Blood Components & Indications for Use

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Professor of Pathology and Medicine
Page ID # 16002
Why are YOU Confused about Transfusions?

• Mixed messages
  • “Blood saves lives…”
  • “BAD Blood”

• Near-total absence of education!!

• Paucity of highly-reliable clinical trial data

• Lack of uniform clinical practice guidelines

• Even published transfusion guidelines are not followed!

• Major barriers to change management persist as does the culture of medical hierarchy
Objectives of Today’s Talk

• Some background thoughts
• Define the 4 basic blood components
• Describe the contents “in the bag”
• High-level overview of indications for use
• Preliminary commentary on Patient Blood Management principles
• Discuss a couple of cases
WW II Medic Administers IV Plasma to Wounded GI: The Value of Blood Transfusion was Recognized Before Randomized Controlled Trials
Blood Transfusion is “Unavoidably Unsafe”

• High volume
• High cost
• High Risk
• Problem prone
## Plan: Scheduled Educational Sessions

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Blood Components &amp; Indications for Use”</td>
<td>July 21, 2017</td>
</tr>
<tr>
<td>“Adverse Effects of Blood Transfusion”</td>
<td>August 17, 2017</td>
</tr>
<tr>
<td>“Specialized Blood Components &amp; Their Indications”</td>
<td>August 28, 2017</td>
</tr>
</tbody>
</table>
## Basic Blood Components

### The potential of Human Blood

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cells</td>
<td>To increase the amount of red blood cells after trauma or surgery or to treat severe anemia.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>To correct a deficiency in coagulation factors or to treat shock due to plasma loss from burns or massive bleeding.</td>
</tr>
<tr>
<td>Concentrate of Platelets</td>
<td>To treat or prevent bleeding due to low platelet levels. To correct functional platenet problems.</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>To treat fibrinogen deficiencies:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Storage Period</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>42 days in the refrigerator or 10 years in the freezer</td>
<td>1 year in the freezer</td>
<td>5 days at room temperature</td>
<td>1 year in the freezer</td>
</tr>
</tbody>
</table>
Components Prepared Sequentially, in a Hermetically Sealed Sterile System
Blood Components

• **Whole blood**

• Separated from whole blood by centrifugation
  ➢ Red Blood Cells ("The Red Stuff")

• **Hemostatic components** ("The Yellow Stuff")
  ➢ Plasma
  ➢ Platelet concentrates
  ➢ Cryoprecipitated AHF
Do Not Pull That Transfusion
“Trigger” Absent Patient Assessment
Develop Transfusion Targets:
Incorporate Laboratory Trigger Numbers with Clinical Judgment
8 Rights of Transfusion Administration

8 RIGHTS:
✓ Product
✓ Patient
✓ Dose
✓ Time
✓ Reason
✓ Site
✓ Documentation
✓ Response
Red Blood Cell Units
Stored in Anticoagulant-Preservative Solution
Stored at 1 – 6° C, 42-day Shelf Life
Content of a Unit of RBC’s?

- Volume = ~ 300 mL
- Red blood cell volume (“mass”) = ~ 185 mL
- Hemoglobin content = ~ 50 grams
- Iron content = 250 mg
- Residual plasma = ~ 15 – 20 mL
- Citrate anticoagulant / preservative = ~ 100 mL
- Transfused to a “70-Kg man”, 1 unit of RBC raises the Hct ~ 3% and Hgb ~ 1.0 g/dL
RBC Dosing
Appropriate Management

• Hemoglobin threshold < 7 g/dL
  ➢ Stable non-bleeding adults for *symptomatic anemias*
  ➢ Includes Hematology / Oncology patients receiving chemotherapy / radiation therapy

• Hemoglobin threshold < 8 g/dL
  ➢ Acute coronary syndrome with ischemia
  ➢ Traumatic brain injury or intracranial hypertension
RBC Dosing
Appropriate Management

• “Don’t Give 2 when 1 will do!”
• Transfuse what patients need, but not more
• Transfuse 1 unit at a time; re-evaluate the patient & the laboratory response
• Generally, most patients do not need to be transfused to ≥ 10 g / dL
Units of Thawed Plasma
On Average, 220 mL – 250 mL
VARIEITES of PLASMA

• **FFP**: Plasma separated from donated whole blood by centrifugation, frozen ≤ 8 hours of collection

• **FP24**: Frozen ≥ 8 hours, but ≤ 24 hours of collection

• “**Thawed**” plasma (5-day shelf life)
# Coagulation “Factors”

<table>
<thead>
<tr>
<th>Factor</th>
<th>Common Name</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>3 – 4 Days</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>2 – 3 Days</td>
</tr>
<tr>
<td>III</td>
<td>Thromboplastin</td>
<td>Available from various tissues, such as lung, brain, kidney</td>
</tr>
<tr>
<td>IV</td>
<td>Ionized Ca^{++}</td>
<td>Ubiquitous</td>
</tr>
<tr>
<td>V</td>
<td>Ac-globulin (proaccelerin)</td>
<td>12 – 36 hours</td>
</tr>
<tr>
<td>VI</td>
<td>Nonexistent</td>
<td>-</td>
</tr>
</tbody>
</table>
Coagulation “Factors”

<table>
<thead>
<tr>
<th>Factor</th>
<th>Common Name</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>Proconvertin (Prothrombin Conversion Accelerator)</td>
<td>3 – 6 hours</td>
</tr>
<tr>
<td>VIIIIC</td>
<td>Antihemophilic Factor</td>
<td>12 hours</td>
</tr>
<tr>
<td>IX</td>
<td>Christmas Factor</td>
<td>24 hours</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Prower Factor</td>
<td>1 – 2 days</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma Thromboplastin antecedent</td>
<td>2 – 3 days</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman’s (contact) factor</td>
<td>2 – 3 days</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin Stabilizing Factor (Profibrinoligase)</td>
<td>3 – 5 days</td>
</tr>
</tbody>
</table>
Vitamin K-Dependent Factors (all synthesized in the liver)

- Factor II
- Factor VII
- Factor IX
- Factor X
- Protein C
- Protein S
Where in the *Classical Cascade* Do the Coagulation Factors “Belong”?

**Extrinsic Pathway**
- Factor I
- Factor II
- Factor V
- Factor VII
- Factor X

**Intrinsic Pathway**
- Factors I, II, V
- Factor VIII:C
- vWF
- Factor IX
- Factor X
- Factor XI
- Factor XII
Defining the INR

- **International Normalized Ratio** = \( \frac{\text{PT}_{\text{patient}}}{\text{Geometric Mean PT Reference Range}} \)^{\text{ISI}}
  where **ISI** = International Sensitivity Index

- **INR** are designed specifically for **Coumadin treatment control**, not as a criterion to transfuse plasma!!

- **ISI** used by local laboratories performing the *ex vivo* PT tests

- The ISI reflects the *responsiveness* of a given thromboplastin to a reduction in Vitamin K-dependent coagulation factors compared to WHO reference material.

- Highly sensitive thromboplastins (ISI ~ 1.0) are now made by recombinant technology with defined phospholipid content
Lab Screening Tests NOT a Trigger to Transfuse Plasma

No increased risk of hemorrhage / oozing if the PT / aPTT is no more prolonged than

1.3 X upper limit of reference range
- or -
1.5 X midpoint of reference range

NOT an INR = 1.5

Lab Abnormality ≠ Clinical Coagulopathy
And What if Plasma is Transfused?

- Mean change of $0.03$ INR units / unit of FFP transfused
- Mildly abnormal PT’s just don’t change much with FFP transfusion
- INR’s above $3$ have a more significant change per unit of FFP
- Mildly prolonged PT values ($13 - 17$ sec) do not correlate with RBC loss
- Only $10\%$ of patients had the PT re-checked after transfusion!!

Holland, et al, Transfusion 2005;45:1234-5
### Retrospective Literature Analysis

**Normal vs. Abnormal Coagulation Tests**

- Pre-procedure coagulation tests are lousy predictors of who is going to bleed
- Prophylactic plasma transfusion does not result in fewer bleeding events

<table>
<thead>
<tr>
<th>Reference/Procedure</th>
<th>Abnormal tests n/N</th>
<th>Normal tests n/N</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 angiography</td>
<td>1/85</td>
<td>15/915</td>
<td></td>
</tr>
<tr>
<td>12 angiography</td>
<td>0/9</td>
<td>0/200</td>
<td></td>
</tr>
<tr>
<td>16 bronchoscopy</td>
<td>3/28</td>
<td>28/218</td>
<td></td>
</tr>
<tr>
<td>17 bronchoscopy</td>
<td>1/14</td>
<td>43/412</td>
<td></td>
</tr>
<tr>
<td>27 liver biopsy</td>
<td>0/27</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>25 liver biopsy</td>
<td>4/76</td>
<td>4/100</td>
<td></td>
</tr>
<tr>
<td>22 liver laparoscopy</td>
<td>4/93</td>
<td>4/85</td>
<td></td>
</tr>
<tr>
<td>13 liver laparoscopy</td>
<td>0/29</td>
<td>1/50</td>
<td></td>
</tr>
<tr>
<td>29 transjugular liver</td>
<td>0/112</td>
<td>0/45</td>
<td></td>
</tr>
<tr>
<td>14 transjugular liver</td>
<td>0/31</td>
<td>0/19</td>
<td></td>
</tr>
<tr>
<td>31 transjugular liver</td>
<td>3/203</td>
<td>0/168</td>
<td></td>
</tr>
<tr>
<td>32 para/thoracocentesis</td>
<td>1/42</td>
<td>18/556</td>
<td></td>
</tr>
<tr>
<td>15 transjugular kidney</td>
<td>2/10</td>
<td>0/15</td>
<td></td>
</tr>
<tr>
<td>33 kidney biopsy</td>
<td>1/9</td>
<td>33/110</td>
<td></td>
</tr>
</tbody>
</table>

The INR of Fresh Frozen Plasma

- The INR of FFP is 1.1 (range 0.9 to 1.3)
- Not surprising that giving FFP will have little effect on minimally elevated PT’s
- FFP will affect the INR only if there is a big difference between the FFP and the patient’s plasma
Whadya Do With an Elevated INR?

• An elevated INR has NEVER been an “indication” to transfuse plasma or platelets!!

• Practice Clinical Correlation:
  - How “elevated” is the value?
  - Why is the PT / INR elevated?
  - Is the patient bleeding?
  - Is the patient at risk for bleeding (e.g. planned invasive procedure)?
  - Is there any evidence that plasma transfusion will improve patient outcome?
  - Decision to transfuse is multi-factorial, never based solely on some “number”.
Review of RCTs on Plasma Effectiveness

**TRANSFUSION PRACTICE**

**BACKGROUND:** The clinical use of frozen plasma (FP) continues to increase, both in prophylactic and in therapeutic settings. In 2004, a systematic review of all published randomized controlled trials (RCTs) revealed a lack of evidence that supported the efficacy of FP use. This is an update that includes all new RCTs published since the original review.

**STUDY DESIGN AND METHODS:** Trials involving transfusion of FP up to July 2011 were identified from searches of MEDLINE, EMBASE, CINAHL, The Cochrane Library, and the UKBT/SNPI Transfusion Evidence Library. Methodologic quality was assessed. The primary outcome measure was the effect of FP on survival.

**RESULTS:** Twenty-one new trials were eligible for inclusion. These covered prophylactic and therapeutic FP use in liver disease, in cardiac surgery, for warfarin anticoagulation reversal, for thrombotic thrombocytopenic purpura treatment, for plasmapheresis, and in other settings, including burns, shock, and head injury. The largest number of recent RCTs were conducted in cardiac surgery; meta-analysis showed no significant difference for FP use for the outcome of 24-hours post-operative blood loss (weighted mean difference, −3% 95% CI: −6% to 0% confidence interval ...Jul 14, 2012.

A recurring theme for transfusion of plasma is variation in practice and uncertainty around the evidence-based indications informing appropriate use. Plasma for transfusion is given primarily for two indications: to prevent bleeding (prophylaxis) or to stop bleeding (therapeutic). Clinical use of frozen plasma (FP) continues to grow, despite a number of publications attesting to questionable practice in many settings. Plasma continues to be commonly used as prophylaxis, before surgery or invasive procedures. Results from a large multicenter prospective observational study in adult critical care, which evaluated just under 2000 admissions, showed that 30% of intensive care unit (ICU) patients had prolongation of prothrombin time (PT) during their admission and that one-third of patients in adult critical care with PT prolongation received fresh-frozen plasma (FFP), but approximately 50% of patients received FFP in the absence of evidence of clinical bleeding. In the United States, the latest data from the National Blood Collection and Utilization Survey showed that 5,780,000 units of plasma were produced for transfusion in 2009. This represented a 0.3% increase from 2006 and a significant (23%) increase from 2005.

In 2004, in parallel to the drafting of guidelines for the use of FFP: cryoprecipitate, and cryosupernatant by the

- 80 trials (1966 – 2012), covering prophylactic & therapeutic plasma use
- Conditions such as liver disease, cardiac surgery, warfarin reversal, burns, shock, head injury
- No significant benefit for use across a range of indications!

*Transfusion 2012;52: 1673-86.*
Prophylactic Plasma Use in Critical Care, A Randomized Controlled Trial (TOPIC)

Fresh frozen plasma (FFP) is effective in correcting multiple clotting factor deficiencies, and transfusion guidelines recommend its use during massive bleeding and such a deficiency. In the past decades, use of FFP has grown steadily. In addition to the use of FFP in actively bleeding patients, substantial amount of FFP is transfused prophylactically to nonbleeding patients with a coagulopathy. Coagulopathy, defined as prolonged prothrombin time (PT) or international normalized ratio (INR), has a high

- Prolonged INR (1.5 – 3.0)
- CV catheter insertion
- Tracheostomy
- Chest tube
- Abscess drainage

Outcomes:
- INR correction
- bleeding complications
- occurrence of lung injury

Plasma (12 mL/Kg) reduced INR to < 1.5 in only 54%
No difference in post-procedural bleeding
No difference in lung injury scores, regardless whether plasma was administered or not

Transfusion 2014, ePub June 9
Plasma Indications
Appropriate Usage
(“Customary Dose” = 12 – 15 mL / Kg)

• Thrombotic microangiopathies (TTP, HUS, etc.)
• Multiple clotting factor deficiencies with INR ≥ 1.7
  ➢ **Bleeding** not related to surgery
  ➢ Ongoing **bleeding**, acute or chronic liver disease
  ➢ Active **bleeding** with DIC
  ➢ Prevention of intra-operative **bleeding** in patients with DIC or liver disease
  ➢ Correction of micro-vascular **bleeding** in massive recipients
  ➢ Single clotting factor deficiencies (specific factors not commercially available)
• To correct congenial deficiencies of clotting factors
Misuses of Plasma

• As a volume expander
• As a nutritional source
• To enhance wound healing
• Not a suitable source of immunoglobulins (e.g., in patients with severe hypogammaglobulinemia)

• Mild to moderate prolongation of PT or aPTT prior to invasive procedures
Platelet Concentrates

- “Random-donor” pools (whole blood-derived)
- Apheresis platelets (“single donor”)


Flavors of Platelet Concentrates

- “Adult Doses”
- “Random-donor” pools (pool size = 4)
- Apheresis platelets (“single donor”)
- Pre-Storage RD Pools (leukoreduced, bacteriologically tested, counted for yield)
- Contents are equivalent (3 x 10^{11} platelets / dose)
Deciding to Transfuse Platelets: Risk Assessment Issues

- Why is your patient thrombocytopenic?
- Medical vs. Surgical patient
- Bleeding vs. Non-bleeding
- Risks in surgical / obstetric patients
  - type and extent of surgery
  - the ability to control bleeding
  - actual / anticipated rate of bleeding
  - factors affecting platelet function, such as medications, renal failure, extra-corporeal circulation (e.g., bypass or ECMO), etc.
Bleeding Risks & Platelet Count are Approximately Correlated

<table>
<thead>
<tr>
<th>Platelet Count (10⁹ / L)</th>
<th>Likelihood of Spontaneous Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>High</td>
</tr>
<tr>
<td>5 – 10</td>
<td>Increased with</td>
</tr>
<tr>
<td></td>
<td>• Trauma</td>
</tr>
<tr>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td>• Ulceration</td>
</tr>
<tr>
<td>10 - 50</td>
<td>Variably Increased</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>Exceedingly Unlikely</td>
</tr>
</tbody>
</table>
# Recommendations for Platelet Transfusion ("Trigger Points")

<table>
<thead>
<tr>
<th>Platelet Count (10⁹ / L)</th>
<th>Transfusion Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>Almost Always</td>
</tr>
<tr>
<td>≤ 10 – 20</td>
<td>Prophylaxis Window for Medical Patients</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Usually Indicated for major surgery, endoscopic biopsies, liver biopsy</td>
</tr>
<tr>
<td>≤ 50</td>
<td>Active bleeding during massive transfusion, cardiopulmonary bypass or DIC</td>
</tr>
<tr>
<td>50 – 100</td>
<td>Based on risk of bleeding</td>
</tr>
<tr>
<td>≥ 100</td>
<td>Uncommonly Indicated: Consider with known platelet dysfunction, anti-platelet drugs &amp; microvascular bleeding</td>
</tr>
</tbody>
</table>
Dose of Prophylactic Platelet Transfusions and Prevention of Hemorrhage


ABSTRACT

BACKGROUND
We conducted a trial of prophylactic platelet transfusions to evaluate the effect of platelet dose on bleeding in patients with hypoproliferative thrombocytopenia.

METHODS
We randomly assigned hospitalized patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumors to receive prophylactic platelet transfusions at a low dose, a medium dose, or a high dose (1.1 x 10^11, 2.2 x 10^11, or 4.4 x 10^11 platelets per square meter of body-surface area, respectively), when morning platelet counts were 10,000 per cubic millimeter or lower.

- 1271 patients with hypoproliferative thrombocytopenia
- Transfusion "Trigger" = 10,000 / µL
- Randomly assigned to 3 doses
  - 1.1 x 10^{11} / meter^2
  - 2.2 x 10^{11} / meter^2
  - 4.4 x 10^{11} / meter^2
- Low dose led to decreased numbers of platelets transfused, but increased transfusions given
- Doses between 1.1 and 4.4 x 10^{11} / meter^2 have no effect on the incidence of bleeding

Avoid Transfusing Platelets

- In thrombocytopenia due to *increased platelet destruction* (immune or microangiopathic)
  - Idiopathic thrombocytopenic purpura (ITP)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Other microangiopathies (HUS, HELLP syndrome)

- In end-stage (cirrhotic) liver disease with splenomegaly

- Platelet transfusion in these settings are rarely indicated and usually *ineffective* – the patient incurs all the risks, all cost, little or no benefit
Cryoprecipitated AHF, Single & Pooled
(Frozen Shelf Life, 1 year; Thawed, 6 hours)

Single-donor Cryoprecipitate, 15 – 20 mL volume / unit

"Adult Dose" =
• Pooled Cryo AHF
• Pool of 5 units
• 80 – 100 mL volume / pool
## Cryoprecipitated AHF: Estimated Concentrations of Plasma Factors

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Approximate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>• 150 mg (minimum) &lt;br&gt;• usually contains ≥ 250 mg of fibrinogen / unit</td>
</tr>
<tr>
<td>Factor VIII:C</td>
<td>&gt; 80 IU (minimum)</td>
</tr>
<tr>
<td>von Willebrand Factor (vWF)</td>
<td>80-120 Units</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>40 – 60 IU</td>
</tr>
</tbody>
</table>
Cryoprecipitated AHF: Clinical Indications

- **Hypofibrinogenemia** (< 200 mg/dL)
  - Fibrinogen deficiency with **active bleeding** or in patients at risk
  - Consumptive coagulopathies (e.g., DIC)
- Uremic bleeding unresponsive to DDAVP
- Evident hemorrhagic stroke or intracranial bleeding in patients receiving TPA
- von Willebrand Disease or Hemophilia A (use **only** when commercial factor concentrates are unavailable)
- Dysfibrinogenemia (normal fibrinogen level)
- Factor XIII deficiency
Transfuse "common sense" instead of blood components...

• In patients with **cirrhosis**:
  - Editorial / review of the use of prophylactic plasma & platelets
  - Speaks to the lack of evidence
    - that transfusion is necessary at all
    - improves outcomes
    - But transfusion actually increases healthcare cost due to adverse events

Hepatology 2016; 63: 368-369
Test Case # 1: RBC Transfusion

- Patient is a 28-y/o female admitted to the Burn ICU
- Toxic epidermal necrolysis (TEN) secondary to drug ingestion
- Patient transfused with 1 unit of RBCs in each of the last 2 days
- AM Hgb ~ 6.6 g/dL; posttransfusion only ~ 6.9 g/dL
- “What’s the matter? Why isn’t my patient responding to transfusion?”
Common Things Occur *Commonly*

Test Case #2

- You’re *on-call* tonight (~ 10:30 PM)
- 76-y/o man with ESLD needs a percutaneous liver biopsy (or tunneled central line placement)
  - Weight = 84 Kg
  - INR = **1.7**
  - Platelet count = **22 K / µL**
- Interventional Radiology *wants*
  - INR of **1.5**
  - Platelet count of **50 K / µL**
- Procedure is scheduled, *to follow*, likely after Noon tomorrow
Ready to Transfuse Plasma?

• To affect laboratory tests results, ~ 1/3 of patient’s PV needs to be replaced

• “Usual & Customary” dose is 12 - 15 mL / Kg

• “How many units of plasma should I order”? [Is the estimated volume of plasma limiting?]

• “Timing is Everything”: What’s the shortest lived coagulation Factor in plasma?

• When should you transfuse plasma?
Ready to Transfuse Platelets?

• Why is the patient thrombocytopenic?
  ➢ End-stage liver disease
  ➢ Portal hypertension
  ➢ Splenomegaly
  ➢ Splenic sequestration
  ➢ What hormone helps “make” platelets?
    o Thrombopoietin
    o Where is it synthesized?
  ➢ Where are the patient’s own platelets?
  ➢ When should you transfuse platelets?
The Rational Use of Blood

The Best Patient Blood Management Recommendation

Blood Transfusion is like marriage:

• It should not be entered upon lightly,
• Unadvisedly or wantonly, or
• More often than is absolutely necessary