

## Brief Communication



# Seroprevalence of Hepatitis A Virus in Pediatric Patients with Hematologic Malignancies after Chemotherapy and Hematopoietic Cell Transplantation

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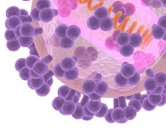
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## ABSTRACT

This retrospective study was performed to determine the seroprevalence of hepatitis A virus (HAV) in children and adolescents with hematologic malignancies after the completion of chemotherapy and hematopoietic cell transplantation (HCT). Of 97 enrolled patients, 60 (61.9%) were seropositive for HAV. The seroprevalences in patients undergoing chemotherapy and HCT were 60.3% (41/68) and 65.5% (19/29), respectively ( $P = 0.628$ ). No significant factors associated with seropositivity for HAV after chemotherapy and HCT were identified. Anti-HAV tests and HAV re-vaccinations can be considered in children and adolescents with underlying hematologic malignancies after chemotherapy and HCT based on the anti-HAV results.

**Keywords:** Chemotherapy; Stem cell transplantation; Hepatitis A virus; Seroprevalence; Child

Curative treatments for hematologic malignancies consist of chemotherapy and hematopoietic cell transplantation (HCT) [1, 2]. Because HCT recipients' immune cells are replaced by progeny of the HCT graft, HCT recipients should be regarded as “never vaccinated,” and therefore, re-vaccination of inactivated vaccines is recommended after HCT [3]. Chemotherapy for hematologic malignancies also causes immunosuppression in the host; however, the suppressed immunity is thought to be restored several months after the completion of chemotherapy [4]. A catch-up vaccination according to the vaccination schedule for immunocompetent persons rather than re-vaccination is recommended in patients receiving chemotherapy [3]. However, the kinetics of loss of immune memories and the necessity of re-vaccination have not been adequately studied in patients receiving chemotherapy. In particular, studies of hepatitis A virus (HAV) vaccinations in children and adolescents receiving chemotherapy as well as undergoing HCT are scarce [5-8]. The survival of children and adolescents with hematologic malignancies has been increasing with improvements in chemotherapeutic strategies and supportive cares, and children and adolescents who are cured of hematologic malignancies are expected to have several decades of life expectancy [1]. During the remaining life, the cured children and adolescents living



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**Conflict of Interest**

No conflicts of interest.

**Author Contributions**

Conceptualization: SBH, JHK. Data curation: JUM, ALH, ESL. Formal analysis: SBH, NGC, DCJ. Methodology: JWJ, BC, DCJ. Writing - original draft: JUM, SKK, SBH. Writing - review & editing: JWJ, BC, JHK.

in highly endemic areas of hepatitis A can be infected by HAV in the community and those living in less endemic areas of hepatitis A can be infected by traveling to highly endemic areas if they lose their protective immunity against HAV after chemotherapy and HCT. Therefore, the restoration of immunity against HAV should be achieved. This study evaluated the seroprevalence of HAV in children and adolescents undergoing chemotherapy and HCT for underlying hematologic malignancies to determine the necessity of re-vaccination against HAV in these patients.

Children and adolescents who underwent chemotherapy and HCT for underlying hematologic malignancies in the Department of Pediatrics, Seoul St. Mary's Hospital, Seoul, Korea were recruited for this study. Among them, those who were consulted for vaccination after completing therapy for hematologic malignancies between January 2015 and June 2018 were included. In our hospital, vaccination after chemotherapy and HCT is considered after  $\geq 1$  year since completing anti-B-cell therapy;  $\geq 3$  months since the last intravenous immunoglobulin administration after HCT; and when graft-versus-host diseases are well-controlled after HCT. Patients receiving additional courses of chemotherapy for their relapsed malignancies after HCT were excluded. Medical records of the enrolled patients were retrospectively reviewed. The total antibody titers to HAV were measured using a commercial electrochemiluminescence immunoassay kit (Elecsys/Modular analytics E170, Roche Diagnostics GmbH, Mannheim, Germany). The antibody titers of  $\geq 20$  IU/L were considered positive according to the manufacturer's guidance. The following factors were also investigated: demographic factors, including age at the time of anti-HAV tests and sex; clinical factors, including the type of underlying hematologic malignancy, HCT donor and stem cell source, year of anti-HAV test, time from the completion of chemotherapy or HCT to the anti-HAV test; and laboratory factors, result of complete blood count on the day of the anti-HAV test. The enrolled patients were divided into seropositive and seronegative groups for HAV, and the investigated factors were compared between the two patient groups. Categorical and continuous factors were compared using the Fisher's exact and Mann-Whitney U tests, respectively. The SPSS 21 program (IBM Corporation, Armonk, NY, USA) was used for statistical analyses, and statistical significance was defined as a  $P$ -value  $< 0.05$ . This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital with a waiver of acquiring informed consent (Approval No.: KC18RESI0503).

Overall 258 patients with hematologic/oncologic diseases were consulted for vaccination after chemotherapy and HCT. Among them, 203 had underlying hematologic malignancies, of whom four receiving additional chemotherapies after HCT were excluded. Among the remaining 199 patients, 97 underwent anti-HAV tests. The enrolled patients were aged a median of 8 years (range: 2-20 years), and 61 (62.9%) patients were male. Anti-HAV tests were performed a median of 3 months (range: 1-48 months) after the completion of chemotherapy in 68 patients and a median of 14 months (range: 12-23 months) after HCT in 29 patients (26 with allogeneic HCT and three with autologous HCT). Anti-HAV results were positive in a total of 60 (61.9%) patients, and seroprevalences of HAV were not significantly different between those in patients undergoing chemotherapy and HCT ( $P = 0.628$ ). The compared demographic, clinical, and laboratory factors showed no significant differences between seropositive and seronegative groups for HAV (data are not shown). Among the 68 patients who received chemotherapy, 41 (60.3%) were seropositive for HAV (Table 1). There were no significantly different factors between the seropositive and seronegative groups in these patients. Among 29 patients who underwent HCT, 19 (65.5%) were seropositive (Table 2). In these patients, no significantly different factors were observed between the seropositive and negative groups.

## HAV seroprevalence after chemotherapy and HCT

**Table 1.** Comparison between seropositive and seronegative patients for hepatitis A virus in patients receiving chemotherapy

Factor	Seropositive (n = 41)	Seronegative (n = 27)	P-value
Sex, male	27 (65.9)	16 (59.3)	0.581
Age, years, median (range) <sup>a</sup>	8 (4–20)	7 (3–17)	0.442
Year of the anti-HAV test			0.987
2015	7 (17.1)	4 (14.8)	
2016	11 (26.8)	7 (25.9)	
2017	18 (43.9)	13 (48.1)	
2018	5 (12.2)	3 (11.1)	
Underlying hematologic malignancy			0.644
Acute lymphoblastic leukemia	34 (82.9)	24 (88.9)	
Acute myeloid leukemia	3 (7.3)	2 (7.4)	
Lymphoma	4 (9.8)	1 (3.7)	
Time from the completion of chemotherapy to the anti-HAV test, months, median (range)	3 (1–14)	3 (1–48)	0.318
Complete blood count results on the anti-HAV test			
White blood cell count, cells/mm <sup>3</sup> , median (range)	6,370 (3,790–13,720)	6,040 (3,070–9,650)	0.502
Absolute neutrophil count, cells/mm <sup>3</sup> , median (range)	3,806 (1,439–10,153)	3,198 (1,535–7,334)	0.113
Absolute lymphocyte count, cells/mm <sup>3</sup> , median (range)	1,901 (714–4,601)	1,939 (1,009–4,173)	0.721
Absolute monocyte count, cells/mm <sup>3</sup> , median (range)	376 (84–960)	372 (0–1,081)	0.945

<sup>a</sup>The ages were at the time of anti-HAV tests.  
HAV, hepatitis A virus.

**Table 2.** Comparison between seropositive and seronegative patients for hepatitis A virus in patients undergoing hematopoietic cell transplantation

Factor	Seropositive (n = 19)	Seronegative (n = 10)	P-value
Sex, male	11 (57.9)	7 (70.0)	0.694
Age, years, median (range) <sup>a</sup>	9 (3–18)	10 (2–17)	0.946
Year of the anti-HAV test			0.813
2015	2 (10.5)	1 (10.0)	
2016	4 (21.1)	3 (30.0)	
2017	6 (31.6)	4 (40.0)	
2018	7 (36.8)	2 (20.0)	
Underlying hematologic malignancy			0.904
Acute lymphoblastic leukemia	11 (57.9)	6 (60.0)	
Acute myeloid leukemia	5 (26.3)	3 (30.0)	
Lymphoma	2 (10.5)	1 (10.0)	
Chronic myeloid leukemia	1 (5.3)	0 (0.0)	
Type of hematopoietic cell donors <sup>b</sup>			0.232
Matched familial donor	2 (14.3)	0 (0.0)	
Matched unrelated donor	5 (35.7)	5 (83.3)	
Mismatched familial donor	3 (21.4)	0 (0.0)	
Mismatched unrelated donor	4 (28.6)	1 (16.7)	
Hematopoietic cell source			0.426
Peripheral blood	14 (73.7)	7 (70.0)	
Bone marrow	2 (10.5)	0 (0.0)	
Cord blood	3 (15.8)	3 (30.0)	
Time from HCT to the anti-HAV test, months, median (range)	14 (12–20)	15 (12–23)	0.668
Time from the completion of immunosuppressant therapy to the anti-HAV test, months, median (range) <sup>c</sup>	7 (1–9)	6 (0–9)	0.610
Complete blood count results on the anti-HAV test			
White blood cell count, cells/mm <sup>3</sup> , median (range)	6,550 (3,680–16,470)	7,305 (5,430–10,200)	0.636
Absolute neutrophil count, cells/mm <sup>3</sup> , median (range)	2,958 (1,707–7,412)	3,330 (2,172–5,100)	0.484
Absolute lymphocyte count, cells/mm <sup>3</sup> , median (range)	2,974 (794–7,082)	3,158 (1,382–4,644)	0.769
Absolute monocyte count, cells/mm <sup>3</sup> , median (range)	402 (88–1,318)	352 (134–714)	0.456

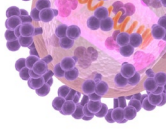
<sup>a</sup>The ages were at the time of anti-HAV tests.

<sup>b</sup>Six patients undergoing cord blood transplantations were excluded.

<sup>c</sup>Immunosuppressants were not administered in three patients undergoing autologous HCT (two in the seropositive and one in the seronegative groups). The anti-HAV was measured during immunosuppressant therapy in each one patient in seropositive and seronegative groups.

HAV, hepatitis A virus; HCT, hematopoietic cell transplantation.

The seroprevalence of HAV after chemotherapy and HCT in children and adolescents with hematologic malignancies was about 60% in this study. Seroprevalences were



not significantly different between patients undergoing chemotherapy and HCT. No demographic, clinical, or laboratory factors were significantly associated with seropositivity for HAV. Patel et al. reported two studies on seroprevalences of vaccine-preventable diseases (VPDs) performed at the same hospital during the same period: one included patients undergoing HCT and the other included patients receiving chemotherapy [9, 10]. In these studies, tetanus and measles seroprevalences were higher in patients receiving chemotherapy than in those undergoing HCT, whereas, the seroprevalence of polio was higher in patients undergoing HCT than in those receiving chemotherapy [9, 10]. Although the degree of immunosuppression may be greater after HCT than after chemotherapy, its effect on VPD seroprevalence may be different in each disease. Therefore, immunosuppressive effects of chemotherapy and HCT on each VPD should be determined separately, considering protective immunity of the HCT donor, previous vaccination history, immunoglobulin administration after HCT, and epidemiology of each disease in the community.

Godoi et al. reported that 11.2% of seropositive patients lost protective immunity against HAV a median of 644 days after HCT [5]. In allogeneic HCT recipients of another study, 87.1% and only 6.5% of seropositive patients for HAV remained seropositive 12 and 54 months after HCT, respectively [7]. Because seroprevalence and vaccination rates for HAV were not determined during hematologic malignancy diagnosis in our hospital, we could not calculate the loss rate of anti-HAV antibodies after chemotherapy and HCT. In Korea, since a hepatitis A outbreak in 2009 [11], most hepatitis A cases are reported in 20-39-year-old adults with an HAV seroprevalence <80% [12]. Therefore, HAV vaccination for children and adolescents undergoing chemotherapy and HCT with 61.9% of HAV seroprevalence may be needed to prevent hepatitis A during young adulthood. Considering the decreasing seroprevalence of VPDs, including HAV, with time after HCT [7, 13], a universal HAV re-vaccination may be considered for patients undergoing HCT. The change in HAV seroprevalence after chemotherapy has not been previously reported. Immune reconstitution may be more profound after chemotherapy than HCT, and therefore, the decreasing tendency of seroprevalence with time after chemotherapy may not be as evident as that after HCT. Future studies should determine the serologic change with time after the completion of chemotherapy. Until then, a selective HAV re-vaccination strategy for seronegative patients based on anti-HAV test results may be appropriate in patients undergoing chemotherapy and HCT.

In Korea, an HAV vaccine was introduced in 1997, and included in the National Immunization Program (NIP) in May 2015. Previous studies on HAV seroprevalence in HCT recipients were performed in countries where HAV vaccinations were not available and where natural HAV infections were the entire source of protective immunity against HAV [5-7]. The HAV vaccination rate in Korean children was 82% in 2013 [14]. Considering that a HAV vaccination was included in the NIP in 2015 and vaccination rates of other existing NIP vaccines were reported >99% in Korean toddlers [14], the HAV vaccination rate may be >99% in the near future, and the kinetics of losing immunity against HAV after chemotherapy and HCT may change with the increasing vaccination rate. Follow-up studies of HAV seroprevalence should be performed periodically, and vaccination strategies for patients undergoing chemotherapy and HCT should be revised.

This study had several limitations including those arising from the retrospective nature of this study. The pre-treatment seroprevalence of HAV was not determined in this study, and therefore, the loss rate of anti-HAV could not be determined. The history of HAV vaccination before the diagnosis of hematologic malignancy was also not determined. The effects of HAV vaccinations and natural HAV infections on the HAV seroprevalence after chemotherapy and HCT could not be determined. The time from the completion of chemotherapy or HCT to the

anti-HAV test may affect the seroprevalence; however, the changes in seroprevalences with time were not determined due to the small number of enrolled patients at each time point. The small number of enrolled patients might restrict the determination of significant factors related to seropositivity for HAV after chemotherapy and HCT. Protective immunity can be achieved with cellular immunity and reactivation of immune memories despite a seronegative status. Although the presence of antibodies against HAV was used as a measure of protective immunity in this study, cellular and memory immunities should be determined in future studies.

In conclusion, about 60% of children and adolescents were seropositive for HAV after chemotherapy and HCT for underlying hematologic malignancies. HAV re-vaccinations can be considered in patients undergoing chemotherapy and HCT based on the anti-HAV results.

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