shifts on Hgb concentration, and to adjust ESA doses with this additional variable in mind.

In conclusion, the findings of the interesting analysis by Szczech *et al.*[1] should be a stimulus for further study. But there are no immediate clinical implications of this observational analysis. Hgb targets during ESA therapy for patients with CHF or diabetes mellitus should remain consistent with current guidelines. An Hgb target of 10–12 or 11–12 g/dl remains a reasonable target that balances improved quality of life with potential cardiovascular risk.

DISCLOSURE

The authors declared no competing interests.

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Hepatitis B virus infection in hemodialysis populations: progress toward prevention

Katherine A. Barraclough[1] and E. Geoffrey Playford[2]

Hemodialysis patients are at increased risk of acquiring hepatitis B virus (HBV) infection. Administration of the standard HBV vaccine is suboptimal as a means of prevention because of an impaired seroconversion response in individuals with chronic kidney disease. Surquin and colleagues describe a novel vaccine adjuvant system that increases speed of seroconversion and duration of seroprotection compared with older vaccine formulations. However, its ability to improve overall seroconversion response remains unproven.

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Over the past few decades, there has been a substantial decrease in the incidence of hepatitis B virus (HBV) infection in hemodialysis patients, probably attributable to screening of blood donors, a decline in blood transfusion requirements with increased erythropoietin use, and authoritative guidelines relating to infection control and vaccination. Despite this progress, hemodialysis patients remain at increased risk of acquiring HBV because of increased exposure to blood products, shared hemodialysis equipment, frequent breaching of skin, immunodeficiency, and continuing high prevalence rates of HBV infection among hemodialysis populations. Although acute infection tends to be mild and asymptomatic in dialysis patients, up to two-thirds may progress to chronic carriage, with significant risk of chronic liver disease, premature death from cirrhosis or liver cancer, and nosocomial transmission within hemodialysis units.[1,2]

[1]*Department of Nephrology, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia and* [2]*Infection Management Services, Princess Alexandra Hospital, Brisbane, Australia*
Correspondence: *K.A. Barraclough, Department of Nephrology, University of Queensland, Princess Alexandra Hospital, 199 Ipswich Road, Brisbane, 4102, Australia.*
E-mail: katherine_barraclough@health.qld.gov.au

When available to healthy individuals, HBV vaccination is an extremely effective means of disease prevention. Administration of three doses of 20 μg of HBV surface antigen (HBsAg) over 6 months achieves seroprotection rates of more than 90%.[2] Alternatively, among chronic kidney disease (CKD) populations, immune responses to HBV vaccination are impaired, proportionally to the degree of kidney failure.[1] Hence, CKD patients experience lower seroconversion rates (32–80%), lower peak antibody titers, and shorter durations of seroprotection (protective antibody titers maintained in 50% of CKD patients compared with 85% of healthy individuals after 1 year).[2,3] Strategies to improve response rates among such patients have included vaccination as early as possible in the course of renal disease, use of double vaccine dose, and a four-dose rather than three-dose schedule.[1,2] These have yielded some, but still suboptimal, improvement, achieving response rates of approximately 70%.[3] Thus, additional strategies to improve vaccination response remain an important and as-yet unmet priority.

The development of protective immunity following administration of vaccine requires the interaction of the innate and adaptive immune systems (Figure 1). Specifically, antigen recognition requires

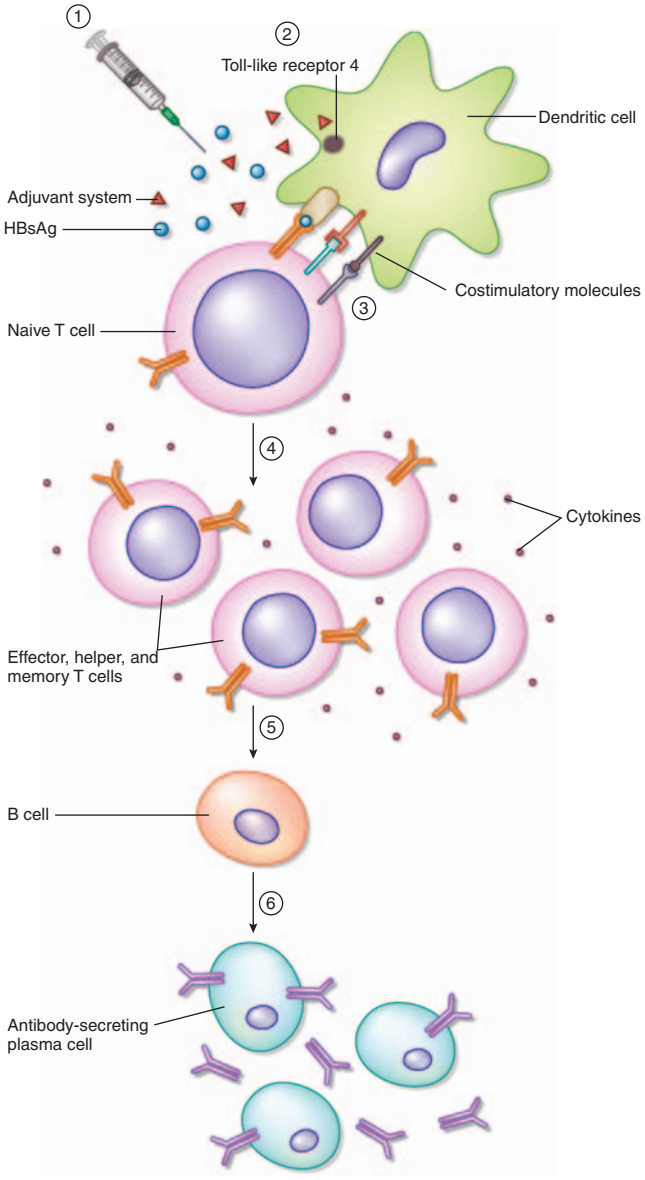

Figure 1 | Hepatitis B virus vaccination. (1) Hepatitis B virus (HBV) vaccine formulation containing hepatitis B virus surface antigen (HBsAg), monophosphoryl lipid (MPL) and QS21 is administered to the patient. (2) The adjuvant (MPL and QS21) stimulates the immune system. It is thought that MPL does this via binding to Toll-like receptor 4 on antigen-presenting cells (APCs), which leads to direct antimicrobial responses, as well as maturation and migration of APCs to draining lymph nodes, increased expression of co-stimulatory molecules and release of cytokines required for the activation and differentiation of T and B cells. QS21 is thought to also improve antigen presentation. (3) APC presents HBsAg to T cells. (4) Recognition of HBsAg in the presence of costimulation leads to activation and proliferation of T cells. (5) T cells secrete cytokines that lead to proliferation and differentiation of B cells into plasma cells. (6) Plasma cells secrete antibodies to HBsAg, thereby providing immunity to HBV.

antigen-presenting cells of the innate immune system (primarily macrophages and dendritic cells) to present antigen to cells of the adaptive immune system (T and B cells). Subsequent T-cell and B-cell stimulation and proliferation lead to the development of an army of immune cells specifically designed to respond to that antigen. The mechanism underlying the impaired response to vaccination in CKD populations is incompletely understood. However, uremia-induced dysfunctional antigen presentation is thought to contribute.[3]

Adjuvants are components added to vaccine formulations to enhance the immunogenicity of antigens.[3] Aluminum is the predominant adjuvant used in many currently available vaccines, including the standard HBV vaccine (Table 1). Its mode of action is incompletely understood, but its known effects include enhanced uptake of antigen by antigen-presenting-cells, stimulation of cytokine release, and increased antigen-specific proliferation of T cells.[4]

Surquin and colleagues[5] (this issue) report an open, multicenter randomized controlled trial comparing the ability of two alternative adjuvant systems, HB-AS04 and HB-AS02, to induce a protective HBV antibody response in CKD patients. HB-AS04 has previously demonstrated the ability to elicit higher and more persistent levels of anti-hepatitis B surface antibodies (anti-HBs) in CKD patients when compared with double doses of standard HBV vaccine,[6,7] leading to its licensing for use in CKD patients in Europe in 2005. While never tested previously in CKD patients, HB-AS02 has been shown to generate strong and persistent humoral and T-cell responses in healthy adults, providing the rationale for a comparative trial with HB-AS04.

HB-AS04 comprises 20 μg recombinant HBsAg, aluminum phosphate, and monophosphoryl lipid (Table 1). Monophosphoryl lipid is a purified, detoxified derivative of the lipopolysaccharide molecule of the bacterial wall of *Salmonella minnesota*, which, like lipopolysaccharide, is thought to bind to Toll-like receptor 4 on antigen-presenting cells. This leads to direct antimicrobial responses, as well as maturation of antigen-presenting cells and their migration to draining lymph nodes, increased expression of costimulatory molecules, and release of cytokines required for the activation and differentiation of T and B cells.[8] In contrast, HB-AS02 is an aluminum-free preparation containing 20 μg recombinant HBsAg, monophosphoryl lipid, and QS21 (Table 1). QS21 is a highly purified immunostimulant extracted from the bark of the South American *Quillaja saponaria* tree. The mechanism of action of QS21 has not been fully elucidated, but *in vitro* experiments suggest that it also improves antigen presentation.[8]

Three hundred patients who were predialysis or receiving hemodialysis or peritoneal dialysis were randomized to receive

Table 1 | Vaccine formulations

Composition	Standard HBV vaccine (Engerix-B)	HB-AS04 (Fendrix)	HB-AS02
Recombinant HBV surface antigen	20 μg	20 μg	20 μg
Adjuvant	500 μg Al^{3+}	500 μg Al^{3+}, 50 μg monophosphoryl lipid	50 μg monophosphoryl lipid, 50 μg QS21
Excipients	Sodium chloride, water	Sodium chloride, water	Oil-in-water emulsion
Volume/dose	1.0 ml	0.5 ml	0.5 ml
Dose[a]	Double	Single	Single
Schedule[a]	0, 1, 2, and 6 months	0, 1, 2, and 6 months	0, 1, and 6 months

[a]Dose administered and schedule followed in the HBV vaccination comparative trials in chronic kidney disease populations.

either three doses of HB-AS02 (at 0, 1, and 6 months) or four doses of HB-AS04 (at 0, 1, 2, and 6 months). Results showed that HB-AS02 was able to induce more rapid antibody responses, higher peak antibody titers, and prolonged duration of seroprotection compared with HB-AS04. Each of these improvements has specific relevance to CKD populations. Rapid seroconversion is clearly beneficial within the dialysis setting, as the sooner a protective antibody titer is obtained, the lower the cumulative risk of infection. The duration of protection afforded by HBV vaccination—directly proportional to the peak antibody level obtained after vaccination[9]—is also important given that isolated cases of clinically significant HBV infection have been documented in immunocompromised persons with waning anti-HBs titers.[1] Given recommendations for annual anti-HBs testing of CKD patients, and, where relevant, administration of booster doses,[1,2] higher initial peak titers and increased duration of seroprotection would decrease the requirement for, and the costs associated with, booster dosing.

The impressive seroprotection rates observed in both arms of this trial are of interest (anti-HBs >10 IU per liter in >90% of participants in both the HB-AS02 and HB-AS04 groups[5]). Although it is tempting to ascribe this to increased immunogenicity of the vaccine formulations, it should be noted that similarly impressive seroprotection rates were seen in both the experimental and the control (standard HBV vaccine) arms of the earlier HB-AS04 trial (91% versus 84%, respectively; P = not significant).[6] Consequently, it must be considered that the characteristics of these studied populations may have differed in some way from those of more typical CKD populations, in whom markedly poorer seroconversion responses are observed. Particularly, a high proportion of participants were predialysis in both the earlier HB-AS04 versus standard HBV vaccine trial[6] and this trial. Additionally, neither trial reported on other factors known to predict seroconversion, such as dialysis adequacy, hemoglobin, serum albumin, or erythropoietin-stimulating agent usage.

Importantly, Surquin *et al.*[5] did not demonstrate an increase in overall seroprotection rate with use of the new vaccine formulation (seroprotection achieved in 96.4% compared with 91.8% of participants in the HB-AS02 and HB-AS04 groups, respectively, over the 12 months of follow-up; difference, 4.55%, 95% confidence interval −1.25 to 11.22). Similarly, in the earlier HB-AS04 trial, there was no significant difference in overall proportion achieving seroprotection with HB-AS04 compared with standard HBV vaccine.[6] This suggests a similar ability of the newer formulations to induce an immune response compared with the standard HBV vaccine. Although isolated cases of HBV infection have been documented in immunocompromised persons with anti-HBs titers $\leqslant$ 10 IU per liter, it is likely that a seroconversion response allows for the development of immunological memory and subsequent protection in most, as is seen in immunocompetent individuals. This is supported by the rapid anamnestic response to booster dosing in those who have responded previously, regardless of humoral immune status.[1] Thus, while more rapid seroconversion and prolonged duration of immunity are definitely advantageous, the overall ability of an HBV vaccine to achieve protective antibody titers should remain the primary focus.

It is also worth pointing out that other HBV vaccination strategies have shown promise in CKD populations. In randomized controlled trial settings, both intradermal HBV vaccination[10] and the addition of granulocyte–macrophage colony-stimulating factor (GM-CSF)[11] have demonstrated improved ability over standard HBV vaccination to generate a seroprotective antibody response. Further, these agents have been tested in cohorts comprising purely dialysis patients nonresponsive to primary HBV vaccination. Being later in the course of renal disease and having already declared themselves as belonging to the more immunodeficient group of non-responders, such individuals collectively represent a more 'troublesome' group. Testing the efficacy of HB-AS02 in this setting would be of considerable interest.

In conclusion, prevention of HBV infection in CKD populations is an important priority, and progress has been made over recent decades. However, infection rates are still unacceptably high, and further work is required. The article by Surquin *et al.*[5] reports an important initiative in providing primary HBV vaccination to CKD patients. The adjuvanted vaccine HB-AS02 shows clear immunological advantage with regard to its ability to increase speed of seroconversion and duration of seroprotection, both of which are important in CKD populations. However, its ability to improve overall seroconversion response compared with HB-AS04 or standard HBV vaccine remains unproven, as does its ability to perform in dialysis patients non-responsive to primary vaccination. Further study of this is required, as are further trials of alternative strategies aimed at improving vaccination response among CKD patient populations (Figure 1).

DISCLOSURE
The authors declared no competing interests.

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