Bacterial translocation in cirrhosis

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The Gut-Liver axis: a bidirectional relation in health and disease
Bologna October 4-5th
Bacterial translocation (BT)

Definition

Bacterial translocation (BT), is defined as the migration of viable bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes (MLNs) or other extraintestinal organs and sites.

R. Wiest et al. Hepatology 2005; 41: 422-33
Bacterial translocation (BT)

Bacterial DNA fragments in mesenteric lymph nodes (MLNs) in cirrhotic rats according to positive cultures from MLNs

M. Ubeda et al. Hepatology 2010; 52: 2086-2095
Bacterial translocation (BT)

Headlines

- Prevalence
- Pathogenesis
- Pathophysiological consequences
- Clinical consequences
- Prevention
Positive cultures from mesenteric lymph nodes in cirrhotic patients (pts) according to the Child-Turcotte-Pugh (CTP) class and selective intestinal decontamination (SID)

Bacterial translocation (BT)

Markers of bacterial translocation

- Bact-DNA
- Bacterial footprints
  - Endotoxins (LPS)
  - LPS binding protein
Plasma levels of lipopolysaccharide (LPS) binding protein (LBP) in patients with cirrhosis and ascites


Bacterial translocation (BT)

Plasma levels of lipopolysaccharide (LPS) binding protein (LBP) in patients with cirrhosis and ascites

Prevalence of Bact-DNA in inpatients with cirrhosis and refractory ascites

Bacteriological tranlocation (BT)

P. Angeli et al. (AASLD Annual Meeting 2010)
Bacterial translocation (BT)

Headlines

- Prevalence
- Pathogenesis
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- Prevention
Bacterial translocation (BT)

Mechanisms of bacterial translocation

R. Wiest et al. Hepatology 2005; 41: 422-433
Small intestine bacterial overgrowth in cirrhotic patients according with the occurrence of SBP

Bacterial translocation (BT)

Bacterial translocation (BT)

The Bifidobacteria/Enterobacteriaceae ratio in patients with decompensated cirrhosis

P <0.01


Phylogenetic groups of E. coli. in patients with cirrhosis and spontaneous bacterial peritonitis and/or bacteremia

Bacterial translocation (BT)
## Bacterial translocation (BT)

**TABLE 1. Prevalence of virulence factor genes among 110 *Escherichia coli* clinical isolates from cirrhotic patients with spontaneous bacterial peritonitis and/or primary bacteremia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Gene prevalence (no. [%] of isolates)</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt; &lt;br&gt; (B2 vs non-B2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All isolates &lt;br&gt; (n = 110)</td>
<td>B2 isolates &lt;br&gt; (n = 53)</td>
</tr>
<tr>
<td>Adhesins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>papAH</em></td>
<td>50 (45)</td>
<td>33 (62)</td>
</tr>
<tr>
<td></td>
<td><em>papC</em></td>
<td>50 (45)</td>
<td>34 (64)</td>
</tr>
<tr>
<td></td>
<td><em>papEF</em></td>
<td>45 (41)</td>
<td>35 (66)</td>
</tr>
<tr>
<td></td>
<td><em>papG</em></td>
<td>41 (37)</td>
<td>34 (64)</td>
</tr>
<tr>
<td></td>
<td><em>sfa/foc</em></td>
<td>23 (21)</td>
<td>21 (40)</td>
</tr>
<tr>
<td></td>
<td><em>focG</em></td>
<td>12 (11)</td>
<td>11 (21)</td>
</tr>
<tr>
<td></td>
<td><em>iha</em></td>
<td>33 (30)</td>
<td>15 (28)</td>
</tr>
<tr>
<td></td>
<td><em>fimH</em></td>
<td>102 (93)</td>
<td>52 (98)</td>
</tr>
<tr>
<td></td>
<td><em>tra</em></td>
<td>39 (35)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Toxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>hlyA</em></td>
<td>23 (21)</td>
<td>22 (41)</td>
</tr>
<tr>
<td></td>
<td><em>crtI</em></td>
<td>20 (18)</td>
<td>20 (38)</td>
</tr>
<tr>
<td></td>
<td><em>sat</em></td>
<td>27 (24)</td>
<td>17 (32)</td>
</tr>
<tr>
<td></td>
<td><em>pic</em></td>
<td>17 (15)</td>
<td>12 (23)</td>
</tr>
<tr>
<td></td>
<td><em>vat</em></td>
<td>50 (45)</td>
<td>47 (89)</td>
</tr>
<tr>
<td>Siderophores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>iroN</em></td>
<td>48 (44)</td>
<td>35 (66)</td>
</tr>
<tr>
<td></td>
<td><em>fyuA</em></td>
<td>78 (71)</td>
<td>52 (98)</td>
</tr>
<tr>
<td></td>
<td><em>ire</em></td>
<td>33 (30)</td>
<td>22 (41)</td>
</tr>
<tr>
<td></td>
<td><em>intA</em></td>
<td>50 (45)</td>
<td>25 (47)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>kpsM II</em></td>
<td>66 (60)</td>
<td>46 (87)</td>
</tr>
<tr>
<td></td>
<td><em>cvaC</em></td>
<td>24 (22)</td>
<td>16 (30)</td>
</tr>
<tr>
<td></td>
<td><em>usp</em></td>
<td>55 (50)</td>
<td>52 (98)</td>
</tr>
<tr>
<td></td>
<td><em>traT</em></td>
<td>64 (58)</td>
<td>35 (66)</td>
</tr>
<tr>
<td></td>
<td><em>ompT</em></td>
<td>77 (70)</td>
<td>53 (100)</td>
</tr>
<tr>
<td></td>
<td><em>iss</em></td>
<td>27 (24)</td>
<td>15 (28)</td>
</tr>
<tr>
<td></td>
<td><em>ibeA</em></td>
<td>11 (10)</td>
<td>11 (21)</td>
</tr>
</tbody>
</table>

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Factors contributing to the bacterial overgrowth in cirrhotic patients

- Reduced gastric acid secretion
- Reduced intestinal peristalsis
- Reduced bile output and/or abnormal bile composition
- Reduced intestinal mucosa secretion and/or abnormal composition
- Deficit of the mucosal immunity
Bacterial translocation (BT)

Drugs used only for a liver-related condition in hospitalized patients with cirrhosis in Spain

Bacterial translocation (BT)

Use of proton pump inhibitors (PPI) in patients with cirrhosis and spontaneous bacterial peritonitis

P <0.0001

Bacterial translocation (BT)

Expression of Paneth cell antimicrobial peptides in control patients (C), patients with liver cirrhosis (LC) and patients with LC and bacterial translocation (LC + BT)

R. Wiest et al. Hepatology 2005; 41: 422-433
Bacterial translocation (BT)

Mechanisms of bacterial translocation

R. Wiest et al. Hepatology 2005; 41: 422-433
Bacterial translocation (BT)

Percentage of urine excretion of a marker of integrity of mucosal barrier in cirrhotic patients

P <0.001

Bacterial translocation (BT)

Mechanisms of bacterial translocation

R. Wiest et al. Hepatology 2005; 41: 422-433
MLC1 regulates ZO-1 exchange in vivo.

Bacterial translocation (BT)

Schematic diagram of the molecular organization of epithelial tight junction

Yu D et al. PNAS 2010;107:8237-8241

Université de Genève 2011
MLCK regulates ZO-1 exchange in vivo.

Bacterial translocation (BT)

Ocludin expression 1 day after ligation of the common bile duct (BDL)

Yu D et al. PNAS 2010;107:8237-8241

MLC1 regulates ZO-1 exchange in vivo.

Yu D et al. PNAS 2010;107:8237-8241

Bacterial translocation (BT)

Schematic diagram of the molecular organization of epithelial tight junction

Yu D et al. PNAS 2010;107:8237-8241

Université de Genève 2011
Bacterial translocation (BT)

Mechanisms of bacterial translocation

R. Wiest et al. Hepatology 2005 ; 41 : 422-433
Bacterial translocation (BT)

Model for a role of Nod1 and Nod2 as cytosolic surveillance proteins of mucosal surfaces

Bacterial translocation (BT)

Nucleotide-binding oligomerization domain containing 2 (NOD2) Variants as a risk factors for spontaneous bacterial peritonitis in patients with cirrhosis

Table 3. Distribution of Risk Alleles of NOD2 Variants

<table>
<thead>
<tr>
<th>Minor Allele Frequencies of NOD2 Variants (%)</th>
<th>p.R702W</th>
<th>p.G908R</th>
<th>c.3020InsC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>6.3</td>
<td>3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>PMN &gt; 250/μL</td>
<td>8.7</td>
<td>5.8</td>
<td>4.8</td>
</tr>
<tr>
<td>PMN &lt; 250/μL</td>
<td>5.1</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Ins, insertion; NOD, nucleotide-binding oligomerisation domain containing; p, protein (amino acid number); PMN, polymorphonuclear neutrophil.

Table 5. Numbers of Carriers of Any NOD2 Risk Allele in Patients With Cirrhosis With and Without SBP (PMN Cell Count >250/μL)

<table>
<thead>
<tr>
<th>(A) Prospective Analysis</th>
<th>SBP (PMN &gt; 250/μL)</th>
<th>No SBP (PMN &lt;250/μL)</th>
<th>P (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD2 risk allele</td>
<td>13</td>
<td>24</td>
<td>0.008</td>
</tr>
<tr>
<td>No NOD2 risk allele</td>
<td>17</td>
<td>96</td>
<td>OR = 3.06</td>
</tr>
</tbody>
</table>

(95% CI 1.31–7.15)

B. Appenrodt et al. Hepatology 2010; 51:1327-1333
Acute (ALF), chronic (CLF) or acute on chronic liver failure (ACLF)

The expressions of TNFα- and IL-10 positive cells within the liver tissue

Bacterial translocation (BT)

Model for a role of Nod1 and Nod2 as cytosolic surveillance proteins of mucosal surfaces

Bacterial translocation (BT)

Myosin II regulatory light chain kinase (MLCK) phosphorylation

Cultured intestinal epithelial cell permeability to 3kD fluorescein isothiocyanate-dextran exposed to IFN-γ followed by TNF-α

Bacterial translocation (BT)

Headlines

- Prevalence
- Pathogenesis
- Pathophysiological consequences
- Clinical consequences
- Prevention
Bacterial translocation (BT)

Endotoxins and proinflammatory cytokines

Increasing rate of BT
Bacterial translocation (BT)

**Bacterial translocation in cirrhosis: clinical consequences**

- Bacterial infections
- Cardiovascular dysfunction
- Renal failure
- Hepatic encephalophaty
Bacterial translocation (BT)

Bacterial translocation in cirrhosis: consequences

Viable Bacteria
Translocation

Bacterial infection

↑ LPS

↑ TNFα

SIRS
Bacterial translocation (BT)

Actuarial probability of severe bacterial infections in patients with cirrhosis and ascites according to the plasma level of lipopolysaccharide-binding protein (LBP)

Bacterial translocation (BT)

Bacterial translocation in cirrhosis: consequences

- Bacterial fragments
- Translocation
- Bacterial infection
- LPS
  - LPS
  - TNFα
  - SIRS

↑ LPS
Tumor necrosis factor α (TNFα) and Interferon γ (INFγ) levels in cirrhotic patients with ascites

Bacterial translocation (BT)

Bacterial translocation (BT)

Molecular translocation persists during i.v. antibiotic treatment of SBP episodes

Bacterial translocation (BT)

Bacterial translocation in cirrhosis: clinical consequences

- Bacterial infections
- Cardiovascular dysfunction
- Renal failure
- Hepatic encephalophaty
### Bacterial translocation (BT)

**Six month follow up of patients with cirrhosis and refractory ascites according to the detection of Bact-DNA in ascites**

<table>
<thead>
<tr>
<th>Event</th>
<th>Bact-DNA+ve (n= 23)</th>
<th>Bact-DNA-ve (n= 14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All complications</td>
<td>96%</td>
<td>64%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HRS 1</td>
<td>26%</td>
<td>0%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Death</td>
<td>46%</td>
<td>14%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*P. Angeli et al. (AASLD Annual Meeting 2010)*
Bacterial translocation (BT)

Endotoxins and proinflammatory cytokines

Further derangement of systemic hemodynamics

Fibrosis progression in the liver and increase in portal pressure

Organ failure(s)
Bacterial translocation (BT)

TLR4 expression in the Bile duct ligated and in the BDL + LPS group

N. Shah et al. Journal of Hepatology 2012 vol. 56 j 1047–1053
Bacterial translocation (BT)

Methamine silver staining of the kidney in the BDL group and in the BDL group administered LPS (BDL+LPS group)

N. Shah et al. Journal of Hepatology 2012 vol. 56 j 1047–1053
Bacterial translocation (BT)

Bacterial translocation in cirrhosis: clinical consequences

- Bacterial infections
- Cardiovascular dysfunction
- Renal failure
- Hepatic encephalopathy
Bacterial translocation (BT)

Activation state of CD103+ dendritic cells in mesenteric lymph nodes of control rats and cirrhotic rats according to the Bact-DNA state and gut viable bacteria translocation (GBT)

L. Munoz et al. Hepatology 2012 (Epub ahead of print)
Bacterial translocation (BT)

Schematic representation of the “in vitro” model of functional monocyte deactivation

GA. Antoniades et al. J. Hepatol. 2008; 49: 945-861
Bacterial translocation (BT)

Recurrent bacterial Translocation

Bacterial Translocation

Bacterial infection

↑ LPS

↑ LPS

↑ LPS

↑ TNFα

Monocyte deactivation

CARS

SIRS
**Bacterial translocation (BT)**

Prognostic model model in patients with cirrhosis who were admitted with or developed a bacterial infection during hospitalization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>OR</th>
<th>OR 95 % CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.9689</td>
<td>1.5511</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD</td>
<td>0.1169</td>
<td>0.0281</td>
<td>1.124</td>
<td>(1.064-1.188)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Albumin</td>
<td>-0.6863</td>
<td>0.3341</td>
<td>0.503</td>
<td>(0.262-0.069)</td>
<td>0.0399</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.0279</td>
<td>0.0120</td>
<td>1.028</td>
<td>(1.004-1.053)</td>
<td>0.0202</td>
</tr>
<tr>
<td>Second infection</td>
<td>1.4852</td>
<td>0.4022</td>
<td>4.4416</td>
<td>(2.007-9.713)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*JS. Bajaj et al. Hepatology 2012 (Epub ahead of print)*
Bacterial translocation (BT)

Actuarial probability of survival in patients with cirrhosis and ascites according to the Bact-DNA state and the MELD score

Bacterial translocation (BT)

Headlines

- Prevalence
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Bacterial translocation (BT)

Aims in the prevention of Bacterial translocation

• to decrease the bacterial overgrowth
• to change the microbiome
• to reduce the intestinal permeability
• to manipulate the immune response
Primary prevention of spontaneous bacterial peritonitis (SBP)

- patients with cirrhosis and low protein ascitic level (15 g/l)
  and one of the following conditions:
  - advanced liver failure (CTP ≥ 9 with total serum bilirubin ≥ 3 mg/dl)
    or
  - impaired renal function (serum creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl)
    or
  - serum sodium level ≤ 130 mmol/l

*J. Fernandez et al. Gastroenterology 2007; 133: 818-824*
Bacterial translocation (BT)

Probability of development of spontaneous bacterial peritonitis

Norfloxacin
Placebo

P < 0.001

J. Fernandez et al. Gastroenterology 2007; 133: 818-824
Bacterial translocation (BT)

Probability of one year survival

Norfloxacin

Placebo

P < 0.01

J. Fernandez et al. Gastroenterology 2007 ; 133 : 818-824
Bacterial translocation (BT)

Probability of hepatorenal syndrome

\[ P < 0.05 \]

\[ \text{J. Fernandez et al. Gastroenterology 2007 ; 133 : 818-824} \]
Bacterial translocation (BT)

Effects on norfloxacin on plasma endotoxins in patients with cirrhosis and ascites

Bacterial translocation (BT)

Norfloxacin and TNF- concentrations in 2 patients with multiple serum samples collected at inclusion (1) and at 15 days and 1, 2, 4, 7, 8, 9, and 10 months, respectively, after inclusion

Effects on norfloxacin on systemic vascular resistance in patients with cirrhosis and ascites

Bacterial translocation (BT)

Before After

(units)

P < 0.05

Bacterial translocation (BT)

Temporal relationship between intracellular levels of norfloxacin or trimethoprim/sulfamethoxazole and NF-

\[ P. \text{ Zapater et al. Gastroenterology 2009;137:1669–1679} \]
Bacterial translocation (BT)

Spontaneous bacterial peritonitis with septic shock sustained by Klebsiella pneumoniae in a patient with cirrhosis

Table 2 Antibiogram of carbapenemase-producing Klebsiella pneumoniae

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (µg/ml)</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin</td>
<td>≥ 128</td>
<td>R</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>≥ 32</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥ 16</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Amikacina</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≥ 8</td>
<td>R</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>S</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration; R, resistant; S, sensitive.

Bacterial translocation (BT)

Rate of bacterial translocation in cirrhotic rats receiving Lactobacillus GG (LGG) or Milk (MILK) or norfloxacin single dose followed by LGG (NOR-LGG) or milk (NOR-MILK)

Cecal colonization with Lactobacillus was achieved in 90% of treated rats

*TM. Bauer et al. J. Hepatol. 2002; 36: 501–506*
Bacterial translocation (BT)

Cumulative probability of developing spontaneous bacterial peritonitis (SBP) in patients with cirrhosis receiving norfloxacin and probiotics and vs patients with cirrhosis receiving norfloxacin and placebo

Bacterial translocation (BT)

Effect of antibiotic, cisapride and placebo on small-intestinal bacterial overgrowth (SIBO) and oro-cecal transit time (OCTT)

Table 3. Effect of Antibiotic, Cisapride and Placebo on SIBO and OCTT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antibiotics</th>
<th>Cisapride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>SIBO (n)</td>
<td>8</td>
<td>6</td>
<td>2*</td>
</tr>
<tr>
<td>OCTT (min)</td>
<td>122 ± 31</td>
<td>117 ± 28</td>
<td>97 ± 38*</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with baseline within the group.

Bacterial translocation (BT)

Aims in the prevention of Bacterial translocation

- to decrease the bacterial overgrowth
- to change the microbiome
- to restore the intestinal mucosal barrier
- to manipulate the immune response
Bacterial translocation (BT)

Prevention of spontaneous bacterial peritonitis by propanolol in non randomized control trials (RCTs) and in non randomized comparative studies

M. Senzolo et al. Liver Int. 2009 ; 29 : 1189-19993
Bacterial translocation (BT)

Effect of splanchnic sympathetcomy (SE) on in vitro phagocytosis index of peritoneal polymorhonuclear lecocytes

M. Worlicek et al. Gut 2010; 59: 1127-1134
Bacterial translocation (BT)

**Aims in the prevention of Bacterial translocation**

- to decrease the bacterial overgrowth
- to change the microbiome
- to restore the intestinal mucosal barrier
- to manipulate the immune response
Rate of bacterial translocation in rats with cirrhosis receiving anti-TNFα monoclonal antibody (anti-TNFα), placebo, or an IgG isotype control (IgG2a), * = p < 0.05 vs Group I.

Effects of pentoxifylline on intestinal bacterial overgrowth (IBO), bacterial translocation (BT) and spontaneous bacterial peritonitis (SBP) in rats with cirrhosis

Pentoxifylline reduced the level of malonyldialdehyde in the cecal mucosa

F. Corradi et al. Dig. Liver Dis. 2012; 44: 239-244