Management Approaches to Hepatitis B Virus Vaccination Nonresponse

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Abstract: Background: Despite the availability of hepatitis B virus (HBV) vaccination, HBV remains a cause of significant morbidity and mortality around the world. Immunologic response and the development of immunity to the HBV vaccine vary significantly among patients. Multiple studies have looked at patients who are at risk of nonresponse and have offered their own approaches to patients who do not respond. This article reviews the best approaches to HBV vaccine nonresponse. **Methods:** We searched the PubMed database for all articles on HBV vaccination response from 1981 to January 2018. Recommended and tested approaches to nonresponse were identified. **Results:** A total of 71 adequate-quality studies with 2354 patients were identified. Repeat vaccination with the same dose increased immunologic seroconversion in 85.7% of patients who previously reported nonresponse and in over 80% of patients with end-stage renal disease, HIV infection, hepatitis C virus (HCV) infection, advanced age, hypoalbuminemia, liver cirrhosis, and hemodialysis (HD) dependence. Patients with inflammatory bowel disease, celiac disease, and diabetes had a milder response (67.5%). Increasing the vaccination dose to 40 µg improved seroconversion in HIV-infected, HCV-infected, and HD patients of initial nonresponse. The use of a subcutaneous injection route increased response by 12% in patients infected with HIV. **Conclusion:** Patients not responding to an initial vaccine series and not actively infected with HBV benefited from reimmunization by repeating the vaccine series or receiving a single-dose vaccine booster. Although the overall response rate was approximately 90% of previous nonresponders, the rate varied among the populations studied.

Hepatitis B virus (HBV) chronically infects up to 2.2 million people in the United States and 240 million people worldwide.[1] Chronic infection may cause liver cirrhosis and hepatocellular carcinoma (HCC). HCC is the sixth most common cancer and the second leading cause of cancer death worldwide.[1,2]

The HBV vaccine is 1 of only 2 available vaccines that can prevent cancer.[1,2] Despite the availability and administration of this vaccine, HBV infection remains a worldwide concern.[1] HBV vaccine nonresponse has been described in the general population as well as in patients with chronic diseases.[1-5] The mechanism of HBV vaccination nonresponse is poorly understood.[1-5] It is estimated that 5% of the general population will not mount a protective response and can be described as nonresponders. Response to HBV vaccine is variable among patients with chronic disease. Some studies have reported a response rate as low as 20% in patients with diabetes and inflammatory bowel disease (IBD).[1,3] Previous studies have looked at HBV vaccine response in different subsets of the population and have individually addressed nonresponse in certain populations.[1-48] Among the populations that have been examined are those with HIV infection, hepatitis C virus (HCV) infection, celiac disease and IBD, diabetes, end-stage renal disease (ESRD), and hemodialysis (HD) dependence. Patients at risk for HBV vaccine nonresponse have been described as at-risk or vulnerable populations in previous studies.[1-50] Thus far, there is no standardized guidance on how to address HBV vaccine nonresponse. Therefore, we reviewed HBV vaccine nonresponse and approaches to patients described as previous nonresponders.

Prevaccination testing for hepatitis B surface antibody (HBsAb) levels is currently recommended for health care workers and at-risk individuals if their history of HBV vaccination is unknown.[51] No prevaccination testing recommendations exist for patients vulnerable or at risk for vaccine nonresponse if they have previously been vaccinated. Hence, if those individuals do not mount an immune response to the vaccine, they may be missed by providers and will be at risk of contracting HBV. The goal of HBV vaccination is to mount an appropriate immune response in case of exposure to HBV. Appropriate immune response is defined as an HBsAb level of greater than 10 IU/L.[49-51] Data suggest that an HBsAb level between 10 IU/L and 100 IU/L may indicate incomplete response to the HBV vaccine and places patients at risk of loss of immunity against HBV.[49-51] An HBsAb level of at least 100 IU/L is considered protective.[48-51] Moreover, patients actively infected with HBV may not develop HBsAbs postimmunization. At the current time, there are no recommendations to check for hepatitis B surface antigen (HBsAg) prior to the initiation of HBV vaccine series or booster dosing in patients who were previously vaccinated. A change in the paradigm of HBV vaccination protocol can, therefore, help in the detection and appropriate management of populations that have been designated as vulnerable or at risk and help eliminate the use of vaccination in patients who were previously vaccinated.

Methods

We searched the PubMed database for all articles published from 1981 (when the HBV vaccine first came into use) to January 2018 that examined HBV vaccination response, including nonresponse, in patient populations that had previously reported decreased response to HBV vaccine, using the following keywords: human immunodeficiency virus, immunosuppressed patient, concurrent hepatitis C, liver cirrhosis, diabetes, hypoalbuminemia, chronic kidney disease, hemodialysis, advanced age, and inflammatory bowel disease. Recommended and tested approaches to nonresponse were identified. Only English peer-reviewed publications were included. Thus, all non-English studies and non–peer-reviewed articles were excluded. The data were extracted from previous studies to an Excel spreadsheet. The articles isolated were verified by 2 of the coauthors (Beshoy Yanny, Lisa M. Najarian).

Definitions

HBV vaccine response was defined as the production of anti-HBsAg, or HBsAb, greater than 10 IU/L. Hypoalbuminemia and advanced age were defined by the primary authors of the original articles. Most authors defined hypoalbuminemia as a serum albumin level of less than 3.4 mg/dL. Most authors defined advanced age as greater than 65 years of age. The duration of loss of immunity was defined by the primary authors. New research has identified an anti-HBsAg titer of at least 100 IU/L as protective and for seroconversion to immune status.[48-51]

Results

A total of 582 studies were identified. After exclusion of repeat articles and non–evidence-based approaches, a total of 71 adequate-quality studies with 2354 patients were found. Tables 1 and 2 compare the most-studied approaches. Table 3 shows the breakdown of the number of patients and studies included. Other suggested strategies, which have a small number of patients and low statistical power to make a meaningful conclusion, are listed in Table 4.

General Population

A total of 10 studies addressed approaches to nonresponders in the general population for a total of 282 patients.[1,8,10-12,14,17,18,42,44] The studies showed that administering a repeat vaccination series with the same dose increased the rate of seroconversion to 85.7% in previous nonresponders in the general population. A single-dose booster with the same vaccination dose of 10 µg to 20 µg (intramuscular formulation) increased seroconversion to 73.2% in the general population.[42-44,52]

Table 1. Comparing Repeat Vaccination Series to Booster in Primary Nonresponse

	Reimmunization With Additional Series	Single-Dose Booster	*P*-Value
General Population	85.7%	73.2%	<.01
HIV	92.0%	91.7%	<.01
Hepatitis C Virus	90.3%	87.3%	<.03
End-Stage Renal Disease and Hemodialysis Dependence	97.2%	92.1%	<.04
Hypoalbuminemia	82.7%	38.2%	<.07
Diabetes	67.5%	43.0%	<.02
Celiac Disease and Inflammatory Bowel Disease	67.5%	N/A	N/A
Advanced Age	87.0%	N/A	N/A

N/A, not available.

Table 2. Comparing Repeat Vaccination Series to Booster in Loss of Immunity

	Reimmunization With Additional Series	Single-Dose Booster	*P*-Value
General Population	95.7%	83.2%	<.01
HIV	91.0%	89.7%	<.03
Hepatitis C Virus	93.3%	77.3%	<.01
End-Stage Renal Disease and Hemodialysis Dependence	97.2%	90.1%	<.01
Hypoalbuminemia	89.7%	48.2%	<.06
Diabetes	87.5%	52.0%	<.04
Celiac Disease and Inflammatory Bowel Disease	77.5%	N/A	N/A
Advanced Age	80.1%	N/A	N/A

N/A, not available.

A single-dose booster using a higher dose of 40 μg increased seroconversion to immune status in 79.7% of nonresponders, and there was no difference when a 60-μg dose was used in the general population, as 78.9% seroconverted. Using adjuncts such as delta inulin, oral mebendazole, albendazole, praziquantel, levamisole, microcrystalline polysaccharide, colony-stimulating factor, and Toll-like receptor-9 agonist did not significantly increase seroconversion. However, the data are very limited, making it uncertain whether meaningful conclusions can be drawn. Using a pre-S core mutant vaccine type also falls in the same category as using adjuncts in the general population. Changing the vaccine route was not addressed in this population (Tables 1 and 2).

HIV-Infected Individuals

A total of 12 studies addressed approaches to HBV vaccine nonresponse in HIV-infected individuals for a total of 398 patients.[2,8,10,11,16-18,23,25,40,42,44] The studies showed that administering a repeat vaccination series with 10 μg to 20 μg (intramuscular formulation) increased the rate of seroconversion to 92.0% in HIV previous nonresponders.[16-18,23,25,40,42,44] A single-dose booster with the same vaccination dose increased seroconversion to 91.7%. However, a single-dose booster using a higher dose of 40 μg increased seroconversion to immune status in 68.7% of nonresponders, and there was no difference when a 60-μg dose was used in HIV-infected individuals, as 68.9% seroconverted. Changing the route of vaccination increased seroconversion to immune status in 12.0% of previous nonresponders. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Hepatitis C Virus–Infected Individuals

A total of 8 studies addressed approaches to HBV vaccine nonresponse in HCV-infected individuals for a total of 302 patients.[10-12,14,17,18,42,44] The studies showed that administering a repeat vaccination series with the same dose of 10 μg to 20 μg (intramuscular formulation) increased the rate of seroconversion to 90.3% in HCV-infected previous nonresponders. A single-dose booster with the same vaccination dose increased seroconversion to 87.3%. In addition, a single-dose booster using a higher dose of 40 μg increased seroconversion to immune status in 88.7% of nonresponders, and there was no difference when a 60-μg dose was used in HCV-infected individuals, as 85.9% seroconverted. Changing the route of vaccination was not studied in this population. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Individuals With End-Stage Renal Disease and Hemodialysis Dependence

A total of 19 studies addressed approaches to HBV vaccine nonresponse in patients with ESRD. Including patients

Table 3. Breakdown of the Number of Studies and Patients and the Corresponding References

	Number of Studies	Number of Patients	References
General Population	10	282	1,8,10-12,14,17, 18,42,44
HIV	12	398	2,8,10,11,16-18, 23,25,40,42,44
Hepatitis C Virus	8	302	10-12,14,17,18, 42,44
End-Stage Renal Disease and Hemodialysis Dependence	19	704	2,8-18,20,23,27, 42,43,47,48
Hypoalbuminemia	4	83	1,2,11,17
Diabetes	14	193	8,11,18,20,23,27-29,42,43,45-48
Celiac Disease and Inflammatory Bowel Disease	12	282	3-7,10,11,15,17, 18,42,44
Advanced Age	7	110	9-11,17,18,42,44

Table 4. Other Suggested Strategies

	Reported Response	Reference(s)
Delta Inulin	Enhances response, exact percentage unclear	19
Oral Praziquantel	Enhances response by approximately 10%	32,33
Oral Levamisole	Enhances response by approximately 7%-10%	28-30
Mebendazole or Albendazole	Enhances response, exact percentage unclear	31
Pre-S Core Hepatitis B Virus Vaccine	Enhances response in animal models, still in clinical trials	24,34
Microcrystalline Polysaccharide	Reported to enhance response, exact percentage unclear	20
Toll-Like Receptor-9 Agonist	Reported to enhance response, exact percentage unclear	21,22
Colony-Stimulating Factor	Reported to enhance response, exact percentage unclear	26

on HD, a total of 704 patients were identified in these studies.[2,8-18,20,23,27,42,43,47,48] The studies showed that administering a repeat vaccination series with the same dose of 10 µg to 20 µg (intramuscular formulation) increased the rate of seroconversion to 97.2% in previous nonresponders with ESRD. A single-dose booster with the same vaccination dose increased seroconversion to 92.1%. In addition, a single-dose booster using a higher dose of 40 µg increased seroconversion to immune status in 93.0% of nonresponders, and there was no difference when a 60-µg dose was used in individuals with ESRD, as the same percent of patients seroconverted. Changing the route of vaccination was not studied in this population. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Individuals With Hypoalbuminemia

A total of 4 studies addressed approaches to HBV vaccine nonresponse in patients with hypoalbuminemia for a total of 83 patients.[1,2,11,17] The studies showed that administering a repeat vaccination series with the same dose of 10 µg to 20 µg (intramuscular formulation) increased the rate of seroconversion to 82.7% in hypoalbuminemia patients who were previously nonresponders. A single-dose booster with the same vaccination dose increased seroconversion to 38.2%. A single-dose booster using a higher dose of 40 µg or 60 µg did not increase seroconversion to immune status in this population. Changing the route of vaccination was not studied in this population. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Individuals With Diabetes

A total of 14 studies addressed approaches to HBV vaccine nonresponse in patients with diabetes for a total of 193 patients.[8,11,18,20,23,27-29,42,43,45-48] The studies showed that administering a repeat vaccination series with the same dose of 10 µg to 20 µg (intramuscular formulation) increased the rate of seroconversion to 67.5% in diabetes patients who were previous nonresponders. A single-dose booster with the same vaccination dose increased seroconversion to 43.0%, whereas a single-dose booster using a higher dose of 40 µg or 60 µg did not increase seroconversion to immune status in this population. Changing the route of vaccination was not studied in this population. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

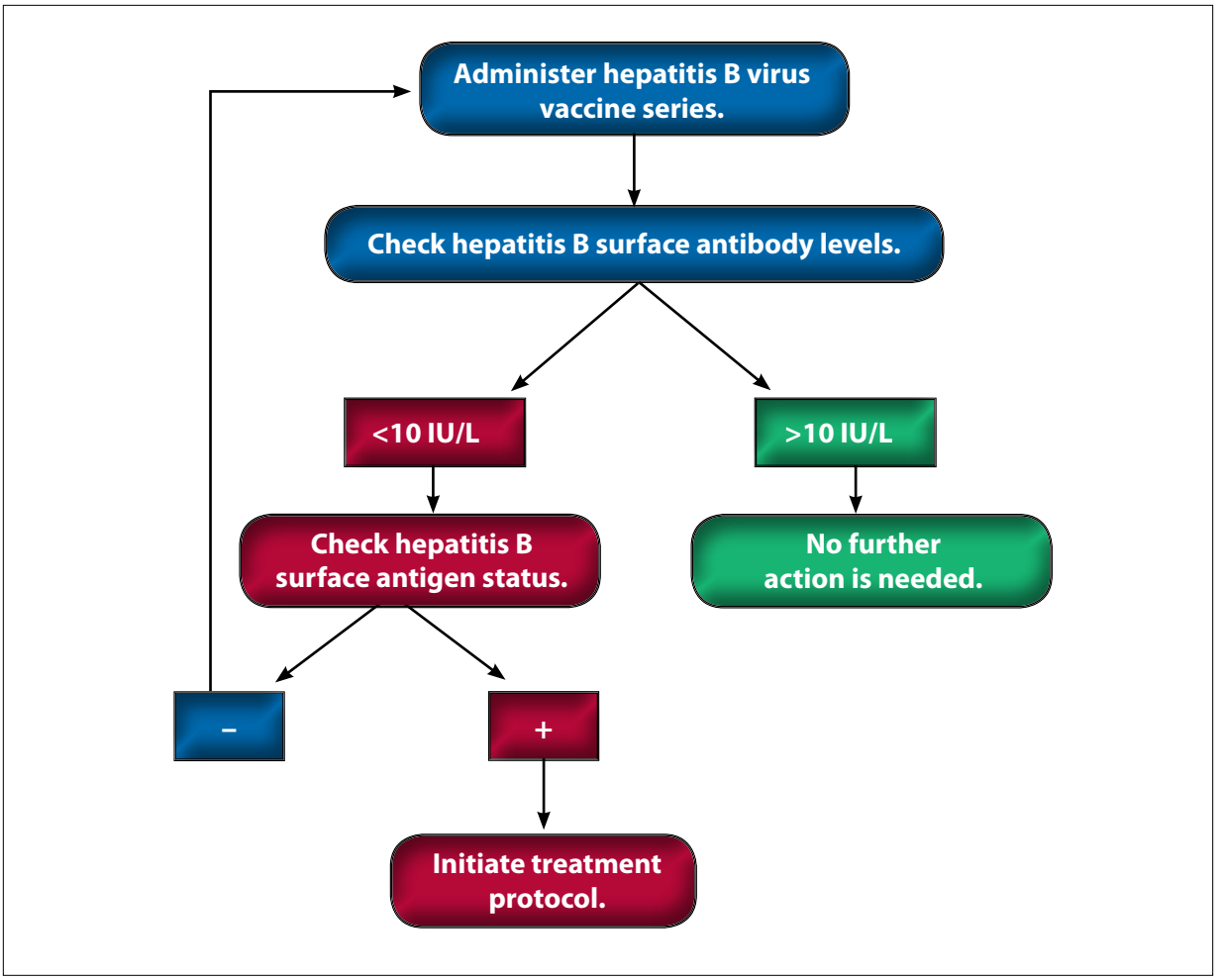

Figure. A proposed approach to at-risk populations.

Individuals With Celiac Disease and Inflammatory Bowel Disease

A total of 12 studies addressed approaches to HBV vaccine nonresponse in patients with celiac disease and IBD for a total of 282 patients.[3-7,10,11,15,17,18,42,44] The studies showed that administering a repeat vaccination series with the same dose of 10 µg to 20 µg (intramuscular formulation) increased the rate of seroconversion to 67.5% in celiac disease and IBD patients who were previous nonresponders. A single-dose booster with the same vaccination dose or a higher dose of 40 µg or 60 µg was not studied in this population, nor was changing the route of vaccination. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Individuals With Advanced Age

A total of 7 studies addressed approaches to HBV vaccine nonresponse in patients with advanced age, which included 110 patients.[9-11,17,18,42,44] The studies showed that administering a repeat vaccination series with the same dose 10 µg to 20 µg (intramuscular formulation) increased the rate of seroconversion to 87.0% in patients with advanced age who were previous nonresponders. A single-dose booster with the same vaccination dose or a higher dose of 40 µg or 60 µg was not studied in this population. Also not studied was changing the route of vaccination. The data for using adjuncts and a pre-S core vaccine type remain scarce, and no meaningful conclusion could be elucidated based on the available studies in this population.

Discussion

The current HBV vaccine is effective; however, response to the vaccine varies significantly in certain populations. Due to the lack of guidance on who to screen postvaccination and how to appropriately manage nonresponders,

we performed this review of approaches to patients who did not respond to the HBV vaccine. Our results suggest that patients with HIV infection, HCV infection, ESRD, hypoalbuminemia, diabetes, celiac disease and IBD, and advanced age should be screened for response postvaccination, and if there is no response, their HBsAg status should be checked for active HBV infection. Careful consideration should be given to health care workers. The vaccine titer should be checked 8 to 12 weeks after administration of the vaccination series. A proposed approach to HBV vaccine nonresponders can be found in the Figure. Based on our findings, administering a repeat vaccination series with the same dose is the most effective approach to HBV vaccine nonresponders, with a seroconversion to immune status approaching 90%. Same-dose booster is effective in patients with HIV infection, HCV infection, and ESRD, also approaching a 90% seroconversion rate to immune status in patients previously reported to be nonresponders. It has been suggested that the half-life of antibodies is much longer when a repeat vaccination series is given. A single-dose booster using a higher dose of 40 µg or 60 µg was not previously studied in individuals with celiac disease and IBD. Changing the route of vaccination from intramuscular to subcutaneous did not significantly increase seroconversion to immune status. The data for using adjuncts and a pre-S core vaccine type remain mixed, and no meaningful conclusion could be elucidated based on the available studies in this population. Tables 1 and 2 show a comparison of single-dose booster vs repeating the vaccination series.

The Centers for Disease Control and Prevention does not recommend checking the post–HBV vaccination titer except in infants born to mothers infected with HBV, immunocompromised individuals, sexual partners of HBV-infected individuals, and health care workers.[48] Many studies have shown multiple vulnerable or at-risk populations, including those with diabetes, HIV infection, ESRD, hypoalbuminemia, celiac disease and IBD, and advanced age.[1-48] Data compiled from previous studies have reported that HBV vaccine response can be as low as 20% in certain vulnerable populations, such as those with HIV infection and diabetes.[2] The highest reported response in a vulnerable population is 78% in patients with celiac disease and IBD.[37] Thus far, there are no recommendations regarding checking HBsAg status in previous vaccine nonresponders. One of the reasons that patients may not respond to HBV vaccination is active infection. Our data suggest that seroconversion rates following repeat vaccination series increase to over 80% in most vulnerable populations. However, these rates would not hold true if the patient has an active HBV infection, which suggests that HBsAg status should be checked in patients who do not respond to the initial HBV vaccine series. The findings also advocate checking the anti-HBsAg titer postvaccination in patients in at-risk populations. Checking the titer and repeating the vaccine series will decrease the global burden of HBV and ultimately decrease the burden of liver cirrhosis, HCC, and chronic liver disease in general.[48-51]

Our study is the only one that has reviewed management approaches to HBV vaccine nonresponse. This was a retrospective review, which limits its findings. Given the nature of the study, cost analysis was not included. The cost-effectiveness of checking immune response in vulnerable populations and repeating a HBV immune titer have not been evaluated. However, this does not undermine the strength of the review given the number of studies and patients included, as well as the benefits of HBV prevention in these high-risk populations.

Conclusion

Based on our findings, the best approach to HBV vaccine nonresponse is repeating the vaccine series at the same dose (10-20 µg) and using the same route in noninfected individuals. HBsAg should be checked after initial nonresponse to the vaccine. It is reasonable to check HBsAb levels 6 to 8 weeks after the vaccination in at-risk populations. A single-dose booster may be effective in certain at-risk populations. There is not sufficient evidence that increasing the dose of the booster, adding oral or intravenous adjuncts to the HBV vaccine, changing the vaccine route to subcutaneous, or using a pre-S core HBV vaccine improves seroconversion to immune status. No cost-effectiveness studies are available to support this approach; thus, more studies are needed.

The authors have no relevant conflicts of interest to disclose.

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