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○ 研究協力

「肝炎ウイルス感染者に対する偏見や差別の実態を把握し、その被害の防止のためのガイドラインを作成のための研究」班
代表　学習院大学法科大学院客員研究員（弁護士）龍岡 資晃

「生活集団の場における肝炎ウイルス感染予防ガイドラインの作成のための研究」班
代表　東京大学大学院生体防御感染症（医師）四柳 宏

全国老人福祉施設協議会
会長　中田 清

全国老人保健施設協会
会長　木川田 典彌

本調査票回答締切日　　平成25年7月12日（金）まで
※同封の返信用封筒にて、東京都健康長寿医療センター研究所・事務局まで、ご返信くださいますようお願い申し上げます。

1．あなた自身についてお伺いします。

性　別	1．男性　　2．女性
年　齢	1．20歳未満　2．20歳～29歳　3．30歳～39歳 4．40歳～49歳　5．50歳～59歳　6．60歳～69歳 7．70歳以上
職　種	1．医師・歯科医師　2．看護師・准看護師 3．薬剤師　4．介護職員（介護福祉士） 5．介護職員（ホームヘルパー）　6．介護職員（その他） 7．生活相談員（社会福祉士）　8．生活相談員（介護支援専門員） 9．生活相談員（その他）　10．リハビリテーション関連職種 11．管理栄養士・栄養士　12．調理師 13．事務職員・その他職員
雇用形態	1．常　勤　　2．非常勤（パート、アルバイトを含む）
勤務形態	1．日勤のみ　　2．夜勤のみ　　3．日勤と夜勤両方ある
経験年数 ※現在の職種に就いてからの延べ年数をお答え下さい。	1．1年未満　2．1年～2年 3．3年～5年　4．6年～10年 5．11年～15年　6．16年～20年 7．20年以上

2．あなたは以下の感染症について、どの程度の理解がありますか。また、それらを保有する利用者を介護、看護するにあたってどのような意識をお持ちですか。それぞれについて、主観的に1つお答えください。

	理解について			介護、看護への意識について		
	よく知っている（感染経路や治療方法を知っている）	少し知っている	ほとんど知らない（名前を聞いたことがある程度）	まったく抵抗感を感じない	少し危険に感じ、抵抗感を感じることがある	自分自身に感染するのではないかと危険に感じる
（例）肺炎	1	②	3	1	②	3
1．インフルエンザ	1	2	3	1	2	3
2．ウイルス性胃腸炎（ノロウィルスを含む）	1	2	3	1	2	3
3．B型肝炎	1	2	3	1	2	3
4．C型肝炎	1	2	3	1	2	3
5．エイズ	1	2	3	1	2	3
6．結核	1	2	3	1	2	3
7．疥癬（かいせん）	1	2	3	1	2	3
8．MRSA感染症	1	2	3	1	2	3
9．多剤耐性グラム陰性桿菌感染症（緑膿菌、アシネトバクターなど）	1	2	3	1	2	3

3-1. あなたが所属する施設内における経験についてお伺いします。手袋をしている状態で以下のことをどの程度経験したことがありますか。それぞれについて、1つお答えください。

	まったくない	今までに1～2度ある	年に1回程度ある	年に2回以上ある
1. 血液を混じた嘔吐物、喀出物に触れる	1	2	3	4
2. 下血に触れる（痔出血、下血）	1	2	3	4
3. 外傷に触れる	1	2	3	4
4. 医療関連事故（針刺し等）	1	2	3	4
5. 患者に噛まれる	1	2	3	4

3-2. 手袋をしていない状態で以下のことをどの程度経験したことがありますか。それぞれについて、1つお答えください。

	まったくない	今までに1～2度ある	年に1回程度ある	年に2回以上ある
1. 血液を混じた嘔吐物、喀出物に触れる	1	2	3	4
2. 下血に触れる（痔出血、下血）	1	2	3	4
3. 外傷に触れる	1	2	3	4
4. 医療関連事故（針刺し等）	1	2	3	4
5. 患者に噛まれる	1	2	3	4

4. あなたは以下の標準的予防対策（スタンダード・プリコーション）について、どの程度実施していますか。それぞれについて、あてはまるもの１つお答えください。

＊仕事上、利用者と直接接する機会が全くない場合は、次ページ問５へお進みください。

	必ず実施する	ほとんど実施する	ときどき実施する	たまに実施しない	ほとんど実施しない
手洗いについて					
1. 血液や排泄物に接触したら衛生学的手洗い※を行う（※速乾性すり込み式手指消毒剤の使用や、指輪や腕時計を外し手首まで洗うことを意味します）	1	2	3	4	5
2. 同一利用者でも、感染の可能性があると感じるものに接触したら、処置の度に手洗いを行う	1	2	3	4	5
3. 手洗い時、センサー等を利用して、蛇口の栓に直接手を触れずに開閉している	1	2	3	4	5
4. タオルの共有を避け、ペーパータオルを使用している	1	2	3	4	5
手袋、ガウン、マスク等について					
1. 血液や排泄物に触れるときは、その度に手袋、ガウン、マスク等を着用・交換している	1	2	3	4	5
2. 使用済み手袋、ガウン、マスク等は所定の方法で処理している	1	2	3	4	5
3. 白衣は適宜交換し、清潔を保つように心がけている	1	2	3	4	5
4. 自分自身に咳が出ているときは、マスクを着用している	1	2	3	4	5

	必ず実施する	ほとんど実施する	ときどき実施する	たまに実施しない	ほとんど実施しない
利用者への対応について					
1. 結核等が疑われる利用者は、特定の感染対策がなされた区域に隔離している	1	2	3	4	5
2. 飛沫感染の疑いのある利用者を他の利用者と隔離できない場合は、パーテーションで区切るなど十分に空間的分離を行っている	1	2	3	4	5
3. 飛沫感染のおそれのある利用者の移送は極力制限し、必要に応じて利用者にマスクを着用させている	1	2	3	4	5
4. 飛沫感染の疑いのある利用者の手が日常的に触れる居室内の部位は消毒用アルコールで清掃している	1	2	3	4	5
5. 飛沫感染の疑いのある利用者が触れた施設内の場所は消毒用アルコールで清掃している	1	2	3	4	5
6. 吐物処理に関しては塩素系消毒薬を使用している	1	2	3	4	5

5. あなたは以下の検査を行なったことがありますか。またご自身の感染状態を把握していますか？それぞれについて、1つお答えください。

	検査をしたことがない	検査をしたことがあるが、結果を忘れている	検査をしたことがあり、結果を知っている	検査をしたかどうかわからない
1. B型肝炎抗原(HBsAg)	1	2	3	4
2. B型肝炎抗体	1	2	3	4
3. C型肝炎抗体	1	2	3	4
4. エイズ(HIV)抗体	1	2	3	4

6. あなたの健康管理についてお伺いします。

6-1. 今までにＢ型肝炎ワクチンの接種を行った事がありますか。	1. はい　2. いいえ 6-2 へ　3. わからない
6-2. Ｂ型肝炎ワクチン接種を行ったのは約何年前ですか。	約　　年前 6-3 へ
6-3. 接種したきっかけ（動機）は何ですか。	1. 所属施設ですすめられた 2. 自発的に接種した 3. その他（　　） 6-4 へ
6-4. この１年間（平成 24 年４月～平成 25 年３月）に定期健康診断（胸部レントゲン検査を含む）を受診しましたか。	1. はい　2. いいえ

6-4 へ

7. あなたは感染症に関する知識を得る際に、参考にしているものについて、それぞれあてはまるものを１つお答えください。

	よく利用する	たまに利用する	あまり利用しない	全く利用しない
1. 専門医学雑誌・教科書	1	2	3	4
2. 従事している施設内部の研修会	1	2	3	4
3. 従事している施設外部の研修会・勉強会・講演会	1	2	3	4
4. 施設職員	1	2	3	4
5. 家族	1	2	3	4
6. 新聞・情報雑誌	1	2	3	4
7. テレビ・ラジオ	1	2	3	4
8. 国や地方公共団体等の公的な HP 等のインターネット	1	2	3	4
9.「８」を除く HP 等のインターネット	1	2	3	4

以上で質問は終わりです。ご協力誠にありがとうございました。

Ⅲ. 研究成果の刊行に関する一覧表

平成24年度 厚生労働科学研究費補助金難病・がん等の疾患分野の医療の実用化研究事業（肝炎関係研究分野） 「集団生活の場における肝炎ウイルス感染予防ガイドラインの作成のための研究」

研究成果の刊行に関する一覧表

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2．総説

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Ⅳ. 主　要　論　文

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Review Article

Infection Control in Healthcare Settings in Japan

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ABSTRACT

In Japan, the practice of infection control in healthcare settings has a short history of less than 3 decades. Before that, infection control practices were far from perfect and even ignored. This review summarizes changes in infection control in Japan since the 1980s and offers some comparisons with practices in foreign countries, especially the United States. Infection control is far better now than 25 years ago, but there remain fundamental issues that limit the development of better infection control practices. These problems include insufficient funding and human resources due to the socialized healthcare insurance system in Japan and the lack of interest in infection control research.

Key words: healthcare-associated infection; infection control; healthcare insurance system

INTRODUCTION

In Japan, infection control in the healthcare setting was not an organized endeavor until the founding of a society for infection control (Japanese Society for Environmental Infections, JSEI) in 1986.[1] During my medical education in the mid-1980s, there was no instruction in infection control. The idea of universal precautions, which became popular in healthcare settings in Western countries, had not yet been introduced to Japan, and procedures with some risk of exposure to blood-borne pathogens, such as phlebotomy and peripheral line insertion, were often done without gloves. This was during the time when methicillin-resistant *Staphylococcus aureus* (MRSA) became prevalent throughout Japan, especially in postoperative patients. Many had diarrhea with a MRSA-positive stool culture, which was diagnosed as MRSA enterocolitis. This disease entity is still debated, but that situation led to the development of a relevant infection control strategy in Japan, something that had never existed before. The key events since 1986 are listed in Table 1. In this article, I describe the changes in infection control in Japan during the last 25 years and discuss the present situation and challenges we currently face.

Table 1. Key events in infection control in Japan

1980s	Increase in the incidence of healthcare-associated MRSA infection
1986	Founding of JSEI
1993	Infection control department established at The University of Tokyo Hospital (first in Japan)
1999	Nationwide surveillance of surgical site infections by JSEI
2000	Nationwide surveillance of multidrug-resistant organisms by MHLW
2000	832 MD and PhD staff certified as Infection Control Doctors (ICD)
2001	18 nurses certified as Infection Control Nurses (ICN)
2004	Mandatory assignment of dedicated infection control personnel at Advanced Treatment Hospitals
2010	Revision of medical reimbursement system: implementation of additional reimbursement for advanced infection control management

The infection control team

For effective infection control, it is necessary to combine personnel who spend a specified fraction of their time—usually expressed in full-time equivalents (FTEs)—on infection control. Therefore, teamwork among infection control personnel is very important. The infection control team (ICT) is a very popular concept among healthcare workers in Japan, in contrast to the situation in the United States, where members of each profession (physicians, nurses, pharmacists, microbiologists, etc) work independently for infection control and are responsible for their designated, specialized areas. Although Japanese law does not require hospitals to have ICTs, they must have an infection control committee (ICC) that includes the chairperson and executive officers of the hospital. The ICC makes the final decisions regarding infection control programs, but this is often just an endorsement.

Program establishment and practice are led by the ICT, which conducts surveillance of multidrug-resistant pathogens and device/procedure-associated infections such as bloodstream infection (BSI), urinary tract infection (UTI), and surgical site infection (SSI). Other activity includes ward audit (rounds), education of healthcare personnel, adherence

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monitoring of hand hygiene and other infection control practices, and investigation of possible outbreaks. The ICT develops and revises infection control policy in their hospital. The work volume is too great for a single individual; thus, the ICT is essential for infection control activities.

Surveillance

Until the mid-1990s, interest in surveillance was very low. Only a small group of people who learned and were inspired by US infection control practices conducted surveillance at the hospital level. In 1998, the JSEI established a surveillance system in Japan, the Japanese Nosocomial Infections Surveillance (JNIS). The system was based on the US National Nosocomial Infection Surveillance (NNIS) system with some modifications and initially focused on SSIs. Eight hospitals participated initially, and more hospitals joined later. Currently, approximately 50 hospitals send their data to the system each year. Aggregated data are analyzed, and feedback is sent to the hospitals by emails that provide detailed data on the respective hospitals and the overall system. Aggregated data are presented at US meetings such as those of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Discussion of data collection, analysis, and other issues related to SSI surveillance takes place at an SSI surveillance meeting, which has been held twice a year since 2002.

The Japanese Ministry of Health, Labour and Welfare (MHLW) administers another surveillance system, the JApan Nosocomial Infection Surveillance (JANIS), which was developed as a public health service and mainly focuses on collecting data on nosocomial infection by multidrug-resistant organisms (MDROs) such as MRSA, although the system was based on similar components in the NNIS system. The main elements are a laboratory component and a hospital-wide MDRO component. For the intensive care unit (ICU) component, hospitals collect device-associated infection data. The denominator of the infection rate was initially device-days but was changed to patient-days of the targeted ICUs. This change was based on data showing that the infection rate was similar using device-days and patient-days as the denominator in this surveillance system.[2] However, this modification made Japanese data incompatible with data from other countries, such as the United States, where device-days remains the denominator in this form of surveillance.

The JNIS system was renamed JHAIS (Japanese Healthcare-associated Infections Surveillance) in 2008 and began monitoring device-associated infection (ie, central line-associated BSI, catheter-associated UTI, and ventilator-associated pneumonia) as well. Approximately 20 hospitals participate in this system.

The professional community

JSEI was established in 1986 with only 231 members. In 2011, only 25 years after its founding, it has more than 6000 members. Among the 3984 members who disclose their occupation to the Society, most are registered nurses (42%). The proportions of physicians, pharmacists, and clinical laboratory technologists are 19%, 16%, and 8%, respectively. Recent annual meetings have attracted more than 5000 attendees, which exceeds the attendance of any of the 3 major Western healthcare epidemiology organizations, ie, the Association for Professionals in Infection Control and Epidemiology (APIC), SHEA in the United States, and the Hospital Infection Society (HIS) in the United Kingdom.

JSEI activity includes an annual meeting (in February) and publication of a journal (6 issues per year). It also has several committees, including editorial, educational, and international committees. The first training course for healthcare epidemiology was held in 2009 by the educational committee.

The organization responsible for the diagnosis and treatment of infectious diseases in Japan is the Japanese Society for Infectious Diseases. The Japanese Society for Chemotherapy oversees antimicrobials, and the Japanese Society for Microbiology is responsible for clinical microbiology.

Certification

Japan has 4 specialized certifications in infection control for different occupations.

Certified Nurse for Infection Control (CNIC)

The Japanese Nursing Association accredits this certification, which requires 6 months of intensive study at a designated educational institution in Japan and a passing grade on the certification examination. Eighteen nurses were certified after the first examination, in 2001, and as of July 2011 there are 1364 CNICs in Japan. In 2011, 10 institutions offer education for this certification. The curriculum in infection control is comprehensive and includes surveillance, practice, microbiology, and planning of infection control programs in healthcare facilities.

Infection Control Doctor (ICD)

The Committee for the ICD accredits this certification. Candidates must be a medical doctor (MD), or have a PhD in a healthcare field, for more than 5 years, be a member of a society approved by the Committee, have experience in infection control in a healthcare setting, and have proof of participation in educational meetings or scientific conferences. An examination is not necessary for certification. A certified ICD is expected to lead infection control activities in a hospital, with the support of the members from each healthcare profession (ie, physicians, nurses, pharmacists, and microbiologists) and administrative staff. In the first year, 2000, a total of 832 persons were certified; as of January 2010, 6815 have been certified.

Board-Certified Infection Control Pharmacy Specialist (BCICPS)

The Japanese Society of Hospital Pharmacists (JSHP) accredits BCICPS certification. Candidates for certification

must: be a licensed pharmacist, be a member of the JSHP, be a certified ICD, be named as an author in 3 abstracts for designated scientific conferences in the pharmacy field (and as first author in at least 1), have 2 publications in the field of infection control (and as first author in at least 1), and pass an examination. Forty pharmacists were certified in the first year, 2005, and 219 have been certified as of April 2011.

This certification system was aimed to designate pharmacists who are routinely involved in infection control activities, provide instruction to the next generation of pharmacists in infection control, and conduct research in the field. However, because the requirements for certification are very high, a new category was created in 2008, namely, Board-Certified Pharmacist in Infection Control (BCPIC), which is less advanced than the BCICPS. Ninety-four pharmacists were certified in the first year, and 364 have been certified as of October 2010.

Infection Control Microbiological Technologist (ICMT)

The Japanese Society for Clinical Microbiology (JSCM) accredits ICMT certification. Candidates must be a clinical technologist and a member of the JSCM and be active in infection control practices in a healthcare setting, among other requirements. In the first year, 2006, 253 technologists were certified, and 411 have been certified as of January 2011.

Public organizations and agencies

The Centers for Disease Control and Prevention (CDC) in the United States and the Health Protection Agency (HPA) in the United Kingdom are 2 of the most famous organizations in the world. At the national level in Japan, infection control in healthcare settings is under the jurisdiction of the Medical Service Division, Health Policy Bureau, MHLW. This division has technical and administrative officers whose main role is to manage rules and regulations, such as laws and bylaws. The National Institute of Infectious Diseases (NIID) is expected to support the MHLW both technically and scientifically and is equivalent to the US CDC and HPA. NIID is designed to function as a research laboratory for various pathogens, a reference laboratory for nationwide research on microbiology, and a laboratory for investigation of numerous drugs, blood products, and vaccines. There is no designated section in NIID for infection control in healthcare settings. It is therefore impossible to create official guidelines for healthcare-associated infections (HAIs) or lead HAI surveillance. Regarding epidemiologic investigation of HAIs, the Field Epidemiology Training Program (FETP) in the NIID investigated approximately 10 HAI outbreaks caused by pathogens such as vancomycin-resistant *Enterococcus*, multidrug-resistant *Pseudomonas aeruginosa* (MDRP), and *Clostridium difficile*. The FETP is a 2-year intensive course in field epidemiology.

Laws and rules

The Japanese healthcare system is regulated by the Medical Service Act (*Iryou-hou* in Japanese). In the 2007 version of the Act, healthcare safety is a primary goal for every hospital and clinic. In addition, in the Ordinance for Enforcement of the Medical Service Act (*Iryou-hou shikou kisoku*), prevention of HAIs is expressly included as part of healthcare safety. Health centers must establish an HAI policy in each facility, form a committee for HAI prevention, educate employees, and take part in HAI surveillance and reporting. It also requires advanced treatment hospitals (ATHs) and teaching hospitals to establish an HAI prevention department and designate a person(s) to staff the department. This regulation is mandatory, and penalties may apply in cases of intentional violations.

Reimbursement

The costs of HAI prevention are paid by hospitals, and, until recently, no reimbursement was given for superior HAI prevention practices. In addition, reimbursement for treatment of HAIs was equal to that of the respective infectious disease, which meant that there was no incentive to implement better HAI prevention practices.

In 1996, hospitals with good infection control practices began to receive an additional reimbursement of 50 yen (0.6 USD) per patient per day. The requirements for this additional reimbursement were minimal, so, within 2 years, 70% of Japanese hospitals had applied for it. In 2000, this reimbursement policy was discontinued and replaced with a new system of penalties for hospitals with insufficient infection control practices. This policy was also discontinued, in 2006.

In 2010, as part of healthcare safety, a reimbursement of 1000 yen (12 USD) per patient per admission was introduced. Before this policy was begun, most hospitals in Japan did not give physicians or CNICs a designated time period for infection control. If a hospital wishes to receive the reimbursement, it must pay the annual cost for the designated work hours for a physician (a salary of 0.5 full-time equivalents [FTEs], about 4 million yen) and a nurse (a salary of 0.8 FTEs, about 4 million yen), which equals approximately 8 million yen (Table 2). This is roughly equal to the amount that would be reimbursed for a hospital with 300 beds and an average length of stay of 15 days. Therefore, generally speaking, this incentive is attractive for hospitals with more than 300 beds but not for those with fewer beds. There are no data on the number of hospitals that have applied for this reimbursement.

Guidelines

Due to the situation regarding the public organization that oversees infection control, there is no official guideline published by the government. The MHLW has a research fund that it is distributed to selected research groups, which create documents similar to guidelines. These are usually prepared based on guidelines published by the CDC with

Table 2. Requirements for additional reimbursement (April 2010)

Division of infection control
Infection control team in division, consisting of the following:
(1) At least 1 infection control nurse with designated training experience and at least 1 infection control physician with designated infection control experience (1 with >80% FTE; the other with >50% FTE)
(2) Infection control pharmacist and infection control microbiology technologist, both with experience in infection control
Policy regarding duties of infection control team
Hospital infection control policy must be distributed to all wards and divisions
Educational lecture for all staff, at least twice a year
Antimicrobial stewardship program

some modifications. Furthermore, research in this field is limited in Japan, so the country has very few data of its own. Therefore, documents published by these groups are more like expert opinions.

Scientific societies and professional organizations have important roles to play. In 1990, the JSEI published *A Guide for the Prevention of Hospital Infection*, the first publication of its kind in Japan. In 2001, the Japanese Nursing Association published *A Guidebook for Infection Control*, which was followed by the *Guideline For Hospital Infection Control* and the *ICD Textbook*, published by the Committee for National University Hospitals and the Committee for the ICD, respectively. These publications are updated regularly and are widely used in the Japanese infection control community. In addition, numerous commercial-based documents have been published.

Education

In general, infection control personnel in hospitals are certified, experienced, and knowledgeable and are responsible for teaching infection control practices to other healthcare workers. The Health Service Act mandates education sessions in every hospital and clinic, and a supplemental document published by the MLHW specifies that the sessions should be held more than twice a year. To fulfill this requirement, large hospitals hold education sessions within their facility; however, in smaller hospitals and clinics, this might be difficult. As an alternative, they can subsidize healthcare workers to attend seminars hosted by a local government, society, university hospital, or even a private company. There are numerous seminars on infection control throughout Japan. However, because many are held in large metropolitan areas, their geographical distribution is uneven.

Education for certification in infection control is provided by each accrediting body, but there is no education in healthcare epidemiology in Japan. Many universities regard infection control as a clinical practice rather than a field of study and do not have a department of infection control in their (graduate) school of medicine. As a result, healthcare epidemiology is made light of by the medical community and is not regarded as fundamental to infection control. The JSEI held its first healthcare epidemiology training course in Japan in 2009. About 50 infection control professionals attended the session, and it will now be held annually. This might increase the number of professionals who are able to conduct high-quality studies in infection control.

Research

Few publications by Japanese researchers in infection control have been published in English. There are several possible reasons for this, namely (1) not many universities have a department of infection control, which means that even in university hospitals, there is inadequate staffing, funding, and time allocated for research, (2) Japan's socialized health insurance system limits staffing and funding resources for infection control, (3) there are few educational opportunities in healthcare epidemiology, and (4) although research groups receive funding from the MHLW, this funding is closely related to government policy, and the areas of interest are limited.

The media and the general public

The media often react hysterically to clusters or outbreaks of multidrug-resistant organisms. For example, in September 2010, a university hospital in Tokyo had an outbreak of multidrug-resistant *Acinetobacter baumannii*. The media reported the case and related issues in the headlines for 1 week and then suddenly stopped covering it, presumably because they had become disinterested. The reporting during that week was full of sensationalism and lacked a scientific understanding of the situation. Indeed, the outbreak was investigated by a scientific body and the police.[3] The Japanese authorities have a tendency to investigate events (and not only HAIs) from a punitive rather than a scientific perspective, and the general public has the same tendency. After the events described above, there were many anonymous online comments criticizing the university hospital.

Challenges in infection control practices in healthcare settings

The most serious fundamental problem in infection control is the lack of personnel assigned to infection control in hospitals. Under the socialized medical insurance system, hospitals tend to assign healthcare personnel to areas that produce direct revenue, and infection control is not such an area.

In the United States, the standard ratio of infection control personnel is about 1 per 250 beds. The figure among hospitals participating in the National Nosocomial Infections Surveillance system is about 1 per 115 beds.[4] However, there are limited data on personnel assigned to infection control. The MHLW conducted a survey of advanced treatment hospitals (*Tokutei Kinou Byouin*). There are 83 ATHs in

Japan, and most are affiliated with faculties of medicine. According to the *Disclosure of Practice Report From ATHs*, which was published in 2009,[5] there were 159 designated personnel in 83 ATHs that had a total of 72 178 beds. This means that, on average, there is 1 infection control specialist per 454 beds, which is far lower than the standard ratio in the United States. Among the 83 ATHs, only 10 had more than 1 specialist per 250 beds. ATHs with more than 1000 beds often had only 1 infection control specialist.

Another survey of healthcare facilities[6] found that, as of October 2008, there were 468 hospitals with more than 500 beds. Among them, 204 (44%) had 1 or more infection control specialist with an FTE of 0.8 or greater (ie, a person almost completely concerned with infection control), and 253 (54%) had 1 or more personnel with an FTE of between 0.2 and 0.8. Eleven hospitals (2%) had no designated personnel. These data show that even in ATHs, which have the resources to assign personnel working in the faculty of medicine (ie, people not employed by the hospital) to infection control in the hospital, few personnel were actually assigned to infection control. The situation in non-AHTs is likely to be much worse in terms of human resources.

Beginning in April 2010, a new reimbursement system came into effect. This gives a hospital about 12 USD per patient if it fulfils MHLW requirements regarding infection control, which mandate an infection control nurse and infection control physician (one at 0.5 FTE; the other at 0.8 FTE), a pharmacist (0.5 FTE), and a microbiologist (0.5 FTE). This revision favors larger hospitals, which are better able to fulfill the requirement and thus receive the reimbursement. Considerable changes in infection control practices are anticipated.

Summary

The present author's experience visiting many US hospitals suggests that infection control practices in Japanese hospitals are as good as those in US hospitals. However, Japan is far behind in terms of research and data collection. More attention and funding are therefore required in these areas.

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MAJOR ARTICLE

Tears From Children With Chronic Hepatitis B Virus (HBV) Infection Are Infectious Vehicles of HBV Transmission: Experimental Transmission of HBV by Tears, Using Mice With Chimeric Human Livers

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(See the editorial commentary by Heiberg and Hogh, on pages 464–5.)

Background. Body fluids such as saliva, urine, sweat, and tears from hepatitis B virus (HBV) carriers are potential sources of HBV transmission.

Methods. Thirty-nine children and 8 adults who were chronically infected with HBV were enrolled. Real-time polymerase chain reaction was used for the quantification of HBV DNA.

Results. HBV DNA was detected in 73.7% of urine samples (14 of 19), 86.8% of saliva samples (33 of 38), 100% of tear samples (11 of 11), and 100% of sweat samples (9 of 9). Mean HBV DNA levels (±SD) in urine, saliva, tears, and sweat were 4.3 ± 1.1 log copies/mL, 5.9 ± 1.2 log copies/mL, 6.2 ± 0.7 log copies/mL, and 5.2 ± 0.6 log copies/mL, respectively. A statistically significant correlation was observed between the HBV DNA level in serum specimens and HBV DNA levels in saliva and tear specimens ($r = 0.88$; $P < .001$). Tear specimens from a child were injected intravenously into 2 human hepatocyte-transplanted chimeric mice. One week after inoculation, both chimeric mice had serum positive for HBV DNA.

Conclusions. The levels of HBV DNA in tear specimens from young children were high. Tears were confirmed to be infectious, using chimeric mice. Strict precautions should be taken against direct contact with body fluids from HBV carriers with high-level viremia.

Hepatitis B virus (HBV) infection causes acute and chronic liver diseases. Fortunately, HBV infection is a vaccine-preventable disease, and as of 2008, 177 countries (92%) have integrated HBV vaccine into routine infant immunization programs. However, Japan and northern European countries, where the endemicity of HBV is low, continue to implement an HBV immunization strategy that targets high-risk groups, rather than a universal vaccination program [1]. Nonetheless, HBV infection by sexual contact and household contact does occur in Japan [2–5]. Children with chronic HBV infection are usually asymptomatic and have high-level viremia. Therefore, it is believed that children with chronic HBV infection may be a major reservoir for spreading HBV to other close susceptible individuals [6–8]. This scenario would especially threaten the countries that adopt an "at-risk" immunization strategy [6, 9–13].

Body fluids such as saliva, semen, urine, sweat, and tears are also potential sources of HBV transmission. Several studies have reported that HBV DNA in these body fluids can be detected by polymerase chain reaction (PCR) [9–18]. Of these body fluids, however, only serum,

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saliva, and semen have been demonstrated to be infectious in humans or experimental animal models [19–21].

In this study, HBV DNA levels in urine, saliva, tears, and sweat were quantified by real-time PCR. Body fluid samples were collected from HBV-carrier children and HBV-carrier mothers. After quantification of HBV DNA levels for each specimen type, we evaluated the infectivity of tears from HBV carriers. Mice with severe combined immunodeficiency, carrying a urokinase-type plasminogen activator transgene controlled by an albumin promoter (uPA/SCID), and with transplanted human hepatocytes have recently been used as an appropriate animal model for studying viral hepatitis due to HBV and hepatitis C virus [22–24]. Using these mice, we evaluated whether tears from HBV-carrier children were infectious.

MATERIALS AND METHODS

Patients and Materials

Eligible patients were chronic HBV carriers who attended our outpatient clinic. Their chronic HBV infection status was routinely evaluated by blood examination. All of the patients were asymptomatic. Serum, urine, saliva, tears, and sweat samples were collected when possible from each patient.

Serum samples were collected in preparation tubes. Each urine sample was collected in a sterile plastic tube. Saliva, tear, and sweat samples were collected using an indicating FTA Micro Card (Whatman, GE Healthcare, Tokyo, Japan) and sterile foam-tipped applicators (Whatman). When children shed tears spontaneously, we collected tear samples using the FTA cards. Serum, urine, saliva, tear, and sweat specimens were collected on the same day. Informed consent was obtained from all patients or all patients' parents. This study was approved by the Research Ethics Committee of Eastern Yokohama Hospital.

HBV DNA Extraction and Real-Time PCR

HBV DNA in serum was measured by COBAS TaqMan HBV DNA test, version 2.0 (Roche Diagnostics, Tokyo, Japan). HBV DNA was extracted from 200 μL of urine, using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). HBV DNA was extracted from saliva, tear, and sweat specimens that were spotted on FTA cards, using QIAamp DNA Mini kit (QIAGEN). Three circles were punched from the FTA card by use of a single-hole paper puncher (Harris Micro Punch 3.00 mm, GE Healthcare) and were used for HBV DNA extraction. The extracted DNA was dissolved in 100 μL of elution buffer.

Quantification of HBV DNA in urine, saliva, tear, and sweat samples was performed using an in-house TaqMan real-time assay. The real-time PCR was performed using a genotype-independent method described previously [25]. PCR was performed in an MX3000P (Stratagene), and the results were analyzed with MxPro software (version 3.0). The lower limit of detection was >100 copies/mL. All assays were performed in duplicate with negative control samples. This assay was standardized using HBV DNA samples of known concentrations measured by the COBAS TaqMan HBV DNA test and recombinant plasmid controls. In this study, the standard of qualification is based on the result of COBAS TaqMan HBV DNA test. Therefore, the conversion factor between HBV copies/mL and HBV IU/mL is considered to be 5.82 copies/IU. Genotyping of HBV was determined by the PCR-Invader assay [26].

Tear Specimen for Experimental Transmission

For experimental transmission, a tear specimen was collected from a 10-month-old girl with chronic HBV infection. The source of her HBV infection was mother-to-child transmission due to the failure of prophylactic treatment. A total of 200 μL of tears were gently collected from her face when she cried, using a 1.0-mL syringe. The 200-μL tear specimen was diluted with 1300 μL of sterile saline, yielding a total volume of 1500 μL. The specimen underwent filter sterilization with a 0.2-μm filter.

Inoculation of Chimeric Mice With Livers Repopulated by Human Hepatocytes

Three male chimeric mice were purchased from PhoenixBio (Hiroshima, Japan). Human hepatocytes were imported from BD Bioscience (Woburn, MA). Of the 3 mice, 2 (mouse 101 and mouse 102) were inoculated once intravenously with 100 μL of the sterilized tear sample. The remaining mouse (mouse 103) was orally inoculated with 100 μL of the sterilized tear sample every 4 weeks. After inoculation, blood samples for real-time PCR assay were collected from the chimeric mouse every week.

HBV DNA Extraction From Mice Samples and Real-Time PCR

A total of 50 μL of whole blood samples were collected from the mice every week after inoculation, and serum was separated. Saliva and tear specimens were collected from chimeric mice, using FTA cards. HBV DNA was extracted from 20 μL of mouse serum, using SMI-TEST EX-R&D (Medical Biological Laboratories, Aichi, Japan). The extracted DNA was dissolved in 20 μL of nuclease-free water. HBV DNA was quantitatively measured using real-time PCR with the TaqMan PCR Core Reagent kit (Applied Biosystems, Foster City, CA). Real-time PCR was performed in a 25-μL reaction mixture containing 0.125 μL Ampli Taq Gold with 0.2 μM primers (forward primer: 5′-CACATCAGGATTCCTAGGAC C-3′ [nucleotides 166-186]; reverse primer: 5′-AGGTTGGTG AGTGATTGGAG-3′ [nucleotides 325-344]), 0.3 μM probe (5′-FAM-CAGAGTCTAGACTCGTGGTGGACTTC-TAMRA-3′ [nucleotides 242-267]), and 5 μL extracted DNA. The nucleotide position was based on GenBank accession number AB300361 (genotype C). After incubation for 2 min at 50°C and for 10 min at 95°C, the PCR cycling program underwent

53 2-step cycles, one at 95°C for 20 seconds and the other at 60°C for 1 minute. TaqMan PCR was performed with an ABI Prism 7500 (Applied Biosystems). In this study, the volume of serum collected from each mouse was 20 μL, which is a very small amount compared with that used in human studies. Therefore, we considered the upper limit of detection of real-time PCR for a small-volume sample to be >10 000 copies/mL, which provided us with more reliable results. This assay was standardized using mouse HBV DNA samples of known concentrations and the recombinant plasmid controls, as previously described [27].

Immunostaining for HBV Surface Antigen (HBsAg) and HBV Core Antigen (HBcAg)

Immunostaining for HBsAg and HBcAg was performed on frozen sections, using the Ventana i VIEW DAB detection kit (Ventana Medical Systems, Tucson, AZ) and the Dako Envision kit (Dako, Tokyo, Japan), respectively. Primary monoclonal antibodies to HBsAg (Santa Cruz Biotechnology, CA), at a 1:100 dilution, and polyclonal antibodies to HBcAg (Dako), at a 1:500 dilution, were used. Liver tissue was taken from mice after they were euthanized, and the tissue was stored at −80°C.

Statistical Analysis

Categorical variables were compared between groups, using the Yates corrected χ^2 test or the Fisher exact test. Noncategorical variables were compared between groups by the Mann–Whitney *U* test. For analysis of the correlation between log HBV DNA level in serum and in saliva and tears, we used the Pearson correlation coefficient. All tests were 2-sided, and a *P* value of ≤.05 was considered to indicate statistical significance. All statistical analyses were performed with StatMate IV for Windows (Advanced Technology for Medicine & Science, Tokyo, Japan) and Microsoft Office Excel 2007.

RESULTS

Patients and Materials

Between August 2009 and September 2010, 39 children and 8 adults who were chronically infected with HBV were randomly enrolled in this study. Twenty-six subjects were male, and 21 were female; the mean age (±SD) was 12.4 ± 12.0 years, and the median age was 9 years (range, 0–47 years. The 47 HBV carriers fell into the following age groups: 0–5 years, n = 18 (16 were HBV e antigen [HBVeAg] positive); 6–10 years, n = 11 (9 were HBeAg positive); 11–19 years, n = 9 (7 were HBeAg positive); and 20–27 years: n = 9 (7 were HBeAg positive). Of the 47 patients with chronic HBV infection, 39 were positive for HBeAg. In addition, 39 patients had serum HBV DNA levels of ≥6 log copies/mL. One, 6, and 40 patients were infected with genotype A, genotype B, and genotype C, respectively. Serum samples were collected from all patients. From the 47 patients, we collected 19 urine samples, 38 saliva samples, 11 tear samples, and 9 sweat samples. One subject provided urine, saliva, and tears only; 3 provided urine, saliva, and sweat only; 10 provided urine and saliva only; 10 provided saliva and tears only; 1 provided urine and sweat only; 1 provided saliva and sweat only; 4 provided urine only; 13 provided saliva only; and 4 provided sweat only. Samples were collected individually at the same time. The characteristics of body fluid samples are shown in Table 1. There were no significant differences in sex, the number of patients with a serum HBV DNA level of >6 log copies/mL, and the prevalence of genotype C among patients supplying different types of samples. However, there was a significant difference in the age of patients supplying the different kinds of samples.

HBV DNA Detection in Body Fluids

All patients were positive for HBV DNA in serum by the COBAS TaqMan HBV DNA test. The levels of serum HBV DNA ranged from 2.1 log copies/mL to >9 log copies/mL. The median HBV DNA level in serum was >9 log copies/mL. HBV DNA was detected in 73.7% of urine specimens (14 of 19), 86.8% of saliva specimens (33 of 38), 100% of tear specimens (11 of 11), and 100% of sweat specimens (9 of 9) (*P* = .07). In patients with a high viral load (ie, >6 log copies/mL), HBV DNA was detected in 85.7% of urine samples (12 of 14), 100% of saliva samples (32 of 32), 100% of tear samples (11 of 11), and 100% of sweat samples (9 of 9) (*P* = .24). Although the frequency of HBV DNA detection in urine was slightly lower than that in other body fluids, there were no significant differences in the frequency of HBV DNA detection among body fluids.

Quantification of HBV DNA From Body Fluids

Figure 1 shows the levels of HBV DNA in body fluids. Mean levels (±SD) of HBV DNA in urine, saliva, tears, and sweat specimens were 4.3 ± 1.1 log copies/mL, 5.9 ± 1.2 log copies/mL, 6.2 ± 0.7 log copies/mL, and 5.2 ± 0.6 log copies/mL,

Table 1. Characteristics of Body Fluid Samples

Characteristic	Body Fluid				
	Urine (n = 19)	Saliva (n = 38)	Tears (n = 11)	Sweat (n = 9)	*P*
Male sex, no. (%)	10 (52.6)	23 (60.5)	8 (72.7)	4 (44.4)	.29
Age, years, median (range)	11 (1–40)	7 (1–38)	1 (0–3)	16 (8–40)	<.05[a]
HBV DNA in serum, no. (%)					
>6 log copies/mL	14 (73.7)	32 (84.2)	11 (100)	9 (100)	.13
Genotype C	14 (73.7)	33 (86.8)	9 (81.8)	9 (100)	.31

[a] Significant difference between urine and saliva, between urine and tears, between saliva and sweat, and between tears and sweat.

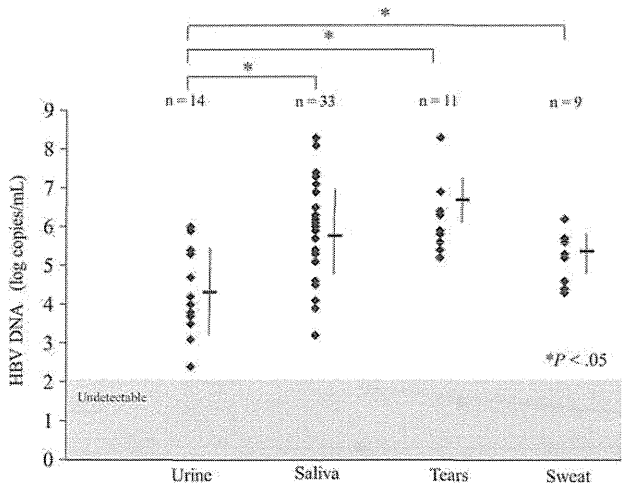

Figure 1. Hepatitis B virus (HBV) DNA levels in urine, saliva, tear, and sweat specimens from 47 patients. The levels of HBV DNA in urine samples were significantly lower than those in saliva, tear, and sweat samples ($P < .05$). The bar indicates the mean of the levels of HBV DNA. SDs are indicated by vertical bars.

respectively. Levels of HBV DNA in urine were significantly lower than those in other body fluids. Levels of HBV DNA in body fluids from patients who had a high viral load (ie, >9 log copies/mL) in serum are shown in Figure 2. Mean levels (±SD) of HBV DNA in urine (n = 10 specimens), saliva (n = 23), tears (n = 8), and sweat (n = 8) were 4.4 ± 0.9 log copies/mL, 6.4 ± 0.9 log copies/mL, 6.4 ± 0.9 log copies/mL, and 5.3 ± 0.6 log copies/mL, respectively. Even after the HBV load in serum was well matched, the HBV DNA levels in urine specimens were significantly lower than those in saliva and tear specimens.

Although there was no significant difference in HBV DNA levels between saliva, tears, and sweat specimens from patients with high viral load in serum, the quantification of HBV DNA in saliva and tear specimens showed almost the same levels (Figure 2). Levels of HBV DNA in the 11 pairs of saliva and tear specimens are shown in Figure 3. Mean HBV DNA levels (±SD) in saliva and tear specimens were 6.1 ± 1.0 log copies/mL and 6.2 ± 0.8 log copies/mL, respectively. The levels of HBV DNA in tear specimens were as high as those in saliva specimens.

The association between the levels of HBV DNA in serum specimens and in saliva and tear specimens was evaluated. Because the upper detection limit of the COBAS TaqMan HBV DNA test was >9 log copies/mL, we used data from patients in whom the levels of HBV DNA in serum ranged from 2.9 to 8.8 log copies/mL. Data from 15 patients (15 serum samples, 15 saliva samples, and 3 tears samples) were available for the correlation analysis. A significant correlation was observed in the levels of HBV DNA between serum specimens and saliva and tear specimens ($r = 0.88$; $P < .001$) (Figure 4*A*). The relationship between HBV DNA in serum specimens and HBV DNA in saliva and tear specimens was described as follows: [log HBV DNA load in saliva and tear specimens] = −3.23 + 1.06 × [log HBV DNA load in serum specimens]. On the other hand, there was no significant

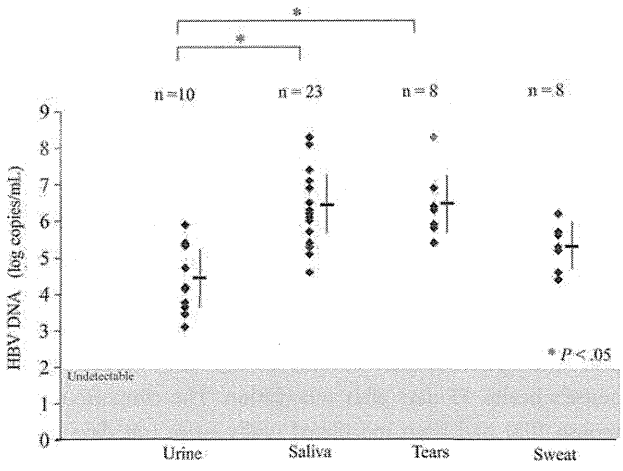

Figure 2. To adjust serum hepatitis B virus (HBV) DNA levels among groups, we show the HBV DNA levels in urine, saliva, tear, and sweat samples from patients whose levels of HBV DNA in serum were ≥9 log copies/mL. Although a significant difference in HBV DNA levels between urine and sweat specimens was not present, HBV DNA levels in urine specimens were significantly lower than those in saliva and tear specimens ($P < .05$). The bar indicates the mean of the levels of HBV DNA. SDs are indicated by vertical bars.

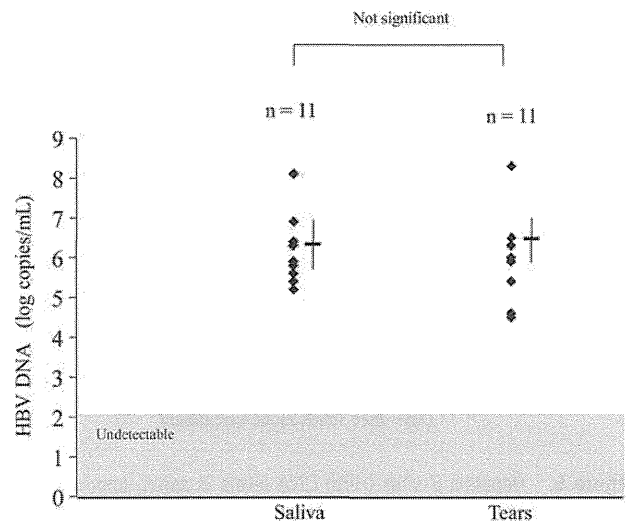

Figure 3. Hepatitis B virus (HBV) DNA levels in saliva and tear samples that were paired. Both groups showed the same HBV DNA levels. The bar indicates the mean of the levels of HBV DNA. SDs are indicated by vertical bars.