Part I: ATTACH SAFETY

A phase IV observational study of the safety of plasma reduced platelet products

part of the

ATTACH program

ATTACH

Analysis of

Thrombocyte

Tr**A**nsfusions in

Cardiothoracic surgery &

Hematology

The ATTACH SAFETY study is part of the ATTACH program. The ATTACH program comprises the following studies:

program	part	study
ATTACH	**I**	**SAFETY** A phase IV observational study of the safety of plasma reduced platelet products
ATTACH	**II**	**EFFICACY** Observational study of the efficacy of (plasma reduced) platelets in **A** **cardiothoracic patients** and **B** **hematologic patients**
ATTACH	**III**	**COST-EFFECTIVENESS** Observational study of the cost-effectiveness of (plasma reduced) platelets in **A** **cardiothoracic patients** and **B** **hematologic patients**

SAFETY study **part I** of the
ATTACH Analysis of **T**hrombocyte **T**r**A**nsfusions in **C**ardiothoracic surgery and **H**ematology **program**

Short title:	the **ATTACH SAFETY** study
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LIST OF ABBREVIATIONS

ATR	adverse transfusion reaction
BC	buffy coat
BTD	bloed transfusie dienst
CT	computer tomografie
DVT	deep venous thrombosis
EIN	eenheid identificatie nummer
EPD	electronisch patiëntendossier
EZIS	electronisch zorg informatie systeem
GBA	gemeentelijke basisadministratie
GLIMS	genomic laboratory information management system
KCD	klinisch consultatieve dienst
LMR	landelijke medische registratie
PACS	picture archiving en communication system
PAS	platelet additive solution
PE	pulmonary embolism
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
TRIP	transfusie- en transplantatiereacties in patiënten
TRIX	transfusie register irregulaire antistoffen en x-proefproblemen

SUMMARY

Rationale Platelet transfusions are used to prevent and treat bleeding in patients with thrombocytopenia or thrombocytopathy. To reduce the number of ATRs, plasma reducing strategies for platelet products have been developed, such as PAS. Currently, both PAS and plasma-stored platelets are used. Studies in relatively small and select patient populations suggest that platelets stored in PAS induce fewer side effects than plasma-stored platelets. However these studies did not examine whether PAS-stored platelets also reduce the risk of adverse reactions in routine clinical practice in non-specified patient populations. This study is designed to compare the incidence of ATRs of PAS-stored platelets and plasma-stored platelets now that PAS-stored platelets are regularly used in the general patient population.

Objectives

1. To assess the occurrence of ATRs of plasma reduced platelet concentrates (PAS / hyperconcentrate) as compared to plasma-stored platelets in patients during hospital stay.
2. To monitor current and possibly also new products in a systematic and continuous way.

Endpoints

Primary endpoint

1. transfusion reactions (including bacteremia) during hospital stay

Secondary endpoints

2. DVT or PE during hospital stay (confirmed by ultrasound of the leg or CT chest imaging respectively)
3. Myocardial infarction or ischemic stroke during hospital stay
4. Mortality within 30 days after a platelet transfusion

Study design and patient population

Methods Routinely collected data will be gathered from electronic files (EZIS, EPD, GLIMS and TRIX) in participating hospitals, the national hemovigilance office (TRIP) and the LMR.

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1. INTRODUCTION AND RATIONALE

1.1 Platelets

Platelet transfusions are used to prevent and treat bleeding in patients with thrombocytopenia or thrombocytopathy.[1] Nationwide, over 57,000 platelet products were transfused in 2012.[2] In the Netherlands, the most commonly used platelet product is prepared from 5 ABO-D identical BCs derived from the whole-blood collection of five donors and the plasma of one of the five donors who must be male and has never received a blood transfusion. This product has a volume of 340 mL with approximately 390 x 10^9 platelets per unit. As an alternative to plasma, it is alternatively possible to add preservation fluid (PAS) in a proportion of 1:2 to the 310 ml, yielding 340x 10^9 platelets. All platelet products are leukocyte reduced (the number of leukocytes is < 1 x 10^6 in 95% of the products). Each donor and donation is tested for several infections according to the national blood bank guidelines and applicable laws to ensure blood product safety. Platelet concentrates are stored at room temperature under constant agitation for a maximum of 5 - 7 days, depending on the type of storage medium (7 days for plasma and PAS III, 5 days for PAS II). Apart from bacterial testing, all products are tested for swirl, pH. and platelet content. Hyperconcentrated platelets, used in some hospitals as a volume and/or plasma reducing strategy, are prepared by adding an extra centrifugation step with resuspension into a smaller volume (15 - 20 mL) of plasma. This hyperconcentrate is put into a syringe and is only usable for 3 hours. Apheresis platelets (single donor platelets) are obtained from one, often selected, donor and used for special indications like IUT or patients with HLA and/or HPA antibodies. For an overview of the above mentioned platelet products, see table 1.[1]

platelet product	specifications	storage time
plasma	340 mL 390 x 10^9 platelets	7 days
PAS	310 mL 340 x 10^9 platelets	5 days (PAS II) 7 days (PAS III)
hyperconcentrate	< 20 mL (adults) 7 - 10 mL (paediatric)	3 hours
apheresis	150 – 400 mL 250 - 500 x 10^9 platelets	7 days

Table 1: Platelet products and their characteristics

1.2 Safety

Transfusion of blood products, in particular platelets, may cause ATRs which can compromise the safety of patients. The most frequent reactions following platelet transfusion are non-hemolytic (febrile) reactions, bacteraemia, allergic reactions, TRALI and TACO.[2] To decrease the incidence of transfusion reactions, and thereby increase product safety, several modifications in production and storage have been applied including leukocyte and plasma reduction. Pathogen reduction techniques have been developed in the past few decades and are currently the subject of clinical trials[3 4 5].

Several studies have suggested that plasma (cytokines and other proteins) in platelet products is an important cause of ATRs.[8] The removal of plasma from the platelet product looked effective in reducing the incidence of adverse reactions.[3] Subsequently, PAS was developed as an alternative to plasma in which to store the platelets. It has been suggested that the use of PAS significantly decreases the occurrence of adverse reactions during platelet transfusions. If this is true, and clinical efficacy is not inferior, it may be beneficial to introduce the use of PAS for all platelet products[6 7 8]. The aim of this study is therefore to compare the occurrence of ATRs between patients treated with platelets stored in PAS with platelets stored in plasma now that PAS-stored platelets are regularly used in the general patient population.

2. OBJECTIVES

1. To assess the occurrence of ATRs of plasma reduced platelet concentrates (PAS / hyper concentrate) as compared to plasma-stored platelets in patients during hospital stay.
2. To monitor current and possibly also new products in a systematic and continuous way.

3. DESIGN

Study design: a phase IV study in 22 Dutch hospitals
Duration: in 2 years (2014 and 2015) data from 2006 to 2015 will be collected
Setting: part of the ATTACH program in which PAS-stored platelets will be compared to plasma-stored platelets with regard to efficacy and cost-efficacy

4. POPULATION

4.1 Hospitals

All patients receiving platelet transfusions between January 2006 and January 2016 in the participating hospitals. We intend to include the following hospitals:

AMC	Haga Ziekenhuis
Maastricht Universitair Medisch Centrum	Isala Klinieken
Erasmus MC	Jeroen Bosch Ziekenhuis
LUMC	Maxima Medisch Centrum
UMC Sint Radboud	Meander Medisch Centrum
UMCG	Medisch Centrum Alkmaar
UMCU	Medisch Centrum Leeuwarden
VU Medisch Centrum	Medisch Spectrum Twente
Albert Schweitzer Ziekenhuis	Onze Lieve Vrouwe Gasthuis
Amphia Ziekenhuis	Sint Antonius Ziekenhuis
Admiraal de Ruyter Ziekenhuis	Sint Elizabeth Ziekenhuis Tilburg
Catherina Ziekenhuis	

4.2 Inclusion and exclusion criteria

Inclusion: all patients receiving a platelet transfusion. There are no exclusion criteria.

4.3 Expected number of inclusions

According to the data of previous years, we estimate that the above mentioned hospitals together transfuse about 40.000 platelets per year. The study is partly retrospectively and partly prospectively and data will be collected from January 2006 until January 2016. It is anticipated that about 17 of the 22 hospitals will and can fully participate, giving 17 / 22 hospitals * 40,000 platelet transfusion yearly * 4 years ≈ 120,000.

4.4 The value of the measured incidences in these populations

The main endpoint is the comparison between the occurrence of adverse transfusions reactions in transfusions with PAS-stored versus plasma-stored platelets. With data of 120.000 platelet transfusions we can make a proper estimation of the actual incidence of transfusion reactions. It is important to notice that there is no null hypothesis that we want to reject or confirm. The expected 95% confidence interval can be calculated with this formula:

$$p \pm 1.96 \times \sqrt{\frac{p\,(1-p)}{n}}$$

In which p is the proportion of transfusion reactions in the study population and n is the number of platelet transfusions in the population.

For plasma-stored platelets, based on the previous TRIP report, we expect a transfusion reaction incidence of 0,006. About 75% of the platelet transfusion in the participating hospitals are with plasma-stored platelets, so the number will be approxemately 90,000. This gives:
0.006 ± 1.96 * √ ((0.006 * 0.994) / 90,000)
0.006 ± 0.000504549
0.006 (0.005495451; 0.006504549)
This means that if this study would be repeated 100 times, 95 of the 100 times the measured incidence of transfusion reactions in plasma-stored platelets would be between 5.5 and 6.5 per 1000 platelet transfusions.

According to two previous studies we expect a reduction of ATRs of about 50% by changing from plasma-stored platelets to PAS-stored platelets[9 10]. If we see a reduction of 50% in this study, this would translate to an expected transfusion reaction incidence of 3 per 1000 in the PAS-stored platelets. About 25% of the platelet transfusions in the participating hospitals are with PAS-stored platelets, so the number will be approximately 30,000 In this case the confidence interval of the incidence of transfusion reactions in PAS-stored platelets would be:
0.003 ± 1.96 * √ ((0.003 * 0.997) / 30,000)
0.003 ± 0.000618876
0.003 (0.002381124; 0.003618876)
This means that if this study would be repeated 100 times, 95 of the 100 times the measured incidence of transfusion reactions in PAS-stored platelets would be between 2.4 and 3.6 per 1000 platelet transfusions.

5. METHODS

5.1 Endpoints

Primary endpoint

1. transfusion reactions (including bacteremia) during hospital stay

Secondary endpoints

2. DVT or PE during hospital stay confirmed by ultrasound of the leg or CT chest imaging respectively
3. Myocardial infarction or ischemic stroke during hospital stay
4. Mortality within 30 days after a platelet transfusion

5.2 Overview of all required data

a) Patient characteristics

parameter	baseline	follow-up	general source	LUMC specific
date of birth	X		BTD	GLIMS
gender	X		BTD	GLIMS
diagnosis	X		BTD, patient dossier	GLIMS
known alloantibodies	X		BTD	GLIMS
previous transfusions	X		BTD	GLIMS
heigth	X		patient dossier	EZIS
weight	X		patient dossier	EZIS
ABO-RhD bloodgroup	X		BTD	GLIMS
bacteraemia	X	X	BacLab	GLIMS
deep venous thrombosis	X	X	leg ultrasound	PACS
pulmonary embolism	X	X	CT chest	PACS
Myocardial infarction	X	X	Troponines, patient dossier	GLIMS, EZIS
Ischemic stroke	X	X	CT-brain	PACS
death	X	X	patient dossier, LMR	EZIS, LMR
erythrocyte transfusion	X	X	BTD	GLIMS
plasma transfusion	X	X	BTD	GLIMS

b) Platelet transfusion characteristics

parameter	baseline	during	post	source
date/time of transfusion	X			BTD / patient dossier
indication	X			BTD / patient dossier
Eenheid Identificatie Nummer unique product number	X			BTD / patient dossier
product type	X			BTD / patient dossier
ABO-Rh D product	X			BTD / patient dossier
donation date	X			Progesa / BTD
irradiated	X			BTD
blood pressure	X	X	X	transfusion report / patient dossier
pulse rate	X	X	X	transfusion report / patient dossier
body temperature	X	X	X	transfusion report / patient dossier
ATR		X	X	BTD / TRIP
ATR symptom(s)				BTD / TRIP
ATR classification (see appendix)			X	BTD / TRIP
ATR severity (see appendix)			X	BTD / TRIP
ATR imputability (see appendix)			X	TRIP

5.3 Study procedure

We will ask the 22 largest hospitals in the Netherlands (in terms of platelet transfusions) to participate in the study. We intend to collate the relevant information, as currently recorded by the (hemovigilance officer in the) participating hospitals, of all platelet transfusions performed in these hospitals. The BTD of every hospital orders blood products from Sanquin and coordinates their issue to the hospital wards. This means that all issued platelet concentrates can be traced via the BTD.

It is important to note that the participating centres will undoubtedly differ with regard to ordering logistics, transport, administration and evaluation of transfusions. Furthermore, patient as well as transfusion data will be collected and registered differently. The study procedures will need to be adapted to align with local systems in each participating centre. This section summarizes the general study procedures applied to the LUMC system (as an example).

5.4 Data collection

5.4.1 Request platelet product

When a doctor orders a blood product, a digital (EZIS) or paper form is completed and sent to the BTD. This transfusion request form includes the requesting ward and the following patient characteristics: patient name, identification number, date of birth and gender. The patient name will not be used in this study and the patient identification number will stay in the hospital. Instead we will link every patient number to a unique study identification number so the data will be handled anonymously once leaving the hospital. The key linking the hospital patient identification number and our study identification number will stay in the hospital concerned. In the request the physician should also state the indication for the transfusion, diagnosis of the patient, and relevant medical history (previous transfusions, pregnancies, organ transplantations and known antibodies) – information which is unfortunately missing on many forms. We will use additional methods to complement the supplied information on the indication and diagnosis: the TRIP form in the case of a reaction, LMR or patient dossier, which in the LUMC is mostly electronic in EZIS although some wards use Metavision or EPD. From the patient dossiers we also intend to record height, weight and medical history.

5.4.2 Processing of the request

When a platelet unit request form arrives at the BTD, the date and time of reception are recorded and the electronic national database TRIX is consulted to ascertain whether there is a history of relevant alloantibodies, hematopoietic stem cell transplantations or problems with previous

transfusions or pregnancies. Furthermore the ABO and Rhesus blood group are determined twice before a compatible platelet unit is issued. Each issued product is accompanied by a form containing the relevant patient data and the following product characteristics: product type (platelets, red blood cells or plasma), platelet storage medium (PAS or plasma), the EIN, which is a unique product identification code), the blood group of the product and whether the product is irradiated. We will collect all the above mentioned data from GLIMS (the electronic laboratory information system used by the BTD) and if necessary from other systems used by the BTD.

5.4.3 Administration of the product

Before the product is administered to the patient, the nurse first checks whether the patient identifiers mentioned on the product bag match the intended patient characteristics (i.e. whether this product is really meant for this patient). Once the blood pressure, heart rate and body temperature are checked, the product is administered to the patient according to the standard procedures. During and following the transfusion, the patient's condition and vital parameters are checked as well (according to the CBO guideline). These data are currently recorded in the patient dossier (EZIS, Metavision or EPD) from which we will collect this information.

5.4.4 Evaluation of the transfusion

After the transfusion has been completed, the nurse completes a transfusion report form to confirm that the product was actually administered and to record whether an ATR occurred. In the case of an ATR, the date, time, symptom(s) and vital parameters are recorded on this form in accordance to the hospital guidelines. All the forms are sent to the BTD and the forms which record occurrence of an adverse reaction are later collected by the hemovigilance officer. The hemovigilance officer will collect additional data to classify and grade the adverse reaction. All adverse reactions will also be reported to the responsible authorities, namely TRIP in all cases, and hospital board of directors as well as the competent authority, the health care inspectorate, in case of any severe adverse reactions. For this study, the hemovigilance officer will link the hospital patient identification number to a unique study identification number and thereby anonymize the patient information. The key between the hospital patient identification number and our unique study identification number will be kept in the concerning hospital. In order to estimate the incidence of ATRs and to gather all relevant additional transfusion information, we will request copies of the transfusion report forms concerning adverse reactions from the hemovigilance employee and the remaining forms from the BTD. After obtaining permission from the participating hospitals, we will request the full reports of transfusion reactions as submitted to TRIP and link these to the relevant EIN numbers.

5.4.5 Follow-up

The follow-up period per patient starts at the time of the first platelet transfusion and ends up to a maximum of 30 days after the last monitored platelet transfusion. During follow-up, we will also register whether the patient received erythrocyte or plasma transfusions. These data will be collected from the BTD. Of all patients who received a platelet transfusion the CT thorax, leg ultrasounds and blood culture reports will be collected to estimate the amount of DVT, PE and bacteraemia. The mortality during follow-up, defined as 30 days after the last platelet transfusion, will be gathered from the LMR.

5.4.6 Data handling

The transfusion report forms will be copied, provided with a unique linked study identification number (thus anonymized). These copied forms will be collected and later imported into a digital secured database. Another option is to enter the information on the form in an anonymized way into a digitally secured database in the concerning hospital itself. Depending on the preference of the local collaborating staff, we will decide which strategy to apply. The data obtained from patient dossiers, TRIP and GBA will be anonymized and stored in a secured digital database as well.

6. RISKS AND BENEFITS

This study does not carry any additional risks for participating patients. The results of this study will lead to further improvement of platelet transfusion strategies, which will be beneficial for future patients.

7. ETHICS & PATIENT PRIVACY

This observational study, monitoring transfusion reactions resulting from blood products that are used for registered and accepted indications according to common practice, is considered to be an observational non-WMO study.

Considering the expected number of included platelet transfusions, we believe it unrealistic to ask each individual patient for explicit permission to inspect and use their medical information[11]. Furthermore the circumstances (in the operation room or intensive care under anaesthesia, during labour and in emergency situations) in which patients receive blood transfusions make it difficult or even impossible to ask the patient for such permission.

Although it is possible to anonymise the data to the point of non-retraceability, this lies beyond our desire. It is likely that, subsequent to the analysis of patient's anonymised records, we will need to retrieve additional data. Thus the set-up, as is, blinds the researcher to the patients' medical records while retaining the ability to trace back any given patient. In addition the digital database will be secured and exclusively accessible to selected, certified individuals involved in the study.

8. TRIAL INSURANCE

This study protocol will not result in extra health risk for the participating patients. No separate patient risk insurance according to the WMO apart from existing hospital insurances is needed.

9. PUBLICATION POLICY

The final outcome of the study will be published by the Study Coordinator(s) on the basis of the statistical analysis performed by the study coordinators. A draft manuscript will be submitted to all co-authors for review. The manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the central study coordinator(s), the lead investigators of the major groups (in case of inter group studies, the statistician(s), and others who have made significant scientific contributions.

Any publication, abstract or presentation based on patients included in this study must be approved by the study supervisor and coordinator(s). This is applicable to any individual patient registered in the trial, or any subgroup of the trial patients.

10. FINANCIAL SUPPORT

This study is funded by Sanquin under the number PPOC12-028PRG.

APPENDIX A: Grading and classification of adverse transfusion reactions

A transfusion reaction is any adverse *event*, meaning any unintended and undesirable event before, during or after transfusion of a blood product which can be related to the administration. An adverse event can be the result of an incident or error and it might or might not result in a reaction in the recipient. However, an adverse *reaction* is an undesirable effect or response in a patient associated with the administration of a blood product. It can be the result of an incident. An *incident* is an event where a patient is transfused with a blood product which did not meet all the requirements for an appropriate transfusion for that patient, or a blood transfusion that was planned for another patient. It can or can not result in an adverse reaction (ISBT, 2011). Figure 1 shows the transfusion reactions in platelet transfusions from 2003 to 2011. From 2003 to 2009, an increase in the number of transfusion reactions is observed, after 2009 a little decrease is seen (TRIP Rapport, 2003-2011).

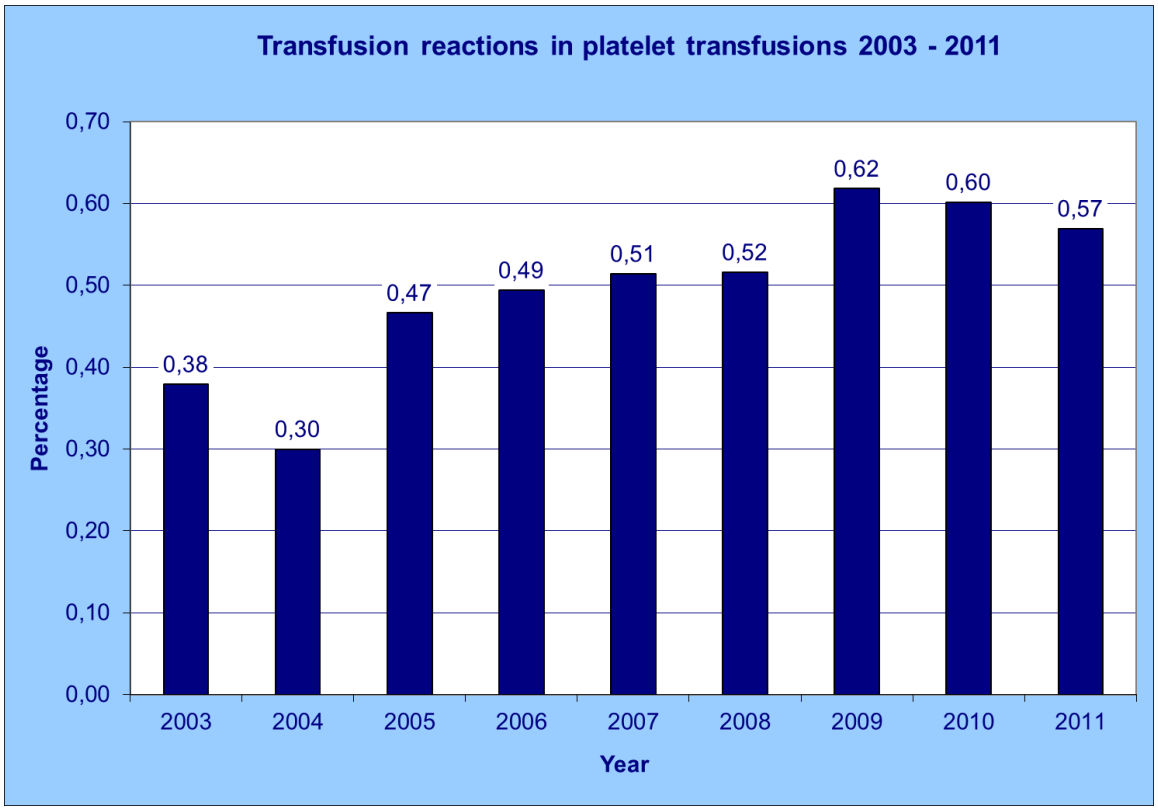

Figure 1: The amount of transfusion reactions in platelet transfusions expressed as percentage of the total number of transfusions from 2003 to 2011 (TRIP Rapport, 2003-2011)

A. Types

Transfusion reactions can be divided in non-infectious and infectious reactions, which can be categorized in the following types (STIR Guide, 2007; CBO, 2011):

Non-infectious:

- acute hemolytic transfusion reactions
- delayed transfusion reactions
- transfusion-associated graft-versus-host disease (TA-GVHD)
- transfusion-related acute lung injury (TRALI)
- transfusion-associated circulatory overload (TACO)
- post-transfusion purpura (PTP)
- (non-systemic) allergic transfusion reaction
- anaphylactic reaction
- non-hemolytic febrile transfusion reaction (NHTR)
- antibodies against blood cell antigens
- immunological effects of blood transfusion

Infectious:

- bacterial/other infection
- post transfusion viral infection
- prions (*variant Creutzfeldt-Jakob* disease)
- parasites

Figure 2 shows the most common types of transfusion reactions in platelet transfusions, expressed as percentage, in 2010 and 2011, which are a (non-systemic) allergic transfusion reaction, non-hemolytic febrile transfusion reaction and 'other' reactions (TRIP Rapport, 2011).

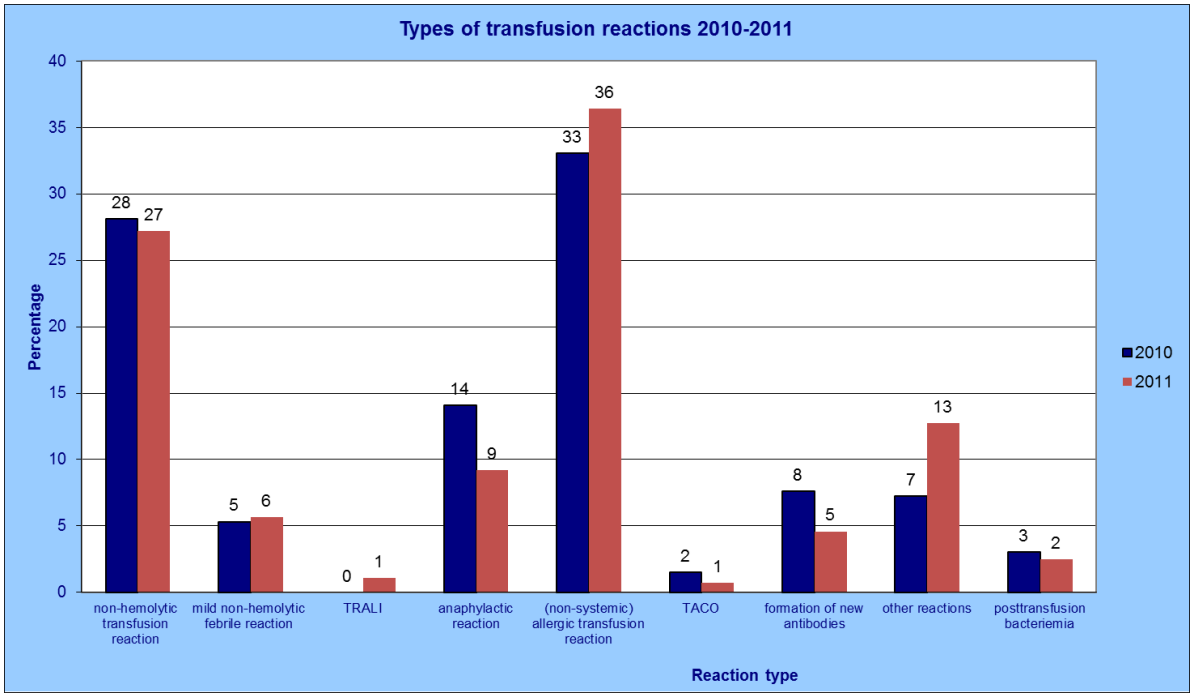

Figure 2: The categorization of transfusion reactions in platelet transfusions, expressed as percentage in 2010 and 2011 (TRIP Rapport, 2011).

(Non-systemic) allergic transfusion reaction

A (non-systemic) allergic reaction occurs within several minutes during transfusion up to several hours after transfusion and is characterized by signs like itching, redness and urticaria and does not involve any respiratory (glottis oedema, asthma, cyanosis), cardiovascular (decrease in blood pressure, tachycardia, arrhythmia, shock and loss of consciousness) or gastro-intestinal symptoms (nausea, vomiting, diarrhea) (Vamvakas 2007). The term “allergic transfusion reaction” assumes that an earlier produced IgE reacts to an allergen, but in fact this has not been investigated. Allergic reactions can also be caused by cytokines derived from platelets of the donor (Kluter 1999).

In about 1 to 3 % (depending on the system of recording) of transfusions with plasma-containing blood products an urticarial reaction happens (Vamvakas 2007). Yearly about 200 “other allergic reactions” are registered by TRIP (“transfusie- en transplantatiereacties in patiënten”) which means an overall ratio of 1:3.000 of short tenable blood products. In platelet concentrates the number is higher (around 1:600) than in plasma (1:1000) and erythrocyte concentrates. The risk of these reactions is not affected by clearance of the product of white blood cells before preservation or by the storage time (Kluter 1999, Uhlmann 2001, Patterson 1998, Sarkodee-Adoo 1998, Kerkhoffs 2006). A decrease in the amount of allergic reactions seems to result if the (70%) plasma in platelet concentrates is replaced by platelet storage solution (PAS) (Kerkhoffs 2006, Rebibo 2008).

(Febrile) non-hemolytic transfusion reaction ((F)NHTR) and mild non-hemolytic febrile reaction

A (F)NHTR is a reaction with a temperature rise ≥ 2 °C with or without chills during transfusion or within the first two hours and with decrease of the temperature to the normal value within 24 hours after transfusion or cold shivers in this period. In this reaction there are no other important signs and no evidence for hemolysis, infection or any other cause. If the temperature rise is just > 1 °C and < 2 °C (during transfusion or within the first two hours following transfusion and normalizing within 24 hours) this is called a mild (F)NHTR. Prior to the start of leuko-reduction the percentage of (F)NHTR ranged from 0,5 to 1 % in regular centers to more than 10% in academic centers that include hemato-oncological patients (Williamson 1999). In 2008 around 1:1000 applied blood products were recorded by TRIP (TRIP rapport 2008). After transfusion of platelets this kind of reaction appears more frequent than after transfusion of erytrocytes (Heddle 2007, 1995, 1993). In platelet transfusion fever develops more often (10-30%) than red cell transfusion (1-2%) (STIR Guide, 2007).

The causes of (F)NHTR are recipient (HLA) antibodies against leukocyte antigens or fragments in the blood product or cytokines which accumulate in the blood component during storage (STIR Guide, 2007). Cytokines can be released from leukocytes during banking of the blood products and (dis)solve in the plasma. The removal of leukocytes from the products reduces the risk of (F)NHTR, but it can also appear after the transfusion of a leuko-reduced blood product (Heddle 2007). Generally no particular cause is demonstrated for (F)NHTR and the clinical signs vanish within 24 hours. It is not established that pre-medication to prevent febrile reactions is effective (Heddle 2007, Kennedy 2008).

Anaphylactic reaction

An anaphylactic reaction is a severe systemic allergic reaction that is rapid in onset and presents with signs of cardiovascular instability including hypotension (pressure drop ≥ 20 mm Hg systolic and / or diastolic, tachycardia, loss of consciousness, cardiac arrhythmia, shock, cardiac arrest, nausea, vomiting, diarrhea and back pain. Sometimes respiratory involvement with dyspnoea and stridor are prominent (STIR Guide, 2007).

Possible causes of such a anaphylactic reaction can be: pre-existent antibodies against serum proteins like IgA, albumine, haptoglobine, alfa-1-antitrypsine, transferrine, C3, C4 or allergens in the donor blood against which the receiver has been earlier sensitized, such as: medication (penicillin, aspirin), food components and substances used in the production and sterilization of blood punction and administration (like formaldehyde, ethyleenoxide). In rare cases passive transfer of IgE-antibodies can occur from donor to receiver.
Not in all cases an anaphylactic reactions is based on an IgE mediated mechanism and in daily practice usually no cause is identified (Vamvakas 2007, Gilstad 2003).

Transfusion-related acute lung injury (TRALI)

TRALI is a severe adverse effect following transfusion of plasma-containing blood components diagnosed per exclusionem in which no immunohematological and bacteriological abnormalities are found. It is characterized by acute respiratory distress and bilaterally symmetrical pulmonary edema with hypoxemia developing within 2 to 6 or 8 hours after a transfusion (Palfi 2001). A chest X-ray shows interstitial or alveolar infiltrates when no cardiogenic or other cause of pulmonary edema exists. It is thought that pulmonary vascular effects occur secondary to cytokines in the transfused product or from interaction between patient white cell antigens and donor antibodies (or vice versa) (STIR Guide, 2007). Immune mediated TRALI is caused by incompatible leukocyte antibodies. Other biologically active substances can also stimulate

leukocytes and give rise to TRALI. These causes can amplify each other (double hit) via a mechanism in which initially stimulus of the pulmonary vascular endothelium is present and subsequently the transfusion provides the second “hit”. According to some authors a immune mediated TRALI develops more severe than TRALI in which no immunological cause is showed (Bux 2005).

Transfusion-associated circulatory overload (TACO)

TACO is a volume overload as a result of the transfusion of a blood component in which respiratory distress, tachycardia (> 100 bpm), ankle edema and increased blood pressure and central venous pressure arise within 6 or 12 hours of the completion of the transfusion. Other non-specific signs can be headache, chest pain and a dry cough. Typical signs of cardiogenic lung oedema in the chest x-ray and a positive fluid balance, or known compromised cardiac status support TACO (STIR Guide, 2007).

Antibodies against blood cell antigens

After transfusion of blood products containing leukocytes and/or platelets antibodies against HLA (human leukocyte antigen) can be produced. If the number of leukocytes in blood products is extremely low because of the leuko-reduction, this is mainly concerning a secondary immune response in female receivers who have become immunized by transplantation, pregnancy and/or transfusion of blood products. The number of this immunization was discovered about 40% in patients with acute leukemia (Sintnicolaas 1995). The number / amount of primary immunizations in this specific patient group is about 7%, in spite of leuko-reduction of erythrocyte and platelet concentrates. These antibodies can cause a non-hemolytic febrile reaction and refractivity to platelets form a random donor. In case of refractivity HLA-compatible platelet transfusions should be administered (van Marwijk Kooy 1991). After pregnancy or administration of blood products containing platelets antibodies against HPA (human platelet antigen) can be produced (Schnaidt 1996).

Post transfusion bacteremia

An estimated 0.4% of erythrocyte and platelet concentrates are contaminated by bacteria. For pooled platelet concentrates that are prepared from different donor units, this percentage can increase to 2% (Blajchman 1998). Platelet concentrates, which are stored at room temperature, are especially components at risk of bacterial contamination (Sanquin Blood Supply Foundation 2001). The risk is decreased by changing the procedure of disinfection and by using the first

milliliters of blood donations to fill the tubes used for the tests (de Korte 2006). Blood products that have been contaminated with bacteria can result in bacteremia in the recipient, which can result in sepsis. Sometimes the symptoms can't be distinguished from a hemolytic transfusion reaction, namely cold shivers, fever, tachycardia, changes in systolic blood pressure (both increase and decrease), shortness of breath, nausea and/or vomiting, lower back pain and shock (Sanquin Blood Supply Foundation 2001). Both the time at which the bacterial contamination manifests itself and the symptoms can vary greatly. In the Netherlands, about three transfusion reactions per year are the result of a blood product contaminated by bacteria (de Korte 2006).

B. Severity grades

In international guidelines transfusion reactions are classified according to severity (TRIP Rapport, 2011). Severity is an assessment of the degree to which the patient developed symptoms and/or signs as a result of the adverse event of the transfusion. The severity of a reaction can be divided in five grades (TRIP Rapport 2011; ISBT, 2011).

Grade 0
If the antibodies are coincidentally, so there were no visible signs or symptoms, noticed after a certain period by means of screening (TRIP).

Grade 1 (Non-Severe):
In this kind of reaction the patient possibly needed medical interventions, not to prevent permanent damage or impairment of a body function, but to treat symptoms.

Grade 2 (Severe):
In this case the reaction caused hospitalization or prolongation of hospitalization and/or the event resulted in permanent or relevant damage; or the recipient required medical intervention to prevent persistent impairment of a body function.

Grade 3 (Life-threatening)
The event necessitated major medical action, to prevent death, like the administration of vasopressors, intubation or admission to the intensive care.

Grade 4 (Death)
The transfusion reaction caused the death of the recipient. This grade should be used only if death is attributed possibly, probably or definitely to the transfusion (reaction).

In 2011 the total number of transfusion reactions reported by TRIP was 2315, from which the severity in 2239 cases (97%) is reported. The severity of 772 reactions was grade 0 (33%), 1344 (58%) grade 1, 104 (4.5%) grade 2, 13 (0.6%) grade 3 and 6 (0.3%) grade 4 (TRIP Rapport 2011).

C. Imputability

Imputability is an assessment of the causal relationship between the transfusion and the adverse event (ISBT, 2011).

Definite:	Convincing evidence shows that the transfusion contributed to the adverse event
Probable:	According to the evidence the adverse event is plausibly attributed to the transfusion
Possible:	According to the evidence the adverse event is indeterminately attributed to the transfusion or another event
Doubtful:	According to the evidence the adverse event is plausibly attributed to a cause other than the transfusion
Excluded:	Convincing evidence beyond reasonable doubt shows that the adverse event can be attributed to a cause other than the transfusion.

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