

Clinical evidence that there can be an association between length of storage and outcome in ICU

Mortality

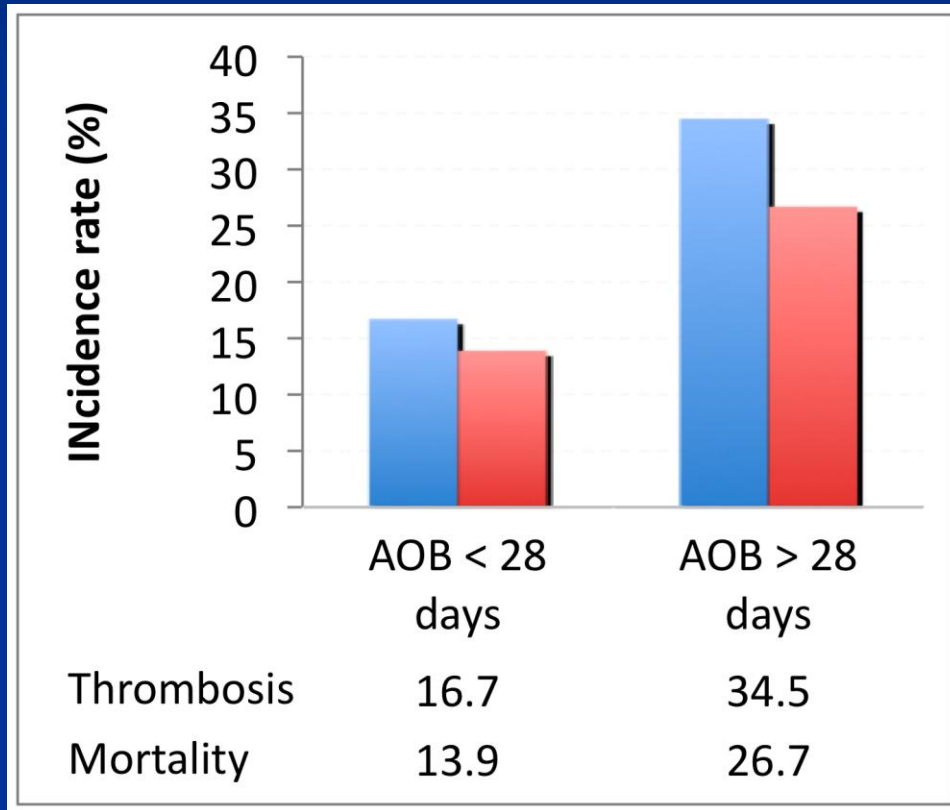
Thrombosis and ischemic lesions

Other outcomes (MODS, etc)

Age of blood and thrombosis

- Possible physiopathology of transfusion-related thrombosis:
 - RBC plugging (deformability, adherence and agregability of RBC).
 - Procoagulant state related to lipids from vesicles.
 - Vasoconstriction caused by Hb-related NO fixation.
 - Platelets activation caused by free Hb (Villagra et al. Blood 2007;110:2166-72).
- Strong laboratory evidence.
 - Higher adherence and aggregation of RBC.
 - Procoagulant in supernatant of RBC older than 21 days.
- Weak clinical evidence:

Age of blood (AOB) and thrombosis



1 versus 1

- Spinella et al. Crit Care 2009;13:R151.
 - Retrospective study.
 - 101 trauma adults who received RBC units > 28 days vs 101 paired recipients of RBC units < 28 days.
 - Thrombosis: $p < 0.006$.
 - Deaths: $p < 0.02$.
- No association found by Katsios et al. (Crit Care 2011:R263) in a prospective study with systematic monitoring of thrombosis.

RBC transfusion and ischemia

- There are data suggesting that RBC transfusion can cause some ischemia.
- Example: Murphy et al reported a strong association between RBC transfusion and ischemia in 8518 adults transfused after a cardiac surgery:
 - Adjusted odds ratio: 3.35 (95% CI: 2.68-4.35).

Table 2. Frequencies of Composite Infection and Ischemic Outcomes

Outcome	Not Transfused			Transfused		
	N	n	%	N	n	%
Infection*	3674	4842
Nadir hematocrit <21	52	1	1.9	982	120	12.2
Nadir hematocrit ≥21 and <24	390	16	4.1	2164	243	11.2
Nadir hematocrit ≥24 and <27	1176	42	3.6	1385	200	14.4
Nadir hematocrit ≥27	2056	82	4.0	311	33	10.6
Ischemia†	3670	4848
Nadir hematocrit <21	52	1	1.9	982	132	13.4
Nadir hematocrit ≥21 and <24	390	13	3.3	2167	307	14.2
Nadir hematocrit ≥24 and <27	1175	40	3.4	1389	231	16.6
Nadir hematocrit ≥27	2053	72	3.5	310	36	11.6

N indicates denominator hematocrit stratum/total; n, number experiencing the outcome.

*737 of 8516 (8.7%) had this outcome (missing for 82); 381 (4.5%) had a respiratory infection; 220 (2.6%) had a wound infection; 136 (1.6%) had both. Eight of 14 patients with septicemia also had a respiratory infection.

†832 of 8518 (9.8%) had this outcome (missing for 80); 543 (6.4%) had renal impairment (142 required dialysis); 77 (0.9%) had a stroke; 134 (1.6%) had a myocardial infarction; 39 (0.5%) had renal impairment and stroke (11 required dialysis); 30 (0.4%) had renal impairment and a myocardial infarction (11 required dialysis); 5 (0.06%) had a stroke and a myocardial infarction; and 4 (0.05%) had renal impairment, stroke, and a myocardial infarction (2 required dialysis).

Murphy et al. Circulation 2007;116:2544-52

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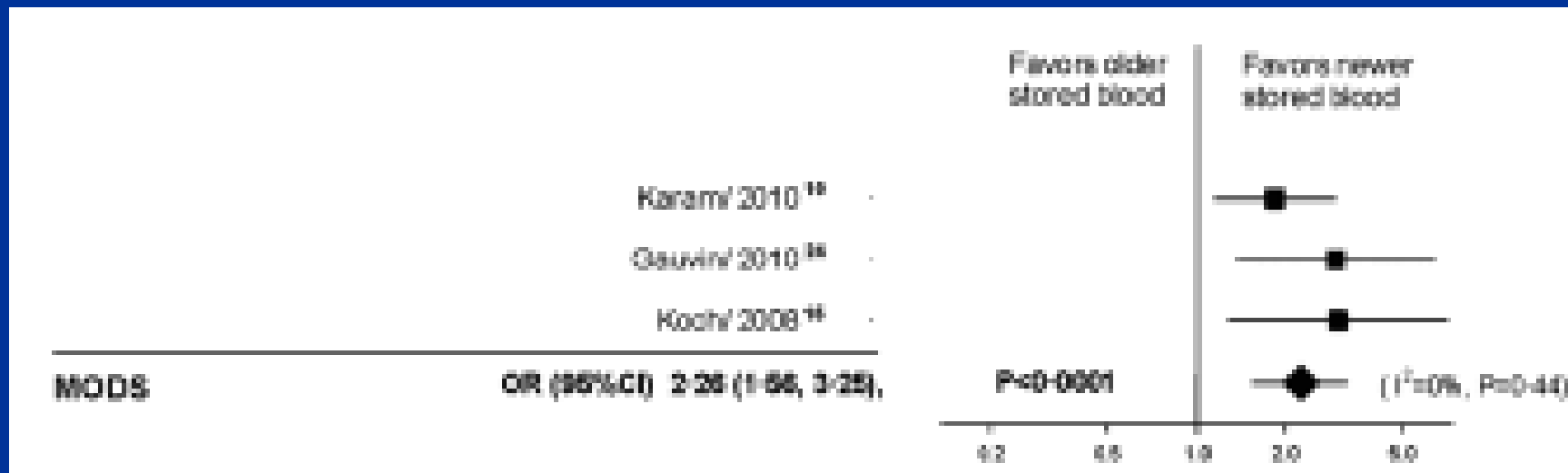
Mortality

Thrombosis and ischemic lesions

Other outcomes (MODS, TRALI, etc)

Association between older RBC units and MODS in ICU patients (TRIM)

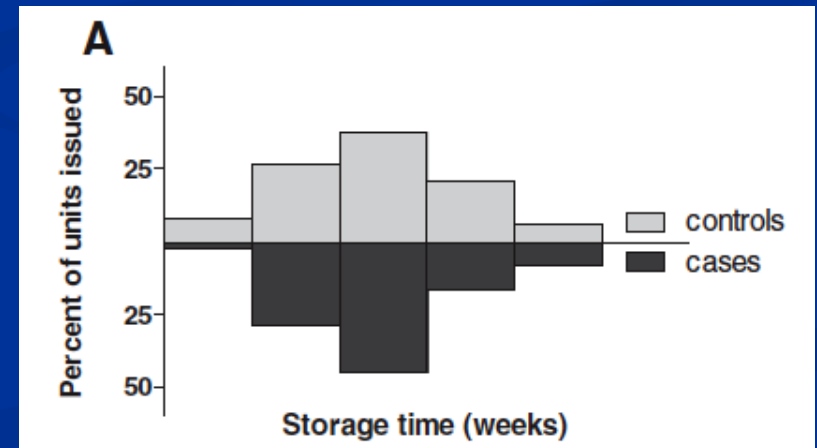
- 3 studies (1 in 63 trauma adults, 2 in PICU children).
- OR to contract a multiple organ dysfunction syndrome (MODS): 2.26 (95%CI: 1.56-3.25).



Wang et al. Transfusion 2012;52: in press

Older RBC units and TRALI

- Vlaar et al. Blood 2011;117:4218-25:
 - 16 cases among 668 cardiac surgery patients.
 - Volume of blood products and TRALI (OR: 1.2; 95%_{CI}: 1.03-1.44)
 - Number of RBC units > 14 days and TRALI (OR: 1.6; 95%_{CI}: 1.04-2.37).
- Middelburgh et al. Transfusion 2012;52:658-67:
 - All RBC receivers in Netherland: 164 with TRALI, 91,602 without TRALI.
 - RBC units stored up to 35 days were not associated with TRALI (figure).



**Clinical evidence that
there can be an
association between
length of storage and
outcome in ICU:
completed randomized
clinical trials**

RCTs examining Age of Blood in the critically ill

- RCT to determine whether age of blood alters gastric mucosal oxygenation or global oxygenation in 22 euvolemic and non hemorrhaging critically ill patients
- Inclusion criteria: Hb < 90 g/L and need for ≥ 2 RBC transfusions
- Intervention: leukodepleted RBC ≤ 5 vs ≥ 20 days old
- Measurements: gastric pHi and gastric to arterial CO₂ gap during transfusion and hourly post transfusion
- Results: no difference in pHi and CO₂ gap between groups and between pre-post transfusion periods.

Walsh et al. Crit Care Med 2004;32:364-71

RCTs examining Age of Blood in the critically ill

- Pilot RCT to examine feasibility of conducting large multi-centre age of blood trial.
- Patients: 66 critically ill and cardiac surgical patients 4 Canadian hospitals.
- Intervention: blood stored ≤ 7 days vs. standard issue.
- Results:
 - It was feasible to get a good difference in length of storage:
 - Fresh arm: median 4 days old RBC units.
 - Standard arm: median 19 days old RBC units.
 - Fresh arm had non-significant higher mortality or serious complication.

Informing fresh versus old red cell management (INFORM) study

- State of progress: pilot-RCT completed (910 patients)*
 - Principal investigators: Nancy Heddle, John Eikelboom, McMaster University.
 - Results: good feasibility; appropriate separation of LOS (10.2 vs 23.8 days).
 - Full multicenter RCT granted by the CIHR in January 2012.
 - Already implemented in Hamilton – should start soon in Australian hospitals.
- INFORM:
 - Basic design: double-blind multicenter pragmatic RCT.
 - Patients: 24,400 anemic hospitalized adults requiring ≥ 1 RBC transfusions.
 - **Waived consent.**
 - Intervention: randomization (1:2) to two experimental groups.
 - 1st group: freshest ABO compatible RBC unit in inventory.
 - 2nd group: oldest ABO compatible RBC unit in inventory.
 - Primary (composite) outcome: in-hospital mortality.

*Heddle et al. Transfusion 2011;51:193A

RCTs examining Age of Blood in the critically ill: TRANSFUSE

- State of progress: pilot-RCT completed (51 patients)*
 - Principal investigator: Jamie Cooper, Melbourne, Australia.
 - Results: good feasibility; appropriate separation of LOS (12.1 ± 3.8 vs 23 ± 8.4 d).
 - Full multicenter RCT financed by ANZICS.
- TRANSFUSE:
 - Basic design: double-blind multicenter pragmatic RCT.
 - Patients: 6000 adults in ICU requiring one or more RBC transfusions.
 - Informed of deferred consent.
 - Intervention: randomization (1:1) to two experimental groups (idem INFORM).
 - 1st group: freshest ABO compatible RBC unit in inventory.
 - 2nd group: oldest ABO compatible RBC unit in inventory.
 - Primary (composite) outcome: 90-day mortality (idem ABLE).
 - TRANSFUSE should start this year.

Age of red blood cell in premature infants (ARIP) (NCT00326924)

- Principal investigator: Dean Fergusson, Ottawa Hospital Research Institute.
- Basic design: double-blind multicenter effectiveness RCT.
 - Patients: prematures < 1250 g birth weight, in neonatal ICU and requiring one or more RBC transfusions (multiple consecutive RBC transfusions is frequent in neonatal ICU).
 - Intervention:
 - Experimental: blood stored ≤ 7 days (these patients will be exposed to fresh RBC units, but to multiple donors).
 - Control (usual care): Pedi-packs (these patients will be exposed to older RBC units, but to less donors).
 - Primary (composite) outcome: mortality, retinopathy, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage.
- Recruitment completed in June 2011 (n=377).
- Analysis: in progress.

Age of Blood Evaluation (ABLE) study (ISRCTN44878718)



The age of RBCs: 1 or 2 questions?

Is old blood harmful?



The question addressed by ABLE: are fresh RBC units (≤ 7 days of storage) better than standard delivery* RBC units?

Is fresh blood beneficial?

* Standard delivery: delivery of the oldest RBC unit {first-in first-out (FIFO) policy} in order to limit wastage of blood products.