

ASIAN MEDICAL JOURNAL

Vol.44 No.1
January
2001

*A Journal of Medical Sciences of
Japan and Other Asian Countries*

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ASIAN MEDICAL JOURNAL

Published by the Japan Medical Association
2-28-16, Honkomagome, Bunkyo-ku, Tokyo 113-8621, Japan
President: TSUBOI, Eitaka, M.D.
Secretary General: KUMAGAI, Fujio, M.D.

Editorial correspondence and contribution to:

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Printed by Japan Printing Co., Ltd.

Subscription Rate: Single Issue: ¥600
One Year: ¥7,200

APPROACH TO RISK MANAGEMENT IN MEDICAL PRACTICE: STANDPOINT OF A HOSPITAL*

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Asian Med. J. 44(1): 1-10, 2001

Abstract: There had been a number of incidences of medical malpractice at Musashino Red Cross Hospital, and since 1995 the hospital has been engaged in “activities to prevent medical malpractice”. In the early days, efforts were focused on quality control (QC) by introducing an incident reporting system that was patterned after risk management techniques developed in the field of aviation. To evaluate these incident reports, a “Committee to Assess Medical Services” (later renamed the Medical Risk Management Committee) was established. Every month this committee reviews each incident from the standpoint of medical technology, medical judgment, human factors, labor conditions, hospital systems, and the supervisory functions of the hospital. The results of these evaluations are used to improve defects in the above system. The committee also conducts medical audits in the hospital. Our approach to the prevention of malpractice is described in this paper.

Key words: Risk management in health care; Medical risk management; Policies to prevent medical malpractice

Introduction

Generally speaking, when an accident occurs in an industry, every effort possible is made to prevent a recurrence, thereby minimizing the risk of recurrence of the same type of accident within that industry. In health care, however, accidents of the same type repeatedly occur in the same hospital. One might even suspect that it is impossible to learn from mistakes in medicine. Confronted with this situation, there is apprehension that doctors in a team practice may lose the trust that the other team members have always placed in them. To improve this situation, hospitals must make efforts systematically to change health care risk management so that medical malpractice can be prevented.

On the other hand, human beings always make mistakes, therefore, making every effort to prevent errors and provide safe and high-quality health care is the most important mission of health care organizations, and the practices employed at the Musashino Red Cross Hospital are described below from this standpoint.

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 5, 2000, pages 622-628).

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The first goal we set in our attempt to prevent medical malpractice was to raise the awareness of those in the frontlines of medical practice. We believed that quality control (QC) activity was the most appropriate means for this purpose and organized a QC group in each work unit in a top-down format. The head of each section was to lead the group, and a total of 11 groups were formed. First, they set the major goal of "prevention of malpractice" and selected topics accordingly. Each group held meetings once a month, from which we learned a great deal. However, the majority of the topics of the QC activities concerned problems related to nurses alone, and because the results of the discussions overlapped accident prevention activities in the nursing section and measures to improve nursing works, the burden on the nurses became even more onerous. After about 2 years, all QC group activities ceased.

These initial efforts, however, established the basis for future activities to prevent medical malpractice in our institution. We came to realize that the QC activities must be reorganized in the original bottom-up format, and we are currently engaged in reorganizing our improvement activities, with the support of the Union of Japanese Scientists and Engineers.

Construction of a Medical Risk Management System within an Organization

1. The nursing section

The nursing section has traditionally been involved in efforts to prevent medical malpractice. In association with this new venture, they revised their accident report forms, organized a "committee to prevent accidents" within the nursing section, reviewed accident reports forwarded from the wards, and fed the results back to the meetings of the chief nurses. The nursing section drew up a manual called "Accident Prevention" within a period of 18 months. Since early 1999, a risk management nurse has been assigned to each ward to gather and analyze information on each incident and send back the details of the analysis in the form of feedback (Fig. 1).

2. Doctors

There are numerous problems concerning doctors, and policies affecting doctors will be mainly presented in this section.

Traditionally, doctors have seemed to regard themselves as privileged and expected everyone else to serve them, this attitude may have helped doctors to become self-righteous. Doctors have tended to avoid disclosing the details of their practice in investigations of medical malpractice, always leaving behind a so-called "gray zone". However, the modern societies offer a wealth of medical information, and the public is better informed than ever. If doctors do not shake themselves free of their arrogant attitude, it may be impossible to prevent recurrences of medical malpractice, and doctors, as leaders of the health care groups, may lose the trust of the other team members. Faced with the situation described above, our programs were undertaken.

Another motivation for starting these programs was doubts about the appro-

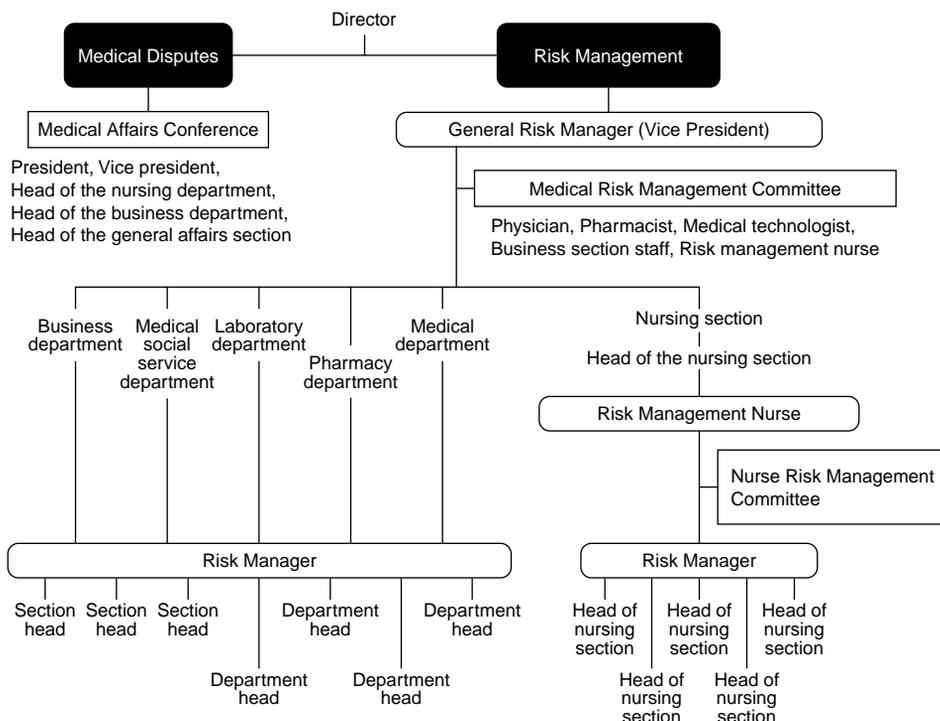


Fig. 1 Organizational chart of medical risk management (Musashino Red Cross Hospital, June 1, 1999)

priateness of our former method of hospital management. There are a number of medical departments within a hospital, and each operates within its own specialty. If each operates independently without regard for the other departments, the cohesion desired in a hospital is lost. Organized health care becomes possible only when the goals and quality of medical service of the hospital as a whole are maintained and managed. We believe that there is a definite need for a system to monitor the health care actions of the hospital as a whole.

Introduction of an Incident Reporting System

Following the advice of Dr. Isao Kuroda, then a professor in the School of Human Science of Waseda University, who suggested “the introduction of risk management technology that had been developed in the field of aviation because malpractice in health care resembles the accidents that occur in association with aviation” (1995), we decided to adopt the risk management incident reporting system for doctors.

There is a well known saying that there is a “chain of events” in aviation accidents, because “3 or more minor incidents always occur in a row before a larger, more serious accident.” Every pilot is instructed to faithfully report every incident that occurs during a flight regardless of its seriousness (including near-miss

Incident/Accident Report (Circle one)				Date:	, 200
Work site	Position	Years of work experience Years	Name (Personal seal)		
Patient's name	Age (male or female)	Diagnosis			
Site of the accident occurred	Ward		Department on an outpatient basis		
Date and time of the accident	Date:	Time:			
Date the accident was discovered	Date:	Time:			
Time treatment was started	Date:	Time:			
Time a report was made to the department head	Date:	Time:			
Type of accident	[Classification] 1. oversight or misunderstanding, 2. misidentification, 3. error in dosage, 4. complication, 5. iatrogenic disease, 6. others				
Process during which the accident happened					
Response and steps taken after the accident					
Explanation given after the accident and the subsequent response of the patient					
Evaluation of the gravity of the risk involved in the accident	Life-threatening: <input type="checkbox"/> very grave; <input type="checkbox"/> grave; <input type="checkbox"/> possible; <input type="checkbox"/> little; <input type="checkbox"/> none Patient's trust: <input type="checkbox"/> greatly damaged; <input type="checkbox"/> slightly damaged; <input type="checkbox"/> not much affected				
Health status of the medical personnel involved	<input type="checkbox"/> good; physically fatigued (<input type="checkbox"/> by work; <input type="checkbox"/> for personal reasons) psychologically fatigued (<input type="checkbox"/> by work; <input type="checkbox"/> for personal reasons) <input type="checkbox"/> others (remarks: _____)				
Views on the cause of the accident	[Classification] 1. lack of observation, 2. delay in testing, 3. delayed diagnosis, 4. inadequate technology, 5. surgical mistake, 6. inadequate communication, 7. inadequate explanation, 8. others				
Thoughts on the steps to be taken in future					

Fig. 2 Incident Report Form

incidents) by filing an incident report. They are assured that filing such reports will in no way affect their chances for promotion or future pay increases. Accident prevention policies have been established and major accidents have been averted by gathering and analyzing these reports describing minor incidents.

When we introduced our incident reporting system, we distributed the following letter to doctors and pharmacists: "We all make mistakes at one time or another. Instead of feeling ashamed and hiding such mistakes, we would like you to share your mistakes with the hospital as valuable experiences that can be accumulated as an organizational asset. Individuals will not be accused of errors, so please report only the facts in the incident reports. The background of the incident or accident will be evaluated, and if a problem of the system in the hospital as a system is uncovered, it will be corrected immediately. The experiences will be used as a common asset to be shared by the entire hospital to enable us to offer safer and higher quality health care services. We hope that you will fill out the reports completely, and we assure you that there will be no personal repercussions."

The form for reporting incidents has been designed to be as simple and easy to fill out as possible. It somewhat resembles the accident report forms now being used by nurses (Fig. 2).

As a rule, the incident report is voluntarily submitted by individuals, but the heads of the department have been assigned the role of risk managers and asked to urge their staff to prepare a report on any medical action that may be a cause for concern. In fact, however, few reports were submitted in the first 3 months. Therefore at a meeting of the department heads, the author stated the following: if there is no incident report from the department involved and a patient files a complaint, the management is forced to question the managerial responsibility of the department head. Department heads must have a thorough understanding of the medical actions of their staff, and if a problem is recognized, the head of the department is to instruct the staff member to file an honest report. I also emphasized that it is a non-punitive reporting system. In addition, when information has become available by some other route, the author has directly contacted the doctors in charge and asked them to submit a report.

As a result, reports started to trickle in. One member of the risk management committee in particular made a special effort to urge his staff to submit reports, and this seemed to have a priming effect. The number of reports has increased since then, and the increase is a reflection of the gradually increasing awareness among doctors that health care accidents can be prevented and that their reports are important in achieving this end. It also shows that the psychological burden of writing a report has gradually been alleviated.

Establishment of the Medical Practice Evaluation Committee

In introducing the incident reporting system, it was recognized that the reports should be evaluated objectively by a third party. Therefore, 11 persons considered capable of rendering sensible judgments were selected from among the department heads and assistant heads actively involved in clinical practice, and assigned to organize a "Medical Practice Evaluation Committee" (later renamed the "Medical Risk Management (MRM) Committee"). At the time the committee was established, its aims were explained at management conferences and department head meetings to obtain a consensus throughout the hospital. It is believed that the process to obtain this consensus was extremely important.

Based on the incident reports, this committee investigates various factors leading up to the occurrence of accidents and they look for answers to health-care-related questions such as: the possible existence of problems in hospital management and steps to correct them; problems related to medical technology; appropriateness of clinical judgments; the working conditions of the medical staff; the psychological condition of the medical staff when the incident occurred; and possible problems related to patients. It was also hoped that the committee would have the function of a medical audit.

Currently, the MRM Committee meets once a month. If a problem is discovered in the hospital system, the general risk manager immediately corrects it. When problems related to medical technology or clinical judgment are uncovered, specific plans to resolve them are studied by the departments involved. In the course of studying these problems, the labor conditions of doctors will inevitably surface, and they should be improved as much as possible through negotiation between the senior leaders and the doctors.

If a single incident involves more than one department, doctors from each of them (other than the committee members) are asked to participate in the investigation. The results of these investigations are transmitted to each department as feedback. If the problem involves the entire hospital, it is reported in the internal hospital newspaper (Musashino Nisseki Shinbun) as a "Report from the Risk Management Committee" so that all hospital employees will be informed.

Thus, the MRM Committee also has the functions of a medical audit.

The Risk Management System

In the United States, risk management is defined as "the science by which the risk for an economic loss is identified, evaluated, and managed". Three approaches to organizing a risk identification system has been reported..

- (1) Incident reporting system: Accident reports are expected to be voluntarily filed by employees: 5 to 30% of all accidents can be identified by this approach.
- (2) Occurrence reporting system: A list of potential accidents is prepared in advance and employees are expected to voluntarily report them whenever they occur. Approximately 40 to 60% of all accidents can be identified by this approach.
- (3) Occurrence screening system: Professional employees identify incidents by chart inspections based on written criteria. It has been reported that 80 to 85% of all accidents can be identified by this approach.¹⁾

The risk management policies adopted in the United States include: (1) protecting the hospital's assets; (2) improve the quality of health care (improvement of patients' safety); and (3) following legally sound risk management policies.

Of the three policies listed above, (2) has been discussed, adopted, and regarded as the most probable approach in Japan at the moment. It appears to conform best to Japanese customs and traditions, which is most important. It is also related to [(1) protection of the hospital's assets]; but more importantly, our efforts should be based on an intent to [(2) improve the quality of health care (and to ensure patient safety)].

Introduction of the Risk Predicting System

To introduce (2) an occurrence reporting system for the risk management system described above, the following steps were taken.

All of the department heads were assigned to the position of risk manager and asked to prepare a list of accidents that are most likely to occur in relation to medical care in their department and to formulate and submit measures to prevent them. These reports have been incorporated into appropriate chapters of the "Manual to Prevent Medical Accidents". As reference material, informed consent to various procedures that are frequently conducted in each department are included (when the consent is written, it is often accompanied by statistics on risk). A list of drug names that are easily confused and photographs and names of ampules containing drugs for parenteral use are included in the manual so errors should not go unnoticed.

It is said that about half of the disputes concerning medical care involve financial settlement, whereas the other half concern the personality of the doctor (appeals are made just to punish doctors for their actions). According to the statistics in the United States, 70% of the medical disputes arise in the absence of errors on the part of the medical staff. These disputes stem from a lack of communication between the patients and doctors or other medical staff members. Apparently, what appears to have been a careless manner of speaking, attitude, or facial expression of the doctor generates distrust on the part of the patient, which eventually leads to medical complaint. With this in mind, the overview section of this "Manual to Prevent Medical Accidents" describes doctors' methods and manner of dealing with patients under the heading of "Basic Rules to Prevent Medical Accidents". In this section, attention is called to basic manners required by doctors, including the need for a patient-oriented medical process, confirmation of each procedure, assuming a humble attitude, with undivided attention given to what the patient wants to talk about, building a good patient-doctor relationship, and providing methods for fill out medical records.

This "Manual to Prevent Medical Accidents" was distributed to all doctors working at the hospital. Doctors are expected to peruse even the sections that do not actually involve them. Their critiques are useful in preparing the next edition, and three revisions were made. It required 8 months to prepare the first edition, which was published in August 1997. The second edition was completed in October 1998. In each of the revised editions we hope to include the experiences of doctors who have learned from the accident prevention steps taken in other departments and re-evaluated and reinforced the accident preventive measures in their own department. We also hope that the manual will be used by all doctors in the hospital, but the process of preparing it is even more important. The author believes that by experiencing the process by which policies to prevent accidents are drawn up, they will become more sensitive to the possibility of accidents. In other words, the manual to prevent medical accidents is most meaningful when each hospital prepares its own unique version.

Introduction of the Occurrence Screening System

The nursing section of our hospital assigned a risk management nurse late in 1999 and prepared its own screening system. We expect good results from this movement.

In the areas in which doctors are involved, the medical care in each department is extremely diverse and the magnitude of the risk involved is several times that of nursing section. Since the area involved is believed to be too large to be managed by a single risk manager, the department heads may have to be asked to act as risk managers; and doctors will be expected to improve their awareness of the need to prevent medical accidents.

Response to the Development of Medical Disputes

When a medical malpractice that might develop into a medical dispute occurs, the basic rule is that the doctor in charge immediately reports the accident to the head of the department, and that the department head in turn reports it to the head of the administrative department, the vice president (general risk manager), or the president of the hospital. The doctor then waits for their directions before responding further.

What is important in these procedures is that those involved express their sincerity and consideration toward the patients and their families by their attitudes and speech. Next, there is a need to establish a single channel to handle the procedures for dealing with patients or their families. At our hospital, the general affairs section is in charge. It is essential that the doctors in charge or the head of the department involved not apologize to patients or their families on their own nor tell them about the possible future response of the hospital based on their own interpretation. Doctors or department heads should always discuss the matter with the management of the hospital before they respond to outsiders. They should explain to them that the matter will be handled by the general affairs section, and then quickly report and discuss any future steps with hospital management through the procedures explained above. The initial response by the doctor in charge or department head often determines future developments.

After taking the steps described above, those who are directly involved in the accident should promptly fill out an "accident report" (a form that has been prepared by an insurance company) and submit it to the general affairs section. Based on this accident report, future steps to be taken will be discussed at the Medical Affairs Conference (composed of the president, vice president, head of the nursing section, business manager, and head of the General Affairs Section). At Red Cross Hospitals, such reports are sent to Red Cross Headquarters and the insurance company.

When the evidence is seized or a patient files a claim leading to a legal dispute, a conference is held between the attorney representing the patient and the insurance company, and the response by the attorney is discussed at a Medical Affairs Conference.

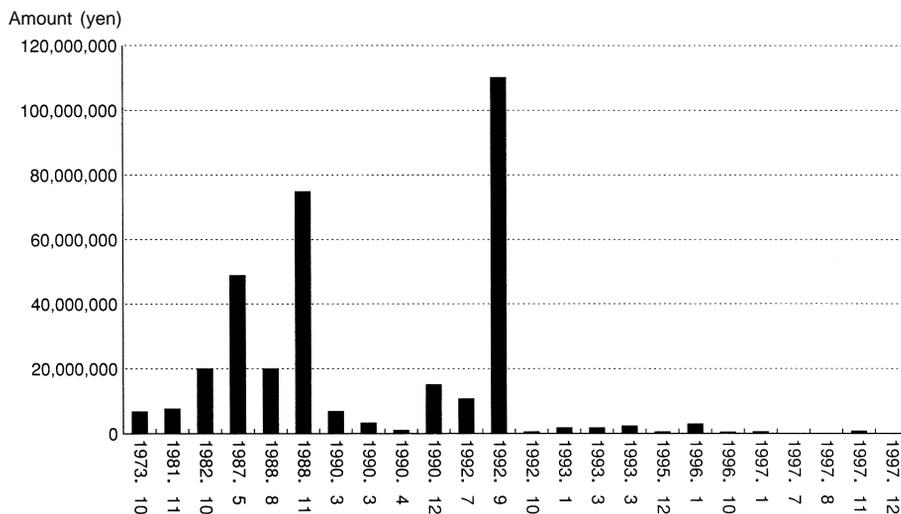


Fig. 3 Changes in total amounts of money paid out for financial settlements annually by Musashino Red Cross Hospital

Conclusion

In reality, personal elements (e.g., personalities or personal attainment) are involved in medical accidents. However, even when an accident appears to have been the fault of a single individual, the cause may be in the management system of the hospital. Therefore, it is important that the person involved report the accident faithfully and that a system capable of evaluating such incidents objectively be in continuous operation in the hospital. When such a practice is established in a hospital, a more trusting relationship between doctors and the hospital management will be established. Backed up by a system such as described above, doctors can be assured of their positions and can concentrate on their own jobs. At the same time, they are reminded that their medical services are being monitored by a third party. Such an environment should produce a change in the doctors' attitude toward the medical care they provide. It is hoped that this change in the doctors' attitude will result in reduced medical malpractice.

It has been five years since we instituted the steps described above to deal with medical accidents. The changes in the amounts of money that our hospital has paid for financial settlements since 1973 are displayed to show the results of our efforts over the years (Fig. 3). Fortunately, no major disputes have occurred (except for one incident early in 1996, when we had just undertaken activities to prevent malpractice). However, valid evaluation should be conducted at 10-year intervals. We hope that the effort by the hospital as a whole will continue.

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APPROACH TO RISK MANAGEMENT IN MEDICAL PRACTICE: STANDPOINT OF THE BLOOD TRASFUSION*

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Asian Med. J. 44 (1): 11–21, 2000

Abstract: In the field of blood transfusion, risk management is defined as assuring the safety of blood transfusion. This includes prevention of errors in the process of collecting blood from donors, examination, and production of blood preparations from the donated blood. Good Manufacturing Practice (GMP) and a system for ensuring compliance with the GMP are thus necessary. Reliable retrospective examination and provision of information, regarding adverse reactions, from medical institutions are essential for prevention of adverse reactions to blood transfusion. On the basis of this information, such measures as highly sensitive screening, including viral nucleic acid amplification, and inactivation and elimination of leukocytes can be implemented. On the other hand, medical institutions need to clearly establish the procedures to be followed when transfusing blood into patients in order to prevent human errors. There should be a system that allows confirmation of good compliance with the procedure. In numerous medical institutions in Japan, the process from placement of orders for blood to actual transfusion of the blood is complicated, thereby increasing the likelihood of errors. Unification of management of the blood transfusion process is necessary. Finally, a system that allows objective monitoring of appropriate production of blood preparations at blood centers, as well as the blood transfusion process at medical institutions, must be established.

Key words: Window period; Error prevention system;
Blood transfusion consent form;
Blood Transfusion Therapy Committee

Introduction

Risk management can be interpreted as a procedure consisting of listing all possible adverse reactions or errors, analysis of the probability of risk onset, evaluation of the seriousness of the risk, and prevention of adverse reactions or accidents by implementing preventive measures or making improvements. Among various adverse reactions to blood transfusion, nonhemolytic reactions have been reported in the largest number, but there have been only a few reports of serious cases. In contrast, transfusion-transmitted infection, post-transfusion graft versus

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 5, 2000, pages 638–644).

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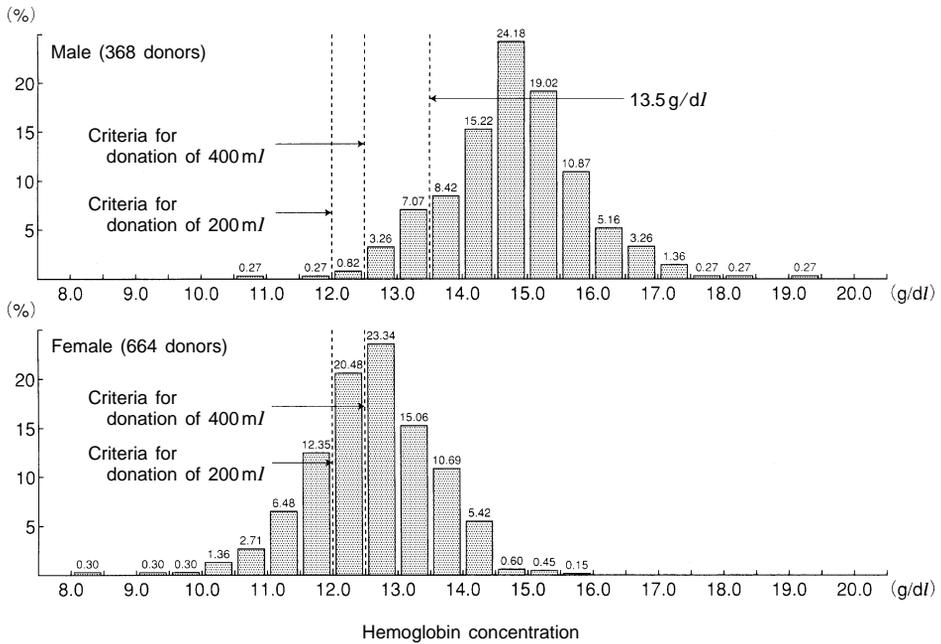


Fig. 1 Distribution of hemoglobin concentrations in blood donors

host disease (GVHD), and hemolytic adverse reactions are infrequent, but can be serious. Therefore, priority should be placed on the more serious reactions in risk management.¹⁾

If we define risk management in blood transfusion as a process to assure its safety, we should consider risk management from the perspective of the providers of blood preparations for transfusion, in other words, blood centers, and risk management at medical institutions where blood transfusion is performed. The former aims at assuring the safety of donors and blood for transfusion, and the latter aims at assuring the safety of blood transfusion recipients.

Risk Management at Blood Centers

1. Assuring donor safety

When donors are females, it is often the case that anemia is suspected due to insufficient specific gravity, making them ineligible as donors. There is a rough correlation between specific gravity and the hemoglobin concentration, but low specific gravity does not necessarily imply anemia. Donors in whom specific gravity is assessed as 1.053 can exhibit a wide range of hemoglobin concentrations, and those with a specific gravity below 1.053 can have quite a high hemoglobin concentration.

In addition, although hemoglobin concentrations in males and females differ physiologically, a specific gravity of 1.053 and a hemoglobin concentration of

Table 1 Systems for Preventing Human Errors

System introduced	Effects
Nationwide unified management of donor information	Reference to past records of blood donation
Automobile-installed reception system	Identification of blood donors
OCR processing system	Prevention of interview sheet omissions
Secondary testing system	Prevention of mistakes with specimens Prevention of input errors of test results

12.5 g/dl or more have been adopted as the criteria for collection of 400 ml of blood in both males and females in Japan. The distribution of hemoglobin concentrations in male donors is shifted toward the higher concentration in comparison to that in female donors. Therefore, it may be necessary to change the criteria for collection of 400 ml of blood to 13.5 g/dl or more for males and 12.5 g/dl or more for females in order to assure donor safety (Fig. 1).

As to carriers of hepatitis viruses detected in screening for blood transfusion, not only notification but also more proactive management of their health is recommended. At our institution, we hold orientations for donors who have been proved to be carriers of hepatitis B virus (HBV) or hepatitis C virus (HCV), and carry out examinations/health consultations two to four times a year under the auspices of the carrier clinic.²⁾ In a sense, this can be regarded as an activity assuring the safety of donors.

2. Systems for preventing human errors

If a reliable quality control system is lacking at blood centers, errors and resultant adverse reactions can occur. The most important task of a quality control system is to minimize human errors. For that purpose, it is important to establish and utilize systems for prevention of human errors, like those listed in Table 1.

Nationwide unified management of donor information, through a system that allows access to information regarding donors from throughout Japan, is useful. However, facilities able to use this system are limited at present. In Hokkaido, a reception system that can be installed in an automobile has been adopted, but the system is unable to collect information regarding donors living outside of Hokkaido. The system for secondary examination is designed to prevent wrong sampling of blood specimens, and errors in data input of the test results of secondary examination, which is carried out manually. The OCR processing system was developed with the aim of preventing omissions of necessary information from the interview sheet. The system examines the interview sheets for any omissions or errors, and temporarily suspends shipment of the blood products for which the blood donation application form and interview sheet are inadequate.²⁾

3. Transfusion-transmitted infection

The major objective of assuring the safety of transfused blood is to reduce adverse reactions. There are four major adverse reactions to blood transfusion;

Table 2 Post-transfusion Infections with Hepatitis Viruses in 1998
(Medical Information Division, Central Blood Center, Japanese Red Cross)

Virus	Voluntary report from medical institution	Retrospective study		Total number
		Fractionation Center NAT-positive	Donor seroconversion	
HBV	6 (4) [1]	11 (5) [2]	5 (4)	22 (13)
HCV	0	3 (3)	4 (3)	7 (6)

(): Number of patients who developed post-transfusion hepatitis

[]: Number of patients who exhibited persistent infection for at least 6 months after infection

transfusion-transmitted infection, post-transfusion GVHD, sensitization with allo-antigens, and non-hemolytic adverse reaction. Because the space is limited, I will confine my discussion to transfusion-transmitted infection in this article. The evolution of the incidence of post-transfusion hepatitis from 1960 until today indicates that, while nearly half of blood transfusion recipients suffered post-transfusion hepatitis in the early days, this has become extremely rare today.³⁾ The possible reasons include the shift from paid blood to donated blood, improvement of the HBV detection system, and establishment of the HCV examination method. In a sense, this can be regarded as an outcome of risk management.

Regarding the incidences of transfusion-transmitted infection with human immunodeficiency virus (HIV), HBV, and HCV during the past five years, only one or two recipients were reported to be infected with these viruses every year between 1994 and 1997, but the number rapidly increased to 14 recipients in 1997, and to 29 recipients in 1998.⁴⁾ These results do not mean that the risk associated with blood transfusion suddenly increased in 1997 and 1998. Instead, it seems more reasonable to interpret these cases as having previously latent infections which manifested in 1997 or thereafter. In the past, voluntary reports by medical institutions were the only major source of reports of post-transfusion infection. Since the end of 1997, however, specimens from all donated blood have been preserved, and nucleic acid amplification test (NAT) of plasma fractions was started, thereby making possible highly reliable retrospective examinations. The reason for voluntary reports increasing in 1998 may be that informed consent to undergo blood transfusion was introduced in this year, and medical institutions came to take great interest in adverse reactions to blood transfusions (Table 2). However, these may represent only the tip of the iceberg, because most of these cases were detected retrospectively. The failure to preserve patients' pre-transfusion specimens made definite identification of the origin of the virus impossible in a great number of patients, and this remains a problem for the future. Preservation of pre-transfusion specimens from patients is important for elucidating the onset mechanisms of adverse reactions, and for preventing these reactions.

4. Screening as countermeasures against transfusion-transmitted infection

Infection can occur despite the viral screening at blood centers. The most important cause relates to blood collected during the window period being used

Table 3 Estimated Risks of Post-transfusion Viral Infection Based on Blood Donated during Window Period

Country	Examination period	HBV	HCV	HTLV-I	HIV-I
Japan (Hokkaido)	1995–1997	1/30,000	1/236,000	1/207,000	—
United States (REDS)	1991–1993	1/63,000	1/103,000	1/641,000	1/493,000
France (VHG/RVG)	1992–1994	1/118,000	1/223,000	1/5,882,000	1/571,000

for transfusion. As shown in Table 3, the risk of infection with blood donated during the window period was calculated according to the method of Schreiber *et al.*⁵⁾ The risks of HCV infection are almost identical in Japan, the United States, and France. This is probably because the percentage of HCV carriers and the sensitivity of the screening technique are almost the same.^{6,7)} In contrast, the risk of infection with human T-cell leukemia virus-I (HTLV-I) is extremely high in Japan. This is because the number of carriers is larger in Japan than in the other two countries. The agglutination method used as a means of HTLV-I antibody screening in Japan is essentially equivalent to the enzyme immunoassay (EIA) in terms of sensitivity.

The risk of HBV infection due to blood transfusion is higher in Japan than in France. The larger number of HBV carriers in Japan and the poor detection sensitivity of the screening method adopted in Japan are the two major reasons for this.^{6,7)} When specimens from blood donors were screened simultaneously with the HBV agglutination system and a highly sensitive chemiluminescence immunoassay for HBsAg (CLIA; CLIA-HBsAg), 5 of the 7 specimens that tested positive only by CLIA turned out to be in the window period when HBc antibody was still negative. They included cases in which the virus could not be detected by NAT of pooled specimens from 500 donors.⁸⁾ The remaining 2 specimens tested positive against HBc antibody, though the antibody titer was low, and are believed to be specimens from chronic carriers. When diluted, these specimens tested negative on NAT, suggesting that such cases may also be overlooked by pooled NAT (Table 4). All specimens tested positive by the agglutination system turned out to be specimens from chronic carriers, and they tested negative on the test employing a pool size other than one fold. These results suggest that NAT will allow detection of HBV in some blood specimens collected during the window period, which are overlooked by the present screening method based on agglutination. However, as long as the test is conducted in a pool of 500 specimens, the technique is not superior to the highly sensitive serology test (CLIA-HBsAg).⁸⁾ Stramer⁹⁾ reported that the HBV test in a pool of 500 specimens is not effective in reducing the window period.

The possibility of infection cannot be ruled out even when blood with an extremely low virus level from HBV carriers is transfused. Moreover, the patient's condition, particularly, the immune state, is believed to be closely associated with the development of infection. A report has revealed that about 10% of recipients infected with HBV as a result of blood transfusion became carriers, and these

Table 4 Sensitivity of HBs Antigen Test by CLIA and Pooled Nucleic Acid Amplification Test (NAT)

	Specimen	HBs antigen CLIA (S/CO +/-)	HBc antibody HI (2n)	NAT pool size							
				×1	×10	×25	×50	×100	×250	×500	
CLIA-HBsAg (+)/ JRC HBV system (-)	1*	+	1.10	-	+	+	+	+	-	-	-
	2*	+	3.59	-	+	+	+	+	-	-	-
	3*	+	1.34	-	+	+	+	+	+	-	-
	4*	+	8.47	-	+	+	+	+	+	+	+
	5*	+	9.18	-	+	+	+	+	+	+	+
	6**	+	7.44	4	+	-	-	-	-	-	-
	7**	+	28.43	4	+	-	-	-	-	-	-
CLIA-HBsAg (-)/ JRC HBV system (+)	1	-	<1.0	9	+	-	-	-	-	-	-
	2	-	<1.0	8	+	-	-	-	-	-	-
	3	-	<1.0	>10	+	-	-	-	-	-	-
	4	-	<1.0	6	+	-	-	-	-	-	-
	5	-	<1.0	6	+	-	-	-	-	-	-
	6	-	<1.0	6	+	-	-	-	-	-	-
	7	-	<1.0	6	+	-	-	-	-	-	-
	8	-	<1.0	7	+	-	-	-	-	-	-

* 1-5: Specimens in the Window Period

** 6,7: Specimens from low-viremic carriers

recipients consisted of elderly people, children, and patients with hematologic disorders in an immunosuppressive state. It goes without saying that, when providing blood without knowing who will be the recipients of that blood, blood with the smallest possible risk should be provided.

As a measure for preventing transfusion-transmitted infection, the Japanese Red Cross has implemented NAT screening against HBV, HIV-1, and HCV using pooled specimens from 500 donors throughout Japan, starting with specimens collected on October 10, 1999. This is expected to improve the safety of blood transfusion (red blood cell preparations and fresh frozen plasma). Supplying platelet preparations with the results of NAT must be implemented despite the limitation that they must be used within a short period of time before expiration. As to HBV screening, the above-described problem of the detection sensitivity of NAT using pools of 500 specimens remains.*

5. Other countermeasures against infection

In addition to screening, inactivation or elimination of viruses are also possible countermeasures.¹⁰⁾ Combining two approaches to safety, i.e., screening and inactivation/elimination of viruses, may greatly enhance countermeasures against infection of blood preparations. While these countermeasures can improve the safety of blood, they may also increase the cost. Opinions of not only those involved in blood transfusion but also those from a variety of fields should be collected with respect to the balance between cost and benefits, in terms of the

* JRC has implemented the 50 pool NAT since February of 2000.

Supply of platelets with the NAT results have been implemented since October of 2000.

safety provided by these measures.

Bacterial contamination of blood preparations should also be taken into consideration. It has been indicated that, in sampling tests, bacterial contamination can be detected in about 0.1% of specimens examined. However, the actual status of adverse reactions to transfused blood preparations contaminated with bacteria remains unknown, and systematic studies have not been conducted in Japan.

6. Retrospective studies of transfusion-transmitted infection

At blood centers, retrospective studies are conducted when patients are suspected of having developed transfusion-transmitted infection, or when NAT-positive blood preparations are suspected to have been given to patients. At blood centers, information regarding the patient is collected from his or her attending physician, and the physician is asked to submit specimens. Then, the patient's specimens as well as specimens from the donor are subjected to detailed examination, and the results are reported to the attending physician. As described earlier, specimens from all donors have been preserved since 1997. When a transfusion-transmitted infection is suspected, the attending physician is requested to follow up the patient's condition, and the blood center cooperates with the physician in carrying out a detailed examination. Persons in charge of medical information at the blood center (Medical Representative) play a central role in these series of examinations.

Risk management at Medical Institutions

Numerous hospital personnel (physicians, nurses, laboratory technicians, and pharmacists, etc.) are involved in blood transfusion therapy, and blood transfusion may be performed at various places such as the general ward, operating room, and outpatient clinic. Therefore, the commitment and cooperation of the entire hospital staff are essential for prevention of errors related to blood transfusion. Moreover, since highly specialized knowledge is required for blood transfusion therapy, accredited specialists and laboratory technicians specializing in transfusion medicine are believed to play important roles in transfusion therapy.

1. Foundation of Blood Transfusion Therapy Committee and its roles

All medical institutions performing blood transfusions should establish a Blood Transfusion Therapy Committee that monitors proper use of blood preparations, examination of blood transfusions, storage and management of blood, actual procedures of blood transfusions, and adverse reactions. The role of such a Blood Transfusion Therapy Committee should be more than nominal. It should constantly monitor whether blood transfusion is carried out in a safe and effective manner for patients, and when any problems are detected, it should demonstrate leadership and responsibility in resolving those problems. Roles of the Blood Transfusion Therapy Committee are summarized in Table 5.

2. Informed consent

In April 1997, it became mandatory that informed consent for blood transfu-

Table 5 Roles of the Blood Transfusion Therapy Committee

1. Indications for blood transfusion therapy
2. Selection of blood preparations
3. Instruction of blood transfusion test
4. Procedures for blood transfusion
5. Storage and management of blood preparations
6. Control of blood preparation usage in the hospital
7. Ensuring proper use
8. Countermeasures against adverse reactions/complications of blood transfusion therapy
9. Others (use of irradiated blood as a countermeasure for GVHD, emergency blood transfusion, 24-hour system for blood transfusion testing)

(Blood Preparation Storage/Management Manual)

sion be obtained from the patients or their guardians before blood transfusion. Physicians should provide detailed information as to why blood transfusion is necessary for the patient, the risks of adverse reactions associated with blood transfusion, what alternative therapies are available, and what risks can be expected if blood transfusion is not provided. Moreover, physicians must confirm that the patients have understood the information, and agree to receive the blood transfusion. In Western countries, there have been cases in which physicians or hospitals were sued because they failed to appropriately obtain informed consent before blood transfusion therapy.¹¹⁾

3. Unified management by the blood transfusion department

Among errors that can occur in hospitals in relation to blood transfusion, the most serious adverse reactions may be induced by transfusion of blood with a different ABO type. On the basis of the results of a study of 981 facilities all over Japan, Shimizu *et al.*¹²⁾ reported that transfusion of blood with the wrong ABO type (major mismatch) occurs 0.11 times a year, and from this figure, they estimated that about 600 cases of blood transfusion with major mismatch occur annually in Japan. As to the cause, transfusions to the wrong patients accounted for the largest percentage (48.3%), followed by wrong sampling (21.6%), and testing errors (18.8%).¹²⁾ Kurata *et al.*¹³⁾ pointed out that many major mismatch transfusions take place during hours other than office hours, such as at night, and that blood transfusion tests during non-office hours are conducted by attending physicians at most institutions. Therefore, countermeasures for preventing these common errors in blood transfusion are urgently required.

First of all, the procedures to be followed during the entire process until the patient receives the proper blood transfusion (i.e., blood collection, testing, and blood transfusion), including the method of confirmation and precautions for preventing mistakes in advance, should be prescribed, and a system for monitoring the appropriate performance of the blood transfusion should be established. Moreover, a system for monitoring adverse reactions to blood transfusion, and for taking appropriate measures in the event of adverse reactions must be established.

Secondly, it is recommended that a blood transfusion department be estab-

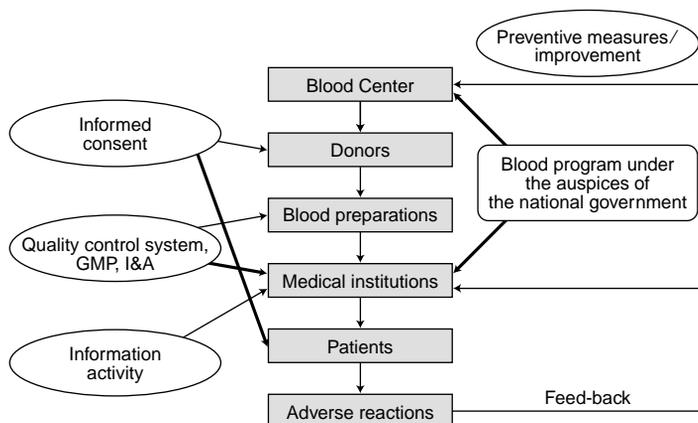


Fig. 2 Risk management in blood transfusion

lished to allow unified management of blood transfusion operations. At most medical institutions in Japan, blood preparations are managed by the pharmacy, and blood transfusion tests are conducted by the laboratory. Therefore, handling of various slips, specimens and blood preparations is complicated during the process following placement of the order for blood transfusion until the actual blood transfusion. Under such circumstances, errors are likely to occur. Unified management is expected to facilitate rapid provision of blood preparations, promote proper use, allow monitoring of recipients of blood transfusion and effective use of blood preparations, as well as control adverse reactions. Unified management by the blood transfusion department is an important aspect of risk management in blood transfusion.

4. Inspection and accreditation (I&A) of blood transfusion procedures

There is a system for objective evaluation by a third party regarding the proper performance of blood transfusion procedures at an institution, and for use of the results to improve procedures at the institution. The Kanto Koshinetsu Block of the Japanese Society of Blood Transfusion has established an I&A Subcommittee to offer this service to institutions that have requested evaluation.¹⁴⁾ This may be another approach to risk management. In the future, the Japanese Society of Blood Transfusion is expected to play a central role in establishing a nationwide I&A system, and in demonstrating its effects.

Conclusion

Risk management in blood transfusion is outlined in Fig. 2. Blood specimens collected from donors are processed into blood for transfusion, then delivered to medical institutions, and finally transfused into patients. At blood centers, errors and other potential causes of adverse reactions may occur during the process of blood collection, testing, and production of preparations. Quality control systems

and Good Manufacturing Practice (GMP) are important in their prevention. Major factors in risk management at medical institutions include establishment of a Blood Transfusion Therapy Committee, informed consent from patients, unified management by the blood transfusion department, and I&A. If the causes are explored and problems identified in the case of adverse reactions to blood transfusion, the information can be given to blood centers and medical institutions as feedback to facilitate the establishment or improvement of preventive measures for the future.

Physicians, nurses, laboratory technicians, and pharmacists of a medical institution will make it possible to provide safe and effective blood transfusions for patients by carrying out their responsibilities and roles, under a cooperative system with the blood center. No matter how far blood transfusion therapy advances, however, potential risks of allogenic blood transfusion can never be completely avoided. Therefore, strategies such as autologous blood transfusion and limiting blood transfusion to the minimum necessary cases should be continued.

Since blood transfusion is a medical practice that is intimately associated with the safety of the general public, establishment of a system under which projects related to blood preparations are carried out under the auspices of the national government is awaited.

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APPROACH TO RISK MANAGEMENT IN MEDICAL PRACTICE: STANDPOINT OF THE CONTROL OF HOSPITAL-ACQUIRED INFECTIONS*

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Asian Med. J. 44 (1): 22-29, 2001

Abstract: As an integral part of risk management in the hospital, the control of nosocomial infections occupies a very important position in the prevention of a poor outcome among patients and hospital employees. In this article, the need for surveillance, reasonable use of antimicrobial agents, and prevention of transmission infections to hospital employees are discussed. Surveillance of hospital-acquired infections begins with collecting data in certain designated areas, such as the ICU or in certain patients with foreign materials. Surveillance should include reporting the rate of the infections rather than just numbers of cases, and the results of surveillance should be returned to each section as a tool for further improvement. The use of antimicrobial agents has an important role in discouraging the emergence of resistant strains. Each hospital should have guidelines for correct usage of antimicrobial agents, including antibiotic prophylaxis to prevent surgical wound infection. Standard precautions and vaccinations are mentioned as a means of protecting hospital employees from infections.

Key words: Surveillance; Antimicrobial agents; Isolation strategies;
Occupational infections

Introduction

Control of the incidence of hospital-acquired infections to the minimum is the essence of infection control, representing an approach to risk management. Although the manifestation of hospital-acquired infection is already beyond the preventive boundary of risk management, treatment of these infectious diseases at onset is of great importance. Preventive measures, however, should be undertaken in each hospital against the occurrence of such nosocomial infections.

This paper describes the necessity of surveillance, standards for the use of antimicrobial agents, isolation strategies, and prevention of nosocomial infections in hospital personnels.

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 5, 2000, pages 645-650).

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		Purulent discharge*	Pain	Swelling	Redness	Fever	Diagnosis by the surgeon	Dehiscence
Skin	Superficial incisional SSI [†]	+	+	+	+	±	+	-
Subcutaneous tissue								
Deep soft tissue (fascia, muscle)	Deep incisional SSI [†]	+	+	+	±	+	+	+
Organ, space	Organ/space SSI [†]	+	+	±	±	+	+	+

*Or microbial growth demonstrated by culture.

[†]Infections occurring within 30 days of a nonimplant procedure or within one year of an implant procedure.

Fig. 1 CDC-diagnostic criteria for surgical site infections (SSI)

Necessity of Surveillance

1. Purpose of surveillance

Surveillance of hospital-acquired infections begins with the collection of data. The purpose of surveillance is to reduce the mortality and morbidity of nosocomial infections by minimizing their incidence. This leads to improvement of the quality of medical care and minimizes the risks associated with nosocomial infections.

2. Target area for surveillance

Whole-hospital surveillance to understand the current status of nosocomial infections may be impractical and confusing. It is therefore recommended (1) that surveillance be conducted in areas where nosocomial infections are frequently encountered, such as ICU and surgical wards, or (2) that attention be focused on patients who are susceptible to infections owing to the use of foreign materials such as a central vascular lines, urinary catheters, and mechanical ventilators. Naturally, attention to both of the aforementioned areas would be acceptable.

3. Common terminology for surveillance

To carry out surveillance of hospital-acquired infections and determine their incidence, it is important to know the definitions of nosocomial infections. For example, the CDC classification of wound infections is shown in Fig. 1.

A bacterial infection associated with urinary catheterization is simply defined as the presence in a urine specimen of a bacterial cell count of 10⁵/ml or more.

The incidence rate of bacteremia associated with central vascular lines is calculated as the number of cases with positive blood culture divided by the total number of cases with central vascular lines.

The incidence rate of bacteremia associated with central vascular lines

$$= \frac{\text{Number of cases with bacteremia associated with central vascular lines} \times 1,000}{\text{The total number of cases with central vascular lines}}$$

Table 1 Antibiotic Prophylaxis

	Medical antibiotic prophylaxis	Surgical antibiotic prophylaxis
Target microorganism	Depending on the disease to be prevented	Normal skin and mucosal flora
Antibiotics	Depending on the disease	Mainly, first-generation cepheems
Duration of treatment	Relatively prolonged	One hour before surgery, and during surgery if necessary
Target disease	Examples: rheumatic fever, endocarditis, tuberculosis, cryptococcal meningitis, malaria	Clean and semi-clean surgery

4. Use of surveillance results

The results of surveillance should be returned to each section of the hospital to enable the staff in the section to draw up measures for reducing the incidence of nosocomial infections. Follow-up surveillance should then be continued. This feedback mechanism helps greatly in reducing the incidence of nosocomial infections and improving their outcome.

Hospital-acquired Infections and the Use of Antimicrobial Agents

Hospital inpatients often have diminished immunological competence, and foreign materials such as central vascular lines and urinary catheters are often used in these patients, making them highly susceptible to infections. These patients often develop fever and frequently receive antibiotic therapy. The relationship between the frequent use of antimicrobial agents and the emergence of drug-resistant strains must be emphasized here.

Before the occurrence of nosocomial infections attracted medical attention, the use of erythromycin and development of erythromycin-resistant hemolytic streptococci was an important issue, as was the use of penicillin and the emergence of penicillinase (β -lactamase)-producing staphylococci.

It has been shown that infection with MRSA (methicillin-resistant *Staphylococcus aureus*) is more closely related to the duration and dose of antibiotic therapy than is infection with MSSA (methicillin-sensitive *Staphylococcus aureus*).

1. Prophylactic antibiotic therapy should be administered only when indicated

Antibiotic prophylaxis is divided into medical and surgical prophylaxis (Table 1). Medical prophylaxis in hospitals is limited. In contrast, surgical antibiotic prophylaxis is administered an hour before operation in clean or semi-clean surgeries. It has been demonstrated that postoperative antibiotic prophylaxis is not helpful in reducing the incidence of postoperative infections. Recent data on the incidence rate of postoperative infection in relation to the time of administration of antimicrobial agents before or after surgery show that antimicrobial therapy given 1 hour before surgery is associated with the lowest incidence rate of postoperative infections.

Table 2 Standards for the Use of Antimicrobial Agents

-
-
1. Gram's staining and bacterial culture, necessary for identifying the etiologic agent, should be carried out before antimicrobial drug treatment.
 2. Antimicrobial therapy should be instituted based on careful examination of the patient with fever, and the antimicrobial agent used must be changed based on the data of sensitivity of the etiologic agent.
 3. Surgical antibiotic prophylaxis should be administered just before clean or semi-clean surgery, and continued during the surgery if necessary. The antimicrobial agent used is usually selected from among first-generation cepheps.
 4. Second- and third-generation cepheps and carbapenem must not be used as first-line drugs for the treatment of community-acquired infections, except when the infection is caused by a strain sensitive to second- and third-generation cepheps or carbapenem alone.
 5. Multiple antimicrobial drug therapy is effective only in limited situations. Combined use of multiple drugs does not necessarily result in synergism.
 6. Fever occurring during antimicrobial therapy should be evaluated bearing the possibility of drug fever in mind.
 7. It would be desirable to consult infectious disease specialists before a third-generation cephem or carbapenem is used.
 8. Vancomycin for MRSA should be used only in infections, and not colonization.
 9. Topical antimicrobial treatment should be avoided.
 10. Monitoring of blood concentrations should be considered when an aminoglycoside and vancomycin are used concomitantly in elderly patients.
-

Prophylactic vancomycin therapy against MRSA colonization facilitates the growth of vancomycin-resistant MRSA, rather than being of any benefit. Continued vancomycin therapy in patients with urinary catheters may result in the appearance of vancomycin-resistant enterococci (VRE).

2. Simple antimicrobial therapy

In general, a single etiological agent is responsible for an infection, and therefore there is no need for multiple antimicrobial therapy. However, multiple antimicrobial therapy is recommended in some situations, e.g., in patients with acute leukemia who have neutropenia and develop fever.

Diarrhea related to antimicrobial therapy, particularly that caused by *Clostridium difficile*, is a common nosocomial infection reported in European and American countries. It has become apparent that *C. difficile*-associated diarrhea is closely related to the administration of certain types of antimicrobial drugs, such as that, in particular, of second- or third-generation cepheps, clindamycin, ampicillin, or amoxicillin. Impudent administration of broad-spectrum antimicrobial agents should be particularly avoided.

3. Laying down standards for the use of antimicrobial agents

To suppress the emergence of resistant strains, each hospital should develop

Table 3 Report of the Sensitivities of In-hospital Isolates
 [Drug sensitivities (%) of species isolated in Tokyo Saiseikai Central Hospital: Monthly report]

		DMPPC	PCG	ABPC	CBPC	PIPC	CEZ	CAZ	CCL	CXM	CPZ	CMZ	LMOX	IPM	AZT	GM	TOB	AMK	MINO	EM	CLDM	CPFX	ST	No. of strains	
<i>Escherichia coli</i>	Inpatient			71		74	91					100	100	100	97	94		100				97	91	35	
	Outpatient			65		83	65					87	100	100	100	100		100					100	100	46
<i>Klebsiella spp</i>	Inpatient			0		89	100					100	100	100	100	100		100					100	100	27
	Outpatient			0		33	78					100	100	100	100	100		100					93	85	14
<i>Enterobacter spp</i> (Excluding <i>E. agglomerans</i>)	Inpatient			0		84	5					5	100	100	95	100		95					100	100	19
	Outpatient			0/3		3/3	0/3					0/3	3/3	3/3	3/3	3/3		3/3					3/3	3/3	3
<i>Serratia spp</i>	Inpatient			0		26	0					20	60	100	67	80		53					53	67	15
	Outpatient			0/7		4/7	0/7					2/7	4/7	6/7	6/7	7/7		4/7					3/7	6/7	7
<i>Proteus mirabilis</i>	Inpatient			91		100	82					100	100	100	100	91		100					91	100	11
	Outpatient			6/6		6/6	5/6					6/6	6/6	6/6	6/6	6/6		6/6					6/6	6/6	6
<i>P. vulgaris</i> , <i>Morganella morganii</i> , <i>Providencia spp</i>	Inpatient			0/2		2/2	0/2					2/2	2/2	2/2	2/2	2/2		2/2					2/2	2/2	2
	Outpatient			0/4		3/4	0/4					0/4	4/4	4/4	4/4	3/4		4/4					3/4	3/4	4
<i>Citrobacter spp</i>	Inpatient			0/2		2/2	0/2					0/2	2/2	2/2	2/2	2/2		2/2					2/2	2/2	2
	Outpatient			0/1		1/1	0/1					0/1	1/1	1/1	1/1	1/1		1/1					1/1	1/1	1
<i>Acinetobacter calcoaceticus</i>	Inpatient			0/3		3/3	0/3					0/3	0/3	3/3	1/3	3/3		3/3					3/3	2/3	3
	Outpatient			1/3		2/3	0/3					1/3	0/3	2/3	3/3	1/3		2/3					3/3	3/3	3
<i>Haemophilus influenzae</i>	Inpatient			83		100			100	100		100											100		12
	Outpatient			4/4		4/4			4/4	4/4		4/4											4/4		4
<i>Pseudomonas aeruginosa</i>	Inpatient				68	77		95				89			91	82	80	91	93					98	44
	Outpatient				5/9	9/9		9/9				9/9			9/9	9/9	8/9	9/9	8/9					7/9	9
<i>Staphylococcus aureus</i> (MRSA)	Inpatient	0	0	0			3					1		10				3	18	55	3	21	11		80
	Outpatient	0	0	0			0					0		0				0	0	38	0	0	8		13
<i>S. aureus</i> (MSSA)	Inpatient	100	0	0			100					100		100				94	96	100	88	100	98		51
	Outpatient	100	42	42			100					100		100				88	96	100	88	96	92		26
<i>S. epidermidis</i>	Inpatient		29	29			79					57		50				57	86	86	64	79	50		14
	Outpatient		36	39			91					82		94				67	85	97	73	88	79		33
<i>Enterococcus faecalis</i>	Inpatient		79	100										100		8					34		25		29
	Outpatient		95	95										100		0					16		11		19

institutional standards for the use of antimicrobial agents (Table 2). The standards should emphasize the need for Gram's staining and restrictions on the use of second- and third-generation cepheims and carbapenem in patients with community-acquired infections. Topical antimicrobial treatment should be avoided.

It is recommended that a table of isolates and their antimicrobial drug sensitivities be prepared in each hospital, and updated regularly (e.g., at 6-month intervals). Such a table will help identify the relationship between the use of antimicrobial agents and the emergence of drug-resistant strains in the hospital (Table 3).

Prevention of occupational infections

The hospital is responsible for not only preventing infections among patients, but also for protecting hospital personnels, including physicians, nurses, and medical technicians, who are in direct contact with patients, against infections.

1. Isolation of patients

Standard isolation precautions have been proposed by the Centers for Disease Control and Prevention (CDC), USA, and must be followed in every inpatient (Table 4). Standard precautions must be followed in the handling of blood, body fluids, secretions (other than perspiration), and non-intact skin and mucosa.

Besides the standard precautions, precautions based on the routes of transmission are also necessary (Table 4). These precautions pertain to three categories of transmission, i.e., airborne, droplet, and contact transmissions. Airborne transmission is the route of transmission of infections such as measles and tuberculosis, and droplet transmission refers to the transmission of diseases via droplets measuring over $5\mu\text{m}$ in diameter generated from the patient. The droplets cause infection when deposited on the hosts' conjunctivae, nasal mucosa, or oral mucosa. Contact transmission refers to the transmission of diseases via direct contact, or contact with a contaminated intermediate object. Precautions against infections by these routes of transmission of infection must also be taken in addition to the standard precautions.

However, to what extent such precautionary measures can be adhered to in hospitals in Japan is an issue of importance.

2. Prevention of tuberculosis

It appears that the number of health care professionals developing tuberculosis as a result of exposure to patients with tuberculosis has recently been increasing. Insufficient knowledge regarding the transmission of tuberculosis underlies such onset of the disease in health care professionals.

Health care professionals should always bear in mind the possibility of tuberculosis when treating patients. When infection is suspected, the patient should be isolated in a private room until the possibility of tuberculosis is eliminated. The hospital manager should keep records of tuberculin skin tests performed in hospital personnel who come in contact with tuberculosis patients. When hospital personnel are exposed to patients with tuberculosis, those with previously negative tuberculin tests should undergo repeat tuberculin testing and chest roentgenography to detect the occurrence of primary infection.

3. Prophylactic vaccination or drug treatment

The hospital manager should set up a system that ensures immediate access to prophylactic vaccination against infections transmitted by accidental needle stick injury, 24 hours of a day. If the accidental needle stick injury involves the risk of contracting type-B hepatitis virus infection, a globulin preparation should be made available immediately. In case of needle stick injury involving the risk of contracting human immunodeficiency virus (HIV) infection, the system should

Table 4 List of Isolation Precautions (CDC Guidelines, 1996)

Type		Standard precautions		
		Precautions against airborne transmission	Precautions against droplet transmission	Precautions against contact transmission
Indications	All patients	Patients with serious illnesses transmitted by airborne droplet nuclei	Patients with serious illnesses transmitted by large particle droplets	Patients with serious illnesses easily transmitted by direct patient contact or by contact with infected material
Representative diseases	All, regardless of the diagnosis	Measles, varicella, tuberculosis	Invasive <i>Haemophilus influenzae</i> type-b disease (meningitis, pneumonia, epiglottitis, and sepsis), Invasive <i>Neisseria meningitidis</i> disease (meningitis, pneumonia, and sepsis), Other serious bacterial respiratory infections spread by droplet transmission [diphtheria (pharyngeal), mycoplasma pneumonia, pertussis, pneumonic plague, streptococcal pharyngitis, pneumonia, or scarlet fever (in infants and young children)], Serious viral infections spread by droplet transmission (adenovirus, influenza, mumps, parvovirus B19, rubella)	Gastrointestinal, respiratory, skin, or wound infections or colonization with multidrug-resistant bacteria judged to be of special clinical and epidemiologic significance, and enteric infections by organisms requiring a low infectious dose or by those capable of prolonged environmental survival (<i>Clostridium difficile</i> , enterohemorrhagic <i>Escherichia coli</i> O157:H7 in diapered or incontinent patients, shigella, hepatitis A, rotavirus, respiratory syncytial virus and parainfluenza virus in infants and young children), Enteroviral infections, Skin infections that are highly contagious or that may occur in dry skin [diphtheria (cutaneous), herpes simplex virus infection (neonatal or mucocutaneous), impetigo, major (noncontained) abscesses/cellulitis/decubitus ulcers, pediculosis, scabies, staphylococcal furunculosis in infants and young children, zoster (disseminated or in immunocompromised hosts)], viral/hemorrhagic conjunctivitis, viral hemorrhagic infections (Ebola, Lassa, or Marburg)
Hand-washing	Wash hands after touching body fluids or other biological materials; immediately after gloves are removed; after patient contact.*1	Same as *1	Same as *1	Same as *1
Gloves	Wear gloves when touching body fluids or other biological materials and when touching mucous membranes and nonintact skin.*2	Same as *2	Same as *2	In addition to *2, wear gloves when entering the room. Change gloves after touching infective material. Remove gloves before leaving the room, and wash hands immediately with an antimicrobial or antiseptic agent.
Mask	Wear a mask to protect the mucous membranes of the eyes, nose, and mouth during procedures that are likely to generate splashes or sprays of body fluids or other biological materials.*3	In addition to *3, wear respiratory protection (N95 mask) when entering the room. Fit test.	In addition to *3, wear a mask when working within 1m of the patient.	Same as *3.
Gown	Wear a gown to prevent soiling of clothing.*4	Same as *4.	Same as *4.	In addition to *4, wear a gown when entering the room when substantial contact with the patient is anticipated. Remove the gown before leaving the room.
Patient-care equipment	Handle used patient-care equipment in a manner that prevents contamination of the mucosae, clothing, and other environments. Ensure that reusable equipment is not used until it is cleaned.*5	Same as *5.	Same as *5.	In addition to *5, dedicate the use of patient-care equipment to a single patient, or adequately disinfect common equipment before use in another patient.
Linen	Handle, transport, and process used linen in such a manner as to prevent contamination of mucosae, clothing, and other environments.*6	Same as *6.	Same as *6.	Same as *6.
Patient placement	Place a patient likely to contaminate the environment in a private room. (If a private room is not available, consult with infection control professionals.)*7	In addition to *7, place the patient in a private room that has monitored negative air pressure, 6 air changes per hour, and appropriate discharge of air outside the room.	In addition to *7, place the patient in a private room or under cohorting, or maintain spatial separation of at least 1m from other patients.	In addition to *7, place the patient in a private room or under cohorting, or consider the epidemiology of the microorganism and the patient population when determining patient placement.
Patient transport		Limit transport of the patient. If transport is necessary, use a surgical mask on the patient.	Limit transport of the patient. If transport is necessary, use a surgical mask on the patient.	Limit transport of the patient.
Others	Take care to prevent needle stick injury.*8	Same as *8.	Same as *8.	In addition to *8, take precautions against contamination of the environment (daily cleaning) and against VRE (vancomycin-resistant enterococci).

allow prompt initiation of anti-HIV, three-drug treatment.

Health care professionals should receive vaccination against influenza virus infection so as to prevent them from becoming sources of infection. Currently, it remains controversial as to whether BCG vaccination is a preventive measure against tuberculosis, particularly in adults. In the author's opinion, BCG vaccination should not be recommended routinely, and follow-up should be conducted by tuberculin testing.

Conclusion

Risk management pertaining to nosocomial infections is difficult to implement properly in Japan, which has poor human resources and hospital economics. However, failure to control nosocomial infections will undermine various aspects of medical care. Beginning with doing what can be done and proceeding steadily to higher levels of infection control is recommended as a way of practicing risk management.

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MUSIC THERAPY AND INTERNAL MEDICINE*

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Asian Med. J. 44(1): 30-35, 2001

Abstract: Music therapy is an alternative and supplemental form of treatment used to treat a variety of diseases in the field of internal medicine, including psychosomatic and lifestyle-related diseases, specifically digestive ulcer, NUD (non-ulcer dyspepsia), chronic pancreatitis, hypertension, bronchial asthma, diabetes mellitus, simple obesity, Basedow's disease, terminal cancer, and senile dementia. It has been used in treating patients undergoing chronic dialysis, blood donation activities, in rehabilitation activities for cerebrovascular accidents (CVA), endoscopic examinations, in intensive care units (ICU), and to stabilize blood pressure, promote sleep, and reduce pain. Music therapy has also been applied in diet therapy using background music (BGM) that is played during meals and karaoke is also a form of music therapy that can be effectively utilized in social situations. It is also utilized in physical and exercise therapy, in rehabilitating patients recovering from CVA and in treating the aged, and in promoting the interpersonal relationship between the patient and the therapist. Music therapy is also effective in promoting the health of professional athletes; and the Awa folk dance in Japan is also used as dance therapy. Rhythmical background music has also been effectively applied using the Walkman.

Key words: Music therapy; Lifestyle-related disease; Diet therapy; Exercise therapy

Introduction

Music therapy has been used to treat numerous diseases in the field of internal medicine, including psychosomatic diseases. In this paper, the correlation between lifestyle-related diseases and diet and exercise is presented.

In this age of advanced technology, the science of medicine alone is unable to cure patients. The art of medicine, as advocated by Hippocrates, effectively utilized music in curing the mind and body of patients. Presently, music therapy is utilized in the fields of medicine, health care, music, education, and social welfare; and its cultural and artistic merits are equally important.

Music therapy allows patients to become directly involved and the benefits of utilizing this method in patience guidance activities is presented in this paper.

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 122 No. 7, 1999, pages 1173-1176).

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Human Beings and Rhythm

Human beings have an inborn love of music and a sense of rhythm. The fetus develops listening to the heartbeat and voice of the mother and infants will change from crying, smiling, to speaking in conjunction with the voice of the mother and other family members and the sounds emanating from the environment. A mother's voice, that is filled with love and affection, is in the alto region and infants are comforted when they are cradled and talked to for about one second in the arms of a mother whose voice is in the alto region.

Human beings maintain their health and live in harmony with melody and rhythm throughout their childhood, adulthood, and the twilight years of their lives. Health is lost when this harmonious balance is destroyed. The human body maintains a pulse, body temperature, respiration, and other vital signs as well as a metabolism and blood flow that functions according to an inherent rhythm. Our behavioral patterns such as eating and sleeping are also based on a consistent rhythm and work activities are synchronized accordingly. The bodily organs are the instruments and the heart is the conductor. The integrated role or function of these instruments are integrated to produce an orchestral performance.

Application and Treatment

Music therapy is widely applied in many areas of health care. However, it is commonly utilized in internal medicine to treat digestive ulcer, NUD (non-ulcer dyspepsia), chronic pancreatitis, hypertension,¹⁾ bronchial asthma, diabetes mellitus, simple obesity, Basedow's disease, terminal cancer,²⁾ and senile dementia.³⁾ It has been used in treating patients undergoing chronic dialysis, blood donation activities, in rehabilitation activities for CVA, during endoscopic examinations,⁴⁾ in intensive care units (ICU), cardiac care unit (CCU), to stabilise blood pressure, promote sleep,⁵⁾ and reduce pain. There are two categories of music therapy—the active form of singing and playing an instrument and the passive form of listening to music. Body sonics, pillows with stereo music, or BGM are the most common forms of the latter category of music therapy.

Music therapy also has supplementary benefits, in addition to being an effective means of treating diseases. Its effectiveness as a form of treatment must be investigated objectively.⁵⁾ It helps rehabilitation activities to be performed more easily and lessens the apprehension of patients undergoing dialysis and other forms of treatment.

In the clinical setting, many hospitals and nursing homes utilize music therapy in their rehabilitation activities for patients recovering from CVA. Blood pressure is lowered and stabilized in patients suffering from hypertension; and orthostatic hypotension is also stabilized with the use of music therapy. In addition, patient compliance has been favorable when music therapy is used in long-term treatment and rehabilitation activities in the aftermath of acute myocardial infarction.⁶⁾

Life-style Related Diseases

The term, lifestyle-related diseases, was initially used and discussed in Japan in 1978 by Dr. Shigeaki Hinohara, President of the Japan Biomusic Association. Recently, the Ministry of Health and Welfare has begun to utilize this term in lieu of the commonly known term, adult diseases.

The fundamental factor to maintaining good health is a balanced diet, moderate exercise, and mental rest. The key to sustaining good health is to maintain an established pattern of activity in our lifestyles. Maintaining a 24-hour daily cyclical rhythm produces a 1/f fluctuation, which induces the feeling of being comfortable. This is because some irregularity exists within lifestyles with an established pattern of activity.

Diet and Music

The most important meal of the day is breakfast, but an increasing number of the younger generation has begun to skip breakfast in recent years and this has become a health issue in Japan. The general intake proportion of meals in Japan is 20 percent for breakfast, 30 percent for lunch, and 50 percent for dinner, in contrast to the ideal proportion of 40 percent for breakfast, 35 percent for lunch, and 25 percent for dinner. Simple obesity and lifestyle related diseases can be prevented if the ideal proportion of food intake is followed. Case examples that may prove useful in explanations to patients regarding the importance of incorporating music in their daily lives have been given below.

1. Rising early in the morning is recommended and late risers should use an alarm clock with a loud buzzer or digital alarm. For those who can get up easily, it may be a good idea to set the time switch on the radio to allow baroque or other kinds of music to play in the morning. This will help such people to wake up quietly and comfortably.

2. After rising, drinking milk or other liquids is recommended, followed by a short walk or light exercise. The added time spent after rising and before breakfast helps to increase the appetite. In addition, fructose derived from fruits that are consumed at breakfast are converted quickly into energy without insulin secretion from the pancreas. Hence, it is said in Japan that fruits which are consumed at breakfast are comparable to gold, fruits eaten at lunch are comparable to silver, and fruits eaten at dinner are comparable to copper.

3. Many people rush through their breakfast, urged on by the time that appears on their television screens. Listening to rhythmical BGM is recommended in the morning. On holidays, it is recommended that the gurgling of small streams, singing birds, and other environmental sounds or refreshing BGM are played during breakfast.

4. Light exercise that induces perspiration, followed by a bath and dinner, is recommended in the evenings. Bathing after an evening meal is not beneficial in terms of blood circulation; and meals consumed late at night increase the onset of lifestyle-related disease, such as hyperlipemia. Therefore, they should be eaten early in the evening. If BGM is played in the evenings, easy listening music that

soothes the mind and body is recommended rather than rock music.

5. Karaoke is the best form of music therapy that Japan can be proud of having developed. It is the optimum form of therapy for relieving stress and for its reinvigorating effects. Aristotle promoted the principle of same quality that promulgates the idea that human beings listen to cheerful music when they are in a happy state of mind and listen to soothing, consoling music when they are sad. The author recommends listening or singing firstly to soulful music, secondly love ballads and lastly rhythmical and cheerful music in the case of karaoke, as the most effective means of alleviating the daily emotional stress.

The above are merely some suggestions and the general rule is to allow the clients or patients to select their favorite music.

Exercise and Music

A good relationship is established between the patient and the therapist when music therapy is utilized during rehabilitation activities for patients recovering from CVA or for the elderly. Generally, 2-beat or 4-beat music is easier for patients to grasp the rhythm and three-beat or rhythmical waltzes can be introduced after patients have become accustomed to the 2-beat music.

The author has arranged and published a music book with CD, entitled "Japanese Songs of the Four Seasons", which include 12 famous Japanese folk songs such as "Haruno Ogawa" (Spring Brook Melody), "Natsuno Omoide" (Summer Memories), "Akatonbo" (Red Dragonfly), and others. The book and CD have been published with the hope that it can be utilized as both an active and passive form of music therapy in hospitals and nursing homes in Japan (Fig. 1).

The author's hometown, Tokushima, is famous for its Awa Dance Festival which is held in the summer. However, the Awa dance can also be enjoyed throughout the year and tourists who visit the town are also able to participate in this dance. In clinical studies of sports medicine, it was discovered that the Awa dance was an ideal type of continuous aerobic exercise that did not strain the heart and lungs.⁷⁾ Dancing is a continuous form of exercise and it is also useful as a form of music therapy that can be adjusted according to the condition of the patients.

In recent years, an increasing number of people in all age groups have joined fitness clubs and taken up aerobic exercises. These sessions provide continuous and effective exercises for 30 to 75 minute periods. When the participants' pulse rate rises to higher than 180 per minute, precautions against overexertion are taken and they are encouraged to rest. In the past, aerobic exercises were mainly high impact exercises with a lot of jumping that placed stress on the knees and ankles. As a result, ankle sprains and foot fractures were often reported. The author has been apprehensive of the burden placed on the knees of middle-aged and overweight people.

Recently, low impact aerobic exercise programs, that utilize a 10 to 24 cm high platform where one foot is always kept on the floor, has become popular. This type of exercise reduces the impact to the knees, ankles, and joints. All aerobic programs utilize music and music is an indispensable factor during the cooling down phase of the program as well. The use of soothing music in a darkened room

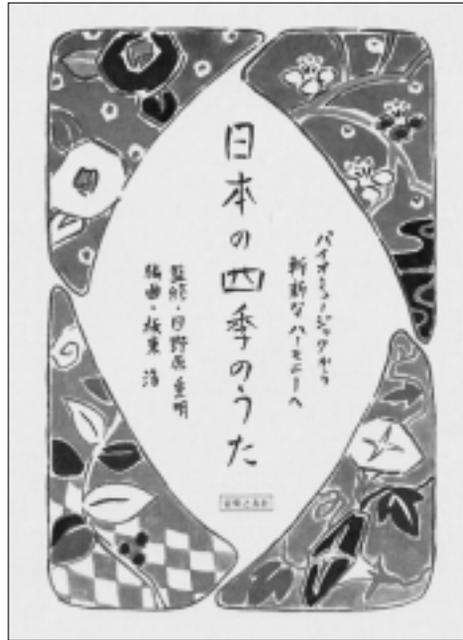


Fig. 1 "Japanese Songs of the Four Seasons" with CD, edited by Shigeaki Hinohara, M.D., arranged by Hiroshi Bando (Published by Ongakuno Tomosha, Tokyo, Japan, January 1998)

heightens the sense of comfort and accomplishment.

Music is also effectively employed in the training programs of athletes. The use of the Walkman when bicycling, walking or running on the treadmill alleviates the monotony of the exercise and helps athletes to continue the training program. The author is a speed skater and an athlete representing Tokushima Prefecture in the Japan National Sports Festival that is held in the winter. The sliding board is used during indoor training activities as part of the training program and the use of the author's own pre-selected music program has been effective for image training exercises.

Conclusion

In this paper, the author has attempted to discuss the importance of maintaining a daily rhythm of diet and exercise and the usage of music therapy in daily life.

In future, the author would like to explore the issue of using music therapy as an effective means of treating diabetic patients in conjunction with diet and exercise. Hopefully, music therapy will be recognized as a means of sustaining a healthy mind and body and as an effective tool in disease prevention.

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INSIGHTS INTO THE PATHOPHYSIOLOGY OF HEART FAILURE BASED ON A NEW CONCEPT*

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Asian Med. J. 44 (1): 36-41, 2001

Abstract: We have reported the increased myocardial expression of cytokines in animal models of heart failure secondary to myocarditis, myocardial infarction, and hypertension and we have shown that the lesions in impaired hearts resemble inflammatory or proliferative changes in some respects. In addition, the occurrence of crosstalk between cytokines and the adrenal axis, as well as between cytokines and the renin-angiotensin or endothelin system, has been suggested. Crosstalk between the sympathetic nervous system, endocrine systems, and the immune system may be important in adaptation and failure of the myocardium caused by various factors, including mechanical overload, ischemia, and viral infection. Elucidation of the mechanisms of these processes may lead to the development of new therapy for heart failure.

Key words: Heart failure; Cardiomyopathy; Cytokines; Immunity

Introduction

Over the years, the concept of heart failure has undergone dramatic changes. At first, heart failure was thought as a disease associated with renal failure due to alteration of cardiac function. Consequently, diuretics were once the mainstay of treatment. Subsequently, cardiotonics and vasodilators were used for this condition, because it was considered to arise from abnormal cardiac metabolism and abnormal circulatory responses, including the peripheral vessels. Recently, beta-adrenergic blockers and ACE inhibitors have become central to treatment because heart failure has considered as a disorder of the neurohumoral system.

Considering heart failure to be based on immune abnormalities, we hope that immunomodulation and anti-cytokine therapy will bring about major progress in its treatment. This article describes our attempts to gain new insights into the pathophysiology of heart failure based on such a viewpoint.

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 121 No. 11, 1999, pages 1745-1748).

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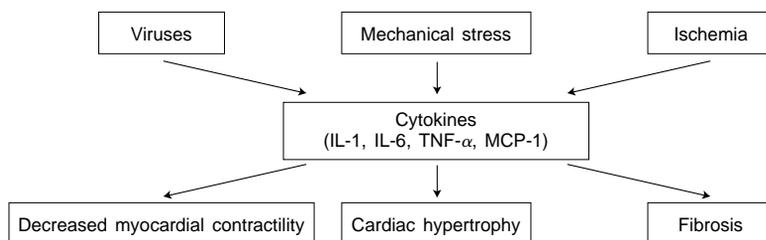


Fig. 1 Production of cytokines in response to various loads

Expression of cytokines in the heart is increased by viral infection, increased hemodynamic load, and ischemia. It has been suggested that cytokines such as IL-1, IL-6, and TNF- α cause a decrease of myocardial contractility, hypertrophy of cardiac myocytes, and myocardial fibrosis.

Cytokines and the Heart

Cytokines are important intercellular mediators, as well as being immunologically active substances. Recently, many cytokines have been shown to influence disorders of cardiac myocytes and cardiac function. This indicates that immunological factors such as cytokines, as well as neural and endocrine factors, may play an important role in the pathology of heart disease, and cytokines have come to attract particular attention.

When cardiac myocytes are injured by viruses, ischemia, and stress, there is an increase in the production of cytokines such as interleukin (IL)-1, IL-2, tumor necrosis factors (TNF- α), and interferon (IFN)- γ . Cytokines are deeply involved in the pathophysiology of heart disease. In addition, it has been shown that cytokines can act on the myocardium to decrease myocardial contractility and to promote myocardial hypertrophy and fibrosis (Fig. 1).¹⁻³⁾

Cytokines and Heart Failure

The relationship between heart disease and cytokines has attracted attention since elevation of blood TNF- α levels in chronic heart failure and an association between TNF- α and cardiac cachexia were reported. We have demonstrated that the blood levels of IL-1 α , IL-1 β , and TNF- α are frequently elevated in myocarditis and the TNF- α level is also frequently elevated in dilated or hypertrophic cardiomyopathy. Such findings strongly suggest that these cytokines play an important role in the pathogenesis of cardiomyopathy.³⁾ In addition, elevation of the blood levels of soluble TNF- α receptor, IL-2 receptor, and IL-1 receptor antagonists in heart failure and cardiomyopathy patients have been reported, and increased expression of myocardial IL-1 β mRNA in patients with dilated cardiomyopathy has also been reported.

In patients with heart failure, the blood levels of chemokines or macrophage chemotactic factors (MCP-1, MIP-1 α , and RANTES) were reported to be elevated and the blood levels of MCP-1 and MIP-1 α were negatively correlated with the left ventricular ejection fraction. There was no evident relationship between the MCP-1 level and the cause of heart failure, but its blood level tended to rise in

patients with coronary disease. When we determined blood levels of MCP-1 in patients with heart failure secondary to dilated cardiomyopathy, however, it was not elevated.

Because the blood MCP-1 level was increased in acute myocardial infarction, however, the possibility that MCP-1 may be related to ischemic heart disease is high. It has been reported that cardiac function (as assessed by echocardiography) was decreased in rats administered TNF- α via an osmotic pump and recovered after administration of TNF- α was discontinued or when soluble TNF- α receptor was administered.

Recently, transgenic mice specifically expressing TNF- α in the myocardium were produced using an α -myosin heavy-chain promoter. These transgenic mice developed myocarditis in both ventricles and atria along with enlargement of the left and right ventricular cavities and a decrease of the ejection fraction. In transgenic mice produced with a similar promoter, myocardium expressing MCP-1 specifically showed infiltration by macrophages, while the heart showed hypertrophy and dilation with a decrease of cardiac function during the chronic phase. These mice are quite interesting models of myocarditis and cardiomyopathy,

To clarify the role of IL-1 β , cardiac function was assessed in dogs receiving intracoronary injection of microspheres coated with recombinant human IL-1 β . Dogs treated in this way with IL-1 β developed persistent cardiac dysfunction. Aminoguanidine, an inducible NO synthase inhibitor, was able to prevent the development of cardiac dysfunction. Thus, dysfunction of the heart caused by IL-1 β was demonstrated *in vivo*.

Cytokines and Heart Failure Secondary to Myocardial Disease

Using a mouse model that develops heart failure secondary to myocarditis caused by infection with EMC virus, we investigated the relationship between the expression of cytokine messenger RNAs (mRNAs) in the myocardium and the severity of heart failure. This study showed that the expression of IL-1 β , IL-2, TNF- α , and IFN- γ mRNA was increased in the acute inflammatory phase, and that these cytokines were still expressed in the chronic phase after three months. These findings strongly suggested that such cytokines were relevant to pathogenesis of myocardial hypertrophy and fibrosis in the chronic phase.⁴⁾

There were positive correlations between the expression of IL-1 β , the heart to body weight ratio, and the extent of fibrosis. In addition, survival was improved when the mice were treated with a high dose of anti-TNF- α antibodies in the early phase of heart failure, while disease progression was seen when cytokines such as recombinant TNF- α were administered. Consequently, IL-1 β and TNF- α were considered to have potential injurious effects on cardiac myocytes that could lead to the aggravation of heart disease.

In recent years, hepatitis C virus (HCV) has been attracting attention as a cause of cardiomyopathy.⁵⁾ In patients with HCV infection, it has been reported that CD4-positive cytotoxic T lymphocytes infected with HCV produce cytokines such as IL-8, TNF- α , IFN- γ , and GM-CSF, while CD4-positive T lymphocytes produce IL-2, IL-4, IL-5, TNF- α , TNF- β , and IFN- γ . In patients with hepatitis

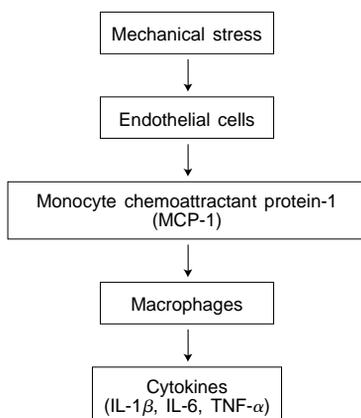


Fig. 2 Hemodynamic loading and the immune response
The hemodynamic load induces synthesis of MCP-1 by vascular endothelial cells, leading to migration and activation of macrophages in the myocardium. The macrophages thus activated may produce cytokines such as IL-1 β .

caused by HCV, elevation of TNF- α and soluble TNF- α receptor in the blood has been reported.

Cytokines and Heart Failure Secondary to Hypertension

We studied the expression of cytokines in Dahl salt-sensitive rats, which develop heart failure secondary to cardiac hypertrophy caused by hypertension. Specimens of the myocardium were obtained from rats in the stages of hypertrophy and heart failure, and the expression of IL-1 β and TNF- α mRNA was investigated. Although expression of TNF- α mRNA was not so remarkable, expression of IL-1 β and MCP-1 mRNA was increased in both stages. Their expression in the stage of heart failure was stronger than in the stage of hypertrophy.⁶⁾ The expression of IL-1 β was positively correlated with the weight and diastolic diameter of the left ventricle, and was negatively correlated with left ventricular fractional shortening. Consequently, IL-1 β appears to play a role in cardiac hypertrophy and heart failure. The infiltration of numerous macrophages in the left ventricular myocardium of Dahl rats suggested that IL-1 β might have been produced by these macrophages and by endothelial cells.

The results of this study on Dahl rats led us to investigate whether mechanical stress could induce the production of cytokines. We studied cytokine production by human umbilical vein endothelial cells (HUVEC) that were subjected to stretching.⁷⁾ This mechanical stretch induced a marked increase in the production of IL-8 and MCP-1 by these cells. This increase showed that vascular endothelial cells can produce MCP-1, a macrophage chemotactic factor, when stimulated mechanically by stretching. The enhanced ventricular expression of MCP-1 in Dahl rats suggested the possibility that infiltration of macrophages into the myocardium would be mediated by MCP-1 (Fig. 2).

Cytokines in Heart Failure after Myocardial Infarction

As described above, the cytokine production can be induced by stresses such as viral infection and hypertension. Whether cytokines can be induced by ischemia was also studied.⁸⁾ In rats, marked expression of the mRNAs for TNF- α , IL-1 β , and IL-6 was noted in the infarcted area at one week after the development of myocardial infarction, and then in the non-infarcted region at 20 weeks after its development. The expression of cytokine mRNAs in the non-infarcted region was correlated with the end-diastolic diameter of the left ventricle. Twenty weeks after infarction, the infarcted region was replaced with scar tissue, while vascular endothelial cells, smooth muscle cells, and macrophages were still IL-1 β positive in the non-infarcted region. In addition, the myocardial collagen content was related to the expression of IL-1 β in the non-infarcted region, suggesting an association between remodeling after myocardial infarction and cytokine expression.⁸⁾ Furthermore, it has been shown that expression of MCP-1 is increased during the acute phase of myocardial infarction, and that administration of anti-MCP-1 antibodies reduces the infarct size.⁹⁾

From these findings, it appears that the expression of cytokines may reflect the development and pathology of heart disease, so cytokines may be of value as diagnostic and therapeutic markers.

Treatment of Heart Failure and Cytokines

Recently, it has been demonstrated that phosphodiesterase inhibitors, which were developed to treat heart failure, can inhibit the production of cytokines. It has been recognized that different inhibitors produced different effects. It has been also recognized that digitalis can increase the production of cytokines.¹⁰⁾ An antiarrhythmic agent amiodarone, which has been shown to improve the long-term prognosis of heart failure, was recently shown to inhibit the production of TNF- α and IL-6.¹¹⁾

Because drugs that control the production of cytokines and signal transduction seem to be effective for the treatment of heart failure, it is expected that immunological response modifiers will be developed as a new form of therapy in the future.

Cytokines and Crosstalk between the Sympathetic Nervous System, Renin-angiotensin System, and Endothelin

The results of recent studies have highlighted the association between the immune system and the central and autonomic nervous systems. It has become clear that increased production of adrenocortical hormones secondary to activation of the hypothalamic-pituitary-adrenal axis reduces the production of cytokines. In heart failure, the sympathetic nervous system is activated, leading to increased secretion of catecholamines, which act on many immune cells such as macrophages and lymphocytes.

Many immune cells, including lymphocytes, macrophages, eosinophils, and neutrophils, possess β -receptors. It has become clear that when β -receptors are

stimulated, the intracellular cAMP level increases and various immune responses are suppressed. Psychological stress is known to increase norepinephrine, which suppresses cellular immunity through modification of helper T-cell functions and also increases humoral immunity.

The renin-angiotensin system and endothelin both play an important role in cardiovascular diseases and both show crosstalk with cytokines. For example, TNF- α increases the production of angiotensinogen by liver cells, while angiotensin II increases the production of IL-6, TNF- α , and MCP-1 by kidney cells. IL-1 β and TNF- α increase the production of endothelin-1, which in turn increases the production of IL-6 by endothelial cells or IL-8 and GM-CSF by bronchial cells.

Thus, it is likely that cytokines form positive feedback circuits with the renin-angiotensin system and endothelin in cardiovascular disease.

Conclusion

In addition to the neural and endocrine factors that have been investigated extensively to date, immunological factors such as cytokines seem to play an important role in cardiovascular disease. If all these systems are taken into consideration, a new strategy for the treatment of heart failure may be designed.

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CONTROL OF TRIGLYCERIDE*

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Asian Med. J. 44 (1): 42-47, 2001

Abstract: Hypertriglyceridemia has been considered to be a risk factor in progressing atherosclerosis because it increases the production of remnant and small dense LDL and frequently reduces HDL. It is also suggested that hypertriglyceridemia is involved in the development of atherosclerosis because it accelerates thrombophilia. Remnant is an atherogenic lipoprotein reported to increase in patients with diseases associated with multiple coronary risk factors, such as insulin resistance syndrome, and such diseases have recently become a matter for concern among medical professionals. Patients with increased remnant often develop hypercholesterolemia, hypertriglyceridemia, and reduced HDL. Remnant, which is abundant in cholesterol and apo-E, is incorporated into cells in a physiological form without being modified oxidatively. All long-term large-scale studies on the preventive effect of fibrates on hypertriglyceridemia have reported that improving the disease inhibits the development of cardiovascular events.

Key words: Triglyceride; Remnant; Syndrome X; HDL

Introduction

Hyperlipidemia has recently attracted widespread attention and it is considered that care should be taken in selecting daily foods to prevent the disease. This trend has occurred because earlier studies revealed that the disease is the most apparent risk factor in developing arteriosclerotic diseases, such as ischemic heart disease. Therefore, determining the upper limit of lipid level that is considered not to cause complications such as atherosclerosis based on the result of epidemiological investigations for the definition of hyperlipidemia would seem to be an appropriate measure. Currently, the consensus of opinion among Japanese medical professionals is that the upper limit of fasting total cholesterol is 220 mg/dL, and that of triglyceride 150 mg/dL. These values are also applied to the new guidelines.

The lifestyles of Japanese people have changed dramatically in the last 50 years: In particular, the changes in eating habits and reduction in the amount of exercise are remarkable. Among the changes in eating habits, the increased intake

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 4, 2000, pages 503-506). The Japanese text is a transcript of a lecture originally aired on June 7, 1999, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

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of animal fat and the reduced intake of dietary fibers have greatly contributed to the increase in the number of hyperlipidemia patients. In addition to these changes in eating habits, the reduction in the amount of exercise has accelerated the tendency toward obesity among Japanese people and had effects on the values of triglyceride and HDL cholesterol, which are important parameters of dyslipidemia. These changes in the parameters are associated with increased caloric intake and reduced energy consumption. Various types of dyslipidemia including hypertriglyceridemia develop as a result of such excessive calorie accumulation.

Patients with mild diabetes mellitus associated with obesity, hyperinsulinemia or glucose intolerance disorder often have underlying insulin resistance as well as glucose intolerance, dyslipidemia, and hypertension simultaneously, although it depends on the predisposition of individual patients. The combined risk factors are regarded to be serious metabolic disorders underlying various modern circulatory diseases. It is also considered that when the severity of combined risk factors aggravated, atheromatous plaque lesions may become unstable, resulting in the earlier development of ischemic heart disease. Hypertriglyceridemia has attracted attention as a hyperglycaemia that plays a central role in the process. The qualitative abnormality of the disease is the increase in remnant.

Hypertriglyceridemia as a Risk Factor of Ischemic Heart Disease

Hypercholesterolemia has been established as an independent risk factor of ischemic heart disease, and aggressive preventive and treatment measures have been taken against it because the causal relationship with ischemic heart disease has been clearly demonstrated in the Framingham Study and investigative studies on primary hyperlipidemia conducted in Japan. Existing epidemiological studies have indicated that increased triglyceride is a risk factor of ischemic heart disease, however, it is considered to be less significant than increased total cholesterol and reduced HDL. Triglyceride often increases in climacteric women.

However, hypertriglyceridemia has recently been attracting the attention of physicians after recent Studies that scrutinized patients with ischemic heart disease have shown that hypertriglyceridemia also developed at a high rate in such patients. The Framingham study also specified increased triglyceride as an independent risk factor of ischemic heart disease in women aged 50 years or older. Moreover, the Helsinki, BIP, and Becaït Studies have also shown that the treatment of hypertriglyceridemia is as important as that of hypercholesterolemia in preventing ischemic heart disease. Care should be taken when treating acute pancreatitis in patients with triglyceride of 1,000 mg/dL or higher.

Hyperlipidemia as a Cause of Atherosclerosis

Atherosclerosis is mainly considered to occur as a result of 2 mechanisms. One is the deposit of ester cholesterol on the vascular wall and the other is cytobiological pathologic response on the vascular wall. Many studies have demonstrated that hypercholesterolemia causes the deposit of cholesterol on the vascular wall, thereby inducing pathologic responses of vascular cells. It is accordingly quite

Table 1 Hypertriglyceridemia and Atherosclerosis

<ul style="list-style-type: none"> • Increase in remnant • Increase in small dense LDL • Reduction of HDL • Increase in thrombophilia • Insulin-resistant pathology
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easy to understand that hypercholesterolemia is a risk factor of ischemic heart disease. It has also been accepted that reduced HDL is a risk factor that accelerates atherosclerosis because HDL removes cholesterol on the vascular wall. Triglyceride is used as a source of energy in the body and therefore cannot be a matrix for the lipid plaque of atherosclerosis because it is not deposited on the vascular wall.

Patients with hypertriglyceridemia frequently show reduced HDL because HDL is produced as a decomposition product of very low-density lipoprotein (VLDL) including triglyceride. Therefore, increased VLDL reduces HDL, making it difficult to deliver cholesterol deposited on the vascular wall to outside the blood vessel, and as a result atherosclerosis occurs. This indicates that, in contrast to cholesterol directly associated with atherosclerosis, triglyceride indirectly induces atherosclerosis.

Remnant, which is a lipoprotein generated when VLDL is hydrolyzed by lipoprotein lipase, is easily incorporated into the vascular wall, and cholesterol in the remnant is deposited on the vascular wall. Therefore, those patients with increased remnant present both hypercholesterolemia and hypertriglyceridemia.

Previously, LDL cholesterol was considered to be the risk factor of ischemic heart disease. Since LDL cholesterol contains remnant, investigators have started to analyze the effect of remnant alone. Some consider that remnant is more important than LDL cholesterol as a risk factor of ischemic heart disease because it contains a larger amount of triglyceride. Increased triglyceride reduces HDL production, thereby accelerating atherosclerosis. Another finding that has recently attracted attention is that small dense LDL, in addition to remnant is also increased in patients with hypertriglyceridemia, thereby accelerating atherosclerosis.

Recent studies have reported that hypertriglyceridemia may be involved in the development of atherosclerosis by inducing thrombophilia. Therefore, hypertriglyceridemia reduces HDL and increases remnant and small dense LDL in blood, thereby inducing the deposit of cholesterol on the vascular wall. At the same time, the disease causes thrombotic formation and induces pathological reactions of the vascular wall to advance atherosclerosis. Thus, hypertriglyceridemia is a very serious risk factor of atherosclerosis when it has occurred in patients with hypercholesterolemia or those with reduced HDL (Table 1).

Remnant

The treatment of patients with diabetes mellitus, obesity, excessive eating, or

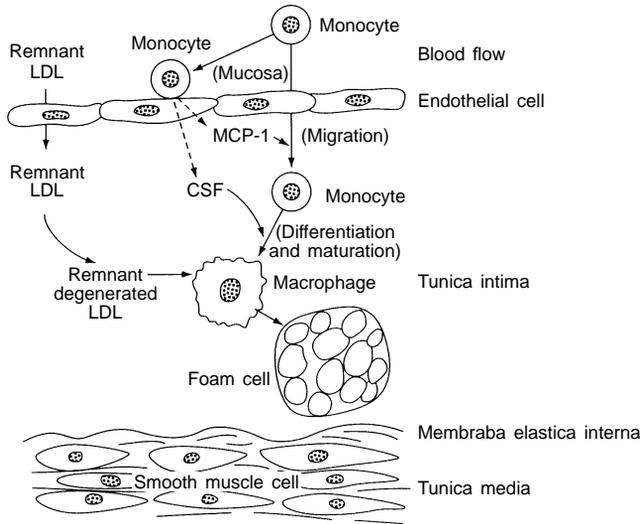


Fig. 1 Incorporation of remnant in the formation of the early lesion of atherosclerosis
MCP-1: monocyte chemoattractant protein 1
CSF: colony stimulating factor, -->: Production, -->: Effect

insulin resistance syndrome associated with multiple coronary risk factors is one of the main concerns among medical professionals. Remnant is an atherogenic lipoprotein that increases in such patients. Those with increased remnant often have hypercholesterolemia, hypertriglyceridemia, and reduced HDL. According to the WHO's type classification, those with increased remnant have complex type, type IIb, or type III hyperlipidemia. Unlike LDL, there is abundant cholesterol and apo-E in remnant which is known to be incorporated into cells through apo-E in physiological form without oxidative modification; it subsequently foams in the cells. Oxidized LDL is atherogenic lipoprotein observed at any time, while remnant is atherogenic lipoprotein that emerges in association with the westernization of lifestyles and the habit of eating excessively (Fig. 1).

Small dense LDL is small LDL with higher specific gravity among LDL fractions. A foreign study has reported that the incidence of coronary heart disease (CHD) in those with high small dense LDL was 3 times as high as that in whom without it. Although small dense LDL generally results from VLDL dysbolism, its mechanism has not been fully understood. The small dense LDL is considered to be atherogenic lipoprotein because it has low affinity with LDL receptors and is susceptible to oxidative degeneration.

Combination of Risk Factors

The risk factors of atherosclerosis include hypercholesterolemia, reduced HDL, hypertension, and glucose tolerance abnormality. The Framingham Study has shown that the combination of these risk factors synergistically increases the

risk of ischemic heart disease. It is important to pay close attention to the combination of such factors in addition to the severity of individual risk factors.

The concept of "syndrome X" or "deadly quartet" has been proposed for a patient group in whom the incidence of ischemic heart disease is high in spite of the mildness of individual risk factors. Both of them indicate a pathological state in which insulin sensitivity has been reduced by obesity, hyperalimentation, lack of exercise, or genetic factors. Those with syndrome X or deadly quartet secrete an excessive amount of insulin to compensate for insufficient insulin effect (insulin resistance), which results in hyperinsulinemia.

The insufficient insulin effect reduces the activity of lipoprotein lipase, increases VLDL, and finally causes hypertriglyceridemia. As described above, HDL is negatively correlated with triglyceride in blood. Therefore, the reduced activity of lipoprotein lipase causes hypertriglyceridemia and reduces the production of HDL, thereby reducing HDL. Moreover, insulin resistance often causes glucose tolerance disorder.

Diagnosis and Treatment of Hypertriglyceridemia

Triglyceride in blood is divided into that derived from the intake of food and that synthesized in the liver. The blood triglyceride value is generally measured after fasting for at least 14 hours (often early in the morning after fasting) because it is easily influenced by that created from the intake of food.

Hyperlipidemia is considered to be primary when it has developed as a result of the predisposition of the patient without the effect of other underlying diseases or drugs. In contrast, the disease is considered secondary when it has developed due to other diseases, such as diabetes mellitus, thyroid diseases, hepatic and bile duct disease, and renal insufficiency, intake of drugs, such as oral contraceptives and hypotensive drugs, drinking, and stress. Secondary hypertriglyceridemia is generally improved by the treatment of such primary diseases and the discontinuance of causatory drugs.

The diseases that frequently develop with hypertriglyceridemia and are important to note in the prevention of ischemic heart diseases include type III hyperlipidemia caused by the increased remnant in association with apo-E abnormality, complex type hyperlipidemia with increased cholesterol, and hyperlipidemia accompanying diabetes mellitus, nephrotic syndrome, and hypothyroidism. It is also necessary to note that excessive drinking causes hypertriglyceridemia.

Hypertriglyceridemia is basically treated with diet therapy. The combination of appropriate diet and exercise therapies is often effective in treating the disease. Care should be taken in starting pharmacotherapy in those with obesity or who have a drinking problem. It is necessary to fully consider the pathological state and risk factors of individual patients before commencing pharmacotherapy. That is, the future progress of atherosclerosis has to be considered in determining therapeutic policy.

Patients with hypertriglyceridemia are divided into high risk and low risk groups. High risk patients are those who have risk factors of ischemic heart disease (hyperlipidemia, hypertension, smoking, diabetes mellitus, men, arteriosclerotic

diseases other than ischemic heart disease, obesity, reduced HDL, and hyperlipoproteinemia (a)) or those with a medical history of ischemic heart disease.

For those who have been affected by hypertriglyceridemia for a long period of time and are classified into the high risk group, it should be considered that atherosclerosis has already progressed, and the main therapeutic target is to reduce atherosclerosis. In such patients, pharmacotherapy should be actively performed. The target value should be set to be as low as possible. The target triglyceride value should be 150 mg/dL or lower.

When hypertriglyceridemia is of low risk with a short affected period and mild risk factors, the treatment should be directed to the prevention of atherosclerosis. In such patients, it is not necessary to hurry the initiation of pharmacotherapy. Rather, it is important to check their compliance with diet therapy and provide instruction for activities of daily living, particularly stopping drinking and adopting a long-term perspective to continued exercise therapy.

Hypertriglyceridemia is mostly a result of excessive eating, lack of exercise, obesity, and excessive drinking. Therefore, it is natural that the disease is complicated by hypertension and diabetes mellitus in a large number of patients. Since the disease is closely related to daily lifestyle, it should be emphasized that patients themselves are responsible for controlling their health on a daily basis, including maintaining ideal body weight, doing moderate exercise, and refraining from drinking, and that favorable control of the above should be most effective in preventing hypertriglyceridemia and other adult diseases. Drugs used for treating the disease include fibrates, niacin preparations, and HMG-CoA reductase inhibitors.

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