

Hepatitis B vaccination in chronic kidney disease (CKD) patients

J-L. Bosmans
F. Van Gompel

3.3. Nierfalen (o.a. nefrotisch syndroom & nierdialyse)

Aanbevolen:

- **influenza** (jaarlijks);
- **hepatitis B**;
- **pneumokokken** (*details, zie fiche Hoge Gezondheidsraad – pneumokokken-vaccinatie bij pediatrische risicogroepen*).

Denk aan het tijdig geven van levend vaccin indien mogelijke evolutie naar transplantatie.

Aanbevolen:

- **influenza** (jaarlijks);
- **hepatitis B** (bij volwassenen: dubbele dosis of geadjuvanteerd hepatitis b vaccin (vanaf de leeftijd van 15 jaar);
- **pneumokokken PPS23V** (*te herevalueren als er meer gegevens over het conjugaatvaccin beschikbaar zijn*).

Denk aan tijdig geven van levend vaccins indien mogelijke evolutie naar transplantatie.

Background-1

- CKD patients are particularly vulnerable to (chronic) hepatitis B infection due to their immunosuppressed status and due to their repeated exposure to blood products (particularly in hemodialysis).
- Acute hepatitis B infection evolves to chronic liver disease in 2/3 of the affected CKD patients (chronic hepB carrier, liver cirrhosis and/or hepatocellular carcinoma)



Background-2

- In response to hepatitis B vaccination, CKD patients have:
 - lower seroconversion rates (32-80% vs > 90% in healthy population)
 - lower peak antibody titers
 - shorter duration of seroprotection (50% seroprotected at 1 year vs 85% in healthy population)



Background-3

- HBV infection in hemodialysis (USA) in 2001:
 - incidence: 0.05%
 - prevalence: 0.9 %
- Measures to reduce HBV infection in CKD:
 - regular serologic testing
 - early HBV vaccination
 - booster vaccination when HBs antibodies < 10 IU/ml
 - screening of blood products for HBV and other viruses
 - EPO treatment and reduction (avoidance) of blood transfusions
 - hygienic measures in dialysis centres



HBV vaccination in CKD: guidelines

- Start early HBV vaccination in HBV negative CKD patients, who are candidate for renal replacement therapy in the future
- Provide a total of 4 injections (at months 0, 1, 2 and 6)
- Check the antibody response at 7 months
- In non-responders (HBsAb < 10 IU/ml) restart a vaccination scheme
- Use double doses of Engerix B (40 µg) or Hevax B Pro (40 µg) or single dosis of Fendrix (20 µg)
- Check annually the AB titre; if < 10 IU/ml give a booster
- HB vaccination **MUST** be performed **BEFORE** transplantation



HBV vaccines available in Belgium

- Engerix-B 20 µg – 26.67 €
- HBvaxpro 40 µg – 61.61 €
- Fendrix 20 µg – 54.28 €

HBV vaccination in CKD: potential issues

- Determinants of response to HBV vaccination in CKD
- Strategies to improve the current response rate in CKD patients
- Cost-effectiveness of systematic early vaccination of elderly CKD patients

HBV vaccination in CKD: determinants of response

- Early vaccination
- Diabetes mellitus
- Nutritional status
- Age



Early HBV vaccination in CKD

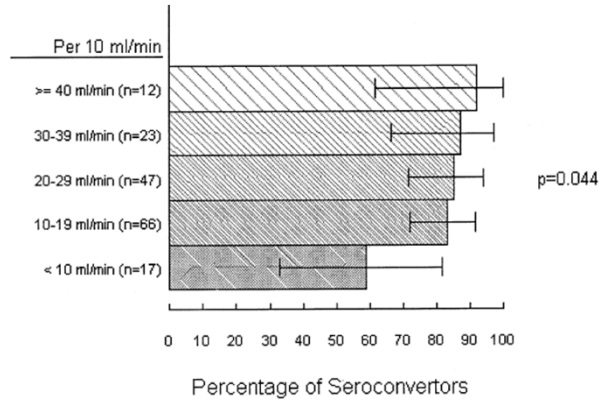
Table 3. Multivariate Modeling Results: Probability of Seroconversion

Variable	Odds Ratio	95% Confidence Interval	P
Model 1			
Age >60 y	0.150	0.050-0.451	0.001
Male sex	0.469	0.168-1.315	0.150
Diabetes	0.273	0.104-0.714	0.008
GFR <10 mL/min	0.103	0.027-0.398	0.001

DaRoza G et al. Am J Kidney Dis 2003; 42(6): 1184-1192
Prospective, single centre study in 165 HBV negative CKD patients



Early HBV vaccination in CKD



DaRoza G et al. Am J Kidney Dis 2003; 42(6): 1184-1192
 Prospective, single centre study in 165 HBV negative CKD patients



Early HBV vaccination in CKD

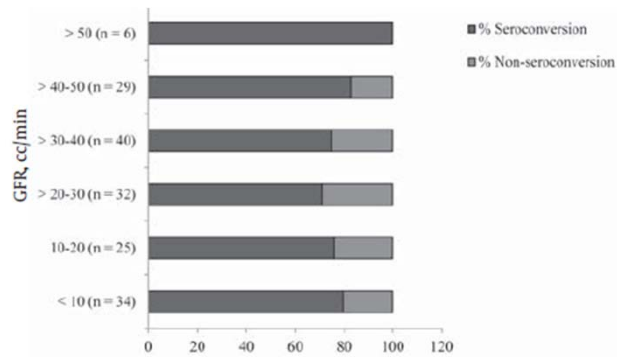


Figure 1. Seroconversion by 10-mL/min Categories of eGFR. $P = 0.693$ (Pearson Chi-Square)

Hashemi B et al. Hepat Mon 2011; 11(10): 816-820.
 Prospective, single-centre study in 167 HBV seronegative CKD patients



Diabetes and HBV vaccination in CKD

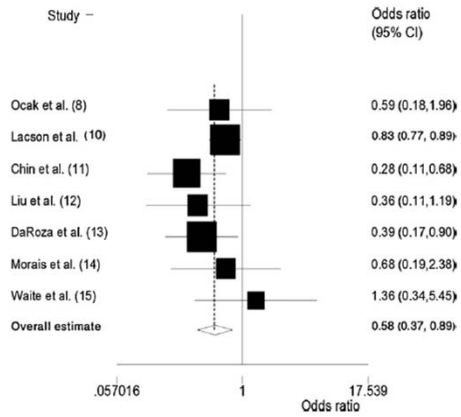


Fig. 2. Summary estimate of ORs of seroprotection rate of HBV vaccine in DM vs. non-DM patients with CKD. Square areas do not correspond to study weights in meta-analysis.

Alavian SM, Tabatabaei SV. Vaccine 2010; 28(22): 3773-3777

Nutritional status and HBV vaccination in CKD

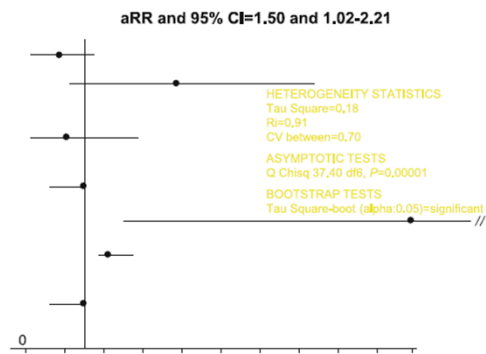


Fig. 1 Estimated RR for each study and 95% Confidence Intervals (95% CI). The vertical line represents the pooled aRR of failure to seroconvert to HB vaccine (random-effects model) according to nutritional status

Fabrizi F et al. Dig Dis Sci 2012; 57(5): 1366-1372

Age and HBV vaccination in CKD

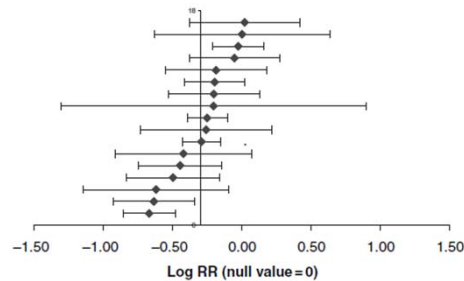


Figure 2. Estimated log risk ratio (logRR) for each study and 95% confidence intervals – the upper bar represents the last study shown in the tables (Singh *et al.*³⁰), the bar at the bottom represents the first study (Crosnier *et al.*¹⁴). The vertical line represents the summary logRR.

Fabrizi F *et al.* Aliment Pharmacol Ther 2004; 20(10): 1053-1062

Determinants of response to HBV vaccination in CKD: Conclusions

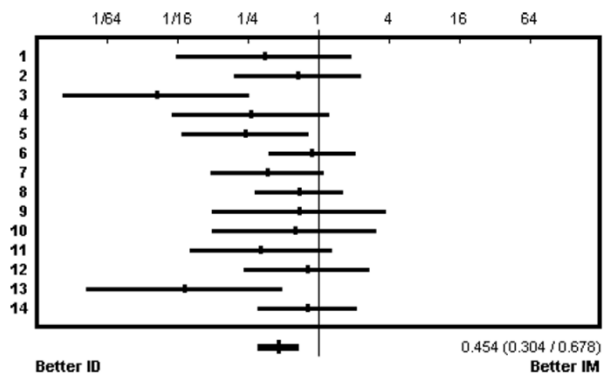
- Response to HBV vaccination is impaired in:
 - CKD patient with diabetes
 - CKD patients with poor nutritional status
 - elderly CKD patients
- Despite conflicting reports, there are strong arguments to start HBV vaccination as soon as the need for renal replacement therapy has been established

HBV vaccination in CKD patients: Strategies to improve the response

- Intradermal injections
- Adjuvant vaccines
- Oral levamisole



Intradermal HBV vaccination in CKD



Seroresponse to HBV vaccine (ID vs IM route): standard plot

Fabrizi F et al. J Viral Hepat 2011; 18(10): 730-737



Adjuvant HBV vaccine in CKD

- Several studies report on a beneficial effect of adjuvant HBV vaccines in terms of acquiring or maintaining seroprotection, either after primary vaccination or after previously failed primary vaccination:
 - Tong NK et al. *Kidney Int* 2005; 68(5): 2298-2303 (HBV-AS04)
 - Kong NC et al. *Kidney Int* 2008; 73 (7): 856-862 (HBV-AS04)
 - Tielemans CL et al. *Vaccine* 2011; 29(6): 1159-1166 (HBV-AS02)
 - Fabrizi F et al. *Aliment Pharmacol Ther* 2010; 32(6): 756-762 (Levamisole p.o. + HBV vaccine: meta-analysis)
 - Alavian SM, Tabatabaei SV. *Clin Ther* 2010; 32(1): 1-10 (Levamisole p.o. + HBV vaccine: meta-analysis)
- However, a recent meta-analysis could not show any benefit



Adjuvant HBV vaccine in CKD: Meta-analysis

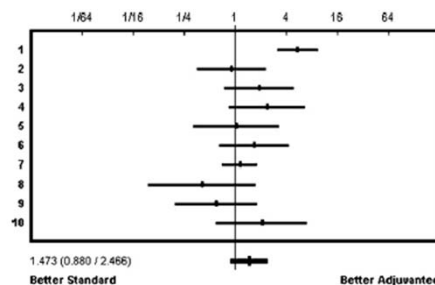


Fig. 1. Response rate to HB vaccine: recombinant vaccine plus adjuvants versus recombinant vaccine alone (standard plot).

Fabrizi F et al. *Vaccine* 2012; 30(13): 2295-2300



Adjuvant HBV vaccine in CKD: Meta-analysis

	Random-effects model OR (95% CI)
All studies (n = 10)	1.473 (0.88; 2.466)
Naive patients studies (n = 4)	1.970 (1.179; 3.292)
Prior vaccine studies (n = 6)	1.167 (0.516; 2.641)
HD patients (n = 5)	1.241 (0.805; 1.914)
Studies from western world (n = 5)	1.142 (0.675; 1.932)

Fabrizi F et al. Vaccine 2012; 30(13): 2295-2300



HBV vaccination in CKD patients: Strategies to improve the response Conclusions

- Despite the absence of good data on long term beneficial effects, intradermal and adjuvant vaccines are promising new strategies that could improve seroprotection against HBV.
- Future studies need to address the combination of these 2 strategies not only in the early phase after vaccination, but also in the long run (loss of seroprotection with time).



Cost-effectiveness of systematic early vaccination of elderly CKD patients

- With the ageing of the general population, there is a steady increase in the incidence of elderly CKD patients.
- Only a small fraction of these patients will ever require renal replacement therapy.
- Early systematic HBV vaccination in elderly CKD patients therefore is potentially not cost-effective. This question needs to be addressed in the future.