CIRCULATORY AND RENAL FAILURE IN CIRRHOSIS

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CIRCULATORY AND RENAL FAILURE IN CIRRHOSIS

Hecker R and Sherlock S, The Lancet 1956
RENAL FAILURE IN CIRRHOSIS
SURVIVAL

Prospective study (2001-2005), n=309)

Median survival = 40 days

Martín-Llahí M et al., unpublished
CIRCULATORY FUNCTION IN EARLY CIRRHOSIS

CIRRHOSIS

\[ \text{Portal hypertension} \]

- Splanchnic arterial vasodilation
  - Decreased systemic vascular resistance
    - Decreased effective arterial blood volume
      - Increased blood/plasma volume
      - Increased cardiac output

MAINTENANCE OF ARTERIAL PRESSURE
CIRCULATORY FUNCTION IN ADVANCED CIRRHOSIS

CIRRHOSIS

Portal hypertension

Splanchnic arterial vasodilation

Decreased systemic vascular resistance

Decreased effective arterial blood volume

Increased blood/plasma volume

Activation of vasoconstrictor systems

Increased cardiac output

Sodium retention/ASCITES

MAINTENANCE OF ARTERIAL PRESSURE
CIRRHOSIS

Portal hypertension

Splanchnic arterial vasodilation

Decreased systemic vascular resistance

Decreased effective arterial blood volume

Increased blood/plasma volume

Activation of vasoconstrictor systems

Increased cardiac output

Renal vasodilator systems

NORMAL KIDNEY FUNCTION
RENAL FAILURE IN CIRRHOSIS
MAIN CAUSES

1. Vasodilation-induced renal failure
   Hepatorenal syndrome (HRS)
   Bacterial infections

2. Hypovolemia-induced renal failure

3. Drug-induced renal failure

4. Intrinsic renal diseases
PATHOGENESIS OF RENAL FAILURE
I. VASODILATION

CIRRHOSIS

Portal hypertension

Disease progression
Bacterial infections
Bacterial translocation?

Splanchnic arterial vasodilation

Decreased systemic vascular resistance

Decreased effective arterial blood volume

Increased blood/plasma volume

Activation of vasoconstrictor systems

Renal vasodilator systems

HEPATORENAL SYNDROME

Increased cardiac output
PATHOGENESIS OF RENAL FAILURE
II. HYPOVOLEMIA

CIRRHOSIS

- **Portal hypertension**
- Splanchnic arterial vasodilation
- Decreased systemic vascular resistance

**Decreased effective arterial blood volume**

- **Increased cardiac output**
- **Activation of vasoconstrictor systems**
- **Increased blood/plasma volume**
- **Renal vasodilator systems**

**Bleeding Overdiuresis**

**RENAL FAILURE / HYPOVOLEMIC**
CIRRHOSIS

- Portal hypertension
- Splanchnic arterial vasodilation
- Decreased systemic vascular resistance
- Decreased effective arterial blood volume
- Increased blood/plasma volume
- Activation of vasoconstrictor systems
- Increased cardiac output

**Renal vasodilator systems**

**RENAL FAILURE**

- NSAIDs
PATHOGENESIS OF RENAL FAILURE
IV. INTRINSIC RENAL DISEASES

CIRRHOSIS

\[ \text{Portal hypertension} \]

\[ \text{Splanchnic arterial vasodilation} \]

\[ \text{Decreased systemic vascular resistance} \]

\[ \text{Decreased effective arterial blood volume} \]

\[ \text{Increased blood/plasma volume} \]

\[ \text{Activation of vasoconstrictor systems} \]

\[ \text{Increased cardiac output} \]

\[ \text{Renal vasodilator systems} \]

Other causes -> RENAL FAILURE -> Glomerulonephritis

Other causes

RENAL FAILURE

IV. INTRINSIC RENAL DISEASES

Pathogenesis

Cirrhosis

- Portal hypertension

  Splanchnic arterial vasodilation

  Decreased systemic vascular resistance

  Decreased effective arterial blood volume

  Increased blood/plasma volume

  Activation of vasoconstrictor systems

  Increased cardiac output

  Renal vasodilator systems

Other causes

RENAL FAILURE

Glomerulonephritis
RENAL FAILURE IN CIRRHOSIS
MAIN CAUSES

1. Vasodilation-induced renal failure
   Hepatorenal syndrome (HRS)
   Bacterial infections

2. Hypovolemia-induced renal failure

3. Nephrotoxicity

4. Intrinsic renal diseases
CIRCULATORY AND RENAL FUNCTION IN HEPATORENAL SYNDROME

CIRRHOSIS
- Portal hypertension
  - Splanchnic arterial vasodilation
    - Decreased effective arterial blood volume
      - Vasoconstrictor systems
        - Cerebral vasoconstriction
        - Renal vasoconstriction
        - Brachial/femoral vasoconstriction
          - Maintenance of effective arterial blood volume

HEPATORENAL SYNDROME
CIRRHOSIS

Portal hypertension

Vasoconstrictors → Splanchnic arterial vasodilation

Decreased effective arterial blood volume

Vasoconstrictor systems

Cerebral vasoconstriction

Renal vasoconstriction

Brachial/femoral vasoconstriction

Maintenance of effective arterial blood volume

HEPATORENAL SYNDROME
CIRRHOSIS

Portal hypertension

Vasoconstrictors → Splanchnic arterial vasodilation

Albumin → Decreased effective arterial blood volume

Vasoconstrictor systems

Cerebral vasoconstriction

Renal vasoconstriction

Brachial/femoral vasoconstriction

Maintenance of effective arterial blood volume

HEPATORENAL SYNDROME
HEPATORENAL SYNDROME
PHARMACOLOGICAL TREATMENT

Drugs used
- Terlipressin, Norepinephrine, Midodrine

Key findings
- Improves renal function in 50-75% of patients
- Response to therapy is associated with improved survival
- Recurrence not constant. Retreatment effective

Unknown issues
- Overall effect on survival
- No comparative studies between different drugs
- Beneficial effect of associated albumin likely but not proved
HEPATOURENAL SYNDROME
TREATMENT WITH TERLIPRESSIN AND ALBUMIN

Survival and response to therapy

Recurrence

Probability
Probability

Days
Days

0.0
0.2
0.4
0.6
0.8
1.0

0.0
0.2
0.4
0.6
0.8
1.0

0
30
60
90

0
30
60
90

Responders
Non responders

p<0.03

Martín-Llahi M et al., unpublished
RENAL FAILURE IN CIRRHOSIS
MAIN CAUSES

1. Vasodilation-induced renal failure
   Hepatorenal syndrome (HRS)
   Bacterial infections

2. Hypovolemia-induced renal failure

3. Nephrotoxicity

4. Intrinsic renal diseases
PATHOGENESIS OF RENAL FAILURE IN BACTERIAL INFECTIONS

CIRRHOSIS

Bacterial infection
Increased cytokine production

Splanchnic arterial vasodilation

Decreased systemic vascular resistance

Decreased effective arterial blood volume

Increased blood/plasma volume

Activation of vasoconstrictor systems

Increased cardiac output

Renal vasodilator systems

RENAL FAILURE
BACTERIAL INFECTIONS AND RENAL FAILURE

Incidence
20-30% of patients with spontaneous bacterial peritonitis or sepsis in the absence of septic shock
40% of cases of renal failure in cirrhosis

Key findings
Reversible or non-reversible
May progress despite infection resolution
Associated with poor outcome
RENAL FAILURE IN CIRRHOSIS
SURVIVAL

- Bacterial infections
- Hepatorenal syndrome

p=NS

Martín-Llahí M et al., unpublished
SPONTANEOUS BACTERIAL PERITONITIS
CIRCULATORY DYSFUNCTION AND RENAL FAILURE

* p<0.05

Plasma renin activity (ng/mL.h)

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<thead>
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<th>Days</th>
<th>No renal failure</th>
<th>Renal failure</th>
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<tr>
<td>0</td>
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<td>8 ± 2</td>
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<tr>
<td>3</td>
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<td>9</td>
<td>4 ± 1</td>
<td>18 ± 3</td>
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Sort et al., N Engl J Med 1999
PATHOGENESIS OF RENAL FAILURE IN BACTERIAL INFECTIONS IN CIRRHOSIS

CIRRHOSIS

Portal hypertension

Bacterial translocation to lymph nodes

Bacterial infection (SBP, sepsis)

Increased cytokine production

Impairment of circulatory function (arterial vasodilation)

Impairment of cardiac function

ALBUMIN

Reduction of effective arterial blood volume

Activation of vasoconstrictor systems

RENAL FAILURE
SPONTANEOUS BACTERIAL PERITONITIS
EFFECTS OF ALBUMIN

Renal failure (%)

Mortality (%)

Cefotaxime
Cefotaxime + albumin

Cefotaxime
Cefotaxime + albumin

p=0.02
p=0.01

Sort et al., N Engl J Med 1999
BACTERIAL TRANSLOCATION IN CIRRHOSIS

Intestinal Bacterial Overgrowth
Dysmotility Delayed transit time

Intestinal Permeability
Mucosal Hypoxia, Acidosis
ATP depletion, NO, LPS, TNF

Impaired Immunity
Impaired chemotaxis, migration, phagocytic function, complement deficiency, etc.

Aerobic bacteria
Anaerobic bacteria
Enterocytes
Lamina propria

Garcia-Tsao et al., Best P Res Clin Gastroenterol 2004
BACTERIAL TRANSLOCATION AND EFFECTS OF NORFLOXACIN

Experimental cirrhosis (%)

Control rats 0%
Cirrhosis with ascites 42%
Placebo 69%
Norfloxacin 31%

Cirrhosis with ascites and hemorrhagic shock

Human cirrhosis (%)

Controls 9%
Child A/B 6%
Child C 31%
Norfloxacin 9%

Patients with cirrhosis

Llovet et al., Hepatology 1996
Cirera et al., J Hepatol 2001
POSSIBLE CONSEQUENCES OF BACTERIAL TRANSLOCATION IN CIRRHOSIS

- Infections due to bacteria from intestinal origin (spontaneous bacterial peritonitis, sepsis)
- Increased cytokine production
- Increased nitric oxide / carbon monoxide production
- Impairment of circulatory / renal function
POSSIBLE CONSEQUENCES OF BACTERIAL TRANSLOCATION IN CIRRHOSIS

- Infections due to bacteria from intestinal origin (spontaneous bacterial peritonitis, sepsis)
- Increased cytokine production
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- Impairment of circulatory / renal function
BACTERIAL TRANSLOCATION
CYTOKINE AND NITRIC OXIDE PRODUCTION

Control

TNFα in lymph nodes (pg/mL)

TNFα in plasma (pg/mL)

Nitric oxide in plasma (10⁻³M)

* p<0.05

Wiest et al., J Clin Invest 1999
CIRCULATORY FUNCTION IN CIRRHOSIS
EFFECT OF SELECTIVE INTESTINAL DECONTAMINATION

Mean arterial pressure (mmHg)

Systemic vascular resistance (units)

Rasaratnam et al., Ann Intern Med 2003
BACTERIAL TRANSLOCATION AND CIRCULATORY / RENAL FUNCTION

CIRRHOSIS

Portal hypertension

→ Bacterial translocation to lymph nodes

Increased cytokine production

Impairment of circulatory function (arterial vasodilation)

Reduction of effective arterial blood volume

Activation of vasoconstrictor systems

HEPATORENAL SYNDROME

SELECTIVE INTESTINAL DECONTAMINATION
SELECTIVE DECONTAMINATION IN CIRRHOSIS
EFFECT ON RENAL FUNCTION AND SURVIVAL

Patients with advanced liver failure and low protein ascites

Fernández et al., unpublished
<table>
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<tr>
<th>Family</th>
<th>Mentors</th>
<th>Collaborators</th>
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<tr>
<td>Núria</td>
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Let every student have full recognition for his work. Never hide the work of others under your own name. Should your assistant make an important observation, let him publish it. Through your students and your disciples will come your greatest honor.

Sir William Osler (1849-1919)