Spontaneous Bacterial Peritonitis
A disease of the gut?
Therapeutic implications

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• Scope of the problem

• Concepts on pathogenesis
  • Bacterial translocation

• Treatment options based on the above
Types of Bacteria Isolated from Hospitalized Cirrhotic Patients

Fernández et al., Hepatology 2002; 35:140
Bacterial Translocation (BT) is the Main Mechanism Implicated in SBP

- **Definition:** migration of viable microorganisms from the intestinal lumen to mesenteric lymph nodes (MLN) and other extraintestinal sites
- BT increases in conditions associated with a high risk of infection by gram-negative organisms (e.g. burns, trauma, hemorrhagic shock, cirrhosis)
- *E. Coli, Klebsiella, enterococci species*
Gut as Source of Bacteria in SBP
Causal Relationship

1. Organisms in SBP are of enteric origin
2. Selective intestinal decontamination (norfloxacin) decreases the development of SBP
3. Cirrhotic rats with positive ascites cultures have concurrent positive MLN cultures, often with the same organism
4. DNA typing of organisms - identity rate of 80% in 5 cases in which bacteria were isolated from both MLNs and ascites

Garcia-Tsao G. Gastroenterology 2001; 120:314
Llovet et al., J Hepatol 1998; 28:307-313
In Experimental Cirrhosis, Bacterial Translocation Increases with Severity of Cirrhosis

Garcia-Tsao et al., Gastroenterology 1995; 108:1835

Submucosal edema & inflammation
Low albumin, high bilirubin

% with positive MLN bacteriological culture

0/12 Normal
0/9 Cirrhosis, no ascites
5/9 Cirrhosis, with ascites
In Humans, Bacterial Translocation Increases with Severity of Cirrhosis

Cirera et al., J Hepatol 2001: 34:32-37
Mechanisms of Bacterial Translocation

Intestinal Bacterial Overgrowth
- Hypomotility-Delayed transit time
- Overactive SNS / NO
- Portal HTN, oxidative stress

Enhanced Intestinal Permeability
- Mucosal Hypoxia, inflammation
- ATP depletion, NO, LPS, TNF

Impaired Immunity
- Local: Impaired chemotaxis, migration, phagocytic function
- Systemic: deficient RES

Garcia-Tsao et al., AGA-GTP 2006
Bacteria in mesenteric lymph nodes

- Bacterial Overgrowth
- Increased Permeability
- Decreased Transit time
- Nonenteric bacteria

Bacteria in mesenteric lymph nodes lead to:

- Bacteremia
  - Impaired RES activity and systemic clearance
  - Reduced ascitic fluid antimicrobial activity

Bacteremia leads to:

- Ascites colonization

SPONTANEOUS BACTERIAL PERITONITIS
Possible Consequences of Bacterial Translocation In Cirrhosis

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

**TNFα in lymph nodes (pg/mL)**
- LC: cirrhosis
- BT: bacterial translocation

**TNFα in plasma (pg/mL)**
- LC: cirrhosis
- BT: bacterial translocation

**Nitric oxide in plasma (10^{-3}M)**
- LC: cirrhosis
- BT: bacterial translocation

*p<0.05*
BACTERIAL TRANSLOCATION, SBP AND CIRCULATORY / RENAL FUNCTION

CIRRHOSIS

- Portal hypertension
- Bacterial translocation to lymph nodes
- Increased NO & cytokine production
- Impairment of circulatory function (arterial vasodilation)
- Reduction of effective arterial blood volume
- Activation of vasoconstrictor systems

Selective intestinal decontamination

Improvement

HEPATOrenal syndrome
CIRCULATORY FUNCTION IN CIRRHOSIS
Norfloxacin 400 mg bid (n=14) vs placebo (n=14)

Mean arterial pressure (mmHg)
Systemic vascular resistance (units)

Therapy 4 weeks

Rasaratnam et al., Ann Intern Med 2003
serum creatinine > 1.2mg/dL, protein levels in ascitic fluid of less than 15 g/L, Child-Pugh score >9, dilutional hyponatremia (serum sodium < 130mEq/L).

Treatment and Prophylaxis of Spontaneous Bacterial Peritonitis

**Therapy**

- **Third-generation cephalosporins**
  - IV cefotaxime or ceftriaxone.

- **Infuse albumin**
  - S bili <68.4 µmol/l and
  - S Cr <88.4 µmol/l can be treated without albumin.

- Treat for 5 – 7 days or until disappearance of signs of infection

**Prophylaxis**

- **GI Bleed**
  - Norfloxacin or IV ceftriaxone – 1 week

- **Previous SBP**
  - Norfloxacin 400 mg

- **Advanced cirrhosis / low protein in ascites (< 15 g/liter):**
  - Norfloxacin 400 mg
Alternatives to antibiotic prophylaxis?
Antibiotic Resistance in SBP

- High rate of infections due to quinolone resistance (65%)

OPTIONS
- Probiotics
  - Animals/humans
- Prokinetics
  - Animals/humans
- Propranolol
  - Animals

Fernández et al. Hepatology 2002; 35:140
Probiotics

- Microorganisms that have beneficial properties for the host
- How they work?
  - Suppression of growth or epithelial binding/invasion by pathogenic bacteria
  - Improvement of intestinal barrier function
  - Modulation of the immune system
- Use in cirrhosis - limited
# Use of Probiotics in Bacterial Translocation

## Use of Probiotics in Bacterial Translocation

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<thead>
<tr>
<th>Author - year</th>
<th>Model</th>
<th>Probiotic</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Bauer - 2002</td>
<td>CCL4 cirrhosis</td>
<td>lactobacillus</td>
<td>Did not prevent BT</td>
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<tr>
<td>Wiest - 2003</td>
<td>Portal vein ligated</td>
<td>lactobacillus</td>
<td>Did not prevent BT</td>
</tr>
<tr>
<td>Chiva - 2002</td>
<td>CCL4 cirrhosis</td>
<td>Lactobacillus &amp; vitamin C + glutamate</td>
<td>Prevented BT</td>
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## Use of Probiotics in Patients

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<th>Patients</th>
<th>Probiotic</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Liu - 2004</td>
<td>Cirrhosis / minimal hepatic encephalopathy</td>
<td>Probiotics and fermentable fiber</td>
<td>Reduced counts of gut flora, blood ammonia &amp; MHE</td>
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<tr>
<td>Loguercio - 2005</td>
<td>Cirrhosis</td>
<td>VSL #3 lactobacillus</td>
<td>Improved liver tests</td>
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<tr>
<td>Rayes - 2002</td>
<td>Liver transplantation</td>
<td>Living lactobacillus &amp; planarum</td>
<td>Decreased post-op bacterial infections</td>
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Prokinetics- Cisapride
Combination RX decreases the incidence of SBP

Problem – pulled from market

PROPRANOLOL
Effects on intestinal bacterial overgrowth and BT in cirrhotic rats

Pérez-Paramo et al. Hepatology 2000
Is Spontaneous Bacterial Peritonitis
A disease of the gut?

Probably yes.

Intestinal factors seem to play a major role in the pathogenesis of SBP, however we need better proof that modulation of intestinal permeability, motility and bacterial overgrowth have a role in the management of patients with cirrhosis and SBP.
## ACKNOWLEDGEMENTS

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