

Age of blood: what do we know?

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*Le centre hospitalier
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Pour l'amour des enfants

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Objective of this lecture

- To review the possible clinical impact of RBC “storage lesions”...
 - In children and...
 - In adults: > 20 observational studies.
- To describe the ABLE study.
- To overview other on-going trials on the question.



Background: length of storage of red blood cell (RBC) units

- Determination of the upper limit of RBC shelf life (maximum length of storage) (FDA, AABB):
 - Based upon an hemolysis $< 1\%$ (0.8% in Europe) and
 - Having $\geq 75\%$ of RBC still alive in circulation of healthy volunteers 24 hours post-transfusion.
 - Criteria advocated in the 40s (Mollison & Young. Quart J Exp Physiol 1942;31:359-92).
- The upper limit of RBC shelf life is **not** based upon...
 - Laboratory or clinical efficacy evaluations.
 - Potential adverse effects of time from storage process.
- It is presently unknown if the efficacy and safety of older RBC units are similar to fresher blood.

Length of storage

Clinical epidemiology

What is the length of storage of transfused RBC units

- In UK, USA and Canada, the standard policy is to deliver to a patient the oldest RBC units first in order to avoid losing outdated products and limit wastage. First-in first-out (FIFO) policy.
- Maximum length of storage:
 - UK: 35 days
 - Canada: 42 days
 - France: 42 days

What is the length of storage (LOS) of transfused RBC units given in ICU?

■ LOS in North-American and Australian ICUs:

■ Adults in ICU:

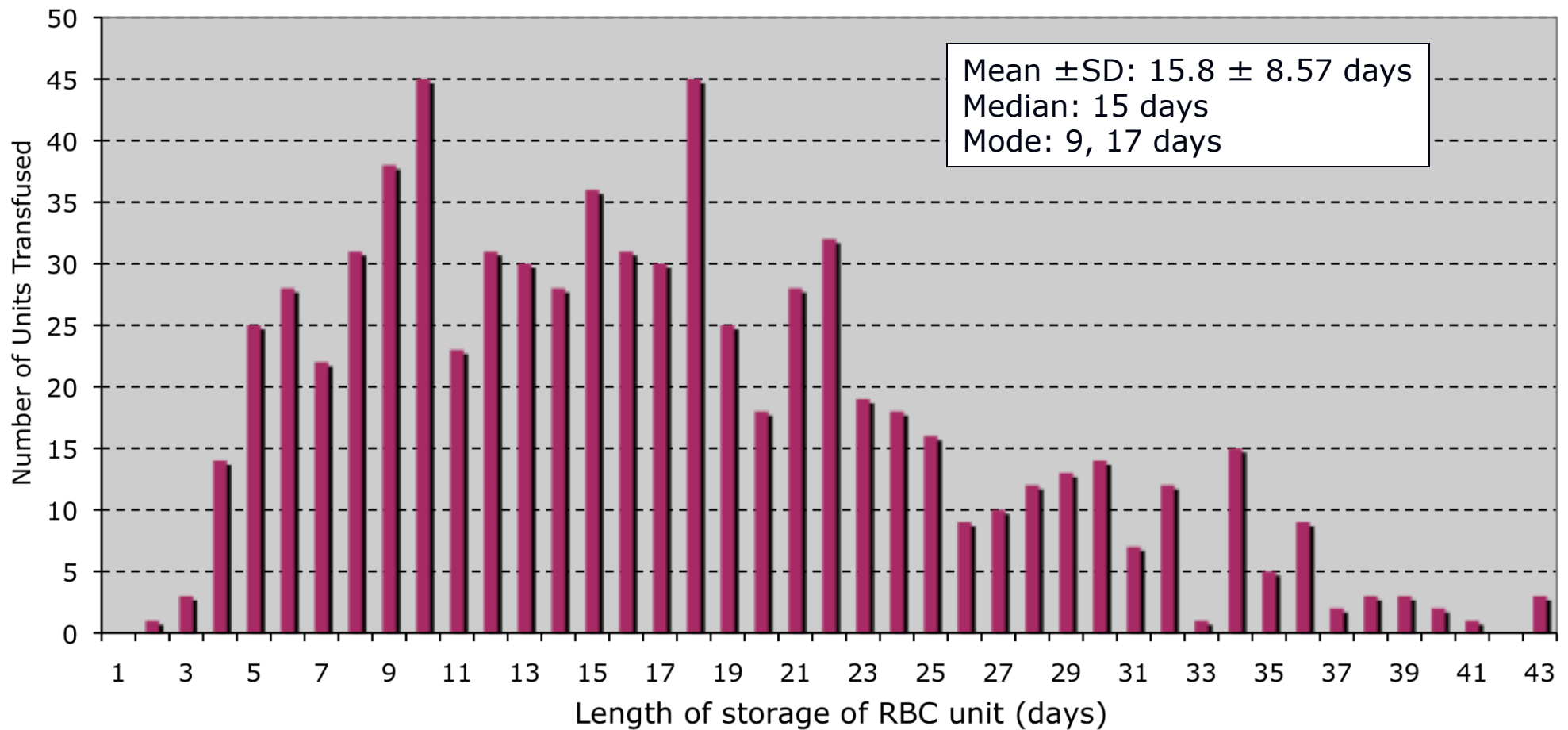
- 757 adults, 47 ICU (Pettita, ANZICS. Crit Care 2011;15:R116) 16 days
- 4892 ICU patients (Corwin. CCM 2004;32:39-52) 21 days
- Trauma center (Denver) (Zallen. Shock 2000;13:29-33) 28 days
- 685 patients, one US military hospital (CCM 2007;35:2576-81) 33 days

■ Children in pediatric ICU (PICU):

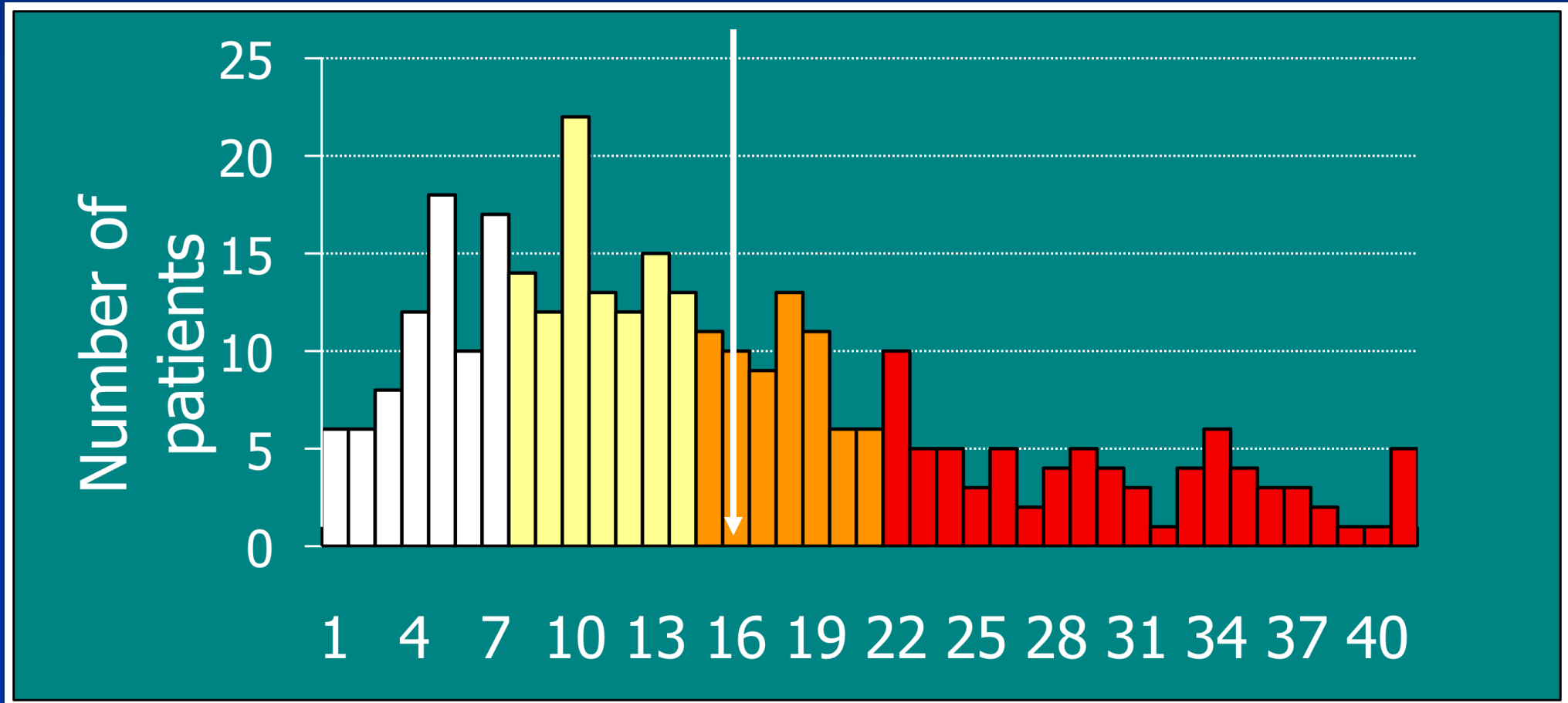
- 296 children in 29 PICU (Karam. Crit Care 2010;14:R57) 18 days
- 456 children (TRIPICU: N Eng J Med 2007;356:1609-19) 16 days

■ What is the distribution of the LOS of RBC units delivered to ICU patients?

Age Distribution of Transfused Red Blood Cells (RBC) in ICU Patients from 2000-2002 (McMaster University, Hamilton)



Length of storage in critically ill children (data from TRIPICU study)



AGEING AND STORAGE LESIONS

Ageing versus storage lesions

■ Ageing:

- Normal life-span of RBC = 120 days.
- RBC ageing is a normal process; however, it is slowed down in stored RBC units.

■ Storage lesions:

- Time-dependent metabolic, biochemical, and molecular changes that stored blood products undergo over time.
- Not a normal process.
- These changes are observed in all stored RBC units.

Storage lesions (in vitro observations)

SUPERNATANT

- High dextrose level.
- High potassium, low sodium.
- Low pH and PaO_2 , high lactate and PCO_2 .
- Inflammatory mediators: cytokines, lipids, etc.
- Procoagulant state (lipids).
- Others.

CELLS

- White blood cells (WBC):
 - Cytokines release.
 - WBC activation.
- Red blood cells:
 - Low ATP.
 - Lysis: free hemoglobin (Hb), iron overload, free lipids, etc
 - Low 2,3-DPG
 - Disturbed RBC rheology.
 - Hb-nitric oxide (NO) interaction and regulation of small blood vessels

Most studies on storage lesions and outcomes were done in ICU patients

- Two concerns are more important in ICU patients than in other patients:
 - Transfusion-related immuno-modulation (TRIM).
 - Disturbed O_2 delivery (DO_2) and O_2 consumption (VO_2), which can boost TRIM.
- TRIM and disturbed DO_2/VO_2 are major concerns because a systemic inflammatory response syndrome (SIRS) and cellular dysoxia are observed in most ICU patients.
 - RBC transfusions may boost up SIRS, cellular dysoxia & TRIM, resulting in more organ dysfunctions and deaths.

STORAGE LESIONS, TRIM, DO_2 and VO_2

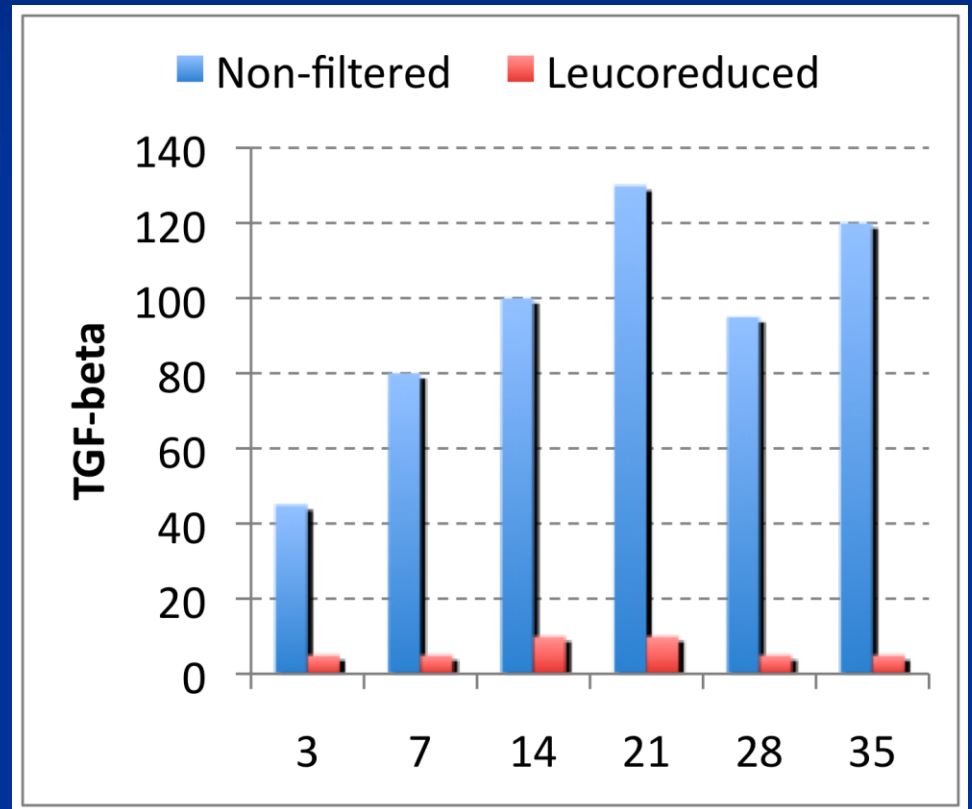
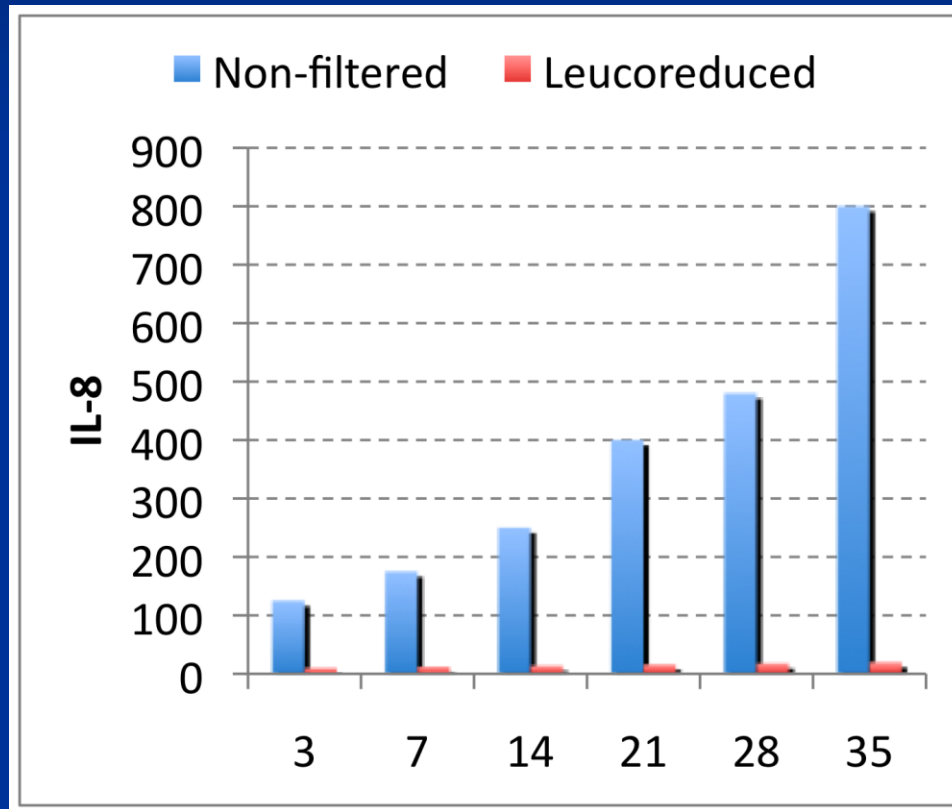
Length of storage and inflammatory mediators

- In the 90s, a progressive increase of many pro-inflammatory mediators (cytokines, O₂-radicals and bioactive lipids) was reported in storage medium of RBC unit.
 - These cytokines increase the risk of SIRS and MODS.
- The increase in cytokines level over time is a lot lower in prestorage leukodepleted RBC units.

Bennett-Guerrero. PNAS 2007;104:/7063-8.

Wadhwa et al. Transfus Sci 2000;23:7-16.

Length of storage and inflammatory mediators in supernatant: IL-8, TGF



Wadhwa et al. Transfus Sci 2000;23:7-16.