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(German Medical Association)

Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives

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4th revised edition

Notice:

Medical science and the public health service are subject to continuous development, entailing that all statements regarding them can only be in accordance with the state of knowledge current at the time of publication.

The utmost care was taken by the authors in compiling and verifying the stated recommendations. Despite diligent manuscript preparation and proof-reading of the typeset, occasional mistakes cannot be ruled out with certainty.

Regarding the choice and dosage of drugs, the reader is requested to consult the manufacturer's package insert and expert information and, in case of doubt, to draw on a specialist.

Liability for any diagnostic or therapeutic application, medication or dosage lies with the reader.

Accordingly, the German Medical Association does not assume responsibility and no subsequent or any other damage that result in any way from the use of information contained in this publication.

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Preface

The appropriate handling of blood components for hemotherapy represents a particular challenge for medical practice. On the one hand, it is essential to optimally apply the blood products available by indicating their therapeutic administration responsibly and critically. On the other hand, because the blood products are a limited resource that was obtained by voluntary blood donations, it is mandatory to use them with particular care.
According to articles 12 a and 18, the *Transfusionsgesetz* (TFG, German Transfusion Act) rules that the German Medical Association (GMA) determines the generally accepted current state of scientific knowledge in medicine and technology regarding the preparation of blood and blood components as well as their application by developing and publishing Guides. According to article 18 TFG, the German Guide for Hemotherapy contains rules and regulations for the administration of blood products. The present Cross-sectional Guidelines contain recommendations regarding the selection of blood components and plasma derivatives as well as their indication and therapeutic administration. In comparison to disease-oriented guidelines, these Cross-sectional Guidelines focus on the critical assessment of a multitude of hemato-therapeutic treatments. This particular character of the publication is expressed in its novel designation as Cross-sectional Guidelines (GMA).
On compiling these Cross-sectional Guidelines, the editors felt the unchanged incentive to submit therapeutic principles and dosages derived predominantly from well-tried clinical experience to critical review and to revise them according to current scientific standards. Similar to the practice regarding the German Guide for Hemotherapy, the Scientific Advisory Board of the German Medical Association has appointed a Working Group, whose members specialize in diverse medical disciplines, to prepare appropriate recommendations.
In particular, the present revision is endeavoring to draft practical guidance and to distinctly point out the respective state of scientific evidence.
The editors thank the Medical Societies, organizations and public institutions for their essential part in developing further these therapeutic recommendations through their statements in the context of the hearing procedure. In particular, we appreciate the methodological advice of the *Ärztliche Zentrum für Qualität in der Medizin* (ÄZQ, Agency for Quality in Medicine). Specials thanks go to the experts of the Standing Working Group of the Scientific Advisory Board "Guidelines for Hemotherapy" who volunteered their expertise and who through their extensive personal dedication have rendered this publication possible in the first place.
To donate blood is an inestimable service of volunteers who contribute every day to help critically ill patients and to preserve life. It shall be particularly emphasized here that the entire medical fraternity is grateful for this service.
The appreciation of such altruistic assistance makes it mandatory for all physicians to apply blood products responsibly. The "Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives" shall contribute towards this goal.

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0 General explanations

0.1 Classification of these Cross-sectional Guidelines

The present publication is called "Cross-sectional Guidelines (GMA)", because recommendations are given regarding the entire range of blood components and plasma derivatives the application of which represents a particular challenge for medical practice. On the one hand, it is essential to optimally apply the blood products available by indicating their therapeutic application responsibly and critically and to prevent risks like transmission of infections. On the other hand, because the blood products are a limited resource that was obtained by voluntary blood donations, it is mandatory to use them with particular care.
Because of this wide range of subjects, the Working Group chose to deviate from the usual practice in guidelines to refer to a single disease entity.
The ambition regarding contents of the present publication corresponds to its special legal position since the present Cross-sectional Guidelines are referred to in the German Guide for Therapy with Blood Components and Plasma Derivatives (Hemotherapy) according to article 18 Transfusion Act (TFG).
It is a result of the special character of these Cross-sectional Guidelines that the methodology used in its compilation is different from the one preferably used by Medical Societies in Germany in developing guidelines or the one used in compiling National Disease Management Guidelines. Regarding several issues, the Working Group has deliberately decided to deviate from the approach used in compiling evidence-based "S2" guidelines. Rather the focus of methodological procedure is on consensus processes that were tried and tested by the Scientific Advisory Board, in particular the comprehensive hearings of the Medical Societies concerned and circles of experts, respectively (see section 0.3).
For these three reasons the present *Cross-sectional Guidelines* form a separate entity.

0.2 Classification of the recommendations

Compared to previous editions, in the present revised edition the refinement of the Guidelines is further systemized. Initially the individual chapters were revised by the authors indicated and adapted to the present state of the art. In doing so the authors were requested to give definite recommendations regarding the selection and indication for administration of a particular blood product and to classify them according to the principles of *Evidence-based Medicine*. On implementation of this classification system, the underlying evidence and the level of the recommendation is demonstrated to the user in a comprehensible manner.
The assignation of quality categories to data and studies on which the recommendations are based followed the system developed for compiling the Guidelines of the American College of Chest Physicians (ACCP) regarding thrombosis prophylaxis and therapy (Guyatt et al 2004[1]).

The recommendations were marked as follows (see **Table 1**):

[1] Guyatt G, Schunemann HJ, Cook D, Jaeschke R, Pauker S: Applying the grades of recommendation for antithrombotic and thrombolytic therapy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126 (suppl 3): 179S-87S.

Designation of the level of recommendation
Recommendations were marked as **level 1** recommendation if, based on present data, the experts were convinced that in compliance to them the benefit for the patient would be greater than a potential risk. Recommendations were marked as **level 2** recommendation if there are no definite data on the risk-benefit ratio.

Designation of the level of evidence
In case the data rely on sufficiently large, prospective, randomized studies, the evidence is designated as level **A.** In case there were several prospective studies with conflicting results or with methodological flaws, the evidence is designated as level **B**. Case reports and non-randomized studies are designated as level **C**. In case the conclusions from such case reports and non-randomized studies are unambiguous and confirmed by several investigations, the evidence is level as **C+**.

Consequences of the recommendations
The *level of evidence* based on the underlying data as well as the *level of recommendation*, in which the risk-benefit ratio is reflected, are significant for the consequences of a recommendation for medical practice. Two aspects are considered in this overall view: on the one hand, in routine clinical practice a risk-benefit assessment is fundamental to medical practice even if ambiguous data were published. On the other hand, if the strategies for treatment are long established and generally approved, it would seem inappropriate to give a recommendation a low level just for lack of a randomized study. For example, medical interventions are rightly categorized as a 1C+ recommendation if they are an inherent part of routine medical care even though corresponding studies have not been performed and will also not be possible in the future, for example because of ethical considerations.
Such a classification takes into account especially those clinical situations where the application of hemotherapeutics must be carefully weighed based on an overall view of a multitude of individual parameters. Therefore it applies in particular to recommendations classified as level 2 that, contrary to the recommendation, the administration of blood products ought to be considered or refused on an individual basis, depending on the particular case.
The recommendations are differentiated into four degrees. For this purpose the classification is expressed by the modal verbs “shall” (strong recommendation), “should” (medium strong recommendation), “can” (weak recommendation) as well as “could” (very weak recommendation) (see **Table 1**).

0.3 Composition and mode of operation of the Working Group

Composition of the Working Group
The Executive Committee of the Scientific Advisory Board of the German Medical Association has appointed the experts listed in the Annex to a membership in the Standing Working Group “Cross-sectional Guidelines (GMA) for Therapy with Blood Components and Plasma Derivatives” and has commissioned them with the composition of this edition.

Dealing with potential conflicts of interest
The authors have been asked to disclose any potential conflicts of interest to the central coordinator of the Working Group and to the chairman of the Scientific Advisory Board. Both chairmen of the bodies have unanimously come to the assessment that there were no conflicts of interests of authors that would compromise the independence or the quality of the guidelines.

Table 1

Level of recommendation	Risk-benefit ratio	Level of evidence	Assessment of the methodological validity of the underlying data	Overall assessment, classification	Implications	key-words
1	Unambiguous	**A**	Randomized, controlled studies without essential methodological flaws with unambiguous results	**1 A**	**Strong recommendation**, valid for most patients	**shall**
1	Unambiguous	**C+**	No randomized, controlled studies, but unambiguous data available	**1 C+**		
1	Unambiguous	**B**	Randomized, controlled study with methodological flaws. Despite unambiguous results of the study it cannot be safely ruled out that methodical flaws have influenced the results	**1 B**	**Strong recommendation**, probably valid for most patients	
1	Unambiguous	**C**	Observational studies without control group, but with convincing results	**1 C**	**Medium strong recommendation**, seems to be plausible, may be changed once improved data become available	**should**
2	Ambiguous	**A**	Randomized, controlled study without methodological reservations, but with conflicting results	**2 A**	**Medium strong recommendation**, depending on the individual case, a different course of action may be indicated. The interpretation of results by the Working Group Guidelines are taken into account in the recommendation.	
2	Ambiguous	**C+**	No randomized, controlled studies, but data can be extrapolated from other studies	**2 C+**	**Weak recommendation**, depending on the individual case, a different course of action may be indicated. The interpretation of results by the Working Group Guidelines are taken into account in the recommendation.	**can**
2	Ambiguous	**B**	Randomized, controlled study with severe flaws	**2 B**	**Weak recommendation**, depending on the individual case, a different course of action may be indicated.	**can**
2	Ambiguous	**C**	Observational studies, case reports	**2 C**	**Very weak recommendation**, depending on the individual case, a different course of action may be indicated.	**could**

Consensus processes and adoption

The chapters prepared by the authors indicated and the individual recommendations were discussed among all members of the Working Group and, if necessary, modified after reaching consensus. Subsequently, in the context of a hearing in written form, the results were presented to the Medical Societies, professional bodies, associations and institutions listed in the Annex who are concerned with issues of applying blood components and plasma derivatives. The Working Group decided after renewed discussion in a consensus process whether the suggestions for alteration received were to be taken into consideration. Afterwards the elaborate Cross-sectional Guidelines were conveyed to the Scientific Advisory Board of the GMA. The comments of the members of the Scientific Advisory Board were again assessed by the Working Group, and the subsequent version consented by the entire Working Group was again conveyed to the Scientific Advisory Board. After consultation and approval of the Cross-sectional Guidelines by the Board they were adopted by the Executive Committee of the GMA on 29 August 2008.

The concept of being a product-related Cross-sectional Guideline has implications for the development process of the guidelines. For instance, clinical algorithms can only be formulated to a certain extent. Nevertheless, the very extensive and consultation-intensive consensus process is characterized by the high degree of balance as well as the broad-based consensus inherent in these guidelines. Editors and authors have attached the greatest importance to presenting the state of scientific knowledge current at the time of the editorial deadline. However, the emergence of new aspects cannot be excluded on implementation of these guidelines to routine clinical practice. For optimization reasons, all users of these Cross-sectional Guidelines are requested to make available their experience in using this publication to the Scientific Advisory Board and its Working Group.

Additional background information on the methodology of compiling the guidelines are summarized in a guideline report ([in German] http://www.baek.de/downloads/ Leitlinien-report_11042008.pdf).

In the interest of obtaining a condensed text of the guidelines, redundancy and overlap were avoided regarding the *German Guide for Obtaining Blood and Blood Components and for Application of Blood Products (Hemotherapy)* http://www.bundesaerztekammer.de/downloads/Haemo2005.pdf [in German]. Therefore the German Guide is referred to regarding the principles in determining the suitability or rather eligibility as a blood donor as well as the laboratory tests performed prior to the release of a donation.

0.4 Legal framework conditions

0.4.1 Application of the German Medicinal Products Act (*Arzneimittelgesetz*, AMG)

In accordance with article 4 paragraph 2 AMG, "blood preparations are medical products which are or which contain, as medically active substances, blood, plasma or serum conserves obtained from blood, blood components or preparations made from blood components."

Thereby it is clearly stated that blood preparations are medical products in terms of article 2 paragraph 1 sentence 3 AMG. Hence, in addition to the TFG, the AMG governs not only the preparation but also the application of blood products.

0.4.2 Expert information

In article 11a the AMG contains extensive regulations on expert information[2].

[2] The relevant passages of article 11a AMG are reproduced in the Annex of this publication.

The present Cross-sectional Guidelines regularly refer to the individual expert information. In case a recommendation regarding the decision for or against treatment deviates from an expert information, this is pointed out and the deviation is accounted for.
General particulars stated in the Cross-sectional Guidelines regarding storage conditions, dosage, intervals between applications, concomitant medication and adverse reactions do not absolve the user from the duty to deal with the specific data in the individual expert information.
Relating to the decision for or against treatment as a consequence of an extensive consensus process performed in the appropriate bodies, the Cross-sectional Guidelines may present recommendations deviating from the expert information of the drug product. For instance, in particular cases the Cross-sectional Guidelines also recommend the application of approved medical products beyond approved indications („Off-Label-Use“).

0.4.3 Up-to-dateness of the Cross-sectional Guidelines

It is not possible to continuously revise these Cross-sectional Guidelines which are thus not always up to date. For this reason the guidelines do not absolve the user from taking into account the data in the expert information (cf. section 0.4.2) of the individual medical products. In terms of article 11a paragraph 2 German Medicinal Products Act (AMG), pharmaceutical entrepreneurs are obliged to keep the expert information up to date with the current state of scientific knowledge. They reflect the information approved by the authorities regarding the application of the medical product. Thus the expert information is of significant pertinence to physicians regarding the safe application of medical products and the therapeutical outcome. Incidentally the statements in the Guideline Report (http://www.baek.de/haemotherapie) [in German] are referred to.

0.4.4 Off-Label-Use

“‘Off-Label Use’ designates the application of an approved pharmaceutical product out of the areas of application (indications) licensed by national or European regulatory authorities. On principle, in Germany pharmaceutical products at the expense of health insurance funds may only be applied in treating those diseases for which a manufacturer has obtained approval from the competent authorities. ‘Off-label Use’ is also referred to as applying a pharmaceutical product beyond the limits of its approved use. The diseases that may be treated with a pharmaceutical product according to its license are specified among other things in the package information leaflet (thus the term ‘label’). The term ‘Off-Label Use’ does not include the application of pharmaceutical products the use of which has not (yet) been approved in Germany.”[3]
“‘Off-Label Use’ […] not only refers to applying an approved pharmaceutical product beyond the limits of its approved indication(s) or to other age groups, but also includes every other parameter specified in the license (e.g. dosage, intervals and mode of administration, duration of treatment and concomitant diseases).”[4]

The treatment with blood components and plasma derivatives often uses medical products in an Off-Label manner. This is done for different reasons: for example in cases of rare indications for which no approved medical product is available. In case legal publications even talk about a “necessary Off-Label Use”, this merely refers back to a decision by the Higher Regional Court (Oberlandesgericht, OLG) in Cologne, Germany, regarding the prescription of

[3] Glossary, Federal Joint Committee (Gemeinsamer Bundesausschuss), über www.g-ba.de or http://www.g-ba.de/institution/sys/english/.
[4] Ludwig, W.-D.: Off-Label-Use von Arzneimitteln, [in German], *Berliner Ärzte*, 2008, issue 7, pp. 14ff.

Aciclovir.[5] According to this, a physician is predominantly considered to be independent with regard to the AMG in his or her decision of whether to prescribe or apply an approved medical product beyond the limits of the approval granted.[6]
Circles of experts who were to deal with the issue of applying medical products exceeding the limits of their approved indication (circle of experts "Off-Label") were established on the basis of article 35b paragraph 3 SGB V (German Code of Social Law, Book V). In doing so, the legislator has taken the fact into account that the licensing procedure established up to that time in the AMG is not completely sufficient in safeguarding the necessary supply with pharmaceutical products for all areas of indication.[7] So far (as of April 2008), however, no recommendations by the circle of experts "Off-Label Use" have been published regarding the pharmaceutical products discussed in this Cross-sectional Guideline.[8]
Physicians who prescribe medical products beyond their approved indication run considerable legal risks: Because on principle the manufacturer is only liable for the application of pharmaceutical products in accordance to regulations, the physician runs a higher risk of liability if he or she prescribes or administers pharmaceutical products exceeding the limits of their approved indication without consent by the manufacturer.
There may be a different ruling in cases where the manufacturer has tolerated the Off-Label Use and has not discouraged this practice, for example by amending the expert information.[9]
In case the terms of the professional indemnity insurance of the physician provide cover regarding "treatment recognized by medical science", such therapies are not excluded on principle. For coverage to be in force it is sufficient to have consensus in medical science in order to be allowed to apply the medical product beyond its authorized use; when in doubt, this issue should be settled together with the individual insurance company.[10]
The recommendations of the present Cross-sectional Guidelines regarding "Off-Label Use" are instrumental in providing the physician concerned with some orientation regarding the application of blood components and plasma derivatives beyond their authorized use. The level of recommendation and its level of evidence are presented in a transparent manner. In particular, a low classification of a recommendation for Off-Label Use requires the physician

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[5] OLG [Higher Regional Court] Köln, *VersR* 1991, 186, as quoted in: Deutsch E, Spickhoff A, Medizinrecht – Arztrecht, Arzneimittelrecht, Medizinprodukterecht und Transfusionsrecht. 6th ed., Heidelberg/Berlin: Springer, 2008, p. 743.
[6] [German Federal Social Court], decision of 30 Sept. 1999, 8 B KN 9/98 KR R, RN 69 with further references.
[7] The circle of experts "Application of medical products beyond the limits of their approved indication" was created by decree of the German Federal Ministry of Health and Social Security [BMGS] dated 17 September 2002. By decree dated 31 August 2005 the circles of experts 'Off-Label Use' located at the German Federal Institute for Drugs and Medical Devices [BfArM] were extended to further medical disciplines. At present there are three circles of experts covering the medical disciplines oncology, infectiology with focus on HIV/AIDS and neurology/psychiatry. According to article 1 paragraph 2 of the establishing decree by the BMGS dated 31 August 2005, the circles of experts Off-Label Use have the following tasks:
a) Submission of assessments regarding the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the AMG. The assessments must be reappraised at reasonable intervals and, if necessary, adapted to the development of the state of scientific knowledge;
b) Inform the German Federal Ministry of Health and Social Security and the Federal Joint Committee according to article 91 SGB V (Code of Social Law, Book V) about the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the AMG.
[8] Recommendations are already available for other medical products in keeping with the regulations according to article 35b paragraph 3 SGB V. The respective decisions by the Federal Joint Committee (G-BA) are reflected in an amendment of Annex 9 of the Guide for Medical Products published by the G-BA which lists medical products that may be prescribed for areas of application not licensed. For example, this relates to Carboplatin-containing medical products.
[9] Deutsch, Spickhoff, loc. cit., p. 743.
[10] Handbuch des Fachanwalts für Medizinrecht [Handbook of the solicitor specialising in medical law], edited by Frank Wenzel, Luchterhand, 2007, p. 151 f. and 582.

concerned to carefully keep records on the specifics of the individual medical case so that in case of doubt he or she will be able document that the pharmaceutical product was applied "in the context of a treatment recognized by medical science".
It was repeatedly the subject of law suits whether or not such pharmaceutical products should be eligible for reimbursement by statutory health insurances. In a leading decision by the German Federal Social Court dated 19 March 2002 (B 1 KR 37/00 R), the following criteria were established for reimbursement of pharmaceutical products applied beyond their licensed indication (Off-Label-Use):
"(1) On principle a licensed pharmaceutical product cannot be prescribed at the expense of health insurance funds for areas of application to which the approval is not extended…
(2) By way of exception, this rule can be deviated from if in the case of a serious illness there are no treatment alternatives and, according to the state of scientific knowledge, there is a well-founded prospect of reaching a therapeutic outcome."
Against the background of the decision by the German Federal Constitutional Court dated 6 December 2005[11], this ruling was refined in particular by the decision of the German Federal Social Court dated 4 April 2006 (B 1 KR 7/05 R) which states among other things:
"In situations similar to emergencies insured persons are entitled, to the extent of narrow preconditions, to receive medical care using imported proprietary pharmaceutical products that are not licensed with regard to the AMG in Germany or throughout the EU."
Prior to applying a pharmaceutical medical product in the Off-Label Use the physician is not only required to perform an individual risk-benefit analysis, but he or she has also particular duties to inform the patient. The information about the lacking authorization and the specific risks connected with this must be particularly pointed out[12].
In case an Off-Label Use for a specific indication was excluded by the manufacturer in the expert information/Summary of Product Characteristics, the product must not be applied contrary to these specifications, unless there is an emergency situation[13].
Incidentally an application in the Off-Label Use is not permitted in cases where the particular prerequisites for "Compassionate Use" or "Unlicensed Use" apply that are regulated in article 21 paragraph 2 sentence 6[14].

[11] BVerfG [German Federal Constitutional Court], decision dated 6 December 2005, reference number: 1 BvR 347/98, via www.juris.de
[12] BGH (German Federal Court of Justice), decision dated 15 March 2005, VI ZR 289/03, *NJW* 2005, pp. 1716 ff.
[13] Deutsch, Spickhoff, loc. cit., p. 743.
[14] (2) "A marketing authorisation *(Zulassung)* shall not be required for medicinal products that
1. […]
6. are made available under the conditions specified to in Article 83 of Regulation (EC) No. 726/2004 for administration to patients with a seriously debilitating disease or whose disease is life-threatening, and who can not be treated satisfactorily with an authorised medicinal product; rules of procedure shall be specified in an ordinance pursuant to article 80." Regarding further details, the article by Ludwig (see footnote 4) is referred to.

1 RBC concentrates

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1.1 Preparation

RBC concentrates are prepared from fresh whole blood or from blood processed in an automated cell separator (apheresis concentrate).

1.1.1 Types of RBC concentrates

Licensed RBC concentrates slightly vary in contents of residual platelets, plasma and additive solution.

1.1.1.1 Leucocyte-depleted RBC concentrates in additive solution

In Germany allogeneic RBC concentrates are licensed only in the leucocyte-depleted form. Leucocyte depletion improves the quality of the RBC concentrates, strongly reduces the risk of immunization against human leucocyte antigens (HLA) and extensively eliminates the risk of infection by intracellular viruses (e.g. CMV) [51]. The plasma content is strongly reduced by employing an additive solution.

1.1.1.2 Washed RBC concentrates

In order to particularly remove residual plasma proteins and platelets from leucocyte-depleted RBC concentrates in additive solution, the erythrocytes are washed repeatedly in isotonic solution in a closed system and subsequently resuspended in isotonic saline solution or additive solution. Washed RBC concentrates are indicated very rarely and have to be transfused immediately [7].

1.1.1.3 Cryopreserved RBC concentrates

Prior to application, cryopreserved RBC concentrates (storage below -80°C) are thawed, washed in a closed system using a suitable solution, resuspended and transfused immediately [7]. Because of the high effort required, few national and international blood banks keep available a limited supply only of selected cryopreserved RBC concentrates of rare blood types.

1.1.1.4 Irradiated leucocyte-depleted RBC concentrates

Irradiation is performed with a mean radiation dose of 30 Gy and must not be less than 25 Gy in any part of the product [7].

1.1.2 Quality criteria

Immediately prior to a transfusion, each unit of RBC concentrates must be subjected to a visual quality control check by the physician performing the transfusion. In particular, attention must be paid to the intactness of the blood bag, clot formation, discoloration (a possible sign of contamination) and/or hemolysis. In addition, the proper labeling and expiration date of the blood product and its correct allocation to the recipient must be carefully controlled. Conspicuous RBC concentrates must not be used [7].
Storage and handling instructions must be strictly followed.

1.2 Active constituents

The active constituents of RBC concentrates are morphologically and functionally intact erythrocytes. Other constituents such as plasma, platelets, anticoagulants and additive solution, the contents of which differ depending on the preparation technique used, do not have a therapeutic effect of their own and do not influence the therapeutic efficacy of the RBC concentrates.

1.3 Physiological function, consequences of storage

Erythrocytes are highly specialized cells without nucleus or mitochondria, with a limited metabolism. They function as carriers of hemoglobin, the substance responsible for exchange and transport of respiratory gases in lungs, blood and tissues. 2–24 hours after transfusion of one RBC unit, in an adult of average weight without increased erythrocyte turnover and without hemorrhage, the hemoglobin concentration can be expected to rise by about 1.0 g/dL (0.62 mmol/L) and the hematocrit by about 3–4 % [79]. The survival time of erythrocytes in the blood is 110–120 days, i.e. the elimination rate is less than 1 % per day. Since RBC concentrates contain erythrocytes of all ages, the mean survival time of transfused compatible fresh erythrocytes is around 58 days. Theoretically, a healthy adult must produce 12 mL of erythrocytes per day to maintain a constant hemoglobin concentration of 10 g/dL (6.2 mmol/L). In the event of complete cessation of erythrocyte production, as in severe aplastic anemia, around 1 unit of RBC (200–250 mL) per week must be transfused to guarantee a constant hemoglobin concentration of 10 g/dL (6.2 mmol/L). In the event of increased degradation a higher erythrocyte consumption is observed, especially in febrile diseases, on evidence of autoimmune antibodies and in splenomegaly.

Storage of erythrocytes outside the body leads to complex changes. Among other things, such damage includes morphological changes of the stored erythrocytes (e.g. development of spherocytes and echinocytes), functional disturbances (e.g. reduction of the 2,3-diphosphoglycerate [2,3 DPG] concentration and a resultant shift to the left of the oxygen dissociation curve, loss of deformability of erythrocytes, increased concentration of lactate, release of components [e.g. potassium, lactate dehydrogenase, hemoglobin] and decrease of the S-nitrosohemoglobin of the erythrocytes [3, 23, 24, 27]). To some extent these storage-related changes in erythrocytes are reversible *in vivo* within 48 to 72 hours after transfusion.

At present, the clinical relevance of such storage-related changes cannot be assessed unambiguously in terms of tissue oxygenation and disease outcome in patients after transfusion. Clinical studies that were performed to determine the consequences of the duration of storage on tissue oxygenation had conflicting results [43, 70]. 2,3-DPG depletion is probably of little relevance for O_2 release from stored erythrocytes and for tissue oxygenation [74]. In some studies involving critically ill trauma patients during intensive care and postoperatively, an association was shown between the duration of storage of transfused RBC concentrates and mortality, morbidity, the occurrence of infections as well as length of stay in hospital [23, 34, 50, 54, 67, 80]. In patients who underwent heart surgery the latest data suggest that the transfusion of erythrocytes that had been stored longer than 14 days was associated with higher complication rates as well as lower survival rates [30]. This is discussed to be caused by storage-related morphological alterations and functional impairment of erythrocytes as well as the presence of cellular and bioactive components in plasma supernatant [3, 23, 27, 48]. However, it must be pointed out that the majority of these studies were performed prior to the implementation of leucocyte depletion. Therefore it is not clear whether the results can be transferred to the present situation.

1.4 Storage and shelf life*

RBC concentrates must be stored at +4°C ± 2°C in a suitable refrigerator or in a cold room with continuous temperature control. RBC concentrates should also be transported at temperatures between +1°C and +10°C (cold chain!) [7].
Concerning their shelf life, the user is referred to the manufacturer's specifications on the product label of the preparations in question.

Within the time frame of licensed storage time, it should **not** generally be requested to obtain RBC concentrates that were stored only briefly.	**1 C**
Under certain conditions briefly stored RBC concentrates should be applied in preterm infants or neonatals (e.g. replacement transfusions, massive transfusion, extracorporeal lung assist).	**1 C**

1.5 Range of application, dosage, mode of administration

1.5.1 Indications

1.5.1.1 General Principles

It is the therapeutic goal of erythrocyte transfusion to avoid the occurrence of an apparent anemic hypoxia. When considering a rational use of transfusion in case of anemia, due to the unspecific character of clinical symptoms in anemia additional criteria have to be taken into consideration besides the concentration of hemoglobin and/or of hematocrit measured. Among those are above all:

- cause, duration and severity of anemia
- extent and rate of blood loss
- an assessment of the individual physiological ability to compensate the reduced O_2 content in the arterial blood
- pre-existing diseases (e.g. cardiac, vascular, pulmonary) of the patient that might limit his or her ability to compensate in case of acute anemia
- the current clinical state of the patient
- symptoms that might indicate the existence of anemic hypoxia (*physiological transfusion triggers*)
- the intravascular volume status because in the case of lowered plasma volume (hypovolemia) the erythrocyte deficit is not reliably recognized and high concentrations of hematocrit are determined (see: acute blood loss).

In addition, the results of clinical studies on the correlation between anemia, transfusion of RBC concentrates and the clinical course of a disease must be considered in a rational decision for or against transfusion.
In any patient with acute or chronic anemia, the attending physician must attempt to identify the cause and to employ causal therapy whenever possible. An RBC concentrate transfusion is justifiable only if in all likelihood the health of the patient would be severely compromised by anemic hypoxia without the transfusion and if there is no at least equivalent therapeutic alternative.
A restrictive RBC transfusion practice avoids the exposition to a heterologous blood transfusion and is not associated with an increased mortality risk in most groups of patients [22, 40, 73].

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* see section 0.4

1.5.1.2 Acute blood loss

On principle, in the case of acute blood loss the overall oxygen delivery can be compensated without leaving permanent damage, while strictly maintaining normovolemia, with hemoglobin concentrations as low as of around 6 g/dL (3.7 mmol/L) and a hematocrit of 18 % by physiologic compensatory mechanisms [(1) increase of cardiac output, (2) increase of oxygen extraction, (3) redistribution of the blood flow favoring heart and CNS] [36, 40, 73]. Clinical symptoms that may indicate anemic hypoxia (*physiologic transfusion triggers*) at maintained normovolemia and confirmed anemia are listed in the following table [39, 61, 63, 78].

Table 1.5.1.2.1: Clinical symptoms that may indicate anemic hypoxia (*physiologic transfusion triggers*) at maintained normovolemia and confirmed anemia

Cardiopulmonary symptoms
• tachycardia
• hypotension
• loss of blood pressure of unknown origin
• dyspnoe
ECG changes typical of ischemia
• newly occurring ST depression or elevation
• newly occurring rhythm disorder
Newly occurring regional myocardial contraction disorder in ECG
Overall indices of an insufficient oxygen delivery
• increase of overall oxygen extraction >50 %
• drop in oxygen uptake >10 % of the initial value
• drop in mixed venous oxygen saturation <50 %
• drop in mixed venous peripheral oxygen <32 mmHg
• drop in central venous oxygen saturation <60 %
• lactate acidosis (lactate >2 mmol/L + acidosis)

When acute blood loss occurs and when there are signs of hypoxia as well as hemorrhagic shock, the timely RBC transfusion is life-sustaining. In these situations the decision to administer RBC concentrates is made on the basis of hemodynamic parameters and symptoms of anemia as well as by considering the actual and future blood loss.

Patients with normal cardiovascular function generally tolerate isovolumetric drops in hemoglobin concentration to approx. 5 g/dL (Hb 3.1 mmol/L; hematocrit 15 %) without clinical signs of a critical decrease of the overall oxygen delivery [36, 77]. At hemoglobin concentrations below 6 g/dL (<3.7 mmol/L) a critical decrease of oxygen delivery that is limited to individual organ systems (e.g. splanchnicus organs) is not safely recognized on the basis of overall indices of oxygen delivery and therefore cannot be ruled out [44]. In case hemoglobin concentration drops below 6 g/dL (3.7 mmol/L), even young and healthy individuals may show ECG alterations [35], have impaired cognitive function and memory [76] as well as subjectively perceive exhaustion and fatigue [65]. These alterations were reversible by increasing hemoglobin concentration beyond 7 g/dL (4.3 mmol/L) or by transiently breathing pure oxygen [75]. The administration of oxygen is therefore recommended as an emergency procedure in cases of acute anemia [75].

Based on clinical observation and taking risk factors into account, a hematocrit value of around 15 % (hemoglobin concentration 5.0–4.5 g/dL = 3.1–2.8 mmol/L) has to be assumed as critical threshold value for the absolute indication for substitution with RBC concentrates [10, 68, 77]. It must be taken into account that in hypovolemic patients the hematocrit value

may be in the normal range even though the erythrocyte volume is reduced; thus the hematocrit value alone cannot be used as transfusion trigger [66].
Critically ill patients, who are monitored and treated in intensive care units, may profit regarding morbidity and mortality from restrictive transfusion strategies employing as target values hemoglobin concentrations of between 7 and 9 g/dL [20, 32].

Table 1.5.1.2.2: Recommendations regarding RBC transfusion in **acute anemia**, taking into account the current hemoglobin concentration (*Hb*), the physiologic capacity to compensate the decreased oxygen content of the blood (*capacity to compensate*) and the presence of cardiovascular risk factors (*risk factors*) and clinical symptoms of an apparent anemic hypoxia (*physiologic transfusion trigger*)

An individual consideration of criteria like hemoglobin concentration, capacity to compensate and risk factors of a patient is recommended in the decision for or against a transfusion of RBC:

Hb range	**capacity to compensate / risk factors**	**transfusion**	**level**
≤6 g/dL (≤3.7 mmol/L)	--- -	**yes****	**1 C+**
>6–8 g/dL (3.7–5.0 mmol/L)	adequate compensation, no risk factors	**no**	**1 C+**
	limited compensation, existing risk factors (e.g. coronary artery disease, cardiac insufficiency, cerebrovascular insufficiency)	**yes**	**1 C+**
	symptoms of anemic hypoxia (*physiologic transfusion trigger*[1]: e.g. tachycardia, hypotension, ECG ischemia, lactacidosis)	**yes**	**1 C+**
>8–10 g/dL (5.0−6.2 mmol/L)	symptoms of anemic hypoxia (*physiologic transfusion trigger**: e.g. tachycardia, hypotension, ECG ischemia, lactacidosis)	**yes**	**2 C**
>10 g/dL (≥6.2 mmol/L)	--- -	**no*****	**1 A**

Note!
- Hemoglobin concentration alone is no adequate measurement of oxygen supply.
- In the case of hypovolemia hematocrit does not correctly reflect erythrocyte deficiency.
- Individual factors may require an indication deviating from the recommendations.

* see Table 1.5.1.2.1
** On an individual basis lower Hb values may be tolerated without transfusion provided that there is adequate compensation and no risk factors.
*** On an individual basis a transfusion might be indicated to increase Hb values to >10 g/dL.

There are insufficient data regarding patients with **cardiovascular diseases**, in particular those with an established coronary artery disease, cardiac insufficiency or cerebrovascular disease, to be able to unambiguously determine a transfusion threshold. Despite the currently limited state of knowledge, it can be concluded that hemodynamically stable patients with cardiovascular risks without symptoms of anemic hypoxia (physiologic transfusion trigger), if their hemoglobin concentration value is between 8 and 10 g/dL, do not profit from RBC transfusion in terms of mortality and morbidity [9, 25, 49]. Hemoglobin concentrations of 7–8 g/dL (4.3–5.0 mmol/L, hematocrit 21–24 %) are tolerated by stable patients with cardiovascular risks without developing lasting hypoxic damage. A decrease of hemoglobin concentration below 7 g/dL (<4.3 mmol/L, hematocrit <21 %) is associated with an increase in morbidity and mortality [6, 10, 11, 12, 17, 19, 20, 21, 55, 71, 72]. The impact of anemia on the quality of life, on functional capacity as well as on long-term mortality of these high-risk

patients was not taken into account in the studies on acute anemia. High-risk patients with cardiovascular diseases and chronic anemia, particularly those with severe cardiac insufficiency, seem to profit from higher hemoglobin concentrations regarding survival, capacity and quality of life [16, 26, 62].
In cases of severe hemorrhage and uncontrolled bleeding (e.g. polytraumatized patient, gastrointestinal bleeding) it might be reasonable in the acute phase to administer, in addition to RBC concentrates, plasma, coagulation products and platelets according to strict regimens [31, 64].
Due to the beneficial effects of higher hematocrit levels on primary hemostasis, hemoglobin concentrations of approx. 10 g/dL (6.2 mmol/L, hematocrit 30 %) should be aimed for in cases of massive uncontrolled hemorrhage (e.g. in large-volume and emergency transfusion) [19].

1.5.1.3 Chronic anemias

Patients with ***chronic anemia*** (e.g. renal insufficiency, cancer-related anemia) normally undergo long-term adaptation processes that under normal conditions secure tissue oxygenation (e.g. increase of erythrocytic 2,3-DPG and a resultant shift to the right of the oxygen binding curve, increase of the left-ventricular volume as well as of the cardiac output, myocardial hypertrophy). In spite of this, chronic anemia can be detrimental to the clinical course of a disease (e.g. cardiac insufficiency) [16, 26, 29, 33, 62]. An increase of the hemoglobin value may therefore improve both objective capacity and subjective well-being of the chronic anemia patients concerned as well as reduce the rate of in-patient treatment [14, 16, 26, 59, 62].
The decision to administer RBC concentrates should be based on an assessment of the overall clinical picture, not on laboratory results alone (hemoglobin, hematocrit, RBC count). If acute blood loss occurs in patients with chronic anemia, the same compensation mechanisms apply as in patients without chronic anemia. Thus pre-existing chronic anemia does not imply that even lower hemoglobin concentrations might be better tolerated. In cases of additional acute decrease of hemoglobin concentration, patients with chronic anemia must be treated according to the same principles as patients without pre-existing chronic anemia.
In chronic anemia patients without cardiovascular disorders, RBC transfusions are not indicated as long as their hemoglobin levels do not fall below 8.0–7.0 g/dL (hematocrit 24–21 % = 5.0–4.3 mmol/L) and the anemia does not lead to clinical symptoms.
Patients with **chronic anemia due to primary or secondary bone marrow deficiency** in whom a future bone marrow/stem cell transplantation cannot be ruled out with certainty should principally receive as few transfusions as possible (see sections 1.5.2 and 1.5.5). The administration of erythropoietin can lower the need for blood transfusion in patients with severe chronic diseases, with malignant diseases or who underwent chemotherapy [13, 53, 69]. According to the current state of knowledge, erythropoietin may have a negative impact in patients with malignant diseases, therefore its administration should be limited to patients undergoing chemotherapy [1, 52, 57]. Frequency of administration and dosage are dependent on the origin and severity of the anemia.

Patients with chronic anemia (hematocrit <24–21 % and hemoglobin concentrations of <8–7 g/dL (<5.0–4.3 mmol/L) should receive RBC transfusions.	**1 C**

Patients **with hemolytic anemia of non-immunological origin** should be treated along the same principles as patients with anemias due to hematopoietic disorders.
Certain peculiarities must be considered in substitution treatment of patients **with warm-type autoimmune hemolytic anemias (AIHA)**. The cross-match is often positive due to free autoantibodies in the patient's serum. However, this serological incompatibility must not pre-

clude the patient from receiving a life-saving transfusion. RBC transfusions together with the appropriate drug therapy can be life-saving in patients with potentially fatal hemolytic crises and very low hemoglobin levels [60]. Accompanying alloantibodies, which may often require difficult and time-consuming diagnostics, should be taken into account.

1.5.2 Indications for special RBC concentrates

1.5.2.1 Irradiated leucocyte-depleted RBC concentrates

The transfusion of blood products containing viable immunocompetent lymphocytes can lead to **graft-versus-host disease (GVHD)** in **immunocompromized patients** (see chapter 11 Adverse reactions). In the presence of a compatible HLA constellation, especially among blood relatives, GVHD can infrequently occur even in the absence of immunosuppression. In all these cases cell-containing blood products must be irradiated with 30 Gy to reliably prevent GVHD [46] (see section 11.4).

1.5.2.2 Washed RBC concentrates

The use of washed RBC concentrates is limited to patients in whom rare transfusion-relevant antibodies against IgA or other plasma proteins have been detected, or if severe non-hemolytic transfusion reactions of unknown origin have repeatedly been observed.

1.5.2.3 Cryopreserved RBC concentrates

Because of their limited availability and demanding storage and handling requirements, cryopreserved RBC concentrates should only be used in patients with complex antibody mixture or with antibodies against high-frequency red blood cell antigens, who cannot be managed otherwise.

1.5.2.4 CMV and parvovirus B19

The availability of CMV-negative RBC concentrates (RBC concentrates from donors without antibodies against CMV) and of RBC concentrates tested for parvovirus B19 is limited (regarding their indication see chapter 11).

1.5.3 Selection and dosage of RBC concentrates

To minimize the potential risks of RBC transfusions, RBC concentrates must be carefully selected on the basis of serological testing and blood grouping. For patients in whom relevant antibodies (anti-D, anti-Kell, etc.) have been detected at any time prior to transfusion, RBC concentrates with erythrocytes lacking the corresponding antigen must always be used, even if the antibody titer has fallen or became undetectable at the time of transfusion. Girls as well as women of reproductive age should not receive RBC concentrates that could lead to immunization against clinically relevant antigens of the Rh system (Rhesus formula) or the Kell factor. Supplementary blood group and antibody testing is performed when indicated.

Immediately prior to transfusion, the ABO identity test (bedside test) is carried out for the recipient by the attending physician or under his or her direct supervision, and the results must be documented in writing [7].

RBC concentrates are transfused according to their ABO identity. In exceptional cases, ABO-dissimilar products, so-called “major compatible” products, may be used for transfusion (see Table 1.5.3). These exceptions must be documented.

Table 1.5.3: Blood group compatible RBC transfusion

Patient's blood group	Compatible RBC concentrates
A	A or O
B	B or O
AB	AB, A, B or O
O	O

Because of the scarcity of RhD-negative blood, it is sometimes impossible to avoid transfusing RhD-positive RBC concentrates to non-immunized RhD-negative patients. Nonetheless, this possibility should be considered only in life-threatening situations (e.g. in emergency and large-volume transfusions) when RhD-negative blood is not available in time and when the patient is a man or a woman of non-reproductive age. RhD-negative RBC concentrates may be transfused to RhD-positive recipients if there is no incompatibility due to Rh antibodies.
RhD-incompatible RBC transfusions must be strictly avoided in RhD-negative girls and in women of reproductive age (except for life-threatening situations). The responsible physician must determine and carefully document in writing the urgency and need for such a transfusion.
In case RhD-positive products were transfused to RhD-negative recipients, a serological follow-up examination should be performed by the subsequently responsible physician 2 to 4 months after transfusion to determine whether any antibody formation has occurred. On determination of corresponding antibodies, the patient concerned must be informed and receive counsel and the fact must be documented in an emergency ID card (see section 4.2.5.8 in [7]).
If a RhD-negative woman patient of reproductive age has received a transfusion of RhD-positive blood, the development of an immune reaction against the D antigen after a transfusion of RhD-positive erythrocytes can be avoided, after consultation with a clinic specializing in transfusion medicine, by the administration of anti-D immunoglobulin (cumulative dose of up to 20 µg/mL RBC concentrates in multiple partial doses i.v.) [45].

1.5.4 Mode of administration

The responsible physician must obtain the patient's informed consent before starting a transfusion (see [7]).
The patient must be adequately monitored during and after the transfusion. After the transfusion, the blood bag with the remaining RBC must be sealed (e.g. through pinching-off) to prevent contamination and stored at 4°C ± 2°C for 24 hours [7].
RBC concentrates are generally transfused via a peripheral vein, preferably using a separate venous access. A transfusion set with a standard filter should be used [7].
The **transfusion rate** has to be adjusted according to the individual needs of the patient. Hypervolemia must be avoided. Severely anemic patients with a stable circulation can receive up to 4 units of RBC (1,000 mL) over a period of 3 to 4 hours if necessary. In patients with cardiac and/or renal failure without bleeding, the transfusion volume per unit of time should be limited to prevent cardiac decompensation.
Warming of chilled RBC concentrates is usually **unnecessary**. Prior warming of the RBC concentrates is indicated in large-volume transfusions of more than 50 mL RBC per minute, in patients with hypothermia already prior to transfusion, in patients with chronic cold agglutinin disease and high titers of cold antibodies, in patients who develop vasospasms when given chilled blood and in neonatal transfusions and replacement transfusions [28]. Only equipment certified for blood warming must be used.

Unsealed ("tapped") packs of blood components must be transfused within 6 hours after opening. It is not permissible to remove blood samples for testing purposes from sealed RBC packs.
It is not allowed to add drugs or solutions for infusion when administering blood products [7].

1.5.5 Special features of RBC transfusion to children

1.5.5.1 Indications

In **preterm infants, neonates and babies** the number and volume of diagnostic blood sampling must be kept to a minimum, because the loss of blood caused by sampling is the most frequent reason for an RBC transfusion at this age [41]. In preterm infants the baseline hematocrit is increased by a delayed sectioning of the umbilical cord and by placing the infant lower than the placenta as well as by a manual drainage of the cord towards the infant [37]. There are only few current reviews and guidelines concerning the specification of indications and/or the determination of optimal RBC dosage [2, 4, 5, 15, 37, 38].

Preterm infants and neonates shall be given RBC concentrates as an acute therapy for a volume deficiency due to loss of blood.	**1 C+**

Apart from that the duration and severity of the anemia, the medical history, the biological as well as the gestational age and the clinical state must be taken into account in the decision whether or not to perform an RBC transfusion [37, 38, 47, 58].

Table 1.5.5.1.1: Indications for the transfusion of RBC concentrates in preterm infants/neonates and babies **up to 4 months of age**

In preterm infants/neonates and babies **up to 4 months of age** RBC transfusions shall be performed in consideration of the following criteria:			**1 C+**
Age (days)	**Mean hematocrit standard value (%)**	**Indication for transfusion: hematocrit threshold value and/or list of indications**	
1 <15 15-28 >28	56 50 45 40	<40 <35 <30 <25	• mechanical ventilation, oxygen requirement (FiO_2) >0.4 or • life-threatening symptoms caused by anemia and/or hypovolemia • intended surgical interventions

Combined treatment with erythropoietin, oral iron substitution, vitamin B12 and folic acid [18, 19] starting in the first week of life can decrease the need for transfusion in **preterm infants** [8, 42].
In **children from 4 months upwards with acute blood loss** and normal cardiovascular function, a decrease of hematocrit down to 20 % and of hemoglobin concentration down to 7–6 g/dL (4.3–3.7 mmol/L) can be compensated by volume replacement. The transfusion threshold in children of this age group with unstable circulation is a hematocrit of 30 %. Children older than 4 months with **chronic anemia** but without symptoms can tolerate hemoglobin values of 8–7 g/dL (5.0–4.3 mmol/L, hematocrit 24–21 %) without needing treatment.
Specific recommendations arise from Table 1.5.5.1.2. In children with cancer receiving chemotherapy, a weekly administration of erythropoietin can considerably lower the need for transfusion [56].

Table 1.5.5.1.2: Indications for RBC transfusion in children **from 4 months upwards**

In children **from 4 months upwards** an RBC transfusion shall be performed by taking into account the following criteria: • pre-operative anemia and hematocrit <24 % • loss of ≥ 25 % of the blood volume • symptomatic anemia and hematocrit <24 % • chemotherapy and/or radiation therapy and hematocrit <24 % • severe cardiac or pulmonary diseases and hematocrit <40 % • symptomatic sickle cell anemia or other hereditary anemias	**1 C+**

A recent randomized study of critically ill children could show that a restrictive transfusion strategy with a hemoglobin concentration threshold of 7.0 g/dL (4.3 mmol/L, hematocrit 21 %) can significantly decrease transfusion requirements compared to a liberal transfusion strategy without increasing adverse outcomes. This is not applicable to preterm infants and children with hypoxemia, hemodynamic instability, active blood loss or cyanotic heart disease [32].

1.5.5.2 Dosage

The normal volume of transfusion in children, especially in preterm infants and neonates, is 5–15 mL/kg body weight [58]. Higher dosage is required in hypovolemic shock, replacement transfusions and surgery with extracorporeal circulation. An administration of 3 mL RBC/kg body weight increases hemoglobin concentration by approx. 1 g/dL (0.6 mmol/L). Transfusion volume can be calculated as follows:

$$\text{Transfusion volume (mL RBC)} = \frac{[(\text{target value hematocrit}) - \text{actual hematocrit}]}{\text{hematocrit of RBC (55–65)}} \times \text{blood volume}$$

blood volume in neonates: approx. 90 mL/kg body weight
blood volume in older children: approx. 80 mL/kg body weight

1.5.6 Contraindications and restricted application

Absolute contraindications are unknown.

Note:
Potential bone marrow or stem cell recipients should never be given RBC concentrates from the transplant donor or her/his close relatives prior to the transplantation.

1.6 Adverse reactions

See chapter 11.

1.7 Documentation

According to article 14 TFG, there is an obligation to perform a patient- as well as product-related batch documentation for RBC concentrates.
For the particulars of documentation and quality management, see German Guide by the GMA for hemotherapy.

1.8 References

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2 Platelet concentrates

2 Platelet concentrates

2.1 Preparation

Platelet concentrates (PC) can be obtained either from whole blood or by apheresis from healthy donors. Two preparations are available. Depending on the number of platelet units used (from 4 to 6 donors), **pooled PCs** generally contain 240 to 360 × 10^9 platelets suspended in 200 to 350 mL plasma or a substitute plasma solution. **Apheresis PCs** generally contain 200 to 400 × 10^9 platelets in 200 to 300 mL plasma from a single donor.
Quality: A low amount (<3 × 10^9) of erythrocytes is present in PC. The content of residual leucocytes is lower than 1 × 10^6 per PC [56].

2.2 Active constituents

Platelet concentrates contain quantitatively enriched and functionally intact blood platelets from one or more blood donors. Platelets are resuspended either in donor plasma or in an additive solution. Depending on the preparation process, there are residual amounts of anti-coagulant, stabilizer, additive solution as well as erythrocytes, plasma and leucocytes which have no therapeutic effect by themselves and do not contribute to the clinical effectiveness of the platelet concentrates.

2.3 Physiological function

Platelets are the cellular elements of the hemostatic system. By adhesion to the subendothelial matrix followed by local aggregation of activated thrombocytes, the resulting platelet plug covers endothelial defects by involving the plasmatic coagulation system, thereby initiating clotting and hemostasis.
Following transfusion, the intact platelets are distributed between circulating blood and the spleen. The recovery rate in peripheral blood therefore amounts to only 60-70 %. The recovery rate is increased in splenectomized patients, but decreased in case of hypersplenism. A reduced recovery rate is also observed in conditions with increased platelet consumption (e.g. sepsis, disseminated intravasal coagulation, presence of antibodies against platelet antigens).
Fresh, non-activated platelets from a healthy donor can be detected for about 7 to 10 days after transfusion in the peripheral blood of a healthy recipient. This mean post-transfusion platelet lifespan decreases with the length of PC storage. The lifespan of blood platelets is markedly reduced in all patients with thrombocytopenia and/or increased platelet consumption, but especially in the presence of antibodies that react with platelets [48].

2.4 Storage and shelf life

Platelet concentrates are stored in special gas-permeable sterile plastic bags at 22°C ± 2°C. When closed collection systems are used during preparation, PC can be stored for up to 5 days under continuous agitation. For optimal transfusion results, platelets should not be stored for long periods. The products should be used according to the manufacturer's instructions on the product label. Transfusion should be initiated as quickly as possible after delivery of PC, any storage below +20°C or above +24°C is to be strictly avoided, since platelets could be damaged by this [61]. Opened bag systems must not be stored [56].

2.5 Range of application, dosage, modes of administration

With a few exceptions, there are no prospective clinical studies on optimal use of platelet concentrates. The levels of evidence and recommendation specified here are based on a Medline search regarding this topic covering the time period since 1990. They are additionally based on a recent review by the medical societies German Society for Transfusion Medicine and Immunohaematology, German Society for Haematology and Oncology as well as Society of Thrombosis and Haemostasis Research [16].
Platelet transfusions are used for prophylaxis and for treatment of platelet-related bleeding. The indication for platelet transfusion depends on the platelet count and function, the bleeding pathology (according to WHO classification: **grade 1,** small hematoma, petechiae, gum bleeding; **grade 2**, minor bleeding not requiring RBC transfusion; **grade 3**, bleeding requiring transfusion; **grade 4**, organ-threatening or life-threatening bleeding), the risk factors for bleeding as well as the underlying disease. Prophylactic platelet transfusions are used to lower the risk of life-threatening bleeding. Data on the transfusion trigger are available from case-controlled clinical studies involving patients with hematologic-oncologic disorders [65]. For all other patient groups, the recommendations are based on case histories and expert opinions.

2.5.1 Platelet transfusion in patients with hematologic-oncologic disorders

Based on clinical aspects, patients can be classified in four groups.

2.5.1.1 Patients with chronic thrombocytopenia (group A)

Patients with chronic thrombocytopenia due to impaired platelet production belong to this group (e.g. aplastic syndrome, myelodysplastic syndrome or hereditary thrombocytopenia).
In outpatients with aplastic anemia no severe bleeding complications occurred by observing the following prospectively determined transfusion triggers:
platelet count <5,000/µL and weekly control; platelet count <10,000/µL in case of recent hemorrhage or fever exceeding 38°C only; platelet count <10,000/µL in case of major bleeding events (World Health Organization grade 3) or before minor surgery only [57].
There is no scientific evidence of any benefit involved in administering platelets to prevent bleeding if platelet count exceeds 5,000/µL.

In **patients with hematologic-oncologic disorders** with chronic and treatment-refractory thrombocytopenia platelet transfusion is recommended in the following cases:	
clinically manifest hemorrhage grade 3 or 4	**1 B**
prior to surgical interventions	**1 C**
prophylactically if platelet count <5,000/µL	**2 B**

2.5.1.2 Patients with elevated platelet turnover (group B)

Patients with thrombocytopenia as a sign of an immunologically or non-immunologically increased turnover rate of platelets belong to this group.
There are no prospective studies available regarding prophylactic platelet transfusions in patients with immune thrombocytopenia. Transfusion of platelets is recommended only in patients with immune thrombocytopenia for the treatment of life-threatening hemorrhages (WHO grade 4). To achieve hemostasis in these cases, high doses of platelets are often necessary. In this case, concomitant treatment is essential, e.g. with high-dose glucocorticoids (2 mg prednisolone/kg body weight) and immunoglobulins (1 g/kg body weight/day on two consecutive days) [15].

In patients with **hemolytic uremic syndrome**, **TTP** or drug-induced microangiopathic hemolysis the administration of platelets is subject of controversy even if there is evidence of bleeding. This also applies in the case of patients with increased turnover in the context of **disseminated intravascular coagulopathy** or sepsis. No prospective studies are available in this regard.

In patients with elevated platelet turnover (group B) platelet transfusion is recommended in the following cases:	
immune thrombocytopenia only in case of severe hemorrhage	**2 C**
patients with hemolytic uremic syndrome and patients with TTP and severe hemorrhage only after all other therapeutic options have been exhausted	**2 C**
patients with sepsis and disseminated intravascular coagulopathy only in case of severe hemorrhage	**2 C**

2.5.1.3 Patients with impaired platelet production due to chemotherapy (group C)

Patients with thrombocytopenia due to impaired megakaryocytopoiesis without concomitant bleeding risk belong to this group.

A trigger of 10,000 platelets/µL is recommended for prophylactic platelet transfusions in adult patients with transient disease- or treatment-induced thrombocytopenia following chemotherapy in the context of malignant hematological neoplasias, in the absence of other risk factors for bleeding. This was predominantly investigated in patients with acute leukemia [68, 75, 81].

In children concomitant risks (e.g. desire to move, danger of falling) should be considered in the decision for or against platelet transfusion.

Only few studies are available regarding prophylactic platelet transfusion in patients undergoing bone marrow transplantation. In these patients bleeding frequently occurs due to additional complications (e.g. mucositis). In patients with stable condition a transfusion trigger of 10,000 platelets/µL is widely accepted [17, 20, 38, 49, 55, 71, 76].

In patients with solid tumors and thrombocytopenia, who underwent radiation or chemotherapy, the same transfusion triggers as in hematologic-oncologic patients are adopted. No prospective studies are available in this regard. If there are manifest bleeding complications (e.g. in patients with necrotizing solid primary tumors) higher platelet amounts are possibly required (>50,000/µL).

In patients with acute platelet-forming disorders (group C) platelet transfusion is recommended in the following cases:	
adult patients with acute leukemia, as prophylactic treatment only below a platelet count of ≤10,000/µL or if manifest bleeding occurs	**1 A**
children with acute leukemia with a low risk of injury, as prophylaxis only below a platelet count of ≤10,000/µL or if manifest bleeding occurs	**1 C**
patients after bone marrow or stem cell transplantation **without** complications like severe graft versus host reaction, mucositis or cystitis only below a platelet count of ≤10,000/µL or if manifest bleeding occurs	**1 C**
patients with solid tumors with no additional risk of bleeding only below a platelet count of ≤10,000/µL or if manifest bleeding occurs	**1 C**

2.5.1.4 Patients with impaired platelet production and additional risks of bleeding (group D)

Group C patients with additional risks of bleeding belong in this group. Certain risk factors for the occurrence of severe bleeding complications have become apparent in patients with

hematologic diseases and also in patients with solid tumors and chemotherapy-associated thrombocytopenia (Table 2.5.1.4).

Table 2.5.1.4 Risk factors for the occurrence of bleeding complications in patients with thrombocytopenia

- infections
- complications (GVHD)
- clinical evidence of hemorrhage (e.g. petechial bleeding)
- fever above 38°C
- leucocytosis
- plasmatic (pro-hemorrhagic) coagulation disorders
- sharp decline in platelet count
- pre-existing necrotic areas

In thrombocytopenic patients with malignant tumors with one or more of these risk factors it is usually recommended to administer platelet concentrates prophylactically if the platelet count is ≤20.000/µL.

In hematologic-oncologic and oncologic patients with impaired platelet production and additional bleeding risks (group D) platelet transfusion is recommended in the following cases:	
patients with additional risks of bleeding (table 2.5.1.4) with a platelet count of <20.000/µL	**2 C**
if manifest bleeding occurs	**1 C**

2.5.2 Platelet transfusion in surgical interventions/medical procedures

2.5.2.1 Invasive diagnostic interventions

In the context of invasive surgical interventions the critical transfusion trigger depends on the patient's individual risk of bleeding, the extent of trauma and the risk exposure involved with possible hemorrhage (Tables 2.5.1.4. and 2.5.2.1.). According to common clinical experience, there is no increased risk of bleeding with a platelet count of ≥ 50.000/µl and normal platelet function [59]. It is indispensable to specifically take a careful medical history regarding bleeding.

In platelet disorders the severity of the disorder determines the transfusion trigger. Typical examples of an isolated platelet disorder are patients treated with glycoprotein IIb/IIIa inhibitors or with combined clopidogrel and aspirin anti-platelet therapy following the implantation of a stent. If it is not possible to wait for the action of the platelet aggregation inhibitors to wear off in these patients, the individual risk of a stent thrombosis has to be weighed against the risk of bleeding. The therapeutic course of action for such patients should be coordinated among diverse medical disciplines (surgery, cardiology, hemostaseology). When a surgical intervention requires discontinuation of combined anti-platelet therapy, at least aspirin therapy should be maintained, if possible. If necessary in emergencies, normalization of platelet function can be achieved by platelet transfusion [21, 26, 41, 60, 74]. There are also reports on the efficacy of desmopressin and antifibrinolytic drugs [4, 22, 72].

In patients without additional risks of bleeding platelet transfusion is recommended prior to invasive surgical interventions if platelet counts are <50,000/µL.	**1 C**

Table 2.5.2.1 Selected drugs influencing platelet function and/or hemostasis

1. Inhibitors of hemostasis
- Platelet inhibitors (e.g. aspirin, clopidogrel, ticlopidin, fibrinogen receptor antagonists, certain non-steroidal antiinflammatory drugs)
- Antibiotics (e.g. penicillin G, ampicillin, cephalosporins, amphotericin B)
- Synthetic colloids (dextrans, highly polymerized hydroxyethyl starch)
- Heparins and heparinoids
- Thrombolytic drugs
- Tricyclic antidepressive drugs, phenothiazine, valproic acid, serotonin uptake antagonists
- lipid suppressors (clofibrate etc.)

2. Improvement of hemostasis
- Antifibrinolytic drugs (e.g. tranexamic acid, aminomethylbenzoic acid)
- Desmopressin acetate

2.5.2.2 Lumbar puncture

Lumbar puncture is associated with a low risk of bleeding [13]. Because of serious consequences of bleeding close to the spinal cord, the majority of experts recommend a threshold platelet count of ≥50.000/µL in elective lumbar puncture [59]. In urgently necessary diagnostic procedures a platelet count of 20,000/µL is considered to be sufficient unless there are symptoms of hemorrhage [59].

In patients with severe sepsis for whom a lumbar puncture is absolutely necessary for confirming or disproving the diagnosis (e.g. if meningococcal sepsis is suspected), lumbar puncture may be performed independent of platelet count. If platelet count is <10.000/µl platelet transfusion should be performed.

Under therapy with combined platelet aggregation inhibitors (clopidogrel and aspirin) it is recommended to administer platelet concentrates prophylactically. If only aspirin 100 mg is administered, lumbar puncture is possible even without platelet transfusion since the risk of bleeding is low.

In lumbar puncture platelet transfusion is recommended under the following circumstances:	
prior to elective lumbar puncture if platelet count is ≤50.000/µl. In emergency situations lumbar puncture should not be delayed if platelet counts are <20,000/µL.	**1 C**
as a prophylaxis in patients treated with combined platelet aggregation inhibitors (clopidogrel and aspirin).	**2 C**

2.5.2.3 Needle biopsy of the liver

Even in patients with severe thrombocytopenia and/or other coagulation disorders transjugular biopsy of the liver can be safely performed without platelet transfusion. If this biopsy procedure is chosen, administration of platelet concentrates prior to intervention is indicated only if platelet counts are <10,000/µL [8].

In case a percutaneous liver biopsy is unavoidable in patients with a risk of bleeding, a platelet count of >50,000/µL is recommended [8].

Prior to transjugular biopsy of the liver platelet transfusion should be performed if platelet counts are <10,000/µL.	**1 C**

2.5.2.4 Aspiration of joints

In patients undergoing aspiration of joints platelet counts and function must be observed. There are no studies determining a safe threshold platelet count prior to aspiration. Unless there is a disposition to bleeding and a platelet function disorder, a platelet count of >20,000/µL is recommended.

Prior to aspiration of joints platelets should be transfused if platelet count is <20,000/µL.	**2 C**

2.5.2.5 Dental extraction and surgery

In patients undergoing dental extraction/surgery platelet counts and function must be observed. There are no studies determining a safe minimum platelet count prior to treatment. Unless there is a disposition to bleeding and a platelet function disorder, a platelet count of >20,000/µL is recommended, in case of dental extraction/surgery a platelet count of >50,000/µL [51, 79].

In most dental interventions with risk of bleeding the local administration of tranexamic acid is sufficient (1 g per glass of water, rinse mouth every 30 min) with or without treating the wound with fibrin sealant. Administration of desmopressin is indicated in platelet function disorders and von Willebrand Syndrome [23, 44, 63].

Prior to surgical dental treatment platelets should be transfused if there is a disposition to bleeding and if platelet counts are <20,000/µL.	**2 C**

2.5.2.6 Gastrointestinal endoscopy

In patients with severe thrombocytopenia gastrointestinal endoscopy can be performed even without platelet transfusion [59]. If it is intended to take a biopsy, platelet substitution is only necessary with platelet counts <20,000/µL. Administration of platelets should be performed immediately prior to the intervention. In cases of combined coagulopathy it is required to treat the plasmatic coagulation disorder in addition to platelet transfusions. In patients pretreated with anti-platelet drugs, these drugs should be discontinued if possible. Administration of platelets is only indicated in the event of bleeding.

In patients undergoing gastrointestinal endoscopy with the intention to take a biopsy platelets should be transfused if platelet counts are <20,000/µL.	**1 C**

2.5.2.7 Bronchoscopy including transbronchial biopsy

Fiberoptic bronchoscopy can be performed without platelet transfusion also in thrombocytopenic patients [77]. Platelet therapy prior to bronchoscopy is indicated if platelet counts are <20,000/µL, and prior to transbronchial biopsy if platelet counts are <50,000/µL [52, 62].

In patients pretreated with anti-platelet drugs it is recommended to discontinue these drugs early enough (at least three half-lives) if a biopsy is intended. Prophylactic platelet transfusion is indicated in emergency situations and if there is a known disposition to bleeding.

Platelet transfusion is recommended under the following circumstances:	
bronchoscopy and platelet count of <20,000/µL.	**1 C**
transbronchial biopsy and platelet count of <50,000/µL.	**1 C**

2.5.2.8 Angiography including coronary angiography

Prior to performing angiography a minimum platelet count of 20,000/µL is required in order to avoid hemorrhage in the puncture area. When platelet counts are lower, administration of platelets is recommended provided the angiography is performed for localisation of a source of bleeding or for elective vascular diagnostics. When angiography is indicated because of acute arterial thrombosis, administration of platelets may pose an additional thrombosis risk for the patient. In such cases administration of platelets is only recommended if increased postoperative bleeding occurs [58].

Prior to angiography including coronary angiography platelets could be transfused if platelet counts are ≤20,000/µL, unless angiography is carried out in the context of an acute arterial thrombotic event.	**2 C**

2.5.2.9 Biopsy of the iliac crest

For bone marrow biopsy no prophylactic platelet transfusions are required, unless there are particular anatomical risks of bleeding [3, 62].

We do not recommend prophylactic platelet transfusion prior to bone marrow biopsies.	**1 C**

2.5.2.10 Central venous catheter

In patients without high bleeding risk and with platelet counts of more than 10,000/µL, central venous catheters can be inserted even without platelet substitution. In patients with clinical disposition to bleeding and platelet counts of ≤20,000/µL prophylactic platelet transfusion is indicated [11, 54, 69].

Prophylactic platelet transfusion on insertion of a central venous catheter could be performed in patients with disposition to bleeding and platelet counts of <20,000/µL.	**2 C**

2.5.2.11 Surgical interventions

If platelet aggregation is normal and platelet counts are >50,000/µL bleeding risk is normal and no preoperative platelet transfusion is required [9, 59].

Surgical interventions with a low risk of bleeding, including the majority of peripheral interventions in which hemostasis can be achieved by compression, can also be performed at platelet counts between 20,000 and 50,000/µL. In case there is already a disposition to bleeding prior to surgery and/or a platelet count of <20,000/µL, platelet transfusion prior to surgery is indicated.

Preoperative platelet transfusion is sometimes recommended in major surgical interventions on falling below a threshold value of 50,000/µL. If values range between 50,000 and 100,000/µL platelet counts should be monitored at close intervals during and after surgery.

A preoperative value of more than 70,000 up to 100,000/µL is recommended for interventions with a particularly high risk of bleeding (e.g. neurosurgical interventions).

Prophylactic platelet transfusions are not required for cardiac surgery and extracorporeal circulation, except in patients with thrombocytopenia <20,000/µl. Upon completion of the cardiopulmonary bypass platelet transfusion is indicated when platelet counts are <20,000/µL. In patients with platelet aggregation disorders replacement may be necessary already with counts <50,000/µL. In patients with microvascular bleeding the post surgery platelet transfusion is recommended until hemostasis is achieved. Subsequently platelet counts between 50,000/µL and 100,000/µL should be maintained.

A threshold platelet count of >80,000/µL is recommended when performing epidural anesthesia. In case this count is not reached, it is recommended to use alternative anesthetic procedures. For spinal analgesia there is a threshold platelet count of 50,000/µL [5, 24, 73]. In national recommendations of Medical Societies of Anesthesiology dual anti-platelet therapy is generally cited as a contraindication for the performance of regional neuro-axial blockade [26, 41]. If necessary, prophylactic platelet transfusions are recommended [41]. Based on the treatment of patients with severe thrombocytopenia or congenital thrombocytopathy, the administration of 4–5 × 10^{11} platelets (2 platelet concentrates) should be sufficient to achieve adequate hemostasis. In these cases platelet counts should be monitored at close intervals.
In acquired platelet aggregation disorders (e.g. in uremia; after cardiopulmonary bypass; dual anti-platelet therapy) transfusion triggers cannot be based on platelet counts but rather on the clinical disposition to bleeding. In individual cases concomitant treatment with antifibrinolytic drugs or desmopressin can be indicated. Platelet aggregation inhibitors (Table 2.5.2.1.) should be discontinued, if possible. Anticoagulation should be carefully monitored in these patients.
Patients treated with platelet aggregation inhibitors have an increased risk of bleeding [58]. In these patients preoperative platelet transfusion is recommended for interventions with a particularly high risk of bleeding (e.g. neurosurgical interventions and surgery in the posterior eye segment).

In the case of surgical interventions platelet transfusion is recommended in the following cases:	
as prophylaxis prior to minor surgical interventions in case of preexisting bleeding due to platelet disorders or if platelet counts are ≤20,000/µL	**2 C**
as prophylaxis in major surgical interventions and interventions with a high risk of bleeding immediately prior to surgery if platelet counts are <50,000/µL	**2 C**
as prophylaxis in interventions with a particularly high risk of bleeding immediately prior to surgery if platelet counts are <70,000/µL to 100,000/µL	**1 C**
in cardiac surgery in the case of increased postoperative bleeding or if platelet count falls below 20,000/µL	**2 C**
as prophylaxis prior to performing epidural anesthesia if the threshold platelet count is <80,000/µL	**1 C**
as prophylaxis prior to performing spinal anesthesia with a threshold count of 50,000/µL	**1 C**

2.5.3 Liver failure

Acute liver failure is often accompanied by a rapid development of severe thrombocytopenia. Platelet administration is recommended if values are <20,000/µL or in case of pronounced petechial bleeding.
In patients with chronic liver failure with platelet counts of >10,000/µL no prophylactic administration of platelets is required unless when preparing for diagnostic or therapeutical interventions. The recommendations for gastrointestinal endoscopy apply here also.

Platelet transfusion is recommended in patients with liver failure in the following cases:	
in acute liver failure if platelet counts are <20,000/µL or if pronounced petechial bleeding occurs	**1 C**
in patients with chronic liver failure if bleeding complications occur or as prophylaxis when preparing for diagnostic or therapeutical interventions if platelet counts are <20,000/µL	**2 B**

2.5.4 Platelet transfusion for treatment of an acute hemorrhage

In cases of acute hemorrhage platelet count and function, the extent of the blood loss as well as the degree of severity of hemorrhage represent the most important transfusion triggers. In case of life-threatening bleeding; risk of organ damage (WHO grade 4) [67]; and bleeding requiring transfusion of ≥1 RBC concentrate per day (WHO grade 3) [43], platelet counts should be maintained at 100,000/µL independent of the cause of bleeding.
Bleeding symptoms not requiring RBC transfusion (WHO grade 1–2: petechia, ecchymosis, occult hemorrhages, intermenstrual bleeding, epistaxis, microscopic hematuria) are usually no indication for platelet transfusion.

Platelet transfusion is recommended in the event of acute hemorrhage:	
in case of life-threatening bleeding to prevent coagulopathy if platelet counts are <100,000/µL	**2 C**
in case of transfusion-dependent bleeding if platelet counts are <100,000/µL	**2 C**

2.6 Monitoring of platelet transfusion

The most important monitoring parameter in acute hemorrhage is cessation of bleeding.
In case of prophylactic platelet transfusion, the increase in platelets (increment) or corrected count increment (see section 6.3.) is a reasonable monitoring parameter.

2.7 Selection of the platelet concentrate

Indications for irradiated platelet concentrates, for CMV antibody-negative platelet concentrates and for parvovirus B19-negative platelet concentrates are summarized in chapter 11, Adverse reactions.

2.7.1 Apheresis platelet concentrates and pool platelet concentrates

Both types of platelet concentrates are effective in treating the bleeding patient [1, 31, 70]. In immunized patients for selection of platelet donors, the appropriate HLA and human platelet antigens (HPA) have to be taken into account (see also section 2.8).
Platelet concentrates obtained by the platelet-rich plasma method (which are not used in Germany) have a reduced platelet recovery and survival compared to apheresis platelet preparations [2]. Also refractoriness developed less frequently with apheresis concentrates [64]. When platelet concentrates obtained by the buffy coat method are transfused, the recipient receives blood from a higher number of donors as compared to the transfusion of apheresis concentrates. The Corrected Count Increment (CCI) in both preparations is reduced by approximately 20–30 % after storage for 5 days [31].
In case of planned stem cell/bone marrow transplantation, transfusion of platelets obtained from the stem cell donor and blood relatives have to be avoided.

In selecting platelet concentrates for transfusion the following is recommended:	
to match the donor for the respective HLA or HPA antigens in immunized patients	**1 C**
prior to allogeneic stem cell/bone marrow transplantation, avoidance of transfusion of platelet concentrates from the stem cell donor (or from blood relatives of the donor)	**1 C**

2.7.2 ABO blood groups and RhD compatibility

In addition to HLA class I and platelet-specific antigens (HPA), platelets carry the ABO blood group [32, 33]. It is still unresolved whether ABO-incompatible platelet transfusions cause clinically relevant immune modulation [6, 7, 18, 19]. In rare cases acute hemolytic transfusion reactions can occur, caused by isoagglutinins (anti-A and anti-B) in the donor plasma. Possibly ABO-incompatible platelets are more rapidly metabolized than ABO-identical ones [12, 30]. Therefore, on selecting platelet concentrates the blood group should be taken into account, if possible.
Platelet concentrates contain small amounts of erythrocytes. Therefore the RhD factor should be also taken into account on selecting platelet concentrates, particularly for girls and women of reproductive age. If the transfusion of RhD-positive platelet concentrates is unavoidable in the case of women of reproductive age, prophylactic i.v. or subcutaneous administration of 150–300 µg anti-D immune globulins is indicated [82].

For selection of the platelet concentrate for transfusion it is recommended:	
to preferentially transfuse ABO-identical platelet concentrates	**1 C**
in patients with HLA or HPA antibodies to select primarily according to HLA/HPA compatibility and only in the second place according to ABO blood group	**1 C**
to preferentially select platelets from RhD-negative donors for RhD-negative patients	**1 C**
in case RhD-negative women of reproductive age receive RhD-positive platelet transfusions, to give Rh prophylaxis (150–300 µg i.v. or s.c. anti-D)	**1 C**

2.8 Management of the refractory patient

2.8.1 Definition

Refractoriness against platelet transfusions is defined as repeated failure to achieve an increase in platelet count despite repeated transfusions of ABO-compatible, fresh (<3 days) platelet concentrates. The origin of refractoriness is often unknown. Non-immune causes (e.g. consumptive coagulopathy in major hemorrhage or in sepsis) are more frequent than immune mechanisms (HLA and HPA antibodies).
Platelet transfusion in these patients should not be based on platelet count but rather on symptoms of blood loss and additional bleeding risks (e.g. invasive surgery). Often a higher platelet dose (e.g. two fresh ABO-identical platelet concentrates) is able to stop bleeding.

2.8.2 Serologic investigations in refractory patients

Antibodies against HLA class I antigens are the most frequent cause for immune mediated transfusion refractoriness [25, 47]. Patient serum should be tested for HLA antibodies using antigen assays, e.g. enzyme immuno assays with immobilized HLA antigens or platelets [28, 36, 42]. The lymphocytotoxicity test can show false positive results (e.g. in patients with autoreactive cytotoxic antibodies or by previous administration of therapeutic antibodies [anti-CD3, ATG]) or false negative results in patients with non-complement-activating HLA antibodies.
In 15–30 % of patients HLA class I antibodies are associated with additional HPA antibodies [18, 66]. Similar to RBC transfusion, a serological compatibility test can be performed prior to platelet transfusion. Hereby donor platelets are tested with the recipient's serum. In patients

in whom platelet-reactive antibodies have been detected, a higher platelet increment is achieved when using matched platelet concentrates [14, 50, 53].

For managing the refractory patient, the following recommendations are made:	
HLA class I antibodies should be ruled out in the patient serum if an immune mechanism of refractoriness is suspected	**1 C**
a complement-independent antigen test rather than the lymphocytotoxic test should be used for HLA class I antibodies	**2 C**
to additionally search for platelet-specific alloantibodies (HPA antibodies) if HLA antibodies are detected and in the case of ineffective HLA-compatible platelet transfusion	**2 C**
to perform a serological compatibility test (crossmatch) in immunized patients, using antiglobulin-binding assay (like ELISA, immunofluorescence test) by using platelets as antigenic substrate	**1 C**
to determine HLA-A and HLA-B antigens of the patient with confirmed HLA antibodies in order to select the donor (high-resolution typing is not necessary).	**2 C**

2.8.3 Selection of compatible platelet concentrates in immunized patients

In patients with confirmed class-I HLA alloantibodies HLA-well-matched compatible platelets should be used for transfusion after verification in a cross-match procedure [14, 40, 53]. In broadly immunized patients (reactivity with more than 80–90 % of the test cells) it is recommended to determine HLA-A and HLA-B antigens of the patient in order to be able to preselect potentially suitable platelet donors (→ apheresis platelet concentrates). HLA- and HPA-compatible donors should be selected for patients who have formed HPA antibodies in addition to HLA class I antibodies [37].
Transfusion outcome should be controlled by determining platelet increment in order to detect additional immunization at an early stage. For this purpose platelet counts are determined prior to transfusion and 1 hour and approx. 20 hours post transfusion. The corrected count increment (CCI) represents a "normalized" measure [10].

CCI = (platelet increment per μL × body surface in m^2)/number of platelets transfused (× 10^{11})

In case of refractoriness corrected increments determined after 1 hour are <7,500, and values determined after 20 hours <4,500.

Regarding management of the refractory patient, it is recommended:	
in patients with confirmed HLA class I antibodies to transfuse HLA-compatible platelets obtained by apheresis.	**1 B**
to transfuse HLA- and HPA-compatible platelets obtained by apheresis in patients who have also formed HPA antibodies.	**2 C**
to control transfusion outcome in immunized patients by determining corrected count increment	**2 C**

2.8.4 Administration of incompatible platelets

If no compatible platelet concentrates are available, high-dosed administration of platelet concentrates (empirically: 5–10 platelet concentrates) can accomplish short-term hemostasis in patients with apparent bleeding.
In cases of life-threatening hemorrhage the administration of recombinant factor VIIa may be indicated (see section 7.4.6).
Intravenous application of high-dose IgG (ivIgG) in combination with platelet transfusion is not more effective than platelet transfusion alone [27, 39].

Regarding management of the refractory patient, in cases of life-threatening hemorrhage large volumes of platelets should be transfused and, in case of failure, rFVIIa should be administered. (Because the application of rFVIIIa would be done in the "Off-Label Use", the reader is referred to the statements in section 0.4.)	**1 C**
In transfusion-refractory patients with life-threatening hemorrhage we discourage the additional transfusion of ivIgG.	**1 B**

2.9 Fetal and neonatal alloimmune thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by immunization of the mother against a fetal platelet antigen and by placental transmission of the maternal antibodies into the fetal circulation [33]. Most frequently, antibodies against human platelet antigens (HPA)-1a and -5b are involved. Antibodies against other HPAs are rare [35]. In the Caucasian population FNAIT occurs in approximately 1:1,000 pregnancies. Untreated neonates have a high risk (up to 25 %) of suffering intracranial hemorrhages [45, 46, 78].
Intracranial hemorrhages can also occur in the fetus [34, 80]. Probably there is already a risk of bleeding if platelet counts are lower than 50,000/µL. Treatment of the mother with i.v. IgG with and without prednisolone seems to reduce the rate of severe thrombocytopenia or intracranial hemorrhage in the fetus (see section 9.5.2.3). Intrauterine platelet transfusion is associated with risks and should be avoided, if possible. After delivery platelet transfusion is the treatment of choice. In a case series of 27 newborns with FNAIT who received platelets from random donors, 24 newborns showed sufficient increase in platelet count [29]. In the past, transfusion of maternal platelets was often preferred to administration of random donor platelets [45]. However, because of organizational reasons, maternal platelets are frequently only available after a considerable time lag. In addition, maternal plasma must be removed and replaced with donor plasma. In recent years several German blood transfusion services have started to offer the possibility of genotyping the platelet antigens [32]. Thus an HPA-1a negative platelet concentrate is often available on short notice. Prior to elective delivery HPA-compatible platelet concentrates should be provided for patients with known NAIT.

In fetal and neonatal alloimmune thrombocytopenia the following is recommended:	
platelet transfusion of compatible HPA-1a- and -5b-negative platelets as prophylaxis if FNAIT is suspected and if there is a risk of bleeding (platelet count <30,000/µL; preterm infants <50,000/µL), if these preparations are available immediately.	**2 C+**
in cases where platelet count is <30,000/µL, or when there is a risk of bleeding, an initial transfusion of random donor platelets if HPA-1a- and -5b-negative platelets are unavailable on short notice.	**1 C**

as prophylaxis HPA-compatible platelet concentrates should be provided prior to delivery and be transfused if bleeding occurs (platelet count <30,000/µL in full-term neonates <50,000/µL in preterm neonates).	**1 C**
We discourage exclusive ivIgG therapy in neonates with NAIT and a risk of bleeding. (Regarding antenatal treatment of FNAIT, see section 9.5.2.3.)	**2 C**

2.10 Adverse reactions

See chapter 11.

2.11 Documentation

According to article 14 TFG, there is an obligation to perform a patient- as well as product-related batch documentation for platelet concentrates.
For details regarding documentation and quality management, see [56].

2.12 References

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3 Granulocyte concentrates

3 Granulocyte concentrates

3.1 Preparation

Granulocyte concentrates (GC) are prepared from the blood of healthy donors by automatic apheresis and are therefore also known as granulocyte apheresis concentrates. To ensure sufficient granulocyte content, donors are pretreated with corticosteroids and/or recombinant growth factors for granulocytes (granulocyte colony-stimulating factor, G-CSF). This pretreatment with G-CSF significantly increases granulocyte yield [5, 7] and prolongs granulocyte survival time [15]. To achieve better separation of granulocytes from erythrocytes, during apheresis the collected blood is supplemented by a sedimenting agent, usually 6 % high-molecular-weight hydroxyethyl starch (HES) [6]. Because of the risk of severe itching following infusion of HES, granulocyte donations are limited to four per donor and year [6, 10]. The specifications of article 9 of the German Transfusion Act (TFG) must be observed regarding pretreatment of donors with G-CSF. Pretreatment of donors with G-CSF should only be performed in the context of notified mobilization programs so that, in case late adverse reactions occur, all pretreated donors can be reached quickly for clarifying follow-up examination.
Regarding donor suitability as well as requirements of product quality, the national and European laws and directives mentioned in chapter 1 are referred to.

3.1.1 Quality criteria

GC must contain a sufficient number of functional neutrophil granulocytes, depending on the weight or rather the body surface of the recipient (see section 3.3). Every GC must be subjected to visual quality control immediately before transfusion. Special attention must be paid to bag integrity, coagulation, aggregate formation, discoloration and hemolysis. GC in any way suspicious may not be transfused. Furthermore, complete labeling, correct assignment to the patient and expiration date of the preparation must be checked.

3.2 Active constituents

The effective components of GC are morphologically and functionally intact neutrophils. Mononuclear leucocytes present in GC possibly contribute to the antiinfective effect attributed to GC [14]. Platelets that are often contained in abundance in GC can alleviate an accompanying thrombocytopenia in the patient. Residual amounts of plasma, anticoagulants, sedimentation accelerators and erythrocytes have no clinical impact.

3.3 Physiological function

Neutrophils are essential for innate immunity. Their main functions are phagocytosis and elimination of microorganisms. Premedicating donors with growth factors for granulocytes significantly enhances antimicrobial activity of granulocytes [21]. Immediately after transfusion a portion of granulocytes first settles temporarily in the pulmonary circulation, causing transfused granulocytes to appear in their entirety in the peripheral blood with a delay of 1–2 hours, where recovery amounts to around 30–50 % [16]. Further temporary pooling takes place in spleen and liver. The increase of granulocyte count in peripheral blood following GC transfusion varies considerably with dosage and recipient and may entirely be lacking in conditions with high granulocyte consumption. Normal physiological half-life of granulocytes is

5–9 hours which is greatly reduced during febrile processes. Granulocytes collected from donors premedicated with G-CSF have a prolonged half-life [8]. Transfused granulocytes migrate from blood vessels into the infected areas and, following a chemotactical gradient, arrive at the focus of infection where they phagocytize and kill the invading microorganisms [1].

3.4 Storage and shelf life

Because of the neutrophils' autolytic tendency *ex vivo*, GC should be transfused as soon as possible after preparation. However, without agitation GC can be stored at room temperature for a maximum of 24 hours without significant loss of their functionality [13, 23].

3.5 Range of application, dosage, mode of administration

3.5.1 Indications

Numerous case reports and phase-II studies reported a beneficial effect of GC transfusion [19, 20].
A meta-analysis of the therapeutic efficacy of GC transfusion in patients with bacterial sepsis, evaluating seven controlled clinical studies of adults and four studies of neonates, also found significant ($P < .05$) benefit when adequate doses of granulocytes were transfused (see below) [26]. Another meta-analysis of eight randomized controlled trials, involving 310 patients with neutropenia who were treated with GC transfusions, confirmed the benefit (RR = 0.64) regarding mortality when taking six of eight trials into account. However, there was evidence of significant statistical heterogeneity in the trials [24]. If only the results of the four studies transfusing granulocyte doses greater than 1×10^{10} were taken into account, the data indicated a significant benefit (RR = 0.37). Regarding rates of reversal of infection, the analysis of data from four studies found the combined RR of 0.94, again with evidence of heterogeneity.
In spite of the benefit reported for GC transfusion, due to the heterogeneity and small size of the clinical studies available, no well-founded, generally valid conclusions can be drawn from the analysis of the studies regarding the significance of GC transfusion for patients with neutropenia and infection.
The same applies to GC transfusion in neonates with sepsis and neutropenia. Meta-analysis of three comparable studies involving a total of 44 patients showed no significant reduction of mortality in favor of GC transfusion compared with placebo or no GC transfusion [17].
Based on their personal experience, clinicians increasingly hold the opinion that, along with the administration of an adequate amount of neutrophils, the particular time of starting the transfusion plays an important role in the outcome of a GC transfusion, i.e. the timely start of GC transfusion as opposed to using it as last resort in the course of a life-threatening infection [12].
A randomized study of prophylactic granulocyte transfusion reported a significant reduction in the number of febrile days and intravenous antibiotics required [2]. A meta-analysis of randomized controlled trials on the efficacy of prophylactic GC transfusion published between 1970 and 1995 showed that a significant reduction in mortality can be achieved by transfusing adequate amounts of granulocytes that were tested normal in serological compatibility tests [27].

Patients with progredient infections and severe neutropenia of less than 500 neutrophils/µL blood, despite optimal antibiotic and antimycotic therapy for more than 48 hours, can be candidates for granulocyte transfusion, provided that these infections can become life-threatening due to the nature of the etiological agent and the expected duration of the neutropenic state. The same applies to patients with neutropenia of <500 neutrophils/µL and a high risk of acquiring a life-threatening bacterial or fungal infection.	**2 B**

In view of the strain involved for the donor (premedication, infusion of HES, time-consuming apheresis) and the lack of more recent randomized application studies, GC should preferably be administered predominantly in the context of studies.

3.5.2 Special indications

Patients suffering from one of the rare hereditary disturbances of granulocyte function, such as chronic granulomatous disease, might profit from a granulocyte transfusion in progredient life-threatening infections even when the absolute granulocyte count in peripheral blood is within normal limits [29].	**2 C**

3.5.3 Dosage

Investigations involving animal experiments suggest that per GC a minimum of $1.5–2 \times 10^8$ granulocytes/kg body weight shall be transfused for anti-infective therapy [4]. Meta-analysis of controlled clinical studies showed a significant beneficial outcome if adults received $>1 \times 10^{10}$ granulocytes and neonates with bacterial sepsis $>0.5 \times 10^9$ granulocytes/kg body weight [26].
The transfusion frequency varies depending on the individual case and on the clinical state of the patient as well as on the efficacy and compatibility of the transfused granulocytes. The transfusion frequency reported ranges between twice daily in acute severe infections and twice per week as prophylactic transfusion after stem cell transplantation [2, 19].
The effectiveness of a granulocyte transfusion is assessed according to clinical criteria and by determining the increase in the number of granulocytes circulating in peripheral blood 2–4 hours after completing transfusion (increment).
The increase in granulocyte count in peripheral blood following GC transfusion varies considerably, depending on the dose and on the recipient, and may completely fail to appear if granulocyte-consuming processes occur. On physiological grounds, the half-life time in the blood is around 7 hours but is substantially shorter in case inflammatory processes occur.
When success is considered inadequate (increment $<500 \times 10^6$/L), especially in prophylactic transfusions, alloimmunization of the recipient against HLA- and granulocyte-specific antigens should be excluded.

3.5.4 Mode of administration

Because of the large numbers of contaminating donor erythrocytes, granulocyte preparations should be transfused ABO and RhD compatible. A cross-match must be performed. To prevent pulmonary transfusion reactions and reduced transfusion efficiency, a leucocyte compatibility test is required [3, 22]. Older publications have claimed that there was a correlation between the simultaneous administration of amphotericin B and granulocyte transfusions and the occurrence of pulmonary transfusion reactions. To avoid this, it has become established practice to observe an interval of 4–6 hours between the administration of amphotericin B and GC transfusion, even if this correlation has later been challenged [9].

Because a case of fatal graft-versus-host disease was reported in the context of a transfusion of granulocytes [11], GC must be irradiated prior to transfusion with 30 Gy.
To prevent immunization, RhD-negative women of reproductive age should be given anti-D immunoglobulin (10 µg anti-D/mL erythrocyte sediment) prophylactically if the transfusion of RhD-positive GC is unavoidable.
CMV transmissions have also been reported in the context of GC transfusions [28]. Therefore, when used therapeutically, it is recommended to give CMV-seronegative GC from donors who were tested negative for CMV to seronegative recipients [18].
GC transfusion is performed using a transfusion set with standard filter (standardized according to the Act on Medical Devices, pore size 170–230 µm).
Since immediately after transfusion a portion of granulocytes first settles in the pulmonary circulation, causing the transfused granulocytes to appear in the peripheral blood with a delay of 1–2 hours (recovery around 30–50 %) [16], a slow transfusion rate is recommended (e.g. 1×10^{10} cells/hour) [10], although it was reported that GC transfusions over 35–60 min were well tolerated [19].

3.5.5 Refractoriness

Refractoriness is defined as the repeated absence of an adequate post-transfusion increase in granulocytes. The origins of refractoriness can be immunological or non-immunological. *Non-immunological* refractoriness can be caused among other things by high fever, sepsis, splenomegaly or antibiotic therapy. *Immunological* refractoriness must be anticipated especially in polytransfused patients and multiparous women. Its origin may be alloimmunization against HLA class I antigens or other granulocyte antigens (human neutrophil alloantigens, HNA). The frequency of alloimmunization against leucocyte antigens after repeated GC transfusion varies between 20–30 % in the case of iatrogenic neutropenia and up to 80 % in patients with aplastic anemia and chronic granulomatous disease [6, 20, 25]. In such cases of immunological refractoriness, HLA- and/or granulocyte-antigen-compatible granulocytes are to be transfused.

3.6 Adverse reactions

GC from donors pretreated with G-CSF is tolerated well [6]. Fever, chills and skin irritations are the most frequently observed reactions. The triggering of a severe, especially pulmonary transfusion reaction that has often been reported in the past in the context of a granulocyte transfusion has become an extremely rare event today when the leucocyte compatibility test has no pathological results. Additional adverse reactions that may principally occur in the context of a blood transfusion are listed in chapter 11.

3.7 Documentation

See chapter 1.

3.8 References

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4 Plasma for therapeutic use

4 Plasma for therapeutic use

Four licensed preparations are available in Germany, **Plasma, fresh frozen (FFP); Solvent-detergent-treated plasma (SDP); Methylene-blue-photoinactivated plasma (MBPIP**); as well as **Lyophilized human plasma (LHP).**

4.1 Preparation and products

FFP is obtained from whole blood from an individual donor by centrifugation and separation of cells or by apheresis (plasmapheresis or as part of a multicomponent donation). If necessary, leucocyte filtration is performed and the plasma is immediately frozen to below -30°C so that activities of factor V and VIII are optimally preserved [29]. To minimize the risk of transmitting HIV, HBV and HCV, quarantine storage of FFP is mandatory, followed by a second examination of the donor for infection markers of these viruses prior to releasing the plasma for treatment purposes.
Like FFP, **LHP** is a single-donor plasma that is lyophilized after quarantine storage and cell filtration and is only solubilized immediately before use.
SDP is prepared by pooling 500–1,600 individual donations. Treatment with the solvent TNBP and the detergent Triton X-100 completely eliminates lipid-enveloped viruses in SDP like HIV, HBV and HCV. The risk of transmitting the non-enveloped viruses HAV and parvovirus B19 is minimized by testing the individual plasma donations using nucleic acid amplification technique (NAT) and by virus neutralization due to the antibodies present in the plasma pool. As is true for all pooled plasma preparations, the residual risk of transmitting the variant Creutzfeldt-Jakob disease (vCJD) is very low but slightly higher compared to that of preparations from individual donations. Because of ultracentrifugation, SDP is virtually free of blood cells [28, 31].
MBPIP is leucocyte-reduced plasma from individual donors to which methylene-blue was added and which was irradiated by infrared light at a wave-length of 590 nm. After irradiation, methylene-blue is largely removed using a special filter and the plasma is frozen. The methylene-blue/light procedure effectively inactivates most of the clinically relevant viruses. Only viruses that might be present at very high titers, like e.g. parvovirus B19, are possibly not completely inactivated [56].

4.2 Quality criteria

FFP units contain all pharmaceutically active compounds, the clotting factors and inhibitors, at an average activity of 100 U/dL or 100 %, respectively, with widely diverging values corresponding to variability between individuals. Levels of the acute-phase proteins fibrinogen and factor VIII in the plasma show particularly wide variation. FFP obtained by apheresis contains substantially greater activities of factors V, VIII, IX and XI than FFP obtained from whole blood [64]. Depending on the manufacturing process, FFP contains small amounts of leucocytes and platelets [9].
Due to the manufacturing conditions, potencies of clotting factors and inhibitor activities in **SDP** are by approx. 10 % lower than in FFP. Activities of factor VIII, plasmin inhibitor (synonym: alpha-2 antiplasmin) and levels of protein S are even lower. Clinical trials, taking into account all indications for plasma except for plasma exchange in neonates, showed that SDP and FFP do not substantially differ in their tolerance and their influence on the levels of clotting factors [30]. However, the studies involved relatively small numbers of cases and therefore lack the statistical power to detect minor differences in efficacy. Like FFP, SDP

contains normal activities of von Willebrand factor Cleaving Protease (vWF:CP, synonym: ADAMTS13; ADAMTS = a disintegrin and metalloproteinase) which is important for treating thrombotic thrombocytopenic purpura (TTP) [71]. Pooling causes a leveling of variation between individuals regarding plasma levels and a dilution of any antibodies that may be present.
Like FFP, **MBPIP** is a single-donor preparation the plasma protein levels of which are subject to natural variation between individuals. Photo-oxidation of fibrinogen in the presence of methylene blue and under the influence of light causes a reduction of coagulable fibrinogen levels and of factor VIII activities by 20–35 % [70]. Activities of coagulation factors V, IX and XI may also decrease by more than 10 %. To date, there are no data derived from large randomized trials regarding MBPIP efficacy and tolerance [70].
In blood group O and A(2) preparations the levels of clotting factor VIII and von Willebrand factor (vWf) are on average lower by approx. 25 % than in blood group A(1), B or AB plasma units.
The plasma preparations described are free of activated clotting factors and can therefore also be used in patients with activated hemostasis, e.g. in disseminated intravascular coagulation (DIC).
To date, no data are published regarding **LHP**.

4.3 Storage, shelf life and transportation

Except for LHP (storage temperature at +4°C to +25°C), plasma preparations have to be stored in suitable deep-freezers or freezers that continually monitor and document the temperature and are fitted with an alarm device. Under no circumstances may the products be thawed, either partially or completely, during transportation, therefore they must be transported in deep-frozen form using validated systems. Deep-frozen plasma units have to be handled with great care to avoid damage to the plastic bags. After thawing or reconstitution with water, respectively, plasma preparations must be administered within six hours.

4.4 Application: general principles, mode of administration, dosage, indications

4.4.1 General principles

Principally plasma therapy is indicated if

- in complex coagulopathies plasma activities of clotting factors and inhibitors have to be raised prior to invasive surgery because of apparent bleeding or the threat of severe hemorrhage and/or
- plasma activities of clotting factors V and XI or of vWF:CP (synonym: ADAMTS13) have to be raised since no licensed concentrates are available yet for substitution.

Other congenital coagulopathies are principally treated with coagulation factor concentrates, e.g. hemophilia A is treated with factor VIII concentrates. If in emergencies the effect of oral anticoagulants or of a severe vitamin K deficiency is to be reversed, the more rapid and more effective prothrombin complex concentrates (PCC) should be used for this purpose. But PCC concentrates are no replacement for plasma when treating complex coagulopathies since they do not contain the following clotting factors: fibrinogen, factor V, factor VIII, vWf, factor XI and factor XIII.

Requirements for an efficient plasma therapy are
- laboratory confirmation of a suspected coagulopathy by using prothrombin time (PT) and, if necessary, activated partial thromboplastin time (aPTT), level of coagulable fibrinogen as well as determination of the single factors in congenital factor V or factor XI deficiency (exceptions: plasma exchange, urgent indication in massive transfusion),
- specification of the dose according to the objective of the therapy
- control of transfusion efficacy following plasma transfusion by laboratory analyses
- specification of suitable transfusion intervals.

For the following reasons it is not very efficient to treat coagulopathy with plasma:
- Some coagulation factors have a short biological half-life (factor V: 12–15 h; factor VII: 3–6 h). The substitution effect is not sustained over long periods of time, therefore short transfusion intervals of 4–12 h are necessary in order to achieve and maintain hemostatically effective levels in plasma.
- Patients with acquired coagulopathies often show increased turnover regarding clotting factors and inhibitors due to consumption and/or loss or dilution and consequently an abbreviated and diminished efficacy of plasma in comparison to patients in the steady-state.
- A significant increase in clotting factor and inhibitor levels in plasma requires the transfusion of large volumes. Often the required dose cannot be administered due to the risk of hypervolemia.

4.4.2 Mode of administration

Transfusion is performed intravenously, using peripheral veins if possible, by using a transfusion device standardized according to the Act on Medical Devices that is provided with a standard filter (usually with a pore size of 170–230 µm) to retain blood clots. Several plasma units can be transfused using the same set of transfusion instruments within 6 hours after thawing of frozen plasma and resolving of lyophilized preparations. Ready-to-use plasma may not be supplemented with drugs or intravenous fluids. On selecting the speed of transfusion and the dose, the risks of **hypervolemia**, **hypothermia** and **citrate intoxication** must be taken into account. Warming of plasma prior to or during transfusion using licensed equipment is required in patients
- undergoing massive transfusion,
- with hypothermia prior to transfusion,
- with chronic cold agglutinin disease,
- with high titers of cold antibodies,
- who develop vasospasms when given chilled blood or
- in preterm and full-term infants and children.

ABO-typed fresh frozen plasma (FFP), lyophilized human plasma (LHP) and SDP are administered as ABO-identical transfusions. Serological compatibility tests are not necessary. Plasma preparations marked as universally compatible can be administered without regard to the ABO blood group. In exceptional cases ABO-typed FFP, LHP or SDP may also be administered as ABO-nonidentical but compatible transfusion. To generally use AB plasma for all patients is out of the question since the amount of AB plasma available is very limited (in Central Europe the prevalence of blood group AB is 4 %).

Table 4.4.2: Compatibility scheme of plasma depending on the ABO blood group of the recipient

Patient blood group	Compatible plasma blood groups
A	A or AB
B	B or AB
AB	AB
O	O, A, B or AB

In case a transfusion is urgent the physician performing the transfusion has to take into account the time needed for thawing of the frozen plasma (around 30 min) and for transport.

4.4.3 Dosage

The necessary dose is calculated as follows:

1 mL plasma/kg body weight increases the factor and inhibitor levels or the prothrombin time (PT)

- by 1 U/dL or by 1 % in cases when increased turnover is lacking
- by 0.5–1.0 U/dL or by 0.5–1.0 % in cases of increased turnover (level of fibrinogen: by 0.02–0.03 g/L or 2–3 mg/dL)

Example: patient with a prothrombin time of 40 %; target level: 60 % (difference 20 %); body weight 75 kg; plasma dose = 75 kg × 20 mL plasma/kg = 1,500 mL, corresponding to 6 units of FFP of 250 mL or 8 units of SDP of 200 mL (dose rounded). When using SDP it is recommended to increase the dose by approx. 10 % in comparison to FFP because of a lower concentration of clotting factors.

Even high doses of plasma only result in a moderate increase of clotting factor and inhibitor activities in the recipient [37]. For an effective plasma therapy a sufficiently high dose is therefore required that has to be transfused rapidly: a minimum of 15 mL/kg body weight, infusion rate 30–50 mL/min. In adults any dose below 600 mL (2 to 3 units) is inadequate. In patients with impaired renal function, severe liver damage or cardiopulmonary insufficiency the plasma dose is limited due to the risk of hypervolemia.

An acute thrombotic thrombocytopenic purpura (TTP) can only be treated effectively by **plasma exchange**. For this purpose the major part of patient plasma is removed using automated plasmapheresis and replaced by FFP or SDP. 100 or 150 % of plasma exchange requires plasma doses of 40 or 60 mL/kg body weight. Plasma exchange can also be necessary in patients with severe factor V and factor XI deficiency prior to major surgery in order to boost factor V and factor XI levels to hemostatically effective plasma levels [3, 51].

There are wide variations in the biological half-life of clotting factors and inhibitors contained in plasma. When treating severe congenital factor V and factor XI deficiency, replacement intervals are calculated according to the half-life of these clotting factors (factor V: 12–15 h; factor XI: 60–80 h). Often TTP is caused by an vWf:CP (ADAMTS13) deficiency or by an inhibitor against this protease whose half-life is 2–4 days [22]. Nonetheless, in cases of the very rare congenital TTP prophylactic plasma transfusions every 2 to 4 weeks are sufficient to avoid TTP episodes [20].

Clinically relevant plasmin inhibitor deficiency has to be treated with antifibrinolytic agents since the concentration of plasmin inhibitor cannot be boosted sufficiently by plasma therapy alone [18].

4.4.4 Indications

As far as there are any controlled trials at all on the treatment of certain clinical pictures with plasma preparations, there are just a few randomized clinical trials on the use of FFP and SDP [67].

4.4.4.1 Loss and dilution coagulopathy in severe acute blood loss

Cohort trials in patients with severe acute blood loss of more than 100 % of the circulating blood volume who were transfused with massive amounts of volume replacement fluids and plasma-poor RBC concentrates showed a hemostatically significant drop in the fibrinogen level to below 1.0 g/L and an prothrombin time values below 50 % [17, 32, 39, 49, 50]. Below these threshold values **diffuse microvascular bleeding** is to be anticipated. However, there are no controlled trials on the determination of effective plasma doses.
In patients with hypothermia it is possible to determine false shortened PT, activated partial thromboplastin time (aPTT) and false low fibrinogen levels since laboratory analysis is performed at 37°C [63]. In case patients receive either hydroxyethyl starch preparations or dextran and the fibrinogen level is determined using the so-called "derived" fibrinogen method, an intervention level of 1.5 g/L instead of 1.0 g/L should be chosen [33].
Based on a number of aspects, plasma transfusion should be indicated early in cases of major continuous blood loss:

- Blood loss is difficult to quantify in routine clinical practice.
- If blood loss is rapid, normovolemia and hemoglobin concentration of at least 60 g/L are difficult to maintain.
- **Consumption** of coagulation factors at the site of large wound surfaces and/or by DIC as well as **hypothermia** and **acidosis** can aggravate loss and dilution coagulopathy derived from crystalloid and colloid volume replacement fluids [15, 27].
- Data on prothrombin time, aPTT and levels of coagulable fibrinogen (and platelet count) are not always available in a timely fashion.

In acute blood loss the transfusion of plasma is indicated under the following circumstances:

- continuous blood loss of more than 100 mL/min or continuous demand for substitution by more than 2 RBC concentrates every 15 min, following transfusion of at least 4–6 RBC concentrates;
- continuous blood loss, in particular due to apparent microvascular bleeding, following transfusion of 4–10 RBC concentrates, if data on PT, aPTT and possibly levels of coagulable fibrinogen are not available in a timely fashion;
- prothrombin time <50 % or aPTT >45 s and/or fibrinogen <1 g/L (method according to Clauss). In this connection it must be taken into account that different reagents show differences in sensitivity to clotting factor deficiencies as well as other interfering factors, e.g. due to heparin or volume replacement fluids, especially for aPTT. The reference range in different aPTT reagents also varies widely.
- Rapid transfusion of plasma with 15–20 mL/kg body weight at a rate of 30–50 mL/min is preferable to a schematic administration of 1 unit of plasma for every 1–3 units of RBC [34].
- The therapeutic goal is to stop diffuse microvascular bleeding or rather to prevent the occurrence of microvascular bleeding by boosting PT to a minimum of 50 % and of the fibrinogen level to a minimum of 1 g/L, and by shortening of aPTT to levels <45 s.

In cardiac surgery the prophylactic postoperative administration of plasma to decrease postoperative blood loss is not indicated [11].

Plasma should be rapidly transfused with a dose of 15–20 mL/kg body weight in patients with severe acute blood loss and apparent or impending diffuse microvascular bleeding that is caused in part by coagulopathy with prothrombin time (PT) <50 % or aPTT >45 s and/or fibrinogen levels of <1 g/L.	**1 C**
Plasma shall **not** be transfused postoperatively as prophylaxis in patients undergoing cardiopulmonary bypass surgery if PT >50 % and fibrinogen levels >1 g/L and in the absence of diffuse microvascular bleeding.	**1 A**

4.4.4.2 Liver damage

End-stage liver disease is accompanied by complex failure of hemostasis, also including thrombocytopenia, platelet dysfunction and accelerated fibrinolysis, in addition to coagulopathy due to impaired synthesis and/or increased turnover of clotting factors and inhibitors [37]. In order to determine the severity of coagulopathy, PT is used and can be expressed in seconds, in percent activity of the standard value, as ratio values (of the clotting time of the patient plasma compared to that of normal pool plasma) and as International Normalized Ratio (INR). In liver disease only PT expression in percent of the standard value is comparable between different thromboplastin reagents and should be referred to, rather than seconds or INR [35, 61]. Since not only coagulation factors but also inhibitors have reduced levels, the disposition to bleeding is often less pronounced than expected from the reduced PT level [44, 69]. In patients with liver disease the following applies for all clinical situations: The threshold value for PT or for other parameters in hemostasis at which bleeding complications are significantly reduced by a therapeutic intervention using plasma has not yet been determined as well as the plasma doses necessary for sufficient hemostasis. Since the intravascular blood volume in patients with liver dysfunctions is often set at high values due to hyperaldosteroism, the risk of hypervolemia is higher after transfusion of large doses of plasma than in other clinical settings.

Liver transplantation is not a mandatory indication for plasma transfusion. In the context of liver transplantation the demand in blood products including FFP or SDP depends primarily on the surgical technique and the duration of surgery. Some centers never require plasma in the context of liver transplantation [14, 55].

In patients with severe liver dysfunction who have to undergo **cholecystectomy**, **laparoscopic cholecystectomy**, **partial hepatic resection** or other **medium or major surgical interventions**, there is an association between PT and postoperative bleeding [2, 21, 43, 65]. The purpose of plasma therapy is to raise PT levels to more than 50 % [43]. To do this, single doses of at least 20 mL/kg body weight are usually required [72]. Clinical observation of patients without severe liver dysfunction suggest that partial hepatic resection can be performed without plasma transfusion even at PT levels between 35 and 40 %, unless major peri- or postoperative bleeding occurs [43, 57, 65].

In **acute liver failure** the prophylactic administration of plasma apparently does not improve the prognosis [23].

Fine-needle liver biopsy under ultrasound guidance and monitored by laparoscopy is not associated with a higher rate of bleeding complications in patients with liver dysfunction and PT levels of below 50 % [12, 16, 46]. Therefore a prophylactic administration of plasma is not indicated prior to liver biopsy at PT levels <50 %, while postoperative monitoring of bleeding from the biopsy channel is advisable. A decrease in the PT level down to 30 % does not lead to a higher rate of bleeding in patients after **paracentesis** or **thoracentesis**, so that the prophylactic administration of plasma is not indicated in these cases [47]. **Central venous cannulation** in patients with PT levels <10 % (INR >5.0) leads to a higher incidence of superficial hematoma, but not to prolonged bleeding from the needle track [19]. The prophylactic transfusion of plasma is not indicated.

In patients with liver dysfunction and coagulation disorders plasma could be transfused when PT is below 50 % and major bleeding occurs at a dose of 20 mL/kg body weight. The objective of treatment is to arrest bleeding and to increase PT to at least 50 %.	**2 C**
In patients with liver dysfunction and coagulation disorders plasma could be transfused when PT is below 50 % and major bleeding occurs at a dose of 20 mL/kg body weight. The purpose of treatment is to increase PT to at least 50 % until primary wound healing is complete.	**2 C**
In patients undergoing liver transplantation with PT ≥50 % plasma should not be administered perioperatively as prophylaxis.	**2 C+**
Plasma shall not be transfused as prophylaxis in patients with liver dysfunction and coagulation disorders in the context of fine-needle liver biopsy, after paracentesis, thoracentesis or central venous cannulation.	**1 C+**

4.4.4.3 Disseminated intravascular coagulation

There are no controlled trials on the efficacy of plasma transfusion in patients with disseminated intravascular coagulation (DIC) except for a small controlled study in neonates with DIC that found no effect regarding survival of either exchange transfusion or administration of fresh-frozen plasma and platelets [26]. In patients with DIC and severe hemorrhage, that are aggravated among other things by severe coagulopathy, high doses of plasma shall be transfused repeatedly, e.g. 20 mL/kg body weight [48]. The purpose of this treatment is maintenance of hemostatically effective minimum levels corresponding to PT levels of around 50 % [10].

Administration of plasma has no beneficial effect on the prognosis of patients with acute pancreatitis without DIC [40, 41].

Plasma could be transfused at a dose of 20 mL/kg body weight in patients with disseminated intravascular coagulation (DIC) and coagulopathy with PT <50 % and/or fibrinogen levels <1 g/L **and** severe hemorrhage.	**2 C**
Plasma should not be administered prophylactically in patients with disseminated intravascular coagulation (DIC) and coagulopathy with PT <50 % and/or fibrinogen levels <1 g/L, who do not have to undergo surgery and have no injuries with a risk of bleeding.	**2 C**
Plasma shall not be transfused in patients with acute pancreatitis without DIC and without coagulopathy with PT <50 %.	**1 A**

4.4.4.4 Thrombotic thrombocytopenic purpura (TTP) and adult hemolytic uremic syndrome (HUS)

TTP and adult HUS are summarized under the **microangiopathic hemolytic anemias (MHA)**. Probably plasma exchange is only effective in the forms of TTP occurring most frequently that are characterized by a vWf cleaving protease (vWf:CP) deficiency (synonym: ADAMTS13) or by an inhibitor against vWf:CP. By exchanging plasma, the antibodies against vWf:CP are removed and lacking vWf:CP is substituted. Since the various clinical pictures cannot be safely differentiated at the time when a decision on the therapy is required, in all cases plasma exchange is started. Plasma exchange has led to a significant reduction in the 2-year mortality from >90 % down to 20–30 % and is clearly superior to plasma transfusion alone [4, 62, 66].

- Daily plasma exchange with 40–60 mL/kg body weight until platelet count is >100/nL and still rising or at least no longer dropping. By this the 2-year mortality of patients with acute

TTP could be reduced from >95 % down to 20–40 %. In contrast to plasma exchange, plasma infusion does not lower the rate of mortality satisfactorily [62].

- Relapses require to repeat a course of daily plasma exchange.
- If the response rate is low an attempt can be made to perform plasma exchange twice per day.
- Plasma infusions are only effective in the very rare **congenital form of TTP** in preventing relapses during remission. In this connection plasma infusions of 10 mL/kg body weight given prophylactically every 1–3 weeks are sufficient, at a biological half-life of vWf:CP of 50–80 h [38].

In patients with acute thrombotic thrombocytopenic purpura (TTP) or adult hemolytic uremic syndrome (HUS) daily plasma exchange shall be performed with 40–60 mL/kg body weight until platelet count is >100,000/µL. If the response rate is low an attempt to perform plasma exchange twice per day is indicated.	**1 A**
In patients with severe congenital von Willebrand factor cleaving protease (vWf:CP; ADAMTS13) deficiency and TTP plasma can be transfused every 1–3 weeks in order to prevent TTP relapses.	**2 C+**

4.4.4.5 Hereditary factor V deficiency and hereditary factor XI deficiency

Severe hereditary factor V deficiency with residual activities below 5 % is a very rare event. Prior to surgery or invasive procedures and in cases of severe hemorrhage 15–20 mL plasma/kg body weight are transfused in order to maintain hemostatically effective factor V levels of at least 15–20 %. Because of the short biological half-life of factor V (12–15 h) plasma has to be transfused in 12-hour intervals [6]. In cases of severe hemorrhage and a risk of volume overload plasma exchange can be necessary, especially in children [3]. The efficacy of an additional therapy with platelet concentrates because of the high amounts of factor V in platelets is doubtful. A therapy with activated recombinant coagulation factor VIIa alone or in addition to plasma may be reasonable [25].

In **severe hereditary factor XI deficiency** (residual activity below 5 %) and **mild factor XI deficiency with a disposition to severe bleeding** 20 mL plasma/kg body weight are transfused prior to surgery, invasive procedures and in cases of severe bleeding in order to achieve a hemostatically effective minimum level of 20 %. Because of the long biological half-life of factor XI (around 60 h) plasma transfusions in 24-hour intervals are usually sufficient [6]. In mild factor XI deficiency with a disposition to severe bleeding plasma has to be transfused when fibrin sealant, desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis. In rare cases plasma exchange may be necessary to avoid volume overload [51]. In Germany factor XI concentrates are not available and are suspected to cause thromboembolic complications [5]. Recombinant factor VIIa could represent an alternative to plasma [52].

In patients with severe hereditary **factor V deficiency** (residual activity <5 %) plasma shall be transfused with a dose of 15–20 mL/kg body weight perioperatively, in the context of invasive procedures or in cases of severe bleeding with the objective of maintaining hemostatically effective plasma levels of 15–20 %.	**1 C+**
Plasma exchange with 40 mL/kg body weight could be performed perioperatively or in the context of invasive procedures in patients with severe hereditary **factor V deficiency** (residual activity <5 %), in whom a hemostatically effective factor V level in plasma cannot be achieved by plasma transfusion.	**2 C**

In patients with severe hereditary **factor XI deficiency** (residual activity <5 %) plasma shall be transfused with a dose of 20 mL/kg body weight perioperatively, in the context of invasive procedures or in cases of severe bleeding with the objective of maintaining hemostatically effective plasma levels of 20 % when local measures (e.g. fibrin sealant), desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis.	**1 C+**
Plasma exchange with 40 mL/kg body weight could be performed perioperatively, in the context of invasive procedures or in cases of severe bleeding in patients with severe hereditary **factor XI deficiency** (residual activity <5 %), in whom a hemostatically effective plasma factor XI level cannot be achieved by plasma transfusion.	**2 C**
In patients with mild hereditary **factor XI deficiency** and a disposition to severe bleeding plasma shall be transfused with a dose of 20 mL/kg body weight perioperatively or in the context of invasive procedures when local measures (e.g. fibrin sealant), desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis.	**1 C+**

4.4.4.6 Special indications in pediatric patients

The prophylactic application of 3–20 mL plasma/kg body weight in **preterm infants** on their first and second day of life has no effect on the frequency and severity of cerebral hemorrhage, mortality and the long-term outcome [54].

Plasma infusions have no beneficial effect on the clinical course of **hemolytic uremic syndrome (HUS)** in children [42, 60].

Partial plasma exchange transfusion has no beneficial effect compared to exchange transfusion with volume substitutes when treating the **hyperviscosity syndrome in neonates with polycythemia** [13, 36, 68].

In newborn infants and small children undergoing **cardiopulmonary bypass surgery** or **extracorporeal membrane oxygenation** RBC concentrates and plasma and possibly platelet concentrates are used as priming fluid, because there is a disparity between the blood volume of the child and the volume used to prime the oxygenator. In a prospective randomized trial comparing plasma with albumin as priming fluid of the heart-and-lung machine there was a tendency to less blood loss in the plasma group [53]. Another very small prospective randomized trial showed no difference between the groups with or without plasma in the prime [45].

For the same reasons as in cardiopulmonary bypass surgery, an **exchange transfusion in neonates** with severe hemolysis or hyperbilirubinemia is performed using RBC concentrates that are mixed with compatible plasma.

In newborn infants and small children undergoing cardiopulmonary bypass surgery or extracorporeal membrane oxygenation plasma combined with RBC concentrates could be used as priming fluid.	**2 C**
An exchange transfusion shall be performed in neonates using RBC concentrates and plasma.	**1 C+**
Plasma shall not be transfused in preterm infants as prophylaxis with the objective of preventing intracerebral hemorrhage.	**1 A**
Plasma shall not be transfused in children with hemolytic uremic syndrome without coagulopathy.	**1 B**
Partial exchange transfusion in neonates with polycythemia and hyperviscosity syndrome shall not be performed using plasma.	**1 B**

4.4.4.7 Lack of indication for therapy with plasma ("non-indication")

In Table 4.4.4.7 below clinical pictures and symptom complexes are listed in which plasma should not be applied or is possibly ineffective.

Table 4.4.4.7: Lacking indications for plasma treatment

• Prophylactic postoperative administration of plasma in patients undergoing cardiopulmonary bypass surgery with PT >50 % or fibrinogen levels >1 g/L and in the absence of signs of microvascular bleeding [11]	**1 A**
• Prophylactic perioperative administration of plasma in patients undergoing liver transplantation if PT ≥50 % [14, 55]	**2 C+**
• Prophylactic administration of plasma prior to liver biopsy, paracentesis, thoracentesis or central venous cannulation in patients with liver dysfunction and coagulopathy [12, 16, 19, 46, 47]	**1 C+**
• Prophylactic administration of plasma in acute liver failure without bleeding complications with the objective of improving the outcome [23]	**1 B**
• Disseminated intravascular coagulation (DIC) without coagulopathy and/or without bleeding complications [26]	**2 C**
• Acute pancreatitis [40, 41]	**1 A**
• Prophylactic administration of plasma in preterm neonates [54]	**1 A**
• Partial plasma exchange transfusion in neonates with polycythemia and hyperviscosity syndrome [13, 36, 68]	**1 B**
• Hemolytic uremic syndrome in children [42, 60]	**1 B**
• Burns in the absence of bleeding complications and without coagulopathy [1, 7, 8]	**1 B**
• Plasma exchange in patients with Guillain Barré syndrome [58, 59]	**1 A**
• Primary volume substitution • Parenteral nutrition • Substitution of immunoglobulins • Coagulation factor and inhibitor deficiencies that can be treated more effectively and with better tolerance using factor concentrates, e.g. hemophilia A and B, severe coumarin-induced hemorrhage, with the exception of emergency situations if concentrates are not available in time or if there are contraindications against concentrates (e.g. PCC in heparin-induced thrombocytopenia type II) • Disorders of hemostasis that on principle cannot be treated effectively with plasma: thrombocytopenia, platelet disorders, hyperfibrinolysis	**1 C+**

4.5 Absolute and relative contraindications

In patients with **plasma intolerance** and confirmed **IgA deficiency** plasma is contraindicated. In the quite frequent hereditary IgA deficiency (prevalence 1:650) anti-IgA antibodies can be present that were implicated to cause anaphylactic reactions to blood products after application of IgA-containing blood products. However, the association is controversial [24].

4.6 Adverse reactions

Citrate intoxication occurs following transfusion of high doses of plasma in the context of a massive transfusion or plasma exchange in patients with impaired liver function. This can be accompanied by reduced ventricular function, arrhythmia and increased neuromuscular excit-

ability. Since citrate is metabolized to bicarbonate, quite often during massive transfusion a **metabolic alkalosis** is observed that is difficult to manage.
There is a risk of **volume overload** in particular in patients with renal insufficiency, cardiopulmonary insufficiency and liver disease as well as in preterm and full-term neonates.
The development of **inhibitors against coagulation factors** following the application of plasma is highly unlikely. Patients with severe factor V or factor XI deficiency must be considered to be at risk if the residual activities of these coagulation factors are below 1 U/dL.
For further particulars, especially regarding transfusion-related acute lung injury (TRALI), see chapter 11.

4.7 Documentation

According to article 14 of the German Transfusion Act, there is an obligation to perform a patient- as well as product-related batch documentation for plasma for therapeutic use.

4.8 References

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5 Human albumin (HA)

5 Human albumin (HA)

5.1 Preparation

Human albumin (HA) is prepared from human pool plasma by alcoholic precipitation [12]. For pathogen inactivation albumin is pasteurized for at least 10 hours at +60°C (see also European Pharmacopoeia).

5.1.1 Quality criteria

Human albumin solutions for transfusion are obtained from human plasma proteins as sterile preparations which, according to the monograph "Human albumin solutions" of the European Pharmacopoeia, must contain a minimum of 95 % albumin. Aside from human albumin, preparations currently available have a sodium concentration between 87 and 160 mmol/L and a potassium concentration below 2 mmol/L. Because of variable electrolyte concentrations contained in albumin preparations it is required to monitor the balance of water and electrolyte, especially when administering large amounts. Up to 3.2 g/L sodium octanoat and up to 4.29 g/L acetyltryptophan are added as stabilizers. All albumin preparations currently available contain less than 200 µg/L of aluminum.
Albumin solutions do not contain isoagglutinins or blood group substances and can thus be administered independent of the recipient's blood group. They do not contain oxygen carriers, coagulation factors or antibodies. Based on the manufacturing process and the pathogen inactivation involved, albumin preparations are considered to carry no risk of transmitting infections.

5.2 Active constituents

Human albumin solutions are manufactured as two preparations, namely as isooncotic (5 %) or as hyperoncotic (20–25 %) infusion solutions. The effective component is human albumin with a molecular weight of around 66 kD consisting of 584 amino acids of known sequence. Albumin preparations intended for clinical use may contain monomers along with dimers and, in small amounts, polymers of albumin. According to the European Pharmacopoeia, a maximum content of 10 % polymers and aggregates is permitted.

5.3 Physiological properties and function

The reference concentration of albumin in plasma ranges between 33 and 52 g/L. Albumin is synthesized exclusively in the liver. The normal rate of albumin synthesis is approximately 0.2 g/kg body weight/day. Extravascular colloid osmotic pressure (COP) in the liver is considered to be the factor regulating synthesis. Albumin synthesis may be suppressed by an exogenous supply of substances affecting COP, i.e. natural or synthetic colloids [36]. A lasting increase in albumin concentration can only be achieved by suitable nutrition therapy.
Under physiological conditions a steady state exists between albumin synthesis and metabolism. The amount of albumin metabolized daily is proportional to the plasma concentration, i.e. a fixed percentage of approximately 10 % of plasma albumin content is metabolized per day [29, 31]. Its half-life changes inversely proportionately to the plasma albumin concentration; i.e. a decreased albumin content results in increasing its half-life, whereas increasing albumin concentrations cause the metabolic rate to increase by up to 50 %.

The distribution of albumin in the human body is adequately described by a 2-compartment model where about 40 % is taken up by the intravascular and 60 % by the extravascular space [29, 36, 47]. The balance between plasma and interstitial space is established at varying rates with respect to the two subcompartments of the extravascular albumin pool [57]. The total exchange rate between intra- and extravascular volume amounts to approximately 5 % of the intravascular albumin content per hour (so-called transcapillary escape rate). The transcapillary escape rate of albumin is increased in arterial hypertension, myxedema, burns, liver cirrhosis and diabetic microangiopathy [38, 39].

The physiological function of albumin can be summarized as follows:
1. volume effect (colloid oncotic effect),
2. transport function

Volume effect (colloid osmotic pressure [COP])
Albumin has a high capacity for binding water (approximately 18 mL/g), an intravasal residence time of approximately 4 hours presupposing physiological capillary permeability [57] as well as an *in vivo* half-life of approx. 18–21 days [29, 31, 57]. At equal concentrations the oncotic (colloid osmotic) effect of albumin is about 2.5 times greater than that of globulins which have an average molecular weight of around 170 kD [28]. Although albumin comprises only about 50–60 % of the total protein content of plasma, it is responsible for about 80 % of intravascular COP.

Transport function
Because of its high net charge albumin possesses excellent binding capacities, among other things for water, calcium, sodium and trace elements. Albumin is also an important transport protein for fatty acids, bilirubin and hormones as well as for many drugs. Although these transport qualities are of physiological and pharmacological importance, no therapeutic indication is documented for administering human albumin to improve the transport function.

5.4 Storage, shelf life, packaging sizes

Human albumin preparations can be stored at room temperature, although storage temperature for human albumin solutions should not exceed 25°C according to expert information (Summary of Product Characteristics, SPC). Therefore it is not possible to administer prewarmed solutions.
The European Pharmacopoeia merely requires storage conditions under protection from light.
Human albumin solutions can be administered by a peripheral or central venous line and are well tolerated. No daily maximum permissible dose is specified for human albumin. It is available as 5 % or 20 % solutions in ampoules or infusion bottles. Therefore no rapid supply ("pressure infusion") is possible with human albumin to rapidly compensate for acute volume loss.

5.5 Indications

Clinical application of albumin derives from its physiological functions. Possible areas of application are:
1. hypovolemia
2. hypoalbuminemia
3. other areas of application (e.g. transport function).

5.5.1 Acute volume replacement

Albumin is the protein with the highest concentration in plasma and is the main factor responsible for maintaining COP. To achieve a normalization or an increase of COP was therefore considered as one possible indication for the administration of albumin solutions. However, this can also be achieved in a similar manner by using synthetic colloids.
A meta-analysis of the "Cochrane Injuries Group Albumin Reviewers" published in 1998 has led to a negative assessment regarding the use of human albumin [51]. The use of albumin was associated with an increased absolute risk of mortality in critically ill patients (one extra death for every 17 patients treated with albumin). The authors concluded that the continued use of human albumin should be challenged. Another meta-analysis investigated the effect of albumin administration on mortality when compared with other plasma substitutes [61]. The analysis included volume substitution in surgery/trauma (27 trials), burns (4 trials), neonates (6 trials), in patients with ascites (5 trials), hypoalbuminemia (5 trials) as well as other non-specified indications (8 trials). A total of 55 trials with a total of 3,504 patients were investigated, and none of the attributes analyzed ("outcome", "mortality") showed a significant difference between the treated groups, not even between sub-groups. In contrast to the meta-analysis of the "Cochrane Injuries Group Albumin Reviewers" of 1998, albumin administration was not associated with excess mortality, but there was also no benefit regarding survival (mortality) when comparing albumin with other volume substitutes (e.g. synthetic colloids).
Note: In cases where administration of human albumin in treating hypovolemia showed no benefit when compared with alternative volume substitution, a "*non-recommendation*" was made based on the fact that it is impossible to perform a rapid infusion ("pressure infusion") of human albumin stored at room temperature. According to the individual level of recommendation, it may be reasonable in particular cases to pursue a deviating course of treatment.

5.5.1.1 Acute volume replacement in the perioperative phase

Neither benefit nor harm was shown when using human albumin for increased hemodynamic stability in the perioperative phase, as compared to a crystalloid or any other colloid volume substitute [5, 6, 57, 61].

Human albumin should not be used as substitute in hypovolemia or for increased hemodynamic stability of adult patients in the perioperative phase.	**2 A**

5.5.1.2 Acute volume replacement in intensive-care patients

The largest trial currently available (approx. 7,000 patients), using a prospective, randomized, double-blind design, compared volume substitution in intensive-care patients by administering either crystalloid substitutes or human albumin 4 % (SAFE Study [18]). No significant beneficial effect of human albumin was determined regarding either morbidity and mortality or days spent in ICU or in hospital.
According to the Guideline for Diagnosis and Therapy of Sepsis [44], it is not recommended to administer human albumin for volume replacement, also in critically ill patients with severe sepsis and septic shock.

Human albumin is not recommended as substitute in hypovolemia or for increased hemodynamic stability of adult intensive-care patients.	**1 A**

5.5.1.3 Acute volume replacement in burn patients

Trauma caused by burning is viewed as a potential indication for administration of albumin solutions, however, not during the first 24 hours after burning. In this context, preference is given to crystalloid solutions as volume replacement [7].

The administration of human albumin for increased hemodynamic stability of burn patients is not recommended during the first 24 hours. In the further course of treatment administration of human albumin may be reasonable.	**2 B**

5.5.1.4 Acute volume replacement in trauma patients

In trauma patients with (severe) hypovolemia no rapid compensation is possible using human albumin (pressure infusion not possible). No benefit regarding survival is documented when compared to other volume substitutes.
In patients with traumatic brain injury a *post hoc* follow-up analysis of data from the SAFE study showed a significantly increased mortality for the group treated with human albumin as opposed to the non-albumin group [48].

The administration of human albumin for increased hemodynamic stability of patients with traumatic brain injury is not recommended.	**2 B**

5.5.1.5 Acute volume replacement in pregnant women

There are hardly any reports on any kind of volume substitution (including human albumin) in pregnant women. Severe hypovolemia during the first months of a pregnancy (e.g. in the context of surgical intervention) is a possible indication for albumin administration. In contrast, administration of modern synthetic volume substitutes is an established procedure in clinics to correct hypovolemia during delivery (e.g. during Cesarean delivery).

In pregnant women human albumin could be administered in cases of severe hypovolemia during early pregnancy.	**2 C**
It is not recommended to administer human albumin exclusively for volume substitution in the course of a Cesarean delivery.	**2 C**

5.5.1.6 Acute volume replacement in cardiac surgery

Human albumin is considered to be indicated for volume replacement in cardiac surgery. In particular, the risk of excessive bleeding when administering older synthetic colloids (dextrane, older HES preparations) is seen as the rationale for the application of human albumin [3, 9, 13, 27], since no relevant substance-specific alterations regarding coagulation have been reported for human albumin use. The majority of the studies reporting benefits when using human albumin solutions in the context of cardiac surgery originate from the United States. However, no modern synthetic colloids with few adverse reactions are available there. Therefore the results of a retrospective analysis of data that reported a lower incidence of mortality in cardiac surgery patients when using human albumin [52] must be interpreted with caution, because no specifics were given for the volume substitutes used as an alternative. In a meta-analysis published in 2001 Wilkes and co-workers [62] compared the risk of post-operative bleeding following administration of older HES preparations (with either high or medium molecular weight [Mw] and a high degree of substitution [MS]) in the context of cardiac surgery. Human albumin and HES, respectively, were administered as volume replacement prior to and after cardiopulmonary bypass (CPB) and also as constituents of the priming fluid of the extracorporeal circuit (heart-and-lung machine, HLM). In nine trials involving 354 patients the effects of a first-generation starch (Mw 450 kD, MS 0.7) and albumin, respectively, were compared. Postoperative blood loss was significantly lower in patients exposed to albumin than in those exposed to HES. If in contrast a more modern synthetic colloid solution was administered (Mw 200 kD, MS 0.5; 8 trials involving 299 patients), there was no longer a statistically significant difference in comparison to albumin under the conditions of the systematic meta-analysis.

In cardiac surgery patients the administration of human albumin for compensation of hypovolemia and for increased hemodynamic stability is not recommended.	**1 A**

5.5.1.7 Acute volume replacement in patients with bleeding disorder and patients with manifest bleeding due to coagulopathy

In patients with altered coagulation (e.g. polytrauma, patients with septicemia) or in patients in whom coagulation disorders are anticipated (e.g. cardiac surgery patients with extracorporeal circulation) the application of albumin is possible since no substance-specific alterations regarding coagulation have been reported for human albumin use. However, in such situations other volume substitutes have also been administered without seriously altered coagulation function. Similarly the administration of large doses of albumin or other volume substitutes leads to hypocoagulopathy due to dilution.

In patients who are at risk of bleeding the administration of albumin for volume replacement is not recommended.	**2 C**

5.5.1.8 Acute volume replacement in hepatic surgery (e.g. liver transplantation)

Compensation of hypovolemia in patients undergoing major liver surgery or liver transplantation has long been considered an indication for human albumin therapy. Meanwhile patients in such situations have also successfully been treated with synthetic colloids, but large-scale prospective trials are lacking [8]. There is also a lack of unambiguous data (controlled, randomized, comparative trials investigating modern synthetic volume substitutes) regarding the significance of substitution by albumin in major liver surgery, e.g. of extended hepatocellular carcinoma.

In cases of liver transplantation the administration of human albumin or synthetic colloids is recommended for volume replacement, subject to the therapy strategy of the particular hepatic surgery center.	**2 C**

5.5.1.9 Acute volume replacement in children

For a long time, administration of human albumin and stored serum has been the treatment of choice regarding volume substitution in children. Meanwhile safe and effective volume substitution in children is also possible by using crystalloid or modern colloid solutions [4, 11, 24, 53, 58]. In general, there are only few publications reporting experiences with the application of albumin or different volume substitutes in neonates, premature infants and children under the age of 12 months. However, some studies showed that in neonates and pediatric patients human albumin that is administered for increased hemodynamic stability can be replaced by other volume substitutes [4, 11, 53, 58].

Routine application of human albumin for volume replacement in children is not recommended.	**2 A**

5.5.1.10 Acute volume replacement in therapeutical plasmapheresis

Administration of human albumin is indicated for volume replacement with albumin in therapeutic plasmapheresis. However, there are no large comparative trials involving other substances for volume replacement that would document a benefit.

Human albumin could be administered in order to balance volume withdrawal in plasmapheresis.	**2 C**

5.5.2 Therapy of hypoalbuminemia

5.5.2.1 Physiology/pathophysiology

Compensation of hypoalbuminemia is considered to be an essential indication for administration especially of highly concentrated albumin preparations. In human plasma albumin concentration ranges around 3.5–4.5 g/dL and amounts to approx. 60 % of the total plasma proteins (6–8 g/dL). Around 30–40 % of the replaceable albumin pool is located in the plasma compartment (approx. 120 g in around 3 L of plasma volume) [25]. Concentration in the tissue spaces is considerably lower (approx. 1.4 g/dL; approx. 160 g in 10–12 L of interstitial volume). Under normal conditions the liver produces around 200 mg/kg per day in albumin, corresponding to around 15 g per day in a man weighing 70 kg. The foremost factor in monitoring the production of albumin is apparently colloid osmotic pressure (COP) in the region of the extravascular space of the liver. In sepsis, infection, trauma or mental strain the albumin level decreases (approx. 1–1.5 g/dL during 3–7 days). Albumin synthesis is also reduced under these circumstances, but with a half-life of around 20 days this cannot explain the rapid drop in serum albumin concentration. The most significant cause of the reduced albumin level is apparently redistribution and/or catabolism. Particularly in patients with sepsis an increased vascular permeability (capillary leak) plays an important role in developing hypoalbuminemia [19].

Following transfusion of human albumin, its distribution within the extravascular compartment is complete after 7–10 days. Approx. 10 % of transfused albumin migrates from the intravascular space within 2 hours [38], 75 % of transfused albumin is distributed into the extravascular space after 2 days [25]. In particular clinical pictures (e.g. in sepsis) this distribution process happens far more rapidly. In this connection capillary permeability of albumin can increase 13-fold compared to its normal level [10].

5.5.2.2 Therapy of hypoalbuminemia in intensive-care patients

Hypoalbuminemia is a predictor of increased mortality and morbidity [29, 31]. Compensation of hypoalbuminemia however showed no benefit regarding morbidity and mortality in comparison to an untreated control group. This was shown for adults as well as for children in meta-analyses [26, 61].

It is not settled yet which albumin level can be considered to be still tolerable and whether there is a “critical” threshold value in hypoalbuminemia below which an administration of albumin is beneficial.

Two prospective randomized studies were able to show that in hypoalbuminemia with levels of <31 g/L, or total protein concentrations of <60 g/L, albumin administration significantly improved organ function (respiratory, cardiovascular and central nervous system function). Also a better tolerance to enteral feeding, an improved oxygenation in acute pulmonary failure and a less positive fluid balance were achieved [14, 30]. Both studies however failed to use for comparison another substance which also increases COP. Furthermore, both studies enrolled only small numbers of patients, therefore they are not comparable with the available meta-analyses enrolling hundreds of patients.

Transfusion of human albumin to balance a state of hypoalbuminemia in critically ill patients is not recommended.	**2 A**

Since a beneficial effect of albumin replacement in critically ill patients with sepsis or those with severe multi-organ failure (MOF) cannot be completely ruled out, it might be reasonable to follow a deviating course of treatment in individual cases [60].

5.5.2.3 Therapy of hypoalbuminemia in undernutrition, malnutrition and enteropathies/malabsorption syndrome

In clinical practice no benefit is shown for the administration of albumin in undernutrition, malnutrition and enteropathies/malabsorption syndrome. Because of the composition of amino acids with a low ratio of some essential amino acids (tryptophan, methionine, isoleucine) as well as its long biological half-life of around 19–21 days, albumin is principally unsuitable for parenteral nutrition.

Administration of albumin in undernutrition, malnutrition, enteropathies and malabsorption syndrome is not recommended.	**1 C+**

5.5.2.4 Therapy of hypoalbuminemia in liver cirrhosis

In cirrhotic patients with ascites there is some evidence that albumin transfusion leads to a reduction in morbidity and mortality [21, 56]. However, as an individual parameter, hypoalbuminemia *per se* is no confirmed indication for substitution in patients with established liver cirrhosis and ascites. The decision on whether volume replacement or albumin substitution are necessary depends on the degree of severity of liver cirrhosis as well as the extent of the hemodynamic, hormonal and immunological deficits.

Three clinical situations are described below where transfusion with human albumin as volume replacement or an albumin substitution may be indicated:

a) spontaneous bacterial peritonitis
b) hepatorenal syndrome
c) post paracentesis.

5.5.2.4.1 Spontaneous bacterial peritonitis (SBP). According to the Guideline by the American Association for the Study of Liver Diseases (AASLD), spontaneous bacterial peritonitis is defined by the detection of neutrophil granulocytes (>250/mm^3 of ascites) in the absence of an intra-abdominal source of infection [45]. A single randomized controlled trial involving patients with ascites and SBP investigated the administration of cefotaxime plus albumin (1.5 g/kg body weight at the time of SBP diagnosis [day 1] and 1 g/kg body weight on day 3) and compared this to treatment with cefotaxime alone without plasma volume expansion [56]. In this connection the incidence of renal impairment could be prevented by the additional use of albumin, and the mortality rate at three months was significantly improved. However, the trial has methodological flaws because the control group did not receive adequately controlled fluid replacement.

In patients with chronic liver failure (e.g. in the context of liver cirrhosis) and drainage of ascitic fluid attention shall be paid to an adequate volume replacement.	**1 C+**

However, a sub-group analysis of the data of the above-mentioned trial showed that the incidence of renal impairment following SBP was almost exclusively in patients with elevated creatinine levels at the time of SBP diagnosis and serum bilirubin levels of at least 4 mg/dL [56]. A randomized unblinded pilot study involving 10 patients compared the administration of 20 % albumin for 6 hours and the administration of hydroxyethyl starch (HES) 200/0.5 for 18 hours regarding the prevention of hemodynamic and renal complications in patients with SBP [17]. There were fewer incidences of renal complications in the human albumin group in comparison with the HES group (3 vs. 5 patients).

Administration of albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) could be carried out in patients with liver cirrhosis and spontaneous bacterial peritonitis as well as elevated serum bilirubin levels (>4 mg/dL) and renal impairment.	**2 C**

5.5.2.4.2 Hepatorenal syndrome (HRS). In patients with hepatorenal syndrome (definition according to [50]) vasoconstrictors are used. In the majority of the trials performed on the treatment of an HRS, vasoconstrictors were in each case combined with albumin [2, 15, 34, 55]. In a prospective, non-randomized study patients receiving terlipressin combined with albumin (1 g/kg body weight on day 1 and 20–40 g albumin/day on consecutive days with a central venous pressure of ≤18 mmHg) were compared with patients receiving terlipressin alone [37]. A considerably increased rate of complete response was found under albumin therapy. However, this trial has methodological flaws in that after the enrolment of 13 patients the protocol (terlipressin plus albumin) was modified: only subsequently, non-randomized, the other patients were treated with terlipressin alone.

In patients with liver cirrhosis and hepatorenal syndrome the treatment with vasoconstrictors should be combined with albumin therapy.	**1 B**

5.5.2.4.3 Post paracentesis. Following paracentesis with drainage of ascitic fluid, i.e. post paracentesis, without volume compensation after puncture there is the risk of developing a so-called post paracentesis syndrome (PPS). PPS is defined as circulatory dysfunction accompanied by activation of the renin-angiotensin-aldosterone system (increase by >50 % of the pre-treatment value to a level >4 ng/mL per h on day 6 post paracentesis) [22].
The incidence of PPS is associated with impaired renal function, a concomitant considerably higher risk of developing renal failure and an overall increased mortality [23, 32]. To prevent PPS, volume substitution shall therefore be performed after each total paracentesis (i.e. drainage of the total volume of ascites) [32, 33].
Regarding the selection of plasma expanders for the prevention of PPS, there are randomized clinical trials comparing albumin (6–8 g/L of ascitic fluid) with dextran 70 [16, 23, 41], polygeline [23, 35, 49], dextran 40 [20] and hydroxyethyl starch [1]. Partly the trials showed considerable differences regarding volume and number of paracenteses performed, the degree of severity of liver disease, the length of follow-up and the definition of clinical complications. So far, a meta-analysis of this issue is only available in the form of an abstract. There were no significant differences between the individual groups regarding mortality and incidence of clinical complications.
Regarding the question of whether the volume of ascitic fluid evacuated played a role in indicating the type of plasma expander therapy, there is only one case-control trial (without incidence of PPS if the volume of ascitic fluid evacuated was <5 L and without plasma expander therapy) [40]. There is also one randomized controlled trial comparing albumin and saline (3.5 %) therapy after paracentesis [54]. The latter trial found a higher incidence of PPS in the total number of patients when 3.5 % saline was used (170 mL/L of ascitic fluid and transfusion rate of 1 L/hour), but not in a subpopulation for whom less than 6 L of ascitic fluid were evacuated. According to a consensus guideline, this evidence is not strong enough to deny plasma expander therapy to those patients in whom less than 6 L of ascitic fluid were evacuated. In this case it is recommended to use synthetic plasma expanders [33].

Following total paracentesis and a volume of ascitic fluid ≥6 L, plasma expander therapy with albumin (6–8 g/L of ascitic fluid) should be performed.	**2 A**
Following paracentesis and a volume of ascitic fluid evacuated of <6 L, saline (3.5 %) should be administered alone or, alternatively, synthetic plasma expander or albumin (6–8 g/L of ascitic fluid) should be used for substitution.	**2 A**

A randomized unblinded clinical trial involving patients with liver cirrhosis and first-onset ascites compared a standard therapy according to a consensus guideline [33] with and without administration of human albumin (25 g/week in the first year and 25 g every two weeks there-

after) [46]. It was found that the albumin-treated group had a significantly greater cumulative survival rate. However, this trial was not placebo-controlled and represented a continuation of a previous trial with a different primary endpoint [21].

In patients with cirrhosis and first-onset ascites albumin therapy at regular intervals could be beneficial.	**2 C**

5.5.2.5 Therapy of hypoalbuminemia in nephrotic syndrome

In nephrotic syndrome albumin is lost via the kidneys. Compensation of the resulting hypoalbuminemia is not reasonable because the transfused albumin is soon eliminated again to the greatest extent.

In cases of nephrotic syndrome the administration of human albumin is not recommended.	**1 C+**

5.5.3 Other applications of albumin

In addition to increasing colloid osmotic pressure (COP) and the volume-stabilizing effect associated with this, numerous other features are assigned to albumin that exceed its function for volume substitution [42, 43].

5.5.3.1 Albumin improving transport capacity for drugs

Albumin serves as a transport protein for many substances (e.g. bilirubin, drugs). It is doubtful whether in the case of hypoalbuminemia there may also be an increase in the "free" unbound (biologically active) fraction of drugs (e.g. coumarin derivatives). Since an increase in the free fraction of a substance is most often followed by a more rapid metabolism or an increased elimination of this substance, no critical increase in the concentration of the free substance in plasma is to be anticipated in case of low levels of albumin. There is no risk of acute toxic effects resulting from hypoalbuminemia because of rapid migration of the unbound fraction of drugs from the intravascular to the extravascular space, so that a (low-level) balance is reached. In addition, apparently binding sites for drugs are lost in the production process of human albumin solutions.

Administration of human albumin to improve the transport capacity for drugs is not recommended.	**2 C**

5.5.3.2 Albumin as free radical scavenger and for binding toxic substances

Physiologically, albumin is assumed to serve as free radical scavenger and is able to bind toxic substances (e.g. free fatty acids). Therefore albumin seems to be indicated in particular in patients with sepsis because toxic oxygen radicals play a role in pathogenesis and maintenance of sepsis [43]. Allegedly albumin can also bind toxins in large-scale burns. Therefore albumin solutions could have a beneficial effect in these patients. However, to date there are no confirmed factual data on the benefit of human albumin therapy regarding morbidity or mortality in humans. It is uncertain whether human albumin preparations currently commercially available have the same (radical scavenger) properties as natural albumin or whether they are altered by the manufacturing process.

Administration of human albumin as free radical scavenger and for binding toxic substances, e.g. in patients with sepsis, is not recommended.	**1 C**

5.6 Adverse reactions

No substance-specific clinically relevant alterations in the coagulation capacity nor alterations in organ function (e.g. renal function) due to albumin therapy have been reported. There is also no risk of retention of albumin. Although albumin is prepared from pooled plasma, albumin preparations currently available are considered to be non-immunogenic due to the manufacturing process.
Investigating the safety of application of human albumin, Vincent et al. [59] showed that from 1990 to 1997 approx. 112 million units of human albumin were administered worldwide; while from 1998 to 2000 approx. 10^7 units of 40 g each were administered. Adverse reactions that were directly associated with albumin were an extremely rare event during this observation period.
A study compared approx. 7,000 critically ill patients who either received 4 percent human albumin or crystalloid solutions (Saline versus Albumin Fluid Evaluation, SAFE study [18]). No serious adverse reactions were reported for the human albumin group in comparison to the crystalloid solution group.

5.7 Absolute and relative contraindications

The only substance-specific contraindication for albumin is an established allergy against human albumin (or rather against the dissolving agent). As any albumin infusion (e.g. to compensate hypovolemia) simultaneously causes increased intravascular volume, any hypervolemic state is to be considered a contraindication. Special caution is necessary in patients with severely restricted cardiac function. As is true for all volume substitutes, the following contraindications apply also to human albumin in general:

- congestive heart failure
- pulmonary edema
- hypocoagulopathy due to dilution

5.8 Documentation

The product type, batch number and recipient of human albumin must be documented in writing in accordance with section 14 of the German Transfusion Act (TFG).

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6 Factor VIII concentrates, factor VIII/von Willebrand factor concentrates, factor IX concentrates, activated prothrombin complex concentrates

6 Factor VIII concentrates, factor VIII/von Willebrand factor concentrates, factor IX concentrates, activated prothrombin complex concentrates

6.1 Preparation

Human factor concentrates are prepared from large plasma pools. In addition, recombinant (genetically produced) human factor VIII and factor IX concentrates are commercially available [8, 36, 56].

6.1.1 Factor VIII concentrates, Factor VIII/von Willebrand factor concentrates

Plasma-derived factor VIII as well as factor VIII/von Willebrand factor concentrates are prepared from **cyroprecipitates** and contain von Willebrand factor and moderately enriched factor VIII. Additional isolation steps include either immunoaffinity chromatography, ion exchange chromatography or precipitation procedures [1, 10, 26, 44]. Precipitation as well as chromatography lead to enrichment with functional von Willebrand factor [12, 43].

6.1.2 Factor IX concentrates

Plasma-derived factor IX concentrates are prepared from the **supernatant of cryoprecipitates** and from PCC prepared from the supernatant. Factor IX is isolated by affinity chromatography or by ion exchange chromatography. The most recent generation of factor IX concentrates contains almost exclusively factor IX in highly purified form and has largely lost its former thrombogenicity [15, 68].

6.1.3 Recombinant factor concentrates

Recombinant factor concentrates are prepared in animal cell cultures using biotechnological procedures. Cells containing the genetic material of the protein in question release the factor which is subsequently isolated. Various products are available which differ by their manufacturing process. Subsequent processing and purification steps require in some cases the addition of plasma proteins (e.g. albumin as stabilizers). In third-generation products the addition of plasma proteins is abandoned during the entire manufacturing process. Factor VIII preparations available contain the natural factor VIII molecule at full length, while one preparation consists of a truncated factor VIII molecule lacking the B domain. A recombinant factor IX preparation is also available.

6.1.4 Activated prothrombin complex concentrates

Activated prothrombin complex concentrates derived from plasma are produced from the **supernatant of cryoprecipitates**. Subsequent to isolation of the factors of the prothrombin complex the controlled activation of the factors II, VII, IX and X is generated as well as the standardization of the factor VIII inhibitor bypassing activity, FEIBA [8, 33, 58].

6.1.5 Quality criteria

The quality of a given hemostatically effective factor concentrate [24, 26, 31, 35, 43, 49, 60] depends on the starting material, the isolation or production processes, the clotting activity, the degree of purity of the concentrate (specific activity, additional protein contamination), the virus inactivation procedure, its immunogenicity and the type of stabilizers employed.

6.2 Active constituents

6.2.1 Factor VIII concentrates

Factor VIII concentrates contain high concentrations of highly purified clotting factor VIII (Factor VIII:C, i.e. factor VIII clotting activity) [10, 33, 43].

6.2.2 Factor VIII/von Willebrand factor concentrates

These concentrates contain factor VIII as well as hemostatically effective von Willebrand factor (vWf), especially its highly polymerized multimers [12, 25].

6.2.3 Factor IX concentrates

Factor IX concentrates contain high concentrations of factor IX [15, 61].

6.2.4 Activated prothrombin complex concentrates

Activated prothrombin complex concentrates contain standardized factor VIII inhibitor bypassing activity (FEIBA) consisting of activated and non-activated clotting factors of the prothrombin complex [8].

6.2.5 Further components

Depending on the particular product, factor concentrates derived from plasma may contain additional plasma proteins in varying concentrations, mainly albumin added as stabilizer, and, in albeit small amounts, fibrinogen, fibronectin, IgG and IgA immunoglobulins [10, 11]. Novel preparations have abandoned the addition of albumin. vWf can also serve as a stabilizer for factor VIII; some preparations contain small amounts of heparin. The degree of purity of a given factor concentrate is stated as **specific activity** in units (U) of the active constituent/mg total protein. The specific activity of presently available factor VIII concentrates ranges from 10-100 U factor VIII/mg protein, that of preparations without albumin as stabilizer can exceed 2000 U/mg. The stabilized specific activity of factor IX concentrates exceeds 200 U/mg [15]. Some factor IX concentrates additionally contain antithrombin and/or heparin.
Some recombinant “first-generation” factor concentrates contain human albumin added as stabilizer. In preparations presently available sugar molecules (e.g. saccharose or trehalose/mannitol) are added as stabilizer.

6.3 Physiological function and deficiency diseases

6.3.1 Factor VIII

Factor VIII is an acute phase protein formed mainly in the liver. It is the cofactor of the serine protease factor IXa, which activates factor X to Xa in the intrinsic coagulation system. Factor VIII is activated by thrombin and is inactivated by activated protein C. Factor VIII activity is reduced in the plasma of patients with hemophilia A. Their proneness to bleed correlates with the degree of factor VIII reduction. The mode of inheritance is X-linked recessive, its prevalence is 1 in 5,000 male births.

Hemophilia A is divided into **three degrees of severity**:

- **Severe hemophilia A** with residual factor VIII activity of ≤1 % shows a marked bleeding tendency. These patients have a disposition for spontaneous bleeding, especially in knee, elbow and ankle joints. Repeated bleeding in the same joint causes reactive chronic synovitis, in turn causing increased bleeding tendency and finally, destruction of the joint (**hemophilic arthropathy**) [3, 44].
- **Moderate hemophilia A** is defined by a residual activity of >1 to ≤ 5 %. Bleeding tendency is less severe; in residual activity of >2 % joint bleeding occurs only rarely.
- **Mild hemophilia A** has a residual factor VIII activity of >5 to ≤ 15 %, subhemophilia A of 15–50 %. In the latter case bleeding often occurs only after severe injury or during surgery.

In patients with hemophilia A the application of allogeneic factor VIII can induce the development of alloantibodies to factor VIII commonly called **factor VIII inhibitors** (hemophilia with inhibitors, mean incidence 25 %) [2, 29, 48]. A very rare event is the development of **spontaneously acquired factor VIII inhibitors** caused by autoantibodies in persons with normal clotting factor concentrations [32].

The biological half-life of factor VIII is about 8-12 hours. Increased requirement for factor VIII or shortened half-life occurs in patients with fresh large wounds, increased factor loss due to persistent bleeding, infections, hyperthyroidism as well as in infants and small children [44].

Pharmacokinetics and clinical effectiveness of recombinant factor VIII preparations do not differ essentially from those of factor VIII preparations from human plasma.

6.3.2 von Willebrand factor (vWf)

The vWf is a high molecular, adhesive glycoprotein with a multimeric structure (molecular weight 500–20,000 kD). It is formed in endothelial cells and alpha granules of platelets and fulfills several functions [12, 46, 52]:

- In primary hemostasis, it connects platelets with collagen of the subendothelial layer of the blood vessel [25]. vWf activity can thus be measured as collagen-binding activity.
- It participates in platelet aggregation by adhesion to platelet membrane receptors. This platelet aggregation can be activated in vitro by the antibiotic **ristocetin**. For this reason the vWf is known as the ristocetin-cofactor and is measured by adding ristocetin to platelet-rich plasma.
- **vWF forms a complex with factor VIII, thereby extending the half-life of factor VIII in plasma. In the absence of vWf the half-life of factor VIII in plasma is drastically reduced.**

The biological half-life of vWf is 6-12 hours; infusion, subcutaneous injection or nasal application of the vasopressin analogue DDVAP (desmopressin) releases vWf and factor VIII from the body's reservoirs and causes an approximately threefold increase over initial plasma

levels. Thus DDVAP can be employed to stop bleeding in mild forms of von Willebrand Syndrome (type 1) and in mild hemophilia A during minor bleeding episodes or minor surgery [12, 38].

Three types of von Willebrand Syndrome can be distinguished [53]:

- In **type 1** the concentration of vWf, its activity and factor VIII are all reduced to 50–10 %.
- In **type 2** the plasma concentration of von Willebrand molecules is normal or slightly reduced but their function is characteristically impaired. There are several subtypes of type 2. Type 2a, in which large and intermediate molecular multimers are lacking, is most frequent. Type 2b is characterized by increased binding of the vWf to the glycoprotein complex Ib of platelets and therefore may go along with thrombocytopenia. Administration of DDVAP may aggravate this condition. Therefore it is required to closely monitor platelet count. The rare type 2M is characterized by a reduced platelet-dependent function with normal distribution of multimers and aberrant triplet pattern. In the type 2N which is also rare the binding capacity of vWf to factor VIII is disturbed, thus imitating a mild form of hemophilia A in diagnostic tests [59]. Type 2N requires treatment with factor VIII/vWf concentrate.
- In **type 3** vWf is lacking while factor VIII:C is markedly reduced to but a few percent of its normal concentration.

Congenital type 1 von Willebrand Syndrome is the most common bleeding disorder (vWf concentrations between 25 % and 50 %, mild form, prevalence in general population 1:100). Type 3 has a prevalence of 1:100,000 [52]. **Acquired von Willebrand Syndrome** has been observed with the use of certain medications (e.g. valproic acid), in lymphoproliferative diseases, less often in myeloproliferative diseases, in monoclonal gammopathies, in hypothyroidism and in certain cardiac defects [46].

6.3.3 Factor IX

Factor IX is the proenzyme of the serine protease factor IXa which activates factor X in the presence of cofactor VIII. Factor IX is formed in liver cells. It is part of the prothrombin complex and thus requires vitamin K for synthesis. Factor IX formation is encoded by a gene on the X chromosome. The half-life of factor IX is 20–24 hours. Factor IX activity is reduced in hemophilia B; the bleeding tendency correlates with the degree of diminished factor IX activity. The classification in degrees of severity corresponds to that of hemophilia A [58]. The prevalence of hemophilia B is 1:30,000 male births. The prevalence of factor IX inhibitors is about 0.5 % in hemophilia B.

Recovery of the recombinant factor IX seems to amount to about 40–50 % below that of natural plasma factor. The half-lives are identical [27, 54].

6.3.4 Activated prothrombin complex

Activated PCC (FEIBA) does not occur *in vivo*. Its impact on hemostasis can be deduced from reduced coagulation times as evidenced by group tests such as APIT or shortened r-time in thrombelastogram. There is, however, no clear-cut correlation between laboratory results and clinical effectiveness [8, 33].

6.3.5 Recombinant activated FVII (rFVIIa)

See chapter 7.

6.4 Storage, shelf life and package sizes*

6.4.1 Storage

Generally, factor concentrates must be stored protected from light. The standard storage temperature for concentrates is +2°C to +8°C. Some factor concentrates can be stored temporarily or over its entire shelf life at up to +25°C or +30°C, respectively. For some concentrates it was documented that the factors were stable for up to 12 hours after preparing the solution. However, from a microbiological perspective, the ready-to-use solution should be used immediately after preparation. The particular instructions for use/expert information are referred to.

6.4.2 Package sizes

The following package sizes are usual:
Factor VIII:
250/500/1000/1500/2000 U/package
Factor VIII/von Willebrand factor:
450/900 and 500/1000 U/package
Factor IX:
200/600/1200 U/package and
250/500/1000 U/package and
300/600/1200 U/package and
500/1000 U/package
Activated PCC (FEIBA):
500/1000 U/package

6.5 Range of application, dosage, mode of administration*

6.5.1 General information

Appropriate clotting factor concentrates are used to treat hemophilia A or B or von Willebrand Syndrome. The following recommendations are based on consensus reports [14, 37, 61, 62, 63] and on review articles on the treatment of hemophilia [7, 17, 26, 47, 58, 63].
Criteria determining indications and dosage are:

- **the principal goals of hemophilia therapy,** namely:
  - prevention of bleeding,
  - treatment of bleeding, its complications and sequelae,
  - maintaining and/or restoring joint functions,
  - integrating hemophiliacs into a normal social life
- **further criteria influencing hemophilia therapy:**

1. patient groups
   - age (e.g. small children and infants require higher doses/kg body weight because of higher relative plasma volume),
   - medical history,
   - degree of severity,
   - inhibitor formation,
   - individual variations in recovery and half-life,

* see also section 0.4.

- adverse reactions of therapy,

2. clinical situation
   - frequency and site of bleeding,
   - state of the particular joints,
   - accompanying diseases (hepatic diseases, especially HCV and HBV; HIV),
   - other individual indications for treatment,
3. social situation, the patients' wishes as well as the physician's experience.

Dosage recommendations listed below with indications and contraindications are average initial doses which should be adapted to individual needs considering the goals and criteria indicated.

On principle treatment shall be carried out at a hemophilia center (so-called "Comprehensive Care Center") or in close cooperation with such an institution [62, 63, 66].	**1 C+**

The German Federal Joint Committee has enacted a guide for out-patient treatment of hemophilia patients in hospitals in accordance with article 116b SGB V (German Code of Social Law, Book V) specifying diagnostic and therapeutic procedures to be offered as well as requirements of the hemophilia center regarding personnel and equipment (Bundesanzeiger no. 73 p. 4003 dated 18 April 2007, see also http://www.g-ba.de).

6.5.2 Indications for replacement therapy using factor concentrates

Treatment principles:

Factor replacement on demand shall be performed during spontaneous or traumatic bleeding episodes at any bleeding site if the bleeding exceeds a minimum degree (e.g. minor skin bleeding) [40, 57].	**1 C+**
Full-time prophylactic replacement therapy shall be carried out mostly in **children and adolescents** with severe hemophilia in the form of physician-controlled self-administered treatment with the main intention of preventing hemophilic arthropathy [23, 30, 41, 51, 67, 69].	**1 A**
Full-time prophylactic replacement therapy can be carried out individually in **adults** with the intention of preventing the development of arthropathies as a late consequence [3, 18, 23, 50].	**2 C+**
Prophylactic therapy to prevent bleeding shall be provided before and after surgical interventions.	**1 C+**
Temporary prophylactic therapy to prevent bleeding should be provided during periods of major physical or psychic stress (e.g. rehabilitation, exams) [61, 63].	**1 C**

- Factor VIII concentrates are administered in hemophilia A when factor VIII activity is reduced or in patients who have developed factor VIII inhibitors.
- Factor VIII/vWf concentrates are administered according to their licensed use in cases of vWf deficiencies, i.e. in congenital or acquired von Willebrand Syndrome, factor VIII deficiency and acquired factor VIII inhibitors.
- Factor IX concentrates are given in hemophilia B (factor IX deficiency).
- Activated PCC and recombinant factor VIIa preparations are predominantly used for treating patients with factor VIII **inhibitors** [8].
- Replacement therapy can be supported by local measures (e.g. mechanical pressure, application of antifibrinolytic drugs, fibrin glue).

6.5.3 Dosage, mode of administration

Several reviews on dosage of replacement therapy in hemophilia A and B as well as in von Willebrand Syndrome have been published in recent years [17, 26, 33, 43, 44, 61, 63], but hardly any dose-finding studies were published. Recommended doses are essentially based on the Consensus Paper on Hemophilia Treatment in Germany, updated in 1999 [63].
The activity of clotting factors is expressed in units (U). One unit of a clotting factor corresponds to "100 % factor activity" and is defined as the activity in 1 mL of pooled plasma from healthy donors.

One unit/kg body weight increases the respective plasma factor concentration by 1–2 %.

The specifications regarding "incremental recovery" are referred to in the expert information provided by the manufacturer.
Frequently patients with severe hemophilia A or B will show an increase of only 1 % after the first injection. After a dose of 1 U/kg body weight an increase of about 2 % can only be expected after an equilibrium between blood and extravascular compartments has been achieved, thereafter the dose may be reduced as appropriate.
Patients with severe or moderate hemophilia A usually require exclusively factor VIII concentrates. In contrast, most patients with mild hemophilia A or von Willebrand Syndrome type 1 can be treated with DDAVP, with the exception of severe bleedings or during major surgery. Prior to administration of DDAVP the rate of biologic response should be tested [22, 38, 54, 59].

- Clotting factor concentrates are usually administered slowly as bolus i.v. injection.
- Because of the stability of currently available factor concentrates, constant plasma levels can be achieved *in many clinical situations by continuous infusion*. By this the total dose can be reduced without sacrificing effectiveness. However, in particular the potentially increased development of inhibitors against the administered factor during continuous infusion is discussed [9].
- The recommended doses represent a range of standard initial doses. Further dosage should be adjusted according to the clinical situation. Calculations for dosage are based on the half-life of the clotting factor and should be monitored by measuring the recovery of the replaced factor in patients' plasma. Numerous bleeding episodes (e.g. bleeding into joints, epistaxis) may be successfully treated with 1–2 injections, if given promptly and in sufficient dose.

6.5.3.1 Replacement in children with hemophilia A, B or von Willebrand Syndrome

Full-time prophylactic replacement therapy to achieve the goals stated under 6.5.1 [33, 58]:

- As a general rule, this treatment is recommended for children with severe hemophilia [62, 71].
- Treatment is to be initiated without delay after the first episode of bleeding into joints or after other frequent bleedings.
- Treatment must be individually adjusted according to the clinical situation and age.

Mean dose: 20–30 U/kg body weight at least 3 times per week. Because of the longer half-life of factor IX, fewer injections/week suffice in hemophilia B [23, 30, 41, 51, 58, 62, 67, 69].	**1 A**

Exclusively referring to clinical trials investigating full-time prophylactic replacement therapy in children with hemophilia, the general international consensus is to give a 1 A recommendation [41, 62]. However, the exact dose of factor infusion, starting time and duration of therapy are still under discussion.

Factor replacement on demand in children:
- Individual dose adjustment according to clinical situation
- Duration: until cessation of bleeding
- Reduction of total dose is possible by means of continuous infusion without loss of effectiveness.

Table 6.5.3.1: Treatment on demand in childhood: mean initial dose

Indication	Mean initial dose U/kg body weight
Bleeding into joints and muscles	30–40
Life-threatening bleeding	80–100
Surgery • major wounds, e.g. tonsillectomy • minor wounds	 80–100 50–100

As a rule, **moderate hemophilia** is treated on demand (doses corresponding to those applied in severe hemophilia). Continuous replacement therapy in moderate hemophilia depends on the frequency of bleeding and on the particular clinical situation and is performed similar to treatment of severe hemophilia.
With the exception of severe bleeding or major surgery, most children beyond the age of 4 years with **mild hemophilia** or **von Willebrand Syndrome type 1** can be treated with the synthetic vasopressin analogue DDAVP (1-desamino-8-D-arginin-vasopressin) at a dose of 0.3 µg/kg body weight or as nasal spray (dosage see expert information) [38, 46, 58]. Because of the danger of hyponatremia and cerebral seizures, DDAVP is not indicated in children under the age of 4 years.
Life-threatening bleeding in patients with **type 1, 2 or 3 von Willebrand Syndrome** is treated with factor VIII/vWf concentrates. Dose and duration of treatment depend on the particular clinical situation.

Furthermore, prior to surgery with risk of bleeding, patients with type 1, 2 or 3 von Willebrand Syndrome should be substituted with factor VIII/vWf concentrates. Dose and duration of the therapy depend on the clinical situation [4, 20, 21, 42, 45].	**1 C**

6.5.3.2 Replacement in adults with hemophilia A, B or von Willebrand Syndrome

As a rule, **moderate hemophilia** is treated on demand. Indication for full-time replacement therapy depends on the frequency of bleeding and the particular clinical situation. Procedure and dosage are similar to those in severe hemophilia.

With the exception of severe bleeding or major surgery, most patients with **mild hemophilia** or **von Willebrand Syndrome type 1** should be treated with the synthetic vasopressin analogue DDAVP (desmopressin) at a dose of 0.3 µg/kg body weight or as nasal spray (dosage see expert information) [38]. **Life-threatening bleeding** in patients with **type 1, 2 or 3 von Willebrand Syndrome** should be treated with factor VIII/vWf concentrates. Dose and duration of treatment depend on the particular clinical situation. Furthermore, prior to surgery with risk of bleeding, patients with severe type 1 von Willebrand Syndrome or with type 2 or 3 von Willebrand Syndrome should also be substituted with factor VIII/vWf concentrates. Dose and duration of the therapy depend on the individual clinical situation [20, 21, 42, 45].	**1 C**

Recommended doses for treatment on demand are: (dose-finding studies have not been published in sufficient number [57]. Recommended doses are essentially based on the Consensus Paper on Hemophilia Treatment in Germany, updated in 1999 [63]).	**1 C+**
Indication/type of bleeding	**Mean initial dose (U/kg BW)***
Bleeding into joints and muscles	20–40
Life-threatening bleeding	50–80
Bleeding into soft tissue	
• severe or extensive bleeding (e.g. cerebral hemorrhage, tongue bite, carpal tunnel syndrome, retroperitoneal bleeding, femoral, calve, muscle hemorrhage)	40–60
• minor bleeding into skin and muscles	15–30
Mucosal bleeding, urogenital bleeding	
• gastrointestinal bleeding and bleeding of the oral cavity	30–60
• epistaxis	20–40
• hematuria	20–40
Surgery	
• major wounds and/or high tendency of bleeding, including tonsillectomy	50–80
• minor wounds (tooth extraction, herniotomia)	25–40

* (exploratory range)

Continuous prophylactic factor replacement therapy can be carried out [3, 17, 18, 23, 50, 61, 63]: • in patients with recurrent bleeding with the danger of irreversible damage, • individually to prevent the development of arthropathies as a late consequence, • under extreme physical or psychological/mental stress, • during rehabilitation **Mean dose: 20–30 U/kg body weight at least 3 x weekly** Because of the longer half-life of factor IX, fewer injections/week suffice in hemophilia B [58]. **Individual adjustment** and maintenance therapy required according to the clinical situation. Duration: until a symptom-free interval of several weeks is attained, or at least until cessation of symptoms. **Continuous infusion over several days** may result in a reduction of the total dose without loss of effectiveness.	**2 C+**

6.5.3.3 Indications and recommended doses for treating patients with factor VIII inhibitors in hemophilia A

General remarks

The recommendations in this section are derived from the following publications [8, 16, 61, 63].

Treatment of acute bleedings (children and adults)

- **Low Responders** (<5 Bethesda units, BU, or the possibility of overriding acute bleedings with factor VIII concentrates):

a) High-dose factor VIII infusions shall be administered up to hemostatically effective factor VIII levels [5, 28].	**1 C+**
b) Activated Prothrombin complex concentrate (FEIBA) shall be given as initial dose: up to 100 U/kg body weight and a maintenance dose of up to 100 U/kg body weight twice daily [6, 19, 28, 65].	**1 A**
c) Alternatively recombinant Factor VIIa shall be given, mean initial dose 90 µg/kg body weight or 270 µg/kg body weight as single dose (see section 7.4) [6, 28].	**1 C+**

- **High Responders (>5 BU):**

a) Activated Prothrombin complex concentrate (FEIBA) shall be given as initial dose: up to 100 U/kg body weight and a maintenance dose of up to 100 U/kg body weight twice daily [6, 19, 28, 65].	**1 A**
b) Alternatively recombinant Factor VIIa shall be given, mean initial dose 90 µg/kg body weight or 270 µg/kg body weight as single dose (see section 7.4) [6, 28, 34, 39, 55, 64, 70].	**1 C+**
c) In emergencies and failure of a) and b) immunoadsorption apheresis should be considered [13].	**1 C**

Inhibitor elimination by inducing immune tolerance

Children:

Low Responders (<5 BU): Even if no clinical symptoms occur factor VIII concentrate could be given 3 times per week at a dose of 50–100 U/kg body weight, until normal recovery and half-life are achieved. Monitoring for inhibitors necessary once or twice per week, followed by continuous therapy [5, 28].	**2 C**
High Responders (>5 BU): Factor VIII concentrate at a dose of 100–200 U/kg body weight shall be given twice daily up to normalization of recovery and half-life over several months, followed by individually adjusted continuous therapy. Combination with FEIBA at a dose of up to 50 U/kg body weight twice daily during inhibitor elimination may be used to reduce the bleeding tendency [5, 6, 28].	**1 C+**
In case of unsuccessful inhibitor elimination, this therapy mode should be discontinued generally after 1 year.	**2 C**

Alternatively, recombinant Factor VIIa can be given (initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose) to treat bleeding tendency during inhibitor elimination.

Adults:

Low Responders (<5 BU): As a rule, elimination therapy is not recommended during continuous therapy with factor VIII concentrate, 50 U/kg body weight three times per week [5, 28].	**2 C**
High Responders (>5 BU): Factor VIII concentrate, dose: 100–150 U/kg body weight should be given twice daily up to normalization of recovery and half-life over several months, followed by individually adjusted continuous therapy. Combination with FEIBA at a dose of up to 50 U/kg body weight twice daily during inhibitor elimination may be used to reduce the bleeding tendency [5, 6, 28].	**1 C**
In case of unsuccessful inhibitor elimination, this therapy mode should be discontinued generally after 1 year.	**2 C**

Alternatively, recombinant Factor VIIa can be given (initial dose 90 μg/kg body weight or 270 μg/kg body weight as single dose) to treat bleeding tendency during inhibitor elimination.

6.5.4 Absolute and relative contraindications

- Correct indications provided, there are no contraindications for factor VIII concentrates, factor VIII/vWf concentrates or factor IX concentrates.
- Activated PCC preparations (FEIBA), recombinant factor VIIa preparations: These preparations may aggravate disseminated intravascular coagulation. In patients with known or suspected coronary heart disease as well as in acute thromboembolic disorders, these preparations should be strictly reserved for cases with life-threatening bleedings.

6.6 Adverse reactions

See chapter 11.

6.7 Documentation

The product type, batch number and recipient of factor VIII concentrates, factor VIII/vWf concentrates, factor IX concentrates and activated prothrombin concentrates must be documented in writing in accordance with section 14 of German Transfusion Act (TFG).

6.8 References

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7 Procoagulators

7 Procoagulators

The factor concentrates discussed below are primarily obtained from clotting factors circulating in plasma. The factors enhancing coagulation are called procoagulators. Fibrin is formed from fibrinogen by activation of procoagulators. Fibrin consolidates the primary clot consisting of aggregated platelets.
The liver is predominantly the place of synthesis of procoagulatory clotting factors. With the exception of factors V, VIII and XIII, all procoagulatory clotting factors are so-called serine proteases (amino acid "serine" at the active site) and circulate in the blood mostly in their inactive form (proenzyme).
Factor VII is also commercially available in its activated form (rFVIIa) as a genetically engineered preparation. There are no single-factor concentrates for factors II and X.
Furthermore, factors V and XI are currently not available in a highly concentrated form in Germany. Therefore fresh frozen plasma (FFP) is used in cases of factor V or XI deficiency relevant towards bleeding (see section 4.4.4.5).
Because of the clinical relevance the application of procoagulators in patients with acquired deficiency and bleeding complications is also discussed in the following chapters, in particular in the sections "Fibrinogen and Prothrombin complex concentrate" as well as "Recombinant Factor VIIa". Regarding the comprehensive management of these acutely ill patients, the reader is particularly referred to a recent review article by Mannucci and Levi [61].

7.1 Fibrinogen

7.1.1 Preparation, quality criteria

The starting material is pooled human plasma. Following the thawing and pooling of plasma, fibrinogen concentrate is obtained from cryoprecipitate (procedure according to Cohn/Oncley).

7.1.2 Active constituents

The effective component of the only concentrate commercially available in Germany contains human fibrinogen (ratio of coagulable protein >80 %), with human albumin added as stabilizer.

7.1.3 Physiological function

Fibrinogen, a glycoprotein with a molecular weight of approximately 340,000 Daltons, is predominantly formed in the liver and stored in both endothelial tissue and platelets. Its biological half-life is 96–120 hours. The normal fibrinogen concentration in plasma is 1.5 to 4 g/L, depending on the particular reference collective.
On the one hand, water-soluble fibrinogen is the substrate of plasmatic blood coagulation; on the other, it functions as an essential ligand in platelet activation and platelet aggregation. Fibrinogen is an acute phase protein; its concentration may rise rapidly within a few hours to more than 10 g/L during infections and postoperatively.
In pregnancy the physiological level of fibrinogen may rise to values up to 6 g/L.

7.1.4 Application

7.1.4.1 Congenital fibrinogen deficiency

Various congenital variants and disorders of fibrinogen formation (hypo- or dysfibrinogenemia) have been described [12, 68]. The individuals concerned may be asymptomatic or have a predisposition to thrombosis. Dysfibrinogenemia is rarely associated with a clinical disposition to bleeding.

The bleeding tendency in **dysfibrinogenemia** is usually mild but can be considerable during and after surgery or particularly post partum. Depending on the size of the wound surface, fibrinogen levels of at least 1 g/L (in cases of severe bleeding at least 1.5 g/L) are generally sufficient during elective surgery.

Congenital afibrinogenemia (i.e. no functional fibrinogen is detectable) must be associated with a severe bleeding tendency so that in individual cases even continuous prophylactic replacement may be indicated.

The widest clinical experience has been gained for years with applying fibrinogen concentrate for the treatment or prevention of bleeding in patients with congenital fibrinogen deficiency [13, 55, 69, 82, 91]. Due to the rarity and heterogeneity of these congenital defects, no controlled trials have been carried out.

7.1.4.2 Acquired fibrinogen deficiency

In daily clinical routine acquired fibrinogen deficiency following increased consumption is found in disseminated intravascular coagulation, loss and dilution coagulopathy [10, 22, 24, 30, 86]. Fibrinogen deficiency induced by increased turnover is also found in reactive or therapeutic hyperfibrinolysis [83]. Acquired fibrinogen deficiency due to impaired synthesis occurs in cases of severe damage of the liver parenchyma or following asparaginase therapy. In cases of pronounced damage of the liver parenchyma acquired dysfibrinogenemia may also occur. A distinctive fibrinogen deficiency may also occur in acute lymphoblastic leukemia, in particular acute promyelocytic leukemia, obstetric complications, burns and states of shock with massive hemorrhage or distinctive disseminated intravascular coagulation [26].

Acquired fibrinogen deficiency may also occur in isolated cases but is frequently accompanied by other hemostatic or fibrinolytic disorders.

A distinctive fibrinogen deficiency can develop in the event of **massive transfusions** in the context of loss and dilution coagulopathy, because primary replacement by crystalloids, colloids and possibly RBC concentrates is performed almost exclusively without plasma. In such situations fibrinogen levels are the first procoagulatory factors to decline, dropping to a critical range of 1 g/L. The other clotting factors and platelets decline later on, i.e. in cases of much more extensive blood loss, below critical threshold values [32, 35].

Severe liver disease with impaired synthesis primarily presents with a complex synthesis disorder of almost all of the proteins relevant for coagulation [79]. Although no trials have been conducted, the administration of FFP is therefore often recommended in cases of bleeding (see chapter 4). However, if a distinct deficiency in factors and cellular components has already developed due to blood loss, large amounts of FFP alone (1–1.5 L) cannot achieve sufficient hemostasis. Regarding fibrinogen, it must be noted that there is not only a drop in fibrinogen levels in severe liver damage, but that dysfibrinogenemia and hyperfibrinolysis may additionally occur. Critical threshold levels for the possible occurrence of spontaneous bleeding are approximately 1 g/L in these diseases.

Hyperfibrinolysis can occur in **disseminated intravascular coagulation** as well as in multiple organ failure, in particular with liver damage but also as an isolated coagulation disorder (e.g. in resection of the prostate or in cardiac, pulmonary, pancreatic or uterine surgery). Not only is the generated fibrin destroyed by endogenous lysis, but also fibrinogen. The primary therapy consists of the interruption of fibrinolysis by antifibrinolytic drugs. The recommended

course of action is the same in both therapeutically induced fibrinolysis and severe hemorrhage. Only in a persisting disposition to massive bleeding and low levels of fibrinogen (<1 g/L, measured not earlier than 8 h after the end of therapy), lysis should be interrupted and fibrinogen substituted.
In **asparaginase** therapy the synthesis of all aspartic acid-containing proteins is impaired. A decrease particularly of AT levels but also of fibrinogen levels is to be anticipated. In the patients concerned thrombosis may occur (if AT deficiency is dominant) and/or bleeding (if fibrinogen deficiency is dominant). In order to avoid these complications, it is reasonable to substitute the respective coagulation components that are lacking. The threshold value for intervention by fibrinogen substitution is also approximately 1 g/L or less. Irrespective of asparaginase therapy, a massive fibrinogen and platelet deficiency may develop in cases of acute leukemia, in particular acute promyelocytic leukemia. In complications during pregnancy and delivery (e.g. atonic uterus) rare but possibly fulminant **defibrination syndromes** may occur [51, 70].

7.1.4.3 Laboratory diagnostics

The two screening tests prothrombin time (PT) and partial thromboplastin time (PTT) also detect fibrinogen. However, it must be pointed out that both tests distinctively demonstrate pathological values only in pronounced fibrinogen deficiency below the critical threshold value of 1 g/L. In cases of acute bleeding or relevant disposition to bleeding it is therefore recommended to determine fibrinogen concentrations directly (method according to Clauss). Furthermore, it must be pointed out that, following the application of colloids, a fibrin polymerization disorder in terms of a clinical disposition to bleeding may occur. In addition, false elevated fibrinogen values may be measured. The coagulometers measuring scattered light are widely used but are prone to measure false elevated fibrinogen values in plasma laced with colloids [36]. It must be ensured in the respective clinical unit that fibrinogen levels can be measured reproducibly and correctly in the range around and below 1 g/L (calibration, quality assurance).
To estimate fibrinogen turnover and synthesis, it may be reasonable to determine the D-dimer and/or a thrombelastogram in addition to fibrinogen concentrations.

7.1.5 Storage, shelf life and package sizes∗

Fibrinogen concentrate should be stored at +4°C to +8°C. The shelf life amounts to 5 years. Ready-to-use solutions must be administered without delay, as they do not comprise of preservatives.
Fibrinogen: 1 g/50 mL dissolving agent or 2 g/100 mL dissolving agent.
Water for injection must be used as solving agent.
Note: According to the manufacturer, no dilution in glucose or sodium chloride solution should be performed.

7.1.6 Indications

7.1.6.1 Substitution in congenital fibrinogen deficiency [19, 40, 55]:

- prophylactic physician-controlled continuous therapy (home treatment) in severe congenital fibrinogen deficiency to prevent frequent recurrent bleeding episodes, during gravidity to maintain pregnancy, also in individual cases of hemorrhagic dysfibrinogenemia,
- perioperatively and in surgical interventions with a risk of bleeding,

∗ see section 0.4

- intermittently and prophylactically to prevent bleeding in known fibrinogen deficiency as well as in hemorrhagic dysfibrinogenemia.

Table 7.1.6.1: Substitution therapy in congenital fibrinogen deficiency

Defect	**Modality**	
congenital **hypofibrinogenemia** (fibrinogen level between 0.5 and 1.5 g/L), congenital, hemorrhagic dysfibrinogenemia	Generally **no** replacement therapy is necessary in congenital hypofibrinogenemia. Prior to **surgery** or to **diagnostic interventions** with an increased **risk of bleeding** (e.g. lumbar or epidural puncture and organ biopsies), a fibrinogen substitution is to be performed if fibrinogen levels <1 g/L. Fibrinogen levels of at least 1 g/L must be aimed for (in severe hemorrhage of at least 1.5 g/L).	**1 C+**
congenital **afibrinogenemia** (no functional fibrinogen is found)	Prior to all **surgical interventions** the concentration of fibrinogen in plasma should be elevated to the reference range of at least 1 g/L (in severe hemorrhage of at least 1.5 g/L) and maintained in this range until wound healing. In rare cases a continuous prophylaxis may be necessary.	**1 C+**

7.1.6.2 Substitution in acquired fibrinogen deficiency

General recommendations:

- The critical threshold values for the occurrence of spontaneous bleeding are <1 g/L (in severe hemorrhage 1.5 g/L).
- The fibrinogen level should always be specifically determined. An indirect determination using PT or PTT is not sufficient for any decisions regarding substitution therapy. The detection limit of the laboratory assay must be taken into account.
- The mean adult dose is around 3–5 g; following administration, the levels should be monitored and maintained above the critical threshold value (approx. 1 g/L).
- In hyperfibrinolysis or disseminated intravascular coagulation the administration of fibrinogen is only indicated following interruption of the coagulation disorder by antifibrinolytic drugs or antithrombin in cases of persistent bleeding and low levels of fibrinogen.

Table 7.1.6.2: Recommendations regarding fibrinogen substitution in **acquired** deficiency:

Fibrinogen can be substituted perioperatively in interventions or lesions with the risk of acute bleeding and confirmed fibrinogen deficiency (massive transfusion, dilution and loss coagulopathy).	**2 C+**
Fibrinogen can be substituted in synthesis disorders (liver damage) with fibrinogen deficiency or in hemorrhagic dysfibrinogenemias as prophylaxis and therapy of hemorrhage and confirmed fibrinogen deficiency.	**2 C+**
Fibrinogen can be substituted as a prophylaxis and therapy of hemorrhage and confirmed fibrinogen deficiency of different origin (e.g. acute leukemia, asparaginase therapy, obstetrical complications, postoperatively).	**2 C+**

7.1.7 Dosage*

The required fibrinogen dose is estimated from the plasma volume (≈ 40 mL/kg body weight) according to the following formula:

fibrinogen dose (g) = desired increase (g/L) × plasma volume (L)

Following fibrinogen substitution, the minimum plasma concentration should be 1.0 g/L plasma. In adults single doses of 3–6 g are usually required [82].

Note:
Administration of 3 g of fibrinogen in a volume of 3 L plasma increases fibrinogen levels by approximately 1 g/L.
In congenital deficiency the half-life (96–120 h) must be considered. When the half-life is shortened, fibrinogen levels should be monitored more frequently.

7.1.8 Absolute and relative contraindications

Overt thrombosis and myocardial infarction preclude fibrinogen use except in cases of life-threatening hemorrhage.

In disseminated intravascular coagulation (DIC) fibrinogen substitution is dangerous because during ongoing fibrin generation it can augment fibrin formation in the microcirculation and thus further the risk of multiple organ failure. Administering fibrinogen is thus indicated only when active intravascular coagulation has ceased and/or when appropriate therapeutic, particularly anticoagulatory, measures have already reduced fibrin turnover in the hemostatic system.

7.2 Prothrombin complex concentrates (PCC) – Prothrombin (factor II), Proconvertin (factor VII), Stuart factor (factor X) and antihemophilic factor B (factor IX)

7.2.1 Preparation, quality criteria

Factors II, VII, IX and X of the prothrombin complex as well as the proteins C, S and Z are isolated from large cryoprecipitate-poor plasma pools, using ion exchange chromatography in combination with various precipitation and adsorption methods.
Prothrombin complex concentrates (PCC, in German: PPSB: **P**rothrombin [factor II], **P**roconvertin [factor VII], **S**tuart factor [factor X] and antihemophilic factor **B** [factor IX]) are standardized with respect to their content in factor IX. Because of the varying recovery and stability of factors II, VII, IX and X during successive production steps, the composition of clotting factor activities in the concentrates inevitably deviates from physiological conditions. Thus the amount of prothrombin and factor X may be double, whereas factor VII may measure only half the activity of factor IX. Protein C, S and Z content similarly exhibits a large range of variation.
Activated clotting factors and activated protein C or plasmin are virtually no longer contained in currently available PCC preparations, so that adverse reactions such as thromboembolic episodes, disseminated intravascular coagulation and/or hyperfibrinolytic bleeding are

* see section 0.4

extremely unlikely, even when larger doses are administered [33, 49, 87]. Thromboembolic events reported to have occurred in the past following application of PCC mainly occurred in patients with hemophilia B, liver disease and/or antithrombin deficiency, particularly following repeated high-dose administration [49]. A distinct prothrombin overload in some PCC which are no longer commercially available is most likely a cofactor in resultant thromboembolic complications [29]. Batch control performed by the Paul-Ehrlich-Institute ensures today's high safety standard. Therefore no general AT substitution is required. According to the rules and regulations of the European Pharmacopeia, all preparations contain heparin (up to 0.5 U/U factor IX) and some contain antithrombin as well (1–2 U/mL) [56, 76].

7.2.2 Active constituents

Prothrombin complex concentrate contains a number of proenzymes (zymogens) of factors of the prothrombin complex, namely the human clotting factors II (prothrombin), VII (proconvertin), X (Stuart-Prower factor), IX (antihemophilic globulin B) as well as the inhibitor protein C, its cofactor protein S and the coagulation regulator Z. This mixture is also known as prothrombin complex concentrate (PCC).

7.2.3 Physiological function

The clotting factors II, VII, IX and X (prothrombin complex) stimulate coagulation, while proteins C and S inhibit it. Protein Z is a plasma protein dependent on vitamin K and represents a cofactor for inactivation of factor X by a protease inhibitor dependent on protein Z. All seven proteins are synthesized in the hepatocytes. Sufficient concentration of intracellular vitamin K and an intact vitamin K metabolism are required for their biosynthesis.

Congenital factor II, VII, IX and X deficiencies predispose the patient to bleeding, depending on the location of the genetic defect, while in contrast congenital protein C and S deficiencies predispose to thromboembolic disorders.

Homozygous carriers of factors II, VII, and X deficiencies are characterized by reduced activity of single factors (<10 %), whereas in heterozygous carriers, activity is reduced by 10 to 50 %. Homozygous carriers of factor deficiencies have a strong propensity to bleeding. Heterozygous carriers of factors II, VII and X deficiencies may be devoid of clinical symptoms, but may be endangered during surgery and in cases of accidents.

Congenital homozygous deficiency of protein C or S is associated with a considerable risk of thromboembolism (Purpura fulminans) as early as during the first year of life. Heterozygous deficiencies can remain clinically inconspicuous for long periods of time.

An acute or chronic **acquired reduction of factors belonging to the prothrombin complex** may be caused by loss or dilution, consumption or limited synthesis. Synthesis of factor V, antithrombin, proteins C, S and Z as well as of other clotting factors and inhibitors may additionally be diminished to various degrees. In cases of acute liver failure, not only is a diminished synthesis observed, but a defective synthesis is to be anticipated along with elimination disorders [80].

If vitamin K is deficient, or if following ingestion of a vitamin K antagonist, the liver cells cease to produce mature clotting factors of the prothrombin complex, a deficiency of plasma factors II, VII, IX, X as well as of proteins C, S and Z may result.

When coumarin derivatives are used for oral anticoagulation, the fact that the synthesis of the four clotting factors depends on sufficient amounts of vitamin K is used therapeutically for prophylaxis of thromboembolic events: the ingestion of such vitamin K antagonists reduces the clotting potential to such an extent that the patients concerned no longer have an increased risk of thrombosis, while the induction of an increased risk of bleeding is also prevented for as long as possible. PCC is used for the short-term specific replacement of vitamin K-depend-

ent clotting factors under the following circumstances: severe bleeding complications caused by overdosing, urgently necessary surgical interventions as well as accidents resulting in severe bleeding.

Half-lives of clotting factors
Half-lives are as follows:

Prothrombin	48–60 hours
Factor VII	1.5–6 hours
Factor IX	20–24 hours
Factor X	24–48 hours
Protein C	1.5–6 hours
Protein S	24–48 hours
Protein Z	24–48 hours

These half-lives may be considerably shorter during pronounced catabolic states, in severe liver damage and in disseminated intravascular coagulation (DIC).
Low-dosed administration of recombinant factor VIIa is an effective alternative.

7.2.4 Storage, shelf life and package sizes*

PCC currently commercially available are to be stored at a maximum temperature of 25°C or at +2°C to +8°C. The ready-to-use solution must be administered immediately. Longer lifetimes of the reconstituted solutions must be avoided for sterility reasons and possible instability of the clotting factors. Attention should be paid to the product information leaflets by the manufacturer.
PCC is available in lots of 200, 250, 300, 500 or 600 U, relating to the factor IX content in the product. Most manufacturers provide the content levels of activated factors II, VII, X and of proteins C and S either based on the specific batch or as average values.

7.2.5 Indications and dosage

Prospective clinical studies for the indications provided are scarcely available. The following recommendations can be provided on the basis of these few studies and of long years of clinical experience:

- In cases of severe liver damage, in disseminated intravascular coagulation and loss or dilution coagulopathy, the prothrombin complex deficiency may be pronounced to such a degree that **in addition** to FFP infusion (see chapter 4) substitution with PCC is required [33].
- While under oral anticoagulation therapy, PCC therapy is the preferred treatment together with vitamin K in patients with episodes of major bleeding, in urgent essential surgery and emergencies [15, 21, 72, 74]. FFP should only be used in cases where PCC is unavailable or contraindicated (e.g. in known heparin-induced thrombocytopenia type II).
- Replacement with clotting factor concentrates is not always necessary in factor II, VII, IX and X deficiencies. Depending on the cause, localization and extent of manifest or imminent bleeding, other therapeutic measures (e.g. vitamin K substitution, inhibition of activation of the clotting system or of hyperfibrinolysis) are primarily indicated [33].
- Prothrombin time is suitable as a screening test. This can also be used for follow-up control. FFP serves as second-line therapy in complex hemostatic disturbances.

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* see section 0.4

It is essential for all indications: Following dissolving the lyophilisate, PCC is administered as an intravenous infusion according to the specifications in the expert information (Summary of Product Characteristics).

7.2.5.1 Congenital prothrombin complex factor deficiency

In congenital deficiency PCC can be administered for the cessation of spontaneous, traumatic and perioperative bleeding when insufficient factor activity prevents hemostasis.	**2 C+**
In congenital deficiency PCC can be administered to prevent bleeding in cases of factor deficiencies, during and after surgery to ensure wound healing and, in individual cases, as prophylactic long-term treatment.	**2 C+**

Note:
Hemophilia B (factor IX deficiency) and congenital factor VII deficiency should always be treated with the respective single factor concentrates. Exceptions: PCC may be employed in emergencies only when factor IX or factor VII concentrates are not available.

Dosage in congenital deficiencies
Dosage and duration of replacement therapy depend on the severity of the disorder, its localization and the extent of bleeding.

As a rule, 1 U of PCC/kg body weight increases the activity of factors VII and IX by 0.5–1 % and the activity of factors II and X by 1–2 %. 1 U PCC/kg body weight increases the thromboplastin time by approximately 1 %.
Depending on each case, the maintenance dose may be half of the initial dose. The respective half-lives as well as minimum activities required for hemostasis should be taken into account.

High initial doses of 40 U/kg body weight are indicated in:
- life-threatening or extensive bleeding (e.g. cerebral bleeding, bitten tongue, retroperitoneal bleeding, compartment syndrome, muscle bleeding, gastrointestinal bleeding and oral cavity bleeding),
- surgery involving large wound surfaces and/or danger of extensive bleeding (including tonsillectomy).

Doses of more than 40 U/kg body weight should be administered as several partial doses.

Low initial doses of 20 U/kg body weight are indicated in
- minor skin, muscle and joint bleeding,
- epistaxis,
- hematuria and
- surgery involving small wound surfaces (e.g. tooth extraction, herniotomy).

After application of the initial dose, activity of deficient clotting factors should be repeatedly determined in order to monitor the therapeutic outcome and to establish a firmer base for further treatment.
In addition to procoagulator therapy, vitamin K should be substituted.

7.2.5.2 Acquired prothrombin complex factor deficiency

In cases of bleeding or for perioperative replacement in surgery involving an increased risk of bleeding PCC is indicated in patients with single or multiple prothrombin complex factor deficiencies when the residual activity of factors II, VII, IX or X or prothrombin time is below 40 %: (INR >2):

- in cases of overdosing oral vitamin K antagonists (prothrombin time in % below therapeutic level, INR above therapeutic level) or at discontinuation of therapy with oral anticoagulants in emergencies (e.g. non-elective surgery),
- in severe liver disease as well as during and following liver transplantation. In these cases complex impairment of hemostasis is to be considered (see ch. 4),
- in vitamin K deficiency (e.g. high-dose antibiotic therapy, persisting diarrhea, resorption disorders) with life-threatening bleeding,
- in life-threatening bleeding in neonates or infants with severe vitamin K deficiency.

Dosage in acquired deficiencies

Dosage and duration of replacement therapy depends on the severity of the hemostatic disorder, localization, extent of bleeding as well as the clinical situation [9, 33, 83].

Prior to administering PCC, clotting analyses are to be performed, provided that the patient's condition permits this. To estimate both initial and maintenance doses, the determination of the prothrombin time (PT) is required.

However, considerable individual variation may occur and the reference values provided here may not be reached. In cases of severe bleeding initial bolus doses of 20–25 U/kg body weight are recommended.

In cases of slight bleeding, slight injury or minor surgery, factor activities of 20–40 % are sufficient (corresponding to a PT value of 30–50 %); whereas in severe injury or major surgery factor activities of 50–60 % (PT value 60–80 %) should be maintained. Higher factor activities may be necessary in individual cases.

Thirty to sixty minutes following the first application a further clotting analysis is necessary. Indication and dosage of further PCC administration depend on the patient's condition and laboratory results.

7.2.5.3 Interrupting the effects of vitamin K antagonists

Bleeding that occurs during anticoagulation therapy with coumarin derivates may be caused either by overdose of anticoagulants or by displacement of the coumarin derivates from albumin binding by other medication, leading to an increase in the concentration of free (and therapeutically effective) coumarin in patients' plasma. Moreover, decreased synthesis of clotting factors in liver disease (e.g. acute hepatitis) can reinforce the effect of anticoagulation therapy with coumarin derivates. Bleeding often results spontaneously from initially minimal lesions.

Therapy consists of

- discontinuing anticoagulants,
- administering vitamin K (10–20 mg) to reverse the effect of anticoagulants,
- PCC is indicated only in cases of acute life-threatening bleeding and emergency surgery. PCC has the advantage of normalizing the clotting defect in the shortest possible time.
- administration of low-dose anticoagulants that are immediately effective (also monitoring of the AT level) in the event that anticoagulation must be continued.

For decisions regarding therapy and for follow-up control, the prothrombin time (PT) should be determined. Regarding the dosage according to the desired PT value (30–50 % in slight bleeding, 60–80 % in severe bleeding), refer to section 7.2.5.2.

In the course of further therapy the half-life of coumarin derivates used (Warfarin 48 h, Marcumar 7 days) should be taken into account. Following further decline of the PT value, additional administration of vitamin K or PCC should be considered.
When INR is referred to in decisions on treatment and follow-up control, the following recommendation applies for the normalization of INR (PT in INR <1.3):

Table 7.2.5.3.1: Recommended dosage

Prothrombin time in INR (at the onset of treatment)	2.0–3.9	4.0–6.0	>6.0
Dosage (factor IX/kg body weight)	25	35	50

A maximum dose of 5,000 U should not be exceeded.

Table 7.2.5.3.2: Level of evidence regarding indication in acquired deficiency

Indication	**Level of evidence**	**Comments**
PCC shall be administered in order to achieve hemostasis in cases of severe bleeding during therapy with vitamin K antagonists. Prior to non-elective major surgery or in trauma (cases of emergency), PCC should be administered as a bleeding prophylaxis.	**1 B**	Vitamin K as supplement
In liver damage PCC could be administered in order to halt bleeding.	**2 C**	FFP as second line therapy
In acquired deficiency of prothrombin complex PCC could be administered in order to halt bleeding.	**2 C**	Vitamin K as supplement

7.2.6 Absolute and relative contraindications

- Disseminated intravascular coagulation (DIC).
- PCC is indicated in DIC with overt bleeding caused completely or partially by prothrombin complex factor deficiency, and only if the cause of the DIC is also being treated. In DIC PCC preparations should not be administered without monitoring and possibly normalizing the AT level [50].
- Heparin-induced thrombocytopenia type II, as almost all Prothrombin complex concentrates contain heparin (exception: currently in Europe only one heparin-free PCC containing antithrombin is commercially available in the Netherlands).
- During pregnancy and lactation PCC should only be used following careful consideration.
- Caution is advised for patients with known sensitivity to compounds contained in the preparation.

7.3 Factor VII concentrate

7.3.1 Preparation, quality criteria

Factor VII is isolated from large cryoprecipitate-poor plasma pools using ion exchange chromatography and adsorption to aluminum hydroxide. The only factor VII concentrate commercially available in Germany is standardized regarding its factor VII contents. The clotting activity is given as International Units (U).

7.3.2 Active constituents

The only concentrate commercially available in Germany contains the proenzyme (zymogen) factor VII that is part of the prothrombin complex (see section 7.2.2).

7.3.3 Physiological function

Clotting factor VII is effective as a procoagulator and is synthesized in the hepatocytes. A sufficient intracellular vitamin K concentration is necessary for its biosynthesis (see section 7.2.3).

7.3.3.1 Congenital factor VII deficiency

Depending on the autosomal recessive genetic defect and the related decrease in factor VII activity, congenital factor VII deficiency predisposes to bleeding.
Homozygous carriers of factor VII deficiency are characterized by a lower activity level (<10 %), while heterozygous carriers show decreased activity levels of between 10 % and 50 %. Although on average factor VII activities are lower in patients with a strong propensity for bleeding, this does not permit any prediction regarding a particular patient's disposition to bleeding. Thus there are asymptomatic patients who demonstrate only a few percent of residual factor VII activity as well as symptomatic patients demonstrating an activity of around 50 % [62]. PT values may even be marginal or only slightly lower.
Heterozygous genetic carriers of the factor VII deficiency may be without pathological findings, however they are at risk of bleeding in the event of surgery or trauma.
The mean **half-life** of factor VII following substitution is 5 h [75].

7.3.4 Storage, shelf life and package sizes*

Factor VII concentrate is generally stored at +2°C to +8°C. The ready-to-use solution should be administered immediately. Longer lifetimes of the reconstituted solutions must be avoided for sterility reasons and possible instability of the clotting factors. Attention should be paid to the product information leaflets provided by the manufacturer.
Package size is 600 U referring to the factor VII content of the preparation.

7.3.5 Application

7.3.5.1 General remarks

Following reconstitution of the lyophilisate, the factor VII concentrate is very slowly infused intravenously.
There are no prospective clinical trials on the indications listed here. Based on long-term clinical experience, the following recommendations are possible:

7.3.5.2 Congenital factor VII deficiency

- Treatment of bleeding disorders that were caused by isolated congenital factor VII deficiency.
- Prophylaxis of bleeding disorders that could be caused by isolated congenital factor VII deficiency.

* see section 0.4

Note:
Congenital factor VII deficiency should now only be treated with highly purified plasmatic or recombinant single factor concentrates. Only in emergencies in the absence of the availability of single factor concentrates is the administration of PCC advisable.

7.3.6 Dosage*

Dose and duration of the substitution therapy depends on the severity of factor VII deficiency as well as on the site and extent of bleeding and the clinical condition of the patient.
An International Unit (U) of factor VII activity corresponds to the activity of factor VII in 1 mL of normal human plasma (= 100 %).
The calculation provided below regarding the factor VII dose required is based on the empirical finding that 1 U of factor VII/kg body weight increases factor VII activity in plasma by approximately 1.7 % referred to the normal activity.

The dose required is determined using the following formula:
Dose U = body weight (kg) × desired increase in factor VII levels (%) × 0.6

The dose and the dosing interval should always be based on the clinical outcome in each individual case.

In patients with congenital factor VII deficiency the administration of factor VII in the event of hemorrhage or of surgical interventions shall be performed in accordance with Table 7.3.6.	**1 C+**

Table 7.3.6: Administration of factor VII in cases of bleeding or in surgical interventions

Grade of bleeding/type of surgical intervention	Factor VII activity levels desired [U/mL]	Duration of therapy
minor bleeding	0.10–0.20	a single dose
major bleeding	0.25–0.40	for 8–10 days or until healing is completed**
minor surgical interventions	0.20–0.30	a single dose prior to intervention or, in case the bleeding risk is assumed to be higher, until wound healing is completed
major surgical interventions	preoperative >0.50 then 0.25–0.45	for 8–10 days or until healing is completed**

**Based on clinical assessment, lower doses may be sufficient in individual cases towards the end of therapy, provided adequate hemostasis is achieved.

Dosing intervals have to be adjusted to the short half-life of factor VII in circulation amounting to approximately 3–5 hours.
Accordingly, the interpretation of levels in plasma must be performed with the full awareness of the precise time of administration (peak level – trough level).

* see section 0.4

In individual cases of congenital factor VII deficiency (severe factor VII deficiency) administration shall be performed as a prophylaxis.	**1 B**

7.3.7 Absolute and relative contraindications

- Factor VII concentrate must be applied with caution in patients with known intolerance to components in the product.
- Factor VII concentrate should be applied only following careful consideration during pregnancy and lactation.

7.4 Recombinant factor VIIa

7.4.1 Preparation, quality criteria

Recombinant factor VII (rFVII) is obtained from cDNA from the human factor VII codon using baby hamster kidney cells. Activation of the single-chain rFVII to double-chain rFVIIa is done by hydrolytic cleavage between positions 152 (arginine) and 153 (isoleucine) of the peptide chain. rFVIIa concentrate does not contain any other activated clotting factors. Further purification of rFVIIa includes several chromatography steps as well as virus inactivation. The purified product is then portioned and lyophilized.

7.4.2 Active constituents

Eptacog alfa (activated) is recombinant clotting factor VIIa (rFVIIa) with a molecular weight of around 50,000 Daltons. Following reconstitution 1 mL of solution contains 0.6 mg of Eptacog alfa (activated). Additional ingredients: sodium chloride, calcium chloride dihydrate, N-glycylglycine, Polysorbate 80, mannitol).
The excipients used have no pharmacological effects.

7.4.3 Physiological function and pharmacological effect

Under physiological conditions only 1 % of factor VII in its activated form circulates in the blood. **By injecting a pharmacological bolus dose of factor VII in its activated form, the factor VIIa concentration is briefly increased numerous times over normal physiological concentrations** so that a maximum number of TF (tissue factor) molecules form complexes with factor VIIa. In doing so, an activation of the clotting system is achieved that is limited to the site of trauma. The supraphysiological factor VIIa level in the blood also has the effect that factor VIIa binds to activated platelets with a lower degree of affinity. In addition, factor VIIa activates factor X to factor Xa irrespective of the presence of TF. As a consequence, thrombin formation is accelerated and amplified. Thrombin formation is able to compensate a deficiency in factor VII, factor IXa-VIIIa complex or factor Va-Xa complex. Thus a pathway for the initiation of coagulation is formed that is independent of a sufficient activation of factors IX and/or VIII. Due to the lower affinity of factor VIIa to activated platelets, a supraphysiological (pharmacological) dose of rFVIIa is necessary to achieve hemostasis.
In contrast, FVIIa has almost no affinity at all to inactive platelets, which may be the reason for the lack of any relevant systemic clotting activation by supraphysiological doses of factor VIIa [31, 42].

7.4.4 Storage, shelf life and package sizes*

Recombinant factor VIIa must be stored at +2°C to +8°C. The preparation is commercially available in three sizes: 1.2 mg, 2.4 mg and 4.8 mg. The units are specific for rFVIIa and incomparable with units of other clotting factors. Shelf life is 3 years. Following reconstitution, rFVIIa may be stored at 2–8°C for 24 hours.

7.4.5 Licensed indication and dosage

General recommendation: The following preconditions apply for the administration of rFVIIa: a fibrinogen level of ≥1 g/L, a platelet count of ≥50,000 (or better ≥100,000) × 10^9/L and a pH value of ≥7.2 [63, 92].

7.4.5.1 Bleeding and prevention of bleeding in patients with inhibitors in congenital hemophilia A

An intravenous bolus dose of 90 µg/kg body weight is recommended as an initial and maintenance dose. The bolus injection should be administered over a period of 2–5 minutes. Due to the short half-life of rFVIIa, therapy intervals are initially 2–3 hours until hemostasis is achieved. In individual cases a shorter interval may be necessary. If therapy is to be continued, therapy intervals can be prolonged gradually to 4 and up to 12 hours, provided the continued treatment is indicated [1, 5, 31, 60, 78, 85].
In individual cases (e.g. in children who have a higher clearance compared to adults [93]) a higher dosage may be necessary. No maximum daily dose for rFVIIa is specified, as e.g. for activated prothrombin complex preparations. rFVIIa may also be administered on an outpatient basis.

In the event of bleeding in hemophilic patients with clotting factor VIII or IX inhibitors, rFVIIa shall be administered at a dose of 90–120 µg/kg body weight as bolus in 2–3-hour intervals until hemostasis is achieved. It is also possible to administer a single injection of 270 µg/kg body weight.	**1 C+**

Due to the shorter half-life of rFVIIa in children, it may be reasonable to increase the dosage levels up to threefold the initial concentration. In clinical trials a dose of up to 270 µg/kg body weight per bolus was found to be safe and at least equal to the repetitive administration of 90 µg/kg body weight. Based on data from trials which included children and adults, it may be expected that the number of necessary venous injections can be reduced by a single bolus megadose [45, 46, 78]. A randomized multicenter double-blind prospective trial on patients with frequently recurring bleeding could demonstrate that the frequency of bleeding episodes was markedly reduced by a dosing regimen of 90 µg/kg body weight per day or 270 µg/kg body weight, respectively, compared to the frequency prior to prophylaxis onset [52].

In the event of bleeding in hemophilic children with clotting factor VIII or IX inhibitors, rFVIIa shall be administered at a dose of 90–270 µg/kg body weight as bolus in 1.5–2-hour intervals until hemostasis is achieved.	**1 C+**

* see section 0.4

7.4.5.2 Bleeding and prevention of bleeding in patients with acquired inhibitors against clotting factors

In patients with inhibitors in acquired hemophilia A spontaneous autoantibodies to factor VIII occur and, in rare cases, to other clotting factors. The highest incidence has been observed in pregnant women, particularly during postpartum, and in older patients in their early seventies. Gender does not play a significant role in the incidence of autoantibodies. In sudden severe bleeding events the laboratory parameters which determine the course of treatment are a prolonged aPTT and, on performing further diagnostics, a positive plasma exchange test. In these patients it is necessary to initiate treatment without delay, in particular **prior** to commencing any surgical interventions [1, 5, 6, 31].

In the event of severe bleeding episodes in patients with inhibitors in acquired hemophilia A, rFVIIa shall be administered at a dose of 90–120 µg/kg body weight as bolus in 2–3-hour intervals until hemostasis is achieved.	**1 C+**

FEIBA can also be used as an alternative treatment of inhibitors in acquired hemophilia A (see section 6.1.4). Regarding dosage, the reader is referred to the recommendations for patients with congenital hemophilia and inhibitors in section 6.5.3.3, subsection "Treatment of acute bleedings (children and adults)".

7.4.5.3 Bleeding and prevention of bleeding in patients with Glanzmann's thrombasthenia with antibodies to glycoprotein IIb/IIIa and/or HLA and with former or current refractoriness to transfusion of platelet concentrates

rFVIIa has successfully been used in achieving hemostasis in patients with severe congenital or acquired allo- or autoantibody-induced thrombopathies and thrombopenias [34].

In patients with Glanzmann's thrombasthenia and severe bleeding a bolus dose (80–120 µg/kg body weight) shall be administered three times in the course of 2 hours.	**1 C+**

Distinctive secondary bleeding episodes have been observed despite primary hemostasis in cases where no treatment with rFVIIa was conducted [71].
There are also anecdotal reports on positive clinical experiences with rFVIIa in patients with Bernard-Soulier syndrome, storage pool disease [4] and immunothrombopenia [17, 34, 94].

In patients with congenital thrombopathies such as e.g. Bernard-Soulier syndrome, storage pool disease and severe bleeding the administration of rFVIIa at a bolus dose of 90–120 µg/kg body weight could be indicated.	**2 C**

Bleeding has been frequently observed to cease following 1 or 2 injections.

7.4.5.4 Bleeding and prevention of bleeding in patients with congenital factor VII deficiency

Investigations on patients with congenital factor VII deficiency have demonstrated that rFVIIa should be generally administered at a dose of 15–30 µg/kg body weight as bolus every 6 hours until hemostasis is achieved, provided that activity levels <10 % and in the event of bleeding. The time interval until the next bolus can be prolonged during the course of treatment, depending on the bleeding pathology. In many instances a subsequent injection regime of twice a day is sufficient [41, 62].

In patients with congenital factor VII deficiency rFVIIa shall be administered at a dose of 15–30 µg/kg body weight as bolus every 6 hours. Administration can also be performed as a prophylaxis.	**1 C+**

7.4.6 Off-Label Use*

Significant effects of rFVIIa administration (200 µg/kg body weight followed by 2 additional bolus doses of 100 µg each/kg body weight after 1 and 3 hours) have been observed in a placebo-controlled phase-2 trial in patients with severe bleeding following blunt trauma. Transfusion requirements of RBC concentrates decreased significantly, and the frequency of massive transfusions as well as the rate of ARDS compared to placebo were significantly reduced. In open trials on the use of rFVIIa in case of massive bleeding [28, 47, 63] 71 trauma patients received mean rFVIIa doses of 90–140 µg/kg body weight per patient using an average of 1.6 bolus injections.
In patients with life-threatening postpartum hemorrhage rFVIIa has led to hemostasis in a number of cases after all other conservative and surgical conventional hemostatic therapies had failed [2, 11, 37], and in one case it was also possible to avoid a hysterectomy. In the majority of cases one or two rFVIIa bolus doses of approx. 20–120 µg/kg body weight were applied.
In several large case studies involving patients with bleeding complications following cardiac surgery, rFVIIa has led to hemostasis after all other conservative and surgical conventional hemostatic therapies had failed [43, 95]. In most cases rFVIIa was administered as a bolus at a dose ranging between 30 and 90 µg/kg body weight.
In case reports and in a controlled trial patients with hematologic oncologic diseases with severe bleeding episodes that were refractory to conventional therapy received rFVIIa; this also included patients following stem cell or bone marrow transplantation [67]. The mean single dose was observed to be just under 90 µg/kg body weight. A recent review article [23] states that bleeding has been halted in many patients following the first injection.
In individual cases of drug-induced life-threatening bleeding (due to factor IIa, factor Xa inhibitors, glycoprotein IIb/IIIa inhibitors), following the failed application of other procoagulatory substances, an administration of rFVIIa may be considered at a dose of 90–120 µg/kg body weight per bolus [8, 38, 88].

7.4.7 Adverse reactions

A risk of thromboembolic events is involved in the employment of genetically engineered activated clotting factor VII (rFVIIa). Such adverse reactions have very rarely been observed (<1:25,000 standard doses) [1] when using rFVIIa as its only indication licensed to date: patients with inhibitors in hemophilia A (see chapter 11). Corresponding clinical trials on children demonstrated no increased rate of thromboembolic complications compared to conventional doses, even when using doses of 270 µg/kg body weight [45, 46, 78].
Due to the ongoing controversies regarding the statistical methods used [3, 58, 66, 90], no ultimate assessment of the registry data published on thromboembolic complications is possible. Thromboembolic events have occurred in the arterial and venous vascular system or in vessels damaged perioperatively or by trauma, in particular in patients receiving rFVIIa for non-licensed indications. Therefore the well-known adverse reactions of rFVIIa have to be specifically pointed out during the informed consent consultation between the physician and

* The legal issues involved in the Off-Label Use are pointed out in section 0.4.

the patient, in particular if the preparation is used accordingly. For an assessment of Off-Label Use of rFVIIa in acute blood loss the reader is referred to an exemplary review article [61].

7.4.8 Absolute and relative contraindications

Simultaneous or almost simultaneous administration of rFVIIa and activated prothrombin complex concentrates should only be performed following a strict risk-benefit analysis. The thrombogenic effect of activated prothrombin complex concentrate can thus be potentiated by simultaneous application of rFVIIa. In individual cases a temporary combined [48] or sequential application [18, 81] of rFVIIa and FEIBA was reported in hemophilia patients with inhibitors with a severe course of the disease who had demonstrated massive bleeding refractory to treatment. However, grave thromboembolic complications have been observed to occur in one patient [77]. Therefore the decision regarding the combined use of these preparations must be made individually and be adjusted to the clinical course.
A known intolerance against murine, hamster or bovine protein can be a contraindication.

7.5 Factor XIII concentrate

7.5.1 Preparation, quality criteria

The starting material is derived from pooled human plasma. The production is performed according to the Cohn/Oncley procedure. Following the separation of the cryoprecipitate and adsorption of the vitamin K-dependent factors of the prothrombin complex, the only factor XIII concentrate commercially available in Germany is obtained by precipitation with ethanol.

7.5.2 Active constituents

The product contains fibrin stabilizing factor XIII as its active component, namely both subunit factor XIII A (containing activity) and subunit factor XIII B (carrier protein); human albumin, sodium chloride and glucose are added as stabilizers.

7.5.3 Physiological function

Activated factor XIII (fibrin-stabilizing factor XIII) is a transglutaminase which cross-links fibrin covalently in the presence of calcium ions, thus increasing the mechanical firmness so that a firm three-dimensional fibrin net is formed resulting in definite hemostasis. In doing so, factor XIII integrates alpha-2 antiplasmin and fibronectin into the clot, thus protecting it on the one hand against premature fibrinolysis and, on the other, serving as chemical lead for fibroblasts immigrating into the wound area. Longitudinal interlinking of the fibrin strands occurs quite rapidly while transversal interlinking representing the actual mechanical stabilization takes several hours. In blood factor XIII is activated by thrombin and binds to fibrinogen, but more strongly to fibrin. Factor XIII is found in plasma, platelets and certain tissues. Its plasma concentration amounts to 22 mg/L; the biological half-life is about 96–120 hours. Factor XIII plays a physiological role in hemostasis, wound healing and in the maintenance of pregnancy during the first weeks after conception.
In the low concentration range the bleeding tendency correlates largely with the degree of factor XIII deficiency. Patients with severe congenital factor XIII deficiency particularly tend to experience umbilical cord stump hemorrhage, impaired wound healing and intracranial bleedings; women have a tendency towards habitual abortion. As in hemophilia, skin, mucous membrane, soft tissue and joint bleedings occur also. In general, there is no spontaneous

bleeding tendency in congenital deficiency and when factor XIII levels exceed 7 % of the normal values. However, single cases of severe hemorrhage and impaired wound healing have been observed in heterozygote patients with factor XIII levels of around 50 %, following surgery or trauma.
Acquired factor XIII deficiency is not rare. It may be caused by increased turnover (e.g. following intravascular clotting, sepsis, inflammatory intestinal diseases, systemic hematological disorders, increased blood loss, hyperfibrinolysis), by increased consumption (e.g. in major surgery) or by reduced synthesis (e.g. in liver disease). In patients with pre-existing coagulation activation prior to surgery (e.g. in tumor patients) a severe factor XIII deficiency might develop during surgery and thus cause massive intraoperative hemorrhage [19, 53, 96]. A typical symptom of a postoperative factor XIII deficiency is scattered secondary hemorrhage several hours following surgery whereas hemostasis during surgery was observed to be completely normal. In addition to severe hemorrhage, acquired factor XIII deficiency may also induce acute postoperative impaired wound healing. This becomes usually apparent 3–7 days following surgery. Chronic wounds such as venous ulcers (Ulcus cruris) or decubitus ulcers may also be linked with factor XIII deficiency.
A rare occurrence is inhibitor (antibody) formation in congenital factor XIII deficiency following replacement therapy or as autoantibodies [19].
Factor XIII is *not* determined by the screening tests PT and PTT because these tests only measure the point in time of onset of fibrin formation but not fibrin interlinking. The suspected diagnosis of factor XIII deficiency should be investigated further by laboratory tests in all cases of bleeding of unknown origin, especially in postoperative scattered secondary hemorrhage several hours following surgery or in intraoperative hemorrhage occurring in patients with activated coagulation.

7.5.4 Storage, shelf life and package sizes*

Factor XIII concentrates should be stored at +4°C to +8°C in the closed cardboard box. The shelf life is 3 years and is indicated on the box and the container. Ready-to-use solutions should be administered immediately, as there are no preservatives included.
Factor XIII concentrate: 250 U/4 mL; 1,250 U/20 mL.

7.5.5 Range of application, dosage, mode of administration*

Congenital factor XIII deficiency
Due to the rarity of the disease, there is only a limited clinical knowledge available. Indications are prevention and therapy of hemorrhage and impaired wound healing. *Controlled studies do not exist due to the rarity of these congenital defects.*

Table 7.5.5.1: Substitution therapy in congenital factor XIII deficiency

Defect	Modality
Severe congenital factor XIII deficiency	Factor XIII concentration must be elevated and maintained within the reference range (>50 %) prior to all surgical procedures until wound healing is complete. Prophylactic continuous therapy is recommended only on an individual basis.

* see section 0.4

Acquired factor XIII deficiency

Consumption of factor XIII may develop in the context of hemostasis and wound healing during and following major surgery (e.g. in general and abdominal surgery or cardiac surgery) [16, 79]. The extent of the decline in factor XIII concentration is also crucial while there is no clearly defined critical threshold either for hemorrhage or for impaired wound healing. In patients with factor XIII deficiency undergoing coronary surgery substitution leads to a significant reduction of drainage volumes and the extent of blood transfusion [27].

In patients with coagulation activation prior to surgery, caused by e.g. a malignant process, factor XIII deficiency becomes manifest intraoperatively rather than postoperatively through secondary bleeding [53, 96].

In patients with therapy-refractory postoperative wound healing disorders and factor XIII deficiency (level <70 %) factor XIII substitution leads to a significant improvement of wound healing, potentially leading to complete healing [64] according to several controlled randomized double-blind trials. In chronic wounds (e.g. venous ulcers or decubitus ulcers) factor XIII therapy has also led to significantly improved healing [7, 97], while the best results were achieved with topical application which is not licensed in Germany [98].

In a pilot study investigating patients with inflammatory bowel disease [59] the substitution of factor XIII led to a decreased bleeding tendency, mitigated pain and reduced stool frequency.

In severe chronic liver disease factor XIII residual activities correlate with the degree of cirrhosis. Low levels of factor XIII (<50 %) in patients during evaluation for liver transplantation is an unfavorable prognostic factor regarding future hemorrhagic episodes and survival [89]. Substitution with factor XIII should be considered if bleeding persists following second line substitution with fresh frozen plasma and/or PCC and if factor XIII levels continue to be markedly lower than the reference range (<50 %) or if secondary bleeding occurs under the same circumstances.

A relevant factor XIII deficiency can develop in patients with leukemia and other hematological systemic disorders. On the one hand, elastase released from leukemia cells unspecifically destroys factor XIII [19]; on the other, factor XIII deficiency is induced by tumor-derived thrombocytopenia as in healthy individuals almost half of the circulating coagulation factor XIII is stored in platelets. In addition, leukemia can cause DIC with increased turnover and consumption of factors and inhibitors. Accordingly, proneness to bleeding in patients with leukemia depends on multiple parameters; the decision regarding substitution with factor XIII must be taken on an individual basis.

Disseminated intravascular coagulation can also result in relevant factor XIII deficiency. In the event of relevant hemorrhage the consumed factors should be substituted.

Indications and dosage

In severe congenital deficiency the substitution of factor XIII has become the most widely established practice. In the majority of cases no continuous substitution is required but rather a perioperative treatment on demand or in cases of bleeding [65].

Factor XIII shall be substituted in congenital factor XIII deficiency in order to treat resulting hemorrhagic diatheses such as bleeding and impaired wound healing and/or prophylactically, e.g. prior to surgery.	**1 C+**

In principle, dosage of factor XIII **in congenital deficiency** follows the same rules as that of factor VIII and IX concentrates:

1 U/kg body weight of factor XIII leads to an increase in plasma activity by 1–2 %.

In cases of severe hemorrhage 10–20 U/kg body weight per day should be administered until hemostasis is achieved. Prior to surgery up to 35 U/kg body weight or more are required until the desired levels are achieved. In major surgery standard levels (>50 %) should be aimed for. In continuous prophylactic administration significantly fewer repeated injections are required than in deficiencies of other factors due to the long biological half-life (100–120 hours). In single cases the half-life of factor XIII may also vary considerably.

Factor XIII substitution for treating hemorrhagic diatheses should be performed if the latter are entirely or in part derived from an acquired factor XIII deficiency.	**2 A**
Factor XIII substitution can be performed as supportive therapy in impaired wound healing, e.g. following extensive surgery and injury, if these are entirely or in part derived from an acquired factor XIII deficiency.	**2 B**

The following rules apply in determining the dosage of factor XIII **in acquired deficiency**:

- In cases of bleeding at least 15–20 U/kg body weight per day until normal levels of factor XIII or hemostasis are achieved.
- In patients with therapy-refractory wound healing disorders 15–20 U each/kg body weight should be administered per day over the course of 3 days (days 0, 1 and 3).

Concluding assessment of factor XIII diagnostics:

- Factor XIII levels are not determined by the screening tests PT and aPTT; if factor XIII deficiency is suspected factor XIII should always be determined separately.
- In case a prompt determination of factor XIII is not possible, the risk of persistent bleeding should be weighed against that of a blind administration of factor XIII, particularly in acute severe hemorrhage.

7.5.6 Absolute and relative contraindications

Known intolerance of the components in the product. In case of fresh thrombosis caution is advised due to the fibrin stabilizing effect. In long-term administration patients should be monitored carefully for the development of inhibitors.

7.6 Fibrin glue

7.6.1 Preparation, quality criteria

The starting material is derived from pooled human plasma. The production is performed according to the Cohn/Oncley procedure.

7.6.2 Active constituents

Active constituents of fibrin sealant are human fibrinogen, human thrombin, human factor XIII, bovine aprotinin and calcium chloride [20].

7.6.3 Storage, shelf life and package sizes*

Factor concentrates should be stored at +2°C to +8°C, and fibrin glue in a deep-frozen state, when required. Information regarding the shelf life can be obtained from the package leaflet. Ready-to-use solutions should be administered immediately.
Fibrin sealants are available in a lyophilized and deep-frozen state.

Dry substances in the combi set:
0.5 mL/1.0 mL/3.0 mL
2 deep-frozen solutions:
0.5 mL/1.0 mL/2.0 mL
Dry substances in the kit:
1.0 mL/2.0 mL/5.0 mL

7.6.4 Range of application and dosage

Fibrin glue has a wide application range in surgery. The immediate hemostatic effect of the sealant is taken advantage of. Sealing by fibrin analogously leads to the final stage of hemostasis, to polymerization of the fibrin monomer, by the addition of the thrombin solution and calcium chloride. The fibrinolysis inhibitor aprotinin is added to the sealant for stabilization of this fibrin lattice. The fibrin lattice resulting from the sealing process is completely metabolized. The use of fibrin sealant in patients with coagulopathy can lead to a reduction in the demand for factor concentrates.
Fibrin sealant is used in surgery to achieve local hemostasis in large bleeding parenchyma areas and by injection surrounding the area of bleeding gastrointestinal ulcers. It is also used for the fixation of transplants and implants (e.g. hernia mesh patches), for joining and fixation of nerve ends, sealing vascular prostheses, in septoplasty, sealing cerebrospinal fluid leaks etc. [44, 73, 84]. These applications are based on retrospective studies.

Local application of fibrin sealant could be performed in patients requiring hemostasis in large bleeding parenchyma areas.	**2 C**
Further local applications of fibrin sealant could be as follows: to halt bleeding arising from gastrointestinal ulcers, fix transplants and implants (e.g. hernia mesh patches), join and fixate nerve ends, seal vascular prostheses, in septoplasty and to seal cerebrospinal fluid leaks.	**2 C**

Biochemical investigations demonstrate distinctive differences in comparison to autologous products [14].

7.6.5 Adverse reactions

Local application of fibrin glue in neurosurgery has reportedly had a proconvulsive effect attributed to tranexamic acid that is possibly contained in fibrin sealant and has an effect on cerebral GABA receptors [25].

* see section 0.4

7.7 Documentation

According to article 14 TFG, there is an obligation to perform a patient- as well as product-related batch documentation for fibrinogen, PCC, factor VII and factor XIII concentrates, fibrin sealant and recombinant factor VIIa.

7.8 References

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8 Inhibitors

8 Inhibitors

8.1 Antithrombin

8.1.1 Preparation

Human antithrombin (AT) concentrates are produced from large pools of human plasma by affinity or ion exchange chromatography followed by further purification steps [20]. Concerning the requirements of the individual blood donor as well as quality criteria required of the product, the reader is referred to the national and European acts and directives/guides listed in chapter 1, section 1.1.

8.1.2 Active constituents

The active constituent is human antithrombin. Human albumin or other substances can be used as stabilizers. Some preparations contain small amounts of heparin.

8.1.3 Physiological function and deficiency disorders

Antithrombin (former designations: antithrombin III, progressive antithrombin, heparin cofactor) belongs to the family of serine protease inhibitors (SERPINS) and is synthesized in the liver. Its synthesis is independent of a sufficient supply of vitamin K. Its concentration in normal human plasma amounts to 0.15–0.39 g/L, which equals an activity relative to standard human plasma between 80 and 120 %. The biological half-life is 1.5–2.5 days. Aside from antithrombin circulating freely in human plasma, most of it is bound to vascular endothelial cells by heparan.
Antithrombin is the most important inhibitor of thrombin and factor Xa. To a lesser extent it also inhibits activated clotting factors IX, XI and XII, as well as factor VIIa to a small extent. The activated clotting factors (proteases) are inhibited by antithrombin by formation of irreversible complexes consisting of antithrombin and the corresponding protease. Under physiological conditions, the affinity of thrombin to its substrate fibrinogen is higher than to antithrombin. Inactivation of the activated clotting factors – thrombin and factor Xa – by antithrombin is a slow process which is, however, exponentially accelerated in the presence of heparin and heparan which act as biological catalysers. After formation of the irreversible antithrombin-protease complex, heparin dissociates itself from the complex and is available for reaction with other antithrombin molecules.
Along with its inhibitory activity in coagulation, antithrombin also has anti-inflammatory properties.
Binding of antithrombin to heparin-like glycosaminoglycans of the endothelial cells causes prostacyclins to be released from endothelial cells. Their secretion causes reduced release of cytokines from activated monocytes and/or of oxygen radicals from granulocytes, as well as an inhibition of platelet adhesion and aggregation.
Congenital antithrombin deficiency is a dominant autosomal hereditary disease characterized by a reduced activity of antithrombin with lowered or normal antithrombin-protein concentrations. The estimated prevalence of the disorder varies between 1:5,000 and 1:40,000. The patients exhibit antithrombin activities of about 50 %. By the age of 50, two thirds of them have experienced a thromboembolic event, especially deep leg and pelvic vein thrombosis and/or lung embolism.

Acquired antithrombin deficiency can result from reduced synthesis, increased consumption or loss. **Reduced synthesis** of antithrombin is caused by acute or chronic damage of the liver parenchyma. In such cases synthesis of both coagulators and inhibitors is equidirectionally reduced. Acute liver failure leads to drastically reduced synthesis. In addition, antithrombin consumption is often increased. In cases of severe liver failure the diagnosis of a disseminated intravascular coagulation (DIC) is often only possible with difficulty, because the concentration of both clotting factors and fibrin cleavage products may be lowered [21, 31, 32].
Increased consumption of antithrombin occurs above all in disseminated intravascular coagulation (DIC) [29, 45]. DIC is not a primary disorder of the clotting system, but rather results from certain diseases such as sepsis, obstetric complications [48], malignant diseases and others. DIC is diagnosed with reference to the status of the primary disease, the clinical situation and unambiguous pathological hematostatic findings (e.g. rapidly decreasing platelet counts, prolonged Activated Partial Thromboplastin Time [aPTT] as well as prothrombin time, increased concentration of D-dimers or fibrin monomers, loss of antithrombin activity).
On the one hand, intravascular activation of clotting can lead to impaired organ perfusion, and, on the other hand, to bleeding caused by loss of clotting factors and platelets followed by reactive hyperfibrinolysis. On the assumption that antithrombin inhibits the activated clotting factors circulating in the vascular system, antithrombin concentrates have been administered in individual cases [29, 44, 48] and in clinical trials [8] with the aim of interrupting DIC and preventing multiple organ failure. In these studies, the duration of DIC could be significantly shortened, certain organ functions were found to be improved, but the mortality of patient groups treated with antithrombin was not reduced significantly. Evidence from prospective controlled clinical trials indicating that the DIC death rate could be reduced by the administration of antithrombin concentrates has not been reported up to now. However, a subgroup analysis demonstrated a beneficial effect [31].
Increased loss of antithrombin occurs in nephrotic protein loss syndrome patients. In the event of ascites a considerable amount of antithrombin may also be lost into ascites fluid.

8.1.4 Storage, shelf life and package sizes*

Depending on the specific product, antithrombin concentrates can be stored in the refrigerator (at temperatures between +2°C and +8°C) or at room temperature. As the stability of the lyophilized products varies between different manufacturers, product information leaflets should be consulted in detail. Ready-to-use solutions must be used immediately, unless the manufacturer provides information on prolonged shelf-life.
Standard package sizes are 500 and 1,000 U.

8.1.5 Range of application, dosage*

8.1.5.1 Indications

8.1.5.1.1 Congenital antithrombin deficiency

Patients with congenital antithrombin deficiency can generally be effectively treated with oral anticoagulants. In cases of thromboembolic events, after an acute treatment with antithrombin and heparins, a treatment with oral anticoagulants on a long-term basis is necessary.

* see section 0.4

The following applications of antithrombin in **particular clinical situations in patients with congenital antithrombin deficiency** are based solely on clinical experience [16]: controlled prospective trials are lacking.

Antithrombin substitution can be applied to optimize heparin therapy, e.g. in extracorporeal circulation or as prophylactic application in recurrent thromboses, until switching to oral anticoagulant is completed.	**2 C+**
Antithrombin substitution can be applied to avoid thromboembolisms in situations associated with an increased risk of thromboembolism (e.g. hip replacement).	**2 C+**
Antithrombin substitution can be applied in neonates with congenital antithrombin deficiency to prevent thromboembolic complications in the postnatal phase.	**2 C+**
In patients with congenital antithrombin deficiency pregnancy poses a particular problem. To avoid thromboembolic complications, therapy with low-molecular heparins is indicated. Additional antithrombin may be indicated for cases with a particular propensity to thrombosis (during the peripartal period, confinement after childbirth, recurrent thrombosis, combinations with other congenital thrombophilic defects, factor V Leiden mutation, prothrombin mutation, protein C and S deficiencies).	**2 C+**

If replacement therapy with antithrombin is indicated, antithrombin activity of >70 % in plasma should be maintained.
The **necessary dose** can be estimated using the following rule:

1 U AT/kg body weight increases AT activity by 1−2 %.

If antithrombin substitution is carried out simultaneously with heparin therapy, a decreased half-life of AT from 1.5−2.5 days to less than 1 day must be taken into account, that is, a substitution therapy with antithrombin may intensify the effect of an ongoing heparin therapy to the extent that increased bleeding episodes may occur due to an overshooting heparin effect.

8.1.5.1.2 Acquired antithrombin deficiency

At any rate, the causes of hemostasis must first be investigated by clinical analysis and laboratory tests before a reasonable and effective therapy with antithrombin can be initiated.

8.1.5.1.2.1 Reduced synthesis

If bleeding occurs due to a deficiency of factors II, VII, IX and X in patients with acute or chronic liver parenchyma damage, Prothrombin complex concentrate (PCC) should be administered (see chapter 7.2). In rare cases a simultaneous antithrombin substitution may be indicated to prevent the activation of clotting.

8.1.5.1.2.2 Increased consumption of antithrombin

8.1.5.1.2.2.1 Antithrombin in case of sepsis

A comprehensive clinical trial was conducted, involving patients with severe sepsis and multiorgan failure who were treated with antithrombin vs. placebo, in order to clinically assess the potential benefit of the anti-inflammatory effect of antithrombin. It was the aim of the trial to mitigate multiorgan failure and other sequelae and to improve the survival rate by administration of antithrombin. The effect of antithrombin administration (30,000 U over 4 days) versus placebo was investigated prospectively in 2,314 patients with severe sepsis. There was no difference in the 28-day mortality (38.9 % in the antithrombin vs. 38.7 % in the placebo group), and the rate of bleeding events was significantly increased in patients treated with

antithrombin (23.8 % vs. 13.5 % in the placebo group). Considering the patients (n=698) without concomitant heparin therapy, mortality was slightly lower in the group treated with antithrombin, however, even under these terms, there was no significant difference [48]. A post hoc analysis of 563 patients involved in the study mentioned, who had received no heparin and who fulfilled the criteria of a DIC diagnosis, found only a difference in the mortality rate 28 days after treatment; mortality rates after 90 days was similar in both groups (29.9 % vs. 32.9 % in the placebo group). However, in patients with severe sepsis and DIC who were treated with antithrombin there was a higher incidence of bleeding complications [31]. When exclusively comparing 229 (out of 563) patients with an established DIC, the mortality rate in the placebo group was 40 % (46/115) whereas only 25.4 % (29/114) of the patients in the antithrombin group died. This difference was significant both after 28 and 90 days.

A high-dosed administration of antithrombin with the aim of using its anti-inflammatory effect is not indicated in patients with severe sepsis without the criteria for a DIC diagnosis.	**1 B**

8.1.5.1.2.2.2 Antithrombin in DIC

There are only few and small-scale trials regarding the application of antithrombin in DIC derived from various causes [24, 29, 30]. Based on the reported data, substitution of antithrombin up to levels >70 % appears justified if the corresponding clinical picture is present (underlying illness predisposing to develop DIC, concomitant organ dysfunction and typical alterations of laboratory parameters). This is supported by the subgroup analysis of the antithrombin–sepsis study [31]. In particular this applies in cases when the administration of coagulation factors is required due to clinically relevant hemorrhage. Substitution of antithrombin is not justified if solely based on low antithrombin activity and without the corresponding clinical pathology.

In clinically established DIC and accompanying antithrombin deficiency antithrombin substitution shall be carried out. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.)	**1 C+**

8.1.5.1.2.3 The administration of antithrombin is not indicated:

- in chronic liver cell damage or reduction of functional liver parenchyma when the hemostatic potential is stable at a low level without signs of DIC and with no risk of bleeding,
- in increased antithrombin loss in nephrotic syndrome and in the presence of ascites, as antithrombin given intravascularly is lost rapidly through the kidneys or diluted into the ascites fluid and thus cannot fulfill its function,
- in hemodilution, as inhibitors and procoagulators are equally reduced by dilution.

8.1.5.2 Absolute and relative contraindications

- In patients with known heparin-induced thrombocytopenia type II, administration of antithrombin concentrates containing heparin is contraindicated,
- in patients with known allergic reactions to any of the constituents of the preparation.

Note:
Replacement therapy with antithrombin may intensify the effect of ongoing heparin therapy to the extent that bleeding may occur due to an overshooting heparin effect.

8.1.6 Adverse reactions

See chapter 11.

8.2 Protein C concentrate

8.2.1 Preparation

Along with the remaining factors of the prothrombin complex, protein C is obtained from cryoprecipitate-poor plasma pools and bound to ion exchangers. Protein C is subsequently isolated in ultrapure form from the eluate by immunoaffinity chromatography using murine monoclonal antibodies, as well as by further production steps using chromatography.
During the manufacturing process the product is virus inactivated using two different methods (polysorbate 80 treatment and vapor heating). However, the separation or inactivation procedure is effective against parvovirus B19 only to a limited extent.

8.2.2 Active constituents

The preparation contains non-activated protein C as well as human albumin as stabilizer.

8.2.3 Physiological function and deficiency syndromes

Protein C which acts as an inhibitor is the precursor of a serine protease – the **a**ctivated **p**rotein **C** (APC) – and belongs to the vitamin K-dependent glycoproteins synthesized in hepatocytes [19].
Protein C is activated to APC by the thrombomodulin/thrombin complex that is expressed on the surface of endothelial cells. With protein S as a cofactor, APC catalyzes the proteolysis of the activated coagulation factors V and VIII. Thereby APC downregulates the subsequent activation of factor X as well as of prothrombin via the so-called prothrombinase. This leads to inactivation of factor X and stops thrombin formation. The activated coagulation comes to a standstill. With decreasing thrombin concentration the thrombin-activatable fibrinolysis inhibitor (TAFI) is also no longer activated, therefore tissue plasminogen activator (tPA) and plasmin can dock at the fibrin clot. In addition, APC also inactivates plasminogen activator inhibitor-1 (PAI-1) and has a pro-fibrinolytic effect by release of tPA.
There are homozygous or heterozygous hereditary protein C deficiencies. The incidence of severe homozygous or compound heterozygous protein C deficiency is specified as lying between 1:500,000 and 1:750,000. Heterozygous protein C deficiency is said to occur in the general population with a frequency of 1:200 to 1:300. Since acquired protein C deficiencies also occur (see below) and since the standard range is wide, diagnosis is often difficult. **In homozygous protein C deficiency** a most severe thrombotic decompensation can occur immediately after delivery, e.g. Purpura fulminans or thrombosis of arterial vessels (kidney). Patients with protein C deficiency have a high risk of recurring arterial and venous thrombosis [15, 25]. When therapy is started with oral anticoagulants belonging to the coumarin group, in these patients necrosis of skin areas can occur resulting from local thrombotic processes of vessel of the skin. This is caused by hypercoagulemia that develops because of the longer half-lives of the procoagulant factors versus the very short half-life of protein C (see chapter 6, 6.3.1).

Acquired protein C deficiencies can result from increased consumption, diminished synthesis or both.

An increased consumption is observed in DIC, in acquired Purpura fulminans on the basis of bacterial sepsis (meningococcal sepsis) or infection with varicella, in severe pre-eclampsia as well as in patients during the acute phase of HELLP Syndrome in the context of Systemic lupus erythematosus (SLE), Colitis ulcerosa and IgG paraproteinemia.
A diminished synthesis is observed in acute and chronic liver diseases that are accompanied by impairment of protein biosynthesis in the hepatocytes, during therapy with oral anticoagulants, in vitamin K deficiency, in healthy neonates as well as during treatment with asparaginase and fluorouracil.
Combined increased consumption and diminished synthesis is found in the postoperative phase following liver transplantation, in chronic hemodialysis and clinical pictures with loss coagulopathy and DIC.
The half-life of protein C is 4.5 to 6 hours. In the case of increased consumption the half-life is significantly shorter.

8.2.4 Storage, shelf life and package sizes*

Protein C concentrates must be stored at +2°C to +8°C, but must not be frozen. Protection from light is necessary, and ready-to-use solutions must be administered immediately. Protein C concentrate in the dissolved state is stable at 30°C for 32 hours under the conditions of continuous infusion and may be diluted with 0.9 % sodium chloride, 5 % glucose or Ringer lactate.
Package sizes of 500 and 1,000 U per vial are available.

8.2.5 Range of application, dosage*

8.2.5.1 Indications
Currently protein C concentrate is licensed for treatment of Purpura fulminans and of coumarin-induced necroses of the skin in patients with severe congenital protein C deficiency [22, 23].
Short-term prophylaxis with protein C concentrate is indicated in patients with severe congenital protein C deficiency, if one or more of the following conditions apply:

In **congenital severe protein C deficiency** protein C substitution should be carried out: • prior to surgery or invasive procedures, • at the start of coumarin therapy, • if coumarin therapy alone is not sufficient, • if coumarin therapy is not possible.	**1 C**

8.2.5.2 Dosage
At the beginning of treatment an activity of 100 % of protein C shall be aimed for, and values beyond 25 % should be maintained during the treatment period.
The manufacturer recommends an **initial dose** of 60–80 U/kg body weight to determine recovery and half-life.
The dosage depends on the results of the determination of protein C activity. In the case of an acute thrombotic event the activity must be determined prior to substitution, followed by 6-hour intervals until the patient is stabilized, followed by twice daily immediately prior to

* see section 0.4

the next injection. If necessary, the interval between determinations has to be shortened, since the half-life of protein C can be significantly shortened in acute thrombotic events like Purpura fulminans, acute thrombosis and coumarin-induced necrosis of skin areas. Therefore the protein C activity should be determined repeatedly when starting therapy with protein C concentrate, and the dosage adjusted accordingly.
After the end of protein C therapy the patients have to be switched over, if possible, to long-term prophylaxis with oral anticoagulants. Substitution therapy with protein C concentrate must be continued until reliable anticoagulation is achieved.

8.2.5.3 Mode of administration

Protein C concentrate is administered as **intravenous injection after solving in sterile Aqua ad injectionem**. The preparation must be administered immediately after reconstitution. **Do not mix with other medical products!**
Protein C concentrate is given at an injection rate of a maximum of 2 mL/min. In children with a body weight of <10 kg the injection rate should not be higher than 0.2 mL/kg/min.

8.2.5.4 Absolute and relative contraindications

Intolerance against one of the components of the preparation, against murine proteins or heparin.

8.2.6 Adverse reactions

See chapter 11.

8.3 Recombinant human activated protein C

8.3.1 Preparation

Recombinant human activated protein C (drotrecogin alfa [activated]) is produced by genetic engineering. The inactive precursor, recombinant human protein C, is produced in the human kidney cell line HEK 293, is secreted by the cells into the surrounding medium and is purified by using column chromatography. Activation of the zymogen is done by thrombin, similar to the process in human plasma. The resulting product, drotrecogin alfa (activated) is identical with the form occurring in human plasma, except for the glycosylation pattern. A second column chromatography produces the ultrapure drotrecogin alfa (activated).

8.3.2 Active constituents

Drotrecogin alfa (activated) is the recombinant form of activated protein C occurring naturally in plasma. It is different from the native molecule only by individual oligosaccharides in the carbohydrate portion.

8.3.3 Physiological function and effects

The treatment concept using supraphysiological levels of activated protein C is distinctly different from substitution with protein C concentrate in congenital deficiency (see section 8.2).
Activated protein C, the physiological inhibitor of clotting activation, is converted from its inactive form, protein C, by thrombin linked to thrombomodulin [28]. Activated protein C has antithrombotic and profibrinolytic effects [3]. The antithrombotic properties are based on the inactivation of the clotting factors Va and VIIIa and the resulting decrease in thrombin formation using a negative feedback mechanism. Activated protein C has a profibrinolytic effect

by inhibiting the plasminogen activator inhibitor-1 (PAI-1) and preventing activation of thrombin-activatable fibrinolysis inhibitor (TAFI).
In phase II trials on activated protein C therapy in patients with severe sepsis a dose-dependent reduction of elevated D-dimer concentrations in plasma and interleukin-6 concentrations in serum was described as well as of other parameters regarding inflammation and coagulation [26]. In investigations that were in part experimental anti-inflammatory [47] and cytoprotective actions have been described [40].
Inactivation of drotrecogin alfa (activated) is done by endogenous plasma protease inhibitors. The half-life of elimination is specified to be 1.6 h; this can be significantly shorter in cases of increased consumption and in sepsis.

8.3.4 Storage, shelf life and package sizes*

Drotrecogin alfa (activated) must be stored at +2°C to +8°C in the refrigerator in a covering box (protection from light). In customary packing the shelf life is 3 years.
Drotrecogin alfa (activated) is available in vials at 5 mg and 20 mg. After reconstitution of the powder in Aqua ad injectionem (2.5 mL for the 5 mg vial and 10 mL for the 20 mg vial, respectively) a stock solution is obtained containing 2 mg of drotrecogin alfa (activated)/mL.
The stock solution is stable at room temperature (15–30°C) for around 3 hours. Subsequently it has to be diluted using sterile 0.9 % NaCl solution to a ready-to-use infusion solution with final concentration of 100 µg/mL or 200 µg/mL. The ready-to-use infusion solution can be used at room temperature for up to 14 hours.

8.3.5 Range of application, dosage*

8.3.5.1 Licensed indication
The approval followed the completion of a phase 3 clinical trial involving 1690 patients. In this trial drotrecogin alfa (activated), at a dose of 24 µg/kg/hour for 96 hours in adult patients with severe sepsis (see Table 8.3.5.1), was associated with a statistically significant reduction (29.4 % drotrecogin vs. 34.6 placebo) in 28-day all-cause mortality [9]. In patients with initial APACHE II scores >25 the survival benefit was still present after 36 months [7]. In cases of single-organ failure or of APACHE II scores <25 there was no significant difference in survival time or survival rates. A follow-up trial, involving patients with sepsis who had single-organ failure due to sepsis or APACHE II scores <25, was terminated early after enrollment of 2,640 patients because a low likelihood of a survival benefit became apparent in an interim analysis (20.7 % drotrecogin vs. 21.9 % placebo). In this trial there was an increased incidence of bleeding episodes during treatment with drotrecogin alfa (activated) (10.9 % vs. 6.4 %) [3, 43]. In an additional single-arm, multicenter clinical treatment trial enrolling 273 patients with severe sepsis and multiorgan failure a higher incidence (6.5 %) of severe bleeding complications was observed [10] in comparison with the above-mentioned trials (3.5 % in [9]).

* see section 0.4

Table 8.3.5.1: ACCP/SCCM definitions for SIRS and sepsis [2]

Systemic Inflammatory Response Syndrome (SIRS) A systemic inflammatory response to various clinical triggers if at least 3 out of 4 of the following conditions are present: • central body temperature ≥ 38°C or ≤ 36°C • heart rate ≥ 90/min, except for patients with a known disease or under medication preventing tachycardia • respiratory rate ≥ 20/min or $PaCO_2$ ≤ 32 Torr or assisted respiration in acute respiratory insufficiency • leucocyte count >12,000 cells/mm^3, <4,000 cells/mm^3 or >10 % immature neutrophile granulocytes
Sepsis Detection of a systemic inflammatory response (SIRS) to a confirmed or suspected infection. An infection is suspected when at least one of the following applies: • Detection of leucocytes in body fluid that is sterile under normal circumstances • Perforation of a hollow organ • Pneumonia confirmed by X-ray in conjunction with production of purulent sputum • Existence of a syndrome with a high risk of infection (e.g. ascending cholangitis)
Severe sepsis Sepsis with at least one of the following five criteria of organ dysfunction: • **Cardiovascular dysfunction:** For at least 1 hour systolic arterial blood pressure ≤90 mmHg or mean arterial blood pressure ≤70 mmHg despite adequate intravascular blood volume or application of vasopressors with the purpose to achieve a systolic arterial blood pressure ≥90 mmHg or mean arterial blood pressure ≥70 mmHg. • **Renal dysfunction:** For at least 1 hour urinary excretion of <0.5 mL/kg body weight despite adequate volume substitution. • **Respiratory dysfunction:** PaO_2/FiO_2 ≤250 mmHg in combination with dysfunction of other organs or ≤200 mmHg in isolated pulmonary failure. • **Hematological dysfunction:** Platelet count <80,000 mm^3 or decrease by 50 % within the past 3 days. • **Metabolic dysfunction:** pH value ≤7.3 or base excess of ≥5.0 mmol/L with elevated plasma lactate levels that are 150 % of the standard level.

In adult patients with severe sepsis, in whom at least two organ systems are failing due to sepsis, application of drotrecogin alfa (activated) shall be performed in addition to standard therapy. Drotrecogin alfa (activated) therapy should be started within 48 hours after the first organ dysfunction due to sepsis.	**1 B**
There is no indication for the intravenous administration of activated protein C (drotrecogin alfa) in patients with sepsis in whom only one organ system is failing due to sepsis or who have an APACHE score of below 25.	**1 B**

8.3.5.2 Dosage, mode of administration

The contents of the vial drotrecogin alfa (activated) 5 mg/20 mg is dissolved in Aqua ad injectionem (0.5 mL/mg) under aseptic conditions. The reconstituted preparation is then diluted with 0.9 % NaCl to a ready-to-use infusion solution. Drotrecogin alfa (activated) is administered as intravenous infusion relating to the body weight (24 µg/kg/h). Drotrecogin alfa (activated) should be administered using a separate intravenous access or a separate vascular lumen of a central venous multi-lumen catheter. The duration of infusion should be 96 hours.

The recommended dose for drotrecogin alfa (activated) is 24 µg/kg/h as a continuous intravenous infusion over a period of 96 hours. If infusion is interrupted, drotrecogin alfa (activated) should be administered again with an infusion rate of 24 µg/kg/h until the entire infusion time span of 96 hours is reached.

Simultaneous administration of heparin (unfractionated *UFH* or fractionated *LMH*) and Drotrecogin alfa (activated) in patients with severe sepsis has led to a higher rate of bleeding events (12.4 % vs. 10.9 %). However, the incidence of ischemic stroke was lower (0.3 % vs. 1.3 %). Simultaneous administration of heparin did not influence the effect of Drotrecogin alfa (activated), based on mortality rates in both groups (28.3 % with heparin vs. 31.9 % without heparin) [36].

In case severe bleeding complications occur, the infusion with drotrecogin alfa (activated) has to be interrupted. If bleeding is successfully arrested the infusion can be restarted after carefully weighing risk and benefit for the patient. Administration of drotrecogin alfa (activated) shall be discontinued 2 hours prior to starting interventions associated with possible risk of bleeding. 12 hours after major invasive procedures or surgery or immediately after uncomplicated minor procedures drotrecogin alfa (activated) can be administered again provided that an adequate coagulation state is reestablished.

During the infusion of drotrecogin alfa (activated) repeated determination of coagulation parameters should be done as part of the routine measures (e.g. Activated Partial Thromboplastin Time [aPTT], prothrombin time [PT], platelet count). In case consecutive analyses of coagulation show an uncontrolled or increasing coagulation disorder, the benefit of continued infusion must be weighed against the potential risk of bleeding in the patients concerned.

8.3.5.3 Absolute and relative contraindications

Drotrecogin alfa (activated) is not licensed to be used for treatment in children. A trial enrolling pediatric patients (<17 years of age) with severe sepsis and respiratory and cardiovascular failure was stopped following an interim analysis after enrolling 400 out of 600 patients (intended number). No difference in overall mortality was to be expected (17.1 % vs. 17.3 %), but instances of CNS bleeding were observed in four children receiving drotrecogin alfa (activated) therapy compared to one child in the placebo group. Three of the four children with CNS bleeding in the drotrecogin alfa (activated)-treated group were younger than 60 days of age.

Drotrecogin alfa (activated) should not be applied in children [41].	**1 C**

Since drotrecogin alfa (activated) can increase the risk of bleeding it is contraindicated in the following cases:

1) active internal bleeding,
2) patients with pathological intracranial alteration, neoplasm or signs of cerebral herniation,
3) simultaneous heparin therapy with ≥15 U/kg/hour,
4) known disposition to bleeding, except for acute coagulation disorder due to sepsis,
5) severe chronic liver disease,

6) platelet count <30,000/µl, even though platelet numbers have been raised by administration of platelet concentrates,
7) patients with an increased risk of bleeding, e.g. in the following clinical situations:
   a) Any major surgery under general anesthesia or spinal anesthesia within 12 hours immediately prior to administration of the drug, in the postoperative period if there are signs of active hemorrhage or if a surgical intervention is planned or likely during administration of the drug.
   b) Severe traumatic brain injury with hospitalization, neurosurgical intervention (cranial or spinal), severe brain injury, intracranial arteriovenous malformation or cerebral aneurysm in the medical history; hemorrhagic stroke within the past 3 months; epidural catheter or need for an epidural catheter during the time of treatment.
   c) Congenital disposition to bleeding.
   d) Gastrointestinal bleeding within the past 6 weeks with clinical intervention, unless a definitive surgical intervention was performed.
   e) Trauma with increased risk of bleeding.

In addition, drotrecogin alfa (activated) is contraindicated in patients with known intolerance of drotrecogin alfa (activated), one of the excipients or bovine thrombin (residual traces due to the manufacturing process).
Since drotrecogin alfa (activated) increases the risk of bleeding, the risks should also be weighed against the anticipated benefit in the following situations:
1) thrombolytic therapy performed within the past 3 days,
2) administration of oral anticoagulants within the past 7 days,
3) administration of acetylsalicyl acid or other platelet aggregation inhibitors within the past 7 days,
4) ischemic stroke within the past 3 months,
5) any other disorder due to which relevant bleeding could occur in the opinion of the attending physician.

8.3.6 Adverse reactions

Drotrecogin alfa (activated) can increase an existing risk of bleeding [10]. All controlled trials performed so far have reported more frequent bleeding events in patients treated with drotrecogin alfa (activated) than in the placebo groups. Therefore the risk of bleeding must always be weighed against the therapeutical benefit for the patient. When life-threatening bleeding occurs the administration of drotrecogin alfa (activated) must be interrupted immediately and the indication reassessed.

8.4 C1 esterase inhibitor concentrate

8.4.1 Preparation

C1 esterase inhibitor (C1-INH) concentrate is produced from cryoprecipitate-poor human plasma by adsorption and ion exchange chromatography. It is available in lyophilized form. In Germany only one pasteurized C1-INH concentrate is licensed so far.

8.4.1.1 Quality criteria

To eliminate and inactivate viruses, the C1-INH concentrate licensed in Germany is subjected to pasteurization (heating in aqueous solution for 10 hours at 60º C), in addition to several purification steps.

8.4.2 Active constituents

The preparation's effective component is human C1 esterase inhibitor (C1-INH). It contains small amounts of aminoacetic acid as stabilizer.

8.4.3 Physiological function

C1-INH is an acute phase protein; its concentration in normal human plasma is 240–270 mg/L. By definition its activity in 1 mL fresh citrate plasma corresponds to 1 unit (1 U). In the event of infections the level can increase up to twofold.
Besides in plasma, C1-INH is also detectable in placenta, liver cells, monocytes and thrombocytes. It achieves its therapeutic effect by replacement of lacking inhibitor activity resulting in the blockade of the initiated cascades.
C1-INH inhibits the classical pathway of activating the complement system by inactivating the enzymatically active compounds C1s and C1r, where the enzymes form a molecular 1:1 complex with the inhibitor. A further biological function of C1-INH is the blockade of contact activation by inhibiting clotting factor XIIa and its fragments. In addition to alpha-2-macroglobulin, C1-INH is thus the most important endogenous inhibitor of kallikrein in plasma.
Pharmacological data from hereditary angioedema patients showed half-lives ranging between 1.1 and 12.4 days; in these patients the median *in vivo* recovery was 82 %. Following application of this preparation detectable C1-INH activity reached maximum levels after approximately 1 hour. Depending on the individual clinical situation, administration of 1 U/kg body weight increases the activity by 1–3 %. In a randomized placebo-controlled double blind study the half-life of a steam-treated C1-INH preparation not licensed in Germany was 38 hours [35].

8.4.4 Storage, shelf life and package sizes*

The preparation is to be stored at +2 to +25°C; shelf life is 30 months. Once dissolved, it must be used immediately.
C1-INH is available in packages of 500 IU.

8.4.5 Range of application, dosage*

8.4.5.1 Indications

8.4.5.1.1 Hereditary angioedema types I and II (HAE I and II)

In hereditary autosomal dominant deficiency of C1-INH, persistent long-lasting swelling may occur, especially in the gastrointestinal tract, in the head or throat area or on the entire integument and particularly at the extremities. Genital edema including paraphimosis can also occur. Laryngeal edema may provoke life-threatening asphyxia by blocking air passages [13].
Laboratory tests show that patients with type I HAE have reduced C1-INH activity and C1-INH antigen levels; patients with type II HAE show reduced C1-INH activity with normal or increased C1-INH antigen levels (functional defect).
A marked increase in bradykinin concentration in plasma during acute attacks has been observed in HAE patients as well as in those with acquired angioedema (AAE). Following infusion of C1-INH, bradykinin concentration decreases rapidly [42].

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* see section 0.4

The effectiveness of C1-INH concentrates for the treatment of type I and II HAE could be shown in two randomized placebo-controlled doubleblind trials [35, 49]. Prophylactic application of steam-treated C1-INH concentrate led to a statistically significantly lower daily symptom score. During acute HAE episodes the interval up to improvement of symptoms was significantly shorter in the C1-INH-treated group as compared to the placebo group (55 vs. 563 min) [49].
These results were confirmed in a further study [35].
C1-INH concentrate can be administered in acute episodes of angioedema, but also prophylactically prior to surgery [4, 5, 18, 34, 39]. There are no therapeutic alternatives to substitution with C1-INH concentrate in patients with acute symptoms such as laryngeal edema, CNS involvement or severe swelling of inner organs [13, 14, 34].

For intervention therapy of the hereditary angioedema (HAE types I and II) during acute episodes or for pre-surgical prophylaxis C1-INH concentrate shall be administered.	**1 C+**

Only few data are available on long-term prophylaxis with C1-INH concentrate [49]. The question of long-term prophylaxis vs. treatment on demand is currently the subject of ongoing clinical investigations.
Initial results from 30 patients receiving long-term prophylaxis with C1-INH concentrates showed that 15 patients were attack-free while the remaining 15 patients experienced a markedly reduced frequency of attacks [37, 38]. For pregnant women or those of reproductive age seeking offspring, children and patients with severe side-effects resulting from chronic androgen therapy, such as liver adenoma, hepatocellular carcinoma, depression, amenorrhea, arterial hypertonus, manifest virilization and hirsutism, therapy on demand or, in the case of recurrent severe symptoms, long-term therapy with C1-INH concentrate represents the only possible therapy to-date [1, 33, 34]. The costs and risks of such long-term replacement therapy with C1-INH concentrate are to be weighed against the known risks and adverse reactions of long-term androgen therapy [12, 18].

8.4.5.1.2 Acquired angioedema

Acquired deficiencies of C1-INH (so-called “acquired angioedema” [AAE]) are rare. They occur in lymphoproliferative diseases, autoimmune diseases or in patients with malignant tumors and in connection with administration of certain drugs like e.g. ACE inhibitors (AAE type 1), occasionally also independent of such primary illnesses (AAE type II with auto-antibodies against C1-INH) and usually appear after the age of 40 [27].
The clinical symptoms of AAE are comparable to those of HAE, severity and frequency of attacks showing a greater variability than in the hereditary form. The primary illness, if known, should be treated first.
Patients with acquired angioedema with severe or life-threatening episodes or prior to surgery have been successfully treated with C1-INH concentrate analogous to the therapy for HAE patients [6, 11, 17, 27]. In patients with antibodies to C1-INH (usually AAE type II) its effectiveness can be attenuated or totally lacking because of rapid inactivation of the administered C1-INH [6, 17, 46]. In patients with acquired deficiency clinical symptoms that have initially improved following long-term therapy with C1-INH concentrates may therefore, under certain circumstances, recur [11].

For intervention therapy of the acquired angioedema (types I and II) C1-INH concentrate can be administered. (Note: Because this indication is not licensed, the application would be done in the “Off-Label Use”. The legal issues involved in this are pointed out in section 0.4.)	**2 C+**

8.4.5.2 Dosage

8.4.5.2.1 Hereditary angioedema types I and II (HAE I and II)

Therapy of acute episodes or pre-surgical prophylaxis (licensed indications): A single dose of C1-INH concentrate is 15–30 U/kg body weight. In children this usually corresponds to 500–1,000 U, and in adults to 1,000–2,000 U of C1-INH concentrate (see expert information).

In cases with life-threatening swelling such as laryngeal edema, the higher dose should be used initially. If the patient's condition does not improve within several hours or the effect fails to persist, a further dose of 500 to 1,000 U should be given. During an acute attack the requirement for C1-INH may be increased because of higher consumption.

Dosage

- Continuous prophylactic administration before/during surgery:

Investigations in adults with HAE during surgery with continuous replacement of C1-INH concentrate have shown that a bolus administration of 1,000 U followed by infusion of 0.5–1 U/kg body weight/hour maintained the plasma level of C1-INH activity within the normal range while no HAE-typical symptoms arose. The advantages are more stable C1-INH activity levels and lower concentrate consumption [37].

- Long-term prophylaxis:

25 U/kg body weight of C1-INH concentrate given every 3rd day leads to a significantly lower symptom-score compared to a placebo group [49]. Preliminary data show that a dose of 500–1,000 U of C1-INH concentrate twice or three times a week can achieve attack-free phases or lead to a markedly reduced frequency of attacks [37, 38].

8.4.5.2.2 Acquired angioedema types I and II (AAE I and II)

Only few data are available on the use of C1-INH concentrate in acquired angioedema. Therapy with this concentrate may be attempted in acute or life-threatening angioedema, or as prophylaxis prior to surgery at a dose delineated for the hereditary form.

Warning:

In the presence of autoantibodies against C1-INH (usually AAE II) the therapeutic effectiveness of the C1-INH concentrate may be weakened or entirely lacking. Whereas in some such cases therapeutic effects have been observed when using extremely high doses of C1-INH concentrate, negative results have been obtained in others [4, 6, 17, 27].

8.4.5.3 Absolute and relative contraindications

So far, no contraindications are known.

8.4.6 Adverse reactions

See chapter 11.

8.5 Documentation

According to article 14 TFG*, there is an obligation to perform a patient- as well as product-related batch documentation for C1-INH, antithrombin and protein C concentrates.

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* The classification of recombinant activated protein C requiring obligatory batch documentation according to section 14 TFG as plasma protein for the treatment of hemostasis disorders is controversial, because it is licensed for the indication “sepsis” and not for the indication “therapy of hemostasis disorders”. In case of doubt it is recommended that the attending physician carries out batch documentation, in particular if the preparation is applied for treatment of hemostasis disorders in the Off-Label Use.

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9 Human immunoglobulins

9 Human immunoglobulins

9.1 Preparation

Human immunoglobulins (Ig) are manufactured from human plasma using various procedures (enzymatic and/or chemical treatment as well as chromatographic techniques) [33, 95, 103, 118]. Donor selection, gentle separation procedures and effective steps for inactivation or elimination of enveloped and non-enveloped viruses are important parameters concerning quality, tolerance and safety. **Preparations for subcutaneous or intramuscular (sc/imIg) and intravenous (ivIg) application differ with respect to manufacturing, protein content and tolerance: in each case the prescribed mode of application must therefore be strictly observed.**

9.1.1 Quality criteria

Immunoglobulins are produced from a pool of donations from at least 1,000 healthy donors. The product must not transmit infections and must, at a protein concentration of 50-120 g/L (ivIg) or 160 g/L and 165 g/L (scIg), contain defined antiviral and antibacterial antibodies at a concentration at least 3fold (ivIg) or 10fold (scIg) above that of the starting material [95]. Furthermore ivIg preparations must have a defined distribution of immunoglobulin-G subclasses as well as display Fc-functions of native immunoglobulins. The proportion of monomeric and dimeric IgG molecules must amount to at least 90 %, the proportion of polymers and aggregates may not exceed 3 %. IvIg products must contain at least 0.5 U anti-HBs antibodies per gram of immunoglobulin [95].

9.2 Active constituents

The effective components of human immunoglobulin preparations are specific antibodies which may be used for prophylactic or therapeutic indications.
Immunoglobulin preparations are available in lyophilized form or in stabilized solution and contain as stabilizers albumin and amino-acids (glycine, proline, isoleucine), as well as diverse sugars (glucose, sucrose, sorbitol, maltose) and nicotinamide in part at high concentrations [33, 41].

9.2.1 Normal immunoglobulins for subcutaneous/intramuscular injection (scIg/imIg) or for intravenous injection (ivIg)

The quality criteria for immunoglobulins (scIg, imIg and ivIg) are set by the European Pharmacopeia. Most of the preparations currently available contain more than 90 % monomeric IgG1–4 and only insignificant amounts of IgM and IgA molecules. A preparation enriched with IgM for special indications contains both 12 % IgM and IgA, as well as 76 % IgG. Currently, several ivIg preparations are available with very low IgA concentration that are predominantly used in patients with manifest clinically relevant antibodies against IgA molecules [25]. As an alternative, subcutaneously administered immunoglobulins can be given in such cases without increased risk of anaphylactic reactions [32, 54].

9.2.2 Specific immunoglobulin preparations (hyperimmunoglobulins)

These preparations have concentrations of the specific antibody that are many times higher

than normal Ig preparations. **They are produced from plasma of selected or immunized donors with higher serum concentrations of specific antibodies (Table 9.2.2.1).**

Table 9.2.2.1: Specific immunoglobulins (according to [95] and further references)

Specificity	Preparations	Protein concentrations (g/L)	Minimum content of specific antibody (IU/mL)*
Anti-D (Rh_0)	imIg ivIg	100–180**	500–1000(= 100–200 µg) 500–750 (=100–150 µg)
CMV	ivIg	50; 100	50
HBV	imIg ivIg	100–180 100	200 50
Rabies	imIg	100–180	150
Tetanus	imIg	100–180	100
VZV	imIg ivIg	100–180 100	100 25

* WHO standard; for lyophilized preparations after dissolving according to instructions
** varying concentrations according to manufacturer

9.3 Physiological function

Human immunoglobulins can be divided into 5 Ig classes: IgM, IgD, IgA, IgG, IgE. IgA is composed of two subclasses (IgA1, IgA2), and the IgG of four subclasses (IgG1, IgG2, IgG3, IgG4). Certain antibody specificities occur preferentially in single classes or subclasses (e.g. antibodies against bacterial polysaccharides in IgG2, antibodies against proteins preferentially in IgG1 and IgG3, neutralizing antibodies against bacterial toxins in the IgM class). 90 % of IgA is secreted by mucous membranes. Commercially available IgG preparations contain >90 % monomeric IgG1–4, low amounts of IgA and IgM and no IgE and IgD.
Because of pool size (donations from >1,000–80,000 healthy individual donors) commercial immunoglobulin preparations contain antibodies to a large number of relevant antigens and toxins of a great variety of pathogens in our environment. In addition there are regulative antibodies (e.g. anti-idiotypes) and also certain autoantibodies in small concentrations. **Thus every IgG batch extracted from a pool of over 1,000 donors contains the "antibody repertoire of the human species"**. A protective effect of immunoglobulin preparations against experimental infections has been demonstrated for all commercially available preparations. Because of considerable variation in the experimental approach, a comparison regarding efficacy between different preparations is impossible. Immunoglobulins selectively neutralize toxins and viruses and "opsonize" bacteria. They strengthen unspecific defense mechanisms and can also modulate the immune response and lead to a temporary blockade of Fc-receptors in the RES [9, 19, 23, 33, 62, 65, 90, 121].
Application of therapeutic doses of ivIg causes a steep rise of serum concentrations, followed by a decrease within 6–12 hours to about half the peak concentration (due to distribution into the extravascular space). Plasma levels thereafter decrease slowly over a period of 2–4 weeks to initial levels. Circulating antibodies appear around 20 minutes after administration of imIg and scIg; maximum antibody titers are reached after about 4 days [33].

9.4 Storage, shelf life and package sizes

ImIg, scIg and ivIg are available in various package sizes in order to allow dose adjustment according to individual indications in children and adults. Shelf life and storage temperature must be declared by the manufacturer.

9.5 Range of application, dosage*

9.5.1 Indications for subcutaneous or intramuscular injection (sc/imIg) of normal immunoglobulins

Sc/imIg can be injected as substitutes for specific immunoglobulins **subcutaneously** or **intramuscularly** (see 9.5.4).
For **continuous substitution in children and adults with primary and secondary immunodeficiency diseases, subcutaneous administration** represents an important and effective alternative to substitution with ivIg (s. sections 9, 9.5.2.1, 9.5.2.2) [22, 33, 46, 48, 55, 67].
Dosage of subcutaneous immunoglobulins: Initially an s.c. "loading dose" of 0.2–0.5 g/kg body weight may be required. The maintenance dose is 0.1–0.15 g/kg body weight per week. Empirically the necessary weekly dose amounts to approx. ¼ of the monthly dose when undergoing ivIg substitution. One or more subcutaneous infusions can be administered in parallel on the abdomen and/or thigh. After appropriate training patients are able to perform self-administered infusion therapy with or without assistance from a special infusion pump [46]. In comparison with i.v. administration, many mostly younger and working patients with antibody deficiency syndrome perceive subcutaneous self-administered infusion to provide a higher quality of life [47, 48, 67].

9.5.2 Indications for intravenous injection (ivIg) of normal immunoglobulins

Provided there is no reference to the contrary, indications in this chapter are licensed for prophylactic or therapeutic administration of immunoglobulins. Indications for prophylactic or therapeutic administration are substitution therapy with ivIg in patients with known impairment of antibody formation and modulation of the humoral immune response in certain autoimmune diseases and some diseases of unknown etiology.
In individual cases recommendations are given for indications in the "Off-Label Use". In this context the comments in section 0.4 on legal issues involved in the "Off-Label Use" are referred to.

9.5.2.1 Primary immunodeficiency diseases

Long-term ivIg substitution with a dose adjusted for serum IgG concentrations has proved as efficient treatment in Bruton's X-linked agammaglobulinemia (XLA), severe combined immunodeficiency (SCID and variants), variable immunodeficiency syndromes (common variable immunodeficiency, CVID) and various forms of hyper-IgM syndrome as the incidence of severe infections and their sequelae are significantly reduced. In other rare immunodeficiency diseases (Wiskott-Aldrich Syndrome, ataxia telangiectasia and in IgG-subclass deficiency etc.), ivIg substitution therapy is indicated only in selected cases presenting with recurrent severe infections and in proven insufficient antibody formation following vaccination (diphtheria, tetanus, hemophilus influenzae B, pneumococci) [18, 19, 49, 118, 134].
Even in patients with isolated IgG-subclass deficiency or in patients with specific antibody deficiency (e.g. against pneumococci) the substitution with immunoglobulins is reasonable only if the patients concerned show a propensity to contract infections and/or a failure to form antibodies following vaccination.
Depending on the time when the immunodeficiency became clinically manifest and was diagnosed, therapy is initiated and usually continued for life [129].
Dosage of ivIg: ivIg 0.4–0.8 g/kg body weight initially. Maintenance dose is 0.4–0.6 g/kg

* see section 0.4

body weight at 2–10-week intervals, depending on the serum concentration and the clinical picture. The patient's clinical course is definitive in determining the maintenance dose. The trough level that is aimed for, of 6 to 9 g/L IgG before the next infusion, serves as reference value which however is not reached in some patients with high IgG catabolism. In particular, it has to be considered that patients with established organ damage (e.g. bronchiectasis) have higher requirements of Ig and therefore need a higher trough level. In addition, severe acute infections may increase the demand in immunoglobulins.

In primary immunodeficiency diseases, accompanied by antibody deficiencies and an increased susceptibility to infections, a continuous therapy with ivIg or scIg **shall** be performed.	**1 C+**

9.5.2.2 Secondary immunodeficiency diseases

Antibody deficiency syndromes in patients with malignant lymphoma, multiple myeloma and in chronically immunosuppressed patients (including patients after allotransplantation)

A clinically relevant antibody deficiency syndrome may be defined in patients with malignant lymphoma, multiple myeloma, certain malignancies and in chronically immunosuppressed patients by the occurrence of at least three severe bacterial infections per year of the respiratory, digestive and/or urinary tract, or by the occurrence of one septicemia. Studies with various doses concur that the prophylactic treatment with ivIg significantly reduces the number of severe bacterial infections [6, 21, 33, 45, 108, 137].

Dosage: Depending on the preparation, 0.2–0.4 mg ivIg/kg body weight at 3–4-week intervals is administered as medium to long-term infection prophylaxis.

In the context of allogeneic bone marrow transplantation ivIg is used in cases of hypogammaglobulinemia as prophylaxis against infections and in order to lower the incidence of acute graft-versus-host disease (GVHD) [110, 133]. IvIg therapy is not indicated to alleviate chronic GVHD in patients with normal serum Ig levels [1, 39, 119, 131].

Dosage in hypogammaglobulinemia following BMT: 0.5 g ivIg/kg body weight per week from day –7 up to 3 months post transplantionem.

Substitution with ivIg **shall** be performed in patients with chronic lymphocytic leukemia (CLL) and multiple myeloma with a secondary antibody deficiency syndrome and a clinically relevant susceptibility to infections.	**1 A**
Substitution with ivIg **should** be performed in patients who are chronically immunosuppressed, patients after stem cell transplantation and patients with malignancies who develop a secondary antibody deficiency syndrome with a clinically relevant susceptibility to infections.	**1 C**

HIV infection in infants and small children

In contrast to HIV infection in adults, severe bacterial infections are more frequently observed in HIV infection in children. Several controlled studies have shown that the rate and severity of infections can be significantly reduced by ivIg therapy [123]. The survival rate in the patients concerned, however, was not improved [84, 85, 114]. Meanwhile standardized highly active antiretroviral combination therapy (HAART) [120] is preventing vertical transmission of infection from HIV-positive mothers to their newborns in up to 99 %. Therefore ivIg therapy in HIV-infected infants and small children is only indicated as supportive measure in individual cases that have an increased susceptibility to bacterial infections and an antibody deficiency despite HAART [128].

Dosage: Depending on the preparation, 0.2–0.4 mg ivIg/kg body weight are administered every 3–4 weeks.

HIV-infected infants and small children who have an increased susceptibility to bacterial infections despite HAART **shall** be treated with ivIg.	**1 A**

9.5.2.3 High-dose ivIg treatment in certain autoimmune diseases and diseases of unknown etiology

The mechanism of action of ivIg treatment in autoimmune diseases is not yet entirely understood. The neutralization of antigen and super-antigen (including autoantigens), the Fc-receptor blockade [62, 90], enhanced catabolism and anti-idiotype regulation of autoantibodies [11, 69] are documented.

Indications:

Autoimmune thrombocytopenic purpura (ITP; M. Werlhof)

The use of ivIg is recommended prior to invasive treatment (e.g. surgery, tooth extraction) [122] for children [12, 16, 17] as well as for adults showing therapy-refractoriness and clinically relevant thrombocytopenic bleeding. The response rate of ivIg therapy in cases of ITP is 90 % in children and 70–80 % in adults. The duration of the response is several days to weeks. Only in rare cases is the therapy curative.

Dosage: day 1: ivIg 0.8–1.0 g/kg body weight, repeated once up to day 3, or 0.4 g/kg body weight daily on consecutive days 2–5 [6]. Therapy may be repeated in episodic recurrences of the disease in patients responding to therapy.

Prior to invasive treatment, patients with ITP **shall** be treated with high doses of ivIg.	**1 A**

Fetal and neonatal alloimmunothrombocytopenia (FNAIT), prenatal therapy

This rare form of immunothrombocytopenia develops if the mother forms alloantibodies against paternal platelet antigens of the fetus. The children are born with thrombocytopenia and can develop petechial bleeding during delivery, at worst intracranial hemorrhage (see chapter 2.9). In case of a corresponding family history and confirmed alloantibodies, the mother should be given 1 g ivIg/kg body weight per week as antenatal therapy of FNAIT [6], starting in the 20^{th}–30^{th} week of gestation. The additional administration of prednisolone (1 mg/kg body weight) appears to reduce the incidence of intracranial hemorrhage. However, this attempted therapy is associated with severe adverse reactions [14, 63]. Platelet transfusions are recommended post delivery to treat neonatal alloimmunothrombocytopenia (see chapter 2.9).

Dosage: 1 g ivIg/kg body weight/week starting in the 20^{th}–30^{th} week of gestation, depending on the severity of thrombocytopenia. The treatment must be discussed and coordinated with specialized neonatal centers.

Female patients with confirmed FNAIT can be treated prenatally with high doses of ivIg. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.)	**2 C**

Posttransfusional purpura (PTP)

In this very rare adverse event following blood transfusion ivIg is considered the therapy of choice, if necessary following administration of corticosteroids [6, 72, 86, 87].

Dosage: ivIg 1 g/kg body weight on two consecutive days, or 0.4 g/kg body weight daily on five consecutive days.

Patients with PTP **shall** be treated with high doses of ivIg. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.)	**1 C+**

Guillain-Barré Syndrome (GBS)

IvIg and repeated plasma exchange have shown similar success rates in older studies [26]. In the rare event of recurrences of the disease repeated treatment is indicated [26, 28]. IvIg therapy is regarded as equivalent to or rather better and more cost-effective than plasma exchange therapy [57, 100, 116, 124].

Dosage in GBS: ivIg 0.4 g/kg body weight for 3–7 days.

Patients with Guillain-Barré Syndrome **shall** be treated with ivIg for 3–7 days.	**1 A**

Kawasaki Syndrome

IvIg combined with acetylsalicylic acid has been recommended during acute phases [73, 89, 91].

Dosage: IvIg 1.6–2.0 g/kg body weight portioned into several doses for 2–5 days, or 2.0 g/kg body weight as a single dose.

Patients with Kawasaki Syndrome **shall** be treated with high doses of ivIg for 2–5 days.	**1 A**

Aplastic anemia and pure red cell aplasia

IvIg therapy is generally not recommended in patients with aplastic anemia. An attempt could be made with ivIg therapy in refractory patients with the immunologically induced form of aplasia (pure red cell aplasia), in particular if this is parvovirus B19 associated [6].

Dosage: ivIg 0.5 g/kg body weight/week for 4 weeks.

In refractory patients with aplastic anemia, in whom an immunosuppressive therapy has failed, an attempt could be made to administer ivIg with some prospect of success. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.)	**2 C**

Toxic epidermal necrolysis (Lyell Syndrome)

In a portion of patients with Lyell Syndrome ivIg therapy has been shown to be very successful. High doses of ivIg are said to block Fas-mediated keratinocyte death *in vitro* and *in vivo* [20, 88, 97, 104, 125].

Dosage: ivIg 0.2–0.75 g/kg body weight for 5 days.

In patients with Lyell Syndrome in whom an immunosuppressive therapy has failed an attempt can be made to administer ivIg with some prospect of success. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.)	**2 C+**

Sepsis and septic shock

In three meta-analyses (based on 55 studies) on polyvalent ivIg therapy in bacterial sepsis and septic shock [5, 71, 74], a significant reduction of mortality was shown for the group of ivIg-treated patients. Although it is not yet possible to make reliable statements regarding benefit because of the low patient numbers involved in the studies, the authors conclude that ivIg might become a promising additional therapy in bacterial sepsis of adults as well as of children. The effect was even more pronounced when using polyvalent ivIg preparations enriched for IgM [71]. A significant benefit was also achieved when treating **sepsis in neonates** with ivIg [61, 94], but not as **infection prophylaxis** in premature infants and neonates [13, 36, 69, 92, 93, 130]. Larger multicentre prospective studies are required for confirmation of these statements. The guideline by the German Sepsis Society [101] as well as the guideline by the International Sepsis Campaign [30] arrive at a recommendation deviating from this, however, they did not include the most recent publications.

IvIg **can** be administered along with simultaneous antibiotic therapy for the selective treatment of sepsis or septic shock in adults, children and neonates.	**2 B**

Relapsing multiple sclerosis (MS)

Long-range ivIg therapy (long-term interval therapy) of this type of MS was shown to improve symptoms and reduce the number of relapses [2, 3, 26, 31, 37, 70, 77, 112, 113, 115, 116]. In patients with high relapse rates and clinical disease progression ivIg therapy is indicated especially during pregnancy and lactation, in childhood and also if interferon-β, Copaxone and Nataluzimab are contraindicated. In refractory patients treated with a licensed therapy option (non-responders) therapy escalation is indicated [3, 15, 40, 50, 51, 53].

Dosage: Dosage is not standardized. IvIg 0.15–0.4 g/kg body weight once per month or every 2 months over 1 or 2 years.

In patients with rapidly progressing relapsing multiple sclerosis and with a contraindication for, or a treatment resistance to, licensed immunosuppressive or immunomodulatory drugs, an attempt should be made with ivIg in the context of a prospective therapeutic concept (e.g. therapy escalation) [116]. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts "Off-Label Use"* in neurology/psychiatry located at the German Federal Institute for Drugs and Medical Devices [BfArM] [http://www.bfarm.de].)	**2 A**

Chronic inflammatory demyelinating polyneuropathy (CIDP)

The application of ivIg is considered to be the first-line, short-term treatment of choice in CIDP. Long-term interval treatment has also been shown to have some beneficial effects [28, 56, 58, 82, 102, 116]. Preliminary investigations have shown a comparable efficacy of subcutaneous (scIg) and intravenous immunoglobulin (ivIg) administration [75].

Dosage: Initially ivIg 0.2–1 g/kg body weight, long-term treatment: 0.2–0.4 g/kg body weight every 4–8 weeks.

In patients with CIDP an induction therapy with ivIg shall be performed in the framework of an overall therapeutic concept.	**1 A**
In patients with CIDP who have shown refractoriness with a licensed therapy ivIg should also be applied as long-term interval therapy.	**2 A**

(Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts "Off-Label Use"* in neurology/psychiatry located at the German Federal Institute for Drugs and Medical Devices [BfArM] [http://www.bfarm.de].)

Multifocal motor neuropathy with conduction blocks (MMN)

There is no licensed therapy for treating multifocal motor neuropathy (MMN) with conduction blocks. The treatment of MMN using ivIg has a distinct effect on the clinical symptoms. This effect decreases with the duration of the disease [38, 76] and may probably be improved by higher doses [28, 126].

Dosage: 0.4 g/kg body weight for 5 days, followed by a long-term interval therapy that is adjusted to the individual case with a dose determined by titration depending on the clinical picture.

Patients with MMN should initially be treated with ivIg therapy. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts "Off-Label Use"* in neurology/psychiatry located at the German Federal Institute for Drugs and Medical Devices [BfArM] [http://www.bfarm.de].)	**2 A**

Myasthenia Syndrome

The classification of the autoimmune Myasthenia Syndrome is still under debate. In most patients with Myasthenia gravis and Lambert-Eaton Myasthenic Syndrome (LEMS) the administration of ivIg is effective, representing an alternative to plasmapheresis. In doing this, the overall therapeutic concept has to be taken into account adjusted to the individual case. There are no controlled trials on the long-term therapy [102].

Acute exacerbation of Myasthenia gravis (AChR-positive or MusK-positive) or so-called seronegative Myasthenia gravis show a response to ivIg therapy [44, 135]. Similarly ivIg therapy has the same effect as plasmapheresis in the case of a myasthenic crisis requiring obligatory intubation. However, ivIg has a more favorable profile regarding adverse reactions [43]. A beneficial effect has also been confirmed by trials in cases of LEMS, a syndrome that has a far lower incidence [7]. A reliable total dose of ivIg is considered to be 1 g/kg body weight [116].

Dosage: 0.4 g/kg body weight for 5 days.

***** The circle of experts "Application of medical products beyond the limits of their approved indications" was created by decree of the German Federal Ministry of Health and Social Security [BMGS] dated 17 September 2002. By decree dated 31 August 2005 the circles of experts 'Off-Label Use' located at the German Federal Institute for Drugs and Medical Devices [BfArM] were extended to further medical disciplines. At present there are three circles of experts covering the medical disciplines oncology, infectious diseases with focus on HIV/AIDS and neurology/psychiatry. According to article 1 paragraph 2 of the establishing decree by the BMGS dated 31 August 2005, the circles of experts Off-Label Use have the following tasks:

a) Submission of assessments regarding the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the AMG. The assessments must be reappraised at reasonable intervals and, if necessary, adapted to the development of the state of scientific knowledge;

b) Inform the German Federal Ministry of Health and Social Security and the Federal Joint Committee according to article 91 SGB V (Code of Social Law, Book V) about the state of scientific knowledge in medicine and technology on the application of approved medical products for indications and areas of indications for which they are not approved according to the AMG.

In patients with seronegative and antibody-positive ***Myasthenia gravis*** and in patients with **Lambert-Eaton Myasthenic Syndrome (LEMS)** ivIg should be used in cases of acute exacerbation. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4. A scientific account on this application of ivIg is being prepared by the circle of experts "Off-Label Use"* in neurology/psychiatry located at the German Federal Institute for Drugs and Medical Devices [BfArM] [http://www.bfarm.de].)	**2 A**

Additional immunologically mediated diseases
In a number of additional diseases favorable outcomes on using ivIg have been reported, mostly in the form of case reports, e.g. autoimmune hemolytic anemia (AIHA), autoimmune neutropenia, Evans Syndrome, Morbus haemolyticus neonatorum, hemolytic transfusion reactions, hemolytic uremic syndrome, heparin-induced thrombocytopenia type II, HIV-associated thrombocytopenia, various forms of vasculitis, bullous dermatosis, uveitis, rheumatoid arthritis, Systemic lupus erythematosus (SLE; e.g. during pregnancy). Representative prospective randomized trials confirming the efficacy of ivIg are still lacking [6, 9, 10, 15, 26, 28, 29, 69, 102, 105, 116, 128].
In case of refractoriness to a licensed treatment protocol successful therapeutic attempts have been documented with ivIg as add-on therapy in several case reports for the following clinical pictures: Stiff-Person Syndrome [27, 28], Opsoclonus-Myoclonus Syndrome, Postpolio Syndrome and Alzheimer's Syndrome [102, 116]. Due to insufficient data, we refrain from making definite therapeutic recommendations. Because this indication is not licensed, the application would be done in the "Off-Label Use". The legal issues involved in this are pointed out in section 0.4.

9.5.3 Licensed indications with conditional recommendation or no recommendation due to new scientific data

Substitution of immunoglobulins in preterm infants, especially prior to week 32 of gestation
The largest prospective multicentre study [36] with over 2400 premature infants has shown that the number and severity of infections could not be reduced by ivIg as prophylaxis. In addition to humoral immunodeficiency, premature infants exhibit cellular immune defects which cannot be corrected by administration of ivIg [8, 36]. This is also confirmed by more recent meta-analyses [92, 93].

IvIg should **not** be used as infection prophylaxis in preterm infants, even though this indication is licensed.	**2 A**

Prophylaxis and therapy of cytomegalovirus (CMV) infections
Clinically manifest CMV infections are frequent complications after bone marrow or organ transplantation. Following the introduction of effective virostatic drugs, the prophylactic or therapeutic use of ivIg or CMV-Ig in treating CMV-derived organic diseases (e.g. CMV pneumonitis) has no longer advantages over an antiviral therapy alone. This also applies for CMV-antibody-negative recipients of a CMV-positive transplant [68, 78, 79, 80, 99, 132, 136].

According to the current state of scientific knowledge regarding prophylaxis and treatment of CMV infections, ivIg or CMV-Ig therapy can **not** be recommended without simultaneous administration of virostatic drugs. This indication is not licensed.	**2 C**

Recurrent miscarriage
Regarding the issue of immunomodulatory effect on recurrent miscarriage (>3 miscarriages) by administration of ivIg and other measures, there is a large number of reports [98] including a meta-analysis [96] and guidelines [59]. Though positive effects have been reported for individual cases, no significant benefit of ivIg has been confirmed to date. Therefore the application is not recommended. Additionally, the indication is not licensed.

Hemophilia complicated by inhibitor formation or confirmed spontaneous or induced factor VIII autoantibodies
In general ivIg therapy is not recommended in patients with hemophilia complicated by inhibitor formation [6]. However, in individual cases ivIg therapy was reported to have been successful [109, 121]. All of the more recent trials and consensus reports recommend ivIg therapy at best as a standby therapy that could be tried after corticosteroids and immunosuppressive drugs have failed [6, 24, 102].
Dosage: ivIg 0.4 g/kg body weight for 2–5 days.

In patients with hemophilia complicated by inhibitor formation a therapy attempt using ivIg is not recommended unless conventional immunosuppressive therapy has failed or in emergency situations. (Note: Because this indication is not licensed, the application would be done in the "Off-Label Use". [The legal issues involved in this are pointed out in section 0.4.])	**1 C**

Application of ivIg in refractory recipients of platelet concentrates
Regarding the simultaneous application of ivIg and platelets in refractory platelet recipients, the reader is referred to section 2.8.

9.5.4 Indications for specific (enriched) immunoglobulins

Regarding specific immunoglobulins, the reader is referred to the current publications by the German Standing Vaccination Committee (STIKO) [cf. 34, 35a,b].
Statements on the application of specific immunoglobulins for RhD prophylaxis can be found in Table 9.5.4.1.

Table 9.5.4.1: Prophylactic application of specific immunoglobulins for RhD

Target group/indications/mode of exposition	Preparation	Current evaluation of indication
Rh(D)-neg. (dd) women		
• after delivery of an Rh-pos. child	Anti-D imIg	prescribed post partum prophylaxis
• during pregnancy	Anti-D imIg	ante partum prophylaxis
• in abortion, after interruption, ectopic pregnancy, amniocentesis, chorion biopsy or cord puncture, in bleeding during pregnancy, after forced inversion, after removal of a hydatid mole, in placenta praevia	Anti-D imIg	prescribed prophylaxis
Rh(D)-incompatible RBC transfusion; granulocyte transfusion Prophylaxis for immunization against D in Rh-neg. (dd) recipients of Rh-pos. (D+) RBC or granulocyte concentrates	Anti-D ivIg	individual cases, for prevention of Anti-D formation, especially for women of reproductive age. Not applicable in emergency transfusion.
Rh (D)-pos. platelet transfusion in Rh(D)-neg. (dd) women	Anti-D ivIg	
Autoimmune thrombocytopenia (ITP)	Anti-D ivIg Anti-D s.c. [83]	Second-line therapy after ivIg. Ineffective after splenectomy [17, 106]. Caution: hemolysis, hemoglobinuria [42]!

9.5.5 Absolute and relative contraindications

- Administration of ivIg or imIg is contraindicated in ***selective IgA deficiency*** and clinically relevant, verified antibodies to IgA. However, these patients can safely be substituted with scIg or, after blocking of the antibodies, with ivIg [4, 32, 54, 107].
- In ***transient hypogammaglobulinemia during childhood***, substitution with Ig preparations is not indicated provided that such children form normal amounts of antibodies following vaccination [19].
- ***Simultaneous parenteral administration of specific immunoglobulins and attenuated live vaccines*** (measles, rubella, mumps, chicken pox, yellow fever) can lead to impairment of active antibody formation. A minimum interval of two weeks between Ig application and vaccination must be observed. Guidelines for dosage and manufacturers' informations are to be followed carefully, especially on administration of specific immunoglobulins.

Note:
Underdosing of sc/imIg or ivIg without precise indication **is always contraindicated**, as this does not lead to effective antibody concentrations. Specifically the intramuscular administration of immunoglobulins as substitution therapy is considered to have become obsolete as the dose necessary for treatment is not achieved.
(Example: 10 mL 16 % sc/imIg ≈ 1.6 g IgG, i.e. ≤2 % of the total body pool of 1 g/kg body weight in adults.)

9.6 Adverse reactions

See chapter 11.

So-called aseptic meningitis [52, 111, 127] with headache, stiff neck, vomiting and fever occasionally occurring after too rapid infusion or too high doses of ivIg does not constitute a contraindication to further infusion therapy. But an interruption of therapy is recommended, as pachymeningitis was also observed to occur under ivIg administration [81]. A slower rate of infusion is recommended and/or switching to a lower-dose ivIg preparation; another possibility is to switch the ivIg preparation. It is not yet clear whether this represents a variant of the drug-induced aseptic meningitis (DIAM) [66] or whether the Fc-concentration or other immunological mechanisms are more likely explanations [60].
Additional rare adverse reactions are to be expected like embolic incidents (cerebral infarction) or renal tubular necrosis [28]. There is also the possibility of ivIg-derived acute polyneuroradiculitis in chronic inflammatory demyelinizing polyneuropathy [64].

9.7 Documentation

According to article 14 TFG, there is an obligation to perform a patient- as well as product-related batch documentation for human immunoglobulins.

9.8 References

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10 Autologous hemotherapy

10 Autologous hemotherapy

Note: Autologous blood or blood components collected prior to surgery are pharmaceutical products and as such are subject to regulations of the *Arzneimittel- und Wirkstoffherstellungsverordnung* (AMWHV), the *Arzneimittelgesetz* (AMG – German Medicinal Products Act), the *Gesetz zur Regelung des Transfusionswesens* (TFG – German Transfusion Act) as well as the German Guide for Obtaining Blood and Blood Components and for Application of Blood Products (Hemotherapy) [11].

10.1 Autologous RBC products

10.1.1 Preparation

Autologous RBC products can be prepared in three ways: by preoperative autologous blood donation, by presurgical normovolemic hemodilution and by salvaging of wound/drainage blood shed during and/or after surgery by means of mechanically processed autologous transfusion (MAT).
The advantages of autologous hemotherapy include: the exclusion of rare adverse reactions like plasma-associated incompatibilities or transfusion-associated GVHD, formation of irregular erythrocyte blood group-specific alloantibodies or delayed hemolytic transfusion reactions and above all the avoidance of transmitting viral pathogens. In view of the considerable progress made in the virus safety of allogeneic blood products, however, this aspect has lost significance [6, 38]. Reduction of postoperative infections after exclusive administration of autologous RBC concentrates in comparison to leucocyte-depleted allogeneic RBC concentrates is subject of discussion [25]. Autologous blood donation and transfusion exposes the patient to principally the same risks as homologous blood donors [11].
The capability of the individual patient to donate autologous blood (see [11]) is to be judged by the attending physician.

10.1.1.1 Preoperative autologous blood donation

Prior to elective surgical interventions with an at least 10 % likelihood of blood transfusion (defined by in-house data) according to German Guide for Obtaining Blood and Blood Components and for Application of Blood Products (Hemotherapy), the patient is to be informed in due course and individually of the risks of homologous blood transfusion, of the possible application of autologous blood and of the potential risks and benefits of autologous hemotherapy [11]. The attending physician is responsible for defining the indication as well as deciding on the amount of blood products required while observing the German Guide in force [11]. Each case of autologous hemotherapy requires exact decisions for or against hemotherapy, taking contraindications into account. Based on the necessary underlying data (blood count and hematocrit, minimum acceptable levels of intra- and postoperative hematocrit/hemoglobin, blood volume, expected loss of blood during the intended procedure according to the hospital's current requisition lists), planning should be started as early as possible [2].
Current investigations document the benefit of preoperative donation of autologous blood, in particular in cardiovascular surgery [15, 29], hip replacement and spinal surgery [20, 23]. In contrast, a prospective, randomized study on the benefit of preoperative autologous blood donation for hip replacement surgery could demonstrate no advantages [5]. The problem of increased wastage of predonated RBC units that were not used should also be taken into account [4]. No general recommendation can be given regarding the use of preoperative

autologous blood donation in primary total knee arthroplasty [18] and in oral and maxillofacial surgery [26, 32, 33].
The essential goal of preoperative autologous blood donation is a substantiated gaining in erythrocyte mass (extracorporeal deposit plus *in vivo* regeneration). The decisive factor for this increase is the concept of blood collection with a minimum time interval of 3 weeks between the last predeposit and elective surgery. Only in this way can an adequate RBC regeneration take place due to the time-dependent physiological basics of erythropoiesis. Because there is an inverse exponential correlation between hematocrit and erythropoietin levels in plasma, erythropoiesis is intensified with declining hematocrit levels. Taking this essential factor into account, conventional concepts for the collection of autologous predeposits (1 unit each with an interval of 1–2 weeks up to shortly before the date of surgery) do not lead to an optimal increase in RBC mass. New, intensified concepts for the collection of autologous predeposits with brief time intervals between the collection of 2 RBC concentrates (within 1 week) results in an increased erythropoietic stimulus and a significant increase in RBC mass compared with the "conventional concept" of collecting RBC [40, 41].

When collecting autologous predeposits, an "intensified" concept for collection is recommended where 2 autologous blood donations are performed within a short time (1 week), provided the clinical status of the patient permits this. In addition to a larger decline in hematocrit levels, there is also a longer time period before surgery, allowing regeneration of erythrocytes.	**1 C+**

The eligibility of a patient for autologous blood donation is examined following the specifications for healthy blood donors [11]. Patients with leucocyte counts of more than 10.5×10^9/L should donate autologous blood only if an infection is unlikely or can be ruled out as the cause. Depending on the clinical state of the patient, an adequate volume substitution should be performed after each autologous blood donation.

Prior to autologous blood donation the hemoglobin level should be at least 11.5 ± 0.5 g/dL (7.13 ± 0.31 mmol/L).	**1 C**

In individual cases the administration of erythropoietin (EPO, in combination with iron supplementation) can become necessary in order to retain endogenous erythrocyte reserves [37, 42, 48]. Iron substitution therapy should be applied if at least 3 autologous blood donations are planned or if the ferritin level is <50 µg/L [51].
Autologous RBC concentrates are prepared from whole blood or by using cell separators. Blood collection follows regulations laid down for the production of homologous RBC units (see chapter 1). Autologous whole blood may also be used unprocessed after inline filtration. By setting a correspondingly low extracorporeal volume (e.g. 250 mL), the cell separator can be adapted for use in children and older patients [34, 35].

It is prohibited to pass on unused units of autologous blood to other patients or to use them for the preparation of other blood products.

Cryopreservation of autologous blood is established only in some centers [31]. Its indication is limited to patients with a complex spectrum of antibodies as well as patients with rare blood groups and the potential risk of forming antibodies against high-frequency antigens.

Quality criteria
On principle, all the requirements of homologous RBC concentrates must be met (see chapter 1). In individual cases it is possible, due to a physician's decision, to deviate from the

requirements of homologous blood donors, especially regarding threshold values for erythrocyte counts and hemoglobin/hematocrit [11].

10.1.1.2 Preoperative normovolemic hemodilution

Preoperative normovolemic hemodilution can be considered for patients with preoperative hematocrit/hemoglobin concentrations at the upper limit of normal and for whom an intraoperative blood loss is anticipated of >50 % of the blood volume, and who are able to tolerate hemodilution-derived anemia due to their general clinical state [27, 43]. Within the framework of any risk-benefit analysis, the physician should also bear in mind that the maximum possible saving (which is only achievable when preoperative hemoglobin concentrations are at the upper limit of normal) does not exceed 1–1.5 homologous RBC concentrates [7, 39].
The patient is to be informed about the risks and benefits of hemodilution.
The blood bag is to be labeled with patient data (last name, first name, date of birth) as well as the time and date of collection and is to be tested for intactness, possible hemolysis and clot formation. Collected autologous blood cannot be stored and must be transfused within 6 hours after collection has started. An ABO bedside test is not mandatory if the products remain in the immediate vicinity of the patient and if no change of personnel happens between blood collection and transfusion. The physician collecting the blood is responsible for proper preparation.

Quality criteria
Stored whole blood must be visually inspected (intactness, hemolysis and clot formation). The German Guide for Hemotherapy must be considered [11].

Preoperative normovolemic hemodilution can only be recommended as a method with a limited effect for patients with hemoglobin concentrations at the upper limit of normal. No reduction in the demand for allogeneic RBC concentrates could be documented in controlled trials.	**1 A**

10.1.1.3 Mechanically processed autologous transfusion (MAT)

The patient is to be informed about the potential risks and benefits of MAT. MAT is especially indicated in operations in which major blood loss is anticipated (e.g. orthopedic or vascular surgery) or occurs unexpectedly (emergency operations) [3, 12]. Although more than 50 % of the blood shed from wounds can be retransfused in this way, the rate of recovery varies considerably, thus it cannot be anticipated and budgeted in preoperative transfusion planning [50].
The blood shed from the wound is mechanically salvaged under sterile conditions and retransfused as a washed RBC suspension. MAT may not be used when bacterial contamination of the aspirated blood is strongly suspected (e.g. in gastrointestinal surgery) as the washing and filtration steps in the preparation process do not eliminate bacteria. As a rule the collected RBC must be retransfused immediately. In exceptional cases RBC collected by MAT can be stored up to 6 hours at +2 °C to +6 °C. This period of time covers the complete process.
The transfusion of salvaged blood shed from wounds or drainage intra- or postoperatively without previous treatment (washing) is not recommended due to the risk of clotting activation or retransfusion of cytokines and possibly endotoxins as well as of other biological active substances.
In tumor patients it is recommended to irradiate MAT blood at 50 Gy before retransfusion [24]. The relevant terms and regulations of the German Medicinal Products Act regarding the operation of a qualified radiation institution must be observed.

Taking the contraindications into account, application of MAT can be recommended when major blood loss is anticipated as well as when acute bleeding occurs during surgery.	**1 C+**
In tumor surgery the application of MAT can be recommended, when the blood shed from the wound is irradiated prior to retransfusion.	**2 C+**

10.1.2 Storage and shelf life

Autologous red blood cell preparations are principally to be stored at +2 to +6°C clearly separated from homologous blood products.
Blood derived from hemodilution or MAT must be retransfused as soon as possible if indicated. The maximum time span between collection and transfusion is 6 hours.

10.1.3 Range of application, dosage and mode of administration

Autologous whole blood concentrates and RBC concentrates are prescription-only medical products and therefore an integral part of medical treatment [11]. Indications for transfusion differ in no way from those for homologous preparations. This also applies to RBC concentrates obtained in the context of acute normovolemic hemodilution.

10.1.4 Adverse reactions

See chapter 11.

10.1.5 Documentation, informed consent

Documentation of administration is done according to article 14 German Transfusion Act (TFG) (patient data, batch number, identification of the preparation, volume administered, time and date of collection, adverse reactions). The German Guide for Hemotherapy should be considered [11].
Before autologous blood donation the patient is to be informed in writing about the individual risk-benefit ratio involved in donating and receiving autologous blood components and about the possibility that homologous blood components may still have to be transfused.

10.2 Autologous platelet preparations, autologous fresh frozen plasma (AFFP), autologous fibrin glue, autologous platelet-rich plasma (APRP)

The use of these blood products is based on reports from isolated centers and is limited to only a few indications. Controlled prospective studies have not been performed. Therefore, no recommendations concerning indications, dosage, quality requirements or mode of administration can be made.

10.2.1 Autologous platelet concentrates

This application is restricted to specific indications.
Autologous platelet concentrates have been used by ophthalmologists to treat macular holes [21, 22, 28]. Single reports have been published about the use of autologous PC in cardiac surgery [52] and as supportive treatment in high dose chemotherapy [45].

10.2.2 Autologous fresh frozen plasma (AFFP)

In the production of autologous RBC concentrates AFFP is routinely produced as part of the separation process and is available during or after surgery [11]. Indications for FFP are described in ch. 4. In elective surgery in which high blood losses can be anticipated (e.g. revision of total hip arthroplasty, spinal surgery), the presurgical collection of several units of AFFP via plasmapheresis in combination with intraoperative MAT is a well-established means of providing "physiological" fluid replacement perioperatively, even in the event of massive blood loss.

10.2.3 Autologous fibrin glue

Various working groups have reported on the preparation and use of autologous fibrin glue in surgery [13, 44, 49]. Standard methods have not yet been established [46].

10.2.4 Autologous platelet-rich plasma (APRP)

Autologous platelet-rich plasma (APRP) is obtained from small amounts (around 10–80 mL) of autologous blood by centrifugation. Usually it is mixed with a few drops of blood from the wound and human bone material or synthetic bone substitute material and is used for filling bone defects in dentistry. The only prospective trial published so far [30] as well as a few case studies or data from animal experiments who reported benefits [1, 16, 47] or no significant effect [17, 19, 36] in the application of APRP or PRP in bone graft surgery do not allow to make recommendations for application beyond clinical trials. Randomized trials on the efficacy of APRP are still lacking.

A general application of autologous platelet-rich plasma beyond clinical trials is not recommended.	**2 C**

10.3 Autologous stem cell preparations

The German Guide for Obtaining Blood and Blood Components and for Application of Blood Products (Hemotherapy) [11], the guides for transplantation of peripheral blood stem cells [9], for bone marrow transplantation [8] and cord blood stem cells [10] as well as the recommendations of the German Society for Transfusion Medicine and Immunohaematology on blood stem cell apheresis [14] should be observed.

10.4 Documentation

See section 10.1.5.

10.5 References

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11 Adverse reactions

11 Adverse reactions

11.1 Clinical classification and immediate measures in acute adverse reactions

Acute adverse reactions include all adverse reactions on administration of blood components that have a direct temporal association with the application, i.e. usually during administration of components or within a 6-hour period after administration of components. Depending on the characteristics of the clinical reaction, these adverse reactions can be classified into three grades of severity (see Table 11.1.1).

The most frequently occurring adverse reactions are fever, chills and urticaria. The most frequently occurring serious adverse reactions are acute hemolytic transfusion reactions (following administration of RBC concentrates), TRALI (following administration of FFP and platelet concentrates) and transfusion reactions caused by bacterial contamination of blood components (especially platelet concentrates are affected).

When adverse reactions occur during transfusion, the transfusion must be interrupted or cancelled, depending on the severity and character of symptoms, and the attending physician performing the transfusion has to be informed immediately. The venous access must be maintained for therapy that might become necessary. If clinically justifiable, the administration of further RBC concentrates or blood components should be discontinued until clarification. The patient requires continuous monitoring until abatement of symptoms is achieved.

The first priority is to confirm or rule out intravascular hemolysis that can be identified by an immediate detection of red staining in plasma and/or urine and that can be objectified by determining the free hemoglobin. Because this parameter is not available in many laboratories, haptoglobin values can be determined as an alternative. However, in this context follow-up monitoring is possibly required since haptoglobin as an acute phase protein is subject to wide variation.

In the interest of an efficient flow of information, in case further diagnostic tests are required, the physician performing the transfusion must take care to send the stored material (sealed blood bag, EDTA blood sample from the patient) with written documentation to the immunohematological laboratory, in accordance with the specifications of the in-house quality assurance system.

Table 11.1.1: Clinical classification of acute adverse reactions

	Clinical signs and symptoms	**Probable causes**	**Immediate course of action**	**Further immediate clarification**
I	urticaria and/or pruritus	allergic reaction	1. interrupt transfusion 2. clinical examination 3. consider antihistamine therapy 4. continue transfusion if no aggravation occurs	none
II	urticaria pruritus fever rigor restlessness tachycardia anxiety palpitations mild dyspnea headaches	allergic reaction febrile nonhemolytic transfusion reaction bacterial contamination of the component	1. interrupt transfusion 2. clinical examination 3. consider antihistamine/ paracetamol therapy 4. monitor the patient 5. in case transfusion is urgently necessary, transfusion of additional components (not of the triggering component) which should be monitored at close intervals	exclusion of hemolysis (section 11.2.1) exclusion of bacterial contamination (section 11.2.4)
III	fever rigor restlessness drop in blood pressure tachycardia dark urine unexplained bleeding chest pains side and back pains pains at the injection site headaches dyspnea	**A) without cardinal respiratory symptoms:** acute intravascular hemolysis; shock in case of bacterial contamination; anaphylaxis **B) with cardinal respiratory symptoms:** hypervolemia; transfusion-associated acute lung injury (TRALI)	1. interrupt transfusion 2. clinical examination 3. immediate emergency measures according to the cardinal symptoms (circulation, respiratory tract)	exclusion of mix-up if necessary, repeat bedside test exclusion of hemolysis (section 11.2.1) exclusion of bacterial contamination (section 11.2.4) with cardinal respiratory symptoms exclusion of TRALI (table 11.1.2 + section 11.2.5)

In problematic cases of hemolytic transfusion reactions an experienced immunohematological laboratory should be contacted. In case of febrile reactions with a temperature rise of more than 1°C as well as any grade III reactions (see table 11.1.1), microbiological cultures from the RBC preparation and from the recipient's blood must be initiated in a microbiological laboratory. In transfusion reactions with cardinal respiratory symptoms TRALI must be ruled out. Because there are no specific symptoms for acute adverse reactions, the acute-care measures to be initiated should first be taken in compliance with clinical parameters:

Table 11.1.2: Clinical differential diagnostics in acute transfusion reaction with cardinal pulmonary symptoms

O_2 saturation	X-ray (mandatory)	Additional important symptoms	Temporal connection with transfusion	Clinically suspected diagnosis
<90 %*	bilateral* pulmonary infiltrate; unremarkable cardiac symptoms		immediately up to 6 h* after transfusion	TRALI**
	pulmonary infiltrates; signs of cardiac decompensation	tachycardia hypertension	up to 12 h after transfusion; possibly following massive transfusion	TACO***
	no infiltrates			TAD****
	no infiltrates	cyanosis stridor	up to 24 h after transfusion	allergic dyspnea

* the diagnosis TRALI is ruled out if one of the criteria is not met
** transfusion-related acute lung injury (TRALI)
*** transfusion-associated circulatory overload (TACO)
**** transfusion-associated dyspnea

11.2 Acute adverse reactions

11.2.1 Hemolytic transfusion reactions of the acute type

Etiology and frequency:
Immediate-type hemolytic transfusion reactions usually occur in the presence of alloantibodies in the recipient's serum against antigens on the transfused RBC. Therefore they typically occur with ABO-incompatible RBC transfusions, mostly when RBC of blood group A are transfused to blood group O recipients. Incompatible transfusions due to incorrect allocation of blood products were most frequently reported to the hemovigilance system in the United Kingdom (61 % of all reports between 1996 and 2002). In an accidental misadministration of an RBC concentrate there is a probability of approximately 33 % that a major incompatible transfusion occurs [28]. The actually observed frequency of acute immunohemolysis due to ABO mix-up ranges between 1:20,000 and 1:40,000, while less than 10 % of major incompatible RBC transfusions have a fatal outcome [7, 27]. Due to the manufacturing process, granulocyte concentrates contain a relatively high percentage of erythrocytes, therefore immediate-type hemolytic transfusion reactions are also observed in ABO-incompatible transfusion of granulocyte concentrates.
Following transfusion of ABO-incompatible plasma-containing blood products (platelet concentrates, fresh frozen plasma), immediate-type hemolytic transfusion reactions can occur when the donor has high titers of hemolytically active isoagglutinins and/or when rather large volumes are transfused, e.g. to neonates and children (minor-incompatible transfusion).
Rarely, preformed alloantibodies in the recipient's serum against other blood group antigens (like RhD) may cause an acute intravascular hemolysis.

Symptoms:
Clinical symptoms are highly variable: fever, sweating, tachycardia, hypotension/shock, chills, restlessness, anxiety, back/side/chest pains, pains at the injection site, facial/trunk flushing, nausea and emesis as well as dyspnea are observed. Following hemolysis, hemorrhage due to disseminated intravascular coagulation, hemoglobinuria and renal failure may occur.

In anaesthetized patients hypotension and unusually severe bleeding from the wound area may be the only symptoms.
Diagnosis:
Check identity of the recipient and the blood product by referring to the accompanying documents. Repeat ABO bedside test using a fresh blood sample from the patient and a fresh sample from the blood component implicated.

Laboratory tests:
Visual inspection of the patient's plasma for red color after centrifugation, free hemoglobin in plasma and in urine. As it is often not possible to determine free hemoglobin in hospital laboratories, haptoglobin and LDH activity can be determined alternatively. Follow-up determination is recommended in order to confirm hemolysis by these laboratory parameters.
If hemolysis has been confirmed, direct antihuman globulin test, serological compatibility testing and antibody detection test with pre- and post-transfusion sample blood from the recipient must also be performed. When coagulation disorders are suspected, specific coagulation investigations are indicated. Where applicable, diagnostic tests should be performed to confirm/rule out disseminated intravascular coagulation.

Differential diagnoses:
Shock due to bacterial contamination (see 11.2.4), anaphylactic reaction (see 11.2.3).

Therapeutic measures:
Discontinue transfusion, maintain venous access. **Immediate** information of the blood bank/ laboratory (another patient might be involved due to cross-wise mix-up!). Secure renal perfusion (forced diuresis, early hemodialysis or hemofiltration if necessary). Monitoring of coagulation status and general shock treatment.
Transfusion of further blood components – if possible – only after clarification of etiology.

11.2.2 Febrile nonhemolytic transfusion reactions

Etiology and frequency:
Release of leucocyte-derived cell components during manufacturing, storage or transfusion is assumed to be the most frequent cause of febrile reactions. These can also occur when the recipient's antibodies against leucocytes (especially HLA antibodies) react with contaminating leucocytes in platelet or granulocyte concentrates [19]. Following the introduction of general leucocyte depletion, febrile nonhemolytic transfusion reactions have become a rare occurrence (<0.1 %) [22, 36, 50].

Symptoms:
Fever (increase of body temperature by more than 1°C), shivering, chills, usually starting 30–60 minutes after beginning of transfusion; hypotension and facial/trunk flushing may also be observed in some cases.

Diagnosis:
No specific diagnostics is available. An acute intravascular hemolysis and, in case of an increase of body temperature by more than 1°C, a bacterial contamination are to be ruled out. In patients needing transfusions for longer periods of time the determination of HLA antibodies and the provision with HLA-compatible (crossmatch-negative) platelet concentrates may be indicated.

Differential diagnoses:

Acute hemolysis, allergic reaction, bacterial contamination of blood components.

Therapeutic and prophylactic measures:
Patients who repeatedly have a febrile nonhemolytic transfusion reaction on administration of cellular blood products can be effectively pretreated with antipyretic drugs [11].

11.2.3 Allergic transfusion reactions

Etiology and frequency:
Antibodies in the recipient's serum against donor plasma proteins are considered the cause of allergic reactions. An allergic reaction is to be anticipated in about 0.5 % of transfused units [10], 90 % of which occur with plasma and platelet transfusions [14, 14a].
In very rare cases recipients with congenital IgA deficiency may form high-titer antibodies against immunoglobulin A, which may cause an allergic transfusion reaction.

Symptoms:
Urticaria, facial and trunk flushing, pruritus, rarely further clinical signs occur of an allergic reaction, like gastrointestinal (diarrhea, emesis) or pulmonary symptoms (cyanosis, stridor). Even more rarely anaphylactic shock occurs. The reactions usually appear immediately after beginning of transfusion.

Diagnosis:
An acute intravascular hemolysis and, in case of an increase of body temperature by more than 1°C, a bacterial contamination of the blood product are to be ruled out.
In severe allergic reactions a congenital IgA deficiency (IgA <0.05 mg/dL) is also to be ruled out by determining IgA concentration in serum from a pre-transfusion blood sample. In absolute IgA deficiency the additional determination of specific antibodies against IgA is recommended [46].

Differential diagnoses:
Acute hemolysis, bacterial contamination of the blood component.

Therapeutic measures:
Discontinue transfusion; maintain venous access. Stage-specific treatment as in other allergic reactions.

Prophylaxis:
In the event of repeated allergic transfusion reactions, premedication (H_1 receptor antagonists, corticoids) of the patient should be considered.
After severe anaphylactic reactions in patients with confirmed absolute IgA deficiency and formation of anti-IgA, transfusion of washed RBC and platelet concentrates may be indicated. Plasma transfusions in these patients may be performed with IgA-deficient plasma.

11.2.4 Transfusion reactions caused by bacterial contamination

Etiology and frequency:
Microorganisms present in the circulating blood or on the skin of the donor can lead to contamination of blood products. At the storage temperature employed, few classes of pathogens can adequately propagate in RBC concentrates, among them typically Yersinia which may provoke an endotoxic shock in the recipient (in individual cases). However, in platelet concentrates the commensal pathogens of the donor's skin flora can propagate, like coagulase-

negative Staphylococci and Propionibacteria, but the clinical relevance of some of these pathogens is not yet clear [25].
For epidemiological purposes one must clearly differentiate between the rate of diagnosed bacterial contamination of blood components (ranging between 0.1 and 0.5 % of all units in platelet concentrates [12, 34]) and the frequency of clinical reactions to contaminated preparations (approx. 1:100,000 [12, 14, 14a]), since a large proportion of contaminated transfused platelet concentrates did not lead to clinical reactions [34].
Specific infections with treponema, borrelia or rickettsia by blood transfusion are extremely rare [4, 8].

Symptoms:
Depending on the degree of severity, the symptoms of a septic reaction may resemble those of an immediate-type hemolytic transfusion reaction or those of a febrile nonhemolytic transfusion reaction (grade II to grade III). Most frequent are fever, chills, emesis and/or diarrhea, pronounced hypotension and tachycardia, which may often occur during transfusion, rarely several hours later.

Diagnosis:
It is most essential to rule out an immediate-type hemolytic transfusion reaction. In all grade II and grade III reactions the microbiological laboratory should first carry out a smear from the blood product using gram staining. In addition, upon suspicion of bacterial contamination microbiological cultures from the transfused units and from the recipient's blood should be performed at suitable temperatures. If the same species of bacteria is detected in the blood component and in the patient sample, a comparison of genome sequences of bacteria should be performed.

Differential diagnoses:
Acute hemolysis, allergic reaction, febrile nonhemolytic transfusion reaction.

Therapeutic measures:
Discontinue transfusion; maintain venous access. Symptomatic therapy, if necessary shock treatment, targeted antibiotic therapy.

Prophylaxis:
Visual control of all blood products immediately prior to transfusion regarding intactness of the blood bag. Bacterial contamination can occasionally be detected by clot and lump formation, discoloration or lack of the "swirling effect" in platelet concentrates (cloudy opalescence on inspection against the light). Control of the expiration date prior to transfusion. Verification of the cold chain in the case of RBC concentrates. On principle, blood components must never be opened except for introducing the transfusion set immediately prior to transfusion. Transfusion of blood components within 6 hours after opening [1].

11.2.5 Transfusion-related acute lung injury (TRALI)

Etiology and frequency:
Transfusion-related acute lung injury (TRALI) is caused by antibodies to patients' leucocytes in donor plasma (rarely in recipients' plasma). The activated leucocytes obstruct the pulmonary microcirculation and cause pulmonary edema. Up to 25 % of afflicted patients die [14, 23]. In rare cases TRALI can also have a non-immunogenic etiology, but in these cases clinical symptoms are mostly insignificant.

Symptoms:
During or up to 6 hours after transfusion rapidly increasing dyspnea develops together with hypoxemia (SpO_2 <90 % on ambient air or $FiO_2 \leq 300$) and bilateral pulmonary infiltrates become apparent in chest X-ray. Sometimes hypotension and fever are observed. 70 % of patients require assisted respiration.

Diagnosis:
In all of the patients developing a distinctive acute dyspnea in the context of transfusion the O_2 saturation (minimum) shall be determined by pulse oxymetry and a chest X-ray shall be made, at least in the posterior-anterior view. In patients with TRALI the O_2 saturation is below 90 % and the X-ray displays newly emerged bilateral infiltrates. Regarding differential diagnosis, see Table 11.1.2.
If TRALI is suspected clinically, the pharmaceutical manufacturer of the blood component must be informed. In cooperation with the attending physician, the manufacturer must identify the product(s) probably triggering the symptoms. Sera from the donors involved must be investigated for the presence of leucocyte-reactive antibodies, in particular antibodies to HLA class I and class II, as well as to granulocyte-specific antigens (HNA). When antibodies are detected in the donor, an identification of the antibodies and a typing of the recipient's antigens should be aimed for. As a rule, it is necessary to determine leucocyte antibodies also from serum of the recipient.

Differential diagnoses:
Transfusion-associated circulatory overload, often accompanied by tachycardia and hypertension (see section 11.2.6); allergic dyspnea accompanying an allergic transfusion reaction that is often accompanied by cyanosis and stridor; transfusion-associated dyspnea, indistinct clinical picture with dyspnea in connection with the transfusion but without infiltrates in the X-ray (see also table 11.1.2).

Therapeutic measures:
It is most important to maintain respiratory functions (approx. 70 % of patients with TRALI need obligatory intubation and assisted respiration) and cardiovascular functions. Infusion therapy alone is often not sufficient in TRALI, additional drug therapy is required. Diuretics are not indicated and the use of corticoids is controversial for lack of evidence [49].

11.2.6 Hypervolemia, transfusion-associated circulatory overload (TACO)

Etiology and frequency:
Especially too rapid transfusion and too large transfusion volumes can lead to acute hypervolemia, strongly depending however on the cardiac capability of the individual patient. The most relevant clinical complication of hypervolemia is acute hydrostatic pulmonary edema. Neonates and children as well as patients older than 60 years of age are most often affected. Incidence is stated as 1–8 % of transfusion recipients, lethality with 3–4 % [39].

Symptoms:
Cough, dyspnea, cyanosis, jugular inflow congestion, headache, tachycardia, cardiac insufficiency and pulmonary edema.

Diagnosis:
In all of the patients developing a distinctive acute dyspnea in the context of transfusion the O_2 saturation (minimum) shall be determined by pulse oxymetry and a chest X-ray shall be made, at least in the posterior-anterior view. Regarding differential diagnosis, see Table 11.1.2.

Therapeutic measures:
If possible bring patients into an upright position; discontinue transfusion or reduce transfusion rate; treatment with oxygen and diuretics.

Prophylaxis:
Hypervolemia can be avoided by restricting the amount transfused to 2–4 mL/kg body weight and hour, in case of particular risk to 1 mL/kg body weight and hour.

11.2.7 Further acute adverse reactions

Hypothermia:
Hypothermia may occur mainly in connection with massive transfusions; the body temperature may decrease to 34–32°C during rapid replacement of 50 % of the blood volume which can provoke or amplify potentially life-threatening disorders [24].
Warming of blood components (RBC concentrates, plasma) using suitable equipment can prevent hypothermia on administration of large transfusion volumes.

Hyperkalemia:
Hyperkalemia may attain clinical significance in rapid massive transfusion of RBC (≥ 60 mL/min). It should also be considered in patients with primarily elevated plasma potassium levels (renal insufficiency!) and possibly in connection with exchange transfusions [24]. High levels of potassium are frequently found in irradiated and stored RBC concentrates.

Transfusion of hemolytic RBC:
Hemolysis can occur to a noteworthy extent when storage is inadequate (accidental freezing!), by incorrect warming or – prohibited! – addition of medications and/or hyper- or hypotonic solutions to the RBC concentrate.
The occurrence of severe coagulation disorders with the danger of DIC cannot be ruled out. Patients must be closely monitored and their clotting status is to be checked repeatedly.

Citrate reactions:
If transfusion of FFP is performed rapidly (more than 50 mL/min), there is a risk of citrate intoxication, particularly in neonates and in patients with well-known dysfunction (restricted liver function, acidosis, hypothermia, shock). In addition to clinical signs, symptoms are long QT syndrome in the ECG, drop in blood pressure and arrhythmia. Calcium gluconate is administered as therapy.

11.3 Adverse reactions of the delayed type

11.3.1 Hemolytic transfusion reactions of the delayed type

Etiology and frequency:
If the recipient has at some time formed alloantibodies to blood-group antigens their concentration may decrease considerably over time and may no longer be detectable in the event of a transfusion at a later date. Further exposure of the immunized recipient acts as a booster fol-

lowed by delayed reappearance of antibodies. The subsequent hemolysis may thus develop within a period of 14 days (or longer) after transfusion. The ratio of fatal outcomes is given as approximately 1:1.8 million transfused units [27].
Because of processing steps, granulocyte concentrates contain a relatively high proportion of erythrocytes. Therefore hemolytic transfusion reactions of the delayed type can also occur in this context.

Symptoms:
Rise in temperature, anemia, jaundice; hemoglobinuria, DIC and renal failure can occur less frequently than in acute immunohemolysis.

Diagnosis:
Suggestive are the positive results of the direct antiglobulin test showing IgG coating of the transfused RBCs (partly also with C3d). Even earlier than its detection in serum, the antibody can be found in the eluate [42]. Most antibodies are directed against antigens of the Rhesus and Kidd system, followed by those against Duffy, Kell and MNS. Occasionally the alloantibodies implicated can only be confirmed in a blood sample collected at a later point in time.
Hemolysis can be verified by measurement of lactate dehydrogenase (LDH) activity and bilirubin over time as well as haptoglobin.
Considerably higher than the incidence of hemolytic transfusion reactions of the delayed type is that of serological transfusion reactions of the delayed type. Although RBC coating with the antibody that was boostered by transfusion can be demonstrated in the laboratory, there are no clinical or laboratory signs of hemolysis.

Therapeutic measures:
Symptom-oriented monitoring of the patient, depending on the clinical course. If necessary, monitoring of coagulation status and second transfusion, taking into account the specific antibody.

Prophylaxis:
Previously established irregular erythrocyte antibodies should be recorded into the patient's emergency identification document and this information should always be available when compatibility testing is carried out in the future.

11.3.2 Post-transfusion purpura

Etiology and frequency:
Post-transfusion purpura is caused by a platelet-specific alloimmune response with an autoimmune portion [47]. It is a very rare transfusion reaction [33] almost exclusively affecting middle-aged or older women with pregnancy or transfusion inducing immunization in their history.

Symptoms:
Acute, isolated thrombocytopenia with bleeding tendency after previously unremarkable thrombocyte count about 1 week after transfusion. Frequently the platelet count decreases below 10,000/µL.

Diagnosis:
Proof of platelet-specific alloantibodies in the patient. Usually the female patient is HPA-1a negative and a strongly reactive anti-HPA-1a-specific antibody can be detected in her serum. If necessary, a heparin-induced thrombocytopenia type II (HIT) must be ruled out in differen-

tial diagnosis.

Therapeutic measures:
Intravenous high-dose immunoglobulin therapy with 1 g immunoglobulins/kg body weight, in portions of 2 doses on 2 days [32]. Platelet transfusions have no effect at all [13].

11.3.3 Transfusion-associated graft versus host disease (TA-GVHD)

Etiology and frequency:
The origin of the very rare transfusion-associated graft versus host disease (TA-GVHD), which is most often fatal, is the transfer of proliferative T lymphocytes from the donor to a usually immunoincompetent recipient. Today TA-GVHD is sometimes observed in neonates with congenital immune deficiency not yet recognized at the time of transfusion. The occurrence of TA-GVHD in immunocompetent recipients has also been described in rare cases where the donor was homozygous for an HLA haplotype of the recipient, especially in transfusion between close relatives or if the donor was homozygous for a common HLA haplotype (z. B. HLA-A1, B8, DR3).

Symptoms:
Fever, maculopapular erythema of the skin, generalized erythrodermia, blister formation, nausea, emesis, massive diarrhea, cholestatic hepatitis, lymphadenopathy, pancytopenia, about 4 to 30 days following transfusion.

Diagnosis:
Detection of donor-cell chimerism in blood and in biopsies of the affected tissue is performed by investigation of suitable DNA microsatellites [43].

Therapeutic measures:
Symptom-oriented therapy [20].

Prophylaxis:
In view of the often fatal outcome of a TA-GVHD, the irradiation of the blood components with 30 Gy must be indicated liberally (indications see section 11.4). Leucocyte depletion alone is not sufficient [30]. Granulocyte concentrates must always be irradiated with 30 Gy due to their high content of T-lymphocytes that are able to proliferate (see chapter 3, section 3.1).

11.3.4 Transfusion-transmitted viral infections

Etiology and frequency:
The cause of viral contamination of RBC concentrates is donor viremia not detected by donor screening despite highly sensitive laboratory test assays. Transmission of viruses – even of those that are as yet unknown – by cellular blood components and fresh plasma cannot be completely ruled out. This also applies to HIV, HBV and HCV. Leucocyte depletion of RBC and platelet concentrates decreases the titer of cellular viruses, e.g. CMV and HHV-8 as well as HTLV-I/II. According to present knowledge, leucocyte depletion for the prevention of transfusion-associated CMV infection is as effective as transfusion of blood components that have been tested anti-CMV-negative. Cellular viruses (like e.g. CMV) may possibly be transmitted by granulocyte concentrates.
Parvovirus B19 can be transmitted by blood products, leading to severe illness in pregnant women (fetal infection) and individuals with immunodeficiency or increased erythropoiesis

(e.g. in hemolytic anemia). Regarding prophylaxis of transfusion-associated CMV and parvovirus B19 infections: see chapter 11.4.

Symptoms:
Occurrence of specific symptoms of the infection in question after expiration of the respective incubation time (characteristic time interval between transfusion and onset of disease!).

Diagnosis:
Determination of specific antibodies, proof of virus genome, if necessary, comparison of viral genome sequences in recipient and donor. Initiation of a recipient-triggered look-back procedure starts by notifying the pharmaceutical manufacturer on the incidence of a confirmed infection following transfusion, based on findings to be collected by the attending physician. The virus infection suspected must be confirmed by reactive results in a serological test system involving a confirmation test and/or detection of the viral genome in two independent test samples. In the event of a suspected virus transmission by blood products, the procedure is regulated by law (article 19 German Transfusion Act) and has been specified in its particulars in an announcement of the Arbeitskreis Blut (National Advisory Committee 'Blood'; http://www.rki.de).

Therapeutic measures:
Specific therapy according to the particular infection.

Prophylaxis:
Despite the low risk of infection, before every transfusion the risk of the recipient to contract a transfusion-transmitted viral infection is to be weighed against its benefits. Regarding prophylaxis to avoid transfusion-associated CMV or parvovirus B19 infections: see chapter 11.4.

11.3.5 Transfusion-transmitted parasitical infections

Etiology and frequency:
In principle parasites can also be transmitted by RBC: especially the pathogen causing malaria (plasmodia), but also trypanosomes, babesias, leishmanias, microfilarias and toxoplasmata [8].

Symptoms:
Occurrence of specific symptoms of the infection in question after expiration of the respective incubation time (characteristic time interval between transfusion and onset of disease!).

Diagnosis:
Antibody diagnosis, pathogen determination.

Therapeutic measures:
Specific therapy according to the particular infection.

11.3.6 Further long-term adverse reactions

Transmission of prions (variant Creutzfeldt-Jakob Disease):
Whereas classical sporadic *Creutzfeldt-Jakob Disease* is probably not transmissible by blood, this is assumed for *variant Creutzfeldt-Jakob Disease* (vCJD). Four cases have been described in the United Kingdom up to the summer of 2007 in whom a probable transmission of vCJD prions occurred by blood transfusion and in three of the cases a subsequent fatal disease developed [29]. At present no risk assessment is possible for Germany since it is not known to what extent vCJD prions might have spread in the human population; therefore the vCJD risk is to be regarded as a theoretical risk.
To prevent the transmission of vCJD prions from latently infected individuals by blood or tissue donations or medical interventions (iatrogenic transmission), the Advisory Group 'Blood' has developed detailed recommendations (see http://www.rki.de). Physicians treating a patient who has received blood products possibly contaminated with vCJD prions or who, as a former blood donor, was him- or herself diagnosed with vCJD shall take or arrange the taking of measures described there concerning information and look-back in order to minimize the risk of transmission to third parties.

Transfusion hemosiderosis (RBC concentrates):
In chronically required transfusions the occurrence of hemosiderosis is to be anticipated after approx. 100 transfused RBC concentrates; it specifically affects the endocrine pancreas, liver and heart. Desferrioxamine is clinically effective and should be applied early when long-term transfusion needs are anticipated.

Inhibitor formation:
The formation of circulating inhibitors is possible in patients with factor deficiencies who received fresh frozen plasma transfusions.

Adverse reactions caused by plasticizers:
At present no final assessment can be made about whether plasticizers represent an additional health risk, particularly for preterm or full-term neonates. Platelets are stored in polyolefine bags without further addition of plasticizers.

11.4 Indications for transfusion of irradiated blood products and indications for transfusion of CMV- and parvovirus B19-screened blood products

11.4.1 Recommendations for irradiation of blood products

The transfusion of blood products containing T lymphocytes capable of proliferation carries the danger of a transfusion-associated Graft-Versus-Host-Disease (TA-GVHD) in immunocompromized recipients or in certain donor/recipient combinations. Irradiation with a mean dose of 30 Gy (with no part of the product receiving less than 25 Gy) causes a reliable inhibition of T cell proliferation, while the clinical efficacy of RBC, platelets and granulocytes does not seem to be significantly affected by irradiation [44]. If the irradiated preparations are stored further, the damage to the erythrocyte membrane causes an increased loss of potassium from the cell into the additive preservative solution and an increased hemolysis [31] which lead to a restriction in storage time of irradiated RBC concentrates.
So far, TA-GVHD has only be observed after transfusion of cellular blood products (RBC, platelet and granulocyte concentrates). In no case was a TA-GVHD following transfusion of FFP documented, regardless of the residual content of leucocytes.

It is **not** recommended to irradiate fresh frozen plasma to prevent a TA-GVHD.	**1 C+**

An irradiation shall be performed **at all events** for the following indications:

All cellular blood components collected by directed donation from blood relatives.
On principle, all cellular blood components collected by directed donation from blood relatives shall be irradiated. In these cases there is a particularly high risk of a one-way HLA match. At least 14 cases of TA-GVHD are documented to have occurred due to directed blood donations collected from blood relatives, all of which had a fatal outcome.

All cellular blood components of directed blood donations collected from blood relatives shall be irradiated prior to transfusion.	**1 C+**

All HLA-matched cellular blood components.
This particularly applies also to HLA-matched platelet concentrates in which there is a considerable risk of a one-way HLA match (approx. 5 %).

All HLA-matched cellular blood components shall be irradiated prior to transfusion.	**1 C+**

All granulocyte concentrates.
Because of manufacturing steps these products contain a large amount of T lymphocytes. At least 16 cases of granulocyte TA-GVHD are documented.

Granulocyte concentrates shall only be transfused after irradiation.	**1 C+**

All cellular blood components for intrauterine transfusion.
At least 3 cases of TA-GVHD are documented to have occurred following intrauterine transfusion with a fatal outcome in 2 cases. Anecdotal reports of children who, after an intrauterine transfusion, received further non-irradiated components and subsequently developed TA-GVHD are documented.

Intrauterine transfusions shall be carried out exclusively with irradiated cellular blood components.	**1 C+**
Following intrauterine transfusion, neonates shall be transfused exclusively with irradiated cellular blood components.	**1 C+**

RBC concentrates for exchange transfusion.
At least 2 cases of exchange transfusion are documented to have occurred without prior intrauterine transfusion, that have led to a fatal TA-GVHD, one of them in a full-term neonate.

Exchange transfusion of neonates should be performed with irradiated cellular blood components.	**1 C**

All cellular blood components for patients with congenital immunodeficiency.
Patients with severe combined immunodeficiency (SCID) have a very high risk of developing a TA-GVHD. At least 3 patients with SCID are documented who developed TA-GVHD. TA-GVHD has also been described in patients with milder forms of congenital immunodefi-

ciency, in particular in patients with purine nucleoside phosphorylase (PNP) deficiency, Wiskott-Aldrich Syndrome and DiGeorge Syndrome.

All patients with SCID shall be treated with irradiated cellular blood components.	**1 C+**
It is recommended to treat patients with congenital immunodeficiency or with suspected congenital immunodeficiency with irradiated cellular blood components.	**2 C**

All cellular blood components for patients prior to collection of autologous blood stem cells and during the period of autologous blood stem cell or bone marrow transplantation.
Several cases of fatal TA-GVHD have been described in patients in connection with autologous bone marrow transplantation. A literature search did not allow to specify evidence-based timeframes of how long before and after autologous transplantation irradiated blood components should be used. The usual time is 14 days prior to collection of autologous blood stem cells and at least 3 months following transplantation or reliable detection of immunological reconstitution.

Patients prior to collection of autologous blood stem cells and all patients during and following autologous blood stem cell or bone marrow transplantation shall be transfused with irradiated cellular blood components.	**1 C+**
It is recommended to treat patients following autologous transplantation with irradiated cellular blood components for at least 3 months.	**2 C**

All cellular blood components for patients with allogeneic blood stem cell or bone marrow transplantation.
There are reports in the literature on fatal outcomes due to TA-GVHD.

Following allogeneic blood stem cell or bone marrow transplantation, all patients shall be transfused with irradiated cellular blood components.	**1 C+**
It is recommended to treat patients following allogeneic transplantation with irradiated cellular blood components for at least 6 months or until immunological reconstitution.	**2 C**
It is recommended to treat patients with GVHD following allogeneic blood stem cell or bone marrow transplantation with irradiated cellular blood components.	**2 C**

All cellular blood components for patients with Hodgkin's lymphoma (all stages).
At least 12 cases of TA-GVHD in patients with Hodgkin's lymphoma are documented, all of them with a fatal outcome. A prospective study on the treatment of Hodgkin's lymphoma in 53 pediatric patients lists 2 cases of TA-GVHD.

Patients with Hodgkin's lymphoma (all stages) shall be transfused exclusively with irradiated cellular blood components.	**1 C+**

All cellular blood components for patients with Non-Hodgkin lymphoma (all stages).
At least 17 cases of TA-GVHD in patients with Non-Hodgkin lymphoma are documented, among them a higher number of Non-Hodgkin lymphoma patients without alternative risks of a TA-GVHD (no therapy with purine antagonists, no one-way HLA match). Some patients have developed chronic GVHD.

Patients with Non-Hodgkin lymphoma (all stages) shall be transfused exclusively with irradiated cellular blood components.	**1 C+**

All cellular blood components for patients during therapy with purine antagonists.
In at least nine patients during Fludarabin therapy and one patient during Cladribin therapy TA-GVHD occurred.

All patients during therapy with purine antagonists shall be transfused exclusively with irradiated cellular blood components.	**1 C+**

Note:
A literature assessment did not supply sufficient evidence to give a recommendation for irradiation of cellular blood products in the following situations:

- Transfusion in preterm neonates
- Transfusion in patients with AIDS
- Transfusion in patients with leukemia
- Transfusion in patients with solid tumors (including neuroblastoma und rhabdomyosarcoma)
- Transplantation of solid organs (including heart transplantation)

Note: When applying inactivation by photochemical treatment for pathogen inactivation it is possible to detect in vitro or in an animal model an inactivation of leucocytes corresponding to that after irradiation with 30 Gy [15, 16].
The expert information (Summary of Product Characteristics) and the product leaflet are referred to.

11.4.2 Recommendations for the safety of blood products regarding CMV and parvovirus B19

Cytomegalovirus (CMV)
The **Cytomegalovirus** (CMV, human herpesvirus 5) can be transmitted transplacentally, by breast milk, body fluids, through mucosal contact or iatrogenically through cellular blood components as well as organ and stem cell transplants. Whereas the infection in immunocompetent individuals mostly remains latent, CMV infection can lead to severe illness in fetuses, pre-term neonates, patients with congenital or acquired immunodeficiencies (AIDS) and patients after organ or stem cell transplantation. After primary CMV infection it is assumed that the virus persists for life. Therefore recipients of organ and especially stem cell transplants are at risk not only by recently transmitted CMV but also by reactivation of the autochthonous latent virus or by the virus latent in the transplant.
Transfusion-associated CMV infections have first been described in the 1960s in patients after cardiopulmonary bypass surgery and in the following years in the above-mentioned patient groups at risk. It is assumed that CMV is transmitted from CMV-seropositive blood donors as a latent virus together with blood leucocytes (monocytes) and circulating hematopoietic progenitor cells. Transfusion-associated CMV infections have not yet been observed after transfusion of FFP [2].
There are two effective measures in preventing transfusion-associated CMV infections:
a) application of cellular blood components from CMV-seronegative donors,
b) leucocyte depletion of cellular blood components.

Both measures result in a reduction in the incidence of transfusion-associated CMV infections in patient groups at risk by approximately 90 % each [45]. In the same meta-analysis the

residual risk despite taking either one of the two preventive measures is stated to be 1.5–3 % for patients after stem cell transplantation [45]. The two preventive measures have been compared directly in just one prospective, randomized trial involving 502 patients after stem cell transplantation [3]. Four cases (1.4 %) of CMV infections have been observed in the patient group receiving CMV-seronegative blood products compared to 6 cases (2.4 %) in the patient group receiving leucocyte-depleted blood products. The authors of the study concluded that both procedures are equivalent. However, all 6 patients in the group receiving leucocyte-depleted blood products developed an apparent CMV disease whereas no patient fell ill in the patient group receiving CMV-seronegative blood products (P = .03).

A meta-analysis including the prospective, randomized trial by Bowden et al. [3] as well as two non-randomized trials (before and after comparison [35, 37]) found a slight benefit when using blood products from CMV-seronegative donors as compared to leucocyte-depleted blood products in patients after stem cell transplantation [45]. There are no comparative clinical trials for other patient groups.

There are also no trials on a combined use of both preventive measures (leucocyte-depletion plus selection of CMV-seronegative donors vs. leucocyte depletion alone). It is also highly unlikely that such a trial will ever be conducted, since the number of patients enrolled would have to be extremely high in order to detect a statistically significant difference (n=6,500 [45]).

The minimum infectious dose (number of latently infected blood leucocytes) in humans is not known. Attempts to quantify CMV genome copies in latently infected blood donors have failed since copy numbers are usually below the detection limit of test assays presently available (1–10 CMV genome copies in DNA from 250,000 blood leucocytes). Only 2 of 1,000 samples had CMV DNA reproducibly detectable by validated methods [40]. Both blood samples were from seropositive donors. Conclusions by analogy from a murine model of transfusion-associated CMV infection suggest that leucocyte depletion using current generations of filters can reduce the number of latently infected leucocytes below the threshold of the infectious dose [41].

In addition to technical and other problems (lack of sensitivity of the antibody detection assay, decrease of the antibody titers under the limit of detection, filtration failure, CMV infection derived from another source with a temporal association with the transfusion therapy etc.), newly infected blood donors in the pre-seroconversion period could be responsible for part of the transfusion-associated CMV infections occurring in spite of preventive measures (window period). In blood donors of all age groups an overall CMV seroconversion rate of 0.55 % per year was detected [18].

In the context of a prospective cohort trial the rate of detection of CMV genome within blood leucocytes ranged from 75 % to 80 % during the first 16 weeks after infection. CMV DNA could be detected in plasma in 25 % to 40 % of the samples between week 8 and 16. In this trial IgG antibodies to CMV were present 6–8 weeks after CMV DNA was detected in blood leucocytes [52]. A different trial has also found CMV DNA in plasma of blood donors in the pre-seroconversion period [9].

CMV viremia in plasma from donors in the serological window period could explain part of the residual infection risk when using blood products from seronegative donors as well as leucocyte-depleted blood products. Theoretically the selection of CMV-seronegative blood donors for patients at risk leads to a doubling of the risk to collect blood in the serological window period which is particularly infection-prone (at a seroprevalence of 50 %).

At present no assessment can be made about whether the risk of a transfusion-associated CMV infection by leucocyte-depleted blood products is higher or lower when CMV-seronegative blood donors are selected. On the one hand, the risk reduction by leucocyte depletion and the risk reduction by selecting CMV-seronegative donors could be cumulative. On the

other hand, the selection of CMV-seronegative donors could lead to a doubling of the number of infectious donors in the window period.
Leucocyte depletion is performed in Germany for all RBC and platelet concentrates: this has caused a reduction of cellular latent cytomegaloviruses and thus has lowered the risk of a transfusion-associated CMV infection for patients at risk by approximately 90 %. At present no assessment can be made about whether the residual risk of these patients could be further reduced by using CMV-seronegative blood donations.

It is **not** recommended to select CMV-seronegative blood donors for collection of leucocyte-depleted blood products in order to prevent a CMV infection.	**2 C**

The Paul-Ehrlich-Institute should be notified of any suspected case of transfusion-associated CMV infection so that it will become possible to develop evidence-based recommendations in the future.
Since granulocyte concentrates also have a large portion of mononuclear cells due tomanufacturing steps, CMV infections have been described following granulocyte transfusions from unselected donors.

Granulocyte concentrates intended for CMV-seronegative recipients shall be collected exclusively from CMV-seronegative blood donors.	**1 C+**

Parvovirus B19
In the majority of cases, infections with the **Erythrovirus/Parvovirus B19**, the etiological agent of fifth disease, are asymptomatic. In patients with hemolytic diseases and immunodeficiency an infection with parvovirus B19 can trigger severe aplastic crises. An intrauterine infection can lead to fetal hydrops due to pronounced anemia (review: [6]). The incidence reported for parvovirus B19 DNA in blood donations ranges between 1:100 to approx. 1:50,000, depending on the epidemiological situation and the detection method. Currently only those donations are used for the production of plasma derivatives and SDP that have less than 10^4 genome equivalents/mL of plasma. In combination with measures for reducing virus titers this has resulted in the fact that today plasma derivatives are considered to be safe regarding a parvovirus B 19 infection.
It has not been explained until today why transfusion-associated parvovirus B19 infections have been observed only rarely despite a high prevalence of the virus in blood donors. Worldwide only anecdotal cases have been reported so far [5, 51]. In the context of a small cohort trial on patients of a hematological ward over a period of 6 months (2,123 blood products, 114 patients) no symptomatic infection was reported [38] although B19 DNA was detected in 1 % of blood products transfused. Over the past 12 years (1995–2006) no suspected cases of parvovirus B19 transmission by blood products were reported to the Paul-Ehrlich-Institute.
It has been proposed to provide patients at risk of developing a symptomatic parvovirus B19 infection exclusively with blood products from donors in whom IgG antibodies against parvovirus B19 have been detected in two separate samples taken at an interval of 6 months [17]. However, recent reports suggested that parvovirus B19 DNA is detectable even several years after seroconversion in the blood of asymptomatic carriers [26]. As the minimum infectious dose for a parvovirus B19 infection by blood products is not known, the efficacy of this measure remains unclear.
Transfusion-associated parvovirus B19 infections might be prevented to a large extent by using blood products from donors who had negative results in sensitive nucleic acid amplification techniques for the detection of viral DNA. However, the sensitivity required for the exclusion of infectious donors is not known.

Because of the lacking evidence on transfusion-associated parvovirus B19 infections in Germany, at present no evidence-based recommendations are possible regarding the indication of blood products with a reduced risk of parvovirus B19 transmission.

Therefore the Paul-Ehrlich-Institute should be notified of any suspected case of transfusion-associated parvovirus B19 infection so that it will become possible to develop recommendations in the future.

11.5 Documentation and reporting

11.5.1 Adverse events

In the case of an adverse event (e.g. incorrect blood component transfused) the physician performing the transfusion informs the person in charge, in accordance to the specifications of the in-house quality assurance system. Under the overall responsibility of the person in charge of transfusion it must be clarified whether this was a matter of an adverse event calling for consequences within the institution (§ 16 paragraph 1 TFG which does not call for the notification of external bodies) or whether this was a matter of an adverse reaction to a drug with the ensuing obligatory notification requirements according to § 16 paragraph 2 TFG.

11.5.2 Suspected adverse reactions

When adverse reactions are suspected the blood donor service or the pharmaceutical entrepreneur is to be informed.

11.5.3 Suspected serious adverse reactions

When serious adverse reactions are suspected the Paul-Ehrlich-Institute must also be informed as higher federal authority responsible.

11.5.4 Suspected transmission of an infection

In the event of a confirmed case of an infectious disease suspected to have been transmitted by a blood transfusion, the pharmaceutical entrepreneur is required to separately notify the Paul-Ehrlich-Institute as well as the appropriate Länder authority.
The notification requirements according to the Protection Against Infection Act and the Laboratory Reporting Ordinance are pointed out.

11.5.5 Responsibilities and documentation

It is advisable to transfer the obligation to notify the authorities in the context of quality management to the person in charge of transfusion and to perform notification centrally and computer based (central documentation and central archiving).
The person in charge in the context of quality management, e.g. the person in charge of transfusion, informs the attending physician about the ultimate assessment of the investigation, and in case of serious adverse reactions the above-mentioned institutions are informed.
The responsible transfusion commission should evaluate the reports on adverse events and reactions and, if necessary, take corrective measures.
Notification is to be written in such a way that possible causes as well as measures taken are comprehensible. They must contain data on the blood product, the manufacturer and the number of the preparation or the batch code, the gender and the date of birth of the recipient.

All adverse events and reactions due to transfusions must be documented comprehensively related to the patient and providing the date and time of transfusion. The written information must be kept in the archive for at least 15 years.

11.5.6 Look back

In the event of a justifiable suspicion that the recipient of blood products has been infected by a blood product with HIV, HCV or HBV or other pathogens potentially leading to serious courses of disease, a look back procedure must be initiated to identify other recipients who might possibly be also affected and to identify the donor in question (§ 19 paragraph 2 TFG). This look back procedure must be carried out according to the announcement by the Advisory Committee 'Blood' currently in force (http://www.rki.de).

11.6 Adverse events and reactions in autologous hemotherapy

11.6.1 Risks of incorrect autologous blood transfusion

In the event of incorrect autologous blood transfusion, basically every adverse reaction that has been described for allogeneic RBC concentrates is possible in autologous hemotherapy.
The occurrence of hemolytic transfusion reactions as well as the transmission of pathogens are particularly clinically relevant.

Prophylaxis:
Prior to starting an autologous transfusion, an ABO identity test (bedside test) using a freshly collected blood sample of the recipient must be performed in addition to verifying the identity of the recipient and of the RBC concentrate. In the case of preparations containing erythrocytes this must also be done for the autologous blood product [53]!

11.6.2 Transfusion reactions caused by bacterial contamination

Etiology and frequency:
Microorganisms present in the circulating blood or on the skin of the patient can lead to contamination of autologous RBC concentrates. Individual cases of septic complications following the administration of autologous RBC concentrates have been described [21].

Symptoms:
Most prominent are fever, chills, emesis, hypotension and tachycardia which often occur while transfusion is still being performed, and rarely occur several hours later.

Diagnostics:
In the event of a temperature increase by more than 1°C or of a grade III reaction, microbiological cultures from the RBC concentrate and from the recipient's blood must be initiated at appropriate temperatures (including 4° and 20°C).

Therapeutic measures:
Symptomatic therapy, if necessary treatment of shock, initiation of an antibiotic therapy.

11.6.3 Febrile non-hemolytic transfusion reactions

Etiology and frequency:
Considering that cytokines released play a role in triggering febrile transfusion reactions, it is conceivable that this reaction occurs also in transfusion of stored autologous RBC concentrates [21].

Symptoms:
Fever, chills, moderate dyspnea, most often 30–60 minutes after starting the transfusion.

Diagnosis:
Immediate-type hemolytic transfusion reactions due to ABO incompatibility must be ruled out.

Therapeutic measures:
Antipyretic drugs can usually suppress the symptoms.

11.6.4 Further adverse reactions

Hypervolemia:
Larger volumes that are transfused too rapidly, especially in the case of neonates and children as well as elderly persons and patients with increased plasma volumes, can lead to acute hypervolemia with coughing, dyspnea, cyanosis, jugular inflow congestion, headache, cardiac insufficiency and pulmonary edema. Treatment with oxygen and diuretics is recommended.
Hypervolemia can be prevented by restricting the volume transfused to 2–4 mL/kg body weight per hour, in particular cases to 1 mL/kg body weight per hour.

Transfusion of hemolytic RBC concentrates:
Hemolysis can occur to a noteworthy extent if RBC concentrates are stored improperly (accidental freezing!), warmed improperly or if there is improper admixture of drugs and hyper- or hypotonic solutions to the RBC concentrate.
It cannot be ruled out that severe coagulation disorders occur with the risk of developing disseminated intravascular coagulation. Patients must be monitored at close intervals and the blood clotting status must be checked repeatedly.

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Annex

Regulations laid down in the German Medicinal Products Act (*Arzneimittelgesetz,* AMG) regarding the expert information

In section 11a the AMG contains extensive regulations regarding the expert information. Section 11a AMG reads as follows:
http://www.pei.de/cln_115/nn_155784/SharedDocs/Downloads/EN/arzneimittelgesetz-en,templateId=raw,property=publicationFile.pdf/arzneimittelgesetz-en.pdf

Section 11a

Expert information

(1) The pharmaceutical entrepreneur shall be obliged to make available upon request to physicians, dentists, veterinarians, pharmacists and, if the medicinal products concerned are not subject to prescription, to other persons practising medicine or dentistry professionally, instructions for use by experts (expert information) for finished medicinal products which are subject to or exempted from the obligation to obtain a marketing authorisation, are medicinal products within the meaning of Section 2 sub-section 1 or sub-section 2 No. 1 and are not released for trade outside of pharmacies. These instructions for expert use shall bear the heading *"Fachinformation"* (expert information) and include the following particulars written in clearly legible type in conformity with the Summary of Product Characteristics approved within the framework of the marketing authorisation, and in the following order:

1. the name of the medicinal product followed by the strength and the pharmaceutical form; Section 10 sub-section 1a shall apply *mutatis mutandis*,
2. information on the qualitative and quantitative composition in terms of active substance and other constituents, knowledge of which is required for proper administration of the product, with the usual common or chemical name indicated; Section 10 sub-section 6 shall apply,
3. pharmaceutical form,
4. clinical particulars:
a) fields of application,
b) posology and method of administration for adults and, in so far the medicinal product is indicated for administration to children, for children,
c) contra-indications,
d) special warnings and precautions for use, and in the case of immunological medicinal products, any special precautions to be taken by persons coming into contact with and administering these medicinal products to patients, together with any precautions to be taken by the patient, if required as a result of conditions imposed by the competent Higher Federal Authority in accordance with Section 28 sub-section 2 No. 1 letter a or if stipulated by an ordinance,
e) interaction with other medicinal products or other products if this is likely to influence the effect of the medicinal product,
f) use during pregnancy and lactation,
g) effects on ability to drive or operate machinery,
h) side-effects,
i) overdosage: symptoms, emergency procedures, antidotes;
5. pharmacological properties:
a) pharmacodynamic properties,
b) pharmacokinetic properties,
c) preclinical safety data;
6. pharmaceutical particulars:
a) list of other ingredients,

b) main incompatibilities,
c) shelf life and where necessary, the shelf life after reconstitution of the medicinal product or after first opening the container,
d) special precautions for storage,
e) nature and contents of the container,
f) special precautions for disposal of an opened medicinal product, or waste materials derived from it, in order to avoid any risk to the environment,
7. marketing authorisation holder,
8. marketing authorisation number;
9. the date of first authorisation or prolongation of the authorisation,
10. date of revision of the expert information.

Additional particulars are admissible if they are related to the use of the medicinal product and do not contradict the information referred to sentence 2; they must be clearly separate and distinct from the particulars referred to sentence 2. Sentence 1 shall not apply to medicinal products, which do not require a marketing authorisation pursuant to Section 21 sub-section 2 or are manufactured according homeopathic procedures.
(1a) In the case of sera, the type of living organism from which they are derived, in the case of virus vaccines, the host system used for virus multiplication and, in the case of medicinal products derived from human blood plasma for fractionation, the country of origin of the blood plasma shall be indicated.
(1b) In respect of radiopharmaceuticals, details of the internal radiation dosimetry, additional detailed instructions for the extemporaneous preparation and the quality control of this preparation shall also be given and, where necessary, the maximum storage time shall also be indicated during which an intermediate preparation, such as an eluate or the medicinal product when ready for use, corresponds to its specifications.
(1c) In the case of medicinal products intended for use in animals, the expert information specified under number 4 'clinical particulars' must include the following particulars:
a) particulars on each target animal species to which the medicinal product is to be administered,
b) instructions for use, specifying the target animal species,
c) contra-indications,
d) special warnings for each target animal species,
e) special precautions for use, including special precautions to be taken by the person administering the medicinal product,
f) side-effects (frequency and seriousness),
g) use during pregnancy, lactation or lay,
h) interactions with other medicinal products and other forms of interaction,
i) dosage and method of administration,
j) overdosage, emergency procedures, symptoms, antidotes, if necessary,
k) withdrawal periods for all foodstuffs, including those for which there is no withdrawal period.
The particulars referred to in sub-section 1 sentence 2 No. 5 letter c are not necessary.
(1d) In the case of medicinal products available only on prescription by a doctor, dentist or veterinarian, the information *"Verschreibungspflichtig"* (prescription only) should also be added, for narcotics the information *"Betäubungsmittel"* (narcotics), in the case of other medicinal products available to consumers only in pharmacies, the information *"Apothekenpflichtig"* (pharmacy only), in the case of medicinal products containing a substance or a preparation referred to in Section 48 sub-section 2 No. 1, the information that these medicinal products contain a substance the effect of which is not generally known in medical science.

(1e) For marketing authorisations of medicinal products in accordance with Section 24b, the particulars referred to in sub-section 1 relating to fields of application, dosages or other objects of a patent can be omitted if they are still covered by patent law at the time of placing on the market.
(2) The pharmaceutical entrepreneur shall be obliged to make all modifications to the expert information, which are relevant for therapy, accessible to the experts in an appropriate form. In so far as necessary, the competent Higher Federal Authority may, by imposition of a condition, stipulate the form in which the changes are to be made accessible to all or to certain groups of experts.
(3) A sample of the expert information and revised versions thereof shall be sent immediately to the competent Higher Federal Authority unless the medicinal product is exempted from the obligation to obtain a marketing authorisation.
(4) The obligations referred to in sub-section 1 sentence 1 can also be fulfilled in the case of medicinal products which are administered exclusively by members of the health professions by including the information referred to in sub-section 1 sentence 2 in the package leaflet. The package leaflet must be headed with the title *"Gebrauchsinformation und Fachinformation"* (instructions for use and expert information).

The following Medical Societies, professional bodies, associations and institutions were heard regarding consideration of the contents of these Cross-sectional Guidelines in the context of a formalized hearing in written form on the basis of the specifications according to §§ 12a and 18 of the TFG:

AOK-Bundesverband
Arbeitsgemeinschaft der Ärzte staatlicher und kommunaler Bluttransfusionsdienste
Arbeitsgemeinschaft der Obersten Landesgesundheitsbehörden (AOLG)
Arbeitsgemeinschaft Plasmaproteine herstellender Unternehmen
Arbeitsgemeinschaft Plasmapherese e. V.
Ärztliches Zentrum für Qualität in der Medizin
Bundesverband der Belegärzte e. V.
Bundesverband Deutscher Krankenhausapotheker e.V.
Bundeszahnärztekammer
Berufsverband Deutscher Anästhesisten e.V.
Berufsverband Deutscher Laborärzte e. V.
Berufsverband Deutscher Neurochirurgen e. V.
Berufsverband der Ärzte für Mikrobiologie und Infektionsepidemiologie e. V.
Berufsverband der Deutschen Chirurgen e. V.
Berufsverband der Deutschen Urologen e. V.
Berufsverband der Fachärzte für Orthopädie e. V.
Berufsverband der Frauenärzte e. V.
Berufsverband der Kinder- und Jugendärzte e. V.
Berufsverband der Niedergelassenen Hämatologen und Onkologen in Deutschland e. V.
Berufsverband Deutscher Internisten e. V.
Berufsverband Deutscher Transfusionsmediziner e. V.
BKK Bundesverband
Bundesarbeitsgemeinschaft Selbsthilfe e. V.
Bundesknappschaft
Bundesministerium für Gesundheit
Bundesministerium der Verteidigung, FüSan I
Bundesverband der Pharmazeutischen Industrie
Bundesvereinigung der Naturwissenschaftler in der Labordiagnostik e. V.

Deutscher Berufsverband der Hals-Nasen-Ohrenärzte e. V.
Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen
Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e. V.
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V.
Deutsche Gesellschaft für Chirurgie
Deutsche Gesellschaft für Gefäßchirurgie
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V.
Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V.
Deutsche Gesellschaft für Hämatologie und Onkologie e. V.
Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V.
Deutsche Gesellschaft für Immunologie
Deutsche Gesellschaft für Infektiologie e. V.
Deutsche Gesellschaft für Innere Medizin e. V.
Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin
Deutsche Gesellschaft für Kinderchirurgie
Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.
Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie e. V.
Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e. V.
Deutsche Gesellschaft für Neurochirurgie e. V.
Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie e. V.
Deutsche Gesellschaft für Thoraxchirurgie
Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie
Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie e. V.
Deutsche Gesellschaft für Unfallchirurgie e. V.
Deutsche Gesellschaft für Urologie e. V.
Deutsche Gesellschaft für Verbrennungsmedizin
Deutsche Hämophiliegesellschaft
Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin
Deutsche Krankenhausgesellschaft e.V.
Deutscher Verband Technischer Assistentinnen/Assistenten in der Medizin e. V.
Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten e. V.
Gesellschaft für Neonatologie und pädiatrische Intensivmedizin
Gesellschaft für Thrombose- und Hämostaseforschung e.V.
Gesellschaft für Virologie e.V.
Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien e. V. (Instand e. V.)
IKK-Bundesverband
Interdisziplinäre Arbeitsgemeinschaft für klinische Hämotherapie e. V.
Kassenärztliche Bundesvereinigung
Paritätischer Wohlfahrtsverband
Paul-Ehrlich-Institut
Robert Koch-Institut
See-Krankenkasse
Spitzenverbände der landwirtschaftlichen Sozialversicherung
Ständige Impfkommission (STIKO) des Robert Koch-Instituts
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