Original article

Blood transfusion-associated anaphylaxis in perioperative- and non-perioperative patients in Western Norway 2002-2021

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Background - Anaphylaxis after blood transfusion is a feared complication accounting for severe morbidity. A retrospective study was performed at Haukeland University Hospital, Bergen, Norway, to investigate the rate and features of transfusion-associated anaphylaxis (TAA) occurring between 2002-2021.

Materials and methods - Identified cases of TAA were studied by an immunologist and an allergist to extract information about general characteristics, amplifying factors, co-morbidity, treatment, and treatment responses. TAA was reported as perioperative or non-perioperative.

Results - We identified 29 cases of TAA: 13 perioperative and 16 non-perioperative. Allergic transfusion reaction had an incidence rate of 34/100,000 transfusions and TAA a rate of 7/100,000 transfusions. The incidence of allergic reactions and TAA increased 2.6- and 6.4-fold during the study period. The first perioperative TAA was discovered 12 years into the study period but was equally frequent as non-perioperative transfusion-associated anaphylaxis in the last five years of the study period. 52% of the TAA cases had relevant co-morbidity and 100% of them had amplifying factors. Although only 38% of the non-perioperative patients received epinephrine as treatment, 94% of them had a good treatment response to their total treatment regimen. Poorer treatment response was observed with higher age, more cardiovascular- and respiratory disease, higher use of amplifying and sedating medications and a higher severity score.

Discussion - Our findings indicate that TAA, especially in the perioperative setting, is underdiagnosed. The increased incidence of TAA in our study is temporally related to the introduction of a national hemovigilance program, introduction of standardized laboratory testing for anaphylaxis and increased multidisciplinary focus on the condition. In conclusion, increased awareness of TAA, and especially in the perioperative setting, is needed. A multidisciplinary approach is necessary to improve identification and reporting of TAA.

Keywords: *anaphylaxis, blood transfusion, perioperative period, transfusion reaction, allergy, transfusion associated anaphylaxis.*

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INTRODUCTION

Allergic transfusion reaction is one of the most common complications of blood transfusion, and the overall incidence is reported to 0.1-3% of all transfusions[1-3]. Some reports estimate that 0.7-10% of all allergic transfusion reactions have a clinical presentation that is anaphylactic, which is defined as a reaction with an acute debut, systemic and generalized symptoms and findings and a severe or even life-threatening course[1,3,4]. In the Serious Hazard of Transfusion (SHOT) reports from the United Kingdom mild allergic- or anaphylactic reactions with major morbidity accounted for between 31.8-39.7% of transfusion reactions after blood transfusion, between 2019-2021[5-7]. Transfusion-associated anaphylaxis (TAA) can occur in all settings where blood components are transfused but recently there has been increased awareness around perioperative TAA[8,9]. Perioperative hypersensitivity of all causes, including blood transfusion, is an important multidisciplinary topic as it is associated with severe life-threatening reactions requiring cardiopulmonary resuscitation in 45% of cases. Plasma has been implicated in up to three percent of perioperative hypersensitivity reactions in an older study[10] but the literature lacks good estimates of the frequency of perioperative anaphylaxis related to blood transfusion.

The mechanism of allergic transfusion reactions is hypothesized to include both recipient and donor factors, and is sometimes described as a two-event model[11]. Recipient related factors may include antibodies in the patient against plasma proteins like immunoglobulin A, complement factor 3, complement factor 4, complement factor inhibitor 1, or haptoglobin or towards other allergens that are present in the blood component given[1,11-13]. Amplifying co-factors like medications, atopic disease or physical stress can also contribute to the anaphylactic course[14]. Donor related factors may include antibodies towards food, aerosols, or medications that are passively transferred to the patient during the transfusion and thereafter, upon exposure to the actual allergen, induce TAA in the recipient of the blood[11,12,15]. The importance of the recipient factors compared to the donor factors when it comes to inducing TAA is unknown. Savage and co-workers have previously reported that only 0.95% of the times when two different patients got apheresis platelets from the same donor, both had an allergic transfusion reaction[16]. This finding suggests that recipient related factors have highest impact on the risk.

Anaphylaxis requires immediate administration of epinephrine and may also necessitate treatment such as positioning on the back with lower extremities elevated, supplemental oxygen, intravenous fluid resuscitation with or without second line medications like antihistamines, bronchodilators, and glucocorticoids[12-14,17]. If a new transfusion is unavoidable, premedication with antihistamine or minimization of plasma content in the unit or use of platelets stored in additive solutions, can reduce the incidence of TAA or decrease the severity if TAA occurs[1,18].

In this study, we aimed to determine the incidence of TAA at our hospital during the last twenty years, and to describe general characteristics, amplifying factors, morbidity inducing factors, treatment and treatment responses in both in perioperative- and non-perioperative patients with this condition.

MATERIALS AND METHODS

Study design and ethical considerations

We conducted a retrospective quality surveillance study identifying all mild allergic- or anaphylactic events among patients with a reported transfusion reaction after receiving a blood component, at Haukeland University Hospital from January 1st, 2002, to December 31st, 2021. The study was approved by the local data protection officer (Personvernombudet; eProtocol No.: 2809-2809).

Data collection

During the study period, suspected transfusion reactions were reported by clinical staff to the Blood Bank at the time of occurrence. When reported, the reactions were evaluated by a specialist in immunology and transfusion medicine on call at the Blood Bank. Since 2004, reporting of transfusion reactions were further reported to the Norwegian Hemovigilance System, first on a voluntary basis, but a new legislation in 2007 made reporting mandatory[3]. The schemes for reporting reactions from the clinical wards records are the transfusion journals for the blood products transfused. In the bottom they contain a section where clinical staff describe signs/symptoms arising during or after the transfusion. These schemes have not changed significantly during the study period. Furthermore, blood products produced and transfused at the hospital remained the same during the study period.

Identification of incidents and inclusion of patients

We went through all reports of unwanted effects from the clinical wards to the blood bank at our hospital in the study period. An allergist and a specialist in immunology and transfusion medicine confirmed all TAA cases before manual extraction of demographic, clinical, laboratory, treatment, and outcome data from the hospitals electronic health record system. In cases of discrepancy, consensus was reached after a discussion of the interpretation of the retrieved data from the health records.

The first inclusion criterium for the study was that the adverse event fulfilled the clinical criteria for anaphylactic reactions as described in the world allergy organization (WAO) 2011 guidelines (*Online Supplementary* **Table S1**)[14]. Furthermore, the imputability of the TAA had to be possible, probable, or certain based on the International Society of Blood Transfusion (ISBT) grading system for adverse events after blood transfusion[19]. Certain imputability was assumed when there was conclusive evidence beyond reasonable doubt that the adverse event could be attributed to the transfusion. One example of TAA with certain imputability is when the patient has reacted allergic to blood products prior or after the TAA incidence and there were no other probable allergens. Probable imputability according to ISBT was defined when the evidence was clearly in favor of attributing the adverse event to the transfusion. We categorized anaphylactic episodes as probable TAA if the blood product was the temporally closest possible allergen. Furthermore, possible imputability was defined when the evidence was indeterminate for attributing the adverse event to the transfusion or an alternate cause. When there were one or two alternative candidates that were equally close temporally to the anaphylactic event as the blood product, we graded the imputability as possible.

Categorization of data

Clinical information was further used to grade the severity of the TAA according to ISBTs criteria[19]. Briefly, non-severe TAA (grade 1) was only symptomatically treated, severe TAA (grade 2) required more intensive care and treatment to prevent permanent damage, life-threatening (grade 3) TAA required vasopressors or intubation to prevent death and the most severe ISBT grade (grade 4) is death.

When several blood products were transfused in close relations (<4 hours) to the TAA, we assumed that it was the blood product transfused closest to the onset of anaphylaxis that induced the reaction.

Medications used by the patient within the last 24 hours were evaluated, as some medications can have a direct mast cell activating effect, some are known cofactors for lowering anaphylaxis threshold and other might influence the consciousness level, and thereby increase morbidity and mortality of an anaphylactic reaction[14]. We judged whether the treatments response was adequate by looking at whether the administered treatment gave a rapid and sufficient effect to alleviate signs/symptoms of TAA[14].

Statistical considerations

Statistical comparisons were made using GraphPad Prism version 9.4. Fisher's exact test, Mann-Whitney U test or Kruskal-Wallis test were employed to investigate statistical significance. p-values <0.05 were considered statistically significant.

RESULTS

Incidence rate of TAA

There were 1,289 reports of all types of transfusion reactions from clinical wards to the blood bank in the study period. We observed an increase in annual number of reports during the period (**Figure 1A**). To determine whether the increase in adverse effects was due to an increase in transfusions at the hospital we quantified transfusion practice at the hospital in this period (*Online Supplementary* **Figure S1**).

Total numbers of transfusions given to patients in our hospital were available from 2005 to 2021, and numbers of plasma transfusions from 2006 to 2021. From 2005 to 2021 a total of 410,743 blood units have been transfused at our hospital, mainly red blood cell concentrates (RBC; 65.5%) but also platelet concentrates (10.8%) and solvent-detergent treated pooled fresh frozen plasma (SD-FFP) units supplied by Octapharma (Octaplasma, Lachen, Switzerland) (23.3%) (*Online Supplementary* **Figure S1**). The amount of plasma transfusion at the hospital has been stable from 2006-2021. RBC transfusions, however, have declined 29% during the same period. As increased transfusion at the hospital could not explain the increased incidence of transfusion reaction reports, we more thoroughly reviewed the last six years of the study period. This evaluation indicated that the main parts of the increase in reports were due to more frequent reporting of

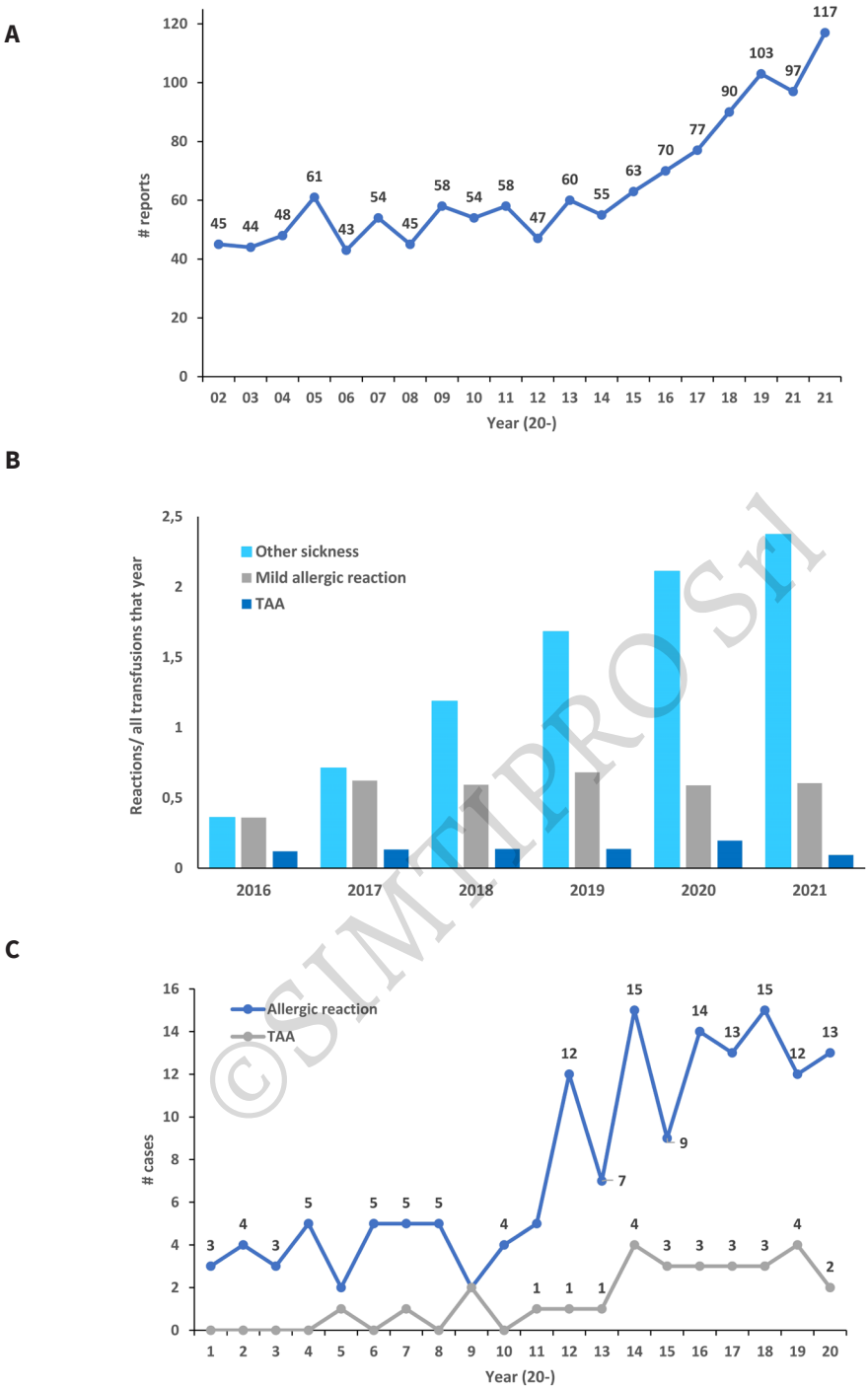

Figure 1 - Occurrence of all types of transfusion reactions, mild allergic transfusion reactions and TAA
A) The graph illustrates the transfusion reports that clinical wards have sent to the blood bank at our hospital from 2002-2021. **B**) The istogram illustrates how the blood bank has judged the transfusion reaction reports they have received from 2016-2021. Some were judged to be a reaction from a disease that is not related to the transfusion (light blue), some to represent mild allergic transfusion reactions (grey) and some were transfusion-associated anaphylaxis (TAA, dark blue). The columns represent the number of reactions of that category divided by all transfusion performed at the hospital that year. **C**) The graph exhibits the number of allergic transfusion reactions (blue line) and the number of TAA (grey line) at the hospital from 2002-2021. TAA: transfusion-associated anaphylaxis.

patient reactions that were not related to the actual blood transfusion. This indicate that the clinical wards had increased awareness around the necessity of reporting transfusion reactions. When we investigated the last six years in the study period, however, the increase seemed to consist mainly of reactions that after evaluation were deemed not related to the transfusion (**Figure 1B**).

We have registered a total of 153 mild allergic reactions (34/100,000 total blood product transfusions) in the study period (**Figure 1C**), and the incidence rate has increased from 5/22,518 blood product transfusions in 2007 to 13/21,498 blood product transfusions in 2021. Totally, 29 TAA episodes in 27 patients have occurred in the study period. The first case of non-perioperative TAA was registered in 2006 while the first perioperative TAA was registered in 2013. The total incidence rate of TAA has increased during the study period (**Figure 1C** and **Figure 2A**). As we have performed 410,743 transfusions totally from 2005-2021, the average TAA rate for this period is 7.06/100,000 transfusions. Total incidence changed from 2.8 TAA per 100,000 blood transfusions in the 2005-2006 period to 13.86 per 100,000 transfusions in the 2017-2021 period. Our incidence rate of perioperative and non-perioperative TAA increased from 0- and 2.8 per 100,000 transfusions in 2005-2006 to 6.47- and 7.39 per 100,000 transfusions respectively in 2017-2021 (**Figure 2A**).

Twenty-four of the TAA cases fulfilled only the first WAO clinical criteria for diagnosing anaphylaxis, four cases both fulfilled the first and the second criteria while one case only fulfilled the third criteria[14] (*Online Supplementary* **Table SI**). Two additional suspected TAA reactions were identified during the inclusion process. Both were perioperative reactions presenting with severe hypotension and respiratory distress in temporally close relation to blood transfusions. However, the patients did not exhibit signs from the skin or mucous membrane or had a history of allergic transfusion reactions and the cases were therefore excluded.

Of the total 29 TAA cases, 16 non-perioperative and 13 perioperative TAA cases have been registered. Of the perioperative cases (defined as a TAA occurring between 3 hours before operation to 24 hours after), one occurred preoperative, six happened intraoperative and six happened postoperative. Ten of the 29 confirmed TAA were not judged by blood bank personnel to be TAA initially and therefore not reported to the Norwegian Hemovigilance group. Because of this only 19 of our TAA cases have been included in previous scientific articles and/or EU reports[3,20].

General characteristics of the TAA patients

The median age of the patients was 55 years (mean: 47, SD: 22.9, min-max: 2-77). Most of the patients (17/29) were between 50-77 years, and no patients were older than 77

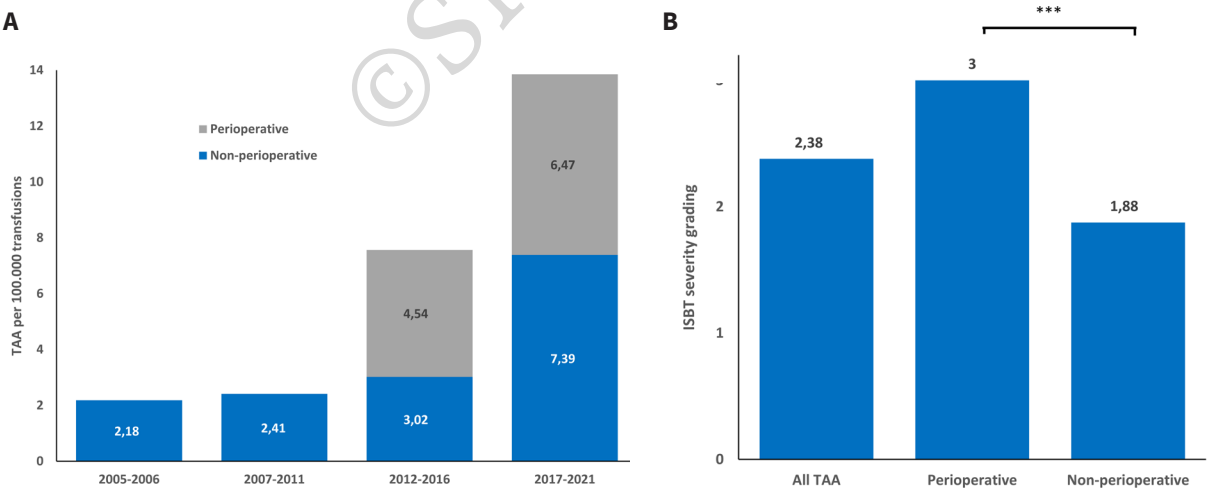

Figure 2 - Incidence rate and severity of perioperative and non-perioperative TAA

The total height of the columns in Figure **2A**) illustrates the rate of TAA per 100,000 transfusions at Haukeland University Hospital from 2005-2006, 2007-2011, 2012-2016 and 2017-2021. The blue parts of the columns are the rate of non-perioperative TAA, and the grey parts represent the rate of perioperative TAA. In Figure **2B**) the columns illustrate the ISBT severity of all TAA patients, perioperative related TAA and non-perioperative related TAA. ISBT: International Society of Blood Transfusion. ***: p<0.001; TAA: transfusion-associated anaphylaxis.

years (*Online Supplementary* **Figure S2A**). Non-perioperative patients with TAA had a median age of 27.5 years (SD: 22.9, min-max: 2-77) while the perioperative patients had a median age of 65 years (SD: 8.3, min-max: 48-72). Eight of the total twenty-nine (27.6%) TAA patients were women and only two of the thirteen perioperative related TAA cases occurred in women. In the non-perioperative group, there were a more balanced distribution (*Online Supplementary* **Figure S2B**).

When we categorized the TAA cases according to the ISBT severity scoring system, the average severity in all TAA events was 2.4. Perioperative TAA cases were more severe than non-perioperative (3.0 *vs* 1.88 respectively) (**Figure 2B**).

TAA associated symptoms and signs

Ninety seven % of the patients had a skin manifestation with flushing and urticaria as the most prevalent findings (**Table I**). Cardiovascular- and respiratory signs and symptoms were second- and third most prevalent. Notably, CNS symptoms only occurred in two perioperative patients and no one had signs/symptoms from the GI system. The two CNS signs occurred after the patients had awoken from general anaesthesia. Also, none of the TAA patients had lingual angioedema, respiratory arrest, diarrhea, bradycardia, cardiac arrest or incontinence reported in their patient journals.

Table I - *Signs/symptoms of transfusion-associated anaphylaxis*

Cutaneous			Cardiovascular			Respiratory		
Sign/symptoms	**No.**	**%**	**Sign/symptoms**	**No.**	**%**	**Sign/symptoms**	**No.**	**%**
	28	**97%**		**27**	**93%**		**23**	**79%**
Flushing	18	62%	Decreased BP	26	90%	Hypoxia	15	52%
Urticaria	18	62%	Tachycardia	17	59%	Dyspnoea	13	45%
Pruritus	14	48%	Feeling faint	12	41%	Tachypnoea	10	35%
Angioedema	9	31%	Shock	10	35%	Throat tightness	9	31%
Morbilliform rash	9	31%	Other	4	14%	Shortness of breath	9	31%
			Chest pain	3	10%	Other	7	24%
						Stridor	7	24%
						Sneezing	4	14%
						Cyanosis	2	7%
Perioperative	**13**	**100%**	**Perioperative**	**13**	**100%**	**Perioperative**	**10**	**77%**
Non-perioperative	**15**	**94%**	**Non-perioperative**	**14**	**88%**	**Non-perioperative**	**13**	**81%**

Central nervous system			Gastrointestinal			Mucosal		
Sign/symptoms	**No.**	**%**	**Sign/symptoms**	**No.**	**%**	**Sign/symptoms**	**No.**	**%**
	12	**41%**		**7**	**24%**		**7**	**24%**
Uneasiness	10	35%	Nausea	7	24%	Other	7	24%
Dizziness	7	24%	Vomiting	1	3%	Swelled lips	1	3%
Headache	1	3%	Abdom. pain	1	3%	Swelled uvula	1	3%
Aura of Impending doom	1	3%						
Altered mental status	1	3%						
Perioperative	**2**	**15%**	**Perioperative**	**0**	**0%**	**Perioperative**	**3**	**23%**
Non-perioperative	**10**	**63%**	**Non-perioperative**	**7**	**44%**	**Non-perioperative**	**4**	**25%**

The patients (No.= 29) are either perioperative (No.= 13) or non-perioperative (No.= 16). Specific signs/symptoms and their occurrence in absolute number and frequency (%) from each organ system, are listed in the rows below the "All" row. The "Sign/symptoms" row sums up all cases that have any sign/symptom in that organ system. "Perioperative" means all symptoms/signs of that category in the perioperative patients. "Non-perioperative" means all symptoms/signs of that category in the non-perioperative patients. No cases were associated with swelling of tongue, respiratory arrest, diarrhoea, bradycardia, incontinence and cardiac arrest.

Probability of an association between transfusion and TAA

The average imputability in our cohort of TAA was 3.4 (**Table II**). Four in score implies certain relationship between the transfusion and the following reaction. Non-perioperative and perioperative TAA reactions had an average score of 3.7 and 3.1 respectively. Four TAA patients had previously experienced allergic reactions to blood transfusion. Of these, three had previously reacted to platelet transfusions and one to a SD-FFP transfusion. Two of the earlier reactions were TAAs. Four patients experienced a new TAA after the first. Both RBC (No.=1), platelets (No.=1) and SD-FFP (No.=2) caused TAA in the four first TAA reactions. TAA debuted 24.4 minutes after start of transfusions on average, and there was no significant difference between debut of perioperative or non-perioperative reactions (mean: 21.9 *vs* 30.3 minutes) or between debut according to type of blood products used.

Blood products associated with TAA

Platelet transfusions were most commonly associated with TAA (*Online Supplementary* **Table SII**). The incidence rates of TAA after SD-FPP-, platelet- and RBC transfusion were 11.47-, 29.38- and 1.86 per 100,000 transfusions of the product type, respectively. TAA episodes were most prevalently associated with SD-FPP transfusion in perioperative reactions (77%), while platelet transfusions were most prevalent in the non-perioperative reactions (69%). Other blood products transfused within four hours prior to the TAA might also be responsible for the reaction and are listed in *Online Supplementary* **Table SII**[14].

Pre-treatment, treatment, and response

TAA developed despite administration of premedication in 59% of the TAA cases (**Table III**). While 92% of the perioperative TAA cases received relevant premedication, only 31% of the non-perioperative did the same. We classify epinephrine as a premedication as this medication probably inhibits the development of TAA[14]. Many of the perioperative patients in this study used this as part of the effort to regulate blood pressure in the perioperative period.

Treatment of TAA was most often glucocorticosteroids, but a majority also received epinephrine, norepinephrine or fenylepinephrine. The latter three were used in all

Table II - *ISBT probability grading of the relationship between anaphylaxis and transfusion*

Temporal association (min)	Allergic TR before (B) or after (A)	Possible allergens beside blood?	ISBT probability grading
Non-perioperative patients			
35	B	No	4
40	B	No	4
40	0	No	4
5	0	No	4
30	0	No	4
50	0	Yes, less likely	3
20	0	Yes, less likely	3
5	A	No	4
10	0	No	4
50	0	No	4
40	0	Yes, less likely	3
5	0	Yes, less likely	3
15	0	Yes, less likely	3
45	A	No	4
50	B	No	4
45	B	No	4
Perioperative patients			
20	0	Yes, less likely	3
15	0	Yes, dextrane	2
10	0	Yes, less likely	3
20	0	No	4
10	A	No	4
20	0	No	4
45	0	Yes, Imovane	2
75	0	Yes, less likely	3
5	0	Yes, protamine	2
50	0	Yes, gentamicin/cefazolin	2
5	0	Yes, less likely	3
5	0	No	4
5	A	No	4

The table describes how we have categorized the reactions with regard to the possibility that it is the blood transfusion that caused the anaphylactic reaction. We have used the proposed International Society of Blood Transfusion (ISBT) categories to achieve this. In the table several of the important factors for this categorization are visualized. We show how temporally close the reaction occurs to the transfusion in minutes (min), we show if the patient had an allergic transfusion reaction (TR) to blood products before (B) or after (A) the TAA, we show whether there are other possible allergens that could have caused the reaction and name them, and lastly, we show what ISBT probability grade we conclude is present in that cases. The boxes are increasingly grey with increased probable relationship between the transfusion and the anaphylactic reaction according to the ISBT grading system (a high number equals high probability that the transfusion caused the anaphylactic reaction). TAA: transfusion-associated anaphylaxis.

Table III - *Pre-treatment, treatment and response*

	All		Perioperative		Non-perioperative		p-value
	No.	%	No.	%	No.	%	
	Pre-treatment						
All types of treatment	**17**	**59**	**12**	**92**	**5**	**31**	**
Epi. /norepi./fenylepi.	13	45	12	92	1	6	***
Glucocorticoid	8	28	4	31	4	25	n.s.
H1 antihistamine	3	10	0	0	3	19	n.s.
	Treatment after reaction						
All types of treatment	**29**	**100**	**13**	**100**	**16**	**100**	n.s.
Epi. /norepi./fenylepi.	19	66	13	100	6	38	***
Glucocorticoid	26	90	13	100	13	81	n.s.
H1 antihistamine	23	79	8	62	15	94	n.s.
O_2 supplement	20	69	13	100	7	44	**
Fluids (clear)	19	66	12	92	7	44	**
Fluids (SD-FFP)	4	14	4	31	0	0	*
Bronchodilators	7	24	3	23	4	25	n.s.
Other vasopressors	12	41	11	85	1	6	***
Treatment response	**23**	**79**	**8**	**62**	**15**	**94**	n.s. (p =0.06)
Recommended future premedication	**15**	**52**	**3**	**23**	**12**	**75**	**

The table shows the pretreatment, treatment, treatment response and possible recommended future pretreatment, that the TAA cases received. The p-value was calculated by statistically testing whether there was a difference between the results from the perioperative group of TAA's, and the non-perioperative group. We judged there to be a treatment response if the response to the treatment was rapid and adequate to alleviate signs/symptoms of severe TAA.
n.s. = not significant; *: p<0.05; **: p<0.01; ***: p<0.001; TAA: transfusion-associated anaphylaxis; Epi: epinephrine, H1: Histamine 1, SD-FFP: solvent-detergent treated pooled fresh frozen plasma.

perioperative TAAs but only 38% of non-perioperative TAAs. O_2 supplementation, fluids therapy and treatment with other vasopressors than epinephrine, norepinephrine or fenylepinephrine, were also more commonly in the reactions associated with surgery, compared to the ones that were not associated with this.

Perioperative TAA seemed less responsive to treatment than non-perioperative (good response in 62 *vs* 94% respectively) but the differences were not significant.

Risk factors and potential amplifying factors for TAA

All the TAA reactions were associated with an amplifying factor (**Table IV**). Most prevalent were some form of stress for the patients (100%) or use of opioids (72%). We defined stress as a substantial increase in physical or mental strain.

Of investigated factors predisposing for a more severe or fatal outcome of the TAA, cardiovascular disease was the most prevalent (52%). This concomitant disease was more frequent in perioperative patients than non-perioperative patients.

DISCUSSION

In this study, we show that awareness, recognition and legal requirements lead to an increase in reports of TAA both in non-perioperative and perioperative patients. The total incidence rate during our study period of twenty years was 7.06 per 100,000 transfusions. Our rate of TAA is in accordance with the rate reported from the Biomedical Excellence for Safer Transfusion (BEST) Collaborative in 2016[1]. The reported TAA in the United States in 2015 and in the United Kingdom between 2019-2021, range between 1.77-3.3 per 100,000 transfusions[5-7,12]. The rate of TAA in Norway has previously been reported to be 2.5 per 100,000 transfusions[3]. We think there are several reasons for the discrepancy between the results: firstly, estimates

Table IV - *Potential amplifying factors and risk factors for severe TAA*

	All		Perioperative		Non-perioperative		p-value
	No.	%	No.	%	No.	%	
Potential amplifying factors							
Stress	29	100	13	100	16	100	n.s.
Opioids	21	72	13	100	8	50	**
Infection	17	59	7	54	10	63	n.s.
Chemotherapy/radiation	14	48	0	0	14	88	***
Anamnestic allergy	14	48	6	46	8	50	n.s.
Cold/heat	12	41	7	54	5	31	n.s.
NSAIDs	8	28	7	54	1	6	**
Alcohol	2	7	2	15	0	0	n.s.
Exercise	2	7	1	8	1	6	n.s.
Risk factors for severe/fatal TAA							
Decreased recog. of symptoms							
Sedatives	9	31	6	46	3	19	n.s.
Sleeping medicines	9	31	9	69	0	0	***
Alcohol	2	7	2	15	0	0	n.s.
Concomitant disease							
Cardiovascular disease	15	52	12	92	3	19	***
Asthma/resp. disease	6	21	4	31	2	13	n.s.
Depression	1	3	0	0	1	6	n.s.
Concurrent medication							
ACE-inhibitor	6	21	4	31	2	13	n.s.
β adrenergic blocker	10	34	7	54	3	19	n.s.

The table is an overview of potentially amplifying factors and risk factors for severe TAA that were present in the patients that experienced the TAA. No persons had very low or very high age as a risk factor. Also, no person in this patient cohort had mastocytosis or used antidepressants. The p-value was calculated by statistically testing whether there was a difference between the results from the perioperative group of TAA's, and the non-perioperative group. n.s. = not significant; *: p<0.05; **: p<0.01; ***: p<0.001; TAA: transfusion-associated anaphylaxis; NSAIDs: nonsteroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme.

from both the United States, the United Kingdom and Norway depend on passive reporting to the national hemovigilance systems by persons with a busy schedule and varying experience with allergy. A more active search for signs and symptoms in the patient's journals by our experts revealed more cases with TAA in our study. Secondly, several studies indicate that intraoperative TAA is probably underreported in the hemovigilance systems[8,9] and our results supports this. The first time we detected a perioperative TAA case was twelve years into the study period (**Figure 2**). The low rate of perioperative TAA might both be attributable to the difficulty of diagnosing, lack of time or motivation to report reactions, or a combination[8,9]. Identification of the blood product as a causal factor for the reaction, when several drugs and substances are administered simultaneously during anaesthesia and surgery, is difficult.

Domen *et al.* found that platelet transfusions are more often associated with TAA than fresh frozen plasma (FFP) and erythrocyte transfusions[2]. Moreover, the incidence of SD-FFP associated TAA is probably even lower than when FFP is used[21]. Our results support this as the probability

of experiencing a TAA in our study is approximately three times higher when receiving platelets compared to SD-FFP and approximately 15 times higher when receiving platelets compared to erythrocyte transfusions.

A retrospective series of allergic- and anaphylactic transfusion reactions in Cleveland, USA from 1993-2001 indicated that 90.5% of patients had a cutaneous sign of the reaction[2]. A United Kingdom study of general perioperative anaphylaxis with different types of allergens identified skin manifestations in 56% of all cases, and it was seldom the presenting feature[22]. In our study most patients had a skin manifestations/mucocutaneous signs. Only one patient without skin manifestations/mucocutaneous signs were included, and this was because the patient in addition to a clear involvement of the cardiovascular- and the central nervous system also previously had experienced a TAA and therefore fulfilled the third WAO criteria. Two other patients were excluded even though they had severe hypotension and signs from the respiratory system shortly after start of transfusion, as the patients did not have symptoms from the skin/mucocutaneous system or previous allergic reaction to blood transfusion. Both reactions occurred in perioperative patients with less possibility to report subjective symptoms and signs. The operative setting can also probably mask modest symptoms from the skin/mucocutaneous system[22].

We observed distinct differences between perioperative and non-perioperative TAA cases. Firstly, perioperative TAA cases appear in an older patient population (*Online Supplementary* **Figure S2A**). This is partly because advanced paediatric surgery is centralized to another Norwegian hospital, Oslo University Hospital. Also, in the perioperative patients requiring blood transfusion, cardiovascular patients are an important group, and they are in general of advanced age. Patients over 80 years old are often denied advanced cardiovascular operations due to increased surgical risk. This might explain the absence of perioperative TAA over 72 years[23].

Perioperative and non-perioperative TAA cases also differed regarding gender in our study. TAA cases predominantly occurred in males (*Online Supplementary* **Figure S2B**) as opposed to the higher frequency of anaphylaxis in adult females reported in literature. Hypothesized reasons for the female predominance is higher levels of female sex hormones (oestrogen and progesterone)[24]. Our results show that the male dominance is especially pronounced in the perioperative TAA. Blood requiring surgery like cardiovascular surgery is more often performed on males than females, and this may be the reason for the high proportion of males among our TAA cases.

Regarding clinical presentation of the TAA, fewer perioperative- than non-perioperative patients exhibit signs and symptoms from the central nervous- and the gastrointestinal system. This is understandable as perioperative patients are often anesthetized (**Table I**). Cardiovascular monitoring is uncommon in non-perioperative TAA patients, and we think this is the reason that cardiovascular sign and symptoms are less often reported in our non-perioperative TAA patients. It is important to know these differences, as lacking recognition of these criteria might lead to delayed clinical diagnosis and treatment.

Both physical and psychological stress are augmenting factors for induction of anaphylaxis[14,25,26]. All our TAA patients experienced stress. Surgery and chemotherapy were common stress inducing factors (in 45% and 48% of all patients respectively)[25]. Mechanisms causing the augmenting effects are poorly understood but increment of plasma osmolarity with following mast cell activation in physical stress, and neuropeptidase stimulation of mast cells in psychological stress, are hypothesized explanations[26-28]. Stress can also affect several aspects of mast cell function, like survival, activation and secretion of various proinflammatory and vasodilatory mediators, such as histamine, cytokines, nitric oxide and proteases[28].

All our patients had a co-factor possibly amplifying the TAA reaction. Co-factors have been documented in about 30% of anaphylactic reactions in one study[29], but all our patients were hospitalized in a tertiary hospital, and this might explain our high number of patients demonstrating co-factors.

It is highly recommended that all patients with anaphylactic reactions should receive prompt intramuscular administration of epinephrine (adrenaline, grade 1A evidence)[1,4,13,14,17]. Only 59% of the reported TAA cases in this study, however, involved early administration of this treatment. 92% of the perioperative patients

received epinephrine, but only 31% of the non-perioperative patients. Swift treatment is especially important in perioperative TAA cases, as these patients more often have cardiovascular- and respiratory diseases, are exposed to amplifying factors, are older, and demonstrate more severe anaphylactic reactions than the non-perioperative patients in our cohort. Together, this makes perioperative patients especially vulnerable[14,30,31] and this might explain that only 64% of these patients had a rapid and good treatment response (**Table III**).

There were no reports of TAA related fatalities among the 410,743 blood transfusions in the study period. This is in harmony with previous reports from the United Kingdom, the United States and Norway[3,5-7].

There are several limitations in our study. Firstly, it is a retrospective and descriptive study, which does not prove causal relationship. Secondly, we have chosen to adhere to the WAO 2011 criteria, although there is no full agreement of all specific criteria for the anaphylaxis diagnosis globally[32,33]. Subsequently, we might not refer all TAA cases that might have been found with different sets of anaphylaxis criteria. Thirdly, the study was conducted at one study location and extrapolation of the results should be done with caution.

CONCLUSIONS

In conclusion, our study indicates that TAA is a more prevalent complication to blood transfusion than currently reported. There is a need for further discussion and harmonization of diagnostic criteria for TAA. A multidisciplinary approach is key to diagnose and evaluate anaphylaxis[1,13]. Furthermore, perioperative associated TAA needs increased awareness. Our results indicate that perioperative TAA: 1) exhibits different clinical signs and symptoms than non-perioperative TAA, 2) often occurs after plasma transfusion, 3) often occurs together with amplifying factors, 4) is associated with risk factors for severe or fatal anaphylaxis and 5) is often more severe than non-perioperative TAA. Despite this, we observed no fatalities, and this might be partly due to the frequent use of epinephrine when these reactions occurred.

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AUTHORSHIP CONTRIBUTIONS

BE: conceptualization, methodology, formal analysis, investigation, data curation, visualization and writing original draft and editing. MBA: validation, data curation, formal analysis, investigation and writing- review and editing. TOA: conceptualization, methodology, writing review and editing, resources, visualization and project administration.

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