VIA MEDICA

ORIGINAL ARTICLE

Journal of Transfusion Medicine
2022, vol. 15, no. 3, 196–209
DOI: 10.5603/JTM.2022.0015

ISSN 1689-6017
e-ISSN 2080-1505

Analysis of the frequency of post transfusion adverse reactions and their association with blood components supplied by the Regional Blood Transfusion Center in Poznań (2011–2018)

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Summary

Background: *Blood component transfusions are common, often life-saving therapies, however they sometimes (0.2–10%) result in adverse reactions (ARs). The study aim was to analyse AR frequency and relation to transfusion in patients treated with blood components as well as to present recipient, donor, and blood component factors that induce ARs.*

Material and methods: *The retrospective analysis included 650 cases of ARs following transfusion which were reported to the Blood Transfusion Center in Poznań in the period 2011–2018. The reported ARs were analysed for their intensity/severity, component modification and storage time prior to transfusion, patient's clinical condition and transfusion history as well as sex and age of both donors and recipients. Finally, for each AR case the imputability with transfusion was assessed.*

Results: *In the study population, ARs were infrequent (< 0.1%) and depended on the type of blood component, age and sex of the recipient and donor as well as on transfusion history. The symptoms observed were found to be related to transfusion in less than 50% of cases. It has been demonstrated that the deaths reported in the study were related to patients whose clinical condition was either severe or fairly/relatively good and who usually manifested severe adverse reactions (SARs) following transfusion.*

Conclusions: *(i) identified ARs were rarely reported. The lower incidence rate as compared to the published data indicates that not all ARs are reported. The reporting procedure needs to be changed. (ii) Confirmed relation with transfusion was determined in less than 50% of cases. (iii) Some donor/recipient/blood component — specific factors may induce certain types of adverse reactions.*

Key words: post-transfusion adverse reactions (P-ARs), imputability level, blood donor, blood component recipient, blood components

J. Transf. Med. 2022; 15: 196–209

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Introduction

Transfusion of blood components is a common therapy. According to the World Health Organization (WHO), each year, various types of blood components are transfused worldwide prepared from 112.5 mln blood donations [1]. Transfusions of red blood cell concentrate (RBC) are estimated at 90 mln units and platelet concentrate (PC) at 10 mln units) [2–3]. In the USA (328 mln inhabitants), 21 mln units of blood components are transfused annually, including 15 mln RBC, 4 mln fresh frozen plasma (FFP) and 2 mln PC. In Poland (38 mln inhabitants), the annual consumption of blood components is 1.5–1.7 mln, including 1.2 mln RBCC, 0.3 mln FFP and 0.12–0.13 mln PCs [4–6].

Though undoubtedly life-saving procedures, transfusions are also burdened with the risk of ARs which may sometimes be life-threatening. ARs are associated with transfusions of 0.2–10% of components and 0.26/100.000 of them are fatal [7–9]. In the USA and France, the AR incidence rate (component type included) was similar (0.2% of all transfusions; 0.2% related to RBC; 0.1% to FFP; 0.4% to PC transfusions). In Poland, post transfusion ARs were distributed as follows: 0.09% were related to RBC; 0.04% to FFP and 0.17% to PC [10–12]. In the USA (2010–2012), 83% of reported ARs were related to febrile nonhemolytic transfusion reactions (FNHTR) and allergies, 6% to alloimmunization, 4% to transfusion-associated circulatory overload (TACO), 3% to hypotension, 2% to delayed haemolytic transfusion reaction (DHTR), 1% to transfusion-associated dyspnea (TAD) and less than 1% to transfusion related acute lung injury (TRALI), acute haemolytic transfusion reaction (AHTR) and infections [10]. According to the data presented by prof. dr hab. n. med. Magdalena Łętowska, during the 09/06/2020 webinar entitled "Adverse reactions in Blood Donors" (Niepożądane reakcje u biorców), the distribution of post transfusion ARs reported in Poland in the years 2006–2017 was as follows: 28% related to FNHTR, 25% to allergy, 3% to TACO, 3% to hypotension, 4% to DHTR, 1% to AHTR, 1% to TRALI, 7% to TAD, 1% to infection, 27% to others.

Adverse reactions are responses of the recipient's immune system to the genetic incompatibility with the transfused component or inflammatory responses most likely due to a combination of overlapping factors related to the donor, blood component and recipient [13]. Therefore it is sometimes difficult to determine a cause-and-effect relationship between transfusion and the observed AR [14].

In view of the above, the study aim was to analyse the frequency rate of ARs and to assess their relationship with transfusions of blood components supplied by the Regional Blood Transfusion Center (RCKiK) in Poznań in the period 2011–2018. The specific objectives were to identify the AR-inducing factors related to the recipient, donor and the transfused blood component.

Material and methods

Study population

The retrospective study included data of patients admitted to the hospitals in the Greater Poland Voivodeship (Województwo Wielkopolskie) in the years 2011–2018 who suffered ARs related to blood component therapy. The ARs were reported to the Regional Blood Transfusion Center in Poznań. The study population comprised 650 persons aged from 2 days to 93 years (median 55). The results are presented in two variants: for adults (n = 525; age: 18–93 years ; median 60; women 56%; men 44%) and for children (n = 125; age: 2 days up to 18 years; median 5; girls 43%; boys 57%). The data come from completed AR/AE (adverse reaction/event) reporting templates which are an appendix to the Announcement of the Minister of Health regarding blood and blood component therapy in medical entities performing therapeutic activities such as stationary/inpatient and 24-hour health services [15].

Methods

Information on blood components issued to hospitals and transfused to patients was obtained from the RCKiK Poznań-database. Modified blood components were included in the study.

Modification refers to additional preparation procedures used in order to strengthen the safety of blood components and to minimize the risk of ARs. The procedures include: filtration (special filters used to obtain leukocyte-reduced RBC and PC), irradiation with γ rays (25–50 Gy) to inhibit proliferative capacity of lymphocytes in cellular blood components (prevention against transfusion-associated graft-vs-host disease, TA-GvHD), washing of RBC and/or PC with 0.9% NaCl or appropriate additive solutions to remove plasma proteins (the potential source of allergens); pathogen reduction in FFP with methylene blue.

Table 1. Correlation between symptoms and AR imputability levels according to Polish criteria [16]

Imputability		Explanation
NA	Not assessable	When there is insufficient data for imputability assessment
0	Excluded	Where there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes
	Unlikely	Where the evidence is clearly in favor of attributing the adverse reaction to causes other than blood or blood components
1	Possible	When the evidence is indeterminate for attributing the adverse reaction either to the blood or blood components or to alternative causes
2	Likely, Probable	When the evidence is clearly in favor of attributing the adverse reaction to the blood or blood component
3	Certain	Where there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the blood or blood component

Among all the reported allergic-type ARs, the study distinguished anaphylaxis as a severe, life-threatening hypersensitivity with symptoms of shock and/or loss of consciousness and dyspnea, and an allergic reaction, mainly skin-type (sporadically accompanied by dyspnea). Each AR was finally assessed in terms of relation to transfusion, according to the criteria accepted in Poland (Table 1) [16].

Statistical analysis

The results were subjected to statistical analysis using software GraphPad Prism v 6. The adult and children group were each divided into four age-dependant quartiles. Chi-squared test (Chi^2) was used in the retrospective analysis. The charts and tables also included the *p value for trend* (full name in the statistical software: *Chi-squared test for trend*). In this case, the p-value shows not so much the trend as the age-dependant differentiation in the number of ARs in adults and children. In short, it shows the percentage difference between the number of ARs in particular age groups (quartiles). A p value of less than 0.05 was considered statistically significant.

Results

The frequency of ARs in the study population was referred to/presented in relation to the number of blood components issued and/or transfused. Age-dependant use of blood components as reported by hospitals included data on the following groups: (i) below 5 years, (ii) 5–14 years, (iii) 15–44 years, (iv) 45–59 years. Separate data for adults over 60 and children below 18 was unavailable, so it was impossible to determine the ARs frequency in these study groups.

AR frequency in the study population and their differentiation in adult and children groups.

ARs occurred most frequently after transfusions of PC or FFP, and FNHTR and allergy prevailed. FNHTR occurred mostly in adults ($p < 0.001$), and allergy in children ($p < 0.0001$) (Table 2).

AR frequency depending on their intensity/severity, the type of the transfused component and the clinical condition of the patient prior to transfusion.

Mild reactions prevailed (Table 3).

Relationship between patient's death, his clinical status prior to transfusion, and intensity of ARs

In the study group of patients (n = 650) with ARs, 15 deaths were reported. Nine among adult patients hospitalized for exacerbation of the underlying disease or comorbidity (cancer, stroke, heart and kidney failure, hemorrhagic shock, advanced pulmonary tuberculosis). Their condition was severe even before transfusion.

Six patients were in fairly good condition prior to transfusion. In this group, one reported fatal case was a six-year-old operated on for a brain/cerebral tumor, who developed thrombocytopenia. The child was transfused with cryoprecipitate with donor HLA (human leukocyte antigen) antibodies class I, detected in LCT test (lymphocytotoxicity test). Five adults died after RBC therapy for anemia or gastrointestinal bleeding. An 89-year-old with gastrointestinal bleeding died of sudden cardiac arrest. Two patients died of pulmonary edema. Two deaths were ascribed to haemolysis: a 57-year-old fol-

Tabela 2. Frequency rate and differentiation of ARs in adults and children in relation to type of blood component

Type of adverse reaction (%) [frequency/100.000]	Adults n (%)	Children n (%)	Adverse reactions following RBCs n (%) [frequency/100.000]		Adverse reactions following FFP n (%) [frequency/100.000]		Adverse reactions following PC n (%) [frequency/100.000]	
			Adults	Children	Adults	Children	Adults	Children
FNHTR n = 278 (43) [29]	254 (48)	24 (19)***	221 (63) [36]	19 (28)****	16 (12) [10]	1 (7)	17 (40) [21]	4 (10)**
Allergy n = 236 (36.3) [25]	159 (30)	77 (62)****	36 (10) [11]	33 (49)****	102 (77) [62]	10 (66)	21 (50) [54]	34 (81)**
TACO n = 28 (4.3) [3]	25 (5)	3 (2)	23 (7) [4]	3 (4)	2 (2) [1]	0	0 [0]	0
Haemolysis n = 25 (3.8) [3]	23 (4)	2 (2)	19 (5) [3]	0	3 (2) [2]	0	1 (2.5) [3]	2 (4)
TAD n = 18 (2.7) [2]	18 (3)	0*	17 (5) [3]	0	1 (1) [1]	0	0 [0]	0
TRALI n = 10 (1.5) [1]	7 (1)	3 (2)	3 (1) [1]	2 (3)	4 (3) [2]	0	0 [1]	1 (2.5)
Anaphylaxis n = 8 (1.2) [1]	4 (1)	4 (3)	0 [0]	0	3 (2) [3]	3 (20)***	1 (2.5) [2]	1 (2.5)
PTP [1] n = 4 (0.6) [0.4]	2 (1)	2 (2)	1 (1) [0.3]	1 (2)	0 [0]	0	1 (2.5) [1]	0
Infections n = 2 (0.3) [0.2]	0	2 (2) **	0 [0.2]	1 (2)*	0 [0.6]	1 (7)**	0 [0]	0
Others n = 41 (6.3) [4]	33 (7)	8 (6)	31 (8) [6]	8 (12)	1 (1) [0.6]	0	1 (2.5) [1]	0
Total n (%)	525 (81) 650 (100) [68]	125 (19)***	351(67) 418 (64) [63]	67 (54)**	132 (25) 147 (23) [82]	15 (12)**	42 (8) 84 (12.8)[2] [84]	42 (34)****

[1]The table does not include PTP after cryoprecipitate transfusion in a child n = 1 (25) [5]; [2]Adverse reactions following PC transfusion 12.8%, following cryoprecipitate transfusion 0.2%; Statistical significance of children vs. adults *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; n — number of adverse reactions; (%) — percentage of adverse reactions for all reports in adults and children by type of blood component. FNHTR — febrile non-haemolytic transfusion reactions; TACO — transfusion associated circulatory overload; TAD — transfusion associated dyspnea; TRALI — transfusion related acute lung injury; PTP — post transfusion (thrombocytopenic) purpura; RBCs — red blood cells; FFP — fresh frozen plasma; PC — platelet concentrate; [frequency/100.000] — frequency per 100 000 transfused blood components

lowing arterial embolization for kidney cancer (no antibodies to RBC antigens detected in laboratory tests) and a 79-year-old woman with leg ulcer and erysipelas of the leg (anti-K antibodies detected 11 days after transfusion of 1 unit of RBC with Kell system antigens DHTR with hyperhemolysis; HHTR — hyperhemolytic transfusion reaction).

The deaths reported for patients who were in severe or fairly good condition prior to transfusion

Table 3. The frequency of ARs related to severity, type of component and the clinical condition of the patient prior to transfusion

	Condition prior to transfusion				Intesity of adverse reaction		
	No entry	Severe	Fairly good	Good	Serious	Mild	Deaths
RBC n = 418 [frequency/100.000]	40	68	282	28	70 [10]	348 [53]	13 [2]
FFP n = 147 [frequency/100.000]	12	23	97	15	15 [8]	132 [74]	1 [0,6]
PC n = 84 [frequency/100.000]	8	7	61	8	5 [5]	79 [79]	0 [0]
Cryo n = 1 [frequency/100.000]	0	0	1	0	1 [5]	0 [0]	1 [5]
Total n = 650 (%) [frequency/100.000]	60 (9)	98 (15)	441 (68)	51(8)	91 (14) [10]	559 (86) [58]	15 (2) [2]

n — number of adverse reactions; (%) — percentage of adverse reactions related to (i) condition prior to transfusion (ii) intensity of the reaction; RBC — red blood cells; FFP — fresh frozen plasma; PC — platelet concentrate; Cryo — cryoprecipitate [frequency/100.000] — frequency per 100 000 transfused blood components

Table 4. Mortality (N = 9) in patients critically ill prior to transfusion (n = 98) depending on the severity of ARs

Intensity of adverse reaction	Serious condition prior to transfusion	Deaths N (%)	p
Serious n (%)	29 (30)	7 (78)	0,0034
[frequency/100.000]	[3]	[0.7]	
Mild n (%)	69 (70)	2 (22)	
[frequency/100.000]	[7]	[0.2]	

n (%) — the number of adverse reactions (%) related to intensity of the reaction; N (%) — the number of fatal adverse reactions (%) related to the intensity of the reaction frequency/100.000] — frequency per 100 000 transfused blood components

Table 5. Mortality (N = 6) in cases of fairly good-condition prior to transfusion (n = 441) depending on the severity of ARs

Intensity of AR	Fairly good condition prior to transfusion	Mortality N (%)	p
Serious n (%)	51 (12)	6 (100)	< 0.0001
[frequency/100.000]	[5]	[0.6]	
Mild n (%)	390 (88)	0 (0)	
[frequency/100.000]	[41]	[0]	

n (%) — number and % of ARs depending on intensity; N (%) — number of ARs ending with death and % of deaths related to the intensity of reaction; [frequency/100.000] — frequency per 100 000 transfused blood components. the chi — square test was used for data analysis

occured more frequently as result of SAR (p<0,01 and p< 0,0001 respectively; Table 4, 5).

Post transfusion ARs broken down into age groups for children and adults

In children of all age groups, allergy was the most frequently reported AR (Fig. 1). The incidence rate was different for 6–11 year olds as compared to the youngest children (p < 0.01). Transfusion associated circulatory overload (TACO) and infections were reported only amongst infants (TACO *p for trend* < 0.05).

FNHTR was reported most frequently amongst adults, but no statistically significant differences were observed between age groups. Age-dependent differences in AR frequency in adult recipients were reported only for allergic reactions which most often occurred in young adults of 18–45 (p for trend < 0.01) and for TACO which mostly occurred in the eldest age group 72–93 (p for trend < 0.0001) (Fig. 2).

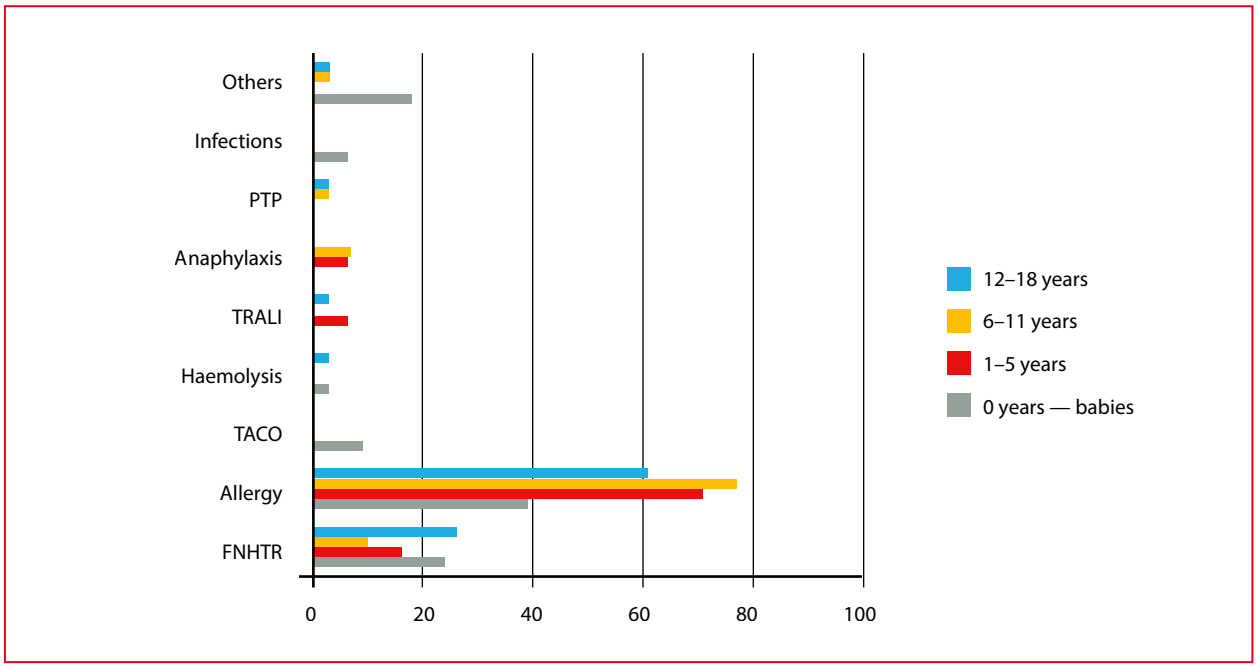

Figure 1. Age-dependent percentage of ARs in children

PTP — post-transfusion purpura; TRALI — transfusion related acute lung injury; TACO — transfusion-associated circulatory overload; FNHTR — febrile nonhemolytic transfusion reaction

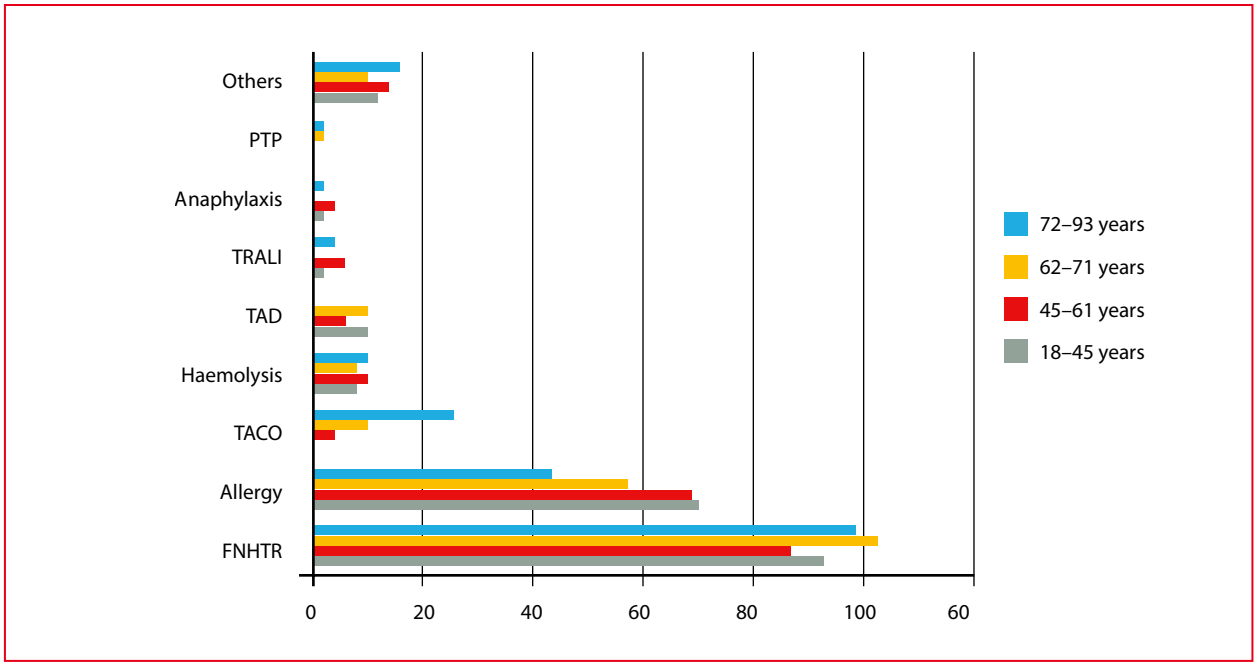

Figure 2. Age-dependent ARs in adults (%)

PTP — post-transfusion purpura; TRALI — transfusion related acute lung injury; TAD — transfusion-associated dyspnea; TACO — transfusion-associated circulatory overload; FNHTR — febrile nonhemolytic transfusion reaction

The abovementioned allergic ARs in the adult groups did not include anaphylaxis and were usually skin allergies sporadically accompanied by dyspnea.

Impact of donor age and sex on the number of reported post transfusion ARs

The highest number of reported ARs was related to blood components from men (n = 512) which correlates with the number of male donors (79%) (Table 6). Haemolytic reactions, TRALI, and anaphylaxis were most often reported following transfusion of blood components collected from women ($p < 0.05$) (Table 6).

All the anti-HLA antibodies found in the immune TRALI cases were detected in blood components from female donors aged 38–45 years (Table 7).

Impact of component modification and pre-transfusion storage time on the incidence rate of ARs

The highest number of adverse reactions related to RBC transfusion referred to unmodified component ($p < 0.0001$) (Table 8 and Table 9). For modified RBCs, the reports of FNHTR, TACO, haemolysis, TAD, etc. were less frequent. No such correlation was found for allergies (Table 8). The smallest number of adverse reactions related to RBC concerned transfusion of RBCs stored for > 28 days of collection (< 14 days vs. > 28 days $p < 0.0001$) — Table 8 and Table 9. For PC transfusions, the highest number of adverse reactions was associated with leuko-reduced PC ($p < 0.0001$) (Table 8 and Table 9). In the period under investigation, 79% of PCs issued for clinical use were subjected to filtration.

The incidence rate of ARs among adults and children, related to type of transfused component and transfusion history

More ARs were reported in patients previously treated with blood components (74% adults, 82% children; Table 10). In both multiple and first-time recipients, the largest number of reported ARs was related to RBC transfusions (Table 10).

Assessment of imputability levels of reported ARs

Conclusive evidence beyond reasonable doubt for attributing the AR to transfusion (imputability level 3) referred to no more than 20% of reported ARs and differed with regard to the type of reaction (Table 11). In the highest number of reports, TRALI was assessed as certain, allergic reactions and anaphylaxis as likely, FNHTR as probable. In 11% of reported AR cases the imputability level with transfusion and symptoms was assessed as unlikely, excluded, or not assessable (Table 11).

Discussion

Adverse reactions are associated with transfusion of 0.2–10% of blood components, and their frequency and reporting-rate depends on the efficiency of the hemovigilnce system (legally sanctioned standardization, implementation of IT tools for transmission and analysis of data) as well as responsibility and involvement of the persons who supervise the reporting of incompatibilities [7, 8, 10, 17–18].

Reports usually refer to symptoms of mild ARs but it is the serious adverse reactions (SARs) that deserve special attention because they are the life-threatening reactions [10, 17].

The most common adverse reactions reported include febrile non-haemolytic transfusion reactions (FNTR) and allergic reactions [19].

Adverse reactions in our study were related to transfusion of < 0.1% of blood components. The ARs were usually mild and mostly classified as FNHTR or allergy (80% in total).

According to literature data, there is a correlation between the type of the transfused component and the frequency of ARs [10, 20]. This is consistent with our results.

Assessment of imputability level with transfusion is often difficult because during and/or after transfusion many patients experience symptoms that may also be attributed to the underlying or concomitant diseases.

Our study results are consistent with the publication of Vidya Shree M. et al. as regards allergic reactions (imputability level: certain 11%, probable 63%, possible 26%) [21], but inconsistent with the results of Harvey et al. (imputability level: certain 52%, probable 30%, possible 18%) [10].

Donor and recipient incompatibility (biological differences) are considered the main factor affecting transfusion outcome [22].

Blood component therapy is always performed in a hospital setting and patients who require transfusion (10% of all patients hospitalized) are a heterogeneous population [23]. Pro-inflammatory mechanisms are confirmed for such diseases as diabetes, obesity, cancer, chronic kidney disorders, hypertension, hypercholesterolaemia, unstable angina pectoris, myocardial infarction, and stroke

Tabela 6. Donor sex-related adverse reactions

Donors (n = 650)	Adverse reaction		p
	Yes (%)	No (%)	
FNHTR (n = 278)			
Men (n = 512)	220 (43)	292 (57)	
Women (n = 138)	58 (42)	80 (58)	0.8430
Allergic reaction (n = 236)			
Men (n = 512)	190 (37)	322 (63)	
Women (n = 138)	46 (33)	92 (67)	0.4130
TACO (n=28)			
Men (n = 512)	24 (5)	488 (95)	
Women (n = 138)	4 (3)	134 (97)	0.3583
Hemolytic reaction (n = 25)			
Men (n = 512)	15 (3)	497 (97)	
Women (n = 138)	10 (7)	128 (93)	0.0193*
TAD (n=18)			
Men (n = 512)	16 (3)	496 (97)	
Women (n = 138)	2 (1)	136 (99)	0.2870
TRALI (n = 10)			
Men (n = 512)	5 (1)	507 (99)	
Women (n = 138)	5 (4)	133 (96)	0.0250*
Anaphylaxis (n = 8)			
Men (n = 512)	4 (1)	508 (99)	
Women (n = 138)	4 (3)	134 (97)	0.0453*
PTP (n = 4)			
Men (n = 512)	4 (1)	508 (99)	
Women (n = 138)	0	138 (100)	0.2976
Infections (n = 2)			
Men (n = 512)	1 (0,2)	511 (99,8)	
Women (n = 138)	1 (1)	137 (99)	0.3190
Others (not classified) (n = 41)			
Men (n = 512)	33 (6)	479 (94)	
Women (n = 138)	8 (6)	130 (94)	0.7810

Statistical significance *p < 0.05; n — number of adverse reactions; (%) — percentage of adverse reactions by donor sex; FNHTR-febrile non-haemolytic transfusion reactions; TACO — transfusion associated circulatory overload; TAD — transfusion associated dyspnea; TRALI — transfusion related acute lung injury; PTP — post transfusion (thrombocytopenic) purpura

Tables 7. Donor age and sex-related anti-HLA antibodies detected in blood components following ARs

Reaction (imputability)	Antibodies detected	Donor sex	Donor age (years)
TRALI (3)	Anti-HLA class I	Woman	43
TRALI (3)	Anti-HLA class I and II	Woman	45
TACO/TRALI (3)	Anti-HLA class II non-complement binding	Woman	38

TRALI — transfusion related acute lung injury; TACO — transfusion associated circulatory overload; HLA — human leukocyte antigens

Table 8. ARs related to the storage time and modification of the transfused blood component

	FNHTR (n = 278)	Allergy (n = 236)	TACO (n = 28)	Hemolysis (n = 25)	TAD (n = 18)	TRALI (n = 10)	Anaphylaxis (n = 8)	PTP* (n = 4)	Infections (n = 2)	Others (n = 41)	Total
RBC	240 (%)	69 (%)	26 (%)	19 (%)	17 (%)	5 (%)	–	2 (%)	1 (%)	39 (%)	418 (100)
No BC	185 (77)	32 (46)	20 (77)	16 (84)	14 (82)	1 (20)	–	–	–	28 (72)	296 (71)
IRBC	22 (9)	–	–	–	–	–	–	–	–	–	22 (5)
LDRBC	–	–	1 (4)	2 (11)	2 (12)	1 (20)	–	1 (50)	–	3 (8)	10 (2)
ILRBC	32 (13)	36 (52)	5 (19)	1 (5)	1 (6)	1 (20)	–	1 (50)	1 (100)	8 (20)	86 (21)
WRBC	1 (1)	1 (2)	–	–	–	2 (40)	–	–	–	–	4 (1)
RBC up to 14 days	89	38	7	9	6	3	–	1	1	21	175 (42)
RBC 14–28 days	115	24	17	6	9	1	–	1	–	13	186 (44)
RBC > 28 days	36	7	2	4	2	1	–	–	–	5	57 (14)
FFP	17 (%)	112 (%)	2 (%)	3 (%)	1 (%)	4 (%)	6 (%)	–	1 (%)	1 (%)	147 (100)
qFFP	16 (94)	106 (95)	2 (100)	3 (100)	1 (100)	4 (100)	4 (67)	–	–	1 (100)	137 (93)
iFFP	1 (6)	6 (5)	–	–	–	–	2 (33)	–	1 (100)	–	10 (7)
PC	21 (%)	55 (%)	–	3 (%)	–	1 (%)	2 (%)	1 (%)		1 (%)	84 (100)
Pooled	9 (43)	7 (13)		1 (33)	–	–	–	–	–	1	18 (21)
LPC	8 (38)	19 (34)	–	2 (67)	–	1 (100)	–	–	–	–	30 (36)
RLPC	1 (5)	17 (31)	–	–	–	–	1 (50)	1 (100)	–	–	20 (24)
LPC-Ap	3 (14)	12 (22)	–	–	–	–	1 (50)	–	–	–	16 (19)
PC 1 day	2	8	–	–	–	–	–	–	1	1	12 (14)
PC 2 days	4	4	–	1	–	1	–	–	–	–	10 (12)
PC 3 days	1	9	–	1	–	–	2	–	–	–	13 (16)
PC 4 days	10	21	–	–	–	–	–	–	–	–	31 (37)
PC 5 days	4	13	–	1	–	–	–	–	–	–	18 (21)

*RBC — red blood cells; BC — buffy coat; IRBC — irradiated red blood cells; LRBC — leukoreduced red blood cells; ILRBC — irradiated, leukoreduced red blood cells; WRBC — washed red blood cells; FFP — fresh frozen plasma; qFFP — quarantine FFP; iFFP pathogen reduced/inactivated FFP; PC — platelet concentrate; LPC — leukoreduced platelet concentrate; RLPC — reconstituted leukoreduced platelet concentrate; LPC-Ap-leukoreduced platelet concentrate from apheresis; FNHTR — febrile non-haemolytic transfusion reactions; TACO — transfusion associated circulatory overload; TAD — transfusion associated dyspnea; TRALI — transfusion related acute lung injury; PTP — post transfusion (thrombocytopenic) purpura

*The table does not include PTP following cryoprecipitate transfusion; n — number of ARs; (%) — percentage of ARs with regard to (i) type of transfused component (white lines) and (ii) pre-transfusion storage time (light gray lines), 100% are data in the dark gray lines RBC, FFP, PC

Table 9. Reported ARs related to storage time and modification of the transfused blood component

Component	Adverse reaction		p
	Yes n (%)	No n (%)	
RBCs			
RBC-no buffy coat	296 (71)	122 (29)	**< 0.0001**
RBC after modification	122 (29)	296 (71)	
RBC related to storage time	***p for trend* < 0.0001**		
< 14 days	175 (42)	243 (58)	
14–28 days	186 (44)	232 (56)	< 14 days vs. 14–28 days 0.9966
> 28 days	57 (14)	361 (86)	< 14 days vs. > 28 days **< 0.0001**
FFP			
After quarantine	137 (93)	10 (7)	**< 0.0001**
After pathogen inactivation	10 (7)	137 (93)	
PC			
Irradiated PC-pooled	18 (21)	66 (79)	**< 0.0001**
Leukocyte reduced irradiated PC	66 (79)	18 (21)	
PC related to storage time			
Up to 3 days	35 (42)	49 (58)	0.5872
More than 3 days	49 (58)	35 (42)	

RBC — red blood cells; FFP — fresh frozen plasma; PC — platelet concentrate; IPC — irradiated platelet concentrate
n = number of ARs; % of ARS; significant statistical values are marked in Bold

Table 10. ARs related to type of blood component, storage time and modification of blood component in adults and children

	Haemolysis (n = 25)	PTP (n = 4)	Allergy (n = 236)	Anaphylaxis (n = 8)	TRALI (n = 10)	TAD (n = 18)	Infections (n = 2)	FNHTR (n = 278)	TACO (n = 28)	Others (n = 41)	Total (n = 650) (%)
Multiple recipients of blood components											
RBC	17	2	49	0	5	11	1	177	15	28	305 (47)
FFP	1	0	85	4	2	0	1	11	2	0	106 (16)
PC	3	1	50	2	1	0	0	20	0	0	77 (12)
Cryo	0	1	0	0	0	0	0	0	0	0	1 (1)
Adults	19	2	119	3	5	11	–	190	15	22	386 (74)
Children	2	2	65	3	3	–	2	18	2	6	103 (82)
First-time recipients of blood components											
RBC	2	0	20	0	0	6	0	63	11	11	113 (17)
FFP	2	0	27	2	2	1	0	6	0	1	41 (6)
PC	0	0	5	0	0	0	0	1	0	1	7 (1)
Adults	4	0	40	1	2	7	0	64	10	11	139 (26)
Children	0	0	12	1	0	0	0	6	1	2	22 (18)

n — number of adverse reactions; (%) — percentage of adverse reactions; RBC — red blood cells; FFP — fresh frozen plasma; PC — platelet concentrate; Cryo — cryoprecipitate; FNHTR — febrile non-haemolytic transfusion reactions; TACO — transfusion associated circulatory overload; TAD — transfusion associated dyspnea; TRALI — transfusion related acute lung injury; PTP — post transfusion (thrombocytopenic) purpura

Table 11. ARs imputability level in the study population (n = 650)

Imputability	FNHTR	Allergy	TACO	Haemolysis	TAD	TRALI	Anaphylaxis	PTP	Infections	Others
	n = 278	n = 236	n = 28	n = 25	n = 18	n = 10	n = 8	n = 4	n = 2	n = 41
NA (n = 2) (0,3%)	1 (1)	0	0	0	0	0	0	0	1 (50)	0
0 (n = 70) (10,7%)	8 (3)	4 (1)	1 (3)	11 (44)	9 (50)	0	0	3 (75)	1 (50)	33 (81)
1 (n = 293) (45%)	201 (72)	59 (25)	12 (43)	3 (12)	9 (50)	0	0	1 (25)	0	8 (19)
2 (n = 168) (26%)	3 (1)	148 (63)	10 (36)	0	0	2 (20)	5 (62)	0	0	0
3 (n = 117) (18%)	65 (23)	25 (11)	5 (18)	11 (44)	0	8 (80)	3 (38)	0	0	0

n — number of adverse reactions; FNHTR — febrile non-haemolytic transfusion reactions; TACO — transfusion associated circulatory overload; TAD — transfusion associated dyspnea; TRALI — transfusion related acute lung injury; PTP — post transfusion (thrombocytopenic) purpura; NA — not assessable ; 0 — excluded, unlikely; 1 — possible; 2 — probable, likely; 3 — certain

[24, 25]. At this point, it is worthwhile to pay attention to such common demographic phenomenon as longer life-span and aging observed in high-income countries. This results i.a. in a higher percentage of elderly recipients of blood therapy (about 80% of components are transfused to patients over 65 [1]. At the same time, the elderly population is diagnosed with numerous age-related pro-inflammatory diseases [24]. Inflammation is also induced by the aging process itself. In literature, "inflammation" and "seno-inflammation" are used to define these relations [24, 26].

Numerous ARs observed after transfusion have confirmed pro-inflammatory background. The transfusion itself may also induce a pro-inflammatory response in the recipient [13, 23, 27].

The response of the immune system to transfusion depends on the clinical condition of the patient, so it is not always easy to determine which reaction results from the underlying disease and which may be ascribed to transfusion of a blood component [28–30].

Patients may be predisposed to the occurrence of some adverse reactions (eg. TACO in neonate, elderly and critically ill patients and high-risk heart patients) [30–32]. Our results are consistent with literature data.

Many studies discuss the potentially harmful effect of RBC transfusions on the recipient's immune system, especially if the patient is critically ill [5, 30]. Retrospective analyses in this population of patients showed that exacerbation of the clinical condition and increase in mortality rate correlates with transfusion of long-stored RBCs [33, 34]. This is not consistent with the observations of other authors [19, 30, 35].

In the population of transfused patients, deaths are more frequently reported than in those who received no blood components (7–10% vs. 3–4%) [36]. For the fatal cases, the authors have demonstrated various intensity of ARs in patients in severe and fairly good clinical condition prior to transfusion.

We also analysed the correlation between the sex of recipient and donor and occurrence of ARs. Adverse reactions were reported in 56% of women and 44% of men (group of adults), and in 57% of boys and 43% of girls (group of children). Similar data is presented by other authors [21].

Literature reports describe severe, life-threatening adverse reactions (SARs) following RBC transfusions mostly to women who had previously developed antibodies against RBCs or platelet antigens (during pregnancy, previous transfusions). The antibodies were undetected before transfusion [29, 37–38].

The correlation between TRALI and transfusion of blood components from women immunized during pregnancy was also confirmed [36, 39, 40]. Three TRALI cases were demonstrated as related to components from 38–45 aged women with anti-HLA antibodies.

According to some authors, ARs occur more frequently in multiple recipients [17]; others are of an opposite opinion, especially as regards allergy/hypersensitivity [41]. Hypersensitivity may therefore be induced no by one factor but a number of overlapping factors that ultimately result in an AR [42–43].

Larger numbers of ARs were reported in multiple transfusion-recipients as compared to patients treated with blood components for the first time (74% vs. 26%).

Although blood components issued for clinical use are liable to specific regulations, principles of good manufacturing practice (GMP) and qualitative tests, they still demonstrate high variability resulting from the differences between individual blood donors [44].

Numerous studies confirm that the origin and type of blood component as well as the preparation method and storage time have big impact on transfusion outcome [5, 20, 23, 44–47].

Over the last 20 years, numerous publications have reported adverse outcome following transfusion of long-stored RBCs [6, 30, 33], and recently also of short-stored RBCs [13, 23, 45]. Some authors, however believe that the storage lesions in RBCs have no influence on transfusion outcome and that oxygen supply to tissues is equally effective regardless of storage time [48].

FFP transfusions are controversial. On the one hand, such transfusions are believed to cause inflammation and damage to endothelial cells (increase of IL-8, IL-1 in TRALI), on the other, improved survival has been reported for trauma patients previously transfused with large volumes of FFP [49–50]. The beneficial effect of FFP transfusion remains unclear, but it seems that plasma transfusion does not induce an inflammatory response but rather has a endothelial cell stabilizing effect [49–50].

Allergic transfusion reactions and FNHTR in patients transfused with platelets stored in platelet additive solutions (PAS) are reported less frequently than reactions following transfusions of platelets stored in plasma. Suspension of platelet concentrate (PC) in a mixture of 30–40% plasma results in reduction of the incidence rate of allergic and FNHTR reactions following PC transfusions [23, 41, 51].

The frequency rate of some ARs can also be reduced by PC filtration prior to storage. This inhibits production of reactive oxygen species (ROS) [19, 41, 52, 53]. We have observed that ARs related to transfusion of unfiltered PCs were less frequently reported than for leukoreduced PCs. This may be attributed to PC filtration during storage as well as to the fact that leukoreduced components have no effect on allergy reactions which are most frequently reportable after PC transfusions [51].

Summary

Adverse reactions observed after transfusion are a rare outcome of blood component therapy. Their intensity/severity and course are affected by a multitude of recipient, donor and blood component — related factors and therefore the consequences of transfusions cannot easily be predicted. In view of the above, the benefits are most likely to outweigh the transfusion-related risks if : (i) blood components are used rationally, (ii) special attention is focused on patients susceptible to specific adverse reactions with the purpose of minimizing their occurrence, (iii) recommendations related to blood component therapy are strictly observed (iv) the knowledge regarding pathophysiology of adverse reactions is sufficient.

Conclusions

1. ARs following transfusion were less frequently reported to the Regional Blood Transfusion Center in Poznań in 2011–2018 than reflected in the published data (< 0.1% percent of transfused blood components).
2. Imputability of < 50% of reportable ARs was likely/probable (level 2) or certain (level 3).
3. Some recipient, donor, and component-related factors induce specific ARs.

Acknowledgments

The authors express their thanks to Prof. dr hab. n. med. Piotr Radziwon for his valuable contribution to the review of Bożena Andrys doctoral dissertation. The comments were referred to during the preparation of this manuscript.

Conflict of interest: none declared

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