CONTINUING MEDICAL EDUCATION

Transfusion of Packed Red Cells

Indications, Triggers and Adverse Events

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SUMMARY

Background: About four million units of packed red cells are transfused in Germany every year. The safety of blood transfusions is further improved by modern production methods and molecular diagnostic techniques.

Methods: This review is based on selected publications, including the German guidelines and regulations and the German Transfusion Act.

Results: Packed red blood cells are transfused to prevent tissue hypoxia. As the clinical manifestations of anemia are nonspecific, the indication for transfusion is based on surrogate parameters, such as the hemoglobin (Hb) concentration, in addition to clinical criteria. For patients with unimpaired cardiopulmonary and vascular function, transfusion is generally indicated at hemoglobin values of 6 g/dL (3.7 mmol/L) or less. Randomized controlled trials have shown that a restrictive transfusion strategy (trigger: Hb 7–8 g/dL) in certain patient groups is as effective as a more liberal strategy (trigger: Hb about 10 g/dL). The most frequent causes for transfusion errors are lack of informed consent, lack of identity checking and/or ABO identity testing, and the drawing of blood samples in unlabelled tubes.

Conclusion: Overtransfusion, undertransfusion, as well as other transfusion errors can be markedly reduced by means of appropriate organizational measures and training.

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The risk of viral transmission via transfusion of packed red blood cells in Germany has reached an all-time low. The reasons comprise the selection of donors and the screening for pathogens such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV) by molecular and serological methods. Transmission of transfusion-relevant viruses via blood products is nowadays a rare event, found only in isolated cases (1). For example, since the introduction of mandatory HCV-PCR (polymerase chain reaction) in Germany in 1999, there has been one single case of transfusion-related HCV transmission in 16 years. At an annual rate of about 4 million units of packed red cells, over 60 million units were transfused in this period (1).

Modern production methods using closed blood bag systems and “inline” leukocyte depletion also contribute towards the safety of modern blood products. All steps of production are subject to quality controls to ensure good manufacturing practice (GMP).

The use of blood preparations is closely regulated by:

- European Union directives
- The German Transfusion Act (TFG; [2])
- The German Medical Association (GMA) guidelines on collection of blood and blood components and use of blood products (hemotherapy) (3)
- The “Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives” of the Scientific Advisory Board of the GMA (4).

Germany as well as other member states of the European Union have carried EU directives over into their own laws and guidelines, so that these regulations and recommendations are largely similar in EU member states. Nevertheless, in English-speaking countries, for example, the bedside test and certain laboratory tests are

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Safety

The risk of viral transmission via transfusion of packed red cells in Germany has reached an all-time low. Transmission of transfusion-relevant viruses via blood products is nowadays a rare event.

BOX 1

Assessment of clinical circumstances before transfusion*

- Acute clinical status (fever?, sepsis?, etc.), cause, duration, and severity of anemia (bleeding?, chronic anemia?, etc.) and comorbidities (cardiac insufficiency?, coronary heart disease?, previous cerebrovascular or pulmonary disease?, etc.)
- Volume status: normovolemia?, hypovolemia?, acute volume displacements that make it more difficult to use Hb concentration or hematocrit as parameters for the decision whether or not to administer packed red cells (4)?
- In acute blood loss: source?, dynamics?, rate?
- Patient's capacity to compensate the loss of erythrocytes (= decreased supply of oxygen to tissues)?
- Physiological transfusion triggers (cf. Box 2)?

* This information can be used in addition to Hb concentration or hematocrit to decide whether or not to transfuse packed red cells (modified from [4]). Here, as in Box 2, we are talking about clinical experience, not the results of randomized studies

not mandatory, but there is a compulsory ID check by means of the patient's wrist band.

Learning goals

After studying this article, the reader should:

- Be acquainted with the indications and triggers for packed red cell transfusion
- Be able to recognize, name, treat, and prevent the adverse events that may occur during transfusion

Indications for the transfusion of packed red cells

The transfusion of packed red cells is carried out to prevent manifest anemia-related tissue hypoxia. The administration of packed red cells is the "ultima ratio" of anemia treatment, employed to achieve the primary treatment goal in cases where causal treatment of the anemia is either not feasible or inadequate.

Preoperative anemia is a risk factor for a poor postoperative outcome in a patient (5). With the exception of emergencies and urgent indications for intervention, anemia should be diagnosed and treated before elective surgery. A retrospective analysis showed a fourfold risk of perioperative mortality for patients with mild anemia

(hematocrit between 29% and 36% in women and between 29% and 39% in men) compared with those without anemia (30-day mortality: 3.52% for mild preoperative anemia versus 0.78% for hemoglobin/hematocrit in the normal range) (5). The diagnosis and causal treatment of preoperative anemia are not within the scope of this article. Because of the low specificity of clinical symptoms of anemia, surrogate parameters such as hemoglobin (Hb) concentration or hematocrit are used as transfusion triggers in addition to clinical criteria. Box 1 shows the clinical criteria, while Box 2 describes the so-called physiological transfusion triggers. The procedures described here are based not on the results of randomized studies, but on clinical observation and experience.

When determining the indications for administration of packed red cells, it is important to distinguish between acute hemorrhage and chronic anemia, e.g., in myelodysplastic syndrome (MLS).

In the case of an acute bleeding event, an important treatment goal is the maintenance or restoration of homeostasis, particularly normovolemia by means of volume replacement. Furthermore, along with the surgical treatment, management of coagulation is crucial to stop bleeding. Together with normothermia, physiological pH and ionized Ca^{2+} within the physiological range, the erythrocytes—particularly in the arterial circulation—contribute to laminar flow and thus to spatial proximity of thrombocytes and von Willebrand factor to the endothelium or endothelial defects, localizing them towards the vessel wall. In acute hemorrhagic shock and in manifest tissue hypoxia, timely administration of packed red cells is a life-saving measure. The dosage depends on the patient's clinical status and on current and anticipated blood loss (4).

The administration of packed red cells has never been systematically investigated in double-blind controlled studies, e.g., in comparison with crystalloid volume replacement.

Transfusion triggers

In a patient with normal cardiopulmonary and vascular performance, an Hb level of 6 g/dL or less (Hb <3.7 mmol/L or hematocrit <18%) is seen as an "absolute" indication for transfusion (4). In individual cases, particularly in the presence of chronic adaptation to anemia, the transfusion trigger may be lower (e.g., Hb 5.5 g/dL).

Indications for transfusion

The transfusion of packed red cells is carried out to prevent manifest anemia-related tissue hypoxia.

Acute bleeding or chronic anemia?

When determining the indications for administration of packed red cells, it is important to distinguish between acute hemorrhage and chronic anemia, e.g., in myelodysplastic syndrome (MDS).

A patient with a stable Hb concentration of over 10 g/dL (Hb >6.2 mmol/L or hematocrit >30%) without acute blood loss will generally gain no benefit from further administration of packed red cells. Here too, however, exceptions may be justified in individual patients. In such cases, the (physiological) transfusion trigger must be documented in the medical record (*Table 1*).

In an adult patient without an increase in red cell destruction, administration of one unit of packed red cells increases the hematocrit or Hb concentration by about 3% or 1 g/dL respectively (4). The standard transfusion rate is one bag per hour. In patients with cardiac or renal insufficiency, transfusion volumes and rates have to be individually adapted or reduced (4, 15).

Clinical studies on restrictive versus liberal transfusion triggers

Judging by the prospective randomized studies published to date, a restrictive transfusion strategy with transfusion triggers at 7 to 8 g Hb/dL seems to be non-inferior to a liberal treatment strategy with higher triggers—usually around 10 g/dL (6–11) in the following patient groups:

- Intensive care patients
- Pediatric and geriatric high-risk patients, the latter before total hip replacement
- Patients with upper gastrointestinal bleeding and moderate liver cirrhosis
- Patients in septic shock.

In special situations, e.g., in upper gastrointestinal bleeding, a restrictive strategy may even be slightly superior (6-week survival rate 95% versus 91% for a liberal strategy) (10). However, a pilot study came to the conclusion that a liberal transfusion strategy achieves a significantly lower 30-day mortality rate in patients with symptomatic coronary heart disease, with a trend towards fewer cardiac events, compared with a restrictive transfusion regimen (12). The findings of a recent study in post cardiac surgery patients are similar (25).

Further prospective randomized studies on restrictive transfusion regimens are required to confirm these early results (13), even though some experts already see a transfusion trigger of 7 g/dL as the new standard for almost all groups of patients (14).

Choice of packed red cells and order details

Packed red cells are usually transfused in an AB0-identical manner. In rare cases, packed cells that

BOX 2

Physiological transfusion triggers that may indicate anemic hypoxia*

● Clinical symptoms

- Newly occurring cardiopulmonary, (cerebro-)vascular, or neurological symptoms for which no other known cause can be found
- (Stress) dyspnea of unknown origin
- Tachycardia of unknown origin/subjectively: cardiac palpitation
- Hypotension of unknown origin despite normovolemia
- Newly occurring cardiac arrhythmia/subjectively: extrasystole of unknown origin
- Orthostatic vertigo or tinnitus of unknown origin—*cave*: unspecific symptoms!
- Headache/neurological symptoms of unknown origin
- Exhaustion/fatigue/tiredness/poor memory or reduced cognitive function of unknown origin

● Newly occurring ECG changes, otherwise unexplained

- ST-segment elevations, ST-segment depressions
- Arrhythmias

● Newly occurring changes in echocardiography that cannot be explained by structural changes

- Regional myocardial contraction disorders

● Global indices of inadequate tissue oxygen supply (some of these can only be measured by means of continuous intensive monitoring)

- Increase in global oxygen extraction >50%
- Decrease of over 10% in global oxygen uptake, calculated from initial value
- Decrease in mixed venous pO₂ to under 32 mm Hg
- Decrease in central venous oxygen saturation to under 60%
- Decrease in mixed venous oxygen saturation to under 50%
- Lactate >2 mmol/L + acidosis

* Provided anemia confirmed by clinical chemistry and normovolemia present;
pO₂ = partial pressure of oxygen
(adapted from [4])

Transfusion trigger

This is the Hb concentration at which administration of packed red cells is initiated.

Patients with cardiac or renal insufficiency

In patients with cardiac or renal insufficiency, transfusion volumes and rates have to be individually adapted or reduced.

TABLE 1

Indication for transfusion of packed red cells depending on Hb concentration, medical history, and clinical findings*

Hb (g/dL; mmol/L)	Clinical decision	Transfusion indicated?
≤ 6 g/dL or ≤ 3.7 mmol/L	Independent of whether cardiovascular risk factors or signs of anemic hypoxia are present	Yes
>6 and ≤ 8 g/dL or >3.7 and ≤ 5 mmol/L	Neither cardiovascular risk factors nor signs of anemic hypoxia present	No
>6 and ≤ 8 g/dL or >3.7 and ≤ 5 mmol/L	Either cardiovascular risk factors or signs of anemic hypoxia present	Yes
>8 and ≤ 10 g/dL or >5 and ≤ 6.2 mmol/L	Signs of anemic hypoxia present	Yes (weak evidence!)
>10 g/dL or >6.2 mmol/L	Independent of whether cardiovascular risk factors or signs of anemic hypoxia are present	No (except in isolated cases)

*Modified from (4)

are AB0 non-identical but AB0 compatible can be transfused (Table 2).

Other blood group characteristics and blood group-specific serological findings have to be taken into account, in particular the following: the Rhesus (Rh) D factor; in certain groups of patients (e.g., regularly transfused patients, patients with known antierythrocytic antibodies, females of child-bearing age) other antigens of the Rh system (C, c, E, e) and the Kell blood group antigen K as well; the results of a recent antibody screening test; relevant data from emergency ID cards and maternity booklets; and the results of serological tolerance testing (cross-matching).

With the exceptions of acute emergencies, particular immunohematological constellations, or acute scarcity of resources, AB0-identical and Rh D-identical packed red cells are transfused (3, 4). Deviations from this rule must be documented. In the event of an acute bleeding crisis in a previously unknown person, packed cells of blood group 0 must be transfused until the patient's blood group has been established by the laboratory. Even in emergencies, blood samples should be taken and sent for blood group determination and an antibody screening test before the transfusion of packed red cells is initiated. As soon as the results are received, transfusion should be switched to packed cells of the patient's own AB0 blood group.

Rh D-negative patients should not receive Rh D-positive packed red cells. In an acute bleeding crisis or in the lack of Rh D-negative packed cells,

however, Rh D-negative, non-Rh D-sensitized recipients may well have to be given Rh D-positive transfusions. There must be no evidence of Rh D-specific antibodies (anti-D) in the patient's medical history (emergency ID card, maternity booklet) or in the antibody screening test.

In the event that Rh D-positive packed red cells have to be administered to an Rh D-negative recipient, this must be documented in the patient's medical record, the patient must be informed, and the discharge letter should include the recommendation for antibody screening within the next 2 to 4 months. If antibodies relevant to transfusion are then demonstrated, the patient must be informed and counseled, and an emergency ID card must be issued. For the rest of his/her life, such antibodies must be considered whenever packed red cells have to be transfused. While such antierythrocytic allo-antibodies are rare in the general population (about or less than 1%), they may be found in up to 10% of regularly transfused patients.

With the exception of life-threatening situations in which no Rh D-negative blood can be obtained quickly enough, Rh D-negative girls and women of child-bearing age must not receive Rh D-positive packed red cells because of the risk of immunization and the subsequent danger of hemolytic disease of the newborn (HDI) (4). Furthermore, the danger of immunization to principal components of the Rh system such as C, c, D, E, or e and to antigen K with subsequent risk of HDI should always be avoided in girls and women of this age group.

Choice of packed red cells and order details

Packed red cells are usually transfused in AB0-identical form. In exceptional cases, packed cells that are AB0 non-identical but AB0 compatible can be transfused.

Acute bleeding crisis

In the event of an acute bleeding crisis in a previously unknown patient, packed red cells of blood group 0 must be transfused until the patient's blood group has been established.

Administration of packed red cells

Before the planned administration of packed red cells—with the exception of emergency transfusion—the treating physician must document the recipient's transfusion history (Box 3). The patient should receive written and oral information about the possible necessity for blood transfusion as early as possible before standard interventions. Standardized information sheets are suitable for this purpose; they are amended to include details discussed between patient and physician, signed by both parties, and the patient receives a copy. The information given to the patient must always include how a transfusion takes place, the risks, potential complications and adverse effects involved, and potential alternatives to transfusion. If the likelihood of perioperative transfusion is estimated as $\geq 10\%$ —according to local experience—the patient should be informed of the options for autologous hemotherapy, such as preoperative collection of the patient's own blood for transfusion.

The written agreement of the patient or his/her legal representative—in children, the parent or legal guardian—must be obtained. Early discussion of transfusion gives the patient enough time to come to a decision. If information cannot be given in advance of transfusion, e.g., in an emergency or if the patient is unconscious, it must be provided at the earliest possible time thereafter.

If there is a realistic chance that a planned invasive or operative procedure will involve a transfusion, the patient's blood group must be known and an antibody screening test carried out (no more than 3 days before the procedure). This "type and screen" strategy is particularly helpful if bleeding complications occur. In this event, the blood group and antibody status are known and the patient's blood is available in the laboratory. If no transfusion-relevant antibodies are currently present or recorded in the patient's medical history, unmatched packed red cells of the patient's AB0 blood group can be used in such a case of emergency. This saves the scarce resources of blood group 0 packed red cells for emergencies in which the recipient's blood group is initially unknown.

A positive antibody screening test is followed by identification of the antibodies present. If any transfusion-relevant antibodies are found or were already known, planned interventions must be preceded by allocation of a quantity of compatible, i.e., antigen-negative packed red cells sufficient not only for the anticipated

TABLE 2

Compatible transfusion of packed red cells (PRC)*

Patient's blood group	Compatible PRC
A	A or 0
B	B or 0
AB	AB, A, B, or 0
0	0

* Modified from (4, 15)

perioperative requirements but also for potential complications. This necessitates close cooperation between the laboratory staff and the treating physicians.

If the planned intervention has a high likelihood of perioperative administration of packed red cells (according to local hospital data), the serological compatibility of the patient's plasma and the packed cells provided should be tested before the intervention (cross-matching).

Ordering packed red cells

The order for packed red cells should generally be placed in writing or electronically. In Germany, blood products require a prescription. This requirement is fulfilled by the physician signing the request form. Requests for emergency transfusions can be made by telephone or fax. The steps involved in an emergency transfusion must be laid down in the local regulations governing transfusion and should be regularly practiced by all parties involved.

The following information should be given on the request form or in the blood bank's electronic module for ordering blood products:

- Patient's family name, given name, date of birth, and treatment number
- Ward and location for delivery (e.g., operating theater)
- Patient's diagnosis and transfusion history (Box 3).
- Type and number of blood products required
- Any special requirements (e.g., irradiated blood products)
- Urgency of transfusion; anticipated further requirements, if any
- Date, physician's signature (legible!), and telephone number.

Pregnancy and HDN

Rh D-negative girls and women of child-bearing age should not receive Rh D-positive packed red cells because of the risk of immunization and the subsequent danger of hemolytic disease of the newborn (HDN).

Antibody Screening Test (AST)

If there is a realistic probability that a planned invasive or operative procedure will involve a transfusion, the patient's blood group must be known and an antibody screening test carried out.

BOX 3

Transfusion history and inspection of packed red cells (PRC) before transfusion

- **Transfusion history: the findings must be recorded in the patient's medical record and transmitted to the immunohematological laboratory**
 - Previous immunohematological findings, if available: ABO blood group, Rh formula, any known transfusion-relevant antibodies, etc.
 - Previous transfusions: when? what? where? any problems?
 - Hematopoietic stem cell transplantation (HSC-Tx)? Bone marrow/peripheral stem cells? When? Blood group before/after HSC-Tx?
 - Emergency ID cards, blood donor cards: transmit any relevant data to the immunohematological laboratory!
 - In women:
 - Pregnancies? Abortions?
 - Anti-D prophylaxis: when? what? where?
 - Transmit any potentially relevant data from maternity booklets to the immunohematological laboratory, even if the pregnancy was many years ago!
- **Confirm that the conditions for transfusions are satisfied and inspect the PRC before transfusion**
 - Is administration of PRC (still) indicated?
 - Has the patient given informed written consent to transfusion of PRC?
 - Is the blood bag intact? Reject any bags with large air bubbles, clots, unusual coloration (black, brownish, etc.), or reddish supernatant in the bag!
 - Are the PRC intended for this patient?
 - Does the blood group of the PRC correspond to that of the patient, or is it at least compatible (see also *Table 2*)?
 - Check the batch number: compare label on PRC with the documented batches on delivery slip/cross-matching form!
 - Check the expiration date of the PRC
 - Is the result of the cross-matching still valid? (no more than 3 days after the day of blood sampling for cross-matching)

Preparation and execution of transfusion, with practical tips

The collection tubes to be filled with blood samples for blood group testing, antibody screening test, and cross-matching must be labeled in advance. Preprinted patient labels can be used for this purpose. The information on each tube must include at least the patient's family name, given name, and date of birth. Should identification be impossible, another means of labeling must be agreed, e.g., the use of sets of labels with serial numbers. Collection of blood samples in unlabeled tubes is one of the principal causes of error and must be avoided.

The patient's identity must be clearly established at the bedside before withdrawal of blood. The person taking the samples must ask the patient for identifying details such as

date of birth, address, family name, and given name. These data are then compared with the labels on the collection tubes and the request form. After collection of the required samples the date and time of withdrawal is added to the request form and the form is signed. If the person who collects the samples is not the physician ordering the blood products, the latter must also sign the request form. The physician always bears responsibility for the request and for the withdrawal of blood, whether delegated or not, and thus for the identity of the sample. Before the administration of packed red cells the checks detailed in *Box 3* must be carried out.

ABO identity testing

ABO identity testing (bedside testing), important for patient safety, must be carried out and documented by

Cross-matching

If the planned procedure has a high likelihood of perioperative administration of packed red cells, the serological compatibility of the patient's plasma and the packed cells provided should be tested preoperatively.

Ordering packed red cells

Blood products have to be prescribed; the physician's signature is required.

TABLE 3a

Prevalence, pathophysiology, treatment, and prophylaxis of adverse effects of packed red cells (modified from [4, 15])^{*1}

Adverse effect	Risk per unit transfused	Pathophysiology and treatment	Prophylaxis
Allergic transfusion reaction	Mild reaction: up to 1 in 200 administrations	Cutaneous reactions, erythema, urticaria, or flush: difficult to distinguish from severe complication. If present, discontinue transfusion. After exclusion of severe complications (e.g., hemolytic reaction) and renewed identity check the transfusion can be resumed, with administration of antihistamines if indicated.	Establish transfusion history; consider antihistamines before transfusion
	Severe reaction: 1 in 10 000 to 1 in 100 000	Immediate discontinuation of transfusion and intensive care necessary in most cases	Recurring severe allergic reactions: check for plasma protein deficit (IgA, haptoglobin, etc.)
Febrile, non-hemolytic transfusion reaction (FNHTR) ^{*2}	<1 in 1000 administrations ^{*2}	Fever or temperature increase >1 °C, sensation of cold, shivering during transfusion of PRC or up to 4 h thereafter; an important differential diagnosis is hemolytic transfusion reaction or reaction to bacterial contamination. After exclusion of mistaken identity the transfusion can be resumed; if the quality of the blood product is in question, the transfusion must be ended and the PRC sent back to the blood bank.	Much less common since the introduction of leukocyte depletion
Hemolytic transfusion reaction of immediate type	Without fatal outcome: 1 in 10 000 to 1 in 100 000	Symptoms ranging up to shock, usually within 24 h; inadequate Hb increase/Hb decrease after transfusion with no other explanation (e.g., bleeding), increase in LDH and bilirubin. In the event of intravascular hemolysis: free hemoglobin in serum (red) and hemoglobinuria; the most common reason is ABO incompatibility due to mistaken identity. End transfusion immediately, initiate intensive care and kidney protection measures. Send blood samples taken before and after transfusion plus PRC for laboratory examination. Early detection and prompt intensive care decrease mortality.	Continuous identity checks from blood withdrawal to transfusion, no blood samples in unlabeled tubes, ABO identity test (= bedside test) before every administration of PRC, even in emergencies! Cross-matching
	Fatal outcome: 1 in 500 000 to 1 in 1 000 000		
Hemolytic transfusion reaction of delayed type	Without fatal outcome: 1 in 10 000 to 1 in 100 000	Occurs days or weeks after transfusion through "boosting" of a pre-existing antibody that was not/no longer detectable at the time of transfusion. Diagnosis is often delayed because LDH and bilirubin increase or Hb decreases after discharge from hospital. Usually no acute treatment is necessary, but renewed administration of PRC is often required.	Pay attention to transfusion history, emergency ID cards! This is one of the reasons why cross-matching is valid for only 3 days.
	Fatal outcome: about 1 in 1 000 000		

^{*1} All figures for risk are estimates. New-variant Creutzfeldt-Jakob disease (vCJD), transfusion-associated parasitosis, post-transfusional purpura, hypothermia, hyperkalemia, and transfusion-associated graft-versus-host disease are not included in this table due to space restrictions.

^{*2} Risk declining in Germany owing to use of leukocyte-depleted blood products (since 2001)

PRC, packed red cells

Transfusion reactions

These are classified into:

- Allergic reactions
- Febrile, non-hemolytic reactions
- Immediate hemolytic reactions
- Delayed hemolytic reactions

Febrile, non-hemolytic transfusion reaction

The symptoms are fever or temperature increase >1 °C, sensation of cold, and shivering during transfusion of PRC or up to 4 h thereafter.

TABLE 3b

Prevalence, pathophysiology, treatment, and prophylaxis of adverse effects of packed red cells (PRC) (modified from [4, 15])^{*1}

Adverse effect	Risk per unit transfused	Pathophysiology and treatment	Prophylaxis
Transfusion-associated circulatory overload (TACO)	On administration of several blood products in risk groups: 1 : 12 or less	(Excessively) large transfusions in certain groups of patients (cardiac insufficiency, renal insufficiency, etc.)	The amount transfused per unit of time should be individually adjusted in vulnerable patients.
Transfusion hemosiderosis	High individual risk with administration of more than 100 units of PRC (lifetime) or more than 20 units/year	Administration of more than 20 units of PRC/year should be accompanied by regular determination of ferritin. If ferritin is >1000 ng/mL or symptoms occur, chelators should be given.	Prophylaxis comprises the administration of iron chelators. In chronic PRC transfusion the increase in ferritin levels must be monitored.
Transfusion-associated lung insufficiency after administration of PRC (TRALI)	<1 in 1 000 000	Mostly triggered by granulocyte-specific antibodies from the donor (often women post pregnancy). Extremely infrequent (isolated cases) after administration of PRC due to a low plasma amount in PRC.	Female donors having given birth are tested for granulocyte-specific antibodies or barred from donating blood products containing plasma (platelet concentrates, therapeutic plasma).
Bacterial contamination of PRC	<1 in 100 000 to <1 in 1 000 000	Extremely infrequent (isolated cases) after administration of PRC	Exclude donors with bacteremia, institute GMP, test blood products for bacteria
Transfusion-associated viral transmissions	HBV (D) ^{*2} about 1 in 500 000 ^{*2}	Isolated cases: Despite NAT (nucleic acid testing = detection of viral nucleic acids by molecular methods such as PCR [polymerase chain reaction]) of blood donated, transfusion-associated transmission of viruses may occur in single cases.	Selection of blood donors, serological testing (antibodies), and NAT (PCR testing for specified viruses)
	HIV (D) ^{*3} <1 in 1 000 000 ^{*3}		
	HCV (D) ^{*4} <1 in 1 000 000 ^{*4}		

^{*1} All figures for risk are estimates. New-variant Creutzfeldt-Jakob disease (vCJD), transfusion-associated parasitosis, post-transfusional purpura, hypothermia, hyperkalemia, and transfusion-associated graft-versus-host disease are not included in this table due to space restrictions.

^{*2} Calculated risk (1997–2005) for German Red Cross blood donation service: HBV risk: 1 : 360 000 (95% CI: 1 : 190 000–1 : 3 360 000; [24])

^{*3} Calculated risk (1997–2005) for German Red Cross blood donation service: HIV-1 risk: 1 : 4 300 000 (95% CI: 1 : 2 390 000–1 : 21 370 000; [24])

^{*4} Calculated risk (1997–2005) for German Red Cross blood donation service: HCV risk: 1 : 10 880 000 (95% CI: 1 : 7 510 000–1 : 19 720 000; [24])

PRC: packed red cells; D: figures for Germany; NAT, nucleic acid testing = detection of viral nucleic acid by molecular biological methods such as polymerase chain reaction (PCR);

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; GMP, good manufacturing practice

the physician at the patient's bedside. Checking the recipient's AB0 blood group is mandatory. The result must be compared with the AB0 blood group of the packed red cells and the blood group recorded in the accompanying documentation. The results of the patient AB0 bedside and identity check must be entered in the medical record with the date, time, and physician's initials. Only for autologous blood products do the packed red cells also have to be tested; for allogeneic transfusions the AB0 bedside testing of the recipient suffices. The AB0 bedside test must be performed every single time packed red cells are given—even in emergencies. The bedside test should be repeated whenever one of the four crucial parameters—physician, patient, place, time—changes.

Administration of packed red cells

Transfusion of packed red cells should always be carried out using a standard transfusion set with a filter (pore diameter 170–230 µm), never with a system that does not include a transfusion filter. Two or more units of packed cells should be given consecutively, not in parallel, with the exception of massive or emergency transfusions. The transfusion should be given via an exclusive venous port; drugs or other infusates should not be mixed with the packed red cells or administered simultaneously through the same port. In the case of transfusion via a central venous catheter, it must be ensured that no other parenteral solution is administered simultaneously via the same lumen.

Practical hints

The collection tubes for blood group determination, antibody screening, and possibly for cross-matching must be labeled in advance. Preprinted patient labels can be used for this purpose.

Identity check

The patient's identity must be clearly established at the bedside before withdrawal of blood. The person taking the samples must ask the patient for identifying details such as date of birth, address, family name, and given name.

The transfusion is initiated by the physician. He/she is responsible for ensuring that the patient is continuously monitored during the administration of packed red cells and thereafter. During and after transfusion a physician must be immediately available for swift intervention should any adverse events occur. Outpatient recipients must be advised of the risk of delayed adverse events. All patients should be observed for about an hour after transfusion.

In the rare event that packed red cells have to be heated to body temperature before transfusion, only certified blood heaters may be used for this purpose. The heated packed cells should then be transfused as soon as possible. Opened bags must be used within 6 h. Following transfusion, the transfusion set has to be closed in sterile fashion and retained, together with the empty bag, for 24 h at a temperature of +1°C to +10°C.

Documentation of packed red cell transfusion

The following information should be documented in the patient's medical record:

- Patient information and clinical indication for transfusion
- Results of identity check and ABO bedside test
- Product designation
- Manufacturer and batch number—together with the product designation, these are summarized in the bar code on the bag
- Date and time of packed red cell transfusion
- If applicable, adverse events and transfusion-related effects such as amelioration of symptoms or increase in Hb concentration.

In parallel with the patient-related documentation, product-related documentation is also required. Nowadays this product-associated batch documentation is often accomplished with the aid of an IT system or in the laboratory. These records are to be preserved for 30 years to enable later reconstruction.

Special products

Irradiated packed red cells

Despite leukocyte depletion, bags of packed red cells may contain a small number of vital donor lymphocytes that can lead to transfusion-associated graft-versus-host disease (ta-GvHD) in immunocompromised recipients (e.g., patients with B-cell non-Hodgkin lymphoma [NHL]). For this reason the packed cells to be used in such circumstances must be irradiated with

at least 30 Gy before transfusion. This information has to be included on the request form sent to the blood bank. Because the irradiation elevates the potassium concentration of the packed red cells, irradiated bags have a reduced shelf life and—especially in children and patients with renal insufficiency—should only be ordered from the blood bank when transfusion is scheduled within the ensuing 24 h. The maximum storage time for irradiated packed red cells depends on the terms of licensing for the individual product and is provided in the manufacturer's product information accompanying every unit of packed cells (*eBox 1*).

Washed packed red cells

Washed packed red cells are rarely indicated. Early contact with the responsible transfusion specialist is recommended.

Cryopreserved packed red cells

Cryopreserved packed red cells are required in extremely rare cases in patients with multiple transfusion-relevant antibodies or antibodies to high frequent antigens. Particularly early contact with the responsible transfusion specialist is essential.

Contraindications, risks, and adverse events

Provided transfusion is indicated and the transfusion triggers are observed, there are no contraindications to the administration of packed red cells. Serological tolerance should be assured by means of the investigations described above. In patients scheduled for hematopoietic stem cell transplantation, administration of packed red cells donated by blood relatives or potential stem cell donors must be strictly avoided. Members of some religious faiths follow particular rules regarding blood and transfusion, and in such cases the patient's wishes must be respected.

Transfusion of cellular blood products, seen as transplantation of the fluid organ blood, represents an immunological challenge for the recipient organism. Whether transfusion-related immunomodulation (TRIM) has a negative influence on the postoperative outcome is currently being investigated. The results of these studies will show whether the connection between TRIM and unfavorable outcome postulated from retrospective observation withstands prospective scrutiny. It must be remembered that preoperative anemia represents an independent correlation factor for elevated perioperative morbidity and mortality.

Administration

Transfusion of packed red cells should always be carried out using a standard transfusion set with a filter (pore diameter 170–230 µm), never with a system that does not include a transfusion filter.

Heating of packed red cells

In the rare event that packed red cells have to be heated to body temperature before transfusion, only certified blood heaters may be used for this purpose.

This has been shown for coronary bypass surgery (16), major non-cardiosurgical interventions (5), and colorectal surgery (17).

Studies from the past 2 years (18–20) show that both preoperative anemia before coronary bypass surgery and transfusion seem to contribute to the perioperative risk. A meta-analysis of the prospective trials on restrictive transfusion triggers (18) concluded that restrictive transfusion strategies appear to lead to fewer periprocedural infections than liberal transfusion strategies. Acute transfusion reactions can be distinguished from delayed reactions, and immunological from non-immunological reactions (*eTable*). The estimated frequencies of occurrence of transfusion-related adverse events together with their pathophysiology, treatment, and prophylaxis are given in *Table 3a, b*.

Apart from documentation in the patient's medical record as described above, the German Transfusion Act requires reporting of adverse effects (2, 3) (*eBox 2*) in the following circumstances:

- If they are suspected of a causal connection with the administration of packed red cells
- If they occur at the time of administration of packed red cells, with or without suspicion of a causal connection.

Conflict of interest statement

Dr. Müller has received consulting fees from Novartis Pharmaceutical Corporation. He has received payments from Fresenius KABI and Cerus for the preparation of scientific training courses. Furthermore, he has received funding from Cerus for research that he initiated.

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Prof. Tonn declares that no conflict of interest exists.

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Irradiated packed red cells

Despite leukocyte depletion, bags of packed red cells may contain a small number of vital donor lymphocytes that can lead to transfusion-associated graft-versus-host disease (ta-GvHD).

Washed packed red cells

Washed packed red cells are rarely indicated. Early contact with the responsible transfusion specialist is recommended.

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[Supplementary material](#)

[eTable and eBoxes:](#)

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Further information on CME

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

A patient of unknown blood group needs an emergency transfusion of packed red cells (PRC). What should you give?

- a) PRC of blood group A
- b) PRC of blood group B
- c) PRC of blood group O
- d) PRC of blood group AB
- e) PRC of all four blood groups (O, A, B, and AB) can be given in an emergency.

Question 2

What do you establish or check in the ABO identity test (bedside test) before administering packed red cells?

- a) Correct result of the serological tolerance test (cross-matching)
- b) ABO antigen characteristics of the patient's red blood cells
- c) Correct result of the antibody screening test
- d) ABO-specific antibodies of the packed red cells
- e) ABO-specific antibodies of the patient

Question 3

Which group of patients must receive Rh (D)-negative packed red cells?

- a) Elderly patients with a history of hematological disease
- b) Rh D-negative patients with demonstrated anti-D antibodies
- c) Young patients after surgical interventions
- d) Postmenopausal women with gynecological hemorrhage
- e) Patients with severe head injury after road traffic accidents

Question 4

What is it crucial to ask about in women scheduled for transfusion?

- a) Date and result of most recent cervical smears
- b) Cross-allergies
- c) Type of childbirth (e.g. cesarean section)
- d) Most recent mammography
- e) Existence of maternity booklet(s)

Question 5

How common are hemolytic transfusion reactions of immediate type without fatal outcome in Germany?

- a) 1 : 10 to 1 : 100
- b) 1 : 100 to 1 : 1000
- c) 1 : 1000 to 1 : 10 000
- d) 1 : 10 000 to 1 : 100 000
- e) 1 : 100 000 to 1 : 1 000 000

Question 6

Erythema and wheals are found in a female patient after transfusion of packed red cells. Severe complications can be excluded and a renewed identity check is negative. What kind of transfusion reaction does she probably have?

- a) Allergic transfusion reaction
- b) Hemolytic transfusion reaction of the immediate type
- c) Hemolytic transfusion reaction of the delayed type
- d) Transfusion-associated viral infection
- e) Transfusional hemosiderosis

Question 7

In which of the following circumstances is there a clear-cut indication for irradiation of packed red cells with gamma radiation at a dose of at least 30 Gy?

- a) Non-Hodgkin lymphoma (NHL)
- b) Prostate carcinoma
- c) Patient with cardiac valve replacement
- d) Septic shock
- e) Multiple trauma

Question 8

In the "type and screen" strategy, which investigations are carried out in the 3-day period preceding a planned intervention?

- a) HLA typing and tumor screening
- b) Ascertainment of tumor type (grading) and prostate-specific antigen (PSA) screening
- c) Blood group determination and antibody screening test
- d) HPA determination and whole-body plethysmography
- e) Cardiac echocardiography and upper abdominal sonography

Question 9

A 28-year-old female patient known to have the blood group B Rh (D) negative suffers a sudden esophageal variceal hemorrhage while in hospital and a transfusion of non-cross-matched packed red cells (PRC) is planned owing to an Hb concentration of 5 g/dL, severe dyspnea, hypotension, and tachycardia. Which of the following products do you choose?

- a) PRC of blood group A Rh (D) negative
- b) PRC of blood group B Rh (D) positive
- c) PRC of blood group AB Rh (D) negative
- d) PRC of blood group O Rh (D) negative
- e) PRC of blood group O Rh (D) positive

Question 10

In a 55-year-old patient who has undergone major surgery with intraoperative blood loss you find an Hb concentration of 8.4 g/dL with anemia.

The patient feels well (BP 135/85 mm Hg, pulse 82/min) and is moving around the ward to the extent allowed by his postoperative status. There are no relevant previous diseases; the postoperative course justifies discharge from hospital; on your pre-discharge examination the patient shows no signs of dyspnea or vertigo and no other clinical abnormalities. How do you proceed?

- a) The patient receives a unit of packed red cells prophylactically, so that he can soon be sent home.
- b) On discharge the patient is given two units of packed red cells to take to his primary care physician for transfusion.
- c) The patient is instructed to attend the day clinic on the day after discharge for transfusion of a unit of packed red cells.
- d) The patient cannot be discharged owing to his pronounced anemia.
- e) After clarification of his home situation, the patient is discharged with no further administration of packed red cells.

Supplementary material to:

Transfusion of Packed Red Cells

Indications, Triggers and Adverse Events

by Markus M. Müller, Christof Geisen, Kai Zacharowski,
Torsten Tonn, and Erhard Seifried

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eBOX 1

Indications for irradiation of packed red cells to prevent ta-GvHD*

- **Transfusion in patients with hematopoietic stem cell transplantation**
 - In autologous transplantation (auto-Tx) at least 14 days before and for at least 3 months after auto-Tx or until demonstration of immunological reconstitution
 - In allogeneic transplantation (allo-Tx) for at least 6 months after allo-Tx or until demonstration of immunological reconstitution
 - In patients with GvHD after allo-Tx regardless of time since allo-Tx
- **Obstetric and pediatric indications**
 - Intrauterine transfusion and transfusion in a newborn post intrauterine transfusion
 - Transfusion in confirmed or suspected severe congenital immunodeficiency
 - Exchange transfusion in neonates or transfusion in neonates and infants with suspected immunodeficiency
- **In all directed transfusions (= donor is family member; now extremely rare in Germany!) or transfusion of HLA-selected blood products and packed granulocytes (irradiation by manufacturer)**
- **Transfusion in patients with Hodgkin disease or Non-Hodgkin lymphoma (in either case, all stages!)**
- **Transfusion in patients being treated with purine analogs (fludarabine, cladribine etc.)**
- **Note that the indication for irradiation applies to all cellular blood products (packed red cells and platelet concentrates).**
- **There is no clear-cut indication for the irradiation of cellular blood products in the following states/diseases:**
 - Premature infants: with the exception of the above-mentioned indications!
 - AIDS patients
 - Leukemia patients (but: observe indication for irradiation indicated in treatment with purine analogs—see above!)
 - Recipients of solid organ transplants (check for immunosuppression!)
 - Patients with solid tumors

(For these five situations it is advisable for the transfusion committee to decide the best procedure and write it into the local regulations governing transfusions.)

*Modified from (4); ta-GvHD, transfusion-associated graft-versus-host disease

eBOX 2

Reporting of adverse events and side effects as stipulated by the German Transfusion Act and prevailing guidelines (2, 3)

- **Adverse event**
 - Report to the departmental transfusion officer or responsible physician
- **(Suspected) adverse effect**
 - Report to the manufacturer of the PRC (blood donation service) and the Drug Commission of the German Medical Association
- **(Suspected) severe adverse effect***
 - Report to the manufacturer of the PRC (blood donation service), the Drug Commission of the German Medical Association, and the Paul Ehrlich Institute (Langen)

* "Severe" = fatal or life-threatening; requiring or prolonging inpatient treatment; leading to persistent or severe disability; leading to invalidity, congenital anomalies, or birth defects
PRC, packed red cells

eTABLE

Classification of adverse drug reactions to packed red cells (from [21])

Pathomechanism	Time of onset	
	Acute (<24 h after transfusion)	Delayed (>24 h after transfusion)
Immunological	<ul style="list-style-type: none"> – Allergic transfusion reaction – Febrile non-hemolytic transfusion reaction (FNHTR) – Transfusion-associated acute lung insufficiency (TRALI) – Hemolytic transfusion reaction of immediate type 	<ul style="list-style-type: none"> – Hemolytic transfusion reaction of delayed type – Transfusion-associated immunomodulation (TRIM) – Transfusion-associated graft-versus-host disease (ta-GvHD) – Post-transfusional purpura (PTP)
Non-immunological	<ul style="list-style-type: none"> – Transfusion-associated circulatory overload (TACO) – Hypothermia – Hyperkalemia – Citrate toxicity 	<ul style="list-style-type: none"> – Transfusional hemosiderosis
Infections	<ul style="list-style-type: none"> – Transfusion-associated bacterial infection 	<ul style="list-style-type: none"> – Transfusion-associated viral transmissions (HIV, HAV, HBV, HCV, HEV, CMV, Dengue, Chikungunya, WNV, etc.) – Transfusion-associated parasitosis (e.g., malaria) – Transfusion-associated new variant of Creutzfeldt-Jakob disease (nvCJD)