Transfusion Medicine & Transformational Change Series
Part 1 Pathogen Reduction

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Disclosures

• None

Transformational Change in Transfusion Medicine

• Pathogen Reduction
• Regenerative Medicine/Cellular Medicine
• Big Data
Pathogen Reduction

• “The historical process of reactive, pathogen-specific test development is not sufficient to protect patients. The time has come for proactive pathogen reduction.”

• “We now have a means to protect patients from existing and emerging blood borne threats – all we need is the will.”

Pathogen Reduction

• Existing and emerging pathogens
  • Viruses
  • Bacteria
  • Protozoa
  • Prions

• Threaten the safety of the blood supply
• Blood collecting facilities
  • Reactive approach
    • Developing and implementing screening tests
    • After potential transfusion transmissible pathogens identified
    • Often a lengthy process – Pathogen transmission through transfusion is inevitable
Pathogen Reduction

- **2008** – Advisory Committee on Blood and Tissue Safety and Availability
  - Advises the Secretary of Health and Human Services
  - “accumulating evidence for the efficacy and safety of pathogen reduction warrants a commitment and concerted effort to add this technology as a broadly applicable safeguard which additionally would provide a reasonable protection against potential emerging infectious diseases.”

### Table: Pathogen-Reduction Technologies Approved and in Development in the United States and Europe

<table>
<thead>
<tr>
<th>Component and Source</th>
<th>Manufacturer and Technology</th>
<th>Treatment Process</th>
<th>Manner of Inhibiting Replication</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets</strong></td>
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<tr>
<td>Individual volunteer donors</td>
<td>Censo Intercept Blood System</td>
<td>Psoralen (photosens) and UVA light exposure</td>
<td>Formation of DNA and RNA monoox adducts and cross-linkage</td>
<td>FDA approved, CE marked</td>
</tr>
<tr>
<td></td>
<td>Terumo BCT Mirasol Pathogen Reduction Technology (PRT) System</td>
<td>Riboflavin and ultraviolet light exposure</td>
<td>Direct DNA and RNA damage and guanine modification</td>
<td>Phase 3 study planned in the United States; CE marked</td>
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<tr>
<td></td>
<td>Macopharma Theraplex ultraviolet platelets</td>
<td>UVC light exposure</td>
<td>Direct DNA and RNA damage and thymine dimer formation</td>
<td>CE marked</td>
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<tr>
<td><strong>Plasma</strong></td>
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<tr>
<td>Pools of volunteer and paid donors</td>
<td>Octapharma Octaplas</td>
<td>Plasma pools treated with solvent, trim-butyl phosphosphate and detergent (octoxynol)</td>
<td>Lipid membrane disintegration of enveloped viruses</td>
<td>FDA approved, CE marked</td>
</tr>
<tr>
<td>Individual and minipools of volunteer donors</td>
<td>Censo Intercept Blood System</td>
<td>Psoralen (photosens) and UVA light exposure</td>
<td>Formation of DNA and RNA monoox adducts and cross-linkage</td>
<td>FDA approved, CE marked</td>
</tr>
<tr>
<td>Individual volunteer donors</td>
<td>Macopharma Theraplex MB Plasma System</td>
<td>Filtration, methylene blue treatment and visible light exposure</td>
<td>DNA and RNA damage by type I and type II redox reactions</td>
<td>CE marked</td>
</tr>
<tr>
<td></td>
<td>Terumo BCT Mirasol PRT System</td>
<td>Riboflavin and ultraviolet light exposure</td>
<td>Direct DNA and RNA damage and guanine modification</td>
<td>CE marked</td>
</tr>
<tr>
<td><strong>Whole blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Individual volunteer donors</td>
<td>Terumo BCT Mirasol PRT System</td>
<td>Riboflavin and ultraviolet light exposure</td>
<td>Direct DNA and RNA damage and guanine modification</td>
<td>Phase 3 studies planned in the United States, completed in Africa</td>
</tr>
<tr>
<td><strong>Red cells</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Individual volunteer donors</td>
<td>Censo Intercept Blood System</td>
<td>Frangible Anchor-Linker Efferer (S103) and glutathione</td>
<td>Formation of DNA and RNA monoox adducts and cross-linkage</td>
<td>U.S. phase 2 and European phase 3 studies complete</td>
</tr>
</tbody>
</table>

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Pathogen Reduction

- Platelets: Bacterial contamination and associated septic transfusion reactions
  - Serious threat to platelet recipients
  - Room temperature storage of platelet components favors bacterial growth
  - Blood collecting facilities: voluntarily test platelet components – FDA-approved bacterial detection techniques

Pathogen Reduction

- Relevant bacterial concentrations
  - 1/3000 platelet units
- Clinical sepsis
  - 1/100,000 platelet transfusions
- To address this substantial risk
- FDA Draft Guidance
  - High false-negative rate of early bacterial testing
  - Outlines: prerelease bacterial screening strategy (e.g., on the day of platelet transfusion)
Pathogen Reduction

- Current screening tests for pathogens
- Limited – Failure to detect low levels of known transfusion-transmissible agents soon after infection (i.e., infectious “window” period)
  - Human immunodeficiency virus (HIV)
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
- Transfusion-transmitted infections
  - HIV, HBV, and HCV – Somewhere between 1 in 800,000 to 1 in 1.5 million transfused blood components

Pathogen Reduction

- Case review – Countries with similar safeguards against transfusion-transmissible agents as USA
  - 6 of 15 HIV and 12 of 19 HBV transmissions were linked to platelets or plasma collected during the window period
- Pathogen reduction technology
  - Inactivate HIV, HBV, and HCV in blood components with low viral loads
Pathogen Reduction

- Past 15 years: Blood centers’ response to transfusion threats
  - Implemented numerous screening tests
- Pathogens continue to emerge
  - Each instance brings transfusion safety into question
- Potential threats
  - Zika, Ebola, Dengue, Chikungunya, hepatitis E, pandemic influenza, severe acute respiratory syndrome (SARS) viruses

Pathogen Reduction

- Proactive pathogen reduction of platelets and plasma
  - Defuse many emerging threats
- In the near future pathogen-reduced red blood cell components should become available
- Continued “reactive approach” addressing transfusion threats
  - Non-viable
- Pathogen reduction
  - New screening tests only necessary for pathogens that lack susceptibility to the techniques or in concentrations that exceed the capacity of the techniques
**Pathogen Reduction**

- Critics concerned it will increase costs
- Adoption of pathogen reduction
  - Allow other costly processes to be discontinued
- Pathogen-reduced blood components
  - Considered safe with respect to:
    - Bacteria
    - Most known transfusion-transmitted viruses
    - Transfusion-associated graft-versus-host disease
    - Eliminating need for bacterial detection, CMV screening, and irradiation

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Amotosalen acts by binding and reacting with nucleic acids upon illumination

- Amotosalen (5-59)
- Targeting
- Helical region of single- or double-stranded DNA or RNA
- Intercalation
- Crosslinking
- UVA Illumination
- Multiple crosslinks block strand separation and replication

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Leukocyte effects: Intercept offers higher safety margin than gamma irradiation

**Gamma irradiation**
Inactivation analyzed using LDA¹²

- **2,500 cGy**
- **1.25-fold**

**Amotosalen/UVA**
Inactivation analyzed using LDA at 1.4 J/cm²³

- **150 μM, 3 J/cm²**
- **3,000-fold**


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**TABLE 7. Frequency of transfusion transmitted bacterial infections of conventional PCs and of INTERCEPT PCs based on national French and Swiss hemovigilance data**

<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional PLTs</th>
<th>INTERCEPT PLTs</th>
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<tbody>
<tr>
<td></td>
<td>Number of units transfused</td>
<td>Transfusion-transmitted infections (fatalities)</td>
</tr>
<tr>
<td>French data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>231,863</td>
<td>4 (0)</td>
</tr>
<tr>
<td>2007</td>
<td>232,708</td>
<td>9 (2)</td>
</tr>
<tr>
<td>2008</td>
<td>239,349</td>
<td>6 (1)</td>
</tr>
<tr>
<td>2009</td>
<td>241,634</td>
<td>9 (0)</td>
</tr>
<tr>
<td>2010</td>
<td>253,149</td>
<td>2 (1)</td>
</tr>
<tr>
<td>2011</td>
<td>267,785</td>
<td>3 (1)</td>
</tr>
<tr>
<td>2012</td>
<td>275,834</td>
<td>7 (2)</td>
</tr>
<tr>
<td>2013</td>
<td>278,234</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Swiss data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>28,900</td>
<td>1 (0)</td>
</tr>
<tr>
<td>2011</td>
<td>6,600</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2,057,046</td>
<td>45 (6)</td>
</tr>
</tbody>
</table>

* One-sided Fisher's exact test analysis provided the following values for the assessment of statistical significance: p value French data = 0.039; p value Swiss data = 0.277; p value combined = 0.006.
† French hemovigilance data, 1994-1996
‡ Swiss hemovigilance data, 2002-2003.
Cost of Pathogen-Reduced Platelets

- Additional cost savings to consider
  - Improved platelet availability
  - Earlier release of products
  - Ease of donor scheduling
  - Reduction of donor deferrals
Pathogen Reduction

- Disruptive technology
  - Innovation
    - Disrupts existing systems and processes
    - Displacing an earlier technology
- Pathogen reduction – Meets this definition
  - Replace or prevent adoption of additional tests against potential pathogen threats
  - Improve platelet availability and improve logistics of providing platelet transfusion therapy
- End result: Transformational Change!

References

Questions or requests…
Email to: MMLHotTopics@mayo.edu

For more information…
Visit MayoMedicalLaboratories.com or call Mayo Laboratory Inquiry at 800-533-1710