Overview: clinical and microbiological characteristics of infections in allogeneic HSCT recipients

Claudio Viscoli
Professor of Infectious Disease
University of Genova, Italy
Potential conflicts of interest

• Received grants as speaker/moderator in national or international meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS, Novartis
• Received grants for participation in national or international advisory boards by Gilead, Astellas, MSD, Pfizer, Novartis
• Obtained research grants for my institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis
• Expert for the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency
• Member of several local boards (Genoa, Liguria, Italy and my hospital) (Hospital Infection Control and Antibiotic Stewardship, HIV, vaccination, Hospital Formulary)
Allogeneic HSCT

A real challenge for transplant physicians and ID consultants, because in the same patient multiple immunodeficiency factors (and consequently multiple pathogens) occur in sequence and sometimes overlap, with the intriguing interplay between a variably compatible grafted immunological system and donor’s tissues.

Contrary to organ transplant, it is the grafted immune system that reacts against the donor not the contrary, and a certain degree of reaction (Graft versus Host Disease (GVHD) is desirable, because of its anti-leukemia effect.
Essential factors affecting susceptibility to infection in allo HSCT

- Patient’s history and underlying disease
  - Reactivation of infections during remission induction
- Conditioning regimen
  - Post-chemotherapy neutropenia and mucositis
- Type of transplant and Graft source
  - Occurrence and severity of GVHD
  - Immunosuppressive therapy for GVHD
- Age
- Donor’s immune competence and past history
GITMO Trapianto Allogenico
Numero Trapianti per principali Patologie
Attività 2011

- Leucemia Mieloide Acuta: 470
- Leucemia Linfatica Cronica: 29
- MielMult/Plasmacell: 77
- Tumori Solidi: 18
- Errori genetici: 14
- Immunodeficienze: 14
- Leucemia Linfatica Acuta: 304
- Leucemia Mieloide Cronica: 34
- Linfomi: 230
- MDS/MPS: 253
- Anemia Aplastica: 65
- Talassemia: 71
Essential factors affecting susceptibility to infection in allo HSCT

- Patient’s history and underlying disease
  - Reactivation of previous infections
- Conditioning regimen
  - Post-chemotherapy neutropenia and mucositis
- Type of transplant and Graft source
  - Occurrence and severity of GVHD
  - Immunosuppressive therapy for GVHD
- Age
- Donor’s immune competence and past history
Conditioning regimens

- Myeloablative
  - Reduced intensity
  - Non-myeloablative
Role of the conditioning regimen

- **Myeloablative**
  - Neutropenia (2-4 weeks) in the early post-transplant period
  - Mucositis (early period)
  - Lymphodepletion (long-term depending on GVHD)
- **Reduced intensity**
  - Shorter primary neutropenia
  - Less intense mucositis
  - Possibly more lymphodepletion
- **Non-myeloablative**
  - Shorter primary neutropenia
  - Secondary neutropenia (graft failure any time postengraftment)
  - Intense lymphodepletion because of higher risk of GVHD
Essential factors affecting susceptibility to infection in allo HSCT

• Patient’s history and underlying disease  
  - Reactivation of previous infections
• Conditioning regimen  
  - Post-chemotherapy neutropenia and mucositis
• Type of transplant and Graft source  
  - Occurrence and severity of GVHD  
  - Immunosuppressive therapy for GVHD
• Age
• Donor’s immune competence and past history
GITMO Trapianto Allogenico
Tipo di trapianto
Attività 2000-2011

N. TRAPIANTI


- HLA id. sib.
- Familiare Match
- Familiare Mismatch
- MUD/CB
GITMO Trapianto Allogenico
Sorgente di CSE
Attività 2001-2011

N. TRAPIANTI


ANNI

BM
PBSC
CB
SCs Comb.
GITMO Trapianto Allogenico

Età al trapianto

Attività 2000-2011

N. TRAPIANTI

0 500 1000 1500

≤20

21-40

40-60

>60

ANNI


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Causes of Death after Transplants Done in 2009-2010

**Unrelated Donor**
- Primary Disease (37%)
- New Malignancy (1%)
- GVHD (18%)
- Infection (18%)
- Other (18%)
- Organ Failure (8%)

**HLA-identical Sibling**
- Primary Disease (49%)
- New Malignancy (1%)
- GVHD (16%)
- Infection (13%)
- Other (16%)
- Organ Failure (5%)

**Autologous**
- Primary Disease (72%)
- New Malignancy (1%)
- Infection (7%)
- Organ Failure (3%)
- Other (17%)
Tomblyn M et al BBMT 2009
CD4+ T cells
### Table 4  Multivariate analysis of factors influencing the risk of transplant-related mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline value</th>
<th>Compared value</th>
<th>RR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ cell number</td>
<td>&gt;86/µl</td>
<td>≤86/µl</td>
<td>1.97</td>
<td>1.7–2.5</td>
<td><strong>0.0017</strong></td>
</tr>
<tr>
<td>Donor type</td>
<td>MSD</td>
<td>ADI</td>
<td>1.47</td>
<td>0.9–1.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Acute GvHD grading</td>
<td>0–I</td>
<td>II–IV</td>
<td>1.59</td>
<td>1.4–1.7</td>
<td><strong>0.0097</strong></td>
</tr>
<tr>
<td>Recipient age</td>
<td>&lt;16</td>
<td>≥16</td>
<td>1.23</td>
<td>0.8–1.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Donor age</td>
<td>&lt;35</td>
<td>≥35</td>
<td>1.2</td>
<td>0.9–1.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>TBI yes</td>
<td>TBI no</td>
<td>1.09</td>
<td>0.7–1.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Disease phase</td>
<td>Early</td>
<td>Advanced</td>
<td>1.11</td>
<td>0.7–1.3</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Berger M et al BMT, 2008
Phase I: Pre-engraftment

- Graft-versus-host-disease: Acute
  - Neutropenia, barrier breakdown (mucositis, central venous access devices)
  - Gram negative bacilli
  - Gram positive organisms
  - Gastrointestinal Streptococci species

Phase II: Post-engraftment

- Impaired cellular and humoral immunity: NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire
  - Encapsulated bacteria
  - Herpes Simplex virus
  - Cytomegalovirus

Phase III: Late phase

- Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies
  - Varicella Zoster virus
  - EBV PTLD
  - Aspergillus species
  - Candida species
  - Pneumocystis

Day 0 - Day 15-45 - Day 100 - Day 365 and beyond

Tomblyn M et al BBMT 2009
Epidemiology and risk factors for bloodstream infections after allogeneic hematopoietic stem cell transplantation

Paola Cappellano¹, Claudio Viscoli², Paolo Bruzzi³, Maria Teresa Van Lint³, Carlos Alberto Pires Pereira¹, Andrea Bacigalupo¹

FIGURE 1 - Cumulative incidence of BSI among 314 recipients of allogeneic HSCT, until day 180 after transplantation.

20.6% 8.9% 8.9%
Outcome

• By 180 days, 87 (27.7%) out of 314 pts had died:
  – 10 (11.5%) with BSI as primary cause of death.
  – 11 (12.6%) with associated cause of death: rejection (2), leukaemia (2), acute GVHD (2), hemorrhage (1) and infection (4).
  – 66 (75.9%) from other causes.
  – 17 (5.4%) pts had recurrence of underlying disease.

• The cumulative risk of death from any cause was 8.9% at 30 days, 13.4% at 60 days, and 27.7% at 180 days.

• The cumulative risk of death due to or associated with BSI was 3.9% at 30 days, 4.9% at 60 days, and 7.2% at 180 days.
Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients

M. Mikulska · V. Del Bono · P. Bruzzi ·
A. M. Ratola · F. Gualandi · M. T. Van Lint ·
A. Bacigalupo · C. Viscoli
Table 4 Variables predicting 7- and 30-day mortality in multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>7-day mortality, n (%)</th>
<th>30-day mortality, n (%)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Acute leukaemia</td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.44 (0.19–1.03)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status of the underlying disease</td>
<td></td>
<td></td>
<td>0.40 (0.08–2.14)</td>
<td>2.34 (0.76–7.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>First complete remission</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission 2nd</td>
<td>2.20 (0.74–6.51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of bloodstream infection</td>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (&gt;20 days after HSCT)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late (&gt;20 days after HSCT)</td>
<td>3.29 (1.15–9.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overall survival

Days after bloodstream infection

First complete remission at HSCT
Remission $\geq 2^o$ at HSCT
Active disease at HSCT
Bloodstream infections, isolated pathogens

<table>
<thead>
<tr>
<th>Year</th>
<th>Gram +</th>
<th>Gram -</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>2005</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>2006</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>2007</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>2008</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>2009</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>2010</td>
<td>10%</td>
<td>90%</td>
</tr>
</tbody>
</table>
BSI 2010, isolates

- S. aureus
- CoNS
- E. faecium
- Other enterococci
- P. aeruginosa
- E. coli
- K. pneumoniae
- Enterobacter
- S. maltophilia
- Other Gram -

Personal experience, HSCT Unit, Genova, Italy
ECIL: literature review and survey

• A literature review on BSI in cancer patients after January 1\textsuperscript{st} 2005 until June 2011 (49 articles)
• Surveillance of BSI in cancer centers of the ECIL network (80 centers, 27 countries).
Results: data on epidemiology & resistance
G+ vs G- ratio

Literature review
60% vs 40%
ranging from 26% vs 74% to
85% vs 15%

ECIL-4 questionnaire
55% vs 45%
ranging from 30% vs 70% to
85% vs 15%
ECIL-4 Surveillance Questionnaire
Rate of various forms of resistance among pathogens isolated in BSI

%
Fungal Pathogens Associated with Infection

Predominant Fungi
- Candida spp
- Aspergillus spp
- Cryptococcus neoformans
- P. jirovecii

Endemic Fungi
- Histoplasma capsulatum
- Blastomyces dermatitidis
- Coccidioides immitis

Rare Fungi
- Fusarium spp
- Trichosporon spp
- Malassezia furfur
- Scedosporium spp
- Zygomycetes
- Dematiaceous moulds
Incidence of IFD after HSCT

Prospective Surveillance for IFI in HSCT Recipients • CID 2010:50
Timing of IFI after HSCT
Epidemiology of Aspergillus infections in BMT

- 158 pts with invasive aspergillosis
  - Increase in incidence from 5.7% to 11.2%
  - Bimodal onset: 16 and 96 days after transplant
- Risk:
  - Within 40 days: underlying disease, donor type, season and no laminar flow
  - After 40 days: age, underlying disease, donor type, GVHD, neutropenia, and steroid use
- Only 31% of pts neutropenic

Wald et al, *JID* 1997;175:1459
Incidence 15% (45/306, 8 proven and 37 probable IA)

Median time to diagnosis after HSCT: 53 days (range: 4-449)

Early IA: 23 (51%),
Late IA: 22 (49%)
Phase I: Pre-engraftment

- Graft-versus-host-disease: Acute
  - Neutropenia, barrier breakdown (mucositis, central venous access devices)

Phase II: Post-engraftment

- Impaired cellular and humoral immunity:
  - NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire

Phase III: Late phase

- Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies

**Bacterial**
- Gram negative bacilli
- Gram positive organisms
- Gastrointestinal *Streptococci* species

**Viral**
- Herpes Simplex virus
- Cytomegalovirus (Seasonal/intermittent)
- Varicella Zoster virus
- EBV PTLD
- Other viruses eg. HHV

**Fungal**
- Aspergillus species
- Candida species
- Pneumocystis

Day 0
Day 15-45
Day 100
Day 365 and beyond
Viral infections

- Herpes viruses
  • HSV, CMV, EBV, HHV6, VZV

- Polyomaviruses
  • BKV, JCV

- Adenoviruses

- Respiratory
  • Influenza, Parainfluenza, RSV

- HBV, HCV
CMV – pre-emptive treatment

**Risk Groups**
- **Cord blood**: Any level, 1000 copies
- **Allograft**
  - High-dose steroids+ or T cell depletion or anti-T cell antibodies: >100 copies/mL, 1000 copies
  - Low-dose steroids or no T cell depletion or anti-T cell antibodies: >500 copies/mL or 5-fold ↑†, 1000 copies
- **Allograft after day 100**: >1000 copies/mL or 5-fold ↑†, 1000 copies if GVHD or based on ↑

**CMV Plasma DNA Level to Start PET at FHRC**
- >100 copies/mL, 1000 copies

**CMV Whole Blood DNA Level to Start PET at Karolinska Institute**
- >500 copies/mL or 5-fold ↑†, 1000 copies

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* Assays performed weekly or twice weekly (highest risk); limit of detection 25 copies/mL.
† If initial level is less than threshold.
** Assays performed weekly, limit of detection 50 copies/mL.

Figure 1. CMV viral load to start preemptive therapy (PET) used at the FHRC in Seattle, WA, and the Karolinska Institute, Stockholm, Sweden.

P. Ljungman and M. Boechk
Essential factors affecting susceptibility to infection in allo HSCT

- Patient’s history and underlying disease
  - Reactivation of previous infections
- Conditioning regimen
  - Post-chemotherapy neutropenia and mucositis
- Type of transplant and Graft source
  - Occurrence and severity of GVHD
  - Immunosuppressive therapy for GVHD
- Age
- Donor’s immune competence and past history
CMV Infection after Transplant from Cord Blood Compared to Other Alternative Donors: The Importance of Donor-Negative CMV Serostatus

Małgorzata Mikulska, Anna Maria Raiola, Paolo Bruzzi, Riccardo Varaldo, Silvana Annunziata, Teresa Lamparelli, Francesco Frassoni, Elisabetta Tedone, Barbara Galano, Andrea Bacigalupo, Claudio Viscoli
Figure 1. Cumulative incidence of CMV infection (180 days) in 2 types of HSCT donors: alternative versus cord blood.
Figure 2. Percent of patients with CMV infection during the first 12 months after transplantation, divided according to donor type.
Figure 5. Cumulative incidence of late CMV infection in CMV seropositive HSCT recipients divided according to donor serostatus and type of transplant. Note: Incidence of late (> 100 days after transplant) CMV infection, both in patients with and without previous early infection, was evaluated in 108 patients who survived more than 100 days after transplant.
I finished
Thank you for your attention
Backup slides
HHV-6

- Beta herpesvirus isolato nel 1986
- Infezione endemica in età infantile
- Sieroprevalenza negli adulti – 90%
- Incidenza di riattivazione del HHV6 - 47%, 1-2 mesi dopo HSCT

Quadro clinico:
- Infezione sistemica - febbre, rash, ritardo di attecchimento
- Encefalite (<2%) - localizzazioni specifiche (sistema limbico) – disturbi di memoria (deficit della memoria a breve termine), disturbi di coscienza, crisi epilettiche, insonnia.
- Terapia: foscarnet, ganciclovir, cidofovir
Adenovirus Infections in Transplant Recipients

- Riattivazione
  - Trapianto allogénico 10%
  - Trapianto autologo 6%
  - Trapianto di fegato 3%

Manifestazioni cliniche:
- Epatite (SOT, HSCT)
- Cistite emorragica (HSCT)
- Diarrea
- Polmonite

- Terapia – cidofovir?, infusione dei linfociti del donatore

Polyomavirus BKV

- Polyoma BK virus (BKV) infetta circa 80% degli adulti e rimane latente nel tratto urinario

Trapianto di rene
- Nefropatia da BKV

HSCT:
- Cistite emorragica (Cause: BKV, JCV, adenovirus, tossicità da farmaci ex ciclofosfamide)

Erard 2004 CID, Erard 2005 Blood, Leung 2005 CID,
Virus respiratori

- Virus respiratorio sinciziale (RSV), parainfluenza, influenza virus

Diagnosi: clinica + ricerca molecolare
- RSV - inverno, infezione delle basse vie aeree nel fino a 50% dei pazienti
- Virus di parainfluenza 3 - tutto l’anno

- Influenza - raramente progredisce verso polmonite; profilassi e terapia con oseltamivir o amantadina
- Prevenzione: isolamento mezzi di bariera e vaccinazioni

- RSV e parainfluenza progrediscono più facilmente all’infezione delle basse vie respiratorie
- Con la mortalità fino a 50% in caso di polmonite da RSV in HSCT
Data on epidemiology and resistance
Conclusions

- Few up-to-date data on etiology & resistance in cancer patients.
- Compared with the published data, the results of the ECIL surveillance suggest:
  - Reduction of the G+ to G- ratio (60%:40% vs. 55%:45%)
  - Increased rates of enterococci and Enterobacteriaceae (11% vs. 5% and 33% vs. 24%, respectively);
  - Decreased rate of \textit{P. aeruginosa} BSI (4% vs. 11%, respectively);
  - Lower resistance rates \textit{all} the pathogens (but still high in absolute terms)
- Significant differences exist among the centers in etiology of BSI and resistance, with patterns also changing over time
- A thorough knowledge of \textit{current local} epidemiology is of utmost importance in guiding the choice of the optimal empirical therapy.
analyzed the lung CT scans (A.B., C.d.B., and K.C.). The following features were noted: nodules with or without halo sign or cavitation (in particular air crescent sign), alveolar consolidation with or without halo sign or cavitation, centrilobular micronodules and tree-in-bud opacities, ground glass opacities, septal thickening, and pleural effusion. Particular attention to radiologic correlations, the presence of a nodule with a halo sign without any airway-invasive features was defined as an angioinvasive disease (Figure 1A). In contrast, the presence of centrilobular micronodules and/or tree-in-bud without any nodule with a halo sign was defined as an airway-invasive disease (Figure 1B).\textsuperscript{7,9,11-13} As consolidations may occur

<table>
<thead>
<tr>
<th>Sign</th>
<th>Allogeneic HSCT (N = 23), no. (%)</th>
<th>AL (N = 22), no. (%)</th>
<th>Others* (N = 10), no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioinvasive†</td>
<td>3 (13)</td>
<td>10 (45)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Airway-invasive‡</td>
<td>10 (44)</td>
<td>3 (14)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Both angioinvasive and airway-invasive‡</td>
<td>3 (13)</td>
<td>2 (9)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Neither angioinvasive nor airway-invasive§</td>
<td>7 (30)</td>
<td>7 (32)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>

*Non-AL patients and no allogeneic HSCT (lymphoma, chronic lymphocytic leukemia, multiple myeloma, myelodysplastic syndrome, hairy cell leukemia).
†At least 1 nodule with halo sign and no sign of airway-invasive disease; other signs allowed.
‡Centrilobular micronodules and/or tree-in-bud without any nodule with halo sign; other signs allowed.
§Consolidations with or without halo sign, cavitated consolidation, macronodule without halo sign, and/or air crescent sign.
Angioinvasive disease was more frequent among
- Acute leukemia patients
- Patients with leukocyte counts less than 100/mm³

Airway-invasive signs were more frequent among non-AL patients
Enterococci, susceptibility

73% of isolates of 2010 presented high-level resistance to aminoglycosides
Literature review
Rate of various forms of resistance among pathogens isolated in BSI

Data from: 13 centres from 8 countries (Brazil, Germany, India, Italy 4, Japan 2, Taiwan 2, Turkey, US).
Data for given resistance reported from median 6 centres, range: 4-9.
Berger M et al BMT, 2008
Post-transplant temporal stage and prevalent type of immunodeficiency

- **Early**
  - Day 0-30
  - Neutropenia

- **Intermediate**
  - Day 30-100
  - Lymphocytopenia

- **Late**
  - Selective lymphocytopenia (CD4+ T cells)
  - Humoral immunity
## Risk factors for early and late IA in multivariable analysis

### Early
- Status of underlying disease at transplant $(p=0.002)$
  - 2nd remission OR 1.9
  - Relapse OR 7.2
- Days to engraftment $(p=0.001)$
  - Each day OR 1.016
- CMV reactivation $(p=0.05)$
  - Yes OR 2.8

### Late
- Chronic GVHD $(p=0.05)$
  - Yes extensive OR 3.6
- Steroids $(p=0.04)$
  - Yes (<2 mg/Kg) OR 7.26
  - Yes (>2 mg/Kg) OR 16.4
- Relapse $(p=0.004)$
  - Yes OR 5.55
- Secondary neutropenia $(P=0.001)$
  - Yes OR 5.01
**Figure 4.** Median time (in days) between the first and last positive CMV antigenemia in CMV seropositive HSCT recipients divided according to donor serostatus and type of transplant.
Etiology of bacterial bloodstream infections (median prevalence with range) reported in the review of the literature published in years 2005-2011.

- S. aureus: 7% (0-24%)
- CNS: 25% (2-60%)
- Viridans: 5% (0-16%)
- Enterococci: 5% (0-38%)
- Other Gram+: 6% (0-21%)
- Enterobacteriaceae: 24% (6-54%)
- P. aeruginosa: 10% (0-30%)
- Acinetobacter: 2% (0-12%)
- Other Gram-: 6% (0-11%)

Etiology of bacterial bloodstream infections (median prevalence with range) reported in the ECIL-4 surveillance study.

- S. aureus: 5% (0-15%)
- CNS: 27% (7-21%)
- Viridans: 7% (0-22%)
- Enterococci: 11% (0-30%)
- Other Gram+: 6% (0-15%)
- Enterobacteriaceae: 33% (8-56%)
- P. aeruginosa: 4% (0-28%)
- Acinetobacter: 1% (0-11%)
- Other Gram-: 6% (0-14%)
Graft sources

- HLA-matched sibling donors (MSD)*
- Matched unrelated donors (MUD)*
- Umbilical cord blood (UCB)
- Mis-matched related grafts (MRG)*

Different rate and severity of GVHD and intensity of immunosuppression

- Bone marrow stem cells or G-CSF-mobilized Peripheral Blood Stem Cells
Time to restoring immunocompetence

Time to immuno competence varies substantially based on GVHD and its therapy

- Neutrophils: 2-4 weeks
- NK cells: 1-2 months
- CD8+ T cells & B cells: 1 year minimum
- CD4+ T cells: YEARS