Post-Hematopoietic Stem Cell Transplantation Immune-Mediated Anemia: A Literature Review and Novel Therapeutics

Tracking no: ADV-2021-006279R1

Yazan Migdady (Oregon Health & Science University, United States) Yifan Pang (National Heart, Lung, and Blood Institute, National Institutes of Health, United States) Shelley Kalsi (NIH, United States) Richard Childs (National Heart Lung and Blood Institute, National Institutes of Health, United States) Sally Arai (Stanford, United States)

Abstract:
Anemia following allogeneic hematopoietic stem cell transplantation (HCT) can be immune- or non-immune mediated. Auto- or alloimmunity due to blood groups incompatibility remain an important cause if post-HCT immune-mediated anemia. ABO incompatibility is commonly encountered in HCT and may lead to serious clinical complications including acute hemolysis, pure red cell aplasia, and passenger lymphocyte syndrome. It remains controversial whether ABO incompatibility may affect HCT outcomes, such as relapse, non-relapse mortality, graft-versus-host disease and survival. Non-ABO incompatibility is less frequently encountered but can have similar complications to ABO incompatibility, causing adverse clinical outcomes. It is crucial to identify the driving etiology of post-HCT anemia in order to prevent and treat this condition. This requires a comprehensive understanding of the mechanism of anemia in blood group incompatible HCT, and the temporal association between HCT and anemia. In this review, we summarized the literature on post-HCT immune-mediated anemia with a focus on ABO and non-ABO blood group incompatibility, described the underlying mechanism of anemia, and outlined preventive and treatment approaches.

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: Y.M. and Y.P. are co-first authors who provided concept and design, wrote, reviewed, and/or revised the manuscript; S.K. reviewed and revised the manuscript; S.A. and R.W.C. are co-senior authors who wrote, revised the manuscript and provided expert guidance.

Non-author contributions and disclosures: Yes; The authors would like to extend their gratitude to the patients reported on this review. A special thanks to Dr. Charles Bolan for his contribution and review of this manuscript.

Agreement to Share Publication-Related Data and Data Sharing Statement: This is a review paper and data sharing is not applicable. For questions, please contact the corresponding author.

Clinical trial registration information (if any):
Title:
Post-Hematopoietic Stem Cell Transplantation Immune-Mediated Anemia: A Literature Review and Novel Therapeutics

Authors
Yazan Migdady¹ and Yifan Pang², Shelley S. Kalsi³, Richard Childs³ and Sally Arai⁴

Affiliations:
¹ Knight Cancer Institute, Oregon Health and Science University, Oregon, USA
² National Heart, Lung, and Blood Institute, National Institutes of Health, Maryland, USA
³ Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, MD, USA
⁴ Division of Blood and Marrow Transplantation, Department of Medicine, Stanford University, Stanford, CA

Running title: Post-HCT Immune Mediated Anemia

Correspondence:
Yazan Migdady
Institution: Oregon Health and Science University
Address: 3181 SW Sam Jackson Park Road, Portland, Oregon 97239
Telephone number: 503-494-5482
E-mail address: migdady@ohsu.edu

Source of support: Not applicable.

Conflict of interest: No conflicts of interest.

Keywords: hematopoietic stem cell transplantation, hemolysis, blood group, ABO, non-ABO

Word count: 3991

Tables: 3

Figures: 4
Abstract

Anemia following allogeneic hematopoietic stem cell transplantation (HCT) can be immune- or non-immune mediated. Auto- or alloimmunity due to blood groups incompatibility remain an important cause if post-HCT immune-mediated anemia. ABO incompatibility is commonly encountered in HCT and may lead to serious clinical complications including acute hemolysis, pure red cell aplasia, and passenger lymphocyte syndrome. It remains controversial whether ABO incompatibility may affect HCT outcomes, such as relapse, non-relapse mortality, graft-versus-host disease and survival. Non-ABO incompatibility is less frequently encountered but can have similar complications to ABO incompatibility, causing adverse clinical outcomes. It is crucial to identify the driving etiology of post-HCT anemia in order to prevent and treat this condition. This requires a comprehensive understanding of the mechanism of anemia in blood group incompatible HCT, and the temporal association between HCT and anemia. In this review, we summarized the literature on post-HCT immune-mediated anemia with a focus on ABO and non-ABO blood group incompatibility, described the underlying mechanism of anemia, and outlined preventive and treatment approaches.
**Introduction**

There are at least 43 recognized blood groups in humans involving 345 red blood cell (RBC) antigens [1]. Approximately 30-50% of HCT are performed across the ABO blood group barrier, and clinically significant hemolysis is encountered in 10-15% of cases [2, 3]. Other complications of ABO mismatched HCT include hemolytic infusion reactions, delayed engraftment, and pure red cell aplasia (PRCA) [4, 5]. Compared with ABO mismatched HCT, complications of non-ABO blood group mismatched HCT are less well-characterized. Recipients and donors are not routinely checked for non-ABO blood group phenotypes unless clinically indicated, such as when there is a known history of alloantibodies or heavy transfusion requirement in the recipient prior to transplant [6]. The incidence of non-ABO blood group mismatch-related immunohematologic complications following HCT is reported below 10% which is likely under reported [7-10].

Auto- or alloimmunity against the RBC are an important etiology of immune-mediated anemia in blood group mismatched HCT. The source of auto- or alloimmunity may be donor- or recipient, such as passive antibody transfusion, passenger lymphocyte syndrome, alloantibodies formed against engrafting hematopoietic cells, or new auto- or alloantibodies due to transfusions (Figure 1, 2).

Antibodies can mediate phagocytosis and cellular toxicity, and activate the complement pathway, resulting in intra- and extravascular hemolysis [11]. Immune-mediated cytopenias can also occur as a manifestation of chronic graft versus host disease (GVHD) [12, 13]. The underlying mechanism of cytopenias in GVHD is unclear but likely from altered T-cell immune reconstitution [14].

The complexity of the post-HCT immune-mediated anemia requires a close collaboration between transfusion medicine, hematology, and transplant services. Detailed knowledge about the recipient/donor blood group phenotypes, and the temporal association between transplant and hemolysis can help identify the underlying mechanism of hemolysis and direct appropriate management. This review summarizes the literature on post-HCT immune-mediated anemia to provide insight into its pathophysiology, clinical manifestations, preventive and proposed therapeutic strategies.

**ABO Mismatch:**

ABO mismatch is categorized into major, minor and bidirectional (Table 1).

**Major ABO Mismatch:**

Major ABO mismatch is characterized by the presence of naturally existing host isohemagglutinins against the donor RBC’s corresponding carbohydrate ABO antigens. The most common scenario is when a group O recipient receives a non-O graft, and less commonly, when group A or B recipients receive a B or A graft, respectively, or an AB graft. The naturally occurring isohemagglutinins in recipients can attack donor RBC ABO antigens early after stem cell infusion or can affect erythroid precursors later in the post-HCT course.

ABO isohemagglutinins are IgM antibodies that can robustly activate the classical complement pathway [15]. Through formation of the membrane attack complex, major ABO incompatibility may cause acute hemolytic transfusion reactions at the time of stem cell infusion, especially when the graft contains a significant volume of RBCs, such as in unmanipulated bone marrow (BM) grafts [16]. Further, recipient isohemagglutinin against donor-derived erythroid precursor cells can lead to reticulocytopenia with subsequent PRCA, which is seen in 8-26% of major ABO mismatch HCT [17]. PRCA usually occurs around 30-90 days post-HCT and is characterized by an absence of erythroid precursor in an otherwise normal BM [18]. As the majority of recipients clear the donor-specific isohemagglutinins within day 120, the development of PRCA has been attributed to residual recipient plasma cells that continue to produce isohemagglutinins (Figure 3) [19]. Patients with PRCA can be transfusion dependent for months, become iron overload and alloimmunization to other blood group antigens [20]. ABO antigens are also expressed on granulocytes and platelets, therefore major ABO
mismatch can also lead to prolonged neutropenia and thrombocytopenia, resulting in severe infections and catastrophic bleeding [21]. Whether major ABO mismatch can affect HCT outcomes, such as survival, relapse, and GVHD is controversial (Table 2). A single center study of 1,502 patients receiving HCT from different graft sources including PB, BM or cord, showed that ABO mismatch was not associated with neutrophil or platelet engraftment delay, incidence of acute or chronic GVHD, overall survival (OS) or non-relapse mortality (NRM), regardless of the graft source [22]. A meta-analysis of seven cohort studies showed that OS was not affected by ABO matching status [23]. On the other hand, in a Center for International Blood and Marrow Transplant Research (CIBMTR) study that included 5179 patients, major ABO mismatch was associated with decreased OS (hazard ratio HR = 1.19; 95% confidence interval, CI = 1.19 – 1.31; p<.001) and increased NRM (HR 1.23, 95%CI 1.08 – 1.4, p=.002) [24]. In a European Blood and Marrow Transplant (EBMT) Acute Leukemia Working Group Registry study that included 837 patients who underwent haploidentical HCT, major ABO mismatch was associated with inferior day 100 engraftment rate, and in BM HCT associated with inferior OS [25].

Patients with ABO mismatch may have lower rates of complications if they receive myeloablative conditioning (MA) [26]. In one study, fludarabine/cyclophosphamide conditioning, compared with total body irradiation-based MA regimen, was associated with delayed full donor erythroid chimerism by a median of 74 days, and increased risk of PRCA. The clearance of anti-donor isohemagglutinins was faster in the latter [26]. Other studies also showed impaired HCT outcomes in ABO mismatch HCT receiving reduced-intensity conditioning (RIC) [27, 28]. ABO mismatch was associated with a 1.7-fold increased risk for extensive chronic GVHD in a cohort of 594 patients who received alemtuzumab-based RIC HCT [28].

Preventive strategies for immunohematologic complications

Although ABO matching is not required for donor selection per current guidelines, it is worthwhile to be taken into consideration when multiple suitable donors are available [29]. Besides using MA regimens when feasible, strategies to prevent complications in major ABO mismatch include graft RBC reduction, and to remove host isohemagglutinin by therapeutic plasma exchange prior to HCT [30-32]. In recipients with anti-donor isohemagglutinin titers ≥ 1:32, RBC depletion should be performed to ensure infused RBC < 20ml. When titers are ≤ 1:16, RBC depletion are generally not required [3].

As ABO antigen can be secreted into the plasma, pretransplant immunoabsorption, i.e., infusing donor type fresh frozen plasma (FFP) that are positive in A or B antigen, in order to neutralize respective isohemagglutinin, is another approach to prevent complications. In one single center study in Singapore 79 of 99 major or bidirectional ABO mismatch recipients were treated with donors’ FFP from day -5 to day -2 prior to transplant, including 70 patients with isohemagglutinin titers > 1:32. Those with a titer level ≤ 1:32 at the time of stem cell infusion did not develop acute hemolysis. Three patients developed PRCA, irrespective of pre- or post-FFP isohemagglutinin levels [33]. In another single center study from Australia, 75 of 110 major or bidirectional ABO mismatch recipients had isohemagglutinin titers > 1:32, and received FFP with or without plasma exchange prior to HCT. The incidence of PRCA was 5%. Risk of PRCA or delayed RBC engraftment was significantly higher in patients with pre-transplant isohemagglutinin titers ≥ 1:128 [17].

Donor-type RBC transfusion is another immunoabsorption method [34, 35]. In a single center study in thalassemia, 20 of 55 major or bidirectional ABO mismatched recipients with isohemagglutinin titer ≥ 1:32 received small incremental doses of uncrossmatched donor RBC during conditioning, 12 had mild hemolysis and none had severe hemolysis or anaphylaxis. In patients who had no hemolytic reaction at the last transfusion or titer were ≤1:32, bone marrow grafts were infused without RBC depletion. No hemolytic reactions were observed post-HCT, and all patients engrafted without delay [34]. Despite the successes, immunoabsorption requires high expertise in transfusion medicine and close patient monitoring, and remains to be validated in larger studies.
**Minor ABO Mismatch:**

Minor ABO mismatch is characterized by the interaction of donor-derived isohemagglutinin with the recipient’s corresponding RBC antigens. These isohemagglutinins may be infused along with the stem cell products, causing acute hemolysis of the recipient RBCs. Alternatively, “passenger” B-lymphocytes from the donor graft proliferate and secrete isohemagglutinins and other RBC antibodies, causing a clinically significant delayed hemolysis called passenger lymphocyte syndrome (PLS) (Figure 4) [36]. PLS typically occurs 1-2 weeks post-HCT, more frequently after peripheral blood (PB) than BM HCT as the former contains a higher concentration of lymphocytes [36, 37]. RIC is associated with a higher risk of PLS because recipient’s antigen may be left intact and subsequently stimulates donor B-cells [38, 39]. Cyclosporine-only GVHD prophylactic regimen has been associated with higher risks of immunohematologic complications because cyclosporin boosts B-cell antibody production [2, 40].

The impact of minor ABO mismatch on HCT outcomes is also controversial (Table 1). Some studies suggest that minor ABO mismatch is a risk factor for acute GVHD, decreased OS and increased NRM [24, 41-43]. In one study, it was associated with a 3-fold increased risk for grade II-IV acute GVHD and 4-fold increased risk for grade III-IV acute GVHD [44]. In a 1737-patient cohort at Stanford University between 1986 and 2011, minor ABO mismatch was an independent risk factor for OS with a HR of 1.56 (95%CI, 1.05 – 2.05, p=.001) [24]. In a CIBMTR analysis, lymphoma patients receiving PB graft, minor ABO mismatch was associated with reduced OS and higher NRM (HR = 1.55 and 1.72, p=.021 and .03, respectively), however, these associations were not observed in patients with acute myeloid leukemia and myelodysplastic syndrome [24].

**Preventative strategies for immunohematologic complications**

In minor ABO mismatched HCT, immediate hemolysis can be prevented by graft plasma volume reduction; this does not prevent PLS because it does not affect the B-cell component in the graft [45]. There is a scarcity of literature how to prevent PLS. Patients need close monitoring for hemolysis especially around 1-2 weeks post-HCT when PLS may occur. Direct anti-globulin test (DAT) may assist early detection of subclinical hemolysis. It is often checked once or twice weekly according to institutional protocols. Maintaining higher hemoglobin levels than normal transfusion threshold is preferred especially during the high-risk period, to avoid nadir in case severe or life-threatening PLS occurs. Collaborative efforts between transfusion and transplant services to ensure the awareness of minor ABO mismatch and transfuse compatible RBC components peri-transplant is very critical.

**Bidirectional ABO Mismatch:**

Bidirectional mismatch occurs when the donor/recipient pair has both a major and minor ABO mismatch, such as type A donor/type B recipient, or vice versa. The recipient is at risk for the complications associated with both directions of incompatibility (Table 1), and preventive methods should address both accordingly.

**Non-ABO blood groups incompatibility:**

Unlike ABO isohemagglutinins which exist in the absence of a previous exposure, alloimmunization to protein antigens only occurs after exposure. The incidence of alloimmunization after transfusion is 2-6%, and most commonly involve the Rhesus (Rh), Kell (K) and Kidd (Jk) blood groups [46-48]. RhD antigen is the most potent non-ABO antigen, followed by K antigen. Patients with history of alloimmunization are at higher risk of developing additional alloantibodies [49]. Although rare, non-ABO blood group alloantibodies may result in poor HCT outcomes [50, 51]. Complement cascade is implicated in immune-mediated anemia in some of the non-ABO mismatched HCT. For example, the IgG or IgM antibodies against the Kidd antigens are able to fix complements and induce intra- or extravascular hemolysis [52]. Mismatch of the Kidd antigen system have been reported to cause severe hemolytic anemia or PLS [8, 53].

RBC alloimmunization due to non-ABO mismatch could originate from the donor, recipient or both, depending on the temporal relationship between the antibody development and the chimerism status.
Donor-derived alloantibodies include the pre-existing antibodies in the graft, and new antibodies produced by passenger or engrafted lymphocytes. Recipient-derived alloantibodies include pre-existing antibodies, or antibodies produced by residual lymphocytes and plasma cells.

Post-HCT, majority of the de novo non-ABO alloantibodies develop within the first month [8]. PLS can also occur in non-ABO blood group mismatch HCT, usually involving the RhD, E, s, Kk2, or Jk2 [53-55]. Table 3 outlines previously described clinically significant non-ABO blood group systems associated with alloimmunization following HSCT.

Patients on chronic transfusion therapy prior to HCT are generally at higher risk of developing auto- and alloimmunization. Patients with sickle cell disease (SCD) have high rates of of RBC alloimmunization (23.8-45.7%) despite leukoreduction and prophylactic antigen matching [56, 57]. Frequent transfusions, lack of phenotypically matched products, inadequate alloantibody testing, and the presence of antigen variations especially in donors of African descent increase the risk of alloimmunization [58]. In one cohort, RBC antibodies were detected in 9 of 61 patients post-HCT (15%), including 3 patients with pre-formed and 6 with new antibodies, 4 patients developed reticulocytopenia or hemolysis [59]. In a cohort of non-MA, matched-sibling HCT for SCT, 31% (11/31) of patients had a history of RBC alloantibodies, which was correlated with a decreased donor T cell chimerism at 1 year than non-alloimmunized patients (median 24% vs 55%, p=.035) [60]. As the number of HCT in SCD is increasing, it remains a challenge to prevent and treat RBC alloimmunization peri-HCT.

Thalassemia is another hemoglobinopathy that requires chronic transfusion therapy. Alloantibodies occur in 5-30% of thalassemia patients, and are more common after splenectomy, long duration of treatment and frequent transfusion [61-64]. The dominant antibodies are against the Rh and Kell groups, each comprises 20-30% of the antibodies [64]. When prophylactically transfusing Rh (D, C, E) and K antigen matched RBC units, alloantibodies were still detected in 32.5% of patients, with an alloimmunization rate of 0.26 antibodies/100 units, and 72.5% of antibodies were directed against Rh [63]. There is limited data on how non-ABO alloantibodies affect the HCT outcome in patients with thalassemia.

Chronic granulomatous disease (CGD) can co-exist with the McLeod phenotype, i.e., reduced expression of the Kell blood group antigens and the absence of the XK protein on the RBCs. This is due to the genetic proximity between the cytochrome B beta subunit gene and the XK gene. Höning et al. reported a case of successful HCT in a CGD/McLeod patient with anti-K and anti-Kx alloantibodies. The patient received rituximab, antithymoglobulin (ATG), MA conditioning, and a K-antigen negative, HLA-matched unrelated graft. The patient had an uneventful HCT course with prompt engraftment. The anti-K alloantibodies remained detectable until 20 months post-HCT [65]. Another patient received MA conditioning with busulfan, cyclophosphamide and ATG, followed by a Kell-negative BM graft. He developed refractory severe hemolytic anemia after day+100 due to anti-Kx and anti-K and was found to have low donor T-cell chimerism, despite B-cell and erythroid conversion. His hemolytic anemia resolved after three doses of donor lymphocyte infusion [66].

Outside of the chronically transfused population, the rate of non-ABO alloimmunization is reportedly low [7, 8, 10]. De la Rubia et al. reported a rate of 3.7% (8/217 patients) of new non-ABO alloantibodies post-HCT, in which 2 patients developed severe immune hemolytic anemia early after HCT; recipient age and ABO incompatibility was associated with the development of non-ABO alloantibodies[10]. Ting et al., reported a rate of 8.7% (13/150 patients) of new RBC alloantibody production from 12 days to 11 months post-HCT [7]. In another retrospective study, the incidence of alloimmune hemolysis post-HCT involving non-ABO antigens was 1% (5/427 patients) [8]. When the alloantibodies are detected timely, these complications may be prevented [8, 67]. In one case, recipient with anti-Jk2 received fludarabine/melphalan conditioning with rituximab, followed by Jk2+ donor PB stem cells without adverse events [67]. Complications related to non-ABO antigen incompatibility are expected to increase given the progressive success in HCT and its wide use in malignant and nonmalignant diseases [68].
**Laboratory investigations in non-ABO blood group mismatched HCT:**

Immunohematologic complications caused by non-ABO blood group mismatch can be under-diagnosed due to inadequate phenotyping of the donor-recipient RBCs. In the absence of known pre-existing alloantibodies in the recipient, testing beyond the ABO and Rh blood group is generally not considered prior to transplant. Some alloantibodies may be not detected, such as the Jk\(^+/\)Jk\(^-\) antibodies, because of fluctuation of the titers [8]. Kidd antibodies are known to have amnestic response such that a patient may test negative initially but have a subsequent re-emergence of antibodies later in the post-HCT course.

Extended serologic RBC phenotype matching is being done for patients receiving frequent transfusions in order to provide appropriate antigen-negative blood products. Despite that, alloantibodies can still form and lead to further challenges in transfusion [69]. Extended genotype RBC matching can detect and predict minor variations in RBC antigens that are hard to identify serologically; it is increasingly utilized in clinical practice [70, 71]. Real-time polymerase chain reaction is another method for quick RBC phenotyping in HCT, especially when the donor-recipient myeloid chimerism status is dynamically changing [72].

**Anemia due to autoimmunity**

Autoimmune-hemolytic anemia (AIHA) occurs in 4-6% of HCT recipients [73, 74]. In one study of T cell-depleted haploidentical HCT in patients with severe combined immunodeficiency, the incidence of AIHA was 19.5% [75]. Patients post-second HCT have higher incidence and earlier presentation of AIHA than post-first HCT [76]. AIHA may occur alone or in conjunction with other immune-mediated cytopenias [74]. RBC phenotyping of the donor and recipient, determined before HCT, can help differentiate auto-immune-mediated anemia from alloimmunity [77]. In different reports, median time of onset ranges from 4 to 10 months post-HCT [76]. Transplant for non-malignant disease is the most consistent risk factor for post-HCT AIHA in the literature; other factors, such as unrelated donor, acute or chronic GVHD, CMV activation and alemtuzumab-containing conditioning regimen, have been reported but inconsistent [73, 77-79].

The pathophysiology of AIHA post-HCT has not been fully elucidated, but may be related to pre-formed autoantibodies and dysregulated immune tolerance. In chronically transfused population, autoantibodies against RBCs has been reported in 7-25% of patients; majority of the autoantibodies are transient but some may lead to clinically significant hemolysis [80]. Patients who develop AIHA are severely lymphopenic, with low numbers of regulatory T-cells; delayed T-cell immune reconstitution, due to either in-vivo or ex-vivo T-cell depletion, may allow autoreactive B-cells to activate and expand without regulation [75, 81]. On the other hand, flowcytometry and cytokine analysis of patients with AIHA post-HCT identified a decreased CD3+CD8+ T cell ratio, and a T-helper cell 2-related cytokine profile, compared with the control patients [77]. Patients who develop autoimmune AIHA are at a higher risk for developing alloimmunity.

**Treatment**

Mild to moderate cases of hemolytic anemia, including PLS, are self-limited and are usually treated with simple transfusions of antigen negative RBCs; however, finding the appropriate RBC unit can be challenging when multiple alloantibodies or antibody to a high frequency antigen are present [82]. Around 50% of PRCA cases resolve spontaneously within 100-200 days post-HCT, but in the cases with prolonged anemia dependent on chronic, frequent transfusions, treatment is necessary to prevent complications such as iron overload [18, 83-85].

Most of the therapeutic options for post-HCT immune-mediated anemia are derived from AIHA, which does not have a licensed treatment itself (Figure 2) [81]. Based on mechanism of action, the options can be categorized into immunosuppression, which include the use of systemic steroids, IVIG, rituximab, cyclophosphamide, azathioprine, and splenectomy in the severe cases, immunoabsorption, RBC or plasma exchange, and stimulation of erythropoiesis using erythropoietin or thrombopoietin.
Eculizumab was effective in one of the three cases reported in literature for antibody autoimmune hemolytic anemia and cold agglutinin disease (Figure 1) [86-90]. For PRCA, the most commonly used therapies are rituximab, erythropoietin and donor lymphocyte infusion (DLI) (Figure 3) [91].

There are reports of efficacy using anti-CD20 monoclonal antibodies such as rituximab to treat PRCA [92]. Since B-cells are responsible for isohemagglutinins or alloantibody production in PLS, rituximab can also be used in severe cases of PLS (Figure 4) [93]. Other immunosuppressive treatments reported to work in refractory cases including Abatacept, a fusion protein that blocks interaction between T cells and antigen-presenting cells [94].

Erythropoietin stimulating agents can increase RBC production and can be used as a therapeutic option in severe hemolytic anemia or PRCA post-HCT [89, 95]. Eltrombopag is a thrombopoietin receptor agonist approved for the treatment of aplastic anemia. It has shown efficacy in refractory acquired PRCA outside of the HCT setting [96]. Busca et al., reported 2 cases of PRCA that were refractory to erythropoietin, plasma exchange, rituximab and bortezomib, who achieved sustained remission of PRCA with eltrombopag [90].

DLI or tapering of immunosuppressants represent unique therapeutic options in the HCT setting. These methods may improve donor chimerism, eliminate recipient plasma cells, and reduce alloreactivity from either donor or recipient directions. The efficacy of either methods in PRCA are ~50% in case reports [84]. In one case report, a patient with PRCA received DLI with a CD34-positive stem cell boost, and achieved normal blood counts after 2 months [97]. However, in a recent multicenter retrospective study, rituximab, DLI and erythropoietin had no impact on the resolution of PRCA [91]. Mesenchymal stem cell infusion has also been utilized in refractory PRCA cases with promising results [98, 99].

Plasma cells are a viable target for therapy because they may contribute to antibody production, especially in refractory hemolytic anemia and PRCA. Bortezomib was reported being effective in 40% of the cases in literature [84]. Compared with other plasma cell-targeted therapy, daratumumab has a more appealing safety profile and mechanism of action [100, 101]. A few case reports have noted its efficacy in refractory post-HCT autoimmune hemolytic anemia and PRCA [102-104]. Daratumumab may have efficacy on other forms of post-HCT immune-mediated cytopenia(s), such as thrombocytopenia or Evan’s syndrome [105]. We have previously reported durable response following daratumumab in a patient with posttransplant thrombocytopenia [106]. Daratumumab impairs the RBC crossmatch testing which necessitates transfusing Kell-negative units post-treatment, unless the RBC phenotype is identified pre-treatment [107]. However, daratumumab is not always effective in post-HCT immune mediated cytopenias, likely due to the suppressive effect of daratumumab on the CD38-positive regulatory T cells [108, 109].

A novel modulatory therapy that is worth testing is the spleen tyrosine kinase (Syk) inhibitor fostamatinib. Its active metabolite, R406, was shown to reduce antibody-mediated platelet destruction. It was FDA approved in April 2018 for patients with chronic ITP who failed one line of therapy. Additionally, it is currently studied in phase III clinical trial for subjects with warm AIHA (NCT03764618) and in an early phase chronic GVHD trial (NCT02611063). The Syk pathway is critical for B-cell activation and proliferation; activated B-cells may trigger T-cell activation and cytokine production [110, 111]. Preclinical reports in xenograft models using peripheral blood mononuclear cell (PBMCs) from patients with active cGVHD showed that Syk inhibitor augments B-cells apoptosis while not affecting normal T-cell function [112].

Therapies targeting the complement pathway are being more frequently utilized in immune-mediated cytopenias. Vo, et al., used eculizumab, a complement C5 inhibitor, to treat heavily alloimmunized patients with platelet transfusion refractoriness. Four of the 10 patients enrolled overcame platelet transfusion refractoriness with one dose of eculizumab [113]. Eculizumab has shown efficacy in warm antibody autoimmune hemolytic anemia and cold agglutinin disease [114, 115]. In post-HCT AIHA, eculizumab was effective in one of the three cases reported in literature [73]. Several other
complement inhibitors, such as pegcetacoplan and sutimlimab, are actively being investigated in complement-mediated hemolytic anemia [116, 117]. These agents may be viable options for refractory hemolytic anemia post-HCT.

Therapies carry their own risks. Infection is the most concerning complication in patients on immunosuppression. In one study analyzing the outcome of 46 patients with PRCA, 22 received treatment other than supportive care, and 7 died of infection [18]. IVIG, rituximab and plasma exchange may cause anaphylactic reactions. Donor lymphocyte infusion may lead to higher incidence of GVHD [118]. Therefore, careful evaluation of the risks and benefits prior to the initiation of therapy is crucial, requiring multidisciplinary collaboration between transfusion medicine, hematology and HCT providers.

Conclusions

Donor-recipient RBC antigen mismatch is commonly encountered which results in clinically significant immunohematologic events complicating the posttransplant course. ABO phenotype is part of the donor-recipient pretransplant work up to plan transfusion needs, clinical laboratory monitoring and possible graft manipulations. Donor-recipient extended phenotyping for non-ABO antigens such as Rh, Kell and Kidd should be considered in high-risk groups, especially those on chronic transfusion therapy. HCT across the barrier of RBC antigen mismatch may lead to acute hemolysis, PLS, and PRCA. Early detection of hemolysis, supportive care with antigen-negative or matched RBC transfusion, and appropriate interventions such as immunosuppression, are necessary to improve clinical outcomes. Active collaboration between the transfusion and transplant services might help with early identification of clinically significant antibodies and prompt necessary treatment interventions.
Acknowledgments

The authors would like to extend their gratitude to the patients reported on this review. A special thanks to Dr. Charles Bolan for his contribution and review of this manuscript.

Authorship

Contribution:

Y.M. and Y.P. provided concept and design, wrote, reviewed, and/or revised the manuscript; S.K. reviewed and revised the manuscript; S.A. and R.C. wrote, revised the manuscript and provided expert guidance.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Yazan Migdady, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239; e-mail: migdady@ohsu.edu
References

1. ISBT ISoBT: Red cell immunogenetics and blood group terminology. In.; 2021.
2. Hows J, Beddow K, Gordon-Smith E, Branch DR, Spruce W, Sniecinski I, Krance RA, Petz LD: Donor-derived red blood cell antibodies and immune hemolysis after allogeneic bone marrow transplantation. Blood 1986, 67(1):177-181.
3. Rowley SD, Donato ML, Bhattacharyya P: Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. Bone Marrow Transplant 2011, 46(9):1167-1185.
4. Griffith LM, McCoy JP, Jr., Bolan CD, Stroncek DF, Pickett AC, Linton GF, Lundqvist A, Srinivasan R, Leitman SF, Childs RW: Persistence of recipient plasma cells and anti-donor isoehaemagglutinins in patients with delayed donor erythropoiesis after major ABO incompatible non-myeloablative haematopoietic cell transplantation. Br J Haematol 2005, 128(5):668-675.
5. Stussi G, Muntwyler J, Passweg JR, Seebach L, Schanz U, Gmur J, Gratwohl A, Seebach JD: Consequences of ABO incompatibility in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2002, 30(2):87-93.
6. Allen ES, Nelson RC, Flegel WA: How we evaluate red blood cell compatibility and transfusion support for patients with sickle cell disease undergoing hematopoietic progenitor cell transplantation. Transfusion 2018, 58(11):2483-2489.
7. Ting A, Pun A, Dodds AJ, Atkinson K, Biggs JC: Red cell alloantibodies produced after bone marrow transplantation. Transfusion 1987, 27(2):145-147.
8. Young PP, Goodnough LT, Westervelt P, Diersio JF: Immune hemolysis involving non-ABO/RhD alloantibodies following hematopoietic stem cell transplantation. Bone Marrow Transplant 2001, 27(12):1305-1310.
9. Abou-Elena AA, Camarillo TA, Allen MB, Barclay S, Pierce JA, Holland HK, Wingard JR, Bray RA, Rodey GE, Hillyer CD: Low incidence of red cell and HLA antibody formation by bone marrow transplant patients. Transfusion 1995, 35(11):931-935.
10. de La Rubia J, Arriaga F, Andreu R, Sanz G, Jiménez C, Vicente A, Carpio N, Marty ML, Sanz MA: Development of non-ABO RBC alloantibodies in patients undergoing allogeneic HPC transplantation. Is ABO incompatibility a predisposing factor? Transfusion 2001, 41(1):106-110.
11. Flegel WA: Pathogenesis and mechanisms of antibody-mediated hemolysis. Transfusion 2015, 55(S2):S47-S58.
12. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D et al: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005, 11(12):945-956.
13. Couriel D, Carpenter PA, Cutler C, Bolanos-Meade J, Treister NS, Gea-Banacloche J, Shaughnessy P, Hymes S, Kim S, Wayne AS et al: Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant 2006, 12(4):375-396.
14. Szanto CL, Langenhorst J, de Koning C, Nierkens S, Bierings M, Huitema ADR, Lindemans CA, Boelens JJ: Predictors for Autoimmune Cytopenias after Allogeneic Hematopoietic Cell Transplantation in Children. Biol Blood Marrow Transplant 2020, 26(1):114-122.
15. Stowell SR, Winker AM, Maier CL, Arthur CM, Smith NH, Girard-Pierce KR, Cummings RD, Zimring JC, Hendrickson JE: Initiation and Regulation of Complement during Hemolytic Transfusion Reactions. Clinical and Developmental Immunology 2012, 2012:1-12.
16. Rowley SD, Liang PS, Ulz L: Transplantation of ABO-incompatible bone marrow and peripheral blood stem cell components. Bone Marrow Transplant 2000, 26(7):749-757.
17. Curley C, Pillai E, Mudie K, Western R, Hutchins C, Durrant S, Kennedy GA: Outcomes after major or bidirectional ABO-mismatched allogeneic hematopoietic progenitor cell transplantation after pretransplant isoagglutinin reduction with donor-type secretor plasma with or without plasma exchange. Transfusion 2012, 52(2):291-297.
18. Hirokawa M, Fukuda T, Ohashi K, Hidaka M, Ichinohe T, Iwato K, Kanamori H, Murata M, Sakura T, Imamura M et al: Efficacy and long-term outcome of treatment for pure red cell aplasia after allogeneic stem cell transplantation from major ABO-incompatible donors. Biol Blood Marrow Transplant 2013, 19(7):1026-1032.

19. Griffith LM, McCoy JP, Bolan CD, Stronccek DF, Pickett AC, Linton GF, Lundqvist A, Srinivasan R, Leitman SF, Childs RW: Persistence of recipient plasma cells and anti-donor isohaemagglutinins in patients with delayed donor erythropoiesis after major ABO incompatible non-myeloablative haematopoietic cell transplantation. British Journal of Haematology 2005, 128(5):668-675.

20. Gmur JP, Burger J, Schaffner A, Neftel K, Oelz O, Frey D, Metaxas M: Pure red cell aplasia of long duration complicating major ABO-incompatible bone marrow transplantation. Blood 1990, 75(1):290-295.

21. Worel N, Greinix HT, Schneider B, Kurz M, Rabitsch W, Knobl P, Reiter E, Derfker K, Fischer G, Hinterberger W et al: Regeneration of erythropoiesis after related- and unrelated-donor BMT or peripheral blood HPC transplantation: a major ABO mismatch means problems. Transfusion 2000, 40(5):543-550.

22. Damodor S, Shanley R, MacMillan M, Ustun C, Weisdorf D: Donor-to-Recipient ABO Mismatch Does Not Impact Outcomes of Allogeneic Hematopoietic Cell Transplantation Regardless of Graft Source. Biol Blood Marrow Transplant 2017, 23(5):795-804.

23. Kanda J, Ichinohe T, Matsuo K, Benjamin RJ, Klumpp TR, Rozman P, Blumberg N, Mehta J, Sohn SK, Uchiyama T: Impact of ABO mismatching on the outcomes of allogeneic related and unrelated blood and marrow stem cell transplantsations for hematologic malignancies: IPD-based meta-analysis of cohort studies. Transfusion 2009, 49(4):624-635.

24. Logan AC, Wang Z, Alimoghadam K, Wong RM, Lai T, Negrin RS, Grumet C, Logan BR, Zhang MJ, Spellman SR et al: ABO mismatch is associated with increased nonrelapse mortality after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2015, 21(4):746-754.

25. Canaani J, Savani BN, Labopin M, Huang XJ, Cicere W, Tischer J, Koc Y, Bruno B, Gülbas Z et al: Impact of ABO incompatibility on patients' outcome after haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia - a report from the Acute Leukemia Working Party of the EBMT. Haematologica 2017, 102(6):1066-1074.

26. Bolan CD, Leitman SF, Griffith LM, Wesley RA, Procter JL, Stronccek DF, Barrett AJ, Childs RW: Delayed donor red cell chimerism and pure red cell aplasia following major ABO-incompatible nonmyeloablative hematopoietic stem cell transplantation. Blood 2001, 98(6):1687.

27. Worel N, Kalhs P, Keil F, Prinz E, Moser K, Schulenburg A, Mitterbauer M, Mannhalter C, Mayr WR, Schwarzinger I et al: ABO mismatch increases transplant-related morbidity and mortality in patients given nonmyeloablative allogeneic HPC transplantation. Transfusion 2003, 43(8):1153-1161.

28. Brierley CK, Littlewood TJ, Peniket AJ, Gregg R, Ward J, Clark A, Parker A, Malladi R, Medd P: Impact of ABO blood group mismatch in alemtuzumab-based reduced-intensity conditioned haematopoietic SCT. Bone Marrow Transplant 2015, 50(7):931-938.

29. Dehn J, Spellman S, Hurley CK, Shaw BE, Barker JN, Burns LJ, Confer DL, Eapen M, Fernandez-Vina M, Hartzman R et al: Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood 2019, 134(12):924-934.

30. Buckner CD, Clift RA, Sanders JE, Williams B, Gray M, Storb R, Thomas ED: ABO-incompatible marrow transplants. Transplantation 1978, 26(4):233-238.

31. Bensinger WI, Buckner CD, Thomas ED, Clift RA: ABO-incompatible marrow transplants. Transplantation 1982, 33(4):427-429.

32. Benjamin RJ, McGurk S, Ralston MS, Churchill WH, Antin JH: ABO incompatibility as an adverse risk factor for survival after allogeneic bone marrow transplantation. Transfusion 1999, 39(2):179-187.
33. Quek J, Lee JJ, Lim FL, Diong C, Goh YT, Gopalakrishnan S, Ho A, Hwang W, Koh M, Loh Y et al: Donor-type fresh frozen plasma is effective in preventing hemolytic reaction in major ABO incompatible allogeneic stem cell transplant. *Transfusion* 2019, 59(1):335-339.

34. Mehta P, Ramprakash S, Raghuram CP, Trivedi D, Dhanya R, Agarwal RK, Faulkner L: Pre-transplant donor-type red cell transfusion is a safe and effective strategy to reduce isohemagglutinin titers and prevent donor marrow infusion reactions in major ABO-mismatched transplants. *Ann Hematol* 2021, 100(8):2071-2078.

35. Scholl S, Klink A, Müge LO, Schilling K, Höffken K, Sayer HG: Safety and impact of donor-type red blood cell transfusion before allogeneic peripheral blood progenitor cell transplantation with major ABO mismatch. *Transfusion* 2005, 45(10):1676-1683.

36. Bolan CD, Childs RW, Procter JL, Barrett AJ, Leitman SF: Massive immune haemolysis after allogeneic peripheral blood stem cell transplantation with minor ABO incompatibility. *Br J Haematol* 2001, 112(3):787-795.

37. Toren A, Dacosta Y, Manny N, Varadi G, Or R, Nagler A: Passenger B-lymphocyte-induced severe hemolytic disease after allogeneic peripheral blood stem cell transplantation. *Blood* 1996, 87(2):843-844.

38. Noborio K, Muroi K, Izumi T, Toshima M, Kawano-Yamamoto C, Otsuki T, Nagai T, Komatsu N, Ozawa K: Massive immune hemolysis after non-myeloablative allogeneic peripheral blood stem cell transplantation with minor ABO-incompatibility. *Leuk Lymphoma* 2003, 44(2):357-359.

39. Worel N, Greinix HT, Keil F, Mitterbauer M, Lechner K, Fischer G, Mayr W, Hocker P, Kalhs P: Severe immune hemolysis after minor ABO-mismatched allogeneic peripheral blood progenitor cell transplantation occurs more frequently after nonmyeloablative than myeloablative conditioning. *Transfusion* 2002, 42(10):1293-1301.

40. Rosenthal GJ, Weigand GW, Germolec DR, Blank JA, Luster MI: Suppression of B cell function by methotrexate and trimetrexate. Evidence for inhibition of purine biosynthesis as a major mechanism of action. *J Immunol* 1988, 141(2):410-416.

41. Vaæzi M, Oulad Damesghdi D, Souri M, Setarehdan SA, Alimoghaddam K, Ghavamzadeh A: ABO Incompatibility and Hematopoietic Stem Cell Transplantation Outcomes. *Int J Hematol Oncol Stem Cell Res* 2017, 11(2):139-147.

42. Ma YR, Wang WJ, Cheng YF, Zhang YY, Mo XD, Han TT, Wang FR, Yan CH, Sun YQ, Chen YH et al: Impact of ABO incompatibility on outcomes after haploidentical hematopoietic stem cell transplantation for severe aplastic anemia. *Bone Marrow Transplant* 2020.

43. Grube M, Wolff D, Ahrens N, Herzberg PY, Herr W, Holler E: ABO blood group antigen mismatch has an impact on outcome after allogeneic peripheral blood stem cell transplantation. *Clin Transplant* 2016, 30(11):1457-1465.

44. Ludajic K, Balavcarza Y, Bickeboller H, Rosenmayr A, Fischer GF, Faé I, Kalhs P, Pohlreich D, Koubia M, Dobrovolina M et al: Minor ABO-mismatches are risk factors for acute graft-versus-host disease in hematopoietic stem cell transplant patients. *Biol Blood Marrow Transplant* 2009, 15(11):1400-1406.

45. Booth GS, Gehrie EA, Bolan CD, Savani BN: Clinical guide to ABO-incompatible allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2013, 19(8):1152-1158.

46. Heddle NM, Soutar RL, O’Hoski PL, Singer J, McBride JA, Ali MA, Kelton JG: A prospective study to determine the frequency and clinical significance of alloimmunization post-transfusion. *Br J Haematol* 1995, 91(4):1000-1005.

47. Hoeltge GA, Domen RE, Rybicki LA, Schaffer PA: Multiple red cell transfusions and alloimmunization. Experience with 6996 antibodies detected in a total of 159,262 patients from 1985 to 1993. *Arch Pathol Lab Med* 1995, 119(1):42-45.

48. Seyfried H, Walewska I: Analysis of immune response to red blood cell antigens in multitransfused patients with different diseases. *Mater Med Pol* 1990, 22(1):21-25.

49. Higgins JM, Sloan SR: Stochastic modeling of human RBC alloimmunization: evidence for a distinct population of immunologic responders. *Blood* 2008, 112(6):2546-2553.

50. Klumph TR: Immunohematologic complications of bone marrow transplantation. *Bone Marrow Transplant* 1991, 8(3):159-170.
562. Lopez A, de la Rubia J, Arriaga F, Jimenez C, Sanz GF, Carpio N, Marty ML: Severe hemolytic anemia due to multiple red cell alloantibodies after an ABO-incompatible allogeneic bone marrow transplant. *Transfusion* 1998, 38(3):247-251.
565. Kay B, Poisson JL, Tuma CW, Shulman IA: Anti-Jk present in red cell adherence but missed by gel testing can cause hemolytic transfusion reactions. *Transfusion* 2016, 56(12):2973-2979.
566. Leo A, Mytilineos J, Voso MT, Weber-Nordt R, Liebisch P, Lensing C, Schraven B: Passenger lymphocyte syndrome with severe hemolytic anemia due to an anti-Jk(a) after allogeneic PBPC transplantation. *Transfusion* 2000, 40(6):632-636.
571. Petz LD: Immune hemolysis associated with transplantation. *Semin Hematol* 2005, 42(3):145-155.
572. Franchini M, Gandini G, Aprili G: Non-ABO red blood cell alloantigens following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004, 33(12):1169-1172.
576. Campbell-Lee SA, Gvozdjan K, Choi KM, Chen YF, Saraf SL, Hsu LL, Gordeuk VR, Strauss RG, Triulzi DJ: Red blood cell alloimmunization in sickle cell disease: assessment of transfusion protocols during two time periods. *Transfusion* 2018, 58(7):1588-1596.
579. Hindawi S, Badawi M, Elsayoum EI, Elgemmezei T, Al Hassani A, Raml M, Alamoudi S, Ghom K: The value of transfusion of phenotyped blood units for thalassemia and sickle cell anemia patients at an academic center. *Transfusion* 2020, 60 Suppl 1:S15-S21.
582. Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM: High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. *Blood* 2013, 122(6):1062-1071.
585. Allen ES, Srivastava K, Hsieh MM, Fitzhugh CD, Klein HG, Tisdale JF, Flegel WA: Immunohaematological complications in patients with sickle cell disease after haemopoietic progenitor cell transplantation: a prospective, single-centre, observational study. *Lancet Haematol* 2017, 4(11):e553-e561.
589. Nickel RS, Flegel WA, Adams SD, Hendrickson JE, Liang H, Tisdale JF, Hsieh MM: The impact of pre-existing HLA and red blood cell antibodies on transfusion support and engraftment in sickle cell disease after nonmyeloablative hematopoietic stem cell transplantation from HLA-matched sibling donors: A prospective, single-center, observational study. *EclinicalMedicine* 2020, 24:100432.
591. Thompson AA, Cunningham MJ, Singer ST, Neufeld EJ, Vichinsky E, Yamashita R, Giardina P, Kim HY, Trachtenberg F, Kwiatkowski JL et al: Red cell alloimmunization in a diverse population of transfused patients with thalassemia. *Br J Haematol* 2011, 153(1):121-128.
592. Datta SS, Mukherjee S, Talukder B, Bhattacharya P, Mukherjee K: Frequency of Red Cell Alloimmunization and Autoimmunization in Thalassemia Patients: A Report from Eastern India. *Adv Hematol* 2015, 2015:610931.
593. Waldis SJ, Uter S, Kavitsky D, Fickinger C, Vege S, Friedman DF, Westhoff CM, Chou ST: Rh alloimmunization in chronically transfused patients with thalassemia receiving RhD, C, E, and K matched transfusions. *Blood Adv* 2021, 5(3):737-744.
594. El-Beshlawy A, Salama AA, El-Masry MR, El Husseiny NM, Abdelhameed AM: A study of red blood cell alloimmunization and autoimmunization among 200 multitransfused Egyptian β thalassemia patients. *Sci Rep* 2020, 10(1):21079.
595. Höning M, Flegel WA, Schwarz K, Freihorst JF, Baumann U, Seltsam A, Debatin KM, Schulz AS, Friedrich W: Successful hematopoietic stem-cell transplantation in a patient with chronic granulomatous disease and McLeod phenotype sensitized to Kx and K antigens. *Bone Marrow Transplant* 2010, 45(1):209-211.
596. Kordes U, Binder TM, Eiermann TH, Hassenpflug-Diedrich B, Hassan MA, Beutel K, Nagy M, Kabisch H, Schneppenheim R: Successful donor-lymphocyte infusion for extreme immune-hemolysis following unrelated BMT in a patient with X-linked chronic granulomatous disease and McLeod phenotype. *Bone Marrow Transplant* 2008, 42(3):219-220.
669. Kim MY, Chaudhary P, Shulman IA, Pullarkat V: Major non-ABO incompatibility caused by anti-Jk(a) in a patient before allogeneic hematopoietic stem cell transplantation. *Immunohematology* 2013, 29(1):11-14.
670. Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, Duarte RF, Dufour C, Falkenburg JH, Farge-Bancel D *et al*: Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. *Bone Marrow Transplant* 2015, 50(4):476-482.
671. Lasalle-Williams M, Nuss R, Le T, Cole L, Hassell K, Murphy JR, Ambruso DR: Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center (CME). *Transfusion* 2011, 51(8):1732-1739.
672. Casas J, Friedman DF, Jackson T, Vege S, Westhoff CM, Chou ST: Changing practice: red blood cell typing by molecular methods for patients with sickle cell disease. *Transfusion* 2015, 55(6 Pt 2):1388-1393.
673. Fasano RM, Chou ST: Red Blood Cell Antigen Genotyping for Sickle Cell Disease, *Thalassemia, and Other Transfusion Complications*. *Transfus Med Rev* 2016, 30(4):197-201.
674. Liu F, Li G, Mao X, Hu L: ABO chimerism determined by real-time polymerase chain reaction analysis after ABO-incompatible haematopoietic stem cell transplantation. *Blood Transfus* 2013, 11(1):43-52.
675. Barcellini W, Fattizzo B, Zaninoni A: Management of refractory autoimmune hemolytic anemia after allogeneic hematopoietic stem cell transplantation: current perspectives. *J Blood Med* 2019, 10:265-278.
676. Miller PDE, Snowden JA, De Latour RP, Iacobelli S, Eikema D-J, Knol C, Marsh JCW, Rice C, Koh M, Fagioli F *et al*: Autoimmune cytopenias (AIC) following allogeneic hematopoietic stem cell transplant for acquired aplastic anemia: a joint study of the Autoimmune Diseases and Severe Aplastic Anaemia Working Parties (ADWP/SAAWP) of the European Society for Blood and Mar. *Bone Marrow Transplantation* 2020, 55(2):441-451.
677. Horn B, Viele M, Mentzer W, Mogck N, Desantes K, Cowan M: Autoimmune hemolytic anemia in patients with SCID after T cell-depleted BM and PBSC transplantation. *Bone Marrow Transplantation* 1999, 24(9):1009-1013.
678. Ahmed I, Teruya J, Murray-Krezan C, Krance R: The incidence of autoimmune hemolytic anemia in pediatric hematopoietic stem cell recipients post-first and post-second hematopoietic stem cell transplant. *Pediatric Transplantation* 2015, 19(4):391-398.
679. Kruizinga MD, Van Tol MJD, Bekker V, Netelenbos T, Smiers FJ, Bresters D, Jansen-Hooogendijk AM, Van Ostaijen-Ten Dam MM, Kollen WJW, Zwaginga JJ *et al*: Risk Factors, Treatment, and Immune Dysregulation in Autoimmune Cytopenia after Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Patients. *Blood and Marrow Transplantation* 2018, 24(4):772-778.
680. O’Brien TA, Eastlund T, Peters C, Neglia JP, Defor T, Ramsay NKC, Scott Baker K: Autoimmune haemolytic anaemia complicating haematopoietic cell transplantation in paediatric patients: high incidence and significant mortality in unrelated donor transplants for non-malignant diseases. *British Journal of Haematology* 2004, 127(1):67-75.
681. Faraci M, Zecca M, Pillon M, Rovelli A, Menconi MC, Ripaldi M, Fagioli F, Rabusin M, Ziino O, Laino E *et al*: Autoimmune Hematological Diseases after Allogeneic Hematopoietic Stem Cell Transplantation in Children: An Italian Multicenter Experience. *Blood and Marrow Transplantation* 2014, 20(2):272-278.
682. Garratty G: Autoantibodies induced by blood transfusion. *Transfusion* 2004, 44(1):5-9.
683. González-Vicent M, Sanz J, Fuster JL, Cid J, de Heredia CD, Morillo D, Fernández JM, Pascaul A, Badell I, Serrano D *et al*: Autoimmune hemolytic anemia (AIHA) following allogeneic hematopoietic stem cell transplantation (HSCT): A retrospective analysis and a proposal of treatment on behalf of the Grupo Español De Trasplante de Medula Osea en Niños (GETMON) and the Grupo Español de Trasplante Hematopoietico (GETH). *Transfus Med Rev* 2018.
684. Adams BR, Miller AN, Costa LJ: Self-limited hemolysis due to anti-D passenger lymphocyte syndrome in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010, 45(4):772-773.
83. Aung FM, Lichtiger B, Bassett R, Liu P, Alousi A, Bashier Q, Ciurea SO, de Lima MJ, Hosing C, Kebriaei P et al: Incidence and natural history of pure red cell aplasia in major ABO-mismatched haematopoietic cell transplantation. *Br J Haematol* 2013, 160(6):798-805.
84. Marco-Ayala J, Gómez-Seguí I, Sanz G, Solves P: Pure red cell aplasia after major or bidirectional ABO incompatible hematopoietic stem cell transplantation: to treat or not to treat, that is the question. *Bone Marrow Transplant* 2021, 56(4):769-778.
85. Stussi G, Halter J, Bucheli E, Valli PV, Seebach L, Gmürr J, Gratwohl A, Schanz U, Passweg JR, Seebach JD: Prevention of pure red cell aplasia after major or bidirectional ABO blood group incompatible hematopoietic stem cell transplantation by pretransplant reduction of host anti-donor isoagglutinins. *Haematologica* 2009, 94(2):239-248.
86. Holbro A, Passweg JR: Management of hemolytic anemia following allogeneic stem cell transplantation. *Hematology Am Soc Hematol Educ Program* 2015, 2015:378-384.
87. Hill QA, Stamps R, Mussey E, Grainger JD, Provan D, Hill A, British Society for Haematology G: Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia. *Br J Haematol* 2017, 177(2):208-220.
88. Silva VA, Seder RH, Weintraub LR: Synchronization of plasma exchange and cyclophosphamide in severe and refractory autoimmune hemolytic anemia. *J Clin Apher* 1994, 9(2):120-123.
89. Santamaría A, Sureda A, Martino R, Domingo-Albós A, Muñiz-Díaz E, Brunet S: Successful treatment of pure red cell aplasia after major ABO-incompatible T cell-depleted bone marrow transplantation with erythropoietin. *Bone Marrow Transplant* 1997, 20(12):1105-1107.
90. Busca A, Dellacasa C, Giaccone L, Manetta S, Biale L, Godio L, Aydin S, Festuccia M, Brunello L, Bruno B: Eltrombopag for the Treatment of Refractory Pure RBC Aplasia after Major ABO Incompatible Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* 2014, 20(4):1765-1770.
91. Longval T, Galimard JE, Lépërte AC, Suarez F, Amiranoff D, Cazaux M, Kaphan E, Michonneau D, Dhedin N, Coman T et al: Treatment for pure red cell aplasia after major ABO-incompatible allogeneic stem cell transplantation: a multicentre study. *British Journal of Haematology* 2021, 193(4):814-826.
92. Helbig G, Stella-Holowiecka B, Krawczyk-Kulis M, Wojnar J, Markiewicz M, Wojciechowska-Sadus M, Koper M, Kruzel T, Najda J, Nowak K et al: Successful treatment of pure red cell aplasia with repeated, low doses of rituximab in two patients after ABO-incompatible allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia. *Haematologica* 2005, 90 Suppl:ECR33.
93. Audet M, Panaro F, Piardi T, Huang P, Cag M, Cinquebre L, Wolf P: Passenger lymphocyte syndrome and liver transplantation. *Clin Dev Immunol* 2008, 2008:715769.
94. Hess J, Su L, Nizzi F, Beebe K, Magee K, Adams RH, Aloussy A: Successful treatment of severe refractory autoimmune hemolytic anemia after hematopoietic stem cell transplant with abatacept. *Transfusion* 2018, 58(9):2122-2127.
95. Taniguchi S, Yamasaki K, Shibuya T, Asayama R, Harada M, Niho Y: Recombinant human erythropoietin for long-term persistent anemia after major ABO-incompatible bone marrow transplantation. *Bone Marrow Transplant* 1993, 12(4):423.
96. Liu X, Cheng L, He Y, Zhang R, Lu R, Zhang J, Hong M, He G, Li J: Eltrombopag restores erythropoiesis in refractory adult acquired pure red cell aplasia. *Int J Hematol* 2021, 114(1):124-128.
97. Selleri C, Raiola A, De Rosa G, Luciano L, Pezzullo L, Picardi M, Rotoli B: CD34+-enriched donor lymphocyte infusions in a case of pure red cell aplasia and late graft failure after major ABO-incompatible bone marrow transplantation. *Bone Marrow Transplant* 1998, 22(6):605-607.
98. Fang B, Song Y, Li N, Li J, Han Q, Zhao RC: Mesenchymal stem cells for the treatment of refractory pure red cell aplasia after major ABO-incompatible hematopoietic stem cell transplantation. *Ann Hematol* 2009, 88(3):261-266.
99. Sergeevichyeva V, Kruchkova I, Chernykh E, Sheveva E, Kulagin A, Gilevich A, Lisukov I, Sergeevichyev D, Kozlov V: Rapid Recovery from Chronic PRCA by MSC Infusion in Patient after Major ABO-Mismatched alloSCT. *Case Rep Med* 2012, 2012:862721.
101. Poon LM, Koh LP: Successful treatment of isohemagglutinin-mediated pure red cell aplasia after ABO-mismatched allogeneic hematopoietic cell transplant using bortezomib. Bone Marrow Transplantation 2012, 47(6):870-871.

102. Tolbert VP: Daratumumab Is Effective in the Treatment of Refractory Post-Transplant Autoimmune Hemolytic Anemia: A Pediatric Case Report. Blood 2016, 128.

103. Chapuy CI, Kaufman RM, Alyea EP, Connors JM: Daratumumab for Delayed Red-Cell Engraftment after Allogeneic Transplantation. N Engl J Med 2018, 379(19):1846-1850.

104. Schuetz C, Hoening M, Moshous D, Weinstock C, Castelle M, Bendavid M, Shimano K, Tolbert V, Schulz AS, Dvorak CC: Daratumumab in life-threatening autoimmune hemolytic anemia following hematopoietic stem cell transplantation. Blood Adv 2018, 2(19):2550-2553.

105. Blenerhasset R, Sudini L, Gottlieb D, Bhattacharyya A: Post-allogeneic transplant Evans syndrome successfully treated with daratumumab. Br J Haematol 2019.

106. Migdady Y, Ediriwickrema A, Jackson RP, Kadi W, Gupta R, Socola F, Arai S, Martin BA: Successful treatment of thrombocytopenia with daratumumab after allogeneic transplantation: a case report and literature review. Blood Adv 2020, 4(5):815-818.

107. Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, Doshi P, Kaufman RM: Resolving the daratumumab interference with blood compatibility testing. Transfusion 2015, 55(6 Pt 2):1545-1554.

108. van de Donk N: Reprint of "Immunomodulatory effects of CD38-targeting antibodies". Immunol Lett 2019, 205:71-77.

109. Krejcik J, Casneuf T, Nijhof IS, Verbit B, Bald J, Plesner T, Syed K, Liu K, van de Donk NW, Weiss BM et al: Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 2016, 128(3):384-394.

110. Mócsai A, Ruland J, Tybulewicz VL: The SYK tyrosine kinase: a crucial player in diverse biological functions. Nat Rev Immunol 2010, 10(6):387-402.

111. Kaur M, Singh M, Silakari O: Inhibitors of switch kinase 'spleen tyrosine kinase' in inflammation and immune-mediated disorders: a review. Eur J Med Chem 2013, 67:343-446.

112. Poe JC, Jia W, Di Paolo JA, Reyes NJ, Kim JY, Su H, Sundy JS, Cardones AR, Perez VL, Chen BJ et al: SYK inhibitor entospletinib prevents ocular and skin GVHD in mice. JCI Insight 2018, 3(19).

113. Vo P, Purev E, West KA, McDuffee E, Worthy T, Cook L, Hawks G, Wells B, Shalabi R, Rother J, Flegel WA et al: A pilot trial of complement inhibition using eculizumab to overcome platelet transfusion refractoriness in human leukocyte antigen allo-immunized patients. Br J Haematol 2020, 189(3):551-558.

114. Gauchy AC, Hentzien M, Wynckel A, De Marcellus V, Rodier C, Delmer A, Quinquenel A: Efficacy of eculizumab in refractory life-threatening warm autoimmune hemolytic anemia associated with chronic myelomonocytic leukemia. Clinical Case Reports 2020, 8(12):2641-2644.

115. Röth A, Bommmer M, Hüttmann A, Herich-Therhißre D, Kuklik N, Rekowski J, Lenz V, Schrezenmeier H, Dührens U: Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial. Blood Advances 2018, 2(19):2543-2549.

116. Röth A, Barcellini W, D’Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt THA, Fruebis J et al: Sutimlimab in Cold Agglutinin Disease. New England Journal of Medicine 2021, 384(14):1323-1334.

117. Hillmen P, Szer J, Weitz I, Röth A, Höchsmann B, Panse J, Usuki K, Griffin M, Kiladjian J-J, De Castro C et al: Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. New England Journal of Medicine 2021, 384(11):1028-1037.

118. Frey NV, Porter DL: Graft-versus-host disease after donor leukocyte infusions: presentation and management. Best Pract Res Clin Haematol 2008, 21(2):205-222.

119. Rowley S, Liang P, Ulz L: Transplantation of ABO-incompatible bone marrow and peripheral blood stem cell components. Bone Marrow Transplantation 2000, 26(7):749-757.
120. Kollman C, Howe CWS, Anasetti C, Antin JH, Davies SM, Filipovich AH, Hegland J, Kamani N, Kernan NA, King R et al: Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood 2001, 98(7):2043-2051.

121. Seebach JD, Stussi G, Passweg JR, Loberiza FR, Gajewski JL, Keating A, Goerner M, Rowlings PA, Tiberghien P, Elfenbein GJ et al: ABO Blood Group Barrier in Allogeneic Bone Marrow Transplantation Revisited. Biology of Blood and Marrow Transplantation 2005, 11(12):1006-1013.

122. Helming AM, Brand A, Wolterbeek R, Van Tol MJD, Egeler RM, Ball LM: ABO incompatible stem cell transplantation in children does not influence outcome. Pediatric Blood & Cancer 2007, 49(3):313-317.

123. Michallet M, Le QH, Mohty M, Prébet T, Nicolini F, Boiron JM, Esperou H, Attal M, Milpied N, Lioure B et al: Predictive factors for outcomes after reduced intensity conditioning hematopoietic stem cell transplantation for hematological malignancies: a 10-year retrospective analysis from the Société Française de Greffe de Moelle et de Thérapie Cellulaire. Exp Hematol 2008, 36(5):535-544.

124. Kimura F, Sato K, Kobayashi S, Ikeda T, Sao H, Okamoto S, Miyamura K, Mori S, Akiyama H, Hirokawa M et al: Impact of ABO-blood group incompatibility on the outcome of recipients of bone marrow transplants from unrelated donors in the Japan Marrow Donor Program. Haematologica 2008, 93(11):1686-1693.

125. Canaani J, Savani BN, Labopin M, Michallet M, Craddock C, Socié G, Volin L, Maertens JA, Crawley C, Blaise D et al: ABO incompatibility in mismatched unrelated donor allogeneic hematopoietic cell transplantation for acute myeloid leukemia: A report from the acute leukemia working party of the EBMT. Am J Hematol 2017, 92(8):789-796.

126. Damodor S, Shanley R, Macmillan M, Ustun C, Weisdorf D: Donor-to-Recipient ABO Mismatch Does Not Impact Outcomes of Allogeneic Hematopoietic Cell Transplantation Regardless of Graft Source. Biology of Blood and Marrow Transplantation 2017, 23(5):795-804.

127. Ataca Atilla P, Akkus E, Atilla E, Gokmen N, Civriz Bozdag S, Kocak Toprak S, Kurt Yuksel M, Ozcan M, Demirer T, Illhan O et al: Effects of ABO-incompatibility in allogeneic hematopoietic stem cell transplantation. Transfusion Clinique et Biologique 2020, 27(3):115-121.

128. Heim MU, Schleuning M, Eckstein R, Huhn D, Siegert W, Clemm C, Ledderose G, Kolb HJ, Wilmanns M, Mempel W: Rh antibodies against the pretransplant red cells following Rh-incompatible bone marrow transplantation. Transfusion 1988, 28(3):272-275.

129. Tasaki T, Sasaki S, Gotoh K, Itoh C, Itokh S, Kuriya S: Multiple red blood cell antibodies produced by donor B lymphocytes after ABO-matched allogeneic bone marrow transplantation. Transfus Sci 1999, 20(2):121-127.

130. Izumi N, Fuse I, Furukawa T, Uesugi Y, Tsuchiyama J, Toba K, Tagashi K, Yamada K, Ohtake S, Saitoh Y et al: Long-term production of pre-existing alloantibodies to E and e after allogeneic BMT in a patient with aplastic anemia resulting in delayed hemolytic anemia. Transfusion 2003, 43(2):241-245.

131. Zupanska B, Zaucha JM, Michalewska B, Malinowska A, Brojer E, Hellmann A: Multiple red cell alloantibodies, including anti-Dib, after allogeneic ABO-matched peripheral blood progenitor cell transplantation. Transfusion 2005, 45(1):16-20.

132. Myser T, Steedman M, Hunt K, Strohm P, Williams M, Kennedy M: A bone marrow transplant with an acquired anti-Le(a): a case study. Hum Immunol 1986, 17(2):102-106.
| ABO Mismatch | Recipient Phenotype | Donor Phenotype |
|--------------|---------------------|-----------------|
| Major        | O                   | A, B, AB        |
|              | A                   | AB, B           |
|              | B                   | AB, A           |
| Minor        | A                   | O               |
|              | B                   | O               |
|              | AB                  | O, A, B         |
| Bidirectional| A                   | B               |
|              | B                   | A               |
| Reference          | Year  | ABO match (N, %): Matched Major | Reduced intensity conditioning (N/%) | Related donor (N/%) | Bone marrow graft (N/%) | GVHD prophylaxis | Engraftment | GVHD rate | Relapse rate | NRM | OS |
|--------------------|-------|----------------------------------|-------------------------------------|-------------------|------------------------|------------------|-------------|------------|-------------|-----|----|
| Rowley, et al.     | 2000  | 0                               | None                                | All related       | --                     | CNI+MTX          | NS          | No data    | No data    | No data     | No data |
|                    |       | 83 (53)                         | 65 (41)                             |                   | 62 (74.7)              |                  |             |            |             |               |       |
|                    |       | 10 (6)                          | 46 (70.8)                           |                   | 7 (70.0)               |                  |             |            |             |               |       |
| Kollman, et al.    | 2001  | No data                         | All matched unrelated               | All BM            | Various regimens       | NS               | No data     | No data    | No data    | No data     | NS    |
|                    |       | 2860 (41)                       | 1670 (24)                           |                   | 587 (8)                |                  |             |            |             |               |       |
|                    |       | 1802 (26)                       | 54 (13)                             |                   | 46 (70.8)              |                  |             |            |             |               |       |
|                    |       | 121 (56)                        | 17 (15)                             |                   | 6 (6)                  |                  |             |            |             |               |       |
| Seebach, et al.    | 2005  | 258 (12)                        | All related                         | All BM            | CNI+MTX                | NS               | No data     | No data    | No data    | No data     | NS    |
|                    |       | 451 (21)                        | 46 (10)                             |                   | 54 (13)                |                  |             |            |             |               |       |
|                    |       | 430 (14)                        | 17 (15)                             |                   | 17 (15)                |                  |             |            |             |               |       |
|                    |       | 114 (4)                         | 12 (5)                              |                   | 12 (5)                 |                  |             |            |             |               |       |
|                    |       | 121 (56)                        | 17 (15)                             |                   | 17 (15)                |                  |             |            |             |               |       |
| Helming, et al.    | 2007  | 0.5% of all subjects           | No data                             | No data            | CNI+/-MTX; MTX alone   | NS               | No data     | No data    | No data    | No data     | NS    |
|                    |       | 40 (19)                         | 86 (71)                             |                   | 86 (71)                |                  |             |            |             |               |       |
|                    |       | 15 (7)                          | 17 (43)                             |                   | 17 (43)                |                  |             |            |             |               |       |
|                    |       | 40 (19)                         | 15 (7)                              |                   | 15 (7)                 |                  |             |            |             |               |       |
|                    |       | 2108 (68)                       | 8 (27)                              |                   | 15 (34)                |                  |             |            |             |               |       |
|                    |       | 587 (8)                         | 16 (73)                             |                   | 16 (73)                |                  |             |            |             |               |       |
| Michallet, et al.  | 2008  | Major 205 (18.5)                 | All subjects                        | All subjects       | CNI only in 430 (39%)  | No data         | No data     | Higher in minor ABO incompatibility | No data | No data | Poorer in minor ABO incompatibility |
|                    |       | Minor 187 (17)                  | 932 (84) of all subjects            |                   | 932 (84)              |                  |             |            |             |               |       |
|                    |       |                                 | 213 (19) of all subjects            |                   | 213 (19)              |                  |             |            |             |               |       |
| Kimura, et al.     | 2008  | 348 (12)                        | No data                             | No data            | CNI+MTX                | NS               | No data     | Higher in major and minor ABO incompatibility | No data | No data | Poorer in major and minor ABO incompatibility |
|                    |       | 1834 (31)                       | 152 (8)                             |                   | 152 (8)               |                  |             |            |             |               |       |
|                    |       | 1202 (20)                       | 136 (11)                            |                   | 136 (11)              |                  |             |            |             |               |       |
|                    |       | 143 (2)                         | 30 (21)                             |                   | 30 (21)               |                  |             |            |             |               |       |
|                    |       | 58 (38)                         | 17 (29)                             |                   | 17 (29)               |                  |             |            |             |               |       |
|                    |       | 30 (19)                         | 8 (27)                              |                   | 8 (27)                |                  |             |            |             |               |       |
|                    |       | 44 (29)                         | 15 (34)                             |                   | 15 (34)               |                  |             |            |             |               |       |
|                    |       | 22 (14)                         | 16 (73)                             |                   | 16 (73)               |                  |             |            |             |               |       |
| Ludajic, et al.    | 2009  | All matched unrelated           | No data                             | No data            | CNI+MTX/MMF, 10% with CNI only | NS               | No data     | Higher acute GVHD rate in minor ABO incompatibility | No data | No data | NS |
|                    |       | 17 (29)                         | 8 (27)                              |                   | 8 (27)                |                  |             |            |             |               |       |
|                    |       | 30 (21)                         | 15 (34)                             |                   | 15 (34)               |                  |             |            |             |               |       |
|                    |       | 17 (29)                         | 16 (73)                             |                   | 16 (73)               |                  |             |            |             |               |       |
| Logan, et al. [24] | 2015  | 526 (30) of all subjects        | 1303 (75) of all subjects           | 727 (42) of all subjects | Various               | No data         | NS          | Higher in minor ABO incompatibility | Poorer in minor ABO incompatibility, especially in bone marrow grafts |
| Stanford           |       | 1053 (61)                       | 297 (17)                            |                   | 297 (17)              |                  |             |            |             |               |       |
|                    |       | 309 (18)                        | 78 (4)                              |                   | 78 (4)                |                  |             |            |             |               |       |
|                    |       | 526 (30) of all subjects        | 1303 (75) of all subjects           | 727 (42) of all subjects | Various               | No data         | NS          | Higher in minor ABO incompatibility | Poorer in minor ABO incompatibility |
|                   |       | 240 (59)                        | 73 (18)                             |                   | 73 (18)               |                  |             |            |             |               |       |
|                   |       | 73 (18)                         | 22 (5)                              |                   | 22 (5)                |                  |             |            |             |               |       |
|                   |       | 238 (55) of all subjects        | None                                | Various            | No data               | NS          | Higher in minor ABO incompatibility | Poorer in minor ABO incompatibility |
|                   |       | 330 (76) of all subjects        | None                                | Various            | No data               | NS          |             |            |             |               |       |
|                   |       | 1448 (28) of all subjects       | Various                             | No data            | NS                   | NS          | Higher in major ABO incompatibility | Poorer in major ABO incompatibility |
|                   |       | 2079 (40) of all subjects       | Various                             | No data            | NS                   | NS          |             |            |             |               |       |
|                   |       | 2333 (45) of all subjects       | Various                             | No data            | NS                   | NS          |             |            |             |               |       |
|                   |       | 2079 (40) of all subjects       | Various                             | No data            | NS                   | NS          |             |            |             |               |       |
**Table 2, continued**

| Reference        | Year | ABO match (N, %): Matched Major | Reduced intensity conditioning (N/%) | Related donor (N/%) | Bone marrow graft (N/%) | GVHD prophylaxis | Engraftment | GVHD rate | Relapse rate | NRM | OS |
|------------------|------|---------------------------------|-------------------------------------|--------------------|------------------------|------------------|-------------|-----------|-------------|-----|----|
| Grube, et al. [43] | 2016 | 252 (49) 105 (21) 117 (23) 38 (7) | 192 (76) 78 (74) 86 (74) 30 (79) | 108 (43) 25 (24) 32 (27) 7 (18) | None | No data | Delayed PLT engraftment in major ABO incompatibility | NS | NS | No data | NS |
| Cannani, et al. [125] | 2017 | 349 (40) 215 (25) 241 (28) 71 (8) | 193 (55) 122 (57) 154 (64) 38 (54) | None | None | CNI-based in 87% of all subjects | NS | Lower grade II-IV acute GCHD rate in major ABO incompatibility | NS | NS | NS |
| Cannani, et al. [25] | 2017 | 522 (63) 127 (15) 150 (18) 38 (5) | 215 (41) 45 (35) 68 (45) 12 (32) | All haploidentical | 279 (53) 76 (60) 83 (55) 19 (55) | No data | Delayed engraftment in major ABO incompatibility | Higher grade II-IV acute GVHD in bidirectional | NS | NS | Poorer in major ABO incompatibility + bone marrow graft |
| Damodar, et al. [126] | 2017 | 704 (47) 324 (22) 372 (25) 102 (7) | 301 (43) 128 (40) 151 (41) 54 (53) | 372 (53) 101 (31) 88 (24) 23 (23) | 296 (42) 87 (27) 73 (17) 19 (19) | No data | Delayed neutrophil engraftment only in bidirectional with umbilical cord blood graft | NS | NS | NS | NS |
| Ma, et al. [42] | 2020 | 114 (57) 47 (24) 38 (19) 0 | All subjects | All haploidentical | Both bone marrow and peripheral blood in all subjects | CNI+MMF+MTX | NS | Grade III-IV acute GVHD more common in minor | No data | No data | No data | NS |
| Ataca Atilla, et al. [127] | 2020 | 590 (59.0) 164 (16.4) 191 (19.1) 55 (5.5) | 110 (17) 32 (20) 35 (18) 18 (33) | 531 (90) 124 (76) 145 (76) 34 (62) | 189 (32) 33 (20) 41 (22) 8 (15) | CNI + MTX/MMF | Neutrophil engraftment delayed in mismatched groups | NS | NS | NS | NS |

Abbreviations: GVHD: graft-versus-host disease; CNI: Calcineurin inhibitor; NRM: non-relapse mortality; OS: overall survival; NS: not significant; MTX: methotrexate; MMF: mycophenolate mofetil; BM: bone marrow; CIBMTR: Center for International Blood and Marrow Transplant Research; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; PLT: platelets
Table 3. Non-ABO blood group systems with potential to cause clinically significant alloimmunization following HCT

| RBC blood group system | Antibodies |
|------------------------|------------|
| Rh System              | Anti-D[^8, 59, 128], Anti-C, Anti-c[^59, 129, 130], Anti-E[^8, 59, 128, 130, 131] |
| Kidd system            | Anti-Jka[^8, 131], Anti-Jkb |
| Kell system            | Anti-K[^51, 59], Jk[^a, 129] |
| MNSs system            | Anti-M[^51], Anti-N[^7], Anti-S, Anti-s[^8] |
| Lewis system           | Anti-Lu[^132], Anti-Le[^a, 59], 79 |
| Diego system           | Anti-Di[^a], Anti-Di[^b] |
| Other blood groups     | Anti-McC[^59], Anti-V[^59], Anti-Knop[^59] |

Figure legend:

Figure 1. Pathophysiology and targeted therapy for post-HCT immune mediated anemia. Post-HCT anemia is multifactorial due to new auto- or alloantibodies in combination with T-cell and cytokine mediated inflammatory processes. There are no formal guidelines in management. Several therapeutic approaches that target different pathophysiological aspects of post-HCT immune mediated anemia are outlined above.

Figure 2. General Approach for Posttransplant Immune Mediated Hemolysis. The graph outlines underlying mechanisms of posttransplant hemolysis, timing posttransplant, preventive methods and treatment strategies. Disclaimer: there is no consensus or guidelines on how to manage posttransplant immune mediated anemia. The management approach listed is based on expert opinions and available literature.

Figure 3. Pure Red Cell Aplasia (PRCA). PRCA is more frequently encountered in major ABO mismatch during the first 1-3 months posttransplant. Management approach is similar to PLS with frequent monitoring and RBC transfusion support. Other pharmacological interventions can be considered in refractory cases.

Figure 4. Passenger Lymphocyte Syndrome (PLS). Proactive approach with identifying patients at risk prior to transplant, alerting the blood bank service, frequent counts monitoring and transfusion support in the first 2 weeks posttransplant is a key for better clinical outcomes.
### Acute Hemolytic Reaction

| Cause | Condition | Onset | Prevention | Treatment |
|-------|-----------|-------|------------|-----------|
| ABO mismatch | Membrane attack complex | Day 0, at the time of stem cell infusion | Red cell reduction of the graft in major ABO mismatch; plasma reduction of the graft in minor ABO mismatch | Supportive care; transfuse recipient-compatible red cell units in major ABO mismatch; transfuse donor-compatible red cell units in minor ABO mismatch |

### PLS

| Minor ABO mismatch | Plasma reduction; in vivo or in vitro lymphodepletion | Supportive care; transfuse donor-compatible red cell units; RBC exchange |

### PRCA

| Residual recipient plasma cells; abnormal immune tolerance | Myeloablative conditioning when able |

### Allo- and Autoimmune Hemolytic Anemia

| Development of new autoantibodies; abnormal immune tolerance; mixed chimerism | Myeloablative conditioning when able |

- Severe cases: treat as AIHA outside of the transplant setting
  - Common: corticosteroids, IVIG, rituximab
  - Others: erythropoietin, splenectomy, Syk-inhibitor, anti-plasma cell, anti-complement, other immunosuppressants
Figure 3

**Identify Patient at Risk for PLS**
- Minor ABO mismatch
- Reduced-intensity conditioning
- Cyclosporine-only GvHD prophylaxis

**Precautions**
- Notify Transfusion Department in Advance
- Check CBC daily
- Preemptive transfusion to maintain Hb>9.5 g/dL

**Treatment**
- Transfusion
- Check post-transfusion Hb
- maintain Hb>9.5 g/dL
- Rule out other causes of anemia such as: TMA, bleeding, infection, graft rejection
  - Refractory hemolysis
    - consider AIHA-like therapy such as IVIG, rituximab
    - rule out mismatch in non-ABO blood groups
  - Transfuse donor blood group-compatible red cell units
Figure 4

Identify Patient at Risk for PRCA

- Major ABO mismatch
- Reduced-intensity conditioning

Notify Transfusion Department in Advance

Assessment

Around Day 30-90 post-HCT
- Residual recipient plasma cells
- Abnormal immune tolerance
- Isohemagglutinin, cytokines
- Engrafting donor erythropoietic cells
- Apoptosis

Treatment

- Transfuse blood unit compatible with both recipient and donor, or as directed by transfusion medicine

Refractory anemia
Consider:
- Donor lymphocyte infusion
- Erythropoietin
- AIHA-like therapy such as IVIG, rituximab
- Plasma cell-directed therapy

- Rule out other causes of anemia such as: nutritional, AIHA, TMA, graft failure
- Bone marrow: absence of erythroid precursors, otherwise normal