Transfusion in Massive Bleeding - A role for fresh blood?

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Historical Background

• Over last 40 years, transfusion therapy evolved from use of predominately whole blood to now largely component therapy.
• Whole blood: still used in many developing countries and in military situations, however
• Component therapy predominates primarily due to resource utilization and safety.
• Change occurred without strong evidence of clinical outcomes between whole blood and component therapy in multiple trauma patients.
The transfusion paradigm in the developed social market economies

- National blood services funded by government
- Provide transfusion needs – through components
- Embedded in the manufacturing/inventory paradigm
  - “Blood factories”
  - GMP, QC etc
  - Detached from clinical environment
Age and gender distribution of transfused patients

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Benin</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>5-14</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>15-44</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>45-59</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>≥60</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Population and GDP/cap (PPP) $:

- **Benin**
  - Population: 9099922
  - GDP/cap (PPP) $: 1481

- **Denmark**
  - Population: 5580413
  - GDP/cap (PPP) $: 37151

Transfusions/10³ population:

- **Benin**: 6.1
- **Denmark**: 9.6

Indications for transfusions: Malaria, trauma, Obstetric haemorrhage, Surgery, Oncology support etc. Whole Blood.
The red cell storage lesion

- ATP depletion
- Lipid peroxidation
- Protein oxidation
- 2,3-DPG depletion

Red blood cells:
- Increased osmotic fragility and haemolysis
- Membrane vesiculation and decreased deformability
- Increased O2 Hb affinity

Storage Medium:
- Increased K+, iron, RBC micro-particles, oxidized proteins and lipids, lactate, cytokines
- Decreased pH

RBC squeezing through a capillary bed
Microhemodynamic aberrations created by transfusion of stored blood
Red cell deformability and elasticity
Transfusion in Man’s Best Friend
Old vs less old blood

A. Survival

B. Lung Injury

C. Shock Score

D. Pulmonary Pressure during Transfusion

Predicted risk of death against maximum age of red blood cells

Lowess smoother

Estimated Probability of Death

Maximum age of red blood

bandwidth = .8

Pettijä et al. Critical Care 2011, 15:R116
The age of red blood cells is associated with bacterial infections in critically ill trauma patients.

Mortality Decrease with Higher FFP:PRBC Ratios

- Low (≤1:8): 90% (56/62)
- Medium (>1:8 and ≤1:3): 49% (47/95)
- High (>1:3 and ≤1:2): 25% (28/111)
- Highest (>1:2): 26% (30/115)

*p<0.01 compared to >1:2
Survival of patients receiving high ratios versus patients receiving low ratios of fresh frozen plasma (FFP) and platelets to PRBCs
Transfusion in Trauma
Patient mortality by transfusion type

<table>
<thead>
<tr>
<th>Variable (Reference Group)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>.32</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>.09</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>.004</td>
</tr>
<tr>
<td>EMS time</td>
<td>.035</td>
</tr>
<tr>
<td>Transfer (no)</td>
<td>.58</td>
</tr>
<tr>
<td>Blood product (whole)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; $^a$Logistic regression analysis was used.

Independent Predictors of Mortality in Adult Patients With Trauma
Fresh blood in battlefield trauma

Survival

Days

0.00  5.00  10.00  15.00  20.00  25.00  30.00

0.50  0.60  0.70  0.80  0.90  1.00

Log-Rank Test, (p=0.002)

WFWB group
CT group
Comparison of “reconstituted” whole blood (1:1:1) to whole blood

<table>
<thead>
<tr>
<th></th>
<th>“Reconstituted” WB(1:1:1)*</th>
<th>WB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume</td>
<td>660 mL</td>
<td>570 mL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>29%</td>
<td>33%-43%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>88 k</td>
<td>130 k – 350 k</td>
</tr>
<tr>
<td>Coagulation factor</td>
<td>65%</td>
<td>86%</td>
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</table>
Whole Blood in the Management of Hypovolemia Due to Obstetric Hemorrhage

Women receiving transfusions for obstetric hemorrhage N=1,540

- Only whole blood given n=659
  - 1,443 units transfused
  - Mean of 2.2 units per woman transfused

- Only packed red blood cells given n=583
  - 1,375 units transfused
  - Mean of 2.3 units per woman transfused

- Combination of blood products given n=288
  - 1,591 units transfused
  - Mean of 5.5 units per woman transfused

Graph shows data for complications:
- Acute Tubular Necrosis
- Pulmonary edema
- Hypofibrinogenemia
- ICU
- Maternal death

Legend:
- WB only
- RCC only
- Combination

Transfusion of fresh whole blood (FWB) versus platelet concentrates (PC) after cardiac operations

- To evaluate FWB vs PC after cardiac operations
- Platelet aggregation on extracellular matrix model
- 24 patients one unit FWB (12 patients) or 10 platelet units (12 patients) after cardiopulmonary bypass.
- One unit FWB restored platelet aggregation on extracellular matrix to preoperative status (3.0 +/- 1.0), eight PC needed for the same result (3.2 +/- 0.8).
- One unit FWB increased platelet count to level achieved by six PC.

*The effect of one unit of FWB on platelet aggregation after cardiopulmonary bypass is equal or superior, to the effect of 8 to 10 PC.*
EXTENDED LIFE PLASMA:
A FRAMEWORK
FOR PREPARATION,
STORAGE AND USE
Protective Effects of Fresh Frozen Plasma on Vascular Endothelial Permeability

- Thawed FFP exerts protective effect on endothelium
- Independent of coagulation factor content
- Decreases over storage
- Argues against storage of thawed FFP
Reiteration – The extinction of fresh whole blood transfusion

- Bigger inventory – One donor - Many patients

- Blood screening
  - Donor recruitment – millions of $€£
  - Donor selection – a million questions
  - Testing – a million tests

- Need for recovered plasma
Reflections

- Much of transfusion practice lacks an evidence base
- In particular, the assumption that transfusion and resuscitation following massive blood loss requires individual stored components needs to be challenged
- Component therapy in the developed economies was an inevitable outcome of recovered plasma manufacture
More reflections

- Fresh whole blood has been rendered extinct but is therapeutically superior

- We suggest that the emerging Patient Blood Management movement represents the future of transfusion

- This can be achieved by closely integrating the transfusion service within the clinical environment
A pragmatic approach to embedding patient blood management in a tertiary hospital

1st Pillar
Optimize erythropoiesis
- Detect anemia
- Identify underlying disorder(s) causing anemia
- Manage disorder(s)
- Refer for further evaluation if necessary
- Treat suboptimal iron stores/iron deficiency/anemia of chronic disease/iron-restricted erythropoiesis
- Treat other hematologic deficiencies
- Note: Anemia is a contraindication for elective surgery

2nd Pillar
Minimize blood loss & bleeding
- Identify and manage bleeding risk
- Minimizing iatrogenic blood loss
- Procedure planning and rehearsal
- Preoperative autologous blood donation (in selected cases or when patient choice)
- Other

3rd Pillar
Harness & optimize physiological reserve of anemia
- Assess/optimize patient's physiological reserve and risk factors
- Compare estimated blood loss with patient-specific tolerable blood loss
- Formulate patient-specific management plan using appropriate blood conservation modalities to minimize blood loss, optimize red cell mass, and manage anemia
- Restrictive transfusion thresholds

Preoperative
- Meticulous hemostasis and surgical techniques
- Blood-sparing surgical techniques
- Anesthetic blood conserving strategies
- Autologous blood options
- Pharmacological/haemostatic agents

Intraoperative
- Timing surgery with hematological optimization

Postoperative
- Stimulate erythropoiesis
- Be aware of drug interactions that can increase anemia

- Vigilant monitoring and management of post-operative bleeding
- Avoid secondary hemorrhage
- Rapid warming/maintain normothermia (unless hypothermia specifically indicated)
- Autologous blood salvage
- Minimizing iatrogenic blood loss
- Hemostasis/anticoagulation management
- Prophylaxis of upper gastrointestinal hemorrhage
- Avoid/treat infections promptly
- Be aware of adverse effects of medication

- Optimize anemia reserve
- Maximize oxygen delivery
- Minimize oxygen consumption
- Avoid/treat infections promptly
- Restrictive transfusion thresholds

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Further reading

# External Financial Aid to Blood Transfusion Services in Sub-Saharan Africa: A Need for Reflection

Ferydoun Ala1, Jean-Pierre Allain2, Imelda Bates3, Kamel Bouket2, Frank Boulton4, James Brandful5, Elizabeth M. Dax1, Magdy El Ekiaby6, Albert Farrugia2, Jed Gorlin1, Oliver Hassali1,11, Helen Lee3, André Loua7, Kathryn Mailand8, Dora Ibbanya9, Zainab Mulkhay10, William Murphy9, Obene Opare-Sem7, Shirley Owusu-Ofori1, Henk Reesink9, David Roberts1,20, Oscar Torres1, Grace Totoe1, Henrik Ullum2, Silvano Wendel4

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# Toward a patient-based paradigm for blood transfusion

Falsification or paradigm shift? Toward a revision of the common sense of transfusion

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Abstract: The current “manufacturing paradigm” of transfusion practice has detached transfusion from the clinical environment. As an example, fresh whole blood in large-volume hemorrhage may be superior to whole blood reconstituted from multiple components. Multicomponent apheresis can overcome logistical difficulties in matching patient needs with fresh component availability and can deliver the benefits of fresh whole blood. Because of the different transfusion needs of patients in emerging economies and the vulnerability of these blood systems to emerging infections, fresh whole blood and multicomponent apheresis can better meet patient needs when compared with transplants of the “manufacturing paradigm”. We propose that patient blood management, along with panels of repeat, paid, accredited apheresis and fresh whole-blood donors can be used in emerging economies to support decentralized blood services. This alternative transfusion–medicine paradigm could eventually also be adopted by established economies to focus transfusion medicine on local patient needs and to alleviate the problem of the aging volunteer donor base.

Keywords: indications, emerging countries, patient blood management

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Reasons for moving toward a patient-centric paradigm of clinical transfusion medicine practice

Eleftherios C. Vamvakas

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The University of Western Australia