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The decades-long fight against HBV transmission to dialysis patients: slow but definite progress

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In the early days of haemodialysis (HD), hepatitis was frequent, both in patients and staff. The discovery in 1963 by Blumberg of the so-called Australia antigen in the serum of an aboriginal carrier, rewarded by the 1976 Nobel Prize, soon made it possible to demonstrate that the hepatitis B virus (HBV) was a major cause of hepatitis in HD. Screening blood donors with increasingly sensitive tests, understanding the routes of nosocomial HBV transmission, isolating HBV carriers in a separate HD room, and vaccinating HD patients and staff undoubtedly all contributed to the subsequent dramatic decrease of HBV incidence and prevalence in HD patients and virtually 0% incidence in staff [1]. Still, nosocomial HBV transmission remains a concern in HD patients, not only in emerging [2,3] but also in Western countries [4].

Many factors contribute to this persistent problem, the first being inadequate adherence to basic hygienic precautions. These are important for the prevention of transmission of all blood-borne pathogens (including HCV and HIV, in addition to HBV) and have recently been reviewed by the Kidney Disease Improving Global Outcomes (KDIGO) Hepatitis C Guidelines [5].

The second factor is the variability of actual vaccination rates. Indeed, in the USA in 2002 [6], only 56% of HD patients were given at least three doses of HBV vaccine. Similarly, in the UK [7], routine vaccination against HBV was even recently not offered to HD patients by most renal units. Interestingly, the reasons explaining this limited coverage include, a.o., a low perceived risk and impression of limited cost-effectiveness of vaccination [7]. Still, 15% of interviewed UK units experienced at least one recent seroconversion for HBV [7], a finding that contradicts the claim of low risk and suggests that vaccinating is indeed cost-effective as compared with the costly and disturbing management of seroconversions or even outbreaks. It should be stressed that suboptimal vaccination rates in HD are probably more common than seems apparent from the few available reports on this topic.
The third factor is the poor response of HD patients to HBV vaccination. Seroprotection rates after standard vaccination schedules with current recombinant HBV vaccines are poor in the dialysis population (32–80%), in contrast to the excellent (>95%) efficacy observed in the young general population [8]. In addition, even in case of response to the vaccine, chronic kidney disease (CKD) and HD patients develop lower peak antibody titres and, consequently, have a shorter duration of seroprotection than healthy subjects (50% vs. 85% 1 year after completion of the vaccination schedule, respectively). The mechanisms of this uraemia-associated immunodeficiency are incompletely understood. A recent study in HD patients has shown a diminished activation of T helper cells and impaired function of dendritic cells that play, as antigen-presenting cells, a key role in the immune response [9]. In addition to uraemia, other factors have a negative impact on the response to HBV vaccines. Two recent meta-analyses showed a clear association between ‘older age’ and non-response to primary HBV vaccine, both in the general population [10] and in end-stage renal disease (ESRD) patients [11]. It should be mentioned that the used cutoff for ‘older age’ was either 40, 50 or 60 years, respectively, in both meta-analyses, rather severe criteria in the face of the current mostly elderly HD population! Other factors predicting a poor response in CKD patients after HBV vaccination are a higher CKD stage, diabetes [12] and some human leucocyte antigen (HLA) alleles [13], but not dialysis modality [14].

Several strategies have been attempted in order to increase the response to HBV vaccination in CKD patients: these include vaccination earlier in the course of renal disease [12], intradermal instead of intramuscular administration of the vaccine in non-responders [15,16] or the administration of higher vaccine doses (either double vaccine doses (40 µg instead of 20 µg) or use of four-dose (at 0, 1, 2 and 6 months) instead of three-dose (at 0, 1 and 6 months) schedules [1]. Despite some improvements, responses remain suboptimal [86% (range 40–98%) for the four-dose schedule versus 64% (range 34–88%) for the three-dose schedule] [1].

In this issue of *Nephrol Dial Transplant*, Chow et al. [17] report the results of a multicentre randomized controlled trial (RCT) of two 3-dose schedules [extra-high (80 µg) versus the currently recommended dose (40 µg)] of intramuscular standard recombinant HB vaccine (Engerix B®, GlaxoSmithKline Biologicals, Rixensart, Belgium), at 0, 1 and 6 months. The trial was performed in Hong Kong [17] in 87 peritoneal dialysis (PD) patients (average age 60 years, 52% diabetics). Seroprotection rates did not differ 3 months (78.6% and 62.2% in patients receiving 40 and 80 µg, respectively) and 12 months (45.2% and 51.1%, respectively) after completion of vaccination. After adjustment for age, diabetes status, dialysis adequacy, co-morbidities, body mass index (BMI) and albumin serum level, only baseline nPNA independently predicted both seroprotection (1.16 ± 0.25 g/kg/day in responders versus 0.96 ± 0.23 g/kg/day in non-responders, P = 0.001) and persistence of seroprotection 12 months after completion of vaccination schedule (1.18 ± 0.24 g/kg/day versus 1.03 ± 0.25 g/kg/day, respectively, P = 0.007). As expected, mean anti-HB titres 3 months after the end of schedule predicted a persistent seroprotection at Month 12 (P < 0.00001). Interestingly, the same group previously reported in an observational retrospective study that 80-µg vaccination was associated with a longer seroprotection [18]. This discrepancy may result from the difference of age of included patients (average 43 years [18] versus 60 years [17]). Alternatively and more likely, it may just underscore that observational studies are hypothesis generating but that some of the generated hypotheses are not confirmed when properly tested in RCT. Thus, RCTs, even with a negative result like the one of Chow et al. [17], contribute to improved, cost-effective, clinical care.

An alternative strategy to improve response rates after vaccination relies on adjuvant substances containing immunostimulants. In a randomized controlled trial, Kong et al. [19,20] vaccinated 153 pre-dialysis and HD patients, with a vaccine containing a novel adjuvant system (AS04), including aluminium and the strongly immunogenic monophosphoryl lipid A (MPL), considered to improve the activity of antigen-presenting cells via binding to their Toll-like receptors. When compared with a four-dose schedule of classical recombinant vaccine (Engerix B® 40 µg), HB-AS04 vaccine (Fendrix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) elicited a faster onset of seroprotection, already apparent 1 month after the first dose, greater peak levels of anti-HB antibodies and longer duration of seroprotection over 42 months of follow up. These differences persisted regardless of the cutoff used for the definition of seroprotection (i.e. ≥10 or ≥100 IU/L). Moreover, significantly fewer subjects primed with the HB-AS04 vaccine needed a booster dose during follow-up (16.7% versus 42.9%). All these effects were observed despite a lower dose of HBsAg in the HB-AS04 vaccine (20 µg). Admittedly, the trial included mostly an Asian relatively young population, a finding that limits the generalizability of the results.

Another adjuvanted but aluminium-free HB vaccine (HB-AS02), containing 20 µg of HBsAg, MPL and a novel adjuvant called QS21 (a highly purified immunostimulant extracted from the bark of the South American *Quillaja saponaria* tree) induced seroprotection rates similar to those obtained with the HB-AS04 vaccine (>90% in both groups 1 month after completion of the schedule) in another multicentre international phase 3 RCT [21] in 300 naïve pre-dialysis, PD and HD patients, 40% of whom were diabetics. The response elicited by HB-AS02 started even earlier than with HB-AS04 (18% versus 7.7%, respectively, 1 month after the first dose) and persisted longer (93.6% versus 78.6% at Month 12), regardless of dialysis status.

In conclusion, several strategies may (and should!) contribute to reduce further the transmission of HBV in HD. These include improving actual adherence to hygienic precautions and vaccination rates in CKD and HD patients together with a wider use of promising regimens like adjuvanted vaccines and intradermal route of administration in patients at high-risk of non-response or non-responders to a primary vaccination. The fight against HBV transmission in HD is continuing, but step by step, additional evidence is accrued that will ultimately contribute to winning the war!
Conflict of interest statement. None declared.

References


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