Vaccination in Transplantation

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Scope

- Vaccination in the transplant recipients :

  pre-transplantation

- Vaccination in the transplant recipients :

  post- transplantation

- Vaccination in the CKD period
- Vaccination of the siblings and contacts
- New vaccines

Introduction

- Transplant recipients are at increased risk of infectious complications.

- Data from the North American Pediatric Renal Transplant Cooperative study show that ***38–42%*** patients transplanted between 1987 and 2002 required hospitalization ***for infections***.

Introduction

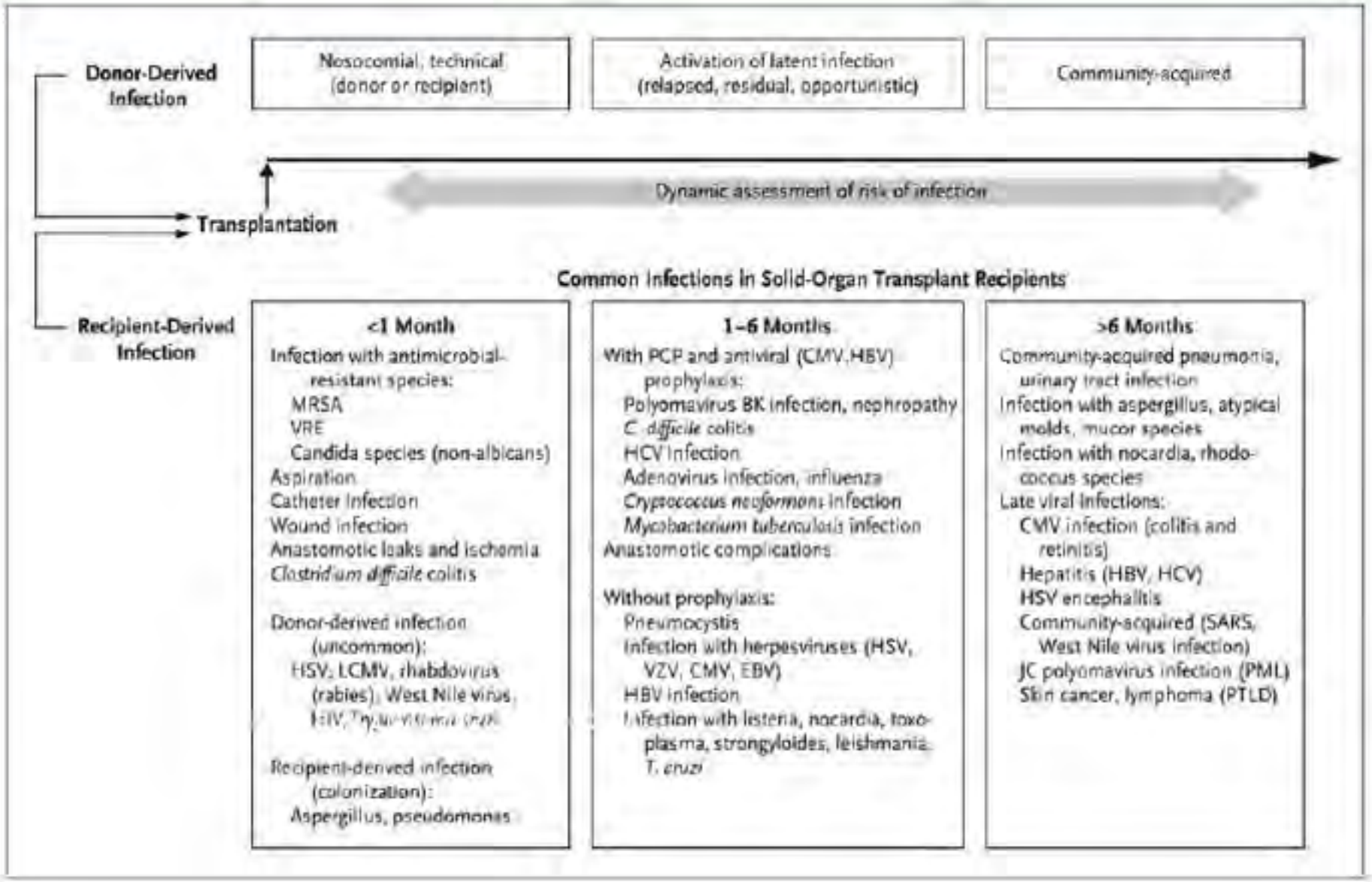
- Infection was the primary cause of hospitalization in the first 2 years after transplantation, exceeding that for rejection.

  Dharnidharka VR et al. Am J Transplant. 2004

- Infection risk is even greater in the pediatric transplant population

  V. Jha, Indian J of Nephrology 2010

Changing Timeline of Infection after Organ Transplantation



Vaccination in SOT

- **Ideally** , the issue of vaccination in pediatric renal transplantation candidates should not be raised before transplantation in the setting of pre-transplant preparation program

- Neither should it be raised in the post transplantation phase !!

- Then when ?

Vaccination in CKD phase

- Vaccination status should be reviewed and evaluated at initial evaluation of chronic kidney disease (CKD).

- Once a pediatric patient is labeled a CKD patient, his vaccination schedule SHOULD be revised and evaluated and all vaccinations recommended for the general population should be administered.

CKD outpatient clinic

Outpatient Follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L)) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Output							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose

Vaccination in CKD phase

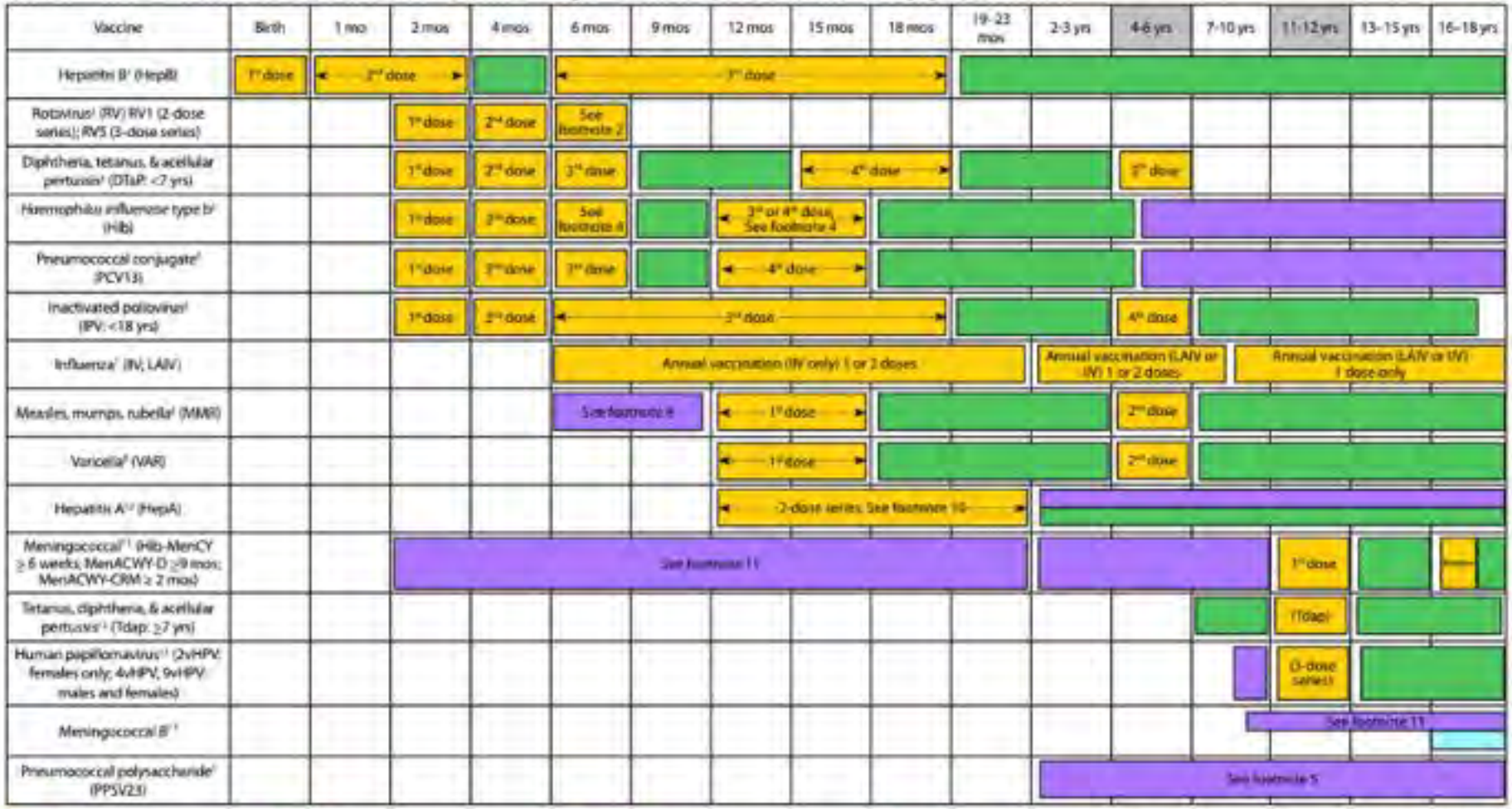
- Type:
  - Recommendations for vaccination in CKD are based largely on data from ***general population.***

- Timing:
  - Vaccines should be administered ***early to CKD patients***, since poor ***immune memory*** in advanced stages of CKD and after transplantation results in weak antibody response.
- Pediatric CKD patients should be vaccinated against varicella, influenza, hepatitis B and *Pneumococcus*.

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2016.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE (FIGURE 2)).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded.



This schedule includes recommendations in effect as of January 1, 2016. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online

Vaccination in CKD phase

- Hepatitis B
  - Dialysis patients, and especially HD are at a significantly increased risk for hepatitis B infection, hence every effort should be taken to minimize that risk with vaccination .

  - Unfortunately, it is well documented that in dialysis:
    - ***Suboptimal response*** to hepatitis B vaccine and
    - ***More rapid decline*** in anti-hepatitis B antibody levels

Vaccination in CKD phase

- Although these data suggest that pediatric CKD patients may benefit from an augmented dose of hepatitis B vaccine, at present the Advisory Committee on Immunization Practices (ACIP) recommends that CKD and dialysis patients younger than 20 years of age receive hepatitis B immunization according to the standard schedule.

- Post-vaccination testing is recommended 1–2 months after the primary series is completed

- The protective antibody levels should be achieved which is >10 mIU/ml .

Vaccination in CKD phase

- Up to three additional doses can be given after completion of the primary series if protective antibody levels (>10 mIU/ml) are not achieved .

- Antibody levels should then be measured ***annually*** and ***booster doses*** provided to patients whose antibody levels fall below protective .

Hemodialysis Follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							
Other							

Vaccination: HBV Ab titer (annually) and not only HBV sAg

*—A = alert; D = drowsy; S = stuporous; C = comatose

Recommendation 1

- Add a Vaccination Sheet to your CKD outpatient clinic
- Make sure to vaccinate the CKD child ***as early as possible*** in his CKD course, using the regular vaccination schedules
- Add a Vaccination Sheet to your HD follow up
- HBV titer should be monitored in HD with extra doses if needed

Vaccination Pre-Transplantation

Vaccination in Pre-Transplantation Phase

- Every effort should be made to ensure that transplant candidates, ***their household members and healthcare workers*** have completed the full complement of recommended vaccinations prior to transplantation.

- Since the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their disease.

Vaccination in Pre-Transplantation Phase

- It is recommended that:
  - vaccination status be reviewed at the time of ***the first transplant clinic visit*** (if not done in CKD clinic) ,
  - a **vaccine strategy** be developed at that time

Transplant Preparation Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration(depth)†							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
CMV HCV HBV HIV							
$Paco_2$							
VCUG Echo CXR							
[illegible]							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							
5% dextrose (mL) in past hour							
[illegible]							
Vaccination:							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose.
†—D = deep; S = shallow; N = normal.

Vaccination in Pre-Transplantation Phase

- the vaccination status **be reviewed** once again at **the time** the patient is listed for transplantation.

- A minimum of 4 weeks between live-virus vaccine administration and transplantation is suggested (III).

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

PEDIATRIC VACCINES

Vaccine	Inactivated/ live attenuated (I/LA)	Recommended before transplant[1]
Influenza	I	Yes
	LA	No
Hepatitis B	I	Yes
Hepatitis A	I	Yes
Pertussis	I	Yes
Diphtheria	I	Yes
Tetanus	I	Yes
Inactivated Polio vaccine	I	Yes
H. influenzae	I	Yes
S. pneumoniae[4] (conjugate vaccine)	I	Yes
S. pneumoniae[4] (polysaccharide vaccine)	I	Yes
N. meningitidis[5]	I	Yes
Human papillomavirus (	I	Yes
Rabies[7]	I	Yes
Varicella (live-attenuated)[8]	LA	Yes
Rotavirus	LA	Yes
Measles[8]	LA	Yes
Mumps[8]	LA	Yes
Rubella[8]	LA	Yes
BCG[9]	LA	Yes
Smallpox[10]	LA	No

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination in Pre-Transplantation Phase

- In general, live vaccines are not administered after transplantation; therefore, it is recommended to administer live vaccines such as measles, mumps, rubella (MMR) and Varicella vaccine prior to transplantation.

- While MMR is the most effective after a year of age when maternal antibody has waned, it can be administered as early as 6 months of age for pediatric patients who may require transplantation.

Vaccination in Pre-Transplantation Phase

- If transplantation has still not occurred by the time the baby is a year of age, the dose should be repeated. The second dose of MMR can be administered as soon as 4 weeks later.

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination in Pre-Transplantation Phase

- Notes:

  "<u>Safe Vaccines</u>"

  - Don't postpone vaccines to post transplantation as even "safe " vaccines ***after transplantation*** may not be sufficiently immunogenic after transplantation.

  <u>Time plan:</u>

  - Accelerated schedules may be less immunogenic (plan ahead of time starting at the first visit)

  - Serial hepatitis B surface antibody titers should be assessed both before and every 6–12 months after transplantation to assess ongoing immunity

Vaccination in Pre-Transplantation Phase

- Notes:
  - All patients aged 11–18 years in the United States and certain patients (properdin deficient, terminal complement component deficient, those with functional or anatomic asplenia) are candidates for the meningococcal vaccine in the United States and Canada

Vaccines and hindrances of special treatment

- Patients undergoing transplant evaluation may be receiving or have recently received immunosuppressive therapies and/ or immunoglobulin (IG) therapy, whether standard or disease specific, which can affect the response to vaccines.

Vaccines and Rituximab

- Rituximab is an anti-CD20 monoclonal antibody that can inhibit the immune response to vaccines.

- The ability of vaccines to stimulate humoral immunity after receipt of rituximab can be impaired for as long as 12 months, although the maximum effect occurs within the first 6 months

- Delay vaccination for at least 6 months after rituximab in order to make the administration of inactivated vaccines effective and live vaccines safe

Vaccines and steroids

- Delaying live virus vaccines for at least 4 weeks in patients receiving 14 days or more of high-dose corticosteroids (≥ 2 mg/kg/day of prednisone or ≥ 20 mg/day in patients over 10 kg)

Vaccines and Other Immunossuppressives

- For Mycophenolate, tacrolimus, cyclosporine, cyclophosphamide, and azathioprine (scarce data):

- it is generally considered that a period of 3 months is required for immune status to be completely restored after the cessation of these medications and therefore before live vaccines can be safely administered

Vaccines and IG

- MMR and varicella vaccines should be delayed at least 2 weeks before and up to 11 months after receipt of IG

- The period of delay is proportional to the dose of IG given. For example, those given a 400 mg/kg dose should delay MMR and varicella vaccines by 8 months. Receipt of doses of 1600 to 2000 mg/kg requires an 11-month deferral

Vaccines and Blood Products Transfusion

- MMR and varicella vaccines should also be delayed in patients who have received blood products.

- For example, those receiving packed red blood cells (10 ml/kg) or platelets/ plasma (10 ml/kg) should wait 5 and 7 months, respectively, before receiving these vaccines .

Vaccination Post-Transplantation

Vaccination in Post-Transplantation Phase

- While every effort should be made to vaccinate prior to transplantation, **inactivated vaccines** are generally safe after solid organ transplantation.

- For inactivated vaccines where there are no data for transplant candidates or recipients, recommendations made by ACIP (Advisory Committee on Immunization Practices) for the general population should be followed.

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination in Post-Transplantation Phase

- Vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic after transplantation.

- There is no evidence to link rejection episodes to vaccination (II-2) .

Avery RK, Michaels M. Am J Transplant 2008

Vaccination in Post-Transplantation Phase

Timing of Post Tx Vaccination :

- While data regarding timing of vaccines after transplantation have not been fully evaluated, most centers restart vaccination at **approximately 3–6 months after transplantation,** when baseline immunosuppression levels are attained.

- **Types of Accepted Vaccines Post Tx:**

PEDIATRIC VACCINES

Vaccine	Inactivated/ live attenuated (I/LA)	Recommended before transplant[1]	Recommended after transplant	Monitor vaccine titers	Quality of evidence
Influenza (2–6)	I	Yes	Yes	No	II-1
	LA	No	No	No	III
Hepatitis B (7–13)	I	Yes	Yes[2]	Yes[2]	II-1
Hepatitis A (14,15)	I	Yes	Yes	Yes	II-1
Pertussis	I	Yes	Yes	No	III
Diphtheria (16–19)	I	Yes	Yes	No	II
Tetanus (16–19)	I	Yes	Yes	Yes	II-1
Inactivated Polio vaccine (16–19)	I	Yes	Yes	No	II-2
H. influenzae (20)	I	Yes	Yes	Yes[3]	II-1
S. pneumoniae[4] (conjugate vaccine) (1,21–25)	I	Yes	Yes	Yes[3]	II-1
S. pneumoniae[4] (polysaccharide vaccine) (1,21–25)	I	Yes	Yes	Yes[3]	II-1
N. meningitidis[5] (1,26) (MCV4)	I	Yes	Yes	No	III
Human papillomavirus (HPV)[6] (1)	I	Yes	Yes	No	III
Rabies[7]	I	Yes	Yes	No	III
Varicella (live-attenuated)[8] (27–30)	LA	Yes	No	Yes	II-1
Rotavirus	LA	Yes	No	No	III
Measles[8] (31–34)	LA	Yes	No	Yes	II-1
Mumps[8] (31,34)	LA	Yes	No	Yes	II-1
Rubella[8] (31,34)	LA	Yes	No	Yes	II-1
BCG[9]	LA	Yes	No	No	III
Smallpox[10] (35)	LA	No	No	No	III

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination in Post-Transplantation Phase

Influenza vaccination

- Among the various flu vaccines, the injectable inactivated vaccine is safe in kidney transplant recipients whereas the nasal live attenuated vaccine is contraindicated in the immunocompromised.

- If an ESRD patient received a live attenuated influenza vaccine, he/she should not be immunosuppressed preferably for the next 4-6 weeks, and at least for not <2 weeks.

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

Vaccination in Post-Transplantation Phase

Influenza vaccination

- After kidney transplantation, routine annual inactivated influenza vaccine administration is recommended in all transplant recipients

- Immunogenicity of the influenza vaccine in kidney transplant recipients varies widely due to many factors, for example, patients on MMF have a lower seroprotective rate.

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

Vaccination in Post-Transplantation Phase

Varicella Vaccine:

- Only a couple of studies demonstrated the safety of varicella and measles vaccines in small number of patients after transplantation, but the balance of opinion suggests that the risks of live vaccines outweigh potential benefits and hence should not be used.

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

- More recent reviews consider this vaccine contraindicated in kidney transplant recipients.

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

Vaccination in Post-Transplantation Phase

Varicella Vaccine:

- It should be administered at least 4-6 weeks before kidney transplantation. If transplant is emergently indicated in a patient who has received a varicella vaccine recently, he/she ***should receive peri-transplant prophylaxis with intravenous acyclovir or oral valacyclovir.***

- The *Zoster vaccine*, composed of a stronger dose of the live attenuated strain, is also contraindicated in kidney transplant recipients.

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

Vaccination in Post-Transplantation Phase

Human papillomavirus vaccination

- Kidney transplant recipients have a 14-fold increased risk of cervical cancer and a 100-fold increased risk of anal cancers, the majority of which are caused by high-risk HPV types

- Cervical carcinoma, the second most common cancer in women worldwide, is nearly always caused by HPV infection: type 16 is responsible for about 60%, while type 18 causes approximately 10% of deaths

Vaccination in Post-Transplantation Phase

Human papillomavirus vaccination

- Initially approved only for females but later expanded to males, the HPV quadrivalent vaccine (types 6, 11, 16, and 18) demonstrated efficacy against the development of HPV-related cancers .

  Brown D, et al. Hum Vaccin 2011

- At the end of 2016, a nine-valent vaccine that targets the quadrivalent types along with HPV types 31, 33, 45, 52, and 58 became available. Given the choice, it is recommended to use the ninevalent HPV vaccine whenever possible

Vaccination in Post-Transplantation Phase

Human papillomavirus vaccination

- HPV vaccination should be completed prior to kidney transplantation. If the vaccination has been initiated pretransplant and could not be completed, additional doses could be administered after 3 months of kidney transplantation when the intensity of immunosuppression is less
- 9-13 years age girls should be primary target of vaccination.
- Similar age boys could also be vaccinated

Vaccination in Post-Transplantation Phase

Human papillomavirus vaccination

- Catch-up vaccination can be administered to those men and women between 11-26 years of age who have not been vaccinated previously.

- **The role of HPV vaccination among male and female kidney transplant recipients may expand in future.**

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

Transplant follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Output							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose

Vaccination in Post-Transplantation Phase

- Vaccines titers

Vaccination in Post-Transplantation Phase

- The ability to mount an immune response will be impacted by the type and amount of immunosuppression after organ transplantation. Accordingly, seroefficacy should be documented by serologic assays where available.

- A minimum of 4 weeks should elapse between vaccine administration and evaluation for seroconversion based on protective titers established in the literature.

- However, given that serology may not be an accurate measure of immunity in the posttransplant period, assays for cellular immunity need further study in this population (III).

Vaccination in Post-Transplantation Phase

- Post-transplant influenza and pneumococcal vaccinations lead to protective antibody titers in a majority of RTRs.

- The antibody response is weak for post-transplant hepatitis B vaccine. Antibody titers should be monitored with booster vaccination once the titers fall below 10 IU/m

Neuhaus TJ. Pediatr Nephrol. 2004

PEDIATRIC VACCINES

Vaccine	Inactivated/ live attenuated (I/LA)	Recommended before transplant[1]	Recommended after transplant	Monitor vaccine titers	Quality of evidence
Influenza (2–6)	I	Yes	Yes	No	II-1
	LA	No	No	No	III
Hepatitis B (7–13)	I	Yes	Yes[2]	Yes[2]	II-1
Hepatitis A (14,15)	I	Yes	Yes	Yes	II-1
Pertussis	I	Yes	Yes	No	III
Diphtheria (16–19)	I	Yes	Yes	No	II
Tetanus (16–19)	I	Yes	Yes	Yes	II-1
Inactivated Polio vaccine (16–19)	I	Yes	Yes	No	II-2
H. influenzae (20)	I	Yes	Yes	Yes[3]	II-1
S. pneumoniae[4] (conjugate vaccine) (1,21–25)	I	Yes	Yes	Yes[3]	II-1
S. pneumoniae[4] (polysaccharide vaccine) (1,21–25)	I	Yes	Yes	Yes[3]	II-1
N. meningitidis[5] (1,26) (MCV4)	I	Yes	Yes	No	III
Human papillomavirus (HPV)[6] (1)	I	Yes	Yes	No	III
Rabies[7]	I	Yes	Yes	No	III
Varicella (live-attenuated)[8] (27–30)	LA	Yes	No	Yes	II-1
Rotavirus	LA	Yes	No	No	III
Measles[8] (31–34)	LA	Yes	No	Yes	II-1
Mumps[8] (31,34)	LA	Yes	No	Yes	II-1
Rubella[8] (31,34)	LA	Yes	No	Yes	II-1
BCG[9]	LA	Yes	No	No	III
Smallpox[10] (35)	LA	No	No	No	III

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination of Contacts and Family Members

- Healthcare workers, close contacts and family members should be immunized fully

- In particular, they should receive influenza vaccine yearly.

- In general, if nonlive vaccine options are available for household members they are preferred. However, with the exception **of smallpox and oral-polio vaccines** there is little to no risk from the family members or close contacts receiving live vaccines.

Vaccination of Contacts and Family Members

- Family members **should NOT take OPV** as the virus may be transmissible to the transplant recipient

Guidelines for vaccination in kidney transplant recipients, Indian J Nephrol 2016

- Household and close contacts may **preferably** be vaccinated against MMR and varicella to prevent the transplanted patient from having contact with wild-type viruses (III)

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

HEALTH CARE WORKERS AND OTHER CLOSE CONTACTS/HOUSEHOLD MEMBERS of TRANSPLANT CANDIDATES/RECIPIENTS

Vaccine	Inactivated/ live attenuated (i/la)	Recommended before transplant[1]	Recommended after transplant	Quality of evidence
Influenza (2–6)	I	Yes	Yes	II-2
	LA	Yes	No	III
Hepatitis B[2] (7–13)	I	Yes	Yes	II-2
Hepatitis A (14–15)	I	Yes	Yes	II-1
H. influenzae (20)	I	Yes	Yes	II-2
Pertussis (Tdap)	I	Yes	Yes	II-2
Varicella (27–30)	LA	Yes	Yes	II-2
Measles (31–34)	LA	Yes	Yes	II-2
Mumps (31,33,34)	LA	Yes	Yes	II-2
Rubella (31,33,34)	LA	Yes	Yes	II-2

Guidelines for Vaccination of Solid Organ Transplant Candidates and Recipients, American Journal of Transplantation 2009

Vaccination of Contacts and Family Members: Varicella vaccine

- There are conflicting opinions on the safety of administration of varicella vaccine in household contacts of transplant recipients.

- Although the American Academy of Pediatrics (AAP) supports the use of the varicella vaccine in household contacts, it recommends ***isolation if rashes develop*** and they should not be in contact of the transplant recipients

- If rashes develop in the transplant recipient, the transplant center should be notified and anti-viral therapy should be administered immediately

Vaccination of Contacts and Family Members: Rotavirus vaccine

- Rotavirus shedding happens after the first vaccination in siblings of transplant recipient receiving rota vaccine .
- However most experts consider the risk of household transmission is less severe than the wild-type rotavirus.
- Rotavirus vaccine can be safely given to infant contacts of the SOT recipient, but because the virus is shed in the infant's stool , SOT recipients should avoid changing the vaccine recipient's diapers for at least 28 days following receipt of vaccine. If this is unavoidable, strict hand hygiene should be enforced

Transplant follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Patient :

Family:

*—A = alert; D = drowsy; S = stuporous; C = comatose

New Vaccines

Drugs. 2016 Nov;76(17):1625-1645.

Cytomegalovirus Vaccines: Current Status and Future Prospects.

Anderholm KM[1], Bierle CJ[1], Schleiss MR[2].

Author information

Abstract

Congenital human cytomegalovirus (HCMV) infection can result in severe and permanent neurological injury in newborns, and vaccine development is accordingly a major public health priority. HCMV can also cause disease in solid organ transplant (SOT) and hematopoietic stem-cell transplant (HSCT) recipients, and a vaccine would be valuable in prevention of viremia and end-organ disease in these populations. Currently there is no licensed HCMV vaccine, but progress toward this goal has been made in recent clinical trials. A recombinant HCMV glycoprotein B (gB) vaccine has been shown to have some efficacy in prevention of infection in young women and adolescents, and has provided benefit to HCMV-seronegative SOT recipients. Similarly, DNA vaccines based on gB and the immunodominant T-cell target, pp65 (ppUL83), have been shown to reduce viremia in HSCT patients. This review provides an overview of HCMV vaccine candidates in various stages of development, as well as an update on the current status of ongoing clinical trials. Protective correlates of vaccine-induced immunity may be different for pregnant woman and transplant patients. As more knowledge emerges about correlates of protection, the ultimate licensure of HCMV vaccines may reflect the uniqueness of the target populations being immunized.

PMID: 27882457 DOI: 10.1007/s40265-016-0653-5

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Cytomegalovirus vaccines under clinical development

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Abstract

Go to:

Congenital cytomegalovirus (CMV) infection is the most common infectious cause of disability in newborn infants. CMV also causes serious disease in solid organ (SOT) and haematopoietic stem cell transplant (HSCT) recipients. In otherwise healthy children and adults, primary CMV infection rarely causes illness. However, even asymptomatic CMV infections may predispose an individual towards an increased risk of atherosclerosis, cancer and immune senescence over the life course, although such associations remain controversial. Thus, although a vaccine against congenital CMV infection would have the greatest public health impact and cost-effectiveness, arguably all populations could benefit from an effective immunisation against this virus. Currently there are no licensed CMV vaccines, but there is increased interest in developing and testing potential candidates, driven by the demonstration that a recombinant CMV glycoprotein B (gB) vaccine has some efficacy in prevention of infection in young women and adolescents, and in CMV-seronegative SOT recipients. In this review, the recent and current status of candidate CMV vaccines is discussed. Evolving concepts about proposed correlates of protective immunity in different target populations for CMV vaccination, and how these differences impact current clinical trials, are also reviewed.

Keywords: CMV, cytomegalovirus, vaccine, pentameric complex, congenital infection, placenta

Table 1. CMV vaccines currently or recently in clinical trials

Vaccine category	Phase	Vaccine	Antigens used	Adjuvant	Parameters evaluated	Manufacturer	Subjects	Serostatus	Age	Identifier
DNA (plasmid) vaccines	1	ASP0113	pp65, gB	CRL1005-BAK	Part 1: pharmacokinetics; Part 2: immunogenicity	Astellas, Vical	Healthy in Part 1, Healthy or dialysis recipients in Part 2	−/+ if healthy, − if dialysis	18–70	NCT02103426
	2	ASP0113	pp65, gB	CRL1005-BAK	Viraemia, safety	Astellas	Allogeneic HTC recipients	N/A	20+	NCT01903928
	2	ASP0113	pp65, gB	CRL1005-BAK	Viraemia	Astellas, Vical	Seronegative recipient of seropositive kidney	Negative	18+	NCT01974206
	2	VCL-CB01	pp65, gB	CRL1005-BAK	Viraemia, T cells	Astellas, Vical	HCT donors/recipients	Positive (HCT recipient)	18–65	NCT00285259
	3	ASP0113	pp65, gB	CRL1005-BAK	Viraemia, CMV end-organ disease; overall mortality	Astellas, Vical	Recipients of allogeneic HCT	Positive	18+	NCT01877655

Attenuated and DISC vaccines	1	V160-001		Merck Aluminum Phosphate Adjuvant or none	Antibodies, adverse effects	Merck	Healthy	Positive and negative	18+	NCT01986010
	1	Towne-Toledo Chimera Vaccines			General safety	CMV Research Foundation, International AIDS Vaccine Initiative	Healthy males with no children <18 yoa in sexual relationship with seropositive individual	Negative	30–50	NCT01195571
	1	VCL-CT02, plus Towne CMV	gB, pp65, IE1		Antibodies, T cells, IFN-γ ELISPOT	UC-SF, Vical	CMV-specific immune response post-Towne vaccine challenge (3000 pfu) in volunteers who received VCL CT02 vaccine in a 3-dose regimen	Negative	18–45	NCT00370006
Vectored vaccines	1	AVX601	gB, pp65, IE1	None	Antibodies, T cells	AlphaVax, Inc (Novartis, GSK)	Healthy	Negative	18–45	NCT00439803
	1	HCMV-MVA Triplex	pp65, UL123/IE1-exon4, UL122/IE2-exon5	None	Optimal dosage (2-dose), immune response, safety	City of Hope, National Cancer Institute	Healthy	Positive and negative	18–60	NCT01941056
	1	HB-101	gB, pp65	None	Safety, optimal dosage, ELISA	Hookipa Biotech	Healthy	Negative	18–45	NCT02798692

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Epstein–barr virus vaccines

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This article has been corrected. See Clin Transl Immunology. 2015 April; 4(4): e36.

This article has been cited by other articles in PMC.

Abstract

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Epstein–Barr virus (EBV) is the primary cause of infectious mononucleosis (IM) and is associated with epithelial cell malignancies such as nasopharyngeal carcinoma and gastric carcinoma, as well as lymphoid malignancies including Hodgkin lymphoma, Burkitt lymphoma, non-Hodgkin lymphoma and post-transplant lymphoproliferative disorder. EBV vaccines to prevent primary infection or disease, or therapeutic vaccines to treat EBV malignancies have not been licensed. Most efforts to develop prophylactic vaccines have focused on EBV gp350, which is the major target of neutralizing antibody. A single phase 2 trial of an EBV gp350 vaccine has been reported: the vaccine reduced the rate of IM but not virus infection. The observation that infusion of EBV-specific T cells can reduce disease due to Hodgkin lymphoma and nasopharyngeal carcinoma provides a proof of principle that a therapeutic vaccine for these and other EBV-associated malignancies might be effective. Most therapeutic vaccines have targeted EBV LMP2 and EBV nuclear antigen-1. As EBV is associated with nearly 200 000 new malignancies each year worldwide, an EBV vaccine to prevent these diseases is needed.

Over 95% of adults are infected with Epstein–Barr virus (EBV); most infections occur in young children and are asymptomatic or cause nonspecific symptoms.[1] EBV is the primary cause of infectious mononucleosis (IM) and is associated with a number of B lymphocyte and epithelial cell malignancies. In a recent study, 37% of students entering a college in the United States were EBV seronegative, 46% of them seroconverted during 3 years of college and 77% of those who seroconverted developed symptoms of IM.[2] Although IM is

Non-human primate studies with EBV gp350

Vaccine	*Adjuvant*	*Study and results*
Purified native gp350	Lipsomes	Cotton top tamarins protected from EBV- induced lymphoma[29]
Purified native gp350	ISCOMs	Cotton top tamarins protected from EBV- induced lymphoma[60]
Purified native gp350	Muramyl dipeptide in squalene	Cotton top tarmarins protected from EBV- induced lymphoma[61]
Adenovirus-gp350	None	Cotton top tamarins protected from EBV- induced lymphoma[30]
Vaccinia-gp350 WR strain	None	Cotton top tamarins protected from EBV- induced lymphoma[31]
Vaccinia-gp350 Wyeth strain	None	Cotton top tamarins not protected from EBV- induced lymphoma[31]
Vaccinia-gp350	None	Common marmosets had decreased virus replication of EBV after challenge[62]
Recombinant gp350	Muramyl dipepide in squalene	Cotton top tamarins protected from EBV- induced lymphoma[63]
Recombinant gp350	Alum	Cotton top tamarins protected from EBV- induced lymphoma[64]
Recombinant gp350	Alum	Common marmosets had decreased virus replication of EBV after challenge[65]

Abbreviations: EBV, Epstein–Barr virus; ISCOMs, immunostimulating complexes WR strain, Western reserve strain.

Human trials of EBV vaccines

Vaccine	*Adjuvant*	*Results*
Prophylactic		
Vaccinia-gp350	None	Induced neutralizing antibody and may have reduced infection[35]
Recombinant gp350	None, alum, or alum/MPL	Induced neutralizing antibody[36]
Recombinant gp350	Alum/MPL	Induced neutralizing antibody; reduced rate of infectious mononucleosis, but not infection[37]
Recombinant gp350	Alum	Induced transient neutralizing antibody in a minority of patients with chronic kidney disease; did not prevent EBV post-transplant lymphoproliferative disorder[38]
EBNA-3A peptide	Tetanus toxoid in oil and water emulsion	Trend toward reduction of infectious mononucleosis but not infection[39]
Therapeutic		
Modified vaccinia Ankara expressing LMP2 and a portion of EBNA-1	None	T-cell responses to LMP2 or EBNA-1 detected in 15 of 18 NPC patients with a three to fourfold increase in T-cell responses[55]
Modified vaccinia Ankara expressing LMP2 and a portion of EBNA-1	None	T-cell responses to LMP2 or EBNA-1 detected in 8 of 14 NPC patients[56]
Autologous dendritic cells pulsed with LMP2 peptides	None	Boosted CD8 T-cell responses to LMP2 in NPC patients; tumor regression observed in two of nine patients[57]
Autologous dendritic cells transduced with adenovirus expressing LMP2 and a portion of LMP1	None	Induced LMP-specific delayed type hypersensitivity responses in 75% of NPC patients, but no increase in LMP1 or LMP2-specific T cells; transient partial response in 1 of 16 patients, and stable disease in 2[58]

Abbreviations: EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; LMP1, latent membrane protein 1; MPL, monophosphoryl lipid A; NCP, nasopharyngeal carcinoma patients.

Conclusion

- Vaccination status should be reviewed and evaluated at initial evaluation of chronic kidney disease (CKD).

- Immune response decreases with CKD advancement , the earlier the vaccination the better.

- In CKD and post Tx , Hepatitis B vaccine shows suboptimal response and more rapid decline in anti-hepatitis B antibody levels. This needs monitoring and extra doses and protective level should exceed 10 mIU/ml

Conclusion

- Many vaccines need to have their titers monitored as HBV, Hib, MMR and Varicella
- After kidney transplantation, routine annual inactivated influenza vaccine administration is recommended in all transplant recipients
- There is no evidence to link rejection episodes to vaccination (II-2) .

Conclusion

- Family members **should NOT take OPV** as the virus may be transmissible to the transplant recipient

- Household may **preferably** be vaccinated against MMR and varicella to prevent the transplanted patient from having contact with wild-type viruses but if rashes occur they should be isolated

Outpatient Follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L)) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Output							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose

Hemodialysis Follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							
Other							

Vaccination: HBV Ab titer (annually) and not only HBV sAg

*—A = alert; D = drowsy; S = stuporous; C = comatose

Transplant Preparation Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration(depth)†							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
CMV HCV HBV HIV							
$Paco_2$							
VCUG Echo CXR							
[illegible]							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							
5% dextrose (mL) in past hour							
[illegible]							
Vaccination:							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose.
†—D = deep; S = shallow; N = normal.

Transplant follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Output							
Urine (mL)							
Other							

*—A = alert; D = drowsy; S = stuporous; C = comatose

Transplant follow-up Sheet

Date: Hour:	0	1	2	3	4	5	6
General information							
Mental status*							
Temperature							
Pulse							
Respiration/depth							
Blood pressure							
Serum glucose (mg/dL)							
Serum ketones							
Urinary ketones							
Electrolytes							
Serum sodium (mEq/L)							
Serum potassium (mEq/L)							
Serum chloride (mEq/L)							
Serum bicarbonate (mEq/L)							
Serum blood urea nitrogen (mg/dL)							
Effective osmolality: 2 (measured serum sodium (mEq/L) + glucose (mg/dL)/18							
Anion gap (mEq/L)							
Arterial blood gases							
pH: venous (V); arterial (A)							
Pao_2							
$Paco_2$							
O_2 saturation							
Insulin							
Units in past hour							
Route							
Intake of fluids/metabolites							
0.45% saline (mL) in past hour							
0.9% saline (mL) in past hour							

Vaccination:

Patient :

Family:

*—A = alert; D = drowsy; S = stuporous; C = comatose

Thank you

Question 1

- ***One answer is correct:***

A) Rota virus and OPV are contraindicated to be given to the household contacts of a Tx recipient

B) IPV is not recommended for Household contact of a transplant recipient

C) Varicella and MMR vaccines can be given to household contacts of a Tx recipient but should be isolated if they develop rash

D) Intranasal Influenza vaccine is highly recommended for both the recipient and his household before every winter

Question 2

- ***One answer is correct:***

A) A case of steroid resistant Nephrotic Syndrome on Neoral and steroid can receive Varicella vaccine after 12 weeks of cessation of these drugs

B) Rituximab delay the possibility of giving MMR vaccine for a period of 3 months

C) It s recommended to give varicella vaccine within 4 weeks to a CKD patient who has just received packed RBC s for severe anemia to guard him against severe infection

D) IVIG are helpful in induction of a strong antibody response to different vaccines especially pneumoccoci

Question 3

- ***One answer is correct:***

A) HCV ab titre should be measured before Tx and every year after Tx to keep the level of protective antibodies

B) Live attenuated vaccines are contraindicated in household contacts

C) Risk of cervical and anal cancer can be reduced by giving a ninevalent HPV vaccine

D) It s better to delay vaccination to pre-transplantation period in order to have the highest antibody titer at the time of transplantation

Patients undergoing transplant evaluation may be receiving or have recently received immunosuppressive therapies and/ or immunoglobulin (IG) therapy, whether standard or diseasespecific, which can affect the response to vaccines. Rituximab is an anti-CD20 monoclonal antibody that can inhibit the immune response to vaccines. The ability of vaccines to stimulate humoral immunity after receipt of rituximab can be impaired for as long as 12 months, although the maximum effect occurs within the first 6 months [11]

. As a general recommendation, most sources suggest delaying vaccination for at least 6 months after rituximab in order to make the administration of inactivated vaccines effective and live vaccines

safe [12].

Delaying live virus vaccines for at least 4 weeks in patients receiving 14 days or more of high-dose corticosteroids (≥ 2 mg/kg/day of prednisone or ≥ 20 mg/day in patients over 10 kg) is generally recommended, although the evidence to

Table 1 Recommended vaccines for pediatric kidney transplant candidates and recipients and recommendations for monitoring vaccine titers after transplantation

Vaccine	Inactivated/live-attenuated (I/LA)	Recommended for candidates	Recommended for recipients	Monitor vaccine titers
Influenza	I	Yes	Yes	No
Influenza	LA	No	No	No
Hepatitis B	I	Yes	Yes	Yes
Hepatitis A	I	Yes	Yes	Yes[1]
Pertussis	I	Yes	Yes	No
Diphtheria	I	Yes	Yes	No
Tetanus	I	Yes	Yes	Yes
IPV	I	Yes	Yes	No
H. influenzae	I	Yes	Yes	Yes
PCV13	I	Yes	Yes	Yes
PPSV23	I	Yes	Yes	Yes
MenACWY	I	Yes	Yes	No
HPV	I	Yes	Yes	No
Varicella	LA	Yes	No[2]	Yes
Rotavirus	LA	Yes	No	No
Measles	LA	Yes	No	Yes
Mumps	LA	Yes	No	Yes
Rubella	LA	Yes	No	Yes

Adapted with permission from Danziger-Isakov and Kumar [7]

[1] Monitoring only if ongoing risk of exposure, for example with planned travel to high-risk areas

[2] May be considered for select transplant recipients; see text for details

Danziger-Isakov L, Kumar D (2013) Vaccination in solid organ transplantation. Am J Transplant 13(Suppl 4):311–317

- For immunosuppressive medications such as mycophenolate, tacrolimus, cyclosporine, cyclophosphamide, and azathioprine, there are even fewer data to guide the proper time interval between medication cessation and safe live vaccine administration. In the rheumatology literature, based on only level D evidence, it is generally considered that a period of 3 months is required for immune status to be completely restored after the cessation of these medications and therefore before live vaccines can be safely administered

- MMR and varicella vaccines should be delayed at least 2 weeks before and up to 11 months after receipt of IG [15]. The period of delay is proportional to the dose of IG given. For example, those given a 400 mg/kg dose should delay MMR and varicella vaccines by 8 months. Receipt of doses of 1600 to 2000 mg/kg requires an 11-month deferral [15]

- MMR and varicella vaccines should also be delayed in patie nts who have received blood products. For example, those receiving packed red blood cells (10 ml/kg) or platelets/ plasma (10 ml/kg) should wait 5 and 7 months, respectively, before receiving these vaccines [15].

- The international organization Kidney Disease Improving Global Outcomes (KDIGO) recommends giving KT recipients all standard non-live vaccines according to routine immunization schedules [21].

- There are specific recommendations in transplant recipients that deviate from the routine schedule, namely for hepatitis B vaccine (HBV), pneumococcal vaccines, and MenACWY. These particularities are discussed below. The importance of HPV in cancer prevention is highlighted. Live vaccines are generally contraindicated in SOT recipients due to the risk of developing disease from the vaccine strain

- Several case reports and small series reported a possible correlation between IIV and graft rejection, but larger studies have not confirmed this [25]

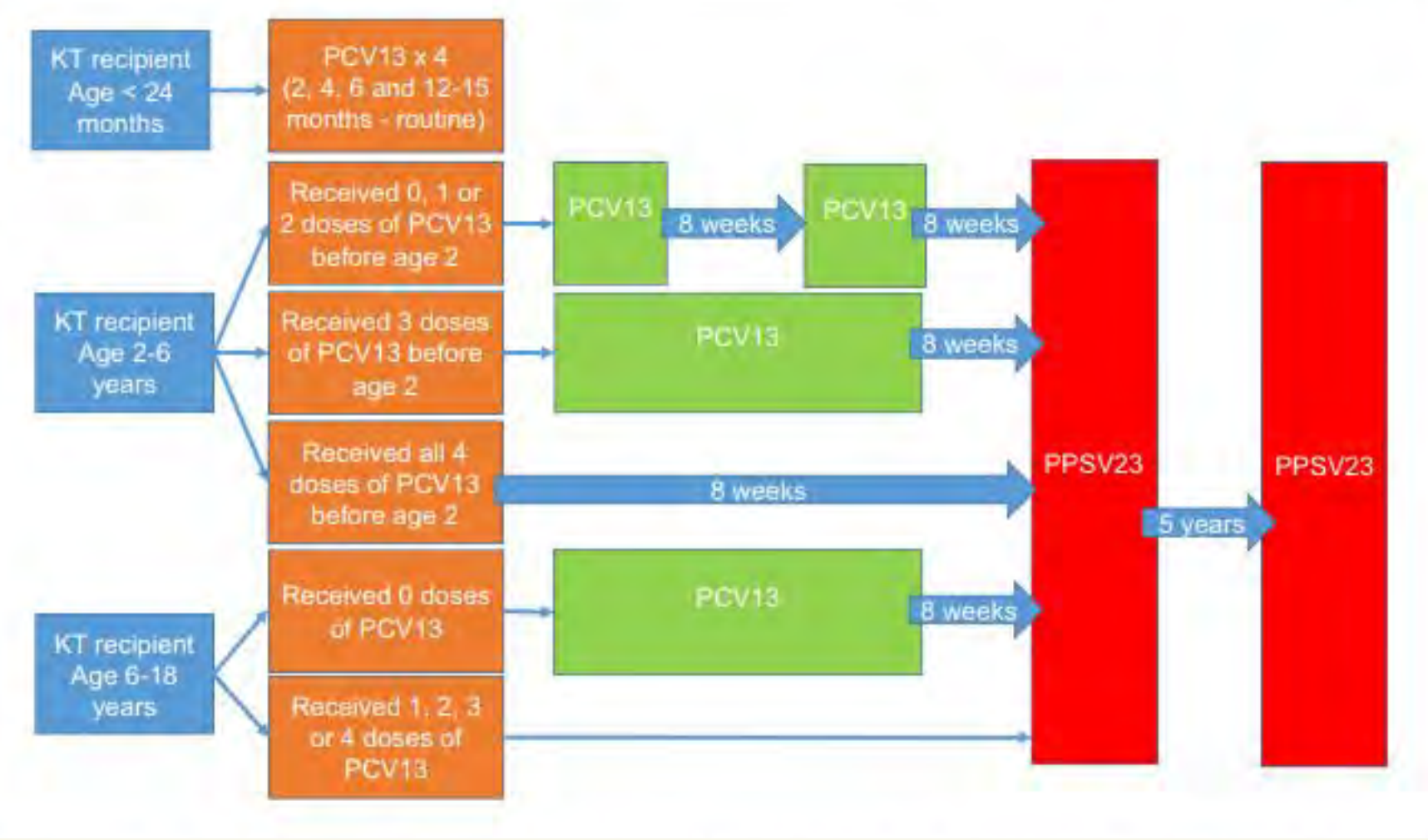
- No cases of rejection were seen, suggesting that during an influenza epidemic or pandemic, IIV is safe and effective in recent SOT recipients. However, some experts recommend that if IIVis administered early after transplantation, consideration should be given to revaccinate 3 to 6 months post KT if the influenza season is ongoing [7].

- In a study looking at adult KT recipients, after 12 months, 25% of patients had lost protective HBsAb titers

Moal V, et al .J Clin Virol 2015

- KDIGO proposed annual anti-HBsAb titers and revaccination if the titer falls below 10 mIU/ml

- it is recommended that pediatric SOT, including KT recipients, also receive the pneumococcal polysaccharide vaccine 23-valent (PPSV23) for expanded serotype coverage, provided that they are at least 2 years of age. PCV13 should always be given before PPSV23 to enhance immunogenicity. PPSV23 should be given at a minimum of 8 weeks after PCV13


KT recipient Age < 24 months
PCV13 x 4 (2, 4, 6 and 12-15 months - routine)
KT recipient Age 2-6 years
Received 0, 1 or 2 doses of PCV13 before age 2
PCV13
8 weeks
PCV13
8 weeks
Received 3 doses of PCV13 before age 2
PCV13
8 weeks
Received all 4 doses of PCV13 before age 2
8 weeks
KT recipient Age 6-18 years
Received 0 doses of PCV13
PCV13
8 weeks
Received 1, 2, 3 or 4 doses of PCV13
PPSV23
5 years
PPSV23

- Among pediatric KT recipients, it is important to identify those patients with specific risk factors for invasive meningococcal infections, as they will require different interventions. This category includes KT recipients with persistent complement component deficiencies due to C3 glomerulopathy or atypical hemolytic uremic syndrome, patients receiving eculizumab (an anti-C5 monoclonal antibody used for treatment of complement-mediated glomerular diseases)