Chapter 7
Adverse Transfusion Reactions in Critically Ill Patients

Federica Tomasella and Luca G. Mascaretti

As transfusion entered routine clinical practice in the mid-twentieth century, it was apparent that the benefits were counterbalanced by unwanted reactions both of infectious and noninfectious nature [1, 2]. Whereas the former received wide attention also by the general population [3], the latter mainly remained of restricted interest to transfusion scientists (and naturally to the patients). It is a well-known fact that in the past 25 years, blood testing and donor selection have had a notable impact on reducing infectious complications [4, 5] and today, noninfectious adverse reactions to transfusion (NIART) are prevalent. If we look at the UK's Serious Hazards of Blood Transfusion hemovigilance data for 2012 [6], of the 538 cases analyzed only 3 were transfusion-transmitted infections; 372 acute transfusion reactions, 42 hemolytic transfusion reactions, 11 transfusion-related acute lung injuries, and 82 transfusion-associated circulatory overload. Hemovigilance data for our region, Friuli Venezia Giulia (North East Italy), are presented in Table 7.1 [7].

F. Tomasella, MD (✉) • L.G. Mascaretti, MD
Transfusion Medicine Department, University Hospital Trieste,
Strada di Fiume 447, Trieste 34149, Italy
e-mail: federica.tomasella@aots.sanita.fvg.it

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Table 7.1 Adverse transfusion reactions in Friuli Venezia Giulia 2007–2012

Adverse transfusion reactions	2007–2009	2010	2011	2012	Total 2007–2012
Febrile nonhemolytic transfusion reactions (FNHTR)	195	52	70	47	**364**
Allergic transfusion reactions (ATR)	140	39	42	49	**270**
Circulatory overload	20	8	1	3	**32**
Hypotension	14	3	3	3	**23**
Severe dyspnea	4	4	3	1	**12**
Delayed hemolytic transfusion reactions (DHTR)	6	0	1	0	**7**
Anaphylaxis	6	2	1	4	**13**
Transfusion-associated graft versus host disease (TA-GVHD)	1	0	0	0	**1**
Transfusion errors	7	0	5	1	**13**
Transfusion-related acute lung injury (TRALI)	2	0	0	0	**2**
Septic complications	0	1	0	0	**1**
Others	77	15	20	12	**124**
Total adverse reactions	**472**	**124**	**146**	**120**	**862**
Total transfused units	**219,129**	**71,147**	**72,728**	**70,488**	**433,492**
Frequency of adverse reaction per unit (%)	**0.22**	**0.17**	**0.20**	**0.17**	**0.20**

The critically ill patient can be affected by both infectious and noninfectious adverse reactions after a transfusion therapy and the importance of diagnosis is remarkable for the severity of clinical conditions usually treated in an intensive care unit. Transfusion reactions, in fact, can be masked by the severity of the main illness and the lack of active collaboration of the patient [8].

The aim of this chapter is to give an overview of the most common adverse transfusion reactions.

7.1 Infectious Adverse Reactions to Transfusion (IARTs)

IARTs can be caused by viruses, bacteria, and protozoa. Potentially, an undefined number of infective agents are liable to transmit a disease after a transfusion, but we shall consider the most frequent and pathogenic. In this field, it is important to know that not all infectious reactions have the same incidence in different countries, and for this reason the policy of detecting tests varies from USA [9] and Europe, and at the same time among European countries (EU). In this paper, we will focus on Italian policy, which is harmonized with EU regulations.

7.1.1 Viruses

The transmission of viruses after a transfusion therapy is usually due to the presence of the infective agent in the circulation of the donor.

In the past 30 years, the risk of transmitting a virus infection with transfusion has greatly decreased because of the development of microbiological research and new detection techniques (serological and nucleic acid testing (NAT)). At the same time,

more restrictive donor selection criteria and pathogen reduction or inactivation technologies are usually employed to further reduce the risk of infection [10]. Residual risk is due to asymptomatic donors who donate in the "window period."

Table 7.2 summarizes information related to the principal virus infections potentially transmitted by transfusion.

7.1.1.1 Management

It is useful for ICU specialists to know the main transfusion-related viral infections. In fact, differently from the main immunological adverse reactions, the symptoms of IARTs can appear some days after transfusion and can be confused with the main disease. Particularly, it is necessary to pay attention to patients with a compromised immunological system who need immediate therapy to stop virus replication.

7.1.2 Bacteria

Bacteria infections following transfusion (Table 7.3) are often derived from microbial flora present on donor skin which contaminate blood products. They can also be due to systemic bacterial infections, though this is a rare event. From 2008, the Italian National Blood Center recommends using the first 40 ml of collected blood for testing, diverting it in tubes during withdrawal.

Regarding the kind of blood components, platelet concentrates are more frequently involved in IARTs, because their storage is at room temperature (22 ± 2 °C). However, medical and nursing staff must inspect the blood component before administration to check for integrity of bags, hemolysis, change in color, gas formation, and clots. Any of these findings must be communicated to the transfusion center to which the product must be returned.

Table 7.2 Main viruses involved in IARTs

Virus	Symptoms	Risk of IARTs	Policy of donor testing and deferral
Hepatitis A virus (HAV) [11]	Only acute phase with jaundice, hepatomegaly, dark urine, anorexia, malaise, fever, nausea, abdominal pain and vomiting	Rare. The transmission is fecal–oral and usually the donor is symptomatic in viral phase. Vaccine is available	No test in routine
Hepatitis B virus (HBV) [11]	The incubation phase is 30–180 days. After this acute phase, sometimes fulminant effect, and in some cases chronic progression (10 %)	Transmission is parenteral, sexual, and perinatal. Vaccine is available	HBsAg serological assay and HBV-DNA NAT
Hepatitis C virus (HCV) [11]	The incubation phase is 15–160 days. The acute phase can be often asymptomatic and chronic progression (50–70 %) is more frequent	Actual residual risk in Italy 0.2×10^6 [12]. Transmission is parenteral, sexual, and perinatal. Vaccine is not available	HCV antibody serological assay and HCV-RNA NAT
Hepatitis D virus (HDV) [11]	The infection is possible only in the presence of HBV. The acute phase can be more severe because of coinfection	Data not available, and in any case lower than hepatitis B	Tests performed for HBV are suitable to prevent the infection

(continued)

Table 7.2 (continued)

Virus	Symptoms	Risk of IARTs	Policy of donor testing and deferral
Human Immunodeficiency Virus (HIV) 1–2 [13]	The incubation phase is 7–28 days. Acute phase with fever, malaise, skin rashes, lymphoadenopathy. After that asymptomatic period for years with persisting viremic phase until the loss of CD4+ lymphocytes	Actual residual risk in Italy 0.4×10^6 [12]. Transmission is parenteral, sexual, and perinatal. Vaccine is not available	HIV 1–2 antibody serological assay and HIV-RNA NAT
Human T-cell Lymphotropic Virus (HTLV) [13, 14]	Most infections are asymptomatic. In some cases tropical spastic paraparesis, T-cell leukemia–lymphoma	Very rare in Italy. Present in tropical areas and Japan. Transmission is parenteral, sexual, and perinatal. Vaccine is not available	Not tested routinely
Cytomegalovirus (CMV) [15]	Acute phase quite asymptomatic or self-limited with fever, malaise, hepatosplenomegaly, and skin rash in immunocompetent patients. The infection is very frequent and increases with age.	Not clinically significant in immunocompetent patients. Dangerous if perinatal and after transfusion in premature infants and hematopoietic stem cell transplantation patients	Serological detection of antibodies in donors and reserved negative blood components for critical situations

West Nile Virus (WNV) [16]	The incubation period is within 28 days after contact and the only acute phase can be asymptomatic or presents fever, headache, vomiting, lymphocytopenia, muscle weakness, and headache. Sometimes sign of peripheral demyelinization and in elderly severe neurological disease	Transmitted through mosquitoes. Vaccine is not available	NAT testing for blood donors coming from endemic areas, usually limited to the warm season
Dengue	The infection is characterized by a different range of outcomes, from asymptomatic viral spread, a mild fever, or a shock syndrome. The first viral phase can be asymptomatic.	Transmitted through mosquitoes in tropical areas. Vaccine is not available	Not tested routinely. NAT testing is available, but usually deferral of donors coming from endemic areas for 28 days

Table 7.3 Main bacteria involved in IARTs

Bacteria	Symptoms	Contamination source and risk	Policy of donor testing and deferral
Treponema pallidum	Agent of syphilis. Incubation period about 7–21 days. Primary phase with the presence of ulcer in the injection site and regional lymphoadenopathy (not present in IARTs). Secondary phase after months with skin rash and later phase after years with neurological and cardiovascular symptoms	Donor blood. Transmission is parenteral, sexual, and perinatal	Antigen serological assay
Staphylococcus spp., *Pseudomonas* spp., *Escherichia coli*, *Enterobacteriacea*	Usually high fever (more than 2 °C), chills, malaise, and diffuse pain	Skin of the donor or devices	Isolation of the agent with microbiological techniques
Borrelia burdgoferi	The agent of Lyme disease. The transmission is by ticks in a sylvatic cycle involving primates. In an early phase a characteristic skin rash is present, while in the later one, after years, neurological and cardiovascular symptoms	Blood of the donor for IARTs.	After tick contact, a donor is deferred for 40 days to donation. If symptoms appear, antibiotic treatment is mandatory until serological resolution

7.1.2.1 Management

Several bacteria are involved in IARTs, but symptoms of infection are usually the same like high fever (an increase >2 °C), chills, malaise, and diffuse pain. If the symptoms appear during transfusion, therapy must be stopped and the residual blood component sent to the transfusion center. It is mandatory to perform a blood culture for identification of microbial agent and begin immediately an antibiotic and antipyretic therapy. Following the laboratory result, pharmacological therapy can be modified to become more effective.

7.1.3 Protozoa

The transmission of protozoa after transfusion is unequivocally due to the presence of the agent in the circulating blood of the donor. Sometimes it is not easy to identify infective donors, because some of these protozoa give no symptoms for years. In Italy, donor selection criteria specify a period of deferral for individuals who were born or visited endemic areas. The main problem with protozoan infections is the globalization in tourism and immigration from countries in which infection is endemic (Table 7.4).

7.1.3.1 Management

A protozoan infection can be detected with a peripheral blood smear which may be followed by a serological assay. The precision of diagnosis is very important for a timely treatment, because often the acute phase is severe and involves different body systems. Chemotherapy is targeted for each different agent and in all cases the diagnosis must be notified to the transfusion center.

Table 7.4 Main protozoa involved in IARTs [17]

Protozoa	Symptoms	Risk of IARTs	Policy of donor testing and deferral
Plasmodium spp.	Agent of different types of malaria. Acute phase of recurrent high fever, hemolysis, chills, jaundice, and hepatosplenomegaly. Possible chronic phase asymptomatic for years	Rare in Italy (not endemic area)	Serological assay, not used routinely. Deferral for 6 months for travellers, 5 years for immigrants from endemic areas. After the disease, the donor is deferred for 3 years after which only plasma for industrial purposes can be donated
Trypanosoma cruzi	Agent of Chagas' disease. Acute phase is self-limited, but chronic phase can be asymptomatic for years until development of gastrointestinal and cardiac symptoms	Rare in Italy (not an endemic area)	Serological assay, not used routinely. Deferral for 3 months for travellers, 5 years for immigrants from endemic areas
Toxoplasma gondii	Acute phase quite asymptomatic in immunocompetent patients. The infection is very frequent and increases with age	Not clinically in immunocompetent patients. Dangerous in pregnancy, immunocompromised individuals like premature infants and hematopoietic stem cell transplantation patients	Serological assay in some donors. Usually leukoreduction of blood components

7.1.4 Emerging Infections

In the past years, numerous emerging infections have been described in different areas of the world. Because of globalization of travel and immigration, it is a challenge for transfusion centers in the prevention of emerging IARTs [18].

The variant of Creutzfeldt–Jakob Disease (vCJD) is transmissible spongiform encephalopathy. Like the primitive CJD, it results from the changing of a prion protein into a protease-resistant form (PrP Sc). Originally, bovine spongiform encephalopathy affected cattle. The use of animal protein in bovine feed diffused the disease in cows. Successively, meat consumption by humans was responsible for the variant of Creutzfeldt–Jakob Disease, which has an earlier onset with neurological manifestations, dementia, and death in 7–38 months. At present, there are no invasive tests available for donors or patients and diagnosis is mainly confirmed postmortem. The policy for blood collection consists in deferring donors who lived in the UK (the area of first onset of the disease) from 1980 to 1992 and donors who present neurological diseases [19].

Severe Acute Respiratory Syndrome (SARS) is a recent disease emerged explosively in Asia in 2004. The coronavirus agent can cause pneumonia with rapid onset and is often fatal. The transmission by transfusion is not clearly detected, but it can be possible in the asymptomatic viral phase. Quarantine and traveler surveillance is employed in airports during the endemic period.

Middle East Respiratory Syndrome (MERS) is due to another *coronavirus* identified in Saudi Arabia in 2012. The virus can affect many types of animals, but recently dromedaries seem to be the most important source of infection for humans. Actually interhuman transmission is not demonstrated. Most infected patients report a severe respiratory disease with acute renal failure and high fatal rates [20]. As during SARS

pandemia, travelers' surveillance in airports is important in the endemic periods.

Xenotropic murine leukemia virus-related virus (XMRV) is a recent discovery and reported in uncertain association with chronic fatigue syndrome (CFS). This disease can potentially be transmitted by transfusion, but more extensive studies are needed to define the pathology [21].

7.1.5 A General Comment

Medical doctors when faced with an infectious disease in a hospitalized patient should always collect an accurate clinical history that must include transfusion of blood components and take into consideration that the viral/bacterial/protozoan infection could be related to a transfusion event. If a transfusion-transmitted infection is suspected, the clinician must contact the transfusion center that will provide a look-back of the blood products and a follow-up of the involved donors.

7.2 Noninfectious Adverse Reactions to Transfusions (NIARTs)

There are many excellent reviews on noninfectious transfusion complications published in journals or as chapters in textbooks [22–24], and this paper does not intend duplicating them. Our aims are to illustrate different criteria with which NIARTs have been classified, mention the most important pathogenetic mechanisms involved, suggest organizational measures that hospitals may adopt to manage NIARTs, and discuss the laboratory's support for NIART diagnosis. Although NIARTs have different grades of severity, it must be underlined that most adverse reactions can occur in critically ill patients.

7.2.1 Classification of NIARTs

There are different ways in which NIARTS can be classified: according to time of presentation (acute, within 24 h or delayed, after 24 h from the transfusion event) or according to pathogenesis (immunologic vs. nonimmunologic). Whereas the former is a more practical classification oriented to clinicians, the latter is of greater interest for the transfusion scientist.

Classification of NIARTs according to pathogenesis (with the exception of transfusion errors, see following paragraph) is presented in Table 7.5.

It may be incorrect to include transfusion errors in Table 7.5, mainly because part of transfusion errors (those which are AB0 incompatible) would be registered under acute hemolytic reactions. However, since transfusion errors are an important source of adverse reactions we believe that it is useful to keep a focus on this type of unwanted event.

Klein and Anstee [24] use a more specific "pathogenetic" classification criterion in that they divide NIARTs into those due to red cell incompatibility, leukocyte antibodies, platelet antibodies, reactions to transfused proteins, and nonimmunological reactions.

7.2.2 Pathogenesis of NIARTs

The aim of this section is to give an overview of the main NIARTs, irrespective of their severity.

Tables 7.6 and 7.7 summarize the main mechanisms responsible for immunological and nonimmunological NIARTs, respectively, as well as the incidences as reported in literature. As far as the latter are concerned, it should be kept in mind that correct estimates are very difficult to obtain and vary according to clinical setting, accuracy of reporting, type of blood component transfused, and whether a transfusion event or number of

Table 7.5 A classification of NIARTS

Mechanism	NIART
Immunological	Acute hemolytic transfusion reaction
	Delayed hemolytic transfusion reaction
	Allergic transfusion reaction
	Anaphylaxis
	Febrile nonhemolytic transfusion reactions (FNHTRs)
	Platelet refractoriness
	Transfusion-associated graft versus host disease (TA-GVHD)
	Transfusion-related acute lung injury (TRALI)
	Posttransfusion purpura (PTP)
	Immunomodulation
Nonimmunological mechanisms	Septic complications
	Red cell hemolysis
	Circulatory overload
	Iron overload
	Hypotension
	Metabolic complications
	Citrate toxicity and hypocalcemia
	Hypothermia
Errors (misidentification, clerical mistakes, etc.)	Transfusion errors (transfusion of a unit to the wrong patient)

units are considered in the denominator. A specific reference is included for all NIARTS.

7.2.3 Transfusion Errors

Transfusion of a RBC unit to the "wrong patient" is a very significant problem in transfusion medicine although it is only part of a wider problem of hospital adverse events due to misidentification [35]. It is estimated that a transfusion error

Table 7.6 Pathogenesis of NIARTs with an immunological mechanism

NIART	Pathogenesis in brief	Incidence
Acute hemolytic transfusion reaction [25]	Binding of recipient antibodies (usually anti-A, anti-B, or anti-A,B) to incompatible RBCs. Activation of complement cascade, intravascular RBCs lysis, release of Hb in plasma. DIC. TRANSFUSION ERRORS MAIN UNDERLYING CAUSE	1:38,000–1:70,000
Delayed hemolytic transfusion reaction [25]	Usually secondary immune response with increase in antibody titres following "re-challenge" with incompatible RBCs. No complement activation or only up to C3. Destruction of RBCs occurs in extravascular space by MPS (mainly spleen and liver). Drop in Hb, increase in bilirubinemia 3–15 days posttransfusion	1:5,000–1:11,000
Allergic transfusion reaction [24]	Mild IgE-mediated reactions against soluble substances present in plasma; release of histamine leads to urticaria and pruritis	1:100–1:33
Anaphylaxis [26]	Severe IgE-mediated reactions against plasma proteins. Histamine and other biological mediators are responsible for severe systemic reactions, which lead to laryngeal edema, lower airway obstruction, hypotension. Recipients with congenital IgA deficiency are particularly at risk; in this case, the reaction is mediated by high-titre anti-IgA	1:20,000–1:50,000
Febrile nonhemolytic transfusion reactions [27]	Anti-HLA or other anti-leukocyte antibodies react with WBCs present in RBC or platelet units. Complement binding leads to WBC lysis and release of pyrogens (TNF-α, Il-1, Il-6). Transfusion of "old units" (mainly platelets) containing cytokines may also be responsible	PLTs:1:100

(continued)

Table 7.6 (continued)

NIART	Pathogenesis in brief	Incidence
Platelet refractoriness [28]	HLA antibodies (due to previous pregnancies, transplants, or transfusions) are more commonly implicated, followed by anti-ABO or anti-HPA. Platelets become coated with HLA antibodies and are then removed by MPS	Not available
Transfusion -associated graft versus host disease [29]	Viable lymphocytes present in transfused unit are not recognized as foreign and exert an alloimmune response toward the recipient's cells leading to rash, abdominal pain, diarrhoea, liver function abnormality, and bone-marrow suppression 2–30 days following transfusion	Not available (very rare)
Transfusion-related acute lung injury [30]	Donor anti-HLA or anti-granulocyte antibodies bind to the host's granulocytes causing pulmonary leucostasis and complement-mediated leucocyte activation. This leads to endothelial damage in pulmonary capillaries through release of proteolytic enzymes and toxic oxygen metabolites from neutrophils. Alternative hypothesis: cumulative effect of 2 conditions: First, adherence of patient's neutrophils to pulmonary vascular endothelium and second, presence of lipids or cytokines or leucocyte antibodies in transfused plasma cause further neutrophil activation and endothelial damage	1:5,000–1:190,000
Posttransfusion purpura [31]	Anti-platelet antibodies (usually anti-HPA-1a) in recipient react with transfused platelets leading to their elimination. The reaction, however, for some as yet unexplained mechanism may also regard the patient's own platelets	Not available (very rare)
Immunomodulation [32]	Is matter of controversy. Donor factors (WBCs or other) would be responsible for immunosuppression in host	Not available

Table 7.7 Pathogenesis of NIARTs with nonimmunological mechanism

NIART	Pathognesis in brief	Incidence
Septic complications [33]	Transfusion of unrecognized septic blood components, mainly platelets	Not available
Red cell hemolysis (nonimmunological) [25]	Transfusion of RBCs damaged by excessive heating or freezing/thawing. Inappropriate administration of medication simultaneously to RBC units. Transfusion of contaminated RBC units or RBCs from donors with congenital RBC defects (G6PD deficiency)	Not available
Circulatory overload [34]	Occurs in patients with compromised cardiac status who cannot cope with increased intravascular volume; if cardiac output cannot be maintained, pulmonary edema results	<1 %
Iron overload [24]	Is seen in multitransfused patients and is due to the fact that iron intake with transfusions is very high compared with the capability of excretion (1 unit contains ~200 mg of iron whereas daily excretion amounts to 1 mg). Chelation therapy is essential to limit damage related to deposit of iron in vital organs (heart, pancreas, liver, gonads, etc.)	In all cases of multitransfused recipients. Variable degree
Hypotension due to ACE inhibitors [23]	Patients receiving ACE drugs may experience hypotension if transfused with components (mainly platelets) filtered with bedside leukoreduction filters. Bradykinin is a vasodilatory peptide which is released when blood comes into contact with negatively charged surfaces	Not available

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Table 7.7 (continued)

NIART	Pathogenesis in brief	Incidence
Metabolic complications [24]	Neonates and small children are mainly at risk. Increase in potassium, ammonium. Acidosis. Changes in RBCs occur as units age (storage lesion)	Not available
Citrate toxicity and hypocalcemia [24]	Transfusion of large volumes of citrated blood may lead to a decrease of ionized calcium levels which can have a negative effect on cardiac contractility	Not available
Hypothermia [24]	May occur when large volumes of cold blood are transfused at high rates mostly to neonates and children	Not available

RBC red blood cells, *Hb* hemoglobin, *HLA* Human Leukocyte Antigens, *WBCs* white blood cells, *HPA* Human Platelet Antigens, *MPS* Mononuclear Phagocyte System, *ACE* Angiotensin Converting Enzyme, *DIC* disseminated intravascular coagulation

occurs about 1:16,000 transfused units, and in the majority of cases it is due to misidentification of the patient. An AB0-incompatible transfusion error will occur 1:33,000 units; 50 % of these will give rise to hemolysis but the mortality incidence due to an incompatible transfusion is calculated as being 1:800,000 [4]. These figures are surely underestimated due to the legal implications of reporting a transfusion-associated mistake. It is interesting to note that the Joint Commission International accreditation system [36] quite rightly consider transfusion errors as "sentinel events," which implies that a thorough root-cause analysis must be performed in the health facility where the event occurs. Today, technology for the prevention of transfusion errors is available [37] and hospitals should consider its implementation.

7.2.4 Organizational Measures for the Management of NIARTs

Every health facility practicing transfusion therapy should have a system in place to ensure the highest possible level of safety for the patients. Figure 7.1 depicts the main critical points for a safe transfusion. Transfusion requests originate in the ward and clinicians first of all should ask themselves whether their patient does in fact need the transfusion. This means that clinicians should rely on guidelines for which there is a wide consensus on the appropriate use of blood. An important role in this regard is played by the Hospital Transfusion Committee, which is the ideal forum in which these documents are prepared and shared by the hospital medical staff. Clinicians should always bear in mind that the safest transfusion is the one which is not performed. A written request form must be made specifying correct patient data (name, surname, place, and date of birth), condition requiring transfusion, ward, type and number of blood components required, urgency of transfusion, blood group and

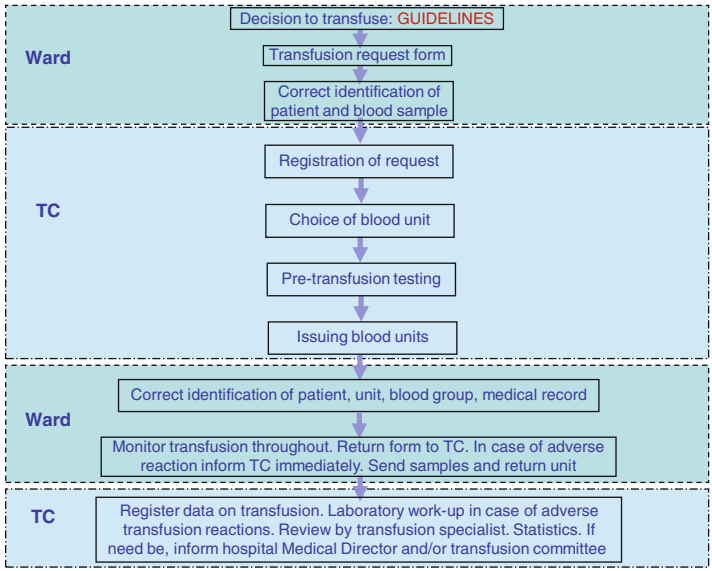

Fig. 7.1 Duties and responsibilities of ward and transfusion center (*TC*) in order to guarantee a safe transfusion

red blood cell antibody status if previously determined, history of sensitization episodes, previous NIARTs, signature of medical doctor. Fulfilling the request form correctly is the first step toward a safe transfusion. The second step relates to withdrawing blood samples; patient must be identified at the bedside; when possible the patient should be asked his/her name and surname and date of birth, otherwise the patient record must be used. Here again it must be pointed out that many transfusion errors are made at this truly critical point. Traceability (an important ingredient of safety) is enhanced by bar codes on the request form and sample labels. Moreover, as far as AB0 and Rh testing is concerned, it should be performed previous to the request form on a separate blood sample. This is to reduce the

risk of mistakes due to swapping of patients. The nurse or medical doctor who withdraws blood should sign the label on blood sample tube to testify that patient identity has been checked.

The request form and sample is then sent to the transfusion center; the date and time of arrival must be registered and the coherence of data reported on the request form and on the sample label checked. Each center should have a policy that clearly states when samples should be rejected. Transfusion centers should have computer software (with adequate backups) on which to store patient data (as already mentioned, barcodes are very useful and should be used whenever possible). The best softwares are those that allow a complete traceability "from vein to vein" (donor to recipient) thus permitting to perform look-back studies should it be necessary.

The transfusion technician should check that the patient for whom blood components are being requested has been tested for AB0 and Rh and has undergone red cell antibody screening (if red blood cells are needed). The transfusion center should have a Standard Operating Procedure (SOP) in place specifying what type of compatibility testing is performed for which type of patient (e.g., type and screen for nonimmunized recipients, cross-matching for immunized patients). The SOP should also specify what tests should be performed in case of very urgent cases. Once the request form is registered, pretransfusion testing can be performed. If we consider safety at 360° as it ought to be, we must also mention that quality of testing plays a major role in transfusion safety. This means that a quality management system should be in place in the immunohematology laboratory foreseeing SOPs for all activities (testing, blood component preparation, and storage), internal quality control on reagents and blood components (including sterility), external proficiency testing (for blood groups, antibody screening, and identification), maintenance program for instruments, a training program for the staff, and a quality improvement scheme.

Once testing is completed (an AB0 direct test should be performed on all samples accompanying the request form), compatible units are chosen according to an SOP; this document should also state in which conditions nonideally compatible units can be issued (e.g., group 0 Rh positive red blood cell units for 0 Rh negative recipients). The issuing of blood components should be registered on the software, which also prints a form that accompanies the units on which patient data number and blood group of unit are reported. This "transfusion form" ideally should be divided in two with one section that must be returned to the transfusion center testifying that the patient has been transfused; should adverse reactions be observed, these should be registered on this form. Units are then sent to the ward (in appropriate containers at controlled temperature). Before transfusion, personnel (in Italy a nurse and medical doctor) should check, with the aid of a checklist, the patient's identity (possibly asking name, surname, and date of birth), blood group on patient record, blood unit label, and transfusion form. This check is pivotal for the safety of transfusion since it is the last chance for a transfusion error to be stopped. In fact, it has been published many times that a superficial pretransfusion check at the patient's bedside is the single most frequent cause of transfusion mistakes.

Transfusion then starts and must be monitored for the appearance of adverse reactions. It is of fundamental importance for clinicians and nurses who are directly involved in transfusing patients to be aware of the different NIARTs in order to recognize them promptly and give appropriate treatment. It is a good measure to register in the patient's record the blood pressure, heart rate, and temperature before and after the end of transfusion. One of the difficulties concerns differential diagnosis of NIARTs in that many signs and symptoms are common to more than one reaction; Table 7.8 reports some signs and symptoms of NIARTs (for a more thorough description see specific references).

Table 7.8 Some signs and symptoms of more common NIARTs

NIART	Onset	Fever	Urticaria/ rash	Shock	Respirat. distress/ dyspnea	(Shaking) chills	Increase bilirubinemia	Drop Hb	Drop PLTs	Hemoglobi-nemia	Hemoglo-binuria	DIC
Acute hemolytic transfusion reaction	Immediate	X		X	X	X				X	X	X
Delayed hemolytic transfusion reaction	3–10 days	X					X	X				
Allergic transfusion reaction	Immediate		X									
Anaphylaxis	Immediate			X	X							
Febrile nonhemolytic transfusion reaction	Immediate	X				X						
Transfusion-associated graft versus host disease	2–30 days		X				X					

(continued)

Table 7.8 (continued)

NIART	Onset	Fever	Urticaria/ rash	Shock	Respirat. distress/ dyspnea	(Shaking) chills	Increase bilirubinemia	Drop Hb	Drop PLTs	Hemoglobi-nemia	Hemoglo-binuria	DIC
Transfusion-related acute lung injury	<6 h	X			X							
Posttransfusion purpura	5–10 days								X			
Circulatory overload	Immediate				X							

A second difficulty concerns the fact that fortunately, the majority of NIARTs are rare events and therefore personnel may have little experience in dealing with them. Third, in some cases (patients in intensive care units for example) symptoms may be heavily modified by the patient's clinical condition (hemoglobinuria may be the only sign of an acute hemolytic transfusion reaction in patients under anesthesia). Finally, for reactions occurring at considerable time period from transfusion (post-transfusion purpura, delayed hemolytic transfusion reaction, transfusion-associated graft vs. host disease), establishing a link between symptoms and the transfusion event may not be so obvious.

Once an acute NIART is suspected or diagnosed (during transfusion), TRANSFUSION MUST BE STOPPED IMMEDIATELY, but a line must be kept for infusion if necessary. The transfusion center must be promptly informed and a blood sample together with the remains of the transfusion unit must be sent to the transfusion center together with a description of signs and symptoms (on transfusion form). Treatment must be started immediately and specialized opinion may be sought from an intensive care unit specialist or from a nephrologists or other specialist. A synthesis of the most important therapeutic and preventive strategies for immunologic NIARTs is shown in Table 7.9. Data regarding any NIART should be registered on the patient's medical record for future preventive measures.

7.3 Concluding Remarks

Blood transfusion is a complex procedure and guaranteeing a safe transfusion requires a joint effort from the clinician and transfusion specialist. As we all know, a "zero risk" transfusion does not exist and thus risk management systems must be implemented since knowing the extent of risk is the first step for

Table 7.9 Therapy and prevention for some immunological NIARTs

NIART	Therapeutic strategy	Preventive strategy
Acute hemolytic transfusion reaction	STOP TRANSFUSION, support blood pressure (low dose dopamine), support urine output (diuretics). Plasma if needed to correct DIC. Analgesics if necessary	Correct patient identification at all stages. Infuse slowly at beginning of transfusion
Delayed hemolytic transfusion reaction	Usually no treatment is necessary. Antipyretics	Patient in successive transfusions must receive cross-match negative, antigen negative RBCs
Allergic transfusion reaction	Interrupt transfusion; administer antihistamines (oral or IV). If urticaria and pruritis disappear, try continuing slowly	Premedication with anti-histamines. Steroids if severe. For refractory cases, use washed RBCs or PLTs.
Anaphylaxis	STOP TRANSFUSION. Epinephrine, antihistamines, steroids, fluids, oxygen	For IgA-deficient patients, use IgA-deficient blood components
Febrile nonhemolytic transfusion reaction	STOP TRANSFUSION, antipyretics	Premedication with antipyretics, leukocyte-reduced components
Platelet refractoriness	Monitor platelet counts at 1 and 24 h posttransfusion. Rule out nonimmunologic factors	HLA compatible platelets or cross-match negative platelets
Transfusion-associated graft vs. host disease	Rarely therapy is effective (steroids, immunosuppressive agents)	Gamma-irradiation of cellular blood components for selected cases
Transfusion-related acute lung injury	STOP TRANSFUSION. Oxygen, support respiration, Intensive Care Unit for intubation	Defer donors implicated in TRALI cases
Posttransfusion purpura	Intravenous immunoglobulin	For successive transfusions, use HPA compatible platelets

controlling it. This means that statistics must be prepared on all types of NIARTs and discussed at the Transfusion Committee. One of the obstacles that prevent NIARTs from being successfully managed is underreporting; this is due to underrecognition in the ward but also due to a reticence from clinicians who may be worried that, for example, a transfusion error may lead to legal problems. An anonymous form for adverse event reporting must be available in the wards. Clinicians must feel adequately supported by the transfusion laboratory which must perform all necessary tests in a timely manner. The final word goes to training; continuous updating and "refresher" courses should be given to both nurses and doctors working at the patient's bedside as well as to personnel working in transfusion centers to allow prompt recognition, laboratory diagnosis, effective treatment, and implementation of prevention strategies in order to guarantee an as-safe-as-possible transfusion for our patients.

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