Immunogenicity of Augmented Compared With Standard Dose Hepatitis B Vaccine in Pediatric Patients on Dialysis: a Midwest Pediatric Nephrology Consortium Study

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Abstract

Background and objectives Patients on maintenance dialysis have a higher risk of unresponsiveness to hepatitis B vaccination and loss of hepatitis B immunity. Adult guidelines recommend augmented dosing (40 mcg/dose), resulting in improved response in adults. We sought to determine whether children on dialysis mount a similar antibody response when given standard or augmented dosing of hepatitis B vaccine.

Design, setting, participants, & measurements This is a retrospective review of patients on dialysis aged <19 years from May 1, 2008 to May 1, 2013 at 12 pediatric dialysis units. Hepatitis B surface antibody (HBsAb) titers $\geq 10$ mIU/ml were defined as protective.

Results A total of 187 out of 417 patients received one or more hepatitis B vaccine boosters. The median age was 13 years; the cohort was 57% boys and 59% white. Booster dose or HBsAb titers were missing in 17 patients. Conversion to protective HBsAb titers was achieved in 135 out of 170 patients (79%) after their first single-dose booster or multidose booster series. In patients receiving a single-dose booster, the response rate was 53% (nine out of 17) after a 10 mcg dose, 86% (65 out of 76) after a 20 mcg dose, and 65% (17 out of 26) after a 40 mcg hepatitis B vaccine dose. In patients receiving a multidose booster series, the response rate was 95% (19 out of 20) after a 10 mcg/dose series, 83% (20 out of 24) after a 20 mcg/dose series, and 71% (five out of seven) after a 40 mcg/dose series. Patients receiving a multidose booster series had a response rate of 86% (44 out of 51), compared with 76% (91 out of 119) in patients receiving a single-dose booster ($P=0.21$). Twenty-seven patients received more than one single-dose booster or multidose series, and 26 out of 27 (96%) eventually gained immunity after receiving one to three additional single-dose boosters or multidose booster series.

Conclusions There was no clear gradient of increasing seroconversion rate with increasing vaccine dose in this cohort of pediatric patients on dialysis.

Current CDC guidelines recommend standard age-appropriate dosing of hepatitis B booster vaccine in children on hemodialysis (5 mcg/dose for age 0–10 years and 10 mcg/dose for age 11–19 years). However, the guidelines also state that “higher doses might be more immunogenic” (5). Adult guidelines recommend augmented dosing (40 mcg/dose), and augmented dosing results in improved response in adults, although the overall response rate is still poor (6). However, no data are available to assess whether higher doses are more immunogenic in pediatric patients on dialysis (7).

Current practice among pediatric nephrologists is varied. Many pediatric nephrology centers in the United States practice augmented single-dose hepatitis B booster vaccination using 20–40 mcg/dose, whereas others use standard age-appropriate dosing or multidose booster series for all patients. Of the 27 Midwest Pediatric Nephrology Consortium centers that responded to a survey, eight centers use standard dosing and 19 use augmented dosing (C. Nailescu, unpublished observations). Given the variation in practice across centers, evidence-based guidelines would be helpful.

The goals of this study were (1) to determine the incidence of loss of primary hepatitis B immunity in children on dialysis, (2) to determine the incidence of hepatitis B immunity after augmented and standard hepatitis B vaccine dosing in children on dialysis, and (3) to determine risk factors for nonresponsiveness to hepatitis B vaccination. We hypothesized that children on dialysis mount a similar antibody response whether given standard or augmented dosing of hepatitis B vaccine.

Materials and Methods

We performed a multicenter retrospective chart review of hepatitis B vaccine response in patients on chronic hemodialysis or peritoneal dialysis aged <19 years, from May 1, 2008 to May 1, 2013 at 12 pediatric nephrology centers in the United States with differing practices in hepatitis B booster vaccine dosing. Patients who had completed their primary hepatitis B vaccine series and who were patients on prevalent dialysis were eligible for inclusion. HBsAb titers are collected at least annually in these pediatric dialysis centers. For patients who did not receive a hepatitis B booster vaccination during the study, the most recent HBsAb titer value was collected, along with other laboratory and clinical data from within 6 weeks of the HBsAb titer. Standard dose hepatitis B vaccination was defined as vaccine dose of 5 or 10 mcg/injection. Augmented dose hepatitis B vaccination was defined as vaccine dose of 20 or 40 mcg/injection. Multidose booster vaccination series was defined as the administration of two or three hepatitis B vaccine injections without checking HBsAb titers between vaccine doses (i.e., a two- or three-dose booster vaccine series). If a patient failed to respond to a single vaccine injection and was given another single vaccine injection, this was entered into the database as two separate single-dose boosters. This would not meet the definition of multidose booster series because titers were checked after the first vaccine injection. If a patient received either two or three vaccine injections in a planned fashion with no titers checked between the vaccine injections, this was counted as one multidose booster series. Some patients received a single-dose booster, failed to respond, and then received a multidose booster series (two or three additional vaccine injections with no titer checked between vaccine injections). We did not separate these patients from patients given a multidose booster series per center protocol.

For multidose booster series, the dose reported represents the dose of each hepatitis B vaccine injection, rather than the cumulative dose. For patients who received one or more hepatitis B booster vaccinations during the study period, HBsAb titer values before and after each vaccine or vaccine series were collected, along with the relevant clinical data nearest the date of the vaccination.

Study data were collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Indiana University. REDCap is a secure, web-based application designed to support data capture for research studies (8). The study was approved by the Institutional Review Board of Indiana University, as well as all of the other participating institutions. All participating institutions belonged to the Midwest Pediatric Nephrology Consortium.

Statistical Analyses

Analyses were carried out using SPSS software versions 22.0 and 24.0. For unadjusted analyses, categorical variables were analyzed with Fisher exact and chi-squared tests, and continuous variables were tested using the Mann–Whitney U test, as each continuous variable was non-normally distributed. Statistical significance was defined as $P<0.05$.

Multivariate analysis was conducted using logistic regression models. The primary outcome was vaccine response, defined as an increase in HBsAb titer from low/negative (<10 mIU/ml) to positive (≥10 mIU/ml). This analysis was on the basis of the first single-dose booster or multidose booster series each patient received during the study period, so that no patient was represented twice in the analysis. Hierarchical models were constructed to choose the most appropriate model. Variables with $P<0.10$ were included in the model as covariates. Variables thought to have a clinical association with the outcome were included in the analysis even if the $P$ value exceeded 0.10.

A second logistic regression model was conducted to investigate factors predictive of which patients required booster vaccination. This secondary outcome was defined as unique patients who required booster vaccination (HBsAb titer <10 mIU/ml) versus those who retained protection from their primary titer and did not receive hepatitis B booster vaccination (HBsAb titer ≥10 mIU/ml without booster vaccination).

Results

We included 417 unique patients at 12 pediatric dialysis units in the United States. The median age was 13 years, 57% of patients were boys, and 59% of patients were white. Dialysis modality was hemodialysis in 52% and peritoneal dialysis in 48% of patients. Median dialysis vintage (time on dialysis) was 0.53 years, and median time since primary hepatitis B vaccine series was 9.2 years.
The hepatitis B vaccine was given as a single-dose or multidose booster series in 187 patients, of which 170 did not receive a booster vaccination. Excluding this center, we observed that 157 (86% of unique patients lost immunity to hepatitis B and received a booster vaccination (Table 1). The rate of immunity loss was 40% (78 out of 196) in patients on hemodialysis, and 41% (77 out of 188) in patients on peritoneal dialysis.

Patients who retained versus those who lost immunity were compared in a multivariate logistic regression model to determine which factors were associated with loss of immunity. Significant factors predicting whether a patient would require booster vaccination were time elapsed since primary series, dialysis adequacy (Kt/V), age and medical center. The proportion of patients requiring booster vaccination at different medical centers varied widely, ranging from 9% to 76%. The predictive capability of the model was not improved by the addition of age, sex, dialysis modality, race/ethnicity, dialysis vintage, dialysis adequacy, serum albumin, white blood cell count, hemoglobin, parathyroid hormone, C-reactive protein, or normalized protein catabolic rate (data not shown).

The hepatitis B vaccine was given as a single-dose or multidose booster series in 187 patients, of which 170 patients had data suitable for analysis (Figure 1). The primary analysis of response to vaccination was on the basis of the first single-dose booster or multidose booster series each patient received during the study period, so that no patient was represented twice in the analysis. The response rate was 79% overall (135 out of 170). Vaccine dose versus serologic response is shown in Figure 2. There was no clear gradient of increasing serologic response with increasing vaccine dose.

Response rate to multidose booster series was 86% (44 out of 51) compared with 76% (91 out of 119) in patients receiving a single-dose booster (P=0.21). In patients receiving a multidose booster series of 10 mcg/dose, the response rate was 95% (19 out of 20) versus 53% (nine out of 17) after a single-dose booster of 10 mcg (P=0.005). The difference was not statistically significant for 20 mcg/dose: 83% (20 out of 24) responded to multidose booster series versus 86% (65 out of 76) to a single-dose booster (P=0.75). Likewise, for 40 mcg/dose, 71% (five out of seven) responded to a multidose booster series versus 65% (17 out of 26) to a single-dose booster (P=0.99).

To investigate which factors were predictive of serologic response to vaccination, a logistic regression analysis was performed with serologic response as the dependent variable. Hierarchical models were constructed to select the most parsimonious model. The following factors were included in the final model: receipt of immunosuppressive medications, age, and a variable combining both vaccine dose and whether the booster was given as a single-dose booster or a multidose booster series (Table 2). The model was significant, with a chi-squared test value of 18.1 (P=0.01). It correctly classified 81% of cases, explaining 16% of the variation in serologic response to vaccination (Nagelkerke pseudo-R² =0.16). Only the variable combining both vaccine dose and whether the booster was given as a single-dose booster or multidose booster series was significant in the model (P=0.04). Receipt of a 10 mcg multidose booster series had a higher odds of vaccine response when compared with a 10 mcg single-dose booster (aOR, 16.3; 95% CI, 1.7 to 153.4; P=0.02). Likewise, 20 mcg single dose had higher odds of resulting in vaccine response than 10 mcg single dose (aOR, 5.2; 95% CI, 1.6 to 16.9; P=0.006), as did the 20 mcg multidose booster series (aOR, 5.1; 95% CI, 1.2 to 22.5; P=0.03). However, neither the 40 mcg single-dose booster nor 40 mcg multidose booster series demonstrated statistically higher odds of seroconversion than the reference 10 mcg single-dose booster (Table 2).

Neither receipt of immunosuppressive medications nor age was a significant contributor to the model—they were included because they are thought to have a clinical association with vaccine response. Immunosuppressive medications received are listed in Supplemental Table 1. The following independent variables did not significantly improve the model and were excluded from the final model: sex, race, ethnicity, dialysis vintage, time since primary series, dialysis adequacy (Kt/V), age×dose

Table 1. Comparison of patients who lost versus retained immunity after primary hepatitis B vaccination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Booster Needed (n=230)</th>
<th>Received Booster (n=157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr*</td>
<td>13 [3–17]</td>
<td>13 [8–16]</td>
<td>0.36</td>
</tr>
<tr>
<td>Boys</td>
<td>56% (129/230)</td>
<td>55% (86/157)</td>
<td>0.84</td>
</tr>
<tr>
<td>White</td>
<td>61% (120/230)</td>
<td>59% (93/157)</td>
<td>0.29</td>
</tr>
<tr>
<td>Modality: peritoneal dialysis</td>
<td>49% (111/229)</td>
<td>50% (77/155)</td>
<td>0.84</td>
</tr>
<tr>
<td>Modality: hemodialysis</td>
<td>51% (118/229)</td>
<td>50% (78/155)</td>
<td>0.84</td>
</tr>
<tr>
<td>Time since primary series, yr*</td>
<td>6.9 [1.1–13.1] (n=214)</td>
<td>10.5 [4.7–13.9] (n=138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis vintage, yr*</td>
<td>0.8 [0.2–1.9] (n=217)</td>
<td>0.4 [0.1–1.2] (n=149)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.6 [9.4–11.9] (n=223)</td>
<td>10.7 [9.6–12] (n=156)</td>
<td>0.34</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6 [3.2–4] (n=223)</td>
<td>3.5 [3.1–3.8] (n=155)</td>
<td>0.07</td>
</tr>
<tr>
<td>Peritoneal dialysis Kt/V, single pool*</td>
<td>1.58 [1.33–1.87] (n=106)</td>
<td>1.53 [1.35–1.8] (n=69)</td>
<td>0.76</td>
</tr>
<tr>
<td>White blood cell count*</td>
<td>7.2 [5.5–9.6] (n=222)</td>
<td>7.2 [5.5–9.5] (n=156)</td>
<td>0.77</td>
</tr>
<tr>
<td>Normalized protein catabolic rate*</td>
<td>1.04 [0.72–1.84] (n=88)</td>
<td>0.98 [0.73–1.2] (n=63)</td>
<td>0.16</td>
</tr>
<tr>
<td>Immunosuppressive medications</td>
<td>21% (11/52)</td>
<td>17% (27/156)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*Continuous variables expressed as medians [25th–75th percentile].
interaction, medical center, serum albumin, white blood cell count, hemoglobin, parathyroid hormone, C-reactive protein levels, and normalized protein catabolic rate. Linearity of the logit was confirmed. There was no evidence of collinearity.

During the study period, 27 of the 170 patients mentioned above received one or more additional hepatitis B boosters, either because they failed to obtain immunity after the first booster or because they responded but then lost immunity. Of these 27 patients, 96% (26 out of 27) eventually responded to vaccination: 20 out of 27 (74%) after one more booster or multidose booster series, four out of 27 after two more boosters or multidose series, and two out of 27 after three more boosters or multidose series.

Hepatitis B booster vaccine dosing patterns at each medical center are shown in Supplemental Table 2 and Figure 3. Each center followed center-specific protocols for booster dose vaccination. For centers that used both standard and augmented dose, the cutoff was often on the basis of age or weight. Some centers routinely gave multidose booster series (two or three doses), whereas others reserved multidose booster series for patients who were unresponsive to a single-dose booster.

Discussion

Our study has three important findings. First, loss of immunity to hepatitis B vaccination is common in pediatric patients on dialysis. Second, there was no clear gradient of increasing serologic response with increasing dose of hepatitis B booster vaccine. Third, nearly all patients eventually seroconverted with persistent repeat hepatitis B booster vaccinations.

Our first major finding was that loss of immunity or primary nonresponsiveness to the hepatitis B vaccination series is common in pediatric patients on hemodialysis and those on peritoneal dialysis. Forty-one percent (157 out of 357) of study participants had a measured HBsAb titer <10 mIU/ml and required booster vaccination at some point after dialysis initiation. Although the CDC recommendations are specific to patients on hemodialysis, our study shows that patients on peritoneal dialysis and patients on hemodialysis lose immunity to hepatitis B vaccination at a similar rate (5). On the basis of our observation of comparable rate of immunity loss, we recommend that pediatric patients on peritoneal dialysis should also receive annual screenings of HBsAb and hepatitis B booster vaccinations.

Our second major finding was that there was not a clear gradient of increasing serologic response with increasing...
vaccine dose. Of the single-dose booster vaccinations, the 20 mcg dose was significantly more effective than either the 10 or 40 mcg doses (Figure 2, Table 2). This suggests that higher doses are not necessarily better, and that factors other than vaccine dose are most likely responsible for the differences in serologic response. The CDC vaccination guidelines currently recommend routine dosing (5–10 mcg/dose) for pediatric patients on dialysis, but state that “higher doses might be more immunogenic” (5). Previous studies have shown a response rate of 94%–97%, although the studies were done in patients who were naïve to the hepatitis B vaccine, representing a population distinct from ours (3,7). Our study included patients who had already received a primary hepatitis B vaccine series, with either loss of immunity or primary nonresponsiveness, and who then received single-dose or multidose booster vaccination as pediatric patients on dialysis. Finally, we found that nearly all patients eventually seroconverted with persistent revaccination. The study included 27 patients who required repeat booster vaccination, either because they failed to respond to the initial booster or because they responded and subsequently lost immunity once more. Ninety-six percent of these patients eventually responded with persistent revaccination. Most responded after one additional booster (20 out of 27), although a significant minority required two or three.

![Figure 2](image-url)

**Figure 2.** Hepatitis B vaccine dose versus response reveals no clear gradient of increasing seroconversion rate with increasing vaccine dose. Comparisons are on the basis of the first hepatitis B booster vaccination strategy (single dose or multidose) received by each patient during the study period. Overall chi-squared was 15.62 ($P=0.008$). Bivariate comparisons made by two-sided Fisher exact test.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mcg single-dose booster</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>10 mcg multidose booster series</td>
<td>16.3 (1.7 to 153.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>20 mcg single-dose booster</td>
<td>5.2 (1.6 to 16.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>20 mcg multidose booster series</td>
<td>5.1 (1.2 to 22.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>40 mcg single-dose booster</td>
<td>2.15 (0.57 to 8.13)</td>
<td>0.26</td>
</tr>
<tr>
<td>40 mcg multidose booster series</td>
<td>2.68 (0.37 to 19.26)</td>
<td>0.33</td>
</tr>
<tr>
<td>Immunosuppressive medications</td>
<td>0.56 (0.21 to 1.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Age</td>
<td>0.95 (0.87 to 1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Logistic regression model; Nagelkerke pseudo-$R^2 =0.16$. The model is significant, with a chi-squared test value of 18.1 ($P=0.01$). The following variables were tested and did not significantly improve the model: sex, race, ethnicity, dialysis vintage, time since primary series, dialysis adequacy (Kt/V), age×dose, medical center, serum albumin, white blood cell count, hemoglobin, parathyroid hormone, and C-reactive protein levels, and normalized protein catabolic rate.
additional boosters. The response to revaccination was therefore still good: 74% (20 out of 27) after the second booster vaccination, 57% (four out of seven) after the third booster vaccination, and 67% (two out of three) after the fourth booster vaccination. Therefore, past unresponsiveness to vaccination should not generally be taken as a predictor of future unresponsiveness.

Our study has a number of strengths. It is the largest study of hepatitis B vaccination in pediatric patients on dialysis, and the only study on vaccine response in pediatric patients on dialysis who had previously received a childhood hepatitis B vaccination series. The multicenter design helps minimize the effects that center-specific factors could have on the final conclusions and increases the validity of the results. Finally, inclusion of all pediatric patients on dialysis at each center through our retrospective study design helps avoid selection bias.

Our study also has several limitations. First, it is a retrospective cohort study, so we could not randomize patients to control for unknown sources of confounding. However, we collected clinical data on known confounders and we carried out multivariate testing to look for differences between groups. Second, our treatment group sizes were unbalanced, with far more patients receiving a 20 mcg dose than either 10 or 40 mcg. This imbalance in group sizes persisted despite targeted recruitment of centers with varying hepatitis B vaccine dosing policies. Third, we were unable to capture side effects of vaccination in this retrospective study, and we were unable to evaluate whether there was an increase in side effects with augmented dosing. Fourth, there was significant heterogeneity between centers, as illustrated by the wide variability in the rate of immunity loss across centers. Finally, we did not have complete laboratory or clinical data for some of the included patients because of varying dialysis and laboratory monitoring practices at different centers.

Although our study demonstrated no clear gradient of increasing serologic response with increasing hepatitis B vaccine dose, a definitive conclusion can only come from a randomized clinical trial. In the meantime, it is reasonable to use either standard or augmented dose hepatitis B booster vaccine in pediatric patients on dialysis, with the caveat that a single 10 mcg dose may be less effective than other dosing strategies. Regarding single-dose versus multidose booster vaccination, we suggest that it is reasonable to give a single dose of the hepatitis B vaccine and then test for antibody titer response, given the discomfort and anxiety surrounding vaccination in children. Our data suggest that patients who do not respond to initial booster vaccination are likely to benefit from revaccination, as the seroconversion rate in previous nonresponders was still good.

Disclosures
None.

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