

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 May 16; 9(14): 3227-3486



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Yun-Jie Ma; Editorial Office Director: Jin-Lei Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

May 16, 2021

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

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# Successful treatment of infantile hepatitis B with lamivudine: A case report

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**Supported by** National Natural Science Foundation of China (General Program), No. 82070610.

**Informed consent statement:**

Informed consent was obtained from the patient's mother.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest to disclose.

**CARE Checklist (2016) statement:**

The authors have read the CARE Checklist (2016), and the manuscript was prepared and

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## Abstract

### BACKGROUND

How to treat infantile hepatitis B virus (HBV) infection remains a controversial issue. The nucleoside analogue lamivudine (LAM) has been approved to treat children (2 to 17 years old) with chronic hepatitis B. Here, we aimed to investigate the benefit of LAM treatment in infantile hepatitis B.

### CASE SUMMARY

A 4-mo-old infant born to a hepatitis B surface antigen (HBsAg)-positive woman was found to be infected by HBV during a health checkup. Liver chemistry and HBV seromarker tests showed alanine aminotransferase of 106 U/L, HBsAg of 685.2 cut-off index, hepatitis B "e" antigen of 1454.0 cut-off index, and HBV DNA of  $> 1.0 \times 10^9$  IU/mL. LAM treatment (20 mg/d) was initiated, and after 19 mo, serum HBsAg was entirely cleared and hepatitis B surface antibody was present. The patient received LAM treatment for 2 years in total and has been followed for 3 years. During this period, serum hepatitis B surface antibody has been persistently positive, and serum HBV DNA was undetectable.

### CONCLUSION



revised according to the CARE Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C  
Grade D (Fair): D  
Grade E (Poor): 0

**Received:** December 12, 2020

**Peer-review started:** December 12, 2020

**First decision:** January 27, 2021

**Revised:** February 8, 2021

**Accepted:** March 3, 2021

**Article in press:** March 3, 2021

**Published online:** May 16, 2021

**P-Reviewer:** Yang SS

**S-Editor:** Zhang L

**L-Editor:** Wang TQ

**P-Editor:** Liu JH



Early treatment of infantile hepatitis B with LAM could be safe and effective.

**Key Words:** Hepatitis B virus; Infant; Lamivudine; Mother-to-infant transmission; Antiviral therapy; Case report

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**Core Tip:** We report a case of infantile hepatitis B that was successfully treated with lamivudine. In addition, we review the clinical characteristics and laboratory tests and compare them with previously reported cases. Lamivudine is safe and effective in the treatment of infantile hepatitis B, and this case report may contribute to the development of relevant clinical guidelines.

**Citation:** Zhang YT, Liu J, Pan XB, Gao YD, Hu YF, Lin L, Cheng HJ, Chen GY. Successful treatment of infantile hepatitis B with lamivudine: A case report. *World J Clin Cases* 2021; 9(14): 3442-3448

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i14/3442.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i14.3442>

## INTRODUCTION

Hepatitis B virus (HBV) is a hepatotropic DNA virus that chronically infects approximately 240 million people worldwide[1]. The majority of people with chronic hepatitis B are infected at birth or in early childhood. Nearly 2 million children under the age of 5 years are newly infected with HBV every year, mainly through mother-to-infant transmission (MTIT)[2]. Reportedly, 80%-90% of infants (< 1 year old) infected by HBV will subsequently develop chronic hepatitis B; in comparison, 20%-30% of children infected between 1 and 5 years old and < 5% of adults will progress to chronic hepatitis B[3]. The main characteristics of infantile HBV infection are high replication and low inflammation during the perinatal period and childhood. Hepatitis B surface antigen (HBsAg), hepatitis B "e" antigen (HBeAg), and high HBV DNA load can be detected in the serum, and alanine aminotransferase (ALT) is normal or slightly elevated[4]. The American Association for the Study of Liver Diseases has already recommended antiviral treatment for children (2 to 18 years old) with chronic hepatitis B[5]. However, because of uncertainty of the natural history of chronic hepatitis B in infants, there is no consensus treatment guidelines available for children under the age of 1 year, which puts doctors in a difficult position when trying to determine the most appropriate clinical practice.

The antiviral compound lamivudine (LAM) is a dideoxynucleoside analog that is a reverse transcriptase inhibitor with great antiviral activity against both human immunodeficiency virus type 1 and HBV. It is utilized in combination with other drugs to treat human immunodeficiency virus infected patients under 3 years old, and it can also be used as a single drug to treat HBV infections, inhibiting the replication of HBV[6]. In 2019, a meta-analysis of the efficacy and safety of LAM in preventing MTIT of HBV led to the authors' strongly recommending use of LAM to prevent vertical transmission of HBV in pregnant women with HBV DNA > 1.0 × 10<sup>6</sup> IU/mL. LAM was safe for both mothers and fetuses[7].

Here, we report a case of infantile hepatitis B treated with LAM. In this case, a baby infected with HBV through MTIT received LAM at 4 mo of age. Serum HBsAg was entirely cleared, and seroconversion was achieved after 19 mo of antiviral therapy. There were no side effects found during the follow-up, which indicated that LAM could be safe and effective in the early treatment of hepatitis B in infants under 1 year old.

## CASE PRESENTATION

### Chief complaints

A 4-mo-old baby boy was hospitalized for HBsAg positivity and abnormal serological indicators of liver function found in a health checkup.

### History of present illness

The patient had no obvious symptoms of discomfort at the time of admission.

### History of past illness

The patient had no history of drug exposure. Furthermore, human immunodeficiency virus, hepatitis A, C, and E, autoimmune hepatitis, Wilson's disease, and other liver-related diseases were excluded.

### Personal and family history

HBV seromarker tests in the patient's mother showed HBsAg > 300 ng/mL, HBeAg 82.79 PEIU/mL, and HBV DNA  $6.47 \times 10^7$  IU/mL. The mother did not take any antiviral drug in the third trimester of pregnancy to block HBV. The infant was injected with hepatitis B immunoglobulin at birth and was vaccinated against hepatitis B at 0 and 1 mo after birth. He was breastfed for 3 mo after birth.

### Physical examination

The patient's physical examination was unremarkable.

### Laboratory examinations

Laboratory examination data are shown in Table 1. Notably, the ALT level was 106 U/L and aspartate aminotransferase level was 107 U/L. HBsAg, HBeAg, and hepatitis B core antibody (HBcAb) were positive, and HBV DNA load was  $> 10^9$  IU/mL. The patient's serum HBV markers were examined with the Roche Cobas E601 electrochemical luminescence analyzer and associated kit (Roche diagnostic, Basel, Switzerland). HBsAg > 1 cut-off index (COI) is positive. Hepatitis B surface antibody (HBsAb) > 10 IU/L is positive. HBeAg > 1 COI is positive. Hepatitis B "e" antibody (HBeAb) < 1 COI is positive. HBcAb < 1 COI is positive. HBV DNA was quantified by real-time Taqman PCR using the Roche LightCycler480 (Roche diagnostic, Basel, Switzerland) and matched kit with detection limit of  $1.0 \times 10^2$  IU/mL.

## FINAL DIAGNOSIS

According to the laboratory examinations and family history, the infant was diagnosed with HBV infection acquired through MTIT.

## TREATMENT

Our patient was treated with 20 mg/d LAM for HBV infection after informed consent was obtained from his mother.

## OUTCOME AND FOLLOW-UP

After 3 mo of antiviral treatment, the patient's serum ALT (38 U/L) dropped into the normal range. HBV DNA load ( $< 1.0 \times 10^2$  IU/mL) was undetectable after 5 mo of treatment. After 19 mo of treatment, HBsAg was completely cleared, and HBsAb level increased to 48.625 mIU/mL. HBeAg was entirely cleared, and seroconversion was achieved after 5 mo of antiviral therapy.

The patient stopped using LAM 2 years after initiation of antiviral therapy and has been followed for 3 years. In February 2020, he received another booster injection of hepatitis B vaccine. There were no side effects and no evidence of HBV reinfection during the antiviral treatment. The boy's last serological indicators are shown in Table 2, and HBV DNA, HBsAg, and HBeAg are all undetectable. Figure 1 depicts the dynamic changes of serum HBsAg, HBsAb, log<sub>10</sub> HBV DNA, and ALT during the treatment. Blood sampling schedule of the patient is shown in Table 3. It should be



**Table 1 Laboratory test results on admission (December 14, 2015)**

Serum marker (unit)	Actual value	Reference range
Alanine aminotransferase (U/L)	106	1-52
Aspartate aminotransferase (U/L)	107	1-40
HBsAg (COI)	685.2	< 1
HBsAb (mIU/mL)	< 2	< 10
HBeAg (COI)	1454.0	< 1
HBeAb (COI)	11.89	> 1
HBcAb (COI)	0.009	> 1
HBcAb-IgM (COI)	2.07	< 1
HBV DNA (IU/mL)	$> 1.0 \times 10^9$	$< 1.0 \times 10^2$

COI: Cut-off index; HBcAb: Hepatitis B core antibody; HBcAb-IgM: Immunoglobulin M antibody to hepatitis B core antigen; HBeAb: Hepatitis B “e” antibody; HBeAg: Hepatitis B “e” antigen; HBV: Hepatitis B virus; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen.

**Table 2 Partial laboratory test results from last reexamination (July 2, 2020)**

Serum marker (unit)	Actual value	Reference range
Alanine aminotransferase (U/L)	18	1-52
Aspartate aminotransferase (U/L)	33	1-40
HBsAg (IU/mL)	< 0.03	< 0.05
HBsAb (mIU/mL)	> 1000	0.0-10.00
HBeAg (PEIU/mL)	< 0.01	0.00-0.11
HBeAb (PEIU/mL)	< 0.1	> 1.10
HBcAb (IU/mL)	< 0.1	> 1.10
HBV DNA (IU/mL)	< 30	< 30
White blood cell ( $10^9/L$ )	5.95	4.0-10.0
Neutrophil ( $10^9/L$ )	2.66	2.00-7.00
Red blood cell ( $10^{12}/L$ )	4.16	3.50-5.50
Platelet ( $10^9/L$ )	306.0	100.0-300.0

HBcAb: Hepatitis B core antibody; HBeAb: Hepatitis B “e” antibody; HBeAg: Hepatitis B “e” antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

noted that due to the different detection methods, the serum HBsAg level of the patient on admission and during treatment were not comparable. In the follow-up tests, Immunalysis ELISA assay was used to test serum HBV markers on a Tecan Freedom EVOlyzer platform (Swiss Tecan Company RSP150/8 pretreatment system and Germany Dade Behring company produces the BEIII post-processing system) according to the manufacturer's specifications. The kit was purchased from Ink New Technology (Xiamen) Co., Ltd. HBsAg > 0.5 ng/mL, HBsAb > 10 mIU/mL, HBeAg > 0.5 PEIU/mL, HBeAb > 0.2 PEIU/mL, and HBcAb > 0.9 IU/mL were considered positive. HBV DNA was quantified by PCR-fluorescent probe method using the Thermo Fisher ABI7500, United States, and the kit was purchased from Da An Gene Co., Ltd. of Sun Yat-Sen University with detection limit of  $1.0 \times 10^2$  IU/mL. In the last test, serum HBV markers were quantified with Cobas E411 (Roche Diagnostics, Mannheim, Germany). HBsAg > 0.05 IU/mL, HBsAb > 10 mIU/mL, HBeAg > 0.11 PEIU/mL, HBeAb < 1.1 PEIU/m, and HBcAb < 1.1 IU/mL were considered positive. HBV DNA was detected by real-time Taqman PCR on the ABI Prism 7000 system (Applied Biosystems, Forster City, CA, United States) and assayed with the matched kit with detection limit of 30 IU/mL.

**Table 3 Blood sampling schedule**

Date	Item
December 14, 2015	ALT, HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
April 1, 2016	ALT
May 3, 2016	HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
August 11, 2016	ALT, HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
November 2, 2016	HBsAg, HBsAb, HBeAg, HBeAb
March 22, 2017	HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
July 20, 2017	ALT, HBsAg, HBsAb, HBeAg, HBeAb
December 11, 2017	ALT, HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
April 8, 2018	HBsAg, HBsAb, HBeAg, HBeAb
July 31, 2018	HBsAg, HBsAb, HBeAg, HBeAb
January 6, 2019	HBsAg, HBsAb, HBeAg, HBeAb
November 27, 2019	ALT, HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA
July 2, 2020	ALT, HBsAg, HBsAb, HBeAg, HBeAb, HBV DNA

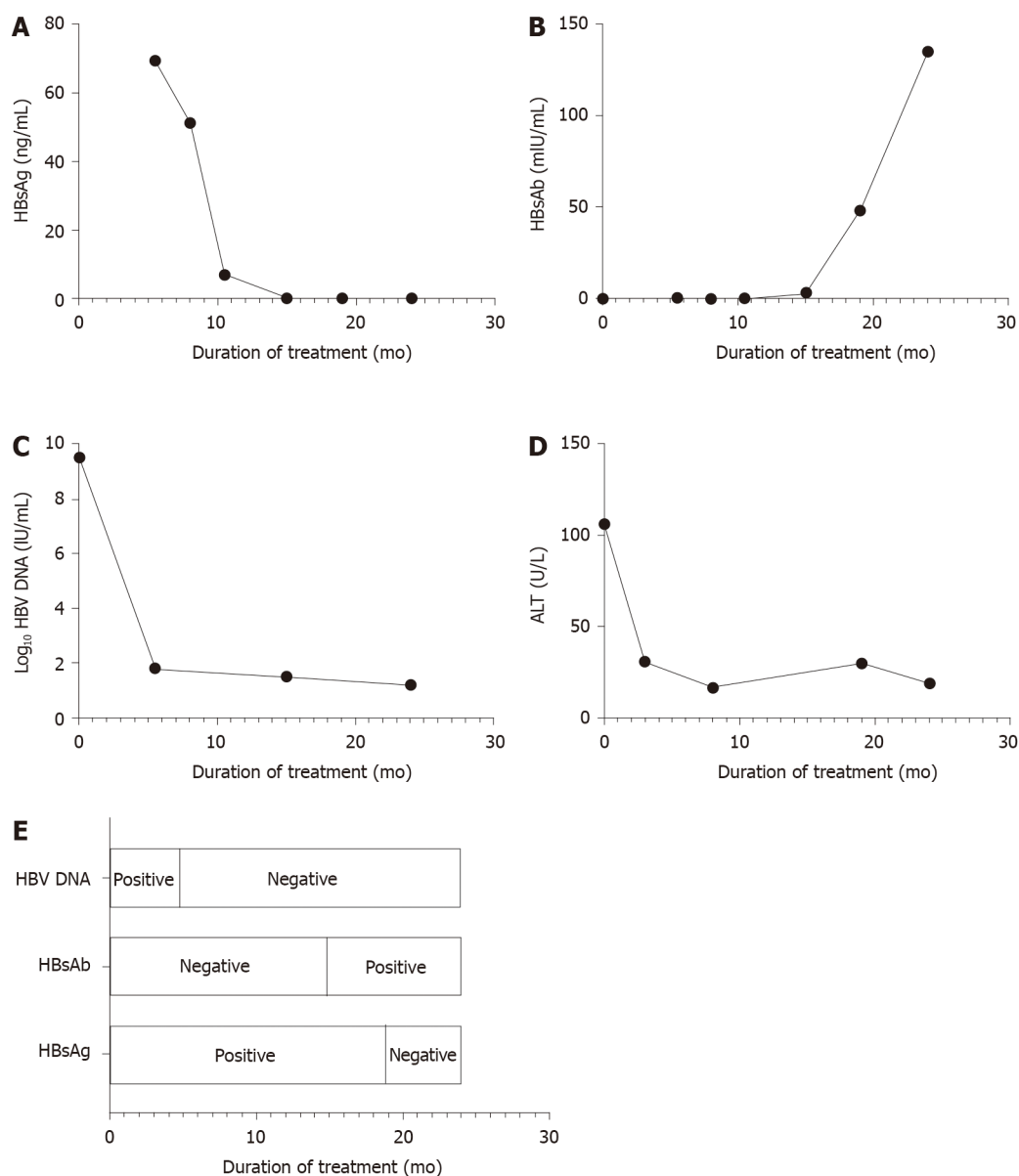
HBeAb: Hepatitis B “e” antibody; HBeAg: Hepatitis B “e” antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

## DISCUSSION

A previous study has shown that the rate of spontaneous loss of HBsAg in Asian infants less than 1 year old is extremely low (between 0.5% and 1.4%)[8]. Our case showed a 4-mo-old infant born to an HBsAg-positive mother who was infected by HBV; serum ALT level on admission was more than twice the normal upper limit, and HBV DNA was  $> 10^9$  IU/mL. Nineteen months after initiating antiviral therapy (LAM), serum HBsAg and HBV DNA were entirely cleared and seroconversion was achieved.

The concept of early treatment for infantile hepatitis B has been reported in recent years and has proven efficacy[9-11]. For infantile hepatitis B, published studies mainly involve LAM therapy. Previously, three cases of infants younger than 1 year old with acute severe hepatitis B, whose serum was HBsAg-positive and HBeAg-negative, were reported. Their serum HBsAg successfully turned to negative within 9 mo after early application of LAM (at initial doses of 8 mg/kg and 3-4 mg/kg, daily) and adjuvant support therapy[12-14]. In 2019, a study by Zhu *et al*[15] showed early antiviral therapy with LAM (4 mg/kg, daily) contributed to the rapid negative conversion of serum HBsAg in infants under 1 year old with HBV DNA  $> 10^5$  IU/mL and ALT more than two times the upper limit of normal. Bertolotti *et al*[9], however, offered a different perspective. They suggested that early antiviral therapy had no role in patients' ALT levels and that the clinical endpoints of the study should not be limited to “obtaining a higher serum HBsAg conversion rate”. Emphasis should be placed on early treatment and the adoption of new treatment strategies to reduce hepatocyte infection and HBV DNA integration in order to avoid the long-term effects of HBV infection.

In this case, HBsAg was completely cleared and HBsAb levels were quantifiably increased after 19 mo of LAM treatment. The immune response to HBV infection in infants has been a controversial topic in recent years. Traditionally, the infant's immune system is considered to be physically immature, and infants are more vulnerable to severe infections than adults. HBV induces an “immune tolerance state” in the host through transplacental HBeAg to produce persistent infections[5]. Recently, however, there is growing evidence showing that infants are neither “immature” nor “immunodeficient”. The innate immune system could display memory features immediately following birth, and specific T cells in infants have the ability to resist viral infection. In other words, the immune system of a newborn is trained or matured and can actually produce a broad-cross protective response to viral antigens[16]. On the other hand, the infant's liver volume is small, and the duration of HBV infection is short. Thus, the absolute amount of HBsAg and HBV DNA load are low, and infection



**Figure 1** Dynamic of hepatitis B surface antigen, hepatitis B surface antibody, log<sub>10</sub> hepatitis B virus DNA, and alanine aminotransferase of the infant after lamivudine treatment. A-D: Dynamic of hepatitis B surface antigen (A), hepatitis B surface antibody (B), log<sub>10</sub> hepatitis B virus DNA (C), and alanine aminotransferase (D); E: Qualitative change of hepatitis B virus DNA, hepatitis B surface antibody, and hepatitis B surface antigen. HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody; HBV: Hepatitis B virus.

of new hepatocytes by HBV is avoided. The plasticity of the early life immune system makes it amenable to therapeutic interventions to combat infection[17]. Therefore, infants with hepatitis B may have better therapeutic outcomes than adults with antiviral therapy.

Nucleoside/nucleotide analogues are the main drugs for the treatment of HBV infection in children. In the treatment of infantile hepatitis B, safety is an important issue that cannot be ignored. Like adults, nucleoside/nucleotide analogues can also cause different degrees of adverse reactions, such as myopathy, nephropathy, neuropathy, and lactic acidosis. Some of these adverse events can be attributed to their effects on mitochondrial dysfunction, and most of the cases have involved LAM and telbivudine treatment. There has been no increase in reported fetal adverse events with LAM treatment[18]. Fortunately, in this case, no adverse reactions occurred throughout the treatment and follow-up period, which is consistent with the findings of Zhu *et al*[15].

## CONCLUSION

Physical examination during pregnancy and timely antiviral therapy are still the main measures to prevent MTIT of HBV. According to several previous reports, HBsAg conversion in infants infected with HBV is higher than that in adults. This was true in the case presented here, and there was no recurrence during the follow-up. In other words, the infant achieved clinical recovery, which indicates that the early application of LAM in the treatment of infants under 1 year old with MTIT of HBV is safe and effective. This case may provide insight into possible adjustment of the current treatment guidelines. More cases are still needed to assess the efficacy of LAM treatment for infantile hepatitis B.

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