Extracorporeal therapies in advanced liver disease: A review of current and future technologies

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10th IFSA Congress/13th Congress de la Asociación Mexicana de Medicina Transfusional
Cancun, Mexico
14 May 2015
Disclosures:

- Baxter Healthcare Acute Therapies Institute (paid consultant)
- I will discuss off-label use of therapy
Objectives:

- Develop a conceptual understanding of liver failure
- Define a rationale for use of extracorporeal therapy in liver failure
- Review current technologies
- Review emerging liver support technologies
Liver failure *types*:

- Acute liver failure
- Acute-on-chronic liver failure
- Cirrhosis
  - Compensated disease
  - Decompensated disease (end-stage)
Acute Liver Failure:

Most widely accepted definition is as follows:

- Coagulopathy (usually INR >1.5)
- Any degree of encephalopathy
- Patient without pre-existing liver disease or cirrhosis
- Duration of illness <26 weeks
- Exceptions:
  - Wilson disease
  - HBV and AIH
Acute Liver Failure:

• Severe systemic inflammatory response
• Cerebral edema leading to herniation
• Multisystem organ failure
• Recovery
• Transplant or death

*e.g.* Acetaminophen toxicity
2000 Patients enrolled  
761 (38%) listed

Spontaneous survivors  
N=864 (43%)

Transplanted  
N=482 (24%)

Died (Not Transplanted)  
N=654 (33%)

Alive  
N=410 (85%)

Died  
N=72 (10%)

Overall survival:  N=1274 (64%)

Data: United States Acute Liver Failure Study Group
Acute on chronic liver failure:

AASLD-EASL Working Definition

“Acute deterioration of pre-existing, chronic liver disease usually related to a preceding event and associated with increased mortality at three months due to multi-system organ failure”
Cirrhosis

Natural History

ACLF

Deranged inflammatory response

Multi-organ dysfunction/failure

Death

Recovery

Prevention

transplant

Death

Liver support?
Early Transplantation?

Olson and Kamath (2011) Current Opinion in Critical Care 17: 165-9
Key concept: Reversibility

Olson and Kamath (2011) *Current Opinion in Critical Care* 17: 165-9
Decompensation of cirrhosis:

• Progressive
• Once established, cirrhosis is essentially irreversible
• Transplant only “curative” therapy
  e.g. Hepatitis C Virus, alcohol, primary sclerosing cholangitis
Prevalence of Cirrhosis in the US

- 0.27% corresponding to 633,323 adults
- 69% were unaware of having the disease
- 30,000 diagnoses per year at tertiary referral centers

Scaglione et al., J Clin Gastroenterol (2014); epub ahead of print
# 20 leading causes of death worldwide

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>Deaths (000s)</th>
<th>% deaths</th>
<th>Deaths per 100,000 population</th>
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<tr>
<td>0</td>
<td>All Causes</td>
<td>55859</td>
<td>100.0</td>
<td>789.5</td>
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<td>Ischaemic heart disease</td>
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<td>13.2</td>
<td>104.0</td>
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<td>2</td>
<td>Stroke</td>
<td>6671</td>
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<td>Chronic obstructive pulmonary disease</td>
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<td>43.9</td>
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<td>Lower respiratory infections</td>
<td>3052</td>
<td>5.5</td>
<td>43.1</td>
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<tr>
<td>5</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1600</td>
<td>2.9</td>
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<td>6</td>
<td>HIV/AIDS</td>
<td>1534</td>
<td>2.8</td>
<td>21.7</td>
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<tr>
<td>7</td>
<td>Diarrhoeal diseases</td>
<td>1498</td>
<td>2.7</td>
<td>21.2</td>
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<td>Diabetes mellitus</td>
<td>1497</td>
<td>2.7</td>
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<td>9</td>
<td>Road injury</td>
<td>1255</td>
<td>2.3</td>
<td>17.7</td>
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<td>10</td>
<td>Hypertensive heart disease</td>
<td>1141</td>
<td>2.0</td>
<td>16.1</td>
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<tr>
<td>11</td>
<td>Preterm birth complications</td>
<td>1135</td>
<td>2.0</td>
<td>16.0</td>
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<tr>
<td>12</td>
<td>Cirrhosis of the liver</td>
<td>1021</td>
<td>1.8</td>
<td>14.4</td>
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<tr>
<td>13</td>
<td>Tuberculosis</td>
<td>933</td>
<td>1.7</td>
<td>13.2</td>
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<td>Kidney diseases</td>
<td>864</td>
<td>1.6</td>
<td>12.2</td>
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<td>Self-harm</td>
<td>804</td>
<td>1.4</td>
<td>11.4</td>
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<td>16</td>
<td>Birth asphyxia and birth trauma</td>
<td>744</td>
<td>1.3</td>
<td>10.5</td>
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<td>17</td>
<td>Liver cancer</td>
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<td>1.3</td>
<td>10.5</td>
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<td>Stomach cancer</td>
<td>733</td>
<td>1.3</td>
<td>10.4</td>
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<tr>
<td>19</td>
<td>Colon and rectum cancers</td>
<td>724</td>
<td>1.3</td>
<td>10.2</td>
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<tr>
<td>20</td>
<td>Alzheimer's disease and other dementias</td>
<td>701</td>
<td>1.3</td>
<td>9.9</td>
</tr>
</tbody>
</table>

Liver Transplantation

- United States:
  - 15,272 individual patients on wait list
  - 6,729 transplants performed in US
- Worldwide
  - ~20,000 +/- liver transplants

Source: UNOS Database
10,000 defined biological functions
• Metabolism and nutrition
• Coagulation
• Drug metabolism
• Immune modulation
Results of advanced liver disease:
Rational need for liver support:

- Significant worldwide disease burden
- Leads to significant loss of life
- Dramatic decrease in quality of life
- Few treatment options
Liver Failure

- Acute Liver Failure
  - Bridge to spontaneous recovery
  - Toxin Removal
  - Bridge to transplant

- ACLF
  - Temporary stabilization?
  - Bridge to transplant

Extracorporeal Liver Support
Is there a role in decompensated cirrhosis?

• Symptom relief?
  • Intractable pruritus
  • Hepatic encephalopathy
• Bridge to transplant??
• Lifelong support-doubtful
Application of extracorporeal therapy in liver disease

- To remove toxins
- Removal of metabolites
- Stabilization of biochemistry
- Metabolic functions
Extracorporeal therapy in liver disease

• Artificial liver support
  • Small molecules, albumin bound compounds, ion exchange
  • e.g. MARS®
• Bioartificial liver (the *ideal* system)
  • All of the above
  • Metabolic removal of waste, synthetic functions
  • e.g. ELAD®, SRBAL
Review of current technologies:
Molecular Adsorbent Recirculating System—MARS®

- Artificial support
- Recirculated albumin
  - Ion exchange cartridge
  - Charcoal cartridge
- FDA Approved in US
MARS® Therapy

Diagram of MARS® Therapy:
- MARS® Flux Dialyzer
- DiaMARS® Adsorption Columns
- DiaFlux Dialyzer

Patient, Blood Circuit, MARS® Albumin Circuit, Dialysate Circuit
Blood is dialyzed of water and protein-bound toxins by albumin dialysate. Albumin dialysate goes first to CRRT for removal of water-soluble toxins, such as ammonia and creatinine, with CVVHDF. Remaining protein-bound drugs and toxins are removed in the charcoal adsorber, while bilirubin is retained in the ion exchanger-resin. Regenerated albumin is recirculated back through MARS FLUX.
Table 1. Removal of Substances During Albumin Dialysis MARS

<table>
<thead>
<tr>
<th>Albumin-Bound Substances</th>
<th>Water-Soluble Substances</th>
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<tbody>
<tr>
<td>Benzodiazepines*†</td>
<td>Ammonia</td>
</tr>
<tr>
<td>Bilirubin, conjugated</td>
<td>Aromatic amino acids</td>
</tr>
<tr>
<td>Bilirubin, unconjugated</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Bile acids</td>
<td>Interleukin 6</td>
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<tr>
<td>Copper</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>Furancarboxylic acid</td>
<td>Tumor necrosis factor alpha</td>
</tr>
<tr>
<td>Indoyxlsulfate</td>
<td>Urea</td>
</tr>
<tr>
<td>Middle- and short-chain fatty acids</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Para-cresol†</td>
<td></td>
</tr>
<tr>
<td>Protoporphyrin</td>
<td></td>
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</tbody>
</table>

Treatment Regimen

- FDA approved for treatment of:
  - (1) ALF due to drugs or toxins
  - (2) Advanced Hepatic Encephalopathy in ACLF

- 8 hours of MARS therapy / day for 3 consecutive days.

- **Albumin dialysate**: 600 ml of 16 % albumin (400 ml of 25% albumin + 200 ml of normal saline)

- Exchange of MARS cartridges after every treatment session

- May continue CRRT portion of circuit after completion of MARS therapy (sodium & ammonia homeostasis)

- Heparin or **citrate** anticoagulation
Beneficial Effects of MARS (*Case reports/series*)

- Improvement of jaundice and pruritis
- Improvement of hemodynamic instability (NO removal?)
- Reduction in portal pressure
- Reduction in ICP in ALF, and hepatic encephalopathy in ACLF
- Improvement of renal function in HRS

*MARS effect on bioavailability of highly protein bound drugs* (including NAC) awaits further study
Plasmapheresis

- Accepted roles in some liver related disease states (e.g. cryoglobulinemia)
- Completed trials in acute liver failure
- Pending multi-national trial in Acute-on-Chronic Liver Failure
Future Technologies
Extracorporeal Liver Support Device--ELAD®

- Bioartificial liver
- C3A hepatoblastoma cell line
- May provide functions of primary hepatocytes
- In phase 3 trials
ELAD System
ELAD Circuit

440 g (~30% liver mass)

Metabolic Support
Glucose & Oxygen

ELAD

ELAD

ELAD

Cartridge Pump

Ultrafiltrate Pump

Ultrafiltrate Generator

Cell Filter

Blood Pump

Heparin Infusion

KU MEDICAL CENTER
The University of Kansas
ELAD Cartridges

- 4 ELAD Cartridges (Bioreactors):
  - Hollow fibers (#8000/cartridge)
  - Pore 0.2µm (allowing exchange of toxins and proteins)
  - 440g Immortalized human C3A liver hepatocytes (Subclone of HepG2 human hepatoblastoma cell line)
ELAD C3A Cells

Allogeneic Cell Therapy

- C3A hepatocytes divide to fill available extra-capillary space in the cartridges
- Plasma flows through semipermeable hollow fibers
  - **Bidirectional diffusion** between UF and C3A cell
- Toxins processed and metabolites secreted across membrane to UF
ELAD Cell Therapy

- **Human:** no animal or safety issues identified
- **Stable:** can be stored, grown in unlimited quantities and shipped worldwide with minimal bedside preparation
- **Immortal:** Retain hepatocyte functions
ELAD Cell Function

---Theroretically retain the function of primary hepatocytes

- Process toxins / metabolites
- Consume large amounts of $O_2$ and glucose
- Active P-450 enzyme system
- Synthesize liver proteins including AFP
ELAD Cell Function: Protein Synthesis

- Albumin
- α-Fetoprotein
- α-1-Antichymotrypsin
- α-1-Antitrypsin
- C3 Complement
- HGF
- Antithrombin III
- Factor V
- Fibrinogen
- Transferrin
- Factor VII
- TGF-α
Spheroid Reservoir Bioartifical Liver—SRBAL

- Bioartifical liver
- Primary porcine hepatocytes
- Experimental trials in pig models of acute liver failure
- Impressive success
Spheroid Reservoir Bioartificial Liver

- Spheroids overcome limitations
  - Stable viability
  - Excellent functionality
  - Increased mass (up to 400g)

Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN
Spheroid Reservoir Bioartificial Liver (SRBAL)

Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN
Results: Survival

Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN
Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press
Results: Survival

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Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press
Results: Survival

- **Standard therapy**
- **ST+No cell BAL**
- **ST+SRBAL**

% survival vs. Hours after D-gal:

- p = 0.01
Results: Intracranial Pressure

- T = 48hrs
- Peak
- Death

<table>
<thead>
<tr>
<th></th>
<th>Standard therapy</th>
<th>ST+No cell BAL</th>
<th>ST+SRBAL</th>
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</thead>
<tbody>
<tr>
<td>mmHg</td>
<td>27</td>
<td>22</td>
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Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press
Results: Intracranial Pressure

<table>
<thead>
<tr>
<th>Time</th>
<th>ST+No cell BAL</th>
<th>ST+SRBAL</th>
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<tr>
<td>T=48hrs</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Peak</td>
<td>39</td>
<td>30</td>
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<tr>
<td>Death</td>
<td>22</td>
<td>30</td>
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</tbody>
</table>

Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN
Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press
Results: Intracranial Pressure

- **T = 48hrs**
  - Standard therapy: 14 mmHg
  - ST+No cell BAL: 22 mmHg
  - ST+SRBAL: 30 mmHg

- **Peak**
  - Standard therapy: 27 mmHg
  - ST+No cell BAL: 39 mmHg
  - ST+SRBAL: 14 mmHg

- **Death**
  - Standard therapy: 30 mmHg
  - ST+No cell BAL: 30 mmHg
  - ST+SRBAL: 7 mmHg

*Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press*
Results: Pig Plasma Ammonia Levels

Slide and data courtesy of Scott Nyberg, M.D., Ph.D. Mayo Clinic Rochester MN
Glorioso JM, Nyberg, SL, et al., Journal of Hepatology in press
THANK YOU!