Transfusion Medicine Update

October 15, 2015
Arkansas Chapters of CLMA and ASCLS

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Medical Director

Oklahoma Blood Institute
Texas Blood Institute
Arkansas Blood Institute

FEEL GOOD. GIVE BLOOD.
Who We Are

- One of the largest non-profit blood centers in America
- Founded by the Oklahoma County Medical Society (OCMS) in 1977
- Led by Don Rinehart, MD (neurosurgeon) and 200 other physicians (OCMS)
- Postponed surgeries and repeated shortages
- Physicians personally fronted the money to start OBI
- Texas Blood Institute
- Arkansas Blood Institute
What I am going to talk about

• Transfusion Medicine (Very Quick) Review
  – Regulatory, Donor Testing, Special Products, Patient Testing
• Patient Blood Management and Transfusion Guidelines
• Massive Transfusion Protocols
Regulatory Issues
Pharmaceutical agents, Medical laboratories

- Code of Federal Regulations (CFR)
- Food and Drug Administration
- Department of Health and Human Services
- Centers for Medicare and Medicaid Services
- AABB
- The Joint Commission
- College of American Pathologists
- Local and state regulations
- US Nuclear Regulatory Commission
Donor Required testing

- ABO
- Rh
- Antibody screening
- ID
Infectious Disease Testing

- HIV
- HCV
- HBV
- HTLV-I/II (Human T-cell lymphotropic virus)
- Syphilis
- West Nile virus
- Chagas disease
# ABO Typing

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red blood cell type</strong></td>
<td><img src="image" alt="A antigen" /></td>
<td><img src="image" alt="B antigen" /></td>
<td><img src="image" alt="AB antigens" /></td>
<td><img src="image" alt="O antigen" /></td>
</tr>
<tr>
<td><strong>Antibodies present</strong></td>
<td>Anti-B</td>
<td>Anti-A</td>
<td>None</td>
<td>Anti-A and Anti-B</td>
</tr>
<tr>
<td><strong>Antigens present</strong></td>
<td>A antigen</td>
<td>B antigen</td>
<td>A and B antigens</td>
<td>None</td>
</tr>
</tbody>
</table>
Patient Testing

- TYPE: ABO and Rh grouping of the recipient and donor
- SCREEN: Antibody screen of the patient’s serum, “unexpected antibodies”
- Antibody ID: if Antibody screen is positive
- RBC Crossmatch
Products

• Red blood cells
• Platelets
• Plasma
• Cryoprecipitate
• Granulocytes
• HPC collections
Specialized Blood Components

- Irradiated blood products
- Leukoreduced blood products
- CMV
- Washing
- Frozen and Deglycerolized RBCs
Irradiated blood products

• **Purpose (only ONE)**
  – Prevent TAGVHD by inhibiting lymphocyte proliferation

• **Does NOT**
  – Prevent transmission of diseases
  – Reduce white cell count
Transfusion Associated Graft vs. Host Disease

- Donor Lymphocytes infiltrate skin, liver, and GI tract.
- Rare except in immunocompromised patients
- Nearly 100% fatal
Irradiated blood products

- Blood Products
  - pRBCs
  - Platelets
  - Granulocytes
- Disadvantage
  - Shelf life shortened to 28 days or original date, whichever is first
  - $K^+$ leak approximately doubled
Irradiated blood products

• **Indication: prevent TAGVHD**
  – Intrauterine, Infants ≤ 4 months of age
  – Patients with cellular immunodeficiency syndromes (SCID, DiGeorge’s syndrome)
  – Bone marrow transplant
  – Hematologic diagnoses (e.g. leukemia, lymphoma)
  – Directed donations
Leukoreduced blood products

- Reduces WBC content to $<5 \times 10^6$ per transfused product
- Purpose
  - reduce febrile transfusion reactions
  - reduce alloimmunization
  - reduce transmission of CMV
- Blood donation products
  - Whole blood: special WBC filters
  - Apheresis: leukoreduced by collection technology
CMV

• **Purpose**
  – To prevent TT-CMV disease in patients at risk for developing severe clinical CMV disease
    • Infants ≤ 4 months
    • Immunocompromised patients
    • Likely to become immunocompromised (allo BMT candidates)

• **Seronegative vs. Leukocyte reduced**
  – Controversy
Washed

• Purpose is to remove plasma
  – Reduce reactions (anaphylactic and severe allergic)
  – Special patients (e.g. IgA deficiency with IgA antibodies)
  – Reduces incompatible plasma
  – Prevent hyperkalemia in patients susceptible to cardiac complications

• Cellular Blood products

• Disadvantages
  – Lose product, functionality
  – 24 hour outdate
  – Takes time
Frozen/Deglycerolized RBCs

- Freezing is done to prolong storage
  - Autologous RBCs (postponed surgery)
  - Rare RBC phenotypes
  - Process: Adding glycerol to donor RBCs, then freeze to -65°C or colder
- Frozen RBC shelf-life 10 years (ID testing issues!!!)
- Deglycerolizing a frozen RBC:
  - Place in a 37°C water bath
  - Wash glycerol off before issuing
  - Resulting product: a RBC “donut”
  - Shelf life of 24 hours
What I am going to talk about

• Transfusion Medicine (Very Quick) Review
  – Regulatory, Donor Testing, Special Products, Patient Testing

• Patient Blood Management and Transfusion Guidelines

• Massive Transfusion Protocols
Do you have a Blood Management Strategy?
Goal of Effective Blood Management

Promote *optimal* use of blood products

Providing: **Right Dose**

**Right Blood Product**

**Right Patient**

**Right Time**
Adverse events occur in 20% of all transfusions

- The most significant opportunity for improvement lies with reducing patient risks
- The most significant risks to patient safety reside outside of infectious disease transmission
The Cost of BLOOD TRANSFUSIONS

Patient Blood Management

- External
  - Consultants
  - Software programs/companies
- Internal
  - Transfusion Committee
  - Physician Champion
  - Patient Blood Safety Officer
Successful Blood Management

• Improves blood utilization by using the best available evidence as an aide in deciding when to transfuse
• Improves patient safety by reducing risks
• Improves outcomes
• Improves the bottom line by reducing costs
How can we help with PBM?

- Ensure adequate inventory levels are established and maintained for transfusion support
- Encourage Blood Management Programs and help identify opportunities for process improvements
- Improve utilization through data review and benchmarking
- Provide Awareness, Education and Best Practice Guidelines
America’s Blood Centers

- Evaluated literature to develop guidelines for transfusion
- Red Cells
- Platelets
- Plasma
Red Blood Cell Transfusion: A Clinical Practice Guideline from the AABB

Prepared by ABC Transfusion Trigger Workgroup

America’s Blood Centers
It’s About Life.

www.AmericasBlood.org ★ 1-888-USBLOOD
Background

- Physicians most commonly use hemoglobin concentration to decide when to transfuse. However, most guidelines emphasize that transfusion should be given for symptoms of anemia and should not be based on hemoglobin concentration alone.

- Previous guidelines have identified patients with coronary artery disease as an important subgroup that may need to be treated differently.

- Most literature currently defines “liberal” transfusion threshold as a hemoglobin of 9-10 g/dL and “restrictive” transfusion threshold as a hemoglobin of 7-8 g/dL.
Question 1

In hospitalized, hemodynamically stable patients, at what hemoglobin concentration should a decision to transfuse RBCs be considered?
Recommendation 1:

- The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL Hgb) in hospitalized, stable patients.
- Grade: strong recommendation; high-quality evidence.
Question 2

In hospitalized, hemodynamically stable patients with preexisting cardiovascular disease, at what hemoglobin concentration should a decision to transfuse RBCs be considered?
Recommendation 2:

- The AABB suggests adhering to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less.

- Grade: weak recommendation; moderate-quality evidence.
Question 3

In hospitalized, hemodynamically stable patients with the acute coronary syndrome, at what hemoglobin concentration should an RBC transfusion be considered?
Recommendation 3:

- The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome.

- Grade: uncertain recommendation; very low-quality evidence.
Question 4

In hospitalized, hemodynamically stable patients, should transfusion be guided by symptoms rather than hemoglobin concentration?
Recommendation 4:

The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration.

Grade: weak recommendation; low-quality evidence.
Hgb g/dL | Recommendation/comments

>10 | RBC Tx NOT indicated

- Rare exceptions may exist, but Tx when Hgb >10 g/dL is generally considered not indicated.
Hgb g/dL  Recommendation/comments

- RBC Tx NOT indicated unless specific clinical signs or symptoms of anemia or risk for ongoing bleeding.
- AABB guideline suggests considering Tx for patients with pre-existing cardiovascular disease who have the following symptoms: chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure.
- AABB does not recommend for or against liberal or restrictive transfusion for hemodynamically stable patients with acute coronary syndrome.
**Hgb g/dL**

7-8

- RBC Tx should be considered in postoperative patients with Hgb <8 g/dL
- RBC Tx is NOT indicated in intensive care unit patients until Hgb <7 g/dL
- AABB recommends restrictive Tx strategy (7-9 g/dL) in hospitalized, stable patients even in presence of pre-existing cardiovascular disease.
- Tx should only be considered after evaluation of clinical context and patient symptoms.
- Same recommendations likely to apply to most medical patients with exception of those with acute coronary syndrome.
Hgb g/dL  Recommendation/comments

<7  

⚠️ RBC Tx likely indicated

⚠️ Exceptions may occur, but generally Tx is considered likely to be indicated when Hgb <7 g/dL
Hgb g/dL | Recommendation/comments

<6 | RBC Tx highly recommended, except in exceptional circumstances
Reference:

Platelet Transfusion: A Clinical Practice Guideline From the AABB

Prepared by ABC Transfusion Trigger Workgroup
# Platelet Components Equivalent to 4-6 Whole-Blood Derived Platelets

<table>
<thead>
<tr>
<th></th>
<th>Apheresis Platelets</th>
<th>Prestorage Pooled Platelets (Acrodose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Single donor exposure</td>
<td>Closed system</td>
</tr>
<tr>
<td></td>
<td>HLA matching possible</td>
<td>Allows pooling 4-6 ABO identical units</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Limited availability</td>
<td>Multiple donor exposures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Matching impractical</td>
</tr>
<tr>
<td><strong>Leukocyte Reduction</strong></td>
<td>Prestorage</td>
<td>Prestorage</td>
</tr>
<tr>
<td><strong>Bacterial Detection</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Shelf Life</strong></td>
<td>5 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Transfusion Therapy. 3rd ed. 2011  

www.AmericasBlood.org ★ 1-888-USBLOOD
Platelet Transfusion-AABB Clinical Practice Guidelines

- Based on a systematic review of randomized, clinical trials and observational studies that reported clinical outcomes on patients receiving prophylactic or therapeutic platelet transfusions.

- Literature search from 1900 to September 2014 with no language restrictions was done.

- Examined outcomes included all-cause mortality, bleeding-related mortality, bleeding, and number of platelet units transfused.

- An expert panel reviewed the data and developed recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Ann Intern Med. 2015;162:205-213
Recommendation 1

_platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in hospitalized adult patients with therapy induced hypoproliferative thrombocytopenia_

Transfusing hospitalized adult patients with a platelet count of 10,000/uL or less to reduce the risk for spontaneous bleeding
Recommendation 1

- AABB recommends transfusing up to a single apheresis unit or equivalent.
- Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective.
- Grade: strong recommendation; moderate-quality evidence.
Recommendation 2

Prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than 20,000/uL

Grade: weak recommendation; low-quality evidence
Recommendation 3

Prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50,000/uL

Grade: weak recommendation; very low-quality evidence
Recommendation 4

Prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50,000/uL

Grade: weak recommendation; very low-quality evidence
Recommendation 5

- Recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass (CPB)
- Suggests platelet transfusion for patients having CPB who exhibit perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction
- Grade: weak recommendation; very low-quality evidence
Recommendation 6

AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous)

Grade: uncertain recommendation; very low-quality evidence
# Therapeutic Transfusions

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Platelet Count (/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral, ophthalmologic or pulmonary hemorrhage</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Thrombocytopenia

 Causes
  - Congenital (e.g., Glanzmann thrombasthenia)
  - Acquired as the result of disease (e.g., myelodysplasia)
  - Drug treatment (e.g., with aspirin or glycoprotein IIb/IIIa antagonists)

 Transfusion Decisions
  - Based upon patient’s clinical status
  - Test platelet function

 Mitigation
  - Discontinue antiplatelet agents prior to surgery

Pre and Post Counts

- Platelet count should be obtained:
  - Before
  - 10 to 60 minutes after transfusion
- Assess the adequacy of response to transfusion

Transfusion 1997; 37: 573-76
Conclusions

- Standard doses are convenient starting points for platelet transfusion in most patients
- Adjustments to dose and frequency are often required because of coexisting clinical factors
Evidence-based Recommendations for Plasma Transfusions

Prepared by ABC Transfusion Trigger Workgroup

America's Blood Centers
It's About Life.
Plasma Administration in Setting of Trauma with Massive Bleeding

Plasma transfusion for massive bleeding is appropriate and should be administered as early as possible in a “balanced” Plasma:Platelet:RBC ratio of 1:1:1 to 1:1:2.


Plasma Transfusion Before Invasive Procedures

- Evidence does not support plasma transfusion based solely on PT/INR values.
- Audit criteria published by AABB used to aid in identifying inappropriate transfusion are PT or PTT >1.7 to 2.0 times the mean of the reference range. This corresponds to an INR>2.0, in a non-bleeding patient scheduled for surgery or an invasive procedure. This suggests that plasma should not be routinely transfused for INR<2.0, even in the setting of prophylactic use for patients with liver disease.

- Segal J, Dzik W. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion:2005 Sep;45(9):1413-25.
Plasma Transfusion for Rapid Reversal of Vitamin K Antagonists (e.g. warfarin) with Elevated INR

- For patients taking Vitamin K antagonists without bleeding, plasma transfusion is not recommended. Vitamin K administration may or may not be suggested.
- For rapid vitamin K antagonist reversal, four-factor prothrombin complex concentrate is recommended. This is likely safer, especially with reference to volume overload and is more rapid acting than plasma (albeit much more expensive). Vitamin K administration is also suggested.

Therapeutic Plasma Exchange

TPE is used to treat many disorders. In thrombotic thrombocytopenic purpura, it decreases mortality significantly and should be initiated as soon as possible after diagnosis. Guidelines for TPE with and without plasma as replacement fluid for other conditions have been summarized by the American Society for Apheresis.

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History

1628 William Harvey M.D. published “An Anatomical Study of the Motion of the Heart and of the Blood in Animals”, described the circulation of blood

1655 Richard Lower M.D. transfuses blood between dogs in England, keeps dogs alive

1818 James Blundell M.D. transfused blood to treat postpartum hemorrhage (donor was husband)

1937 Bernard Fantus M.D., Cook County, established first blood bank

1994 Bickell M.D. *Immediate versus delayed fluid resuscitation for Hypotensive patients with penetrating torso injuries*
Definition – Massive Transfusion

• AABB Technical Manual
  – “For this chapter”
    • 8-10 RBCs in an adult patient in less than 24 hours
    • 4-5 RBC units in 1 hour
    • Exchange transfusion in an infant
Definition

• No consensus
  – Most commonly used
    • > 10 RBC units within 24 hours
    • Conceptually a whole blood volume in a 70 kg patient
  – Define massive transfusion by how many units were issued before hemorrhage control
    • Small number of patients reach ICU before the threshold of 10 units but have significantly decreased mortality risk
    • Make mortality risks more uniform
Trauma Resuscitation

• Literature on this topic has more than doubled

• Three important lessons
  – 25% of severely injured trauma patients enter the hospital with coagulopathy
  – Massive crystalloid resuscitation causes compartment syndromes (abdominal, intracranial and limb)
  – Early treatment of coagulopathy may improve outcome
Trauma Centers

• Level I
  – Highest level of surgical care
  – Full range of specialists
  – Education program
  – Research
Trauma Centers

• Level II
  – Similar to Level I
  – Works with a Level I center
  – No research or residency program requirements

• Level III
  – Emergency resuscitation, surgery, intensive care
  – Transfer to Level I or II

• Level IV
  – Triage and transfer
Literature Reviews

• Survivor bias
  – 90% who receive more than 8 units of RBCs die in the first hour of care
  – 80% of those who will bleed to death have done so within 6 hours of admission
Literature Reviews

• Randomized controlled trials for acceptance of new clinical procedures
• Severely injured
  – Can’t give informed consent
  – Urgency of triage - Rapid enrollment
  – Determining control arm
  – Inclusion and exclusion criteria
  – Timely activation of research team and blood bank
Formula Driven vs. Laboratory Driven

• Formula driven
  – Transfuse by ratios of products
  – Blood bank supplies the products in the ratios that were predetermined

• Laboratory driven
  – Red cells for hemoglobin levels
  – Plasma for INR levels
  – Platelets for platelet levels
  – Cryoprecipitate for fibrinogen levels
  – Continue lab evaluation at set intervals
Pilot Study

• Level I trauma center in Toronto
• Inclusion criteria
  – Adult trauma patients (16-90)
  – Penetrating or blunt injury
    • Bleeding expected massive transfusion
    • Hypotension
Pilot Study

• Level I trauma center in Toronto

• Exclusion criteria
  – Assessed > 6 hours after injury
  – Received more than 2 units before arrival
  – Brain injury, head injury
  – Shock unrelated to hemorrhage
  – Known coagulopathy unrelated to trauma
  – Unsalvageable injuries
Pilot Study

• Formula-Driven
  – 1:1:1 ratio
    • 4 FFP : 4 RBCs : 4 pooled platelets
    • Thawed plasma was not available
    • RBCs could be transfused earlier if clinically indicated
  – Up to 12 hours or terminated by surgeon
Pilot Study

• Laboratory-Guided
  – RBCs: Hgb < 7
  – FFP: 3-4 units for INR > 1.8
  – Platelets: One pool at a time for plt < 50
  – Cryo: Ten units at a time for fibrinogen < 100
  – Labs performed at least every 2 hours
Figure 1. Patient flow diagram for TRFL study (study period: July 6, 2009, to May 31, 2010).
Pilot Study

• Conclusions
  – Random controlled trial can be done
  – Challenges with the study population
  – Overcome by organization
    • Initial 5 months many patients were missed
    • Eventually the blood bank personnel identified patients who could be included in the study
Evaluation of MTP

- Note that what was issued in the massive transfusion protocol was not followed
- Survivor bias
- Laboratory data not available
- Next Up
  - Joint Theater Trauma Registry (JTTR)
  - Prospective, Observational, Multicenter, Major Trauma Transfusion Study (PROMMTT)
  - Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR)
JTTR

• Joint Theater Trauma Registry (2004)
  – Injury characteristics
  – Clinical practices
  – Military trauma outcomes
• Operation Iraqi Freedom
• Operation Enduring Freedom
JTTR

- Retrospective review
- March 2003 – 2012
- Received at least one transfusion
- First 24 hours of care
JTTR

– Red Blood Cells (RBCs)
– Fresh Whole Blood (FWB)
– Fresh Frozen Plasma (FFP)
– Apheresis Platelets (PLT)
– Not evaluated
  • Cryoprecipitate
JTTR

• Age
• Sex
• Injury Severity Score (ISS)
• Glasgow Coma Scale (GCS)
• INR, hemoglobin, platelet count
• Blood pressure, heart rate, temperature
• Heart rate
• Conclusions
  – Coagulopathy was present on presentation
  – High transfusion ratios correlated with higher survival
• Supports damage control resuscitation
PROMMTT

• The Prospective, Observational, Multicenter, Major Trauma Transfusion Study
• 10 Level I trauma centers
• 1245 Study patients (of 34362 trauma admissions, 12560 initial patients)
PROMMTT

• Timing of products transfused to assess association of timing and amount of blood products with mortality
• Higher plasma and platelet ratios early associated with decreased mortality at 24 hours
• Survivors at 30 days not associated with the ratios of plasma or platelets
PROPPR

• Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients with Severe Trauma
• 12 Level 1 Trauma Centers
• Randomized trial (August 2012 – December 2013)
• 24 hour and 30 day mortality
PROPPR

• No significant differences in 24 hour or 30 day mortality
• 1:1:1 group achieved hemostasis more often and less died from exsanguination at 24 hours
References

- Copes WS, Sacco WJ, Champion HR, Bain LW, "Progress in Characterising Anatomic Injury", In Proceedings of the 33rd Annual Meeting of the Association for the Advancement of Automotive Medicine, Baltimore, MA, USA 205-218
- Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974; 81-84.

Questions?