Microbial Epidemiology and Outcome of Posttransplant Bloodstream Infection: An Analysis of 222 Consecutive Liver Transplant Recipients

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Background

- Effective antimicrobial prophylaxis strategies
  - ↓ incidence of infections among liver transplant recipients
- Morbidity and mortality due to infectious complications are major problems
- Bloodstream infection (BSI): Bacteremia
  - Most frequently occurring infectious complication after liver transplantation (LT) (incidence 21~49%)
  - Significant predictor for Posttransplant death

Del Pozo et al. World J Gastroenterol 2008; Bert F et al. Liver transpl 2010
Background

- Most BSI are caused by
  - Intra-abdominal sepsis or biliary tract infections
  - Hematogenous spread from the portal blood
- Other sources of BSI
  - Respiratory, urinary, central venous catheter-related or wound infections
- Growing concern for the increased resistance to antimicrobial agents
  - Multi-drug resistant Gram (+) and G (-) pathogens are emerging with increased antimicrobial resistance.

Background

- Detailed knowledge of posttransplant BSI
  - Improve empirical antimicrobial strategies
  - Aid in overcoming antimicrobial resistance
  - Help infection control practices

- The aim of this study
  - To assess the frequency, source, timing and antimicrobial resistance of bacterial pathogens responsible for BSI during 1\textsuperscript{st} year after LT
  - To evaluate the associated risk factors of BSI and mortality in LT recipients with BSI
Materials and Methods

- Patients who were performed LT from February 2005 to May 2011
- Ajou University Hospital
- 231 LT operations including
  8 re-transplantation in 222 recipients
- 11 ABO-incompatible LT since 2007
- 33 salvage LT after hepatic resection for HCC
Materials and Methods

- **Definition of Bloodstream infection**
  - A positive blood culture with a pathogenic organism
    - At least 2 sets of blood culture for potential skin contaminant
  - Each isolated organisms were counted as a single case

- **Definition of source of BSI**
  - The same organism found in the blood culture is isolated from a clinically significant site of infection (eg. Bile, urine, intravascular catheter, liver aspiration…)

Definitions by CDC criteria

### Demographic Characteristics of the Study Population (N=222)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>49.1 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Gender, <strong>male</strong>, N. (%)</td>
<td>168 (75.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B virus</strong></td>
<td>170 (76.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>58 (26.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td>106 (47.7%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Acute hepatic failure</td>
<td>5 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>5 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>4 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (1.8%)</td>
<td></td>
</tr>
</tbody>
</table>
Demographic Characteristics of the Study Population (N=222)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>9.3</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>MELD score</strong></td>
<td>18.9</td>
<td>10.4</td>
</tr>
<tr>
<td><strong>Broad-spectrum antibiotics in 1 month</strong></td>
<td>125</td>
<td>(56.3%)</td>
</tr>
<tr>
<td>Salvage liver transplantation</td>
<td>33</td>
<td>(14.8%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>23</td>
<td>(10.3%)</td>
</tr>
</tbody>
</table>
Materials and Methods

- **Antimicrobial prophylaxis**
  - Cefoperazone/sulbactam (2005~2007)
  - Piperacillin/tazobactam (2007~) for 3~5 days
  - **Vancomycin** for 3~5 days
  - **Amphotericin B deoxycholate** (2005~2009)
    - Liposomal Amphotericin B (2009~) for 5 days
  - **Gancyclovir**
  - Selective bowel decontamination
  - Trimethoprim/sulfamethoxazole

- **Immunosuppression**
  - Tacrolimus or cyclosporine, prednisone, basiliximab
Materials and Methods

- **Pretransplant variables**
  - Age, gender, B-viral hepatitis, alcoholic liver cirrhosis, CTP\(^1\) score, MELD\(^2\) score, HCC\(^3\), DM\(^4\), broad spectrum antibiotics in 1 month

- **Operative variables**
  - Living donor graft, pRBC transfusion, op time, ABO-I\(^5\), splenectomy

- **Posttransplant variables**
  - Posttransplant hemodialysis, reoperation within 3 months, acute rejection, Intensive care unit (ICU) stay, admission days, retransplantation, biliary complications

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\(^1\) Child-Pugh-Turcotte, \(^2\) Model of end stage liver disease, \(^3\) hepatocellular carcinoma, \(^4\) Diabetes mellitus, \(^5\) Incompatible
Results

**Frequency**

- **28.8%** (64 of 222) of LT recipients underwent 112 episodes of BSI
  - 50.4 BSI episodes per 100 patients 1 YR posttransplant

- One patient can have more than one episode
  - 1 BSI in 59.3% (38 /64) of patients
  - **Multiple BSI in 40.6%** (26 /64) of patients

**Total follow-up days in median with range:**
1306 with 2-1803 days
Results: Timing

- Most BSI episodes occurred within a month after LT

- Median time with interquartile range from the day of LT to the day of BSI
  - Total (n=134): 28 days with 6-89 days
  - GPC (n=44): 40 days with 19-113 days
  - GNB (n=71): 23 days with 6-66 days
  - Fungi (n=19): 12 days with 5-95 days

- The median time to onset (median with IQR)
  - *K. pneumoniae*, the earliest: 8 with 4-83 days
  - Enterococcus, the last: 101 with 24-153 days
## Causative pathogens of BSI

<table>
<thead>
<tr>
<th>Organisms (n=135)</th>
<th>N. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positives n= 44 (32.8%)</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>14 (10.4)</td>
</tr>
<tr>
<td>Coagulase negative <em>Staphylococcus</em></td>
<td>5 (3.7)</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>24 (17.8)</td>
</tr>
<tr>
<td>Other GP</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td><strong>Gram negatives n=72 (52.9%)</strong></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>19 (14.2)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>17 (11.9)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>6 (4.4)</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>14 (10.4)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>12 (8.9)</td>
</tr>
<tr>
<td>Other GN</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td><strong>Fungi n=19 (14.2%)</strong></td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>9 (6.7)</td>
</tr>
<tr>
<td><em>Candida tropicalis</em></td>
<td>5 (3.7)</td>
</tr>
<tr>
<td>Other candida species</td>
<td>5 (3.7)</td>
</tr>
</tbody>
</table>
Antimicrobial susceptibility of bloodstream infection

- Most pathogens were highly multi-drug resistant
  - *Enterococcus faecium*: 38% (8/21) Vancomycin-R
  - *K. pneumonia*: 68.4% (13/19) ESBL-producing
  - *Escherichia coli*: 82.3% (14/17) ESBL-producing
  - *S. aureus*: 92.8% (13/14) Methicillin-R
  - *A. baumannii*: 92.8% (13/14) Carbapenem-R
  - *P. aeruginosa*: 91.6% (11/12) Carbapenem-R

- All candida were susceptible to fluconazole.
  Carbapenem-R enterobacteriaceae or Vancomycin-R S. aureus were not identified.

ESBL, extended spectrum beta-lactamase
Source of Bloodstream infection

- Source of infection and the m/c causative pathogen
  - **Biliary 36.2%** (49/135 isolates): Enterococci
  - **Abd/wound 28.1%** (38/135): *K. pneumoniae*
  - **IVC related 18.5%** (25/135): *Candida*
  - **Lung 5.9%** (8/135): *Pseudomonas*
  - **Urinary 2.2%** (3/135), Unknown 8.9% (12/135)

IVC, intravascular catheter; m/c most common
Patient survivals

Kaplan-Meier Survival Curves

<table>
<thead>
<tr>
<th></th>
<th>Patients with BSI</th>
<th>Patients without BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1YR Surv rate</strong></td>
<td>60.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td><strong>30 D Mortality</strong></td>
<td>22.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td><strong>1YR Mortality</strong></td>
<td>40.0%</td>
<td>10.5%</td>
</tr>
<tr>
<td><em>P</em> &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Without BSI

GP

GN

Fungi

polymicrobial

Fungal BSI

Non-fungal BSI

Poly microbial

Mono microbial

1YR SR

35.7%

66.1%

26.7%

69.1%
Risk factors for Posttransplant Bloodstream infection

- **Univariate Analysis**
  - CTP score, MELD score, transfusion, posttransplant HD, re-op episodes, postop ICU stay, total postop adm days, retransplantation and biliary complication.

- **Multivariate Analysis**
  - **Biliary Complication**: OR 2.91, CI 1.29-6.59; \( P=0.010 \)
  - **Longer ICU stay**: OR 1.04, CI 1.00-1.08; \( P<0.001 \).
## Predictor for Death after LT

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Patients with BSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.97-1.03</td>
</tr>
<tr>
<td>B-viral hepatitis</td>
<td>0.51</td>
<td>0.28-0.95</td>
</tr>
<tr>
<td>HCC</td>
<td>2.14</td>
<td>1.20-3.82</td>
</tr>
<tr>
<td>Post-transplant HD</td>
<td>3.38</td>
<td>1.70-6.70</td>
</tr>
<tr>
<td>ICU stay after LT</td>
<td>1.02</td>
<td>1.00-1.04</td>
</tr>
<tr>
<td>Post-transplant adm</td>
<td>0.97</td>
<td>0.95-0.98</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>3.92</td>
<td>2.22-6.91</td>
</tr>
<tr>
<td>Candidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial BSI</td>
<td></td>
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</tr>
</tbody>
</table>
Discussion

- Clinical significance of BSI during 1 yr after LT
  - **Common Cx: 28.8%** (64/222) of recipients
  - Strongest predictor for death: HR 3.92, CI 2.22-6.91; \( P<0.001 \)
  - BSI group **1YR SR 60.0%** (vs 89.5% of non-BSI group)
  - Particularly high mortality in patients with candida or polymicrobial BSI

- Relatively **higher** rate of BSI
  - **Poor general condition**: higher MELD (18.9) and CTP score (9.3)
  - Possible **learning curve effect** in the early transplant period
Discussion:

- **Common type of BSI**
  - Enterococcemia originated from *biliary infection* in the later posttransplant period
  - Enteric GN bacilli or nonfermenting GN bacteremia from abdominal or/and wound infection
  - Candidemia or *A. baumannii* bacteremia originated from *the intravascular catheter infection*
    - 18.5% of posttransplant BSI was Catheter related: CRBSI is *nosocomial* that warrants additional action for infection control practices
Discussion

- Most pathogens were highly MDR
  - **ESBL**: 68.4% *K. pneumoniae*, 82.3% *E. coli*
  - **VRE**: 38% *E. faecium*
  - **Methicillin-R**: 92.8% MRSA, 100% MRCoNS
  - **Carbapenem-R**: 92.8% *A. baumannii*, 91.6% *Pseudomonas*

- Factors increase MDR
  - Extensive exposure to **broadspectrum antibiotics** before LT
  - Routine use of **broadspectrum antibiotics** as a prophylaxis: Antipseudomonal penicillin + Vancomycin

- Posttransplant hemodialysis as a significant predictor for death
  - Cautious and selective use of **nephrotoxic agents** including antimicrobial prophylaxis for LT
Conclusion

- Posttransplant BSI occurred frequently during 1 year after LT and it leads to low patient survival rate.
- **Biliary complication** was the strongest predictor for BSI and **biliary origin enterococccemia** was the most common type of BSI after LT.
- **Fungal and polymicrobial BSI** showed particularly high mortality.
- Most of the pathogens in BSI were **highly MDR**.
- This study provides detailed microbiology and clinical feature of posttransplant BSI which help **to guide selection of antimicrobial therapy** in LT recipients with suspected BSI and to improve infection control practices.