Blood Transfusion is Associated with Adverse Outcomes in Pediatric Oncology Patients Following Tumor Resection

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Blood Transfusion

- **Can be a life saving intervention in a variety of clinical settings**
- **Perioperatively, typically used to replace blood (specifically hemoglobin) lost and to improve oxygen carrying capacity**
- **PRBC transfusion – Proimflammatory and immunosuppressive effects**
  - **IL-6, IL-10, TNF- alpha, lipids, T-cell activation**
  - **Transfusion related immunomodulation (TRIM)**

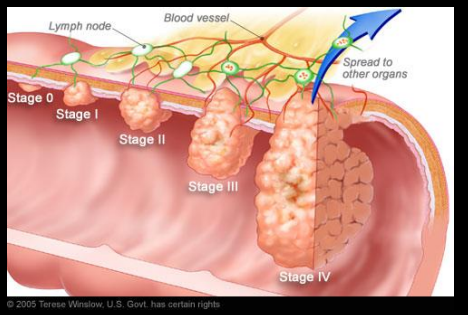




Vincent, *Crit Care Med* 2006
Karam et al. *Transfusion* 2009
Baumgartner et al. *J Am Coll Surg* 2009
Silliman et al. *Transfusion* 2011

Adult Oncology Patients

- **PRBC transfusion in perioperative period**
  - Increased infectious complications
  - Increased tumor recurrence rate
  - Increased mortality

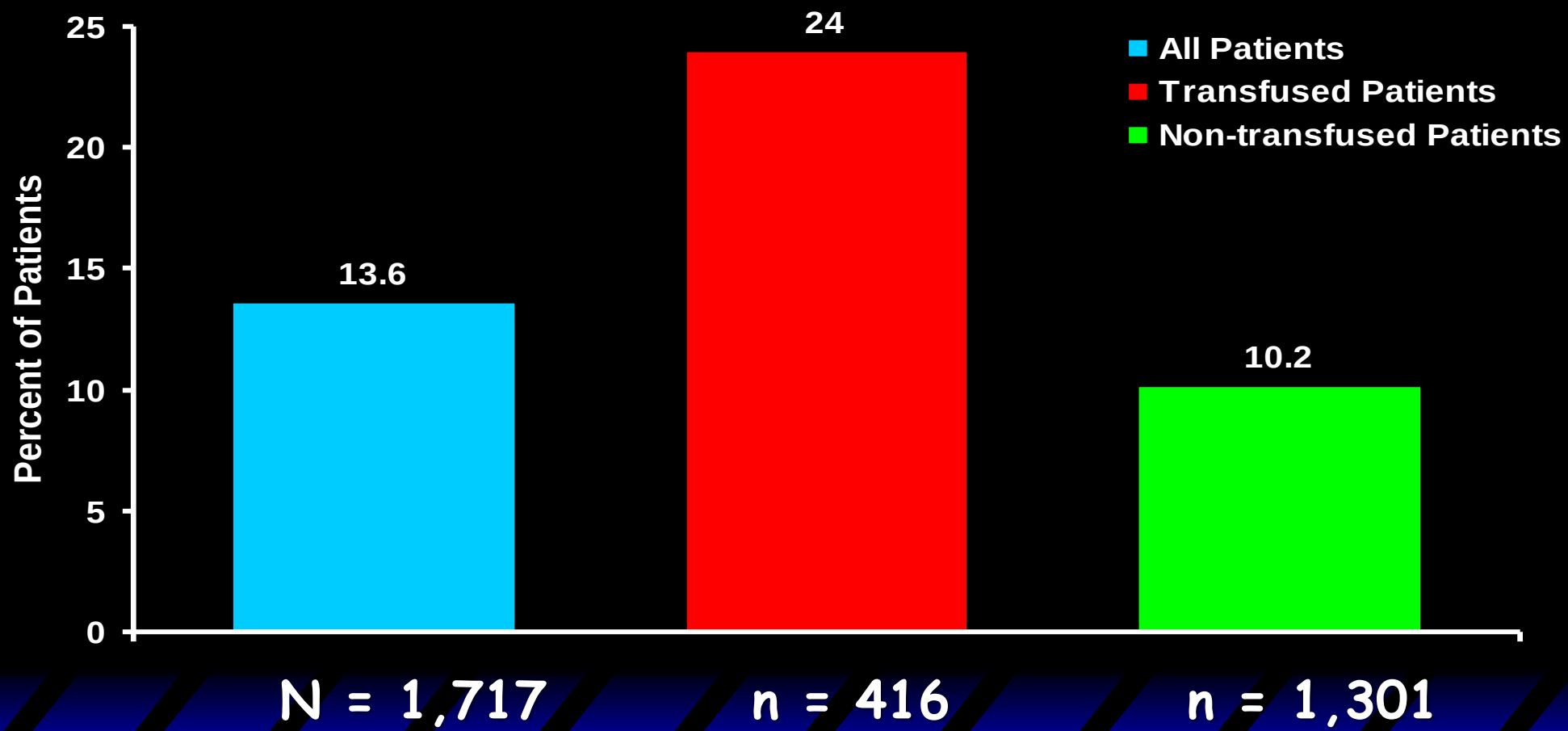


- **Mechanisms?**
  - Mobilization of malignant cells intraoperatively
  - Depressed host defenses - TRIM
  - Physiologic stress/inflammatory response to surgery



Cata et al. *Br J Anaesth* 2013
Acheson et al. *Ann Surg* 2012
Wang et al. *Ann Thorac Surg* 2014

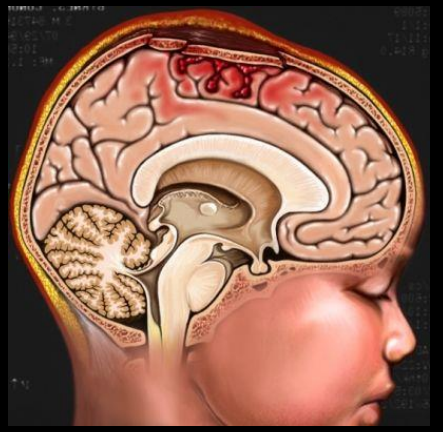
MORTALITY IN CRITICALLY ILL PATIENTS



Taylor RW et al. Crit Care Med 2002; 30:2249

PRBC Transfusion in Children

- **Traumatic brain injury**
  - Increased mortality
  - Increased in hospital infectious complications
  - Increased need for long term rehab and dependent on caregivers



- **Cardiac surgery**
  - Longer mechanical ventilation
  - Increased postoperative complications
  - Longer hospital stay

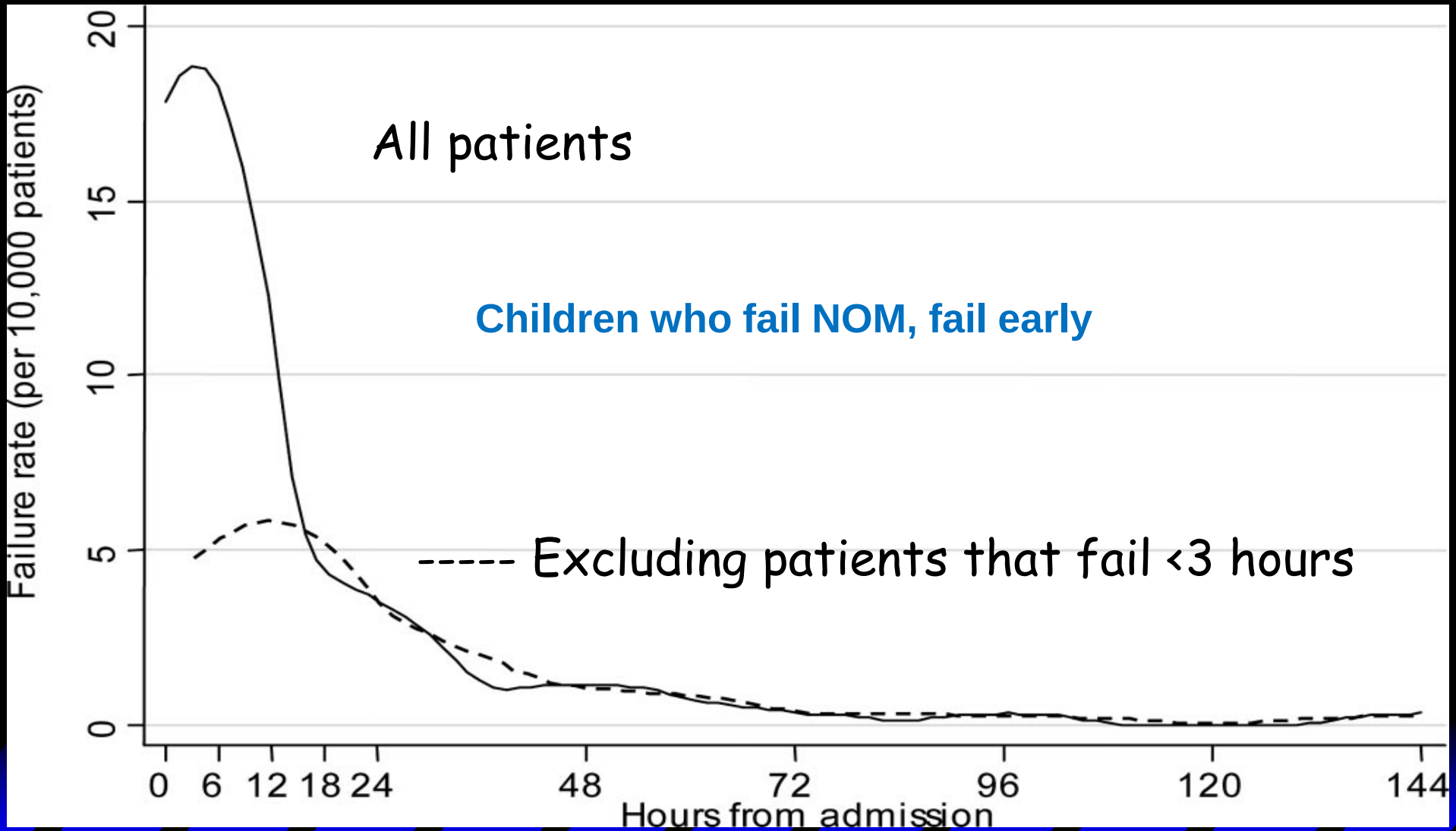


- **Critically ill non-cardiac patients**
  - Independently associated with increased mortality

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Partrick et al. *J Trauma Acute Care Surg* 2014
Iyengar et al. *Ann Thorac Surg* 2013
Kneyber et al. *Intensive Care Med* 2007

Non-operative management of solid organ injury is successful in 95% of cases but is <u>not 100%</u>!



Who's at risk of NOM failure

Table 4 Risk of Failure and Injury Severity

Injury Severity	Relative Risk (95% CI)	*p* Value
ISS ≤ 9	Reference	—
ISS = 10–14	1.83 (0.66–5.10)	NS
ISS = 15–24	3.33 (1.53–7.22)	<0.01
ISS ≥ 25	14.95 (7.50–29.79)	<0.001
GCS ≤ 8	5.09 (3.04–8.52)	<0.001

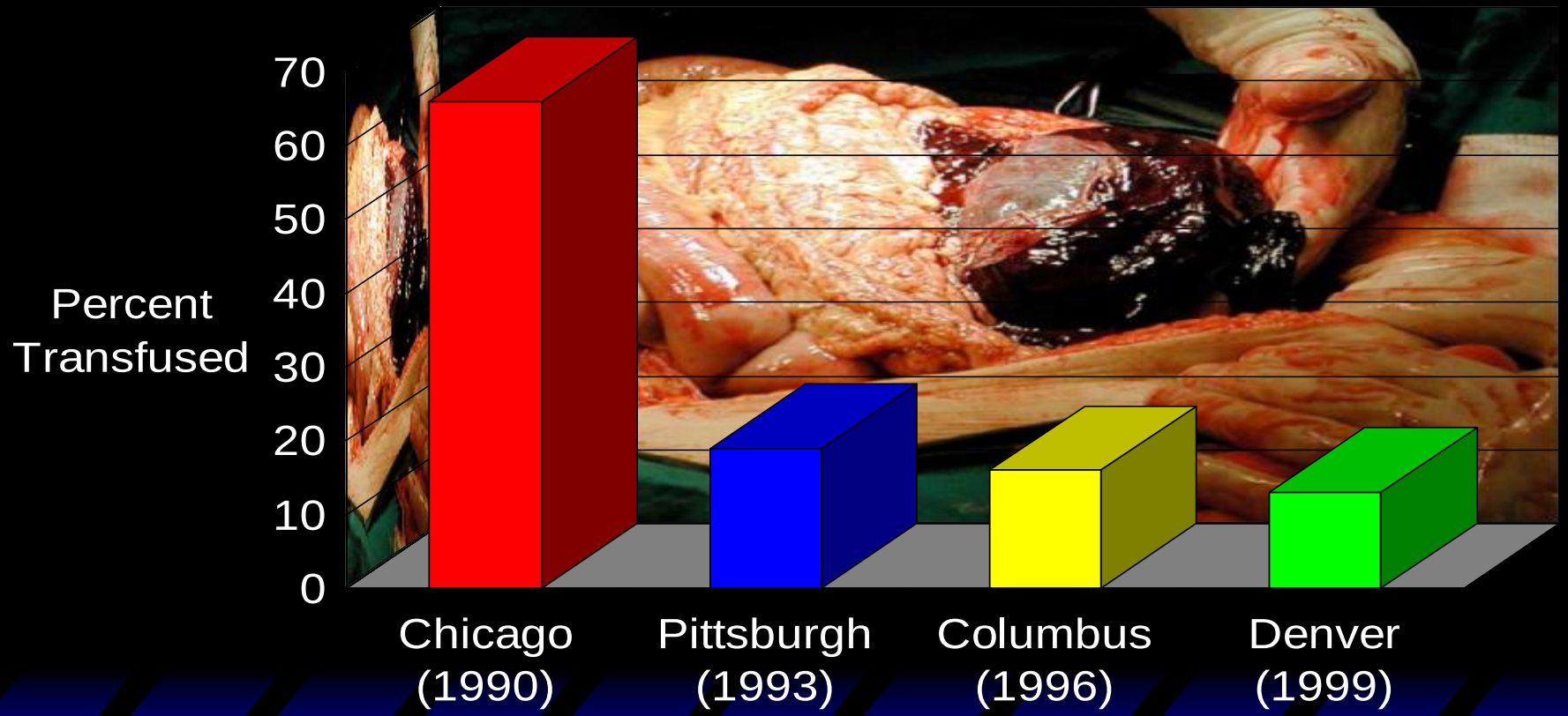
Multi-system injury

Severity of injury

Table 5 Risk of Failure and Organ Injury Severity

Injury Grade	Relative Risk (95% CI)	*p* Value
Isolated grade 1	Reference	—
Isolated grade 2	1.66 (0.56–4.89)	NS
Isolated grade 3	2.10 (0.71–6.19)	NS
Isolated grade 4	5.00 (1.78–14.06)	<0.01
Isolated grade 5	57.89 (19.42–172.54)	<0.001
sAIS ≥ 4	6.84 (4.26–10.99)	<0.001

Does nonoperative management lead to excessive blood transfusion?



Is nonoperative management applicable in combined adult/ pediatric trauma centers?

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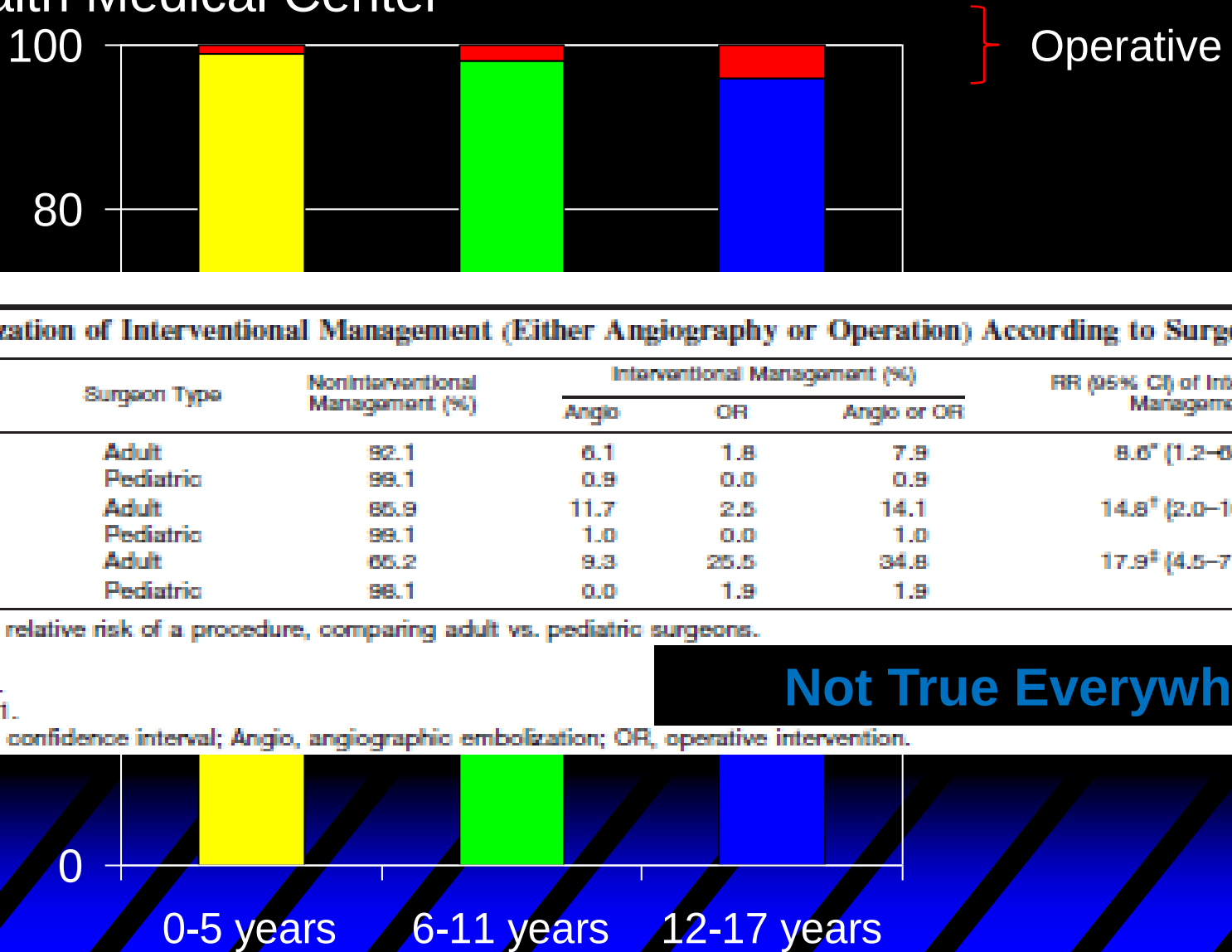


Table 2 Utilization of Interventional Management (Either Angiography or Operation) According to Surgeon Type

Scenario	Surgeon Type	Noninterventional Management (%)	Interventional Management (%)			RR (95% CI) of Interventional Management
			Angio	OR	Angio or OR	
Isolated SOI	Adult	92.1	6.1	1.8	7.9	8.6* (1.2–65.1)
	Pediatric	99.1	0.9	0.0	0.9	
Multiple SOI	Adult	85.9	11.7	2.5	14.1	14.8† (2.0–108.1)
	Pediatric	99.1	1.0	0.0	1.0	
SOI and ICH	Adult	65.2	9.3	25.5	34.8	17.9‡ (4.5–71.6)
	Pediatric	98.1	0.0	1.9	1.9	

RR denotes relative risk of a procedure, comparing adult vs. pediatric surgeons.
* $p < 0.05$.
† $p < 0.001$.
‡ $p < 0.0001$.
CI indicates confidence interval; Angio, angiographic embolization; OR, operative intervention.

Not True Everywhere

Does nonoperative management lead to excessive blood transfusion?

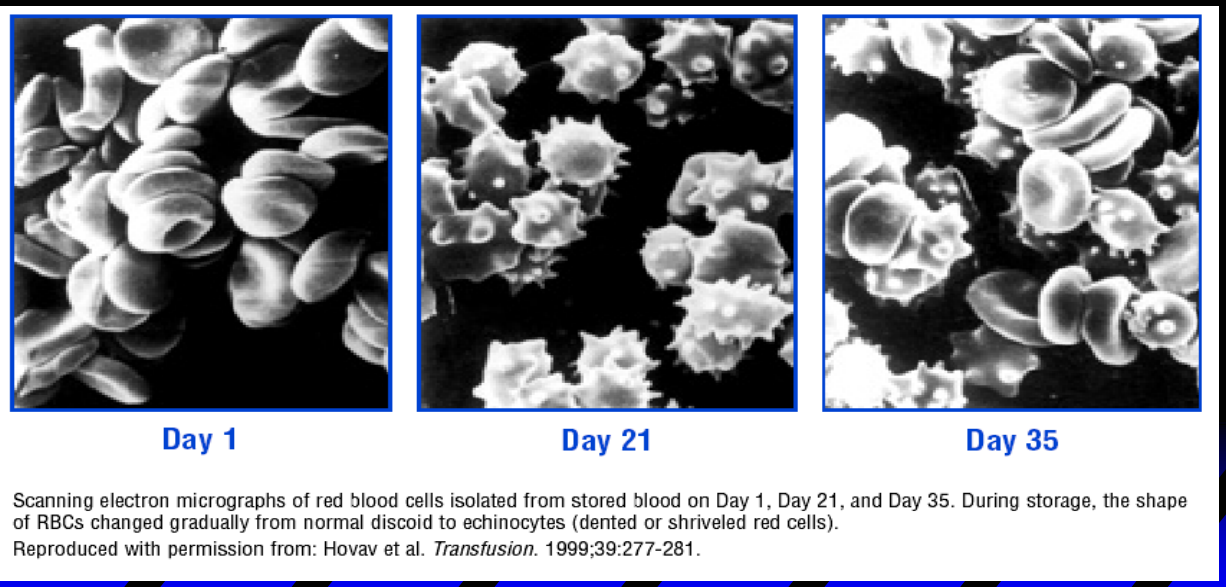
Table 3 Transfusion Failure Threshold as Function of Surgeon Type

Transfusion Failure Threshold	Adult Surgeon N = 167 (n, cumulative %)	Pediatric Surgeon N = 114 (n, cumulative %)	p
Any transfusion	22 (13.3)	2 (1.2)	<0.001
After 10 mL/kg	18 (24.1)	0 (1.2)	
After 20 mL/kg	78 (71.1)	28 (25.5)	
After 30 mL/kg	16 (80.7)	16 (40.5)	
After 40 mL/kg	29 (98.2)	51 (88.2)	
After 50 mL/kg	3 (100)	12 (100)	

Difference in transfusion threshold

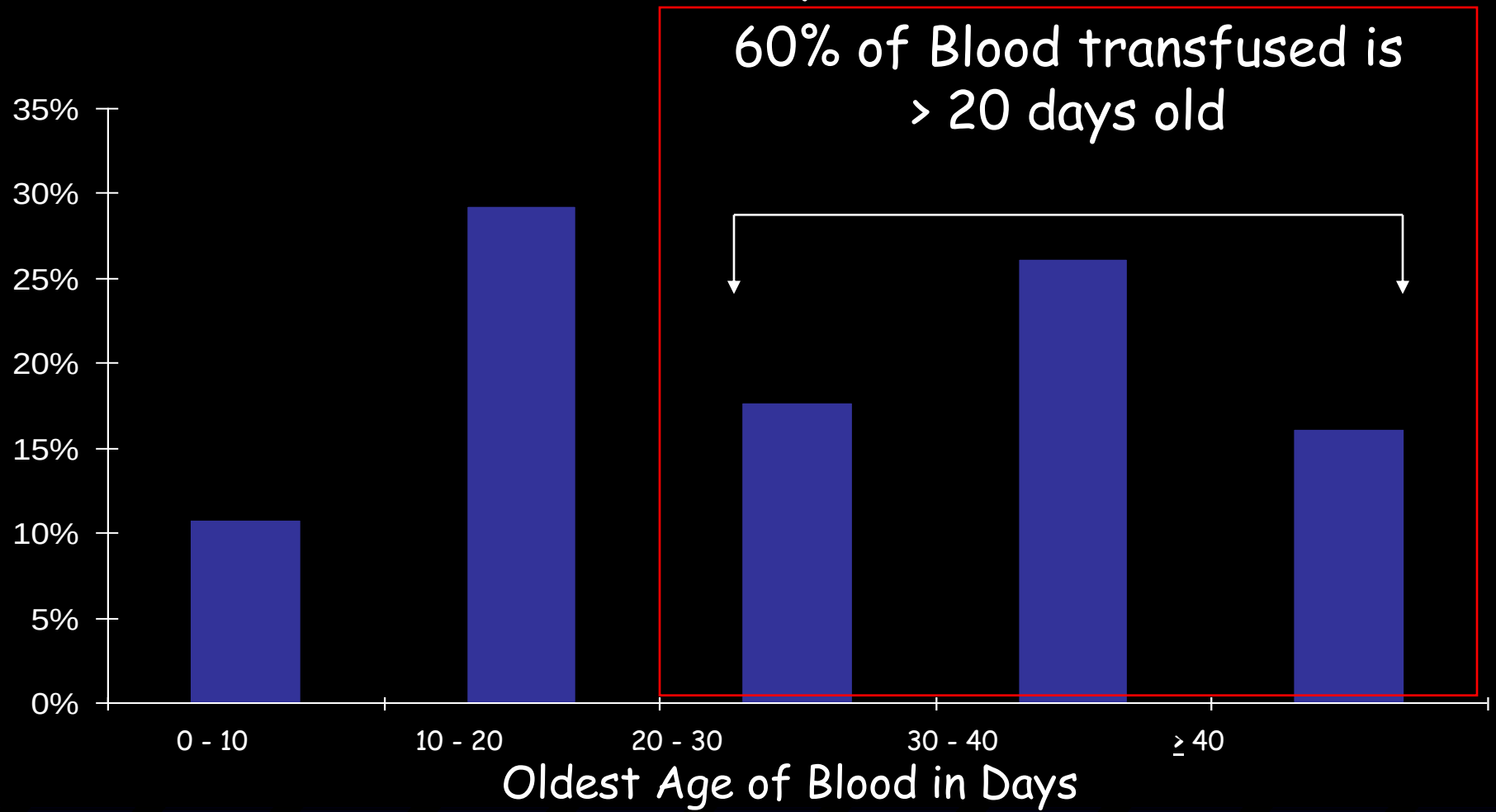
Stored RBCs

- Decreased RBC deformability
- Decreased 2,3, DPG
- Metabolic acidosis
- Altered oxygen carrying capacity
- Increased red cell death with increased age of blood (~30% dead)
- No improvement in oxygen utilization at the tissue level



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.

Distribution of Transfused Units by Age of Blood CRIT Study



In Trauma Subset, 68% of blood is > 20 days old

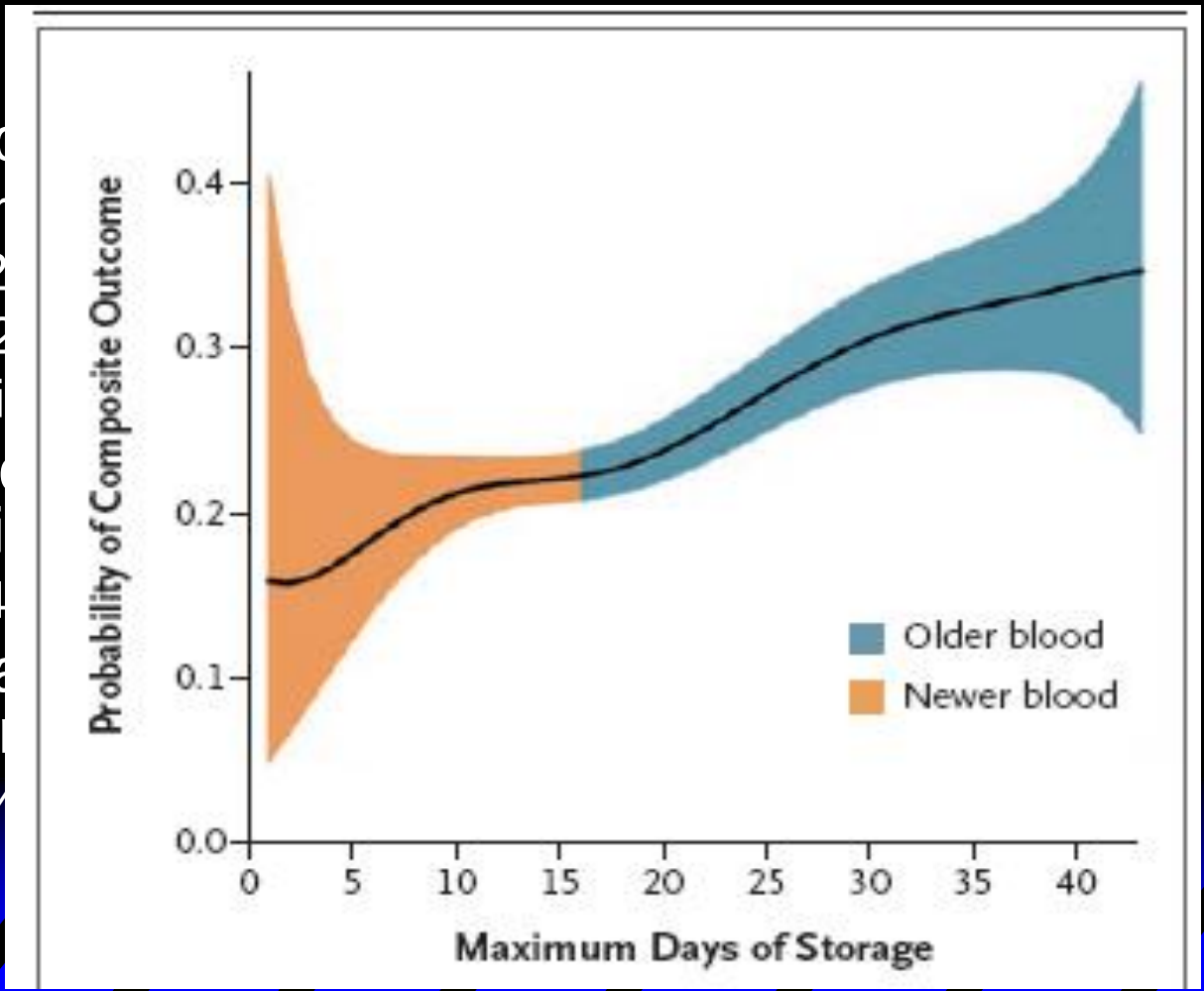
EDITORIALS

New Blood, Old Blood, or No Blood?

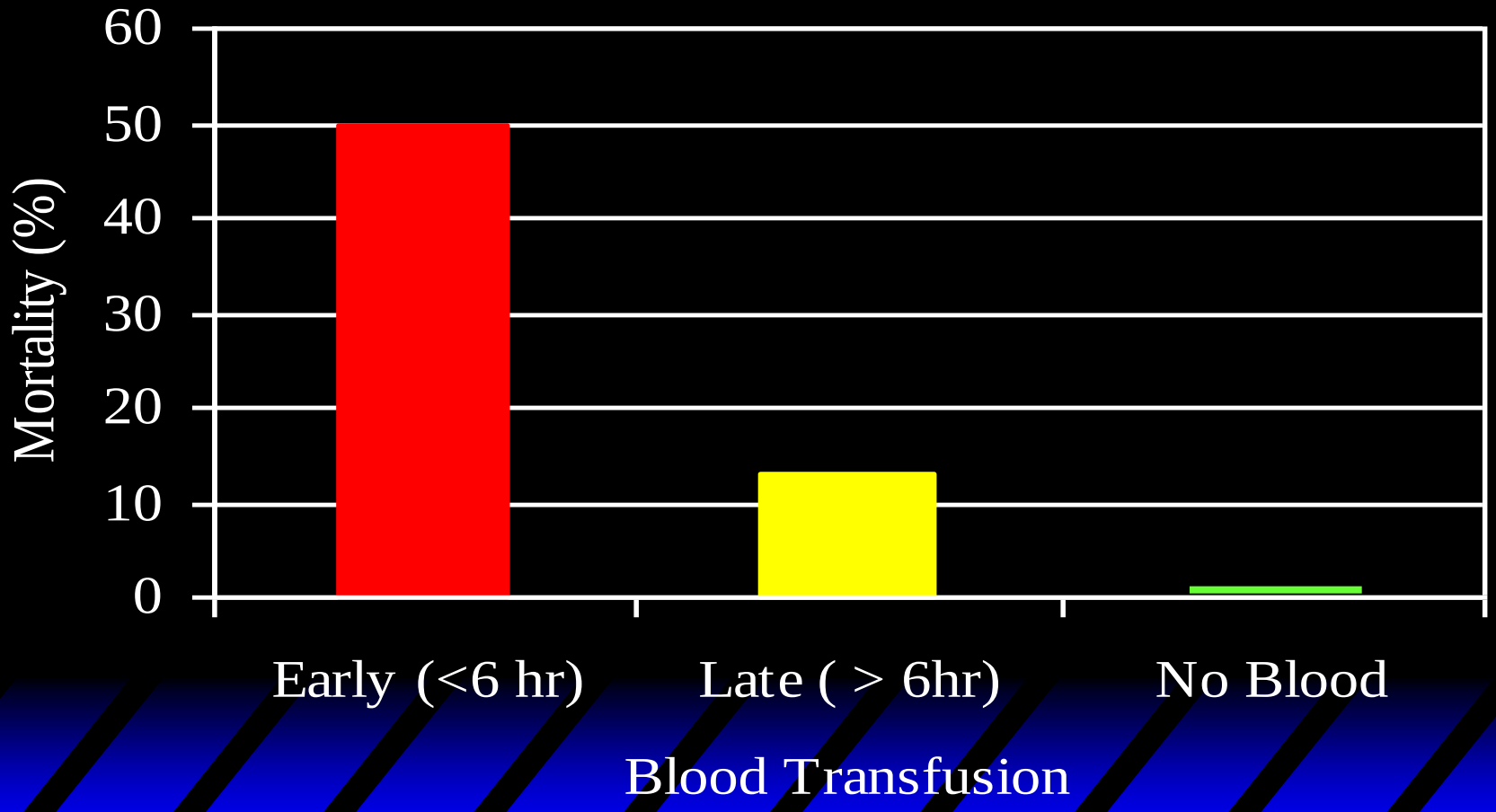
John W. Adamson, M.D.

N Engl J Med 2008;358:1229-39.

- Patients given c
  - In-hospital mor
  - Intubation > 72
  - Renal failure- 2
  - Sepsis or septi
- Composite of c
  common in pati
  - 25.9% vs. 22.4
- At 1 year, morta
  in patients giver
  - 7.4% vs. 11.0%



Both Early and Late blood transfusion are associated with an increased risk of death in children



Restrictive Blood Transfusion in Children Undergoing Surgery Appears Safe

- The TRIPICU study
  - prospective randomized controlled trial
  - critically ill children receive transfusion if their hemoglobin dropped below either 7.0 g/dL (restrictive) or 9.5 g/dL (liberal).
- No significant differences
  - MODS
  - 28-day mortality
- A difference between groups for PICU length of stay
  - 7.7 days for the restrictive group
  - 11.6 days for the liberal group

TABLE 3. Intervention (Red-Cell Transfusion), Suspension, and Cointerventions*

	Restrictive	Liberal	*P*
	60	64	
Red-cell transfusion and hemoglobin concentration after randomization			
Lowest Hb level (g/dL) per day in PICU	8.4 ± 1.0	10.8 ± 1.0	<0.01
Data on transfused patients			
No. transfused patients: total (%)	30 (50)	62 (97)	<0.01
Patients with 1 red-cell transfusion (%)	25 (42)	38 (59)	
Patients with 2 red-cell transfusions (%)	3 (5)	15 (23)	
Patients with more than 2 red-cell transfusions (%)	2 (3)	9 (14)	
Volume (mL/kg) per transfused patient	13.9 ± 5.6	17.6 ± 8.2	0.07
Data on first red-cell transfusion			
Days from randomization to first transfusion	0.9 ± 1.6	0.5 ± 1.7	0.11
Hb level before first transfusion (g/dL)	6.6 ± 0.5	8.0 ± 0.9	<0.01
Hb level after first transfusion (g/dL)	9.4 ± 1.3	11.0 ± 1.1	<0.01

TABLE 5. Secondary Outcome Measures

	Restrictive	Liberal
	60	64
Measures of severity of organ dysfunction‡		
Highest number of organ dysfunctions	1.3 ± 1.2	1.3 ± 1.0
PELOD score over all PICU stay§	4.0 ± 7.1	3.5 ± 3.8
PELOD score on day 1§	5.3 ± 6.3	4.9 ± 5.4
Highest daily PELOD score after day 1§	7.4 ± 9.6	7.6 ± 8.8
Change in PELOD score§	2.1 ± 6.3	2.8 ± 6.7
Average daily PELOD score§	4.0 ± 7.1	3.5 ± 3.8
Clinical outcomes: no. patients (%)		
No. deaths in PICU	1 (2)	0 (0)
No. deaths 28 d post PICU	0 (0)	1 (2)
Overall 28-d mortality	1 (2)	1 (2)
No. nosocomial infections	14 (23)	20 (31)
Other clinical outcomes (d)¶		
Length of mechanical ventilation		
After randomization	5.5 ± 5.2	6.6 ± 5.6
Total PICU stay	6.9 ± 5.5	7.6 ± 6.1
Length of stay from entry to PICU discharge	7.7 ± 6.6	11.6 ± 10.2

Lacroix et al. *N Engl J Med* 2007

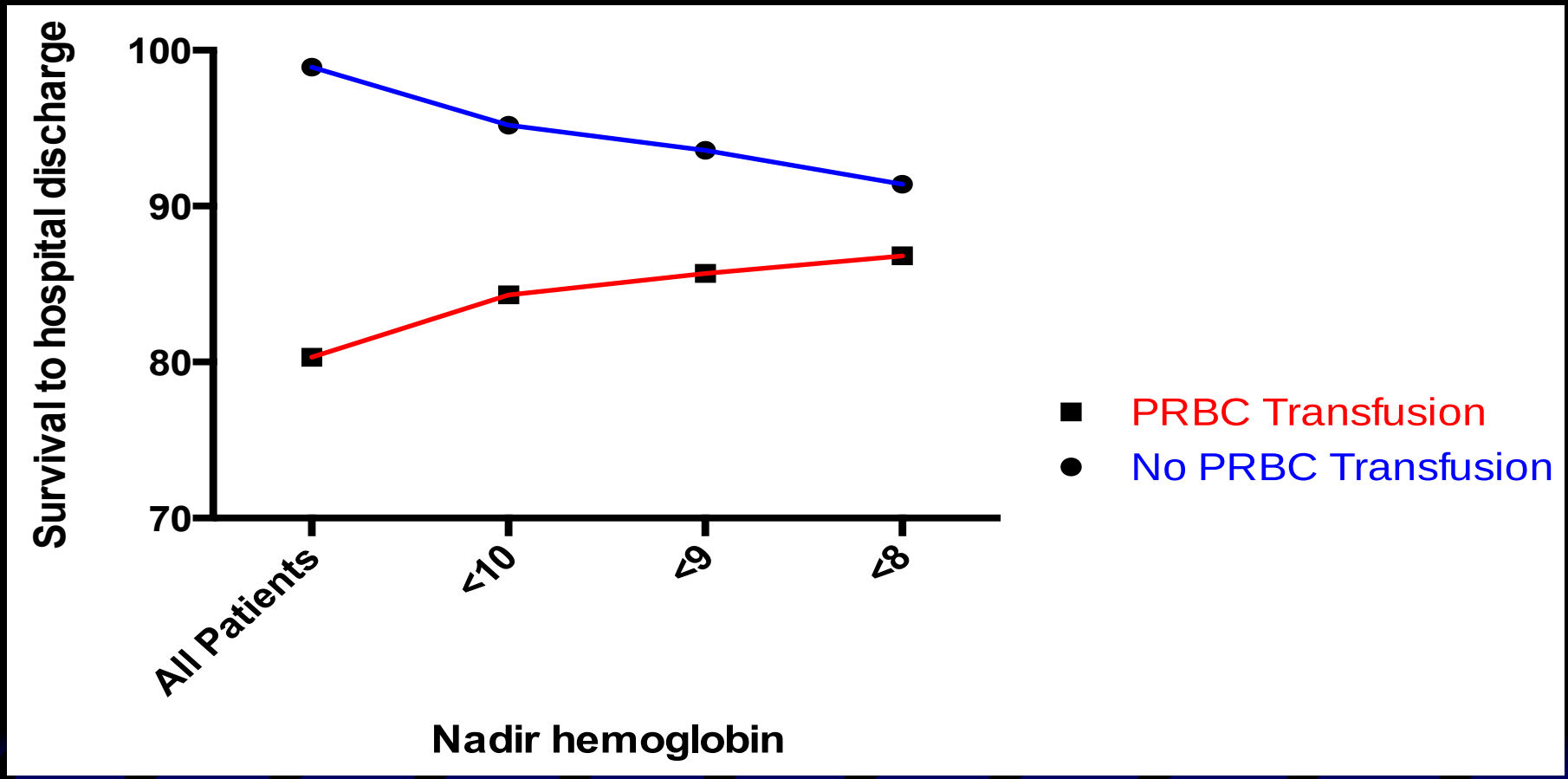
Implementation of a restrictive transfusion policy in children

	Transfused	Out of Protocol	Not Transfused	Total
ISS <15	10 (2%)	4 (40%)	416	426
ISS 16-25	9 (17%)	1 (11%)	44	53
ISS >26	24 (72%)	4 (17%)	9	33

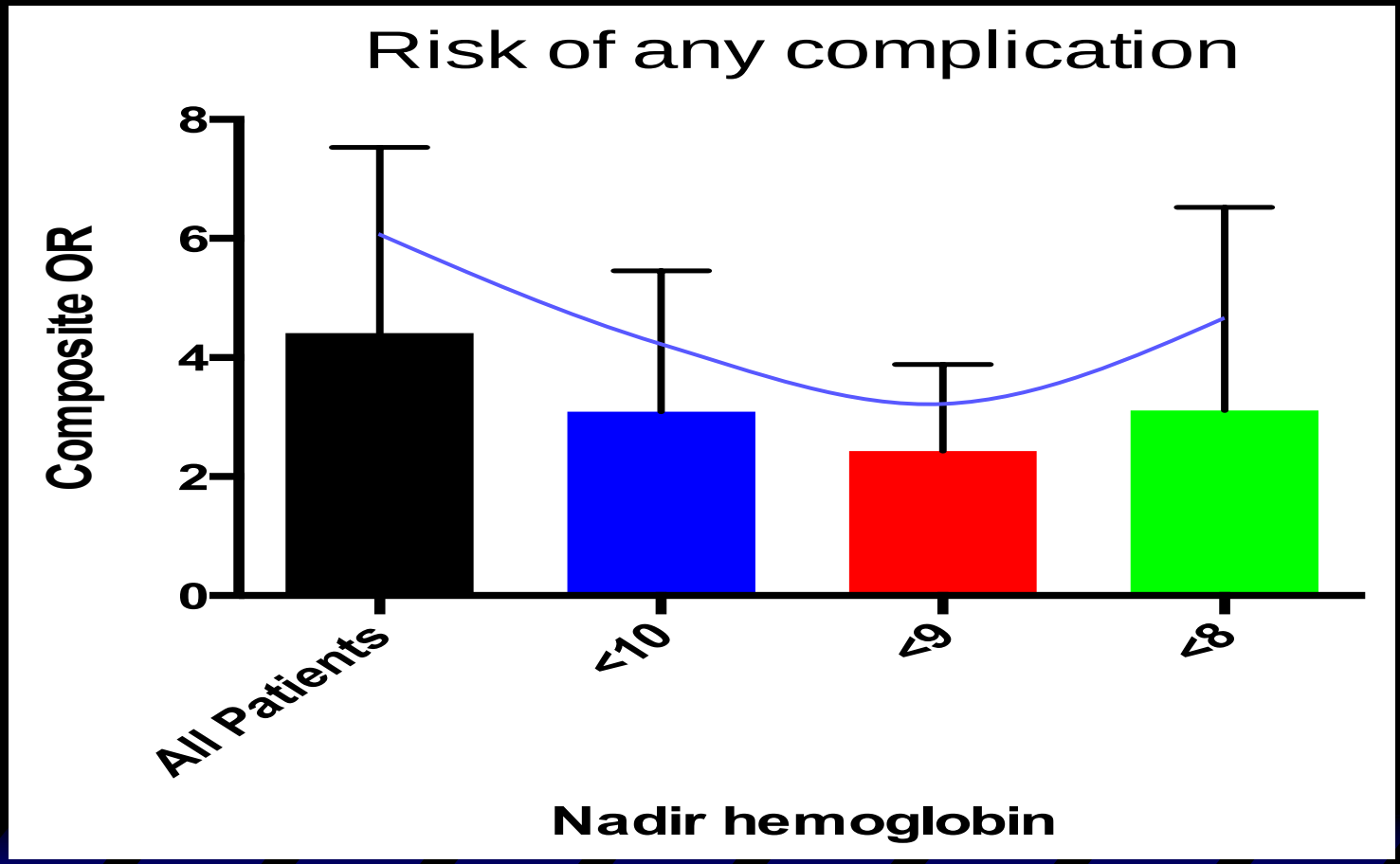
8% of injured children received blood transfusion; 2% out of protocol (4 TBI, 4 Replant)

➔ 0.6% did not meet exception criteria

Identifying the opitimal transfusion trigger in children suffering TBI?



The optimal transfusion trigger in pediatric TBI = 8-9?



Phlebotomy

Are they bleeding or are we bleeding them?



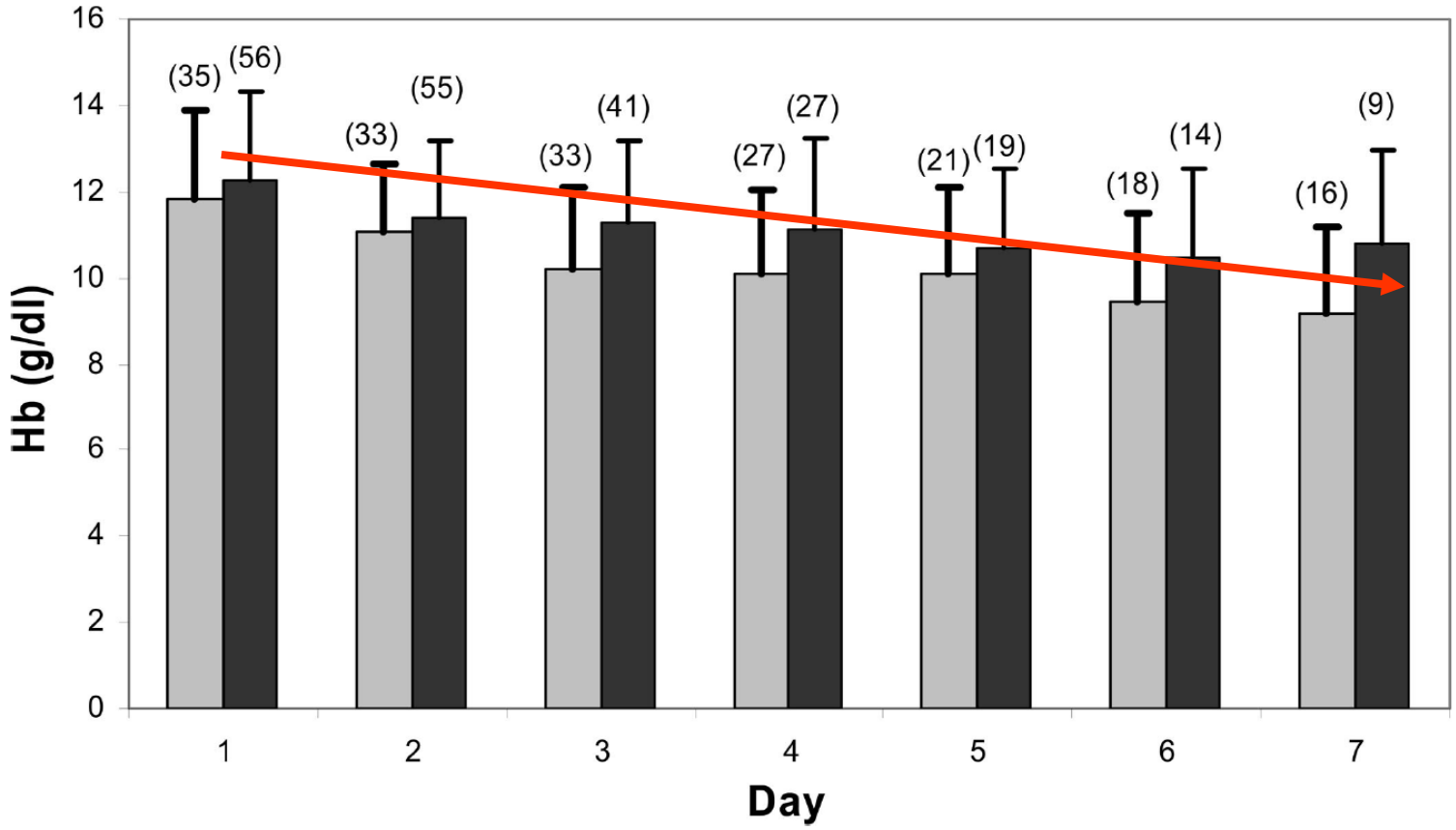


Figure 1. Time course of hemoglobin concentrations over the first 7 days in septic (*gray bars*) and nonseptic (*black bars*) patients. (Numbers of patients in parentheses). From Ref. 6 with permission.

Summary

- Know your ABCs
- Directed resuscitation and evaluation
- Most solid organ injuries are managed successfully non-operatively
- Employ restrictive transfusion strategies and avoid excessive phlebotomy

Hypothesis

- Children with malignant solid tumors who receive a PRBC transfusion within 30 days of tumor resection have higher rates of tumor recurrence, mortality, and infectious complications

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Methods

- Retrospective review
  - All children who underwent operative resection of a solid tumor malignancy at Children's Hospital Colorado between 1/02-1/13
- Data collected
  - Demographic information
  - Operation performed
  - Postoperative course
  - Any PRBC transfusion within 30 days of tumor resection
    - Age of any unit transfused

Analysis

- Comparison of five outcome variables between transfusion and no transfusion groups
  - Hospital length of stay (LOS)
  - Postoperative infectious complications
  - Disease free interval
  - Tumor recurrence
  - Mortality
- Age of transfusion
  - Compared outcomes among those patients who received any unit stored >20 days and those patients who only received units stored <5 days

Demographic characteristics

	No Transfusion (n=175)	Transfusion (n=197)	P value
Male (%)	97 (55%)	101 (51%)	0.42
Median age (years)	4	4	0.13
Postoperative ICU (%)	10 (6%)	69 (35%)	<0.001
Median nadir Hgb	10.3	7.9	<0.001
Operative location			<0.001
Chest/Abdomen/Pelvis	140 (80%)	135 (69%)	
Extremity (%)	23 (13%)	57 (29%)	
Head/Neck (%)	12 (7%)	5 (2%)	

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Outcomes

	No transfusion (n=175)	Transfusion (n=197)	Unadjusted p value	*Adjusted p value
Hospital LOS (days)	5	7	<0.001	0.05
Infectious complications	5 (3%)	27 (14%)	<0.001	0.09
Disease free interval (mths)	39	30	<0.001	0.113
Tumor recurrence	19 (11%)	61 (31%)	<0.001	0.001
Mortality	11 (6%)	43 (22%)	<0.001	0.01

*Adjusted for postoperative ICU admission, nadir hemoglobin, and operative location

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Relationship between age of blood and outcomes

	Any unit >20 days (n=93)	All units <5 days (n=25)	P value
Hospital LOS (days)	7	7	0.92
Infectious complications	15 (16%)	1 (6%)	0.19
Tumor recurrence	34 (37%)	4 (16%)	0.06
Mortality	28 (30%)	3 (12%)	0.08

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Summary

- Perioperative blood transfusion is associated with:
  - Longer hospital length of stay
  - Higher mortality
  - Higher tumor recurrence rates
- Transfusion of PRBCs stored >20 days is associated with a trend towards higher rates of tumor recurrence and mortality

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Conclusion

- Perioperative blood transfusion is associated with adverse outcomes in children
- Larger database is needed to
  - Validate these findings
  - Determine if the effects are tumor and stage specific
  - Evaluate the effect of aged blood

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Questions ?

