Prevention of infections and vaccination in HSCT patients

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Background

Infection is primary cause of death in

- 17% - 20% of allogeneic HCT recipients
- 8% of autologous HCT patients
Risk factors for infection

- Severe immune suppression
- Barriers breakage – mucositis
- Foreign bodies (central lines)
- TPN
- Prolonged hospitalization
- Antibiotic treatment
Origin of infections

- Environment (water, air, food)
- Donor (HIV, HBV, HCV, HTLV-I/II, West Nile virus, CMV, EBV, toxoplasmosis, etc)
- Community (contagious diseases)
- Patient
HEPA filters: 99.97% efficiency for removing particles ≥0.3 µm (esp. during construction)
Consistent positive air pressure, ≥12 air exchanges/hour
Well-sealed rooms
Self-closing doors to maintain constant pressure differentials
Protective Environment: rooms
Phase I: Pre-engraftment

- 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

Phase III: Late phase

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

Bacterial

- Herpes Simplex virus
- Respiratory and enteric viruses (Seasonal/intermittent)
- Varicella Zoster virus
- EBV PTLD

Viral

- Aspergillus species
- Candida species

Fungal

- Pneumocystis

Day 0
Day 15-45
Day 100
Day 365 and beyond
Bacterial infections prevention

✓ 13% to 77% of HSCT recipients develop blood stream infection (BSI)
✓ 12 - 42% mortality
✓ 25-70% Gram-negative pathogens
✓ Resistance to antibiotics is growing
Bacterial infections prevention

- **Central line management:**
  - hand hygiene, full barrier precautions, cleaning the insertion site with chlorhexidine, avoiding femoral sites for insertion, and removing unnecessary catheters
Bacterial infections prevention

- **Antibacterial prophylaxis:** fluoroquinolone for anticipated neutropenic periods of 7 days or more

Because of lack of data, there are currently no antimicrobial prophylactic regimens that can be recommended for children.
Outbreaks of resistant bacteria in HSCT units

Clinical Infectious Diseases 1999; 29: 1268–73
An Outbreak of Vancomycin-Dependent Enterococcus faecium in a Bone Marrow Transplant Unit

Journal of Hospital Infection 77 (2011) 76–92
Clusters of infection due to metallo-β-lactamase-producing Pseudomonas aeruginosa in stem cell transplant and haematology units

Clinical Infectious Diseases 2000; 30: 195–7
Outbreak of Stenotrophomonas maltophilia Bacteremia in Allogenic Bone Marrow Transplant Patients: Role of Severe Neutropenia and Mucositis

Infection Control and Hospital Epidemiology November 1999
Outbreak of Stenotrophomonas maltophilia Bacteremia Among Patients Undergoing Bone Marrow Transplantation: Association With Faulty Replacement of Handwashing Soap
Infectious control for resistant bacteria

**Institutional measures**

- A campaign to improve hand hygiene
- Review of procedures that lead to nurses, physicians and ancillary staff (e.g., radiography technicians) failing to use contact isolation precautions
Infection control for resistant bacteria

- Institute **contact isolation** precautions, particularly if clonal spread is demonstrated.

- Identify colonized patients by use of **rectal swabs** plated onto selective media (ESBL, KPC, VRE).

- Patients who have gastrointestinal tract colonization as well as those with frank infection should undergo **contact isolation**.

- Evaluation for the presence of a common environmental source of infection.

- **Closure of the ward**.
Know Your Bugs!
Late post-engraftment bacterial disease (>100 days after HCT)

- Pathogens: Encapsulated bacteria: *S. pneumoniae, H. influenzae*

- Prolonged antibiotic prophylaxis with **penicillin** - if chronic GVHD or low IG (prevention of *S. pneumoniae*)

- monthly **IVIG** - if severe hypogammaglobulinemia (IgG <400 mg/dL) (risk of bacteremia or recurrent sinopulmonary infections)

- Vaccinations
Prevention of fungal infections

Hepatosplenic candidiasis

Pulmonary aspergillosis

Risk factors:
- Neutropenia
- Mucositis
- Central lines
- Impaired cellular immunodeficiency
- GVHD/treatment for GVHD

Antifungal prophylaxis

CNS aspergillosis
PCP (*Pneumocystis jiroveci* pneumonia)

- Sulfamethoxazole (TMP-SMX)
- Timing: from engraftment until at least 6 months after HCT (AII) or longer than 6 months in patients who continue to receive immunosuppressive drugs
- protection against Toxoplasma, Nocardia, some respiratory pathogen.
Prevention of viral infections

• Herpes viruses (HSV, CMV, EBV, VZV)

• Adenovirus

• Common respiratory viruses (Influenza, Respiratory Syncytial Virus, Human Metapneumovirus, Parainfluenza)
Herpes viruses

HSV mucositis

CMV retinitis

PTLD (EBV)

CMV pneumonitis
Prevention of viral infections: Herpes viruses/ Adeno

- Recipient origin - reactivation
- Donor origin - Transmitted with graft
- Environmental
Prevention of viral infections
Herpes viruses

• Donor/recipient status

• Prevention of re-infection: behaviors that decrease HSV exposure, leukocyte filtration (CMV), vaccination of health care workers, family members, household contacts (VZV)

• If exposed to varicella (chickenpox or shingles): VZIG or VariZIG as soon as possible and no later than 96 hours
Prevention of viral infections
Herpes viruses/adeno

• Acyclovir prophylaxis
• Preemptive approach for CMV, EBV, adeno: PCR weekly
• Preemptive treatment: reduction in immunosuppression, ganciclovir (CMV), rituximab (EBV), cidofovir or ribavirin (adeno, in selected high-risk patients)
CRV: Influenza, Respiratory Syncytial Virus, Human Metapneumovirus, Parainfluenza

- Significant cause of morbidity and mortality
- Progression to lower RTI (LRTI), respiratory failure, and fatal outcome, especially when certain risk factors present, as lymphopenia and steroid treatment
- Mortality 0-70%
- Prolonged shedding (7 to 84 days)
- Nosocomial transmission and outbreaks in HSCT units

CRV: Influenza, Respiratory Syncytial Virus, Human Metapneumovirus, Parainfluenza

- Determine the etiology of a URI
- Contact precautions for patients with URTI/LRTI
- Good personal hygiene (frequent hand washing, cover of the mouth when coughing & sneezing, and safe disposal of oral & nasal secretions).
- Avoid contact with individuals showing symptoms or signs of influenza-like illness or acute respiratory infection
- Vaccination of contacts

ECIL4, 2011
Questions about vaccinations

• Why to vaccinate?
• What is the evidence of efficacy in this population?
• Which vaccine?
• When to vaccinate?
Questions about vaccinations

• Why to vaccinate?

• What is the evidence of efficacy in this population?

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• Which vaccine?
Risk for infections later after HSCT

**Risk factor:** cellular and humoral immune deficiency (hypogammaglobulinemia, GVHD)

**Duration:** years
Antibody titers against vaccine preventable diseases
(Geometric means and 95% confidence intervals)

Poliovirus

Parkkali APMIS 1996
Antibody titers against vaccine preventable diseases (Geometric means and 95% confidence intervals)

**Diphtheria antitoxin**

![Graph showing antibody titers over time](image-url)

Parkkali APMIS 1996
Antibody titers against vaccine preventable diseases (Geometric means and 95% confidence intervals)

*Haemophilus influenzae* type b
Invasive pneumococcal infection (IPI)

**Overall incidence rate of IPI**

- 0.09/1000 persons in healthy adults
- 6-8/1000 in patients with HSCT
- 18.85/1000 in case of GVHD

**Mortality 13% - 20%**
Haemophilus influenzae B infections after HSCT

- Allogeneic HSCT almost exclusively
- Sinusitis, bronchitis, pneumonia
- Related to low anti-PRP Ab levels
"In general, post-HSCT patients should be viewed as "never vaccinated" patients regardless of the pre-HSCT vaccination history of the patient or the donor."
Post-HSCT active immunizations are recommended for:

- Specific infections (higher risk in HSCT)
- Outbreak of infections
- Recovering of childhood immunizations
Questions about vaccinations

• Why to vaccinate?
• What is the evidence of efficacy in this population?
• Which vaccine?
• When to vaccinate?
First vaccination, 1796
Prevenar efficacy: **Invasive** Pneumococcal Disease Rates in Children <5 years

In children < 2 years (per 100,000)

1999: 188 cases
2001: 59 cases
~ 70% decline

Whitney, *NEJM* 2003
Crude Invasive Pneumococcal Disease Mortality Rates/100,000 Children <2 Years, U.S.

Redelings et al, Arch Pediatr Adolesc Med, 159:195-6, 2005
Number of patients needed to demonstrate a benefit of a vaccine in pneumococcal disease

Incidence in allo: 8 / 1,000 transplants

**Hypothesis**: if a vaccine works, it will reduce the risk from 8 to 2 / 1,000 HSCT

......You should enroll > 5000 patients!

Just impossible to run such a study!

- 158 patients included in the largest prospective study on antipneumococcal vaccine in HSCT recipients
- Antibody concentration used to assess vaccine efficacy

Serum antibodies before/after (re)vaccination
- absent or mild cGVHD (○)
- moderate to severe cGVHD (△)

The mean concentrations and their 95% confidence intervals
Questions about vaccinations

• Why to vaccinate?
• What is the evidence of efficacy in this population?
• Which vaccine?
• When to vaccinate?
Pneumococcal vaccines

- Polysaccharide vaccines 23-valent (PS23)
- Conjugate vaccines 13-valent (Prevnar 13)
Polysaccharide vaccine

✓ 23-valent (PS23)

✓ Non T-cell dependent response

✓ Poor response, especially if chronic GVHD and in patients <5 years or >65 years old

✓ No memory = no boost effect

✓ Repeated doses of PPV23 can induce immune tolerance and hyporesponsiveness when any subsequent pneumococcal vaccines are given

O’Brien Lancet Infect. Dis. 2007
Poolman Expert Rev. Vaccines 2011
Cordonnier Exp Rev Vacc 2013
Conjugate vaccines (Prevnar-13)

- Covalent coupling of the PS with protein
- T-cell dependent response
- Better primary response
- Longer lasting antibody response
- Boost effect
- Response (protective antibody levels) 64-75%
- Cover fewer antigens
- More we wait, the better the response

Questions about vaccinations

• Why to vaccinate?
• What is the evidence of efficacy in this population?
• Which vaccine?
• When to vaccinate?
Early (3 months) to a late (9 months) immunization with PCV7 after allogeneic myeloablative HSCT

Response assessed 1 month after the 3rd dose of PCV7
Early (3 months) to a late (9 months) immunization with PCV7 after allogeneic myeloablative HSCT

Response assessed 1 month after the 3rd dose of PCV7

Study Flow Chart

Early group

Late group

Prevenar

23-valent polysaccharide vaccine

79%

82%
Early (3 months) to a late (9 months) immunization with PCV7 after allogeneic myeloablative HSCT

Response assessed 24 month after the HSCT
Pneumococcal vaccine

- 3 doses of PCV13, 3-6 months after HSCT
- 1 dose of PPSV23, 12 months after HSCT
  - extends the serotype coverage to additional pneumococci not included in PCV7
  - increases the response rate to the serotypes included in the PCV7 conjugate vaccine

- 4th dose of PCV13, 12 months after HSCT, for patients with chronic GVHD
Influenza
Outbreak of pandemic 2009 influenza A/H1N1 infection in the hematology ward: fatal clinical outcome of hematopoietic stem cell transplant recipients and emergence of the H275Y neuraminidase mutation

Futoshi Iioka · Ryuichi Sada · Yoshitomo Maesako · Fumihiko Nakamura · Hitoshi Ohno

Outbreak of novel influenza A (H1N1) in an adult haematology department and hematopoietic cell transplantation unit: Clinical presentation and outcome

A multicenter evaluation of pandemic influenza A/H1N1 in hematopoietic stem cell transplant recipients


Mortality 19%

7 patients, 3/7 died

Mortality 3/8
TIV trivalent inactivated = killed vaccine in HSCT

The humoral immune response is generally poor (less than 50%)

<table>
<thead>
<tr>
<th>Hemagglutination-inhibition antibodies</th>
<th>Before vaccination N=78</th>
<th>3-4 weeks after 1st vaccination N=77*</th>
<th>3-4 weeks after 2nd vaccination N=43**</th>
</tr>
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<tbody>
<tr>
<td>≥1:40</td>
<td>14 (17.9%)</td>
<td>34 (44.2%) p&lt;0.001</td>
<td>21 (48.8%) p&lt;0.001</td>
</tr>
</tbody>
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significantly associated with higher lymphocyte counts, higher HI baseline titers and sibling donor (allogeneic HSCT)

Humoral response induced by the adjuvanted influenza A/H1N1pdm2009
Influenza vaccination to HSCT recipients

Yearly vaccination with seasonal TIV:

• HSCT patients

• Family members, close contacts annually as long as the recipient is at risk

• HCW

Post-exposure anti-viral prophylaxis (oseltamivir)
Live vaccines are (theoretically) contraindicated after HSCT?

- VZ virus
- Measles, mumps, and rubella
- Yellow fever
- Tuberculosis

Consider Risk versus Benefit
Live attenuated varicella vaccine

- 46 VZV seronegative allo HSCT patients
- <20 years old, CD4 cell count $\geq 200/\mu l$, off immunosuppression, and responded to $\geq 1$ post-HCT vaccines
- Median time to vaccination was 4 years
- Median follow-up of 29.1 (range: 6.9-167.1) months
- 64% seroconverted following 1 immunization
- 3/44 - self-limited varicella-like rash within 2.5 weeks of immunization
Measles, Mumps, and Rubella vaccines

• None of these diseases really « opportunistic »
• Lost of specific Ab during the 1st year after Allo or Auto
• Severe measles reported
• Risk at school, epidemics
• Data limited to administration at 2 years, only in children with no GVHD, no immunosuppressive drug (Ljungman 1989 and 1994)
• Response rate in seronegative patients: 65-75%
  -> Restricted, but good indications +++
International guidelines for immunization after HSCT

**NOT RECOMMENDED VACCINES**

- BCG
- Oral Polio
- Rotavirus
- Intranasal influenza vaccine
- Cholera
- Typhoid, oral vaccine

*Ljungman et al. BMT, 2009*
Do GVHD and immunosuppressive drugs contraindicate immunization with a non-live vaccine?

1) Are non-live vaccines dangerous in patients with GVHD or receiving IS drugs? **NO**
   - no serious side effect reported
   - no vaccine-induced thrombocytopenia
   - no worsening of GVHD
2) Is the efficacy of non-live vaccines impaired by GVHD?

- Yes for pneumococcal PS vaccine
  *(poor IgG2 response)*
- Yes for conjugate pneumococcal *(IDWPO1)*
- Yes for diphteria if early vaccination
  *(4 months)*
- No for conjugate Hib vaccine
- Conflicting data for polio
Recommendations for vaccinations after allogeneic HSCT for children and adolescents

Pneumovax
12 months

DTaP-IPV-HBV/Hib
PCV

Seasonal influenza vaccination (start 4-6 months after HSCT; each year)

MMR*

Optional immunizations:
- Meningococcal type C conjugate
- Hepatitis A virus
- Human papillomavirus
- Tick-borne encephalitis
- Varicella zoster virus (>= 24 months after SCT)*

*only immunocompetent patients
Thanks!
Is it beneficial to prime the donor?

  - NO

- Conjugate pneumococcal vaccine (Molrine 2003) 
  - Y/No

- Conjugate-Hib vaccine (Molrine 1996, Storek 2004) 
  - YES

  - YES