Re-Immunization Post-Transplant: Who, When, What With?

Susannah E. Koontz, Pharm.D., BCOP
Clinical Pharmacy Specialist
The Children’s Cancer Hospital at The University of Texas M. D. Anderson Cancer Center

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Objectives

- Summarize key literature relating to re-immunization of patients following hematopoietic stem cell transplants.
- Discuss risks and benefits of selected vaccination administration in hematopoietic stem cell transplant recipients.
- Summarize re-immunization recommendations and schedules for hematopoietic stem cell transplant recipients.
- Identify immunization recommendations for close household contacts and health care providers of hematopoietic stem cell transplant recipients.

Background

- Hematopoietic stem cell transplantation (HSCT) increasingly common procedure
- Preparative regimens impose a state of combined immunodeficiency through impairment of host defenses
Background

- **B-Cell and T-Cell immunity**
  - Reconstitution after HSCT resembles the development of immunity in normal infant
  - Delayed by the presence (treatment) of GVHD
  - Transference from donor to recipient (?)

Storek J. *BMT* 1992;9(6):395-408
Ljungman P. *Blood* 1994;84(2):657-663
Mackall CL. *Stem Cells* 2000;18(1):10-18

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**Background**

- **0-30 days following HSCT**
  - Neutrophil recovery
  - Phagocytic function
- **6 months following HSCT**
  - “Humoral immunity”
  - Immune globulin levels normalize
- **12 months following HSCT**
  - “Cellular immunity”

Antin JH. *BBMT* 2005;11(1):43-45
Background

**Figure 2.** Median B Cell Recovery following T cell depleted or T-replete Unrelated HCT.

Small TN. *BBMT* 2008;14(1 Suppl 1):54-58

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Background

**Figure 3.** Median CD4+ cell count/ul following T cell depleted or T-replete Unrelated BMT: Children Versus Adults.

Small TN. *BBMT* 2008;14(1 Suppl 1):54-58
Background

- Loss of antibody titers to vaccine preventable diseases during the first four years following HSCT has been documented.
- Vaccine preventable diseases do occur in HSCT patients, most commonly:
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae* type b
  - Influenza A
  - Varicella zoster

Background

- Successful vaccination causes the development of:
  - High-affinity antibodies which neutralize a specific pathogen and/or
  - High concentration of memory effector T cells
Tetanus

- Loss of antibodies over time
  - 48 alloHSCT patients
    - 77% of recipients and 71% of donors were seropositive for tetanus toxoid before HSCT
    - At one year post HSCT, only half of previously immune patients had detectable antibodies

Ljungman P. *J Infect Dis* 1990;162(2):496-500

Tetanus

- Response rates of vaccination
  - Decrease in mean concentration of antibodies based on time of vaccination
    - Vaccine at 6 months → 90% immunity
    - Vaccine at 18 months → 70% immunity
  - In late group recipients, antibody response after 1st and 2nd dose correlated with antibody levels of donors

Parkkali T. *BMT* 1997;19(9):933-938
Tetanus

- Stem cell source
  - Decline in antibodies over 1 year
    - Auto BMT 58% → 29%
    - Auto PBSCT 66% → 47%
  - Likelihood of immunity loss not influenced by age, disease, or stem cell source in multivariate analysis

Hammarstrom V. BMT 1998;22(1):67-71

Tetanus

- Successful immunization achieved with 3 doses of vaccine regardless of GVHD status
  - More than 1 dose must be given to achieve lasting IgG levels
  - Vaccination should start 6-12 months post HSCT

Ljungman P. J Infect Dis 1990;162:496-500
Parkkali T. BMT 1997;19(9):933-938
Tetanus

- GVHD effects
  - aGVHD
  - cGVHD

- Donor vaccination can improve response

Parkkali T. *BMT* 1997;19(9):933-938
Ljungman P. *J Infect Dis* 1990;496-500

Diphtheria

- Loss of antibodies after HSCT
  - Only 50% of patients retained levels after transplant

- Multiple doses more effective than single dose
  - Demonstrated in allo HSCT without GVHD

- Effects of cGVHD on response

Li Volti S. *BMT* 1994;14(2):225-227
Diphtheria

- Successful immunization achieved with 3 doses of vaccine
  - Vaccination should start 6-12 months post HSCT
  - Lack of data to say exactly when to start

Pertussis

- Routine vaccination not recommended in adult HSCT patients
  - Few cases reported
  - No data on loss of antibodies
  - Should this be readdressed?

- Vaccination for pediatric patients less than 7 years old

Kochethu G. *BMT* 2006;37(8):793-794
Haemophilus Influenza Type b

- Important cause of infection
  - Early 1980’s French group reported it as a leading cause of morbidity and mortality and main cause of pneumonia ≥ 90 days post HSCT
  - Recent reports are lacking

Cordonnier C. Cancer 1986;58(5):1047-1054

Haemophilus Influenza Type b

- Timing appears to be important
  - Early immunization (3-6 months) produced higher levels of antibody titers vs. late vaccination (12 months), yet efficacy similar
  - Donor vaccination improved responses in recipients

Barra A. J Infect Dis 1992;166(5):1021-1028
Vance E. BMT 1998;22(8):735-741
Molrine DC. Blood 1996;87(7):3012-3018
Storek J. BMT 2004;33(3):337-346
Haemophilus Influenza Type b

- Two doses produced 80% immunity
  - Might be improved by giving a dose before stem cell harvest
- Start 6-12 months after HSCT with 3 doses

Guinan EC. Transplantation 1994;57(5):677-684
Vance E. BMT 1998;22(8):735-741

Pneumococcus

<table>
<thead>
<tr>
<th>Patients</th>
<th>Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winston DJ 1973-1977 AIM 1983;143(9):1735-37</td>
<td>7 of 26 (27%)</td>
<td>&gt; 7 mos</td>
</tr>
<tr>
<td>Guenther C 1979-1996 Blood 1997;90(Suppl 1) 368b Abstr 4405</td>
<td>20 of 54 (37%)</td>
<td>Med 2.2 yrs (6 mos – 5 yr)</td>
</tr>
</tbody>
</table>
Pneumococcus

- EBMT Survey (July 1994 – Dec 1997)
  - Increased incidence in allo vs. auto
    - 12.2/1000 vs. 4.6/1000 (p < 0.001)
  - Increased risk of invasive infection in patients with cGVHD vs. no cGVHD
    - 18.85/1000 vs. 8.25/1000 (p = 0.015)
    - Functional hyposplenism
    - Decreased IgG and antigenicity

Engelhard D. *Br J Haematol* 2002;117(2):444-450

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Pneumococcus

- Less immunogenic vaccine in HSCT patients compared to other vaccines
  - Polysaccharide vs. conjugate

- Immune responses
  - Improvement with multiple doses?
  - Giving before stem cell harvest?
  - Donor vaccination?

Guinan EC. *Transplantation* 1994;57(5):677-684
Spoulou V. *J Infect Dis* 2000;182(3):965-969
Antin JH. *BBMT* 2005;11(3):213-222
Pneumococcus

- Conjugate
  - 96 patients and their donors randomized to donor vaccination vs. no donor vaccination
  - All recipients received 3 doses of conjugate vaccine at 3, 6, and 12 months
  - Response after 1st dose
    - Donor + = 67% vs Donor - = 36% (p = 0.05)
    - No difference in response after 3rd dose


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Pneumococcus

- Vaccination should occur at 12 months for all patients (2nd dose “boost”)
- Conjugate vaccine for young children (less than 7 years old) and patients with cGVHD
  - Can consider subsequent polysaccharide dose
- Antibiotic prophylaxis should occur in patients with cGVHD
- Testing of immunity every 2-3 yrs in patients with cGVHD

Kulkarni S. *Blood* 2000;95(12):3683-3686
Polio

- Titers are progressively lost after transplant
- Efficacy
  - Schedules of immunization (6, 8 and 14 mos vs. 18, 20 and 26 mos) in alloHSCT
  - Both similar in immunogenicity
  - aGVHD vs. cGVHD

Ljungman P. BMT 1991;7(2):89-93
Engelhard D. BMT 1991;8(4):295-300
Parkkali T. BMT 1997;20(8):663-668

Polio

- Duration of immunity after HSCT
  - 134 patients alloHSCT
    - 15.6% became seronegative to at least one of the polio virus subtypes after a median follow-up of 8 years (range 1-19 years)
    - cGVHD had only a minimal effect
    - Risk factor: age

Ljungman P. BMT 2004;34(2):1067-1069
Polio

Seronegative Patients According to Age

- <10 yrs
- 10-30 yrs
- >30 yrs

Ljungman P. *BMT* 2004;34(2)1067-1069

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**Polio**

- All HSCT patients should receive 3 doses starting 6-12 months after transplant
- Re-checking of titers?
- Avoid the use of live, attenuated vaccine
  - No reports of vaccine associated poliomyelitis in HSCT patients
Measles, Mumps, Rubella

- Measles
  - Severe and fatal infections reported in HSCT patients
  - Loss of immunity after transplant
    - Probability of immunity
      - 3 years = 47%
      - 5 years = 27%
      - 7 years = 20%

Machado CM. *Blood* 2002;99(1):83-87
Spolou V. *BMT* 2004;33(12):1187-1190

Measles, Mumps, Rubella

Fig. 2. Kaplan-Meier probability for immunity in patients who had previous measles disease or who were immunized against measles before BMT is shown. Triangles represent immune and nonimmunized patients at the time of last follow-up.

Ljungman P. *Blood* 1994;84(2)657-663
Measles, Mumps, Rubella

- **Mumps**
  - No evidence that disease produces severe infection in HSCT patients
  - Routine use not recommended but it is included in vaccine with measles and rubella

- **Rubella**
  - Low risk of development
  - No severe cases reported in HSCT patients
  - Main focus is prevention of congenital rubella
Measles, Mumps, Rubella

- Seroconversions not as high in HSCT patients as in normal controls
- Safe and immunogenic in allo recipients ≥ 24 months after HSCT when not immunosuppressed or with active cGVHD
  - Concern for side effects
  - Has been given safely after 1 year
  - Loss of immunity over time

Machado CM. *Blood* 2002;99(1):83-87

Influenza

- Flu epidemic involving 68 patients requiring hospitalization (1991-1992)
  - 28 patients developed acute respiratory infection (18 auto and 10 allo)
    - 8 cases of documented influenza A (5 auto and 3 allo)
      - All had URI symptoms
      - 6 cases complicated by pneumonia (1 death)
  - Risk factors
    - Infection after HSCT prior to engraftment
    - cGVHD

Influenza

- Inactivated influenza not effective when given within 1st 6 months after HSCT
- Second dose not useful
- AlloHSCT should receive prior to influenza season and then yearly as long as on immunosuppression
- AutoHSCT?
- Sargramostim adjunct therapy?

Engelhard D. BMT 1993;11(1):1-5
Hepatitis B

- Safe when given post-transplant
  - 8 pairs of donors/recipients of TCD HSCT
  - All donors negative for antibody to core and surface antigen as well as Hep B surface antigen
  - Donors immunized → all recipients seroconverted to anti-HBs
  - Recipients were given 3 doses post HSCT

Ilan Y. Hepatology 1993;18(2):246-252

Hepatitis B

- Effect of immunity
  - 50 auto and allo HSCT patients received standard vaccination schedule post HSCT
    - 100% seroconverted when vaccinated 1 year post HSCT
    - Almost 60% lost their immunity 1 year after vaccination
      - Children and absence of cGVHD influenced ability to keep immunity
    - Time to vaccination did not affect response to vaccine or duration of immunity

Hepatitis B

- Recommendations
  - For children and high risk adults?
  - Patients receive series of 3 vaccinations starting 6-12 months after HSCT
  - Higher doses warranted
  - Titers should be checked 1-2 months after 3rd dose
  - Series repeated if no response

Varicella

<table>
<thead>
<tr>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Locksley et al</td>
<td>231 of 1394 (16.6%)</td>
<td>Risk Factors: alloHSCT, GVHD, ≥ 10 yrs old, dx other than CML, postHSCT ATG</td>
</tr>
<tr>
<td>(1969-1982)</td>
<td>80% within 9 months after HSCT</td>
<td></td>
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<tr>
<td>Seattle, WA</td>
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</tbody>
</table>

| Han et al         | 216 of 1186 (18%)          | 62% of cases resulted in shingles                                         |
| (1974-1989)       | 4 days – 10.8 yrs          | Auto = Allo Risk Factors: ≥ 10 yrs old, XRT                              |
| Minneapolis, MN   |                            |                                                                          |

| Koc et al         | 41% of allo patients       | Median 227 days (45-346 days)                                            |
| (1992-1997)       |                            |                                                                          |
| Boston, MA        |                            |                                                                          |

Locksley RM. *J Infect Dis* 1985;152(6):1172-1178
Han CS. *BMT* 1994;13(2):277-283
Koc Y. *BBMT* 2000;6(1):44-49
Varicella

- Seronegative patients
  - Prevents chicken pox
  - Consider prior to transplantation (?)
  - Administer 2 years after transplant if no GVHD or ongoing immune suppression

- Seropositive patients
  - Prevents zoster
  - Not routinely indicated since safe, effective antiviral prophylactic measures exist

Varicella

- Licensed live varicella vaccine is contraindicated in HSCT recipients
  - Use may result in disseminated infection with vaccine strain VZV
  - If benefits > risks, give only to VZV seronegative patients

- Heat inactivated varicella vaccine has shown promise

  Redman RL. *J Infect Dis* 1997;176(3):578-585
  Sauerbrei A. *BMT* 1997;20(5):381-383
  Hata A. *NEJM* 2002;347(1):26-34
  Ljungman P. *Sup Care Cancer* 2003;11(1):739-741
**Hepatitis A**

- Routine use not recommended
  - Dignani et al did show that 15% of recipients lost antibodies after median time of 12 months (1-51 months)
- Consider using in patients living in or traveling to endemic areas
  - 2 doses given

  Dignani MC. *BMT* 2003;31(9):809-812

**Meningococcal**

- Not routinely recommended
- Consider in high risk patients
  - Data exists using tetravalent polysaccharide vaccine
  - No data for conjugate vaccine against group C

  Parkkali T. *BMT* 2001;27(1):79-84
Serological Testing

- Techniques vary
- Poorly defined antibody levels which confer “protective” immunity
- Cost

Ljungman P. *BMT* 2005;35(8):737-746
Singhal S. *BMT* 1999;23(7):637-346

Serological Testing

- Testing before vaccination
  - Not necessary for vaccines recommended for all patients (tetanus, diphtheria, polio, influenza, pneumococcal, haemophilus)
  - Recommended before eventual vaccination for hepatitis B, varicella, measles and mumps

Ljungman P. *BMT* 2005;35(8):737-746
Singhal S. *BMT* 1999;23(7):637-346
Serological Testing

- Testing for vaccine response
  - Not recommended in vaccines proven to produce a good response (tetanus, diphtheria, polio and haemophilus) or when a second dose is not advantageous (influenza)
  - Recommended for hepatitis B, measles and varicella
  - Consider for pneumococcal polysaccharide vaccine recipients due to high risk for poor response

Ljungman P. BMT 2005;35(8):737-746
Singhal S. BMT 1999;23(7):637-346

Survey of Practices

- NMDP (1994)
  - US centers performing alloHSCT
  - Most centers gave vaccines
  - Schedules widely varied
    - 3-11 different schedules per vaccine

- EBMT (1995)

Henning KJ. JAMA 1997;277(14):1148-1151
Consensus, Please!

- Design flaws
  - Small number of patients
  - Few randomized trials
  - Variability of administration timing
  - Serological endpoints vs. clinical effectiveness

- Vaccine problems
  - Immnuogenicity (live vs. attenuated)
  - Incidence of diseases/"Herd immunity"

Vance E. *BMT* 1998;22(8):735-741
Gandhi MK. *BMT* 2001;28(8):775-781

Consensus, Please!

- Type of transplant
  - Auto vs. Allo
  - Nonmyeloablative

- Source of stem cells
  - Bone marrow vs. PBSC vs. UCB

- Presence of GVHD/immunosuppression

Vance E. *BMT* 1998;22(8):735-741
Gandhi MK. *BMT* 2001;28(8):775-781
Small TN. *Blood* 2004;104(11):Abstract 2226
**Recommendations**

- CDC/IDSA/ASBMT
- EBMT

CDC. *MMWR Morb Mortal Wkly Rep* 2000;49(RR-10):1-128
Ljungman P. *BMT* 2005;35(8):737-746

**Donors**

- Studies have shown that recipient response can be improved by donor vaccination
  - *S. pneumoniae* (conj)  Tetanus
  - *H. influenzae* type B  Hepatitis B
  - Diphtheria (?)

Molrine DC. *Blood* 1996;87(7):3012-3018
Small TN. *Blood* 2004;104(11):2226
Storek J. *BMT* 2004;33(3):337-346
Donors

- HLA-Identical sibling donors of 111 BMT recipients
- Randomized to receive T-d/Hib/IPV or not 2-10 weeks before harvest
- All recipients immunized with same vaccines at 3, 6 and 12 months post HSCT

Parkkali T. *BMT* 2007;39(3):179-188

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Donors

- Dip/Hib concentrations higher in the group where donors immunized
- Tetanus and PV concentrations were not different
- Varying effects of GVHD
- Beneficiaries
  - Donors with low titers
  - Recipients at high risk for GVHD

Parkkali T. *BMT* 2007;39(3):179-188
Donors

- Things to consider
  - When will patients be at risk for infection?
  - Against which agents will transfer of donor immunity be protective for the recipient?
  - What is the time frame?
  - What are the ethical issues?

Close Contacts

- Influenza A
- Polio
- MMR
- Varicella
- Hepatitis A

CDC. MMWR Morb Mortal Wkly Rep 2000;49(RR-10):1-128
Ljungman P. BMT 2005;35(8):737-746
Passive Therapies

- Intravenous immunoglobulin
- Varicella-zoster immunoglobulin
- Cytomegalovirus immunoglobulin
- Respiratory syncytial virus immunoglobulin/monoclonal antibody
- Hepatitis B immunoglobulin
- Tetanus immunoglobulin

CDC. MMWR Morb Mortal Wkly Rep 2000;49(RR-10):1-128

Looking Forward

- Populations
- Early start schedules
- Boosters for certain populations
- Donor vaccinations
- New vaccines
- Provision of temporary protection vs. restoring loss of immunity

Patel SR. CID 2007;44(5):625-634
Miesel R. Blood 2007;109(6):2322-2326
Acknowledgements

- Laura L. Worth, MD, PhD
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- and ...

Questions and Discussion

Thank you!

skoontz@mdanderson.org
General Reviews

- Small TN. *BBMT* 2008;14(1 Suppl 1):54-58