Bridge therapies:
Auxiliary Grafts to MARS

Sharan Rambarran
Acute Liver Failure 11th May 2019
Concept

Bridge to transplant

Vs

Bridge to recovery

Hepatic encephalopathy

Imminent herniation

Inflammatory mediators /cytokines / toxins / SIRS
Time is running out…

Clinical Practice Guidelines

Table 11. (A) Acute Liver Failure Poor Prognosis Criteria in use for selection of candidates for Liver Transplantation. (B) Criteria for emergency liver transplantation.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aetiology</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Encephalopathy†</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bilirubin*</td>
<td>–</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Coagulopathy†</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

King’s College criteria

ALF due to paracetamol
- Arterial pH <7.3 after resuscitation and >24 h since ingestion
- Lactate >3 mmol/L or
- The 3 following criteria:
  - Hepatic encephalopathy >grade 3
  - Serum creatinine >300 µmol/L
  - INR >6.5

ALF not due to paracetamol
- INR >6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice-encephalopathy >7 days
  - Bilirubin >300 µmol/L
  - INR >3.5

Beaujon-Paul Brousse criteria (Clichy)
- Confusion or coma (hepatic encephalopathy stage 3 or 4)
- Factor V <20% of normal if age <30 year or
- Factor V <30% if age >30 year

† Factors common to all prognostic models.
* Bilirubin not included in paracetamol criteria.
Acute liver failure
Bridge to recovery
Bridge to transplant

Hypothermic
Normothermic
Machine perfusion devices

Orthotopic liver transplant
Cadaveric
Whole
Split
Reduced
Living donor
Adult to child
Adult to adult
Right vs left
ABO Incompatible
Extended Criteria donor

Xenografts
Porcine ex vivo
In vivo

Auxiliary grafts
HALT
APOLT
Left
Right

Liver assist
MARS
Prometheus
SPAD

Ventilation
Dialysis
ICP monitors
Antibiotics
Cardiac

ICU support

Tissue Engineering and Regenerative medicine
BioArtificial Liver
Hepatocyte transplantation

Total Hepatectomy

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Tissue Engineering and Regenerative medicine
BioArtificial Liver
Hepatocyte transplantation

Total Hepatectomy
Auxiliary grafts

• Surprisingly long history - since 1990

• Organ shortage - partial grafts

• High acute liver failure waitlist death

• Borne out of necessity due to lack of current immunosuppression

• Ability to STOP immunosuppression once native liver recovers

• Toxic liver and risk of handling vs ICP

Belghiti J et al HPB 2004 vol 6 number 2
Heterotopic Auxiliary Liver Transplant

Stamfl DA et al reported the first HALT in acute liver failure

15 year female with fulminant Wilson’s disease

Elevation of intracranial pressures prevented any manipulation of the native liver

Right lobe used

Needed ABOI orthotopic transplant 27 days later

But.. showed that the procedure could be lifesaving and was feasible

Stamfl DA et al Gastroenterology 1990
Auxiliary partial orthotopic liver transplant

Issues with HALT:
- Space
- Competing venous flow
- PGN

**APOLT:**
- 2 cut surfaces!
- Space
- Preserves enough liver to regenerate
- Technically tricky

G Gubernatis et al

LLS APOLT in 2 year old with acute Hep A
Recovery

- Native liver remnant
- Immunosuppression for at least 6 months
- Confirm native hepatic recovery and growth
- HIDA scan and serial CT imaging
- Slow withdrawal of immunosuppression
- Induced rejection and atrophy of graft
- Graft hepatectomy if needed
Pick your patient…

• Young adults and children higher regenerative ability
• Preserved hepatic scaffold / pure hepatocyte lost
• Pathologic processes most suitable:
  • Hepatitis A and E viral infection
  • Paracetamol overdose
  • Mushroom poisoning
Ideal artificial liver

- 1. Detoxification
- 2. Biosynthesis
- 3. Regulation

- Allow bridge to recovery or transplant
- Purification vs detoxification
## Definition of extended criteria donors

- Advanced age
- Macrovesicular steatosis
- DCD
- Organ dysfunction at procurement
  - ICU stay greater than 7 days
  - Hypernatremia greater than 165
  - Bilirubin greater than 3
  - Elevated aspartate aminotransferase/alanine aminotransferase
  - Vasopressor use
- Cause of death: anoxia, cerebrovascular accident
- Disease transmission
  - HBcAb+
  - HBsAg+
  - Hepatitis C virus
  - CDC high-risk donors
  - HIV positive
  - Extrahepatic malignancy
- CIT greater than 12 hours

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I Vokin A Kuo  
Clin Liver Dis 21 (2017) 289–301
Static storage vs Machine Perfusion
Ischaemic-Reperfusion-Injury

Ischaemic injury

- Glycogen consumption
- Adenosine triphosphate (ATP) depletion
- Lack of oxygen
- Parenchymal cell death, release of reactive oxygen species (ROS), proteases and damage-associated molecular patterns (DAMPs)

Reperfusion injury

- Reactive oxygen species (ROS) production
- Activation of the inflammatory immune innate response
- Release of inflammatory mediators (cytokines, chemokines, adhesion molecules, reactive oxygen species (ROS) and proteases)

Reperfusing-modalities of machine perfusion shorten the ischaemic period, whereas they inevitably trigger the detrimental pathways associated with reperfusion. Pharmacological and non-pharmacological interventions may mitigate the injury associated with reperfusion.

Or

Non-reperfusing-modalities of machine perfusion optimise the mitochondrial oxidative function and replenish cellular energy stores

Or

Ischaemia-free organ transplantation may prevent completely ischaemia-reperfusion injury
Machine Perfusion systems
Liver Transplantation After *Ex Vivo* Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial

- Infusions:
  - Heparin
  - Insulin
  - Bile Salts
  - Prostacyclin
  - Nutrients

- Components:
  - Soft-shell Reservoir
  - Pinch Valve
  - Flow Sensor and Bubble Detector
  - Oxygenator
  - Pinch Valve
  - Hepatic Artery
  - Portal Vein
  - Centrifugal Pump
  - Inferior Vena Cava
  - Flow Sensor

- Recirculation:
  - Ascites

OrganOx metra

Machine perfusion devices

(A, B) Photograph of Organ Recovery Systems Inc. LifePort® Liver Transporter prototype. (C) ECOPS device (Organ Assist®). (D) The OrganOx® metabTM device.
Machine Perfusion Options and trials on the go…

<table>
<thead>
<tr>
<th>Variables</th>
<th>HMP</th>
<th>HOPE</th>
<th>EHOPE</th>
<th>DHOPE</th>
<th>SMP</th>
<th>COR</th>
<th>NMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>0–12</td>
<td>0–12</td>
<td>0–12</td>
<td>0–12</td>
<td>25–34</td>
<td>25–34</td>
<td>35–38</td>
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<tr>
<td>Oxygen</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Perfusion route</td>
<td>PV</td>
<td>PV</td>
<td>PV + HA</td>
<td>PV + HA</td>
<td>PV/PV + HA</td>
<td>PV/PV + HA</td>
<td>PV/PV + HA</td>
</tr>
<tr>
<td>Perfuseate</td>
<td>Solution</td>
<td>Solution</td>
<td>Solution</td>
<td>Solution</td>
<td>Oxygen carrier</td>
<td>Oxygen carrier</td>
<td>Oxygen carrier</td>
</tr>
<tr>
<td>Bile production</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Metabolism</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Decreased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Intervention site</td>
<td>Recipients site</td>
<td>Recipients site</td>
<td>Recipients site</td>
<td>Recipients site</td>
<td>Recipients site</td>
<td>Recipients site</td>
<td>From donor to recipients site</td>
</tr>
<tr>
<td>Main mechanism</td>
<td>Metabolism delay, decreased oxygen need</td>
<td>Metabolism delay, energy recovery</td>
<td>Metabolism delay, energy recovery</td>
<td>Metabolism delay, energy recovery</td>
<td>Graft reconditioning, energy recovery</td>
<td>Graft reconditioning, energy recovery</td>
<td>Mimic physiology, energy charge, initiate repair process</td>
</tr>
</tbody>
</table>


Recent clinical trials of NMP:

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Experimental groups</th>
<th>MP Time</th>
<th>Observation parameters</th>
<th>Device, perfusate, route and oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravikumar (2016) [16]</td>
<td>NMP (n = 20) vs SCS (n = 40)</td>
<td>3.5–18.5 h</td>
<td>30-d graft survival, ALT/AST</td>
<td>OrganOx, blood based solution, HA (60–75 mmHg) and PV, oxygen (maintain normal pH and PO₂)</td>
</tr>
<tr>
<td>Mergental (2016) [17]</td>
<td>NMP (n = 5)</td>
<td>255–564 min</td>
<td>Lactate, bile production, hospital stay, 6-mon survival</td>
<td>Liver Assist and OrganOx, blood based solution, PV and HA, oxygen (no details)</td>
</tr>
<tr>
<td>Selzner (2016) [18]</td>
<td>NMP (n = 10) vs SCS (n = 30)</td>
<td>340–580 min</td>
<td>Lactate, bile production, ALT/AST, ICU stay, hospital stay, complications</td>
<td>OrganOx, Steen solution, PV and HA, oxygen (no details)</td>
</tr>
<tr>
<td>Watson (2017) [19]</td>
<td>NMP (n = 12)</td>
<td>122–530 min</td>
<td>Post-reperfusion syndrome, vasoplegia, PNF, oxygen tension</td>
<td>Liver Assist, blood based solution, PV (660–1130 ml/min) and HA (208–390 ml/min), oxygen (621–671 mmHg or 153–187 mmHg)</td>
</tr>
<tr>
<td>Bral (2017) [20]</td>
<td>NMP (n = 10) vs SCS (n = 30)</td>
<td>3.3–22.5 h</td>
<td>ALT/AST, lactate, 1-mon graft survival, ICU and hospital stays</td>
<td>OrganOx, blood based solution, PV (500 ml/min) and HA (150 ml/min), oxygen (no details)</td>
</tr>
</tbody>
</table>


Tissue Engineering and Regenerative Medicine

- 3 decades of research - proper studies rare
- Compared to orthotropic liver transplant benefits minimal
- Tissue revascularisation and integration into host circulation
- Safe metabolically active source of cells
- Hepatocyte transplantation and tissue engineering methods
- Hepatocyte transplantation for metabolic disorders maybe acute liver failure

Liver support strategies: cutting-edge technologies
B. Struecker, N. Raschzok & I Sauer *Nature Reviews Gastroenterology & Hepatology*
03/2014
Tissue Engineering and Regenerative Medicine

M. Cesaretti et al. / Transplantation Reviews 33 (2019) 72–76
Current status of Xenotransplantation

- Pioneered in the 1960’s
- Until 2012 longest recorded survival 9 days
- Pig to Non-human Primate (baboon)
- XenoTX immunosuppression protocol developed
- Survival >900 days possible
- Interspecies immune modulated thrombosis and coagulopathy
Albumin Dialysis

- Plasma exchange

- Liver support systems (biological or adsorbent) should only be used in the context of RCT (evidence level II-1, grade of recommendation 1).

- Plasma exchange in RCT, has been shown to improve transplant-free survival in patients with ALF, and to modulate immune dysfunction (evidence level I, grade of recommendation 1).

- Plasma exchange may be of greater benefit in patients who are treated early and who will not ultimately undergo LTx (evidence level I, grade of recommendation 2).

- Fractionated plasma separation and adsorption Prometheus
Conclusion

Liver transplant for fulminant failure

Many options when organs few and far between

Most still outside the realms of current clinical practice

Guidelines govern current practice

The arsenal of the liver transplant team continues to grow

Development of skills and understanding should be concentrated

Refer your patient early
WITS TRANSPLANT
Progressive medicine, exceptional care.