Benefits of pathogen inactivation

with focus on apheresis platelets in the US

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Pathogen Inactivation: risks incurred vs. risks averted

**Potential Risks Incurred**

- Decreased platelet effectiveness
- Acute recipient adverse reaction
- Chronic Toxicity

**Risks Averted**

- TTI reduction
  - Known pathogens
    - bacteria, CMV
    - close infectivity windows
  - Potential inactivation of emerging pathogens
- Leukocyte Inactivation
  - TA GVHD
  - Reduction of Tx reactions
Risk Benefit Comparison
A faulty comparison if risk estimates are taken from the literature

A

\[ \text{Incurred risks Per Patient} \]

\[ \text{Averted risks Per Unit} \]

\[ \text{Underestimated} \]

B

\[ \text{Incurred risks Per Patient} \]

\[ \text{Averted risks Per Patient} \]
Mean AP dose for a given patient

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>PC Type</th>
<th>Years</th>
<th>Patients</th>
<th>Dose per Patient</th>
<th>Patient Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT(^1)</td>
<td>US</td>
<td>Conv.</td>
<td>‘02-'04</td>
<td>327</td>
<td>6.2</td>
<td>HSCT&amp; Hem/Onc</td>
</tr>
<tr>
<td>PLADO(^2)</td>
<td>US</td>
<td>Conv.*</td>
<td>‘04-'07</td>
<td>423</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Routine(^3)</td>
<td>France</td>
<td>INTERCEPT</td>
<td>‘06-'08</td>
<td>6996</td>
<td>6.4</td>
<td>All Types</td>
</tr>
<tr>
<td>EFS ALSACER</td>
<td>Europe 20 Centers</td>
<td>INTERCEPT</td>
<td>‘03-'10</td>
<td>4067</td>
<td>4.7</td>
<td>All Types</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.8</td>
<td>HSCT</td>
</tr>
</tbody>
</table>


* Medium Dose

- Our estimate from these cumulative data is a mean per HSCT/HemOnc patient platelet dose of **6 AP**
Infectious risks of platelet transfusion averted by PI

• Bacterial infection and septic transfusion reactions (STR)
• CMV
• Unknown Emerging Infectious Agents (EIA)
• Aggregate risk estimates
• Window period infection with known viruses (HIV, HCV, HBV, WNV) and occult infection with HBV
  – Current risks are very low and will not be discussed further
Bacterial contamination in PC at expiration

* No Day 0 Culture, **Point of Release Assay (in-date units)

Per patient bacterial risk

• There are now 5 independent studies\(^1\) performed on platelets at expiration (4), or time of issue (1) indicating that the rate of bacteria infection undetected by early culture is \(~ 1:1500\) units

• Thus the platelet recipient transfused with an average platelet dose of 6AP has a risk of \(~ 1:250\) to receive a contaminated unit during a cycle of treatment

• INTERCEPT platelets will alleviate virtually all this risk*  

*possible exception of some bacterial spore formers

### Active vs passive surveillance for STRs
*(f/u of culture positive units from 1991-2006)*

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Active (n=102,998)</th>
<th>Passive (n=135,885)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial contamination</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Septic Tx reaction</td>
<td>16 (0.016%)</td>
<td>2 (0.0015%)</td>
</tr>
</tbody>
</table>

STR rate from active HV was 10.56 fold higher than by passive reporting

Risk estimate for post-transfusion sepsis

- Current risk for clinically detectable post-tx sepsis range from 1:50,000 - 1:80,000 AP units transfused based on passive reporting\(^1\)
- However, such septic events are not always reported or appreciated
  - May be misdiagnosed or unrecognized due to patient’s general health status
  - Delayed events will be missed
- Passive reporting is sub-optimal
  - Active HV over a 15 year period (1991-2006) at a single institution\(^2\) showed sepsis to be 10-fold more common than by passive reporting
- This projects to a current per unit sepsis risk of 1:5,000 to 1:8,000 and a per patient risk (dose of 6 AP per patient) of 1:833 - 1:1,333

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Current bacterial risk: what is the relevant measure?

• It’s a matter of judgment which risk (bacterially contaminated unit *versus* clinically symptomatic disease) should be considered in a risk/benefit analysis
  – Estimated at 1 in 250 (0.4%) versus 1 in 1000 (0.1%)

• Here is one opinion: (*Murphy WG, Transfusion 2010*)
  – “It is unthinkable that a manufacturer of other intravenous medications could eschew reasonable methods to eradicate possible contamination on the basis that only organisms of questionable clinical significance persisted in the preparations infused.”
Modeling the risk of an emerging pathogen entering the Canadian blood supply

Kleinman S, Cameron C, Custer B et al.
Transfusion 2010; 50: 2592-2606
Estimating prevalence of an emerging infectious agent (EIA) in donor units

- Prevalence rates estimated by reviewing the literature on other emerging TTIs as well as historical blood donor screening data
- Estimates might be marginally higher for the US
- A new agent may either be chronic (HIV-like) or acute (WNV-like):

  **Chronic agent**
  - most likely 0.045%
  - min. 0.01%
  - max. 0.08%

  **Acute agent**
  - most likely 0.025%
  - min. 0.007%
  - max. 0.075%
Estimating the risk period for EIA transmission

- Risk period is defined as the time from the pathogen entering the blood supply to the time of an effective intervention (e.g., donor screening assay)

**Chronic agent**
- min. 3 year
- max. 10 years
- most likely 5 years

**Acute agent**
- min. 1 year
- max. 2 years
- most likely 1.5 years
Risk estimates need to include emerging infectious agents

Patient Exposure

[Units Transfused over Lifetime] \times [Risk per Unit]
CMV Risk: Historical data and recent studies

Vamvakas

Wu et al.

Thiele et al.

Estimate

~ 50% CMV seronegative patients at risk

Risk of exposure to an IA with potential clinical sequelae for hem-onc platelet tx recipients

<table>
<thead>
<tr>
<th>Infection</th>
<th>Per Unit Estimate</th>
<th>Per Patient Estimate (6 AP Exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Contamination (Clinical Sepsis)</td>
<td>1 in 1500</td>
<td>1 in 250</td>
</tr>
<tr>
<td></td>
<td>(1 in 5,000-1 in 8,000)</td>
<td>(1 in 1,000)</td>
</tr>
<tr>
<td>TT-CMV</td>
<td>1 in 1000</td>
<td>1 in 300 (50% suscep pts)</td>
</tr>
<tr>
<td>Emerging agent</td>
<td>1 in 14,000 – 1 in 1,250</td>
<td>1 in 2,400 – 1 in 210</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1 in 583 – 1 in 400</strong></td>
<td><strong>1 in 250</strong> (bacteria baseline estimate)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>1 in 80</strong> (bacteria, CMV, and EIA highest estimate)**</td>
</tr>
</tbody>
</table>

Real Life Examples of TTI Risk from Acute and Chronic EIAs

<table>
<thead>
<tr>
<th>Example</th>
<th>Acute TTI</th>
<th>Chronic TTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV In San Francisco Early 1980s</td>
<td>Up to 1%</td>
<td>Up to 6%</td>
</tr>
<tr>
<td>Dengue in PR: Sept, 2010</td>
<td>Up to 0.35%</td>
<td>Up to 2.1%</td>
</tr>
</tbody>
</table>
Replacement of Gamma irradiation to prevent Transfusion-associated GVHD

- TA-GVHD is rare but nearly universally fatal
- Traditionally prevented through gamma irradiation of platelets (T-cell inactivation) used for at-risk patients
- Targeted strategy may miss susceptible patients:
  - improper patient diagnosis
  - unrecognized risk for an entire group of immunosuppressed patients
- PI can inactivate T cells 2000-fold more effectively
- PI of all components eliminates missing susceptible patients
- No TA-GVHD observed to date after PI PC transfusion
Hemovigilance data show significant reduction of adverse reactions for PI platelets

<table>
<thead>
<tr>
<th>Preparation Method</th>
<th>Component</th>
<th>Number</th>
<th>Adverse Reactions /10^6 PC</th>
<th>Reduction %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis</td>
<td>EFS Alsace</td>
<td>16,494</td>
<td>2182</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>National*</td>
<td>385,049</td>
<td>6220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffy Coat Pools</td>
<td>EFS Alsace</td>
<td>26,312</td>
<td>2166</td>
<td>32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>National*</td>
<td>117,795</td>
<td>3179</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excludes EFS Alsace
Unknown Toxicity or Undetected Severe Adverse Effects
Less Likely as More Products are Transfused

![Graph showing an increase in unknown toxicity or undetected severe adverse effects from 2006 to 2012. The graph is color-coded with blue for Plasma, red for Platelets, and green for Dual.]
Pros and cons (benefits and risks) of PI

**Pros**
- kills most relevant viruses, bacteria, and parasites
- a precautionary paradigm for EID agents
- Additional:
  - Replace gamma irradiation
  - Replace CMV testing
  - Reduce FNHTR
  - Reduce alloimmunization?

**Cons**
- does not kill all agents (prions, some viruses, spores)
- concern about adverse reactions and long term toxicity - unproven
- US regulators have thus far shown precaution for the use of this new intervention