Acute liver failure

Yvon Calmus, Paris
Hôpital Saint-Antoine
Université Paris 5 Descartes
**Acute liver failure (ALF) : Classification**

<table>
<thead>
<tr>
<th></th>
<th>Factor V</th>
<th>Encephalopathy</th>
<th>Time from jaundice to encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate ALF</td>
<td>50-75%</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>Severe ALF</td>
<td>&lt;50%</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>Fulminant ALF</td>
<td>&lt;50%</td>
<td>present</td>
<td>&lt;2 weeks</td>
</tr>
<tr>
<td>Subfulminant ALF</td>
<td>&lt;50%</td>
<td>present</td>
<td>&gt;2 weeks</td>
</tr>
</tbody>
</table>
ALF: Natural history

Prothrombine rate (%)

Days

enkephalopathy

LT in emergency
Acute hepatitis

Acute liver failure (ALF)
(TP<50%)

(sub) Fulminant hepatitis
(enkephalopathy, cerebral edema)

Recovery

100 pts

< 10

< 1
Acute liver failure: mechanisms

- Hepatocellular necrosis or apoptosis
- Cellular or mitochondrial dysfunction
- Steatosis

hepatocellular necrosis or apoptosis, cellular or mitochondrial dysfunction, steatosis
Signs of Severe ALF

F. Coagulation <50%
Encephalopathy
Jaundice
Hypoglycemia +++
Circulatory hyperkinetic syndrome
Portal hypertension
± Renal failure
± Metabolic disorders
± Acute respiratory distress syndrome (ARDS),
Reduced metabolism of drugs

Cerebral edema
Infections bactériennes
Hémorragie digestive
Ascite
Hypophosphorémie
Pancrétatite aiguë
<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Signs of Encephalopathy</th>
<th>EEG changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Prodrome)</td>
<td>Slowness of mentation; mild disturbed sleep wake cycle</td>
<td>Minimal</td>
</tr>
<tr>
<td>II</td>
<td>Drowsiness, confusion, inappropriate behavior, disorientation, mood swings</td>
<td>Generalized slowing of rhythm</td>
</tr>
<tr>
<td>III</td>
<td>Very sleepy, but arousable, unresponsive to verbal commands, increased reflexes</td>
<td>Grossly abnormal</td>
</tr>
<tr>
<td>IV (Coma)</td>
<td>Unconscious, abnormal posture in response to pain, or no response at all</td>
<td>Appearance of δ waves, decreased amplitudes</td>
</tr>
</tbody>
</table>
Acute liver failure

- Enkephalopathy
- Jaundice
- Vasoplegia
- Renal failure
- Reduced coagulation factors
- Bacterial infections
Signs of Severe ALF

- F. Coagulation <50%
- Encephalopathy
- Jaundice
- Hypoglycemia +++
- Circulatory hyperkinetic syndrome
- Portal hypertension
- ± Renal failure
- ± Metabolic disorders
- ± Acute respiratory distress syndrome (ARDS),
- Reduced metabolism of drugs

- Cerebral edema
- Infections bactériennes
- Hémorragie digestive
- Ascite
- Hypophosphoré mie
- Pancréatite aiguë
# The three subtypes of acute liver failure

<table>
<thead>
<tr>
<th></th>
<th>Hyperacute</th>
<th>Acute</th>
<th>Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from jaundice to encephalopathy</td>
<td>0–1 week</td>
<td>1–4 weeks</td>
<td>4–12 weeks</td>
</tr>
<tr>
<td>Severity of coagulopathy</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Severity of jaundice</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Degree of intracranial hypertension</td>
<td>++</td>
<td>++</td>
<td>+/–</td>
</tr>
<tr>
<td>Survival rate without emergency liver transplantation</td>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Typical cause</td>
<td>Paracetamol, hepatitis A and E</td>
<td>Hepatitis B</td>
<td>Non-paracetamol drug-induced liver injury</td>
</tr>
</tbody>
</table>
ALF: Prognosis according to evolution

ALF: Prognosis according to aetiology

**Etiology**

**VIRUS**
- Hepatotrophic virus
- Others: CMV, HSV, hemorrhagic fever viruses, Paramyxovirus, EBV

**PREGNANCY-RELATED**
- Acute fatty liver of pregnancy
- HELLP syndrome

**DRUGS TOXINS**
- Amanita phalloides toxin
- Bacillus cereus toxin
- Cyanobacteria toxin
- CCl₄
- Yellow phosphorus

**VASCULAR**
- Ischemic hepatitis
- Budd-Chiari syndrome
- Veno-occlusive disease
- PV thrombosis
- Hepatic arterial thrombosis

**METABOLIC**
- Alpha1 antitrypsin deficiency
- Wilson disease

**MALIGNANCY**
- 1º: HCC, (CHCA)
- 2º: adenocarcinoma, lymphoma, leukemia

**AUTOIMMUNE HEPATITIS**

**MISCELLANEOUS**
- Adult-onset Still disease
- Heat stroke
- Graft nonfunction
## Acute liver failure

*William Bernal, Georg Auzinger, Anil Dhawan, Julia Wendon*

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol</th>
<th>DILI (non-paracetamol)</th>
<th>HAV</th>
<th>HBV</th>
<th>HEV</th>
<th>Unknown</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK 1999–2008</strong></td>
<td>57%</td>
<td>11%</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>USA 1998–2001</strong></td>
<td>39%</td>
<td>13%</td>
<td>4%</td>
<td>7%</td>
<td>0%</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Pakistan 2003–05</strong></td>
<td>0%</td>
<td>2%</td>
<td>7%</td>
<td>20%</td>
<td>60%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Germany 1996–2005</strong></td>
<td>15%</td>
<td>14%</td>
<td>4%</td>
<td>18%</td>
<td>0%</td>
<td>21%</td>
<td>28%</td>
</tr>
</tbody>
</table>

*Lancet 2010; 376: 190–201*
Prognosis of Fulminant (and subfulminant) hepatitis without liver transplantation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Survival (global)</th>
<th>Survival if FV&lt;15% + coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>45 %</td>
<td>15 %</td>
</tr>
<tr>
<td>HBV</td>
<td>26 %</td>
<td>10 %</td>
</tr>
<tr>
<td>DILI</td>
<td>15 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Phalloid amanites</td>
<td>50 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>40 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>25 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>12 %</td>
<td>9 %</td>
</tr>
</tbody>
</table>
Hepatitis A

- Worldwide distribution
- Risk of ALF 0.1-1%
- Usually hyperacute
- Anti-HAV IgM 95%
- Spontaneous survival relatively high (40-60%)
Hepatitis B

- ALF ~ 1%
- Risk: women, older
- Diagnosis (Dx) frequently hampered by vigorous immunologic response (rapidly clears virus)
  - HBsAg (30-50%), HBeAg, HBV DNA may be absent
- Dx: anti-HBc IgM and/or anti-HBsAb
Hepatitis E

• almost exclusively in developing country
• Northern Africa and Southern Asia
• young adults
  pregnant women esp. 3\textsuperscript{rd} trimester
Hepatitis E Virus Infection

Typical Serologic Course

Symptoms

ALT

IgG anti-HEV

IgM anti-HEV

Virus in stool

Titer

Weeks after Exposure
Systemic viral infection

- Herpes virus
  - all members
  - neonates, immucompromised, pregnancy
  - Dx: serology, DNA in blood, liver biopsy
  - HSV: mucocutaneous vesicles, ALF, DIC, death

- HHV-6, EBV, CMV, Adenovirus, Coxsackie B virus, Ebola, Yellow fever, Lassa fever, Dengue
## Drug-induced Liver Injury (DILI)

### Drug-induced ALF

<table>
<thead>
<tr>
<th>Feature of ALF</th>
<th>Intrinsic hepatotoxin</th>
<th>Idiosyncratic hepatotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose dependence</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Incidence</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Latent period</td>
<td>consistent, usually days</td>
<td>variable, often weeks</td>
</tr>
<tr>
<td>Clinical course</td>
<td>hyperacute</td>
<td>subacute</td>
</tr>
<tr>
<td>Survival without transplantation</td>
<td>relatively good</td>
<td>poor</td>
</tr>
</tbody>
</table>
Acetaminophen

Å suicidal overdoses and unintentional cases
  ï clinical and outcome similar
Å clinical average-risk patients
  ï > 7-10 g/D (100 mg/kg/D)
  ï hepatic necrosis 7-8 g, hepatotoxicity 15 g, severe liver injury 21 g
Å Dx: history of potentially toxic ingestion, detection of acetaminophen in serum, markedly elevated AST and ALT
  high index of suspicion
Therapeutic Misadventures

ingestion of therapeutic doses of acetaminophen ( > 2 g/D) in

Å habitually drink alcohol to excess
  ﲠ acute hepatic injury 40% < 4 g, 60% < 6 g

Å fasting or malnourished

Å taking drugs that interact with metabolism of acetaminophen
Acetaminophen

- Glucoronide moiety (non-toxic)
- Sulfate moiety (non-toxic)
- NAPQI (toxic)
- Mercapturic acid (non-toxic)

Conjugation:
- CP450 2E1, IA2, 3A4
- GSH transferase
- INH, alcohol, fasting

Covalent binding:
- phenytoin
- fasting, alcohol

Fasting, AZT
Paracetamol

Conjugation

N-Acetyl-cystein

Glutathione

Cytochrome P<sub>450</sub>

Toxic reactive metabolite

Non toxic metabolites

Non toxic metabolites

Non toxic metabolites
Acetaminophen: NAC

- Oral 140 mg/kg then 70 mg/kg q 4 hr
- Until INR < 1.5
- IV 150 mg/kg in 5DW 250 cc. over 15 mins,
  50 mg/kg in 5DW 500 cc. over 4 hr
  100 mg/kg in 5DW 1000 cc. over 16 hr,
  100 mg/kg in 5DW 1000 cc. over 24 hr
- Until INR < 1.5
Acetaminophen

Â hyperacute (begin 36 hr, peak 72 hr)
Â LFT
  ï transaminases rise within 12-24 hrs.
  ï AST > ALT : level higher than other etiologies
  ï peak transaminases and PT usually in D3
  ï bilirubin lower than other etiologies, B > 10 mg/dL unusual
Â 70% oliguric or non-oliguric renal failure within 24-72 hrs.
Â higher spontaneous survival, lower LT
Non-paracetamol-based drugs causing ALF in patients requiring emergency transplantation in USA, 1987–2006

- **Antituberculosis:**
  - Isoniazid (48)
  - Isoniazid plus another anti-tuberculosis drug (2)

- **Anti-epileptics:**
  - Phenytoin (20)
  - Valproate (20)
  - Carbamazepine (3)
  - Single case: Felbamate

- **Antibiotics:**
  - Nitrofurantoin (12)
  - Ketoconazole (8)
  - Amoxicillin and clavulanate (5)
  - Trimethoprim-sulfamethoxazole (2)
  - Minocycline (2)
  - Single cases:
    - Terbinafine
    - Ciprofloxacin
    - Telithromycin
    - Levofloxacin
    - Itraconazole
    - Moxifloxacin

- **Non-steroidal anti-inflammatories:**
  - Diclofenac (3)
  - Bromfenac (2)
  - Ibuprofen (2)
  - Single cases:
    - Etodolac
    - Naproxen
    - Indometacin

- ** statins:**
  - Atorvastatin (3)
  - Cerivastatin (2)
  - Simvastatin (2)
  - Single cases:
    - Pravastatin
    - Ezetimibe
    - Fluvastatin

- **Other drugs:**
  - Propylthiouracil (19)
  - Disulfiram (9)
  - Halothane (8)
  - Herbal (6)
  - Amitriptyline (2)
  - Nefazodone (2)
  - Methotrexate (5)
  - Troglitazone (4)
  - Methyldopa (5)
  - Mercaptopurine or azathioprine (3)
  - Fialuridine (3)
  - Single cases*
Acute fatty liver of pregnancy

- Microvesicular fatty liver disease
- Unknown pathophysiologic mechanisms
  - Inherited LCHAD deficiency
- Late pregnancy (34-37 wks),
- Rarely 19-20 wks, after delivery.
- Primiparous, multiple gestations, male fetuses
Acute fatty liver of pregnancy

- N/V, abdominal pain, pruritus
- FHF, coagulopathy, HE
- premature labor, vaginal bleeding, decreased fetal movement
- PT, fibrinogen, leukocytosis
- AST, ALT moderately elevated (≤750 U/L), jaundice (common)
- elevations creatinine, BUN, uric acid, hypoglycemia and hyperammonemia
Acute fatty liver of pregnancy

microvesicular fatty infiltration, most in zone 3
HEELP syndrome

- Microangiopathic Hemolysis, Elevated serum aminotransferase levels, and Low Platelets
- Chest, epigastric, RUQ pain, N/V, headache, blurred vision, hypertension, proteinuria
- Hemolysis, LDH, AST, ALT, low level bilirubin
- Complication: intrahepatic hemorrhage and infarction
HEELP syndrome
ALF: Indications of LT

severity

Early decision

- Mortality
- Surgical complications
- "Futile" transplantations

Late decision

- Mortality
- Surgical complications
- "No futile" LT
ALF: Criteria for LT

**Clichy criteria**
- Confusion / coma
- and factor V < 30% if age > 30 or factor V < 20% if age < 30

**King's College criteria**
- Acetaminophen
  - pH < 7.3
  - Or 3 among: INR > 7, creat > 300 µmol/L, enkephalopathy 3 or 4
- Non ACM
  - INR > 7
  - Or 3 among: age < 10 ou > 40, bilirubin > 300 µmol/L, INR > 3.5, non A non B or DILI, jaundice-enkephalopathy > 7 days
## Liver transplantation for ALF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Time before LT (days)</th>
<th>ABO incompatibility</th>
<th>Survival</th>
<th>Followup (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peleman RR</td>
<td>1987</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>54%</td>
<td>-</td>
</tr>
<tr>
<td>Bismuth H</td>
<td>1987</td>
<td>17</td>
<td>1,9</td>
<td>5/17</td>
<td>71%</td>
<td>2-15</td>
</tr>
<tr>
<td>Vickers C</td>
<td>1988</td>
<td>16</td>
<td>2,5</td>
<td>3/16</td>
<td>56%</td>
<td>16</td>
</tr>
<tr>
<td>Rakela J</td>
<td>1989</td>
<td>8</td>
<td>1,7</td>
<td>2/8</td>
<td>63%</td>
<td>-</td>
</tr>
<tr>
<td>Gallinger S</td>
<td>1989</td>
<td>18</td>
<td>1,8</td>
<td>3/18</td>
<td>72%</td>
<td>1-2</td>
</tr>
<tr>
<td>Emond JC</td>
<td>1989</td>
<td>19</td>
<td>2</td>
<td>2/19</td>
<td>74%</td>
<td>15</td>
</tr>
</tbody>
</table>
Survival after liver transplantation for acute liver failure by date of surgery in Europe, 1984–2008 Data from the European liver transplant registry
Results of LT for ALF: 1991-2007

120 patients; 10-year survival: 59%
# ALF: Specific therapies

<table>
<thead>
<tr>
<th>Cause</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Herpes virus</td>
<td>acyclovir</td>
</tr>
<tr>
<td>Budd Chiari</td>
<td>anticoagulant</td>
</tr>
<tr>
<td>Wilson</td>
<td>D-penicillamin</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>steroids</td>
</tr>
<tr>
<td>AFL of pregnancy</td>
<td>Early delivery</td>
</tr>
</tbody>
</table>
Non specific therapies

1. N Acetyl Cystein
2. Controlled hypernatremia
3. Controlled hypothermia
4. Xenotransplantation
5. Ex-vivo xenoperfusion
6. Albumin dialysis
7. Bioartificial liver
N-Acetyl-Cystein and ALF not related to acetaminophen

<table>
<thead>
<tr>
<th></th>
<th>NAC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=81</td>
<td></td>
<td>n=92</td>
</tr>
<tr>
<td>Global survival</td>
<td>70%</td>
<td>66%</td>
</tr>
<tr>
<td>Survival w/o LT</td>
<td>40%</td>
<td>27%</td>
</tr>
<tr>
<td><em>HE I-II</em></td>
<td>52%</td>
<td>30%</td>
</tr>
<tr>
<td><em>HE III-IV</em></td>
<td>9%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Lee, Gastroenterology 2009*
Controlled hypernatremia: 145-155 mmol/L

30 patients with ALF and enkephalopathy grade III-IV

<table>
<thead>
<tr>
<th></th>
<th>Hypertonic saline (n=15)</th>
<th>Controls (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>12/15</td>
<td>12/15</td>
<td>ns</td>
</tr>
<tr>
<td>Age</td>
<td>36</td>
<td>36</td>
<td>ns</td>
</tr>
<tr>
<td>INR</td>
<td>7.9 ± 1.4</td>
<td>4.7 ± 0.6</td>
<td>ns</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>110 ± 24</td>
<td>147 ± 62</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinin (μmol/L)</td>
<td>250 ± 34</td>
<td>256 ± 37</td>
<td>ns</td>
</tr>
<tr>
<td>ICP initial (mmHg)</td>
<td>17.2 ± 2.3</td>
<td>16.9 ± 3.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

Controlled hypernatremia


Hypertonic saline

ICP

Survival ? Survival w/o LT?
Controlled hypothermia
Rationale

Â Reduced production of cerebral glutamine

Â Reduced cerebral hyperhemia

Â Improved autoregulation of cerebral blood flow
ALF: hypothermia

14 patients on the waiting list for ALF
13/14 acetaminophen
hypothermia 32-33°C
13/14: LT

Hypothermia and traumatic cerebral edema

<table>
<thead>
<tr>
<th></th>
<th>hypothermia</th>
<th>normothermia</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients</td>
<td>199</td>
<td>193</td>
<td></td>
</tr>
<tr>
<td>Bad neurologic prognosis</td>
<td>57%</td>
<td>57%</td>
<td>ns</td>
</tr>
<tr>
<td>Mortality</td>
<td>28%</td>
<td>27%</td>
<td>ns</td>
</tr>
<tr>
<td>ICP &gt; 30 mmHg</td>
<td>45</td>
<td>59</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>78 ± 22</td>
<td>70 ± 29</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Albumin dialysis (MARS®)

Å ALF : accumulation of substances potentially responsible for the signs of ALF

ï Hydrosoluble substances

ï Protein-linked substances (albumine)

ÅBilirubin

ÅBiliary acids

ÅEndogenous benzodiazepins

ÅFree fatty acids

ÅCytokines (TNF alpha, IL6, IL 10)

Åé é é é é ..
Albumin dialysis (MARS®)

diaMARS® IE250 adsorber (Anionic exchanger)
diaMARS® AC250 adsorber (Activated carbon adsorber)
MARS for ALF

Controlled study in 13 malades

<table>
<thead>
<tr>
<th></th>
<th>MARS (n=8)</th>
<th>Controls (n=5)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta SVR</td>
<td>+ 46%</td>
<td>+6%</td>
<td>0.006</td>
</tr>
<tr>
<td>Delta cardiac index</td>
<td>-20%</td>
<td>-7%</td>
<td>ns</td>
</tr>
<tr>
<td>Delta MAP</td>
<td>+20%</td>
<td>0%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>lactates</td>
<td>+4%</td>
<td>-9.5%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Schmidt LE et al. Liver Transpl 2003; 9: 290
MARS and ALF

Non controlled study in 22 PATIENTS

22 patients treated by MARS
2 applications, duration: 7.6 h (+/- 2.6 h)

Results:
- Improvement in encephalopathy
- Improvement in coagulation
- Improvement in MELD score while on waiting list: 29% (vs 9% in historical controls)

*Camus C et al. Intensive Care Med 2007*
MARS and ALF

The randomized, controlled Fulmar study

- 102 patients with ALF
- 2 groups: MARS vs conventional renal replacement therapy
- Acetaminophen (ACM) : 38%
- LT : 68 patients (41% ACM, 83% non-ACM)
- Mean delay registration on the waiting list-LT : 16 h
- 7 patients transplanted before MARS, 7 patients : too short duration of MARS

Results :
  - Same survival at 6 months in the 2 groups
  - Similar side effects

Saliba, abstract AASLD 2008
MARS : limits

1 kit = 1900 €
+ albumin
x 5-6 applications
Installation +
connexion = 1h30-2h
# MARS®: Conclusions

<table>
<thead>
<tr>
<th>Feature</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance in case of ALF</td>
<td>good</td>
</tr>
<tr>
<td>Improved hemodynamics</td>
<td>?</td>
</tr>
<tr>
<td>Improved neurologic status</td>
<td>?</td>
</tr>
<tr>
<td>Reduced ICP</td>
<td>yes</td>
</tr>
<tr>
<td>Reduced pretransplant mortality</td>
<td>no</td>
</tr>
<tr>
<td>Reduced posttransplant mortality</td>
<td>no</td>
</tr>
<tr>
<td>Superiority to high-speed hemofiltration</td>
<td>no</td>
</tr>
</tbody>
</table>

Few (no ?) indication for MARS in ALF
## Bio-artificial liver

<table>
<thead>
<tr>
<th>system</th>
<th>origin</th>
<th>hepatocytes</th>
<th>Blood/plasma</th>
<th>Controlled study</th>
<th>Improved survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELAD</td>
<td>USA</td>
<td>human</td>
<td>blood</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>HepatAssist</td>
<td>USA</td>
<td>porcine</td>
<td>plasma</td>
<td>yes</td>
<td>no*</td>
</tr>
<tr>
<td>TECA-HALSS</td>
<td>China</td>
<td>porcine</td>
<td>plasma</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>BLSS</td>
<td>USA</td>
<td>porcine</td>
<td>blood</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>RFB</td>
<td>Italy</td>
<td>porcine</td>
<td>plasma</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>LSS/MELS</td>
<td>Germany</td>
<td>porcine/human</td>
<td>plasma</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>AMC-BAL</td>
<td>Nederland</td>
<td>porcine</td>
<td>plasma</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>HBAL</td>
<td>China</td>
<td>porcine</td>
<td>plasma</td>
<td>no</td>
<td>-</td>
</tr>
</tbody>
</table>

* But in a subgroup
Initial Evaluation

Lab:

- to identify cause: anti-HAV IgM, HBsAb, anti-HBcAb, anti-HCV, anti-HDV, drug screen, Doppler sonogram, ANA, SMA, ceruloplasmin, serum Cu
- to assess severity: PT, bilirubin, ABG, F V and VII, phosphate, arterial lactate
- to assess complications: Cr, CXR, cultures, electrolytes, BS, plasma osmolarity, arterial ammonia
- requiring for OLT listing: anti-HIV, anti-CMV, EBV, echocardiogram, blood type and cross match
Current care: stage 0

- Prevent the worsening of liver failure and enkephalopathy
  - Avoid hepatotoxic agents (acetaminophen)
  - Avoid nephrotoxic agents (NSAID, aminosides)
  - Correct hypovolemia
  - Avoid sedatives
Current care: stage 1

- Enkephalopathy grade 3-4 w/o signs of cerebral edema, w/o renal failure, w/o multi-organ failure
  - Think liver transplantation
  - Endotracheal intubation, nasogastric tube
  - Sedation
  - Invasive measurement of MAP
  - Antibioprophylaxis, Antisecretory agents
  - Hydration (> 2 L/j)
  - Prevent hyponatremia
  - Correct hypophosphoreemia
  - N-acetyl cystein
  - No frozen plasma
Current care: stage 2

- Signs of intracerebral hypertension (w/o renal failure)
  - trunk and heat elevation (30°)
  - Bolus of mannitol (0.5-1 g/kg/4hours)
  - Improve ventilation
    - Hypocapnia (Paco₂ 27–34 mm Hg)
    - Avoid high intra-thoracic pressure
    - Avoid peep (positive end-expiratory pressure)
Current care: stage 3

 Signs of intracerebral hypertension and renal failure:

- Renal replacement therapy (continuous > intermittent): hemofiltration, hemodiafiltration
- Invasive PAM monitoring
- Maintain PAM > 70 mmHg
Current care: stage 4

Å Refractory intracerebral hypertension

- Controlled hypothermia (32-33°C)?
## Treatments of unproven efficacy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Awaited results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin</td>
<td>Prevent micro-thrombi/DIVC</td>
</tr>
<tr>
<td>Prostaglandin E1</td>
<td>Hepatic regeneration</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Prevent infraclinic comitial seizures</td>
</tr>
</tbody>
</table>