Maintaining Hepatitis B Protection in Immunocompromised Pediatric Rheumatology and Inflammatory Bowel Disease Patients

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Abstract

Objective: Hepatitis B virus (HBV) infection remains a significant public health challenge, particularly for immunocompromised patients. Our aim was to evaluate the serologic immunity in immunocompromised rheumatology and inflammatory bowel disease (IBD) patients, assess factors for serologic non-immunity and evaluate their response to one HBV booster dose.

Methods: Immunocompromised rheumatology and IBD patients with completed HBV screening were identified. A chart review was performed to collect demographics, clinical information, baseline HBV serology results, and serologic response to booster vaccination. Serologic non-immunity was defined as a negative/indeterminate hepatitis B surface antibody (anti-HBs) level.

Results: Among 580 patients, 71% were non-immune. The highest portion of non-immune patients were 11-18 years old (p 0.004). There was no significant difference between immune and non-immune patients with regards to diagnosis (p 0.342), age at diagnosis (p 0.639), duration of treatment (p 0.069) or type of medications (p 0.080). Sixty-two percent of those who received a booster vaccine were re-screened, and most (68%) seroconverted. In those 18 years or older, only half seroconverted.

Conclusion: Results of this study support the benefit of HBV screening in immunosuppressed patients. Beginning at age 11 years most patients lacked serologic immunity to HBV. Seroconversion for most patients 11-18 years occurred after one booster vaccine. Thus, for immunocompromised patients without recent HBV serologic data, obtaining the HBV serology beginning at age 11 years might be considered. Those 18 years and older were least likely to seroconvert after one booster, indicating that they may benefit from receiving the three-dose HBV vaccine series.

Introduction

Advances in the understanding of the mechanisms of inflammation involved in rheumatic disorders and inflammatory bowel disease have led to the invention of new target-specific medications referred to as “biologics”. Biologic agents are designed to inhibit specific components of the immune system such as cytokines and their complex interactions. The use of biologics alone or in combination with other immunosuppressive medications such as corticosteroids, methotrexate, 6-mercaptopurine, have dramatically improved the outcome for children with rheumatic disorders and inflammatory bowel disease, allowing for improved disease control and maintenance of remission. However, enthusiasm for improved outcomes must be tempered by the fact that chronic immunosuppression may lead to an increase in vaccine-preventable illnesses and reactivation of previous infections (1-3). Furthermore, biologic agents have been associated with a higher risk of serious infections when compared with the non-biologic disease-modifying anti-rheumatic medications (4).

In particular, hepatitis B virus (HBV) is a significant concern for patients considered immunocompromised by either their medications or underlying disease condition. While universal vaccination against HBV was implemented in the US in 1991, evidence shows that 10% of HBV vaccine recipients fail to demonstrate a serologic response to the vaccine (5). In addition, use of biologic agents has been shown to accelerate the natural decline in the protective antibody levels against HBV (6). For example, when evaluating previously vaccinated pediatric patients with inflammatory bowel disease, 50% were found to no longer have serologic immunity to HBV (6).

Acute HBV infection as well as reactivation of HBV in immunocompromised patients entails considerable risk for the patient. In addition to elevated transaminase levels, and clinical signs of hepatitis, patients may suffer serious complications, such as liver failure, liver cirrhosis or hepatocellular carcinoma (7, 8). Reactivation of HBV is defined as abrupt increase in HBV replication in a patient with current or past HBV infection(9). Hepatitis B reactivation while receiving biologic therapy has been known to result in 5-25% mortality (7, 10). Data on the rate of past or chronic HBV infections in immunocompromised children is not available. But there is data that when screened prior to starting biologic treatment, up to 6% of adult rheumatology patients have evidence of past HBV infection (8). Therefore, the Advisory Committee on Immunization Practices recommends that all patients receiving immunosuppressive therapy for rheumatology or gastroenterology disorders should be screened for HBV infection and/or immunity and receive repeat vaccinations as needed (11). This screening recommendation is endorsed by multiple professional societies (10).

Therefore, our study aimed to describe the prevalence of serologic immunity against HBV among a single-center cohort of immunocompromised patients with pediatric-onset IBD and rheumatologic diseases, investigate the potential factors associated with lack of immunity, and evaluate the response to a single HBV vaccine booster.

Methods

Population and Study Design

We conducted a retrospective chart review on patients seen in the rheumatology and IBD clinics at Cincinnati Children's Hospital Medical Center (CCHMC). Patients included in this study were identified as immunocompromised via the electronic medical chart using a unique logic defined

by the following: (Meds: Current, by grouper OR Problems by grouper OR HM: Modifier). This logic has been validated elsewhere (12). The time range for the data collected was between January 1, 2011 and January 25, 2017. Patients who lacked hepatitis B surface antibody (anti-HBs) were excluded. The primary outcome measure was anti-HBs positivity (serologic immunity). The following data items were collected: sex, age at diagnosis, age at start of immunosuppressive medications, age at HBV screening, immunosuppressive medications at the time of HBV screening, initial HBV serology results and time, time and type of HBV booster doses, time and results of HBV serology after booster doses. Patients were divided into the following categories as per their diagnosis: IBD (including Crohn's disease and ulcerative colitis), autoimmune arthritis (mainly juvenile idiopathic arthritis), auto-inflammatory disease (including systemic juvenile idiopathic arthritis, periodic fever syndrome, Behcet's disease, chronic recurrent multifocal osteomyelitis), connective tissue disease/vasculitis (including systemic lupus erythematosus, scleroderma and vasculitides), other (including uveitis and myositis). Immunosuppressant medications taken at the time of HBV screening were recorded and categorized as biologics, non-biologic disease-modifying anti-rheumatic drugs ("DMARDs"; which include hydroxychloroquine, methotrexate, mycophenolate, azathioprine, tacrolimus) or as none if the patient was not on any immunosuppressants at the time of HBV screening or the three months prior. Patients who received intravenous or subcutaneous immunoglobulins were eliminated from this study. This study was approved by the Cincinnati Children's Institutional Review Board (IRB) (2016-6462).

Hepatitis B serology

At CCHMC the rheumatology and inflammatory bowel disease (IBD) divisions implemented a quality improvement initiative to standardize HBV screening and repeat vaccinations for their immunocompromised patients in 2015.

The recommended serologic screening for HBV includes hepatitis B surface antigen (HbsAg), hepatitis B core antibody (anti-HBc), and anti-HBs. In our lab, these serologies are analyzed by chemiluminescent microparticle immunoassay and reported as positive, negative, or indeterminate. Negative values were those <10 mIU/mL. Indeterminate for anti-HBs was considered negative. Different patterns of HBsAg or anti-HBc can represent active infection, chronic inactive carrier, or previous infection. If HBsAg or anti-HBc are positive, they are referred to Hepatology and monitored closely. If anti-HBs is positive, then the patient is considered immune and no further action is needed. If anti-HBs is negative, then the patient is vaccinated per the 2013 Infectious Disease Society of America (IDSA) guidelines. Initial attempts at gathering primary vaccine records were extremely time-consuming and largely unsuccessful, and therefore, patients were assumed to have completed the primary HBV vaccine series.

Data Analysis

Descriptive statistics were calculated for all variables. R software was used to perform analyses. For continuous variables, mean and standard deviation are reported, and comparisons were calculated using two-sample t-tests. For categorical variables, frequencies and percentages are reported, and comparisons were calculated using chi-square tests.

Results

Demographic and Clinical Characteristics of Patients

A total of 580 patient charts were reviewed for this study. Of those, 354 (61%) were from the rheumatology clinic, while 226 were from the IBD clinic (Table 1). There were 237 (41%) males and 343 (59%) females in the cohort. The age range at the time of screening was 4-29 years of age. The mean age at screening was 16 years for rheumatology patients and 15 years for IBD patients. The majority of patients from either clinic were exposed to an anti-tumor necrosis factor (anti-TNF) biologic agent, chiefly infliximab. Of the rheumatology patients, 213 (60%) were diagnosed with juvenile arthritis, 93 (26%) had a connective tissue disease or vasculitis, 18 (5%) had an autoinflammatory disease, and 30 (9%) had other rheumatologic diagnoses.

Hepatitis B Serology Results and Seroconversion Rates

The majority of patients (71%) were serologically non-immune to HBV upon screening. The highest portion of non-immune to immune patients (75%) were in patients between the ages of 11 and 18 years of age (p 0.004) (Figure 1A). The percent of non-immunity was approximately equal between the rheumatology and IBD clinics (73% and 67% respectively). After providing one booster dose of HBV vaccine to 291 out of 409 serologically non-immune patients (71%), we found that 68% of patients seroconverted. This response varied by age, where patients above the age of 18 years had the highest portion of non-immunity (47%; p 0.010) after the booster dose (Figure 1B). A subset of those patients in rheumatology clinic received the rest of the HBV vaccination series as per the clinical algorithm followed at the rheumatology clinic (Figure 2). The serologic data is collected during one visit and the booster is given to those that need it at the next visit. The majority of the 118 that had not received HBV booster for lack of serologic immunity

had not yet returned for follow-up clinic visit at the time the data was analyzed. Further data about their response to the 3-dose series was not available.

Factors Associated with Lack of Serologic Immunity to Hepatitis B

Several factors were assessed for their impact on the status of serologic immunity for HBV (Table 2). Being between the ages of 11 and 18 years was significantly associated with serologic non-immunity (p 0.004). Neither age at diagnosis (p 0.639) nor duration of treatment (p 0.069) had an impact on HBV serology upon screening. The risk of lacking serologic immunity was not different between the different disease categories (p 0.342) or between the different classes of immunosuppressant medications (p 0.080). In addition, the same factors were taken into account to assess seroconversion and only age showed statistical significance (Table 3).

Among the patients screened during this period of time, one patient was found to have evidence of exposure to HBV infection indicated by the presence of anti-HBc. The patient was reported to have completed HBV primary vaccination. It was thought that HBV was transmitted perinatally since the mother has history of HBV. This patient was on infliximab upon screening and continues to be closely monitored by rheumatology and hepatology for any clinical or laboratory evidence of HBV reactivation while continuing to receive infliximab.

Discussion

This study revealed that the majority (71%) of patients classified as immunocompromised in our pediatric rheumatology and IBD clinics lacked serologic immunity against HBV. Other cohorts with pediatric IBD patients also reported serologic non-immunity in more than half of their patients (5, 13). Upon stratification by age in our cohort, patients between the ages of 11 and 18 years stood out as the group most likely to lack immunity, as well as the age range most likely to

respond to a single booster vaccine. Thus, preemptive administration of HBV booster vaccine may be appropriate for those between 11 -18 years of age, in particular when recent HBV serologic data is not available.

The use of anti-TNF agents was not associated with lack of protective anti-HBs in this analysis. This was also the case in a pediatric IBD cohort by Moses et al (5). However, our analysis is limited, since only the current use of medications was documented, and recent history of medications was not accounted for. The lack of TNF response in this population is underscored since TNF plays an important role in the suppression of viral replication and the proliferation of HBV-specific cytotoxic T lymphocytes (14, 15). As a result, several studies reported cases of HBV reactivation in patients on anti-TNF therapy (7, 16-18).

Most of our patients who returned for repeat testing (68%) seroconverted after a single dose of HBV vaccine. This rate of seroconversion is comparable to other pediatric rheumatology and IBD cohorts as well as rheumatoid arthritis (RA) patients (5, 19-21). In one of the pediatric IBD cohorts, Urganci et al. compared seroconversion after HBV booster in IBD patients and healthy controls and found rates of 70.2% and 90% respectively (19). This implies the presence of IBD-related factors that contribute to lack of immunogenicity of the vaccine when compared to healthy subjects. These can be attributed to the disease itself or the use of immunosuppressant medications. Exploring factors contributing to seroconversion rates in the immunocompromised population can be of great value. Previously, the use of prednisone, DAMRDs, or biologic medications had no influence on HBV vaccine immunogenicity in rheumatology patients (20, 22). However, the use of anti-TNF agents in IBD cohorts was associated with a significantly lower seroconversion rate (23, 24). It is important to note that with regards to HBV reactivation,

the type of immunosuppressive therapy impacts the risk. This has led to risk-stratification per the type of immunosuppressive therapy (10, 25).

In our cohort, age was identified as the only relevant factor. Several studies in healthy populations have also reported age as a factor that negatively affects HBV seroconversion rates (26-28). Accordingly, we propose that future work determine if those 18 years and older should all receive the complete three-dose series as opposed to an initial booster with repeat serology per the algorithm (Figure 2). The overall rate of seroconversion after a three-dose HBV vaccine series has yielded a higher seroconversion rate of 93-97% in rheumatology patients (22, 29). At the time of analysis of this study, only a minority of patients had completed the three-dose series. Therefore, an overall assessment of the rate of seroconversion after the full series is not available.

Patients with rheumatic diseases are particularly at high risk for HBV reactivation. Changes in T-cell lymphocyte dynamics and homeostasis seen in rheumatoid arthritis (RA) patients (30, 31) could point to a potential inherent susceptibility to HBV reactivation in rheumatic patients. In addition, the use of immunosuppression in patients with rheumatic diseases is largely linked to HBV reactivation, as it influences cellular and humoral responses essential for fighting HBV (32).

Although HBV reactivation has been reported in a patient with adequate anti-HBs levels on immunosuppressive treatment (33), lack of anti-HBs antibodies has been linked to HBV reactivation (34-36). While this highlights the importance of positive surface antibody serology for protection against HBV, further studies are needed to understand the long-term impact of serologic immunity in immunocompromised patients. This is distinctly important as immunocompetent individuals may continue to have immunologic memory despite declining

anti-HBS levels (37). The Center for Disease Control and Prevention's (CDC) recommendations to screen patients for HBV include those who are about to commence immunosuppressive treatment (38). Despite this, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) do not include screening for HBV as part of their current guidelines (39, 40). The guidelines note that HBV vaccination can be safely administered to patients who are at general risk of contracting HBV (intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel, or living in endemic areas) (39, 40). In clinical practice, the rate of HBV universal screening for rheumatology patients undergoing immunosuppressive treatment varies. In a survey administered to members of the ACR, 69% reported performing universal screening for HBV prior to starting biologics, and 42% prior to DMARDs (41). The lack of consensus on HBV screening for this patient population is likely behind the low numbers reported. It is ideal to screen and vaccinate patients prior to initiation of immunosuppression therapy. This is encouraged and outlined in several other societies' guidelines (10, 25, 42). However, this may not be possible due to timing, and so screening can still be sought after therapy has started. Screening of oncology patients has been shown to be cost-effective in those starting rituximab among other immunosuppressive agents (43). A decision model developed by Eckman et al highlighted the cost-effectiveness of universal screening for HBV in the general population even when the prevalence is 0.3% (44). This further emphasizes the ultimate need for comprehensive HBV screening in immunosuppressed patients. We demonstrated that the rate of past infection is 0.2% in our pediatric cohort. This low rate is presumed to be a result of the universal vaccination that started in 1991. However, thorough screening with history and laboratory investigation should not be undermined specially in immunocompromised populations.

In summary, this study emphasizes the need for comprehensive screening with HBsAg, anti-HBc as well as anti-HBs to thoroughly assess for immunity and risk of HBV. Ideally this HBV serologic screening would be performed prior to the initiation of immunosuppressive therapy. However, we have demonstrated in this study that the useful results are obtained during immunosuppressive therapy as well. Beginning at age 11 years most patients lacked serologic immunity to HBV. Regardless of current immunosuppressive medications, the administration of HBV vaccine resulted in seroconversion after one booster dose in the majority of those between the age of 11 and 18 years who had follow-up testing. Thus, for those immunocompromised rheumatology and IBD patients who do not have recent HBV serologic data, one might consider obtaining this serologic screening at age 11 years. Because only half of patients who were 18 years and older seroconverted following one booster vaccine, this age group may benefit from receiving the complete HBV vaccine series. Efforts should be directed towards expanding and then sustaining the screening process for HBV into routine clinical care, in this immunocompromised population.

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References

1. Davies HD, Committee On Infectious D. Infectious Complications With the Use of Biologic Response Modifiers in Infants and Children. Pediatrics 2016;138
2. Horneff G. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep 2015;17:66
3. Shobha V. Common anti-infective prophylaxis and vaccinations in autoimmune inflammatory rheumatic disease. Indian Journal of Rheumatology 2012;7:21-8
4. McKinnon JE, Maksimowicz-McKinnon K. Autoimmune disease and vaccination: impact on infectious disease prevention and a look at future applications. Transl Res 2016;167:46-60

5. Moses J, Alkhouri N, Shannon A, Raig K, Lopez R, Danziger-Isakov L, et al. Hepatitis B immunity and response to booster vaccination in children with inflammatory bowel disease treated with infliximab. Am J Gastroenterol 2012;107:133-8
6. Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. Curr Rheumatol Rep 2015;17:46
7. Perez-Alvarez R, Diaz-Lagares C, Garcia-Hernandez F, Lopez-Roses L, Brito-Zeron P, Perez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011;90:359-71
8. Feuchtenberger M, Schafer A, Philipp Nigg A, Rupert Kraus M. Hepatitis B Serology in Patients with Rheumatic Diseases. Open Rheumatol J 2016;10:39-48
9. Hoofnagle JH. Reactivation of hepatitis B. Hepatology 2009;49:S156-65
10. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: Just the tip of the iceberg? Hepatology 2015;61:703-11
11. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. 2008;
12. Favier LA, Smitherman EA, Furnier A, Ting T, Watts A, Kramer S, et al., editors. Use of Electronic Medical Record to Identify Immunocompromised Patients in a Pediatric Rheumatology Clinic; 2016; HOBOKEN. WILEY.
13. Nguyen HT, Minar P, Jackson K, Fulkerson PC. Vaccinations in immunosuppressive-dependent pediatric inflammatory bowel disease. World J Gastroenterol 2017;23:7644-52
14. Herbein G, O'Brien WA. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis. Proc Soc Exp Biol Med 2000;223:241-57
15. Kasahara S, Ando K, Saito K, Sekikawa K, Ito H, Ishikawa T, et al. Lack of tumor necrosis factor alpha induces impaired proliferation of hepatitis B virus-specific cytotoxic T lymphocytes. J Virol 2003;77:2469-76
16. Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. Clinical rheumatology 2010;29:1021-9
17. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. Int J Rheum Dis 2013;16:527-31
18. Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor-alpha therapy. J Rheumatol 2009;36:2416-20
19. Urganci N, Kalyoncu D. Immunogenecity of hepatitis A and B vaccination in pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;56:412-15
20. Nerome Y, Akaike H, Nonaka Y, Takezaki T, Kubota T, Yamato T, et al. The safety and effectiveness of HBV vaccination in patients with juvenile idiopathic arthritis controlled by treatment. Mod Rheumatol 2016;26:368-71
21. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis 2002;61:623-5
22. Kasapcopur O, Cullu F, Kamburoglu-Goksel A, Cam H, Akdenizli E, Calykan S, et al. Hepatitis B vaccination in children with juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1128-30
23. Gisbert JP, Villagrasa JR, Rodriguez-Nogueiras A, Chaparro M. Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. Am J Gastroenterol 2012;107:1460-6

24. Andrade P, Santos-Antunes J, Rodrigues S, Lopes S, Macedo G. Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients. J Gastroenterol Hepatol 2015;30:1591-5
25. Indolfi G, Abdel-Hady M, Bansal S, Debray D, Smets F, Czubkowski P, et al. Management of Hepatitis B Virus Infection and Prevention of Hepatitis B Virus Reactivation in Children With Acquired Immunodeficiencies or Undergoing Immune Suppressive, Cytotoxic, or Biological Modifier Therapies. J Pediatr Gastroenterol Nutr 2020;70:527-38
26. Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. Clin Infect Dis 2002;35:1368-75
27. Havlichek D, Jr., Rosenman K, Simms M, Guss P. Age-related hepatitis B seroconversion rates in health care workers. Am J Infect Control 1997;25:418-20
28. Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. Sci Rep 2016;6:27251
29. Kuruma KA, Borba EF, Lopes MH, de Carvalho JF, Bonfa E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus 2007;16:350-4
30. Wagner UG, Koetz K, Weyand CM, Goronzy JJ. Perturbation of the T cell repertoire in rheumatoid arthritis. Proc Natl Acad Sci U S A 1998;95:14447-52
31. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proc Natl Acad Sci U S A 2000;97:9203-8
32. Wursthorn K, Wedemeyer H, Manns MP. Managing HBV in patients with impaired immunity. Gut 2010;59:1430-45
33. Sera T, Hiasa Y, Michitaka K, Konishi I, Matsuura K, Tokumoto Y, et al. Anti-HBs-positive liver failure due to hepatitis B virus reactivation induced by rituximab. Intern Med 2006;45:721-4
34. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis 2011;70:1719-25
35. Watanabe T, Fukae J, Fukaya S, Sawamukai N, Isobe M, Matsuhashi M, et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2019;22:574-82
36. Paul S, Dickstein A, Saxena A, Terrin N, Viveiros K, Balk EM, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis. Hepatology 2017;66:379-88
37. Banatvala JE, Van Damme P. Hepatitis B vaccine – do we need boosters? Journal of Viral Hepatitis 2003;10:1-6
38. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67:1-31
39. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1-26
40. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39-52
41. Stine JG, Khokhar OS, Charalambopoulos J, Shanmugam VK, Lewis JH. Rheumatologists' awareness of and screening practices for hepatitis B virus infection prior to initiating immunomodulatory therapy. Arthritis Care Res (Hoboken) 2010;62:704-11
42. Kobayashi I, Mori M, Yamaguchi K, Ito S, Iwata N, Masunaga K, et al. Pediatric Rheumatology Association of Japan recommendation for vaccination in pediatric rheumatic diseases. Mod Rheumatol 2015;25:335-43

43. Zurawska U, Hicks LK, Woo G, Bell CM, Krahn M, Chan KK, et al. Hepatitis B virus screening before chemotherapy for lymphoma: a cost-effectiveness analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:3167-73
44. Eckman MH, Kaiser TE, Sherman KE. The cost-effectiveness of screening for chronic hepatitis B infection in the United States. Clin Infect Dis 2011;52:1294-306

Table 1. Demographics and clinical characteristics of patients by clinic.

	Rheumatology (n=354)	GI (n=226)
Female, n (%)	256 (72%)	87 (38%)
Age at diagnosis in years, mean (SD)	10 (5)	13 (4)
Age at the start of treatment in years, mean (SD)	10 (5)	13 (4)
Age at screening in years, mean (SD)	16 (5)	15 (4)
Medications at the time of HBV screening[a], n (%)	144 (41%)	99 (44%)
Anti TNF biologic	37 (10%)	-
Anti-IL-6 biologic	34 (10%)	3 (1%)
Other biologics	100 (28%)	24 (11%)
Non-biologic DMARDs	39 (11%)	100 (44%)
No biologics/DMARDs		

[a] Percentages are representing the proportions of medication within each column.

Abbreviations: SD: standard deviation; DMARDs: disease-modifying anti-rheumatic drugs.

Table 2. Demographics and clinical characteristics by initial serologic immunity status.

	Non-immune (n=409)	Immune (n=171)	*p*-value
Age at screening in years, n (%)			
4-10 years	57 (67%)	28 (33%)	0.004
11-18 years	263 (75%)	86 (25%)	
> 18 years	89 (61%)	57 (39%)	
Female, n (%)	240 (59%)	103 (60%)	0.799
Age at diagnosis in years, mean (SD)	11 (5)	11 (5)	0.639
Duration of treatment in years, mean (SD)	4.5 (5)	4 (4)	0.069
Clinic, n (%)			0.141
Rheumatology	258 (73%)	96 (27%)	
GI	151 (67%)	75 (33%)	
Diagnosis, n (%)			
Auto-immune arthritis	153 (72%)	60 (28%)	0.342
Auto-inflammatory diseases	14 (78%)	4 (22%)	
Connective tissue diseases/vasculitis	66 (71%)	27 (29%)	
IBD	151 (67%)	75 (33%)	
Others	25 (83%)	5 (17%)	

Medications at the time of HBV screening[a], n (%)			
Anti-TNF biologic	163 (67%)	80 (33%)	0.080
Anti-IL-6 biologic	29 (78%)	8 (22%)	
Other biologics	21 (57%)	16 (43%)	
Non-biologic DMARDs	90 (73%)	34 (27%)	
No biologics/DMARDs	106 (76%)	33 (24%)	

[a] Percentage of non-immune patients out of total patients in each age group.

Abbreviations: SD: standard deviation; IBD: inflammatory bowel disease; DMARDs: disease-modifying anti-rheumatic drugs.

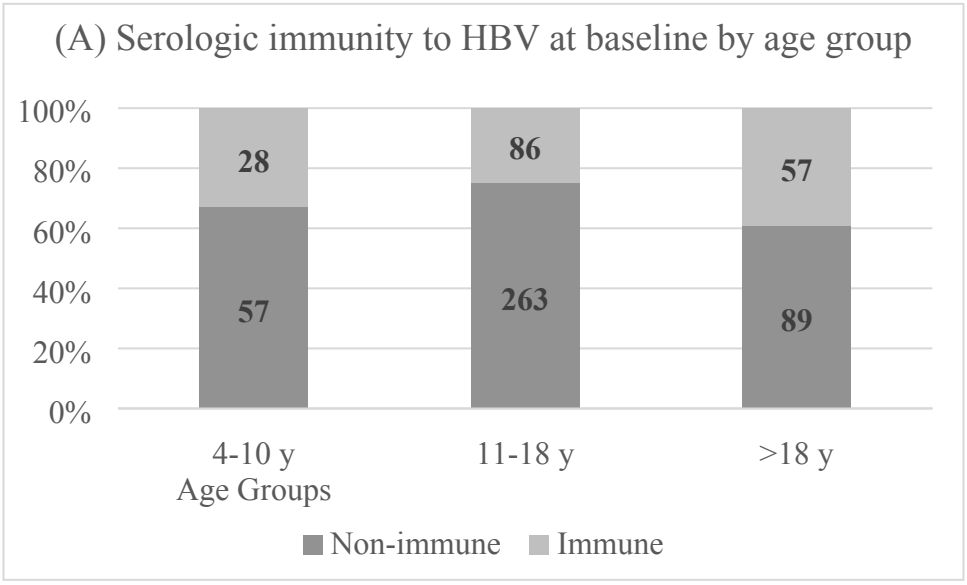
Table 3. Demographics and clinical characteristics by serologic immunity status after one booster dose of HBV vaccine.

	Non-immune (n=57)	Immune (n=122)	*p*-value
Age at screening in years, n (%)			0.010
4-10 years	6 (32%)	13 (68%)	
11-18 years	25 (24%)	80 (76%)	
> 18 years	26 (47%)	29 (53%)	
Female, n (%)	32 (56%)	75 (61%)	0.606
Age at diagnosis in years, mean (SD)	12 (4)	11 (4)	0.628
Duration of treatment in years, mean (SD)	4 (4)	3 (4)	0.064
Clinic, n (%)			0.689
Rheumatology	38 (33%)	76 (67%)	
GI	19 (20%)	75 (80%)	
Diagnosis, n (%)			0.910
Auto-immune arthritis	19 (31%)	43 (69%)	
Auto-inflammatory diseases	3 (43%)	4 (57%)	
Connective tissue diseases/vasculitis	11 (34%)	21 (66%)	
IBD	19 (29%)	46 (71%)	
Others	5 (38%)	8 (62%)	
Medications at the time of screening[a], n (%)			0.658
Anti TNF biologic	31 (29%)	76 (71%)	
Anti IL-6 biologic	6 (46%)	7 (54%)	

Other biologics	3 (38%)	5 (62%)	
Non-biologic DMARDs	13 (31%)	29 (69%)	
No biologics/DMARDs	4 (44%)	5 (56%)	

[a] Percentage of non-immune patients out of total patients in each age group.

Abbreviations: SD: standard deviation; IBD: inflammatory bowel disease; DMARDs: disease-modifying anti-rheumatic drugs.



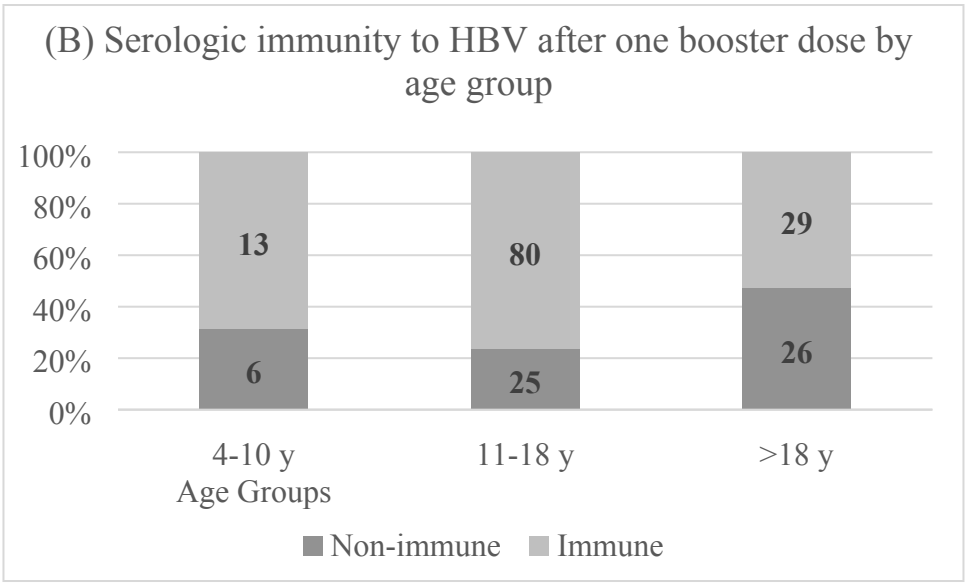


FIGURE 1. Serologic immunity to HBV by age group. Y-axis indicates percentage levels. Absolute numbers of immune and non-immune patients are outlined within bars. Panel (A) shows the initial hepatitis B virus serologic immunity across age groups. Panel (B) shows the serologic immunity response to one dose of HBV vaccine across age groups.
HBV: hepatitis B virus.

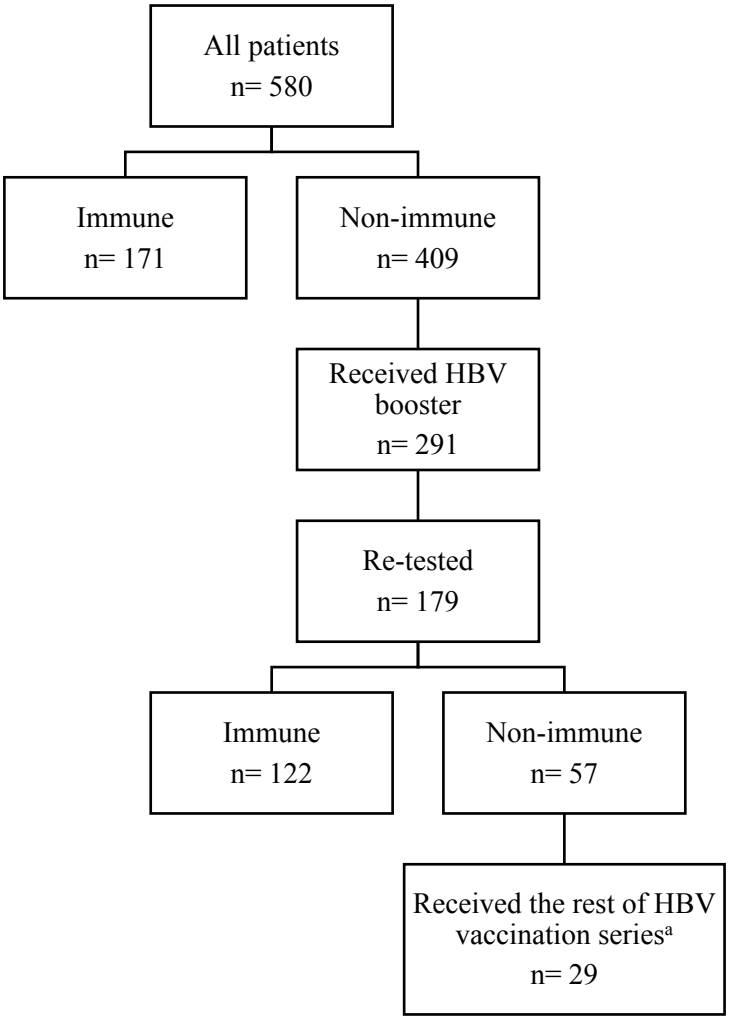


FIGURE 2. Flowchart of rheumatology and IBD patients in this cohort through screening and immunization for HBV.
[a] For a total of 3 doses.