TREATMENT OF ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS

Pere Ginès, MD
Liver Unit, Hospital Clínic
Barcelona, Catalunya, Spain
### Functional Renal Abnormalities in Cirrhosis

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Clinical Consequence</th>
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<td>Sodium retention</td>
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FUNCTIONAL RENAL ABNORMALITIES IN CIRRHOSIS

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ASCITES
Pathogenesis and therapeutic interventions

LIVER TRANSPLANTATION → CIRRHOSIS

TIPS → Portal hypertension

Splanchnic arterial vasodilation

Reduced effective arterial blood volume

Stimulation of antinatriuretic/vasoconstrictor systems

DIURETICS → Increased tubular sodium reabsorption

Sodium retention

LARGE-VOLUME PARACENTESIS → ASCITES
CIRRHOSIS WITH ASCITES

Clinical types
- Non-refractory
  Moderate (grade 2)
  Large (grade 3)
- Refractory
MANAGEMENT OF LARGE ASCITES
Comparison of large-volume paracentesis plus albumin and diuretics

Efficacy (%) Side effects (%)

<table>
<thead>
<tr>
<th>Large-volume paracentesis + albumin</th>
<th>Diuretics</th>
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<tr>
<td>Hyponatremia</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>20</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>100</td>
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</table>

P<0.05

Ginès et al., Gastroenterology 1987
REFRACTORY ASCITES
Pathogenesis and therapeutic interventions

LIVER TRANSPLANTATION → CIRRHOSIS

TIPS → Portal hypertension → Splanchnic arterial vasodilation → Reduced effective arterial blood volume → Stimulation of antinatriuretic/vasoconstrictor systems

DIURETICS → Increased tubular sodium reabsorption → Sodium retention

LARGE-VOLUME PARACENTESIS → ASCITES
### TIPS vs PARACENTESIS FOR REFRACTORY ASCITES

#### Summary of studies

<table>
<thead>
<tr>
<th></th>
<th>Control of ascites</th>
<th>Hepatorenal syndrome</th>
<th>Hepatic encephalopathy</th>
<th>Cost</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebrec et al., J Hepatol 1997</td>
<td>Better with TIPS</td>
<td>-</td>
<td>No difference</td>
<td>-</td>
<td>Worse with TIPS</td>
</tr>
<tr>
<td>Ginès et al., Gastroenterology 2002</td>
<td>Better with TIPS</td>
<td>Less frequent with TIPS</td>
<td>Worse with TIPS</td>
<td>Greater with TIPS</td>
<td>No difference</td>
</tr>
<tr>
<td>Sanyal et al., Gastroenterology 2003</td>
<td>Better with TIPS</td>
<td>-</td>
<td>Worse with TIPS</td>
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<td>No difference</td>
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<td>Salerno et al., Hepatology 2005</td>
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<td>-</td>
<td>Better with TIPS</td>
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Salerno et al., Hepatology 2005
REFRACTORY ASCITES
Treatment strategy

Initial therapy
- Total paracentesis plus i.v. albumin (8 g/L of ascites)
- Partial paracentesis (<5 L) with artificial plasma expanders if albumin is not available
- Consider liver transplantation

Maintenance therapy
- Repeated paracentesis plus i.v. albumin when necessary
- TIPS is not the treatment of choice. Better control of ascites should be weighed against increased risk of severe encephalopathy and higher costs
ASCITES / DILUTIONAL HYponatremia
Pathogenesis and therapeutic interventions

CIRRHOSIS

Portal hypertension

Splanchnic arterial vasodilation

Reduced effective arterial blood volume

Stimulation of vasoconstrictor systems

Renin-aldosterone system

Spironolactone (aldosterone receptor) Sodium retention

Dilation

Antidiuretic hormone (vasopressin)

Vasopressin V2 receptor (solute-free water retention)

V2 receptor antagonists

ASCITES

DILUTIONAL HYponatremia
### V₂ RECEPTOR ANTAGONISTS IN CIRRHOSIS WITH ASCITES AND HYponatremia

- Double-blind, randomized, parallel group comparison of fixed doses of Satavaptan with placebo

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<th>Screening period</th>
<th>Treatment period</th>
<th>Post-treatment follow-up</th>
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<tr>
<td>7 days</td>
<td>14 days</td>
<td>7 days</td>
</tr>
</tbody>
</table>

- **Placebo**
- **Satavaptan 5 mg/day**
- **Satavaptan 12.5 mg/day**
- **Satavaptan 25 mg/day**
- **Spironolactone 100 mg/day**
V₂ RECEPTOR ANTAGONISTS IN CIRRHOSIS WITH ASCITES AND HYponatremia

Body weight (Kg)  Serum sodium (mmol/L)

Ginès et al., EASL 2006
SPONTANEOUS BACTERIAL PERITONITIS

Key findings
- Wide clinical spectrum: from asymptomatic cases to septic shock
- Diagnosis based on increased neutrophil count in ascitic fluid
- High resolution rate with third-generation cephalosporins
- High hospital mortality (10-20%)
- Poor long-term outcome

Important clinical issues
- Hepatorenal syndrome common, even after infection resolution
- Adrenal insufficiency frequently associated
- Prevention in high risk patients
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SBP-INDUCED CIRCULATORY AND RENAL FAILURE
Proposed mechanism

SPONTANEOUS BACTERIAL PERITONITIS

Arterial vasodilation (cytokines, NO, CO)

Albumin

IMPAIRMENT OF EFFECTIVE ARTERIAL BLOOD VOLUME

ACTIVATION OF VASOCONSTRICTOR SYSTEMS

REDUCED RENAL PERFUSION

HEPATORENAL SYNDROME

DECREASED SURVIVAL
SPONTANEOUS BACTERIAL PERITONITIS
Effects of plasma volume expansion with albumin

Hepatorenal syndrome (%) - p=0.02
Mortality (%) - p=0.01

Sort et al., N Engl J Med 1999
SPONTANEOUS BACTERIAL PERITONITIS

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ADRENAL INSUFFICIENCY AND SEPSIS IN CIRRHOSIS

Adrenal insufficiency and outcome (%)

- Renal failure: 35% (No adrenal insufficiency), 79% (Adrenal insufficiency)
- Hemodynamic instability: 24% (No adrenal insufficiency), 73% (Adrenal insufficiency)
- Mortality: 37% (No adrenal insufficiency), 81% (Adrenal insufficiency)

Septic shock: survival according to treatment of adrenal insufficiency

- Treatment (n=25): p=0.003
- No treatment (n=50)

Tsai et al., Hepatology 2006
Fernández et al., Hepatology (in press)
SPONTANEOUS BACTERIAL PERITONITIS

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SELECTIVE INTESTINAL DECONTAMINATION

SPONTANEOUS BACTERIAL PERITONITIS
Pathogenesis and prophylactic interventions

CIRRHOSIS

Sinusoidal portal hypertension

Intestinal bacterial overgrowth
Impaired intestinal motility
Impaired intestinal barrier

Bacterial translocation to lymph nodes

Reduced activity of the reticuloendothelial system (severe liver failure)

Spontaneous bacteremia

Colonization of ascitic fluid

Reduced antibacterial activity of the ascitic fluid (low-protein ascites)

SPONTANEOUS BACTERIAL PERITONITIS
EFFECT OF LONG-TERM NORFLOXACIN ADMINISTRATION IN SBP RECURRENCE IN CIRRHOSIS

Ginès et al, Hepatology 1990
SELECTIVE DECONTAMINATION IN CIRRHOSIS
EFFECT ON RENAL FUNCTION AND SURVIVAL

Fernández et al., unpublished

Patients without previous SBP with advanced liver failure and low protein ascites

Hepatorenal syndrome

Survival

Probability

Probability

Days

Days

Norfloxacin

Placebo

p=0.02

p=0.05
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