Evidence Based Transfusion Medicine

Dr Rajesh B Sawant MD
Outline

• EBM definition and concept
• Evidence based aspects in:
  - Donor Selection
  - Quality of blood components
  - Transfusion triggers for RBC & Platelet components
  - Improving platelet transfusion therapy
  - PBSC and Granulocyte harvests
  - Patients safety
## The Six Essential Elements

1. Blood and blood products are used and managed in accordance with national evidence based guidelines
2. A program is in place to reduce the risks associated with blood and blood products and to improve safety and quality
3. Adverse events, incidents and near misses relating to transfusion practice are reported and feed into risk management processes
4. Transfusion details are documented in the patient clinical record
5. Blood and blood products are managed appropriately
6. Informed consent is documented for transfusions
Why do we need evidence?

To encourage practitioners and patients to pay due respect to current best evidence in making decisions.
History of EBM:

• Dr James Lind - first recorded randomized controlled trial to evaluate the efficacious treatment of scurvy.
• Dr Archibald Cochrane’s book entitled *Effectiveness and Efficiency: Random Reflections on Health Services*
• Establishment of the Cochrane Collaborative
• Development of new methodological techniques such as meta-analysis.
• Dr David Sackett (1981) from McMaster University in Hamilton, Canada coined the phrase ‘critical appraisal’
• Dr Gordon Guyatt suggested the term ‘evidence-based medicine’.
Definition:

• Evidence-based medicine is defined as the “integration of best research evidence with clinical expertise and patient values.”

• The practice of evidence-based medicine means integrating individual expertise with the best available external evidence from systematic research.
• The highest level of support for evidence based decisions is the randomized controlled trial (RCT)

• Decision making in transfusion medicine occurs in many different settings, under a variety of circumstances, and involves a variety of issues related to blood donors, blood recipient diagnosis and management, laboratory interpretations, and policy issues.
Essential components of evidence based decision making
CAN POLICY DECISIONS IN TM BE EVIDENCE-BASED?
• Evidence for quality of blood components
DTM-Environmental Surveillance
CONFIRMING THAT IRRADIATION OCCURRED

- Radiation-sensitive indicator labels
- Range: 15Gy to 50Gy and
RED CELL HEMOLYSIS DURING PROCESSING AND STORAGE
Levels of free Hb in Red cell concentrates at different storage durations
CONCLUSION

• Haemolysis of red cells increases due to processing for component preparation and during storage

• It is maximum during the first week

• Visual inspection may lead to unnecessary discard of Red cell units

• Evaluation of haemolysis is relevant for
  • Transfusion recipients safety
  • Adherence to GMP
Bacterial Contamination of Platelets – A neglected hazard of Transfusion
The Impact

• **Change in Policy**
  • A policy to use SDP units collected after repeat venepuncture within 24 hours of collection or after bacteriological clearance was subsequently implemented.

• **Bacterial Detection Study with the Pall e BDS system**: Purpose
  • Determine bacterial contamination rates of blood components associated with recipient transfusion reaction
  • Identify pathogens associated with contamination
  • Identify risk factors for bacterial contamination
Conclusion

• Simple measures like a **vigilant visual examination** of platelet units and **pH** measurement in suspicious cases can facilitate the detection of bacterial contamination.

• Better surveillance and reporting are needed in the efforts to improve blood product safety.
What quality of red blood cells shall we offer the transfused patient?

- RBCs can vary widely in their benefit to recipients depending on:
  - how the unit is prepared and the duration
  - quality of pretransfusion storage
  - haemoglobin (Hb) concentration of the donor blood
  - volume of the collection
  - leucocyte depletion procedures
  - composition of the additive

- Haemoglobin content of viable RBCs in an individual blood unit collected within current standards may range from as little as 30 g to as much as 90 g

- Transfusing physician is generally unaware of this fact
Standardization of the red cell product

Joseph D. Sweeney *

Brown University, Transfusion Services and Coagulation, Lifespan Academic Medical Center, Providence, RI 02904, United States

Received 28 November 2005; accepted 29 November 2005
• Measure and label the potency of each red cell product, allowing some degree of recipient defined product choice by the transfusion service.

• The current situation where red cell products are prescribed in non-standard ‘units’ is outdated and unscientific.
• Most adult clinicians assume that a ‘unit’ of red cells will increase the hemoglobin by 1 g/dL or the hematocrit by 3%

• The amount of hemoglobin necessary to achieve this increment in an adult with stable normovolemic anemic and an intravascular volume of 5 L (50 dL) would be 50 g

• Prescribing physicians could be taught to grasp the concept of a fixed amount of hemoglobin per unit and encouraged to prescribe in relation to the blood volume of the recipient
Evidence base for Donor selection criteria.
The threshold Hb: Problems

1 Sample site – earlobe-stick blood has higher Hb values than finger-stick blood, which are generally closer to venous blood Hb (Chambers & McGuff, 1989)

2 Variations between Hb from different fingers (often over 10% – Boulton, Nightingale & Reynolds, 1994)

3 Limitations because of methodology and performance variables (Walters & Garrity, 2000). Reported differences between capillary (finger-stick) and venous blood Hb (Vuk et al., 1998; Neufeld et al., 2002; Darragh et al., 2006) may be unreliable because each sample-type was analysed on different apparatus calibrated separately

4 Environmental conditions at blood donation sessions may be associated with less reliable staff performance (Boulton et al., 2001);
EVALUATION OF HEMOGLOBIN
OF BLOOD DONORS DEFERRED
BY THE COPPER SULPHATE METHOD
FOR HEMOGLOBIN
OBSERVATIONS

• **16.2%** of the donors who failed the copper sulphate test had Hb level $\geq 12.5$ g/dL

• **9.2%** of the donors who passed the copper sulphate test had true Hb level $< 12.5$ g/dL

• **32.8%** of the deferred donors had their Hb level between 12 and 12.5 g/dL
CONCLUSION

- The finger-prick copper sulphate specific gravity method gives a high incidence of false negative results leading to unnecessary deferrals

- This method can be used as an initial screening method for selecting suitable donors

- All the donors deferred with this method should be further evaluated by alternate screening methods using venous blood samples to recruit more healthy donors for donation

- Lowering of the Hb threshold for blood donation to 12 g/dL should be considered
Retesting the deferred donor’s Hemoglobin: does it help?
OBJECTIVE

- Compare CuSO₄ method with the Hemocue (Hb 201) photometer method

- Evaluate the impact of the new strategy of retesting deferred donor’s Hb.
Results

(With Hb values between 12-12.4 g/dl)

(accepted back for blood donation.)
CONCLUSION

• The Hemocue method can be used reliably with capillary samples for donor hemoglobin estimation.

• The Hb retesting strategy helps in recruiting additional eligible donors for blood donation.
THE CONFIDENTIAL UNIT EXCLUSION (CUE) -

DOES IT REALLY ENHANCE BLOOD SAFETY?
## RESULTS

<table>
<thead>
<tr>
<th>TTI</th>
<th>CUE</th>
<th>No. of Donors</th>
<th>No. of reactive</th>
<th>% reactive</th>
<th>Sensitivity</th>
<th>PPV</th>
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<td>922</td>
<td>1.08</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
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<td>286</td>
<td>04</td>
<td>1.3</td>
<td>0.00432</td>
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CONCLUSIONS

- **CUE procedure** - poor sensitivity and PPV and thus may prevent the transfusion of a very small number of units in the window period

- **CUE option** – loss of many safe blood units

- Newer and more effective donor history elicitation tools and meticulous counseling strategy is essential

- Approaches to validation of the donor questionnaire and quality assurance of donor screening procedures is warranted
TTI - Related counselling in a blood transfusion service

Training:
Staff, Volunteers
New recruits

Pre-donation education

Queries related to TTI’s

Pre-donation counselling

Consent

Risk not detected:
Consent
Medical exa.
Blood donation
Screening of blood units for TTI’s

Positive
Post-donation counselling
Referral to post-test
Counselling and testing

Negative
Blood unit accepted
For transfusion

Risk detected
Donor deferral
Status of EBM for transfusion practice

• Red blood cells

• The ‘transfusion trigger’ for perioperative RBC use has been recommended in the USA at 7 g/dl for patients with no history of cardiac or respiratory disease but that level remains controversial, for both surgical and medical, including cardiac patients

• The Canadian Transfusion Requirements in Critical Care (TRICC) trial fuelled this controversy by showing that a more restrictive transfusion trigger for patients in intensive care units (ICU) is actually more beneficial than a liberal trigger

• Meta-analysis concluded that patients in ICUs who receive transfusion have ‘significantly poorer outcomes than do patients not receiving such transfusions …’
Red blood cell transfusion:

**Transfusion Medicine Reviews**

Vol 16, No 3  July 2002

Transfusion Triggers: A Systematic Review of the Literature

Jeffrey L. Carson, Suzanne Hill, Paul Carless, Paul Hébert, and David Henry

Most clinical practice guidelines recommend restrictive red blood cell (RBC) transfusion practices with the goal of minimizing transmission of blood-borne pathogens. The purpose of this review is to compare clinical outcomes in patients randomized to restrictive versus liberal transfusion thresholds (triggers). We conducted a search of OVID Medline, Current Contents, the Cochrane Library, and bibliographies of published studies. Our search strategies used a combination of key-word terms as text and MeSH headings relating to transfusion triggers. We included trials if the comparison groups were assigned on the basis of a clear transfusion trigger or threshold, and the study was randomized with a concurrent control group. Eligibility of studies was assessed by 2 independent raters, with disagreements resolved by consensus. Disagreements not resolved by consensus were referred to a third party for review. Two raters assessed the methodologic quality of the trials modified from the methods of Schultz. The main study outcomes are probability of receiving an RBC transfusion, volume of RBCs transfused, hematocrit levels, mortality, and length of hospital stay. Ten trials, which reported outcomes for a total of 1,780 patients, were included. Five studies were in surgical patients, 3 were in the setting of acute blood loss and trauma, and 2 involved intensive care unit patients. Transfusion triggers varied between 7 and 10 g/dL (most often they were 8 or 9 g/dL). Being randomized to a restrictive transfusion trigger group had the following average effects: the probability of receiving an RBC transfusion was reduced by 42% (relative risk, 0.58; 95% confidence interval [CI] 0.47, 0.71), the volume of RBCs was reduced by 0.93 units (95% CI 0.36, 1.5 units), and hematocrit values were 5.6% lower (95% CI 3.5, 7.7%). Mortality, rates of cardiac events, morbidity, and length of hospital stay were unaffected. The limited published evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease. However, most of the data on clinical outcomes were generated by a single trial. The effects of conservative transfusion triggers on functional status, morbidity, and mortality, particularly in patients with cardiac disease, need to be tested in further large clinical trials. In countries with inadequate screening of donor blood, the data may constitute a stronger basis for avoiding transfusion with allogeneic RBCs.

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Retrospective audit of Transfusion practices:
Transfusion trigger: Red blood cells

Medical Speciality

Surgical Speciality
Transfusion trigger: Platelets

- Platelets < 10000: 36%
- 10000 < Platelets < 20000: 21.3%
- Platelets > 20000: 31%
• Therapeutic Apheresis Procedures:
Correlation of CD34$^+$ cell yield in PBPC product with the pre-harvest cell counts
Practical Challenges

1) To find if pre-harvest CD34\(^+\) cell concentration in PB correlates with CD34\(^+\) cells in leukapheresis product.

2) To find a threshold concentration of pre-leukapheresis PB- CD34\(^+\) cells necessary to obtain at least $2 \times 10^6$/Kg CD34\(^+\) cells in a single leukapheresis procedure.
Results

Correlation of pre-leukapheresis PB-CD34+ cell count with PBPC product CD34+ cell content

Allogeneic

Autologous
Results

Correlation coefficient between PB cell counts and PBPC CD34⁺ cell counts:

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<tr>
<td>MNC</td>
<td>0.340</td>
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<tr>
<td>CD34⁺ cells</td>
<td>0.656</td>
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* PB WBC and MNC = 0.373

Prediction of PBPC product yield based on pre-leukapheresis PBCD34⁺ cell counts:

<table>
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<tr>
<th>PBPC CD34⁺ cells</th>
<th>PB CD34⁺ ct</th>
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<tr>
<td>&lt; 1x10^6</td>
<td>5x10³</td>
</tr>
<tr>
<td>2x10^6</td>
<td>20x10³</td>
</tr>
<tr>
<td>&gt;2x10^6</td>
<td>50x10³</td>
</tr>
</tbody>
</table>
Conclusion

• The number of CD34\(^+\) cells in PB - useful as predictor for timing of apheresis and estimating PBPC yield

• When PB CD34\(^+\) cell counts are > 20x10\(^3\)/ul a PBPC yield of 2x10\(^6\) CD34\(^+\) cells/Kg can be obtained

• PB CD34\(^+\) cell counting pre- leukapheresis can facilitate efficient organization of leukapheresis procedures
Improving Platelet Therapy

Proposed research is focused on three major areas:

- To determine the appropriate dose of platelets to prevent bleeding.
- To assess whether the storage time of platelets can be extended.
- To develop techniques of preventing alloimmunization in multi-transfused patients.

Significance:
- Decrease platelet requirement
- Reduce cost &
- Ensure continual supply of platelets
Plasma – Depletion of Single Donor Platelet Concentrates : Is it essential ?
Results

- Volume of SDP was reduced to $25 \pm 5\% (60-80 \text{ ml})$ of original volume with PR procedure.

- Platelet loss upto $15+2\%$ occurred with PR.

- There was no significant alteration in the MPV, p H and swirling of platelets due to PR.

- $4\%$ of the plasma reduced SDPs showed presence of high titer of ABO antibodies.

- CCI at 1 hour was found to be equivalent in group specific and PR ‘O’ SDP transfusions in patients with matched clinical conditions.

- At 24 hrs the increment was better with ABO identical transfusions but was not statistically significant.
Conclusion

• Plasma reduction is associated with significant loss of platelets and is labor intensive, time consuming and reduces the available shelf life of platelets.

• Assessment of Ab titers in ‘O’ group SDPs should be considered prior to plasma reduction. This shall ensure the safety of ‘out-of-group’ platelet transfusions.
Transfusion of non group specific platelets: Does antibody titration help?

Policy regarding transfusion of ABO incompatible platelets is lacking currently in our country.

• Screening the samples from platelet donors for anti-A and/or anti-B titres & study the outcome of transfusion of incompatible platelets in patients.
• **Results:**
• 31% of group O donors had high titre of both IgG and IgM antibodies.
• The **CCI was equivalent** with transfusion of O group Plasma Reduced (PR) single donor platelets (SDP’s) & ABO incompatible SDP’s with low antibody titre transfusions in patients with matched clinical conditions.
• **No severe adverse events** were reported in both groups.
• **Conclusion:**
  
  • High titre ABO antibodies and hemolysins are present in a high proportion of donors (especially group O donors).
  
  • Antibody titration reduces the need of further interventions like PR prior transfusion of SDP’s across the ABO barrier.
Comparison of therapeutic efficacy of whole blood derived vs Apheresis platelet transfusion
**Corrected count increment 1 hour & 24 hour in RDP, SDP transfusion- Compatible vs Noncompatible**

<table>
<thead>
<tr>
<th></th>
<th>RDP 1hr CCI</th>
<th>SDP 1hr CCI</th>
<th>P value</th>
<th>RDP 24hr CCI</th>
<th>SDP 24hr CCI</th>
<th>P value</th>
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<td><strong>Compatible</strong></td>
<td>14331±5250</td>
<td>19452±2954</td>
<td>0.40</td>
<td>17998±2782</td>
<td>11790±876</td>
<td><strong>0.006</strong></td>
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<tr>
<td><strong>Non compatible</strong></td>
<td>28900±13680</td>
<td>12709±1354</td>
<td>0.272</td>
<td>12598±1332</td>
<td>11131±1038</td>
<td>0.38</td>
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</table>
CCI with shelf life of product

$p=0.575$, 1 hr CCI

$p=0.24$, 24 hr CCI
Conclusion:

• Calculating the CCI in multiply transfused patients helps one to understand the in vivo efficacy of platelet transfusions.

• A Significantly greater 24 hour CCI is the only clinically relevant advantage found to be associated with SDP transfusions.

• A final conclusion regarding the superiority of SDP preparations cannot be drawn based on the above findings.

• Further studies to evaluate the utility of pooled, leucodepleted RDP transfusion versus RDP & SDP transfusions are needed to derive conclusive evidence.
Special Components
What has universal leucodepletion given us: evidence from clinical trials?

- Non-hemolytic febrile transfusion reactions
- Leukocyte-transmitted infections
- Platelet-refractoriness
- Immunomodulation
EFFECTS OF GAMMA IRRADIATION ON PRODUCT QUALITY AND STABILITY.
POTASSIUM EFFLUX AND RED CELL HEMOLYSIS AFTER GAMMA IRRADIATION: CORRELATION WITH STORAGE AND TIMING OF GAMMA IRRADIATION
Results

• K+ efflux and hemolysis showed significant (p < 0.001) increase with the increase in storage period post - GI.

• K+ levels were significantly (p < 0.001) higher in RCC in Protocol I when compared with RCC of similar age in Protocol II.

• K+ levels and PFH increased significantly after 7 days of storage in GI RCC.
Conclusion

- Gamma irradiation of RBC units is associated with an increase in hemolysis and $K^+$.  
- The permissible storage period of 28 days post gamma irradiation needs to be re-looked at since the extent of hemolysis exceeds the 0.8% threshold.  
- RCC GI just prior to their issue have significantly lesser $K^+$ efflux and hemolysis compared to RCC stored after GI on day 1.  
- GI of RCC older than 14 days results in significantly higher $K^+$ efflux and hemolysis and should therefore be avoided.
Granulocyte Transfusion

• **Current Situation**
• Evidence of efficacy
• No clear answer from published uncontrolled experience
• Most trials show no efficacy for established mold infection
• Good argument for clinical equipoise

• **Practice**
• Anecdotes and unpublished series abound: many clinicians convinced that 1) they don’t work, or 2) they do work
• Has become standard practice in many centers
## Clinical Efficacy

- Assorted case reports of success
- Small uncontrolled series

<table>
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<tr>
<th>#Pts</th>
<th>Clinical Response</th>
<th># of Patients</th>
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<tr>
<td>Hester (95) 15</td>
<td>60%</td>
<td>11 M, 4 Y</td>
</tr>
<tr>
<td>Grigg (96) 11</td>
<td>100%</td>
<td>3 B</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>3 P</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>5 inv F</td>
</tr>
<tr>
<td>Peters (99) 30</td>
<td>82%</td>
<td>17 B</td>
</tr>
<tr>
<td></td>
<td>54%</td>
<td>13 F</td>
</tr>
<tr>
<td>Price (00) 19</td>
<td>100%</td>
<td>4 B</td>
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<tr>
<td></td>
<td>57%</td>
<td>7 Y</td>
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<tr>
<td></td>
<td>0%</td>
<td>8 inv M</td>
</tr>
<tr>
<td>Lee (01) 25</td>
<td>40%</td>
<td>21 local, 4 sepsis</td>
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<tr>
<td>Rutella (03) 20</td>
<td>50%</td>
<td>11 B, 7 F, 2U</td>
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### Effects on Recipient Hematologic Values

**Most reports**

- Post-transfusion PMN increments large
- Prolonged PMN survival

<table>
<thead>
<tr>
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<th>#Pts</th>
<th>PMN Dose (x10⁹)</th>
<th>1 hr Increment (x10³/µl)</th>
<th>24hr PMN (x10³/µl)</th>
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<tr>
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<td>41</td>
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<td>Adkins</td>
<td>10</td>
<td>51</td>
<td>1.0</td>
<td>25-37 h dur</td>
</tr>
<tr>
<td>Peters</td>
<td>26</td>
<td>45</td>
<td>1.5</td>
<td></td>
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<tr>
<td>Price</td>
<td>19</td>
<td>82</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>S/R</td>
<td>G-CSF</td>
<td>n</td>
<td>Donor PMN (x10^3/μl)</td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>----------------</td>
<td>----</td>
<td>----------------------</td>
</tr>
<tr>
<td>Bensinger</td>
<td>R</td>
<td>5ug/kg/d</td>
<td>58</td>
<td>15-40</td>
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<tr>
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<td>S</td>
<td>300ug</td>
<td>22</td>
<td>20</td>
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<tr>
<td>Leitman</td>
<td>S</td>
<td>5ug/kg</td>
<td>7</td>
<td>28</td>
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<td>5ug/kg/d</td>
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<td>Price</td>
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<td>600ug</td>
<td>175</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dexe 8mg</td>
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Determinants of PMN Yield

- Volume of Blood Processed
- Efficiency of Collection
- Donor’s Blood PMN Count
Pool and Store Platelets – Augmenting Quality Platelet Supply To Meet Transfusion Requirements

• Can the quality of apheresis or single donor platelets (SDP) be considered comparable to WB-d or BC platelets that are pooled prior to storage?

• Can platelet products be pooled to consistently provide platelet counts that are comparable to those found in an SDP product?

• Is donor exposure, to mediators of morbidity inherent in any one donor, increased by pooling to the point where it causes significant concern?

• Can quality bacteria detection be applied to ensure the safety of the platelet product?
• Summary
  • SDPs have long held a preferred position among transfusion experts. However, the evidence presented suggests a new perspective, with P&S platelet products reasonably viewed as a complementary strategy to meet platelet transfusion needs.
  • In vitro and in vivo data reviewed here suggest that SDP and P&S platelets, ABO-matched and pooled in a manner consistent with cGMP are comparable in quality, and using 4 to 5 unit pools, P&S platelets can be prepared to consistently provide comparable platelet counts. Since the advent of NAT, the concern over donor exposure to viruses is not as clinically meaningful as it once was. Bacteria testing has further increased the safety of platelet transfusions.
  • It is well known that apheresis donors are sometimes more difficult to recruit as evidenced by the fact that not all blood centers can satisfy their platelet requirements with single donor products. P&S platelets will provide a product to meet the needs of platelet transfusion requirements that cannot be satisfied with SDP products alone.
EBM and Patient Safety:

- Examples of certain evidence based practices to improve safety are:
  - Decreased verbal orders
  - Work hour limitations
  - Critical value notification
  - Removing certain harmful chemical agents from the routine inventory
Summing Up...

• Implementation requires a mind shift and the willingness to utilize the tools that are available
• Can slowly be incorporated into the routine system
• Will lead to a better decision-making process that will benefit patients and the healthcare set-up.
• **Recommended References:**

• The Evidence-Based Medicine Working Group: *Users’ Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*; Guyatt G, Rennie D (eds.), Chicago, IL, AMA Press, 2002


• Slichter SJ, Grabowski M, Townsend-McCall D, Bolgiano D: Prospective randomized transfusion trial to directly compare fresh and stored apheresis platelets and pooled random donor platelet concentrates in thrombocytopenic patients. *Blood* 1998; *92*(Suppl. 1):672a


• Heddle NM: Controversy concerning platelet dose. *ISBT Science Series* 2007; *2*:220–225

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</tbody>
</table>

* These resources have an annual fee but are often available at no charge to faculty through the medical library.
THANK YOU

When we accept tough jobs as a challenge and wade into them with joy & enthusiasm, miracles happen!

Gilbert Writer