Pathogen Inactivation: Beyond The Consensus Conference

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Full Disclosure

I receive $0

David Anstee receives $

Blackwell Publishing receives $$$$$
Transfusion Process

Product

- Recruit
- Screen donor
- Collect and prepare
- Infectious Disease tests
- Compatibility testing
- Medical reason for Tx
- Issue
- Administer (bedside)
- Monitor and evaluate

Blood donor

Quarantine
Reducing the Risk of Infection

- Donor history
- Donor examination
- Testing
- Diversion
- Leukoreduction
- Component inspection
- Post donation information
- Donor deferral registries
- Limit exposures
- Hemovigilance
INCIDENCE OF POST-TRANSFUSION HEPATITIS OVER THREE DECADES

26.9%

1967-1970
n=160

All Volunteer HBsAg Testing

8.6%

1970-1973
n=244

3rd gen HBsAg

5.6%

1974-1976
n=320

ALT Testing

11.0%

1977-1978
n=237

HIV Testing

5.5%

1979
n=163

Anti-HBc Testing

4.7%

1980
n=299

5.2%

1981
n=96

3.7%

1985-1986
n=218

Anti-HCV 1st gen

0.6%

1987-1990
n=170

Anti-HCV 2nd gen

0.3%

1990-1992
n=342

0

1992-1994
n=287
HIV Viremia during early infection

Peak viremia: $10^6$-$10^8$ gEq/mL

Ramp-up viremia
$DT = 21.5$ hrs

“blip” viremia

Viral set-point: $10^2$-$10^5$ gEq/mL
HCV Transmission by Blood Donation Negative by NAT

• Donation 8 weeks prior to SC donation
• HCV transmission by platelet concentrate (~50mL plasma) but not RBC (~5mL plasma)
• NAT studies of FFP, incl. “enhanced input” PCR assays, negative for HCV RNA
• Conclusion: “Even a negative NAT test cannot completely prevent transmission of HCV.”
• GenProbe HCV dTMA (+) in 2 of 3 replicates; NGI Ultraqual PCR (-) on all 3 replicates
West Nile Virus

West Nile Virus Transmission Cycle

Mosquito vector

West Nile virus

Bird reservoir hosts

Incidental infection

West Nile virus

Incidental infection

Mosquito
West Nile Virus Activity: 1999-2002

1999

2000

2001

2002

Human WNV infections
West Nile Virus Activity - 2007

[Map showing West Nile Virus activity across the United States with states colored to indicate human disease cases and avian, animal, or mosquito infections.]
Our Greatest Concern

That an unknown agent, of unknown origin, coming from an unknown location at an unknown time and working through unknown mechanisms might enter the blood supply and cause a disease of unknown, but significant consequences. Basically that a tragedy of AIDS proportions might repeat itself.

Both the moral imperative and the litigious fear stemming from this concern form the paradigm that has driven blood safety initiatives since 1985.

Harvey J. Alter
2002
Projected Risk of HIV-1 Infection in San Francisco

- First TA-AIDS case reported; high-risk donor deferral initiated
- First hemophilia-associated AIDS
- First AIDS cases reported
- HIV discovered; progressive impact of high-risk donor education
- Anti-HIV screening implemented

Year of transfusion

Risk of HIV per unit (%)

TA-AIDS = Transfusion-Associated-AIDS
Adapted from Busch MP et al. The Transfusion Safety Study.
Classification of Infectious Threats to Blood Safety

**Emerged** – HBV, HCV, Plasmodia, CMV

**Emerging** - HIV, vCJD, ? SARS, ? Bird flu

**Re-emerging** – WNV, bacteria, T. cruzi, babesia

**Submerging** – HGV/GVB-C, TTV, SEN-V

**Protective Triad**
- Donor Selection
- Blood Screening
- Pathogen Inactivation

**Residual Risk**
Bacterial Contamination of Blood

• First recognized transfusion-transmitted infection
• Frequency reduced by refrigerated storage and closed, sterile system technology
• With improved donor screening and viral testing, bacterial sepsis regained position as most frequent infectious agent
Risk of Bacterial Sepsis / Contamination in Platelets

Pre-Intervention

Ness et al. USA 1:13,000
Perez et al. France 1:30,000
Kuehnert et al USA 1:100,000

Post-Culture

Fang et al * USA 1:5,000

*confirmed positive aerobic culture
Residual Risk from Bacteria: ARC Passive Surveillance of Apheresis Platelets*

• Pre-intervention
  1:40,000 septic reactions
  1:240,000 fatalities

Post-intervention

  1:75,000 septic reactions
  1:500,000 fatalities

\[ \sim 50\% \text{ decrease} \]

*Eder et al. Transfusion 2007
BacT/ALERT (Culture) False Negative Rate

**ARC** (Eder et al. Transfusion 2007)
20 Septic reactions – 3 fatal
1,004,000 tested components

**Canada** (Ramirez-Arcos et al. Transfusion 2007)
2 septic reaction – 1 fatal
82,004 tested components

**Netherlands** (Boekhorst et al. Transfusion 2005)
2 septic reactions
28,104 pools tested

**Germany** (Schmidt et al. Vox sang 2007)
2 septic reaction – 1 fatal
11,037 components tested
The Urban Wilderness
Babesia microti and Borrelia burgdorferi
# Major Tick-Borne Diseases in U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td>spirochete</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td><em>Borrelia</em> spp.</td>
<td>Spirochete</td>
</tr>
<tr>
<td>Tularemia</td>
<td><em>Francisella tularensis</em></td>
<td>Bacteria</td>
</tr>
<tr>
<td>RM spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td>Rickettsia</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td><em>Ehrlichia</em> spp.</td>
<td>Rickettsia</td>
</tr>
<tr>
<td>Colorado tick fever</td>
<td>Coltivirus</td>
<td>Virus</td>
</tr>
<tr>
<td><em>Babesiosis</em></td>
<td><em>Babesia microti, WA1</em></td>
<td>Protozoa</td>
</tr>
<tr>
<td></td>
<td><em>B. divergens,</em></td>
<td></td>
</tr>
<tr>
<td>Tick paralysis</td>
<td>Toxin</td>
<td>Neurotoxin</td>
</tr>
</tbody>
</table>

*After Spach et al., NEJM, 1993*
SARS and the Blood Supply

• Severe acute respiratory syndrome with > 5% mortality
• Blood transmissibility unknown
• Window unknown
• Isolated from blood
Chikungunya virus

Alpha virus with dengue-like
Presentation — epidemic in
Africa and Asia

Mosquito-borne transmission

Present in blood and transmitted
by organ transplant

Health worker infected from
needlestick
Other Vector-Borne Infections

T. cruzi
Chagas and Transfusion

Parasite survives in stored blood

7 transmissions detected in N.A.

1 in 4,655 donors confirmed positive
In high-risk areas (ARC 148,000 samples in 6 mos.)

Risk increasing in U.S. with population movement and focus on Latino donors

No effective treatment for chronic disease – Screening recently introduced
Leishmania infected 2,500 U.S. troops in Iraq and Afghanistan during the last 4 years.
Leishmania species

- intracellular flagellated protozoan
- etiologic agent of leishmaniasis
  - cutaneous ↔ mucocutaneous ↔ visceral
- transmitted by sandflies
- endemic to tropical and subtropical areas:
  - Africa, Asia, Mediterranean Coast of Europe, Middle East, Central and South America
- worldwide 350 million at-risk and 2 million new infections each year
- 50 documented transfusion transmissions—1 yr. donor deferral in U.S.
Malaria

• From the Italian: “mala”, bad; “aria”, air
• Mosquito-borne transmission
• Most important TTD worldwide
• 1 case / 4 million units annually in the U.S.

One U.S. transfusion cases in this century (Houston, 2003 – Ghanian donor

Few U.S. cases from travelers
Deferrals Because of Travel to Malarial Area

Data from the New York Blood Center
vCJD and Transfusion

Agent likely present in all components
- 3 transfusion cases and 1 transmission alone
- Transmissions by leukoreplete RBC
- Recipient susceptibility unknown
- Second transfusion case in U.K. and sheep data raise fear of second and third “waves”
- Disease in deer and elk in the U.S.
Impact of vCJD Deferrals

• Big issues: confusion and self deferrals
• Numbers
  – ARC ~ 600,000
  – ABC ~ 300,000
  – Euroblood (NYBC) ~140,000
  – Military (25%) ~ 30,000
  – Total loss ~ 1.1 million donors, 1.7 million units
Guess who’s coming to dinner
Simian Foamy Virus (SFV)

- Highly prevalent primate virus that infects human cells, replicates, cell-free virus
- Broad tropism, T, B lymphs, fibroblasts, endothelial cells, kidney cells
- 1% in southern Cameroon have antibody *
- 2-5% of U.S. animal handlers**

*Wolfe et al. Lancet 2004
**Switzer et al. J Virol 2004
Simian foamy virus

- Persistent viremia detected in PBL
- 11 SFV-infected workers known blood donors
- SFV transfusion transmission not identified in 4 recipients (3 RBC, 1 Pl) – Boneva et al. Transfusion 2002
- No evidence of human disease – but risk of recombination with persistent infection
Donor Testing for Infectious Disease in the U.S.

- Syphilis (1938)
- HBsAg
- Anti-HIV
- Anti-HBc
- Anti-CMV
- ALT
- Anti-HTLV
- Anti-HCV
- HIV Ag
- HIV HCV NAT
- HBV NAT
- WNV
- Chagas
- Malaria
- HHV8
- Babesia
- Leishmania
- Monkeypox
- Foamy viruses
- HEV
- LCT
- CHIKV
- Dengue
- Ebola
Blood Contaminants – I.D. Future

- Screening out all contaminated units would result in an inadequate blood supply
- Risk assessments for all of these agents in all of these populations is an unachievable task.

Donor lymphocytes
Parvo B19
HGV
Leishmania
T. cruzi
Babesia microti
Plasmodium sp.
West Nile Virus
Dengue
Chikungunya
Foamy viruses
Ebola
Bacteria
“Next” pathogen(s)

TTV
HHV-8
EBV
CMV
HEV
HPV
HIV
HAV
HCV
HTLV
LCT
Pathogen Reduction
New Paradigm

"I'm not trying to change you, Ronald. I'm trying to change your paradigm."
Biopharmaceutical Pathogen Reduction/Clearance Technology

- Pasteurization
- Fractionation
- UV/Propiolactone
- Low pH
- AHF Heat
- Solvent-Detergent
- Affinity Purification
- Nanofiltration
- Product NAT

No HIV, HBV, HCV Transmissions since 1987

No WNV
Pathogen Reduction in Transfusion Products - Risks vs Benefits

Risks
- damage to transfusion product
- toxicity to recipient
- toxicity to processing personnel
- toxicity to environment

Benefits
- reduction of known viruses
- reduction of bacteria
- reduction of parasites
- potential reduction of emerging and unknown pathogens

From Jaroslav G. Vostal. M.D., Ph.D.
Power Calculation for Adverse Events

• For an SAE occurring 1/1000 patients:
  – Requires 4,800 patients for a 95% chance of any practitioner observing > 1 event
  – One treated patient per day, every day, for 18 years
Seronegative Patients

CMV Infected

Pregnancy
35%

Cerebral Palsy
Mental Retardation
Sensorineural Loss

“Healthy” Patient
No effect?

Immunocompromised

Pneumonitis
Retinitis
Neurologic Disease
Death

Underlying Medical Condition
No Effect?

“Healthy” Patient
No effect?
HGV Virology

- Viremia = Genomic RNA in serum
- Persistent viremia for years ~ 20% - 50%
- Viremia ranges from $10^4$ – $10^7$ GEq/mL
- Virus replicates in lymphocytes
- No known disease association
Concern of HGV in the Blood Supply

- 180,000 patients exposed annually to HGV
- ~ 36,000 become chronically infected
- High viremia maintained for years
- Lymphocyte tropism including CD4\(^+\) Cells

- Should a virus remain in the blood supply until proven dangerous?
- Should a virus be screened out or inactivated until proven safe?
Viral Inactivation: Lessons Learned

- Efficacy of component well maintained
- Toxicity not encountered
- Immunogenicity seldom encountered
- Viral “safety” achieved
  - Methods that kill 4-5 logs did NOT eliminate HCV infectivity
  - Methods that kill $\geq$6-7 logs provided safety
Pathogen-Inactivated Transfusion Components

• Goal: Eliminate transmission of viruses

• Secondary Drivers
  – Bacteria, Parasites

• Added Value
  – GVHD


Additional Considerations Applicable to Single Donor Components

- Higher viral concentration
- More proteins to consider (FFP)
- Limited ability to purify
- Cells more fragile
- Bags are not tanks
Principal Methods Applied to Components

• Single Donor Plasma
  – Solvent Detergent (SD, Octaplas)*
  – Methylene blue*

• Cellular components
  – S-59 (psoralen)*
  – Riboflavin
  – S-303
  – (Inactine)**

*approved/licensed  **abandoned
Reasons for Slow Acceptance

• Current safety of the volunteer blood supply
• No single method to treat all components
• Success of surveillance and screening in dealing with emerging pathogens
• Inability of current technologies to inactivate all agents (small, non-encapsulated viruses, spores, high-titer viremia, and prions)
• Potential risks from the residual chemical agents
• Cost
Consensus Development Conference*
Toronto - March 29 - 30

• Topic Identified – Background materials
• Steering Committee - Crafts questions, identifies speakers, appoints panel
• Speakers - Outline issues – 1 day
• Panel - Deliberates and produces statement
• Draft Consensus Statement – public review
• Panel refines - Consensus Statement

*Supported by CBS, Héma-Québec, BEST
Consensus Panel

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Queen’s University Kingston ON

Fiona Smaill
McMaster University Health Sciences, Hamilton ON
1. **Is the current risk of transfusion-transmitted diseases acceptable in relation to other risks of transfusions?**

   • **Dramatic recent advances in transfusion safety**

     • Estimated residual risk (Canada): HIV = 1 in 7.8 million, HCV = 1 in 2.3 million, HBV = 1 in 153,000, HTLV = 1 in 4.3 million

     • Risk of bacterial contamination: ~1 in 41,000 (passive reporting in Canada) after introduction of screening cultures. ARC reports sepsis ~1/50,000 units tested negative – Canada ~1/33,000 in uncultured WBD platelets

     • Hemovigilance data suggest that aggregate infectious risks << current non-infectious risks of transfusion (e.g. acute hemolysis, delayed hemolysis, TRALI)
• Based on these data alone, the Panel does not recommend introduction of pathogen inactivation (PI) with its attendant unknown risks. **However,**

  • Active surveillance cannot account for the risk of an emerging transfusion-transmitted pathogen.
  • Emerging agents have been detected in blood donors at an increasing rate since the HIV epidemic.
  • The reactive strategy of surveillance, identification, and test development permits an agent to disseminate widely before clinical disease is recognized.
  • In addition to causing morbidity and mortality, such an event undermines public confidence in the blood supply.

• The Panel recognizes that such risks require a proactive approach in accordance with the precautionary principle.
a) If so, under what new circumstances should pathogen inactivation be implemented?

PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available.

The Panel acknowledges that non-infectious hazards of transfusion can entail serious safety issues which deserve specific attention.

*Introduction of PI technology should not preclude efforts to reduce these non-infectious risks.*
## Estimated Costs to Reduce Non-infectious Hazards†

<table>
<thead>
<tr>
<th>Cost Drivers</th>
<th>Patient Barcode</th>
<th>Unified Online Database</th>
<th>TRALI: Exclusion/Testing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental Cost/unit</td>
<td>$10-20/unit</td>
<td>$3-6/unit</td>
<td>$1 -2 /unit</td>
<td>$14 – 28</td>
</tr>
<tr>
<td>27 million units*</td>
<td>$392 million</td>
<td>$90 million</td>
<td>$40 million</td>
<td>$432 mil</td>
</tr>
<tr>
<td>Major events (hemovigilance)*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>295</td>
</tr>
<tr>
<td>$ per event avoided</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$1.5 mil</td>
</tr>
</tbody>
</table>

†Adapted from S. Dzik as presented  *Stainsby et al Transfusion Med Rev 2006 20:273
b. Should the criteria be the same for RBCs, Platelets, and FFP?

- The same criteria of safety, feasibility, and efficacy should apply to all blood components.

- A single method to inactivate pathogens in all blood components would be ideal.

- However, absence of an integrated system does not imply that PI of any one component should be delayed until a method is proven satisfactory for all components.
c. Should different criteria be used for certain patient populations?

• The treated product should be used universally.

• Traditionally, premature infants, children, and pregnant women have been considered “vulnerable populations”. However, these patients may be at particular risk for transfusion-transmitted pathogens and might arguably derive special benefit from PI components.

• Few current data available on which to individualize risk-benefit assessment. Additional new information may identify groups of patients who should not receive the PI product.
2. What minimum acceptable safety and efficacy criteria should be put into place for the pre-approval assessment of pathogen inactivated products?

Specifically:

a) What criteria should govern acceptable toxicology standards and how should they be assessed?

The Panel endorsed rigorous application of standards for safety and efficacy, particularly in the area of toxicology. The Panel strongly recommended the use of well-designed randomized clinical trials using clinically relevant endpoints.
b) What type of post-marketing surveillance should be required (if any) with the implementation of pathogen inactivated blood components?

The Panel recognizes the difficulty of post-marketing surveillance:

Specific studies should be mandated by the regulatory authorities and supported by the manufacturers or the blood suppliers.

Post-marketing surveillance for adverse reactions to PI products should be linked to national hemovigilance systems.

Annual reports on adverse reactions to specific products should be performed and analyzed.

Comparisons should be made to historical rates of adverse reactions with non PI products.

The Panel recommends sharing of hemovigilance data across jurisdictions.
# Estimates of Study Size to rule out an adverse event frequency

<table>
<thead>
<tr>
<th>Study Size to rule out an adverse event*</th>
<th>Adverse event frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1/33</td>
</tr>
<tr>
<td>300</td>
<td>1/100</td>
</tr>
<tr>
<td>1,000</td>
<td>1/333</td>
</tr>
<tr>
<td>3,000</td>
<td>1/1000</td>
</tr>
<tr>
<td>10,000</td>
<td>1/3,333</td>
</tr>
<tr>
<td>225,000</td>
<td>1/75,000</td>
</tr>
</tbody>
</table>

*95% upper confidence limit

From Hanley JA JAMA 259:1743-5 1983
3. For pathogen inactivation technologies that have been approved by the regulatory authorities, what implications should be considered prior to their widespread adoption?

A number of implications for blood services (and beyond) as well as unintended consequences.

• Suppliers will require a process to select the most appropriate PI technology.
• Logistical issues
• The process should include the detailed review of the available safety and effectiveness data along with determination of how the adoption of a new technology will impact the processes of the organization.
• Cost-effectiveness studies should be conducted by agencies such as CADTH.
4. If pathogen inactivation were to be implemented for all components; in principle, what criteria would allow:

a) Changes in donor deferral or testing?

Specifically

i. The relaxation of any current donor deferral/exclusion policies?

The regulatory agencies and blood collectors should review the donor screening questionnaire to eliminate or modify questions that are thought to be of marginal value such as tattooing and certain travel deferrals.
ii. What criteria would allow the cessation of any currently undertaken screening tests?

1. Screening tests for agents that are not readily transmissible by transfusion; for example, T. pallidum (syphilis).

2. Screening tests for agents of low infectious titer and high log kill by PI. For example, West Nile Virus.

3. Screening tests for agents sensitive to PI and for which redundant safety measures are in place, such as CMV, HTLV, and anti-HBc.

4. Screening tests for agents that are exquisitely sensitive to PI and for which the current tests have poor specificity and sensitivity, such as bacteria.

5. Although not a screening test, gamma irradiation of cellular blood components could be eliminated if nucleic acid-targeted PI technology were introduced.
a) What criteria would allow a decision not to implement new screening tests for agents susceptible to pathogen inactivation?

A candidate agent shown to be adequately inactivated by an implemented PI technology would not require testing implementation, unless of unusually high infectious titer.

b. Should multiple inventories be considered for each component and if yes how should allocation be decided?

The Panel recommended universal implementation of PI (or universal implementation of a particular component if PI methods for all components are not available). The Panel recommended against multiple inventories.
5. How should the costs/benefits of pathogen inactivation be assessed?

• Implementation of PI should not be based solely or on the results of an economic analysis; the costs are currently unknown and the benefits are difficult to quantify.

• Costs and benefits should be assessed using a societal perspective, examining both direct and indirect costs in accordance with published recommendations.

• Methods and models should be transparent with assumptions highlighted and tested for their effect on the results.

• Uncertainty about these analyses should be considered, not only for the incremental cost-effectiveness ratio (ICER) but also for the budget impact.
How should these be aligned with other blood safety interventions and/or other health care interventions?

• A judgment about whether the extra benefits outweigh the extra costs is context specific.
• It may be inappropriate to assign a single number as a cutoff threshold for the cost-effectiveness analysis.
• Decision makers should clearly state their reasoning for decisions with emphasis on budget impact, the extra cost for improved patient outcome, and opportunity costs.
• Reasoning used for past decisions may not be applicable for current or future decisions for new, expensive tech.
• Decisions about scarce resources must be consistent with the values of the decision makers and their patients.
6. What other information, considerations, and research-related questions would need to be answered in order to decide whether/when a particular pathogen inactivation procedure should be implemented?

The Panel recommends that consideration be given to robust governmental support for a large scale investment in developing an integrated PI technology for all blood components.

Mathematical modeling should be used to develop credible scenarios for the unknown pathogen risk. These models could be used in economic analysis of candidate PI technologies to support decisions about investment for the research agenda.

Large, adequately powered, randomized clinical trials should be done to evaluate and/or confirm the effectiveness of any new PI technology.
• Post-licensure phase IV studies should be integrated with hemovigilance systems to enhance detection of adverse events.

• Introduction of PI technologies might have unanticipated consequences to the health care system. For example, the development and availability of screening tests for new agents might be compromised.

• Prion diseases have not been addressed by current PI technologies. New PI technologies should be investigated to address these and other resistant agents. Research should address the relative risks and benefits of PI pooled components versus PI single donor components.

• Research initiatives should be directed toward a PI technology suitable for implementation in developing countries.
January 28, 2008

Donald Wright, M.D. M.P.H.
Acting Assistant Secretary for Health
200 Independence Avenue, SW
Washington, D.C. 20201

Dear Dr. Wright:

The HHS Advisory Committee on Blood Safety and Availability met in Washington, DC on January 9 and 10, 2008. The Committee heard from a number of authorities regarding current risks of transfusion, available testing strategies and supplier capability for developing new tests. We also heard reports on systems designed to inactivate a wide range of potential blood-borne pathogens including toxicity data, clinical efficacy data from clinical trials and ongoing European experience as well as a summation of a recent Canadian consensus conference of pathogen inactivation. The Committee felt that further development of these systems and a move toward implementation is warranted. The Committee's resolution follows.
"The Advisory Committee on Blood Safety and Availability (ACBSA) finds that accumulating evidence for the efficacy and safety of pathogen reduction warrants a commitment and concerted effort to add this technology a broadly applicable safeguard which additionally would provide a reasonable protection against potential emerging infectious diseases. This would result in a proactive, pre-emptive strategy that would broadly render most known agents non-infectious and prevent emerging agents from becoming transfusion risks.”
Potential Benefits

1. Reduction of current risks of known infectious agents
2. Protection against the risk of emerging infectious agents including shielding the nation from introduction of biological threats into our blood supply
3. Avoiding obligate blood recipient infectious risk before emerging infectious diseases are detected and new assays are developed
4. Increase the availability of blood supply by avoiding unnecessary loss as an undesired outcome of false-positive infectious disease tests and non-specific donor screening strategies
5. Avoidance of the need to develop new screening assays for emerging and/or localized infectious agents
6. Mitigation of non-viral threats associated with blood transfusion, such as transfusion-related acute lung injury (TRALI), bacterial contamination, graft-versus-host disease (GVHD) and human leukocyte antigen (HLA) alloimmunization
Recommendations

a) Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implement as they become available.

b) Provide resources to overcome current barriers to development and validation of pathogen reduction technologies.

c) Ensure adequate safety monitoring of pathogen reduced blood products post-marketing using an active national hemovigilance system.

d) Ensure that other efforts to improve blood safety and availability are not compromised by these efforts.
Technologies of PATHOGEN REDUCTION

Helinx (S-303) Mechanism of Action

DNA or RNA of pathogen
Physiologic pH
Docking & Crosslinking
Unreactive By-product

Amotosalen Mechanism of Action

Amotosalen (S-59)
DNA or RNA of pathogen
Intercalation
Cross-linking
UVA Illumination

Add riboflavin to product
Illuminate product
Collect blood component
Store and transfuse
I think we agree, the past is over

George W. Bush
Single Donor Blood Components Pathogen Inactivation/Removal Steps

Riboflavin/light: Platelets, FFP, RBC

INACTINE: RBC

FRALE: RBC

Amotosalen/UVA: FFP

Amotosalen/UVA: Platelets

MB-FFP

SD Plasma

Leukofiltration

Gamma-Irradiation
Principal Methods Applied to Plasma

- Marketed
  - Solvent Detergent (SD, Octaplas)
  - Methylene blue
  - (quarantine plasma)

- Investigational
  - S-59 (psoralen)
  - Riboflavin
SD-Plasma: Current Status

• Licensed by FDA
  – Unavailable in the U.S.
  – Quarantine plasma offered
  – Black box warning re liver disease

• Widely available in Europe
  – 650,000 units/year
  – Likely eliminates TRALI risk from plasma
    • Alternatives: male donors; HLA screening
  – Pricing: 110 Euros vs 66 Euros for quarantine plasma in France

• Uniplas
The Theraflex System

Plasmaflex PLAS 4

Methylene Blue Pillow

Illumination bag

Blueflex Methylene Blue depletion filter

Plasma Storage bag

MacoPharma

W. Walker
MACOTRONIC

- 8 sodium low pressure, high energy lamps
- Emission max. 590nm
- Documentation of light intensity
- 15 – 20 min. illumination

- Double sided illumination
- 4 bags / cycle
- Agitation of plasma under controlled temperature
- Full GMP-Procedure
## Usage of Theraflex MB Plasma in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Registration</th>
<th>Routine use</th>
<th>Centres</th>
<th>Units/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Registered</td>
<td>since 2004</td>
<td>4</td>
<td>90.000</td>
</tr>
<tr>
<td>UK</td>
<td>Registered</td>
<td>since 2003</td>
<td>4</td>
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<tr>
<td>Greece</td>
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<td>since 2002</td>
<td>1</td>
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<td>Italy</td>
<td>Registered</td>
<td>since 2002</td>
<td>5</td>
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</tr>
<tr>
<td>Spain</td>
<td>Registered</td>
<td>since 2000</td>
<td>6</td>
<td>100.000</td>
</tr>
<tr>
<td>France</td>
<td>Registered</td>
<td>in preparation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>in preparation</td>
<td>in preparation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Austria</td>
<td>in preparation</td>
<td>in preparation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Switzerland</td>
<td>in preparation</td>
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</table>
MB-Plasma Trends

- Usage appears to be increasing
  - Has replaced SD-Plasma in Belgium
  - Sole plasma product used in UK for pts born after Jan 1, 1996
  - Poised to replace quarantine plasma in France
    - vCJD
- Concerns over toxicity/carcinogenicity likely overstated
- Pricing: 40-100 Euros/200 mL
Observed Viral Safety

Routine Use

• Enveloped viruses
  – Neither SD-Plasma nor MB-Plasma have documented transmissions of HIV, HBV, or HCV

• Non-enveloped viruses
  – SD-Plasma + B19 NAT has not transmitted parvovirus or HAV
Conclusions

- PI-Plasmas are here to stay
- Cell-Associated Agents not a Problem
- Thorough investigation
  - Excellent safety/efficacy profiles demonstrated
  - Demonstrated virucidal potency indicates that there is a good chance that new virus transmissions will be greatly reduced/eliminated
Psoralen (Amotosalen, S-59) For Platelets and Plasma

- Helinx technology intercalates between bases of double-stranded nucleic acid
- Photo treated with UV-A light crosslinks strands and produces reactive $O_2$ species
- Absorbing resin removes S-59 and adducts
- Platelet loss and damage noted in clinical trials
INTERCEPT Plasma Photochemical Treatment

Integrated Container Set

1. Collected Plasma
2. Amotosalen (S-59) Container
3. Illumination Container
4. Flow CAD
5. Final Storage Containers

UVA Illumination Device

Cerus
L. Corash
The Intercept System (S-59) and Platelets

- Platelets suspended in a plasma-reduced medium
- UVA treatment and S-59 absorption
- Inactivates 5-6 log HIV, HCV, HBV and a wide range of other agents
- 166 thrombocytopenic patients (Europe) with PC and BC, adequate increments and few reactions
- 645 thrombocytopenic patients (U.S./SPRINT) equivalent hemostasis and reaction profile*
- Licensed and in use in much of Europe

### Completed INTERCEPT Plasma Clinical Trials

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<th>Phase</th>
<th>Objective</th>
<th>Patients</th>
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<td>I</td>
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<td>II</td>
<td>Factor VII Kinetics</td>
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## I-FFP: Patient Experience

<table>
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<tr>
<th>Study</th>
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<tr>
<td>Congenital Defects</td>
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<td>Acquired Defects</td>
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<td>Plasma Exchange</td>
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<td>3,185</td>
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</table>
Frangible Anchor Linker Effector (FRALE, S-303)

- Used for RBC pathogen reduction
- Tricyclic compound with an alkylating effector
- Intercalates and crosslinks nucleic acid
- Alkylates proteins and membrane proteins
- Removed by resin absorption
Red Cells and Pathogen Reduction

- 2 SC patients receiving Inactine-treated RBC and 2/17 chronically transfused with S-303 developed apparent neoantigen/antibody formation (+ DAT)
- 74 cardiac surgery patients received S-303 treated RBC (with 74 controls)*
  - Equivalent treatment-related morbidity/mortality
  - Equivalent RBC use and HCT rise
  - 2 DAT in each group
  - Increased constipation, less SVT in treated group

*Benjamin et al. Transfusion 2005; 45:1739
Riboflavin (vitamin B2)
Essential nutrient, recommended daily allowance 1.7 mg
Normal viral DNA

Riboflavin is added to blood product. It intercalates into viral DNA.

Blood product is exposed to light, causing chemical reaction which snaps viral DNA spine.
The Mirasol™ PRT Process

- 90% Plasma, 10% Solution
- 50μM riboflavin
- UV + visible light
  Broad spectrum
- 5J/cm² = 6.2 J/ml
  8-10 minutes
- Illumination and storage in one container (ELP)

Navigant
R. Goodrich
Cautions Regarding Pathogen Reduction Technology

- Each technology is different
  - Chemical/biological characteristics
  - Spectrum of pathogen reduction
  - Activity for specific pathogens - “log reduction”
  - Activity in specific components
  - Adducts and metabolites
  - Profile of adverse reactions (toxicity)
Preliminary Results with Prion Filtration

After 300 days, 0/20 hamsters injected with filtered RBC developed scrapie vs. 2/18 controls.
Summary

• Blood in the U.S. and in other developed countries is extraordinarily safe

• Pathogen reduction technologies could add an additional layer of safety, especially for window period infections
Summary

For a “tolerable” Benefit-Risk Profile, a Pathogen reduction Technology should offer:

1. Broad inactivation spectrum
2. Minimal damage to cells
3. Little toxicity potential to the most vulnerable patients
4. A failsafe manufacturing system
Summary

• Pathogen reduction technology is no guarantee against the “next” virus or emerging pathogen

• Geography, blood donor characteristics, the robustness of the health care delivery system may alter the benefit-risk calculus
Steering Committee

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Héma-Québec

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Publications

