Changes in the Symbiotic Microbial Community and Its Impact on Health and Disease

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Perturbations of the Gut Microbiota and its Relevance to Infections of Immunocompromised Individuals

Memorial Sloan-Kettering Cancer Center
New York, New York
Allogeneic hematopoietic stem cell transplantation (allo-HSCT)

- **Intensive Treatment**
  - Chemotherapy
  - Total body irradiation
  - Antibiotics

- **Complications**
  - Bloodstream infections
  - *Clostridium difficile* infection (CDI)
  - Graft-versus-host disease (GVHD)
Timeline of early allo-HSCT

WBC (K/mcL)

Prophylactic and/or Treatment Antibiotics

Conditioning Regimen

Hospital Admission (Day -7)

Stem cell infusion (Day 0)

Pre-Engraftment
Mucositis
Neutropenia

Engraftment (day +10 to +35)

Post-Engraftment
Graft-versus-host disease
Opportunistic infections
Timeline of early allo-HSCT

**Conditioning Intensity**
- Non-myeloablative (NMA)
- Reduced intensity (RIC)
- Myeloablative (MA)

**Stem cell sources**
- Related donor
- Unrelated donor
- Umbilical cord blood

**T-lymphocytes**
- T-cell depleted cells
- Conventional

**Antibiotics**
- Prophylaxis
- Empiric treatment
- Targeted therapy
Timing of bloodstream infections during allo-HSCT

10% incidence of bloodstream infection

MSKCC allo-HSCT data, 1999-2012
Bacteremias during early allo-HSCT (MSKCC, 1999-2012)
MSKCC allo-HSCT data, 1999-2011

- **S. viridans**
- **VRE**
- **Gram Negative**

Proportion of Early BSIs

Year

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Initial Study of 5 allo-HSCT recipients

• Fecal biospecimen protocol
  – 94 allo-HSCT patients
  – 439 fecal specimens
  – Examination of microbiota
  – Correlation with clinical factors and outcomes
Loss of Microbial Diversity During Transplant
Proteobacteria (Gram Negatives)

Streptococcus

Bacteria phylotypes
- other Bacteria
- other Firmicutes
- other Bacteroidetes
- Proteobacteria
- Granulicatella
- Lactococcus
- Veillonella
- Sporacetigenium
- Coprococcus
- Parabacteroides
- Roseburia
- unclassified Lachnospiraceae
- unclassified Firmicutes
- Coprobacillus
- Staphylococcus
- Dorea
- Lactobacillus
- Blautia
- Streptococcus
- Enterococcus

Antibiotics
- Fluoroquinolone
- Metronidazole
- Beta-lactam
- Vancomycin
Cumulative incidence of intestinal domination
Hierarchical clustering of fecal samples

Enterococcus domination

Biodiverse microbiota

Proteobacteria domination

Streptococcus domination

pre-transplant
post-transplant
Microbial state transitions, by Circos plot
Clinical Characteristics
• Conditioning
• Antibiotics

Microbiota
• Diversity
• Taxonomy

Clinical Outcomes
• Bloodstream infection
# Clinical Risk Factors for Bacterial Domination

<table>
<thead>
<tr>
<th>Clinical Predictor</th>
<th>Enterococcus (VRE) Domination</th>
<th></th>
<th>Streptococcus Domination</th>
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<th>Proteobacteria (Gram negative) Domination</th>
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<tbody>
<tr>
<td>Clinical Characteristics</td>
<td>Relative risk(95% CI)</td>
<td>P-value</td>
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<td>P-value</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>1.01 (0.97 - 1.06)</td>
<td>0.567</td>
<td>1.00 (0.96 - 1.04)</td>
<td>0.836</td>
<td>0.98 (0.93 - 1.03)</td>
<td>0.434</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.86 (0.35 - 2.00)</td>
<td>0.726</td>
<td>0.94 (0.34 - 2.58)</td>
<td>0.909</td>
<td>1.17 (0.30 - 4.58)</td>
<td>0.811</td>
</tr>
<tr>
<td>Underlying Diagnosis (Leukemia vs. other)</td>
<td>1.86 (0.80 - 4.60)</td>
<td>0.151</td>
<td>1.18 (0.41 - 3.49)</td>
<td>0.763</td>
<td>0.64 (0.15 - 2.40)</td>
<td>0.507</td>
</tr>
<tr>
<td>Conditioning Regimen (MA/RIC vs. NMA)</td>
<td>0.75 (0.28 - 2.45)</td>
<td>0.599</td>
<td>0.51 (0.16 - 2.08)</td>
<td>0.317</td>
<td>3.08 (0.37 - 399.74)</td>
<td>0.363</td>
</tr>
<tr>
<td>T-cell depleted graft</td>
<td>1.02 (0.40 - 2.47)</td>
<td>0.973</td>
<td>1.19 (0.38 - 3.46)</td>
<td>0.759</td>
<td>1.72 (0.43 - 6.90)</td>
<td>0.430</td>
</tr>
<tr>
<td>Stem cell source (cord vs. donor)</td>
<td>1.05 (0.37 - 2.63)</td>
<td>0.926</td>
<td>0.75 (0.21 - 2.29)</td>
<td>0.625</td>
<td>0.98 (0.21 - 3.88)</td>
<td>0.980</td>
</tr>
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**Dominations:**
- **≥30% relative abundance**

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**Clinical Characteristics**
- Age (years)
- Sex (female)
- Underlying Diagnosis (Leukemia vs. other)
- Conditioning Regimen (MA/RIC vs. NMA)
- T-cell depleted graft
- Stem cell source (cord vs. donor)
## Antibiotic Risk Factors for Bacterial Domination

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<tr>
<td>Vancomycin (IV)</td>
<td>2.10 (0.67 - 10.14)</td>
<td>0.228</td>
<td>5.08 (0.52 - 693.34)</td>
<td>0.196</td>
<td>0.95 (0.33 - 3.75)</td>
<td>0.931</td>
<td></td>
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<tr>
<td>Metronidazole</td>
<td>3.40 (1.66 - 6.75)</td>
<td>0.001</td>
<td>1.73 (0.41 - 6.04)</td>
<td>0.425</td>
<td>1.94 (0.81 - 4.31)</td>
<td>0.130</td>
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</tr>
<tr>
<td>Fluoroquinolone</td>
<td>1.09 (0.49 - 2.25)</td>
<td>0.824</td>
<td>0.09 (0.00 - 0.75)</td>
<td>0.020</td>
<td>1.19 (0.52 - 2.61)</td>
<td>0.673</td>
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<td>Beta-lactam</td>
<td>1.19 (0.47 - 3.45)</td>
<td>0.724</td>
<td>0.64 (0.15 - 3.27)</td>
<td>0.574</td>
<td>3.56 (0.83 - 33.20)</td>
<td>0.094</td>
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# Domination and Risk Factors for Bacteremia

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<th>Domination by</th>
<th>VRE Bloodstream infection</th>
<th>Gram negative bloodstream infection</th>
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<td>Relative Risk (95% CI)</td>
<td>P-value</td>
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<tr>
<td><strong>Enterococcus</strong> (VRE)</td>
<td>9.47 (2.46 - 46.00)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Proteobacteria</strong> (Gram negative)</td>
<td>0.76 (0.01 - 6.20)</td>
<td>0.842</td>
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<tr>
<td><strong>Streptococcus</strong></td>
<td>0.22 (0.00 - 1.77)</td>
<td>0.188</td>
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Conclusions

• Extreme microbiome shifts occur during allo-HSCT
• Intestinal domination by a single species can occur
• Domination is influenced by antibiotics
• Intestinal domination precedes bloodstream infection in these patients
Other studies microbiome in immunocompromised

- *Clostridium difficile*
- Leukemia
- Graft-versus host disease
- Ipilimumab
- Patients on total parenteral nutrition
Lucille Castori Center for Microbes, Inflammation, and Cancer

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Melissa Kinnebrew
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Eric Littman
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