表2 輸血管理料取得状況の年次推移

		2010年				2011年				2012年				2013年			
		施設数		比率(%)		施設数		比率(%)		施設数		比率(%)		施設数		比率(%)	
300床未満	輸血管理料Ⅰ取得	519	87	17.78	2.98	544	68	15.14	1.89	856	87	25.77	2.62	927	89	49.33	4.74
	輸血管理料Ⅱ取得		432		14.80		476		13.25		769		23.15		838		44.60
	取得していない	2,399		82.22		3,049		84.86		2,466		74.23		952		50.66	
300～499床	輸血管理料Ⅰ取得	206	98	46.60	22.17	222	108	48.28	23.48	374	156	78.72	32.84	392	168	85.96	36.84
	輸血管理料Ⅱ取得		108		24.43		114		24.78		218		45.88		224		49.12
	取得していない	236		53.39		238		51.74		101		21.26		64		14.04	
500床以上	輸血管理料Ⅰ取得	139	120	50.00	43.17	140	125	52.04	46.47	247	185	86.28	65.37	256	197	92.75	71.38
	輸血管理料Ⅱ取得		19		6.83		15		5.58		62		21.91		59		21.38
	取得していない	139		50.00		129		47.96		36		12.72		20		7.25	
全体	輸血管理料Ⅰ取得	864	305	23.75	8.38	906	301	20.96	6.96	1,477	428	36.20	10.49	1,575	454	60.32	17.39
	輸血管理料Ⅱ取得		559		15.37		605		14.00		1,049		25.71		1,121		42.93
	取得していない	2,774		76.25		3,416		79.04		2,603		63.80		1,036		39.68	

看護師でもまだ大規模施設の32.7%，全施設の4.7%の配置率であった（表3）．輸血用血液による副作用の報告体制は大・中規模施設では95%以上の施設で整備されていたが，小規模の施設では64.3%の整備率だった．

3. 輸血検査の実施状況

ABO式血液型検査は300床以上の施設では97%の施設で院内の検査技師が担当していたが，300床未満の施設の約36%で院外の検査機関に委託されていた．検査内容も前者ではほぼ必要事項を満たしていたが，後者ではウラ検査の未実施率が約12%だった．交差適合試験は300床以上の施設では98%で院内検査技師が行っていたが，300床未満の施設では72%であった．不規則抗体スクリーニングでは300床以上の施設では94%で院内検査技師が実施していたが，300床未満の施設の56%で院外に委託されていた．輸血前の感染症検査は入院時検査と同時に行っている場合を含め84%の実施率であり，輸血前検体保管は300床以上の施設では97%で実施しているが，300床未満の施設では64%の実施率であった．輸血後感染症検査は，必ず実施している施設は28%のみで最近6年間でほとんど変化がなく，輸血後の検体保存も20%程度であった．これらの輸血前後の感染症検査や検体保存に関するマニュアルがある施設は全体の49%であった．

4. 血液製剤使用状況

本調査での輸血実施率・輸血実施患者数から日本全体での輸血実施患者数を推計したところ1,035,611人となり，昨年とほぼ同様ながらわずかに(約10,500人)減少した．一方自己血輸血推計患者数は110,360人であり，2010年以降減少傾向が続いている．自己血輸血が減少している理由は手術時の出血量減少(40%)，外科医の方針変更（21%）と共にその他（33%）も多く，その内容は手術件数の減少（整形外科，泌尿器科，婦人科等），適応症例の減少(80歳以上の高齢者の増加，重度の大動脈弁狭窄症・貧血例の増加)，貯血期間の短縮(来院から手術までの日数が短縮)などであった．今回初めて調査した，輸血を準備するも実際には実施しなかった推計患者数（T&Sを含む）の比率（輸血準備率）は，小規模施設では12%であったが，病床規模が大きくなるほど増加する傾向があり，大規模病院では輸血患者数の42%に達した（図2）．

2013年は日赤からの総供給量としては赤血球製剤は減少，血小板製剤は増加，血漿製剤はほぼ横ばいという状況であったが，本調査での血液製剤使用量の年次推移をみると赤血球製剤ではほぼ横ばい，血小板製剤と血漿製剤では微増傾向，アルブミン製剤はほぼ横ばい，免疫グロブリン製剤は増加，自己血輸血は減少傾向を示した（図3）．特に最近は免疫グロブリン製剤の増加と自己血輸血の減少が目立った．診療科別の血液製剤使用状況は前年と同様の傾向を示し，赤血球製剤は血液内科と心臓血管外科での使用が多く，血小板製剤では血液内科，血漿製剤では心臓血管外科の使用が突出して多かった．等張アルブミン製剤は外科系診療科で，高張アルブミン製剤は消化器系診療科で多く使用された．免疫グロブリン製剤は神経内科での使用量が顕著であった．

病床群毎の1施設当たりの年間血液購入量と廃棄率を図4に示した．病床数が多くなるに従い血液製剤購入量も増加し，赤血球製剤と血漿製剤ではその廃棄率が減少する傾向がみられたが，血小板製剤では500床台の病院群での廃棄率が最も低かった．

都道府県別に各血液製剤の使用量(1病床当たりの年間使用量）を比較すると，最も格差の少ない製剤は赤

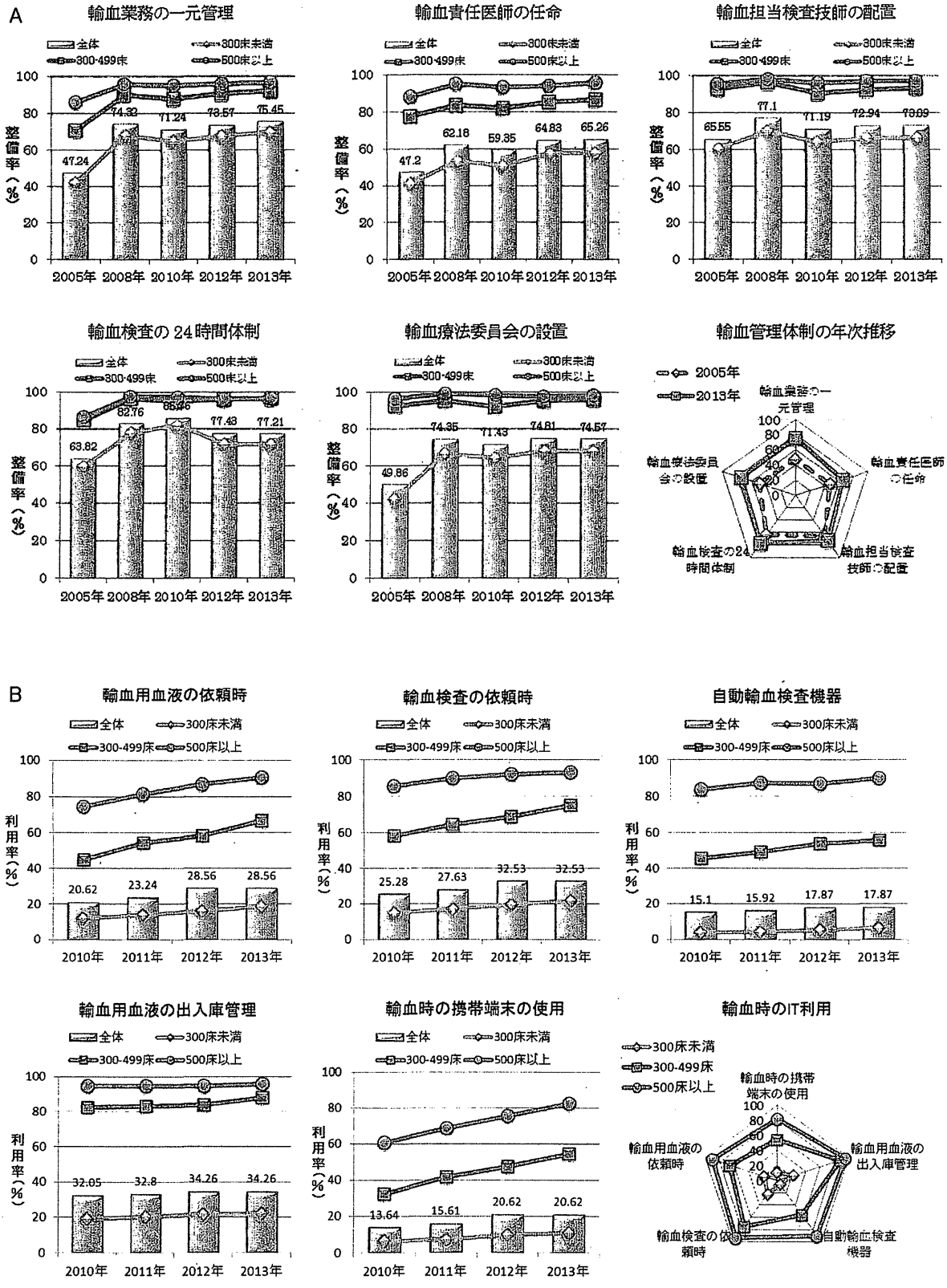

図1　輸血管理体制とコンピュータシステムの整備状況
A　輸血管理体制の年次推移
B　コンピュータシステム導入率の年次推移

表3 学会認定看護師の整備状況

項目	0床		1～299床		300～499床		500床以上		全体	
	施設数	比率	施設数	比率	施設数	比率	施設数	比率	施設数	比率
学会認定・臨床輸血看護師	0	0.00%	37	1.40%	38	8.32%	90	32.73%	165	4.68%
学会認定・自己血輸血看護師	0	0.00%	34	1.28%	32	7.03%	63	22.99%	129	3.65%
学会認定アフェレーシスナース	0	0.00%	7	0.26%	4	0.87%	28	10.29%	39	1.11%

*比率は各病床群で「いる」と回答した施設の比率を示す

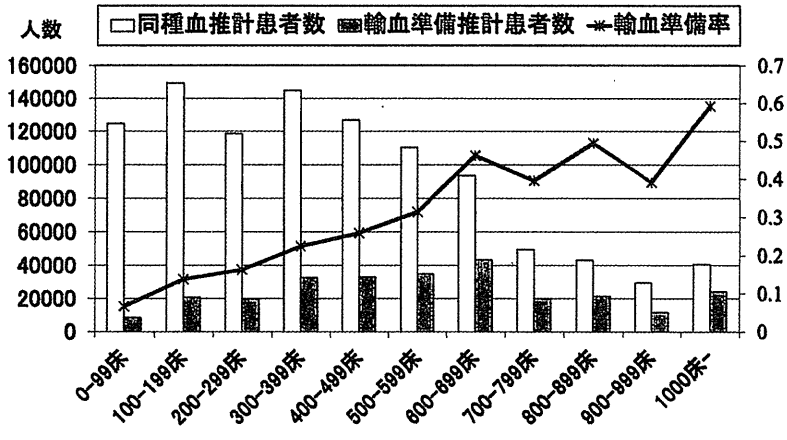

図2 輸血推計患者数と準備未実施推計患者数

血球製剤で約2倍，血小板製剤，FFP，アルブミン製剤には約4倍の格差がみられた．免疫グロブリン製剤は最も格差が大きく，約6倍であった．

血液製剤使用基準の遵守率は赤血球製剤で79%，血小板製剤で81%，血漿製剤で77%，アルブミン製剤で77% とほぼ同様であり，施設の規模による差異もあまりみられなかった．

考　察

本調査は2008年以降，国内の全輸血実施医療機関を対象に行われているが，2013年は過去6年間で最も高い回答率であり，報告された全血液製剤使用量は日赤からの総供給量の76% を示した．今回は19床以下の小規模施設の回答数も増えたが回答率は40% を下回っており，さらに回答を促すような調査方法について考えてゆく必要がある．特に診療所などでは年間の輸血回数は少ない場合も多く，地域に密着した対策が求められる．

安全でかつ適正な輸血療法を実施するために輸血管理体制の整備が重要であることは論を俟たないが，小規模施設で整備が進んでいないことが課題である．2008年以降は輸血責任医師の任命を筆頭に整備率にほとんど変化がみられないが，人的要件や院内設備に制約がある中では改善が困難なことが推測される．この状況を解決してゆくには，草の根的な取り組みが有効と思われる．福島県では「合同輸血療法委員会」が小規模施設への研修会や検査業務のサポートを行い，施設間ネットワークの構築を推進している[6]．関東甲信越ブロック血液センターでは本年より東京都での中小病院向けの検査実技講習を含む研修会を開始した．また石川県合同輸血療法委員会では「小規模医療施設向け輸血マニュアル」を作成し，ホームページ上で公開している[7]．これは医師1人，看護師1人の施設で，輸血検査を自施設で実施しないことを前提とした斬新な内容であり，注目に値する．「輸血療法の実施に関する指針」の中では輸血を実施する医療機関で輸血検査を行うことが明記されているが，実際には小規模施設の約40% で外注されており，この現実をふまえた上で今後の対応を議論するべきと思われる．このような様々な活動が広がり，小規模施設の輸血医療の改善につなげてゆくことが期待される．

輸血管理料は2012年4月の診療報酬改定で施設基準と適正使用加算に分かれたため，取得施設が大幅に増えた．これ自体は望ましいことであるが，適正使用基準については根強い不公平感がある．確かに診療科別の使用量をみると，FFPは心臓血管外科，消化器外科，救急科，血液浄化療法科等で，アルブミン製剤は消化器外科，心臓血管外科，消化器内科等で多いので，そ

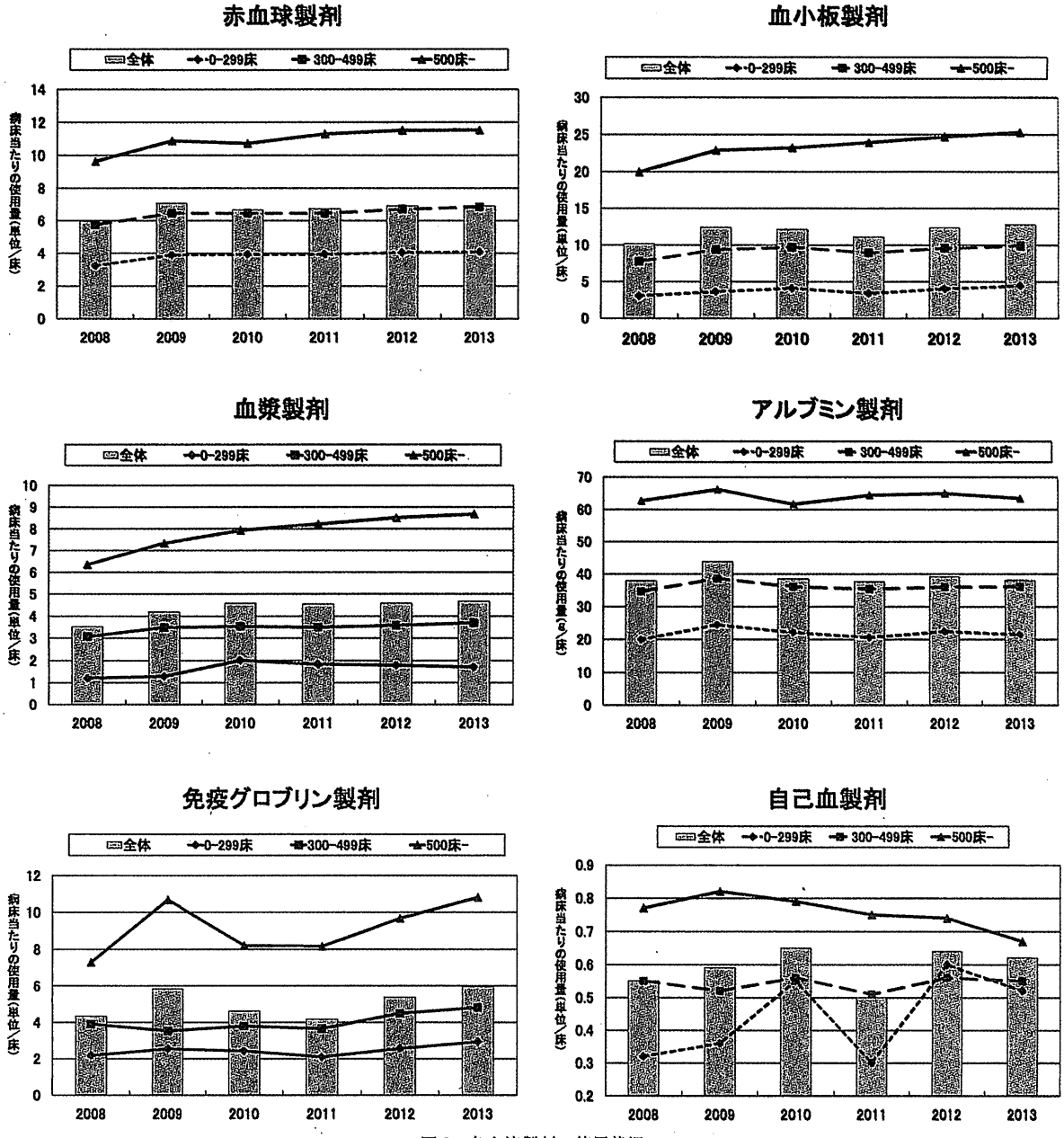

図3　各血液製剤の使用状況

れらの診療科の患者数・重症度などが影響することは否めない．現在「科学的根拠に基づく輸血ガイドラインの策定等に関する研究」班（研究代表者：松下正）の作業が進行しているが，アルブミン製剤については肝疾患の合併症に対する治療（大量腹水穿刺廃液後や細菌性腹膜炎等）[8,9]や凝固因子の補充を必要としない（自己免疫性神経疾患等）治療的血漿交換療法時[10]において高いエビデンスが示されており，本来は病態毎に適正使用の評価がなされるべきであろう．しかし全ての施設を統一基準で評価するには簡便性も重要であり，それらをどのように両立させてゆくかが今後の課題である．

輸血後感染症の発生頻度は年間10件程度で推移しており，非常に低い頻度となってきた．しかしながら，昨年12月には約10年ぶりにHIV感染症の報告があり，ごくまれながら劇症肝炎の発生例[11]も報告されている．後者についてはHBVにより起こった事例だが，輸血後95日目にはすでに全身状態が悪化しており，重症化の防止という観点では輸血後2カ月前後での検査が推奨されるべきかもしれない．但し，献血者のHBc抗体のカットオフ値の厳密化と個別NAT検査の導入により，今後の輸血後HBV感染症は年間1～2件程度に減少す

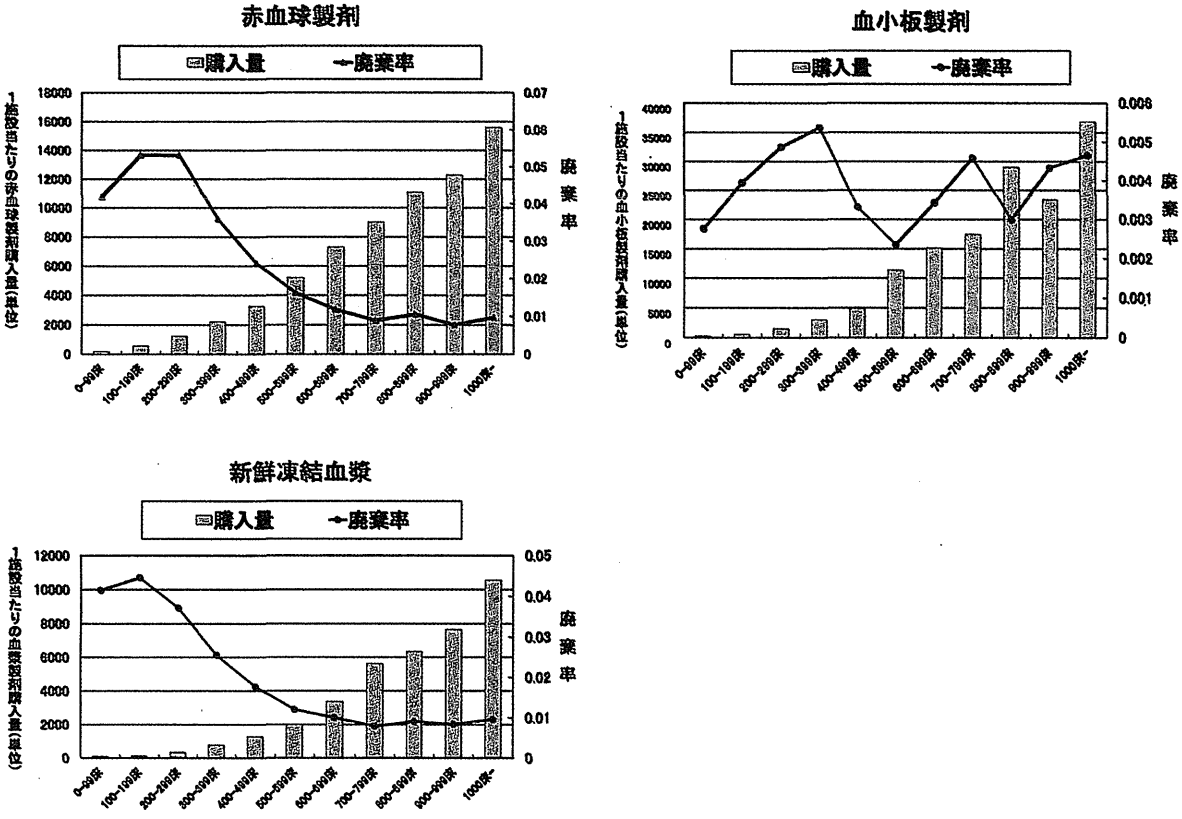

図4　各血液製剤の病床別購入量と廃棄率

ることが予想されている．また全血献血の場合には，分割されたFFPについては6カ月の貯留保管期間があるため，もう一方の赤血球製剤での感染が輸血後感染症検査により判明すれば，感染症を未然に防げるという利点も考慮すべきであろう．

自己血輸血の使用量は4年前より減少傾向であるが，その原因を調べたところ，手術時の出血量減少と外科医の方針変更が多かった．前者では心臓外科領域でのオフポンプ手術や泌尿器科・消化器外科・婦人科などでの内視鏡・腹腔鏡手術の普及などが影響していると考えられる．自己血輸血件数の減少について検討した論文では，主に整形外科で輸血を行う必要のない患者においての自己血貯血が減少したことが原因と考察している[12]．従って，自己血輸血の推進が後退したというよりも必要性が減ってきた結果という側面が大きいと考えられた．しかし日本で独自の発展を遂げてきた自己血輸血は，同種血の削減効果も期待できるので，今後も推進する方向性は維持すべきと思われる．

各血液製剤の都道府県別使用量には約2〜6倍の格差があるが，その意義を一律に表現することは困難である．有効活用の一方法として平均的なレベルから明らかに乖離して多い場合には，適正輸血から逸脱している可能性を考慮して対策を練ることなどは考慮してよいと思われる．

結　語

安全でかつ適正な輸血医療を推進するためには，輸血管理体制を整備し，輸血療法を改善する仕組みが必要である．毎年実施されている輸血使用実態調査は医療現場における輸血業務に関する問題点を把握し，最新の状況を踏まえた対策を検討することを目的としている．本報告を各医療機関や合同輸血療法委員会，地域での取り組みなどに有効活用いただくことを希望する．

著者のCOI開示：本論文発表内容に関連して特に申告なし

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す.

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NATIONWIDE QUESTIONNAIRE SURVEY OF TRANSFUSION MEDICINE IN FISCAL YEAR 2013

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Abstract:

In the survey conducted in 2013, among the 11,015 Japanese institutions receiving blood supply from the Japanese Red Cross Blood Center (JRCBC), the 4,894 institutions, which responded to the questionnaire, were enrolled. Blood management systems such as a unified management system were developed in Japan from 2005 through 2008. However, no significant improvement in efficiency of blood management has been observed since their implementation. In cases of small institutions (less than 300 beds), only 60% were able to implement a system. Nurses authorized by the Japan Society of Transfusion Medicine and Cell Therapy were present in only 32.7% of large institutions (more than 500 beds) and in only 4.7% of all institutions. The modifications regarding the requirements of facilities resulted in a large increase in the number of institutions which were able to establish criteria for obtaining hospital fees for transfusion management. In fact, the acquisition rate of hospital fees increased from 49.7% (2011) to 88.5% (2013) in medium to large institutions (more than 300 beds). Moreover, the introduction of a computer system to transfusion practice has increased gradually over the past 5 years, including implementation of a bar code-based identification system. Compared with fiscal year 2012, the numbers of blood products used according to the number of beds in fiscal year 2013 have changed as follows: Red blood cells and fresh frozen plasma, almost unchanged; platelet products, slightly increased; human albumin products, slightly decreased; intravenous immunoglobulin, increased; autologous blood products, decreased. There was no significant difference in the rates of adherence to the national guidelines of each blood product (77%-80%). Taken together, these observations suggest the importance of promoting the establishment of a blood management system in small institutions and to facilitating the appropriate use of blood products.

Keywords:

nationwide questionnaire survey on transfusion medicine, transfusion management system, appropriate blood transfusion

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ORIGINAL PAPER

A retrospective observational study to assess adverse transfusion reactions of patients with and without prior transfusion history

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Vox Sanguinis

Background and Objectives This study compares the frequency of adverse transfusion reactions (ATRs) after first transfusions with the frequency of ATRs for subsequent (non-first) transfusions.

Materials and Methods Five hospitals agreed to systematically collect and share 2 years of data. This was a retrospective observational analysis of data including the number of transfusion episodes and ATRs for red blood cells (RBCs), fresh frozen plasma (FFP) and platelet concentrates (PCs) given to first-time transfusion recipients and to those previously transfused.

Results First transfusion ATRs to RBCs, FFP and PCs were 1·08%, 2·84% and 3·34%, respectively. These are higher than ATR incidences to RBCs (0·69%), FFP (1·91%) and PCs (2·75%) on subsequent transfusions. Specifically, first transfusion incidences of febrile non-haemolytic transfusion reactions (FNHTRs) to RBCs (0·43%) and allergic reactions to FFP (2·51%) were higher than on subsequent transfusions (RBCs: 0·23%, FFP: 1·65%).

Conclusion There are risks of ATRs on the first transfusion as well as transfusions of patients with transfusion history.

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Key words: adverse transfusion reaction, allergic reaction, first transfusion, haemovigilance, transfusion episode.

Introduction

Although blood transfusion is regarded as an essential and life-saving therapy, significant clinical risks are attributed to the allogeneic origin of blood components. Also, concerns have been expressed about adverse transfusion reactions (ATRs) attributed to cytokines that accumulate in stored autologous blood. As transfusion-transmitted infections decrease due to improved donor screening and blood testing [1], non-infectious ATRs attract greater concern. In fact, the risk of transfusion-transmitted infectious diseases has decreased approximately 10 000-fold [2], while deaths attributed to transfusion-related acute lung injury (TRALI) and haemolytic transfusion reactions now account for approximately 72% of all transfusion-related fatalities reported to the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration [3]. Although blood components in Japan – as elsewhere – can be considered as highly safe, transfusion-associated ATRs have not been eliminated. Indeed, the overall incidence of ATRs per transfused unit was 1·53% in Japan [4]. But, the incidences of ATRs per unique patient per year are still high: to red blood cells (RBCs), 2·61%; to fresh frozen

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plasma (FFP), 4·32%; and to platelet concentrates (PCs), 13·24% [4].

While the majority of ATRs are not serious, these reactions can lead to hospitalization for outpatients or prolonged hospital stays for inpatients. This is a burden to patients, their families and to healthcare under any system of delivery and reimbursement. For these reasons, preventive strategies should be embraced. To this end, it is prudent to quantify ATRs, search for causality and investigate mechanisms.

National haemovigilance systems began in France in 1994 [5] and in the United Kingdom in 1996 [6], although these two systems differ greatly. With the advent of Directive 2002/98/EC [7], the introduction of haemovigilance systems has become a priority throughout the European Community. The recently established US Biovigilance Network commenced data collection in 2008 [8]. Less well known, the Japanese Red Cross Society (JRCS), as a monopoly provider of allogeneic blood, recognized its duty to co-ordinate blood safety and established a haemovigilance system in 1993. In summary, the emergence of haemovigilance systems is a global phenomenon.

Although most of these systems report the incidence of ATRs on a per-transfused unit basis, the incidence of reactions from first vs. subsequent transfusions has not been published, even though some ATRs are associated with prior transfusion. Previous exposure to allogeneic blood may sensitize patients to foreign plasma proteins [9] as well as cell surface alloantigens. Even so, the impact of prior transfusion on subsequent ATRs is not well defined. Herein we report the incidence of first transfusion ATRs vs. subsequent (non-first) transfusion ATRs from five hospitals over 2 years and consider the factors that may account for any differences.

Patients and methods

Study set-up

Data from standardized records were collected by the Department of Transfusion Medicine, Aichi Medical University, from its own and four hospitals. The data covered January 2010 through December 2011 and were assembled in February 2012.

Study design

This was a retrospective observational analysis of data from standardized records in 5 Japanese hospitals with established haemovigilance systems (Aichi Medical University Hospital, Keio University Hospital, Osaka University Hospital, Shinshu University Hospital, and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital) from January 2010 through December 2011, covering transfusions and associated ATRs for red blood cells (RBCs), fresh frozen plasma (FFP) and platelet concentrates (PCs). The study was approved by the Aichi Medical University Institutional Review Board, which is guided by local policy, national law and the World Medical Association Declaration of Helsinki. For each type of blood component, the data included the total number of first transfusion episodes on patients without any transfusion history and the total number of subsequent transfusion episodes for those with transfusion history, as well as the total number of transfusion-related ATRs per blood component with respect to both first and subsequent transfusions. We can identify first transfusions because physicians and nurses routinely solicit transfusion history from patients or family members and check hospital databases and medical records. We have defined a transfusion episode as any number of units of the same type administered within 24 h of each other. Therefore, if a patient with no transfusion history received more than one type of blood component within 24 h, a 'first transfusion' for each type of blood component was recorded. Any blood components thereafter would belong to a subsequent (non-first) transfusion.

Physicians and nurses monitored patients after the start of each transfusion for the occurrence of any ATRs and reported to the transfusion medicine service of each hospital whether or not an ATR had occurred. ATRs were investigated by a physician trained in transfusion medicine, and additional clinical and biological information was collected to facilitate diagnosis and assessment of severity. Adverse reactions were deemed ATRs according to professional assessment of imputability based on clinical and laboratory data.

A standard ATR assessment form included the following 16 items as shown in Table 1. A febrile non-haemolytic transfusion reaction (FNHTR) was diagnosed if fever, chills/rigours and feverishness (subjective feeling of warmth or glow) occurred during or within 4 h following transfusion without any other cause such as haemolysis, bacterial contamination or underlying disease. Allergic reactions consisted of skin symptoms or signs such as pruritus, skin rash and urticaria within 6 h of transfusion, after other potential etiologies of an allergic reaction were excluded. Any additional findings or comments, including suspected transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) or transfusion-transmitted viral and bacterial infection, could be entered as free text, and were later analysed. The definitions of all signs, symptoms and specific clinical syndromes used by the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) are based on

Table 1 Signs, symptoms and clinical diagnoses of ATRs

Signs/Symptoms	Clinical diagnoses
Fever (more than 38°C and more than 1°C increase after a transfusion)	Serious allergic reaction
	TRALI
Chills/Rigor	TACO
Feverishness (feeling of warmth or glow)	PTP
Pruritus	GVHD
Skin rash	Haemolytic transfusion reaction
Urticaria	Acute
Respiratory distress	Delayed
Nausea/Vomiting	Transfusion-transmitted infection
Headache	HBV
Chest/flank/back pain	HCV
Hypotension (a decrease of more than 30 mmHg after a transfusion)	HIV
	Bacteria
Hypertension (a increase of more than 30 mmHg after a transfusion)	Others
Tachycardia	
Vein pain	
Disturbance of consciousness	
Haemoglobinuria	
Others	

ATR, adverse transfusion reaction; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; PTP, post-transfusion purpura; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

documents issued by the International Society of Blood Transfusion (ISBT) Working Party for Haemovigilance [10], which also defined the criteria for grading the severity of ATRs, as follows: grade 1, the absence of immediate or long-term consequences; grade 2, long-term morbidity; grade 3, immediate vital risk; and grade 4, death of the recipient. Serious ATRs were defined as grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance.

Blood components

Blood collection, preparation and testing were performed according to protocols of the Blood Service Headquarters of the JRCS. Types of blood donation were 200 ml or 400 ml of whole blood and apheresis of platelets or plasma. Since January 2007, only prestorage leucoreduced blood components ($<1 \times 10^6$ leucocytes per unit) have been manufactured. After venipuncture, the first 25 ml of blood is diverted to decrease the risk of bacterial contamination, although not all units were tested for bacterial contamination. All blood components were screened using serological testing for infectious diseases. Furthermore, all blood components were screened using 20-mini-pool nucleic acid testing to reduce the risk of transfusion-transmitted infectious diseases (hepatitis B virus, hepatitis C virus and human immunodeficiency virus). RBCs are prepared with the additive solution MAP (mannitol adenine phosphate) and stored for up to 21 days at 5°C. All PCs are collected from single donors by apheresis, suspended in 200 ml of plasma and stored for up to 4 days at 22°C with agitation. FFP is prepared from whole blood plasma or by apheresis from single donors. Final volumes of FFP derived from 200 to 400 ml whole blood donations are approximately 120 and 240 ml, respectively, whereas the volume of FFP derived from single donor apheresis is around 450 ml. All blood components excluding FFP are irradiated with 15–50 Gy to prevent transfusion-associated graft-versus-host disease.

Statistical analysis

Data were analysed for first transfusion episodes and for subsequent transfusion episodes. To calculate the frequency of ATRs, the number of confirmed ATRs was correlated with the total number of first and subsequent transfusion episodes. All statistical analyses were performed by the chi-squared test, with Yates's correction for continuity and/or a Student's t-test. P values below 0·05 were considered statistically significant.

Results

Basic transfusion data set

During this study, there were 7594 RBC, 2469 FFP and 2127 PC first transfusion episodes (Table 2). As for the

Table 2 Number of transfusions

	First transfusion	Subsequent transfusion
No. of transfusion episodes		
RBC	7594	31 767
FFP	2469	6652
PC	2127	25 866
Gender ratio (female/male)		
RBC	0·8 (3380/4214)	0·6 (12 452/19 315)
FFP	0·7 (1031/1438)	0·6 (2463/4189)
PC	0·7 (896/1231)	0·6 (9533/16 333)
No. of units per episode[a]		
RBC	2·0	1·6
FFP	2·6	3·0
PC	1·2	1·1

[a]The values are averages.

gender distribution of first transfusion episodes, the female-to-male ratios for each blood component were at or near 0·7. On the subsequent transfusion episodes, the female-to-male ratios for each blood component were all 0·6. Thus, the gender distributions are quite similar for each blood component in both categories of transfusion episode. Furthermore, none of the differences in the number of units per episode for each blood component between first and subsequent transfusions was statistically significant.

ATRs following transfusion of blood components

As shown in Table 3, the incidence of ATRs to RBCs was significantly higher on first (1·08%) vs. subsequent (0·69%) transfusion episodes ($P = 0·0004$). Also, the incidence of ATRs to FFP was significantly higher on the first than on subsequent transfusion episodes: 2·84% vs. 1·91%, respectively ($P = 0·006$). Furthermore, although there was no significant difference in the incidence of ATRs to PC between first and subsequent transfusion episodes, the incidence of ATRs to PC trended higher on first vs. subsequent transfusion episodes (3·34% vs. 2·75%, respectively, but without statistical significance ($P = 0·10$).

When the incidence of ATRs to each blood component was investigated among males, the frequency of ATRs to RBCs on first transfusion episodes was found to be significantly higher than that on subsequent transfusion episodes ($P = 0·002$) (Table 3). The incidences of ATRs to FFP and PCs on first transfusion episodes were slightly higher than those on subsequent transfusion episodes. On the other hand, for females, the incidence of ATRs to FFP on first transfusion episodes was significantly higher than that on subsequent transfusion episodes ($P = 0·018$). Also, the incidences of ATRs to RBCs and PCs on first transfusion episodes were slightly higher than those on subsequent transfusion episodes among females.

Table 3 Incidence of ATRs on first transfusion and subsequent transfusion episode bases

	First transfusion		Subsequent transfusion		
	Number	Incidence (%)	Number	Incidence (%)	*P* value[a]
RBC					
Male	39	0·93	103	0·53	0·002
Female	43	1·27	117	0·94	0·08
Total	82	1·08	220	0·69	0·0004
FFP					
Male	34	2·36	75	1·79	0·18
Female	36	3·49	52	2·11	0·018
Total	70	3·24	127	1·91	0·006
PC					
Male	40	3·25	440	2·69	0·28
Female	31	3·46	271	2·84	0·30
Total	71	3·34	711	2·75	0·10

ATR, Adverse transfusion reaction.

[a]*P* values are for difference of incidences of ATRs between first transfusion and subsequent transfusion episodes.

Characteristics of clinical signs and symptoms associated with ATRs

When the incidence of various ATR types to RBCs was investigated, the frequency of FNHTR (0·43%) and other reactions (0·26%) on first transfusion episodes was found to be significantly higher than on subsequent transfusion episodes (FNHTR: 0·23%; $P = 0·001$, other reactions: 0·15%; $P = 0·03$) (Table 4). The first transfusion incidence of allergic reactions (0·47%) was slightly higher than for subsequent transfusion episodes (0·37%). Furthermore, first transfusion incidence of allergic reactions (2·51%) to FFP was significantly higher than that on subsequent transfusion episodes (1·65%, $P = 0·01$). On the other hand, there were no significant differences in the frequency of FNHTR, allergic reactions and others to PCs on first transfusion episodes vs. subsequent transfusion episodes (FNHTR: 0·33% vs. 0·23%, allergic reactions: 2·82% vs. 2·49%, others: 0·33% vs. 0·12%).

During the study, serious ATRs to RBCs and FFP were 3 (0·04%) and 4 (0·16%), respectively on first transfusion episodes (Table 4). On subsequent transfusion episodes, serious ATRs to RBCs, FFP and PCs were 5 (0·02%), 2 (0·03%) and 7 (0·03%), respectively. The proportions of serious ATRs among all ATRs to RBCs, FFP and PCs were low on first and subsequent transfusion episodes; thus, the majority of ATRs were not serious.

Discussion

One factor thought to influence the risk of ATRs is transfusion history. Despite this, previous reports about ATRs have not distinguished first from subsequent transfusions in their analysis. In the present study, incidences of ATRs to RBCs, FFP and PCs per first transfusion episode were 1·08%, 2·84% and 3·34%, respectively. On the other hand, the incidences of ATRs on subsequent transfusion episodes to RBCs, FFP and PCs were 0·69%, 1·91% and 2·75%, respectively. Thus, the risk of ATRs for patients with no transfusion history trended higher compared to patients who had already been transfused. In particular, the first transfusion incidences of ATRs to RBCs and FFP are significantly higher than those for subsequent

Table 4 Clinical characteristics of ATRs on first transfusion and subsequent transfusion episodes

	RBC			FFP			PC		
	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]
FNHTR	33 (0·43)	73 (0·23)	0·001	7 (0·28)	6 (0·09)	0·07	7 (0·33)	60 (0·23)	0·35
Allergic reaction	36 (0·47)	108 (0·34)	0·09	62 (2·51)	110 (1·65)	0·01	60 (2·82)	643 (2·49)	0·31
Others	20 (0·26)	48 (0·15)	0·03	5 (0·20)	17 (0·26)	0·63	7 (0·33)	31 (0·12)	0·16
Serious ATR[d]									
Serious allergic reaction	2 (0·03)	5 (0·02)	0·28	4 (0·16)	2 (0·03)	0·18	0	7 (0·03)	0·46
TRALI	0	0	–	0	1 (0·01)	–	0	0	–
Delayed haemolytic reaction	1 (0·01)	0	–	0	0	–	0	0	–

ATR, Adverse transfusion reaction; FNHTR, Febrile non-haemolytic transfusion reaction.
The values are the number of ATRs (%).
[a]First transfusion episodes.
[b]Subsequent transfusion episodes.
[c]*P* values are for difference of incidences of ATRs between first transfusion and subsequent transfusion episodes.
[d]Serious ATRs were defined as grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance and include serious allergic reaction, transfusion-related acute lung injury (TRALI) and haemolytic transfusion reaction.

transfusion episodes ($P < 0·01$). Furthermore, the first transfusion incidences of FNHTR to RBCs (0·43%, $P = 0·001$) and allergic reactions to FFP (2·51%, $P = 0·01$) were higher than those on subsequent transfusion episodes (RBCs: 0·23%, FFP: 1·65%). Therefore, the higher frequencies of ATRs to RBCs and FFP on the first transfusion vs. subsequent transfusions could be traced to the higher incidences of FNHTRs to RBCs and allergic reactions to FFP on the first transfusion.

Previous work has reported that the risk of ATRs for patients who had already been transfused trended higher compared to patients with no transfusion history [11]. In general, Japanese physicians and nurses must obtain transfusion histories from patients or their family members and the physicians in transfusion medicine check this history against hospital database records. Furthermore, they infer whether or not patients have received any previous transfusions based on the patients' diseases. Thus, in the present study, almost all patients in the first transfusion category are considered to be reliably categorized. Another possible reason for this discrepancy comes from a previous study that surveyed ATRs to only PCs and did not reach statistical significance in the incidences of ATRs for patients with no transfusion history vs. any transfusion history. Indeed, in the present study, although the first transfusion incidence of ATRs to PCs trended higher than for subsequent transfusions, the difference did not reach statistical significance ($P = 0·10$). It is suspected that although the data in this study were not analysed for the characteristics of transfused patients, such as underlying condition, age and pregnancy history, there are risks of ATRs on the first transfusion.

Heddle *et al.* [12, 13] have reported that FNHTRs to blood components are caused by white blood cell (WBC) antigen–antibody interaction and cytokines, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-α, released from WBCs and accumulated in blood components during storage. There is general agreement that prestorage leucoreduction will decrease the frequency of FNHTRs [14, 15]. However, leucoreduction dose not completely reduce the amount of CD154 (CD40 ligand), implicated in FNHTRs and elaborated by platelets. Thus, it is unlikely that leucocyte filtration by itself can completely eliminate the risk of FNHTRs. Furthermore, a recent study revealed that some cytokines start accumulating in stored whole blood within hours after donation [16]. In this study, although all blood components were leucocyte reduced before storage, a low rate of FNHTRs to blood components persisted both on first transfusion and subsequent transfusion episodes. In particular, the incidence of FNHTRs per first transfusion episode to RBCs, which contain relatively more WBCs than other blood components, was significantly higher than on subsequent transfusion episodes.

Furthermore, the number of RBC units per episode for the first transfusion was slightly more compared with that on subsequent transfusion episodes. In particular, the number of RBC units per episode for the first transfusion tended to be more than that on subsequent transfusion episodes for males (data not shown). Therefore, it is suspected that FNHTRs to blood components are not influenced by previous allogeneic exposure from transfusion and one risk of ATRs on the transfusion was correlated with the number of transfusion units per episode.

It is thought that allergic reactions to blood components are influenced by previous allogeneic exposure from transfusion. Tobian *et al.* [17] described that patients must be exposed to plasma multiple times before having an allergic reaction. In addition, the incidence of ATRs per patient was influenced by the number of transfusions per patient [4, 11]. However, in this study, the incidences of allergic reactions to RBCs, FFP and PCs were 0·47%, 2·51% and 2·82%, respectively on the first transfusion though these patients were not previously exposed to allogeneic transfusion (Table 4). Furthermore, there were 6 serious allergic reactions associated with first transfusions. Putative mechanisms underlying allergic reactions include biological response modifiers (BRMs) such as inflammatory cytokines and chemokines that accumulate during storage and enter the circulation during transfusion, leading to allergic reactions [18–22]. On the other hand, Savage *et al.* [23] showed that certain donors donated PCs that resulted in an allergic reaction rate of 5·8%, which was greater than the overall incidence of allergic reactions (1·72%). A recent study observed 1616 (1·72%) allergic reactions among 93 737 transfusions and found that 30% of recipients with an allergic reaction had allergic reaction rates of more than 5% [23]. Furthermore, in 630 instances where split PCs were given to two patients in whom one had a reaction, there were only six instances where the other patient also had a reaction [23]. On the other hand, Ahmed *et al.* [24] reported that pregnancy history directly correlates with the risk of allergic reaction on initial transfusion. Indeed, although the data analysis in this study did not consider pregnancy for female patients, the incidence of ATRs (3·49%) per first transfusion episode to FFP was significantly higher than on subsequent transfusion episodes (2·11%, $P = 0·018$, Table 3). Thus, it is suspected that blood component factors, donor factors and patient factors including pregnancy may contribute to allergic reactions. Therefore, as the present study shows, risks of allergic reactions to blood component exist in patients without previous allogeneic exposure from transfusion.

The incidences of allergic reactions to blood components on the first transfusion were higher or almost the same compared to subsequent transfusion episodes. In particular, the frequency of allergic reactions to FFP (2·51%) on the first transfusion was significantly higher compared to subsequent transfusion (1·65%, $P = 0·01$). It is possible that this pattern is due to an increased use of premedication among patients with reactions to a previous transfusion. However, most studies performed to date have failed to demonstrate that premedication is effective in preventing allergic transfusion reactions [25–28]. Furthermore, in the present study, although most patients receiving RBCs and PCs were premedicated, the first transfusion incidences of allergic reactions to RBCs and PCs were not significantly higher than for subsequent transfusions. Another possibility is that serial exposure to blood components may desensitize recipients. A recent study revealed that recurrent exposure to PCs caused recipients to become less likely to experience allergic reactions [29]. Furthermore, experiments show a desensitization effect on repeat exposure to reconstituted donor serum [30]. It is thought that desensitization is mediated by two mechanisms, the suppression of proallergic innate effectors and the upregulation of regulatory T-cell activity. Proallergic innate effectors could undergo rapid desensitization against allergens [31]. In addition, functional allergen-specific regulatory T cells can attenuate allergic responses through suppression of mast cells, basophils and eosinophils; suppression of allergen-specific T cells; and reduction of IgE production [31]. Indeed, Jo *et al.* [32] showed the acquisition of tolerance to cow's milk allergens during childhood is associated with the suppression of proallergic innate effectors' activity and activity of regulatory T cells. Taken together, these findings help explain why the incidence of allergic reactions to blood components on first transfusions could exceed that of subsequent transfusions.

We conclude that there are risks of ATRs on the first transfusion as well as transfusions of patients with transfusion history. It is suspected that FNHTRs are not so much provoked by previous allogeneic transfusion exposure as by the number of transfusion units per episode. On the other hand, with regard to allergic reactions, although both atopic susceptibility in the recipient as well as particular donor and component characteristics are risk factors, the first transfusion itself appears to be an important risk. Thus, despite the limitations of this study, it suggests the need for more elaborate analyses of patient data to further improve transfusion therapy. In particular, ATR risk factors elucidated here and elsewhere might refine clinical indications for washing PCs.

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Conflict of interest

The authors declare no conflict of interests.

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Repeated exposure rather than the total volume of transfused components may influence the incidence of allergic transfusion reactions

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BACKGROUND: The plasma fraction of blood components has an essential role in the etiology of allergic transfusion reactions (ATRs). The difference of incidences of ATRs between fresh-frozen plasma (FFP) and platelet concentrates (PCs), in which plasma is the main component, is not clearly understood. This study compares the frequency of ATRs to FFP versus PCs on both first and subsequent (nonfirst) transfusions and considers the factors influencing the risk of ATRs.

STUDY DESIGN AND METHODS: Five hospitals agreed to systematically collect and share 2 years of data (January 2010 through December 2011). This was a retrospective observational analysis of data including the number of transfusion episodes and ATRs for FFP and PCs on first-transfusion patients (without transfusion history) and previously transfused patients.

RESULTS: The incidence of ATRs to PCs (2.51%) was significantly higher than to FFP (1.68%) on subsequent transfusions ($p < 0.001$). On the other hand, there were no significant differences in the incidences of ATRs to FFP (2.67%) and PCs (2.82%) on first transfusions. This discrepancy was most pronounced among males: FFP versus PCs on first transfusions, 2.02% versus 2.60% ($p = 0.30$); and on subsequent transfusions, 1.58% versus 2.46% ($p = 0.0007$). Among females, FFP versus PCs on first transfusions was 3.59% versus 3.13% ($p = 0.61$) and on subsequent transfusions was 1.87% versus 2.61% ($p = 0.029$).

CONCLUSION: Repeated exposure rather than the total volume of transfused components may influence the incidence of ATRs.

Although blood transfusion is regarded as an essential and life-saving therapy, significant clinical risks are attributed to blood components' allogeneic origin. In particular, adverse reactions (ARs) are frequent in patients receiving transfusions of platelet concentrates (PCs).[1] We have previously demonstrated that the incidence of ARs to PCs per transfused unit was 3.8%.[2] It was also shown that the incidence of ARs to PCs per patient was 13.2%. Furthermore, most ARs to PCs were allergic transfusion reactions (ATRs).

ABBREVIATIONS: AR(s) = adverse reaction(s); ATR(s) = allergic transfusion reaction(s); PC(s) = platelet concentrate(s).

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ATRs are the most common AR to transfused PCs and have an incidence of approximately 1% to 3%.[3-5] Most reactions are mild and are usually associated with cutaneous manifestations such as urticaria, rash, pruritis, and flushing. Severe ATRs, such as anaphylactic shock, are rare. ATRs are classically thought of as Type I hypersensitivity reactions due to immunoglobulin (Ig)E antibodies interacting with allergens to activate mast cells and basophils. However, the mechanisms involved are not understood in the majority of cases. Paglino and colleagues[6] reported a significant decrease in the frequency of febrile nonhemolytic transfusion reactions—although not ATRs—for red blood cells (RBCs) and PCs after the introduction of universal prestorage leukoreduction. Furthermore, washing PCs and RBCs substantially reduces ATRs;[7] hence the suspicion that the plasma fraction of blood components has an essential role in etiology of ATRs.

However, although plasma is the main component in fresh-frozen plasma (FFP) and PCs, the incidence of ATRs to PCs is higher than that of FFP.[2,8] The reason for this difference between FFP and PCs is not clearly understood. Thus, a mediator in plasma may be necessary, but not sufficient, to cause an ATR. Herein we report an incidence matrix of ATRs to FFP versus PCs on first versus subsequent (nonfirst) transfusions, using data from five hospitals over 2 years and consider factors influencing the risk of ATRs.

MATERIALS AND METHODS

Study set-up

Data from standardized records were collected by the Department of Transfusion Medicine, Aichi Medical University, from its own and four hospitals. The data covered January 2010 through December 2011 and were assembled in February 2012.

Study design

This was a retrospective observational analysis of data from standardized records of five Japanese hospitals with established hemovigilance systems (Aichi Medical University Hospital, Keio University Hospital, Osaka University Hospital, Shinshu University Hospital, and Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital) from January 2010 through December 2011, covering FFP and PC transfusions and associated ATRs. The study was approved by the Aichi Medical University Institutional Review Board, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. For each type of blood component, the data included the total number of first-transfusion episodes on patients without transfusion history and the total number of subsequent transfusion episodes for those with transfusion history, as well as the total number of ATRs per blood component with respect to both first and subsequent transfusions. We can identify first transfusions because physicians and nurses routinely solicit transfusion history from patients or family members and check hospital databases and medical records. We have defined a transfusion episode as any number of units of the same type administered within 24 hours of each other. Therefore, if a patient with no transfusion history received more than one type of blood component within 24 hours, a "first transfusion" for each type of blood component was recorded.

Physicians and nurses monitored the patients after the start of each transfusion for the occurrence of any ARs and reported the results to the transfusion medicine service of each hospital whether or not an AR had occurred. Physicians and nurses more readily identified ARs by using a standard monitoring form during strictly defined observation periods during and after transfusion. ARs were investigated by a physician trained in transfusion medicine, and additional clinical and biological information was collected to facilitate diagnosis and assessment of severity. ARs were deemed ARs according to professional assessment of imputability based on clinical and laboratory data. If ARs had occurred in patients who had received multiple blood components within 6 hours of an AR, specialist physicians identified blood components related to the ARs based on clinical and laboratory data. No data were collected regarding pretransfusion medications and washing of PCs.

An ATR was defined as having two or more of the following symptoms or signs occurring during the transfusion: skin rash; urticaria; pruritus; localized angioedema; edema of lips, tongue, and uvula; conjunctival edema; and hypotension. An ATR could also include respiratory or gastrointestinal signs and/or symptoms. All ATRs were within 6 hours of transfusion and other potential etiologies of an allergic reaction were excluded. The definition of ATRs used by the Japan Society of Transfusion Medicine and Cell Therapy is based on documents issued by the International Society of Blood Transfusion (ISBT) Working Party for Haemovigilance,[9] which also defined the criteria for grading the severity of ATRs as follows: Grade 1 = the absence of immediate or long-term consequences; Grade 2 = long-term morbidity; Grade 3 = immediate vital risk; and Grade 4 = death of the recipient. Serious ATRs were defined as Grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance.

Blood components

Blood collection, preparation, and testing were performed according to protocols of the blood service headquarters of the Japanese Red Cross Society. Types of blood donation were 200 or 400 mL of whole blood and apheresis of platelets (PLTs) or plasma. Since January 2007, only prestorage leukoreduced blood components (less than 1×10^6 white blood cells/unit) are manufactured. After

venipuncture, the first 25 mL of blood is diverted to decrease the risk of bacterial contamination, although units are not routinely tested for bacterial contamination. All blood components were screened using serologic testing for infectious diseases. Furthermore, all blood components were screened using 20-minipool nucleic acid testing to reduce the risk of transfusion-transmitted infectious diseases (hepatitis B virus, hepatitis C virus, and human immunodeficiency virus). All PCs are prepared from single donors by apheresis; the products are suspended in 200 mL of plasma and stored for up to 4 days at 22°C with agitation. FFP is prepared from whole blood plasma or by apheresis from single donors. Final volumes of FFP derived from 200- and 400-mL whole blood donations are approximately 120 and 240 mL, respectively, whereas the volume of FFP derived from single-donor apheresis is around 450 mL. All blood components excluding FFP were irradiated with 15 to 50 Gy to prevent transfusion-associated graft-versus-host disease.

Statistical analysis

Data were analyzed for first-transfusion episodes and for all transfusion episodes. To calculate the frequency of ATRs, the number of confirmed ATRs was correlated with the total number of first and total transfused episodes. All statistical analyses were performed by the chi-square test, with Yates's correction for continuity and/or a test. p values below 0.05 were considered significant.

RESULTS

Basic transfusion data set

During this study, 9121 FFP transfusion episodes involved 3497 patients and 27,993 PC transfusion episodes involved 4052 patients. Of 3497 patients who received FFP, 2469 patients (70.6%) were receiving their first transfusion (Table 1). In contrast, of the 4052 patients who received PCs, only 2127 (52.5%) were receiving their first transfusion. Thus, patients receiving blood for the first time accounted for more than half of all transfused patients regardless of blood component.

As for the sex distribution of first transfusion episodes, the female-to-male ratios for FFP and PCs were both 0.7. On the subsequent (nonfirst) transfusion episodes, the female-to-male ratios for FFP and PCs were both 0.6. Thus, the sex distributions are quite similar for either blood component in either category of transfusion episode. Furthermore, the number of FFP and PC units per episode for first transfusions were 2.6 and 1.2 units, respectively. The number of FFP and PC units per subsequent transfusion episode were 3.0 and 1.1, respectively. Thus, the mean number of FFP units transfused was slightly greater than the number of PC units transfused in both categories of transfusion episode.

TABLE 1. Basic transfusion data

Characteristic	FFP	PC
Number of transfusion patients		
Total transfusion	3497	4,052
First transfusion	2469	2,127
Subsequent transfusion	1028	1,925
Number of units per patient	7.7	7.4
Male	8.2	7.7
Female	7.1	7.0
Number of episodes per patient	2.6	6.9*
Male	2.8	7.2*
Female	2.4	6.5*
Number of transfusion episodes		
First transfusion	2469	2,127
Subsequent transfusion	6652	25,866
Sex ratio (female/male)		
First transfusion	0.7	0.7
Subsequent transfusion	0.6	0.6
Number of units per episode		
First transfusion	2.6	1.2
Subsequent transfusion	3.0	1.1

* $p < 0.01$ compared with FFP.

The mean numbers of FFP and PC transfusion units per patient were 7.7 and 7.4, respectively. On the other hand, the mean numbers of FFP and PC transfusion episodes per patient were 2.6 and 6.9, respectively. Thus, although the mean number of units per patient was almost the same for either blood component, PC transfusion episodes (6.9 per patient) were significantly greater than FFP transfusion episodes (2.6 per patient, $p < 0.01$). Furthermore, there was no significant difference in the number of units or number of transfusion episodes per patient by sex in each blood component (number of FFP units per patient, male and female, 8.2 and 7.1; number of PC units per patient, male and female, 7.7 and 7.0; number of FFP episodes per patient, male and female, 2.8 and 2.4; number of PC episodes per patient, male and female, 7.2 and 6.5).

ATRs after transfusion of blood components

During the study, the number of serious ATRs to FFP was 4 (0.16%) on first transfusion episode (Table 2). On subsequent transfusion episode, the numbers of serious ATRs to FFP and PCs were 2 (0.03%) and 7 (0.03%), respectively. The proportions of serious ATRs among all ATRs to FFP and PCs were low for first and subsequent transfusion episodes; thus, the majority of ATRs were not serious.

Among first transfusions, 66 of 2469 episodes of FFP (2.67%) and 60 of 2127 episodes of PC (2.82%) transfusion were associated with an ATR. Furthermore, 62 episodes (2.51%) experienced mild ATRs to FFP and 60 episodes (2.82%) to PC. Thus, there were no significant differences in the incidences of ATRs to FFP and PCs on the first transfusion. On the other hand, on subsequent transfusions, 112 of 6652 episodes (1.68%) of FFP transfusions

TABLE 2. Incidence of ATRs on first-transfusion and subsequent transfusion episode bases

	FFP		PC		
ATR	Number	Incidence (%)	Number	Incidence (%)	p value*
First transfusion	2469		2,127		
Mild	62	2.51	60	2.82	0.46
Serious	4	0.16	0	0	
Total	66	2.67	60	2.82	0.72
Subsequent transfusion	6652		25,866		
Mild	110	1.65	643	2.49	<0.0001
Serious	2	0.03	7	0.03	
Total	112	1.68	650	2.51	<0.0001

* p values refer to differences of incidences of ATRs between FFP and PCs.

TABLE 3. Incidence of ATRs for males and females

	FFP		PC		
Transfusion	Number	Incidence (%)	Number	Incidence (%)	p value†
First					
Male	29/1438*	2.02	32/1,231	2.60	0.30
Female	37/1031	3.59	28/896	3.13	0.61
Subsequent					
Male	66/4189	1.58	401/16,333	2.46	0.0007
Female	46/2463	1.87	249/9,533	2.61	0.029

* The number of ATRs/transfusion episodes.
† p values refer to differences of incidences of ATRs between FFP and PCs.

experienced ATRs (Table 2). In contrast, 650 of 25,866 episodes (2.51%) experienced ATRs to PCs. Also, 110 episodes (1.65%) experienced mild ATRs to FFP and 643 episodes (2.49%) to PCs. The incidence of ATRs to PCs was significantly higher than that to FFP on the subsequent transfusion ($p < 0.001$).

When the incidence of ATRs to each blood component was investigated among males, the frequency of ATRs to FFP (2.02%) was found not to be significantly different from PCs (2.60%) on first transfusion episodes ($p = 0.30$; Table 3). Similar to the result for males, there was no significant difference in the incidence of ATRs to FFP (3.59%) versus PCs (3.13%) on first transfusions for females ($p = 0.61$). In contrast, the frequency of ATRs to PCs (male, 2.46%; female, 2.61%) was significantly higher than to FFP (male, 1.58%; female, 1.87%) for both males and females for subsequent transfusion episodes (male, $p = 0.0007$; female, $p = 0.029$).

DISCUSSION

We retrospectively analyzed ATRs with stringent criteria and standardized case reporting forms across five study sites, over a period of 2 years. The incidence of ATRs to PCs (2.51%) was significantly higher than that to FFP (1.68%) in subsequent transfusions ($p < 0.001$). On the other hand, there were no significant differences in the incidences of ATRs to FFP (2.67%) and PCs (2.82%) on the first transfusion. Furthermore, this discrepancy was for both males and females.

Although the pathophysiology of ATRs has not been fully elucidated, both the plasma fraction of blood components and the various recipient factors play a role in ATRs.[4] Patient hypersensitivities resulting from severe deficiencies of IgA,[10] haptoglobin,[11] and C4[12] have been described, but these deficiencies are too rare to explain the high incidence of ATRs. Previous studies have demonstrated that ATR incidence is dependent on the dose of plasma in blood components.[7,13] Biogenic amines, eosinophil and neutrophil chemotaxic factors, enzymes, prostaglandin, and numerous cytokines have all been found in the plasma and implicated in ATRs.[13] In this study, the incidences of ATRs to FFP and PCs in which plasma is the main component were significantly higher than to RBCs in which plasma comprises less than 10% of the volume (data not shown). Furthermore, there were no significant differences in frequencies of ATRs to FFP (2.67%) and PCs (2.82%) on the first transfusion (Table 2). Thus, this study confirms that blood component factors may contribute to ATRs as shown by analysis of the incidence of ATRs to FFP and PCs on patients without prior exposure to allogeneic transfusion. It is suspected that the plasma component of FFP and PCs has an essential role in the etiology of ATRs.

The present and previous studies[2,8,14] have reported that PCs give rise to statistically more ATRs than FFP (2.51% vs. 1.68%, $p < 0.001$) on subsequent transfusion episodes. On the other hand, there were no significant

differences in the incidences of ATRs to FFP and PCs on first-transfusion episodes. Thus, although plasma is the main constituent in both FFP and PCs, the incidences of ATRs to each blood component differed according to the category of transfusion episode. One possible reason is that compared with FFP recipients, PC recipients are more likely to be hematology patients sensitized to plasma through other blood components. Indeed, in this study, the mean number of PC transfusion episodes (6.9 episodes per patient, i.e., 27,993 episodes/4052 patients) was more than those for FFP (2.6 per patient, i.e., 9121 episodes/3497 patients; Table 1). On the other hand, the mean numbers of FFP (7.7 units per patient, i.e., 26,968 units/3497 patients) and PC (7.4 units per patient, i.e., 73,541 units/4052 patients) transfusion units per patient were almost the same. Tobian and coworkers[7] described that patients must be exposed to plasma multiple times before having an ATR. In addition, the incidence of ARs per patient was influenced by the number of transfusions per patient.[2,15] Therefore, we speculate that repeated exposure rather than total volume of blood transfused can influence the incidence of ATRs.

Furthermore, these different incidences of ATRs to FFP and PCs on subsequent transfusions were strongly significant for males and slightly significant for females (males, 1.58% vs. 2.46%, $p = 0.0007$; females, 1.87% vs. 2.61%, $p = 0.029$; Table 3). We might attribute this to female patients having long-term exposure to allogeneic molecules through pregnancy before ever being transfused. Ahmed and colleagues[16] reported that the frequency of fetal exposure directly correlates with the risk of ATR on initial transfusion. Previous work reported that the positivity rates for anti-human leukocyte antigen antibodies were significantly higher among females than among males for both patients who have experienced ARs and donors associated with ARs.[17] Seftel and colleagues[18] reported that the factors that predict PLT alloimmunization were a history of pregnancy and/or transfusion and receipt of 13 or more PLT transfusions. Therefore, we speculate that this study includes female recipients whose ATRs were not significantly influenced by the number of transfusions because of their prior alloexposure. Nevertheless, the different incidences of ATRs to FFP and PCs on subsequent transfusions were significant for females. Therefore, this study supports the concept that one factor predicting occurrence of ATRs could be exposure by repeated transfusion.

However, previous studies[19,20] have reported that increases in the number of PC transfusions are associated with decreases in the number of ATRs. Indeed, in this study, the incidence of ATRs to FFP (1.68%) on subsequent transfusion was lower compared to first-transfusion episodes (2.67%, $p < 0.01$). A possibility is that preexposure to blood components may desensitize recipients. It is thought that desensitization is mediated by two mechanisms, the suppression of proallergic innate effectors and the up regulation of regulatory T-cell activity. Proallergic innate effectors could undergo rapid desensitization against allergens.[21] In addition, functional allergen-specific regulatory T cells can attenuate allergic responses through suppression of mast cells, basophils, and eosinophils; suppression of allergen-specific T cells; and reduction of IgE production.[21] On the other hand, the subsequent transfusion incidence of ATRs to PCs (2.51%) was not significantly lower than for first-transfusion episodes (2.82%, $p = 0.31$). PC recipients, most of whom suffer from hematologic diseases, may be leukocytopenic due to their diseases and chemotherapy. It is thought that although PC recipients on subsequent transfusions have allergen-specific IgE due to repeated exposure by multiple transfusions, regulatory T cells on most PC recipients are decreased by leukocytopenia. Therefore, we suspected that compared with FFP recipients, PC recipients may have become more sensitized to plasma through other blood components. However, the data in this study do not completely support these concepts, so they are, for now, purely speculative. Taken together, these findings support the fact that hematologic diseases, food allergy, history of pregnancy, and such modulate recipients' susceptibility to ATRs.

We conclude that repeated exposure rather than total amount of transfusion by blood components might influence the incidence of ATRs. It is summarized by Savage and coworkers[13] that both atopic susceptibility in the recipient as well as particular donor and component characteristics are unique risk factors for the development of ATRs. Thus, despite the limitation of this study, it provides insight into risks of ATRs among transfused patients. In the future, more elaborate analyses of the data collected from individual patients may allow recommendations to be made for improvements in transfusion therapy.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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