Incidence and severity of adverse effects related to platelet transfusion: a narrative review of the literature and the recent hemovigilance data of Japan

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Abstract: Platelet transfusions are given to prevent or treat bleeding in patients with quantitative or qualitative platelet disorders. Despite these lifesaving roles, certain complications are unavoidable even with best practices. Administration of platelet components has various risks, including allergic and anaphylactic transfusion reactions, febrile non-hemolytic transfusion reactions (FNHTRs), bacterial and viral infections, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-associated graft-versus-host disease (TA-GVHD) etc., some of which can be fatal. Among them, allergic and anaphylactic transfusion reactions, FNHTRs are frequent with platelet and plasma transfusions. Due to storage at room temperature, bacterial infections are more frequently caused by platelet transfusions than red blood cell or plasma transfusions. To prevent these adverse events related to platelet transfusions, various safety measures are being applied, which include well-organized donor-selection protocol, skin disinfection, sample diversion, leukoreduction, detection of bacterial contamination by culture and/or immunoassay, plasma replacement with platelet additive solution, platelet washing, and pathogen reduction technology. In contrast to other developed countries, the situation of platelet transfusions in Japan is unique in that the shelf-life of leukoreduced single-donor apheresis platelets is limited to 3 days and bacterial culture screening and pathogen reduction technologies are not implemented so far. In this article, incidence and severity of various adverse effects of platelet transfusions in Japan are described by referring to the recent data collected by two existing hemovigilance systems at the national level. Moreover, existing literatures inside and outside Japan regarding epidemiology, clinical manifestation, treatment, and mitigation strategies of adverse events associated with platelet transfusions are reviewed, which can help clinicians' appropriate use of platelet components and management of related adverse events.

Keywords: Platelet transfusion; adverse transfusion reaction; transfusion-transmitted infection (TTI); hemovigilance

Introduction

In clinical practice, platelet transfusions are indicated for prevention or treatment of bleeding in patients with either low platelet counts or poor platelet function (1-3), the majority of which comprise of prophylactic transfusion for patients with chemotherapy or hematopoietic progenitor cell transplantation to reduce the risk of spontaneous bleeding (4-7). Other cases, mostly in general medicine, cardiac surgery, intensive care unit etc., require therapeutic platelet transfusions for treating acute hemorrhage (6,7). Platelets can be collected by isolating and pooling platelets from units of donated whole blood (pooled whole-blood-derived platelets) or by apheresis directly from a donor (single-donor apheresis platelets) (1,8). Compared to red blood cells (RBCs) and plasma, which are stored at 4 ℃ for 5 to 6 weeks and at –20 ℃ for about 1 year, respectively, platelets are stored at room temperature (20 to 24 ℃) in gas permeable bags with constant agitation to preserve the viability. Thus, in most of developed countries, platelet shelf-life is limited to no longer than 5 days because of the bacterial infection risk that increases in relationship to the storage duration (9,10).

Transfusion practice is inseparable from adverse events, which include adverse transfusion reactions and transfusion-transmitted infections (TTIs). Incidence of the frequent adverse reactions to any blood components is estimated to be about one in 100 transfusions, and some reactions can be fatal, although very rare, occurring in about one in 200,000 to 420,000 units (11,12). Incidence of adverse reactions associated with platelet transfusions is approximately 1% to 4%, which is higher compared with those with RBC or plasma transfusions (13-16). According to the definition of adverse transfusion reactions by the International Society of Blood Transfusion (ISBT) Working Party for Hemovigilance (17), most of reactions related to administration of platelet concentrate (PC) are classified as either allergic transfusion reactions (ATRs) or febrile non-hemolytic transfusion reactions (FNHTRs) (16,18). These major reactions have been shown to be caused by the supernatant plasma in which units are stored (19,20). As for TTIs, bacterial infections are relatively more common with platelet transfusions than with RBC or plasma transfusions due to storage of platelets at warmer temperature.

Leukoreduction is a major safety measure to prevent adverse events related to platelet transfusions that has been widely implemented in developed countries, which is beneficial for reducing FNHTRs, bacterial and viral infections (12,21-23). Replacement of plasma in PC bags with platelet additive solution (PAS) and platelet washing are safety measures to prevent ATRs (23-27). The common preventive strategies for transfusion-transmitted bacterial infection (TTBI) include well-organized donor-selection protocol, skin disinfection, sample diversion, leukoreduction, and detection of contamination by culture and/or immunoassay (12,23,28-32). Pathogen reduction technology (PRT) has been proven to reduce the residual risk of TTIs (8,12,28,33,34). There is an inter-country variation in adopting safety measures for preventing adverse events of platelet transfusions, and the situation in Japan is unique (35-37). However, information regarding platelet transfusion in Japan has been poorly described in existing literatures.

This article aims at reviewing existing literatures inside and outside Japan regarding epidemiology, clinical manifestation, treatment, and mitigation strategies of adverse events associated with platelet transfusions. Additionally, this article provides incidence and severity of these events in Japan using the recent data collected by two existing hemovigilance systems at the national level. This article is presented in accordance with the narrative review checklist (available at http://dx.doi.org/10.21037/aob-20-90).

Literature search strategy

The medical literatures for published observational/investigational studies, randomized controlled trials or systematic reviews and meta-analyses regarding adverse events related to platelet transfusions were analyzed. The PubMed/Medline electronic database was searched in November 2020 using the primary phrases such as "platelet transfusion", "adverse transfusion reaction", "transfusion-transmitted infection", "incidence", "severity". Further search was performed with additional key terms such as "allergic transfusion reaction", "febrile non-hemolytic transfusion reaction", "anaphylactic transfusion reaction", "bacterial infection", "mitigation strategy", "safety measure". Moreover, a hand search of *ISBT Science Series* and *Annals of Blood* was also added. English language, peer-reviewed articles were considered and no constraints on publication type or date were imposed. Titles/abstracts of retrieved articles were checked for relevance, and other relevant papers were identified by manual searching of reference lists and the authors' personal literature collections. When similar findings were reported in

Table 1 Comparisons of TTBI mitigation strategies and PC shelf-life

Area	Country	Shelf-life, days	Bacterial screening, implementation	Pathogen inactivation, implementation	Fatal TTBI, cases/1M bags	Ref.
Europe	Belgium	7	+	Universal	0/0*	(22,46)
	France	7	–	Universal	3.5/0*	(22,46)
	Switzerland	5	–	Universal	19.1/0*	(22,46)
	United Kingdom	7	+	–	2.3	(22,46)
America	United States	5	+	Available	1.3	(43)**
	Canada	7	+	Available	2	(44,47)
Asia/ Pacific	Australia	5	+	Available	0	(29)
	New Zealand	7	+	–	0	(45)
	Japan	3	–	–	0.1	(36)***

*, before/after implementation of pathogen reduction technology; **, can be extended to 7 days if negative by rapid immunoassay; ***, all single-donor apheresis platelets are inspected visually. TTBI, transfusion-transmitted bacterial infection; PC, platelet concentrate.

multiple articles, priority was given to those most recently published.

Production and supply of PCs in Japan

The Japanese Red Cross Society (JRCS), as a sole operator of blood services, controls blood collection, processing and supply of blood products nationwide (38,39). In Japan, all PCs transfused are leukoreduced single-donor apheresis platelets. Of 4,707,951 voluntary non-remunerated donations in 2018, platelet apheresis donations accounted for 620,414 (13.2%), and 808,179 PC bags were distributed nationwide (40,41).

Eligibility criteria for platelet apheresis donation are as follows: age of 18 to 69 for male, 18 to 54 for female, body weight of 45 kg or more for male and 40 kg or more for female, hemoglobin level of 12 g/dL or more, and platelet count from 0.15 to 0.6 million/μL. After donor's skin disinfection with 10% povidone-iodine followed by 70% isopropyl alcohol and the diversion of the initial 25 mL portion of blood, up to 600 mL of platelets suspended in plasma can be collected by any of three collection systems: CCS (Haemonetics), Terusys-S (Terumo), and Trima (Terumo) (36,39). More than 0.2, 0.4, 1.0, 2.0, 3.0, 4.0 $\times 10^{11}$ platelets are contained in 1-, 2-, 5-, 10-, 15-, 20- unit PC bags respectively, and 10-unit PC bags (volume of about 200 mL) are the most commonly used in clinical practice (35). All PCs are leukoreduced before storage, stored at 20 to 24 ℃ with agitation, and visually inspected for the presence of aggregates and/or swirling before issue (36).

ABO-identical, single-donor apheresis platelets are routinely supplied by the JRCS, however, human leukocyte antigen (HLA) and/or human platelet antigen (HPA) matching is given priority over ABO compatibility when there is a need for HLA- or HPA-matched platelets. Currently, approximately 70% of supplied HLA-matched platelets are ABO-identical. Non-ABO-identical HLA- or HPA-matched platelets with high ABO antibody titers (>1:128) are administered at the physician's discretion (42).

The JRCS has already implemented universal leukoreduction and initial flow diversion, but not bacterial culture screening or PRTs so far (36). For reducing clinically relevant risk of sepsis due to TTBIs, the shelf-life of PC is presently limited to 3 days. This is the shortest when compared to other developed countries (22,29,43-45), where bacterial screening of PC bags and/ or PRTs are being implemented as strategies to mitigate TTBIs (*Table 1*). This "3-day limitation policy" has contributed to the low incidence of fatal TTBI related to platelet transfusion in Japan, which is currently estimated to be 0.1 in 1 million PC bags (36).

Reflecting effectiveness of decreasing the volume of plasma for preventing ATRs, which contains inflammatory cytokines and protein components (48-50), the JRCS started to provide washed PCs in 2016 (51). In contrast to Western countries, PAS-PCs, in which about 70% of plasma is replaced with PAS, are not available so far in Japan.

Table 2 Hemovigilance data by the JRCS during 2010–2018: mean frequencies of adverse reactions

Adverse reactions	PC		RBC		FFP	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Allergic reaction	35.86	22.31–49.41	4.45	3.62–5.29	11.97	9.68–14.27
Severe allergic reaction	25.02	22.29–27.73	2.72	2.04–3.41	8.73	8.19–9.27
Fever	5.58	4.37–6.79	3.66	2.85–4.47	0.62	1.06–1.48
Respiratory distress	5.16	3.915–6.399	2.42	2.03–2.80	1.21	0.91–1.52
Hypotension	2.59	2.214–2.970	1.37	1.17–1.57	1.27	0.33–0.91
TACO	0.48	0.203–0.749	0.58	0.33–0.83	0.22	0.08–0.36
TRALI	0.36	0.225–0.503	0.12	0.04–0.17	0.14	0.05–0.22
Others	3.81	2.649–4.974	2.09	1.53–2.65	0.62	0.42–0.82
Total	78.98	65.32–92.62	17.52	15.51–19.53	24.83	22.40–27.25
No. of bags distributed in Japan*	819,691	808,885–830,497	3,364,908	3,310,163–3,419,653	961,589	945,373–977,804

Mean frequencies of adverse events per 100,000 transfusion bags. *, derived from hemovigilance data by the JRCS (35). JRCS, Japanese Red Cross Society; PC, platelet concentrate; RBC, red blood cell; FFP, fresh frozen plasma; CI, confidence interval; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

Recent hemovigilance data of Japan

Two existing hemovigilance systems

Presently, two hemovigilance data are available in Japan, one gathered by the JRCS (40), and the other by the National Institute of Infectious Diseases (NIID) of Japan and the Hemovigilance Committee of the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT). The JRCS established a hemovigilance system in 1993, in accordance with Pharmaceuticals and Medical Devices act of Japan. The system can provide surveillance of transfusion adverse reactions and infections nationwide (52), with voluntary paper-based reports from domestic hospitals and information from blood donors. Since that, approximately 2,000 suspected cases with moderate to severe adverse events have been reported annually (40), however, the largest and voluntary reporting system has precluded surveillance of mild adverse events (38).

Thereafter, to collect comprehensive data on adverse transfusion reactions nationwide, an online reporting system for transfusion-related adverse events was introduced in 2007 by the NIID and the JSTMCT (38,51). With voluntary participation of academic hospitals and small-scale hospitals, the incidence of adverse events to PCs recorded in the online system was shown to be comparable to the rates reported in other countries (38,51). The surveillance by the online reporting system has been so far monitoring about 10% of the bags distributed in Japan (53).

The hemovigilance situations on monitoring adverse events to blood transfusion vary from country to country. It is mandatory to report fatal cases in the US (54), serious or unexpected adverse reactions in Canada (44), serious adverse reactions and events in the UK and Belgium (55,56), any suspected transfusion reactions in France and Switzerland (57,58). On the other hand, in Australia and New Zealand, reporting of serious adverse reactions is performed on a voluntary basis, as is in Japan (45,59).

Hereafter in this article, the online hemovigilance data by the NIID (53) from 2010 to 2018 was evaluated mainly in terms of mild adverse events associated with platelet transfusions. During this period, approximately 40 to 50 hospitals per year {academic hospitals: median 43 [34–46]; small-scale hospitals: median 4 [3–5]} participated in the online surveillance by the NIID. The paper-based data by the JRCS (40) from 2010 to 2018 was used to evaluate mainly severe adverse events.

Frequent adverse events related to platelet transfusions in Japan

Table 2 shows the incidence of adverse reactions reported to the JRCS from 2010 to 2018. The mean numbers of PC, RBC, and fresh frozen plasma (FFP) bags distributed yearly in Japan were 819,691 (95% CI: 808,885–830,497),

Table 3 Hemovigilance data by the NIID during 2010–2018: clinical diagnoses of adverse events

Clinical diagnoses	PC		RBC		FFP	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Non-hemolytic transfusion reactions*	3,156.93	2,810.37–3,503.48	636.32	589.38–683.26	1,117.35	971.58–1,263.12
Other non-hemolytic reaction	3,120.57	2,780.86–3,460.28	627.81	580.85–674.77	1,095.87	952.15–1,239.58
Severe allergic reaction	33.93	22.53–45.34	14.23	–1.02 to 29.48	19.10	14.36–23.84
TRALI	1.53	0.78–2.28	0.62	0.26–0.98	1.48	0.14–2.82
TACO	0.89	0.27–1.52	1.29	0.95–1.62	0.91	0.29–1.53
GVHD	0.00	–	0.00	–	0.00	–
PTP	0.00	–	0.00	–	0.00	–
Hemolytic reaction*	0.00	–	1.29	0.46–2.11	0.00	–
Acute hemolytic reaction	0.00	–	0.67	0.18–1.17	0.00	–
Delayed hemolytic reaction	0.00	–	0.62	0.13–1.10	0.00	–
Infectious diseases*	0.51	–0.03 to 1.06	0.06	–0.05 to 0.17	0.23	–0.07 to 0.52
Bacterial infection	0.38	0.00–0.76	0.00	–	0.00	–
HBV infection	0.13	–0.12 to 0.38	0.00	–	0.23	–0.07 to 0.52
HCV infection	0.00	–	0.00	–	0.00	–
HIV infection	0.00	–	0.00	–	0.00	–
Other infections	0.00	–	0.06	–0.05 to 0.17	0.00	–
Total*	3,157.44	2,811.05–3,503.82	637.67	591.04–684.29	1,117.58	971.92–1,263.24
No. of bags reported to the NIID	109,389	100,965–117,812	242,846	223,527–262,164	124567	112,644–136,490
% of bags reported/ distributed	13.35	12.39–14.27	7.22	6.69–7.73	12.95	11.82–14.05
No. of bags distributed in Japan**	819,691	808,885–830,497	3,364,908	3,310,163–3,419,653	961,589	945,373–977,804

*, mean frequencies of adverse events per 100,000 transfusion bags; **, derived from hemovigilance data by the JRCS (35). NIID, National Institute of Infectious Diseases; PC, platelet concentrate; RBC, red blood cell; FFP, fresh frozen plasma; CI, confidence interval; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; GVHD, graft-versus-host disease; PTP, post-transfusion purpura.

3,364,908 (95% CI: 3,310,163–3,419,653), and 961,589 (95% CI: 945,373–977,804), respectively. The mean incidences of all adverse reactions associated with PC, RBC, and FFP were 78.98 (95% CI: 65.32–92.62), 17.52 (95% CI: 15.51–19.53), and 24.83 (95% CI: 22.40–27.25) per 100,000 distributed bags, respectively. Thus, according to the JRCS data, ATRs were the most frequent adverse events of platelet transfusions, with an incidence of 0.03% (35.86 per 100,000 bags).

Table 3 shows the clinical diagnoses of adverse events reported online to the NIID from 2010 to 2018. The mean numbers of PC, RBC, and FFP bags transfused at participating hospitals were 109,389 (95% CI: 100,965–117,812), 242,846 (95% CI: 223,527–262,164), and 124,567 (95% CI: 112,644–136,490), respectively, accounting for 13.35%, 7.22%, and 12.95% of bags distributed in Japan, respectively. The mean incidences of all adverse reactions associated with PC, RBC, and FFP were 3,157.44 (95% CI: 2,811.05–3,503.82), 637.67 (95% CI: 591.04–684.29), and 1,117.58 (95% CI: 971.92–1,263.24) per 100,000

Table 4 Hemovigilance data by the NIID during 2010–2018: clinical signs of adverse events

Clinical signs	PC		RBC		FFP	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Urticaria	2,339.95	2,066.45–2,613.44	215.97	194.20–237.74	921.92	782.78–1,061.06
Pruritus	1,336.07	1,178.77–1,493.37	78.41	71.36–85.46	446.46	363.87–529.06
Rash	392.67	345.56–439.77	66.37	60.19–72.55	220.45	178.05–262.85
Fever	278.49	242.86–314.11	201.07	184.91–217.24	71.63	57.11–86.14
Feverishness	105.38	95.54–115.20	54.83	48.81–60.86	52.18	41.72–62.65
Chill, rigor	100.02	88.99–111.04	40.44	35.23–41.64	37.97	28.18–47.77
Respiratory distress	87.64	74.62–100.65	22.74	20.25–25.23	40.59	32.93–48.25
Hypotension	64.55	55.02–74.08	34.05	29.00–39.10	66.05	56.27–75.84
Nausea, vomiting	50.65	43.38–57.90	29.01	25.36–32.66	34.90	24.01–45.80
Hypertension	41.08	32.72–49.42	49.23	41.28–57.18	16.03	11.18–20.89
Tachycardia	35.85	30.15–41.54	16.97	14.76–19.19	20.24	17.29–23.18
Chest, flank or back pain	15.18	12.61–17.74	9.41	6.67–12.15	6.48	4.26–8.70
Headache	14.54	10.96–18.12	9.24	7.22–11.26	4.43	2.48–6.38
Consciousness disturbance	5.49	3.58–7.38	0.95	0.26–1.64	0.45	–0.03 to 0.94
Venous pain	2.93	1.62–4.23	14.56	13.00–16.13	0.34	–0.13 to 0.81
Hematuria	1.15	0.61–1.67	1.68	0.73–2.63	0.57	0.08–1.05
Others	42.23	31.50–52.95	15.85	10.58–21.13	27.06	15.45–38.67
Total	4,913.86	4,381.31–5,446.40	860.81	802.83–918.78	1967.76	1,669.63–2,265.89

Mean frequencies of adverse events per 100,000 transfusion bags. NIID, National Institute of Infectious Diseases; PC, platelet concentrate; RBC, red blood cell; FFP, fresh frozen plasma; CI, confidence interval.

bags, respectively. Thus, according to the NIID data, non-hemolytic reactions, mostly ATRs and FNHTRs, were the most frequent adverse events of platelet transfusions, with an incidence of 3.16% (3,156.93 per 100,000 bags).

Table 4 shows the clinical signs of adverse events reported online to the NIID from 2010 to 2018. Urticaria, pruritus, rash, fever, and feverishness were the most frequently reported signs, with incidences of 2,339.95, 1,336.07, 392.67, 278.49, and 105.38 per 100,000 bags, respectively. ATR-related signs (urticaria, pruritus, rash) represented about 80% of all reported adverse events.

This big difference in the incidence of mild adverse reactions, such as ATRs and FNHTRs, between the JRCS and the NIID data might be dependent on the different scopes of each reporting system. Since most clinicians report suspected cases of adverse events to the JRCS with the intent to have the causal relationship investigated, the reported cases tend to be of moderate to severe intensities, and mild cases are usually underreported. Reflecting the nationwide coverage of the JRCS reporting system, it is suitable for the analysis of moderate to severe adverse events in Japan. On the other hand, mild adverse reactions are better collected by the online reporting system of the NIID, through passive surveillance (60), where the blood users of the participating hospitals register the whole hemovigilance data (38).

Severe adverse events related to platelet transfusions in Japan

Table 5 shows the severe adverse events related to all blood components reported to the JRCS from 2010 to 2018, which included fatal cases and non-fatal cases that required intensive treatment. The numbers of cases with TTI, severe

Table 5 Severe adverse events reported to the JRCS during 2010–2018

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Severe allergic reaction	326	353	357	280	464	497	405	360	347	3,389
TRALI*	9 [2]	14	6	9	2 [1]	7	4	5	4	60 [3]
p-TRALI*	15 [1]	10	4	10	7	6	3	4	1	60 [1]
TACO	0	0	26	29	44	63	45	47	55	309
Cardiogenic pulmonary edema	47	48	44	35	33	38	40	35	49	369
Respiratory distress total*	71 [3]	72	80	83	86 [1]	114	92	91	109	798 [4]
Bacteria infection										
Suspicious	28	21	31	25	17	25	20	21	23	211
Confirmed*	0	1	1	1	0	2	1	3 [1]	4	13 [1]
HBV infection										
Suspicious	36	40	50	52	27	14	18	20	13	270
Confirmed*	11	13	6	7	2	0	1	1	1	42
HCV infection										
Suspicious	27	29	40	32	26	35	28	21	17	255
Confirmed*	2	0	0	1	0	0	0	0	0	3
Other infections										
Suspicious	7	6	10	16	11	19	14	12	19	114
Confirmed*	1	1	4	2	4	4	3	4 [1]	7	30 [1]
Infection total										
Suspicious	98	96	131	125	81	93	80	74	72	850
Confirmed*	14	15	11	11	6	6	5	8 [2]	12	88 [2]
No. of transfusion bags distributed**	5,197,025	5,237,637	5,287,450	5,243,088	5,160,350	5,103,352	5,060,832	5,041,752	4,984,201	46,315,687

*, no. of confirmed cases [No. of fatal cases]; **, total no. of distributed bags including PC, RBC, and FFP, derived from hemovigilance data by the JRCS (35). JRCS, Japanese Red Cross Society; TRALI, transfusion-related acute lung injury; p-TRALI, possible TRALI; TACO, transfusion-associated circulatory overload; HBV, hepatitis B virus; HCV, hepatitis C virus.

allergic reaction, and respiratory distress were 88, 3,389, and 798, respectively, with the incidence of 0.17, 7.31, and 1.38 per 100,000 transfusion bags (including PC, RBC, and FFP). During the period, a total of six fatal cases were reported, which included one case of TTBI (*E. coli*), one case of viral infection [hepatitis E virus (HEV)], three cases of TRALI, and one case of possible TRALI (p-TRALI). Data regarding fatal TACO cases was unavailable in this period mainly because TACO reporting criteria of the surveillance by the JRCS were under consideration.

Management of frequent adverse events related to platelet transfusions

ATRs and FNHTRs are frequent adverse reactions associated with platelet transfusions, and these incidences are reported to be higher than those associated with RBC or plasma transfusions (16,18,61,62).

ATR

ATRs are the most frequent adverse events of platelet

transfusions (62), with a reported incidence of 3% to 7% (12,63). Typical symptoms such as urticaria, rash, pruritus, and localized angioedema are usually mild, however, anaphylaxis, the severe form of ATRs, sometimes occur (refer to Anaphylaxis section). The main underlying mechanism is type I hypersensitivity reactions by interaction of allergens within the donor plasma with preformed immunoglobulin (Ig) E antibodies in the recipient (62,64).

Prompt cessation of transfusion and administration of antihistamine agent are required for symptomatic relief (21,65). Premedication with antihistamine agents for reducing the incidence of ATRs has been shown to have suboptimal efficacy (66,67). For patients with a history of ATRs, close monitoring during subsequent transfusions is required (12).

Two observational studies in the US showed that PAS-stored apheresis platelets could reduce the incidence of allergic reactions by about 50%: ATR incidences of 1.01% for PAS-platelets versus 1.85% for platelets in plasma from the study by Tobian *et al.* (26), and incidences of 0.29% for platelets in PAS-C versus 0.82% for platelets in plasma from the study by Cohn *et al.* (62).

Platelet washing has also been shown to be beneficial for preventing ATRs (50,51,68-70). One observational study in Japan revealed that ATR to apheresis platelets decreased after the release of washed PCs: ATR incidences of 0.36% for washed PCs versus 3.44% for unwashed PCs (51).

FNHTR

FNHTRs, clinically presented as a temperature increase (above 38 ℃ or more than 1 ℃ increase above baseline) during or shortly after transfusion, are also frequent adverse events, which occur in 4% to 6% of platelet transfusions (23,62). Transient symptoms such as chills, rigors, tachypnea, anxiety, and headache can be accompanied, which are not specific to FNHTRs, hence FNHTRs should be diagnosed by exclusion (21). In case of developing fever, immediate cessation of platelet transfusion and assessment of infection or hemolysis are required (12,71) (refer to TTBI section). Fever can be managed with antipyretics, but premedication to prevent FNHTRs has been reported to be ineffective (72-75).

Multiple factors such as donor leucocytes, cytokine accumulation during storage and leucoagglutinins in the donor or recipient are thought to cause FNHTRs (23,64,76). One observational study in the US showed that prestorage leukoreduction of buffy-coat pooled whole-blood-derived

platelets is effective enough to decrease FNHTR risk by about 90%: FNHTR incidence of 0.15% for leukoreduced pooled platelets versus 2.18% for untreated pooled platelets (77). Additionally, both PAS-stored apheresis platelets and whole-blood-derived platelets have been shown to reduce FNHTR rate compared to plasma platelets (62,78). Washed platelets have also been reported to efficiently mitigate FNHTRs (79), but in an observational study in Japan, washing of single-donor apheresis platelets had no effect on reducing FNHTR incidence (51). Hence, the exact effect of platelet washing on reducing FNHTRs is controversial (63).

Management of severe adverse events related to platelet transfusions

Severe adverse events associated with platelet transfusions include TTBI, anaphylaxis, respiratory distress including transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) (23,80,81).

TTBI

Bacterial infection has long been the highest TTI risk associated with platelet transfusion (23,47,82). Platelets are stored at room temperature mostly due to negative impact of cold storage on platelet function and survival (83-85), which poses platelet components at a high risk of bacterial contamination compared to RBC and plasma component (31,36,86,87). Septic transfusion reactions caused by TTBI are of great concern due to the fatality and severity even if transfusion-related infectious complications are less common than noninfectious complications (44,54,55).

Since the bacterial infection risk increases in relationship to the storage duration, the shelf-life of platelets stored at room temperature is generally shorter than that of other components, with most countries adopting the 5 days. Recently, the large-volume, delayed-sampling bacterial screening algorithm has been implemented in the UK and in Canada (32,88), which significantly reduced the risk of bacterial transmission, and allowed the extension of the PC shelf-life to 7 days. The US Food and Drug Administration also approved the 7-day extension of the PC shelf-life, provided a secondary bacterial testing, through the conventional testing or by a rapid test, is performed, or the large-volume, delayed-sampling bacterial screening algorithm is applied (89). Estimates of TTBI incidence with

platelet transfusions are variable between pooled platelets and single-donor apheresis platelets, ranging from 10 to 70 in million units (87,90), and the incidence is estimated to be higher than incidence of transfusion-transmitted human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infections (about one in two million units transfused) (91,92).

Typical clinical manifestations of TTBI include fever, rigors, tachycardia, hypertension and hypotension (23,87), which require differentiation from ATRs, FNHTRs and other causes. In some cases, abdominal pain, back pain, nausea, vomiting and hypothermia can be presented. The duration between completion of transfusion and appearance of related symptoms is short with a median of 30 minutes, depending on multiple factors such as bacterial inoculum size, bacterial virulence and immune status of the recipient (87,90).

Once TTBI is suspected, prompt cessation of transfusion and evaluation for the presence of bacterial contamination in all transfused products are required (93). Bacterial cultures should be taken before empiric treatment with broad-spectrum antibiotics is initiated (65). Antibiotic treatments should be adjusted based on subsequent culture results.

Due to the low sensitivity of surrogate markers such as pH, glucose and/or platelet swirling for bacterial detection, post-collection automated culture methods have been widely implemented in developed countries (23,94). Bacterial screening by automated culture systems such as BacT/Alert and eBDS has shown increased sensitivity for bacterial detection (71,95-101). Another option for mitigating bacterial contamination is rapid immunoassay, which can detect bacterial wall components. Combination of bacterial culture and immunoassay tests has been shown to increase sensitivity for bacterial detection, however, there still remains a residual TTBI risk (71,82,102,103).

PRT, a method relying on an ultraviolet photo activation system, is an available option for pathogen reduction in platelets. It is currently used to varying degrees in most developed countries (*Table 1*) (9,10,23), which have been shown to contribute to decrease of fatality by TTBI (46). Although recent reports have shown that current PRT can decrease platelet recovery following transfusion (34,104), PRT might also be beneficial for risk reduction of agents where screening tests do not exist or have poor sensitivity (10,104,105).

In Japan, where single-donor apheresis platelets are transfused under "3-day limitation policy" with no bacterial culture testing, investigation of 86 suspected TTBI cases during 2007 to 2018 revealed that the short shelf-life of PC is associated with a low TTBI incidence: one, six and ten TTBI cases were caused by Day 1, 2 and 3 PCs, respectively (36). From the hemovigilance data provided in *Table 5*, incidence of suspected and confirmed bacterial contamination is as low as 0.46 and 0.03 per 100,000 transfusion bags (including PC, RBC, and FFP). Under the circumstance, visual inspection of PC bags prior to and during the transfusion for identifying aggregates in the bag or filter clogging seems to be crucial in preventing TTBIs.

Anaphylaxis

Anaphylactic reactions, the most severe ATRs occurring in eight per 100,000 units, usually present as respiratory distress, bronchospasm and hypotension (106). Immediate cessation of transfusion and prompt intramuscular epinephrine administration with supportive care are required for treatment of anaphylactic reactions (65,72,107). Other medications to be considered are H_1 antihistamine agents, bronchodilators, glucocorticoid and H_2 antihistamine agents (65). For patients with past history of anaphylactic reactions, specific serum protein deficiency such as IgA and haptoglobin should be investigated (65).

For IgA-deficient patients who have anti-IgA antibodies without previous anaphylactic reactions, transfusion of IgA-deficient or washed blood components can be applied (65,108). In Japan, after the release of washed PCs by the JRCS in 2016, no severe allergic reactions to washed single-donor-apheresis PCs have been reported (51).

TRALI

TRALI is a rare but potentially fatal respiratory complication of blood component transfusion, which is caused by activated pulmonary neutrophils (12,109-111). Traditionally, TRALI was defined as newly-developed pulmonary distress within 6 hours of completion of transfusion when the recipient had no other risk factors for acute respiratory distress syndrome (111). Recipient risk factors for TRALI are liver transplantation surgery, chronic alcohol abuse, shock, higher peak airway pressure while being mechanically ventilated, current smoking, higher interleukin (IL)-8 levels and positive fluid balance, whereas blood component risk factors for TRALI are high-plasma-volume blood components, increased volume of transfused HLA class II antibody or anti-human neutrophil

antigen (HNA) antibody (23,112-114). Although TRALI had been the leading cause of transfusion-associated fatalities, occurring in 1 in 3,891 units transfused (115), implementation of mandated strategies such as deferral of multiparous female donors was successful in the risk reduction with the incidence of 1 in 12,345 units (114).

Development of immune TRALI had been thought to fit for a "two-hit" model, in which the first hit is a clinical disorder that causes activation of the pulmonary endothelium, leading to the sequestration and priming of neutrophils in the lung, and the second hit is the transfusion of blood components, especially plasma (116). However, as TRALI can also occur in the absence of demonstrable antibodies, recently-proposed "multicausal model" might better describe TRALI pathogenesis (117).

Despite recently revised definition of TRALI (118), accurate diagnosis of TRALI is still challenging. Clinical symptoms of TRALI include dyspnea, tachypnea, and hypoxemia, sometimes accompanied by rigors, tachycardia, fever, hypothermia, and hypotension or hypertension, which require differentiation from TACO, anaphylaxis and septic reaction (110,114). Treatment of TRALI is mainly supportive care with supplemental oxygen or mechanical ventilation as needed. Additionally, both fluid and transfusion restriction can be preventive (12,114).

In Japan, since 2004, suspected cases of TRALI are submitted to the JRCS, where a case record auditing by lung specialist physicians is conducted to evaluate if the clinical and radiological findings meet the criteria of TRALI. In addition, for the further investigation of the adverse event, various types of tests, including HLA and HNA antibody screening, peripheral blood leukocyte crossmatch, measurement of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and screening for anti-plasma proteins and plasma protein deficiencies, are conducted (39,119,120). The annual numbers of confirmed TRALI and p-TRALI cases from 2010 to 2018 were 4–14 and 1–15, respectively, and in the recent years, a decreasing trend is observed (*Table 5*). Among the 120 cases of TRALI and p-TRALI diagnosed during the period, four cases were fatal (121).

TACO

TACO is the most frequent but underdiagnosed and underreported pulmonary complication of any blood component transfusion, including platelets (23,110,122). It

typically occurs in patients receiving transfusion of a large volume of blood over a short period of time, or in those with underlying diseases (12,123,124). Risk factors for TACO have been reported to include cardiac, pulmonary, or renal disease, older age (over 70 years), low body weight, and pre-transfusion positive fluid balance (123-126), however, other factors including inflammation are supposed to cause TACO (110). The estimated frequency of TACO varies from 1% to 11%, depending on clinical settings (110,127-129). The recent reports from UK and US showed that TACO is one of the leading causes of transfusion-related fatalities (54,55).

The definition of TACO has recently been revised by the ISBT, the International Hemovigilance Network, and AABB, requiring new onset or acute exacerbation of three or more of the following, within 12 hours of transfusion: respiratory distress, raised brain natriuretic peptide (BNP or NT-pro-BNP), increased central venous pressure, left heart failure, positive fluid balance, or pulmonary edema (12,126). Despite the revised diagnostic criteria, precise diagnosis of TACO is mostly difficult due to overlapping of clinical symptoms with TRALI, septic transfusion reaction and acute HTR (12).

Treatment of TACO requires prompt cessation of transfusion, oxygen supplementation, and administration of diuretics as needed (125,130). For at-risk patients, slow infusion rates and pre-transfusion administration of diuretics can reduce the incidence of TACO (12,23,130). The benefit of diuretics before or during the transfusion for patients with a history of TACO is being investigated (131,132).

Since 2012, when the JRCS started evaluating the suspected TACO cases, the number of definite TACO cases has increased year by year, reaching 55 cases in 2018 (*Table 5*). Among the 798 suspected cases of TRALI, 309 were classified as TACO, but the remaining 369 cases were classified as cardiogenic pulmonary edema (*Table 5*), which suggests that circulatory overload may be overlooked in the clinical practice (39).

Other adverse events to be considered

Other adverse events to be considered are HTR, TTI other than TTBI, transfusion-associated graft versus host disease (TA-GVHD) and post-transfusion purpura (PTP). Platelet transfusion refractoriness due to alloimmunization is also of concern, which is reviewed in another article in the same

issue of *Annals of Blood* journal.

HTR

As with the cases with TRALI, TACO, FNHTRs and ATRs, amounts of incompatible donor plasma in PC bags can cause hemolysis in recipients (23). Clinical manifestation of acute HTRs associated platelet transfusions is less severe than those with incompatible RBCs (133). Since platelets are often transfused without respecting the ABO compatibility in most Western countries due to the limited stock availability (81), a sizable number of minor ABO-incompatible platelet products are routinely issued (133-136). Although minor ABO-incompatible platelet transfusions rarely cause recipient intravascular hemolysis, underreporting of HTRs due to minor ABO-incompatible platelet transfusions is of concern (135,137). Screening of platelet components for titers of anti-A and anti-B antibodies is a mitigation strategy for recipient hemolysis, but consensus on methods or thresholds for "high-titer" is not well established so far (23,138).

Even if ABO-identical platelet transfusions result in a higher platelet increment, the role of ABO matching in platelet transfusions is still an issue of debate (139,140). Considering a high burden of issuing ABO-identical platelets (140), other mitigation strategies such as utilization of PAS-PC or washed PC seem to be more reasonable to minimize the risk of ABO-minor incompatible reactions.

In the Japanese practice, ABO-incompatible PCs can be supplied only in case there is a need to prioritize HLA-matching. But even in such cases, blood group O PC is never supplied to patients of other blood group types, and antibody titers are measured and only those with low antibody titers are supplied in case of major mismatch between donor and recipient, e.g., blood group A PC to a blood group B patient. Recent hemovigilance data of Japan showed that all recent cases of HTRs associated platelet transfusions were due to the administration of ABO-incompatible HLA-matched platelets, with an incidence of 0.0021% (1 per 47,800 HLA-matched PC bags) (42).

TTI other than TTBI

Improvement of donor testing over the past few decades, including nucleic acid-amplification technologies (NATs), has contributed to significant reduction of TTIs by HIV, hepatitis B virus (HBV) and HCV (23,28). Current estimates of these TTI rates are reported to be 1 in 2 to 3 million units (28).

Adoption of NAT screening for other viruses such as West Nile virus, Zika virus, and HEV varies depending on the country or the region (141-149). Leukoreduction has been shown to reduce risks of transfusion-related transmission of cytomegalovirus, human T-lymphotropic virus and human herpesvirus 8 (23,150-152).

In Japan, NAT testing of HIV, HBV and HCV was implemented in 1999, initially with a mini-pool of 500, then reduced to 50 in 2000, to 20 in 2004, and 10 years later, in 2014, the individual NAT was implemented. Recent estimated risk of HBV transmission is 1 in 2 million units, and those of HCV and HIV transmission are immeasurably small (35). Selective screening of *Trypanosoma cruzi* and individual NAT testing for HEV started in August 2016 and in August 2020, respectively. Testing for *Babesia microti*, West Nile virus and Zika virus are not routinely performed.

TA-GVHD

TA-GVHD is an extremely rare adverse event caused by transfusion of cellular components containing viable donor lymphocytes that engraft in the transfused recipient and attack the recipient's organs (12,23,153). The mortality rate of TA-GVHD is as high as 90%, and blood products from biologically related donors (partial HLA matching) and immunocompromised recipients are two major risk factors for TA-GVHD (23,154,155).

Within 5 to 10 days after transfusion, erythema, fever, abdominal pain, diarrhea, nausea, and vomiting develop with abnormal laboratory results such as pancytopenia, abnormal liver function, and electrolyte disturbances. Subsequently, bone marrow aplasia develops within 21 days. Most of fatal TA-GVHD cases are attributable to infections (154).

The preferred prevention of TA-GVHD is irradiation of cellular blood components with gamma-rays or X-rays, which has been successful in dramatic decrease of TA-GVHD incidence (153,155-157). PRTs have also been considered as an alternative method to prevent TA-GVHD development in some countries (154,158).

As the highest incidence of TA-GVHD had been reported in Japan, the supply of irradiated blood products was introduced nationwide by the JRCS in 1998, reflecting the revised guidelines for the irradiation of blood to prevent post-transfusion GVHD by the Japan Society of Blood

Transfusion (former JSTMCT), which recommended transfusion of irradiated blood for at-risk patients (157). Thereafter, in principle, irradiation of all cellular components is recommended in the present guidelines for the appropriate use of blood products released by the Japanese Ministry of Health, Labor and Welfare. Hospitals may request irradiated blood to the JRCS or irradiate at their own service prior to transfusion. No TA-GVHD cases by blood components distributed by the JRCS have been confirmed in Japan since 2000 (40,156).

PTP

PTP is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. It mostly affects HPA-1a-negative individuals who have been alloimmunized by previous pregnancy and/or transfusion while other HPA antigens might be involved (12,159). Typically, thrombocytopenia is severe but resolves spontaneously within several weeks. The diagnosis is confirmed by the detection of platelet specific alloantibodies. PTP is treated with intravenous Ig, corticosteroids, and plasmapheresis (12,159). To prevent PTP recurrence, HPA-compatible platelets are indicated (160).

Limitations and future perspective

This article has several limitations. First, the incidence of each type of adverse reaction, referred from the literatures outside Japan, might be affected by the inter-country difference of reporting systems. Second, the difference of reporting systems and participants might limit the direct comparison of the two hemovigilance data of Japan. And underreporting might affect both collected data due to their nature of passive surveillance. Considering each advantage for collecting transfusion-related adverse events, integration of two hemovigilance systems seems reasonable. Third, the descriptions related to transfusion practice in Japan could be insufficient, as the number of literatures from Japan is limited. Fourth, this article could not cover all literatures outside Japan regarding adverse effects to platelet transfusion due to the nature of narrative review.

Implementation of bacterial culture screening and PRT, and supply of PAS-PC are under consideration in Japan. For ensuring safe and appropriate blood transfusion in Japan, both observational and investigational researches should be encouraged.

Summary

The unique situation of transfusing leukoreduced single-donor apheresis platelets in Japan is highlighted as the short shelf-life of 3 days and visual inspection before issue, with no implementation of bacterial culture screening and pathogen reduction technologies. From two recent hemovigilance data of Japan during 2010 to 2018, non-HTRs including ATRs and FNHTRs are the most frequent adverse events related to platelet transfusions in Japan, with an incidence of 3.16%. The incidence is also higher than that with RBC (0.64%) and plasma transfusions (1.11%). Severe adverse events related to any of blood components are anaphylaxis, respiratory distress including TRALI and TACO, and TTIs, with the incidence of, 7.31, 1.38, and 0.17 per 100,000 transfusion bags, respectively. During the period, a total of six fatal cases were reported, which included one case of TTBI by *E. coli*, one case of HEV infection, 3 cases of TRALI, and one case of p-TRALI. Even under the unique situations in Japan, incidence of adverse events related to platelet transfusions is mostly consistent with previous related reports outside Japan.

Various risk mitigation strategies have been successful for securing safety of platelet transfusions, however, there is still room for further improvement. This can be achieved by patient blood management strategies, including appropriate use of blood products, with adherence to evidence-based transfusion guidelines, minimizing unnecessary transfusions and regularly performing reflection on transfusion practices. ATRs including anaphylaxis can be mostly mitigated by the use of PAS reposition or washed platelets. Bacterial screening of PC and/or PRT are being applied for the prevention of TTBI, and good results have been shown with the large-volume, delayed-sampling bacterial screening algorithm implemented in the UK and Canada, which may be superior to the strategy applied in Japan. TRALI and TACO are conditions that can be prevented or treated, provided the condition is appropriately recognized and managed. Thus, it is essential that clinicians recognize the adverse events that may occur during or after the platelet transfusion, and understand the appropriate management of each condition.

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