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

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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
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

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*Fig. 1  Distribution of hemoglobin concentrations in blood donors*
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. 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.

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;
transfusion-transmitted infection, post-transfusion GVHD, sensitization with alloantigens, 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>
<thead>
<tr>
<th>Virus</th>
<th>Voluntary report from medical institution</th>
<th>Retrospective study</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fractionation Center</td>
<td>Donor NAT-positive</td>
</tr>
<tr>
<td>HBV</td>
<td>6 (4) [1]</td>
<td>11 (5) [2]</td>
<td>5 (4)</td>
</tr>
<tr>
<td>HCV</td>
<td>0</td>
<td>3 (3)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

\(\) : Number of patients who developed post-transfusion hepatitis
\[\] : Number of patients who exhibited persistent infection for at least 6 months after infection
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. 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. 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. 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. 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). Stramer 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>
<thead>
<tr>
<th>Country</th>
<th>Examination period</th>
<th>HBV</th>
<th>HCV</th>
<th>HTLV-I</th>
<th>HIV-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan (Hokkaido)</td>
<td>1995–1997</td>
<td>1/30,000</td>
<td>1/236,000</td>
<td>1/207,000</td>
<td>—</td>
</tr>
<tr>
<td>United States (REDS)</td>
<td>1991–1993</td>
<td>1/63,000</td>
<td>1/103,000</td>
<td>1/641,000</td>
<td>1/493,000</td>
</tr>
<tr>
<td>France (VHG/ RVG)</td>
<td>1992–1994</td>
<td>1/118,000</td>
<td>1/223,000</td>
<td>1/5,882,000</td>
<td>1/571,000</td>
</tr>
</tbody>
</table>
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

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

<table>
<thead>
<tr>
<th>Specimen</th>
<th>HBs antigen</th>
<th>HBc antibody</th>
<th>NAT pool size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLIA (+/−)</td>
<td>(S/CO value)</td>
<td>HI (2n)</td>
</tr>
<tr>
<td>CLIA-HBsAg (+)/JRC HBV system (−)</td>
<td>1*</td>
<td>+</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td>+</td>
<td>3.59</td>
</tr>
<tr>
<td></td>
<td>3*</td>
<td>+</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>4*</td>
<td>+</td>
<td>8.47</td>
</tr>
<tr>
<td></td>
<td>5*</td>
<td>+</td>
<td>9.18</td>
</tr>
<tr>
<td></td>
<td>6**</td>
<td>+</td>
<td>7.44</td>
</tr>
<tr>
<td></td>
<td>7**</td>
<td>+</td>
<td>28.43</td>
</tr>
</tbody>
</table>

* 1–5: Specimens in the Window Period
** 6,7: Specimens from low-viremic carriers

* 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-
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-
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. 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.

REFERENCES
