Vaccination after Solid Organ Transplantation

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Vaccination after Solid Organ TP

Background

Rationale

Inactivated vaccines

Contra-indicated vaccinations

Conclusions

Background

- Solid Organ Transplant: Kidney, Liver, Heart, Lung, Pancreas, Intestine, Combinations
- Usual maintenance immunosuppression (> 6 post TP month)
  - Tacrolimus
  - Mycophenolate mofetil
  - Steroids
  - Induction therapy (ATG – anti IL2R)
- Acute rejection rates < 15% (90% < 3 post TP month)
- The price to pay
  - Increased incidence of viral infections
  - Increased incidence of opportunistic infections
  - Increased incidence of cancer
  - ...... And so, profound immunodepression ....
Vaccination after Solid Organ TP

1. **Background**

2. **Rationale**

3. **Inactivated vaccines**

4. **Contra-indicated vaccinations**

5. **Conclusions**

### Rationale

- Whenever possible, vaccines should be administered before TP (even before dialysis initiation for renal graft recipients)
- Little or no harm has been described with the use of inactivated vaccines
- Most vaccines produce an antibody response, albeit diminished
- The potential benefits of vaccination with inactivated vaccines outweigh the harm of immunization
- Serious infection can result from live vaccines
- Vaccinations are more likely to be effective when immunosuppression is the lowest (> 6 post TP months)

Am J Transpl 2009; 9 (Suppl 3) : S41-43
Bally et al Nephrol Ther 2009; 5 : 265-79
Avery RK & Michaels M Am J Transplant 2008 ; 8 : 9-14*
Vaccination after Solid Organ TP

- Background
- Rationale
- Inactivated vaccines
- Contra-indicated vaccinations
- Conclusions

- Limited number of studies available
- No evidence that vaccination lead to an increased risk of rejection
  - Common practice is to propose vaccination > 6 post TP months (except for Influenza)
- Response to post TP vaccination is diminished compared to immunization prior TP
  - Optimal timing for vaccination is prior TP
- Repeated vaccinations post TP are often necessary
- Vaccination of relatives and family members should not be forgotten
Recommended vaccines

Diphteria-pertussis-tetanus *
Haemophilus influenza (children <16 y.o. *)
Hepatitis A (for travel, occupational and liver Tp candidates, HBV,HCV)
Hepatitis B *
Pneumococcal (children <16 y.o. *)
Inactivated polio *
Influenza
Meningococcus * (adults : administer if patient is at high risk)
Typhoid Vi (for travel in at-risk areas)
HPV *

* Standard vaccination

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Diphteria – Pertussis- Tetanus Vaccination

- Immunity in adults SOT good for tetanus; less for diphteria
- Waning of antitoxin titers after TP
- Good response to booster vaccines, mainly for tetanus (~100 %) ; less for diphteria : 89 % after the booster, 62 % at one year
  
  *Huzly D et al Transplantation 1997 ; 63 : 839-45*

- **Post TP Recommendation :**
  - Immunization : single booster ; booster interval : 10 years (shorter intervals if travel ; monitoring of titers !)
  - No immunization : 3 series – interval between doses : 4 weeks, 6-12 months after second dose ; booster interval : 10 years (shorter intervals if travel ; monitoring of titers !)

  *Stark K et al Lancet 2002 ; 359 957-65*
  *Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009 ; 5 : 46-53*
  *Bally et al Nephrol Ther 2009; 5 : 265-79*
Inactivated polio

- Immunity in adults SOT good for polio
- Good response to vaccine, similar to healthy controls
  
  Huzly D et al Transplantation 1997; 63: 839-45
  Balloni A et al Vaccine 1999; 17: 2507-11

- Repeat immunization every 5 to 10 yrs; mainly if travel in high-risk areas
  
  Bally et al Nephrol Ther 2009; 5: 265-79
  Stark K et al Lancet 2002; 359: 957-65
  Huzly D et al Transplantation 1997; 63: 839-45

Influenza vaccination

- Can cause significant morbidity and mortality in SOT recipients
- Responsible for up to 42% of upper and 48% of lower respiratory tract infections in SOT recipients
  
  Kumar D et al Lancet Infect Dis 2010; 10: 521-6
  Gottlieb J et al Transplantation 2009; 87: 1530-7

- 1 to 4% of SOT infected annually
  
  Ison MG et al J Heart Lung Transplant 2008; 27: 282-8

- Risk of surinfection (bacterial and fungal) – Acute hepatitis in liver TP
  
  Rubin RH Transplant Infect Dis 2002; 1: 175-6
  Duchini A et al Liver Transplant 2000; 6: 531-42

- In lung recipients, influenza may mediate acute allograft rejection and bronchiolitis obliterans syndrome
  
  Khalifah AP et al Am J Respir Crit Care Med 2004; 170: 181-7
**Influenza vaccination**

- Variability in response to vaccine, ranging from 15 to 93% 
  
  
  Cordero E et al. Transplantation 2012; 93: 847-54

  - Lower response in lung recipients
  - Higher response in long-term renal recipients
  - Efficacy superior in paediatrics

- > 1 post-TP month (mainly if SOT recipient has received induction therapy)

- Recommendation: yearly vaccination before start of influenza season

- Strategies to improve response
  - Intradermal administration?
  - Additional doses?
  - Use of adjuvants?

  *Bally et al. Nephrol Ther 2009; 5: 265-79*
  
  
  *Stark K et al. Lancet 2002; 359: 957-65*
  
  *Cohn J & Blumberg EA Nature Clin Pract Nephrol 2009; 5: 46-53*

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**H1N1 vaccination**

- Variability in response to vaccine
  - Vaccination in 21 controls, 53 HD pts and 11 Renal Tp pts
  - Sampling before and one month after a single dose of Pandremix vaccine
  - Proportion of responders: 90% for controls, 57% for HD and 44% for renal TP pts

Hepatitis B

- Still remains a matter of concern in SOT: infection is severe under IS and disease likely to become chronic in SOT (renal and liver)
- Cost of Ig (liver TP) and anti-viral drugs – emergence of resistance
- Post-TP vaccination yields a low response: 32-36% of kidney graft recipients after the 40 ug four-dose schedule; 7 to 23% after liver TP
  
  Bruguera M et al Vaccine 1990; 8: S47-S49
  Loinaz C et al Hepatogastroenterol 1997; 44: 235-36

- Vaccination prior dialysis initiation in patients with renal failure; on waiting lists for all
  
  Bally et al Nephrol Ther 2009; 5: 265-79
  Stark K et al Lancet 2002; 359: 957-65

- Level of immune protection? Acute HBV infection reported in vaccinated patients with low ab titers or rapidly decreasing titers
  
  Goffin E et al Lancet 1995; 345: 263

- Significant rate of HBV reactivation in patients with anti-HBc ab and low or undetectable anti-HBs ab

  Renal TP at St Luc between 1/1995 and 12/2007: 764 → 93 pts with resolved HBV infection
  Graft was negative for HBV infection
  HBsAg reversion occurred in 6 pts; one pt died during follow-up (sepsis)
  
Hepatitis B

- Recommendations for non-immunized SOT patients
  - 3-4 (double ?) doses
  - Recommended schedule: month 0, 1, (2), 6
  - Monitoring response after 6th dose; additional dose recommended if anti-HBS ab < 10 IU/L
  - Regular monitoring of ab (eg every 12 months)
  - Booster doses necessary if ab < 10 IU/L and/or if ab titer decreases rapidly

- Center practice
  - Maintaining anti-HBs ab > 100 IU/L
  - Idem in patients with resolved HBV infection
Pneumococcal vaccine

- Pneumococcal infection cause pneumonia, bacteraemia and meningitis in SOD pts
- Risk of invasive pneumococcal disease 12.8 fold greater than in the general population
  
  *Kumar D et al Am J Transplant 2011; 11 : 2020-30*

- Most SOT recipients develop titers (lower than in general population) : 83 and 80 % for 23-valent and conjugated vaccines, respectively
- Ab titers decrease similarly with both types of vaccination
  
  *Kumar D et al 2003 J Infect Dis 187 : 1639-45*

- No enhanced immunogenicity after a prime-boost strategy (PCV-7) followed by PPV-23 (liver TP recipients)
  
  *Kumar D et al Clin Infect Dis 2008 ; 47 : 885-92*

- Pneumovax 23 injection (14 serotypes) in 43 renal graft recipients ;
  - Ab measured before, and at 4 weeks
  - Response in all patients (increase from 9 (0-13) to 13 (3-14) in serotypes recognized)
  - Ab titers lower than in the general population (84 % of healthy controls)
  
  *Lindemann M et al Transplantation 2010 ; 90 : 1463-7*

  Decrease in ab titers less in younger pts, females, pts given CyA and if better renal function
  
  *Lindemann M et al Transplantation 2012 ; 94 : 50-6*
Pneumococcal vaccine (ACIP recommendations – WWWR Oct 2012)

- **Vaccine-naïve persons**
  - A dose of PCV13 (Prevenar) first, followed by a dose of PPSV23 (Pneumovax) at least 8 weeks later
  - Subsequent doses of PPSV23 (5 years)

- **Previous vaccination with PPSV23**
  - One dose of PCV13 > 1 year after the last PPSV23 dose was received
  - Additional doses of PPSV23 no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23

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Contra-indicated vaccinations after TP

- Varicella zoster
- BCG
- Smallpox
- Live oral typhoid
- Measles (except during an outbreak?)
- Mumps
- Rubella
- Oral polio
- Live Japanese B encephalitis vaccine
- Yellow fever

- Live vaccines use
  - Attenuated viral strains
  - Strain thought to be less pathogenic
- Data on their use is limited raising therefore concerns about both the safety and efficacy of these vaccines in SOT recipients
- For experts, the risks outweigh the potential benefits
- Travel in areas where Yellow Fever is endemic is not advised; if travel, certificate of vaccine contra-indication is required; local protections!
- Pre-TP vaccination (e.g. Varicella)
Primary varicella versus reactivation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Immunization N=13</th>
<th>No Immunization N=19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths n (%)</td>
<td>2 (15)</td>
<td>4 (21)</td>
<td>0.99</td>
</tr>
<tr>
<td>Visceral complication n (%)</td>
<td>4 (31)</td>
<td>5 (26)</td>
<td>0.99</td>
</tr>
<tr>
<td>Initial symptoms n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>6 (75)</td>
<td>15 (100)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (25)</td>
<td>4 (27)</td>
<td>0.99</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>0.35</td>
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</tbody>
</table>

Risk factor for mortality

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Alive n=39</th>
<th>Dead n=17</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 (20)</td>
<td>35 (22)</td>
<td>0.37</td>
</tr>
<tr>
<td>Visceral complication n (%)</td>
<td>23 (68)</td>
<td>17 (53)</td>
<td>0.022</td>
</tr>
<tr>
<td>VZV IgG negative preTP n (%) (n=42)</td>
<td>11 (40)</td>
<td>2 (50)</td>
<td>0.68</td>
</tr>
<tr>
<td>Induction treatment n (%)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Immunosuppression reduction n (%)</td>
<td>29 (74)</td>
<td>7 (63)</td>
<td>0.38</td>
</tr>
<tr>
<td>Aza vs MMF n (%) (n=43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aza</td>
<td>22 (51)</td>
<td>4 (24)</td>
<td>0.74</td>
</tr>
<tr>
<td>MMF</td>
<td>21 (49)</td>
<td>13 (76)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (19)</td>
<td>51 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>21 (17)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin n (%) (mg/dL)</td>
<td>34 (39)</td>
<td>25 (14)</td>
<td>0.28</td>
</tr>
<tr>
<td>Triamcinolone vs methylprednisolone n (%)</td>
<td>22 (86)</td>
<td>21 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>18 (95)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0 (0)</td>
<td>23 (63)</td>
<td>0.27</td>
</tr>
<tr>
<td>Rejection n (%)</td>
<td>7 (18)</td>
<td>5 (29)</td>
<td>0.74</td>
</tr>
<tr>
<td>Treatment time since negative n (%)</td>
<td>3 (5)</td>
<td>7 (41)</td>
<td>0.48</td>
</tr>
<tr>
<td>Additional treatment n (%)</td>
<td>34 (87)</td>
<td>13 (76)</td>
<td>0.7</td>
</tr>
<tr>
<td>Time between TP and onset of</td>
<td>1.9 (1.4 - 3.2)</td>
<td>4.1 (3.0 - 6.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>varicella (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between onset of symptoms and treatment (days)</td>
<td>3.0 (1.9 - 4.5)</td>
<td>2.3 (2.0 - 5.0)</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Varicella (Medline search 1985-2011: 56 renal TP adults with disseminated cutaneous or visceral VZV)

Kanaan N et al Transplant Proc 2012; 44: 2814-7

Survival rate after admission for disseminated VZV infection

64% seroconversion rate in adults on dialysis


Vaccination in seronegative infants results in fewer (12 vs 45%) and milder episodes after renal TP compared with no vaccination (n: 704 pts – observational study)

62% ab at one year and 42% after 10 yrs

Broyer M et al Pediatrics 1997; 99: 35-39
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**Conclusions**

- Inactivated vaccinations schedules should be respected in Solid Organ Transplant candidates; vaccinations while on waiting list better than after TP
- Good evidence to encourage post-TP Influenza and Pneumococcal vaccinations
- Travel vaccinations: hepatitis A, polio and typhoid, meningoccal vaccines
- Hepatitis B:
  - Repeated booster if anti-HBs ab < 100 UI/L
  - And in pts with resolved HBV infection who lost their anti-HBs ab
- Varicella vaccine prior TP in pts without ab