port on a phase II trial of a recombinant HEV vaccine administered to a group of volunteers, mostly male (>99%), in the Nepalese Army.[10] The selection of the target population for vaccine studies such as this one is challenging, since the subjects must not have acquired immunity to HEV yet must be at high risk for exposure to the pathogen, and the community must be supportive of research. The volunteers, consisting of 896 subjects in the vaccine group and 898 in the placebo group, received three doses (at 0, 1, and 6 months) of recombinant HEV capsid protein or saline, respectively. The protective efficacy against clinically overt HEV infection (the study's primary end point) was 95.5% in subjects who received all three vaccine doses and 85.7% after two doses. No obvious safety concerns were identified in a randomly selected reactogenicity subgroup of subjects. All the HEV-vaccinated subjects were anti-HEV seropositive a month after the third vaccination, but only 56.3% maintained a level of anti-HEV antibody at the end of study without an increase in the rate of clinically overt HEV infection among vaccinees.

The results from this trial of a recombinant HEV vaccine are encouraging with respect to the prevention of clinically overt HEV infection. However, Purcell et al.[8] observed that an HEV vaccine in rhesus monkeys demonstrated vaccine-induced protection against HEV disease but incomplete protection against HEV infection. Since the vaccine that was used in the study by Shrestha et al. appears to be similar or identical to the one used by Purcell et al., the effect of vaccination on human HEV infection requires further study.

The primary end point of the study by Shrestha et al. was the prevention of clinically overt HEV infection. The use of vaccine to prevent asymptomatic HEV infection was not investigated because only trial subjects who presented with clinical illness were tested for HEV RNA. It is conceivable, therefore, that the vaccine may not have prevented subclinical HEV infection. Asymptomatic HEV infection may be important because the vaccinated subjects without clinical symptoms may continue to shed virus and thus maintain an environmental reservoir of HEV. Evidence of persistent contamination of water supplies in disease-endemic regions is supported by environmental virologic studies that showed the presence of HEV RNA in wastewater and sewage samples.[11]

These data suggest that HEV vaccine may be useful for people traveling from the developed world to hepatitis E–endemic regions. Since HEV infection may cause fatal disease in pregnant women, determining the safety and efficacy of HEV vaccine in this group should be a high priority. As long as questions remain with respect to the length of the protective efficacy of the vaccine, its use in children and adolescents in hepatitis E–endemic countries requires further study. The cost of the vaccine will be an important factor in determining its availability in the developing world, where it is most needed.

In conclusion, the study by Shrestha et al. shows in a group of almost exclusively male subjects that recombinant HEV vaccine effectively prevents clinical hepatitis E, although the duration of the induced immunity remains unknown, as does the efficacy of the vaccine in preventing asymptomatic HEV infection. It will be important to define how this vaccine may affect the reservoir and transmission of HEV, thus determining the overall public health benefit.

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The views expressed in this editorial are those of the author and do not necessarily reflect the views or policies of the Centers for Disease Control and Prevention.

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Performance Measurement in Search of a Path

Rodney A. Hayward, M.D.

In this issue of the *Journal*, Landon and colleagues report on a Herculean undertaking — a study of quality-improvement interventions conducted at 44 community health centers.[1] This study showed a modest improvement in some process measures and no improvement in intermediate or end-stage outcomes — results that are similar to those of most previous large-scale quality-improvement initiatives. As the authors correctly note, improved processes may not be accompanied by discernible improvements in outcomes for several reasons. A particularly important problem is that the majority of Health Plan Employer Data and Information Set–style performance measures used to guide most large-scale quality-improvement activities represent inefficient and sometimes counterproductive standards for improving clinical outcomes.

The shortcomings of current approaches to performance measurement are distressing, since it may be the single most important health policy tool for improving health care. Our experience with performance measurement over the past two decades has generally shown that "what you measure improves," but unfortunately, we often settle for measuring that which is simple and easy to gauge and then sit back and celebrate the improvements in our "measures." As a result, we risk wasting both resources and opportunities. With the current interest in pay-for-performance programs, this is an opportune time to revisit the principles and rationale underlying meaningful performance measurement.

First, it is critically important to understand that performance measurements are inherently and fundamentally different from clinical guidelines.[2-4] In a guideline (an educational tool designed to aid clinicians in providing optimal care), it might be perfectly acceptable to recommend glycated hemoglobin levels of less than 7% (or even <6.5%) as a goal or to recommend annual eye screening for patients with diabetes. However, for many reasons that have been chronicled over the years,[2-7] basic guidelines are rarely appropriate as "all-or-nothing" performance measures. The reasons that guidelines often make poor performance measures are nonintuitive and easily forgotten by those who do not take care of patients. Indeed, in the very political and high-stakes process of selecting performance measures, influential parties often have strong incentives to advocate that these measures be aligned with idealized goals. For example, even the most pure-hearted persons and groups with a vested interest in issues related to diabetes (such as the American Diabetes Association, diabetes "experts," and the diabetes sections of the National Institutes of Health and the Centers for Disease Control and Prevention) have a natural and justifiable tendency to want more attention and resources for their cause and will logically want to push for the most care for patients with this disease.[8] It sounds terrible when we hear that 50% of recommended care is not received, but much of the care recommended by subspecialty groups is of modest or unproven value, and mandating adherence to these recommendations is not necessarily in the best interest of patients or society. For example, it has been estimated that it would take a primary care physician almost 8 hours per workday just to provide the interventions recommended by the U.S. Preventive Services Task Force, leaving no time to deal with acute conditions.[9]

At the heart of this problem is our wish to keep efforts at quality improvement and cost containment separate. When selecting quality measures, leaders of the performance-measurement process nationally tend to ignore the issues of the burden imposed on patients, patients' preferences, and costs, preferring instead to construct a separate cost "report card." One leader in a national performance-measurement organization told me that it is irrelevant how much benefit accrues from performance measurement, "just as long as it's recommended by a respected professional group

平成18年度厚生労働科学研究費補助金肝炎等克服緊急対策研究事業
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平成18年度　総括研究報告書

主任研究者　三代　俊治

補遺

（落丁のあった研究報告書の追加）

平成19年(2007)4月

御詫び

2006年度末に編集・印刷・製本し發行した本研究班の報告書に重大な落丁がありました。鈴木一幸班友(岩手醫科大學第一内科教授)から頂戴した2006年度研究報告書原稿を、編集責任者である私が、版組みのプロセスの過程で逸失してしまったのが其の落丁の原因です。意図的な脱落では断じてありません。鈴木先生に夛大なる御迷惑を御掛けしたことを心より御詫び申し上げます。

幸いにも鈴木先生の玉稿が手許に保管してありましたので、ここに『補遺』を上梓して、皆様に配布する次第です。發行済みの報告書に此の補遺を合冊したものが、本研究班の2006年度報告書の正編であると、御理解頂きたく存じます。

印刷会社にも他の誰彼にも責任は全くなく、一切の責任は私にあります。

平身低頭して御詫び申し上げます。

2007.04.16

主任研究者　三代　俊治

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厚生労働科学研究費補助金(肝炎等克服緊急対策研究事業)
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治療に関する研究
平成18年度
班友研究報告書

岩手県におけるE型肝炎の動向(2006年)

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研究要旨：2006年に当科で経験した急性E型肝炎2例について臨床像、感染経路、予後などを検討した．2例とも肝予備能は比較的保たれていたが高度の黄疸を呈し肝機能の正常化までに長期間を要した．また、いずれも感染経路は不明であったが、遺伝子型はIII型であった．急性E型肝炎は少数ながら毎年散発性に発生しており．その早期の血清学的診断法の普及が急務であり、感染源の解明に向けた取組みが今後とも必要と思われる．

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A. 研究目的

E 型肝炎ウイルス（HEV）による急性 E 型肝炎（E-AH）は人畜共通感染症(Zoonosis)として位置づけられてきている．さらに、HEV 感染の発生頻度の高い北海道地区では輸血後 E 型肝炎の報告もなされてきている．

我々の施設でも毎年少数例ながらHEVによる急性E型肝炎例を確認しており、これまで経験した急性 E 型肝炎例の臨床学的特徴や病態解析を行ってきた．

今年度は、2006 年に経験した急性 E 型肝炎について臨床経過、感染経路、予後などを検討し、E 型肝炎診療の問題点を明らかにする．

B. 研究方法

2006 年 1 月より 2006 年 12 月までに岩手医科大学第一内科において入院加療を受けた急性肝障害患者のうち血清学的に E-AH と診断（血中 HEV-RNA 陽性）されたのは 2 例であった．これら 2 例について、感染経路との関わり、臨床像の特徴を検討した．なお、HEV の確定診断は血中 HEV-RNA の陽性で行い、同時に遺伝子型も測定した．

C. 研究結果

1) 症例 1(52 歳、男性)

臨床経過：平成 18 年 1 月 5 日より感冒様症状を認め、近医受診．消炎鎮痛薬、抗生物質などの投与を受ける．さらに、1 月 10 日より心窩部痛、嘔気が出現し同医にて消化器病薬の処方を受け、全身倦怠感は残るものの他の症状は軽快してきていた．1 月 16 日に職場の同僚に皮膚黄染を指摘され、県立 S 病院を受診．血液生化学検査にて肝機能異常を認め薬剤性肝障害ないしウイルス性肝炎の疑いにて入院．しかし、入院後も黄疸が増強してきたため、1 月 23 日に当科に紹介入院となる．輸血歴、海外渡航歴なし．飲酒歴では最近 10 年間は日本酒換算 1 日 1~2 合であるが、23 歳時より 5~10 年間は 1 日 5 合程度の飲酒歴を認める．入院時肝機能検査では血清ビルルビンは高値(T-Bil.26.8mg/dl)を示していたが、肝予備能は保たれ、血清トランスアミナーゼ値(AST 29, ALT 42 IU/L)は低値であり、胆汁うっ滞性肝障害の病態を示していた．各種薬剤に対する DLST 試験は陰性であり、A~D 型肝炎ウイルスおよび肝炎ウイルス以外のウイルスマーカ、自己抗体もすべて陰性であった．1 週間の経過観察後、IgM-HEV 抗体が陽性であることが判明し、遺伝子型を検索（自治医科大学感染・免疫学講座ウイルス学部門岡本宏明教授）したところ、genotype III であった．

治療としてプレドニン 30mg/day より開始したが、明らかな減黄は見られず、UDCA 療法、グルカゴン―インスリン療法などを漸次施行し、最終的に 3 月 24 日退院した．

2) 症例 2(68 歳、男性)

平成 18 年 9 月 25 日に尿の濃染に気づき、10 月 4 日に易疲労感、6 日に皮膚の掻痒感が出現し、近医を受診．肝機能異常を認め、某総合病院を紹介されたが、プロトロンビン時間の低下(45%)を認めたため、劇症化も懸念されたため当科紹介入院となる．輸血歴、海外渡航歴なし．飲酒は 1 日日本酒換算 0.5 合程度．入院時検査成績では、A~D 型肝炎ウイルスおよび肝炎ウイルス以外のウイルスマーカ、自己抗体はすべて陰性であった．肝機能検査では T-Bil.7.9mg/dl、血清 AST 2159 IU/L、ALT 2875 IU/L、PT53%であったため 2 日間抗凝固療法を施行した．その後、黄疸が増強し、T-Bil.25.9mg/dl に達したが、一般肝庇護療法のみでゆっくりと改善し平成 19 年 1 月 19 日軽快退院となった．HEV の感染経路は不明であったが、genotype III であった．

D. 考察

2006 年に経験した 2 例の E-AH 例

は重症化(PT40%以下)には至らなかったが、いずれも高度黄疸を呈し、肝機能の改善までに長期間を有した例であった．当科では、毎年少数ながら散発性に E-AH の発生を確認しているが、いずれの例も前医での確定診断が得られておらず、当科受診後に始めて E-AH の確定診断がなされている．この原因には、E-AH の診断に必須の IgM または IgA-HEV 抗体の測定が保険診療で認められていないため、第一線の医療機関では診断が困難なことによる．

感染経路については，今回の経験した 2 例では生肉摂取など Zoonosis を疑うような食行動歴もなく、感染源を特定するまでには至らなかった．患者からの詳細な病歴聴取を行い、HEV の未知の感染源を明らかにするためにも早期の確定診断が必要であると思われる．

E-AH の多くはこれまで我々が報告してきたように予後良好で慢性化する例は認めていない．しかしながら，まれに重症化や劇症化する例が認められる．また，我々が既に指摘したように重症化あるいは劇症化の要因に薬剤の関与が疑われる例も多い．最近，劇症化に関わるウイルス側の因子として HEV ウイルスの遺伝子型およびその塩基配列の違いが密接に関係することが報告されている．また、我々は高度の胆汁うっ滞を示した E-AH の経過中に薬剤過敏症とサイトメガロウイルスの再活性化を認めた1例を報告した．今後、E-AH の病態や重症に関わる因子の解明を更に進める必要がある．

D. 結論

当科で経験した 2006 年における急性 E 型肝炎例について臨床的検討を行った．今後、E 型肝炎の早期の血清学的診断法の普及が望まれる．

E. 健康危険情報

特記すべきことなし．

F. 研究発表

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Hepatology Research 2007; 37: 158–165 doi: 10.1111/j.1872-034X.2007.00021.x

Case Report

A case of acute hepatitis E associated with multidrug hypersensitivity and cytomegalovirus reactivation

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A 65-year-old Japanese man was hospitalized because of acute hepatitis and severe cholestasis due to hepatitis E virus (HEV) infection combined with a drug reaction to a cold preparation. He died of disseminated intravascular coagulation and severe intestinal bleeding due to systemic cytomegalovirus reactivation following the development of severe eruptions with marked eosinophilia due to drug hypersensitivity to taurine and ursodeoxycholate preparations. The close interaction between viral infection or reactivation and drug hypersensitivity was considered as a pathophysiology in this case, which emphasizes the need for further study of the immunological mechanism of the interaction.

Key words: cholestasis, drug hypersensitivity, eosinophilia, eruption, hepatitis E, hypersensitivity syndrome

INTRODUCTION

SOME VIRAL SPECIES, such as the Epstein–Barr (EB) virus,[1–3] induce drug hypersensitivity associated with eruptions. Cases of severe eruptions caused by viral reactivation, usually by human herpesvirus-6 (HHV-6), induced by primarily occurring drug hypersensitivity, have recently been reported and designated as hypersensitivity syndrome (HS).[4] The association between viral infection or reactivation and drug allergy is therefore a major area of concern in studying the immunological mechanism of hypersensitivity. Here, we report a case demonstrating multidrug hypersensitivity and cytomegalovirus reactivation following acute hepatitis E virus (HEV) infection.

CASE REPORT

THE PATIENT WAS a 65-year-old Japanese man. He took a commercially available medicine for a common cold, Jikinin, because of his rhinorrhea and coughing in the middle of February, 2004. He noted dark urine and pruritus of the whole body on 1 March, and visited Iwate Prefectural Ohfunato Hospital on 9 March. He was hospitalized on the day of his visit with a diagnosis of acute hepatitis from the clinical findings of overt jaundice and elevated levels of liver enzymes (Table 1). The laboratory data obtained at this stage demonstrated acute hepatic injury with cholestasis, but without any sign of hepatic failure. He was then transferred to the Iwate Medical University Hospital on 12 March because of further elevation in the levels of serum bilirubin and liver enzymes.

On admission, he showed marked jaundice on the bulbar conjunctiva and skin, but no abnormality in consciousness and vital signs. Laboratory findings showed a marked increase in serum bilirubin level and a moderate increase in the levels of liver enzymes, but no abnormality in total protein concentration, albumin level or blood coagulation test results (Tables 1 and 2). Leukocyte bands showed no abnormal classification, and no eosinophilia was found at this stage. Serological screening tests for viral hepatitis revealed that he had acute hepatitis E virus (HEV) infection, and the genotype III HEV RNA was detected in the serum sample. This isolate designated HE-JA42 and the sequence of the open reading frame 2 region (412 nucleotides) was registered as the accession number of AB218721 for the DNA databank of Japan, and showed a relatively close identity of approximately 92% with isolates from

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Table 1 Laboratory findings on admission in former hospital

Hematology		Blood chemistry	
Neutrophil	56.6%	D.Bil.	15.7 mg/dL
Lymphocyte	27.6%	AST	1548 IU/L
Monocyte	14.0%	ALT	1483 IU/L
Eosinophil	0.6%	LDH	744 IU/L
Basophil	1.2%	γ-GTP	224 IU/L
White blood cell	4900/μL	T.Bil.	22.2 mg/dL
Red blood cell	436×10^4/μL	Al-P	1644 IU/L
Haemoglobin	13.7 g/dL	TBA	197.6 μM/L
Hematocrit	39.8%	T.P.	6.3 g/dL
Platelet	26.2×10^4/μL	IgG	1430 mg/dL
		IgA	494 mg/dL
Electrolytes and renal function		IgM	236 mg/dL
Na	141 mEq/L	CRP	1.0 mg/dL
K	4.4 mEq/L		
Cl	107 mEq/L	Blood coagulation	
Urea nitrogen	16.1 mg/dL	PT	145%
Creatinine	0.6 mg/dL	HPT	110%
		Fibrinogen	338 mg/dL
		Antithrombin	156%
		FDP D-dimer	1.1 μg/mL

T.Bil., total bilirubin; D.Bil., direct bilirubin; AST, asparate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltranspeptidase; Al-P, alkaline phosphatase; TBA, total bile acid; T.P., total protein; Ig, Immunoglobulin; CRP, C-reactive protein; PT, prothrombin time; HPT, hepaplastin test (normotest); FDP, fibrin and fibrinogen degradation products.

Table 2 Laboratory findings on admission in Iwate Medical University

Hematology		Blood chemistry		Virus markers	
Neutrophil	46.0%	D.Bil.	26.3 mg/dL	HBsAb	(-)
Lymphocyte	22.0%	AST	427 IU/L	HCVAb	(-)
Monocyte	23.0%	ALT	765 IU/L	EBVCA IgG	(+)
Eosinophil	4.0%	LDH	295 IU/L	EBVCA IgM	(-)
Basophil	1.0%	γ-GTP	295 IU/L	EBNA Ab	(+)
White blood cell	4530/μL	T.Bil.	29.0 mg/dL	HBsAg	(-)
Red blood cell	493×10^4/μL	Al-P	1716 IU/L	CMV IgG	(+)
Haemoglobin	15.1 g/dL	T.P.	7.0 g/dL	CMV IgM	(-)
Hematocrit	44.2%	Albumin	3.7 g/dL	HEV IgG	(+)
Platelet	24.6×10^4/μL	IgG	1780 mg/dL	HEV IgM	(+)
		IgA	563 mg/dL	HEV RNA	(+)
Electrolytes and renal function		IgM	240 mg/dL	Genotype III	
Na	136 mEq/L	CRP	0.7 mg/dL		
K	4.6 mEq/L			Autoantibodies	
Cl	102 mEq/L	Blood coagulation		ANA	(-)
Urea nitrogen	15.3 mg/dL	PT	114%		
Creatinine	0.8 mg/dL	PT-INR	0.85	Others	
		HPT	115.4%	AFP	2.7 ng/mL
Urinalysis		Fibrinogen	245.8 mg/dL	HGF	0.44 ng/mL
pH	6.0	Antithrombin	112%	4/8 CD	5.25
Sp.G.	1.015	FDP D-dimer	0.5 μg/mL		
Protein	(-)				
Sugar	(-)				

PT-INR, prothrombin time-international normalizaion ratio; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; EBVCA, Epstein-Barr virus capsid antigen; EBNA, Epstein-Barr virus nuclear antigen; HEV, hepatitis E; ANA, antinuclear antibody; AFP, alpha fetoprotein; HGF, hepatocyte growth factor; 4/8 CD, ratio of clusters of differentiation 4 to 8.

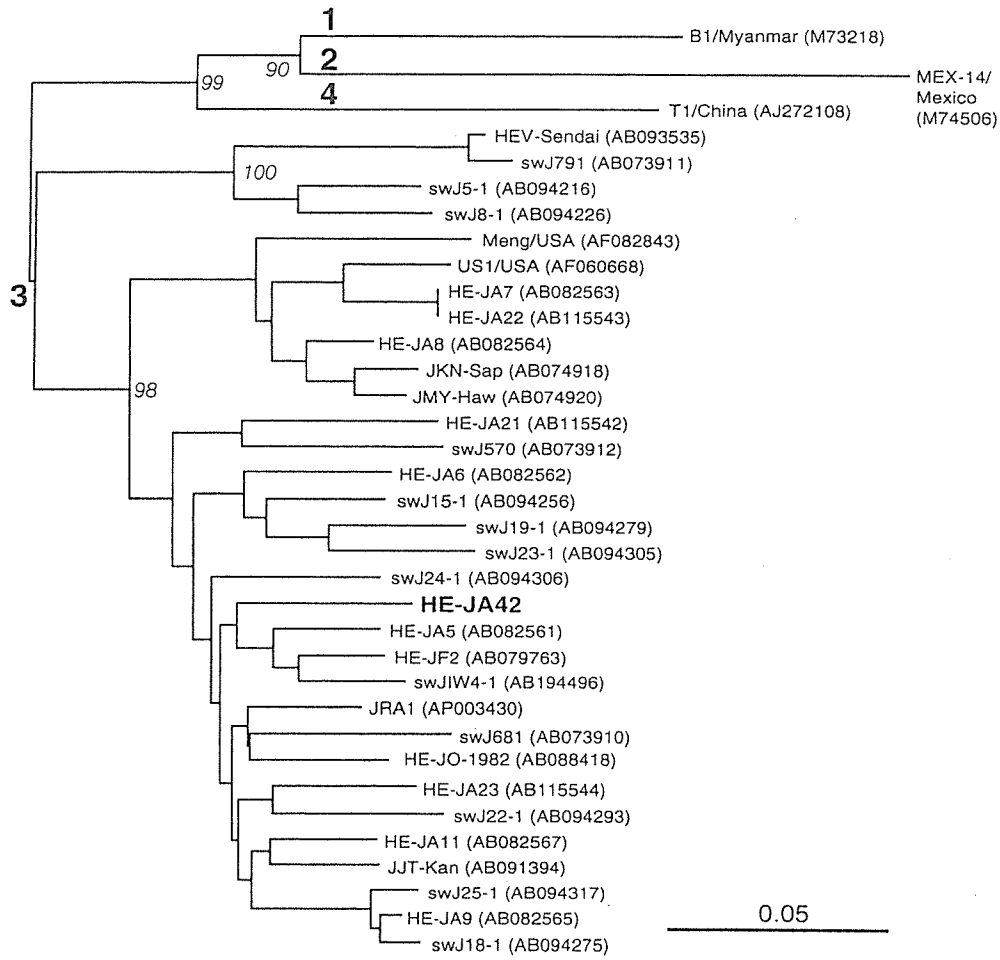

Figure 1 Phylogenetic tree constructed by neighbor-joining method on the basis of partial nucleotide sequence of open reading frame 2 region (301 nucleotides; nt 6037–6337 of the HE-JA10 genome [AB089824]) of reported human and swine genotype III HEV isolates. The HEV isolated from this patient is in bold face (HE-JA 42).

humans (HE-JA5 and HE-JF2) and swine (swJIW4-1) in Iwate prefecture (Fig. 1). Furthermore, a drug-induced lymphocyte stimulation test (DLST) showed a positive result for the drug, Jikinin, which he took for a common cold four weeks before the test. The DLST was carried out as follows: 1×10^6 peripheral blood lymphocytes of the patient per reaction were prepared using Ficoll–Paque, cultured and stimulated by medium with and without the drug solution. Lymphocyte proliferation measured by ^{3}H-incorporation to the DNA was 2.04-fold higher in drug-stimulated lymphocytes than in control. The drug Jikinin is a popular over-the-counter medicine for the common cold, containing some antiphlogistic and analgesic agents as shown in Table 3. Therefore, it was not clear which of these agents was responsible for the hypersensitive response.

Table 3 Active agents and additives included in the drug, Jikinin

Active agents
Dihydrocodeine phosphate
dL-Methylephedrine
Acetaminophen
Chloropheniramine maleate
Anhydrous caffeine
Liquorice extract
Additives
Talc
hydroxypropylcellulose
D-mannitol
Magnesium stearate
Cellulose
Sucrose

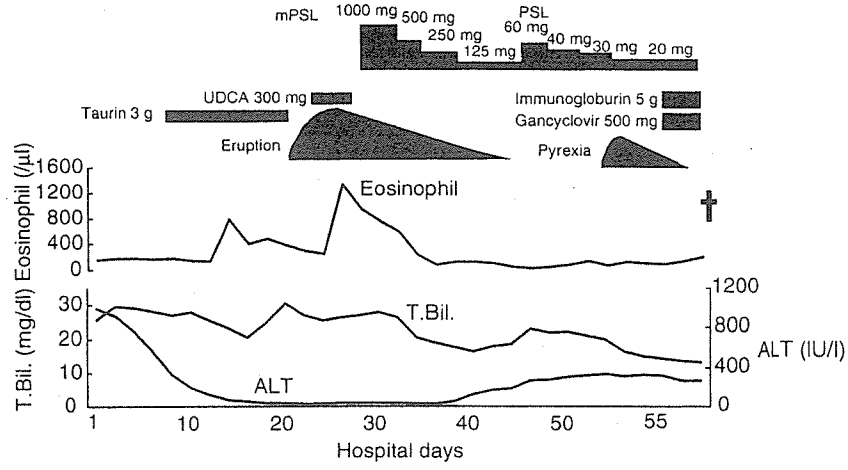

Figure 2 Clinical course of patient. ALT, alanine aminotransferase; mPLS, methylprednisolone; PLS, prednisolone; T. Bil., total bilirubin.

Abdominal computed tomography (CT) scan showed no signs of hepatic failure, such as liver atrophy, density irregularities or ascites, but showed the collapse and thickening of the wall of the gall bladder. Galactose receptor scintigraphy showed no decrease in functional liver mass. From these laboratory and imaging results, he was diagnosed to have acute hepatitis with intrahepatic cholestasis due to acute HEV infection and drug reaction to Jikinin.

Because the serum bilirubin level was maintained at approximately 30 mg/dL despite the smooth decrease in aminotransferase level after admission, 3 g/day taurin was administered on the tenth hospital day (HD) to induce choleresis (Fig. 2). Although the bilirubin level transiently decreased to 20 mg/dL after taurin administration, the level increased to 30.4 mg/dL on the 27th HD following an increase in eosinophil count up to 784/mL on the 13th HD, with numerous pruritic eruptions and erythema exsudativum multiforme appearing on his whole body on the 23rd HD (Fig. 3). Histopathological examination of his thigh lesion showed the presence of slight spongiosis and cell degradation in the epidermis, and marked eosinophilic infiltration around vessels and hair follicles in the upper dermis (Fig. 4). Taurin administration was stopped on the 23rd HD with the assessment of a possible allergic reaction to taurin. Instead, Ursodeoxycholic acid (UDCA) preparation was given on the 31st HD. However, the eosinophil count increased up to 20% on the 33rd HD, two days after the start of UDCA administration, followed by pyrexia (38.5°C), severe eruptions on the whole body with pruritus and facial edema. With a diagnosis of multidrug hypersensitivity despite the negative result of the DLST for taurin and UDCA, 1000 mg/day methylprednisolone was administered for three days, from the 35th to the 37th HD, and tapered by switching to oral prednisolone administration. Since the start of methylprednisolone treatment, symptoms of pyrexia, eruptions and facial edema improved, but urea nitrogen and creatinine levels gradually elevated. When the dose of prednisolone was tapered to 30 mg/day on the 54th HD, a high fever (39.5°C) abruptly developed. Although the administration of ganciclovir and immunoglobulin preparation was started on the 58th HD with a positive result for blood cytomegalovirus (CMV) antigen, the pyrexia did not subside and was followed by hemorrhagic shock originating from multiple hemorrhagic duodenal ulcers. Although an emergency hemostatic treatment was performed through gastrointestinal endoscopy, hemorrhage did not subside and the patient died from multiple organ failure associated with disseminated intravascular coagulation (DIC) on the 68th HD.

Autopsy and subsequent histopathology showed a number of findings indicating DIC and CMV infection: (i) gangrenous necrosis of the whole intestine with multiple fibrin thrombi in small vessels and microscopic infarction in the spleen with fibrin thrombi (Fig. 5a); (ii) multiple fresh infarcts in the liver, skin in the thumb tip and spleen (Fig. 5b); (iii) multiorgan CMV infection including the duodenum, small and large intestines and bilateral lungs (Fig. 6); and (iv) diffuse alveolar damage of both lungs.

DISCUSSION

THE PATHOPHYSIOLOGICAL FEATURES of the patient precipitating into death was not due to liver failure but to drug hypersensitivity and severe CMV reactivation, although the initial symptoms were those of

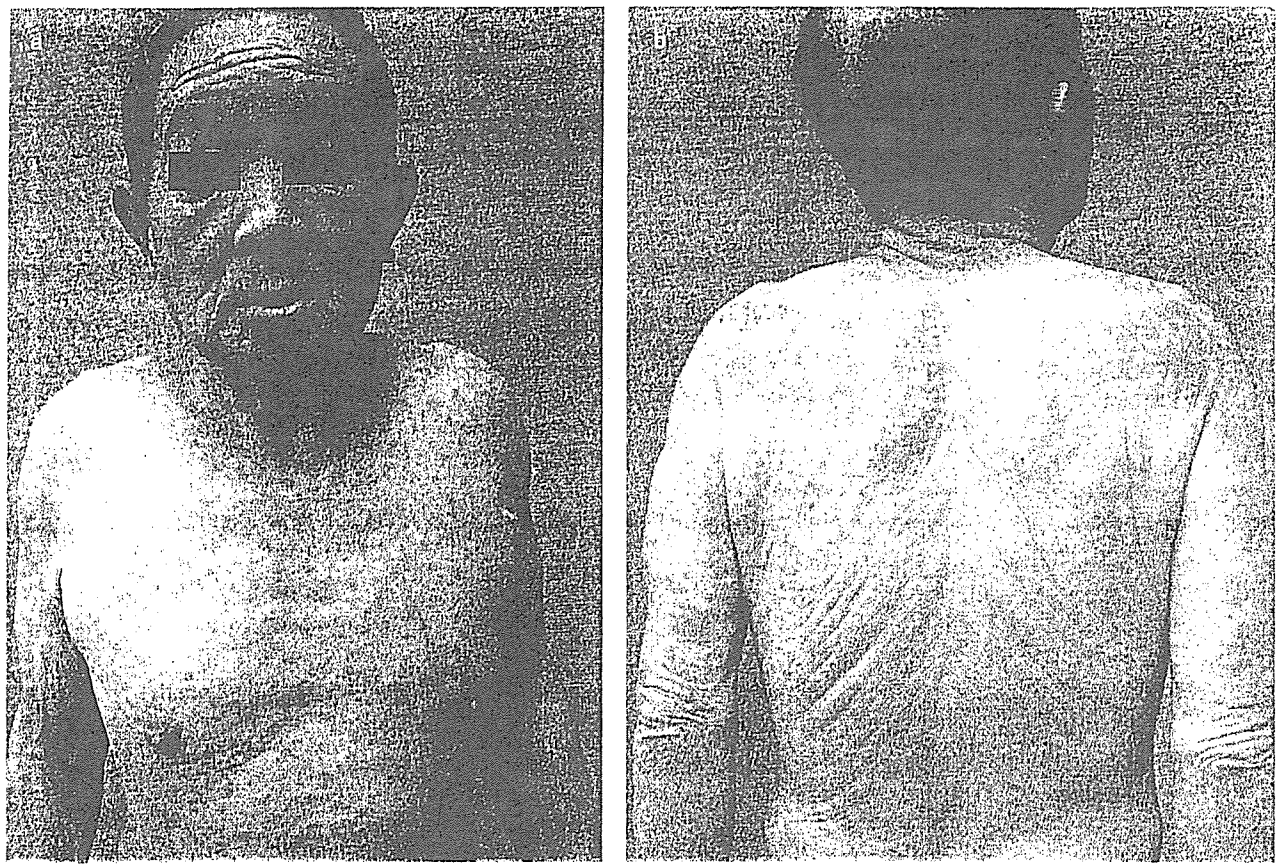

Figure 3 Clinical features of skin. Erythropapular eruptions and erythema exudativum multiforme were observed with icterus

acute hepatitis due to HEV infection, which is recently regarded to be endemic in Japan[7] and occasionally causes fatal hepatic failure.[6] The eruptions were multiform exudative erythema-type, and histopathologic finding of these eruptions showed marked eosinophilic infiltration. These findings indicated typical allergic dermatitis. The acute onset of rashes associated with pyrexia and eosinophilia following the start of taurin or UDCA administration suggests that allergic reactions to these drugs are responsible for the eruptions. However, neither taurin nor UDCA is listed as a high-risk compound for drug allergy.[1] Therefore, the condition of this patient at the onset of eruptions was considered to be highly susceptible to drug hypersensitivity.

A number of reports have shown a strong relationship between drug hypersensitivity and viral infection.[1–4] In both interactions, that is viral infection-induced drug hypersensitivity and drug hypersensitivity-induced viral reactivation, lymphocyte activation is considered to play an important role in the pathophysiology, although the precise mechanism of this role has not yet been elucidated. The EB virus, which infects B-lymphocytes and induces the development of infectious mononucleosis,[5] induces allergic reaction to ampicillin.[1,3] A reactivation of HHV-6, which infects T-lymphocytes and induces the development of exanthem subitum during the initial infection,[8] is hypothesized to induce the pathogenesis of hypersensitivity syndrome following the intake of specific drugs such as anticonvulsants and alloprinol.[4] In our patient, neither such a virus nor drugs were accounted for, at least during the initial phase of the disease. The CMV virus, which persistently infects white blood cells, endothelial cells and other cells, causing a symptomatic disease in an immunocompromised host, was remarkably activated only in the late phase of the disease, after the glucocorticoid therapy.

Therefore, hypersensitivity to multidrugs such as taurin and UDCA in this case cannot be categorized in any known disease entity of drug allergy. One of the issues in this case was whether HEV infection alone was sufficient to cause drug hypersensitivity, or whether an unfortunate coincidental HEV infection and independ-

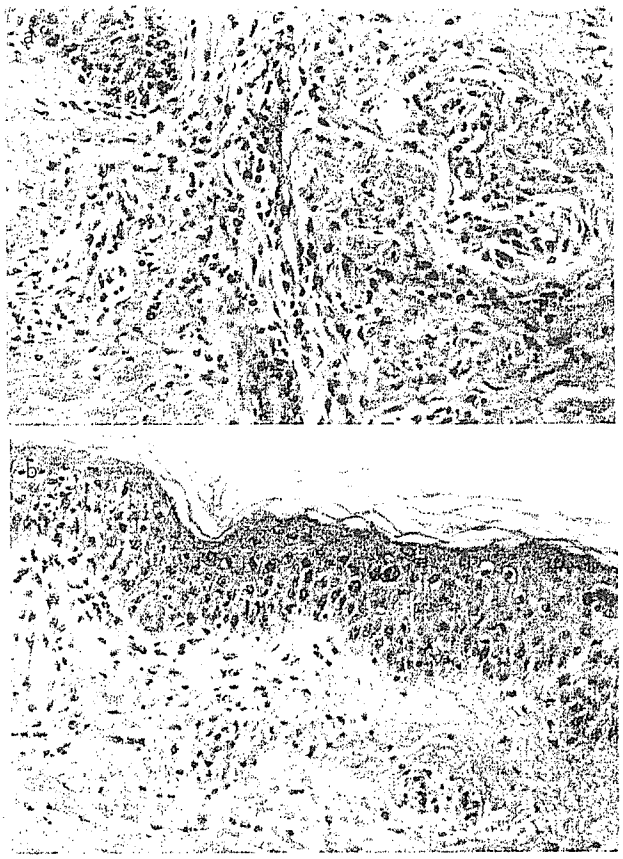

Figure 4 Marked eosinophilic infiltration around vessels and hair follicles were observed in upper dermis (hematoxylin-eosin staining, 200×).

ent reaction to Jikinin led to an accidental hypersensitive reaction. The other issue was whether the glucocorticoid therapy alone led to the severe CMV reactivation in the late phase.

The feature of hepatic injury in this case was marked cholestasis, which is unusual in HEV hepatitis[9] but common in drug-induced hepatitis.[10] Drug-induced hepatitis accounts for approximately 10% of all cases of fulminant hepatitis in Japan.[11] The use of some drugs during the early stages of acute hepatic injury may be implicated in the progression of such an injury to acute liver failure.[12,13] These findings suggest that drugs act not only as the primary cause, but also as the aggravating cofactor of acute liver injury. Although the precise mechanism by which drugs induce hepatic injury remains to be elucidated, two major types of hepatic injury are known: toxic hepatic injury and immunoallergic hepatitis.[14] In this case, the primary cause of liver injury might have been acute HEV infection, as shown by the positivity for the IgM anti-HEV antibody and HEV RNA; and the initial symptoms such as a cold might have been the onset symptom of acute hepatitis. The marked cholestasis associated with acute hepatitis might have been a result of drug reaction to Jikinin superimposed to acute HEV hepatitis, although it is not clear whether the HEV infection accelerated drug hypersensitivity or whether the HEV infection was just coincidental. Nagasaki *et al.* have recently reported that two patients with acute HEV hepatitis demonstrated acute onset autoimmune hepatitis-like features such as positivity for the antinuclear antibody and an elevated serum immunoglobulin G level.[15,16] This indicates the possibility that HEV infection induces an excessive immune response or aggravates asymptomatic autoimmune dis-

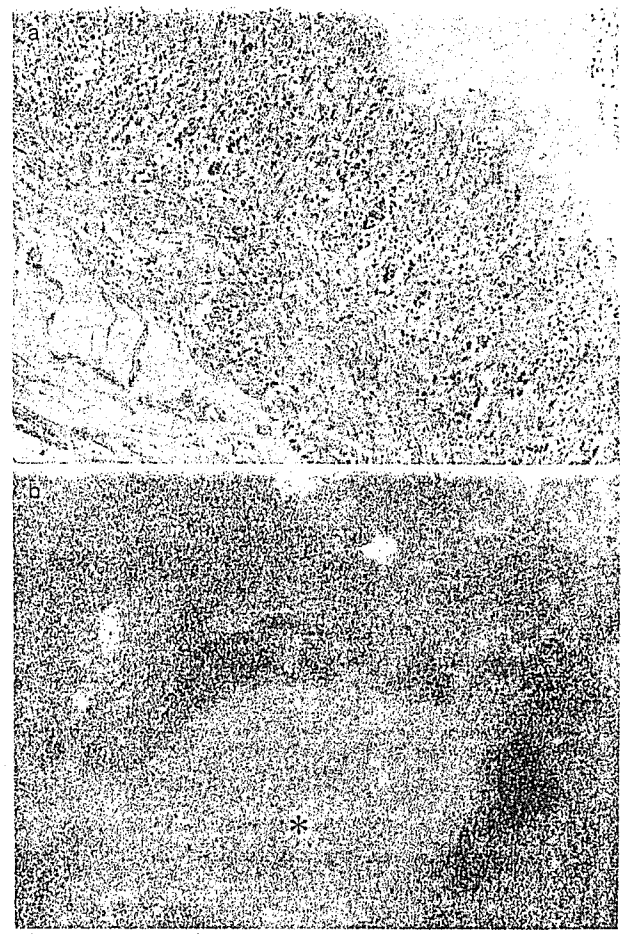

Figure 5 Histopathology of small intestine (a) and spleen (b). Multiple fibrin thrombi were observed in small vessels of the small intestine and spleen. Small infarcts (*) were observed in the spleen.

Figure 6 Histopathology of lung (a) and duodenum (b). Multiple inclusion bodies of cytomegalovirus were observed in epithelial cells.

eases, which supports the possible mechanism of HEV-induced drug hypersensitivity in this case. Indeed, a case of hepatitis E-associated hypersensitivity to dapsone, an antileprosy drug, was reported.[17] Besides HEV infection, many extrahepatic symptoms associated with acute and chronic viral hepatitis have been reported in relation to immunoallergic mechanisms such as Guillain–Barré syndrome[18] and Schönlein–Henoch purpura.[19] However, there is no report demonstrating the association between drug hypersensitivity and the hepatitis virus, although a close relationship between drug hypersensitivity and acute infection or reactivation of herpesviruses, HHV-6,[4] EBV[20] and CMV[21] has been reported.

The pathophysiologies leading to the death of the patient were DIC and a massive hemorrhage from duodenal ulcer, both of which were induced by CMV reactivation in multiple organs. CMV infects many types of cell including lymphocytes,[5] remains latent within the host and reactivates when the host's immune system is compromised.[22] On the other hand, CMV is considered as one of the causative viruses of hypersensitivity syndrome, as with other herpesviruses. Indeed, Aihara *et al.*[21] reported a case of hypersensitivity syndrome associated with CMV reactivation, which developed jaundice, renal failure and DIC, similarly to our present case. Therefore, CMV reactivation in this case may be induced by not only glucocorticoid therapy but also pathogenic mechanism that is the same as that underlining HHV-6 reactivation in hypersensitivity syndrome.

In summary, this case suggests the possibility that HEV infection is a cause of multidrug hypersensitivity, and that drug hypersensitivity induces CMV reactivation instead of HHV-6. These findings emphasize the need for further study of the immunological mechanism of the interaction between drug hypersensitivity and viral infection.

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Influence of Genotypes and Precore Mutations on Fulminant or Chronic Outcome of Acute Hepatitis B Virus Infection

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The outcome of acute hepatitis B virus (HBV) infection is variable, influenced by host and viral factors. From 1982 through 2004, 301 patients with acute HBV infection entered a multi-center cross-sectional study in Japan. Patients with fulminant hepatitis (n = 40) were older (44.7 ± 16.3 vs. 36.0 ± 14.3 years, $P < .0017$), less predominantly male (43% vs. 71%, $P = .0005$), less positive for hepatitis B e antigen (HBeAg) (23% vs. 60%, $P < .0001$), less infected with subgenotype Ae (0% vs. 13%, $P < .05$), and more frequently with Bj (30% vs. 4%, $P < .0001$) than those with acute self-limited hepatitis (n = 261). Precore (G1896A) and core-promoter (A1762T/G1764A) mutations were more frequent in patients with fulminant than acute self-limited hepatitis (53% vs. 9% and 50% vs. 17%, $P < .0001$ for both). HBV infection persisted in only three (1%) patients, and they represented 2 of the 23 infected with Ae and 1 of the 187 with the other subgenotypes (9% vs. 0.5%, $P = .032$); none of them received antiviral therapy. In multivariate analysis, age 34 years or older, Bj, HBeAg-negative, total bilirubin 10.0 mg/dL or greater, and G1896A mutation were independently associated with the fulminant outcome. In *in vitro* transfection experiments, the replication of Bj clone was markedly enhanced by introducing either G1896A or A1762T/G1764A mutation. In conclusion, persistence of HBV was rare (1%) and associated with Ae, whereas fulminant hepatitis was frequent (13%) and associated with Bj and lack of HBeAg as well as high replication due to precore mutation in patients with acute HBV infection. *Supplementary material for this article can be found on the HEPATOLOGY website (http://interscience.wiley.com/jpages/0270-9139/suppmat/index.html).* (HEPATOLOGY 2006; 44:326-334.)

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; EIA, enzyme immunoassay; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; ALT, alanine aminotransferase.

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The nucleotide sequences of HBV DNA isolates used in this study have been deposited in the international DNA database under accession numbers AB249373-AB249636.

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Approximately 3 billion people, one half of the world population, have been exposed to hepatitis B virus (HBV), of whom approximately 350 million are persistently infected with it.[1] Acute infection with HBV resolves in the great majority but can induce fulminant hepatitis or go on to become chronic. Host and viral factors may influence fulminant or chronic outcome of acute HBV infection, but they are not fully defined.

Eight genotypes have been detected by a sequence divergence greater than 8% in the entire HBV genome of approximately 3,200 nucleotides (nt), and designated by capital alphabet letters from A (HBV/A) to H in the order of documentation.[2-5] They have distinct geographical distributions associated with severity of liver disease as well as response to antiviral therapies.[6-8] Furthermore, subgenotypes have been reported for HBV/A, B, and C and named Aa/A1 (Asian/African type) and Ae/A2 (European type),[9] Bj/B1 (Japanese type) and Ba/B2 (Asian type),[10] as well as Cs/C1 (Southeast Asian type) and Ce/C2 (East Asian type).[11-13] Increasing lines of evidence indicate that subgenotypes of HBV/A and B influence the replication of HBV and bear clinical relevance.[14-16] Furthermore, genotypes affect mutations in precore region and core promoter, thereby influencing the expression of hepatitis B e antigen (HBeAg).[8,17]

During the 23 years from 1982 to 2004, a multi-center cross-sectional study was conducted throughout Japan on 301 patients with acute hepatitis B. We examined the influence of genotypes/subgenotypes on their fulminant or chronic outcome. Furthermore, the influence of G1896A or A1762T/G1764A on replication of HBV was evaluated in an *in vitro* replication model.

Patients and Methods

Patients With Acute Hepatitis B. During 1982 through 2004, 336 consecutive cases of acute hepatitis B were registered in 16 hospitals throughout Japan. These hospitals were from the following eight areas: Hokkaido (represented by J.-H. K. and S.H.), Tohoku (T.K. and K.S.), Kanto (H.T., Y.A. and K.I.), Koshin (E.T. and S.O), Tokai (A.O., Y.T., E.O., M.S., R.U., M.M., and S.K.), Kinki (T.O.), Honshu/Shikoku (Y.M., K.H., and M.O.), and Kyushu (H.Y. and H.S.). The diagnosis of acute hepatitis B was contingent on a sudden onset of clinical symptoms of hepatitis and detection of high-titered antibody to hepatitis B core antigen (anti-HBc) of IgM class in serum. Patients with initial high-titered anti-HBc (≥90% inhibition by a 1:200 diluted serum) were excluded; they were diagnosed as exacerbation of chronic hepatitis B. Patients with acute hepatitis A, hepatitis C, or human immunodeficiency virus co-infection, and drug- or alcohol-induced acute hepatitis also were excluded; hepatitis D virus infection was not examined because of its extreme rarity in Japan.[18] Most of them were followed for clinical outcomes until the disappearance of hepatitis B surface antigen (HBsAg) during 24 weeks or longer after the presentation. The criteria of fulminant hepatitis are based on the report by Trey et al.,[19] with a slight modification in 1981 (Inuyama symposium, Aichi, Japan): coma of grade II or higher and prothrombin time less than 40% developing within 8 weeks after the onset. Serum samples were collected at the presentation and had been stored at −80°C. HBV genotypes, HBV DNA, and HBeAg were determined, and clinical outcomes of acute hepatitis were analyzed. The study protocol conformed to the 1975 Declaration of Helsinki, and was approved by the Ethics Committees of the institutions. Every patient gave an informed consent for this study.

Serological Markers of HBV Infection. HBsAg was determined by hemagglutination (MyCell; Institute of Immunology Co., Ltd., Tokyo, Japan) or enzyme immunoassay (EIA) (Axsym; Abbott Japan, Tokyo, Japan), and HBeAg by enzyme-linked immunosorbent assay (F-HBe; Kokusai Diagnostic, Kobe, Japan) or chemiluminescent EIA (Fujirebio Inc., Tokyo, Japan). Anti-HBc of IgM and IgG classes were determined by radioimmunoassay (Abbott Japan).

Genotypes and Subgenotypes of HBV. The six major HBV genotypes (A-F) were determined serologically by EIA using commercial kits (HBV GENOTYPE EIA; Institute of Immunology). The method depends on the combination of epitopes on preS2-region products detected by monoclonal antibodies, which is specific for each of them.[20] HBV/G was determined by a slight modification of the polymerase chain reaction (PCR) with specific primers.[21]

Subgenotypes of HBV/A designated Ae prevalent in Europe and Aa frequent in Africa as well as Asia,9 which corresponds to subgroup A′ originally reported by Bowyer et al.,[22] were determined by PCR restriction fragment length polymorphism (RFLP) involving nucleotide conversions in an immediate upstream of the precore region that are specific for each of them.[16,23] HBV/Bj (Japanese type) lacking the recombination with C over the precore region and the core gene and Ba (Asian type) with the recombination were determined by its absence or presence on HBV DNA sequences, as well as RFLP based on specific nucleotide substitutions, after the methods described previously.[15,24]

Subgenotypes of HBV/C, Cs (Southeast Asian type) found only in Southeast Asia, including Vietnam, Myanmar, Thailand, Laos, Bangladesh, Hong Kong, and Southern China, and Ce (East Asian type), found in Far