with low viral load that can escape detection by NAT.[3] Interestingly, the lookback program of the Japanese Red Cross (JRC) demonstrated that low viral load donations in the window phase were more than 10-fold more often implicated in HBV transmission reports than were occult carriers with anti-HBc titers below the exclusion limit of the anti-HBc hemagglutination inhibition screening assay.[3] Bearing in mind the relatively high infectivity of HBV in the window phase, exact knowledge on early dynamics of HBV replication is important for residual risk estimations.[4-7] It will determine the threshold of NAT in identifying blood donors during the preacute phase of HBV infection, which is important for planning and executing evidence-based hepatitis B blood screening strategies.[7,8] In this context, the relative infectivity of HBV in the early window phase is an important factor for measuring the effect of NAT screening systems on the residual risk of HBV transmission by blood transfusion.[7-9]

Chimpanzees are the only experimental animals susceptible to human hepatitis viruses and have been very useful in transmission studies.[10] As early as the mid-1970s, it was demonstrated that blood units from HBV carriers, especially those positive for the presence of hepatitis B e antigen (HBeAg), have a tremendously high infectious potential and can transmit infection to chimps by intravenous inoculation with 1 mL of plasma diluted to 1:10^8.[11] Now that NAT enables detection of HBV DNA in blood donors even in individual-donation format, it can be estimated by mathematical modeling what the residual risk would be depending on the minimum copy number required for infection.[9] More conservative risk modeling assumes that a single copy of HBV, if it successfully reaches a hepatocyte in susceptible hosts, may be enough to establish infection.[5] To pursue strategies for preventing HBV infections by blood transfusions, additional information on the infectivity of HBV is crucially required. It is imperative to define not only the minimum copy number of HBV DNA or number of virions required for transmission of HBV, but also the early dynamics of HBV replication in the circulation of infected hosts. This can be established more accurately in chimpanzee experiments. In this report on experimental transmission of hepatitis B in chimps, the minimum infectious dose was determined separately for HBV of genotypes A and C, and the copy number of HBV DNA for establishing infection was defined for each of them. Moreover, the doubling time and logarithmic time of HBV DNA were determined by following the viral dynamics in the preacute phase of chimpanzees who had received the minimum infectious dose of HBV.

MATERIALS AND METHODS

Chimpanzees

Six chimps entered this study. Their age, sex, and weight, as well as the HBV inocula that they received are listed in Table 1 along with the infection outcome. Every chimp was kept in an individual cage and received humane care in accordance with all relevant requirements for the use of primates in an approved institution. None of the six chimps had serologic or molecular biologic evidence of past or present HBV infection prior to the inoculation. They were also not infected with hepatitis C virus (HCV) and human immunodeficiency virus type-1. Chimps were inoculated intravenously while they were under anesthesia by intramuscular injection with ketamine hydrochloride. After the inoculation, serum samples were obtained once a week or more frequently as required, until 16 weeks or longer. They were tested for HBV DNA, HBsAg, anti-HBc, anti-HBs, and alanine aminotransferase as well as aspartate aminotransferase.

Inocula containing HBV

The chimpanzees received four kinds of inocula (Table 1). Inocula I and III were fresh-frozen plasma (FFP) units from blood donors acutely infected with HBV genotypes A and C, respectively. Inocula II and IV were plasma samples from chimps infected with inoculum I of genotype A and inoculum III of genotype C, respectively (see Figs. 1A and 1B). Inocula II and IV were: 1) recovered in the preacute phase of HBV infection before immune responses of the host had developed; 2) positive for the presence of HBV DNA in the highest titer before anti-HBc developed; and 3) taken with utmost care to maintain the infectious activity and avoid attenuation during serial processing from blood collection until storage. Immediately after blood drawing

TABLE 1. Six chimpanzees and HBV inocula and HBV infection outcomes

Chimpanzee	Age, sex, weight	HBV DNA copies	Outcome
Inoculum I: FFP from a human donor in the preacute phase of HBV infection of genotype A			
1 Chimp 246	13 years, male, 60.7 kg	1 mL (6.9 × 10^4 copies/mL)	Infected
Inoculum II: Preacute-phase plasma of Chimp 246 containing HBV (2.6 × 10^6 copies/mL)			
2 Chimp 272	9 years, male, 58.7 kg	1 mL (1:10^6 dilution)	Not infected
3 Chimp 279	8 years, male, 51.4 kg	1 mL (1:10^6 dilution)	Not infected
3 Chimp 279	Reinoculation	1 mL (1:10^5 dilution)	Infected
4 Chimp 280	8 years, male, 39.4 kg	1 mL (1:10^5 dilution)	Infected
Inoculum III: FFP from a human donor in the preacute phase of HBV infection of genotype C			
2 Chimp 272	Reinoculation	5 mL (5.3 × 10^5 copies/mL)	Infected
Inoculum IV: Preacute-phase plasma of Chimp-272 containing HBV (3.0 × 10^6 copies/mL)			
5 Chimp 269	11 years, male, 62.5 kg	1 mL (1:10^6 dilution)	Not infected
6 Chimp 285	7 years, male, 41.1 kg	1 mL (1:10^6 dilution)	Not infected
5 Chimp 269	Reinoculation	1 mL (1:10^5 dilution)	Infected
6 Chimp 285	Reinoculation	1 mL (1:10^5 dilution)	Infected

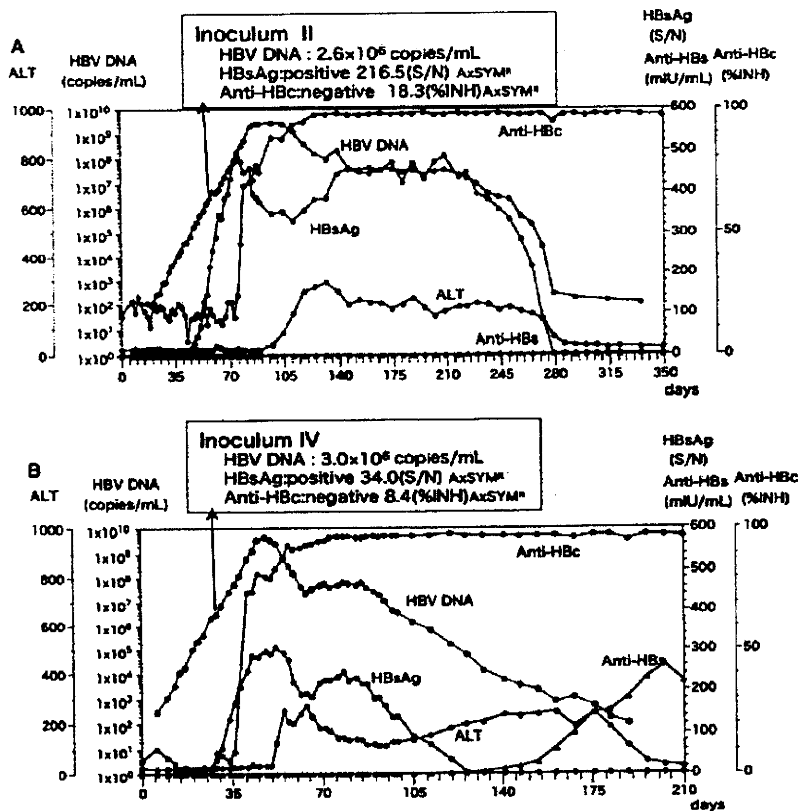

Fig. 1. Time course of HBV serum markers in chimps used as a source of inoculation of HBV genotype A and genotype C. (A) Chimp 246 was inoculated with human plasma of HBV genotype A. Inoculum II for chimp infectivity studies was harvested in the ramp-up phase of viremia before anti-HBc seroconversion at the time HBV DNA had reached a concentration of 2.6 × 10⁶ copies per mL and the HBsAg response had increased to a signal-to-noise (S/N) ratio of 216.5 (cutoff S/N = 2.0). (B) Chimp 272 was inoculated with human plasma of HBV genotype C. Inoculum IV was harvested in the ramp-up phase of viremia before anti-HBc seroconversion at the time HBV DNA had reached a concentration of 3.0 × 10⁶ copies per mL and HBsAg had increased to an S/N ratio of 34.0.

from chimps, plasma samples were separated. They were divided into 15 tubes in 1-mL aliquots, snap-frozen in liquid nitrogen, and kept in a deep freezer at −80°C until used for transmission experiments. For each experiment, the plasma in one tube was thawed gently by immersing it in a water bath at 37°C, and the required amounts were used.

Laboratory tests

HBsAg, anti-HBc, and antibody to HBsAg (anti-HBs) were determined by chemiluminescent immunoassay (CLIA) with commercially available kits (AxSYM, Abbott Japan, KK, Tokyo, Japan), with the index of 2.0 (signal-to-noise [S/N]), 50 percent inhibition, and 5.0 mIU per mL as cutoff values, respectively. Qualitative assay for HBV DNA was performed by polymerase chain reaction (PCR) with primers deduced from the S region of HBV DNA.[12] HBV DNA was quantitated by the PCR (TaqMan, Roche Diagnostics KK, Tokyo, Japan) with a sensitivity of 100 copies per mL. Quantitative assays for HBV DNA were performed simultaneously for an accurate comparison of data.

Calculation for doubling time and logarithmic time of HBV DNA

To calculate the doubling time and the logarithmic time (time for reaching 10 times the amount) of HBV DNA at ramp-up after the infection, HBV DNA copy numbers were evaluated statistically by log linear regression analysis. The comparison of regression slope (the doubling time and the logarithmic time) between HBV genotypes was evaluated by growth curve analysis (Vonesh-Carter-Ohtaki method).[13,14]

RESULTS

Inocula and copy numbers of HBV genotype A or genotype C recovered from chimpanzees in the preacute phase of infection

Chimp 246 was injected intravenously with 1 mL of FFP from a blood donor in the preacute phase of HBV infection (Table 1); the donor had been screened by NAT at a JRC Blood Center. His plasma sample contained 6.9×10^4 copies per mL of HBV DNA genotype A and was positive for the presence of HBsAg but negative for the presence of anti-HBc (inoculum I). Plasma was harvested from Chimp 246, in the preacute phase of HBV infection 57 days after inoculation (inoculum II). It contained 2.6×10^6 copies per mL HBV DNA and was positive for the presence of HBsAg but still negative for the presence of anti-HBc and anti-HBs (Fig. 1A).

Likewise, Chimp 272 was injected intravenously with 5 mL of FFP from a blood donor in the preacute phase of HBV infection who had been screened by NAT at JRC (Table 1). It contained 5.3×10^5 copies per mL of HBV DNA genotype C and was positive for the presence of HBsAg but negative for the presence of anti-HBc and anti-HBs (inoculum III). Thus, Chimp 272 was inoculated with

2.7×10^6 copies of HBV genotype C. The preacute plasma sample was collected from Chimp 272 29 days after challenge (inoculum IV). It contained 3.0×10^6 copies per mL HBV DNA and was positive for the presence of HBsAg but still negative for the presence of anti-HBc and anti-HBs (Fig. 1B).

Estimates of HBV DNA copy numbers in serial 1-in-10-fold dilutions and inocula below the HBV NAT detection limit

Serial 1-in-10 dilutions of inoculum II of genotype A were prepared in preinoculation serum sample from each chimp (e.g., Chimp 272, Chimp 279, and Chimp 280, respectively). Dilutions were delivered to three tubes each in 1-mL aliquots and snap-frozen in liquid nitrogen. Concentration of HBV DNA was determined in one of the three tubes in each dilution so as to guarantee copy numbers of HBV DNA in the other two vials that were inoculated into chimps. These samples had been stored in a deep freezer at −80°C until inoculation.

Table 2 shows the measured HBV DNA concentrations in 1-in-10 dilutions of inoculum II (genotype A). The quantitative HBV DNA results starting from 2.6×10^6 copies per mL in the undiluted sample varied between 2.0×10^5 to 2.3×10^5, 2.0×10^4 to 2.4×10^4, 1.6×10^3 to 2.0×10^3, and 1.7×10^2 to 2.8×10^2 copies per mL, respectively, in the 1:10, $1:10^2$, $1:10^3$, and $1:10^4$ dilutions. These quantitative results are an indication of the accuracy of the dilution and assay procedure. On the premise that dilutions beyond $1:10^4$ had been performed properly, further dilutions to $1:10^5$ and $1:10^6$ would have contained 16 to 28 and 1.6 to 2.8 HBV DNA copies per mL (ranges estimated by variations of HBV DNA measurements in lower dilutions), respectively, although they were below the detection limit of the PCR method used.

Likewise, serial 1-in-10 dilutions of inoculum IV (genotype C) were prepared in the plasma sample from Chimp 269 and Chimp 285. HBV DNA in 3.0×10^6, 3.5×10^5 to 3.8×10^5, 3.6×10^4 to 3.9×10^4, 3.6×10^3 to 4.6×10^3, and 4.3×10^2 to 4.6×10^2 copies per mL were detected in the original serum samples at 1:10, $1:10^2$, $1:10^3$, and $1:10^4$ dilutions thereof, respectively (Table 3). Thus, further experiments were performed on the assumption that serial dilutions of $1:10^5$ and $1:10^6$ of inoculum IV would have contained 35 to 46 and 3.5 to 4.6 HBV DNA copies per mL, respectively.

Determination of the minimum copy number required for transmission of HBV genotype A or genotype C to chimpanzees

When Chimp 272 and Chimp 279 were inoculated intravenously with 1.0 mL of inoculum II diluted $1:10^6$ (equivalent to 1.6 to 2.8 copies of HBV DNA in an in vitro assay), HBV infection did not develop in either of them during monitoring for 119 days (17 weeks) and thereafter. Chimp 279 was then rechallenged with 1.0 mL of inoculum II diluted $1:10^5$ (equivalent to 16-28 copies). He then became infected and developed HBV DNA in his serum 55 days (8 weeks) after the inoculation. Chimp 280 was also inoculated intravenously with 1.0 mL of inoculum II diluted $1:10^5$ (equivalent to 16 to 28 copies of HBV DNA). He developed HBV DNA in the circulation 76 days (11 weeks) after infection. In view of the incubation period of 55 to 76 days (8-11 weeks) for $1:10^5$ dilution of inoculum II, HBV infection would probably not have occurred in chimps who received $1:10^6$ dilution if they had been followed longer than 119 days (17 weeks).

Chimp 269 and Chimp 285 were inoculated with 1.0 mL of inoculum IV diluted $1:10^6$ (equivalent to 3.5-4.6 copies of HBV DNA in an in vitro assay). During follow-up

TABLE 2. Quantification of HBV DNA in serial 1-in-10 dilutions of the standard serum for HBV genotype A (inoculum II)*

		Serial dilutions in preinoculation serum samples of each chimpanzee					
Chimpanzee	Undiluted	1:10	$1:10^2$	$1:10^3$	$1:10^4$	$1:10^5$	$1:10^6$
272	2.6×10^6	2.3×10^5	2.0×10^4	2.0×10^3	1.7×10^2	Not done	<100
279	2.6×10^6	2.0×10^5	2.4×10^4	2.0×10^3	2.4×10^2	<100	<100
280	2.6×10^6	2.3×10^5	2.3×10^4	1.6×10^3	2.8×10^2	<100	Not done

* Data are reported as copies per mL.

TABLE 3. Quantification of HBV DNA in serial 1-in-10 dilutions of the standard serum for HBV genotype C (inoculum IV)*

		Serial dilutions in preinoculation serum of each chimpanzee					
Chimpanzees	Undiluted	1:10	$1:10^2$	$1:10^3$	$1:10^4$	$1:10^5$	$1:10^6$
Chimp 269	3.0×10^6	3.8×10^5	3.9×10^4	3.6×10^3	4.6×10^2	<100	<100
Chimp 285	3.0×10^6	3.5×10^5	3.6×10^4	4.6×10^3	4.3×10^2	<100	<100

* Data are reported as copies per mL.

for 112 days (16 weeks), however, no HBV infection occurred in either of them. Subsequently, they were rechallenged with 1.0 mL of inoculum IV diluted 1:10^5 (equivalent to 35-46 copies of HBV DNA) 17 weeks after the initial inoculation. They developed HBV DNA in the circulation 35 and 50 days thereafter, respectively, indicating that both of them were infected. Therefore, the 50 percent chimp infectious dose (CID_{50}) for both genotype A and genotype C lies between the lowest infectious dose of approximately 30 copies and the subinfectious dose of approximately 3 copies or at approximately 10 HBV DNA copies.

HBV infection resolved in all six chimps and they never became carriers. Within a few weeks after the peak HBV DNA titer was reached, serum levels of transaminase increased slightly, within 3 times the upper limit of normal.

Replication velocity of HBV DNA in the preacute phase of infection

Doubling time and logarithmic time of HBV genotype A

Figure 2A illustrates the appearance of HBV genotype A in the circulation, when HBV DNA reached more than 10^2 copies per mL, as well as its early dynamics in Chimp 246, Chimp 279, and Chimp 280 during the preacute phase of exponential replication. HBV DNA emerged in the circulation earlier in Chimp 246 than the other two chimps, but

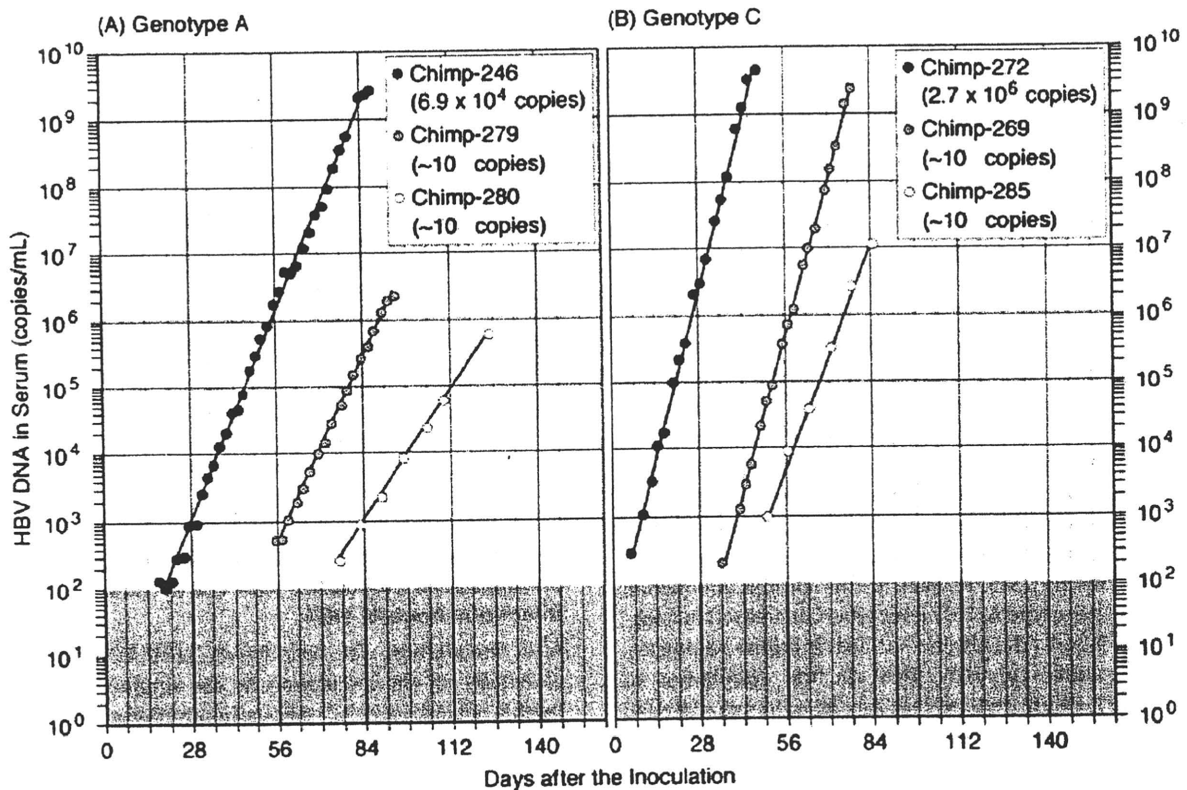

Fig. 2. Log-linear increase of HBV DNA in the circulation of chimpanzees during the early exponential replication phase. (A) Dynamics in the early ramp-up phase of viral DNA for three chimps inoculated with HBV genotype A: one chimp (Chimp 246) received 1 mL of human plasma containing 6.9 × 10^4 copies and the other two chimps (Chimps 279 and 280) received 1 mL of a 100,000 dilution of chimp plasma taken in the HBsAg ramp-up phase just before appearance of anti-HBc, which dilution contains a measured amount of 16 to 28 copies. (B) Graph summarizes the viral load dynamics for three chimpanzees inoculated with HBV genotype C: one chimp (Chimp 272) received 5 mL of human plasma with 2.7 × 10^6 copies of HBV DNA and the two other chimps (Chimps 269 and 285) received a measured amount of 35 to 46 copies (1:100,000 dilution) of preacute-phase chimpanzee plasma. Shaded areas are below the detection limit of NAT (<100 copies/mL). Only the phase of exponential replication is shown, and HBV DNA decreased after it reached peak values of 5.7 × 10^5 to 2.8 × 10^9 copies per mL in three chimps inoculated with HBV genotype A and 1.1 × 10^7 to 4.6 × 10^9 copies per mL in three chimps inoculated with HBV genotype C.

this animal had received more than a 1000-fold larger amount of copies of HBV than the other two chimps. Despite the 1000-fold higher infectious dose, the log-linear increase of HBV DNA in Chimp 246 was the same as in Chimp 279, who had received the minimum infectious dose. In Chimp 246, HBV DNA replicated exponentially from 21 to 97 days (3-13 weeks) until it peaked and then declined. Even though the same minimum infectious dose of HBV was inoculated, Chimp 279 developed detectable HBV DNA about 21 days (3 weeks) earlier than Chimp 280, in whom HBV replicated slightly slower. Despite differences in HBV doses and individual variation, the replication velocity was constant for HBV genotype A in the preacute phase of infection, before innate immune responses of the host developed, while the virus replicated at an exponential rate. The doubling time and the logarithmic time, in the early exponential viral replication phase, were calculated to be 2.7 to 4.4 and 9.0 to 14.7 days, respectively (see Table 4).

TABLE 4. Estimated doubling times and logarithmic times for HBV genotypes A and C with log-linear and growth-curve analysis

Genotype	Doubling time (days)	Logarithmic time (days)	y = a × exp(b × x) a	b	R^2
Genotype A					
Chimp 246	2.71	9.01	0.8491	0.2556	0.997
Chimp 279	3.05	10.14	0.0015	0.2271	0.998
Chimp 280	4.43	14.73	0.0022	0.1563	0.999
Genotype C					
Chimp 272	1.68	5.58	0.2074	0.413	0.998
Chimp 269	1.79	5.96	0.0002	0.3863	0.999
Chimp 285	2.5	8.31	0.0009	0.2771	0.997

TABLE 5. Comparing the replication velocity of HBV DNA between the two genotypes estimated by a growth curve

Genotype	Doubling time (95% CI), days	Logarithmic time (95% CI), days	y = a × exp(b × x) a*	b (95% CI)	p Value
A	3.44 (2.64-4.89)	11.42 (8.80-16.26)	2.299	0.2017 (0.14-0.26)	<0.01
C	1.9 (1.63-2.27)	6.3 (5.41-7.54)	2.299	0.3654 (0.31-0.43)	

* To evaluate the difference of "b" (that is, slope) between the two genotypes, the growth curve model is assuming that "a" is identical.[13]

Doubling time and logarithmic time of HBV genotype C

The replication velocity in the preacute phase of infection in chimpanzees inoculated with genotype C inocula was faster than in the chimps infected with HBV of genotype A (Fig. 2B). Again, slight variation in log-linear increase of HBV DNA was found, and HBV DNA appeared in serum earlier in Chimp 272 who was inoculated with a 100,000-fold higher infectious dose than was administered to Chimps 269 and 285. As seen in the chimps inoculated with HBV genotype A, HBV genotype C increased in a log-linear fashion in the absence of host immune responses. Doubling times of HBV DNA in the circulation of Chimp 272, Chimp 269, and Chimp 285 were calculated to be 1.7 to 2.5 days and logarithmic times were 5.6 to 8.3 days as determined with the regression formula shown in Table 4.

When comparing the replication velocity of HBV DNA between the two genotypes estimated by a growth curve, the difference was significant ($p < 0.01$, Table 5). That is, the doubling time of replications of HBV DNA with genotype A was estimated to be 3.44 days (95% confidence interval [CI], 2.64-4.89 days) and the logarithmic time was estimated to be 11.42 days (95% CI, 8.80-16.26 days). By contrast, those with HBV genotype C were estimated to be 1.90 days (95% CI, 1.63-2.27 days) and 6.30 days (95% CI, 5.41-7.54 days), respectively.

TABLE 6. Window periods before HBV DNA and HBsAg developed in the circulation of chimpanzees inoculated with the minimum infectious dose of genotype A or genotype C

HBV inoculated	Chimp infected	Markers of HBV infection: HBV DNA (days)	HBsAg (days)
Genotype A	279	55	69
	280	76	97
Genotype C	269	35	50
	285	50	64

Window periods of HBV DNA and HBsAg in chimpanzees inoculated with the minimum infectious dose of HBV

After inoculation, the time before HBV DNA becomes detectable in the circulation by the single-sample NAT (with a sensitivity of 10^2 copies/mL) and the time before HBsAg was detected by CLIA after inoculation are listed in Table 6. The HBV DNA (<100 copies/mL) NAT window was 55 and 76 days, respectively, in Chimp 279 and Chimp 280 inoculated with the lowest infectious dose of HBV genotype A (approx. 30 copies). These NAT window periods were longer than the 35 and 50 days, respectively, found in Chimp 269 and Chimp 285 inoculated with the lowest infectious amounts of HBV genotype C (approx. 30 copies). Likewise, the HBsAg window was longer in Chimp 279 and Chimp 280 infected with genotype A than in Chimp 269 and Chimp 285 infected with genotype C (69 and 97 days, respectively, vs. 50 and 64 days, respectively).

DISCUSSION

Animal models sensitive to human hepatitis viruses offer robust advantages in obtaining basic data of viral infectivity.[10] By experimental infection of chimps with HCV, we have been able to determine the minimum infectious dose of HCV required for establishing infection.[15,16] The doubling time of HCV was determined to be 6.3 to 8.6 hours in two chimps inoculated with the minimum infectious dose of approximately 10 copies of HCV RNA. During the first 5 days after inoculation, HCV RNA did not increase above the NAT detection limit of 10^2 copies per mL in the circulation.[16] It would not be possible to detect HCV infection during the initial few days after exposure, even if 1-mL samples were used for individual NAT.

In this study, we have determined the minimum infectious dose for two standardized inocula containing defined copy numbers of HBV DNA. They were plasma passages of HBV in chimps harvested during the preacute phase of infection and had been processed with the utmost care for maintaining infectious activity. The minimum infectious dose of HBV or the dose where 50 percent of the chimps would be infected lies between 1-in-1 million and 1-in-100,000 dilution of the original inocula and is estimated to be of the order of 10 copies, as was the case for HCV.[15] On the basis of HBV DNA concentrations measured in serial dilutions of inocula (Tables 2 and 3), the minimum infectious dose can be determined to be 16 to 28 copies for HBV genotype A and 35 to 46 copies for HBV genotype C.

There are two definitions of the minimum infectious dose of HBV. Theoretically, it is a single copy of HBV. Not all HBV virions entering the circulation of recipients, however, will succeed in reaching hepatocytes, because some of them are phagocytized by circulating macrophages and Kupffer cells in the sinusoids of the liver. In a mathematical window-phase risk model, Weusten and colleagues[9] have proposed a minimum infectious dose approximately 10 copies of HBV, on the basis of the CID_{50}.[17-19] Recently the inocula derived from chronic HBV carriers used in older chimpanzee studies[17,18] were requantified by Hsia and coworkers[20] with real-time TaqMan PCR. The estimated HBV copy number per CID_{50} (geq) was 169 for genotype A *adw*, 78 for genotype D *ayw*, and 3 for genotype C *adr*, calculated by mathematical division, respectively. These viral load data, performed on cryopreserved aliquots from an inocula derived from a chronic HBV carrier (i.e., HBsAg- and anti-HBc–positive), were derived retrospectively several decades after the chimp titration studies. These results are different from the results obtained in our study, where the inocula was derived from the early ramp-up phase of viremia (HBsAg is positive but anti-HBc is negative) and the chimp titration and viral load analyses were performed prospectively. Hence, the minimum infectious dose defined as a single copy, proposed on a theoretical basis, would deserve revisiting in practical HBV infections. The window period of HBV infection changes with the size of the inoculum. The more copies of HBV inoculated therefore the shorter the incubation period in experimental transmission studies in chimps.[11] An inverse correlation is reported, also, between time before HBsAg appears in serum and the HBV dose in human beings.[21] In accordance with these reports, we also found that the NAT window was shorter in chimps receiving larger sizes of inocula both for genotypes A and C (Fig. 2). The NAT (<100 copies/mL) window period was approximately 1 week with an inoculum of 2.7×10^6 copies of genotype C, approximately 3 weeks with 6.9×10^4 copies of genotype A, 5 to 7 weeks when inoculating 35 to 46 copies of genotype C, and 8 to 11 weeks when inoculating 16 to 28 copies of HBV genotype A, while no infection was observed during 16 to 17 weeks of observation with an inocula of approximately 3 copies of genotype A or B. Theoretically, HBV infection might have become detectable after 17 weeks, but this is unlikely when extrapolating the data above. Inoculation with HBV in large amounts, as happens with transfusion with HBsAg-positive blood units, has been largely excluded since introduction of HBsAg testing in 1972. Barker and Murray[21] have shown that inoculation of lower infectious doses of HBV in the range of 10^4 to 10^7 diluted icteric plasma no longer caused clinical hepatitis in healthy individuals, while infection still occurred with up to a 10^7 diluted inoculum, as detected by an HBsAg complement fixation test. Our study showed that HBV DNA levels increase 6.5×10^3 to 2.2×10^5 copies per mL at the time of the first HBsAg-reactive sample in six chimpanzees in whom blood samples were taken at intervals of 2 to 7 days. These amounts are enough to cause clinical hepatitis B.[21] Indeed, Satake and coworkers[3] found that transmission of 5,000 to 50,000 copies of HBV by blood components with a low viral load in the pre-MP-NAT window phase could cause clinical hepatitis B. Transfusion-transmitted HBV after introduction of individual-donation or small-pool NAT (<10) is still possible, but would involve relatively low infectious doses of HBV of approximately 10 to 100 CID_{50}.

In the chimps inoculated with approximately 30 copies of HBV, the NAT window was determined by individual-donation NAT having a sensitivity of 10^2 copies per mL, while the HBsAg window was established by CLIA with the highest sensitivity presently available.[5,12] The NAT window was 55 to 76 days and HBsAg window was 69 to 97 days, respectively, in Chimp 279 and Chimp 280 who had been inoculated with approximately 30 copies of HBV genotype A. In contrast, the NAT window was 35 to 50 days and the HBsAg window was 50 to 64 days, respectively, for Chimp 269 and Chimp 285 inoculated with approximately 30 copies of HBV genotype C. Thus, neither

the NAT nor the HBsAg window phases overlapped between minimum-dose infections of HBV genotypes A and C; they were longer for genotype A than genotype C. It may be that the NAT window is longer for genotype A, prevalent in Western countries, than genotype C common in Japan. It cannot be excluded, however, that the results observed in our inoculation studies with a limited number of chimpanzees were influenced by the host rather than the genotype of the virus. The duration of the NAT and HBsAg windows are influenced at least by three factors: 1) the infectious dose, 2) individual variation among recipients, and 3) distinct HBV genotypes.

We found the replication velocity of HBV in the preacute phase of infection remarkably different between genotypes A and C. From three chimps infected with HBV genotype A, the doubling time was estimated to be 3.44 days (95% CI, 2.64-4.89 days) and the logarithmic time 11.42 days (95% CI, 8.80-16.26 days). From three chimps infected with HBV genotype C, the doubling time was estimated to be 1.90 days (95% CI, 1.63-2.27 days), and the logarithmic time 6.30 days (95% CI, 5.41-7.54 days). Also in chimeric mice with the liver replaced by human hepatocytes, genotype A was found to replicate much slower than genotype C in the initial weeks of HBV infection.[22]

The replication velocity of HBV in the circulation, indicated by the viral doubling time, is an important factor when calculating the window-period reduction provided by NAT screening systems. Biswas and colleagues[5] calculated a doubling time of 2.56 days (95% CI, 2.24-2.97 days) based on a seroconversion panel of 23 HBV infections. Yoshikawa et al.[4] followed 93 donors in preacute phase HBV infections who had been identified by the routine NAT screening program on 50-MPs at JRC Blood Centers. They estimated a median doubling time of HBV at 2.6 days (range: 1.3-15.2).

Kleinman and Busch[7] have assessed the HBsAg window period based on the HBV doubling time of 2.56 days documented by Biswas and colleagues.[5] They estimated an HBsAg window at 38.3 days (95% CI, 33.0-43.7 days) by the CLIA HBsAg seroconversion point at a concentration of 1650 copies per mL, while Minegishi and coworkers[12] determined the HBsAg seroconversion point at 2100 copies per mL. We found the HBsAg seroconversion with AxSYM occurred when the HBV DNA concentration reached a level of 6.5×10^3 to 2.2×10^5 in six chimpanzees. The differences in HBV levels at HBsAg seroconversion in CLIA may be related to the genotype, but also could reflect differences in the calibration of HBV quantitative assays in genome copies.

It is not known if the chimpanzee model is as susceptible for HBV infection as human beings. As a result, the minimum dose of HBV for transmitting infection to man is, in fact, not precisely known. Nevertheless, a minimum human infectious dose of approximately 10 HBV DNA copies, as indicated by our chimpanzee infectivity experiments, seems a reasonable assumption for modeling the HBV transmission risk in the pre-HBV-NAT window period.

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B型・C型ウイルス肝炎へのアプローチ
その1
実地医家に必要な基本的知識

ウイルス肝炎の疫学

わが国の肝炎ウイルス罹患状況と推定キャリア数

田中純子
広島大学大学院医歯薬学総合研究科疫学・疾病制御学／たなか・じゅんこ

わが国の肝癌死亡の年次推移・地理的分布

わが国の肝癌による死亡実数および人口10万人対死亡数を図1に示す(肝及び肝内胆管の悪性新生物，人口動態統計)．1970年代前半までは1万人以下であった死亡実数は増加の一途を辿り，1995年の国際疾病分類の改正(ICD-10)に伴い3万人を超えた後，さらに微増したが，2002年に至ってようやく頭打ちの状態となった(2002年34,637人，2004年34,510人，2006年33,662人)．人口10万人対死亡数を見ると，男女とも1970年代後半から増加傾向が認められること，男性は女性のほぼ2倍以上の高い死亡数を示していることが特徴的である(2006年，人口10万人対：男性36.7，女性17.2)．

日本肝癌研究会による調査成績[1)]および人口動態統計資料を基に算出した成因別の肝癌死亡(人口10万人対)の年次推移をまとめて図2に示す．

HBV(B型肝炎ウイルス)の持続感染に起因する肝癌(B型の肝癌)による死亡は，1970年代から今日に至るまでほぼ増減がないまま，人口10万人対3～4の状態で推移しており，HBVの持

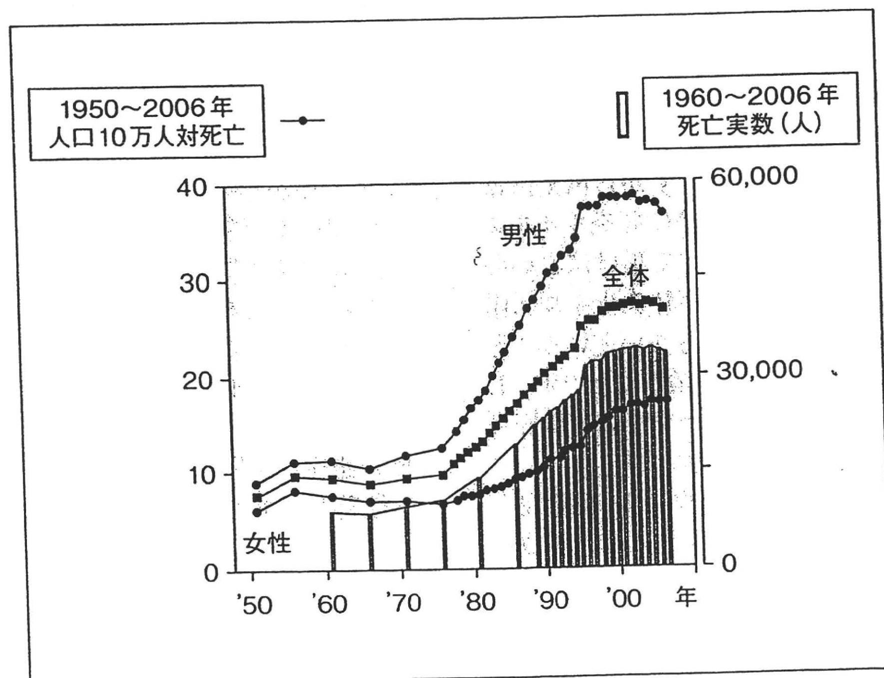


図1　わが国における肝癌*人口10万対死亡数および死亡実数の推移
*肝及び肝内胆管の悪性新生物(死因簡単分類：02106)

1345-1551/08/￥100/頁/JCLS

- *わが国の肝癌による死亡実数は頭打ちの状態となった.*
- *わが国の「肝及び肝内胆管の悪性新生物」による死亡数は33,662人(2006年)(人口10万人対：男性36.7, 女性17.2).*
- *B型の肝癌による死亡は, 人口10万人対3〜4. 非B型の肝癌の約80〜90%はC型の肝癌である.*

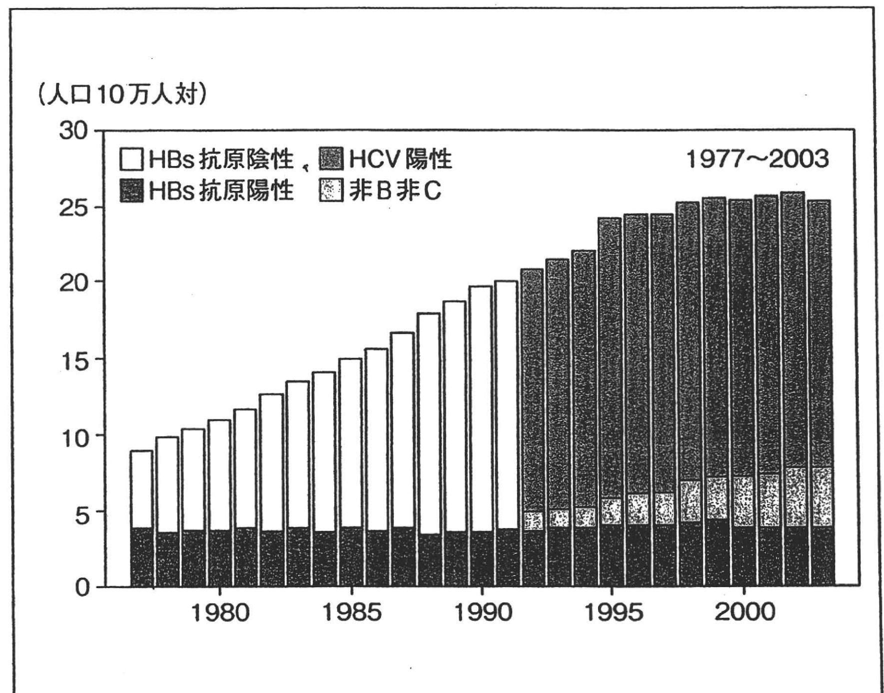


図2 わが国における成因別肝癌死亡の推移
(厚生労働省大臣官房統計情報部：人口動態統計. 日本肝癌研究会：全国原発性肝癌追跡調査報告の数値を用いて概算)

続感染によらない肝癌(非B型の肝癌)による死亡が死亡率全体の増加に寄与していることがわかる. また, HCV(C型肝炎ウイルス)感染の確定診断が可能になった1992年以降についてみると, それまで非B型の肝癌とされてきた集団の約80〜90%はHCVの感染に起因する肝癌(C型の肝癌)であることが明らかとなっている[2).

全国市町村別の肝癌標準化死亡比を三つの時期に分け図3に示す(年齢の偏りと小さい人口集団への偏りを補正したベイズ法による標準化死亡比推定量[3)). 人口10万人あたりの肝癌死亡数が9人程度に止まり, B型の肝癌が全体の約半数を占めていた1970年代前半のSMR地理分布と比べ, 人口10万人あたりの肝癌死亡が27人を超え, 非B型の肝癌が全体の80%以上を占めるに至った2000年代前半のSMR地理分布では, 非B型の肝癌(すなわちC型の肝癌)死亡の増加による時間的変化とともに, 肝癌死亡の多発地域は駿河湾沿岸, 大阪湾沿岸, 中国地方の瀬戸内沿岸, そして九州北部を中心とした市町村への偏りが顕在化

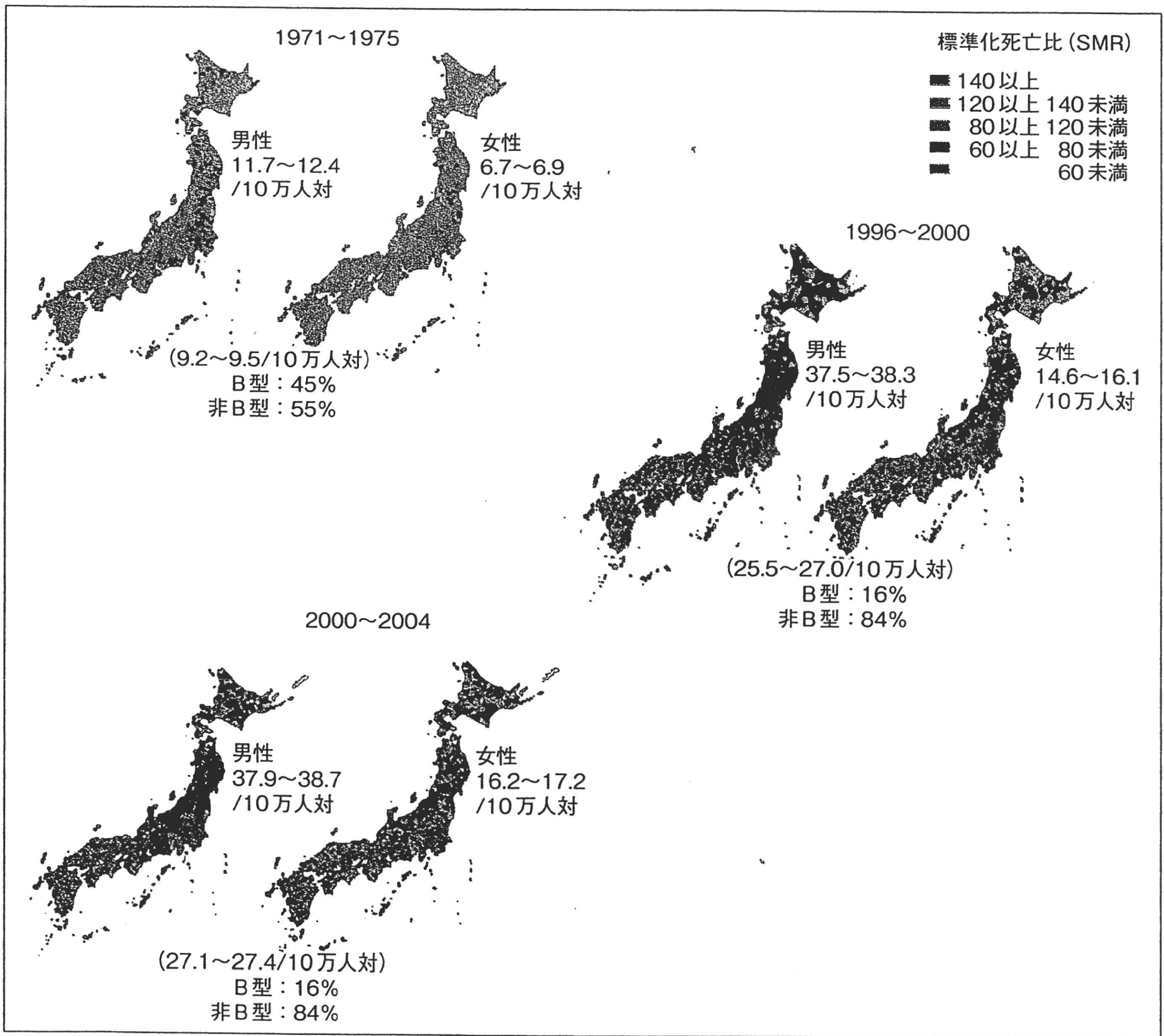


図3　市町村別にみた肝癌標準化死亡比(Bayesian method)の推移
(厚生労働省：肝炎疫学研究班より)

- 約350万人にのぼる初回供血者集団を対象とした調査から,
  - HBVキャリア率は全体では0.6%,50歳代(2000年時点)の年齢集団では1.5%である.
  - 北海道地区および,近畿以西の西日本地区ではHBVキャリア率はやや高い値を示す.
  - HCV抗体陽性率は全体では0.5%,年齢が高い集団で高い値を示す.
  - 西日本地域の40歳以上の年齢集団におけるHCV抗体陽性率は高い値を示す.

していることがわかる.

一方,肝癌による死亡率が高い都道府県順に1993年から2006年の14年間分を集計すると,県ごとの年齢構成を調整していない粗死亡率での比較となるが,10位以内にランクされる県の7割が中国・四国・九州地域に位置し,近畿を含む西日本地域に拡大すればそのほとんどすべてを占めることがわかる.肝癌による死亡が人口割合でみて高頻度に起こっている地域は西日本地域に偏在していることを示している.

性,年齢,地域別にみたHBs抗原陽性率とHCV抗体陽性率

わが国のいわゆる一般集団における肝炎ウイルス(HBV,HCV)の感染率は,唯一,日本赤十字血液センターの献血者の資料を元にして算出することができる.血液センターでは,毎年約600万本の献血された血液が輸血用血液の安全性を確保する目的で,全国一律の基準により同一の試薬を用いて検査されている.

厚生労働省肝炎に関する疫学研究班と日本赤十字社との協力のもと,1995年から2000年までの6年間に全国の血液センターで初めて献血した3,485,648人(初回献血者)を対象として,地域別,2000年の時点における年齢に換算した年齢階級別にHBs抗原陽性率,HCV抗体陽性率を算出した成績[4)]を図4a,bに示す.

HBs抗原陽性率を全体でみると0.6%であるが,年齢階級別にみると50歳代までは年齢が高い集団で高い値を示す傾向がみられる.日赤基幹血液センターの所在地を中心に8つに分けた地域別にみると,北海道地区では他の地域と比べて高いHBs抗原陽性率(1.5%)を示している.また,近畿以西の西日本地区では関東・中部地域と比べて,やや高い値を示し(0.6~1.1%),50歳代のみならず40歳代においてもHBs抗原陽性率が高値を示す傾向がみられる.

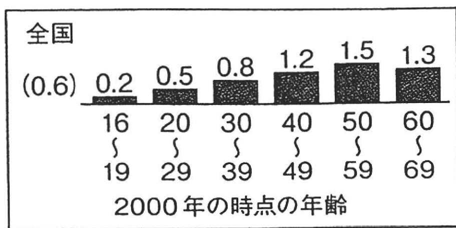
HCV抗体陽性率は全体でみると0.5%であり,年齢が高い集団で高い値を示す傾向がみられる.0~20歳代では0.2%以下の低い値を示すが,年齢が高い集団,特に,60歳以上の年齢集団では3%を超える値を示している.地域別にみると,肝癌多発地域である西日本の各地域,すなわち九州,中国・四国,近畿地方の40歳以上の年齢層におけるHCV抗体陽性率が他の地域・年齢層に比べて高い値を示す傾向が認められる.

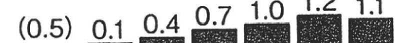
性,年齢,地域別にみたHBVキャリア数(推計)と,HCVキャリア数(推計)

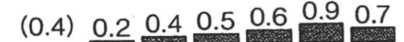
現在,社会に存在しているHBVキャリアおよびHCVキャリアは,「すでに患者として入院,または通院している」キャリアと,「自覚症状がないまま社会に潜在している」キャリアとに分けることができる.前者については,現時点におけるわが国では,各種の患者調査成績を元に患者数の概数を推計しても,実際の慢性肝疾患患者数の近

a　地域別，年齢階級別にみたHBs抗原陽性率

日本赤十字社　初回供血者
1995.1～2000.12　3,485,648人
2000年の時点の年齢に換算

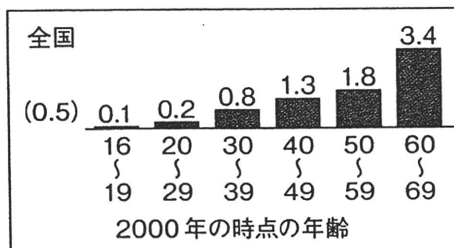


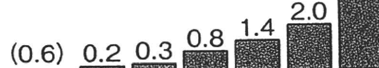


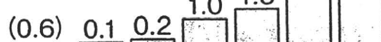


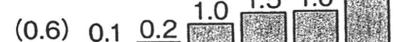
b　地域別，年齢階級別にみたHCV抗体陽性率

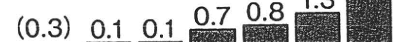
日本赤十字社　初回供血者
1995.1～2000.12　3,485,648人
2000年の時点の年齢に換算

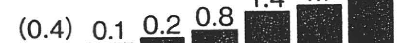












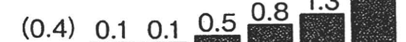


図4　地域別，年齢階級別にみたHBs抗原陽性率，HCV抗体陽性率
（厚生労働省：C型肝炎疫学研究班より）

- 2000年時点の人口約9,332万人(15歳から69歳)中,「本人が自覚しないままの状態で社会に潜在している」キャリア数の推計値は,
  - HBVキャリア数：96.8万人(80.7〜112.9万人)
  - HCVキャリア数：88.5万人(72.5〜104.5万人)

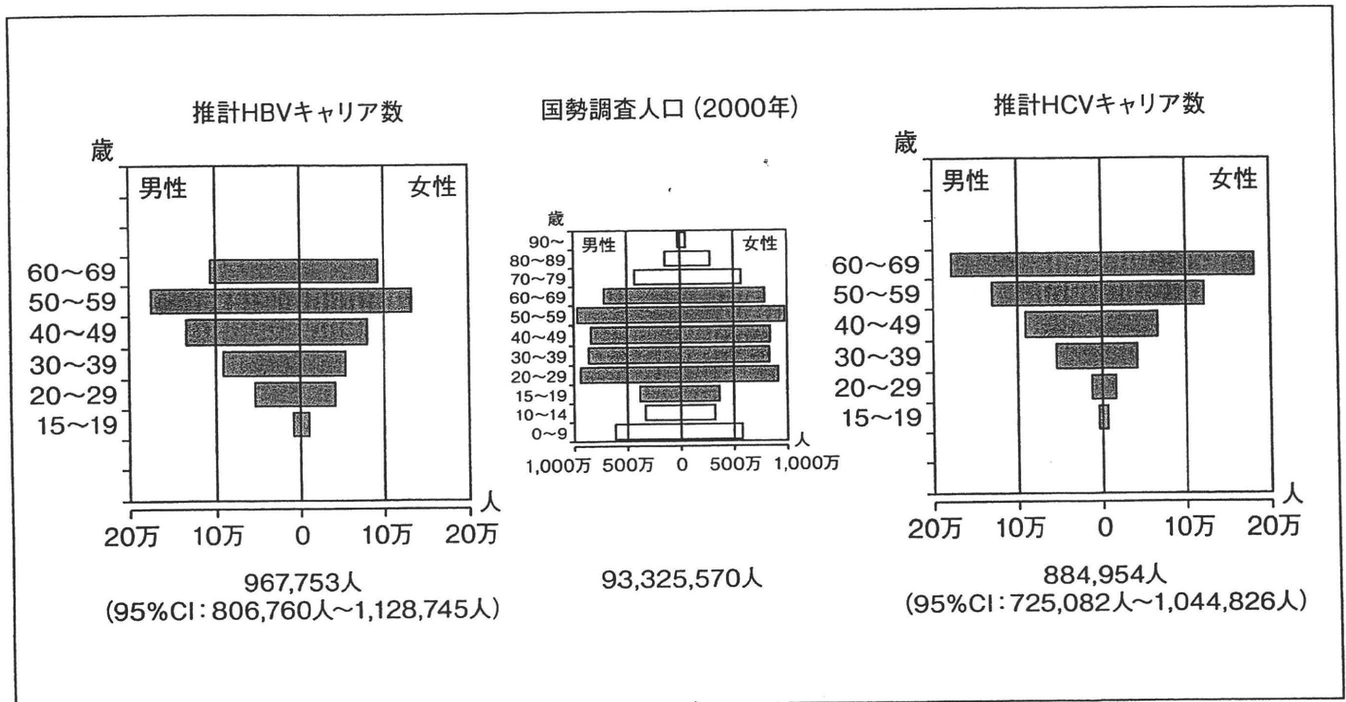


図5 わが国の人口ピラミッドと各年齢階級別にみた推計HBVキャリア数，HCVキャリア数 —15〜69歳の年齢層における推計値—

似値を得ることはやや困難と考える.

一方，後者については，前項で示した日赤血液センターにおける献血者からみた年齢階級別のHBs抗原陽性率，HCV抗体陽性率と，HCV抗体陽性者の中に占めるHCVキャリア率(HCV抗体陽性者の70%)および，国勢調査資料から得られる年齢階級別人口から算出が可能[4]である．以上のことから，後者，すなわち「自覚症状がないまま社会に潜在している」HBVキャリア数，HCVキャリア数について推計したもの[4]を，2000年の時点におけるわが国の人口ピラミッドと併せて図5に示す.

2000年時点の15歳から69歳の人口約9,332万人の中に，本人が自覚しないままの状態で社会に潜在しているHBVキャリア数は96.8万人(80.7〜112.9万人：95%信頼区間)，HCVキャリア数は88.5万人(72.5〜104.5万人：95%信頼区間)と推計された．なお，この中には病・医院

● *肝発癌のリスクが高いと考えられる年齢層(40〜69歳)において,「本人が自覚しないままの状態で社会に潜在している」キャリアの推計値は,71.4万人(HBV),75.9万人(HCV).*

へ通院もしくは入院しているウイルス肝炎の患者は含まれていないこと,また,献血時の問診により肝炎ウイルスに感染しているリスクのある人などはあらかじめ除外されることから,ここに推計したキャリア数は実態よりもやや低く見積もる可能性がある.しかし,約350万人にのぼる大規模調査の感染率を基に推計したキャリア数をbaseに,「通院・入院患者数」,「70歳以上の年齢層におけるキャリア数」などを加算することで,わが国のキャリア数全体を概算することができる.

2002年度から開始された肝炎ウイルス検診の対象年齢であり,肝発癌のリスクが高いと考えられる40歳から69歳の年齢層に限って,キャリア数を算出すると,当該人口約5,100万人中にHBVキャリアは71.4万人,HCVキャリアは75.9万人となった.これは,推計したキャリア数全体のそれぞれ,73.8%,85.8%と高率を占め,この年齢層にキャリアが偏在している[5]ことがわかる.また,図表には示していないが,推計キャリア数を地域別にみると,人口密度の高い関東地区,近畿地区,九州地区に多いことが明らかとなっている[5].

人口10万人あたりの肝癌死亡数は西日本地域で高い値を示したが,2006年当該死因による死亡実数33,662人のうち,大阪3,014人,東京2,851人,福岡2,024人,兵庫1,857人,神奈川1,782人,埼玉1,479人であり,前述の地域と重なることがわかる.

一方,広島県赤十字血液センターにおいて献血を契機に見出されたHCVキャリアに対する初診時の肝臓専門医による臨床診断の成績から,約52%が慢性肝炎と診断され,かつそのうち半数は初診後ただちに治療を開始したこと[6]からも,検診などを契機にみつかった自覚症状がないキャリアに対する診断・治療を的確に行う必要があると考えられる.

おわりに

わが国では,HBV母子感染予防対策事業による若年者集団(22歳以下)におけるHBVキャリア率の低下や,輸血用血液の安全性の向上などに加え,過去10年余にわたる広汎な血清疫学的調査[7]の結果から,特別な場合[8,9]を除き,新たなHBVキャリア,HCVキャリアの発生が低率である[10,11]ことが明らかとなっている.

これらの疫学的根拠と肝炎,肝癌治療の進歩を背景に,肝癌死亡の減少をめざしたキャリア対策の一環として,2002年から40歳以上の地域住民を対象とした肝炎ウイルス検査が開始されている.厚生労働省担当課の集計では,5年間にHBVキャリア100,983人,HCVキャリア99,950人が見出されている(受診者はそれぞれ約870万人,約863万人)が,肝炎ウイルス検診受診率,検診により見出されたキャリアの病・医院受診率は必ずしも十分ではない状況であることなどから,2008年度以降,国は医療補助も含めて「新し

い肝炎総合対策」を推進している状況にある．

今後は，地域・年齢ごとに潜在・偏在するキャリアの分布を念頭において，肝炎ウイルス検診の実施体制も含めた受診率の向上，キャリアの拾い上げから適切な治療に至る組織的な対応策を地域単位で確立し，実施に移すことが求められている．

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透析医療施設における HCV 感染対策

田中 純子[1)]，熊谷 純子[1)]，小宮 裕[1)]，
頼岡 徳在[2)]，吉澤 浩司[3)]
[1)] 広島大学大学院 疫学・疾病制御学
[2)] 広島大学大学院 腎臓病制御学
[3)] 広島大学 名誉教授

◆1．はじめに

これまでの調査から，近年の我が国の一般集団におけるC型肝炎ウイルス（HCV）の新規感染は，ごく稀に起こるに過ぎないことが明らかになっている[1)2)]．しかし，透析医療施設など日常的に観血的処置を行っている医療現場におけるHCV感染のリスクは，国際的にみても高い値を示すことが知られており[3)]，感染予防対策を立てることが必要とされている．

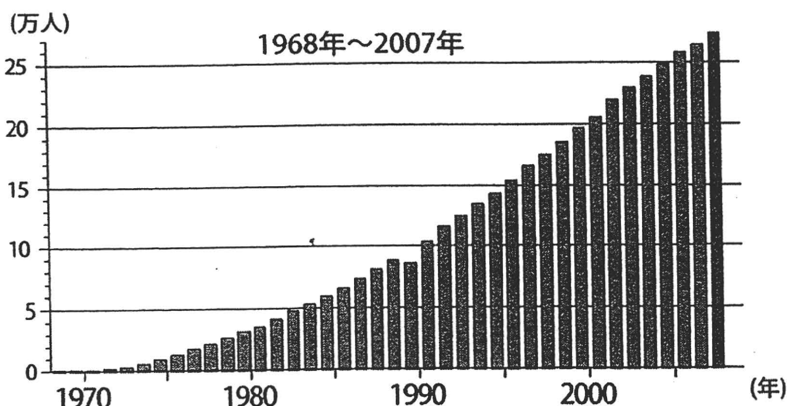

図1　わが国の透析患者数の推移（文献[6)]より作図）

HCV感染とB型肝炎ウイルス（HBV）感染は，血液を介する感染であること，ウイルスの持続感染状態（キャリア）を持つこと，肝発がんとの関連が認められることなどの共通点が認められるが，C型肝炎ウイルスはRNA型，B型肝炎ウイルスはDNA型のウイルス構造を呈し，その感染病態は大きく異なる．

HCVに感染した場合，その70％前後がキャリア化することから，閉鎖された集団において感染のリスク行為が繰り返された場合，感染源としてのHCVキャリアが累積し最終的には，その集団内にHCVの感染爆発がおこることが，田辺らの調査成績[4)]から明らかとなっている．

本稿では，HCVキャリア率が高い環境下で観血的処置を繰り返すことから，感染発生のリスクが高いことが知られている透析医療施設における実態を把握することを目的とした前向き調査の成績[5)]と，感染予防対策のあり方，およびパイロットスタディの結果について紹介してみたい．

◆2. 慢性透析患者数の推移

日本透析医学会の統計調査委員会から出されている資料[6)]によると，慢性透析療法を受けている患者数はこの20年間，年々1万人余ずつ増え続けており，2007年末の時点における患者数は27万5119人に達していることが明らかとなっている（図1）．また，透析導入に至った原因疾患は1998年を境に糖尿病性腎症が第一位となり，2007年には全体の43.4％を占めるに至っていることが明らかとなっている（慢性糸球体腎炎24.0％）．

◆3. 血液透析患者集団におけるHCVキャリア率

著者らは，透析医療施設におけるHCV感染の実態を把握し，その感染予防対策を確立することを目的として3年余にわたる前向き調査を行った．1999年11月から3ヵ月ごと，計14回にわたっ

表1　調査時期および対象者数（男女別）

調査	調査時期	全体対象者数	男性			女性		
			対象者数	年齢（歳）	透析歴（年）	対象者数	年齢（歳）	透析歴（年）
1	1999年11月	1,664	989	59.3 ± 12.9	6.1 ± 6.5	675	61.8 ± 12.7	6.4 ± 6.2
2	2000月 2月	1,677	993	59.4 ± 12.9	6.3 ± 6.6	684	61.8 ± 12.7	6.5 ± 6.3
3	5月	1,712	1,019	59.5 ± 13.0	6.3 ± 6.5	693	61.9 ± 12.8	6.6 ± 6.4
4	8月	1,736	1,027	59.8 ± 13.0	6.3 ± 6.5	709	62.0 ± 12.7	6.6 ± 6.3
5	11月	1,775	1,044	60.0 ± 13.0	6.3 ± 6.5	731	62.3 ± 12.7	6.5 ± 6.4
6	2001年2月	1,808	1,071	60.4 ± 13.0	6.3 ± 6.5	737	62.6 ± 12.7	6.6 ± 6.4
7	5月	1,820	1,080	60.6 ± 12.8	6.4 ± 6.6	740	62.6 ± 12.9	6.6 ± 6.3
8	8月	1,758	1,046	60.5 ± 12.7	6.6 ± 6.6	712	62.7 ± 12.8	6.8 ± 6.4
9	11月	1,774	1,051	60.7 ± 12.8	6.5 ± 6.6	723	63.0 ± 12.6	6.8 ± 6.4
10	2002年2月	1,805	1,060	61.0 ± 12.9	6.6 ± 6.6	745	63.2 ± 12.7	6.8 ± 6.4
11	5月	1,842	1,082	61.2 ± 12.8	6.6 ± 6.7	760	63.3 ± 12.8	6.8 ± 6.4
12	8月	1,859	1,091	61.4 ± 12.7	6.7 ± 6.7	768	63.3 ± 12.8	6.9 ± 6.4
13	11月	1,870	1,094	61.7 ± 12.7	6.7 ± 6.7	776	63.4 ± 12.9	6.8 ± 6.5
14	2003年2月	1,882	1,103	61.7 ± 12.7	6.8 ± 6.8	779	63.6 ± 13.0	6.9 ± 6.6
	全調査期間を通じた対象者数	2,744	1,613	63.3 ± 13.1	6.7 ± 6.4	1,131	65.7 ± 13.2	6.7 ± 6.5

て9つの透析医療施設の全患者を対象としてHCVマーカーを統一的に測定し，HCVキャリア率，HCVの新規感染発生率を算出した．調査対象者数は個人の重複を除くと計2,744例であるが，調査期間内には患者の新規参入と転院，死亡等による離脱があるため，対象者数は調査回ごとに異なっている．それぞれの調査回ごとの対象患者数，平均年齢，平均透析期間は**表1**に示した通りである．平均年齢，平均透析期間のいずれも調査の経過とともに高齢，長期化している．

第14回目，2003年2月の時点におけるHCV RNA陽性者（HCVキャリア）率を年齢階級別に整理してみると（**図2**），HCVキャリア率は40歳以上の群ではいずれの年齢層も9～14％と高い値を示しており，40歳以上の年齢群間での際立った差は認められない．

一方，透析導入後の期間別に整理してみると（**図3**），透析期間が20年以上経過した群におけるHCVキャリア率は40％以上ときわめて高い値を示

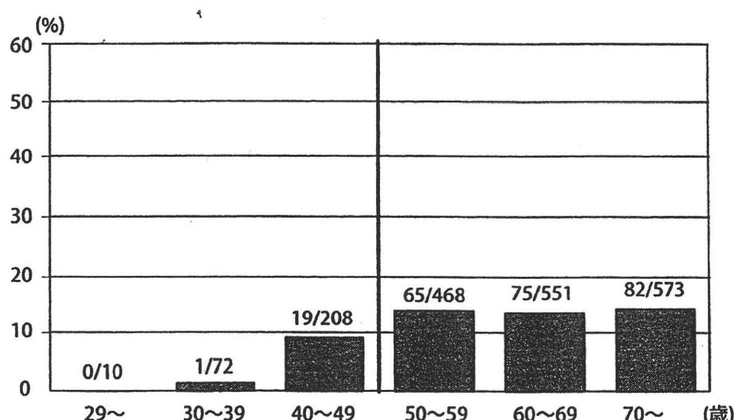

図2　年齢別にみたHCV RNA陽性率（2003.2 N =1,882）

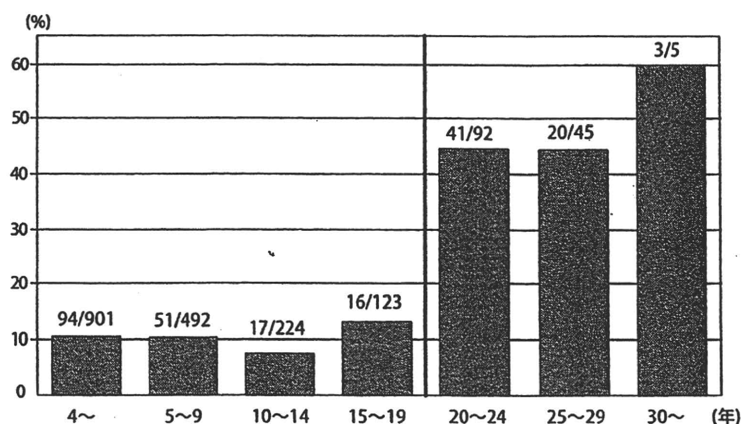

図3　透析開始後の年数別にみたHCVキャリア率（2003.2 N =1,882）

表2 透析導入後の期間別にみたHCV RNA陽性率および背景 調査14（2003年2月）1,882例

透析導入後の期間（年）	例数	HCV RNA 陽性者数（%）	透析導入年齢	輸血後肝炎	
				時期	発生率
30～	5	3(60)	56.0 ± 6.4	1968～1972	16.20%
25～29	45	20(44.4)	58.4 ± 6.9	1973～1977	9.60%
20～24	92	41(44.6)	56.9 ± 9.3	1978～1982	19.30%
15～19	123	16(13)	60.1 ± 10.9	1983～1987	12.30%
10～14	224	17(7.6)	58.7 ± 11.1	1988～1992	3.10%
5～9	492	51(10.4)	62.0 ± 13.3	1993～1997	およそ0%
0～4	901	94(10.4)	64.8 ± 13.3	1998～2002	およそ0%

1989 輸血用血液のHCV c100-3抗体スクリーニング導入
1990 ヒトエリスロポエチン（rHuEPO）健康保険適応
1992 輸血用血液のHCV抗体検査（第二世代）スクリーニング導入

していることがわかる．しかし，透析期間が20年未満の群においてもHCVキャリア率が10%前後の値を示し，これまでに得られている献血者集団や肝炎ウイルス検診受診群等の一般集団における年齢階級別にみた値[7),8)]と比較すると，目立って高い値を示していることがわかる．

そこで，透析導入時期と，それぞれの時期における輸血後肝炎発生率のデータ[9)]，および透析期間別にみたHCVキャリア率とを対比してみた（**表2**）．

Watanabe Jら（1993）によれば，わが国では1972年までは全輸血後肝炎例の約60%，1973年～1976年までは約80%，また，1977年～1987年には約96%がそれぞれHCVの感染に起因していたことが明らかとなっている[10)]．さらに1989年以降は，輸血用血液のスクリーニングのためにHBc抗体検査が追加導入され，輸血に伴うHBVの感染はほとんどみられなくなった．

一方，1989年11月からは第一世代のHCV C100-3抗体検査が，また1992年2月からは第二世代のHCV抗体検査が輸血用血液のスクリーニングのために取り入れられ，さらに1999年11月からは核酸増幅検査（Nucleic acid amplification test: NAT）が追加再入されたことにより，これ以降は輸血に伴うHCVの感染もほぼ駆逐されるに至ったことが明らかとなっている[11)]．1990年には，腎性貧血を改善するためのヒトエリスロポエチンが保険適用となった．

以上のように，血液の安全性が向上し，輸血に伴うHCV感染のリスクがほとんどゼロに近い状態となったことに加えて，エリスロポイエチンの導入により，輸血を受ける機会も減少した1990年以降に透析を開始した患者集団でもHCVキャリア率が10%前後と，高い値を示している．このことは，この集団内において，輸血以外の経路によるHCVの新規感染がその後も起こり続けていたことを示すものであると言える．

◆4. 血液透析患者集団におけるHCVキャリアの新規発生率と新規発生数の推移

調査開始時の検査でHCV抗体あるいはHCV RNAが陰性であり，かつ3ヵ月以上に亘る追跡が可能であった計2,114例の患者集団を対象として，前向きコホート調査を行った結果，3年間の調査期間内に16例のHCVキャリアの新規発生（0.33/100人年）が認められた[5)]．それぞれの調査時点におけるHCVキャリアの新規発生数の推移は**図4**に示した通りであり，調査回がすすむにつれて，その発生数は減少する傾向がみられている．これは，調査中に得られた結果をその都度それぞれの施設に報告し，毎年1～2回の検討会を開催し討議を行ったことにより，本調査がすすむにつれて，各施設においてHCVの感染予防に関する認識が深まり，透析環境の整備や改善，また，スタッフの感染予防への意識が高まったことの反映と考えることができる．

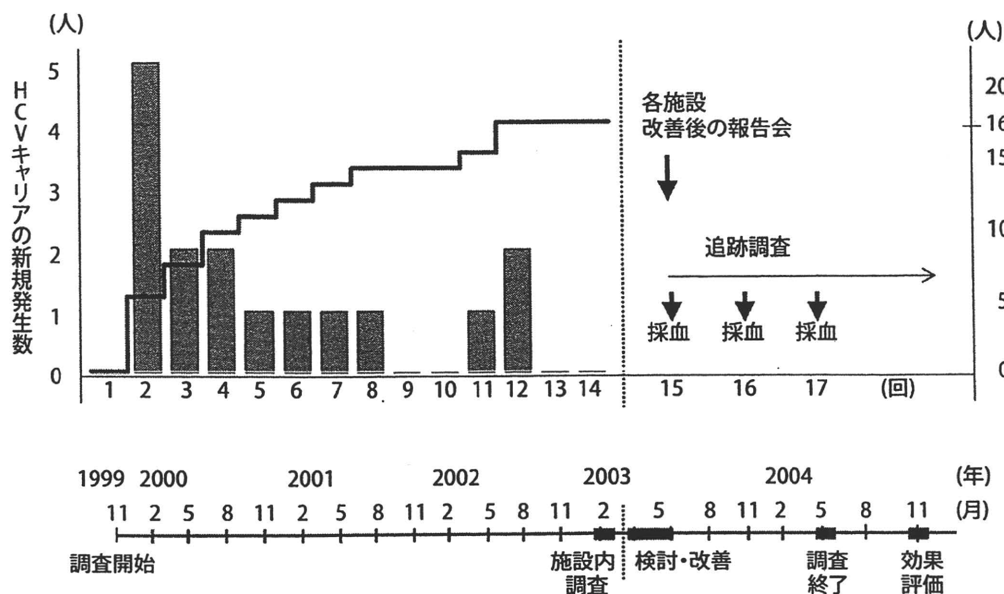

図4 血液透析患者集団におけるHCVキャリアの新規発生数および感染防止のための改善とその効果評価

◆ 5. 透析医療施設におけるHCV感染の防止のための介入とその効果評価

血液透析施設におけるHCVの感染防止対策は，「血液を介した汚染が起こる可能性のあるすべての経路を遮断すること」が基本となる．具体的には，透析室の環境整備，設備の改善，器具・機材の見直しと適切な配備，およびスタッフへの教育，訓練の実施などを挙げることができる（**表3**）．

透析室の環境整備，設備の改善としては，透析室の区域化，患者グループごとの使用ベッドの固定，ベッド間隔の確保，手洗い場の改善，廃棄物置き場の改善など，また，器具機材の見直しと適切な配備としては，コッヘルや駆血帯などの十分量，かつ適正な配備，透析開始時・終了時に使用する消耗品類のセット化などを挙げることができる（**表3**）．

また，スタッフへの教育，訓練は，各種の操作を行う際に，手指，器具，機材，およびカルテや筆記用具などを介した汚染が広がらないようにするための教育や訓練を，実際に即したわかりやすい教材[12]を効果的に用いて，定期的に繰り返して行うことが大切であると言える（**写真1～3**）．

2003年5月から7月にかけて，以上の対策を実

表3 血液透析施設におけるHCV感染防止のための指針

(1) 設備，環境などの見直しと改善
1) 透析室の区域化
2) 患者グループ毎の使用ベッドの固定
3) ベッド間隔の確保
4) 手洗い場の改善（→**写真1**）
・手洗い場の増設
・手動式カランから足踏み式，自動式カランへの変更
・ペーパータオルの設置
5) 廃棄物置き場の改善
・廃棄物運搬の動線距離の短縮
・清潔域と不潔域の区分の徹底
6) 器具，機材の改善
・透析回路をニードルレスタイプとする
・鉗子（コッヘル），駆血帯の適正配備（→**写真2**）
7) 消耗品のセット化
・透析開始時，終了時の消耗品のセット化
(2) スタッフへの教育、訓練
1) 清潔域，不潔域の区分の徹底
・清潔物と不潔物との扱いの習得
・清潔域，不潔域での各種操作手順の習得
2) 手洗いの意味とタイミングの習得
3) 手袋着脱の意味とタイミングの習得
4) 予防衣着脱の意味とタイミングの習得
5) 環境，機械，器具，用具を介した汚染拡大の防止法の習得 （→**写真3**）
・床，テーブル等の適宜清拭
・透析終了後ごとのコンソールの清拭
・記録用紙，ペン等を介した汚染拡大の防止
6) 写真集を用いた繰り返し講習の実施
・無菌操作の実際を習得