REASONS FOR MOVING TOWARD A PATIENT-CENTRIC PARADIGM OF CLINICAL TRANSFUSION MEDICINE PRACTICE

Eleftherios C. Vamvakas
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KUNH’S CONCEPTS OF “PARADIGM” AND “PARADIGM SHIFT”

- At any point in time, scientific thinking is reflected in a set of accepted and shared beliefs which is called a “paradigm”
- Scientific thinking goes through long periods of stable, unquestioned status quo punctuated by “paradigm shifts”:
  - During such paradigm shifts, the existing, dominant paradigm is brought under increasing pressure until it is replaced by another paradigm
- A change in paradigm amounts to no less than a scientific revolution
- Once adopted as a paradigm, no theory is regarded as being testable by any quantitative tests that it has not already passed
COMPONENT-CENTRIC TRANSFUSION MEDICINE PARADIGM

• **Blood component therapy:**
  – Each whole-blood donation is *split* into red blood cells (RBCs), platelets, and plasma to meet the transfusion needs of 3 different patients with, respectively, anemia, thrombocytopenia, and coagulopathy

• **Focus on the blood component:**
  – Each blood component meets or exceeds specified **standards** for that **component** (i.e., respectively, minimum hemoglobin content and proportion of RBCs surviving at 24 hours, minimum platelet content, or minimum content of coagulation factors)

• **Primacy of inventory:**
  – The **longest-stored** compatible blood component in inventory is routinely issued for transfusion to **avoid outdates** of units and **any shortages** of blood components that could result from such outdates
“ESTABLISHED COMMON SENSE” OF TRANSFUSION: “UNTESTABLE” TENETS OF THE COMPONENT-CENTRIC PARADIGM

• Blood component therapy:
  – Each blood component is a drug that, until its expiration date, will equally benefit every recipient

• Focus on the blood component:
  – Centralized blood systems excel at a manufacturing culture adhering to current good manufacturing practice regulations and aiming at the production of blood components that meet uniform standards

• Primacy of inventory:
  – The objective of a country’s centralized blood supply system is to avoid blood shortages and to always meet all transfusion needs of all patients
“ORDINARY” COMMON SENSE WOULD DICTATE EXPOSURE TO AS FEW ALLOGENEIC DONORS AS POSSIBLE IF:

- The transfusion needs of patients having acute blood loss could be met by transfusing actual fresh whole blood rather than whole blood “reconstituted” from the RBCs and plasma of different donors.
- The transfusion needs of patients requiring multiple and various blood components could be met by transfusing RBCs, platelets, and/or plasma collected from the same donor during the same multicomponent apheresis donation.

BECAUSE: As currently manufactured, each blood component is one allogeneic donor exposure potentially associated with:

- Infectious (i.e., transfusion-transmitted infection [TTI]), and/or
- Immunologic (e.g., transfusion-related acute lung injury [TRALI]) complications.
“ORDINARY” COMMON SENSE WOULD DICTATE AVOIDANCE OF COMPONENTS ASSOCIATED WITH INCREASED RISKS, I.E.:

- **Old RBCs**: Compared with fresh RBCs, old RBCs are:
  - Associated with *known* or *purported*, but *rare*, fatal complications of transfusion, that is, respectively, transfusion-associated sepsis (TAS) and TRALI, owing (respectively) to proliferation of psychrophilic bacteria or accumulation of bioactive lipids over time
  - An inferior-quality product concerning their ability to deliver oxygen to tissues, *regardless of whether old RBCs are associated (or not) with the disputed “common” adverse effects of old blood (i.e., increased mortality, infection, and/or multiple-organ failure)*

- **Old platelets**: Compared with fresh platelets, old platelets are associated with:
  - a *higher* risk of TAS owing to proliferation of bacteria over time
  - a *lower* post-transfusion corrected count increment (CCI)
• Dividing each whole-blood unit into 3 components and using the two “by-products” of RBC collection (i.e., whole-blood-derived [WBD] platelets and recovered plasma) was necessary to:
  – avoid blood shortages;
  – subsidize the cost of manufacturing all the various blood components needed by the entire population of a country
  – supplement source plasma as a source of Factor VIII, to ensure that all needs of patients with hemophilia were met

• The risk from the non-availability of blood components needed by a bleeding patient FAR exceeded (and exceeds):
  – The infectious and/or immunologic risks of unnecessarily exposing a bleeding patient to multiple allogeneic donors
Percent of all deaths reported to the FDA, 2005-2010

- TRALI: 145%
- HTR: 75%
- TACO: 37%
- TAS: 24%
- Babesiosis: 11%
- Anaphylaxis: 11%
- GVHD: 4%
THE IMPACT OF THE NEXT FATAL TTI

• Although mortality from established complications of transfusion is currently very low, a novel and fatal TTI could emerge in the future and reproduce the HIV catastrophe that caused some 1,000 deaths in the 1980s
• 3 fatal TTIs have emerged in the last 30 years secondary to:
  – HIV
  – vCJD (variant Creutzfeldt-Jakob disease) prions
  – West Nile Virus (WNV)
• It is not prudence but common sense to assume that what happened in the past can happen again in the future
• The next major TTI to emerge represents the cardinal threat to transfusion safety today:
  – If a new “HIV-like” pathogen were to emerge, it could cause more deaths than TRALI, TAS, and HTRs combined
DO THE CONSTRAINTS THAT IMPOSED THE 20TH-CENTURY “COMMON SENSE OF TRANSFUSION” STILL APPLY IN THE 21ST CENTURY?

- Technology for Patient Blood Management (PBM) and multicomponent apheresis is now available that permits us to follow our “ordinary” common sense rather than the previously-established “common sense of transfusion” which had been imposed on us by considerations of supply and cost.

- **PRESENTATION OBJECTIVE:** To show that PBM and multicomponent apheresis can reduce both the infectious and immunologic risks of transfusion by at least two-fold, because (compared with the component-centric transfusion-medicine paradigm) they can reduce exposure of transfusion recipients to allogeneic donors by at least two-fold.
“ORDINARY” COMMON SENSE DICTATES THAT WE STRIVE TO REDUCE THE RISK OF TRANSFUSION TO AN AS LOW AS REASONABLY ACHIEVABLE (ALARA) LEVEL

• Interventions that jeopardize the supply of needed blood components in order to reduce risk are not reasonable
• Interventions that exceed the cost per quality-adjusted life year (QALY) saved that society is willing to pay for blood safety are also not reasonable

If adopted, Patient Blood Management (PBM) and multicomponent apheresis could either decrease or increase the total cost of transfusion; similarly, they could either decrease or increase the total supply of blood components:

• Both predictions are plausible and both predictions have been made in the literature
• The impact of PBM and multicomponent apheresis on total supply and cost remains to be quantified by future research
PATIENT BLOOD MANAGEMENT

PBM identifies a patient at risk of transfusion and formulates a multidisciplinary and multimodal, yet individualized, plan for reducing the need for allogeneic transfusion:

– anemia and coagulopathy are treated before admission by pharmacologic alternatives to transfusion
– iatrogenic blood losses are minimized
– intraoperative cardiac output, ventilation, and oxygenation, and perioperative bleeding, are optimized
– blood-sparing surgical and anesthetic blood-conservation techniques, blood recovery, and acute normovolemic hemodilution (ANH) are used where indicated
– transfusion is given only if proven (based on RCTs using clinical endpoints) rather than postulated (based on pathophysiology) benefit can be expected
**“BLOODLESS SURGERY” IN JEHOVAH’S WITNESSES: ANH FOR LIVER RESECTION**

<table>
<thead>
<tr>
<th></th>
<th>No allogeneic transfusion group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>65</td>
<td>179</td>
</tr>
<tr>
<td>Proportion receiving allogeneic transfusion</td>
<td>0%</td>
<td>44%</td>
</tr>
<tr>
<td>Mean (range) number of RBCs transfused</td>
<td>0</td>
<td>3.3 (1 - 15)</td>
</tr>
<tr>
<td>Mean (range) age</td>
<td>47 (18 - 75)</td>
<td>55 (16 - 82)</td>
</tr>
<tr>
<td>Mean (range) preoperative hct</td>
<td>37.5 (28.6 - 50)</td>
<td>39 (22 - 48.4)</td>
</tr>
<tr>
<td>Mean (range) postoperative hct</td>
<td>31 (22.6 - 40.2)</td>
<td>31.3 (27.9 - 41.2)</td>
</tr>
</tbody>
</table>

MULTICOMPONENT APHERESIS

• Multicomponent apheresis can collect any combination of RBCs, platelets, and/or plasma from a single donor during the same donation, and reserve all components collected during the same donation for transfusion to the same recipient
• Common protocols used in multicomponent apheresis collect:
  – 2 (or 3) units of single-donor platelets
  – 3 units of fresh frozen plasma (FFP)
  – 2 RBC units
  – 1 RBC unit and 2 FFP units
  – 1 unit of single-donor platelets and 2 FFP units
• When multitransfused patients (e.g., patients with acute blood loss) need transfusion of both RBCs and FFP (and perhaps platelets as well), multicomponent apheresis can reduce their number of donor exposures by >2-fold
Rate of moderate or severe reactions per 10,000 donations made to Blood Systems in 2007

Based on data reported by Kamel et al. Transfusion 50:556, 2010
Prevalence of known TTIs per 100,000 ARC collections, 2004-2008
Based on data reported by Zou et al. *Transfusion* 50:1487, 2010
PATIENT-CENTRIC TRANSFUSION MEDICINE PARADIGM

• **Patient blood management** (vs. blood component therapy):
  – Each patient’s transfusion needs are met through an **individualized** combination of approaches aimed at avoiding as many allogeneic donor exposures as possible

• **Focus on the individual patient** (vs. on the component):
  – Our focus is **not** on the quality of the component but on the quality of the **medical** service that we provide **each** patient through **optimally** combining PBM modalities

• **Primacy of individual needs** (vs. primacy of inventory):
  – The overriding concern is **not** to avoid blood shortages **but** to **reduce** the transfusion risk for each patient to a level **as low as the ALARA risk**
THE CHANGE TO THE INFRASTRUCTURE OF THE CURRENT BLOOD PROCUREMENT SYSTEM WILL BE SO PROFOUND AS TO AMOUNT TO A REVOLUTION

• Activity (and reimbursement) move from blood centers to hospital blood banks and other departments involved in PBM:
  – multidisciplinary, multimodal **approaches** replace the **dispensing** of blood components
  – multicomponent apheresis collections are planned and performed **locally** around the needs of **specific** patients

• A **medical** culture succeeds a **manufacturing** culture:
  – decentralized decision-making, by clinicians close to patients and by the **patients themselves**, supplants centralized decision-making by blood systems
  – a patient who has already been exposed to a particular **allogeneic donor** is entitled to **all** the components harvested from that donation if s/he needs them
PATIENT-CENTRIC PLATELET TRANSFUSION PARADIGM

- Only **single-donor (apheresis)** platelets collected from **male** donors or **screened** female donors (without a history of pregnancy or shown not to have white-blood-cell [**WBC**] antibodies) are used for transfusion.
- Platelets **and** plasma (**and/or** RBCs) collected from the **same** donor during the **same** multicomponent apheresis collection are reserved for transfusion to the **same** recipient.
- Only **single-donor (apheresis)** platelets collected from **male** donors or **screened** female donors are subjected to **pathogen reduction (PR)** if PR systems become licensed by the US Food and Drug Administration (FDA).
PROVIDED THAT RESEARCH INTO THE LOGISTICS SHOWS THAT THE PARADIGM CHANGE DOES NOT:
1) JEOPARDIZE THE SUPPLY OF NEEDED COMPONENTS; OR
2) EXCEED THE COST/QALY SAVED THAT SOCIETY IS WILLING TO PAY FOR BLOOD SAFETY,

IS SUCH A RADICAL CHANGE IN PLATELET TRANSFUSION NECESSARY TO ACHIEVE A TRANSFUSION RISK AS LOW AS THE ALARA RISK?
I.

AS-LOW-AS-REASONABLY-ACHIEVABLE (ALARA)

RISK OF TRALI
THEORIES OF TRALI PATHOGENESIS

ANTIBODY HYPOTHESIS
Preformed anti-WBC antibodies
• anti-HLA class I and/or II, and/or
• anti-neutrophil antibodies circulating in the donor’s plasma owing to alloimmunization by previous transfusion/pregnancy

Directed against a WBC antigen(s) on the transfusion recipient’s WBCs

Attack the recipient’s WBCs in the microcirculation of the lungs

PREVENTION BY EXCLUDING ALLOIMMUNIZED DONORS

LIPID HYPOTHESIS
PATIENT’S CLINICAL CONDITION:
First hit: initial insult to pulmonary vascular endothelium attracts/primed neutrophils adhering to endothelium

PLUS

Second hit: lipids accumulating progressively during storage in the supernatant of RBCs and platelets

Activation of sequestered neutrophils → Endothelial damage

PREVENTION BY LIMITING STORAGE TIME OR WASHING RBCs & PLATELETS
Percent of transfusion recipients developing TRALI/possible TRALI in the Leucocyte Antibody Prevalence Study II

Based on data reported by Kleinman et al. 
*Transfusion* 51:2078, 2011

\[ p > 0.05 \text{ in both cases} \]
IF DONOR WBC ANTIBODIES CAUSE TRALI,

**future** SINGLE-DONOR PLATELETS collected *solely* from:

– male donors, or
– female donors without a history of pregnancy or shown **not** to have white-blood-cell (WBC) antibodies

should be associated with a **lower** risk of TRALI than our **current PWBD** platelets
Percent of donors and components implicated in ALL TRALI cases in the Netherlands, 2005-2007

Based on data reported by van Stein et al. *Transfusion* 50:213, 2010
"Male-only": male donors with or without screened female donors

Based on data reported by van Stein et al. *Transfusion* 50:213, 2010
II. 
AS-LOW-AS-REASONABLY-ACHIEVABLE (ALARA) 
RISK OF TTIs
MODELING THE IMPACT OF THE NEXT FATAL TTI

• In 1984 (the year before blood-donor testing was introduced), the prevalence of HIV infection in US blood donors exceeded 1 per 1,000

• Because of current surveillance systems, it is unlikely that a new pathogen causing chronic infection could go undetected for as long as HIV went undetected

• Therefore, infection with the new pathogen would be unlikely to reach a prevalence of 1 per 1,000 US blood donors before measures were introduced to interrupt its transmission through transfusion

• Nonetheless, the next “HIV-like” pathogen could reach a prevalence one order of magnitude less than HIV (i.e., a prevalence of 1 per 10,000 US blood donors)
PREVALENCE OF **SUBCLINICAL VARIANT CREUTZFELDT-JAKOB DISEASE (vCJD)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases of clinical vCJD</th>
<th>Presumed prevalence*</th>
<th>Estimate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>170</td>
<td>100</td>
<td>1 per 10,000</td>
</tr>
<tr>
<td>Ireland</td>
<td>2(4)</td>
<td>17</td>
<td>1 per 60,000</td>
</tr>
<tr>
<td>France</td>
<td>25</td>
<td>14</td>
<td>1 per 70,000</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>3</td>
<td>6.5</td>
<td>1 per 150,000</td>
</tr>
<tr>
<td>Portugal</td>
<td>2</td>
<td>6.5</td>
<td>1 per 150,000</td>
</tr>
<tr>
<td>Spain</td>
<td>5</td>
<td>4</td>
<td>1 per 250,000</td>
</tr>
<tr>
<td>Italy</td>
<td>2</td>
<td>1</td>
<td>1 per 1,000,000</td>
</tr>
</tbody>
</table>

* Based on the **relative incidence** of clinical disease by the end of **2009** between each country and the UK

† **Approximation.** Based on a combination of the published appendix/tonsil surveys: 4/43,907
RISK OF ACQUIRING CLINICAL vCJD FROM A TRANSFUSION IN THE UK

For codon-129 prion-protein-gene methionine homozygotes (13) who survive for ≥5 years after a transfusion (32):

1 per 100,000

IF:

• the probability of developing transfusion-acquired disease is 23% (3/13); and

Based on data reported by Houston et al.  
*Blood* 112:4739, 2008
PREVENTING DEATHS FROM THE NEXT FATAL TTI

• An epidemic of transfusion-acquired disease could be prevented only if an effective and safe PR system(s) suitable for all blood components (RBCs, plasma, and platelets) were introduced before the next major transfusion-transmitted pathogen accumulated in blood donors.

• Absent such an all-encompassing (as well as effective and safe) PR system, an epidemic can be only contained by minimizing allogeneic donor exposures through:
  – cessation of production of all pooled blood components
  – substitution of PBM and multicomponent apheresis for the component-centric transfusion-medicine paradigm
PREVENTABLE ALLOGENEIC-DONOR EXPOSURES IN THE US OWING TO THE CONTINUED USE OF PWBD PLATELETS

2.021 million apheresis-equivalent units transfused in 2008:
— 1.761 million (87.1%) as single-donor platelets
— 0.260 million (12.9%) as PWBD platelets

For platelet doses transfused as PWBD platelets:
— 1.3 million donors were used, with platelets and RBCs/FFP from each “window-period” donation infecting different transfusion recipients
— these patient needs could have been met instead by 260,000 donors of single-donor platelets,

thereby avoiding 1.04 million allogeneic donor exposures
Annual increase in the number of TTIs in the US because of 1.04 million preventable allogeneic-donor exposures.
IF THE NEXT “HIV-LIKE” PATHOGEN TO EMERGE ATTAINED A PREVALENCE OF 1 PER 10,000 DONORS, THERE COULD BE FROM 26 TO 130 TRANSFUSION TRANSMISSIONS IN THE YEAR PRECEDING THE INTRODUCTION OF TESTING, DEPENDING ON HOW THE 260,000 PLATELET DOSES (NOW PROVIDED AS POOLS) WERE OBTAINED:

- **13,000** apheresis donors donating **10** times a year and whose **every** donation is split generate (13,000 times 10 times 2 divided by 10,000) **26** recipient infections
- **34,667** apheresis donors donating **5** times a year and whose **half** the donations are split **also** generate **26** recipient infections
- **650,000** whole-blood donors donating **2** times a year (and whose **1.3 million** donations produce **260,000** platelet pools) generate **130** recipient infections
AN ALL-APHERESIS PLATELET SUPPLY IS AN “ALARA” RATHER THAN “ZERO-RISK” INTERVENTION

• Although the risk confronted is “theoretical”, a 5-fold reduction in the risk from pools can be reasonably achieved:
  – moving from 87.1% to 100% of platelet doses transfused as apheresis is logistically and economically feasible and should pose no risk to either patient or donor
• The only question open to debate is whether it is reasonable to anticipate that a novel “HIV-like” pathogen could emerge
• If this is a reasonable possibility, the precautionary principle (enshrined in European Union law) states that:
  – when a purported risk represents a threat of “serious or irreversible damage”, complete evidence of risk does not have to exist to justify the institution of measures to protect individuals and society from that risk
PATHOGEN REDUCTION (PR) SYSTEMS FOR PLATELETS BASED ON CHEMICALLY-INDUCED CROSSLINKING/PHOTOINACTIVATION OF NUCLEIC ACIDS

• Have been licensed in Europe to prevent:
  – >90% of cases of TAS (except for TAS due to some rare spore-forming bacteria): UK 2010 risk-reduction estimate
  – TTIs due to pathogens containing nucleic acids
• Concerning TAS, there is now an alternative solution:
  – a second bacteria detection test performed at the time of issue of the component to prevent 70-90% of cases of TAS
• Concerning both TAS and TTIs, IF SHOWN TO BE SAFE, PR should replace the bacteria detection tests and become part of the patient-centric paradigm
• The time to implement PR has not yet come, which gives further immediacy to the need for reducing donor exposures by moving toward PBM and multicomponent apheresis
Vamvakas E. *Vox Sang* 104:302, 2012
PR SYSTEMS WERE DEVELOPED BEFORE PLATELETS WERE KNOWN TO CONTAIN SIGNIFICANT AMOUNTS OF FUNCTIONALLY IMPORTANT NUCLEIC ACIDS

- Platelets retain a diverse mRNA transcriptome from their megakaryocytic precursors, so that up to a third of all human genes are present in platelets at the mRNA level.
- Platelets make use of their mRNAs to template de novo protein synthesis both in the circulation and during platelet storage in the blood bank: e.g., integrin β3
- Platelets also contain a particularly abundant and diverse array of microRNAs (small, 19- to 24-nucleotide-long, non-coding RNAs) and a functioning microRNA pathway that regulates mRNAs and platelet protein gene transcription, and may thus also regulate platelet protein translation and platelet function

HYPOTHESIS

Crosslinking by PR of the double-stranded precursors of platelet microRNAs

“Perturbation” caused by PR

Release of microRNAs from platelets:
- directly into the supernatant
- inside microvesicles

Reduced synthesis of microRNAs by platelets following PR

Reduced microRNA content

Impaired protein synthesis during storage in the blood bank after PR

Impaired function of PR-treated platelets

Increased bleeding despite the compensatory platelet transfusions given to make for the known platelet losses caused by PR

Osman A, Hitzler W, Hellstern P, Vamvakas E & Provost P. 4th StKB Future Workshop, Mainz, Germany, April 20, 2012
CONCLUSIONS

• PBM and multicomponent apheresis:
  – can meet a patient’s transfusion needs with at least 2-fold fewer donor exposures,
  – thereby reducing the risk of infectious and immunologic transfusion complications by at least 2-fold

• The reduction in risk includes:
  – the leading cause of transfusion-related mortality (TRALI) and
  – the cardinal threat to transfusion safety (the next “HIV-like” pathogen to emerge in the future)
POLICY RECOMMENDATION

Once it is determined that PBM and multicomponent apheresis can replace the current blood-procurement system at a “reasonable” cost and without jeopardizing the supply of needed components, the patient-centric paradigm should replace the current component-centric paradigm to fulfill the purpose of PBM and multicomponent apheresis, i.e.,

TO REDUCE THE TRANSFUSION RISK FOR ALL PATIENTS TO THE LEVEL OF THE “ALARA” RISK
FURTHER POSSIBLE REASONS FOR MOVING TOWARD A PATIENT-CENTRIC PARADIGM:

• To prevent transfusion of “old” RBCs:
  – if old RBCs are found to be associated with “common” adverse patient outcomes (i.e., increased mortality, infection, and/or multiple-organ failure)

• To expose trauma victims to 1 (rather than 2) allogeneic donors for each dose of both plasma and RBCs:
  – if a 1:1 plasma-to-RBCs ratio for resuscitation is found to improve survival

REGARDLESS OF WHETHER THESE PURPORTED BENEFITS (OF FRESH RBCs OR A 1:1 RATIO) MATERIALIZE:

– the decrease in established complications thanks to the reduction in donor exposures is a sufficient reduction in risk for changing the transfusion-medicine paradigm