Vaccines: What’s new and hot

Hayley Gans, M.D.
Stanford University Medical Center
International Pediatric Transplant Association
8th Congress
Disclosures

• None
Goals and Objectives

• Understand the current strategies for pre and post transplant vaccination
• Become familiar with unique strategies for protecting transplant patients through vaccination
• Learn what to do for exposures or in outbreak situations
Infectious Burden

• Higher rates of infection than rejection\textsuperscript{1}
  – 52% vs 46%

• Infection caused more deaths than rejection\textsuperscript{1}
  – 5.6% vs 0.6%

• Younger age is correlated with higher incidence of infection and severity\textsuperscript{2}
  – Higher rates of primary infection in young children

• Viral infections increase risk of subsequent infections\textsuperscript{3}
  – After varicella in Liver transplant, increased risk for bacteremia in following year:

• Infection and colonization increase the risk of rejection

Vaccine General Issues

- Vaccines are underutilized even pretransplant
  - 20-30% of transplant candidates are UTD
  - While possibly suboptimal 2° to chronic dis before transplant vaccines are definitely subimmunogenic after
  - Live viral vaccines typically not given posttransplant
  - Accelerated schedules are encouraged

- Continue vaccination posttransplant as appropriate

- Immunization has decreased morbidity and mortality in the post-transplant period

- Cocoon patient by optimizing family vaccination status
Vaccine General Issues

• Waning humoral immunity well documented, cell mediated not well studied

• Evidence that responses of boosters post-transplant better than primary series initiated after transplant

• Well documented studies to reject the idea that there is an excess incidence of rejection at least with Flu vaccine
Table 1. Suggested accelerated schedule for vaccination of solid organ transplant candidates

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum age for vaccination</th>
<th>Minimum interval between doses</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td></td>
<td></td>
<td>2nd and 3rd, 8 wk and after 24 wk of age</td>
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<tr>
<td>DTaP</td>
<td>6 wk</td>
<td>1st and 2nd, 4 wk</td>
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<td></td>
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<td>2nd and 3rd, 4 wk</td>
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<tr>
<td></td>
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<td>3rd and 4th, 6 months, and after age 12 months</td>
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<tr>
<td></td>
<td></td>
<td>4th and 5th, 6 months and after age 4 yr</td>
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<tr>
<td></td>
<td></td>
<td>1st and 2nd, 4 wk</td>
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<td></td>
<td></td>
<td>2nd and 3rd, 4 wk and after age 6 months</td>
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<tr>
<td></td>
<td></td>
<td>3rd and 4th, and after age 4 yr</td>
</tr>
<tr>
<td>IPV</td>
<td>6 wk</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td></td>
<td></td>
<td>2nd and 3rd, 4 wk</td>
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<tr>
<td>Hepatitis A</td>
<td>6 months</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td>Hib</td>
<td>6 wk</td>
<td>1st and 2nd, 4 wk</td>
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<td></td>
<td></td>
<td>2nd and 3rd, 4 wk</td>
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<tr>
<td></td>
<td></td>
<td>3rd and 4th, 8 wk, and after age 12 months</td>
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<tr>
<td>Rotavirus</td>
<td>6 wk</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td>(live vaccine – do not give if &lt;1 month anticipated to transplant)</td>
<td></td>
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<tr>
<td>Influenza</td>
<td>6 months</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td></td>
<td></td>
<td>2nd and 3rd, 4 wk</td>
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<tr>
<td>MCV</td>
<td>9 months</td>
<td>1st and 2nd, 12 wk</td>
</tr>
<tr>
<td>MMR</td>
<td>6 months</td>
<td>1st and 2nd, 4 wk</td>
</tr>
<tr>
<td>(live vaccine – do not give if &lt;1 month anticipated to transplant)</td>
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</tr>
<tr>
<td>Varicella</td>
<td>6 months</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td>PCV 13</td>
<td>6 wk</td>
<td>1st and 2nd, 4 wk</td>
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<td></td>
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<td>2nd and 3rd, 4 wk</td>
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<td></td>
<td></td>
<td>3rd and 4th, 8 wk</td>
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<td></td>
<td></td>
<td>If between 12–23 months and unvaccinated, give 3 doses, 8 wk apart</td>
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<tr>
<td></td>
<td></td>
<td>If between 24 months to 5 yr and unvaccinated, give one dose</td>
</tr>
<tr>
<td>MMR8</td>
<td>2 yr</td>
<td>1st and 2nd, 4 wk</td>
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<tr>
<td>Tdap</td>
<td>7 yr</td>
<td>1st and 2nd, 4 wk</td>
</tr>
<tr>
<td>HPV</td>
<td>9 yr</td>
<td>2nd and 3rd, 12 wk</td>
</tr>
</tbody>
</table>
Rationale for Immunization Before with booster after

- Heart transplant several years prior
- Primed responses significantly higher
- Longevity of response unknown
- Booster timing has not been studied, adult recs extrapolated to children = q 5 yrs

Blumberg, CID, 2001
Flu season shaping up to be bad one, CDC says

By Julianne S. Chen, CNN

Updated 9:21 AM EST, Thu January 16, 2015

CDC says flu shots may not be good match for 2014-15 virus

By Julie Sternhagen

CHICAGO — Wed Dec 3, 2014 8:23pm EST

A sampling of flu cases so far this season suggests the current flu vaccine may not be a good match for the most common seasonal flu strain currently circulating in the United States, the U.S. Centers for Disease Control and Prevention said...
Respiratory Viruses

- Higher incidence in immunocompromised patients
- Higher hospitalization rates in infected patients
- Higher rates of LTI and mortality
  - SCT > SOT
  - Age < 1 yr
- RSV > PIV > AdV > IV
  - Motility highest with ADV

Pediatr Transplantation 2013: 17: 133–143
Influenza

- Annual incidence
  - Incidence highest in lung transplant recipients
- Risk of infection not affected by time from transplant
  - Average ~ 3 years posttransplant
- Hospitalization rates reported as high as 70% in SOT and 40% in SCT
- LT disease and pneumonia in 32% and ICU admissions in 16%
- Morality 4% SOT and 6% SCT
- Graft rejection in lung transplant and some reports in kidney, liver

Curr Opin Organ Transplant 2012, 17:601–608
JAMA 2009; 302: 1872–79.
• Current recommendations
  – Annually TIV as early as 1 mo after SOT and
• Novel strategies
  – Adjuvanted TIV
  – Transdermal vs subcutaneous administration
  – Booster dosing: pretransplantation and posttransplantation
  – High dose vs standard dose

Curr Opin Organ Transplant 2012, 17:601–608
All transplant recipients had pretransplant TIV and 2 postransplant doses 28 days apart.

Significant rise after 1st and 2nd TIV doses in transplant recipients.

Is there a role for 2 doses especially the first year posttransplant?
Randomized, double-blind comparison of standard-dose vs. high-dose trivalent inactivated influenza vaccine in pediatric solid organ transplant patients

- Phase I safety trial: 2010-2011, TIV HD vs SD
- 38 patients, mean age 11 yrs, 2 yrs post-transplant
- 42% renal, 26% heart, 21% liver, 5% lung and intestinal
- High dose safe and well tolerated
- Higher % of ≥4 fold rise for H3N2, met all WHO criteria for influenza vaccine efficacy
- Phase 2 study to be performed with higher numbers to assess immunogenicity

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>SD</th>
<th>GMT difference between HD and SD estimate (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A/California/7/2009 H1N1</strong></td>
<td></td>
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<tr>
<td>% with ≥1:40</td>
<td>95.5% (21/22)</td>
<td>80% (12/15)</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>% with ≥4-fold rise</td>
<td>68% (15/22)</td>
<td>47% (7/15)</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Prevaccine GMT (95% CI)</td>
<td>77.5 (35.2–170.5)</td>
<td>62 (20.9–155.1)</td>
<td>15.5 (–94.5–113.8)</td>
<td></td>
</tr>
<tr>
<td>Post-vaccine GMT (95% CI)</td>
<td>773.2 (374.6–1363.3)</td>
<td>310.3 (124–718.4)</td>
<td>462.9 (–85.9–1112.4)</td>
<td></td>
</tr>
<tr>
<td>GMT difference estimate (95% CI)</td>
<td>695.7 (305.3–1299.2)</td>
<td>248.3 (32.9–681.9)</td>
<td></td>
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</tr>
<tr>
<td><strong>A/Perth/16/ 2009 H3N2</strong></td>
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<tr>
<td>% with ≥1:40</td>
<td>86% (19/22)</td>
<td>80% (12/15)</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>% with ≥4-fold rise</td>
<td>54% (12/22)</td>
<td>13% (2/15)</td>
<td></td>
<td><strong>0.011</strong></td>
</tr>
<tr>
<td>Prevaccine GMT (95% CI)</td>
<td>34.7 (21–55.7)</td>
<td>93.3 (47.4–195.5)</td>
<td>–58.6 (–146.1 to –8.6)</td>
<td></td>
</tr>
<tr>
<td>Post-vaccine GMT (95% CI)</td>
<td>131.7 (76.7–233.5)</td>
<td>136.1 (71.8–254)</td>
<td>–4.4 (–131–113)</td>
<td></td>
</tr>
<tr>
<td>GMT difference estimate (95% CI)</td>
<td>97 (35.8–194)</td>
<td>42.8 (–64.4–170.5)</td>
<td></td>
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<tr>
<td><strong>B/Brisbane/60/2008</strong></td>
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<tr>
<td>% with ≥1:40</td>
<td>46% (10/22)</td>
<td>47% (7/15)</td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>% with ≥4-fold rise</td>
<td>18% (4/22)</td>
<td>33% (5/15)</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Prevaccine GMT (95% CI)</td>
<td>19.6 (14.2–26.8)</td>
<td>21.1 (11.4–48.9)</td>
<td>–1.5 (–26.7–11.4)</td>
<td></td>
</tr>
<tr>
<td>Post-vaccine GMT (95% CI)</td>
<td>36.8 (23.3–60.6)</td>
<td>36.2 (18.9–83.2)</td>
<td>0.6 (–42.6–32.4)</td>
<td></td>
</tr>
<tr>
<td>GMT difference estimate (95% CI)</td>
<td>17.2 (1.9–42.4)</td>
<td>15.1 (–15.4–62.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Boldface indicates significance.
Randomized trial: no previous IV
- No pretransplant dose, 180d dose recipient (n=38)
- Pretransplant + 180d dose recipient (n=44)
- Pretransplant donor + 180d recipient (n=40)
• Donor TIV did not significantly increase recipient influenza titers
• Recipient pretransplant vaccine significantly increased posttransplant titers of H1 and H3 up to d180
• All groups had poor response to posttransplant TIV
• Pretransplant vaccine efficacy was 65% against disease
Antiviral therapy provided within 48 hours of symptom onset was associated with decreased ICU admissions (20% vs 80%) and mortality (1% vs 6%)

- **Role for both prophylaxis for exposures and early treatment with symptoms**
Respiratory Syncytial Virus

- Leading cause in bronchiolitis in children < 2y
- Second leading cause of RVI in transplant, but associated with LTD and rejection
- Of SOT ~40% < 5yr, ~15% <1yr

-97% used Palivizumab
-72% during the first RSV season
-25% used it for two seasons
-93% used in 0-12
-79% up to 24 mo

Many centers moving to 5 doses for candidates and recipients <24mo

RSV Disease: Prophylaxis: 4/109 (4%)  No Prophylaxis: 22/195 (11%)  P=.03
2015 MEASLES OUTBREAK IN THE UNITED STATES

The unvaccinated, by the numbers

By Josh Leve, CNN
Updated 8:05 PM ET, Wed February 4, 2015

Source: Centers for Disease Control

Different states, different numbers

By Holly Yan, CNN
Live Viral Vaccines

• Documented more severe cases in immunocompromised
  – Documented break through disease despite
• Theoretical risk of adverse outcomes when immunized when immunosuppressed
• Overall few studies, but growing in number
  – 5 MMR and 8 Varicella
• Variable response rates and no studies looking at pre and post responses systematically
Live Viral Vaccines

- Stringent criteria for immunization
  - >2yr PT, good immune function, low levels of immunosuppressant Rx

- Well tolerated
- Break through varicella in 3 which was mild
- Waning immunity at 5 yrs: Me (60%), Mu (73%), V (40%), but not rubella
Multiple doses given posttransplant: well tolerated

Vaccine elicited good T cell immunity
Post-exposure Prophylaxis

• Exposure to measles case
  – IVIg within 6 days\(^1\): 400mg/kg

• Exposure to varicella
  – Access immunity
    • If seronegative: give varicella IgG preferably before 96 hours but up to 10 days\(^2\)

1. Cochrane Database Syst Rev. 2014 Apr 1;4
2. MMWR / July 19, 2013 / Vol. 62 / No. 28
Summary

• Infections including vaccine preventable diseases cause higher rates of morbidity and mortality in transplant recipient and now surpass rejection as primary source of mortality

• Pretransplant vaccination is the most effective strategy for protection posttransplant
  – The more doses pretransplant the better
  – Evidence supports better booster effects when doses have been given pretransplant followed by doses posttransplant

• Many potential strategies under investigation and will likely influence trends in vaccine usage over time
Conclusions

• **Immunize**
  – Remember the Household!

• **Aim for full series before transplant and before chronically ill**
  – Use accelerated schedule if necessary

• **Boost with all non-live vaccines in post-transplant time**
  – Maintenance immunosuppression
  – Follow titers to determine time to next boost
  – Consider live vaccines (especially measles, no Tx) with informed consent, no cases reported
    • Monitor exposure closely, immune correlate not established for transplant recipients