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### 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 (table 11.1).

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), transfusion-related acute lung injury (TRALI; following administration of fresh frozen plasma (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.

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 (table 11.1), 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...

| Table 11.1. Clinical classification of acute adverse reactions |
|---------------------------------|-----------------|-----------------|-----------------|
| Clinical signs and symptoms      | Probable causes | Immediate course of action | Further immediate clarification |
| I                               | allergic reaction | 1) interrupt transfusion | exclusion of hemolysis (section 11.2.1) |
| urticaria and/or pruritus        |                 | 2) clinical examination | exclusion of bacterial contamination (section 11.2.4) |
| II                              | allergic reaction febrile nonhemolytic transfusion reaction bacterial contamination of the component | 1) interrupt transfusion 2) clinical examination 3) consider antihistamine therapy/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 | |
| urticaria, pruritus, fever, rigor, restlessness, tachycardia, anxiety, palpitations, mild dyspnea, headaches | | | |
| III                             | without cardinal respiratory symptoms: acute intravascular hemolysis; shock in case of bacterial contamination; anaphylaxis | 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) |
| 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 | | | |
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 11.2).

### 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 RBCs. Therefore, they typically occur with ABO-incompatible RBC transfusions, mostly when RBCs 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 UK (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 [29]. 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, 28]. 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, FFP), 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 anesthetized 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 lactate dehydrogenase (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 (DIC).

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

<table>
<thead>
<tr>
<th>O₂-saturation</th>
<th>X-ray (mandatory)</th>
<th>Additional important symptoms</th>
<th>Temporal connection with transfusion</th>
<th>Clinically suspected diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;90%*</td>
<td>bilateral* pulmonary infiltrate; unremarkable cardiac symptoms</td>
<td>immediately up to 6 h* after transfusion</td>
<td>TRALI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pulmonary infiltrates; signs of cardiac decompensation</td>
<td>up to 12 h after transfusion; possibly following massive transfusion</td>
<td>TACO</td>
<td></td>
</tr>
</tbody>
</table>

| no infiltrates | cyanosis, stridor | up to 24 h after transfusion | TAD                           |

TRALI = transfusion-associated lung injury; TACO = transfusion-associated circulatory overload; TAD = transfusion-associated dyspnea.

*The diagnosis TRALI is ruled out if one of the criteria is not met.
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 leukocyte-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 leukocytes (especially HLA antibodies) react with contaminating leukocytes in platelet or granulocyte concentrates [20]. Following the introduction of general leukocyte depletion, febrile nonhemolytic transfusion reactions have become a rare occurrence (<0.1%) [23, 37, 50].

Symptoms:
Fever (increase of body temperature by more than 1 °C), shivering, chills, usually starting 30–60 min 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 of the blood product are to be ruled out. If the patient repeatedly has a febrile nonhemolytic transfusion reaction, haemoglobinuria 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, 15].

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 [47].

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, pre-medication (H1 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 [26].

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, 35]) and the frequency of clinical reactions to contaminated preparations (approximately 1:100,000 [12, 14, 15]), since a large proportion of contami-
nated transfused platelet concentrates did not lead to clinical reactions [35].

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’s 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 h after opening [1].

11.2.5 Transfusion-Related Acute Lung Injury

**Etiology and frequency:**
TRALI is caused by antibodies to patients’ leukocytes in donor plasma (rarely in recipients’ plasma). The activated leukocytes obstruct the pulmonary microcirculation and cause pulmonary edema. Up to 25% of afflicted patients die [14, 24]. 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 h after transfusion, rapidly increasing dyspnea develops together with hypoxemia (SpO₂ ≤ 90% on ambient air or FiO₂ ≤ 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 O₂ 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 O₂ saturation is below 90% and the X-ray displays newly emerged bilateral infiltrates. Regarding differential diagnosis (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 leukocyte-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 leukocyte 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 (approximately 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 and lethality with 3–4% [40].

**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 oximetry, 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/h, in case of particular risk to 1 ml/kg body weight/h.

### 11.2.7 Further Acute Adverse Reactions

**Hypothermia:**
Hypothermia may occur mainly in connection with massive transfusions; the body temperature may decrease to 32–34 °C during rapid replacement of 50% of the blood volume which can provoke or amplify potentially life-threatening disorders [25].

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 concentrates (≥ 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 [25]. High levels of potassium are frequently found in irradiated and stored RBC concentrates.

**Transfusion of hemolytic RBC concentrates:**
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 followed 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 1:1.6 million transfused units [28].

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 [43]. 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 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 [48]. It is a very rare transfusion reaction [34], 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/\mu l.

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 must be ruled out in differential diagnosis.

Therapeutic measures:
Intravenous high-dose immunoglobulin therapy with 1 g immunoglobulins/kg body weight, in portions of 2 doses on 2 days [33]. Platelet transfusions have no effect at all [13].

11.3.3 Transfusion-Associated Graft-versus-Host Disease

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 erythrodernia, 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 [44].

Therapeutic measures:
Symptom-oriented therapy [21].

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). Leukocyte depletion alone is not sufficient [31]. Granulocyte concentrates must always be irradiated with 30 Gy due to their high content of T lymphocytes that are able to proliferate (see 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. Leukocyte 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, leukocyte 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 erythrocytosis (e.g. in hemolytic anemia). Regarding prophylaxis of transfusion-associated CMV and parvovirus B19 infections, see section 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; Transfusionsgesetz; TFG) and has been specified in its particulars in an announcement of the Arbeitskreis Blut (National Advisory Committee ‘Blood'; 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 section 11.4.
11.3.5 Transfusion-Transmitted Parasitical Infections

Etiology and frequency:
In principle parasites can also be transmitted by RBCs: 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 UK 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 [30]. 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 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 approximately 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 FFP 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 polylefine 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 TA-GVHD in immunocompromised 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 [45]. 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 [32] 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 leukocytes.

It is not recommended to irradiate FFP 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 con-
centrates in which there is a considerable risk of a one-way HLA match (approximately 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.

| Intraterine transfusions shall be carried out exclusively with irradiated cellular blood components. 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 patients with SCID shall be treated with irradiated cellular blood components.

| 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. It is recommended to treat patients following autologous transplantation with irradiated cellular blood components for at least 3 months. | 1 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. It is recommended to treat patients following allogeneic transplantation with irradiated cellular blood components for at least 6 months or until immunological reconstitution. It is recommended to treat patients with GVHD following allogeneic blood stem cell or bone marrow transplantation 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 immunodeficiency, in particular in patients with purine nucleoside phosphorylase (PNP) deficiency, Wiskott-Aldrich syndrome and DiGeorge syndrome.

| All 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. | 2 C |
Patients with Hodgkin’s lymphoma (all stages) shall be transfused exclusively with irradiated cellular blood components. **1C+**

_all cellular blood components for patients with non-Hodgkin’s lymphoma (all stages):_ At least 17 cases of TA-GVHD in patients with non-Hodgkin’s lymphoma are documented, among them a higher number of non-Hodgkin’s 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’s lymphoma (all stages) shall be transfused exclusively with irradiated cellular blood components. **1C+**

All cellular blood components for patients during therapy with purine antagonists: In at least 9 patients during fludarabin therapy and in 1 patient during cladribin therapy TA-GVHD occurred.

All patients during therapy with purine antagonists shall be transfused exclusively with irradiated cellular blood components. **1C+**

**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 leukocytes corresponding to that after irradiation with 30 Gy [16, 17]. 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**

**11.4.2.1 CMV**

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, preterm 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 leukocytes (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:
- application of cellular blood components from CMV-seronegative donors,
- leukocyte 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 [46]. 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 [46]. 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 leukocyte-depleted blood products. The authors of the study concluded that both procedures are equivalent. However, all 6 patients in the group receiving leukocyte-depleted blood products developed an apparent CMV disease, whereas no patient fell ill in the patient group receiving CMV-seronegative blood products (p = 0.03).

A meta-analysis including the prospective, randomized trial by Bowden et al. [3] as well as two non-randomized trials (before and after comparison [36, 38]) found a slight benefit when using blood products from CMV-seronegative donors as compared to leukocyte-depleted blood products in patients after stem cell transplantation [46]. There are no comparative clinical trials for other patient groups.

There are also no trials on a combined use of both preventive measures (leukocyte depletion plus selection of CMV-seronegative donors vs. leukocyte 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) [46].
The minimum infectious dose (number of latently infected blood leukocytes) 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 leukocytes). Only 2 of 1,000 samples had CMV DNA reproducibly detectable by validated methods [41]. Both blood samples were from seropositive donors. Conclusions by analogy from a murine model of transfusion-associated CMV infection suggest that leukocyte depletion using current generations of filters can reduce the number of latently infected leukocytes below the threshold of the infectious dose [42].

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 [19].

In the context of a prospective cohort trial the rate of detection of CMV genome within blood leukocytes ranged from 75 to 80% during the first 16 weeks after infection. CMV DNA could be detected in plasma in 25–40% 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 leukocytes [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 leukocyte-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 leukocyte-depleted blood products is higher or lower when CMV-seronegative blood donors are selected. On the one hand, the risk reduction by leukocyte 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.

Leukocyte depletion is performed in Germany for all RBC and platelet concentrates: this has caused a reduction of cellula latent CMV 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 leukocyte-depleted blood products in order to prevent a CMV infection.

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 to manufacturing 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.

11.4.2.2 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 [reviewed in 6]. The incidence reported for parvovirus B19 DNA in blood donations ranges between 1:100 to approximately 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 single-donor platelets 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 B19 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 [39] although parvovirus 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 [18]. However, recent reports suggested that parvovirus B19 DNA is detectable even several years after seroconversion in the blood of asymptomatic
carriers [27]. 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 (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 al-
logeneic 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 [22].

**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 [22].

**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 Nonhemolytic 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 [22].

**Symptoms:**
Fever, chills, moderate dyspnea, most often 30–60 min 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/h, in particular cases to 1 ml/kg body weight/h.

**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 hyperv- 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.

**References**


