Workshop
The Liver and the Kidney - 2

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Liver support

- Synthesis
- Regulation
- Detoxification

Liver cells
- albumin
- amino acids
- glucose, lipids
- coagulation factors
- unknown substances

Adsorber
- ammonia
- bilirubin
- endotoxins
- aromatic amino acids
- toxins
- acid-base-status
- electrolytes
- amino acids
- CNS energy supply
- CNS transmitter precursors
Renal support

Dialysis therapies

- Peritoneal dialysis
- Intermittent HD/HF/HDF
- Hybrid techniques
- CAVHF
- CVVHF
- CVVHF high volume
  - plasma exchange
Peritoneal dialysis

**Acute or AonCLD**

- **advantage**
  - no anticoagulation
  - glucose based

- **disadvantages**
  - clearance
  - fluid balance
  - hyponatraemic
  - changes in cardiac filling
Cerebral perfusion during PD

MAP mmHg

- epinephrine
- norepinephrine
- GTN
- colloid

- fixed dilated pupils
- cardiac arrest & death

CCPD

2 l cycles

0 4 8 12 16 time (hrs)
Peritoneal dialysis

CLD

- awaiting transplantation
  - risk of peritonitis ?
  - splenic vein thrombosis

- not for transplantation
  - no increased infection risk
  - no increased protein losses
Cerebral edema
Start of hemodialysis

During hemodialysis

End of hemodialysis

### capillary
- **urea**
- **↓↓↓↓ urea**
- **↓↓ osmolality**

### CSF
- **urea**
- **↓↓ urea**
- **↓ osmolality**

### brain
- **urea**
- **↓ urea**
- **↑ idiogenic osmoles**
- **↑ osmolality**

### Water Flow
- **H₂O**
- **H₂O**
Brain water post hemodialysis

Measured brain water L/kg dry wt

uremic controls slow fast urea hemodialysis high Na

dogs 2 hrs hemodialysis plasma urea 72→24 mmol/l
* p < 0.05

gray matter white matter

Arieff et al KI 1973
Ammonia clearance

Arterial NH₃ ug/l

CVHHF

SJUH
45 yr pt
Acetaminophen
CVVHF
1.5 /h
65 yr pt
4 hr HD
CLD
CVVH for acute liver failure

Matsubara et al CritCareMed 1990

HPLC elution profile

plasma

filtrate

Tohoku Univ Sendai, Japan
ALF
CVVH
Polysulfone 0.6m²
500-600 ml/min
Nafamostat 30-40 mg/h
Apnoeas during haemodialysis

DeBacker et al AmRevRespirDis 1987

Cumulative no of apnoeas

Duration of haemodialYSIS (min)
During dialysis, the concentration of $\text{HCO}_3^-$ in the capillary increases, leading to a decrease in pH. The bicarbonate is converted into water and carbon dioxide, resulting in a decrease in pH in the brain. The increase in pH causes an increase in $\text{H}^+$ and idiogenic osmoles.
Changes in ICP with HD

MAP mmHg

ICP mmHg
Change in ICP with falling MAP

Time min

ICP mmHg

ABP mmHg

SJO₂ % ICP mmHg

13.02 13.04 13.06
CVVH vs intermittent HD

John et al Nephrol Dial Transplant 2001

Univ Frankfurt
Univ Erlangen
Nürnberg
30 pts septic shock AKI
PS/heparin
Qb 250 ml/min mean (SD)
* p < 0.05

Change in Systolic BP mmHg

CVVHF
2 l/h lac

4 h HD bie
UF 0.25-0.5 l/h

Baseline 0.5 2 4 24
time hr
DYYNAMICS OF BLOOD VOLUME RESPONSE

BV (%) vs time (min) for different UFR values:

- UFR = 2 l/h
- UFR = 0.85 l/h
- UFR = 0.3 l/h

Lopet et al. Hemodial Int 2000
Slope RBV with UF

![Graph showing RBV and UFR over time with Na values 136, 142, and 147 marked on the graph.](image-url)
CRRT for acute liver failure

Mean ICP mmHg

0   4    8  12  16  20 24 28  32  36 40  44 48 52 Time h

0
5
10
15
20
25
30

24 yr old pt acetaminophen CVVHF 1.5 /h

CVVHF
RBV change %

treatment time (mins)

ACTUAL BV (%)

DESIRED BV (%)

UF rate l/h

UF rate
Biofeedback controlled HD - Hemocontrol

Objective

Actual value

Upper tolerance

Lower tolerance

Ideal trajectory
Sudden catastrophic hypotension

MAP mmHg

duration of treatment min

pre 2 4 6 8 10 12

SJUH
10 pts sham CVVH PAN 69 mean
Cardiac perfusion

Chesterton LJ et al. Hemodial Int 2009
Hothi MD thesis UCL 2009
Elapsed time

Oxygen saturation %

Jones et al. Nephrol Dial Transplant 1992
Hypersensitivity reaction

Blood - membrane interaction

Diluted Blood - Membrane interaction

Patient acidosis

Rinsing solution (pH, buffer, dilution)

Dialysate

Composition (acetic acid ...)

Bacterial contamination exotoxins

Water treatment system

Heparins
Plasma kallikrein activity kinetics with AN69 membrane: Influence of diluted plasma pH

Plasma Kallikrein (UKK/l)

- pH = 7.2
- pH = 7.4
- pH = 7.6
- pH = 7.8

Time (min)
Heparin reactions

- Very charged membrane

C3a ← C3
C5a ← C5
bradykinin
HMW+ kininogen

plasma kallikrein

plasma prekallikrein

Contact coagulation pathway

XI
XII
XIIa
XIa
Cirrhotic cardiomyopathy

Osmotic demyelination syndrome

Central pontine myelinosis

Image from WebPath, courtesy of Edward C. Klatt MD, Florida State University College of Medicine.
Recovery of Brain Osmolytes

A patient with serum sodium 101 mEq/L
10 days after correction of hyponatremia
2 months after correction of hyponatremia

Haussinger, Gastroenterology 1994;107:1475-1480
Correction of hyponatraemia


Serum sodium mmol/l

CAVHF

Birmingham adult F CLF

time days
Extracorporeal liver support

CRRT

• homeostasis
  ♦ electrolytes
  ♦ acid–base
  ♦ fluid balance
  ♦ cardiovascular stability
Liver failure

- hydrophilic toxins
  - Ammonia

- lipophylic or hydrophobic toxins
  - Protein bound
Albumin Infusion prevents Renal Failure in patients with *Spontaneous Bacterial Peritonitis*

Sort et al. NEJM, 1999, 126 patients with SBP
Antibiotics vs Albumin+Antibiotics in SBP

**RENAL IMPAIRMENT**
- Cefotaxime alone: 21 (33%)
- Albumin + Cefotaxime: 6 (10%)  \( p<0.002 \)

**Mortality (In hospital)**
- Cefotaxime alone: 18 (28%)
- Albumin + Cefotaxime: 6 (10%)  \( p<0.01 \)
Why albumin?

albumin binds
  • nitric oxide
  • hormones

• Liver Failure
  - aromatic amino acids
  - bilirubin
  - bile acids
  - copper
  - free fatty acids
  - indoles
  - mercaptans
  - phenols
Detoxification Efficiency

Healthy Control
MODS, Sepsis
Liver Failure

DTE (%)
Albumin “Dialysis”

Open loop circuit

Thermodynamic limitation
Non selective losses
Costs

Plasma exchange
SPAD

Closed loop circuit

Equilibrium limitations
Effective perfusion time

MARS™
Prometheus™
Single pass albumin dialysis

**RESULT**

+ elimination of albumin bound toxins
+ Substitution: pathological modified & inadequately synthetised albumin

(+) No elimination of water soluble toxins
- No synthesis, metabolism, biotransformation or immunity
Single pass techniques

SPAD

PE+HD

no trial data

abstract (Heidelberg - Paed Nephrol 2009)

9 children

3 Rx MARS all died

4 Rx PE & HD 75% survived
High volume CRRT and daily PE

Yokai et al
Transfusion Apheresis 2009


table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow rate</td>
<td>200-250 ml/min</td>
</tr>
<tr>
<td>Plasma removal rate</td>
<td>500-700 ml/hr</td>
</tr>
<tr>
<td>FFP infusion rate</td>
<td>500-700 ml/hr</td>
</tr>
<tr>
<td>Dialysate flow rate</td>
<td>300-500 ml/min</td>
</tr>
<tr>
<td>Ultrafiltration rate</td>
<td>200-500 ml/hr</td>
</tr>
</tbody>
</table>

chart:

- Acute:
  - Non-HFCHDF (n=18): 50.0%
  - HFCHDF (n=27): 40.7%
  - n.s.

- Subacute:
  - Non-HFCHDF (n=21): 4.8%
  - HFCHDF (n=17): 23.5%
  - n.s.

- Total:
  - Non-HFCHDF (n=39): 25.6%
  - HFCHDF (n=44): 34.1%
  - n.s.
Is all albumin equal?

Stange et al

- Albumin binding capacity %
  - globulin and fatty acid free HSA
  - serum preparation
  - HSA (with stabilizers)
  - HSA after deligandization
blood flow

60 kD cut off

albumin dialysate

anionic resin

activated charcoal

high flux dialyzer

MARS™

spent dialysate

fresh dialysate + glucose

fresh dialysate + glucose

spent dialysate

neutral resin

anionic resin

high flux dialyzer

Prometheus™

SC albumin 0.6
MARS in hyperacute liver failure

Schmidt et al. Liver Transplant 2003

Rigshospitalet Copenhagen
13 pts ALF
8 MARS single Rx
5 cooled controls (ice packs)
mean * p < 0.05
Rigshospitalet
24 patients
cirrhosis

<table>
<thead>
<tr>
<th>MAP mmHg</th>
<th>Pre Rx</th>
<th>Post Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>75.2 ±7</td>
<td>76.6 ±5</td>
</tr>
<tr>
<td>MARS</td>
<td>68.9 ±4</td>
<td>78.1 ±5*</td>
</tr>
<tr>
<td>Prometheus</td>
<td>74.0 ±4</td>
<td>74.4 ±5</td>
</tr>
</tbody>
</table>

Dethloff et al WorldJGastroenterol 2008
**MARS in acute liver failure**

**Non randomised**

<table>
<thead>
<tr>
<th>survival</th>
<th>MARS</th>
<th>Standard Medical Rx</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>with OLTx</td>
<td>94%</td>
<td>77%</td>
<td>p=0.06</td>
</tr>
<tr>
<td>No OLTx</td>
<td>66%</td>
<td>40%</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Death due to cerebral herniation</td>
<td>4%</td>
<td>18%</td>
<td>p=0.014</td>
</tr>
</tbody>
</table>
## MARS trial vs SMT

*Hassanein et al Hepatol 2007*

<table>
<thead>
<tr>
<th></th>
<th>1-5 days</th>
<th>6-10 days</th>
<th>11-180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMT</strong></td>
<td>5 (16%)</td>
<td>2 (8%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td><strong>MARS+SMT</strong></td>
<td>5 (13%)</td>
<td>4 (12%)</td>
<td>10 (33%)</td>
</tr>
</tbody>
</table>
## FULMAR study – French multicentre

<table>
<thead>
<tr>
<th>mortality</th>
<th>MARS</th>
<th>Medical Rx Supportive</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>8/53</td>
<td>12/49</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>POD</td>
<td>3/20</td>
<td>6/10</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
189 patients randomised to MARS (95) vs SMT (94)
Bilirubin > 5 mg/dl AND hepatic encephalopathy II-IV or HRS
or bilirubin > 20 mg/dl
Early drop out
19 MARS 4 SMT
Precipitant of AonCLF
SBP 16.4% MARS vs 7.1% SMT (p=0.05)
HELIOS trial  (Prometheus AonCLF)

- 145 patients randomised to Prometheus (77) vs SMT (68)
- 8-11 Prometheus 4 hour treatments
- 56% EtOH 20% viral hepatitis

Sub group Analysis possible benefit
HRS type 1 MELD >30
p=0.04
The UCL Liver Dialysis Device
Incorporates Endotoxin removal + Albumin Exchange

Subject
In Vitro plasma
Pig
Patient

Additional Albumin Infusion

Albumin Rich Dialysis Soln.

ENSOS membrane

P2SX

Albumin Dialysis

Dialysate

Waste

Plasma Flow
Risk
Bleeding vs Clotting

Do liver failure patients need to be anticoagulated?
<table>
<thead>
<tr>
<th>Liver synthesis</th>
<th>Liver synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro-coagulant vs Anticoagulant</strong></td>
<td><strong>Pro-coagulant vs Anticoagulant</strong></td>
</tr>
<tr>
<td>Natural anticoagulants</td>
<td>Clotting factors</td>
</tr>
<tr>
<td>- Antithrombin</td>
<td>- Complement</td>
</tr>
<tr>
<td>- Proteins S &amp; C</td>
<td>- Fibrinogen</td>
</tr>
<tr>
<td>- Heparin CoF-II</td>
<td>- PAI-1</td>
</tr>
</tbody>
</table>
CRRT circuit life

**groups**

- **liver**
  - ALF
  - AonCLD
  - post LTx

- **controls**
  - systemic sepsis
  - haematological malignancy
CRRT circuit life

- Haem
- ALF
- CLD
- LTx
- SS
Number of CRRT circuits in 48 hrs

- Haem
- ALF
- CLD
- LTx
- SS

* indicates significant difference.
Anticoagulation?

![Bar chart comparing none and anticoagulation]
<table>
<thead>
<tr>
<th>TEG</th>
<th>ALF</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R time min</strong></td>
<td>12.1 (9-28)</td>
<td>14 (10.8-20)</td>
</tr>
<tr>
<td><strong>K time min</strong></td>
<td>5.2 (3.0-22.5)</td>
<td>5.6 (4.9-13.1)</td>
</tr>
<tr>
<td><strong>angle</strong></td>
<td>40 (13-56)</td>
<td>35.7 (24.2-42.6)</td>
</tr>
<tr>
<td><strong>Max Ampl mm</strong></td>
<td>41.2 3.6</td>
<td>51.6 4.6</td>
</tr>
<tr>
<td><strong>G dyne/s</strong></td>
<td>4.2 0.6</td>
<td>6.2 0.9</td>
</tr>
<tr>
<td><strong>EPL %</strong></td>
<td>0(0-0.15)</td>
<td>0 (0-0.05)</td>
</tr>
<tr>
<td>Thrombin generation</td>
<td>ALF</td>
<td>Sepsis</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>ETP</td>
<td>1033 111</td>
<td>1355 86*</td>
</tr>
<tr>
<td>peak</td>
<td>154 16</td>
<td>239 25 **</td>
</tr>
<tr>
<td>Time to peak</td>
<td>5.0 0.4</td>
<td>5.4 0.3</td>
</tr>
<tr>
<td>slope</td>
<td>68.4 8</td>
<td>110 16*</td>
</tr>
<tr>
<td>ETP (MP)</td>
<td>949 121</td>
<td>1267 85*</td>
</tr>
</tbody>
</table>
Anticoagulants for ALF and AonCLD

Options depend upon institution

- **Japan**
  - nafamostat maleate

- **Europe**
  - prostanoids
  - citrate
  - heparin

- **USA**
  - heparin
  - citrate
acknowledgements

• Sherlock Hepatobiliary, pancreatic & Liver Transplantation Unit
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  - D Thorburn
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  - J Dooley
  - M Singer
  - B Agarwal
  - S Shaw