Currently available…(1)
Currently available …(2)
Overview... Literature is Poor

- **Uncontrolled/historical controls**
  - Natural history of disease
  - Effects of standard therapy
  - Few RCT
    - Heterogenous patient samples
    - Small patient samples
    - Single centre

- **Bertani et al Int J Artif Organs 2002;25:903-10** Literature review on artificial liver support in ALF

- **Human Studies**
  - Non-Biological Liver support
    - 32 papers, 2 RCT; both no benefit.
  - Biological Liver support
    - 9 papers; 1 RCT; no benefit

- **Effects of therapy poorly studied /reported**

- **Bilirubin reduction; frequent outcome measure**
  
  *Kramer et al Int J Artif Org 2002;25:918-22*

  - Influence of hydroxyethyl starch (HES) infusion (10ml/kg) on bilirubin levels in cirrhotic patients (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>HES</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>19.5</td>
<td>15.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heamatoctrit</td>
<td>26.7</td>
<td>23.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Systematic review of liver support
Pascher et al Xenotransplantation 2002 9(5):309

- Systematic review 1994-2000
- 198 patients - long term survival 28% (as per standard of care)
- Independent predictors of positive outcome
  - Age < 20 years  p<0.029
  - Coma < III/IV  p<0.003
  - Perfusion time > 10 hours  p<0.024
  - Use of human or baboon livers  p<0.02
Systematic review: JAMA 2003;289 (2):217: liver support

• Of 528 references: 12 randomised trials in 483 patients
• 10 acute or AOC liver disease, 2 acute liver failure
• Overall support systems had no effect on mortality compared with standard care (RR 0.65 CI 0.65-1.25)
• 5 haemodiasorption, 2 MARS, 2 cellular and remaining exchange techniques
• Meta regression suggested that effect was dependant on type of liver failure (p=0.03)
• In stratified meta analysis support systems decrease mortality in AOCL but not in ALF
Support of the liver

Options

Treat sepsis: procalcitonin monitoring
Appropriate fluid and vasoactive therapies
Pharmacological therapy: antioxidants
Metabolic control and feeding

- Liver Transplantation: whole, split, auxiliary, hepatocytes
- Bio-artificial Systems (Cell based therapies)
  - ELAD, BAL, MELS, Organ in a bucket
  - Hepatocytes infusion
- Extra-Corporeal Methods (Dialysis methods)
  » Charcoal adsorbents: perfusion
  » Albumin dialysis (MARS, Prometheus-Helios, SPAD)
  » Ash (Biologic BT)
  » Plasmapheresis
  » HVHF
Manipulations in the splanchnic bed

- Don’t ignore it!
- Physiological interventions may effect splanchnic blood flow, hepatocyte function and energy dependant transporters
  - Beta and alpha agents, Other pressor drugs
    - Enoximone vs dobutamine in sepsis: increased spl D02, V02 (p<0.05) and decreased inflammatory response. *(TNF release)* *Kern et al Crit Care Med 2001;29(8):1519*
    - Adrenaline: variable spl D02, decreased spl V02, increased metabolism glu turnover, increased lactate. *Meier Hellman et al 1997 Crit Care Med*
    - Iloprost: increased spl D02, decreased glu production, NS increase in spV02. *Keifer P Int Care Med 2001 27(7):1110*
    - Phenylephrine vs Noradrenaline

- Volume loading
  - Supply Dependancy
  - Increased metabolic activity
Role of CVP in transplant setting

Schroeder J Cardiothoracic Vascular Anaesthesia 2004;18:4

- Retrospective 2 centre study - 73 and 78 patients over 19 mnths
- Low cVP < 5 mmHg, SBP > 90: fluid restriction, pressors & GTN
- Normal cVP (7-10): no manipulation, MAP > 75, minimal constrictors

<table>
<thead>
<tr>
<th>Low cVP</th>
<th>Normal cVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor function</td>
<td>8</td>
</tr>
<tr>
<td>Non function</td>
<td>2</td>
</tr>
<tr>
<td>Peak Creatinine</td>
<td>3.2±0.3</td>
</tr>
<tr>
<td>Post op RRT</td>
<td>5 (6.8%)</td>
</tr>
<tr>
<td>LOS ICU</td>
<td>3±0.7</td>
</tr>
<tr>
<td>Hospital</td>
<td>15.8±1.4</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>Operative time</td>
<td>7.3±0.9</td>
</tr>
</tbody>
</table>
ACS and HV outflow

- Rats, IAP up to 30 cm H2O for 90’ then decompress then Bx at 30’
- In vivo GSH decreased in liver
- Decreased hepatocyte survival on culture
- Decreased in vitro GSH  
  \[ \text{Hsu J Trauma 2004 57(3):569} \]

- Post liver transplant \( n=108 \), IAP > 25 mmHg X 2
- Observed in 32% of patients on day 1 and 2 post-op
- Renal dysfunction 32 vs 8%  \( \text{RR with IAP >25 is 9.8} \)
- \( \text{PaO2/FiO2 ratio pre extubation 164 vs 271 mmHg *} \)
- Slower extubation
- Critical value IAP 23-25 on ROC for renal and respiratory dysfunction  
  \[ \text{Biancofiore Trans Proc 2004 36; 547} \]
NAC

- Has it translated ……not really
- 60 patients NAC during anhepatic phase; no difference in haemodynamics, graft function Liver Transplant Surg 1998 4(2).
- NAC + PGI2 1 hours post reperfusion: n=25, no difference in survival Peak ALT lower, median LOS shorter Paediatric Transplant 2001 5(4):274
- NAC pre and post reperfusion, n=20, No effect on lactate/pyruvate ratio, hydroxybutyrate/acetoacetate. Decreased circulating ICAM -1 and VCAM 1 at 24 hours, decreased rise in alpha glutathione transferase Transplantation 2001 72(4):694
- NAC in SIRS and sepsis: Decreased neutrophil oxidative burst after E Coli stimulation, Increased phagocytosis - potentially good for ischemia reperfusion, less so for sepsis Crit Care Med 2001 29(2):272
Glucose and metabolic control

Van de Berghe et al NEJM 2001; 345:1359-67

- 1548 patients - post surgery including Tp
- SOC : aim for 10-11 mmol/l IIT : aim for 4.4 - 6.1 mmol/l
- Mortality : 35 (4.6%) vs 63 (8%) : risk reduction 42% (22-62%)
- Similar effect for all groups and APACHE bands
- Intensive insulin therapy effect more pronounced in patients staying > 5 days in ITU : 10.6 vs 20.2% ITU mortality  p=0.005

- % vasopressor and inotropic support the same (74.8 & 75%)
- Less hyperbilirubinaemia (>35 mmol/l) in IIT group (27 vs 22%) *
- Decreased ventilation (>5/7 ITU stay) 12 vs 10 days **
- Greater 14 days ventilation 11.9 vs 7.5 % ***
- Renal impairment : RRT 8.2 vs 4.8 % **
- Bacteraemia 7.8 vs 4.2 % ** > 10 days antibiotics 17 vs
Hepatocyte mitochondrial ultrastructure: protection with strict glucose control
Vanhorebeck Lancet 2005 365:53

- Examine cytopathic hypoxia in critical illness
- 74 patients who died underwent liver and muscle Bx
- 18 from each group matched for demographics, APS, interventions

Abnormal enlarged mitochondria, disarrayed cristae + reduced electron density of matrix in A/B :liver in CIT
Seen in 20-30% hepatocytes in 78% of livers
C : skeletal muscle

D/E IIT hepatocytes :
Mitochondrial structure normal
In 91%

Maintained Complex 1 activity in IIT
Holy Grail of Liver Support Systems

- Safety
- Efficacious
- Ease of access/ Speed of Delivery
- Cost Effective
Multiple species extracorporeal liver perfusion  *Abouma 1970*

- 1 patient with hepatorenal and chronic hepatitis
  - 16 perfusions over 10 weeks
  - patient died awaiting liver transplant
- organs used
  - 10 pigs
  - 3 baboons
  - 1 calf
  - 1 monkey
  - 1 human …… ??? zoo keeper

*Abouna Transplantation 1999 67;12 : 1576*

*Levy 2000 Transplantation 69;2:272* 2 cases ALF

*Levy 2000 Transplantation 69;2:272* 14 patients

Decrease in ICP, ammonia, bilirubin

Labour intensive and expensive
Haemoperfusion

Uncontrolled study
- 75 patients with ALF and grade III encephalopathy
- 10 hrs of charcoal haemoperfusion
- 65% survival in treated patients
- 15% survival in historical controls

O’Grady JG et al Gastroenterology 1988;94:1186-92
Controlled study
- 62 patients with ALF and grade IV encephalopathy
- No perfusion/ 10 hrs perfusion daily
- Survival 39.3% vs. 34.5% (non-significant)
- No survival benefit
Biologic-DT; randomised controlled studies: Haemodiasorption


- 10 patients with ALF: 5 treated (5 6 hour treatments), 5 controls
  - Treated: No change in ammonia, lactate, bile acids, encephalopathy
  - Increased ACT, reduced fibrinogen, platelets
  - Survival: Treated 1/5 (20%), Controls 3/5 (60%)

- 10 patients with AAH and encephalopathy,
  - 5 treated (3 6 hour treatments), 5 controls
  - No change in ammonia, bilirubin, TNF-a, IL-8, encephalopathy


- 20 patients with cirrhosis and encephalopathy > grade II
- Randomised to 6 hrs treatment with Biologic-DT or SMT.
- Treated: No change in bilirubin, ammonia, no change in encephalopathy grade, Reduced platelets, increased INR, lactate, IL-6, TNF
- Controls; no changes
Extracorporeal Liver Assist Device (ELAD)

- Human Hepatoblastoma Cell line (400g)
- Whole blood perfusion (1 column)
- Initial encouraging case series, not supported by RCT (no clin/biochem benefit)
- ‘New ELAD’
- 1 further clinical report (Millis et al. Transplantation 2002;74(12):1735-46)
- Safe, no adverse incidents, metabolic activity sustained
- Refinanced
Use of discarded human livers in bioreactors

Sauer et al Int J Artif Organs 2002  25(10) :1001
Busse et al, Arch Surg 1999 384:588

- Bioreactor module with 3D-capillary structure containing 1.8-4.0 \times 10^{10} (up to 500g) pig hepatocytes. Kept perfused on stand-by for up to 3 weeks. Now switched to Human Hepatocytes.
- 20-25% of livers not used as transplants
- 54 human livers not used due to steatosis, cirrhosis, fibrosis and other reasons
- 36 reactors were produced of which 10 were used to treat 8 patients
- Treatment period 7 to 144 hours
- No adverse events reported
• Bioartificial liver - radial flow 3D high density
• 7 patients treated on 8 occasions
• Age 21 - 56 years Grade III/IV HE
• Treated for 8 - 35 hours
• 6/7 proceeded to OLT
• 1/7 improved - no OLT required

• Plasmapheresis and subsequent exposure to cells (230g)
• 7 patients treated on 8 occasions
• HBV n=3, primary non-function n=3, 1 abdominal trauma and liver surgery
• 6/7 proceeded to OLT
• 1/7 recovered
• Improved encephalopathy, decreased ammonia, decreased AST
Bioartificial Liver

- Hollow fibre cartridge
- 50 g pig hepatocytes on collagen coated microcarriers
- Incorporated into an extracorporeal circuit
  - 2 charcoal columns
  - heater
  - oxygenator
  - plasma resevoir
- Plasma (centrifugation) perfusion

- Applications of 6 to 7 hours
- Non-Randomised studies suggest benefit
23 patients with acute liver failure:

<table>
<thead>
<tr>
<th></th>
<th>Pre-</th>
<th>Post-</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>9.2±0.8</td>
<td>7.8±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.4±0.7</td>
<td>4.2±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>ICP</td>
<td>17±2</td>
<td>11±1 mmHg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP</td>
<td>69±2</td>
<td>74±2 mmHg</td>
<td>0.04</td>
</tr>
<tr>
<td>Ammonia</td>
<td>159±8</td>
<td>133±16 µmol/l</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>21±1</td>
<td>22±1</td>
<td>NS</td>
</tr>
</tbody>
</table>

- 13 patients with acute liver failure
- 3 not treated - 2 improved, 1 transplanted
- GCS 6.5±3.7 to 9.6±4.4 (p<0.02) related to volume of plasma exchange
- Decreased bilirubin (p<0.0005)
- 6 patients had transient haemodynamic instability
- 5 had bleeding complications
- 2 died post OLT; 8 survived
Phase III study with BAL

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
<th>Control* [n (%)]</th>
<th>BAL* [n (%)]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>171</td>
<td>53/86 (62)</td>
<td>60/85 (71)</td>
<td>0.259</td>
</tr>
<tr>
<td>FHF/SHF</td>
<td>147</td>
<td>44/74 (59)</td>
<td>53/73 (73)</td>
<td>0.117</td>
</tr>
<tr>
<td>PNF</td>
<td>24</td>
<td>9/12 (75)</td>
<td>7/12 (58)</td>
<td>0.667</td>
</tr>
</tbody>
</table>

*Survivors/total patients.
FHF, fulminant hepatic failure; SHF, subfulminant hepatic failure; PNF, primary nonfunction post-transplantation; BAL, bioartificial liver.
• Co-variate time dependent proportional hazard model of time to account for impact of transplantation
  • RR for BAL for all patients (171) 0.67 NS
  • RR for FHF/SHF (148) was 0.56 p=0.048
• Similar incidence of serious adverse events in each group
• No differences seen for neurological function
• Effect of multiple centres and variable management
MARS therapy

Figure 2. Schematic drawing of the MARS.
## MARS in acute on chronic liver disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Controlled</th>
<th>Improvements</th>
<th>Biochem</th>
<th>CVS</th>
<th>CNS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorkine 2001</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>(Yes ?)</td>
<td></td>
</tr>
<tr>
<td>CCM 9(7) 1332-36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stange 1999</td>
<td>13</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Artif Organs 23(4) 319-30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 2001</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Liv Trans:7(8) 709-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitzner 2000</strong></td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Liv Trans:6(3) 277-86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heemann 2002</strong></td>
<td>24</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Hepatology:36:949-58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jalan 2003</td>
<td>8</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>J Hepatol;38:24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sen et al 2004</strong></td>
<td>18</td>
<td>Yes</td>
<td>Bili</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Liver Transplant;10:1109</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biochemical improvements:** Reduced Bilirubin, bile acids, creatinine, ammonia,
### MARS Therapy

*Mitzner et al Liver Transpl 2000;6:277-286*

<table>
<thead>
<tr>
<th></th>
<th>MARS (8)</th>
<th>HDF (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creat(mg/dl)</td>
<td>3.8±1.6 to 2.3±1.5 **</td>
<td>4.4±1.3 to 3.8±0.5</td>
</tr>
<tr>
<td>Bilirubin(mg/dl)</td>
<td>26.8±11.6 to 17.3±7.5 *</td>
<td>24±18.6 to 22.2±12.</td>
</tr>
<tr>
<td>Prothrombin (%)</td>
<td>32±13 to 44±12 **</td>
<td>36±19 to 42±22</td>
</tr>
<tr>
<td>Sodium(mmol/ L)</td>
<td>130±8 to 139±7</td>
<td>124±8 to 131±7</td>
</tr>
</tbody>
</table>

Survival; MARS mean 25 days, 5 days controls (p<0.05)

Long term survival (30 days) in MARS group (8%)
MARS: Heemann et al Hepatology 2002;36:949-58

24 patients with cirrhosis and ‘acute liver injury’

- Randomised to SMT with MARS (6 hour sessions) or SMT alone (RRT for life threatening electrolyte abnormalities)
- MARS group; reduced bile acids, bilirubin, encephalopathy
- No difference in albumin or prothrombin
- Controls; no change in biochemistry, worsening encephalopathy
- 30 day Survival
  - MARS 11/12, SMT 6/12 (P<0.05) ITT p =0.069, PP p=0.02
  - 6 mnth survival 6/12 MARS and 4/11 in control group

- Trial stopped early due to benefit in treatment group
- Concerns raised: Definitions, Matching, End-point, Statistical validity of cessation. (Editorials accompanying paper)
MARS therapy in CLD and encephalopathy

• Hassanein et al
American Association for Study of Liver Disease,
Boston 2/10/04
  – Multi-centre PRCT
  – Acute on Chronic Liver Disease n=70
  – MARS+SMT vs. SMT
  – Analysis by intention to treat
• Significant improvements in encephalopathy grade
• No differences in survival
MARS in AoCLD

Sen et al Liver Transplant 2004;10:1109

• 18 patients with alcohol related AoCLD randomized to MARS or SMT over 7 days
• Significant improvement in encephalopathy
• No change in renal function or creatinine
• No change in ammonia or cytokine levels (TNF, IL-6, IL-10, IL-8)
• No change in plasma malondialdehyde (MDA)
• Significant fall in bilirubin in MARS group
• Significant fall in N0x levels in MARS group
• MELD score decreased significantly in both groups
Effects of MARS treatment on encephalopathy and ammonia

Mortality 5/9 in each group
## MARS in acute liver disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Controlled</th>
<th>Biochem</th>
<th>CVS</th>
<th>CNS</th>
<th>ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awad 2001</td>
<td>9</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>*Surgery:*130:354-62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novelli 2001</td>
<td>10</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>*Trans Proc:*33,1942-44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biochemical improvements:** Reduced ammonia, fatty acids, bilirubin.

Helsinki group have used the system in a significant number of patients with acute liver dysfunction: no controlled data at present. Data suggests haemodynamic and neurological stability.

Larsen et al: increase in SVRI, no fall in ammonia.
• 11 patients with AoCLD, C-P score 9-13
• Treated on 2 consecutive days for > 4 hours
• Significant decrease in:
  – conjugated bilirubin 252±224 to 153±138, 
  – bile acids 68±54 to 39±36, 
  – ammonia 45±30 to 27±18, 
  – cholinesterase (p<0.04), creatinine (p<0.001) and pH
• No change in platelets, factor II, V, fibrinogen (p=0.01)

• 2 patients showed decrease in MAP (septic) and one demonstrated bleeding 16 hours post Rx
• 3 discharged 8 died
Plasmapheresis

Advantages:
- Removes all molecules
- Substitutes plasma products
  - coagulation factors
- Is well tolerated
  - Improves HE, CMRgl and O2
  - increases CPP and CBF
  - No effect upon ICP,
  - Increases MAP & SVRI
  - Decreases CI/DO2 but not VO2
  - Increases splanchnic removal NH4+

Disadvantages:
- Limited transport of water-soluble substances
- Unselective removal substances
- Requires donor plasma

Clemeson et al Hepatology 1999;29:327
Does HVP improve survival in ALF?

*Preliminary findings in 1.interim analysis after 61 patients (now 99 patients included)*

![Cumulative percentage surviving graph](Image)

- **+LTx/+HVP** (n=11)
- **+LTx/non-HVP** (n=12)
- **non-LTx/+HVP** (n=25)
- **non-LTx/non-HVP** (n=13)

\[ p < 0.001 \]
High volume isovolaemic haemofiltration

Honore et al Crit Care Med 2000 28:3581

- 20 patients with refractory septic shock
- STHVHF: 450 ml/min blood flow, 35 L UF over 4 hrs
- Inclusion criteria
  - MAP < 55, CI < 2.5, vasopressor dose > 0.5 µg/kg/min, pH < 7.15, lactate > 5, Pa02/Fi02 ratio < 100.
- Responder: (11/20)
  - at 2 hrs > 50% CI, > 25% increase mixed venous satn,
  - at 4 hrs pH > 7.3, 50% reduction in vasopressor dose
- No differences for h/d, severity scores (Apache II: 30.6 vs 31.1), physiological measurements, vasopressor dose, volume treatment pre entry
- Responders weighed less than Non-Responders
  - 66 vs 81 kg (p<0.003)
- Ultrafiltrate dose
  - 0.53 ± 0.07 L/kg vs 0.43 ± 0.07 L/kg (p<0.003)
  - Delay time (ICU admission to time zero)
  - 6.5 (3-12hrs) vs 13.5 (9.6-17.5 hrs)
HVHF vs CVVHF (ALF)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HVHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived no OLT</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Died no OLT</td>
<td>13 (72%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Underwent OLT</td>
<td>4 (22%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Time of OLT (hrs)</td>
<td>34 (27-36)</td>
<td>51 (22-83)</td>
</tr>
</tbody>
</table>

\[p<0.08\]

\[p<0.08\]
A Bridge?

- ✗ Safe
- ✔ Cheap
- ✗ Widely accessible
- ✗ Efficacious
A Bridge?

- Safe (but beautiful)
- Cheap
- Widely accessible
- Efficacious
A Bridge?

- ? Safe (so far)
- ✔ Cheap
- ✔ Widely accessible
- ✔ Efficacious
The Bridge

- Cheap
- Safe
- Widely accessible
- Efficacious

- And it cleans up after itself!
- Thankyou, any questions?
Where are we now?

- New generation of support systems available.
- Do not forget the basics when enthused for the new and exciting!
- Improvements in
  - Biochemical parameters improve
  - Decreased HE in AoCLD
  - Haemodymics variable
  - Mortality - seen in small studies in CLD at 30 days
  - Concern that findings are not applicable to all patient grps
    - Coagulopathy, sepsis
    - Other systems are likely to have similar side effect profile
- Need for well designed trials before general application
- Concern in regard to drug clearances
MARS treatment and post-operative liver failure and septic multiple organ dysfunction

Rittler et al Liver Int 2004;24(2):136

• 5 patients with post-op liver failure and “MOF”
• 13.4±1.9 treatments were undertaken
• FFP and platelets given to maintain levels
• Significant fall in Bilirubin
• No falls in ammonia
• Increased transfusion requirements, bleeding
• Severe abdominal infection
• All patients died
• Worsening coagulation parameters (APTT)

Doria et al Clinical transplantation 2004;18:365
Extra-Corporeal Liver Assist Device (ELAD)

- Human Hepatoblastoma cell line (C3A)
- Cell Mass 400g
- Extra-capillary space of hollow-fibre dialysis cartridges
- Whole blood perfusion; ultrafiltration across cells
- 80% survival (vs. 0%) in Animal Models
- Encouraging case series
Clinical Trials

Ellis et al Hepatology 1996;24:1446-51

- RCT
- ALF patients
- Group 1; n=17; 30-50% chance of recovery
- Group 2; n=7; 10% chance of recovery
- Median duration of Rx; 62 hours
- Examined safety, efficacy
Clinical Trials

• Safety
  – No change in MAP
  – Mild thrombocytopenia
  – 1 case of ? Tachyphalaxis
  – 1 case of DIC
Clinical Trials

• Function
  – Ammonia; no differences
  – Lactate; no differences
  – Bilirubin; no differences
  – Factor V; no differences
  – GEC; higher in ELAD group
  – Progression of encephalopathy;
    • 3/12 ELAD 7/12 Controls (p=0.09)
Clinical Trials

Fig. 1. Survival figures for ELAD-treated and control patients in Group 1 and Group 2.
Clinical Trials

- ELAD
  - Laudable trial
  - Safe
  - No clinical/biochemical benefits
  - Extensive subsequent modifications
  - 1 Further abstract report (2000)
    - Uncontrolled observations in 4 patients
  - Company bankrupt
  - Relaunched
• Human hepatoblastoma cell line (C3A)
• Grown to confluence in the extracapillary compartment of a hollow fibre filter
• Venous-venous access, No oxygenator
• Blood pumped through the lumen of the bioreactor hollow fibre
• Microfiltrate re-infused
• Continuous system
Blood Lactate during Treatment with ELAD

Ellis et al, Hepatology 1996; 24: 1446-1451

No difference for: Bilirubin, AKBR, INR, factor V, galactose clearance, NH4

Hepatoblastoma cell line: new system developed but not available