Scoping review

Hepatitis B vaccination in patients with stage 4/5 chronic kidney disease – a scoping review

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Keywords chronic kidney disease, Hepatitis B virus, clinical practice guidelines, stage 4/5 CKD, Hepatitis B vaccination


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Abstract

Aim This scoping review aims to identify and map the extent of published literature on Hepatitis B vaccination in stage 4/5 chronic kidney disease (CKD) and dialysis patients, the availability of standardised practice guidelines, the optimal CKD stage to commence the vaccination for efficient response, and seroconversion rate.

Background Hepatitis B vaccination remains ‘standard-of-care’ in the haemodialysis (HD) population despite immunological challenges. CKD patients have decreasing immunity as the disease progresses, prompting further research to investigate the response of Hepatitis B vaccination in earlier stages of CKD for better response rate prior to requiring dialysis.

Method This scoping review was conducted using the Arksey and O’Malley (2005) five-stage approach: 1) identifying the research question; 2) identifying the relevant studies; 3) selecting the studies; 4) data charting; and 5) collating, summarising and reporting the results. Medline, PubMed, PubMed Central (PMC) and Cochrane databases were used to access research literature published between 2012–2022.

Results Of the 602 eligible articles, 183 full text papers were identified. There were 41 studies retained for this review which were sorted out into domains relating to the vaccine immunogenicity, vaccine response and clinical practice guidelines. Although there were studies suggesting immunosuppression in declining renal function leads to low vaccine response, most of the studies were focused on HD patients. There have been no large, randomised control trials on optimal vaccination policy in CKD patients. This scoping review provided important knowledge for future studies to explore the efficiency of commencing vaccination at an earlier stage of CKD before reaching dialysis.

Background

Chronic kidney disease

Chronic kidney disease (CKD) is a leading global public health epidemic disease. The global prevalence, as reported in 2019, is estimated to be 13.4% (Lv & Zhang, 2019). In Australia, CKD is a major health concern. The Australian Institute of Health and Welfare (AIHW) report in 2020 showed an estimated 1.7 million Australians over 18 years old have CKD (AIHW, 2020), with a
9% prevalence among non-Indigenous adults and 18% among Aboriginal and Torres Strait Islander people. CKD is a major risk factor for cardiovascular disease, kidney failure and other complications (Usherwood & Lee, 2021). The most common causes of CKD are diabetes (38%), glomerular disease (16%), and hypertension (13%) as reported in July 2020 (AIHW, 2020). CKD is defined as a decline in kidney function due to structural damage. The estimated glomerular filtration rate (eGFR) measures the level of kidney function and determines the stage of kidney disease. The eGFR can be calculated from the blood creatinine result, age, body size and gender using the Modification of Diet in Renal Disease (MDRD) method (Levey, Coresh & Greene, 2006) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, Stevens & Schmiel, 2009). The eGFR is used globally to classify CKD into five stages according to the degree of kidney damage. Figure 1 summarises the five stages of CKD with corresponding eGFR (Kidney Health Australia, 2020).

Renal replacement therapy (RRT) or kidney transplantation is required when the progressive loss of kidney function develops from CKD to end stage kidney disease (ESKD) with uremic symptoms presented as cardiovascular, mental and gastrointestinal disturbances. The RRT includes various forms of dialysis, such as haemodialysis (HD) involving blood purification via a dialysis machine, peritoneal dialysis (PD) using special fluids and the peritoneal membrane, or pre-emptive kidney transplant (Phadke & Khanna, 2011). According to the 44th annual Australia New Zealand Dialysis and Transplant Registry (ANZDATA) report on data collected to 31 December 2020, there is a total of 14,554 patients on dialysis, with 82% on HD and 18% on PD in Australia (ANZDATA Registry, 2021).

Immunodeficiency associated with ESKD has been identified as early as 1999 (Girndt et al., 1999). It is noted in contemporary literature that immune dysfunction in CKD predisposes patients to the increased risk of infection and diminished vaccine response (Syed-Ahmed & Narayanan, 2019; Ma et al., 2021; Fabrizi et al., 2021).

Cohen (2020) explained that kidney failure results in reduced renin, erythropoietin (EPO) and vitamin D production, causing adverse effects on the immune system. The retention of uremic toxins as a result of reduced glomerular filtration in kidney failure can compromise immune cells (Cohen, 2020). Thus, in CKD, especially patients with ESKD undergoing HD, there is increased risk for contracting viral infection due to recurrent blood exposure to the dialysis machine and skin breaches; the most common viral infection is Hepatitis B (Bernieh, 2015).

**Hepatitis B virus**

The Hepatitis B virus (HBV) is a double-stranded DNA blood-borne virus. This covalently closed circular (ccc) DNA virus has a long-lived minichromosome that is resistant to antiviral therapy and can persist on environmental surfaces for up to 7 days. The incubation of HBV is 45–100 days. The virus consists of three primary structural antigens – ‘surface’ (HBsAg), ‘core’ (HBCAg) and ‘e’ (HBeAg). Hepatitis B surface antigens (HBsAg) play a central role in the HBV infection diagnosis (McMahon, 2014; Holt, Locqmrini & Sasadeusz, 2021).

The World Health Organization (WHO) reported chronic HBV infection globally in 296 million people in 2019 (WHO, 2021), with high prevalence (8%) in Africa and South East Asia, intermediate prevalence (2–8%) in Eastern Europe, Japan and Russia, and low prevalence (<2%) in Western Europe, South America and Australia. According to the WHO classification of HBsAg, prevalence is determined as low (<2%), intermediate (2–8%) and high (>8%). Although Australia is classified as low prevalence, higher rates of HBsAg are reported in high-risk groups such as the Aboriginal population and migrants from high-risk countries. In 2022, 0.9% of the Australian population, i.e., an estimated 222,559 people, were living with chronic Hepatitis B infection (B-Positive, 2022).

The spread of HBV infection consists of horizontal and perinatal transmission modes. The horizontal mode is predominantly due to mucosal exposure to infected blood, saliva, seminal and vaginal fluids as well as the re-use of injections or tattooing equipment and body piercing (Bernieh, 2015; Nelson,

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**Figure 1. Classification of CKD according to corresponding eGFR. Reproduced with permission from Kidney Health Australia (2020)**

ACR: albumin-to-creatinine ratio

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Easterbrook & McMahon, 2016). The perinatal transmission is a vertical mode of mother to child at childbirth (Nelson et al., 2016; Veronese et al., 2021).

The consequences of Hepatitis B infection can be acute or chronic. An acute infection can be symptomatic or asymptomatic with the presence of jaundice. Chronic HBV infection is at high risk of cirrhosis and liver cancer (Cancer Council Victoria, 2016). A systemic review by Schweitzer showed 15–25% of people with chronic HBV die from cirrhosis or liver cancer (Schweitzer, 2015).

The most protective method against HBV infection is by vaccination against HBV. The first generation of HBV vaccines consisted of inactivated plasma-derived HBsAg from the asymptotic HBV carrier (Bernieh, 2015). Due to concerns over the transmission of HIV through plasma products, the first generation HBV vaccines were replaced by the second generation vaccines that used synthetic recombinant DNA technique (Jilg et al., 1986; Koumadakis et al., 2018). A third generation recombinant HBV vaccine containing pre-S1 and pre-S2 antigen expressed in mammalian cells has been developed and licensed in some countries only (Schouval, Roggendorf & Roggenden, 2015; Fabrizi, Donato & Messa, 2017; El Hanan et al., 2018). Current vaccination is safe and effective.

A Hepatitis B surface antibody (HBsAb) titre of >10mIU/mL is defined as achieving seroprotection. In healthy individuals, seroprotection levels of 93% have been attained and long lived. The WHO and the Centers for Disease Control and Prevention (CDC) recommend a 6-month vaccination schedule of 20ug at 0, 1, 6 months (Holt et al., 2021).

In Australia, Hepatitis B vaccines are available as monovalent (Engerix-B or H-B-Vax II) or combined vaccines. The recommended dosing for healthy adults is a 6-month schedule of 20ug at 0, 1, 6 months (Department of Health and Aged Care, 2022).

**Hepatitis B in CKD**

Data from the Dialysis Outcomes and Practice Patterns Studies (DOPPS) reported HBV infection prevalence of 0–6.6% in Western Europe, Japan and USA. In the Asia Pacific regions (including Australia and New Zealand) prevalence ranged from 1.3% to 14.6% (Burdick et al., 2003).

In the CKD population, HBV infection is more prevalent in HD patients due to the exposure to blood handling, broken skin integrity from needling and sharing of dialysis equipment, as well as frequent hospitalisation for surgical procedures related to the HD vascular access. Holt et al. (2021) pointed out that HBsAg can also be found in PD fluids; however, transmission in PD populations seems rare (Holt et al., 2021).

In a systemic review of HBV outbreaks in dialysis units between 1992–2014, Fabrizi et al. (2015) reported 16 outbreaks in 12 papers involving 118 HD patients, demonstrating that despite rigorous measures, the risk of HBV infection still presents amongst HD patients in more recent years (Fabrizi et al., 2015; Victorian Renal Clinical Network, 2017). Rigorous practice of universal precaution is the single most important method of transmission prevention. Edey et al. (2010) pointed out the risk of infection is also increased when infected HD patients are likely to become carriers (Edey et al., 2010; Ghadini et al., 2012). Active vaccination remains vital against the virus (Garthwaite et al., 2019). As indicated in the literature, as the immune system’s abnormalities directly correspond to the degree of kidney failure, it would be beneficial to conduct a scoping review on the available knowledge relating to Hepatitis B vaccination in the high-risk HD group and stage 4/5 CKD before dialysis sets in as well as exploring for the most effective CKD stage to commence the vaccine.

**Aim**

This scoping review aims to identify and map the extent of published literature relating to Hepatitis B vaccination in stage 4 CKD, stage 5 CKD and dialysis patients. The broad nature of the scoping review focuses on summarising the breadth of evidence to ensure further research in this population group is beneficial. It adds to existing knowledge and informs future research study design, program and policy.

**Methods**

This scoping review was conducted according to the five-stage approach described by Arksey and O’Malley (2005): 1) identifying the research question; 2) identifying the relevant studies; 3) selecting the studies; 4) data charting; and 5) collating, summarising and reporting the results.

**Stage 1: identifying the research questions**

The broad research questions in the scoping process include:

- What is known about Hepatitis B vaccination in chronic kidney disease?
- What is the immunogenicity of the Hepatitis B vaccine in CKD?
- What is the Hepatitis B vaccination response in CKD?
- What is known about Hepatitis B vaccination in stage 4/5 CKD?
- What is the availability of established clinical practice guidelines for Hepatitis B vaccination in CKD?

**Stage 2: identifying the relevant studies**

Medline, PubMed, PubMed Central (PMC) and Cochrane databases were used to access research literature published between 2012–2022 on Hepatitis B vaccination for patients with CKD. Some historical literature that set milestones on Hepatitis B vaccine were also included (CDC, 1982; Jilg et al., 1986; Girndt et al., 1999). An example of a search strategy for the PubMed database included using search terms “Chronic
Kidney Disease”, “Hepatitis B Virus”, “Immunisation”, and “Guidelines”.

Inclusion criteria:
• Population: adults with stage 4/5 CKD including dialysis.
• Study designs: full text published literature, systemic reviews, meta-analysis, case reports.
• Literature vintage: all peer reviewed studies that describe Hepatitis B vaccination in CKD published in English between 2012–2022 and grey literature such as fact sheets.

Exclusion criteria:
• Hepatitis B vaccination related to renal transplant recipients.
• Studies related to paediatric CKD patients.
• Studies older than 10 years.
• Studies not published in English.

Stage 3: selecting the studies
Studies and reviews that reported relevant data on Hepatitis B vaccination for CKD patients were included. Items such as immunogenicity of Hepatitis B, Hepatitis B vaccination response in stage 4/5 CKD patients, published clinical practice guidelines for Hepatitis B vaccination were included. Article selection progress is shown in Figure 2.

Stage 4: data charting
The following data from eligible articles was abstracted: the surname of the first author, year of publication, study design, study population, study setting, brief findings, outcomes and recommendations.

Stage 5: collating, summarising and reporting the results
The database search identified 602 articles; after screening titles and abstracts, 183 full-text papers were assessed for eligibility and 41 studies were retained for this review. The papers were further sorted out into the five content domains as shown in Table 1:

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Hepatitis B vaccination in CKD</td>
</tr>
<tr>
<td>2</td>
<td>Immunogenicity of Hepatitis B vaccines in CKD</td>
</tr>
<tr>
<td>3</td>
<td>Hepatitis B vaccination response in CKD</td>
</tr>
<tr>
<td>4</td>
<td>Hepatitis B vaccination in stage 4/5 CKD</td>
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<tr>
<td>5</td>
<td>Clinical practice guidelines for Hepatitis B vaccination in CKD</td>
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</tbody>
</table>

Discussion
Hepatitis B vaccination in CKD
Since its inception in 1982, the Hepatitis B vaccine remains the best protection against HBV (CDC, 1982). Grzegorzewska reported a 99% response rate in the general population with long lived immunity, while in patients with CKD it is less effective and does not provide sustained immunity (Grzegorzewska, 2012). Fabrizi et al., pointed out CKD patients have suboptimal response. Studies have demonstrated multiple approaches and effects to improving Hepatitis B vaccination in HD patients – Holt suggested increasing vaccine dose from 20ugm to 40ugm (Holt et al., 2021) while others proposed to increase the frequency from 0, 1, 6 months to 0, 1, 2, 6 months (Fabrizi et al., 2015; da Silva et al., 2018; Komadakis et al., 2018). A systemic review by Yousef et al. (2015) on intradermal (ID) versus intramuscular (IM) technique demonstrated the ID technique enhanced vaccine response by direct dendritic cell stimulation; however, this study only included those who did not respond to the primary dose given using the IM technique, so it is not clear whether the ID technique was effective if given as the primary dose (Yousef et al., 2015). The use of
Table 1. Collating, summarising and reporting the results in five domains

<table>
<thead>
<tr>
<th>Domain 1: Hepatitis B vaccination in CKD</th>
<th>Author / year</th>
<th>Study design</th>
<th>Study area</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Grzegorzewska (2012)</td>
<td>Review article</td>
<td>CKD</td>
<td>Indications for when, why and how to vaccinate CKD patients</td>
<td></td>
</tr>
<tr>
<td>Yousaf et al. (2015)</td>
<td>System review</td>
<td>HD</td>
<td>ID stimulate dendritic cells to promote vaccine response</td>
<td></td>
</tr>
<tr>
<td>Kosmadakis et al. (2018)</td>
<td>Narrative review</td>
<td>HD</td>
<td>Suggest higher doses and increase frequency</td>
<td></td>
</tr>
<tr>
<td>Haddiya (2020)</td>
<td>Discussion</td>
<td>CKD</td>
<td>Varied protocols, absence of optimal vaccination policy</td>
<td></td>
</tr>
<tr>
<td>Nadeem et al. (2021)</td>
<td>Observational</td>
<td>HD</td>
<td>Short study (4 months), unsatisfactory vaccination status</td>
<td></td>
</tr>
<tr>
<td>Holt et al. (2021)</td>
<td>Meta analysis</td>
<td>HD</td>
<td>Suggest higher dose 40μg/m vs 20μg/m</td>
<td></td>
</tr>
<tr>
<td>Fabrizi et al. (2021)</td>
<td>Narrative review</td>
<td>CKD</td>
<td>Multiple approaches in Hepatitis B vaccine</td>
<td></td>
</tr>
<tr>
<td>Ma et al. (2021)</td>
<td>Review article</td>
<td>CKD</td>
<td>Current state of knowledge regarding vaccination in CKD</td>
<td></td>
</tr>
<tr>
<td>Hettenbaugh et al. (2021)</td>
<td>Quality improvement</td>
<td>HD</td>
<td>Low response rates in HD patients, consider earlier start</td>
<td></td>
</tr>
<tr>
<td>Mysore et al. (2021)</td>
<td>Quality improvement</td>
<td>CKD</td>
<td>Vaccination strategies typically target HD patients</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain 2: Immunogenicity of Hepatitis B vaccines in CKD</th>
<th>Author / year</th>
<th>Study design</th>
<th>Study area</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somi &amp; Hajpour (2012)</td>
<td>Review</td>
<td>HD</td>
<td>Impaired immune response to HBV in HD patients</td>
<td></td>
</tr>
<tr>
<td>Poovorawan et al. (2012)</td>
<td>Long-term study</td>
<td>Healthy population</td>
<td>20-year study on healthy population</td>
<td></td>
</tr>
<tr>
<td>Ni et al. et al. (2012)</td>
<td>Long-term study</td>
<td>Healthy population</td>
<td>25-year study on healthy population</td>
<td></td>
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<tr>
<td>Mendy et al. (2013)</td>
<td>Long-term study</td>
<td>Healthy population</td>
<td>20-year study on healthy population</td>
<td></td>
</tr>
<tr>
<td>Betjes (2013)</td>
<td>Review</td>
<td>HD</td>
<td>Uremia is associated with lymphoid cell dysfunction</td>
<td></td>
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<tr>
<td>Bruce et al. (2016)</td>
<td>Long-term study</td>
<td>Healthy population</td>
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<tr>
<td>Gasim et al. (2015)</td>
<td>Review</td>
<td>HD</td>
<td>Immune response explained, various means to improve response, including adjuvants in HD patients</td>
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</tr>
<tr>
<td>El Hanan et al. (2018)</td>
<td>RTC</td>
<td>HD</td>
<td>Factors relating to defective immunity, HD patients</td>
<td></td>
</tr>
<tr>
<td>Fabrizi et al. (2017)</td>
<td>Systemic</td>
<td>CKD</td>
<td>Higher doses of vaccine required for HD patients</td>
<td></td>
</tr>
<tr>
<td>Cohen (2020)</td>
<td>Review</td>
<td>Immunology renal</td>
<td>Uremic toxins exert detrimental effects on immune cells</td>
<td></td>
</tr>
<tr>
<td>Ma et al. (2021)</td>
<td>Review</td>
<td>CKD</td>
<td>Explain immunogenicity of HBV vaccines</td>
<td></td>
</tr>
<tr>
<td>Fabrizi et al. (2021)</td>
<td>Review</td>
<td>Pathophysiology</td>
<td>Use of adjuvant, use of boosters</td>
<td></td>
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<tr>
<th>Domain 3: Hepatitis B vaccination response in CKD</th>
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<th>Study area</th>
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<tbody>
<tr>
<td>Ghadiani et al. (2012)</td>
<td>Prospective study</td>
<td>CKD stages 3–4 HD and staff</td>
<td>Various response rate in three groups</td>
<td></td>
</tr>
<tr>
<td>Asfar (2013)</td>
<td>Retrospective study</td>
<td>HD Patients</td>
<td>EPO resistance and HBV vaccine response</td>
<td></td>
</tr>
<tr>
<td>Grzegorzewska (2012)</td>
<td>Review</td>
<td>HD patients</td>
<td>Response rate 40–50%</td>
<td></td>
</tr>
<tr>
<td>Malaki (2017)</td>
<td>Cross section study</td>
<td>HD patients</td>
<td>Factors affecting seroprotection</td>
<td></td>
</tr>
<tr>
<td>da Silva et al. (2018)</td>
<td>RCT</td>
<td>CKD patients</td>
<td>T cell defects contributed to impaired seroconversion</td>
<td></td>
</tr>
<tr>
<td>Udomkarnjananun et al. (2020)</td>
<td>Systemic review</td>
<td>HD patients</td>
<td>Factors associated with response in dialysis patients</td>
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<tr>
<td>Mysore et al. (2021)</td>
<td>Quality improvement</td>
<td>CKD patients</td>
<td>Nurse-led approach to improve vaccination</td>
<td></td>
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<tr>
<td>Han et al. (2021)</td>
<td>Retrospective study</td>
<td>HD patients</td>
<td>Poor vaccine response is associated with short sleep</td>
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<tr>
<th>Domain 4: Hepatitis B Vaccination in stage 4/5 CKD</th>
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<th>Study area</th>
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<tbody>
<tr>
<td>Hettenbaugh et al. (2021)</td>
<td>5-year study</td>
<td>Stage 4 CKD</td>
<td>Conversion rate 33–60%</td>
<td></td>
</tr>
<tr>
<td>Ghadiani et al. (2012)</td>
<td>Prospective study</td>
<td>CKD stages 3–4 HD and staff</td>
<td>Recommend vaccination as soon as CKD is diagnosed</td>
<td></td>
</tr>
<tr>
<td>Mysore et al. (2021)</td>
<td>Quality improvement</td>
<td>Stage 4–5 CKD</td>
<td>Aim to promote awareness</td>
<td></td>
</tr>
<tr>
<td>Mulley et al. (2017)</td>
<td>Quasi randomised</td>
<td>CKD 3–5</td>
<td>Double dose vs standard dose</td>
<td></td>
</tr>
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</table>

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<tr>
<th>Domain 5: Clinical practice guidelines for Hepatitis B vaccination in CKD</th>
<th>Author / year</th>
<th>Study design</th>
<th>Study area</th>
<th>Findings</th>
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<tbody>
<tr>
<td>National Kidney Foundation (2013)</td>
<td>Guidelines (NKF-KDOQI)</td>
<td>CKD</td>
<td>No recommendations for Hepatitis B vaccination</td>
<td></td>
</tr>
<tr>
<td>KDIGO (2017)</td>
<td>Guidelines</td>
<td>CKD</td>
<td>Suggest vaccination just prior to dialysis initiation</td>
<td></td>
</tr>
<tr>
<td>Jardine et al. (2019)</td>
<td>Guidelines (KHA-CARI)</td>
<td>CKD</td>
<td>Screening at dialysis initiation or inter-unit transfers</td>
<td></td>
</tr>
<tr>
<td>Garthwaite et al. (2019)</td>
<td>Guidelines (UK Renal Association)</td>
<td>HD patients</td>
<td>Recommend commencing vaccination 2 years before dialysis</td>
<td></td>
</tr>
<tr>
<td>AIHW (2020)</td>
<td>Guidelines</td>
<td>CKD and HD</td>
<td>Recommend larger doses for CKD</td>
<td></td>
</tr>
<tr>
<td>Haddiya (2020)</td>
<td>Review</td>
<td>CKD and HD</td>
<td>Varied global immunisation protocols with absence of optimal vaccination policies</td>
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</table>
an adjuvant (e.g. Levamisole) to increase seroprotection rate was also explored by Fabrizi et al. (2021) and Ma et al., (2021). Fabrizi et al. (2021) also emphasised the importance of vaccination in HBV infection management, but only focused on dialysis patients, providing little data on stage 4/5 CKD patients (Fabrizi et al., 2021; Mysore et al., 2021).

**Immunogenicity of Hepatitis B vaccine in CKD**

CKD and ESKD patients have suboptimal response and shorter duration of seroprotection due to immune deficiency (Somi & Hajpour, 2012; Betjes, 2013; Grzegorzewska, 2014). Fabrizi et al. (2021) pointed out that it remains unclear how the immune response of CKD patients to HBV can be boosted (Fabrizi et al., 2021). The importance of exploring the immunogenicity of the Hepatitis B vaccine in CKD patients was highlighted by Ma et al. (2021) who explained that for an effective immunisation response, both innate (genetic or natural) immunity and adaptive (acquired) immunity are required. The reduced vaccination response is due to various immunological dysfunctions in CKD such as impaired monocytes endocytosis and maturation, defective antigen, impaired T cell activation and proliferation leading to decreased T cell cytokines and reduced B cell memory (Ma et al., 2021).

Long-term studies in healthy adults have demonstrated sustained immunity for up to 30 years in an Alaskan study (Bruce et al., 2016), 25 years in a Taiwanese study (Ni et al., 2012), 20 years in a Thai study (Poovorawan et al., 2012), and 24 years in a Gambian study (Mendy et al., 2013). However, there was limited long-term immunity study in CKD patients. One article was identified describing a 13-year follow-up study by Pin et al. (2009) on 136 HD patients; the study reported that 32% of responders lost their immunity, with only 18% of the responders remaining seroconverted for 6 years (Pin et al., 2009).

**Hepatitis B vaccination response in CKD**

Ghadiani et al. classified response rates using anti-HBs titres, with <10mIU/mL as non-seroconversion, >10mIU/mL as seroconversion and >100mIU/mL as seroprotective (Ghadiani et al., 2012). da Silva et al. conducted a RCT describing the serological and cellular response to hepatitis vaccination in CKD, and concluded that T cell defects contributed to impaired seroconversion (da Silva et al., 2018). Mysore et al. noted that Hepatitis B vaccination strategies for CKD patients typically target patients on dialysis (Mysore et al., 2021). Response rate in dialysis had been shown to be 40–50% (Grzegorzewska, 2012; Mysore et al., 2021) compared to a 90% response rate in the general population, with 50% of the dialysis responders losing their immunity quicker than the healthy population (Grzegorzewska, 2012).

Elevated serum urea due to a decline in kidney functions has an adverse effect on vaccine response rate (Malaki, 2017). Other factors affecting vaccine response were also investigated; however, the studies were limited to dialysis patients only, such as the systemic review and meta-analysis conducted by Udomkarnjananun et al. (2020) that identified 61 studies that explored the factors associated with immune response in the dialysis patients. This review identified multiple factors affecting the immune response – older age, diabetes, HLA-DR3 status, shorter dialysis time leading to lower dialysis adequacy, poor nutritional status, lower parathyroid hormone (PTH) and lower haemoglobin levels (Udomkarnjananun et al., 2020). EPO use for treating low haemoglobin was also studied by Afsar (2013) in the Turkey Konya State Hospital on 97 HD patients to analyse the relationship between anti-HBs response and EPO resistance. It was concluded there was no association between EPO resistance and Hepatitis B vaccine response (Afsar, 2013). In a retrospective study, Han et al. studied the effect of sleep in adaptive Hepatitis B vaccination response and demonstrated that short sleep duration was associated with poor antibody response to the vaccine (Han et al., 2021).

**Hepatitis B vaccination in stage 4/5 CKD**

Amongst various strategies to improve response rates, commencing the vaccination at earlier CKD stage has been suggested. For example, commencing vaccination earlier at stage 4 CKD (16–29ml/min/1.73m2) and stage 5 CKD (<15ml/min/1.73m2) before dialysis commences, as about 40% of dialysis patients do not develop protective titre of antibodies due to compromised immune system (Grzegorzewska, 2012). However, there was limited literature on commencing vaccination in stage 4/5 CKD. Ghadiani et al. (2012), one of the early proponents of vaccination at an early CKD stage, conducted a study on three groups of participants – Group A: HD patients; Group B: stage 3–4 CKD patients; Group C: healthy medical staff (as control group). The vaccination consisted of a regime of four doses of 40ug on a 6-month schedule (0, 1, 2 and 6 months), IMI in the Deltoid muscle. Results demonstrated seroconversion rates of 44% (Group A), 89.7% (Group B) and 96.2% (Group C) (Ghadiani et al., 2012). Although early CKD stage was studied, Group B consisted of stage 3–4 CKD patients who have a wide range of eGFR spanning from 16–60ml/min/1.73m2. From this data it is difficult to judge if commencing at stage 3 or at stage 4 is more beneficial or effective. Mulley et al. conducted a systemic review on stage 3–5 CKD comparing standard dose vaccination to double dosing, but found no increase in seroconversion in the double dose vaccination (Mulley, Le & Ives, 2017).

A more current study by Hettenbaugh et al. investigated the vaccination at stage 4/5 CKD over a 5-year period in Omaha, USA. A total of 198 patients were screened, with 56 eligible and 37 completing the course. The seroconversion rate ranged...
from 33–60%, with one of two US FDA approved vaccines (ReCombivex™ or Engerix™). The study concluded the importance of awareness by nephrologists and nursing staff to vaccinate patients at earlier stage of CKD, at stage 4/5, prior to the onset of dialysis (Hettenbaugh et al., 2021).

Clinical practice guidelines in Hepatitis B vaccination in CKD

HBV causes serious disease such as acute hepatitis, liver fibrosis and liver cancer. Hepatitis B infection is difficult to treat, so prevention by vaccination is the most effective way. Despite widespread HBV vaccine use since 1982 with a clear benefit to Hepatitis B vaccination in CKD patients – in particular the immunocompromised HD patients who are at higher risk of the infection due to frequent blood exposure and skin breaches – there have been limited published studies on vaccination implementation strategies and clinical practice guidelines (Mysore, 2021). Vaccination regime variations and a lack of optimal policy between countries continues to be recognised in recent literature (Haddiya, 2020; Nadeem et al., 2021). Although the CDC guidelines strongly recommend all CKD patients should be vaccinated against HBV, studies have shown the range of CKD patients vaccinated to vary greatly, between 20–73.1%: 20% in Pakistan (Nadeem et al., 2021); 31% in Belgium (Boey et al., 2020); 46% in the UK (Ray et al., 2002); and 73.1% in the US (Ayoila et al., 2019).

Global organisations such as the National Kidney Foundation Kidney Dialysis Outcome Quality Initiative Guidelines (NKF-KDOQI) (National Kidney Foundation, 2013) and Kidney Disease Improving Global Outcomes (KDIGO, 2017) are involved in developing and implementing evidence-based clinical practice guidelines in kidney disease. The NKF-KDOQI showed no recommendations for Hepatitis B vaccination amongst other 13 published renal guidelines (National Kidney Foundation, 2013). The KDIGO guidelines have developed 11 clinical practice guidelines on renal topics since 2008 to 2017; however, there is no specific practice guidelines on Hepatitis B vaccination except to suggest vaccination just prior to initiation of dialysis. The UK Renal Association recommends screening all patients starting HD, preferably to commence vaccination 2 years before dialysis as well as vaccinating patients returning to HD from failed PD (Garthwaite et al., 2019). No recommendations were noted in the Canadian Society of Nephrology or the European Best Practice Guidelines.

In Australia, the Australian Immunisation Handbook (Department of Health and Aged Care, 2018) recommend HD patients and CKD patients nearing dialysis to receive larger than usual doses of Hepatitis B vaccine (40ugm in CKD patients compared to 20ugm in the general population); however, there is no further clarity to what CKD stage to commence vaccination, nor the booster regime for non-responders <10IU/mL (Department of Health and Aged Care, 2018). The Australian renal guideline (the Kidney Health Australia: Caring for Australian with Renal Impairments (KHA-CARI) guidelines) for infection control for HD units recommended standard precautions, screening of HBV at the start of HD or transferring between units (Jardine et al., 2019).

Conclusion

From the literature presented, the immune system abnormalities correlate with the degree of kidney failure – CKD patients not yet on dialysis may have a stronger immune system and higher antibody response to the HBV vaccine. This review provided awareness about why it is so important to continually vaccinate against HBV; although there has been a substantial decline in HBV infection in HD patients – likely due to blood donor screening and reduced use of blood transfusions requirement related to correction of renal anaemia with EPO use (Somi & Hajpour, 2012) – outbreaks of Hepatitis B still occur despite rigorous precaution measures (Victoria Renal Clinical Network, 2017). There have also been studies showing that Hepatitis B vaccination was not routinely implemented. In the UK, a published study showed only 46% of dialysis units were routinely immunising patients according to the Renal Association’s recommendation, while only 20% patients were vaccinated in a study conducted in Pakistan (Nadeem et al., 2021). Besides preventing transmission in the dialysis unit, successful Hepatitis B vaccination also allows for renal transplantation recipient from an anti-HBc positive donor (Holt et al., 2021). Moreover, it is important to note that not only HD patients are at high risk of the infection, they are also at increased risk for becoming HBV carriers (Edey et al., 2010; Ghadini et al., 2012).

This scoping review provided broad knowledge to fulfil the research questions as set out in the aims of the review as well as identifying the parameters and gaps in the literature. There was ample literature describing Hepatitis B vaccination in CKD, the immunogenicity of the vaccine, and the diminishing response as the kidney function declines with escalated inflammatory and immunological changes. In order to improve the vaccine response, many strategies such as increasing the dosing, increasing the frequencies, variations of schedules, and the use of adjuvants were found in the literature. There were also few recommendations in commencing the vaccine in earlier stages of CKD; however, the optimal strategy for vaccination remains unclear, with limited standardised clinical practice guidelines available to guide clinicians. The results of the review indicated the need for further studies to define a stage of CKD and standardise clinical practice guidelines for optimal Hepatitis B vaccination management.

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