September
22th & 23th

2017

7th EUROPEAN
CONFERENCE
ON INFECTIONS IN
LEUKAEMIA

Guidelines for vaccination of patients with hematological malignancies and HSCT recipients

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INTRODUCTION

Common issues to vaccination in hematology patients (1/2)

- An area often neglected by hematologists
- Few or no data with some vaccines
- Number of patients needed to show a clinical efficacy of vaccines in rare diseases: impossible to reach
- Efficacy mostly defined on biological parameters whose protective effect was established in healthy individuals. Clinical pertinence of such parameters unknown in immunocompromised pts
- Many hematological diseases = many different types of immunodeficiencies: difficult to transfer data from one population to another
- Treatments of hematological diseases fastly evolve

Common issues to vaccination in hematology patients (2/2)

- Lower vaccine response than healthy people of the same age range
- Few or no data on the durability of the response
- Live attenuated vaccines (LAV) contra-indicated, *with some exceptions*

- **Timing is crucial**

Main reasons to vaccinate hematology patients

- Higher risk than healthy individuals of the same age to acquire community infections (eg. Pneumococcal disease, Flu)
- Higher risk of infection-related hospitalization, respiratory failure, ICU stay, and death for most vaccine-preventable infections
- Risk that the infection delays or precludes the treatment of the underlying disease
- Decreased herd immunity in countries where vaccination is not mandatory

Many infections observed in hematology patients are vaccine-preventable

Vaccines may preclude - or at least decrease the severity of - the disease

Two different goals of vaccination in hematology patients

- ✓ To protect the patient against specific infections whose risk is clearly increased by the disease and/or the treatment procedures when compared to the healthy individuals

  eg. S pneumoniae and HSCT, Influenza infection

- ✓ To offer him/her, as soon as possible, the same protection as healthy individuals for vaccines recommended in their country: individual and community benefit

ECIL 7 guidelines developed…

- ✓ ***For non-transplanted hematology patients (Part I)***:
  - by underlying disease

- ✓ ***For HSCT patients (Part II)***:
  - by type of vaccine

Outside the scope of this review: primary immune deficiencies, splenectomy, non-malignant hematological diseases

Grading system

(According to ESCMID)

Strength of a recommendation

Grade A	ECIL	strongly supports a recommendation for use
Grade B		moderately supports a recommendation for use
Grade C		marginally supports a recommendation for use
Grade D		supports a recommendation against use

Quality of Evidence

Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

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*Added index:

$_r$: Meta-analysis or systematic review of randomized controlled trials.

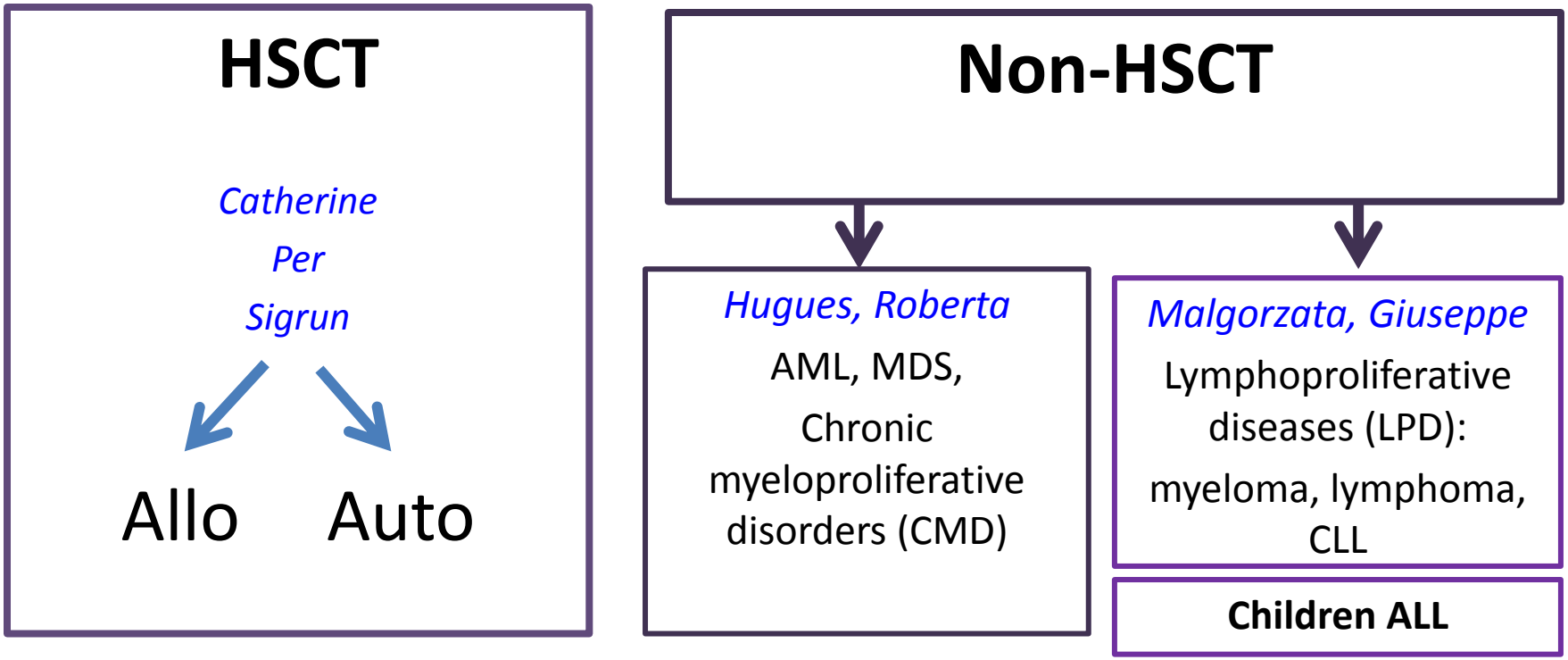
$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.

$_h$: Comparator group is a historical control.

$_u$: Uncontrolled trial.

$_a$: Published abstract (presented at an international symposium or meeting).

Roadmap


HSCT
Catherine
Per
Sigrun
Allo
Auto
Non-HSCT
Hugues, Roberta
AML, MDS,
Chronic myeloproliferative disorders (CMD)
Malgorzata, Giuseppe
Lymphoproliferative diseases (LPD):
myeloma, lymphoma, CLL
Children ALL
Pediatric specificities: Simone, Dan
Side effects
Christina, Dan
Live vaccines
Simone, Giuseppe

Part I: Vaccination of non-transplanted patients with hematological malignancies

- I A: Myeloid diseases
- I B: Lymphoproliferative diseases
- I C: Children Acute lymphoblastic leukemia (ALL)

Part II: Vaccination in HSCT recipients

Part I A: Vaccination in patients with myeloid diseases

- Acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)
- Chronic myeloid leukaemia (CML)
- Myeloproliferative disorders (MPDs)

Vaccination data in myeloid diseases

Important aspects:

- The effect of treatment is determinant on vaccine efficacy:
  - Standard intensive chemotherapy
  - Tyrosine Kinase Inhibitors (TKI) (CML)
  - JAK inhibitors (MPDs)
- Little data on vaccination in these groups of patients

Available influenza vaccines

Inactivated (IIV), usually trivalent (Trivalent inactivated vaccine: **TIV**), but possibly also quadrivalent (evaluable from the 2014-2015 season in some EU/EEA countries) or monovalent (e.g. against 2009 H1N1 pandemic strain), containing

- The whole virus
  - Non adjuvanted (Intramuscular, Intradermal)
  - Adjuvanted (with squalene, i.e. MF59, or AS03 - squalene and α-tocopherol, or aluminium phosphate gel)
  - Cell-based influenza vaccines which can be given to egg-allergic individuals (not available in all EU/EEA countries)
- Split-influenza virus products
- Subunit influenza products

Live attenuated quadrivalent influenza vaccine **(LAIV)** for intranasal use, approved in the EU/EEA for children and adolescents (2-17 years of age) in 2011 (Fluenz tetra™) .

THE LAIV is contra-indicated in HSCT recipients

(safety issue, no data in HSCT, and IIV alternatives exist)

All data presented in the next slides only concern IIVs

Vaccination data in adult patients with MDS

- No published data
- Median age of MDS patients is 75 years and as such, they should receive vaccination against influenza and pneumococcus
- However disease heterogeneity should be taken into account: for instance infections in CMML > RCMD (Refractory Cytopenia with Multilineage Dysplasia)

Vaccination in AML

Influenza

- Slightly increased incidence of influenza in comparison to the general population

HBV

- Acute HBV hepatitis has been associated with delays in chemotherapy
- In low HBV prevalence setting, there is very low risk of de novo HBV infection due to safe blood products
- Risk of de novo HBV infection exists in some high HBV prevalence countries due to high rates of horizontal transmission (blood transfusions, interventional procedures, etc.)

Other

- No sufficient data for VZV, MMR, DTP, meningococcus and pneumococcus in adults

Ljungman et al. BJH 2005; Cherif et al. Eur J Haematol, 2013; Spickermann et al. Leukemia and Lymphoma 1994; Titmarsh et al. Cancer Epidemiology 2014; Metafuni et al, MJHID, 2017; Pullucku et al. Int J of Inf Dis, 2008; Mallet, ECIL-5 guidelines, Lancet Infect Dis 2016

Other vaccination data in AML: paediatric population, summary and impact on adult AML patients

- Loss of previous immunity is less pronounced in AML than in ALL children (in line with adult setting, e.g. tetanus)
- However, **if revaccinated, both groups mount a satisfactory response once treatment is finished**
- Extrapolation to adult population: revaccination of selected adult AML patients after completion of chemotherapy might be successful and may have clinical benefit, for example given low residual immunity to tetanus following AML chemotherapy

Hammarstrom et al. Support Cancer Care 1998; Bochennek et al., Vaccine 2014; Patel et al. CID 2007; Cheng et al. Arch Dis Child 2012; Patel et al. Arch Dis Child 2012; Spickermann et al. Leukemia and Lymphoma 1994

Chronic myeloid diseases

Infection incidence in CML patients on Tyrosine Kinase Inhibitors (TKI)

- CML patients in pre TKI era had an increased risk of respiratory and skin infections *(Titmarsh 2014)*

- TKIs further increase this risk, but precise data not available
  - Risk of reactivations of hepatitis B with TKIs have been repeatedly reported leading to a recommendation of the EMA to screen all patients for HBV before starting TKI
  - Case reports on dasatinib-induced opportunistic infection *(Chang, IJID 2014)*

- **TKI treatment might lower the vaccine efficacy**

- Response to pneumococcal vaccination was lower than in healthy controls
- Reponses to influenza vaccination (inactivated and adjuvanted) was similar to healthy controls

Titmarsh et al. Cancer Epidemiology 2014; Rubin et al. CID 2013; Chang et al. Int J Infect Dis. 2014; de Lavallade et al. Blood 2013; de Lavallade et al. Haematologica 2011

Myeloproliferative disorders (MPD) and ruxolitinib

- Data suggest no increased risk of infection in patients with MPDs in the pre-JAKi era
- Ruxolitinib is associated with an increased risk of infections, and in particular HZ and opportunistic infections
- **JAKi treatment might lower the vaccine efficacy**
- No data on the efficacy of vaccination in patients on JAKi

ECIL 7 guidelines on vaccination

Myeloid diseases: AML

- Indications based on age or comorbidities according to country recommendations should be taken into account
- Patients after the end of intensive chemotherapy: a single dose of inactivated influenza vaccine is recommended as long as considered immunocompromised (B IIu)
- In high HBV prevalence setting, where high risk of HBV transmission during CT is present, HBV vaccination, starting before and continuing during CT, can be performed, similar to what recommended in paediatric ALL (C II u)
- AML patients 3-6 months after the end of CT should be vaccinated according to country recommendations
  - Paediatric AML population should follow the recommendations for paediatric ALL patients

ECIL 7 guidelines on vaccination in chronic myeloid diseases: CML on TKI, MPD on ruxolitinib

- Indications based on age or comorbidities according to country recommendations should be taken into account
- Influenza vaccination is recommended in CML patients (B II u), although the precise risk is unknown and dual BCR-ABL/src inhibitors (dasatinib, bosutinib) might be more immunosuppressive

  One dose seems sufficient to induce seroprotection
- CML patients should be vaccinated against pneumococcus (C II t)
- Live vaccines are contraindicated in patients treated with ruxolitinib or TKIs (D III)

Part IB: Vaccination in patients with Lymphoproliferative diseases

Vaccination data in lymphoproliferative disorders (LPD): chronic LPD and ALL

Diseases

- Multiple myeloma (MM)
- Lymphoma (HD and NHL)
- Chronic lymphocytic leukemia (CLL)
- Acute lymphoblastic leukemia (ALL)

Particular aspects

- Use of anti CD-20 MoAbs
- High vs low intensity treatment for MM and lymphomas
- Novel drugs: e.g. bortezomib, carfilzomib, brentuximab, ibrutinib, idelalisib, lenalidomide
- Low probability of restoring long term immunity in diseases such as MM or CLL without allogeneic HSCT, but high probability after favourable response in diseases such as aggressive lymphomas (e. g. diffuse large B-cell lymphoma, ALL)

Multiple myeloma

Multiple myeloma and the risk of invasive pneumococcal disease (IPD)

- Increased risk of any bacterial infections (**HR = 7.1; 95% CI 6.8-7), especially** during **the 1st year following diagnosis.**
- The risk increased during the last decades (new treatments, autologous HSCT)
- Infections cause approx. 22% of all deaths in MM patients

Blimark et al. 2015 Haematologica, Hsu et al. Medicine (Baltimore) 2015

- Patients with MM have the highest incidence of IPD compared to other LPD and controls (incidence /1000 person years)

Myeloma	11 – 22
Any leukemia	4.1
CLL	4.3
Non-Hodgkin's lymphoma	1.7
Hodgkin's lymphoma	0.9
MGUS	0.12
General population	0.15

Lindstrom et al. Infect Dis 2016, Backhaus et al. BMC InfectDis2016

MM and pneumococcal vaccination, summary

Response rate to PPSV23: between **33-57%.** However:

- Most patients off therapy or during plateau phase > not representative of current treatments
  - » *Chapel Lancet 1994; Hargreaves J Clin Pathol 1995, Robertson Br J Cancer 2000; Hinge APMID 2012*

Response rate to PCV: a single study: **MM: 63% vs controls 100%**

- **Ab function test (OPA): MM: 8% vs** controls: **55%**
  - » *Karlsson Trials in Vaccinology 2013*

Response to vaccination variable, possibly better on lenalidomide

- » *Noonan Clin Cancer Res 2012*

No safety issues

No data on the duration of immunity induced by vaccination

MM and influenza vaccination, summary

Risk of influenza increased in MM: HR=6.1

» *Blimark et al. Haematologica 2015*

Trivalent inactivated vaccine (TIV)

Seroconversion **0% to 83%** (5/6 pts), most frequently approx. **20-25%***

Robertson et al. Br J Cancer 2000; Rapezzi et al. Eur J Haematol 2003; Ljungman et al. Br J Haematology 2005; Hahn et al. Haematologica 2015; Cherif et al. Eur J Haematol 2013; Sanada et al. Japanese Journal of Clinical Oncology 2016;

Improving efficacy:

- **No clear benefit of 2nd dose of TIV or of an adjuvanted vaccine**

Ljungman et al. Br J Haematol, 2005; Sanada et al. Jap J Clin Oncol 2016; Monkman et al. Leuk Lymph 2011

- **Possible benefit of 2 doses of high dose or adjuvanted vaccine**

Cherif et al. Eur J Haematol 2013; Branagan et al. Clin LymphMyel Leuk. 2017

No safety issues

MM and Haemophilus influenzae B (HiB) vaccination

- **Unknown current risk of the HiB disease in MM**
- **Contradictory results on the rate of protective Abs vs. controls**
  - *Karlsson et al. CVI 2011; Nix et al. CVI 2012*
- **Response to HiB as healthy**
  - *Robertson Br J Cancer 2000*

PRP, polyribosylribitol phosphate

MM and Herpes zoster (HZ)

- **Increased risk of HZ infection: 4-14 fold**
  - *Hansson et al. 2017 Br J Cancer; Blimark et al. 2015 Haematologica*
- **Risk of HZ particularly high in patients treated with bortezomid**
  - *Chanan-Khan et al. J Clin Oncol. 2008*
- **No specific data on HZ vaccination in MM available**
  - Heat inactivated HZV, 4 doses, 30 days apart, randomized vs. placebo: 262 patients including **22 pts with MM** (7 no HSCT, 14 after ASCT, 1 after alloHSCT); immune response in IFN-γ ELISPOT was present in HM cohort
    - *Mullane et al JID 2013*

Lymphoma

Risk of infections in lymphoma

Very heterogenous disease

Increased risk of invasive pneumococccal disease: 5-10 fold

Lindstrom et al. Infect Dis 2016; Wong et al. Epidemiol Infect 2010

Increased risk of influenza

Increased risk of Herpes Zoster: 2-3.5 fold

Hansson et al. Br J Cancer 2017, Yenikomshian et al. BMC Infect Dis 2015, Forbes et al. BMJ 2014

HBV: In low endemicity settings de novo infections rare, while reactivation is more frequent, thus appropriate screening and prophylaxis or treatment should be provided

HPV: increased risk, particularly in case of HD or pelvic irradiation

Klosky et al. Cancer 2009

Pneumococcal vaccination and lymphoma

PPSV23

- Many data from splenectomised patients: good response (45%, 72%, 80%), similar to other patients undergoing splenectomy, if vaccinated before CT

Petrasch et al. Clin Diagn Lab Immunol 1997; Landgren et al. J Intern Med 2004, Cherif et al. Vaccine 2006, Grimfors et al. Eu J Haematol 1990; Ammann et al. Rev Infect Dis 1981

- Titres waned at 3 years > revaccination at 2 years might be beneficial
  - » *Grimfors et al. Eu J Haematol 1990*

PCV

- Better response to conjugate HiB than polysaccharide vaccine to PPSV23
  - » *Svensson et al. Br J Haematol 2012*
- No data in lymphoma with PCV7 or PCV13
- The benefit of the conjugated vaccine in this population is expected

Response to influenza vaccination in lymphoma, summary of 15 studies

- **Response to TIV highly variable (3%-95%, in median approx. 30%*), lower than controls**

  Nordøy et al. Medical Oncology 2002; Rapezzi et al. Eu J Haematol 2003; Ljungman et al. Br J Haematol 2005; Mazza et al. Clin Med Res 2005; Brydak et al. Vaccine 2006; Centkowski et al. Clin Immunol 2007; Bedognetti et al. J Immunol 2011; Ide et al. Human Vaccines & Immunother. 2014; Sanada et al. Japanese Journal of Clinical Oncology 2016

- **Similar response to TIV and an adjuvanted vaccine**

  Mackay et al. JCV 2011; Monkman et al. Leuk & Lymph 2011; Villa et al. Leuk & Lymph 2013; De Lavallade et al. Haematologica 2011; Yri et al. Blood 2011

- **Possible benefit of a 2nd dose, particularly of an adjuvanted vaccine**

  Ide et al. Human Vaccines & Immunother. 2014; De Lavallade et al. Haematologica 2011; Villa et al. Leuk & Lymph 2013; Hottinger et al. Oncologist 2012

- **Not affected by chemotherapy, but no clear data on high intensity regimens**
  - *Centkowski et al. Clin Immunol 2007, Hottinger et al. Oncologist 2012*

- **Response strongly impaired by rituximab (ongoing and at least during the previous 6-10 months): no response at all reported in most studies *(See next)***
  - *Ljungman 2005, Yri 2011, De Lavallade 2011, Ide 2014*

Role of rituximab on the immune response to vaccination in lymphoma 1/2

Most data on influenza vaccination

- **During rituximab**
  - Response approx. **0**
    - even if rituximab used in monotherapy
    - even in case of 2 doses or adjuvanted vaccine

    Yri Blood 2011; Hottinger et al. Oncologist 2012; De Lavallade et al. Haematologica 2011; Mackay CVI 2011; Ide et al. Human Vaccines & Immunother. 2014

- **After rituximab therapy**
  - Within **6 months after last rituximab**: **very low response (0-29%)**
  - No response in 7 pts treated with rituximab within the previous **10 months**

    De Lavallade et al. Haematologica 2011
  - Best response in a study of 31 pts with a median of **29 months** (7-65) between rituximab and TIV: **3-29%**

    Bedognetti et al. J Immunol. 2011

Role of rituximab on the immune response to vaccination in lymphoma 2/2

No data of the duration of response after pre-rituximab vaccination

Few data on other vaccines in CLD receiving rituximab

- **PPSV23**: 1/9 response when given at 6-12 mo after rituximab
- **Act-HiB**: 5/9 response when given at 6-12 mo after rituximab

Svensson et al. 2011

In small series, some studies suggest that **rituximab could mainly affect the response to primary** antigens and not or to lower extent to recall antigens

Takata et al. J Clin Exp Hematop. 2009, van der Kolk et al. Blood 2002

However, in all studies with healthy controls, the response to recall antigens remain always lower than the one of the controls

Takata et al. J Clin Exp Hematop. 2009; Bedognetti et al. J Immunol. 2011

CLL

Risk of infections in CLL

- In a recent cohort of 263 pts, mainly treated with novel drugs, **72%** had an infectious complications and infections were responsible for **38% of deaths**

Williams et al. Leuk Lymph 2017

- Historically, higher rate of **pneumococcal** and **HiB** infections and **inverse correlation between IgG levels and the incidence and severity of infections**

- Higher rate of **HZ**

- Suboptimal responses to vaccines due to
  - impaired antibody production
  - defects in antigen presentation
  - higher plasma histamine levels (> studies of vaccination with concomitant ranitidine which blocks the histamine type-2 receptors)

Pneumococcal vaccination in CLL, summary

Response to PPSV23:

- Poor, ranging from 0% to 21%
- Always lower than controls
- Better in early stage disease
  - » *Hartkamp et al. Vaccine 2001; Sinisalo et al. BJH 2001; Van der Velden et al. Eur J Haem 2007; Safdar et al. Cancer 2008*
- No benefit of ranitidine or of GM-CSF
  - » *Van der Velden et al. Eur J Haem 2007; Safdar et al. Cancer 2008*

Response to PCV: better

- PCV7: 20-47%, better in early stage disease *(Sinisalo et al. Vaccine 2007)*
- PCV13: 58% in patients naïve of any treatment *(Pasiarski et al. PLOS One 2014)*
- Poor in case of ibrutinib, but very experienced pts *(Andrick BJH 2017)*

With both vaccines: clinical protection and duration of the response unknown

Influenza vaccination in CLL, summary

Response to TIV was low in two studies: **5-30%**; but as high as **72%-95%** in a single study, which included, among others, 60 CLL patients, mainly **treatment naïve**

Van der Velden Eu J Inter Med 2001, Rapezzi Eur J Haematol 2003, Centkowski J Clin Immunol 2007

Little benefit of 2nd dose of TIV but good response to 2 doses of adjuvanted vaccine, particularly in early stage CLL

Van der Velden Eu J Inter Med 2001, Ljungman Br J Haematol 2005<; De Lavallade Haematologica 2011

Poor response (8%-26%) to TIV in patients treated with **ibrutinib, even in case of high dose TIV**

Sun JAMA Oncology 2016; Douglas Haematologica 2017

CLL and response to other vaccines

HiB:

- Response rate variable 21-92%

  Jurlander 1995; Hartkamp 2001; Sinisalo 2001; Sinisalo 2002; Van der Velden 2007

- 52% in a recent study, better with ranitidine vs. 28% without

  van der Velden 2007

- Better response associated with younger age, early-stage disease and normal Ig levels

  Hartkamp 2001; Sinisalo 2001; Sinisalo 2002

Heat inactivated HZ vaccine, no data specifically for CLL:

Two studies of 4 doses in a mixed cohort of patients with HM (27 and 12with CLL) elicited specific T-cell responses n IFN gamma ELISPOT assays

Mullane et al. 2013; Parrino et al. 2017

ECIL 7 guidelines for vaccination of patients with CLD (1/2) *(myeloma, lymphoma, CLL)* *Comments*

- Inactive vaccines are safe but might not be effective, especially in case of
  - severe hypogammaglobulinemia
  - current or previous, even > 12 months before, treatment with rituximab
- In particular, vaccination is futile in patients who are receiving or have received within the previous 6 months rituximab, as they do not respond. Similar negative impact is expected with other B-cell MoAbs.
- All these patients should benefit from other protective measures, especially during CT and in the following year: droplet precautions, antiviral prophylaxis, Ig, household vaccination, etc.

- After the active phase of treatment (i.e. during maintenance or plateau) or within 3-6 months after the end of treatment, the vaccine history should be individually reviewed in order to plan the vaccination program and apply the country recommendations for inactivated vaccines according to the patient's age and comorbidities.
  - Abs titres (e.g. tetanus, HBV) assessed 3-6 months after the end of chemotherapy or > 6 months after the end of rituximab treatment can help in designing a tailored program

ECIL 7 guidelines for vaccination of patients with CLD *(myeloma, lymphoma, CLL)* (2/2)

Vaccine and population	Timing	ECIL 7 recommendation
Pneumococcal		
PCV13 and **PPSV23** (at least 8 weeks after PCV) in CLD	if possible at diagnosis, or during maintenance or plateau phase	**B II u, t**
Influenza		
Inactivated^	Annually, as long as considered immunocompromised	**A II u**
Influenza vaccination should be postponed in patients who are receiving or have received during the previous 6 months **anti-CD20 Abs** due to the absence of response		**B II u**
HPV In lymphoma survivors	As in healthy population	**B II t**
Live-attenuated vaccines (LAV)		
Do not administer as long as considered immunocompromised, usually at least 3 months after the end of CT or at least 6 months from rituximab		**D III**

° Protective response is not expected during high intensity chemotherapy or within 6 months from the end of rituximab administration; ^ Better response might be obtained administering a 2nd dose and/or using an adjuvanted* or high dose vaccine**; **Data from monovalent pandemic vaccine; no data from regular adjuvanted vaccine. **Unavailable in Europe; One dose unless specified otherwise*

2017

Areas of research

- MDS - no data > collaborative/multicentric research projects should be encouraged
- MPD - no data on vaccine efficacy > collaborative/multicentric research projects should be encouraged

- Pneumococcal vaccination:
  - Duration of protection
  - Benefit of > 1 dose of PCV
  - Need for PPSV23 after PCV, and 5-year PPSV23 booster

- Any inactivated vaccine:
  - Vaccine response during treatment with new drugs
  - Identification of parameters to predict high probability of immunological response
  - Optimal timing of vaccination after anti-CD20 therapy

- Role of HPV vaccination after oral-neck or pelvic irradiation

- Efficacy of new inactivated HZ vaccines (heat inactivated and recombinant)

Part IC: Vaccination in Pediatric ALL

Issues in vaccination in pediatric ALL

- ✓ Increased risk of
  - ✓ Influenza: incidence relatively low, but higher morbidity and mortality, and a delay of CT
  - ✓ IPD over 10 fold than healthy population
  - ✓ VZV

- ✓ Risk of losing long term immunity after CT (a need for booster in previously vaccinated patients)
  - ✓ Chemotherapy variably reduces seropositivity rates
  - ✓ In a systematic review: protective titres after chemotherapy
    - ✓ 17-98% for diphtheria
    - ✓ 27-82% for *Bordetella pertussis*
    - ✓ 20-98% for tetanus
    - ✓ 62-100% for poliomyelitis
    - ✓ 35-100% for HiB
    - ✓ 29-92 % for mumps, 29-60% for measles, 72-92% for rubella

Carr SB 2012 Pediatr Infect Dis J; Kersun LS 2010 Pediatr Blood Cancer; Chisholm 2001 Arch Dis Child; Tasian SK 2008 Pediatr Blood Cancer; Yöntem Y 2013 Pediatr Hematol Oncol; Zeller B2011 Acta Paediatr; Babor F 2012 Transpl Infect Dis; Zignol M 2004 Cancer; A. van der Does-van den Berg, 1981 Pediatrics; Ek T 2004 J Pediatr Hematol oncol; ; Ek T 2005 Pediatr Blood Cancer; Smith S 1995 J Pediatr; Ercan TE 2005 J Pediatr Hematol Oncol; Bochenek 2014, Kwon 2012, Calaminus 2007, Patel 2012; Ek Acta Ped 2006, Nillson Pediatrics 2002; van Tilburg Leukemia 2006 (systematic review)

CT, chemotherapy

Response to influenza vaccination

Inactivated influenza vaccine is safe and might reduce respiratory infections and hospitalization in children with leukemia or lymphoma

Cheuk DK 2011 Cochrane Database Syst Rev

Wide range of response to vaccination with **TIV during maintenance:** H1N1 **22%** - 72%; H3N2 34% - 88%; B 35% - **88%**

Shahgholi E 2012 Pediatr Blood Cancer; Hsieh YC 2002 J Formos Med Assoc; Chisholm 2001 Arch Dis Child; Relly A 2010 J Pediatr Hematol Oncol; Porter CC2004 Pediatr Blood Cancer; Wong-Chew RM 2012 Oncol Lett; Brydak LB 1997 Leuk Lymphoma

No benefit of high dose or adjuvanted vaccine vs TID

Hakim H 2016 Vacicne; McManus M 2014 Pediatr Blood Cancer

Response rate lower than in healthy controls

Porter CC 2004 Pediatr Blood Cancer

Adverse events: only mild (mostly local)

Pneumococcal vaccination in pediatric ALL

✓Seropositivity rates after vaccination **during (mainly maintenance) chemotherapy :**

PCV 7, 2 doses:	86%-100% (depending on serotypes) [7]
PCV 10 , 1 dose:	33%-89% (depending on serotypes) [1]
PCV 13, 1 dose (50% pts with ALL):	46%-87% (depending on serotypes) [6]

✓Seropositivity rates after vaccination **post -chemotherapy**:

PCV 13, 1 dose:	64%-100% (depending on serotypes) [6]

1- Crawford 2015 Vaccine Reports; 2- Lehrnbecher 2011 British J Haematol
3- Patel SR 2010 BMJ; 4- Ridgway 1993 Leukemia and lymphoma
5- Wong 2010 Epidemiol infect; 6- Hung TY 2017 Cancer; 7- Cheng FW 2010 Arch Dis Child

HBV infection and vaccination

- **Countries with high prevalence of HBV**
  - High incidence of de novo HBV infection in, mainly related to hospitalization (unsafe transfusions, in-hospital transmission,…) [1]
  - HBV infection results in delaying full CT course and a reduction of doses with higher mortality rates (7-40%) [2]

- In the setting with **low risk of HBV transmission**, the reactivation of chronic HBV infection is the main risk and should be prevented pharmacologically

1- Hwang JP 2017 cancer; Al-Jadiry MF 2013 East Mediterr Health; 2- Guruprasad 2014 Pediatr Bood Cancer; 3- Karaman S 2011 Ann audi Med; 4- Zignol M 2005 Cancer; Fioredda F 2005 Eur J Haematol

DTP, HiB, IPV, meningococcus

DTP

✓Seroconversion rate is lower in case of vaccination during maintenance compared to post-CT

✓Seroconversion rate post-CT: diphtheria **71%-96%, tetanus 90 - 100%, pertussis 69%**

HiB

- ✓ Comparable seroconversion rate with vaccination during maintenance or 3 months after the end of CT
- ✓ Seroconversion rate post-CT: **87% – 100%**

Poliomyelitis

✓Seroconversion rate post-CT: **68-100%**

Meningococcus

✓Response to MenC (conjugated vaccine) 6 months post-CT: **12-96%**

Zengin E 2009 Pediatr Blood CancerLehrbecher et al BJH 2011; Patel SR 2007 Clin Infect Dis

HPV vaccination

Cancer survivor women are at higher risk of HPV related complications

There are no study on HPV vaccination in ALL patients

James L. Klosky 2009 Cancer

VZV infection and vaccination in ALL patients

- Higher incidence and severity of VZV infections
- 41% of VZV infections occur during maintenance therapy
- In low income countries - fatality risk of VZV reported of 3.4% - 10%
- Seroconversion rate:
  - During maintenance: 1 dose: 19%-54%; 2 doses: 94%
  - Post CT: 1 dose 39.6%; no data for 2 doses
- Vaccination was effective during maintenance, but it requires suspension of CT 1 week before and 1 week after, or longer in case of post-vaccination rash (which occurred up to 33% of patients)
- Recent data from 35.128 ALL children: 20 fatal cases (only 4 during maintenance CT), including 1 death attributed to varicella vaccination

Lin CH 2016 Medicine (Baltimore); Hansson E 2017 Br J Cancer; Ojha RP 2015 Eur J Pediatr; Kim SK 2016 Blood Res; Streng A 2016 Pediatric Hematology and Oncology; Austgulen R 1985 Postgrad Med J; Ninane J 1985 Postgrad Med J.; Bochennek 2014 Vaccine; Faeya 2016 Pediatr Neonatol; Brown AE 2016 World J Pediatr; Caniza Ped Blod Cancer 2012; Diaz PS 1991 Pediatrics; Cakir FB 2012 Pediatr Hematol Oncol; LaRussa P 1996 J Infect Dis; Leung TF 2004 Eur J Haematol

MMR in pediatric ALL

Measles:

- High risk of severe complications in oncology pts (deaths reported) [1];
- Outbreak in hematological pts is associated with high mortality and morbidity [3];
- No treatment or preventive measure available

Mumps:

- Few data available,
- Mild infection reported in ALL pts [2]

Rubella:

- Almost no data available,
- 1 case report of persistent rubella infection in pt vaccinated during maintenance [4]

1 - Kaplan LJ 1992 JAMA; 2- de Boer AW 1989 de Vaan GA. Eur J Pediatr; 3- Ge YL 2017 Chin Med J (Engl); 4- Geiger R 1995 J Med Virol.

ECIL 7 guidelines for vaccination of children with ALL

INDUCTION and REINDUCTION PHASES

Vaccine	Timing and doses	ECIL 7 recommendation	Comment
In the setting of **high HBV prevalence** and **high risk of acquiring HBV infection during CT**			
HBV in HBsAb and HBcAb seronegative patients	Double dose	**B II u**	Different schedules of 3-5 doses can be used
Co-administration of HBV specific HBIg might improve protection		**C II u**	
All live vaccines (including VZV) are contraindicated		**D II u**	

^ Better response might be obtained administering a 2nd dose and/or using an adjuvanted* or high dose vaccine**
**Data from monovalent pandemic vaccine; no data from regular adjuvanted vaccine. **Unavailable in Europe*
One dose unless specified otherwise

ECIL 7 guidelines for vaccination of children with ALL

MAINTENANCE THERAPY

Vaccine	Timing and doses	ECIL 7 recommendation
Inactivated vaccines are feasible but suboptimal response might be present > most vaccinations should be postponed to 3-6 months after the end of CT in order to achieve better and longer lasting protection		
Inactivated influenza vaccine	Yearly 2 doses if ≤ 9 years	**A II u,** **t for dose**
PCV13	1 dose	**B II u**
VZV	CT suspended for at least 1 week before and after, longer if vaccine-related rash	**C II u**
Postpone VZV vaccination to 3-6 months after CT, and provide alternative protective measures during maintenance therapy (acyclovir, isolation, vaccination of household contacts, etc.), in consideration of the potential risk of ALL relapse		**A III**
Live vaccines other than VZV are contraindicated		**D II u**

ECIL 7 guidelines for vaccination of children with ALL

3-6 MONTHS FROM THE END OF CHEMOTHERAPY

Vaccine	Dose	ECIL 7 recommendation
Inactivated influenza	From the end of maintenance CT and as long as considered immunocompromised	**B II u**
Patients fully vaccinated before ALL diagnosis		
DTaP, IPV, HiB	Irrespective of Ab titres* 1 dose **	**A II u**
HBV	Irrespective of Ab titres* 1 dose according to country recommendations	**A II u**
PCV13	1 dose	**A II u**
MenC/ACWY	1 dose according to country recommendations	**B III**
MenB	1 dose according to country recommendations	**C III**
HPV	According to country recommendations	**B III**
VZV in seronegative patients	2 doses (or 2° only if seronegative 4 weeks after 1st)	**A II u**
MMR	Irrespective of Ab titres or when seronegative 1 dose in previously vaccinated	**A II u**
Patients not vaccinated before CT should be revaccinated with full courses, according to country's recommendations		**A II u**

**Titres may decline over time; ** In high risk patients, suboptimal response to 1 dose might occur*

Areas of research on vaccination in children ALL

- Vaccination schedules in children who did not complete the full course of primary vaccination cycles: full revaccination or boosting?
- The possible role of inactivated VZV or inactivated HZ vaccines
- The role of PPSV23

Part I: Vaccination of non-transplanted patients with hematological malignancies

- I A: Myeloid diseases
- I B: Lymphoproliferative diseases
- I C: Children Acute lymphoblastic leukemia (ALL)

Part II: Vaccination in HSCT recipients

ANTIBACTERIAL VACCINES AFTER HSCT

Streptococcus pneumoniae

Invasive pneumococcal disease (IPD) after HSCT

Mainly pneumonia and bacteremia, 21 - 57% occurring during the first 12 months after transplant

Mortality rate after HSCT # 11-22%

The risk correlates with the decrease of specific Abs (IgG, especially IgG2 and IgG4, and IgM) levels and opsonic activity (OPA) after HSCT.

Although HSCT recipients are at higher risk after Allo than after Auto, **all HSCT patients are at risk**.

Main risk factors:

- After allo: chronic GVHD
- After auto: total body irradiation (TBI)

There is no data about the present risk of IPD in autologous HSCT with actual conditioning without TBI, or in those receiving post-transplant maintenance treatment

Winston DJ et al. Ann Int Med 1979; Sheridan JF et al, Blood 1990; Kulkarni S et al. Blood 2000; Engelhard D et al. BJH 2002; Youssef S et al. Medicine 2007; Olarte L et al. TID 2017

Antipneumococcal vaccines available

- **23-valent polysaccharidic (PS) vaccine (PPSV23, Pneumo23®)**

  Poorly immunogenic, T-cell independent response, no boost effect

- **13-valent** (replacing the previous 7-valent (2001-2010)) **conjugate vaccine (PCV 13, Prevenar®)**

  Highly immunogenic, due to the conjugation of each PS to a protein carrier (diphtheria CRM197 protein) which confers a T-cell dependence to the immune response, and consequently a stronger, longer-lasting Ab response, and a boost effect

- 10-valent pneumococcal non-typeable *H influenzae* protein D vaccine (PHiD-CDn, Synflorix®) available in some countries

PPSV23 after allogeneic HSCT

- The immune response to PPSV23 alone is poor, (<55%) even when given from 12 months, and especially in case of chronic GVHD or ongoing steroids *(Gandhi et al. BMT 2001; Kumar et al. CID 2007)*

- The response to one dose given at 8 or at 20 months after allogeneic HSCT is not different *(Parkkali T et al. BMT 1996)*

- However, when given at 12 or 18 months after 3 doses of PCV, the response rate to specific PPSV23 antigens is in the range of 83-89% and additionally increases the response to the PCV antigens *(Cordonnier C et al. Vaccine 2010)*

Immune response rates to the PCV vaccines *(PCV7 and PCV13) in prospective studies* after allogeneic SCT

Ref.erence	Vaccine	No. Pts (No. evaluable pts)	Immunization schedule	Definition of response	% of responders and comments
Molrine *Blood 2003*	**PCV7**	**96 (65)**	**3 doses at 3, 6, 12 mo (+/- donor (D) vaccination)**	≥ 0.5 µg/mL for all 7 serotypes	At 13 months: **64-75%** Benefit of D vaccination for the response to the first 2 doses, not for the 3rd
Kumar *CID 2007*	**PCV7**	**64 (44)**	**1 dose of either PPV23 or PCV7 at 6 mo (1 dose of PPV23 or PCV7 to the D), assessed at 12 mo**	≥ 0.35 µg/mL for ≥ 1 serotype	**38.6%** after PCV7 *0% after PPV23* Better immunogenicity of PCV7 vs PPV23
Meisel *Blood 2007*	**PCV7**	**53 ped. (43)**	**3 doses at 1 mo. interval from 6-10 mo**	≥ 0.5 µg/mL for all 7 serotypes	**74%**
Cordonnier *CID 2009*	**PCV7**	**158 (114)**	**3 doses: Early (3, 4, 5 mo.) *or Late* (9, 10, 11 mo) after HSCT**	≥ 0.15µg/mL ≥ 0.5 µg/mL for all 7 serotypes	**79** (E) vs **82** (L) **%** **56** (E) vs **54** (L) **%** **Early not inferior to late**
Cordonnier *CID 2015*	**PCV13**	**251 (207)**	**3 doses from 4 mo, then a 4th dose at 9 mo.**	IgG GMFR and > 0.35 µg/mL for all 13 serotypes	**89.7%–98.0%** *No ≠ betwen MA and non-MA conditioning regimens*

GMFR: Geometric Mean Fold Rise; MA: myeloablative

Main conclusions about pneumococcal vaccination after HSCT

- Poor response to the PPSV23 during the 1st year of transplant, especially in patients with GVHD and/or receiving steroids

- The PCV is much more immunogenic than the PPSV23 *(Kumar et al. CID 2007)*

- The PCV should always be administered before the PPSV23:
  - because a previous exposure to PS may induce hyporesponsiveness to subsequent administration of the conjugate vaccine including the same antigens
  - because the immune response of HSCT patients is much better and much earlier after PCV than after PPSV23

- The administration of the PPSV23 after 3 doses of PCV:
  - Increases the serotype coverage
  - Allows a significant number of previously non-responder patients to respond

Main conclusions about pneumococcal vaccination after HSCT

- Response rates to PCV are in the range of 54-98% after 3 doses over the first 12 months after transplant
- Intervals of 1 month between each PCV dose provides a regular increase of the Ab titers
- Early vaccination (from 3 months, 3 x PCV) is not inferior to late (from 9 months) vaccination after allogeneic HSCT. *Considering the risk of IPD starts early after transplant, it is crucial to achieve protective Ab titers as soon as possible. Therefore, an early vaccination is recommended.*

- No large data on long-term duration of immunity

Meisel R Blood 2007, Cordonnier CID 2009, Cordonnier CID 2015

Pneumococcal vaccination

ECIL 7 guidelines for allogeneic HSCT recipients (1/2)

From 3 months after transplant

3 doses of PCV13 at 1 month interval **A I**

A 4th dose given 6 months after the 3rd one can be considered in case of GVHD ***BII r***

At 12 months:

- 1 dose of PPSV23 * if no GVHD **B I**

** No earlier than 8 weeks after the last PCV*

No large data to support recommendations after the initial program

The assessment of Ab titers to the main conjugate and PS vaccine serotypes may help in defining the best option at a given time for a patient

Pneumococcal vaccination

ECIL7 guidelines for autologous HSCT recipients (1/1)

From 3 months after transplant

3 doses of PCV13 at 1 month interval **B III**

At 12 months:

1 dose of PPSV23 **B III**

No large data to support recommendations after the initial program

The assessment of Ab titers to the main conjugate and PS vaccine serotypes may help in defining the best option at a given time for a patient

Pneumococcal vaccination
Pediatric specificities

- Pediatric patients respond better than adults
- Their responses are close to those of healthy children *(Meisel et al. Blood 2007)*
- More post-vaccine fever, more local reactions than adults

  (Cordonnier et al. CID 2015)
- **Same schedule recommended fo children and adults**

Haemophilus influenzae B

Immune response to Hib vaccination after allogeneic HSCT

- Although the subclass Ig response is different, the overall response to 1 dose of Hib-conjugate was not different at 6-8 or at 18-20 months *(Parkkali T et al. BMT 1996; Parkkali T et al. BMT 1999)*

- The response rates (#85%) to 2 doses starting between 4-9 months or between 10-17 months were not different *(Barra et al. JID 1992)*

- After 3 doses given over the first 2 years, the response rate varied between 47-81% *(Molrine et al. Blood 1996; Parkkali et al. BMT 2007)*

- A 3rd dose increases the GMCs of specific Abs *(Molrine et al. Blood 1996, Parkkali et al. BMT 2007)*

Immune response to Hib vaccination after allogeneic HSCT

- The Hib conjugate vaccines are highly immunogenic after HSCT
- GVHD seems to have a low impact on the immune response
- High immune responses are observed with young donors and in young recipients.
- Hib conjugate vaccines are safe after HSCT: No SAE reported

Anti-Hib vaccination

ECIL 7 guidelines for HSCT recipients

The same schedule is recommended after allogeneic or autologous HSCT

Considering the timing of Hib infections after transplant and that patients can respond to the vaccine from 3 months, it is recommended to give **3 doses of conjugate vaccine at 1 month interval from 3 months after transplant** **BII r**

In order to give a combined vaccine and decrease the overall number of vaccine doses, an alternative is to give 3 doses of a DTP-Hib vaccine from 6 months **B II r**

Although there is no prospective comparison, the type of the conjugated protein (tetanus vs diphtheria) does not seem to impact on the response in HSCT patients

The optimal subsequent anti-Hib vaccination program after the 3 initial doses after transplant remains to be determined.
The assessment of specific Ab titers may help in defining the best option at a given time and at an individual level.

Hib vaccination
Pediatric specificities

- Better vaccine response than in adults *(Pao et al. BBMT 2008)*
- Same schedule recommended fo children and adults

Neisseria meningitidis

Meningogoccal vaccination after HSCT
Data on vaccine response

- Available data: only in children or young adults

- After 1 dose of MCV-4 given a median time of 2.3 (0.6-5.2) y after transplant: (retrospective study, 46 allo-HSCT aged 9-25y), only 65% responded either to the 4 (15%) or ≥ 1 (31-56%) serogroup. In the 16 non-responders, a second dose elicited a response in 8 of them (*Malher MB BBMT 2012)*

- After 3 doses of MCV-C given at 1 month interval: (prospective trial, 23 patients aged 2-17y) from 12 (auto) or 18 months (allo) after transplant, the response rate was 100% both in auto- and allogeneic HSCT recipients *(Patel SR CID 2007)*

- No data on the MenB vaccines after HSCT sofar

Meningococcal vaccination

ECIL 7 guidelines for allogeneic and autologous HSCT recipients

Vaccination with Meningo vaccines is recommended, regardless of any previous vaccination, from 6 months after transplant, at least 2 doses, in accordance with country recommendations and local prevalence for the healthy population for a given age and particularly for risk groups such as students living in campus, travellers or soldiers :

- with either a Men-C or a tetravalent vaccine **B II u**

AND

- with a Men-B vaccine **BIII**

Meningococcal vaccination
Pediatric specificities

- Main population at risk
- Guidelines based on the pediatric population
- Same recommendations in adults and in children

Tetanus vaccine after HSCT

- 3 doses are needed *(Ljungman et al. JID 1990).* Excellent tolerance, no SAE.
- Excellent response (85-100%) after 3 doses given at 1-2 months interval from 6-12 months.
- Comparable response after Allo *(Ljungman et al. JID 1990; Parkkali et al. BMT 1997; Parkkali et al. BMT 2007; Inaba et al. BJH 2012)* or Auto HSCT *(Vance et al. BMT 1998)* , except in NHL patients who had received Rituximab before and/or after Auto *(Small T et al. BBMT 2009)*
- Comparable responses after RIC *(Meerveld-Eggink et al. BBMT 2009)* or cord blood transplant when vaccinated at 7-45 months *(Shah et al. BBMT 2015)*
- No difference in response when vaccinated early (6, 8, 14 months) or late (18, 20, 26 months)*(Parkkali et al. BMT 1997)*
- Responses are not or only weakly affected by GVHD

Diphtheria vaccine after HSCT

- 3 doses are needed *(Parkkali et al. BMT 2007).* Excellent tolerance, no SAE.
- Excellent response (70-100%) to 3 doses given at 1-2 months interval from 6-12 months after Allo *(Parkkali et al. BMT 2007; Olkinuora et al. Acta Pediatr 2012; Inaba et al. BBMT 2012)*
- Limited data after Auto HSCT *(Nordoy et al BMT 2001; Small T et al. BBMT 2009)*
- No specific data after RIC
- Response after cord blood in the same range as BM or PBSC when vaccinated at 7-45 months *(Shah et al. BBMT 2015)*
- Responses are not or only weakly affected by GVHD
- A trend for lower long-term immunity with Td than with DT in allogeneic HSCT children and young adults *(Inaba et al BJH 2012)*

Diphtheria-Tetanus vaccination

ECIL 7 guidelines for allogeneic and autologous HSCT recipients

- 3 doses at 1-2 months interval from 6 months, both for allogeneic and autologous HSCT B II u
- Prefer DT to Td both in children and adults C III
- Boost doses to administer according to country recommendations

DT vaccination
Pediatric specificities

- Better response in children than in adults

- Same recommendation in adults and in children

Bordetella pertussis

Main data on pertussis vaccination after HSCT

Reference	Vaccine (Pertussis Toxoid content/ µg)	No. evaluable patients Type of HSCT (age range)	Immunization schedule	Definition of response	% of responders
Papadopoulos Blood 2008 (Abstract ASH)	**Tdap** (2.5)	**41 pts ALLO** *(1)* **(10-64y)**	**1 dose, at a median of 4.5 y post-transplant**	**≥ 2 fold Ab titers from pre-vaccine titers**	**7/41 (17%)**
Small BBMT 2009	**Tdap** (2.5)	**28 pts AUTO** *(2)* **(20-73y)**	**1 dose, at a median of 4.5 y post-transplant**	**«**	**2/28 (7%)**
Inaba BJH 2012	**DTaP** (25)	**30 children ALLO ≤ 7 y evaluable for long-term FU with 3 Ab assessments**	**3 doses planned at 12, 15 and 18 months** *(4)*	**EIA index values> 1.19**	**Each of the 3 doses increased Ab titers At 5 years post-HSCT: only 5/16 (31%) were protected**
Shah BBMT 2016	**Tdap** (8) **in adults DTaP** (25) **in children**	**63 pts ALLO Cord Blood (0.9-64)**	**2 or 3 doses at 1 month interval, started at a median of 17 (range: 7-45) months***(3)*	**Seroconversion in a seroneg patient or >2 fold rise Ab titer**	**Children (n=16): 100% Adults (n= 44): 54%**

(1) 59% of the patients were transplanted with T-cell depleted grafts
(2) 84% of the patients had received Rituximab before and/or after autologous HSCT
(3) Vaccination was post-poned in case of chronic GVHD, CD4 <200/µL and IgG <5g/L
(4) Vaccination was post-poned in case of chronic GVHD

Pertussis vaccination

ECIL 7 guidelines for allogeneic and autologous HSCT recipients

- ***The vaccination mainly aims at avoiding pertussis transmission by HSCT patients in the community***

- **The addition of pertussis toxoid to the tetanus-diphtheria vaccine** *(recommended as BII),* **3 doses at 1-2 month interval from 6 to 12 months, should be considered after transplant**

CIII

- Although there is no specific study with DTaP in adult HSCT recipients, considering the poor response to Tdap, **the DTaP** which contains a higher dose of PT than the Tdap **should be preferred both in children and adult**s

CIII

Pertussis vaccination
Pediatric specificities

- Response significantly better in children than in adults *(Shah et al. BBMT 2016)*
- Previously unvaccinated HSCT infants should be vaccinated as soon as possible
- Same recommendations in older children and in adults

ANTIVIRAL VACCINES AFTER HSCT

- Influenza
- Poliomyelitis
- Hepatitis B
- Human papillomavirus (HPV)

- Varicella-zoster virus (VZV)
- Measles-mumps-rubella (MMR)

In purple: Live attenuated vaccines (LAV)

Influenza after HSCT

- Morbidity and mortality
- H1N1-pandemic: 6% mortality in HSCT recipients
- Pneumonia=main complication of influenza, 29-33% of HSCT-recipients with influenza acquire pneumonia.
- Mortality rate of Flu pneumonia after HSCT: 6-28%

Ljungman et al 2011 , Nichols et al 2004

Inactivated influenza vaccine in HSCT patients
Summary

- One study shows the clinical efficacy of 1 dose of TIV in HSCT pts vaccinated more than 6 months after transplant (Machado et al. BMT 2005)
- Response rates to 1 dose given > 6 mo.: 10-74% for TIV, 44-64% for H1N1
- Response improves with time after transplant
- No clear benefit of adjuvanted vs. non adjuvanted vaccines
- Conflicting data exist on the benefit of a 2nd dose
- There is marginal benefit of GM-CSF and of high-dose of antigen
- Transient (early) benefit of pretransplant donor or recipient vaccination

Predictors of poor immune response to IIV after HSCT

- **Shorter time between transplant and vaccination-***(Natori 2017, Engelhard 1993, Mohty 2011, Issa 2011, Karras 2013)*
- **Low lymphocyte counts at vaccination**
  (Engelhard 2011, Fukatsu 2016)
- **Low IgG, IgA or IgM at vaccination** *(Fukatsu 2016, Mohty 2011)*
- **Chronic GVHD** *(Fukatsu 2017)*
- **Use of of calcineurin inhibitors or other immunosuppressive drugs** *(Mohty 2011, Natori 2017)*
- **Use of rituximab last 12 months** *(Issa, 2011)*

- **Local vaccine reaction associated with better immune response**
  (Gelinck, 2009)

ECIL 7 guidelines for seasonal inactivated influenza vaccination (IIV) in HSCT-recipients

- In allogeneic HSCT recipients: Annual seasonal IIV, 1 dose, at the beginning of flu season in all patients > 6 months after transplant and pursued during the first years following transplant, at least until 6 months after stopping any IS and:
  - as long as the patient is jugded to be immunosuppressed **A II r**
  - Or life-long **B II r**
- In autologous HSCT-recipients: Annual seasonal inactivated influenza vaccination, 1 dose, at the beginning of flu season in all patients > 6 months after transplant, at least as long as the patient is judged to be immunosuppressed **B II r**

- **In children ≥ 9 y and in adults, a 2nd dose of vaccine** after 3-4 weeks may have a marginal benefit and should preferably be considered in patients with severe GVHD or low lymphocyte counts **B II r**

- **In the setting of a community outbreak**: IIV can be given both to allo- and auto-HSCT-recipients, from 3 months after transplant. In that case, considering waning of immunity ober time, a 2nd dose is likely to be beneficial **B II r**

Influenza vaccination of HSCT recipients
Pediatric specificities

- Children 6 months through 8 years, receiving influenza vaccination for the first time after transplant should receive a second dose at least 4 weeks after the first dose

B II

Main data of the literature on Inactivated Polio Vaccine

- **3 doses are needed. Response: 80-100% after 3 doses given from 6-12 mo.** *(Ljungman 1991, Pauksen 1994, Parkkali BMT 2007; Olkinuora Acta Pediatr 2012; Inaba BBMT 2012)*
- **Vaccination equally immunogenic when started at 6 or 18 months after alloSCT** *(Parkkali 1997).* Well tolerated, no SAE reported
- **More limited data after Auto HSCT** *(Nordoy BMT 2001; Small T BBMT 2009)*
- **No specific data after RIC**
- **Response after cord blood in the same range of those of other stem cell sources when vaccinated at 7-45 months** *(Shah et al. BBMT 2015)*
- **Response not or only weakly affected by GVHD** *(Parkkali 1997)*
- **Long-term immunity well retained, except in children (<10y at time of transplant)** *(Ljungman 2004)*
- **Small benefit of donor vaccination** (*Parkkali 2007)*

ECIL guidelines for polio vaccination of HSCT recipients

- 3 doses of inactivated polio vaccine at 1-2 months interval, starting from 6-12 months post HSCT

  BII u

- Oral polio vaccine should not be given after HSCT

  DIII

Poliovirus inactivated vaccination
Pediatric specificities

- Better response in children than in adults

- **Higher risk for loosing immunity in the years after initial vaccination if transplanted before 10 years old**

  => Regular Polio-Ab assessment may be useful in children

- Same recommendations in children and in adults

Hepatitis B virus vaccination (3/3)

Before transplant:

Donor anti-HBc+ for Recipient all negative: Pt vaccination if possible **B III**

Additional antiHBV immuneglobulins may be combined with vaccination

After transplant:

- Pts who were all negative before transplant ***and*** patients who were vaccinated before transplant but lost their immunity at 6 mo. should be vaccinated according to country recommendation and age (3 doses: 0, 1, 6 mo, from 6-12 months)

  B II t

- Pts previously infected with HBV before HSCT (AntiHBc +) should be followed for antiHBs and be vaccinated if they have unprotective titers in order to prevent reverse seroconversion

  B III

After vaccination, HSCT recipients may be assessed for antiHBs titers between 1-2 months after the 1st series of 3 doses. If antiHBs< 10mIU/mL: an additional series of 3 doses should be considered but the benefit of a 2nd series is uncertain

HPV and HSCT

Savani et al, BBMT, 2008

35 female allo-pts,
Cervical cytology testing 45-163 months after transplant
43% had abnormal cytology
34% had HPV-related squamous intraepithelial lesions (high-grade: 20%)
Highest risk in chronic GVHD

HPV vaccine and HSCT

MacIntyre et al. Vaccine 2016

59 immunocompromised children (5-18y) including 20 HSCT recipients
3 doses of quadrivalent vaccine from 6 months after transplant, within 2-6 months
Seroconversion rate after 3 doses: 89 to 100% according to type

ECIL-guidelines for HPV-vaccination in HSCT-recipients

- Follow recommendations for general population in each country from 6-12 months after transplant

BIIu

No specific safety issue expected in this patient population

Side effects of inactivated vaccines

Conclusions for HSCT recipients

Vaccinations are safe in HSCT pts: No evidence that side effects of vaccines after HSCT are increased compared to healthy controls or to donors

Mohty et al Haematologica 2011, Molrine et al. Blood 2003, Kumar et al. CID 2007, Gelinck et al. Vaccine 2009

Most AE (local reactions, myalgia, fever, fatigue) quickly resolved

Most SAE not related to vaccines

Mohty B. et al. Haematologica 2011, Halasa et al. BMT 2015, Cordonnier CID 2015

No evidence that vaccination triggers or worsens GVHD after allogeneic HSCT *Engelhard et al. Vaccine 2011*

Risk of Varicella-Zoster infections in HSCT patients

- VZV infections may be severe, even life-threatening, after HSCT, and require hospitalization
- Risk of primary **varicella infection** (chickenpox) in seronegative patients
- High risk of **zoster infection** (VZV reactivation/shingles) in previously seropositive patients (23-59%), especially:
  - during the 1st year, and persistent thereafter
  - in patients with GVHD
- High risk of postherpetic neuralgia (35%) in this population *(Onazawa M, BBMT 2009)*

Vaccines for VZV infections

VACCINES COMMERCIALY AVAILABLE:.

- **Live attenuated VARICELLA vaccines** (LAVV): low-titer VZV-vaccine (#10 ^{3}PFU), indicated in healthy individuals for:
  - Vaccination of individuals > 12 mo *or* recent (3 days) exposure to varicella (Varivax®): 2 doses at ≥1 mo. interval
  - Vaccination of seroneg adolescents and adults (> 13 y): (Varilrix ®)2 doses at 6 w interval

- **Additionally: LAV combining Measles, Mumps, Rubella, and Varicella**

- **Live attenuated ZOSTER vaccine**: high-titer VZV-vaccine (≥19x10 ^{3}PFU), indicated in sero + healthy individuals of > 50 y for :
  - Prevention of zoster
  - Prevention of zoster-related post-herpetic neuralgia

VACCINES NOT YET COMMERCIALLY AVAILABLE:

- Adjuvanted VZV-subunit vaccine *(submitted to FDA and EMA approval)*
- Inactivated VZV-vaccine (V212)

PFU: Plaque-forming unit

Severe adverse events following varicella or zoster LAV

Fatal disseminated VZV infections due to the vaccine strain have been reported in HSCT patients after live attenuated varicella vaccine, even when vaccinated several years after HSCT *(Bhalla CID 2015),* and in non transplanted, hematology patients under chemotherapy *(Schrauder A, Lancet 2007)* or in primary immunedeficient children *(Leung, Hum Vaccine Immunother 2014)*

Fatal disseminated zoster infections have been reported after live attenuated zoster vaccine, both in HSCT recipients and in other, non-transplanted hematology patients (*Curtis KK, J Gen Intern Med 2008)* even in pts whose CT had been stopped 6 months before (Costa, BMJ case report 2015)

The timing ($\geq$ 24 mo after transplant) is not a sufficient condition to use LAAV in HSCT patients. Other conditions are required.

Inactivated Zoster vaccine (ZVIN, V212) in Autologous HSCT

A phase III, double-blind, randomized, placebo-controlled, multicenter clinical trial to study safety, tolerability, efficacy and immunogenicity of inactivated VZV-vaccine(ZVIN) in recipients of autologous HSCT)

- 4 doses (1st within 30 days before auto-HSCT, dose 2-4: d30, 60, 90 post HSCT)
- 3 randomization groups:
  - ZVIN (n=560)
  - ZVIN high antigen (n=160)
  - Placebo (n=564)

Results

- **Herpes zoster(HZ) significantly reduced with ZVIN vs. placebo**

  42/538 (**7.8%**) **vs** 113/535 (**21%**) (p<.0001)

- SAE, and vaccine-related SAEs: Similar between ZVIN and placebo group (32.9% vs 32.7%, and 0.8% vs 0.9%, respectively)

Cornely A et al. Abstracts EBMT 2017

Main conclusions on VZV-vaccination in HSCT recipients

- Antiviral prophylaxis (Acyclovir/valacyclovir) is still the primary mode of prevention: effective, cheap and safe. It should be given for at least one year after allogeneic HSCT and for 3-6 months after autologous HSCT

- **Live attenuated Varicella-vaccine**: immunogenicity to 1 dose given at 12-38 months: 13-64%. Risk of vaccine-related varicella. Can be considered, with great care, in a carefully selected population after HSCT for prevention of varicella *(Ljungman 2003, Aoki 2015, Sasadeusz 2014)*

- **New inactivated zoster vaccine (V212)**(not yet commercially available): - safe in HSCT recipients
  - promising data in auto-HSCT *(Cornely , EBMT abstract 2017, paper not published):* clinically efficient in reducing zoster
  - but poorly immunogenic in allo-HSCT recipients *(Mullane 2013)*

ECIL-guidelines for VZV-vaccination after HSCT

- Live-attenuated **Varicella** vaccine (LAVV) is contraindicated in HSCT-recipients with active GVHD, relapse of the underlying disease, or ongoing immunosuppression

DIII

- **1** dose **(adults)** of LAVV can be considered in a clinically well, **seronegative patient** > 24 months after transplant, no GVHD, no IS, no relapse of the underlying disease, and no Ig since at least 8 months

BIIr

- The addition of a 2nd dose in adults may be considered in patients who were seronegative before HSCT or had no history of VZV infection

- Live-attenuated **Zoster** vaccine is not recommended in HSCT-recipients

DIII

Pediatric specificities on live-attenuated Varicella Vaccine

- Two doses (instead of 1 dose in adults) of LAVV can be considered in children meeting the same limitation criteria than in adults

BIIr

- The interval between 2 doses should be the one recommended in the official label

Measles, Mumps, Rubella

Measles after HSCT: often severe, pneumonia, encephalitis, possibly fatal

Mumps: No severe morbidity reported after transplant

Rubella: No severe morbidity reported. The main goal of vaccination is to ***prevent vertical transmission*** in fertile women

Probability to be seronegative at 5 years after allo: **60%, 73% and 52%,** for measles, mumps and rubella, respectively (*Ljungman Blood 1994)*

High risk in pts with previous aGVHD or vaccination prior to HSCT instead of natural infection *(Ljungman BMT 2004)*

Only live-attenuated vaccines available:

Measles (alone), measles+mumps, measles+rubella, MMR, MMR+LAVV (varicella)

ECIL-guidelines for MMR vaccination

- HSCT recipients should be tested for MMR Ab titers **from 24 months** after transplant

  BIIu

- Seronegative patients for measles should receive 1 dose of MMR from 24 mo. after transplant, if no GVHD, no IS, no relapse of the underlying disease, and no IG since at least 8 months

  BIIu

- Seronegative women for Rubella and of childbearing potential should receive 1 dose of MMR with the same precautions

  CIIu

- In case of measles outbreak, MMR could be considered from 12 mo. after transplant in patients with low grade IS **CIII**

Pediatric specificities

- Lower response in children - > Consider 2 doses in children, with an interval of at least 4 weeks

Rituximab and vaccination after HSCT

AUTOLOGOUS SCT: Ritux given for maintenance after Auto: acceptable – although impaired – vaccine response with T-cell dependent (ie. Tetanus, PCV, HiB) antigens but not with T-cell independent Ags (ie. PPSV23) when vaccinated > 6-8 months after last dose of Ritux *(Horwitz Blood 2004, Pao BBMT 2008)*

ALLOGENEIC HSCT:

- Very limited data
- Ritux greatly impairs the vaccine response, even when vaccine given 28 mo. after last dose

(Issa BBMT 2011, Malher BBMT 2012, Roll Infection 2012, Shah BBMT 2015)

ECIL GUIDELINE:

- HSCT who have received Ritux from transplant should have their **vaccine program delayed at least more than 6 months after the last dose**
- Ab response is uncertain even with T-cell dependent vaccine. Specific Ab assessment after vaccination can be helpful
- Similar issues are expected with other anti-B MoAbs.

Specific questions on Recipient vaccination

- Non-severe, controlled GVHD has limited effects on the response to most vaccines and should not delay starting vaccination

- Assessment of individual Abs is encouraged after most vaccines, especially in patients who are likely to have a suboptimal response (severe GVHD, Rituximab)

Summary ECIL 7 guidelines for vaccination in adult ALLOGENEIC HSCT recipients (I/II)

Vaccine	3-6 mo.	6-12 mo.	12 -24	> 24 mo.	Grading
PCV	3 doses				AI
«		*A 4th dose if GVHD*			BIIr
HiB	3 doses	*Or* 3 doses of DTP-HiB combined vaccine			BII r
PPSV23			1 dose at 12 mo if no GVHD		BI
DTpolio ***+ pertussis***		3 doses from 6-12 mo			BII u *CIII*
MenC MCV4 **Men B**		≥2 doses 2 doses			***CR*** BIIu BIII

CR*: According to country recommendation and age*

Summary ECIL 7 guidelines for vaccination in adult ALLOGENEIC HSCT recipients (II/II)

Vaccine	3-6 mo.	6-12 mo.	12 -24	> 24 mo.	Grading
Inact. influenza		At the beginning of Flu season			1 dose: AII r 2 doses: BII r
HPV		No. doses according to official label			***CR*** BIIu
HBV		In pts all neg for HBV before HSCT ***and*** in pts vaccinated before HSCT but with antiHBs<10IU/L			***CR*** BII t
«		In pts previously infected and antiHBS <10IU/L			BIII
Varicella LAV				Seroneg, no GVHD, no IS, no relapse	BII r
MMR					BII u

***CR**: According to country recommendation and age*

Summary ECIL 7 guidelines for vaccination in adult AUTOLOGOUS HSCT recipients (I/II)

Vaccine	3-6 mo.	6-12 mo.	12 -24	> 24 mo.	Grading
PCV	3 doses				BIII
HiB	3 doses	*Or* 3 doses of DTP-HiB combined vaccine			BII r
PPSV23			1 dose at 12 mo		BIII
DTpolio ***+ pertussis***		3 doses from 6-12 mo			BII u *CIII*
MenC or MCV4 **Men B**		≥2 doses 2 doses			***CR*** BIIu BIII

CR*: According to country recommendation and age*

Summary ECIL 7 guidelines for vaccination in adult AUTOLOGOUS HSCT recipients (II/II)

Vaccine	3-6 mo.	6-12 mo.	12 -24	> 24 mo.	Grading
Inact. influenza		At the beginning of Flu season			1 dose: AII r 2 doses: BII r
HPV		No. doses according to official label			***CR*** BIIu
HBV		In pts all neg for HBV before HSCT ***and*** in pts vaccinated before HSCT but with antiHBs<10IU/L			***CR*** BII t
«		In pts previously infected and antiHBS <10IU/L			BIII
VZV				Seroneg, no IS, no relapse	BII r
MMR					BII u

***CR**: According to country recommendation and age*

DONOR VACCINATION

Benefit of donor vaccination before harvest on the recipient response to inactivated vaccines

Vaccine	Benefit	Comments	References
Tetanus	Yes	Improves the response of early (d-1, d50) R vaccination	*Storek 2004*
Diphtheria	Yes	Improves the Ab concentrations	*Storek 2004, Parkkali 2007*
Polio	No	Good response in the group with no D vaccination	*Parkkali 2007*
Pertussis	*Unknown*		
PPV23	No		*Storek 2004, Kumar 2007*
PCV	Yes	Improved after early vaccination, no more significant at 12 months	*Molrine 2003, Kumar 2007*
Hib	Yes	Improves the response of early (d-1, d50) R vaccination	*Storek 2004*
Influenza	No	No difference on Flu Abs of the R during the first 6 months after transplant . No improved response of the R when vaccinated at 6 months	*Ambati 2015*
HBV	Conflicting results	Poor response to HBsAg with or without D vaccination in Storek et al. Improved response to KLH in Wimperis et al.	*Storek 2004* *Wimperis 1990*

Donor vaccination
LAV to avoid before harvest

LAV should be avoided before harvest, due to the risk of transmitting the pathogen with the graft.

All these vaccines (MMR, VZV, yellow fever, LAV flu vaccine) are contra-indicated in the donor in the weeks preceeding donation.

Although the duration of vaccine-induced viremia is shorter for some of these vaccines, excluding any LAV 4 weeks before stem cell harvest should reasonably exclude any risk of transmission
(Rubin et al. CID 2014)

Vaccination of the healthcare personnel in the hematology ward

ECIL 7 guidelines

- Hospital staff working with immunocompromised patients should receive inactivated influenza vaccine (IIV) annually

A II t

- Hospital staff working with hematology or HSCT patients should be vaccinated according to the country recommendations and additionally to the hospital guidelines

- Care holders who are seronegative for Measles or for VZV should be vaccinated. In case of post-vaccine rash, they should avoid any contact with immuncompromised patients

Vaccination of household members of HSCT recipients
ECIL 7 guidelines

Individuals who live with HSCT recipients should be either immunized or vaccinated according to their age and country recommendations, especially for VZV and MMR

Individuals who live with HSCT recipients should receive inactivated influenza vaccine (IIV):

- beginning season before transplant and first season after transplant **AIII**
- and annually as long as the patient is judged to be severely immunosuppressed **C III**

The live attenuated influenza vaccine (LAIV) should not be used in individuals living with a HSCT recipient in the first months of transplant or with GVHD. ***BIII***

Infants 2-7 months in close contacts with HSCT recipients should be vaccinated for rotavirus but the HSCT recipient should have no contact with the stools or diapers of the vaccinated children for 4 weeks following vaccination

Areas of research on vaccination in HSCT

- ✓ Early vaccination programs in specific HSCT populations: Cordblood, Haplo
- ✓ Predictors of the very poor response to vaccine (in order to develop alternatives)
- ✓ Optimal timing to vaccinate SCT patients after rituximab
- ✓ Efficacy and safety of combined vaccines
- ✓ Need for long-term immunization programs
- ✓ New vaccines to be assessed in this very specific population
- ✓ LAV for traveler HSCT recipients

These slides are open for public consultation until November 1st, 2017

Any comment, question, suggestion, should be sent by @mail to

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