ORIGINAL REPORT

Hemovigilance and the Notify Library

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Hemovigilance systems allow reporting of adverse occurrences associated with blood transfusion to a central database where events can be reviewed and analyzed for the benefit of patients and donors. Hemolytic and serologic transfusion reactions are among the many types of reactions reported to these systems. The Notify Library, a database of adverse events associated with medical products of human origin, has incorporated hemovigilance into its didactic resources. Students and practitioners are encouraged to use the electronic library and to further enhance this resource through review and recommendation of additional publications in the area of immunohematology. ***Immunohematology* 2017;33:159–164.**

Key Words: biovigilance, hemovigilance, transfusion reactions, hemolytic transfusion reactions, serologic transfusion reactions

Advances in science and health care technology have led to the development of replacement medicine, with many human body components being collected for the preparation of medical products of human origin (MPHO). These collections encompass a wide range of medical products—from cells (e.g., human stem cells from peripheral blood, bone marrow, or cord blood; gametes) and tissues (e.g., corneas, musculoskeletal tissues) to blood and blood components and organs, from anatomical components to secretions (e.g., breast milk) and excretions—all originating from the human body. Donated by a human with the goal of benefitting others, these MPHO have indeed saved and improved human lives through their clinical application.

Vigilance is a powerful tool for improving safety and quality. Vigilance includes monitoring and reporting adverse events and outcomes associated with therapeutic treatments. Originating from hemovigilance for blood components, *biovigilance* is the term used for the monitoring of adverse outcomes associated with all MPHO. Sharing the lessons learned from adverse outcomes can allow for significant process improvements for the greater protection of donors and patients. These benefits apply not only to the institution where the incident occurred but also to other institutions where an identical or similar incident might occur. Detection, investigation, and communication of adverse events provide the transparency and openness that these uniquely sourced medical treatments demand.

The World Health Organization (WHO) promotes the governance of MPHO in a manner that acknowledges their exceptional nature. From donation to the follow-up care of the recipient, MPHO have a shared exposure to risks from breaches of ethical, legal, and safety standards—for example, the risk of disease transmission and consequent morbidity or mortality. Ensuring the protection of the donor, the recipient, and society as a whole requires establishment of globally consensual principles to govern the use of MPHO, such as the noncommercial nature of the human body and its parts and strict traceability associated with vigilance and surveillance. The Notify Library[1] is the first WHO initiative that covers vigilance across the full MPHO scope.

Hemovigilance

Hemovigilance of blood transfusions encompasses a set of surveillance procedures that cover the entire collection to transfusion process: from the donor and donation, to the processing of the donor's blood and its components, to their provision and transfusion to patients, to patient follow-up. Hemovigilance includes the monitoring, reporting, investigation, and analysis of adverse events related to the donation, processing, and transfusion of blood, as well as the development and implementation of recommendations to prevent occurrence or recurrence.[2]

Hemovigilance systems arose as a response to the threat to the blood supply from emerging infections, such as HIV and the hepatitis viruses. Hemovigilance was first developed in Japan and then in France in 1993, featuring mandatory reporting. The UK developed the first voluntary system in 1996, called Serious Hazards of Transfusion (SHOT).[3] Over the years, systematic analyses from these systems and subsequent process improvements have led to enhanced patient safety.[3–5] In 2002, the European Union (EU) Commission Directive 2002/98/EC set standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amended Directive 2001/83/EC, thereby mandating hemovigilance in the EU. Subsequently, other countries around the world have established hemovigilance systems, adopting either active or passive hemovigilance reporting. Systems engaging in active

hemovigilance require a confirmation of a transfusion reaction or the lack thereof after every transfusion. In 1998, the European Haemovigilance Network was established; in 2009, it evolved into the International Haemovigilance Network to share common definitions, findings, and interventions and to promote transfusion safety worldwide.

The Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) has developed transfusion reaction definitions (Tables 1 and 2) and imputability criteria (Table 3). Imputability is the strength of the relationship between the transfusion and the adverse transfusion reaction and is usually determined through a thorough investigation of the adverse reaction. Standard definitions for hemolytic transfusion reactions include acute hemolytic transfusion reactions (AHTRs), delayed hemolytic transfusion reactions (DHTRs), and delayed serologic transfusion reactions (DSTRs) (Table 1).[2] Non-hemolytic transfusion reactions are described in Table 2.

Notify Library

The Notify Library is a database developed through a collaboration of WHO and the Italian National Transplant Center (CNT).[6] It supports the sharing of published vigilance information for teaching purposes and for greater public transparency on the use of MPHO. The library aims to support three key audiences: the general public (especially potential donors or recipients), health professionals working in donor detection and selection or in the clinical application of MPHO, and health authorities responsible for vigilance systems. It aims to be comprehensive, describing all types of reactions or events that might have teaching value and assist in the estimation of risk.

The core of the Notify Library Web site (www.notifylibrary.org) includes an online publicly accessible relational database of adverse occurrences collected and analyzed by dedicated editorial groups of international experts, regulators, and clinicians. The database is not a vigilance reporting program but rather a collection of information identified primarily by review of published articles in scientific journals and/or books. It also includes case reports from regulatory or professional vigilance programs (gray literature). Sources include events that may have occurred in procurement and processing, as well as in the clinical application, of blood, organs, tissues, and cells used in transfusion, transplantation, and assisted reproduction. For each adverse occurrence type, at least one reference is cited. The project's collaborating international experts provide a structured analysis, focused in particular on how the adverse occurrence was recognized and how it was shown to have been associated with the donation, processing, or clinical application of MPHO. Categories of occurrences that are analyzed include transmitted infections, malignancies, donor reactions, clinical complications, and process-associated incidents.

Currently, each database entry is given a title and a unique numeric identifier. Through the case analysis, the entry is assigned an adverse occurrence type; an MPHO type; the time to detection; alerting signs, symptoms, and evidence of occurrence; the estimated frequency; demonstration of imputability and imputability grade; keywords; copy of the reference; and any expert comments about the reference or occurrence. To facilitate a structured database search, all cases have been classified according to a taxonomy of two main

Table 1. Hemolytic transfusion reaction definitions developed by the Haemovigilance Working Party of the International Society of Blood Transfusion[2]

Adverse transfusion reaction	Definition
Hemolytic transfusion reactions (general)	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.
Acute hemolytic transfusion reaction (AHTR)	AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of hemolysis are present. 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.).
Delayed hemolytic transfusion reaction (DHTR)	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 manifest as an inadequate rise of post-transfusion hemoglobin level or unexplained fall in hemoglobin after a transfusion. Blood group serology usually shows abnormal results.
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.

Table 2. Non-hemolytic transfusion reaction definitions developed by the Haemovigilance Working Party of the International Society of Blood Transfusion[2]

Adverse transfusion reaction	Definition
Febrile non hemolytic transfusion reaction (FNHTR)	There is a FNHTR in the presence of one or more of the following: fever (≥38°C oral or equivalent and a change of ≥1°C from pretransfusion value), chills/rigors. These may be accompanied by headache and nausea. Symptoms 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).
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 antihistamine 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 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.
Transfusion associated graft-versus-host disease (TA-GVHD)	TA-GVHD is a clinical syndrome characterized 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.
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.
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 (all five criteria should be met): 1) Acute onset 2) Hypoxemia of PaO2/FiO2 <300 mmHg, or oxygen saturation of <90% on room air, or other clinical evidence 3) Bilateral infiltrates on frontal chest radiograph 4) No evidence of left atrial hypertension (i.e., circulatory overload) 5) No temporal relationship to an alternative risk factor for ALI, during or within 6 hours of completion of transfusion Alternate risk factors for ALI include: direct lung injury (aspiration, pneumonia, toxic inhalation, lung contusion, near drowning) or indirect lung injury (severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, drug overdose). Note: 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 earlier). In such a circumstance, TRALI should be indicated with a *possible* imputability to transfusion. TRALI is therefore a clinical syndrome and neither presence of HLA or HNA antibodies **in donor(s)** nor confirmation of cognate antigens **in recipient** is required for diagnosis.
Transfusion associated circulatory overload (TACO)*	TACO is characterized by any 4 of the following occurring within 6 hours of completion of transfusion: 1) Acute respiratory distress 2) Tachycardia 3) Increased blood pressure 4) Acute or worsening pulmonary edema on frontal chest radiograph 5) Evidence of positive fluid balance. An elevated brain natriuretic peptide (BNP) is supportive of TACO.
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.
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.
Haemosiderosis	Transfusion-associated haemosiderosis is defined as a blood ferritin level of ≥ 1000 micrograms/L, with or without organ dysfunction in the setting of repeated RBC transfusions.

Table 2. Non-hemolytic transfusion reaction definitions developed by the Haemovigilance Working Party of the International Society of Blood Transfusion[2] (continued)

Adverse transfusion reaction	Definition
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.
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 reaction type and with no risk factor other than transfusion and no other explaining cause.

*The definition of TACO is currently undergoing revision by the working party.

HLA = human leukocyte antigen; HNA = human neutrophil antigen; RBC = red blood cell.

Table 3. Imputability criteria developed by the Haemovigilance Working Party of the International Society of Blood Transfusion[2]

Imputability category*	Definition
Definite (certain)	There is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the transfusion.
Probable (likely)	The evidence is clearly in favor of attributing the adverse event to the transfusion.
Possible	The evidence is indeterminate for attributing the adverse event to the transfusion or an alternate cause.
Unlikely (doubtful)	The evidence is clearly in favor of attributing the adverse event to causes other than the transfusion.
Excluded	There is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to causes other than the transfusion.

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

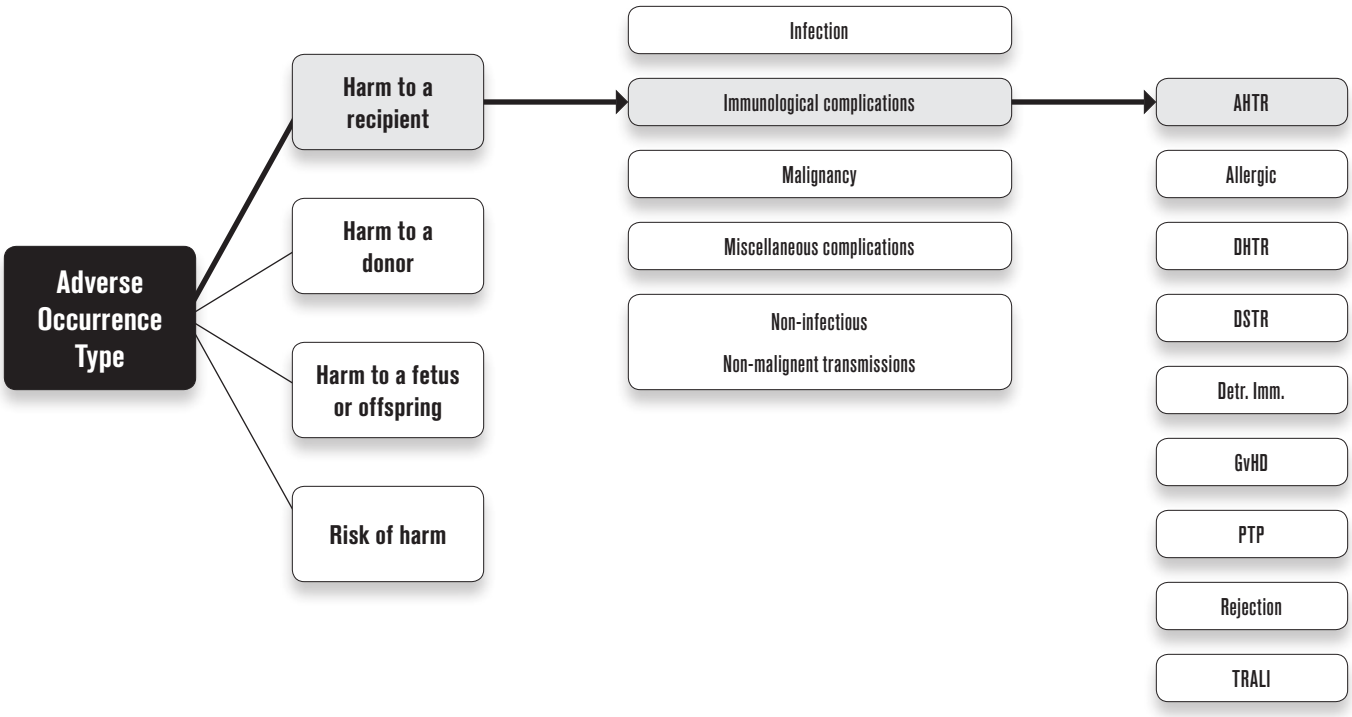

Fig. 1 Adverse occurrence type taxonomy (extract). AHTR = acute hemolytic transfusion reaction; DHTR = delayed hemolytic transfusion reaction; DSTR = delayed serologic transfusion reaction; Detr. Imm. = detrimental immunization; GvHD = graft-versus-host disease; PTP = post-transfusion purpura; TRALI = transfusion-related acute lung injury.

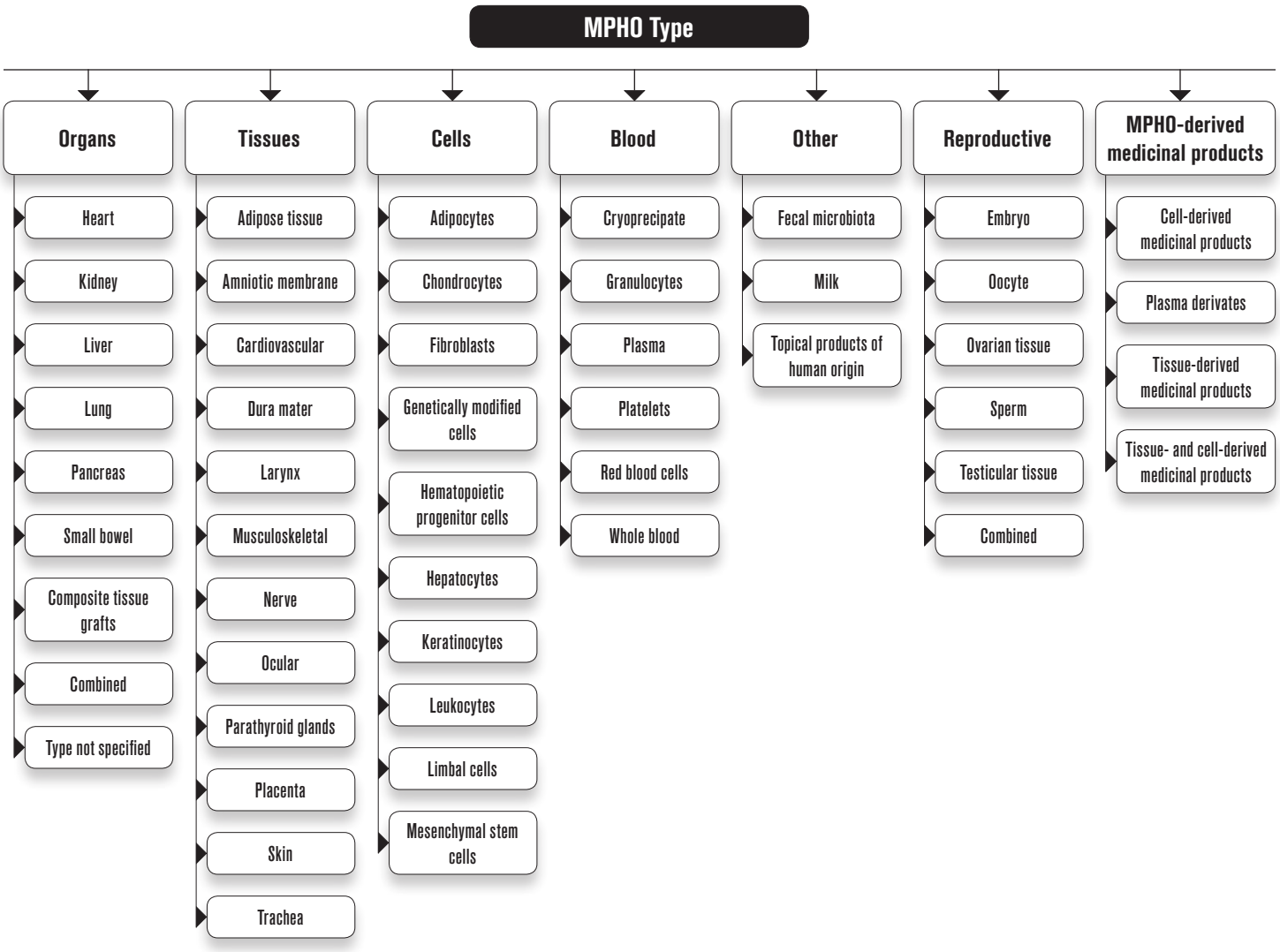

Fig. 2 Medical products of human origin (MPHO) type taxonomy.

groups—adverse occurrence type (harm to a recipient, harm to a donor, harm to a fetus or offspring, risk of harm) and MPHO type (organs, blood, cells, tissues, etc.). Figure 1 provides an extract of the taxonomy for adverse occurrence type. For example, immunological complications are further categorized into AHTRs, allergic reactions, DHTRs, DSTRs, detrimental immunization, graft-versus-host disease, post-transfusion purpura, rejection, and transfusion-related acute lung injury (TRALI). Figure 2 provides the taxonomy applied for MPHO type. This predefined classification enables searching by adverse occurrence type, by MPHO type, or both, as well as by using free text or key words.

Of the current searchable entries in the Notify Library, 68 percent are classified as harm to recipient, 18 percent are classified as harm to donor, 13 percent are classified as risk of harm, and the remaining 1 percent are classified as harm to fetus or offspring. Not surprisingly, among entries relating to recipient harm, 52 percent are subsequently categorized as relating to infection and 17 percent as relating to immunological complications. Of the 331 reports of adverse occurrences associated with the MPHO of blood, 57 percent are related to transfusion of red blood cells, 21 percent to platelets, 11 percent to plasma, 7 percent to whole blood, and 1 percent to granulocytes; the remaining are not specified. Of the 89 percent of blood reports of the occurrence type harm to recipient, 49 percent of reports are immunological in nature (Fig. 3), including DHTRs, AHTRs, DSTRs, TRALI, and allergic reactions.

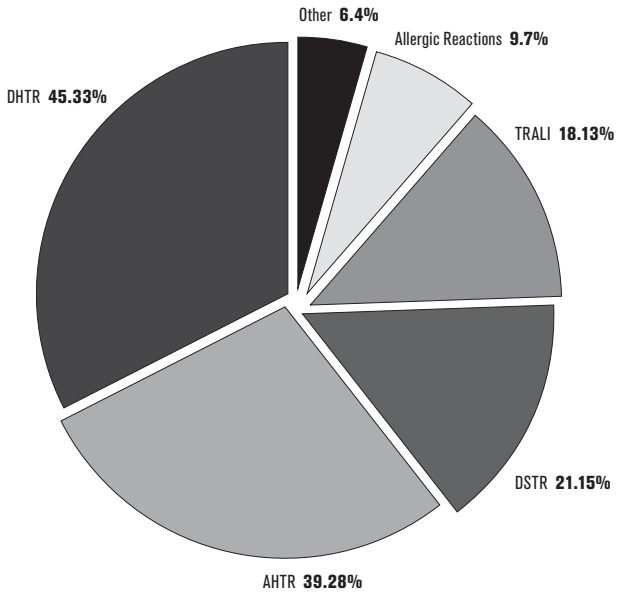

Fig. 3 Immunologic complications described in the Notify Library. TRALI = transfusion-related acute lung injury; DSTR = delayed serologic transfusion reaction; AHTR = acute hemolytic transfusion reaction; DHTR = delayed hemolytic transfusion reaction.

Current Notify Library Activities

Competent authorities for blood, tissues, and cells in the 28 countries of the EU have been approached through the Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART) Joint Action supported by the European Commission and coordinated by CNT (since VISTART includes a specific Work Package on Vigilance Communication dedicated to the Notify Library). Moreover, a directory of vigilance is being created through the WHO regional offices to associate all competent authorities for MPHO at a global level to facilitate member states' access and contribution to the Notify project, building a global network of experts who are learning from each other.

Since the beginning of the project, annual consultations have been organized and, thanks to the collaboration of all editorial group members, the database is regularly updated and the Web site continues to improve. Further tools to support vigilance have been developed over the years, including a comprehensive vigilance document available for download through the related section (Notify Booklet, currently in revision for the inclusion of hemovigilance data) and the ability to access a panel of experts providing support and advice on request via the Notify Web site.

Invitation to Join and Contribute

The Notify Library and the team of professionals associated with its creation and maintenance are a global resource in the area of biovigilance that encourages broad global participation in the project. Access is open to the public. Individual users are encouraged to search and review the contents of the Library. Clinical and laboratory practitioners and students are invited to identify information that might be still missing, to refer new cases, propose new entries, involve students and clinicians from domains outside transfusion and transplantation, recommend references, and even join an editorial group to review new cases. All organizations, authorities, or professional societies that work on the safety and quality of MPHO are invited to support and contribute to this didactic initiative.

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