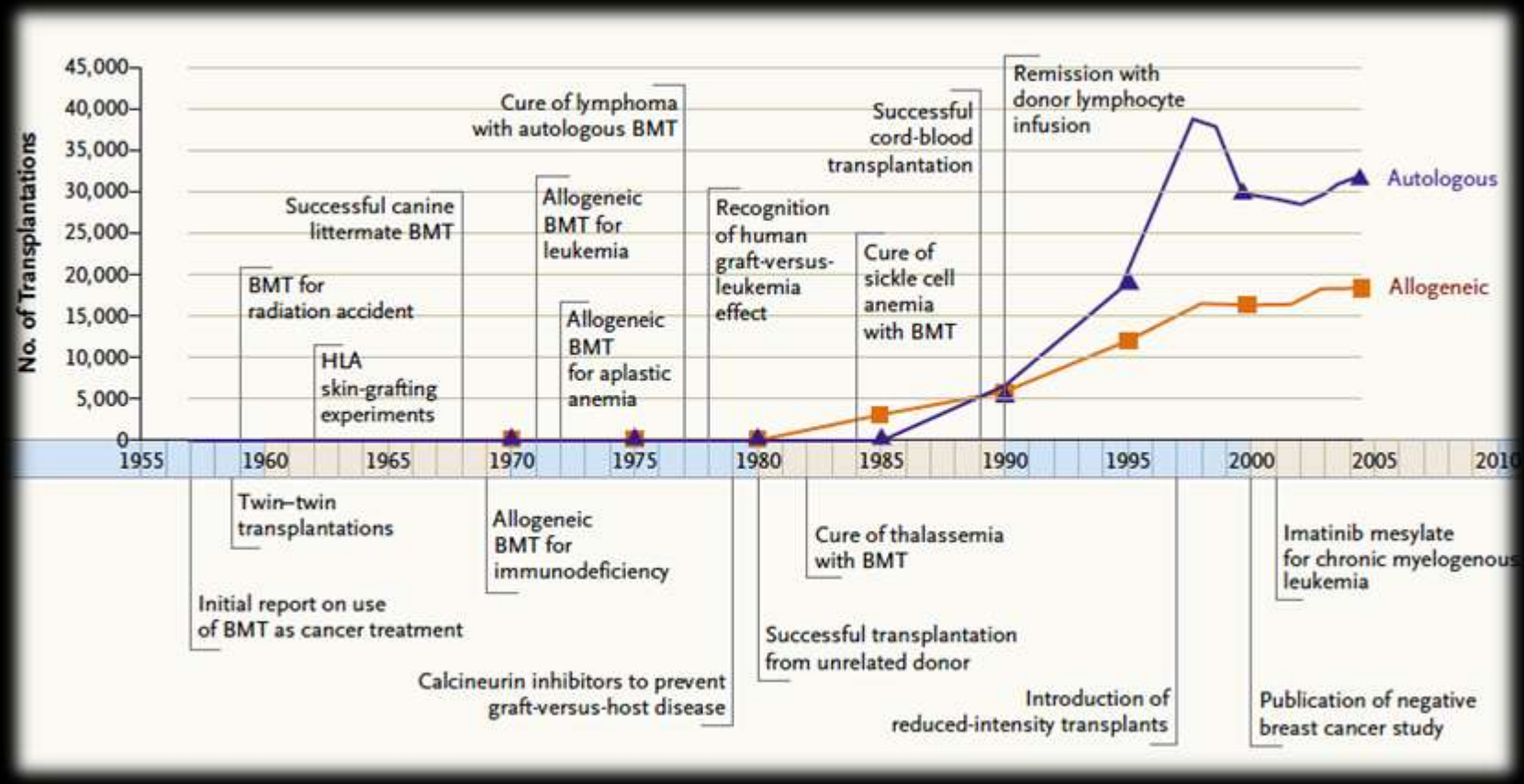
XV CORSO NAZIONALE
DI AGGIORNAMENTO
SIdEM

SIdEM

ATTUALITÀ NELL'USO DELLE PIASTRINE INATTIVATE

Angelo Ostuni

Pia Fondazione di Culto e Religione Card. G. Panico
Azienda Ospedaliera – Tricase (Lecce)
U.O.C. Medicina Trasfusionale

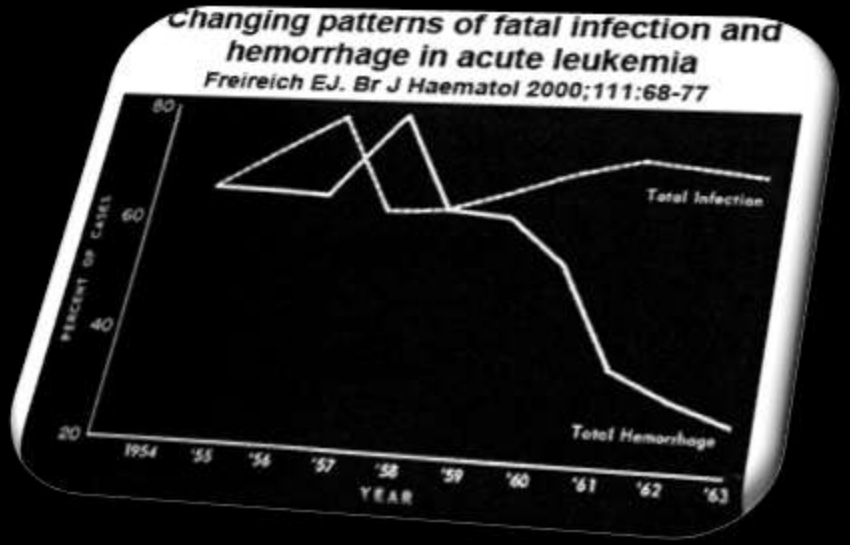


PIASTRINE

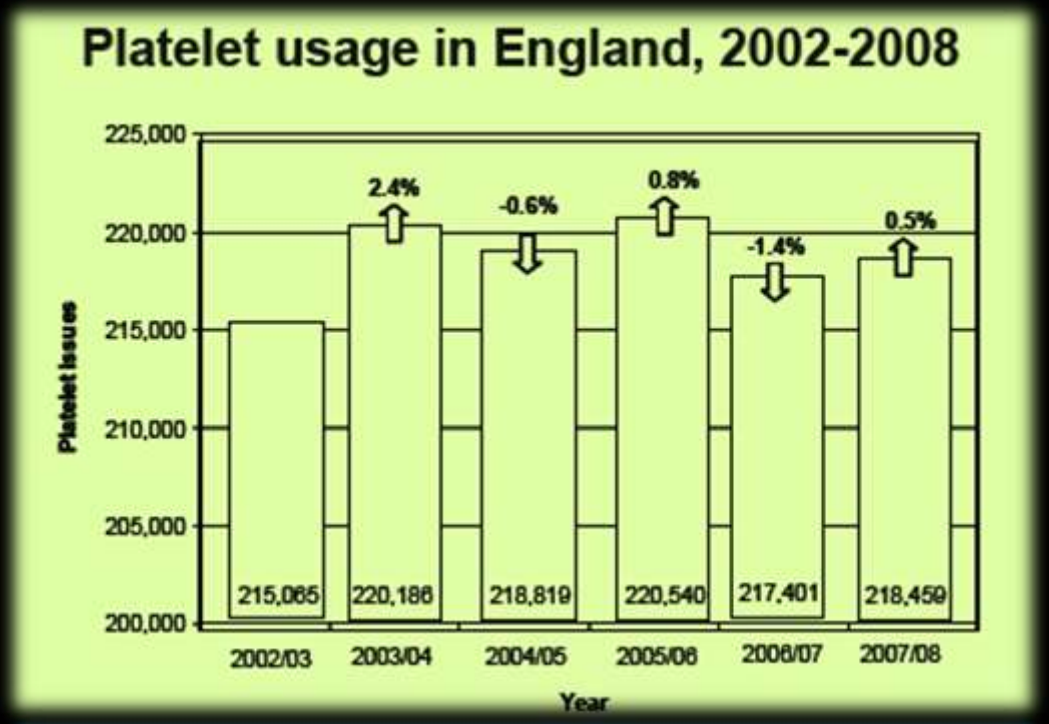
emocomponente indispensabile per i pazienti piastrinopenici …

Hersh et al. JAMA 1965;193:99-103
- **414 patients over 10 years from 1954-1963**
- **Fatal hemorrhage reduced from 67% to 37%**

Han et al. Cancer 1966;19:1937-1942
- **Post-mortem examinations on 57 patients with acute leukaemia between 1963 and 1965**
- **19/27 (63%) died due to bleeding before platelet transfusions in 1964 and 4/30 (15%) after their introduction (p = < 0.001)**



1. *Whatis the **correct dose**ofplatelets, and howoftenshouldtheybegiven?*
2. *Whatshouldbe the '**trigger**' forprescribingprophylacticplatelets?*
3. ***Prophylaxis** versus **no prophylaxis**?*



Audit of the use of platelets in hematology in UK, 2006

Major clinical specialty user is adult hemato-oncology (approx 40% of all platelet transfusions)

2,125 cases from 174 hospitals - median 13/site

Reason for transfusion:

- **55%: prophylaxis**
- **12%: prior to invasive procedure**
- **26%: treat bleeding**
- **7%: none documented**

http://hospital.blood.co.uk/library/pdf/Platelet_%20Audit_St_Elsewhere's_NHS_Foundation_Trust.pdf

Murphy et al. *Transfusion Clinique et Biologique* 2007;14: 509 -513

Mike Murphy,
Professor ofBloodTransfusion Medicine,
National Blood Service, Oxford RadcliffeHospitals

Trasfusione di PIASTRINE → +40% ≈ ultima decade

L'impiego di strategie terapeutiche *intensive* ha determinato un incremento della *domanda*

Aspetti organizzativi ed elegibilità dei Donatori possono costituire un *problema* nel reclutamento dei candidati alla donazione in aferesi

... sicurezza dei prodotti ...

EVENTI AVVERSI POST-TRASFUSIONALI

(Giustini C *et al*, 2006)

INFEZIONI VIRALI

THE PARADOX

Bloodhasneverbeensafer

Safeisnotenough

(AJ Alter)

Despite this, the safety of blood supply remains a source of major public health concern, which requires continuous effort so as to achieve zero risk probability of infection, through advances in molecular screening, improved serology, and viral inactivation technology.

(Velati C et al. *Transfusion*, 2008)

DM 03/03/05 (modifiche DM 27/03/08)

Art. 10 – Validazione biologica delle unità di sangue e/o di emocomponenti

Allegato 7 – parte B

Sierodiagnosi per la lue

HIV-1/2 Ab

HBsAg

NAT HIV

HCV Ab

NAT HBV

NAT HCV

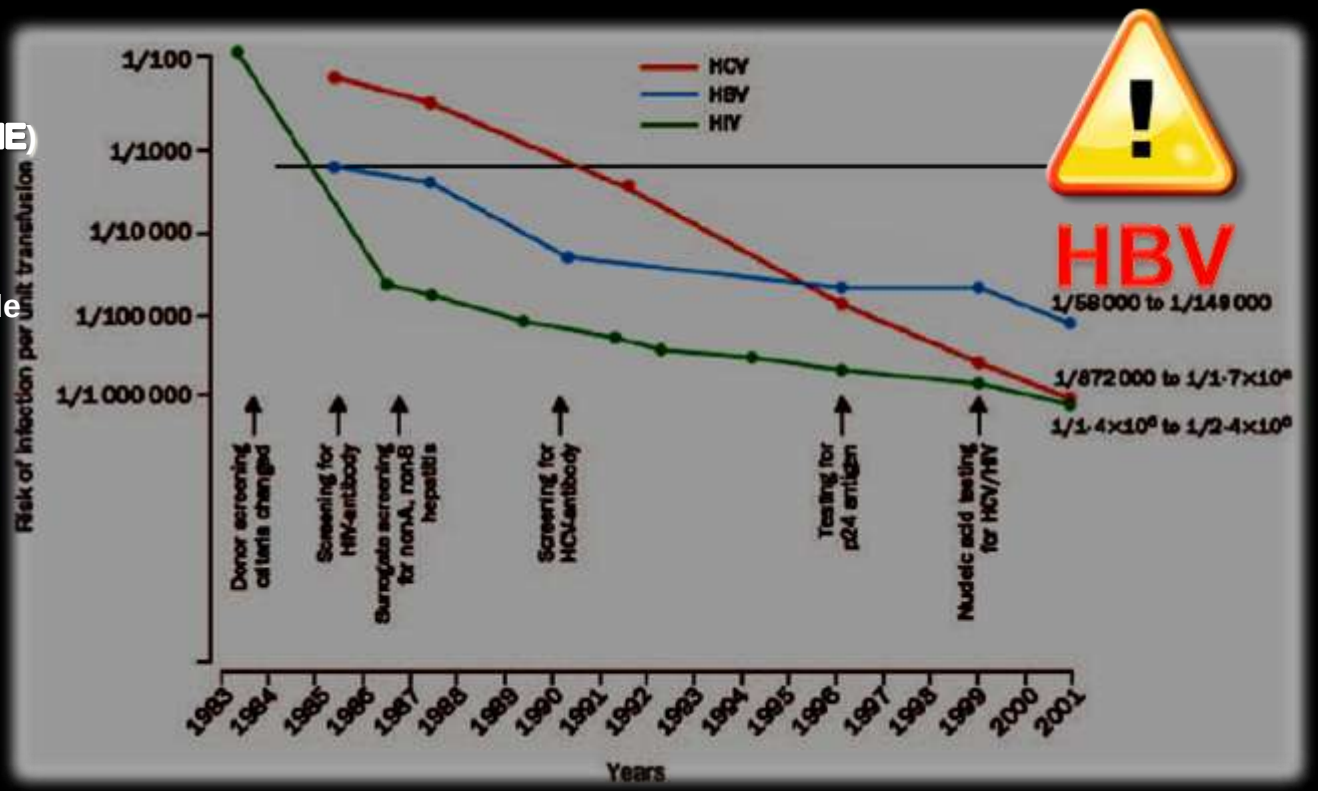
SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare

Riskofinfectiousdiseasetransmission per unittransfusedbyyear, 1983 to 2001
(Brecher ME, Hay SN, 2005)

Contaminazione Batterica(**PIASTRINE**)

Sepsi (piastrine)

Sepsicon esitofatale (**PIASTRINE**)



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Società Italiana di Emaferesi e Manipolazione Cellulare

Impact of nucleic acid testing for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus on the safety of blood supply in Italy: a 6-year survey

Transfusion. 2008 Oct;48(10):2205-13

Claudio Velati, Luisa Romanò, Laura Fomiatti, Lorella Baruffi, Alessandro Remo Zanetti, and the SIMTI Research Group

The **residual risk** for the **three major viral infections** (i.e., HBV, HCV, HIV) **is currently so low** that it can **no longer be assessed** by means of **conventional approaches** such as prospective follow-up and retrospective lookback studies of recipients. Measurement is presently **calculated through mathematical modeling** based on the **incidence of infections among donors** and on the **length of the window phase** of the viral infection.

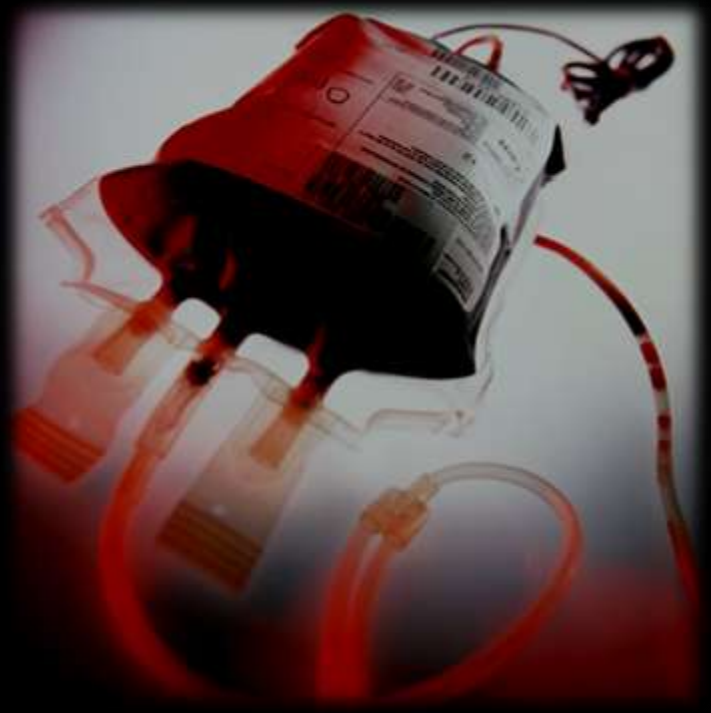
EVENTI AVVERSI POST-TRASFUSIONALI

(Giustini C *et al*, 2006)

Sepsi batteriche

Reazioni brivido-ipertemiche non emolitiche

Reazioni emolitiche acute/ritardate



Disturbi circolatori

Infezioni protozoarie

Reazioni allergico-anafilattiche

Porpora trombocitopenica post-trasfusionale

Immunodepressione

Infezioni Virali

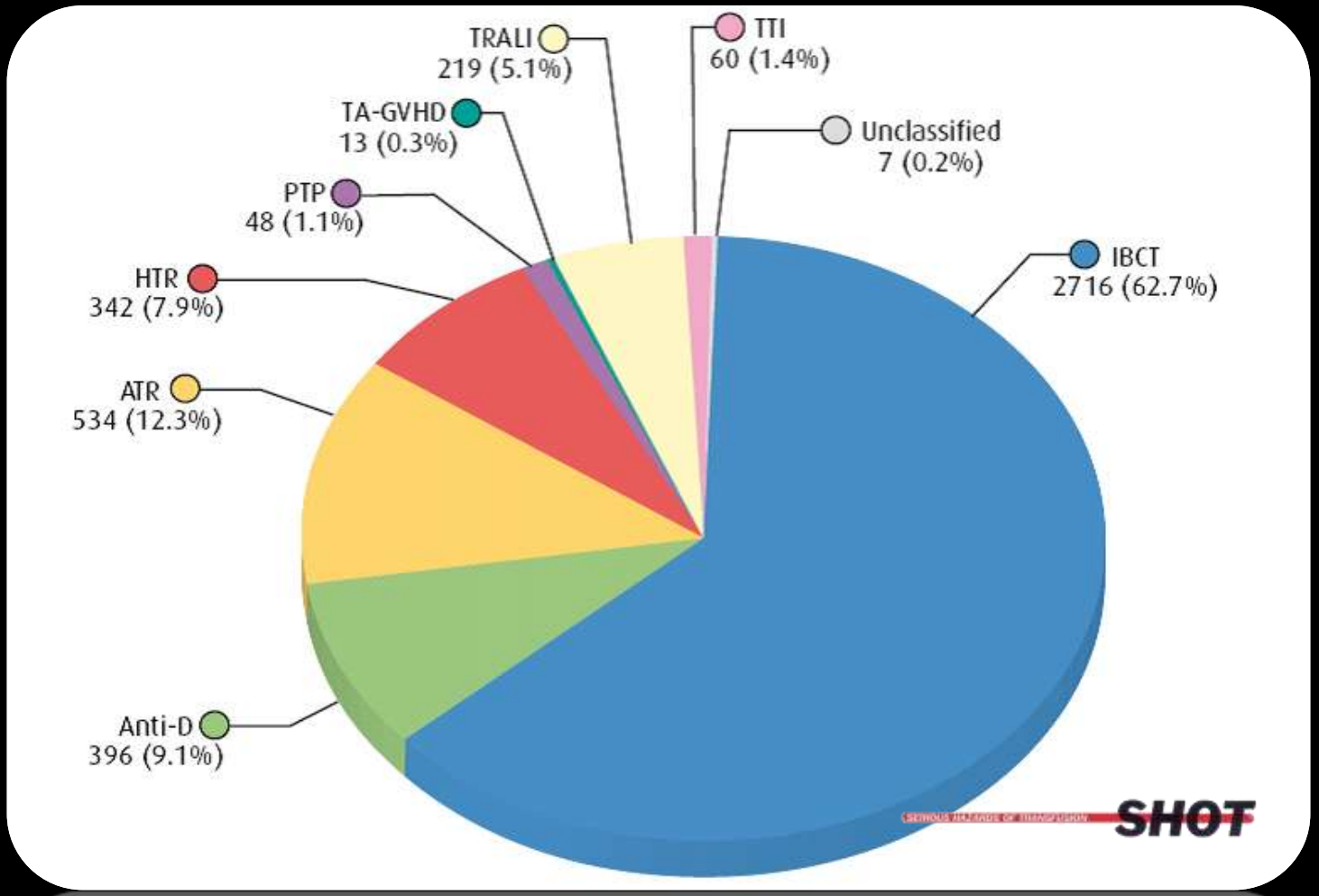
TRALI

(transfusionassociated acute lunginjury)

TA-GvHD

(transfusionassociatedgraft versus hostdisease)

Cumulative data 1996 – 2007 (4335 cases)



Cumulative TTI data shown by SHOT report year

	1996-1997	1997-1998	1998-1999	1999-2000	2000-2001	2001-2002	2003	2004	2005	2006	2007	Total	Death (due to infection)	Major morbidity	Minor morbidity
Bacteria	3	1	6	5	4	5	3	0	2	2	3	34	8	23	3
HAV	1	0	0	0	0	0	1	0	1	0	0	3	0	2	1
HBV	1	2	2	1	1	0	2	0	1	0	0	10	0	10	0
HCV	1	0	1	0	0	0	0	0	0	0	0	2	0	2	0
HEV	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1
HIV	1	0	0	0	0	0	1	0	0	0	0	2	0	2	0
HTLV	0	0	0	0	1	1	0	0	0	0	0	2	0	2	0
Malaria	1	0	0	0	0	0	1	0	0	0	0	2	1	1	0
Prion	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0
vCJD	0	0	0	0	0	0	1	0	1	1	0	3	3	0	0
Total	8	3	9	6	6	6	9	2	5	3	3	60	12	43	5

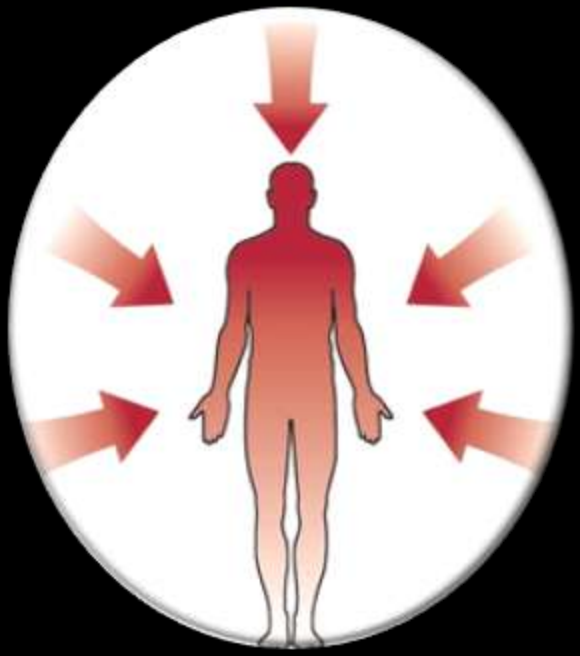
Attualirischiassociatiallatrasfusione

Batteri

rischioditrasmissione con emocomponenticontenenti*piastrine*

Patogeni nuoviedemergenti

Rischioreale e non eliminabile



Limitidei test di screening

Periodofinestra e test di screening

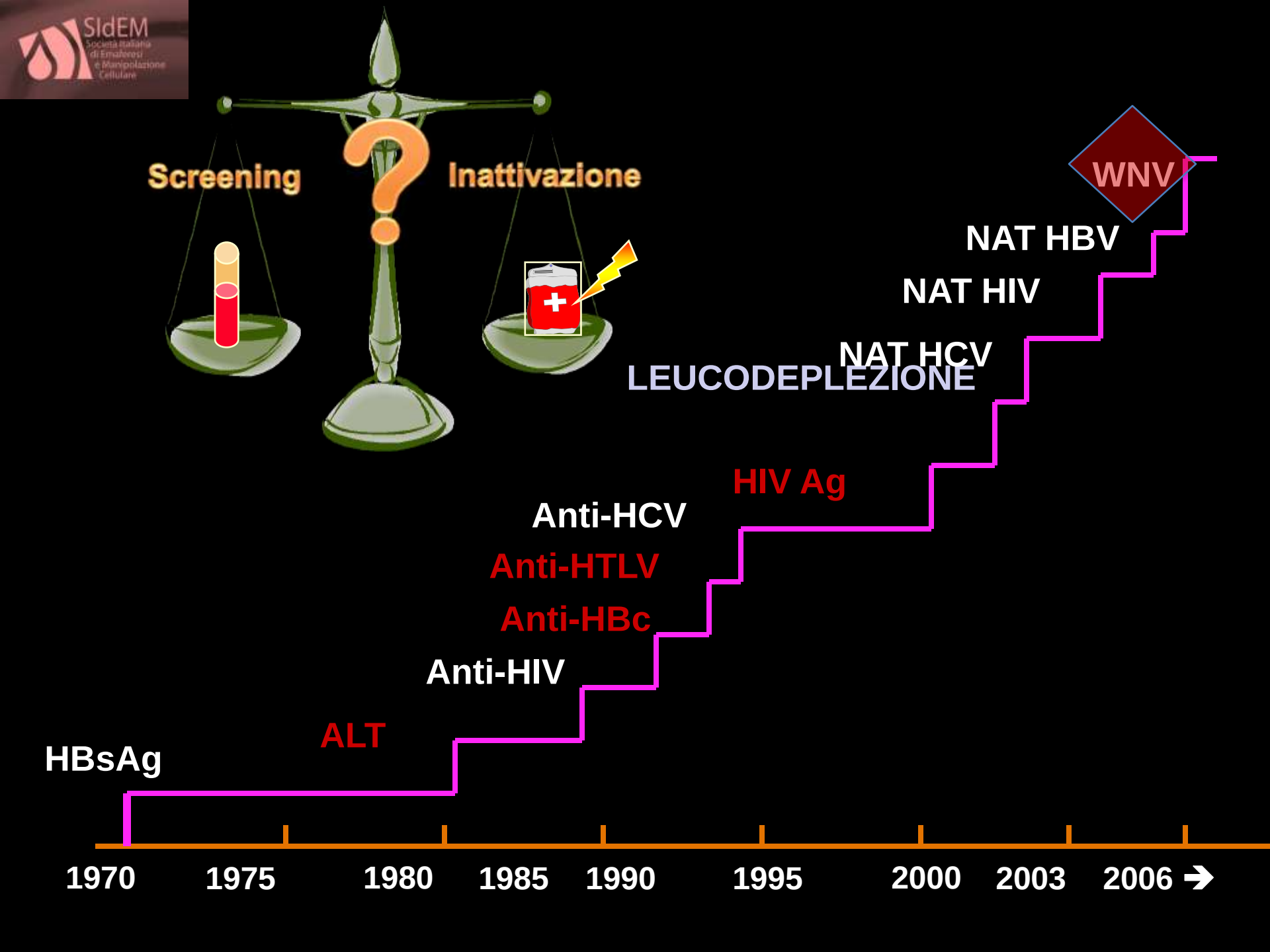
Leucociti

rischiodireazione post-trasfusionale

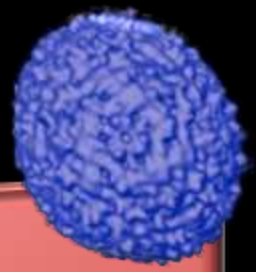
Patogenisconosciuti

Assenzadi test validi? Investimenti ?

La maggior parte deipazientisonoaffettidagravi patologie con sistemaimmunitariocompromesso


SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare
Screening
Inattivazione
WNV
NAT HBV
NAT HIV
NAT HCV
LEUCODEPLEZIONE
HIV Ag
Anti-HCV
Anti-HTLV
Anti-HBc
Anti-HIV
ALT
HBsAg
1970
1975
1980
1985
1990
1995
2000
2003
2006

West Nile Virus



INFEZIONI CORRELATE A TRASFUSIONI NEGLI USA:

2002: 23 casi di infezione trasfusionale dimostrati (GR, PLT, PFC)

2003: su circa 1milione di donazioni testate, lo 0,03% è risultato positivo (la maggior parte dei donatori sono rimasti asintomatici)

Dal 2003, tutte le donazioni in USA sono testate con NAT-WNV

Nel 2008, WNV fa la sua comparsa in Italia...

Parasites and Blood

Althoughasmanyas 25 knownpathogensmaybepresent in blood, **onlyHIV – HCV – HBV and a fewothers are requiredtobescreenedaftercollection.**Detection tests are notyetdeveloped or implementedforallrecognizedpathogens, includingparasites.

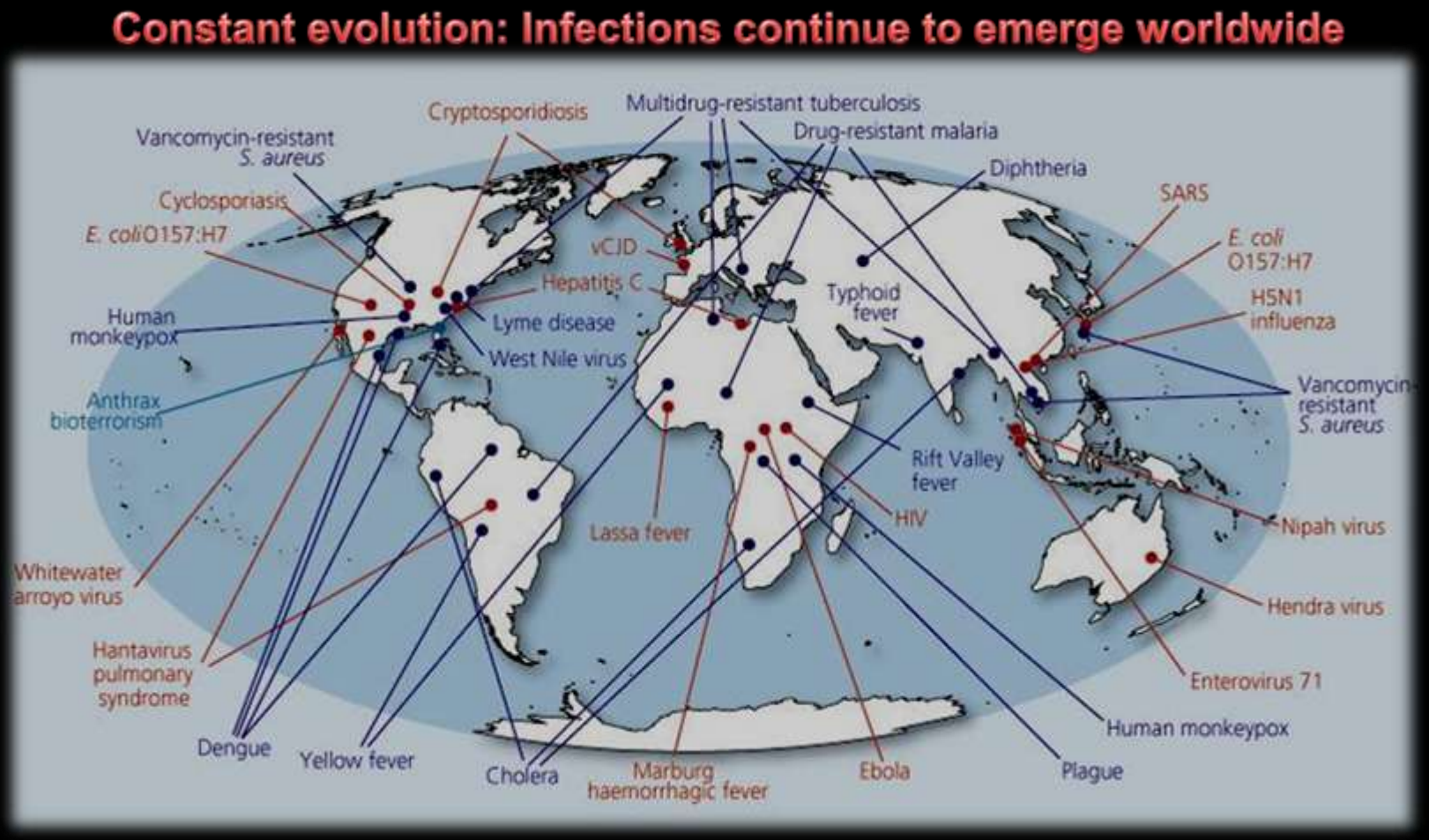
Risksfromparasites: withthe increase in global travel and migrationover the last 20 years, blood-borneparasiticdiseasessuchas malaria and Chagas' diseaseshavebecome more common in bloodtransfusionsthroughoutEurope. Parasite screening tests are notroutinelyused, and donorinterviewsremain the primarydefenseagainstsuchinfections

Malaria: Globally, malaria isestimatedtoinfect 300 - 500 million people everyyear in tropicalregions. Thoughprimarily spread by mosquito bite, the **disease can betransmittedthroughbloodtransfusion**, whichaccountedfor**91 cases in the US between 1963 and 1999**. Currently, donorswhohavevisitedareas in which malaria isendemicmaybedeferredfromdonatingbloodforsixmonths.

Chagas' Disease*Trypanosomacruzi*, the causative agentofChagas' disease, isendemic in muchof South America. Although the **disease can betransmittedthroughbloodtransfusionand hasbeendocumented in the US and Canada**, routine screening ofbloodfor*T. cruzi*isnotperformed. Studies in the US (Los Angeles, California) haveindicatedthat in some regionsasmanyas 1 in 7500 blooddonors show evidenceofinfection.

Leishmaniasis: causedby the *Leishmania sp.*, is a seriousillnessendemictosubtropicalregions. Recentstudiesof Leishmania/HIV co-infectionhaverevealedthat the trueprevalenceof Leishmania in Spain and SouthernEuropemaybeunder-reported and the parasite can pose a serioushealthrisktoimmunocompromisedpatients

... uno scenario alquanto complesso ...



Newly emerging diseases (Red)

Re-emerging/resurging diseases (Blue)

elevato rischio contaminazione batterica

CONCENTRATI di PIASTRINE

terrenodicoltura

Acqua +

Proteine +

Medium +

Zuccheri +

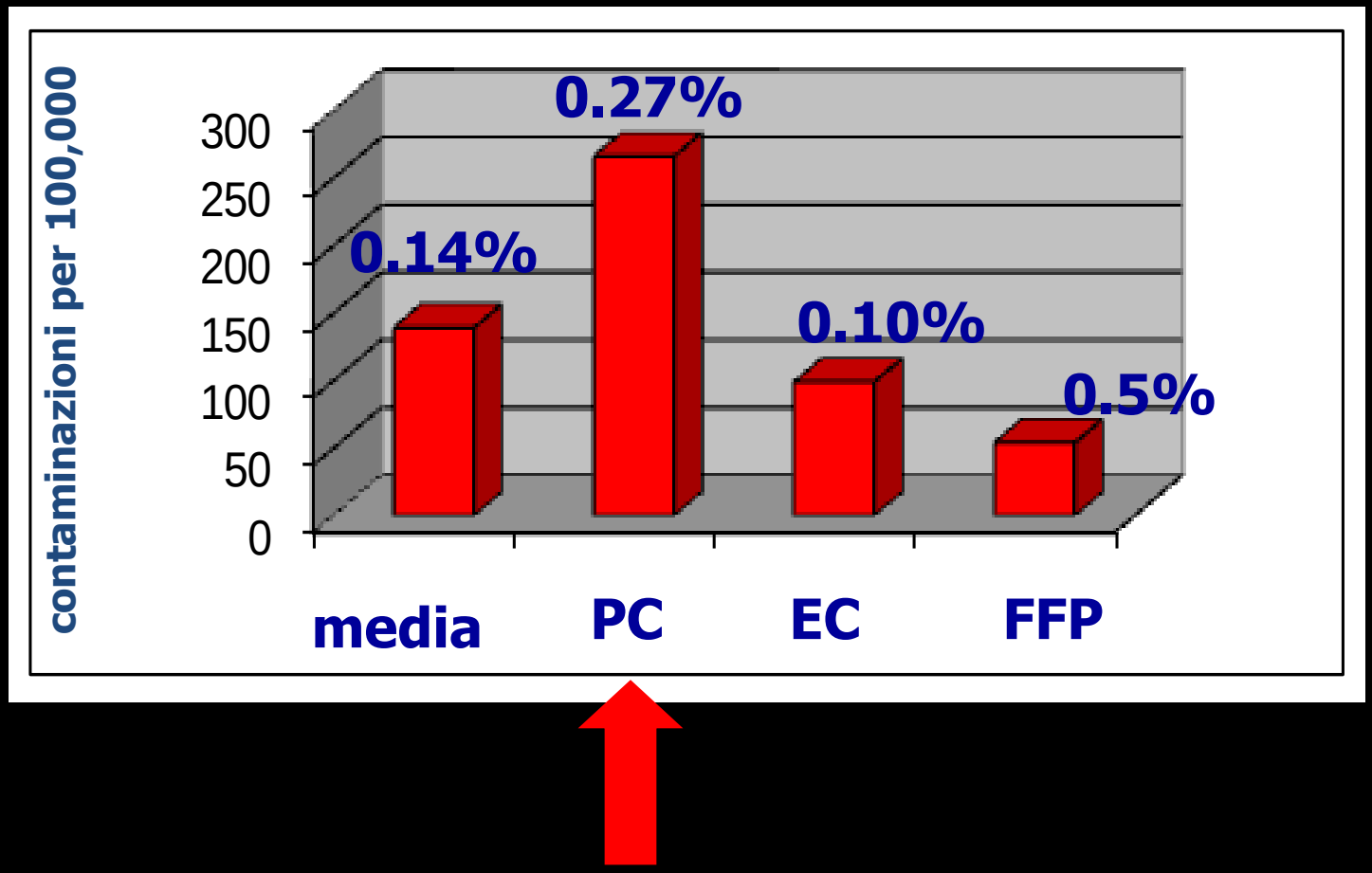
Vitamine +

Sali …

Germania, Survey 2001: contaminazione batterica emocomponenti

6.234.637 emocomponenti prodotti

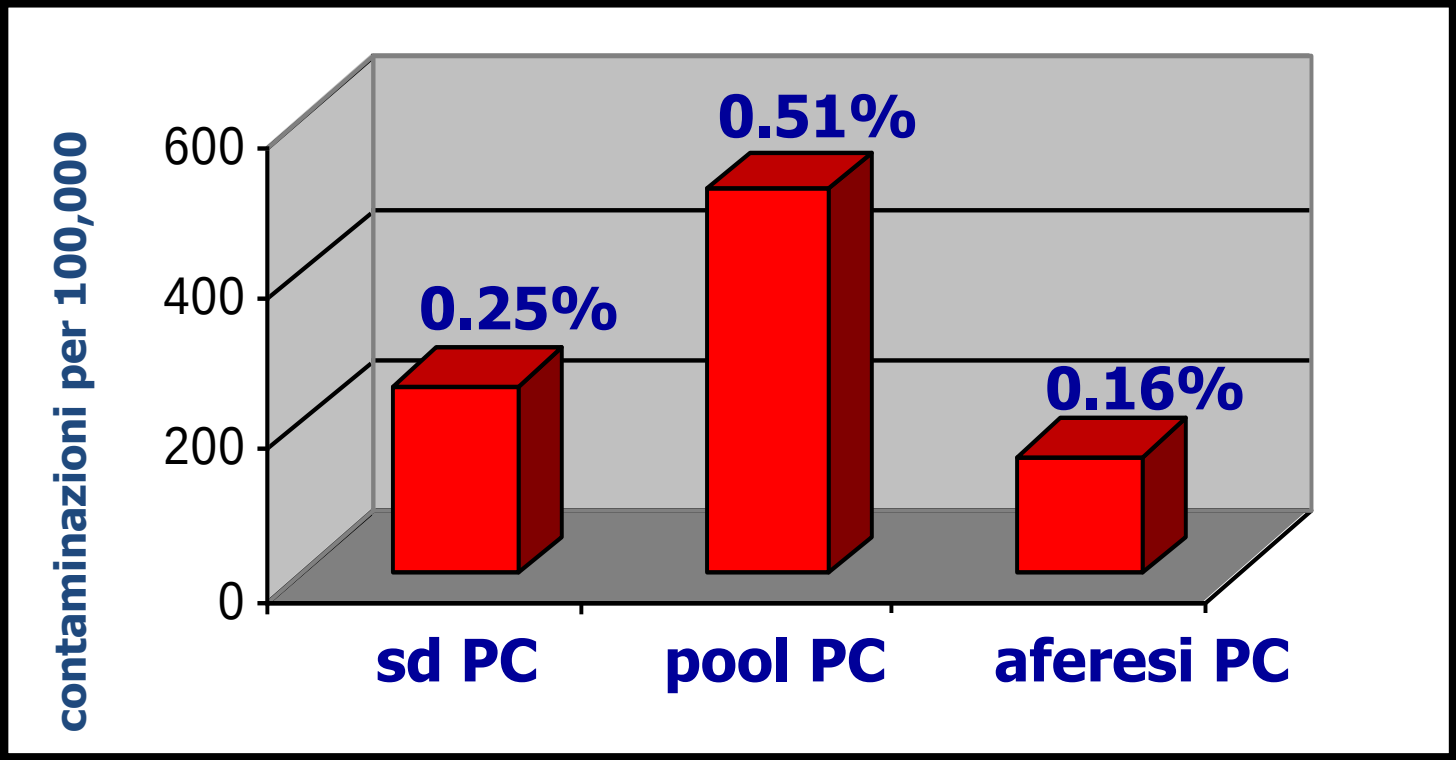
63.844 testati secondo le linee guida nazionali



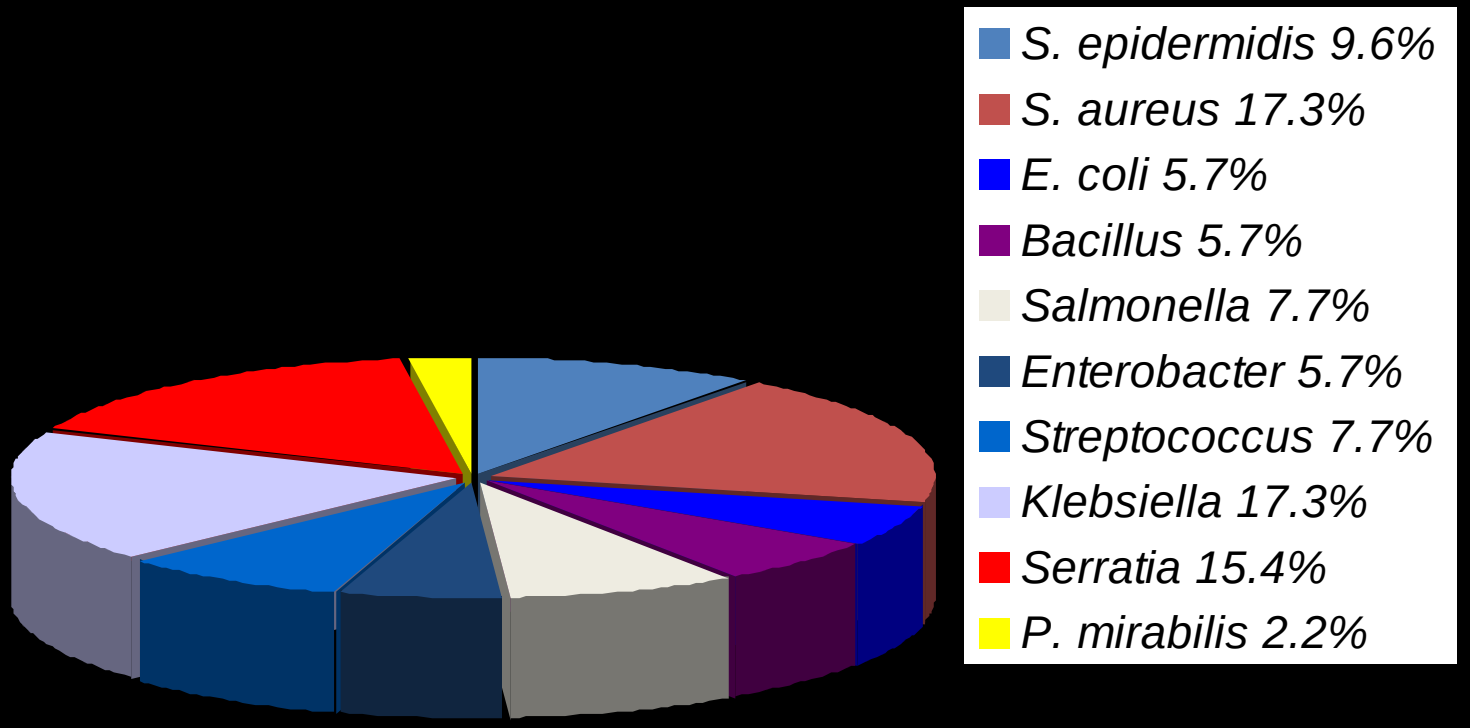
Germania, Survey 2001: Contaminazione batterica delle piastrine

315.218 piastrine prodotte

11.097 (3.5%) testate secondo le linee guida nazionali

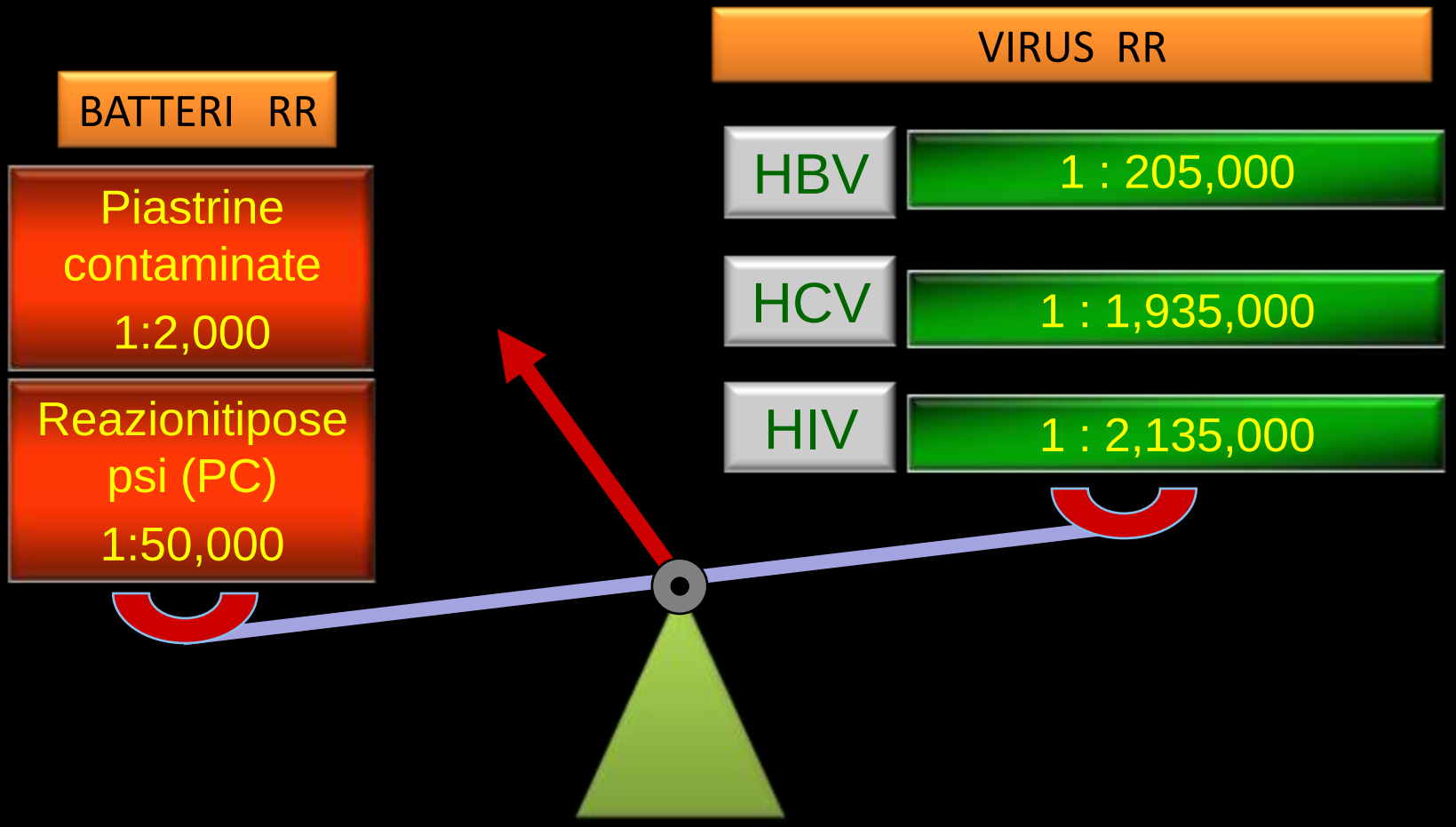


Bacterial species in platelets implicated in septic fatalities reported to the FDA (1976-1998)



Transfusion 2001;41:1493-99; www.shot.demon.co.uk/toc

Rischioresiduo



Evoluzione di un percorso finalizzato alla riduzione del rischio

- Criteri di selezione dei Donatori
- Diversione del volume iniziale di sangue prelevato al momento della raccolta
- Sistemi per la verifica della sterilità del prodotto
- Test di screening e test di amplificazione genica
- Inattivazione/Riduzione dei patogeni

Riduzione del rischio …

individuare i *singoli* agenti patogeni trasmissibili con il sangue e gli emocomponenti?

limitare la trasmissione attraverso sistemi in grado di *inattivare/ridurre* i patogeni?

Criteri di selezione dei Donatori

DM 3 marzo 2005 / Legge 219/05 ➔ criteri di selezione del Donatore per ridurre il rischio di trasmissione di patogeni

Interventi *specifici* del Centro Nazionale Sangue e delle strutture regionali (CRAT) ➔un ulteriore contributo al raggiungimento dell'obiettivo su indicato (es. West Nile … Dengue … Chikungunya …)

Diversione del volume iniziale di sangue prelevato al momento della raccolta

Table II

Reduction of the percentage of bacterial contamination of blood components achieved with different volumes of diversion in studies from 1995 to 2007

Reference	Year of publication	Country	Production procedure/blood component analysed	Volume of diversion (mL)	Reduction of contamination of the blood components (%)
Olthuis H[34]	1995	The Netherlands	Plasmapheresis	10	88
Bruneau C[37]	2001	France	Whole blood	15 (+15)	72
Schneider T[38]	2002	France	PC from BC pools	Not stated	58
Bos H[39]	2002	The Netherlands	PC from BC pools	10	53
Yedema T[40]	2003	The Netherlands	PC from BC pools	20	60
de Korte D[41]	2002	The Netherlands	Whole blood	10	40
McDonald CP[45]	2004	United Kingdom	Whole blood	20	47
Robillard P[46]	2005	Canada	PC from whole blood	40	90
De Korte D[44]	2007	The Netherlands	PC from BC pools	20–30	49
Eder AF[33]	2007	USA	Platelets from apheresis	40–50	47

PC, platelet concentrates; BC, buffy coat.

G.M. Liumbruno et al., Blood Transfusion, 2009 Aprile; *Reduction of the risk of bacterial contamination of blood components through diversion of the first part of the donation of blood and blood components*

De Korte D et al.,Transfusion. 2006 Mar;46(3):476-85: *Effectsofskindisinfectionmethod, deviation bag, and bacterial screening on clinicalsafetyofplatelettransfusions in the Netherlands.*

Murphy et al., Vox Sanguinis 2008: *Screening platelet concentrates for bacterial contamination: low numbers of bacteria and slow growth i contaminated units mandate an alternative approach to product safety.*

valutazione del rischiodicrescitabatterica

- È universalmentericonosciutoche la conservazione a temperaturaambienterappresentaunacondizionefavorevole per la crescitabatterica➔
- Questorappresenta un limite ➔ conservazionedellepiastrine a 5 giorni (…)
- La necessitàdisupportareipazienti con un numeroelevatodi CP fasìcheilrischiosiasottostimato: una media di 6 8 trasfusionicorrispondono ad un rischiopari a 1:340 (*)
- Il rischiodisepsirisultaessere fatale in 1 casosu 4 ([1])

*Using per unit rate of 1:1,000–3,000 from Yomtovian R. *Transfusion*. 2004; **44**:450–60.

1. Kuehnert MJ, et al. *Transfusion.* 2001;**41**:1493–99.

Sistemi per la verifica della sterilità del prodotto

Bacterial Contamination of Platelets for Transfusion: Recent Advances and Issues

Chelsea A. Sheppard, MD; Cassandra D. Josephson, MD; Christopher D. Hillyer, MD

Posted: 12/15/2006; Laboratory Medicine. 2006;36(12):767-772. © 2006 American Society for Clinical Pathology

Table 1. Description of Tests Capable of Detecting Bacteria

Methodology	Comments
Culture-based methodology:	
BacT/ALERT 3D Automated Microbial Detection System (bioMérieux, Durham, NC)	Detects CO_2 production by bacteria; FDA approved for quality control; Semi-closed system; Detects 5-10 CFU/mL (12-26 hr incubation);4 mL required
Culture-based methodology:	
(Pall eBDS, Pall Corporation, East Hills, NY)	Measures O_2 consumption by bacteria; FDA approved for quality control; Completely closed system; Requires 5-6 mL (concentrated to 2-3 mL)
DNA/RNA-based amplification and non-amplification, Chemiluminescence systems	Highly sensitive and specific; Requires highly conserved target by all bacteria or multiple primers and large inoculum; In experimental use only
Tests detecting changes in metabolic parameters or physical elements (glucose concentration, pH, platelet swirling)	Low sensitivity and specificity; Platelet concentration of the sample can affect results; Can be used at point of issue; Validation and QC difficult
Flow or static cytometry:	
(Scansystem, Hemosystem, Marseilles, France [laser-based, solid-phase cytometry])	Recently approved in Europe; Rapid (30 hr incubation and 90 min test time); Acceptable sensitivity and specificity; Requires reagent antibody to highly conserved common antigen or multiple reagent antibodies; 3 mL required
Bacterial cell wall component detection systems:	
(Platelet PGD test, Verax Biomedical, Worcester, MA)	Rapid (20 minutes); Lateral flow format; Sensitivity (10^3 to 10^4) in preliminary trial; 0.5 mL required In experimental use only

Sistemi per la verifica della sterilità del prodotto

BACTERIAL DETECTION in PLATELETS

Although BacT/ALERT in widespread use:

- Different sampling times and volumes!
- Different incubation times!
- Differences in culture media - some use aerobic only - others also include anaerobic!
- Detect gross contamination or low level organisms?
- Some release 'negative-to-date' - others wait for a minimum defined incubation period!
- Different reasons for testing - risk reduction - extended shelf life to 7 days - both?

Very confusing situation!

TEST DI SCREENING E TEST DI AMPLIFICAZIONE GENICA

L'efficacia della ***BIOLOGIA MOLECOLARE*** nel ridurre il periodo finestra sierologico dipende dalla cinetica di replicazione nella fase di "*ramping*": tanto minore è il tempo di replicazione, tanto più efficace è la riduzione del periodo finestra

Tempo di raddoppiamento del virus nel plasma

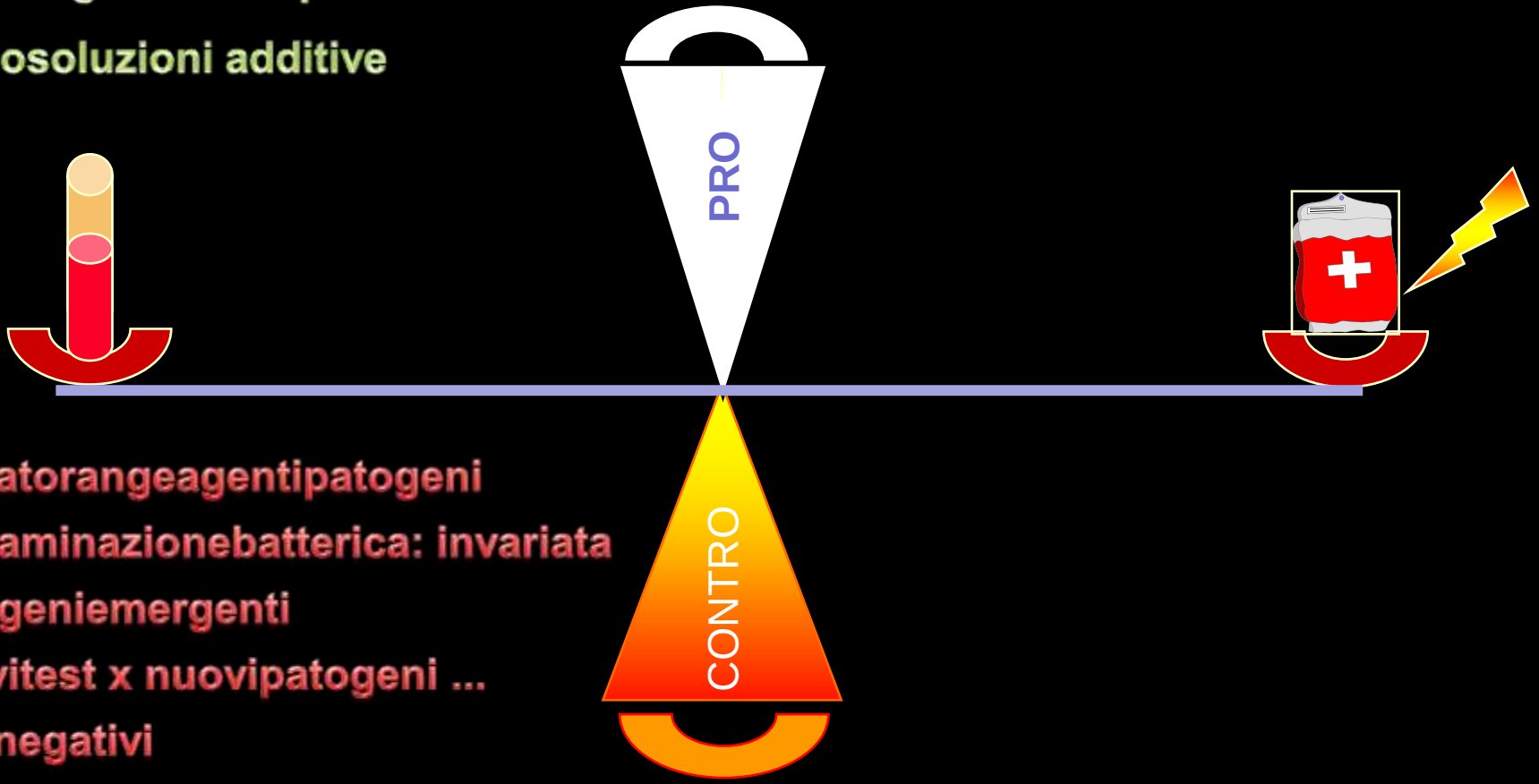
- HCV: 15 ore (da 66 a 7-14 giorni)
- HIV: 20 ore (da 21 a 11 giorni)
- HBV: 2,6 giorni (da 56 a 46 giorni con NAT in MP, a 30 giorni con NAT in singolo)

VIRUS (???)

siamo autorizzati a pensare che, in presenza di un reale rischio di infezione da parte di patogeni non noti o non presenti fino a quel momento in un determinato Paese, vi sia una percezione soggettiva del rischio trasfusionale troppo elevata rispetto al dato oggettivo?

Test di screening

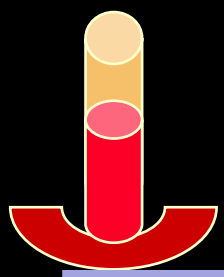
- Tutti gliemocomponenti
- Nosoluzioni additive

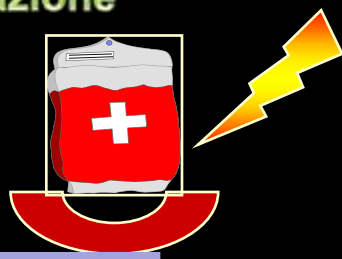


- limitatorangeagentipatogeni
- contaminazionebatterica: invariata
- patogeniemergenti
- nuovitest x nuovipatogeni ...
- falsinegativi
- falsipositivi
- tempiautorizzazione per ilrilascionuovitest
- costi

Inattivazione dei patogeni

- Ampiorange di patogeni
  + Patogeniemergenti
  + Leucociti
- Sostituiscegamma-irradiazione, CMV test
- Aumentatitempiconservazione





PRO

CONTRO

- Non disponibilità per tutti gliemocomponenti
- Non efficacecontrospore, HAV, prioni
- Impiego di sostanze additive
- Costi

Metodiche di inattivazione/riduzione dei patogeni nei prodotti trasfusionali labili

Transfusion Vol. 50, August 2010; Editoriale: Kills 99% ok knowngerms

TABLE 1. Current status of PRTs

Product	Company	Compound/filter	Clinical trial/regulatory status
RBCs	Cerus/Baxter	S303	Redesign at Phase II
	GambroBCT	Riboflavin + light	Phase III
	Vitex (Pall)	Inactine	Abandoned
RBC prion filter	Macopharma	P-Capt	CE Marked September 2006
	Pall	Leukotrap Affinity Plus	CE Marked February 2010
PLTs	Cerus/Baxter	Amotosalen + UV	CE Marked 2002
	Gambro	Riboflavin + UV	CE Marked October 2007
	Macopharma	UV light	Phase III
Plasma	Cerus/Baxter	Amotosalen + UV	CE Marked November 2006
	Gambro	Riboflavin + UV	CE Marked August 2008
	Octapharma	Solvent Detergent	Licensed (1998 in UK)

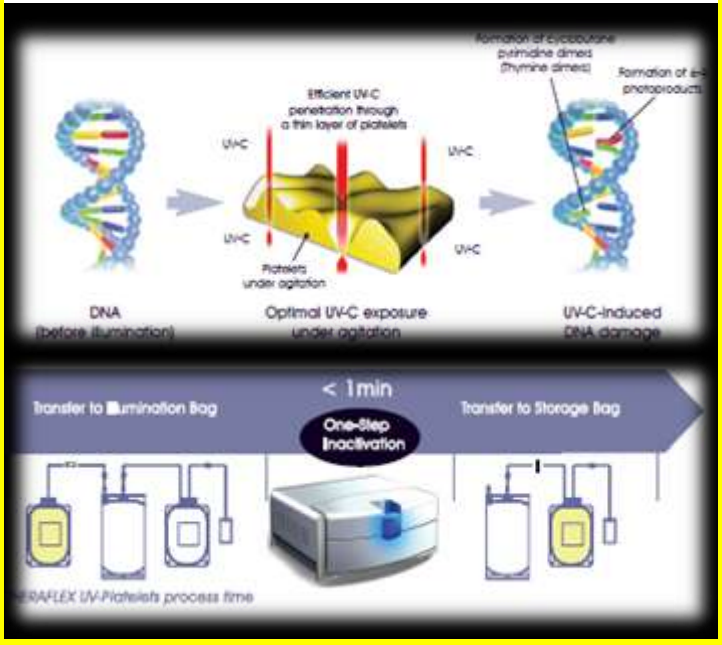
Chris V. Prowse, Scottish National Blood Transfusion Service;
William G. Murphy Irish Blood Transfusion Service, Dublin, Ireland

Sistemi di inattivazione dei patogeni nei concentrati piastrinici

INTERCEPT BLOOD SYSTEM | BE SURE

FIG.1

THERAFLEX UV-Platelets



Mirasol PATHOGEN REDUCTION TECHNOLOGY

Table 1. Inactivation of pathogens in platelet concentrates after photochemical treatment with amotosalen and UVA light

Pathogen	Log-reduction in organisms
Enveloped viruses	
HIV (cell-free)	> 6.2
HIV (cell-associated)	> 6.1
CMV	> 5.9
Hepatitis B virus	> 5.5
Hepatitis C virus	> 4.5
Duck hepatitis B virus	> 6.2
Bovine viral	
Hum	
	6.1-6.
virus B	4.0-4.9
negative bacte	
cherhia coli	> 6.4
erratia marcescens	> 6.7
bsiella pneumoniae	> 5.6
domonas aeruginosa	4.5
ella choleraesuis	
erocolitica	
Gra	
Staph	
Staphylococc	6.6
Streptococcus pyogenes	> 6.8
Listeria monocytogenes	> 6.3
Corynebacterium minutissimum	> 6.3
Bacillus cereus	> 6.0
Gram-positive anaerobic bacteria	
Lactobacillus species	> 6.9
Propionibacterium acnes	> 6.7
Clostridium perfringens	> 7.0
Bifidobacterium adolescentis	> 6.5
Protozoa	
Trypanosoma cruzi	> 5.3
Plasmodium falciparum	> 7.0
Leishmania mexicana	> 5.2

Data are summarized from Lin,[14] Lin et al,[15,16,18] Van Voorhis et al,[19,20] Dupuis et al,[21] Savoor et al,[22] and Sawyer et al.[23]

*Preliminary data; inactivation was performed in 35% B19-infected plasma and 65% PAS III (platelet additive solution III) in the absence of platelets. Studies included a 15- or 30-minute rest between addition of amotosalen and UVA treatment.

SISTEMI DI INATTIVAZIONE

SISTEMI DI INATTIVAZIONE

Sistemi di inattivazione: capacità depletive espresse in logaritmi

Virus Enveloped

(log deplezione)

	Theraflex	INTERCEPT	Mirasol
HIV	~1	> 6.2	5.9
HBV		> 5.5	1.5
HCV		> 4.5	
PRV	~ 3	> 5.1	2.5 – 3.0
WNV		> 6.0	5.1
SAR-CoV		> 6.3	
Influenza		> 5.9	> 5.3
Chikungunya		> 6.4	
Dengue		> 5.0	
Vaccinia		> 5.2	
DHBV		> 6.2	
BVDV	~ 3	> 6.0	
VSV	> 4		≥ 6.3

Virus non Enveloped

	Theraflex	INTERCEPT	Mirasol
Parvo B19	-	4.0 - > 5.5	
Adeno 5	-	> 5.7	
Calicivirus	-	1.7 – 2.4	
SV15/SV40	~ 1	0.7 – 2.3	
Poliovirus	-		
Blue tongue	-	6.1 – 6.4	

Virus Intracellulari

	Theraflex	INTERCEPT	Mirasol
HIV		> 6.1	4.5
HTLV-I		4.7	
HTLV-II		5.1	
CMV		> 5.9	

Sistemi di inattivazione: inattivazione batteri (in logaritmi)

Batteri Gram-Positivi

	Theraflex	Intercept	Mirasol
Staphylococcus epidermidis	> 4, 5-6	> 6.6	≥ 4.2
Staphylococcus aureus	> 4, 5-6	6.6	3.6 – 4.8
Streptococcus pyogenes	5-6	> 6.8	-
Listeria monocytogenes	-	> 6.3	-
Corynebacterium minutissimum	-	> 6.3	-
Bacillus cereus (vegetative)	3, 5-6	> 6.0	1.9 – 2.7
Lactobacillus sp.	-	> 6.9	-
Bifidobacterium adolescentis	-	> 6.5	-
Propionibacterium acnes	5-6	> 6.7	-
Clostridium perfringens	-	> 7.0	-
Streptococcus mitis	-	-	3.7

BatteriGram - negativi

	Theraflex	Intercept	Mirasol
Escherichia coli	> 4, 5-6	> 6.4	> 4.4
Serratia marcescens	-	> 6.7	4.0
Klebsiella pneumoniae	5-6	> 5.6	-
Pseudomonas aeruginosa	-	4.5	4.5 - > 4.7
Salmonella choleraesuis	-	> 6.2	-
Yersinia enterocolitica	-	> 5.9	-
Enterobacter cloacae	-	5.9	-
Orientia tsutsugamushi	-	> 5.0	> 5.0
Spirochete			
Treponema pallidum	-	6.8 - 7.0	-
Borrelia burgdorferi	-	> 6.8	-

Parassiti

	THERAFLEX	INTERCEPT	MIRASOL
Plasmodium falciparum	-	≥ 6.0	-
Trypanosoma cruzi	-	> 5.3	> 5.0
Barbesia microti	-	> 5.3	> 4.0
Leishmania mexicana	-	> 5.0	-
Leishmania major Jish	-	> 4.3	-
Leishmaniadonovaniinfantum	-	-	> 5.0

Leucociti

	THERAFLEX	INTERCEPT	MIRASOL
T-cell	-	> 5.4	~ 2


Piastrine
inattivate
Dati clinici
Piastrine
non
inattivate

Inattivazione dei patogeni e PIASTRINE

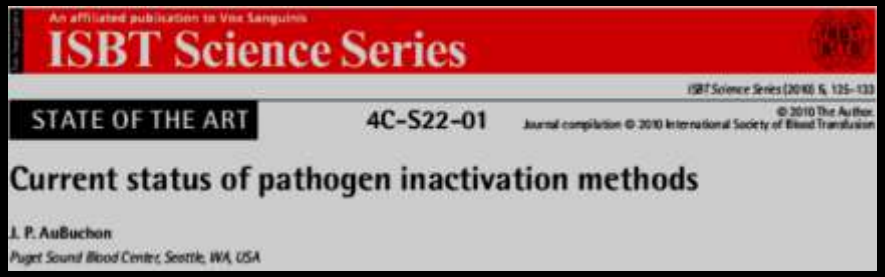
Transfusion, Volume 49, Issue 6, 2009 - Pages 1262-1268

Research opportunities for pathogen reduction/inactivation of blood components: summary of an NHLBI workshop

Morris A. Blajchman et al. for NHLBI Working Group on Research Opportunities for the Pathogen Reduction/Inactivation of Blood Components

National Institutes of Health, and Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, Bethesda, Maryland; Johns Hopkins Hospital, Baltimore, Maryland; and McMaster University, Hamilton, Ontario, Canada.

[…]Intercept (Cerus Corporation, Concord, CA) platform and the Mirasol PRT system (CaridianBCT Biotechnologies, Lakewood, CO). A randomized, controlled, double-blind Phase III clinical trial of PLT prophylaxis performed in the United States **demonstrated equivalence to untreated control PLTs using a clinical bleeding endpoint**. An analysis of adverse events raised concern about a possible increased risk of pulmonary complications in recipients of PR/PI PLTs, although mortality associated with acute lung injury was actually lower in the recipients of PR/PI-treated PLTs than those in the control group. **Both systems have a broad spectrum of antimicrobial action**. As with Intercept, in vitro and animal studies suggest that the Mirasol PRT system process will also **substitute for gamma irradiation in preventing transfusion-associated GVHD**. Data from experimental animal studies suggest that these types of PR/PI technology **reduce the risk of alloimmunization** and induces tolerance in an organ transplant model, perhaps by inactivating donor WBCs or donor dendritic cells.



*Therapeuticefficacy and safetyofplateletstreatedwith a photochemicalprocessforpathogeninactivation: **the SPRINT Trial**. Blood 2004; 104:1534–1541*

*Transfusionofpooledbuffycoatplateletcomponentspreparedwithphoto-chemicalpathogeninactivation treatment: the **euroSPRITE trial**. Blood 2003; 101:2426–2433*

Clinicaleffectiveness and safetyofpooled, randomdonorplateletconcentrates, leucoreduced and stored up tosevendays in either plasma or additive solutionwith and withoutpathogenreduction in hemato-oncologicalpatients. Transfusion 2009; 49:2A–3A

A multi-centerstudyoftherapeuticefficacy and safetyofplateletcomponentspreparedwithpathogeninactivation (InterceptTM) storedfor 6 or 7 daysprior to transfusion. Miguel Lozano, personal communication, March, 2010.

The Mirasol Clinical Evaluation Study Group: A randomized controlled clinical trial evaluating the performance and safety of platelet treated with Mirasol pathogen reduction technology. Ray Goodrich, personal communication, March, 2010

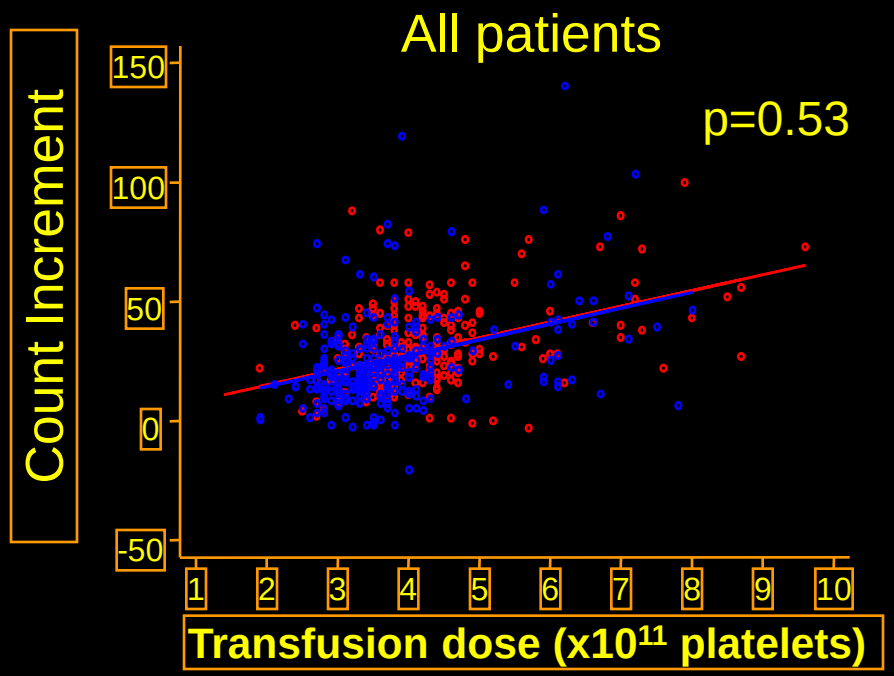
SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare

Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: the euroSPRITE trial

Dick van Rhenen, Hans Gulliksson, Jean-Pierre Cazenave, Derwood Pamphilon, Per Ljungman, Harald Klüter, Hans Vermeij, Mies Kappers-Klunne, Georgine de Greef, Michel Laforet, Bruno Lioure, Kathryn Davis, Stephane M[illegible], Véronique Mayaudon, Jocelyne Flament, Maureen Conlan, Lily Lin, Peyton Metzel, Don Buchholz, and Laurence Corash

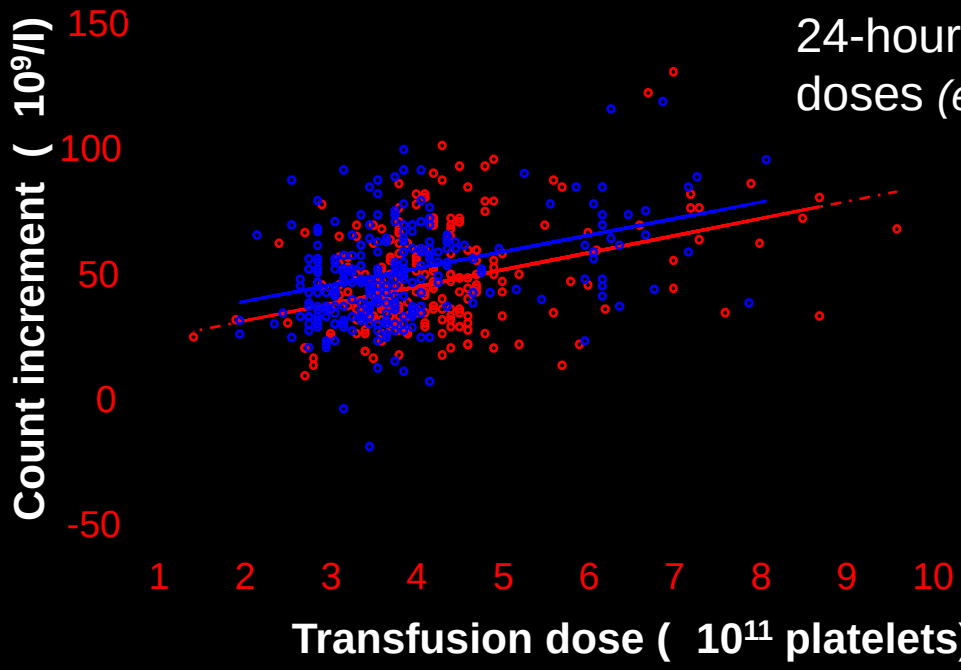
BLOOD, 15 MARCH 2003

the euroSPRITE trial, used the corrected platelet count increment (CCI_{1hr}) as its primary outcome measure [45]. This was no different with platelets treated with amotosalen and UV light (Intercept®) when compared to untreated platelets. However, as the PI process resulted in fewer platelets being transfused, the PI platelet recipients required a proportionately larger number of platelet units to be transfused and reached their transfusion threshold again more quickly.



After 1 h, the increase of platelet count in response of INTERCEPT platelets (o) was indistinguishable* from the response of control platelets (o)

*analyzed by longitudinal regression analysis



24-hour CI: comparable for equivalent doses *(endpoint 2)*

INTERCEPT (n=311)
Control (n=256)
p= 0.19

Nessuna differenza in termini di CI/CCI $1_{hr}/24_{hr}$ delle piastrine inattivate vs piastrine non-inattivate

Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial

Primary Endpoint: Proportion of patients with Grade 2 bleeding (WHO criteria)
Study Sites: 12 blood centers in the United States

Table 7. Mean platelet responses following platelet transfusions

	PCT; n = 318	Control; n = 327
Before transfusion		
Platelet count, × 10^9/L	15.1	15.2
1 h after transfusion		
Platelet count, × 10^9/L	36.5*	49.5
Count increment, × 10^9/L	21.4*	34.1
Corrected count increment, × 10^3	11.1*	16.0
24 h after transfusion		
Platelet count, × 10^9/L	27.9*	36.1
Count increment, × 10^9/L	13.2*	21.5
Corrected count increment, × 10^3	6.7*	10.1

*$P < .001$ compared with control.

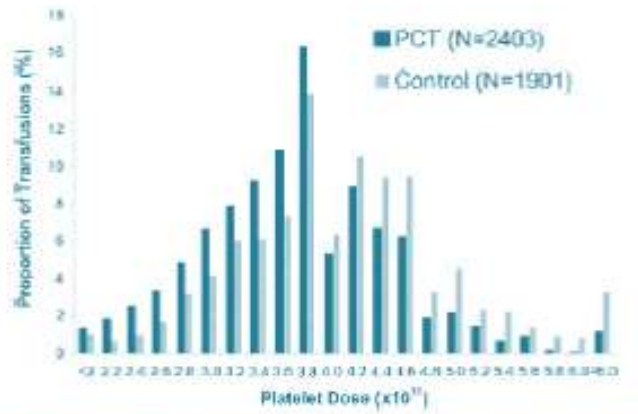


Figure 2. Distribution of transfused platelet doses. A greater proportion of doses were less than 3.0×10^{11} in the PCT group compared with the control group ($P < .01$).

The SPRINT trial in the United States followed the bleeding outcomes in 645 patients randomized to either control platelets or those treated with amotosalen and UV light [46]. As before, the patients in the PI group received fewer platelets per transfusion (3·7 PI vs. $4·0 \times 10^{11}$ control; $P < 0·001$) and, not surprisingly, more transfusions (8·4 vs. 6·2; $P < 0·001$). Although the CCIs were lower in the PI group, comparison of CCIs among patients receiving similar doses of platelets indicated no difference. The primary outcome measure, the proportion of patients experiencing Grade 2 (or greater) bleeding, was not different between the groups nor was the time to such a bleeding episode. Although many patients experienced an adverse event at some time during the course of their illness, the frequency of any significant event did not appear to be different except for that of respiratory distress (which was noted in five patients in the PI group and none in the control group).

Table 9. Adverse events during the study

	PCT, %; n = 318	Control, %; n = 327	*P*
Any adverse event*	99.7	98.2	.12
Grade III or IV adverse event	78.9	78.6	.92
Serious adverse event†	27.0	24.8	.53
Treatment-related adverse event‡	26.4	29.4	.43
Death§	3.5	5.2	.34

Nessuna segnalazione riguardo un incremento degli eventi emorragici (grado 1-2) nei pazienti trasfusi con piastrine inattivate

CONCLUSIONS: These data support the conclusion that INTERCEPT platelets may be used according to standard transfusion guidelines whenever platelet transfusions are required. INTERCEPT platelets appear to be safe and effective in management of thrombocytopenic patients.

The Mirasol® Pathogen Reduction Technology system and quality of platelets stored in platelet additive solution

BloodTransfus 2010

HåkonReikvam, SusanneMarschner, TorunnOvelandApelseth, Ray Goodrich, TorHervig

toevaluate low plasma buffy coatplateletconcentratesobtainedfrom the OrbiSac System and toexamine the effects on the developmentofplateletstoragelesionduringstorage in platelet additive solution.

Efficacia clinica sovrapponibile delle Plt da buffy-coat inattivate rispetto alle Plt non-trattate

Kills 99% ofknowngerms

Transfusion August 2010
C.V.Prowse, W.G. Murphy

Given that cost and toxicity (to the patient and to the product) are issues that can be addressed separately, the problem of efficacy (of microbiologic sterilization) remains to be defined. A purchaser of PRT would expect robust security:

• From the known problems—window period donations for services that have testing in place for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus using nucleic acid technology (NAT);

• From known transfusion-transmissible infections we do not test for: CMV, parvovirus B19, Chikungunyavirus, dengue, malaria, babesiosis, (WNV, Chagas, HTLV-I/II);

• From agents in the community that cause concern rather than known disease—simian foamy virus, XMRV, otheremergingretroviruses;

• And from the unknown unknowns: there are many diseases with a probable, but unknown, environmental cause that may need to be covered in the future

- **Riduzione del rischio in termini di trasmissione di agenti patogeni**

99.34% of INTERCEPT platelet administrations were without a related transfusion reaction. Adverse events following INTERCEPT platelet transfusions classified as related to transfusions were infrequent, mild in severity, and representative of the events expected withplatelettransfusion.

Osselaer et al: Transfusion 2008;48:1061-1071
Osselaer et al: Vox Sang 2008;94:315-323

…transfusion of platelet components treated with INTERCEPT to a broad patient population for a spectrum of indications was well tolerated in routine practice. The incidence of adverse events was less than untreated platelet components suspended in plasma.
INTERCEPT offers the potential to improve the safety and availability of platelet components for transfusion. Importantly, an increase in the total platelet dose and RBCC transfused to patients in this study was not observed.

Cazenaveet al., *Vox Sang 2008*

Emovigilanza:
Non sono riportati eventi avversi significativi

Dati SIT Tricase

intercept

Pool PLT da buffy-coat		
	Pre-inattivazione	Post-inattivazione
Pltx 10^3/uL	1155,8 ± 234	1148,9 ± 216,96
Plt x 10^{11}	3,78 ± 0,9	3,64 ± 0,7

PLT da aferesi		
	Pre-inattivazione	Post-inattivazione
Pltx 10^3/uL	1278,9 ± 306	1271,2±280,51
Pltx 10^{11}	4,05± 1,0	3,91±0,8

Programma di raccolta, produzione e inattivazione di concentrati piastrinici
- 2009 -

DipartimentodiMedicinaTrasfusionale Pescara
DipartimentodiMedicinaTrasfusionale Lazio Ovest
ServiziodiMedicinaTrasfusionalediTricase

Caretteristiche dei Pazienti	
Pazienti ***n°***	***548***
Età	***56,12±20.8***
Sesso	***(M/F)313/235***
Diagnosi	
AML/ALL	***141/46***
Aplasia	***10***
*Linf****oma***	***124***
Leucemia *Cronica*	***27***
*Mi****eloma*** *Multiplo*	***61***
MDS	***59***
Tumori Solidi	***80***

Dati su efficacia delle PLT inattivate vs PLT non-Inattivate				
	Total	Inattivate	Non-Inattivate	P
Trasfusioni n°	5894	1770	4124	
Plt-pre 10^9/L	14379 ±13955	11949 ±10894	15698 ± 5220	< 0.0001
Plt-post 10^9/L	27408 ± 20656	21793 ± 8435	30610 ± 1169	< 0.0001
AI 18-24 h 10^9/L	12969 ± 16714	9600 ± 15229	15041± 7245	< 0,0001
Intervallo Trasfusionale (gg)	2,32 ± 1,64	2,22 ± 1,59	2,37 ± 1,66	<0.67

Analisi statistica

Variabile	OR (IC 95%)	P
Dose Infusa	1,30 (1,19-1.41)	<0.0001
Conservazione (d)	0,90 (0,85-0,95)	<0.0001
Unità non divise	1,62 (1,33-1,97)	<0.0001
Inattivazione	0,44 (0,37-0,52)	<0.0001
AB0 matching		
Plt AB0 match	1.24 (0,93-1,66)	0.13
Plt AB0 identiche	1,54 (1,23-1,93)	<0.0001
Plt AB0 mismatched	1,0 (rc)	
Sesso		
Femm.le	*1,74 (1,49-2,04)*	<0.0001
Maschile	*1,0 (cr)*	
Età	0,992 (0,988-0,995)	<0.000

COMMENTO ALLO STUDIO

- Studio retrospettivo - dati del 2009
- Analisistatistica: inattivazionecome un fattore “negativo” indipendentenellavalutazionedell’efficacia (CI = variabiledipendente)
- Efficaciaclinicasovrapponibile per entrambiigruppi
- Non sisonoosservatieventiavversineipazientitrattati con Pltinattivate. Sono state segnalate 5 reazioni moderate in pazientitrasfusi con Plt non-Inattivate.

Aspetti normativi

Legge 219/05 – Capo II°

art. 5 (LEA)

- 1a - 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 da trasfusione"

7 Days platelets

COMMISSION DIRECTIVE 2004/33/EC

of 22 March 2004

implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components

ANNEX IV

STORAGE, TRANSPORT AND DISTRIBUTION CONDITIONS FOR BLOOD AND BLOOD COMPONENTS

(as referred to in Article 5)

1. STORAGE

1.1. **Liquid storage**

Component	Temperature of storage	Maximum storage time
Red cell preparations and whole blood (if used for transfusion as whole blood)	+ 2 to + 6 °C	**28** to **49** days according to the processes used for collection, processing and storage
Platelet preparations	+ 20 to + 24 °C	**5** days; may be stored for **7** days in conjunction with detection or reduction of bacterial contamination
Granulocytes	+ 20 to + 24 °C	**24** hours

CE 7 days

INTERCEPT PROCESSING SET

For use with INTERCEPT Illuminator
For use with an apheresis kit with InterSol Solution or
INTERCEPT Preparation Set for Apheresis Platelets

Each set is wrapped in a tamper-evident package and includes one 15ml 3mM amotosalen hydrochloride solution container (Formula : Amotosalen HCl 101mg - Natr. chlorid. 924mg - Aqua ad iniect. ad 100ml), one illumination container, one container with Compound Adsorption Device (CAD), one INTERCEPT platelet storage container. The set is sterilized by a combination of steam and radiation.

Indications and Usage

This set is used with an INTERCEPT Illuminator to inactivate a broad spectrum of viruses, bacteria and leukocytes in apheresis platelets. INTERCEPT platelets are indicated for support of patients requiring platelet transfusions, according to clinical practice guidelines. INTERCEPT Platelets may be stored up to 7 days from time of collection, at 20-24°C with continuous agitation. INTERCEPT Platelets stored up to 7 days have been shown to adequately prevent and control bleeding. Any extension of platelet storage time from current blood center limits should be evaluated per Directive [2004/33/EC] and validated according to local blood bank procedures.

Gammarradiation
CE Marc

Form

Change Notification
Approval of Significant Change

TÜV SÜD Product Service

This form is to be filled in by TÜV Product Service only.

TÜV Project No.:	71333755	**Department:**	MHS 2
Applicant:	Cerus Corporation	**Client No.:**	60562
Contact Person:	Jennifer Yonemura	**Fax:**	001 925 603 1684
Change Notification ID:	008 Plasma/013 Platelets	**Date:**	2008-01-23
Affected Certificate(s):	G7 07 11 60562 007, G7 07 11 60562 008, G1 07 11 60562 006		
Subject:	INTERCEPT System for Plasma or Platelets, Expansion of labelling claim		

Classification of the change:

☒ Significant Change, new or updated certificate **does not need** to be issued (approval by MHS)

☐ Significant Change, new or updated certificate **needs** to be issued (approval by Certification Body CRT2)

Comments:

The Change Notification has been evaluated in internal Clinical Report No. 71333755 dated 2008-04-09.

Summary: No TA-GVHD was reported in pre-approval clinical trials and extensive post-approval routine use clinical experience, where hematology/oncology patients at risk for TA-GVHD were supported with INTERCEPT platelets without gamma irradiation. Fresh Frozen Plasma is not routinely irradiated prior to transfusion. Thus, treatment of plasma with INTERCEPT will add an additional measure of safety. The in vitro data are very comparable to the INTERCEPT platelet data for T cell inactivation which is used in clinical practice in place of gamma irradiation. Therefore, data provided support the rationale that pathogen inactivation using the INTERCEPT Blood System can be used as an alternative to gamma irradiation to prevent TA-GVHD.

From a clinical point of view, the risk-to-benefit ratio can be assessed to be positive. The requirements of the Directive are fulfilled.

HHS Advisory Committee on Blood Safety and Availability – January 2008 Recommendations

DEPARTMENT OF HEALTH AND HUMAN SERVICES Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

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.

CONCLUSIONI

L'impiego di PLT inattivate costituisce un approccio differente per affrontare la problematica della sicurezza trasfusionale

È stata dimostrata l'efficacia clinica delle PLT inattivate: le variazioni del CI- CCI 1-24$_{hr}$ post-trasfusionale (PLT inattivate vs PLT non-inattivate) non significative

Non sono state evidenziate reazioni avverse alle soluzioni additive

Efficacia clinica in termini di "eventi emorragici" sovrapponibile

Minore carica virale/batterica degli emocomponenti inattivati

XV CORSO NAZIONALE
DI AGGIORNAMENTO
SIdEM

SIdEM

GRAZIE

Angelo Ostuni

Pia Fondazione di Culto e Religione Card. G. Panico
Azienda Ospedaliera – Tricase (Lecce)
U.O.C. Medicina Trasfusionale