Introduction to Transfusion Medicine: with Recent Advances

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What is Transfusion Medicine

• A field of medicine concerning the care of patients and donors related to blood products and apheresis blood procedures

• Touches on patients from all disease specialties
  – Including healthy people (allogeneic donors)

• Includes aspects of
  – Laboratory management
  – Patient/donor care
  – Regulatory compliance
Transfusion Medicine Encompasses:

- Hospital transfusion services
- Blood collection, processing, and testing
  - Whole blood and apheresis
- Immunohematology and genomics testing
- Cellular therapies
- Therapeutic apheresis
- Tissue banking
- HLA testing
- Coagulation and management of hemostasis
Transfusion Medicine Specialists Include

- Hematologists
- Clinical pathologists
- Anesthesiologists
- Pediatricians
- Nurses
- Other allied health professionals
FIGURE 4.1 Blood center physician oversight.
FIGURE 18.2  Transfusion Service Physician Oversight.
Advances in the Pipeline

**Donor**
- Target recruitment to hospital needs
- African American and minority: Hemoglobin S and Leukoreduction
- Adverse events: Prevention
  - Pre and Post donation care
- Education
- Decrease DEHP

**Processing**
- Better blood products
  - Improve storage
  - Pathogen inactivation
- Automation
- Storage bags - DEHP free
- Testing
- Personalized products (link donor-patient)
- Cellular therapy
- Tissue banking

**Patient**
- Adverse outcomes
  - Infectious: Babesia, Dengue, XMRV
  - Non infectious: TRALI, TACO
- Pediatrics
- Massive transfusion/ETIC
- Evidence Based Transfusion

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New York Blood Center
Improvements in Transfusion Safety
Risks and Benefits of Transfusion

• Weighing the risks and benefits of transfusion
  – Pro
    • Alleviate patients signs/symptoms
  – Con
    • Risk of adverse event
    • Resource use
## Window period and residual risk

<table>
<thead>
<tr>
<th>Test</th>
<th>Window period (days)</th>
<th>Residual Risk of transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV MP NAT</td>
<td>9</td>
<td>1:1,467,000</td>
</tr>
<tr>
<td>HIV EIA</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>HCV MP NAT</td>
<td>7</td>
<td>1:1,148,000</td>
</tr>
<tr>
<td>HCV EIA</td>
<td>51 – 58</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>30-38</td>
<td>1:280,000-1:357,000</td>
</tr>
<tr>
<td>HBV NAT</td>
<td>40-50 (MP) &amp; 15-34 (ID)</td>
<td>1:350,000-1:470,000</td>
</tr>
<tr>
<td>HTLV</td>
<td>80</td>
<td>1: 2,700,000</td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td>1 reported case in the US in the last 50 years (last case 1966)</td>
</tr>
<tr>
<td>Chagas Disease</td>
<td></td>
<td>7 reported cases in the US prior to screening</td>
</tr>
<tr>
<td>WNV NAT</td>
<td></td>
<td>6 reported cases in the US 2004-11.</td>
</tr>
<tr>
<td>Sepsis (Bacterial)</td>
<td></td>
<td>1:25,350 Whole Blood Derived Platelets &amp; 1:74,807 Apheresis Platelets</td>
</tr>
</tbody>
</table>
## Risks in Perspective

<table>
<thead>
<tr>
<th>Activity/Cause</th>
<th>~Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Death(^1)</td>
<td>1:130</td>
</tr>
<tr>
<td>Accidents (unintentional injuries)(^1)</td>
<td>1:2,700</td>
</tr>
<tr>
<td>MVA(^2)</td>
<td>1:6,000</td>
</tr>
<tr>
<td>Homicide(^1)</td>
<td>1:17,000</td>
</tr>
<tr>
<td>Being struck by lightning(^3)</td>
<td>1:700,000</td>
</tr>
</tbody>
</table>

\(^1\)(MMWR 55(50): 1363 (2006) - 2004 Data  
\(^2\)CDC Fast facts – 2005 Data  
\(^3\)USA Today online
Historical and New “Trends”
Pathogen Inactivation

• Current testing/screening has made the blood supply the safest it has ever been.

• However:
  – Bacterial contamination (plts) can still occur
  – New infectious diseases constantly emerging
  – Current testing paradigm limited and reactionary
  – PI is a proactive strategy
Methods of Pathogen Inactivation (PI)

• INTERCEPT
  – Amotosalen + UVA light
    • Disruption of nucleic acids via intercalation and crosslinking of pyrimidine bases (C, T, U)

• MIRASOL
  – Riboflavin + UVA/UVB light
    • Disruption of nucleic acids (Guanine) via free oxygen radicals

• Theraflex-UV
  – UVC
    • Dimerization of pyrimidines
Table 1
Degree of reduction of pathogens in log (adapted from [24] with Permission).

<table>
<thead>
<tr>
<th></th>
<th>Amotosalen/UVA</th>
<th>Riboflavin/UV</th>
<th>UVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enveloped virus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>&gt;5.5</td>
<td>2.3</td>
<td>na*</td>
</tr>
<tr>
<td>HCV</td>
<td>&gt;4.5</td>
<td>3.2</td>
<td>na</td>
</tr>
<tr>
<td>HIV (cell free)</td>
<td>&gt;6.2</td>
<td>&gt;5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>HIV (cell-associated)</td>
<td>&gt;6.1</td>
<td>&gt;4.5</td>
<td>na</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>4.7</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>CMV (cell-associated)</td>
<td>&gt;5.9</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>&gt;6.0</td>
<td>&gt;5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>&gt;6.4</td>
<td>2.1</td>
<td>na</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>&gt;5.9</td>
<td>&gt;5</td>
<td>na</td>
</tr>
<tr>
<td><strong>Nonenveloped virus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV</td>
<td>0</td>
<td>1.8</td>
<td>na</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>3.5 to 5.0</td>
<td>&gt;5</td>
<td>5.46</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>≥6.6</td>
<td>≥4</td>
<td>&gt;4.8</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>≥6.6</td>
<td>4.2</td>
<td>4.8</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>4.5</td>
<td>4.6</td>
<td>4.9</td>
</tr>
<tr>
<td>E. coli</td>
<td>≥6.4</td>
<td>4.4</td>
<td>&gt;4</td>
</tr>
<tr>
<td><strong>Spirochaete bacteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. pallidum</td>
<td>&gt;6.8</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>B. burgdorferi</td>
<td>&gt;6.8</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td><strong>Parasite</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. cruzi</td>
<td>&gt;5.3</td>
<td>6</td>
<td>na</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>&gt;6</td>
<td>&gt;3.2</td>
<td>na</td>
</tr>
</tbody>
</table>

* Information not available.
FDA Approved: The INTERCEPT Blood System for Platelets & Plasma

**INTERCEPT Blood System for Platelets**

For the ex vivo preparation of pathogen-reduced apheresis platelet components in order:
- To reduce the risk of TTI, including sepsis
- To potentially reduce the risk of TA-GVHD

**INTERCEPT Blood System for Plasma**

For the ex vivo preparation of pathogen-reduced, whole blood derived or apheresis plasma in order to reduce the risk of TTI
Blood Management Programs
Blood Management

*Patient blood management is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion.*

*Getting started in patient blood management, AABB, 2011*

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**IMPROVED PATIENT OUTCOMES**

- Interdisciplinary Blood Conservation Modalities
- Anemia Management
- Optimizing Coagulation
- Patient-Centered Decision Making
Tenets of Blood Management

Evidence Based Transfusion

- Restrictive transfusion protocol
  - Hb < 70–80 g/l
- Correction of anaemia
  - Iron, B₁₂, folic acid, rHuEpo
- Blood conservation programme
- Reduction of blood loss
  - Tranexamic acid, sealants and glues
- Autologous blood
  - Preoperative autologous donation
  - Normovolaemic haemodilution
  - Perioperative cell salvage
Is a liberal transfusion strategy better than a restrictive transfusion strategy?

• Multiple randomized clinical trials have addressed this question:
  – A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials (TRICC)
  – Transfusion Strategies for Patients in Pediatric Intensive Care Units (TRIPICU)
  – Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)
Creation of Evidence Based Transfusion Guidelines
### Evidence-based transfusion triggers-EXAMPLE

<table>
<thead>
<tr>
<th>Blood component</th>
<th>Commonly accepted indications</th>
<th>Typical increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>Hb &lt; 7.5 gm/dL except with CAD</td>
<td>Hb: 1 gm/dL</td>
</tr>
<tr>
<td></td>
<td>Hb &lt; 8.5 gm/dL with CAD</td>
<td>Hct: 3%</td>
</tr>
<tr>
<td></td>
<td>Hb &lt; 10 gm/dL with acute CAD</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt; 100,000/µL neurosurgery</td>
<td>30-60,000/µL</td>
</tr>
<tr>
<td></td>
<td>&lt; 50,000/µL if surgery, invasive procedure, or active bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 20,000/µL if febrile/septic or central venous catheter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 10,000/µL</td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Warfarin-related ICH (with 3-factor PCC)</td>
<td>10-15 mL/kg increases factor levels by ~25%</td>
</tr>
<tr>
<td></td>
<td>Massive transfusion (RBC:FFP 1:2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INR &gt; 2.0 prior to invasive procedure</td>
<td></td>
</tr>
<tr>
<td>1 cryoprecipitate unit</td>
<td>Fibrinogen &lt; 150 mg/dL with bleeding Factor XIII deficiency* (purified FXIII product now available)</td>
<td>~7 mg/dL increase in fibrinogen per unit</td>
</tr>
</tbody>
</table>
GRADE

• A systematic and explicit approach to making judgments about quality of evidence and strength of recommendations

• Used by Cochrane Collaborative and many medical societies including AABB

• Strength of recommendation
  – Strong (1)
  – Weak (2)

• Quality of evidence
  – High (A)
  – Intermediate (B)
  – Low (C)
Extended red blood cell antigen matching for transfusions in sickle cell disease: a review of a 14-year experience from a single center

Michele LaSalle-Williams, Rachelle Nuss, Tuan Le, Laura Cole, Kathy Hassell, James R. Murphy, and Daniel R. Ambruso

99 patients
Phenotyped and receiving serological matched for: ABO; Rh (C, c, D, E, e); Kell (K, k); Duffy (Fya, Fyb); Kidd (Jka, Jkb); Lewis (Lea, Leb); and MNS (M, N, S, s)

<table>
<thead>
<tr>
<th>Period, reference</th>
<th>Patient group</th>
<th>Matching</th>
<th>Percentage of patients immunized</th>
<th>Rate (antibodies/100 units transfused)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1978 (control), Ambruso et al.⁴</td>
<td>Chronic transfusions n = 85</td>
<td>ABO, D</td>
<td>34%</td>
<td>3.4</td>
</tr>
<tr>
<td>1979-1983, Ambruso et al.⁴</td>
<td>Chronic transfusions n = 12</td>
<td>Extended matching</td>
<td>25%</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All had previously received</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABO, D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983-1990, Ambruso et al.²²</td>
<td>Chronic transfusions n = 13</td>
<td>Extended matching only</td>
<td>8%</td>
<td>0.08</td>
</tr>
<tr>
<td>1993-2006, Present report</td>
<td>Chronic and intermittent n = 99</td>
<td>Extended matching</td>
<td>All—7%†</td>
<td>0.10†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eliminate D mosaic—4%†</td>
<td>0.06†</td>
</tr>
</tbody>
</table>

* Patients described in each period group were analyzed separately and not included in the summary for any other group.
† Different from historical control, p < 0.00005.
Massive Transfusion Protocols
Trauma

- Injury is the leading cause of death worldwide in those age 5-44 years
- 5 million people die from trauma worldwide each year
- 4th leading cause of death; 120,000 deaths in the US/year

Fig. 1. Timing and mechanism of traumatic death.
Massive Blood Loss and Coagulopathy

Multiple Definitions

• Replacement of patient’s blood volume within 24 hours
• Replacement of more than 50% of the patient’s blood volume in 3 hours
• Transfusion of more than 10 RBC units in 24 hours
• Transfusion of more than 4 RBC units in 1 hour
Predicting Massive Transfusion

- Penetrating mechanism (0 no, 1 yes)
- ED SBP of 90 mm Hg or less (0 no, 1 yes)
- ED HR of 120 bpm or greater (0 no, 1 yes)
- Positive FAST (0 no, 1 yes)

![Graph showing rate of massive transfusion by ABC score with AUROC values for TASH, ABC, and McLaughlin scores.](image)
Massive Transfusion requires MTP

• Why

  – Prevent the lethal triad of acidosis, hypothermia, and dilutional coagulopathy

  – Optimize logistics of blood product delivery to the patient and communication between transfusion service and trauma team

  – Mitigate errors which occur in critical and fast-moving environments

  – Create standardization to patient care
### MTP Examples

<table>
<thead>
<tr>
<th>Study</th>
<th>Package 1</th>
<th>Package 2</th>
<th>Package 3</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dente et al.</td>
<td>6 RBC units 6 AB plasma units</td>
<td>6 RBC units 6 plasma units 1 SDP unit</td>
<td>6 RBC units 6 plasma units 10 cryo units</td>
<td>rFVIIa upon request</td>
</tr>
<tr>
<td>Cotton et al.</td>
<td>10 RBC units 4 AB plasma units 2 SDP units</td>
<td>6 RBC units 4 plasma units 2 SDP units</td>
<td>Repeat package 2</td>
<td>Cryo upon request</td>
</tr>
<tr>
<td>O’Keeffe et al.</td>
<td>5 RBC units 2 AB plasma units</td>
<td>5 RBC units 2 plasma units 1 SDP unit</td>
<td>5 RBC units 2 plasma units 10 cryo units rFVIIa</td>
<td></td>
</tr>
<tr>
<td>Nunez et al.</td>
<td>10 RBC units 6 AB plasma units 2 SDP units</td>
<td>Repeat package 1</td>
<td>Repeat package 1</td>
<td></td>
</tr>
<tr>
<td>Riskin et al.</td>
<td>6 RBC units 4 plasma units 1 SDP unit</td>
<td>Repeat package 1</td>
<td>Repeat package 1</td>
<td>rFVIIa considered</td>
</tr>
</tbody>
</table>
MTP Blood Products

• **Type**
  – Blood types to be used
  – Type of product to be used

• **Amount**
  – Decide on ahead of time
  – Each round the same
  – First round with increased products
MTP Blood Product choices

- Whole blood (military)
- RBC
  - Group O
    - Rh pos
    - Rh neg
- Plasma
  - Group AB
  - Group A
    - ? Low titer
- Platelets
  - Platelet additive solution
- Cryoprecipitate
- Coagulation factors
• Prospective RTC
• 1:1:1 (Plasma:Plts:RBCs) vs 1:1:2
• 680 trauma patients in 12 level 1 trauma centers
• Initial product delivery within 10 min of arrival

• Primary outcome – 24 hour and 30 day mortality
• Secondary outcomes
  – Hemostasis achieved
  – Blood products transfused
  – Complications

Holcomb, et al, JAMA 2015
PROPPR results

• NO significant difference in primary outcomes
  – 24 hour mortality
    • 12.7% vs 17%, diff -4.7% (-6.9% to 1.1%)
  – 30 day mortality
    • 22.4% vs 26.1%, diff -3.7% (-10.2% to 2.7%)
• Improved hemostasis
  – 86% vs 78% (p=.006)
• Decreased death due to exsanguination, 24 hours
  – 9.2% vs 14.6%, diff -5.4% (-10.4 to -.5%)
• Complications not different between groups

Holcomb, et al, JAMA 2015
Apheresis

• Collection-allogeneic (Donor)

• Therapeutic
  – TPE
  – RBCex
  – WBC reduction
  – Plt reduction

• Donor Patients
  – PBMCs for transplant
  – Cellular Therapy

• Interaction with patients and donors!
Evidence Based Guidelines for TA

- American Society for Apheresis
- Evidence based treatment guidelines
- 78 Fact Sheets
- ASFA Categories
- GRADE
- Published every 3 years
Cellular Therapies

• The ultimate personalized (precision) medicine
• Use cells from a patient (or specially selected donor) to cure disease
• Often use BM derived cells
  – PBMCs
• Other sources possible
  – Cord Blood
  – Embryonic Stem Cells
Personalized Vaccines-Education of Cells

• Collect MNCs (T-cells, DCs)
• Co-culture with patient’s tumor cells or tumor antigens, activator molecules…
• Re-infuse “educated” immune cells
• Examples
  – Breast Cancer (Trials, tumor used)
  – Ovarian Cancer (Trials, tumor used)
  – Prostate Cancer (Dendreon, recombinant antigen used)
CAR T Cells

- CAR – Chimeric Antigen Receptor
- Genetically engineered T-Cells
- Fusion of TCR signaling domains with antibody toward target of interest
- Turning a patients T-cells against their cancer

Figure from June et al, Cancer Immunol Immunother (2014)
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.
CART 19

- 30 patients (children and adults)
  - 15 had failed PBSCT
- Refractory or relapsed ALL
- 90% achieved complete remission
- 67% 6-month event free survival
- 78% overall survival
- All had cytokine-release syndrome
  - Tocilizumab (anti-IL-6) was effective treatment
- CART 19 cells detectible in blood up to 11 months

Maude et al., NEJM, 2014, 371:16 p1507
Why did I choose TM?

• Interesting laboratory issues
• Direct patient care
• Wide variety of disease states
• Amenable to basic, clinical and translational research
Why do I stay in TM?

• I oversee interesting issues in the clinical lab
• I care for patients and donors
• I see a wide variety of disease states
• I get to do basic, clinical and translational research
• I am NEVER bored!