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BRIEF ARTICLE

Influence of chronic HBV infection on superimposed acute hepatitis E

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Abstract

AIM: To investigate the influence of chronic hepatitis B virus (HBV) infection [based on the status of hepatitis B e antigen (HBeAg), HBV DNA, and cirrhosis] on superimposed acute hepatitis E.

METHODS: A total of 294 patients were recruited from the Department of Infectious Diseases of the Third Affiliated Hospital, Sun Yat-sen University, from January 2003 to January 2012. The patients were classified into two groups: an HBV + hepatitis E virus (HEV) group (a group with chronic HBV infection that was superinfected with acute hepatitis E, n = 118) and an HEV group (a group with acute hepatitis E, n = 176). We retrospectively analyzed and compared the clinical features of the two groups. Statistical analyses were performed using the χ^2 test or Fisher's exact test for categorical variables and the Student's t test for continuous variables. A P value < 0.05 was considered statistically significant.

RESULTS: The peak values of prothrombin time, serum total bilirubin, and Model for End-Stage Liver Disease scores were significantly higher in the HBV + HEV group. More patients in the HBV + HEV group had complications (39.8% *vs* 16.5%, P = 0.000) and developed liver failure (35.6% *vs* 8.5%, P = 0.000). Additionally, the mortality of the HBV + HEV group was significantly higher (20.3% *vs* 7.4%, P = 0.002). Further analysis of the HBV + HEV group showed that there were no significant differences in complication occurrence, liver failure incidence, or mortality between patients with different HBeAg and HBV DNA statuses. However, in patients with underlying cirrhosis, complication occurrence and liver failure incidence significantly increased. In total, 12.7% of the patients in the HBV + HEV group received anti-HBV treatment, but this therapy failed to reduce mortality in patients who developed liver failure.

CONCLUSION: The presence of underlying cirrhosis in chronic HBV infection results in more severe clinical outcomes with superimposed acute hepatitis E. Anti-HBV treatment cannot improve the prognosis of liver failure caused by HBV-HEV superinfection.

Key words: Chronic hepatitis B virus infection; Acute hepatitis E; Superinfection; Clinical profile; Anti-hepatitis B virus treatment

Core tip: Previous studies have shown that chronic hepatitis B virus (HBV) infection has a negative impact on superimposed acute hepatitis E. However, it remains unknown whether the disease severity of acute hepatitis E correlates with the underlying HBV replication status or with liver histological lesions. Our study

showed that the disease severity of acute hepatitis E correlated not with the HBV replication status (based on the status of hepatitis B e antigen and HBV DNA), but rather with the presence of underlying cirrhosis. This finding raised the question of whether anti-HBV treatment improves the outcome of liver failure caused by HBV-hepatitis E virus superinfection. We found that anti-HBV treatment could not improve the prognosis of such liver failure.

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INTRODUCTION

Infection by hepatitis B virus (HBV) is a serious public health problem worldwide. Two billion people worldwide have been infected with HBV, including more than 240 million cases of chronic infection[1,2]. During the chronic course of HBV infection, there is a chance that patients may be sporadically superinfected with other viruses, such as hepatitis E virus (HEV). HEV is mainly endemic in tropical and subtropical developing countries, including China. Studies of serum epidemiology in China showed that HEV superinfection in patients with chronic hepatitis B is present in 17.6% of these patients[3].

HEV generally causes an acute, self-limiting illness, followed by a complete recovery. Recent studies have shown that HEV can result in severe disease in patients with underlying chronic HBV infection and even liver failure[4-7]. In the chronic course of HBV infection, there are different statuses of hepatitis B e antigen (HBeAg) and HBV DNA, and certain patients have a higher probability of developing cirrhosis. No previous studies are available regarding whether these different chronic statuses have different influences on the superinfection of HBV and HEV.

Liver failure related to HBV activation remains a rapidly progressive and frequently fatal condition. Traditional treatment is generally supportive. International HBV treatment guidelines recommend initiating nucleos(t)ide analogs as early as possible in this patient population[8,9]. Studies on the efficacy of nucleoside analogs have been emerging in recent years. Recent studies have shown that anti-HBV treatment could improve the outcome of this patient population[10-13]. Superinfection with HEV is another common cause of liver failure in patients with chronic HBV infection, accounting for 20% of cases in regions endemic for HEV[4]. Importantly, such liver failure caused by HBV and HEV results in high mortality rates. However, there are still no data on anti-HBV treatment for liver failure caused by the superinfection of HBV and HEV, as previous studies did not consider patients with superinfection.

The aim of our study was to investigate the impact of chronic HBV infection on superimposed acute hepatitis E, particularly the influence of the status of HBeAg, HBV DNA, and cirrhosis on disease severity. Furthermore, we evaluated the effect of anti-HBV treatment on HBV-HEV superinfection. The use of a single liver function index is limited in assessing liver function, but the Model for End-Stage Liver Disease (MELD) score[14], which combines multiple indices, can play a useful role in this assessment. The MELD score system has been used extensively for the allocation of donor livers worldwide[15] and has been validated for use in chronic hepatitis B (CHB)[16]. Thus, the MELD score was applied for a comprehensive analysis of liver function.

MATERIALS AND METHODS

Patients

This work was approved by the local ethics committee of our university. A total of 294 patients were recruited from the Department of Infectious Diseases of the Third Affiliated Hospital, Sun Yat-sen University, from January 2003 to January 2012. Among these patients, 118 were diagnosed with acute hepatitis E and chronic HBV superinfection (HBV + HEV group), and 176 patients were diagnosed with acute hepatitis E alone (HEV group). Acute hepatitis E was diagnosed when patients were hospitalized with typical symptoms of acute viral hepatitis and the presence of anti-HEV serum IgM and IgG. The presence of HBsAg and the absence of anti-HBc IgM established a diagnosis of chronic HBV infection. The diagnosis of liver failure was based on the Guidelines for Diagnosis of Liver Failure (2006)[17] and included the presence of two or more of the following: an international normalized ratio (INR) $\geq$ 1.5, serum total bilirubin (TBil) > 10 times the upper limit of normal, ascites, hepatic encephalopathy, decreased liver size, or hepatorenal syndrome. The complications that were observed were ascites, peritonitis, hepatic encephalopathy, gastrointestinal bleeding, and hepatorenal syndrome.

Detection

Anti-HEV serum IgM and IgG were detected with an enzyme-linked immunosorbent assay (Genelabs Technologies, Singapore). HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb were detected with an automatic rapid immunoassay system (AxSYM; Abbott, United States). HBV DNA levels were determined by real-time polymerase chain reactions using commercial diagnostic kits (Da-an GeneCo., Guangzhou, China) with a lower detection limit of 500 copies/mL. Liver function tests were performed using an automatic biochemical analyzer (AU 640; Olympus, Japan). In this study, prothrombin time (PT)-INR (PT/reference PT) = international sensitivity index. The PT was measured using the detection reagent STA-Neoplastine(r) CI PLUS with an automatic coagulometer (STA-R) (Diagnostica Stago, France). A diagnosis of underlying cirrhosis was made based on clinical,

Table 1 Demographic and clinical characteristics of the hepatitis B virus + hepatitis E virus group and hepatitis E virus group

	HBV + HEV group (n = 118)	HEV group (n = 176)	P values
Age (yr)	44.5 ± 13.8	54.1 ± 15.8	0.000[1]
Sex			0.000[1]
Male	109 (92.4)	140 (79.5)	
Female	9 (7.6)	36 (20.5)	
ALT (U/L)	266.0 ± 227.3	262.9 ± 212.9	0.905
AST (U/L)	228.9 ± 207.1	228.4 ± 213.1	0.986
PT (s)	22.1 ± 11.3	16.8 ± 7.9	0.000[1]
PTA (%)	57.3 ± 26.6	77.2 ± 24.9	0.000[1]
TBil (μmol/L)	334.7 ± 228.0	277.5 ± 217.4	0.031[1]
MELD score	20.0 ± 9.7	15.1 ± 8.6	0.000[1]
Complications	47 (39.8)	29 (16.5)	0.000[1]
Liver failure	42 (35.6)	15 (8.5)	0.000[1]
Death	24 (20.3)	13 (7.4)	0.002[1]

[1]Denotes significant P value. Data are expressed as absolute n (%) or mean ± SD. HBV: Hepatitis B virus; HEV: Hepatitis E virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; PTA: Prothrombin activity; TBil: Serum total bilirubin; MELD: Model for End-Stage Liver Disease.

biochemical, and ultrasonographic findings. Sample collection, transportation, preservation, and processing were performed according to the manufacturer's instructions.

Calculation of MELD scores

MELD score = 3.8 × $\log_e$ [serum bilirubin (μmol/L) × 0.058] + 11.2 × $\log_e$ (PT-INR) + 9.6 × $\log_e$ [serum Cr (μmol/L) × 0.011] + 6.4 × (0 or 1) (cholestatic or alcoholic cirrhosis: 0; other liver diseases: 1)[14].

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, United States). The χ^2 test or Fisher's exact test were used for categorical variables, and the Student's t test was used for continuous variables. Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as the percentage (number). P values < 0.05 were considered statistically significant.

RESULTS

Demographic characteristics

The demographic characteristics of the 294 patients are shown in Table 1. The males outnumbered the females in both groups. The mean ages at admission were 44.5 and 54.1 years in the HBV + HEV and HEV groups, respectively.

Laboratory findings

Liver function tests were performed at admission and regularly after admission. We compared the most severe laboratory abnormalities in the biochemical profile between the two groups (Table 1). The mean peak values of PT (22.1 s *vs* 16.8 s, P = 0.000) and TBil (334.7 μmol/L *vs* 277.5 μmol/L, P = 0.031), as well as the mean MELD score (20.0 *vs* 15.1, P = 0.000), were significantly higher in the HBV + HEV group compared with the HEV group. In contrast, the mean values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) did not differ significantly between the two groups.

Clinical outcomes

As shown in Table 1, the incidences of complications, liver failure, and death were compared between the two groups with respect to clinical outcomes. Complications were noted in 39.8% (47/118) and 16.5% (29/176) of the patients in the HBV + HEV and HEV groups, respectively, and the occurrence of complications in the HBV + HEV group was significantly higher than that in the HEV group (P = 0.000). The incidence of liver failure was significantly higher among patients with superinfection than among patients with acute hepatitis E alone (35.6% *vs* 8.5%, P = 0.000). The mortality rates were also significantly different between the two groups (20.3% in the HBV + HEV group and 7.4% in the HEV group).

Influence of chronic status of HBV infection on acute hepatitis E

To evaluate the influence of chronic HBV infection (based on the status of HBeAg, HBV DNA, and cirrhosis), we performed further analysis of the HBV + HEV group (Table 2). Of the 118 patients in the HBV + HEV group, 16.9% (20/118) were HBeAg-positive, 55.1% (65/118) were HBV DNA-positive, and 14.4% (17/118) had underlying cirrhosis. The occurrence of complications, liver failure, and death did not differ significantly between the HBeAg (+/-) and HBV DNA (+/-) subgroups. Patients with underlying cirrhosis had a significantly higher incidence of complications and liver failure. The mortality rate was 23.5% in the cirrhosis subgroup and 19.8% in the non-cirrhosis subgroup, which was not a significant difference.

Anti-HBV treatment in the HBV + HEV group

Of the 118 patients in the HBV + HEV group, only 15 (12.7%) patients took oral anti-HBV agents. Three of these patients received lamivudine, and the other 12 patients received entecavir. In the HBV + HEV group, 42 patients developed liver failure, and 28.6% received anti-HBV treatment. Only 3.9% of patients without liver failure received anti-HBV treatment.

The mean mortality rates among the 42 patients with liver failure were 66.7% and 53.3% for patients who were and were not receiving anti-HBV treatment, respectively, which were not significantly different (Table 3).

DISCUSSION

Due to the high prevalence of both HBV and HEV infection and the lack of cross-immunity between the two viruses, HBV-HEV superinfection is common[3,18].

In our study, patients with acute hepatitis E superimposed on chronic HBV infection had higher peak laboratory abnormalities and poorer outcomes. There was also

Table 2 Influence of chronic hepatitis B virus infection on acute hepatitis E *n* (%)

	HBV + HEV group								
	Status of HBeAg			Status of HBV DNA			Status of cirrhosis		
	+ (*n* = 20)	- (*n* = 98)	*P* value	+ (*n* = 65)	- (*n* = 53)	*P* value	+ (*n* = 17)	- (*n* = 101)	*P* value
MELD score	17.0 ± 7.0	20.6 ± 10.1	0.131	21.5 ± 10.6	18.3 ± 8.3	0.074	24.7 ± 12.2	19.2 ± 9.1	0.03[1]
Liver failure	5 (25)	37 (37.8)	0.317	25 (38.5)	17 (32.1)	0.563	11 (64.7)	31 (30.7)	0.01[1]
Complications	7 (35)	40 (40.8)	0.803	25 (38.5)	22 (41.5)	0.850	16 (94.1)	31 (30.7)	0.00[1]
Death	2 (10)	22 (22.4)	0.359	14 (21.5)	10 (19.9)	0.820	4 (23.5)	20 (19.8)	0.748

[1]Denotes significant *P* value. HBV: Hepatitis B virus; HEV: Hepatitis E virus; HBeAg: Hepatitis B e antigen; MELD: Model for End-Stage Liver Disease.

Table 3 Anti-hepatitis B virus treatment in patients with liver failure in the hepatitis B virus + hepatitis E virus group

	Patients receiving anti-HBV treatment (*n* = 12)	Patients not receiving anti-HBV treatment (*n* = 30)	*P* value
HBV DNA (log_{10} copies/mL)	4.99e7 ± 9.82e7	2.35e8 ± 9.20e8	0.495
MELD score	33.2 ± 9.4	28.3 ± 9.2	0.129
Mortality	8 (66.7)	53.3 (16/30)	0.506

Data are expressed as absolute *n* (%) or mean ± SD. HBV: Hepatitis B virus; HEV: Hepatitis E virus; MELD: Model for End-Stage Liver Disease.

a higher prevalence of liver failure among those patients. The present study confirmed the previous finding that acute HEV infection can cause severe liver injury in patients with chronic HBV infection[4-7]. This result indicates that chronic HBV infection has a negative impact on the clinical features of acute hepatitis E. However, it remains unknown whether the disease severity of acute hepatitis E correlates with the underlying HBV replication status or liver histological lesions. Our further analysis of the superinfection group showed that the disease severity of superimposed acute hepatitis E correlated not with the HBV replication status (based on the status of HBeAg and HBV DNA), but rather with the presence of underlying liver histological lesions (liver cirrhosis).

It has long been suggested that patients with chronic HBV infection are immunologically different from people without HBV infection. For instance, patients with chronic HBV infection have been reported to have impaired cell-mediated immunity[19-22], decreased peripheral-blood T cell numbers[23,24], impaired interferon production[25,26], and imbalanced cytokine levels[27,28] and may have other currently unrecognized differences. The severity of acute viral hepatitis has been suggested to be dependent on host immune factors rather than on the direct toxicity of the virus. Thus, with impaired and imbalanced immunity in chronic HBV infection, HEV may trigger an excessive immunological response and then induce severe damage in hepatocytes. Alternatively, hepatocyte impairment may accumulate during the chronic course of HBV infection. Thus, with preexisting liver lesions, especially due to cirrhosis, hepatocytes may be limited in their ability to regenerate. This limitation contributes to more severe liver injury in patients with acute hepatitis E superimposed on chronic HBV infection.

According to our data, most patients in the HBV + HEV group were HBeAg-negative, and nearly 50% were HBV DNA-negative. Further analysis showed that the disease severity of acute hepatitis E did not correlate with the status of HBeAg or HBV DNA. This finding indicates that in the superinfection of HBV and HEV, chronic HBV infection is inactive, and HEV is the main trigger factor for severe disease. Thus, the finding raises the question of whether anti-HBV treatment improves the outcome of HBV-HEV superinfection, which requires further investigation.

Acute exacerbation frequently occurs in the natural course of chronic HBV infection. In the case of acute exacerbation caused by spontaneous HBV activation, anti-HBV treatment can strongly suppress HBV replication, and most patients can recover. However, certain patients may develop liver failure, which is named HBV-related acute-on-chronic liver failure (HBV-ACLF). HBV-ACLF remains a rapidly progressive and frequently fatal condition for which mortality reaches 25% to 35%. International guidelines recommend initiating nucleos(t)ide analogs as early as possible in this patient population[8,9]. Recent studies have shown that anti-HBV treatment can improve the outcome of HBV-ACLF[10-13]. Superinfection with HEV is another common cause of liver failure in chronic HBV infection and is present in 20% of cases in regions endemic for HEV[4]. Importantly, such liver failure caused by HBV and HEV results in high rates of mortality. However, for the liver failure caused by the superinfection of HBV and HEV, there are still no data on anti-HBV treatment. In our study, we evaluated the results of anti-HBV treatment administration to the HBV + HEV group. Of the 76 patients without liver failure, only 3.9% took anti-HBV drugs, but the prognosis of this patient population was good. This finding indicates that it is not necessary to administer anti-HBV treatment as soon as possible to patients with HBV-HEV superinfection in mild disease. The necessity of anti-HBV treatment for HBV infection should be re-evaluated by monitoring the HBV DNA level and liver function tests after recovery from acute hepatitis E.

As shown by our data, up to 28.6% of patients received anti-HBV treatment once superinfection caused liver failure. The mortality rate among patients receiving anti-HBV treatment was 66.7%, which was not significantly different from the mortality rate of patients not receiving anti-HBV treatment. Thus, anti-HBV treatment

was unable to improve the outcome of the liver failure caused by HBV-HEV superinfection. As mentioned previously, HEV infection plays the most important role in the disease. The infection triggers strong immunological injury in hepatocytes, which results in liver failure. Anti-HBV treatment can inhibit HBV replication but cannot stop the strong immune activity, so the therapy cannot improve the outcome of this patient population.

In conclusion, our study indicates that acute hepatitis E is associated with more severe disease in patients with chronic HBV infection and that disease severity correlates with the underlying cirrhosis in chronic HBV infection. Anti-HBV treatment cannot improve the prognosis of liver failure caused by HBV-HEV superinfection. As HBV vaccination is being aggressively pursued worldwide, HEV vaccination should also be considered in endemic areas when a vaccine becomes available[29]. Additionally, preventive measures are important to the related morbidity and mortality, such as the consumption of boiled water and well-cooked food.

The main limitation of the present study is its retrospective nature. HEV-RNA levels were not regularly checked, so we are not convinced that there is no substantial contribution of HEV load to the disease severity of HBV-HEV superinfection. Additionally, underlying cirrhosis was mainly assessed by ultrasonography. Thus, it is possible that early-stage underlying cirrhosis was missed. Despite these limitations, our study is significant because the work provides preliminary support for not administering anti-HBV treatment in HBV-HEV superinfection, as chronic HBV replication status (based on the status of HBeAg and HBV DNA) does not determine the outcome of HBV-HEV superinfection.

COMMENTS

Background

Hepatitis B virus (HBV)-hepatitis E virus (HEV) superinfection is common. Recent studies have shown that HEV can result in severe disease in patients with underlying chronic HBV infection and even liver failure. However, whether the disease severity of acute hepatitis E correlates with the underlying HBV replication status (based on the status of HBeAg and HBV DNA) or liver histological lesions and whether anti-HBV treatment can improve the outcome of HBV-HEV superinfection are unknown.

Research frontiers

The present study investigated the influence of chronic HBV infection (based on the status of HBeAg, HBV DNA, and cirrhosis) on superimposed acute hepatitis E. Furthermore, the study evaluated the effect of anti-HBV treatment on HBV + HEV superinfection.

Innovations and breakthroughs

The disease severity of superimposed acute hepatitis E correlated not with the HBV replication status (based on the status of HBeAg and HBV DNA), but rather with the presence of underlying cirrhosis. Anti-HBV treatment did not improve the prognosis of liver failure caused by HBV-HEV superinfection.

Peer review

This study is of great interest and offers useful implications for the treatment of HBV-HEV superinfection.

REFERENCES

1 Fact sheet N°204 of World Health Organization. Available from: URL: http://www.who.int/mediacentre/factsheets/fs204/en/

2 **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107 [PMID: 14996343 DOI: 10.1046/j.1365-2893.2003.00487.x]

3 **Xiong LS**, Cui SF, Zhou JG, Xing Y. [Detection and analysis of HAV-HEV, HGV infection in patients with viral hepatitis]. *Zhonghua Ganzangbing Zazhi* 2004; **12**: 395-396 [PMID: 15268800]

4 **Kumar M**, Sharma BC, Sarin SK. Hepatitis E virus as an etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease. *J Gastroenterol Hepatol* 2008; **23**: 883-887 [PMID: 18070014 DOI: 10.1111/j.1440-1746.2007.05243.x]

5 **Ke WM**, Li XJ, Yu LN, Lai J, Li XH, Gao ZL, Chen PJ. Etiological investigation of fatal liver failure during the course of chronic hepatitis B in southeast China. *J Gastroenterol* 2006; **41**: 347-351 [PMID: 16741614 DOI: 10.1007/s00535-005-1781-y]

6 **Zhang GS**, Feng FM, Li YL, Yuan JX, Shang H. A study of chronic hepatitis B infection superinfected with hepatitis E infection. *Zhonghua Ganzangbing Zazhi* 2006; **14**: 906-908 [PMID: 17196134]

7 **Ramachandran J**, Eapen CE, Kang G, Abraham P, Hubert DD, Kurian G, Hephzibah J, Mukhopadhya A, Chandy GM. Hepatitis E superinfection produces severe decompensation in patients with chronic liver disease. *J Gastroenterol Hepatol* 2004; **19**: 134-138 [PMID: 14731121 DOI: 10.1111/j.1440-1746.2004.03188.x]

8 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227-242 [PMID: 19054588 DOI: 10.1016/j.jhep.2008.10.001]

9 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: 19669255 DOI: 10.1007/s12072-008-9080-3]

10 **Miyake Y**, Iwasaki Y, Takaki A, Fujioka S, Takaguchi K, Ikeda H, Kobashi H, Sakaguchi K, Shiratori Y. Lamivudine treatment improves the prognosis of fulminant hepatitis B. *Intern Med* 2008; **47**: 1293-1299 [PMID: 18628576 DOI: 10.2169/internalmedicine.47.1061]

11 **Jochum C**, Gieseler RK, Gawlista I, Fiedler A, Manka P, Saner FH, Roggendorf M, Gerken G, Canbay A. Hepatitis B-associated acute liver failure: immediate treatment with entecavir inhibits hepatitis B virus replication and potentially its sequelae. *Digestion* 2009; **80**: 235-240 [PMID: 19828954 DOI: 10.1159/000236009]

12 **Huang K**, Hu JH, Wang HF, He WP, Chen J, Duan XZ, Zhang AM, Liu XY. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. *World J Gastroenterol* 2011; **17**: 3448-3452 [PMID: 21876637 DOI: 10.3748/wjg.v17.i29.3448]

13 **Garg H**, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011; **53**: 774-780 [PMID: 21294143 DOI: 10.1002/hep.24109]

14 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541]

15 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

16 **Chan HL**, Chim AM, Lau JT, Hui AY, Wong VW, Sung JJ.

Evaluation of model for end-stage liver disease for prediction of mortality in decompensated chronic hepatitis B. *Am J Gastroenterol* 2006; **101**: 1516-1523 [PMID: 16863555 DOI: 10.1111/j.1572-0241.2006.00659.x]
17 **Liver Failure and Artificial Liver Group**, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Diagnostic and treatment guidelines for liver failure. *Zhonghua Ganzangbing Zazhi* 2006; **14**: 643-646 [PMID: 16995974]
18 **Coursaget P**, Buisson Y, N'Gawara MN, Van Cuyck-Gandre H, Roue R. Role of hepatitis E virus in sporadic cases of acute and fulminant hepatitis in an endemic area (Chad). *Am J Trop Med Hyg* 1998; **58**: 330-334 [PMID: 9546413]
19 **Dudley FJ**, Fox RA, Sherlock S. Cellular immunity and hepatitis-associated, Australia antigen liver disease. *Lancet* 1972; **1**: 723-726 [PMID: 4111197 DOI: 10.1016/S0140-6736(72)90234-6]
20 **Huang CF**, Lin SS, Ho YC, Chen FL, Yang CC. The immune response induced by hepatitis B virus principal antigens. *Cell Mol Immunol* 2006; **3**: 97-106 [PMID: 16696896]
21 **Rehermann B**. Chronic infections with hepatotropic viruses: mechanisms of impairment of cellular immune responses. *Semin Liver Dis* 2007; **27**: 152-160 [PMID: 17520515 DOI: 10.1055/s-2007-979468]
22 **Shimizu Y**. T cell immunopathogenesis and immunotherapeutic strategies for chronic hepatitis B virus infection. *World J Gastroenterol* 2012; **18**: 2443-2451 [PMID: 22654441 DOI: 10.3748/wjg.v18.i20.2443]
23 **Chu CM**, Liaw YF. Peripheral T-cell subsets in asymptomatic hepatitis B-virus carriers. *Cell Immunol* 1986; **98**: 533-537 [PMID: 3489555 DOI: 10.1016/0008-8749(86)90312-6]
24 **Tian Y**, Qiu ZF, Li TS. Difference and significance of peripheral blood T-lymphocyte subsets in patients with chronic hepatitis B and asymptomatic HBV carriers. *Zhonghua Yixue Zazhi* 2005; **85**: 3354-3358 [PMID: 16409844]
25 **Ikeda T**, Lever AM, Thomas HC. Evidence for a deficiency of interferon production in patients with chronic hepatitis B virus infection acquired in adult life. *Hepatology* 1986; **6**: 962-965 [PMID: 2428724 DOI: 10.1002/hep.1840060525]
26 **Akpolat N**, Yahsi S, Godekmerdan A, Demirbag K, Yalniz M. Relationship between serum cytokine levels and histopathological changes of liver in patients with hepatitis B. *World J Gastroenterol* 2005; **11**: 3260-3263 [PMID: 15929178]
27 **Dunn C**, Brunetto M, Reynolds G, Christophides T, Kennedy PT, Lampertico P, Das A, Lopes AR, Borrow P, Williams K, Humphreys E, Afford S, Adams DH, Bertoletti A, Maini MK. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell-mediated liver damage. *J Exp Med* 2007; **204**: 667-680 [PMID: 17353365 DOI: 10.1084/jem.20061287]
28 **Akcam FZ**, Tigli A, Kaya O, Ciris M, Vural H. Cytokine levels and histopathology in chronic hepatitis B and chronic hepatitis C. *J Interferon Cytokine Res* 2012; **32**: 570-574 [PMID: 23067363 DOI: 10.1089/jir.2012.0048]
29 **Zhu FC**, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Wang H, Yang CL, Jiang HM, Cai JP, Wang YJ, Ai X, Hu YM, Tang Q, Yao X, Yan Q, Xian YL, Wu T, Li YM, Miao J, Ng MH, Shih JW, Xia NS. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 2010; **376**: 895-902 [PMID: 20728932 DOI: 10.1016/S0140-6736(10)61030-6]

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