PERCORSI DIAGNOSTICO-TERAPEUTICI
NEL PAZIENTE CON EPATOPATIA

Chianciano Terme
26-28 gennaio 2012

INSUFFICIENZA EPATICA ACUTA

Maria Torrani
INSUFFICIENZA EPATICA ACUTA:

ACUTE LIVER FAILURE (ALF)

ACUTE ON CHRONIC LIVER FAILURE (ACLF)
The sudden loss of hepatic function in a person without preexisting liver disease defines ALF.\textsuperscript{1,2} The most reliable signs of severe acute liver injury are the presence of coagulopathy (international normalized ratio [INR] $\geq 1.5$) and any degree of hepatic encephalopathy, the length of illness being considered anything $\leq 24$ weeks.
**ALF Prognostic definition**

- **HAV and HEV-related ALF** good prognosis compared with HBV-ALF
- **ALF of unknown origin**: poor prognosis

- **HE**: patients admitted with coma have an especially poor prognosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperacute</th>
<th>Acute</th>
<th>Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jaundice to encephalopathy</strong></td>
<td>0-7</td>
<td>8-28</td>
<td>29-84</td>
</tr>
<tr>
<td>Cerebral oedema</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Early</td>
<td>Late</td>
<td>Late</td>
</tr>
<tr>
<td>Ascites</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td>Marked</td>
<td>Marked</td>
<td>Modest</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Moderate</td>
<td>Poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>

O’Grady, Gastroenterology, 1989
Bernal, Lancet 2002
Baquerizo, Transplantation 2003
Dabos, Transplantation 2004
Schmidt, Hepatology 2005
Figure 1. Etiology of fulminant hepatitis in transplanted patients in Europe (1972-2007).
Acute deterioration in liver function

(manifesting as jaundice and coagulopathy)

over a period of 2 - 4 weeks

in a patient with pre-existing chronic liver disease

usually associated with a precipitating event

leading to severe deterioration in clinical status
CIRRHOSIS

Insult

INFLAMMATORY RESPONSE

Persistence

Resolution

Organ Injury

Immune Failure

MOF

Recovery

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

ACLF
**ACLF prognosis**

- ACLF leads to a **short-term mortality of 50-90%**
- In patients with ACLF who overcome the acute decompensation, the **difference in survival tends to attenuate to the same level of chronic decompensated cirrhosis**

*Katoonizadeh A; Gut 2010*
ALF/ACLF

ELEMENTI COMUNI:

• **vie fisiopatologiche** (SIRS/CARS/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 microcirculatoria multiorgano che caratterizza la cirrosi**
ACLF : worsening of Multiorgan circulatory disfunction in cirrhosis
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
Principles of Liver Intensive Care

1. Identification and removal of cause of hepatic injury

2. Optimization of conditions for hepatic regeneration

3. Anticipation and prevention of complications

4. To improve the function of the individual end-organs

5. Early identification and transplantation of “non-survivors”

Volk ML; Liver Transplantation 2007; 13: 1515
Sarin SK; Hepatol Int 2009; 3:269
Abeles D; Hepatology 2009; 50: 565
ALF iter diagnostico

- esclusione di epatopatia cronica preesistente:
  presupposto per la definizione di ALF e l'inserimento in LAT con codice “0”
  eventuale necessità di più metodiche strumentali e/o istologia
- indagini eziologiche: per valutare terapie specifiche ove possibile per escludere controindicazioni a OLT mediche o psicosociali
- Assetto delle funzioni vitali multi organo con attenzione mirata alle principali cause di morte nell’ALF:
  - edema cerebrale → aumento pressione intracranica (ICP) con possibilità di danni irreversibili da erniazione cerebrale o ischemia da ridotta pressione di perfusione
  - sepsi alla presentazione o nel decorso
ALF: HE grade and survival after OLT

KCH 1996
Clichy 1995

ALF

- ALT
- BILIRUBINA
- INR
- ENCEFALOPATIA EPATICA

- relazione ittero / inizio di Encefalopatia!

1° NON PERDERE TEMPO !!!

CONTATTARE CENTRO TRAPIANTO

Nel frattempo:
- orientamento diagnostico e prognostico
- profilassi antibiotica empirica ad ampio spettro
  dopo invio screening es colturali
- lactulosio
- monitoraggio neurologico
- no correzione coagulopatia!!
<table>
<thead>
<tr>
<th><strong>Investigations</strong></th>
<th><strong>clinical biolog histol e radiol</strong></th>
<th><strong>Etiology</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Virological test</strong></td>
<td>Anti-HAV IgM*</td>
<td>HAV</td>
</tr>
<tr>
<td></td>
<td>Anti-HBeAg IgM.* hepatitis B surface antigen.+</td>
<td>HBV</td>
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<tr>
<td></td>
<td>Anti-HBcAg IgM.+ HBV DNA.+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-HV IgM.† HEV RNA†</td>
<td>HEV</td>
</tr>
<tr>
<td></td>
<td>Anti-VZV IgM.† VZV DNA†</td>
<td>VZV</td>
</tr>
<tr>
<td></td>
<td>Anti-HSV IgM.† viral blood cultures,† HSV parovirus B19 DNA†</td>
<td>HSV</td>
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<tr>
<td><strong>Serological tests</strong></td>
<td>HIV serological*</td>
<td>Immunodepression status</td>
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<tr>
<td></td>
<td>Microagglutination test (if suspicion only)†</td>
<td>Leptospirosis</td>
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<td></td>
<td>IgM, IgC antibodies to dengue (if suspicion only)†</td>
<td>Dengue</td>
</tr>
<tr>
<td><strong>Biochemical/immunological tests</strong></td>
<td>Cupremia,† cupruria, ceruloplasmin†</td>
<td>Autoimmune liver disease</td>
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<tr>
<td></td>
<td>Anti-nuclear antibody,† anti-smooth muscle,†</td>
<td>Toxic origin-related fulminant hepatitis</td>
</tr>
<tr>
<td></td>
<td>anti-liver/kidney microsome antibody,† IgG‡</td>
<td></td>
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<tr>
<td><strong>Toxicological screening</strong></td>
<td>Benzodiazepines,* tricyclic antidepressants,*</td>
<td></td>
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<tr>
<td></td>
<td>ecstasy,† amphetamine,* paracetamol,*</td>
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<td></td>
<td>nonsteroidal anti-inflammatory drugs,</td>
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<tr>
<td></td>
<td>aminosalicylates,* carbamazepine</td>
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<tr>
<td><strong>Cardiac/pulmonary exploration</strong></td>
<td>ECG (arrhythmia),* arterial pressure monitoring,* Doppler echocardiography (cardiac output),† pulmonary arterial catheter (if suspicion only),† SaO₂,* pulmonary radiography*</td>
<td>Acute liver ischemia§</td>
</tr>
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<tr>
<td><strong>Medical imaging</strong></td>
<td>Liver ultrasound,* computed tomography†</td>
<td>Chronic liver disease</td>
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<tr>
<td><strong>Hematologic testing</strong></td>
<td>Complete blood count*</td>
<td>Viral infection</td>
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<tr>
<td><strong>Histological examination</strong></td>
<td>Transjugular liver biopsy+/− immunohistochemical staining†</td>
<td>Neoplastic infiltration of the liver (liver metastasis, acute lymphoblastic leukemia, lymphoma)</td>
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<td>Massive invasion of tumor cells in the liver parenchyma (leukemia, metastatic tumors, or primary hepatic lymphomas)</td>
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<td>Presence of underlying liver disease</td>
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<td></td>
<td>Purple nuclear inclusions with a clear halo in hepatocytes and presence of multinucleated hepatocytes</td>
<td></td>
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</tbody>
</table>
Cause-specific interventions

- **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 1 g/Kg/die iv and NAC

- **HVB:** lamivudine, entecavir

- **HSV, HZV:** acyclovir 30 mg/Kg/die iv

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

- **Pregnancy-related disease:** expeditious delivery

*(m di Wilson s. di Budd Chiari)*

Polson, Hepatology 2005
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

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

2. In the United States, systemic inflammatory response, sepsis, and septic shock are common reasons for intensive care unit admission. Intensive care management of these patients serves as a template for the management of patients with acute liver failure.

3. Acute liver failure is attended by high mortality. Although intensive care results in improved survival, the key treatment is liver transplantation. Intensive care unit intervention may open a “window of opportunity” and enable successful liver transplantation in patients who are too ill at presentation.

4. Intracranial hypertension complicates the course for many patients with acute liver failure. Initially, intracranial hypertension results from hyperemia, which is cerebral edema that reduces cerebral blood flow and eventuates in herniation. The precepts of neurocritical care—monitoring cerebral perfusion pressure, cerebral blood flow, and cortical activity—with rapid response to hemodynamic abnormalities, maintenance of normoxia, euglycemia, control of seizures, therapeutic hypothermia, osmotic therapy, and judicious hyperventilation are key to reducing mortality attributable to neurologic failure.
**EPS Conventional therapy**

**Grade I/II HE**
- Brain CT: rule out other causes of decreased mental status
- Avoid stimulation and sedation
- Lactulose: possibly helpful
- Follow closely glucose, acid-base balance, Na⁺

**Grade III/IV HE**
- Intubate trachea
- Elevate head of bed
- Adequate sedation
- Consider placement of **ICP monitoring device**
- Immediate treatment of seizures
- Renal replacement therapy
- Hyperventilation (PaCO₂ 30-35 mmHg)

**Severe elevation ICP**
- **Therapeutic hypothermia** (32-33°C): slows body metab, reduces systemic production and cerebral uptake of ammonia, improves systemic haemodynamic variables
- Adverse effects: coagulation disturbance, impairment of hepatic regeneration, increased infection risk

Mannitol (20% 0.25-0.5 g/Kg)
Hypertonic saline (NaCl 30% → [Na⁺ 145-155 mEq/L])
ALF Gestione MOF

1) EPS e protezione vie aeree
   in ALF può sottintendere l’edema cerebrale e l’aumento dell’ICP; il rischio correla con il grado di EPS (> III_IV°), i livelli di ammoniemia e la presenza di SIRS/SEPSI (⇒ indicazione a profilassi AB).
   Segni neurologici (ipertensione sistemica, bradicardia, alterazione riflessi pupillari, rigidità da decerebrazione) **tardivi**
   Bassa sensibilità della TAC
   **monitoraggio ICP** con modalità invasive o non è l’unico sistema per la diagnosi precoce
   **soglia precoce di necessità di IOT per la protezione vie aeree** (eventuale iperventilazione finalizzata all’ipocapnia)
   **cautela nell’uso dei farmaci vasopressori** per la perdita dell’autoregolazione del flusso cerebrale

**MONITORAGGIO CEREBRALE FONDAMENTALE PRIMA DELL’EVENTUALE INSERIMENTO IN LISTA OLT E DURANTE L’ATTESA DELL’ORGANO**
**ALF gestione MOF**

- **Instabilità emodinamica** (SIRS +/- SEPSI) e funzione renale
  - **volemizzazione** (adeguata a rischio edema cerebrale)
  - **vasopressori** MAP > 65 mmHg
    - NORA +/- teripressina (dopamina)
  - valutare insufficienza corticosurrenalica
  - evitare farmaci nefrotossici
  - dialisi

- **Funz respiratoria**
  - *acute lung injury/ARDS*
    - < soglia x edema polmonare
    - Ipercapnia può indurre > ICP

- **Alterazioni metaboliche/emogasanalitiche**
  - acidosi/ipersodiemia/ipoglicemia

*CVC /SCV 02 linea arteriosa catetere vescicale PiCCo/ Swan Ganz*
### Liver transplantation: criteria

**O'Grady, Gastroenterology 1989**

**Paracetamol:**
- Arterial pH < 7.3 (after volume filling)
- HE III/IV
- INR > 6.5
- Creatinine > 3.4 mg/dL

**Non-Paracetamol:**
- Any grade HE and INR > 6.5
- Any grade HE and any 3 of:
  - INR ≥ 3.5
  - Bilirubin >17.5 mg/dL
  - Age < 10 or > 40 years
  - Unfavourable origin (drug related, indeterminate)
  - Jourdice to HE time > 7 days

**Patients < 30 years:**
- HE III/IV
- FV < 20%

**Patients > 30 years:**
- HE III/IV
- FV < 30%

**Bernuau, Hepatology 1991**

**progressione EPS**

**instabilità emodinamica**

**SIRS criteri**
Between 1995 and 2005, 90,445 candidates for liver transplantation were listed in the United States. During this time, ALF accounted for 3.9% of overall listings.36
MICROCIRCULATORY DISFUNCTION

FUNCTIONAL CELL MASS

OXIDATIVE STATUS
Steatosis, Alcohol, Iron

RELATIVE HYPOVOLEMIA/HYPOXEMIA

PORTAL HYPERTENSION

PORTO-SYSTEMIC SHUNTS

MICROCIRCULATORY DISFUNCTION

PARENTERAL NUTRITION

CHRONIC SIRS

CHRONIC ENDOTOXAEMIA

BOWEL TRANSLOCATION

DEFENSIVE MECHANISMS AGAINST INFECTIONS IMPAIRMENT

ACLF underlying picture
ALCOHOLIC HEPATITIS

HBV FLARE
AIH FLARE

DRUGS/TOXINS/
ALCOHOL

INFECTIONS
VIRAL
BACTERIAL/FUNGAL
SBP/UTI/skin
secondary bacteremia

G.I BLEEDING

TIPS
VASOPRESSORS
PORTAL TROMBOSIS
SHOCK

SURGERY

ALCOHOLIC HEPATITIS
HBV FLARE
AIH FLARE

local proinflammatory and antiinflammatory reaction

Cytokine storm
SIRS/CARS
PMN disfunction

>> macro and microcirculation alterations

MOF
ENDOTOXIN

Toll-like receptors

Proinflammatory cytokines TNF α IL 6

Vasodilation

Effective arterial blood volume

Vasoconstrictor system

Renal perfusion

Hepatic stellate cells contraction

Impaired sinusoidal perfusion

Hypertensive circulatory state

Intrahepatic vascular resistance

Worsening liver function

PLTS aggregation

Coagulation cascade/fibrinolysis

Endogenous heparinoids release

Worsening haemostasis

Portal pressure

VARICEAL BLEEDING

HRS

ET1
ACLF

Hepatotoxic factor: Viruses, Alcohol, ...

Shock, Sepsis, Endotoxins...

ET₁

NO-

Microcirculatory dysfunction
Bile secretion impairment

Splanchnic vascular tone

Intra-renal vascular tone

Systemic vascular tone

Lung vascular tone

Cerebral vascular tone

HRS

Intrahepatic vascular tone

Hepatoxic factor Viruses, Alcohol,...

Shock, Sepsis, Endotoxins,...
ALCOHOLIC HEPATITIS
HBV FLARE
AIH FLARE

DRUGS/TOXINS/
ALCOHOL

INFECTIONS
VIRAL
BACTERIAL/FUNGAL
SBP/UTI/Skin
secondary bacteriemia

G.I BLEEDING
TIPS
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SURGERY

ALCOHOLIC HEPATITIS
HBV FLARE
AIH FLARE

ACLF diagnosis
Infection is the most common cause of mortality

Katoonizadeh A; Gut 2010
### Table 4: Similarity between sepsis and liver failure

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

**Difficult early recognition of infection**
✓ Worsening
- haemodinamic,
- liver function/haemostasis
- renal function

✓ EPS
✓ variceal bleeding
✓ Previous SBP

- < GB ≤ > GB < PLTS

Suspect infection!!
INFECTIONS
VIRAL
BACTERIAL/FUNGAL
SBP/UTI/Skin secondary bacteriemia

G.I BLEEDING
EXCLUDE INFECTION!!

TIPS
VASOPRESSORS
PORTAL TROMBOSIS
SHOCK

DRUGS/TOXINS/
ALCOHOL

SURGERY

ALCOHOLIC HEPATITIS
HBV FLARE
AIH FLARE

ACLF diagnosis
**MOF in ACLF**

- Circulatory failure
- Acute renal failure
  - 27-33% (SBP)
  - prerenal/HRS/ischemic acute tubular necrosis
- Respiratory failure
  - < lung expansion (abdominal/pleural ascites, chest wall edema)
  - < alveolar macrophage antibacterial activity
  - altered capillary permeability
  - altered consciousness
  - cytokines and NO hyperproduction → ARDS risk
  - mortality among cirrhotic pt requiring mech ventilation 50-100%
- Coagulation failure
  - < V VII X prothrombin / prot C prot S ATIII
- Neurological failure
Sepsis in Cirrhosis

**Clinical Evaluation**
- Assess airway
- Assess breathing
- Respiratory rate
- Signs of respiratory distress
- Pulse oximetry
- Circulation
- Hear rate, blood pressure
- Skin

**Laboratory Evaluation**
- Arterial oxygenation and tissue perfusion
- Arterial blood gases
- Arterial lactate
- Peripheral white blood cell count

**Management**
- Assess airway
- Intubation for high-risk patients
- Assess breathing
- Oxygen administration
- Mechanical ventilation if needed
- Assess circulation
- Monitoring: arterial and central venous catheterization
- Fluid challenge, vasopressors
- Hydrocortisone therapy?

**Identify SIRS (s)**

**Identify source of infection (symptoms)**
- Ascites (SBP)
- Respiratory (pneumonia empyema)
- Pyelonephritis
- Skin (cellulitis)

**Identify source of infection**
- Ascitic fluid neutrophil count (culture in hemoculture bottles)
- Culture and Gram’s staining of sputum, urine + hemocultures
- Chest radiography
- Ultrasonography, CT scan

**Start drug therapy**
- Adequate broad-spectrum antibiotics
- Control source of infection
- Surgical or radiological interventions if needed

**Assess organ function**
- Liver
  - Jaundice, hematoma, bleeding
  - Encephalopathy
  - Kidney
  - Urine output

**Assess organ function**
- Liver
  - Bilirubin, INR, AST/ALT, alkaline phosphatase
  - Kidney
  - Electrolytes, creatinine, BUN
  - Others
  - Coagulation (platelets, aPTT)
  - Blood glucose

**Management of organ failure**
- Liver
  - Extracorporeal liver support?
- Cardiovascular system
  - Cardiac monitoring (echography or invasive assessment)
- Kidney
  - Renal replacement vs. liver support?
  - Vasoconstrictor therapy plus IV albumin if type 1 hepatorenal syndrome
- Lung
  - Protective ventilation
Early Goal-Directed Therapy
management of infected patient

Suspected infection
Appropriate cultures

The high-risk patient:
SBP < 90 mmHg after 20–40 cmH2O
volume challenge or lactate > 4 mmol/l

Antibiotics within 1 h and source control

CVP

< 8 mmHg

Crystalloid and colloid

MAP

> 65–90 mmHg

Vasoactive agent(s)

ScvO2

> 70%

Packed red blood cells to Hct > 30%

> 70%

No

Ionotrope(s)

Decrease oxygen consumption

CVP, central venous pressure; Hct, hematocrit; MAP, mean arterial pressure; SBP, systolic blood pressure; ScvO2, surrogate central venous oxygen saturation.

Sepsis Management in cirrhosis

• **Antibiotics**
  Prompts initiation of empiric broad spectrum non nephrotoxic AB after diagnostic tests.
  Cultures neg 30-50% pt with cirrhosis and sepsis AB regimen to be narrowed after ABG!

• **Haemodynamic**
  PAM > 65 mmHg/ PVC 8-12 mmHg, Ht > 30%, CVO2 sat > 70%*: specific goals to be established in cirrhotics

**Fluids/ vasopressors/ blood transfusion**

Colloid/cristalloid controversy: *albumin benefit*
proven to maintain IV volume and renal haemodynamics

> after large volume paracentesis, in PBS, in HRS.

* > O2transport/ < extraction ratio →
> mixed venous O2 saturation in cirrhotics
Sepsis Management in cirrhosis

- Haemodynamic
  Optimal CENTRAL EFFECTIVE intravascular volume
  organ perfusion/ threshold for pulmonary edema

- Hypoproteidemia
- < capillary permeability

PVC: end diastolic pressure/increase intraabdominal pressure

Portal venous pressure reflect CVP → bleeding risk!
Sepsis Management in cirrhosis

- **Ventilation**: IV/ NIV
- **Hydrocortisone**: 50 mg iv/6h (Corticotrophin test non responders) adrenal insufficiency 51-68% in cirrhotics with septic shock
- **Nutrition**: (parenteral/enteral)
- **Glycemic control**: hyperglycemia/insulino resistance hypoglicemia
- **Renal failure**: fluids/vasopressors
  - NB large-volume paracentesis with reduction of intraabdominal pressure
  - **IF INTRAVASCULAR VOLUME IS MAINTAINED.** Hemodyalisis (+/- isovolemic): reduction of inflammatory mediators. Controversy about when to start (before renal failure??), doses., membrane selection, frequency of filter changes
- **(Activated Protein C)**
Antibiotic therapy after severe sepsis evidence

- Each hour of delay of antibiotic therapy decreases survival by 7.6% (Rivers; NEJM 2001;345:1368-77)
- Empiric antbiiotherapy must be adapted to local epidemiology (Kumar; CCM 2006; 34:1589-1596)
The SOFA score calculated 24 hours after ICU admission was found to be the most reliable scoring system to discriminate between hospital survivors and nonsurvivors.
SOFa Score

### Variables/score

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<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td><strong>Respiratory</strong> (PaO₂/FiO₂, mmHg)</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200</td>
<td>≤100</td>
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<tr>
<td><strong>Coagulation</strong> (PLT×10³/µL)</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤100</td>
<td>≤50</td>
<td>≤20</td>
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<tr>
<td><strong>Liver</strong> (Bilirubin, mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2–5.9</td>
<td>6–11.9</td>
<td>&gt;12</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong> (µg/kg/min)</td>
<td>MAP&lt;70</td>
<td>Dop≤5</td>
<td>Dop&gt;5</td>
<td>Epi&gt;0.1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(Epi≤0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>CNS</strong> (GCS)</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>Renal</strong> (Creatinine, mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2–3.4</td>
<td>3.5–4.9</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure, Dop: dopamine, Epi: epinephrine, GCS: Glasgow coma scale

It quantifies organ dysfunction and failure
CIRRHOSIS and ICU: 6 mo. F.U. Mortality risk

- SOFA < 8: 4%
- SOFA > 8: 88%

Wehler Hepatology 2001;34:255-61
<table>
<thead>
<tr>
<th>Points</th>
<th>16</th>
<th>15</th>
<th>13</th>
<th>11</th>
<th>9</th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
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<tbody>
<tr>
<td>Pulse</td>
<td>&lt;40</td>
<td>40-49</td>
<td>70-79</td>
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<tr>
<td>Mean BP</td>
<td>&lt;33</td>
<td>33-33.4</td>
<td>33.5-33.9</td>
<td>34-34.9</td>
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<tr>
<td>Temperature</td>
<td>&lt;6</td>
<td>6-11</td>
<td>12-13</td>
<td></td>
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<tr>
<td>PaO₂ *</td>
<td>&lt;50</td>
<td>50-69</td>
<td>70-79</td>
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<tr>
<td>A-aDO₂ *</td>
<td>&lt;1</td>
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<tr>
<td>Haematocrit</td>
<td>&lt;41</td>
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<tr>
<td>WBC</td>
<td>&lt;1.0</td>
<td>1.0-2.9</td>
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<tr>
<td>Creatinine-No ARF**</td>
<td>micromol/l</td>
<td>(mg/100 ml)</td>
<td>&lt;43</td>
<td>44</td>
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<tr>
<td>Creatinine-ARF**</td>
<td>micromol/l</td>
<td>(mg/100 ml)</td>
<td>&lt;43</td>
<td>44</td>
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<tr>
<td>Urine output</td>
<td>&lt;400</td>
<td>400-599</td>
<td>600-899</td>
<td>900-1499</td>
<td>1500-1999</td>
<td>2000</td>
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<tr>
<td>BUN</td>
<td>mmol/l</td>
<td>(mg/100 ml)</td>
<td>&lt;1</td>
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<tr>
<td>Sodium</td>
<td>mmol/l</td>
<td></td>
<td>&lt;139</td>
<td>120-134</td>
<td>135</td>
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<tr>
<td>Albumin</td>
<td>g/l</td>
<td></td>
<td>&lt;19</td>
<td>20-24</td>
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<tr>
<td>Bilirubin</td>
<td>micromol/l</td>
<td>(mg/100 ml)</td>
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<tr>
<td>Glucose</td>
<td>mmol/l</td>
<td>(mg/100 ml)</td>
<td>2.2-33</td>
<td>&lt;2.2</td>
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</table>
ACLF prognostic scores

Liver function is not the main determinant of outcome in ACLF...

MELD score: Model for end stage liver disease. It is reliable for predicting outcome in pts with decompensated cirrhosis.

Child-Pugh score: It only looks liver functions; it is not versatile at detecting daily changes.

These scores are not able to predict ACLF survival.

The MELD Model, UNOS Modification

In the following model, survival probability of a patient with end-stage liver disease is estimated based on the following variables. Please enter data in the corresponding boxes.

- What is the INR? 
- What is the bilirubin? (mg/dl)
- What is the creatinine? (mg/dl)
- Has the patient had dialysis at least twice in the past week?
  - No
  - Yes

Compute

**MELD score:**
Liver transplantation
ACLF e Trapianto

Paziente mai valutato prima per OLT:
• Valutazione rapida prognosi/eventuali controindicazioni
• Non possibilità di iscrizione in lista con codice urgente
• Priorità in base a MELD secondo l’orientamento del centro

Paziente già in lista:
• rivalutare l’eleggibilità a OLT secondo la “tollerabilità del rischio” del centro Trapianti di riferimento
5 years SURVIVAL BENEFIT

- Graph showing the relationship between life expectancy (years) and MELD score.
- Graph indicating the transplant benefit over different MELD score ranges.

Schaubel DE. Am J Transpl, 2009
Criterio del Transplan Benefit: l’allocazione andrà al paziente che riceve il miglior beneficio e che non necessariamente è il più grave.

MELD $\geq 30$: il primo organo disponibile nella macrozona (AIRT NITP OCST) viene allocato al paziente con il MELD più alto. L’organo va restituito alla regione.

MELD 15-29 (Area Standard): viene lasciata ai centri una flessibilità giustificata nel rispetto del transplant benefit.
### Key points gestione ALF/ACLF

#### ALF
- Identificazione dell’eziologia per valutare terapia specifica e potenziali controindicazioni a OLT
- Monitoraggio e terapia intensiva o rianimatoria (secondo grado di EPS e MOF) incentrati sulla gestione neurologica e sulla prevenzione delle infezioni (evento scatenante o complicazione secondaria)

- Precoce contatto centro Trapianti di riferimento

- Ridefinire indicazione a OLT, nell’attesa dell’organo, secondo la funzione cerebrale

#### ACLF
- Identificazione dell’eziologia per valutare terapia specifica e potenziali controindicazioni a OLT
- Monitoraggio e terapia intensiva MOF incentrati sulla disfunzione emodinamica e sul riconoscimento precoce della sepsi come evento scatenante o complicazione secondaria

- Nuova valutazione o rivalutazione indicazione/idoneità a OLT (per pazienti già in lista) secondo transplant benefit e tollerabilità di rischio del Centro di riferimento

- Comunicazione in ambito trapiantologico tuttora attraverso MELD score
Figure 1 Interactions of genetic and other host factors, specific causes of hepatocellular necrosis and hepatic microenvironment determine outcomes in acute liver failure with medical or surgical management.
MICROCIRCULATORY DISFUNCTION
RELATIVE HYPOVOLEMIA/HYPOXEMIA
OXYDATIVE STATUS (Steatosis, Alcohol, Iron)
PORTAL HYPERTENSION
PORTO-SYSTEMIC SHUNTS
FUNCTIONAL CELL MASS
PARENTERAL NUTRITION
CHRONIC SIRS
CHRONIC ENDOTOXAEMIA
BOWEL TRANSLOCATION
DEFENSIVE MECHANISMS AGAINST INFECTIONS IMPAIRMENT
PORTAL HYPERTENSION
ACLF underlying picture