Vaccination Schedules in Hematopoietic Stem Cell Transplant (HSCT) Patients

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1. Introduction

Patients undergone hematopoietic stem cell transplantation (HSCT) after a myeloablative conditioning regimen, experience an extended period of dysfunctional immunity, during which an increased risk of infections leads to significant morbidity and mortality.[1] Immunizations are a minimally invasive, cost-effective approach to reducing the incidence of Vaccine-preventable infections (VPIs). Nevertheless, the efficacy of immunization in immunocompromised patients is imperfect due to previous exposure to cytotoxic agents and the dysfunctional immunity in the post transplantation period. Moreover, immune system response to vaccines is significantly reduced in the early post transplantation setting, which embodies the period of highest risk for infection. The Infectious Diseases Society of America recommends to consider HSCT recipients as never vaccinated; This highlights the need to offer a full vaccination schedule according to age and country recommendations that take into account local epidemiology. As a result, after a careful review of different vaccination guidelines belonging to various centers around the world, we gathered the upcoming recommendations and modified them according to the health care resources in our country.

2. Recommendations

2.1. General principles

2.1.1. Many vaccines are administered by intramuscular route, which can be a problem for severe thrombocytopenic patients (less than 50 × 10^9platelets/L). For severe thrombocytopenic patients, some vaccines can be safely administered SC (inactivated poliomyelitis, conjugate pneumococcal vaccine) or even intradermic route (for influenza vaccine).

Clinical experience suggests that intramuscular injections are safe if the platelet count is ≥30 to 50 × 10^9/L, a ≤23-gauge needle is used, and constant pressure is maintained at the injection site for 2 min.[2]

2.1.2. The dose of vaccine used is the same for general population, with some exceptions.

2.1.2.1. HBV: After post transplant vaccination, if anti-HBs is <10 mIU/ml, an additional three doses should be considered. For adolescents and adults, a high dose of vaccine (40 μg) is recommended for these booster doses.

2.1.3. The presence of GVHD or ongoing immune suppressor (IS) treatment has been associated with a decrease in vaccine response, particularly for polysaccharide-based vaccines. Some vaccine responses seem to be not impaired by the presence of GVHD/IS treatment. This is the case of conjugated Haemophilus vaccine, conjugated pneumococcal vaccine, conjugated meningococcal vaccine, inactivated polio vaccine, and diphtheria-tetanus vaccine. If patients receive prednisone>0.5 mg/kg bodyweight as part of a combination therapy or a three-agent IS treatment is given, vaccination may be postponed until IS is reduced to a double combination or prednisone <0.5 mg/kg bodyweight in order to achieve better vaccine response. In any case, IS therapy should not lead to postponing vaccination for more than 3 months, and this applies for patients with ongoing active or resolved cGVHD of any severity grade.[3]

2.1.4. The use of rituximab decreases serological vaccine response at least to tetanus and influenza. Patients who have received rituximab from transplant should have their vaccine program delayed at least more than 6 months after the last dose.[4]

2.1.5. For inactivated vaccines, IVIG do not inhibit immune responses. For live virus vaccine, vaccination should be at least 5 months post last dose of IVIG. For inactivated "dead" virus vaccine, vaccination should be at least 2 months post last dose of IVIG.

2.1.6. If patient is on disease-associated maintenance therapy that can affect T or B cell numbers, then before beginning vaccination check CD 19 or CD 20 B cells to determine > 20/μL and check CD4 T cells to determine > 200/μL.

2.1.7.

2.2. Pre-HSCT vaccination

Pre-HSCT vaccination in both donors and recipients is an attractive strategy to prevent infections to pathogens that can cause significant morbidity and mortality. However, despite the possibility of augmented immunity, there remain logistical, ethical and medical concerns about such a vaccination strategy.[5] The pretransplant vaccination is not effective to maintain a prolonged post transplant immunity. Post-HSCT patients should be viewed as "never vaccinated" regardless of the pre-HSCT vaccination history of the patient or the donor.[6]

2.3. Post-HSCT vaccination

2.3.1. Streptococcus pneumonia

2.3.1.1. Start vaccination three months after autologous HSCT and six months after allogeneic HSCT

2.3.1.2. Three doses of Pneumococcal 13-valent Conjugate Vaccine (Prevnar 13) administered at 1–2 month intervals

2.3.1.2.1. A fourth dose of Prevnar 13 in patients with CGVHD who are unlikely to respond to Pneumovax[7]

2.3.1.3. One dose of pneumococcal 23-valent polysaccharide vaccine (Pneumovax 23) 6 months after the last dose of Prevnar 13.

2.3.1.4. Booster doses every 5 years or sooner if the antibody checked after 2 or 3 years would be inadequate.

2.3.2. Neisseria meningitides

2.3.2.1. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.2.2. Two doses (three for children) of the conjugated quadrivalent vaccine (Menveo-MCV4) administered at 1–2 month intervals

2.3.3. Pentavalent vaccine

2.3.3.1. Each dose of 0.5 ml contains: Diphtheria Toxoid, Tetanus Toxoid, B. pertussis (whole cell), HBsAg (rDNA) and Purified capsular Hib Polysaccharide (PRP)

2.3.3.2. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.3.3. Three doses administered at 1–2 month intervals

2.3.3.4. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the third dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second three dose series.[8]

2.3.4. Inactivated poliomyelitis vaccine

2.3.4.1. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.4.2. Three doses administered at 1–2 month intervals

2.3.4.3. Because of the risk of post-vaccinal poliomyelitis with the oral live-attenuated vaccine, only inactivated poliomyelitis vaccine should be used.

2.3.5. Inactivated influenza vaccine (IIV)

2.3.5.1. From 6 months after transplantation a seasonal IIV dose should be administered annually at the beginning of flu season, after the first years following transplant, and at least until 6 months after stopping any immunosuppressor and as long as the patient is judged to be immunocompromised or life-long

2.3.5.2. A second dose administered 3–4 weeks after the first one could be considered in patients with severe GvHD or low lymphocyte counts

2.3.5.3. In the setting of a community outbreak, IIV can be administered 3 months after transplantation, in which case, a second dose administered 3–4 weeks later is likely to be beneficial

2.3.5.4. In children aged six months to nine years who are receiving influenza vaccination for the first time post-HSCT: they require two doses four weeks apart. Those who have received only one dose in the first year should receive two doses in the following year.

2.3.5.5. Lifelong yearly renewal is necessary.

2.3.6. Measles, mumps, and rubella (MMR) vaccine

2.3.6.1. Not until 2 years post HSCT and >1 year off all immunosuppressive therapy (IST) and at least 5 months since last dose of IVIG or most recent plasma transfusion (2-1-5 Rule)

2.3.6.2. A second dose after a two month interval is administered in children younger than nine years.

2.3.6.3. The administration of MMR vaccine should be at least 6 months away from the time of administration of Rituximab.

2.3.7. Haemophilus Influenzae type B (HIB)

2.3.7.1. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.7.2. Three doses with an interval of one to two months

2.3.8. Hepatitis B virus (HBV) vaccine

2.3.8.1. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.8.2. Two doses with an interval of two months and the third dose with an interval of six months from the first dose

2.3.8.3. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the third dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second three dose series.

2.3.9. diphtheria/tetanus (Td)

2.3.9.1. Start vaccination six months after autologous HSCT and twelve months after allogeneic HSCT

2.3.9.2. Three doses with an interval of one to two months

2.3.9.3. Booster vaccination at 5 years post-transplantation

2.4.Family members, close contacts and health care workers

2.4.1. Prior to stem cell transplantation, it is recommended to determine if family members and close contacts have completed their vaccination scheme including booster doses.

2.4.2. Administration of Live attenuated vaccine such as MMR vaccine is not contraindicated for family members and close contacts, but it is advisable

to avoid contact with the transplanted patient if the vaccinated person develops rash or fever.

2.4.2.1. If close contacts take oral poliomyelitis vaccine , isolation should be performed up to 12 weeks.

2.4.3. It is recommended that family members and close contacts of HSCT recipients be vaccinated with IIV at the start of autumn before transplantation and first season after HSCT and annually as long as the patient is considered immunocompromised.

2.5. Posttransplant Vaccination of Primary Immunodeficiency Disorders (PID)

2.5.1. PID patients will be considered as candidates for vaccination at 1 year after transplant.

2.5.2. For vaccines to be effective, IVIG should be discontinued for at least three months. IVIG can be discontinued if the patient has no history of infection in the past 6 months (this should be done in a season where the prevalence of viral respiratory infections is low).

2.5.3. Vaccination can be started if IVIG can be discontinued and all of the following criteria are concurrent: Trough IgG > 600 mg/dL on standard IVIG dosing AND Detectable serum IgA (> 6 mg/dL) AND Donor B cell count > 200 per microliter AND Donor CD4 T cell count > 200 per microliter

2.5.4. If the above criteria is fullfilled:

Vaccines	0	Month 2	Month 4	Month 10	Month 24
Influenzae (IIV)*					
Pneumococcal conjugate (Prevnar 13)**					
Pneumococcal polysaccharide (Pneumovax 23)					
Pentavalent vaccine (Pentavac)***					
IPV					
Measles/ Mumps/ Rubella (MMR)****					

- *In 6 months to 9 years old patients Influenza vaccine should be repeated once 4 weeks after the first dose.
- **A fourth dose of Prevnar 13 in patients with CGVHD with 1 to 2 months interval
- *** Haemophilus influenza, Td and Hepatitis B vaccines in age ≥ 7 years
- *** In patients ≤ 9 years old MMR vaccine should be repeated once two months after the first dose.

Vaccination Tables

Post Allo-HSCT Vaccination Schedule for patients ≤ 7 y/o

Vaccines	Time after HSCT							
	6 Month	8 Month	10 Month	12 Month	14 Month	16 Month	18 Month	24 Month
Influenzae (IIV)*								
Pneumococcal conjugate (Prevnar 13)**								
Pneumococcal polysaccharide (Pneumovax 23)								
MCV4								
Pentavalent vaccine (Pentavac)								
IPV								
Measles/Mumps/ Rubella (MMR)***								

*** In 6 months to 9 years old patients Influenza vaccine should be repeated once 4 weeks after the first dose.**
****A fourth dose of Prevnar 13 in patients with CGVHD with 1 to 2 months interval**
***** In patients ≤ 9 years old MMR vaccine should be repeated once two months after the first dose.**

Post Allo-HSCT Vaccination Schedule for patients > 7 y/o

Vaccines	Time after HSCT							
	6 Month	8 Month	10 Month	12 Month	14 Month	16 Month	18 Month	24 Month
Influenzae (IIV)*	■							
Pneumococcal conjugate (Prevnar 13)**	■	■	■					
Pneumococcal polysaccharide (Pneumovax 23)							■	
MCV4				■	■			
Td				■	■	■		
Hepatitis B virus (HBV)				■	■		■	
H. Influenzae type B				■	■	■		
IPV				■	■	■		
Measles/Mumps/ Rubella (MMR)***								■

*** In 6 months to 9 years old patients Influenza vaccine should be repeated once 4 weeks after the first dose.**
****A fourth dose of Prevnar 13 in patients with CGVHD with 1 to 2 months interval**
***** In patients ≤ 9 years old MMR vaccine should be repeated once two months after the first dose.**

Post Auto-HSCT Vaccination Schedule for patients ≤ 7 y/o

Vaccines	Time after HSCT				
	6 Month	8 Month	10 Month	18 Month	24 Month
Influenzae (IIV) *					
Pneumococcal conjugate (Prevnar 13)					
Pneumococcal polysaccharide (Pneumovax 23)					
MCV4					
Pentavalent vaccine (Pentavac)					
IPV					
Measles/Mumps/Rubella (MMR)**					

*** In 6 months to 9 years old patients Influenza vaccine should be repeated once 4 weeks after the first dose.**
**** In patients ≤ 9 years old MMR vaccine should be repeated once two months after the first dose.**

Post Auto-HSCT Vaccination Schedule for patients > 7 y/o

Vaccines	Time after HSCT					
	6 Month	8 Month	10 Month	12 Month	18 Month	24 Month
Influenzae (IIV)*						
Pneumococcal conjugate (Prevnar 13)						
Pneumococcal polysaccharide (Pneumovax 23)						
MCV4						
Td						
Hepatitis B						
H. Influenzae type B						
IPV						
Measles/Mumps/Rubella (MMR)**						

*** In 6 months to 9 years old patients Influenza vaccine should be repeated once 4 weeks after the first dose.**
**** In patients ≤ 9 years old MMR vaccine should be repeated once two months after the first dose.**

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