Pathophysiology and management of end-stage cirrhosis

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‘Todo o nada’: everything or nothing…

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Normal Liver
Cirrhosis, the end-stage result of chronic liver disease
What is Fibrosis and Cirrhosis?

*Fibrosis* - reversible accumulation of scar
- *fibrillar collagens*
- *sulfated proteoglycans*
- *glycoproteins*

*Cirrhosis* - scar with distortion of liver architecture and *nodule formation*
Cirrhosis

Fibrosis

Regenerating Nodule
Hepatic Fibrosis is the Liver’s Wound Healing Response

- Hepatitis Viruses
- Inherited Metabolic Disorders
- Excess Vitamin A
- Cholestatic Disorders
- Immune Disorders
- Alcohol
- Drugs
Hepatic Stellate Cells (HSC)-perisinusoidal cells of normal liver

Courtesy S Friedman
INITIATION
• Transcriptional events
• Paracrine stimulation
• Early ECM changes

INJURY
- Oxidative Stress, cFn
- PDGF
- ET-1
- TGF-β1

PERPETUATION
• Increased cytokine secretion
• Receptor tyrosine kinase upregulation
• Accelerated ECM remodeling

PROLIFERATION
• PDGF
• ET-1
• TGF-β1
• MMP-2

CONTRACTILITY
• Fibrogenesis
• Matrix Degradation

REVERSION?

REVERSION?

RESOLUTION
• MCP-1
• PDGF, MCP-1
• PDGF, Serum

WBC
Chemoattraction

HSC
Chemotaxis

Retinoid Loss

Courtesy S Friedman
Cirrhosis

Increased intrahepatic vascular resistance

Portal hypertension

Increased production of vasodilators eg. NO

splanchnic vasodilatation

arterial underfilling

stimulation of vasoconstrictor systems

varices

Secondary hyperaldosteronism
Na and water retention
Impaired free water excretion

Renin angiotensin system

Sympathetic nervous system activation

Intense Renal Vasoconstriction

Renal vasoconstrictors > vasodilators

Hepatorenal Syndrome (HRS)

Dilutional hyponatraemia
Ascites
The possible players

- **Vasodilators:**
  - Nitric oxide
  - Vasodilator prostaglandins
  - Prostacyclin
  - PGE1, PGI2
  - VIP
  - Calcitonin
  - Glucagon
  - Atrial naturetic factor
  - Platelet activating factor
  - Ferritin
  - Estrogens

- **Vasoconstrictors:**
  - Tyrosine
  - Serotonin
  - Endothelin
### Cirrhosis: Childs-Pugh grading

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>encephalopathy (grade)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
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<tr>
<td>ascites</td>
<td>Nil</td>
<td>Min</td>
<td>Moderate</td>
</tr>
<tr>
<td>bilirubin (µg/l)</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>albumin (g/l)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Prothrombin (secs over)</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
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*CP A=0-5, B=>5-10, C=>10*
Complications:

- Hepatorenal syndrome
- Portal hypertension
  - Oesophageal/ gastric varices
  - Ascites
  - Spontaneous bacterial peritonitis (SBP)
- Hepatocellular failure.
  - Hepatic encephalopathy
  - Nutrition
- [Hepatocellular carcinoma]
Probability of Survival among Patients with Cirrhosis, Refractory Ascites, and the Hepatorenal Syndrome

Renal failure in cirrhosis

- Multiple potential aetiologies
  - severe dehydration (pre-renal failure) [up tp 49% Balleste 2005]
  - HRS
  - shock (septic, hemorrhagic)
  - ATN
  - nephrotoxic drugs (aminoglycosides, NSAIDS)
  - contrast nephropathy
  - glomerulonephritis (cryoglobulinemia)

- Other renal diseases
  - diabetes, vascular disease, hypertension
Hepatorenal syndrome

- Functional renal failure characterized by
  - intense vasoconstriction of the renal circulation
  - major disturbances in circulatory function → ↓ renal perfusion pressure

- Occurs in setting of advanced cirrhosis
  - Ascites, oedema, +/- dilutional hyponatremia
  - Elevated Cr > 1.5 mg/dl
  - Low urine Na < 10 meq/L
  - Lack of improvement after volume expansion
Treatment Options

- Vasoconstrictors +/- volume expansion
  - Vasopressin analogues
  - Alfa Adrenergic agonists eg midodrine
- TIPS
- Dialysis?
- Liver Transplantation
Vasoconstrictors

- **Vasopressin Analogues** (splanchnic vasoconstrictors)
- **Terlipressin (Glypressin)**
  - More effective in combination with albumin
  - Terlipressin - 50-75% response for type 1 HRS
    - Response over 10 - 14 days
    - Ischemic side effects in 5-10%
    - Expensive, not available in many countries (USA)
    - Need monitored environment?
    - 1 mg BD 5-15/7 62% vs 20% survival *(Gluud CHBG 2005)*

- **Octreotide** - ? no effect, weak constrictor
Acute oesophageal variceal bleeding
Uncontrolled variceal bleeding
Acute variceal bleeding

Goals of therapy

• restore blood volume
• stop bleeding rapidly → ENDOSCOPY
• prevent early rebleeding
• prevent and treat complications
• prevent deterioration of liver function
Improving prognosis following a first variceal haemorrhage over 4 decades

- 1475 patients included in ‘placebo’ arms of 28 RCTs 1960 – 2000
- Over 40 years observation : a fall in variceal bleeding related mortality
- From 65% to 40% (p = 0.024)

McCormick PA, O’Keefe C Gut 2001
Acute variceal bleeding

Factors associated with early mortality: 50% at 6/52

- severity of liver disease (Gines et al., 2005)
- active bleeding (Ben Ari et al., 1999)
- failure to control bleeding (Ben Ari et al., 1999)
- infection (Bernard et al., 1995; Goulis et al., 1998; Bernard et al., 1999)
- renal dysfunction
- concomitant cardiorespiratory disease
Terlipressin (Glypressin) for acute variceal bleeding

20 studies identified (n = 1609)

7 studies (n = 443) comparing terlipressin with placebo

Full publication: Walker 1986
Freeman 1989
Soderlund 1990
Pauwels 1994
Levacher 1995

Abstract: Brunati 1996
Patch 1999

Terlipressin associated with significant mortality benefit
RR 0.66, 95% CI 0.49 to 0.88

Kalambokis et al 2005
Sengstaken Blakemore tube
TIPSS- transjugular intrahepatic porto-systemic shunt
Ascitis in Cirrhosis
Complex pathogenesis -
- ↑ sinusoidal pressure
- ↑ salt and water retention
- ↓ oncotic pressure

Treatment
- Low Na diet + fluid restriction
- Diuretics: spironolactone, frusemide
- Aggressive treatment of SBP
  - norfloxacin prophylaxis
  - Cefatriazone
- Paracentesis LVP 4g/l vs 8g/l equivocal (Alessandria 2005)
- Surgery - peritoneal venous shunting
- TIPS (PTFE shunts)
- Orthotopic liver transplantation
Encephalopathy

Global ↓ in CNS function: complex neuropsychiatric syndrome
- Subclinical mostly
- West Haven criteria - Grade 0 - 4

Pathogenesis - Multifactorial? Ammonia interorgan transport
- Disturbed blood brain barrier / cerebral oedema
- Altered cerebral blood flow
- Gut derived neurotoxins - ammonia-glutamate production
  phenols / amino acids / fatty acids / tryptophan
- Changes in neurotransmitters -Glutamate ↑
  GABA ↑ or ↓
  False neurotransmitters
Diagnosis of exclusion
Eliminate precipitant: GI bleed/sepsis etc

- ↓ absorption neurotoxins low protein diet ?
  Lactulose / lactilol?
- Antibiotics - neomycin / metronidazole / vancomycin
- Branch chain amino acids / levodopa / flumazenil
- Role of hyponatremia 3.2 x *(Torre et al 2005)*
- Role for liver support devices eg MARS
- L- Ornithine-L-Aspartate LOLA *(Abid et al 2005)*
  - Increases increases muscle detoxification
2 recent studies focusing on hepatic encephalopathy reviewed

- Systematic review of 22 randomized trials focusing on benefits of nonabsorbable disaccharides, such as lactulose
- Randomized trial of protein restriction during episodic hepatic encephalopathy

Perhaps these therapies are ‘urban myth’

Key Messages

Complications of cirrhosis have high mortality:

- Proactive management
- Optimise organ perfusion
- Low threshold for antibiotics [antifungals]
- Use of vasopressin analogues (glypressin)
- Attention to nutritional issues
- Meticulous management of fluid balance
- Normal protein diet

Areas of controversy exist - lactulose
Multidisciplinary management essential
Avoid nihilistic approach