Acute Liver Failure: management and bridging to transplant

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Acute Liver failure

Definition

- **US Definition**
  - Coagulation abnormality: INR $\geq 1.5$
  - Encephalopathy: any degree
  - Illness < 26 weeks of duration

- **French definition**
  - Fulminant: Hepatic encephalopathy, PT or Factor V < 50%
    - Subfulminant, Subacute: according to delay: Jaundice-HE

- **UK definition**
  - Hyperacute, acute, subacute: according to delay: Jaundice-HE

- **Preexisting healthy liver**

- **Without pre-existing cirrhosis except for:**
  - Wilson disease
  - Vertically acquired HBV
  - Autoimmune hepatitis

Bernuau J, Benhamou JP. Semin Liver Dis 1986
O’Grady J. Gastroenterology 1989; 97: 439
Etiology of Acute Liver Failure in Adults
Changes over Time in France
(Hôpital Paul Brousse 1986 - 2006)

1986-1995 (198 patients)
- Acetaminophen: 38%
- Drugs: 4%
- HAV: 25%
- HBV: 3%
- Indeterminate: 8%

1996-2005 (285 patients)
- Acetaminophen: 12%
- Drugs: 10%
- HAV: 13%
- HBV: 32%
- Indeterminate: 14%
- other: 19%

* p<0.05
Etiology of Fulminant Hepatitis in Adults
Changes over time in US

Pittsburgh 1983 - 1995
(177 patients)

USA* 1998 - 2001
(308 patients)

* 17 tertiary care centers

Acetaminophen
HAV
HBV
Indeterminate
other

Paracetamol (Acetaminophen)  
Acute Liver Failure

1. Suicide attempt:
   - Doses > 10g, 24-48 hrs before hepatitis, high paracetamolemia

2. Treatment of pain:
   doses > 6g/day on several successive days

3. Therapeutic doses: 2-4g/day:
   - In chronic alcoholic patients after fasting
   - In patients with liver failure: HAV, Ischemic hepatitis, …
   - High paracetamolemia missing
Etiology and Prognosis of Fulminant Hepatic failure in Adults

in the absence of LTx

- Spontaneous rate of death: 80-85%
- Bad prognosis
  - Hepatitis B: 75-85%
  - Hepatitis D: 80-85%
  - Drug-induced: 85%
  - Undeterminate: 90%
- Better prognosis
  - Hepatitis A: 30-50%
  - Paracetamol overdose: 40-50%
Progressive and rapid evolution within few days to

- hepatic encephalopathy grade 1,2
- hepatic encephalopathy grade 3,
  - cerebral oedema 25-35%
- hepatic encephalopathy grade 4 coma
  - cerebral oedema 65-75%
- massive brain oedema
- cerebral herniation
- Irreversible coma and death
Management of ALF in the ICU (1)

- Maintenance of a good haemodynamic & CPP > 60 mmHg
  - If needed: Noradrenaline is the first choice
- Avoid vascular Overload (Swan-Ganz if haemodynamic unstable)
- In early stages of HE avoid sedation
- In patients with progressive HE grade III and IV
  - Head between 20-30°
  - Consider endotracheal intubation
  - Sedation with Propofol, Fentanyl
- Avoid factors/drugs which may increase ICP:
  - Fever, Convulsions, Agitation
  - Tracheal aspiration
  - Rotation of the head, jugular compression
  - Vasodilators ie. Trinitrine
Management of Brain Oedema

- If signs of cerebral oedema:
  - Hyperventilation to maintain PaCO2 level between 25-30 mmHg
  - Hypothermia: 32-34°C
  - Mannitol: 0.5-1g/Kg IV repeated every 4 hours if needed
  - Hypertonic saline 30%: Na between 145-155 mEq/L
  - ICP monitoring could be considered in severe forms
    - ICP < 20-25 mmHg
    - CPP > 50-60 mmHg
- If seizures:
  - Phenytoine and low dose benzodiazepines
  - Short acting barbiturates (thiopental or pentobarbital) for refractory seizures
Effect of Hypothermia on ICP (32-33°C)
Management of ALF in the ICU (2)

- High risk of bacterial and fungal infection
  - Antioprophylaxis once under mechanical ventilation
  - Fungal prophylaxis: lipid formulations or echinocandins

- If renal failure or if cerebral oedema:
  - Continuous veno-venous hemofiltration or hemodiafiltration
  - Plasmapheresis
Specific Treatments of ALF

- Herpetic Hepatitis
  - Acyclovir IV

- Paracetamol overdose
  - N-AcetylCysteine
    - Action at the P450 level in the glutathion reductase system
    - More efficient if administered early, but should always be given

- N-Acetyl-Cysteine for all types of hepatitis?
  - Efficacy proven in patients with ALF on non paracetamol origin and mild HE
  - However, non toxic, frequent absorption of paracetamol during hepatitis of other causes (Paracetamol blood level ++++)
N-acetylcysteine (IV) in the treatment of ALF non due to Paracetamol

- A prospective, randomised, multicenter, double blind study: 173 patients
  - Group N-acetylcysteine (NAC) \([n = 81]\)
  - Group Placebo \([n = 92]\)

<table>
<thead>
<tr>
<th>Group</th>
<th>1-2*</th>
<th>3-4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17/56 (30 %)</td>
<td>8/36 (22 %)</td>
<td>25/92 (27 %)</td>
</tr>
<tr>
<td>NAC</td>
<td>36/58 (52 %)</td>
<td>2/23 (9 %)</td>
<td>32/81 (45 %)</td>
</tr>
</tbody>
</table>

* EH 1-2: \(p = 0.021\)

Transplanted patients: placebo 45 %, NAC 32 %

Lee W et al for The ALF study group
Liver Transplantation

- The need for LT should be evaluated as soon as possible
- Liver transplantation is the gold standard treatment for these patients and dramatically improved the survival rate since 1986.
- Liver transplantation in ALF is an emergency procedure
- When a liver graft is available
  - The indication for transplantation should be reevaluated
  - If criteria are still present, transplantation should be performed immediately
• Confusion or coma associated to factor V level < 30% in a patient ≥ 30 years

• Confusion or coma associated to factor V level < 20% in a patient < 30 years

→ Spontaneous Mortality > 90%

King’s College Criteria for Liver transplantation

- For Paracetamol FHF
  - Arterial lactate > 3.5 mmol/l after fluid resuscitation
  - Arterial pH < 7.3 or arterial lactate > 3.0 mmol/l after fluid resuscitation
- Or concurrently:
  - Creatinine > 300 µmol/l and
  - INR > 6.5 and
  - Encephalopathy ≥ grade 3

- Se: 81 %, Sp: 95 %, predictive accuracy: 92 %

W Bernal Lancet 2002; 359: 558-563
Patient survival after LT according to the main indication
(Paul Brousse experience)

Total Log Rank test p > 0.0001

Cirrhose: 1037
Cancer: 448
Hépatite aigue: 331

p Log Rank:

Hépatite aigue vs Cirrhose: 0.0001
Cancer vs Cirrhose: 0.0001
Hépatite aigue vs Cancer: 0.04 (Wilcoxon test)
Patient survival of patients with ALF according to the period of transplantation Paul Brousse Experience
Survival of patients with ALF after Liver Transplantation
Results from the FULMAR study (n=66)

Survival curve for ITT patients with LT

CONV (n=27, 3 deaths)
MARS (n=39, 4 deaths)
Logrank test : $p=0.96$

$89.4\%$
Acute Liver Failure

Optimal Medical Care

Liver Support Systems

Bridge

Liver Transplantation

Liver Regeneration

Recovery/Survival

Patient improvement
Neurological
Hemodynamic
Biological
Liver, kidney
Inflammation/Sepsis
ELAD studies in ALF
Combined P1/2 Studies (1999-2003, USA/UK)

- 41 evaluable patients
  - Fulminant hepatic failure without chronic disease
  - Average time to transplant – 3 days
  - 28 treated, 13 control

- Total of 11 patients died
  - 6/26 ELAD®, 5/15 control

- Bridge to transplant/recovery
  - p = 0.021
HepatAssist 2000 System® (Circe biomedical)

Paul Brousse Hospital experience

HepatAssist-2® (Arbios Inc)

Bioreactor
Hollow fibers
Cryopreserved porcine hepatocytes
Charcoal columns

HepatAssist-2®
15 billion hepatocytes

Demetriou AA, 1995
HepatAssist 2000 System
Results n = 171

Time to death in FHF/SHF

Survival rates of Transplanted vs nontransplanted patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>BAL</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplanted patients</td>
<td>80%</td>
<td>89%</td>
<td>0.22</td>
</tr>
<tr>
<td>n= 94 (55%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-transplanted Patients</td>
<td>38%</td>
<td>50%</td>
<td>0.38</td>
</tr>
<tr>
<td>N = 77 (45%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Albumin Dialysis devices

- **MARS®**: (Gambro®, ex Teraklin®)
  Molecular Adsorbent Recirculating System

- **PROMETHEUS** (Fresenius®)

- **SPAD**: Single Pass Albumin Dialysis
Efficacy of MARS in ALF

• Several uncontrolled studies performed in patients with Acute liver failure demonstrated that albumin dialysis with MARS® showed:
  
  ➢ Improvement of hepatic encephalopathy
  ➢ Increased mean arterial pressure
  ➢ Reduction of ICP and cerebral oedema
  ➢ Increased cerebral blood perfusion
  ➢ Removal of some cytokines increased in ALF:
    ➢ TNF-α, Interleukine 6, interleukine β

- Sen S, Crit Care Med 2006;34:158-64;
## Main reported Studies of patients with ALF treated with MARS

<table>
<thead>
<tr>
<th>Author</th>
<th>Etiology</th>
<th>n</th>
<th>LT n</th>
<th>Survival free of LT</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt LE et al, 2003</td>
<td>HBV/Acetaminophen/drug</td>
<td>MARS:8</td>
<td>2</td>
<td>3 (37.5%)</td>
<td>62.5%</td>
</tr>
<tr>
<td></td>
<td>Control:5</td>
<td>Control:5</td>
<td>0</td>
<td>3 (60%)</td>
<td>60%</td>
</tr>
<tr>
<td>Felldin M et al, 2003</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>Guo LM et al, 2003</td>
<td>Mixed</td>
<td>ALF :11</td>
<td>-</td>
<td>-</td>
<td>37.5%</td>
</tr>
<tr>
<td>Tsai MH et al, 2005</td>
<td>Hepatitis B virus</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>Lai WK et al, 2005</td>
<td>Paracetamol / NANB/drug</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>Koivusalo AM et al, 2005</td>
<td>Toxic/unknown/other</td>
<td>56</td>
<td>17</td>
<td>30</td>
<td>84%</td>
</tr>
<tr>
<td>Lee KH et al, 2005</td>
<td>Drug (herb)</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>15%</td>
</tr>
<tr>
<td>Lai LK et al, 2005</td>
<td>Drug/NA-NB hepatitis</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>Doria C et al, 2006</td>
<td>Mixed</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>85.7%</td>
</tr>
<tr>
<td>Camus C et al, 2006</td>
<td>Mixed</td>
<td>22</td>
<td>10</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Sein Anand J et al, 2007</td>
<td>Mushroom poisoning</td>
<td>14</td>
<td>1</td>
<td>10</td>
<td>71%</td>
</tr>
<tr>
<td>Pugliese F et al, 2008</td>
<td>Mixed</td>
<td>43</td>
<td>-</td>
<td>-</td>
<td>72%</td>
</tr>
<tr>
<td>Kantola T et al, 2008</td>
<td>Mixed</td>
<td>113</td>
<td>33 (29%)</td>
<td>53 (66%)*</td>
<td>75%** 61%</td>
</tr>
<tr>
<td></td>
<td>Hist. control: 46</td>
<td>26 (57%)</td>
<td>8 (40%)</td>
<td>75%** 61%</td>
<td></td>
</tr>
<tr>
<td>Wang M et al, 2009</td>
<td>Mostly HBV</td>
<td>44</td>
<td>5</td>
<td>50%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

* statistically significant. ** Overall survival at 6 months.
MARS in HBV-ALF

Meta Analysis of 149/252 HBV patients from 14 centers in China

• 149 HBV patients
  – Age: $44.3 \pm 13.2$ (range from 15-80)
  – Average MARS treatment: 2.33/patient
  – ALF (11%), SALD (8%), AoCLD (81%)

Bio-chemical and clinical data before and after MARS treatments

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. of patients</th>
<th>Pre-MARS</th>
<th>Post-MARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB (μmol/L)</td>
<td>149</td>
<td>332.4±97.2</td>
<td>218.6±78.7**</td>
</tr>
<tr>
<td>PTA (%)</td>
<td>149</td>
<td>31.7±14.0</td>
<td>38.7±13.1*</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>92</td>
<td>235.7±110.3</td>
<td>163.2±77.6*</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>92</td>
<td>9.8±2.6</td>
<td>4.9±2.3**</td>
</tr>
<tr>
<td>S-sodium (mmol/L)</td>
<td>92</td>
<td>140.8±5.2</td>
<td>145.3±3.9*</td>
</tr>
<tr>
<td>Ammonia (mmol/L)</td>
<td>117</td>
<td>121.4±6.9</td>
<td>89.7±5.4**</td>
</tr>
<tr>
<td>NO (μmol/L)</td>
<td>30</td>
<td>44.2±17.8</td>
<td>29.9±16.7*</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>43</td>
<td>2.70±1.8</td>
<td>1.99±1.29*</td>
</tr>
<tr>
<td>IL-6 (μmol/L)</td>
<td>24</td>
<td>41.1±19.7</td>
<td>26.3±18.9*</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>24</td>
<td>101.8±98.2</td>
<td>79.9±53.7*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87</td>
<td>75.1±8.3</td>
<td>81.8±6.9*</td>
</tr>
<tr>
<td>CTP (point)</td>
<td>98</td>
<td>10.3±2.3</td>
<td>8.2±2.0*</td>
</tr>
<tr>
<td>HE (grade)</td>
<td>98</td>
<td>2.9±1.2</td>
<td>1.5±1.1*</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01 compared with Pre-MARS.

## MARS Meta Analysis: survival rate

<table>
<thead>
<tr>
<th>Type</th>
<th>Case</th>
<th>Recovered</th>
<th>LTx</th>
<th>Rec+LT alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALF</td>
<td>16</td>
<td>8</td>
<td>5</td>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>SALF</td>
<td>12</td>
<td>8</td>
<td>1</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>AoCLF Early</td>
<td>24</td>
<td>20</td>
<td>3</td>
<td>22 (91.7%)</td>
</tr>
<tr>
<td>AoCLF Middle</td>
<td>32</td>
<td>21</td>
<td>5</td>
<td>24 (75%)</td>
</tr>
<tr>
<td>AoCLF Late</td>
<td>65</td>
<td>18</td>
<td>4</td>
<td>20 (30.8%)</td>
</tr>
</tbody>
</table>

Randomized controlled multicentre trial evaluating the efficacy and safety of albumin dialysis with MARS® in patients with fulminant and subfulminant hepatic failure

- **FULMAR study**: 16 transplant centers in France
- **Eligible patients were randomized:**
  - **Conventional Group (CONV)**: Intensive Care Medical Treatment*
  - **MARS® Group (MARS)**: Intensive Care Medical Treatment* + Albumin dialysis with MARS (Treatment with MARS® < 12h randomization)
- **Stratification**: per Paracetamol etiology
- **Independent safety board committee**
- **Institutional study** (National Clinical research Project, Assistance Publique-Hôpitaux de Paris)
  
  clinicaltrials.gov N° NCT00224705

* F. Saliba et al

* including acute hemodialysis if necessary : CVVH - CVVHD
**Patient account**  
**Aug 2004 - Dec 2007**

RANDOMISATION  
110 patients

**CONV**  
- n=53  
- 33 NP - 20 P

Excluded: 4 patients  
3 pts: absence of consent  
1 pt: decompensated alcoholic cirrhosis

- n=49  
- 30 NP - 19 P

- **MARS**  
- n=57  
- 35 NP - 22 P

Excluded: 4 patients  
2 pts: absence of consent  
2 pts: decompensated alcoholic cirrhosis

- n=53  
- 33 NP - 20 P

14 patients  
7 pts No MARS, 7 pts: <4h session

- n=39  
- 23 NP - 16 P

- **102 pts ITT**

- **88 pts PP**

ITT: intent to treat analysis, PP: per protocol analysis, P: paracetamol etiology, NP: Non-paracetamol etiology
## Patient Characteristics / Etiology

**ITT population n=102**

<table>
<thead>
<tr>
<th></th>
<th>CONV</th>
<th>MARS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 49</td>
<td>n= 53</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>(38.7%)</td>
<td>37.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Paracetamol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>(61.2%)</td>
<td>62.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Viral</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>(12.2%)</td>
<td>15.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Autoimmune</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>(16.3%)</td>
<td>7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Drug induced</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>(14.2%)</td>
<td>5.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mushroom</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>(6.1%)</td>
<td>9.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Toxic</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>(8.1%)</td>
<td>3.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unknown</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>(6.1%)</td>
<td>9.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>(4.0%)</td>
<td>13.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Timing to Liver Transplantation (LT)

**ITT population n= 66/102**

<table>
<thead>
<tr>
<th>Timing (hours)*</th>
<th>CONV n= 49</th>
<th>MARS n= 53</th>
<th>Total n=102</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delay Random/Listing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (hours)</td>
<td>1.6 ± 7.4</td>
<td>5.4 ± 18.4</td>
<td>3.7 ± 14.6</td>
</tr>
<tr>
<td>Median</td>
<td>0.8</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Delay Listing/LT (incision)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (hours)</td>
<td>22.9 ± 14.4</td>
<td>18.5 ± 13.4</td>
<td>21.3 ± 13.8</td>
</tr>
<tr>
<td>Median</td>
<td>20.1</td>
<td>15.4</td>
<td>16.2</td>
</tr>
</tbody>
</table>

- 75% of the patients were transplanted within 24h
- 89.4% of the patients were transplanted within 48h

*p= NS
Results: Primary Endpoint
12 months patient survival (ITT analysis)

CONV n=49: 12 deaths
MARS n=53: 9 deaths

Logrank test: p=0.35

Primary Endpoint
12 months patient survival (ITT analysis)

CONV n=49: 12 deaths
MARS n=53: 9 deaths

Logrank test: p=0.35

Results:
Primary Endpoint
12 months patient survival (ITT analysis)

CONV n=49: 12 deaths
MARS n=53: 9 deaths

Logrank test: p=0.35
Results of Primary Endpoint per Etiology
6 months survival (ITT analysis)

Non Paracetamol
Survival curve for ITT patients with non paracetamol etiology

Paracetamol
Survival curve for ITT patients with paracetamol etiology

Logrank test: p=0.45

Logrank test: p=0.46
Transplant Free survival according to Etiology

(ITT population (n=102))

Probability of Survival

Days

non paracetamol n=63: 8 survivors w/t LT
paracetamol n=39: 15 survivors w/t LT

Logrank test : p=0.002
Transplant Free survival by number of therapeutic sessions

Within MARS group
n = 53

All ITT population
n = 102
## Predictive factors of Transplant Free survival

### Results of the multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>IC95</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score &lt; 37</td>
<td>7.6</td>
<td>2.2 - 26.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment with MARS® ≥ 3 sessions</td>
<td>6.3</td>
<td>1.4 - 27.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Fibrinogen (normal or high)</td>
<td>3.2</td>
<td>1.3 - 8.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>
ICU management in specialized centers is essential in ALF patients

Importance of early evaluation of etiology for the prognosis

Treat etiology:
  - if early stage of coma, start N-acetylcysteine
  - Avoid drug toxicity (cerebral, liver, kidney)
  - Prevent and treat cerebral oedema

Consider listing in High emergency group immediately once the criteria of LT are met

Emergency liver transplantation remains the treatment of choice
> Bioartificial liver support are not yet available.
> Artificial liver support mainly MARS® are of major interest but should be more evaluated in patients who have
> A paracetamol ALF etiology
> Prolonged waiting-time period awaiting graft
> Absence of transplantation possibility
> A contra-indication to liver transplantation
> Poor quality of the graft ie. high risk donors: severe steatosis, fibrosis...