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• VIRAL HEPATITIS •

# Pathogenicity of GB virus C on virus hepatitis and hemodialysis patients

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## Abstract

**AIM:** To determine the pathogenicity of GB virus C (GBV-C) on liver and the effects of its co-infection on the clinical features and prognosis of patients with hepatitis B and C.

**METHODS:** Cross-sectional study was carried out in 413 patients with acute, chronic hepatitis B or liver cirrhosis, and in 67 hemodialysis patients. A 20-month prospective cohort study was carried out in 95 hepatitis B and 80 hepatitis C patients. A reverse transcriptase nested polymerase chain reaction (RT-nPCR) of the 5'-noncoding region was used to detect circulating GBV-C RNA. Liver function was determined by an automated analyzer for all patients.

**RESULTS:** The prevalence of GBV-C in the high-risk populations with the virus transmitted via blood was high, ranging from 16.2 to 28.8 %. Co-infection with GBV-C in hepatitis B patients did not affect the clinical features of the disease or liver function. The dialysis patients infected with GBV-C alone did not develop functional changes to the liver. Prospective cohort study showed that GBV-C co-infection did not affect the clinical features, prognosis or negative serum conversion rate of chronic hepatitis B and C.

**CONCLUSION:** The results suggest that GBV-C has no marked pathogenicity on liver, so it may not be a hepatitis virus.

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## INTRODUCTION

Hepatitis B and C viruses (HBV, HCV) jointly contribute to 90 % of cases of post-transfusion non-A, non-B hepatitis (HNANB). The remaining 10 % of cases could not be attributed to any of the other known hepatitis viruses or other factors such as alcohol, drug, or any disease related causes[1,2]. These cases are named non-A-E hepatitis (HNA-E) and may be caused by an unknown viral agent. In 1995 and 1996, GB virus-C (GBV-C) and hepatitis G virus (HGV) were cloned by Simons *et al.* and Linnen *et al.*, respectively, in the United States[3,4]. Sequence analysis revealed that these two viruses had 85 % and 95 % identical nucleotide and amino acid sequences, respectively. And now these two viruses are named as GBV-C. Initially, GBV-C was isolated from the serum of patients with HNA-E[3,4]. However, there are still a lot of arguments up to now on the pathogenicity of GBV-C on liver and on whether GBV-C is an aetiological agent of HNA-E[5,6]. The prevalence of GBV-C in patients with chronic hepatitis B or chronic hepatitis C is very common, because of the similar transmission routes[7-12]. In the present study, we investigated the prevalence of GBV-C and evaluated its pathogenicity on liver with a cross-sectional study in 413 patients with acute, chronic hepatitis B, or liver cirrhosis, and in 67 hemodialysis patients. We also carried out a 20-month prospective cohort study in 95 patients with chronic hepatitis B and 80 patients with chronic hepatitis C. The results suggest that GBV-C has no marked pathogenicity on liver, so it may not be a new hepatitis virus.

## MATERIALS AND METHODS

### *Patients*

A total of 413 inpatients with confirmed diagnoses of acute, chronic hepatitis B or liver cirrhosis in two hospitals for infectious diseases in Beijing from January to December 2000 were enrolled in this study. Anti-HAV IgM, anti-HCV, anti-HDV and anti-HEV antibodies were all negative in these patients. Serum samples of the inpatients were collected and tested to assess liver biochemical characteristics on the day of admission. The rest serum was tested and stored at -80 ℃ for pathogen analysis.

Serum samples of hemodialysis patients with renal failure were collected from 67 patients in 3 general hospitals from December 2001 to March 2002 in Beijing. All samples were stored at -30 ℃ before analysis.

A cohort of 95 patients with chronic hepatitis B and 80 patients with chronic hepatitis C was enrolled from villages of a county in Zhoukou area, Henan Province. All patients were infected with HBV or HCV from 1991 to 1992 as a consequence of blood donation. All the patients had persistently elevated serum alanine aminotransferase (ALT) (at least 1.5 times the upper limit of the normal level) and were positive for serum HBV DNA or HCV RNA as detected by PCR or RT-PCR, respectively. All the patients were negative for serum anti-HAV IgM and anti-HEV. The average disease course of these patients was 3 years when investigation and confirming diagnosis were carried out in April 1994. All the patients of the cohort showed no evidence of liver cirrhosis or hepatocellular carcinoma in regular ultrasonic graphic examinations. All the patients were followed up twice, i.e., 6 and 20 months after the first investigation.

### *Laboratory examination*

For GBV-C RNA detection, RNA was first extracted from 50 μl of serum using a commercial RNA extraction kit (Promega, Z5110). Reverse transcriptase and nested polymerase chain reactions (RT-nPCR), 35 cycles for two round, were performed using a PCR machine (SABC Thinker Series II, Sino-American Biotechnology Company, China). The primers used were from

the 5' -noncoding region of the GBV-C genome, outer primers (sense, 5' -TCTTGGTAGCCACTATAGGTG-3' , and antisense, 5' -GGCAAAGCCTATTGGTCAAG-3' ), and inner primers (sense, 5' -AGAAAGAGCACGGTCCACAG-3' , and antisense, 5' -CCACTGGTCCTTGTCAACTC-3' ). The amplified product (158 base pairs) was visualized under ultraviolet light after gel electrophoresis and stained with ethidium bromide. GBV-C RNA was assessed in duplicate sera and scored as positive only when consistent results were obtained. Liver biochemistry tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), direct bilirubin (DBil), total protein (Tp), and serum albumin/globulin ratio (A/G) were measured with an automated analyzer.

### *Statistical analysis*

Data in the text and tables were expressed as $\bar{x}\pm s$. Student' s *t*-test and one-way analysis of variance were used for statistical analysis according to the data obtained. For all tests, *P* values less than 0.05 were considered to be statistically significant, and *P* values less than 0.01 were considered to be greatly statistically significant.

## RESULTS

Of the serum samples from 413 patients infected with HBV, 67 were co-infected with GBV-C (16.22 %). 169 cases had integrated clinical data. The patients suffering from acute, chronic hepatitis B or liver cirrhosis were grouped on the basis of the presence or absence of GBV-C co-infection, and the levels of ALT, AST, TBil, DBil, Tp of the different groups were compared (Table 1).

Results shown in Table 1 indicated that there was no significant difference in the serum biochemistry characteristics of 3 types of patients (acute, chronic hepatitis B and liver cirrhosis) between GBV-C RNA infected group and non-infected group ($P>0.05$).

11 of the 67 dialysis patients were GBV-C RNA positive (16.42 %) and the positive rate of GBV-C RNA increased with the number of times of dialysis. The comparison of serum ALT and AST levels in 67 patients infected with different viruses is shown in Table 2.

**Table 2** Comparison of serum ALT and AST in dialysis patients with different virus infection

| Group | *n* | Average dialysis times | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ |
|---|---|---|---|---|
| (1) HBV DNA(+) HCV RNA(-) GBV-C RNA(-) | 11 | 243.75±224.53 | 31.63±22.32 | 35.12±18.06 |
| (2) HBV DNA(-) HCV RNA(+) GBV-C RNA(-) | 6 | 306.67±296.41 | 30.67±9.45 | 25.00±12.28 |
| (3) HBV DNA(-) HCV RNA(-) GBV-C RNA(+) | 8 | 353.40±309.45 | 20.67±11.72 | 17.00±1.00 |
| (4) HBV DNA(-) HCV RNA(-) GBV-C RNA(-) | 37 | 116.45±103.02 | 15.37±6.83 | 20.00±7.04 |

**Table 1** Comparison of biochemistry characteristics in all types of patients with or without GBV-C infection

| Group | *n* | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ | TBil/μmol·L$^{-1}$ | DBil/μmol·L$^{-1}$ | Tp/g·L$^{-1}$ |
|---|---|---|---|---|---|---|
| Acute hepatitis B | | | | | | |
| GBV-C RNA(+) | 13 | 1173.92±961.98 | 565.69±405.32 | 5.18±3.47 | 3.54±2.66 | 68.44±12.14 |
| GBV-C RNA(-) | 33 | 1380.27±906.14 | 620.06±405.32 | 6.52±6.61 | 4.57±4.51 | 67.84±12.42 |
| Chronic hepatitis B | | | | | | |
| GBV-C RNA(+) | 24 | 366.33±237.36 | 289.42±201.32 | 6.48±7.34 | 3.98±4.50 | 71.30±8.57 |
| GBV-C RNA(-) | 35 | 312.91±432.82 | 227.29±292.17 | 3.29±5.58 | 2.21±4.24 | 71.06±7.66 |
| Liver cirrhosis | | | | | | |
| GBV-C RNA(+) | 30 | 71.67±74.13 | 96.73±87.21 | 5.54±7.44 | 3.62±5.33 | 66.46±8.75 |
| GBV-C RNA(-) | 34 | 92.68±80.33 | 106.15±94.81 | 7.67±10.30 | 5.20±5.80 | 62.58±10.99 |
| Total | | | | | | |
| GBV-C RNA(+) | 67 | 400.51±585.36 | 255.22±301.71 | 5.73±6.81 | 3.69±4.46 | 68.80±9.61 |
| GBV-C RNA(-) | 102 | 578.63±807.04 | 314.98±345.05 | 5.85±7.85 | 3.87±4.80 | 67.21±10.92 |

No significant difference ($P>0.05$) was found in all the biochemistry characteristics between hepatitis B patients with or without GBV-C infection.

**Table 3** Comparison of biochemistry characteristics between chronic hepatitis B patients with or without GBV-C infection

| GBV-C RNA | *n* | A/G | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ | TBil/μmol·L$^{-1}$ |
|---|---|---|---|---|---|
| (1) Positive group | 24 | 1.65±0.26 | 90.84±48.43 | 43.21±31.56 | 5.91±1.86 |
| (2) Negative group | 71 | 1.63±0.21 | 95.36±51.96 | 44.45±38.07 | 7.66±1.95 |

No significant difference ($P>0.05$) was found in all the biochemistry characteristics between the two groups.

**Table 4** Comparison of biochemistry characteristics between chronic hepatitis C patients with or without GBV-C infection

| GBV-C RNA | *n* | A/G | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ | TBil/μmol·L$^{-1}$ |
|---|---|---|---|---|---|
| (1) Positive group | 23 | 1.82±0.30 | 110.23±59.61 | 45.96±40.11 | 4.53±1.55 |
| (2) Negative group | 57 | 1.65±0.25 | 97.65±56.74 | 52.94±48.00 | 5.77±1.73 |

No significant difference ($P>0.05$) was found in all the biochemistry characteristics between the two groups.

On statistic analysis, ALT levels were significantly different between groups 1 and 4 ($P<0.01$) and groups 2 and 4 ($P<0.05$). AST levels were also significantly different between groups 1 and 4 ($P<0.01$). The results showed a significant elevation in the levels of ALT and AST in hemodialysis patients infected with HBV or HCV compared with that in those not infected with the two viruses. Significant difference ($P<0.05$) was found in dialysis times between groups 2 and 4, and groups 3 and 4. Three patients had abnormal liver function (ALT>40 IU/L, AST>40 IU/L), among them one was infected with HCV, the other two were infected with HBV. Serum ALT and AST levels were normal in patients with GBV-C infection alone.

A cohort study was carried out in 95 patients with chronic hepatitis B and 80 patients with chronic hepatitis C enrolled from villages in Henan Province. Serum GBV-C was positive in 24 (25.26 %) chronic hepatitis B patients and 23 (28.75 %) chronic hepatitis C patients (Tables 3 and 4).

When following up the patients 6 months later, we found that 23 of the 95 chronic hepatitis B patients (24.21 %) became HBV DNA negative and 21 of the 80 (26.25 %) chronic hepatitis C patients became HCV RNA negative. GBV-C RNA could not be detected in 12.50 % (3/95) chronic hepatitis B patients and in 17.39 % (4/80) chronic hepatitis C patients. Table 5 and Table 6 show the biochemistry characteristics of chronic hepatitis B and C patients.

**Table 5** Comparison of biochemistry characteristics between chronic hepatitis B patients with or without GBV-C infection at the 6-month follow-up

| Group | *n* | A/G | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ | TBil/μmol·L$^{-1}$ |
|---|---|---|---|---|---|
| (1) HBV DNA(+) GBV-C RNA(+) | 14 | 1.74±0.19 | 93.29±60.67 | 29.14±13.87 | 7.64±5.47 |
| (2) HBV DNA (+) GBV-C RNA (-) | 58 | 1.73±0.18 | 62.33±41.67 | 27.68±11.99 | 6.10±2.09 |
| (3) HBV DNA (-) GBV-C RNA (+) | 7 | 1.61±0.11 | 30.00±7.80 | 21.57±8.18 | 7.57±3.41 |
| (4) HBV DNA (-) GBV-C RNA (-) | 16 | 1.64±0.14 | 32.65±17.01 | 26.65±11.96 | 7.71±2.76 |

Significant difference ($P<0.05$) was found only in ALT between group 1 and group 3, group 2 and group 4. No significant difference ($P>0.05$) was found in other biochemistry characteristics among the 4 groups.

**Table 6** Comparison of biochemistry characteristics between chronic hepatitis C patients with or without GBV-C infection at the 6-month follow-up

| Group | *n* | A/G | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ | TBil/μmol·L$^{-1}$ |
|---|---|---|---|---|---|
| (1) HCV RNA(+) GBV-C RNA(+) | 11 | 1.76±0.17 | 127.11±82.12 | 41.13±19.07 | 7.49±5.82 |
| (2) HCV RNA(+) GBV-C RNA (-) | 48 | 1.82±0.20 | 71.62±47.74 | 26.05±12.49 | 7.97±3.91 |
| (3) HCV RNA (-) GBV-C RNA(+) | 8 | 1.60±0.13 | 33.11±8.08 | 22.97±9.78 | 7.26±4.25 |
| (4) HCV RNA (-) GBV-C RNA (-) | 13 | 1.60±0.14 | 30.74±20.01 | 24.65±11.84 | 7.65±3.23 |

Significant difference ($P<0.05$) was found both in ALT between group 1 and group 3, group 2 and group 4, and in AST between group 1 and group 4. No significant difference ($P>0.05$) was found in other biochemistry characteristics among the 4 groups.

At the 20-month follow up, the biochemistry characteristics of chronic hepatitis B and C patients were compared between two groups: one with and the other without GBV-C co-infection (Tables 7 and 8). At this time point, 26.0 % (25/95) chronic hepatitis B patients and 20.0 % (16/80) chronic hepatitis C patients were lost in the follow up.

**Table 7** Comparison of biochemistry characteristics between chronic hepatitis B patients with or without GBV-C infection after 20 months

| Group | *n* | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ |
|---|---|---|---|
| (1) HBV DNA(+) GBV-C RNA(+) | 8 | 52.13±44.90 | 44.25±28.42 |
| (2) HBV DNA (+) GBV-C RNA (-) | 30 | 44.40±37.26 | 34.67±24.23 |
| (3) HBV DNA (-) GBV-C RNA (+) | 8 | 28.14±15.36 | 25.29±17.21 |
| (4) HBV DNA (-) GBV-C RNA (-) | 24 | 25.15±11.59 | 25.73±13.16 |

Significant difference ($P<0.05$) was found only in ALT and AST between group 1 and group 3, and group 2 and group 4.

**Table 8** Comparison of biochemistry characteristics between chronic hepatitis C patients with or without GBV-C infection after 20 months

| Group | *n* | ALT/IU·L$^{-1}$ | AST/IU·L$^{-1}$ |
|---|---|---|---|
| (1) HCV RNA(+) GBV-C RNA(+) | 6 | 72.24±73.87 | 49.29±48.49 |
| (2) HCV RNA(+) GBV-C RNA (-) | 22 | 42.43±39.10 | 32.91±30.57 |
| (3) HCV RNA (-) GBV-C RNA(+) | 7 | 26.98±24.47 | 25.11±19.07 |
| (4) HCV RNA (-) GBV-C RNA (-) | 29 | 25.39±13.16 | 26.74±16.99 |

Significant difference ($P<0.05$) was found only in ALT and AST between group 1 and group 3, and group 2 and group 4.

After 20-month follow up, correlation was seen between the abnormal levels of the liver biochemistry characteristics and HBV DNA in chronic hepatitis B patients. However, no correlation was found between the abnormal levels of the liver function and co-infection with GBV-C. The same result was found in chronic hepatitis C patients. During the period of follow up for 20 months, 50.00 % (8/16) hepatitis B patients with GBV-C infection and 44.44 % (24/54) hepatitis B patients without GBV-C infection became HBV DNA undetectable. 53.85 % (7/13) hepatitis C patients with GBV-C infection and 56.86 % (29/51) hepatitis C patients without GBV-C infection became HCV RNA undetectable. The rates of negative serum conversion of HBV DNA and HCV RNA were not significantly different between the two groups.

## DISCUSSION

Since GBV-C was cloned, there have been a lot of arguments on the pathogenicity of GBV-C. Although a number of reports have indicated that GBV-C can induce acute, chronic, and even fulminant hepatitis[13-16], most of the clinical observations have demonstrated that GBV-C infection alone has little significance in causing liver damage in human[17-20]. There were 363 research publications on GBV-C/HGV in MEDLINE database from 1999 to February 2001, among which only 8 supported GBV-C pathogenicity on the liver. Most researches implicated that no correlation existed between GBV-C and liver diseases. Patients with HBV or HCV co-infected with GBV-C did not have different clinical manifestations and outcomes when compared with patients with HBV or HCV infection alone[21-23].

GBV-C, HBV and HCV have a similar route of transmission. Many of the reports limited their research on the prevalence of GBV-C in hepatitis B and hepatitis C patients and had relatively small numbers of cases. Therefore, it was difficult for them to draw a definite conclusion on GBV-C pathogenicity on the liver. The subjects of this study were a large sample in the high-risk population with GBV-C infection (hepatitis B, hepatitis C and hemodialysis patients). This work combined the cross-sectional and prospective cohort studies and applied the methods of cross-experimental design and analysis. Therefore, it could analyze more reasonably the pure effects of GBV- C infection on liver.

All data in this study were pooled from experiments carried out by many graduate students and repeated many times. Hepatitis B, hepatitis C and hemodialysis patients belonged to the high-risk population transmitted via blood. Previous investigations have shown that there was no significant difference between the prevalence rates of GBV-C in patients with HNA-E and of the aforementioned high-risk population ($P$>0.05)[23-25]. So these findings do not support the argument that GBV-C was the etiological factor of HNA-E. No significant difference was seen in the abnormal level of liver biochemistry characteristics between positive and negative serum GBV-C RNA in acute, chronic hepatitis B or liver cirrhosis patients ($P$>0.05). But the abnormal level of liver biochemistry characteristics correlated well with HBV DNA. Therefore, these results demonstrated that co-infection with GBV-C did not affect the liver biochemistry characteristics and illness. Infection with HBV or HCV could elevate the level of liver enzymes (ALT and AST) in hemodialysis patients, but infection with GBV-C did not demonstrate such effects. So these results showed that the hemodialysis patients had no abnormal liver biochemistry characteristics when infected with GBV-C alone without the known hepatitis virus co-infection. The dynamic observation in 3 follow-ups of the cohort of chronic hepatitis B and C patients during a period of 20 months indicated that co-infection with GBV-C did not significantly affect the illness, outcome or rate of negative serum conversion. In summary, this work demonstrates that, though GBV-C is highly prevalent in high-risk populations with virus infection via blood, it seems to have no pathogenicity on the liver and therefore may not be a hepatitis virus.

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## REFERENCES

1 **Alter HJ,** Seeff LB. Transfusion associated hepatitis. In: Zuckerman AJ, Thomas HC, eds. Viral Hepatitis. *London: Churchill Livingstone* 1998: 489-513
2 **Karayiannis P,** Pickering J, Zampino R, Thomas HC. Natural history and molecular biology of hepatitis G virus / GB virus C. *Clin Diagn Virol* 1998; **10**: 103-111
3 **Simons JN,** Leary TP, Dawson GJ, Pilot-Matias TJ, Muerhoff AS, Schlauder GG, Desai SM, Mushahwar IK. Isolation of novel virus-like sequences associated with human hepatitis. *Nat Med* 1995; **1**: 564-569
4 **Linnen J,** Wages J Jr, Zhang-Keck ZY, Fry KE, Krawczynski KZ, Alter H, Koonin E, Gallagher M, Alter M, Hadziyannis S, Karayiannis P, Fung K, Nakatsuji Y, Shih JW, Young L, Piatak M Jr, Hoover C, Fernandez J, Chen S, Zou JC, Morris T, Hyams KC, Ismay S, Lifson JD, Kim JP. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. *Science* 1996; **271**: 505-508
5 **Grassi M,** Mammarella A, Sagliaschi G, Granati L, Musca A, Traditi F, Pezzella M. Persistent hepatitis G virus (HGV) infection in chronic hemodialysis patients and non-B, non-C chronic hepatitis. *Clin Chem Lab Med* 2001; **39**: 956-960
6 **De Filippi F,** Lampertico P, Soffredini R, Rumi MG, Lunghi G, Aroldi A, Tarantino A, Ponticelli C, Colombo M. High prevalence, low pathogenicity of hepatitis G virus in kidney transplant recipients. *Dig Liver Dis* 2001; **33**: 477-479
7 **Halasz R,** Weiland O, Sallberg M. GB virus C / hepatitis G virus. *Scand J Infect Dis* 2001; **33**: 572-580
8 **Kleinman S.** Hepatitis G virus biology, epidemiology, and clinical manifestations: Implications for blood safety. *Transfus Med Rev* 2001; **15**: 201-212
9 **Li G,** Ma HH, Lau GK, Leung YK, Yao CL, Chong YT, Tang WH, Yao JL. Prevalence of hepatitis G virus infection and homology of different viral strains in southern China. *World J Gastroenterol* 2002; **8**: 1081-1087
10 **Yan J,** Chen LL, Luo YH, Mao YF, He M. High frequencies of HGV and TTV infections in blood donors in hangzhou. *World J Gastroenterol* 2001; **7**: 637-641
11 **Yan J,** Dennin RH. A high frequency of GBV-C / HGV coinfection in hepatitis C patients in Germany. *World J Gastroenterol* 2000; **6**: 833-841
12 **Yan J**, Chen LL, Lou YL, Zhong XZ. Investigation of HGV and TTV infection in sera and saliva from non-hepatitis patients with oral diseases. *World J Gastroenterol* 2002; **8**: 857-862
13 **Kocabas E,** Antmen B, Yarkin F, Serin M, Aksungur P, Tanyeli A, Kilinc Y, Aksaray N. Prevalence of GB virus C / hepatitis G virus infection in pediatric patients receiving multiple transfusions in southern Turkey. *Turk J Pediatr* 1999; **41**: 81-90
14 **Tanaka T,** Hess G, Tanaka S, Kohara M. The significance of hepatitis G virus infection in patients with non-A to C hepatic diseases. *Hepatogastroenterology* 1999; **46**: 1870-1873
15 **Yoshiba M,** Okamoto H, Mishiro S. Detection of the GBV-C hepatitis virus genome in serum from patients with fulminant hepatitis of unknown aetiology. *Lancet* 1995; **346**: 1131-1132
16 **Xu JZ,** Yang ZG, Le MZ, Wang MR, He CL, Sui YH. A study on pathogenicity of hepatitis G virus. *World J Gastroenterol* 2001; **7**: 547-550
17 **Sathar M,** Soni P, York D. GB virus C / hepatitis G virus (GBV-C / HGV): still looking for a disease. *Int J Exp Pathol* 2000; **81**: 305-322
18 **Pessoa MG,** Terrault NA, Detmer J, Kolberg J, Collins M, Hassoba HM, Wright TL. Quantitation of hepatitis G and C viruses in the liver: evidence that hepatitis G virus is not hepatotropic. *Hepatology* 1998; **27**: 877-880
19 **Sarrazin C,** Ruster B, Lee JH, Kronenberger B, Roth WK, Zeuzem S. Prospective follow-up of patients with GBV-C / HGV infection: specific mutational patterns, clinical outcome, and genetic diversity. *J Med Virol* 2000; **62**: 191-198
20 **Shindo M,** Arai K, Okuno T. Long-term follow-up of hepatitis G virus / GB virus C replication in liver during and after interferon therapy in patients coinfected with hepatitis C and G viruses. *J Gastroenterol* 1999; **34**: 680-687
21 **Fattovich G,** Ribero ML, Favarato S, Azzario F, Donato F, Giustina G, Fasola M, Pantalena M, Portera G, Tagger A. Influence of GB virus-C / hepatitis G virus infection on the long-term course of chronic hepatitis B. *Liver* 1998; **18**: 360-365
22 **Kao JH,** Chen PJ, Lai MY, Chen W, Chen DS. Effects of GB virus-C / hepatitis G virus on hepatitis B and C viremia in multiple hepatitis virus infections. *Arch Virol* 1998; **143**: 797-802
23 **Yu ML,** Chuang WL, Dai CY, Lu SN, Wang JH, Huang JF, Chen SC, Lin ZY, Hsieh MY, Tsai JF, Wang LY, Chang WY. The serological and molecular epidemiology of GB virus C / hepatitis G virus infection in a hepatitis C and B endemic area. *J Infect* 2001; **42**: 61-66
24 **Li P,** Zhu WF, An WF, Li ZJ, Wang SP, Zhuang H. Cohort study on pathogenicity of hepatitis G virus mixed infection with hepatitis B and C virus. *Zhongguo Gonggong Weisheng* 2002; **18**: 911-913
25 **Huang J,** Zhu WF, Li Z, Sun JY, Hao W, Wang XM, Li P, Zhuang H. Pathogenicity study of hepatitis G virus mixed infection in chronic hepatitis B and C patients. *Ziran Kexue Jinzhan* 2002; **12**: 307-310

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