"SANGUE FRESCO vs SANGUE CONSERVATO"

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“SANGUE brevemente conservato vs SANGUE lungamente conservato”

"Storage Lesion"

Table 4. Selected Changes Characteristic of the "Storage Lesion" and Their Consequences*

Storage Effects	Consequences
Decreased 2,3-diphosphoglycerate	Increased oxygen affinity and decreased oxygen unloading by hemoglobin
ATP depletion	Erythrocyte shape changes Increased osmotic fragility Decreased deformability
Microvesiculation and loss of lipid membrane	Decreased erythrocyte viability
Lipid peroxidation	Cellular injury and death
Bioactive substance generation	
Neutrophil/platelet enzymes	Febrile transfusion reactions
Histamine	Neutrophil priming/endothelial activation
Cytokines	Cellular injury/monocyte priming
Arginase	Transfusion-related acute lung injury
Lipids	Possible multiple organ failure

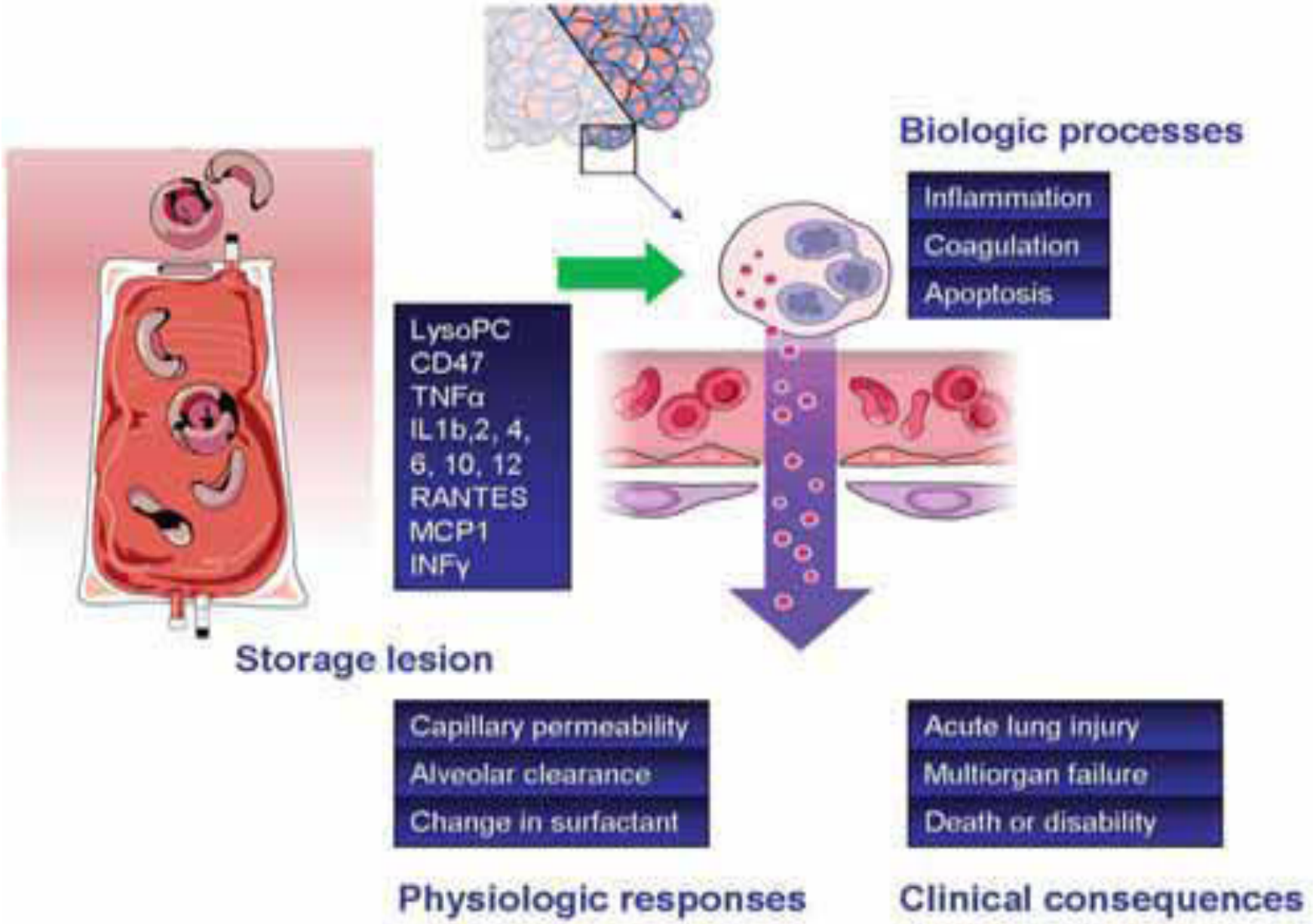
*ATP indicates adenosine triphosphate.

“Storage Lesion” da componenti indesiderate

Rilascio di sostanze bioattive:

a) leucociti
b) piastrine

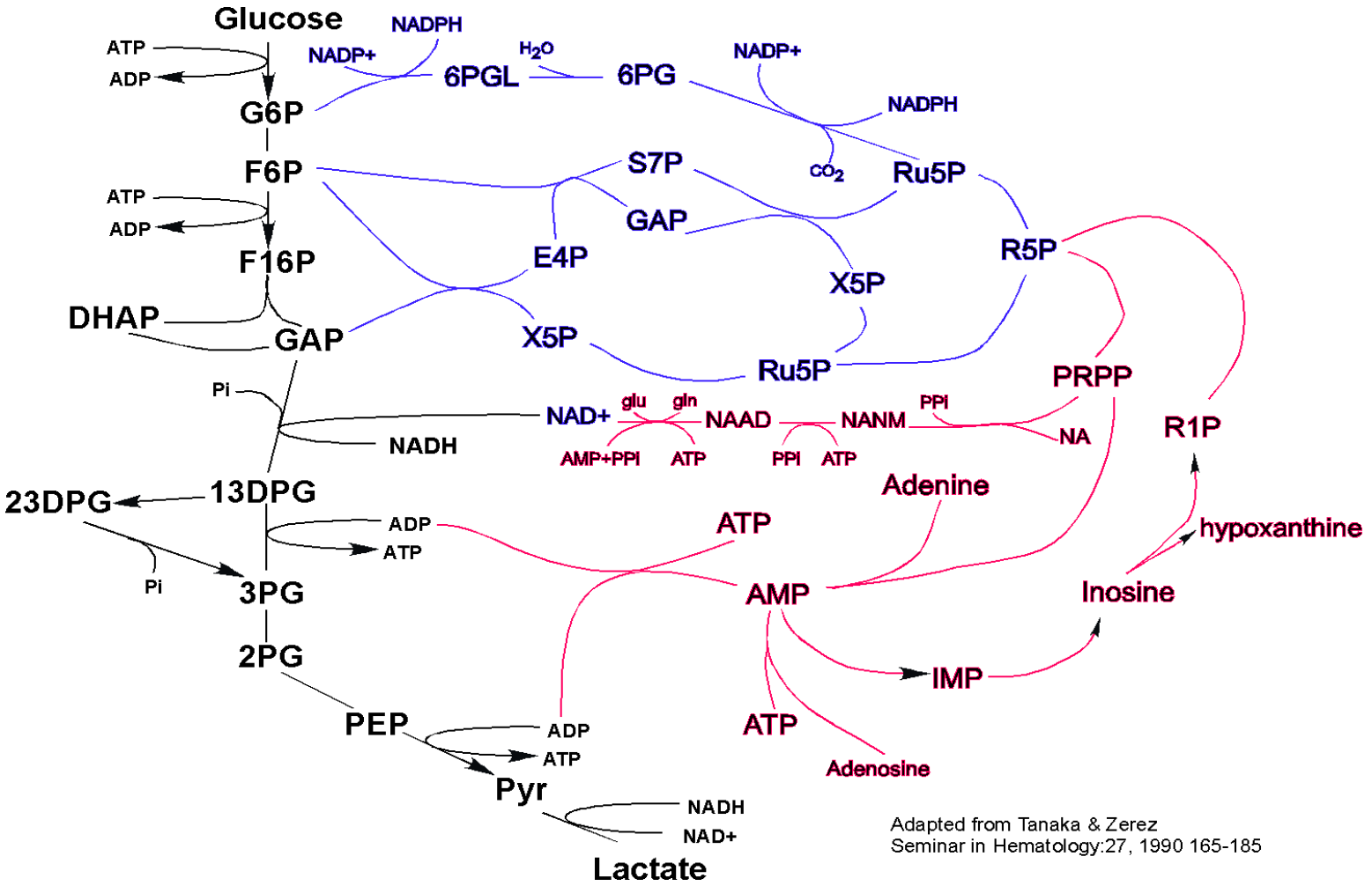
Rilascio di mediatori



Conservazione degli eritrociti

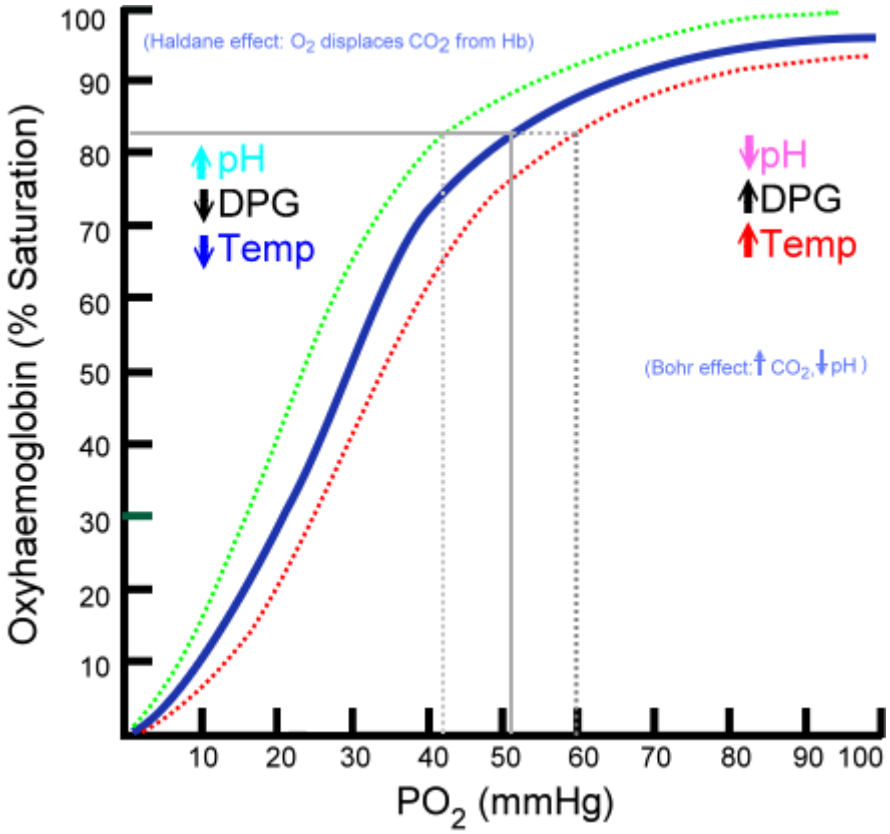
- *Integrita' metabolica*
- *Integrita' di membrana*
- *Proprieta' di membrana*
- *Rilascio di mediatori*

RBC metabolic pathways

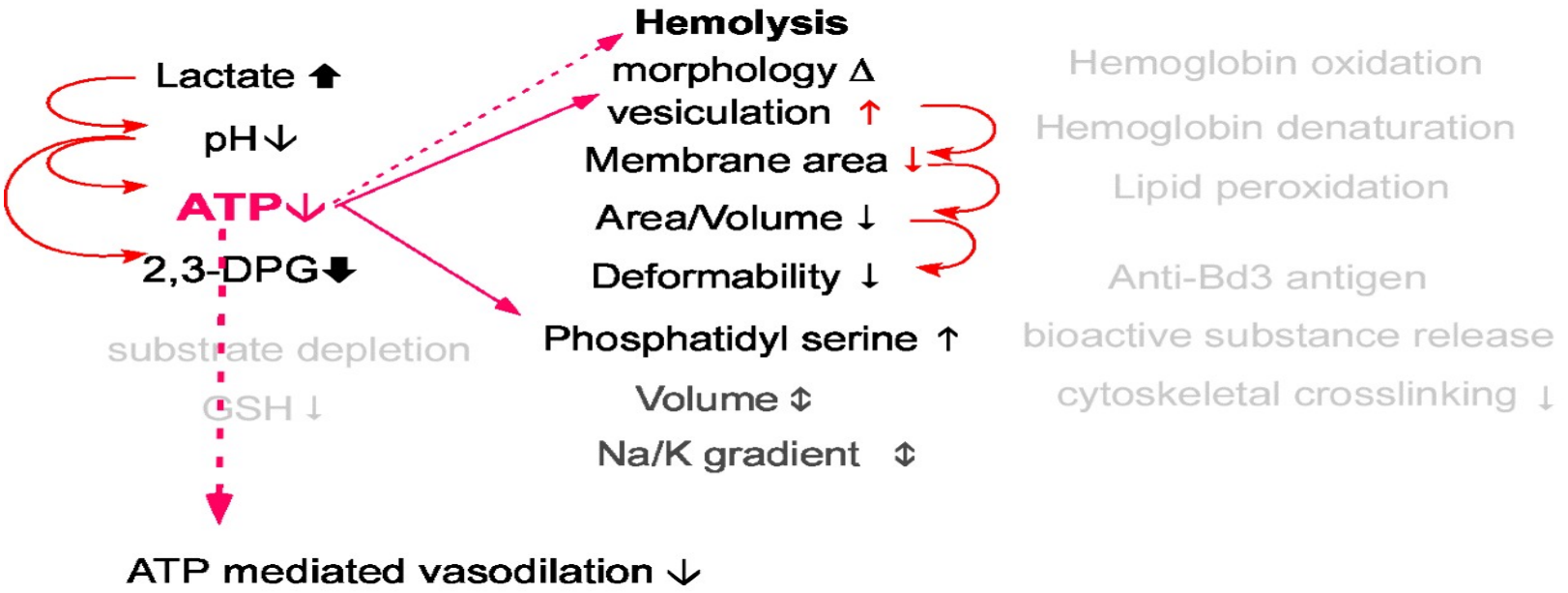


Adapted from Tanaka & Zerez
Seminar in Hematology:27, 1990 165-185

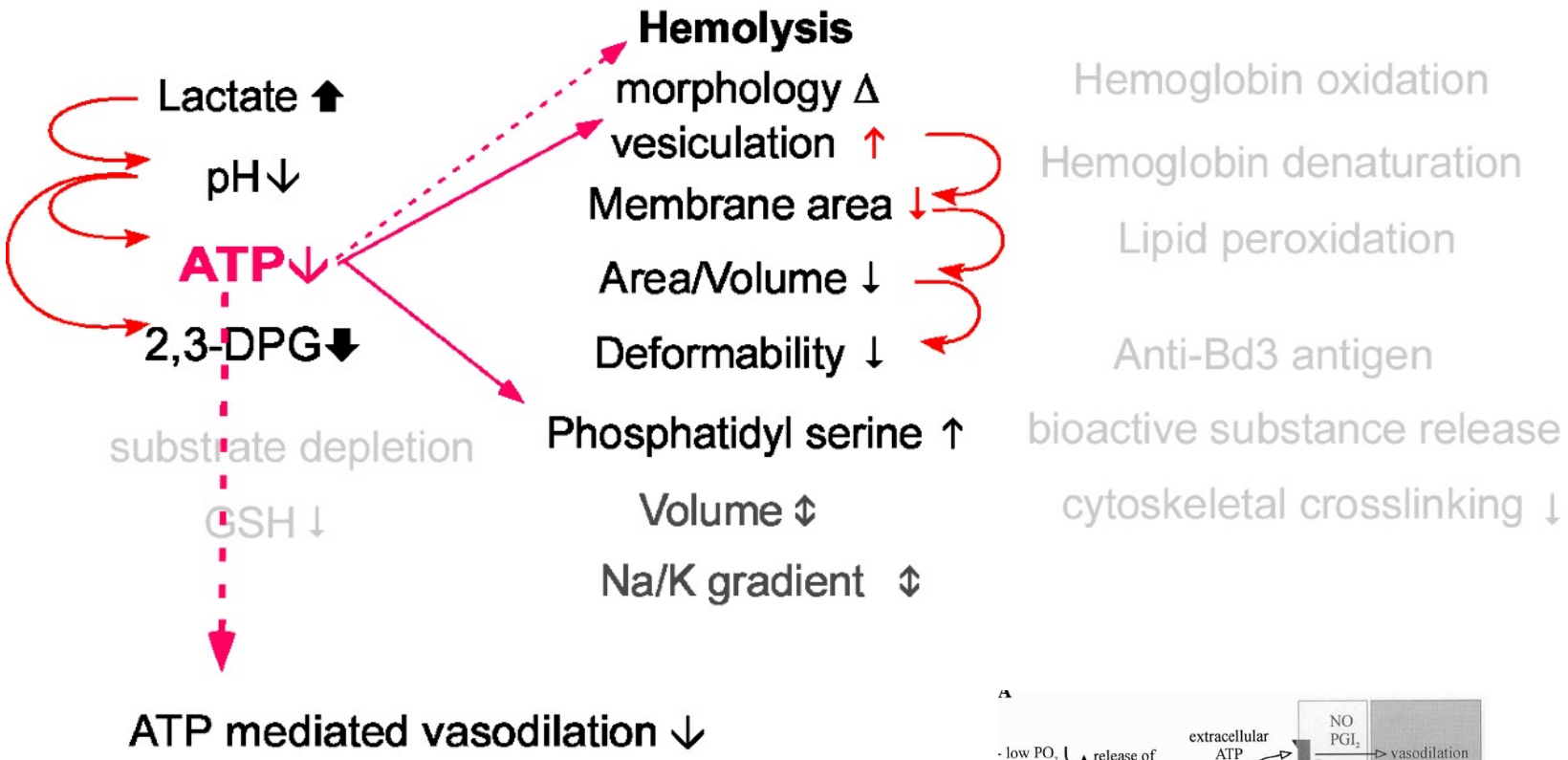
Integrita' metabolica

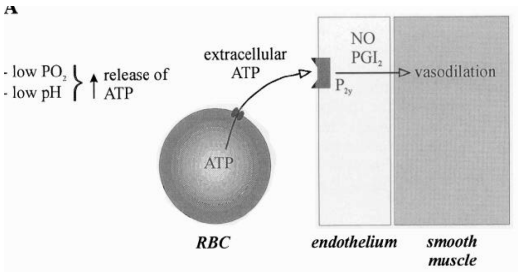


Consequences of ATP depletion

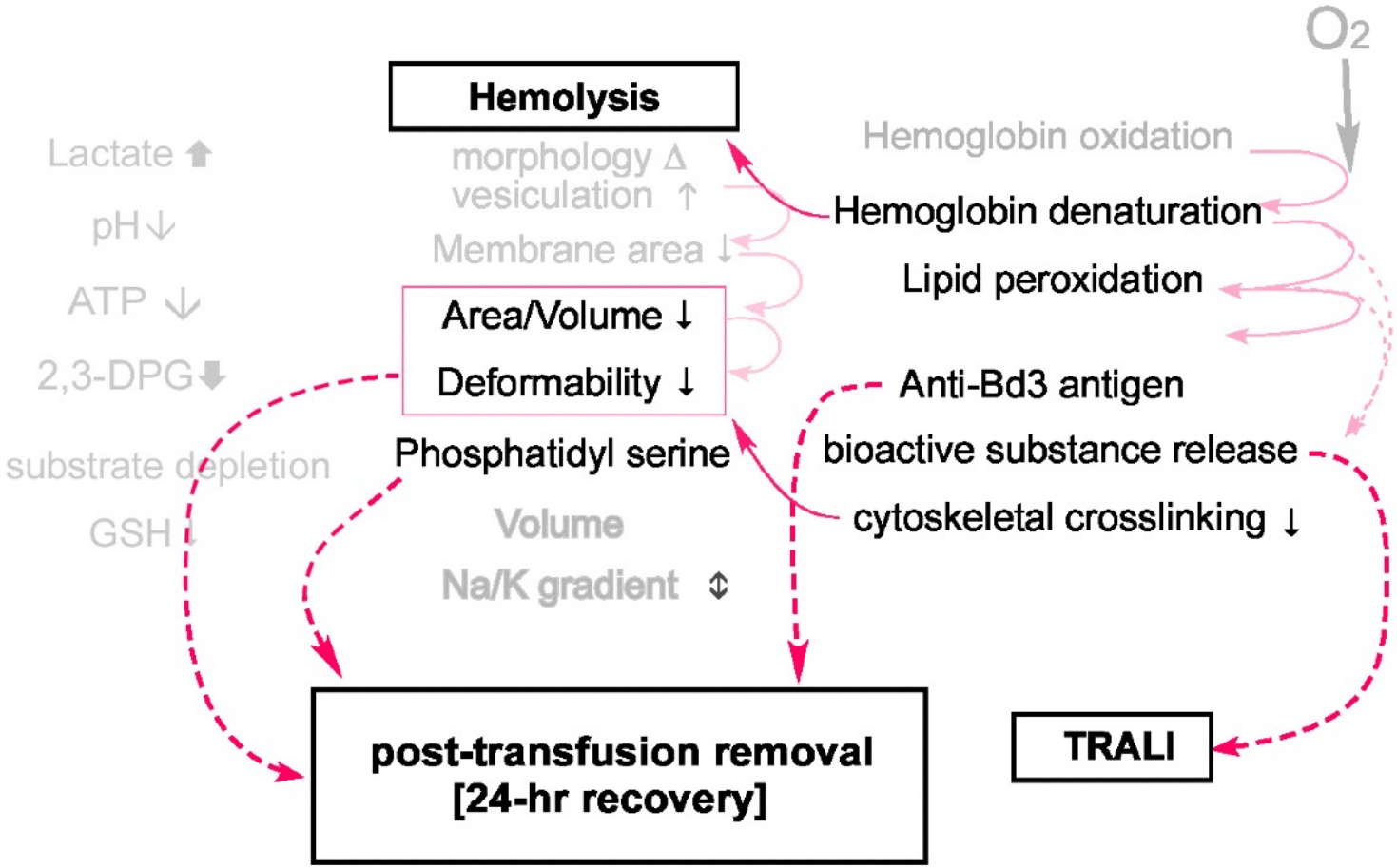


Regulation of microvascular perfusion mediated by ATP

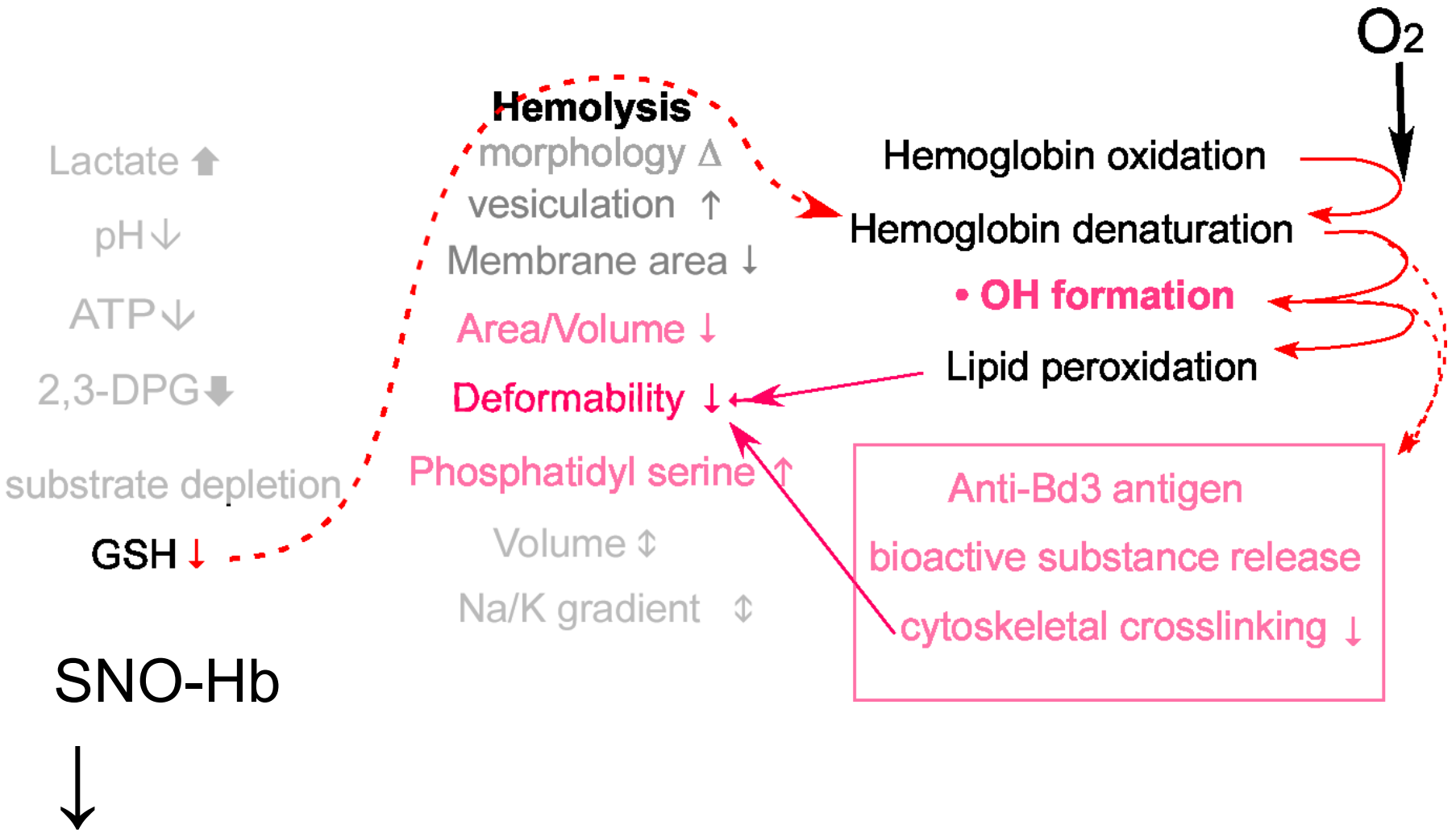




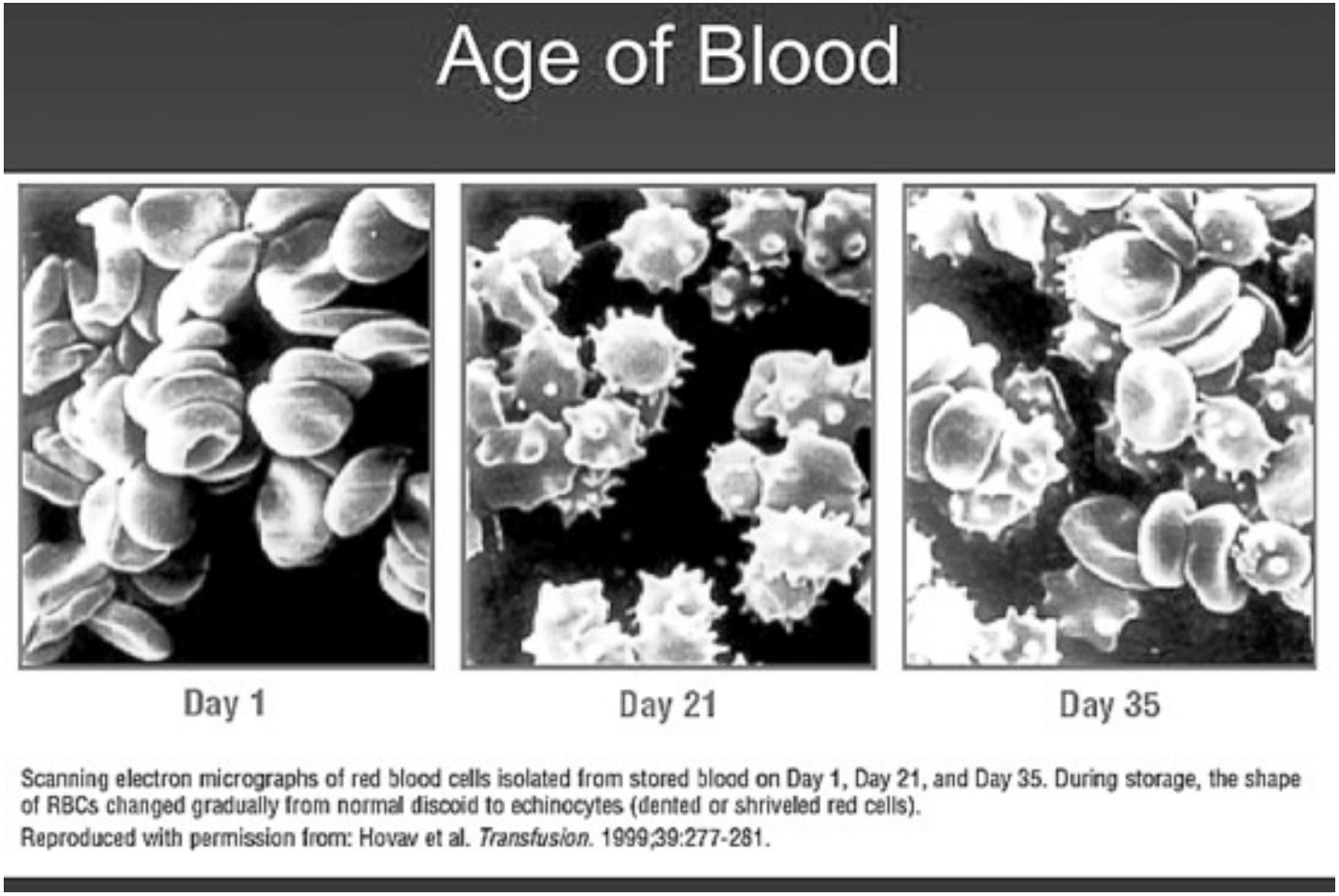
Consequences: oxidative damage



Storage lesions linked to oxidative damage



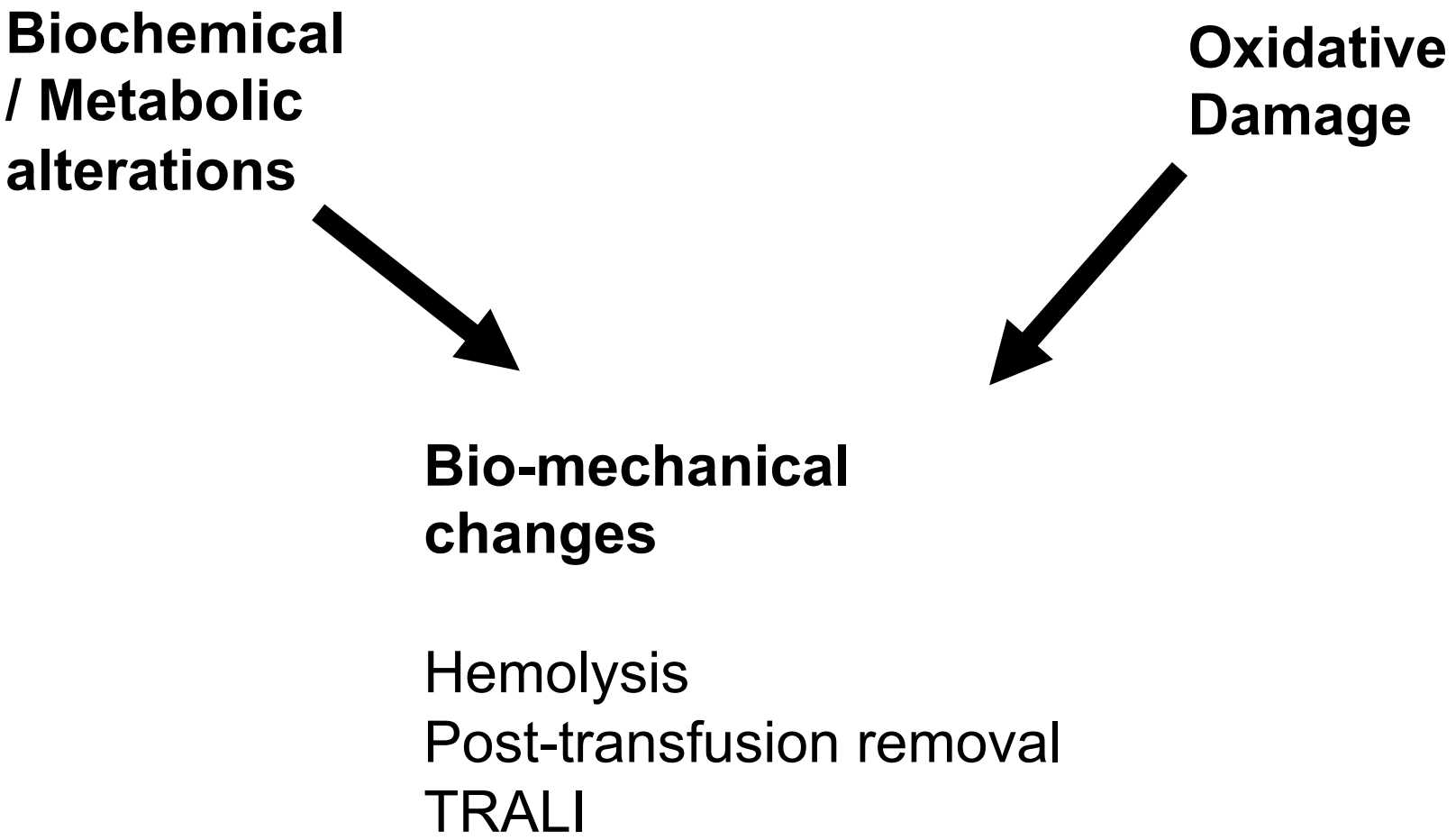
Integrita' di membrana



Scanning electron micrographs of red blood cells isolated from stored blood on Day 1, Day 21, and Day 35. During storage, the shape of RBCs changed gradually from normal discoid to echinocytes (dented or shriveled red cells).

Reproduced with permission from: Hovav et al. *Transfusion*. 1999;39:277-281.

Damage pathways



Concentrazione del Glutatione ridotto negli eritrociti concentrati conservati per > 40 gg in condizioni di stress ossidativo

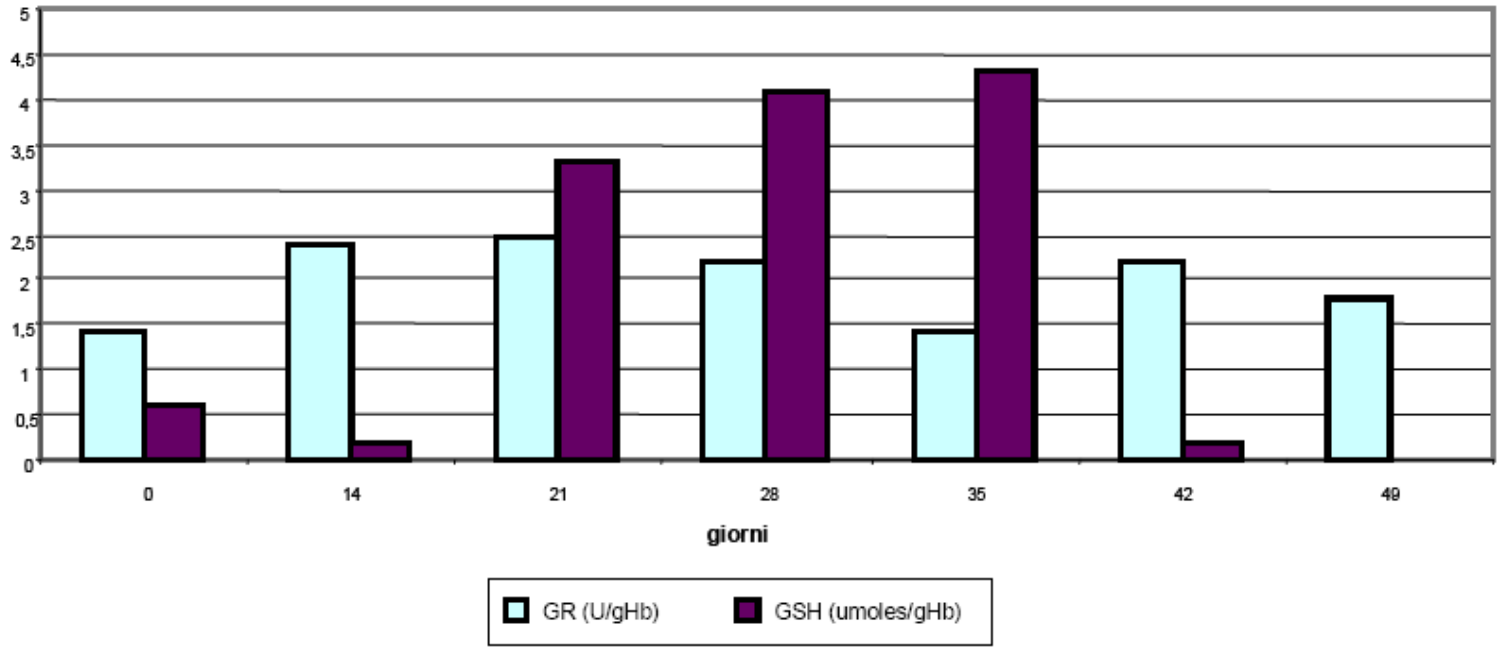


Figura 2. Variazioni dei livelli di GSH intraeritrocitario e dell'attività dell'enzima GR dopo stress ossidativo *in vitro* di eritrociti conservati in SAG-M fino a 49 giorni

Proteine di membrana negli eritrociti concentrati conservati per > 40 gg in condizioni di stress ossidativo

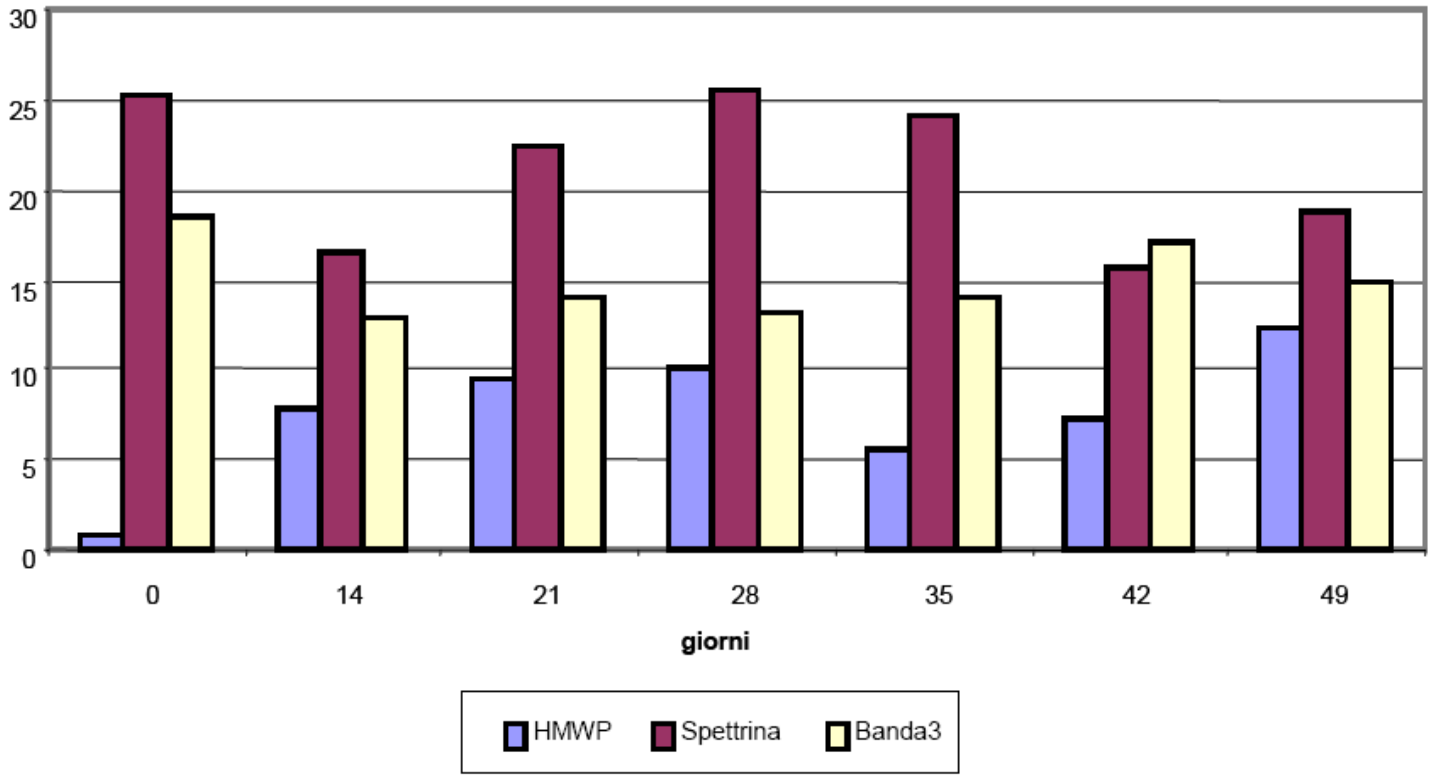
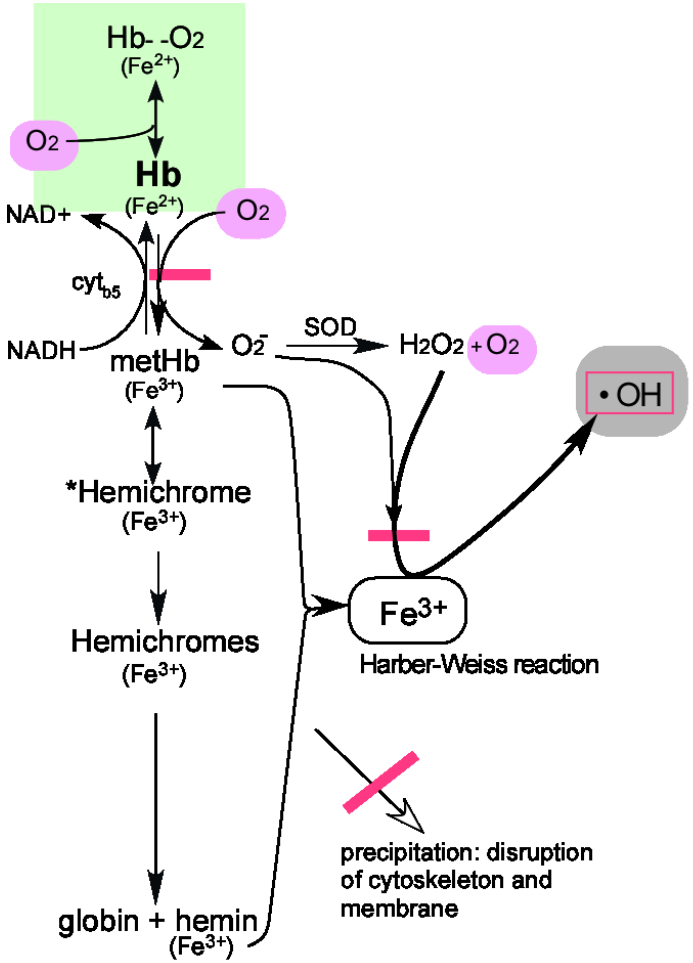


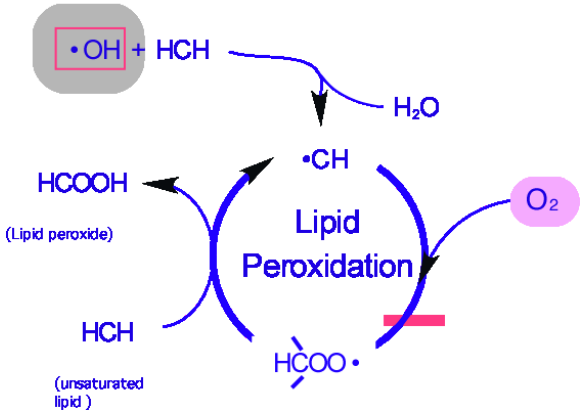
Figura 6. Valori percentuali delle proteine di membrana di emazie concentrate dopo stress ossidativo *in vitro* durante la conservazione

Reduction of oxidative damage: storage under anaerobic condition



Store RBC without oxygen

- *Stop hydroxyl radical-mediated peroxidation cycles*
- *Prevent hemoglobin denaturation*



Rejuvenation

Post-storage metabolic manipulations

Mixture of pyruvate, inosine, Pi, adenine, PEP etc

- *Rejuvesol (Cytosol Laboratory Inc)*
  - *37°C incubation followed by cell washing]*
- *Experimental*
  - *PEP*

Sangue poco conservato vs sangue lungamente conservato : risultati dei RCT

Vamvakas EC Transfusion 2010; 50: 600-610

TABLE 1. RCTs investigating effects of prolonged RBC storage

RCT	Comparison arms	Sample size: patients included in the intention-to-treat vs. the as-treated analysis	Conclusions	Other findings or comments
Schulman et al.[35]	Trauma patients receiving at least 2 units of <11-day-old vs. >20-day-old WBC-reduced RBCs	24 vs. 17 (seven subjects received 0 or 1 RBC unit)	Conduct of an RCT is *not* feasible in a single-center US setting	Recipients of fresh RBCs received 9.3 units and had four deaths; recipients of old RBCs received 10.6 units and had two deaths ($p > 0.05$)
Hébert et al.[31]	Cardiac-surgery *or* ICU patients receiving <8-day-old vs. standard-issue RBCs (but randomized only when >15-day-old RBCs were available in the blood bank) after implementation of universal WBC reduction	66 vs. 57 (five and two subjects randomized to receive fresh or old RBCs, respectively, were not transfused; two patients allocated to receive fresh RBCs did not receive RBCs stored for <8 days and were also excluded)	Conduct of an RCT is feasible in a multicenter Canadian setting, since 1) the median storage time was 4 or 19 days, respectively, in recipients of <8- or >15-day-old RBCs, and 2) 59 and 91%, respectively, of the subjects allocated to receive <8- or >15-day-old RBCs received the appropriate component >90% of the time	Compared with the recipients of old RBCs, recipients of *fresh* RBCs had *more* in-hospital deaths (Fig. 1; $p = 0.45$), as well as more in-hospital deaths and life-threatening complications (27% vs. 12%; $p = 0.31$), but they were 5 years older on average as well as sicker (comorbid illness[es] present in 85% vs. 65%), and they thereby received a higher transfusion dose (5.5 vs. 3.3 units)
Mou et al.[37]	Infants with congenital heart disease undergoing circuit priming with *fresh* whole blood (stored for 45.8-50.7 hr) vs. RBCs stored for 117.0-162.7 hr and reconstituted with fresh-frozen plasma	205 vs. 200 (infants with a median age of 2.7 months and a median weight of 4.3 kg many of whom underwent the equivalent of a complete exchange transfusion with 1 whole-blood unit used for priming)	Based on intention-to-treat analysis, recipients of *fresh* whole blood had a *longer* LOS in the ICU and more generalized edema ($p < 0.05$); transfusion requirements, postoperative bleeding, and indicators of myocardial injury or systemic inflammation did not differ between the arms	Study excluded ex post facto from the meta-analysis, because 1) both arms had received RBCs <7 days old; 2) component allocation based on RBC length of storage was not maintained for the infants' further transfusion needs (mean of 2.25 additional donor exposures); and 3) CPD whole blood was compared to Adsol RBCs, which contain additional preservatives (adenine and mannitol)

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Un OR > 1 dimostrerebbe un influenza negativa degli eritrociti lungamente conservati sulla mortalita' in regime di ricovero

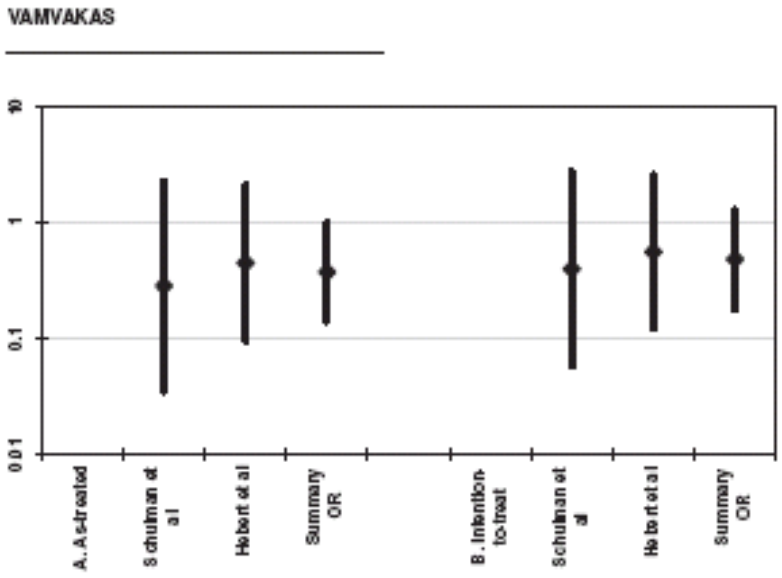

Fig. 1. RCTs investigating the association of RBC storage with in-hospital mortality.[21,28] For each RCT, the figure shows the OR of occurrence of the adverse outcome in recipients of old versus fresh RBCs. Provided that the difference is significant, an OR of greater than 1 indicates that old RBCs are associated with a *worse* outcome, and an OR of less than 1 indicates that old RBCs are associated with a *better* outcome. Each OR is surrounded by its 95% CI. If the CI does not include the null value of 1, the effect of RBC storage is significant ($p < 0.05$). The figure also shows the summary OR across the two studies.[21,28] Both studies had reported only as-treated analyses. Accordingly, only the data shown for the as-treated analyses (A) were extracted from both publications, and the intention-to-treat analysis (B) is shown solely for the purpose of illustration. For the latter analysis, it was assumed that all seven randomized trauma patients who received transfusion of 0 or 1 RBC unit in the study of Schulman and colleagues[28] (and were excluded from the as-treated analysis of that study[21]—Table 1) survived.

Pz . Cardiochirurgici, sopravvivenza ad 1 anno 92,6% Pz trasf con GR<2 sett.,89% con GR> 2 P>0.001

N Engl J Med 20 Marzo 2008

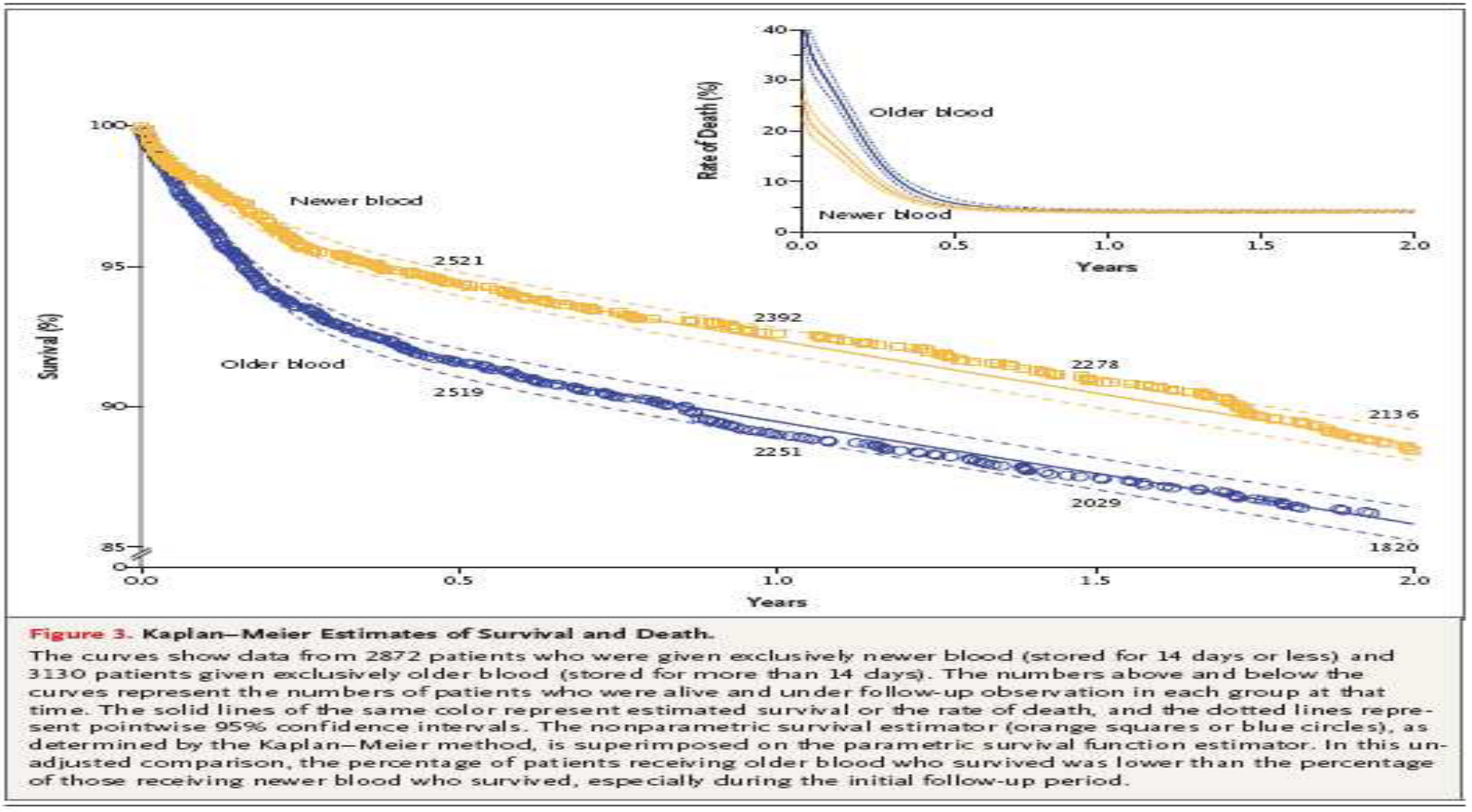

Figure 3. Kaplan–Meier Estimates of Survival and Death.

The curves show data from 2872 patients who were given exclusively newer blood (stored for 14 days or less) and 3130 patients given exclusively older blood (stored for more than 14 days). The numbers above and below the curves represent the numbers of patients who were alive and under follow-up observation in each group at that time. The solid lines of the same color represent estimated survival or the rate of death, and the dotted lines represent pointwise 95% confidence intervals. The nonparametric survival estimator (orange squares or blue circles), as determined by the Kaplan–Meier method, is superimposed on the parametric survival function estimator. In this unadjusted comparison, the percentage of patients receiving older blood who survived was lower than the percentage of those receiving newer blood who survived, especially during the initial follow-up period.

Increased Rate of Infection Associated With Transfusion of Old Blood After Severe Injury

Patrick J. Offner, MD, MPH; Ernest E. Moore, MD; Walter L. Biffl, MD; Jeffrey L. Johnson, MD; Christopher C. Silliman, MD, PhD

Patients: Sixty-one trauma patients with an Injury Severity Score greater than 15, age older than 15 years, and survival longer than 48 hours who were transfused with 6 to 20 U of red blood cells in the first 12 hours after injury were studied. By means of blood bank records, the age of each unit of blood was determined.

Table 1. Selected Patient Data Stratified by Presence or Absence of Infection*

	Major Infection	No Infection	*P* Value
Patient age, y	39 ± 4	36 ± 3	.48†
Sex, No. M/F	25/7	24/5	.75‡
Injury Severity Score	33 ± 2	29 ± 2	.12§
Mechanism of injury, No. blunt/penetrating	22/10	16/13	.30‡
Base deficit, mEq/L	10.3 ± 1	10.1 ± 1	.89§
Serum lactate, mmol/L‖	5.3 ± 0.5	4.3 ± 0.4	.15§
PRBCs transfused in the first 12 h	12.8 ± 0.9	10.4 ± 0.8	.04†

*Values are mean ± SEM unless otherwise specified. PRBCs indicates packed red blood cells
†Mann-Whitney test.
‡χ^2 Test.
§*t* Test.
‖To convert to milligrams per deciliter, divide by 0.111.

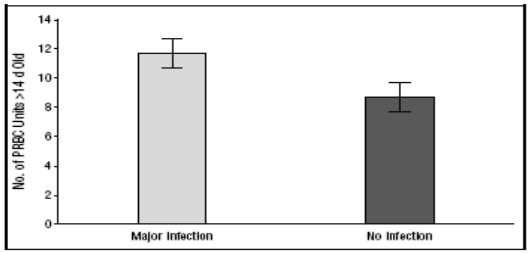

Figure 1. Number of packed red blood cells (PRBCs) more than 14 days old in patients who developed major infections after injury vs those who did not. Patients who did develop major infections received significantly more units (*P* = .02, *t* test).

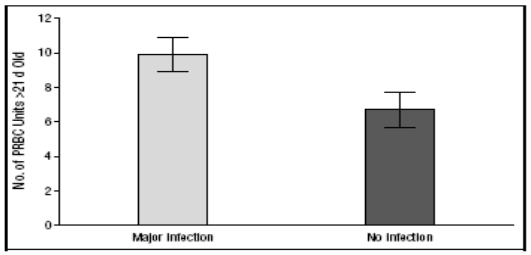

Figure 2. Number of packed red blood cells (PRBCs) more than 21 days old in patients who developed major infections after injury vs those who did not. Patients who did develop major infections received significantly more units (*P* = .02, *t* test).

Table 2. Multivariate Analysis Results*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Model 1		
Patient age, y	1.01 (0.98-1.04)	.54
Sex	0.805 (0.19-3.42)	.77
Mechanism	0.628 (0.18-2.24)	.47
Injury Severity Score	1.044 (0.97-1.12)	.24
No. of Units >14 d Old	**1.127 (1.01-1.26)**	**.03**
Model 2		
Patient age, y	1.007 (0.98-1.04)	.67
Sex	0.95 (0.22-4.05)	.94
Mechanism	0.565 (0.16-2.03)	.38
Injury Severity Score	1.037 (0.96-1.11)	.32
No. of Units >21 d Old	**1.13 (1.00-1.27)**	**.04**

*Boldface type indicates statistical significance.

Table 3. Results Stratified by Total RBC Transfusion Requirement*

	Infection	No Infection	*P* Value
Total RBCs: 6-10 U (n = 34)			
Total RBCs	8.5 ± 0.40	7.7 ± 0.34	.12
RBCs >14 d old	7.8 ± 0.60	5.9 ± 0.60	.04
RBCs >21 d old	6.6 ± 0.72	4.8 ± 0.81	.11
Total RBCs: 11-15 U (n = 12)			
Total RBCs	13.5 ± 0.5	13.1 ± 0.5	.67
RBCs >14 d old	10.5 ± 3.5	12.5 ± 0.6	.44
RBCs >21 d old	8 ± 3	11.4 ± 0.8	.19
Total RBCs: 16-20 U (n = 15)			
Total RBCs	18.3 ± 0.6	19.3 ± 1.2	.46
RBCs >14 d old	17.4 ± 1	15 ± 2.9	.33
RBCs >21 d old	15 ± 1.4	7.3 ± 1.3	.02

*Values are mean ± SEM. RBC indicates red blood cell.

ity between the total number of RBC units transfused and the number of units greater than 14 and 21 days old. Regression models incorporating variables with near collinearity may yield unreliable or impossible results. Analysis after stratification by total transfusion requirement avoids this problem (**Table 3**). In the subgroup receiving 6 to 10 U of packed RBCs, patients developing major infections received more RBCs greater than 14 days old. Similarly, patients receiving 16 to 20 U and developing a major infection received significantly more RBCs greater than 21 days old. No differences were seen in patients receiving 11 to 15 U; however, the groups were small, limiting the power of detecting any differences between them.

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Effetto confondente del carico trasfusionale negli studi osservazionali

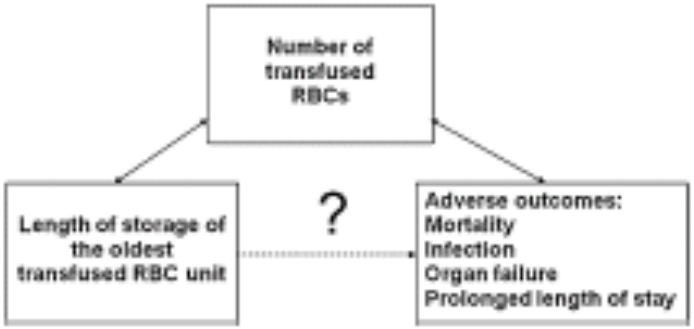

Fig. 3. Confounding of the association between the *oldest* RBC unit transfused to each patient and adverse outcomes by the number of transfused RBCs in observational studies. In these studies, unlike the mean storage of all transfused RBCs, the length of storage of the *oldest* transfused RBC unit is bound to be associated with adverse outcomes because it is associated with the number of transfused RBCs (see text and Fig. 2 in the report of van de Watering and colleagues[31]). The number of transfused RBCs in turn is always associated with adverse outcomes,[27-30] thereby linking the length of storage of the oldest transfused RBC unit to these adverse outcomes.

Outcome e carico trasfusionale

World J Surg
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Outcome Analysis of Blood Product Transfusion in Trauma Patients: A Prospective, Risk-Adjusted Study

Grant V. Bochicchio · Lena Napolitano · Manjari Joshi · Kelly Bochicchio · Walter Meyer · Thomas M. Scalea

Conclusion

There is a dose dependent correlation between blood product transfusion (PRBCs, FFP) and adverse outcome (mortality, infection) in critically ill trauma patients after appropriate stratification for all other variables that affect trauma outcome. All efforts to reduce blood transfusion in critically ill trauma patients should be implemented.

Table 5 Outcome analysis stratified by blood product transfusion versus no transfusion

	Blood product transfusion ($n = 786$)	No blood product transfusion ($n = 386$)	p value
Infection	230 (34%)	46 (9.4%)	<0.001
Ventilator days	12.9 ± 12	6.3 ± 6	<0.001
Hospital days	18.6 ± 14	9 ± 7	<0.001
ICU days	13.7 ± 11	7 ± 5	<0.001
ICU admission	724 (74%)	249 (26%)	<0.001
Hospital mortality	147 (21.4%)	32 (6.5%)	<0.001

Table 6 Risk of infection, hospital and ICU LOS, and mortality stratified by blood product type (adjusted for age, ISS, and admission GCS)

	PRBCs OR (CI)	FFP OR (CI)	Platelets OR (CI)
Infection	2.8 (1.96–3.94)*	1.02 (1.01–1.04)*	0.94 (0.96–1)
Hospital LOS	8.1 (6.6–9.03)*	1.3 (1.3–1.41)*	−0.15 (−0.023 to 0.07)*
ICU LOS	5.6 (4.2–7.06)*	1.25 (1.2–1.31)*	−0.08 (−0.14 to 0.01)*
Mortality	1.05 (1.03–1.07)*	1.03 (1.02–1.05)*	1.03 (1.02–1.04)

* $p < 0.001$

LOS, length of stay; ICU, intensive care unit; PRBCs, packed red blood cells; FFP, fresh frozen plasma; OR, odds ratio; CI, confidence interval

Ipotesi di lavoro per un miglioramento dell'outcome in soggetti candidati alla trasfusione di pRBC in ambito chirurgico

DIAGNOSI	ESA +/- PABD (media)	ANH	PBC (volume medio reinfuso)	N °UNITA' "FRESCHE" (media)	CARICO OMOLOGO RESIDUO Paz. Unita' (media)
COXARTROSI (44)	SI (2 unità) SI (ESA) 61.2%	NO	SI (270ml)	1 30%	30% dei paz. 0.29 unita' 8.8%
GONARTROSI (95)	SI (1 unità) 27%	NO	SI(600ml)	2.5 67.5%	19% dei paz. 0.2 unita' 5.5%
NEFRECTOMIA (compl. IOP) (16)	SI (2unità) SI ESA 38%	NO	SI (850 ml)	3 58%	40% dei paz. 0.2 unita' 4%
A. A. A. (45)	NO	SI (2 unita') 30%	SI (552 ml)	4 60%	70 % dei paz 2.75 unita' 40%
DISSEZIONE AORTICA (7)	NO	SI (2 unita') 22%	SI (870 ml)	5 55%	100% dei paz. 4 unita' 45%

Grazie per l'attenzione

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