

Blood Transfusion Guideline

INITIATIVE:

National Users' Board Sanquin Blood Supply

ORGANISATION:

CBO

MANDATING ORGANISATIONS

- Netherlands General Practitioners' Association (NHG)
- Netherlands Internists' Association
- Netherlands Orthopaedic Association
- Netherlands Association of Anaesthesiology Employees
- Netherlands Association of bioMedical Laboratory Employees
- Netherlands Association for Anaesthesiology
- Netherlands Association for Blood Transfusion
- Netherlands Association for Cardiology
- Netherlands Association for Surgery
- Netherlands Association for Haematology
- Netherlands Association for Intensive Care
- Netherlands Association for Paediatric Medicine
- Netherlands Association for Clinical Chemistry and Laboratory Medicine
- Netherlands Association for Medical Microbiology
- Netherlands Association for Obstetrics and Gynaecology
- Netherlands Association for Thoracic Surgery
- Transfusion Medicine in Academic Hospitals
- Association of Haematology Laboratory Research
- Nurses & Carers of the Netherlands

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Colophon: **Blood Transfusion Guideline**



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CBO
PO Box 20064
3502 LB UTRECHT
Tel.: 030 – 284 39 20
E-mail: mwr@cbo.nl

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The National Users' Board advises the Board of Directors of Sanquin Blood Supply about logistics and service in blood provision. Sanquin Blood Supply is a not-for-profit organisation that ensures blood provision and promotes transfusion medicine in such a way that the highest requirements for quality, safety and efficiency are met. Sanquin Blood Supply provides components and services, performs scientific research and provides education, training and in-service and refresher courses.

The CBO, located in Utrecht, aims to support individual professionals, their professional organisations and care facilities in improving patient care. The CBO offers programmes and projects that provide support and guidance in systematic and structured measurement, improvement and quality assurance of patient care.

Information accompanying the English translation

Since we made significant use of foreign guidelines (usually in English) in the creation of this guideline, we thought it would be a good idea to make our guideline accessible to foreign colleagues by translating the guideline into English. We are extremely grateful to the Sanquin Blood Supply Foundation for financing this translation.

As certain parts of the Guideline are specific to the situation in the Netherlands, we have decided not to translate these. This concerns a chapter about legislation and paragraphs/addenda about transfusion outside the hospital, aprotinin, the cost-efficacy of alternatives for allogeneic blood transfusions during elective surgical interventions, transfusion policy for Jehova's witnesses, tools for setting up a quality system for the transfusion process in the hospital, an Addendum concerning new and amended recommendations with respect to the previous Guideline, description of the literature search for specific topics and recommendations for further research. Partly due to the costs, we have also decided not to translate the Transfusion Guide (summary of the most important recommendations to doctors and nurses) and have not created a new list of abbreviations and Index for the English translation.

Hb in mmol/L and conversion factor

In the Netherlands the Hb is expressed as mmol/L. Because some recommendations (e.g. the so-called 4-5-6 rule) use mmol/L we have left the Hb values in mmol/L in the English translation. To obtain g/dl instead of mmol/L one has to multiply the mmol/L value by 1.6.

We hope that many foreign colleagues will enjoy reading this English translation of the Dutch guideline on Blood Transfusion.

On behalf of the working group for revision of the Blood Transfusion Guideline

René de Vries and Fred Haas, Chairmen

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COMPOSITION OF THE WORKING GROUP

Composition of core group (as part of the working group)

F.J.L.M. Haas, Chairman *
Prof. D.J. van Rhenen
Prof. R.R.P. de Vries, Chairman *
Mrs M.A.M. Overbeeke
Dr V.M.J. Novotny
Dr Ch.P. Henny

* F.J.L.M. Haas, clinical chemist, member of the Sanquin Blood Supply Medical Advisory Board and Prof. R.R.P. de Vries, internist-blood transfusion specialist, Leiden University Medical Centre, IHB department, Leiden were proposed as Chairmen by the National Users' Board of Sanquin Blood Supply

Together with one or more core group members, the following **working group members were responsible** for the revision of the following **chapters**:

Ms H. de Bruijn-van Beek (Ch1)
Dr E.A.M. Beckers (Ch2)
Dr J. Slomp (Ch3)
Dr J.J. Zwaginga (Ch5)
Prof. A. Brand (Ch6)
Dr M.R. Schipperus (Ch7)
Dr A.W.M.M. Koopman-van Gemert (Ch8)

Composition of working group per association

Netherlands Internists' Association

Prof. A. Brand, internist-haematologist, manager of research & education, Sanquin Blood Supply Region SW department of Research & Education, Leiden

Sanquin Blood Supply Foundation

Ms H. de Bruijn-van Beek, general secretary Board Sanquin Blood Supply, Amsterdam
Dr C.L. van der Poel, transfusion doctor-epidemiologist, Secretary for medical affairs, Sanquin Blood Supply, Group personnel, Amsterdam
Dr E.A.M. Beckers, transfusion specialist, University Medical Centre, Haematology Department, Maastricht

Nurses & Carers of the Netherlands

T. Reker, transplant coordinator University Medical Centre, Groningen [until 01-05-2009]
Ms N.W.M. Gerrits, senior nurse haematology/oncology, Onze Lieve Vrouwe Gasthuis, ward C6, Amsterdam

Netherlands Association for Anaesthesiology

Dr Ch.P. Henny, anaesthesiologist, Academic Medical Centre, Anaesthesiology department, Amsterdam
Dr A.W.M.M. Koopman-van Gemert, anaesthesiologist-intensivist, Albert Schweitzer Hospital, location Dordtwijk, Anaesthesiology department, Dordrecht

Netherlands Association for Intensive Care

Dr A.W.M.M. Koopman-van Gemert, anaesthesiologist-intensivist, Albert Schweitzer Hospital, location Dordtwijk, Anaesthesiology department, Dordrecht

Netherlands Association for Blood Transfusion

Dr V.M.J. Novotny, internist-haematologist / blood transfusion specialist, St. Radboud University Medical Centre, Haematology department, Nijmegen

Mrs M.A.M. Overbeeke, biologist, head of Immunohaematology department, Sanquin Blood Supply, Diagnostics Division, Amsterdam

Netherlands Association of bioMedical Laboratory Employees

Mrs M. Smelt, haemovigilance employee, St. Antonius Hospital, Clinical Chemistry Laboratory, Nieuwegein

Transfusion Medicine in Academic Hospitals

Dr M.R. Schipperus, internist-haematologist, Haga Hospital, Haematology department, The Hague

Netherlands Association for Thoracic Surgery

Dr J. Schönberger, cardiothoracic surgeon, Catharina Hospital, Department of Cardiothoracic Surgery, Eindhoven

Netherlands Association for Paediatric Medicine

Dr R.Y.J. Tamminga, paediatrician, oncologist-haematologist, University Medical Centre, Beatrix Children's Clinic, Groningen

Dr C.H. van Ommen, paediatrician-haematologist, Academic Medical Centre, department of Paediatric Haematology, Amsterdam

Dr E. Lopriore, paediatrician-neonatologist, Leiden University Medical Centre, department of neonatology, Leiden

Association of Haematology Laboratory Research

Dr R.C.R.M. Vossen, clinical chemist, Orbis Medical Centre, clinical chemistry & haematology laboratory, Sittard

Dr J. Slomp, clinical chemist, Medical Spectrum Twente, Laboratory, Enschede

Netherlands Association for Haematology

Prof. D.J. van Rhenen, internist-haematologist, division director Sanquin Blood Supply, SW Region, Rotterdam

Dr J.J. Zwaginga, staff member blood transfusion service, head of stem cell therapy centre, Leiden University Medical Centre, department of Immunohaematology, Leiden

Dr B.J. Biemond, internist-haematologist, Academic Medical Centre/University of Amsterdam, department of Internal Medicine, Amsterdam

Dr J.Th.M. de Wolf, internist-haematologist, University Medical Centre, Groningen (until 01-04-2009)

Dr R.E.G. Schutgens, internist-haematologist, University Medical Centre, Utrecht (as of 15-04-2009)

Netherlands Association for Medical Microbiology

Dr P.J. Kabel, physician-microbiologist, Regional Laboratory for Public Health, LMMI department, Tilburg

Netherlands Association for Obstetrics and Gynaecology

Dr G.C.M.L. Page-Christiaens, perinatologist, University Medical Centre, Obstetric department, Utrecht

Netherlands Association for Clinical Chemistry and Laboratory Medicine

Dr J.G. Loeber, clinical chemist, head of laboratory, RIVM, LIS department, Bilthoven (Chapter 9: Indicators)

Dr A. Castel (up to and including February 2009)

Dr Y.B. de Rijke, (as of March 2009), clinical chemist, Erasmus Medical Centre, department of Clinical Chemistry, Rotterdam

Netherlands Association of Anaesthesiology Employees

H.E. Polak, anaesthesiology nurse, Via Sana Clinic, Mill

Netherlands Association for Surgery

Prof. R.J. Porte, University Medical Centre, department of Surgery, Groningen

Netherlands Orthopaedic Association

W.G. Horstmann (up to and including March 2009)]

D.B. van der Schaaf, orthopaedic surgeon, Sint Maartens Clinic, Orthopaedics department, Nijmegen (as of April 2009)

Advisor in a personal capacity

Prof. E. Buskens, Professor MTA, UMCG department of Epidemiology, Groningen

H. Vrielink, Sanquin Blood Supply, Amsterdam (as of 01-04-2008)

With special thanks to

Prof. W.G. van Aken, internist n.p. The core group thanks Mr van Aken for his critical evaluation of the draft texts and his suggestions for improvements.

Acknowledgements

Ms R. Ditz-Kousemaker, Leiden University Medical Centre, Leiden

Ms J.C. Wiersum-Osselton, TRIP

Ms J.S. von Lindern, paediatrician-neonatologist, Groene Hart Hospital Gouda, department of paediatric medicine

A.R.J. Verschoor (coordinator Hospital information service for Jehova's Witnesses)

Publisher Reed business, Elsevier healthcare

Dr J.L. Kerkhoffs, internist-haematologist, Haga Hospital, The Hague

L.M.G. van de Watering, physician-investigator. Sanquin Blood Supply South-West Region

Dr L. van Pampus, haematologist, UMC St Radboud, Nijmegen

CBO, Utrecht

Mrs D.M. Schipper, CBO advisor, project leader (until 31 October 2010)

Dr P.N. Post, CBO senior advisor, physician-epidemiologist

Mrs C.J.G.M. Rosenbrand, physician, CBO senior advisor (as of 31 October 2008)

Dr J.J.E. van Everdingen, dermatologist, CBO senior advisor (up to and including 31 October 2008)

GENERAL INTRODUCTION

This guideline consists of recommendations for the blood transfusion practice and the underlying arguments for these recommendations. They were created through study of the literature and subsequent opinion forming within a multi-disciplinary working group with delegated representatives from the various professional organisations involved in blood transfusion.

Introduction

Blood and blood components have a special place within the Dutch healthcare system. Whereas most other 'consumables' in medicine are supplied by commercial companies, blood is provided without compensation by voluntary donors (nearly 3 % of the Dutch population). The health and safety of both patients and donors is central in blood transfusions. This requires advanced production methods, strict procedures, stringent quality requirements and checks, regulations and monitoring during the administration. Every donation is tested, thereby minimising the risk of blood-transferable infections through blood components. However, despite all precautions, there is still a very small risk of contamination by blood transfusion. This is part of the reason why caution is advised in the use of blood and blood components. Claims for damages by patients who received HIV infected blood were responsible for an international understanding that the liability for the safety of blood components needed to be improved. What does this mean in practice? In the Netherlands, Sanquin Blood Supply is responsible for donor care, donor-component linkage and the safety and efficacy of the component. But what is safe and what is effective? The hospitals are responsible for effective and correctly indicated use of blood components, the compatibility study, the component-patient linkage and the registration thereof, but what is effective and correctly indicated use and how does a patient receive the correct blood component? The current revision of the Blood Transfusion Policy guideline aims to answer these questions.

Motivation

The Blood Transfusion Policy guideline is the first guideline created under the auspices of the Medical Scientific Board of the CBO in 1982. Several revisions have taken place since then. As a result, this guideline has become a standard work, viewed as a manual by everyone in the blood transfusion world. Research has also been performed into the extent to which the guideline is actually followed. One of the most important recommendations from the first guideline (1982) was that the use of full blood should be limited as far as possible and that the use of erythrocyte concentrate should be stimulated as much as possible. This policy has been implemented, but other recommendations from the guideline have not been followed so successfully. This is due in part to the burden of proof from the literature cited, but also due to the extent to which risks are deemed acceptable in relation to costs incurred. On 8 January 2007, the CBO received a letter from the Sanquin Blood Supply National Users' Board, requesting a revision of the Blood Transfusion Policy guideline from 2004.

The revision emphasised in particular a further strengthening of clinical thinking and acting in the field of blood transfusion.

Aim

The aim of the revision was to update the multi-disciplinary guideline on transfusion policy of blood and blood components from 2004. This consisted of the evaluation of the relevance of new research data, subjects that were not discussed in the previous version and developments in the social debate, and incorporation of these matters into the new guideline.

Part of this involves making recommendations that stimulate a more uniform clinical thinking and acting in the field of blood transfusion. Confirming the role of nurses in blood transfusions and incorporating new national initiatives – such as the creation of the TRIX database for irregular red cell antibodies – were also important focal points for the revision.

The clinical evaluation of transfusion and clinical transfusion research to support the basis for guideline development were promoted, and skills improvement of employees involved in blood transfusion is aimed for, with a focus on the hospital situation. This involves technicians, nurses and doctors.

Where there continues to be a lack of evidence based knowledge on certain subjects despite new literature, the working group has – based on discussion and consensus – formulated suggestions and recommendations.

This revision also aimed to provide a brief summary of the clinical guideline in pocket-format. Such booklets (also called Transfusion Guides) have) has previously been developed by many hospitals. The aim of the present booklet is to nationalise such a pocket guideline.

Parallel to the revision of the guideline, a set of internal indicators based on the guideline has been developed, aiming for the effective and safe use of blood components. Such indicators were not present in the 2004 guideline.

An important part of the revision was the development of a more accessible digital version of the guideline with a uniform and balanced layout of the chapters, clearly showing what has changed.

In order to improve the accessibility, a search function was implemented from the table of contents in the PDF guideline document. When the reader clicks the cursor on the desired paragraph in the table of contents, he/she will be linked to the relevant paragraph.

Target group

The guideline is aimed at all care providers involved in blood transfusions. This guideline is authorised by the associations that contributed to the development of this guideline. As a result, this guideline has become part of the professional standard of the members of these associations.

Although this guideline primarily relates to procedures and actions performed in a hospital setting, the recommendations also apply to blood transfusions outside the hospital, for example in the independent treatment centres (ITC) and via home care organisations.

Composition of the core group and working group

The blood transfusion policy guideline working group has a multi-disciplinary composition: as many professionals as possible from various disciplines – involved in blood transfusion – were asked to participate. In composing the working group, a balanced representation was sought of the various disciplines involved, the geographical distribution of the members and the proportion of academic to non-academic institutions. Members of the working group were invited to take part in the working group via the relevant (scientific) associations based on their personal expertise and/or affinity with the subject. They did not receive any payment and/or reimbursement of travel costs for their presence at working group meetings. A small core group was formed from the members of the working group. The working group was chaired by two chairmen, who also acted as chairmen for the core group. The working group members and core group members acted independently and were mandated by their association for participation in the working group. No relationships relevant to this guideline of working group members with the pharmaceutical industry were reported.

Core group working method

The primary task of the core group was to monitor the progress of the entire process, including the results of the working group. The core group members were each responsible for the end result of one or more chapters. The core group also collaborated with the CBO in the final editing of the guideline.

Working group working method

The working group worked on the creation of a draft guideline over a period of two and a half years. The entire working group met on several occasions for plenary discussion, development and approval of the draft texts. The working group worked in small sub-groups outside the plenary meetings on the revision of chapters for the guideline. Some working group members were involved in the revision of several chapters. For each chapter, one working group member was responsible for the revision of the chapter, supported by the core group member(s) with ultimate responsibility.

A literature search was performed for each question according to the Evidence-Based Guideline Development (EBGD) method, in cooperation with an advisor from the CBO. The initial search looked for evidence-based guidelines and reviews in the period from the end date for inclusion of the literature in the previous revision (early 2003) up to and including February 2008. The guidelines and reviews that were found were evaluated for quality by the chairmen with the aid of the AGREE instrument. If a valid guideline and/or review was found, the evidence from the guideline was used to answer the initial questions. Next, the working group members searched for additional studies per chapter from the moment at which the search in the guideline and/or review ended.

The project also offered scope for the CBO to develop seven initial questions. The CBO information specialist performed a systemic literature search from the moment at which the search in the guideline and/or review ended. This was performed based on search criteria set by the sub-working group in advance. The sub-working group, which studied the relevant

question, then selected the articles based on the quality and content, after which the CBO information specialist wrote the draft evidence text. These draft evidence texts were then evaluated by the relevant sub-working groups and supplemented with other considerations from the practical setting and recommendations based on the conclusions from the scientific literature and these other considerations.

All draft texts were discussed several times in the plenary working group, commented on and eventually approved.

Working method for guideline development

The Blood Transfusion Policy guideline project was financed by The Netherlands Organisation for Health Research and Development (ZonMw) within the programme Knowledge Policy Quality of Curative Care. Members of the working group and the core group worked on the development of the guideline for more than two and a half years (November 2007 – July 2010).

The revision started with an inventory of the bottlenecks observed in practice with the Blood Transfusion guideline from 2004, which served as a starting point for the revision. The working group members were asked to consult their association members to name and create an inventory of these bottlenecks. The relevant patient groups (see also under 'patient perspective') were also asked to name and create an inventory of the bottlenecks that they experience in the practical situation. Once the bottlenecks had been collected, they were categorised in the relevant chapter. Seven initial questions were distilled from the prioritised bottlenecks for elaboration by a CBO advisor. As a result, the working group decided to change the layout of the guideline and divide the chapters according to specific problems, whilst still maintaining the indications. This was also done to improve the accessibility of the guideline.

The guideline was then revised according to the procedure described under 'core group working method' and 'working group working method'. Texts developed by the working group were then edited by the core group and the CBO to form the draft guideline. Prof. W.G. van Aken, internist n.p. read the draft texts in the final phase critically and made suggestions for improvement.

The draft guideline, which could be consulted via the CBO website, was submitted to the relevant associations with mandated representatives in the working group for a consultation round. The relevant groups listed under 'patient perspective' were also specifically asked to comment on the Blood Transfusion draft guideline. The resulting comments were processed in the definitive draft guideline. Following inclusion of the comments, the draft guideline was submitted to the associations for authorisation and it was approved on 1 August 2011.

Composition of the guideline

Although the Blood Transfusion guideline covers a large section of the use of blood components, we did not strive for all-inclusiveness and this guideline should not be viewed as a manual for transfusion medicine. The reader should also realise that previous recommendations have not always been repeated in this revision if they have not been changed. In other cases, where recommendations in a certain area have changed, only the changed recommendations have been included in this guideline. Nevertheless, this guideline contains more than 500 recommendations, of which nearly half are new and approximately one quarter have been amended. Any **amended** and **new** recommendations compared to the previous version of the Blood Transfusion guideline have been marked in the text in **turquoise** and **yellow** respectively.

Most of the chapters in the guideline follow a set layout, as described below. The aim of this is to make the guideline transparent, so that every user can see on which literature and considerations the recommendations are based. A more descriptive layout of a certain chapter/section was chosen only for those chapters/sections where little or no scientific high-quality literature has been published.

As this guideline is very extensive and is intended for use by various types of care providers in the blood transfusion chain, we have used colours to mark a number of different sections, so that the various types of users can find the sections relevant to them more easily.

The largest part of this guideline is intended for doctors from many disciplines and has a blank background. As this guideline is the first to focus specifically on the transfusion policy in neonates and children, these sections (Chapter 4 paragraphs 4.5 and 4.6, Chapter 5.4.7 and 5.4.8, Chapter 6 paragraphs 6.2, 6.3, 6.6.2 and 6.6.3) have been marked **light green**. There are also several sections that focus respectively on nurses (Chapter 2 paragraph 2.4 to 2.4.2 inclusive) and laboratory employees (Chapter 3). These have been marked **light pink** and **light blue** respectively.

Introduction

The introduction provides a brief description of the subject for the chapter and which specific problems will be discussed in that chapter.

Scientific support

Where possible, the recommendations in this guideline have been based on proof from published scientific research. Relevant articles were found by performing systematic search actions in the Cochrane Library, Medline and Embase. The languages were limited to Dutch, English, German and French. Manual searches were also performed. The search was performed from 2003 (Medline) and for some questions also in Embase or Cinahl up to and including February 2008. The set-up of the literature search has been summarised in appendix 2.

After the literature search, the result was evaluated by the working group members and the articles were evaluated for clinical relevance. If there was a possibility that the initial question could be answered with the article, the article was included in the selection. The selected articles were evaluated by the working group for quality of the research and graded according to extent of proof, with the following categorisation being used.

Table 1. Categorisation of methodological quality of individual studies

	Intervention	Diagnostic accuracy of research	Damage or adverse effects, etiology, prognosis*
A1	Systematic review of at least two studies performed independently of each other at level A2		
A2	Randomised, double-blind, comparative clinical study of good quality and sufficient size	<i>Research with respect to a reference test (a 'golden standard'), with previously defined limits and independent evaluation of the results of test and gold standard, concerning a sufficiently large series of consecutive patients who have only had the index test and reference test</i>	Prospective cohort study of sufficient size and follow-up, with adequate checks for 'confounding' and sufficient exclusion of selective follow-up.
B	Comparative study, but not with all the characteristics as mentioned under A2 (these also include patient-control study, cohort study)	Study compared to a reference test, but not including all the characteristics mentioned under A2	Prospective cohort study, but not including all characteristics as mentioned under A2 or a retrospective cohort study or patient-control study
C	Non-comparative study		
D	Expert opinion		

*** This classification only applies in situations where controlled trials are not possible due to ethical or other reasons. If these are possible, then the classification for interventions applies.**

Level of conclusions

	Conclusie gebaseerd op
1	Research of level A1 or at least 2 studies performed independently at level A2, with consistent results
2	1 study of level A2 or at least 2 studies performed independently at level B
3	1 study at level B or C
4	Expert opinion

Other considerations

In order to make a recommendation, in addition to scientific proof, there are also other important aspects such as patient perspective, organisational aspects and costs. These were discussed under the heading Other considerations.

Recommendation

The recommendation that was ultimately formulated is the result of the scientific conclusion, which also included the other considerations.

Literature

Each chapter ends with a literature list of the references cited in that chapter.

Patient perspective

There is no specific patient organisation that looks after the interests of the population of patients undergoing blood transfusions. Therefore, there was no representative from a specific patient organisation in the blood transfusion guideline working group. There are specific patient groups who are confronted with blood transfusions to a greater extent. Therefore, it was decided in this revision, to include these patient groups in the inventory of the bottlenecks which formed the basis for the revision, and to submit the draft guideline for commentary to these same patient groups during the consultation phase. The aim was to guarantee the input of patient groups involved in blood transfusion during the revision process. The following patient groups were approached and cooperated in this matter:

- OSCAR Netherlands (sickle cell disease and thalassaemia)
- Association for Parents, Children and Cancer
- Contact Group for Kahler and Waldenström Patients
- National Association for Dialysis and Transplantation
- Association for Parents of Incubator Children
- Kidney Patients' Association of the Netherlands

As Jehovah's Witnesses have a specific stance against blood transfusions due to religious convictions, the Association of Jehovah's Witnesses was also approached to think about bottlenecks in the practical situation and to comment on the draft guideline during the commenting phase.

Authorisation, dissemination and implementation

The draft guideline was submitted for authorisation to all scientific and professional associations involved. The guideline was then authorised by the relevant associations and authorities. The guideline was then initially disseminated through the websites of these parties that were involved and made available through the website of the CBO www.cbo.nl. The direct link is www.cbo.nl/bloedtransfusie. The definitive guideline will be disseminated amongst the associations and will be available in digital format. The recommendations of the guideline will be presented at scientific meetings of the relevant scientific associations. An announcement of this guideline will be submitted for publication to the Netherlands Journal of Medicine, the Journal for Blood Transfusion and the Netherlands Journal of Clinical Chemistry and Laboratory Medicine.

In order to stimulate the implementation and evaluation of this guideline, internal indicators have been developed, which allow for the implementation to be measured by random sampling. In general, indicators give the care providers the opportunity to evaluate whether they are providing the desired care. This enables them also to identify subjects for improvement of the care provision. The internal indicators that were developed for this guideline are discussed in chapter 9 of this guideline.

Legal significance of guidelines

Guidelines are not legal instructions, but rather scientifically substantiated and/or broadly accepted insights and recommendations that care providers should follow in order to offer good quality care. As guidelines are based on 'the average patient', care providers can, if necessary, deviate from the recommendations in the guideline in individual cases. Sometimes it may even be essential to deviate from guidelines if the patient's situation demands this. However, if a conscious decision is made to deviate from the guideline, a case must be made for this and it must be documented. One should also consider whether this should be discussed with the patient, or whether the patient should be informed.

Revision

This guideline will be evaluated for relevance no later than the end of 2015. If necessary, a new working group will be created to revise (parts of) the guideline. The validity of the guideline will expire sooner if new developments form a reason to start the revision process. We have asked the Netherlands Association for Blood Transfusion, the Association for Haematological Laboratory Research and the National Users' Board of Sanquin Blood Transfusion to develop a structural approach for the stimulation of the implementation of the Guideline – particularly by the clinical departments such as monitoring the relevance – and for the revision of this Guideline or parts thereof.

CHAPTER 2: BLOOD COMPONENTS: CHARACTERISTICS, INDICATIONS, LOGISTICS AND ADMINISTRATION

Introduction

This chapter discusses the characteristics (2.1), general aspects of indications and dosage (2.2), logistics (2.3) and administration (2.4) of the short shelf-life blood components, the application of which is discussed in the next chapters. The logistics includes a discussion of storage conditions, shelf-life and transport. The administration of short shelf-life blood components is performed mainly by nurses and this is discussed in detail for the first time in this guideline.

As the evidence of the matters discussed in this chapter is limited, the recommendations which were formulated are based on considerations from the practical situation rather than from scientific research. The layout of the chapter is similar to the other chapters, but the term 'Recommendation' is only used if it is based on evidence, In the other cases it is indicated as 'Recommendation*'. The Sanquin Blood Index part 1 was used as a source and the conclusions and recommendations in this chapter are obtained primarily from the knowledge and practical experience of the working group for the Revision of the Blood Transfusion Guideline. The recommendations were based on consensus within the working group.

In order to improve the legibility, it was decided to use the common component names for the blood components instead of the official Sanquin name. A table of the component names used in this guideline and the corresponding Sanquin name is provided in the addendum to this chapter.

Table 2 is a summary of the most important points from paragraphs 2.1 through 2.3:

Table 2: Short shelf-life blood components: characteristics, shelf-life and most important indications

Component	Characteristic	Specifications (average)	Shelf-life	Indication
Erythrocytes , leukocytes removed in storage solution	erythrocytes that have undergone filtration to remove most leukocytes and platelets	270 mL Ht 0.57 L/L < 1 x 10 ⁶ leukocytes <20 mL plasma	35 days at 2 – 6 °C (in special blood storage refrigerator)	Symptoms of shortage of oxygen transport capacity, either due to blood loss or as a result of severe anaemia
Erythrocytes , leukocytes removed and irradiated , in storage solution	ditto, irradiated (25 Gy)	ditto	irradiated < 14 d after collection: max 28 d; irradiated > 14 d after collection max 24 h	See table 2.1
ditto for paediatric use (Pedi-bag)	ditto O RhD neg. or O RhD pos.	60 mL Ht 0.57 L/L	35 days at 2 – 6 °C	Ditto for neonates
ditto for paediatric use irradiated (Pedi-bag)	ditto, irradiated (25 Gy)	ditto	24 hours after irradiation at 2 – 6 °C	See table 2.1
Erythrocytes, leukocytes removed, in added citrate plasma (exchange)	erythrocytes (< 5 days), where storage solution has been replaced by AB plasma	Volume: 365 mL Ht 0.45 L/L	24 hours after preparation at 2 – 6 °C	Exchange transfusion
Erythrocytes Leukocytes removed and washed , in storage solution	erythrocytes from which as much plasma as possible has been removed by washing	260 mL Ht 0.57 L/L <1x10 ⁶ leukoc. <0.2 mL plasma	5 days at 2 – 6 °C	Allergic reaction to plasma proteins (2x wash) IgA deficiency with anti-IgA antibodies etc. (5x wash)

Table 2: Short shelf-life blood components: characteristics, shelf-life and most important indications

Component	Characteristic	Specifications (average)	Shelf-life	Indication
Platelets leukocytes removed in storage solution (irradiated or not)	platelets with strongly reduced leukocyte levels made from the buffy coat of the blood from 5 donors	310 mL 340×10^9 platelets $< 1 \times 10^6$ leukocytes $< 5 \times 10^9$ erythrocytes storage solution: PAS II (65 %)	administer as soon as possible after receipt, but no more than 6 hours after receipt	1. Thrombocytopenia 2. In case of severe bleeding due to thrombocytopathy NB Preferably administer ABO compatible (platelets), RhD compatible for women < 45 years of age
Platelets, Leukocytes removed in plasma	ditto	340 mL 340×10^9 platelets $< 1 \times 10^6$ leukocytes $< 5 \times 10^9$ erythrocytes	ditto	ditto
Apheresis platelets, leukocytes removed	platelets produced via apheresis procedure from one donor in storage solution or plasma	320 mL 360×10^9 platelets leukocytes $< 1 \times 10^6$	ditto	for HLA and/or HPA typed platelets among others
Apheresis platelets, leukocytes removed for paediatric use	platelets in plasma or storage solution produced via apheresis procedure	65 ml 58×10^9 platelets	ditto	platelets for neonates
Platelets hyperconcentrate	leukocytes removed from platelets in plasma, concentrated	adults < 20 mL paediatric 7 – 10 mL	administer as soon as possible (< 3 hours after production)	ABO incompatibility, volume overload, allergic reactions to plasma
Plasma, apheresis, fresh frozen	minimum ½ year in quarantine for storage leukocytes removed	325 mL $< 1 \times 10^6$ leukocytes > 70 % of all clotting factors	administer as soon as possible after thawing and within 6 hours	see 2.2.3
Plasma, apheresis, fresh frozen split	ditto	75 ml ditto	ditto	ditto

2.1 Characteristics and blood components

2.1.1 Blood components: characteristics, general

Blood components in the Netherlands are obtained from voluntary, altruistic donations by Dutch blood donors. Every donor and each donation is subjected to compulsory tests according to the current national Sanquin guidelines and the relevant laws and regulations (see Chapter 1: Legislation), thereby guaranteeing both donor and blood component safety. Blood donors are categorised as full blood donors and apheresis donors (for plasma and platelet apheresis).

One whole blood donation of 500 ml, treated with anticoagulant citrate-phosphate-dextrose (CPD), yields one unit of erythrocytes, one buffy coat and one unit of plasma. Following removal of the buffy coat and plasma, the storage solution Saline (NaCl 0,9%) and Adenine Glucose Mannitol (SAGM) is added to the erythrocytes. The erythrocyte suspension is then filtered through a leukocyte removal filter.

Five buffy coats of identical ABO/D blood groups are used in the production of one pooled unit of platelets. The plasma component, obtained from whole blood donation, is frozen and used as the raw material for fractionation. Plasma donors donate 650 mL of plasma per donation, obtained after centrifugation of whole blood treated with the anti-coagulant Na-citrate. Two units of 325 mL are obtained from each donation, frozen and kept in quarantine for at least 6 months. The plasmapheresis components can be destined for plasma components for administration to patients or as raw material for fractionation. Platelet apheresis of donors is only performed on indication.

Leukocyte removal is performed for all blood components in the Netherlands ($< 1 \times 10^6$ per unit in 95 % of the components and $< 5 \times 10^6$ per unit in 100 %).

2.1.2 Erythrocytes¹, characteristics

Leukocytes removed, in storage solution

This standard component contains 135 – 180 mL of erythrocytes (40 – 54 gHb), fewer than 10^6 leukocytes, very few platelets, 90 – 100 mL SAGM (storage solution) and low amounts (10 – 20 mL) of plasma, and therefore hardly any clotting factors and citrate. The volume depends on the number of erythrocytes in the donation and usually varies between 270 and 290 mL with a haematocrit of 0.50 – 0.65 L/L. The component contains virtually no calcium ions. The potassium level depends – among other factors – on the duration of storage, the sodium level (approximately 168 mmol/L) and the glucose level (approximately 25 mmol/L) are higher than the physiological values. Administration to an adult weighing 70 kg should result in an increase in Hb of approximately 0.5 to 0.6 mmol/L.

Longer storage results in gradual changes, such as a decrease in pH, increase in potassium level of the storage solution and a decrease in the glucose level. The concentration of the 2,3 Di-Phospho-Glycerate (2,3-DPG) in the erythrocytes, which is virtually zero after approximately ten days of storage, recovers within several hours of transfusion.

Leukocytes removed, in storage solution, irradiated (irradiated erythrocytes)

This component has the same specifications as the standard component of leukocytes removed, in storage solution. As an extra processing step, the component is irradiated with gamma radiation at 25 Gy, aimed at preventing GvHD. Gamma radiation causes breaks in the DNA/RNA structures, which makes cell division impossible. Irradiation does cause some damage to the erythrocytes, which means that different requirements for shelf-life apply (see paragraph 2.3. Storage conditions, shelf-life and transport).

Leukocytes removed, in storage solution, paediatric component

This component has the same specifications as the standard component leukocytes removed, in storage solution, from which a maximum of four paediatric units can be prepared. The volume is 50 mL. Only components obtained from blood group O, RhD-neg or O, RhD-pos are used .

Leukocytes removed, in storage solution, paediatric component, irradiated

This component has the same specifications as the standard component leukocytes removed, in storage solution, from which a maximum of four paediatric components can be prepared. The volume is 50 mL. Only components obtained from blood group O, RhD-neg or O, RhD-pos are used.

As an extra processing step, the component is irradiated with gamma radiation at 25 Gy. Irradiation does cause some damage to the erythrocytes, which means that different requirements for shelf-life apply (see paragraph 2.3. Storage conditions, shelf-life and transport).

Leukocytes removed, in added citrate plasma, for exchange transfusion

This component is obtained by removing the storage solution from a unit of erythrocytes – leukocytes removed – and then adding a specific quantity of thawed citrate-Q (= quarantine) plasma from another donor.

As a rule, this component is used for exchange transfusions in newborns and therefore the erythrocytes used in the preparation may not have been stored for more than 120 hours (five days) after collection from the donor. The antigen typing should be compatible with mother and child. The added plasma has blood group AB and contains no clinically relevant irregular erythrocyte antibodies. The component has the same characteristics as erythrocytes – leukocytes removed – and contains a varying quantity of citrate plasma instead of erythrocyte storage solution (SAGM). The haematocrit value can be adjusted upon request to a range of 0.40 to 0.70 L/L, by varying the amount of added citrate plasma. The volume of the final component, which depends on the volume of the original erythrocyte component and the desired haematocrit, is usually approximately 300 mL. At least 135 mL erythrocytes (40 g Hb) are present. The remaining number of leukocytes is less than 1×10^6 ; platelets are not present. The component contains virtually no free calcium ions, concentration of citrate ions is 5 – 10 mmol/L, the potassium and glucose levels are physiological, the sodium level is elevated to approximately 168 mmol/L. The pH is approximately 6.9 and 2,3-DPG is present at a level of at least 50 % as the erythrocytes that are used may not be more than 5 days old.

Leukocytes removed, washed (washed erythrocytes)

Plasma proteins have been removed from the standard component (erythrocytes, leukocytes removed, in SAGM) as much as possible by washing with NaCl 0.9 % or SAGM, after which the erythrocytes are resuspended in approximately 100 mL SAGM. The number of erythrocytes is at least 135 mL (40 g Hb), the haematocrit is 0.50 – 0.65 L/L. Due to the washing, the unit contains very little IgA, allergens and complement. The number of washes performed is either 2 (prevention of allergic reactions) or 5 (prevention of reactions due to IgA deficiency).

If the washing is performed for a patient with IgA deficiency, the plasma protein in the final component should be < 30 mg.

Leukocytes removed, frozen stored and thawed

Erythrocytes that are eligible for freezing are obtained from selected donors who lack certain blood group antigens; or from designated autologous collections (patients) in specific situations. The component is prepared by removing the storage solution from a unit of erythrocytes (either buffy coat removed, or leukocytes removed) and adding glycerol as a cryo-protectant. These units are stored centrally in the Sanquin Bank of Frozen Blood (SBFB). The erythrocytes are selected for antigen typing, leukocytes removed and stored at -80 °C or -196 °C after the addition of glycerol. After thawing, the units are washed with physiological saline solution with decreasing concentrations of glucose. Finally, they are resuspended in SAGM.

The quantity of erythrocytes is at least 135 mL (40 g Hb) in physiological saline, with minimal traces of glycerol. The volume is usually 210 – 225 mL, with a haematocrit of 0.55 – 0.65 L/L. As a result of the washing, the unit contains very few plasma proteins and little extra-cellular potassium, sodium and glucose. Depending on the original erythrocyte component, the number of leukocytes is 1×10^6 or less and there are no platelets present (see also paragraph 2.2.1).

CMV negative / Parvo B19 safe

Although erythrocytes – leukocytes removed – can be considered Cytomegalovirus (CMV) safe, tests for the presence of CMV antibodies are performed if there is a specific indication. The absence of CMV antibodies indicates CMV antigen negativity. A validated test is used for this purpose. This is a characteristic of the component and not the donor. Each component should be tested again.

Parvo B19 safe blood components are obtained from donors who are positive for antibodies targeted against the Parvo B19 virus. The presence of anti-Parvo B19 is determined by 2 tests, spaced at least 6 months apart. This is a characteristic of the donor and not the component. Repeat testing is not necessary.

2.1.3 Platelet characteristics

Introduction

The common platelet component in the Netherlands is prepared from the 'buffy coats' of five different donors or an apheresis component from one donor. A unit of plasma or a specific volume of platelet storage solution (platelet additive solution type II (PAS II)) is added during the production of 'buffy coat' platelets. Apheresis techniques are used if an HLA/HPA typed platelet component is required. Either plasma or storage solution can be added to apheresis platelet components.

The use of storage solutions

The benefits of the use of storage solutions instead of plasma for platelet concentrates are reduction of transfusion reactions and less use of plasma. A disadvantage is a decreased platelet yield of 15 – 20 % in the final component.

The amount of useful literature about storage solutions for platelets is limited. An observational multi-centre study of 51 patients (277 transfusions) found no difference in yield between plasma and PAS II storage solution components (Van Rhenen 2004). A randomised study of 21 patients (322 transfusions) found a decreased yield for platelet components in PAS II storage solution (De Wildt-Eggen 2000). A larger, randomised Dutch study of 168 patients (765 transfusions) also found decreased 1-hour and 24-hour Corrected Count Increments (CCIs) after administration of platelet components in PAS II versus plasma, of 13.9 and 11.2 (difference 19.7 %) and 8.4 and 6.8 (difference 17.8 %) respectively. No differences in bleeding complications or transfusion interval were observed. Significantly fewer (milder) transfusion reactions were observed in the group transfused with PAS II platelet components, 5.5 % and 2.4 % respectively (Kerkhoffs 2006).

Conclusion 2.1.3

Level 3	An observational multi-centre study found no difference in yield between plasma and PAS II storage solution components. C <i>Van Rhenen 2004</i>
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Level 1	Platelets in PAS II have a decreased yield compared to platelets in plasma, but this does not result in more bleeding complications or a shorter transfusion interval. A2 <i>De Wildt-Eggen 2000; Kerkhoffs 2006</i>
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Level 2	Platelets in PAS II cause fewer transfusion reactions than platelets in plasma. A2 <i>Kerkhoffs 2006</i>
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Recommendation 2.1.3

PAS II + plasma can be used instead of plasma as a storage solution for platelets.

Transfusion reactions by anti-A and anti-B in plasma-incompatible platelets

Scientific support

A haemolytic transfusion reaction is a rare, but severe (sometimes fatal) complication of transfusion of so-called 'out-of-group' platelets, in which a minor ABO incompatibility occurs (plasma-incompatible platelets). Published case reports concern patients who were transfused with single-donor apheresis platelet components, from donors with high anti-A and/or anti-B titres. A retrospective study found one haemolytic transfusion reaction for over 9,000 plasma incompatible apheresis platelet components (Mair 1998). A recent systematic

review concluded that ABO identical platelet transfusions for haemato-oncology patients provided a higher yield and that ABO non-identical platelet transfusions were not associated with more transfusion reactions (Shehata 2009). Five cases of fatal haemolysis due to plasma-incompatible platelet components were reported to the FDA over a period of four years. Fatal reactions were observed primarily in patients with a relatively low circulating plasma volume, who received relatively large amounts of incompatible plasma over a short period of time. Neonates and children have a relatively low plasma volume and therefore form a separate risk group. Transfusion of ABO non-identical platelet components in cardiac surgery patients was not associated with decreased survival, increased tendency to bleed, or decreased yield (Lin 2002). The prevalence of anti-A/A,B IgM titres higher than 64 was 28 % in a group of apheresis donors (Harris 2007).

Conclusions 2.1.3

Level 3	<p>ABO identical platelets provide a higher yield than ABO non-identical platelets.</p> <p>C <i>Shehata 2009</i></p>
Level 3	<p>There are indications that fatal haemolyses from plasma-incompatible platelet transfusions occur primarily in patients with a relatively low plasma volume who receive relatively large quantities of incompatible plasma over a short period of time.</p> <p>C <i>Mair 1998</i></p>
Level 3	<p>As a result of a relatively low plasma volume, neonates and children form a risk group for fatal transfusion reactions following the administration of plasma-incompatible platelets.</p> <p>C <i>Mair 1998</i></p>
Level 3	<p>Transfusion of ABO non-identical platelet components in cardiac surgery patients is not associated with decreased survival, increased tendency to bleed, or decreased yield.</p> <p>C <i>Lin 2002</i></p>
Level 3	<p>The prevalence of anti-A/A,B IgM titres higher than 64 was 28 % in a group of apheresis donors.</p> <p>C <i>Harris 2007</i></p>

Other considerations

The anti-A and anti-B titres vary according to the determination method used. The difference in IgM and IgG class antibodies should also be taken into consideration. Titre determinations can show intra-individual and inter-individual variations. The determination of the correct anti-A and anti-B titres should take place according to a set protocol, using a standardised

method. Sanquin Blood Supply performs titre determinations using the salt technique. In the case of transfusion with incompatible plasma in neonates, the anti-A and/or anti-B titre should be less than 128. The acceptable limit of a dilution of 1:64 for anti-A/B antibodies measured in salt is in line with internationally used methods and limits. (International Forum 2005).

Recommendation 2.1.3

1. Neonates and children should preferably be transfused with ABO identical platelets.

Recommendation* 2.1.3

1. The determination of the anti-A and anti-B titres in blood components should take place according to a set protocol, using standardised methods.
2. When used in newborns up to and including the age of 3 months, combined platelet components (in plasma or PAS II) or apheresis platelet components may not contain anti-A IgM or anti-B IgM antibodies at a dilution greater than 1:64.

Leukocytes removed, five buffy coats combined in PAS II (platelets or platelets in storage solution)

The component is prepared by combining five buffy coats from identical ABO and RhD blood group with a mixture of plasma and platelet storage solution (PAS II) in a ratio of 1:2. The cells are then centrifuged to achieve sedimentation so that the upper platelet suspension can be separated and filtered. The volume of the component is 150 – 400 mL, the number of platelets is at least 250×10^9 and no more than 500×10^9 . The remaining number of leukocytes is less than 1×10^6 .

Leukocytes removed, five buffy coats combined in plasma (platelets or platelets in plasma)

The component is prepared by combining five buffy coats from never-transfused male donors with identical ABO and RhD blood group with plasma from one of these 5 donors. The cells are then centrifuged to achieve sedimentation so that the upper platelet suspension can be separated and filtered.

As a general rule of thumb, the dose for an adult is one platelet concentrate. The volume of the component is 150 – 400 mL, the number of platelets is at least 250×10^9 and no more than 500×10^9 . The remaining number of leukocytes is less than 1×10^6 .

Leukocytes removed, apheresis (apheresis platelets)

Apheresis platelets (single donor platelets) are obtained from one donor. The donor is often selected, for instance for CMV sero-negative status if the component is to be used for an IUT or HLA and/or HPA identical or compatible to match a patient with HLA and/or HPA antibodies and refractory for combined platelet components. An apheresis machine is used to harvest platelets from a donor, which are then suspended in plasma from the donor or in a mixture of plasma and platelet storage solution. Leukocyte removal takes place using the apheresis machine, or by passing the concentrate through a leukocyte removal filter. The volume of the component is 150 – 400 mL, with a target value for the number of platelets of at least 250×10^9 and no more than 500×10^9 . The remaining number of leukocytes is less than 1×10^6 . The volume of storage medium is adjusted to maintain the pH between 6.8 and

7.4 and to guarantee the presence of the 'swirling effect', a visual check for normal morphology of the platelets by swirling the component.

The more plasma the storage medium contains, the more plasma proteins are present. However, labile clotting factors are virtually absent, the potassium concentration is physiological, the sodium concentration is slightly elevated, the glucose level varies between physiological and slightly elevated – depending on the storage medium. There are virtually no free calcium ions present, the citrate concentration varies from 15 to 25 mmol/L. The pH and the glucose level decrease during storage and the lactate concentration increases.

The component contains leukocyte antigens and platelet antigens from only one donor. In the case of apheresis components from selected donors, the apheresis component may not meet the current guideline in all requirements, for example the dosage. If this is the case, the treating doctor should be consulted to decide about the use after considering availability and safety.

Paediatric use

This blood component can be split for paediatric use, with a minimum dose of 50×10^9 platelets in a volume of 40 – 70 mL. In that case, the plasma may not contain any clinically relevant irregular antibodies targeted against erythrocytes. If incompatible plasma (for example from an O donor to an A or B patient) must be used for a neonate, the titre of anti-A IgM and/or anti-B IgM must be less than 128.

2.1.4 Platelet hyperconcentrate

A platelet hyperconcentrate is obtained by taking a platelet component (obtained from apheresis or after centrifugation of five donor buffy coats) and perform further concentration by extra centrifugation and then resuspending it in a small volume of plasma (15 – 20 mL). The component is drawn up into a syringe. Depending on the desired amount of platelets to be administered, the entire component or part thereof is used (paediatric 7 – 10 mL). Due to the very limited shelf-life of only 3 hours for this component, it is prepared only upon indication.

Platelet component in 100 % PAS II

One tenth (10 %) volume ACD (acid citrate dextrose) is added to a 5-donor platelet component in PAS II. This component is concentrated after centrifugation to a platelet "pellet", which is then resuspended in PAS II storage solution. This component contains virtually no plasma. Due to the very limited shelf-life of only 3 hours for this component, it is prepared only upon indication (following consultation with the KCD of Sanquin Blood Supply).

2.1.5 Plasma, characteristics

In the Netherlands, the component: fresh frozen plasma, virus-protected by means of a quarantine method, is used for administration to patients. This component is also abbreviated as FFP (fresh frozen plasma) and any further mention of "plasma" in the text refers to this component. Plasma is obtained by plasmapheresis of male donors without a transfusion history.

Other (commercial) plasma components (including ESDEP) are also available. The position of these components with respect to the quarantine plasma supplied by Sanquin Blood Supply is not yet clear and this should be investigated. Also see Chapter 6 Platelet and plasma transfusion policy.

Plasma contains normal levels of stable clotting factors, protease inhibitors, immunoglobulins and albumin. The concentration of factor VIII and other unstable clotting factors is at least 0.70 IU/mL.

The volume of one unit is approximately 325 mL. The protein concentration and the potassium concentration are physiological, the sodium concentration is elevated to approximately 168 mmol/L and the glucose level is physiological if sodium citrate is used. The citrate concentration is between 15 and 25 mmol/L. As a result of the use of citrate anticoagulant, the component contains virtually no free calcium ions.

The component contains fewer than 1×10^6 leukocytes and virtually no platelets. If prepared by means of plasmapheresis using a 'cell free' apheresis method, the component contains fewer than 1×10^8 erythrocytes. In that case, the risk of RhD immunisation¹ by the component is considered negligible (see 3.9).

The unit of plasma is released for administration to patients if the donor has been tested with all the current tests for infectious diseases for a second time, at least 6 months after the donation, and subsequent tests have again proved to be negative.

1: Comment: Transfusions of cellular blood components, transplantations and/or pregnancies form risks of immunisation against blood cells.

Recommendation* 2.1.5

Other (commercial) plasma components (including ESDEP) are also available. The position of these components with respect to the quarantine plasma supplied by Sanquin Blood Supply is not yet clear and this should be investigated.

2.1.6 Granulocytes, characteristics

Granulocyte components are collected in a few university hospitals and supplied by Sanquin Blood Supply as an "extemporaneous component".

No fixed component specifications have been agreed upon due to the large individual donor and patient variation. However, regarding the number of granulocytes per component and in accordance with the European Guidelines, a minimum of 1×10^{10} granulocytes per component is advised (Guidelines for the preparation, use and quality assurance of blood components; Council of Europe). The initial dose of granulocytes per kilogram of body weight for the patient is preferably $> 8 \times 10^8$ /kg.

Granulocytes are obtained by means of granulocyte apheresis from selected family members or donors who are otherwise related to the patient. The granulocytes need to be mobilised in the peripheral blood prior to the apheresis procedure. This is achieved by administering G-CSF (5 µg/kg subcutaneous) and if a greater yield is required this is combined with dexamethasone (8 mg oral). Hydroxy ethyl starch (HES) is used to optimise the centrifugal separation of granulocytes and erythrocytes. The component is harvested in

plasma and – in addition to the HES – contains the anti-coagulant sodium citrate necessary for the apheresis.

The possible HLA incompatibility of donors related to the patient and the immunocompromised situation of the patient make irradiation (at least 25 Gy) of the granulocyte component essential. The time required for donor preparation and donor approval is 24-48 hours; the component can only be supplied after this time. See also 2.2.8.

An alternative source that will not be discussed here is the preparation of granulocyte transfusions from pooled buffy coats generated by the preparation of the whole blood component from regular blood donors.

2.2 Indications for blood components

2.2.1 Erythrocytes

Introduction

The indication for administering erythrocytes is based on medical factors and is aimed at treating or preventing the symptoms of a lack of oxygen transport capacity by the blood.

The Hb value at which transfusion is deemed necessary varies greatly with the age of the patient and additional illness(es), and is ultimately determined by the treating doctor. A distinction is made between acute and chronic anaemia. Different Hb values apply for intra-uterine transfusions and transfusions in neonates (see Chapter 4. Chronic anaemia and Chapter 5. Acute anaemia due to blood loss). The standard component for erythrocyte transfusion is: erythrocytes, leukocytes removed, in storage solution.

Transfusion of erythrocytes can also be used to promote haemostasis in the case of ongoing blood loss.

Dosage indication for an adult patient: 1 unit of erythrocytes results in an increase in Hb of 0.5 to 0.6 mmol/L. Also see Chapter 4. Chronic anaemia and Chapter 5. Acute anaemia due to blood loss.

Recommendation* 2.2.1

The indication for administering erythrocytes is based on medical factors and is aimed at treating or preventing the symptoms of a lack of oxygen transport capacity by the blood.

Exchange transfusion

The most important indication for exchange transfusions is severe hyperbilirubinaemia (unconjugated bilirubin) due to blood group antagonism in neonates.

For neonates, the total volume of blood that needs to be exchanged (with the aid of a syringe) is ± 160 mL/kg body weight ($\pm 2x$ the circulating volume). A special blood warmer should preferably be used. During each exchange round – at a speed of 2 – 3 minutes/round – blood is removed from the child and an equal volume of donor blood is returned. Each round consists of an exchange of 10 mL for a child weighing 1000 – 1500 grams, 15 mL for a child weighing 1500 – 2250 grams and 20 mL for a child weighing more than 2250 grams.

The platelet number is maintained above $100 \times 10^9/L$ during the exchange transfusion procedure. The platelet number is approximately halved during the exchange. Therefore, the

platelets are substituted during and after the exchange transfusion procedure, if necessary, using apheresis platelets from one donor. Specific precautions and follow-up checks apply during exchange transfusions for neonates (see Chapter 4. Chronic anaemia).

However, in addition to blood group antagonism, there can also be other causes for increased haemolysis. Polycythaemia (Ht > 0.65 L/L in venous blood) can form an indication for partial exchange transfusion (exchange transfusion with physiological saline). Another indication for exchange transfusions is severe sickle cell crisis (see paragraph 4.4.1 Acute indications for blood transfusion in sickle cell disease).

Recommendation 2.2.1

1. Exchange transfusions are indicated in case of severe hyperbilirubinaemia (unconjugated bilirubin) due to blood group antagonism in neonates and severe sickle cell crisis (see paragraph 4.4.1 Acute indications for blood transfusion in sickle cell disease). Polycythaemia (Ht > 0.65 L/L in venous blood) can form an indication for partial exchange transfusion (exchange transfusion with physiological saline).
2. It is recommended that the platelet number be maintained above $100 \times 10^9/L$ during and after the exchange transfusion procedure in neonates.
3. There are specific precautions and follow-up checks for exchange transfusions. Please refer to Chapter 4.5 Anaemia in neonates for this information.

Washed erythrocytes

The aim of washing is to remove plasma proteins. There are few indications for washed components. Components are washed 2 times for patients with a severe allergic reaction to plasma proteins. Patients with IgA deficiency may have an indication for erythrocyte components that have been washed 5 times (see also Chapter 7.2.3 Anaphylactic transfusion reaction).

Recommendation* 2.2.1

The washing of erythrocyte components is recommended for patients with a severe allergic reaction to plasma proteins (wash 2 times) and for patients with IgA deficiency (wash 5 times).

Frozen, stored and thawed

If a patient has (or has had) clinically relevant, rarely occurring irregular antibodies against a very frequently occurring blood group (HFA = high frequency antigen), or against a rare combination of blood groups, this forms an indication for the administration of erythrocytes that are negative for the corresponding antigen(s). Such rare compatible erythrocytes are not present in the regular stocks of Sanquin Blood Supply, but are frozen and stored at a central location: Sanquin Bank of Frozen Blood. (Auto-transfusion or designated donation can be considered as alternatives.) Information about frozen, stored erythrocytes can be obtained through the Clinical Consultation Service of Sanquin Blood Supply.

In addition to filtered erythrocytes, the stock of frozen erythrocytes also contains erythrocytes, buffy coat removed. These components do not meet the criteria for general leuko-reduction, because approximately 10^9 leukocytes were present before freezing. It is

possible that – due to the erythrocyte typing, these non-leukocyte removed erythrocytes are the only suitable option. The treating doctor will have to decide between transfusing this component and not performing the transfusion (in the absence of an alternative). A doctor's declaration is required if a non-leukocyte removed component needs to be supplied.

Recommendation* 2.2.1

The working group is of the opinion that the administration of frozen, stored and thawed erythrocytes that are negative for the corresponding antigen is indicated if the patient has (or has had) clinically relevant, rarely occurring irregular antibodies against a very frequently occurring blood group (HFA = high frequency antigen), or against a rare combination of blood groups.

2.2.2 Platelets

General

The administration of platelets aims to improve primary haemostasis in order to decrease the tendency to bleed or to treat an existing bleed in patients with thrombocytopenia or thrombocytopathy.

It is important that the cause of the thrombocytopenia or thrombocytopathy is established first.

For invasive procedures, the risk of the procedure in relation to blood loss should be established. Only then can the correct treatment be selected, in which the administration of platelets can play a role, in addition to other (medicinal, surgical) measures that reduce the blood loss.

The standard component is platelets that have been obtained from the buffy coats of five ABO/RhD identical donors, in plasma or PAS II.

Dosage indication for adults: 1 unit of platelet concentrate yields a platelet increase of 20 – 50 x 10⁹/L within 10 minutes or a CCI of > 7.5. Also see Chapter 6 Platelet and plasma transfusion policy.

Recommendation* 2.2.2

1. The cause of the thrombocytopenia or thrombocytopathy should always be established before opting for the administration of platelets.
2. For invasive procedures, the risk of the procedure in relation to the tendency to bleed should be established first. The correct treatment is then selected. In addition to medicinal and/or surgical measures to reduce blood loss, the administration of platelets can be considered.

Platelet hyperconcentrate

Recommendation* 2.2.2

The use of platelet hyperconcentrate can be considered for neonatal and paediatric use in order to prevent volume overload. Minor ABO incompatibility, allergic reactions to plasma and volume overload can be considered as indications for the use of platelet hyperconcentrate. (see Chapter 6. Platelet and plasma transfusion policy for details)

2.2.3 Plasma

Plasma is indicated for substitution of deficient clotting factors in:

- Thrombotic Thrombocytopenic Purpura = TTP (ADAMTS-13) and non-STECHUS¹/atypical Haemolytic Uraemic Syndrome = atypical HUS (factor H)

Plasma can be indicated in:

- bleeding associated with combined clotting factor deficiencies due to:
 - loss/dilution with crystalloids and/or colloids during massive transfusions or plasmapheresis
 - acute disseminated intravascular coagulation
 - severe liver insufficiency
 - isolated deficiency of factor V (non-recombinant/purified available)
- to counteract the effect of fibrinolytics (recombinant tissue plasminogen activator, streptokinase and urokinase) and L-asparaginase therapy;
- during plasmapheresis for thrombotic micro-angiopathies other than TTP or atypical HUS in adults.

¹: STEC HUS = Shiga-like toxin-producing E. coli-associated HUS

Other considerations

As a rule of thumb, a coagulation profile is performed to determine the extent of deficiency for all indications, with the exception of TTP. However, in clinical practice there are situations (such as massive blood loss) in which it is not feasible to wait until clotting deficiencies have been demonstrated before administering plasma. The doctor can also decide to administer plasma components based on his/her observations, without test results. With respect to the frequently mentioned target value of 1.0 g/L for fibrinogen, this value may possibly be sub-optimal for effectively stopping uncontrolled blood loss or adequately compensating for blood loss, see also 5.3.2.3. Evaluation of the effect of the administration of plasma can be performed afterwards in this case.

Dosage indication for adults: 10 – 15 mL/kg. See also Chapter 6 Platelet and plasma transfusion policy.

The effect of administration of plasma should be evaluated based on a coagulation profile.

Recommendation* 2.2.3

Plasma is indicated for substitution of deficient clotting factors in:

- Thrombotic Thrombocytopenic Purpura = TTP (ADAMTS-13) and non-STECHUS¹/atypical Haemolytic Uraemic Syndrome = atypical HUS (factor H)

Plasma can be indicated in:

- bleeding associated with combined clotting factor deficiencies due to:
 - loss/dilution with crystalloids and/or colloids during massive transfusions or plasmapheresis
 - acute disseminated intravascular coagulation
 - severe liver insufficiency
 - isolated deficiency of factor V (non-recombinant/purified available)
- to counteract the effect of fibrinolytics (recombinant tissue plasminogen activator, streptokinase and urokinase) and L-asparaginase therapy;
- during plasmapheresis for thrombotic micro-angiopathies other than TTP or atypical HUS in adults.

¹: STEC HUS = Shiga-like toxin-producing E. coli-associated HUS

Determination of the extent of deficiency by means of a coagulation profile is recommended before the administration of plasma. Exceptions to this rule are thrombotic thrombocytopenic purpura (TTP) and acute massive bleeding where waiting for clotting deficiencies to be demonstrated is not an option (see also Chapter 6.6 plasma transfusions in non-surgical patients).

It is recommended that the effect of administration of plasma be evaluated by means of a coagulation profile (also see Chapter 6.6).

2.2.4 Indication for irradiated blood components¹

Gamma radiation (25 Gy) damages the cells in the blood that are capable of cell division (monocytes, lymphocytes) to such an extent that they can no longer multiply. As a result, the Mixed Lymphocyte Culture (MLC) response also disappears.

This prevents the occurrence of so-called Graft-versus-Host disease – caused by the presence of immuno-competent lymphocytes in the donor blood – from occurring in patients who are severely immuno-compromised. It is not known how many immuno-competent lymphocytes are required to elicit such a Transfusion-Associated Graft-versus Host Disease (TA-GvHD). Whether and to what extent leukocyte-removed components protect against the occurrence of TA-GvHD has not been studied. Data from the British haemovigilance programme (serious hazards of transfusion, SHOT) suggest a decrease in the incidence of TA-GvHD after the implementation of leukocyte filtration for all blood components. In addition, SHOT emphasises the importance of irradiated blood components for the defined indications. Indications for the use of irradiated blood components were taken from international guidelines and observations by haemovigilance systems and are listed in the table below (Table 2.1). There are differences between parts of the various guidelines, for example in the most recent version of the German Guideline (Transfusion Medicine and Hemotherapy 2010;36: 345-484) it is recommended that irradiation is performed for patients with all stages of Hodgkin's lymphoma (the Dutch Guideline says only for stages 3 and 4) and also for patients with non-Hodgkin's lymphomas.

Other considerations

The length of time after stem cell transplantation for which irradiated blood components are indicated varies per centre in the Netherlands. There are no controlled studies. The working group is of the opinion that this should concur with the international guidelines. In this case, the British guidelines were followed and can be viewed as a minimum duration. The duration of use of irradiated blood components can also be extended depending on the clinical condition, such as persistent leukopaenia or in the presence of GvHD.

¹ If the term blood components is used in this paragraph, this refers to erythrocyte concentrates, with the exception of cryo-preserved erythrocytes, and platelet concentrates, so no plasma or fractionated plasma components.

When using new (possibly) immuno-suppressive medicines in a study setting on (particularly haemato-oncological) patients, it is important to consider whether these patients may be at greater risk of TA-GvHD. If that is the case, these patients should also receive irradiated blood components.

Table 2.1: Indication for the use of irradiated blood components

- | |
|--|
| <ol style="list-style-type: none"> 1. Intra-uterine transfusions, thereafter until 6 months after the due date 2. Premature babies (< 1500 gram birth weight) and/or pregnancy, <32 weeks (up to 6 months after due date) 3. Children with congenital combined immuno-deficiency (SCID) 4. Acquired immuno-deficiency as is the case with: - allogeneic stem cell transplantation (for at least 6 months after transplantation if total body irradiation formed part of the conditioning; see other considerations; - autologous stem cell transplantation (for at least 3 months after re-infusion; see other considerations). 5. After use of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) for 1 year after transfusion 6. Transfusion between 1st up to and including 3rd degree relatives of cell-containing blood components 7. Leukaemia treatments, where this is required in the protocol (see other considerations) 8. Peripheral blood stem cell apheresis: from mobilization until after collection 9. Bone marrow collection: from 6 weeks prior to collection until after collection 10. HLA compatible platelet concentrates 11. Use of purine/pyrimidine antagonists and related medication (e.g. Fludarabine, Pentostatin, Cladribine) for a year after cessation of the therapy 12. In the case of anti-T cell treatment (ATG, anti-CD52 and other T cell monoclonals) for aplastic anaemia or leukaemia: from the start of the administration through to half a year after completion of the treatment 13. Granulocyte transfusions 14. Hodgkin's lymphoma stage III or IV (with bone marrow infiltration) |
|--|

Recommendations* 2.2.4

- | |
|--|
| <ol style="list-style-type: none"> 1. It is deemed useful to follow the British guideline from the BCSH for the indications of administration of irradiated blood components. Please refer to table 2.1 Indications for the use of irradiated blood components. 2. The international guidelines are also followed for premature babies as they can have cellular immune disorders. 3. Patients who are participating in a study protocol using (possibly) immuno-suppressive medicines and who are therefore (possibly) at increased risk of Transfusion-Associated Graft versus Host Disease (TA-GvHD) should receive irradiated blood components. |
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2.2.5 Indication for CMV-safe and CMV (sero)-negative components

The CMV-virus is primarily associated with lymphocytes. Therefore, leukocyte-removed blood components are considered CMV-safe (Kuhn 2002, James 1997, Adler 1988, Smith 1993, Roback 2000). CMV sero-negative tested components are components that have been tested for the presence of CMV antibodies and have been found negative. The title CMV negative is a characteristic of the component and not a donor characteristic. In one controlled study, primary CMV infections were found in 1.3% of recipients of CMV sero-negative tested blood components and in 2.4% of the recipients of leukocyte-reduced blood; this difference was not statistically significant (Bowden 1995). Leukocyte-removed components can therefore be considered as CMV-safe (Preiksaitis 2000, Laupacis 2001).

Conclusion 2.2.5

Level 1	Leukocyte-removed blood components are considered as CMV-safe. A2 <i>Kuhn 2002, James 1997, Adler 1988, Smith 1993, Roback 2000, Bowden 1995, Preiksaitis 2000, Laupacis 2001</i>
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Other considerations

The risk of CMV contamination is very low with general leuko-reduction, but can never be eliminated completely. This is one of the reasons why, in the case of intra-uterine transfusions, the treating experts wish to administer cellular components that not only have had the leukocytes removed, but also are CMV tested sero-negative to (immuno-compromised) foetuses.

Extremely premature babies (< 32 weeks and/or < 1500 g) are also considered severely immuno-compromised. For these reasons and due to the risk of sepsis-like illness, various Western countries opt to administer only CMV sero-negative components to extremely premature babies.

Recommendations* 2.2.5

1. With the exception of cellular blood components destined for intra-uterine transfusions, it is not deemed useful to test leukocyte-removed blood components for Cytomegalovirus (CMV).
2. Prior to administration, cellular blood components destined for intra-uterine transfusions should be tested for the presence of Cytomegalovirus (CMV) antibodies and found to be sero-negative for CMV.

2.2.6 Indication for Parvo B19 safe components

The Parvo virus B19, abbreviated to B19, is a single-strand DNA virus. In children, an acute B19 infection is known as the “fifth disease” (erythema infectiosum). The course of B19 infection is mild in most children. However, B19 can cause serious health problems in some groups of patients. A B19 infection in a pregnant woman who does not have protective antibodies can result in virus transmission to the foetus. The risk of damage to the foetus is greatest during the first and particularly the second trimester of the pregnancy, and results in an increase in prenatal mortality of 10% and in hydrops foetalis in 3% of cases. Roughly a third of the unborn children with hydrops foetalis recover without intervention and one third die *in utero*. In the remaining cases, intervention in the form of intra-uterine blood transfusion resulted in a survival of more than 80% of the foetuses (Health Council 2002).

Another group of patients for whom B19 can cause problems is the patients with haemolytic disorders such as hereditary spherocytosis, thalassaemia, sickle cell anaemia, erythrocyte abnormalities due to enzyme deficiencies or auto-immune haemolytic anaemia. In patients with these haematological disorders, B19 can result in an aplastic crisis. In patients with a cellular immune deficiency, for example due to infection with HIV or due to treatment with immuno-suppressants following organ transplantation, the B19 infection can persist. This can cause long-term bone marrow damage and aplasia, not only of the erythrocytes, but also of other cell types.

A blood component is only characterised as “B19-safe” if two separate blood samples provided by the donor over an interval of at least 6 months are shown to contain no IgG

antibodies against B19. IgG antibodies against B19 neutralise the virus and give lifelong immunity. The risk of transfer of B19 through blood components from a donor with these antibodies is therefore extremely low.

The following Parvo-safe components are available: erythrocytes, platelets and plasma.

The indications summarised in table 2.2 are listed in the publication by the Health Council 'Blood components and Parvo virus B19' (Health Council 2002). The evidence for this is level D (expert opinion).

Table 2.2: Indications for Parvo B19 safe blood components (Health Council 2002)

- | |
|---|
| <ol style="list-style-type: none">1. Unborn babies receiving intra-uterine transfusions (IUT)2. Premature babies (< 32 weeks and/or < 1500 grams)3. Neonates following IUT, for 6 months after the due date4. Pregnant women (only in case of transfusion during pregnancy)5. Patients with congenital or acquired haemolytic anaemia, who do not have antibodies against B19.6. Patients with a cellular immune deficiency, who do not have antibodies against B19. |
|---|

Recommendations* 2.2.6

The working group supports the indications for administration of Parvo B19 safe blood components from the Health Council Report of 2002. These indications are:

1. Unborn babies during intra-uterine transfusions (IUT)
2. Premature babies (< 32 weeks and/or < 1500 grams)
3. Neonates following IUT, for 6 months after the due date
4. Pregnant women (only in case of transfusion during pregnancy)
5. Patients with congenital or acquired haemolytic anaemia, who do not have antibodies against B19.
6. Patients with a cellular immune deficiency, who do not have antibodies against B19.

2.2.7 Indication for washed cellular components and IgA deficient plasma

There is an indication for washing of cellular components in patients who (could) experience a severe transfusion reaction against plasma proteins. The aim of the washing is to reduce the remaining plasma protein level in the unit. See also Chapter 7.2.3 Anaphylactic transfusion reaction.

Recommendation* 2.2.7

Washing of cellular components for administration to patients who (could) experience severe transfusion reactions against plasma proteins is recommended. The aim of the washing is to reduce the remaining plasma protein level in the unit. See also Chapter 7.2.3 Anaphylactic transfusion reaction. Also refer to recommendation 2.2.1 Washed erythrocytes.

2.2.8 Indication for granulocyte transfusions

Introduction

Neutrophilic granulocytes play a crucial role in combating infections. However, in the case of congenital or acquired granulocytopenia or agranulocytosis – for example, following stem cell transplantation – severe bacterial or mycotic infections can be treated adequately in most cases with antibiotics and/or antimycotic agents. If a life-threatening infection remains present despite adequate antimicrobial therapy, treatment with granulocyte components can bring the infection under control (Atallah 2005, Price 2007, Graham 2007, van de Wetering 2007, Sachs 2006, Sharon 2008). Granulocyte transfusions can also be used prophylactically to maintain granulocyte numbers during haematopoiesis-suppressing treatments at such a level that previous life-threatening infections cannot recur. However, there are no published RCTs that irrefutably prove the effect of such treatment (Stanworth 2005, Massey 2009). A dose-effect relationship has been suggested and a granulocyte number of at least 1×10^{10} per unit is considered optimal (Stanworth 2005). The problem of obtaining sufficient evidence for this therapy is that prospective RCTs and certainly double-blind RCTs are probably not feasible for the patients in which this therapy could be useful (Seidel 2006).

Conclusions 2.2.8

Level 3	<p>There are indications that – if a life-threatening infection remains present in patients with granulocytopenia or agranulocytosis despite adequate antimicrobial therapy – treatment with granulocyte components can bring the infection under control.</p> <p>C <i>Atallah 2005, Price 2007, Graham 2007, Van de Wetering 2007, Sachs 2006, Sharon 2008</i></p>
Level 3	<p>There are no published RCTs that irrefutably prove the effect of granulocyte transfusions that are used prophylactically to maintain granulocyte numbers during haematopoiesis-suppressing treatments at such a level that previous life-threatening infections cannot recur.</p> <p>C <i>Stanworth 2005, Massey 2009</i></p>
Level 3	<p>There are indications that there is a dose-effect relationship between the prophylactic use of granulocyte transfusions so that previous life-threatening infections cannot recur.</p> <p>A granulocyte number of at least 1×10^{10} per unit is considered the optimum number.</p> <p>C <i>Stanworth 2005</i></p>
Level 4	<p>It is expected that (particularly double-blinded) prospective RCTs to substantiate the evidence-based efficacy of prophylactic use of granulocyte transfusions are probably not feasible in patients who could benefit from</p>

	this therapy.
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	D <i>Seidel 2006</i>
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Safety aspects of donor approval of granulocyte transfusions

In accordance with the EBMT/Sanquin Blood Supply guidelines, the donors are tested for the following blood-transmissible diseases: HIV, hepatitis B and C, HTLV-I/II and syphilis. As granulocyte concentrates still contain many erythrocytes, the ABO and the RhD blood group typing are also matched and any irregular antibodies (both HLA and blood group antigens) are determined for donor and patient. Cross matching for erythrocytes and (if HLA antibodies are present also) granulocytes must be performed. Major ABO incompatibility does not form an absolute contra-indication, but based on titres donor-matched plasma or RBC reduction of the granulocyte transplant is required. Acute or delayed haemolytic transfusions are a risk in this case.

Reactive HLA and/or Human Neutrophil Antigen (HNA) antibodies between donor and patient are a contra-indication for the use of that donor. For the patient, granulocyte transfusions can result in the formation of HLA or granulocyte antibodies; once present these antibodies can cause a TRALI. However, the risk of immunisation and new antibody formation is probably lower in the immuno-compromised patients involved.

For the donor, the short-term side effects of G-CSF, dexamethasone and HES should be taken into consideration. However, possible long-term effects of G-CSF also may not be excluded. Donor centres should formulate a follow-up policy for possible undesirable severe adverse effects (SAEs) in donors. Due to its invasive nature, the use of citrate (with a risk of hypocalcaemia) and sometimes significant decreases in the number of platelets, the apheresis procedure itself forms a burden for the donor. The placement of a central line in a donor for this “compassionate need” procedure, without sufficient evidence for efficacy, is ethically disputable.

A described and recorded information procedure – concluding with informed consent of the donor – is essential. A maximum of G-CSF stimulations per donor (usually three times) has been set.

Legislation

The Dutch Central Committee for Research Involving Human Subjects (CCMO) considers granulocyte transfusions as cell therapy. Cell therapies may only be administered within a clinical study protocol tested by the CCMO itself. This does not include “compassionate patient care”. However, the entire donor procedure must always be tested by a Medical Ethics Committee.

Other considerations

In the Netherlands, a clinical guideline has been drafted for paediatric patients – supported by the SKION – in order to achieve uniformity of the granulocyte transfusion treatments. This guideline: “Granulocyte transfusion in the paediatric immuno-compromised patient undergoing intensive chemotherapy or stem cell transplantation with life-threatening bacterial and/or fungal infection”, describes the donor-related activities, the apheresis procedure, the component qualifications, and the methods and follow-up of the patients involved. Within the NVvH working group for Non-Oncological Haematology, this guideline is

currently being amended for granulocyte transfusions in adults. The aim is also to use a central database to monitor all granulocyte transfusions and – if possible – to compare the treated patients with matched controls who do not receive granulocyte transfusions despite having a potential indication. Such a case-control study will hopefully generate more evidence for the efficacy of granulocyte transfusions.

Recommendations 2.2.8

1. Despite the theoretical importance and case reports that suggest the benefit of granulocytes as adjuvant therapy for severe systemic and treatment-resistant infection in granulocytopenic patients, there is insufficient convincing scientific evidence to support or reject this treatment.
2. So far, granulocyte transfusions have to be considered as a “compassionate need” treatment that is not without risks.
3. Experience concerning donor approval, donor information, donor care (during mobilisation and collection), donor follow-up, additional component preparation, patient selection and follow-up are of utmost importance.
4. For the entire granulocyte transfusion chain from donor to patient, the aim is to achieve uniform treatment guidelines (SKION / NVvH) and to combine and exchange data.
5. Granulocyte transfusions should preferably take place in the framework of (inter)national studies.

If a granulocyte transfusion is to be performed:

1. Donors should be tested for the blood-transmissible diseases HIV, hepatitis B and C, HTLV-I/II and syphilis.
2. ABO and RhD matching is essential, as is the determination of irregular erythrocyte and HLA antibodies, and the performance of erythrocyte cross matches and (in the case of HLA antibodies) granulocyte cross matches.
3. Major or minor ABO incompatibility does not form an absolute contra-indication, but does create a risk of acute or delayed haemolytic transfusion reactions. In the case of major or minor incompatibility between the donor and the patient, measures (tailored to antibody titres) should be implemented to reduce the number of red blood cells and plasma if relevant.
4. Reactive HLA and/or HNA antibodies between donor and patient should be considered as a contra-indication for the donor involved.
5. The short and long term risks to the donor of the administration of G-CSF and side effects of HES should be taken into consideration.
6. A described and recorded information procedure – concluding with informed consent of the donor – must be present. A maximum number of G-CSF stimulations per donor (usually three times) should also be set. Donor centres should also formulate a follow-up policy for possible undesirable severe adverse effects (SAEs) in donors.

2.3 Storage conditions, shelf-life and transport

2.3.1 Introduction

The storage conditions, the shelf-life and the requirements for the transportation of blood components are set by Sanquin Blood Supply . Storage systems for blood components must

meet the requirements for Good Manufacturing Practice (GMP). This includes the requirement that it must be fitted with a (continuous) temperature registration system and an acoustic alarm, so that measures can be taken to secure the required temperature. The requirements for minimum and maximum temperatures must also be guaranteed during transport to the hospital and during storage in the hospital.

There are various storage and transport systems available. These must be validated before use. The shelf-life of the blood components – as indicated on the label by the supplier – applies as long as the component has been stored and transported correctly. The storage conditions to guarantee the shelf-life of the various blood components must be indicated exactly under all conditions (both storage and transport) and must be recorded in working instructions. The temperature of the blood component is recorded from the moment of donation (whole blood and plasma).

Materials or components other than blood components may not be stored in the blood storage systems. So-called household refrigerators are not suitable for the storage of blood components for transfusion.

Recommendations* 2.3.1

1. Storage systems for blood components must meet the requirements for Good Manufacturing Practice (GMP).
2. Storage and transport systems must be validated before use.
3. The storage conditions for blood components must be indicated exactly for all conditions and must be recorded in a working instruction.
4. The temperature of the blood component is recorded from the moment of donation (whole blood and plasma).
5. Materials or components other than blood components may not be stored in the blood storage systems. So-called household refrigerators are not suitable for the storage of blood components for transfusion.

2.3.2 Storage conditions, shelf-life and transport of erythrocytes

As far as biochemical composition and shelf-life are concerned, it has been proven that the best storage temperature for erythrocytes is between 2 °C and 6 °C. The risk of bacterial growth is also acceptably low at this temperature. The temperature during storage and transport may never be lower than 1 °C. Unless stated otherwise, erythrocytes have a maximum shelf-life of 35 days.

If a validated storage system is not in use, erythrocytes should be administered to the patient within 6 hours of receipt.

The aim should be to keep the component outside the refrigerator (temperature > 10 °C) for no longer than half an hour before administration to the patient. This can mean that departments where blood is stored (both operating rooms and recovery rooms) for a longer time (maximum of 24 hours) before transfusion must be fitted with validated blood storage refrigerators. The hospital is responsible for developing a policy for this.

After opening or inserting a needle/spike into the system, the maximum storage time is limited to a maximum of 6 hours due to the risks of bacterial growth.

Erythrocyte components that have reached a temperature exceeding 10 °C after storage may not be returned to storage and must be administered within 6 hours or otherwise they

must be destroyed. Erythrocyte components must be destroyed if the storage temperature has exceeded 25 °C (Sanquin Guideline Blood Components 2008).

Recommendations* 2.3.2

The standard erythrocyte component :	
1.	Should be stored at a temperature between 2 °C and 6 °C. The temperature during storage and transport may never be lower than 1 °C.
2.	May not be kept outside the refrigerator for longer than approximately half an hour before administration to the patient.
3.	Has a maximum shelf-life of 35 days, unless stated otherwise.
4.	Has a maximum shelf-life of 6 hours after opening or insertion of a needle in the system, due to the risks of bacterial growth.
5.	May not be returned to storage and must be administered within 6 hours if the component has warmed to above 10°C after storage, or otherwise must be destroyed.
6.	Must be destroyed if the temperature of 25 °C has been exceeded.

Storage duration of erythrocytes in relation to clinical course

The initial observation that the storage duration of erythrocyte concentrates is associated with the clinical course was published in 1994 (Martin 1994). Many observational studies have been published since then and only 1 RCT that examined the associations between storage duration and the prognosis. The RCT was a pilot study, which does not provide definite answers due to the limited size (Hebert 2005). Many of the observational studies reported their results without correcting for the known risk factors, such as the total number of erythrocyte concentrates administered (Purdy 1997, Zallen 1999, Offner 2002, Murrel 2005, Weinbert 2008, Koch 2008). Studies that did correct for this revealed virtually no independent associations after correction, even though these often were present before correction (Vamvakas 2000, Leal-Noval 2003, Gajic 2004, Van de Watering 2006, Leal-Noval 2008, Yap 2008, Dessertaine 2008, Kneyber 2009).

The only statistically significant, independent association that was reported concerns the occurrence of pneumonia after CABG (Vamvakas 1999). Although the (long) storage time in this study was associated with the occurrence of pneumonia, a follow-up analysis revealed no association with respirator time, ICU stay or hospital stay.

At the time of this revision several RCTs were taking place in North America studying the effects of the storage time of erythrocyte concentrates in specific patient groups. Fergusson and Lacroix examined 90 day mortality in high risk ICU patients (Fergusson ongoing study, Lacroix ongoing study). Gajic examined pulmonary functioning and immune activation in ventilated ICU patients (Gajic ongoing study). The study by Koch has changed design regularly “during inclusion” and has been extended by a further 2 years at the time of this revision (Koch ongoing study).

Conclusion 2.3.2

Level 2	The current literature provides no indication for reducing the maximum storage time of erythrocyte concentrates from 35 days.
	<i>B Vamvakas2000; Leal-Noval 2003; Gajic 2004; Van de Watering 2006; Leal-Noval 2008; Yap 2008; Dessertaine 2008; Kneyber 2009,</i>

Leukocytes removed, washed

If resuspended in SAGM storage solution with the aid of a closed system, washed erythrocytes can be stored for a maximum of five days at a temperature between 2 °C and 6 °C in a blood storage refrigerator (Sanquin Guideline Blood Components 2008).

Recommendation* 2.3.2

If resuspended in SAGM storage solution with the aid of a closed system, the washed component leukocytes removed, erythrocyte concentrate can be stored for a maximum of five days at a temperature between 2 °C and 6 °C in a blood storage refrigerator.

Leukocytes removed, frozen stored and thawed

Erythrocytes with a rare typing are stored by Sanquin Blood Service in the Sanquin Bank of Frozen Blood (SBFB) at a temperature below -150 °C (older procedure) or below -80 °C (newer procedure), using a cryo-preservative. These frozen units can be stored for a maximum of 10 years. The maximum storage time after thawing and washing is a of 24 hours (older procedure) or 48 hours (newer procedure), if the component is stored in a blood storage refrigerator at 2 °C – 6 °C.

Recommendation* 2.3.2

Frozen erythrocytes from the Sanquin Bank of Frozen Blood, once thawed may be stored in a blood storage refrigerator between 2 °C and 6°C, for:

- a maximum of 24 hours after being frozen at a temperature below -150 °C (older procedure);
- a maximum of 48 hours after being frozen at a temperature below -80 °C (newer procedure);

Erythrocytes for intra-uterine and exchange transfusions

Erythrocytes destined for intra-uterine administration and erythrocytes for exchange transfusions have specific shelf-life requirements.

Recommendations* 2.3.2

1. Pooled blood (consisting of erythrocytes less than 5 days old, from which the storage solution has been removed and to which citrate plasma has been added) destined for exchange transfusion should be administered as soon as possible. However, pooled blood can be transfused up to 24 hours after preparation, provided it has been stored in a blood storage refrigerator at 2 °C – 6 °C.
2. Irradiated exchange components can – as is the case with non-irradiated components – be stored for 24 hours after preparation (and irradiation), provided they are stored in a blood storage refrigerator at 2 °C – 6 °C.
3. Once erythrocytes have been made suitable for intra-uterine administration, the component can no longer be stored and should be administered immediately.

2.3.3 Storage conditions, shelf-life and transport of platelets

Introduction

The environmental temperature may not drop below 18 °C during the entire storage period, including transportation, up to the transfusion; this means that platelets may not be stored in the refrigerator. Cooled platelets undergo irreversible membrane changes and are immediately intercepted by macrophages in the spleen, meaning that the yield is virtually zero.

Metabolic changes, such as a decrease in pH and glucose level and an increase in lactate levels occur during storage. In order to combat these storage effects, the platelet component is contained in a semi-permeable (oxygen-permeable) storage bag and it must be stored on a shaker/mixer in a platelet storage cupboard (under continuous temperature monitoring). Platelets are stored at a temperature between 20 °C and 24 °C. Under these conditions, platelet components can be stored for a maximum of seven days in plasma and a maximum of 5 days in PAS II.

A number of hospitals have facilities for optimum storage of platelets (temperature-controlled shaking equipment). If these facilities are available, the expiry date and time listed on the component can be adhered to. Shaking should be resumed as soon as possible after receipt in the hospital.

Platelets should be administered immediately after release by the blood transfusion laboratory. After opening or inserting a needle/spike into the system, the maximum administration time is limited to 6 hours due to the risks of bacterial growth.

If the component is not shaken during storage, this will result in glycolysis with lactate production, bicarbonate depletion and CO₂ accumulation, which will cause the pH of the component to drop. Research into in vitro parameters (such as pH, CD62P expression, morphology scores and hypotonic shock response) of non-shaken platelets showed that platelet components that have been kept without continuous agitation for a maximum of 24 hours still maintain acceptable in vitro parameters (Van der Meer 2007). Platelet components stored without shaking for a longer period retained a pH that was permanently too low. If the so-called 'swirling' remains present, unshaken (for a maximum of 24 hours) platelets can also be administered. The use of gamma irradiation on platelet components does not affect the maximum storage duration; the above-mentioned facts therefore relate to both non-irradiated AND irradiated platelet components.

If contamination has occurred, the storage method (between 20 °C and 24 °C under continuous agitation and oxygen exchange) can easily result in bacterial overgrowth within platelet concentrates. As part of improving the bacterial safety of platelet components, each unit is screened immediately after preparation for aerobic and anaerobic bacterial contamination using the BacT/ALERT system. A representative sample is cultured for 7 days. The result of the bacterial screening is checked automatically at the time of release by Sanquin Blood Supply. All components that have had a negative screening up to that point are released ("negative-to-date"). If the BacT/ALERT gives a positive signal after release, the hospital involved will be informed. The hospital should have a policy that guarantees that the platelets – already released by Sanquin Blood Supply, but not administered yet – suspected of bacterial contamination can be destroyed. In situations where already administered platelets with a possible bacterial contamination are involved, the consequences for the patient should be determined.

Recommendations* 2.3.3

1. Platelets should be stored at a temperature between 20 °C and 24 °C. There is a maximum storage time of 7 days for platelets in plasma and 5 days for platelets in PAS II.
2. Platelets should be administered immediately after release by the blood transfusion laboratory. After opening or inserting a needle/spike into the system, the maximum administration time is limited to a maximum of 6 hours due to the risks of bacterial growth. This applies to both non-irradiated and irradiated platelets.
3. If the so-called 'swirling' remains present, unshaken platelets can also be administered (for a maximum of 24 hours). This applies to both non-irradiated and irradiated platelets.
4. The hospital should have a policy that guarantees that the platelets – already released by Sanquin Blood Supply, but not administered yet – suspected of bacterial contamination can be destroyed. In situations where already administered platelets with a possible bacterial contamination are involved, the consequences for the patient should be determined.

Platelet hyperconcentrate

Recommendation* 2.3.3

Platelet hyperconcentrate is supplied in a 20 mL syringe and can be kept (at room temperature) for a maximum of 3 hours.

Platelets in 100% PAS II

Recommendation* 2.3.3

Once processed, platelets in 100% PAS II can be kept for 3 hours in a platelet storage bag, placed in a platelet storage cupboard under continuous agitation at 20 – 24 °C.

2.3.4 Storage conditions, shelf-life and transport of plasma

In order to maintain the activity of the clotting factors, this component should be stored at a temperature of -25 °C or lower. The shelf-life in that case is a maximum of two years. During transportation, the component temperature should not exceed -18 °C.

The plasma should be thawed in a designated and validated piece of equipment, such as a special microwave oven, plasmatherm or in a waterbath, at a maximum of 37 °C (temperature monitoring is required).

A loss of activity of the clotting factors occurs upon thawing, which means that the storage duration of the thawed component is limited. Dutch (Lamboog 2007) and foreign studies show that the activity of ADAMTS13 did not decrease significantly for two weeks after thawing, provided the plasma was stored at 2 °C – 6 °C. Factor V and Factor VIII activity decreased by 25 – 35% and 50% respectively. The fibrinogen level decreased by 8% (Buchta 2004, Downes, 2001, Woodhams, 2001. According to the 'Guide to the preparation, use and quality assurance of blood components, 13th ed' from the Council of Europe, the plasma

component should contain > 70% of the activity of the fresh component after thawing (Council of Europe 2007). This requirement is not met for the FVIII activity in the thawed component that is stored at 2 °C – 6 °C for 14 days. Nevertheless, we can conclude that this component can be deemed suitable for adequate support of haemostasis following trauma or massive blood loss, with the exception of FVIII deficient patients. Thawed plasma components should preferably be administered as soon as possible, however the fact that sufficient clotting factor activity is maintained means that the component can also be stored at 2 °C-6 °C for at least 24 hours.

During the storage of thawed frozen plasma, the concentration of the lipophilic plasticiser in the plastic bag – the di(2-ethyl hexyl) phthalate (DEHP) increases in the plasma over time, most significantly at room temperature and to a lesser extent at 4 °C (Luban 2006). This DEHP has toxic effects on fertility and the foetal development. (Commission Directive 2001, (http://www.noharm.org/lib/downloads/pvc/DEHP_Exposure_of_Infants.pdf)).

Due to the lack of alternatives, the benefits of thawed plasma “on the shelf” for trauma surgery (among others) must be weighed against the disadvantages of DEHP toxicity. It is preferable to administer the plasma within two hours after thawing.

When stored at room temperature and after opening or inserting a needle/spike into the system, the maximum storage time is limited to 6 hours due to the risks of bacterial growth. During this period there is no significant difference in activity or level of clotting factors. Plasma that has been thawed may not be frozen again.

Conclusions 2.3.4

Level 3	<p>Provided storage takes place at 2 °C – 6 °C, the activity of ADAMTS13 in plasma did not decrease significantly for 2 weeks after thawing. Factor V and Factor VIII activity decreased by 25 – 35% and 50% respectively. The fibrinogen level decreased by 8%.</p> <p><i>C Downes 2001, Woodhams 2001, Buchta 2004, Lamboo 2007</i></p>
Level 3	<p>The concentration of the toxic Di(2-ethyl hexyl) phthalate (DEHP) increases during the storage period of thawed frozen plasma.</p> <p><i>C Luban 2006</i></p>

Recommendations 2.3.4

1.	In order to maintain the activity of the clotting factors, plasma should be stored at a temperature of -25 °C or lower. The shelf-life in that case is two years.
2.	During transportation, the temperature of the plasma should not exceed -18 °C.
3.	The plasma should be thawed in a designated and validated piece of equipment, such as a special microwave oven, plasmatherm or in a waterbath, at a maximum of 37 °C. Temperature monitoring is required.
4.	It is recommended that thawed plasma components be administered as soon as possible. However, the fact that sufficient clotting activity is maintained means that the component can also be stored at 2 °C – 6 °C for at least 24 hours.

5. When stored at room temperature and after opening or inserting a needle/spike into the system, the maximum storage time is limited to 6 hours due to the risks of bacterial growth.
6. Plasma that has been thawed may not be frozen again.

2.3.5 Shelf-life of irradiated components

The irradiation of blood components can cause damage, even to non-dividing cells. In addition to biochemical changes to the erythrocyte – such as potassium leakage and decreased ATPase activity – functional abnormalities also occur, such as decreased deformability. As a consequence the storage time for erythrocytes in particular is shortened. As components that were collected recently incur damage less quickly than components that have been stored for a longer period, the storage times will differ. In all cases the expiry date/time is indicated on the bag.

More stringent standards apply for neonates and for young children receiving massive transfusions. Therefore, irradiated erythrocytes and irradiated blood for exchange transfusions may not be used more than 24 hours after irradiation (see also under exchange transfusions). The use of irradiated components and the accompanying shelf-life means that the intention to use several splitcomponents from one donor cannot always be met.

Table 2.3: Age¹ of erythrocyte component at time of gamma irradiation and shelf-life after gamma irradiation

Patient group	Age of component at time of gamma irradiation	Shelf-life after gamma irradiation
Intra-uterine transfusion	Maximum 3 days	Maximum 6 hours
Neonates and children with massive transfusions	Maximum 5 days	Maximum 24 hours
Adults and children	Less than 14 days	Maximum 28 days
Adults and children	More than 14 days	Maximum 24 hours

Recommendation* 2.3.5

Please refer to table 2.3 'Age of erythrocyte component at time of gamma irradiation and shelf-life after gamma irradiation' for the recommendations concerning the shelf-life of gamma irradiated blood components .

2.3.6 Shelf-life of CMV negative / Parvo B19 safe components

Both specifications do not have any effect on the shelf-life, storage time or transport conditions for the blood components.

¹ Age = time calculated from the collection

Shelf-life of granulocytes

The granulocyte component has a short shelf-life, with infusion within 6 hours of collection being preferable. The maximum shelf-life is 24 hours (Drewniak 2008, Hubel 2005).

Recommendation* 2.3.6

The granulocyte component has a short shelf-life, with infusion within 6 hours of collection being preferable. The maximum shelf-life for granulocyte components is 24 hours.

2.4 Nursing aspects

2.4.1 Nursing aspects, general

Many practical matters concerning transfusions of blood components are based on habit and experience, they are rarely evidence-based. Systematic research would be very desirable. In addition to nurses, perfusionists and anaesthesiology assistants are the professionals who perform the blood transfusion. These employees are the last link in the long transfusion chain and they have specific responsibilities; they are subject to specific requirements.

Based on a number of frequently asked questions, the working group has formulated "recommendations*" (opinion of the working group) based on international (UK, Australia) guidelines and manuals (see literature list).

A number of these recommendations* apply mainly to transfusions in non-acute situations on non-surgical wards. Peri-operative and/or acute blood loss sometimes requires deviation from these recommendations.

Requirements for the nurse who administers a transfusion

Recommendations* 2.4.1

1. The employee who performs the blood transfusion must be authorised and skilled, as described in the BIG Law. Nurses must have a BIG registration for this and other employees (anaesthesiology assistants, perfusionists) are deemed authorised and skilled due to their training.
2. It is essential that the nurse has access to clear procedures and is regularly involved in the administration of blood components.
3. It is recommended that nurses involved in blood transfusions be given regular training concerning blood transfusion and the possible side effects.

Recommendations* 2.4.1

1. The employee who administers the blood component is responsible for checking the blood component, patient identification, information and the entire procedure surrounding the administration.
2. The person who actually administers the transfusion is responsible for recording the information in the (electronic) patient file and for reporting any transfusion reaction according to the hospital protocol.
3. The Board of Directors, or an official (haemovigilance officer or blood transfusion commission) appointed by the board, is responsible for the correct process when reporting transfusion reactions to the various responsible institutions and for recording the procedures within the institution.

Use of self-protection measures due to the risk of transmission of infection

In the Netherlands, donors are checked for a number of important blood-transmissible diseases (Hepatitis B and C, HIV, HTLV and Lues) when they donate blood. This ensures that blood components pose a low risk of transmission of infection.

If transported carefully, there is no contact with the blood component. Careful handling is advised when inserting a needle/spike into the blood component, inserting and removing an infusion needle/spike, or removing the empty unit after transfusion as needle stick accidents can occur.

2.4.2 Nursing aspects; administration

Administration methods

In general, blood components can be administered safely via a peripheral indwelling catheter, a Central Venous Catheter (CVC), Peripherally Inserted Central Catheter (PICC) or Port-a-Cath.

There is no minimum or maximum diameter for the transfusion canula (standard 18 Gauge to 24 Gauge (small lumen)). The size and quality of the blood vessel determines the size of the canula.

In general, a transfusion via a thin canula will take longer, which means the desired result also takes longer. In general, an 18 to 20 Gauge canula is advised for adults and a 22 to 24 Gauge canula for children.

Recommendations* 2.4.2

1. Blood components can be administered via a peripheral indwelling catheter, Central Venous Catheter (CVC), Peripherally Inserted Central Catheter (PICC) or Port-a-Cath.
2. An 18 to 20 Gauge transfusion canula is recommended for adults and a 22 to 24 Gauge canula for children, the size of the canula is partly determined by the size and quality of the blood vessel. There is no minimum or maximum diameter for the transfusion canula.

Infusion pumps and syringe pumps

Recommendations* 2.4.2

1. The use of a volume-controlled infusion pump or syringe pump is recommended for small infusion volumes and/or slow administration.
2. Infusion pumps and syringe pumps may be used for the transfusion of blood components if this is specifically mentioned in the manufacturer's specifications of the pump. Upon request, the manufacturer must also be able to demonstrate that use of the pump does not result in haemolysis or damage to the blood component.
3. In general, erythrocytes, platelets and plasma can be administered safely via a volume-controlled infusion pump.

- The working group is of the opinion that the infusion pump or syringe pump and the volume administered should preferably be checked at least 1x per hour during a transfusion of a unit of erythrocytes.

Filters

A coarse filter (170 – 200 µ) removes the minimal clots and precipitate that can form during the preparation process of the blood component.

Recommendation* 2.4.2

Blood administration systems should be fitted with a coarse filter (170 – 200 µ filter)

Administration systems

Recommendations* 2.4.2

- Administration systems may be used for the administration of a blood component if the manufacturer's specifications indicate that the system is suitable for this purpose.
- The combination of the administration system and the pump that is used should also be described in the manufacturer's specifications.
- Special paediatric administration systems are available for transfusions in children, or a syringe linked to a 170 – 200 µ filter is used. The syringe is labelled with the patient's details.

Replacement of administration systems

Administration systems for blood components pose a risk of bacterial growth. A study by Blest describes that this risk is reduced by replacing the administration system every 12 hours and at the end of the administration (Blest 2008).

Conclusion 2.4.2

Level 3	The risk of bacterial growth is minimised by replacing the administration system for blood components every 12 hours. C <i>Blest 2008</i>
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Recommendation 2.4.2

Administration systems for blood components should be replaced every 12 hours and as soon as possible after the end of the administration.

The clean blood administration system should be filled with NaCl 0.9% before the start of the transfusion in order to prevent the blood component from “sticking” to the wall of the system as much as possible.

Should the administration system be rinsed with NaCl 0.9% after each blood component?

There is no recent literature available about rinsing the administration system after each blood transfusion. Glucose 5% can cause haemolysis and may never be used to fill and/or rinse an administration system. Calcium-containing solutions interact with a citrate-

containing blood component and are therefore strongly discouraged. An isotonic calcium-free solution could be used, but it is safer to use NaCl 0.9% solution as the exact contents of other solutions is usually not known.

Recommendation* 2.4.2

The working group is of the opinion that:

- The blood administration system should be (visually) clean before the start of a transfusion.
- The blood administration system should be filled with NaCl 0.9% before the start of the transfusion.
- The blood administration system should be rinsed with NaCl 0.9% after each transfusion episode.

Administration of platelets and erythrocytes via the same administration set

If platelets are administered via the same administration system that has previously been used for **erythrocytes**, the precipitate in the filter from the first transfusion will trap the platelets and hamper their administration. In practice, the administration of **erythrocytes after transfusion of** platelets does not pose any problems.

Recommendation* 2.4.2

The working group is of the opinion that platelets should always be administered via a clean (unused) administration system.

Warming of erythrocytes and/or plasma before administration

Recommendations* 2.4.2

1. The warming of erythrocytes and/or plasma before transfusion is recommended in the following cases only:
 - for administration > 50 mL/kg/hour for adults;
 - for administration > 15 mL/kg/hour for children;
 - for exchange transfusion in neonates and children;
 - for patients with clinically proven, strong cold antibodies, which have been demonstrated – *in vitro* – at 37 °C.
2. The warming of erythrocytes is performed exclusively upon prescription of the treating doctor (following advice from the blood transfusion laboratory).
3. Erythrocytes and plasma should only be warmed in equipment validated specifically for that purpose. Erythrocytes and plasma should never be warmed in a standard microwave oven, in warm water or on a central heating radiator.

Administration speed of the various short shelf-life blood components in neonates, children and adults

Recommendation* 2.4.2

The administration speeds as listed in table 2.4 are recommended for neonates, children and adults:

Table 2.4: Administration speeds

	erythrocytes	platelets	quarantine plasma
neonates	15 mL/kg in 3 hours	$10 \times 10^9/\text{kg}$ (10 mL/kg) in $\frac{1}{2}$ an hour	10 – 15 mL/kg maximum in 3 – 4 hours
children	10 – 15 mL/kg in 3 – 4 hours	$10 \times 10^9/\text{kg}$ (10 mL/kg) in $\frac{1}{2}$ an hour	10 – 15 mL/kg maximum in 3 – 4 hours
adults	1-6 ¹ hours/unit	20 minutes	20 – 30 minutes

¹: If the infusion speed needs to be so low that the entire unit cannot be administered within 6 hours, this could form a reason to transfuse smaller quantities (paediatric units).

Other considerations

Slow administration and the possible use of a diuretic are advised for cardiac-compromised patients (see Recommendation 4 under 7.2.7).

Identification of the correct component for the correct patient

Recommendation* 2.4.2

Prior to every transfusion, the following information should be checked by the blood transfusion laboratory employee before transfer to the nursing ward:

- patient's name
- date of birth
- identification number
- request and component
- component number
- blood group
- presence of antibodies

The blood transfusion laboratory employee should sign for the above-mentioned checks before release, and an authorised person on the nursing ward must sign for receipt.

Identification of patient by employee administering the transfusion.

The most crucial step in preventing incompatible transfusions is the bedside patient identification (surname, initials, date of birth, gender, patient identification number) and compatibility check (component blood group). This check takes place visually/in writing and is performed by two individuals, of whom at least one is an authorised employee or doctor. If identification checks are performed by means of scanning barcodes, then the process can be performed by one person.

If a student administers a blood component, this must be performed under direct supervision. The person who performs the transfusion is ultimately responsible for the accuracy of the identification.

Recommendations* 2.4.2

1. The nurse should check prior to every transfusion that the component for transfusion matches the information on the request and that there are no abnormalities (such as damage, unusual discolouration or turbidity, the presence of large clots) upon visual inspection. If abnormalities are detected, the transfusion component is not transfused.
2. This check must be performed once more at the patient's bedside prior to administration by the person who administers the transfusion, together with another person. This last check should be performed at the same time as the patient identification, with initials being placed again, unless the identification checks are performed by means of scanning the barcodes.
3. If the identification at the bedside reveals any discrepancies for which no explanation has been given on the compatibility declaration, the unit of blood component should not be transfused. The blood transfusion laboratory must be informed of this and the unit should be returned.

Recording of vital parameters before, during and after transfusion.

No distinction is made between the various blood components for the checking of vital parameters. Vital parameters recorded for blood transfusion are:

- temperature;
- heart rate;
- blood pressure;
- evaluation of the patient's condition.

These four vital parameters are also recorded after the blood transfusion. In addition, the following is also recorded after the blood transfusion:

- which component was administered;
- transfusion reaction yes/no.

The patient should be monitored closely, particularly during the first 5 to 10 minutes of the transfusion, because severe reactions (anaphylactic reactions), haemolysis due to ABO incompatibility, TRALI and the effects of bacterial toxins) are usually exhibited shortly after the start of the transfusion. The severity of the reaction is proportional to the quantity administered at that moment. Therefore, it is advisable not to administer more than 20 mL of blood component during the first 10 minutes.¹ If no abnormalities are observed, the transfusion can then continue at the agreed administration speed.

1: Obviously a smaller volume applies for neonates who receive a small component volume.

Recommendations* 2.4.2

1. The patient should be observed for the first 5 to 10 minutes of the transfusion.
2. It is recommended that no more than 20 mL of the blood component be administered during the first 10 minutes of the transfusion. If no abnormalities are observed, the transfusion can then be continued at the agreed administration speed.
3. Please refer to table 2.5 for the vital parameters that should be recorded before, during and after blood transfusion.

Table 2.5: Recording of vital parameters

	before transfusion	5 – 15 minutes after start of transfusion	during transfusion reaction	during disconnection	after transfusion
temperature	+	+	+	+	+
heart rate	+	+	+	+	+
blood pressure	+	+	+	+	+
evaluate condition of patient	+	+	+	+	+
recording of administration					+
recording presence/absence of transfusion reaction					+

Recording the effect of the transfusion

The doctor can request that the effect of a transfusion be measured.

Erythrocyte transfusion: in an adult, an increase of 0.5 – 0.6 mmol/L Hb is expected after administration of one unit of erythrocytes. One should wait at least 15 minutes after transfusion of an erythrocyte concentrate to measure the effect on Hb concentration.

Platelet transfusion: the effect can be determined 10 – 60 minutes (so-called 1-hour value) and/or 16 – 24 hours (so-called 24-hour value) after administration (see also paragraph 2.2.2). If the 24-hour value is insufficient ($< 5 - 10 \times 10^9/L$ increment), a 1-hour measurement must also be performed after the next platelet transfusion.

Plasma transfusion: the effect is measured by determining PT, aPTT and (in exceptional circumstances) the fibrinogen concentration.

Comment: Clinical circumstances – such as prematurity, dysmaturity or a low birth weight – can hamper blood collection from a child to determine the efficacy of the erythrocyte or plasma transfusion; however, the effect of the platelet transfusion should be determined.

Recommendation* 2.4.2

One should wait at least 15 minutes after an erythrocyte transfusion to determine the effect of the transfusion.

The simultaneous administration of blood components with intravenous medications through a single lumen infusion system

Due to the possible occurrence of a reaction between the medicine and the blood component it is not recommended to administer blood components simultaneously with intravenous medication solutions through a single lumen infusion system. Undesirable immediate effects such as haemolysis and/or agglutination depend among other factors on the type of blood component, dosage of the medication and the duration of the contact between the two (van den Bos 2003). This and other studies show that the extent of haemolysis as a result of the simultaneous administration in the conditions examined is acceptable. However, it is difficult to extrapolate *in vitro* study results to clinical relevance (Murdock 2009). Further research on this subject is desirable.

Other considerations

The recommendation that medication and a blood component may not be administered simultaneously via a single lumen infusion system regularly causes practical problems. Further research on this subject is desirable.

Recommendations* 2.4.2

1. Medication may never be administered simultaneously with blood components via a single lumen infusion system.
2. Medication can only be administered via a single lumen infusion system if a second administration system with a three-way stop cock is used whilst the administration of the blood component is halted temporarily.
3. The infusion system (peripheral infusion) must be rinsed thoroughly before and after the administration of medication using an indifferent infusion solution such as NaCl 0.9%, before the transfusion can resume.
4. The transfusion may not be interrupted for longer than 2 hours and the transfusion line may never be disconnected in the meantime due to the risk of bacterial contamination.
5. *In general*, double or triple lumen catheters are suitable for the simultaneous administration of blood components and medication. It is advisable to reserve one lumen specifically for the administration of blood components.
6. Further research into the effect of the simultaneous administration of blood components and intravenous medication through a single lumen infusion system is recommended.

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ADDENDUM

Bloodcomponents : characteristics, indications, logistics and administration

Table 2.6: Translation table component names

<i>CBO Guideline</i>	<i>Alternative name</i>	<i>Sanquin Blood Guide</i>
Erythrocytes	Erythrocyte concentrate (EC)	Erythrocytes in SAGM
Irradiated erythrocytes		Erythrocytes in SAGM, irradiated
Washed erythrocytes		Erythrocytes in SAGM, washed
Platelets (in plasma)	Platelet concentrate (TC)	Platelets comb., in plasma
Platelets (in storage solution)		Platelets comb., in PAS II / plasma
Apheresis platelets		Platelets apheresis, in plasma
Plasma	Quarantine plasma	Plasma, apheresis, fresh frozen
	FFP (fresh frozen plasma)	

Price indication standard blood components (price indication January 2011)	
component	tariff
erythrocytes	€ 210,50
platelets (5 DU) prepared from buffy coats	€ 508,60
plasma	€ 181,00

CHAPTER 3: LABORATORY ASPECTS

Set up

This third chapter of the guideline discusses the laboratory aspects of the blood transfusion process. The following will be discussed consecutively: request of blood and blood components (3.1), the laboratory examination (3.2), compatibility study (3.3), how to handle data from third parties (3.4), the release and transfer of blood components (3.5), selection of erythrocyte concentrate (3.6), selection of erythrocyte concentrate in special patients (3.7), the release of platelets (3.8) and the release of plasma (3.9).

3.1 Accessory conditions for processing of requests for blood and blood components

Scientific support

The developments in clinical chemistry and haematology laboratories over the past decades – with both the number of requests and the complexity of the examination requested increasing – means that high standards apply to correct administrative processing and the associated logistics processes. This applies in particular to all transfusion-related requests for examination and release of blood components. Linden, Williamson, Love and Stainsby analysed the blood transfusion incidents that were reported in the state of New York from 1990 to 2000 (Linden 2000, Linden 1992) and similar reports in England from the British Haemovigilance Service SHOT (Williamson 1999), from 1996 to 2000 (Love 2001) and from 1996 to 2003 (Stainsby 2005). These analyses show that over 50% of the reported incidents were caused by administrative errors¹. Of these administrative errors, 10 – 50% were due to collection for the wrong patient or incorrect identification of the blood sample.

Dzik et al showed in 2003 in an international study in 10 countries of 700,000 samples for transfusion laboratories that for 1:2000 samples the blood group did not match a previous determination (Dzik 2003). This was confirmed by Murphy et al in 2004 (Murphy 2004).

The reports from the TRIP National Haemovigilance Office from 2003 through till 2007 show that for the total of 317 reported near-accidents, more than 50% were caused by identification errors in sample or patient. Of the wrongly administered blood components in that period, 29% was destined for a different patient. The TRIP reports also show that 15% of the wrong components were not irradiated by mistake (TRIP 2003 through 2009). This corresponds to the analyses by Love et al (Love 2001).

¹: other definition than used by TRIP

Conclusions 3.1

	Incorrectly identified blood samples are an important source of errors in blood transfusion incidents.
Level 3	
	C <i>TRIP reports 2003 through 2009, Stainsby 2005, Murphy 2004, Dzik 2003, Love 2001, Williamson 1999, Linden 1992</i>

	When requesting blood components , the correct blood component is not always requested.
Level 3	
	C <i>TRIP reports 2003 through 2007, Love 2001</i>

Other considerations

Upon receipt of blood samples and/or transfusion requests, the blood transfusion laboratory has a verifying role. Upon receipt, they check whether the request and/or the blood sample meet the criteria set and demanded by the institution.

The procedures set out for this stipulate at least the following points:

unambiguous identification of the blood sample and the patient is guaranteed. This means that tubes of blood are labelled in the presence of the patient. These labels contain immediately legible information and at least two characteristics that are unique and can be traced independently to the patient, namely the full name, date of birth and/or social security number or another unique number from a patient identification system. In addition to immediately legible information, it is preferable to use barcodes and/or RFIDs (radio frequency identification) .

If the patient identification and the linking of patient identification to the blood sample always occurred correctly, in theory only one collection would suffice for the definitive determination of the ABO/RhD blood group. However, in practice, the state-of-the-art procedure is to determine ABO/RhD blood group definitively using two independent blood collections in order to trace any errors in the identification process. This often leads to discussions about organisational and logistical matters. Each collection is determined by the three “**W**”s: **who** (phlebotomist), **where** (outpatient department or inpatient ward) and **when** (date/time). In this context “independently” means that at least one of the three **Ws** differs during the two collections with complete patient identification. The blood transfusion laboratory cannot perform the compatibility study if the transfusion request does not meet the criteria set by the institution. This includes that the ABO/RhD blood group must be determined using two blood samples, with an unambiguous link between the sample and the patient.

- The requesting doctor is responsible for the correct component selection. In consultation with the treating doctor, the blood transfusion laboratory records in the transfusion database whether there is an indication for specific blood components and the time-frame that applies to these components – for example, irradiated blood components– and checks that the request conforms to these requirements. In such an event, the blood transfusion laboratory can use the transfusion database, as recorded in the own written and/or digital blood transfusion database, to check whether the requested component matches the historical information, such as typed, irradiated, washed et cetera. The patient’s antibody history is consulted with each request for a cellular blood component and also TRIX for every new treatment (period).
- The name and date of birth and/or identification number of the patient (identified according to an emergency procedure if necessary) and the name of the requesting doctor are recorded.
- In order to prevent unnecessary time loss in case of cito requests, everyone who is involved in the transfusion chain must be familiar with a clear and workable cito procedure.

- Due to the frequency at which administrative errors play a role in – among others – the transfusion of ABO incompatible units, thorough documentation of the procedures surrounding the determination of the blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum.

Recommendations 3.1

1. The blood transfusion laboratory only accepts samples that have a label that unambiguously links the tube to the patient. This means that tubes of blood are labelled in the presence of the patient. These labels contain immediately legible information and at least two characteristics that are unique and can be traced independently to the patient, namely the full name, date of birth and/or social security number or another unique number from a patient identification system. In addition to immediately legible information, it is preferable to use barcodes and/or RFIDs (radio frequency identification).
2. Upon receipt of blood samples and/or transfusion requests, the blood transfusion laboratory has a verifying role. The blood transfusion laboratory only accepts requests for transfusion if the identification of the patient on the request is identical to that of the blood sample. Differences, however small, due to writing errors should be verified.
3. At least two independent collections of blood samples must be performed for the definitive determination of the ABO/RhD blood group. Independent means that the two collections with complete patient identification must be performed at different times, different locations or by different phlebotomists. For both samples there must be an unambiguous identification of the patient and an unambiguous link between the sample and the patient. An ABO/RhD blood group is only definitively determined if this requirement has been met without the discovery of any discrepancies.
4. If there is any doubt, a new sample should always be collected and the ABO/RhD blood group determination should be repeated. Based on the outcome of a careful analysis of all available data, the blood transfusion laboratory can consider the result from this sample as a first or second blood group determination.
5. The cause of discrepancies between ABO/RhD blood group determinations should always be examined.
6. The blood transfusion laboratory will not process any transfusion requests that do not meet the criteria set by the institution. This includes that the ABO/RhD blood group must be determined using two blood samples, with an unambiguous link between the sample and the patient.
7. The requesting doctor should supply relevant clinical information (about antibodies (allo and/or auto), pregnancies, transplants, haemoglobinopathies, etc.) to the transfusion laboratory.
8. The requesting doctor is responsible for the choice of blood component .
9. All care providers involved in the transfusion chain must be familiar with a clear and workable cito procedure.
10. In consultation with the treating doctor, the blood transfusion laboratory records in the transfusion database whether there is an indication for specific blood components and the time-frame that applies to these components and checks that the request conforms to these requirements.

11. In the case of a request by telephone, at least the name and date of birth and/or identification number of the patient (identified according to an emergency procedure if necessary) and the name of the requesting doctor are recorded.
12. The patient's antibody history must be consulted with each request for a cellular blood component and TRIX should also be consulted for each new treatment (episode) (see chapter 3.3.3 and chapter 7.2.2).
13. Due to the frequency at which administrative errors play a role in – among others – the transfusion of ABO incompatible units, thorough documentation of the procedures surrounding the determination of the blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum.

3.2 Laboratory examinations

3.2.1 Blood group determination

ABO blood group determination in adults and children older than three months

Scientific support

The ABO blood group system is the most important blood group system for the transfusion practice (Issit 1998). Transfusion of an ABO incompatible erythrocyte concentrate can have severe – sometimes fatal – consequences for a patient (Stainsby 2005, Wilkinson 2005, Linden 1992, Sazama 1990). The chance of a fatal reaction occurring depends partially on the quantity of blood transfused and the strength of the antibody (Sazama 1990). Severe transfusion reactions with ABO incompatibility can be explained by the fact that ABO antibodies are present in virtually all individuals from the age of three months that are targeted against the missing ABO antigens and therefore no prior immunisation is required. In addition, antibodies – both IgM and IgG – against ABO antigens are very efficiently able to activate the complement system and thereby cause intra-vascular haemolysis. Therefore, the ABO blood group determination of these antigens should meet the highest quality requirements. This entails that the ABO blood group determination should be performed in its entirety. This means that the presence or absence of the antigens of the ABO system on the erythrocytes of the patient should be determined using test reagents and the presence or absence of anti-A and anti-B antibodies in the plasma/serum of the patients should be determined using test erythrocytes (Guide Council of Europe 2008).

Based on the data from the SHOT reports for the period 1996 – 2003, Stainsby calculated a risk of ABO incompatible transfusion of 1:100,000 and a chance of 1:600,000 of this incompatibility resulting in a fatality (Stainsby 2005). According to the data from the French haemovigilance programme, the risk of death is 1:800,000 (Andreu 2002). Analysis of the TRIP reports for the period 2003 – 2007 revealed that the risk of an ABO incompatible blood transfusion is 1:125,000 and the risk of death as a result was less than 1:3,000,000 (TRIP 2003 through 2007). SHOT reports that in approximately 50% of the cases there was more than one error and that approximately 70% of these errors are made outside the laboratory (Williamson 1999).

Conclusions 3.2.1

	Transfusion of an ABO incompatible erythrocyte concentrate can have severe – sometimes fatal – consequences for a patient and should therefore be avoided.
Level 3	
	C <i>Stainsby 2005, Wilkinson 2005, Linden 1992, Sazama 1990, Williamson 1999, Andreu 2002</i>

	The chance of a fatal reaction occurring depends partially on the quantity of blood transfused and the strength of the antibody.
Level 3	
	C <i>Sazama 1990</i>

	The ABO blood group system is the most important blood group system for transfusions and an ABO blood group determination should therefore meet the highest quality requirements. This includes that the ABO blood group determination should be performed in its entirety. This means that the presence or absence of the antigens of the ABO system on the erythrocytes of the patient should be determined using test reagents and the presence or absence of anti-A and anti-B antibodies in the plasma/serum of the patient should be determined using test erythrocytes.
Level 3	
	D <i>Guide Council of Europe 2008</i> C <i>Issit 1998</i>

Recommendations 3.2.1

1. For adults and children older than three months, the ABO blood group determination should be performed in its entirety. This means that the presence or absence of the antigens of the ABO system on the erythrocytes of the patient should be determined using test reagents and the presence or absence of anti-A and anti-B antibodies in the plasma/serum of the patients should be determined using test erythrocytes.
2. See also paragraph 3.1, recommendations 1 through 5.

ABO blood group determination in children up to the age of three months

The ABO blood group antigen determination usually cannot be confirmed in neonates and children up to the age of three months, due to the presence/absence of the corresponding antibodies anti-A and/or anti-B. The agglutinating IgM antibodies often can only be demonstrated from three months after birth. Any IgG antibodies that are present are usually from the mother. The number of A and/or B antigens in neonates is a factor 2 to 3 lower than in adults (Klein 2005, BCSH 2004, SBBTS 2009, Daniels 1995).

Conclusion 3.2.1

	The ABO blood group antigen determination usually cannot be confirmed in neonates and children up to the age of three months, due to the presence/absence of the corresponding antibodies anti-A and/or anti-B.
Level 3	
	C <i>SBBTS 2009; Klein 2005; BCSH 2004; Daniels 1995</i>

Other considerations

Due to the above-mentioned facts, an ABO/RhD blood group determined from two independent samples from a neonate is preliminary in nature until the ABO blood group has become definitive, but it may be used for the selection of ABO/RhD identical blood components.

In the case of cord blood, it is important to rule out a false positive result due to the Wharton's jelly that can cause pseudo-agglutination.

Due to the frequency at which administrative errors play a role in – among others – the transfusion of ABO incompatible units, thorough documentation of the procedures surrounding the determination of the blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum.

Comment: If clinical circumstances – such as prematurity, dysmaturity or low birth weight – hamper a blood collection from the child in order to perform a second ABO/RhD determination, the required second blood group determination can be omitted. The child may then only receive transfusions of O- erythrocyte concentrate.

Recommendations 3.2.1

1. In neonates and children up to the age of three months after birth, the determination of A and B antigens will suffice for the ABO blood group determination. For cord blood, a false positive result due to the Wharton's jelly must be ruled out.
2. The registration of the ABO blood group in neonates and children up to the age of three months after birth is preliminary in nature, until the ABO blood group has become definitive.
3. This preliminary ABO blood group can be used for identical transfusion of blood components.
4. See also paragraph 3.1, recommendations 1 through 5.

3.2.2 Rhesus D blood group determination

Scientific support

After the ABO blood group system, the rhesus blood group system – and particularly the Rhesus D antigen (RhD) – is the most important blood group system in transfusion practice (Issit 1998, Daniels 1995). This is because the RhD blood group is very immunogenic (Gonzales-Porras 2008, Klein 2005), antibodies against RhD can cause haemolytic transfusion reactions and during pregnancy it can be responsible for haemolytic disease in the foetus and neonate. For the transfusion practice it is therefore important to prevent RhD negative patients (recipients) being typed as RhD positive.

The number of RhD antigens on the erythrocyte membrane can vary significantly from person to person (Daniels 1995). The most well-known quantitative RhD antigen abnormality is the 'weak' RhD antigen. Patients with a weakened (low number) but completely intact RhD antigen are RhD positive and unable to produce alloantibodies against the RhD antigen. In addition to quantitative variations, a large number of qualitative variants of the RhD antigen have also been described. Patients with an RhD variant (incomplete RhD antigen) can form

allo-anti RhD antibodies against the epitopes of the RhD antigen that they do not possess (Klein 2005). The most frequently occurring RhD variant is RhD class VI with an incidence of 1:5,000 to 1:6,800 (Caucasian population). This is also the only RhD variant for which it has been described that an alloantibody against the missing part of the RhD has caused haemolytic disease of the newborn. Most of the other RhD variants are much rarer (<1:60,000) in the Caucasian population (Flegel 1996).

Immunisation can occur during pregnancy because foetal erythrocytes enter the mother's circulation. The IgG antibodies formed in this manner can then cross the placental barrier and cause breakdown of the foetal erythrocytes. In severe cases, this can result in haemolytic disease of the foetus and newborn (Klein 2005). Since 1969 in the Netherlands, in order to prevent RhD immunisation, anti-RhD immunoglobulin has been administered prophylactically to RhD negative women who give birth to an RhD positive child. Therefore, when determining the RhD blood group in neonates, both the weak RhD antigens and RhD variants are detected and this determination therefore differs from the RhD determination for patients.

Conclusions 3.2.2

	The RhD blood group is very immunogenic. Antibodies against Rhesus D antigen (RhD) can cause haemolytic transfusion reactions.
Level 3	
	C <i>Gonzales-Porras 2008, Klein 2005.</i>

	The number of RhD antigens on the erythrocyte membrane can vary significantly from person to person.
Level 3	
	C <i>Daniels 1995</i>

	Immunisation can occur during pregnancy because foetal erythrocytes enter the mother's circulation. The IgG antibodies formed in this manner can then cross the placental barrier and cause breakdown of the foetal erythrocytes. In severe cases, this can result in haemolytic disease of the foetus and newborn.
Level 3	
	C <i>Jones 2004</i>

Other considerations

Tracing of very weak RhD antigens in blood recipients is not clinically relevant: if a recipient has in an exceptional case incorrectly been typed as RhD negative, then RhD negative blood will be administered, which will have no negative consequences for the patient. The tracing of very weak RhD antigens in pregnant women also has no clinical importance. In rare cases the recipient could erroneously be typed as RhD negative and will then unnecessarily be administered anti-RhD immunoglobulin. This will not result in clinical problems.

Tracing of very weak RhD antigens using the anti-globulin test in recipients of blood is strongly discouraged. If there are sensitised (IgG coated) erythrocytes present (positive

direct anti-globulin test (DAT)) one might erroneously conclude that the recipient is RhD positive. A recipient with an RhD variant antigen that is determined to be D positive runs the risk during transfusion of an RhD positive erythrocyte concentrate of forming antibodies against the parts of the RhD antigen that he/she is lacking. The chance of this (and an additional chance of haemolytic disease of the foetus and newborn) is mainly present in recipients with a RhD-VI variant. Due to the frequency at which the RhD-VI variant occurs it is important to take this into consideration when selecting the reagents. This does not apply to the other RhD variants.

The sensitive RhD determination in the anti-globulin test causes false positive results in people who have *in vivo* bound antibodies on the erythrocytes (DAT).

Due to the frequency at which administrative errors play a role in blood transfusions, thorough documentation of the procedures surrounding the determination of the RhD blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum.

Recommendations 3.2.2

1. Due to the chance of anti-RhD formation and future haemolytic transfusion reactions, it should be prevented that patients who are RhD negative are erroneously labelled RhD positive.
2. For the RhD blood group determination, the hospital should distinguish between two groups, namely: recipients of blood and neonates (due to the administration of anti-RhD immunoglobulin to the mother).
3. For the determination of the RhD blood group in recipients of blood, the use of one anti-RhD reagent will suffice, provided the RhD-VI variant has been shown to be RhD negative.
4. Due to the administration of anti-RhD immunoglobulin to the mother, the determination of the RhD blood group in neonates should use anti-RhD reagents that show RhD-VI variant and weak RhD antigens to be RhD positive.
5. If the neonate is the recipient of a blood component, the use of one anti-RhD reagent will suffice, see also recommendation 3 above.
6. For the RhD determination in recipients of blood, it is not recommended to expand the test with an anti-globulin phase if the anti-RhD reagent produces a negative reaction.

3.2.3 Actions in case of ABO blood group discrepancies

Scientific support

We can distinguish two types of discrepancies with the ABO blood typing: (1) the ABO blood group does not match a previously determined blood group in the patient (Stainsby 2005, Schulman 2001), or (2) there are discrepancies in the results of the blood group determination itself (the results of the antigen determination on the erythrocytes does not match the ABO antibodies found in the serum) (Brown 2005).

The most important causes for the occurrence of ABO blood group discrepancies in the first group are administrative errors. Errors in the identification of the patient or the blood sample occurred in 0.05% and 0.09% respectively of all blood collections (Dzik 2003, IGZ 2001, Ibojie 2000, Linden 2000). In addition, errors can also occur in the processing of blood

samples, the reading or data entry of results, the selection or release of the blood component and the administration to the (correct) patient (Schulman 2001, Baele 1994, Linden 1992, Sazama 1990). Patients who have undergone an allogeneic bone marrow transplantation form a particular risk group, because their original blood group has changed (Brown 2005).

The actions to be taken in the case of ABO discrepancies are determined at the time that the error is discovered. Data from the TRIP database for the period 2003 through 2007 show that for the transfusion reactions (8683) that were reported, approximately 3% were the result of the administration of an incorrect blood component (272) (TRIP 2003 through 2007).

Due to the small number of incidents in the Netherlands and the resulting lack of statistical proof, the results of the British SHOT programme were also examined (Love 2001). The data from the SHOT programme differs markedly from the Dutch data, partly due to a different definition of "incorrect blood component transfusion" (IBCT). Rough risk estimates can be made from the cumulative SHOT reporting over eight years. The percentage of IBCT is approximately 70% of all reports. Of these IBCT, approximately 14% are due to an ABO incompatible transfusion. Based on calculations using the SHOT figures, the risk of an IBCT is approximately 1:15,000 transfused units and the risk of an ABO incompatible transfusion is approximately 1:100,000 (Stainsby 2006, 2005).

Conclusions 3.2.3

	Transfusion with ABO incompatible blood is usually the result of administrative errors.
Level 3	
	C <i>Love 2001, Dzik 2003, IGZ (Healthcare Inspectorate) report 2001, Linden 2000, Ibojie 2000</i>

	In addition, errors can also occur in the processing of blood samples, the reading or data entry of results, the selection or release of the blood component and the administration to the (correct) patient.
Level 3	
	C <i>Schulman 2001, Baele 1994, Linden 1992, Sazama 1990</i>

	Errors in the identification of the patient or the blood sample occur in 0.05% and 0.09% respectively of all blood collections.
Level 3	
	C <i>Dzik 2003, IGZ (Healthcare Inspectorate) report 2001, Ibojie 2000, Linden 2000</i>

	A specific group at risk for transfusion with an ABO incompatible blood component is the group of patients who have undergone an allogeneic bone marrow transplantation, which has resulted in a change from the original blood group.
Level 3	

	C <i>Brown 2005</i>
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	Of the 8683 transfusion reactions reported to TRIP in the period 2003 – 2007, approximately 272 (3%) were the result of the administration of an incorrect blood component.
Level 3	
	C <i>TRIP 2003 through 2007</i>

	The data from the British SHOT programme differs markedly from the Dutch data, partly due to a different definition of “incorrect blood component transfusion” (IBCT). Rough risk estimates can be made from the cumulative SHOT reporting over eight years: the risk of an IBCT is approximately 1:15,000/transfused units and the risk of an ABO incompatible transfusion is approximately 1:100.000.
Level 3	
	C <i>Stainsby 2006, 2005</i>

	Only considering the ABO blood group as definitive once it has been confirmed using two samples collected independently of each other – without any discrepancies detected – can reduce the risk of an incorrect ABO blood group determination to a minimum.
Level 4	
	D <i>IGZ (Healthcare Inspectorate) report 2001</i>

Other considerations

Due to the frequency with which administrative errors play a role in – among others – the transfusion of ABO incompatible units, thorough documentation of the procedures surrounding the determination of the blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum. If any discrepancies are discovered, one must examine whether this is due to a sample mix-up or a patient mix-up. Depending on this analysis, the follow-up examination should take place in accordance with the protocol that applies for the institution.

Recommendations 3.2.3

1. If any ABO discrepancies are discovered, one must examine whether this is a case of sample mix-up or a patient mix-up. Depending on this analysis, the follow-up examination should take place in accordance with the protocol that applies for the institution.
2. Due to the frequency at which administrative errors play a role in – among others – the transfusion of ABO incompatible units, thorough documentation of the procedures surrounding the determination of the blood group and strict adherence to these procedures is essential. The number of manual administrative procedures should be kept to a minimum.

3.3 Compatibility study in transfusion of erythrocytes

3.3.1 Antibody screening

3.3.1.1 Quality requirements

Scientific support

Prior to each blood transfusion, the serum/plasma of the recipient should be examined with the aid of selected test erythrocytes for the presence of irregular erythrocyte antibodies using a panel of test erythrocytes that meet the set requirements. Various techniques are available for this antibody examination, each with a specific sensitivity for certain categories of antibodies. Traditionally, in the Netherlands, the indirect anti-globulin test (IAT) was used, performed in test tubes with bovine albumin. In the literature, most of the techniques were compared to the IAT in albumin or in 'low ionic strength solution' (LISS) and PEG (Weisbach 1999, Man 1990).

Antibodies can react more weakly to test erythrocytes that express an antigen heterozygously than to test erythrocytes with homozygous expression of that antigen. In order to detect clinically relevant antibodies, the test erythrocytes must therefore be homozygous for the following clinically relevant antigens: C, c, D, E, e, k, Fy^a, Fy^b, Jk^a, Jk^b, M, S, s (Weisbach 1999, Bromilow 1993, Man 1990).

The K-antigen must be present at least in the heterozygous state. (AABB 2008, BCSH 2004). The presence of the C^w, Lu^a, Wr^a and Kp^a antigens on the test erythrocytes is not compulsory.

Conclusions 3.3.1

	Antibodies can react more weakly to test erythrocytes that express an antigen heterozygously than to test erythrocytes with homozygous expression of that antigen. In order to detect clinically relevant antibodies, the test erythrocytes must therefore be homozygous for the following clinically relevant antigens: C, c, D, E, e, k, Fy ^a , Fy ^b , Jk ^a , Jk ^b , M, S, s.
Level 4	
	<i>D Man 1990, Weisbach 1999</i>

	The K-antigen must be present at least in the heterozygous state.
Level 4	
	<i>D AABB 2008, BCSH 2004</i>

Recommendations 3.3.1

1. The antigen screening must be performed using a technique that is – as far as demonstrating the clinically relevant antibodies is concerned – at least as sensitive as the indirect anti-globulin test using bovine albumin (IAT-albumin).
2. The following antigens must be present in homozygous state on at least one of the test erythrocyte suspensions: C, c, D, E, e, **K**, Fy^a, Fy^b, Jk^a, Jk^b, M, S, s.
3. The K-antigen must be present at least in the heterozygous state.

1: ruling out anti-k (anti-Cellano) using homozygous test erythrocytes, change compared to 2004 version

3.3.1.2 Validity of antibody screening

Scientific support

Antibody formation usually takes place within three months of a transfusion or pregnancy. However, a secondary immunisation can take place quickly (Shulman 1990). Based on data from the literature and taking into consideration the increased sensitivity of the test systems, there is general consensus that the period between antibody screening and transfusion should be no more than 72 hours, because antibodies can be demonstrated within this period.

If the patient has not had a transfusion or pregnancy in the past three months, then the antibody screening is (as a general rule) valid until the next blood transfusion, provided the anamnesis is absolutely reliable. If a cross match is performed for the patient in the IAT, the same terms of validity apply to the cross match (Schonewille 2006, Schonewille 2006, Redman 1996, Shulman 1990).

Conclusion 3.3.1.2

	Antibody formation usually takes place within three months after transfusion or pregnancy, but in the case of secondary immunisation antibodies can be detected after only 72 hours.
Level 3	
	C Redman 1996, Shulman 1990, Schonewille 2006, Schonewille 2006

Recommendations 3.3.1.2

1. The maximum time between antibody screening and blood transfusion should be 72 hours.
2. After transfusion or pregnancy, an antibody screening and cross match in the indirect anti-globulin test is valid for a maximum of 72 hours after collection of the sample for up to three months after the event.
3. If one is absolutely certain that there has been no transfusion or pregnancy during the past three months, then the antibody screening (as a general rule) is valid **until the next blood transfusion.**

3.3.2 Compatibility study

Compatibility study according to the Type & Screen strategy

A compatibility study according to the Type & Screen strategy tests the ABO compatibility between donor and patient. The antibody screening should be valid and negative (Williamson 1999, Hedde 1992, Shulman 1990).

If the Type & Screen strategy is used, then the following requirements must be met:

- The ABO blood group and the RhD antigen for both the patient and the donor(s) must be definitively confirmed (see § 3.2.1).
- Screening for irregular erythrocyte antibodies in the patient using a three cell panel of test erythrocytes must be negative.

- Checking the compatibility of the ABO blood group of the patient and the donor must be part of the release procedure (AABB 2008).

Scientific support

American research shows that the chance of missing an antibody with the use of T&S instead of an indirect antiglobulin test (IAT) cross match is approximately 1:5,500 per sample or 1:10,000 per cross match (Garratty 2003). The risk of a severe haemolytic transfusion reaction is 1:260,000 cross matches (Shulman 1990). Antibodies such as anti-Jk^a, anti-C, anti-c, anti-Wr^a and anti-Kp^a cannot be demonstrated with the screening, which means that the chance of AHTR due to antibodies against low frequency antigens is estimated at 1:650,000 cross matches (Shulman 1984). As the occurrence of the low frequency antigens can differ according to race and geographical location, research was performed on the Dutch population in the period before and after the introduction of T&S. In this study by Schonewille of 1795 patients with 2257 erythrocyte transfusions, the risk of an incompatible transfusion due to antibodies against low frequency antigens was 1:204,000 and no transfusion reactions due to antibodies against low frequency antigens were observed (Schonewille 2003).

As ABO incompatibility can cause a direct acute haemolytic transfusion reaction with fatal consequences (Issit 1998), the ABO compatibility between donor and patient is of critical importance. The hospital is responsible for the compatibility between donor and patient, including the release of compatible blood components (IGZ 2001). The blood bank is responsible for the contents of the component, in accordance with the label.

Conclusions 3.3.2

	American research shows that the chance of missing an antibody with the use of T&S instead of an indirect antiglobulin test (IAT) cross match is approximately 1:5,500 per sample or 1:10,000 per cross match.
Level 3	
	C <i>Garratty 2003</i>

	Further research into the effects of 1.3 million transfusions with negative T&S and short cross match revealed five reports of an acute haemolytic transfusion reaction (AHTR) (risk of 1:260,000 cross matches). The responsible antibodies, such as anti-Jk ^a , anti-C, anti-c, anti-Wr ^a and anti-Kp ^a could not be demonstrated with the screening, which meant that the change of AHTR due to antibodies against low frequency antigens is estimated at 1:650,000 cross matches.
Level 3	
	C <i>Shulman 1990</i>

	A Dutch study of 1795 patients with 2257 erythrocyte transfusions found the risk of an incompatible transfusion due to antibodies against low frequency antigens was 1:204,000 and no transfusion reactions due to antibodies against low frequency antigens were observed.
Level 3	
	C <i>Schonewille 2003</i>

Level 3	<p>During compatibility studies according to the Type & Screen strategy, the ABO compatibility between donor and patient is tested and the antibody screening should be valid and negative.</p> <p>C <i>Heddle 1992, Williamson 1999, Shulman 1990</i></p>
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Other considerations

Internationally, the ABO blood group compatibility between donor and patient is checked during a compatibility study according to the Type & Screen strategy using one of the following methods:

- A short cross match in salt between the erythrocytes of the donor and the serum/plasma of the patient.
- The computer (ABO check of both the recipient and the donor based on recorded data).
- An ABO check of both the recipient and the donor using test reagents (AABB 2008).

The above-mentioned methods have both advantages and disadvantages, which means that an exact description of the accepted method is essential.

The exclusive checking of the ABO compatibility using a computer (electronic cross match) without prior control tests of the blood group is insufficient.

Recommendations 3.3.2

1. For the compatibility study according to the Type & Screen strategy, the antibody screening should be valid and negative.
2. If the Type & Screen (T&S) strategy is used, then the following requirements must be met:
 - the ABO blood group and the RhD antigen must be known both for the patient and the donor(s);
 - screening for irregular erythrocyte antibodies in the patient using a three cell panel of test erythrocytes;
 - checking the compatibility of the ABO blood group of the patient and the donor must be part of the release procedure.
3. The working group recommends that for the compatibility study according to the Type & Screen strategy, the ABO blood group compatibility between donor and a recent sample (max. 72 hours old) of the patient be tested by:
 - a short cross match in salt between the erythrocytes of the donor and the serum/plasma of the patient;
 - or
 - the computer. To achieve this, ISBT-128 barcodes on the donor units are used and an ABO blood group check using test reagents is performed on the patient's erythrocytes. The ABO blood group of the donor unit must have been checked once before– using test reagents – in the blood transfusion laboratory of the hospital. This check should be documented in the computer. The exclusive checking of the ABO compatibility using a computer (electronic cross match) without prior control tests of the blood group is insufficient.

or

- **ABO blood group checks using test reagents of recipient and donor for each release of erythrocytes.**

Patients who are not eligible for the Type & Screen strategy and for whom a cross match in the indirect anti-globulin test (IAT) is essential

Scientific support

A number of patient categories, discussed below, are not eligible for the Type & Screen strategy and the performance of a cross match in the indirect anti-globulin test (IAT) is essential in these cases (BCSH 2004).

In unborn children and neonates up to the age of three months, passively acquired antibodies – obtained from the mother – against a low frequency antigen can be present that will not be detected by the test erythrocytes. These antibodies are demonstrated in a cross match in the IAT between the erythrocytes of the donor and preferably the serum/plasma of the mother. After the first transfusion there is also plasma from the donor present in the child's circulation. The donor plasma can also contain antibodies against a low frequency antigen. This means that in subsequent erythrocyte transfusions, the cross match must be performed using the serum/plasma both from the mother and the child. Antibodies against low frequency antigens occur primarily in patients who already have IgG antibodies in their circulation. Therefore, for this group of patients, these antibodies also need to be traced in a cross match in the IAT between the donor's erythrocytes and the serum/plasma of the patient (BCSH 2004).

A cross match in the indirect anti-globulin test is not strictly necessary for patients with clinically irrelevant alloantibodies. A cross match can be used to select compatible donor erythrocytes (see table 3.6.2). In practice, it is usually not possible to find a negative cross match in IAT for patients with autoantibodies (Lee 2007, Engelfriet 2000).

Patients who have undergone transplantation of a vascularised organ (does not include: skin, cornea or bone to name a few examples) in the three months prior to blood transfusion can have anti-A or anti-B antibodies derived from circulating donor lymphocytes in their circulation, which can only be detected by performing cross matches in the IAT (BCSH 2004).

Such a situation – in which anti-A or anti-B antibodies occur – can persist for a longer period and can recur after long periods of time in patients who have undergone an ABO incompatible bone marrow / stem cell transplant. Therefore, a cross match in the IAT will always have to be performed for these patients. If a cross match in IAT must be performed, this test should have at least the same sensitivity as an IAT in bovine albumin (BCSH 2004).

Conclusions 3.3.2

	For neonates, it is essential that the compatibility of an erythrocyte unit is checked with a cross match in the indirect anti-globulin test between the erythrocytes from the donor and serum/plasma from the mother and – after transfusion – also the serum/plasma from the child.
Level 4	

	<i>D</i> <i>BCSH 2004</i>
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Comment: If clinical circumstances – such as prematurity, dysmaturity or a low birth weight – hamper a blood collection from the child in order to perform cross matches, the required cross match with the serum of the child can be omitted.

	For patients with clinically significant alloantibodies, it is essential that the compatibility of an erythrocyte unit be checked by means of a cross match in the indirect anti-globulin test between the erythrocytes from the donor and the serum/plasma of the patient.
Level 4	
	<i>D</i> <i>BCSH 2004</i>

	A cross match in the indirect anti-globulin test is not strictly necessary for patients with clinically irrelevant alloantibodies and autoantibodies. A cross match can be used to select compatible donor erythrocytes. In practice, it is usually not possible to find a negative cross match in the indirect anti-globulin test (IAT) for patients with autoantibodies.
Level 3	
	<i>C</i> <i>Lee 2007, Engelfriet 2000</i>

	For patients who have undergone transplantation of a vascularised organ, it is essential to check the compatibility of an erythrocyte unit by means of a cross match in the indirect anti-globulin test between the erythrocytes from the donor and the serum/plasma from the patient in the subsequent period of three months.
Level 4	
	<i>D</i> <i>BCSH 2004</i>

	In patients who have undergone an ABO incompatible bone marrow / stem cell transplantation , a situation in which antibodies against A and/or B are formed can persist for a longer period and can recur after a long time.
Level 4	
	<i>D</i> <i>BCSH 2004</i>

Other considerations

Transfusion in the presence of antibodies against low frequency antigens will have a greater effect on neonates than on adults. In this perspective, a cross match using the serum/plasma from the mother and – if the neonate has already received transfusions – also the serum/plasma from the child is essential (see above-mentioned comment).

Recommendations 3.3.2

Patients who are not eligible for the Type & Screen strategy and for whom a cross match in the indirect anti-globulin test must be performed are:

1. recipients of intra-uterine transfusions (both mother and neonate);

2. neonates up to and including the age of three months (perform cross match using at least serum/plasma from the mother and after transfusion of the neonate also using serum/plasma from the child), see other considerations;
3. patients with known, clinically relevant, irregular alloantibodies (see table 3.3);
4. recipients of transplants of vascularised organs (this does not include skin, cornea or bone to name some examples) for three months after transplantation.
5. Patients who have undergone a bone marrow / stem cell transplant.

3.3.3 Antibody Identification Study

Scientific support

If the antibody screening or the cross match is positive, the cause of this must be found. A blood transfusion with a unit of erythrocytes that is positive for the antigen against which the antibodies are targeted can cause a (delayed) haemolytic transfusion reaction.

Patients with clinically significant erythrocyte alloantibodies should therefore only receive erythrocytes that are negative for the relevant blood group antigens, see 3.6.2. Therefore, if there are irregular erythrocyte antibodies, the antibodies must be identified.

In order to identify an alloantibody with certainty, the study must meet the following requirements:

- The antibody identification is primarily performed using the technique with which the antibodies were demonstrated. Additional techniques can be useful to the identification, but are not essential.
- The antibody identification must be performed according to the Fisher exact method (p value < 0.05) or must adhere to the following principle: at least 2 antigen positive cells that respond and at least two negative cells that do not respond, per demonstrated antibody, are required for a reliable identification using a panel of at least 8 cells for which requirements have been set.
- If there are irregular erythrocyte antibodies present, the erythrocytes of the patient must also be checked for the absence of the antigen against which the antibodies are targeted.
- In each case, underlying antibodies must be excluded at least once – preferably twice – with erythrocytes that are negative for the relevant antigen against which the antibodies are targeted; antibodies against the C, c, D, E, e, K¹, Fy^a, Fy^b, Jk^a, Jk^b, M, S and s antigens must be ruled out using homozygous test erythrocytes, and antibodies against the K antigen can be ruled out using heterozygous test erythrocytes. If an anti-D antibody is present, the presence of anti-C and anti-E antibodies may be ruled out heterozygously. An anti-E may also be ruled out heterozygously in the presence of an anti-c, and an anti-C may be ruled out heterozygously in the presence of an anti-e.

¹: see comment 3.3.1

Patients with irregular antibodies have been proved to have a good immune response: therefore, one should be aware with each new transfusion of the presence of underlying antibodies, and these antibodies should be ruled out using test erythrocytes with a maximum validity of 72 hours (Schonewille 2006, BCSH 2004, Fluit 1990).

Identification studies can be extremely complicated in patients with clinically relevant autoantibodies. The chance of the presence of alloantibodies or alloantibody formation is

relatively large (in excess of 30%) in patients with autoantibodies (Ahrens 2007, Engelfriet 2000). Therefore, it is important for this group that the presence of alloantibodies be ruled out (as far as possible), for example using adsorption techniques (Leger 1999, Engelfriet 2000). If this study is not possible due to time constraints, it is preferable to transfuse the patient with donor erythrocytes that are compatible with the Rhesus phenotype, the K antigen and the antigens of the Kidd system. Matches for Duffy and Ss antigens are also preferably indicated (in order of importance), also see other considerations.

In patients with alloantibodies, the chance of additional alloantibody formation is also 20 – 25%, which is similar to AIHA patients.

As antibodies against erythrocytes can decrease in concentration over time and can then no longer be demonstrated, it is important to accurately record the data concerning clinically significant erythrocyte antibodies (Schonewille 2000, Sazama 1990). This registration concerns the archiving in the laboratory system, the patient's medical file and a transfusion card that is given to the patient. Since May 2007, the start of TRIX (Transfusion Register for Irregular antibodies and X match problems) in the Netherlands made it possible to store these data in a national database that can be consulted online by the transfusion laboratories 24 hours a day (Beunis 2004, TRIX 2009). In the interests of patient safety and quality considerations, the aim should be to implement rapid national coverage of the participating laboratories in TRIX. The patient information concerning irregular alloantibodies and allogeneic stem cell and bone marrow transplants is registered in TRIX. HPA antibodies and IgA antibodies are also recorded.

Every participating laboratory is authorised to consult TRIX and to register patients in TRIX. Laboratories that meet the set requirements are authorised to enter irregular antibody data in TRIX, provided the TRIX criteria have been met (Beunis 2004).

Conclusions 3.3.3

	For antibody studies, it is important that the specificity of the antibody be clearly defined and that the presence of other antibodies be unambiguously ruled out.
Level 4	
	<i>D BCSH 2004</i>

	For patients who are known to have irregular erythrocyte antibodies, one should be aware for each new transfusion of the occurrence of underlying antibodies and these antibodies should be ruled out with test erythrocytes – with a maximum validity of 72 hours.
Level 4	
	<i>D Schonewille 2006, BCSH 2004, Fluit 1990</i>

	In patients with clinically relevant autoantibodies, the possibility of underlying irregular erythrocyte alloantibodies should be taken into consideration before transfusion.
Level 3	
	<i>C Leger 1999, Engelfriet 2000, Ahrens 2007</i>

Level 3	Antibodies against erythrocytes can decrease in concentration over time
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and therefore no longer be detectable.

C Schonewille 2000, Sazama 1990

Other considerations

The antigens of the Rhesus, Kell, Kidd and Ss systems can usually be detected serologically with monoclonal reagents in patients with warm autoantibodies, provided the person has not received a transfusion in the past three months. For all other cases (antigens in the Duffy system and typing of individuals who have received a transfusion in the last three months) there is the possibility of typing at DNA level (Rozman 2000).

In the case of complex antibody identification, for example due to a combination of several antibodies, or antibodies targeted against high frequency antigens, the use of various panels of test erythrocytes is essential. In these types of situations it is desirable to consult a specialised laboratory.

Recommendations 3.3.3

1. In order to identify an alloantibody with certainty, the study must meet the following requirements:
 - * the antibody identification should primarily be performed using the technique with which the antibodies were demonstrated. Additional techniques can be useful to the identification, but are not essential.
 - * in order to be able to identify an antibody, the antibody identification must be performed according to the Fisher exact method ($p < 0.05$) or the patient serum/plasma must react with at least two antigen-positive test erythrocytes and at least two negative cells that do not react per demonstrated antibody;
 - * if there are irregular erythrocyte antibodies present, the erythrocytes of the patient must also be checked for the absence of the antigen against which the antibodies are targeted;¹
 - * underlying antibodies should be ruled out at least once and preferably two times. This includes: antibodies against the C, c, D, E, e, K², Fy^a, Fy^b, Jk^a, Jk^b, M, S and s antigens must be ruled out using homozygous test erythrocytes, and antibodies against the K antigen can be ruled out using heterozygous test erythrocytes. If an anti-RhD antibody is present, the presence of any anti-C and anti-E antibodies may be ruled out using heterozygous test erythrocytes. In the presence of an anti-c, the presence of an anti-E may be ruled out using heterozygous test erythrocytes and if an anti-e is present, the presence of an anti-C antibody may be ruled out in the same manner.
2. In patients with clinically relevant autoantibodies, the presence of underlying irregular erythrocyte antibodies must be ruled out as far as possible before transfusion and – as a preventative measure – erythrocytes should be chosen that are compatible with antigens in the Rhesus system and K. If this exclusion study cannot be performed (completely), erythrocytes that are compatible for Kidd, Duffy, S and s can also be considered as a preventative measure.
3. The validity of the result of the antibody identification study is a maximum of 72 hours after collection of the sample during the first three months after transfusion or pregnancy.
4. The presence of clinically relevant irregular erythrocyte antibodies should be

- recorded accurately. The working group is of the opinion that this should occur:
- * in the archives of the blood transfusion laboratory;
 - * in a report from this blood transfusion laboratory to the treating doctor for registration in the medical file;
 - * on a transfusion card that is given to the patient with an explanation that can be understood by people without a medical background;
 - * in TRIX.
5. In the case of complex antibody identification – for example due to a combination of several antibodies, or antibodies targeted against high frequency antigens – the working group deems the use of various panels of test erythrocytes to be essential. In these types of situations the working group deems it desirable to consult a specialised laboratory.

¹: Possibly unreliable result with recent transfusions, unless the units were negative for the relevant antigen.

²: see comment 3.3.1

3.3.4 The use of serum or plasma in antibody screening and cross matches

Scientific support

When screening for the presence of erythrocyte antibodies, clinically relevant antibodies (IgG and IgM antibodies reactive at 37 °C) must be demonstrated, whilst non-specific positive reactions need to be avoided. Some weak antibodies targeted against antigens in the Kidd system, for example, can only be demonstrated because they bind complement (Klein 2005). This means that – if less sensitive techniques are used – sufficient complement (in fresh serum) must be present in the test material in order to demonstrate these antibodies. Complement-binding alloantibodies – particularly Kidd – are clinically very important, because they can cause an intravascular haemolytic reaction (Nance 1987).

Hazenberg has demonstrated that the ‘poly-ethylene glycol’ (PEG)-antiglobulin test and column method and ‘solid phase’ method are sensitive enough for demonstrating weak Kidd antibodies (Hazenberg 1990). The bovine albumin-IAT and the salt-IAT are not sensitive enough to demonstrate weak Kidd antibodies, if the ability of these antibodies to activate complement is not used (Klein 2005, Vucelic 2005, AABB 2008). The sensitivity of the various techniques can be described as follows:

Table 3.3.4:

Technique	Sensitivity
Salt-IAT in tubes	least sensitive
Bovine albumin-IAT in tubes	sensitive
LISS column test	most sensitive
LISS ‘solid phase’	most sensitive
PEG-IAT in tubes	most sensitive

Conclusions 3.3.4

	Complement-binding alloantibodies (particularly Kidd antibodies) are clinically very important, because they can cause a haemolytic reaction.
Level 3	
	C <i>Klein 2005, Nance 1987</i>

	The method and technique used to demonstrate the presence of erythrocyte antibodies must be sufficiently sensitive to demonstrate Kidd antibodies.
Level 3	
	C <i>AABB 2008, Klein 2005, Vucelic 2005</i>

	'Poly-ethylene glycol (PEG)-anti-globulin test', 'LISS column' and 'LISS solid phase' methods are sensitive enough for the detection of weak Kidd antibodies.
Level 3	
	C <i>Hazenberg 1990</i>

Recommendations 3.3.4

1. The Poly-ethylene glycol (PEG)-anti-globulin tests and LISS column and LISS 'solid phase' methods are recommended by the working group for demonstrating the presence of weak Kidd antibodies as these are the most sensitive for demonstrating weak Kidd antibodies.
2. Only serum should be used for antibody screening and cross matches with salt-IAT and bovine albumin-IAT. Serum, heparin-plasma or EDTA-plasma can be used with the LISS techniques ('column' and 'solid phase') and with PEG-IAT.

3.4 How to handle data from third parties

General

This chapter proposes that the blood transfusion laboratory is responsible for the release of compatible blood components. In that framework:

- the blood transfusion laboratory may not assume that the label on the blood component indicates the correct ABO/RhD blood group;
- the ABO blood group of the patient must be determined using two, unambiguously identified blood samples;
- known clinically relevant erythrocyte alloantibodies must be taken into consideration.

Other considerations

In order to meet these requirements, every blood transfusion laboratory carefully records whether the ABO/RhD blood group has been determined (and has been unambiguously confirmed) for the relevant patient, which blood transfusions this patient has received and which irregular antibodies – if any – have been demonstrated in the own laboratory or elsewhere (i.e. ask for a transfusion card). Prior to each transfusion period, the own hospital-related database and the (online) national database TRIX must be consulted. The TRIX database is particularly important in relation to the increasing patient mobility, which means that the hospital archive alone cannot meet the set requirements.

In practice, we can distinguish between four situations in which data from third parties is important:

- The ABO/RhD blood group of the patient has been determined at another institution.
- The patient is registered at another institution as having irregular erythrocyte alloantibodies.
- Transfusion of neonates who were transfused at another institution (intra-uterine).
- Allogeneic stem cell and bone marrow transplantation, which can change the ABO/RhD blood group of the patient.

Recommendations 3.4

1. The working group is of the opinion that – for the release of compatible blood components – every blood transfusion laboratory should carefully record whether the ABO/RhD blood group has been determined (and has been unambiguously confirmed) for the relevant patient, which blood transfusions this patient has received and which irregular antibodies – if any – have been demonstrated in the own laboratory or elsewhere (i.e. ask for a transfusion card). This hospital-related database and the (online) national database TRIX should be consulted for verification prior to each transfusion.
2. In emergency situations, an ABO/RhD blood group determined by a third party may be considered as a one-off independently determined blood group if the blood transfusion laboratory has access to (a copy of) an official (i.e. visibly authorised) report with the correct identification data and the definitive blood group.
3. There must be a procedure in place in the hospital to record the result of irregular erythrocyte antibodies determined by third parties as such with source reporting.
4. For an intra-uterine transfusion and/or (exchange) transfusion in a neonate, the blood transfusion laboratory should check – if necessary – whether the mother’s (recent) transfusion history is known.

3.5 Release and transfer of blood components

3.5.1 Procedure for release and transfer of erythrocyte concentrate

Scientific support

Most haemolytic transfusion reactions with a fatal outcome are due to (administrative) errors that result in erythrocytes with the wrong ABO blood group being administered to patients (McClelland 1994, Sazama 1990). Some of the errors (6 – 20%) were made by the selection of blood components from the stock and during the transfer of these components from the blood transfusion laboratory to the ward (Williamson 1999, Linden 1992).

Further analysis of the “incorrect blood component transfusion” reports in SHOT showed that in approximately 50% of the cases there was more than one error and that approximately 70% of the errors were made outside the laboratory (on the nursing ward) (Stainsby 2006, 2005).

Conclusions 3.5.1

	The cause of most haemolytic transfusion reactions with a fatal outcome was (administrative) errors.
Level 3	
	C <i>McClelland 1994, Sazama 1990</i>

	Six to twenty percent of the errors were made during the selection of blood components from the stock and during the transfer of these components from the blood transfusion laboratory to the ward.
Level 3	
	C <i>Williamson 1999, Linden 1992</i>

Other considerations

When blood components that have been declared compatible are released to the ward, there is a transfer of the responsibility from the blood transfusion laboratory to the ward. The procedure up to and including the administration of blood components should be recorded and registered within legal parameters using a sound administrative system. Checks are performed to prevent administrative mix-ups.

Examples of such a checking procedure for the release of blood components from the blood transfusion laboratory to the ward are described in table 3.5 below.

Table 3.5: Example of a checking procedure for release of blood components from the blood transfusion laboratory to the ward in order to prevent administrative mix-ups

Advice	Objective
The blood transfusion laboratory employee compares (birth) name, date of birth and identification number of the patient with the details on the compatibility form and/or with the label on the blood component , preferably electronically by comparing the barcodes	Tracing of errors in identification of patient
The blood transfusion laboratory employee compares the blood component` number on the unit with the number on the compatibility form and/or the label, preferably electronically by comparing the barcodes	Tracing label mix-ups
The blood transfusion laboratory employee checks the blood component for the following characteristics before release to the nursing ward: <ul style="list-style-type: none"> • requested component • expiry date (electronic) • visual inspection for colour, clots and leakage 	Release of the correct blood component
The blood transfusion laboratory employee initials for the above-mentioned checks for release and an authorised individual on the ward initials for receipt	Traceability of the transfer of the responsibility
<p>In order to prevent errors, it is preferable that one unit of blood component is released per patient, per time by the blood transfusion laboratory to a ward, instead of several units simultaneously. Exceptions are made for wards that have a validated and monitored blood storage refrigerator. Each blood component is then accompanied by a form. For the administration, it is also important that there is a sound registration process – preferably using an electronic transfusion monitoring system – that shows which blood component has actually been administered to which patient at which time. In accordance with European legislation, this registration is stored for a minimum of 30 years.</p>	

Recommendations 3.5.1

1. The procedure for the transfer of blood components from the blood transfusion laboratory to the ward should be recorded in writing.
2. This procedure should describe checks that are performed to prevent possible administrative mix-ups. An example of a checking procedure is described in table 3.5.
3. If possible, the blood transfusion laboratory releases one unit of blood component per patient, per time to a ward. Exceptions are made for wards that have a validated and monitored blood storage refrigerator.
4. The blood transfusion laboratory must supply an (electronic) accompanying form to the ward with each blood component.
5. A sound registration procedure – preferably using an electronic transfusion monitoring system – should take place that shows which blood component was actually administered to which patient at which time. In accordance with European legislation, this administration should be stored for 30 years.

3.6 Selection of erythrocyte concentrate

3.6.1 Selection of ABO/RhD compatible units (standard notation RhD)

Scientific support

In the case of an ABO/RhD identical blood transfusion, the donor blood has the same ABO/RhD blood group as the recipient. In the case of an ABO/RhD compatible blood transfusion, the donor erythrocytes do not have any A or B antigens to which the recipient has antibodies and the RhD antigen should be absent if the recipient is RhD negative. An RhD positive recipient can receive both RhD positive and RhD negative donor blood transfusions.

Consequently, a blood group O RhD negative erythrocyte concentrate is compatible for all recipients. If the patient's blood group is not yet known, blood group O RhD negative blood will then be given for safety reasons.

Approximately 7.6% of the recipients are blood group O RhD negative. However, practical experience from Sanquin Blood Supply shows that a much higher percentage of blood group O RhD negative units is used, 13.1% in 2008 (Sanquin 2008). The use of O RhD negative units is therefore higher than expected based on statistical calculations. As a result, this places an additional burden on the donor population with this specific blood group (11.6%) and a shortage of erythrocyte concentrates of this blood group could occur. Maximum efforts by hospitals to transfuse ABO/RhD identical units can relieve this tension between donor availability and blood group specific demand for erythrocyte concentrates (Sanquin Annual Report 2008).

Table 3.6.1: Preferential choice when selecting ABO-Rhesus-D-compatible units

Recipient	Donor erythrocyte concentrate							
	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th
O pos	O pos	O neg						
O neg	O neg							
A pos	A pos	A neg	O pos	O neg				
A neg	A neg	O neg						
B pos	B pos	B neg	O pos	O neg				
B neg	B neg	O neg						
AB pos	AB pos	AB neg	A pos	A neg	B pos	B neg	O pos	O neg
AB neg	AB neg	A neg	B neg	O neg				

The following paragraphs discuss specific patient groups, for whom additional requirements apply to the selection of ABO/RhD compatible units of erythrocyte concentrate.

Conclusions 3.6.1

	An extra burden is placed on the donor population with blood group O RhD negative. A shortage of erythrocyte concentrates of this blood group can occur.
Level 4	
	<i>D Practical Experience Sanquin Blood Service</i>

	Maximum efforts by hospitals to transfuse ABO/RhD identical units can relieve this tension between donor availability and blood group specific demand for erythrocyte concentrates.
Level 4	
	<i>D Practical Experience Sanquin Blood Service</i>

Other considerations

1. The risk of anti-RhD formation in patients who have received RhD incompatible transfusions is 20 – 30% (Frohn 2003, Yazer 2007, Gonzales-Porrez 2008)
2. The chance of the presence of anti-RhD antibodies is smaller in male RhD negative patients than in female RhD negative patients, who can become immunised through pregnancy.
3. The clinical importance of the development of anti-RhD antibodies is less important in RhD negative men than in RhD negative women < 45 years of age. In RhD negative women of childbearing age, the presence of anti-D antibodies can cause complications for the foetus during pregnancy and can also have consequences for the neonate. For the selection of RhD identical units, it is recommended that negative units be selected for women younger than 45 years if the RhD blood group has not been determined with certainty. For men with a negative antibody screening, the selection of RhD identical units can be considered for a one-off RhD determination. In emergencies, women over the age of 45 years and men with unknown RhD blood group can also receive RhD positive units (Gonzalez 2008).

Recommendations 3.6.1

1. Patients should preferably receive transfusions with ABO and RhD identical erythrocytes.
2. It is essential that the hospitals take the necessary logistical measures to reduce the unnecessary use of blood group O RhD negative erythrocytes.
3. For the selection of RhD identical units, it is recommended that negative units be selected for women younger than 45 years if the RhD blood group has not been determined with certainty. For men with a negative antibody screening, the selection of RhD identical units can be considered after a one-off RhD determination. In emergencies, women over the age of 45 years and men with unknown RhD blood group can also receive RhD positive units.

3.6.2 Selection of blood components for patients with irregular antibodies

Scientific support

Clinically relevant allo (erythrocyte) antibodies (see table 3.6.2) are erythrocyte antibodies that have been described in the literature as being able to cause haemolytic transfusion reactions (Issitt 1998). For patients known to have clinically relevant allo-erythrocyte antibodies, only blood from which the relevant antigen is missing will be selected. In addition to the use of typed erythrocytes, a cross match in the IAT is also performed. This is performed, among other reasons, to rule out any incompatibility due to antibodies targeted against specific (private) antigens that are not routinely present on test erythrocytes. If the transfusion cannot wait for the result of the antibody identification or the selection of typed units, the treating doctor and blood transfusion specialist must weigh the risk of transfusion reactions. IgG antibodies usually cause extravascular haemolysis and rarely cause intravascular haemolysis, with the exception of complement-binding antibodies against – for example – Vel, Tja and Kidd (Klein 2005). For patients with clinically irrelevant erythrocyte antibodies, a cross match – performed in the IAT – that has proved negative is sufficient for the selection process (BSCH 2004). Table 3.3 indicates for which antibodies typed erythrocytes must be selected, when a cross match in IAT is always necessary and when a cross match in IAT can be used as a selection method (Daniels 2002).

After anti-RhD, Caucasian patients most readily form antibodies against K, E and c. It is therefore recommended that rhesus phenotype and K compatible erythrocytes be administered as a preventative measure to recipients with clinically relevant alloantibodies, in order to prevent further antibody formation. Rhesus phenotype and K matching in immunised patients reduces additional antibody formation by 71%, addition of Fy^a, Jk^b and S reduces antibody formation by 93% (Schonewille 2006).

Table 3.6.2: Summary of antibodies. Source: Daniels 2002

Specificity	clinically relevant	antigen negative	X match IAT	X match IAT
anti			compulsory	selection
A, B, AB	yes	yes	N/A	N/A
C	yes	yes	yes	N/A
c	yes	yes	yes	N/A
D	yes	yes	yes	N/A
E	yes	yes	yes	N/A
e	yes	yes	yes	N/A
Cw	37 °C reactive	no	N/A	yes
other rhesus	yes	yes	yes	N/A
A1	37 °C reactive	no	N/A	yes
M	37 °C reactive	yes	yes	N/A
M	not reactive 37 °C	no	N/A	yes
N	37 °C reactive	no	N/A	yes
S	yes	yes	yes	N/A
s	yes	yes	yes	N/A
U	yes	yes	yes	N/A
other MNSs	yes	consult ref. lab	N/A	N/A
P1	37 °C reactive	no	N/A	yes
Lu ^a	37 °C reactive	no	N/A	yes
Lu ^b	yes	yes	yes	N/A
other lutheran	yes	yes	yes	N/A
Le ^a	37 °C reactive	no	N/A	yes
Le ^b	37 °C reactive	no	N/A	yes
K	yes	yes	yes	N/A
k	yes	yes	yes	N/A
other Kell	yes	yes	yes	N/A
Fy ^a	yes	yes	yes	N/A
Fy ^b	yes	yes	yes	N/A
other Duffy	yes	yes	yes	N/A
Jk ^a	yes	yes	yes	N/A
Jk ^b	yes	yes	yes	N/A
other Kidd	yes	yes	yes	N/A
Wra	37 °C reactive	yes, optional	N/A	yes
Yt ^a	yes (strong)	yes	yes	N/A
Yt ^a	no (weak)	no	N/A	yes
Colton b	37 °C reactive	no	N/A	yes
LW	yes	no	N/A	yes with D neg
Chido/Rodgers	no (weak)	no	N/A	yes
H	yes (allo)	yes	N/A	N/A
H, IH,	37 °C reactive (auto)	no	N/A	N/A
Knops en Cost	no	no	N/A	yes
P, Tja	yes	yes	yes	N/A
Vel	yes	yes	yes	N/A
LFA (other)*	consult reference lab	N/A	N/A	N/A
HFA (other)**	consult reference lab	N/A	N/A	N/A

* LFA = Low frequency antigen, ** HFA = High frequency antigen

Conclusion 3.6.2

Level 3

The clinically relevant allo (erythrocyte) antibodies included in table 3.6.2 are antibodies that can cause haemolytic transfusion reactions.

C *Daniels 2002*

Patients who have previously formed a clinically relevant antibody will – as a general rule – form a second antibody against a foreign antigen more quickly. In a Dutch patient population of nearly 1000 patients with various conditions, the chance of additional antibody formation was 20 – 25% (Schonewille 2006, 2009).

Recommendations 3.6.2

1. For patients known to have clinically relevant allo-erythrocyte antibodies, only blood from which the relevant antigen is missing should be selected. **In addition to the use of typed erythrocytes, a cross match in the IAT should also be performed.**
2. For patients with clinically irrelevant alloantibodies against erythrocytes, a negative cross match performed in the indirect agglutination test is sufficient if this result is negative.
3. For patients with known erythrocyte antibodies, the treating doctor must weigh the risk of transfusion reactions due to non-selected units against the risk of delaying the blood transfusion until compatible units have been found.
4. Patients who have previously formed a clinically relevant antibody will – as a general rule – form a second antibody against a foreign antigen more quickly. **In order to rule out antibodies against specific (private) antigens**, a complete cross match (including indirect anti-globulin phase) should always be performed during the compatibility study.
5. **It is recommended that rhesus phenotype and K compatible erythrocytes be administered to recipients with clinically relevant alloantibodies, in order to prevent further antibody formation.**

3.7 Selection of erythrocytes for specific patient categories

In addition to the patients with clinically relevant alloantibodies discussed above – for whom compatible units must be selected with the aid of table 3.6.2 – there are other specific patient categories, for whom additional requirements are set:

1. Girls and women younger than 45 years
2. Patients with haemoglobinopathies, such as sickle cell anaemia or thalassaemia
3. Patients with an auto-immune haemolytic anaemia
4. Patients with a myelodysplastic syndrome (MDS)
5. Patients exposed to hypothermia

3.7.1 Selection of cEK-compatible erythrocytes for women of childbearing age

Scientific support

The use of cEK-compatible blood for girls and women younger than 45 years of age relates to the prevention of antibody formation and thereby prevention of haemolytic disease of the newborn. In addition to RhD antibodies, other irregular antibodies can also be responsible for this. The most commonly occurring non-D antibodies in Caucasian patients – responsible for the haemolytic disease of the newborn – are anti-K and anti-c and to a lesser extent anti-E (Koelewijn 2009, Castel 1996, van Dijk 1991, Contreras 1991).

In the Caucasian population, 91% is negative for the K-antigen and 9% is positive. The large majority of the Dutch donor population is typed for the rhesus phenotype (C, c, D, E and e) and the K-type (K negative or K positive). (communication Sanquin BloodSupply).

A Health Council Committee on Pregnancy Immunisation concluded in its report in 2009 that it is recommended to give erythrocytes that are compatible with regard to the antigens c, E and K during blood transfusion to girls and women up to the age of 45 years (Health Council 2009). It was left up to the professionals to determine how this recommendation is implemented.

Conclusions 3.7.1

	The most commonly occurring non-RhD antibodies – responsible for haemolytic disease of the newborn – are anti-K and anti-c and to a lesser extent anti-E.
Level 3	
	<i>B Koelewijn 2009</i>
	<i>C Castel 1996, Van Dijk 1991, Contreras 1991</i>

	In the Caucasian population, 91% is negative for the K-antigen and 9% is positive.
Level 4	
	<i>D Communication Sanquin Blood Service</i>

Recommendation 3.7.1

In order to reduce the number of cases of haemolytic disease of the newborn due to anti-K, anti-c and anti-E as much as possible, all women aged 45 years and younger should be transfused with **K, c and E compatible** units. It is not necessary to type these women for the K antigen first. **If the typing of the K antigen for the patient is known, then K compatible blood can also be transfused.**

3.7.2 Selection of erythrocytes for patients with haemoglobinopathies (see also Chapter 4)

Scientific support

In patients with haemoglobinopathies (sickle cell anaemia or thalassaemia) who regularly require transfusions, there is a high degree of allo-immunisation when unselected blood is administered. The study by Ness et al has shown this to 10% in children and up to 50% in adults with sickle cell anaemia (Ness 1994). Olujohungbe et al state a figure of 76% allo-

immunisation in patients with sickle cell anaemia in the United Kingdom (Olujohungbe 2001), primarily caused by racial differences between donor and recipient (Vishinski 1990).

What probably played a role in these studies is the fact that a group of primarily Negroid patients was transfused with blood from white donors, who have different frequencies of blood groups. This was also the case in the Netherlands. Spanos described a similar phenomenon in patients with thalassaemia (Spanos 1990). Therefore, transfusion-dependent patients with haemoglobinopathies should be typed as early as possible for the blood groups of the Rhesus, Kell, Duffy, Kidd and MNS systems, and the very rare S and s negative patients should also be typed for blood group U (BCSH 2008).

There are no control studies that examine the effect of matching to prevent alloantibody formation. Three observational studies support the matching for the complete rhesus phenotype and blood group K (Wayne 1995, Pearlman 1994, Russel 1984).

In the case where patients have already been transfused, typing of the Rhesus, Kell, Duffy, Kidd and Ss antigens is possible at DNA level (BCSH 2004, Armeen 2003; Ribeiro 2009, Castilho 2002, 2002, Rozman 2000).

The degree of immunisation in these patients decreases as a result of selection of rhesus phenotype compatible and K negative blood. (BCSH 2004, Armeen 2003). A recent study has also shown that the blood groups Fy^a, Jk^b, S and s are also important (in order of importance). By selecting Fy^a, Jk^b, S en s negative erythrocytes respectively for patients who are negative for these antigens (in order of importance), the degree of immunisation can be decreased significantly (Schonewille 2006). **As the frequency of Jk^b neg (51%) is greater than Jk^a neg (8%) in patients with sickle cell anaemia, particularly Jk^b compatible transfusions are important for these patients in order to prevent immunisation.** Extensive selection of blood negative for these antigens can result in far-reaching reduction of allo-immunisation (Schonewille 2006, Castro 2002, Tahhan 1994).

Conclusions 3.7.2

	Transfusion-dependent patients with haemoglobinopathies should be typed as early as possible for the blood groups of the Rhesus, Kell, Duffy, Kidd and MNS systems and the very rare S and s negative patients should also be typed for blood group U.
Level 4	
	<i>D</i> <i>BCSH 2008</i>

	Three observational studies support the matching for the complete rhesus phenotype and blood group K.
Level 2	
	<i>B</i> <i>Wayne 1995, Pearlman 1994, Russel 1984</i>

	If the patient has already been transfused, typing of Rhesus, Kell, Duffy, Kidd and Ss antigens at DNA level is possible. The degree of immunisation in these patients decreases as a result of selection of rhesus phenotype compatible and K negative blood.
Level 2	
	<i>B</i> <i>Ribeiro 2009, BCSH 2004, Armeen 2003, Castilho 2002, Rozman 2000</i>

	By selecting Fy ^a , Jk ^b , S and s negative erythrocytes respectively for patients who are negative for these antigens (in order of importance), the degree of immunisation can be decreased significantly.
Level 3	
	C <i>Schonewille 2006</i>

	For patients with sickle cell anaemia, the frequency of Jk ^b neg (51%) is greater than Jk ^a neg (8%). Therefore, Jk ^b compatible transfusion is important for these patients in order to prevent immunisation. More extensive selection of blood negative for these antigens can result in far-reaching reduction of allo-immunisation.
Level 3	
	C <i>Schonewille 2006 (B), Castro 2002, (C) Tahhan 1994</i>

Other considerations

The selection choice of the compatible units is partly determined by the antigen determinations performed and the availability of typed units in the blood bank.

Recommendations 3.7.2

1. Transfusion-dependent patients with haemoglobinopathies should be typed as early as possible for the blood groups of the Rhesus, Kell, Duffy, Kidd and MNS systems and the very rare S and s negative patients should also be typed for blood group U.
2. Rhesus phenotype, K and Fy^a compatible blood should be selected for (potentially) transfusion-dependent patients with sickle cell anaemia or thalassaemia. If possible, it is also recommended to select Jk^b, S and s negative erythrocytes (in order of importance) for patients who are negative for these antigens.

3.7.3 Selection of erythrocytes for patients with auto-immune haemolytic anaemia (AIHA)

Scientific support

Due to the presence of clinically relevant autoantibodies in patients with AIHA, the chance of the presence of alloantibodies or alloantibody formation is significant (over 30%) (Engelfriet 2000).

See also paragraph 4.4.5.

Conclusion 3.7.3

	Selection of rhesus phenotype and K compatible blood decreases the incidence of allo-immunisation in patients with AIHA.
Level 3	
	C <i>Engelfriet 2000</i>

Other considerations

As the chance of alloantibody formation is relatively large in patients with AIHA due to clinically relevant autoantibodies, it is important for this group to prevent (as far as possible) the formation of alloantibodies by transfusion with erythrocytes that are Rhesus phenotype and K compatible. Preferably, matches for Kidd, Duffy and Ss antigens are also indicated (in order of importance), if the presence of alloantibodies cannot be ruled out. The antigens of the Rhesus, Kell, Kidd and Ss systems can usually be detected serologically with monoclonal reagents if the patient has not received a transfusion in the past three months. For all other cases (antigens in the Duffy system and typing of individuals who have received a transfusion in the last three months) there is the possibility of typing at DNA level (Rozman 2000).

Recommendation 3.7.3

If possible, rhesus phenotype and K compatible blood should be selected for patients with AIHA in order to prevent alloantibody formation.

3.7.4 Selection of erythrocytes for patients with myelodysplastic syndrome

The available literature is ambiguous, but according to an analysis based on this literature, the risk of immunisation in patients with myelodysplastic syndrome (MDS) varies between 14 and 59% - average of 23% - and is comparable to SCD and thalassaemia (Schonewille 2008). It is therefore recommended to select rhesus phenotype and K compatible blood for these patients (Fluit 1990, Novaretti 2001, Stiegler 2001, Schonewille 1999, Arriaga 1995).

Conclusion 3.7.4

	The immunisation risk for patients with MDS varies between 14 and 59%.
Level 3	C Fluit 1990, Arriaga1995, Novaretti 2001, Stiegler 2001; Schonewille 1999

Other considerations

In two Dutch studies of patients with myeloproliferative neoplasms (MPN), in which 44 (Schonewille 1999) and 16 (Fluit 1990) patients respectively were included, the immunisation risk was on average 17%. No new studies with larger patient groups have been published.

Recommendation 3.7.4

Taking into consideration the immunisation risk in patients with MDS, it is preferable to transfuse these patients with rhesus phenotype and K compatible blood.

3.7.5 Selection of erythrocytes for surgical procedures with hypothermia in patients with cold antibodies

Clinically relevant cold antibodies in patients undergoing interventions with hypothermia such as cardiac surgery can cause transfusion reactions (Hoffman 2002). The transfusion reactions described in older publications only occurred with strong cold antibodies and/or deep (~15 °C) hypothermia. Strong cold antibodies can cause problems in the standard

compatibility tests and deep hypothermia is now only used in combination with specific interventions.

There is no evidence in the literature to support pre-operative screening for cold antibodies at room temperature for all patients being exposed to mild hypothermia (~ 30 °C). (Judd 2006).

Conclusions 3.7.5

	Clinically relevant cold antibodies in patients being exposed to severe hypothermia – for example during cardiac surgery – can cause transfusion reactions.
Level 4	
	<i>D Hoffman 2002</i>

	There is no evidence in the literature to support pre-operative screening for cold antibodies at room temperature for all patients being exposed to mild hypothermia.
Level 4	
	<i>D Judd 2006</i>

Other considerations

The transfusion reactions described in the literature only occurred in the case of the presence of strong cold antibodies and/or in surgery involving deep hypothermia. Following consultation with the anaesthesiologist, it may be desirable in some cases to determine the frequency of the clinically relevant cold antibody.

Recommendation 3.7.5

It is not necessary to perform pre-operative screening for cold antibodies at room temperature on patients undergoing a surgical procedure with mild hypothermia (~ 30 °C).

3.8 Release of platelet concentrates

3.8.1 ABO compatibility of platelets

3.8.1.1 Major ABO incompatible transfusions

Scientific support

Major ABO incompatible platelets have a 10 – 35% lower post-transfusion yield than major ABO compatible platelets (Lee 1989, Heal 1993, Shehata 2009, Julmy 2009). After several ABO incompatible transfusions, the recipient's anti-A and/or anti-B titre can increase and for an IgG and/or IgM titre > 128, the yield and survival of A1, B and A1B incompatible platelets is often insufficient. This was demonstrated in 2 randomised studies (Lee 1989, Heal 1993) and confirmed by 2 large observational studies (TRAP 1997, Julmy 2009). Ogasawara et al found very high expression of the A1 antigen in 7% of the donors. (Ogasawara 1993). This figure is not known for Caucasian donors. Transfusion reactions and intravascular platelet degradation can occur at very high anti-A and/or anti-B titres and in the presence of haemolysins in the recipient. This can result in transfusion failure. (Brand 1986). Only A1 platelets are degraded, whilst A2 platelets behave as blood group O. ABO/RhD compatibility

is not always possible in HLA-typed transfusions and therefore the anti-A and/or anti-B titre should be monitored regularly (particularly in the case of poor yield).

Level 3	Both the quantity and the biological activity of anti-A and/or anti-B antibodies in the recipient and the density of the ABO antigens on the membrane of the donor platelets determine the final yield of the platelets. <i>B Ogasawara 1993</i>
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Level 1	Major ABO incompatible platelets have a 10 – 35% lower post-transfusion yield than major ABO compatible platelets. <i>A2 Lee 1989, Heal 1993</i> <i>B Shehata 2009, Julmy 2009</i>
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Level 1	After several ABO incompatible transfusions, the recipient's anti-A and/or anti-B titre can increase and for an IgG and/or IgM titre > 128, the yield and survival of A1, B and A1B incompatible platelets is often insufficient and can sometimes be associated with transfusion reactions. <i>A2 Lee 1989, Heal 1993</i> <i>B TRAP 1997, Julmy 2009,</i> <i>C Brand 1986</i>
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Other considerations

If the expected increase in platelet number is not achieved in a stable patient, the CI (count increment) or CCI (corrected count increment) should be determined after transfusion with (fresh) ABO compatible platelets.

In the case of an ABO incompatible platelet transfusion, it is important to be aware of individual variations in the extent to which ABO incompatible platelets are degraded (variation in anti-A and anti-B respectively in the recipient and antigen density in the donor).

Table 3.8.1: Preferential choice selection of platelets

Recipient	Donor platelet concentrate			
	1 st	2 nd	3 rd	4 th
O	O	B or A		
A	A	O	B*	
B	B	O	A*	
AB	(AB)	A	B	O

Option * only after consultation with the head of the transfusion department (double incompatibility)
 Comment: Platelet hyper-concentrates are also available for blood group incompatibilities (see also paragraph 2.1.4).

Recommendations 3.8.1.1

1. For transfusion of platelets in plasma, it is advised to transfuse **ABO-identical** where possible (see table 3.8.1), this is particularly important for neonates.
2. **If ABO-incompatible donor plasma with a platelet transfusion is administered to a neonate, the titre for anti-A or anti-B must be lower than 128 (see also paragraph 2.1.3).** All paediatric components meet these requirements.

3.8.1.2 Minor ABO incompatible transfusions

Scientific support

Following minor ABO incompatible platelet transfusion, a positive direct anti-globulin test (DAT) can be the result of transfusion of incompatible plasma. This is usually associated with slight haemolysis, although in an estimated 1 in 9000 patients minor incompatible platelet transfusions can cause severe – even fatal – haemolysis and renal failure (Mair 1998, Larsson 2000, Lozano 2003, Harris 2007). The amount of incompatible plasma can be reduced by 30% by using platelet storage solutions, or 95% of the plasma can be removed by hyper-concentration. Even this can be insufficient in the case of high anti-A and/or anti-B titres (Valbonesi 2000). It is advisable to avoid incompatible plasma for patients receiving multiple transfusions simultaneously or for children for whom the transfusion volume is ≥ 10 mL/kg body weight of the recipient. If this is not possible, the plasma should contain a relatively low antibody titre. In the Netherlands, it has been decided on practical and theoretical grounds to set a titre smaller than 128. The anti-A, anti-B titre determination is difficult to standardise (Harris 2007, Aubuchon 2008). There are no (inter)national guidelines for the quantity of incompatible plasma that may be administered with platelets. A survey of 3152 American transfusion services revealed that 83% have an ABO minor incompatibility policy. This policy can vary greatly, from warning the treating physician to volume reduction of platelets (Fung 2007). In the UK, all platelet components are screened and if the antibody titre is > 100 (approximately 10% of the components), only ABO identical components are transfused. (NBS 2006). See also Chapter 2.1.3.

In large series, the yield of O platelets (in plasma) to A/B recipients is slightly lower compared to ABO identical platelets, possibly due to soluble immune complexes that bind to Fc γ receptors on platelets (Heal 1993).

Conclusions 3.8.1.2

	Minor incompatible platelet transfusions can cause a positive anti-globulin test (DAT) in the recipient. This is usually associated with slight haemolysis, but in approximately 1 in 9000 patients minor incompatible platelet transfusions can cause severe – even fatal – haemolysis and renal failure.
Level 3	
	<i>B Mair 1998</i> <i>C Larsson 2000, Lozano 2003, Harris 2007</i>

	The transfusion of platelets in incompatible plasma can be largely reduced by the use of platelet storage solutions or by the removal of plasma. There are indications that these measures may be inadequate for very high anti-A and/or anti-B titres.
Level 3	
	<i>C Valbonesi 2000</i>

Recommendations 3.8.1.2

1. It is recommended to transfuse preferably ABO identical units in the case of platelets from donors with high (or unknown) anti-A and/or anti-B titres.
2. There should be a hospital guideline that describes how to act in the case of ABO minor incompatible platelet transfusions.
3. In the case of minor ABO incompatible transfusions, an anti-A and/or anti-B titre lower than 128 is recommended for patients who receive multiple transfusions simultaneously or for children/neonates for whom the transfusion volume is ≥ 10 mL/kg of body weight. If ABO identical components are not available, a reduction of the anti-A and anti-B antibodies can be achieved by selection based on screening of the titre in the component, the use of storage solutions or by plasma volume reduction.

3.8.2 RhD compatible platelets

Scientific support

Although platelets do not express RhD antigens, RhD immunisation is possible due to erythrocytes present as contamination in platelet units.

The minimum amount of erythrocytes capable of causing primary RhD immunisation is 0.03 mL (Mollison 1997, Cid 2005). Platelets prepared from buffy coat can contain 0.4 – 0.6 mL of erythrocytes whereas platelet units from apheresis generally contain fewer red blood cells (Zeiler 1994). If the platelet suspension is pink in colour it contains more than 0.3 mL of erythrocytes. The risk of RhD immunisation in patients who are immune suppressed is between 0 and 19% (Goldfinger 1971, Lozano 2003, Atoyebi 2000). This is an underestimate as antibodies can be demonstrated long after transfusion, on average 184 days (45 – 450 days). Unlike RhD, irregular erythrocyte antibodies due to platelet transfusions are rare, but cases have been described.

Platelet transfusions should preferably be RhD compatible. RhD negative female patients < 45 years old should receive only RhD negative platelet concentrates; if transfusion of RhD positive platelet concentrate is unavoidable, possible immunisation should be avoided by the administration of an ampoule of anti-RhD immunoglobulin containing 375 international units (IU) (Lozano 2007).

Conclusion 3.8.2.2

	There are indications that the minimum quantity of erythrocytes that can cause primary RhD immunisation is 0.03 mL.
Level 3	
	C <i>Mollison 1997, Cid 2005</i>

	Anti-RhD antibodies are found in 0 – 19% of immune suppressed patients. The actual immunisation frequency is probably higher because anti-RhD antibodies can only be demonstrated long after transfusion.
Level 3	
	B <i>Goldfinger 1971</i> C <i>Lozano 2003, Atoyebi 2000</i>

Recommendation 3.8.2.2

It is recommended that platelet transfusions should preferably be RhD compatible. Female RhD negative patients under the age of 45 years should only receive RhD negative platelet concentrates. If this cannot be achieved, an ampoule of anti-RhD immuno-globulin containing 375 international units (IU) should be administered (provides roughly 10 weeks of protection) to prevent RhD immunisation.

3.9 Release of plasma

Plasma is released as blood group ABO compatible, as plasma can contain antibodies against blood group antigens A and B. A recent cohort study showed that transfusion of ABO incompatible plasma after organ transplantation was associated with more multi-organ damage and that – in a surgical population – administration of ABO compatible but not ABO identical plasma was associated with a higher mortality than administration of ABO identical plasma (Benjamin 1999, Shanwell 2009). This could be caused by soluble immune complexes of soluble A and/or B + anti-A and/or anti-B antibodies (Shanwell 2009).

The ABO blood group of the recipient should be determined and confirmed using at least two independently collected samples (see paragraph 3.2.1 and 3.2.2). If the ABO blood group is unknown or has only been determined once, AB plasma should be administered. As the apheresis plasma in the Netherlands is prepared using a method in which the remaining erythrocyte number is less than 1×10^8 /unit, the RhD blood group does not have to be taken into consideration. All donors are tested for irregular antibodies and are negative or have a titre lower than 32. (Vrieling 2004).

Conclusion 3.9

	Two studies suggest that transfusion of non-identical ABO plasma causes more multi-organ damage and a higher mortality.
Level 3	
	C Benjamin 1999 B Shanwell 2009

Other considerations

European legislation means that it is compulsory for the RhD blood group to be stated on the label of the plasma component.

Table 3.9: Selection of ABO compatible plasma

Recipient	Donor fresh frozen plasma			
	1 st	2 nd	3 rd	4 th
O	O	A	B	AB
A	A	AB		
B	B	AB		
AB	AB			

The working group deems it important that a visual inspection for colour (due to contamination with erythrocytes), clots and leakage of the bag takes place before release of a unit of plasma.

Recommendations 3.9

1. Plasma should be administered ABO blood group compatible (see table 3.9 Selection of ABO compatible plasma).
2. Further investigation to determine whether plasma transfusions need to be ABO identical is recommended. For plasma transfusion, it is not necessary to take into consideration the RhD blood group.
3. The unit of plasma is checked for colour, clots and leakage before release.

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CHAPTER 4: CHRONIC ANAEMIA

Introduction

This guideline discusses the treatment of anaemia and in particular the erythrocyte transfusion policy in two chapters, Chapter 4: Chronic anaemia and Chapter 5: Acute anaemia.

In this guideline, chronic anaemia refers to anaemia that is not the result of acute blood loss. That means that acute anaemia is defined as: anaemia due to acute blood loss. An iron-deficiency anaemia due to chronic blood loss is therefore considered to be chronic anaemia. Acute anaemias that are not the result of bleeding fall outside these definitions. Somewhat arbitrarily, ICU patients with acute anaemia that is not the result of bleeding are discussed in Chapter 5 under acute anaemia and, for example, patients with acute anaemia due to an auto-immune haemolytic anaemia (AIHA) are discussed in this chapter.

A short introduction about the pathophysiology of anaemia is followed by general guidelines for the treatment of chronic anaemia (4.1). Next, forms of anaemia that are the result of production disorders of erythrocytes are discussed (4.2). The use of erythropoietin (EPO) and related medicines (ESAs) in production disorders are discussed separately (4.3). Forms of anaemia due to haemolytic disorders are discussed next (4.4). The chapter concludes with two paragraphs about the erythrocyte transfusion policy in neonates (4.5) and children (4.6) respectively.

The most important indication for the administration of erythrocyte concentrates (RBCs) is the recovery or maintenance of an adequate oxygen supply, matching the needs of the tissues.

The oxygen supply is determined by cardiac output (CO), haemoglobin concentration (Hb) and the arterial oxygen saturation.

Oxygen use at rest is about 250 mL/min. This means that if the supply is 1,000 mL/min, the oxygen extraction ratio is 25%. The oxygen use may increase due to increased extraction above 25% and the oxygen supply can be increased by increasing the Hb concentration and/or increasing the cardiac output. A low Hb can be compensated for by increasing the oxygen extraction and/or the cardiac output.

An increase in cardiac output may be achieved by an increase in stroke volume and/or heart rate. The stroke volume can be increased by increasing the cardiac contractility and/or by decreasing the peripheral resistance and by decreasing blood viscosity ('afterload' reduction). In general, the cardiac output may increase at an Hb < 5.5 – 6.0 mmol/L, but sometimes this will happen at a lower level (Hb < 4.5 – 5.0 mmol/L).

4.1 General guidelines for giving erythrocyte transfusions for chronic anaemia

The Hb does not need to be increased as long as the usual reserves and compensation mechanisms are sufficient to meet the oxygen demands of the tissues. However, when oxygen demand threatens to exceed supply, it is necessary to administer erythrocytes.

The decision to give a blood transfusion to a patient with chronic anaemia is based on the patient's symptoms that indicate a lack of oxygen-transport capacity and a number of clinical

parameters such as patient age, the speed at which the anaemia occurred, the cause of the anaemia, cardiac and/or pulmonary disease resulting in decreased oxygen reserves and/or the ability to compensate for the lack of oxygen transport capacity. The Hb can also be included in this.

Research has shown that a low Hb is often tolerated well. In 32 healthy, resting volunteers, undergoing acute iso-volemic haemodilution to an Hb of 3 mmol/L an adequate oxygen supply was maintained (Weiskopf 1998). In 134 adult Jehovah's Witnesses with an Hb < 5 mmol/L, deaths due to anaemia only increased at an Hb below 3 mmol/L (Viele 1994).

Other considerations

Recently, a number of studies have been published that show that pre-operative anaemia is a risk factor for post-operative mortality.

Please refer to the CBO guideline 'The pre-operative course', 2010 (www.cbo.nl), for recommendations on treatment of pre-operative anaemia.

The following recommendations are not evidence-based, but are based on expert opinion (opinion of the working group) and international guidelines.

Recommendations 4.1

1. The only indication for a therapeutic erythrocyte transfusion in the case of chronic anaemia is a symptomatic anaemia*.
2. An Hb < 3 mmol/L is an absolute indication for an erythrocyte transfusion.
3. Prophylactic erythrocyte transfusions can be indicated for asymptomatic chronic anaemia in a patient without cardio-pulmonary limitations and an Hb < 4 mmol/L.
4. Prophylactic erythrocyte transfusions can be indicated in the case of limited cardio-pulmonary compensation abilities or risk factors in accordance with table 5.2, lines 4, 5 and 6, in Chapter 5.
5. If there are no obvious limited cardio-pulmonary compensation abilities or risk factors, the following Hb triggers can be maintained for prophylactic erythrocyte transfusions for chronic anaemia:

Age (years)	Hb trigger (mmol/L)
< 25	3.5- 4.5
25-50	4.0 -5.0
50-70	5.5
> 70	6.0

The following applies to recommendations 1, 3 and 4: provided no better treatment alternatives are available.

*symptoms of anaemia: tachycardia, dyspnoea, palpitations, angina pectoris, dizziness, syncope, *de novo* ST depression or elevation on the ECG and new arrhythmia on the ECG

4.2 Production disorders

4.2.1 Essential nutrient deficiencies (iron, folic acid, vitamin B12)

Iron deficiency

Iron deficiency occurs in the First World countries too; approximately 10% of women and elderly people are iron deficient (Looker 1997). In the Netherlands, iron deficiency in childhood occurs primarily in ex-premature children, children of foreign parents who drink a lot of cow's milk, asylum seekers and teenagers with a limited diet that is deficient in nutrients. A prospective study of 100 elderly orthopaedic patients revealed that 18% had pre-operative iron-deficiency anaemia (Hb < 7.5 mmol/L). After four weeks of iron substitution, the Hb concentration had improved significantly with an average of 0.7 mmol/L. The patients without anaemia were randomised between four weeks of iron medication (pre-operative and post-operative) and no medication. The group treated with iron (Fe) had a significantly higher (> 0,5 mmol/L) Hb during the first post-operative week than the group that did not receive Fe, without a significant difference in the need for transfusion during the surgery (Andrews 1997). A comparable randomised study of asymptomatic patients with colorectal cancer also showed a higher initial Hb concentration in the group with iron supplementation, but also a significant decrease in the number of transfused units (average 2 to 0) (Liddler 2007). Munoz showed that intravenous administration of iron to patients who had pre-operative anaemia resulted in an increase in Hb level of 2.0 g/L (1.2 mmol/L) (Munoz 2009). Another study examined the effect of post-operative administration of oral iron for 3 weeks after total knee arthroplasty; there was no clear difference in the level of Hb and recovery after surgery (Mundy 2005). A recent study showed no correlation between the pre-operative iron status and the need for peri-operative or post-operative transfusion. However, the pre-operative Hb level did appear to have a predictive value for the peri-operative and/or post-operative need for transfusion (Fotland 2009).

Nutritional megaloblastic anaemia can be caused by:

- Folic acid deficiency caused by nutritional deficiency and/or alcoholism, increased use such as in haemolysis and pregnancy, medication (trimethoprim and methotrexate) and malabsorption.
- Vitamin B12 deficiency caused by malabsorption due to pernicious anaemia, gastritis or following gastrectomy or due to nutritional deficiency with strict veganism.

The blood can also be macrocytic in the case of myelodysplasia and auto-immune haemolytic anaemia.

Megaloblastic anaemias only become symptomatic at very low Hb levels (< 3 – 4 mmol/L) due to the slow development and associated compensation of oxygen transport. If megaloblastic anaemia is suspected, treatment consists of the administration of vitamin B12 and folic acid, with blood being collected first for diagnosis. A transfusion indication only occurs in patients who cannot compensate for anaemia such as severe heart failure or instable angina. Administration of vitamin B12 for such severe anaemia will not guarantee fast correction, meaning that a transfusion could be indicated. In all other cases, transfusion should be avoided.

Conclusions 4.2.1

Level 4	Anaemias caused by nutritional deficiency only form an indication for blood transfusion at extremely low Hb levels. <i>D Expert opinion</i>
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Level 2	The pre-operative Hb level influences the peri-operative need for transfusion. Pre-operative screening and substitution of iron-deficiency anaemia can improve the post-operative Hb. <i>B Fotland 2009, Munoz 2009, Liddler 2007, Andrews 1997</i>
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Recommendations 4.2.1

<ol style="list-style-type: none">1. Anaemia caused by iron deficiency does not form an indication for transfusion, unless the severity of the anaemia reaches the absolute transfusion indication (HB < 3 mmol/L) or if hypoxic symptoms occur at rest.2. In patients undergoing elective, major surgical procedures it is recommended to treat any iron-deficiency anaemia for a minimum of four weeks prior to surgery.
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4.2.2 Bone marrow insufficiency

Bone marrow aplasia inducing treatments

Particularly in haemato-oncology, aplasia-inducing treatments can cause anaemia in a short period of time, which is why some haematologists will give erythrocyte transfusions at an earlier stage (i.e. at a higher Hb). In addition, these patients often have a deep thrombocytopenia, meaning that a higher Hb is desirable for good haemostasis. A restrictive erythrocyte transfusion policy (Hb trigger 4.5 – 5.5 mmol/L, depending on age and symptoms) compared to a more liberal trigger (Hb 6.0 mmol/L) did not result in more platelet transfusions or bleeding complications (Jansen 2004).

Solid tumours

Anaemia in non-haematological malignancies is usually the result of a chronic disease and not the suppression of haematopoiesis by bone marrow metastases.

Chemotherapy, radiotherapy, haemolysis (micro-angiopathy), coagulopathy and bleeding can contribute to the occurrence of anaemia. With solid tumours there is also a (relative) shortage of erythropoietin (Miller 1990). Not all patients with solid tumours develop anaemia. An average of 12% (95% relative odds ratio (CI): 9 – 34) of the adult patients receive transfusions with first line chemotherapy, whilst 18 – 52% will receive blood transfusions in their lifetime (Skilling 1999/1993). Anaemia is more common during platinum-based chemotherapy (Wood 1995, Skilling 1993). There are no randomised studies about the relationship between the level of Ht and the effect of chemotherapy and/or radiotherapy on the disease. Patients with cancer often receive transfusions at an Hb < 6 mmol/L, particularly if they have an active lifestyle, but this limit is not based on research.

Other considerations

A separate point of discussion is whether or not allogeneic transfusions can inhibit the patient's immunity against tumours and thereby promote relapse of the cancer after surgical treatment that should be curative (see Chapter 7.2.12).

Recommendation 4.2.2

Randomised study of the relationship between anaemia and any decreased efficacy of chemotherapy / radiotherapy is desirable.

Lymphatic malignancies

Approximately 70% of patients with multiple myeloma (MM) and approximately 25% of patients with non-Hodgkin's lymphoma develop anaemia during treatment.

Patients with chronic lymphatic leukaemia (CLL) can develop anaemia due to autoantibodies (immune haemolysis (AIHA), see paragraph 4.4.5), by suppression of erythropoiesis or by chemotherapy. Patients with immune-mediated haemolysis are treated according to the protocols that have been developed for patients with idiopathic AIHA (see paragraph 4.4.5). If anaemia is the result of bone marrow suppression, it will improve upon response to treatment. No studies of Hb triggers for transfusion have been performed for this condition.

Recommendation 4.2.2

1. Patients with immune-mediated haemolysis due to CLL should be treated according to the protocols that have been developed for patients with idiopathic AIHA. See also paragraph 4.4.5.

Transfusion risks (see also Chapters 2 and 7)

For irradiation of erythrocytes: see Chapter 2.2.4 (Table 2.1)

Patients with lympho-proliferative diseases receive fewer transfusions than patients with myeloid conditions. There are also data that point to a decreased immune response to allo-antigens (due to the nature of the treatment or not) (Schonewille 1999, Fluit 1990). Therefore, the risk of the occurrence of irregular erythrocyte antibodies in patients with lympho-proliferative conditions is small.

Myeloid conditions

In general, patients with acute myeloid leukaemia receive multiple erythrocyte and platelet transfusions; in the case of chronic myeloid leukaemia transfusions are necessary following transplantation or in the (pre)terminal stages of the disease. Patients with myelofibrosis – who often have splenomegaly – benefit less from erythrocyte transfusions. The greatest chronic need for transfusion exists with myelodysplasias. There are no studies of optimal transfusion triggers for these conditions. There is also no evidence for a specific transfusion policy of red blood cells for acute myeloid leukaemia (Milligan 2006).

Patients with myelodysplasia are usually older (on average 68 years) at the time of diagnosis. More than 90% require erythrocyte transfusions (20 – 30 units / year), often without treatment alternatives. Iron chelation therapy should be given, depending on the type of myelodysplastic syndrome (MDS) and the life expectancy (see Chapter 7).

4.2.3 Anaemia with chronic renal insufficiency

See NFN guideline *Anaemia with chronic renal insufficiency 2009, with an update in 2010* (<http://www.nefro.nl/home/richtlijnen>)

4.2.4 Anaemia with chronic illness, excluding renal failure / malignancy

With chronic anaemia, there is an increase in the 2,3-DPG level in the erythrocytes, with a right shift of the O₂ dissociation curve. Therefore, it is generally not necessary to transfuse above an Hb level of 5.0 mmol/L, except if there are signs of decreased oxygenation (Liumbruno 2009).

HIV infection

With HIV infection there are various causes of anaemia – not all of which are understood – such as autoantibodies, protease inhibitors, bone marrow infiltration and ‘anaemia with chronic illness’.

These are associated with elevated levels of TNF-alpha and IL-6 and an inadequate erythropoietin response to anaemia, particularly in the advanced stage of the infection.

Anaemia is not such a big problem with the use of the new generation of protease inhibitors. Despite T-cell deficiency in HIV infection, there has never been a report of TA-GvHD. Therefore, irradiation of blood components is not indicated for HIV patients.

Inflammatory bowel disease (IBD)

In IBD, anaemia can occur due to ‘anaemia with chronic illness’, blood loss and malabsorption. The Hb concentration can drop to < 5 mmol/L, but because the patients are often young and do not have any symptoms of hypoxaemia, transfusions are generally not indicated. The Hb improves in > 50% of the patients with iron supplementation (Gasche 1997).

Older observational studies show that blood transfusions – administered during bowel surgery for Crohn’s disease – have a favourable immune-modulating effect and extend the interval until the next exacerbation. However, a meta-analysis of 4 of the 7 historical studies found insufficient evidence for this (Hollaar 1995).

Conclusions 4.2.4

Level 3	In chronic illness, a right shift of the oxygen dissociation curve causes a lower transfusion threshold. C Liumbruno 2009
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Level 3	TA-GvHD has never been reported in HIV infected patients, despite the administration of not irradiated blood components. C Collier 2001 D SHOT-rapporten 1996-2009
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Level 3	In IBD, adequate iron supplementation can result in an improvement in Hb in > 50% of patients. C Gasche 1997
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Recommendations 4.2.4

1. Anaemia with chronic illness rarely results in a transfusion indication at an Hb > 5.0 mmol/L.
2. Inflammatory bowel disease (IBD) patients with anaemia should be tested for iron deficiency and if diagnosed, should receive adequate iron supplementation.
3. The working group is of the opinion that an HIV infection is not an indication for irradiation of blood components.

4.2.5 Anaemia during pregnancy

There is little or no controlled research that adequately answers essential questions about transfusion policy in pregnancy. The current guidelines are based mainly on consensus (KNOV guideline 2010, BCSH BTTF 1998, Simon 1998, ACOG 1994). Within the gynaecological setting, transfusions are mostly given peri-operatively; the indications are identical to those applied in general surgery. The chronic anaemia caused by menstrual abnormalities also does not differ from other situations of chronic iron-deficiency anaemia (see paragraph 4.2.1).

The aim of iron supplementation in pregnancy is to achieve a ferritin level of > 80 µg/L (Elion-Gerritzen 2001). Little is currently known about the treatment of anaemia with erythropoietin during pregnancy. The same applies to the treatment of post-partum anaemia (Dodd 2004).

For the diagnosis of anaemia in pregnancy, please refer to the 2010 KNOV guideline (KNOV guideline 2010).

Approximately 30 – 35% of Dutch pregnant women are of foreign descent and have a higher incidence of haemoglobinopathy (refer to transfusion problems in pregnancy for patients with sickle cell anaemia, paragraph 4.2.2.2).

Component choice

During pregnancy, transmission of certain viruses via donor blood (in particular Parvo-B19) should be avoided in order to prevent foetal morbidity and mortality (Health Council: see paragraph 2.2.6, Hofmeyr 2001, BCSH BTTF 1998).

There are no data concerning transmission of Parvo-B19 via blood transfusions to pregnant women. It is known that Parvo-B19 infection during the first term of pregnancy causes approximately 10% intra-uterine death due to hydrops (Tolfvenstam 2001). The Health Council advised in 2002 that sero-negative pregnant women should receive Parvo-B19 safe transfusions in the first and second term of pregnancy (Health Council report 2002). See Chapter 2.2.6 for the guidelines on prevention of Parvo-B19.

Women of pre-reproductive and reproductive age should receive cEK compatible erythrocytes in order to prevent antibody formation, which can cause haemolytic disease of the newborn (see also Chapter 3.7.1, selection of cEK compatible erythrocytes for women of childbearing age).

Conclusions 4.2.5

Level 3	Parvo-B19 infection during the first term of pregnancy causes approximately 10% intra-uterine death due to hydrops. <i>C Tolfvenstam 2001</i>
Level 4	During the first and second terms of pregnancy it is advisable to select Parvo-B19 safe components for transfusion to sero-negative pregnant women in order to prevent transmission of Parvo-B19. <i>D Health Council 2002</i>
Level 3	The aim of iron suppletion during pregnancy is to achieve a ferritin level > 80 µg/L. <i>C Elion-Gerritzen 2001</i>

Other considerations

There are many similarities in the guideline for transfusion to pregnant women, but there is very little scientific evidence to support it. Therefore one may conclude that the precautionary principle is leading.

Recommendations 4.2.5

1. The need for a transfusion during pregnancy should be considered per individual patient, depending on underlying disease and the health of the foetus.
2. **Iron supplementation can be considered** for iron-deficiency anaemia in pregnancy.
3. Parvo-B19 safe transfusions are recommended for sero-negative pregnant women (see Chapter 2.2.6).
4. **A woman of (pre) fertile age should receive cEK compatible erythrocyte transfusions (see also Chapter 3.7.1).**

4.2.6 Bone marrow / stem cell transplants

Haemolysis due to major ABO incompatibility

Transfusion reactions can occur due to antibodies from the recipient against cells from the donor; this usually involves anti-A and/or anti-B antibodies.

Particularly in bone marrow, there is a large quantity (> 700 mL, approximately 40% of the bone marrow volume) of erythrocytes present. There are various options to prevent/reduce transfusion reactions caused by haemolysis due to blood group incompatibility (Klumpp 1995). Every centre has developed its own empirical method (Lapierre 2000). In adults the only measure is usually to reduce the erythrocyte volume of the bone marrow / stem cell component to < 15 mL if the patient has an IgG and/or IgM titre greater than 16 in combination with slow administration and good hydration of the patient. The administration speed must be adjusted according to the anti-A and/or anti-B titre of the patient (the higher the titre, the slower the administration). Further reduction of the erythrocyte volume to < 10

mL is recommended in children (Rowley 2000). The height of the IgG/IgM titre has not been standardised between the various centres. In the case of major ABO incompatibility, the isoagglutinins of the recipient can persist until after day 200 (Herschko 1980) and the titre can still rise during the first three weeks after transplantation (Sniecinski 1988, Ochelford 1982). In addition to delayed haemolytic reactions, complications include prolonged aplasia and 'pure red cell aplasia' (Fitzgerald 1999, Salmon 1999, Lyding 1999, Laurencet 1997, Oziel-Taleb 1997, Bornhauser 1997, Moog 1997, Toren 1996, Greeno 1996, Lopez 1994, Sniecinski 1988, Hows 1986, Warkentin 1983).

Haemolysis due to minor ABO incompatibility

In the case of minor ABO incompatibility, some centres recommend the removal of plasma if the donor has an IgG and/or IgM titre ≥ 128 . The consensus by Société Française de Greffe de Moelle even recommends washing of the transplant at a titre > 32 . A good compromise is plasma reduction at a titre > 32 (Rowley 2000, Lapierre 2000).

Anti-A/anti-B antibodies from the donor can also be stimulated by (tissue) expression of blood group A and/or B in the patient. Prospective follow-up shows that approximately 25% of the recipients develop a positive DAT during the first 3 weeks after bone marrow transplantation (BMT) / peripheral blood stem cell transplantation (PBSC) (Lapierre 2000, Rowley 2000, Hows 1997).

Passenger B-cells in the transplant are usually stimulated after 7 – 14 days. The antibody production usually extinguishes several weeks after transplantation. Life threatening haemolysis has been described between day 5 and day 14 after transplantation – in particular after non-myelo-ablative conditioning and PBSC – in which the entire circulating RBC volume of the recipient is broken down in 1 – 3 days (Lapierre 2000, Bolan 2001, Salmon 1999, Hows 1997, Laurencet 1997, Oziel-Taleb 1997, Toren 1996, Greeno 1996, Lopez 1994, Gajewski 1992, Warkentin 1983), as are compatible donor transfusions as 'innocent bystander'.

Non-ABO blood group specific antibodies

These can come from the donor or the recipient and are targeted against the stem cell donor, the recipient or the blood donor. Multiple specificities such as D, c, Cw, e, E, Jka and Le have been found (Lapierre 2001, Bornhauser 1997, Godder 1997, Lopez 1994).

A randomised study revealed that irregular antibodies formed more frequently after PBSC (3/21) than after BMT (0/28) (Lapierre 2001). The identification of the specificity is easier if the pre-transplant erythrocyte typing of donor and recipient is known.

Non-specific autoantibodies

These can occur > 2 years after transplantation, in association with immune deficiency, CMV infection, unrelated donors and GvHD. The frequency is approximately 4% (Sanz 2007). As a rule, the autoantibody formation is self-limiting if immunological recovery is achieved, although the condition is fatal in 50% of patients due to haemolysis, multi-organ failure or refractory thrombocytopenia (Horn 1999, Chen 1997, Drobyski 1996, Lord 1996).

Conclusions 4.2.6

Level 3	<p>Every centre has developed its own empirical method for preventing/reducing haemolytic reactions with stem cell / bone marrow transplants. In adults the RBC volume is usually reduced to < 15 mL, if the patient has an IgG and/or IgM titre > 16, in combination with slow administration and good hydration of the patient. In children, the RBC volume is reduced to < 10 mL.</p> <p>C <i>Rowley 2000, Lapierre 2000</i></p>
Level 3	<p>In the case of minor ABO incompatibility, some centres recommend the removal of plasma from the stem cell / bone marrow transplant if the donor has an IgG and/or IgM titre \geq 128. The consensus by Société Française de Greffe de Moelle even recommends washing of the transplant at a titre > 32. A good compromise is plasma reduction at a titre > 32.</p> <p>C <i>Rowley 2000, Lapierre 2000</i></p>
Level 3	<p>After BMT/PBSC, blood components that are ABO/RhD compatible with the donor AND the recipient should be used for transfusion.</p> <p>C <i>Klump 1995; Rowley 2000; Hershko 1980; Chan 1983; Ockelford 1982; Sniecinski 1988; Warkentin 1983; Bornhauser 1997; Toren 1996¹; Greeno 1996; Laurencet 1997; Oziel-Taleb 1997; Fitzgerald 1999; Salmon 1999; Lopez 1994; Hows 1997; Lapierre 2001; Gajewski 1992; Bolan 2001; Godder 1997; Lapierre 2000; Hows 1996; Heal 1999; Benjamin 1999</i></p>
Level 3	<p>When transplanting stem cells / bone marrow from a non-related donor/haplo-identical donor – and if donor and recipient are both CMV sero-negative – some centres also select CMV sero-negative blood donors. In addition, from the start of conditioning, cellular blood components should be irradiated in order to prevent GvHD.</p> <p>C <i>Labar 2000</i></p>

Other considerations

The working group members are of the opinion that it is important to have access to complete pre-transplantation data if possible, also in the case of a non-related donor due to post-transplantation haemolysis.

In order to prevent antibody-mediated haemolysis of erythrocytes it is recommended to transfuse with either O erythrocytes or erythrocytes that are compatible with donor and recipient in case of minor and major blood group antagonism.

In France, national protocols are maintained and evaluated for the transfusion policy after transplantation. It would be desirable to achieve the same in the Netherlands.

Recommendations 4.2.6

1. In order to prevent haemolysis during the administration of a major ABO-incompatible stem cell / bone marrow transplant to an adult recipient, the transplant should contain < 15 mL erythrocytes if the IgG and/or IgM titre is > 16. The administration speed should be adjusted according to the titre. For children, a volume of < 10 mL erythrocytes is recommended.
2. For minor ABO incompatibility, plasma reduction of the transplant is recommended at a titre > 32.
3. Blood components for stem cell transplant patients should be irradiated (see also table in Chapter 2.2.4).
4. Stem cell transplant centres should have guidelines how to act in case of ABO incompatibility between donor and recipient.
5. National agreement on the guidelines mentioned under recommendation 4 is desirable.

4.3 The use of ESAs/EPO for production disorders

Erythropoiesis Stimulating Agents (ESAs or erythropoietic growth factors) is a collective term for medications that stimulate the production of erythrocytes. By far the most important ESA is erythropoietin (EPO). There are several types of EPO: epoetin alpha, epoetin beta and darbepoietin alpha, which has a longer half-life than epoetin alpha and epoetin beta. In this chapter we will use ESA if the relevant literature uses Erythropoiesis Stimulating Agents or ESA and EPO if the literature refers to erythropoietin, epoetin, darbepoietin or EPO.

4.3.1 Use of ESAs in patients with anaemia due to cancer

With solid tumours and non-myeloid haematological malignancies, there is a (relative) shortage of erythropoietin (Miller 1990), although no link was found between the erythropoietin level and the response to EPO (Oberhoff 1998).

The effect of EPO on the need for transfusion (and the Hb concentration) in patients who have received chemotherapy because of solid tumours has been examined in randomised studies. The percentage of patients that received transfusions was significantly lower in the EPO groups (Oberhoff 1998). The Cochrane reviews by Bohlius examined the efficacy of ESAs on the need for transfusions in patients with anaemia and cancer (both solid tumours and haematological malignancies) (Bohlius 2004, 2006 en 2009). In 57 randomised studies of 9,353 patients, it was found that ESAs significantly reduced the need for blood transfusions compared to the control treatment, which consisted of a placebo or no erythropoietin (RR 0.64 (0.60 – 0.68)) (Bohlius 2006). The quality of life, which was examined in a number of studies, showed a statistically significant improvement with treatment with EPO (Littlewood 2001, Jones 2004).

A review of the studies on the effect of recombinant erythropoietin in children treated with chemotherapy for cancer was recently published. This review concluded that EPO results in an increase in the Hb level, decreases the need for allogeneic blood and has no effect on

the quality of life or survival. Based on these results, general use of EPO is however not recommended (Marec-Berard 2009).

The use of EPO resulted in a statistically significant reduction in the percentage of patients needing transfusion, but the decrease in the number of erythrocyte concentrates (EC) administered was relatively small. For the dosage and duration of administration used in these studies, EPO resulted in a reduction of 1 unit of EC or less. In 2002 a working group from the American Society for Haematology (ASH) and the American Society of Clinical Oncology (ASCO) released guidelines for the clinical practitioner that are based on 22 randomised studies, six of which were performed in a double-blind manner. The advice is to consider EPO, at the lowest possible dosage, when the Hb concentration is < 6.2 mmol/L (Rizzo 2002, 2010). The guideline from the 'European Organisation for Research and Treatment of Cancer' (EORTC) focuses on the use of ESAs in patients with cancer who are being treated with chemotherapy and/or radiotherapy (Bokemeyer 2007). The guideline is based on 43 studies. A lower requirement for blood transfusion (up to 20% compared to control individuals) is reported in 29 studies of chemotherapy, with four studies being randomised and double-blind. The quality of life was examined in 35 studies, of which three were randomised and double-blind. These three studies found an improvement of undefined magnitude in the haemoglobin level with EPO (epoietin alpha or recombinant human erythropoietin). No difference in mortality was found in six studies in which this was reported. No randomised, double-blind study of the transfusion requirements and quality of life has been performed for patients receiving radiotherapy.

A randomised study is necessary to be able to make definitive conclusions about the quality of life, blood conservation and cost efficacy by erythropoietin, with a similar Hb as a target value in both arms of the study group.

Conclusions 4.3.1

Level 1	<p>The erythropoiesis stimulating agents (ESAs) significantly reduce the need for blood transfusions in patients with chemotherapy-associated anaemia due to solid tumours or haematological malignancies compared to the control treatment consisting of a placebo or no erythropoietic growth factor (RR 0.64 (0.60 – 0.68)).</p> <p><i>A1 Bohlius 2006, 2004</i></p>
Level 1	<p>Observational and randomised studies show that the administration of erythropoiesis stimulating agents (ESAs) is associated with a significantly higher Hb, reduction of the number of patients requiring transfusion and a decrease in the erythrocyte volume administered to patients with solid tumours and haematological malignancies and a chemotherapy-associated anaemia. However, the number of transfusions saved is small (< 1 unit EC per treatment cycle).</p> <p><i>A2 Littlewood 2001, 2003, Oberhoff 1998</i></p>

Level 4	<p>The ASH/ASCO and EORTC advice is to consider erythropoiesis stimulating agents (ESAs) for patients with cancer being treated with chemotherapy and/or radiotherapy at an Hb < 6.2 mmol/L.</p> <p><i>D Bokemeyer 2007, Rizzo 2010</i></p>
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Recommendations 4.3.1

1. Erythropoiesis stimulating agents (ESAs) should only be used for the treatment of patients with chemotherapy-induced anaemia due to cancer with the aim of saving on blood transfusions (see also recommendation 1 under 4.3.2).
2. The treating doctor should discuss the potential dangers (thrombosis, decreased survival time) and benefits (fewer transfusions) of ESAs and the potential dangers (severe infections, immunological side effects) and benefits (rapid increase in Hb) of blood transfusions with the patient.
3. The use of EPO in patients with cancer for indications other than the treatment of chemotherapy-induced anaemia is not recommended.

4.3.2 The effects of ESAs on mortality and survival of patients with cancer

It has been demonstrated that EPO in patients with solid tumours and chemotherapy-induced anaemia reduces the need for transfusions and also reduces the number of units that need to be administered. However, it has also been shown that EPO increases the risk of thrombo-embolic complications (Bohlius 2006). It is not clear whether and how EPO influences the response of the cancer to therapy and what the long-term consequences are.

Scientific support

A search was performed for systematic reviews of RCTs into the effect on mortality and long-term survival in EPO-treated patients.

A Cochrane review from 2006 showed that EPO reduced the need for transfusion (Relative Risk = RR 0.64; CI 0.60 – 0.68; 42 trials, N = 6510), but the risk of thrombo-embolic complications increased (RR 1.67; CI 1.35 – 2.06; 22 trials; n – 6769). There was uncertainty about the effect on survival (HR 1.08; 95% CI 0.99 – 1.18) (Bohlius, 2006).

A very recent meta-analysis – based on data from individual patients – showed that mortality was elevated both during the active study period (Hazard Ratio = HR 1.17; CI 1.06,1.30) and in the long term (HR 1.06; CI 1.00, 1.12). This effect was less pronounced for patients treated with chemotherapy: HR mortality in study period 1.10; CI 0.98 – 1.24 and HR long-term survival 1.04; CI 0.97 – 1.11. However, the test for interaction between EPO and chemotherapy on survival was not significant ($p = 0.42$), indicating a similar effect as in the total group of patients (Bohlius, 2009), but it should be noted that chemotherapy-induced anaemia has a different origin and therefore cannot be compared directly to the total group of cancer patients with anaemia that is not caused by chemotherapy.

Conclusion 4.3.2

Level 1	Use of EPO in cancer patients increases mortality by approximately 17% (6% - 30%) and also decreases survival after 6 months. Chemotherapy-treated cancer patients with anaemia had an increased risk of mortality of 10%, and a decreased long-term survival.
	A1 <i>Bohlius 2009</i>

Other considerations

In view of the fact that the favourable effects of EPO have, to date, only been demonstrated in adult patients with solid tumours and chemotherapy-associated anaemia (see 4.2.1 and 4.2.3) and the fact that the increase in mortality has also been demonstrated in patients with cancer not receiving chemotherapy (this paragraph: 4.2.2), the working group is of the opinion that there is only an indication for the use of EPO in patients with solid tumours and chemotherapy-induced anaemia.

Recommendations 4.3.2

1.	The therapeutic indication for EPO should be strictly adhered to. In other words, treatment with EPO is only indicated in adult patients with chemotherapy-induced anaemia with a non-myeloid malignancy. The starting Hb should be ≤ 6.2 mmol/L and the target Hb 6.2 – 7.4 mmol/L.
2.	The treatment with EPO should be stopped at an Hb > 8.2 mmol/L.

Table 4.3.2: Evidence table

author, year	study design	level quality /	population	study characteristics	Results
Bohlius, 2006	systematic review and meta-analysis	A1 search, selection, quality evaluation, analysis +	6510 patients from 42 trials		Risk of thrombo-embolic complications was elevated (RR 1.67; 95% CI 1.35 – 2.06; 35 trials; n=6769) Uncertainty about the effect on survival (HR 1.08; 95% CI 0.99 – 1.18; 42 trials, n=8167)
Bohlius, 2009	systematic review; individual patient data meta-analysis	A1 search, selection, quality evaluation, analysis +	13933 cancer patients from 53 trials	21 – 63000 IU* EPO/week for 8-52 weeks; median follow-up 6.2 months; active study period 3.7 months	EPO increased mortality during active study period (HR 1.17; 95% CI 1.06 – 1.30) and decreased survival (HR 1.06; CI 1.00 – 1.12). For chemotherapy-treated patients, the HR was HR 1.10; CI 0.98 – 1.24 and for the survival 1.04; 95% CI 0.97 – 1.11. interaction: p = 0.42

* darbepoietin: 100 – 157.5 μ g/week

RR relative risk

HR hazard ratio

CI confidence interval

4.3.3 The use of erythropoiesis stimulating agents (ESAs) for myeloid conditions

There has been limited evidence with respect to the effect of ESAs on myeloid conditions due to the possible risk of stimulating the growth of malignant cells. Cases have also been reported about complications due to ESAs, such as splenomegaly and splenic infarction due to extra-medullary myelopoiesis (Cazzola 1992, Iki 1991, Motoji 1990).

Most of the experience with ESAs has now been gained from myelodysplasias. In 11 phase I or II studies, a total of 382 patients were treated with 75 to 3,000 U/kg/week (Cazzola 1996, Rose 1995, Musto 1995, Isnard 1994, Goy 1993, Aloe Spiriti 1993, Stenke 1993, Zeigler 1993, Ludwig 1993, Shapiro 1993, Jones 1992). An improvement in Hb was found in 13.6% of the patients, particularly those with refractory anaemia or refractory anaemia with ring sideroblasts. Only 6% of the patients who previously required transfusions became independent of transfusions. Hellstrom-Lindberg (1995) confirmed that only a small portion of the total group of patients with MDS treated with EPO showed a favourable effect. Only one randomised, placebo-controlled study with 87 patients has been performed (Italian MDS Study Group 1998). In this study, the Hb of (60% of the) patients with non-transfusion-dependent myelodysplasia (mainly refractory anaemia and refractory anaemia with sideroblasts) improved due to ESAs; the percentage of transfused patients remained the same in both groups. To summarise, it can be said that the administration of an ESA for this condition only results in an increase in Hb concentration and a decrease in the need for transfusion for a minority of patients (Rizzo 2002). However, the endogenous epoietin level and the transfusion history can be used to select patients who have a greater chance of a good response to ESAs (Hellstrom et al, Brit J. of Hematology 120: 1037 -1046).

Conclusion 4.3.3

Level 2	<p>The treatment of all myelodysplasia patients with an erythropoiesis stimulating agent (ESA) has only a slight (< 10%) effect on the transfusion need of transfusion-dependent patients. Selected patients, with an EPO level < 500 U/ml are more likely to respond to treatment with an ESA.</p> <p>A2 <i>Italian MDS study group 1998</i> B <i>Rizzo 2002, Hellstrom-Lindberg 1995, 1997, 2003</i> C <i>Rose 1995, Musto 1995, Isnard 1994, Goy 1993, Aloe Spiriti 1993; Stenke 1993, Zeigler 1993, Ludwig 1993, Shapiro 1993, Jones 1992</i></p>
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Other considerations

There are no curative treatment options for older patients with myelodysplasia. The identification of patients with a potentially favourable response to ESAs – in combination with GM-CSF or not – is of great importance (Thompson 2000).

Recommendations 4.3.3

1. EPO is not recommended for the treatment of patients with myelodysplasia with a high (> 500 mg/L) endogenous EPO level.
2. Research into the identification of responders to EPO is desirable, in order to assign EPO a possible role in the treatment of myelodysplasia patients.

4.3.4 The use of EPO for anaemia as a result of renal insufficiency

See guideline 'Anaemia due to chronic renal insufficiency' for adults (NFN guideline Anaemia 2009, update 2010) <http://www.nefro.nl/home/richtlijnen>.

4.3.5 Use of erythropoiesis stimulating agents (ESAs) for anaemia due to chronic illness: rheumatoid arthritis, HIV infection and Inflammatory Bowel Disease (IBD)

Rheumatoid arthritis

The results of three randomised studies show that symptoms of fatigue and quality of life improved significantly when the Hb increased as a result of treatment with EPO in patients with rheumatoid arthritis (Peeters 1996/1999, Nordstrom 1997, Murphy 1994). There are also indications that ESAs have a favourable effect on disease activity (Peeters 1996/1999). No relevant new references were found on this subject.

HIV infection

Treatment of HIV patients with an ESA reduces the need for transfusion by 40%. 'Responders' have erythropoietin levels < 500 mg/L (Henry 1998, Kreuzer 1997).

Inflammatory Bowel Disease (IBD)

For patients with Inflammatory Bowel Disease (IBD) who do not respond sufficiently to iron supplementation, the administration of ESA results in a significant increase in Hb and an improvement of the quality of life with less fatigue (Gasche 1997, Lopez, Use of agents stimulating erythropoiesis in digestive diseases. World 2009). In a randomised study (Fe + epoetin versus Fe + placebo) of 34 patients, it was observed that after 12 weeks the Hb had increased in 82% of the IBD patients in the EPO group, versus only 24% in the placebo patients. The Hb response to iron supplementation alone takes much longer than the response after iron supplementation combined with EPO (Schreiber 1996).

Conclusions 4.3.5

Level 2	Erythropoiesis stimulating agents (ESA) improve both the Hb and the quality of life in patients with rheumatoid arthritis (and anaemia) and may also decrease the disease activity. <i>B</i> Peeters 1999, Nordstrom 1997, Peeters 1996, Murphy 1994
Level 3	Treatment of HIV patients with an erythropoiesis stimulating agent (ESA) reduces the need for transfusion by 40%. 'Responders' have erythropoietin levels < 500 mg/L. <i>C</i> Henry 1998, Kreuzer 1997

Level 2	<p>For patients with Inflammatory Bowel Disease (IBD) who do not respond sufficiently to iron supplementation, the administration of ESA results in a significant increase in Hb and an improvement of the quality of life with less fatigue.</p> <p><i>B Gasche 1997, Lopez 2009</i></p>
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Other considerations

In the case of anaemia due to chronic illness such as rheumatoid arthritis, HIV and IBD, there is a relative shortage of erythropoietin and inhibition of erythropoiesis by pro-inflammatory cytokinins, such as TNF-alpha and interferon. Both factors are corrected by ESAs. The increase in Hb caused by ESAs is much greater than the target value with transfusions, EPO does not result in relevant transfusion savings for rheumatoid arthritis and IBD.

Recommendations 4.3.5

1. EPO is not yet a generally accepted indication for anaemia due to rheumatoid arthritis or inflammatory bowel disease (IBD).
2. **In the case of HIV infection, the endogenous erythropoietin level should be included in the decision to treat with erythropoiesis stimulating agents (ESAs). Studies show that 'responders' have erythropoietin levels < 500 mg/L.**
3. In the case of HIV infection with anaemia, the position of EPO in relation to a relatively low erythropoietin level should be examined further.

4.3.6 Use of erythropoiesis stimulating agents (ESAs) for aplastic anaemia

A number of clinical studies have examined the efficacy of EPO for aplastic anaemia. The most recent article (Zeng 2006) revealed that the addition of growth factors (EPO plus G-CSF) to immuno-suppressive therapy does not result in improved outcomes when compared to immuno-suppressive therapy alone. Bessho (1997) compared G-CSF + EPO to EPO alone, but did not include an appropriate comparison with immuno-suppressive therapy, whilst this is the current standard treatment for aplastic anaemia. Shao (Shao 1998) compared immuno-suppressive therapy with G-CSF plus EPO. The limitations of this study compared to the study by Zeng are that the Shao study was smaller in size and measured response rate instead of survival. The studies by Zeng and Zhao both had the limitation that EPO plus G-CSF was administered, which meant that the effect of EPO alone could not be determined.

Conclusion 4.3.6

Level 3	<p>The working group is of the opinion that the use of erythropoiesis stimulating agents (ESAs) is not sufficiently substantiated as a supportive therapy for severe aplastic anaemia.</p> <p><i>C Bessho 1997, Shao 1998, Zeng 2006</i></p>
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Recommendation 4.3.6

The use of erythropoiesis stimulating agents (ESAs) is not recommended as a supportive therapy for severe aplastic anaemia.

4.4 Breakdown disorders

4.4.1 Congenital: Sickle cell disease

Sickle cell disease (SCD), caused by a point mutation in the β -globin gene, is a very heterogeneous disease with anaemia and vasculopathy, characterised by increased viscosity, adhesion of erythrocytes to the endothelial cell surface resulting in vaso-occlusion, clotting activation, leukocyte activation, platelet activation and haemolysis. The most important causes of morbidity and mortality in SCD are recurring vaso-occlusive crises, severe anaemia, infections, acute chest syndrome (ACS) and multi-organ failure. 40% of patients die during an acute episode (Wanko 2005, Mancini 2003).

Transfusions for SCD have two aims: 1) improving the oxygen transport and 2) improving or preventing organ damage by decreasing the number of circulating sickle cells. Although a large number of patients with SCD are treated with transfusions – either occasionally or chronically –, there are only 5 randomised studies that have examined the effect of transfusion in certain situations (prevention of CVA, pregnancy and acute chest syndrome) in patients with SCD (Styles 2006, Adams 2005, Adams 1998, Vichinsky 1995, Koshy 1988). Due to the limited number of prospective studies for the indication for blood transfusion in sickle cell disease, some of the recommendations have been formulated based on expert opinion (evidence level 4).

The indications for blood transfusion will be discussed consecutively in acute situations (4.4.1.1), elective indications (4.4.1.2) and the chronic transfusion policy (4.4.1.3). In addition a number of complications associated with transfusions for SCD will be discussed (4.4.1.4).

4.4.1.1 Acute indications for blood transfusion in sickle cell disease

Patients with homozygous sickle cell disease usually have an Hb between 4.0 and 6.0 mmol/L under normal conditions; these values in themselves do not form a transfusion indication. Blood transfusions for anaemia are only indicated in the case of symptomatic anaemia (see also paragraph 4.1).

An acute deterioration of the anaemia in sickle cell disease can be due to a number of factors other than blood loss: acute aplastic crisis, acute sequestration in the liver and/or the spleen, or due to a haemolytic crisis.

Threatened anaemia due to aplastic crisis

An aplastic crisis is usually caused by a Parvo virus B19 infection. The parvo virus inhibits haematopoiesis, which due to the short circulation time of erythrocytes in patients with sickle cell disease, results in a threatened anaemia with noticeable reticulopaenia. A large

observational study revealed that more than 75% of children with sickle cell disease and a Parvo B19 infection require a transfusion (Smith-Whitley 2004).

Threatened anaemia due to acute liver and/or spleen sequestration

Acute liver and/or spleen sequestration usually occurs in early childhood and is a rapidly developing and potentially fatal complication. In these cases the blood is withdrawn from the circulation, which results in acute severe anaemia, hypovolaemia and rapid progressive splenomegaly. Transfusions are recommended in symptomatic cases of acute sequestration and it should be taken into consideration that a portion of the erythrocytes will return to the circulation after sequestration, which can cause a rapid increase in Hb with associated hyperviscosity (Ohene-Frempong 2001, Josephson 2007, Wahl 2009).

Threatened anaemia due to haemolytic crisis

Infections – whether viral, bacterial or parasitic (e.g. malaria) in nature – can result in an acute increase in haemolysis (haemolytic crisis). Acute blood transfusion can be indicated in order to treat or prevent cardiac decompensation (Wanko 2005).

Conclusions 4.4.1.1

Level 3	<p>Acute blood transfusion is only indicated in patients with sickle cell disease for (impending) cardiac or respiratory symptoms. There is no specific Hb trigger for administering a blood transfusion, but patients should not be transfused at an Hb over 6.5 mmol/L due to hyperviscosity.</p> <p>C <i>Alexy 2006</i> D <i>Josephson 2007, Wahl 2009</i></p>
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Level 4	<p>An urgent blood transfusion is indicated in symptomatic cases of acute liver or spleen sequestration in sickle cell patients. This transfusion should take into consideration the fact that a portion of the erythrocytes return to the circulation after sequestration and can cause hyperviscosity.</p> <p>D <i>Ohene-Frempong 2001, Josephson 2007</i></p>
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Level 3	<p>Acute aplastic crisis, defined as acute anaemia in a sickle cell patient without elevated numbers of reticulocytes, is an indication for transfusion. Parvo B19 infection is the most important cause. A large observational study revealed that more than 75% of children with sickle cell disease and a Parvo B19 infection require a transfusion.</p> <p>C <i>Smith-Whitley 2004</i></p>
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Recommendations 4.4.1.1

1.	<p>Blood transfusions are indicated in patients with sickle cell disease if cardiac or respiratory symptoms develop as a result of anaemia. There is no specific Hb trigger at which transfusions must be given.</p>
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2. When giving a blood transfusion to patients with sickle cell disease, one must ensure that the Hb remains < 6.5 mmol/L in order to prevent hyperviscosity.

4.4.1.2 Acute chest syndrome

The 'acute chest' syndrome (ACS), defined as a new lung infiltrate on the chest X-ray in combination with chest pain, dyspnoea or hypoxia can be caused by an infarction, an infection or a combination of both. The pathogenesis is complex, with inflammation, hypoxia, vaso-occlusion, fatty emboli and hypoventilation playing a role. The rationale for transfusion is the improvement of oxygenation. Several non-controlled studies have shown a rapid clinical improvement after transfusion (Mallouh 1988, Emre 1995). A recent review recommended that adult sickle cell patients with ACS be given exchange transfusions immediately at a $pO_2 < 60$ mmHg and children at a $pO_2 < 70$ mmHg, where the aim is to achieve an HbS% lower than 30% (Josephson 2007). A more recent retrospective study of the treatment results for ACS found no difference between a simple transfusion and an exchange transfusion (Turner 2009). A recent Cochrane review concluded that no studies could be found that were of sufficient quality to answer the question whether blood transfusions aid in the treatment of acute chest syndrome (Alhasihimi 2010).

Conclusions 4.4.1.2

Level 2	Based on observational studies, the advice is to give a blood transfusion for the treatment of acute chest syndrome. <i>B Mallouh 1988, Emre 1995</i>
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Level 4	Despite the lack of randomised studies, exchange transfusions are recommended for severe hypoxaemia ($pO_2 < 60$ mmHg in adults and $pO_2 < 70$ mmHg in children), the aim being to achieve an HbS% < 30%. <i>D Josephson 2007</i>
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Recommendation 4.4.1.2

It is advised to treat patients with sickle cell disease and an acute chest syndrome with a blood transfusion. Exchange transfusions are recommended for severe hypoxaemia ($pO_2 < 60$ mmHg in adults and $pO_2 < 70$ mmHg in children), the aim being to achieve an HbS% < 30%.

4.4.1.3 Acute cerebrovascular accident

A cerebrovascular accident (CVA) occurs in 11% of patients with sickle cell disease, with the highest incidence in children . between the ages of 2 and 9 years (Powars 2000, Ohene Frempong 1998). Immediate blood transfusion following an acute CVA does not appear to influence neurological functioning in the long term (Ohene-Frempong 1991). However, based on theoretical considerations, a blood transfusion following an acute CVA can improve the perfusion and oxygenation of brain tissue and so prevent the risk of irreversible ischaemia and further expansion of the ischaemic area. A retrospective cohort study of the

acute treatment of children with an acute CVA showed that an exchange transfusion as initial treatment was more effective in preventing a second CVA than a normal transfusion (Hulbert 2006). Despite the absence of comparative studies between transfusing or not, all experts are of the opinion that an acute CVA is an absolute indication for transfusion (Charache 1992, Ohene-Frempong 1991). Based on the above-mentioned study by Hubert et al, the advice is to perform an exchange transfusion to decrease the HbS to < 30% (Charache 1992, Ohene-Frempong 1991, Hulbert 2006).

Conclusion 4.4.1.3

Level 3	In the event of an acute CVA, the advice is to perform an exchange transfusion immediately, aiming to achieve an HbS% < 30%. <i>B Hulbert 2006</i> <i>D Charache 1992; Ohene-Frempong 1991</i>
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Recommendation 4.4.1.3

In patients with sickle cell disease and an acute CVA, the advice is to perform an exchange transfusion immediately, aiming to achieve an HbS% < 30%.

4.4.1.4 Multi-organ failure

Multi-organ failure in sickle cell disease is defined as severe organ failure of at least two organ systems in the setting of a vaso-occlusive crisis.

A large retrospective study evaluated 17 episodes of multi-organ failure, in which an aggressive transfusion policy using 8 units of erythrocytes or more was associated with a better survival and recovery from organ damage (Hassell 1994). Due to the large number of transfusions for these patients, the advice is to perform an exchange transfusion with a target HbS of < 30%.

Conclusion 4.4.1.4

Level 3	For sickle cell patients with multi-organ failure – defined as severe organ dysfunction of at least two organ systems in the setting of a vaso-occlusive crisis, the advice is to perform an exchange transfusion with a target HbS of < 30%. <i>B Hassell 1994</i>
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Recommendation 4.4.1.4

Sickle cell patients with multi-organ failure – defined as severe organ failure of at least two organ systems in the setting of a vaso-occlusive crisis – should undergo an exchange transfusion.

4.4.1.5 Priapism

Priapism is defined as an involuntary erection without sexual stimulation that persists for at least 4 hours. Priapism occurs frequently with sickle cell disease, particularly during puberty.

Persistent priapism is painful and can lead to structural erectile dysfunction and must be viewed as a medically urgent complication. There is ongoing debate about whether acute blood transfusion can play a role in the treatment of acute priapism by reducing the HbS%. A meta-analysis was published in 2006 on all clinical studies and case reports about the treatment of priapism in which no difference was found in the duration until symptoms disappeared (Merritt 2006).

Conclusion 4.4.1.5

Level 3	There is no indication for (exchange) transfusion as a treatment for priapism. <i>B Merritt 2006</i>
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Recommendation 4.4.1.5

There is no indication for (exchange) transfusion in the acute treatment of priapism.

4.4.1.6 Acute painful (vaso-occlusive) crisis

There is no indication for acute transfusion or exchange transfusion for an uncomplicated vaso-occlusive crisis. In fact, an observational study (Platt 1991) revealed a positive correlation between the level of Hb and the occurrence of a vaso-occlusive crisis, probably due to the increased viscosity. There are no data on the efficacy of exchange transfusions for an acute sickle cell crisis. Experts indicate in various reviews that an acute painful crisis is not an indication for (exchange) transfusion (Josephson 2007, Ohene-Frempong 2001).

Conclusion 4.4.1.6

Level 4	There are no arguments for transfusion during acute painful crises. <i>D Ohene-Frempong 2001, Josephson 2007</i>
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Recommendation 4.4.1.6

There is no indication for performing (exchange) transfusions for the treatment of an acute painful crisis in patients with sickle cell disease.

4.4.2 Elective indications for blood transfusion in patients with sickle cell disease

4.4.2.1 Pre-operative preparation in patients with sickle cell disease

There is much discussion about the need to perform exchange transfusions prior to surgery (in order to reduce the HbS%). A prospective, randomised, multi-centre study of patients with sickle cell disease undergoing mainly gall bladder, ENT and orthopaedic surgery – in which an aggressive (target HbS < 31%) pre-operative transfusion policy was compared to a conservative “on top of transfusion” (target Hb of 6.2 mmol/L) transfusion policy – showed that the frequency of post-operative complications and ‘acute chest’ syndrome was the same for both groups, but that twice the number of complications due to the transfusion occurred in the group with the aggressive pre-operative transfusion policy (Vichinsky 1995). This study did not examine whether the complete omission of prophylactic transfusions was also justified. As far as HbSC (double heterozygous sickle cell disease) is concerned, there are

two retrospective studies that both show a strongly reduced incidence of sickle cell related complications in patients who received a pre-operative blood transfusion versus patients who did not receive a transfusion (Koshy 1995, Neumayr 1998). It is important to mention that various experts advise that the Hb concentration should not exceed 6.5 mmol/L in order to prevent hyperviscosity (Vichinsky 2001, Ohene-Frempong 2001). No randomised studies, however, have been performed on this matter. Mainly patients with HbSC sickle cell disease and a relatively high risk of post-operative complications (abdominal surgery) appeared to benefit greatly from pre-operative blood transfusion (0% versus 35% complications) (Neumayr 1998).

Conclusions 4.4.2.1

Level 2	<p>There is no prospective comparative study on the value of blood transfusion as pre-operative preparation for sickle cell patients. A prospective randomised study revealed no difference in post-operative complications between an aggressive transfusion policy and an “on top of” transfusion policy.</p> <p>A2 <i>Vichinsky 1995</i></p>
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Level 3	<p>For patients with double heterozygous sickle cell disease (HbSC), two large retrospective studies have shown a lower incidence of sickle cell related complications in patients undergoing an elective surgical procedure when they were transfused preoperatively. The authors advise that the Hb in this patient group should not be allowed to exceed 6.5 mmol/L.</p> <p>C <i>Koshy 1995, Neumayr 1998</i> D <i>Vichinsky 2001, Ohene-Frempong 2001</i></p>
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Recommendation 4.4.2.1

Despite the lack of prospective randomised studies, the administration of pre-operative blood transfusions to **a maximum Hb of 6.5 mmol/L** should be considered for sickle cell patients undergoing surgery with an intermediate risk (abdominal surgery such as cholecystectomy, Caesarian section, appendectomy, splenectomy or extensive orthopaedic surgery.).

4.4.2.2 Pregnancy in patients with sickle cell disease

Sickle cell disease causes an increased risk of maternal and foetal death. A randomised, prospective study from 1988 on the effect of prophylactic transfusions during pregnancy in sickle cell disease showed that mortality of both mother and child in the treatment group was the same as for the group that did not receive transfusion. However, a significant reduction in painful crises was observed in the group that received prophylactic transfusions (Koshy 1988).

Based on these benefits concerning sickle cell related complications such as vaso-occlusive crises, experts advise that prophylactic blood transfusions should only be considered for a pregnancy with an increased risk of complications, such as a multiple pregnancy and pregnancies in women with a history of perinatal mortality (Wayne 1995, Koshy 1995).

Conclusions 4.4.2.2

Level 2	There is no indication for the prophylactic transfusion of pregnant women with sickle cell disease. <i>A2 Koshiy 1988</i>
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Level 4	It is advised to consider prophylactic blood transfusion in high risk pregnancies, such as multiple pregnancies and for women with a history of perinatal mortality. <i>D Koshiy 1988; Wayne 1995</i>
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Recommendation 4.4.2.2

There is no indication for prophylactic transfusion of patients with sickle cell disease during pregnancy. Prophylactic transfusions can be considered only in sickle cell patients with an increased risk of complications, such as women with multiple pregnancies or a history of perinatal mortality.

4.4.2.3 Chronic transfusion policy in patients with sickle cell disease

4.4.2.3.1 Prevention of cerebrovascular accidents in patients with sickle cell disease

A prospective, randomised clinical study of children with sickle cell disease with an increased risk of CVA (identified as a cerebral blood flow speed > 200 m/s by means of transcranial Doppler ultrasound) determined that patients who received chronic blood transfusions developed 90% fewer CVAs than children without transfusions (Adams 1998).

The duration of the chronic transfusion programme in patients with sickle cell disease is a topic of discussion. Various studies demonstrate an increased risk of CVAs for these patients after stopping the transfusions, even 12 years after the initial CVA (Wang 1991, Wilimas 1980). This suggests that a long-term transfusion programme in children with sickle cell disease is necessary. The STOP trial demonstrated that stopping the chronic transfusion policy even after the normalisation of the cerebral blood flow speed resulted in more CVAs than in the patients who continued receiving the blood transfusions (Adams 2005).

The prophylactic action of chronic blood transfusions after experiencing a CVA has not been examined prospectively for adult patients. It is also not clear whether the chronic transfusion policy should be continued into adulthood for children who have suffered a CVA. A small observational study of children with sickle cell disease and a history of CVA revealed that children could stop the chronic transfusion policy upon reaching adult age without any problems (Rana 1997). Another approach that was examined was to make the transfusion programme less intensive over time, once children have reached adult age and have not had a recurrence for four years. In a study from 1992, no new CVAs occurred in patients with sickle cell disease at a target HbS of < 50% and who had been neurologically stable for the past four years (Cohen 1992).

“Silent infarctions” are defined as asymptomatic cerebral infarctions that can be demonstrated by means of imaging (MRI) in patients with sickle cell disease. There are indications that these infarctions are related to decreased neuro-cognitive functioning (Armstrong 1996). There are currently no studies that support the chronic transfusion of

these patients. Therefore, silent infarctions do not form an indication for chronic blood transfusion.

Conclusions 4.4.2.3.1

Level 2	<p>Children with an increased risk of CVA – defined as a cerebral blood flow speed > 200 m/s using transcranial Doppler – have an indication for chronic blood transfusion with a target HbS of < 30%.</p> <p>A2 <i>Adams 1998</i></p>
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Level 2	<p>Chronic transfusion policy for the prevention of a (recurrent) CVA should be continued throughout childhood.</p> <p>A2 <i>Adams 2005</i> B <i>Wang 1991, Wilmas 1980</i></p>
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Level 2	<p>It is not clear whether the chronic transfusion policy should be continued for patients with sickle cell disease and an increased risk of CVAs once they have reached adulthood. There are arguments for increasing the target HbS to 50% in patients who have been stable for a long period (> 4 years) and an observational study showed that the chronic transfusion policy could even be stopped without problems upon reaching adulthood.</p> <p>B <i>Cohen 1992, Rana 1997</i></p>
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Level 4	<p>Sickle cell patients with silent cerebral infarction – defined as asymptomatic cerebral infarctions diagnosed by means of imaging – do not have an indication for a chronic transfusion policy.</p> <p>D <i>Ohene-Frempong 2001</i></p>
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Recommendations 4.4.2.3.1

1.	Children with sickle cell disease and an increased risk of a CVA – defined as an elevated flow rate of the cerebral blood vessels of > 200 m/s confirmed using transcranial Doppler – or with a history of CVA have an indication for chronic transfusion policy with a target HbS of < 30%.
2.	For children with an increased risk of CVA or a history of CVA, the chronic transfusion policy should be continued at least until reaching adulthood.
3.	Once adulthood has been reached, cessation or reduction of the intensity can be considered, provided that the patient has been neurologically stable for at least 4 years.

4.4.2.3.2 Prevention of acute chest syndrome (ACS)

The acute chest syndrome (ACS) is a potentially fatal complication of sickle cell disease. The treatment of choice in the prevention of a recurring ACS in patients with sickle cell disease is hydroxy urea. For patients with recurrent episodes of ACS despite hydroxy urea,

a chronic (exchange) transfusion schedule is advised with a target HbS of < 50%. A retrospective study showed a strong reduction in the incidence of ACS in patients with sickle cell disease who received chronic transfusion therapy (Hankins 2005). An earlier prospective study of the effects of chronic blood transfusion on the incidence of CVAs in a high risk population of children with sickle cell disease also showed a strong reduction in the number of episodes of ACS (Miller 2001). It should be noted that this last study – though prospective in nature – was not primarily designed for this query.

Conclusions 4.4.2.3.2

Level 3	In patients with a recurring acute chest syndrome (ACS) under hydroxy urea, a chronic transfusion policy with a target HbS of < 50% can be considered. The efficacy of chronic transfusion for the prevention of ACS was observed in a comparative study on the effect of chronic transfusion in the prevention of CVAs in children with sickle cell disease. <i>B Miller 2001</i>
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Level 3	A retrospective analysis also found a marked reduction in the incidence of acute chest syndrome (ACS) in a group of children with a history of severe or frequent ACS who received chronic transfusion therapy. <i>B Hankins 2005</i>
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Recommendation 4.4.2.3.2

A chronic (exchange) transfusion with a target HbS of < 50% can be considered in patients with sickle cell disease with recurring acute chest syndrome (ACS) despite treatment with hydroxy urea.

4.4.2.3.3 Prevention of recurrent vaso-occlusive crises

A randomised study has shown that the number of admissions for the treatment of a painful vaso-occlusive crisis in patients with sickle cell disease reduced significantly with the use of hydroxy urea (Charache 1995). There are no prospective randomised studies available concerning the effect of chronic transfusion on the incidence of painful vaso-occlusive crises. Analysis of a study of the effects of chronic transfusion during pregnancy did show that chronic blood transfusion was associated with a significant decrease in the number of painful vaso-occlusive crises (14 versus 50%) (Koshy 1988). In a prospective randomised study of the effects of chronic blood transfusion on the incidence of CVAs, further analysis also showed a decrease in the number of painful vaso-occlusive crises, however, the intention to treat analysis showed that this difference was not significant (Miller 2001). However, one should weigh the disadvantages of chronic blood transfusion such as allo-immunisation, iron accumulation and the risk of transfusion-related infections against these potential benefits.

Conclusions 4.4.2.3.3

Level 2	Treatment with hydroxy urea reduces the number of clinical admissions for
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	<p>vaso-occlusive crises in patients with sickle cell disease and a high admission frequency of >2/year for the treatment of painful vaso-occlusive crises.</p> <p>A2 <i>Charache 1995</i></p>
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<p>Level 3</p>	<p>Studies of the effect of a chronic transfusion policy for the prevention of neurological and pregnancy-related complications in patients with sickle cell disease showed a reduction in the number of painful vaso-occlusive crises. Based on this, a chronic transfusion policy could be considered in the treatment of sickle cell patients with severe and frequent recurring painful vaso-occlusive crises who do not respond to hydroxy urea.</p> <p>B <i>Miller 2001</i> C <i>Koshy 1988</i></p>
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Recommendation 4.4.2.3.3

A chronic transfusion policy for the prevention of frequent recurring vaso-occlusive crises without response to hydroxy urea can be considered for patients with sickle cell disease. Despite the proven efficacy, the negative consequences of a chronic transfusion policy (allo-immunisation, iron accumulation and the risk of transmission of infectious diseases) for this indication should be included in the decision-making process before implementing chronic blood transfusions.

4.4.2.4 Complications of chronic blood transfusion in patients with sickle cell disease

4.4.2.4.1 Allo-immunisation

See Chapter 3.7.2.

4.4.2.4.2 Iron accumulation

Iron accumulation only occurs in patients with sickle cell disease as a result of blood transfusions; there is no increased iron resorption as is the case in patients with thalassaemia.

SCD patients with a chronic transfusion policy have an indication for chelation therapy (see Chapter 7.2.10, secondary haemochromatosis). Chelation therapy can be prevented by opting for an erythrocytapheresis policy (exchange transfusion) instead of a chronic transfusion policy.

4.4.2.4.3 Aplastic crisis

An aplastic crisis is usually caused by a Parvo virus B19 infection. The parvo virus inhibits haematopoiesis, which due to the short circulation time of erythrocytes in patients with sickle cell disease, results in a threatened anaemia with noticeable reticulopaenia. A large observational study revealed that more than 75% of children with sickle cell disease and a Parvo B19 infection require a transfusion (Smith-Whitley 2004).

Recommendation 4.4.2.4.3

For patients with sickle cell anaemia who are Parvo B19 IgG negative, a Parvo B19 negative blood component is recommended for the prevention of an aplastic crisis (see also Chapter 2.2.6).

4.4.3 Congenital breakdown disorder: homozygous beta thalassaemia

Beta thalassaemia is an autosomal recessive disorder of the haemoglobin production. Several mutations and deletions of the β globin gene have been described, which result in a complete or partial deficiency of β globin chains resulting in an excess of α globin chains. The excessive number of α globin chains results in ineffective erythropoiesis and this in turn results in severe anaemia and compensatory erythroid hyperplasia in the bone marrow (Olivieri 1999). This pathology is most pronounced in homozygous beta⁰ thalassaemia, in which a transfusion indication occurs at a very early age. Intermediate thalassaemia results in a marked decrease in beta globin production, which can result in clinical symptoms in some of the patients and results in a transfusion indication in some cases. Iron accumulation due to increased absorption from the bowel can occur in patients with intermediate thalassaemia without a transfusion indication.

The decision to start regular blood transfusions for beta thalassaemia is based on the severity of the symptoms of anaemia and bone marrow expansion. Early implementation of transfusions appears to reduce the frequency of allo-immunisation. The UK guideline advises to start transfusing before the age of three (UK Thalassaemia society 2008).

Chronic transfusion therapy – with a target Hb of 5.6 – 6.2 mmol/L – results in an improvement of the clinical course of homozygous beta thalassaemia, suppression of the erythroid bone marrow expansion and less iron accumulation than a hypertransfusion schedule with a target Hb of 6.2 – 7.4 mmol/L (Cazzola 1997). Adequate chelation therapy results in a significantly better life expectancy and less secondary organ damage in patients with beta thalassaemia with a chronic transfusion indication (Brittenham 1994). Patients with an average serum ferritin concentration < 2500 μ g/L had significantly less heart failure than patients with a higher average ferritin (Borgna-Pignatti 2004).

Patients with homozygous beta thalassaemia can be cured using allogeneic stem cell transplantation, which should preferably be performed at the youngest possible age. Various transplant studies all over the world have now achieved thalassaemia-free survival percentages of between 85 and 90% and a long-term survival of 76 – 100% depending on the age and risk factors, such as liver fibrosis and iron accumulation (Robberts 1997, Di Bartolomeo 1997, Boulad 1998, Lawson 2003).

Conclusions 4.4.3

Level 3	For patients with homozygous beta thalassaemia, chronic blood transfusion with a target Hb of 5.6 – 6.2 mmol/L results in a good clinical improvement and less iron accumulation than with a hypertransfusion schedule with a target Hb of 6.2 – 7.4 mmol/L. <i>B Cazzola 1997</i>
Level 2	Adequate chelation therapy in patients with beta thalassaemia and a chronic transfusion indication results in fewer organ complications and better survival. <i>B Brittenham 1997, Borgna-Pignatti 2004</i>
Level 2	Haematopoietic stem cell transplantation in childhood for homozygous beta thalassaemia results in a cure in 85 – 90% of the cases and long-term survival in 76 – 100% of the cases. Important risk factors for complications are the age of the patient, the extent of iron accumulation and the presence of liver fibrosis and/or hepatomegaly. <i>B Roberts 1997, Di Bartolomeo 1997, Boulad 1998, Lawson 2003</i>

Recommendations 4.4.3

<ol style="list-style-type: none">1. The clinical symptoms of anaemia and bone marrow expansion are the basis of the decision to start a chronic transfusion policy in patients with homozygous beta thalassaemia or intermediate thalassaemia.2. A target Hb of 5.4 – 6.2 mmol/L is recommended for chronic transfusion therapy for beta thalassaemia patients.3. A chronic transfusion policy in beta thalassaemia patients should be complemented by adequate chelation therapy with a target average ferritin level < 2500 µg/L. This prevents heart failure and organ damage due to iron accumulation.

4.4.4 Breakdown disorder: paroxysmal nocturnal haemoglobinuria (PNH)

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired haemolytic anaemia that is caused by clonal expansion of a haematological progenitor cell due to an acquired mutation in an X-linked gene. Haemolysis occurs because erythrocytes are more sensitive to complement activation due to the absence of Glycosyl Phosphatidyl Inositol (GPI) anker proteins. In addition, thrombotic complications and bone marrow failure occur, with thrombosis being the most common cause of death. The average survival is 10 to 15 years (Hillmen 1995).

PNH is a chronic condition in which the clinical symptoms differ per individual and during the course of the illness. As a result we can distinguish haemolytic PNH and thrombotic PNH (both referred to as classical PNH) and PNH associated with bone marrow failure or hypoplastic PNH.

The diagnosis PNH can be confirmed by means of flow cytometry by which both normal and PNH cells can be detected. In addition to flow cytometry, a small population of PNH cells can also be detected using fluorescent pro-aerolysin (Brodsky 2000).

The treatment depends on the type of PNH. In the case of hypoplastic PNH with severe aplastic anaemia an allogeneic bone marrow transplant is a potentially curative treatment; in some cases, immunotherapy is given first in the form of anti-thymocyte globulin and cyclosporine. Haemolysis and thrombosis are foremost in classic PNH. In the past an allogeneic bone marrow transplant was the only effective therapy for these patients, but recently eculizumab has been proven to be effective in the treatment of haemolysis due to classic PNH (Hillmen 2004, Hillmen 2006, Brodsky 2008).

Eculizumab is a humanised monoclonal antibody against the complement protein C5 that inhibits complement activation. The first pilot study of 11 classic PNH patients showed that eculizumab is able to reduce haemolysis and the need for transfusion: the average need for transfusion dropped from 1.8 to 0 units per month (Hillmen 2004). A randomised double-blind placebo-controlled study (the TRIUMPH study) in 87 patients with classic PNH showed a reduction in the number of transfused units from 10 to 0 in the eculizumab arm: 51% of the patients treated with eculizumab became transfusion-free (Hillmen 2006). The SHEPHERD study in 79 classic PNH patients showed that eculizumab improved the haemolysis in 87% of the patients, reduced the need for transfusion by 52% (from 12.3 to 5.9 units per patient) and there was a complete absence in the need for transfusion in 51% of the patients (Brodsky 2008). In addition, it appears that the long-term use of eculizumab reduces the risk of thrombotic complications from 7.4 to 1.1 events per 100 patient years (Hillmen 2007).

No Hb trigger is mentioned for transfusion indication in the literature.

There is no contra-indication for plasma (containing blood components) and no indication for washed erythrocytes (Brecher 1998, Fitzgerald 1994, Sirchia 1990).

Conclusions 4.4.4

Level 1	<p>Studies show that eculizumab reduces the need for transfusion in patients with classic transfusion-dependent PNH.</p> <p>A2 <i>Brodsky 2008, Hillmen 2006</i></p>
Level 2	<p>A study of 79 patients with classic paroxysmal nocturnal haemoglobinuria (PNH) showed that eculizumab improved haemolysis in 87% of the patients.</p> <p>A2 <i>Brodsky 2008</i></p>
Level 2	<p>There are no indications for an unfavourable effect of plasma (containing blood components) or for a favourable effect of washed erythrocytes.</p> <p>B <i>Brecher 1998, Fitzgerald 1994, Sirchia 1990</i></p>

Recommendations 4.4.4

1. Plasma containing blood components are not contra-indicated in PNH.
2. There is no indication for washed erythrocytes in PNH.
3. **In a patient with classic transfusion-dependent PNH, treatment with eculizumab should be considered as a means of reducing the need for transfusions.**

4.4.5 Breakdown disorder: Auto-Immune Haemolytic Anaemia (AIHA)

4.4.5.1 Classification of (auto) immune haemolytic anaemia (AIHA)

(Auto) Immune Haemolytic Anaemia (AIHA) is an etiologically, pathogenically, serologically and clinically heterogenous group of acquired immune-mediated haemolytic anaemias with a substantial mortality (> 10 – 20%), particularly in patients in the acute phase and in treatment-resistant cases (Domen 1998, Chen 1997, Sokol 1981, Petz 1980). AIHA is a rare disease: prevalence of 1:80,000 (Mauro 2000, Engelfriet 1987, Sokol 1981, Petz 1980).

There are three categories of AIHA: 1. auto-immune (primary and secondary), 2. medication-associated and 3. transplant(allo) associated. Although strictly speaking only category 1 can be referred to as an auto-immune haemolytic anaemia (AIHA), the term is also applied to categories 2 and 3. In this chapter we will use AIHA for all 3 categories. Within the various categories there is often a sub-division according to the mechanism of haemolysis.

Unless references are mentioned (always at level 3 or 4), the extensive recommendations mentioned at the end of this paragraph are based on level 3 and/or level 4 evidence from the standard work by Petz and Garraty (Acquired immune hemolytic anemias, Church Livingstone, New York 1980) and the following reviews: Engelfriet 2000, Mauro 2000, Hashimoto 1998, de Silva 1996, Jefferies 1994, Virella 1990, Petz 1982.

There are detailed instructions concerning laboratory techniques (see among others Leger 1999, Engelfriet 2000), but only the principles are discussed in this guideline (see Chapter 3).

1. Auto-Immune Haemolytic Anaemia (AIHA) in the strict sense

- 1.1. Warm type AIHA (WAIHA): approximately 80% of the cases of AIHA are the so-called warm type (WAIHA) (Packman 2008). WAIHA is caused by antibodies that react most strongly at 37 °C. These are usually IgG antibodies, sometimes in combination with complement and sometimes these are incomplete (IgM) warm antibodies. WAIHA is rarely caused by IgA autoantibodies alone or by warm IgM agglutinins or mixtures of IgM (cold) and (warm) IgG antibodies. These rare autoantibody combinations often cause severe AIHA (Mauro 2000, Hashimoto 1998, Domen 1998, Engelfriet 1987, Sokol 1981, Petz 1980).
- 1.2. The cold type AIHA represents approximately 20% of the AIHA. This involves complete IgM antibodies, which react more strongly in cold (room temperature or lower) conditions (Engelfriet 2000, Mauro 2000, Hashimoto 1998, De Silva 1996, Jefferies 1994, Virella 1990, Petz 1982).
- 1.3. AIHA with biphasic haemolysins, involving IgG antibodies binding at lower temperatures and then activating complement at higher temperatures (37 °C). AIHA with biphasic haemolysins forms approximately 2% of the AIHA (Engelfriet 1987).

AIHA can occur in isolation or in combination with other diseases:

- (a) With malignancy. The most frequent association is with CLL, in which AIHA occurs in over 4% of cases (Mauro 2000).
- (b) With other auto-immune diseases, for example systemic lupus erythematous (SLE), rheumatoid arthritis (RA), Sjogren's disease, immune thrombocytopenia (ITP), pure red cell aplasia (PRCA), hypothyroidism, Addison's disease or primary biliary cirrhosis.
- (c) With viral (including, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Human Immunodeficiency Virus (HIV)), bacterial (including syphilis, legionnaires' disease, mycoplasma) or parasitic (including leishmaniasis) infections.

The clinical course of AIHA in the strictest sense varies from acute and fatal to chronic and mild. Prednisone is the therapy of choice in classic WAIHA. Recent research has shown that Rituximab is also effective (Garvey 2008), but more research is needed on the position of this new medication .

2. Medication-associated AIHA

More than 15% of AIHA is medication-associated. There are three forms:

- 2.1. Haptene type (e.g. penicillin).
- 2.2. Immune complex type (e.g. diclofenac).
- 2.3. A type in which the medication does not form an antigenic determinant, but disrupts immune regulation (e.g. alpha methyl dopa, fludarabine, gold).

Medication-associated AIHA can also be hyperacute and fatal (particularly the immune complex type).

3. Transplant-associated AIHA

Following stem cell or organ transplantation, the haemolytic antibodies can be donor-derived or recipient derived. The antibodies can be of the warm, cold, biphasic or mixed type. A positive Direct Antiglobulin Test (DAT) occurs in approximately 25% of the recipients of allogeneic bone marrow / blood stem cell transplants. The incidence of AIHA following transplantation is 3 – 4.4%. It can occur within two weeks to more than two years after transplantation (Sanz 2007, O'Brien 2004, Chen 1997, Drobyski 1996).

Risk factors for the development of transplant-related AIHA are T-cell removed bone marrow / stem cell transplants, an unrelated donor, chronic graft-versus-host-disease and transplantation for a non-malignant illness (Sanz 2007, O'Brien 2004). The AIHA can start acutely or slowly, approximately 10% is chronic in nature and is therapy-resistant (Hashimoto 1998, Drobyski 1996).

4.4.5.2 Treatment of AIHA

There is consensus that the confirmation of the type of autoantibody or medication-dependent antibody is relevant for the clinical course and the choice of treatment of AIHA. In general, there is no relationship between the antibody titre and the extent of haemolysis.

As the diagnosis and compatibility study of AIHA requires extensive serological testing, which is not performed routinely (see Chapter 3), the requesting doctor should supply relevant clinical information (including but not limited to information about haemolysis/haemoglobinuria, medication, recent transfusions and any other conditions such as Chronic Lymphatic Leukaemia (CLL) (Engelfriet 2000, Mauro 2000).

Both the requesting doctor and the responsible people in the laboratory should realise that transfusion must take place for vital indications, despite compatibility problems and positive cross matches (Salama 1992, Petz 1980, Jefferies 1994, Garraty 1993).

Recommendations 4.4.5

1. The suspicion of auto-immune haemolytic anaemia (AIHA) should be stated with the request for diagnosis and transfusion.
2. In the case of auto-immune haemolytic anaemia (AIHA) in the acute phase, urgent diagnosis is often indicated for determining the type and specificity of antibodies and the exclusion of alloantibodies (see also Chapter 3.7.3).
3. For a new patient, the specificity of the autoantibodies should be examined because of possible selection of typed, compatible donors for transfusion.
4. The presence of alloantibodies should be ruled out.

Recommendations 4.4.5

Warm types of Auto-Immune Haemolytic Anaemia (AIHA)

1. Prednisone is recommended as the therapy of choice for the classic warm type auto-immune haemolytic anaemia (WAIHA).
2. Splenectomy is effective in patients older than six years of age with classic warm type auto-immune haemolytic anaemia (WAIHA) that have relapsed or are resistant to prednisone. Splenectomy is only indicated in patients older than six years of age because of the risk of infection.
3. Rituximab can be considered in prednisone-resistant patients.

Cold types of Auto-Immune Haemolytic Anaemia (AIHA)

1. The cold types of auto-immune haemolytic anaemia (AIHA) are resistant to prednisone, unless administered in high pulse dosages.
2. Splenectomy has been shown to be ineffective for the cold types of auto-immune haemolytic anaemia (AIHA).

Medication-associated auto-immune haemolytic anaemia (AIHA):

1. Medication-associated auto-immune haemolytic anaemia (AIHA) of the haptene and immune complex types generally improve within a week of stopping the offending medication.
2. However, fludarabine-associated auto-immune haemolytic anaemia (AIHA) can cause haemolysis for weeks.

Recommendations 4.4.5

1. In the case of (beginning) auto-immune haemolytic anaemia (AIHA), the Hb should be determined frequently (every 4 hours), particularly if there is no reticulocyte response (yet) and in the event of an aplastic crisis.
2. The critical Hb limit (< 3 mmol/L) for transfusion (see paragraph 4.1) also applies to auto-immune haemolytic anaemia (AIHA), unless there is symptomatic hypoxaemia despite bedrest and oxygen.
3. Serological analysis may never delay an indicated transfusion.

4. The transfusion policy for auto-immune haemolytic anaemia (AIHA) should be restrictive. Transfusions contribute to disseminated intravascular coagulation, kidney and organ failure. In the acute phase, the Hb should be maintained between 3 and 4 mmol/L, with no more than ½ - 1 unit of erythrocytes per transfusion.
5. In the acute phase, the amount of transfused blood should be kept as small as possible and should never exceed 1 unit (5 mL/kg in children), under constant monitoring.
6. Erythrocyte transfusions should only be given to treat hypoxaemia.
7. If there are no cerebral/cardiac hypoxaemic symptoms in rest, it is permissible to withhold therapy if the Hb is > 3 mmol/L.
8. For warm types of auto-immune haemolytic anaemia (WAIHA), the survival of donor erythrocytes is as short as that of those of the patient (unless there are specific autoantibodies and the transfusion is compatible). For the chronic cold agglutinin syndrome, caution is advised in the correction of moderate to severe chronic anaemia by means of transfusions. Donor erythrocyte survival is shorter than autologous erythrocytes.
9. Plasmapheresis and/or erythrocyte apheresis can be considered for therapy-resistant life threatening auto-immune haemolytic anaemia (AIHA), possibly in combination with intravenous immunoglobulin.
10. In the case of severe cold auto-immune haemolytic anaemia (AIHA), ECs should be administered via a warming system.
11. Exhaustion of the complement cascade can occur in the case of complement-mediated auto-immune haemolytic anaemia (AIHA) combined with intravascular haemolysis. Administration of 'fresh frozen plasma' (FFP) can then make the haemolysis worse.

4.4.6 Haemolytic disease of the foetus and the newborn

The last breakdown disorder discussed in this chapter is the haemolytic disease of the newborn. As both the prevention and treatment of this disease involve not only treating the neonate, but also pregnant women and foetuses, we will discuss this subject here in paragraph 4.4 (Breakdown disorders) instead of paragraph 4.5 (Anaemia in neonates).

4.4.6.1 Prevention and treatment of haemolytic disease of the foetus

If a pregnant woman is found to have RhD antibodies or other alloantibodies that can cause a haemolytic disease of the foetus/neonate, the specificity and immunoglobulin class should be determined. In the case of potentially clinically relevant antibodies, the homozygous/heterozygous presence of the relevant antigen is checked in the father. A large study in the Netherlands on the consequences of non-RhD antibodies found during the 12th week of pregnancy showed that only anti-RhC and anti-K antibodies result in severe disease in the foetus and neonate, which necessitated intra-uterine transfusions (IUT) or exchange transfusions. This involved only 3.7% of all irregular antibodies found (Koelewijn 2008). If the father is homozygous for the relevant antigen, then – if possible – the biological activity of the antibodies is tested using the 'antibody dependent cellular cytotoxicity' (ADCC) test (see also: NVOG Guideline haemolytic disease of the neonate, 2010). If the father is heterozygous, then it is often desirable to know the blood group determination of the foetus.

For an increasing number of blood groups it is now possible to determine the blood group of the foetus in the mother's plasma and this is the case of the clinically relevant Rhesus and K antigens. The clinical condition of the foetus can be monitored using echo Doppler of the flow speed in the Mid Cerebral Artery as a measure of anaemia, if necessary in combination with amniocentesis to estimate the extent of haemolysis or a cord blood puncture to measure foetal Hb. Severe haemolysis with hydrops is often (> 80%) the result of RhD antibodies. Treatment with 2 – 4 weekly intra-uterine transfusions (IUT) is possible from week 18 – 22 for the prevention of hydrops. Large cohort studies have shown that this treatment is effective and more than 90% of these children are born alive (Van Kamp 2004). Blood group antagonism, which results in severe anaemia before the 22nd week – as is a possibility with K antagonism – has a poorer prognosis (Vaughan 1998, Weiner 1996). In the Netherlands, treatment with IUT is centralised in the Leiden University Medical Centre (LUMC), as the occurrence of complications from the procedure is strongly associated with experience (Van Kamp 2004).

As a result of foeto-maternal transfusion during IUT, the mother has an increased (10 – 25%) chance of developing additional irregular antibodies (Viator 1994, Schonewille 2007). The compatibility study is therefore only valid for 24 hours in these women (Van Kamp 1999, Health Council 1992). IUT suppresses the production of erythrocytes in the foetus. As a result, the foetus has primarily erythrocyte antigens from the donor at birth.

Conclusions 4.4.6.1

Level 3	<p>Blood group antagonism in pregnancy should be detected and – if this is checked according to a protocol – it can prevent severe foetal hydrops.</p> <p><i>C Health Council report 1992, Koelewijn 2008, Van Kamp 2004</i></p>
Level 3	<p>Foetal anaemia resulting in hydrops can be treated effectively in more than 90% of cases using intra-uterine transfusions (IUT) if the procedure is performed in a clinic with experience.</p> <p><i>C Van Kamp 2004, Van Kamp 1999</i></p>
Level 3	<p>Following intra-uterine transfusion (IUT), the mother has a 10 – 25% risk of developing additional erythrocyte alloantibodies.</p> <p><i>C Schonewille 2007; Viator 1994</i></p>

Other considerations

Foetal hydrops often has causes other than blood group antagonism (including alpha thalassaemia and Parvo B19 infection).

Recommendations 4.4.6.1

1. The detection and monitoring of irregular antibodies during pregnancy should occur according to a protocol.
2. Severe blood group antagonism resulting in hydrops is an absolute indication for intra-uterine transfusions (IUT); in order to limit complications, foetal transfusions should be performed in a centre with maximum experience.
3. Women undergoing intra-uterine transfusions have a strongly increased risk of blood group immunisation. **It is recommended to perform the compatibility after prior intra-uterine transfusions (IUT) with a sample that is as fresh as possible (< 24 hours old).**

4.4.6.2 Prevention and treatment of haemolytic disease of the neonate

Phototherapy and exchange transfusion are widely used in the treatment of haemolytic disease of the neonate. Despite this, there is limited scientific evidence of the exact bilirubin level or increase at which these interventions should take place (Smits-Wijntjens 2008).

4.4.6.2.1 Exchange transfusion

Virtually the only indication for exchange transfusion is hyperbilirubinaemia, in order to prevent kernicterus. Kernicterus in a full term neonate usually does not occur at < 400 $\mu\text{mol/L}$ bilirubin, but in premature infants kernicterus can occur at a lower bilirubin concentration. An exchange transfusion indication often exists if the bilirubin level rises faster than 20 $\mu\text{mol/L/hour}$ (despite adequate intensive phototherapy). A 2x blood volume exchange reduces the bilirubin level by 45 – 50%, however, the bilirubin level can rise rapidly again after transfusion due to equilibration with the extravascular pool. The exchange volume is approximately 160 – 200 mL/kg. In the Netherlands, exchange blood consists of erythrocytes < 5 days old, blood group compatible with the mother, the child and the plasma donor (See also Chapter 2.2.1). There has only been one more or less randomised study that compared heparin and citrate blood for exchange transfusion (Petaja 2000). Significant metabolic changes occur during and after exchange transfusion with citrate blood: the sodium level rises, osmolality increases, glucose level rises and (ionised) calcium decreases. Approximately 50% of the circulating platelets are also removed.

Mortality due to exchange transfusions is estimated at 2 – 3/1,000 and higher (2%) if there is no experience and/or the children are severely ill (Ip 2004, Jackson 1997). The risks are: cerebral haemorrhage (hypernatraemia, hyperosmolality and coagulopathy) and arrhythmias (acidosis, hyperkalaemia), particularly in premature babies. Permanent electrocardiographic (ECG) monitoring is essential during exchange transfusion. Levels of Na, K, Ca, bilirubin, blood gases, Hb and platelet count should be measured before the start of the exchange (if platelets become < $100 \times 10^9/\text{L}$ halfway through or after the exchange, administer a platelet transfusion so that thrombocytopenia < $50 \times 10^9/\text{L}$ does not occur during the exchange). Levels of Ca, Hb and platelets should be checked halfway through the exchange transfusion and after the exchange transfusion electrolytes, blood gases, glucose and Ca, as well as Hb, platelets and bilirubin. The glucose level should be monitored during the first few hours after the exchange transfusion due to rebound insulin production and hypoglycaemia. The administration of Ca-gluconate or laevulate (never through the same needle as the citrate blood) for the prevention of hypocalcaemia is controversial. (Petaja 2000, Maisels 1974).

Blood for exchange transfusions for premature babies < 32 weeks or < 1,500 grams should be irradiated (25 Gy).

In addition to phototherapy and exchange therapy, the intravenous administration of immunoglobulins (IVIG) is also used. However, the value of this intervention (IV-Ig) is the subject of discussion. Therefore, the literature was searched using systematic reviews to examine the effect of IVIG on haemolytic disease of the neonate. The quality of the reviews was evaluated based on the following items : search strategy, selection of articles, quality evaluation and analysis method.

Two good systematic reviews were found, including a Cochrane review. Gottstein et al performed a systematic review and meta-analysis of RCTs on the effect of IVIG on haemolytic disease of the neonate (Gottstein 2003). Compared to phototherapy alone, IVIG significantly reduced the number of required exchange transfusions, but the number of erythrocyte transfusions required for anaemia occurring at a later stage turned out to be higher in IVIG treated patients (Gottstein 2003). Alcock et al drew similar conclusions in their Cochrane review (Alcock 2002). However, they emphasised that the conclusions were based on only 3 trials with a total of 189 patients. In addition, only 1 trial met the criteria for high quality. Absence of randomly assigned treatment was a significant shortcoming in the other trials. None of the trials used a placebo and there was also no blinding. The Cochrane reviewers concluded that – due to these limitations – the value of IVIG is uncertain and that this treatment cannot be recommended as a routine treatment, also due to the absence of information about the long-term safety (Alcock 2002).

A recent double-blind, placebo-controlled, randomised study of the efficacy of IVIG in haemolytic disease of the neonate found no difference between the IVIG and placebo groups (Smits-Wintjens, Pediatrics 2011, in press).

Conclusions 4.4.6.2

	Phototherapy and/or exchange transfusions are the interventions of choice for preventing brain damage by kernicterus due to haemolytic disease of the neonate. It has not been thoroughly investigated at which bilirubin level(s) these interventions should be started.
Level 3	
	<i>C Smits-Wintjens 2008</i>

	An exchange transfusion is usually given if the bilirubin level rises more rapidly than 20 µmol/L/hour despite adequate phototherapy.
Level 4	
	<i>D Expert opinion</i>

	During exchange transfusions – particularly in premature babies – the greatest possible attentions should be paid to electrolyte and osmolality imbalances that are relevant to the occurrence of cerebral haemorrhages and arrhythmias.
Level 3	
	<i>C Petaja 2000, Jackson 1997</i>
Level 3	In haemolytic disease of the neonate, the administration of intravenous

	<p>immunoglobulin (IVIG) compared to phototherapy alone strongly reduced the number of exchange transfusions required. However, the number of erythrocyte transfusions required at a later stage for anaemia was greater in the IVIG treated patients.</p> <p><i>B Gottstein 2003</i></p>
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	<p>There is insufficient evidence to support the value of administration of intravenous immunoglobulin (IVIG) in haemolytic disease of the neonate.</p>
Level 2	
	<p><i>B Alcock 2002</i> <i>A2 Smits- Wintjens 2011</i></p>

Evidence table of interventions in haemolytic disease of the neonate								
Author, year	Study population	Design	Level, quality	Intervention (I)	Control (C)	Outcome	Result I vs C	Comments
Gottstein, 2003	Neonates with iso-immune haemolytic disease	Review + meta-analysis	Good included RCTs moderate	High dose IVIG + phototherapy	Phototherapy alone	# children with exchange transfusions	RR 0.28; CI 0.17 – 0.47	
“	Only Rhesus disease	“	“	“	“	“	RR 0.21; CI 0.10 – 0.45	
Alcock, 2002	Neonates with iso-immune haemolytic disease	Cochrane review	Good; included RCTs moderate	High dose IVIG + phototherapy	Phototherapy alone	Use of exchange transfusions	RR 0.28; CI 0.17 – 0.47	Only 3 moderate RCTs with a total of 189 patients
“	“	“	“	“	“	Ordinary transfusions after the 1 st week	RR 11; CI 0.62 – 195	Triggers for transfusion varied
“	“	“	“	“	“	Duration of phototherapy	WMD –22; CI – 35,-9.9	Long-term safety unknown
Smits-Wintjens, 2011	Neonates with iso-immune haemolytic disease	Double-blind, placebo-controlled RCT	Good	High dose IVIG + phototherapy	Placebo + phototherapy	# children with exchange transfusions	No difference in exchange transfusions between both groups	
						Duration of phototherapy, maximum bilirubin level	No difference in phototherapy days or bilirubin level between both groups	

Recommendations 4.4.6.2

1. Intensive phototherapy and – if necessary – exchange transfusion(s) should be considered in neonates with hyperbilirubinaemia due to haemolytic disease of the neonate, in order to prevent brain damage.
2. If the bilirubin level rises more rapidly than 20 $\mu\text{mol/L/hour}$ despite adequate phototherapy, this is an indication for exchange transfusion.
3. Permanent ECG monitoring and periodic monitoring of electrolytes, glucose and platelets are required with exchange transfusion.
4. Routine administration of intravenous immunoglobulin (IVIG) for the treatment of haemolytic disease of the neonate is not recommended.

4.5 Anaemia in neonates*

* for haemolytic disease of the neonate, see 4.4.6.2

The normal Hb level for neonates born full-term is 12 mmol/L (SD: 1.4), of which 60 – 80% is HbF. The switch to adult Hb starts in the 32nd week after conception. In premature neonates, the normal Hb at birth is lower and this decreases in a linear fashion proportional to the duration of the pregnancy (Jopling 2009, Nicolaidis 1989). The Hb concentration decreases after birth due to:

- an increase in 2,3 diphosphoglycerate (2,3-DPG);
- a shortened life span of HbF containing red cells;
- rapid expansion of the blood volume;
- decrease in the epoietin level (due to increase in arterial pO_2);
- blood sample collections;
- clamping the umbilical cord too soon.

In a full-term neonate, the Hb drops to a physiological level of 6.8 mmol/L (SD: 1.2) after approximately 8 weeks. Transfusions are almost never indicated, nor is the routine administration of iron effective (Franz 2000, Irigoyen 1991, Heese 1990). In premature babies < 1,500 grams, the Hb concentration can decrease from 10 to 5 mmol/L after 4 – 8 weeks, partially due to blood sample collection for diagnostic tests. Enteral iron administration (in the form of ferrous fumarate, 6 mg/kg/day in 3 doses) is useful for premature babies as soon as complete enteral feeding is possible and this reduces the need for transfusions after the second week of life (Franz 2000). Intramuscular iron has no benefits over oral iron supplementation (Heese 1990). Most transfusions are given to 'very low birth weights' (VLBW) children after a pregnancy of 24 to 32 weeks; this involves 1 – 1.5% of all births, in other words 2,000 – 3,000 per year in the Netherlands. A lot of research has been performed on the administration of epoietin to premature infants (Aher 2006, Ohlsson 2006). The reduction of the quantity of allogeneic erythrocytes administered was usually the primary measure of outcome. Two Cochrane meta-analyses showed that the clinical significance of both early and late administration of epoietin is very limited (Aher 2006, Ohlsson 2006, Aher 2006). Particularly with late administration of epoietin there is an average reduction of the transfusion volume of 7 mL/kg (< 1 neonatal unit EC) (Aher 2006). Both Cochrane reviews concluded that there is insufficient proof to recommend epoietin

administration for neonatal anaemia (Aher 2006, Ohlsson 2006, Aher 2006). Epoietin administration can be considered in special cases, such as Jehovah's Witnesses.

There are two important strategies for reducing anaemia in the (premature) neonate and thereby reducing the number of blood transfusions, namely:

1. late clamping of the umbilical cord at birth;
2. limiting the number of blood sample collections.

Ad 1. Various meta-analyses have shown that late clamping of the umbilical cord (at least 30 seconds to a maximum of 2 or 3 minutes after birth) is important in reducing anaemia, both in premature (Rabe 2008, 2004) and full-term neonates (Hutton 2007). In addition to reducing anaemia and the need for blood transfusions, late clamping also results in a decrease in intracranial haemorrhages (RR: 1.74; 95% - CI 1.08 – 2.81) (Rabe 2004) without an increase in polycythaemia or hyperbilirubinaemia that would require treatment (Ultee 2008, Mercer 2006, Ceriani Cernadas 2006).

Ad 2. Blood loss in premature infants due to blood sample collections varies from 1.1 to 3.5 mL/kg/day (Alagappan 1998, Obladen 1988, Nexo 1981, Kakaiya 1979). Micro methods for laboratory blood analysis are important in reducing blood loss due to blood sample collections (Widness 2005, Lin 2000, Ringer 1998). Reduction of blood loss results in a reduction in the number of blood transfusions (Madan 2005).

4.5.1 Explanation of component choice for neonates

Components for neonates have special storage instructions and irradiation indications. This paragraph briefly explains why this is the case.

Although the cellular immune response develops normally and allogeneic cells are rejected, some sick premature infants are at risk of TA-GvHD, particularly following intra-uterine transfusions (Parkman 1974). Therefore, premature infants should receive irradiated cellular blood components in certain situations (see 2.2.4).

The premature liver metabolises bilirubin and citrate insufficiently.

The compensatory mechanism for volume depletion is reduced in premature infants. After approximately 10% volume depletion there is no increase in the cardiac output, but the peripheral resistance increases in order to maintain the blood pressure. This results in poor tissue oxygenation, increased levels of lactate and acidosis .

The premature infant is also sensitive to relatively large amounts of potassium (Hall 1993).

4.5.2 Transfusion triggers in neonates

The haemoglobin (Hb) limit (trigger) at which it is decided to perform blood transfusion varies internationally and also between neonatal intensive care units (NICUs) in the Netherlands. Few RCTs have been performed to determine the optimal transfusion limits in neonates and these studies are often hard to compare due to the various approaches in methodology (Ross 1989, Brooks 1999, Bell 2005, Kirpalani 2006). The characteristics and results of

these studies can be found in the evidence table. The study by Bell et al (Bell 2005) was downgraded as the reporting appeared to have been extremely selective. Ultimately, an effect was only found for a liberal transfusion policy with an unusual measure of outcome. The better RCT by Kirpalani et al (Kirpalani 2006) (the so-called PINT study; Premature Infants in Need of Transfusion)

found no difference between an algorithm with a low Hb trigger and a high Hb trigger for various clinically relevant measures of outcome. In the group with a low Hb trigger, fewer children required one or more blood transfusions than in the group with a high Hb trigger, 89% versus 95% respectively, $p = 0.04$. Although no significant difference was found between both groups in relation to the long-term psychomotor development, a post-hoc analysis showed a better mental development in the group with a higher Hb trigger (Whyte 2009).

Due to the scarcity of good studies, it is not possible to make reliable recommendations concerning optimal transfusion triggers in neonates. Further study (with follow-up) of a more restrictive transfusion policy in premature neonates is essential.

Commonly used transfusion triggers in the Dutch NICUs (not based on research) are:

- Maintaining Hb = 8 mmol/L with ventilation, whilst avoiding an Ht > 0.50 L/L (Strauss 1995, Brown 1990).
- Maintaining an Hb > 7 mmol/L in stable neonates with cardiopulmonary abnormalities and use of oxygen (Strauss 1995, Brown 1990).
- Maintaining Hb > 6 mmol/L in stable premature infants < 4 weeks, particularly in the first four weeks of life when anaemia and tissue hypoxia can lead to apnoea.
- Maintaining Hb > 4.5 mmol/L in stable premature infants > 4 weeks (Strauss 1995, Brown 1990).

Table 4.5.2: Evidence table triggers for erythrocyte transfusion in neonates

*Aspects of quality: S sequence generation; A allocation concealment; B blinding of participants, personnel and outcome assessors I incomplete outcome data; R selective outcome reporting.

Author NB	year	Study design	level	Quality aspects*	Study population	n	Intervention	outcome	Other considerations
Kirpalani ²⁶	2006	RCT	A2	S, A, C, R: OK B: Blinding outcome assessors only partly	Premature neonates < 31 wks; <1000 g	451	Algorithm of low vs. high Hb trigger (restrictive vs. liberal transfusion policy)	No difference in blood transfusions; OR composite outcome (mortality, severe bronchopulmonary dysplasia, retinopathy of prematurity or cerebral damage 1.30 (0.83, 2.02)	
Bell ²⁵	2005	RCT	B	S, A, B, C: OK R: Selective reporting!	Premature neonates; 500-1300 g	100	Algorithm of low vs. high Hb trigger (restrictive vs. liberal transfusion policy)	No difference in blood transfusions; Fewer cases of grade IV intraventricular haemorrhage or periventricular leukomalasia 0% vs 12% (p=0.012)	Artificial combined neurological measure of outcome only thought of post-hoc. Many methodological queries concerning interpretation of the secondary measures of outcome.
Brooks ²⁸	1999	RCT	B	Risk of bias cannot be assessed	Premature neonates < 1251 g	50	Ht 0.20 – 0.30 L/L+ specific medical criteria vs. Ht ≥0.40	No difference in retinopathy: 83%; vs. 73%; CI 52%, 88%. (p=0.38).	
Ross ²⁹	1989	RCT	(B)	Risk of bias cannot be assessed	Premature neonates < 32 weeks	16	Transfusion to Ht of 0.40 L/L vs no transfusion for 3 days	No differences	Small study; duration of study only 3 days: not relevant

4.5.3 Dosage of erythrocytes, administration and component choice

Correction of anaemia

In the Netherlands, different dosages are used for the correction of anaemia, varying from 10 to 20 mL/kg. Khodabux et al found no difference in efficacy between 15 and 20 mL/kg (Khodabux 2009). The current recommendation is to transfuse 15 mL/kg at an administration speed of 5 mL/kg/hour. For these 'top-up' transfusions, an erythrocyte component in storage

solution is not a problem even at the end of the storage duration (35 days), despite the high potassium concentration (> 50 mmol/L). In order to reduce the number of donor expositions, an erythrocyte concentrate from one donor can be split into a number of so called pedi-packs (usually 4 pedipacks of 50 ml) (Widness 1996, Andriessen 1993, Patten 1991). A premature infant receives an average of two (range: 0-10) pedi-packs. Please see *Chapter 3.3.3.2, compatibility study* for further details concerning the compatibility study for blood transfusions.

During the initial care of a neonate with very severe anaemia due to acute bleeding, it is possible to increase the immediate post-partum Hb without causing volume overload by means of a partial exchange transfusion using uncrossed O-RhD negative erythrocytes

Conclusions 4.5

	Particularly premature infants < 1,000 grams virtually always receive several erythrocyte transfusions. Use of epoietin in premature infants / neonates is not recommended, but could possibly reduce the transfusion volume for late anaemia (after 4 weeks); there is virtually no effect on early anaemia, particularly in severely ill, ventilated children.
Level 1	
	A1 <i>Aher 2006, Ohlsson 2006</i>

	Late clamping of the umbilical cord results in a reduction of anaemia and blood transfusions – without further negative consequences – in both premature infants and full-term neonates.
Level 1	
	A1 <i>Rabe 2004, Hutton 2007</i>

	Limiting iatrogenic blood loss by blood sample collections results in a reduction of anaemia and blood transfusions in premature infants.
Level 2	
	A2 <i>Widness 2005</i> B <i>Madan 2005</i> C <i>Lin 2000</i>

	It is not clear whether a more restrictive transfusion policy in premature neonates is better than a liberal transfusion policy.
Level 2	
	A2 <i>Kirpalani 2006</i> B <i>Bell 2005, Whyte 2009, Brooks 1999</i>

Recommendations 4.5

1. Clamping the umbilical cord of premature and full-term neonates should only take place after at least 30 seconds and no more than 2 – 3 minutes after birth.
2. Iatrogenic blood loss due to blood sample collections in premature neonates should be reduced by using – among others – micro-analysis techniques and by limiting the number of blood tests.

3. Maintaining an Hb > 8 mmol/L is advised in ventilated (premature) neonates with respiratory insufficiency.
4. Maintaining an Hb > 7 mmol/L is advised in stable neonates with cardiopulmonary abnormalities and use of oxygen.
5. For neonates < 4 weeks the transfusion trigger is 6 mmol/L; for neonates > 4 weeks the transfusion trigger is > 4.5 mmol/L; if there are clinical symptoms of hypoxia, a transfusion may be necessary sooner.
6. Further studies (with follow-up) using a more restrictive transfusion regimen in premature babies are essential.
7. Pedi-packs from one donor (15 mL/kg in 3 hours) should preferably be used in premature neonates for the correction of anaemia; there are no further limitations as to storage duration or storage solution, provided the transfusion speed does not exceed 5 mL/kg/hour.
8. For massive transfusions (> 80 mL/kg/24 hours or administration speed > 5 mL/kg/hour), erythrocytes < 5 days old should be selected; extra monitoring (electrolytes, blood gases) is necessary particularly in the case of liver or renal insufficiency.

4.6 Anaemia in children

Approximately 3.5 – 4.2% of all erythrocyte transfusions are given to children, defined here as patients younger than 18 – 20 years (Cobain 2007, Stainsby 2008). In 69% of the children receiving a transfusion, the number of transfusions remains limited to one (Slonim 2008). A 'complication' as a result of a transfusion occurs in less than 1% of these patients (Slonim 2008). An English report was published recently about severe side effects of blood transfusion, specifically in children (Stainsby 2008). The incidence of severe side effects is estimated in this report at 18:100,000 transfusions for children aged 1 – 18 years and double that for children < 1 year. Examples of severe side effects are (in order of decreasing frequency): incorrect blood component administered, acute or delayed transfusion reaction, TRALI, graft versus host disease and transmission of infection. Children over the age of four months primarily receive erythrocyte transfusions in the ICU, peri-operatively, due to blood loss after trauma, because of (treatment of) cancer, sickle cell disease, thalassaemia or a primary bone marrow condition associated with (among others) insufficient red cell production. Erythrocyte transfusions for neonates are discussed in paragraph 4.5, erythrocyte transfusions in acute situations are discussed in Chapter 5.

There are few – if any – studies that compared various erythrocyte transfusion triggers for children over the age of four months. As a result, guidelines for this category of children are based largely on empirical evidence or have been extrapolated from studies in adults. The best and most recent guideline concerning erythrocyte transfusions for neonates and older children is from the United Kingdom (Gibson 2004). Usually, erythrocyte transfusions are given at Hb values between 4.0 and 5.0 mmol/L; the indication is partly determined by the symptoms (Wong 2005, Gibson 2004, Slonim 2008).

4.7 Specific Diseases

Bone marrow failure / cancer: see paragraph 4.2.

Anaemia due to chronic renal insufficiency (see also paragraph 4.2.3)

The normal values for Hb are lower in children. There is no evidence as yet that the upper limits for Hb that are maintained for adults with renal insufficiency should also apply to children.

Sickle cell disease: see paragraph 4.4.1.

Thalassaemia: see paragraph 4.4.3.

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CHAPTER 5: transfusion policy for acute anaemia

Acute anaemia is defined in this guideline as anaemia due to acute blood loss, as opposed to the erythrocyte transfusion policy for chronic anaemia (defined as not being the result of acute blood loss) discussed in Chapter 4. The policy for ICU patients with acute anaemia – that is not (only) the result of blood loss – is also discussed in this chapter.

After a general introduction about acute blood loss (5.1), we will first (5.2) discuss the erythrocyte transfusion policy for acute – but not massive – blood loss (the so-called 4-5-6 rule). This is followed by a discussion on massive blood loss (5.3) with a distinction being made between a decompensated or uncontrolled shock situation (5.3.1) and a controlled situation (5.3.2). For the compensated situation, we will discuss separately the erythrocyte transfusion policy (5.3.2.1), the platelet transfusion policy (5.3.2.2) and the further clotting correction policy (5.3.2.3). A paragraph about the side effects of massive transfusions (5.3.3) is followed by general recommendations for the transfusion policy in the case of massive blood loss (5.3.4).

We will then discuss the transfusion policy for acute blood loss in a number of specific situations (5.4): in obstetrics (5.4.1), in the ICU (5.4.2), in cardiovascular conditions and cardiac surgery (5.4.3), in cerebral trauma (5.4.4), anaesthesia (5.4.5), in the post-operative situation (5.4.6), in children (5.4.7) and massive transfusions in neonates (5.4.8). Finally, we will discuss the so-called pre-operative blood ordering lists (5.4.9).

5.1 Acute blood loss: introduction

In acute blood loss, depending on the volume and speed of the blood loss on the one hand and the physiological ability to compensate on the other hand, symptoms occur based on loss of circulating volume.

5.1.1 Estimating blood loss based on symptoms

A reasonable estimate of the loss of circulating volume in an average adult can be made based on the clinical symptoms according to ATLS categorisation (American College of Surgeons 2008), as shown in table 5.1.1. There is a slightly different score for children, with only three shock classifications and different volumes.

Table 5.1.1: Classification of blood loss based on symptoms

	Class 1	Class 2	Class 3	Class 4
Blood loss (ml);% CV (70 kg adult)	< 750 < 15%	750-1500 15 – 30%	1500-2000 30 – 40%	>2000 > 40%
Heart rate	< 100	>100	>120	>140
Blood pressure	Normal	Normal	↓	↓
Pulse pressure	Normal	↓	↓	↓
Respiration frequency	14-20	20-30	30-40	>40
Urine output (ml/hour)	>30	20-30	5-15	< 5
CNS	Agitated	Anxious	Confused	Drowsy

5.1.2 Compensation mechanisms of acute blood loss

In conscious patients, the oxygen transport is maintained by (Hebert 1999, Consensus Conference 'Perioperative Red Blood Cell Transfusion 1988):

- Increase in cardiac output, the heart rate increases, viscosity increases, systemic vascular resistance (SVR) decreases, venous return and myocardial contractility increase.
- Redistribution of the blood flow to the brain and myocardium at the expense of hepatic, splanchnic and (ad)renal perfusion; the bowel is the first to suffer hypoxic damage (American College of Physicians 1992).
- Increased capillary blood flow due to recruitment within the vascular bed and a decrease in pre-capillary oxygen loss.
- Increase in oxygen extraction.
- Right shift in the Hb dissociation curve due to elevation of 2,3-diphosphoglycerate (2,3-DPG) does not play a role in the acute phase; a shift can occur under the influence of pH or temperature changes.

With the help of compensatory mechanisms, healthy adults can lose up to 30% of the circulating volume without going into shock. Cardiopulmonary compromised patients have a limited capacity to accommodate for blood loss and do not tolerate acute anaemia as well. The compensatory mechanisms can also be compromised by age, hypothermia, fever, medication such as negative inotropics and some types of anaesthetics.

Insufficient compensation of acute blood loss causes:

- haemodynamic instability or shock;
- tissue hypoxia: ischaemia, anaerobic glycolysis, acidosis and necrosis;
- organ damage, particularly bowel ischaemia and acute tubular necrosis;
- hypothermia;
- electrolyte imbalances: hypocalcaemia, hypomagnesaemia, hyperkalaemia;
- disruption of the pH.

5.2 Transfusion triggers for erythrocyte transfusions for acute anaemia due to non-massive blood loss: the 4-5-6 rule

Most patients with acute anaemia have or had blood loss, but not massive bleeding. Their blood loss can be compensated by physiological mechanisms and/or therapy. The erythrocyte transfusion policy in this situation can be based on Hb values.

In patients with burn wounds who were transfused at either an Hb < 6 mmol/L or an Hb < 4 mmol/L respectively, no difference was found in survival, hospital stay or cardiac decompensation (Sittig 1994). In a study in patients undergoing coronary bypass surgery, one group received a transfusion at a haematocrit (Ht) < 0.32 L/L and the other group at an Ht < 0.25 L/L. No difference was found in fluid requirement, haemodynamic parameters or in-hospital complications (Johnson 1992). A randomised study in patients undergoing aortic valve replacement surgery, showed no difference in survival or acid-base abnormalities between the group receiving blood at an Hb of 5.5 mmol/L and the group receiving blood at an Hb of 4 mmol/L (Lilleaasen 1978). The duration of ventilation in intensive care (ICU) patients did not differ for the group who were transfused at an Hb < 6 mmol/L compared to the group who received transfusions at an Hb < 4 mmol/L (Hebert 2001). This demonstrates that a relatively low Hb is well tolerated.

Too liberal transfusion policy can also be harmful. In a prospective randomised study in 838 adult ICU patients who needed (non-leukocyte reduced ECs: see also 5.4.2) transfusions, the aim was to maintain an Hb between 4.5 and 5.5 mmol/L in the one group and an Hb between 6 and 7.5 mmol/L in the other group. The group with the higher transfusion trigger – the group receiving more blood – suffered significantly more myocardial infarctions and pulmonary oedema. Transfusion trigger was defined in this case as the Hb at which erythrocyte transfusions were administered. The 30-day mortality was the same in both groups, but the mortality was significantly lower in a sub-group of younger patients (< 55 years) and less severe disease, if the Hb was maintained at between 4.5 and 5.5 mmol/L (Hebert 1999). Various organisations, including the National Institutes of Health, the American College of Physicians, the American Society of Anaesthesiologists, the Canadian Medical Association, the British Committee for Standards in Haematology (Royal College of Surgeons of England, the Royal College of Physicians and the Royal College of Anaesthetists) have published guidelines over the past years concerning the use of erythrocytes. These guidelines assume that a blood transfusion will have few positive effects at an Hb > 6 mmol/L, that a transfusion is often beneficial at an Hb < 4 mmol/L and that – at an Hb between 4 and 6 mmol/L – it depends on patient characteristics whether or not the transfusion is expected to have a positive effect. The so-called 4-5-6 rule was developed based on this information, including important factors for the decision to transfuse:

- Can the patient compensate for the anaemia (cardiopulmonary status)?
- Is there increased use of oxygen (fever, sepsis)?
- Are there signs of atherosclerosis (brain, heart, kidneys, intermittent claudication)?
- Is there continuous active blood loss and – if so – how much?

Please refer to table 5.2 for the 4-5-6 rule.

Table 5.2: : The 4-5-6 rule for erythrocyte transfusion for acute normovolemic anaemia

Consider a transfusion if the following occurs at an **Hb < 4 mmol/L**:

- acute blood loss in a healthy individual (ASA I, see table 5.1.3) < 60 years, normovolemic, blood loss at 1 location

Consider a transfusion if one of the following situations occurs at an **Hb < 5 mmol/L**:

- acute blood loss in a healthy individual (ASA I, see table 5.1.3) of > 60 years and normovolemic, blood loss from 1 location
- acute blood loss in healthy individuals < 60 years, normovolemic, bleeding from several locations (poly-trauma patients)
- patient < 60 years, pre-operative, with an expected blood loss > 500 mL
- fever
- post-operative phase following open heart surgery, uncomplicated
- ASA II and ASA III

Consider a transfusion if one of the following situations occurs at an **Hb < 6 mmol/L**:

- ASA-IV patients
- patient who is unable to increase the heart minute volume to compensate for haemodilution
- septic* and toxic patient
- patient with severe lung disease
- patient with symptomatic cerebrovascular disease

* See 5.10 for differentiation

Table 5.2 b: ASA criteria

The ASA criteria are:

- I healthy individuals
- II patients with a mild systemic abnormality, without limitation of function
- III patients with a severe function-limiting systemic abnormality
- IV patients with a systemic abnormality that is constantly life threatening
- V patients who are moribund and would probably die within 24 hours with or without surgery

Recommendation 5.2

It is recommended that the so-called 4-5-6 rule (see table 5.2: the 4-5-6 rule) be maintained as a guideline for an erythrocyte transfusion **in acute normovolemic anaemia.**

5.3 Massive blood loss: introduction

Various definitions are used for 'massive blood loss':

- more than 10 units of erythrocyte concentrate transfused into an adult patient in a 24-hour period;
- the patient loses his or her circulating blood volume more than once over in a 24-hour period (Drummond 2001, CMA Expert Working Group 1997);
- the patient loses 50% of the circulating volume in 3 hours, or;
- the (adult) patient has a blood loss of > 150 mL/min (Stainsby 2000)

In the case of massive blood loss, it is important to recognise the **uncontrolled situation with impending exsanguination and hypovolemic shock** in a timely manner. Typical patient categories with massive blood loss and impending exsanguination are patients with severe trauma, a ruptured aortic aneurysm, post partum haemorrhage or patients with

digestive tract bleeding, who meet the ATLS shock classifications III/IV. Resuscitation is required. However, this is a small category, seen in only a few percent of civilian traumas, but is more common in military calamities.

The first two definitions of massive blood loss – as mentioned above – often involve less rapid blood loss, which is easier to compensate for. With slower blood loss there is usually no resuscitation situation and a component policy can be implemented based on laboratory values such as Hb, Ht, platelets and clotting parameters. A **compensated situation** with massive blood loss can occur – for example – peri-operatively or in the intensive care unit.

In both the compensated and decompensated situation, with massive blood loss, a **coagulopathy** due to dilution, use of pro-coagulant factors and activation of anti-coagulant and fibrinolytic factors can further compromise the haemostasis.

Supplementing the lost blood volume with only ECs or physiological saline or colloids causes a dilution of the clotting factors and platelets. This “dilution coagulopathy” further compromises the blood clotting in the bleeding patient.

A loss of 1 – 1.5 times the circulating blood volume and supplementation with fluids or ECs alone causes a shortage of clotting factors and a decrease in the fibrinogen level. This is associated with elongation of the Prothrombin Time (PT) (see table 5.3: Clotting disorders due to massive blood loss) (Murray 1995, Hippalla 1995). A critical drop in the number of platelets only becomes evident at a later stage and is reached at a blood loss of more than 2 – 3 times the circulating blood volume (Murray 1995). However, there is a wide distribution. The extent and time at which these shortages occur depend partly on the rate of blood loss (Koopman-van Gemert 1996, Hirschberg 2003).

Table 5.3: Clotting disorders due to massive blood loss

First author	Study design	Results
Murray 1995	Spondylodesis; blood loss only compensated with erythrocyte concentrates (n = 32)	50% loss of Circulating Volume: aPTT (activated Partial Thromboplastin Time) and PT (Prothrombin Time) 2x longer, clotting abnormalities clinically manifest, platelets still normal
Hippala 1995	Surgery with a lot of blood loss (n = 60) Measurements performed used to extrapolate when critical limit of clotting factors would be reached	Fibrinogen. 1 g/L with loss of 142% CV Factor II = 20% with loss of 201% CV Factor V = 25% with loss of 229% CV Factor VII = 20% with loss of 236% CV Platelets < 50 x 10 ⁹ /L with loss of 230% CV
Koopman-van Gemert 1996	Theoretical mathematical model of the effect of rapid blood loss (BL) on dilution of plasma proteins	Massive BL 1 litre per accident: rapid; with 3 litres of BL still 29% plasma proteins remaining BL of 0.5 litre per accident: slow; with 5 litres of BL still 24% plasma proteins remaining
Geeraedts 2007	The actual plasma and platelet transfusions given to multi-trauma patients were compared to the calculated amount required for optimum haemostasis corrections	82% of the patients were found to have received about 50% too few platelets and plasma. The ratios improved with more RBC transfusions. .

In traumatology and with massive blood loss, there is also another type of coagulopathy disorder, which is often referred to as “trauma induced coagulopathy” in the literature of the English-speaking world (Hess 2008, Brohi 2008, Davenport 2009, Fries 2009, Lier 2008, Ganter 2008, Rossaint 2010). Research on animals and studies in battle situations have shown that significant tissue trauma – particularly in combination with perfusion abnormalities or low flow situations – triggers the endothelium to increase expression of thrombomodulin. This elevated expression results in the binding of thrombin. Thrombin is withdrawn from the system and this results in decreased fibrin formation. Activation of protein C (aPC) results in inactivation of co-factors V and VIII and therefore causes anti-coagulation. In addition, aPC amplifies fibrinolysis by inactivation of Plasminogen Activator Inhibitor type 1 (PAI-1). However, thrombin bound to thrombomodulin can also activate the Thrombin Activated Fibrinolysis Inhibitor, which results in inhibition of fibrinolysis.

In the case of “trauma induced coagulopathy” there is probably competition between the binding of Protein C and TAFI, which can result in various situations. Brohi found an image particularly of anti-coagulation and hyperfibrinolysis, which suggests that the elevated inactivation of PAI-1 is clinically more significant than the activation of TAFI.

Ganter showed that exocytosis of Weibel-Palade bodies takes place with this type of bleeding, which contain among others vWF (von Willebrand Factor) and angiopoietin 2, which in turn correlates with increased complement activation and endothelial dysfunction.

In addition, a tissue-(plasminogen)activator is released with extended hypotension, acidosis and ischaemia (Lier 2008). Liver function abnormalities, consumption of clotting factors, activated plasmin and fibrin breakdown components contribute to the further deterioration of haemostasis. Furthermore, the colloid plasma expanders – particularly dextran and high molecular weight HES – are known to compromise haemostasis with more blood loss via a decrease in vWF. This phenomenon should be taken into consideration with the infusion of all colloids in large quantities (for example > 1.5 L). This is even more applicable if there are pre-existing abnormalities in haemostasis (Levi 2010).

The vicious circle that is created in this is also referred to as “The bloody vicious circle”. It has been demonstrated that these clotting abnormalities are difficult to correct. Recovery of the hypoperfusion is probably the first point of intervention (Brohi 2009).

The **hypothermia** (decrease in core body temperature < 35 °C) that often occurs in poly-trauma patients can perpetuate blood loss by influencing clotting **and acidosis**. Hypothermia causes a strongly decreased functioning of both the clotting factors and the platelets (Mc Donald 2008, Tieu 2007, Fries 2002).

5.3.1 Massive blood loss: the decompensated/hypovolemic shock situation

Particularly in the case of the last definition of massive blood loss as mentioned above (blood loss > 150 mL/minute in adult patients), there is a life threatening situation due to exsanguination. These are the situations in which rapid (within 1 hour, the so-called “golden hour”) resuscitation is of great importance for survival. This situation is the most well known in the case of massive uncontrolled blood loss in multi-trauma patients and battle field situations. This also occurs in the case of large gastro-intestinal, obstetric and arterial haemorrhages. The policy is aggressive, pragmatic, pro-active and based on an estimate of the blood loss that has already occurred and is still expected to occur (Geeraedts 2009).

The recognition and treatment of patients with uncontrolled blood loss is essential and falls under shock/resuscitation protocols. The European guideline on this subject (Rossaint 2010) is a usable example of this.

Please refer to table 5.1.1 in paragraph 5.1.1 for clinical recognition. The haemodynamic reaction to intravenous filling is also an indication for the existing deficit in circulating volume. Laboratory values usually lag significantly behind the rapidly changing condition in the case of persistent bleeding. However, laboratory tests should be performed as soon as possible, even if only to have the initial data to allow for better estimates of the situation. The base excess and the lactate level are important values used to estimate the extent of hypoperfusion and the degree of shock.

The infusion and transfusion policy in the initial phase is based on an estimate of the circulating volume lost and still expected to be lost until the bleeding has been stopped or can be controlled. This phase should be implemented as soon as possible after the bleeding or the trauma occurs and usually takes place at the site where the trauma occurred, during transport to the hospital, in the Emergency Department or early on during corrective surgery. Optimisation of the circulating volume and the haemostasis – so that the bleeding can be stopped most effectively – are key points in this.

5.3.1.1 The treatment/resuscitation of hypovolemic shock in a patient with uncontrolled bleeding

Particularly in the poly-trauma patient, it is important that the resuscitation is started soon after the accident. The implementation of ‘advanced trauma life support’ (ATLS) within the so-called “golden hour” has resulted in a better prognosis for these patients (Beekley 2008). In unstable poly-trauma patients with massive blood loss, stopping the bleeding – often from various locations – very quickly is foremost (Kaasjager 2001). In order to prevent loss of time, the system of “damage control” surgery was developed for this (Poortman 2000, Martin 1997). This means that the patient undergoes a brief operation to stop the bleeding, after which he/she is stabilised and optimised in the ICU for the eventual operation(s). A recent European guideline (Rossaint 2010) emphasises the particular importance of a multi-disciplinary approach for the best possible resuscitation and “damage control” surgery, now called “damage control resuscitation”.

The aim of the resuscitation is to optimise the circulation blood volume and oxygen transport further. The estimated blood loss (see table 5.1.1 in paragraph 5.1.1) and the haemodynamic parameters can be used to calculate volume correction.

Maintaining blood pressure during resuscitation is now considered less crucial. Although insufficiently evidence-based, accepting a “permissive hypotension” due to restrictive fluid infusion is an accepted strategy. This can decrease blood loss in the event of massive blood loss (Fowler 2002, McIntyre 2002, Hiippala 1998, Bickel 1994, Brimacombe 1994/1993, Crawford 1991, Johansen 1991).

The oxygen transport and haemostasis should also be optimised (Fries 2002, Corazza 2000, Hiippala 1998). Finally, it is important to maintain the patient’s body temperature. Hypothermia, clotting abnormalities and acidosis (lethal triad) negatively affect the prognosis (Eddy 2000).

Conclusions 5.3.1.1

Level 3	Resuscitation and ‘damage control surgery’ are central in massive blood loss in poly-trauma patients (decompensated situation). <i>C Kaasjager 2001, Martin 1997</i> <i>D Poortman 2000</i>
Level 3	In poly-trauma patients (decompensated situation), it is important that the resuscitation is started soon after the accident. The implementation of ‘advanced trauma life support’ (ATLS) within the so-called “golden hour” has resulted in a better prognosis for these patients. <i>B Beekley 2008</i>
Level 3	A multi-disciplinary approach is deemed important for the best possible resuscitation and damage control surgery, now called “damage control resuscitation”. <i>C Rossaint 2010</i>
Level 3	It is likely that the acceptance of ‘permissive hypotension’ due to restrictive fluid infusion can reduce the blood loss in the case of massive blood loss in a decompensated situation. <i>C McIntyre 2002, Bickel 1994, Johansen 1991</i> <i>D Fowler 2002, Hiippala 1998, Brimacombe 1994, 1993, Crawford 1991</i>
Level 3	In poly-trauma patients (decompensated situation), it is important to optimise the oxygen transport and haemostasis and to correct any hypothermia and acidosis. <i>C Fries 2002, Corazza 2000, Hiippala 1998</i>

5.3.1.2 The “blind” transfusion policy for uncontrolled blood loss: estimated correction of the circulating volume and haemostasis

In the case of a severe uncontrolled bleed in a patient, a blind transfusion policy must be started based on clinical symptoms; firstly to prevent hypovolemia, but also to prevent further compromise of the clotting and haemostasis due to dilution and coagulopathy. This can be achieved by transfusing erythrocytes, platelets and plasma. In addition to platelets and plasma, erythrocyte transfusions also play an important haemostatic role. Erythrocytes mediate the radial transport of platelets to the vascular wall and the co-activation of platelets by ADP (adenosine-di-phosphate) release. At a haematocrit of < 0.3 L/L, the platelet adhesion is decreased – particularly in the vascular bed – with high flow speeds (Valeri 2000, Anand 1994, Blajchman 1994, Escolar 1988, Nunez 2009). This decrease will become greater as the Ht becomes lower (Hardy 2004).

A number of studies have appeared in the last few years that concluded that – in addition to the basic measures of resuscitation – a transfusion policy with set ratios between erythrocytes/plasma/platelets increases survival. There are indications that this is due to prevention and/or correction of the dilution coagulopathy (Beekley 2008, Gonzalez 2007, Hardy 2004, Holcomb 2008, Johansson 2009, Johansson 2010).

In the study by Johansson (2009), for example, the following transfusion schedule was used: 5 erythrocytes units: 5 plasma units: 2 platelet units (from 5 donors) in bleeding patients who received > 10 erythrocyte units/24 hours. For the Dutch situation this equates to a ratio of 3: 3: 1. This strategy of administering several components is usually referred to as multi-component transfusions or as the administration of transfusion packages (Madjdpour 2006, Hirschberg 2008, Holcomb 2008).

Apart from the logical reasoning that this strategy proactively prevents haemostatic dilution in massively bleeding patients, these studies do not clearly show which volume of fluid/colloids or erythrocyte transfusion should be started with. It is also not clear which ratios of erythrocytes to plasma are optimum. These ratios are based on retrospective studies (Borgman 2007, Ho 2005, Murad 2010, Roback 2010, Johansson 2010, Saltzherr 2011) where – as mentioned – large amounts of erythrocytes and fluids have already been administered. Studies of battle field situations also use fresh full blood transfusions or erythrocyte transfusion < 15 days old. The improved survival due to a transfusion policy with a relatively high plasma-erythrocyte ratio has also not been confirmed in all situations of massive blood loss (Scalea 2008, Dirks 2010). Finally, there is discussion about whether the association of a high ratio of plasma-erythrocytes with improved survival is the result of improved survival (bias) instead of the other way around (Snyder 2009).

Prospective randomised research is desirable before definitive exact recommendations can be made (Johansson 2010).

Conclusions 5.3.1.2

Level 3	Multi-component transfusions in patients with massive blood loss can often have underestimated dilution coagulopathy. <i>C Hirschberg 2008, Johansson 2009,2010, Holcomb 2008</i>
Level 3	Multi-component transfusions in patients with massive blood loss are associated with improved survival. However, the nature of this association is still the subject of discussion. <i>C Hirschberg 2008, Holcomb 2008, Murad 2010, Roback 2010, Snyder 2009</i>
Level 3	A transfusion policy with set ratios of erythrocytes/plasma and platelets appears to increase survival in the case of decompensated massive blood loss when combined with the basic measures of resuscitation. <i>C Johansson 2009, Murad 2010, Roback 2010, Johansson 2010, Saltzherr 2011</i>

Level 3	<p>There are indications that transfusion of erythrocytes and plasma units in equal quantities, together with approximately one third of that volume in platelet units (concentrate from 5 donors), results in improved survival. However, it is not yet clear what the optimum ratio is and when is the best time to start a multi-component policy for massive blood loss.</p> <p>C <i>Johansson 2009 en 2010, Beekley 2008, Holcomb 2007, Gonzalez 2007; Hardy 2004, Saltzherr 2011</i></p>
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5.3.2 Transfusion policy for massive blood loss in the compensated situation

In a compensated situation, the policy must be tailored to the laboratory values as soon as possible. Transfusion of individual components should also be implemented again.

5.3.2.1 Erythrocyte transfusion policy for massive blood loss in the compensated situation

Massive blood loss can be tolerated for a long period if the speed of blood loss is relatively slow. If a normovolemic (and oxygenated) state can be maintained, the patient will not go into shock and this is called a compensated situation. The lowest acceptable limit for acute anaemia due to blood loss has not been determined in humans, because this depends on the speed of blood loss and the physiological capacity and the therapeutic measures to accommodate for the blood loss. The Hb value is only reliable once the circulating blood volume has been restored.

If the blood loss has been controlled by optimising haemostasis, the erythrocyte mediated oxygen transport becomes the major factor in the policy. However, it is not yet possible to measure accurately the transfusion-related improvement of low oxygen transport and tissue oxygenation. The oxygen extraction ratio (O₂ER) was examined as a possible surrogate marker (Orlov 2009). However, the O₂ER is only a measure of the systemic oxygen extraction. As the local (from organ to organ) oxygen extraction at a tissue level (particularly in the case of sepsis and ischaemic multiple organ failure) can differ from the systemic oxygen extraction, it may be necessary in future to consider basing the decision to transfuse and the monitoring of the efficacy on oxygenation measured in target organs (Stowell 2009).

There are data available about the critical limits for tissue oxygenation in experiments with acute normovolemic haemodilution; this is a compensated situation with corrected circulating volume (normovolemia), good oxygenation and normothermia. Based on these data, there are indications that the tissue oxygenation generally remains adequate down to an Hb of 3 – 5 mmol/L. This applies to these circumstances in healthy volunteers, for both the heart function and the brain function (Weiskopf 1998). Administration of 100% oxygen can temporarily bridge an Hb deficit of 1 mmol/L. In the case of acute blood loss – with another dilution step to follow – it appears to be better not to allow the Hb to drop to 3 mmol/L. This concentration is mentioned in the literature as the limit below which cerebral function abnormalities occur (Madjdpour 2006).

Conclusions 5.3.2

Level 2	<p>There are indications that in the compensated situation of massive blood loss, adequate tissue oxygenation in healthy individuals is generally guaranteed for both cardiac function and cerebral function to an Hb of 3 – 5 mmol/L. A prerequisite is that normovolemia, normothermia and oxygen supply are maintained.</p> <p><i>B Weiskopf 1998, Madjdpour 2006</i> <i>C Madjdpour 2006</i></p>
Level 3	<p>There are indications that the Hb level is reliable as soon as the circulatory blood volume has been restored.</p> <p><i>C Elizalde 1997, Wiesen 1994</i></p>
Level 3	<p>There are indications that cerebral function abnormalities occur at an Hb level lower than 3 mmol/L.</p> <p><i>C Madjdpour 2006</i></p>

Partly due to the limited value of the Hb measurement, particularly in the case of persistent bleeding, there is little evidence to indicate the Hb concentration at which erythrocytes need to be transfused. The decision to start a transfusion therefore also depends on the blood loss already suffered (but often difficult to estimate), the estimated speed of blood loss and still expected blood loss, as well as the comorbidity such as cardiovascular reserves (Murphy 2001, Simon 1998, Ekeroma 1997, CMA Expert working group 1997, Hebert 1997, ASA TFBCT 1996). Also refer to the 4-5-6 rule (table 5.2, paragraph 5.2).

5.3.2.2 Platelet transfusions for massive compensated blood loss

Reviews and guidelines usually recommend to maintain the platelet count $> 50 \times 10^9/L$ with persistent blood loss and $> 100 \times 10^9/L$ in the case of direct vital haemorrhages, for example intracranial (Fries 2002, McDonald 2008, CMA Expert Working group 1997, Rossaint 2010).

5.3.2.3 Specific clotting-modulating measures for massive blood loss

As far as the clotting parameters are concerned, the aim has long been to achieve aPTT and PT values up to 1.5x normal and a fibrinogen level > 0.8 g/L. With respect to the frequently mentioned target value of 0.8 g/L for fibrinogen, this value is probably sub-optimal for effectively stopping uncontrolled blood loss. As a pre-emptive measure, an initial determination of fibrinogen at 0.8 – 1.0 g/L in a bleeding patient should always be considered too low, as this value will decrease further due to dilution and use (Fenger-Eriksen 2008, Thomas 2010, Bolliger 2010). In a bleeding patient – taking into consideration the delay in determination – a measured fibrinogen of 1.5 g/L is probably already an indication for specific fibrinogen elevating and clotting factor correcting treatments. It is becoming increasingly accepted that – in the case of a large loss of circulating volume – the coagulopathy (due to loss and dilution) can be severe and in particular fibrinogen decreases to critical levels sooner than other clotting factors (Chowdhury 2004, Corazza 2000, Murray 1995, Hiipala 1995). Based on a mathematical model, it appears that fibrinogen – particularly

if the pre-dilution initial value is on the low side of normal – is the first factor to fall below the critical value for normal haemostasis in the case of normovolemic haemodilution (Singbartl 2003). The effect of the dose can be calculated (Solomon 2010). A pilot study of cardiothoracic surgery patients suggested that with dosage based on the result of TEM or TEG could result in a more than 50% decrease in the use of clotting factors (Westbrook 2009).

Of course, medicines that inhibit haemostasis – such as heparin, coumarins and platelet inhibitors – should be stopped (temporarily) or reduced.

Conclusions 5.3.2.3

Level 3	<p>There are indications that the decrease in fibrinogen in massively bleeding and transfused patients makes it the first clotting factor to reach a critical level. Administration of 30 – 50 mg/kg fibrinogen concentrate appears to be associated with improved outcome.</p> <p><i>C Johansson 2010, Chowdhury 2004, Corazza 2000, Murray 1995, Hiipala 1995</i></p>
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Level 3	<p>There are indications that supplementation of clotting factors BEFORE aPTT and PT values > 1.5x normal and/or a fibrinogen level < 1.0 g/L are measured results in less blood loss.</p> <p><i>C Fenger-Eriksen 2009, 2008, Rossaint 2010</i></p>
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Fibrinogen preparations are usually not necessary with a multi-component transfusion policy (so-called transfusion packages with set ratios erythrocytes/plasma/platelets), provided these are used aggressively and in a timely manner. However, the advice is increasingly to provide extra and faster compensation of the clotting-dependent haemostasis if surgical haemostasis cannot be achieved in the short term.

The use of anti-fibrinolytics (tranexamic acid) appears to have a positive effect on mortality due to massive blood loss with severe trauma. A recent multi-centre RCT (CRASH-2) of trauma patients revealed that the administration of tranexamic acid resulted in a significant reduction of both overall mortality and mortality due to bleeding (CRASH-2 trial collaborators 2010). However, confirmation of this in a setting more similar to that in the Netherlands is desirable before a definitive recommendation of tranexamic acid in trauma patients.

The administration of 4-factor concentrate or recombinant factor VIIa as clotting factor at an early stage of obvious dilution coagulopathy was also considered, but there are no studies that show a favourable effect. Also refer to Chapter 8.1.3.6 for the possible use of recombinant factor VIIa for massive blood loss.

Conclusion

Level 2	<p>There are indications from a large RCT that tranexamic acid provides a reduction in overall mortality and mortality due to bleeding with severe trauma. Research to confirm this – in a setting more similar to the Dutch situation – is recommended, focusing on thrombotic side effects.</p> <p>A2 <i>CRASH-2 trial collaborators 2010</i></p>
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When interpreting laboratory tests (Hb, Ht, platelets, aPTT, PT, fibrinogen) – particularly in the case of persistent blood loss – one must take into account the fact that these values lag behind the clinical situation. Point of care determinations should, in theory, limit this delay. Retrospective studies found that the use of blood components decreased if thromboelastography (TEG) was used to direct the transfusion policy (Johansson 2009, Anderson 2006). It should be noted that directing the transfusion policy based on thromboelastography/elastometry has never been validated.

It is crucially important to have a good agreement with the laboratory about the communication and the procedure to be followed for massive blood loss. A “massive blood loss protocol” and the agreement of a telephone number, on which the laboratory and the ICU/OR can maintain direct contact, have been recommended in various guidelines (Stainsby 2000, Rossaint 2010, O’Keefe 2008).

5.3.3 Side effects of massive transfusions

Clotting factor deficiencies and thrombocytopenia due to dilution

As was discussed in paragraph 5.3, dilution of clotting factors and platelets occurs when only fluids and erythrocyte transfusions are used. As a result, haemostasis is compromised.

Citrate intoxication

In the case of massive plasma transfusion, citrate intoxication can occur, which is characterised by hypotension, increase in end ventricular diastolic pressure and increase in central venous pressure. On an electrocardiogram a prolonged QT interval, widening of the QRS complex or shallow T-tops due to hypocalcaemia may be seen. In patients with liver failure, citrate is metabolised more slowly and the risk of hypocalcaemia is greater. It is therefore recommended to monitor the (ionised) calcium concentration and ECG changes and supplement calcium if necessary (Vivien 2005, Perkins 2008, Rossaint 2010).

Hyperkalaemia

Potassium release from erythrocytes takes place during storage which raises the potassium concentration in the storage solution; this should be taken into consideration in the case of massive transfusions, particularly in patients with renal insufficiency.

General recommendations for massive blood loss 5.3.1

For acute massive blood loss in a **decompensated situation** (imminent exsanguination, shock), the following is recommended:

1. Start resuscitation quickly according to the 'advanced trauma life support' (ATLS) protocol. **Accept so-called 'permissive hypotension'. Ensure good intravenous access and if necessary place an intra-osseous needle.**
2. Take measures to stop blood loss as soon as possible.
3. In the case of severe continuing blood loss, consider rapid 'damage control' surgery and/or a radiological intervention (see also Chapter 8.1.1).
4. Aim for normothermia, **adequate oxygenation** and avoid acidosis.
5. **Consider possible extramural transfusions.**
6. **Correct haemostasis with multi-component transfusions in ratios as listed under recommendation 7. Fibrinogen preparations are indicated early on in the treatment of extreme blood loss (ATLS IV) and in case of coagulopathy.**
7. **Administer multi-component transfusions, for example in a 3:3:1 ratio between erythrocytes/plasma/platelets.**
8. Preheat blood components and infusion solutions in order to prevent hypothermia.
9. **Consider tranexamic acid – preferably in a study setting – in the case of massive blood loss following severe trauma.**

General recommendations for massive blood loss 5.3.2

The following is recommended in the case of massive blood loss **in a compensated situation** (no danger of exsanguination):

1. Take measures to stop bleeding as soon as possible.
2. Normalise the circulating blood volume with fluid therapy.
3. **Optimise the oxygen transport.**
4. Aim for normothermia (**preheat blood components and infusion solutions if possible**).
5. **Correct the calcium level with Ca-gluconate when administering large quantities of transfusion components that contain citrate.**
6. **If a cell saver is present, consider washing the erythrocytes for transfusion; this can lower the potassium level.**
7. Base transfusion policy on laboratory determinations as soon as possible especially in the case of less severe blood loss or when the delay between sample collection and test result is acceptable. The erythrocyte transfusion policy can then be based on the 4-5-6 rule (see Table 5.2). Additional single component transfusions can be used to achieve an activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT) < 1.5 times prolonged, platelets > 50 x 10⁹/L and fibrinogen > 1.0 – 1.5 g/L.
8. **If the first fibrinogen measurement is < 1.5 g/L and severe bleeding is still continuing, increase the fibrinogen level by using plasma or a fibrinogen preparation.**
9. **The value of TEG and TEM as point-of-care haemostasis screening methods should be validated further in a study setting.**

5.4 Transfusion policy for acute blood loss

5.4.1 Acute or massive blood loss in pregnancy and surrounding birth

Acute, massive blood loss can occur both during pregnancy and during or just after childbirth (Hofmeyr 2001, Bonnar 2000, Nolan 1991). Examples are placental abruption, intra-abdominal blood loss due to an ectopic pregnancy, uterine rupture or placenta percreta. Due to the increased number of caesarian sections, a number of causes of blood loss - such as uterine rupture, placenta praevia, placenta increta and placenta percreta –occur more frequently. There are also more women with co-morbidity which can disrupt uterine contraction after childbirth (uterine atonia); Acquired or congenital clotting abnormalities can also make blood loss during childbirth or post partum more severe. Trauma to the birth canal, uterus atonia or (partial) retention of the placenta are examples of causes of post-partum haemorrhage.

The occurrence of ample post-partum blood loss is an important predictive factor for blood loss in subsequent pregnancies, both for immediate blood loss during childbirth (8 – 28%) and for later post-partum blood loss (Kominiarek 2007).

Disseminated intravascular coagulopathy should always be considered in pregnant women with massive blood loss. During pregnancy, childbirth or post-partum clotting abnormalities—depending on the severity – should be corrected before further (surgical) action can be taken (Seeley 1995).

In addition to the general treatment for shock with rapid intravenous infusion of crystalloids and/or colloids (Hofmeyr 2001), blood and blood components, adequate diagnosis and treatment of the underlying cause is essential (Huissoud 2009, Ahonen 2010, Charbit 2007). The measurement of the blood loss in this setting – provided that the uterus is contracting properly – is easier than the multi-site blood loss of a trauma patient. Calamities occur often because an expectative approach is maintained for too long (Bonnar 2000, Ekeroma 1997, Ahonen 2010, Mercier 2010). Hidden blood loss, for example in the uterus, can contain a large portion of the total blood volume before a decrease in Hb occurs and changes in blood pressure and heart rate are observed (Seeley 1995). In Great Britain, 16% of maternal deaths were associated with massive blood loss (Seeley 1995). Klapholz et al described 30,621 births in which 0.09% of women (n = 28) received more than eight units of blood (Klapholz 1990). Favourable results have been described using washed vaginally suctioned blood (autotransfusion) (Thomas 2005). Multi-component transfusions and tranexamic acid can be considered in the case of massive blood loss (Ahonen 2010, Mercier 2010).

Conclusion 5.4.1

Level	<p>In the case of acute, massive blood loss during pregnancy and surrounding childbirth – in addition to the rapid administration of infusion solutions and blood components – adequate diagnosis and treatment of the underlying cause are essential. Calamities occur often when an expectative policy is maintained for too long. In the perinatal situation the occurrence of disseminated intravascular should be kept in mind</p> <p>C <i>Hofmeyr 2001, Bonnar 2000, Ekeroma 1997, Seeley 1995, Huissoud 2009, Ahonen 2010, Charbit 2007, Mercier 2010</i></p>
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Other considerations

If uterotonic agents do not work, external uterine compression, aortic compression or intra-uterine tamponade using gauze sponges or a balloon can be used to try to stop the bleeding. Radiological embolisations can sometimes prevent hysterectomy in the case of severe arterial bleeding (Kwee 2006). The experience with the latter procedures is based on the treatment of uterine myomas.

Recommendations 5.4.1

Please refer to the general recommendations for acute massive blood loss in paragraph 5.3.4.

Specific recommendations concerning acute massive blood loss in pregnancy and childbirth are:

1. Always consider a disseminated intravascular coagulopathy (DIC) in case of blood loss and abnormal haemostasis post-partum.
2. Anticipate severe blood loss in high risk patients (for example, patients with retained placenta).
3. Consider the use of a cell saver (autotransfusion) (see also Chapter 8.2.2).
4. In the obstetric setting – particularly in the case of ongoing and uncontrolled bleeding – also consider radiological embolisation or other radiological interventions to prevent hysterectomy.

5.4.2 Transfusion policy for acute anaemia in the intensive care unit (ICU)

Introduction

Due to the cardiovascular risks of acute anaemia, blood transfusions are an important part of the treatment of anaemic patients in the intensive care unit (ICU). Critically ill patients may also be more sensitive to the immunosuppressive and microvascular complications of blood transfusions. Therefore, it is important to know which transfusion policy is associated with the lowest mortality and morbidity.

Method

A search was performed for systematic reviews of RCTs that examined the effect of a liberal versus a restrictive blood transfusion strategy. Based on these reviews, the large (> 200 patients) RCTs were evaluated separately.

Results

Of the 16 potentially relevant reviews, three were evaluated in detail. Two reviews were of good quality, but related to the same set of RCTs. One review by Gould et al performed a systematic literature search, but no systematic methods were reported (Gould 2007). Studying the RCTs discussed in the reviews resulted in three studies with > 200 patients. This turned out to be one large RCT by Hebert et al (1999), in which two additional analyses reported the effect of the different policies in a specific sub-population within the same trial. A restrictive transfusion policy (transfusion if Hb < 4.3 mmol/L and subsequently maintaining the Hb between 4.3 and 5.6 mmol/L), resulted in a similar 30-day mortality rate in ICU patients when compared to a liberal transfusion policy (trigger < 6.2 mmol/L; maintenance Hb 6.2 – 7.4 mmol/L). There may even have been a lower total death rate during hospital stay (odds ratio (OR) 0.72, confidence interval (CI) 0.50 – 1.07). There was also marginally less multi-organ failure in the restrictive group (Gould 2007). Less sick patients (APACHE-II <=20) and patients < 55 years of age showed improved survival with a restrictive transfusion policy. A sub-group analysis of 200 trauma patients in this trial by McIntyre et al showed similar results (OR 0.86, CI 0.34 – 2.22) (2004). The restrictive strategy also resulted in a significant reduction in the number of blood transfusions – for example in the sub-group of trauma patients – from 5.4 (SD 4.4) units during ICU admission with the liberal strategy to 2.3 (SD 4.3) units in the restrictive group (McIntyre 2004). However, it should be noted that the erythrocyte component studied by Hebert et al was not leukocyte-reduced, therefore extrapolation to the Dutch situation may not be possible.

Conclusion 5.4.2

Level 2	A restrictive transfusion policy with a transfusion trigger of Hb < 7 g/dL (= 4.3 mmol/L) in ICU patients without a compromised cardiac status resulted in a strong reduction in the use of blood, with a similar or possibly even a lower 30-day mortality when compared to a liberal transfusion policy with an Hb trigger < 10 g/dL (= 6.2 mmol/L).
	A2 <i>Hebert 1999</i>

Other considerations

In retrospective studies – such as the so-called CRIT study – the number of transfusions is often correlated to decreased survival (Corwin 2004, Vincent 2002); however, a causal link should be interpreted with caution with this type of data and always be examined with a thorough multi-variant analysis. This association may not be present then and death following transfusion may rather be associated with a patient who was in worse condition to begin with (Vincent 2008).

However, several studies justify a restrictive policy, although there may still be patients who require an individualised transfusion regimen. These are patients with existing compromised tissue perfusion and/or oxygen transport capacity. Cardiac and pulmonary co-morbidity reduce this capacity and will undoubtedly influence the optimal transfusion trigger in such patients. Therefore, it is important to continuously check for signs indicating that the restrictive transfusion policy may be too restrictive.

A possible generally applicable concept was recently described in patients with pre-existing anaemia prior to cardiac surgery. It was demonstrated that these patients with a lower

baseline (pre-operative) Hb value were better able to tolerate a lower post-operative Hb value. In other words, the greater the Hb difference pre-operatively and post-operatively, the greater the mortality risk. This concept that requires further elucidation suggests that it is not so much the post-operative Hb value that should determine whether or not to give a transfusion, but rather the decrease in post-operative Hb as compared to the pre-operative Hb that seems to be critical (Karkouti 2008).

Recommendations 5.4.2

1. A restrictive transfusion policy should be implemented for ICU patients without an elevated metabolism or cardiac and/or pulmonary co-morbidity. It is recommended to maintain a transfusion trigger of Hb < 4.3 mmol/L.
2. However, all ICU patients – particularly those with cardiovascular and/or pulmonary disease or patients with an elevated metabolism – should be monitored constantly for signs that indicate that the restrictive transfusion policy may be too restrictive. This type of co-morbidity decreases tissue perfusion and/or oxygen transport capacity.*

* These recommendations are compatible with the 4-5-6 rule (see paragraph 5.2)

Table 5.4.2: Evidence table for transfusion triggers on the ICU

Author, year	Study population	Design	Level, quality	Intervention (I)	Control (C)	Outcome	Result I vs C	Comments
Reviews								
Hill, 2002 Carson, 2002	Children or adults Major surgery/ICU	Meta-analysis of 10 RCTs	A2, only 1 large RCT	restrictive trigger: variation between 7 and 9 g/dL or Ht 25 – 30%	liberal trigger: Variation between 9 and 10 g/dL or Ht 32 – 40%	30-day mortality	RR 0.80 (CI 0.63 – 1.02)	Most included RCTs were of moderate quality

Large RCTs								
Hebert, 1999	838 ICU patients with Hb < 9 g/dL	RCT	A2, randomisation, concealment + blinding?	Transfusion at Hb < 7.0 g/dL	transfusion at Hb < 10.0 g/dL	30-day mortality	19% vs 23% OR 0.72; CI 0.50 – 1.07	Multi-organ failure marginally better in restrictive strategy
McIntyre, 2004	203 ICU patients with trauma	RCT; sub-study of Hebert, 1999	A2, see Hebert, 1999	transfusion at Hb < 7g g/dL	transfusion at Hb < 10 g/dL	30-day mortality	OR 0.86; CI 0.34 – 2.22	Except for # transfusions, no difference in other outcomes
Hebert, 2001	357 ICU patients with cardiovascular disease	RCT; sub-study of Hebert, 1999	A2, see Hebert, 1999	transfusion at Hb < 7g g/dL	transfusion at Hb < 10 g/dL	30-day mortality	OR 1.14; CI 0.66 – 1.96	No difference in other outcomes

RR relative risk; OR odds ratio; SD standard deviation

5.4.2.1 Special patients on the intensive care unit (ICU): acute anaemia with sepsis

An analysis of the available literature in 2002 resulted in the recommendation that an Hb trigger of 7 – 9 g/dL (4.5 – 5.5 mmol/L) can be maintained for erythrocyte transfusions in septic patients in the ICU – also when circulation has been restored (Dellinger 2008, Zimmerman 2004). Liberal limits may still be used in special circumstances, such as simultaneous coronary insufficiency, hypoxaemia, acute bleeding and lactate acidosis (Dellinger 2008). Prior to the sepsis recommendation in 2008 (Dellinger 2008), a survey of intensivists in Canada showed that more than 75% already implemented a restrictive policy (Hb < 80 g/L = 5.0 mmol/L) in early sepsis in ICU patients (McIntyre 2007).

Conclusion 5.4.2.1

Level 3	It is not yet clear whether there is an optimal transfusion trigger for erythrocyte transfusions in septic patients in the ICU.
	<i>B</i> <i>Zimmerman 2004</i>
	<i>C</i> <i>Dellinger 2008, Vincent 2008</i>

Other considerations

Micro-circulatory imaging (under the tongue) has thusfar not shown large effects of erythrocyte transfusions in sepsis. The capillary perfusion only appears to improve in patients with abnormal initial values (Sakr 2007). Experiments in animal models show that particularly the transmyocardial oxygen extraction (O_2ER) and the associated myocardial metabolism are better conserved with transfusions at higher triggers (Bloos 1999).

In the case of sepsis, the venous mixed saturation (SvO_2) may be used in addition to the Hb in determining the transfusion trigger (Vallet 2007). For example, a higher Hb trigger is considered at an $SvO_2 < 70\%$ (McIntyre 2007).

Sepsis is characterised by severe morbidity with a pathological redistribution of the perfusion and capillary leakage, resulting in abnormal tissue perfusion. As has been demonstrated in studies, the latter can probably be negatively influenced by haemodilution, but conversely this situation is not necessarily positively affected by transfusions. In this setting, it is very important that the actual transfusion-related improvement of a decreased oxygen consumption can be measured. A measure of oxygen use is the oxygen extraction ratio (O_2ER). It was shown that only O_2ER values that are too low can be improved by erythrocyte transfusions, but that transfusions at normal O_2ER values can even negatively influence the O_2ER value (Orlov 2009). However, the O_2ER is only an overall measure of the systemic oxygen extraction. In the case of sepsis, where there is ischaemia and perfusion redistribution at tissue level in one or more organs, the oxygen extraction measured locally in these organs can differ from the systemic value. In the future – it may become possible to measure oxygen consumption in target organs which may in turn be a base for deciding on a transfusion regimen (Stowell 2009).

Despite the lack of convincing scientific research on the effect of a restrictive transfusion policy in patients with sepsis, there appear to be enough indicators that point to the benefits of a more liberal transfusion policy, particularly in the acute unstable phase.

Recommendations 5.4.2.1

1. In the case of acute anaemia in combination with sepsis the use of the Hb value alone as erythrocyte transfusion trigger is too simple a concept due to the severe morbidity. At this time it is as yet recommended to maintain an Hb value of 6 mmol/L as erythrocyte transfusion trigger following the 4-5-6 rule (see paragraph 5.2).
2. In the case of acute anaemia and sepsis, one can consider including the systemic oxygen extraction ratio (O₂ER) and/or SvO₂ determinations in the decision whether or not to transfuse and the measurement of the subsequent result. A transfusion should be considered sooner in the case of lower values. More research is needed to formulate specific guidelines about this.

5.4.3 Acute anaemia and cardiovascular disease

Anaemia in cardiovascularly compromised patients can result in myocardial ischaemia. This is particularly true for patients with symptomatic coronary sclerosis, especially in situations where the oxygen requirement of the heart is increased, such as exertion or in situations in which the availability of oxygen for the heart is decreased, such as tachycardia.

In older patients who have recently suffered a myocardial infarction, the mortality increases significantly when the haematocrit value is below 0.3 L/L (Wu 2001). So-called silent ischaemia can occur in surgical patients with an Hb of 4.3 – 6.0 mmol/L (Goodnough 1995, Mangano 1990, Parsloe 1990). In animal experiments, it has been determined that the critical limit for myocardial ischaemia due to anaemia with coronary sclerosis is elevated in comparison to the situation with normal coronary arteries (Wahr 1998, Spahn 1994, Levy 1993, 1992).

5.4.3.1 Tolerance for anaemia in patients with cardiovascular conditions in the post-operative phase following cardiac surgery

Three RCTs with a total of 567 cardiac surgery patients showed that it is likely that a post-operative Hb of 5 mmol/L or an Ht of 0.20 – 0.25 L/L is not associated with an increase in post-operative complications, compared to an Hb of 5.5 mmol/L or higher and an Ht of 0.32 L/L or higher respectively (Bracey 1999, Paone 1997, Johnson 1992, Roblee 2002, Carson 2002).

In a retrospective analysis of 224 coronary artery bypass grafting (CABG) patients, Doak et al found no difference in complications between a post-operative Hb of 3.7 and 4.3 mmol/L (1995).

A cohort study by Spiess et al of 2,202 post-CABG patients showed that the risk of myocardial infarction and left ventricle dysfunction increased with an Ht > 0.34 L/L (Spiess 1998). Haematocrit values lower than 0.34 L/L were better tolerated (see table 5.4.3.a Tolerance anaemia post-CABG). In a recent study (the TRACS RCT), the authors concluded that there was no inferiority for 30-day mortality and there was severe morbidity for a restrictive erythrocyte transfusion policy in CABG patients. Careful consideration of the study makes this conclusion less clear (Hajjar 2010).

It was demonstrated recently that cardiac surgery patients with a low pre-operative Hb are better able to tolerate a lower post-operative Hb than patients with a high pre-operative Hb. (Karkouti 2008). This interesting concept requires further testing, but suggests that it is not

so much the absolute post-operative Hb value that should determine whether or not to administer transfusions, but that the decrease in Hb during and after the surgery should also be taken into consideration.

5.4.3.2 Tolerance for anaemia in non-cardiac surgery patients with cardiovascular conditions

In a retrospective cohort study of patients who refused a blood transfusion for religious reasons, Carson et al found that the odds ratio for mortality was 4.3 times higher if the patient had cardiovascular disease (see table 5.10.2: Relationship between peri-operative anaemia and cardiovascular conditions). If the Hb was < 3.7 mmol/L, the mortality in patients with cardiovascular disease was 8 times higher than in patients without cardiovascular disease (Carson 1996).

In older patients who recently suffered from a myocardial infarction, the mortality increases significantly when the haematocrit value is lower than 0.3 L/L (Wu 2001).

Table 5.4.3a: Tolerance of anaemia post-CABG

First author	Study set-up	Result	Evidence class
Johnson	RCT: Ht 0.32 vs Ht < 0.25 L/L (n = 39)	No difference in rehabilitation	A2
Paone	Observational cohort: Transfusion trigger SvO ₂ < 55%, Ht < 0.20 L/L, clinical (n = 100)	No complications	B
Bracey	RCT: Transfusion trigger Hb < 8 g/dL (4.5 mmol/L) or Hb < 9 g/dL (5.5 mmol/L) (n = 428)	No difference in morbidity, mortality or fatigue	A2
Doak	Retrospective observational cohort: Multivariate analysis between Hb and myocardial ischaemia measured via lactate flux. (n = 224)	Hb 58 – 172 g/L (4.5 – 10 mmol/L) no association with ischaemia. Not detrimental up to Hb 60 – 70 g/L	B
Spieß	Prospective observational cohort: Ht ≥ 0.34 vs Ht 0.25 – 0.33 vs Ht ≤ 0.24 L/L (n = 2,202)	Myocardial infarction: 8.3 vs 5.5 vs 3.6%, p < 0.03 LV dysfunction: 11.7 vs 7.4 vs 5.7%, p = 0.006	B
Robblee	Observational vs. historic cohort: Hb < 8 g/L (4.5 mmol/L) vs liberal policy (n = 29)	No difference in lung function tests and cardiopulmonary tests	B
Carson, 2002	Systematic review: 2 small studies show better outcome in high risk CVD patients	Insufficient evidence to decide on conservative or liberal policy	A1
Karkouti, 2008	Retrospective cohort study (n= 10,179 cardiac surgery patients)	A 50% decrease in Hb was correlated to a composite poor outcome. (adjusted odds ratio, 1.53; 95% confidence interval, 1.12 – 2.08; p = 0.007)	B

Hajjar 2010	RCT of restrictive vs more liberal policy in CABG patients	Restrictive policy not inferior as far as 30-day mortality and severe morbidity are concerned.	A2

Table 5.4.3b: Relationship between (peri-operative) anaemia and cardiovascular conditions

First author	Study set-up	Results	Evidence class
Wu Acute myocardial infarction	Retrospective observational cohort: Relationship between Ht and mortality (n = 78,974)	30-day mortality: Ht = 5 – 24% mortality 38.7% OR = 0.22 Ht = 30 – 33% mortality 30% OR = 0.69 Ht > 33% mortality < 25% OR = 1.13	B
Carson Jehovah's Witnesses	Observational cohort: (n = 1,958)	Mortality 1.3% at Hb > 12 g/dL (7.4 mmol/L); 33.3% at Hb < 6 g/dL (3.7 mmol/L); the mortality increases more than two-fold with a decrease in Hb > 4 g/dL (2.5 mmol/L).	B

Conclusions 5.4.3

Level 1	<p>In cardiac surgery patients, a post-operative Hb of 4.5 mmol/L is not associated with an increase in post-operative complications, compared to an Hb > 5.4 mmol/L. The extent of decrease of the postoperative Hb compared to the pre-operative Hb is possibly associated with a poorer outcome.</p> <p>A1 Carson 2002 A2 Johnson 1992, Bracey 1999 B Paone 1997 C Roblee 2002, Karkouti 2008</p>
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Level 3	<p>There are indications that – for coronary artery bypass grafting (CABG) patients – there is no difference in complications between a post-operative Hb of 3.7 mmol/L compared to 4.3 mmol/L.</p> <p>B Doak 1995</p>
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Level 3	<p>In older patients who have recently suffered a myocardial infarction, the mortality increases significantly when the haematocrit value is lower than 0.3 L/L.</p> <p>B Wu 2001</p>
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Level 3	There are indications that the risk of myocardial infarction and left ventricle
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	dysfunction increases in post-CABG patients at an Ht > 0.34 L/L.
	<i>B Spiess 1998</i>

Level 3	There are indications that the odds-ratio for mortality is 4.3 times higher in patients with cardiovascular disease who refused a blood transfusion than in patients without cardiovascular disease who refused a blood transfusion. At an Hb < 3.7 mmol/L, the mortality appears to be 8 times higher in patients with cardiovascular disease than in patients without cardiovascular disease.
	<i>B Carson 1996</i>

Other considerations

To summarise, the above-mentioned conclusions were based on old studies in which the erythrocyte components were not yet leukocyte-reduced. Furthermore, the aggregate of studies appears to point to a range for an optimal Hb and Ht: both high and lower Hb and Ht values appear to be associated with higher morbidity. It is particularly difficult to determine the lower limit of these ranges per individual patient. As already described in paragraph 5.10.1 “Transfusion policy in the ICU for acute anaemia and acute anaemia in combination with co-morbidity”, the indication for transfusion is not only based on the Hb value. Due to the supposed correlation between mortality and the difference between the post-operative and pre-operative Hb values, the absolute decrease in Hb post-operatively compared to pre-operatively should be considered as a transfusion trigger also in patients with cardiovascular disease.

Recommendations 5.4.3

1. A critical limit for anaemia cannot be determined for the individual cardiovascularly compromised patient; an optimal range of Hb values must be taken into consideration. The 4-5-6 rule (see paragraph 5.2) provides a guideline.
2. Due to the supposed correlation between mortality and the difference in post-operative versus pre-operative Hb, the absolute Hb decrease post-operative versus pre-operative should also be included in the decision whether or not to transfuse.

5.4.4 Acute anaemia and cerebral trauma

An isovolemic Hb decrease to Hb values from 4.3 to 3.4 mmol/L showed a clear decrease in cerebral function (Weiskopf 2006). In healthy volunteers, the cerebral function improved after transfusion at Hb values between 3.1 – 3.7 mmol/L to 5.0 mmol/L (Weiskopf 2005).

A retrospective study found that the mortality in trauma patients with severe cerebral injury and an Ht < 0.30 L/L was four times higher than in patients with an Ht > 0.30 L/L. However, Carlson et al demonstrated that patients had better neurological outcomes after longer periods with an Ht < 0.30 L/L (2006).

McIntyre found that in a sub-group analysis of the results from a previous randomised trial by Hebert et al (1999), for patients with moderate to severe brain trauma, there was no

difference in 30-day mortality and multiple organ failure between a liberal and a restrictive transfusion policy (2006).

In a prospective study by Zygun et al, 30 patients with severe cerebral trauma were randomised between transfusion of 2 units of erythrocyte concentrate (EC) in 2 hours at an Hb trigger of 8, 9 or 10 g/dL (5.0, 5.6 or 6.2 mmol/L). The brain-tissue oxygenation 1 hour after transfusions was the only primary endpoint for the short term. Transfusions improved the brain tissue oxygenation in 57% of the patients, with the extent of improvement correlating to the Hb increase. This improvement was not correlated to the pre-transfusion Hb. However, the brain metabolism – measured as lactate-pyruvate ratio and the brain pH as secondary endpoints – did not improve with transfusion at these Hb values (Zygun 2009). Patients with elevated cerebral pressure due to trauma or with a cerebral haemorrhage can theoretically experience damage due to elevated cerebral perfusion caused by haemodilution (Hebert 1997).

Conclusions 5.4.4

Level 2	Brain functions in healthy volunteers decreased with an isovolemic Hb decrease to 5 – 6 g/dL (3.1 – 3.7 mmol/L) and can be corrected with transfusions. <i>B Weiskopf 2005, 2006</i>
Level 2	Transfusions for cerebral trauma patients at a transfusion trigger of 8, 9 or 10 g/dL (5.0, 5.6 or 6.2 mmol/L) increased the brain tissue oxygenation in 57% of the cases. <i>A2 Zygun 2009</i>

Other considerations

In the literature – and particularly as far as retrospective studies are concerned – it appears that for patients with cerebral trauma, the initial severity of the clinical situation act as a confounder to severely cloud the conclusions when the aim is to correlate outcome on the one hand and Hb, Ht and transfusions on the other hand. Of continuing and great importance is that low Hb values with haemodilution in healthy volunteers results in decreased ability to react and memory dysfunction (Zygun 2009). It seems likely that particularly the damaged brain can be extra sensitive to an Hb < 6 mmol/L.

Recommendation 5.4.4

It is recommended for patients with cerebral trauma to implement transfusion at an Hb below 5 mmol/L with a target value of Hb 6 mmol/L.

5.4.5 Acute anaemia in combination with anaesthesia

Various anaesthetics, analgesics and sedatives have a positive, dosage-related effect on tissue oxygenation with acute anaemia (Van der Linden 2000/1998, Schou 1997, Bissonnette 1994, Lugo 1993, Mangano 1992, Shibutani 1983). Analgesia reduces the oxygen transport (the DO_2) and the oxygen consumption (VO_2) without decreasing the oxygen extraction ratio (Ickx 2000, Van der Linden 1994, Boyd 1992, Rouby 1981). Sedatives reduce the VO_2 more than the DO_2 (Mangano 1992).

General anaesthesia results in a lowering of the metabolism, which causes oxygen consumption to decrease by approximately 10%. Local anaesthetics also influence the micro-circulatory compensation as far as anaemia and hypoxia are concerned. Anaesthetics affect thermoregulation, resulting in hypothermia (also see Chapter 8: Blood-saving techniques and medicines, table 8.1.2 Anaesthesiological measures to decrease blood loss) (Johansson 1999, Bissonnette 1994).

5.4.5.1 Decreased tolerance for blood loss with acute anaemia in combination with anaesthesia

Anaesthetics also affect the compensatory mechanisms activated with acute anaemia. In the case of severe blood loss, lowering of the viscosity, regional hypoxaemia and humero-neuronal changes – that occur during acute anaemia – activate a large number of different compensatory mechanisms that result in a large tolerance of anaemia (Ickx 2000, Van der Linden 2000, 1998, Habler 1998, Trouwborst 1998, Bissonnette 1994, Boyd 1992, Trouwborst 1992, van Woerkens 1992, Van der Linden 1990).

In an awake patient with anaemia, the increase in cardiac output (CO) is caused by a combination of an increase in stroke volume and an elevation of the heart rate and an increase in oxygen extraction ratio.

In patients with acute anaemia under general anaesthesia, there is a far less pronounced increase in heartrate; the compensatory mechanism is increase in stroke volume due to an increase in preload and an increase in oxygen extraction ratio (Ickx 2000).

Under these conditions of activated compensatory mechanisms during severe blood loss, one should exercise caution with the combination of strongly negative inotropic anaesthetics or other medications. Animal studies have shown that the use of halothane is associated in a dose-dependent manner with a smaller increase in cardiac output upon haemodilution. With the use of anaesthetics, the Hb could also not be lowered as far with haemodilution, and the oxygen transport became compromised at an earlier stage (Van der Linden 2003).

Conclusions 5.4.5

Level 2	<p>It is likely that various anaesthetics, analgesics and sedatives have a dosage-related positive effect on tissue oxygenation in case of acute anaemia.</p> <p>A2 <i>Van der Linden 2000</i> B <i>Van der Linden 1998</i> C <i>Lugo 1993, Shibutani 1983, Schou 1997, Bissonnette 1994, Mangano 1992</i></p>
Level 2	<p>Anaesthetics can have a negative effect on the compensatory mechanisms activated by acute anaemia.</p> <p>A2 <i>Van der Linden 2000</i> B <i>Van der Linden 1998</i> B/C <i>Ickx 2000, Habler 1998, Trouwborst 1998, Bissonnette 1994, Boyd 1992, Trouwborst 1992, Van Woerkens 1992, Van der Linden 1990</i></p>

Other considerations

Under anaesthesia, it is hard to estimate whether a transfusion trigger needs to be adjusted up or down. On the one hand the tissue oxygen requirement and capillary bleeding tendency are often influenced favourably under anaesthesia, on the other hand anaesthesia can compromise the haemodynamic compensation for blood loss.

Recommendations 5.4.5

1. With acute anaemia under anaesthesia, one should consider **more factors than only a target Hb or Ht**. Other parameters that reflect tissue perfusion, such as oxygen delivery and oxygen consumption should preferably be included in the transfusion policy.
2. Research needs to be performed in order to formulate concrete guidelines for this situation.

5.4.6 Acute post-operative anaemia

Pathophysiology

Low Hb and Ht values are common in the post-operative phase. Usually, the oxygen transport capacity is maintained by the various compensatory mechanisms. In addition to pre-existing co-morbidity, the following factors are important post-operatively:

- Continuing action of hypnotics, sedatives and opioids may either decrease or increase oxygen consumption ;some loco-regional techniques inhibit the ability of the sympathetic nervous system to activate the compensatory mechanisms (see paragraph 5.4.6 and 8.1.2).
- Elevated oxygen requirement post-operatively due to shivering, hypothermia, pain, fever and anxiety.
- The additional morbidity due to the surgery.

The evaluation of the oxygen status, the filling state and the haematocrit of the patient can be difficult in the immediate post-operative phase due to ongoing blood loss, inter-compartmental shifts and dilution due to infusion therapy. In order to detect and treat hypoxia and tissue ischaemia at an early stage, continuous monitoring of the arterial oxygen saturation, circulatory and pulmonary parameters , frequent repeat measurements of Hb or Ht and clinical observation of the patient are essential.

Tolerance

There are no indications that a low Hb negatively influences wound healing (Bracey 1999). In a number of randomised studies on various forms of surgery and in a number of retrospective studies, it has been shown that a low Hb down to 4.5 – 5.0 mmol/L in the post-operative phase does not negatively influence general recovery (Slappendel 2001, Weber 2000, Bowditch 1999, Hogue 1998, Carson 1998, 1998, Spiess 1998, Paone 1997, Bush 1997, Doak 1995, Shahar 1991, Johnson 1991, Bracey 1999). These low values apply to young men with a normal to high-normal body weight; others (the elderly, women and patients with a low body weight) have a greater transfusion need (see table 5.13). (Paone 1997).

Although a liberal transfusion policy after hip operations in elderly patients did not result in improved rehabilitation, a restrictive policy was associated with more cardiovascular complications and a higher mortality (Foss 2009).

The same was found in a retrospective study in patients who underwent open vascular surgery and who had a history – or were thought to suffer from – coronary artery disease (Dunkelgrün 2008).

Table 5.4.6: Tolerance for post-operative anaemia

First author	Study set-up	Result	Evidence class
After CABG			
Bracey ¹	RCT: Hb trigger < 8 g/dL or < 9 g/dL (n = 428)	No difference in morbidity, mortality, fatigue or wound healing	A2
Johnson ²	RCT: Ht 0.32 versus < 0.25 L/L (n = 39)	No difference in rehabilitation	A2
Spieß ³	Observational cohort: Recovery of patient with: Ht > 34 versus 25 – 33 vs < 24% (n = 2.202)	Myocardial infarction: 8.3 vs 5.5 vs 3.6%, p < 0.03; LV dysfunction: 11.7 vs 7.4 vs 5.7%; p = 0.006 Mortality: 8.6 vs 4.5 vs 3.2%; p < 0.001	B
Doak ⁴	Retrospective observational cohort: Hb 5.8 – 17.2 g/dL + lactate measurement + myocardial VO ₂ (n = 224)	No differences Hb 60 – 70 g/L is safe	B
Paone ⁵	Retrospective observational cohort: Trigger SvO ₂ < 55%, Ht < 0.20, clinical indication (n = 100)	No complications	B
Dunkelgrün 2008	Retrospective observational cohort: open vascular surgery (N = 1211), with known or suspected coronary artery disease. Cardiac outcome measured 30 days and 5 years in relation to anaemia (Hb < 13 g/dL for men; < 12 g/dL for women); divided into mild (men: 12.2 – 13.0 g/dL; women: 11.2 – 12.0 g/dL), moderate (11.0 – 12.1 vs 10.2 – 11.1 g/dL) and severe (7.2 – 11.0 vs 7.5 – 10.1 g/dL) Multi-variant and Cox regression analysis	30 days: 74 major cardiac events (6%) 5 years: 199 (17%) Anaemia: 399 patients 30 days: mild anaemia: HR 1.8 moderate: HR 2.3 severe: HR 4.7 5 years: Mild: HR 2.4 Moderate: HR 3.6 Severe: HR 6.1	B

After orthopaedic surgery			
Carson ⁶ Hip fractures	Systemic review of literature: Trigger Hb < 8 g/dL or symptoms versus Hb < 10 g/dL	No difference in morbidity, mortality or rehabilitation	A2
Carson ⁷ Hip fractures	Retrospective cohort study: (n = 8.787)	Hb ≥ 8 g/dL well tolerated, no difference in morbidity or mortality	B
Bowditch ⁸ Primary THP	Retrospective cohort study: BMI > 30 versus < 26 (n = 80)	BMI > 30 mean BV 380 ml more (200 – 560)	B

After vascular surgery			
Bush ⁹ Major vascular surgery	RCT Trigger Hb 10 versus 9 g/dL (n = 99)	No difference in morbidity, mortality or VO ₂	A2
Shahar ¹⁰ Carotid surgery	Case study: (n = 2)	Neurological abnormalities at Hb < 5 – 6 g/dL Immediate recovery after BT	C
After urological procedures			
Hogue ¹¹ Radical prostatectomy	RCT: PAD vs ANH versus epoietin (n = 190)	Ht < 0.28 L/L significantly more peri-operative ischaemic periods, more tachycardia	A2
Foss 14 Hip operations	RCT: 120 elderly patients randomised Hb 10 vs Hb 8 g/dL	Liberal policy fewer cardiovascular complications 2 vs 10% and less mortality 0 vs 8%	A2 ?

Conclusions 5.4.6

Level 1	<p>It is likely that in young men with a normal to high-normal body weight, an Hb down to 4.5 – 5.0 mmol/L in the post-operative phase does not negatively influence general recovery.</p> <p>A2 <i>Hogue 1998, Carson 1998, Bush 1997, Johnson 1991</i> B <i>Spiess 1998, Carson 1998, Paone 1997, Doak 1995</i> C <i>Shahar 1991, Slappendel 2001, Weber 2000, Bowditch 1999</i></p>
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Level 3	<p>There are indications that the elderly, women and patients with a low body weight have a greater need for transfusions.</p> <p>B <i>Paone 1997</i></p>
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Recommendations 5.4.6

See 4-5-6 rule paragraph 5.2

5.4.7 Blood transfusion guidelines/triggers for children in the intensive care unit

Introduction

There is a large variation in the administration of erythrocyte transfusions in the paediatric intensive care units (Nahum 2004, Laverdiere 2002). The difference in patient population between the intensive care units does not provide sufficient explanation. Factors that are associated with the administration of an erythrocyte transfusion in practice are: anaemia (Hb < 6 mmol/L), cardiac or severe critical condition (PRISM score > 10 upon admission) and damage to multiple organs (Armano 2005). Furthermore, it has been described that the administration of erythrocyte transfusions to children on an intensive care unit is independently associated with a longer stay in the intensive care unit, longer duration of ventilation, longer administration of vaso-active medications and a higher mortality (Bateman 2008, Kneyber 2007). It is therefore desirable to come to a guideline based on literature.

Method

A search was performed for randomised, controlled trials (RCTs) (since 1985) or observational studies (since 2001), in which the value of a certain limit or clinically relevant outcome was compared to another policy. The quality of the studies was evaluated according to the new “Cochrane tool for assessing risk of bias”.

Scientific support

One RCT and one observational study were found. The RCT in which only “stable” severely ill children without cardiovascular problems participated, revealed that for a liberal strategy with transfusion at an Hb < 6 mmol/L the occurrence of multi-organ failure was similar to that of transfusion at an Hb < 4.4 mmol/L (Lacroix 2007). In the observational study – performed in children with extensive burn wounds (approximately 30% of total body surface area) – there was no difference in duration of stay in the hospital and mortality between transfusion at an Hb < 4.4 mmol/L or transfusion at an Hb < 6.3 mmol/L (Palmieri 2007).

Table 5.4.7

Author	Year	Study design	Level	Quality aspects*	Study population	n	Intervention	Outcome result
Lacroix ⁶	2007	RCT	A2	S, A, C, R: OK B: Blinding unclear	Critically ill children 3 – 14 years old; Hb < 9.5 g/dL	637	Hb Threshold 9.5 vs 7 g/dL	No difference in multiple organ dysfunction syndrome (MODS) or progression of MODS: absolute risk reduction 0.4% (CI – 4.6, 5.5) after 28 days of follow-up.
Palmieri ¹⁰	2007	historical cohort	B	No difference in baseline severity and other characteristics	Children with burn injury	1140	Hb ≥ 7g/dL vs Hb ≥ 10g/dL	No difference in length of stay, mortality rates; traditional group had twice the number of pulmonary complications

* S Sequence generation; A Concealment of allocation; B Blinding (of participants, personnel and outcome assessors); C Completeness of outcome data; R Selective outcome reporting

Conclusion 5.4.7

	A trigger of Hb < 4.4 or Hb < 6.3 mmol/L for erythrocyte transfusion in children does not appear to affect outcomes such as mortality, morbidity and duration of admission.
Level 2	
	A2 <i>Lacroix 2007</i> B <i>Palmieri 2007</i>

Recommendation 5.4.7

For the time being, the same policy that applies to adults can be maintained for children on the ICU. Please refer to these recommendations in paragraph 5.4.2.

5.4.8 Massive transfusion in the (premature) neonate

The erythrocyte transfusion policy for neonates – including triggers – is discussed in paragraph 4.5. This paragraph discusses a number of aspects of massive erythrocyte transfusion in neonates, because this occurs relatively often in this patient category.

The term massive transfusion in neonates applies to transfusions of > 80 mL/kg < 24 hours or for a transfusion speed > 5 mL/kg/hour. Massive transfusions are given during exchange transfusions, priming of the extracorporeal membrane oxygenation (ECMO, used for severe lung failure) and during cardiac surgery to correct congenital defects. A potassium concentration of 8 mmol/L or higher causes arrhythmias and is fatal above 10 mmol/L (Hall 1993). Due to the high potassium concentration and the low 2,3-DPG concentration in blood that has been stored for a longer period, it is recommended in these situations to use erythrocytes with a maximum storage duration of 5 days (Kreuger 1976).

Conclusion 5.4.8

	Erythrocyte components that have been stored for more than 5 days are dangerous for neonates when used in massive transfusions due to the high potassium concentration and the low 2,3-DPG concentration.
Level 3	
	C <i>Kreuger 1976, Hall 1993</i>

Recommendation 5.4.8

In the case of massive transfusions (> 80 mL/kg/ < 24 hours or administration speed > 5 mL/kg/hour) for neonates, erythrocytes < 5 days old should be selected.

5.4.9 Pre-operative surgical blood order lists

Estimating the intraoperative blood loss – which depends on the extensiveness and type of intervention – has resulted in a more accurate pre-operative ordering of blood. However, there is great heterogeneity in this practice, both between individuals within one hospital and between hospitals.

Retrospective studies, particularly in orthopaedic and cardiac surgery patients, show that women of higher age and with a low body surface area in general appear to require more transfusions (Khanna 2003). In coronary artery bypass grafting (CABG) patients, pre-existing renal insufficiency and the urgency of the operation were found to be important risk factors for a higher transfusion requirement (Shehata 2007).

Conclusion 5.4.9

Level 1	Risk groups can be defined per operation who are more likely to need transfusions. <i>A1 Shehata 2007</i> <i>B Khanna 2003</i>
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Other considerations

Due to the “Type and Screen” policy (see paragraph 3.3.2, Compatibility study) currently implemented by most hospitals, it is only necessary to order pre-operative blood components(notably erythrocytes) for a limited number of procedures and patients (for example, those with erythrocyte antibodies).

Recommendations 5.4.9

1.	The working group recommends that a hospital drafts written guidelines on when a “Type and Screen” should be performed and when pre-operative blood components should be requested or reserved. These guidelines are called pre-operative blood order lists.
2.	The implementation and the use of these pre-operative blood order lists should be evaluated periodically.

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CHAPTER 6: PLATELET AND PLASMA TRANSFUSION POLICY

Set up

This chapter discusses the platelet transfusion policy for thrombocytopenia and thrombocytopathies (6.1 through 6.5) as well as the plasma transfusion policy (6.6) for coagulopathies and thrombotic micro-angiopathies (TMAs) in non-surgical patients.

Following a general introduction about the causes of thrombocytopenia and thrombocytopathy and indications for platelet transfusion (6.1), we will then discuss the platelet transfusion policy for neonates (6.2), children (6.3) and adults (6.4). This section concludes with a paragraph about platelet transfusions in practice: refractoriness, ABO compatibility and supporting treatments (6.5).

Paragraph 6.6 discusses the plasma transfusion policy in non-surgical patients. The plasma transfusion policy for surgical patients and in the case of massive blood loss was discussed in Chapter 5. This paragraph has the same set-up as paragraphs 6.1 through 6.4, discussing the plasma transfusion policy in (non-surgical) neonates, children and adults in that order. This paragraph concludes with a sub-section on plasma component choice and blood group compatibility.

6.1 Transfusion policy in thrombocytopenia and thrombocytopathy: general introduction

A platelet count of $< 150 \times 10^9/L$, has been defined as thrombocytopenia which means that the patient has a shortage of circulating platelets. If a patient has functionally abnormal platelets, this is referred to as thrombocytopathy.

Thrombocytopenia and thrombocytopathy can result in bleeding that can vary in severity from skin bleeds to fatal bleeding. Various grades of severity are used to objectify bleeding. The WHO classification according to Miller as shown in table 6.1 is relatively simple (Miller 1981).

Table 6.1: WHO classification severity of bleeding with thrombocytopenia

Grade 1	Petechiae, mouth-nose/vaginal bleeding	No effect on Hb
Grade 2	Severe melaena, haematuria, haemoptysis, haematemesis	Results in Hb decrease $< 1.2 \text{ mmol/L/24 hours}$ without transfusion indication
Grade 3	All bleeding	EC transfusion indication
Grade 4	Fatal bleeding due to extent / localisation	Includes non-fatal cerebral or retinal bleeding with loss of function

6.1.1 Causes of thrombocytopenia and thrombocytopathy

Before starting the treatment and the transfusion policy, it is important to diagnose the cause of the thrombocytopenia or thrombocytopathy. The categories provided below form a guideline in setting the policy: see table 6.1.1.

Table 6.1.1: Pathophysiology of thrombocytopenia and thrombocytopathy

Pathophysiology	Classification	Cause
Production disorder +/- pathy	Congenital	Bone marrow disorders
		Disrupted thrombopoiesis
	Acquired	Aplastic anaemia, MDS ¹ , leukaemia
		Iatrogenic: chemotherapy / radiotherapy
Use	Micro-angiopathy	HUS
		TTP
		HELLP
		VOD ² , aGVHD ³ CAPS ⁴
		DIC
		Sepsis (low grade)
		Shock, hypoxia, haemolysis
	Thrombo-emboli	Amniotic embolism
		HIT(T) ⁵ ;
Breakdown	Immunological	Auto-immune
		Medication-mediated
		Allo-immune (PTP ⁶ , passive)
Pooling	Splenomegaly	Portal hypertension
		Malignant infiltration
		Extramedullary haematopoiesis
Haemodilution	Massive blood substitution	Trauma, surgery
Haemodilution +/- pathy	Extracorporeal circulation	ECMO ⁷ / cardiac surgery

1 MDS= myelodysplastic syndrome

2 VOD= Veno-occlusive Disease

3 GVHD=Graft Versus Host Disease

4 CAPS= Catastrophic Anti-Phospholipid Syndrome

5 HIT(T)=Heparin Induced Thrombocytopenia (and Thrombosis)

6 PTP=Post-transfusion thrombocytopenia

7 ECMO= Extra-corporeal membrane oxygenation

Perinatal

In neonates, maternal causes (eclampsia, auto or allo platelet antibodies) or foetal asphyxiation during birth can also play a role immediately post partum (< 72 hours). Congenital thrombocytopenia or thrombocytopathy – such as Glanzmann's thrombasthenia and storage pool diseases – are rare. Thrombocytopenia > 72 hours post partum is often due to infections.

A pregnant woman can suffer from mild (platelets > 80 x 10⁹/L) 'gestational' thrombocytopenia; this does not require diagnosis or treatment.

6.1.2 Indications for platelet transfusion in thrombocytopenia and thrombocytopathy

The following recommendation is based on non-comparative research and conforms to international guidelines (evidence level C/D).

Recommendation 6.1.2

When balancing the indication for a platelet transfusion, the aim of the transfusion must be compared to the cause of the thrombocytopenia or thrombocytopathy. Prevention of spontaneous bleeding, prevention of bleeding during procedures or treatment of manifest (severe) bleeding > grade 2 are possible aims of platelet transfusions in thrombocytopenia or thrombocytopathy. The working group recommends that the **indication definition according to Table 6.1.2** is used as a guideline.

Table 6.1.2: Indications for platelet transfusions in thrombocytopenia and/ or

	Acquired thrombocytopenia +/- thrombocytopathy caused by:				Congenital Thrombocytopathy
	Haemodilution	Production disorder	Splenomegaly	Breakdown/ use	
Prevention spontaneous bleeding	Yes	Yes	Consider	No	No
Prevention during procedures	Yes	Yes*	Yes	Possibility	Possibility*
Bleeding > grade 2	Yes	Yes	Yes	Yes	Yes

thrombocytopathy; see recommendation 6.2.1 and table 6.4.2 for triggers

* unless contra-indicated, see paragraph 6.4.4

6.2 Platelet transfusion policy in neonates

6.2.1 Indications for transfusion in neonates

Thrombocytopenia occurs in approximately 1% of all neonates. The incidence is highest in severely ill premature neonates (20% to 35%) (Josephson 2009, Strauss 2008, Roberts 2008). Neonates with haemolytic disease of the newborn also frequently have thrombocytopenia (van den Akker 2009). In addition to thrombocytopenia, the occurrence of platelet function abnormalities is also described mainly with prematurity in the first few days after birth (Bednarek 2009).

Not enough randomised clinical research has been performed to substantiate the optimal platelet transfusion policy in neonates. This applies both to thrombocytopenia in a clinically stable neonate and to bleeding or invasive procedures.

The platelet limit (trigger) at which the decision is made to give a platelet transfusion varies between different centres (Josephson 2009). A randomised study of premature neonates compared the use of prophylactic platelet transfusion at a transfusion trigger of < 150 x 10⁹/L

to a transfusion trigger of $< 50 \times 10^9/L$. No difference was found in the incidence of intracranial bleeding (Andrew 1993).

Conclusion 6.2.1

	Prophylactic platelet transfusion in premature neonates at a transfusion trigger of $< 150 \times 10^9/L$ does not reduce the incidence of intracranial bleeding compared to a transfusion trigger of $< 50 \times 10^9/L$.
Level 2	
	A2 Andrew 1993

Other considerations

Most guidelines advise maintaining a platelet count of $> 50 \times 10^9/L$ in neonates with manifest (intracranial) bleeding. A trigger of $> 50 \times 10^9/L$ platelets is recommended for surgical procedures in neonates (Strauss 2008, Roberts 2008). These recommendations are based on evidence level C/D. The recommended trigger for prophylactic transfusions varies per guideline and review. For the sake of uniformity, the working group advises that only the following triggers be used: 20, 50 and $100 \times 10^9/L$.

Recommendation 6.2.1

Table 6.2.1: Platelet threshold values as indication for platelet transfusion in neonates during the first month of life

Patient groups	Platelet transfusion trigger
Birth weight $< 1,500$ g and < 32 weeks	
Stable	$20 \times 10^9/L$
Sick	$50 \times 10^9/L$
Manifest bleeding / procedure	$50 \times 10^9/L$
Birth weight $\geq 1,500$ g or ≥ 32 weeks	
Sick or not sick	$20 \times 10^9/L$
Manifest bleeding / procedure	$50 \times 10^9/L$
Special circumstances	
Exchange transfusion (ET)*, before ET	$100 \times 10^9/L$
During extra-corporeal membrane oxygenation	$100 \times 10^9/L$

*If the platelet count is $< 100 \times 10^9/L$ before the ET, then give platelet transfusion half-way through the ET. If the platelet count is $< 50 \times 10^9/L$ after the ET, then also give a platelet transfusion.

6.2.2 Platelet transfusion policy for foetal/neonatal allo-immune thrombocytopenia (FNAIT)

Incidence

Foetal / neonatal allo-immune thrombocytopenia (FNAIT) is a thrombocytopenia of the foetus / neonate due to maternal IgG alloantibodies targeted against a paternal platelet-specific antigen (HPA = Human Platelet Antigen). The incidence of the antigens involved in FNAIT varies among the different races (Von dem Borne 1990, Porcelijn 1999). Caucasians are negative for HPA-1a in 2% of cases. Thrombocytopenia due to anti-HPA-1a antibodies occurs in Caucasians in approximately 1 in 1100 pregnancies (Jaegtvik 2000, Williamson 1998). Most cases of FNAIT in Caucasians are caused in the order anti-HPA-1a (~ 75%), anti-HPA-5b (~ 10 – 15%) and HPA-3a or other antigens (Porcelijn 1999).

Conclusions 6.2.2

	The incidence of antigens involved in foetal / neonatal allo-immune thrombocytopenia (FNAIT) varies between the different races. Most cases of FNAIT in Caucasians are caused by anti-HPA-1a (approx. 1 in 1100 pregnancies), anti-HPA-5b and anti-HPA-3a respectively.
Level 2	
B	<i>Porcelijn 1999, Jaegtvik 2000, Williamson 1998</i>

Bleeding tendency

The frequency of intracranial haemorrhage (ICH) with FNAIT is 11 – 25% (Mueller-Eckhardt 1989, Ghevaert 2007). Two large prospective population studies of pregnant women (25,000 in Cambridge, UK (Williamson 1998) and 10,000 in Norway (Jaegtvik 2000)) together reported two severe ICH and 1 mild ICH (1: 10,000 – 20,000 pregnancies). Most neonates show no symptoms, or only petechiae or bleeding from puncture sites. ICH occurs primarily *in utero*, mainly in the 3rd term and occasionally before the 20th week of pregnancy. (Radder 2003, Spencer 2001, Bussel 1988, Symington 2010, Kamphuis 2010). In contrast to erythrocyte allo-immunisation, 50% of first born children are affected by FNAIT (Ghevaert 2007, Spencer 2001). In most cases FNAIT is only diagnosed after the birth of an affected child. In a subsequent pregnancy of a child with the same HPA antigens, the thrombocytopenia is usually similar or more severe (Radder 2003, Bussel 1988). Following the birth of a child with ICH, the chance of ICH in a subsequent HPA-(1a) positive child is approximately 80%. If a previous child did have thrombocytopenia, but did not have ICH, the risk of ICH in a subsequent child is estimated at 7 – 13% (Radder 2003).

Conclusion 6.2.2

	There are indications that – after the birth of an HPA-1a positive child with intracranial haemorrhaging (ICH) – the risk of ICH in a subsequent HPA-1a positive child is approximately 80%. If a previous child did have thrombocytopenia but did not have ICH, the risk of ICH in a subsequent child is estimated at 7 – 13%.
Level 3	
	<i>B Radder 2003</i>

Treatment

<p>The treatment should distinguish between a neonate with unexpected thrombocytopenia and a pregnancy involving an HPA incompatibility after a previous child with FNAIT. Diagnostic tests for FNAIT should be started if a full term neonate has thrombocytopenia without indications for congenital abnormalities, infections, haemolytic disease of the neonate or auto-immune thrombocytopenic purpurae (ITP) in the mother. A bleeding tendency should be transfused according to table 6.2.1 (see paragraph 6.2.1), with the understanding that HPA compatible platelets should preferably be given whilst awaiting the results of diagnostic tests (Mueller-Eckhardt 1989). The study by Te Pas showed that in the case of thrombocytopenia of $< 50 \times 10^9/L$ in full term neonates with FNAIT, HPA matched platelets provided the fastest and most durable platelet increase. (Te Pas 2007). As a general rule, Sanquin Blood Supply always has HPA-1a and 5b negative platelet components available for unexpected cases of FNAIT. Kiefel et al demonstrated in a study of 27 neonates with FNAIT that random transfusions provide a very reasonable short-term yield and can safely be administered until HPA compatible platelets become available (Kiefel 2006). Other treatment options (corticosteroids, intravenous immunoglobulin (IVIG)) work more slowly (Allan 2007, Mueller-Eckhardt 1989, Te Pas 2007) and are not recommended as the treatment of first choice.</p> <p>If there is known HPA incompatibility and a history of FNAIT, then the mother is generally treated with intravenous immunoglobulin (IVIG) during pregnancy. This causes the platelet count of the neonate to increase and decreases the incidence of ICH to such an extent that this policy is more favourable compared to the risk of an invasive policy with intra-uterine (HPA compatible) platelet transfusions (Radder 2001, Bussel 1988, Birchal 2003, Berkowitz 2006, van den Akker 2007).</p> <p>At birth – by elective Caesarian section or vaginal delivery – HPA compatible platelets must be available (International Forum Vox Sanguinis 2007, Akker 2007).</p>
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Conclusions 6.2.2

	In the case of thrombocytopenia due to foetal / neonatal allo-immune thrombocytopenia (FNAIT), there are indications that HPA compatible platelets produce the fastest and most durable increase in platelets.
Level 3	
	<i>C Mueller-Eckhardt 1989, Te Pas 2007</i>

	In the case of thrombocytopenia $< 20 \times 10^9/L$ and/or haemorrhaging due to foetal / neonatal allo-immune thrombocytopenia (FNAIT), random transfusions whilst awaiting HPA compatible transfusions can provide a reasonable (temporary) yield without negative consequences.
Level 3	
	C <i>Allan 2007, Kiefel 2006</i>

	A non-invasive policy with maternally administered intravenous immunoglobulin (IVIG) for foetal / neonatal allo-immune thrombocytopenia (FNAIT) after a previous child with or without ICH does not increase the risk of foetal ICH or severe bleeding compared to an invasive policy of intra-uterine platelet transfusions.
Level 3	
	C <i>Radder 2001, International Forum 2007, Akker 2007</i>

Recommendations 6.2.2

1. In the treatment of foetal / neonatal allo-immune thrombocytopenia (FNAIT), a distinction should be made between a neonate with unexpected thrombocytopenia and a pregnancy after a previous child with thrombocytopenia due to FNAIT.
2. Diagnostic tests for foetal / neonatal allo-immune thrombocytopenia (FNAIT) should be started if a full term neonate has thrombocytopenia without indications for congenital abnormalities, infections, allo-immune haemolytic disease or auto-immune thrombocytopenic purpurae (ITP) in the mother. If there is a bleeding tendency, the neonate should be transfused according to table 6.2.1 (see paragraph 6.2.1). (HPA) compatible platelets should preferably be given (in other words, HPA negative for the antigen against which the antibody is targeted).
3. If HPA compatible platelets are not immediately available, random transfusions are not **contra-indicated** whilst awaiting HPA compatible transfusions.
4. In an elective delivery of a child with foetal / neonatal allo-immune thrombocytopenia (FNAIT), HPA compatible platelet transfusions concentrates should be available immediately.
5. Foetal / neonatal allo-immune thrombocytopenia (FNAIT) is preferably treated non-invasively (with intra-uterine transfusions) during the pregnancy.
6. It is recommended that doctors contact the Leiden University Medical Centre – the national centre for foetal-maternal allo-immune diseases – for advice about treatment options for FNAIT.

6.2.3 Platelet transfusion policy in neonates if the mother has an auto-immune thrombocytopenic purpura (ITP)

Incidence of auto-immune thrombocytopaenic purpurae (ITP)

Auto-immune thrombocytopaenic purpura (ITP) is a rare condition (6:100,000). A history or presentation of ITP in pregnancy occurs in approximately 1 to 5 per 10,000 pregnant women. The perinatal mortality with ITP is 0.6% (Burrows 1992). There are no maternal treatment options for ITP that also improve the thrombocytopenia in the child (Marti-Carvajal 2009).

Bleeding complications in auto-immune thrombocytopaenic purpura (ITP)

In contrast to thrombocytopenia due to foetal / neonatal allo-immune thrombocytopenia (FNAIT), severe *in utero* bleeds have not been described with IPT of the mother. Neonatal thrombocytopenia of $< 50 \times 10^9/L$ is found in 9 – 15% of newborns. This is not related to the maternal platelet count (Valat 1998, Payne 1997, Garmel 1995, Burrows 1992, Samuels 1990, Kaplan 1990). The risk of ICH is present mainly during or after birth, with a risk of 0 – 1.5%. The advice is to aim for a non-traumatic birth (George 1996, Cook 1991). After birth, the platelet count decreased during the first week in 30% of the children, thereby increasing the risk of bleeding (Valat 1998, Letsky 1996, Burrows 1993). Neonatal thrombocytopenia $< 50 \times 10^9/L$ during the course of a previous pregnancy predicts a similar degree of thrombocytopenia in a subsequent pregnancy in approximately 70% of cases (Christiaens 1997). Thrombocytopenia in a child can sometimes persist for months (Webert 2003). Treatment with IVIG, alone or in combination with (methyl) prednisolone, may be necessary. The treatment of newborns with passive ITP has not been described in large series or controlled studies. Practice guidelines mention treatment with platelet transfusions, intravenous immunoglobulin (IVIG) and prednisolone – alone or in combination – depending on the severity of the thrombocytopenia and presence of bleeding (Gernsheimer 2007). Platelet transfusions are given in combination with IVIG, particularly in the case of severe thrombocytopenia and/or bleeding (George 1998, Burrows 1992).

Conclusions 6.2.3

	Auto-immune thrombocytopaenic purpura (ITP) in the mother causes neonatal thrombocytopenia $< 50 \times 10^9/L$ in 9 – 15% of children; this is not related to the maternal platelet count and does not improve with maternal treatment.
Level 3	
	C <i>Burrows 1992, Valat 1998, Payne 1997, Garmel 1995, Samuels 1990, Kaplan 1990, Mart-Carvajal 2009</i>

Level 3	In 30% of children born to a mother with IPT, the platelet count will decrease in the first week after birth thus increasing the risk of bleeding.
	C <i>Valat 1998, Letsky 1996, Burrows 1993</i>

Level 4	Experts postulate that platelet transfusions – alone or in combination with intravenous immunoglobulin (IVIg) – are indicated in neonates with passive ITP depending on the severity of the thrombocytopenia and the presence of bleeding.
	D <i>Gernsheimer 2007</i>

Recommendations 6.2.3

1. If the mother has a history of auto-immune thrombocytopenic purpura (ITP), the aim should be to have a non-traumatic birth, as far as possible.
2. In a neonate born to a mother with IPT, the platelet count should be checked for at least 5 days post partum to check for the occurrence of thrombocytopenia.
3. Intravenous immunoglobulin (IVIg) is recommended as the treatment of choice for neonates with passive idiopathic auto-immune thrombocytopenia (ITP) and platelet count $< 50 \times 10^9/L$ without clinical bleeding; to be combined with (methyl) prednisolone in the case of persistent thrombocytopenia.
4. Platelets transfusion – alone or in combination with intravenous immunoglobulin (IVIg) – is recommended for neonates with passive IPT and $< 20 \times 10^9/L$ platelets and/or bleeding.

6.2.4 Dosage and volume of platelet transfusions in neonates

There have been no randomised clinical studies on the optimal dosage of platelet concentrate and the effects of various platelet components on neonates. Most studies and guidelines advise a dosage of $10 \times 10^9/kg$ (Strauss 2008). Others suggest giving higher dosages, namely $20 \times 10^9/kg$ (Roberts 2008). In order to reduce donor exposure, the advice is to use platelets obtained from one donor instead of a pooled platelet component (Roberts 2008).

Conclusions 6.2.4

Level 4	There have been no randomised clinical studies on the optimal dosage for platelets in neonates; experts recommend dosages of both $10 \times 10^9/kg$ and $20 \times 10^9/kg$
	D <i>Strauss 2008, Roberts 2008</i>

	In order to reduce donor exposure, the advice is to use platelets obtained from one donor instead of a pooled platelet component.
Level 4	
	<i>D Roberts 2008</i>

Other considerations

In the Netherlands, there are three platelet components that can be supplied for neonates: platelets in plasma (approx. $1 \times 10^9/\text{mL}$), in storage solution (approx. $0.8 \times 10^9/\text{mL}$) and hyperconcentrated (approx. $5 \times 10^9/\text{mL}$) in plasma. There has been no research to determine which platelet component should preferably be administered to neonates.

Recommendations 6.2.4

1. It is recommended to administer platelets to neonates at a dosage of **at least** $10 \times 10^9/\text{kg}$ body weight.
2. For a platelet transfusion in neonates, the platelet component for transfusion should be obtained from one donor.
3. **Further research is essential, for example on the optimum dosage and/or the various platelet components in the platelet transfusion policy in neonates.**

6.3 Platelet transfusion policy for thrombocytopenia and thrombocytopathy in children (> 1 month after full term birth)

The correct platelet transfusion policy can only be selected once the cause of the thrombocytopenia or thrombocytopathy has been determined and only then can the role of platelet transfusions be determined.

6.3.1 Platelet transfusion policy in the case of congenital thrombocytopenia and thrombocytopathy in children

Congenital thrombocytopenia and thrombocytopathy are a rare cause of an increased bleeding tendency in children. As a result, guidelines for its treatment are mostly based on case reports, small case series and expert opinion (Bolton-Maggs 2006).

Treatment options consist of anti-fibrinolytic agents (tranexamic acid), desmopressin, recombination factor VIIa and platelet transfusions. The advice is to maintain a restrictive policy for platelet transfusions because of the risk of alloimmunisation. Platelet transfusions should only be given in case of severe bleeding or if the other treatment options are not effective (Almeida 2003, Bolton-Maggs 2006).

Consideration

Congenital thrombocytopathic diseases are rare. It can be considered to select pre-emptive HLA identical donors for this small group in case of elective procedures that require platelet transfusions.

Conclusion 6.3.1

	In the case of congenital thrombocytopenia and thrombocytopathy, platelet transfusions are only indicated in the case of severe bleeding and if other treatment options for the relevant condition – such as tranexamic acid, desmopressin and recombinant factor VIIa – are not effective.
Level 3	
	C Bolton-Maggs 2006

Recommendations 6.3.1

1. In the case of congenital thrombocytopenia and thrombocytopathy, it is advisable to limit the administration of platelet transfusions because of the development of alloantibodies.
2. In the case of congenital thrombocytopenia and thrombocytopathy, platelet transfusions are only indicated in the case of severe bleeding and if other treatment options for the relevant condition are not effective.

6.3.2 Children with thrombocytopenia due to leukaemia (treatment)

Prophylactic platelet transfusions

There are few studies that provide sufficient evidence for a prophylactic platelet transfusion policy in children with leukaemia. Three prospective randomised trials have compared prophylactic to therapeutic platelet transfusions in children with leukaemia (Higby 1974, Murphy 1982, Solomon 1978). The study by Murphy involved 56 children with **acute lymphatic leukaemia** (ALL) or **acute non-lymphocytic leukaemia** (ANLL) (Murphy 1982). A meta-analysis of these studies showed no difference in overall mortality, mortality due to bleeding, remission, the frequency of blood transfusions or the duration of hospital admission (Stanworth 2004). Prophylactic platelet transfusions were associated with a risk reduction of 0.49 (95% CI, 0.28 – 0.87) for major and severe bleeding (Stanworth 2004). However, the three studies were performed more than 20 years ago. In those days, aspirin was still widely used to combat pain and fever, which may have affected the results. The patient numbers in this study were also small.

Randomised studies of both children and adults show that the limit of $10 \times 10^9/L$ platelets is just as safe as $20 \times 10^9/L$ for preventing mortality and severe bleeding in stable patients with leukaemia or after stem cell transplantation (Stanworth 2004, Heckman 1997, Rebullá 1997, Zumberg 2002). The study by Zumberg was performed on children and adults (aged 3 – 70 years) after stem cell transplantation. The studies by Heckman and Rebullá were performed on adults following the diagnosis of leukaemia and subsequent treatment with chemotherapy.

In the case of sepsis, hyperleukocytosis, very rapid decrease in platelet count or other abnormalities in haemostasis, the American Society of Clinical Oncology (ASCO) and the British Committee for Standards in Hematology (BCSH) advise to increase the trigger to $20 \times 10^9/L$, without supporting this with any results from studies (BSCH 2004, ASCO 2001).

Conclusions 6.3.2

	The current prophylactic transfusion policy is based on older studies with small numbers of patients and possibly biased by aspirin use. There is no evidence of any benefit from the prophylactic transfusion of platelets in children with leukaemia without powerful chemotherapy or stem cell transplantation in terms of overall mortality, mortality due to bleeding, remission, the frequency of blood transfusions and the duration of hospital admission. Prophylactic platelet transfusions were associated with a risk reduction of 0.49 (95% CI, 0.28 – 0.87) for major and severe bleeding. <i>A1 Stanworth 2004</i>
Level 1	

	In children in a stable situation being treated with high dose chemotherapy for leukaemia or after stem cell transplantation, a platelet transfusion trigger of $10 \times 10^9/L$ is as safe as $20 \times 10^9/L$ in preventing mortality and severe bleeding. <i>A2 Heckman 1997, Rebullá 1997, Zumberg 2002</i>
Level 1	

	In the case of sepsis, hyperleukocytosis, a very rapid drop in platelet count or other abnormalities in haemostasis, experts advise to increase the transfusion trigger for prophylactic platelet transfusions from $10 \times 10^9/L$ to $20 \times 10^9/L$. <i>D Schiffer 2001, Gibson 2004</i>
Level 4	

Recommendations 6.3.2

1. For children in a stable situation with leukaemia being treated with high dose chemotherapy or after stem cell transplantation, the working group advises a prophylactic platelet transfusion trigger of $10 \times 10^9/L$.
2. In children with leukaemia, being treated with high dose chemotherapy or after stem cell transplantation and with an increased risk of bleeding due to platelet use – as is the case of sepsis, hyperleukocytosis, a very rapid drop in platelet count or other abnormalities in haemostasis – a platelet transfusion trigger of $20 \times 10^9/L$ is advised.

6.3.3. Platelet transfusion policy for severe aplastic anaemia (SAA) in children

There is no literature available about platelet transfusions in young children with severe aplastic anaemia (SAA). There is 1 retrospective analysis performed on 25 adolescents and adults (aged 15 – 76 years) (Sagmeister 1999). It appeared safe to follow a restrictive prophylactic platelet transfusion policy in patients with SAA. A transfusion trigger of $< 5 \times 10^9/L$ is recommended for stable patients and a transfusion trigger of $< 10 \times 10^9/L$ is recommended for sick patients with infections, fever or sepsis. (Sagmeister 1999). The BCSH (British Committee for Standards in Haematology) advises to maintain a restrictive policy for platelet transfusions in children with severe aplastic anaemia (Gibson 2004). However, during treatment with anti-thymocyte globulin (ATG), a transfusion trigger of $20 \times 10^9/L$ (BCSH 2004) or $30 \times 10^9/L$ (Marsh 2009) is recommended for prophylactic platelet transfusion. This is due to the increased consumption of platelets during ATG administration (Gibson 2004). It is advisable not to administer the platelets and ATG simultaneously (Marsh 2009).

Conclusions 6.3.3

	There are indications that it is safe to follow a restrictive prophylactic platelet transfusion policy in adolescents and adults (15 – 76 years) with severe aplastic anaemia (SAA). A trigger of $5 \times 10^9/L$ is recommended for stable patients and a trigger of $10 \times 10^9/L$ is recommended for sick patients with infections, fever or sepsis.
Level 3	
	<i>C Sagmeister 1999</i>

	Experts advise a restrictive policy for platelet transfusions in children with severe aplastic anaemia (SAA). However, during treatment with anti-thymocyte globulin (ATG), a transfusion trigger of $20 \times 10^9/L$ – preferably $30 \times 10^9/L$ – is recommended for prophylactic platelet transfusion.
Level 4	
	<i>D Gibson 2004, Marsh 2009</i>

Other considerations

There are no studies on children with SAA. Therefore, the same recommendations that apply to adults are made for the time being.

Recommendations 6.3.3

1. In stable children with severe aplastic anaemia (SAA), it is recommended to maintain a restrictive prophylactic platelet transfusion policy and maintain a trigger of – for example – $5 \times 10^9/L$.
2. In children with severe aplastic anaemia (SAA) and infections, fever or sepsis, a platelet transfusion trigger of $10 \times 10^9/L$ is advised for prophylactic platelet transfusions.
3. In children being treated with anti-thymocyte globulin (ATG), prophylactic platelet transfusions are advised at a platelet transfusion trigger of $20 \times 10^9/L$.

6.3.4 Platelet transfusion policy for thrombocytopenia due to accelerated breakdown or consumption in children

6.3.4.1 Auto-immune thrombocytopaenic purpura (ITP)

In the case of auto-immune thrombocytopaenic purpura (ITP), autoantibodies cause the accelerated breakdown of both transfused platelets and autologous platelets. The treatment of ITP consists of suppressing the formation of autoantibodies or interfering with the breakdown of platelets by administering corticosteroids, intravenous immunoglobulin, rituximab or by performing a splenectomy. Platelet transfusions are only indicated for severe bleeding. They are then combined with a high dose intravenous immunoglobulin (IVIg) (Spahr 2008). There is no literature available about the effect of this therapy in children.

6.3.4.2 Thrombocytopenia due to disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) can occur during sepsis, in the presence of malignancies, in case of intoxication, haemolysis and severe trauma. In DIC, the clotting system is activated. This results in increased use of clotting factors and platelets. International guidelines advise to give prophylactic platelet transfusions to children with DIC at a platelet count of $< 20 \times 10^9/L$, although this is not supported by evidence (Gibson 2004).

6.3.4.3 Thrombotic thrombocytopaenic purpura (TTP), haemolytic uraemic syndrome (HUS) and heparin-induced thrombocytopenia (HIT(T))

In most cases, the administration of platelet transfusions for Thrombotic thrombocytopaenic purpura (TTP), haemolytic-uraemic syndrome (HUS) and heparin-induced thrombocytopenia (and thrombosis) (HIT(T)) results in very little yield and may even result in a deterioration of the clinical situation by promoting a tendency of developing thrombosis. However, platelet transfusions have proven successful for life threatening bleeding in TTP, HUS and HIT(T), with transfusions preferably being given after treatment for the underlying cause has been started (Gibson 2004).

Conclusions 6.3.4

	In the case of auto-immune thrombocytopaenic purpura (ITP), the administration of platelet transfusions generally has no use.
Level 3	Platelet transfusions are only indicated for severe bleeding. They are then combined with a high dose intravenous immunoglobulin (IVIG).
	<i>C Spahr 2008</i>

	Experts are of the opinion that – for children with thrombocytopenia due to disseminated intravascular coagulation (DIC) – prophylactic platelet transfusions should be given at a platelet trigger of $20 \times 10^9/L$.
Level 4	
	<i>D Gibson 2004</i>

	Experts are of the opinion that the administration of platelet transfusions for thrombotic thrombocytopaenic purpura (TTP), haemolytic-uraemic syndrome (HUS) and heparin-induced thrombocytopenia (and thrombosis) (HIT(T)) results in very little yield and may even result in deterioration of the clinical situation. In the case of life threatening bleeds due to TTP, HUS or HIT(T) platelet transfusions can halt the bleeding.
Level 4	
	<i>D Gibson 2004</i>

Recommendations 6.3.4

1. For thrombocytopenia due to increased breakdown or consumption in the case of auto-immune thrombocytopaenic purpura (ITP), disseminated intravascular coagulation (DIC), thrombotic thrombocytopaenic purpura (TTP), haemolytic-uraemic syndrome (HUS) or heparin-induced thrombocytopenia (and thrombosis) (HIT(T)), the transfusion of platelets is only indicated for life threatening bleedings.
2. For life threatening bleedings in the case of auto-immune thrombocytopaenic purpura (ITP), the advice is to administer platelet transfusions in combination with intravenous immunoglobulin (IVIG).
3. For children with thrombocytopenia due to disseminated intravascular coagulopathy (DIC), one can consider prophylactic platelet transfusions at a platelet trigger of $20 \times 10^9/L$.

6.3.5 Platelet transfusion policy for thrombocytopenia due to invasive procedures in children

There are insufficient study data available concerning the trigger for transfusion of platelets for children with thrombocytopenia undergoing invasive procedures, such as bone marrow biopsy, lumbar puncture, insertion of central venous catheters, biopsies or major surgery. This does not apply to lumbar punctures in children with leukaemia which will be discussed separately in the paragraph below (6.3.5.1). For the other invasive and surgical procedures a general trigger of $50 \times 10^9/L$ is accepted. This limit is based on a study by Bishop et al in which 95 adult patients underwent a total of 167 operations and invasive procedures (Bishop 1987). . In the case of neurosurgery, cardiopulmonary surgery and intracranial surgery, one

usually aims for a platelet count $> 100 \times 10^9/L$ (see paragraph 6.4: adults). According to American and English guidelines, a bone marrow biopsy can be performed without platelet transfusion (Schiffer 2001, Gibson 2004).

Conclusion 6.3.5

	With the exception of children with leukaemia, who underwent lumbar puncture, there are no paediatric data available on the transfusion limit for platelets in children with thrombocytopenia undergoing invasive procedures.
Level 4	

Other considerations

As there is no evidence for other invasive procedures, the recommendations for adults can be followed (see paragraph 6.4).

Recommendation 6.3.5

There is insufficient literature available concerning the platelet transfusion policy for invasive procedures and surgical procedures other than lumbar punctures in children with thrombocytopenia. Therefore, the working group advises that, for the time being, the recommendations for adults should be followed for such procedures (see paragraph 6.4).

6.3.5.1 Platelet transfusion policy for a lumbar puncture (LP) in the presence of thrombocytopenia

Most lumbar punctures (LP) with thrombocytopenia are performed on children with leukaemia for diagnosis of any meningeal metastases and/or for the administration of intrathecal medication.

The complications that can occur are related to bleeding. Spinal and/or intracranial bleeding with the risk of neurological damage is rare and also occurs after LPs in children with normal platelet counts and intact coagulation.

In addition, there is a risk of introducing leukaemic cells into the central nervous system (CNS) if there are blasts present in the peripheral blood.

There are no prospective studies that examine the platelet trigger when performing LPs in children. There are retrospective, observational studies and case series. The largest observational studies on the occurrence of complications with LP and thrombocytopenia were performed in children with **acute lymphatic leukaemia** (ALL) (Gaydos 1962).

Van Veen et al performed a retrospective review of 226 ALL patients; 135 patients had a platelet count $< 50 \times 10^9/L$ and 129 had an LP, of which 72 without transfusion (9 patients had a platelet count of $< 10 \times 10^9/L$, 22 patients with $10 - 20 \times 10^9/L$ and 41 patients with $21 - 50 \times 10^9/L$). There were no complications (Van Veen 2004). These findings confirm previous findings by Howard et al: stable children with ALL without blasts in the peripheral blood and without severe spinal or cranial bleeding can safely undergo LP at a platelet count of $> 10 \times 10^9/L$ (Howard 2002, 2000).

Gajjar et al compared the chances of survival in 546 children with ALL with traumatic and non-traumatic LPs. The survival was worse in children with a traumatic diagnostic LP and

blasts in the peripheral blood (Gajjar 2000). Howard et al analysed the risk factors for a traumatic LP based on multiple regression analysis of 5609 LPs in 956 children with ALL. Fewer traumatic punctures occurred at a platelet trigger $> 50 - 100 \times 10^9/L$ (Howard 2002).

Conclusions 6.3.5

	There are indications that – for children with acute lymphatic leukaemia (ALL) and blasts in the peripheral blood – at a platelet count of $> 50 - 100 \times 10^9/L$, there are fewer iatrogenic metastases of the leukaemia in the central nervous system (CNS) as a result of a traumatic lumbar puncture (LP).
Level 3	
	<i>C Gajjar 2000, Howard 2002</i>

	There are indications that in children with acute lymphatic leukaemia (ALL), without blasts in the peripheral blood and who do not have severe spinal or cranial bleeding, a lumbar puncture can be performed safely at a platelet count of $> 10 \times 10^9/L$.
Level 3	
	<i>C Howard 2000, 2002; Van Veen 2004</i>

Other considerations

Other factors also play a role, particularly whether general anaesthetic is used or not and the experience of the surgeon. A higher platelet transfusion trigger can be considered if general anaesthesia cannot be used when performing an LP in children (please refer to the Guideline PSA for children in locations outside the OR (NVA, NVK 2010) for the accessory conditions concerning the use of anaesthesia and/or procedural sedation and/or analgesia (PSA) when performing an LP) and/or if the physician who performs the LP is inexperienced.

Recommendations 6.3.5

1. A platelet count of $> 50 \times 10^9/L$ is recommended for a lumbar punctures (LP) in children with acute lymphatic leukaemia (ALL) with blasts in the peripheral blood.
2. In stable children with acute lymphatic leukaemia (ALL), without blasts in the peripheral blood, a lumbar puncture (LP) can be performed safely at a platelet count of $> 10 \times 10^9/L$.
3. A higher platelet transfusion trigger should be considered if general anaesthesia cannot be used on a child undergoing a lumbar puncture (LP) and/or if the physician who performs the LP is inexperienced. Please refer to the Guideline PSA for children in locations outside the OR (NVA, NVK 2010) for the accessory conditions concerning the use of anaesthesia and/or procedural sedation and/or analgesia (PSA) when performing an LP.

6.3.6 Dosage of platelets in children

In general, the dosage for children is calculated based on the body weight, using the formula $5 - 10 \times 10^9$ platelets/kg. There is limited data available about the effects of different doses of platelets on the transfusion outcomes in children (Roy 1973, Norol 1998).

In 1973, Roy et al compared two doses (0.2 versus 0.4×10^{10} platelets/kg) in children with **acute lymphatic leukaemia** (ALL). The yield after 1 hour was 17 and $25 \times 10^9/L$ respectively. The incidence of bleeding was the same (Roy 1973).

In 1998, Norol et al examined three different dosages of platelets (medium group: 0.1×10^{11} platelets/kg), high group: 0.15×10^{11} platelets/kg and extra high group: 0.22×10^{11} platelets/kg) in 13 children with thrombocytopenia following bone marrow transplantation. There was a clear-dose effect relationship: the higher the dosage, the greater the increase in the number of platelets 12 hours after transfusion. The transfusion interval was 2.5 days, 3.4 days and 4.4 days respectively. This study did not examine the risk of bleeding (Norol 1998).

Conclusions 6.3.6

	In children with acute lymphatic leukaemia (ALL) who were given 0.2×10^{10} platelets/kg or 0.4×10^{10} platelets/kg, the yield after 1 hour was $17 \times 10^9/L$ and $25 \times 10^9/L$ respectively. The incidence of bleeding was the same.
Level 3	
	<i>B Roy 1973</i>

Level 3	There are indications that transfusion of a higher dose of platelets in children with thrombocytopenia following bone marrow transplantation results in a greater increase in the number of platelets 12 hours after transfusion and a longer interval to the next transfusion.
	<i>B Norol 1998</i>

Recommendation 6.3.6

The old dosage advice for platelet transfusion in children – namely one paediatric unit of 50 to $100 \times 10^9/10$ kg ($= 5 - 10 \times 10^9/kg$) is maintained.

6.4 Platelet transfusion policy in adults

6.4.1 Platelet transfusion policy for congenital thrombocytopenia / thrombocytopathy

Congenital platelet function disorders are rare conditions and usually have already been diagnosed and treated by the paediatrician. In the case of congenital thrombocytopenia / thrombocytopathy, transfusions for the prevention of spontaneous bleeding are not indicated due to the risk of allo-immunisation (Fujimori 1999). However, transfusions may be necessary in the case of bleeding, refractory to other treatments such as desmopressin

(DDAVP), tranexamic acid and activated recombinant factor VIIa and for elective procedures, if medicinal correction of the bleeding time produces insufficient effect (Bolton-Maggs 2006, Almeida 2003, 1996, Manco-Johnson 2001, 1996, Mannucci 1997, Weiss 1996, Fujimori 1999).

6.4.1.1 Von Willebrand Disease (vWD)

Von Willebrand Disease (vWD) is the most common congenital coagulation abnormality with a frequency of approximately 1%. This is a quantitative (types 1 and 3) or qualitative (type 2) defect of the von Willebrand factor (vWF). vWD type 1 is most common and is treated with desmopressin and/or vWF + FVIII (Haemate P). There are many sub-types of type 2 vWD and desmopressin is contra-indicated for type 2B because it can cause platelet aggregation and thrombocytopenia. Type 2A is treatable with desmopressin. Desmopressin is not effective for the very rare type 3. Platelet transfusions are very rarely necessary (Mannucci 1997).

Conclusions 6.4.1

Level 3	<p>Transfusions for the prevention of spontaneous bleeding are not indicated for congenital thrombocytopenia / thrombocytopathy due to the risk of allo-immunisation resulting in the patient becoming refractory for platelet transfusions.</p> <p><i>C Fujimori 1999, Bolton-Maggs 2006</i></p>
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Level 3	<p>For patients with a congenital thrombocytopathy / thrombocytopenia, platelet transfusions are only indicated for a procedure or in case of bleeding ,if medicinal treatment is insufficient.</p> <p><i>C Bolton-Maggs 2006, Almeida 2003, Manco-Johnson 2001, 1996, Mannucci 1997, Weiss 1996, Fujimori 1999</i></p>
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Other considerations

Allo-immunisation is extremely undesirable in patients with congenital thrombocytopathy or thrombocytopenia, since platelet transfusions may be necessary in the event of severe acute bleeding. The pre-emptive selection of HLA compatible platelets should be considered for an elective procedure requiring platelet transfusions.

Recommendations 6.4.1

1.	For patients with a congenital thrombocytopathy and/or thrombocytopenia the advice is to limit the administration of platelet transfusions as much as possible due to the development of alloantibodies, which can destroy the effect of platelet transfusions.
2.	Prophylactic platelet transfusions are not indicated in case of congenital thrombocytopenia and thrombocytopathy.
3.	In congenital thrombocytopenia and thrombocytopathy platelet transfusions are indicated for procedures and in case of severe bleeding if other treatment modalities are not effective.

6.4.2 Platelet transfusion policy for thrombocytopenia due to acquired production disorders

This includes all acquired production disorders such as aplastic anaemia, myelodysplasia, suppression due to leukaemic infiltration and iatrogenic bone marrow inhibition due to chemotherapy and/or radiotherapy.

6.4.2.1 Platelet transfusions for the prevention of spontaneous bleeding versus therapeutic transfusions

Three randomised studies compared prophylactic and therapeutic transfusions in leukaemia patients (Murphy 1982, Solomon 1978, Highy 1974). In a meta-analysis of these older randomised studies, Stanworth (2004) concluded that there was fewer large and severe bleeding when prophylactic transfusions were given. One observational study of autologous stem cell transplant patients with transient thrombocytopenia only administered therapeutic transfusions. Mild to moderately severe bleeding occurred in 19% of the patients. Transfusions were not required for 30% of the patients (Wandt 2006). The same group found a higher incidence of cerebral haemorrhage in the therapeutic group in a randomised study of 161 AML patients with thrombocytopenia due to induction or consolidation therapy (Wandt 2009).

Conclusions 6.4.2.1

Level 1	Fewer severe haemorrhages occurred with the use of prophylactic platelet transfusions in leukaemia patients. <i>A1 Stanworth 2004</i>
Level 3	A therapeutic transfusion policy may be safe in furthermore healthy patients with transient thrombocytopenia. This does not apply to AML treatment. <i>C Wandt 2006, A2 Wandt 2009</i>

Other considerations

The meta-analysis by Stanworth based their conclusion – that prophylactic use of platelet transfusions resulted in fewer severe haemorrhages – mainly on older studies in which the use of aspirin cannot be ruled out. Wandt et al (Wandt 2006) studied patients following autologous stem cell transplantation: these patients are less sick and have only transient thrombocytopenia compared to the patients from the meta-analysis by Stanworth (Stanworth 2004).

Recommendation 6.4.2.1

Prophylactic platelet transfusions are recommended for patients with thrombocytopenia due to an acquired production disorder. **A therapeutic transfusion policy can be considered for furthermore healthy patients experiencing a short period of pancytopenia.**

6.4.2.2 The platelet transfusion trigger for prophylactic platelet transfusions for the prevention of spontaneous haemorrhage

The only study on the relationship between the platelet count and spontaneous bleeding is a study in 20 non-transfused patients in whom the loss of erythrocytes in the faeces was measured in relation to the platelet count. The findings were as follows (Slichter 1978):

- at a platelet count of $< 5 \times 10^9 /L$: $50 \text{ mL} \pm 20 \text{ mL/day}$
- at a platelet count of $5 - 9 \times 10^9 /L$: $9 \text{ mL} \pm 7 \text{ mL/day}$
- at a platelet count of $10 - 25 \times 10^9 /L$ $< 5 \text{ mL/day}$

The standard platelet transfusion trigger in the United States is $20 \times 10^9 /L$. Observational cohort studies reported that transfusion triggers lower than $20 \times 10^9 /L$ did not result in a higher incidence and/or increased severity of bleeding (Slichter 1978, Gaydos 1962, Gmur 1991, Wandt 1998, Sagmeister 1999, Gil-Fernandez 1995, Navarro 1998, Lawrence 2001, Callow 2002, Nevo 2007a).

A retrospective analysis of patients treated with a myelo-ablative allogeneic haematopoietic stem cell transplant compared patients who were transfused at a platelet transfusion trigger of $10 \times 10^9 /L$ with a historic group of 170 patients transfused at a trigger of $20 \times 10^9 /L$. In the lower trigger group there were significantly more patients with deep thrombocytopenia $< 10 \times 10^9 /L$ (19% versus 7%). In both cohorts, deep thrombocytopenia was associated with higher mortality; however, this was not due to bleeding (Nevo 2007). In a retrospective study in **acute myeloid leukaemia** (AML) patients, Kerkhoffs et al found an association between poor post-transfusion yields and a higher non-bleeding related mortality. (Kerkhoffs 2008). However, it was not demonstrated that increasing the platelet transfusion threshold to $20 \times 10^9 /L$ had any effect on this non-bleeding related mortality. The recent PLatelet transfusion And DOsis (PLADO) study – a randomised study on dosage – showed that there was a 25% risk of bleeding on the same day the platelet count was $< 5 \times 10^9 /L$. There was no correlation between the platelet count and the bleeding risk at a platelet count $\geq 10 - 80 \times 10^9 /L$ (Slichter 2010).

Four randomised studies in patients treated because of a haemato-oncological malignancy and/or stem cell transplantation compared transfusion triggers of $10 \times 10^9 /L$ and $20 \times 10^9 /L$ (Heckman 1997, Rebullá 1997, Zumberg 2002) and $10 \times 10^9 /L$ and $30 \times 10^9 /L$ (Dietrich 2005). None of the studies showed any difference in incidence of bleeding. The same 3 studies (Heckman 1997, Rebullá 1997, Zumberg 2002) were included in the Cochrane analysis in 2004. This meta-analysis concluded that equivalence between a trigger of 10 and 20 or 30 $\times 10^9 /L$ had not (yet) been demonstrated (Stanworth 2004).

American (ASCO), British (BCSH) and Dutch (CBO) guidelines advise increasing the platelet transfusion trigger to $20 \times 10^9 /L$ in clinical situations that can promote bleeding (sepsis, fever, high blast count, extensive endothelial damage, recent bleeding). This has not been supported by research (ASCO 2001, BCSH 2003, CBO 2004). At least 3 analyses of large study populations on the risk of bleeding show that it is not the platelet count but the occurrence of a bleeding in the preceding five days that is the most important risk factor for bleeding. (Callow 2002, Nevo 2007, Slichter 2004). However, in practice, the transfusion threshold is increased to $20 \times 10^9 /L$ almost everywhere in the case of a severe bleeding. This can be the reason that bleeding occurs primarily at higher platelet counts in these analyses.

The optimal threshold level for platelet transfusions has not been examined for patients who are taking anti-coagulant medication.

Table 6.4.2: Literature summary of prophylactic transfusion triggers in adults with thrombocytopenia due to a production disorder

First author	Number of patients	Disease	Intervention/measure of outcome	Result	Evidence class
Rebulla ¹	255	Acute Myeloid Leukaemia (median age in years: 51; extremes 16 – 76)	Transfusion parameter < 10 x 10 ⁹ /l vs < 20 x 10 ⁹ /l primary frequency severe bleeds	No difference in severe bleeds 21.5 % lower transfusion requirement	A2
Heckman ²	78	Acute leukaemia	Transfusion parameter < 10 x 10 ⁹ /l vs < 20 x 10 ⁹ /l Bleeding episode Number of platelet transfusions	No difference in number of bleeding episodes Higher use of transfusions in < 20 x 10 ⁹ /l group	A2
Wandt ³	105	Acute myeloid leukaemia	Transfusion parameter = 10 x 10 ⁹ /l vs = 20 x 10 ⁹ /l Bleeding episode Number of platelet transfusions	No relationship between severe bleeding and platelet count Fewer platelet transfusions in < 10 x 10 ⁹ /l group	B
Gmur ⁴	102	Acute leukaemia	Transfusion parameter = 5 x 10 ⁹ /l vs = 10 x 10 ⁹ /l vs = 20 x 10 ⁹ /l *both groups had higher risk profile	31 bleeding episodes in 1.9 % of 5 x 10 ⁹ /l group 0.07 % of 10 x 10 ⁹ /l group	B
Gil-Fernandez ⁵	190	Bone marrow transplantation	Comparison of transfusion regime with respect to severe bleedings Number of platelet transfusions	No difference between 10 or 20 x 10 ⁹ /l groups Fewer platelet transfusions	B

Conclusions 6.4.2.2

Level 2	<p>In randomised studies– usually performed in patients with standard risk – there was no difference in bleeding complications at a platelet transfusion trigger of 10 x 10⁹/L versus 20 or 30 x 10⁹/L. However, the studies were too small to conclude that the various triggers are equal.</p> <p><i>B Rebulla 1997, Heckman 1997, Zumberg 2002, Dietrich 2005</i></p>
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Level 3	<p>In patients following allogeneic myelo-ablative haematopoietic stem cell transplantation, maintaining a platelet transfusion trigger of 10 x 10⁹/L was associated with significantly more periods of deep thrombocytopenia than when a platelet transfusion trigger of 20 x 10⁹/L was maintained (19% versus 7%). In both cohorts, deep thrombocytopenia was associated with higher mortality, however, this was not due to bleeding.</p> <p><i>C Nevo 2007</i></p>
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Level 4	<p>In clinical situations that can promote bleeding (sepsis, fever, high blast count, extensive endothelial damage) consensus guidelines advise increasing the platelet transfusion trigger to $20 \times 10^9/L$. This is not supported by research.</p> <p><i>D ASCO 2001, BCSH 2003, CBO 2004</i></p>
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Level 3	<p>There are indications that patients who have experienced severe bleeding in the preceding 5 days are at increased risk of recurrent bleeding.</p> <p><i>C Callow 2002, Slichter 2004, Nevo 2007a</i></p>
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Other considerations

In patients with an indication for anti-coagulant therapy and administration of anti-thymocyte globulin (ATG), there was consensus in the Netherlands that the platelet transfusion trigger should be increased to $40 \times 10^9/L$ for the first 2 days of ATG treatment. (CBO Blood Transfusion Guideline 2004). The working group deems that the number of platelet triggers should be reduced (namely 10, 20, 50 and $100 \times 10^9/L$), as there is very little evidence supporting the various triggers. Therefore, the current consensus recommends $50 \times 10^9/L$ for patients with an indication for anti-coagulant therapy. A trigger of $20 \times 10^9/L$ is recommended during administration of anti-thymocyte globulin (ATG).

Although the platelet count does not appear to be related to an increased risk of recurrent bleeding in patients who have experienced severe bleeding in the preceding 5 days, most experts still feel that for the present it is safer to increase the platelet transfusion trigger to $20 \times 10^9/L$ for such patients.

Recommendations 6.4.2.2

1. In the case of a standard risk of bleeding, a transfusion trigger of $10 \times 10^9/L$ is recommended for prophylactic platelet transfusions.
2. If there are additional clinical complications that promote bleeding, it is recommended that the platelet transfusion trigger be increased to $20 \times 10^9/L$ for prophylactic platelet transfusions.
3. For patients with an indication for anti-coagulant treatment, it is recommended to increase the platelet transfusion trigger to $50 \times 10^9/L$ in order to prevent spontaneous bleeding; this is not evidence based.
4. For patients who have recently (past 5 days) experienced a WHO > grade 2 bleed, it is recommended to increase the threshold for a platelet transfusion to $20 \times 10^9/L$ and to analyse or remove other risk factors.

6.4.2.3 Platelet transfusion dose in platelet transfusions for the prevention of spontaneous bleeding

In the literature, the dose of prophylactically transfused platelets varies from 2×10^{11} to $7 - 8 \times 10^{11}$. In the Netherlands, the standard component is a platelet concentrate prepared from several buffy coats or apheresis, with a dose of $3 - 4 \times 10^{11}$. Various randomised studies compared a low, standard and high transfusion dose for prophylactic platelet transfusions (Goodnough 2001, Klumpp 1999, Norol 1998, Sensebe 2005, Tinmouth 2004). A meta-analysis of these 5 studies by Cid in 2007 compared a dose of $< 3 \times 10^{11}$ versus $> 3 \times 10^{11}$.

Use of the higher dose resulted in a significantly longer interval to the next transfusion and a higher post-transfusion value. However, no difference was observed in occurrence of bleeding (Cid 2007). Since then, two randomised studies have been performed with bleeding as end point. A Canadian study was halted prematurely due to more WHO grade 4 bleeds (5.2% versus 0%) in the low dose arm (Heddle 2009). The American PLADO (PLatelet transfusion And DOsis) study – in which a low, standard and high dose were compared in more than 1200 patients – was recently completed and showed no difference in bleeding (> 60% WHO grade ≥ 2 bleeds irrespective of dose) between the 3 arms (Slichter 2009).

Conclusions 6.4.2.3

Level 1	For prophylactic transfusion of platelets, the use of a dose $> 3 \times 10^{11}$ significantly increased the interval to the next transfusion and resulted in higher post-transfusion values compared to a dose $< 3 \times 10^{11}$. However, no difference was seen in the occurrence of bleeding. <i>A1 Cid 2007</i>
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Level 2	The PLatelet transfusion And DOsis (PLADO) study on more than 1200 patients showed no difference in bleeding between low, standard and high doses, with > 60% WHO grade ≥ 2 bleeds in all 3 arms. <i>A2 Slichter 2009</i>
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Recommendation 6.4.2.3

A dose of approximately 3.5×10^{11} (this is the dose of a standard preparation and contains 5×10^9 platelets/kg for a patient of 70 kg) is recommended for prophylactic platelet transfusions in adults.

6.4.2.4 Platelet transfusion policy for the prevention of bleeding in (elective) procedures

The bleeding incidence is not known for most of the procedures that are frequently performed on patients with thrombocytopenia. Certain rules of thumb are provided based on empirical data and consensus. Use of the bleeding time to determine the indication for platelet transfusions during procedures is unreliable (Lind 1991). Thorough preparation for the procedure, checking for medications that interfere with haemostasis, monitoring the level of clotting factors, discontinuing anti-coagulant medication if necessary and avoiding hypothermia of the patient are advised (Bain 2004, Valeri 2007). Various studies have examined bleeding during procedures.

Bone marrow aspiration

The ASCO and BCSH guidelines advise performing a bone marrow aspiration without correction of haemostasis (ASCO 2001, BCSH 2003). A survey in the UK found a complication frequency due to bleeding of 0.1% for bone marrow aspiration/biopsy, caused by thrombocytopenia and/or an INR that was too high (Eikelboom 2005).

Central Venous Catheters (CVC)

Various studies have been performed on the effect of inserting Central Venous Catheters (CVC) (Ray 1997, Tercan 2008). Mild bleeding was observed at platelet counts $< 50 \times 10^9/L$, primarily increases in further bleeding of the insertion site (Doerffler 1996, Mumtaz 2000, Ray 1997). Another study found no relationship between bleeding and a platelet count of $6 - 37 \times 10^9/L$ (Stecker 2007). Corrections of haemostasis are not required for the removal of a CVC, even in the case of thrombocytopenia the insertion wound rarely requires more than 15 minutes of compression (Stecker 2007).

Liver biopsy

A retrospective study reported 3.4% bleeding after liver biopsy performed at a platelet count between 50 and $100 \times 10^9/L$; this incidence is no higher than in patients with normal platelet counts (Sharma 1982, McVay 1990). The largest series reported no increase in bleeding during ultrasound-guided biopsies, despite a platelet count $< 50 \times 10^9/L$, with or without additional clotting abnormalities (Caturelli 1993). Most guidelines advise a platelet count $> 50 - 80 \times 10^9/L$ for percutaneous liver biopsy.

High risk operations

Various guidelines advise platelet target values $> 100 \times 10^9/L$ for high risk operations, such as heart, brain or eye surgery (excluding cataract surgery). (ASCO 2001, BCSH 2007, Schiffer 2001, Bosley 2007). These platelet target values are not supported by research.

Conclusion 6.4.2.4

Level 3	The threshold values advised in the literature or guidelines for platelet transfusions for the prevention of bleeding during procedures are based on non-comparative research and/or expert opinion.
	<i>C</i> Caturelli 1993, Doerffler 1996, Eikelboom 2005, McVay 1990; Mumtaz 2000, Ray 1997, Sharma 1982, Tercan 2008, Valeri 2007 <i>D</i> Bosley 2007, ASCO 2001, BCSH 2007, Grant 1999, Schiffer 2001

Other considerations

The CBO Blood Transfusion Guideline from 2004 recommends 40 , 60 and $100 \times 10^9/L$ platelets as target values for platelets during various procedures. These target values were not based on comparative research with bleeding as end point. As revision of the recent literature found no indications that more or fewer bleeds would occur at 40 versus $60 \times 10^9/L$ and a platelet count of $50 \times 10^9/L$ is recommended as trigger/threshold value elsewhere in this guideline, the working group has decided to maintain a platelet count of $50 \times 10^9/L$ instead of 40 or $60 \times 10^9/L$. The target value of $100 \times 10^9/L$ is maintained for high risk procedures. The aim of this is purely to simplify matters.

Recommendation 6.4.2.4

The following table can be used as a rule of thumb for platelet target values to prevent bleeding during common, elective procedures.

Table 6.4.2 Target values for platelets during procedures

PROCEDURE	Platelets x 10 ⁹ /L
Arthrocentesis	>50
Ascites / pleural puncture (thin needle)	N/A
Ascites drain, pleural drain and pericardial drain	>50
Bone marrow aspiration	N/A
Bone marrow biopsy (Jamshidi needle)	N/A
Blind organ biopsy or puncture	>50
Bronchoscopy with biopsy or brush	>50
Insertion of central venous catheter	>50
Removal of central venous catheter	N/A
Small intestine biopsy	>50
EMG	>20
Endoscopy + deep loop biopsy or polypectomy large polyp	>50
Endoscopy without biopsy	>20
Endoscopy with "ordinary biopsy"	>50
ERCP with papillotomy	>50
Eye surgery (except cataract)	>100
Laparoscopy without biopsy	>50
Laparoscopy with biopsy or procedure	>50
Laser coagulation (not retina)	N/A
Liver biopsy (percutaneous)	>50
Lumbar puncture	>20*
Myelography, saccography	>50
Neurosurgery	>100
Pacemaker implantation	>50
Percutaneous Transhepatic Cholangiography	>50
Plexus anaesthesia, epidural	>50
Seldinger arterial	>50
Muscle biopsy	>50
Sclerosing oesophageal varices	>50
Tooth/molar extractions	>50
Thoracoscopy/arthroscopy	>50

* In the case of leukaemic blasts in the peripheral blood: > 50 x 10⁹/L

6.4.2.5 Platelet transfusions for the treatment of bleeding

With bleeding \geq WHO grade 3, the aim is usually to increase the platelet count to > 50 x 10⁹/L. As to bleeding in enclosed spaces of vital organs – such as brain, nervous system and eye – the aim is often to increase the count to > 100 x 10⁹/L. Further transfusion above this level is not deemed useful (Rebulla 2005, BCSH 2003). These target values are not supported by studies.

Conclusions 6.4.2.5

Level 4	With bleeding \geq WHO grade 3, the aim is usually to increase the platelet count to $> 50 \times 10^9/L$. <i>D Rebutla 2005, BCSH 2003</i>
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Level 4	For bleeding in vital organs such as the brain, nervous system and the eye, experts usually advise to aim for a platelet count of $> 100 \times 10^9/L$. Further transfusion above this level is not deemed useful. <i>D Rebutla 2005, BCSH 2003</i>
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Recommendations 6.4.2.5

1.	In the case of a severe bleed (\geq WHO grade 3), platelets should be transfused until the bleeding stops and/or the platelet count is $> 50 \times 10^9/L$.
2.	With respect to bleeding in enclosed spaces of vital organs – such as the brain, the nervous system and the eye – the advice is to transfuse platelets to a platelet count of $>100 \times 10^9/L$.

6.4.3 Peripheral thrombocytopenia due to antibodies

6.4.3.1 Auto-immune thrombocytopaenic purpura (ITP)

Prophylactic platelet transfusions for the prevention of spontaneous bleeding are not indicated for auto-immune thrombocytopaenic purpura (ITP) (DiGeorge 1996, BCSH 2003). Transfused platelets are broken down more rapidly – in the same way as autologous platelets – due to the presence of autoantibodies.

Treatment with prednisolone or administration of intravenous immunoglobulin (IVIg) is advised as preparation for elective operations in patients with ITP. Platelet transfusions may be necessary if there is no response or if there is a need for emergency surgery such as a splenectomy. In an elective procedure, platelets should preferably be administered after a therapeutic dose of IVIg. In the case of splenectomy with thrombocytopenia, it is also recommended – if possible – to start platelet transfusions only after clamping the splenic artery (BSCH 2003).

For childbirth, the British guideline recommends a platelet transfusion trigger of $> 30 \times 10^9/L$ for vaginal deliveries and $> 50 \times 10^9/L$ for Caesarian sections (BCSH 2003). The Dutch guideline on neuraxis blockade and anti-coagulants advises a platelet count of $> 50 \times 10^9/L$ in the case of epidural analgesia (NVA 2004). The aim is to achieve a non-traumatic birth, particularly in the interests of the child.

The British guideline advises a target platelet count of $> 80 \times 10^9/L$ for epidural analgesia. This recommendation is based on a study in which no complications occurred in ITP patients with a platelet count $> 69 \times 10^9/L$ (Gernsheimer 2007). Unfortunately, there were no observations on patients with lower platelet counts.

In ITP patients with severe bleeding (WHO \geq grade 3), who are refractory for maximum titrated treatment, platelet transfusions are often the only short-term option and this also

applies when there is not enough time to wait for the effect of a therapeutic dose of IVIG. High doses (3 – 7 therapeutic units corresponding to 15 – 35 donor units) in combination with IVIG resulted in a (temporary) improvement of the platelet count to $> 50 \times 10^9/L$ and halted the bleeding (Salama 2008, Spahn 2008).

Conclusions 6.4.3.1

Level 4	<p>Platelet transfusions for the prevention of spontaneous bleeding are not indicated in the case of auto-immune thrombocytopenic purpura (ITP).</p> <p><i>D</i> <i>BCSH 2003, DiGeorge 1996, working group</i></p>
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Level 3	<p>Severe ($>$ WHO grade 2) bleeding with therapy-resistant auto-immune thrombocytopenic purpura (ITP) can be treated with (multiple) platelet transfusions in combination with intravenous immunoglobulin (IVIG).</p> <p><i>C</i> <i>Salama 2008, Spahn 2008</i></p>
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Recommendations 6.4.3.1

1. Prophylactic platelet transfusions for the prevention of spontaneous bleeding are not indicated in auto-immune thrombocytopenic purpura (ITP).
2. For elective procedures in auto-immune thrombocytopenic purpura (ITP) patients, the recommended treatment is prednisolone or intravenous immunoglobulin (IVIG), alone or in combination with platelet transfusions if necessary.
3. With auto-immune thrombocytopenic purpura (ITP), platelets should preferably be administered after intravenous immunoglobulin (IVIG).
4. In patients with auto-immune thrombocytopenic purpura (ITP) and severe WHO grade > 2 bleeding, (high dose) platelet transfusions are recommended and this is also the case if it is not possible to wait for the effect of a therapeutic dose of intravenous immunoglobulin (IVIG).
5. See also table 6.7. Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)(T)).

6.4.3.2 Post-transfusion purpura (PTP)

Post-transfusion purpura (PTP) – a rare transfusion reaction – causes thrombocytopenia 5 – 15 days after a blood transfusion of erythrocytes and/or platelets. The thrombocytopenia is often very severe. The cause of this is a strong reaction by platelet-specific alloantibodies that reach a high titre in a short period of time, with the autologous platelets being broken down as innocent bystanders. In $> 80\%$ of cases this involves the alloantibodies against HPA-1a. Random transfusions cause transfusion reactions and sustain antibody formation and platelet breakdown (McCrae 1996), HPA-matched transfusion are broken down as quickly as the patient's own platelets. The treatment consists of high dose IVIG, but additional HPA-compatible platelets can be life-saving in refractory patients with severe bleeding (Win 1995).

Conclusion 6.4.3.2

Level 3	In the case of severe bleeding in post-transfusion purpura (PTP) patients, refractory after intravenous immunoglobulin (IVIG), severe bleeding could be halted with HPA-compatible platelet transfusions. C <i>Win 1995</i>
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Recommendations 6.4.3.2

1. Random platelet transfusions are contra-indicated for post-transfusion purpura (PTP).
2. High dose intravenous immunoglobulin (IVIG) is recommended as treatment for PTP.
3. In the case of severe bleeding with PTP, HPA-compatible transfusions are recommended in addition to intravenous immunoglobulin (IVIG).
4. See also table 6.4.4. Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)(T)).

6.4.4 Peripheral thrombocytopenia due to consumption in Thrombotic Thrombocytopenic Purpura (TTP), Haemolytic Uraemic Syndrome (HUS), Haemolysis Elevated Liver enzymes and Low Platelets (HELLP), Disseminated Intravascular Coagulopathy (DIC) and Heparin-Induced Thrombocytopenia (and Thrombosis) (HIT(T))

6.4.4.1 Thrombotic Micro-Angiopathy (TMA)

Thrombotic Thrombocytopenic Purpura (TTP), Haemolytic Uraemic Syndrome (HUS) and Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) all have thrombotic micro-angiopathy (TMA) as a common characteristic. In this paragraph the abbreviation TMA will be used to refer to TTP, HUS and HELLP.

6.4.4.2 Prophylactic platelet transfusions in the prevention of spontaneous bleeding in TMA

Prophylactic platelet transfusions are not indicated in the prevention of spontaneous bleeding in TMA patients. Guidelines even mention thrombotic thrombocytopenic purpura (TTP) as a contra-indication for prophylactic platelet transfusions, because the occurrence of cerebral infarction has been described following platelet transfusions (Harkness 1981, Lind 1987, Bell 1991, Kennedy 2000). A review of the literature – including their own series of 33 patients who received platelet transfusions, with or without prior plasmapheresis – shows that there is no convincing evidence of damage due to platelet transfusions in TTP patients. The efficacy of prophylactic platelet transfusions for TTP has also not been demonstrated (Swisher 2009).

Conclusions 6.4.4.2

Level 3	Cerebral infarctions have been described after platelet transfusions in patients with thrombotic thrombocytopenic purpura (TTP). <i>C Harkness 1981, Lind 1987, Bell 1991, Kennedy 2000</i>
Level 3	There is no convincing evidence for damage caused by platelet transfusions to thrombotic thrombocytopenic purpura (TTP) patients. The efficacy of prophylactic platelet transfusions for TTP has not been demonstrated. <i>B Swisher 2009</i>

Recommendations 6.4.4.2

1. Prophylactic platelet transfusions are not indicated for thrombotic micro-angiopathies (TMAs)
2. In the case of thrombotic thrombocytopenic purpura (TTP), prophylactic platelet transfusions to prevent spontaneous bleeding are even discouraged due to a possible risk of occurrence or exacerbation of thrombo-emboli.
3. See also table 6.4.4. Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)(T)).

6.4.4.3 Prevention of bleeding during procedures in patients with thrombotic micro-angiopathy (TMA)

Platelet transfusions are not recommended during simple procedures such as the insertion of a central venous catheter (CVC) in patients with thrombotic thrombocytopenic purpura (TTP), particularly if treatment with plasma has not been started yet. This is because it may promote thrombotic complications (Swisher 2009, Harkness 1981; Lind 1987; Bell 1991; Kennedy 2000). No thrombotic complications of platelet transfusions have been described for classic haemolytic uraemic syndrome (HUS) or disseminated intravascular coagulation (DIC), but it remains to be seen whether these transfusions are effective. Elective procedures should be postponed as long as possible, until treatment of the underlying disease has started.

In the case of haemolysis elevated liver enzymes and low platelets (HELLP) syndrome and in the rare case of HUS before delivery, platelet transfusions are given to prevent or treat blood loss during delivery. In the case of HELLP, it is essential to terminate the pregnancy in order to stop the disease. Non-evidence based guidelines advise to aim for $> 50 \times 10^9/L$ platelets for a Caesarian section and $> 20 \times 10^9/L$ for a vaginal delivery (Van Dam 1989, Sibai 1990, Sibai 2004, Baxter 2004, Haram 2009). Platelet transfusions have no therapeutic effect on the disease. Corticosteroids (particularly antenatally administered dexamethasone) improve the platelet count more quickly, without affecting the clinical outcomes for mother and child (Woudstra 2010).

Conclusions 6.4.4.3

Level 3	<p>There are indications that for haemolytic uraemic syndrome (HUS) and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, a platelet count of $> 50 \times 10^9/L$ can be considered safe for a Caesarian section and a platelet count of $> 20 \times 10^9/L$ can be considered safe for a vaginal delivery.</p> <p>C <i>Sibai 1990, Van Dam 1989, Sibai 2004, Baxter 2004, Haram 2009</i></p>
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Level 2	<p>There are indications that women with HELLP syndrome have a faster post-partum recovery of the platelet count after (antenatal) administration of corticosteroids. In the absence of clear gain on clinical outcomes, corticosteroids are not recommended as a matter of routine.</p> <p>A2 <i>Woudstra, Cochrane 2010</i></p>
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Other considerations

Platelet transfusions are not recommended for simple procedures in the case of thrombotic thrombocytopenic purpura (TTP), unless there is a strongly increased risk of bleeding as is the case in extreme obesity or severe thrombocytopenia of $< 5 \times 10^9/L$.

Whether a vaginal delivery is aimed for or not, one should always consider that an indication for a Caesarian section may arise, it is therefore recommended to keep the platelet count during childbirth $> 50 \times 10^9/L$ (the recommended platelet count for a Caesarian section). According to the Dutch guidelines, this platelet count is also suitable for the use of epidural analgesia. The same target value ($> 50 \times 10^9/L$) can also be adhered to for other procedures.

Recommendations 6.4.4.3

1. For relatively simple procedures such as the insertion of a central venous catheter (CVC) in the case of thrombotic thrombocytopenic purpura (TTP), platelet transfusions are not recommended unless there is a strongly increased risk of bleeding, as is the case in severe obesity and severe thrombocytopenia $< 5 \times 10^9/L$. If it is decided to give platelet transfusions, the recommendation is to start preferably with the administration of plasma.
2. In use and/or breakdown disorders other than thrombotic thrombocytopenic purpura (TTP), platelet transfusions are recommended for the prevention of bleeding during emergency procedures or vaginal delivery and Caesarian section in order to achieve a platelet count of $> 20 \times 10^9/L$ or $> 50 \times 10^9/L$ respectively.
3. See also table 6.4.4. Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)).

6.4.4.4 Heparin induced thrombocytopenia (and thrombosis) HIT(T)

In the case of heparin induced thrombocytopenia (and thrombosis) (HIT(T)), there are usually no typical symptoms of thrombocytopenia such as skin and mucous membrane haemorrhages. In large series, thrombotic complications are listed more frequently than bleeding complications (Shantsila 2009). However, in patients on the intensive care unit,

severe internal bleeding was described in more than 50% of the patients, possibly due to anti-coagulant therapy that was too aggressively titrated (Wester 2004). Risk factors for bleeding with HIT(T) were analysed in a series of 269 patients, who were treated with the anti-coagulant Argatroban. Severe bleeding occurred in 7.1% of the patients (Warkentin 2004). In addition to thrombosis and other factors, a prolonged (> 90 seconds) **activated partial thromboplastin time** (aPTT) is an important risk factor for bleeding (Keeling 2006, Hursting 2008).

In the case of HIT(T), expert reviews usually advise not to administer platelet transfusions due to the risk of thrombosis (Warkentin 2004, Keeling 2006). However, confirmed cases of thrombosis have not been described, whilst there have been case reports in which bleeding (in 4 patients) was stopped after platelet transfusion without thrombotic events (Hopkins 2008).

Conclusions 6.4.4.4

Level 4	Experts advise not to give platelet transfusions in the case of heparin induced thrombocytopenia (and thrombosis) (HIT(T)) because of the risk of thrombosis. <i>D Warkentin 2004, Keeling 2006</i>
Level 3	There are case reports on heparin induced thrombocytopenia (and thrombosis) (HIT(T)) that showed that platelet transfusions can stop bleeding without causing thrombotic events. <i>C Hopkins 2008</i>

Recommendations 6.4.4.4

1. There is no absolute contra-indication against a platelet transfusion in the case of WHO > grade 2 bleeding in a patient with heparin induced thrombocytopenia (and thrombosis) (HIT(T)) and adequate therapeutic treatment with alternative anti-coagulants.
2. See also table 6.4.4. Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)).

Table 6.4.4: Indications and contra-indications for platelet transfusions in thrombocytopenia caused by consumption and/or breakdown disorders (TTP, HUS, HELLP, DIC, ITP, PTP and HIT(T)).

	Prophylaxis	Procedures	Grade > 2 bleeding
TTP	Contra-indication	If there is an increased risk, preferably after starting plasma therapy	Consider
HUS	No indication	Consider	Indication
HELLP	No indication	Childbirth > 20 –	Indication

		50 x 10 ⁹ /L	
DIC	No indication	Consider	Indication
ITP	No indication	Consider (+ IVIG or prednisolone)	Indication (+ IVIG)
PTP	Contra-indication	Contra-indication	HPA matched
HIT(T)	No indication	Consider provided (alternative) anti-coagulants	Provided (alternative) anti-coagulants

6.4.5 Platelet loss due to pooling in splenomegaly

Upon repeat, multivariate analyses showed that splenomegaly is an important cause of insufficient yield in platelet transfusions (Bishop 1991, Slichter 2007, Kerkhoffs 2008, 2010).

Conclusion 6.4.5

Level 2	<p>Splenomegaly is an important cause of (excessively) low post-platelet transfusion increments.</p> <p><i>B Bishop 1991, Slichter 2007, Kerkhoffs 2008, 2010.</i></p>
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Other considerations

With normal spleen size, approximately 1/3 of the platelets are withdrawn from circulation. In the case of splenomegaly – depending on size and cause – this part can increase to 90%. With a normal bone marrow reserve, the platelet count can drop to approximately 60 x 10⁹/L in the case of splenomegaly.

In the case of an enlarged spleen, the platelet dose should be increased in order to achieve the desired increment or to stop bleeding.

Recommendation 6.4.5

For patients with thrombocytopenia due to splenomegaly, higher dosages of platelet transfusions are essential for the prevention and treatment of bleeding. Depending on the size of the spleen, 2 – 4 times the standard dose should be administered for a therapeutic transfusion.

6.4.6 Acquired thrombocytopathy

In various conditions – such as uraemia, hyperviscosity due to para-proteinaemia, liver cirrhosis and myelodysplasia – acquired platelet function disorders can result in an increased risk of bleeding. As a general rule, prophylactic platelet transfusions are not indicated, unless there is also thrombocytopenia. Anticipation of any bleeding during procedures and treatment of manifest bleeding is essential.

Uraemia

In 75% of patients with uraemic thrombocytopenia, the bleeding time is corrected after administration of Desmopressin. This effect starts immediately and reaches a maximum after 4 hours (Manucci 1983). The effect is exhaustible and the interval between 2 doses should be at least 24 hours. . Uraemia may be treated with dialysis. Platelet transfusions are rarely necessary.

Para-proteinaemia

Hyperviscosity with para-proteinaemia can result in inhibition of platelet adhesion and/or aggregation, resulting in prolongation of the bleeding time. This also applies to transfused platelets. Treatment consists of plasmapheresis.

The para-protein can also have antibody activity against specific clotting factors. One example is acquired von Willebrand Disease (vWD) due to autoantibodies against **von Willebrand Factor** (vWF) in **monoclonal gammopathy of undetermined significance** (MGUS) (Rinder 1997). Plasmapheresis is a category I (proven efficacy) indication for hyperviscosity syndrome according to the criteria of the American Society For Apheresis (ASFA) (ASFA 2010).

Liver cirrhosis

In addition to thrombocytopenia due to splenomegaly and a shortage of thrombopoietin, thrombocytopenia may occur in liver cirrhosis (Roberts 2009). Platelet transfusions are not administered for the prevention of spontaneous bleeding. A trigger of $> 50 \times 10^9/L$ is usually maintained for procedures (BSCH 2003), although the role of (plasma and) platelet transfusions for liver biopsy or insertion of a central venous line remains controversial (Bravo 2001, BCSH 2004, Lisman 2010).

Myelodysplasias (MDS)

In the case of Myelodysplasia (MDS), thrombocytopenia can occur in addition to thrombocytopenia, caused by acquired von Willebrand Disease (vWD), function abnormalities of the collagen receptor and/or autoantibodies (Rinder 1997). As is the case with congenital thrombocytopenias, Desmopressin is the treatment of choice for the correction of a bleeding tendency (Manucci 1997).

Conclusions 6.4.6

Level 3	In thrombocytopenia caused by uraemia, Desmopressin corrects the bleeding time in approximately 75% of the patients, with a maximum effect after 4 hours. <i>B Manucci 1983</i>
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Level 3	In order to reduce bleeding in patients with a hyperviscosity syndrome, plasmapheresis is effective and platelet transfusions are ineffective as the transfused platelets are also inhibited in their functioning. <i>B ASFA 2010</i>
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Level 3	<p>In the case of liver cirrhosis and thrombocytopenia $< 50 \times 10^9/L$, platelet transfusions can be considered for procedures (percutaneous liver biopsy) and/or bleeding $>$ grade 2.</p> <p><i>B Bravo 2001,</i> <i>C/D BSCH 2003, 2004</i></p>
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Level 3	<p>Desmopressin is the treatment of choice for correction of a bleeding tendency in acquired von Willebrand Disease (vWD), except for type 2B.</p> <p><i>C Manucci 1997</i></p>
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Other considerations

The effect of Desmopressin has not been examined in thrombocytopenia $< 50 \times 10^9/L$ and is not authorised for use in pregnancy or with suspected cerebral haemorrhage. Desmopressin is also contra-indicated in cardiac decompensation. Cerebral and cardiac infarction have been described as complications in renal patients. It is useful to determine the bleeding time to monitor the effect of Desmopressin.

Recommendations 6.4.6

1. In the case of acquired thrombocytopenia, the patient may be treated depending on the cause and the severity of the bleeding or the nature of the scheduled procedure.
2. For thrombocytopenia $< 50 \times 10^9/L$ and thrombocytopenia, platelet transfusions are advised for procedures and bleeding and before administration of Desmopressin.
3. Plasmapheresis is recommended for thrombocytopenic bleeding with hyperviscosity syndrome caused by a para-protein.
4. One should take into consideration that the effect of Desmopressin becomes exhausted after a procedure and that a second dose should therefore be administered after 24 hours.

6.4.6.1 Thrombocytopenia due to use of medication

Anti-platelet agents are used in the (primary) prevention of thrombotic processes in patients with an increased risk or for secondary prevention of thrombo-embolism. In the case of thrombocytopenia with use of Acetyl salicylic acid, Clopidogrel or monoclonal antibodies against the IIb/IIIa receptor (Reopro), platelet transfusions are only considered for the prevention of bleeding during (emergency) procedures or for the treatment of bleeding.

Acetyl salicylic acid

Acetyl salicylic acid irreversibly inhibits prostaglandin synthesis. In a meta-analysis of 30 studies (1966 – 2002), Fijnheer et al showed that for most procedures there was no (life threatening) major blood loss with the use of acetyl salicylic acid (Aspirin). The authors advise that acetyl salicylic acid be stopped 5 – 10 days before a procedure only for those procedures in which even slight bleeding can have disastrous consequences (enclosed spaces), such as brain surgery (Fijnheer 2003).

In volunteers, a prolonged bleeding time due to Aspirin could be corrected with low doses of platelets (Valeri 2002).., Desmopressin improved platelet function and thereby coagulation

in animal studies using Aspirin (Peter 2002). It is controversial – in the case of a cerebral haemorrhage in patients using platelet inhibitors – whether platelet transfusions can reduce the extent of the cerebral haemorrhage (Creutzfeldt 2009, Sansing 2009, Naidech 2009). This question is being studied in the Netherlands (PATCH study).

Dipyrimadole

In general, it is not necessary to stop using Dipyrimadole before procedures.

Clopidogrel

Clopidogrel (Plavix) – in combination with Aspirin – is frequently administered after PTCA and/or stent placement. This component inhibits platelet aggregation at the level of the megakaryocyte and affects platelet function for up to 5 – 7 days. Clopidogrel is not thought to affect transfused platelets (Quin 1999, Bennett 2001). The guideline on neuraxis blockade and anti-coagulants states that the risk of neuraxis blockade with the use of clopidogrel is barely increased, provided no other anticoagulant medication is used and there is no history of bleeding (NVA 2004). A meta-analysis in cardiac surgery patients using Clopidogrel and Aspirin with an indication for emergency surgery concluded that this was associated with more bleeding, more transfusions, more post-operative complications and an increased number of re-thoracotomies (Despotis 2008). A dose-dependent inhibition of platelet aggregation was found in volunteers using a combination of Plavix and Ascal. Higher doses of donor platelets (2 – 3 platelet transfusions, 10 – 15 donor units) were needed for correction of the *in vitro* platelet aggregation (using mixing tests) when using Clopidogrel (Vilahur 2006). This is not supported by clinical research.

IIb/IIIa inhibitors/Abciximab

Abciximab (Reopro)/Eptifibatide and Tirofiban hydrochloride – a human Fab fragment from chimeric monoclonal antibodies – block the IIb/IIIa receptor and function as fibrinogen receptor antagonist. Severe thrombocytopenia of $< 20 \times 10^9/L$ within 24 hours occurs in 0.2 – 1% of patients receiving Abciximab for the first time and more often with repeat administration. This is caused by antibodies against platelets with Abciximab on their surface (Curtis 2002). After stopping the medication, the platelet count increases by $> 20 \times 10^9/L$ per day. Platelet transfusions are only given in the case of severe bleeding and emergency procedures and have a limited result (Curtis 2002). The guideline on neuraxis blockade and anti-coagulants states that every form of neuraxis blockade is contra-indicated with IIb/IIIa inhibitors (NVA 2004).

In acute surgery in patients on Abciximab, (large numbers of) platelet transfusions are administered before surgery in order to absorb the antibodies. Desmopressin is thought to increase the absorption and may reduce the number of required platelet transfusions (Reiter 2005). The latter has not been clinically proven.

Other considerations

Anti-platelet agents are often used. There has only been limited clinical experience on the effect of platelet transfusions in the case of bleeding or invasive interventions. Usually it involved patient-dependent, multi-disciplinary treatment advice that was determined by the absolute indication for anti-platelet agents (recent cerebral infarction, unstable anginous symptoms, recent stent) and the risk of bleeding during an intervention (in enclosed spaces of vital organs such as the brain and eye) or biopsy in a parenchymatous organ, in which it is

hard to stop the bleeding.. We have provided only a general overview of the indications for platelet transfusions with respect to the use of anti-platelet agents. Please refer to Chapter 8 for blood-saving measures in the peri-operative situation. For recommendations on regional analgesia, please consult the Guideline on neuraxis blockade and anti-coagulants (NVA 2004).

Conclusions 6.4.6

Level 1	<p>It has been demonstrated that the use of acetyl salicylic acid (Aspirin) and/or Clopidogrel in cardiac surgery patients with an indication for emergency surgery is associated with more bleeding, more transfusions and more post-operative complications and re-thoracotomies.</p> <p><i>A1 Despotis 2008</i></p>
Level 3	<p>It is likely that the use of acetyl salicylic acid does not result in (life threatening) major blood loss during most procedures. For procedures in enclosed spaces – in which even slight bleeding can have disastrous consequences, such as brain surgery – the use of aspirin should be halted 5 – 10 days before the procedure.</p> <p><i>C Fijnheer 2003</i></p>
Level 3	<p>In patients using platelet inhibitors and who experience a cerebral haemorrhage, it is not known whether the administration of platelet transfusions can limit the extent of the bleeding.</p> <p><i>C Sansing 2009, Naidech 2009, Creutzfeldt 2009</i></p>
Level 3	<p>Large quantities of platelet transfusions are often required for correction of thrombocytopenia due to anti-IIb/IIIa inhibitors in the case of an acute procedure.</p> <p><i>C Reiter 2005</i></p>

Recommendations 6.4.6

1. If there are indications not to stop the use of acetyl salicylic acid (Aspirin) and Clopidogrel before a cardiovascular procedure, one should take into account that increased blood loss can occur.
2. In the case of procedures in non-critical locations, the use of Aspirin does not need to be halted before the procedure.
3. For elective surgery in critical (enclosed space: brain, eye, inner ear, etc.) locations, the use of Aspirin should be halted at least 5 days before the procedure.
4. For emergency procedures or bleeding under Aspirin therapy, a standard dose platelet transfusion should be sufficient; at least 2 doses are necessary in the case of combined use with Clopidogrel.
5. Research is necessary to determine the benefit of platelet transfusions in (cerebral) haemorrhage during the use of platelet inhibitors.
6. Platelet transfusions – alone or in combination with Desmopressin – are necessary in the case of an acute intervention with the use of anti-IIb/IIIa inhibitors in order to absorb the antibodies.

6.5 Platelet transfusions in practice

6.5.1 Platelet transfusion failure (refractoriness)

6.5.1.1 Definition and determination of refractoriness

The yield of transfused platelets is determined by the increment (CI = count increment), or more precisely and universally, the increment corrected for blood volume of the recipient and the administered dose, the “corrected count increment” (CCI) using the formula: $CCI = (\text{post minus pre platelet count (in } 10^9/L)) \times (\text{body surface area in } m^2 / \text{number of platelets administered (in } 10^{11}))$.

The CCI after approximately 1 hour (measured after 10 – 75 minutes) is partially determined by spleen size, the presence of antibodies, use and quality of the component. In order to determine survival in the circulation, the CCI is repeated after 18 – 24 hours; this value should be > 4.5 and is primarily determined by clinical factors. The definition of refractoriness has been met if the CCI is < 7.5 twice in a row 1 hour after transfusion of qualitatively good ABO compatible platelets. An adequate CCI after approximately 1 hour and an inadequate value after approximately 20 hours is often seen in conditions with low grade disseminated intravascular coagulation, such as in sepsis and graft versus host disease. The quality of the component also plays a role. (Legler 1997).

6.5.1.2 Causes of platelet refractoriness

In practice, transfusion failure or refractoriness occurs in 30 – 60% of platelet transfusions. In two thirds of cases, refractoriness is caused by clinical factors such as fever, sepsis, medication, endothelial damage, etc. An immunological cause is found in one third of cases (Legler 1997). In the absence of explanatory clinical factors, tests should be performed for allo-immunisation and/or the administration of suspected medications should be stopped. The most common cause of immunological transfusion failure is antibodies against HLA antigens. Antibodies against platelet specific antigens (HPA) rarely form an isolated cause

of transfusion failure, but occur frequently in combination with HLA antibodies (Schnaidt 2000). The removal of leukocytes from platelet components has significantly reduced HLA immunisation (> 80% reduction in primary immunisation and 40% reduction in secondary booster immunisation) (TRAP 1997, Novotny 1995, Sintnicolaas 1995). Despite this, HLA antibodies still occur in approximately 20% of recipients, but these antibodies do not always result in transfusion failure. (Novotny 1995, TRAP 1997). Approximately 5% of patients – usually with strong multi-specific HLA antibodies – exhibit transfusion refractoriness. After previous pregnancies, women have an increased risk of forming HLA antibodies and platelet refractoriness. (Novotny 1995, Sintnicolaas 1995). Leukocyte depletion of erythrocyte components does not prevent HLA immunisation (Van de Watering 2003).

The presence of HLA and/or HPA antibodies can be demonstrated using screening tests, usually ELISA based. HLA reference laboratories determine the specificity of HLA antibodies and – for the purposes of donor selection – the HLA antigens against which antibodies are not present. If the 1-hour CCI is insufficient despite HLA and ABO compatible transfusions, it is useful to look for HPA specific antibodies using a sensitive test in a reference laboratory (the **Monoclonal Antibody Immobilization of Platelet Antigen (MAIPA)**).

6.5.1.3 Selection of HLA (HPA) compatible donors

Sanquin Blood Supply has a large HLA (partially HPA) typed database of voluntary donors and a selection programme to select available donors for an immunised patient. The donor must be called up for platelet apheresis and the blood must then be tested for transmissible infections. Sometimes there are only a few suitable donors and donors with “acceptable” mismatches are selected. The 1-hour yield for these transfusions is essential in determining whether subsequent transfusions with the same mismatch are useful.

Conclusions 6.5.1

Level 2	<p>Several analyses have shown that platelet transfusion failure (refractoriness) is caused by clinical factors – such as fever, sepsis, medication, extent of endothelial damage – in the majority of cases, and only a minority of cases have an immunological cause.</p> <p><i>B</i> Novotny 1995, Slichter 1997, Legler 1997</p>
Level 3	<p>There are indications that antibodies against platelet specific antigens (HPA) occur frequently in combination with HLA antibodies, but that these are rarely an isolated cause of transfusion failure.</p> <p><i>C</i> Schnaidt 2000, Novotny 1995,</p>
Level 2	<p>It is likely that the removal of leukocytes from platelet components significantly reduces HLA immunisation.</p> <p><i>A2</i> TRAP 1997 <i>B</i> Novotny 1995</p>

Level 2	Transfusion of erythrocytes – leukocytes removed does not prevent HLA immunisation. A2 <i>Van de Watering 2003</i>
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Other considerations

As the logistics of HLA (and possibly HPA) matched platelet transfusions are complicated, good clinical follow-up is very important for the further policy concerning donor selection. Good communication between treating doctor, hospital transfusion service and the Clinical Consultative Service of the Blood Supplier is essential for effective implementation and support of HLA and/or HPA immunised patients.

Recommendations 6.5.1

1. Screening for HLA antibodies is recommended if the 1-hour Corrected Count Increment (CCI) of a fresh ABO compatible platelet transfusion is **< 7.5 twice** in a row in a patient without clinical factors that could explain this (this is then a case of platelet refractoriness).
2. **If ABO and HLA compatible transfusions result in a Corrected Count Increment (CCI) < 7.5 – in the absence of clinical factors that could explain this – serological analysis for platelet specific antigens (HPA) is recommended.**
3. **The working group is of the opinion that communication between treating doctor, hospital transfusion service and the Clinical Consultative Service of the Blood Supplier is essential for effective implementation and support with HLA matched platelet transfusions.**

6.5.2 ABO/Rh-D selection

See 2.1.3 and 3.8.1

6.5.3 Supporting treatments for therapy-resistant bleeding

6.5.3.1 Erythrocyte transfusion, inhibition of fibrinolysis and recombinant F VIIa

Erythrocyte transfusions

In patients with renal insufficiency and anaemia, an inverse relationship between the level of the haematocrit and the tendency to bleed has been found. In a bleeding thrombocytopaenic patient, correction of the anaemia to a haematocrit above 0.30 L/L can contribute to limiting the blood loss (Fernandez 1985, Livio 1982).

Inhibition of fibrinolysis (see also 8.1.3.2 tranexamic acid)

Inhibition of fibrinolysis by intravenous or oral administration of fibrinolysis-inhibiting medication appears to have varying success in limiting blood loss during ENT procedures, gastric bleeding, prostate surgery and cardiac surgery. Theoretically, it seems sensible to use fibrinolysis inhibition for thrombocytopaenic patients, particularly if they exhibit a tendency to bleed from mucous membranes or wound surfaces, which are known to have a high local fibrinolytic activity. However, only a few studies have been performed and tranexamic acid has no effect (Fricke 1991) or only a moderate effect (Bartholemew 1989,

Garewal 1985) in severe thrombocytopenia. Fibrinolysis inhibition is contra-indicated in haematuria due to the risk of thrombus formation in the urinary tract (Bartholemew 1989, Garewal 1985).

Recombinant factor VIIa (rFVIIa) (see also 8.1.3.6 rFVII-a in the perioperative phase)

Recombinant factor VIIa is still used “off label” for non-surgical blood loss. As the thrombin generation by factor VIIa is platelet-dependent, its use in patients without functional platelets is a point of discussion. Recently, Leebeek & Eikenboom published 6 randomised studies (RCTs of non-surgical bleeding (Leebeek 2008). Most of the studies had end points of blood loss, need for transfusion and – although the size of the studies was insufficient for this purpose – thrombo-embolic complications. Two RCTs involved patients with thrombocytopenia after mainly allogeneic haematopoietic stem cell transplants, with improvement of the WHO bleeding score as end point (Pihusch 2005). The first study found no difference in blood loss and need for transfusion. Thrombo-embolic complications occurred in 6/77 patients receiving rFVIIa and 0/23 in the non-treatment group (no significant difference). A second study involved 25 patients with a dengue fever infection and severe bleeding. There was no effect on the need for erythrocyte and platelet transfusions. Recently, a total of 18 published ITP cases were described in a review by Salama. The bleeding stopped in 17 of the 18 patients (Salama 2009). Kristensen examined the effect on the bleeding time in 47 patients with thrombocytopenia of different etiologies, including **auto-immune thrombocytopenic purpura** (ITP). In patients with a platelet count < 20 x 10⁹/L, there was a reduction in bleeding time in 32% of the patients after infusion of rFVIIa (Kristensen 1997).

Conclusions 6.5.3.1

Level 3	<p>There are indications that the tendency to bleed in patients with thrombocytopenia can be reduced by increasing the haematocrit above 0.30 L/L.</p> <p><i>C Fernandez 1985, Livio 1982</i></p>
Level 3	<p>There are indications that inhibition of fibrinolysis by intravenous or oral administration of fibrinolysis-inhibiting agents has varying success in limiting blood loss during ENT procedures, gastric bleedings, prostate surgery and cardiac surgery.</p> <p><i>C Bartholemew 1989, Garewal 1985, Fricke 1991</i></p>
Level 2	<p>No significant difference was found with respect to the improvement in WHO bleeding score in patients with thrombocytopenia following allogeneic haematopoietic stem cell transplantation with or without the use of recombinant factor VIIa (rFVIIa).</p> <p><i>A2 Pihusch 2005</i></p>
Level 2	<p>Based on the literature, it is not possible to reach a conclusion on the role</p>

	of recombinant factor VIIa (rFVIIa) in the treatment of (major) bleeding in patients with thrombocytopenia.
A2	<i>Leebeek 2008</i>
C	<i>Salama 2009, Kristensen 1997, Pihush 2005</i>

Other considerations

Recombinant factor VIIa (rFVIIa) is used in practice in multi-therapy resistant life threatening bleeding with thrombocytopenia. It is highly desirable for this to occur in a study context.

Recommendations 6.5.3.1

1. For patients with thrombocytopenia and bleeding – who cannot be, or are poorly, corrected with platelet transfusions, it is recommended to consider increasing the haematocrit to > 0.30 L/L in order to reduce the tendency to bleed.
2. In patients with thrombocytopenia and mucous membrane bleeding (bleeding from nose and gums, menorrhagia), anti-fibrinolytic medication can be considered to reduce the tendency to bleed. Fibrinolysis inhibition is contra-indicated in haematuria because of the risk of thrombus formation in the urinary tract.
3. It is recommended that a (preferably national) registration takes place of the use of recombinant factor VIIa (rFVIIa) for bleeding in patients with thrombocytopenia and that protocols be developed for evaluation and reporting of the effect of the use of rFVIIa for this indication.

6.5.3.2 Intravenous immunoglobulin (IVIG)

In a small randomised study in 12 patients with HLA antibodies, the administration of random platelets resulted in only a temporary increased recovery (better 1-hour *Corrected Count Increment* (CCI) and no difference in 24-hour CCI) after administration of intravenous immunoglobulin (IVIG). (Kickler 1990). In the case of HLA antibodies, high dose IVIG resulted in a varying effect on the count after incompatible platelet transfusions. There may also have been autoantibodies or HPA antibodies present (Zeigler 1987, Kekomaki 1984, Schiffer 1984, Knupp 1985, Siemons 1987).

Conclusions 6.5.3.2

Level 3	In patients with HLA antibodies, high dose intravenous immunoglobulin (IVIG) resulted in a favourable effect or no improvement of the count . after incompatible platelet transfusions.
	C <i>Schiffer 1984; Zeigler 1987; Kekomaki 1984; Knupp 1985; Siemons 1987</i>

Level 2	<p>There are indications that – for patients with HLA antibodies – the administration of random platelets results in only a temporary increase in recovery (better 24-hour <i>Corrected Count</i> Increment (CCI), no difference in -hour CCI) after administration of intravenous immunoglobulin (IVIG).</p> <p>A2 <i>Kickler 1990</i></p>
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Other considerations

Intravenous immunoglobulin (IVIG) is a very expensive treatment, which is used in post-transfusion failure due to demonstrated or suspected alloantibodies. The success described in certain cases may be due to the simultaneous presence of autoantibodies or antibodies against Human Platelet Antigens (HPA). The working group deems the positive result of IVIG with HLA antibodies (the most frequent cause of immunological transfusion failure) as insufficient evidence to justify this treatment.

Recommendation 6.5.3.2

Administration of intravenous immunoglobulin (IVIG) before a platelet transfusion is not recommended in the case of refractoriness due to HLA antibodies.

6.6 Plasma transfusions for non-surgical patients

6.6.1 General aspects

Administration of plasma can be indicated in the case of bleeding if there is also a shortage of clotting factors (see Chapter 2.2.3 and Chapter 5 for plasma use with surgical bleeding). However, plasma is often used incorrectly for the prevention of bleeding during a scheduled procedure or for the treatment of bleeding in the absence of the recommended indications. In addition, the dosage of plasma is often too low even when there is a good indication (see Chapter 2). Systematic reviews revealed very little evidence for the use of plasma (Stanworth 2004, Roback 2010). In general, a shortage of clotting factor(s) must be demonstrated before administering plasma (see Chapter 5 for exceptions). The initial coagulation profile is used together with the anamnesis (see Chapter 2).

In this chapter we will primarily discuss plasma therapy for reasons other than correction of haemostasis.

Conclusion 6.6.1

Level 1	<p>Evidence for the administration of plasma was only found for a limited number of indications.</p> <p>A1 <i>Stanworth 2004, Roback 2010</i></p>
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Recommendations 6.6.1

Indications for plasma: see 2.2.3

6.6.2 Plasma transfusions in neonates

The haemostasis in neonates is insufficiently developed. The level of certain clotting factors (FXII, FXI, prekallikrein (Fletcher factor) and high molecular weight (HMW) kininogen) in full term neonates is 40 – 50% of the level in adults. In premature infants this is only 30 – 40%. The vitamin K dependent factors (FII, FVII, FIX, FX) show similar percentages, as do the anti-coagulation factors anti-thrombin and proteins C and S. Apart from rare, isolated deficiencies (for example factor V .), plasma is administered to neonates primarily in exchange transfusions (see Chapter 2 and 4.4.6.2.1), during surgical procedures (see Chapter 5) and to full term and premature neonates in the case of bleeding and severely prolonged coagulation times. There is no evidence to support prophylactic plasma transfusions to premature infants with the aim of preventing cerebral haemorrhage (NNN 1996).

Conclusion 6.6.2

	There is no evidence to support the prophylactic administration of plasma to premature infants with the aim of preventing cerebral haemorrhage.
Level 4	
	<i>D Opinion of the working group</i>

6.6.3 Plasma transfusions in children

Very little research has been performed on plasma transfusions in children. In this paragraph, the use of plasma transfusions – alone or in combination with plasmapheresis – is described for two diseases, namely HUS and TTP. In the absence of any research, please refer to the paragraph on plasma transfusions in adults for other situations (paragraph 6.6.4).

Haemolytic Uraemic Syndrome (HUS)

In children, haemolytic uraemic syndrome (HUS) is often the result of bacterial (Shiga toxin producing) bowel infections. Treatment with plasma(pheresis) does not contribute to recovery from diarrhoea-associated (d+) HUS (Loirat 2001, 1988). In contrast, plasma transfusion / plasmapheresis does result in improvement in the case of familial HUS, atypical (d^{neg}) HUS due to complement dysregulation and recurrent HUS in a transplanted kidney (Heuvelink 2001, Loirat 2001, Barbot 2001, Filler 2004, Noris 2009).

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) in children is usually caused by a congenital deficiency of ADAMTS-13. Chronic recurrent and familial TTP and recurrent primary TTP due to anti-ADAMTS-13 antibodies is an indication for regular (generally 2-weekly) plasma transfusions in young children (Loirat 2009).

Conclusions 6.6.3

	In children, haemolytic uraemic syndrome (HUS,) is usually the result of a shiga toxin producing <i>E. coli</i> infection ((d+) HUS) and treatment with plasma(pheresis) does not contribute to recovery.
Level 2	
	C <i>Loirat 1988</i> B <i>Loirat 2001, Ariceta 2009</i>

	Plasma transfusion did result in improvement of atypical (d ^{neg}) haemolytic uraemic syndrome (HUS) and recurrent HUS in a transplanted kidney.
Level 3	
	C <i>Heuvelink 2001, Bestbas 2006, Ariceta 2009, Norris 2010</i>

	Thrombotic thrombocytopenic purpura (TTP) in children is usually caused by a congenital deficiency of ADAMTS-13, which is an indication for plasma(pheresis).
Level 3	
	C <i>Barbot 2001, Filler 2004, Loirat 2009, Besbas 2006</i>

Recommendations 6.6.3

1. Treatment with plasma or plasmapheresis is generally not indicated in children with d+ haemolytic uraemic syndrome (HUS).
2. Treatment with plasma or plasmapheresis is recommended for children with atypical (d^{neg}) HUS or recurrent HUS in a transplanted kidney.
3. After therapeutic plasma administration, prophylactic plasma transfusions are indicated in children with thrombotic thrombocytopenic purpura (TTP) caused by a congenital ADAMTS-13 deficiency.

6.6.4 Plasma transfusions in adults

6.6.4.1 Plasmapheresis for primary TMAs

Thrombotic micro-angiopathies (TMAs) in adults – such as thrombotic thrombocytopenic purpura (TTP), Haemolytic uraemic syndrome (HUS) and Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) –all present as a direct anti-globulin test (DAT) negative micro-angiopathic haemolytic anaemia and thrombocytopenia (Rock 2000, Rock 1998, George 2000).

TMAs are the result of a multitude of factors that lead to a common end point via endothelial damage: clots in the micro-vasculature (Eldor 1998, Ruggerenti 1996). Between primary TTP – caused by antibodies against ADAMTS-13 – and congenital ADAMTS-13 deficiency and classic d+ HUS, or atypical HUS caused by dysregulation of the complement system, there is still a grey area of TTP/HUS that will hopefully be clarified in future. TTP (Eldor 1998, Ruggerenti 1996), HELLP (Egerman 1999, Magann 1999) and (postnatal) HUS (Ruggerenti 1996) occur in and around pregnancy (Fakhouri 2010, Stella 2009).

The administration of plasma results in an impressive improvement in survival of TTP, yet mortality after 6 months is still 16 – 29% (Byrnes 1977, Bukowski 1997). Plasma is the therapy of choice for all primary forms of TTP, irrespective of the level of ADAMTS-13 and

for atypical (d^{neg}) HUS (Amorosi 1966, Bell 1991, Norris 2010, Ariceta 2009). The effect of plasmapheresis in the case of HELLP is not clear, as this disease generally improves spontaneously within 3 days after birth (Egerman 1999, Magann 1999, Egerman 1999). Favourable results have been described for plasmapheresis in HELLP syndrome that persists for > 72 hours post-partum or that occurred or deteriorated post-partum. (Martin 1990, Eser 2005). Randomised studies have not been performed. TTP can also occur during pregnancy or post-partum and is also an indication for plasmapheresis. The same applies to post-partum HUS (Egermann 1999b).

Two randomised studies of TTP showed improved results following plasmapheresis when compared to plasma transfusion (Rock 1991, Henon 1991). A retrospective study of a small patient group had previously demonstrated no difference between plasmapheresis and plasma transfusion (Novitsky 1994).

Choice of plasma component or product

In a non-randomised, sequential study, the group treated with cryo-supernatant plasma (CSP) had a better survival than the group treated with Fresh Frozen Plasma (plasma) (13/18 versus 9/19) (Owens 1995). In a group of 18 patients who had not responded to plasma exchange after 7 days, a good response was achieved 7 days after CSP in 61% and 82% were still alive after one month. In contrast, 67% of patients treated with plasma were still alive after one month (Rock 1996). However, these studies were not continued. (CSP is not a standard component in the Netherlands, but can be supplied by Sanquin Blood Service with a doctor's declaration).

Successful use of plasma treated with solvent and detergent (SD plasma) has been described in several patients with therapy-resistant TTP (Moake 1994, Harrison 1996). No difference was found in a small series that compared SD plasma to Fresh Frozen Plasma (plasma) (Horowitz 1998). In a somewhat larger cohort study, SD plasma was as effective as cryo-supernatant plasma (Scully 2007), but the study was not large enough to be certain that the use of SD plasma did not require more plasmapheresis and/or a larger plasma volume. The same applies to a randomised study with pathogen-inactivated (amotosalen/UVA) plasma (Mintz 2006). A retrospective study, from Spain, suggested that plasma treated with methylene blue is probably inferior to plasma, both in achieving complete remission of TTP and the volume required to achieve remission (Rio-Garma 2008, Alvarez-Larran 2004).

Systematic reviews by Brunskill and Michael concluded that more research is necessary before conclusions can be drawn on the efficacy and adverse effects of the various plasma components and components (Brunskill 2007, Michael 2009).

Conclusions 6.6.4.1

Level 2	Plasma is the therapy of choice for all primary forms of thrombotic thrombocytopenic purpura (TTP) and atypical (d ^{neg}) HUS. <i>B Amorosi 1966, Bell 1991, Norris 2010, Ariceta 2009, ASFA 2010</i>
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Level 3	Doubt has been cast over treatment with plasma for Haemolysis Elevated Liver enzymes and Low Platelets (HELLP), as the disease generally improves spontaneously within three days after birth.
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	C <i>Magann 1999, Egerman 1999a, Egerman 1999b</i>
Level 3	Favourable results have been described for plasmapheresis in progressive Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) that persists longer than three days post-partum or that deteriorates. Favourable results have also been described for HELLP syndrome that occurs post-partum. However, randomised studies have not been performed. C <i>Martin 1990, Eser 2005</i>
Level 3	There are indications that early plasmapheresis has a favourable effect on the course of post-partum HUS. C <i>Egermann 1999, Fakhouri 2010, Stella 2009</i>
Level 1	In the case of thrombotic thrombocytopenic purpura (TTP), plasmapheresis provides better results than plasma transfusion. A2 <i>Rock 1991, Henon 1991</i> B <i>Novitsky 1994</i>
Level 3	There are indications that complete remission is achieved less often with methylene blue treated plasma and that more volume is required than is the case with standard plasma to achieve complete remission with <i>thrombotic thrombocytopenic purpura (TTP)</i> . C <i>Alvarez-Larran 2004, Rio-Garma 2008</i>

Other considerations

The working group is not convinced by the favourable results described for cryo-supernatant plasma compared to standard plasma (FFP). No randomised research is available concerning the choice between the various plasma components; Q-FFP, CSP and SD plasma contain similar amounts of ADAMTS-13 (Scot 2007 Michael 2009).

Recommendations 6.6.4.1

1. Treatment of *Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome with plasma(pheresis) is not recommended, unless there has been either no improvement or deterioration has occurred > 72 hours post-partum.*
2. Plasma administration is recommended as therapy of choice for *thrombotic thrombocytopenic purpura (TTP) and for atypical (d^{neg}) haemolytic uraemic syndrome (HUS).*
3. Plasma administration / plasmapheresis is **indicated** for *thrombotic thrombocytopenic purpura (TTP) and HUS before or shortly after childbirth.*

4. Plasmapheresis is preferred to plasma transfusion for the treatment of *thrombotic thrombocytopaenic purpura (TTP)* or *atypical (d^{neg}) HUS*.
5. For the time being, methylene blue treated plasma is not recommended for the treatment of thrombotic micro-angiopathies (TMA) / *thrombotic thrombocytopaenic purpura (TTP)*.

6.6.4.2 Secondary TMAs

Secondary thrombotic micro-angiopathies (TMAs) are TMAs that occur as part of an underlying illness. The level of ADAMTS-13 is often much less . reduced than in primary TTP. TMA associated with malignant tumours and their treatment has been described extensively in a number of reviews (Lohrmann 1973, Murgu 1987, Gordon 1997). We can distinguish between the effect of the malignancy itself, the effect of chemotherapy and TMA as a complication of stem cell transplantation (SCT) (Kwaan 2001). The following secondary TMAs will be discussed consecutively:

- with malignancies;
- after chemotherapy and bone marrow or stem cell transplantation;
- after administration of medications (including cyclosporin, tacrolimus, quinine, ticlopedine and Clopidogrel);
- as a complication of bacterial and viral infections;
- as a complication of .the anti-phospholipid syndrome.

Extensive metastasised carcinoma

TMA as a complication of extensively metastasised carcinoma has been described in 6 – 28% of the patients in a number of case series, which were however, difficult to compare .(Lohrmann 1973, Murgu 1987, Gordon 1997). The use of plasmapheresis is usually disappointing, but has not been examined in a RCT (Kaplan 2000). The ASFA guideline gives this indication a category III (role of plasmapheresis has not been demonstrated) (ASFA 2010).

Bone marrow / stem cell transplantation (SCT/BMT)

TMA has been described in various case series with an incidence of 6 – 26% (Pettitt 1994, Verburch 1996, Fuge 2001). The clinical image is very variable and has been described after an interval of 2 weeks to > 1 year after SCT (Pettitt 1994, Schriber 1997). It remains difficult to distinguish from the usual post-transplant complications (Graft-versus-host disease (GvHD), disseminated infections, cyclosporin) (Daly 2002). The results of treatment vary greatly and have not been examined in RCTs. Mortality is high, namely > 75% (George 2004). In general, plasmapheresis is ineffective (category III in ASFA criteria, i.e. effect not demonstrated). It appears that better results are being achieved with prompt administration of Rituximab (Au 2007, George 2006).

Medication

TMA is associated with the use of various medications (Medina 2001, Pisoni 2001). An overview of the most important agents for which the effect of plasmapheresis has been examined is provided here.

Cytostatics

Several cytostatics (including mitomycin-C, bleomycin, cisplatin, anti-VEGF components, gemcitabine) have been linked to TMA (Gordon 1997, Medina 2001, Pisoni 2001, Frangie 2007, Kapteijn 2007). The clinical course is similar to severe TTP/HUS and mortality is high. Plasmapheresis is not effective (ASFA 2010), but could have a favourable effect in combination with protein A column apheresis, although this has not been studied in RCTs (Kaplan 2000, Schriber 1997).

Cyclosporin A and tacrolimus (FK 506)

TMA has been described primarily with the use of cyclosporin A for kidney transplants (Medina 2001). The prognosis is good once cyclosporin has been stopped or the dose has been reduced. Use of plasma has hardly been described and is not favourable (Medina 2001, Pisoni 2001). No RCTs have been performed.

Quinine

Quinine can cause TMA by an immune-mediated mechanism; the antibodies are not targeted against ADAMTS-13 (Gottschall 1994, 1991). The ASFA deems that there is no effect of plasmapheresis (category IV).

Ticlopedine and Clopidogrel

TMA was found to be an adverse effect of ticlopedine, with an estimated incidence of 1 in 1500 – 8000. Plasmapheresis resulted in rapid remission in some cases, but has not been examined in an RCT (Medina 2001, Steinhubl 1999). The related component Clopidogrel, which has largely replaced ticlopedine, can also cause TMA, but the incidence is much lower than for ticlopedine (Hankey 2000). The ASFA has assigned these TMAs to category I (indicated and effective).

Other medication-associated TMAs

TMA cases have been described with statins, valacyclovir, pentostatin, cephalosporin, dipyridamole and levonogestrol. The discontinuation of the medication – alone or in combination with a few sessions of plasmapheresis – usually resulted in a rapid response (Sundram 2004).

TMA as a complication of infections

Bacterial infections

TMA as a complication of infections with verocytotoxin producing *E. coli* is the most common cause of haemolytic uraemic syndrome (d+ HUS) in childhood (van de Kar 1998). Plasma does not need to be used in the treatment of children (Loirat 2001, 1988, Ariceta 2009, Besbas 2006). Improved survival has been reported for the use of plasma compared to historically untreated patients in adults with d+ HUS (Dundas 1999).

TMA has been described as a complication with various other infections (Eldor 1998). There are no known systematic studies concerning the use of plasma. Streptococcus pneumoniae induced HUS is fairly rare, with the Thomson Friedreichsen (T) antigen on erythrocytes (and on other tissues, including glomerular endothelium) being activated by the splitting of sialic acid residues from the membrane. The DAT is positive in this case. This form of HUS usually occurs in children, but has also been described in adults (Oliver 2010). As is the case with

d+ HUS, plasma(pheresis) is not indicated. Although controversial, it is recommended that erythrocyte transfusions are washed (once) (Vanderkooi 2003, 2010).

Viral infections

Various viral infections are associated with TMA (Eldor 1998). The best described association is with HIV. TMA in HIV infections responds well and quickly to plasma(pheresis) (Hymes 1997, Man 1997, Abraham 2001). This has not been examined in a RCT.

Catastrophic anti-phospholipid syndrome

TMA can occur in the case of anti-phospholipid syndrome. Several cases of catastrophic anti-phospholipid syndrome presenting with the classic TTP pentad, low ADAMTS-13 and anti-ADAMTS-13 antibodies have been described (Diaz-Cremades 2009, de Carvalho 2009) and the two diseases may be difficult to distinguish from each other (Thachil 2010). Plasmapheresis can be considered in the presence of schistocytes and insufficient response to conventional therapy (anti-coagulants) (ASFA 2010).

Conclusions 6.6.4.2

Level 3	The use of plasmapheresis for thrombotic micro-angiopathy (TMA) as a complication of an extensively metastasised carcinoma is usually disappointing, but has not been examined in a RCT. <i>C Kaplan 2000</i>
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Level 3	The effect of plasmapheresis has not been demonstrated for thrombotic micro-angiopathy (TMA) that is not caused by cyclosporin toxicity following bone marrow transplantation. <i>C Schriber 1997, Pettitt 1994, Fuge 2001, Zeigler 1996, Au 2007, George 2006, ASFA 2010</i>
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Level 3	Cyclosporin A and tacrolimus-associated thrombotic micro-angiopathy (TMA) recovers after stopping the medication and does not respond favourably to plasma. <i>C Medina 2001, Pisoni 2001</i>
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Level 3	Thrombotic micro-angiopathy (TMA) was found to be a side effect of ticlopedine, with an estimated incidence of 1 in 1500 – 8000 and to a lesser extent with Clopidogrel. Plasmapheresis produces a rapid and favourable effect. <i>C Medina 2001, Steinhubl 1999, Hankey 2000, ASFA 2010</i>
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Level 3	The combination of TTP and catastrophic anti-phospholipid syndrome has
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	<p>been described and plasmapheresis can be considered in the case of obvious TMA with insufficient response to standard (anti-coagulant) therapy.</p> <p>C <i>Diaz-Cremades 2009, ASFA 2010</i></p>
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Level 3	<p>There are indications that the use of plasma results in improved survival – compared to historical patients not treated with plasma – for adults with haemolytic uraemic syndrome (d+ HUS) as a complication of infections with verotoxin producing E. coli.</p> <p>C <i>Dundas 1999</i></p>
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Level 3	<p>Thrombotic micro-angiopathy (TMA) in HIV infection responds well to plasma(pheresis), but this has not been studied in a RCT.</p> <p>C <i>Hymes 1997, Man 1997, Abraham 2001</i></p>
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Recommendations 6.6.4.2

1. Plasma(pheresis) is not recommended for thrombotic micro-angiopathy (TMA) associated with extensively metastasised carcinoma.
2. Plasma(pheresis) is not recommended for post stem cell transplant (SCT) and post bone marrow transplant (BMT) induced thrombotic micro-angiopathy (TMA).
3. Plasma(pheresis) is not recommended for thrombotic micro-angiopathy (TMA) caused by cytostatics.
4. Plasma(pheresis) is not recommended for cyclosporin A or tacrolimus (FK 506) induced thrombotic micro-angiopathy (TMA).
5. Plasmapheresis is recommended for thrombotic micro-angiopathies (TMA) induced by ticlopedine, Clopidogrel and a number of other medications.
6. Plasmapheresis is recommended for HIV induced thrombotic micro-angiopathy (TMA).
7. Plasmapheresis can be considered in the rare combination of TMA and catastrophic anti-phospholipid syndrome if standard treatment provides insufficient effect.

6.6.4.3 Supplementation of clotting factors for deficiencies

Dilution coagulopathy due to plasmapheresis

Please refer to Chapter 5 for use of fresh frozen plasma (FFP) with dilution coagulopathy for surgical indications.

Dilution coagulopathy can occur in the case of daily plasmapheresis (or every other day) with a non-plasma substitution agent. This concerns all clotting factors, including fibrinogen and anti-thrombin; it takes approximately 2 – 3 days for the factors to reach starting values. Thrombosis has been described incidentally with the use of albumin as a substitution liquid; the estimated incidence is 0.060 – 0.14% (Ziselman 1984). Bleeding has very rarely been described. In the case of diagnostic (e.g. kidney biopsy) or other surgical procedures or for

pulmonary bleeding with Goodpasture's syndrome and Wegener's Myeloma, the level of clotting factors and fibrinogen should be checked before or during . plasmapheresis. It is advisable to administer plasma (15 – 30 mL/kg based on coagulation screening) at the end of plasmapheresis (Kaplan 1999).

Tapering oral anti-coagulants

With an INR > 7, vitamin K is given orally without bleeding and intravenously in the case of bleeding. Pro-thrombin complex (4 factor concentrate) is given in the case of severe bleeding.

Tapering fibrinolytics

It is recommended to administer tranexamic acid and repeat it after six hours if necessary. Plasma (or fibrinogen concentrate) should be administered based on the aPTT and the fibrinogen level if the activated partial thromboplastin time (aPTT) is prolonged and the fibrinogen level is decreased. This can be repeated if necessary (Van Aken 1991).

Conclusions 6.6.4.3

Level 3	Dilution coagulopathy can occur with daily plasmapheresis treatment (or every other day) if plasma is not used as substitution liquid. <i>C Kaplan 1999</i>
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Level 3	Tranexamic acid is the component of choice for tapering anti-fibrinolytics. Plasma or a fibrinogen preparation can be administered – based on aPTT and fibrinogen level – in the case of bleeding with a prolonged activated partial thromboplastin time (aPTT) and a low fibrinogen level. <i>C Van Aken 1991</i>
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Recommendations 6.6.4.3

1.	In the case of procedures, it is recommended to take into consideration the dilution coagulopathy due to plasmapheresis treatment with a daily frequency (or every other day) without plasma as substitution liquid.
2.	Treatment with plasma does not have a role in vitamin K deficiency and/or the tapering of oral anti-coagulants(vit.K antagonists).
3.	For the tapering of anti-fibrinolytics in the case of bleeding, it is recommended to administer plasma or a fibrinogen preparation – based on aPTT and fibrinogen level – in addition to tranexamic acid in the case of an prolonged activated partial thromboplastin time (aPTT) and a low fibrinogen level.

6.6.4.4 Plasma transfusion policy for severe disseminated intravascular coagulation (DIC) with bleeding

Disseminated intravascular coagulation (DIC) occurs in many different clinical situations including sepsis, trauma, haemolysis, malignancies – particularly with metastases – leukaemias and with severe obstetric complications. The most important therapeutic aim for DIC is the treatment of the underlying disease. If this does not provide sufficient result, extra supportive measures may be necessary.

In the framework of this guideline, only the role of plasma for patients with severe DIC who are bleeding will be described.

The use of plasma in patients with DIC who are bleeding has not been examined in a RCT. In the many reviews on DIC, the recommendations are based on theoretical considerations and expert opinions. There are few indications that the supplementation of clotting factors enhances the process of DIC (Levi 2009). Sometimes large quantities of plasma are necessary to supplement the clotting factors. In American literature, cryo-precipitate is often administered, but this is not available in the Netherlands and fibrinogen concentrate is an option for the reduction of the amount of plasma required (10 – 15 mL plasma/kg body weight is required for a 0.5 g increase in fibrinogen). The efficacy and safety of recombinant factor VIIa (rFVIIa) has not been demonstrated (Levi 2009).

Conclusions 6.6.4.4

Level 4	In the case of severe disseminated intravascular coagulation (DIC) with bleeding, the use of fibrinogen concentrate can reduce the plasma requirement. <i>D</i> <i>Levi 2009</i>
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Recommendation 6.6.4.4

In patients with disseminated intravascular coagulation (DIC) who are bleeding, need to undergo an invasive procedure or have some other severe risk of bleeding, treatment with plasma, supplemented by a fibrinogen concentrate if necessary, should be considered.

6.6.5 Plasma component choice and blood group incompatibility

6.6.5.1 Plasma component choice

Various types of plasma components are available. In the Netherlands, we use quarantined fresh frozen plasma (FFP), obtained exclusively from male non-transfused donors since 2007. If this guideline refers to plasma, it is referring to this component. In neighbouring countries, methylene blue treated plasma (MB-FFP) is used and – in a study context – photodynamically inactivated plasma is used, also obtained from individual donors.

Solvent-detergent treated (SD) plasma is a pooled plasma component and has fewer allergic side effects compared to plasma from individual donors, including Transfusion Related Acute Lung Injury (TRALI). A disadvantage is that not all pathogens are inactivated by SD treatment, for example vCJD. The use of a specific prion-removal filtration step during the preparation process of SD plasma is promising but has not yet resulted in an authorised component.

The choice of plasma component depends strongly on the indication and whether a small amount of plasma is required or massive amounts as in the case of TTP or DIC, in which SD plasma has some benefits. There is hardly any research available to make evidence-based choices in relation to the indication (Bianco 1999).

Conclusions 6.6.5.1

Level 4	Experts are of the opinion that the choice of plasma component depends strongly on the indication and whether a small quantity of plasma is
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	<p>required or massive amounts – as is the case in thrombotic thrombocytopenic purpura (TTP), in which case Solvent-detergent (SD) plasma has some benefits.</p> <p><i>D</i> <i>Bianco 1999</i></p>
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Level 4	<p>There is hardly any research available to make considered choices for a certain plasma preparation in relation to the indication.</p> <p><i>D</i> <i>Bianco 1999</i></p>
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6.6.5.2 Blood group incompatibility

A recent cohort study showed that transfusion of ABO minor incompatible plasma after organ transplantation was associated with more multi-organ damage and that – in a surgical population – administration of ABO compatible but not ABO identical plasma was associated with a higher mortality than administration of ABO identical plasma (Benjamin 1999, Shanwell 2009). This could be caused by soluble immune complexes of soluble A and/or B + anti-A and/or anti-B antibodies (Shanwell 2009).

Conclusion 6.6.5.2

Level 3	<p>Two studies suggest that transfusion of ABO incompatible plasma causes more multi-organ damage and a higher mortality.</p> <p><i>C</i> <i>Benjamin 1999</i> <i>B</i> <i>Shanwell 2009</i></p>
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Recommendations 6.6.5

1.	Further research is essential to be able to recommend the optimal plasma component in relation to indication and patient.
2.	Further research on the effects of ABO compatible but not ABO identical plasma is recommended and it is preferable to transfuse in an ABO identical manner.

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CHAPTER 7: TRANSFUSION REACTIONS AND RELATED CONDITIONS

7.1. Set up

Following a general introduction about adverse effects of transfusion of blood components and the differential diagnosis and treatment of acute transfusion reactions (7.1), this chapter will then discuss non-infectious complications (7.2) and infectious complications (7.3) of blood transfusions.

7.1.1 General introduction

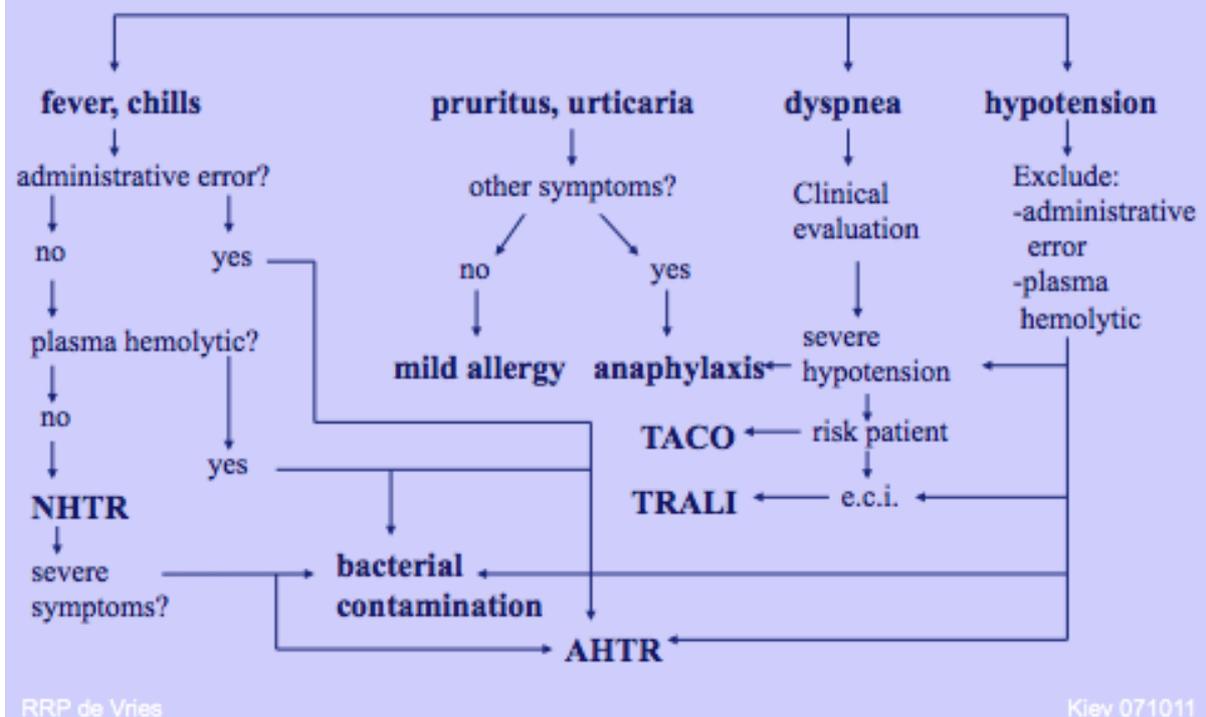
The timely recognition and treatment of transfusion reactions and related conditions is of great importance for clinicians, nurses, the laboratory and the blood bank alike (Andrzejewski 2007). This justifies a separate section in this guideline. Chapter 9 discusses the requirements that a hospital must meet concerning the monitoring of the transfusion chain, such as having access to a functioning blood transfusion committee, a haemovigilance official, a haemovigilance employee, and a training and further education program for all those involved in the transfusion chain.

Transfusion reactions can be divided in several ways. For this guideline, it was decided to divide according to cause, namely into non-infectious and infectious complications. In addition, the categorisation into acute symptoms during or within 24 hours of the transfusion and non-acute symptoms more than 24 hours after the transfusion is also used. All acute reactions – except those due to bacterial contamination – are non-infectious. Acute reactions require an acute diagnostic and – if necessary – treatment policy. For this reason, we will first focus on the diagnosis and treatment of acute transfusion reactions.

7.1.2 Differential diagnosis for (suspected) acute transfusion reactions

Figure 7.1: Differential diagnosis and treatment of acute transfusion reaction¹

1: example of existing protocol



HTR = haemolytic transfusion reaction. FNHTR = febrile non-haemolytic transfusion reaction
 TACO = transfusion-associated circulatory overload. TRALI = Transfusion Related Acute Lung Injury

Explanation of figure 7.1:

1. **Hypotension:**
 - Rule out acute haemolytic transfusion reactions (see point 3)
 - Consider bacterial contamination, sepsis (see point 3)
 - Consider anaphylactic reaction (see points 2 and 3)
 - Consider TRALI (see point 2)
 - Consider non-transfusion related cause
2. **Dyspnoea:**
 - Rule out overfilling based on clinical symptoms. Monitor fluid balance. Chest X-ray if indicated; if overfilling/TACO (Transfusion Associated Circulatory Overload) is diagnosed, remove excess fluid and if the response is good, consider slow administration of the component
 - Consider anaphylactic reaction (skin symptoms, glottis oedema), (see point 4)
 - If there is no anaphylactic reaction or overfilling, consider Transfusion Related Acute Lung Injury (TRALI), chest X-ray
3. **Fever:**
 - ≥ 2 °C temperature increase and/or cold shivers: consider bacterial contamination, take blood cultures (aerobic/anaerobic) from patient and

component; in the case of sepsis, treat as such and start antibiotics; consider haemolytic transfusion reaction (see paragraph 7.2); all negative: see paragraph 7.2. ((F)NHTR).

- < 2 °C increase without cold shivers: can this be explained by patient's clinical condition? (take note of temperature curve); has the patient used non-steroidal anti-inflammatory drugs (NSAIDs) or other anti-pyretic medication (paracetamol)?; If there are no indications for bacterial contamination or mix up and haemolysis has been ruled out: give paracetamol if necessary and consider resuming the transfusion if the patient's temperature decreases and he/she is in good condition.

4. *Itching/urticaria:*

- If there are no anaphylactic symptoms (such as glottis oedema, hypotension, shock): consider administering an anti-histamine. Transfusion can be resumed with adequate response.

The recommendations provided below are based on the opinions of experts and international guidelines (evidence level 4).

Recommendations 7.1.2

1. A nurse must observe the patient for **5 to 10 minutes** after starting the transfusion of each new unit. The vital functions should be recorded at the end of this period. Clearly define which parameters should be monitored (heart rate, temperature, blood pressure, etc.) during transfusion and at what frequency..
2. In the case of a (suspected) transfusion reaction other than itching or urticaria, the transfusion should be stopped and the unit disconnected if necessary, in consultation with the treating physician. The infusion system should be left in place. Rapid and targeted examination by the blood transfusion laboratory is also required.
3. The treating physician should be contacted for the differential diagnosis and treatment of acute transfusion reactions. It is recommended that the treating physician follows the above-mentioned algorithm (7.1) "suspected acute transfusion reaction" (including explanation) or the hospital's own schedule that has been adapted to the local situation. For more detailed recommendations for (suspected) specific reactions: see paragraph 7.2.
4. If anaphylactic symptoms (such as glottis oedema, hypotension, shock) are present: disconnect the unit immediately, connect a neutral infusion solution (e.g. 0.9% NaCl) and treat as an anaphylactic reaction: anti-histamines, corticosteroids and adrenalin, if necessary. Consult the transfusion specialist about diagnosis of IgA deficiency. See also paragraph 7.2.3.
5. Before disconnecting the unit, it should first be sealed ('clamped'), in order to prevent the reflux of blood from the patient to the donor unit.
6. If the blood component is disconnected, it should be returned to the blood transfusion laboratory as soon as possible for further examination. The hospital must provide instructions for disconnection, transport & storage conditions, and the method of sampling and these instructions must be followed.
7. Reporting: Transfusion reactions must first be reported to the treating doctor and the blood transfusion laboratory. Sanquin Blood Supply should be contacted as soon as possible with each suspected transfusion reaction or incident that may have

consequences for other components from this donor (these donors) (for example: suspected bacterial or viral contamination of a unit, suspected Transfusion Related Acute Lung Injury (TRALI)) The haemovigilance official of the hospital reports all reactions and incidents to the TRIP (Transfusion Reactions in Patients) National Haemovigilance Office. Severe reactions or calamities must also be reported to the Health Care Inspectorate (IGZ). See www.tripnet.nl for reporting and definitions of severity.

8. The blood sample for compatibility testing (also called cross-match blood) must be stored for seven days at a maximum of 4 °C to 8 °C for testing of possible transfusion reactions.
9. Systematic training of nurses in the field of prevention, recognition and treatment of transfusion reactions is indicated.
10. In addition to a haemovigilance official, each hospital should also have a haemovigilance nurse/employee. An important task of the haemovigilance nurse/employee is the training of all people involved in the prescription and administration of blood components (see Chapter 9.3).
11. The working group is of the opinion that haemovigilance should encompass both transfusions of (short shelf-life) blood components and blood-saving techniques.

7.2 Non-infectious complications of transfusions

The recommendations formulated in 7.2 are also largely based on level 4 evidence – i.e. expert opinions, international guidelines and manuals. If the evidence is stronger than level 4, this is indicated in the text.

7.2.1 Acute haemolytic transfusion reaction

An acute haemolytic transfusion reaction is defined as increased breakdown of erythrocytes occurring within several minutes after the start to 24 hours after the end of a transfusion. Symptoms can include: decrease in blood pressure ≥ 20 mmHg systolic and/or diastolic, fever/cold shivers, nausea/vomiting, back pain, dark or red urine, no or only slight increase in Hb or unexpected decrease in Hb.

Scientific support

An acute haemolytic transfusion reaction is usually the result of a transfusion involving (an) ABO incompatible blood component(s) due to administrative errors (Rudmann 1995, Mollison 1997, Sazama 1990, Linden 2000, SHOT 2008). The risk of a fatal reaction occurring depends, among other factors, on the amount of transfused blood, the clinical condition of the patient and the time lapsed between the start of the transfusion and the start of the treatment (Rudmann 1995, Sazama 1990, SHOT 2008). Incompatible units of plasma and platelet concentrates can also cause haemolysis due to antibodies and in rare cases can cause an acute haemolytic transfusion reaction. Antibodies (both IgM and IgG) against ABO antigens are very efficiently able to activate the complement system and thereby cause severe haemolysis.

Other antibodies can also cause an acute haemolytic transfusion reaction. Activation of the complement system causes the release of anaphylatoxins (C5a, C4a, C3a), serotonin and histamine, which in turn cause some of the clinical symptoms associated with an acute haemolytic transfusion reaction. Various mechanisms activate the clotting cascade and this

results in disseminated intravascular coagulation. The release of haemoglobin in plasma results in haemoglobinuria; the acute renal insufficiency is caused primarily by renal ischaemia (Rudmann 1995, Mollison 1997).

Fortunately, the acute haemolytic transfusion reaction is rare, but the true incidence is hard to determine due to under-reporting and the diagnosis can also be missed because the clinical symptoms are not specific. . TRIP reports 2003-2007 show an incidence of 1 per 43,796 administered blood components (TRIP reports).

The clinical symptoms of an acute haemolytic transfusion reaction can occur even after transfusion of a minimal amount of incompatible blood; however, the most severe reactions are usually seen after transfusion of larger quantities (> 200 mL). The most common symptoms are fever and cold shivers, but sometimes a transfusion reaction starts with a feeling of general malaise and back pain. In addition, dyspnoea, a light-headed feeling, pain at the infusion site or chest pains and nausea can occur. Sometimes haemoglobinuria is the first symptom. The most severe cases are accompanied by hypotension and shock, acute renal insufficiency with anuria and a (strongly) elevated tendency to bleed due to disseminated intravascular coagulation. In unconscious patients or patients under general anaesthesia, an increased tendency to bleed can be the first (or only) symptom of an acute haemolytic transfusion reaction.

Differential diagnosis should include auto-immune haemolytic anaemia, cold agglutinin syndrome and non-immunological causes such as transfusion of a strongly haemolytic erythrocyte concentrate (e.g. due to freezing or heating of the erythrocyte unit), the infusion of hypotonic solutions, haemolytic anaemia due to erythrocytic enzyme deficiencies (G-6-PD, Pyruvate kinase), paroxysmal nocturnal haemoglobinuria, haemolysis due to artificial heart valves, micro-angiopathic haemolytic anaemia (e.g. HUS), medication-induced intravascular haemolysis and infections such as malaria or clostridium.

Conclusions 7.2.1

Level 3	<p>The occurrence of symptoms such as fever, cold shivers, flushing, hypotension and/or dyspnoea soon – within several minutes to hours – after starting a transfusion of a blood component may indicate an acute haemolytic transfusion reaction.</p> <p><i>C Rudmann 1995, Mollison 1997</i></p>
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Level 3	<p>Acute haemolytic transfusion reactions are rare, but can be very severe and are usually the result of administrative errors in the transfusion procedure. The risk of a fatal reaction occurring depends, among other factors, on the amount of transfused blood, the clinical condition of the patient, and the time lapsed between the start of the transfusion and the start of the treatment.</p> <p><i>C Rudmann 1995, Sazama 1990, SHOT 2008</i></p>
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Level 3	<p>Treatment of an acute transfusion reaction consists of stopping the transfusion immediately, maintaining adequate renal function and</p>
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combating the consequences of any disseminated intravascular coagulation (DIC) and/or increased tendency to bleed.

C *Rudmann 1995, Mollison 1997*

Recommendations 7.2.1

1. In the case of a (suspected) acute haemolytic transfusion reaction, the transfusion should be stopped immediately and the unit must be disconnected, blood must be collected for serological testing, Hb and haemolysis parameters must be tested and treatment (see recommendation 2) must be started.
2. The treatment of an acute haemolytic transfusion reaction begins with measures that maintain diuresis:
 - NaCl 0.9% infusion
 - Administer diuretics (furosemide), consider mannitol
 - In the case of shock, consider using inotropic agents
 - The further treatment is symptomatic, with special attention paid to possible disseminated intravascular coagulation (DIC)
 - There is no role for the administration of corticosteroids
3. The remainder of the relevant blood component should be returned to the blood transfusion laboratory immediately in order to determine the cause of the transfusion reaction.
4. Administrative and laboratory examination into the cause of the transfusion reaction should be performed/requested as soon as possible.
5. If it is suspected that the supplied blood component was labelled incorrectly, Sanquin Blood Supply should be contacted urgently.
6. Depending on the nature of the transfusion reaction, a report will be submitted to TRIP / Sanquin Blood Supply / the Health Care Inspectorate in accordance with the relevant hospital protocol.

7.2.2 Postponed (or delayed) haemolytic transfusion reaction

A postponed (or delayed) haemolytic transfusion reaction is defined as increased breakdown of erythrocytes occurring longer than 24 hours after a transfusion to a maximum of 28 days after transfusion. Symptoms such as unexplained decrease in Hb, dark urine, fever/cold shivers and jaundice are characteristic of a delayed haemolytic transfusion reaction.

Scientific support

The transfusion of blood components – both erythrocytes and platelets – can result in the formation of antibodies against antigens on transfused erythrocytes. Following transfusion of erythrocytes, 8.4% of the recipients develop clinically relevant antibodies targeted against erythrocyte antigens (Redman 1996). IgG alloantibodies targeted against erythrocytes can – over the course of time – become so weak that they can no longer be detected. When erythrocytes with the relevant antigen are subsequently administered, the antibodies will be produced in large quantities in a short period of time (boosted) – a so-called secondary immune response – causing the transfused erythrocytes to be broken down. A well-known example are Kidd antibodies. This can be expressed in the form of clinical symptoms such

as fever, cold shivers, haemoglobinuria and a decrease in Hb with abnormal haemolysis parameters (LDH), an increase in unconjugated bilirubin and a decrease in haptoglobin (Issitt 1998). Therefore, confirmed clinically relevant alloantibodies against erythrocytes should be taken into consideration for all further transfusions during the entire life-span of the recipient. This also applies if the antibodies can no longer be detected, due to the risk of a delayed haemolytic transfusion reaction due to boosting of the antibodies. When demonstrating clinically relevant antibodies, it is recommended to check the patient and/or the laboratory history for the occurrence of any delayed haemolytic transfusion reaction.

Conclusions 7.2.2

Level 3	The formation of antibodies against erythrocytes is a frequent complication of blood transfusions. <i>C Redman 1996</i>
Level 3	There are indications that 8.4% of the recipients of erythrocyte transfusions develop clinically relevant antibodies targeted against erythrocyte antigens. <i>C Redman 1996</i>
Level 3	Patients who have IgG alloantibodies against erythrocytes that are no longer detectable can develop a delayed haemolytic transfusion reaction after transfusion of erythrocytes with the relevant antigen. <i>C Issitt 1998</i>

Other considerations

Knowledge of the patient's erythrocyte antibody history is very important, both when requesting a blood transfusion and when searching for a diagnosis of undefined transfusion reactions and/or unexplained blood breakdown. This information should be directly accessible for the entire life of the patient. The TRIX database for irregular red cell antibodies is a national database in which confirmed irregular antibodies (see 3.3.3) can be registered. It is of great importance that all hospitals are linked to this system, contribute to the registration and consult this register prior to transfusion. Although a transfusion card – given to a patient if he/she has irregular antibodies – is an aid, in practice this is not conclusive.

Recommendations 7.2.2

1.	Data concerning the presence of erythrocyte antibodies should be included in the patient's transfusion history.
2.	The patient's antibody history and TRIX (the TRIX database for irregular red cell antibodies) should be consulted with each request for a cellular blood component (see 3.3.3).
3.	Irregular erythrocyte antibodies should be registered in TRIX.

4. If clinically relevant antibodies are detected after a recent transfusion, it is recommended to check the patient and/or the laboratory history for the occurrence of any delayed haemolytic transfusion reaction.

7.2.3 Anaphylactic transfusion reaction

An anaphylactic transfusion reaction is defined as a rapidly progressing allergic reaction that occurs within several seconds after the start to shortly after the end of a transfusion and is characterised by systemic (respiratory, cardiovascular or gastro-intestinal) symptoms. Symptoms that can occur include: stridor, decrease in blood pressure ≥ 20 mm Hg systolic and/or diastolic, nausea/vomiting, diarrhoea, back pain. If an allergic reaction is associated only with itching and/or skin symptoms (urticaria), this is referred to as an “other allergic reaction”. This is discussed in the next sub paragraph 7.2.4.

Scientific support

A potentially severe reaction can occur within a few seconds to several minutes after the start of a transfusion, which includes possible allergic skin symptoms (itching, urticaria) and also systemic symptoms such as airway obstruction (glottis oedema, bronchospasm, cyanosis), circulatory collapse (decreased blood pressure, tachycardia, arrhythmia, shock and loss of consciousness), or gastro-intestinal symptoms (nausea, vomiting, diarrhoea). Causes of such an anaphylactic transfusion reaction can include: pre-existing antibodies against serum proteins such as IgA, albumin, haptoglobin, alpha-1 anti-trypsin, transferrin, C3, C4 or allergens in the donor blood against which the recipient has been sensitised in the past, such as: medicines (penicillin, aspirin), food ingredients, substances used in the production and sterilisation of blood collection and blood administration systems (formaldehyde, ethylene oxide). In rare cases, passive transfer of IgE antibodies from the donor to the recipient can occur.

An IgE mechanism is not always the cause of an anaphylactic transfusion reaction and in practice the cause is usually not found (Vamvakas 2007, Gilstad 2003).

Anaphylactic transfusion reactions are an important cause of transfusion-related morbidity. Annually, approximately 18 anaphylactic reactions of severity grade 2 (see definitions as used by TRIP on www.tripnet.nl) or higher are reported to TRIP (roughly 1:40,000 blood components (TRIP report 2007). They are reported for all types of blood components, but occur relatively more often with the administration of platelets or plasma (TRIP report 2007).

Anaphylactic transfusion reactions can occur due to pre-existing anti-IgA antibodies (both IgE and IgG) in a recipient with IgA deficiency (< 0.05 mg/dL) or due to pre-existing subclass or allotype specific anti-IgA in a recipient with a normal IgA titre (Vamvakas, Sandler). IgA deficiency occurs in 1 in 500 – 700 Caucasians (Yuan). Not every individual who is IgA deficient has antibodies and even if anti-IgA is present, this does not mean that an anaphylactic transfusion reaction will always occur. Up to 20% of the anaphylactic transfusion reactions could be attributable to anti-IgA. However, until 2007, anti-IgA was rarely shown to be the cause of the anaphylactic transfusion reactions that were reported (to TRIP) (Gilstad 2003, TRIP rapporten 2003-2007, Sandler 1995). Tests should be performed for anti-IgA after a severe anaphylactic transfusion reaction and if positive, washed blood components should be administered in case of future transfusions. If there is a need for

transfusion of platelets or plasma, one could consider using components obtained from IgA deficient donors (Sandler 1995, Council of Europe 2007).

Haptoglobin deficiency with anti-haptoglobin of IgG and IgE specificity was found in 2% of Japanese patients who were examined after an anaphylactic transfusion reaction. Rare cases of anaphylactic reactions have also been described in deficiencies of plasma factors, such as complement and von Willebrand factor (Shimada 2002).

Conclusions 7.2.3

Level 3	<p>A cause is found in only a minority of anaphylactic transfusion reactions. Antibodies against IgA are the most frequently described cause of anaphylactic reactions to (blood) components that contain plasma.</p> <p><i>C Vamvakas 2007, Sandler 1995</i></p>
Level 4	<p>Anaphylactic transfusion reactions are reported for all types of blood components but occur relatively more often with the administration of platelets or plasma.</p> <p><i>D TRIP rapport 2007</i></p>
Level 3	<p>Haptoglobin deficiency with anti-haptoglobin of IgG and IgE specificity was found in 2% of Japanese patients who were examined after an anaphylactic transfusion reaction. Rare cases of anaphylactic reactions have also been described in deficiencies of plasma factors, such as complement and von Willebrand factor.</p> <p><i>C Shimada 2002</i></p>

Recommendations 7.2.3

1.	<p>In the case of a (suspected) anaphylactic reaction, the transfusion should be stopped immediately (see schedule 7.1) and treatment must be started. Deficiency of IgA and presence of anti-IgA and anti-IgA sub class antibodies should be considered.</p>
2.	<p>A five times washed erythrocyte concentrate – from which plasma proteins have been virtually completely removed (see 2.2.1) – should only be used for subsequent transfusions in the case of a proven anaphylactic reaction due to antibodies against IgA or a demonstrated IgA deficiency (< 0.05 mg/dL (= 0.5 mg/L)).</p>
3.	<p>In the case of proven anaphylactic reactions due to antibodies against IgA or demonstrated IgA deficiency (< 0.05 mg/dL (= 0.5 mg/L)), one should consider using IgA deficient donors for platelet transfusion and transfusion of fresh frozen plasma. (see 2.2.7)</p>
4.	<p>If severe anaphylactic reactions to erythrocyte concentrates still occur, which cannot be explained by an IgA deficiency or anti-IgA, one should consider administering twice washed erythrocyte concentrates in future (see 2.2.1).</p>

7.2.4 Non-systemic allergic transfusion reactions

If allergic symptoms occur within several minutes during transfusion up to several hours after transfusion, which are limited to the skin – such as itching, redness and urticaria – then a different (i.e. non-anaphylactic) allergic transfusion reaction should be considered. Such a different reaction does not involve any respiratory, cardiovascular or gastro-intestinal symptoms.

Scientific support

Allergic skin symptoms – such as itching, redness and urticaria – can occur within several minutes to hours after transfusion, without the presence of systemic allergic symptoms such as airway obstruction (glottis oedema, asthma, cyanosis), circulatory collapse (decrease in blood pressure, tachycardia, arrhythmia, shock and loss of consciousness), or gastro-intestinal symptoms (nausea, vomiting, diarrhoea) (Vamvakas 2007).

The name ‘allergic transfusion reaction’ assumes an interaction between an allergen and a previously formed IgE, but in practice this has not been studied. Cytokines originating from donor platelets can also cause such reactions (Kluter 1999).

Urticarial reactions can (depending on the method or registration) occur in approximately 1 – 3% of transfusions with plasma-containing blood components (Vamvakas 2007). Approximately 200 ‘other allergic reactions’ are reported annually to TRIP: this is an overall ratio of 1:3,000 short shelf-life blood components supplied. The frequency is higher for platelet concentrates (roughly 1:600) than for plasma (1:1,000) and erythrocyte concentrates.

The frequency of allergic reactions is not reduced by the removal of leukocytes prior to the storage of platelet concentrates. The storage duration of platelets also does not seem to affect the risk of allergic transfusion reactions (Kluter 1999, Uhlmann 2001, Patterson 1998, Sarkodee-Adoo 1998, Kerkhoffs 2006).

The use of platelet concentrates in which 70% of the plasma has been replaced by platelet storage solution (PAS) appears to result in a reduction of allergic transfusion reactions (Kerkhoffs 2006, Rebibo 2008).

Conclusions 7.2.4

Level 3	The name ‘allergic transfusion reaction’ assumes an interaction between an allergen and a previously formed IgE, but in practice this is not investigated. Cytokines from donor platelets can also result in such reactions. <i>C Kluter 1999</i>
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Level 3	Urticarial reactions can (depending on the method or registration) occur in approximately 1 – 3% of transfusions with plasma-containing blood components. <i>C Vamvakas 2007</i>
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Level 3	<p>The frequency of allergic reactions is not reduced by the removal of leukocytes prior to storage. The storage duration for platelets also does not appear to influence the risk of allergic transfusion reactions.</p> <p><i>C Kluter 1999, Uhlmann 2001, Patterson 1998, Sarkodee-Adoo 1998, Kerkhoffs 2006</i></p>
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Level 3	<p>The use of platelet concentrates in which 70% of the plasma has been replaced by platelets storage solution (PAS) appears to result in a reduction of allergic transfusion reactions.</p> <p><i>C Kerkhoffs 2006, Rebibo 2008</i></p>
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Other considerations

In most international guidelines, recommendations are made based on expert opinion (evidence level 4) to administer an anti-histamine for other – i.e. mild and non-anaphylactic – allergic reactions; usually the transfusion can then proceed with caution. After one (or more) allergic reaction(s), an anti-histamine can be administered as pre-medication for future transfusions.

Rare cases of clusters of allergic reactions have been observed, associated with certain materials used in the processing of donor blood. The so-called “red eye syndrome” was associated with allergic symptoms and conjunctivitis in recipients of erythrocytes that were treated with a certain filter for the removal of leukocytes (Centers for disease control and prevention 1998). It is important to recognise such a pattern in a timely manner, by reporting this type of transfusion reaction.

Recommendations 7.2.4

1. **It is recommended to administer an anti-histamine in the case of a mild and non-anaphylactic allergic transfusion reaction; usually the transfusion can proceed with caution.**
2. **After one (or more) mild and non-anaphylactic allergic transfusion reaction(s), an anti-histamine can be administered as pre-medication for future transfusions.**
3. For patients with mild and non-anaphylactic allergic transfusion reactions, the blood components for administration do not need to undergo any extra processing steps, such as washing.

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

A non-haemolytic (also called febrile) transfusion reaction (NHTR) is defined as a temperature increase ≥ 2 °C with or without cold shivers (CS) during or in the first two hours after transfusion, with normalisation of the temperature within 24 hours after transfusion or CS within this same period. During a non-haemolytic transfusion reaction, there are no other relevant signs/symptoms and there are no indications for haemolysis, an infectious cause or any other cause.

A mild non-haemolytic febrile reaction is defined as an increase in temperature $> 1\text{ }^{\circ}\text{C}$ ($< 2\text{ }^{\circ}\text{C}$) during or within the first two hours after transfusion, with normalisation of the temperature within 24 hours after transfusion. A mild non-haemolytic febrile reaction also does not produce any other relevant complaints/symptoms and there are no indications for haemolysis, an infectious cause or any other cause.

Scientific support

The incidence of NHTR before the introduction of leuko-reduction varied from 0.5 – 1% in a general hospital to more than 10% of patients in an academic hospital or a centre that treats haemato-oncological patients (Williamson 1999). A frequency of approximately one per 1,000 administered blood components was reported to TRIP in 2008 (TRIP report 2008). NHTR occurs more often after transfusion of platelets than after transfusion of erythrocytes (Heddle 2007, 1995, 1993).

A NHTR or mild non-haemolytic febrile reaction can be caused by:

- antibodies against leukocyte antigens (HLA antibodies);
- accumulation of pyrogenic substances during storage of the blood component .

During the storage of blood components , pyrogenic substances can be released from leukocytes and these substances dissolve in the blood plasma. Leuko-reduction does reduce the occurrence of NHTR, but these reactions can also occur after the administration of leukocyte reduced blood components (Heddle 2007).

Fever or CS can also be the first symptom of a haemolytic transfusion reaction or post-transfusion bacteraemia due to bacterial contamination of a blood component . A Transfusion Related Acute Lung Injury (TRALI) can also be associated with fever, as is the case for an allergic reaction. When evaluating the cause of an increase in temperature during blood transfusion, the patient's entire clinical condition should be analysed, including the construction of a temperature curve.

Usually no specific cause is found for the NHTR and the symptoms disappear within 24 hours. Anti-pyretic medication (paracetamol, NSAIDs) can be administered to combat the symptoms.

There is no sound evidence to support the standard administration of pre-medication to prevent febrile reactions (Heddle 2007, Kennedy 2008). A small randomised, double blind study of 315 haematology and oncology patients transfused with (a total of) 4199 'bedside' leuko-reduced erythrocyte concentrates or platelet concentrates showed that the use of pre-medication consisting of 500 mg paracetamol and 25 mg diphenhydramine did not change the risk of developing a transfusion reaction (1.44% versus 1.51% with placebo), but there was a slight decrease in the number of febrile reactions (0.35% versus 0.64, $p = 0.08$) (Kennedy 2008). The role of pre-medication seems more useful for patients who have had a previous NHTR.

Conclusions 7.2.5

Level 3	There are indications that non-haemolytic transfusion reactions (NHTR) occur more often with transfusion of platelets than the administration of erythrocytes.
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	<i>C Heddle 2007</i>
Level 3	<p>There is no sound evidence to support the standard administration of pre-medication to prevent febrile reactions during transfusions.</p> <p><i>C Heddle 2007</i> <i>B Kennedy 2008</i></p>
Level 3	<p>There are indications that the use of pre-medication with 500 mg paracetamol and 25 mg diphenhydramine results in an unchanged risk of the occurrence of a transfusion reaction (1.44% versus 1.51% for placebo), but there is a slight decrease in the number of febrile reactions (0.35% versus 0.64, $p = 0.08$).</p> <p><i>B Kennedy 2008</i></p>
Level 3	<p>Leukocyte reduction does not prevent non-haemolytic transfusion reactions (NHTR), but does reduce the frequency.</p> <p><i>C Heddle 2007</i></p>

Recommendations 7.2.5

1. The diagnosis of non-haemolytic transfusion reaction (NHTR) is a diagnosis based on exclusion.
2. A non-haemolytic transfusion reaction (NHTR) is never life-threatening, but transfusion reactions that are life-threatening – such as acute haemolysis transfusion reaction (AHTR), bacterial contamination and Transfusion Related Acute Lung Injury (TRALI) – must be ruled out before the diagnosis of NHTR may be made.
3. When evaluating the cause of an increase in temperature during blood transfusion, the patient's entire clinical condition should be analysed, and a temperature curve should be constructed.
4. Anti-pyretic medication (paracetamol, NSAIDs) can be administered to combat the symptoms of a non-haemolytic transfusion reaction (NHTR).
5. The transfusion can be resumed once an acute haemolytic transfusion reaction (AHTR), bacterial contamination and Transfusion Related Acute Lung Injury (TRALI) have been ruled out.

7.2.6 Transfusion Related Acute Lung Injury (TRALI)

Transfusion Related Acute Lung Injury (TRALI) is a severe lung complication of plasma-containing blood components (Palfi 2001). TRALI is associated with symptoms of acute lung injury, such as dyspnoea and hypoxia, which occur during or within six hours after a transfusion. The chest X-ray shows bilateral interstitial abnormalities.

Scientific support

TRALI is an adult respiratory distress syndrome (ARDS) or acute lung injury (ALI) that occurs within six hours after a transfusion of blood components (TRIP definition: symptoms of acute lung damage – such as dyspnoea and hypoxia – that occur during or within six hours after a transfusion, with bilateral interstitial abnormalities on the chest X-ray, immunohaematological and bacteriological tests showing no abnormalities).

An international consensus meeting of the TRALI consensus panel in Canada in 2004 set criteria to meet the definition of (TR)ALI. Other causes for dyspnoea or hypoxia (transfusion-related or not) – in particular volume overload – should be ruled out. If there is a known risk factor for ALI (e.g. sepsis, pneumonia, massive blood transfusion or the use of a heart-lung machine), the Canadian consensus group suggests using the name ‘possible TRALI’. (Kleinman 2004). According to the working group of the American National Heart, Lung and Blood Institute, the diagnosis of TRALI can be made despite the presence of other ALI risk factors if there is a strong time relationship (within six hours after start of transfusion) to the transfusion (Kopko 2007, Goldman 2005).

Since 2005, approximately 20 reports of TRALI are made annually to TRIP that fall under the above-mentioned definition. According to the literature, the mortality of TRALI (5 – 15%) is lower than ALI due to other causes. In the period 2005 through 2007, TRIP received a total of six reports of death following a TRALI (imputability possible, probable or certain). As is the case in the United States and The United Kingdom, TRALI is therefore the most important transfusion-related cause of death in the Netherlands (Goldman 2005, SHOT 2007, FDA 2008).

TRALI with an immunological cause (“immune-mediated TRALI”) is caused by incompatible leukocyte antibodies.

Other biologically active substances in blood components can also activate leukocytes and cause TRALI. Both causes can amplify each other (double hit) via a mechanism in which a trigger is initially present in the endothelium of the lung vasculature. The transfusion then supplies the second ‘hit’. According to some authors, immune-mediated TRALIs are generally more severe than a TRALI for which no immunological cause has been demonstrated (Bux 2005).

Since 2007, only plasma from male (never transfused) donors is used for fresh frozen plasma in the Netherlands (due to the increased risk of the presence of HLA antibodies in women as a result of pregnancy). In addition, only plasma from male donors is added to combined platelet concentrates. It is expected that in the course of 2011, apheresis platelets for use in paediatric situations will also be obtained exclusively from male donors.

It is estimated that this has resulted in the total number of TRALI reports decreasing by one third (TRIP report 2010).

Conclusions 7.2.6

Level 3	<p>Adult Respiratory Distress Syndrome (ARDS) or Acute Lung Injury (ALI) that occurs in a patient within six hours of the administration of plasma-containing blood components is possibly a Transfusion Related Acute Lung Injury (TRALI).</p> <p>C Kleinman 2004</p>
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Level 3	<p>Immune-mediated Transfusion Related Acute Lung Injuries (TRALIs) are possibly more severe than TRALIs for which an immunological cause has not been demonstrated.</p> <p>C <i>Bux 2005</i></p>
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Other considerations

Although leukocyte serological testing is not essential to confirm the diagnosis of TRALI (Kleinman 2004), the findings can support the donor policy (e.g. future donations from involved donors). As TRALI is a donor-linked reaction, the reaction should be reported both to TRIP and to Sanquin Blood Supply and also to the Health Care Inspectorate if the reaction is severity grade 2 or higher.

Recommendations 7.2.6

1. A chest X-ray should be made for every suspected case of Transfusion Related Acute Lung Injury (TRALI).
2. (Possible) Transfusion Related Acute Lung Injury (TRALI) is a clinical diagnosis.
3. Other causes of dyspnoea or hypoxia (transfusion-related or not) – particularly volume overload – should be ruled out before making the diagnosis Transfusion Related Acute Lung Injury (TRALI).
4. Transfusion Related Acute Lung Injury (TRALI) must be reported both to TRIP and to Sanquin Blood Supply.
5. For each transfusion reaction that meets the definition of Transfusion Related Acute Lung Injury (TRALI), the donor(s) and the patient (in the case of administration of a leukocyte-containing blood component) must be examined for antibodies against HLA and/or granulocytes. Sanquin Blood Supply will coordinate this testing.

7.2.7 Volume overload / Transfusion Associated Circulatory Overload (TACO)

Volume overload or overfilling as the result of transfusion of a blood component is also called Transfusion Associated Circulatory Overload (TACO). TACO is diagnosed if the patient develops one or more of the following symptoms during or within six hours after transfusion: dyspnoea, orthopnoea, cyanosis, tachycardia > 100 bpm, ankle oedema or elevated central venous pressure. Other non-specific symptoms include headache, a feeling of tightness across the chest and a dry cough. Volume overload due to transfusion causes acute pulmonary oedema as a result of overfilling. The chest X-ray (if performed) shows an image consistent with overfilling in the case of TACO.

Scientific support

Transfusion Associated Circulatory Overload (TACO) forms part of the group of lung complications and should be distinguished from Transfusion Related Acute Lung Injury (TRALI) and the anaphylactic reaction. The frequency for this transfusion complication is between 2 and 8%, with a mortality of 5 – 20% (Popovsky 2007, 1985, Audet 1998, Gajic 2006, Rana 2006, Robillard 2008, FDA 2008, Li 2009). Both the Canadian and the French

haemovigilance systems have reported that volume overload is an important cause of transfusion-related mortality (Robillard 2008, Affsap 2007).

In severely ill patients, TACO is sometimes hard to distinguish – clinically and radiologically – from TRALI. Acute lung injury (ALI) and TACO could also occur simultaneously. The NTproBNP (N-terminal pro-brain natriuretic peptide) determination is also not specific enough to differentiate between the two entities (Li 2009). Volume overload can occur after transfusion of only one unit of erythrocyte concentrate.

It is important to treat TACO as early as possible. Treatment consists of stopping the transfusion, administering oxygen and anti-diuretics, getting the patient to sit upright and performing bloodletting, if necessary. For patients who are sensitive to TACO, it is recommended to transfuse slowly in future, e.g. 1 mL/kg/hour and/or administer diuretics before and/or during the transfusion.

Conclusions 7.2.7

Level 2	<p>Transfusion-associated circulatory overload (TACO) or volume overload occurs as a complication of blood transfusion and manifests itself as a pulmonary complication. It is important to distinguish TACO from transfusion-related acute lung injury (TRALI) and an anaphylactic reaction. The incidence of this transfusion complication is between 2 and 8%, with a mortality of 5 – 20%.</p> <p><i>B Gajic 2006, Rana 2006</i> <i>C Popovsky 1985, Audet 1998, Robillard 2008, FDA 2008, Li 2009</i> <i>D Popovsky 2007</i></p>
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Level 3	<p>Transfusion-associated circulatory overload (TACO), also called volume overload, appears to be an important cause of transfusion-related mortality.</p> <p><i>D Affsap 2007</i> <i>C Robillard 2008</i></p>
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Recommendations 7.2.7

<ol style="list-style-type: none"> 1. If dyspnoea, orthopnoea, cyanosis, tachycardia > 100 bpm, ankle oedema or elevated central venous pressure occurs during or within six hours after transfusion, one should always consider Transfusion Associated Circulatory Overload (TACO) (also called volume overload) next to Transfusion Related Acute Lung Injury (TRALI) or anaphylactic reaction. 2. One should consider taking a chest X-ray for each suspected case of Transfusion Associated Circulatory Overload (TACO) (also called volume overload). In the case of TACO, the chest X-ray will give an image consistent with cardiac decompensation. 3. If Transfusion Associated Circulatory Overload (TACO) (also called volume overload) is diagnosed, treatment should start as early as possible. The transfusion should be stopped immediately and the treatment can consist of the administration of oxygen and diuretics. Bloodletting may also be considered.
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4. In patients who are susceptible to Transfusion Associated Circulatory Overload (TACO) (also called volume overload), it is recommended to transfuse slowly in the future, e.g. 1 mL/kg/hour and/or administer diuretics before and/or during the transfusion.

7.2.8 Post-transfusion purpura (PTP)

Post-transfusion purpura (PTP) is a severe transient thrombocytopenia in a patient with a history of pregnancy and/or transfusion.

Scientific support

Post-transfusion purpura (PTP) is characterised by the occurrence of severe, transient thrombocytopenia – with or without bleeding – an average of nine (range 1 – 24) days after a transfusion of erythrocytes and/or platelets in a patient with a history of pregnancy or transfusion. The thrombocytopenia is often very severe, with the platelet count dropping below $10 \times 10^9/L$ in 80% of the patients. These are patients older than 15 years, usually (> 85%) women. In many cases the patients are negative for the platelet specific antigen HPA-1a and antibodies against HPA-1a can be detected, usually with a high titre. Occasionally, HPA antibodies with a different specificity are also detected (Mc Farland 2007).

It is not yet clear why PTP results in the breakdown of autologous platelets. Soluble platelet antigens from a donor may adhere to the patient's own platelets and/or there is epitope distribution. This could cause an auto-immune response against non-polymorphic epitopes on the membrane of the platelets (Shulman 1991, Watkins 2002, Taaning 1999).

The incidence of PTP in the United Kingdom has decreased since the introduction of general leuko-reduction in 1999 from 3.7 per 1,000,000 cell-containing components to 0.8 in the period 1996 through to 2005 (Williamson 2007). In the Netherlands, general leuko-reduction was implemented in 2001, before registration of TRIP started.

The laboratory diagnosis is important for the diagnosis of PTP and consists of – among others – the testing for HPA antibodies and performing HPA typing.

The differential diagnosis for suspected PTP includes auto-immune thrombocytopenia (ITP), sepsis, disseminated intravascular coagulation (DIC), bone marrow suppression, medication-induced thrombocytopenia (particularly heparin-induced thrombocytopenia (HIT)), passive transfer of platelet antibodies and thrombotic thrombocytopenic purpura (TTP).

High dose intravenous immunoglobulin (HD-IVIG) is the treatment of choice for PTP (Mueller-Eckhardt 1988). Plasma exchange transfusion with fresh frozen plasma was used frequently in the past, but is now only considered for those patients who do not respond to treatment with IVIG. There is no evidence that additional treatment with corticosteroids is effective (McFarland 2001). Platelet transfusions are only considered in case of life-threatening haemorrhages, as the transfused platelets (HPA-1a positive or HPA-1a negative) are broken down rapidly. A favourable result using transfusion of HPA-1a negative platelets has only been reported occasionally (Lippman 1988).

Mortality in the acute phase (Kroll 1993, Taaning 1994) is in the order of magnitude of 5 – 8% and is primarily caused by cerebral haemorrhages. If these do not occur the patient usually makes a full recovery. If a patient has experienced a period of PTP, there is a limited chance of recurrence with subsequent blood transfusions. For this reason, if these patients experience severe bleeding, it is advisable – after a period of PTP – to give platelets obtained from donors who are negative for the antigen (usually HPA-1a) against which the antibody is targeted (Kroll 1993).

Conclusions 7.2.8

Level 3	<p>Post-transfusion purpura (PTP) is a severe, potentially lethal adverse effect, characterised by severe, transient thrombocytopenia – with or without bleeding – that occurs an average of nine (spread 1 – 24) days after a transfusion of cellular blood components in a patient with a history of pregnancy or transfusion. These are patients older than 15 years, usually (> 85%) women.</p> <p><i>C McFarland 2001</i></p>
Level 3	<p>In many cases, patients with post-transfusion purpura (PTP) are negative for the platelet specific antigen HPA-1a and antibodies against HPA-1a can be detected, usually with a high titre. Occasionally, HPA antibodies with a different specificity can also be detected.</p> <p><i>C McFarland 2001</i></p>
Level 3	<p>High dose intravenous immunoglobulin (HD-IVIG) is the treatment of choice for post-transfusion purpura (PTP).</p> <p><i>C Mueller-Eckhardt 1988, McFarland 2001</i></p>
Level 3	<p>Prophylactic platelet transfusions are not indicated for post-transfusion purpura (PTP). Transfusion using platelet concentrates obtained from donors negative for the relevant HPA antigen (usually HPA-1a) can be considered in the case of severe bleeding. (See also Chapter 6).</p> <p><i>C Kroll 1993</i></p>

Other considerations

In surgical patients with thrombopenia who have had a transfusion, post-transfusion purpura (PTP) should be included in the differential diagnosis along with suspected heparin-induced thrombocytopenia (HIT).

Recommendations 7.2.8

1. The diagnosis of post-transfusion purpura (PTP) must be considered in every patient who develops severe thrombocytopenia within three weeks after a blood transfusion.

2. In the case of suspected post-transfusion purpura (PTP), HPA typing should be performed on the patient in addition to the determination of HPA antibodies.
3. Intravenous immunoglobulin (IVIg) is the treatment of choice for patients with post-transfusion purpura (PTP).
4. Prophylactic treatment with platelet transfusions is not indicated for post-transfusion purpura (PTP). Transfusion with HPA-1a negative platelet concentrates should only be considered in the case of severe bleeding.
5. Once a patient has experienced post-transfusion purpura (PTP), it is recommended for future platelet transfusions to administer platelets obtained from donors who are negative for the antigen against which the antibody is targeted.

7.2.9 Transfusion-associated 'graft-versus-host' disease (TA-GVHD)

Transfusion-associated graft-versus-host-disease (TA-GVHD) is characterised by the occurrence of clinical symptoms such as centrally initiating erythema, watery diarrhoea, fever, elevated liver enzymes and pancytopenia one to six weeks (usually eighteen days) after the administration of a T-lymphocyte containing and non-irradiated blood component (AABB 2006). The diagnosis TA-GVHD can be made with the aid of histological examination of a skin biopsy and a liver biopsy if necessary. Confirmation of the diagnosis is obtained by demonstrating an HLA discrepancy between DNA obtained from lymphocytes and that of nails or hair, or by demonstrating two different DNA profiles in the blood of the patient. Patients with decreased cellular immunity are the typical risk patients, but TA-GVHD can also occur in immune competent recipients (see Chapter 2).

Scientific support

Unfortunately, there are no pathognomonic symptoms in TA-GVHD (AABB 2006) and the diagnosis will often be missed as a result of the extensive differential diagnosis (including reaction to medication, viral and bacterial infection). On the other hand, the literature describes only a few real 'proven' TA-GVHD reactions, as only allogeneic T-lymphocytes demonstrated by molecular biological techniques can formally confirm the diagnosis (Hayakawa 1993, Ohto 1996).

The implementation of general leuko-reduction in 1999 in the United Kingdom has reduced the (slight) risk of TA-GVHD, as is evident from the reports to SHOT; they have received no further reports of TA-GVHD since 2001. As leukocyte reduced cellular components still contain enough T-lymphocytes to cause TA-GVHD, this measure alone is not enough (Williamson 2007, Council of Europe 2008) and irradiated components will always have to be used for patients at-risk. In the future, pathogen inactivation may eliminate the risk of TA-GVHD (Dwyre 2008). In the Netherlands, there have been no reports of TA-GvHD since the start of TRIP in 2001.

Conclusions 7.2.9

Level 4	Each T-lymphocyte containing blood component(including leukocyte-reduced) can cause a 'graft-versus-host' reaction.
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	<i>D AABB 2006, Hayakawa 1993, Ohta 1996, Williamson 2007, Raad van Europa 2008</i>
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Level 4	<p>Only allogeneic T-lymphocytes demonstrated by molecular biological techniques can formally confirm the diagnosis of transfusion-associated 'graft-versus-host' disease (TA-GVHD).</p> <p><i>D Hayakawa 1993, Ohta 1996</i></p>
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Other considerations

Following irradiation of cellular blood components with 25 Gy, the T-lymphocytes present in these components are no longer able to divide and therefore no longer able to cause GvHD.

Recommendation 7.2.9

In order to prevent a transfusion-associated 'graft-versus-host' reaction (TA-GVHD), T-lymphocyte containing blood components must be irradiated (25 Gy) before administration to patients at-risk (see Chapter 2 for indications for irradiated blood components).

7.2.10 Secondary haemochromatosis (haemosiderosis)

Secondary haemochromatosis (haemosiderosis) is defined as iron accumulation, with a ferritin level of at least 1000 µg/L, with or without organ damage caused by frequent erythrocyte transfusions.

Scientific support

Secondary haemochromatosis (haemosiderosis) is primarily the result of frequent blood transfusions. (Malcovatti 2007, Modell 2000, Borgna-Pignatti 2005). One unit of erythrocyte concentrate contains approximately 200 mg of iron, whilst no more than 1 – 2 mg of iron is absorbed from the diet by the intestines on a daily basis (Andrews 1999). Symptoms of haemochromatosis can occur after administration of approximately twenty erythrocyte concentrates. Often, the ferritin level is higher than 1000 µg/L. In general, it can be said that organ damage due to iron accumulation with transfusions occurs more quickly than with primary haemochromatosis (iron accumulation due to a congenital defect).

Iron accumulation can result in fibrosis and cirrhosis of the liver (Deugnier 2008), heart failure and cardiac arrhythmias (Buja 1971), diabetes mellitus, hypothyroidism, hypoparathyroidism and hypogonadism (Allen 2008). Disseminated pigmentation in the skin may occur as a result of an increase in melanocytes.

The diagnosis of iron accumulation starts with the determination of the ferritin level in the blood. As ferritin is an acute phase protein, it can also be elevated in the case of inflammation and tissue damage without iron accumulation. Tests to determine organ damage consist of laboratory tests for liver enzymes and α-foetoprotein (with cirrhosis), FSH, LH, testosterone, oestradiol, growth hormone, cortisol, prolactin, calcium, phosphate and glucose. The organ damage can also be evaluated by means of an ECG, MRI or

ultrasound of the liver and/or heart and bone densitometry (Wood 2008). A liver biopsy can be performed to determine the extent of iron accumulation and to demonstrate signs of fibrosis or cirrhosis.

Iron chelation should be started (see Chapter 5) if the ferritin level is > 1000 µg/L, or if more than 20 erythrocyte concentrates have been administered, the patient remains transfusion-dependent and the patient's life expectancy is more than one year. In the Netherlands, there are three authorised types of medication available for iron chelation: deferoxamine, deferiprone and deferasirox. The aim of iron chelation therapy is to achieve a safe iron concentration in the tissues and to neutralise free oxygen radicals. The aim is to achieve a ferritin level < 1000 µg/L and to normalise the MRI pattern of the liver. Deferoxamine is generally the component of choice, due to the many years of experience with this component and the mild side effects (Roberts 2005). Deferiprone should preferably be used in the case of cardiac iron accumulation (Piga 2006).

Conclusions 7.2.10

Level 3	<p>Secondary haemochromatosis (haemosiderosis) is primarily the result of frequent blood transfusions.</p> <p><i>C Malcovati 2007, Modell 2000, Borgna-Pignatti 2005</i></p>
Level 3	<p>It is very important to monitor and treat iron accumulation due to blood transfusions. Adequate iron chelation can prevent organ damage.</p> <p><i>C Malcovati 2007, Modell 2000, Borgna-Pignatti 2005</i></p>
Level 1	<p>In the case of iron accumulation due to secondary haemochromatosis (haemosiderosis), deferoxamine is generally the component of choice, due to the many years of experience and the mild side effects.</p> <p><i>A1 Roberts 2005</i></p>
Level 2	<p>In the case of cardiac iron accumulation due to secondary haemochromatosis (haemosiderosis), deferiprone is the preferred treatment, in combination with deferoxamine if necessary.</p> <p><i>A2 Piga 2006</i></p>

Other considerations

Experts recommend deferasirox if the patient does not tolerate deferoxamine or deferiprone, or in the case of poor therapy compliance resulting in insufficient iron chelation.

Recommendations 7.2.10

1. **Due to iron accumulation caused by secondary haemochromatosis (haemosiderosis), every patient who has received more than 20 erythrocyte units, remains transfusion-**

- dependent and has a life expectancy of more than one year must be started on iron chelation and the ferritin level in the blood must be monitored.
- 2. Iron chelation must be started in transfusion-dependent patients with a ferritin level > 1000 µg/L and a life expectancy of more than one year.
- 3. The aim of iron chelation is to achieve a ferritin level < 1000 µg/L and to normalise the MRI pattern of the liver.
- 4. Deferoxamine is recommended as the component of choice. Deferiprone is recommended in the case of cardiac iron accumulation, possibly in combination with deferoxamine. Deferasirox is recommended if the patient does not tolerate either of these iron chelators, or in the case of poor therapy compliance resulting in insufficient iron chelation.

7.2.11 Antibodies against blood cell antigens

PM For diagnosis and policy for antibodies against erythrocytes, see Chapter 3

Antibodies against HLA/HPA antigens

Scientific support

Antibodies against HLA antigens can be formed after transfusion of blood components that contain leukocytes and/or platelets. As the number of leukocytes in blood components is now extremely low due to the routine use of leukocyte reduction, this mainly relates to the secondary immune response in female recipients who have become immunised by pregnancy, transplantation and/or the transfusion of blood components. The frequency of this secondary immunisation was found to be approximately 40% in patients with acute leukaemia (Sintnicolaas 1995). The frequency of primary immunisation in these patients is approximately 7%, despite leukocyte reduction of erythrocyte and platelet concentrates. HLA antibodies can result in non-haemolytic febrile reactions and refractivity to random donor platelet transfusions. In the latter case, HLA compatible platelet transfusions should be given (van Marwijk Kooy 1991).

HPA antibodies can be formed after transfusion of platelet-containing blood components or through pregnancy.

HPA-1a antibodies can result in post-transfusion purpura (PTP) (see paragraph 7.2.8) and are also involved in neonatal allo-immune thrombocytopenic purpura (FNAITP, see Chapter 6). HPA antibodies can result in refractivity to random donor platelet transfusions. This usually involves a combination of HLA and HPA antibodies and in that case, HLA and HPA compatible platelet concentrates are required (Schnaidt 1996).

Conclusions 7.2.11

Level 2	The formation of HLA and HPA antibodies is a complication of transfusion of leukocyte and/or platelet containing blood components or a result of pregnancy. <i>B Sintnicolaas 1995, Van Marwijk Kooy 1991</i>
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Level 3	The formation of HPA antibodies is a complication of transfusion of platelet containing blood components or a result of pregnancy.
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Other considerations

Knowledge of the patient's HLA and HPA antibody history is very important both when requesting a platelet or granulocyte component for transfusion and when diagnosing a case of undefined thrombocytopenia after transfusion. This information should be directly accessible for the entire life of the patient, preferably in the TRIX database for irregular red cell antibodies.

Recommendations 7.2.11

1. The patient's antibody history – including HLA and HPA antibodies – should be consulted with each request for a platelet or granulocyte component (see also Chapters 3 and 6).
2. Data concerning the presence of HLA and/or HPA antibodies should be included in the patient's transfusion history.

7.2.12 Immunological effects of blood transfusion**Scientific support**

Many studies have been performed on the immunological effects of blood transfusions. Although these studies demonstrate that blood transfusions can (permanently) affect the recipient's immune system, more research is necessary to determine the clinical significance of many of these findings. A brief overview of the immunological effects of blood transfusion:

Blood transfusion and immune suppression

Studies of patients with long term use of blood components (haemophilia patients, poly-transfusion patients and patients with renal insufficiency) show that the mononuclear cells in the peripheral blood of these patients react with a lower antigen-specific and non-specific lectin response. This is associated with a decreased ability to secrete interleukin (IL) 2 (Hay 1990, Blumberg 1989). Administration of transfusions during surgery results in a temporary reduction of NK cells and an increase in the surgery-associated shift to a Th2 type immune response (Nielsen 1991, Jensen 1992, Kalechman 1990, Heiss 1997, Gharehbaghian 2004).

Blood transfusions and post-operative infections

Meta-analyses of observational studies show that peri-operative transfusions are associated with a higher incidence of post-operative infections, even after correction for other risk factors (Houbiers 1994). Various blood components were compared in a randomised study and this revealed great variation in the number of infections, particularly with abdominal surgery (see table 7.2.12) (Jensen 1992, Houbiers 1994, Jensen 1996, Tartter 1998, Titlestad 2001, van Hilten 2004). A meta-analysis of these studies was not possible due to the heterogeneity of the data (Vamvakas 2007).

Table 7.2.12: Randomised controlled studies on the effect of filtration of erythrocyte components on post-operative infections after abdominal surgery

1 st author	Study design	Number patients	Study arm	Control arm	% post-operative infections Study arm vs control arm
Jensen ⁴	one centre	197	LD	full blood	14 vs 63% ? p < 0.05
Houbiers ⁷	multi-centre	697	LD	RBCwbc	36 vs 32% ‡ n.s.
Jensen ⁸	one centre	586	LD	RBCwbc	11 vs 30% ? p < 0.05
Tarter ⁹	one centre	221	LD	RBC+bc	16 vs 44% ? p < 0.05
Tittlestadt ¹⁰	one centre	279	LD	RBCwbc	38 vs 45% ? n.s.
Van Hilten ¹¹	multi-centre	560	LD	RBCwbc	22 vs 23% ‡ n.s.

LD = leukocyte-reduced by means of filtration; RBC = erythrocyte concentrate;
wbc = without 'buffy coat'; +bc = with 'buffy coat';
?= analysis limited to transfused patients; ‡ analysis in randomisation groups

On average, patients undergoing open heart surgery receive a greater number of transfusions compared to other surgical procedures. The randomised studies in these patients are less heterogeneous, with meta-analyses showing significantly fewer post-operative infections when filtered components are used (Vamvakas 2007, van de Watering 1998, Wallis 2002, Bracey 2002, Boshkov 2004, Bilgin 2004, Blumberg 2007).

Blood transfusions and mortality in cardiovascular surgery

Prospective randomised research performed in the Netherlands found a significant reduction in post-operative mortality if transfusions with leukocyte-reduced erythrocytes were given instead of standard erythrocytes from which only the 'buffy coat' was removed (van de Watering 1998, Bilgin 2004). Meta-analyses show improved survival with the use of filtered erythrocytes only for cardiovascular procedures (Vamvakas 2007).

Blood transfusions and negative effects on cancer

The proposed negative effect of blood transfusions on recurrence of a cancer that was cured is based on the hypothesis (Gantt 1981, Blumberg 1989) that the growth of metastases or local recurrence is partly under immunological control. Evaluating only those studies in which multi-variant analysis for known risk factors was applied, most studies did not anymore appear to show a negative effect of peri-operative transfusions. The renewed Cochrane analysis of studies on patients with colorectal cancer also failed to demonstrate a link (Amato 2008). A large observational Scandinavian study found no increased incidence of cancer in recipients of a blood transfusion (Hjalgrim 2007).

A retrospective study showed a favourable effect of blood transfusions on the prevention of relapse of leukaemia after chemotherapy in patients with acute myeloid leukaemia (graft-versus-leukaemia effect, Bilgin 2004). Various large case-control studies show that it is likely that particularly low grade and intermediate non-Hodgkin's lymphomas occur at a frequency of up to two times higher after an interval of approximately 10 years after the transfusion of full blood or erythrocytes with leukocytes (Cerhan 2008, Erber 2009), but not after transfusion of 'buffy coat'-depleted components (Blumberg 2007, Vamvakas 2007).

Blood transfusions and transplantation tolerance

There are many factors that play a role in transplantation survival. A number of studies have demonstrated that pre-transplantation blood transfusion is an important favourable factor for transplantation survival, not only for kidney transplantation (Opelz 1972, Vincenti 1978,

Opelz 1997), but also for heart (van der Mast 1997, Katz 1987), liver and combined kidney-pancreas (Waanders 2008) transplantation. The larger studies still demonstrate a favourable effect of transfusions (Terasaki 1995).

Conclusions 7.2.12

Level 1	<p>Leukocyte reduction for open heart surgery – in which large amounts of transfusions are given – has a significantly favourable effect on the prevention of post-operative infections.</p> <p>A2 <i>Bilgin 2004,</i> A1 <i>Vamvakas 2007</i></p>
Level 2	<p>There are no indications that the immuno-suppressive effect of blood transfusions forms a risk for the recurrence of cancer following curative surgery for colon cancer.</p> <p>A2 <i>Amato 2008</i></p>
Level 2	<p>Blood transfusions using full blood or leukocyte-containing erythrocyte concentrate are associated with a maximum two-fold higher incidence of low grade and intermediate non-Hodgkin's lymphoma in particular than after transfusion of 'buffy coat'-reduced components.</p> <p>B <i>Blumberg 2007, Vamvakas 2007</i></p>

Other considerations

The clinical significance of the changes in cellular immunity caused by blood transfusions is unknown. Thanks to the current immuno-suppressants, the transplantation results are so good that immune-modulating transfusions – with the accompanying disadvantages (10 – 30% antibodies) – are no longer worth the slight gain in transplant survival (Koneru 1997, Alexander 1999).

Recommendations 7.2.12

1. Research on the mechanisms and causal factors of immune suppression by blood components is recommended.
2. Immune-modulating pre-transplantation blood transfusions should only take place as part of a clinical protocol. This research should be set up to achieve informative end points.

7.3 Infectious complications of blood transfusions

7.3.1 Infection due to bacterial contamination of blood components

Scientific support

An estimated 0.4% of erythrocyte and platelet concentrates are contaminated by bacteria (Sanquin Blood Supply Foundation 2001, Blajchman 1998). This figure can increase to 2%

for pooled platelet concentrates that are prepared from several donor units. Dutch research (Sanquin Blood Supply Foundation 2001) confirms that – in particular – platelet suspensions, which are stored at room temperature, are components at risk of bacterial contamination. The risk has been decreased by changing the method of disinfection and by using the first millilitres of blood donations to fill the test tubes (de Korte 2006). All platelet components are cultured by Sanquin Blood Supply and only released if the culture has remained negative until the time of release. Blood components that have been contaminated with bacteria can result in transient bacteraemia in the recipient, but also in sepsis. Sometimes the symptoms cannot be distinguished from a haemolytic transfusion reaction, namely fever, cold shivers, tachycardia, changes in systolic blood pressure (both increase and decrease), nausea and/or vomiting, shortness of breath, lower back pain, shock (Sanquin Blood Supply Foundation 2001). Both the symptoms themselves and the time at which the bacterial contamination manifests itself can vary greatly, which hampers the formation of a protocol.

In the Netherlands, approximately three transfusion reactions per year are probably or definitely the result of a blood component contaminated by bacteria (de Korte 2006).

Infected components should be traced by means of a good haemovigilance system (de Korte 2006, TRIP report 2008) and a report should be sent back to Sanquin Blood Supply immediately.

TRIP distinguishes three reporting categories with respect to bacterial complications (see www.tripnet.nl):

- A. Blood cultures must be collected from the patient and from the (remainder of the already) transfused blood component, the bag being sealed and stored in the correct manner, for a reliable diagnosis of a bacterial infection caused by blood components. Instead of or in addition to – blood cultures may also be taken from other blood components prepared from the same donation. The strains detected in the patient and the blood component should be identical. Genetic testing may be required, depending on the type of bacteria.
- B. If symptoms are observed in a patient and a positive blood culture is found in the patient, this is referred to as a post-transfusion bacteraemia/sepsis: defined by TRIP as: ‘the occurrence of clinical symptoms of bacteraemia/sepsis during, following or some time after a blood transfusion, where a relevant positive blood culture is obtained from the patient and with or without a causal link being made to an administered blood component’.
- C. If the detection of bacterial contamination in a (partially) transfused blood component is the trigger for reporting, we call this a bacterial contamination of a blood component (with sub category if the patient showed symptoms), which is defined by TRIP as: using relevant techniques to detect a relevant quantity of bacteria in a (remaining portion of a) blood component or the bacteriological screening culture of a platelet component – or material from the same donation – using laboratory techniques and preferably with typing of the relevant bacterial strain(s).

Conclusions 7.3.1

Level 3	Platelet suspensions in particular, which are stored at room temperature, are components at risk of bacterial contamination. <i>C Blajchman 1998, Schrezenmeier 2007</i>
Level 3	Infected components should be traced by means of a good haemovigilance system and a report should be sent back to Sanquin Blood Supply immediately. <i>C De Korte 2006</i> <i>D TRIP rapport 2008</i>

Other considerations

The limit for a febrile reaction – and therefore also for a standard collection of a blood culture – has been set at an increase of ≥ 2 °C and/or cold shivers. Two independent collections are performed as standard procedure, in order to increase the chance of a positive blood culture.

In order to reduce the risk of contamination to a minimum, instructions for the collection of a blood culture, the disconnection, transport and storage conditions and method of sampling of a blood component must be present in the hospital and these instructions must be followed.

Recommendations 7.3.1

1. One bacterial culture from the component and two blood cultures from the patient must be performed in case of a febrile reaction ≥ 2 °C and/or cold shivers. For a febrile reaction < 2 °C, blood cultures should be taken depending on the doctor's 'clinical judgement'.
2. The hospital must provide instructions for disconnection, transport & storage conditions and the method of sampling, and these instructions must be followed.
3. Infected blood components should be traced by means of a good haemovigilance system. (Suspected) cases of bacterial contamination of blood components should be reported to Sanquin Blood Supply as soon as possible.
4. If a report of bacterial contamination of a blood component is sent to Sanquin Blood Supply (or another manufacturer) and the blood component has already been administered or is being administered at the time, it is essential to monitor the patient for symptoms of bacteraemia/sepsis.

7.3.2 Post-transfusion viral infection

A post-transfusion viral infection has occurred if the viral infection can be traced to an administered blood component, with the virus being typed and identical virus strains demonstrated in recipient and donor or (related) blood component, and where contamination via another route is unlikely.

The risk of transmission of a viral infection by blood transfusion in the Netherlands is very low (TRIP report 2007, 2008). Every infection has a 'window period' in which the virus is

present in the blood, but cannot be detected yet by the tests that are used. In addition to performing laboratory tests on donor blood, it is important to ask questions during the donor anamnesis about increased risk, so that – together with voluntary, non-paid donors – this guarantees the optimum safety of blood components .

The transmission of an infection can also be suspected if a blood transmissible viral infection is detected in a transfused patient and there is no other obvious cause for this infection. If there is a realistic suspicion, Sanquin Blood Supply will test the relevant donors. Conversely, if a blood transmissible infection is found in a donor, doubt can be cast over the safety of previous donations. Even if the stored samples from the previous donations are found to be negative after additional testing, the relevant hospitals will be contacted in ‘look-back’ procedures. If relevant, the patient should undergo additional testing.

Conclusion 7.3.2

Level 4	The risk of a viral infection as a result of transfusion of a blood component (in the Netherlands) is very low. <i>D TRIP rapport 2007</i>
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Recommendation 7.3.2

A realistic suspicion of a post-transfusion viral infection should be reported to Sanquin Blood Supply immediately.

7.3.2.1 Transfusion-associated cytomegalovirus (CMV) infection

Scientific support

A transfusion-associated cytomegalovirus (CMV) infection can run a mild course (fever, malaise) or can cause severe complications such as congenital defects of the central nervous system in an initial infection of the mother (primary infection) during pregnancy (Ho 1995). In immune-compromised or dysmature neonates, CMV infection can cause severe pneumonitis. CMV complications in these patient groups can be caused by reactivation of a previous infection, transmission from mother to child, transmission through a transplant, horizontal transmission (by contact transmission), but also through blood transfusion. (Hamprecht 2001). The highest incidence of CMV in the population is found during the perinatal period and the sexually mature period. Approximately 40 – 60% (Northern Europe, North America and Australia) to nearly 100% (South East Asia and Africa) of adults are CMV carriers (Ho 2008).

CMV is primarily lymphocyte-bound. Leukocyte reduction makes donor blood CMV safe (Kuhn 2000, James 1997, Adler 1988, Smith 1993, Roback 2000). Another approach in the prevention of transfusion-associated CMV infection is the use of anti-CMV seronegative screened blood (Bowden 1995, Preiksaitis 2000). In controlled studies, primary CMV infections were reported in 0% of the recipients of anti-CMV serum negative screened blood and in 1 – 2% of the recipients of leukocyte-reduced blood (not significantly different) (Laupacis 2001). Since January 2002, all platelet and erythrocyte concentrates in the Netherlands are leukocyte-reduced. There is no international consensus on departing from

the previous policy of CMV tested blood following the implementation of leuko-reduction. However, there is no evidence to support anti-CMV testing of leukocyte-reduced blood (Preiksaitis 2000, Laupacis 2001, Blajchman 2001).

Conclusions 7.3.2.1

Level 3	<p>Primary cytomegalovirus (CMV) infection can be transmitted via blood components and can result in severe complications in certain patient groups.</p> <p><i>C Hamprecht 2001</i></p>
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Level 3	<p>In controlled studies, primary cytomegalovirus (CMV) infections were reported in 0% of the recipients of anti-CMV negative screened blood and in 1 – 2% of the recipients of leukocyte-reduced blood. This was not significantly different.</p> <p><i>B Laupacis 2001</i></p>
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Level 3	<p>There is no evidence to support an anti-CMV test of donor blood following the implementation of leukocyte reduction.</p> <p><i>C Blajchman 2001, Preiksaitis 2000</i> <i>B Laupacis 2001</i></p>
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Other considerations

To date, leukocyte reduction has been maintained as the intervention of choice for the preparation of CMV-safe cellular blood components.

In the case of intra-uterine transfusions, the treating experts wish to administer blood that is leukocyte-reduced AND anti-CMV serology negative.

Recommendations 7.3.2.1

1. If a primary cytomegalovirus (CMV) infection in the recipient of a blood component is likely, this should also be reported to Sanquin Blood Supply.
2. Leukocyte-reduced blood components are considered CMV-safe (see also Chapter 2), but in order to avoid all risks during intra-uterine transfusions the donor should also be anti-CMV seronegative.

7.3.2.2 Transfusion-related Parvo B19 infection

Scientific support

Acute infection with Parvo virus B19 (abbreviated: B19) usually occurs in childhood; the most characteristic symptom is that of the 'fifth illness' (erythaema infectiosum), which is characterised by fever and skin rash and recovery without problems. If the infection occurs during pregnancy – with or without clinical symptoms – the foetus can become infected in the uterus, sometimes resulting . in foetal anaemia or intra-uterine death . (Health Council 2002, de Haan 2008). A *de novo* B19 infection is dangerous in people with chronic

haemolysis and decreased immunity, because of the risk of haematopoiesis inhibition. (Health Council 2002, van Dam 2008). It is estimated that more than 50% of adults in the developed world have antibodies against B19, pointing to previous infection.

A study of pooled plasma obtained from asymptomatic Dutch blood donors and random testing of individual donors estimated the incidence at 0.56% per year. The data pointed to high viral load ($> 10^9$ copies/mL) in the first days of the infection, followed by a decrease in viral load ($< 10^6$ copies/mL) for two weeks (Zaaijer 2004).

Retrospective testing of 5020 regular donations in the United States found B19 in 0.88% of the samples using a sensitive PCR test. Specific IgG was present in all cases and IgM in 23% of these donations; the presence of IgM was correlated to a higher level of B19 DNA and may be consistent with the recovery phase of an acute infection (Kleinman 2007). A study of 2.8 million donations (2004 – 2006) in Germany and Austria found B19 DNA in 2.7% of donations during a high-incidence period, with a titre of 10^5 IU/mL in 0.012%. IgG antibodies were also present in all donations with a low titre and these antibodies are thought to have a neutralising effect on the Parvo virus B19 (Schmidt 2007).

Antibody development and replication of the virus were demonstrated in recipients of plasma with a high titre of the Parvo virus B19 (Health Council 2002, Plentz 2005); however, clinical consequences have not been described. Some cases of B19 infections that resulted in clinically severe inhibition of haematopoiesis have been reported in the Netherlands following the administration of standard blood components. It is remarkable to note that a number of studies have demonstrated the long term presence of B19 in the bone marrow, which persisted after the appearance of IgG antibodies.

B19-safe blood components can be acquired from Sanquin Blood Supply, obtained from donors who were found to have IgG antibodies against B19 twice with an interval of at least six months. Risk groups have been defined for the use of these components and B19-safe components must be requested for patients with an increased risk (Health Council 2002). See Chapter 2, paragraph 2.6 for specific risk groups.

Conclusions 7.3.2.2

Level 3	<p><i>A de novo</i> Parvo B19 viral infection is dangerous in people with chronic haemolysis and decreased immunity, due to the risk of haematopoiesis inhibition.</p> <p>C Zaaijer 2004, D Gezondheidsraad 2002</p>
Level 4	<p>Blood components obtained from donors who have demonstrated IgG antibodies on two subsequent occasions with an interval of at least six months are considered B19-safe. Risk groups have been defined for the use of these components and B19-safe components must be requested for these patients.</p> <p>D Health Council 2002</p>

Recommendation 7.3.2.2

B19-safe components must be requested for patients with an increased risk of severe detrimental consequences of a B19 infection from transfusion of standard short shelf-life blood components (see Chapter 2, paragraph 2.6).

7.3.2.3 Viral Post-transfusion Hepatitis (PTH)

Scientific support

The incidence of viral post-transfusion hepatitis (PTH) has been reduced significantly over the last few decades due to intensive donor selection, the eradication of paid donations (from abroad) and the implementation of sensitive tests for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies (Goodnough 1999, Glynn 2000, van der Poel 1998). In addition, since July 1999 all donations in the Netherlands are tested using a nucleic acid amplification test (NAT) for hepatitis C virus (HCV). Since 2009, a NAT test is also performed for Hepatitis B virus (HBV).

The risk of transmission of HBV or HCV via blood transfusion is determined primarily by the 'window' phase, the 'false serum negative' period during early infection of the donor and is also a derivative of the incidence of (*de novo*) HBV or HCV infections in regular donors. (Schreiber 1996). For the Netherlands, the remaining chance of infection with HBV by transfusion of a short shelf-life blood component can be calculated as 1 per 800,000 donor units and for HCV (after the implementation of NAT) as 1 per 3 million donor units (van de Bij 2006).

The definition 'post-transfusion' points to chronology and does not rule out causes other than blood transfusion. Therefore, hospital infections should also be taken into consideration. In the majority of the reports of post-transfusion HBV, further investigation shows that blood transfusion cannot be marked as the cause (SHOT 2007). Since the early 1990s, Sanquin Blood Supply stores a sample from each donation for two years, in order to perform further testing, for example following reports of PTH.

Conclusions 7.3.2.3

Level 3	<p>The incidence of viral post-transfusion hepatitis (PTH) has been reduced significantly over the last few decades due to intensive donor selection, the eradication of paid donations (from abroad) and the implementation of sensitive tests for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies.</p> <p><i>C Goodnough 1999, Glynn 2000, van der Poel 1998</i></p>
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Level 2	<p>For the Netherlands, the remaining chance of infection with HBV through transfusion of a short shelf-life blood component can be calculated as 1 per 800,000 donor units and for HCV (after the implementation of the nucleic acid amplification test (NAT)) as 1 per 3 million donor units.</p>
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	A2 <i>Van de Bij 2006</i>
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Level 4	In the majority of the reports of post-transfusion HBV, further investigation shows that blood transfusion cannot be marked as the cause. <i>D SHOT 2007</i>
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Recommendations 7.3.2.3

1. In the case of viral hepatitis, the (small) possibility of transmission by a blood transfusion should also be considered.
2. Each case of viral post-transfusion hepatitis (PTH) – for example by HBV or HCV – with a positive blood transfusion history should also be reported to Sanquin Blood Supply.

7.3.2.4 Post-transfusion HIV infection/AIDS

Scientific support

Following the implementation in 1985 of the test for human immunodeficiency virus (HIV antibodies) for every blood donation, the risk of transmission of HIV by blood transfusion (Goodnough 1999, Glynn 2000) in the Netherlands is extremely low, partly due to careful donor selection procedures (TRIP rapporten, www.tripnet.nl). The incubation period for HIV is six months to 10 years. In order to limit the incidence of HIV in known donors, the policy since 1983 has been to exclude individuals with an increased HIV risk from donating blood. The risk of transmission of HIV through blood transfusion is determined by the ‘window’ period – the period during which the serum test(s) is (are) false negative – during early infection and also by the chance that a known donor experiences a *de novo* HIV infection, the ‘incidence’ (Schreiber 1996).

In the case of fresh frozen plasma, this plasma is only released once the donor has been tested again after at least six months and has been found to be negative: such plasma is referred to as ‘quarantine’ plasma. This virtually eliminates the risk for infection during the ‘window’ phase for fresh frozen plasma, as is the case with inactivated SD plasma. Such a long quarantine period is not possible for cellular components such as erythrocytes and platelets. However, the ‘window’ phase for HIV has been reduced significantly with the implementation of the nucleic acid amplification test (HIV-NAT), which was added to the tests on all donations of blood components in 2000.

The theoretical remaining risk of post-transfusion HIV/AIDS can be calculated from the ‘window’ phase and the incidence, and is presented in table 7.3.2.4. One should take into consideration a risk of HIV transmission of 1 in 5 million with the transfusion of blood cells from a donor in the early phase of infection. This is an extremely low risk, but severe in the public perception.

Table 7.3.2.4: Risk of transmission of various blood transmissible diseases

Virus	‘Window’ period	Average incidence	Risk of infection
	in days	1993 – 2002 (van de Bij 2006)	per 100,000 donations
HBV	59 excl. NAT	1.27	0.21

HIV	11 incl. NAT	0.59	0.02
HCV	12 incl. NAT	0.71	0.02

NAT = nucleic acid amplification test

Conclusions 7.3.2.4

Level 3	<p>The risk of HIV transmission by transfusion of blood cells is very low in the Netherlands, partly due to thorough donor selection procedures and is currently estimated at 1 in 5 million.</p> <p><i>C Goodnough 1999; Glynn 2000,</i> <i>D Jaaroverzichten Sanquin Bloedvoorziening</i></p>
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Level 4	<p>The risk of HIV transmission by transfusion of fresh frozen plasma - secured according to the quarantine method or inactivated by SD treatment – is negligible in the Netherlands.</p> <p><i>D Opinion of the authors</i></p>
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Recommendations 7.3.2.4

<ol style="list-style-type: none"> 1. In the case of an HIV infection, the recipients transfusion history over the past 10 years should be checked. 2. Each case of HIV infection with a positive blood transfusion history should also be reported to Sanquin Blood Supply.
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7.3.3 Post-transfusion malaria infection

Scientific support

Malaria can be transmitted by blood transfusion. This rarely occurs in non-endemic areas. In the Netherlands, transfusion transmission of malaria (compulsory reporting to the RIVM) has not been reported since the 1950s. In the United States, the risk is estimated at 1 in 4 million transfusions (Nahlen 1991). Recent cases of malaria transmission in the United States and the United Kingdom were primarily due to donations from individuals who had previously had a long term stay in malaria-endemic areas and had recently visited a malaria-endemic area again . (Eliades 2003, Kitchen 2005). The current prevention in the Netherlands is based on the one hand on the exclusion of donors who have recently visited malaria-endemic areas and on the other hand by allowing donors who have had malaria to donate, provided they have a negative test result (at least three years after recovery) . for the presence of malaria antibodies.

Conclusion 7.3.3

Level 4	<p>The risk of transmission of malaria by a blood transfusion in the Netherlands is theoretically present, but almost negligible.</p> <p><i>D Sanquin Blood Supply annual reports, RIVM bulletins, TRIP annual reports</i></p>
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Recommendation 7.3.3

In the case of malaria in a recipient of erythrocyte transfusions, the (extremely small) possibility of post-transfusion malaria must be considered if other causes have been ruled out.

7.3.4 Post-transfusion variant Creutzfeldt Jakob Disease (vCJD) infection

Scientific support

Creutzfeldt Jakob Disease (CJD) belongs to a group of conditions called Transmissible Spongiform Encephalopathies (TSE), which are characterised by a long to very long incubation period and severe, irreversible damage to the central nervous system, resulting in, among other conditions, dementia (Collins 2004). CJD has an incidence of approximately 1 per million inhabitants and the disease starts at an average age of 65 years.

CJD has been shown in a number of case control, look back and surveillance studies not to be transmitted by blood or plasma components (Dorsey 2009).

Since the early 1980s, bovine spongiform encephalopathy (BSE) has been increasingly detected in cattle in the United Kingdom (UK) and later also in various other countries. Following measures in the cattle breeding and food industry, the incidence was strongly reduced. Subsequently since 1996, a number of patients – particularly in the United Kingdom – have been diagnosed with an abnormal (variant) form of CJD (vCJD). By the end of 2008, a total of over 160 people in the United Kingdom had died of vCJD. Animal experiments have shown that this variant form of CJD – vCJD – can be transmitted by blood (Collins 2004).

In December 2003, the first possible case of transmission of vCJD by blood transfusion in humans was reported in the United Kingdom. This transfusion of an erythrocyte concentrate took place in 1996 when the donor was still healthy. After the donor died of vCJD in 2000, the recipient of his blood was also diagnosed with vCJD in 2003. Since then, a further two cases of vCJD have been diagnosed in the United Kingdom in recipients of (non-leukocyte reduced) erythrocyte concentrates, obtained from donors who developed vCJD after their donation (Hewitt 2006). Although it is theoretically plausible that the disease was caused in all individuals by the consumption of contaminated beef components, the chance that transmission occurred via blood is statistically much greater. In a fourth recipient of an erythrocyte concentrate from a contaminated donor, prion proteins characteristic of vCJD were found in the spleen after her death (Hewitt 2006). To date, three cases of vCJD have been diagnosed in the Netherlands; these people were neither blood donor, nor had they ever received blood components (Health Care Inspectorate 2010).

Since there is no inactivation method yet and there is no reliable screening test or confirmation test for tracing vCJD in blood, two precautionary measures have been taken in the Netherlands to limit the risk of transmission of vCJD via blood and blood components (van Aken 2001). These are:

- Donor exclusion, i.e. rejecting donors who resided in the United Kingdom for a period of six months or more between 1980 and 1996 (since 2001) and donors who have themselves received an allogeneic blood transfusion since 1980 (since 2005).

- Leukocyte reduction of all short shelf-life blood components (since 2001).

As far as the safety of plasma components is concerned, the literature shows that virtually all examined process steps during the preparation have a TSE removing or inactivating effect (Foster 2000). At the end of 2008 there was a report of a haemophilia patient who had received a clotting factor preparation over 11 years ago in the United Kingdom, prepared from a batch containing plasma from a donor who developed vCJD. The haemophilia patient never displayed neurological symptoms, but prion proteins were demonstrated in the spleen after his death from other causes. As there are many patients who have received components prepared from human plasma, there is no reason as yet – based on this case – to suppose transmission via the component (Health Protection Agency 2009).

Conclusions 7.3.4

Level 3	<p>The transmission of the variant form of Creutzfeldt Jacob Disease (vCJD) via cellular blood components is theoretically possible and also likely based on epidemiological research.</p> <p><i>C Collins 2004, Hewitt 2006</i></p>
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Level 3	<p>As far as the safety of plasma components is concerned, the literature shows that virtually all examined process steps during the preparation have a Transmissible Spongiform Encephalopathies (TSE) removing or inactivating effect.</p> <p><i>C Foster 2000</i></p>
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Recommendation 7.3.4

If the diagnosis of Creutzfeldt Jakob Disease (CJD) or variant Creutzfeldt Jakob Disease (vCJD) is made, one should verify whether the patient ever received a transfusion of blood components and whether he/she ever donated blood. If yes, this should be reported to the Health Care Inspectorate and in the case of blood donation also to Sanquin Blood Supply.

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CHAPTER 8: BLOOD SAVING TECHNIQUES AND MEDICATIONS

Introduction

This chapter describes techniques and medications that can reduce the use of short shelf-life allogeneic blood components in case of acute anaemia, particularly during the perioperative period .

In general, the use of allogeneic blood transfusions for acute anaemia can be limited in three ways:

- Pre-operative treatment of any existing anaemia (see Chapter 4 and for a recent review: Goodnough 2010)
- Limiting the blood loss (8.1) by:
 - surgical measures (8.1.1)
 - anaesthesiological measures (8.1.2)
 - medication (8.1.3)
 - haemodilution (8.1.4)
- The use of autologous blood transfusion techniques (8.2):
 - pre-operative autologous donation (8.2.1).
 - peri-operative and post-operative auto-transfusion (8.2.2)
- A separate paragraph is dedicated to combinations of techniques (8.3)

The working group also recommends haemovigilance of blood saving techniques: see Chapter 7.1.2, Recommendation 11

8.1 Techniques to limit blood loss during surgical procedures

8.1.1 Surgical techniques to limit peri-operative blood loss

The following techniques are essential in limiting blood loss during surgical procedures: anatomical dissection according to non-vascular surfaces, thorough haemostasis, the ligation of blood vessels before they are severed, immediate control of bleeding, non-traumatic handling of tissues and peri-operative time planning. In trauma surgery, blood loss can be limited by phased surgery with damage control (Beekley 2008, Spahn 2007).

8.1.1.1 Surgical haemostatic instruments

An electrocautery (electrosurgery) is a surgical haemostatic instrument that can contribute to the limitation of blood loss during surgical procedures. The electrocautery supplies electrical current that is used to heat the tip of the instrument that is being used. This singes the capillary vessels and arterioles shut.

Argon beam

Argon gas allows for faster and more efficient haemostasis than with electrosurgery alone. One of the benefits of using argon gas is the minimal tissue damage. This technique can be particularly valuable in surgery on the spleen, liver and kidneys (Gombotz 1998, Ross 1997, Idowu 1998, Rees 1996).

Laser surgery

A laser burner works according to the same principles as an electrocautery, but it uses laser energy instead of electrical current to separate tissues and simultaneously coagulate (Wyman 1993, Cornford 1997).

Water jet dissector

The water jet dissector is an instrument that uses water at high pressure to separate tissues and causes relatively little tissue damage (Rau 1995, Baer 1993, Wu 1992).

Ultrasonic dissector

An ultrasonic dissector is an instrument that uses the mechanical energy created by ultrasonic vibrations to perform precise surgical incisions, which in combination with controlled haemostasis limits the damage to surrounding tissues to a minimum (Hoenig 1996, Epstein 1998).

Local haemostatics

The local application of haemostatic pharmacological agents such as fibrin glue (see 8.1.3.4.) can limit blood loss during surgical procedures. Another option to halt localised bleeding is infiltration with epinephrine (Kuster 1993, Sheridan 1999), phenylephrine or the local application of cocaine (Berde 2000, Riegler 1992). The (capillary) bleeding can be halted by the vaso-constrictive effect of these agents.

8.1.1.2 Minimally invasive surgical techniques

Minimally invasive surgical techniques can limit blood loss. These include surgical techniques that limit the size of the procedure – such as laparoscopy and thoracoscopy – and techniques that replace conventional surgery or limit the extent of the surgery, such as endoluminal techniques and interventional radiology. Laparoscopy and thoracoscopy make large incisions and extensive surgical dissection largely redundant, thereby reducing blood loss and tissue damage (O'Reilly 1996, Caprotti 1998, Kerbl 1994). The last few years have seen increasing use of radiological intervention to simplify, limit or even replace surgical procedures. Examples are arterial embolisation, trans-jugular intrahepatic porto-systemic shunts (TIPS) and stents.

For example, arterial embolisation of the iliac vessels can halt bleeding in a poly-trauma patient with massive exsanguination shock. In the case of blunt injury to the spleen and liver, the bleeding vessel can be traced and embolised with the aid of selective angiography (Holting 1992, Ben-Menachem 1991, Agolini 1997, Willmann 2002, Spahn 2007). The concept of “damage control surgery” combined with radiological intervention means that severe trauma patients can be stabilised much faster and at an earlier stage. Definitive (surgical) treatment can take place semi-electively at a later stage, once the patient is haemodynamically and pulmonologically stable and any acidosis, electrolyte and clotting abnormalities and hypothermia have been corrected (Beekley 2008, Spahn 2007). See also Chapter 5.

Arterial embolisation can also be used for non-traumatic bleeding. During elective surgery, pre-operative embolisation of a richly vascularised tumour can often limit the final resection and minimise blood loss.

A trans-jugular intra-hepatic porto-systemic shunt (TIPS) can be used for bleeding from oesophageal varices. The success rate is around 90% and this is a method where the blood loss is controlled relatively quickly, which limits the number of blood transfusions and means that surgical intervention can usually be avoided (McCormick 1994, Orloff 1994).

Radiological intervention is increasingly being used for both atherosclerotic stenosing vascular disease and aneurysmatic vascular disease for the insertion of stents (also in patients with increased cardio-pulmonary risk) and coils (also in patients with aneurysms of cerebral vessels).

Cryo-surgery

This uses instruments that allow malignant tumours to be frozen to low temperatures (down to minus 100 °C) and then be removed. Cryo-therapy is much less invasive than conventional surgery and is used primarily for liver and prostate surgery.

Radio-surgery

Developments both in the field of radiology and radiotherapy means that in some cases malignancies can be treated using localised radiotherapy. An example of this is brachytherapy as adjuvant treatment for breast cancer and . prevention of local tumour recurrence in rectal and prostate cancer (Ragde 1998).

Conclusion 8.1.1

Level 4	There are no studies available that demonstrate the efficacy of surgical techniques to limit peri-operative blood loss. <i>D Opinion of the authors</i>
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Recommendation 8.1.1

For each operation, one should consider defining a surgical strategy – including the accompanying surgical techniques to be used – to limit the peri-operative blood loss.
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8.1.2 Anaesthesiological measures to reduce peri-operative blood loss

Positioning of the patient/use of tourniquet

Careful positioning of the patient in order to prevent venous stagnation is a simple measure that can be taken to reduce blood loss. (Simpson 1992). The use of a tourniquet to remove blood from extremities is an efficient method of limiting blood loss in the surgical area (Snyder 1997, Mathru 1996).

Normothermia

Maintaining a normal body temperature (normothermia) contributes to reducing blood loss. Hypothermia reduces the function of both clotting factors and platelets (Drummond 2001). This increases the tendency to bleed (Corazza 2000, Fries 2002, Spahn 2007, Eastridge 2006).

Neuro-axial analgesia techniques

Neuro-axial analgesia techniques, such as sympathetic nerve block, can limit peri-operative blood loss. A reduction of allogeneic blood transfusions up to 50% has been described. Sympathetic nerve block causes peripheral vasodilation and regional flow redistribution (Sharrock 1996, Kleinschmidt 2001, Rodgers 2000).

Controlled hypotension by pharmacological methods

Blood pressure can be lowered in a controlled manner using pharmacological methods and this can contribute to decreased blood loss. The following agents can be used for this: sodium nitroprusside, nitroglycerin, nicardipine and a combination of a vasodilator and an alpha or beta receptor blocker (see table 8.1) (Suttner 2001, Hersey 1997, Shapira 1997, Boldt 1999).

Table 8.1: Efficiency of controlled hypotension as blood transfusion saving method

First author	Study set-up	Result	Evidence class
Kleinschmidt ⁸	Review of 5 RTs: hypotension vs no hypotension	in 2 studies reduction BT: 12 vs 44%; 9 units vs 0 units	A1
Suttner ¹⁰ Radical prostatectomies	Group 1: Na-nitroprusside average 50 mmHg Group 2: Na-nitro + ANH Group 3: standard (n = 42)	Blood loss: (p < 0.05) Group 1: 788 ml Group 2: 861 ml Group 3: 1,355 ml Allogeneic PC (p < 0.05) Group 1: 3 units Group 2: 2 units Group 3: 17 units	A2
Hersey ¹¹ Scoliosis operations	Grade 1: Na-nitroprusside Grade 2: nicardipine (n = 20) (not double blind)	Blood loss (p < 0.05) Grade 1: 761 ml Grade 2: 1,297 ml Recovery of normal blood pressure (p < 0.01) Grade 1: 26.8 min Grade 2: 7.3 min	A2
Shapira ¹² Major orthopaedic surgery	Grade 1: ANH to 20% + hypotension (mean 50 mmHg) Grade 2: target mean \pm 20% initial value n = 16	Allogeneic BT (p < 0.05) Grade 1: 225 ml Grade 2: 2,650 ml	A2
Boldt ¹³ Radical prostatectomies	Grade 1: ANH Grade 2: hypotension mean 50 mm Hg with Na-nitroprusside Grade 3: control (n = 60)	Blood loss: + no BT (p < 0.05) Grade 1: 1,820 ml + 75% Grade 2: 1,260 ml + 55% Grade 3: 1,920 ml + 40%	A2

ANH: acute normovolemic haemodilution (see Chapter 8.2.2)

Conclusions 8.1.2

Level 4	Careful positioning of the patient, aimed at preventing venous stagnation, can limit peri-operative blood loss. <i>D Simpson 1992</i>
Level 4	Maintaining a normal body temperature (normothermia) contributes to reducing blood loss. <i>D Corazza 2000, Fries 2002, Spahn 2007, Eastridge 2006</i>
Level 1	Controlled hypotension, in combination with acute normovolemic haemodilution (ANH) can reduce the number of peri-operative allogeneic blood transfusions. <i>A1 Kleinschmidt 2001</i> <i>A2 Suttner 2001, Hersy 1997, Shapira 1997, Boldt 1999</i>
Level 4	The use of a tourniquet to remove blood from the extremities is an efficient method of limiting blood loss in the surgical area. <i>D Snyder 1997</i>
Level 4	Neuro-axial analgesia techniques, such as sympathetic nerve block, can limit peri-operative blood loss. <i>D Sharrock 1996, Kleinschmidt 2001, Rodgers 2000</i>

Recommendations 8.1.2

The following anaesthesiology technique(s) should be applied – or at least considered – in order to reduce peri-operative blood loss:

1. Position the patient in such a way to prevent venous stagnation in the surgical area.
2. Cooling of the patient should be avoided as much as possible.
3. **Consider controlled hypotension, preferably in combination with acute normovolemic haemodilution (ANH) (see also 8.1.4).**
4. Where relevant: use blood removal techniques (tourniquet) and neuro-axial techniques such as sympathetic nerve block.

8.1.3 Medicines

8.1.3.1 Aprotinin

During the BART study – a randomised study of cardiac surgery patients with a high surgical risk – the interim analysis showed an increase in mortality (1.5x higher) and complications in the group treated with aprotinin (Fergusson 2008). Therefore, the study was stopped. Partly due to an analysis by the FDA of 67,000 files, it was then decided to remove aprotinin from the market (Hiatt 2006, Fergusson 2008). As a result of this, the Medicines Evaluation Board (MEB) consulted with the company Bayer and the Health Care Inspectorate in 2007 and

decided that Trasylol (aprotinin) may no longer be used until the definitive analysis results are known.

8.1.3.2 Tranexamic acid (Cyclokapron®)

Properties and adverse effects

Tranexamic acid is a synthetic lysine analogue that exerts an anti-fibrinolytic effect by reversibly blocking lysine binding sites on plasminogen (Dunn 1999, Fraser 2008). The binding of both plasminogen and plasmin (which can still be formed) to fibrin are inhibited by this. Tranexamic acid may also have an anti-inflammatory effect (Jimenez 2007). Tranexamic acid is effective after both oral and intravenous administration. Tranexamic acid is excreted by the kidneys.

Applications

Peri-operative

The use of tranexamic acid during cardiac surgery, orthopaedic procedures, during liver transplants and prostate surgery significantly reduces blood loss, the number of blood transfusions and the number of transfused patients (see table 8.1.3.2). The Cochrane database – in which 46 of the 53 studies used a transfusion protocol – calculated that 1.12 fewer units of erythrocyte concentrate were transfused in the intervention arm of all included studies. In the intervention arms of studies that did not use a transfusion protocol, the number of allogeneic transfusions was higher than in the trials that determined the transfusion indication based on a protocol (37 versus 25%) (Henry 2007).

The use of tranexamic acid during orthopaedic procedures is based on the fact that the use of a tourniquet provides a bloodless peri-operative surgical field during knee surgery, but that post-operative blood loss is amplified by local fibrinolysis activation (Engel 2001).

The use of tranexamic acid during prostate surgery is based on the fact that primary fibrinolysis due to the release of plasminogen is one of the causes of peri-operative blood loss.

Not much is known about the use of anti-fibrinolytics during liver resections. Elevated or amplified fibrinolysis may occur during liver resections. During liver transplants, tranexamic acid at a low dose suppresses fibrinolysis without reducing the number of blood transfusions, in contrast to a high dose regime where the number of transfusions is thought to increase (Groenland 2006, Molenaar 2007). See also table 8.1.3.2.

Gynaecology

Tranexamic acid is effective in women with menorrhagia caused by coagulopathies such as von Willebrand Disease, being a carrier of haemophilia and thrombocytopenia/thrombocytopenia due to menorrhagia caused by hormonal therapy or peri-menopausal and other types of dysfunctional menorrhagias (Fraser 2008, Kadir 2006, Bongers 2004, Duckitt 2007, Phupong 2006, Kriplani 2006). Tranexamic acid should not be administered in the case of nephrogenic haematuria, because of possible urethral thrombosis. The medication is also effective at inhibiting placental bleeding and post-partum

bleeding, as well as reducing blood loss during Caesarian sections and cervix surgery (Gai 2004, Martin-Hirsch 1999, Caglar 2008). See also table 8.1.3.2.

Neurosurgery/neurology

Reduction of recurrent bleeding (45%) following administration of tranexamic acid for sub-arachnoid haemorrhages has been described (Roos 2008, Liu-DeRyke 2008). See also table 8.1.3.2.

However, the risk of cerebral ischaemia was elevated in five studies in the group treated with anti-fibrinolytics, with considerable heterogeneity between the studies in which measures to prevent ischaemia were taken (Roos 2008, Carley 2005).

As a result, tranexamic acid therapy does not improve the clinical result, because the benefit of preventing recurrent bleeding does not outweigh the increase in consequences of cerebral ischaemia. There are no data that support the routine use of tranexamic acid for this indication.

Digestive tract bleeding

Older studies suggest that tranexamic acid reduces mortality with digestive tract bleeding. A meta-analysis from 1989 of six studies showed a reduction in the number of operations by 40%, a reduction in mortality of 40% and a decrease in recurrent bleeding by 20 – 30% (Henry 1989). Inclusion of a study with high mortality due to cimetidine use may have distorted results (Gluud 2007). A recent meta-analysis revealed that tranexamic acid reduces overall mortality (RR 0.61), but not blood loss, the bleeding-related mortality, the number of transfusions or the number of operations (Gluud 2008).

Two case reports of two patients with GAVE (Gastric Antral Vascular Ectasia) describe that the number of bleeding episodes and the number of blood transfusions decreased after administration of tranexamic acid (Selinger 2008).

Side effects

Reported side effects of tranexamic acid use are vasospasm, gastro-intestinal symptoms, orthostatic hypotension and thrombosis.

Gastro-intestinal symptoms (nausea, diarrhoea, stomach cramps) have only been described with oral therapy (Faught 1998).

A change in skin colouration is occasionally reported. If this happens, treatment with the medication should be stopped.

In the randomised studies performed to date in cardiac surgery, orthopaedics and liver transplants, no significant difference was seen in the incidence of myocardial infarction, thrombosis or cerebrovascular accidents (see table 8.1.3.2). This was confirmed by the large retrospective studies by Mangano and Karkoutie and in the BART study. The use of tranexamic acid therapy is also not associated with an increased short or long term mortality (Mangano 2006 en 2007, Karkouti 2006, Fergusson 2008).

The administration of tranexamic acid with liver transplantation appears to be safe, without elevated risk of thrombo-embolic complications (Molenaar 2007).

Clot formation in the bladder during trans-urethral prostatectomies (TURP) has been described, as have fatal pulmonary emboli during retropubic prostatectomies. It is not clear

whether adequate thrombosis prophylaxis was given in these cases. The same applies to patients with macroscopic haematuria.

Table 8.1.3.2: Reduction in the number of blood transfusions and side effects due to tranexamic acid in meta-analyses and RCTs

Author (year)	Level	Study set-up	Reduction in number of blood transfusions ³	Side effects
Cardiac surgery				
Brown (2007)	A1	22 RCT CABG; 1966 – 2006; n = 2429	RR 0.75	n.s.
Umscheid (2007)	A1	Cardiac surgery 1966 – 2007 TXA vs placebo; n = 1905; AT vs TXA n = 1825	RR 0.65 vs AT RR 0.98	n.s.
Henry; (Cochrane 2007)	A1	CABG: 1966 – 1999; 15 RCT; n = 1151	RR 0.69 (EC)	n.s.
Jimenez (2007)	B / A2	CPB inflammatory response. Case control n = 165; RCT n = 50		Inflammatory response ↓; 17 vs 42% (p = 0.047) Significant reduction shock, vasopressors, artificial ventilation, RD, D-dimer.
Orthopaedics				
Henry; (Cochrane 2007)	A1	Non-cardiac; 21 RCT orthopaedics; n = 993; 2 RCTLT n = 296	Ortho: RR 0.44 LT: n.s.	n.s.
Gynaecology				
Lethaby; (Cochrane 2000)	A1	Menorrhagias; 7 RCT 1966 – 2004. n = 193	Reduction BL: WMD 94%.	n.s.
Martin-Hirsch; (Cochrane 1999)	A1	Surgery for cervical intra-epithelial neoplasia; 4 RCT 1966 – 1999. Prophylactic TXA. (i.v. and/or oral); n = 910 P.S.: older studies	Reduction secondary bleeding OR 0.23 Reduction volume BL 1 week: – 55.66%	n.s.
Gai (2004)	A2	Caesarian section; RCT TXA oral vs none; n = 180	BL up to 2 hours post-partum 88 ml less (p = 0.002)	n.s.
Phupong (2006)	A2	Bleeding in Norplant implantations; RCT TXA oral vs placebo; double blind; 1 week	Irregular bleeding stopped in week 1: 64.7 vs 35.3% Only effect during	n.s.

		therapy, then stop; n = 68	use of TXA	
Kriplani (2006)	A2	Menorrhagia; RCT TXA oral vs MPA; n = 100; 6 months follow-up	BL reduction: 60.3 vs 57.7%	hysterectomy 4 vs 17.8%
Caglar GS (2008)	A2	Myomectomy; RCT TXA i.v. vs Saline; n = 100	n.s.	n.s.
Other				
Roos (Cochrane 2008)	A1	Sub-arachnoid bleeding. 8 RCT TXA 1966 – 2002; n = 1360	Reduction in re-bleeding: OR 0.55	outcome: no benefit OR 1.12 mortality: OR 0.99 risk of ischaemia increased in 5 trials: OR 1.39, with heterogeneity in 1 study with ischaemia prevention (Roos 2000) Hydrocephalus: n.s.
Glud (2008)	A1	Upper digestive tract bleed. 7 RCT TXA vs placebo; n = 1754.	n.s.	Mortality 5 vs 8% Thrombo-emboli: n.s.
Molenaar (2007)	A1	LT: 1966 – 2005; 23 RCT; n = 306	EC: SMD 0.42 U FFP: SMD 0.30	n.s.

1. AT= Aprotinin Therapy; BL = Blood Loss; CABG = Coronary Artery Bypass Graft; EC = Erythrocyte Concentrate; FFP = Fresh Frozen Plasma; i.v. = intravenous; LT = Liver Transplant; n.s. = not significant; MPA = MedroxyProgesterone Acetate; OR = Odds Ratio; RCT = Randomised Controlled Trial; RD = Renal Dysfunction; RR = Relative Risk; SMD = Standardised Mean Difference; WMD = Weighted Mean Difference; U = Unit.

2. All results are significant, unless specifically mentioned.

TXA versus control/placebo. Only the significant data were presented.

Conclusions 8.1.3.2

Level 1	<p>Tranexamic acid is a safe and effective agent to reduce blood loss and the resulting number of allogeneic blood transfusions in cardiac surgery and orthopaedic surgery and during liver transplants (with the exception of the hypo-fibrinolytic phase).</p> <p>A1 <i>Henry 2007, Brown 2007, Molenaar 2007, Umscheid 2007</i></p>
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Level 1	<p>Tranexamic acid reduces blood loss in menometrorrhagias, post-partum bleeding, Caesarian section, cervix surgery, digestive tract bleeding and trans-urethral prostatectomies.</p> <p>A1 <i>Martin-Hirsch 2008, Lethaby 2008, Gluud 2008, Gai 2004, , Phupong 2006</i></p> <p>A2 <i>Kriplani 2006</i></p>
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Level 1	<p>The use of tranexamic acid with sub-arachnoid haemorrhages results in an increased risk of cerebral ischaemia.</p> <p>A1 <i>Roos 2008</i></p>
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Recommendations 8.1.3.2

1. Peri-operative and post-operative use of tranexamic acid to reduce blood loss during cardiac surgery and during knee and hip surgery is recommended.
2. Peri-operative use of tranexamic acid to reduce blood loss during liver transplants should be considered except in the case of hyper-coagulability.
3. The administration of tranexamic acid to reduce blood loss should be considered in the case of digestive tract bleeds, menorrhagia and post-partum bleeding.
4. **Macroscopic haematuria is a contra-indication for tranexamic acid therapy with all the above-mentioned indications.**
5. **Tranexamic acid administration is not recommended for trans-urethral prostatectomy (TURP) and in the case of sub-arachnoid bleeding.**

8.1.3.3 Desmopressin

Desmopressin is the synthetic analogue 1-deamino-8-D-arginine vasopressin (DDAVP) of the hormone vasopressin. Following intravenous administration, desmopressin increased the plasma concentration of von Willebrand Factor, factor VII and tissue plasminogen activator by mobilisation from the storage sites. Depletion of the depots then takes place and the clotting factors need to be produced once more. In addition, desmopressin has an anti-diuretic effect without vaso-active side effects (Hashemi 1990).

Efficacy as blood saving method

Two meta-analyses (Laupacis 1997, Levi 1999), a Cochrane study (Henry 2001) and two RCTs (Oliver 2000, Ozkizacik 2001) show that desmopressin administered peri-operatively in cardiac surgery does not result in a decrease in the number of allogeneic blood transfusions.

Conclusions 8.1.3.3

Level 1	<p>Following intravenous administration, desmopressin increases the plasma concentration of von Willebrand factor, factor VIII and . tissue plasminogen activator. In addition, desmopressin has an anti-diuretic effect without vaso-active side effects.</p>
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	A1 Hashemi 1990
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Level 1	It has been shown that desmopressin does not reduce the number of allogeneic blood transfusions in cardiac surgery.
	A1 Laupacis 1997, Levi 1999, Henry 2001
	A2 Oliver 2000, Ozkizacik 2001

Other considerations

International guidelines recommend the use of desmopressin to improve platelet function in patients using medication that inhibits platelet function (for example, Clopidogrel and acetylsalicylic acid), in patients with uraemia, kidney or liver function abnormalities and in patients with von Willebrand Disease types 1 and 2A (Ferrari 2007, Anonymous 2006; see also Chapter 6.4.1).

8.1.3.4 Fibrin glue and platelet gel

Fibrin glue

Fibrin glue has been described since the 1970s as a medication that promotes adhesion of tissues and has local haemostatic properties. As a result of this latter characteristic, fibrin glue could be used as a method to save on allogeneic blood transfusions.

Component composition

Fibrin glue consists of 2 components, namely a cryoprecipitate and thrombin. The cryoprecipitate contains concentrated clotting factors and a high concentration of fibrinogen. The addition of thrombin converts fibrinogen to fibrin. The current commercially available components sometimes contain anti-fibrinolytics, such as aprotinin or tranexamic acid, to inhibit fibrinolysis. There is also equipment available on the market to produce peri-operative autologous fibrin glue. Fibrin glue does not contain growth factors.

Currently, there are also materials available on the market that contain thrombin and fibrinogen on their surface, which can be placed on the wound. Fibrinogen activation takes place upon contact with water or blood and this creates fibrin, which controls the bleeding.

Efficacy

A recent Cochrane analysis – in which 18 RCTs involving 1,406 patients are described – shows that the local application of fibrin glue in the surgical field significantly reduced the number of peri-operative allogeneic blood transfusions by 37% and resulted in an average 161 mL reduction in blood loss (Carless 2009). However, only a few studies were of good quality and only 18% of the studies were performed in a blinded manner. It was not possible to formulate a conclusion on side effects.

Conclusion 8.1.3.4

Level 1	The use of fibrin glue can reduce the use of peri-operative allogeneic blood transfusions. However, the extent of benefit in saving on allogeneic blood transfusions for various procedures has not been studied in qualitatively and quantitatively good studies.
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Recommendation 8.1.3.4

The local application of fibrin glue is an option to reduce peri-operative blood loss.

Platelet-leukocyte enriched gel (PLG)*Definition*

Platelet-leukocyte enriched gel (PLG) is a gelatinous mass that is formed within 10 seconds when autologous “platelet rich plasma” (PRP) and thrombin are mixed. PRP is prepared from the buffy coat, which – in addition to platelets – also contains a more than three-fold higher concentration of leukocytes. The addition of thrombin activates the platelets in the PRP and causes the release of various platelet growth factors (PDGF-ab, VEGF, EGF, TGF-beta) (Marx 2001).

Efficacy and use

In addition to use in wound healing, PLG also appears to be effective as a haemostatic and could therefore result in fewer allogeneic blood transfusions (Everts Devilee 2006).

Area of application

In the early 1990s, PLG was positioned as an alternative to fibrin glue to improve haemostasis in cardiac surgery patients (Ferrari 1987, Rubens 1998). However, the efficacy of PLG as a haemostatic agent in cardiac surgery has not been examined in RCTs. Incidental studies report that PLG reduced the use of allogeneic blood transfusions in orthopaedic surgery (Everts Devilee 2006).

Conclusion 8.1.3.4

Level 3	<p>There are indications that – in addition to a favourable effect on wound healing – platelet-leukocyte enriched gel (PLG) may also have a haemostatic effect and might therefore result in fewer allogeneic blood transfusions.</p> <p>C <i>Everts, Devilee 2006 , Everts Jakimovitch 2007, Ferrari 1987, Rubens 1998</i></p>
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Other considerations

There are no comparative studies on the efficacy and side effects of PLG and other local haemostatics, . such as fibrin glue.

The use of bovine thrombin to activate PLG is not recommended, partly due to the development of . antibodies (Chouhan 1997).

Recommendation 8.1.3.4

There is not enough data available to be able to make a recommendation concerning the use of platelet-leukocyte enriched gel (PLG) as a local haemostatic.

8.1.3.5 Erythropoietin (EPO)

Properties, dosage and side effects

Erythropoiesis Stimulating Agents (ESAs or erythropoietic growth factors) is a collective term for medications that stimulate the production of erythrocytes. By far the most important ESA is erythropoietin (EPO). There are two types of EPO: epoetin and darbepoietin alpha, which has a longer half life than epoetin. In this guideline, we will use ESA if the relevant literature uses the term Erythropoiesis Stimulating Agents and EPO if the literature refers to erythropoietin, epoetin, darbepoietin or EPO.

Please refer to Chapter 4, section 4.3 for the use of EPO in chronic anaemia and Chapter 5, section 5.9.2 (Use of EPO in ICU patients) and 5.8 (acute or massive blood loss in pregnancy and surrounding childbirth) for use with anaemia in the Intensive Care Unit and in Obstetrics.

This section discusses the peri-operative use of EPO. The use of EPO results in an increase in Hb in patients with pre-operative anaemia or patients who donate autologous blood pre-operatively .

Around 8 – 24 hours after subcutaneous administration of EPO, a peak concentration is achieved that is lower but persists longer than following intravenous administration (Muirhead 1995). The half life following intravenous administration is 4 -5 hours and after subcutaneous administration is 19 – 22 hours. Following multiple intravenous administrations in study subjects, the half life tends to decrease faster than with a one-off high intravenous dose, because the elimination is accelerated after multiple doses (Markham 1995, Goldberg 1996, Adamson 1996).

Various dose regimes are used for EPO, varying from a total dose of 300 IU/kg to 6,400 IU/kg subcutaneous or intravenous over 5 – 30 days, in combination with oral or intravenous iron supplementation. The optimum total dose for peri-operative use is not known. The lowest effective dose has also not been sufficiently researched and is currently not known, although a dose lower than 150 IU/kg appears to be less effective (Laupacis 1998). It is confusing that the total dose of supplemented iron differs in various studies. Sufficient iron supplementation is important to obtain an increase in Hb, particularly in patients with pre-existing iron deficiency or an oncological or chronic disease process.

It has been demonstrated that iron depletion decreases the therapeutic effect of EPO, particularly in patients with anaemia of non-renal origin (Iperen 2000). During treatment with EPO, the transferrin saturation should be $\geq 20\%$ and the ferritin concentration $\geq 100 \mu\text{g/L}$. Normally, the intake of 200 mg elemental iron per day should be sufficient. If oral iron administration provides insufficient effect, or if the patient is unable to take oral medication, one can consider intravenous administration of iron. It is advisable to take vitamin C together with oral iron, as vitamin C promotes the absorption of iron (Iperen 2000). It has not been demonstrated whether this also promotes the effect of exogenously administered EPO. The same applies to vitamin B12 and folic acid.

Side effects

Hypertension

EPO can cause hypertension. The underlying mechanism is not well known, but an increase in viscosity of the blood, the neutralisation of reflex hypoxic vasodilation or direct vasoconstriction could be an explanation (Esbach 1991, Faught 1998).

Deterioration of pre-existing hypertension has been described during peri-operative use of high dose EPO (3 of the 200 patients) (Laupacis 1998, Faught 1998). In all other studies, no differences in complications were described for this indication between the study group and the placebo group (Faught 1998). (see also table 8.1.3.5.)

Thrombo-embolic complications

EPO can cause thrombo-embolic complications (myocardial infarction, CVA, TIA) in patients with renal failure. (Weiss 2005). The occurrence of these complications is described separately for the various applications (see also table 8.1.3.5).

Contra-indications

Allergy to EPO or one of its ingredients, severe atherosclerosis of the coronary arteries or peripheral vessels, uncontrolled hypertension, recent myocardial infarction, CVA or cardiovascular conditions and situations in which a contra-indication for adequate anti-thrombotic prophylaxis exist are absolute contra-indications for pre-operative use of EPO (Weiss 2005). Relative contra-indications are: epilepsy, chronic liver insufficiency and a predisposition to deep vein thrombosis.

Applications

Cardiac surgery

A systematic review of nine randomised studies about the use of EPO in cardiac surgery procedures – alone or in combination with peri-operative autologous donation – showed that the use of EPO increases the number of autologous units of blood collected and significantly reduces the number of allogeneic blood transfusions (Alghmadi 2006, Laupacis 1998).

There is not enough scientific data available to draw definitive conclusions about the risk of thrombotic or vascular complications in this group of patients. Therefore, use in cardiac surgery patients is often only advised in combination with pre-operative autologous donation (PAD).

Orthopaedic surgery

An older systematic review of 21 randomised double blind studies shows that in orthopaedic surgery, the pre-operative administration of EPO (sometimes in combination with PAD) also caused a significant increase in the number of autologous units of blood collected and a decrease in the use of allogeneic blood transfusions (Laupacis 1998). See also table 8.1.3.4. No new meta-analysis has appeared since, but several RCTs and one large observational study do confirm the above-mentioned data (Moonen 2008, Rosencher 2005, Weber 2005, Karkouti 2005).

Intravenous administration of EPO was not significantly more effective than subcutaneous administration (odds ratio 0.52 and 0.32 respectively). The studies do not provide a clear advice on the dosage (the most commonly used dosage was 600 IU/kg once a week).

There are indications that fewer injections are also effective (Rosencher 2005, Karkouti 2005), which could save on costs.

In the studies described above, no significantly increased risk of thrombo-embolic complications was found.

Oncological surgery

EPO has been examined for various types of surgery, with the aim of increasing the preoperative Hb and reducing the number of peri-operative blood transfusions. A recent meta-analysis demonstrated that – for colorectal surgery – EPO did not significantly reduce the number of blood transfusions. There were no differences in mortality or morbidity between the two groups (Devon 2009). This may be different for patients undergoing a radical prostatectomy or a gynaecological radical surgery (Dousias 2005, Gaston 2006). However, these studies were too small to be able to draw definitive conclusions.

People who reject transfusions for religious reasons

EPO (provided it is not dissolved in human albumin) is accepted by people who reject transfusions on religious grounds (Ball 2008). See further 8.4 Jehovah’s Witnesses.

Post-operative anaemia

For the treatment of post-operative anaemia, EPO combined with intravenous (i.v.) iron did not appear to be more effective than i.v. iron or placebo therapy (Karkouti 2006).

Post kidney transplant

Following kidney transplantation, EPO resulted in a faster increase in Hb, after 4 months, however there were no differences compared to a placebo group. (Van Biesen 2005). Another smaller study showed that low dose EPO is sufficient in these patients (Baltar 2007). Erythropoietin did not affect the kidney function.

Pre-operative Autologous Donation (PAD)

Various studies have shown that EPO during PAD increases the number of units for collection and results in a higher initial Hb immediately before and after surgery (see PAD and extensive table 8.1.3.5 below) (Bovy 2006, Hyllner 2005, Hardwick 2004, Deutsch 2006, Keating 2007).

Table 8.1.3.5: Data from clinical trials concerning the use of erythropoietin therapy aimed at saving on peri-operative allogeneic blood transfusions

Author (year)	Level	Study set-up ¹	Result ²	Side effects ²
Orthopaedics				
Laupacis 1998	A1	Meta-analysis 1966 – 1997. Epo + PAD: 16 studies; 5 x cardio; 9 x ortho. Epo + Ortho: 3 studies Epo + cardio: 2 studies	OR BT with epo + PAD: - Ortho: 0.42 OR epo only: - Ortho: 0.36 No difference i.v. or s.c.	Possibly more thrombo-embolic complications in several small studies. Not significant

Moonen 2008	A2	RCT, THP / TKP. Epo (4) vs drain blood N = 100	THP - BT 7 vs 30% TKP - BT 0 vs 25% At least 1 EC less	none
Weber 2005	A2	RCT Epo (4; n = 460) vs control (n=235)	- BT 12 vs 46% - Hb - No effect: duration of admission, infections, walking BT + vs BT -: - Walking: 3.8 vs 3.1 days - Duration of admission: 12.9 vs 10.2 days	none
Karkouti 2005	C	Prospective THP / TKP 1999 – 2003. n = 770 with Hb < 7.8 mmol/L: 214 epo vs 556 not 1 – 3 x 20,000 U (< 70 kg) resp 40,000 U (> 70 kg) in week before OR	- BT 16.4 vs 56.1%	
Cardiac surgery			-	
Alghamdi 2006	A1	Meta-analysis 11 RCTs n=708	- Epo + PAD BT RR = 0.28 - Epo only: BT = 0.58	Not significant
Laupacis 1998	A1	Meta-analysis 7 RCTs	- Epo + PAD: OR chance of 1 BT: 0.25 - Epo only: OR 0.25	
Oncological surgery				
Devon Cochrane 2009	A1	Meta-analysis colorectal surgery 1966 – 2008. 4 RCTs	- No differences BT	No difference in mortality, thrombotic complications.
Dousias 2005	A2	RCT. Gyn. radical extripation. Epo n= 20, control n=18	- Hb 11.9 vs 10.9 g/dL - BT: 0 vs 3 patients	None
Gaston 2006	A2	RCT rad prostatectomy epo n=25, control n=25	- Ht 4% higher - BT = 4 vs 4%. - QoL: n.s.	None
Pre-operative Autologous Donation epo vs PAD				

Hardwick 2004	A2	RCT ortho Epo (2 x) n = 19 vs PAD n = 21 + cell saver intra-operative	Total BT (allogeneic and autologous) - 16% (90 mL/p.p.) vs 52% (340 ml/p.p.) - 11 vs 14% allogeneic BT: n.s. - PAD group 62% more mL allogeneic - Hb 14.6 vs 12.6 g/dL - Hb post-op day 1: 11.5 vs 9.8 g/dL (also higher on other days)	None
Deutsch 2006	A2	RCT ortho Epo (2 x) (n=25) vs PAD (n = 25)	- Hb 13 vs 11 g/dL - BT 8 vs 28% n.s.	None
Keating 2007	A2	RCT ortho Epo (4 x 600 U/kg) (n=130) vs PAD (n=121) BT trigger 8 g/dL also for autologous	- Hb 14.2 vs 12.1 g/dL - Allogeneic BT 3 vs 17% - Vigor score epo group higher - Hand grip strength: n.s. - BT trigger 8.13 vs 8.97 g/dL n.s. - 31% autologous blood discarded (49 U)	None
Rosencher 2005	A2	RCT Epo (to Ht = 40%) vs PAD (to Ht < 33%) N = 93	- 65% had Ht = 40% after 2 inj. - 45% 2 PAD - BT 6 vs 12% (allogeneic); n.s. - Epo: Ht post-op ↑ - Energy score: epo ↑	none
Epo + PAD vs PAD				
Bovy 2006	A2	RCT orthopaedic Epo (3 x 600 U/kg) + PAD n=11 vs epo + PAD (3x 300 U/kg) n=11 vs placebo + PAD n=10	- 4.6 units PAD vs 4.1 vs 3.6 (4.6 vs 3.6 is significant)	None
Hyllner 2005	A2	RCT radical hysterectomy PAD + epo (n=15) vs PAD - epo (n=15)	- Hb pre-op: 11.8 vs 10.6 g/dL - Hb day 1 post-op: 10.1 vs 9.2 g/dL - IL-6 and IL-8: n.s.	
Aksoy 2001	A2	RCT, deblinded. ortho PAD + Epo (n=20) PAD + placebo (n=20)	- 48 vs 49 units collected - Allogeneic EC 7 vs 13 units	
Other				
Post kidney transplant				
Van Biesen 2005	A2	RCT. Post kidney	- Target reached: 52.6 vs	

		transplant Epo (100 IU/kg, 3 x week to Hb 12.5 g/dL) (n =22) vs control (n=18)	66.5 days - No difference after 3 months - Not efficient from cost point of view.	
Baltar 2007	C	Open label; following kidney transplant. Epo to Hb 11 g/dL. N=24	- Hb correction in 86%. Graft survival: 71% benefited from epo; no graft survival: 50% benefited from epo. - Epo had no effect on renal function.	
Post-operative anaemia				
Karkouti 2006	A2	RCT, blinded. Post-op Hb for cardio and ortho with Hb 7 – 9 g/dL. i.v. Fe (200 mg on days 1,2,3; n=11) vs i.v. Fe + epo (n=10; day 1 and 3 post-op) vs placebo (i.v. and s.c. n=10)	- No significant reduction in anaemia	
Ferraro 2004	C	CT, plastic surgery, randomisation not pure. Epo (3 x) (n=15) vs control (n=15)	- Hb pre-op 14.9 vs 12.9 g/dL - Hb day 1 post-op: 11.7 vs 9.6 g/dL - BT: 0 vs 1.6 units (average)	

BT = Blood Transfusions; C = Control group; EC = Erythrocyte Concentrate; Epo = erythropoietin, marketed as various preparations; Hb – haemoglobin level in g/dL, conversion to mmol/l is x 0.6206; HF = Heart Failure; Ht = haematocrit; n = number of patients; n.s. = not significant; OR = Odds Ratio; RCT = Randomised Controlled Trial; RR = Relative Risk; SMD = Standardised Mean Difference; The results are significant, unless specifically mentioned. Erythropoietin versus control.

Conclusions 8.1.3.5

Level 1	Pre-operative therapy with EPO increases both the number of autologous donations for collection in the case of pre-operative autologous blood donation (PABD) and the peri-operative Hb. A1 <i>Laupacis 1998</i> A2 <i>Bovy 2006</i>
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Level 1	Administration of EPO reduces the number of allogeneic blood transfusions administered peri-operatively in orthopaedic surgery, provided sufficient iron supplementation is started in a timely manner. A1 <i>Laupacis 1998</i> A2 <i>Moonen 2008, Weber 2005</i> C <i>Karkouti 2005</i>
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Level 1	Administration of EPO in cardiac surgery – with or without pre-operative autologous blood donation (PAD) – reduces the number of allogeneic transfusions administered, provided iron therapy is started in a timely manner. A1 <i>Laupacis 1998, Alghamdi 2006</i>
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Level 1	Administration of EPO for colorectal surgery does not reduce the number of allogeneic blood transfusions. There are indications that this is the case for prostatectomy, radical hysterectomy, plastic surgery and kidney transplants. A1 <i>Devon 2008</i> A2 <i>Dousias 2005, Baltar 2007</i>
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Recommendations 8.1.3.5

1. EPO can be administered pre-operatively to increase the yield of pre-operative autologous donation or to reduce the use of allogeneic blood transfusion during major orthopaedic procedures in patients with moderate blood loss.
2. For patients who refuse transfusions on principle, epoietin can be administered in the peri-operative phase.
3. EPO should be combined with iron therapy that should be started as soon as possible.
4. Due to the risk of complications (mainly thrombo-embolic), EPO injections should be stopped as soon as the Hb is > 9.4 mmol/L.

8.1.3.6 Recombinant factor VIIa (rFVIIa) in the peri-operative phase

Based on new insights into the action of blood clotting *in vivo*, recombinant factor VIIa (rFVIIa, Eptacog alpha, NovoSeven) has been developed as a pro-haemostatic agent. Improvement in blood clotting by means of pharmacotherapeutic intervention with rFVIIa is a registered treatment for bleeding in haemophilia patients with antibodies against factor VIII or factor IX. The efficacy in the case of the above-mentioned clotting disorders has resulted in the hypothesis that administration of rFVIIa in patients with a normal blood clotting system and severe blood loss due to major trauma or a major surgical procedure could result in a reduction of blood loss and blood transfusion. The off-label use of rFVIIa is largely based on case reports and smaller studies (Kenet 1999, Vlot 2000, White 1999, Ejlsen 2001, Martinowitz 2001, Hardy 2005, Hoyt 2004, Lynn, Spahn 2005, ASA Task force on blood component therapy 1996, Levi 2005, Diprose 2005).

A recent review of 17 RCTs for various indications demonstrated that with routine administration of rFVIIa, the blood-saving effect was demonstrable in three of the pilot studies, but was not confirmed in large randomised studies (Boffard 2005). See also table 8.1.3.6. rFVII appears to be more effective for blunt trauma than sharp trauma and could save 2 – 6 units of allogeneic blood. No significant difference was found in thrombo-embolic complications, except for patients with an intracranial haemorrhage. A decrease in intracranial blood volume was found in these patients, but this was associated with a significant increase in arterial and venous thrombo-embolic complications. In patients with

normal blood clotting, routine use of rFVIIa in the peri-operative phase was possibly associated with an increase of thrombo-embolic complications (Johansson 2008).

A transfusion protocol was described in nine of the 17 studies, but three of these only provided guidelines for the transfusion of erythrocytes. With the exception of one study, traditional parameters were mainly used for the transfusion of plasma and platelets. Another point of comment is that there was a difference in the platelet transfusion trigger. However, conditions for an optimal effect of rFVIIa are a sufficient number of platelets and an adequate fibrinogen level (Boffard 2005).

rFVIIa has a role as a rescue medication in the treatment of massive blood loss (see Chapter 5), if all other conditions have been met and if there are sufficient opportunities present to form a clot (platelets > 100 x 10⁹/L and fibrinogen > 1.0 g/L). The optimum dose for this indication is not known. A low dose (20 – 90 µg/kg) appears to be effective (Vincent 2006). European guidelines (ESA and ESICM) recommend a dose of 200 µg/kg, followed by 100 µg/kg at 1 and 3 hours after the trauma. If the administered dose is effective, the dose can be repeated once. If administration has not resulted in an effect, there is no point in administering a second dose.

Table 8.1.3.6: Results of RCTs concerning rFVIIa for various indications

Author	Search	Results BT	Side effects	Level
Johansson 2008	1966 – 2007 RCTs use of rFVIIa: 17 RCTs	BT = blood transfusion BL = blood loss	TE = thrombo-embolism ATE: arterial thrombotic complications	A1
	Stem cell transplant	N = 100, 73 rFVIIa. No difference	TE 3. 1 in each rFVIIa group	
	Intra-cerebral haemorrhage	2 studies; N = 48 + 399 Reduction haematoma	TE 6/48 and 19/21 ATE: 16/16 Only in rFVIIa groups	
	Dengue Fever	N = 25, 16 rFVIIa. No difference		
	Cirrhosis	N = 245, no difference		
	Prostatectomy	N = 36. No difference in blood loss. BL in control group extremely high.		
	Pelvic trauma	N = 48. no difference		
	Liver transplant	N = 172 + 82. no difference	TE: 27/172 and 12/48 evenly distributed over both groups	
	Liver resection	N = 185 + 221. no difference	TE: 9 / 185 and 2 / 221 evenly distributed over both groups	
	Cardiovascular surgery	N = 20. no difference	4 / 20 evenly distributed over both groups	
	Congenital heart surgery	N = 76. no difference		
	Burn wounds	N = 18 50% fewer BT in rFVIIa group		
	Spinal column	N = 49. Less BL	TE 2/49 in rFVIIA group	

	surgeries			
	Trauma	Blunt: N = 143 Sharp: N = 134 Initially no difference. Planned after 48 hours post hoc blunt: 2 – 6 U less.	TE: 5/143 and 7/134. evenly distributed over both groups.	

Mayer also showed in a RCT that the outcome did not improve despite a decrease in intra-cerebral haematoma.

Conclusions 8.1.3.6

Level 1	The use of recombinant factor VIIa (rFVIIa) in patients with bleeding resulted in a decrease in the bleeding, but was associated with a significant increase in arterial and venous thrombo-embolic complications. <i>A1 Johansson 2008, Levi 2010, Mayer 2008 (A2)</i>
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Level 1	There is insufficient evidence to prove that the routine use of recombinant factor VIIa (rFVIIa) in trauma patients reduces the peri-operative use of allogeneic blood transfusions. <i>A1 Johansson 2008</i>
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Other considerations

There are indications that the use of rFVIIa at a low dose can limit the blood loss due to blunt trauma and that it could play a role as rescue medication in the case of major blood loss. This only applies if abnormal coagulation has been corrected, the platelet count is $> 100 \times 10^9/L$, the fibrinogen level $> 1.0 \text{ g/L}$, and acidosis and hypothermia have been corrected. More research is desirable, as is the implementation of national registration of rFVIIa use for non-registered indications.

Recommendations 8.1.3.6

1.	One can consider using recombinant factor VIIa (rFVIIa) as rescue medication for massive blood loss, provided the platelet count is $> 100 \times 10^9/L$ and the fibrinogen level is $> 1.0 \text{ g/L}$, and any acidosis and hypothermia have been corrected.
2.	The recommended dose of recombinant factor VIIa (rFVIIa) as rescue medication for recommendation 1 is $90 - 120 \mu\text{g/kg}$. The administration may be repeated once if an effect is observed.
3.	If no effect is seen after administration of recombinant factor VIIa (rFVIIa) as rescue medication as mentioned under recommendation 1, repeat administration is not recommended.
4.	In the case of off-label use of recombinant factor VIIa (rFVIIa is not authorised as a rescue medication), the patient must be closely monitored for the occurrence of thrombo-embolic complications.

8.1.4 Haemodilution

(Intentional) haemodilution is defined as the artificial reduction of the erythrocyte count in the blood by dilution with crystalline or colloidal fluids. The treatment is aimed at reducing blood loss.

8.1.4.1 Acute normovolemic haemodilution (ANH)

In acute normovolemic haemodilution (ANH), a number of units of blood are collected from a large vein, immediately pre-operatively after the patient is under anaesthesia, until the desired Hb has been reached (Ferrari 2008, Anonymous 2006, Wolowczyk 2005). The blood is replaced volume for volume with a plasma substitute (normovolemia). This technique has been used for many years in orthopaedic surgery, urology and general surgery, but particularly in cardiac surgery.

For non-cardiac surgical procedures, ANH is used with the aim of lowering the number of circulating erythrocytes by dilution, resulting in a smaller net loss of erythrocytes (Bennet 2006). This also applies to cardiac surgical procedures, whilst also preventing the collected blood from being exposed to activation by the use of the cardiopulmonary bypass machine (Reents 1999).

The quantity of blood that can be collected depends on the initial Ht of the patient and the estimated blood volume. The normograms by Zetterstrom can be used as a guideline. (Zetterstrom 1985). The blood collected under sterile conditions can be stored at room temperature for a maximum of 6 hours and at 4 °C for 24 hours (AABB 1997). The platelet function of the collected blood will be lost with storage at 4 °C. If this blood has not been tested (in the same way as blood from random donors), it should be stored in a separate refrigerator. Return of the blood takes place in reverse order, because the unit that was collected first contains the highest number of erythrocytes, platelets and clotting factors ('last out, first in').

Efficacy and indications for ANH

The efficacy of ANH increases with increasing "initial Hb" and decreasing "ANH target Hb" (Weiskopf 2001, Matot 2002). Randomised trials have demonstrated the efficacy of ANH for non-cardiac surgical procedures such as liver surgery (Matot 2002, Jamagin 2008), urology (Monk 1999) and orthopaedics (Goodnough 2000, Goodnough 1999) and approximately 30% fewer allogeneic transfusions are given, but the results vary (among others Hohn 2002, Ramnath 2003, see Table 8.1.4.1). As far as the efficacy of ANH for cardiac surgical procedures is concerned, there are contradictory study results (Bryson 1998, Carless 2004). See also table 8.1.4.1. Licker (2004, 2004, 2005, 2007) demonstrated that patients undergoing haemodilution had fewer post-operative complications, possibly due to improved tissue perfusion and oxygenation. See also table 8.1.4.2. The recently developed American Clinical Practical Guideline for blood-saving techniques states that ANH can be used effectively in cardiac surgery and advises the combination of ANH with other blood-saving techniques such as peri-operative auto-transfusion (Ferrari 2007).

Safety of ANH

The reduction in viscosity causes vasodilation and increases cardiac output (Suttner 2001, Jamnicki 2003). It is recommended to monitor patients with cardiac conditions closely using

ultrasound Doppler or via cardiac output monitoring (Suttner 2001, Jamnicki 2003, Licker 2004, Licker 2004). ANH can also result in an extension of the neuro-muscular block when using rocuronium, but not with cisatracurium (Dahaba 2006).

Dilution can cause the concentration of clotting factors to decrease. The use of large quantities of plasma expanders can cause coagulopathy, not only related to the effect of dilution but also dependent on the component used (Levi 2007). Recent research has demonstrated that in the case of infusion of colloids according to a protocol, this aspect is less important (Hobisch-Hagen 1999, Ickx 2003, Jalali 2008). The coagulopathy .due to plasma expanders was not observed . with the use of ANH during partial liver resections (Matot 2002). Measurements of the plasma volume and erythrocyte volume using advanced techniques have shown that a part of the infused plasma substitute or the protein solution used disappears into the “endothelial surface plasma layer” (Glycocalix) and another part leaves the circulation. This explains the fact that approximately 15% more plasma substitute is required to replace the collected volume of blood (Rehm 2001, Jacob 2005). See also table 8.1.4.2.

ANH is a cheap and easy technique to apply (Haynes 2002, Davies 2006).

Contra-indications of ANH

The contra-indications for the application of ANH are: pre-operative anaemia, sepsis, heart failure or ischaemic heart disease, myocardial infarction, cardiogenic shock and severe pulmonary disease. .Licker 2005).

8.1.4.2 Hypervolemic haemodilution (HVH)

In the case of hypervolemic haemodilution (HVH), the haematocrit is artificially reduced by infusion of plasma substitutes/crystalloids to increase the circulating volume. Very little research is available on this topic. One study shows a comparable result for HVH and ANH. Singbartl and Saricaoglu recently demonstrated that HVH can be used as an alternative blood-saving technique for patients who lose less than 40% of their circulating volume; ANH is preferable if greater blood loss is expected (Saricaoglu 2005, Singbartl 2000).

Table 8.1.4.1: Efficacy of acute normovolemic haemodilution (ANH)

First author	Study set-up	Result	Evidence class
General			
Bryson 1998	Meta-analysis RTs 1966 – Aug. 1996	Chance of BT reduced OR = 0.31 Chance of number of units reduced: - 2.2 U Studies with strict BT protocol do not confirm this Results may be flattered by study set-up	A1
Carless 2004	Meta-analysis 1966 – 2002 68 RCTs and 812 observational studies N = 34,000	BT –effect: PAD: 63% ↓ CS: 42% ↓ ANH: 31% ↓	A1
Orthopaedics			

Olsfanger 1997	RCT TKP ANH to Ht = 28 – 30% vs none. In ANH group, randomised to 2 or 6 hour post-operative re-infusion of autologous blood (n = 30)	21 units PC vs 5 – 7 in ANH group. No difference if ANH blood is returned 2 or 6 hours post-operative. (p < 0.024)	A2
Saricaoglu 2005	RCT THP ANH + 6% HES (10) vs HHD + HES (n=10) vs control (N=10)	BT 20 vs 40 vs 100%	A2
Bennett J 2006	RCT Ortho THP ANH (n=78) vs Control (n=77) BT trigger: Hb < 8 g/dL	19 vs 29% BT n.s.; 33 vs 63 EC n.s. OR 0.60 (p = 0.23) Complications: 18 vs 38% (p = 0.009)	A2
(Cardio)Vascular surgery			
Kahraman 1997	RCT CABG ANH 500 mL vs 1,000 mL vs none (n = 42)	Fewer allogeneic BT (p = 0.01) 2.3 vs 2.1 vs 3.1 units	A2
Höhn 2002	RCT CABG ANH + CS + aprotinin (n=40) vs CS + aprotinin (n=40)	No difference in saving BT So ANH no added benefit	A2
McGill 2002	RCT Cardiac surgery CS (n=75) vs CS + ANH (n=74) vs control (N=88)	BT: 26 vs 43 patients EC: average 0.68 vs 1.07/pp ANH no added benefit	A2
Ramnath 2003	RCT CABG ANH (in heparin) (n=50) vs ANH (in citrate) (n=48) vs control (n=46)	no saving in BT	A2
Wolowczyk 2003 and 2005	RCT AAA ANH + CS (n=16) vs control + CS (n=18)	No difference in BT Inflammatory response the same	A2
Jalali 2008	Case control, prospective CABG; control clotting ANH + NaCl substitution (n=50) vs control (n=50)	EC 17 vs 46 FFP 10 vs 47 No difference in coagulation parameters	B
Ramnarine 2006	Cardio 2006 ANH in citrate (n=14) vs ANH after heparinisation (n=13)	Platelet function better in heparinised collected blood	A2
Other surgery			
Hans 2000	craniosynostosis children ANH to Ht 0.25 vs none (n = 34)	No difference in BT	A2
Suttner 2001	RCT prostatectomy Controlled Hypotension + ANH (n=14) vs ANH (n=14)	BT effect ANH + CH equal to ANH alone. EC: 2 vs 2 vs 7 units	A2

	vs control (n=14)		
Matot 2002	RCT liver lobe resection ANH (n=39) vs control (n=39). BT trigger: Ht = 0.20 L/L	BT: 10 vs 36% No side effects	A2
Ickx 2003	RCT abdominal ANH + HES 130/0.4 (n=20) vs ANH + HES 200/0.5 (n=20)	Both equally effective.	A2
Sanders 2004	RCT: gastro-intestinal surgery ANH: 3 units (n=78) vs control (n=82)	ANH: increase in median anaesthesia time 55 vs 40 minutes Oliguria: 47 vs 67% BT: no difference	A2
Jarnagin 2008	RCT liver lobe resection (≥ 3 segments) ANH (n=63) vs control (n=67) BT trigger < 8 g/dL	EC total: 12.7 vs 25.4% EC intra-op: 1.16 vs 10.4% BL > 800 ml: FFP: 21.1 vs 48.3%	A2

Table 8.1.4.2: Physiology and pharmacology ANH

Physiology and pharmacology			
Rehm 2001	cervical cancer ANH + albumin vs ANH + 6% HES (n = 20)	After collection of 1,500 mL, 15% more colloids were required to compensate loss of CV.	
Licker 2004	RCT: patients with severe aortic stenosis ANH Ht 28% (n=14) vs control (n=12)	ANH: improved venous return, higher pre-load, increased beat volume, significant decrease in LV stroke work	A2
Licker 2004	RCT: patients with severe coronary conditions ANH to Hb = 8.6 gr/dL/Ht 27% (n=12) vs control (n=10)	ANH: beat volume, CVD increased significantly; HF decreased significantly. Conclusion: ANH to Hb 8.6 g/dL well tolerated.	A2
Licker 2005	RCT CABG ANH Ht 28% (n=41) vs control (n=39)	Troponine-i 1.4 vs 3.8 ng/mL CK 29 vs 71 U/L Inotropic requirement 7/41 vs 15/39 Cardiac complications 12/41 vs 26/39	
Dahaba 2006	ANH + rocuronium (n=28) matched with control (n=28).	Rocuronium dose 26% lower in ANH group. Distribution volume enlarged, T1/2 longer.	
Dahaba 2006	RCT ANH + cisatracurium	No significant extension block	

	(n=30) vs control (n=30)		
Licker 2007	RCT aortic valve replacement ANH (n=20) vs control (n=20)	Epo levels: 13.6 vs 7.3 mU/mL HF: - 11% ANH vs control group Troponine-i: 1.7 vs 3.7 ng/mL CK: 22 vs 45 U/L Significantly less inotropics required in ANH group: 43 vs 96 mg ANH group fewer cardiac complications: 4 vs 13	
Dahaba 2008	RCT ANH + BIS + extra O ₂ (n=15) ANH + BIS + air (n=15) Control (n=15) All TCI propofol	ANH: short decrease BIS for induction ANH: less propofol required for induction O ₂ no extra effect	A2

Table 8.1.4.3: Comparing efficiency ANH with other techniques or combinations

First author	Study set-up	Result	Evidence class
Orthopaedics			
Oishi 1997	RCT. THP Gr 1 ANH + PAD + Cell Saving (CS) Gr 2 PAD + CS (n = 33)	% PAD blood that was used: Grade 1: 41% Grade 2: 75% (p < 0.05)	A2
Xenakis 1997	RCT, THP and TKP Group 1 CS Group 2 CS + PAD Group 3 control (n = 208)	Allogeneic BT Group 1 – 2.7 U (No p value) Groep 2 – 1.7 U Groep 3 – 4.2 U	A2
Goodnough 1999	RCT THP PAD vs ANH TOT 28% (n = 32)	No difference in BT between both groups (p = 0.45)	A2
Goodnough 2000	RCT THP PAD vs ANH TOT 28% (n = 48)	No difference in BT between both groups (p = 0.30)	A2
Gombotz 2000	RCT THP Group 1 EPO Group 2 EPO + ANH Group 3 PAD (n = 60)	Allogeneic BT required: group 1 – group 2 – group 3: 6 – 4 – 8 patients (ns)	A2
Urology			
Boldt 1999	RCT, prostatectomy Group 1 = ANH	Blood loss in group 2 < group 3:	A2

	Group 2 = controlled hypotension (MAP = 50 mmHg) Group 3 = control (n = 60)	-1,260 vs 1,920 mL (p < 0.05) PC group 1 vs group 3: - 21 – 14 – 28 U Conclusion: group 2 most effective (p < 0.05)	
Monk 1999	RCT, prostatectomy Group 1 = PAD Group 2 = EPO + ANH Group 3 = ANH + placebo (n = 79)	No BT group 1 – group 2 – group 3 85 – 81 – 96% no	A2

Conclusions 8.1.4

Level 1	Acute normovolemic haemodilution (ANH) is a safe and cheap technique that can save on allogeneic blood transfusions, if the expected blood loss is at least 40% of the circulating volume. The efficacy increases with increasing pre-operative Hb. A1 <i>Ferrari 2007, Bryson 1998</i> A2 <i>Matot 2002</i>
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Level 2	Hypervolemic haemodilution (HVH) is a technique that can be used to reduce the number of allogeneic transfusions if blood loss is less than 40% of the circulating volume. Acute normovolemic haemodilution (ANH) is preferred if greater blood loss is expected. A2 <i>Saricaoglu 2005</i> B <i>Singbartl 2000</i>
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Other considerations

ANH is a technique that is easy to apply. In order to achieve an optimum effect, one should realise that fresh blood is collected, which contains clotting factors and platelets. In order to maintain platelet function, the collected blood should be stored at room temperature ..

If the blood is kept near the patient in the operating room, there is very little chance of a mix-up. The collected blood is not tested for various blood-transmissible infections and appropriate precautionary measures should be taken, including measures to protect the (para) medical staff present in the operating room (The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists 2007).

As with ANH, the contra-indications for HVH in non-cardiac surgical procedures are: pre-operative anaemia, sepsis, heart failure or ischaemic heart disease and severe pulmonary disease.

These contra-indications also apply to cardiac surgery procedures. HVH is also contra-indicated in cardiac surgical procedures if the patient has unstable symptoms or an acute myocardial infarction, or is in cardiogenic shock. Complications of HVH can include: pulmonary oedema and heart failure (expert opinion).

In ANH, the collected blood is not tested for blood-transmissible micro-organisms.

Recommendations 8.1.4

1. Consider acute normovolemic haemodilution (ANH) in case of surgery with expected severe blood loss and definitely in case > 40% of the total blood volume is expected to be lost.
2. Hypervolemic haemodilution (HVH) can also be considered if (expected) peri-operative blood loss is < 40% of the blood volume.
3. When collecting blood for acute normovolemic haemodilution (ANH), carefully note the patient's name and date of birth, the order of collection (bag I, II, etc.) and the time of collection.
4. If possible, store autologous blood (shelf-life < 6 hours) at room temperature because of platelet viability.
5. In cardiac risk patients, monitor the cardiac output during acute normovolemic haemodilution (ANH).
6. Always monitor cardiac output thoroughly in the case of hypervolemic haemodilution (HVH) and watch for signs of overfilling.
7. Do not use the acute normovolemic haemodilution (ANH) in patients who are known carriers of hepatitis B or C or HIV.

8.2 Pre-operative and peri-operative autologous blood transfusion techniques

8.2.1 Pre-operative autologous (blood) donation (PAD)

In a pre-operative autologous (blood) donation (PAD), the patient is his/her own donor and he/she donates one or more units of blood. The components prepared from this donation are transfused peri-operatively.

PAD is used relatively infrequently in the Netherlands. Elsewhere, PAD is primarily used prior to elective orthopaedic, vascular and cardiac surgical procedures.

Safety

In the Netherlands, PAD patients are screened according to the standard donor criteria, which may explain why few side effects are seen following autologous donation, in contrast to other countries (Torella 2001, Freedman 2008, Davies 2006). The blood group and Rhesus factor should be determined for each collected unit, to be compared to the recipient's blood before administration of the autologous blood. This may be performed both by means of a short cross match or by means of the computer method, as described in Chapter 3.

Efficiency

Use of PAD decreases the amount of allogeneic units administered by 64% (Carless 2004). Compared to ANH, PAD is equally efficient, but more expensive (Goodnough 2000). Recent research shows that the efficacy of PAD can increase if the donation takes place at least one month prior to a scheduled operation, so that the Hb has time to recover to a normal level (Singbartl part I 2007). Blood collection should be combined with iron supplementation (Bovy 2006, Singbartl part I 2007). Preferably, the total amount of autologous blood should be collected in one session (Singbartl part II 2007). If PAD is combined with EPO therapy (see

paragraph 8.1.3.5), the number of units that can be collected . increases and the Hb immediately before surgery is higher (see tables 8.2.1 and 8.2.2) (Bovy 2006, Hyllner 2002, Hyllner 2005, Aksoy 2001, Bouchard 2008). A good indication . and good logistic procedures are important (Freedman 2008, Dietrich 2005). Often, not all the units are returned. It is estimated that roughly 25% of the units are not used and that – on the other hand – 25% of patients require an allogeneic blood transfusion after all (Henry 2008). Recent research reveals an even greater waste for total knee arthroplasty: only 11.3% of the collected units were transfused and 1.9% received an allogeneic blood transfusion (Regis 2008).

There are insufficient data known to be able to draw conclusions about the effect of PAD on mortality, infections, CVA, thrombosis or pulmonary emboli. A PAD donor receives relatively more blood transfusions (autologous and allogeneic, but mostly autologous), often due to a broader indication setting, thereby increasing the risks, for example the risk of a mix-up (Henry 2008, Carless 2004).

On the other hand, there are indications that the number of infectious complications are less with PAD than with allogeneic transfusions (Heiss 1997, Innherhof 2005).

PAD can also be indicated in the treatment of high risk patients, such as:

- in situations where compatible donor blood is not or hardly available;
- in the case of a previously demonstrated haemolytic transfusion reaction without a clear cause.

See also Chapter 2

An alternative to pre-operative autologous blood donation (PAD) is a pre-operative erythrocyte apheresis (Rubens 1998, Shulman 1998).

Table 8.2.1: Efficiency of pre-operative autologous blood donation (PAD) as a blood transfusion saving technique

First author	Study set-up	Result	Evidence class
Forgie 1998	Meta-analysis of 6 RTs and 9 cohort control studies	Chance of allogeneic blood transfusion strongly reduced: RT arm: OR = 0.17 (is chance of allogeneic BT) Cohort arm: OR = 0.19	A1
Carless 2004	Meta-analysis 1966 – 2002 68 RCTs and 812 observational studies N = 34,000	BT –effect: PAD: 63% ↓ CS: 42% ↓ ANH: 31% ↓	A1
Henry CD 003602	Cochrane analysis of all RTs through to January 2004	PABD reduces the chance of transfusion with allogeneic blood by 64% (RR = 0.36) Chance of receiving a transfusion (also autologous) is greater RR = 1.33 Hb PAD donor 0.7 mmol/L < not donor A1	

Bouchard 2008	RCT cardiac surgery PAD (n=25) vs control (n=23) All + aprotinin and cell saver	8% (n=2) AP, therefore PAD stopped Allogeneic BT: 16% (1 x FFP, 3 x TC) vs 39.1% (6 x EC, 5 x FFP, 4 x TC, 1 x cryo) PAD group: 47.8% BT vs 39.1% n.s. Fibrinogen higher in PAD pre-op and day 1 post-op (1 gr)	A2
Dietrich 2005	Observational cardiac surgery PAD (n=84) vs control (n=3476)	BT allogeneic: 13 vs 48% 1 PAD: chance of BT 24% 2 PAD: chance of BT 14% 3 PAD: chance of BT 9% cost-benefit achieved at 2 units	B
PAD vs ANH			
Goodnough 2000	RCT ortho PAD 3 U (n=25) vs ANH 3 U or Ht = 0.28 (n=23)	Ht pre-op 39.7 vs 41.8% n.s. BT 0 vs 17% p = 0.30 ANH cheaper	A2

Table 8.2.2: Combination pre-operative autologous blood donation (PAD) with epoietin (EPO)

First author	Study set-up	Result	Evidence class
Bovy 2006	RCT Placebo (n=10), Epo 330 IU/kg (n=11), Epo 600 IU/kg (n=11) + Oral iron therapy	EC collected: 4.5 vs 4.1 vs 3.5 U Oral iron absorption correlated to erythropoiesis	A2
Hyllner 2005	RCT radical hysterectomy PAD + epo (n=15) vs PAD – epo (n=15) 3 U per patient	- Hb pre-op: 11.8 vs 10.6 g/dL - Hb day 1 post-op: 10.1 vs 9.2 g/dL - IL-6 and IL-8: n.s.	A2
Hyllner 2002	RCT radical hysterectomy PAD + epo (19) vs PAD – epo (n=18)	PAD not successful, decreased from 17.8 to 3.4%	A2
Aksoy 2001	RCT ortho Gr 1 PABD +EPO Gr 2 PABD+placebo (n = 40)	Number of allogeneic BT: Gr 1: 7 U Gr 2: 13 U P not given	A2
Other			
Innerhof 2005	Orthopaedic, prospective observational PAD (n=85) vs leukoreduction allogeneic (n=100) vs no BT (n=101)	Infections: 1.2 vs 12 vs 6.9% Allogeneic BT predictive infection: OR 23.65	B2

Table 8.2.3: Erythrocyte apheresis as an alternative to PAD

First	Study set-up	Result	Evidence
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author			class
Rubens ¹ Open heart surgery	Meta-analysis apheresis of platelet-rich plasma through to Aug. 1997 17 articles: Group 1 apheresis (n = 694) Group 2 control (n = 675)	Blood loss: Group 1 102 mL < group 1 (p < 0.0001) Group 0.33 U PC < group 2 (p < 0.0001) Effect greater in studies of marginal quality (OR = 0.33) than in studies with optimal study set-up (OR = 0.83)!!	A1
Shulman ² Spondylodesis	Group 1 Haemapheresis: platelet-rich plasma and erythrocytes + CS Group 2 CS Transfusion trigger Ht = 24% (n = 160)	Group 1: 0.7 allogeneic erythrocyte concentrates/patient (p < 0.001) 0.3 U allogeneic FFP/patient (p < 0.05) 0 platelet concentrate Group 2: 3.2 allogeneic PC/patient 1.6 U allogeneic FFP/patient 24 platelet concentrate (total) Admission duration in group 1 was 23% shorter than in group 2 (6.3 vs 8.4 days p < 0.04)	A2

Conclusions 8.2.1

Level 2	It is likely that the use of pre-operative autologous blood donation (PAD) reduces the number of allogeneic units administered by 64%. A2 <i>Carless 2004</i>
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Level 2	It is likely that the efficacy of pre-operative autologous blood donation (PAD) can increase with donation at least one month prior to the operation, so that the Hb can return to pre-donation levels .. A2 <i>Singbartl part I 2007</i>
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Level 1	It has been demonstrated that pre-operative autologous blood donation (PAD), combined with iron supplementation started at least one month prior to the procedure results in the administration of fewer allogeneic transfusions than PAD without iron supplementation. A2 <i>Bovy 2006, Singbartl part I 2007</i>
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Level 1	Pre-operative autologous blood donation (PAD) results in a higher number of administered blood transfusions (autologous and allogeneic combined) per patient and therefore a greater transfusion risk. A1 <i>Henry 2008, Carless 2004, Forgy1998</i>
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Level 3	There are indications that the number of infectious complications are less with PAD than with allogeneic transfusions.
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	C <i>Heiss 1997, Innherhof 2005</i>
Level 1	Pre-operative autologous blood donation (PAD) combined with EPO increases the number of units that can be collected and increases the pre-operative initial Hb. A2 <i>Bovy 2006, Hyllner 2002/2005, Aksoy 2001</i>
Level 1	Pre-operative autologous blood donation (PAD) requires a good indication setting in order to prevent wasting blood. A1 <i>Henry 2008, Carless 2004</i> B <i>Regis 2008, Dietrich 2005</i> C <i>Freedman 2008</i>
Level 1	An alternative to pre-operative autologous blood donation (PAD) is pre-operative erythrocyte apheresis. A1 <i>Rubens 1998</i> A2 <i>Shulman 1998</i>

Other considerations

PAD is an efficient way of saving on allogeneic blood transfusions, provided there is a good indication setting. For an optimal effect, a transfusion trigger comparable to that used for allogeneic blood transfusions should be adhered to. Due to the more complex logistics of PAD and the fact that the collected plasma normally is not used, the technique is more expensive and no more safe (also documented by TRIP: see annual reports) than . allogeneic blood transfusions and also results in the wasting of plasma.

Recommendations 8.2.1

1. Use of pre-operative autologous blood donation (PAD) as a blood saving technique requires a good indication setting in order to avoid wasting the collected units.
2. Due to the complex logistics, the relatively high costs, the lack of safety . and the wasting of plasma, the working group recommends a restrictive policy for the use of pre-operative autologous blood donation (PAD) as a blood-saving technique.
3. Other indications for pre-operative autologous blood donation (PAD): situations in which compatible donor blood is not or hardly available and in the case of a previous erythrocyte transfusion with a demonstrated haemolytic transfusion reaction without a clear cause.
4. If it is decided to perform pre-operative autologous blood donation (PAD), it is recommended to combine the PAD with iron supplementation. This should be started at least one month before the procedure.
5. If it is decided to perform pre-operative autologous blood donation (PAD), one should consider not only iron supplementation, but also combining this with EPO therapy in order to further increase the efficiency.

6. The blood group / rhesus factor must be determined for each pre-operative autologous blood donation (PAD) unit. Checks before transfusion are according to the rules that apply to an allogeneic blood transfusion.

8.2.2 Peri-operative auto-transfusion

Technology

Peri-operative auto-transfusion is a type of autologous blood transfusion in which the blood lost peri-operatively is returned to the patient during or immediately after the operation.

Peri-operative auto-transfusion is a safe and effective way of saving on donor blood, with a reduction of 33 to 58%, depending on the type of operation (Carless 2006).

There are two methods of peri-operative auto-transfusion:

1. Unprocessed auto-transfusion.

The blood is usually filtered, but re-infused without washing. Currently, auto-transfusion of unwashed blood is almost always performed post-operatively .. It involves the re-infusion of drain blood. This can be done up to 6 hours post-operatively – after connection of the drain and excluding one hour required for the re-transfusion (Faught 1998, Huët 1999). Although studies have not been performed, a limit is used for post-operative unprocessed auto-transfusion in adults of no more than 15% of the circulating blood volume, with a maximum of 1,500 mL.

Re-infusion of unwashed peri-operatively collected blood has in the past resulted in severe complications (see paragraph on Quality and Safety below). Currently, there is a component on the market that is used for unwashed peri-operatively collected blood. The safety and associated maximum amount of blood to be collected has not been studied sufficiently as yet .. A severe complication has already been described (Trip report 2009: www.tripnet.nl, Stachura 2010).

2. Processed auto-transfusion

Processed auto-transfusion is a method in which the peri-operatively collected blood is washed and separated by a machine. The final component consists of concentrated erythrocytes in NaCl 0.9%. The method can be continued post-operatively for up to 6 hours after connection of the wound drain. Under certain conditions, the post-operative period can be extended to 18 hours. The temperature at which the blood is stored becomes important in that case. (Guidelines AABB 1997, British committee for standards in haematology 1998, Ferrari 2007).

Quality and safety

When blood leaves the circulation and comes into contact with other tissues, the clotting factors and the complement system are activated. This is also the case with re-infusion of unwashed peri-operatively collected blood (Stachura 2010). Leukocytes and erythrocytes are destroyed in the process. Suctioning of blood increases cell damage by contact with air (foaming) and by turbulence. Re-infusion of unprocessed blood can result in severe organ damage (Faught 1998). Complications following re-infusion include: ARDS, DIC, renal function abnormalities, multi-organ failure ('blood salvage' syndrome), air emboli and

coagulopathies. . This has resulted in the development of techniques by which washed erythrocyte concentrates were produced. The above complications do not occur if the blood is washed by a machine (processed auto-transfusion). The quality and survival of erythrocytes after processing is normal. (Thorley 1990, Kent 1991, Wixson 1994).

During the washing, free Hb and added heparin are removed for up to 95% and 98% respectively (Koopman-van Gemert 1993). The efficiency of the washing procedure remains stable, even after multiple procedures using the same set (Vermeijden 2008).

Patients with a dysfunctional metal hip prosthesis have higher plasma concentrations of cobalt and chrome, of which approximately 80% is removed by the washing (Reijngoud 2008). Fat is also evacuated during orthopaedic procedures. Solid fat is filtered out or remains stuck to the tubing. Liquid fat is not removed completely during the washing. Filtration of the washed blood over a 40 µ microfilter removes the fat. Filtration through a surface filter (leukocyte filter) or fat filter is more effective than through a screen filter (Ramirez 2002). A leukocyte filter is more effective than a fat filter (de Vries 2003, 2006).

Drain blood

Drain blood contains free Hb, activated clotting factors, activated leukocytes, fat and various mediators such as interleukins. There is almost no fibrinogen present. Therefore, an anti-coagulant is not required for the collection of such blood. It has been demonstrated that prolonged contact between erythrocytes and leukocytes in the drain blood results in damage to the erythrocytes. This can be prevented by removal of the leukocytes by filtration at the start of the collection of the drain blood (Dalen 1999).

A lot of research has been performed on the consequences of the re-infusion of the collected drain blood (see table 8.2.2.2). There has been much discussion about the safety of drain blood. Currently, processed auto-transfusion is a much used technique in cardiac surgery and orthopaedics. For more details, please refer to the specific indication areas. With normal use, one does not need to worry about bacterial contamination of the equipment used (Wollinsky 2007, Bowley 2006).

In a Dutch study of 1819 patients undergoing hip or knee replacement surgery, an average of 460 ml autologous, filtered drain blood was re-infused. The volume was > 1,500 mL (1550 – 1900) in 9 patients (0.5%). Side effects occurred in 65 patients (3.6%, of which 17 hip and 48 knee surgeries). In most cases these were minor reactions such as fever (> 38.5 °) or shivering. Severe side effects occurred in 2 patients (0.1%), one episode of brief asystole and one of atrial fibrillation with respiratory insufficiency (pulmonary embolism; history of deep vein thrombosis) during the transfusion of 30 ml and 50 ml respectively of autologous blood. Clots formed in the collected blood in 0.3% and the re-infusion could not take place due to a technical problem in 1% of cases. Allogeneic blood transfusion took place in 18% of patients with hip operations and 9% of knee operations (Horstmann 2009).

There is insufficient data available about the maximum quantity of drain blood that can be re-infused safely. In most clinical studies, no more than 1.5 litres of unprocessed blood was re-infused. Others advise a maximum of 15% of the circulating blood volume (Krohn 2001, Sinardi 2005). There is no data available for children and this method is not recommended for them.

Indications

In general, all operations associated with significant blood loss form an indication for peri-operative auto-transfusion. The benefit of the various types of auto-transfusion with respect to the reduction in allogeneic transfusion depends on the type of surgery. Known indication areas include cardiac surgery procedures, vascular surgery, orthopaedic surgery, liver surgery, trauma surgery and surgical procedures in Jehovah's Witnesses. (see also addendum 3 to Chapter 8).

Applications

Cardiac surgery

Re-infusion of the blood evacuated during surgery and the drain blood lost post-operatively is an efficient way of saving on donor blood (Ferrari 2007, Klein 2008). The use of a technique involving washing appears to be more efficient than a technique without washing (RR washed units transfused = 0.61 versus unwashed = 0.87) (Huët 1999, Carless 2006). Drain blood re-infusion is used a lot in cardiac surgery.

It has been shown that this blood, if re-infused without washing:

- results in more cognitive dysfunction (15% versus 6% (Djaiani 2007));
- causes haemodynamic instability, probably due to infusion of cytokines (Marcheix, Boodwhani 2008);
- causes complement activation (Marcheix, Boodwhani 2008);
- can disrupt function tests, for example to demonstrate a myocardial infarction (Pleym 2005);
- gives laboratory abnormalities consistent with increased fibrinolysis or DIC (Krohn 2001, Sinardi 2005). These are usually without clinical relevance (Krohn 2001, Sinardi 2005), but some authors have demonstrated an increase in post-operative blood loss (Schönbergen 1992, Wiefferink 2007). Other authors are unable to confirm this (Schroeder 2007, Sirvinskas 2007).

Washing of the collected blood, which significantly reduces these complications, must definitely be performed if the blood is suctioned peri-operatively (Carrier 2006, Westerberg 2005, Djaiani 2007, Svenmarker 2004).

Orthopaedics

Re-infusion of peri-operatively suctioned washed blood and (un)washed blood lost post-operatively was shown in most studies to be an efficient way of saving on donor blood (Huët 1999, Tylman 2001, Jones 2004, Carless 2006, Tsumara 2006, Smith 2007, Zacharopoulos 2007, Amin 2008, Tripkovic 2008; Muñoz 2010, see table 8.2.2.2).

Approximatley 75% of post-operative blood loss takes place in the first 6 hours post-operative. (Wood 2008). This corresponds to the time normally maintained for the interval in which drain blood can be re-infused. There are indications that a 6-hour period results in better wound healing than when a longer period is maintained (Wood 2008). The Hb of the collected drain blood is around 5 mmol/L.

According to some (So-Osman 2006, Kirkos 2006, Hendrych 2006), re-infusion of the unwashed blood causes a mild febrile reaction, although other authors cannot confirm this (Moonen 2008). This febrile reaction may depend on an increase in the IL-6 concentration.

This concentration is elevated in collected blood in the first 6 hours and even increases 7-fold over the next 6-hour period (Handel 2006). Filtration of the unwashed blood over a leukocyte filter reduces the quantity of interleukins (IL-8 and TNF- α), but causes complement activation (Dalen 1998).

Re-infusion of unwashed blood does not alter lung perfusion (Altinel 2007). A slight decrease in the platelet count does occur (de Jong 2007).

A study of 120 patients undergoing orthopaedic prosthetic surgery looked at the immunological response to: no blood transfusion (BT), BT (non-leukocyte reduced), BT (leukocyte reduced), PAD blood and unwashed auto-transfusion blood. The number of Natural Killer (NK) cells and the interferon gamma level decreased due to surgery and blood loss, except in the auto-transfusion group where the concentrations were higher. The IL-10 concentration remained the same. The higher concentration of interferon gamma could point to improved immunity after re-infusion of unwashed drain blood (Gharehbaghian 2004).

Vascular surgery

Auto-transfusion of washed blood is used frequently during major vascular surgery. It is an efficient method of reducing donor blood transfusions (RR 0.55) (Hüet 1999, Carless 2006). Despite this, few randomised studies have been published, including Wong 2002, Takagi 2007; (see table 8.2.2.2).

Obstetrics

Auto-transfusion of washed blood is used during ectopic pregnancies and Caesarian sections (Thomas 2005, Selo-Ojeme 2007). See also table 8.2.2.2.

The evacuated amniotic fluid contains substances that can cause DIC or amniotic fluid emboli. It has been demonstrated that these harmful substances are removed by washing (Thomas 2005). One has to realise that erythrocytes from the child can also be evacuated. Re-infusion of erythrocytes from the child can promote antibody formation in the mother. Most Caesarian sections result in very little blood loss, so that routine use is not indicated. However, a cell saver can save lives in the case of major bleeding.

Urology

Auto-transfusion of washed blood is often used during radical cystectomies and prostatectomies, without irradiation of the blood. Various studies have demonstrated that the survival is the same as for surgical patients who did not receive auto-transfusion (Nieder 2004, 2007, Davis 2003, Ford 2007, Gallina 2007, Stoffel 2005, Waters 2004). PSA-expressing cells were demonstrated in the evacuated blood (Stoffel 2005). None of the studies were randomised.

Traumatology

Auto-transfusion of washed blood is often used in traumatology. Especially in the case of hepatic or splenic ruptures. No randomised studies have been published as yet.

In general, a bowel perforation forms a relative contra-indication. A recent randomised study of patients with abdominal trauma with perforation of the bowel found that – with the use of auto-transfusion – significantly fewer blood transfusions (6.47 U versus 11.17 U) were

required in the auto-transfusion group whilst there was no difference in morbidity and mortality (Bowley 2006). All operations were performed under antibiotic prophylaxis. Blood visibly contaminated by faecal matter was suctioned into a different container. This means that auto-transfusion can be used under these conditions in emergencies (Bowley 2006).

Contra-indications

Contra-indications for peri-operative auto-transfusion are: rinsing with toxic substances, locally used haemostatics, bacterial contamination (relative), tumour surgery (relative) and sickle cell anaemia. Bacteria are not washed away completely (Thomas 1999). In emergency situations, antibiotics can be given in the case of bacterial contamination.

In general, tumour surgery forms a contra-indication to auto-transfusion due to the risk of haematogenic metastasis of tumour cells. Centrifugation and washing does not result in removal of all tumour cells and results in less than 1 log reduction of the other cells (Hanssen 2002, 2004, 2004, 2006, Thomas 1999, Stoffel 2005). See also table 8.2.2.4. The tumour load in peri-operatively suctioned blood can be up to 10^7 cells per liter (Hanssen 2002, 2006). Leukocyte filtration results in 1 log reduction (Thomas 1999, Hanssen 2004, 2006), but irradiation of washed blood with 50 Gy results in at least a 10 log reduction of the number of viable tumour cells (Thomas 1999, Hansen 2002). A combination of leukocyte filtration followed by irradiation effectively disables active tumour cells (Poli 2008).

Experiences of peri-operative auto-transfusion (including safety) have now been described for over 700 oncological surgery procedures (Hanssen 2004, Valbonesi 1999).

Auto-transfusion can be life-saving during oncological surgery in Jehovah's Witnesses (Nieder 2004). The patient must be consulted in advance to discuss the possible risks. If a radiation unit is not available, a leukocyte filter should be used.

Table 8.2.2.1: Meta-analysis of auto-transfusion

Author	Study set-up	Results	Comments	Evidence class
Carless Cochrane CD 001888	Meta-analysis 1966 – 2009 75 RCT, n=3857 Ortho: N = 36 Cardio: n= 33 Vasc: N = 6 Washed: N = 27 Unwashed: n = 40 Other: N = 8 60 with BT protocol (of which 59 trigger): - 55 post-operative, -21 also intra-operative 15 without BT	Overall: RR = 0.62 Ortho: RR = 0.46 Cardio: RR = 0.77 Vasc: RR = 0.63 n.s. 0.68 unit EC less Ortho washed RR 0.48 vs uwashed RR = 0.47 in combination with other techniques RR = 0.63 Cardio washed RR 0.66 vs unwashed 0.85 Combination (6) in + post-op: RR 0.n.s.	Mortality, re-operation, wound infection, thrombosis, stroke, infarction, duration of admission n.s. Infection: trend lower in auto-transf. group RR 0.68, n.s. (wound infection equal) Any infection, non- fatal myocardial infarction in control group, trend lower in auto-transf. group (5.1 and 4.8%)	A1

	protocol	With BT protocol: RR = 0.61 Without BT protocol: RR = 0.56;		
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RR = Relative Risk of allogeneic blood transfusion

Table 8.2.2.2: Efficiency of auto-transfusion for the various indication areas

Author	Study set-up	Results	Comments	Evidence class
Cardio:				
Huët 1999	Meta-analysis Unwashed; 12 RCT. total 984 patients;	RR = 0.85	Reported in 11 studies In 1 study median of 750 mL, other study average < 400 mL	A1
Svenmarker 2004	RCT peri-operative cardio CS (n = 30) vs unwashed (n = 30) protein S100B as marked of brain damage and 3 memory tests	Unwashed significant increase S100B (1.42 vs 0.25)	No clinical difference demonstrated in memory tests	A2
Pleym 2005	RCT cardio 2005 post-operative. Unwashed (n = 23) vs none (n = 24). 8 hours Effect on biochemical parameters, myocardial damage	CK-MB significantly higher immediately post-op. Rest trend.		A2
Westerberg 2005	RCT peri-operatively washed (n = 15) vs unwashed (n = 15) Immunological consequences	SVR 12 vs 28% decrease Significant decrease in TBF- α .C3a after washing IL-6 tended to be lower in washed blood	Washing reduces the harmful vaso-active substances. This is expressed in more stable haemodynamics	A2
Carrier 2006	RCT cardio CS (n=20) vs unwashed (n=20)	S100B 0.51 vs 1.48 No difference in CVA		A2
Allen 2007	RCT peri-operative Washed (n = 18) vs unwashed (n = 19) and immunological response	Cytokines, TNF significantly lower in washed group		A2
Djaiani 2007	RCT cardio peri-operative CS (n=112) vs unwashed (n=114) 12-hour study of cog. dysfunction and emboli	BT EC and TC n.s. FFP: 25 vs 12% Cognitive dysfunction 6 weeks p.o. 6 vs 15%		A2

		Emboli count: 90 vs 133 n.s. INR 1.59 vs 1.47 Platelet count 120 vs 130		
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Sirvinskas 2007	RCT cardio unwashed (n=41) vs control (n=49)	Procalc. 33.3 vs 58.3% CRP 71.74 vs 93.5. BT 14.6 vs 38.8% Infections 2.4 vs 16.3% admission 9.3 vs 16.45 days	No indications for increase in complications, on the contrary	A2
Wiefferink 2007	RCT peri- and post-operative Washed (n=15) vs unwashed (n=15)	FDP higher in unwashed group: 279 vs 4131 ng/mL Post-op blood loss significantly higher in the unwashed group ≥ 2 PC 13 vs 47%		A2
Marcheix 2008	RCT control (n=25) vs VACPb (n=25) vs CS (n=25) vs CS + VACPb (n=25) Effects on immunology All aprotinin	Washing of the blood reduces inflammatory response and complement activation		A2
Klein 2008	RCT Washed (n=102) vs control (n=111)	BT 32% in both groups re-operation due to further bleeding not included: chance BT RR 0.71		A2

Boodhwani 2008	RCT peri-operative washed (n = 132) vs unwashed (n = 134) + haemodynamics	In washed group: better haemodynamics; CI 2.6 vs 2.3, p = 0.004. Worse correlation with quantity unwashed blood Trend towards shorter ventilation in washed group 11 vs 13.9, p = 0.12		A2
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Orthopaedics				
Huët1999	Meta-analysis Orthopaedics 16 RTs: n= 478. 7 washed technique, 9 unwashed technique	RR = 0.35 for the unwashed technique and RR = 0.39 for the washed technique	In 10 studies, protocol maximum average quantity unwashed blood 946 mL; all others < average 700 mL	A1
Handel 2001	Prospective n=81 TKP IL-6 measurements	IL-6: level increased to average 6.5 ng/mL first 6 hours	3 febrile reactions: IL-6 11 ng/mL	B

	Unwashed, 6 + 6 hours (2 times re-infusion with the same set)	Thereafter to 47 ng/mL		
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Tylman 2001	RCT unwashed (n = 7) vs washed (n = 7) vs no BT (BL < 400 ml) interleukins	Washed blood resulted in lower levels in patient		A2
Dalen 1999	RCT unwashed with leukocyte filter (n=11) vs unwashed without (n=12) Immunology	IL-8, TNF- α , leukocyte count lower in leukocyte filter group. Leukocyte filter triggers complement activation		A2
Jones 2004	Prospective CT unwashed (n=94) vs control (n=92)	BT 21 vs 45.7% Duration of admission: 11 vs 12.6 days (p = 0.0248)	Transfusion costs similar 182.70 vs 196.75 pounds	B
De Jong 2006	Unwashed (n=12) vs no (n=12). Immunological consequences	Platelet activation in drain blood. No measurable effect after re-infusion. Drop in platelet count: 14.2 vs 2.5% And increase in prothrombin fragments F1 + 2: 24.3 vs 3.7 nmol/L		A2

Hendrych 2006	Unwashed (n=88) vs control (n=44) Trigger: re-infusion maximum 800 ml	BT 31 vs 100% 2% temp > 38.5 °C in unwashed group		A2 or B (could not be determined due to language)
Kirkos 2006	RCT unwashed (n=78) (sub group + corticosteroids 53 vs not 25) vs control (n=77).	BT EC: Peri-op: 0 vs 0.57 Post-op: 0.54 vs 1.06 U Fever: 50 vs 61% In group unwashed + cort. vs not: 47 vs 56%	Complications: Allogeneic BT: 4 x (1 x serum reaction, 2 x allergic reaction, 1 x embolism) Auto-transfusion: 4 x (3x clot, so no re-infusion possible; 1x haemolysis due to too small drain)	A2
So 2006	RCT ortho unwashed (n = 23 system A and 24 system B) vs none (n=22)	No difference in BT	30% auto-transfusion group mild febrile reaction after infusion	A2

Tsumara 2006	RCT ortho unwashed (n=106) vs NaCl with adrenalin via drain and 1 hour clamping without re-infusion	BL post-op 352 vs 662 ml BT 1 vs 3 patients n.s.	none	A2
Abuzakuk 2007	RCT unwashed (n=52) vs control (n=52)	No reduction BT		A2
Altinel 2007	RCT unwashed (n=16) vs control (n=16) + examination lung damage	BT 300 vs 685 mL No difference in lung perfusion		A2
Tripovic 2008	RCT ortho unwashed (n=30) vs control (n=30) BT trigger Hb < 100 g/L	BT 12 vs 80%	none	A2
Moonen 2007	Unwashed (n= 80) vs not (n=80) BT trigger 8.1 – 8.9, 9.7 g/dL rule	BT 6 vs 19% TKP 2 vs 16% p = 0.04 THP 11 vs 21% n.s. Febrile reaction 18 vs 20% n.s.		A2
Smith 2007	RCT unwashed (n=76) vs control (n=82)	14 vs 44 U BT Patients: 8 vs 21% Post-op Hb < 9 g/dL: 8 vs 20%		A2

Zacharopoulos 2007	RCT unwashed (n=30) vs control (n=30) BT trigger < 9 g/dL or symptoms	Allogeneic BT 80% ↓	Expenses 36% ↓	A2
Amin 2008	RCT unwashed (n=92) vs control (n=86)	No difference in BT		A2
Wood 2008	RCT unwashed drain removed 6 hours post-op (n=40) vs 24 hours (n=40) BT trigger < 8 g/dL or symptoms	BL no difference 75% of the BL takes place in the first 6 hours Allogeneic BT 17.5 vs 5%. Volume of auto-transfusion THP 250 ml, TKP 500 ml. THP (15%) more BT than TKP (7.5%) despite auto-transfusion. Hb equal in both groups. 6-hour group tended to have better wound healing		A2

Vascular surgery				
Wong 2002	RCT AAA: ANH + washed (n = 74) vs control group: (n = 71) BT trigger < 8 g/dL or ischaemia on ECG	BT 43 vs 56%	None	A2
Takagi 2007	Meta-analysis AAA 1966 – 2005 4 RCTs; n=292	RR 0.63		A1
Obstetrics				
Thomas 2005	Report debates about controversy	- markers of amniotic fluid, such as tissue factor, completely removed during washing. - Lamellar bodies removed by leukocyte filter	Cell Saver not necessary during routine Caesarian	C
Selo 2007	EUG RCT cs (n=56) vs none (n=56)	Ht 0.29 vs 0.26 L/L With CS, 3x higher chance of discharge Ht ≥ 0.27 L/L		A2

Table 8.2.2.3: Quality of auto-transfusion blood

First author	Study set-up	Results	Comments	Evidence class
Thorley 1990 Kent 1991	RCT AAA: washed (n = 6) vs unwashed (n = 6) vs control group: (n = 6) healthy volunteers Erythrocyte survival	<i>No difference in survival</i>		A2
Wixson 1994	Unwashed: 28 THP 22 TKP: erythrocyte survival (¹¹¹ In: ⁵¹ Cr ratio) coagulation abnormalities	No difference in survival. No clinical signs of DIC, despite demonstrable increase in clotting breakdown components and haemolysis parameters	Average 450 ± 261 mL autologous blood re-infused	C
Wollinsky 1997	RCT TPH n=40 No AB prophylaxis (n=20) vs with (n=20)	Surgical field and wound drain blood no bact. Contamination. Some suction tips did (6 vs 3). Collection bag (8 vs 0) Re-infusion bags (8 vs 3; 3 vs 0; 0 vs 0) Low pathogenic	Antibiotic prophylaxis reduces contamination of suction tips and collection bags.	A2
Krohn 2001	Orthopaedic n=9 clotting factors	α2-antiplasmin 31% of pre-op value, Plasmin-antiplasmin concentration elevated, D-dimer elevated in collected	Caution: further bleeding due to plasmin overload	C

		blood and after re-infusion in patient's plasma.		
Ramirez 2002	Orthopaedics 8 filters tested for fat filtration	Fat, leukocytes and micro-aggregates removed by surface filters and not effective with screen filters.		C
Reijngoud 2009	Revision of metal-on-metal prosthesis. Removal Cr and Cobalt.	Cr 76.3% and Co 78.6% removed	Patients have high plasma levels of Cr and Co due to re-absorption of metal particles in the circulation.	
Vermeijden 2008	Cardiac surgery Washing efficiency with several runs n=42	Based on IL-6 and free Hb washing efficiency constant also with several runs		B

Table 8.2.2.4: Auto-transfusion and tumour surgery or contaminated surgical field

First author	Study performed	Result	Comments	Evidence class
Thomas 1999	Systematic review of 84 articles that appeared about this	Some authors claim 100% removal by filtration However, sensitivity of the measurement methods of these authors is dubious Filtration takes 40 minutes Irradiation with 50 Gy appears effective and safe Few clinical studies have been performed		A1
Hansen	Can demonstrate 1 tumour cell amongst 10 ⁸ mononuclear cells In other words, 10 tumour cells in 500 mL blood	In suctioned blood from oncological surgeries, the number of tumour cells varies between 10 and 10 ⁷ cells. The cells are viable. Only 21% of the patients had circulating tumour cells in venous sample. Centrifugation and washing of the blood does not remove the cells	...	
Hansen ³⁴	Test with 10 cell lines and 14 tumour preparations Irradiation of blood with 50 Gy	At least 10 ¹⁰ log reduction tumour cells No DNA metabolism	...	
Hansen Valbonesi	Experience in > 700 patients	No metastases or increase in local recurrence Disadvantage: takes 6 – 15 minutes depending on location of irradiation unit	...	
Hansen ³⁶	9 different leukocyte filters tested	4 – 5 log reduction for tumour cell lines and 3 log reduction for cells from solid tumours	...	

First author	Study performed	Result	Comments	Evidence class
Stoffel 2005	Analysis of blood samples 112 CS procedures with rad. prostatectomy. 48 CS and 64 not	PCR: PSA expressing cells in 88% of the CS reservoir and 13% of the pre-operative blood samples. No PSA expressing cells in peripheral blood 3 – 5 weeks post-op. (19 vs 28 follow-up). 16 vs 4% PSA in blood immediately post-op. n.s.	Auto-transfusion not related to survival. 40 months follow-up	
Nieder 2007	Rad. cystectomy retrospective 1 surgeon; CS used if BL > 700 mL CS (n=65) vs not (n=313)	Follow-up median: 19.1 vs 20.7 months Survival 72.2 vs 73% n.s.		B
Waters 2008	Rad. prostatectomy prospective cohort Washed (n=26) vs PAD (n=26)	Allogeneic BT no difference BL 1134 vs 891 mL (so difference in both groups)		B
Contamination				
Bowley 2006	RCT abdominal trauma with perforation. CS (n=21) vs control (n=23) All antibiotic prophylaxis	EC: 6.47 vs 11.17. Survival: 35 vs 33% n.s. Bowel injury 85 vs 75%	Grossly contaminated blood was not suctioned.	

Conclusions 8.2.2

Level 1	<p>Peri-operative auto-transfusion is a safe and effective technique to reduce the transfusion of allogeneic blood varying from 33 to 58%, depending on the type of surgery.</p> <p><i>A1 Carless 2006</i></p>
Level 1	<p>Peri-operatively, cell savers in which blood is washed, can be used safely and without limitation.</p> <p><i>A2 Carrier 2006, Westerberg 2005, Djaiani 2007, Svenmarker 2004</i></p>
Level 1	<p>Post-operatively, both a technique in which blood is washed before being returned and a technique in which it is not washed can be used safely up to 6 hours after connection of the drain (excluding 1 hour required for infusion).</p> <p><i>A1 Moonen 2008</i></p>

Level 1	<p>Blood evacuated peri-operatively during cardiac surgery should be washed before re-infusion in order to prevent complications.</p> <p>A2 <i>Djaiani 2007, Westerberg 2005</i> A2 <i>Carrier 2006</i></p>
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Level 3	<p>Auto-transfusion of washed blood can be used safely for obstetric bleeding. The washing step removes harmful substances that can cause DIC or amniotic fluid embolism.</p> <p>C <i>Thomas 2005</i></p>
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Level 3	<p>Auto-transfusion of washed blood during tumour surgery is safe, provided the blood for re-infusion is irradiated at 50 Gy, with or without the use of a leukocyte filter.</p> <p>C <i>Hansen 2004, Poli 2008</i></p>
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Other considerations

Auto-transfusion of blood lost peri-operatively is the most commonly used blood saving technique in the Netherlands. One advantage of this technique is that the blood can be collected first and one can decide at a later stage whether it should be processed and/or returned to the patient. This significantly reduces the costs.

In the Netherlands, the equipment is usually operated by anaesthesiology technicians or – in the case of post-operative use – recovery room nurses / ward nurses which does not require additional specialised personnel.

The safety of re-infusion of peri-operatively collected unwashed blood has not been demonstrated or published in large series. Therefore, this can currently not be recommended as a standard technique.

Recommendations 8.2.2

1. Consider the use of peri-operative auto-transfusion techniques for expected major blood loss.
2. Bacterial contamination poses a contra-indication for use of peri-operative auto-transfusion. This is relative in emergencies, administration of antibiotic prophylaxis is indicated.
3. Oncological surgery is a relative contra-indication for the use of peri-operative auto-transfusion. The technique can be used, provided the blood is irradiated at 50 Gy before re-infusion, **with or without** a leukocyte filter.
4. **Peri-operative auto-transfusion can be life-saving during oncological surgery on Jehovah's Witnesses. The patient must be consulted in advance in order to consider the risks. See also recommendation 3.**
5. **It is currently recommended to wash peri-operatively collected blood.**

6. Post-operative re-infusion of unwashed drain blood in cardiac surgery and orthopaedics should be limited to 15% of the circulating blood volume in adults, with a maximum of 1,500 mL. A 40 µ filter is recommended for re-infusion.
7. Use of the unwashed peri-operative auto-transfusion technique is not recommended in children.

8.3 Combination of blood saving techniques

The total yield increases with a combination of various blood saving techniques: see table 8.3. The number of units of pre-operative autologous blood donation (PAD) can be increased by administering EPO injections (see also paragraph 8.2.1, table 8.2.2). Acute normovolemic haemodilution (ANH) is also often combined with other techniques and medication (see also paragraph 8.1.4, table 8.1.4.3). The preferred combination depends on the expected quantity of blood loss, the initial Hb of the patient, the condition of the patient and the nature of the procedure. For example, for an orthopaedic procedure the combination EPO/PAD/tranexamic acid and peri-operative auto-transfusion is often used. For heart operations, the combination of acute normovolemic haemodilution and peri-operative auto-transfusion and tranexamic acid is often used. See table 8.3 for an overview of the studies in this field.

For all combinations, the peri-operative transfusion trigger that is used largely determines the expected yield (Weber 2000).

Table 8.3: Combination of techniques

First author	Study set-up	Result	Evidence class
Tempe ⁴ CABG	Group 1 ANH + CS Group 2 ANH Group 3 none (n = 150)	Allogeneic BT required Group 1 – group 2 – group 3: 15 U – 90 U – 102 No transfusion required: group 1 78%, other groups 14%	A2
Price ⁵ Orthopaedics	Group 1: EPO/PAD Group 2 Placebo/PAD N = 173	PAD collected Group 1: 4.5 U Group 2: 3.0 U No transfusion Group 1 80% (p = 0.09) Group 2 69%	A2
Oishi ⁶ Prim THP	Group 1 ANH + PAD + CS Group 2 PAD + CS (n = 33)	% PABD blood that was used: group 1 41% Group 2 75%	A2
Xenakis ⁷ Prim THP or TKP	Group 1 CS Group 2 CS + PAD Group 3 control (n = 208)	Allogeneic BT Group 1 – 2.7 U Group 2 – 1.7 U Group 3 – 4.2 U	A2
Shapira ⁸ Major orthopaedic surgery	Group 1: ANH to 20% + hypotension (mean 50 mmHg) Group 2: target mean ± 20% initial value	Allogeneic BT Group 1: 225 mL Group 2: 2,650 ML	A2
Boldt ⁹ Radical	Group 1: ANH Group 2: hypotension mean	Blood loss: + no BT Group 1: 1,820 ml + 75%	A2

prostatectomies	50 mmHg with Na nitroprusside Group 3: control N = 60	Group 2: 1,260 ml + 55% Group 3: 1,920 ml + 40% No BT	
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First author	Study set-up	Result	Evidence class
Borghi ¹⁰ THP, TKP, primary and revision	Combination PAD and CS Transfusion trigger: clinical or Hb < 6 g/dL (n = 2.303)	89.9% PAD possible (2 – 3 U) 82.3% intra-op CS (228 mL ave.) 96.7% post-op CS (421 mL ave.) 92% no transfusion	C
Goodnough ¹¹ TKP	PAD vs ANH TOT 28% (n = 32)	No difference in BT between both groups	A2
Vd Jagt ¹² Target group Hb ≥ 6.2 mmol/L Hb < 8.2 mmol/L Whether 2 injections are sufficient	Study group (n = 51- 43 and 48) 300 IU/kg vs 600 IU/kg vs 750 IU/kg; 2 injections + Fe oral Control group (n = 55) Placebo + Fe oral 1x auto-transfusion peri-operative; 8x haemodilution; 9x auto-transfusion post-operative	Study of EPO, however combination of techniques used Not clear in study what the effect of this was on the results	A2
Monk ¹³ Radical prostatectomy	Group 1 = PAD Group 2 = EPO + ANH Group 3 = ANH + placebo (n = 79)	No BT group 1 – group 2 – group 3 85 – 81 – 96%	A2
Goodnough ¹⁴ Prim THP	PAD vs ANH to 28% (n = 48)	No difference in BT between both groups	A2
Gombotz ¹⁵ Prim THP	Group 1 EPO Group 2 EPO + ANH Group 3 PAD (n = 60)	Allogeneic BT req. Group 1 – group 2 – group 3: 6 – 4 – 8 patients (ns)	A2
Aksoy ¹⁶ TPH	Group 1 PABD + EPO Group 2 PABD+ placebo (n = 40)	PAD collected group 1: 48 U group 2: 49 U Allogeneic transfusions Group 1 7 U Group 2 13 U	A2
Stover ¹⁷ Open heart surgery	Group 1 epsilon amino hexanoic acid + platelet rich plasma Group 2 epsilon amino hexanoic acid (n = 55)	Group 1 0% platelet concentrate (p < 0.01) 31% PC = 0.7 U/pat (p = 0.35) Group 2 28% platelet concentrate 45% erythrocyte concentrate = 1.2 U/patient	A2

Suttner ¹⁸	group 1: Na nitroprusside	Blood loss:	A2
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Radical prostatectomies	mean 50 mmHg group 2: Na-nitro + ANH group 3: standard (n = 42)	group 1: 788 ml group 2: 861 ml group 3: 1,355 ml Allogeneic PC group 1: 3 units group 2: 2 units group 3: 17 units	
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CS: cell saving

Conclusions 8.3

Level 1	Use of a combination of blood saving techniques is generally more efficient than the use of a single technique. <i>For references and evidence level (14x A2 and 1x C): see table 8.3</i>
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Level 3	For all combinations of blood saving techniques, the peri-operative transfusion trigger that is used largely determines the expected yield. C Weber 2000
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Other considerations

Each technique has its own contribution to prevent allogeneic blood transfusion. By using each specific effect and by careful planning, it is possible to compensate for blood loss over 5 litres without a single allogeneic blood transfusion.

For an optimal yield, it is important to determine a strategy in advance, which takes into account the nature of the procedure, the Hb and the expected blood loss.

The working group is of the opinion that a specific recommendation per procedure would exceed the scope of the Blood Transfusion Guideline.

Recommendations 8.3

1.	Where possible, use a combination of techniques to reduce the number of allogeneic blood transfusions.
2.	For an optimal yield of any combination of blood saving techniques and medications for surgical procedures, it is recommended to determine a strategy beforehand, which takes into consideration the nature of the procedure, the Hb and the expected blood loss.

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CHAPTER 9: QUALITY SYSTEM AND INDICATORS

Introduction

Paragraph 4 contains general information about the use of quality indicators. In addition, suggestions are made for possible indicators, which could provide insight into the quality of every step. The guideline working group is of the opinion that every hospital should determine for itself how the blood transfusion process should be monitored, depending on the local conditions. However, comparison is made possible if hospitals (also) use the same indicators. The guideline working group is convinced that this will promote transparency and contribute to improving the quality, including the indication setting.

9.4 Quality indicators

9.4.1 Introduction

Monitoring the quality of blood transfusions is essential. The aim of this monitoring is not so much providing external accountability, but more the systematic search for possibilities to improve the system. Indicators can play a role in this. Indicators are measurable elements of the care provided, which provide a measure of the quality of the care provided. Indicators can be divided into 3 categories:

- *Structural indicators*

Structural indicators provide information about the (organisational) boundary conditions within which the care is provided. An example of a structural indicator is “the presence or absence of a blood transfusion committee”.

- *Process indicators*

Process indicators provide information about the actions that are performed within a care process to provide quality. The characteristic of process indicators is that they can be influenced directly: they measure how (often) something is done. An example of a process indicator is: “The percentage of erythrocyte transfusions with a pre-transfusion Hb > 6.0 mmol/L within 24 hours before transfusion”.

- *Outcome indicators*

Outcome indicators provide information about the outcome of care processes measured at a patient level. Outcome indicators depend on many factors and are therefore often hard to trace back to direct patient care. An example of an outcome indicator is: “the percentage of patients with a transfusion reaction of severity grade 2 or higher”.

Outcome indicators best approach the aim of indicators (measuring the quality of care). Structural and process indicators can provide further insight into possible conditions or processes that could improve care.

A number of the indicators mentioned in this chapter can only be implemented if both the hospital and the transfusion laboratory have adequate IT services and/or if adequate agreements are made about the coding of patient categories in diagnosis treatment combinations (DBC) or ICD-10 codes. Unfortunately, this is not yet the case in every hospital.

In addition to generating directing information, one must also ensure that action is taken based on this information to improve the quality of care. There must be support among the employees in the primary process as well as management to facilitate the setting up of data collection, the actual implementation and the monitoring of improvement actions.

9.4.2 Why internal indicators?

An indicator has a type of signalling function: it is not a direct measure of quality, but points to a certain aspect of the functioning and can be a cause for further investigation. It concerns the core of quality care: the actual measurement of aspects related to the quality of care and – based on this measurement – the implementation of improvements aimed at targeted improvement of the quality of care.

Indicators can give care providers insight into the results of their own care process and assist in the internal guidance and improvement of this process. Indicators with this goal are called internal indicators. On the other hand, indicators can serve to provide accountability of the quality of care, for example to government authorities, health care insurers or patients. These are called external indicators, because they serve an external goal. Indicators can also be used to compare the performance of care providers or institutions (benchmarking). These are then termed internal or external indicators, depending on the goal for which and by whom they are used.

The indicators formulated for the current Blood Transfusion Guideline were developed by and for care providers and are aimed at improving the quality of the transfusion process. Therefore, these are internal indicators.

9.4.3 How were the indicators created?

The indicators that are to be developed should provide insight into the quality of care. This can include various quality domains, such as: efficacy, safety, efficiency or timeliness.

The Blood transfusion internal indicators were generated by following the steps in the “Indicator Development Manual”. An extensive description of these steps is provided in the “Indicator Development Manual”, available on the website of the CBO (www.cbo.nl). This manual is derived from the AIRE instrument (Appraisal of Indicators, Research and Evaluation). The AIRE instrument is a methodological instrument that serves as an evaluation and testing framework for indicators. All relevant elements from the AIRE instrument were applied in the drafting of the indicators.

The blood transfusion guideline working group was asked to form a sub working group consisting of a small number of individuals who could focus on the development of the internal indicators during the last phase of the revision of the guideline (the phase of

discussing and approving the recommendations). Eventually, a sub working group of three working group members was formed who – supported by the CBO – worked on the development of the internal indicators.

Based on the draft Blood Transfusion Guideline, the sub working group created an inventory of potential indicators related to the aspect of quality of care surrounding blood transfusion practices. A search was also performed for international indicators that have already been developed. These potential indicators were submitted to the entire guideline working group and the working group members were asked to comment on, to prioritise and to indicate which aspects of the care – with a (supposed) relationship to the quality of care – they deemed important. These aspects were processed for possible translation into an indicator. This resulted in a ‘list’ of indicator topics, which were discussed in various meetings of the sub working group and via e-mail. Next, the indicators were prioritised. This prioritisation was performed based on methodological requirements (think of validity, discerning ability and reliability), but arguments such as recordability and the extent to which the indicators meet the specific goals set by the working group during the revision of the guideline also played a role. The argumentation for scrapping potential indicators was documented.

The selected indicators were worked out in fact sheets ([see paragraph 9.4.5 Elaboration of indicators in fact sheets](#)). The characteristics of the indicator are described in a fact sheet, such as the type of indicator (process, structural, outcome) and the quality domain to which the indicator is related. The concept fact sheets were discussed by the core group involved in the guideline and submitted to the guideline working group for comments. The indicators were then submitted to the scientific and professional organisations together with the guideline for consultation. A pilot was also performed by TRIP, in which the indicators were tested to check that they are unambiguous and feasible. Once the results from the pilot and the comments from the consultation round were processed, the scientific and professional organisations (see the introduction to this guideline) authorised the resulting internal indicators.

9.4.4 Use and implementation of indicators

A verdict on the quality of care during blood transfusions can only be made if one can measure whether the quality criteria – as described in the guideline – have been met. The indicator sub working group deems it possible to survey the quality of care as an individual care provider using the indicators related to the Blood Transfusion Guideline, as developed by the indicator sub working group. For the selected and detailed indicators, the indicator sub working group expects that the detailed indicators are valid (*expert validation*), that the indicators can be measured reliably and that the indicators will provide (more or less) the same results under constant conditions. The indicator sub working group is also of the opinion that the indicators discriminate sufficiently, as there appears to be enough variation in practice. Finally, the working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups. Ultimately, the results of the indicators can also provide an incentive to modify or update the Blood Transfusion Guideline.

The actual implementation and measurement of these indicators falls beyond the responsibility of the indicator sub working group.

9.4.5 Elaboration of indicators in fact sheets

The fact sheets of the indicators are presented in this paragraph.

Indicator 1. Blood Transfusion Committee	
Relationship to quality	<p>The Care Facility Quality Law demands reliable care at all times for all patients.</p> <p>Efficacy and safety play an important role in the optimisation of the quality of blood transfusions.</p> <p>The quality requirements that blood transfusions should meet in order to be safe and effective have been formulated in the current Blood Transfusion Guideline. The Board of Directors is responsible for ensuring that the medical staff of the institution evaluates the quality of the blood transfusions performed. A locally appointed blood transfusion committee is charged with translating the national guidelines into a local protocol and with evaluating the quality of the blood transfusion chain and guaranteeing the quality. The data about safety and efficacy of blood transfusions collected in evaluations can be discussed by this blood transfusion committee, including the causistics. This can result in rapid amendment of the local protocol. This should result in the principles as stated in the guideline actually being implemented in practice.</p> <p>In accordance with the Care Facility Quality Law, every hospital must have a blood transfusion committee. It is recommended that this blood transfusion committee meets at least 4 times per year.</p>
Operationalisation	<p>A. Does your care facility have a blood transfusion committee?</p> <p>Possible answers:</p> <p>Yes, there is a blood transfusion committee</p> <p>No, there is no blood transfusion committee</p> <p>B. If yes, how often has the blood transfusion committee convened in the past calendar year?</p> <p>Possible answers:</p> <p>... times</p>
Definitions	Not applicable
Inclusion and exclusion criteria	Not applicable
Type of indicator	<p>A. Structural indicator</p> <p>B. Structural indicator</p>
Quality domain	Efficacy, safety and efficiency

The aim of the indicator

A blood transfusion committee can ensure the implementation and monitoring of the guideline. The working group expects a positive correlation between the presence of an active Blood Transfusion Committee and positive/good scores for the other indicators.

The organisational link to which the indicator is related

The indicator relates to the care facility as a whole and to all disciplines involved in blood transfusions. The following disciplines and institutions should preferably be included in a blood transfusion committee: all disciplines that use blood, blood transfusion laboratory, haemovigilance official and haemovigilance employee, nurses and CCS (Clinical Consultative Service) doctor of Sanquin Blood Supply.

This means that the most important disciplines involved in blood transfusions should be represented in this committee. The working group is of the opinion that in each hospital, a blood transfusion committee is charged with protocol development, testing of the implementation of the agreements in the policy, evaluation of blood transfusions and the drafting of quality standards for a training plan for all involved employees in the hospital and the testing of this plan. The Board of Directors, by law, sets the criteria and monitors the committee.

Background and variation in quality of care

No similar research has been performed from which one could conclude that an active blood transfusion committee improves the quality of blood transfusions. However, in order to achieve adequate implementation and regular evaluation of the guideline in every care facility, a central blood transfusion committee appears to be an obvious choice.

The institution (Board of Directors) is responsible for ensuring that the medical staff of the institution evaluates the quality of the blood transfusions performed. The aim should be to guarantee the quality of all blood transfusions performed in the Netherlands by a local committee.

Possibilities for improvement

If no blood transfusion committee exists (indicator 1A), one can be appointed. If a blood transfusion committee does exist, but they meet less than 4 times per year, benchmarking of indicator 1B can contribute to making the committee more active. The working group expects that most hospitals will have a blood transfusion committee, but that this committee convenes less than 4 times per year.

Minimal bias / description of relevant case mix

No meaningful case mix problems are expected.

Literature

1. Wet inzake bloedtransfusie, Kwaliteitswet Zorginstellingen.
2. "Sanguis sanus sanat". Veiligheid van bloedverstrekking en bloedgebruik in de Nederlandse ziekenhuizen. Inspectie voor de Gezondheidszorg, oktober 2001.

Indicator 2. Haemovigilance employee

Relationship to quality	<p>Haemovigilance is the complex of measures required to gain insight into the safety and quality of the blood transfusion chain. Haemovigilance aims to provide this insight in order to improve the quality of the blood transfusion chain and thus the relevant care.</p> <p>The responsibility for haemovigilance rests on all professionals involved in blood transfusion, each in his or her own field. The local blood transfusion committee is responsible for the transfusion policy in the hospital and the quality control. On record should be who is responsible for which link in the chain and how feedback is arranged. On record should be who is (ultimately) responsible for the data collection surrounding blood transfusion and the reporting of related complaints and deviations.</p> <p>The current Blood Transfusion Guideline recommends the appointment of a haemovigilance employee in institutions where blood transfusions are administered (see paragraph 9.1.3 and Chapter 7).</p>
Operationalisation	<p>A. Does your hospital have a haemovigilance employee?</p> <p>Possible answers: YES / NO</p> <p>B. If yes: how many hours per week does this person spend on haemovigilance tasks?</p> <p>Possible answers: ... hours per week</p>
Definitions	<p>Haemovigilance employee: The TRIP definition of haemovigilance is the systematic monitoring of side effects and unfavourable incidents in the entire transfusion chain from donor to patient and everything else that can contribute to a safer and more efficient use of blood components.</p> <p>The definition of haemovigilance from the “EU Blood Directive 2002/98/EC” is: a group of associated surveillance procedures related to severe unfavourable or unexpected incidents or reactions in donors or recipients and the epidemiological follow-up of blood donors.</p> <p>A haemovigilance employee is a person whose task it is to implement the above-mentioned aspects.</p>
Inclusion and exclusion criteria	Not applicable
Type of indicator	A. Structural indicator B. Structural indicator
Quality domain	Efficacy, safety and efficiency

The aim of the indicator

The aim of the indicator is to determine whether the institution has a haemovigilance employee whose task it is to perform the series of measures required to obtain insight into the safety and quality of the blood transfusion chain. Haemovigilance and the activities of a haemovigilance employee are aimed at learning from these measures in order to improve

the quality of this care. Therefore, the working group expects a positive correlation between the activities of a haemovigilance employee in an institution and a positive/good score on the other indicators

The organisational link to which the indicator is related

The indicator is related to all departments and other business sections of care facilities that are involved in the blood transfusion chain in the care facility.

Background and variation in quality of care

The Care Facility Quality Law demands systematic monitoring, control and improvement of the quality of care. In order to achieve this, the entire transfusion chain must be documented from donor to patient. (Sanquin) Blood Supply, hospital laboratories and clinical departments each have their own responsibilities. The processes should be synchronised with each other. There is a legal obligation to report all (serious) side effects of transfusion. The working group is of the opinion that an adequate hospital haemovigilance system and the appointment of a haemovigilance employee are important factors that can contribute to this systematic monitoring, control and improvement of the quality of (Dutch) blood transfusion practice.

Possibilities for improvement

The working group expects that – in the Netherlands – not every hospital will have a haemovigilance employee employed for at least 8 hours per week. It is also expected that there will be opportunities for improvement of this point.

Minimal bias / description of relevant case mix

The indicator is a structural indicator that does not depend on the case mix. Finally, the working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups.

Indicator 3. Operationalisation: laboratory information system.

Relationship to quality	Without an electronic Hospital Information System and an electronic information system of the Blood Transfusion Laboratory, the sampling of process indicators is a lot of work that will hardly – if ever – take place in practice. The working group is of the opinion that process indicators, such as indicators 5 through 7 are an extremely useful tool to chart and where necessary improve the quality of the blood transfusion chain in a hospital.
Operationalisation	Which of the following process indicators can you generate using your hospital or (blood transfusion) laboratory information system? Possible answers Indicator 5: YES / PARTIALLY / NO Indicator 6: YES / PARTIALLY / NO Indicator 7: YES / PARTIALLY / NO
Definitions	Not applicable
Inclusion and exclusion criteria	Not applicable
Type of indicator	Structural indicator
Quality domain	Efficacy, efficiency

The aim of the indicator

The aim of this indicator is to gain insight into the extent to which the indicators in question can be generated from the hospital or blood transfusion laboratory information system. The derivative aim is to achieve optimum arrangement of the registration of data allowing for a targeted search for quality indicators.

The organisational link to which the indicator is related

This indicator is related to all care facilities in which blood components are administered to patients.

Background and variation in quality of care

Without an electronic Hospital Information System and an electronic information system of the Blood Transfusion Laboratory, the sampling of process indicators is a lot of work that will hardly – if ever – take place in practice. The working group is of the opinion that process indicators mentioned in the operationalisation are an extremely useful tool to chart and, where necessary, improve the quality of the blood transfusion chain in a hospital.

Possibilities for improvement

The working group expects there to be many opportunities for improvement in the (Dutch) hospitals in the field of optimisation of registration of care-related parameters, such as process indicators for the quality of the transfusion chain in the hospital.

Minimal bias / description of relevant case mix

Not applicable.

Literature

1. The specification and use of Information Technology (IT) systems in Blood Transfusion Practice British Committee for Standards in Haematology, Blood Transfusion Task Force. 2006 <http://www.bcshguidelines.com/>.
2. Guideline on the Administration of Blood Components British Committee for Standards in Haematology 2009 <http://www.bcshguidelines.com/>.

Indicator 4. Electronic pre-transfusion identification check	
Relationship to quality	Experience with quality systems in countries such as The United Kingdom, France and the Netherlands shows that a significant proportion of the severe transfusion reactions is caused by administrative errors, mix-ups and human error. Automated systems can contribute to preventing this and to improving safety. Automation of processes can also create new problems. Therefore, these should be evaluated prior to their introduction. The current Blood Transfusion guideline recommends that an electronic identification check is performed on patients and units of blood components prior to blood transfusions (see Chapter 3).
Operationalisation	In your institution, is an electronic identification check used at the bedside – prior to blood transfusions – to link the unit of blood component to the patient? Possible answers: YES / On a limited number of clinical wards / NO
Definitions	Electronic identification check = check for identity of the patients and blood components by means of an automated system.
Inclusion and exclusion criteria	Not applicable
Type of indicator	Structural indicator
Quality domain	Efficacy, safety and efficiency

The aim of the indicator

The aim of the indicator is to measure whether an automated system is used in the institution for identification checks of patients and blood components prior to blood transfusions. As automated systems can contribute to the prevention of errors and thereby increase the safety of care, the derivative aim of this indicator is the stimulation of the implementation of such an automatic system in institutions. The working group expects to see a (negative) correlation of the indicator with haemolytic transfusion reactions reported to TRIP and/or near-misses per hospital.

The organisational link to which the indicator is related

This indicator is related to all care facilities in which blood components are administered to patients.

Background and variation in quality of care

The Care Facility Quality Law demands systematic monitoring, control and improvement of the quality of care. In order to achieve this, the entire transfusion chain must be documented from donor to patient. (Sanquin) Blood Supply, hospital laboratories and clinical departments each have their own responsibilities. The implementation of an automated system for

identification checks of patient and blood components can contribute significantly in (Dutch) blood transfusion practice to the monitoring, control and improvement of the quality of care.

Possibilities for improvement

The working group expects that very few (Dutch) hospitals will have implemented an automated system for identification checks of patients and blood components prior to blood transfusion, but that many hospitals will have plans to implement such a system in future. It is also expected that there will be opportunities for improvement of this point.

Minimal bias / description of relevant case mix

The indicator is a structural indicator that does not depend on the case mix. Finally, the working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups.

Indicator 5. Indication setting for erythrocyte transfusions	
Relationship to quality	<p>Erythrocytes are transfused to combat or prevent the symptoms of a lack of oxygen transport capacity of the blood. In patients with symptoms of anaemia, the transfusion of erythrocytes can be beneficial and in some cases even life-saving. The value of the haemoglobin level at which transfusion is deemed necessary varies greatly with the age of the patient and additional illness(es) and is ultimately determined by the treating doctor.</p> <p>Despite the growing development in research and literature about the restrictions and the number of complications with the transfusion of erythrocytes and the availability of Guidelines (see Chapters 4 and 5), the widespread and random use of erythrocyte transfusions still occurs. (Gombotz 2007).</p> <p>The current Blood Transfusion Guideline provides recommendations for both the indication setting and the follow-up of erythrocyte transfusions. Experts agree that a transfusion 'is almost always indicated' in patients with an Hb < 4 mmol/L and 'rarely indicated' for patients with an Hb > 6 mmol/L. In patients with an Hb between 4 and 6 mmol/L, the decision to transfuse or not to transfuse will have to be based on the 'risk of complications due to inadequate oxygenation'. This estimate should be based on the doctor's clinical judgement. In the Blood Transfusion Guideline, this is translated into the so-called 4-5-6 rule as a recommendation for transfusion triggers for acute anaemia (Chapter 5). Triggers based on age are recommended for chronic anaemia (Chapter 4), the highest trigger being 6 mmol/L. However, the literature reveals that erythrocyte transfusions are regularly given to patients with an Hb of 6 – 7.5 mmol/L. For the operationalisation of this indicator, a window of 72 hours prior to transfusion was selected mainly due to practical reasons, so that both outpatients and inpatients can be included.</p>
Operationalisation	The percentage of erythrocyte transfusions with a pre-transfusion Hb ≤ 6.0 mmol/L within 72 hours before transfusion.
Numerator	The number of erythrocyte transfusions with a pre-transfusion Hb ≤ 6.0 mmol/L within 72 hours before transfusion.
Denominator	Number of administered erythrocyte units

Definitions	Pre-transfusion Hb = lowest Hb < 72 hours prior to transfusion. The numbers may also be obtained from a representative random sample.
Inclusion and exclusion criteria	Exclusion criterion: Paediatric units and exchange transfusions.
Type of indicator	Process indicator
Quality domain	Safety, timeliness, efficiency

The aim of the indicator

The aim of this indicator is to obtain an insight into the percentage of clinically indicated transfusions of erythrocytes.

The organisational link to which the indicator is related

This indicator is related to the hospital-wide implementation of erythrocyte transfusions.

Background and variation in quality of care

Various organisations have published guidelines over the last few years relating to the use of erythrocytes. These guidelines assume that a blood transfusion will have few positive effects at an Hb > 6 mmol/L, that a transfusion is often beneficial at an Hb < 4 mmol/L and that – at an Hb between 4 and 6 mmol/L – it depends on patient characteristics whether or not the transfusion is expected to have a positive effect. The present Dutch Blood Transfusion guideline also supports this hypothesis.

The working group assumes that – as is the case elsewhere in Europe (. Gombotz 2007) – transfusions of erythrocytes occur in (Dutch) hospitals that do not conform to the current guidelines, despite what has been laid down in the Dutch and international guidelines. The usual period of 24 hours prior to transfusion was not selected here, so that outpatients' Hb checks could also be included. This is expected to result in variation in use and an improvement in the quality of care in this area.

Possibilities for improvement

There are opportunities for improvement by following the recommendation not to administer an erythrocyte transfusion at a pre-transfusion Hb > 6 mmol/L. The working group expects that the opportunities for improvement are great, because compliance with the guideline on this point is not widespread in practice in the (Dutch) hospitals.

Minimal bias / description of relevant case mix

This is a process indicator that does not depend strongly on the case mix. The working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups.

Literature

1. American College of Physicians. Practice strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;116:403-6.
2. British Committee for Standards in Haematology. Guidelines for the clinical use of red cell transfusions. *Br J Haematol* 2001;113:24-31.
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11. Maki T. Optimizing blood usage through benchmarking. *Transfusion* 2007 Aug;47(2 Suppl):145S-8S.

Indicator 6. Indication setting and measuring the effect of platelet transfusions

Relationship to quality	<p>The administration of platelets aims to improve primary haemostasis in order to decrease the tendency to bleed or to treat an existing haemorrhage in patients with thrombocytopenia or thrombocytopathy. The current Blood Transfusion guideline provides extensive recommendations for platelet triggers and target values for prophylactic and therapeutic platelet transfusions. However, in practice, platelet transfusions are (often incorrectly) given without determining the platelet count before and/or after the transfusion.</p> <p>Ideally, the platelet count prior to transfusion should be determined as close as possible to the transfusion and a post-transfusion value 10 minutes to 1 hour (1-hour value) or 16 – 24 hours (24-hour value) after the transfusion. As clinical patients often have blood samples collected only once a day (in the morning), a 12 hour period is maintained for the pre-transfusion value. The post-transfusion value should be measured within 24 hours after transfusion.</p> <p>As some patients receiving platelets (for example, due to massive blood loss) may have an indication for platelet transfusions without the pre-transfusion value being known, the working group has chosen to include only haematology – oncology patients for this indicator.</p>
Operationalisation	The percentage of platelet transfusions for which the platelet count was measured < 12 hours prior to transfusion and < 24 hours after transfusion.
Numerator	The number of platelet transfusions for which the platelet count was measured < 12 hours prior to transfusion and < 24 hours after transfusion.
Denominator	Number of administered platelet units
Definitions	Not applicable
Inclusion and exclusion criteria	Inclusion criterion: Haematology or oncology patients receiving a platelet transfusion.
Type of indicator	Process indicator
Quality domain	Safety, timeliness, efficiency

The aim of the indicator

The aim of this indicator is to gain insight into the percentage of platelet transfusions to haematology or oncology patients for whom both a pre-transfusion value and a post-transfusion value and/or grading of bleeding was measured. This charts the proportion of platelet transfusions that were correctly indicated and correctly evaluated.

The organisational link to which the indicator is related

This indicator applies to the hospital-wide use of platelet transfusions in haematology and oncology patients.

Background and variation in quality of care

The administration of platelets should take place based on a medical indication. For this reason, it is important to determine the need for transfusion prior to the transfusion by means of a pre-transfusion measurement and a post-transfusion measurement. The value after the transfusion should be measured to evaluate the effect of the transfusion.

Possibilities for improvement

The working group expects that the opportunities for improvement are great, because compliance with the guideline on this point is not widespread in practice in (Dutch) hospitals.

Minimal bias / description of relevant case mix

This is a process indicator that does not depend strongly on the case mix. The working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups.

Literature

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Indicator 7: Traceability

Relationship to quality	Blood is a valuable component with a limited supply. The Blood Transfusion guideline contains a large number of recommendations to minimise the squandering of blood components. If the legal requirement (EU Directive) that all blood components must be traceable is met, insight can be obtained into the extent of wastage. The working group is of the opinion that many hospitals do not meet this requirement.
Operationalisation	For what percentage of units not returned to the blood transfusion laboratory has the laboratory received confirmation of administration?
Numerator	Number of units for which confirmation of administration has been sent to the blood transfusion laboratory.
Denominator	Total number of units released and not returned to the blood transfusion laboratory.
Inclusion and exclusion criteria	none
Type of indicator	Process indicator
Quality domain	Efficiency

The aim of the indicator

The aim of indicator 7 is to determine whether the EU requirements concerning traceability of blood components have been met. The information obtained from this indicator shows whether the institution meets the set legal requirements. Ideally, every institution should be able to answer 100% to this question. However, it is expected that not all institutions can meet this requirement. Indicator 7 must provide information about the efficiency of the traceability in the hospital.

The organisational link to which the indicator is related

This indicator applies to the hospital-wide use of (short shelf-life) blood components.

Background and variation in quality of care

For the traceability of all short shelf-life blood components in the hospital, it is important to implement a system that works well for the confirmation of administration of a unit.

Possibilities for improvement

The working group expects that the opportunities for improvement are great, because compliance with the guideline on this point is not widespread in practice in (Dutch) hospitals.

Minimal bias / description of relevant case mix

This is a process indicator that does not depend strongly on the case mix. The working group does not think it necessary to monitor for differences in demographic and socio-economic composition or health status of patient groups.

Literature

1. College of American Pathologists Q-Tracks program'.
2. EU Directive 2002/98/EG.
3. "Sanguis sanus sanat". Veiligheid van bloedverstrekking en bloedgebruik in de Nederlandse ziekenhuizen. Inspectie voor de Gezondheidszorg, oktober 2001.
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