Workshop
The Liver and the Kidney

Professor Rajiv Jalan
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Renal dysfunction of Cirrhosis

• Classical HRS
  – Hemodynamic derangements in Cirrhosis
  – Pathophysiological basis of Classical HRS
  – Approaches to therapy

• Pathophysiological basis of renal dysfunction in Acute on Chronic Liver Failure
  – Hemodynamics and renal failure

• Role of Albumin
  • Liver Dialysis Device: Beyond MARS
Pathophysiology of Renal Dysfunction in cirrhosis

Severity of Liver Disease

Severity of Circulatory Disturbance

CLINICAL SYNDROME

- Pre-ascitic
- Diuretic responsive ascites
- Refractory ascites
- Hepatorenal Failure
HEPATOrenal SYNDrome

**TYPE 1:**
Doubling of initial creatinine to > 2.5 mg/dl or reduction in GFR by 50% in 2 weeks

**TYPE 2:**
The renal failure does not have a rapidly progressive course
HEPATOrenal Syndrome

Evidence for a Functional Disorder

- Histology by biopsy or autopsy: Normal
- Liver transplantation
- Kidney donation
- Postmortem renal arteriogram
PERIPHERAL VASODILATION HYPOTHESIS OF ASCITES AND RENAL DYSFUNCTION

CIRRHOSIS

Portal Hypertension

Splanchnic Arterial Vasodilation

Reduced Effective arterial Blood Volume

Activated Vasoconstrictor systems

Vasoconstriction of Extrasplanchnic Vascular Beds

Renal Vasoconstriction

Activation of renal vasodilators

Maintained renal perfusion

Imbalance of vasoactive factors

HEPATORENAL SYNDROME
Cardiac Output and Systemic Vascular Resistance

Renal Blood Flow and Resistive Index

Whole body Nitric Oxide production in Cirrhosis

Jalan et al. Unpublished
## Chronology of Circulatory Disturbances

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-asc.</th>
<th>Refractory ascites</th>
<th>HRS</th>
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</thead>
<tbody>
<tr>
<td><strong>Noradrenaline</strong></td>
<td>1.4 (0.3)</td>
<td>1.1 (0.4)</td>
<td>2.9 (0.4)*</td>
<td>5.9 (0.3)**</td>
</tr>
<tr>
<td>(nmol/ml)</td>
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<tr>
<td><strong>Angiotensin II</strong></td>
<td>3.2 (0.9)</td>
<td>45.4 (7.2)*</td>
<td>235 (30)**</td>
<td>342 (43)*****</td>
</tr>
<tr>
<td>(pg/ml)</td>
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<tr>
<td><strong>Endothelin-1</strong></td>
<td>1.9 (0.4)</td>
<td>2.3 (0.5)*</td>
<td>5.3 (0.4)*****</td>
<td>11.2 (0.3)*****</td>
</tr>
<tr>
<td>(pg/ml)</td>
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</tbody>
</table>

Severity of portal hypertension and renal blood flow

Hepatorenal Reflex

Renal Blood Flow and Portal Pressure

Shunt occluded

Shunt released

Renal Blood flow (ml/min)

Time (min)

Jalan et al Gut 1997;40:664-70
Renal Blood Flow
Autoregulation is disturbed in Cirrhosis

Gastroenterology, 2008
‘Resetting’ of Renal Blood Flow autoregulation by TIPSS

Gastroenterology, 2008
SUMMARY

Pathophysiologcal Mechanisms

- Splanchnic Vasodilation: ? NO related
  - Consequent activation of neurohumoral systems
- Renal Vasoconstriction
- Portal Hypertension
- Altered Renal Blood Flow Autoregulation
PERIPHERAL VASODILATION HYPOTHESIS OF ASCITES AND RENAL DYSFUNCTION

- CIRRHOSIS
  - Portal Hypertension
  - Splanchnic Arterial Vasodilation
  - Reduced Effective arterial Blood Volume
  - Activated Vasoconstrictor systems
- Vasoconstriction of Extrasplanchnic Vascular Beds
- Renal Vasoconstriction
  - Activation of renal vasodilators
  - Maintained renal perfusion
- Imbalance of vasoactive factors
- HEPATORENAL SYNDROME

Liver Support
- TIPSS
- Vasopressors
- albumin
- ET antagonists/NO donors

Liver Support
Brensing et.al Gut 1997

- Improvement in renal function
- Reduced need for haemodialysis

But

- Mortality remained high

? Because of worsening in
  - Liver Function
  - Cardiovascular Haemodynamics
Vasopressin analogue, Terlipressin in cirrhosis

Mean arterial pressure: +21%
Systemic Vascular Resistance: +61%
Portal Pressure: -17%
Renal Blood Flow: +17%
Hepatic Blood Flow: -29%
Terlipressin in HRS, Type 1
Moreau et al. Gastro 2002;123:2160

99 patients, retrospective, 24 centres, Rx: 12 days

• Renal Function
  – Creatinine - 46%
  – Creatinine <130umol/L or decrease > 20% 58%

• Survival
  – Median 21 days
  – 13 patients underwent OLT

13 patients with ischemic side-effects
Terlipressin vs Placebo in HRS-1
Solanki et al. J Gastro Hep 2003;18:152-156

24 patients, randomised, End-point: survival at 15 days

• Renal Function
  – Creatinine (day 8), p<0.05
    • Placebo 390umol/L
    • Terlipressin 160umol/L

• Survival (day 15), p<0.05
  • Placebo 0/12
  • Terlipressin 5/12

5/12 patients with ischemic side-effects
Midodrine+Octreotide+Albumin v IV Dopamine  
(Angeli et al. Hepatology 1999;29:1690-7)

- **13 patients with HRS-Type 1, non-randomised**

- **Renal Function**
  - Dopamine: Persistent HRS in 8/8
  - Midodrine: Recovered to allow discharge in 3/5

- **Survival**
  - Dopamine: 1/8 (transplant)
  - Midodrine: 3/5 (2 transplant)
Noradrenaline+Frusemide+Albumin (Duvoux et al. Hepatology. 2002;36:374-80)

- 12 patients, NA (0.5-3mg/h) for 10 days, HRS, Type 1

- **Renal Function**
  - Creatinine Pre: 356 Post: 145 p<0.001
  - Reversal of HRS in 10/12 patients

- **Survival**
  - Median 29 days
  - Overall 4/12 (1 transplant)
The obvious next step is to combine...........

**Vasoconstrictor**: Increase renal perfusion pressure (*Midodrine*)

**Reduce Splanchnic Vasodilation**: Increase Blood Pressure (*Octreotide*)

**Increase Circulating Volume** (reduce sympathetic drive): *Albumin*

**Reduce Oxidative Stress**: *Albumin*

**Reduce Portal Pressure**: *TIPSS*

**Shift Autoregulation curve to the left**: *TIPSS*

Wong et al. Hepatology, 2004
Fig. 1. Clinical course of the 14 patients who were enrolled in the study. M, months.
Fig. 2. Serum creatinine in both the responders and the nonresponders during the medical treatment phase. *$P < .05$ versus pretreatment; $\#P < .01$ versus pretreatment. Non-R, nonresponders.
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Acute Deterioration of ‘Stable Cirrhosis’ vs Chronic Decompensation

The Clinical Concept

Acute Insult

Threshold for organ failure

?Too late!

Elements of Working Definition of Acute-on-Chronic Liver Failure

- Acute deterioration of Cirrhosis over a defined period: upto 3 mo.
  - Defined Precipitant: Hepatic/Non-Hepatic
  - Deterioration despite specific intervention to treat precipitating factor
  - Presentation with Organ Failure
    - Organ Failure (one or more)
      - High Bilirubin
      - Renal Failure
      - Severe Hepatic Encephalopathy

Subclassification
- Type 1: Those that have decompensated liver disease prior to current presentation
- Type 2: Those that were previously well-compensated

Prognosis: Determined by SOFA score

Jalan and Williams. Blood Purification, 2002
In-hospital mortality: 53%
Deaths related primarily to Liver Failure
Time from organ failure to death: 10 days (1-40)
What are the haemodynamic characteristics of ACLF?

Clinical
Biochemical
Cytokines
Haemodynamics
Swan/HVPG/Hepatic Blood Flow

Molecular Targets for diagnosis and treatment
Endotoxin Albumin
Ammonia Cytokines Albumin
ADMA Nitric Oxide
Oxidative Stress Albumin
Nitric Oxide Albumin
Relationship between HVPG and Cardiac output

![Graph showing the relationship between HVPG and Cardiac output. The graph includes data points for compensated, decompensated, and ACLF states.]
Relationship between HVPG and HBF

- Compensated
- Decompensated
- ACLF
Relationship between HBF, HVPG and Noradrenaline levels
Model for End-Stage Liver Disease Score and Systemic Inflammatory Response Are Major Prognostic Factors in Patients with Cirrhosis and Acute Functional Renal Failure

Dominique Thabut,^1^ Julien Massard,^1^ Alice Gangloff,^2^ Nicolas Carbonell,^3^ Claire Francoz,^4^ Eric Nguyen-Khac,^5^ Christian Duhamel,^2^ Didier Lebrec,^4,6^ Thierry Poynard,^1^ and Richard Moreau^4,6^
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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%)  \( p<0.01 \)
Terlipressin v Terlipressin + Albumin in Hepatorenal Syndrome

N=21
Type 1: 16
Type 2: 5

Terlipressin:
0.5mg/4hr to 2 mg/4hr

Albumin:
1 g/kg: first day and 20-40 g/d thereafter

Ortega et al. 2002;36:941-948
Process of FA binding is provided by a change of the molecular conformation – a reversible process, being repeated several times.
Detoxification Efficiency

Simplification needed for clinical utility
IMAR predicts risk of death in decompensated cirrhosis

Is IMAR a useful biomarker in multiorgan failure in Cirrhosis?

Davies et al. Hepatology; 2009, in press
DASIMAR: A novel biomarker in ACLF

- Cirrhotic patients
- ACLF patients (survivors)
- ACLF patients (non-survivors)
The MARS circuit

Blood from patient

To patient

MARS membrane

Albumin dialysate

Anion Exchange Resin

Activated Charcoal

Dialysis membrane

Haemofiltration / Haemodialysis circuit
Randomized Controlled Study of Extracorporeal Albumin Dialysis for Hepatic Encephalopathy in Advanced Cirrhosis

Tarek I. Hassanein,1 Flemming Tofteg,2 Robert S. Brown, Jr.,3 Brendan McGuire,4 Patrick Lynch,5 Ravindra Mehta,1 Finn S. Larsen,2 Jeff Gornbein,6 Jan Stange,7 and Andres T. Blei3

Survival: No Difference

P < 0.01

Survival: No Difference

p=0.045
The UCL Liver Dialysis Device
Incorporates Endotoxin removal + Albumin Exchange

Subject
In Vitro plasma
Pig
Patient

Additional Albumin Infusion

Albumin Rich Dialysis Soln.

Subject
In Vitro plasma
Pig
Patient

ENSO membrane

P2SX

Albumin Dialysis

Dialysate

Waste

Plasma Flow
Summary

• The occurrence of renal dysfunction of cirrhosis is associated with poor prognosis
• The classical HRS is pathophysiologically and clinically distinct from renal dysfunction in ACLF
• Current diagnostic strategies are outdated and insensitive
  – Biomarker development for novel therapies
• Current therapy is based around the syndrome being treated
  – Classical
    • Vasopressors, Albumin, TIPSS, Transplantation
  – ACLF
    • Albumin, Liver Support, Transplantation