

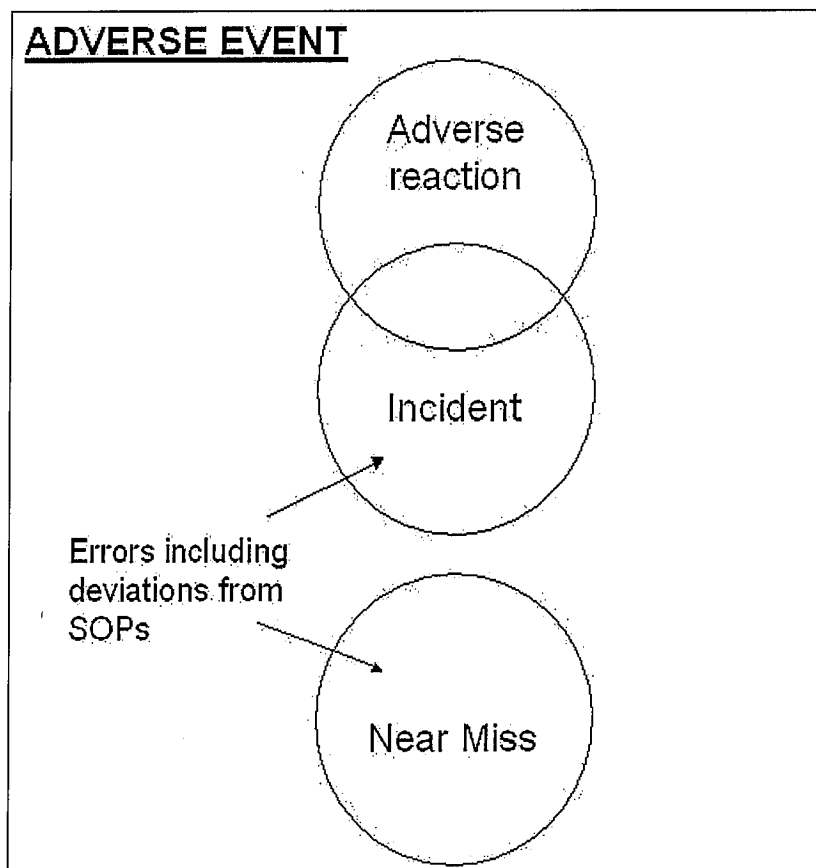
1 GENERAL DEFINITIONS OF ADVERSE EVENTS

An **adverse event** is an undesirable and unintended occurrence before, during or after transfusion of blood or blood component which may be related to the administration of the blood or component. It may be the result of an error or an incident and it may or not result in a reaction in a recipient.

An **incident** is a case where the patient is transfused with a blood component which did not meet all the requirements for a suitable transfusion for that patient, or that was intended for another patient. It thus comprises transfusion errors and deviations from standard operating procedures or hospital policies that have lead to mistransfusions. It may or may not lead to an adverse reaction.

A **near miss** is an error or deviation from standard procedures or policies that is discovered before the start of the transfusion and that could have led to a wrongful transfusion or to a reaction in a recipient.

An **adverse reaction** is an undesirable response or effect in a patient temporally associated with the administration of blood or blood component. It may, but need not, be the result of an incident.



2 HEMOLYTIC TRANSFUSION REACTIONS

A hemolytic transfusion reaction is one in which symptoms and clinical or laboratory signs of increased red cell destruction are produced by transfusion. Hemolysis can occur intravascularly or extravascularly and can be immediate (acute) or delayed.

2.1 Acute hemolytic transfusion reaction (AHTR)

An AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of hemolysis are present.

Common signs of AHTR are:

- Fever
- Chills/rigors
- Facial flushing
- Chest pain
- Abdominal pain
- Back/flank pain
- Nausea/vomiting
- Diarrhea
- Hypotension
- Pallor
- Jaundice
- Oligoanuria
- Diffuse bleeding
- Dark urine

Common laboratory features are:

- Hemoglobinemia
- Hemoglobinuria
- Decreased serum haptoglobin
- Unconjugated hyperbilirubinemia
- Increased LDH and AST levels
- Decreased hemoglobin levels

Not all clinical or laboratory features are present in cases of AHTR.

Blood group serology usually shows abnormal results but absence of immunological findings does not exclude AHTR. AHTR may also be due to erythrocyte auto-antibodies in the recipient or to non immunological factors like mechanical factors inducing hemolysis (malfunction of a pump, of a blood warmer, use of hypotonic solutions, etc.).

2.2 Delayed hemolytic transfusion reaction (DHTR)

A DHTR usually manifests between 24 hours and 28 days after a transfusion and clinical or laboratory features of hemolysis are present. Signs and symptoms are similar to AHTR but are usually less severe. DHTR may sometimes manifests as an inadequate rise of post-transfusion hemoglobin level or unexplained fall in hemoglobin after a transfusion. Blood group serology usually shows abnormal results.

2.3 Delayed serologic reaction (DSTR)

There is a DSTR when, after a transfusion, there is demonstration of clinically significant antibodies against red blood cells which were previously absent (as far as is known) and when there are no clinical or laboratory features of hemolysis. This term is synonymous with alloimmunization.

3 NON HEMOLYTIC TRANSFUSION REACTIONS

3.1 Febrile non hemolytic transfusion reaction (FNHTR)

There is a FNHTR in the presence of one or more of:

- fever ($\geq 38^{\circ}\text{C}$ oral or equivalent and a change of $\geq 1^{\circ}\text{C}$ from pretransfusion value),
- chills/rigors

This may be accompanied by headache and nausea.

occurring during or within four hours following transfusion without any other cause such as hemolytic transfusion reaction, bacterial contamination or underlying condition.

FNHTR could be present in absence of fever (if chills or rigors without fever).

FOR THE PURPOSE OF INTERNATIONAL COMPARISONS ONLY THE MOST SERIOUS CASES OF FNHTR SHOULD BE ACCOUNTED FOR:

- fever ($\geq 39^{\circ}\text{C}$ oral or equivalent and a change of $\geq 2^{\circ}\text{C}$ from pretransfusion value) and chills/rigors

3.2 Allergic reaction

An allergic reaction may present only with mucocutaneous signs and symptoms:

- Morbilliform rash with pruritus
- Urticaria (hives)
- Localized angioedema
- Edema of lips, tongue and uvula
- Periorbital pruritus, erythema and edema
- Conjunctival edema

occurring during or within 4 hours of transfusion. In this form it usually presents no immediate risk to life of patient and responds quickly to symptomatic treatment like anti-histamine or steroid medications. This type of allergic reaction is called 'minor allergic reaction' in many hemovigilance systems.

For the purpose of classification this type of allergic reaction would be graded as 1, i.e. non-severe.

An allergic reaction can also involve respiratory and/or cardiovascular systems and present like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous systems there is airway compromise or severe hypotension requiring vasopressor treatment (or associated symptoms like hypotonia, syncope). The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing/bronchospasm, hypoxemia). Such a reaction usually occurs occurring during or very shortly after transfusion.

For the purpose of classification this type of allergic reaction would be graded as 2 (severe), 3 (life-threatening) or 4 (death) depending on the course and outcome of the reaction.

An allergic reaction classically results from the interaction of an allergen and preformed antibodies. A rise of mast cell tryptase can support the diagnosis of an allergic reaction. IgA deficiency and/or anti-IgA in the recipient has been associated with severe allergic reactions but is only one infrequent cause out of many others.

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

TA-GVHD is a clinical syndrome characterised by symptoms of fever, rash, liver dysfunction, diarrhea, pancytopenia and findings of characteristic histological appearances on biopsy occurring 1-6 weeks following transfusion with no other apparent cause.

The diagnosis of TA-GVHD is further supported by the presence of chimerism.

3.7 Post transfusion purpura (PTP)

PTP is characterized by thrombocytopenia arising 5-12 days following transfusion of cellular blood components with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system.

3.3 Transfusion-related acute lung injury (TRALI)

In patients with no evidence of acute lung injury (ALI) prior to transfusion, TRALI is diagnosed if a new ALI is present:

- Acute onset
- Hypoxemia
 - $PaO_2 / FiO_2 < 300$ mm Hg or
 - Oxygen saturation is $< 90\%$ on room air or
 - Other clinical evidence
- Bilateral infiltrates on frontal chest radiograph
- No evidence of left atrial hypertension (i.e. circulatory overload)
- No temporal relationship to an alternative risk factor for ALI

during or within 6 hours of completion of transfusion.

Alternate risk factors for ALI are:

- Direct Lung Injury
 - Aspiration
 - Pneumonia
 - Toxic inhalation
 - Lung contusion
 - Near drowning
- Indirect Lung Injury
 - Severe sepsis
 - Shock

- Multiple trauma
- Burn injury
- Acute pancreatitis
- Cardiopulmonary bypass
- Drug overdose

It has been suggested by the Toronto TRALI Consensus Panel to add a category of *possible TRALI* that would have the same definition as TRALI except for the presence of a temporal relationship to an alternative risk factor for ALI (as described above). In such a circumstance TRALI should be indicated with a *possible* imputability to transfusion.

TRALI is therefore a clinical syndrome and presence of anti-HLA or anti-HNA antibodies in recipient nor confirmation of cognate antigens in donors are required for diagnosis.

3.6 Transfusion associated dyspnea (TAD)

TAD is characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should be the most prominent clinical feature and should not be explained by the patient's underlying condition or any other known cause.

3.4 Transfusion associated circulatory overload (TACO)

TACO is characterized by any 4 of the following:

- Acute respiratory distress
- Tachycardia
- Increased blood pressure
- Acute or worsening pulmonary edema on frontal chest radiograph
- Evidence of positive fluid balance

occurring within 6 hours of completion of transfusion.

An elevated BNP is supportive of TACO.

3.5 Hypotensive transfusion reaction

This reaction is characterized by hypotension defined as a drop in systolic blood pressure of ≥ 30 mm Hg occurring during or within one hour of completing transfusion **and** a systolic blood pressure ≤ 80 mm Hg.

Most reactions do occur very rapidly after the start of the transfusion (within minutes). This reaction responds rapidly to cessation of transfusion and supportive treatment. This type of reaction appears to occur more frequently in patients on ACE inhibitors

Hypotension is usually the sole manifestation but facial flushing and gastrointestinal symptoms may occur.

All other categories of adverse reactions presenting with hypotension, especially allergic reactions, must have been excluded. The underlying condition of the patient must also have been excluded as a possible explanation for the hypotension.

3.6 Other transfusion reactions

a) Haemosiderosis

Transfusion-associated haemosiderosis is being defined as a blood ferritin level of ≥ 1000 micrograms/l, with or without organ dysfunction in the setting of repeated RBC transfusions.

b) Hyperkalemia

Any abnormally high potassium level (> 5 mmol/l, or ≥ 1.5 mmol/l net increase) within an hour of transfusion can be classified as a transfusion-associated hyperkalemia.

c) Unclassifiable Complication of Transfusion (UCT)

Occurrence of an adverse effect or reaction temporally related to transfusion, which cannot be classified according to an already defined ATE and with no risk factor other than transfusion and no other explaining cause.

4 Severity

Grade 1 (Non-Severe):

- the recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function.

Grade 2 (Severe):

- the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or
- the adverse event resulted in persistent or significant disability or incapacity; or
- the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.

Grade 3 (Life-threatening):

- the recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death

Grade 4 (Death)

- the recipient died following an adverse transfusion reaction

Grade 4 should be used only if death is possibly, probably or definitely related to transfusion. If the patient died of another cause, the severity of the reaction should be graded as 1, 2 or 3.

5 Imputability

This is, once the investigation of the adverse transfusion event is completed, the assessment of the strength of relation to the transfusion of the ATE.

Definite (certain): when there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the transfusion

Probable (likely): when the evidence is clearly in favor of attributing the adverse event to the transfusion

Possible: when the evidence is indeterminate for attributing the adverse event to the transfusion or an alternate cause

Unlikely (doubtful): when the evidence is clearly in favor of attributing the adverse event to causes other than the transfusion

Excluded: when there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to causes other than the transfusion

Only possible, probable and definite cases should be used for international comparisons.

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INTRODUCTION

The definitions proposed in this document were prepared by a sub-group of members of the ISBT Working Party on Haemovigilance comprising:

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The definitions were inspired from a document written by Dr Juergen Bux on proposed definitions by the European Haemovigilance Network, from existing definitions in various haemovigilance systems and from published literature. The definitions were reviewed and adopted by the ISBT Working Party on Haemovigilance at its meeting in Capetown on September 2, 2006. Case scenarios from actual haemovigilance reports were developed and volunteers from various haemovigilance systems agreed to classify the cases using the standard definitions. Good agreement was obtained for the case definitions but a less good agreement was obtained for imputability grading. It was decided to keep imputability grading as developed because already in use in multiple haemovigilance systems.

These definitions are for the sole purpose of surveillance of adverse events related to the transfusion of blood components in haemovigilance systems. They are not intended as strict diagnostic criteria. Standard definitions are essential if comparisons from different haemovigilance systems are to be made. The purpose of this document is to provide such standard definitions that need to be simple yet precise enough to be able to classify most adverse transfusion events.

We first propose general definitions of adverse transfusion events, near misses, incidents and reactions. The non infectious reactions are then addressed with hemolytic and non hemolytic reactions followed by a proposed classification of severity and imputability (strength of association with transfusion) of adverse events.

This document does not provide categories and definitions for types of transfusion errors and near misses.

The proposed definitions of adverse reactions apply to the adult population of patients. Adaptations of the definitions will have to be made by institutions for the pediatric patient population and especially for neonates.

We hope this document will help the various haemovigilance systems to classify the adverse reactions reported to them in order to generate data that will be comparable at an international level.

Pierre Robillard, MD
Chair, ISBT Working Party on Haemovigilance



WORKING PARTY ON HAEMOVIGILANCE

PROPOSED STANDARD DEFINITIONS FOR SURVEILLANCE OF NON INFECTIOUS ADVERSE TRANSFUSION REACTIONS

JULY 2011



INTERNATIONAL HAEMOVIGILANCE NETWORK