) così definita:

- ✓ Comparsa di encefalopatia di grado II in grave insuff epatica a meno di 8 settimane dall'esordio della malattia epatica
  o alcuni dei seguenti sintomi:
- ✓ flapping tremor (asterixis)
- ✓ bilirubinemia > 15 mg/dl
- ✓ PT > 20 sec o INR > 2,5
- ✓ ipoglicemia

Altre indicazioni:

- PNF (Primary non function) (< 7 gg dal precedente Tx)
- Trombosi dell'a. epatica (< 15 gg dal precedente Tx)
- Trauma acuto dell'organo
- Insufficienza acuto su morbo di Wilson

Il pz **NON** può essere inserito in lista in Status1 se esiste una delle seguenti condizioni:

- ❖ Positività per HIV (eccetto in protocolli sperimentali nazionali nei centri indicati)
- ❖ Età > 70 aa
- ❖ Decerebrazione

CONTROINDICAZIONI ASSOLUTE AL TX EPATICO IN URGENZA:

- Neoplasie extraepatiche in atto
- Infezione da HIV al di fuori del Programma Nazionale Trapianto di fegato in HIV per i Centri dedicati;
- Infezioni batteriche in atto
- Dipendenza o uso corrente di stupefacenti o abuso alcoolico attivo
- Malattie psichiatriche/neurologiche gravi

CONTROINDICAZIONI RELATIVE AL TX EPATICO IN URGENZA:

- Coesistenti malattie CV o polmonari avanzate (valutazione collegiale)
- Livelli di HBV-DNA > 11 X 10^5 copie/ml al momento del Tx
- Presenza di neoplasie maligne pregresse con risposta completa al trattamento e con follow-up < 5 anni (valutazione collegiale)

Caratteristiche cliniche ed eziologia: ALF study group 1147 casi (Lee 2011)

Table 1. Etiology and Clinical Characteristics of 1,147 Cases of ALF

Feature	Acetaminophen (n = 532)	Drugs (n = 133)	Indeterminate (n = 161)	Hepatitis A (n = 31)	Hepatitis B (n = 83)	All Others (n = 207)
Age (years)*	37 (28–45)	46 (33–56)	38 (26–50)	47 (40–57)	42 (29–54)	42 (29–56)
Female Sex	76%	67%	58%	45%	42%	76%
Jaundice to Coma (days)*	0 (0–1)	9 (3–20)	9 (2–20)	3 (1–8)	7 (2–14)	7 (1–17)
Coma grade ≥ 3	52%	38%	50%	55%	54%	41%
ALT (U/L)*	4067 (2138–6731)	600 (260–1537)	847 (396–2111)	2404 (1367–3333)	1707 (745–2815)	650 (172–1867)
Bilirubin (mg/dL)*	4.5 (2.9–6.6)	20.2 (12.1–28.3)	23.0 (9.2–29.7)	11.9 (9.7–27.5)	19.7 (12.4–25.6)	15.3 (6.3–26.7)
Spontaneous Survival	65%	29%	25%	58%	25%	34%
Transplantation	9%	41%	43%	29%	47%	33%
Death Without Transplantation	26%	31%	32%	13%	28%	33%

Summarized and updated (after the workshop) from the ALF Study Group database, 1998-2007.[3,4]

* Median values (Q_1-Q_3).

Prognosi del pz con ACLF e gestione in ICU (Gines, J Hepatol 2012)

Prima dell'evento acuto precipitante:

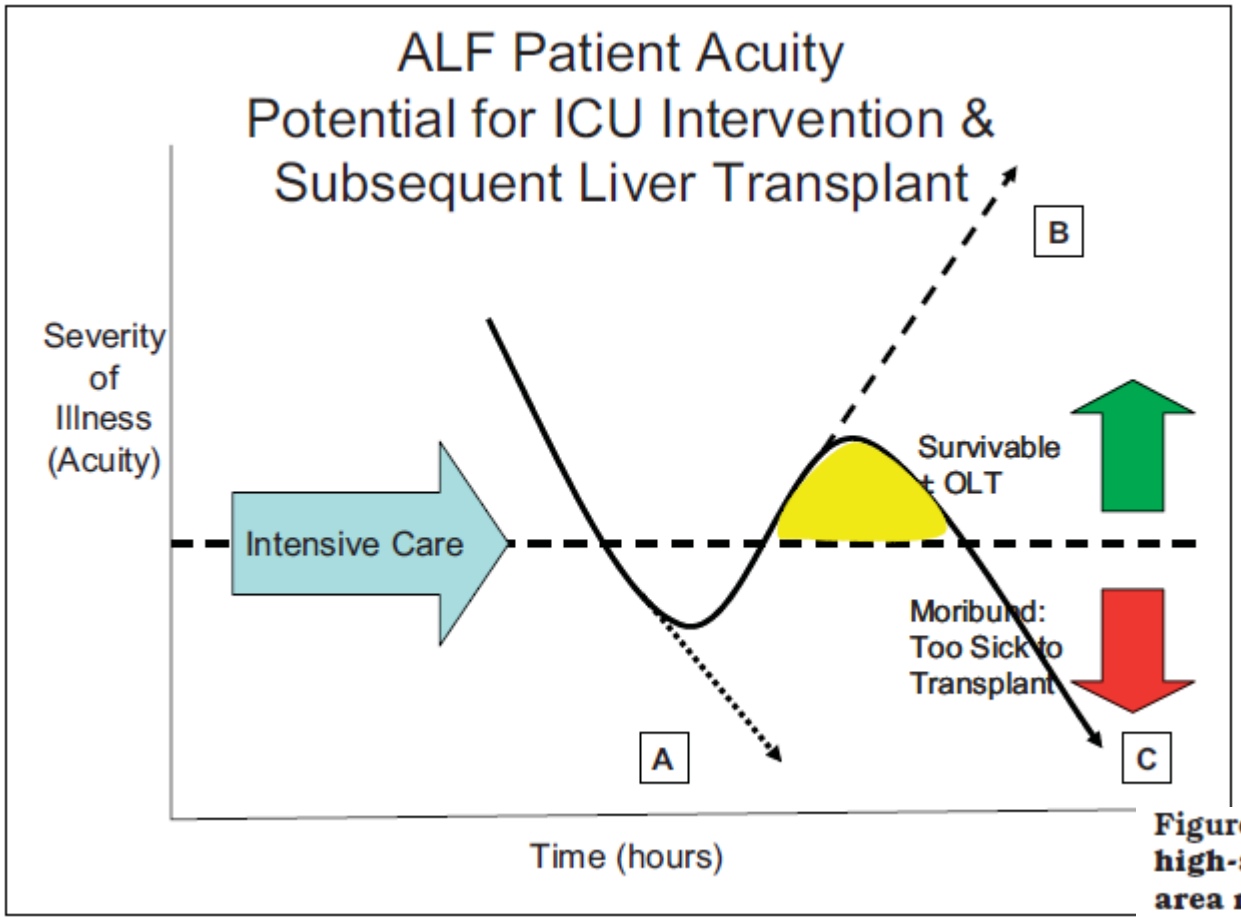
-Pazienti con MELD > 30 o con ≥3 organi non funzionanti senza possibilità di Tx di salvataggio potrebbero non essere considerati per la ICU

-Pz con MELD < 15 certamente considerati per la ICU

-Pz con MELD intermedio con anche ≥3 organi non funzionanti vanno gestiti in ICU

Proposta: valutazione basale della prognosi e dopo 3 gg di trattamento intensivo (3-day trial) per valutare recupero o progressione dell'insufficienza d'organo
→ Identificare la causa del peggioramento acuto ed eventualmente attuare tp specifica, valutare grado di disfunzione epatica/MOF all'ingresso

OLT rimane al momento tp di scelta sebbene il timing rimanga ancora dipendente da molti fattori, tra cui l'esperienza locale



Concludendo….

Figure 2. Impact of ICU intervention in high-acuity acute liver failure. The yellow area represents a time-limited window of opportunity for the high-acuity patient with ALF to undergo successful liver transplantation. Boxes A, B, and C refer to the following possible outcomes for such patients: (A) patient death with insufficient ICU intervention, (B) survival after ICU intervention ± liver transplantation, and (C) patient death despite ICU intervention (transplantation precluded by social or medical factors, donor not identified in time, or failed transplant attempt). Abbreviations: ALF, acute liver failure; ICU, intensive care unit; OLT, orthotopic liver transplantation.

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AASLD/ILTS SYLLABUS

Application of Intensive Care Medicine Principles in the Management of the Acute Liver Failure Patient

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Transplant Critical Care Service, Department of Transplantation, Mayo Clinic, Jacksonville, FL

“…il fegato ha più di 500 funzioni,
ma non è della Apple
quindi non gliene frega niente a nessuno!!!!”

“Cit.”

Grazie!