Table 1. Previously reported cases of confirmed bacterial contaminated blood components in Japan

Year	Detected bacteria species		Caused blood component
	Patient	Blood component	
1993	*Bacillus subtilis*	NT	RC-MAP
1994	*Serratia marcescens*	NT	PC
1995	*Acinetobacter calcoaceticus*	NT	RC-MAP
1996	*Staphylococcus aureus*	NT	PC
1996	G(+) rod	NT	RC-MAP
1998	*Morganella morganii*	NT	PC
2000	*Bacillus cereus*	*Bacillus cereus*	RC-MAP
2000	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	PC
2003	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Yersinia enterocolitica*	*Yersinia enterocolitica*	RC-MAP
2006	*Staphylococcus aureus*	*Staphylococcus aureus*	PC

RC-MAP, erythrocyte concentrate in mannitol-adenine-phosphate solution; PC, platelet concentrates; NT, not tested.

Therefore, preventive measures involving particle agglutination (PA) were implemented in 1986. Moreover, a second generation of PA methods was released for donor screening. Inaba et al. evaluated the efficacy of this screening and HTLV-I prevalence in blood donors after screening estimated the prevalence to be 1 in 45,560 (0.0022%) (18). No confirmed case transmitted by blood components has been reported to the JRC; however, its long latent period and transmission routes other than transfusion make the prevention rate uncertain.

3-1-5. Bacteria

Transfusion-transmitted bacterial contamination of platelets is the most common cause of fatality-related blood components, because the storage of platelets at room temperature to maintain its function is also suitable for bacterial growth. Therefore, numerous countries have introduced culturing-based screening methods to detect bacterial-contaminated platelets. However, after the implementation of these methods, death from bacterial sepsis has continued to be reported because erythrocytes are not screened for bacteria, and current screening methods based on culturing are not entirely satisfactory.

In the United States (US), before the implementation of culturing methods, an average of 11.7 deaths from sepsis per year were reported, whereas 7.5 per year were reported after these detection methods were introduced (19). According to the 6 years' experience of using the BacT/ALERT system in the US, between 0.03 and 0.12% of platelet concentrates (PCs) with a negative culturing test result were still contaminated with bacteria, i.e., false negatives were reported (20).

In Japan, screening methods for platelets have not yet been introduced. We evaluated the efficacy of DOX™ (Daikin Industries, Osaka, Japan), a commercially available system which has been developed to detect contaminated food by measuring the oxygen potential for contaminated PCs. Six species were inoculated into PC, and their dissolved oxygen potentials were measured consecutively (21,22). As a result, this system detected aerobic bacteria in PC within 20 h if their initial concentration was more than 10^1 CFU/ml.

Fatalities from bacterial sepsis are extremely rare and have been reported once every few years (23). However, we have experienced two fatalities from bacterial-contaminated platelet recently. One case was reported in 2000, caused by *Streptococcus pneumoniae* (24), and another case occurred in 2003, caused by a *Staphylococcus aureus*-contaminated platelet (25). In both cases, the patients suffered from malignant hematological diseases. Reported cases of bacterial contamination in Japan are described in Table 1. Since 2007, pre-storage leukocyte-reduction procedure and diversion of initial blood flow have been introduced in Japan. According to the JRC's report, nearly 6,000 blood aliquots from whole blood collected by either the conventional method or from the initial drawn blood flow were cultured using an automated culture system. As a result, the detected rate of bacterial contamination was remarkably reduced from 7 of 2,967 samples (0.24%) to 2 of 2,890 samples (0.07%) after implementation of the diversion (26).

National Blood Service (NBS) in the United Kingdom (UK) also reported that diversion together with improved donor arm disinfection has improved the reduction rate in contamination from 47 to 77% (27).

3-1-6. Prion and other emerging pathogens

Variant Creutzfeldt-Jacob disease (vCJD) was first identified in 1996 in the UK (28,29), and it is considered to be the result of human exposure to the BSE agent. Since then, vCJD patients have been identified in many European countries, especially in the UK. In 2004, the reports showed that vCJD can be transmitted by blood transfusions (30,31). The strategy for preventing trasmission through transfusion has been difficult because there is no effective screening method to determine if a blood donor is infected, and this disease has a long incubation period. Therefore, patients probably received blood products from donors who were asymptomatic at the time of donation. The US instituted a policy in which donations from people who spent at least 6 months in certain western European countries or 3 months in the UK between 1980 and 1996 were excluded. A similar policy has been applied to potential donors in many countries. In Japan, people who spent even one day in the UK from 1980 to 1996 and cumulative periods of 6 months in western European countries where BSE is epidemic were rejected as blood donors.

Consequently, donor deferral was roughly o 6% as a result of this policy. Recently, a number of companies have been developing prion removal filters. Asahi Kasei Medical Co., Ltd. (Tokyo, Japan) has developed an integrated filter which has the functions of prion removal and leukocyte reduction (32,33).

Pall Co., Ltd. (East Hills, N.Y., USA) gained a Council of

Europe (CE) mark for their device "Pall Leukotrap Affinity Prion Reduction Filter (LAPRF)," a new leukocyte reduction filter for the removal of infectious prion from erythrocyte concentrates in 2005 (34,35). Pathogen Removal and Diagnostic Technologies, Inc. (PRDT), which is a joint venture company of the American Red Cross and ProMetic BioSciences, established "P-Capt," which has high prion-binding affinity and also received CE mark in 2006, in cooperation with Macopharma (36).

Some pathogen agents carried by mosquitoes, such as chikungunya virus in the Indian Ocean, West Nile virus in the US, and malaria are widely known as transmitted infectious pathogens (37). Fortunately, this is not an issue of concerne in Japan at present, but potential donors move frequently throughout the world, and some materials imported from abroad may carry mosquitoes. We are collecting information carefully, and we have to manage them in the near future.

Similarly, HEV has been considered to be an imported infectious disease from its epidemic area in the developed countries. However, the epidemiologic study revealed that 2-14% of healthy populations were anti-HEV IgG positive (38), and approximately 13% of the non-A, -B, and -C acute hepatitis cases in Japan were caused by HEV (39). Moreover, the discovery in 2001 of an indigenous Japanese strain of HEV, JRA1, from a patient who had never been abroad, had a great impact on blood safety in our country (40,41). Under these circumstances, HEV screening using a real-time reverse transcription (RT)-polymerase chain reaction (PCR) system has continued as a trial in the Hokkaido district, northern part of Japan.

Blood is also tested for CMV Ab and provided to patients who are at an increased risk for CMV disease in Japan.

3-2. Non-infectious reactions

3-2-1. Hemolytic reactions

Hemolytic reactions are classified into acute hemolytic reactions and delayed hemolytic reactions. Most important hemolytic reactions involve incorrect blood components (IBCT). IBCT has rarely been reported to JRC as an adverse reaction, because it is regarded as a transfusion error. The surveillance of ABO-incompatible blood transfusions was conducted based on an anonymous questionnaire by the Japanese Society of Blood Transfusion for 5 years from 2000 to the end of 2004 (42). This surveillance targeted 1,355 hospitals in Japan, and data were obtained from 829 hospitals among them (61.2%). According to the data, 60 cases of ABO-incompatible transfusion were reported, and 31 of them involved erythrocyte concentrates. Of 31 cases, 22 were due to major mismatches, and others were due to minor mismatches. The current incidents collection system used by JRC is based on voluntary reporting; therefore, the number of reported IBCT cases might be underestimated.

3-2-2. Non-hemolytic reaction

Minor allergic reactions such as urticaria, fever, and dyspnea make up a major portion of non-hemolytic reactions. These include transfusion-associated graft versus host diseases (TA-GVHD) and TRALI.

3-2-3. TA-GVHD

Once TA-GVHD occurs, it is almost always fatal with a very rapid and fulminant course. The mechanism of this condition involves the activation of donor lymphocytes against recipient human leukocyte antigens (HLA). The risk increases in proportion to the degree of HLA haplotype-sharing between donors and patients. In Japan, this condition is a serious problem. Indeed, its incidence is 5-10 times higher than in European countries (43,44). JRC collected information and conducted a national survey in 1991, and a microsatellite DNA assay to identify TA-GVHD has also been developed (45-47). Consequently, JRC has begun the practice of irradiating the blood components supply throughout the country. Since 2000, no confirmed TA-GVHD case has been reported to JRC.

3-2-4. TRALI

TRALI is a serious clinical syndrome involving shortness of breath, hypoxemia and non-cardiogenetic pulmonary edema, associated with HLA/Abs or neutrophil antigens. JRC has gathered information on TRALI since 1997. As knowledge of TRALI has grown, the number of reported TRALI cases has increased. However, the definition of TRALI remains controversial, and it is likely that only a portion of TRALI cases are collected. Other similar serious symptoms which are not included in the definition occur, and treatments have not been developed. Supportive diagnostic evidence includes identifying neutrophil or HLA Abs in the donor or recipient plasma. Among the blood donors, multiparous women frequently have these antibodies. Therefore, in many developed counties, women are not permitted to be plasma donors. In Japan, however, this policy has not been applied.

4. Traceability of causal relationship between blood components and incidents by JRC

JRC has conducted the following tests on residual blood products, plasma derivatives, and recipient blood to identify the causes of adverse reactions and infectious diseases. The contents of the current tests to trace such causes are described in Table 2 (48).

Table 2. Currently conducted tests to identify the causal relationship between blood products and adverse reaction after transfusion according to the classification of reaction type

1. Transmitted infectious diseases
A. Virus
1. Serological test: serological markers related to suspected infections
2. NAT: (1) Detection of suspected viral genome
(2) Evaluation of viral genome sequence homology
B. Bacteria
1. Detection of bacteria by methods based on blood culturing
2. Identification of bacterial species by Gram's stain
3. Detection of endotoxins of Gram-negative bacteria
2. Non-infectious diseases
A. Non-hemolytic adverse reaction
1) Allergic reaction
1. Anti-human leukocyte antigen antibody
2. Anti-platelet antibody
3. Anti-granulocyte antibody
4. Anti-plasma protein antibody: against 6 plasma proteins, including anti-haptoglobin (HP) antibody and anti-immunoglobulin A (IgA) antibody
5. Plasma protein deficiency
2) TA-GVHD
1. Micro-satellite DNA assay
2. Chimerism test on recipient blood
B. Hemolytic adverse reaction
1. Re-check of the blood group and Coombs test
2. Detection of irregular antibody

NAT, nucleic acid amplification tests; TA-GVHD, transfusion-associated graft versus host diseases.

5. Detection strategy versus pathogen reduction for transmitted diseases

At present, detection strategies such as screening tests for known pathogens for which the methods have already been developed are added yearly to maintain the blood components' safety. However, the current strategy does not prevent all of the transfusion-transmitted pathogens. Considering that the use of human blood as a raw biological source is unsafe, screening tests alone cannot exclude all of the potential pathogens. Therefore, we have to consider the introduction of some alternative or additional preventive measures. Some pathogen reduction systems to damage pathogen nucleic acids to proliferate have been developed and some are now under development. Pathogen inactivation (PI) technology using methylene blue plus visible light or solvent-detergent treatment for plasma has been introduced in some European countries and has a track record of more than 10 years (49-51). Similar technologies involving amotosalen (S-59) plus ultraviolet (UV) A light have recently become available for plasma (52). Only amotosalen and riboflavin UV light treatment have obtained the CE mark in Europe, and they have been under evaluation for use with platelets (53,54). With regard to these methods, concern remains regarding cost, process operation changes, ability to inactivate, and ineffectiveness against prions, non-enveloped viruses, spore-formed bacteria and viruses which exist in exceedingly high concentrations in blood. Damage to the products which results in reduction of coagulation factor activities, deterioration of platelets, toxicity, and mutagenicity in recipients is also controversial (55-57). These residual risks are still a major concern to the public, politicians, regulatory agencies, and blood component providers. A recent consensus conference recommended that PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available (58-60).

In Japan, the delegates on behalf of the Japanese Society of Transfusion Medicine and Cell Therapy (JSTMCT) visited some European countries and collected the current information. Additional detection strategies and undeveloped pathogen reduction technology will be extensively debated over the next few years. But it is obvious that TTI is not static and new agents continue to emerge; therefore, we have to carefully watch the circumstances and collect worldwide information.

6. Hemovigilance

Since the AIDS epidemic, developed countries, especially in Europe, took swift action to try to keep records related to transfusion therapy to help ensure blood safety. One method for doing so is called hemovigilance, which is a system for collecting information on unexpected events from donors after drawing blood to the adverse reactions of the patients after transfusion. Various hemovigilance models are usede around the world, depending on social security and national priorities (61-64). JRC has collected transfusion reaction and infectious disease transmission data since 1993, in accordance with the Pharmaceutical Affairs Law. Reporting by medical institutions is voluntary and targets relatively moderate to severe adverse events.

In 2007, JSTMCT established a hemovigilance committee to cooperate with medical institutions and JRC. Seven university hospitals agreed to report all adverse transfusion events

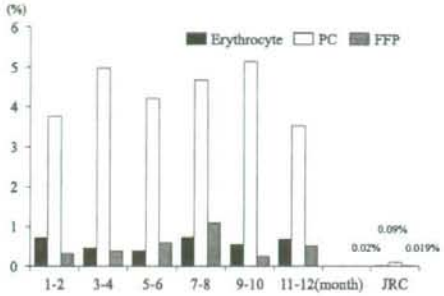

Fig. 2. Bimonthly variability in the reporting rate according to the responsible blood components. PC, platelet concentrates; FFP, fresh frozen plasma.

bimonthly through an anonymous, secure, online portal. Participants also entered the total number of blood products issued over each reporting period. Online access and data entry were made easy, with 16 categories of symptoms and 8 diagnoses. Adverse event rates were calculated automatically and were provided to the participants continuously. As a result of this pilot study, the total number of blood products issued corresponded to about 1% of the total issued in Japan. Six hundred seventy-five transfusion-related adverse events were reported in 2007 by 7 hospitals. Most of them were non-hemolytic transfusion reactions. The reported reaction rates were 0.54 and 0.63% for erythrocytes and plasma, respectively, and 3.4% for PCs in this trial. On the other hand, 0.02% for erythrocytes, 0.018% for plasma, and 0.09% for PCs were nationally reported to JRC (Fig. 2). Hemovigilance such as in this system by a third-party service through an anonymous online portal revealed a high incidence of adverse events, including relatively mild reactions, which physicians previously thought unnecessary, meaningless, or bothersome to report to JRC. Easy online access, anonymity, and the motivation of participating institutions likely contributed to this outcome. This system and the preexisting JRC hemovigilance will complement each other, or rather achieve a better harmonization for future hemovigilance systems (65,66).

7. Conclusion

Current multifocal approaches to blood safety have dramatically reduced the risks related to blood transfusion. However, residual low risks are still a major concern, and we are under pressure to maintain blood product safety. Current approaches have had limited success, and the source of the blood products is raw human blood. In order to improve the safety of blood products, we need to adopt safer alternatives and/or additional preventive measures. Each country has its own circumstances, such as politics, manufacturing, medical resources, and social services, related to transfusion medicine, and each country must develop its most suitable solution.

Consequently, one action taken in one country would not necessarily be an appropriate procedure in another country. It is important to share information and develop standards in transfusion medicine worldwide. However, it is important to remain focused on blood product safety and to track the effectiveness of our policies at all times.

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