L'inattivazione dei patogeni: tecnologie e prospettive

Silvano Rossini
silvano.rossini@hsr.it
Servizio di Immunomatologia e Medicina Trasfusionale
**Il percorso di oggi**

I patogeni emergenti in Medicina Trasfusionale

(Massimo Clementi)

Infezione occulta da Virus dell’Epatite B

(A. Tagger)

I patogeni storici riemergerenti

(G. Gesu)

Cosa possiamo fare?
Transfusion safety

- recruit
- screen donor
- collect & prepare
- infection disease

Risk of infection per unit transfused

Criteria changed
HBV antobody screening began
 HBV antibody screening began
HCV antibody Screening began
HCV antibody Screening began
Testing for HIV and hepatitis B began
NAT for HCV and HIV began

Year

W. Dzik, 2003

S. Rossini
Il problema infettivo

Il rapporto costo/beneficio

Le tecnologie per l’inattivazione
**Screening limitations**
Gaps in current defenses exits, due to the window period and limited screening sensitivity

**New ed emerging pathogens**
A risk that current safety Measures cannot eliminate
**Screening limitations**
Gaps in current defenses exits, due to the window period and limited screening sensitivity

**New ed emerging pathogens**
A risk that current safety Measures cannot eliminate

**Know pathogens**
Routine testing covers only a limited number

**Leukocytes**
Residual cells and cytokines can cause harmful post-transfusion reactions

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Bacteria
The most frequent transfusion-transmitted infection

Screening limitations
Gaps in current defenses exits, due to the window period and limited screening sensitivity

Know pathogens
Routine testing covers only a limited number

New ed emerging pathogens
A risk that current safety measures cannot eliminate

Leukocytes
Residual cells and cytokines can cause harmful post-transfusion reactions

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Il rischio sepsi

- Prevalence of contaminated platelets:
  - 1:2500 random platelet concentrates
  - 1:5000 singol donor platelets (SDP)

- Risk of sepsis
  - 1:50000 with SDP

Castro E. et al., Trasfus Med 3005, Palavecino El et al., Transfusion 2006
Il “Challenge”

- Agenti infettivi nuovi continuano ad emergere
- Agenti infettivi nuovi migrano rapidamente da ospiti non-umani all’uomo
- L’identificazione di patogeni emergenti, la comprensione dell’epidemiologia, lo sviluppo di test diagnostici e la protezione del sangue richiede tempo
Il problema infettivo

Le tecnologie per l’inattivazione

Il rapporto costo/beneficio
<table>
<thead>
<tr>
<th></th>
<th>Acellular Products</th>
<th>Cellular Products</th>
</tr>
</thead>
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<tr>
<td>Plasma and derivatives</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Solvent-detergent</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>Yes</td>
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</tr>
</tbody>
</table>

**Technique targeting nucleic acid**

**Technique targeting membrane**

**Solvent-detergent**

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**Methylene Blue**

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</table>
La (complessa) biologia piastrinica
Gli acidi nucleici come bersaglio per bloccare la proliferazione dei patogeni
Le tecnologie proposte

Intercept – Cerus

Mirasol – Navigant

Macopharma – Theraflex
Intercept (I)

Meccanismo d’ Azione di S-59

S-59

DNA or RNA of pathogen

Intercalation

UVA Activation

Permanent Crosslinking
Intercept (II)

Concentrati piastrinici

Integrated Container Set

SCD

Collected Platelets

Step 1 S-59

Step 2 Illumination

Step 3 CAD

Step 4 Final Storage

UVA Illumination Device
### Table 2. Inactivation of Viruses and Microbial Pathogens by Treatment With Amotosalen and UV-A Light* 109–113

<table>
<thead>
<tr>
<th>Viral Pathogens</th>
<th>Genome</th>
<th>Enveloped</th>
<th>Infectivity Log Reduction</th>
<th>Amotosalen/UV-A Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency 1/2</td>
<td>ss-RNA</td>
<td>+</td>
<td>&gt;6.2 cell free; &gt;6.1 cell associated</td>
<td></td>
</tr>
<tr>
<td>Human T-cell lymphotropic I/II</td>
<td>ss-RNA</td>
<td>+</td>
<td>4.7/5.1 cell associated</td>
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</tr>
<tr>
<td>Hepatitis B</td>
<td>ds-DNA</td>
<td>+</td>
<td>&gt;5.5</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>ss-RNA</td>
<td>+</td>
<td>&gt;4.5</td>
<td></td>
</tr>
<tr>
<td>West Nile</td>
<td>ss-RNA</td>
<td>+</td>
<td>&gt;6.0</td>
<td></td>
</tr>
<tr>
<td>Human erythro B19</td>
<td>ss-DNA</td>
<td>−</td>
<td>4.0–4.9</td>
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</tr>
<tr>
<td>Cytomegalovirus</td>
<td>ds-DNA</td>
<td>+</td>
<td>&gt;5.9 ± 0.3 cell associated</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microbial Pathogens</th>
<th>Gram</th>
<th>Aerobes Vs Anaerobes</th>
<th>Infectivity Log Reduction</th>
<th>Amotosalen/UV-A Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>Neg</td>
<td>Aerobe</td>
<td>&gt;6.4 ± 0.1</td>
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</tr>
<tr>
<td>Serratia marcescens</td>
<td>Neg</td>
<td>Aerobe</td>
<td>&gt;6.7 ± 0.1</td>
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</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>Neg</td>
<td>Aerobe</td>
<td>&gt;5.6 ± 0.2</td>
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</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Neg</td>
<td>Aerobe</td>
<td>4.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Salmonella choleraesuis</td>
<td>Neg</td>
<td>Aerobe</td>
<td>&gt;6.2 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>Neg</td>
<td>Aerobe</td>
<td>&gt;5.9 ± 0.2</td>
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<tr>
<td>Enterobacter cloacae</td>
<td>Neg</td>
<td>Aerobe</td>
<td>5.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Pos</td>
<td>Aerobe</td>
<td>6.6 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>Pos</td>
<td>Aerobe</td>
<td>&gt;6.6 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Pos</td>
<td>Aerobe</td>
<td>&gt;6.8 ± 0.1</td>
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<tr>
<td>Listeria monocytogenes</td>
<td>Pos</td>
<td>Aerobe</td>
<td>&gt;6.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium minutissimum</td>
<td>Pos</td>
<td>Aerobe</td>
<td>&gt;6.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Pos</td>
<td>Aerobe</td>
<td>&gt;5.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus species</td>
<td>Pos</td>
<td>Facultative anaerobe</td>
<td>&gt;6.4 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>Pos</td>
<td>Facultative anaerobe</td>
<td>&gt;6.2 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Pos</td>
<td>Anaerobe</td>
<td>&gt;6.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium adolescentis</td>
<td>Pos</td>
<td>Anaerobe</td>
<td>&gt;6.0 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microbial Pathogens</th>
<th>Class</th>
<th>Infectivity Log Reduction</th>
<th>Amotosalen/UV-A Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treponema pallidum</td>
<td>Spirochete</td>
<td>6.8–7.0</td>
<td></td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Spirochete</td>
<td>&gt;6.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>Protozoa</td>
<td>&gt;5.3</td>
<td></td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Protozoa</td>
<td>&gt;7.0</td>
<td></td>
</tr>
<tr>
<td>Leishmania mexicana</td>
<td>Protozoa</td>
<td>&gt;5.0</td>
<td></td>
</tr>
<tr>
<td>Leishmania major</td>
<td>Protozoa</td>
<td>&gt;4.5</td>
<td></td>
</tr>
</tbody>
</table>
Intercept: utilizzo clinico

- Marchio CE
- 3 trial clinici in Europa (euroSPRITE)
  - 166 pazienti
    - Comparable post transfusion platelet count increment
- Trial SPRINT
  - 645 pazienti
    - 4719 trasfusioni
    - PCT platelet were hemostatically equivalent to the control platelets
La Sicurezza Trasfusionale – Milano, 8 Aprile 2009

**SARS: un patogeno emergente**
**Implicazioni per la sicurezza del sangue**

Amotosalen photochemical inactivation of severe acute respiratory syndrome coronavirus in human platelet concentrates

D. Pinna*, A. Sampson-Johannes†, M. Clementi‡§, G. Poli*§, S. Rossini¶, L. Lin† and E. Vicenzi* 1

Transfusion Medicine. 2005, 15. 269-276

HSR: experimental evaluation
L’epidemia di SARS è stata contenuta, tuttavia....

- Non ci sono farmaci antivirali
- Non c’è un vaccino
- Non è stato identificato l’ospite naturale
- Nessuno può garantire che non possa riemergere

SARS Coronavirus è presente nel sangue degli individui infettati
### Inattivazione di SARS-CoV HSR1 dopo Trattamento con 150 µM S-59 e 3 J/cm² UVA in Concentrati Piastrinici

<table>
<thead>
<tr>
<th>SARS-CoV</th>
<th>Pre-trattamento (pfu/mL)</th>
<th>Volume testato (mL)</th>
<th>Riduzione (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrati piastrinici N = 5</td>
<td>$10^{4.7}$</td>
<td>100 mL (no virus)</td>
<td>&gt; 7.4</td>
</tr>
</tbody>
</table>
Inattivazione del **SARS-CoV-2** da INTERCEPT

Prima

Dopo
**HSR: Clinical evaluation**

<table>
<thead>
<tr>
<th>N. Pit X 10^3/ml average /range</th>
<th>Dose X 10^{11} average /range</th>
<th>CI in 1°h X 10^3/ml average /range</th>
<th>CCI 1°h effectiveness</th>
<th>CI 24°h X 10^3/ml average /range</th>
<th>CCI 24°h effectiveness</th>
<th>Temperature</th>
<th>Haemorrhage</th>
<th>Viral therapy</th>
<th>Antiinfective therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets with treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9862</td>
<td>3,16</td>
<td>7058</td>
<td>14/29</td>
<td></td>
<td></td>
<td>13/29</td>
<td>9/29</td>
<td>22/29</td>
<td></td>
</tr>
<tr>
<td>5000-17000</td>
<td>2,3-3,54</td>
<td>11400-3000</td>
<td></td>
<td></td>
<td></td>
<td>2/29</td>
<td></td>
<td>1/24</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets without treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10000</td>
<td>2,72</td>
<td>9837</td>
<td>18/24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000-16000</td>
<td>1,95-3,5</td>
<td>15000-4000</td>
<td></td>
<td></td>
<td></td>
<td>1/24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
CCI = \frac{(Posttransfusion \ count - Pretransfusion \ count) \times Body \ surface \ area \ (m^2)}{Platelet \ dose \ (x \ 10^{-11})}
\]

Effectiveness is proved whenever:
- **CCI 1° h > 7.5 \times 10^9/L**
- **CCI 24° h > 2.5 \times 10^9/L**

S. Rossini
Pathogen inactivation allows timely release of platelet units to maximize shelf-life

Collection →
Day 0 →
Day 1 →
Day 2 →
Day 3 →
Day 4 →
Day 5 →
Day 6 →
Outdate →

Before culture →
Serology/NAT →
Release →
Bacterial culture →
Pre-incubation →
Begin culture →
Release →
“negative to date” →
Final result →

INTERCEPT →
Inactivation →
Release →

Five years of experience with INTERCEPT blood system in routine use.

Dr. E. Castro

Cada vez más cerca de las personas
Le tecnologie proposte

Intercept – Cerus

Mirasol – Navigant

Macopharma – Theraflex
Mirasol

**RIBOFLAVIN**  
**Vitamin B2**

- Essential nutrient. RDA ~1.3-1.7mg/d
- Intake 1>10-50mg/d in food
- I/V therapy ~ 30-50mg/d
- Up to 1000mg/d ‘safe’.
- Plasma level $m_{24}$, range 9-79nM [USA]†

- **LUMICHROME** formed naturally in riboflavin solutions
- Dose in IV preparations. 5-25mg/d
- Normal plasma level $m_{11}$; range 0-75nM [USA] †

- **Phototherapy of Neonatal Jaundice.**
- ~2-3d @ 420-470nm; 4μW/cm².
- Lumichrome etc formed *in vivo*.
- Riboflavin supplements given; 300-400 μg/kg/d IV or PO, 4+d

- No harmful effects. No excess neoplasia
- [Olsen et al 1996, Cancer Causes & Control, 7, 411-414; 55120 children followed 16 years]
The Mirasol PRT system applies light* and riboflavin to reduce the pathogen load in labile blood products by several mechanisms including the three distinct modes of action shown below.

In blood products, viral, bacterial, and parasitic nucleic acids absorb low wavelength photons (hv) resulting in nucleic acid damage (direct UV light effect).

Riboflavin interacts with nucleic acids, causing additional irreversible nucleic acid damage through electron transfer chemistry, primarily between riboflavin and guanine.

In all blood products, “Reactive Oxygen Species” (ROS) are generated by riboflavin and light, resulting in irreversible nucleic acid damage through various oxidative reactions.

*The Mirasol PRT system uses low wavelength light.
MIRASOL PRT system

1. Transfer PLT product to Mirasol Illumination bag

2. Add Riboflavin Solution (2nd sterile dock)

3. Illuminate for ~ 10 min.

S. Rossini
• Safe – Use of a natural compound with known safety profile

• Effective against broad range of viruses, bacteria, parasites, as well as white cells

• Simple – Process does not require removal of compounds
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<tr>
<td>Human immunodeficiency 1/2</td>
<td>ss-RNA</td>
<td>+</td>
<td>5.93 ± 0.20 cell associated and cell free; 4.46 ± 0.39 intracellular</td>
</tr>
<tr>
<td>West Nile</td>
<td>ss-RNA</td>
<td>+</td>
<td>5.19 ± 0.50</td>
</tr>
<tr>
<td>PPV (surrogate for human erythro B19)</td>
<td>ss-DNA</td>
<td>-</td>
<td>≥5.03</td>
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<td><em>Escherichia coli</em></td>
<td>Neg</td>
<td>Aerobe</td>
<td>≥4.38</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>Pos</td>
<td>Aerobe</td>
<td>≥4.5</td>
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<tr>
<td><em>Leishmania donovani infantum</em></td>
<td>Protozoa</td>
<td>≥5.0</td>
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</table>

* Apheresis platelets were treated with 50µM riboflavin and 6.2 J/mL UV-A light. PPV indicates porcine parvovirus; ss, single stranded; ds, double stranded; +, presence of an envelope; −, no envelope; Neg, gram negative; and Pos, gram positive.
Le tecnologie proposte

Intercept – Cerus

Mirasol – Navigant

Macopharma – Theraflex
Theraflex

- Short wave UVC (254 nm)
Theraflex Kit

Apheresis / Buffy-coat derived Platelet Concentrate

Transfer of plasma-reduced platelet concentrates in SSP+

UVC Illumination (< 60 sec)

Storage/Transfusion

Highly UV transparent polyolefin acetate bag for irradiation

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THERAFLEX UV System for Platelets

MACOTRONIC UV Illuminator (CE pending)
Status / Planning –
THERAFLEX UV Platelets:

Preclinical phase A
- efficiency (bacteria, viruses, leucocytes)
  - platelet quality

- Preclinical Phase B
  - neoantigens,
  - cytokines, parasites

- Clin. Phase I study (recov. & survival)
- Clin. Phase I, full unit, Volunteer, Tolerance Study
- Phase III Clinical Study (Thrombocytopenic Patients)

- CE registration
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<tr>
<td>Methylene Blue</td>
<td>Yes</td>
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<tr>
<td>Psoralen (S59) Amotosalen</td>
<td>Yes</td>
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<tr>
<td>Riboflavin</td>
<td>Yes</td>
</tr>
<tr>
<td>UV-C</td>
<td>Yes</td>
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<td>Acellular Products</td>
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<tr>
<td></td>
<td>Plasma and</td>
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<tr>
<td></td>
<td>derivatives</td>
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### Tecnique targeting nucleic acid

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<th>Amotosalen</th>
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<th>UV-C</th>
<th>FRALE ( S503)</th>
<th>Inactine</th>
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</thead>
<tbody>
<tr>
<td>Solvent-detergent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Methylene Blue</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Psoralen ( S59)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
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<tr>
<td>Amotosalen</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Riboflavin</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
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<td></td>
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<td>UV-C</td>
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<td></td>
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<tr>
<td>FRALE ( S503)</td>
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<td></td>
<td>Yes</td>
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<tr>
<td>Inactine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
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<td></td>
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</table>
Rapporto costo/beneficio

Il problema infettivo

Tecnologie per l’inattivazione
Pathogen reduction: risks versus benefits

➢ Risks
  • Damage to transfusion product
  • Toxicity to processing personnel
  • Toxicity to recipient

➢ Benefits
  • Reduction of known viruses
  • Reduction of bacteria
  • Reduction of parasites
  • Potential reduction of unknown pathogens
  • Eventually elimination of lymphocytes
Inattivazione: si o no?

opzione scientifica

risorse disponibili

(vincolo economico)

paziente

legge

(vincolo legale)
Blood Bank: a new perception

- Organization providing a community service to patients, hospital and donors

HIV

- Drug manufacturing firms that produce and distribute a variety of injectable products.
Legge 21 ottobre 2005, n. 219
"Nuova disciplina delle attività trasfusionali e della produzione nazionale degli emoderivati"

ORGANIZZAZIONE DEL SISTEMA TRASFUSIONALE

Art. 5.

(Livelli essenziali di assistenza sanitaria in materia di attività trasfusionale)

i servizi e le prestazioni erogati dalle strutture del Servizio sanitario nazionale in rapporto alle specifiche competenze disciplinari, con esenzione dalla partecipazione alla spesa, in materia di attività trasfusionali comprendono:

4) esecuzione delle indagini di laboratorio e delle procedure di inattivazione dei patogeni finalizzate alla certificazione dei requisiti di qualità e sicurezza previsti dalla legislazione vigente per le unità di sangue e gli emocomponenti, con particolare riferimento alla prevenzione delle malattie trasmissibili con la trasfusione;
**Inattivazione: un problema di economia sanitaria?**

- **Assessment of the economic value of the Intercept blood system in Belgium.**
  - K. Moeremans, Transfusion Medicine, 2006; 16, 17-30
  - 3459200 € - 195364 € Quality Adjusted Life Years (QALY)
  - NAT: 2-3 million per lifeyear

- **Cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherland.**
  - 554000 € net cost per life year gained (LYG)
La decisione sulle nuove tecnologie

- Il ruolo delle Società Scientifiche
- Consensus Conference – Canada (2007)
  - Is the current risk of transfusion-transmitted disease acceptable in relation to other risk of transfusion?
  - What minimum acceptable safety and efficacy criteria should be put into place for the pre-approval assessment of pathogen-inactivated products?
  - For PI technologies that have been approved by the regulatory authorities, what implications should be considered prior to their widespread adoption?

Large adequately powered randomized clinical trials should be performed to evaluate and/or to confirm the effectiveness of any new PI technology. Post-licensure phase IV studies should be integrated with haemovigilance systems to enhance the ability to detect adverse events.
The Canadian Consensus Conference on Pathogen Inactivation in March 2007

- During the Consensus Conference on Pathogen Inactivation the consulting panel of experts recognized that based on the relatively low rates of post-tranfusion infections with the most well-known agents (e.g. HIV or HBV), pathogen reduction cannot be recommended.

- However, the same panel acknowledged that emerging pathogens have been detected in blood donors at an increasing rate since the HIV epidemic.

- The strategy of surveillance, identification and development of test, allows a new agent spread widely even before the disease can be recognized. Such situations undermine confidence in the safety of blood supply when they reach public opinion.
A proactive approach in accordance to the precautionary principle would lead to the reduction of the theoretical risk, and help to sustain public confidence in the blood supply.

The precautionary principle is a different way of making decisions to manage great risks when there is significant scientific uncertainty, to meet society expectations that the risk is covered.

The panel believes that pathogen inactivation should be implemented, when feasible technologies were available and were capable of inactivating a broad spectrum of infectious agents.
L’inattivazione dei patogeni:
una nuova sfida per la nostra mission

Quality in the clinical use of blood products implies administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of process and the outcome

Blood safety in the European Community:
An initiative for optimal Use 20-22 May 1999, Germany

S. Rossini
….Waiting for the future of

tranfusion medicine .......

Thank you