



**Es convenient
restringir les
transfusions? Els
umbrals de transfusió:
“Less is more”.**

“Less is More: Red Cell Transfusion Therapy “

**II Jornada De Medicina Transfusional de la Societat
Catalano-Balear de Transfusió Sanguínia
Barcelona (Can Caralleu)**



- Signs and symptoms relate to
 - Severity
 - Effectiveness of physiologic compensatory mechanisms

- Clinical judgment regarding transfusion
 - Experience and acumen

- Diagnostic tests for determining transfusion
 - Lack sufficient predictive value
 - Lactate levels
 - Mixed venous oxygen saturation
 - Central venous oxygen saturation
 - Cardiac ischemic markers

- Available data for making decisions
 - Patients refusing transfusions for religious beliefs
 - Two RCT's
 - Acute coronary syndrome and Hb levels
 - Multiple observational cohort studies
 - Orthopedic surgery patients



▪ Hemoglobin

- $P_{50} = 26.3$ mmHg

Varies (higher P_{50} decreased Hb – O_2 affinity)

$CO_2 \uparrow$

pH \downarrow

2,3 DPG \uparrow

Temperature \uparrow

- Nitric Oxide (NO)

○ Hb – NO = nitrosothiol (SNO)

○ Deoxygenation: NO release from SNO

Vasodilatation

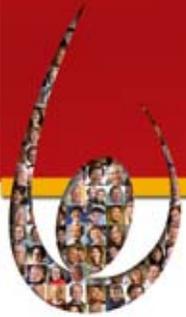
Blood flow, O_2 delivery \uparrow

○ SNO lost during RBC storage



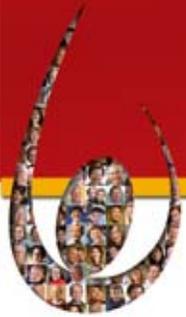
- Oxygen Delivery (DO_2)
 - $DO_2 = CO \times C_aO_2$
 - Oxygen delivery = cardiac output x arterial O_2 content
 - DO_2 crit = tissue metabolic demands not met (lactic acidosis, ischemic ECG changes, neurologic dysfunction)
 - Anemia => $\downarrow DO_2$

- Oxygen Consumption (VO_2)
 - Oxygen consumption may not change (compensatory mechanisms)
 - VO_2 does not increase p txf if txf given > DO_2 crit.



▪ Compensatory Mechanisms

- ↑ O₂ extraction (20% - 30% → 60%+)
 - Myocardium = 60%
 - Brain = 30%
 - Skin, kidney = 10%
- ↑ Cardiac output
 - Conscious = C.O.↑ (↑ heart rate)
 - Anesthetized patients = C.O.↑ (↑ SV)
 - ↑ HR = hypovolemia
- Shunting from hi flow; lo extraction to hi oxygen requirement
- 2,3 DPG ↑



Critical Hb Concentration

- Jehovah's Witness' patients

- n = 2,083
- surgical procedures (13 hospitals, 1981-1994)
- average age = 57 years

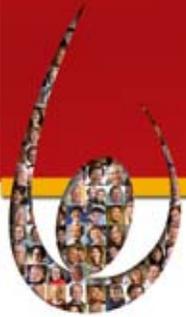
Hb Concentration	Morbidity *	Mortality Rate
7.1 – 8.0 g/dL	9.4%	0%
6.1 – 7.0	22.0%	8.9%
5.1 – 6.0	28.6%	9.3%
4.1 – 5.0	57.7%	34.4%
3.1 – 4.0	52.6%	25.0%
2.1 – 3.0	91.7%	54.2%
1.1 – 2.0	100%	100%

* Arrhythmia, CHF, M.I., bacteremia, pneumonia, wound infection, death



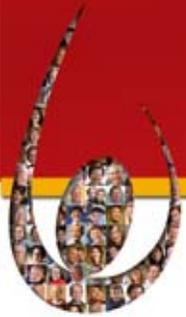
- Animal Models
 - Hb 3.5 – 5.0 g/dL

- Hemodilution Studies
 - 19 – 33 y.o. conscious volunteers
 - Hemodilution to 5.0 g/dL
 - Oxygen consumption did not change
 - Systemic vascular resistance ↓
 - HR ↑ (75% of C.O.↑)
 - SV ↑ (25% of C.O.↑)
 - Cardiac index ↑
 - DO_2 crit not approached despite Hb 5.0 g/dL



▪ Hemodilution Studies

- Hb reduced to 5 – 6 g/dL
 - Loss of cognitive function: reaction time, immediate delayed memory
- Hb reduced to 5 g/dL
 - 3/55 subjects, age 27 +/- 5 years
 - ECG ST-segment depression
 - HR ↑
 - No sx's

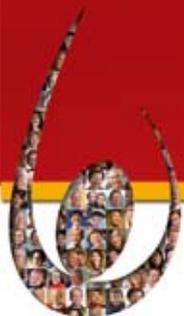


Hemoglobin Concentration & Time to Death

Re-analysis of *Transfusion* 2002; 42:812

<u>Hb Concentration</u>	<u>Median Days Prior to Death</u>
4.1 – 5.0 g/dL	11
3.1 – 4.0 g/dL	2
2.1 – 3.0 g/dL	2.5
< 2.0 g/dL	1.0

- Temporal latitude exists for treating profound anemia
- Only 10% developed cardiac arrhythmias
- Absence of cardiac sx's understates poor clinical outcome

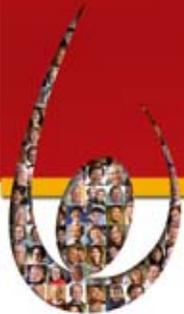


Clinical Studies in Anemia

Transfusion Requirements in Critical Care (TRICC)

RCT critically ill Canadian ICU patients at 25 hospitals

	<u>Restrictive</u>	<u>Liberal</u>
N	418 patients	420
Hb Trigger	7.0 g/dL	10.0
Maintenance Hb	7-9 g/dL	10-12
Leuko Reduction	No	No
RBC txf'd	2.6 units	5.6 p=0.01
No txf \bar{p} randomization	33%	0% p<0.01
Primary Outcome		
▪ Death within 30 days	18.7%	23.3% p=0.11
▪ Cardiac events (pulmonary edema, M.I.)	13.2%	21.0% p<0.001



Transfusion Requirements in Critical Care (TRICC) - continued

RCT, critically ill Canadian ICU patients at 25 hospitals

Sub-group analysis – 30 day mortality

	<u>Restrictive</u>	<u>Liberal</u>
APACHE II scores <20	8.7%	16.1% p<0.03
Age <55 years	5.77%	13.07% p=0.02

Conclusion: 7.0 g/dL threshold (7-9 g/dL maintenance) - effective



Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)

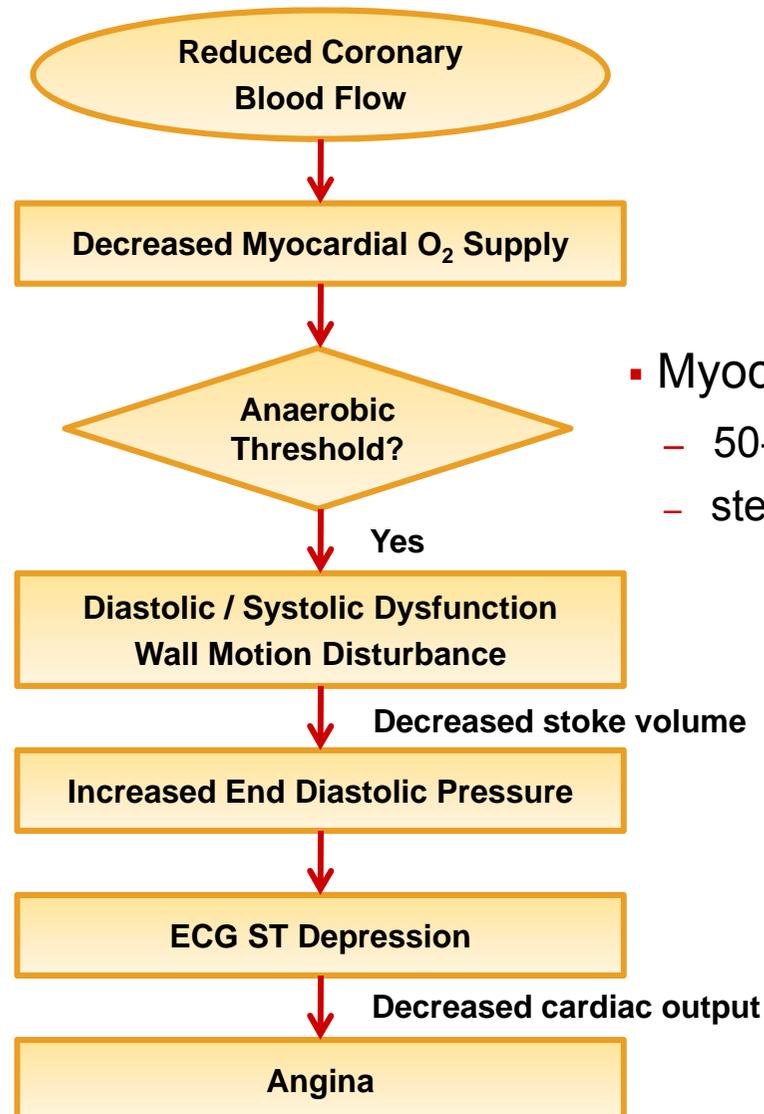
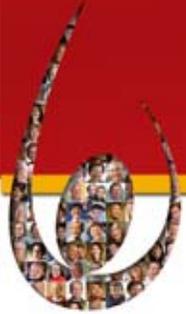
RCT

Primary Outcome: Death or inability to walk across a room without assistance 60 days \bar{p} randomization.

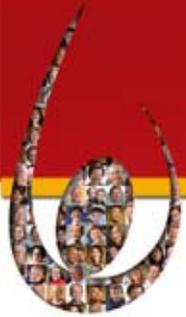
Multicenter Study: 2,016 patients
Average age 81.6 years
82% \uparrow BP
40% coronary artery disease
25% diabetes mellitus

Transfusion Trigger	Hb <10 g/dL	Hb <8 g/dL or sx's
Hb prior to txf	9.2 g/dL	7.9 g/dL
Median RBCs txf'd	2 units	0
Mortality Rate	7.6%	6.5% (95% CI 0.70-1.86)
Hospital Re-admits	Same	same

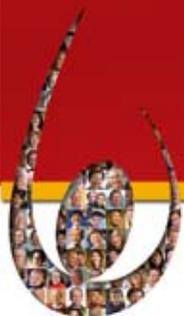
Impaired Cardiac Function



- Myocardium:
 - 50-60% oxygen extraction ratio
 - stenotic lesions impair ability to ↑ blood flow



- Medicare beneficiaries (n=78,974)
 - >65 years old
 - Acute M.I. (72% without ST elevation)
 - 4.7% received txf
 - Abstracted record review excluded patients who died within 48 hours
 - Lower *admitting* HCT = higher 30 day mortality
 - Txf reduced death: HCT <30-33%



Impaired Cardiac Function

[continued]

- Anti-platelet agent treated patients (n=24,112)
 - Acute coronary syndrome without ST elevation
 - 2,401 received txf p bleeding
 - Included patients <65 years old
 - Txf – time-dependent covariate
 - On-going record review

<u>Nadir Hct</u>	<u>30-day Mortality Odds Ratio</u>
35%	292
30%	169
25% *	1.13
20%	1.59

* Benefit when Nadir Hct <25% during hospitalization



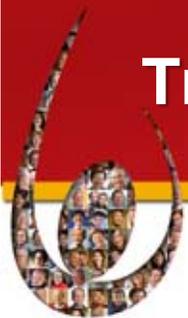
- CRUSADE (n=74,271)
 - Non-ST elevation acute coronary syndrome without surgery
 - 1.3% received txf – more severely ill
 - Subset analysis (n=44,242)
 - 27-30% - higher mortality
 - 24-27% - no benefit – blood txf
 - < 25% - lower mortality



- Animal Model

- Acute M.I. (72% without ST elevation)

- Acute coronary ligation
 - Anemic rats
 - Infarct size reduced; cardiac function improved – Hb ↑'d to 10 g/dL
 - No benefit txf = Hb >10 g/dL



Transfusion Requirements after Cardiac Surgery (TRACS)

Prospective, randomized, non-inferiority controlled trial

Elective cardiac surgery with bypass

Single hospital, San Paulo, Brazil

February 9, 2009 – February 1, 2010

Liberal (Hct <30%) vs. Restrictive (Hct < 24%) transfusion strategy

Transfuse one unit and obtain Hct

Non, LR – RBC's

Median 3-day storage

	Restrictive = 255	Liberal = 257
Received txf	47%	78% (p<0.001)
Median RBC txf	0	2
FFP	27%	21%
Plt	9%	10%
Cryo	4%	4%
30-day Mortality/Morbidity	11%	10%
Median ICU Stay	3 days	3 days
Median Hospital Stay	9 days	9 days

Conclusion: Hct ~ 24% is as safe as Hct ~ 30% with respect to composite end points, 30 day mortality and inpatient clinical complications.



Variation in Transfusion in CABG Surgery

N = 102, 470 patients

CABG surgery with bypass

Calendar year 2008

798 U.S. Sites = Society of Thoracic Surgeons Adult Cardiac Surgery Database

RBC txf rate 7.8% – 92.8%

FFP txf rate 0% – 97.5%

Platelet txf rate 0.4% – 90.0%

Transfusion rates varied by

11.1% of Variation	{	Geographic location (West South Central higher)	(p = 0.007)
		Academic status (higher)	(p = 0.03)
		Hospital Volume (inverse)	(p < 0.001)

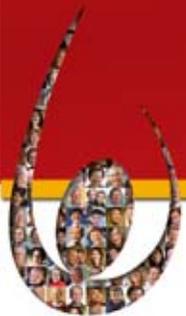
20.1% of variation Case Mix

No association between RBC txf rates and all-cause mortality

Enormous variability remains despite > 20 years attention to this finding



- Summary:
 - Human and animal studies
 - Despite conflicting data
 - Outcomes appear improved by restricting transfusions for patients with acute coronary syndromes to 8 g/dL or Hct 25%
 - Unclear if outcome different re: ST or non-ST elevation



Observational Studies

12 studies; more than 2,000 patients

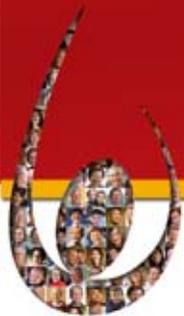
Anemia and Blood Transfusions in Critical Care (ABC) European ICU's

	<u>Txf'd</u>	<u>Non-Txf'd</u>	
Mortality Rate	22.7%	17.1%	P=0.02
Pre-txf Hb	8.4 g/dL		
Leukocyte – reduced	variable		



Sepsis Occurrence in Acutely Ill Patients (SOAP) European ICU's (same study design as ABC)

	<u>Txf'd</u>	<u>Non-Txf'd</u>
Pre-txf Hb	Not provided	
Txf	5.5 units	
Leukocyte – reduced	yes	
Mortality rate	Lower (hazard ratio 0.73) – attributed to LR	



CRIT Study Anemic and Blood Transfusion in Critically Ill

	<u>Txf'd</u>	<u>Non-Txf'd</u>
N (U.S. ICU's)	2,152	2,740
Pre-txf Hb	8.6 g/dL	
\bar{X} age RBC	21.2 days (no correlation with mortality)	
Mortality Rate	25%	10%
• 1-2 units	OR 1.5	
• 3-4 units	OR 2.6	
• 4+ units	OR 4.0	



Nosocomial Infection in Critically Ill Patients

	<u>Txf'd</u>	<u>Non-Txf'd</u>
N	428	1,657
Nosocomial Infection (central line, bacteremia, cystitis, pneumonia)	14.3%	5.8%
Pre-txf Hb	7.6 g/dL	
\bar{X} units txf'd	3.7 dL	

Infection rate non-statistically lower – Leukocyte reduced RBC's



- Anemia and Quality of Life
- Three (3) hospitals – The Netherlands
- Secondary analysis of a previously conducted RCT
- Mean age = 70.4 years
 - Investigated relationships between QoL, fatigue, and Hb levels
 - 603 consecutive patients total hip and knee replacement surgery

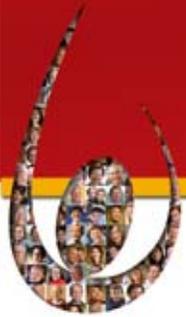
Hb day+7

10.5

Hb day+ 14

11.4

- QoL – at most 4% of variability explained by Hb ($R^2 < 0.04$)
- Conclusion:
 - Hb levels do not correlate with QoL scores in immediate post-op period following lower limb joint replacement surgery.
 - Different results than Conlon (2008); Halm (2003), Foss (2009)
 - Fewer number of patients
 - Hb not always measured simultaneously with QoL questionnaire
 - Data not reproduced
 - Observational study not confirmed by RCT (no difference Hb 8 or 9)



Perioperative Risk for Myocardial Infarction / Mortality in Hip and Knee Arthroplasty: Role of Anemia

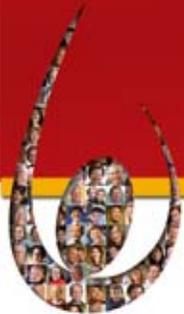
Mayo Clinic:

- 20 year case: control study (1:1)
 - Control no myocardial infarction/mortality, matched demographically
- 391 cases:
 - 228 deaths
 - 103 non-fatal M.I.
- Mean age: 78 years
- Few patients hemoglobin <10.0 g/dL
- Lower pre-op Hb
 - Significant risk for death (univariate analysis)
OR 1.38 p = 0.04
 - Multivariable analysis – pre-op anemia and m.i./mortality risk
 - OR 0.81 (95% CI 0.54-1.20), p=NS
 - Pre-op co-morbidities most important
 - Cardiovascular
 - Cerebrovascular
 - Pulmonary Disease
 - Diffuse as metastatic malignancy



Conclusion

- Underlying conditions more important than anemia in risk of myocardial infarction / death in hip/knee arthroplasty
- Separating risk of anemia vs. risk from transfusion – difficult in patients with moderate anemia
- Beattie (2009), Wu (2007), Carson (1996) – pre-op anemia: risk factor for outcome
 - Fewer deaths (sample size)
 - Small effect (OR 1.03)
 - More heterogeneous study populations



Effects of Transfusion vs. Need for Transfusion (underlying condition)

- Mayo Clinic:
 - Anemia associated with poor outcome and underlying disease
 - Underlying disease is cause of poor outcome
 - Transfusion more common in cases (53%) vs. controls (37%)
 - Does transfusion cause poor outcome or does transfusion negate effect of anemia in outcome?
- FOCUS Study:
 - No difference in mortality or serious cardiac events between liberal strategy vs. symptomatic trigger
- Why transfuse?
 - Anemia slows post-op recovery?
 - Dutch study: Hb recovers quickly in healthier patients
Hb 10.5 to 11.4 g/dL in 10 days

Conclusion

- No good evidence that moderate pre-op or post-op day 14 anemia substantially adversely affects outcomes hip/knee replacement surgery
- Cannot extrapolate to more severe degrees of anemia



Summary

- RCT (TRICC and FOCUS)
 - Pre-txf Hb < 8 g/dL
 - Results equal or better than higher levels
- Cardiac Patients
 - Conflicting data
 - Overall – restrict txf for patients with acute coronary syndrome to 8 g/dL or Hct 25%
- Observational Studies
 - Mortality rate higher in txf'd patients probably correlates with illness severity
 - Txf does not improve outcome when pre-txf Hb > ~ 8 g/dL
- Anemia and Outcomes in Orthopedic Surgery
 - Separating effect of transfusion from need for transfusion - difficult

Conclusion

- Maximizing transfusion effectiveness focuses on prescribing txf at Nadir 7-8 g/dL
- In patients with acute coronary artery syndrome, txf's above 25% hematocrit may be detrimental and above 33% hematocrit are hazardous

US Transfusion Rates per thousand population ¹

Red Cells

- 2004: 48.5
- 2006: 48.9
- 2008: 49.3
- 2010: **? Reduction**

Pheresis Platelet Equivalents

- 2004: 5.6
- 2006: 5.8
- 2008: 6.6

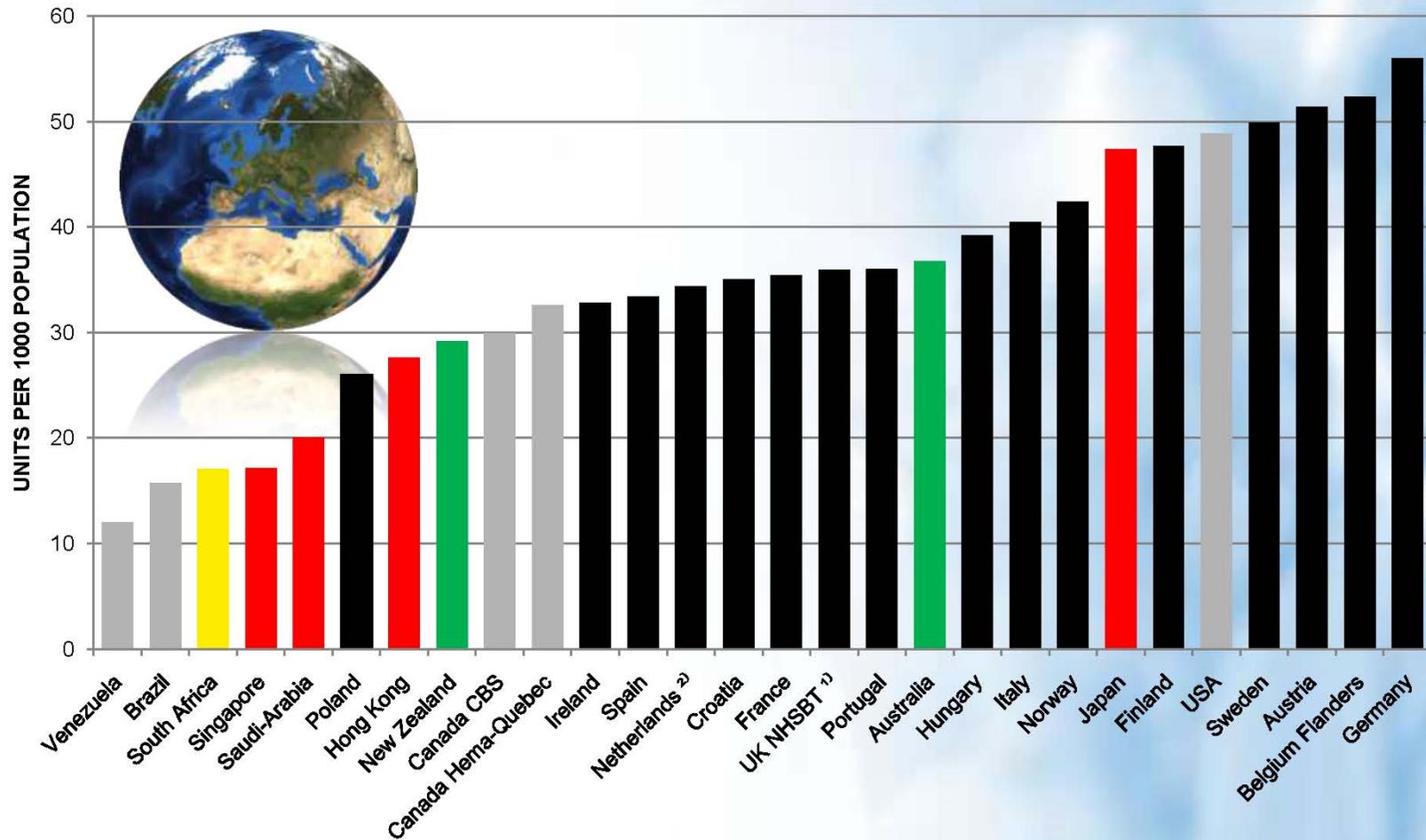
FFP

- 2004: 14.0
- 2006: 13.4
- 2008: 14.7

Red Cell & Platelet
transfusion rates have
been rising

¹ Source: *The National Blood Collection and Utilisation Survey Reports, US Dept of Health & Human Services*

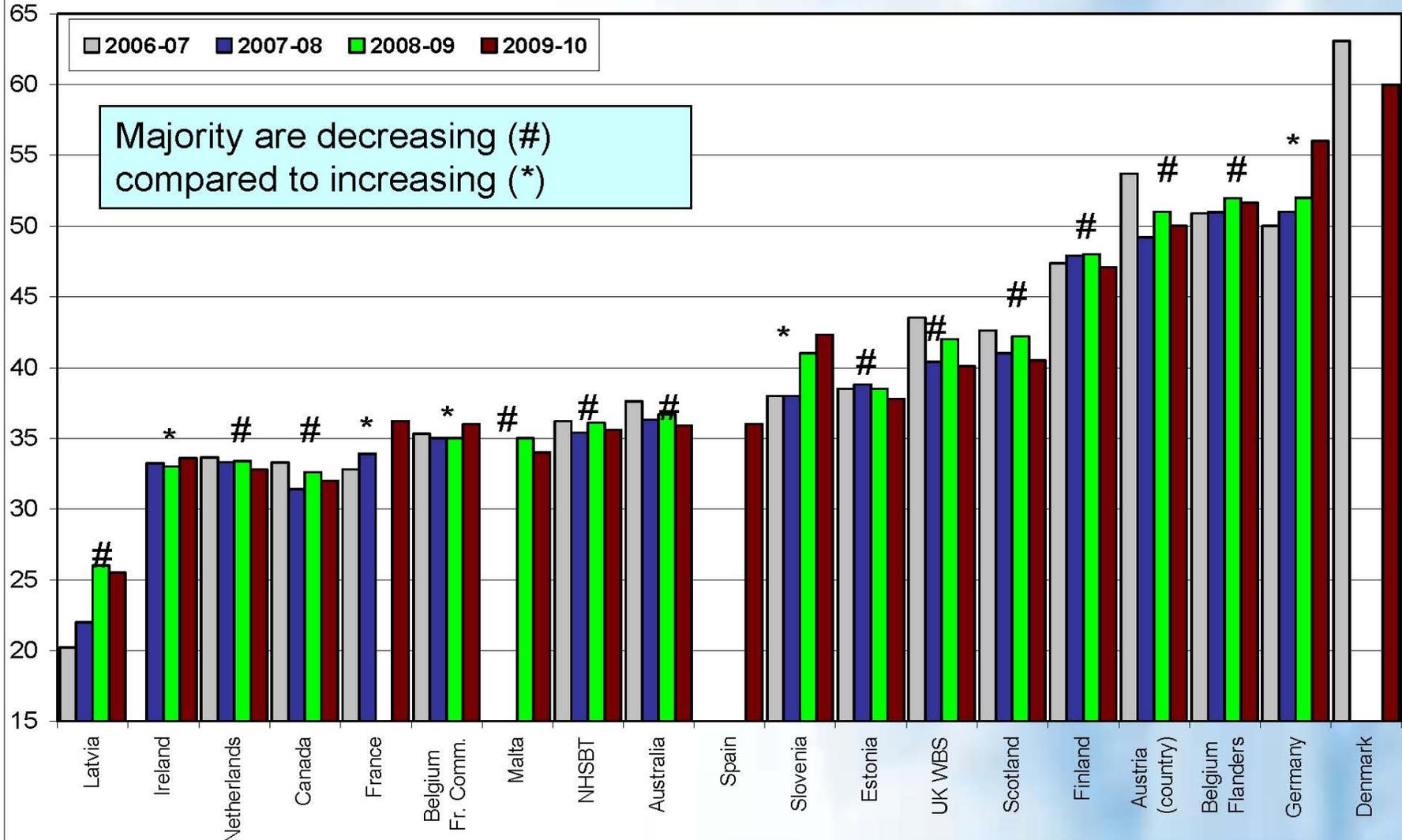
Global Red Cell Utilization Rates: 2008-09



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Source: D. V. Devine et al.: International Forum / Inventory Management, Vox Sanguinis 2009; DOI: 10.1111/j.1423-0410.2009.1252.x

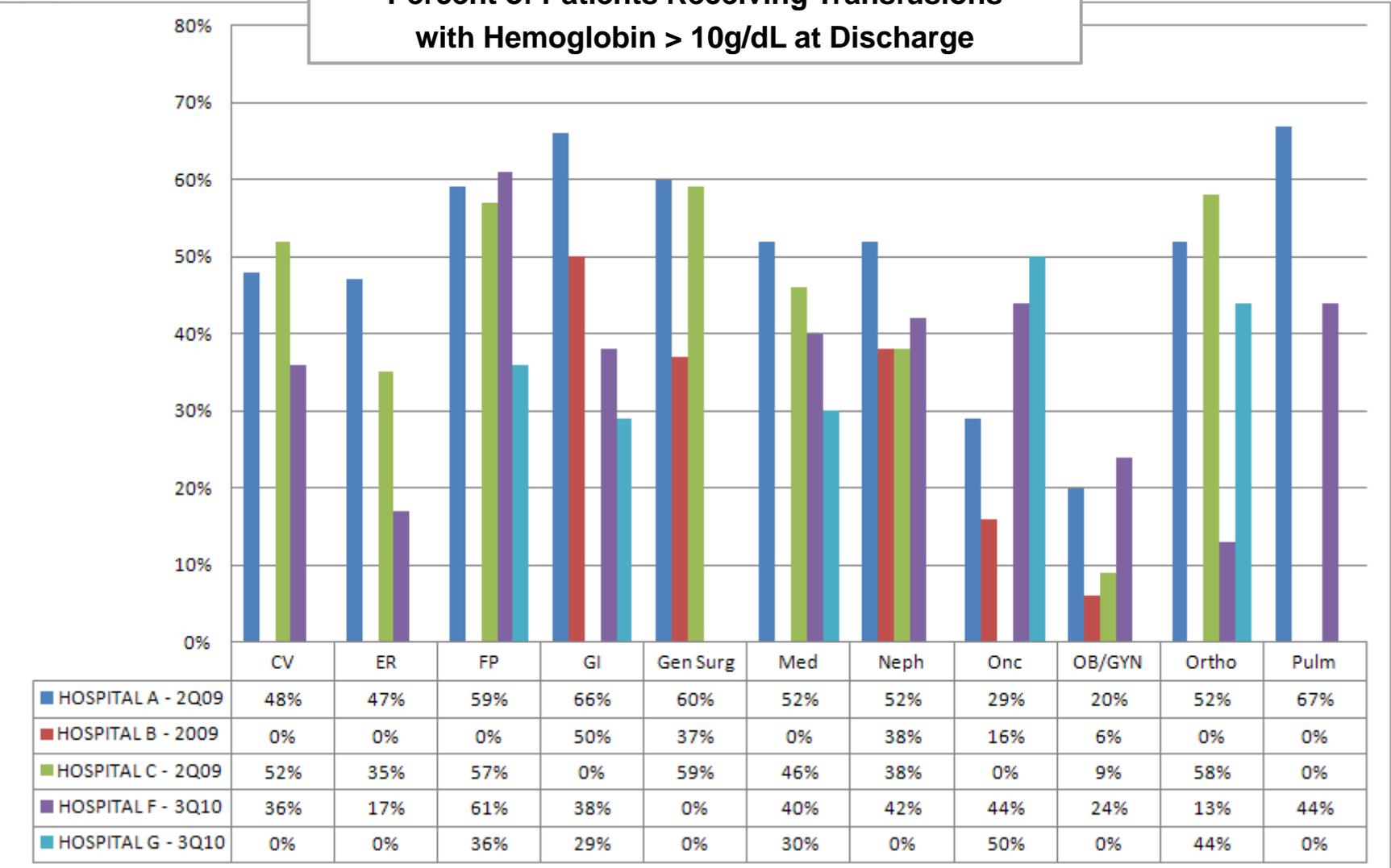
ABO Red Cell Issues per 1,000 of Population

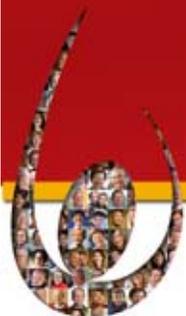




CBC Served Hospitals

Percent of Patients Receiving Transfusions with Hemoglobin > 10g/dL at Discharge





Transfusion Costs

- Cost of transfusion in surgical setting
- Activity-based costing study
- Four Hospitals – Three Countries
- Cost of transfusion for surgical procedures higher than previously reported

	<u>New Jersey</u>	<u>Rhode Island</u>	<u>Switzerland</u>	<u>Austria</u>
Cost per Unit	\$1,183	\$726	\$611	\$522
Consent Requirements	2.5%	2.5%		
Outsource In-Hospital Management			- 4%	- 4%
Indirect Costs	40%	40%	33%	33%
	Blood Management			
	Bloodless Surgery			



Transfusion Costs

[continued]

SHANDER ET AL.

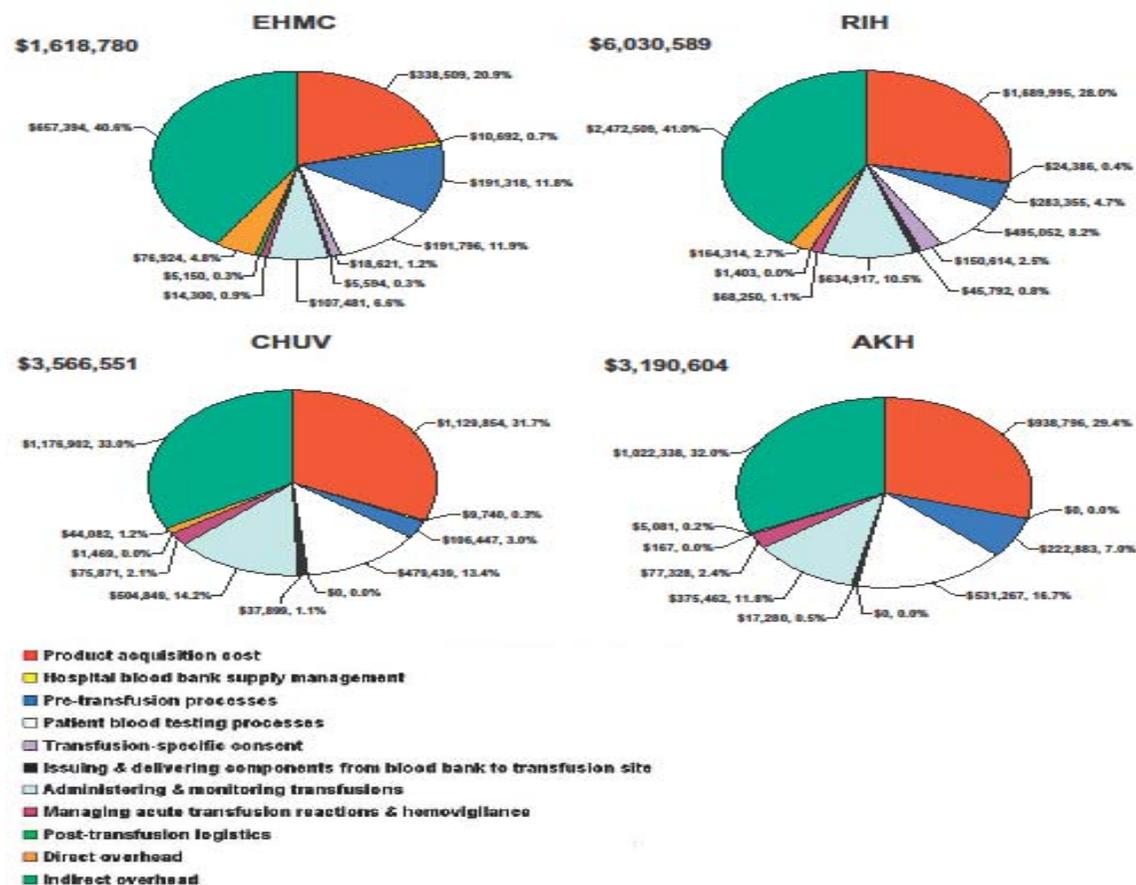
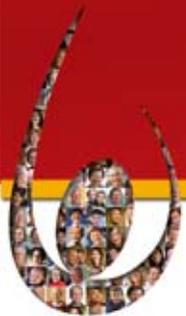


Fig. 3. Total costs of blood transfusions showing all contributing cost elements at two US and two European hospitals in 2007. Costs at CHUV (SF_r) and AKH (€) converted to \$USD using 1-year currency conversion average (May 2008–May 2009). Percentages of each contributing element shown next to \$USD amount.



■ “Storage Lesion”

- Loss of 2,3 DPG
- Biconcave disk shape → echinocytes and spherocytes (deformability loss)
- Spectrin-actin protein 4.1 oxidation and lipid peroxidation
- Vascular endothelium adhesion
- Decreased NO
- Increased pro-inflammatory agents
- Free Hb release



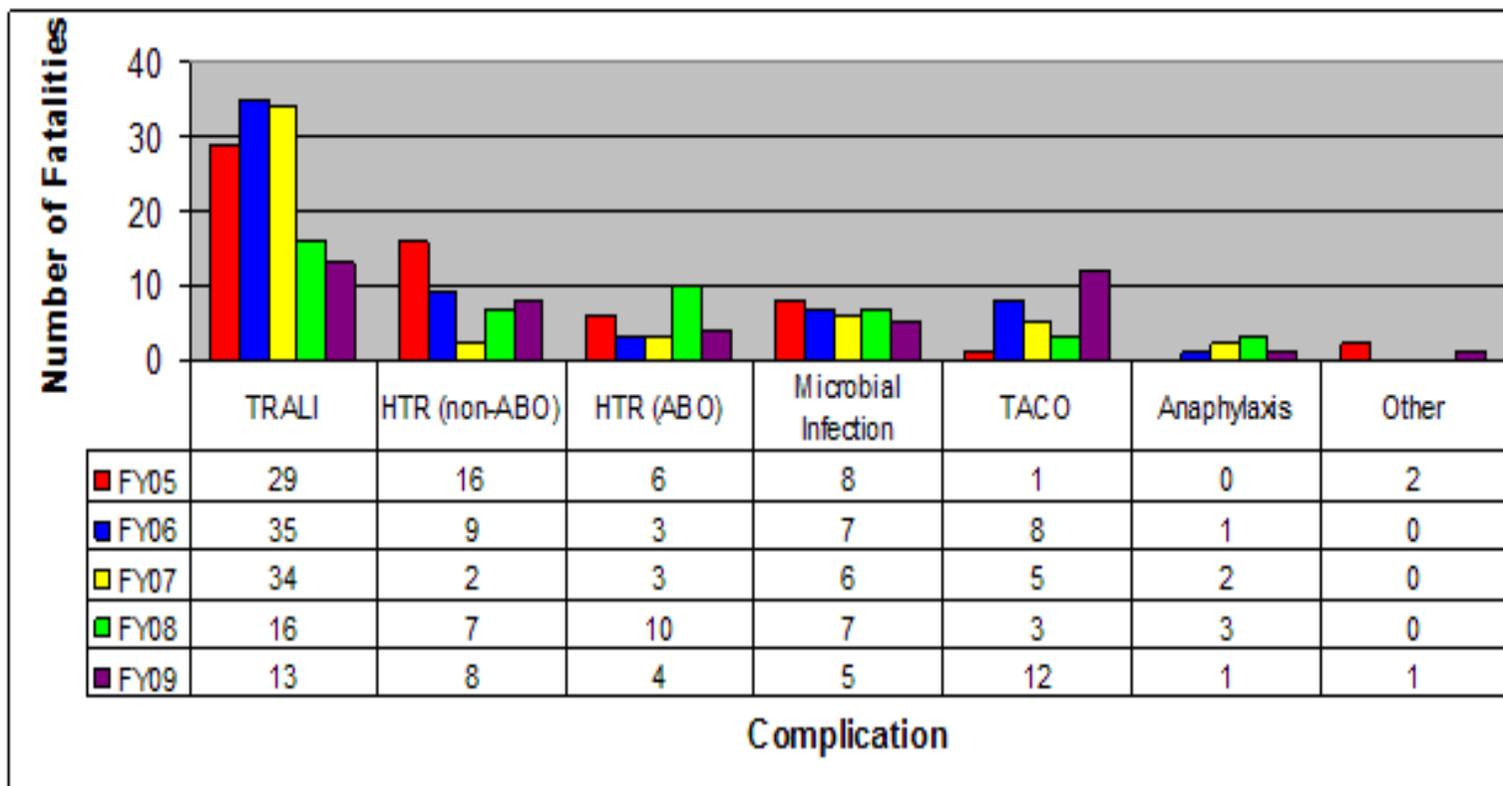
- Multiple Studies – Conflicting data, study design and end-points
 - RCT – No difference 19 versus 28 day storage
 - Neurocognitive Changes – No difference 3.5 versus 23 days
 - Cardiac Surgery Patients
 - Mortality Rate: Storage <11 days = 1.7%; Storage >20 days = 2.8%
 - However, study design: multiple conflicting variables
 - Two multicenter RCT's in progress
 - Age of blood evaluation - Canadian ICU's (<8 d versus standard practice)
 - Red Cell Storage Duration Study – United States (≤ 10 days versus ≥ 21 days)

In light of on-going RCT's and conflicting published reports, premature to change practice regarding storage interval.

- Weiskopf R, et al
Transfusion 2008; 48:2026
- Koch C, et al
N Engl J Med 2008; 358:1229
- Dzik W, et al
Transfusion 2008; 18:206
- Walsh T, et al
Crit Care Med 2004; 32:364
- Hebert P, et al
Anesth Analg 2005; 100:1433

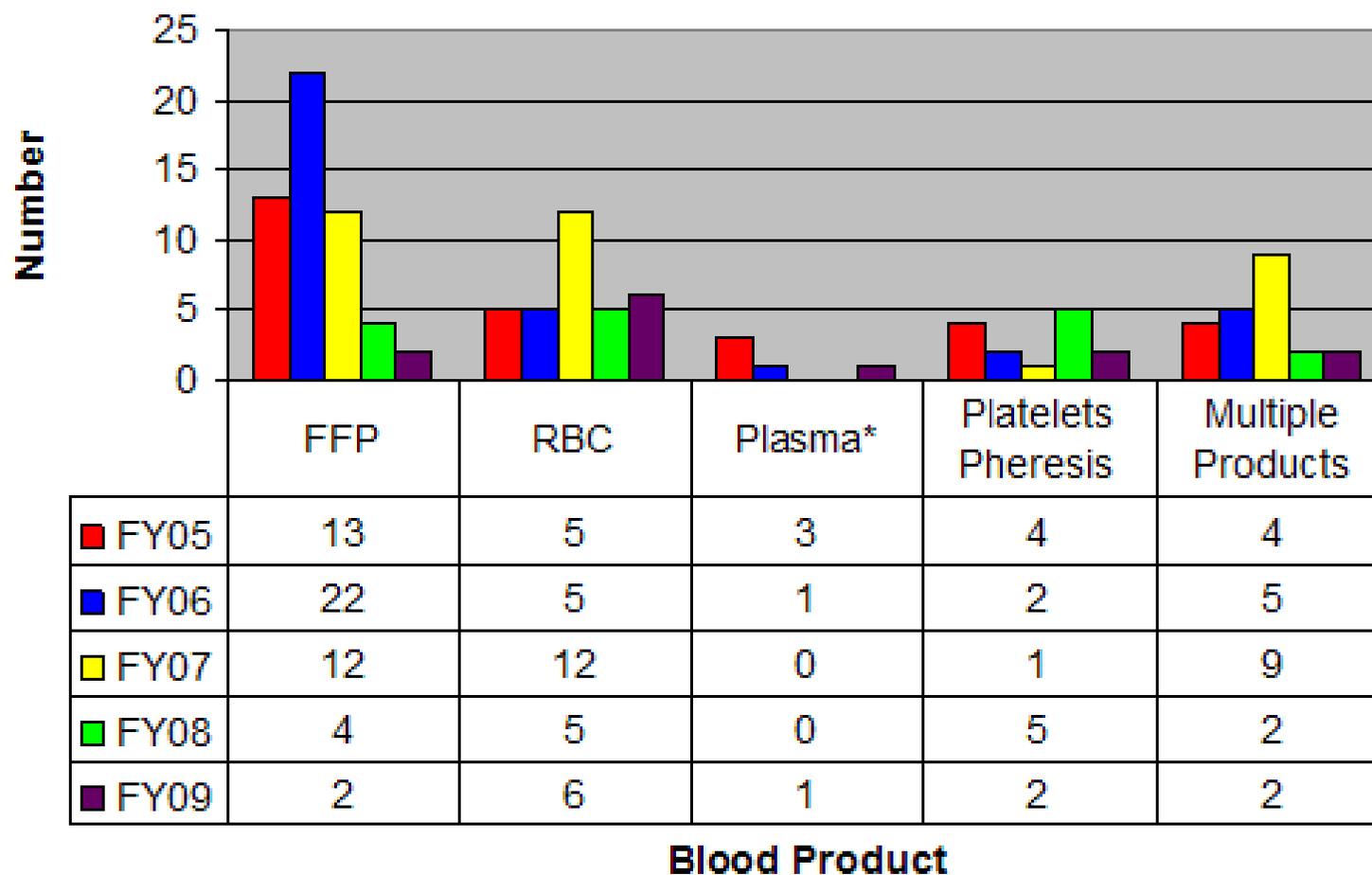


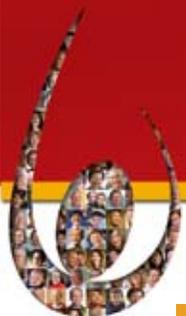
Fatalities Reported to FDA





FDA Reported Fatalities: TRALI





Infectious Disease Risks

Infectious Agent Risks	Risk of Infection Per Unit
Hepatitis A	One in 1,000,000
Hepatitis B	< One in 400,000
Hepatitis C	One in 1,600,000
HIV (AIDS)	One in 2,000,000
HTLV	One in 3,000,000
Chagas Disease	Rare
Bacterial Contamination (deaths)	Red Cells = One in 2,000,000 Platelets = One in 75,000
vCreutzfeldt Jakob Disease (vCJD)	No reports from transfusion in the U.S.
Malaria	< One in 4,000,000
West Nile Virus	Rare
Babesia	~ 100 TA - deaths
Dengue	Rare



Infectious Disease Risks

[continued]

Non-Infectious Serious Hazards of Transfusion	Risk Per Unit
ABO Incompatibility	One in 38,000
Anaphylaxis	One in 70,000
Acute Lung Injury	One in 15,000
Circulatory Overload	Varies by Patient
Iron Overload	Risk begins at 20 units or more

The table above cites the risk per unit. In practice, patients receive an average of 3 to 5 units of blood per transfusion episode.

References:

Menitove JE, Fiebig EW, Busch MP. Transfusion-transmitted diseases (Chapter 154). *Hematology Basic Principles* – 5th Edition. Ronald Hoffman, Edward J. Benz, Sanford J. Shattil, Bruce Furie, Leslie E. Silberstein, Philip McGlave, Helen Heslop (eds). Elsevier Churchill Livingstone, Philadelphia PA 2009, pgs 2277-2290

Zou S, Drosey KA, Noturo IP, (eds). Prevalence, incidence, and residual risk of human immune deficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion* 2010; 50: 1495-1504

Dumont LJ, Kleinman S, Murphy JR. Screening of single-donor apheresis platelets for bacterial contamination: The PASSPORT study results. *Transfusion* 2010; 50: 589-599

Vamvakas EC and Blachman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for the prevention. *Blood* 2009; 113: 3406-3417



- Point of care testing for bacterial contamination
 - At least, 50% of bacterially contaminated platelets detected by current methods
 - Verax PGD
 - Qualitative immunoassay for detecting aerobic and anaerobic Gram \ominus ive and Gram \ominus ive bacteria
- XMRV / MLV
 - Xenotropic murine leukemia retrovirus / murine leukemia virus
 - Linked to Chronic Fatigue Syndrome, prostate cancer
 - 4% - 7% of healthy blood donors
- Babesia (tick-borne)
 - Endemic = mid-Atlantic and northern Midwest
 - 100 transfusion associated deaths
 - Geography-based selective testing
- Dengue (mosquito-borne)
- What is really needed?
- Pathogen reduction!!



Questions and Answers



Community Blood Center

Save a Life. **Right Here, Right Now.**

For more information visit:

www.savealifenow.org

