

## Q: What is the hepatitis B vaccination regimen in chronic kidney disease?

**A:** For patients age 16 and older with advanced chronic kidney disease (CKD), including those undergoing hemodialysis, we recommend a higher dose of hepatitis B virus (HBV) vaccine, more doses, or both. Vaccination with a higher dose may improve the immune response. The hepatitis B surface antibody (anti-HBs) titer should be monitored 1 to 2 months after completion of the vaccination schedule and annually thereafter, with a target titer of 10 IU/mL or greater. For patients who do not develop a protective antibody titer after completing the initial vaccination schedule, the vaccination schedule should be repeated.

### RECOMMENDED DOSES AND SCHEDULES

#### Recommendation 1

Give higher vaccine doses, increase the number of doses, or both.

**Rationale.** Patients with CKD, especially those on hemodialysis, are in an immunocompromised state and thus are less likely to achieve protective anti-HBs levels after vaccination with standard dosages.<sup>1-3</sup> Two main vaccine formulations are available (Table 1). Recombivax-HB contains 40 µg/mL and is given in a 3-dose schedule at 0, 1, and 6 months. Engerix-B contains a standard dose of 20 µg/mL and should be given in a 4-dose schedule at double the standard dose (ie, a total of 40 µg/mL). Both regimens are recommended in the 2017 update of the United States Advisory Committee on Immunization Practices (ACIP) recommendations for adult immunization schedule.<sup>4</sup>

#### Recommendation 2

A 4-dose regimen may provide a better antibody response than a 3-dose regimen. (Note: This recommendation applies only to Engerix-B; 4 doses of Recombivax-HB would be an off-label use.)

**Rationale.** The US Centers for Disease Control and Prevention reported that after completion of a 3-dose vaccination schedule, the median proportion of patients developing a protective antibody response was 64% (range 34%–88%) vs a median of 86% (range 40%–98%) after a 4-dose schedule.<sup>3</sup>

Lacson et al<sup>5</sup> compared antibody response rates after 3 doses of Recombivax-HB and after 4 doses of Engerix-B and found a better response rate with the 4-dose schedule. The rate of persistent protective anti-HBs titer after 1 year was 77% for Engerix-B vs 53% for Recombivax-HB.

Agarwal et al<sup>6</sup> evaluated response rates in patients who had mild CKD (serum creatinine levels 1.5–3.0 mg/dL), moderate CKD (creatinine 3.0–6.0 mg/dL), and severe CKD (creatinine > 6.0 mg/dL). The seroconversion rates after 3 doses of 40-µg HBV vaccine were 87.5% in those with mild CKD, 66.6% in those with moderate CKD, and 35.7% in those with severe disease. After a fourth dose, rates improved significantly to 100%, 77%, and 36.4%, respectively.

#### Recommendation 3

In patients with CKD, vaccination should be done early, before they become dependent on hemodialysis.

**Rationale.** Patients with advanced CKD may have a lower seroconversion rate. Fraser et al<sup>7</sup> found that after a 4-dose series, the seroprotection rate in adult prehemodialysis patients with serum creatinine levels of 4 mg/

Use higher doses, more doses, or both strategies, and vaccinate at earlier stages of CKD

dL or less was 86%, compared with 37% in patients with serum creatinine levels above 4 mg/dL, of whom 88% were on hemodialysis.<sup>7</sup>

In a 2003 prospective cohort study by DaRoza et al,<sup>8</sup> patients with higher levels of kidney function were more likely to respond to HBV vaccination, and the level of kidney function was found to be an independent predictor of seroconversion.<sup>8</sup>

A 2012 prospective study by Ghadiani et al<sup>9</sup> compared seroconversion rates in patients with stage 3 or 4 CKD vs patients on hemodialysis, with medical staff as controls. The authors reported seroprotection rates of 26.1% in patients on hemodialysis, 55.2% in patients with stage 3 or 4 CKD, and 96.2% in controls. They concluded that vaccination is more likely to induce seroconversion in earlier stages of kidney disease.<sup>9</sup>

#### ■ MONITORING THE RESPONSE TO VACCINATION AND REVACCINATION

Testing after vaccination is recommended to determine response. Testing should be done 1 to 2 months after the last dose of the vaccination schedule.<sup>1-3</sup> Anti-HBs levels 10 IU/mL and greater are considered protective.<sup>10</sup>

Revaccination with a full vaccination series is recommended for patients who do not develop adequate levels of protective antibodies after completion of the vaccination schedule.<sup>2</sup> Reported response rates to revaccination have varied from 40% to 50% after 2 or 3 additional intramuscular doses of 40 µg, to 64% after 4 additional intramuscular doses of 10 µg.<sup>3</sup> Serologic testing should be repeated after the last dose of the vaccination series, as serologic testing after only 1 or 2 additional doses appears to be no more cost-effective.<sup>2,3</sup>

To the best of our knowledge, no data exist to indicate that in nonresponders, further doses given after completion of 2 full vaccination schedules would induce an antibody response.

#### ■ ANTIBODY PERSISTENCE AND BOOSTER DOSES

Antibody levels fall with time in patients on hemodialysis. Limited data suggest that in patients who respond to the primary vaccination series, antibodies remain detectable for 6 months in 80% to 100% (median 100%) of

TABLE 1

#### Recommended vaccination regimens for hepatitis B virus in chronic kidney disease

| Vaccine              | Regimen  |
|----------------------|--|
| <b>Recombivax-HB</b> | 40 µg intramuscularly, at 0, 1, and 6 months   |
| <b>Engerix-B</b>     | 40 µg (ie, double the standard 20-µg dose) intramuscularly, at 0, 1, 2, and 6 months |

patients and for 12 months in 58% to 100% (median 70%) of patients.<sup>3</sup> The need for booster doses should be assessed by annual monitoring.<sup>2,11</sup> Booster doses should be given when the anti-HBs titer declines to below 10 IU/mL. Limited data indicate that nearly all such patients would respond to a booster dose.<sup>3</sup>

#### ■ OTHER WAYS TO IMPROVE VACCINE RESPONSE

Other strategies to improve vaccine response, such as the addition of adjuvants or immunostimulants, have shown variable success.<sup>12</sup> Intradermal HBV vaccination in patients on chronic hemodialysis has also been proposed. The efficacy of intradermal vaccination may be related to the dense network of immunologic dendritic cells within the dermis. After intradermal administration, the antigen is taken up by dendritic cells residing in the dermis, which mature and travel to the regional lymph node where further immunostimulation takes place.<sup>13</sup>

In a systematic review of four prospective trials with a total of 204 hemodialysis patients,<sup>13</sup> a significantly higher proportion of patients achieved seroconversion with intradermal HBV vaccine administration than with intramuscular administration. The authors concluded that the intradermal route in primary nonresponders undergoing hemodialysis provides an effective alternative to the intramuscular route to protect against HBV infection in this highly susceptible population.

Additional well-designed, double-blinded, randomized trials are needed to establish clear guidelines on intradermal HBV vaccine dosing and vaccination schedules. ■

**In CKD, vaccinate against HBV early, before the patient becomes dependent on hemodialysis**

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