日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2015

Safety Vigilance Division, Technical Department,
Blood Service Headquarters

Table of Contents

Haemovigilance system of Japanese Red Cross Society

The haemovigilance system is defined as a set of surveillance procedures intended to identify and prevent further transfusion-related adverse effects from blood collections, through testing, processing, distribution, up to follow-up of recipients by analysing and evaluating the causes, and to conduct appropriate safety measures. The Japanese Red Cross Society (hereinafter referred to as "JRCS") has addressed donor adverse reactions, transfusion-transmitted infections (hereinafter referred to as "TTIs") and transfusion-related adverse reactions since the start of the blood service, by having specified an internal procedure for reporting donor adverse reactions in 1982, and by deploying medical representatives (hereinafter referred to as "MRs") in all JRC blood centers across Japan in 1983 to deal with the problems of transfusion-related adverse reactions and infections. In the meantime, JRCS has also introduced the tests of donated blood for hepatitis and HIV markers as a measure against TTI, and established a nationwide integrated system to collect and analyse information on transfusion-related adverse reactions and infections in 1993. In addition, a specimen storage system of storing aliquot of all donated blood for analysis for 11 years started in 1996. This specimen storage enabled investigation of blood components for transfusion mainly related to TTIs to confirm the causal relationship between TTIs and transfusion, in addition to being useful for further studies of newly emerging adverse reactions and infections. Furthermore, the expired repository samples could be used for research and development in accordance with the policy described in the PFSB Notification No. 0801-1 "Guideline on the use of donated blood in R&D" issued by the Director of Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare on August 1, 2012. The appropriateness of their use in R&D should be evaluated by the Steering Committee for Blood Services of the Pharmaceutical Affairs and Food Sanitation Council under the Ministry of Health, Labour and Welfare.

On the other hand, blood components for transfusion are categorized as "prescription drugs" in Japan. Based on the revision of the Pharmaceutical Affairs Law on November 25, 2014, they have since been regulated by the "Pharmaceuticals and Medical Device Act (PMD Act)." JRCS has the marketing approval for such blood components for transfusion same as for other prescription drugs. JRCS is the only body that is authorized to collect and supply blood and blood components for transfusion in Japan. In addition, JRCS provides source plasma to domestic manufacturers of plasma derivatives. For the manufacturing and distribution of blood and blood components for transfusion prepared from donated blood, JRCS observes the PMD Act and its Enforcement Regulations, the "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs, Good Manufacturing Practice (GMP)," and the "Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Regenerative Medicine Products, Good Quality Practice (GQP)." Concerning the necessary post-marketing measures, based on the "Ministerial Ordinance on Standards for Post-Marketing Safety Assurance for Drug, Quasi-drugs, Cosmetics, Medical Devices and Regenerative Medicine Products; Goop Vigilance Practice (GVP)", the Blood Service Headquarters (as marketing authorization holders, including the General Safety Management Division), each blood center and the Central Blood Institute (both are part of the Safety Implementation Division) cooperate to take necessary measures. MRs deployed at each blood center are responsible to collect information of adverse reactions and/or TTIs and to provide information on blood components to health care professionals. The General Safety Management Division is responsible to analyse and evaluate the information. It also reports severe cases of transfusion-related adverse reactions and TTIs to the Pharmaceutical and Medical Devices Agency (hereinafter referred to as "PMDA") in accordance with the PMD Act and conducts a series of activities including management of basic data on safety measures, withdrawal of inappropriate blood components, and revision of package inserts (Precautions). Additionally, the JRCS conducts epidemiological studies for blood safety, and reports the results to the Steering Committee for Blood Services and/or the Safety Technology Research Committee, the Pharmaceutical Affairs and Food Sanitation Council under the Ministry of Health, Labour and Welfare, contributing to the government to establish safety measures for blood components for transfusion.

The pharmacovigilance system applies to prescription drugs. The WHO defines pharmacovigilance as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems," which is in close agreement with the post-marketing safety assurance activities stipulated by the GVP Ordinance in Japan. In addition, the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) developed the E2E Guideline, "Pharmacovigilance

Planning," which has been implemented since 2005, in parallel with complete enforcement of the amended Pharmaceutical Affairs Law in April 2005. Thus observation of the Ordinances of GQP and GVP became the licensing requirements forMarketing Authorization Holders.

It seems that the concept of "haemovigilance" developed in Western countries, where blood and blood components for transfusion are mostly regulated separately from prescription drugs, and a safety monitoring system for blood and blood components for transfusion has to be prepared separately from that for prescription drugs. On the other hand, as blood and blood components for transfusion are categorized as prescription drugs in Japan, the same pharmacovigilance as for prescription drugs is applied to blood and blood components for transfusion. Therefore, the haemovigilance system in Japan is similar to the pharmacovigilance system, which is the significant feature.

1. Reports on adverse reactions and TTIs

Figure 1 shows the number of case reports of transfusion-related adverse reactions and infectious diseases which were reported by medical institutions between 2006 and 2015. Note that cases assessed as unrelated to transfusion are included.

In 2015, the JRCS received 1,563 case reports of adverse reactions (1,533 cases were classified as non-hemolytic adverse reactions, 28 as hemolytic adverse reactions, and 2 as suspected transfusion associated GVHD), and 93 case reports of suspected TTIs by medical institutions across Japan. Severe cases which were evaluated by reporting physicians and/or the JRCS were submitted as individual case safety reports (ICSRs) to the PMDA in accordance with the Pharmaceuticals and Medical Device Act. (The breakdown of the ICSRs is 773* non-hemolytic adverse reactions, 18* hemolytic adverse reactions, and 93* infections.) Some cases of adverse reactions that have not been reported voluntarily to the JRCS by medical institutions may be presented in the literature and/or at academic conferences, and when JRCS obtains such information, JRCS additionally investigates the concerned medical institutions regarding the severity. (see "3 Information about individual cases of transfusion adverse reactions and TTIs obtained from the literature or academic conference").

*Note that some cases included multiple categories were overlapped, eg, one case had non-hemolytic and hemolytic reactions.

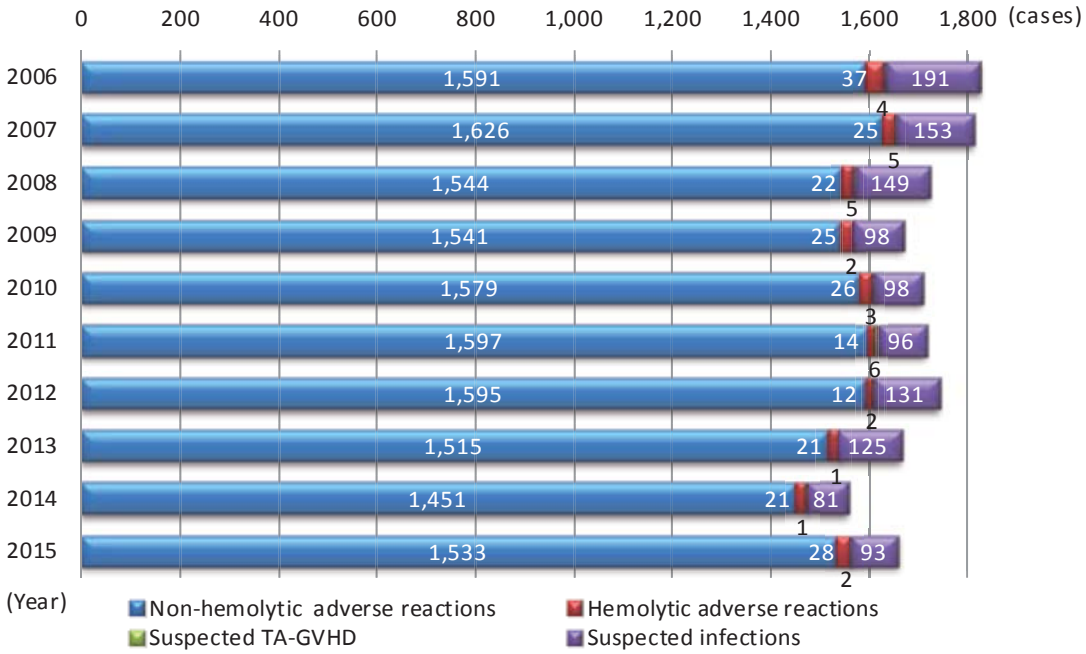


Figure 1. Changes in the number of voluntary reports of transfusion-related adverse reactions and infectious diseases*
*Excluded cases that were obtained from the literature or academic conference.

1) Transfusion-related adverse reactions

(1) Non-hemolytic adverse reactions

Table 1 shows the number of cases reported as non-hemolytic adverse reactions by medical institutions between 2006 and 2015. Figure 2 shows the breakdown of adverse reactions by symptom reported in 2015. Figure 3 shows the breakdown of cases evaluated as severe adverse reactions and the annual changes in number of severe and non-severe adverse reactions. The cases of TRALI (transfusion-related acute lung injury) and TACO (transfusion-associated circulatory overload) were included under dyspnea.

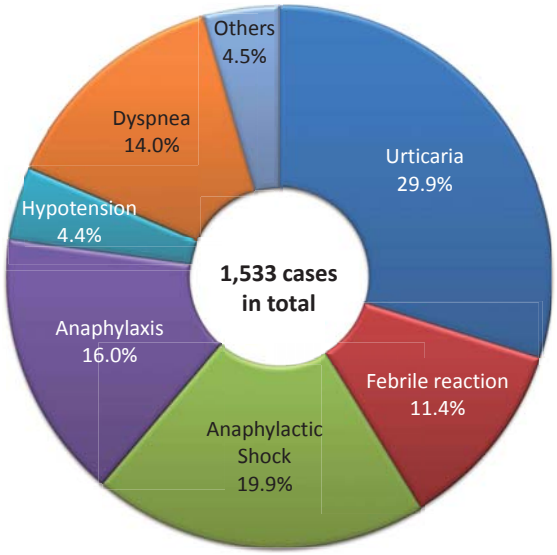


Figure 2. Breakdown of reported cases of non-hemolytic adverse reactions in 2015

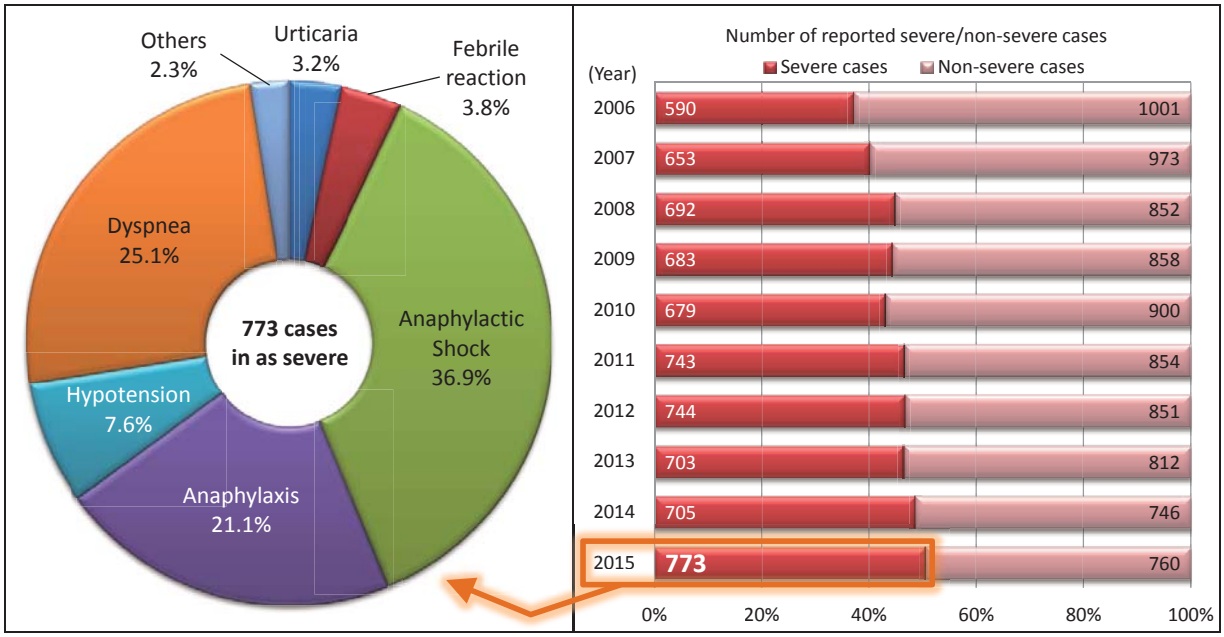


Figure 3. Breakdown of cases evaluated as severe non-hemolytic adverse reactions* in 2015 and annual changes in number of severe and non-severe cases

*severe cases: cases reported as severe adverse reactions by reporting physicians, and/or cases evaluated as severe according to the symptoms by JRCS although the case was reported as non-severe.

Table 1. The number of reported cases of non-hemolytic adverse reactions by symptom

Symptom \ Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Urticaria	529	578	535	523	612	606	572	608	468	458
Febrile reactions	238	197	157	176	175	140	190	174	149	175
Anaphylactic Shock	246	293	269	280	253	275	242	218	277	305
Anaphylaxis	173	155	152	128	117	129	156	110	245	245
Hypotension	62	47	57	62	70	78	90	92	74	67
Dyspnea*1	245	217	224	231	219	232	229	248	189	214
Others	98	139	150	141	129	135	116	65	49	69
Excluded*2	0	0	0	0	4	2	0	0	0	0
Total	1591	1626	1544	1541	1579	1597	1595	1515	1451	1533

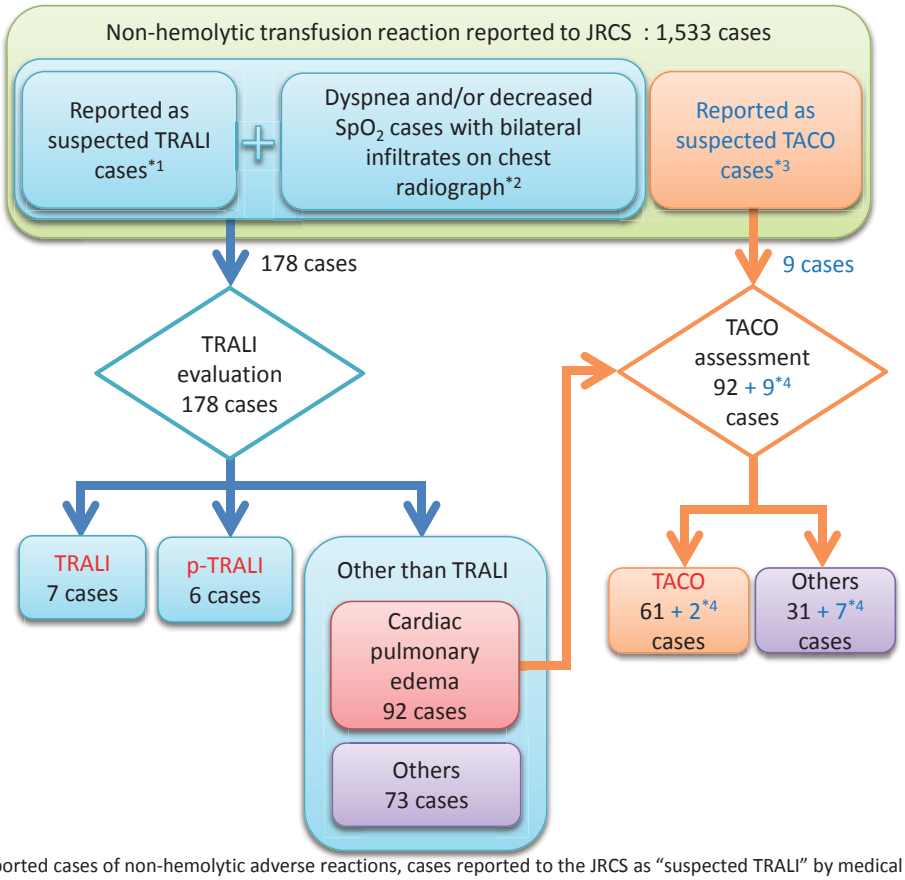
*1 TRALI, possible-TRALI and TACO cases are included in dyspnea.

*2 Cases excluded that were evaluated as being unrelated to transfusion by reporting physitians afterwards.

Evaluation of TRALI and TACO cases

Cases reported as suspected cases of TRALI or TACO by medical institutions and cases suspected to be TRALI or TACO based on symptoms of dyspnea were evaluated using the TRALI diagnostic criteria/TACO assessment criteria.

Figure 4 shows the flowchart of evaluation of cases with suspected TRALI or TACO and the number of cases in 2015.



*1 Of the reported cases of non-hemolytic adverse reactions, cases reported to the JRCS as "suspected TRALI" by medical institutions.

*2 Of the reported cases of non-hemolytic adverse reactions, cases reported to the JRCS as "dyspnea," "acute lung injury," "respiratory failure," "hypoxemia (decreased SpO_2)", and "anaphylaxis," etc. cases associated with bilateral infiltrates on chest x-ray. The cases in which the infiltrates are not confirmed due to unavailability of chest radiograph image are excluded from the evaluation of TRALI.

*3 Of the reported cases of non-hemolytic adverse reactions, cases reported to the JRCS as "suspected TACO" by medical institutions.

*4 Of the reported cases of suspected TACO to the JRCS, two cases were assessed as TACO, and rest of the 7 cases were assessed as other adverse reactions .

Figure 4. Flowchart of evaluation for TRALI and TACO

TRALI

Evaluation for TRALI is based on the diagnostic criteria (Figure 5) that were proposed at the Consensus Conference held in 2004 (Transfusion. 2004; 44(12):1774-89.).

- Of the 1,533 cases of non-hemolytic adverse reactions reported in 2015 by medical institutions, 178 cases were subjected to evaluation for TRALI. TRALI evaluation was performed on cases with dyspnea and hypoxemia (decreased SpO_2), associated with bilateral infiltrates on chest x-ray, as well as cases reported as suspected TRALI.
- TRALI evaluation revealed 7 cases of TRALI, and 6 cases of possible TRALI.
- Of the 165 cases that were not diagnosed as TRALI, 92 cases had suspected cardiogenic pulmonary edema, and they were also evaluated for TACO.
- The remaining 73 cases included cases in which data of the required diagnostic criteria were insufficient (including images of chest radiography and data of respiratory function before transfusion), and cases which did not meet the diagnostic criteria (including substantially exceeded the criteria for the time of onset and acute respiratory failure observed before transfusion), in addition to cases which were evaluated as other adverse reactions (including allergic and anaphylactic dyspnea).

TRALI Criteria

- TRALI is defined as a new episode of ALI that occurs during or within 6 hours of a completed transfusion, which is not temporally related to a competing etiology for ALI.
- possible-TRALI that would have the same definition as TRALI except for the presence of a temporal relationship to an alternative risk factor for ALI .

a. Acute Lung Injury (ALI)
- **I. Acute onset**
- **II. Hypoxemia**
  - **PaO_2/FiO_2 ≦300mmHg or**
  - **SpO_2＜90%(room air)**
  - **or other clinical evidence of hypoxemia**
- **III. Bilateral infiltrates on frontal chest radiograph**
- **IV. No evidence of left atrial hypertension (i.e., circulatory overload)**

b. No preexisting ALI before transfusion
c. During or within 6 hr of transfusion
d. No temporal relationship to an alternative risk factor for ALI*

*Risk factors for ALI…Direct lung injury (Aspiration, pneumonia, toxic inhalation, lung contusion, and near drowning), Indirect lung injury (Severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, and drug overdose)

(Transfusion. 2004;44(12):1774-89.)

Figure 5. Diagnostic criteria for TRALI

TACO

Dyspnea due to transfusion overload has been known as a transfusion-related complication since the 1950s. Among the activities of the International Society of Blood Transfusion (ISBT) to establish definitions of transfusion-related adverse reactions and standardize their evaluation criteria from the mid-2000s, some criteria have been defined for the diagnosis of TACO, but there are no universally accepted diagnostic criteria for TACO on which consensus has been reached as for TRALI. To clarify whether only transfusion causes circulatory overload, and to investigate whether TACO may occur even if transfusion is conducted appropriately, the JRCS has started assessment in April 2012, using the original TACO assessment criteria (Figure 6). JRCS's TACO criteria exclude cases with complications under which circulatory overload tends to occur, such as cardiac failure, hemodialysis or artificial heart lung machines.

- In 2015, there were 63 cases assessed to have TACO, of which 61 cases were classified as cardiogenic pulmonary edema when evaluated for TRALI and were then further assessed for TACO, and 2 cases were reported by the medical institution to have suspected TACO.
- Figure 7 shows the gender of the patients and blood components used in cases assessed as TACO in 2015, and Figure 8 shows the data of JRCS on TACO evaluation from April 2012 to 2015. TACO appears to occur in elderly and female patients. For females, because of a lower body weight and smaller circulatory volume than males, circulatory overload is likely to occur. RBC was the most commonly involved component in up to 90% of TACO cases, including cases with multiple components.

ISBT haemovigilance working party TACO Criteria	JRCS TACO assessment criteria
TACO is characterized by any 4 of the following: **a. Acute respiratory distress** **b. Tachycardia** **c. Increased blood pressure** **d. Acute or worsening pulmonary edema on frontal chest radiograph** **e. Evidence of positive fluid balance** ● occurring within 6 hours of completion of transfusion. ● An elevated BNP is supportive of TACO.	**1. Acute respiratory failure** **PaO_2/FiO_2 ≦300mmHg or** **SpO_2＜90%(room air)** **2. Pulmonary congestion on chest radiograph** **3. Evidence of transfusion and/or fluid overload** **4. Occurring during transfusion or within 6 hours of completion of transfusion** 5. Increased blood pressure 6. Tachycardia 7. Elevated BNP or NT-pro BNP within 24 hours of completion of transfusion **From 1 to 4 are essential** **Exceptional features** (excluded if one of them is met) ● Patient on hemodialysis ● Patient undergoing cardiopulmonary bypass ● Patient on extracorporeal support ● Patient undergoing treatment for cardiac failure or respiratory failure

Figure 6. Diagnostic/assessment criteria of TACO

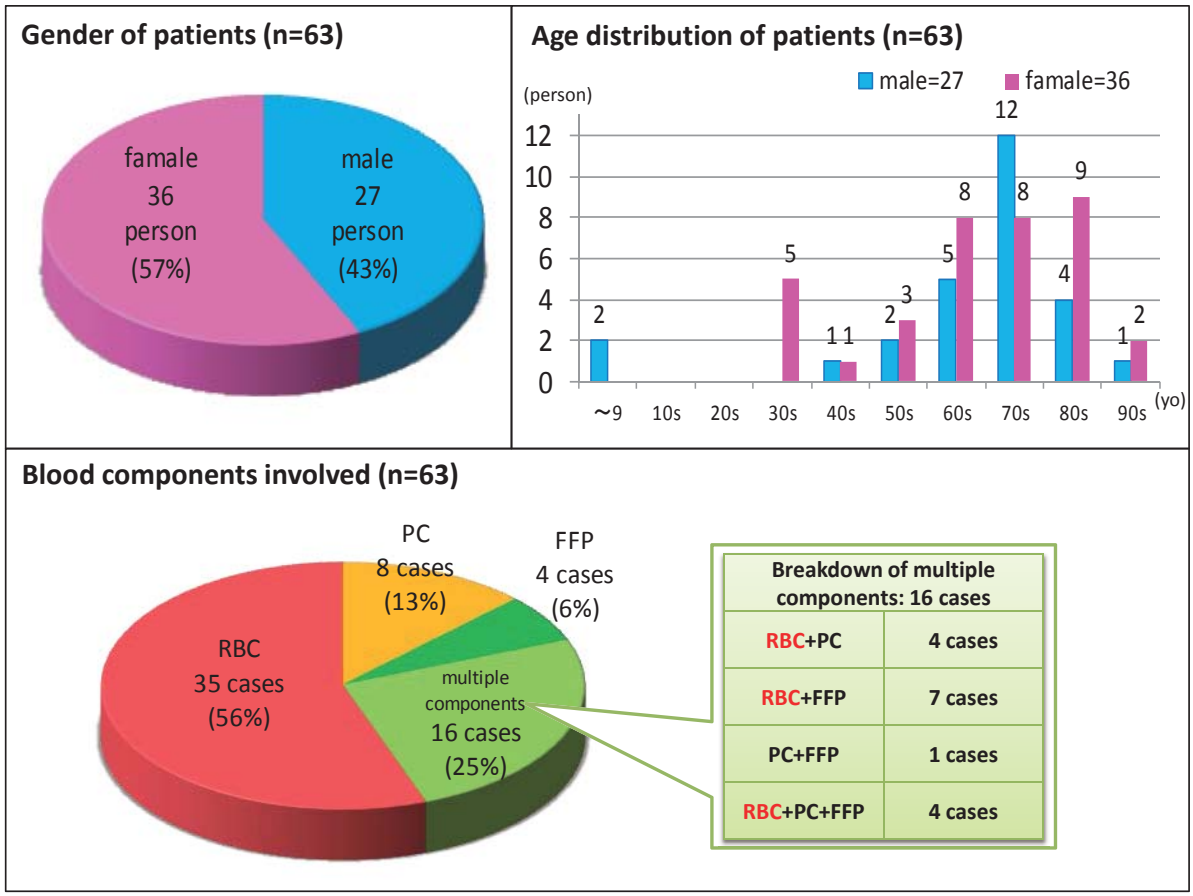


Figure 7. Gender of patients and blood components used in cases assessed as TACO (2015)

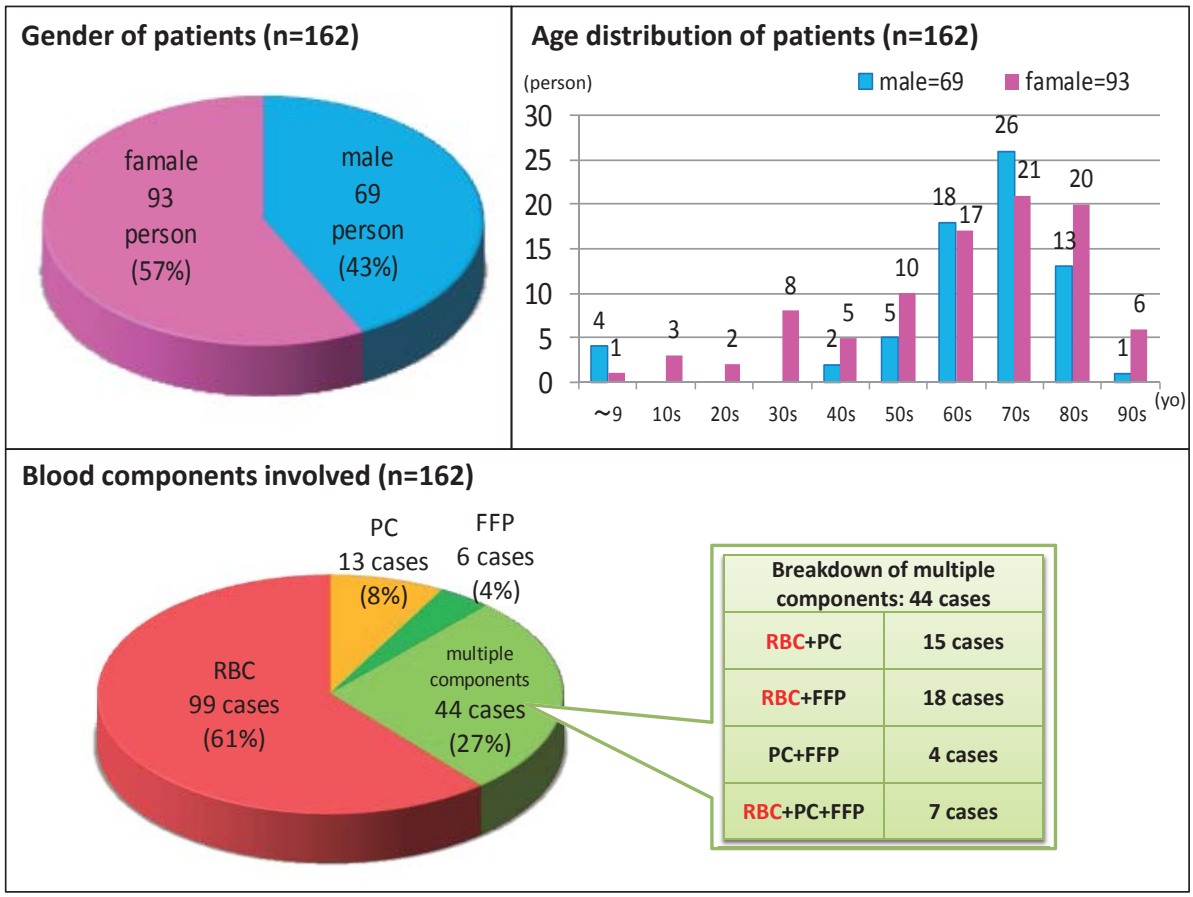


Figure 8. Gender of patients and blood components used in cases assessed as TACO (April 2012–2015)

Discussion and future tasks for TRALI and TACO

- Compared to the number of case reported as suspected TRALI, the rate of cases actually diagnosed as TRALI has been decreasing. There were no cases that were diagnosed as fatal TRALI in 2015.
- As a measure against TRALI, the JRCS continues the preparation of FFP derived from 400 mL of whole blood donations, mainly from male donors. It is also considered to introduce tests for anti-leukocyte antibodies and to add the item of taking pregnancy history to the medical history.
- The JRCS started TACO assessment in 2012. When the "Practical guideline for transfusion medicine" was revised in March 2012, TACO was added to the section of "transfusion-related adverse reactions/complications." Therefore, TACO is becoming more widely recognized. However, most cases that were reported as "TRALI" by medical institutions were classified as cardiogenic pulmonary edema by the JRCS's TRALI evaluation, and were afterwards determined to be "TACO" based on assessment for TACO (Figure 4). Although the number of cases evaluated as TACO has been on the increase (Figure 9), a similar number of cases were evaluated as cardiogenic pulmonary edema before assessment for TACO started. It is not considered that TACO cases have actually increased as rapidly as it seems.
- TACO is a condition of cardiac failure due to circulatory overload. To transfuse at-risk patients who have potential cardiac and/or renal failure, it is necessary to reduce the transfusion rate and volume, and to monitor the patients closely during the transfusion.
- Future tasks to be considered for TACO cases include an association between weight and transfusion volume and transfusion rate, concomitant use of diuretics, and regimen of diuretics after the onset of TACO.
- Since the number of cases evaluated as TACO has been on the increase, JRCS prepared and distributed the "Transfusion Information" (Figure 10) that included TACO's pathophysiology, clinical presentation, risk factors, and treatment to call the attention of healthcare professionals.
- For a correct differential diagnosis of TRALI and TACO, the Study Group (Study on the preparation of a guideline for early diagnosis and treatment of TRALI and TACO as severe adverse reactions of transfusion therapy) of the Ministry of Health, Labour and Welfare has made efforts since 2012 to establish a guideline that is clinically easy to use and consistent with domestic and international diagnostic criteria, and allows an objective diagnosis. The Study Group asked for public comments, verified TRALI and TACO cases reported to JRCS and completed the final plan in 2015 after several modifications ("A Guideline for the Differential Diagnosis of TRALI and TACO", Japanese Journal of Transfusion and Cell Therapy. 2015;61(4):474-479). JRCS continues to make efforts to contribute to the prevention, diagnosis, and treatment of TRALI and TACO in cooperation with the Study Group of the Ministry of Health, Labour and Welfare as well as academic societies.

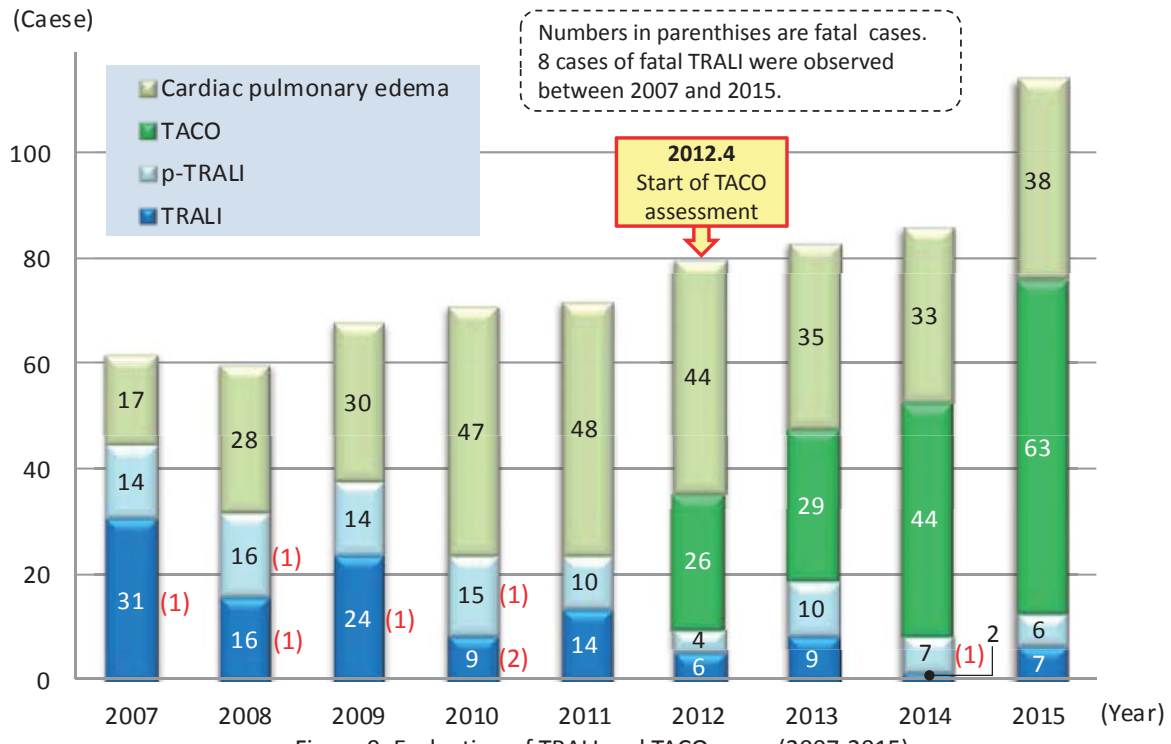
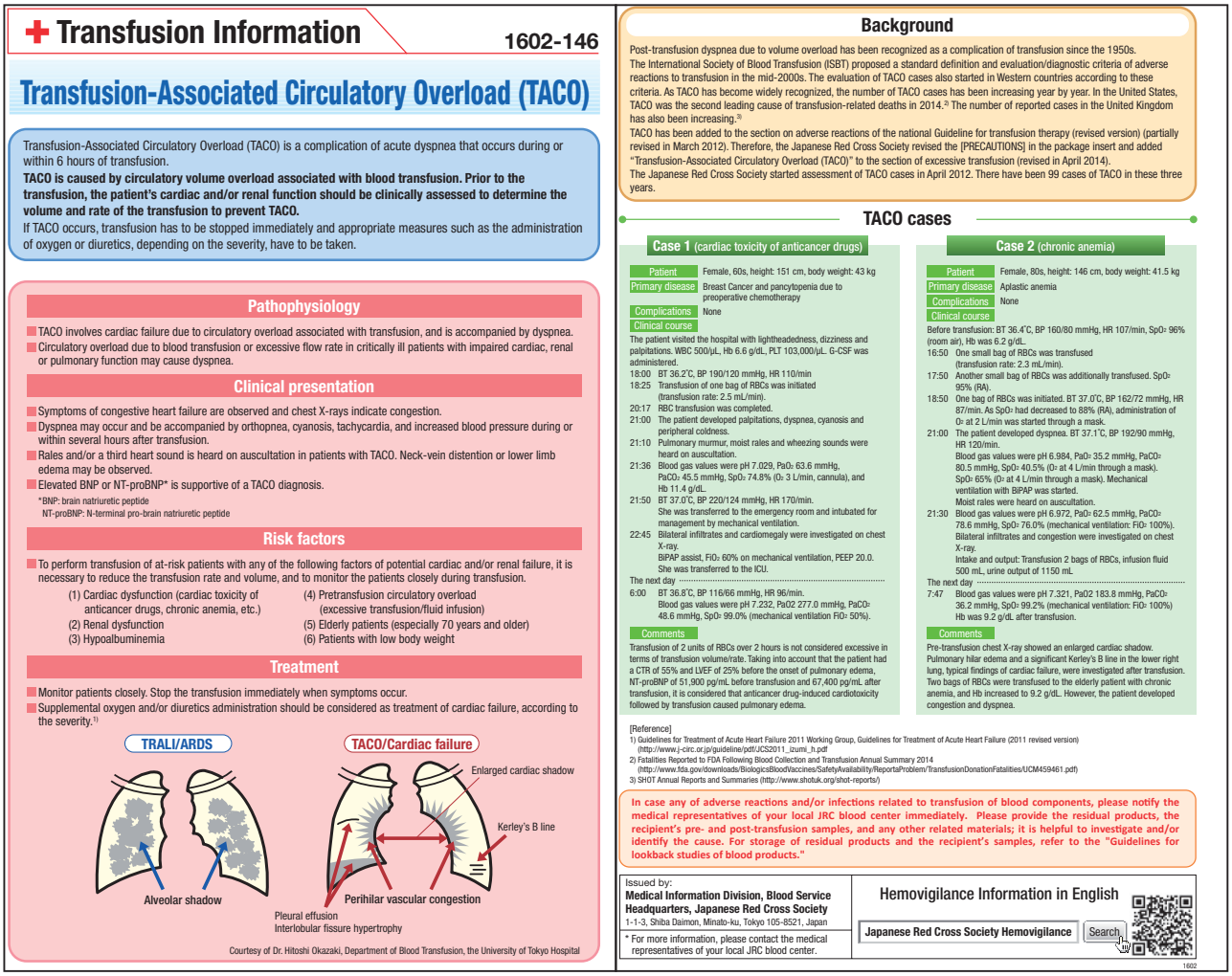


Figure 9. Evaluation of TRALI and TACO cases (2007-2015)



Transfusion Information 1602-146

Transfusion-Associated Circulatory Overload (TACO)

Transfusion-Associated Circulatory Overload (TACO) is a complication of acute dyspnea that occurs during or within 6 hours of transfusion.
TACO is caused by circulatory volume overload associated with blood transfusion. Prior to the transfusion, the patient's cardiac and/or renal function should be clinically assessed to determine the volume and rate of the transfusion to prevent TACO.
If TACO occurs, transfusion has to be stopped immediately and appropriate measures such as the administration of oxygen or diuretics, depending on the severity, have to be taken.

Pathophysiology
- TACO involves cardiac failure due to circulatory overload associated with transfusion, and is accompanied by dyspnea.
- Circulatory overload due to blood transfusion or excessive flow rate in critically ill patients with impaired cardiac, renal or pulmonary function may cause dyspnea.

Clinical presentation
- Symptoms of congestive heart failure are observed and chest X-rays indicate congestion.
- Dyspnea may occur and be accompanied by orthopnea, cyanosis, tachycardia, and increased blood pressure during or within several hours after transfusion.
- Rales and/or a third heart sound is heard on auscultation in patients with TACO. Neck-vein distention or lower limb edema may be observed.
- Elevated BNP or NT-proBNP* is supportive of a TACO diagnosis.

*BNP: brain natriuretic peptide
NT-proBNP: N-terminal pro-brain natriuretic peptide

Risk factors
- To perform transfusion of at-risk patients with any of the following factors of potential cardiac and/or renal failure, it is necessary to reduce the transfusion rate and volume, and to monitor the patients closely during transfusion.
  (1) Cardiac dysfunction (cardiac toxicity of anticancer drugs, chronic anemia, etc.)
  (2) Renal dysfunction
  (3) Hypoalbuminemia
  (4) Pretransfusion circulatory overload (excessive transfusion/fluid infusion)
  (5) Elderly patients (especially 70 years and older)
  (6) Patients with low body weight

Treatment
- Monitor patients closely. Stop the transfusion immediately when symptoms occur.
- Supplemental oxygen and/or diuretics administration should be considered as treatment of cardiac failure, according to the severity.[1]

Courtesy of Dr. Hitoshi Okazaki, Department of Blood Transfusion, the University of Tokyo Hospital

Background

Post-transfusion dyspnea due to volume overload has been recognized as a complication of transfusion since the 1950s. The International Society of Blood Transfusion (ISBT) proposed a standard definition and evaluation/diagnostic criteria of adverse reactions to transfusion in the mid-2000s. The evaluation of TACO cases also started in Western countries according to these criteria. As TACO has become widely recognized, the number of TACO cases has been increasing year by year. In the United States, TACO was the second leading cause of transfusion-related deaths in 2014.[2] The number of reported cases in the United Kingdom has also been increasing.[3]
TACO has been added to the section on adverse reactions of the national Guideline for transfusion therapy (revised version) (partially revised in March 2012). Therefore, the Japanese Red Cross Society revised the [PRECAUTIONS] in the package insert and added "Transfusion-Associated Circulatory Overload (TACO)" to the section of excessive transfusion (revised in April 2014).
The Japanese Red Cross Society started assessment of TACO cases in April 2012. There have been 99 cases of TACO in these three years.

TACO cases

Case 1 (cardiac toxicity of anticancer drugs)

Patient: Female, 60s, height: 151 cm, body weight: 43 kg
Primary disease: Breast Cancer and pancytopenia due to preoperative chemotherapy
Complications: None
Clinical course:
The patient visited the hospital with lightheadedness, dizziness and palpitations. WBC 500/μL, Hb 6.6 g/dL, PLT 103,000/μL. G-CSF was administered.
18:00 BT 36.2°C, BP 190/120 mmHg, HR 110/min
18:25 Transfusion of one bag of RBCs was initiated (transfusion rate: 2.5 mL/min).
20:17 RBC transfusion was completed.
21:00 The patient developed palpitations, dyspnea, cyanosis and peripheral coldness.
21:10 Pulmonary murmur, moist rales and wheezing sounds were heard on auscultation.
21:36 Blood gas values were pH 7.029, PaO_2 63.6 mmHg, $PaCO_2$ 45.5 mmHg, SpO_2 74.8% (O_2 3 L/min, cannula), and Hb 11.4 g/dL.
21:50 BT 37.0°C, BP 220/124 mmHg, HR 170/min.
She was transferred to the emergency room and intubated for management by mechanical ventilation.
22:45 Bilateral infiltrates and cardiomegaly were investigated on chest X-ray.
BiPAP assist, FiO_2 60% on mechanical ventilation, PEEP 20.0.
She was transferred to the ICU.
The next day
6:00 BT 36.8°C, BP 116/66 mmHg, HR 96/min.
Blood gas values were pH 7.232, PaO_2 277.0 mmHg, $PaCO_2$ 48.6 mmHg, SpO_2 99.0% (mechanical ventilation FiO_2 50%).
Comments:
Transfusion of 2 units of RBCs over 2 hours is not considered excessive in terms of transfusion volume/rate. Taking into account that the patient had a CTR of 55% and LVEF of 25% before the onset of pulmonary edema, NT-proBNP of 51,900 pg/mL before transfusion and 67,400 pg/mL after transfusion, it is considered that anticancer drug-induced cardiotoxicity followed by transfusion caused pulmonary edema.

Case 2 (chronic anemia)

Patient: Female, 80s, height: 146 cm, body weight: 41.5 kg
Primary disease: Aplastic anemia
Complications: None
Clinical course:
Before transfusion: BT 36.4°C, BP 160/80 mmHg, HR 107/min, SpO_2 96% (room air), Hb was 6.2 g/dL.
16:50 One small bag of RBCs was transfused (transfusion rate: 2.3 mL/min).
17:50 Another small bag of RBCs was additionally transfused. SpO_2 95% (RA).
18:50 One bag of RBCs was initiated. BT 37.0°C, BP 162/72 mmHg, HR 87/min. As SpO_2 had decreased to 88% (RA), administration of O_2 at 2 L/min was started through a mask.
21:00 The patient developed dyspnea. BT 37.1°C, BP 192/90 mmHg, HR 120/min.
Blood gas values were pH 6.984, PaO_2 35.2 mmHg, $PaCO_2$ 80.5 mmHg, SpO_2 40.5% (O_2 at 4 L/min through a mask).
SpO_2 65% (O_2 at 4 L/min through a mask). Mechanical ventilation with BiPAP was started.
Moist rales were heard on auscultation.
21:30 Blood gas values were pH 6.972, PaO_2 62.5 mmHg, $PaCO_2$ 78.6 mmHg, SpO_2 76.0% (mechanical ventilation: FiO_2 100%).
Bilateral infiltrates and congestion were investigated on chest X-ray.
Intake and output: Transfusion 2 bags of RBCs, infusion fluid 500 mL, urine output of 1150 mL
The next day
7:47 Blood gas values were pH 7.321, PaO_2 183.8 mmHg, $PaCO_2$ 36.2 mmHg, SpO_2 99.2% (mechanical ventilation: FiO_2 100%)
Hb was 9.2 g/dL after transfusion.
Comments:
Pre-transfusion chest X-ray showed an enlarged cardiac shadow. Pulmonary hilar edema and a significant Kerley's B line in the lower right lung, typical findings of cardiac failure, were investigated after transfusion. Two bags of RBCs were transfused to the elderly patient with chronic anemia, and Hb increased to 9.2 g/dL. However, the patient developed congestion and dyspnea.

[Reference]
1) Guidelines for Treatment of Acute Heart Failure 2011 Working Group, Guidelines for Treatment of Acute Heart Failure (2011 revised version) (http://www.j-circ.or.jp/guideline/pdf/JCS2011_izumi_h.pdf
2) Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary 2014 (http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf)
3) SHOT Annual Reports and Summaries (http://www.shotuk.org/shot-reports/)

In case any of adverse reactions and/or infections related to transfusion of blood components, please notify the medical representatives of your local JRC blood center immediately. Please provide the residual products, the recipient's pre- and post-transfusion samples, and any other related materials; it is helpful to investigate and/or identify the cause. For storage of residual products and the recipient's samples, refer to the "Guidelines for lookback studies of blood products."

Issued by:
Medical Information Division, Blood Service Headquarters, Japanese Red Cross Society
1-1-3, Shiba Daimon, Minato-ku, Tokyo 105-8521, Japan
* For more information, please contact the medical representatives of your local JRC blood center.

Hemovigilance Information in English
Japanese Red Cross Society Hemovigilance Search

1602

Figure 10. English translation of distributed leaflet of TACO (Transfusion Information 1602-146)

(2) Hemolytic adverse reactions

Table 2 shows the breakdown of case reported as hemolytic adverse reactions by medical institutions in 2015. Case investigation by the JRCS revealed 11 cases with irregular antibodies in the patients' specimens which consisted of 4 acute reactions and 7 delayed reactions (Table 3). In addition, 3 patients with an acute reaction and 4 patients with delayed reactions had a history of transfusion.

The acute reaction case (No. 4) and the delayed reaction cases (Nos. 1, 2 and 6) were evaluated as "compatible" in the pre-transfusion crossmatch test conducted by the medical institutions but were evaluated as "incompatible" in the test results conducted by JRCS due to confirmed weak agglutination. Note that, in the acute reaction case (No.1), agglutination was observed with a saline method at room temperature in the pre-transfusion crossmatch test conducted by the medical institution; since reactivity was not observed at 37°C, it was evaluated as "compatible", on the other hand, since weak agglutination was observed at 37°C in the test results conducted by JRCS, it was evaluated as "incompatible".

Table 2. Number of case reports of hemolytic adverse reactions in 2015

	Severe	Non-severe	Total
AHTR	10	5	15
DHTR	8	5	13
Total	18	10	28

Acute Hemolytic Transfusion Reaction (AHTR) : Onset within 24 hours of a transfusion
Delayed Hemolytic Transfusion Reactions (DHTR) : Onset after 24 hours of a transfusion

(Continued on the following page.)

(3) Transfusion-associated graft-versus-host disease (TA-GVHD)

- Two cases with suspected TA-GVHD were reported in 2015. However, microsatellite DNA analysis of the patients' blood revealed no chimerism, thus TA-GVHD was ruled out.
- There have been no confirmed cases of TA-GVHD which were caused by blood components for transfusion distributed by the JRCS since 2000.

Table 3. Positive cases of irregular blood antibodies

		Component	Patients	Symptoms	Test results conducted by JRCS after onset					
					Pre-transfusion			Post-transfusion		
					Crossmatch	Patient's serum	DAT	Crossmatch	Patient's serum	DAT
Acute	1	RBC	F 90s	Fever, Hemolysis	Incompatible	Pos.*1	weak Pos.	Incompatible	Anti-M	Pos.
	2	RBC	F 60s	Hemolysis	n/t	n/t	n/t	n/t	Anti-Jk^{b} Anti-Di^{a}	Neg.
	3	RBC	F 70s	Chills, Fever, Vomiting, Hemolysis	n/t	Anti-M	Pos.	Compatible	Anti-M	Pos.
	4	RBC	F 90s	Chills, Shivering, Hemolysis, Tachycardia, Fever	Incompatible	Anti-M	n/t	Incompatible	n/t	Pos.
Delayed	1	RBC	M 80s	Fever, Urticaria, Dyspnoea, Hematuria	Incompatible	Anti-M Anti-Le^{a}	Neg.	Incompatible	n/t	Neg.
	2	RBC	M 80s	DHTR	Incompatible	Anti-E	n/t	Incompatible	Anti-E	Neg.
	3	RBC	M 50s	Hemolysis, LDH increased, Fever	n/t	Neg.	n/t	n/t	Anti-C Anti-e	Neg.
	4	RBC	F 40s	Hemolysis	Compatible*2				Anti-E	Pos.
	5	RBC	F 30s	Hemolysis, Hematuria	Compatible	Anti-c	Neg.	Incompatible	Anti-c Anti-Jk^{a}	Neg.
	6	RBC	F 80s	Hemolytic anaemia	Incompatible	Anti-Di^{a}	n/t	Incompatible	Anti-Di^{a} Anti-M	Pos.
	7	RBC	M 50s	Hemolysis	Compatible	n/t	n/t	Incompatible	Anti-E Anti-c	Pos.

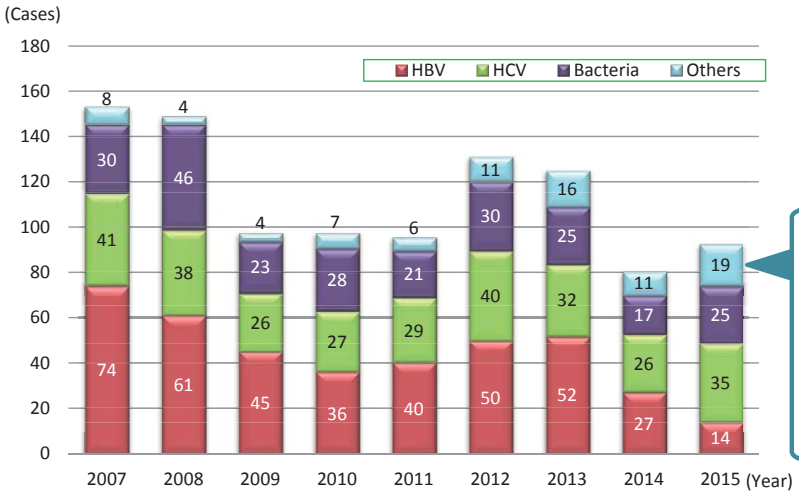
*1 Irregular blood antibodies were not identified.
*2 Test result obtained from medical institutions. Patient's specimen was unavailable for the testing at JRCS.
DHTR: Delayed Hemolytic Transfusion Reaction

2) Transfusion transmitted infections

(1) Cases reported as suspected post-transfusion transfusion-transmitted infections

Figure 11 shows the breakdown of cases of suspected post-transfusion transfusion-transmitted infections (including reported cases by medical institutions and cases of post-donation information) reported in 2015 and annual changes in the number of cases.

Confirmed cases include cases in which pathogens such as viruses were found both in the transfused blood components and in the post-transfusion patients' blood. Viral homology was confirmed by viral genome sequence analysis, while consistency of bacterial strain was confirmed by genotype (PFGE: Pulsed Field Gel Electrophoresis), drug susceptibility, and toxinotype.



Pathogen	Number of reported cases	Number of confirmed cases
HBV	14	0
HCV	35	0
Bacteria	25	2
CMV	10	0
HEV	4	3
HAV	1	0
HSV	1	0
HIV	1	0
HTLV-1	1	0
Parvovirus B19	1	1
Total	93	6

Figure 11. Breakdown of cases of suspected transfusion-transmitted infections by pathogen in 2015 and annual changes in the number of cases

(2) Summary of cases reports identified as TTIs

A summary of cases identified as TTIs is described as follows:

HEV

Voluntary reports: Cases reported by medical institutions as transfusion-transmitted viral infection

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		ALT		Recipient's outcome
					Test items	Test results	Period to transfusion	Positive conversion items	Interval after transfusion	Maximum (IU/L)	Interval after transfusion	
1	Myeloma	Ir-PC-LR (2015. 2)	50s	F	HEV-RNA IgA-HEV-Ab IgM-HEV-Ab IgG-HEV-Ab	Neg.	6 days	HEV-RNA IgA-HEV-Ab IgM-HEV-Ab IgG-HEV-Ab	16 wks	449	16 wks	Recovery
2	Hodgkin's lymphoma	Ir-PC-LR (2015. 3)	60s	M	HEV-RNA IgA-HEV-Ab IgM-HEV-Ab IgG-HEV-Ab	Neg.	21 days	HEV-RNA IgA-HEV-Ab IgM-HEV-Ab IgG-HEV-Ab	16 wks	646	15 wks	Recovery

Post-donation information: A case reported by a medical institution based on Lookback studies on positive conversion identified in the HEV-NAT trial*

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		ALT		Recipient's outcome
					Test items	Test results	Period to transfusion	Positive conversion items	Interval after transfusion	Maximum (IU/L)	Interval after transfusion	
3	Acute myeloid leukaemia	Ir-PC-LR (2014.12)	70s	M	HEV-RNA IgM-HEV-Ab IgG-HEV-Ab	Neg.	5 days	HEV-RNA	2 wks	615.5	10 wks	Remission

*An experimental and investigational nucleic-acid amplification test (NAT) for HEV has been conducted exclusively in Hokkaido, the prevalence of HEV is high, to eliminate HEV-RNA positive blood donation. Consequently, an investigational look-back study is performed based on a HEV positive conversion donation. (see the "Guideline on look-back studies on blood products" (partially revised in July 2014)).

Bacteria

Voluntary report: Cases reported by medical institutions as suspected transfusion-transmitted bacterial infection

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Blood culture results of post-transfusion		Symptoms	Onset time (after administration)	Recipient's outcome
					Blood components	Recipient's blood			
1	Acute myeloid leukaemia	Ir-PC-LR (2014.12)	Under 10	M	*Escherichia coli*	*Escherichia coli*	Fever, chills, tachycardia, hypoxemia, hypotension	25 min.	Recovery
2	Neuroblastoma	Ir-PC-LR (2015. 6)	Under 10	F	*Staphylococcus aureus*	*Staphylococcus aureus*	Fever, generalized edema, weight gain, worsening heart failure	Unknown	Recovery, with sequelae

Parvovirus B19

Voluntary report: A case reported by a medical institution as a suspected transfusion-transmitted viral infection

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		Recipient's outcome
					Test items	Test results	Period to transfusion	Positive conversion items	Interval after transfusion	
1	Diabetic nephropathy	Ir-RBC-LR (2015. 8)	60s	M	B19-DNA	Neg.	1 day	B19-DNA	3 wks	Recovery

3) Information about individual cases of transfusion adverse reactions and TTIs obtained from the literature or academic conference

Table 4 shows domestic case reports found by the periodical searching of the literature and academic conference in 2015. The domestic cases in Table 4 were only reported in the literature or at academic conferences, and not to the JRCS. For these cases, the JRCS investigated the severity of adverse reactions and the blood components used by the medical institutions via JRCS's MRs. If the cases were classified as severe adverse reactions, we submitted them as ICSR to PMDA.

Since the blood components for transfusion prepared by the JRCS are distributed only in Japan, we collect and investigate the case reports on adverse reactions and TTIs caused by foreign blood components that are therapeutically equivalent in accordance with PMD Act. Overseas cases of TTIs and unknown severe adverse reactions are submitted as ICSR to PMDA. Table 5 shows the overseas cases collected in 2015.

Table 4. Domestic cases of transfusion-related adverse reactions obtained in the literature search in 2015 (including cases not submitted ICSR to PMDA)

No.	Suspected Component	Age	Sex	Symptoms	Journal etc.
1	Ir-RCC-LR	82	M	Hemolytic transfusion reaction	Journal of Japanese Association for Acute Medicine. 2014; 25(8): 577.
2	Ir-RCC-LR	65	M	Delayed haemolytic transfusion reaction	Journal of Japanese Association for Acute Medicine. 2014; 25(8): 577.
3	RBC-LR Ir-RBC-LR Ir-PC-LR FFP-LR240	35	F	Transfusion-related ci rculatory overload	Kanto Journal of Obstetrics and Gynecology. 2014; 51(3): 423.
4	Ir-RCC-LR	73	F	Delayed haemolytic transfusion reaction	The Bulletin of Hiroshima Association of Medical Technologists. 2015; 44(1): 30.
5	Ir-RCC-LR	68	F	Delayed haemolytic transfusion reaction	Kanto-Koshin regional meeting of JAMT prog. 2014; 51th: 140.
6	Ir-RBC-LR	65	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2015; 61(1): 62.
7	Ir-RCC-LR	80	M	Delayed haemolytic transfusion reaction, Hematuria, Fever, Acute renal failure	Japanese Journal of Transfusion and Cell Therapy. 2015; 61(2): 235.
8	RBC-LR	52	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2015; 61(2): 344.
9	RCC-LR	58	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2015; 61(2): 350.
10	Ir-RCC-LR	81	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2015; 61(2): 357.
11	Ir-RCC-LR	79	F	Delayed haemolytic transfusion reaction	Japanese Journal of Medical Technology. 2015; 64(Suppl): 242.
12	Ir-RBC-LR	42	F	Delayed haemolytic transfusion reaction	Japanese Journal of Medical Technology. 2015; 64(Suppl): 242.
13	Ir-RBC-LR	62	F	Delayed haemolytic transfusion reaction	Japanese Journal of Medical Technology. 2015; 64(Suppl): 242.
14	RCC-LR Ir-RCC-LR	80s	M	Delayed haemolytic transfusion reaction	Japanese Journal of Medical Technology. 2015; 64(Suppl): 243.
15	Ir-RCC-LR	83	F	Hyperkalaemia, Pulseless electrical activity	Journal of the Japanese Society of Intensive Care Medicine. 2015; 22(4): 257-260.
16	Ir-PC-LR	70	F	Redness generalized, Hypotension , Anaphylactic Shock	Cardiovascular Anesthesia. 2015; 19(Suppl): 373.

RCC-LR : Red Cells Concentrates Leukocytes Reduced
RBC-LR : Red Blood Cells, Leukocytes Reduced
Ir-RCC-LR : Irradiated Red Cells Concentrates Leukocytes Reduced
Ir-RBC-LR : Irradiated Red Blood Cells, Leukocytes Reduced
Ir-PC-LR : Irradiated Platelet Concentrate, Leukocytes Reduced
FFP-LR240 : Fresh Frozen Plasma, Leukocytes Reduced, 240mL

(Summary)

- Many of transfusion-related adverse reactions obtained in the literature research were hemolytic reactions due to irregular antibodies (Nos. 1, 2, 4-14). Among the irregular antibodies detected, anti-E and anti-c antibodies were often observed, followed by the Kidd system (anti-Jk^b), and Duffy system (anti-Fy^a and anti-Fy^b). The investigation results for these cases responded by medical institutions showed that the most cases were not severe, but one case (No. 7) developed uremia from acute kidney failure and required dialysis treatment.
- The transfusion-associated circulatory overload (TACO) case (No. 3) seemed to be due to massive transfusion of platelet components to a patient with myelodysplastic syndrome (MDS) who was refractory to platelet transfusion.
- In the case (No. 15) of hyperkalemia and pulseless electrical activity (PEA), PEA was thought to be caused by elevated blood potassium due to massive transfusion of irradiated red cell components in which the supernatant potassium concentration was likely to increase during storage.

Table 5. Overseas cases obtained in the literature search in 2015 that have been submitted ICSR to PMDA

No.	Country	Suspected blood product	Age	Sex	Symptoms	Journal etc.
1	Brazil	Platelet	56	M	Dengue fever	Transfusion. 2015; 55(5): 961-964.
2	Singapore	Packed Red cells	37	F	Dengue fever	Transfusion. 2015; 55(7): 1655-1661.
3	Italy	Packed Red cells	36	F	Yersinia sepsis	Blood Transfus. 2015; 13(3): 528-531.
4	China	Whole blood	61	M	Plasmodium malariae infection	Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi 2014; 32(6): 458, 461.
5	Canada	Platelet	Unknown	M	Bacterial infection	Transfusion. 2015; 55(10): 2384-2389.
6	U.S.	Platelet	79	F	Human anaplasmosis	Vox Sanguinis. 2015; 109(Suppl.1): 243-244.
7	Thailand	Packed Red cells	Unknown	M	HIV infection	Vox Sanguinis. 2015; 109(Suppl.1): 226.
8	Sweden	Packed Red cells Platelet Plasma	63	M	Hepatitis E	Journal of Medical Case Reports. 2015; 9(180): 1-6.
9	Argentina	Packed Red cells	10	F	Posterior reversible encephalopathy	Archivos argentinos de pediatria. 2015; 113(5): e271-e274.
10	U.S.	Packed Red cells	75	F	Babesiosis	Orthopedics. 2015; 38(9): e852-e855.
11	U.S.	Packed Red cells	0	Unknown	Babesiosis	Transfusion. 2015; 55(Suppl.3): 185A.
12	Belgium	Packed Red cells	7	M	Chagas' disease	PLoS Negl Trop Dis 2015; 9(10): e0003986.
13	U.S.	Packed Red cells	75	M	Dengue hemorrhagic	Transfusion. 2016; 56(1): 215-222.
14	France	Platelet	10	Unknown	Bacterial infection	Arch Pediatr. 2016; 23(1): 86-89.
15	Spain	Platelet	24	M	HIV infection	Transfusion. 2016; 56(4): 831-836.

(Summary)

- Of 3 cases with Dengue virus infection (Nos. 1, 2 and 13), the donors developed symptoms of fever after the blood donation to the 2 cases (Nos. 1 and 2), and the look-back studies revealed dengue virus infections in the recipients of blood components derived from these donors. Investigation of the patient, who received transfusion of blood components that were determined to be dengue virus positive in the look-back study, showed that one case (No. 13) had met case-defining criteria for dengue hemorrhagic fever.
- Two cases of babesiosis (Nos. 10 and 11) presented with symptoms of fever, fatigue, and thrombocytopenia after transfusion. One case (No. 10) recovered after the administration of azithromycin (antibacterial drug) and atovaquone (antimalarial drug). In another case (No. 11), protozoa were observed in red blood cells of the patient's blood after transfusion and were identified as *Babesia microti* by PCR test. The involved donor lived in an endemic area of *B. microti* and had a history of multiple tick bites, and also tested positive for *B. microti*.
- Of 3 cases with bacterial infection (Nos 3, 5 and 14); one case (No. 3) died due to worsened general condition after transfusion. The patient was diagnosed with septicemia (multiple organ failure) due to *Yersinia enterocolitica* after death. Investigation of the involved blood donors revealed that one donor was antibody positive for *Y. enterocolitica*. The second case (No. 5) died of septicemia on the day following transfusion. *Staphylococcus epidermidis* was detected both in the post-transfusion blood culture of the patient and in the residual platelet components, and their sensitivity to antibiotics and rRNA matched. The third case (No. 14) developed chills and vomiting after the start of transfusion, but these symptoms improved with medication, but when the transfusion was restarted, the symptoms of chills and vomiting re-appeared and the patient's general condition worsened. As *Citrobacter koseri* was detected in the transfused platelet components, transfusion-associated bacterial infection was suspected.
- Two cases with HIV infection (Nos. 7 and 15) were both TTI cases caused by HIV-pool NAT negative blood components. In one case (No. 7), the look-back studies on a donor who experienced positive conversion HIV antibody revealed that the recipient of the relevant red blood cell component tested positive for HIV antibody. In another case (No. 15), positive conversion of HIV antibody was observed in the patient who had received frequent transfusions. In the look-back study, it was determined by an individual NAT that HIV-RNA positive blood had been contained in the blood components transfused in the past. In both of the 2 cases, the viral genome sequence of detected from donors and patients was consistent.
- The quartan malaria case (No. 4) presented with frequent fever after transfusion, and *Plasmodium malariae* was detected in the patient's blood. *P. malariae* was also detected in the involved donor and their genome sequence was also consistent. Since the involved donor was from a malaria endemic country, but did not have a history of malaria or overseas travel in the past three years, the donor was considered to be an asymptomatic carrier.
- The human anaplasmosis case (No. 6) presented with fever after the transfusion of platelet components, and *Anaplasma phagocytophilum* was detected in the patient blood. Investigation of the involved donor revealed that the donor lived in an endemic area for *Ixodes scapularis*, the vector of *A. phagocytophilum* and tested positive for *A. phagocytophilum* by PCR as well as for anti-*A. phagocytophilum* IgG and IgM antibody.
- The hepatitis E case (No. 8) received transfusion at the time of heart transplant surgery and developed elevation of liver enzymes after the start of immunosuppression therapy. Detailed investigation revealed that HEV-RNA was positive. Since the HEV infection was confirmed, the dosage of immunosuppressive drug was reduced, and the patient recovered with administration of ribavirin. Investigation of 12 donors involved in the blood components transfused revealed that one donor had a high titer of HEV-IgG.
- In the Chagas' disease case (No. 12), the look-back studies of a donor who tested positive for *Trypanosoma cruzi* antibody revealed that the recipients of red blood cell components derived from this donor was positive for *T. cruzi* antibody and *T. cruzi* DNA.
- One case (No. 9) was diagnosed with reversible posterior encephalopathy (RPE), with seizure and a decreased level of consciousness observed after the transfusion of red blood cell components, and high intensity areas were investigated in the parieto-occipital cortex and both frontal lobes on head MRI. Since this patient had concomitant risk factors for the development of RPE (mass administration of steroid and intravenous administration of gamma globulin) besides transfusion, it was difficult to identify the pathogenesis of RPE.

2. Reports on measures in foreign countries and reports of studies

Reports on measures in foreign countries are submitted when the JRCS obtains information concerning the enforcement of measures to prevent health hazards from occurring or spreading, including discontinuation of manufacturing, importing or distributing, or recall or disposal of foreign pharmaceutical products. Reports of studies are submitted when the JRCS obtains information concerning study reports showing that cancer or another serious disease, disorder, or death was possibly caused by a relevant pharmaceutical product or a foreign pharmaceutical product, or infection due to its use, or that the incidence of adverse reactions to the relevant pharmaceutical product or foreign pharmaceutical product or infection by its use has significantly changed, or that the relevant pharmaceutical product did not show its approved efficacy or effect.

Reports on measures in foreign countries and reports of studies are submitted based on Article 68-10 of the PMD Act and Article 228-20 of the Enforcement Regulations of the PMD Act even if the blood components manufactured by JRCS are not marketed (supplied) in other countries. Intended products involve products used in other countries that have the same active ingredients as the blood components manufactured or distributed by the JRCS, including such products with a different administration route and dosage, or efficacy and effect.

Table 6 shows the measures in foreign countries that have been reported in 2015. There were no reports of studies to be reported in 2015.

Table 6. Reports on measures in foreign countries obtained in 2015

Source	Title
France (ANSM)	Plasma therapeutique securise par solvant-detergent : changement de statut juridique - Point d'Information 27/01/2015
U.S. (FDA)	Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products - Draft Guidance for Industry(May 2015)
	Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products - Guidance for Industry(Dec 2015)
U.S. (FDA)	Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in Response to Ebola Virus; Draft Guidance for Industry December 2015
U.K. (NHSBT, JPAC)	The Update. For Action. 1.4 Points of note from the National Commissioning Group for Blood Wednesday, 25 November 2015
	NHSBT Board Papers. Implementation of the Supply of Hepatitis E Virus (HEV) Tested Components November 26 2015
	HEV Letter to Hospital Transfusion Teams. Introduction of Hepatitis E Virus (HEV) screened negative components 2016/01/28*
	NHSBT Hepatitis E Virus (HEV) Factsheet for Hospital Transfusion Teams 2016/01*
	Change Notification UK National Blood Services No.12-2016 2016/01/27*

*Consecutive information obtained in 2016 were submitted as addendum report.

(Summary)

- (No. 1) The French National Agency for Medicines and Health Products (ANSM) announced that solvent detergent (SD) plasma should no longer be considered as a labile blood product, but as a blood derived medicinal product from January 31, 2015 and only pharmaceutical companies can produce and distribute these products. The French Blood Establishment (EFS), a public blood organization that does not have the status of a pharmaceutical establishment, will no longer be authorized to produce and distribute SD plasma. The pharmacovigilance system will be applied as the system of surveillance, but haemovigilance is also applied in the meantime.
- (No. 2) A Draft Guidance titled, "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission," was issued by the FDA in May 2015. The FDA revised its recommendation from the indefinite deferral for male donors with a history of sexual contact with another man since 1977to the 12-month blood donor deferral after the last sexual contact with another man. Since then, the final version was issued

in December 2015, and reflected public comment on the draft. In the final version, FDA recommends indefinite deferral to an individual with hemophilia or related clotting factor deficiencies requiring treatment with clotting factor concentrates for reasons of donor safety, rather than based on the risk of HIV infection from clotting factor concentrates, and the FDA no longer recommends deferral to donors who have had sex contact with such a patient.

- (No. 3) A Draft Guidance for Industry titled "Recommendations for Assessment of Blood Donor Suitability, Donor Deferral and Blood Product Management in response to Ebola Virus" was issued by the FDA. Those who had a history of Ebola virus (EBV) infection or disease (EVD), who had contact with Ebola patients, or who had a history of travelling to a country with widespread Ebola cases may be in a state before the onset of symptoms or during an asymptomatic incubation period. The viremia and infectivity in such a state are not yet known, but FDA recommends indefinite deferral for donors with a history of Ebola virus infection or disease, 8 weeks' deferral from the date of his/her departure for donors who have travelled to a country with widespread Ebola virus disease, and also 8 weeks' deferral for donors who have a history of close contact with a person confirmed to have Ebola virus infection or disease over the previous 8 weeks to reduce the risk of infection.
- (No. 4) Based on the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) recommendation that "the use of HEV tested components is recommended for patients having solid organ and allogenic (donor) stem cell transplantation." released in July 2015, the National Health Service Blood and Transplant (NHSBT) in the UK decided to start the supply of HEV negative components for transfusion from March 14, 2016. HEV negative components are supplied for transfusion to neonates and infants regardless of the order of the medical institutions. A premium of 17.18 sterling pound is applied to each unit as an additional requirement.

3. Safety measures against blood components for transfusion

Safety measures are taken based on cases of transfusion related adverse reactions and TTIs reported by medical institutions and the results of assessment and evaluation of post-donation information obtained from donors. The following are the safety measures taken in 2015:

1) Approach to determine the cause of cytomegalovirus (CMV) infection in neonates (especially in very-low-birth-weight infants)

In 2013, JRCS distributed a leaflet about suspected cases of transfusion-transmitted CMV infection to provide information to perinatal healthcare professionals that CMV antibody-negative blood is available for transfusion to very-low-birth-weight infants as appropriate. In addition, in April 2014, JRCS voluntarily revised the package inserts of all blood components for transfusion except plasma components to add the risk of CMV infection (see "Haemovigilance by JRCS 2013").

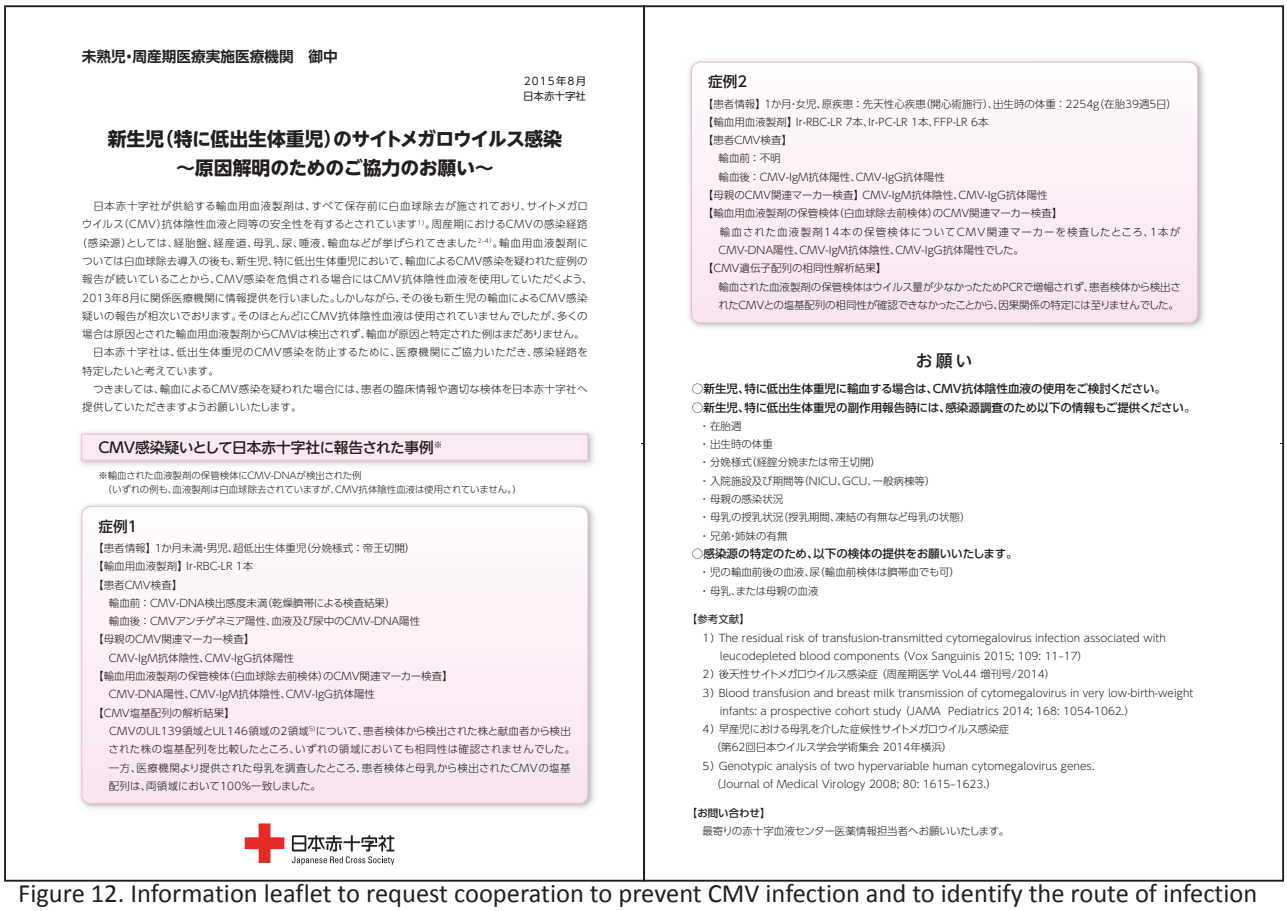
After information provision and revision of the precautions in package inserts, JRCS has received continuous reports of suspected cases of transfusion-transmitted CMV infection in neonates. Although CMV antibody-negative blood was not used in most of these cases, no cases identified as TT-CMV (as of March 2015).

Based on these observations, JRCS decided to ask for cooperation, requesting medical institutions to provide clinical information on infant patients with appropriate samples when any transfusion-related CMV infection is suspected in low-birth-weight infants so that JRCS can identify the route of infection to determine the infectious risk. To this end, JRCS provided a leaflet (Figure 12) to medical institutions with departments for immature babies and perinatal healthcare in August 2015. Figure 13 shows the samples and other materials requested to be provided for the investigation.

"Case 1" shown in the leaflet (Figure 14) was a case of strongly suspected CMV infection due to breast milk found among suspected cases of transfusion-related CMV infection reported to JRCS. Investigation of the repository sample* of pre-storage leukocyte-reduced blood components used for transfusion revealed that it was CMV-DNA positive but the viral genome sequence was not consistent with that of the CMV detected in the patient's sample after transfusion but 100% consistent with that of CMV detected in the breast milk of the mother (Transfusion. 2016; 56(6):1305-1310).

Currently, all blood components for transfusion supplied by JRCS are treated with leukocyte reduction procedure before they are stored, and they are considered as safe as CMV antibody negative blood (Vox Sang. 2015; 109 (1):11-17). In addition, since some reports show that the risk of infection from breast milk is higher than that from transfusion in low-birth-weight infants (JAMA Pediatr. 2014; 168 (11):1054-1062), it is recommended to investigate breast milk when a transfusion-related CMV infection is suspected.

*JRCS stores samples of all blood donations for 11 years to investigate adverse reactions. These repository samples were not treated with leukoreduction procedure.



未熟児・周産期医療実施医療機関　御中

2015年8月
日本赤十字社

新生児（特に低出生体重児）のサイトメガロウイルス感染 ～原因解明のためのご協力のお願い～

日本赤十字社が供給する輸血用血液製剤は、すべて保存前に白血球除去が施されており、サイトメガロウイルス（CMV）抗体陰性血液と同等の安全性を有するとされています[1]。周産期におけるCMVの感染経路（感染源）としては、経胎盤、経産道、母乳、尿、唾液、輸血などが挙げられてきました[2-4]。輸血用血液製剤については白血球除去導入の後も、新生児、特に低出生体重児において、輸血によるCMV感染を疑われた症例の報告が続いていることから、CMV感染を危惧される場合にはCMV抗体陰性血液を使用していただくよう、2013年8月に関係医療機関に情報提供を行いました。しかしながら、その後も新生児の輸血によるCMV感染疑いの報告が相次いでおります。そのほとんどにCMV抗体陰性血液は使用されていませんでしたが、多くの場合は原因とされた輸血用血液製剤からCMVは検出されず、輸血が原因と特定された例はまだありません。

日本赤十字社は、低出生体重児のCMV感染を防止するために、医療機関にご協力いただき、感染経路を特定したいと考えています。

つきましては、輸血によるCMV感染を疑われた場合には、患者の臨床情報や適切な検体を日本赤十字社へ提供していただきますようお願いいたします。

CMV感染疑いとして日本赤十字社に報告された事例※

※輸血された血液製剤の保管検体にCMV-DNAが検出された例
（いずれの例も、血液製剤は白血球除去されていますが、CMV抗体陰性血液は使用されていません。）

症例1
【患者情報】1か月未満・男児、超低出生体重児（分娩様式：帝王切開）
【輸血用血液製剤】Ir-RBC-LR 1本
【患者CMV検査】
輸血前：CMV-DNA検出感度未満（乾燥臍帯による検査結果）
輸血後：CMVアンチゲネミア陽性、血液及び尿中のCMV-DNA陽性
【母親のCMV関連マーカー検査】
CMV-IgM抗体陰性、CMV-IgG抗体陽性
【輸血用血液製剤の保管検体（白血球除去前検体）のCMV関連マーカー検査】
CMV-DNA陽性、CMV-IgM抗体陰性、CMV-IgG抗体陽性
【CMV塩基配列の解析結果】
CMVのUL139領域とUL146領域の2領域[5]について、患者検体から検出された株と献血者から検出された株の塩基配列を比較したところ、いずれの領域においても相同性は確認されませんでした。一方、医療機関より提供された母乳を調査したところ、患者検体と母乳から検出されたCMVの塩基配列は、両領域において100%一致しました。

日本赤十字社
Japanese Red Cross Society

症例2
【患者情報】1か月・女児、原疾患：先天性心疾患（開心術施行）、出生時の体重：2254g（在胎39週5日）
【輸血用血液製剤】Ir-RBC-LR 7本、Ir-PC-LR 1本、FFP-LR 6本
【患者CMV検査】
輸血前：不明
輸血後：CMV-IgM抗体陽性、CMV-IgG抗体陽性
【母親のCMV関連マーカー検査】CMV-IgM抗体陰性、CMV-IgG抗体陽性
【輸血用血液製剤の保管検体（白血球除去前検体）のCMV関連マーカー検査】
輸血された血液製剤14本の保管検体についてCMV関連マーカーを検査したところ、1本がCMV-DNA陽性、CMV-IgM抗体陰性、CMV-IgG抗体陽性でした。
【CMV遺伝子配列の相同性解析結果】
輸血された血液製剤の保管検体はウイルス量が少なかったためPCRで増幅されず、患者検体から検出されたCMVとの塩基配列の相同性が確認できなかったことから、因果関係の特定には至りませんでした。

お願い

○**新生児、特に低出生体重児に輸血する場合は、CMV抗体陰性血液の使用をご検討ください。**
○**新生児、特に低出生体重児の副作用報告時には、感染源調査のため以下の情報もご提供ください。**
・在胎週
・出生時の体重
・分娩様式（経腟分娩または帝王切開）
・入院施設及び期間等（NICU、GCU、一般病棟等）
・母親の感染状況
・母乳の授乳状況（授乳期間、凍結の有無など母乳の状態）
・兄弟・姉妹の有無
○**感染源の特定のため、以下の検体の提供をお願いいたします。**
・児の輸血前後の血液、尿（輸血前検体は臍帯血でも可）
・母乳、または母親の血液

【参考文献】

1）The residual risk of transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components (Vox Sanguinis 2015; 109: 11-17)
2）後天性サイトメガロウイルス感染症（周産期医学 Vol.44 増刊号/2014）
3）Blood transfusion and breast milk transmission of cytomegalovirus in very low-birth-weight infants: a prospective cohort study (JAMA Pediatrics 2014; 168: 1054-1062.)
4）早産児における母乳を介した症候性サイトメガロウイルス感染症（第62回日本ウイルス学会学術集会 2014年横浜）
5）Genotypic analysis of two hypervariable human cytomegalovirus genes. (Journal of Medical Virology 2008; 80: 1615-1623.)

【お問い合わせ】
最寄りの赤十字血液センター医薬情報担当者へお願いいたします。

Figure 12. Information leaflet to request cooperation to prevent CMV infection and to identify the route of infection

(Extract of the information medium in Figure 12)

- Please consider the use of CMV negative blood components for the transfusion to neonates, especially for low-birth-weight infants.
- Please provide the following information to investigate the source of infection when submitting a case report of adverse reactions in neonates, especially low-birth-weight infants:
  - Number of gestational weeks
  - Body weight at birth
  - Mode of delivery (vaginal delivery or Caesarean section)
  - Inpatient facility and period of hospitalization (NICU, GCU, general ward, etc.)
  - Maternal infection status
  - Status of breast feeding (duration of breast-feeding, administration of breast milk including freezing or not)
  - Existence of siblings
- Please provide the following samples to identify the source of infection:
  - Blood and urine samples of the infant before and after transfusion (umbilical cord blood is acceptable as a sample before transfusion)
  - Breast milk or blood of the mother

Figure 13. Contents of the request for cooperation to medical institutions

(Extract of the information medium in Figure 12)

[Patient]
Male, under 1 month old, very-low-birth-weight infant (mode of delivery: Caesarean section)
[Blood components transfused]
1 bag of Ir-RBC-LR
[CVM tests on the patient]
Pre-transfusion: Below the detection sensitivity of CMV-DNA (tested with dried umbilical cord)
Post- transfusion: CMV antigenemia positive, blood and urine CMV-DNA positive
[CMV tests of the mother]
CMV-IgM antibody negative, CMV-IgG antibody positive
[CMV tests of repository samples of blood components (samples without leukoreduction)]
CMV-DNA positive, CMV-IgM antibody negative, CMV-IgG antibody positive
[CMV genome sequence analysis]
When the genome sequences of the CMV UL139 genes and UL146 genes detected in the patient's sample was compared to that of the donor's sample, homology was not confirmed in both genes. On the other hand, when the breast milk of the mother provided by the medical institution was examined, the two CMV gene sequences detected in the breast milk were 100% consistent with that detected in the patient's sample.

Figure 14. A strongly suspected case of CMV infection due to breast milk

4. Donor adverse reactions

1) Cases of donor adverse reactions

More than 70% of donor adverse reactions are vasovagal reactions (VVR), which have the highest incidence among all cases of donor adverse reactions. Symptoms of mild VVR include feeling bad, pallor facial, cold sweat, and symptoms of severe VVR include loss of consciousness (including associated falling), or convulsions in addition to the symptoms found in mild cases.

Table 7 shows the cases of donor adverse reactions in FY2015, and Figure 15 shows the breakdown by symptoms.

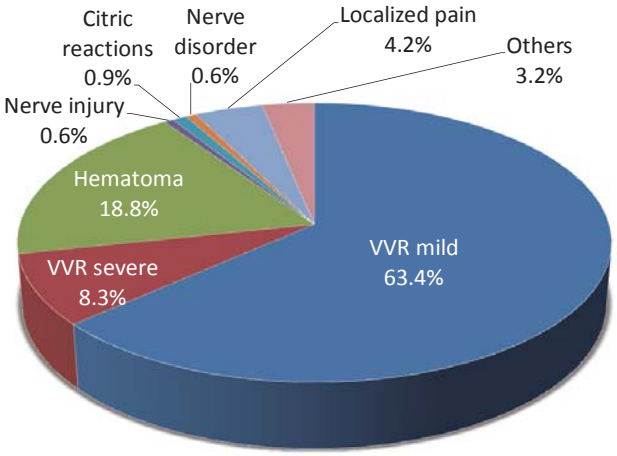


Figure 15. Breakdown of donor adverse reactions that occurred in FY2015

Table 7. Number of donor adverse reaction cases in FY2015

Category	Number of cases	Incidence
VVR mild*	29,689	0.608%
VVR severe*	3,863	0.079%
Hematoma	8,814	0.180%
Nerve injury	264	0.005%
Citric reactions	421	0.009%
Nerve disorder	298	0.006%
Localized pain	1,967	0.040%
Others	1,505	0.031%
Total	46,821	0.959%

Total donation	4,883,587

*Evaluation and categorization of VVR

Severity	Category	sBP(mmHg) pre-donation → post donation	Heart rate(/min) pre-donation → post donation	Respiratory rate(/min)
mild	Feel bad, palor, yawn, nausea, vomiting, cold sweat	120< → 80< <119 → <70	60< → 40< <59 → <30	10<
severe	In addition to mild ones, Loss of conciousness, convulsion, Incontenence, defecating	120< → <79 <119 → <69	60< → <39 <59 → <29	<9

Notice) Accident accompanied with faint should be categolized to severe.

2) Actions against donor adverse reactions

Nationwide introduction of leg muscle tension exercise

The internal working group of donor adverse reactions was established in 2012. A study entitled “Leg muscle tension exercises as a VVR preventive action” was introduced at 27 blood centers across Japan from July 2013, and verified the effect of leg muscle tension exercises to decrease the incidence of VVR. The results confirmed that the leg muscle tension exercises were effective to decrease the incidence of VVR in whole blood donation (see “Haemovigilance by JRCS 2014”).

Therefore, the introduction of leg muscle tension exercises to all donors has been launched all over Japan since October 2015 (Figure 16). After its introduction, a decreasing trend in the general VVR incidence was observed, especially due to a decrease in the VVR incidence with 400 mL whole blood donation (Figure 17). Regarding the effect of leg muscle tension exercises to decrease the VVR incidence with apheresis blood donation, a slight decreasing trend in the VVR incidence was seen in the results of the verification described above, but the effect was not significant. However, since apheresis process repeats blood drawing and returning and it takes a longer time to complete, it cannot be said that the blood circulation dynamics is the same as whole blood donation and apheresis donation. In addition, different timing of the start of leg muscle tension exercises were used for the verification of whole blood donation and apheresis donation. JRCS will continue to examine the effect of leg muscle tension exercises with amended method to decrease the incidence of VVR with apheresis donation.

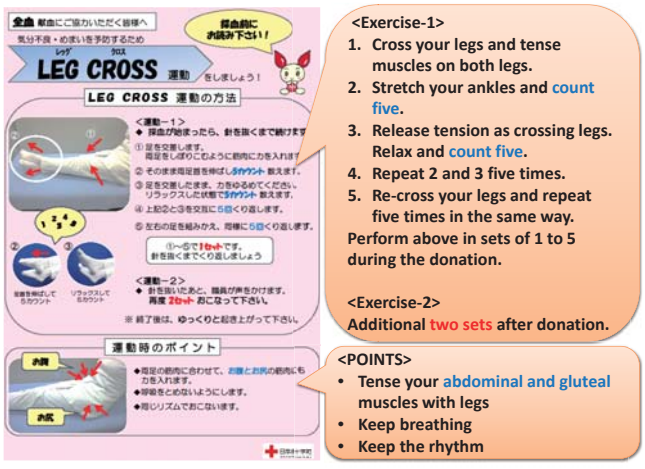
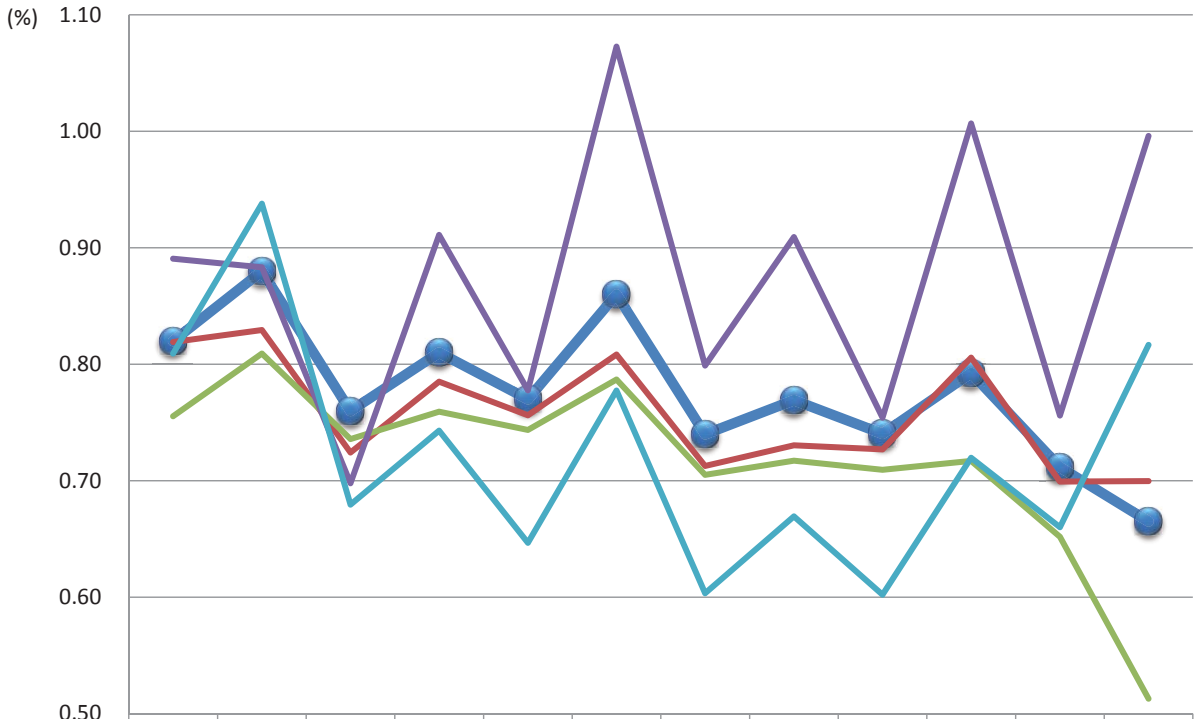


Figure 16. Leaflet for “leg muscle tension exercise”



	1H FY 2010	2H FY 2010	1H FY 2011	2H FY 2011	1H FY 2012	2H FY 2012	1H FY 2013	2H FY 2013	1H FY 2014	2H FY 2014	1H FY 2015	2H FY 2015
Total	0.82	0.88	0.76	0.81	0.77	0.86	0.74	0.77	0.74	0.79	0.71	0.67
WB (200mL)	0.82	0.83	0.72	0.79	0.76	0.81	0.71	0.73	0.73	0.81	0.70	0.70
WB (400mL)	0.76	0.81	0.74	0.76	0.74	0.79	0.71	0.72	0.71	0.72	0.65	0.51
Apheresis (platelets)	0.89	0.88	0.70	0.91	0.78	1.07	0.80	0.91	0.75	1.01	0.76	1.00
Apheresis (plasma)	0.81	0.94	0.68	0.74	0.65	0.78	0.60	0.67	0.60	0.72	0.66	0.82

1H FY: April to September
2H FY: October to March

Figure 17. Changes in the incidence of VVR

Afterword

This annual report describes information including those on transfusion-related adverse reactions and infectious diseases reported by medical institutions nationwide to JRC Blood Centers, and infectious cases based on post-donation information as well as other safety information. This report also summarises the safety measures conducted through evaluation and analysis of the safety information in accordance with the Pharmaceutical Affairs Law and GVP ordinance.

We extend our sincere appreciation for the cooperation of health care professionals and members of JRC Blood Centers to conduct these safety vigilance activities.

The JRCS will contribute to haemovigilance in Japan and the international community in compliance with the applicable laws and regulations, and endeavor to improve the safety of transfusions.

"Haemovigilance by JRCS 2015"

Issued by
Safety Vigilance Division, Technical Department, Blood Service Headquarters, Japanese Red Cross Society
Manager of Safety Vigilance Division:
Rikizo Taira
(Safety Management Supervisor)
Issued in
November 2016
Safety Vigilance Division, Technical Department, Blood Service Headquarters, Japanese Red Cross Society
1-2-1, Shiba-koen, Minato-ku, Tokyo, 105-0011
Japan