Transfusion Medicine

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DISCLOSURES

Off-Label Usage
  • None

Interests
  • None
Topics

- Blood Group Alloantigen Systems Relevant to Common Clinical Problems
- Blood Components
- Transfusion Practices in Common Hematologic Disorders
- Adverse Effects of Transfusion
ABH Blood Group Antigens

- Antigens of Blood Group A and Blood Group B are trisaccharides with a terminal immunodominant group
- Group A ‘s sugar is N-acetylgalactosamine
- Group B ‘s sugar is galactose
- Group O lacks the addition of these sugars to the glycolipid
- ABO genes on Chromosome 9 and code for transferases that covalently links the saccharide to subterminal galactose
Biochemistry of ABH Antigens

Blood Group Antigens

- O Antigen
  - Gne Gal GalNAc Gal Fuc

- A Antigen
  - GalNAc
  - Gne Gal

- B Antigen
  - Gal
### ABO Immunology

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Isoagglutin Abs in serum</th>
<th>Class of Ab</th>
<th>All ABO Abs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-B</td>
<td>IgM &amp; IgG</td>
<td>Fix complement</td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
<td>IgM &amp; IgG</td>
<td>Agglutinate RBCs</td>
</tr>
<tr>
<td>O</td>
<td>Anti-A</td>
<td>IgM &amp; IgG</td>
<td>Cause I.V. Hemolysis</td>
</tr>
<tr>
<td></td>
<td>Anti-B</td>
<td></td>
<td>“Naturally Occurring”</td>
</tr>
<tr>
<td>AB</td>
<td>None</td>
<td>IgM &amp; IgG</td>
<td></td>
</tr>
</tbody>
</table>
Implications of ABO Immunology

- Group O packed cells universal donor
- Group O plasma cannot be given to Group A, B or AB recipients
- Platelets from Group O donor given to Groups A, B, AB may cause hemolysis (250 ml of Group O plasma in Plt bag)
- Group O marrow donor to Groups A,B or AB may cause hemolysis due to production of anti A, B acting on patients own remaining RBCs (see below)
- Passenger lymphocytes in solid organ transplants may make issoagglutins and cause hemolysis
Biochemistry of ABH, Rh(D)
Rhesus Blood Group

- Antigen System Comprised of D, C, c, E, e…… NO (d)
- Rh D is the most immunogenic and all recipients are typed for D (15% are Neg)
- The Rh proteins are integral to RBC membrane
- Absence of Rh proteins lead to Rh Null state, associated with stomatocytes and hemolysis
- If make Abs to these Ags give antigen (-) blood (HbS patients) match before make an antibody to C,c,E, e)
- In Warm Auto Immune Hemolytic Anemia- Auto Ab directed toward these proteins
Blood Groups & Disease Associations

- Rh Null cells - stomatocytes, chronic hemolytic anemia
- Duffy Antigen – Receptor for Plasmodium vivax; Duffy A negative, B Negative less likely for malaria, BUT 40% more likely to contract HIV.
- Colton - associated with water transport protein
Key Points on Blood Groups

- The ABO system is the most important for blood compatibility
- Rh (D) compatibility is necessary because of high immunogenicity and potential role in hemolytic disease of the newborn and delayed reactions
- Other relevant Blood groups include kell, kidd, Duffy and MnS
Direct Antiglobulin Test (Coombs Test)

Deters about 100 molecules of IGG per red cell!!
Test done using anti-IGG and third component of complement

Antiglobulin Testing detects nonagglutinating Abs --IgG or complement
Used to detect Abs in the serum
Most Alloantibodies are non-agglutinating (incomplete)
A technique used to do compatibility testing
Also used to type for minor antigens (Rh, Kell, Duffy)
Causes of Positive Direct Antiglobulin Test

- Autoantibodies to intrinsic red cell antigen
- Alloantibodies in a recipient’s circulation, reacting with antigens on recently transfused red cells * Hallmark of Hemolytic Transfusion Reaction
- Antibodies directed against drugs that bind to red cell membranes
- Nonspecifically adsorbed proteins including immunoglobulins associated with hypergammaglobulinemia
- Passive administration of alloantibodies in IGIV
- Antibodies produced by passenger lymphocytes in transplanted organs or hematopoietic components
- Red cell bound complement. This may be due to complement activation by alloantibodies, drugs or bacterial infection
Blood Components
Blood Components
What are their contents?

- RBCs
- Platelets
- Pheresis Plts
- FFP
- Cryoprecipitate

- Hct ≤ 80%
- > 5.5 \times 10^{10}
- 3 \times 10^{11}
- 250 ml
- 150 mg fibrinogen

High WBC contamination of RBCs and Platelets, remove to prevent febrile reactions, HLA abs, CMV
## Red Cell Components: Characteristics & Indications

<table>
<thead>
<tr>
<th>Component</th>
<th>Characteristics</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed Cells, stored up to 42 days</td>
<td>250 ml with Hct of 80%</td>
<td>Red Cell Deficit</td>
</tr>
<tr>
<td>Leucocyte Reduced</td>
<td>&lt; 10,000,000 WBC</td>
<td>Prevent Febrile reactions; HLA alloimmunization; Reduces CMV transmission</td>
</tr>
<tr>
<td>Washed Red Cells</td>
<td>Plasma depleted</td>
<td>Prevent severe allergic reactions</td>
</tr>
<tr>
<td>Frozen Red Cells</td>
<td>150 ml of RBC; plasma and WBCs depleted</td>
<td>Rare donor or autologous storage</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>450 ml</td>
<td>Massive transfusion, exchange transfusion</td>
</tr>
</tbody>
</table>
Leucodepletion through Blood Filtration

Leucocyte poor advantageous in reducing febrile reactions, alloimmunization, second line approach in prevention of CMV, may reduce immunosuppressive effects of transfusion
RBC Transfusions in Selected Clinical Situations

- Transfusion of Transfusion Dependent Patients, for example myelodysplastic patient or sickle cell anemia. *How far to match for antigens other than ABO & Rh(D)?*

- Transfusion of Autoimmune Hemolytic Anemia. *Do not be afraid to transfuse if needed!*

- Transfusion in HPSCT. *Remember ABO, minor and major mismatches determine course of action*
Supplying Red Cells to Transfusion Dependent Patients

APPROACHES--- Rationale- with repetitive transfusion patients make red cell antibodies leading to difficult crossmatching

- Provide antigen negative blood after the patient has made an alloantibody (the traditional approach)
- Provide phenotype matched blood after the patient makes the first Ab
- Provide blood matched for D, C, E, K antigens prior to alloAb forming
- Provide blood with extended phenotype matching to include D, C, E, c, e, K, Fy, Kidd

CONSIDERATIONS—
The approach a joint decision of consulting hematologist, transfusion service director, and blood donor centers.

It may not be possible for the community to meet the request
Autoimmune Hemolytic Anemia

- All crossmatches will be incompatible
- Lab ABO and Rh types patient, if unable give Group O, Rh Neg
- If patient previously transfused, should exclude the possibility of an alloantibody
- This is done by autoabsorbing the patient’s serum with autologous RBCs
- May need to give extended phenotype blood
- For Cold Autoimmune Hemolytic anemia- use blood warmer
Transfusion Support in Hematopoietic Stem Cell Transplant

- Prevent CMV, serologically negative blood products, or leukocyte depleted products
- Gamma irradiated to prevent GVHD
- Leucocyte depleted blood products to prevent HLA alloimmunization
- What ABO type of Red cells, plasma should be given? Major & Minor Incompatible Transplants
Major ABO Incompatibility

- Occurs when the recipient has ABO antibodies against the Donor Red Cells
- The HPC can be processed to remove RBCs thereby reducing risk of immediate hemolytic reaction
- The group O recipient who gets Group A graft may make anti A, & B for 3-4 months
- Will delay RBC engraftment
- Group A RBCs will appear in circulation when isoagglutins disappear
- Transfuse with RBCs that are compatible with donor and recipient, to avoid confusion we use Group O
Delayed RBC engraftment in the recipient of a Major ABO incompatible SCT

The appearance of mature RBC corresponded to the disappearance of isoagglutinins.
Minor ABO Incompatibility

- Minor ABO incompatibility occurs when the graft makes antibodies against the recipient RBCs
- For example a Group O donor to a Group A recipient
- Clinical hemolysis abrupt onset at 7-10 days and may last 2 weeks
- Transfuse with Group O cells and use plasma compatible with Donor and Recipient
- We start to transfuse Group O cells prior to transplant
Severe Hemolysis in a Minor Incompatible SCT: The Donor was Group O, and Recipient Group A.

Serologically the Direct Antiglobulin Test is Positive with IgG, C3d and an eluate from the RBCs showed Anti - A.
Adverse Effects of Transfusion

- Infectious
- Immunological
- Metabolic
- Volume
Warning Transfusions are Hazardous
Package Insert

- Disease transmission
- Hemolysis
- Febrile reactions
- Allergies
- Metabolic abnormalities
- Volume overload
- Death

- AIDS
- Malaria
- Immune suppression
- Sepsis
- GVHD
- Dementia (?)
- Hepatitis
- CMV
Disease Transmission by Transfusion
Blood Tested For:

HIV-1, HIV-2 - Test for antibodies to HIV-1 and HIV-2 (Human Immunodeficiency Virus)

HBc - Test for antibody produced during and after infection with HBV (Hepatitis B)

HCV - Test for antibody to HCV (Hepatitis C)

HTLV-I and HTLV-II - Test for antibodies to HTLV-I and HTLV-II (Human T-cell Lymphotropic Virus)

HBsAg (Hepatitis B Surface Antigen — Screens for HBV)

PKTP (Syphilis) - Test for syphilis
Nucleic Acid Testing – Detects Viremia Before Antibody Testing

NAT (Nucleic Acid Testing) - NAT is a technology that can detect the genetic material of Hepatitis C virus, HIV and West Nile Virus faster and more accurately than other tests, which react to antibodies of those viruses.

All of the blood collected by the American Red Cross for transfusion is now subjected to NAT for Hepatitis C, HIV and West Nile Virus.
Infectious Risk of Transfusions Due to Viruses

<table>
<thead>
<tr>
<th>Viral Agent</th>
<th>Estimated Risk/Unit</th>
<th>Estimated % infected units that transmit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 &amp; 2</td>
<td>1:2,300,000</td>
<td>90</td>
</tr>
<tr>
<td>HTLV 1 &amp; 2</td>
<td>1:2,930,000</td>
<td>30</td>
</tr>
<tr>
<td>HAV</td>
<td>1:1,000,000</td>
<td>90</td>
</tr>
<tr>
<td>HBV</td>
<td>1:220,000</td>
<td>70</td>
</tr>
<tr>
<td>HCV</td>
<td>1:1,800,000</td>
<td>90</td>
</tr>
<tr>
<td>B19 Parvoviurs</td>
<td>1:40,000</td>
<td>low</td>
</tr>
</tbody>
</table>

West Nile virus- estimated risk- depends upon location
**Infectious Risk Due to Bacteria**

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>Estimated Risk/Unit</th>
<th>Estimated % if infected units that transmit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBCs</strong></td>
<td>1:1,000</td>
<td>1:10,000,000 fatal</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>1:2,000</td>
<td>1:2,500 result in sepsis</td>
</tr>
<tr>
<td><strong>Platelets Pheresis</strong></td>
<td>1:2,000</td>
<td>1:13,400 result in sepsis</td>
</tr>
</tbody>
</table>
Estimated Risk of Collecting Blood During the Infectious Window Period (repeat donors)

- HCV, Ab test only
- HCV, + NAT
- HIV AB + p24
- HIV AB + NAT
- HTLV
- HBV

- 70 days
- 10 days
- 16 days
- 11 days
- 51 days
- 59 days
# Infectious Risks of Transfusion Due to Parasites

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Estimated Risk/Unit</th>
<th>Estimated % infected units that transmit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria and Babesia</td>
<td>&lt;1:4,000,000/ Babesia 1,800 in endemic areas</td>
<td>unknown</td>
</tr>
<tr>
<td>Trypanosoma Cruzi</td>
<td>1:42,000</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Transfused patient with fevers and babesia
Immunologic Transfusion Reactions
Immunologic Reactions

- Hemolytic
- Allergic
- WBC & Cytokine mediated
- GVHD
- Transfusion Related Acute Lung Injury
- Anaphylactic
- Immune suppression
Hemolytic Transfusion Reactions

• Acute Hemolytic: ABO mismatched blood, and some IgG antibodies to other Alloantigens, such as E, C, e, Fy
• Delayed Hemolytic Reactions: IgG antibodies form anamnestically in previously immunized people
• Passive administration of isoagglutins in FFP and platelets
ABO Hemolytic Reactions

- Acute pain, arm, back
- Fever, chills
- DIC, in O.R. unexplained bleeding
- Hemoglobinuria, and hemoglobinemia
- DAT positive for Complement
Intravascular Hemolysis

HEMOGLOBINURIA

Urine, red
Centrifuge, if RBC all sediment; if hemoglobinuria, supernant red

HEMOGLOBINEMIA

Intensely pigmented plasma, after centrifugation, hemoglobin cleared in several hours
Conditions Mimicking a Hemolytic Reaction

- Over heating of blood in blood warmer
- Adding hypotonic solutions to blood
- Mechanical Trauma of membrane oxygenator or ventricular assist device
- Addition of medications to bag of blood that lysis red cells
- Unit of blood is from a G6PD deficient donor
Lab Findings of A Hemolytic Transfusion Reaction

• Positive direct antiglobulin test, due to isoagglutins on red cells and or complement on the red cells

• Repeat incompatible crossmatch

• New blood specimen typically shows an ABO discrepancy

• Hemoglobinemia, hemoglobinuria

• DIC
Delayed Hemolytic Transfusion Reactions (DHTR)

- Seen in previously transfused or pregnant patients
- The Ab is below detection in pretransfusion testing
- 7-10 days post-TRX the Ab titer increases resulting in extravascular hemolysis
- At this time the DAT and Indirect DAT are Positive
Spherocytes in Delayed Transfusion Reactions
Laboratory Findings in Delayed Hemolytic Reaction

- Antibody screening positive – this signals a alloantibody is present
- Next step is to identify the antibody – is it Anti E, Kell, Duffy a etc.
- This identification is done by performing a specificity panel by testing the patient serum against a panel of 10 well phenotyped red cells.
- Those cells that do not react, yield the identification of the antibody
What a RBC Panel Looks Like

From a panel of red cells one can identify the specificity of the antibody. This takes specialized medical personnel to do. Multiple antibodies may do, and is not something a hematologist is credentialed to do.

*
Clinical Issues of DHTR

- Fever, jaundice, spleen may increase
- Renal failure unlikely
- Falling hematocrit, increased Reticulocyte count
- Need to give RBCs lacking the Ags promoting the immune response
- For example if have anti E, and Kell give blood negative for these antigens
- Give the patient a card stating the patient has these ABs
Febrile Reactions

- Due to patients HLA or antigranulocyte antibodies
- Cytokines from WBCS in blood
- Prevent by giving leucocyte depleted blood
- Antipyretics: no clinical trials showing efficacy
- If have febrile reaction: STOP TRANSFUSION AND WORKUP
### Transfusion Reactions – Most Common Immunologic

<table>
<thead>
<tr>
<th>Usual Urgency</th>
<th>Reaction Type</th>
<th>Approx Incidence</th>
<th>Clinical significance/ Burn points</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>Acute Hemolytic</td>
<td>1: 12,000-35,000</td>
<td>~50-75% of Txn fatalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1:100,000 – 600,000)</td>
</tr>
<tr>
<td>+</td>
<td>Delayed Hemolytic</td>
<td>1: 1000-12,000</td>
<td>• Severe symptomatic hemolysis: 1: 250,000; death: rare;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑ risk sickle cell</td>
</tr>
<tr>
<td>+/- to</td>
<td>Febrile</td>
<td>0.5-1.4%</td>
<td>• Frequent: 43- 75% of Txn Rxns</td>
</tr>
<tr>
<td>++</td>
<td>Non-Hemolytic</td>
<td>15% recur</td>
<td>• Frightening to patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Specters of AHTR + bacterial sepsis</td>
</tr>
</tbody>
</table>
Allergic Reactions

- Hives
- Caused by allergy to proteins, or some substance in the donor cells
- Prevent by giving antihistamines
- Washed RBCs for persistent, severe allergic reactions
Anaphylactic Reactions

- Antibodies to IgA in totally IGA deficient patient
- May occur in previously untransfused patient
- Give IgA deficient plasma products, extensively washed RBCS
- May occur due to antibodies to haptoglobin
Transfusion Related Acute Lung Injury (TRALI)

- severe respiratory compromise (clinically ARDS: severe hypoxemia + non-cardiogenic pulmonary edema)
- Occurs within 4-6 hrs of txn; no other cause evident

Other usual clinical concomitants:
- Rapid onset: 15-20 mins
- Fever almost invariable
- ↑ bp initially; most severe → ↓ bp
- ↑ pulmonary artery pressures
- Resolution usually rapid (hrs) ≠ ARDS
Transfusion Related Acute Lung Injury (TRALI)

Caused by antigranulocyte/HLA antibodies being passively administered in blood products

Donor usually Multiparous female
Donor anti-WBC antibodies (abs) definitely seem to be a significant cause of TRALI: Other factors, cytokines, biologically active lipids

**Pathogenesis:**

Passive donor → React with recipient’s WBCs

C’ activation

Pulmonary leukosequestration

Non-cardiogenic pulmonary edema

Prevention, limit plasma production from mulitparous women??
Transfusion Associated GVHD

- Seen in severe immune suppressed patients
- Patients with congenital cellular immunodeficiencies
- Premature babies
- Give irradiated blood to these patients
- Patient groups, BMT, Lymphoma, leukemias undergoing induction therapy
### Other Adverse Effects of Transfusion

<table>
<thead>
<tr>
<th>Usual Urgency</th>
<th>Reaction Type</th>
<th>Approx Incidence</th>
<th>Clinical significance/Burn points</th>
</tr>
</thead>
<tbody>
<tr>
<td>- - ++++</td>
<td>Volume overload</td>
<td>? 1:100</td>
<td>Rarely fatal</td>
</tr>
<tr>
<td>+++</td>
<td>Hypotension from bedside filters</td>
<td>?</td>
<td>• Bradykinin implicated; ↑ risk ACE inhibitors</td>
</tr>
<tr>
<td>++</td>
<td>Non-Immune Hemolysis</td>
<td>Rare</td>
<td>• Hypotonic solutions; intra-op salvage; defective warmers; rarely serious</td>
</tr>
<tr>
<td>++ -</td>
<td>Metabolic imbalances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+++</td>
<td>• ↑ K</td>
<td>Rare</td>
<td>Rapid infusion of old RBCs; renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Acidosis</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ Ca++ (Mg++)</td>
<td>Rare</td>
<td>• Massive transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Special attn: young children</td>
</tr>
</tbody>
</table>
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<thead>
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<th>Reaction Type</th>
<th>Approx Incidence</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>Hypothermia</td>
<td>-</td>
<td>• Massive Txn; trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Fe++ overload</td>
<td>-</td>
<td>Chronic Txn -250 mg/unit</td>
</tr>
</tbody>
</table>
Hemoglobin Carriers

- Solutions of Hb from outdated Human RBCs or Cows (Biopure: what vets use)
- The Hb is chemically modified to make the molecule larger to prevent renal clearance
- Some interfere with NO leading to hypertension
- None approved clinically, yet but available on IND
• Blood Group Alloantigen Systems Relevant to Common Clinical Problems
• Blood Components
• Transfusion Practices in Common Hematologic Disorders
• Adverse Effects of Transfusion
• Reducing the Risks of Transfusion
The Discoverer of the ABO Blood Group
Nobel Laureate
Karl Landsteiner