Vaccination Post-HSCT

Jackrapong Bruminhent, MD
Division of Infectious Diseases
Department of Medicine
Faculty of Medicine Ramathibodi Hospital
Mahidol University

CLINICAL GUIDELINE

Annals of Internal Medicine

Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2018*

David K. Kim, MD, MA; Laura E. Riley, MD; and Paul Hunter, MD; on behalf of the Advisory Committee on Immunization Practices†

American Journal of Transplantation 2013; 13: 311–317
Wiley Periodicals Inc.

doi: 10.1111/ajt.12122

Special Article

Vaccination in Solid Organ Transplantation

L. Danziger-Isakov[a,*], D. Kumar[b] and the AST Infectious Diseases Community of Practice

IDSA GUIDELINES

2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Lorry G. Rubin,[1] Myron J. Levin,[2] Per Ljungman,[3,4] E. Graham Davies,[5] Robin Avery,[6] Marcie Tomblyn,[7] Athos Bousvaros,[8] Shireesha Dhanireddy,[9] Lillian Sung,[10] Harry Keyserling,[11] and Insoo Kang[12]

ASBMT American Society for Blood and Marrow Transplantation

GUIDELINES

Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective

Marcie Tomblyn, Tom Chiller, Hermann Einsele, Ronald Gress, Kent Sepkowitz, Jan Storek, John R. Wingard, Jo-Anne H. Young, Michael A. Boeckh

Biol Blood Marrow Transplant 15: 1143-1238 (2009) © 2009 American Society for Blood and Marrow Transplantation

คำแนะนำการให้วัคซีนป้องกันโรคสำหรับผู้ใหญ่และผู้สูงอายุ

(Recommended Adult and Elderly Immunization Schedule)

สมาคมโรคติดเชื้อแห่งประเทศไทย ปี พ.ศ. 2561

blood®
Leading the way in experimental and clinical research in hematology

BLOOD, 9 JUNE 2016 • VOLUME 127, NUMBER 23

How I Treat

How I vaccinate blood and marrow transplant recipients

Paul A. Carpenter[1-3] and Janet A. Englund[2,3]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [2]Department of Pediatrics, University of Washington, Seattle, WA; and [3]Seattle Children's Hospital, Seattle WA

FAQ 11: how soon after BMT can I give the flu shot?

Administer at ≥6 months post-BMT regardless of conditioning regimen or BMT type. During community outbreaks flu vaccine may be given at 3 to 4 months post-BMT, in which case a second dose is given 1 month later.[14]

Carpenter PA. Blood. 2016 Jun 9;127(23):2824-32.

Prevent of Infection

Pre-HSCT

-Treat active infection
-Define risk of infection
-Immunization
    Inactivated vaccines
    Live-attenuated vaccines

Post-HSCT

-Prevention of infection
    Prophylaxis
    Preemptive Rx
-Optimize immunosuppression
-Active immunization
    Inactivated vaccines
    +/- Live-attenuated vaccines
-Passive immunization (IVIG)

What is your recommendation?

Mr. Ake

A 25 yo M AML
s/p HSCT 6 months ago without GVHD
asked you about pneumococcal vaccination

Uncle Yuth

A 55 yo M CLL
s/p HSCT 2 years ago
s/p rituximab, IVIG
asked you about MMR vaccination

Ms. Gade

A 20 yo F who will start her work as a nurse in BMT unit, asked for varicella vaccination.

Vaccines in Immunocompromised Hosts

1. Vaccine-preventable diseases continue to cause morbidity & mortality
2. Vaccination is a the most important strategy
3. Inactivated vaccines may be suboptimal
4. Live vaccines may result in serious infection

What you need to know more? (1)

1. Live attenuated vs. inactivated vaccine
2. Time after HSCT
3. Immune reconstitution: B cell, CD4 T cell > 200/mL
4. Immunosuppression: recent, ongoing
   - Conditioning regimen
   - GVHD prophylaxis
   - Treatment of GVHD (moderate to severe)
   - Functional or anatomic asplenia
   - IVIG, rituximab
   - Others (azacytidine, lenalidomide, imatinib, sorafenib)

Carpenter PA. Blood. 2016 Jun 9;127(23):2824-32.

What you need to know more? (2)

5. Anti-viral agents: acyclovir
6. Donor or recipient's vaccination history
7. Current outbreak: influenza

Available Vaccines

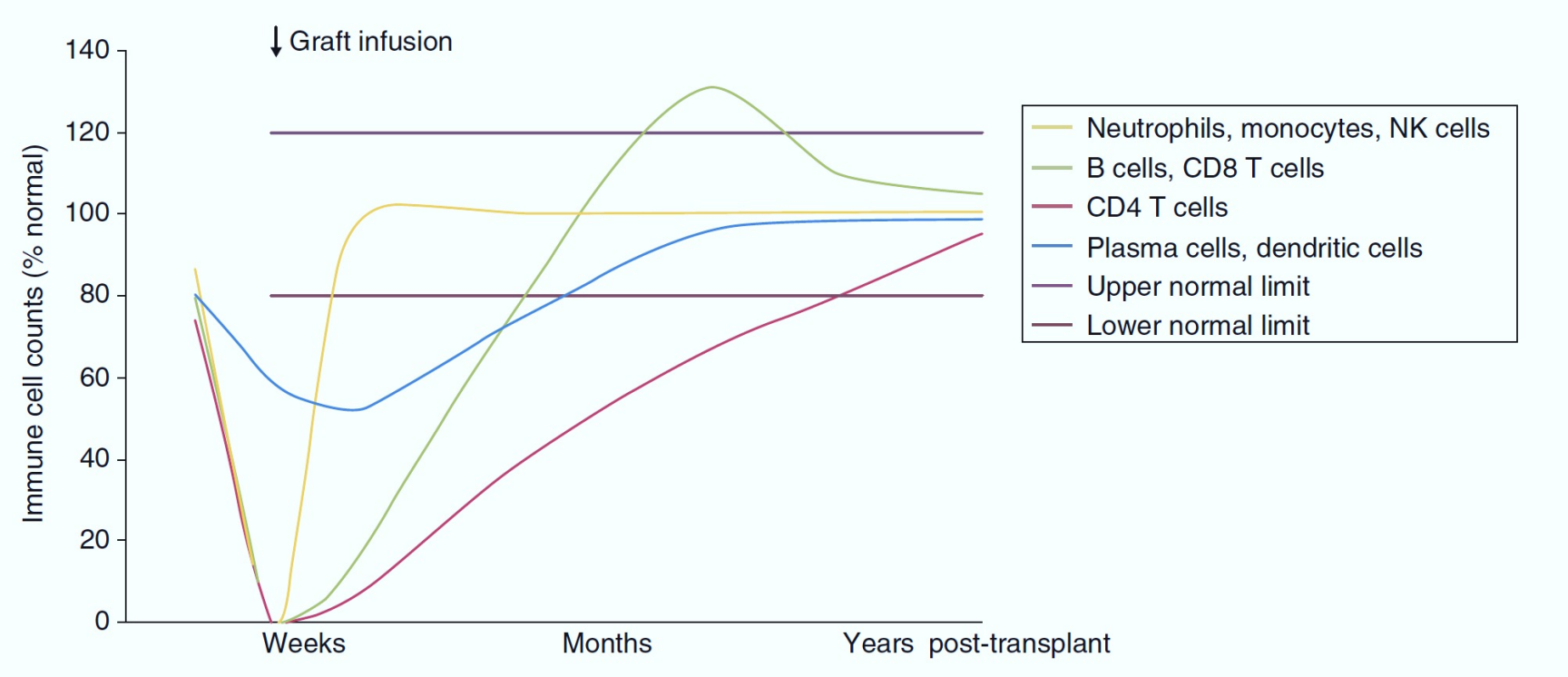
Live-attenuated vaccines

- MMR
- Varicella
- Zoster
- Rotavirus
- Polio (oral)
- Yellow fever

Inactivated vaccines

- Influenza
- DTaP/Tdap/Td
- Pneumococcus
  - Conjugated (PCV13)
  - Polysaccharide (PPSV23)
- HAV/HBV
- Meningococcus (ACWY)
- Hib
- HPV
- Polio (injected)

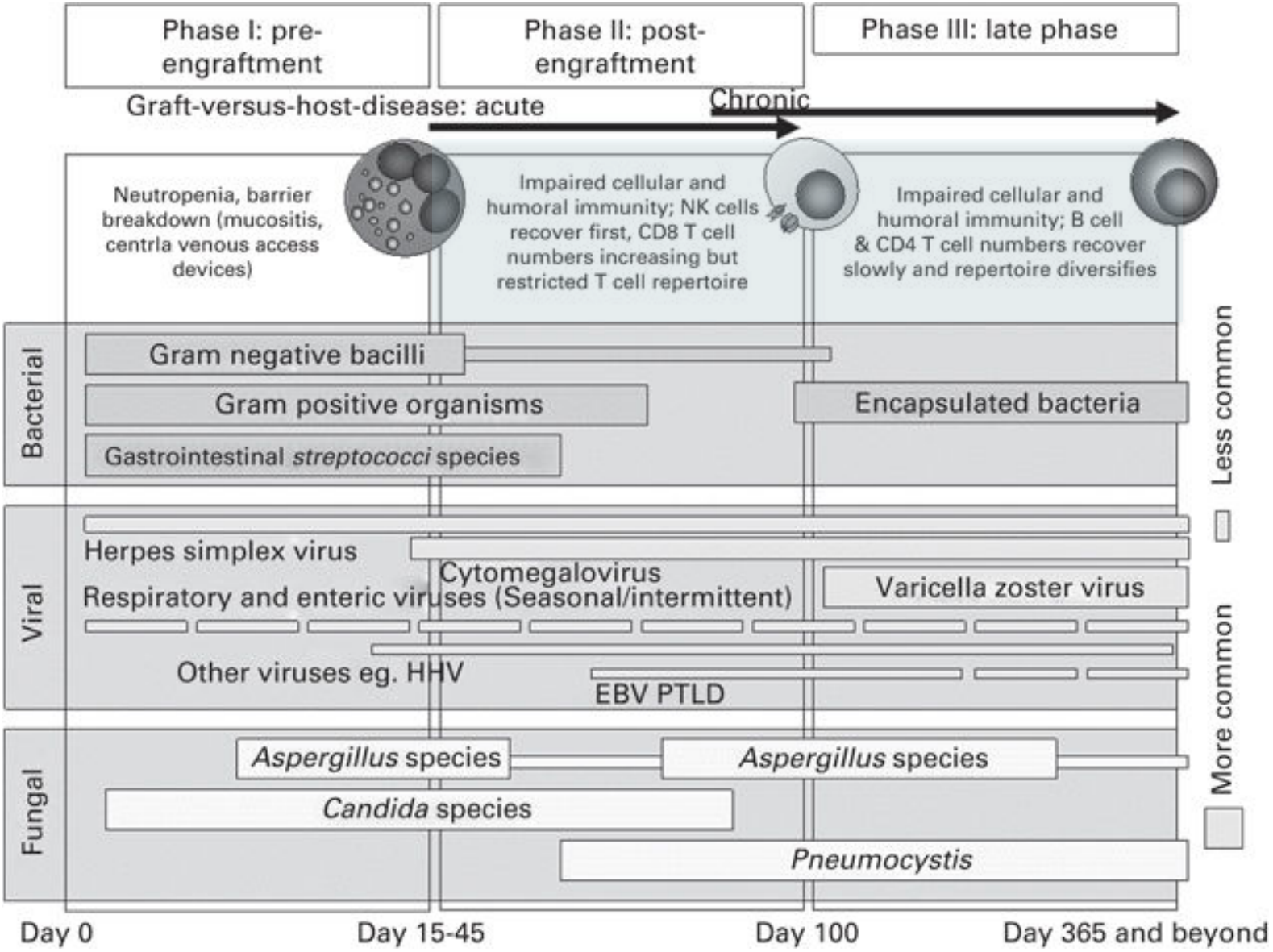
Immune Reconstitution after HSCT



CD4+ counts may provide the most readily available and predictive marker for the restoration of immune competence after HCT

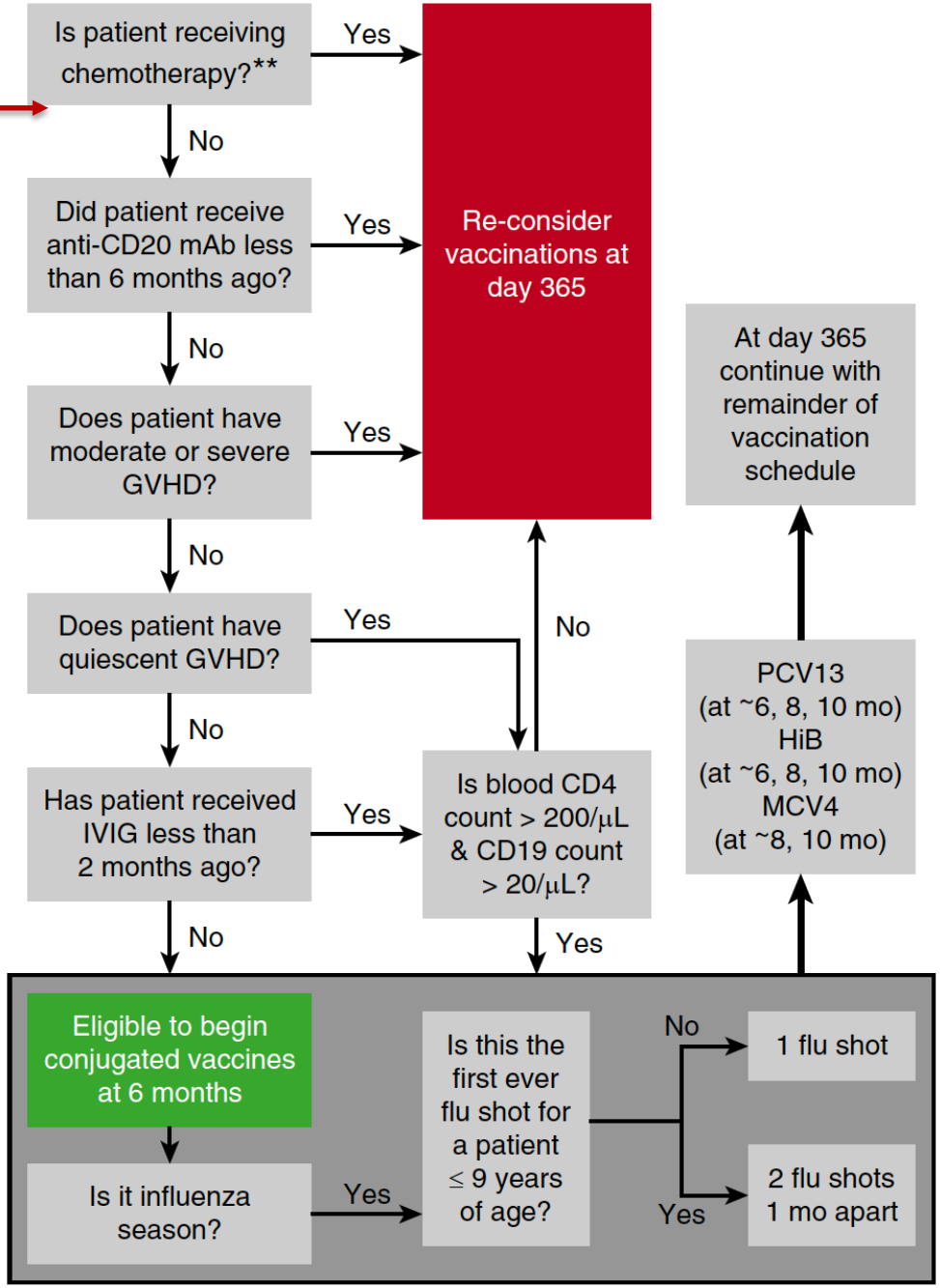
Mackall C. Bone Marrow Transplant. 2009 Oct;44(8):457-62.

Time for Inactivated Vaccine = ~6 (3-12) months after HSCT
Time for Live Vaccine = 24 months after HSCT

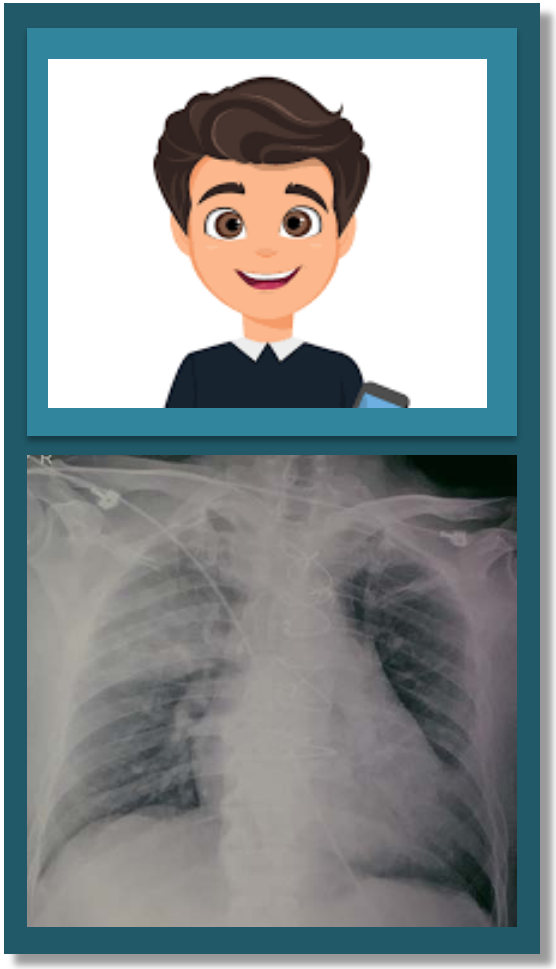


Mackall C. Bone Marrow Transplant. 2009 Oct;44(8):457-62.

Think about Vaccination at 6 Months post-HSCT



A 25 yo M AML HSCT 6 months ago No GVHD



Pneumococcal vaccination

A. No need for vaccine

B. PCV13 (now) → PPSV 23 (8 weeks later)

C. PCV 13 x 3 doses (now) → PPSV 23 (8 weeks after)

D. PCV13 (at 2 years after HSCT) → PPSV 23 (1 year after)

E. Call ID service

Pneumococcal Vaccines in HSCT

- **No GVHD**
  - PCV13 x 3 doses at 3-6 months after HSCT
  - PPSV23 x 1 dose at 12 months after HSCT
- **GVHD**
  - PCV13 x 3 doses at 3-6 months after HSCT
  - PCV13 **(4th dose)** at 12 months after HSCT
  - PPSV23 x 1 dose at 12 months after HSCT

*PCV13 should be completed 8 weeks prior to PPSV23

Vaccines for HSCT Recipients (1)

Vaccine	Type	For Whom?	Dose and Timing	Comments
Influenza	Injected, non-live	All recipients	1 yearly dose at least 6 mo post-HSCT	Can give at 1 mo post-HSCT in outbreak setting.
Hepatitis B	Injected, non-live	All recipients	3 doses; 0,1,and 6 mo starting 6-12 mo post-HSCT	May check anti-HBs titer and reimmunize if failure to seroconvert
HPV	Injected, non-live	Ages 11-26 y	3 doses, starting 6-12 mo post-HSCT	Little evidence in this population as yet
PPSV-23	Injected, non-live	All recipients if no chronic GVHD	1 dose at 12 mo	As long as no chronic GVHD
PCV-13	Injected, non-live	All recipients	3 doses starting 3-6 mo post-HSCT	Can give a fourth dose at 12 mo if chronic GVHD
HIB	Injected, non-live	All recipients	3 doses starting 6-12 mo post-HSCT	-

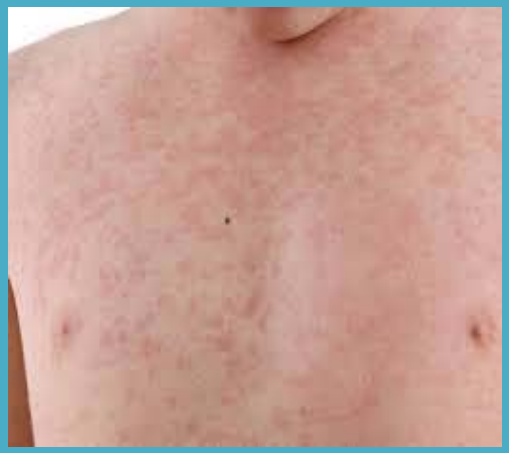
Chong PP. Clin Ther. 2017 Aug;39(8):1581-1598.

Vaccines for HSCT Recipients (2)

Vaccine	Type	For Whom?	Dose and Timing	Comments
Quadrivalent meningococcal	Injected, non-live	Ages 11-18 y or exposure risk of per country-specific guidelines	2 doses starting 6-12 mo post-HSCT	Besides the age range listed: planned travel to endemic area, incoming college freshmen (booster dose at age 16-18 y if first doses received at age 11-15 y)
Polio vaccine	Injected, non-live	All recipients	3 doses starting 6-12 mo post-HSCT	-
Tetanus and diphtheria-containing vaccine	Injected, non-live	All recipients	3 doses starting 6 mo post-HSCT	-
MMR	Injected, live	If seronegative, no GVHD and not on immunosuppression	2 doses, 24 mo post-HSCT	Wait 8-11 mo after last dose of IVIG or earlier if there is a measles outbreak
Varicella vaccine	Injected, live	If seronegative, no GVHD and not on immunosuppression	2 doses, 24 mo post-HSCT	-
Zoster vaccine	Injected, live	Not recommended	-	-

Chong PP. Clin Ther. 2017 Aug;39(8):1581-1598.

A 55 yo M CLL s/p HSCT 2 years ago s/p rituximab, IVIG



MMR vaccination

“6812”

Give live vaccine

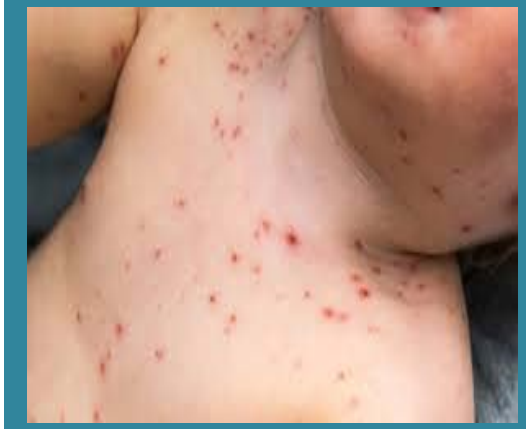
6 months after rituximab

8 months after IVIG

1 year after stop IS

2 year after HSCT

A 20 yo F who will start her work as a nurse in BMT unit



Varicella vaccination

A. Check her VZV IgG first

B. No need for vaccine

C. She should not receive varicella vaccine

D. She should, but should be furloughed

Live Vaccines in Household Contacts of Transplant Recipients

Vaccine	Give on Schedule to Household Contact?	Comments
MMR	Yes	Household transmission not an issue
Rotavirus	Yes	Avoid handling diaper for 4 wk
Varicella	Yes	Only seronegative transplant recipient Risk of transmission very low; except child develops a rash (consider avoiding direct contact, or antiviral for 21 d)
Zoster	Yes	As above for varicella vaccine
Yellow fever	Yes	Possibly shed in breast milk, administer except to women who are nursing
Oral typhoid	Yes	Household transmission not an issue
LAIV	Yes (unless severely immunocompromised HSCT)	Not currently recommended due to suboptimal efficacy
Oral polio	No	No longer use in United States

Chong PP. Clin Ther. 2017 Aug;39(8):1581-1598.

Vaccination Post-SCT

1. Consider HSCT recipients as never been vaccinated
2. Inactivated vaccine given after ~6 (3-12) months
3. PCV after HSCT: use 3 or (4 if +chronic GVHD)
4. Live vaccine can be given after 24 months if no intense immunosuppression e.g. chronic GVHD
5. Be cautious given live vaccine in close contacts
6. Role of vaccination in HSCT donor is unclear

“6812”

Thank you

Email: jbruminhent@gmail.com

Pearls: Vaccines in HSCT

Patients	Suggestions
HSCT candidates	Avoid live vaccine within 4 weeks prior to HSCT
	Avoid inactivated vaccine within 2 weeks prior to HSCT
HSCT donor	Avoid live vaccine within 4 weeks prior to harvest
HSCT recipients	Waiting 3-12 months post-HSCT (inactivated vaccine), 24 months post-HSCT (live vaccine)

Rubin LG. Clin Infect Dis. 2014 Feb;58(3):e44-100.

Pearls:

Vaccines in Immunocompromised Hosts (2)

Vaccines	Suggestions
Live/inactivated vaccines	Avoid within 6 months after receiving rituximab
	Avoid during chemotherapy
	Can be given 3 months after CMT
MMR, varicella vaccines	Ok in HSCT after 24 months with neither chronic GVHD nor ongoing immunosuppression
	8–11 months (or earlier if there is a measles outbreak) after the last dose of IVIG
Rotavirus	HSCT recipients whose household receiving rotavirus should avoid handling diapers for 4 weeks after the infant has been vaccinated
-MMR -Varicella vaccine	Recent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product)
-Varicella vaccine -Zoster vaccine live	-Receipt of acyclovir, famciclovir, or valacyclovir 24 hours before vaccination -Avoid use of these antiviral drugs for 14 days after

Rubin LG. Clin Infect Dis. 2014 Feb;58(3):e44-100.

Pearls:

Vaccines in Immunocompromised Hosts (4)

Scenario	Suggestion
Can we vaccinate MMR, VAR or Zoster vaccines on the same day? If not able to complete on the same day, how would you recommend?	MMR may be administered together with VAR or LZV on the same day. If not, separate live vaccines by at least 28 days.
A 40 yo M with Bell's palsy s/p oral prednisolone 40 mg/day for 1 month then stopped 1 month ago.	Vaccination should be deferred for at least 1 month after discontinuation of immunosuppressive steroid therapy (daily receipt of 20 mg or more prednisone or equivalent for ≥ 2 weeks).

\

Rubin LG. Clin Infect Dis. 2014 Feb;58(3):e44-100.

ภาพ

- Screening questions to determine early
- vaccination candidacy. Note: B-cell numbers are low in
- the first 1 to 2 months and normalize during months 3 to 12.
- B-cell recovery is delayed by at least 6 months after anti-B-cell
- antibody therapy. Antigen-specific responses are impaired also
- because of limited capacity to undergo somatic mutation and
- isotype switch during the first year. Normalization of IgA levels
- can be indicative of isotype switching and is unaffected by IVIG
- replacement therapy. CD4 counts are generally ,200/mL
- during the first 3 months. Thereafter, recovery is highly variable,
- generally .200/mL by 6 to 9 months if age ,18 years and no
- chronic GVHD. Adults with chronic GVHD may take .2 years.
- For these reasons, some institutions defer vaccination until the
- peripheral CD4 count is .200/mL and the CD19 (B-cell) count
- is .20 /mL.
- Most circulating T cells at year 1 (especially in
- adults) are memory/effector T cells derived from infused T cells.
- These cells can respond to antigens encountered by the donor
- pre-BMT. Na¨ıve T cells that respond to neoantigens are
- generated only at 6 to 12 months (earlier in young children, later
- in old adults). Only limited data exist for the settings of unrelated
- cord blood and haploidentical HCT or after reduced intensity
- regimens, and so, for the sake of simplicity, the algorithm does
- not make further adjustments on these bases. The double
- asterisk (**) indicates that which agents are sufficiently immunosuppressive
- to prevent effective vaccination has not been
- studied. Other than the seasonal flu shot, most vaccinations
- are avoided when BMT recipients are receiving azacytidine,
- lenalidomide, or rituximab. We tend to still administer vaccines if
- patients have little or no chronic GVHD and are on kinase
- inhibitors (eg, imatinb or sorafenib).

- They still pose increased risks for BMT recipients until immunity is fully restored.
- With exception of viruses exhibiting latency outside the hematopoietic system (eg, varicella), BMT recipients should be revaccinated against pathogens contained in childhood primary immunization schedules.

- Live vaccine in household
- If there is an inactivated vaccine, use it .
- oral polio vaccine x 5 with IPV x 1 available in Thailand
- intranasal live attenuated influenza vaccine (LAIV)

- It is considered safe to give live attenuatedMMR when
- recipients are 2 years out from BMT, 1 year off all systemic IST,
- And 8months out from any prior IVIG dose (the **"2-1-8"** mnemonic).
- Relaxation of this rule to some extent is considered when community
- outbreaks occur. Unvaccinated adults need only 1 dose of MMR. Antibody titers are unnecessary before or after vaccination.
- PCV13, a T-cell-dependent vaccine, is more immunogenic than
- PPSV23 because it triggersmemory response that leads tomore durable
- protection than PPSV23, which confers only 3 to 5 years of protection.
- It is worth remembering that PPSV23 is particularly ineffective in
- young children age ,2 years.

- One dose of PPSV23 is then given 6 to 12
- months (minimum 8 weeks) after the last PCV13.
- FAQ 18: are there exceptions or modifications to the
- pneumococcal vaccination schedule in FAQ 17? Yes. When a
- BMT recipient remains heavily immunocompromised, a fourth dose of
- PCV13 is given rather than PPSV23 because PCV13 should induce
- better T-cell collaboration and anamnestic response via generation of
- memory B cells (see FAQ 5).
- Elderly BMT recipients also need PPSV23 booster immunization
- because of their increased vulnerability to IPD. The baseline assumption
- is that these individuals earlier completed 3 post-BMT doses of
- PCV13 and 1 dose of PPSV23, or 4 doses of PCV13. ACIP
- recommends 1 dose of PCV13 for all adults $65 who have not yet
- received this, followed by a booster PPSV23 6 to 12 months later or a
- repeat dose of PPSV23 5 years after the last dose of PPSV23. Injection
- site reactogenicity to PPSV23 is less of an issue if boosting is done
- infrequently at a time when antibody levels have waned.

Live attenu

- Vaccination with Varivax (Merck & Co. Inc.) to
- prevent chicken pox is only recommended for VZV-seronegative
- recipients without a history of chickenpox or varicella vaccination
- because BMT does not eradicate latent VZV in the sensory
- nerve ganglia of previously infected individuals (ie, those with a
- history of chicken pox) or previously vaccinated individuals.
- Latent VZV is thought to provide ongoing antigen exposure that
- obviates the need for revaccination with standard Varivax.

Inactivated vaccines

- If we restrict the use of a 3-shotDTaP
- series to,7 year olds, the testable question remainswhether 3 doses of
- Tdap would be better than Tdap/Td/Td for those over 7 years of age.
- HAV same
- HBV needs high dose (double =40 mcg Engerix
- how soon after BMT can I give the flu shot?
- Administer at 6 months post-BMT regardless of conditioning
- regimen or BMT type. During community outbreaks flu vaccine may
- be given at 3 to 4 months post-BMT, in which case a second dose is
- given 1 month later.14
- Influenza
- Yes, but only for children aged$6months
- and,9 yearswho never had flu vaccine posttransplant; these children
- need 2 flu shots given$1month apart.
- **Conjugate vaccines are more immunogenic and stimulate long-lived memory B cells.**

What is your recommendation?

Mr. Ake

A 25 yo M AML
s/p HSCT 6 months ago
asked you about
pneumococcal
vaccination

Ms. Gade

A 35 yo F AML
s/p HSCT 2 year ago
without GVHD asked
you about MMR
vaccination

Uncle Yuth

A 67 yo M lives with
HSCT recipients who
has chronic GVHD
asked you for a
permission for
vaccination