



Pediatric Oncology: Vaccination After Therapy

**Family Practice Oncology CME Day
November 2017**

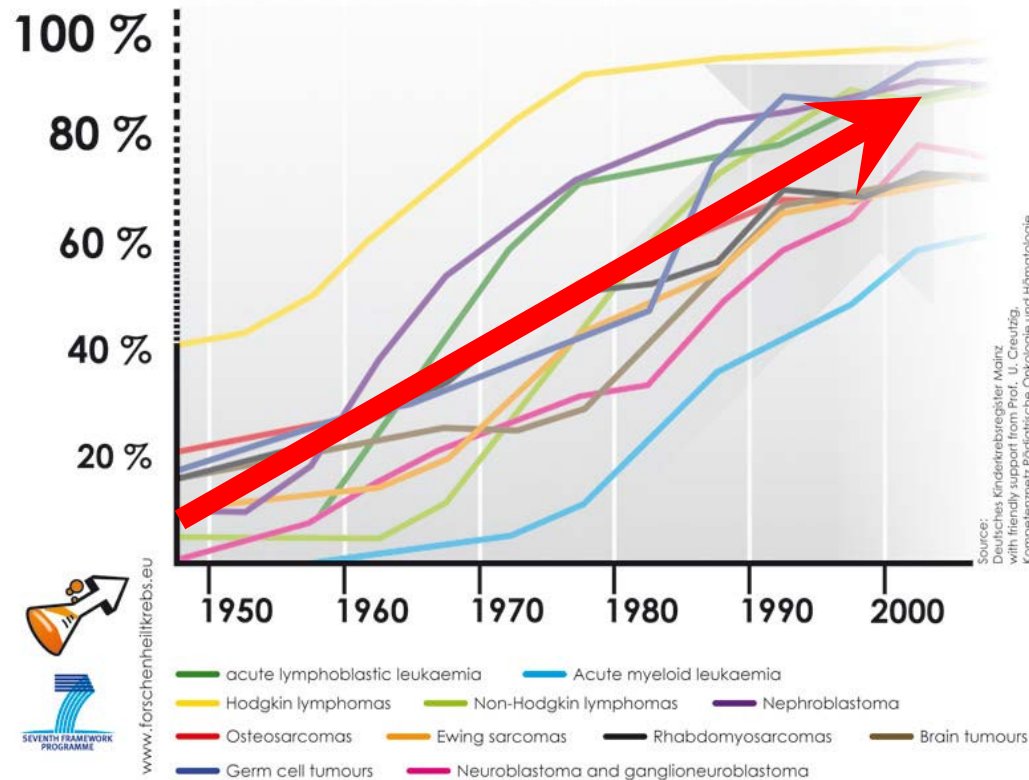
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Objectives

- Discuss the immune system and vaccination in immunocompromised children
- Discuss how to immunize post therapy for cancer
- Discuss special groups within oncology that need different vaccination guidelines
- Review the change in practice in British Columbia as to how we re-immunize post therapy

More children survive cancer

Survival Rates of Children and Young Adults Suffering from Cancer



■ Increase from 30% in 1960s to over 80% today

Ellison et al. *Eur J Cancer*. 2007 Sep;43(13):1967-75.

Vaccination in Peds Onc – What is Known?

- Very little actual hard data to tell us what to do
 - Most guidelines are based on expert opinion and are based on extrapolated data from healthy children
- Wide variation in approaches to re-vaccination post therapy in childhood cancer
 - When ? (Vaccinate during therapy or post therapy?)
 - How ? (start new, continue as before, or booster?)
 - Who ? (Any extra vaccines? Special groups?)

Vaccination – Timing

■ North America

- No sooner than 3 months post chemo
- No sooner than 12 months post SCT

■ Europe

- Start at 6 months post chemo or SCT

■ UK

- Boosters for kids 6 months post chemo
- Complete re-immunization 12 months post SCT (auto or AlloSCT with sibling donors)
- Complete re-immunization 18 months post SCT (allo with unrelated donors)

Immune system and Cancer Therapy

- Both cellular and humoral immune systems suppressed by cancer & its treatment
- A few studies show that immunoglobulin levels as well as specific antibody concentrations are normal at the time of a child's diagnosis
 - Therefore past vaccines are likely protective for these kids at time and diagnosis and possibly through treatment
 - We check viral serologies at time of new patient diagnosis
 - Help us decide who will get VZIG in case of exposure

Immune system and Cancer Therapy

- Humoral immunity is affected during therapy
 - Leukemia patients had low levels of IgA and IgM at end of therapy but these normalized by 6 months post treatment
 - IgG levels normal throughout
 - Thought that the immune system normalizes around 3 to 6 months post therapy
- Cellular immunity appears to take longer
 - Conflicting info on how long it takes for reconstitution of T, B and NK cells
 - CD8+ cells regenerate 3-12 months post Rx
 - CD4+ lymphocyte cells is not improved until 6m post therapy

Contraindicated Vaccines

■ Absolute Contraindications include:

- Live viral vaccines are contraindicated
- Oral Polio
- Intranasal Influenza
- Oral Typhoid
- Yellow Fever
- BCG vaccine

■ Relative contraindications include:

- MMR vaccinations
- Varicella vaccines

Influenza Vaccine

- Should try and give to all families and to patients
- Current Guidelines in BC:
 - Give to children on therapy as long as ANC over 0.5
 - Family should be vaccinated
 - Do not use live intranasal vaccine in patients or household contacts

Varicella Vaccination

- Children with ALL have been vaccinated during maintenance chemotherapy (in outbreaks, or if living in area of low vaccination rates)
 - Good immune responses seen in short term
 - Safe to give with mild complications similar to healthy children
 - Concerns if immunity will be maintained lifelong
 - Current guidelines in BC:
 - Do not immunize during therapy but suggest a booster dose post therapy

Varicella Vaccination

- 7 Studies over last 3 decades in childhood ALL
 - Would stop chemo for 2 weeks to give live vaccine during maintenance chemo
 - Give only if Lymphocyte count > 0.7 and plts > 100
- Overall effective seroprotection & no impact on cancer relapse
- However concerns about:
 - Stopping chemotherapy for 2 weeks
 - 20 to 50% would develop vaccine strain disease
 - Impact on infection control and isolation in clinic
 - Case reports of death due to vaccine strain in patients given vaccine during induction chemotherapy
 - Can use VZIG and acyclovir in case of varicella exposure

Varicella Vaccination

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Vaccination post chemo – UK Experience

- 59 children with leukemia
- Vaccinated with single dose of boosters for Hib, tetanus, diphtheria, acellular pertussis, mening C, polio, and MMR starting at 6 months post therapy
- Prevaccination levels were protective for:
 - Tetanus 100%
 - H Influenza B 87%
 - Measles 71%
 - Men C 12% (40% had been given this)
 - Polio 11%

Vaccination post chemo – UK Experience

- Booster increased to 90%+ for all children except polio that increased to 85%
- Testing one year later showed that this immunity was still present at similar levels one year later
- Conclusion:
Revaccination with a single booster 6 months post therapy gives excellent immunity levels

Vaccination post chemo – Australian Experience

- Guidelines to do boosters in survivors 6m post therapy (2 yrs for HSCT patients)
- Wanted to look at compliance with this in Australian survivors of childhood cancer
- Results showed very poor compliance:
 - 39% had no vaccines given post therapy
 - 47% had at least one influenza vaccine

Special Populations – Stem Cell Transplant

- Type of Stem cell transplant matters for immune reconstitution
 - Autologous
 - Allogeneic
 - Cord Blood
 - Related Donor
 - Matched Unrelated Donor
 - Haploidentical stem cell donor
 - T-cell depleted or not ?
 - Conditioning regimen
 - GVHD prophylaxis medications

Special Populations – Stem Cell Transplant

- Which Vaccine preventable diseases are SCT children at risk for post therapy?
 - Varicella Zoster
 - Hemophilus Influenza Type B
 - Pneumococcus
 - Meningococcus

- Problem is the biggest risk is in the first 100 days before immune reconstitution
 - Studies have shown minimal response until minimum 6 months post SCT

Vaccination – Italian Guidelines

- Systematic review performed
 - All papers in English language from 1980 to 2013
- Expert panel convened
 - Reviewed each vaccine individually
 - Small working groups for each vaccine
 - Reported back to larger group at two concensus meetings
 - Levels of evidence attached to each recommendation (using IDSA guidelines)

TABLE 2: Summary of level of evidence and recommendations for paediatric patients during and after chemotherapy.

Vaccine	During chemotherapy		After chemotherapy	
	Level of evidence, Reference	Concise recommendation	Level of evidence and reference	Concise recommendation
Poliomyelitis	C III [21, 23]	Benefit of herd immunity Postpone if lymphocyte count $<1.0 \times 10^9/L^{**}$	B II, [10, 11, 57, 85, 87–89, 91]	Booster or vaccination 6 months after stopping chemotherapy
Diphtheria	C III [21, 24]	As above, passive immunoprophylaxis and antibiotic prophylaxis in case of epidemic	B II [10, 11, 14, 26, 61, 86–91]	Booster or vaccination 6 months after stopping chemotherapy (adult type vaccine for age >6 years)
Tetanus	C III [21, 24]	Postpone if lymphocyte count $<1.0 \times 10^9/L^{**}$ Passive immunoprophylaxis, thorough washing and disinfection of wound, and antibiotic therapy for wounds at risk	B II [11, 14, 26, 56, 61, 86, 87, 89, 91–93]	Booster or vaccination 6 months after stopping chemotherapy
Pertussis	C III [21, 25]	Postpone if lymphocyte count $<1.0 \times 10^9/L^{**}$ Passive immunoprophylaxis and antibiotic prophylaxis in case of epidemic	B II [10, 26, 86, 87, 90, 92]	Booster or vaccination 6 months after stopping chemotherapy
Hepatitis A virus	C III [21, 27–30]	Vaccination of the seronegative patients before starting chemotherapy in highly endemic areas; alternatively, passive immunoprophylaxis	C III [29]	Booster or vaccination 6 months after stopping chemotherapy
Hepatitis B virus*	B II [21, 28, 31, 32, 34, 35]	As above	B II	Booster or vaccination 6 months after stopping chemotherapy

Influenza	B II [21, 36–51, 53]	Vaccination yearly during fall; postpone if lymphocyte count $<1.0 \times 10^9/L$;** Vaccination of family members Not administered to infants <6 months of age	B II [14, 46, 49, 51, 52]	Fall Season vaccination after 3 months from stopping intensive chemotherapy Not administered to infants <6 months of age
Meningococcus [§]	C III [21, 56, 57]	Recommended vaccination prior to splenectomy Postpone vaccination if lymphocyte count $<1.0 \times 10^9/L$ ** Not administered if age <2 years	B II [87]	Not administered if age <2 years Booster or vaccination 6 months after stopping chemotherapy Booster after 3 years if vaccinated at age of 2–6 years
Haemophilus influenzae	C III [21, 24, 58, 61]	Not administered if age <2 months Recommended vaccination prior to splenectomy Postpone vaccination if lymphocyte count $<1.0 \times 10^9/L$ °	B II [11, 14, 87, 89]	Not administered if age <2 months Booster or vaccination 6 months after stopping chemotherapy
Pneumococcus ^{§,§§}	C II [20, 41, 55–58]	Recommended vaccination prior to splenectomy Postpone vaccination if lymphocyte count $<1.0 \times 10^9/L$ **	B II [87]	Booster or vaccination 6 months after stopping chemotherapy
Measles, Mumps, Rubella	D III [21, 64]	Not administered if age <12 months Passive immunoprophylaxis in case of contact Vaccination of seronegative family members	B II [11, 12, 56, 61, 86, 87, 89, 92]	Not administered if age <12 months Booster or vaccination 6 months after stopping chemotherapy
Measles	CIII (if epidemics) [64]	In case of epidemic, patient vaccination if adequate CD4+ immune recovery °		

TABLE 2: Continued.

Vaccine	During chemotherapy		After chemotherapy	
	Level of evidence, Reference	Concise recommendation	Level of evidence and reference	Concise recommendation
Varicella	C II [21, 63, 67, 69–73]	Postpone if lymphocyte count $<0.7\text{--}1.2 \times 10^9/\text{L}^{**}$ or the patient is not in remission for 12 months or is doing radiotherapy Not administered if age <12 months Vaccination of family members at risk; Postexposure prophylaxis within 96 hours from contact: hyperimmune Ig (0.2 mL/kg, max 10 mL) 96 hours after contact Acyclovir 4×20 mg/kg/day from the 7th to 21st days ^{**}	B II [11, 57, 65, 89]	Not administered if age <12 months Booster or vaccination 6 months after stopping chemotherapy
Human papilloma virus	No data		C III [22]	Not administered if age <9 years Booster or vaccination 6 months after stopping chemotherapy
Rotavirus	No data		No data	

Vaccination for Asplenic patients

- Who is at risk for encapsulated bacteria (who needs pneumococcal and meningococcal vaccinations)?
 - Surgically asplenic
 - Functionally asplenic
 - Chronic Graft vs Host Disease
 - Radiation to the spleen (Neuroblastoma, Wilms, Hodgkins)
 - Total Body irradiation (eg: Allogeneic Stem Cell Transplantation)

Evidence for Vaccine Boosters

■ Zignol et al

- 192 children with cancer
- Post chemo loss of serum antibodies in 52%
- Hep B immunity lost in 46%
- MMR immunity lost in 25%

■ Fioredda et al

- 70 children treated with leukemia
- Found 85% had antibody titers similar to their peers

1. Zignol et al Cancer 2004
2. Fioredda et al, Pediatr Blood and Cancer 2009

Vaccination of family members

- Parents/Siblings should be vaccinated to protect the immunocompromised child
 - Influenza (avoid nasal live vaccine)
 - Inactivated vaccines
 - Avoid oral polio vaccine (give inactivated polio vaccine)
 - Can give MMR vaccine
 - Varicella vaccine if not immune for siblings
 - No need for isolation but look for skin outbreaks
 - No transmission reported other than in cases where rash noted and transmitted by direct contact
 - Can give MMR and Varicella vaccines

Vaccine Paperwork.....

- Current system in British Columbia is cumbersome and paperwork heavy
 - Heavy workload on nurses at BCCH, and Public Health Nurses
 - Paperwork that needs to be signed by Oncologists
 - Only good for 3 months
 - Separate forms for varicella, MMR, and regular vaccines
 - Relies on families to go to public health to get vaccinations

- However a new solution may be on its way...

Future Directions

■ New Clinic at BCCH

**\$15-million donation
funds immunization
clinic at B.C. Children's
Hospital**



BCCH Family Immunization Clinic



- 2nd of its kind in the world, 1st in Canada
- Opening October 16th
 - Flu shots only initially
 - All publicly-funded vaccines from Jan
 - Vaccine referrals to ID will be seen here – no need to re-refer
- Ambulatory Care Building, main floor, opp. clinic 7
- 8.30 am – 5.00 pm Mon-Fri
- Drop-in and pre-booked appointments
- Not intended for staff
 - PHSA staff immunization clinics on site Oct 18 – Dec 5
 - Details: www.phsa.ca/staff-resources/staff-influenza-resources
- Please send your patients, pregnant women, family members and their visitors

Current Canadian Research Study

- Vaccination in survivors of childhood ALL
- Wide variation of vaccination protocols in Canada
 - 5 centers give no extra vaccines
 - 5 centers give boosters (either based on titers or to all)
 - Only 4 of the above sites give pneumococcal vaccination (PCV13)
- Prospective study open labeled trial of PCV13 (Pneumovax) + PCV23 (Pneumovax) and DTaP-IPV-Hib (Pediatrix) in kids done therapy
 - Assess baseline immune status and response to vaccines, 6 months post therapy

Vaccination – What we used to do

- Used to check Vaccine titers at 1, 3 and 5 years post therapy
 - Vaccinate when titers drop
 - Miss those who don't come to follow up
 - Do titers stay high over time?

Vaccination – What we do now

- No more checking of vaccine titers routinely
- Catch up vaccines that the children missed
- Give booster vaccine for every all vaccines
- Think about IVIG (esp in allo-SCT patients)

- Are they in special group of survivors?
 - Allogeneic SCT
 - Start from scratch
 - Autologous SCT
 - Start from scratch
 - Asplenic
 - Prevnar, Pneumovax, Meningococcal vaccines

Vaccination

- Boosters starting 3 - 6 months post chemo
 - Inactivated vaccines first
 - Ideally with normal lymphocyte count
- MMR and VZIG 24 months post SCT if there is no active GVHD and no immunosuppression

Take Home Points

- No live vaccines during therapy
- Flu shots during therapy (not intranasal)
- 6 months post therapy start boosters (in most)
- Think about Asplenic patients post therapy
- Stem Cell Transplantation need full re-immunization protocol
- Herd Immunity is important for our kids!!!
 - Critical to keep immunization rates high
 - In BC only 68% of two year olds are up to date
 - Canada ranks 28th out of 29 industrial countries for vaccination rates
- New Vaccination clinic at BCCH

Questions?

“This anti-vaxx movement has a lot of things that I love: star power, science denial, and hipster appeal. Cause Penny-farthings and handlebar moustaches are cool, but nothing is more vintage than dying of Rubella.”

Stephen Colbert

