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Access to Treatment of Acute Hepatitis B and Chronic Hepatitis B Acute Exacerbation

Akut Hepatit B ve Kronik Hepatit B Akut Alevlenmede Tedaviye Erişim

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ABSTRACT

Objectives: Acute hepatitis B (AHB) and chronic hepatitis B acute exacerbation (CHBAE) can lead to liver failure, necessitating careful monitoring and urgent intervention. This study aimed to evaluate patients diagnosed with AHB and CHBAE, the antivirals initiated, and the methods of accessing these treatments.

Materials and Methods: This study included patients monitored at our hospital over a 5 year period with diagnoses of AHB and CHBAE. Clinical symptoms of the patients, potential etiologies leading to infection or exacerbation, laboratory values, possible diagnoses, indications for antiviral treatment, methods of treatment access, and disease course were retrospectively evaluated.

Results: Seven patients diagnosed with AHB and 12 with CHBAE were included in the study. Antiviral therapy was initiated in nine patients (47.4%). Among these patients, four began antivirals for coagulopathy, one for pregnancy, one for cessation of previously used antivirals for CHB, and three for ongoing liver function test abnormalities and hepatitis B virus-DNA positivity. Only two patients had swift access to treatment through health insurance coverage, while others pursued alternative routes, such as off-label drug approval. None of the patients developed fulminant hepatitis.

Conclusion: The treatment indications for AHB are clearly established based on the guidelines. Some studies recommend initiating treatment for all CHBAE cases, whereas others suggest treatment only when signs of liver failure are present. Access to treatment for patients who require urgent intervention may be delayed due to non-compliance with healthcare reimbursement

ÖZ

Amaç: Akut hepatit B (AHB) ve kronik hepatit B akut alevlenme (KHBAA) karaciğer yetmezliğine sebep olabilecek, dikkatle izlenmesi ve gerektiğinde acil müdahale edilmesi gereken patolojilerdir. Çalışmamızın amacı AHB ve KHBAA tanılarıyla izlenen hastaları, başlanan tedavileri ve tedaviye erişim yollarını değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 5 yıllık süre içinde hastanemizde AHB ve KHBAA tanılarıyla izlenen hastalar dahil edilmiş ve bu hastalara ait bilgiler retrospektif olarak taranmıştır. Hastaların klinik belirtileri, bulaşa veya alevlenmeye sebep olabilecek olası etiyolojileri, laboratuvar değerleri, olası tanıları, antiviral başlanıp başlanmadığı, başlandıysa endikasyonu ve tedaviye ulaşım şekli ile hastalık seyri değerlendirilmiştir.

Bulgular: AHB tanısıyla izlenen yedi (%36,8) ve KHBAA tanısıyla izlenen 12 (%63,8) hasta çalışmaya dahil edilmiş, bu hastaların da dokuzuna (%47,4) antiviral tedavi başlanmıştır. Hastaların dördüne koagülopati, birine gebelik, birine alevlenme öncesi KHB nedeniyle başlanan antivirali kesmiş olması nedeniyle tedavi başlanmış, kalan 3 hastaya ise izlemlerinde devam eden karaciğer fonksiyon testlerindeki anormallik ve hepatit B virüsü-DNA pozitifliği nedeniyle tedavi başlanmıştır. Hastaların yalnızca ikisine geri ödeme kapsamında ilaç raporu çıkarılarak tedaviye hızlıca erişmeleri sağlanmış, diğerleri için endikasyon dışı ilaç onayına başvurmak gibi farklı yollara başvurulmuştur. Hastaların hiçbirinde fulminan hepatit gelişmemiştir.

Sonuç: AHB ve KHBAA karaciğer yetmezliğine sebep olabilecek patolojilerdir. AHB tanısıyla izlenen hastalar için tedavi endikasyonları

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regulations. Adjustments in health insurance coverage for antiviral therapies are necessary to mitigate such delays.

Keywords: Hepatitis B virus, acute hepatitis, acute exacerbation, health insurance, antiviral therapy

rehberler tarafından belirlenmiştir. Çalışmaların bir kısmında KHBAA hastalarının tamamına, bir kısmında ise özellikle karaciğer yetmezliği bulguları olduğunda tedavi başlanması önerilmektedir. Acil tedavi ihtiyacı gelişebilecek bu hastaların tedaviye erişimleri ise sağlık uygulamaları tebliğinin gereklerini karşılamadıkları için gecikebilmektedir. Bu gecikmenin önüne geçebilmek için antiviral tedavilerinin geri ödeme koşullarında düzenlemelerin yapılması gerekmektedir.

Anahtar Kelimeler: Hepatit B virüsü, akut hepatit, akut alevlenme, sağlık sigortası, antiviral

Introduction

Hepatitis B virus (HBV) infection remains one of the leading causes of liver cirrhosis and hepatocellular carcinoma, despite effective vaccines and treatments. It is estimated that 880,000-1.89 million people in the US and more than 250 million people worldwide are infected with HBV. In 2021, 2045 cases of acute hepatitis B (AHB) were reported in the USA, suggesting approximately 13,300 new cases (1). In Turkey, one in every three people is infected with HBV (2).

Patients infected with HBV may present asymptomatically or with no-specific symptoms, such as nausea and vomiting, or with more serious conditions, such as fulminant hepatitis. Although 90% of acute HBV infections in newborns become chronic, this rate is around 5-10% in adults (3). Acute exacerbations are not uncommon in the course of chronic hepatitis B (CHB), with an annual cumulative incidence ranging from 10-30% (4). Immune clearance, spontaneous immune reactivation, discontinuation of nucleos(t)ide analog therapy, use of immunosuppressive therapies, pregnancy, and other conditions can cause exacerbations during the course of CHB. These attacks can be asymptomatic or symptomatic (5,6).

In our country, the criteria for initiating antiviral treatment for CHB are clearly regulated by the Ministry of Health. Treatment recommendations for patients with AHB or CHB acute exacerbation (CHBAE) difficulties in accessing treatment may arise from time to time due to the lack of reimbursement for antiviral treatments in this patient group. The aim of our study was to evaluate the clinical follow-up of patients diagnosed with AHB and CHBAE, the treatments initiated for these patients, and the procurement process of these treatments.

Materials and Methods

Our study included patients followed up with the diagnosis of AHB and acute exacerbations of CHB in of CHB in Recep Tayyip Erdoğan University Training and Research Hospital infectious diseases and clinical microbiology clinic over the past 5 years. Patients with a follow-up duration of >1 year were additionally evaluated to observe the progression of their conditions. Patient age, sex, possible diagnoses, serological test results related to HBV, HBV-DNA levels during follow-up, peak alanine aminotransferase (ALT), bilirubin, international normalized ratio (INR), and the time taken for these values to return to normal ranges were evaluated. Furthermore, if applicable, along with the treatments received, indications, treatment durations, and how these treatments were procured were retrospectively recorded from the hospital data system. Symptoms and signs of patients, potential transmission routes for AHB, such as suspected sexual contact, piercing, surgical operations, invasive procedures, blood transfusions, or conditions that could lead to exacerbations of CHBAE, such as discontinuation of antiviral therapy, pregnancy, use of herbal supplements, or hepatotoxic drug use, were documented based on their medical histories. Additionally, patients were evaluated for the presence of Delta hepatitis or other viral, bacterial, or parasitic infections that could contribute to CHBAE exacerbation.

Acute exacerbation was defined as an abrupt increase in ALT levels to three times the basal level or five times the upper limit of normal (whichever is higher) (7,8).

Chemiluminescent microparticle immunoassay (CMIA) was used for qualitative determination of Hepatitis B-surface antigen (HbsAg), Hepatitis B-e antigen (HBe-Ag) and anti-Hepatitis B-core immunoglobulin M (anti-HBcIgM), immunoglobulin G (anti-HBc IgG), and anti-HBe antibodies. Anti-HBs antibody was quantitatively detected using CMIA. HBV-DNA levels were assessed using real-time polymerase chain reaction.

To determine the possible diagnosis of patients, previous serological test results, high-risk exposure history, serum anti-HBc IgM positivity and titers at the time of diagnosis, anti-HBc IgG positivity and titers, HBV-DNA level, and ALT levels were evaluated.

The decision to initiate antiviral therapy was based on the patient's clinical and laboratory findings, and nucleos(t)ide analog antiviral therapy was initiated for patients with signs of liver failure. If patients' conditions met the criteria of health application regulations for initiating antiviral treatments, drugs were prescribed accordingly. Otherwise, attempts were made to provide drugs by applying for off-label use to the drug-pharmacist association. During this period, medications were procured without prescriptions to avoid delays.

Statistical Analysis

The age was distributed normally, shown as mean ± standard deviation. The distribution of gender, diagnoses, signs and symptoms was presented as percentiles.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of Recep Tayyip Erdoğan University Non-interventional Clinical Research Ethics Committee (approval number: 2024/06, dated: 04.01.2024.)

Results

During the study period, a total of 19 hospitalized patients with diagnoses of AHB and CHBAE were identified in our hospital. The mean age of the patients was 45.3±14.5 years, with 6 (31.6%) women. Seven patients (36.8%) were diagnosed with AHB, while 12 patients (63.2%) were diagnosed with CHBAE. The most common reasons for patient admission were fatigue (63%), loss of appetite (37%), nausea/vomiting (31.5%), jaundice (21%), and high fever (21%). Six patients (31.5%) were asymptomatic, and liver function abnormalities were detected during routine tests. Three of the patients diagnosed with AHB had a history of risky contacts that could lead to transmission, whereas one patient diagnosed with CHBAE was pregnant, one had a COVID-19 infection, and one had exacerbation possibly due to discontinuation of antiviral therapy. Delta virus co/super-infection was not detected in any of the patients (Table 1). All patients included in the study were positive for hepatitis B surface antigen, and anti-HBs positivity was detected in two of them. The highest ALT, INR, total bilirubin, and HBV-DNA levels during the initial follow-up period are presented in Table 2.

Treatment was initiated for one of the AHB patients (14.3%) and eight of the CHBAE patients (66.6%). Four patients were started on antiviral therapy for coagulopathy and one for pregnancy. One of the patients was restarted on antiviral treatment, which he had left voluntarily and was faced with acute exacerbation, and the remaining three patients were initiated on antivirals due to ongoing liver function abnormalities and high DNA levels with the diagnosis of CHB. Four patients with CHBAE did not receive antiviral treatment due to lack of follow-up after discharge and one patient was anti-HBs positive. Among the patients who started treatment, four received disoproxil fumarate, three received alafenamide fumarate, and two received entecavir. Immediate health insurance coverage was provided to only two out of the nine patients who received treatment. One of these patients had previously been

Table 1: Characteristics, risk factors, and signs of patients followed up with a diagnosis of AHB and CHBAE

					Risk factors					Signs				
	Age	Gender	CHB	Possible diagnosis	Discontinuation of antiviral therapy	Pregnancy	Herbal	Hepatotoxic drugs	Other risk factors	Jaundice	Loss of appetite	N/V	Fever	Malaise
Patient 1	63	F	-	AHB	-	-	-	-	-	-	-	-	-	+
Patient 2	62	M	-	AHB	-	-	-	-	CABG	-	-	-	-	-
Patient 3	47	M	+	CHBAE	-	-	-	-	-	-	-	-	-	+
Patient 4	60	M	-	CHBAE	-	-	-	-	-	-	+	+	-	+
Patient 5	46	M	+	CHBAE	+	-	-	+	-	-	-	-	-	-
Patient 6	54	M	+	CHBAE	-	-	-	-	-	-	-	+	+	-
Patient 7	58	M	+	CHBAE	-	-	-	-	-	-	-	-	-	-
Patient 8	24	F	-	CHBAE	-	+	-	-	-	-	-	-	-	-
Patient 9	46	M	+	CHBAE	-	-	-	-	-	-	-	-	-	-
Patient 10	27	M	+	CHBAE	-	-	-	-	-	+	+	-	+	+
Patient 11	23	F	+	CHBAE	-	-	-	-	-	+	+	+	-	+
Patient 12	35	M	+	CHBAE	-	-	-	-	COVID-19	-	-	-	+	+
Patient 13	27	F	+	CHBAE	-	-	-	-	-	-	+	+	-	+
Patient 14	35	M	-	AHB	-	-	-	-	Risky sexual contact	-	-	-	-	+
Patient 15	38	M		CHBAE										
Patient 16	49	M	-	AHB	-	-	-	+	-	+	+	-	+	+
Patient 17	69	M	-	AHB	-	-	-	-	-	+	+	+	-	+
Patient 18	37	F	-	AHB	-	-	-	-	Piercing	-	-	-	-	+
Patient 19	60	F	-	AHB	-	-	-	-	-	-	+	+	-	+

F: Female, M: Male, AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, CHB: Chronic hepatitis B, CABG: Coronary artery by-pass great operation, COVID-19: Coronavirus disease 2019; N/V: Nausea/Vomiting

Table 2. Laboratory values of patients and normalization time for abnormal findings

	Possible diagnose	Laboratory Values				Serology						Normalization time (wk)			Seroconversion to anti-HB antibodies	Anti HBs-time (wk)	Viral eradication (wk)
		ALT-max. (IU/mL)	INR-max.	Bilirubin-max. (mg/dL)	HBV-DNA (IU/mL)	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc IgM	Anti-HBc IgG	ALT	INR	Bilirubin			
Patient 1	AHB	1157	0.9	1.5	198200000	+	-	+	+	+	+	12	-	8	+	28	28
Patient 2	AHB	867	1.6	2.0	41937505	+	-	+	-	+	+	16	8	8	+	52	28
Patient 3	CHBAE	2401	1.5	2.5	80778027	+	-	-	+	-	+	6	6	2	-	-	52
Patient 4	CHBAE	1659	1.4	2.4	742	+	+	+	+	+	+	5	1	5	+	0	6
Patient 5	CHBAE	1094	1.1	0.8	6407404	+	-	-	+	-	+	16	-	-	-	-	16
Patient 6	CHBAE	647	1.2	1.1	69424617	+	+	-	+	-	+	12	-	-	+	0	
Patient 7	CHBAE	601	1.2	1.6	1407	+	-	-	+		-	52	-	-	-	-	84*
Patient 8	CHBAE	990	1.2	0.8	83227075	+	-	-	+	-	+	6	-	-	-	-	8
Patient 9	CHBAE	702	1.2	1.0	332130	+	-	-	+		+	76	-	-	-	-	72
Patient 10	CHBAE	1213	1.0	0.5	32431592	+	-	-	+	-	+	8	-	-	-	-	
Patient 11	CHBAE	3279	2.1	9.2	105615	+	-	-	+	+	+	8	1	8	+	14	16
Patient 12	CHBAE	916	1.5	0.6	708	+	-	-	+	-	+	NI	NI	NI	NI	NI	NI
Patient 13	CHBAE	877	1.4	1.4	248700000	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 14	AHB	537	0.9	2.2	1201	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 15	CHBAE	1145	1.0	1.2	1240000	+	-	-	+	-	+	NI	NI	NI	NI	NI	NI
Patient 16	AHB	3509	1.1	7.2	15650000	+	-	-	+	+	+	8	-	4	-	-	13
Patient 17	AHB	1573	1.2	1.7	51722666	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 18	AHB	1559	1.0	3.9	1229545	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 19	AHB	1408	1.1	8.5	719400	+	-	-	+	+	+	5	0	6	-	-	NI

*HBV-DNA levels were negative on the third month of antiviral treatment, AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, wk: Week, NI: No information, max.: Maximum, ALT: Alanine aminotransferase, IU: Interantional unit, INR: International normalised ratio, HBV-DNA: Hepatitis B virus DNA level, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B-e antigen, Anti-HBe: Antibody to hepatitis B-e antigen, Anti-HBc IgM: Immunglobulin M antibody to hepatitis B core antigen, Anti-HBc IgG: Immunglobulin G antibody to hepatitis B core antigen

using antivirals with a diagnosis of CHB, and one was pregnant. Treatment was initiated for the remaining three patients by applying for off-label drug approval, and one patient was started because of a lack of reimbursement coverage (Table 3). None of the patients developed fulminant hepatitis, and there was no need for liver transplantation.

Discussion

Nineteen patients diagnosed with AHB and CHB with CHBAE were included in our study, and antiviral therapy was initiated in nine of them. Only three of these patients were able to access treatment early with health insurance coverage, whereas for others, treatment was attempted through other ways like off-label drug approvals or buying medicines for a fee. Notably, access to antiviral therapy was hindered by the lack of reimbursement coverage for these treatments. Importantly, none of the patients experienced liver failure, transplantation requirement, or death.

AHB and CHBAE are diseases that require careful monitoring and prompt intervention because they are acute pathologies that can lead to liver failure, transplantation, or even death (9). It may be difficult for patients who develop an indication for "urgent" antiviral treatment during the follow-up period to access treatment due to reasons such as the expensiveness of the treatments and the fact that the drugs are not covered by health insurance. Although antiviral indications are determined in the guidelines for these conditions, challenges in accessing treatment due to lack of reimbursement coverage under the current healthcare system regulations can pose significant obstacles.

Although the incidence of symptomatic disease in the acute phase of HBV infection is not high, exacerbations can occasionally occur in the chronic phase due to various reasons. Therefore, a higher incidence of CHBAE was expected among patients presenting to the acute hepatitis clinic (4,5), which was consistent with our study.

Table 3. Treatment indications and treatment access

	Possible diagnose	Indication for treatment	Antiviral treatment	Access to treatment	Special conditions	Treatment duration (wk)
Patient 1	AHB	-	-			-
Patient 2	AHB	Coagulopathy	ENT	OLDA		52
Patient 3	CHBAE	Coagulopathy	ENT	Non-HI	Treatment was started immediately, and health insurance coverage was obtained after liver bx in the 1st month of follow-up	Going on
Patient 4	CHBAE	Coagulopathy	TDF	OLDA	Anti HBs positive HBV-DNA positive	24
Patient 5	CHBAE	CHB	TAF	HI	Exacerbation due to discontinuation of antiviral therapy	Going on
Patient 6	CHBAE	-	-			-
Patient 7	CHBAE	CHB	TAF	HI	Treatment was started after liver biopsy on the 18th month of follow-up	Going on
Patient 8	CHBAE	Pregnancy	TDF	HI	Treatment was stopped after pregnancy	16
Patient 9	CHBAE	CHB	TAF	HI	Treatment was started after liver biopsy in the 10th month of follow-up	Going on
Patient 10	CHBAE	-	-			-
Patient 11	CHBAE	Coagulopathy	TDF	OLDA		24
Patient 12	CHBAE	-	-		Follow-up time is insufficient	
Patient 13	CHBAE	-	-		Follow-up time is insufficient	
Patient 14	AHB	-	-		Follow-up time is insufficient	
Patient 15	CHBAE	CHB	TDF	HI	Treatment was started after liver biopsy in the 3rd month of follow-up, and the follow-up time was insufficient	Unfollowed
Patient 16	AHB	-	-		Follow-up time is insufficient	
Patient 17	AHB	-	-		Follow-up time is insufficient	
Patient 18	AHB	-	-		Follow-up time is insufficient	
Patient 19	AHB	-	-		Follow-up time is insufficient	

AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, CHB: Chronic hepatitis B, ENT: Entecavir, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, OLDA: Off-label drug approval, HI: Health insurance, wk: Week, non-HI: Treatment not covered by health insurance, HBV-DNA: Hepatitis B virus DNA level

Among the patients diagnosed with AHB, three had a history of risky contacts, and one underwent coronary artery bypass grafting, potentially indicating postoperative complications or nosocomial exposure. Many of these patients presented with jaundice, a typical clinical manifestation of AHB infection (8). In contrast, patients with CHBAE exhibited a diverse clinical profile and milder symptoms, such as nausea, vomiting, and loss of appetite. Several patients had histories of hepatotoxic drug use, concurrent viral infections, pregnancy, or discontinuation of antiviral drugs, raising the possibility of intensifying chronic liver disease.

Routine antiviral therapy is not recommended for adult patients with AHB, as only 5-10% develop CHB and there is a chance of spontaneous resolution. However, antiviral therapy with nucleos(t)ide analogs is recommended in severe cases with evidence of coagulopathy (INR≥1.5 or prothrombin time prolonged by 4 seconds), prolonged hyperbilirubinemia (elevated bilirubin levels persisting for more than 4 weeks), or signs of hepatic encephalopathy (5,10). In our study, one of the seven patients with AHB received entecavir due to coagulopathy, whereas the others recovered with supportive treatment.

Exacerbations can occur at any stage of chronic HBV infection due to various reasons, such as immunological factors and superinfections, with spontaneous exacerbations being more common, especially in HBeAg negative stage (10-12). Most of the patients included in our study were monitored for CHBAE, and only one tested positive for HBeAg. Due to the risk of decompensation and mortality associated with underlying chronic liver disease, antiviral therapy initiation and continuation are recommended for this patient group (6,9,13). Some studies have emphasized the importance of antiviral therapy, particularly in patients with severe hepatitis causing coagulopathy (8). A significant proportion of patients diagnosed with CHBAE and followed up in our study were started on antiviral therapy.

Among the nine patients included in our study who started antiviral drugs, only two of them were able to access treatment promptly under health insurance reimbursement coverage; other

patients had access through alternative means, leading to delays in early intervention. Despite challenges in treatment access, several patients showed favorable responses to antiviral therapy, as evidenced by seroconversion to anti-HBs and suppression of HBV-DNA levels.

Study Limitations

The limitations of limitations of this study include inadequate follow-up duration for some patients, limited assessment of long-term treatment efficacy and virological response durability, and small number of patients.

Conclusion

Overall, our findings highlight the complex clinical presentation and treatment challenges of patients with AHB and CHBAE. The lack of reimbursement coverage for antiviral therapies under current healthcare regulations in Turkey remains a significant barrier to treatment access and continuity, particularly in emergency situations where immediate treatment initiation is crucial. Updating healthcare regulations is essential to ensure equitable access to essential therapies for hepatitis B management.

Ethics

Ethics Committee Approval: Ethical Approval was obtained from the Recep Tayyip Erdoğan University Non-interventional Clinical Research Ethics Committee (approval number: 2024/06, dated: 04.01.2024.)

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Concept: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Design: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Data Collection or Processing: A.Ö., T.İ., S.M.Ç., Analysis or Interpretation: A.Ö., T.İ., Literature Search: A.Ö., Writing: A.Ö., T.İ., S.M.Ç.

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