ABO Incompatibility and Other Transfusion-Related Issues in Hematopoietic Transplantation

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DISCLOSURES

Off-Label Usage

• None

Interests

• None
Focus of Presentation

- ABO blood group in blood transfusions
  - Red cells versus platelets
- ABO blood group in transplantation
  - Selection of blood products
  - Graft manipulation
  - Consequences of major and minor mismatch in
    - Solid Organ
    - Hematopoietic Stem Cell transplants
Importance of ABO Blood Group in Donor-Recipient Compatibility and Safety

Blood Transfusion
- FIRST: ABO (also for many solid organ transplants)
- NEXT: Infection

Hematopoietic Stem Cell Transplantation
- FIRST: HLA
- NEXT: Graft source, Infection testing and screening
- NEXT to LAST: Donor age, gender
- LAST: ABO compatibility
ABO Antigens

- A and B antigens → carbohydrate oligosaccharides coded by glycosyltransferases
- Cell surface density of A antigens approximately 20 to 40% higher than B
- Caucasians 45% 0, 40% A, 11% B
  - B is relatively more common in other ethnic groups
ABO Antigens and Antibodies

- Anti-thetical antibody (antibody to the AB antigen lacking in the patient) consistently present after infancy (isohemagglutinin)
  - Does not require prior RBC exposure
  - High titer IgM, IgG’s that can fix complement
  - Immunohematology not fully understood
  - Titers may be increased by pregnancy, transfusion
- Anti-A isohemagglutinins fix complement more efficiently than anti-B
ABO Serological Assays

“Forward type” for A and B antigens
- Tests pt. RBC with standard anti-sera
- Provides information about hematopoiesis and/or transfusion of red cells

“Reverse type” for anti-A and anti-B isohemagglutinin
- Tests pt. serum with standard A and B RBC
- Provides information about immune system and/or transfusion of plasma
ABO Forward and Reverse Types

- Based on cell clumping due to antibody binding (weak, 1+, 2+ etc)
- Graded according to intensity of reaction and...
- Presence of non-clumped cells
  "mixed field"

**EACH SERVES TO CROSS-CHECK THE OTHER RESULTS**

- High impact, routine tests performed prior to every RBC transfusion
- Very useful in ABO mis-matched transplants and other clinical scenarios
## ABO Type

- Involves both forward and reverse type
- Forward and reverse type should “agree”

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Anti-body</th>
<th>Fwd type</th>
<th>Rev type</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>anti-B</td>
<td>A</td>
<td>A</td>
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<tr>
<td>B</td>
<td>anti-A</td>
<td>B</td>
<td>B</td>
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<tr>
<td>neither (O)*</td>
<td>anti-A, anti-B</td>
<td>O</td>
<td>O</td>
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<tr>
<td>both (A+B)**</td>
<td>neither</td>
<td>AB</td>
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* universal RBC donor
** universal plasma donor
<table>
<thead>
<tr>
<th>Patient’s RBC + reagent anti-A</th>
<th>Patient’s RBC + reagent anti-B</th>
<th>Interpretation</th>
<th>Patient’s serum + reagent A cells</th>
<th>Patient’s serum + reagent B cells</th>
<th>Interpretation</th>
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Other important serologic assays

- Isohemagglutinin titer
  - Highest serial dilution with anti-A or anti-B present
- Direct antibody test
  - Polyclonal, detects either human IgG or C3D
  - Use specific reagent if positive
- Indirect antibody test (antibody screen)
  - Check serum with panels of group O cells to detect antibodies against other antigens
- Eluate
  - Wash cells with positive DAT to determine specificity
  - Uses group O rbc in cell panel unless specified
ABO Incompatible Transfusions

- **Major Mismatch** - usually A or B → O
  - patient plasma incompatible with donor red blood cells
  - most common cause of death from RBC transfusion
  - after TRALI, the most common cause of transfusion-related death

- **Minor Mismatch** - usually O → A or B
  - donor plasma incompatible with recipient red blood cells
ABO Incompatible Transplantation

a. Major mismatch = host *immune system* incompatible with donor ABO type
   \[A, B \text{ or } AB \text{ into } O, AB \text{ into } A \text{ or } B\]

b. Minor mismatch = donor *immune system* incompatible with host ABO type
   \[O \text{ into } A, B \text{ or } AB\]

c. Bi-directional mismatch: both a and b apply
   \[A \text{ into } B, B \text{ into } A\]
Three Step Approach to ABO Incompatible HSCT

1. Graft processing prior to infusion
   - Remove incompatible red cells or plasma
2. Appropriate blood product selection
3. Immunohematalogic events caused by recipient and/or donor immune cells
   - Hemolysis (minor ABO mismatch)
   - Pure red cell aplasia (major ABO mismatch)
1. Graft Infusion Management for ABO Incompatible HSCT Grafts

PBSC and marrow contain RBC and plasma
- May cause immune mediated events when infused into the recipient
- **Major mismatch**
  - Remove incompatible RBC
- **Minor mismatch**
  - Remove incompatible plasma
- **Bidirectional mismatch**
  - Remove both red cells and plasma
Major ABO Mismatch

The recipient has pre-formed antibodies against the donor. Recipients are at risk of immediate hemolysis, pure red cell aplasia and delayed hemolytic reactions.

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>Preferred Choice of RBC</th>
<th>Platelets/Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>A</td>
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Minor ABO Mismatch

The donor can generate antibodies against the recipient. Recipients are at risk of delayed hemolytic transfusion reactions from “passenger lymphocytes “in the graft.

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<td>AB</td>
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Bidirectional Mismatch

Recipients are at risk of immediate and delayed hemolysis.

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Choice of blood components in ABO-incompatible transplants. O type RBCs are usually provided either from the start of conditioning or from the transplant date, depending on individual transfusion service policies.

- **Major mismatch** – donor RBC incompatible with host immune system
  (A or B into O; AB into B, A or O)
- RBC: type O
- Plasma: donor compatible

- **Minor mismatch** – donor immune system incompatible with host rbc
  (O into A, B or AB; A or B into AB)
  - RBC: donor compatible
  - Plasma: host compatible

- **Major/minor (bi-directional) mismatch**
  (A into B, B into A)
  - RBC: type O
  - Plasma: type AB
Case History

- 55 yo male - day 9 after infusion of PBSC
- PMH - CLL x 2 yrs, s/p fludarabine therapy
  - Good performance status
  - Gangrenous gall bladder 1985
- “Mini-transplant” - Cy/flu conditioning
  - High CD34 content, T replete graft
History - 2

- Phenotypically matched donor (daughter)
- Donor/Recipient ABO incompatibility
  - Donor O pos  Recipient A pos
- Cyclosporine for GVHD prophylaxis
History - 3

- Uncomplicated course day 1-5
- Day 6 - fever
- Day 7 - fever, ↑ LDH, ↑ bilirubin
- Day 8 - fever, ↑↑ LDH, ↑↑ bili, hypotension
- Day 9 - hemodynamic instability, transferred to ICU
Assessment: Day 9

- Patient
  - Toxic; tachypneic, tachycardic, anuric
- Laboratory
  - HGB ↓ from 9.2 to 3.4 over 24 hrs, HCT 5.4%
  - LDH 1364, T Bili 8.7, WBC 6.4, PLTs 246
  - PT 19, PTT > 2 min, NI TT, fibrinogen
- Peripheral smear
  - no schistocytes, occasional spherocytes, no feathered edge, adequate platelets
Acute, Massive Hemolysis

Differential Diagnosis

I. Immune
   A. ABO Incompatibility
   B. Drug Related

II. Non-Immune
   A. Infection
Serologic Testing - Day 9

- **Direct Antibody Test (Coomb’s Test)**
  1+ IgG, 2+ C3d  Eluate: Anti-A

- **Isohemagglutinin assay**
  Positive for Anti-A 1:8

- **Indirect Antibody Screen**
  Negative to a panel of antigens on O cells
Consequences of Massive Immune Hemolysis due to ABO Incompatibility

- Cell Lysis, Hemoglobinemia
  - Severe anemia, anoxia
  - Activation of coagulation cascade (DIC)
  - Activation of complement cascade
- Release of vasoactive mediators
- Hemoglobinuria
- Renal, multi-organ system failure
Therapy

- **Transfusions**
  - Group O, crossmatched PRBC

- **Vigorous hydration**
  - Forced diuresis (if not anuric)

- **Expectant management** (K, PO₄, acidosis)
  - Dialysis

- **Supportive measures**
  - Pressors, antipyretics, analgesics
  - Steroids (inflammation and cytokine storm)
  - Red cell or plasma exchange
Time course of changes in LDH, HCT and WBC after minor-ABO Incompatible HSCT

Days after PBSC infusion
Risk Factors for Hemolysis in Minor ABO Mismatched HSCT

- Non-HLA matched sibling donor
- CsA without MTX
- Use of PBSC graft instead of marrow
  No cases described for cord blood
- Inappropriate RBC transfusion
  Use DONOR COMPATIBLE (usually O)
- Approach:
  Maintain hgb $\geq$ 9.5 g/dL
  Use donor-compatible rbc
  May start 10-14 days prior to conditioning
Immune Hemolysis after Minor ABO Incompatible Solid Organ Transplant

- Similar time course, risk factors as HSCT
  1. Increases with ↑ lymphocyte content
     Heart lung > liver > kidney
  1. Increases with CsA alone
  2. Treat with donor compatible rbc

AKA: “passenger lymphocyte syndrome”
Non-ABO Blood Group Transplant Associated Hemolysis

- Milder, delayed (after day 14)
- Occur with donor pre-formed antibodies
- No fatalities reported
- Diagnosis:
  - DAT
  - Donor and recipient red cell phenotype for minor blood group antigens
Effects of Major ABO Incompatibility in Transplantation

- ABO antigens are present on liver, kidney, heart, lung and other tissues, and on early bone marrow red cell precursors
- Consequences of major ABO mismatch differ in HSCT vs solid organ transplants
  - **Solid organ**: graft rejection
  - **HSCT**: pure red cell aplasia*
    - Profound reticulocytopenia with normal wbc and platelets
PRCA after Major ABO Incompatible HSCT

- Associated with persistent host isohema-glutinins against donor rbc
- Cause reticulocytopenia due to inhibition of donor rbc erythropoiesis
- Other cell lines recover normally
- Resolve when antibody forming cells are destroyed by conditioning or by graft
- More frequent with high pre-transplant isohemagglutinin titer and with regimens that do not attack host plasma cells
Pure Red Cell Aplasia after Major ABO Mismatched HSCT

- Frequent descriptions after ablative regimens
  - Hows - ↓ recovery all cell lines SAA (1983)
  - Snicienski - prca 5/28 CsA, 0/30 MTX (1988)
  - Gmur (1991) - prca in 3/15 cases, up to 600 days

- May occur more frequently after reduced intensity conditioning
Figure 1.

Figure 2:

A. Onset of Donor RBC Chimerism (d) vs. Time to Host Antidonor Isohemagglutinin ≤ 1+ (d)

R² = 0.7519

B. Time to Host Anti-Donor Isohemagglutinin ≤ 1+ (d) vs. Pretransplantation Host Antidonor Isohemagglutinin Titer

R² = 0.5638
Figure 3.
Therapy for PRCA

- Isohemagglutinins are related to plasma cell chimerism of donor
  - May resolve “spontaneously”
  - Some series, related to GVH, CsA taper
- “High and standard dose” epo not usually effective (similarly rituximab not effective)
- Plasma exchange +/-
- Donor Lymphocyte Infusions, risk of GVHD
Working out problems with ABO Incompatible HSCT

- Map out donor and recipient ABO type
  - Forward type for cells and hematopoiesis
  - Reverse type for antibodies/immunology
- Graft processing
  - Remove host incompatible rbc and plasma
- Blood product selection
  - Major mismatch – group O rbc, donor compatible plasma
  - Minor mismatch – donor compatible rbc, host compatible plasma
Immunohematologic Consequences of ABO Incompatible HSCT

- Minor ABO incompatibility (Hemolysis, esp with PBSC, CsA alone, MUD graft)
  - HGB > 9.5/g/dL with donor type rbc. DAT prn,
- Major ABO incompatibility (PRCA; esp with high pre-HSCT titer, reduced conditioning)
  - Pre-HSCT assessment of erythropoietic function
  - Monitor reticulocyte counts, isoheamagglutinins
- Watch also for hemolysis from minor mismatched solid organ transplant
ABO Incompatible Solid Organ Transplants

- Major ABO mismatch: **graft rejection**
  - some but not all organs

- Minor ABO mismatch: **immune hemolysis**
  - “passenger lymphocyte syndrome as in HSCT”
  - ↑ with ↑ graft lymphocyte content (heart/lung > liver > kidney)
  - ↑ with use of cyclosporine without antiproliferative agent
  - More common after O→A than O→B
Some useful resources


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