EVIDENCE FOR VACCINATION POST HSCT

BSBMT EDUCATION DAY OCTOBER 2015
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Overview

- JACIE Standards + BSBMT vaccination survey
- Antibody levels and infection post transplant
- Assessing vaccines
- Influenza vaccine
- Pneumococcal vaccine
- Future Directions
BSBMT Vaccination Survey

- Comprehensive review of UK vaccination practice
- Collecting data until end of October
- www.smartsurvey.co.uk/s/vaccinationsurvey
SOPs should include post-transplant vaccination schedules and indications

100% (25) centres recommend revaccination

92% (23) Vaccination SOP
Antibody levels post-transplant

- Decline in Ab levels to vaccine preventable diseases (VPDs) Ljungman 1990, 1994; Engelhard 1991.

Infection from VPD post HSCT

- VPDs post transplant
  - Most relatively rare in the community
  - Limited number of cases post HSCT
    - Pertussis – Suzuki 2004, Kochethu 2006
    - Measles – Machado 2002

- HSCT recipients more susceptible to
  - Influenza Virus infection – Whimbey 1994; Nichols 2004; Ljungman 2001; Nichols 2004
Developing and Assessing Vaccines
Correlates of Protection
Developing and Assessing Vaccines

• Immunogenicity
  – Does vaccine provoke a quantifiable immune response?

• Clinical Efficacy
  – Does immune response help to reduce rate and/or severity of infection?

• Clinical Effectiveness
  – Does the vaccine work in the real world?
Correlate of Protection (CoP)

- Immune response correlated with clinical outcome
- Influenza – HAI Assay
  - Seroprotection $\geq 1:40$
- Pneumococcus – ELISA IgG Anti Capsular Ab
  - Seroprotection $\geq 0.35$ ug/ml
Difficulties with CoP?

• Derived from specific study populations
  – Applicable across age groups?
  – Applicable in immunosuppressed?

• Is an absolute cut-off meaningful?
  – Continuum of protection
Seasonal Inactivated Influenza Vaccine
Seasonal Inactivated Influenza Vaccine
2013 IDSA

• One dose IIV administered annually to:-
  – persons aged ≥6 months
  – starting 6 months after HSCT
  – or 4 months if community outbreak

• Children aged 6-8 months, 2 doses should be administered
<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>REGIMEN</th>
<th>POPULATION</th>
<th>TIMING OF VACCINATION</th>
<th>SEROCONVERSION/PROTECTION RATES</th>
<th>OTHER FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelhard et al, 1993</td>
<td>2 doses</td>
<td>n=48 Adult + Paeds Allo HSCT</td>
<td>2-82 months</td>
<td>&lt;6 month 0% SC  &gt;24 months – similar to immunocompetent</td>
<td>Time to Vaccination  GvHD</td>
</tr>
<tr>
<td>Pauksen et al, 2000</td>
<td>1 dose</td>
<td>n=117 Age&gt;16 50 Allo HSCT</td>
<td>4-24 months</td>
<td>&lt;12 months 9-31% SC  &gt;12 months 20-40% SC</td>
<td>GM-CSF significantly higher Influenza B seroconversion rates</td>
</tr>
<tr>
<td>Gandhi et al 2001</td>
<td>1 dose</td>
<td>n=50 Adult 29 AutoPBSCT 12 AutoBMT 9 AlloBMT</td>
<td>11-16 months</td>
<td>Allo – 0% SP AutoBMT – 10% SP AutoPBSC – 13% SP</td>
<td>Response equivalent AutoPBSCT + BMT</td>
</tr>
<tr>
<td>Avetisyan et al 2008</td>
<td>1 dose</td>
<td>n=14 Adult Allo HSCT</td>
<td>5 &lt; 6 months  9 &gt;6 months</td>
<td>H1N1 - 29% SP H3N2 / Influenza B – 0% SP</td>
<td>B+T Cell response as early as 2 months</td>
</tr>
<tr>
<td>Karras et al, 2013</td>
<td>1 v 2 dose regimen</td>
<td>n=73 Adult + Paeds Allo HSCT</td>
<td>2-236 months</td>
<td>&lt; 12 months 0-8% SP  &gt;12 months 39-64% SP</td>
<td>Time to vaccination  No benefit from 2 doses</td>
</tr>
</tbody>
</table>
Seasonal Trivalent IIV

- Minimal serological response before 6 months and impaired beyond 12 months
- Cellular response as early as 2/12
- GvHD associated with lower response rates
- No benefit from 2 dose regimen
Pneumococcal Vaccine
Pneumococcal Vaccine

• PSV - Pneumococcal Polysaccharide
  – T lymphocyte independent response
  – Low-affinity Ab and limited immune memory
  – 23 Valant

• PCV - Pneumococcal Conjugate
  – Polysaccharide + protein carrier
  – T lymphocyte dependent response
  – High affinity Ab and immune memory
  – 7 and 13 valent
Pneumococcal Vaccine – 2013 IDSA

- 3 doses of PCV13 should be administered to adults and children at 3-6 months after HSCT

- At 12 months after HSCT, 1 dose of PSV23 should be given provided patient does not have cGVHD

- For patients with cGVHD, a fourth dose of PCV13 can be considered
### Pneumococcal Vaccine

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<th>TIMING OF VACCINATION</th>
<th>CoP + RESPONSE RATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinan et al 1994</td>
<td>PSV 1 v 2 dose</td>
<td>n=35 Paeds + Adults Auto + Allo</td>
<td>12 or 12+24 months</td>
<td>&gt;0.30ug/ml 19% No difference 1 v 2 dose cGVHD assoc with poor response</td>
</tr>
<tr>
<td>Kumar et al 2007</td>
<td>PSV23 v PCV7</td>
<td>n=64 Adults Sib AlloHSCT Donor and Recip pairs</td>
<td>6 months</td>
<td>&gt;0.35ug/ml Low rates complete seroprotection to at least one serotype:- PSV23 = 56% PCV7 = 90.9%</td>
</tr>
<tr>
<td>Meisel et al 2007</td>
<td>PCV7</td>
<td>n=53 AlloHSCT Paediatric</td>
<td>6-9 months</td>
<td>&gt;0.5ug/ml 2 dose= 55.8% 3dose= 74.4% complete seroprotection</td>
</tr>
<tr>
<td>Cordonnier et al 2009</td>
<td>PCV7 3 dose</td>
<td>n=158 AlloHSCT Adult and Paeds</td>
<td>3,4+5 months v 6,7+8 months</td>
<td>&gt;0.5ug/ml Early=79% Late = 82% Complete seroprotection</td>
</tr>
<tr>
<td>Cordonnier et al 2010</td>
<td>PCV7 3 dose + PSV23</td>
<td>n=101 AlloHSCT Adult and Paeds</td>
<td>PCV7 3,4+5 + PSV23 at 12 or 18 months</td>
<td>&gt;0.5ug/ml No difference early v late Broadened response to include Pn1+Pn5 Increase response to PCV7 serotypes</td>
</tr>
</tbody>
</table>
PCV 13 – 4 dose schedule - Cordonnier 2014
Pneumococcal Vaccine

• PCV more immunogenic than PSV23

• cGVHD assoc with poor response to PSV23

• 3 x PCV7 or PCV13 immunogenic from 3 months

• PSV23 after 3xPCV7 boosts response to shared serotypes and broadens serotype coverage
Summary

- PCV provokes seroprotective response from 3 months

- IIV immunogenicity negligible before 6 months and impaired until at least 12 months

- But what about clinical efficacy?
Future Directions

• Vaccine development
  – Novel adjuvants
  – Alternative delivery methods eg intradermal
  – Universal influenza vaccines

• New CoP
  – Subpopulations (eg young, elderly, immunosuppressed)
  – Novel correlates of protection (eg Cellular response)

• HSCT population
  – Should we vaccinate all HSCT recipients alike?
  – Individualized schedules immune reconstitution?
  – Efficacy studies
References

- Cordonnier, C., Labopin, M., Chesnel, V., Ribaud, P., Camara, R. D. La, Martino, R., ... Ljungman, P. (2010). Immune response to the 23-valent polysaccharide pneumococcal vaccine after the 7-valent conjugate vaccine in allogeneic stem cell transplant recipients: Results from the EBMT IDWP01 trial. *Vaccine, 28*(15), 2730–2734.
- Gandhi, M. K., Egner, W., Sizer, L., Inman, I., Zambon, M., Craig, J. I., & Marcus, R. E. (2001). Antibody responses to vaccinations given within the first two years after transplant are similar between autologous peripheral blood stem cell and bone marrow transplant recipients. *Bone Marrow Transplantation, 28*(June), 775–781.


THANK YOU QUESTIONS?
2009 Pandemic H1N1 Monovalent IIV

• Adjuvanted vaccine

• SP rates 48-84% with 2 dose regimen and equivalent to single dose in healthy controls – de Lavallade 2011; Mohty 2011; Dhedin 2014; Gueller 2011; Engelhard 2011

• Time from HSCT to vaccination associated with higher response rates – Issa 2011; de Lavallade 2011; Mohty 2011; Dhedin 2014

• Poorer response rates if Active GvHD or immunosupression – Mohty 2011; Gueller 2011; Dhedin 2014