

ABO-Incompatible Allogeneic Hematopoietic Stem Cell Transplants From Collection to the Bench



Heart of America Association of Blood Banks

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HAABB Fall Meeting – September 10, 2019



**PATHOLOGY
DEPARTMENT**
SAINT LOUIS UNIVERSITY



Disclosures

None

Objectives

- History and Basic Theory
- Terminology
- Blood Bank Management
- Blood Bank Case

#WeAllBleedBlue



QUESTION #1

Which of the following has the most impact on clinical survival outcomes for allogeneic stem cell transplants?

- A. HLA match
- B. Graft source
- C. ABO-incompatibility
- D. Donor age and gender

QUESTION #2

True or False?

In contrast to HSCT,
ABO-incompatible
solid organ transplant
can be a barrier?

- A. True
- B. False

QUESTION #3

Which of the following are considered a major ABO-mismatch?

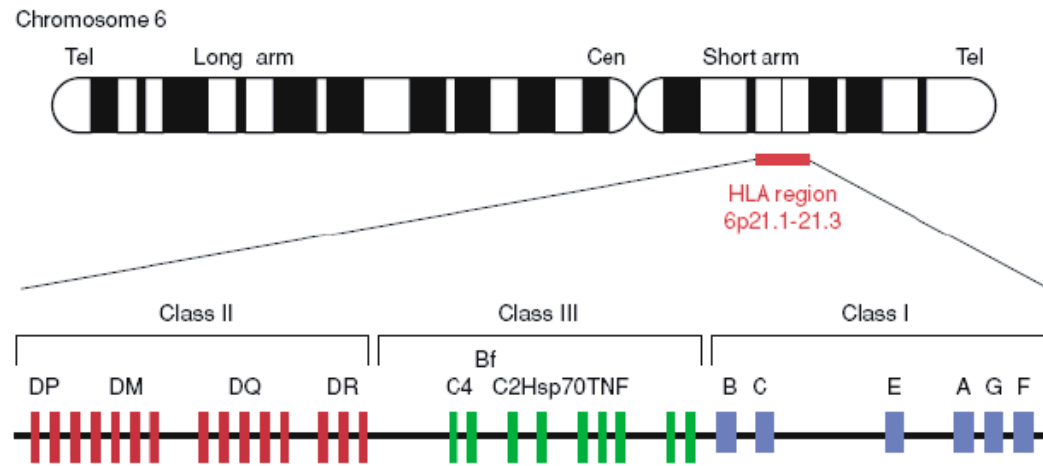
- A. O recipient, A donor
- B. O recipient, AB donor
- C. A recipient, O donor
- D. A recipient, AB donor

Human Major Histocompatibility Complex

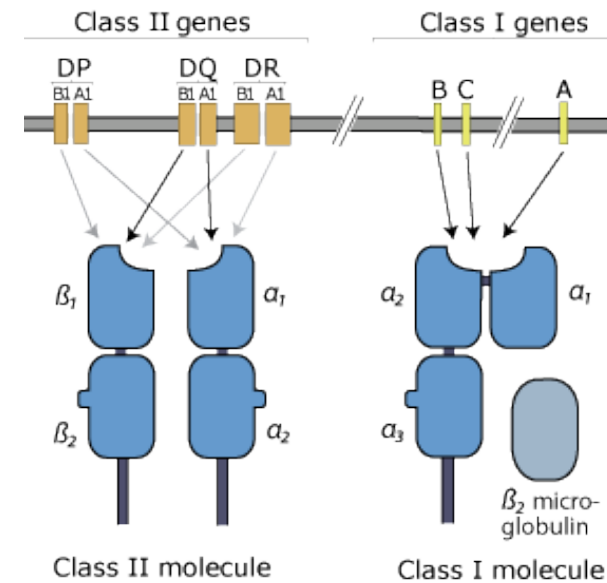
3 regions on chromosome 6p21

Rates of engraftment influenced by degree of match

HLA antigens expressed on immature pluripotent stem cells



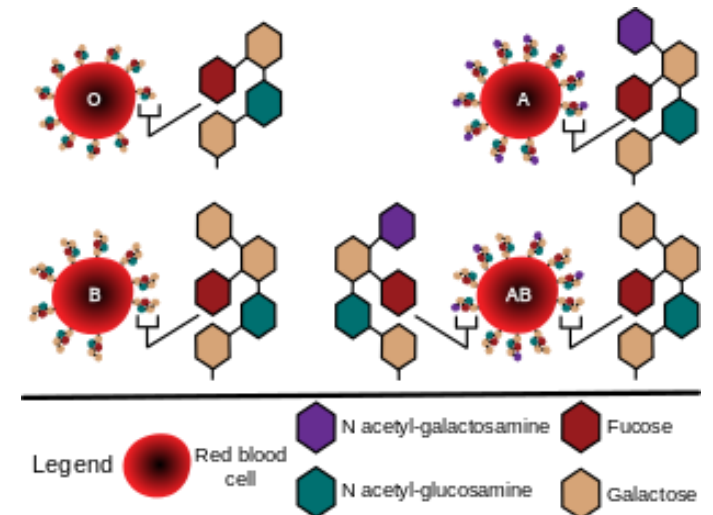
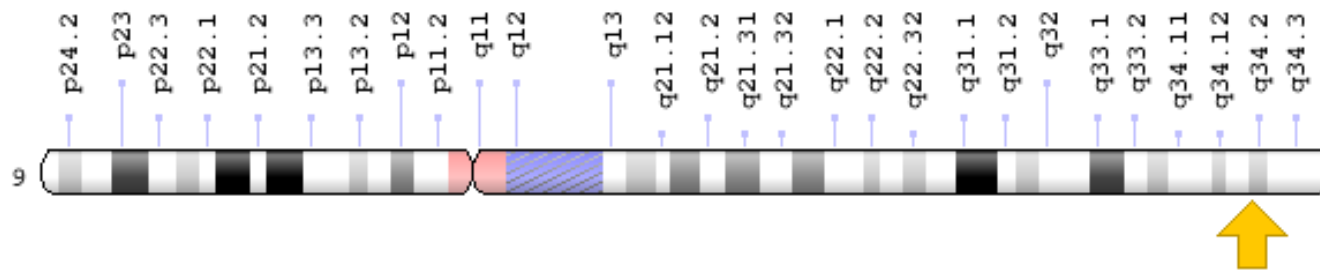
https://www.researchgate.net/figure/Gene-map-of-the-human-leukocyte-antigen-HLA-region-The-HLA-region-spans-410-6_fig1_226487979



http://medweb4.unige.ch/immunologie/home/HSC/transplantation_barriers/structures_recognized/major_histocompatibility_antigens/genetic.php

ABO Carbohydrate Glycosyltransferases

- Located on chromosome 9q34
- Inherited independently of HLA
- ABO antigens are NOT expressed on pluripotent stem cells
- ABO antigens are expressed on mature RBCs, WBCs, **vascular and organ endothelium** and plasma



Landsteiner's Law

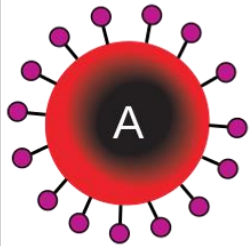
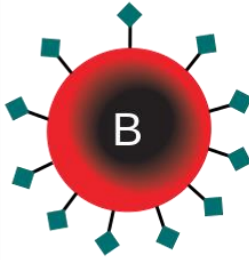
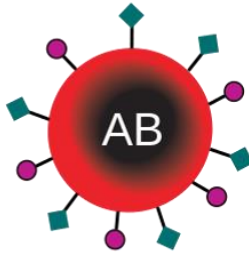
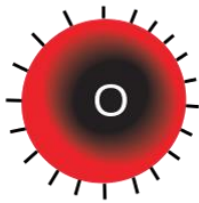
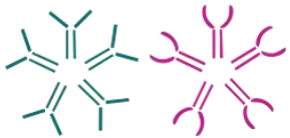
Dr. Karl Landsteiner

Discovered the ABO Blood Group System in 1901

1927 he discovered new blood groups: M, N, and P

Received the Nobel Prize on
Dec. 11, 1930

Landsteiner's Law

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

ABO- Incompatibility

25-50% of transplants are ABO-incompatible

Both ABO-identical and ABO-incompatible HSCT require extensive transfusion support

ABO-mismatch results in complication caused by the interactions between the ABO antigens and isohemagglutinins in the plasma

Clinical outcomes: degree of HLA match, graft source, risk of infection and donor age and gender

Survival after ABO-Incompatible HSCT

Study Authors	Year	Survival after ABO-Incompatible HCT Transplantation			Risk of Graft-versus-Host Disease
		Major	Minor	Bidirectional	
Kimura et al. [3]	2008	Decreased	Decreased	No difference	Increased with minor or major ABO mismatch
Helming et al. [13]	2007	No difference*	No difference*	No difference*	No difference*
Erker et al. [15]	2005	No difference	Decreased	Decreased	No difference
Kim JG et al. [12]	2005	No difference	No difference	No difference	No difference
Stussi et al. [14]	2002	Decreased	No difference	No difference	Increased with minor ABO mismatch
Benjamin et al. [18]	1999	Decreased [‡]	Decreased [‡]	No difference	No difference with minor or major mismatch
Bacigalupo et al. [19]	1988	–	–	–	Increased with minor ABO mismatch
Benisnger et al. [41]	1982	No difference	–	–	No difference with major ABO mismatch
Buckner et al. [17]	1978	–	No difference	–	No difference with minor ABO mismatch

Transplantation Time Periods



Phase 2



Initiation of induction
chemotherapy

RBCS: When DAT is negative and
anti-donor isohemagglutinins
and recipient RBCs are not
detected (Front and Back Type
match ABO-Type of Donor)

ABO-Incompatible Classification

Table 1. ABO Matching of Donor and Recipients

Donor	Recipient			
	A	B	AB	O
A	Compatible	Major/Minor	Minor	Major
B	Major/Minor	Compatible	Minor	Major
AB	Major	Major	Compatible	Major
O	Minor	Minor	Minor	Compatible

ABO-INCOMPATIBLE CLASSIFICATION

Where are the antibodies?

MAJOR

DONOR: Type A, B, AB

RECIPIENT: Type O

Anti-A, Anti-B

Anti-donor antibodies

MINOR

DONOR: Type O

Anti-A, Anti-B

Incompatible transfer of
donor antibodies

RECIPIENT: Type A, B, AB

BIDIRECTIONAL

DONOR: Type A or B

Anti-A or Anti-B

RECIPIENT: Type A or B

Anti-A or Anti-B



“Minor is from A to O, plasma reduction is the way to go”

“Major is from O to A, RBC reduction will save the day”

MAJOR

Major ABO-Incompatibility

DONOR: Type A, B, AB

RECIPIENT: Type O

Anti-A, Anti-B

ANTI-DONOR antibodies

Clinical Manifestations

- Immediate hemolysis
- Delayed engraftment
- Pure RBC aplasia

Preventative Measures

- TPE prior to transplantation to remove recipient's isoagglutinins

RBC Engraftment

Absolute reticulocyte count of more than $30 \times 10^{12}/L$ ($>1\%$), independent of RBC transfusion

100% donor RBC chimerism in the marrow

Coincides with disappearance of recipient isoagglutinins

Delayed engraftment can occur with or without PRA

Delayed engraftment can occur even when full PLT, neutrophil and T-cell engraftment

RBC engraftment ranges from 40-114 days depending on myeloablative vs nonmyelablative regimens

Longer time period for ABO-mismatch compared to identical

PRCA

Reticulopenia (<1%) lasting more than 60 days after HPC transplant



Absent erythroid precursors in the marrow, engrafted myeloid, lymphoid and megakaryocyte precursors



3-29% of major ABO-mismatch

Preparative regimen

Posttransplant
immunosuppression

Isoagglutinin specificity

MINOR

Minor ABO-Incompatibility

DONOR: Type O
Anti-A, Anti-B
Incompatible transfer of
donor antibodies
Anti-RECIPIENT
antibodies
RECIPIENT: Type A, B, AB

Clinical Manifestations

- Acute hemolysis of recipient RBCs
- Delayed (5-15 days after transplant) **Passenger lymphocyte syndrome (PLS)**: Ab-producing immune cells contained in donor graft

Preventative Measures

- Plasma reduction on HPC product to remove donor antibody, prevents acute hemolysis
- Replacement of recipient RBCs with donor type via RBC exchange, rituximab

Passenger Lymphocyte Syndrome

Viable B lymphocytes present in the HPC product producing isohemagglutinins directed against residual RBCs

Hemolysis occurs between Days 5-15 posttransplant

Recipient DAT may be positive, but only 10-15% DAT-positive develop hemolysis

Monitor recipient for hemolysis indices (Bilirubin, LDH, Hb/Hct)

Approach to ABO- Incompatible HSCT

Evaluation

Phase I

Donor and recipient laboratory analysis

Evaluate ABO/Rh status, presence or absence of antibodies

1.) Two independent peripheral blood samples for ABO/Rh typing and antibody screen

a.) Determination of clinical significance or insignificance of all non-ABO minor RBC antibodies (eg, anti-K versus anti-N)

b.) Determination of ABO-incompatibility type: major, minor, bidirectional, or none

2.) Communication with clinical teams regarding transfusion support and risk for hemolysis

Approach to ABO- Incompatible HSCT

HPC acquisition and potential manipulation

Confirmation of ABO-incompatibility and stem cell dose.

1.) Major mismatch: RBC depletion

2.) Minor mismatch: plasma depletion

3.) Bidirectional: consider both product modifications in appropriate clinical context



From Collection to the Bench

Step 1: Determine Blood Unit Selection for ABO-Mismatch

- If the ABO types of the patient and donor are different, the following chart will guide transfusion starting at Day 0 until the change of patient blood type.

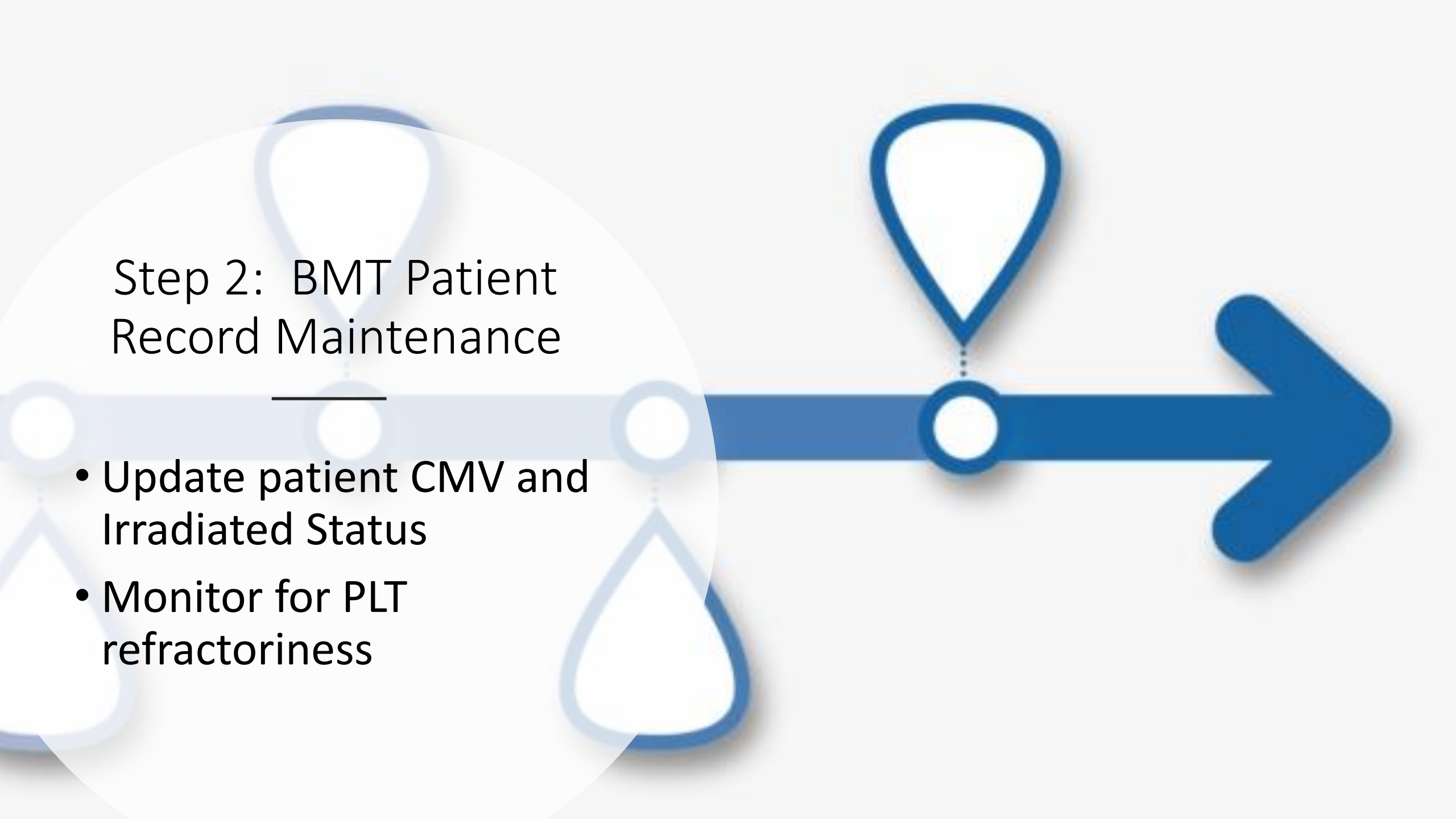


Red Cell Selection for HSCT Patients

RED CELL SELECTION for HSCT Patients

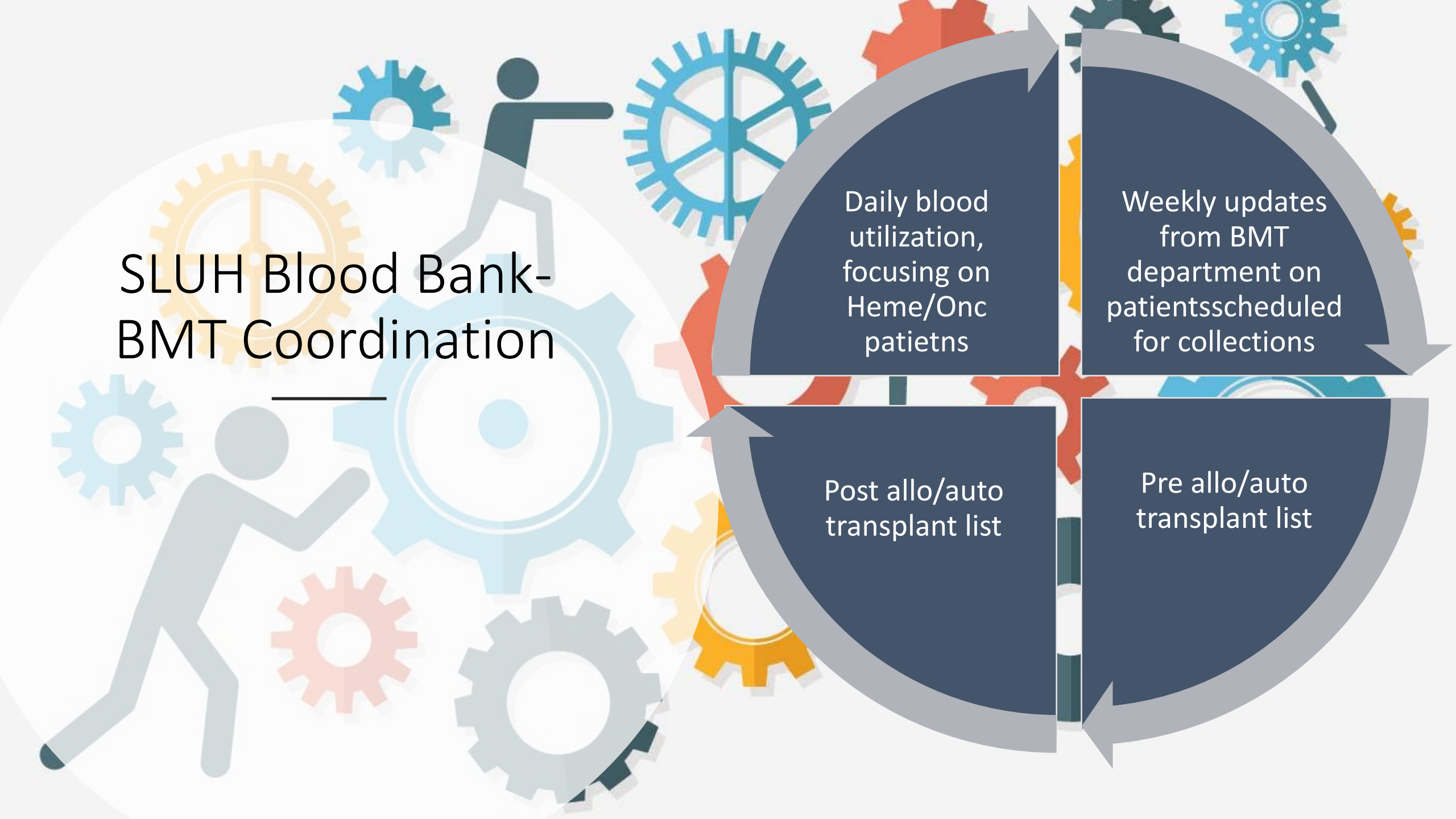
Recipient Type	Donor Type	Transplant Incompatibility	Transfuse: Red Blood Cells	Plasma
A	O	Minor	O	A, AB
A	B	Major	O	AB
A	AB	Major	A, O	A, AB
B	O	Minor	O	B, AB
B	A	Major	O	AB
B	AB	Major	B, O	B, AB
O	A	Major	O	A, AB
O	B	Major	O	B, AB
O	AB	Major	O	AB
AB	O	Minor	O	AB
AB	A	Minor	A, O	AB
AB	B	Minor	B, O	AB

Step 2: BMT Patient Record Maintenance

A decorative background featuring a large blue arrow pointing to the right, with several teardrop-shaped outlines in blue and light blue scattered around it. A semi-transparent white circle is positioned on the left side of the image, partially overlapping the arrow and the text.

- Update patient CMV and Irradiated Status
- Monitor for PLT refractoriness

SLUH Blood Bank- BMT Coordination



Daily blood
utilization,
focusing on
Heme/Onc
patients

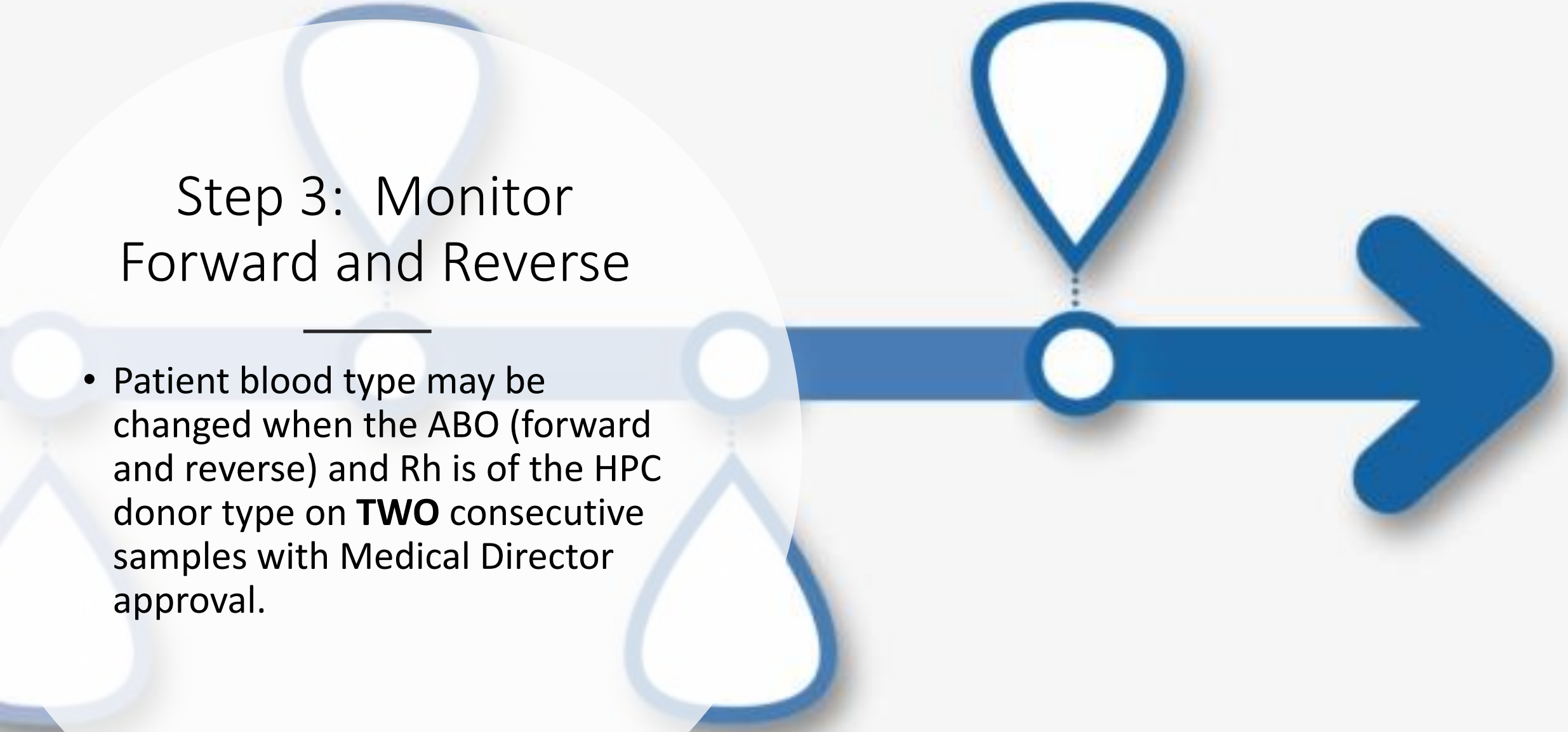
Weekly updates
from BMT
department on
patients scheduled
for collections

Post allo/auto
transplant list

Pre allo/auto
transplant list

Step 3: Monitor Forward and Reverse

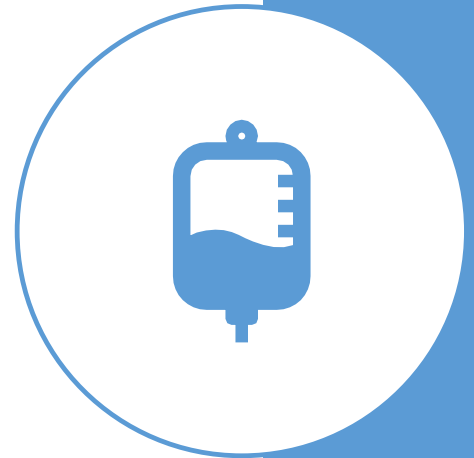
- Patient blood type may be changed when the ABO (forward and reverse) and Rh is of the HPC donor type on **TWO** consecutive samples with Medical Director approval.



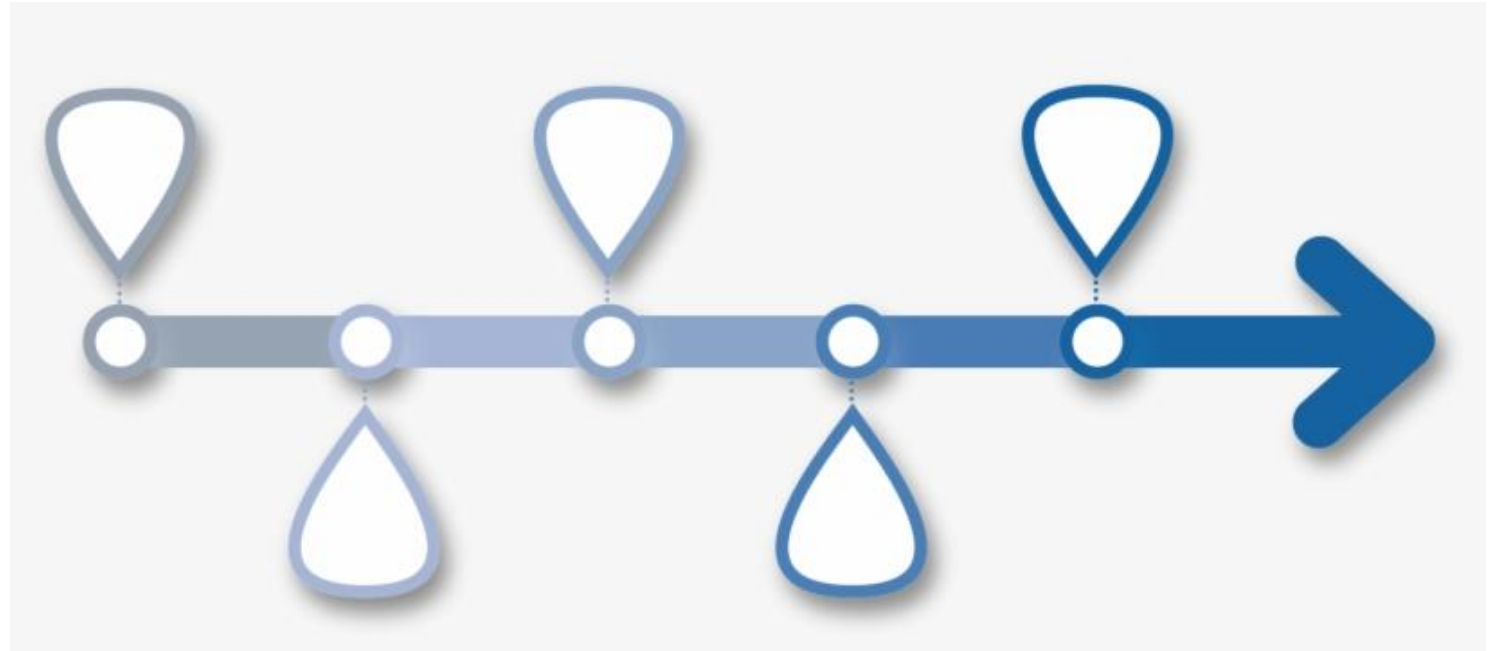
Blood Bank Case

- 9-month boy who underwent unrelated allogeneic umbilical cord blood transplant for juvenile myelomonocytic leukemia
- Original recipient blood type of the patient was O-positive
- Donor was AB-positive

What type of ABO-mismatch?



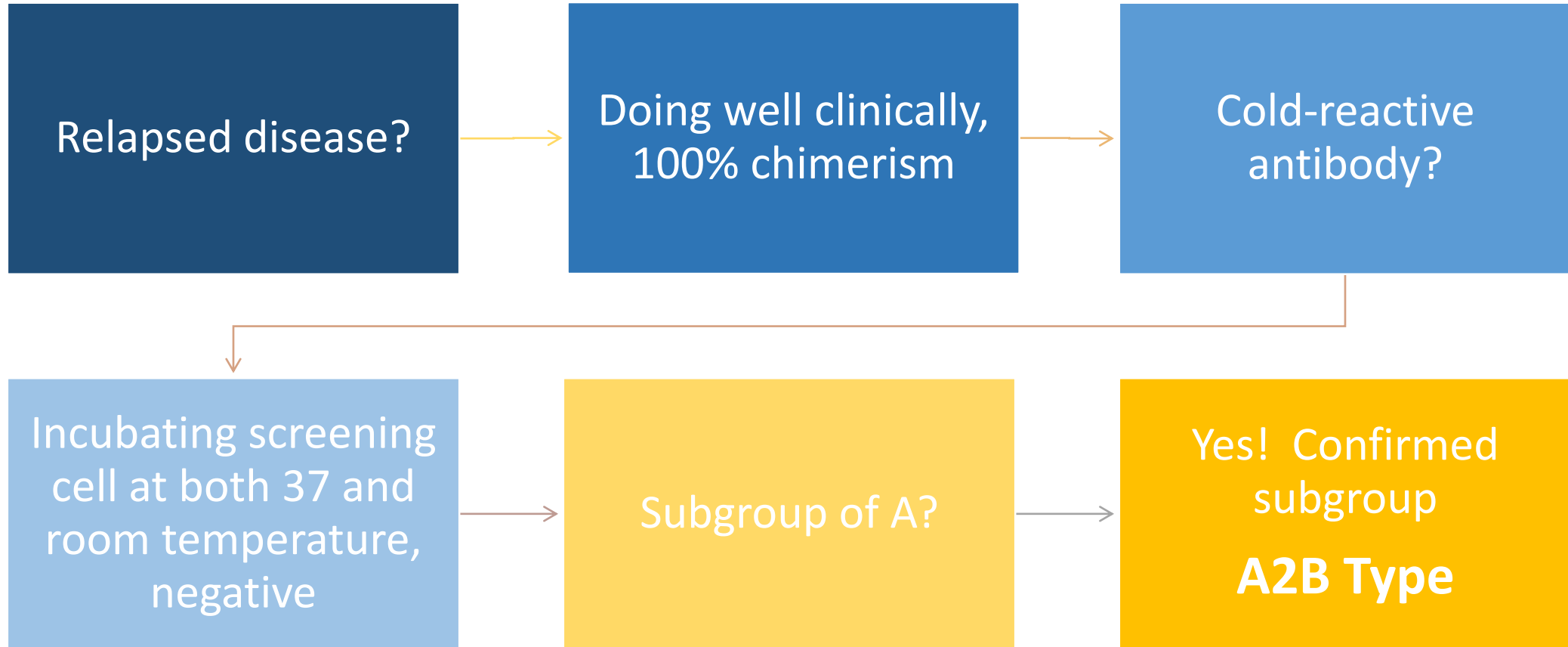
Timeline



- During first 60 days, patient was heavily transfused
- Received 19 O-type RBCs and 38 AB platelet products, all units CMV negative and irradiated
- Neutrophil engraftment (ANC > 500) Day 18
- Platelet engraftment (untransfused PLT count >20,000K) Day 55

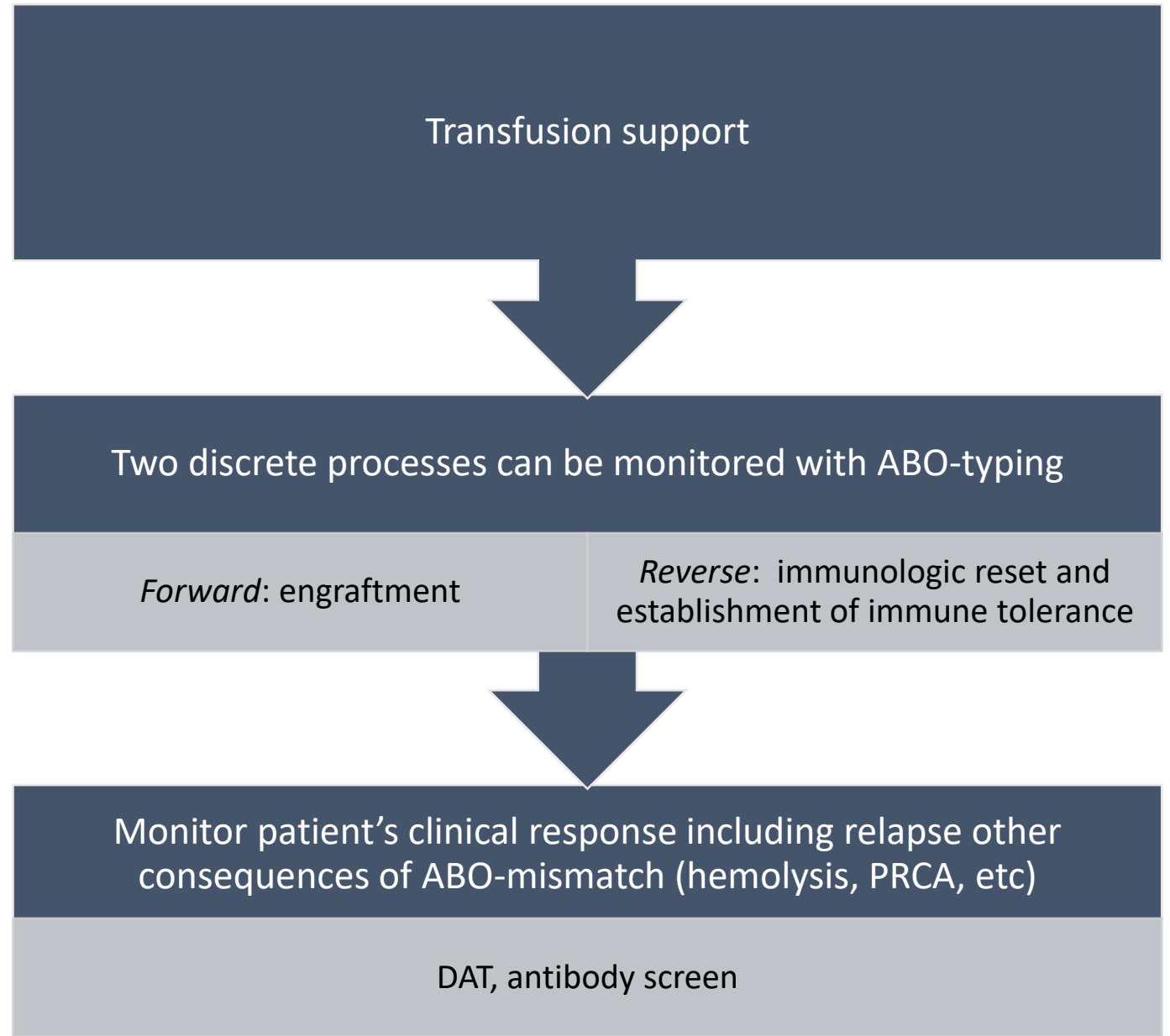
Timeline

TRANSPLANT DAY	FORWARD		REVERSE		OBSERVATION
	A	B	A cell	B cell	
0	0	0	3	2	Pre-transplant
+25	mf w+	mf	2+	0	Forward– conversion
+50, +54, +60	mf	mf	0	0	Reverse – conversion Change recipient ABO-type
+66	4	4	2	0	Typing discrepancy



Unexpected Results

Blood Bank Support



Research Interests

Monitoring

Monitoring RBC engraftment

Generating

Generating better software systems for BMT patients

Integrating

Integrating surveillance with PLT refractoriness

Enhancing

Enhancing our Transfusion Medicine Consult Note for HSCT patients

QUESTION #1

Which of the following has the least impact on clinical survival outcomes for allogeneic stem cell transplants?

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- B. Graft source
- C. ABO-incompatibility
- D. Donor age and gender

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True or False?

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#Blooducation on Twitter

← **Daniela Hermelin, MD**
3,779 Tweets



Daniela Hermelin, MD
@HermelinDaniela

Physician. Assist Prof Pathology. #SLUPath. Bloody passionate for Transfusion Medicine. Member @AABB eLearning Committee. Wife. Mom of 6. My own opinions 🙌🙌🙌

📍 St Louis, MO 🔗 about.me/hermelinmd 🎂 Born December 28, 1977
📅 Joined December 2017

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📍 Midwest, USA 🔗 haabb.org 🎂 Born May 11 📅 Joined May 2018

Thank you for your attention!



Learn more about ABO-Incompatible HSCT

1. Rowley SD, Donato ML, Bhattacharyya P. Red blood cell-incompatible allogeneic hematopoietic progenitor cell transplantation. *Bone Marrow Transplant*. 2011;46(9):1167-1185.
2. Booth GS, Gehrie EA, Bolan CD, Savani BN. Clinical guide to ABO-incompatible allogeneic stem cell transplantation. *Biology of Blood and Marrow Transplantation*. 2013;19(8):1152-1158.
3. Wingard JR, American Association of Blood Banks. *Hematopoietic stem cell transplantation : a handbook for clinicians*. Bethesda, Md.: American Association of Blood Banks; 2009.
4. Kollman C, Spellman SR, Zhang M-J, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*. 2016;127(2):260-267.
5. Daniel-Johnson, J, Schwartz, J. How do I approach ABO-incompatible hematopoietic progenitor cell transplantation? *Transfusion*. 2011; 51:1143-1149.