Epidemiology of bacterial infections in transplantation

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Reduced mortality after allogeneic hematopoietic-cell transplantation (FHCRC-Seattle)

There were significant decreases in the risk of disease caused by viral, fungal and bacterial infections over the two study periods.

Granulocytes (log$_{10}$ 1x 10$^6$/L)

Risk periods for bacterial infection following HSCT

- PRETRANSPLANT
- PRE-ENGRAFTMENT
- EARLY POST-ENGRAFTMENT
- LATE POST-ENGRAFTMENT

Bacterial infections

Encapsulated bacteria

Granulocytes (log$_{10}$ 1x 10$^6$/L), Temperature °C

Risk periods for bacterial infection following HSCT:

- **PRETRANSPLANT**
- **PRE-ENGRAFTMENT**
- **EARLY POST-ENGRAFTMENT**
- **LATE POST-ENGRAFTMENT**

**Bacterial infections**

- Stem cells
- acute GvHD
- chronic GvHD
- low IgG

**NEUTROPENIA**

Temperature chart with days, weeks, and months indicated.
Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-engraftment (n= 100)</th>
<th>Post-engraftment (n= 89)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo-HSCT</td>
<td>43%</td>
<td>86%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GVHD</td>
<td>1%</td>
<td>44%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Corticoesteroids</td>
<td>14%</td>
<td>47%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neutropenia (&lt;500)</td>
<td>96%</td>
<td>19%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MASCC (≥ 21)</td>
<td>80%</td>
<td>42%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior ATB (30 d)</td>
<td>36%</td>
<td>68%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe mucositis</td>
<td>20%</td>
<td>4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Concomitant infection</td>
<td>4%</td>
<td>20%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

189 bacteremias (Jan 2006 - Aug 2013)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-engraftment (n=100)</th>
<th>Post-engraftment (n=89)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>5%</td>
<td>21%</td>
<td>.001</td>
</tr>
<tr>
<td>Adequate initial ATB therapy</td>
<td>63%</td>
<td>68%</td>
<td>NS</td>
</tr>
<tr>
<td>ICU admission</td>
<td>7%</td>
<td>25%</td>
<td>.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4%</td>
<td>14%</td>
<td>.015</td>
</tr>
<tr>
<td>Early case-fatality rate (48 h)</td>
<td>2%</td>
<td>10%</td>
<td>.017</td>
</tr>
<tr>
<td>Overall case-fatality rate (30 d)</td>
<td>4%</td>
<td>25%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Causative organisms in 189 episodes of BSI in HSCT recipients (2006-2013)

- CoNS
- S. pneumoniae
- VGS
- S. aureus
- E. faecium
- E. coli
- P. aeruginosa
- K. pneumoniae
- GPB
- GNB

Early-onset and Late-onset infection

Pre-engraftment

Post-engraftment

Gudiol C. Bone Marrow Transplant 2014
### Source of BSI in HSCT recipients (2006 – 2013)

<table>
<thead>
<tr>
<th>Source</th>
<th>Pre-engraftment</th>
<th>Post-engraftment</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n= 100)</td>
<td>(n= 89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter related</td>
<td>48%</td>
<td>37%</td>
<td>.13</td>
</tr>
<tr>
<td>Endogenous source</td>
<td>32%</td>
<td>20%</td>
<td>.076</td>
</tr>
<tr>
<td>Unknown source</td>
<td>8%</td>
<td>10%</td>
<td>.080</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1%</td>
<td>14%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe mucositis</td>
<td>10%</td>
<td>2%</td>
<td>.027</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1%</td>
<td>6%</td>
<td>.10</td>
</tr>
</tbody>
</table>
Serious complications of bacteremia caused by viridans group streptococci (VGS) in neutropenic patients with cancer

485 Bacteremias

VGS 88 (18%)

78 (89%)

10 (11%)

Patients with complications

Shock
ARDS
Skin rash
Renal failure

Marron A. Clin Infect Dis 2000
<table>
<thead>
<tr>
<th>Variable</th>
<th>Case patients</th>
<th>Control patients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in y (range)</td>
<td>38.5 (16–71)</td>
<td>43.2 (16–73)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (60)</td>
<td>23 (57.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>4 (40)</td>
<td>17 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>4 (40)</td>
<td>15 (37.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>6 (60)</td>
<td>25 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Allogeneic BMT</td>
<td>4 (40)</td>
<td>4 (10)</td>
<td>.040</td>
</tr>
<tr>
<td>Severe oral mucositis</td>
<td>7 (70)</td>
<td>13 (32.5)</td>
<td>.036</td>
</tr>
<tr>
<td>High-dose therapy with cyclophosphamide</td>
<td>6 (60)</td>
<td>10 (25)</td>
<td>.043</td>
</tr>
<tr>
<td>High-dose therapy with cytosine arabinoside</td>
<td>3 (30)</td>
<td>21 (52.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Prophylactic norfloxacin</td>
<td>7 (70)</td>
<td>33 (82.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Isolated <em>Streptococcus</em> species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. mitis</em></td>
<td>7 (70)</td>
<td>31 (77.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>3 (30)</td>
<td>9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Penicillin resistance</td>
<td>5 (50)</td>
<td>16 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Cured</td>
<td>2 (20)</td>
<td>33 (82.5)</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>8 (80)</td>
<td>7 (17.5)</td>
<td></td>
</tr>
</tbody>
</table>
BSI in allogeneic hematopoietic stem cell transplant recipients: reemergence of GNB and increasing antibiotic resistance

168 episodes of BSI in 132 pts (median, 10 days after HSCT) and 182 pathogens isolated (2004 – 2007), Genoa, Italy

Mikulska M. Biol Blood Marrow Transplant 2009
BSI in allogeneic hematopoietic stem cell transplant recipients: reemergence of GNB and increasing antibiotic resistance

- All patients received routine fluoroquinolone prophylaxis
- There was a significant decrease in GPB/GNB ratio over time, from 2.4 in 2004 to 1 in 2007 (p = .043)
- Among GPB, staphylococci decreased from 64% in 2004 - 2005 to 23% in 2006 - 2007
- The incidence of *E. coli* among GNB increased from 20% in 2004 to 62% in 2007 (p = .003)
- Fluoroquinolone-resistance was common, both among GPB (81%) and GNB (74%)
- Mortality at 7 days after BSI was 11%, reaching 39% for *P. aeruginosa*
Enterococcal bacteremia in recipients of allogeneic hematopoietic stem cell transplantation

- 93 of 752 pts who received allo-HSCT (2004-2008) at the University of Minnesota had enterococcal BSI during the first year
- Vancomycin resistance was observed in 66% and 31% of isolates in adults and children, respectively
- Colonization with VRE and delay in engraftment were risk factors for VRE bacteremia
- The hazard ratio for all-cause mortality up to 1 yr after transplant was 4.2 (95% CI, 3.1 - 6.9) for pts with VRE and 2.7 (1.4 - 5.1) for pts with VSE
Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients

**Design:** retrospective nested case-control study

**Objective:** to describe the epidemiology, timing and risk factors for CDI

**Setting:** the Johns Hopkins Hospital, Baltimore, Maryland

**Population:** 999 HSCT adult recipients

**Overall 1-year incidence of CDI:** 9.2%

**Median time to CDI:** autologous *6.5 days*; allogeneic *33 days*

Alonso CD. Clin Infect Dis 2012
Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients

Risk factors for CDI in allo-HSCT:
- Chemotherapy prior to conditioning
- Broad-spectrum ATB
- Acute GVHD
- GI GVHD ➔ recurrent CDI

Alonso CD. Clin Infect Dis 2012
Overall patient survival by first SOT in the Swiss Transplant Cohort Study (2008 – 2011)

Koller MT. Eur J Epidemiol 2013
Occurrence of infection episodes in the Swiss Transplant Cohort Study (1.5.2008 – 30.9.2011)

<table>
<thead>
<tr>
<th>Patients with any infectious event [n (%)]</th>
<th>1,048 (62%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any proven infection or viral syndrome</td>
<td>521 (31%)</td>
</tr>
<tr>
<td>Average number of infectious events in subjects with at least one infection, median</td>
<td>4.17</td>
</tr>
<tr>
<td>Average number of proven infections or viral syndrome in subjects with at least one such episode</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Koller MT. Eur J Epidemiol 2013
Changing timeline of infection after SOT

Donor-Derived Infection
- Nosocomial, technical (donor or recipient)
- Activation of latent infection (relapsed, residual, opportunistic)
- Community-acquired

Transplantation

Recipient-Derived Infection
- <1 Month
  - Infection with antimicrobial-resistant species:
    - MRSA
    - VRE
    - Candida species (non-albicans)
    - Aspiration
    - Catheter infection
    - Wound infection
    - Anastomotic leaks and ischemia
    - Clostridium difficile colitis
  - Donor-derived infection (uncommon):
    - HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, Trypanosoma cruzi
  - Recipient-derived infection (colonization):
    - Aspergillus, pseudomonas

- 1-6 Months
  - With PCP and antiviral (CMV, HBV) prophylaxis:
    - Polyomavirus BK infection, nephropathy
    - C. difficile colitis
    - HCV infection
    - Adenovirus infection, influenza
    - Cryptococcus neoformans infection
    - Mycobacterium tuberculosis infection
    - Anastomotic complications
  - Without prophylaxis:
    - Pneumocystis
    - Infection with herpesviruses (HSV, VZV, CMV, EBV)
    - HBV infection
    - Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, T. cruzi

- >6 Months
  - Community-acquired pneumonia, urinary tract infection
  - Infection with aspergillus, atypical molds, mucor species
  - Infection with nocardia, rhodococcus species
  - Late viral infections:
    - CMV infection (colitis and retinitis)
    - Hepatitis (HBV, HCV)
    - HSV encephalitis
    - Community-acquired (SARS, West Nile virus infection)
    - JC polyomavirus infection (PML)
    - Skin cancer, lymphoma (PTLD)

1,677 patients (2008-2011)
## Bloodstream Infections Among Transplant Recipients: Results of a Nationwide Surveillance in Spain

<table>
<thead>
<tr>
<th></th>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Lung</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplants (n)</td>
<td>1400</td>
<td>1012</td>
<td>291</td>
<td>167</td>
<td>65</td>
</tr>
<tr>
<td>Episodes (n)</td>
<td>121</td>
<td>134</td>
<td>32</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>102</td>
<td>105</td>
<td>24</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>8.6</td>
<td>13.2</td>
<td>11</td>
<td>10.2</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Crude mortality was 7.8%, being highest in liver recipients (16%).

Moreno A. Am J Transpl 2007
Etiology of 321 Episodes of Bacteremia in SOT Recipients

- **CNS**: 284 episodes (37%)
- **E. coli**: 127 episodes (17%)
- **A. baumanii**: 60 episodes (8%)
- **Pseudomonas spp**: 47 episodes (6%)
- **Enterococcus spp**: 46 episodes (6%)
- **S. aureus**: 37 episodes (5%)
- **Klebsiella spp**: 29 episodes (4%)

Moreno A. Am J Transpl 2007
Bloodstream Infections Among SOT Recipients
Proportion of Resistant Organisms (2003-2005)

- Enteric bacilli: 14.5%
- No-fermentative: 9.7%
- S. aureus: 16.2%

Overall, 12% of isolates were MDR
Risk Factors and Outcomes of Bacteremia Caused by Drug-Resistant ESKAPE Pathogens in Solid-Organ Transplant Recipients

276 cases of bacteremia

130 (47%) ESKAPE bacteremia

Non-rESKAPE

76 cases

rESKAPE

54 cases (19.6%)

Hospital de Bellvitge (Jan 2007- Dec 2012)

Bodro M. Transplantation 2013
84 bacteremias (30.4%) were due to ESBL-producing *E. coli*
Risk factors for rESKAPE bacteremia in SOT recipients by multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior transplantation</td>
<td>3.1</td>
<td>1.1 – 9.4</td>
</tr>
<tr>
<td>Prior antibiotic therapy</td>
<td>4.0</td>
<td>1.5 – 10.6</td>
</tr>
<tr>
<td>Septic shock</td>
<td>2.8</td>
<td>1.4 – 5.7</td>
</tr>
</tbody>
</table>

Median time from transplantation was shorter in bacteremia due to rESKAPE pathogens compared with bacteremia due to other organisms (59 vs. 331 days; p = 0.003)
Antibiotic therapy and outcomes of SOT recipients with rESKAPE Bacteremia

<table>
<thead>
<tr>
<th>Variable</th>
<th>rESKAPE</th>
<th>Other</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate ATB therapy</td>
<td>41%</td>
<td>22%</td>
<td>.01</td>
</tr>
<tr>
<td>ICU admission</td>
<td>52%</td>
<td>25%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>39%</td>
<td>17%</td>
<td>.001</td>
</tr>
<tr>
<td>Overall case-fatality rate (30d)</td>
<td>35%</td>
<td>14%</td>
<td>.001</td>
</tr>
</tbody>
</table>

Bodro M. Transplantation 2013
Bacterial Urinary Tract Infection After SOT in the RESITRA Cohort

- Bacterial urinary tract infection, kidney transplant vs. others in the RESITRA cohort (4388 pts).
- 192 pts (4.4%) with 249 episodes of urinary infection (0.23 episodes/1000 transplant days).
- 156 pts were kidney or kidney/pancreas recipients (7.3%).
- *Escherichia coli* (58%), 26% were ESBL-producing strains.
- Risk factors: age, female sex, and posttransplant dialysis.
Risk Factors for Infection with Extended-Spectrum and AMpC β-Lactamase-Producing Gram Negative Rods in Renal Transplantation

- A cohort observational study (2003-2006).
- 417 kidney transplant recipients (61 kidney/pancreas).
- Incidence of ESBL-producing and desrepressed AMpC β-Lactamases was 11.8% (49 patients).
- The most frequent bacteria was *E. coli* (35/60) followed by *Klebsiella spp* (12/60).
## Risk Factors for ESBL-Producing and Desrepressed AmpC β-lactamase GNB Infection in Kidney Recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney-Pancreas Tx</td>
<td>3.5</td>
<td>1.6 – 7.8</td>
</tr>
<tr>
<td>Prior antibiotic use</td>
<td>2.1</td>
<td>1.1 – 4.1</td>
</tr>
<tr>
<td>Posttransplant dialysis</td>
<td>3.1</td>
<td>1.5 – 6.4</td>
</tr>
<tr>
<td>Posttransplant urinary obstruction</td>
<td>5.8</td>
<td>2.2 – 14.9</td>
</tr>
</tbody>
</table>

Linares L. Am J Transpl 2008
Infection with KPC-producing *Klebsiella pneumoniae* in Solid Organ Transplantation

- Outbreak of 12 cases of KPC-2 producing KP in Sao Paulo.
- Incidence: 26% KT (6); 17% HT (2); 13% LT (4). Median time to infection: 20 days.
- Site of infection: urinary tract (4), bacteremia (4), pneumonia (2), SSI (2).
- All but 1 patient had received prior antibiotic therapy (30 days).
- Treatment: Tige + PB (3); PB + carbapenem (3); PB (3); Tige + Imip (1)
- Overall 30-day mortality: 42%.
**Clostridium Difficile Colitis: Increasing Incidence, Risk Factors, and Outcomes in Solid Organ Transplant Recipients**

**Population:** 1331 SOT recipients, Canada (1999 – 2010).

**Incidence of CDAD:** 4.5% (1999), 21.1% (2005), 9.5% (2010).

**Independent risk factors for CDAD:** age > 65 yrs (HR 1.47), induction with ATG (1.43), and transplant other than KT (1.41).

**Independent predictors of CCDC:** WBCC >25000 and evidence of pancolitis on CT.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence of CDAD</td>
<td>165</td>
<td>12.4</td>
</tr>
<tr>
<td>Incidence of CCDC</td>
<td>26</td>
<td>15.8</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>14</td>
<td>8.5</td>
</tr>
<tr>
<td>Overall graft loss</td>
<td>13</td>
<td>7.9</td>
</tr>
<tr>
<td>Recurrent CDC</td>
<td>14</td>
<td>8.5</td>
</tr>
</tbody>
</table>
Summary

• Bacterial infections continue to be a major cause of morbidity and mortality among HSCT patients and SOT recipients.

• The increasing prevalence of antibiotic resistance among organisms causing BSI in these patients is cause for concern.

• CDAD is emerging as a significant problem in some centers.

• Need to improve prevention strategies and to optimize antimicrobial use.