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

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Vaccine failure

Failure to vaccinate ↔ Vaccine failure

(incorrect use of vaccine) (host- or vaccine-related)

↓

incomplete strain coverage,
escape mutants, manufacturing, etc.

→ host related vaccine failure

- clinical → VPD in correctly vaccinated individual
- immunological → 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

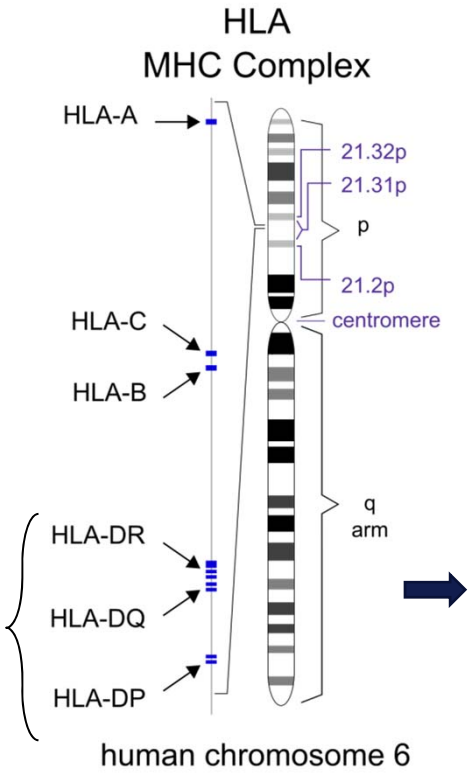
Behavioural factors:

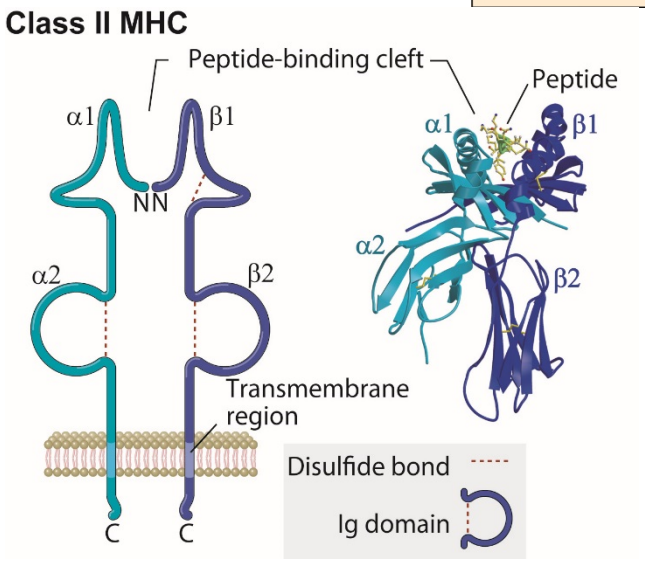
- Smoking
- Stress

Intrinsic risk factors - **Genetics**

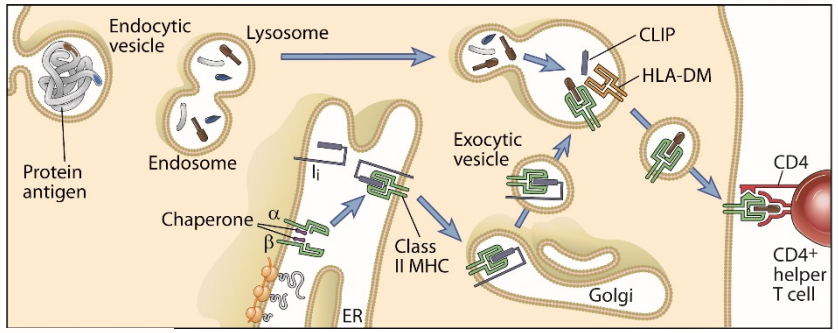
HLA genes - encode MHC Class II proteins on APCs

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





APC



Abbas, Cellular & Mol. Immunology, 7th Ed.

HLA haplotype → distinct conformation of MHCII α1 & ß1 chain

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

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-repsonders 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-y 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-ß 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**

Immunosenscence = 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
Boraschi et al, Sciene Trans Med 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
  (Wagner, Garner-Spitzer et al, Sci Rep. 2018)

  - 43% low/non-responders after 2 doses of neo-antigen (0-1mo)
  - reduced ag-specific IFN-y, expanded B & T-cell memory subsets

  → prominent in CMV+ eldery vacinees

- 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)

Factor	Level	Number of HCW[a]	Number (%) no-responders	Odds ratio[b]	95% (c.i.)	*p*-Value
Age (years)	<35	1221	57 (4.67)	1.0		
	35–49	643	63 (9.80)	2.22	(1.53, 3.22)	<0.001
	≥50	175	38 (21.71)	5.66	(3.62, 8.85)	<0.001

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

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

- **genetic & epigenetic regulation**

  immune related genes on X chr → polymorphisms & damaging mutations - ↑ 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
Klein et al, Trans R Soc Trop Med Hyg 2015

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)
- ↑ incresase only in obese males (↓ testosteron levels)

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

- Hep B – higher Ab titers in females (children & adults) (Jilg et al, Lancet 1984; Fang et al, J Trop Peditr 1994)
- 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
- positve energy balance → accumulation of WAT
→ functions as endocrine organ

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

Kanneganti et al, NR Imm 2012
Abella et al, NR Rheuma 2017

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

Nutritional risk factors – **BMI**

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)

- **Averhoff et al, Am. J Prev. Medicine 1998; Simo et al, Vaccine 1996**
  Confirmation of obestiy 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
  (ul-Haq et al, Vaccine 2003; Estevez et al, J Int Assoc Biol Stand 2007; Young et al, PLoS ONE 2013)

- ***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 %

Intrinsic risk factors – **Co-morbidities**

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 Gastoenterology 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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