1976 and has surveyed the incidence of this disease in Japan since 1983. During the last two decades, a considerable number of cases of FH have been documented. We describe the culmination of this survey, including trends in etiology, survival and treatment responses in the period before the substantial introduction of liver transplantation for treatment, to provide basic data for comparison with those in transplantation era.

2. Material and methods

2.1. Study centers

A written questionnaire was sent annually to 313 centers affiliated with the councilors of the Japanese Society of Gastroenterology and the Japan Society of Hepatology. The recovery rate since 1989 has been 66–74%; the data on the recovery rate before 1989 was unavailable.

2.2. Patients

FH was diagnosed according to Japanese diagnostic criteria [13,14], that is, the disease was diagnosed when grade II or worse encephalopathy developed within 8 weeks of the first symptom due to impaired liver functions in patients with acute hepatitis [15], and the plasma prothrombin time was 40% or less. We included only patients with viral or drug-induced hepatitis. Hepatitis B virus (HBV) carriers who developed the disease were also included, except those with liver cirrhosis. Patients with other causes of hepatic failure such as acute exacerbation of autoimmune hepatitis or Wilson's disease, acute fatty liver of pregnancy, and alcoholic hepatic injury were excluded.

Over the course of 15 years, 1324 patients were diagnosed as having FH according to these criteria. We finally selected 1309 patients for this study, excluding 15 patients who were younger than 15 years old.

2.3. Definition of disease type

FH was classified as the acute type, in which 10 days or less had elapsed from the onset of illness to the development of grade II or worse encephalopathy, and the subacute type, in which 11 or more days had elapsed [16].

2.4. Definition of causes

Patients positive for the serum IgM anti-hepatitis A antibody (IgM anti-HA detected by radioimmunoassay (RIA) or enzyme immunoassay (EIA)) were regarded to have the hepatitis A virus (HAV); those positive for the serum IgM anti-hepatitis B core antibody (IgM anti-HBc detected by RIA or EIA) had HBV; those without a history of drug exposure and negative for both of these antibodies had non-A, non-B hepatitis; those with a history of drug exposure closely related to the onset of hepatitis and negative for both antibodies were classified as having drug-induced hepatitis; those in which the IgM anti-HA or -HBc antibody was not assayed were classified as having FH of unknown cause.

In a subset of patients, other hepatitis markers were also measured, that is, the anti-hepatitis C virus antibody (detected by RIA or EIA), hepatitis C virus (HCV) RNA (detected by branched DNA probe assay or PCR), anti-hepatitis D virus antibody (detected by EIA), hepatitis E virus RNA (PCR) and GBV-C/HGV RNA (PCR).

2.5. Infection routes of HBV

We examined the possible routes of transmission of HBV since 1995. We classified the routes into acute exacerbation in HBV carriers, sexual transmission, iatrogenic or drug abuse, and unknown, on the basis of the history of chronic HBV infection, sexual contact with HBV carriers, and exposure to HBV such as through the use of contaminated injection needles, respectively.

2.6. Statistical analyses

Examination variables and age are expressed as median values with ranges. The statistical significance of differences between groups was assessed using the Mann-Whitney U test and chi-square test. All statistical analyses were performed using an SPSS version 11 computer software program (SPSS Japan Inc., Tokyo).

3. Results

3.1. Clinical findings

Over a period of 15 years, 1309 patients were studied. Approximately 100 patients were registered per year; the lowest annual number of patients was 60 in 1992, and the highest was 116 in 1983.

Among these 1309 patients, 674 (51.5%) were classified as having the acute type of disease and the other 635 (48.5%) the subacute type. The men:women ratio was higher for the acute type (343:331) than for the subacute type (277:358) ($P < 0.01$). The patients ranged in age from young adults to the elderly, and the median age at FH onset was 48 years. The median age was higher for the subacute type (51 [38–63]; median with [25–75th percentile]) than for the acute type (45 [31–57]) ($P < 0.001$). The overall survival rate was 25.9% and the survival rate was significantly higher for the acute type (36.2%) than for the subacute type (15.0%) ($P < 0.001$) (Table 1).

3.2. Causes

The cause of FH was identified as HAV, HBV or drug-induced in about 40% of the patients (536/1309). The causes

Table 1
Clinical findings of the patients

	Acute type	Subacute type	Total
Age (median [range] years)	45 [15–85]	51 [15–84]	48 [15–85]
Men/women	343/331	277/358	620/689
Survival rate (%)	36.2	15.0	25.9
HBV carrier rate (%)	6.4	14.4	10.4

Table 2
Causes of fulminant hepatitis

	Acute type	Subacute type	Total
HAV	85 (12.6)	17 (2.7)	102 (7.8)
HBV	242 (35.9)	69 (10.9)	311 (23.8)
Probable HBV	82 (12.2)	98 (15.4)	180 (13.8)
Non-A, non-B hepatitis	106 (15.7)	277 (43.6)	383 (29.3)
Drug-induced	56 (8.3)	67 (10.6)	123 (9.3)
Unknown	103 (15.3)	107 (16.9)	210 (16.0)
Total	674 (100)	635 (100)	1309 (100)

No. of patients (%).

in the remaining 60% (773/1309) of the patients were classified as non-A, non-B hepatitis, probable HBV, or unknown (Table 2). The proportion of patients with an unknown cause of the disease has decreased since 1989, when viral markers began to be routinely measured. The annual incidence of HAV varied from 1.1% in 1987 to 20.6% in 1991, with an average of 7.8% for all patients and years. HBV infection was responsible in about 24% of patients; when probable HBV infections were included, this value increased to 37%. During the 15-year study period, there was no decrease in the proportion of patients with HBV (Fig. 1). We could determine the route of transmission in 60 cases out of 112 patients with HBV and probable HBV registered since 1995. Among 38 HBV patients, in 17 (45%), sexual transmission was the route of infection, and in 9 (24%), the disease developed as an acute exacerbation in HBV carriers; in contrast, in 13 of 22 patients with probable HBV (59%) the disease developed as an acute exacerbation in HBV carriers. Drug exposure was implicated in about 10% of all patients; this value did not change markedly during the study period (Fig. 1).

Table 3
Positivity of HCV antibody and HCV RNA

Cause	HCV-positive case/total case (%)
HAV	3/66 (4.5)
HBV	5/175 (2.9)
Probable HBV	5/70 (7.1)
Non-A, non-B hepatitis	20/233 (8.6)
Drug-induced	1/59 (1.7)
Unknown	2/42 (5.6)
Total	36/645 (5.6)

The causes of FH differed significantly between the acute type and subacute type (Table 2) ($P < 0.001$). Since 1989, HAV and HBV infections accounted for about 60% of acute type, whereas non-A, non-B infection was responsible for about 60% of subacute type. The distribution of the number of days from the onset of illness until the development of encephalopathy (onset-coma days: OCD) is shown according to the cause in Fig. 2. In non-A, non-B FH and drug-induced FH, the distribution is wide, ranging from a few days to more than 50 days, in contrast to the narrow distribution of within 10 days in the case of HAV and HBV infections. Survival rate clearly decreased in the cases with longer than 10 days duration before the onset of encephalopathy for any causes except HBV. In the case of HBV infection, survival rate did not decrease until duration of 20 days before the onset of encephalopathy occurred (Fig. 2).

HCV markers (anti-HCV antibody and HCV RNA) were measured in 645 of 727 patients since 1989. Thirty-six patients (5.6%) were positive for at least one of these. HCV marker positivity rate according to the cause is shown in Table 3. None of the patients were positive for the markers of hepatitis D or hepatitis E virus. The presence of GBV-C/HGV RNA before the administration of blood products was tested

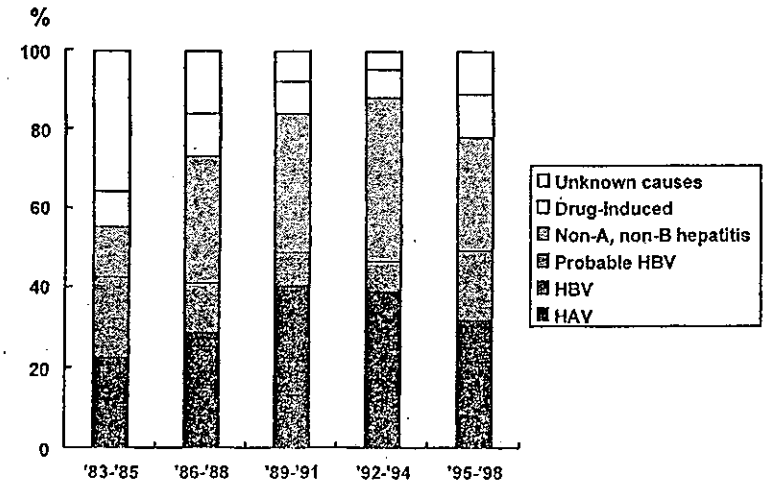


Fig. 1. Changes in distribution of causes. Bar graphs show distribution of causes in percentages in each 3-year period. The numbers at the bottom represent the number of patients in each period.

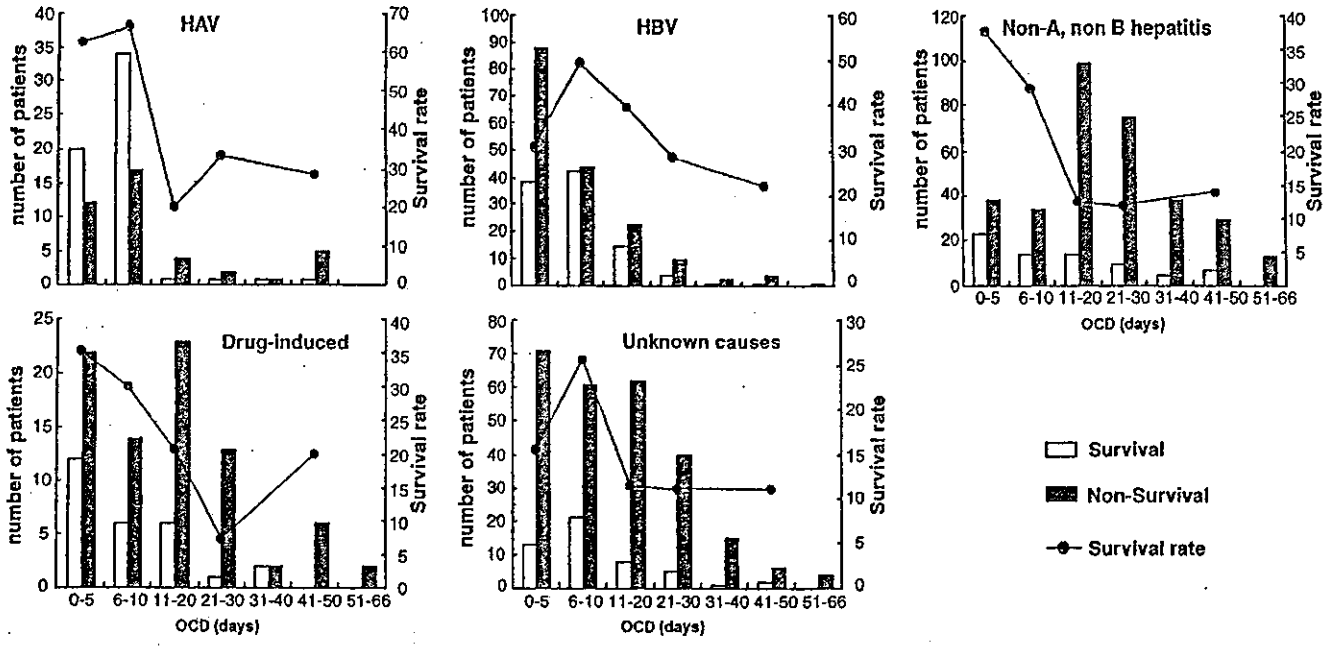


Fig. 2. Histograms of OCD according to cause. Each graph shows the distribution of OCD for each cause. Bar graphs represent the number of patients in each 5–10-day interval divided into survivors (white area) and non-survivors (gray area). The line graph represents survival rate for each OCD value.

in 63 of 180 patients since 1996 and a positive result was obtained in 5 of 63 patients (7.9%).

3.3. Changes in survival

Survival rate is shown for three 5-year periods (period I, 1983–1987; period II, 1988–1992; period III, 1993–1997) in Table 4. Although there was no significant improvement in overall survival rate ($P = 0.087$), survival rate for the acute type was significantly different among the three periods. However, when survival was analyzed according to the cause, there was no improvement in any subgroup.

For the entire study period, the survival rates according to the cause were as follows: HAV, 57.8%; HBV, 37.6%; probable HBV, 16.7%; non-A, non-B hepatitis, 18.5%; drug-induced, 23.6%; unknown, 17.1%. The survival rate was significantly higher for HAV than for other causes (Table 3) ($P < 0.001$).

Table 4
Changes in survival rate

Period (*n*)	1983–1987 (497)	1988–1992 (369)	1993–1997 (443)
Total	22.5	28.7	27.3
Disease type			
Acute	28.6	38.9	43.3
Subacute	15.4	17.9	12.3
Cause			
HAV	60.0	56.4	58.1
HBV	34.3	40.4	35.8
Probable HBV	16.5	10.5	21.1
Non-A, non-B hepatitis	18.8	20.1	16.8
Drug-induced	21.2	23.1	26.7
Unknown	15.5	27.3	14.3

Survival rate (%).

3.4. HBV-related FH

The clinical characteristics were compared between 311 patients with HBV infection who were IgM anti-HBc-positive and 68 patients with probable HBV infection who were confirmed to be IgM anti-HBc-negative and identified from 180 patients with probable HBV infection. As compared with the patients with HBV infection who were IgM anti-HBc-positive, the patients with probable HBV infection who were IgM anti-HBc-negative included a significantly higher proportion of men, elderly patients, HBV carriers, those with the subacute type, and those with a poor prognosis (Table 5).

3.5. Therapies and complications

The frequency of applying each therapy to FH patients is shown for five 3-year periods in Table 6. The frequency of plasma exchange, and interferon and anticoagulant treatment

Table 5
Differences in clinical findings between the patients with acute HBV infection and probable HBV infection

	HBV	IgM HBc-negative probable HBV	*P*
Age (median [range])	40 [16–83]	50 [20–83]	<0.001
Sex (men/women)	159/152	50/18	<0.001
Disease type (acute/subacute)	242/69	20/48	<0.001
Underlying disease (%)	23.2	38.1	<0.05
HBV carrier (%)	12.2	73.8	<0.001
Survival (%)	36.7	20.6	<0.05

Table 6
Changes in therapies for fulminant hepatitis in pretransplantation era

	1983–1985	1986–1988	1989–1991	1992–1994	1995–1997
Fischer's solution	79.7	86.6	92.8	87.9	66.8
Glucagons–insulin therapy	82.0	87.7	84.2	79.7	65.7
Glucocorticoid	56.4	54.0	43.7	54.7	69.7
Cyclosporin	–	–	7.5	13.7	16.1
Anticoagulant therapy	50.5	69.6	–	71.4	65.1
Prostaglandins	–	–	41.4	43.4	37.4
Interferon	5.9	3.6	17.1	15.2	15.9
Plasma exchange	77.4	82.7	85.6	88.4	89.1
Hemodiafiltration	–	–	–	–	56.0
Charcoal perfusion	13.8	9.4	12.2	10.5	2.3

Table 7
Influence of complications on prognosis of fulminant hepatitis

Complications	Incidence (%)	Survival rate (%)	
		With complications	Without complications
Infection	39.1	14.9	34.8***
Gastrointestinal bleeding	36.1	13.8	34.6***
Renal failure	47.1	10.9	39.5***
Disseminated intravascular coagulation	49.7	13.1	40.9***

*** $P < 0.001$ as compared with survival rate in patients with complications.

increased and those of glucagons–insulin therapy and the administration of Fischer's solution decreased over the study period. Glucocorticoids were administered to approximately 60% of FH patients in the early 1980s. The frequency of the administration of glucocorticoids transiently decreased to about 40% around 1990 and increased again to more than 60% in the late 1990s. In the late 1990s, hemodiafiltration therapy was developed and became popular, and was performed on about 60% of patients, particularly on those with the acute type (74% in 1997). None of these therapies significantly improved survival rate in each individual chi-square analysis (data not shown). Only three patients with the subacute type received living-related donor liver transplantation in 1997 and all of them were alive at the time of survey.

In regard to complications, we examined the frequencies and effect on the prognosis of infections, gastrointestinal bleeding, renal failure and disseminated intravascular coagulation. There were no significant changes in the frequencies of these complications during the 15-year study period (data not shown). Any of these complications significantly decreased survival rate (Table 7).

4. Discussion

In many countries, liver transplantation is accepted as the only effective therapy for FH and is performed routinely [1,17], because the survival rate following liver transplantation is much higher than those following conservative therapies. However, FH is a potentially reversible condition [18] and the liver after recovery from FH is usually normal [19], whereas almost all patients who undergo liver transplantation experience some restrictions to their lifestyle [20]. Therefore, the quality of life after a full recovery is much better for patients who were treated by conservative therapies than those treated by liver transplantation. In addition, a living-donor also has some physical, economical and social disadvantages following liver transplantation [21]. From these points of view, efforts should be made to treat FH patients by conservative therapies at least at the start of treatment. In Japan, powerful artificial liver support systems for the treatment of FH have been developed [22,23] and were widely used despite the lower frequency of liver transplantation. The increased frequency of plasma exchange combined with hemodiafiltration therapy in the 1990s may be implicated in the tendency for survival rate to increase for the acute type FH. However, it was difficult to evaluate the efficiency of the therapy by a randomized controlled trial (RCT) [24], because FH patients were seriously ill and the number of patients in single institutions was small, which may be why the efficiency of liver transplantation for FH patients has also not been tested by RCT. Fortunately, we have gathered nationwide data regarding the epidemiology, treatment and outcome of FH patients over 15 years; therefore, we can compare these aspects of FH between before and after the substantial introduction of liver transplantation. The main object of this report is to provide a summary of the Japanese Nationwide survey on FH in the pretransplantation era.

The principal findings in this survey were that HBV was consistently responsible for FH in about one-third of all patients throughout the study period and that the etiology remains obscure in approximately one-half patients with FH. Because the presence of the IgM anti-HBc antibody reflects recent immune response to HBV, it is considered useful in the diagnosis of hepatitis caused by HBV [25]. However, patients with hepatitis caused by HBV and who were negative for the IgM anti-HBc antibody have been identified, re-emphasizing the potential role of HBV in hepatitis of unknown etiology [26,27]. In addition, many cases of FH associated with carrier reactivation due to HBV virus mutations or immunosuppressive or cytotoxic therapy have been described [28–30]. Therefore, we separately classified probable HBV

and classical HBV or non-A, non-B hepatitis, to elucidate the importance of HBV as a cause of FH. FH related to HBV infections, including HBV and probable HBV infections, accounted for 37.6% of all cases, and this proportion did not decrease during the 15-year survey period. These data show that HBV remains a major cause of FH. In the period before 1989, when anti-HBc antibody assay was adopted as a screening test for donated blood, 24% of FH due to HBV was post-transfusion hepatitis [14]. In contrast, the introduction of the screening test for donated blood seems to have considerably eliminated post-transfusion hepatitis [31], although the problem of the occurrence of hepatitis after the transfusion of blood from a donor in the window period of acute HBV infection still remains unsolved [32], even after improvements in screening methods using nucleic acid amplification testing [33,34].

Our results regarding the routes of transmission of HBV indicate that at present, sexual transmission from HBV carriers is a major route for FH patients positive for the IgM anti-HBc antibody. In contrast, in most patients with probable HBV, FH was considered to develop as an acute exacerbation in HBV carriers. In either case, the monitoring of HBV carriers is most important for reducing the incidence of HBV-related FH. Therefore, screening and vaccination programs for adolescents and education programs for infection prevention as well as the prevention of mother-to-child transmission, would play an important role in decreasing the incidence of FH caused by HBV. The preventive administration of HBV hyperimmune globulin and vaccination against HBV to neonates born to HBV carrier mothers has been being practiced nationwide since 1985 in Japan [35]. Therefore, the HBV carrier rate in the population has significantly decreased [36] and as a result, a marked decrease in the incidence of FH caused by HBV is expected in the next generation.

In about 45% of patients with FH, the etiology remains obscure. Although the roles of HCV, GBV-C/HGV and TTV have been discussed [37–41], neither HCV nor GBV-C/HGV appeared to be a major cause of FH in our study. However, the positivity (5.6%) for the anti-HCV antibody in patients with non-A, non-B FH was much higher than that in the general population in Japan (1.3% in men, 1.5% in women) [36]. Therefore, this indicates that HCV is not a major cause of non-A, non-B FH, but is responsible for some of the cases [42]. To elucidate the extent by which HCV causes FH, the establishment of a new method to distinguish acute HCV infection from that developing in carriers is expected. Recently, it has been reported that domestic hepatitis E virus (HEV) infection is implicated in acute hepatitis and occasionally in FH even in developed countries including the USA and Japan [43,44]. Therefore, the involvement of HEV hepatitis in non-A, non-B FH is expected to be clarified by a national survey.

From the viewpoint of disease type and prognosis, non-A, non-B FH may include at least two types with unknown causes as shown in Fig. 2. One of these exhibits a course similar to HAV or HBV infection (the acute type) and has a comparatively good prognosis, and the other develops into the subacute type and has a poor prognosis. The elucidation of the cause(s) of FH of unknown etiology is urgently required not only for improving the survival rate of patients with the subacute type but also for the prevention of the development of FH with poor prognosis.

Regarding the outcome of conservative treatment of FH patients survival rate remains poor, although it tended to increase in patients with the acute type. Furthermore, long-term conservative therapies appear not only to be of limited benefit, but also to have the potential to induce fatal complications. Therefore, the prognosis for FH patients in the earlier stage needs to be highly accurate to facilitate making a decision regarding liver transplantation.

In conclusion, our results suggest an urgent need for the elimination of the transmission routes of HBV infection and identification of the virus causing FH of unknown origin to reduce the incidence of FH in Japan. To improve the prognosis of FH, the increased use of liver transplantation should be promoted in the treatment of FH with efforts to establish an accurate prediction model of prognosis.

Acknowledgments

This study was conducted and supported by the Ministry of Health and Welfare as an official project. The authors are indebted to many physicians who provided valuable clinical data.

References

[1] Shiødt FV, Atillasoy E, Shakil O, et al. Etiology and outcome for 295 patients with acute liver failure in United States. Liv Transplant Surg 1999;5:23–34.
[2] Tandon BN, Joshi YK, Tandon M. Acute liver failure. Experience with 145 patients. J Clin Gastroenterol 1986;8:664–8.
[3] Paraevangelos G, Tassopoulos N, Roumeliotou-Karayannis A, Richardson C. Etiology of fulminant viral hepatitis in Greece. Hepatology 1984;4:369–72.
[4] McNeil M, Hoy JF, Richards MJ, et al. Aetiology of fatal viral hepatitis in Melbourne. A retrospective study. Med J Aust 1984;141:637–40.
[5] Rakela J, Lange SM, Ludwig J, Baldus W. FH: Mayo clinic experience with 34 cases. Mayo Clin Proc 1985;60:289–92.
[6] Christensen E, Bremmelgaard A, Bahnsen M, Andreasen PB, Tygstrup N. Prediction of fatality in fulminant hepatic failure. Scand J Gastroenterol 1984;19:90–6.
[7] Bernuau J, Goudeau A, Poynard T, et al. Multivariate analysis of prognostic factors in FH B. Hepatology 1986;6:648–51.
[8] O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–45.
[9] Frohburg E, Stolzel E, Lecz K, Schafer J-H, Tung LC, Riechen E-O. Prognostic indicators in fulminant hepatic failure. Z Gastroenterol 1992;30:571–5.
[10] Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of King's criteria. J Hepatol 1997;26:62–8.

[11] Fujiwara K. Japanese national survey of FH in 2000. The 2001 Annual Report of Research Group of Intractable Hepatitis. Tokyo: The Ministry of Health and Welfare of Japan 2002;87–96 (in Japanese).
[12] Lee WM. Acute liver failure. Semin Liver Dis 2003;23:217–26.
[13] The Proceedings of the 12th Inuyama Symposium. Hepatitis Type A FH. Tokyo: Chugai Igaku-sha 1982 (in Japanese).
[14] Takahashi Y, Shimizu M. The study group of FH. Aetiology and prognosis of fulminant viral hepatitis in Japan: A multicenter study. J Gastroenterol Hepatol 1991;6:159–64.
[15] Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, editors. Progress in Liver Disease, vol. III. New York: Grune & Stratton; 1970. p. 282–98.
[16] Takahashi Y. Acute hepatic failure in special relation to treatment. Jpn J Med 1983;22:140–5.
[17] Caraceni P, Van Thiel DH. Acute liver failure. Lancet 1995;345:163–9.
[18] Trey C, Lipworth L, Dabidson CS. Parameters influencing survival in the first 318 patients reported to the fulminant hepatic failure surveillance study. Gastroenterology 1970;58:306.
[19] Horney JT, Galambos JT. The liver during and after fulminant hepatitis. Gastroenterology 1977;73:639–45.
[20] Kita Y, Umeshita K, Gotoh M, et al. Quality of life in adult Japanese patients undergoing liver transplants overseas. Transpl Proc 1996;28:1934–6.
[21] Humar A. Donor and recipient outcomes after adult living donor liver transplantation. Liv Transpl 2003;9(Suppl 2):S42–4.
[22] Yoshiba M, Inoue K, Sekiyama K, et al. Favorable effect of new artificial liver support on survival of patients with fulminant hepatic failure. Artif Organs 1996;11:1169–72.
[23] Sadahiro T, Hirasawa H, Oda S, et al. Usefulness of plasma exchange plus continuous hemodiafiltration to reduce adverse effects associated with plasma exchange in patients with acute liver failure. Crit Care Med 2001;29:1386–92.
[24] Kjaergard LL, Liu J, Als-Nielsen B, et al. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA 2003;289:217–22.
[25] Lemon SM, Gates NL, Simms TE, Bancroft WH. IgM antibody to hepatitis B core antigen as a diagnostic parameter of acute infection with hepatitis B virus. J Infect Dis 1981;143:803–9.
[26] Wright TL, Manish D, Combs C, et al. Hepatitis B virus and apparent fulminant non-A, non-B hepatitis. Lancet 1992;339:952–5.
[27] Fukai K, Yokosuka O, Fujiwara K, et al. Etiologic considerations of fulminant non-A, non-B viral hepatitis in Japan: analyses by nucleic acid amplification method. J Infect Dis 1989;178:325–33.
[28] Lok ASF, Liang RHS, Chiu EKW, Wong K-L, Chan T-K, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Gastroenterology 1991;100:182–8.
[29] Bang BK, Yang CW, Yoon SA, et al. Prevalence and clinical course of hepatitis B and hepatitis C liver disease in ciclosporin-treated renal allograft recipients. Nephron 1995;70:397–401.
[30] Omata F, Ide H, Ito T, Shibayama Y, Takahashi H, Ueno F. Interferon therapy for FH associated with precore region mutation in hepatitis B virus carrier. Am J Gastroenterol 1996;91:1673–5.
[31] Japanese Red Cross Non-A, non-B hepatitis Research, Group. Effect of screening for hepatitis C virus antibody and hepatitis B virus core antibody on incidence of post-transfusion hepatitis. Lancet 1991;338:1040–1.
[32] Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. New Engl Med 1996;334:1685–90.
[33] Japanese Red Cross NAT Screening Group. Nationwide nucleic acid amplification testing of hepatitis B virus, hepatitis C virus and human immunodeficiency virus type 1 for blood transfusion and follow-up study of nucleic acid amplification positive donors. Jpn J Infect Dis 2000;53:116–23.
[34] Minegishi K, Yoshikawa A, Kishimoto S, et al. Superiority of minipool nucleic acid amplification technology for hepatitis B virus over chemiluminescence immunoassay for hepatitis B surface antigen screening. Vox Sang 2003;84:287–91.
[35] Eto T, Shiraki K. National project on the prevention of mother-to-infant infection by hepatitis B virus in Japan. Acta Paedatr Jpn 1989;31:681–4.
[36] Yoshizawa H. Blood screening to prevent post-transfusion hepatitis in Japan: effective for prevention as well as revealing the epidemiology of HBV and HCV infection in healthy subjects. Int Hepatol Commun 1996;5:79–87.
[37] Muto Y, Sugihara J, Ohnishi H, Moriwaki H, Nishioka K. Anti-hepatitis C virus antibody presents in fulminant hepatic failure. Gastroenterol Jpn 1990;25:32–5.
[38] Wright TL, Hsu H, Donegan E, et al. Hepatitis virus not found in fulminant non-A, non-B hepatitis. Ann Intern Med 1991;115:111–2.
[39] Yoshiba M, Okamoto H, Mishiro S. Detection of the GBV-C hepatitis virus genome in serum from patients with FH of unknown aetiology. Lancet 1995;346:1131–2.
[40] Kuroki T, Nishiguchi S, Tanaka M, Enomoto M, Kobayashi K. Does GBV-C cause FH in Japan? Lancet 1996;347:908.
[41] Okamoto H, Nishizawa T, Kato N, et al. Molecular cloning and characterization of novel DNA virus (TTV) associated with post-transfusion hepatitis of unknown etiology. Hepatol Res 1998;10:1–16.
[42] Yoshiba M, Dehara K, Inoue K, Okamoto H, Mayumi M. Contribution of hepatitis C virus to non-A, non-B fulminant hepatitis in Japan. Hepatology 1994;19:829–35.
[43] Kwo PY, Schlauder GG, Carpenter HA, et al. Acute hepatitis E by a new isolate acquired in the United States. Mayo Clin Proc 1997;72:1133–6.
[44] Suzuki K, Aikawa T, Okamoto H. Fulminant hepatitis E in Japan. N Engl J Med 2002;347:1456.

歯学部並びに歯科衛生士学校の学生を対象に実施したB型及びC型肝炎に対しての意識調査

[1]久留米大学先端癌治療研究センター・肝癌部門，[2]北海道医療大学歯学部口腔衛生学講座，
[3]久留米大学医学部第2内科学講座
長尾由実子[1]　千葉　逸朗[2]　佐田　通夫[1][3]

(平成16年4月9日受付)
(平成16年5月11日受理)

Key words：　hepatitis C virus (HCV), hepatitis B virus (HBV), dental treatment, standard precautions

要　旨

現在，わが国では，輸血に起因するB型肝炎ウイルス（HBV）やC型肝炎ウイルス（HCV）の感染はほとんど見られなくなった．しかし，全国調査によると散発性のB型やC型急性肝炎例の発生が毎年報告され，医原性感染によるウイルス肝炎も報告されている．私共は，歯科診療時の肝炎ウイルスに対する感染予防対策についての教育や啓発が重要であると考え，某大学歯学部と歯科衛生士学校の学生全352名を対象にB型肝炎やC型肝炎に関連した知識や感染予防についての認識度についてアンケート調査を実施した．全体の35.5%の学生が，交叉感染の防御よりも術者自身の感染防御を重要視していた．さらに，ディスポーザブルの手袋や局所麻酔薬のカートリッジを再使用してもよいと考える学生の割合は，各々13.1%（46/352名），14.8%（52/352名）であった．HBVやHCVが血液だけでなく唾液などの体液からも検出されるという認識を持つ学生は65.3%に留まっており，肝炎ウイルスの知識や器具の消毒と滅菌に関する理解が低い実態が明らかになった．

国内の歯科治療における院内感染防止の標準化を目指したガイドラインの早急な作成と歯科医療に従事する学生に対する感染のリスクマネージメントを重視したカリキュラムの導入と教育が必要である．さらに，歯科医療にスタンダードプレコーションの考えを普及することが重要な課題であると思われる．

〔感染症誌　78：554～565，2004〕

序　文

B型肝炎ウイルス（HBV）やC型肝炎ウイルス（HCV）は，肝細胞癌（以下肝癌）の発生要因として最も重要であることが明らかにされている[1]．現在，わが国では肝癌撲滅をめざして2002年4月からHBs抗原とHCV抗体の測定によるウイルスキャリアの同定，精密検査と治療による肝発癌リスクの低下を目標とした肝癌撲滅のための国家的事業が推進されている．HBVやHCVの感染は，血液を介して起こることから，日本赤十字社では，1999年より全献血血液のスクリーニング検査に世界に先駆けて核酸増幅検査（NAT）を導入した．したがって現在，わが国では，輸血によってHBVやHCV感染が起きる頻度は極めて低い．一方，急性肝炎の全国調査によれば散発性のB型やC型急性肝炎例の発生は毎年報告されており[2]，平成14年度の厚生労働省「C型肝炎ウイル

別刷請求先：(〒830-0011) 福岡県久留米市旭町67
久留米大学先端癌治療研究センター・肝癌部門　長尾由実子

スの感染者に対する治療の標準化に関する臨床的研究班」の報告によると，その感染ルートの30%が医原性感染に起因している可能性があると報告されている[3]．歯科治療もその一つにあげられている．歯牙を切削する高速回転の器具は，唾液や血液を周囲にまき散らすことが多く，医療従事者自身が感染に留意するだけでなく，交叉感染が起きないように留意することも非常に重要である．しかし，平成15年1月～2月に実施された日本歯科医師会員の無作為抽出法による全国アンケート調査では，歯科治療時に患者毎に手袋を交換する歯科医師は，24.6%(87/361名)に過ぎず，午前午後の一日2回のみしか手袋を交換しない歯科医師の存在も明らかにされている[4]．そこで，歯科診療時の肝炎ウイルスに対する感染予防対策に対する啓発，教育が重要であるとの認識を持ち，某大学歯学部と大学付属歯科衛生士学校の学生を対象に，HCV並びにHBVとその感染予防対策に対する認識度や現状を明らかにするために，調査を行った．

対象と方法

某大学歯学部の学生253名（3年生；93名，4年生；76名，6年生；84名）と大学付属歯科衛生士学校の学生99名（1年生；58名，2年生；41名）の計352名を対象に，HCV並びにHBVに対する知識や認識度及びその感染予防対策に対する認識度についてアンケート調査を行った．アンケートは，「はい」か「いいえ」による無記名による回答方式で，2003年11月13日（歯学部学生3年生），同年11月28日(歯学部学生4年生と6年生，歯科衛生士学校の学生1年生)，2004年1月8日(歯科衛生士学校の学生2年生)に実施した．下記がアンケートの設問内容である．

1. C型肝炎ウイルスやB型肝炎ウイルスは，血液中だけでなく体液（たとえば唾液）からも検出されると思う．

2. 歯科治療中に手袋を着用する目的は，術者の感染防御よりも交叉感染の防止の方が重要であると思う．

3. 局所麻酔用のカートリッジ（通常1.8ml/本）を半分しか使用しなかった場合，次の患者には，通常新しい針に変えて残りを使用する．

4. 感染症ではない患者にディスポーザブルの手袋を使用するとき，血液が付着しなかったり，穴があいていなければ，手袋を洗い再使用した方がコスト削減に有効であると思う．

5. 次の患者を診察する時に，新しい手袋をして診察するなら，とくに毎回の手洗いはしなくてもよいと思う．

6. C型肝炎の患者を診察した後では，グルタールアルデヒドで手洗いをすると水平感染を防ぐことができる．

7. クロルヘキシジンは，ウイルスに対しては効果がない．

8. C型肝炎やB型肝炎の患者に使用した器具のうち，プラスティック製やゴム製のもので，オートクレーブにかけることのできないものは，消毒用エタノール（100%）を使用すればよいと思う．

9. 患者が感染症（肝炎ウイルスキャリアやAIDS患者など)でなければ，治療用のピンセットで直接綿球をつかみ，薬液ビンにつける行為はとくに問題にはならないと思う．

10. 自分の血液にC型肝炎ウイルスの抗体が検出されれば(HCV抗体陽性)，C型肝炎に罹患する心配はないと思う．

11. インターフェロン療法によって，C型肝炎ウイルスの持続感染が駆除できた患者の歯科診療では，「感染症」として取り扱う必要性はない．

12. スタンダードプレコーションという言葉を知っていますか？

成　績

HCVやHBVが血液だけでなく唾液などの体液からも検出されるという認識を持つ学生は，全体の65.3%(230/352名)で，6年生でも75%(63/84名）に留まっていた（Fig. 1)．全体の64.5%(227/352名）の学生が，歯科治療における手袋着用の目的を術者自身の感染防御よりも交叉感染の防御として重要視していた．つまり35.5%の学生は自己の感染防衛を重要視していることになる(Fig. 2)．歯科治療で使用する麻酔注射薬はディスポーザブルのカートリッジに入っているが，Fig. 3に示すように6年生でも6%(5/84名)が廃棄せ

平成16年7月20日

Fig. 1 Question 1 : "You think that HCV and HBV are detected from body fluid such as saliva as well as blood."

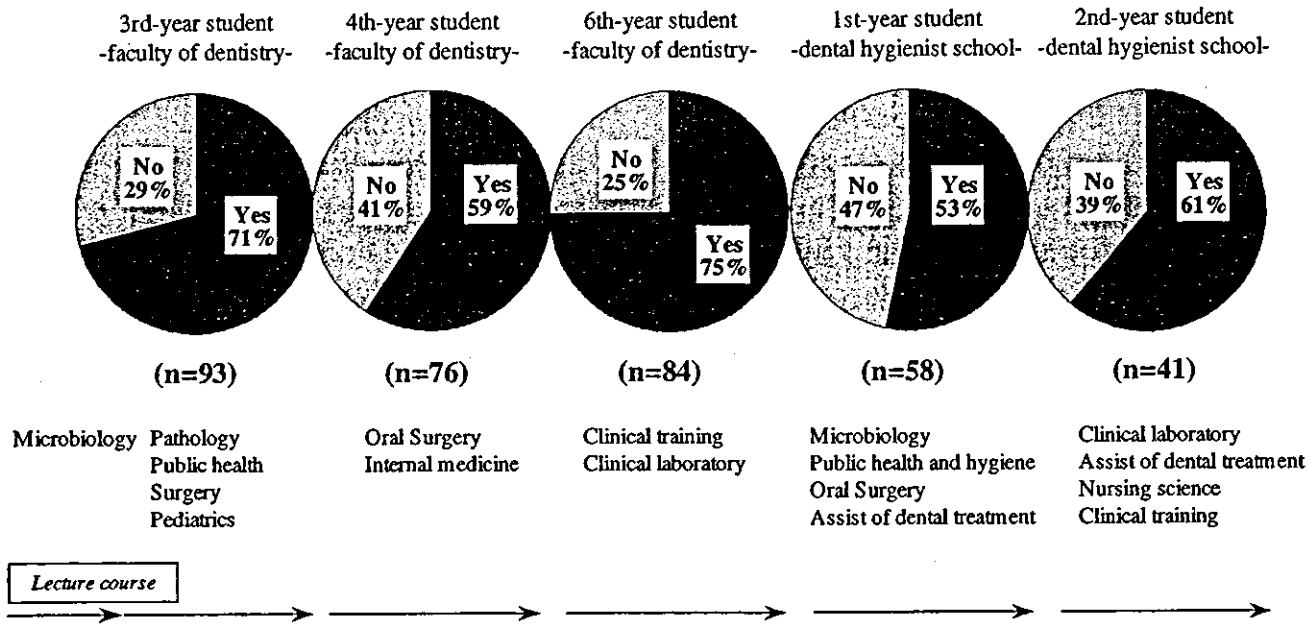
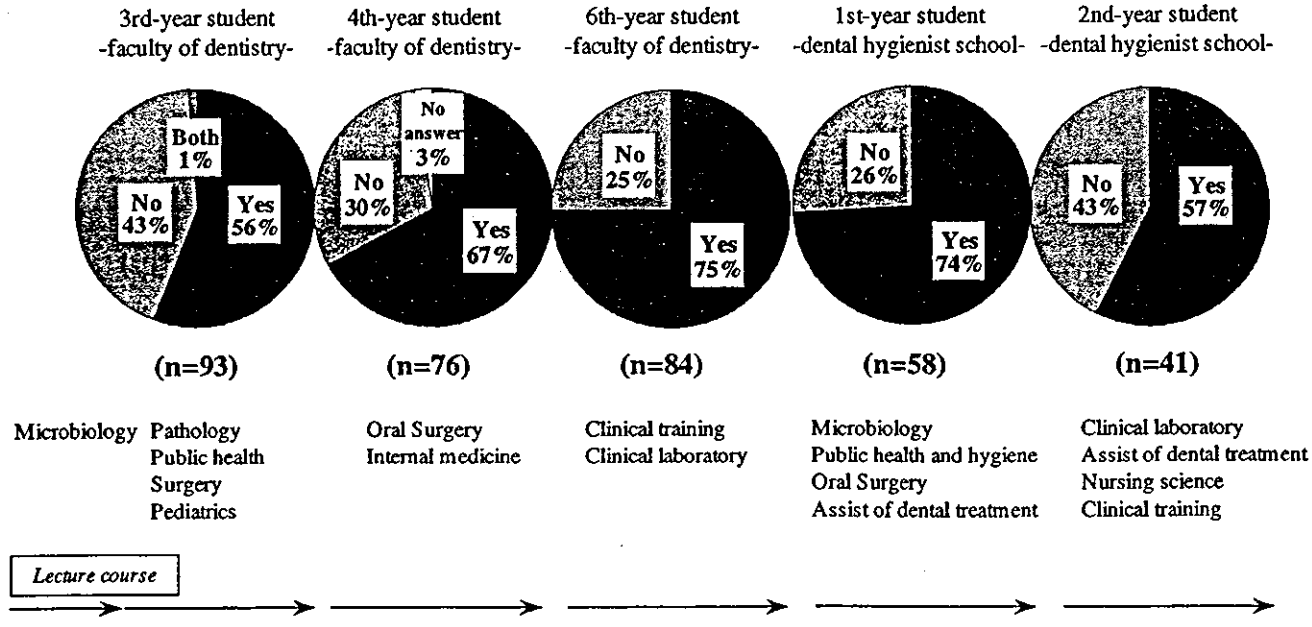


Fig. 2 Question 2 : "You think that prevention of cross transmission is more important than defense yourself against infection in terms of purpose to wear gloves during dental treatment."



ずに再使用すると答えていた．また，ディスポーザブルの手袋を再使用するかという設問は，学年が進むにつれて「はい」と答えた学生の割合が高くなっていた(Fig. 4)．手袋をはずした際に毎回の手洗いを励行する意識は強いが (Fig. 5)，HCV感染者の診察後にはグルタールアルデヒドで手洗いをすると答えた学生が過半数を占め (54.5%, 192/352 名, Fig. 6)，クロルヘキシジンがウイルス

Fig. 3 Question 3 : "You think to permit recycle of a disposer cartridge of a local anesthesia if even a new needle is changed"

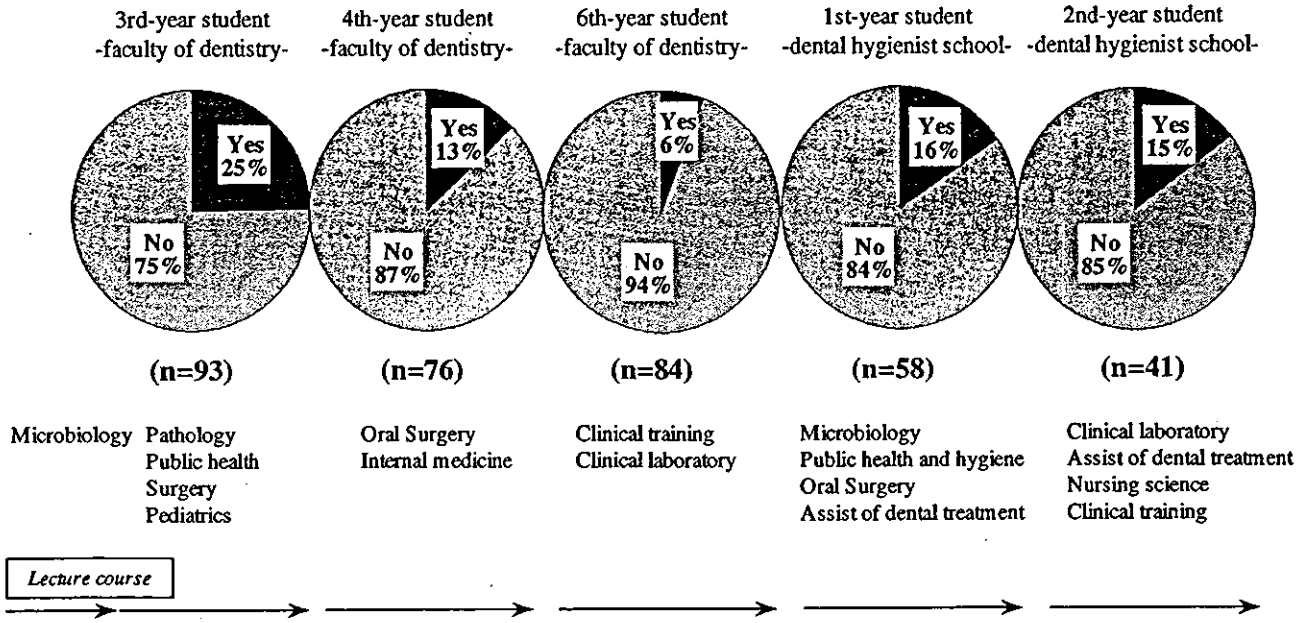
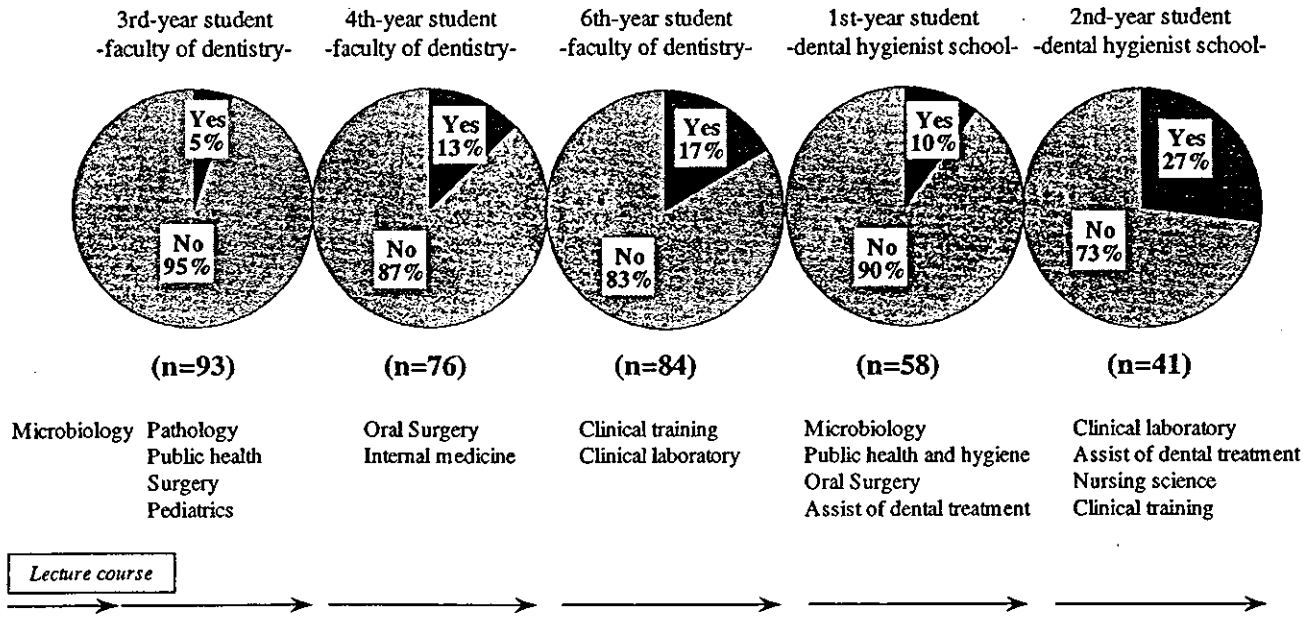


Fig. 4 Question 4 : "You think that recycle of disposer gloves is useful as cost reduction if you don't attach blood to gloves or you don't puncture a hole in gloves."



に効果を示すと答えた学生も40.3%を占めた(142/352名, Fig. 7). HCVやHBVに汚染した器具のうちオートクレーブによる高圧滅菌が不可能なプラスティック製の器具について, 22.7% (80/352名) の学生がエタノールを使用すればよいと考えていることも明らかになった(Fig. 8). 実際に器具の消毒や滅菌操作を行う歯科衛生士の学生では, 17.2% (17/99名) の学生がエタノールを使用すればよいと考えていた. また10.2% (36/352名) の学生は, 感染症ではない患者であれば, 治

平成16年7月20日

Fig. 5 Question 5 : "You think that there is no need to wash hands for examination of the next patient if you pull on disposer gloves."

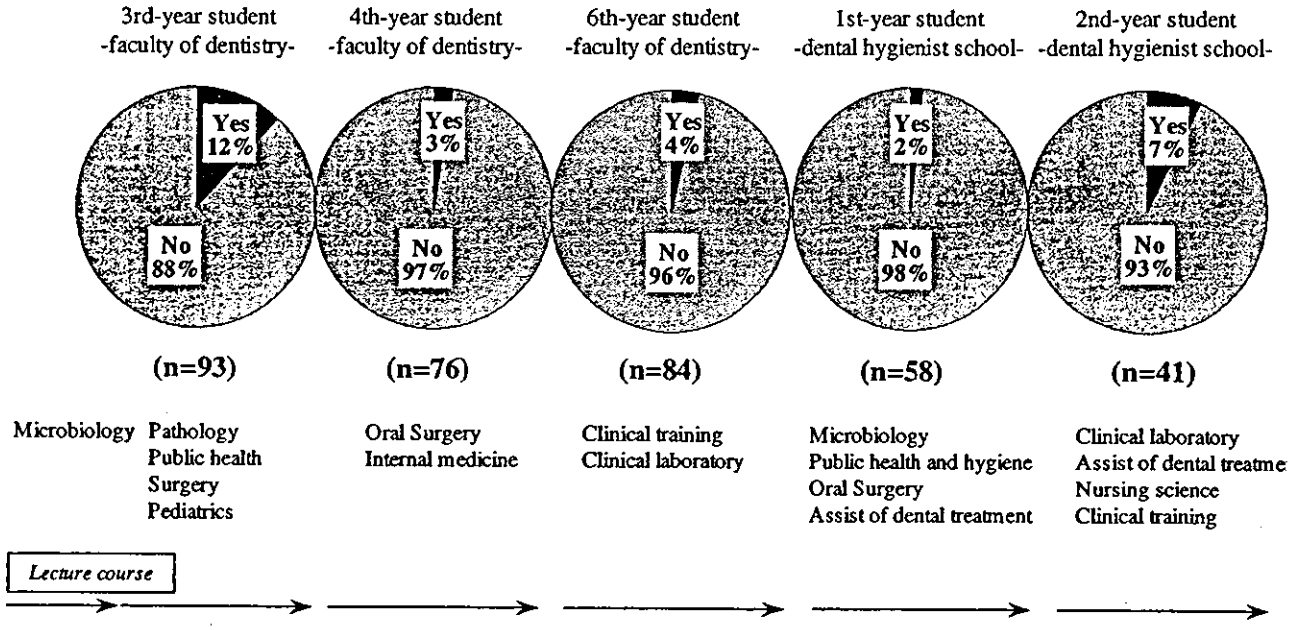
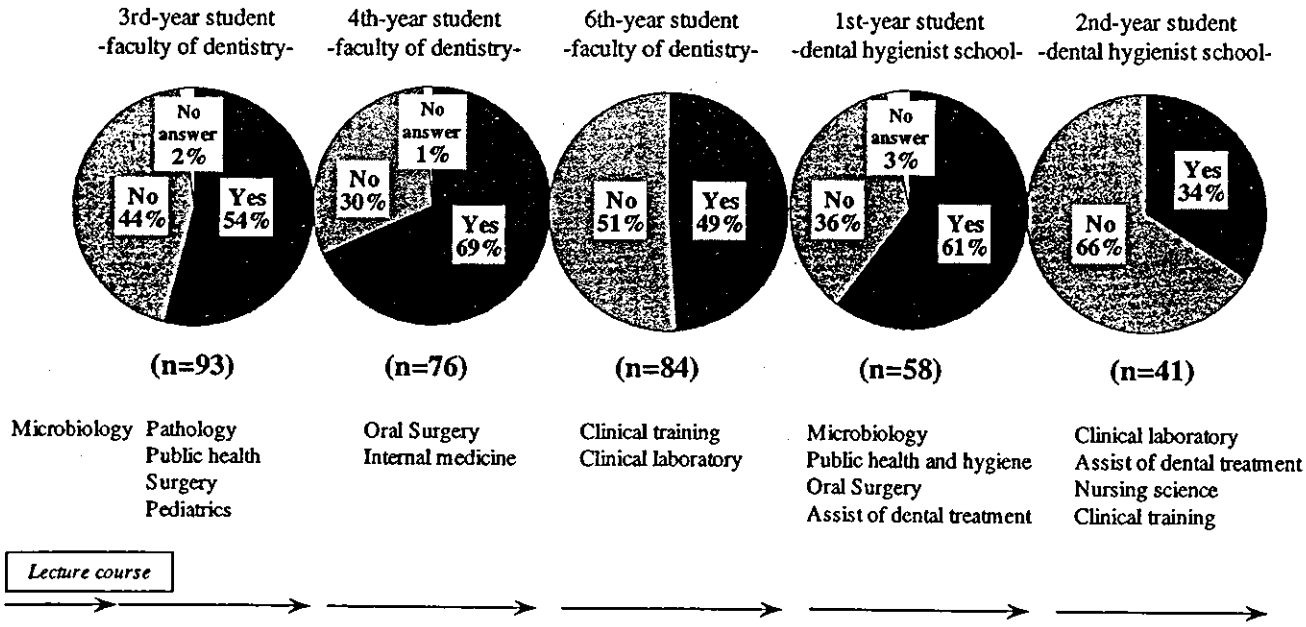


Fig. 6 Question 6 : "You think that you can prevent cross transmission by hand-washing using glutaraldehyde after you examined the patient of hepatitis C."



療用の器具で薬液ビンから薬液を取り出す行為は問題ないと考えていた (Fig. 9). また, Fig. 10 に示すようにHCV抗体を中和抗体として捉える学生が全体の29.5% (104/352名) にも及び, HCV抗体陽性患者を感染症ではないと考えている可能性も明らかになった. インターフェロン療法によってHCVを駆除することのできた所謂ウイルス持続陰性化 (Sustained Viral Response : SVR) 症例でも, 大半の学生が感染症として取り扱うと答えており (82.9%, 299/352名, Fig. 11),

Fig. 7 Question 7 : "You think that chlorhexidine is ineffective in killing the virus."

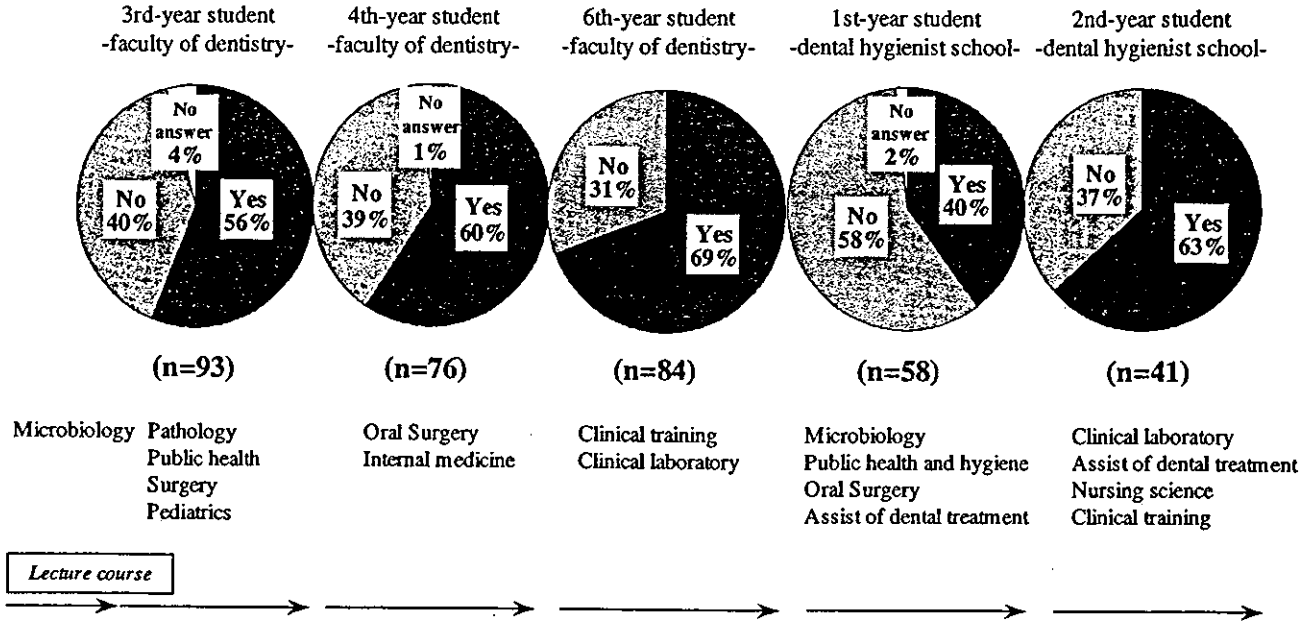
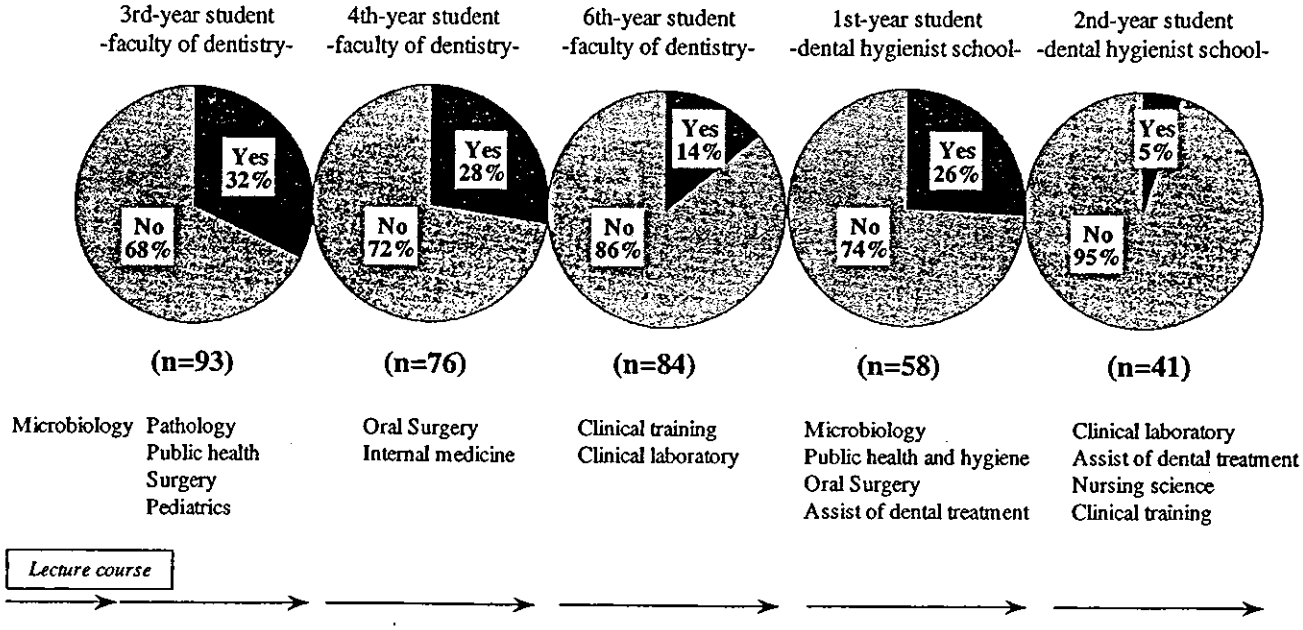


Fig. 8 Question 8 : "You think that you use 100% ethanol as effective sterilization of plastic or rubber instruments which can not sterilize by autoclave among instruments contaminated by HCV or HBV."



HCV RNA が持続陰性化しても歯科治療では感染症として捉えられている可能性が高い．スタンダードプレコーションという言葉を，6年生以外はほとんど聞いたことがないという実態も明らかになった（Fig. 12）．

考　察

わが国の肝癌による死亡者数は増加の一途をたどり，この傾向は2015年まで続くと考えられている[5]．肝癌の原因の約80%が，HCV に起因するものであり，HCV による肝癌患者の増加がわが国に

平成16年7月20日

Fig. 9 Question 9 : "You think that there is nothing wrong with catching directly pledget by used pincette, and with getting used pincette into medicine bottle if the patient don't have infectious disease"

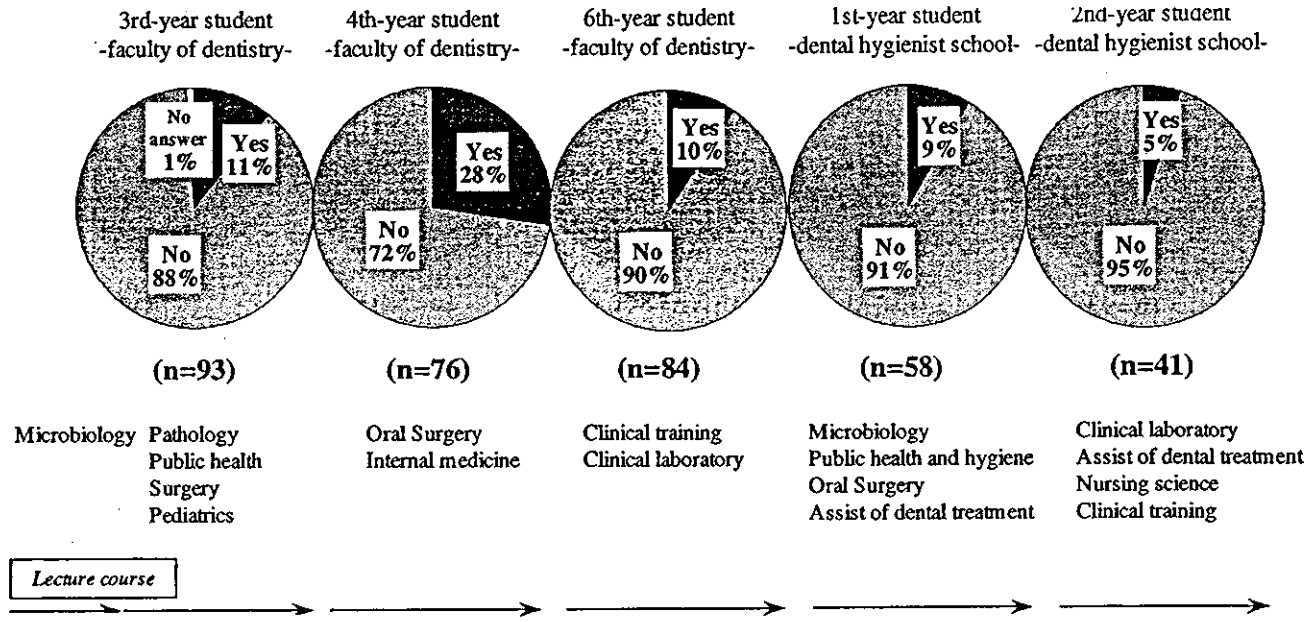
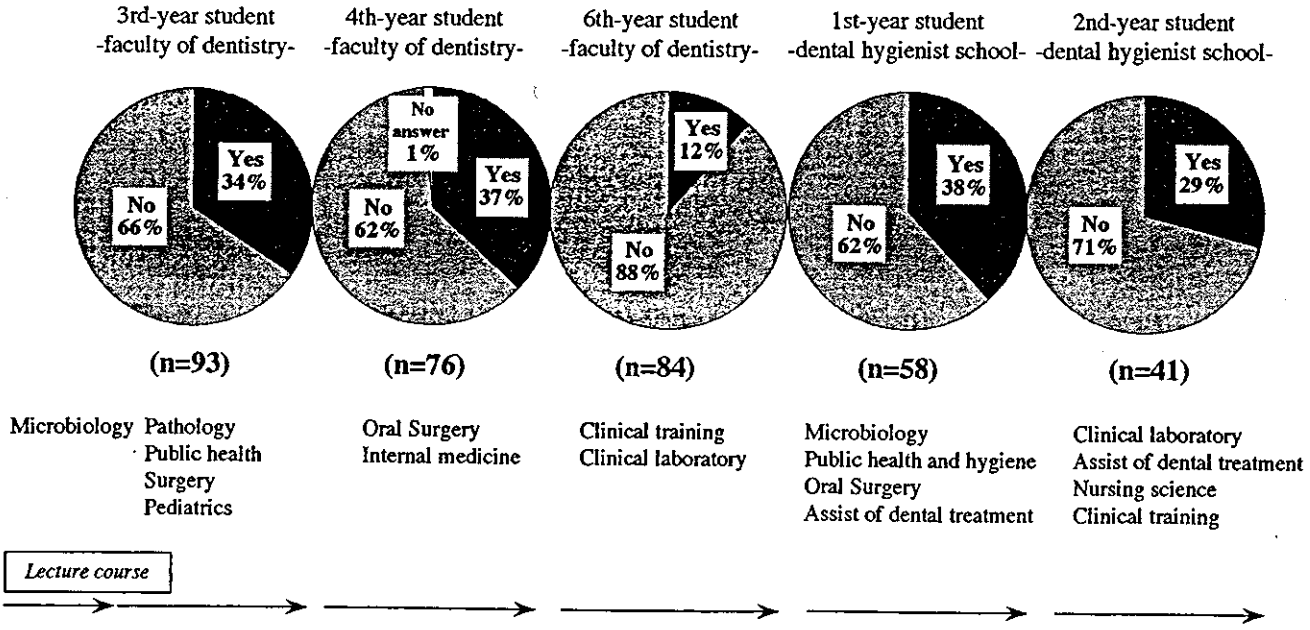


Fig. 10 Question 10 : "You think that you won't need to worry about contraction of hepatitis C if an anti-HCV antibody is detected within blood (in other words anti-HCV positive)."



おける肝癌死亡者数の増加の原因である．現在，わが国では年間34,000人が肝癌で死亡しており，日本人の死亡原因の第三位を占めている．平成14年度から老人保健法に基づいて40歳から70歳までの5歳刻みの節目の年齢者や過去に肝機能異常を指摘されたことのある者は，節目あるいは節目外検診としてHCV並びにHBVのキャリアの発見と肝発癌抑制を見据えた効率の高い検診を受け

Fig. 11 Question 11 : "You think that you don't need to treat the patient whom exterminated HCV RNA in serum by interferon therapy as high-risk infectious patient in dental treatment"

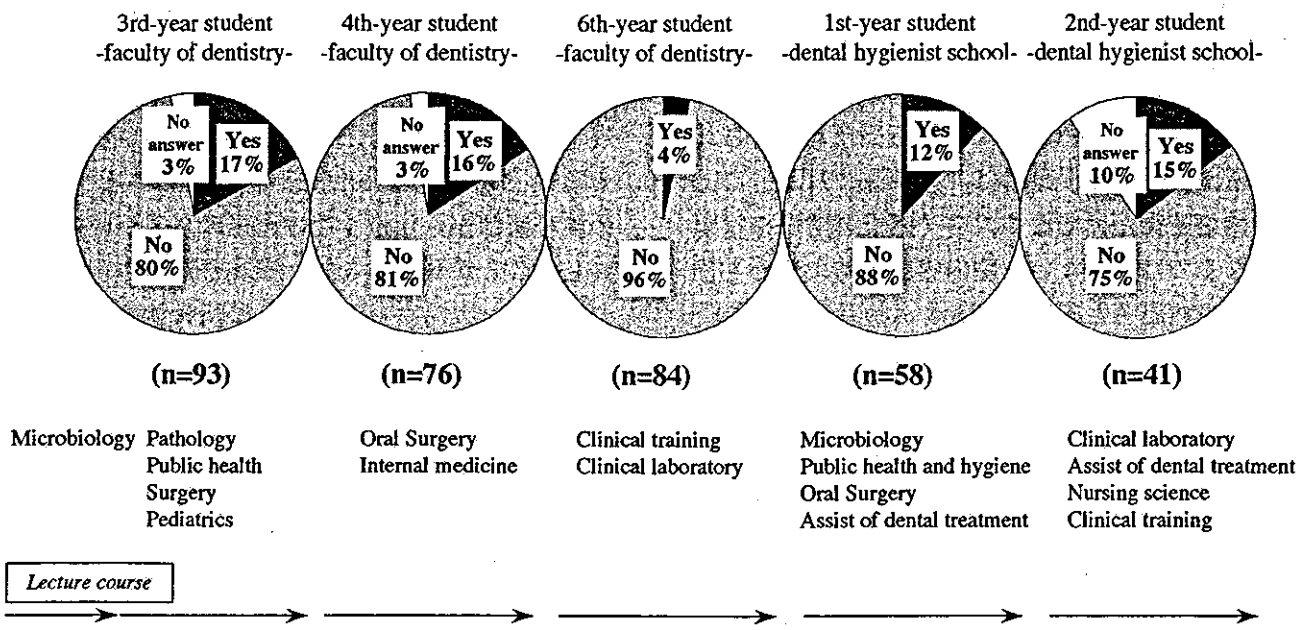
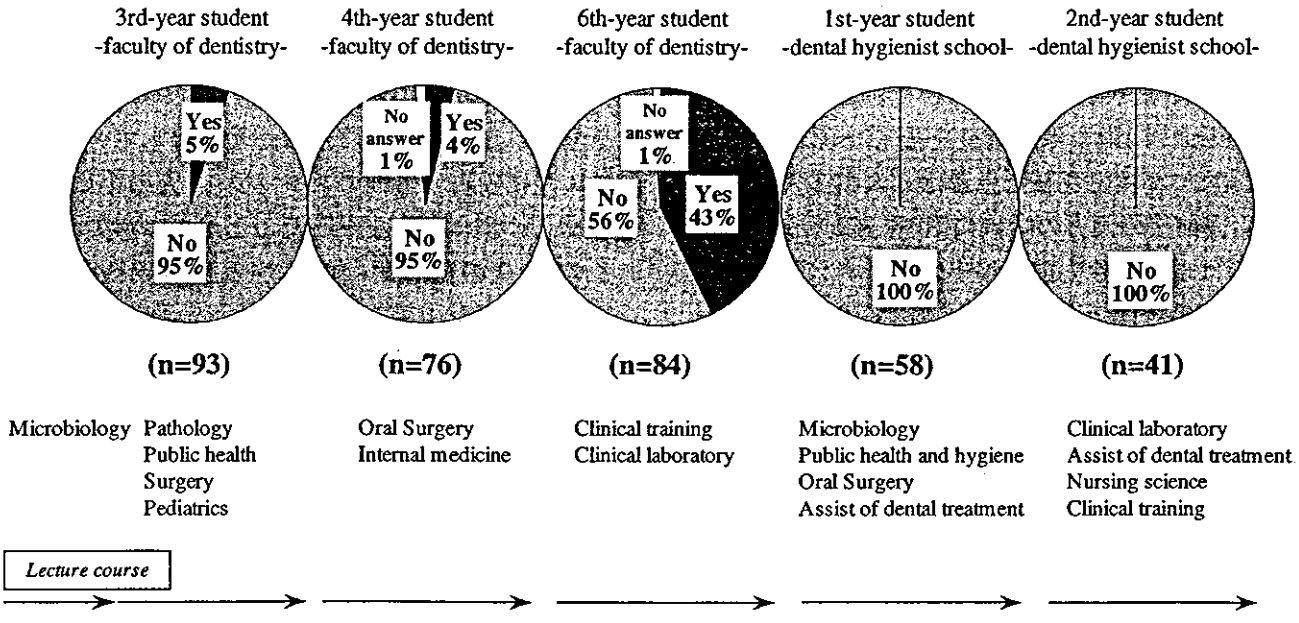


Fig. 12 Question 12 : "Do you know the word of standard precautions?"



られるようになった．現在，肝癌撲滅の事業は国家レベルで推し進められている．日本は，世界的にみてもこのHCV感染が高い国である．そして，その感染率は東日本よりも西日本に高く，したがって西日本は肝癌死亡率も高い．このような社会的背景を，医療に携わる者は周知する必要がある．

平成14年度の厚生労働省の肝炎研究班は，全国調査に基づくC型急性肝炎の感染経路および治療に関する研究報告の中で，その感染ルートとして医原性感染の可能性が30% (33/109名) を占めていることを報告した[3]．この33名の中で感染

平成16年7月20日

ルートを詳細に解明できた症例は存在しないが，感染ルートの内訳として外科手術34%（11/33名），輸血15%（5/33名），静脈注射12%（4/33名），観血手技9%(3/33名)，内視鏡検査9%(3/33名)，歯科治療9%（3/33名），透析3%（1/33名），詳細不明9%(3/33名)であったと報告されている．我々医療従事者は，感染源に対して自己への感染防御だけでなく，交叉感染の防御を重要視しなくてはならない．院内感染の防止策の主目標は，当然患者と患者，患者と医療従事者間の交叉感染防止に力が注がれなければならない．

歯科治療では，鋭利な器具が使用されるだけでなく，歯牙切削時に容易に歯肉から出血するため，血液を扱うことは多い[6]．感染源となる血液が混じった唾液を，高速回転の器具や電気エンジンによって診療室内に飛沫させており，細心の注意が必要である．HBVやHCVが唾液からも検出されるという論文は数多く存在する[7][8]．したがって，歯科医療従事者は，歯科治療を通じて肝炎ウイルスに感染するリスクが高いが，その一方で，交叉感染防止に努める義務がある．我々は，HCVキャリアの歯石除去前後の唾液に含まれるHCV RNAを検出した[9]．歯石除去前後を通じて唾液中からHCV RNAが検出された患者は6人中3人であった．除去前後の両方の唾液にHCV RNAが検出された者は1人，除去前に検出された者は1人，除去後の検出者は1人であった．HCVキャリアの歯科治療では，HCV RNAが歯肉溝滲出液，印象採得時の印象材，診療台の作業台，エアータービンのハンドピース，ホルダー，吸引嘴管，鉗子，デンタルミラー，切削バーからも検出されることが報告されているだけでなく[4][10][11]，HCV感染者に使用された歯科治療器具の表面に付着した器具からHCV RNAが数日間検出され続けたという報告もある[12]．ディスポーザブルの局所麻酔用のカートリッジの残液を再使用することは，逆流させた吸引血液によってHBVやHCVを感染拡大させる極めて危険性の高い行為である．このように卒業を控えた歯学部の6年生や歯科衛生士学校の2年生でさえも，滅菌に対する知識が不足している実態が明らかとなり，早急に汚染した器具の消毒や滅菌の正しい知識を身につけさせる必要がある．肝疾患の病態や感染予防対策に関する講義は，Fig. 1～Fig. 12に示すように講義や実習では行われているが，その理解は完全なものではない．

歯科医師が患者にHCVを感染させた事例は報告されていないが，HBVを感染させた事例は存在する[13]．1977年のRimlandらの報告では[13]，1人の歯科医師から治療を受けた患者2名が肝炎を発症したことが発端となり，調査が進められた．この地方で2カ月から6カ月前に歯科治療を受けた後に肝炎を発症した71名を調査したところ，55名がある特定の口腔外科医から治療を受けていることが判明した．46歳の口腔外科医は，13年にわたり口腔外科を標榜し，治療にあたっていたが，肝炎の既往はなく，後にHBs抗原陽性，HBe抗原陽性であることがわかった．彼は，週250人～300人の患者を診察し，その95%が抜歯であった．彼は指先によく傷をつくることがあったが，手袋をせずに治療にあたっていた．その後，この歯科医師はHBs抗原が陰性になるまで歯科治療を休診し，手袋を着用して治療を再開したところ，1年1カ月の間の約8,000人の患者診察において肝炎を発症した患者はいなかったと報告している．歯科医院に勤務する他のスタッフ13人の中にHBVキャリアが存在しなかったことから，感染経路はこの46歳の歯科医師の手からHBVが患者の抜歯創に侵入したと考えられ，hemo-oral transmissionと推定されている．

わが国の歯科診療では，手袋の着用は義務づけられていないし，たとえ着用していても患者毎に交換する歯科医師は僅か24.6%だと申告されているため[4]，歯科治療を通じてHBVやHCVを交叉感染させる潜在的可能性は高いのではないかと推察される．現在，わが国で手袋を着用する歯科医師の多くは，「破損したら交換する」か「1日2回の交換（午前1回午後1回）」であり（46.2%，167/361名），診察時にマスクさえ着用しない歯科医師は5.8%（21/361名）とされている[4]．1982年チンパンジーの両眼にHBVを滴下させ，9週間後にHBV感染が成立した実験結果が報告された[14]．Bondらは，この論文内で歯科医師のような感染

のハイリスク者は眼をガードする必要があるとよびかけている．したがって，歯科診療時には手袋，マスク，アイガードの使用は必須である．わが国では，篠崎らが主に肝炎やAIDSに関する歯科領域での感染防止とその対策について著書にまとめているが，日本の歯科診療のガイドラインとして普及しているわけではない[15]．米国疾病管理予防センター（CDC，Centers for Disease Control and Prevention）の歯科診療のガイドラインでは，雇用者は従業員にHBVワクチンを打つことを義務づけている．1987年のCDCの医療従事者の感染防止ガイドラインの中では，感染の有無が明らかであるか否かに係わらず，いかなる患者でも血液や体液は感染症の可能性があるということを前提として取り扱いに注意を払うというユニバーサルプレコーションという考えが盛り込まれた[16]．HBVやHCVキャリアの多くは，無症状であり，自分自身がキャリアであることを知らない患者も多い．また感染者かどうかは，患者の自己申告によるため，歯科診療前に全ての患者について感染の有無を把握することは不可能である．したがってユニバーサルプレコーションもしくはスタンダードプレコーションという概念で治療を進めることは大切である[17]．

歯科医療従事者とくに歯科医師の肝炎の罹患率は，どうだろうか？　わが国では，篠崎らが1978年から1982年までに歯科一般開業医998名の採血を行い，HBs抗原陽性率は3.7%（37/998名），HBs抗体陽性率は42.1%（420/998名）であったと述べている[18]．この際，九州よりも北海道の歯科医師の方が，HBs抗体陽性率が有意に高いことも述べている（北海道；47.4%，中国・四国；38.2%，九州36.7%）．その後，篠崎らは1986年～1994年までの間に歯科医師から採取された凍結血清を用いてHCV感染率を分析し，その抗体陽性率が2.6%（10/382名）であったと報告している[19]．しかし当時採取された歯科医師の平均年齢の記載がないため，詳細は不明である．海外での報告では，1991年にKleinらはニューヨークの歯科医師のHCV感染率は（1.75%，8/456名），コントロールよりも（0.14%，1/723名）高く，特に口腔外科医はHCV感染率が高いと報告した（9.3%，4/43名）[20]．このように歯科医師の中でもその専門領域の違いにより，罹患率が異なることを明らかにしている．血液に曝露されやすい職種程肝炎ウイルスの感染を受けやすい．またわが国では東日本よりも西日本にHCV感染率が高いため，この地域で歯科医療に従事する者は自身の健康管理だけでなく交叉感染のリスクに一層の注意を促さなければならない．

2001年8月に日本歯科医師会は，「一般歯科診療　C型肝炎予防対策Q&A」という感染防止マニュアルを作成し，全国の会員約65,000人に配布した．それによると，汚染された器具のうち，オートクレーブにかけることのできない器具に付着したHCVを死滅させる薬液として，次亜塩素酸ナトリウム，グルタールアルデヒド，アルコールの3種を推奨して紹介しているが，消毒用アルコールの有効性についてはその効果が確かめられていないため，HBVと同様に有効でないという前提に立って対処すべきである．したがって，このマニュアルは早急に訂正すべきである．またこの度の歯学部のアンケートや2003年に実施された全国歯科医師のアンケートを通じて，消毒や滅菌に対する知識や感染予防対策が，実際の臨床では実践されていない可能性が非常に高いことも判明した．歯科治療行為がHBVやHCVの感染ルートにならないように歯科医師への教育と啓発普及活動が必要であると共に，学生教育に感染予防についての徹底した教育を導入する必要があると考えられた．さらに，雇用者となる歯科医師は，自己の健康管理だけでなく従業員の健康管理も把握し，適切な注意と指導も必要である．また誤って針刺し事故を起こした場合の事故対応に関してもすぐに行えるだけの知識と能力が必要とされる．現時点の歯科の保険診療内では，厳重な感染対策を盛り込むことは，経済的にも時間的にも困難と思われるが，国内の歯科治療における院内感染防止の標準化を目指したガイドラインを早急に作成すべきである．また，各県市町村の歯科医師会が，院内感染予防対策の充実を図ると同時に，各歯科医療機関が院内感染予防対策に対して認識を深めるこ

平成16年7月20日

とが不可欠である．HCVの高感染地区である佐賀県や福岡県では，県としての歯科診療における院内感染マニュアルは存在しない．

本論文中の対象者には，アンケート実施後にその集計結果だけでなくHCV・HBVと正しい消毒・滅菌法について解説し，各質問に対して各々解答した．歯学部の学生に対しても，感染に対するリスクマネージメントの重要性を教育する統一化されたカリキュラムを作成し，徹底した教育をする必要がある．現行の歯科医師の卒後臨床研修では，「歯科医師は，免許取得後も1年以上，臨床研修を行うよう努めるものとする」という努力義務が定められているが，必修ではない．歯科医師の臨床研修の義務化は2006年（H18）4月からの施行予定である．開業した歯科医師は，感染の知識を得る場が少ない．したがって，学生と歯科医師を対象に生涯教育を目指したinfection controlの教育が最も重要な課題であると思われる．

文　献

1) Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, *et al.*：A multivariate analysis of risk factors for hepatocellular carcinogenesis：a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993；18：47—53.
2) 矢野右人：散発性急性肝炎におけるHEVの関与．新興・再興感染症研究事業　非A非B型肝炎の臨床的総合研究．平成12年度総括・分担研究報告書　2001；p. 106—8.
3) 佐田通夫：全国調査に基づくC型急性肝炎の感染経路および治療に関する知見．肝炎等克服緊急対策研究事業（肝炎分野）「C型肝炎ウイルスの感染者に対する治療の標準化に関する臨床的研究」　平成14年度総括・分担報告書　2002；p. 24—7.
4) 古屋英毅：C型肝炎疑い症例の歯科診療実態調査．肝炎等克服緊急対策研究事業（肝炎分野）「歯科診療におけるC型肝炎の感染リスク低減に関する研究」平成14年度総括・分担報告書　2002；p. 6—11.
5) Yoshizawa H：Hepatocellular carcinoma associated with hepatitis C virus infection in Japan：projection to other countries in the foreseeable future. Oncology 2002；62 Suppl 1：8—17.
6) Siew C, Gruninger SE, Miaw CL, Neidle EA：Percutaneous injuries in practicing dentists：a prospective study using a 20-day diary. J Am Dent Assoc 1995；126：1227—34.
7) Davison F, Alexander GJ, Trowbridge R, Fagan EA, Williams R：Detection of hepatitis B virus DNA in spermatozoa, urine, saliva and leucocytes, of chronic HBsAg carriers. A lack of relationship with serum markers of replication. J Hepatol 1987；4：37—44.
8) Komiyama K, Moro I, Mastuda Y, Morshed SA, Nishioka M, Hayashi N, *et al.*：HCV in saliva of chronic hepatitis patients having dental treatment. Lancet 1991；338：572—3.
9) Nagao Y, Seki N, Tamatsukuri S, Sata M：Detection of hepatitis C virus in saliva before and after scaling of dental calculus. Kansenshogaku Zasshi 2000；74：961—5.
10) Piazza M, Borgia G, Picciotto L, Nappa S, Cicciarello S, Orlando R：Detection of hepatitis C virus-RNA by polymerase chain reaction in dental surgeries. J Med Virol 1995；45：40—2.
11) Maticic M, Poljak M, Kramar B, Seme K, Brinovec V, Meglic-Volkar J, *et al.*：Detection of hepatitis C virus RNA from gingival crevicular fluid and its relation to virus presence in saliva. J Periodontol 2001；72：11—6.
12) Fong TL, Charboneau F, Valinluck B, Govindarajan S：The stability of serum hepatitis C viral RNA in various handling and storage conditions. Arch Pathol Lab Med 1993；117：150—1.
13) Rimland D, Parkin WE, Miller GB Jr, Schrack WD：Hepatitis B outbreak traced to an oral surgeon. Hepatitis B outbreak traced to an oral surgeon. N Engl J Med 1977；296：953—8.
14) Bond WW, Peterson NJ, Favero MS, Ebert JW, Maynard JE：Transmission of type B viral hepatitis via eye inoculation of a chimpanzee. J Clin Microbiol 1982；15：533—4.
15) 篠崎文彦：肝炎とAIDS—歯科診療での感染防止とその対策—．砦林，東京，1987；p. 1—138.
16) Update：universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep 1988；24；37：377—82, 387—8.
17) Kohn WG, Collins AS, Cleveland JL, Harte JA, Eklund KJ, Malvitz DM：Centers for Disease Control and Prevention（CDC）：Guidelines for infection control in dental health-care settings—2003. MMWR Recomm Rep 2003；19；52（RR-17）：1—61.
18) 篠崎文彦，早津良和，岩井正行，熊谷茂宏，小浜源郁：わが国における歯科医師のB型肝炎ウイ

ルス感染に関する疫学的調査．日口外誌 1983；29：1865—71.
19) 篠崎文彦，早津良和，福田てる代，末次正康，水垣雄三：わが国における歯科医師のC型肝炎ウイルス感染に関する疫学的調査．口科誌 1995；44：438—41.
20) Klein RS, Freeman K, Taylor PE, Stevens CE：Occupational risk for hepatitis C virus infection among New York City dentists. Lancet 1991；338：1539—42.

Survey of Hepatitis B and C in Students of Faculty of Dentistry and Dental Hygienist School

Yumiko NAGAO[1], Itsuo CHIBA[2] & Michio SATA[1)3)]
[1)]Research Center for Innovative Cancer Therapy, Kurume University School of Medicine
[2)]Department of Preventive and Community Dentistry,
Health Sciences University of Hokkaido School of Dentistry
[3)]Second Department of Medicine, Kurume University School of Medicine

At present, in Japan, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection by blood transfusion rarely happens. However, according to the national survey, outbreak of sporadic acute hepatitis B and C is reported every year and viral hepatitis induced by iatrogenic infection is also reported. We think that education and enlightenmen for measures of infection control for hepatitis virus in dentisal medical care are important. Therefore, we carried out a questionnaire survey about measures of an infection control including hepatitis B and C for 352 students of a certain faculty of dentistry and a dental hygienist school. 35.5% of the total students thought the defense of oneself against infection was more important than defense of cross infection. Furthermore, the prevalence of the student who thought to permit recycle of a disposer glove and a disposer cartridge of a local anesthesia was 13.1% (46/352), 14.8% (52/352), respectively. The prevalence of students who recognized that HCV and HBV were detected from not only blood but also body fluid such as saliva remained in 65.3%. Consequently, the reality that knowledge of hepatitis virus and understanding about sterilization and disinfection of instruments were low became clear.

In conclusion, immediate making of the guideline that aimed at standardization of prevention of hospital infection in domestic dental treatment and education to introduce the curriculum with a high regard for risk management of infection for students of dentistry will be required. In addition, it is an important problem to spread thoughts of standard precautions for dentistry.

平成16年7月20日

Lamivudine Therapy of Hepatitis B in Japan

Michio Sata

Second Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan

Introduction

HBV carrier rate is now 0.67% in Japanese population. The most prevalent HBV genotype is genotype C (85%) in patients with chronic HBV carriers in Japan. Hepatitis activity is more severe and response to anti-viral therapy is poor in genotype C compared with genotype B. There are questions whether we should use lamivudine for long-term.

There are two ways regarding the methods of administration of lamivudine in the treatment of chronic hepatitis B. One is to administer continuously for a long time over several years, and the other is to complete administration in 6 months to 1 year. The effectiveness of long-term administration is demonstrated by the increases in seroconversion rate from HBeAg to HBe antibody (HBeSC) and in the normalization rate of ALT value, with the prolongation of duration of administration. On the other hand, the occurrence of YMDD mutation increases with time [1,2].

Therefore, we decided to analyse patients who received lamivudine at least for one year.

Results

The HBeSC Rate and Negativization of Serum HBV DNA

In our 57 patients who received lamivudine continuously for the one year or more, the he HBeSC rate and negativization of serum HBV DNA ceased to increase after 18 months for the former and 9 months for the latter (Fig. 1 & 2). This is probable related to the appearance of YMDD mutant viruses. Then, we explored the conditions associated with post treatment flare [3], and appearance of YMDD mutant viruses [4-6].

Patients with eAg Positive Chronic Hepatitis B

Fig.3 shows results of analyses of 41 patients with eAg positive chronic hepatitis B at the beginning of lamivudine treatment. In all of the cases analyzed, HBV

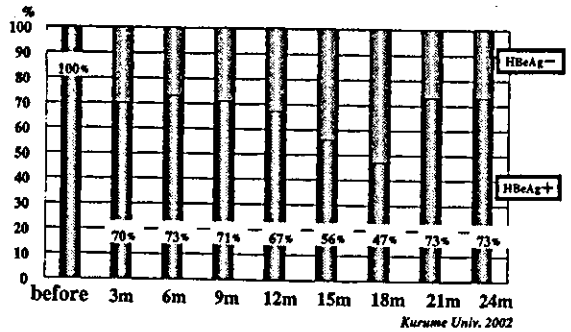


Fig. 1. Changes in HBeAg positive rate by a lamivudine. This figure shows that positive rate of HBeAg in the chronic hepatitis B patients loss by lamivudine treatment. Positive rate of HBeAg became 67% in 12 months after a lamivudine treatment and decreased to 47% in 18 months after a lamivudine treatment.

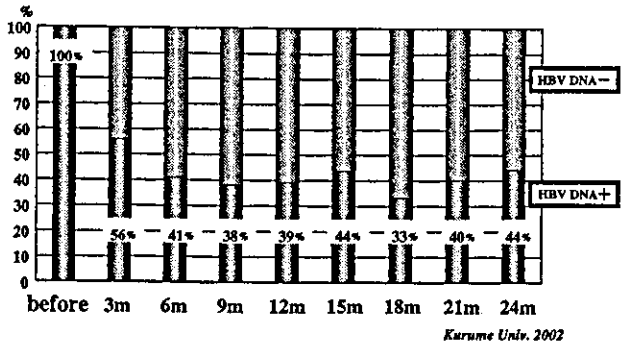


Fig. 2. Changes in HBV DNA positive rate: patients positive for HBeAg by a lamivudine treatment. This figure shows that serum HBV DNA of the chronic hepatitis B patients with HBeAg positive loss by lamivudine treatment. Positive rate of HBV DNA became 39% in 12 months after a lamivudine treatment and decreased to 33% in 18 months after a lamivudine treatment.

genotype was C. Negativization of HBeAg was seen in 13 (32%) and HBeSC occurred in 11 cases. In the remaining 28 cases who did not show negative turn of eAg, 10 became negative for HBV DNA (Fig. 3).

Of 41 patients treated with lamivudine, 16 patients discontinued the treatment. Post treatment flare occurred in 11 out of the above 16 (69%) patients (Fig. 3) [3]. While ALT values were elevated to 500 IU or above in some cases during post treatment flare, no jaundice or hepatic dysfunction developed. On the other hand, post treatment flare occurred in 5 out of 9 (56%) patients of HBe antibody positive at the beginning of treatment (date not shown).

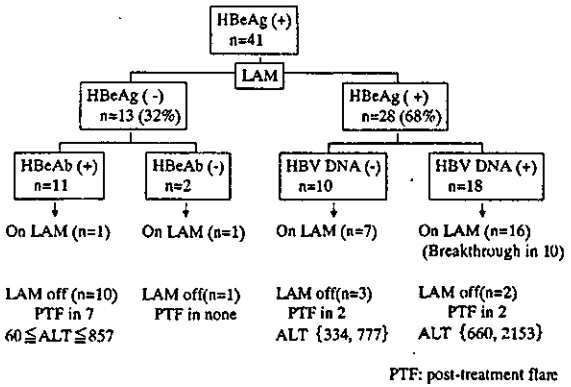


Fig. 3. Analyses of 41 eAg positive patients treated with lamivudine

Post Treatment Flare and Breakthrough Hepatitis (BKh)

We examined patients with breakthrough hepatitis (BKh) (Table 1) [7]. Analyses of factors associated with breakthrough (BK) in HBe antigen-positive patients (n=41) demonstrated clear differences between the two groups, one with BK (n=10) and the other without (n=31). They were the duration of administration, disappearance of HBV DNA and patients' age. The HBV DNA levels before treatment was not a predictor of BK, implying that the risk for BK increases with the period of administration even in those with lower HBV DNA at baseline. A total of 25 patients were still on lamivudine with a mean administration period of 22.1+/-10.5 months. The incidence of BK was 40 % (10/25) in patients who were initially HBe antigen-positive and were continuously treated with the drug (Fig. 3). All the patients with BK were positive for HBe antigen as well as for HBV DNA as determined by Amplicor PCR at the time of BK. Lamivudine was discontinued in 14 patients as they became negative for HBV DNA for longer than 6 months and in 2 patients the drug was discontinued despite being positive for HBV DNA (Fig. 3).

Table 1. Factors associated with breakthrough hepatitis

	Bk-hep (+)	Bk-hep (-)	P*value
Number of cases	n=10	n=31	
HBV DNA (LGE/ml): pre treatment	7.82±0.76	7.66±0.95	p=0.48
ALT (IU/l): pre treatment	145.9±84.1	154.6±98.3	ns
Duration of Treatment (mo.)	28.0±7.2	14.5±8.6	p=0.0005
DNA negative (yes/no): during treatment	3 / 7	24 / 7	p=0.0175
CH / LC: pre treatment	8 / 2	26 / 5	ns
Sex (M/F)	7 / 3	21 / 10	ns
Age (y)	50.2±10.5	45.0±12.5	p=0.0444

Kurume Univ. 2002

After stopping the drug, post-treatment flare (PTF) of hepatitis occurred in 7 patients (70%) who achieved HBe seroconversion, in 2 patients (67%) who were negative for HBV DNA and positive for HBe antigen, and 2 patients (100%) who were both positive for HBV DNA and HBe antigen. Overall incidence of PTF was 68.8 % (11/16). The flare was higher in those who were positive for both HBV DNA and HBe antigen at discontinuation of the drug.

In HBe antigen-negative patients (n=16), 7 patients were still on lamivudine with a mean period of 17.0+/- 9.2 months and in the rest of 9 patients lamivudine was stopped as HBV DNA continued to be negative by the PCR assay for more than 6 months. There were one BKh patients in patients who was HBe antigen-negative at baseline and continuously treated with the drug (1/7, 14.3%). Overall incidence of BKh was 34.4% (11/32). PTF in those who were initially negative for HBe antigen occurred in 5 patients. In these patients, the flare of serum ALT was relatively lower (180+/-66.7 IU/L, range 72 - 276).

Real Time PCR for HBV DNA During Lamivudine Therapy[8]

Changes in the level of HBV DNA were investigated using a real-time PCR method with a detection limit of 1.7 log copies/ml (50 copies/ml) in order to clarify its clinical significance, particularly the association between HBV DNA levels and the emergence of YMDD mutants. Twenty-four patients who had received lamivudine therapy for more than one year were studied. HBV DNA levels were determined using transcription-mediated amplification (TMA)[9] for sera with > 3.7 log genome equivalents/ml, the Roche Monitor kit for sera with ≥2.6 log copies/ml, and real-time PCR for sera with <2.6 log copies/ml (the detection limit was 1.7 log copies/ml). Patients were classified into 3 groups by the minimum HBV DNA level attained during lamivudine therapy: the <1.7 log copies/ml group (8 patients), the 1.7-2.5 log copies/ml group (5 patients), and the ≥2.6 log copies/ml group (11 patients). Pretreatment HBV DNA levels were significantly lower in the <1.7 group than in the other 2 groups (P<0.05). Neither the emergence of YMDD mutants nor a virologic breakthrough of serum HBV DNA was observed in any of the 8 patients in the <1.7 group. In contrast, in the 1.7-2.5 and ≥2.6 groups, virologic breakthroughs due to the emergence of YMDD mutants were observed in 2 of 5 and all 11 patients, respectively (P<0.001) (Table 2). Virologic breakthroughs were observed at a mean of 49.6±18.4 weeks in 11 the patients in the ≥2.6 group, and in the 107th and 115th weeks in 2 patients in the 1.7-2.5 group (Fig.4). The real-time PCR method is useful for predicting the emergence of YMDD mutants and the estimated time of their emergence.