Non-responsiveness to Hepatitis B vaccination - host risk factors (genetics, age, sex, BMI, Vitamin D...)

Primary vaccine failure to routine vaccines: Why and what to do?
Wiedermann et al, Human Vaccines & Immunotherapeutics 2016

VHPB Technical Meeting, April 25th-26th in Vilnius, Lithuania

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Vaccine failure

Failure to vaccinate $\leftrightarrow$ Vaccine failure

(incorrect use of vaccine) $\leftrightarrow$ (host- or vaccine-related)

$\downarrow$

incomplete strain coverage, escape mutants, manufacturing, etc.

$\rightarrow$ host related vaccine failure

- clinical $\rightarrow$ VPD in correctly vaccinated individual
- immunological $\rightarrow$ no serological correlate of protection
  - primary – lack of seroconversion
  - secondary – quickly waning immunity

*Heiniger et al, Vaccine 2012
Wiedermann et al, Human Vaccines & Immunotherapeutics 2016*
Host risk factors for Hep B non-responsiveness

*Intrinsic* factors:
- Genetics
- Age
- Sex
- Co-morbidities

*Nutritional* factors:
- BMI
- Vitamin D

*Behavioural* factors:
- Smoking
- Stress
Intrinsic risk factors - **Genetics**

HLA genes - encode MHC Class II proteins on APCs

- MHC II + Ag peptide complex → recognized by TCR of CD4+ Th cells

HLA haplotype → distinct conformation of MHCII α1 & β1 chain

→ potential effect on Ag presentation?
→ cause for limited responses?

Abbas, Cellular & Mol. Immunology, 7th Ed.
Intrinsic risk factors - **Genetics**

Certain HLA haplotypes - associated with poor immune response to HBsAg vaccine

*McDermott et al, Tissue Antigens 1997*
HLA typing of HBs Ag vaccine NR – DRB1*0701, DQB1*02

*Desombere et al, Tissue Antigens 1998*
DRB1*0701, DPB1*1101, DQB1*02
DRB1*03 – when in combination with DQB1*02

*Desombere et al, Clin Exp Imm 2005*
Investigation of non-responders with DRB1*03 & DRB1*07 HLA subtypes
→ **not** caused by defective Ag uptake & presentation or lack of co-stimulation (CD86)

*Kruger et al, Clin Exp Imm 2005*
DRB1*0701, DRB1*0301 subjects
→ no defect in HBs Ag peptide binding to these MHCII molecules

→ post-genetic factors for lack in T-cell responses?
→ differences in T-cell recognition, TCR arrangement?
Intrinsic risk factors - Genetics

Immunologic characterization of TBE and Hepatitis B Non-responders
(Garner-Spitzer et al, J Immunol 2013)

→ booster vaccination with TBE & Influenza vaccine (Ag-specific?)

**TBE non-responders:**
→ no/low humoral & cellular responses to TBE, but sufficient to Influenza vaccine

**Hepatitis B non-responders:**
→ unimpaired humoral responses to both unrelated vaccine Ags
→ abrogated T-cell proliferation in-vitro (no IL-2 and IFN-γ production)
→ DRB1*0701, DQB1*02 overrepresented, ↑ IL-10 base line levels
→ increased B-reg precursors before booster,
  possibly contribute to ↑ baseline IL-10 and induction of Tregs post booster

- Hep B NR → genotype of high TGF-β and IL-10 secretion (Jarroson et al, Vaccine 2005)
- functional polymorphism in IL-10 promoter → negative influence on Ab titers
  (Höhler et al, Hepatology 2005)

→ impaired responses to Hep B vaccine due to IL-10 inhibited T-cell activation?
Intrinsic risk factors - Age

Immunosenescence = age-related changes of the immune system

- enhanced basal inflammation (“inflammaging”) → increase of down-regulatory mechanisms
- ↓ innate responses, TLR signaling & activation of APC
  → impaired Ag-presentation

- ↓ naïve vs. ↑ memory compartments (B- and T-cells)
- reduced diversity of naïve B-cell & antibody repertoire
- reduced TCR diversity & signaling

  → defective T-cell help & impaired T-cell dependent B-cell responses
  → poor IgG responses to protein antigens

- ↓ naïve vs. ↑ terminally differentiated memory CD8 T-cells
  (due to latent viral infections, e.g. CMV, reside in BM niches)

  → decreased persistence of Abs (loss of survival niches for PZ?)

Goronzy & Weyland, Nature Review 2013
Intrinsic risk factors - Age

Immunosenescence → affects responsiveness to several vaccines
e.g. HepA, HepB, Diphteria, Tetanus, PPV23, TBE, TIV
(Review Zimmerman & Curtis, Clinical Microbiology Reviews, 2019)

Consequences for primary & booster vaccination:
- more frequent booster vaccinations in subjects >60 a (TBE, DTaP in Austria)
- ISPTM – study on primary vaccination with JE vaccine in elderly >65 a
  • 43% low/non-responders after 2 doses of neo-antigen (0-1mo)
  • reduced ag-specific IFN-γ, expanded B & T-cell memory subsets
    → prominent in CMV+ elderly vaccinees

- primary Hepatitis B vaccination in elderly subjects (Tohme et al, Vaccine, 2011)
  • seroprotection rate 88% ≤60a vs. 12% ≥90a
Intrinsic risk factors - Age

Percentage of non-responders after Hevac-B or Engerix B in HCW (0-1-4, titer 1-6 mo post 3rd vacc) *(Sabidò et al, Vaccine 2007)*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level</th>
<th>Number of HCW</th>
<th>Number (%) no-responders</th>
<th>Odds ratio</th>
<th>95% (c.i.)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;35</td>
<td>1221</td>
<td>57 (4.67)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35–49</td>
<td>643</td>
<td>63 (9.80)</td>
<td>2.22</td>
<td>(1.53, 3.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥50</td>
<td>175</td>
<td>38 (21.71)</td>
<td>5.66</td>
<td>(3.62, 8.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Integrated analysis: age –response to Engerix B *(Van Der Meeren, Human Vaccin Immunother 2015)*

SPR 98.6% in adults vaccinated at age 20–24 a vs. 64.8% at age >65 y
Predicted SPR → 90% up to 49 y and 80% up to 60 y

Meta-analysis *(Yang et al, Sci Rep 2016)*: evaluation of relative risk (RR) for decreased response

Adults ≥ 30a - RR: 1.77
≥ 40a - RR: 1.86
≥ 60a - RR: 1.30

→ Hep B vaccination at a young age to achieve long-lasting immunity

Duration of protection and anamnestic response after booster in children vaccinated in infancy *(Salalma et al, Egypt J Imm 2014)*

- n= 898; 9 mo to 16 a; 58% have sero-protective titers (> 10 IU/L)
- non-protective titers in children < 5 years (11.1%) vs. > 10 years (64.8%)
- 92% had anamnestic response, pre-booster titer < 3.3 IU/L = predictor for NR
Intrinsic risk factors - **Sex**

m/f → differences in innate and adaptive immune responses

→ more robust humoral (and cellular) immune responses to infection and vaccination

→ higher Ab titers to TIV, YF, MMR, Hep A and B, HSV2, rabies, smallpox

- **steroid sex hormones** - estrogens, testosterone, progesteron

  ERα/β - expressed on many immune cells
  - estrogens → increased Th2 activation, expanded B-cell proliferation & higher Ab titers

  testosterone & progesteron - inhibitory effects on Ab production
  \( \uparrow \) testosterone - \( \downarrow \) neutralizing TIV Ab titers (*Furman et al, PNAS 2014*)

- **genetic & epigenetic regulation**

  immune related genes on X chr → polymorphisms & damaging mutations - \( \uparrow \) effect on males
  hormones influence epigenetic regulation of gene expression
  mi RNAs - repress mRNA translation or trigger degradation (80 encoded on X, 2 on Y chr)

- **microbiome** sex-specific relationship microbiome ↔ immune phenotype

  bacteria metabolize sex hormones → active/inactive steroids

*Klein et al, Lancet Inf. Dis 2010*
Intrinsic risk factors - **Sex**

ISPTM – study data support m/f difference in vaccine responses

1) **TBE booster in allergic cohort** *(Garner-Spitzer et al, Vaccine 2018)*

   - ↑ fold increase in female controls, but no gender difference in allergic group (males - Th2 bias)

2) **TBE booster in obese** *(Garner-Spitzer et al, in manus)*

   - ↑ fold increase in obese, but faster decline of neutralizing Abs (6 mo)
   - ↑ increase only in obese males (∨ testosteron levels)

**m/f differences in response to Hep B vaccine** *(Klein et al, Lancet Inf. Dis, 2010)*

- also for Hep A/B *(Van der Weilen, Vaccine 2006; Höhler, Vaccine 2007)*
- decline rate until 10 a - not different between boys and girls *(Wu, J Infect Dis 1999)*
- > 60a - similar SCR to Hep A/B in m/f *(Wolters, Vaccine 2003)*
- Proposed meta-analysis of sex differences in response to childhood vaccines *(Voysey et al, BMJ open 2016)*

→ results pending
Nutritional risk factors – **BMI (body mass index)**

**Obesity** - BMI ≥ 30 obese
- positive energy balance → accumulation of WAT
  → functions as endocrine organ

obese: ↓ adiponectin (anti-inflammatory)
  ↑ leptin (pro-inflammatory)

LEPR - expressed in CNS (to regulate food intake)
- on Mph, NK, T- & B-cells
  → direct impact on IS, promotes Th1/pro-inflammatory cytokines
  → chronic inflammation & immune dysfunction

**Co-morbidities** - T2D, cardiovascular disease, etc. & increased susceptibility to infections
  ↓ humoral vaccine responses to **Hep A/B, Tetanus, Rabies**
  ↓ CTLs and faster Ab decline - **Influenza** *(Sheridan et al, Int. J Obesity 2012)*

**ISPTM** - **TBE booster vaccination** in obese subjects *(Garner-Spitzer et al, in manuscript)*
- obese show higher fold increase & faster decline of Abs – shorter duration of protection?
- correlated to BMI, leptin, insulin

*Kanneganti et al, NR Imm 2012
Abella et al, NR Rheuma 2017*
Hepatitis B vaccination in obese subjects *(Review by Painter et al, Vaccine 2015)*

- **Roome et al, JAMA 1993** - investigation of recombinant Hep B vaccines
  
  BMI 25–35 kg/m² → 11 % ≤10 mIU/mL  
  BMI ≥ 35 kg/m² (severly obese) → 61.5% ≤10 mIU/mL, 45% ≤2 mIU/mL

- **Wood et al, JAMA 1993**
  
  Obesity - independent risk factor (p < 0.01) for non-protective anti-HBs titers (Recombivax HB)

  
  Confirmation of obesity as risk factor also for reduced Ab levels to Engerix-B vaccine

- **Continuing evidence for obesity as risk factor** for diminished/non-protective anti-HBs titers over time

- **Fan et al, Vaccine 2016** - 15 studies in meta analysis, 3122 participants
  
  → obese population significantly associated with non-response to Hep B vaccination
  
  - unadjusted OR: 1.99, 95% (CI: 1.47–2.69)
  - adjusted OR: 2.46, 95% (CI: 1.50–4.03)
Intrinsic risk factors – **Co-morbidities**

1) Chronic renal disease (CRD), ESRD (requiring haemodialysis)

CRD/uraemia → inflammation - activation of innate IS (Mono, Mph, granulocytes)  
→ immune deficiency - depletion of DC, naïve and central memory T cells, B cells  
- impaired phagocytic function of neutrophils & monocytes  

*(Vaziri et al, J Ren Nutr. 2013)*

**HD patients - high risk of Hep B infection (frequent parenteral interventions) → vaccination crucial!**

- SCR to HBV vaccine in long term HD patients– 77 % *(Cordova et al, Ann IG, 2017)*  
  - SCR 93 % when ↑ serum albumin (in younger vaccinees)  
  - higher GFR - better response → vaccination at onset of CRD

- 16.5 % non-responders to HBV vaccine in HD patients *(Asan et al, Int Urol Nephrol 2017)*  
  - more in Hep C positive patients, BMI >30, >65 a, duration of HD >5 years

- different vaccination routes/schedules in NR HD patients *(Barraclough, American Journal of Kidney Diseases 2009)*  
  - 5µg i. d. weekly (8x) - SCR 79 %  
  - 40µg i. m. 0 + 8w (2x) - SCR 40 %
2) Diabetes mellitus (DM)
   • in children and adults with DM - lower Ab responses to Hep B vaccination
      (Zimmerman & Curtis, Clinical Microbiology Reviews, 2019)
   • Meta analysis by Schillie at al, Diabetes Care 2012
      Hep B vaccination in children and young adults with DM (US standard administration [0-1-6, 0-1-2-12])
      → similar responses as age-matched, non-diabetic controls
      → adults with DM - reduced response, particularly with coexisting CRD

3) Celiac Disease (CD)
   • lower Ab responses to Hep B vaccination & more rapid waning of Abs in children
      (overview of literature - Zimmerman & Curtis, Clinical Microbiology Reviews, 2019)
   • meta-analysis Hep B vaccination in CD patients (Opri et al, Vaccine 2015)
      - retrospective studies - SCR 54% (82% in controls) n=832
      - prospective studies - SCR 66% (90% in controls) n=184

   → influence of microbiome?
Nutritional risk factors – Vitamin D deficiency

**Vitamin D & immune function (Hewis et al, PNAS 2011)**
- immune cells - convert precursor 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D
- Vit D promotes antimicrobial responses in macrophages & regulates APC maturation
  → control of T-cell function, crucial for Treg induction

**Vit D deficiency & TIV vaccine responses**
- conflicting data
- in HD patients - higher TIV Ab levels with vitamin D supplementation

**Vit D deficiency & ↓ Hep B Ab responses ?**
- highly prevalent in patients with chronic kidney disease
- **Zitt et al, Vaccine 2012** - retrospective study, 200 patients after Hep B vaccination
  Vitamin D <10 ng/mL in 35.5 % of patients, show 45% SCR; ≥10 ng/mL → 64% SCR (p=0.011)
- **Jhorawat et al, Indian J of Gastroenterology 2016**
  60 patients with peritoneal- or hemo-dialysis
  Vit D levels not different between responding & non-responding dialysis patients
**Behavioural risk factors - Smoking, Stress**

- **smoking** leads to lower Ab responses to Hep B vaccination in some, but not all studies

- **stress**
  - mostly investigated with respect to TIV
  - influence of stress on Hep B vaccination – conflicting data:
    - several studies → lower Ab responses in young adults with stressful life events
    - 1 study → higher antibody responses to Hep B vaccination in young adults with chronic stress
    - some studies – no association

*(Review Zimmerman & Curtis, Clinical Microbiology Reviews, 2019)*
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