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# Transfusion in Transplantation

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.69260>

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## Abstract

Hematopoietic stem cell transplantation is increasingly performed in several diseases; majority of them are hematologic malignancies. Hematopoietic stem cell transplantation is not an instant procedure; contrarily, its unique clinical and laboratorial consequences may take life-long time. Blood product transfusion is an inevitable and critical component for the management. Hematopoietic stem cell transplant patients have different requirements regarding blood products transfusion because of their immune status, long-term cytopenias and especially HLA and ABO incompatibilities. Health-care staff who take a part in the management of those patients should be aware of specific and specialized transfusion requirements.

**Keywords:** transfusion, hematopoietic stem cell transplantation, allogeneic, autologous, blood products

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## 1. Introduction

### 1.1. Definition of hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is the procedure that is transplantation of multipotent hematopoietic stem cells, which are derived from bone marrow, peripheral blood, or umbilical cord blood [1]. Autologous HSCT (Auto-HSCT) is transplantation of stem cells, which are collected from the patient by apheresis and stored in a freezer for a while. Before re-transplantation of patients own stem cells, patient should be treated with high-dose chemotherapy (sometimes also with radiotherapy) in order to eradicate malignant cell population in the body. According to the intensity of chemo and radiotherapy to destroy bone marrow, this procedure may be partial or complete myeloablative. After myeloablation, bone marrow

Leukemias	Lymphoid malignancies	Other diseases
AML	DLBCL	Acquired SAA
ALL	MCL	Acquired AA/PNH
CML	FL	Constitutional SAA
		<ul style="list-style-type: none"><li>• Fanconi anemia</li><li>• Dyskeratosis congenita</li></ul>
Myelofibrosis	WM	Germ cell tumors
MDS	TCL	Ewing's sarcoma family of tumors
CLL	Primary CTCL	Multiple sclerosis
	HL	Systemic scleroderma
	MM	Systemic lupus erythematosus
	AL	Crohn's disease
		Rheumatoid arthritis
		Vasculitis
		Polymyositis-dermatomyositis
		Cytopenias

*Note:* AA = aplastic anemia, AML = acute myeloid leukemia, ALL = acute lymphoid leukemia, AL = amyloidosis, CML = chronic myeloid leukemia, CLL = chronic lymphocytic leukemia, CTCL = cutaneous T-cell lymphoma, DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, HL = hodgkin lymphoma, MCL = mantle cell lymphoma, MDS = myelodysplastic syndrome, MM = multiple myeloma, PNH = paroxysmal nocturnal hemoglobinuria, SAA = severe aplastic anemia, TCL = T-cell lymphoma, WM = waldenstrom macroglobulinemia.

**Table 1.** Indications of HSCT for adults.

is supposed to be free of malignant cells. Patient's own stem cells then reinfused via his/her venous vascular access in order to locate bone marrow and maintain normal hematopoiesis. Patient have the risk of infection during leukopenia, but it is lower in auto- than allo-HSCT because imunosuppression is milder in auto-HSCT. Graft versus host disease (GVHD) is the condition in which white blood cells in the graft (donated blood product) recognize the host as a foreign particle and attack the host's cells. GVHD is so rare but possible in auto-HSCT although the host and the graft are genetically same. Donor in allo-HSCT is another healthy person whose HLA (human leukocyte antigen) type is matched with the recipient. HLA gene complex encodes the major histocompatibility complex (MHC) cell-surface proteins, which regulate immune system. Transplant reactions occur according to the compatibility of HLAs between donor and the recipient. Allogeneic transplant donors can be syngeneic (identical twin), HLA-identical sibling, other family member or unrelated donor (from a volunteer). 10/10 or 8/8 identical donor based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1) is defined as well-matched unrelated donor. A mismatched unrelated donor means that at least one allele at HLA-A, -B, -C or -DR are mismatched [2]. Related donors are relatives or siblings of the patient. Unrelated donors are available by national or

Hematological malignancies	Non-malignant disorders; solid tumors
AML	Primary immunodeficiencies
ALL	Thalassemia
CML	Sickle cell disease (high risk)
NHL	Aplastic anemia
HL	Fanconi anemia
MDS	Blackfan-Diamond anemia
	Chronic granulomatous disease
	Kostman's disease
	MPS-1H Hurler
	MPS-VI Maroteaux-Lamy
	Osteopetrosis
	Autoimmune diseases
	Germ cell tumor
	Ewing's sarcoma
	Soft tissue sarcoma
	Neuroblastoma
	Wilm's tumor
	Brain tumors

AML = acute myeloid leukemia, ALL = acute lymphoid leukemia, CML = chronic myeloid leukemia, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, MDS = myelodysplastic syndrome, MPS = mucopolysaccharidosis.

**Table 2.** Indications of HSCT for children.

international bone marrow donor programs. Syngeneic donor means the monozygotic twin of the patient who is full HLA-matched. Umbilical cord blood is an alternative source for hematopoietic stem cell. It is a kind of allo-HSCT which is usually limited to children and the dose of the infused cells are very low [3]. Because of the similarity between allo-HCST, we will not separately discuss transfusion in umbilical cord blood transplantation.

## 1.2. Indications for HSCT

HSCT is widely performed in hematologic malignancies but also indicated in other solid tumors, and non-malignant diseases. Here are the lists of indications of HSCT for adults and children according to the sixth report from the European Society for Blood and Marrow Transplantation (EBMT) [2] (**Tables 1** and **2**). Because of the wide range of under-investigation indications, we only list diseases for which HSCT is standard of care, generally indicated in suitable patients or clinical option that can be carried after careful assessment of risks and benefits.

## 2. Transfusion in transplantation

HSCT patients need transfusion of blood products before, during and after the transplantation period. As a consequence of increase in the number of HSCTs, need for transfusions increased in the hospitals where transplantations are performed and also other health care centers that are involved in managing these patients. Transfusion in HSCT has unique features such as alloimmunization, ABO-mismatched transplantations, infections and more that will be discussed in detail.

### 2.1. Before transplantation

Recipients of HSCT require special blood components such as leukocyte-reduced, cytomegalovirus (CMV) negative and  $\gamma$ -irradiated blood components [4, 5].

#### 2.1.1. Leukocyte-reduced erythrocyte and platelet components

Leukocyte reduction from erythrocyte and platelet products prevents febrile, nonhemolytic transfusion reactions, alloimmunization to HLA antigens and transfusion-transmitted cytomegalovirus (CMV) infections. HLA alloimmunization means formation of antibodies against non-self HLA antigens. Anti-HLA antibodies are inducible by multiple pregnancies and transfusion of blood products (especially if they are not leukocyte-reduced). These antibodies are problematic in HSCT recipient because of the resistance or refractoriness to platelet/erythrocyte transfusion and also cause cross-match positivity against HLA antigens [6]. HLA crossmatch positive allo-HSCT may result with primary graft rejection [6]. Leukocyte reduction filters are not completely effective, some leukocytes and membrane fragments are able to pass through them [5]. In spite of insufficiency to prevent HLA alloimmunization, transfusing only leukocyte-reduced erythrocyte and platelet components to pretransplantation patients is one of the few tools available to potentially reduce the risk of platelet transfusion refractoriness [7].

#### 2.1.2. CMV infection

CMV serology status of both donor and the recipient is important components of transplantation. CMV transmission from blood products into immunocompromised patients such as transplant recipients can cause fatal infection. Current technologies in prevention of transmission include: provision of CMV-seronegative blood components; postdonation leukocyte reduction filters; and pathogen inactivation, for example, photodynamic therapy with psoralens and UV or visible light [8]. The American Association of Blood Banks states that levels of less than  $5 \times 10^6$  leukocytes per blood component may significantly reduce transfusion-transmitted CMV infection [9]. There are also contrary results that support the use of CMV-seronegative products to be superior to leukocyte reduction filters in preventing CMV transmission [10, 11]. The last survey of current practice for prevention of transfusion-transmitted CMV in the United States reported wide variability in the use of leukoreduction versus CMV-seronegative products [12]. CMV serology should be tested for the donor and the

recipient. If the recipient is seropositive, the most common CMV infection is reactivation of latent infection; for this reason, using seronegative blood products has little importance. If HSCT is HLA-matched sibling or autologous transplantation, CMV positivity of the patient may be overcome by preemptive antiviral treatment (ganciclovir, foscarnet) with or without high-dose intravenous immunoglobulin [13–15]. CMV infection risk is the highest when CMV seropositive patients receive transplantations from unrelated, HLA-mismatched, or sibling-matched (matched other than genotypic) donors and T lymphocyte-depleted or cord blood allografts [7]. For this reason, most centers routinely administer anti-CMV prophylactic therapy to HSCT recipients in whom immunocompetence is delayed (haploidentical, T-lymphocyte-depleted, and cord blood transplantations) [7]. The risk for CMV infection is so low in seronegative HSCT recipient exposed to only seronegative blood products and CMV negative donor. Obtaining CMV negative blood products is not always easy, and urgent transfusions should not be delayed until seronegative products are available [7].

### *2.1.3. Transfusion-related graft versus host disease and gamma irradiation*

Transfusion-related graft versus host disease (TR-GVHD) is a complication of blood product transfusion, which contains donor T lymphocytes that engraft in susceptible immunosuppressed host and trigger an immune response against it [16]. TR-GVHD usually develops 4–30 days after the blood transfusion. Viable donor lymphocytes attack recipient's antigen-presenting tissues. The attack is manifested in skin, liver, gastrointestinal tract and bone marrow. Bone marrow involvement distinguishes TR-GVHD from transplantation-related disease. In HSCT, bone marrow is the nest for donor cells so privileged from the attack [17]. Usually donor lymphocytes are destroyed by the recipient's immune system; however, this protection does not work in two conditions: immunodeficiency in the recipient and specific type of partial HLA matching between the donor and the recipient. Examples for immunodeficient states are hematologic cancers, lymphoproliferative disorders, patients with solid tumors and rheumatologic diseases who are immunosuppressed because of chemotherapy or radiotherapy, Congenital immune deficiency, and AIDS [18–20]. Second setting for susceptibility to TR-GVHD is that recipients of blood who are heterozygous for an HLA haplotype for which the donor is homozygous [21]. Donor lymphocytes are not detected as foreign particles by recipient, since the only HLA antigens seen by the host lymphocytes are shared by the recipient. But donor lymphocytes recognize the host's tissues as foreign and initiate an immune attack which is named as TR-GVHD. Blood products associated with TR-GVHD are nonirradiated whole blood, packed red cells, platelets, granulocytes, and fresh and non-frozen plasma. TR-GVHD is not associated with frozen, deglycerolized red cells, fresh frozen plasma, or cryoprecipitate. The early clinical features are fever, maculopapular skin rash, diarrhea and hepatitis occurring 1–2 weeks after transfusion. Later, bone marrow involvement produces severe hypoplasia with profound pancytopenia [22]. Diagnosis is generally made by the biopsy of the affected organs such as skin, gut, and liver, showing evidence of persistence of donor lymphocytes. In order to prove the donor lymphocytes in the host tissue, polymerase chain reaction in peripheral blood [23] or short tandem repeat analysis using peripheral blood and skin biopsies from affected and non-affected sites in the patient, and peripheral blood samples from the implicated donors [24] can be used. The major way



for prevention from TR-GVHD is gamma or X-irradiation of blood components, by validated systems. The minimum dose achieved in the irradiation volume should be 25 Gy, not exceeding 50 Gy. Blood components that should be irradiated for at-risk patients are all red cell, platelet, and granulocyte components except cryopreserved red cells after deglycerolization. There is no need to irradiate fresh frozen plasma, cryoprecipitate or fractionated plasma. Also all transfusions from first- or second-degree relatives should be irradiated, even if the patient is immunocompetent. All recipients of allo-HSCT must receive irradiated blood components from the time of initiation of conditioning chemoradiotherapy and should be continued while the patient keeps receiving GVHD prophylaxis. If chronic GVHD exist or immunosuppressive treatment is continued, irradiated blood components should be given. Allo-HSCT donors (peripheral blood or bone marrow) should be transfused with irradiated blood 7 days prior to or during the harvest. Auto-HSCT patients should receive irradiated cellular blood components during and for 7 days before the harvest to prevent the collection of viable allogeneic T lymphocytes, which can potentially resist cryopreservation. Otherwise auto-HSCT patients should receive irradiated cellular blood components from initiation of conditioning therapy until 3 months from transplantation (6 months if total body irradiation was used in conditioning) [22].

## 2.2. Peritransplantation

The peritransplantation period begins with immunosuppressive preparation regimen, including stem cell infusion, and until engraftment. HSCT donor must be screened of blood group serology, HLA groups, CMV serology status, donor-recipient size disparity, and donor health. Donor and recipient ABO/Rh (D) types are preferred to be compatible but if not, it does not exclude the HSCT donor volunteering. Nearly one-half of all HSCT involve recipient-donor ABO incompatibility [25].

### 2.2.1. ABO Incompatibility

*Major ABO Mismatch:* Donor's erythrocytes are incompatible with recipient's plasma. It occurs most frequently in group O patients who are receiving HSCT from group A, group B, or group AB donors and also when group A and group B recipients receive grafts from group AB donors. Erythrocyte content in the HSC graft should be minimal in order to prevent significant hemolysis after HSCT transfusion. Erythrocytes can be extracted from the donor's bone marrow by Hetastarch separation, mononuclear cell concentration by machine, or through density gradient separation [26]. If a major ABO incompatibility exists, hematocrit should be less than 2% during apheresis collection [7].

*Minor ABO Mismatch:* Donor's plasma is incompatible with recipient's erythrocytes. ABO minor incompatibility may occur in such conditions: (1) if a patient of AB blood group receives HSCT from a non-AB blood group donor, which contains anti-A, anti-B, or both; (2) if a patient from group A receives a B or an O HSCT, which contains anti-A; or (3) if a group B patient receives an A or O transplantation, which contains anti-B [25]. In order to minimize the risk plasma-depleted HSCT products will be collected. The removed plasma volume

is proportional to the titer of the offending antibody(s) and the ratio of plasma-to-recipient erythrocyte volume [7].

### 2.2.2. Transfusion thresholds in peritransplantation period

Threshold for platelet transfusion is generally 10,000/ $\mu$ L in most transplantation centers [27, 28]. Nevertheless, patient's clinical condition must be the basic determinant for transfusion requirements. Bleeding is common and multifactorial in HSCT patients such as mucositis, hemorrhagic cystitis, GVHD, veno-occlusive disease (VOD), and diffuse alveolar hemorrhage. If the patient has another factor for bleeding, platelet transfusion threshold must be personalised. In HSCT patients, platelet rise may be less efficient than other patient groups as a result of alloimmunization. HLA-matched or crossmatched apheresis platelets are required to overcome alloimmunization.

Hemoglobin threshold for erythrocyte transfusion also varies for different clinical conditions. It can be summarized as follows [29]:

- Hemoglobin < 6 g/dL—transfusion recommended except in exceptional circumstances.
- Hemoglobin 6–7 g/dL—transfusion generally likely to be indicated.
- Hemoglobin 7–8 g/dL—transfusion may be appropriate in patients undergoing orthopedic surgery or cardiac surgery, and also for patients with underlying cardiovascular disease, after evaluation of the patient's clinical needs.
- Hemoglobin 8–10 g/dL—in general, transfusion is not required, but some populations such as patients with symptomatic anemia, with active bleeding, suffering from acute coronary heart disease, and with hematological or oncological malignancies those having thrombocytopenia and at risk of bleeding may need erythrocyte transfusions.
- Hemoglobin > 10 g/dL—transfusion generally not indicated except in exceptional circumstances.

The impact of erythrocyte transfusions on outcome and the hemoglobin threshold in HSCT patients are not well understood. In a recent study, patients with a hematologic malignancy requiring HSCT were randomized to either a restrictive (hemoglobin threshold <7 g/dL) or liberal (hemoglobin threshold < 9 g/dL) erythrocyte transfusion strategies between Day-0 and Day-100. The use of a restrictive red blood cell (RBC) transfusion strategy is compared with a liberal strategy in patients undergoing HSCT as the HRQOL (health-related quality of life) is similar and there are no appreciable differences in HSCT-associated clinical outcomes [30].

### 2.2.3. Recommendations for ABO/Rh(D) matching

In HSCT, blood group matching is not required between donor and the recipient, but there are unique transfusion rules that exist. ABO incompatibility is classified as either major, minor, or bidirectional [25] (**Table 3**).

The clinical consequences and management of ABO incompatibilities are discussed below.



Mismatch type	ABO blood type		Potential clinical consequence	Etiology	Potential interventions
	Recipient	Donor			
Major	O	A, B	<ul style="list-style-type: none"> <li>Acute hemolysis</li> </ul>	<ul style="list-style-type: none"> <li>Transfusion of incompatible erythrocytes</li> </ul>	<ul style="list-style-type: none"> <li>Erythrocyte reduction of stem cell product</li> </ul>
Major	A	AB	<ul style="list-style-type: none"> <li>Delayed erythrocyte engraftment</li> </ul>	<ul style="list-style-type: none"> <li>Patient anti-donor isohemagglutinins</li> </ul>	<ul style="list-style-type: none"> <li>Therapeutic plasma exchange in recipient to reduce isohemagglutinins before transplantation</li> </ul>
Major	B	AB	<ul style="list-style-type: none"> <li>Delayed engraftment of granulocyte and Platelets</li> <li>Pure red blood cell aplasia</li> </ul>	<ul style="list-style-type: none"> <li>Loss of immature stem cells from processing</li> <li>Loss of immature stem cells from processing with ABO antigens expressed on granulocytes and platelets</li> </ul>	<ul style="list-style-type: none"> <li>Promote donor erythropoiesis via erythropoietin administration</li> </ul>
Minor	A	O	<ul style="list-style-type: none"> <li>Acute hemolysis</li> </ul>	<ul style="list-style-type: none"> <li>Donor plasma with elevated isohemagglutinin titers/small blood volume recipient</li> </ul>	<ul style="list-style-type: none"> <li>Plasma reduction</li> </ul>
Minor	B	O	<ul style="list-style-type: none"> <li>Delayed hemolysis secondary to passenger lymphocyte syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Passenger lymphocytes producing isohemagglutinins</li> </ul>	<ul style="list-style-type: none"> <li>Continual clinical monitoring between days 5 and 15 for signs/symptoms of hemolysis and laboratory monitoring (LDH, bilirubin, complete blood count, DAT)</li> </ul>
Minor	AB	O, A, B			
Bidirectional	A	B	<ul style="list-style-type: none"> <li>Combination of major and minor consequences</li> </ul>	Combination of major and minor etiologies	Combination of major and minor
Bidirectional	B	A			Bidirectional B A interventions

Note: LDH = lactate dehydrogenase; DAT = direct antiglobulin test.

**Table 3.** Types of donor-recipient ABO incompatibilities.

## 2.3. After transplantation

ABO-mismatched allo-HSCTs have some complications such as immediate or delayed hemolytic reactions, delayed erythrocyte engraftment and red cell aplasia. Immediate immune hemolysis is usually after HPC transplantation infusion and is due to major ABO mismatch (because of the antibodies in the recipient), whereas delayed hemolysis is a consequence of minor ABO-mismatch (because of donor blood group antibodies) [7]. Several clinical conditions that can mimic immune hemolysis include veno-occlusive disease, GVHD, and thrombotic thrombocytopenic purpura. Direct antiglobulin positivity is highly suspicious for transplant-related immune hemolysis. **Table 4** demonstrates an overview to hemolysis in patients after HSCT [7].

### 2.3.1. Passenger lymphocyte syndrome

Passenger lymphocyte syndrome (PLS) occurs when transplanted B lymphocytes produce incompatible blood group antibodies after transplantation [31]. Hemolysis due to PLS may be delayed by 5–15 days after transplantation but is rare after 6–8 weeks [32, 33]. PLS includes ABO incompatibility; additionally, incompatibility in the Rh, Kell, Duffy, or Kidd blood group systems has been reported [34–37]. It is wise to expect higher PLS in peripheral HSCT than bone marrow HSCT because of the higher lymphocyte content in peripheral blood but reports regarding this are mostly anecdotal [7]. Other risk factors for PLS are the use of cyclosporine alone in the absence of an antiproliferative agent, such as methotrexate, for posttransplantation GVHD prophylaxis [38, 32], and the use of a reduced-intensity preparative regimen. After 5–15 days, hemolysis limits itself as the incompatible erythrocytes are eliminated and switched by donor or transfused erythrocytes. “Bystander” immune hemolysis is the term, when hemolysis is more extensive than expected from patient’s erythrocytes alone, attributed to hemolysis of transfused compatible erythrocytes [38]. Plasma reduction does not diminish the B lymphocyte content of HSC material and, for this reason, does not affect the incidence of PLS. Rituximab may be used in PLS prevention [39]. Pretransplantation red cell exchange procedures to reduce the volume of donor incompatible erythrocytes in the recipient before infusion are found to be ineffective and associated with a relatively large fraction of residual recipient red cells [40].

The major complications of major ABO-incompatible transplantation include delayed red cell engraftment and pure red cell aplasia (PRCA). Major ABO incompatibilities may cause delay in RBC engraftment. The diagnosis of PRCA is established if reticulocytopenia persists for more than 60 days and erythrocyte precursors are absent in the bone marrow aspirate. In addition, an inverse correlation between ABO hemagglutinin titers and reticulocyte counts exists. In some major ABO incompatible allo-HSCTs, donor hematopoietic stem cells’ conversion and RBC production are inhibited by isohemagglutinins produced by recipient plasma [41]. The primary pathology is disruption of normal bone marrow maturation by the recipient isohemagglutinins at the colony-forming-units-erythroid stage [42]. Time for recovery of erythropoiesis depends on the pretransplantation titer of antidonor isohemagglutinins, quantity of target antigen available, rate of clearance of isohemagglutinins, presence of GVHD, transplantation-conditioning regimen, and the native recipient erythropoietic function [43, 44]. Resolution of

Diagnosis	Pathophysiology	Serologic findings
<b>HSC graft-related immune hemolysis</b>		
Major ABO incompatibility between HSC donor and recipient	Hemolysis of transfused erythrocytes, delay in erythrocyte engraftment	DAT positive for C3d, IgG or both; anti-A and/or anti-B present in eluate
Minor ABO incompatibility between HSC donor and recipient	Hemolysis of patient's erythrocytes caused by transfused donor's plasma or by passenger lymphocyte-derived isohemagglutinins	DAT positive for C3d, IgG or both; anti-A and/or anti-B present in eluate
Major incompatibility: other blood group antigens	Hemolysis of transfused donor's erythrocytes	DAT positive for C3d, IgG or both; antibody to non-ABO red blood cell antigen(s) identified in eluate and patient plasma
Minor incompatibility: other blood group antigens	Hemolysis of patient's erythrocytes caused by alloantibodies in transfused donor plasma or by passenger lymphocyte-derived alloantibodies	DAT positive for C3d, IgG, or both; antibody to non-ABO red blood cell antigen(s) identified in eluate and patient plasma
<b>Transfusion-related immune hemolysis</b>		
Transfusion of erythrocytes incompatible with donor or patient	Hemolysis of transfused erythrocytes caused by patient's native or graft-derived antibodies	DAT positive for C3d, IgG or both; anti-A and/or anti-B or antibody to other RBC antigen identified in eluate and patient plasma
Transfusion of plasma incompatible with donor or patient	Hemolysis of patient and/or donor erythrocytes	DAT positive for C3d, IgG or both; anti-A and/or anti-B or antibody to other RBC antigen identified in eluate and patient plasma
<b>Other causes of immune hemolysis</b>		
Autoimmune hemolytic anemia	Hemolysis and serologic incompatibility of (all) crossmatched donor erythrocytes	DAT positive for C3d, IgG or both; panagglutinin present in eluate and patient plasma
Drug-induced hemolytic anemia	Autoantibody formation induced by drug, hapten mechanism, or drug modification of erythrocyte membrane	DAT positive for C3d, IgG or both; eluate may react with drug-treated erythrocytes
<b>Nonimmune hemolysis</b>		
TTP	Microangiopathic hemolytic anemia	DAT and antibody screen negative
Cryopreserved stem cell products infusion	Nonimmune hemolysis may be observed during infusion of DMSO-cryopreserved HSC preparations	DAT negative
Clostridium perfringens sepsis	C perfringens-produced hemolysin toxins cause nonimmune intravascular hemolysis	DAT negative

*Note:* HSC = hematopoietic stem cell, DAT = direct antiglobulin test, C3D = complement factor 3D, DMSO = dimethyl sulfoxide, IgG = immunoglobulin G, RBC = red blood cell, TTP = thrombotic thrombocytopenic purpura.

**Table 4.** Differential diagnosis of hemolysis in HSCT patients.

PRA usually takes a few weeks or months but rarely continues for 5 years [45]. Management of PRA includes tapering immunosuppression, using erythropoietin, steroids, plasma exchange, rituximab, and donor lymphocyte infusions [46–48].

## **2.4. Post-engraftment period**

There are some clinical conditions specific to post-engraftment of stem cells, which may increase the requirement for blood products.

### *2.4.1. Graft-versus host disease*

In acute GVHD cytopenias of 1–3 cell lines and an immune-based hemolytic anemia may occur; also, gastrointestinal GVHD may cause bleeding because of ulcers in gastrointestinal system, and severe liver GVHD may also develop the clotting disturbances [49]. Blood product support during GVHD is essential.

### *2.4.2. Hemorrhagic cystitis*

Hemorrhagic cystitis is a toxicity related with cyclophosphamide; however, several viral etiologies, including adenovirus and BK virus, have been reported [50]. HSCT patients with hemorrhagic cystitis may require RBC replacement proportional to its loss and platelet transfusion if the patient is thrombocytopenic. Tranexamic acid should be avoided because of possible clotting within the ureters. Bladder irrigation and platelet transfusion are the mainstay of the treatment.

### *2.4.3. Hepatic veno-occlusive disease*

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, is a major complication of HSCT and carries a high mortality risk. Many different risk factors for VOD have been described, including platelet transfusions containing ABO-incompatible plasma [51]. Incompatible isoagglutinins to ABO blood-group antigens on hepatic sinusoidal endothelial cells may cause toxic injury initiating a sequence of biological events that may lead to circulatory compromise of centrilobular hepatocytes, fibrosis, and obstruction of blood flow, resulting in VOD [7]. It is wise to think that all platelet transfusions after HSCT should be ABO-compatible with both donor and recipient blood types. In VOD, the need for platelet transfusion is increased as a result of activated coagulation and portal hypertension-related thrombocytopenia.

### *2.4.4. Donor lymphocyte infusion*

Donor lymphocyte infusion (DLI) is one of the strategies for managing relapsed hematologic malignancy after HSCT. This procedure is the infusion of lymphocytes from the original stem cell donor after the transplant to augment an antitumor immune response or to be sure that the donor HSCs remain engrafted. Aim is to initiate the process called the graft-versus-tumor effect. T cells of donor are supposed to attack residual cancer cells.

#### 2.4.5. Granulocyte transfusion

Granulocyte transfusion is not routine procedure, but larger doses of granulocytes collection became possible after the discovery and availability of recombinant granulocyte colony-stimulating factor (G-CSF) increased the interest for the issue [52]. It is possible to collect  $5\text{--}10 \times 10^{10}$  granulocytes at once [53–55]. Some authors recommend granulocyte transfusion in patients meet that criterion regardless of the cause of neutropenia [56]:

- Absolute neutrophil count  $<500$  cells/ $\mu\text{L}$ , except in the case of chronic granulomatous disease.
- Evidence of bacterial or fungal infection (i.e., clinical symptoms of infection, positive cultures, pathological diagnosis of infection from biopsies, radiographic evidence of pneumonia).
- Unresponsiveness to antimicrobial treatment for at least 48 hours (except in extreme circumstances with life-threatening infection)

Chemotherapy and HSCT are the most common indications for granulocyte transfusion even though their use is rare in daily practice. Family members and community donors both can donate granulocytes; however, donor must fulfill some criterion. Donors must be ABO and Rh-matched to the recipient, negative for all blood transfusion-associated infectious disease markers within 30 days of granulocyte donation, having good vascular access, and not be pregnant and having hemoglobinopathy. G-CSF (300 mcg subcutaneously) and dexamethasone (8 mg orally) are administered on the day prior to each collection [54]. Granulocyte harvesting by apheresis is performed by removing granulocytes and returning erythrocytes and plasma to the donor. Adverse reactions associated with granulocyte transfusion are pulmonary adverse reactions [57], transfusion-associated GVHD [58], alloimmunization [59], and infections [60], especially CMV [61].

#### 2.4.6. Erythrocyte chimerism

Allo-HSCT patients should be assessed with chimerism studies in order to detect the genotypic origin of posttransplant hematopoiesis. This study serves to define engraftment, graft failure, and relapse. Complete chimerism means hematopoiesis is entirely from the donor; mixed chimerism is the condition that a variable ratio of donor- to recipient-derived cells, and engraftment failure means cells are all from the recipient. Blood group chimerism is an important issue in allo-HSCT patients. According to ABO matching, varied incidences of ABO-grouping discrepancies or mixed field-agglutination reactions have been reported [7]. Antierythrocyte antibodies are measured to document erythrocyte chimerism, once the patient's blood becomes full-donor chimera, recipient-derived antierythrocyte antibodies disappear. Then, blood products consistent with donor ABO typing should be used. After establishing full donor engraftment, the onset of mixed erythrocyte chimerism (circulating erythrocytes typing with mixed field-donor recipient ABO groups) may be signaling for the relapse and/or graft failure [62].

Transfusion-support recommendations for ABO incompatible HSCT are summarized in **Table 5** [25].

Recipient	Donor	Phase 1	Phase 2						Phase 3			
			All products	RBC's	Platelets		Plasma		RBC's	Platelets	Plasma	
					1st Choice	2nd Choices	1st Choice	2nd Choices			1st Choice	2nd Choices
O	A	Recipient	O	A	AB, B, O	A	AB	Donor	A	AB, B, O	A	AB
O	B	Recipient	O	B	AB, A, O	B	AB	Donor	B	AB, A, O	B	AB
O	AB	Recipient	O	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
A	AB	Recipient	A	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
B	AB	Recipient	B	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
A	O	Recipient	O	A	AB, B, O	A	AB	Donor	A	AB, B, O	A	AB
B	O	Recipient	O	B	AB, A, O	B	AB	Donor	B	AB, A, O	B	AB
AB	O	Recipient	O	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
AB	A	Recipient	A	AB	A, B, O	AB	NA	Donor	AB	A, B, O	AB	NA
AB	B	Recipient	B	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
A	B	Recipient	O	AB	B, A, O	AB	NA	Donor	AB	B, A, O	AB	NA
B	A	Recipient	O	AB	O, A, B	AB	NA	Donor	AB	A, B, O	AB	NA

*Note:* NA = not applicable; Phase 1 = time period between diagnosis and transplantation; Phase 2 = time period between transplantation and RBC engraftment; Phase 3 = engraftment established, as indicated by direct antiglobulin testing being negative, along with two consecutive separate samples with the forward and reverse typing showing donor ABO status.

**Table 5.** Transfusion support recommendations for ABO incompatible HSCT.



Autologous and allogeneic HSCT are associated with pancytopenia in the pre-, peri-, and posttransplant period. Blood product transfusion is an inevitable and critical component for the patient management. HSCT patients have special requirements regarding blood products transfusion. Transfusion services, hospitals, physicians, and other health care staff who take care of transplant patients should be aware of that those patients have specific and specialized transfusion requirements.

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