Adverse Transfusion Reactions: The 3 Ts: TACO, TRALI & TRIM

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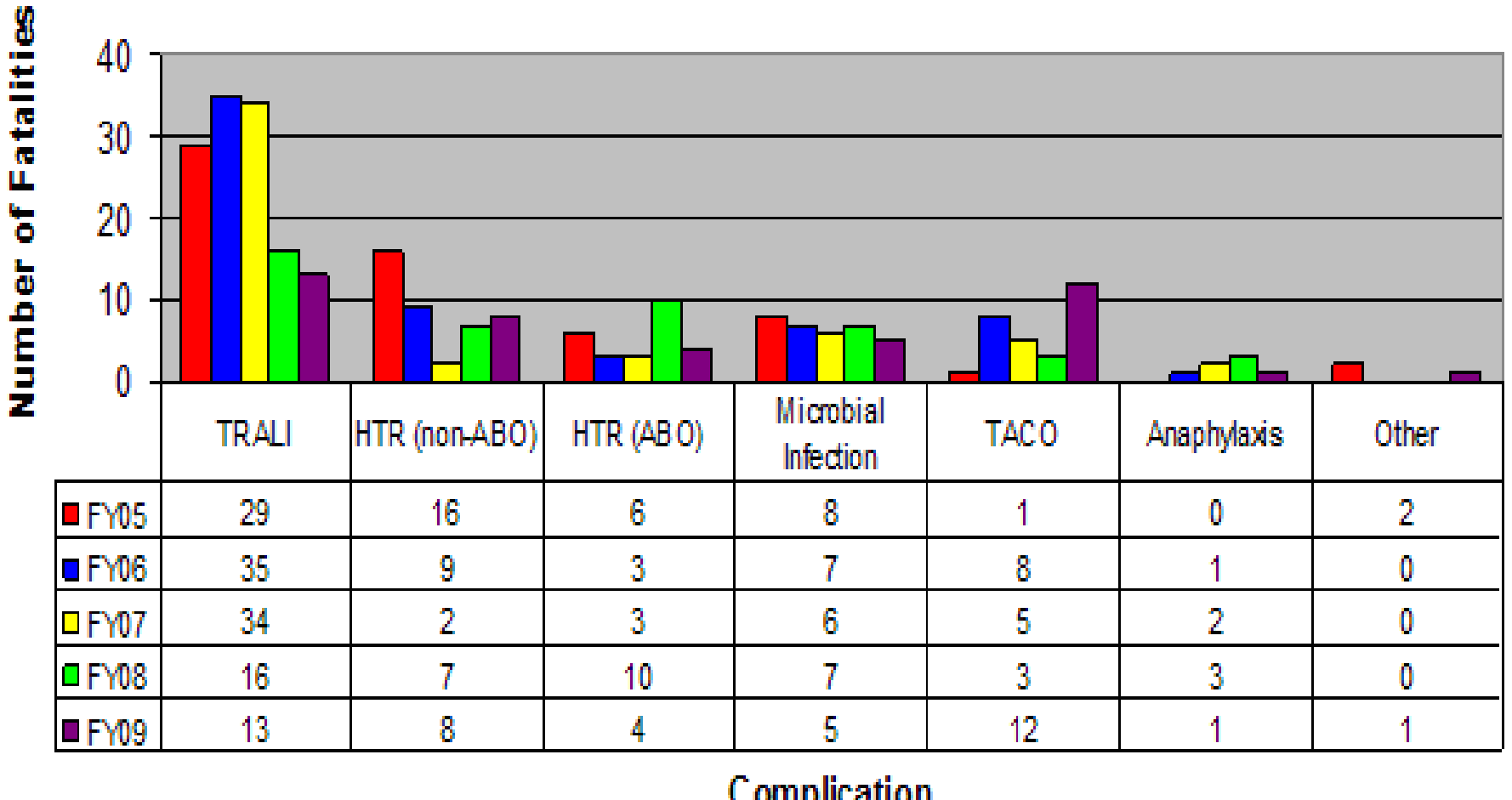
Other Transfusion Reactions

- Febrile Nonhemolytic (1-4:100)
- Delayed Hemolytic (1:2,500)
- TRALI (1:5000)
- TACO (frequent)
- TRIM (frequent)
- Acute Hemolytic (1:38,000)
- Blood delivery errors (1:12,000)
- Fatal Hemolytic reaction (1:1,000,000)
- Anaphylactic (1:150,000)
- Decreased Erythropoiesis Always
- Bacterially contaminated PLT (1:10,000)

Transfusion-Related Fatalities by Complication, FY2005 through FY2009 – Reported to the FDA



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1

Transfusion Associated Circulatory Overload

Transfusion Associated Circulatory Overload

- Most often with rapid administration and large volume transfusions
- Often in patients with co-morbid Cardio-Pulmonary and renal disease
- SOA and other symptoms of fluid overload with increase SBP and MAP
- 2nd most common cause of transfusion-associated mortality

TACO

- Monitoring rate and volume of transfusion in at-risk populations, identify “early signs”
- Consider diuretics between units
- Use of BNP or NT-proBNP to aid in differentiating from other acute lung injury syndromes

TRALI vs. TACO

	TRALI	TACO
Time of onset	Acute onset, within 6 hours	May be more gradual onset
Dyspnea and SOB	Yes	Yes
BP changes	Hypotension likely	Hypertension likely
Fever	Likely	Unlikely
JVD/Pedal Edema	Unlikely	Likely
CVP/PAWP	Likely normal	Elevated
Chest X-ray	Bilateral infiltrates	Bilateral infiltrates
BNP	Likely normal	Elevated

Transfusion-Related Acute Gut Injury (TRAGI)

- Recent studies in pediatric literature associate NEC with transfusion
- Timing of transfusion may be an important factor
- Association with certain blood types

Transfusion – Associated Dyspnea

- Defined as respiratory distress within 24 hours of a transfusion, not meeting the criteria for TRALI, TACO or allergic reactions
- Not explained by underlying or pre-existing medical condition
- Graded as per Hemovigilance Network System i.e. Grades 1-4
- Non-severe, severe, life-threatening, death

Transfusion Related Acute Lung Injury

Transfusion: Related Acute Lung Injury (TRALI)

- Acute lung injury associated within 6 hours of transfusion with exclusion of other forms of injury secondary to CP decompensation, SIRS etc.
- Estimated 1:5,000 – 1:10,000 transfusions
- UNDER-RECOGNIZED AND UNDER-REPORTED

TRALI

- Symptoms include SOA, pulmonary edema, fever, hypotension, tachycardia, signs of ARDS
- Majority of patients have resolution of symptoms within 96 hours
- May see a drop in white count
- Most common cause of transfusion-associated death reported to the FDA

TRALI

- One-hit and Two-hit theories
- Ab-mediated, anti-neutrophil and/or HLA
- Most common with plasma products
- Associated with multigravid female donors
- Use of male-only donors for plasma-containing products has decreased the incidence and number of deaths
- UK SHOT Study decrease incidence of TRALI with use male-only plasma

TRALI

- Rx with supportive care/measures
- AVOID unnecessary transfusion especially those with high volume plasma content
- First episode does not necessarily imply at risk for a second similar reaction
- Must differentiate from TACO and other causes for pulmonary complications

TRALI: Consensus Definition NHLBI

The acute onset of non-cardiogenic pulmonary edema:

- Profound hypoxemia: PaO_2/FiO_2 ratios < 300 mmHg
- Chest x-ray with bilateral, fluffy infiltrates

- New ALI temporally related to transfusion with or without a predisposing condition(s) for development of ALI
- Worsening of pulmonary function temporally related to transfusion

Toy, Crit Care Med, 2005

NHLBI Definition Allows For

- Worsening of pulmonary function caused by transfusion
- Eliminates the confusion of the classification of “possible TRALI”
- TRALI is acute lung injury caused by transfusion and too stringent a definition may mask the adverse effects of transfusion especially in the critically ill

TRALI

- Most common cause of transfusion-related mortality
- Linked to the infusion of plasma containing blood products
- Higher volume plasma components increased incidence, especially fatal TRALI
- PRBCs responsible for 19% of fatal TRALI!
- What is in the plasma that causes acute lung injury?

Antibodies Directed Against HLA Class I or Granulocyte Antigens

- Infusion of an anti-HLA-(Class I) or anti-granulocyte antibody
- Complexes with the recipient antigen on the PMN
- Complement activation?
- Pulmonary sequestration and PMN-mediated injury of endothelium and ALI
- Recipient antibody against transfused PMNs

(Popovsky, Transfusion, 1985 Granulocyte antibody papers)

In Vivo Model of Antibody-Mediated (one-hit) TRALI

- Monoclonal antibody against murine MHC Class I antigens:
  - Concentration: 4.5 mg/kg; lower doses no injury
  - 50% mortality rate
- Pulmonary edema at 2 hours:
  - Antibodies on the surface of vascular endothelium
  - Required PMNs and Fc receptors
- Identical model does not always cause injury

(Fung, Blood, 2010)

In Vivo Model of Antibody-Mediated (one-hit) TRALI

- 10% of all IgG in 1 unit of FFP must be directed against MHC Class I antigens
- This model inconsistent with clinical TRALI
  - High mortality rate
  - Amount of antibody/plasma required
  - Immune complex disease?
- One case of a lung transplant with transfusion of an antibody against HLA Class I (B44) expressed by the transplanted lung

(Dykes, 2000)

Look Back Studies

- Van Buren (1990) donor with an HLA-2b antibody:
  - Most patients did not develop TRALI
  - Clinical condition of the patient is important
- Kopko (2002) donor with an HNA-3a antibody:
  - 8 unrecognized TRALI reactions
  - 27 patients no TRALI even with a known antigen: antibody paring
- Toy (2004) donor with multiple antibodies:
  - No patients developed TRALI

Two Event Pathogenesis

- First event: clinical factors that cause pulmonary sequestration of PMNs
- Second event: the infusion of something in the plasma that activates the sequestered PMNs causing PMN – mediated endothelial damage and ALI
- What are these biologic response modifiers and how do they work?
- Is TRALI PMN-mediated?

Patient Predisposition

- Prospective study two groups:
  - Hematologic malignancies undergoing induction chemotherapy
  - Cardiac disease requiring bypass
- Proposed risk factors:
  - Recent surgery (24 hours)
  - Acute active infection
  - Massive transfusion
  - HUS/TTP

(Silliman, 1997, 1999, 2003; Roffey, 2003; Kopko, 2003; Toy, 2007; Vlaar, 2010)

TRALI in the Critically Ill

- Highest incidence is in the critically ill and approaches 8%
- GI bleeders admitted to the MICU:
  - 16.7% developed ALI and met the clinical definition
  - 29% of patients with end-stage liver disease developed ALI post transfusion
- TRALI is common in this patient population

(Gajic, 2007; Benson, 2008, 2009)

Second Events
or
What Might Be in the Plasma

Problems With Antibody-mediated Model

- Little is known about the antibodies:
  - Titer?
  - Class?
  - Specificity to what epitope?
  - Cytotoxic, pro-inflammatory?
- The role of non-specific antibodies undefined
- Antibody-negative TRALI exists (Silliman 1997, 2003, American Red Cross M & M reports, etc.)
- Autologous TRALI reported (Covin 2004)

TRALI Secondary to Antibodies Against HLA Class II Antibodies

Antibody-mediated Pathogenesis: HLA Class II Antibodies

- Infusion of antibodies directed against specific HLA Class II antigens
- Activation of monocytes ± endothelium
- Synthesis of pro-inflammatory cytokines and lipids
- Activation of pulmonary endothelium
- PMN sequestration & PMN-mediated ALI
- IPRL with human monocytes and antibodies confirmed these interactions could cause ALI

(Kopko 2003, Nishimura 2006 & 2007, Sachs 2010)

TRALI Secondary to BRMs Which Accumulate During Routine Storage of Cellular Blood Components

Bioactive Lipids From Stored Blood Components

- Accumulate during routine storage:
  - PRBCs(100), WB(20), WB-Plts(160), A-Plts(50)
- Maximal and outdate/mirror the storage lesion
- Rapidly prime the PMN oxidase
- Two Classes (identified by GC/MS/MS):
  - Non-polar lipids
  - Lysophosphatidylcholines

Two-Event Model: Human Studies

- Antibody-negative TRALI:
  - 96% of the reactions were antibody-negative including antibodies to HLA Class I & II and granulocyte antigens
  - Patients had a predisposing clinical disorder
  - Most reactions to whole blood derived platelets
  - TACO, urticarial reactions and bacterial contamination were ruled out
  - No ABO incompatibility

Problems With Lipids and Other BRMs

- Are generated in cellular components
- Complex etiology and only a few labs are equipped to test for their presence
- Many products are transfused much younger than those in the studies that defined these agents; so relevance to many is not obvious

PMN Priming

- All implicated products have PMN priming activity including significantly greater activity than in the components that do not cause reactions
- Antibodies to granulocyte antigens and murine antibodies against rat MHC Class I Antigens prime PMNs

Conclusions: TRALI

- Most likely is the result of two events:
  - Susceptible host: endothelial activation
  - Infusion of antibodies, lipids and/or sCD40L
- PMN-mediated
- The ability of implicated agents to prime PMNs appears vital to cause TRALI
- A number of agents have the capacity to cause TRALI as the second event

Transfusion Related Immunomodulation

Transfusion Related Immunomodulation (TRIM)

- Dose-dependent reduction in cellular immunity

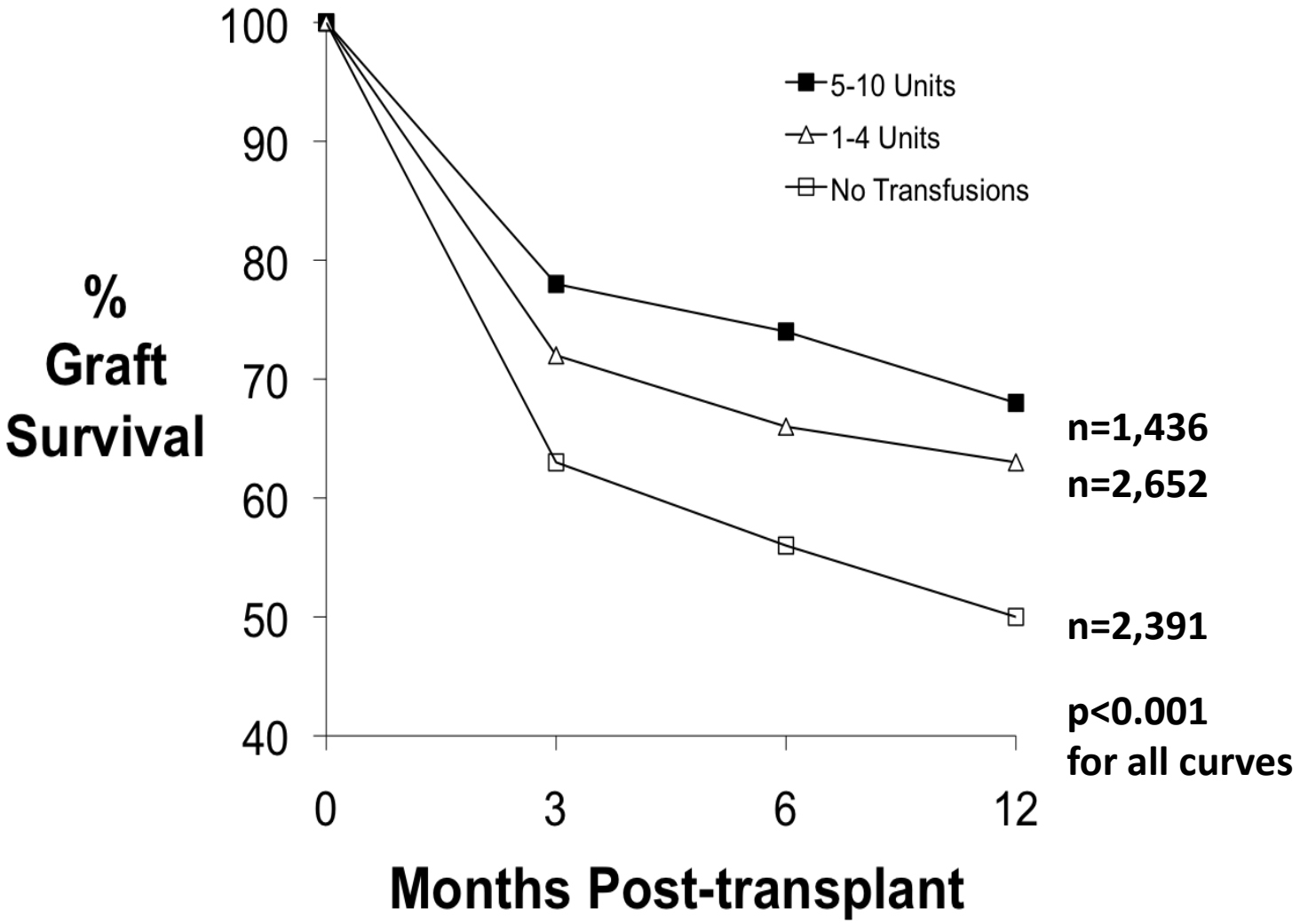
  - Decreases in NK cell and macrophage activity, activation of T-suppressor cells (anergy)

  - Effect has been known and well-documented for years

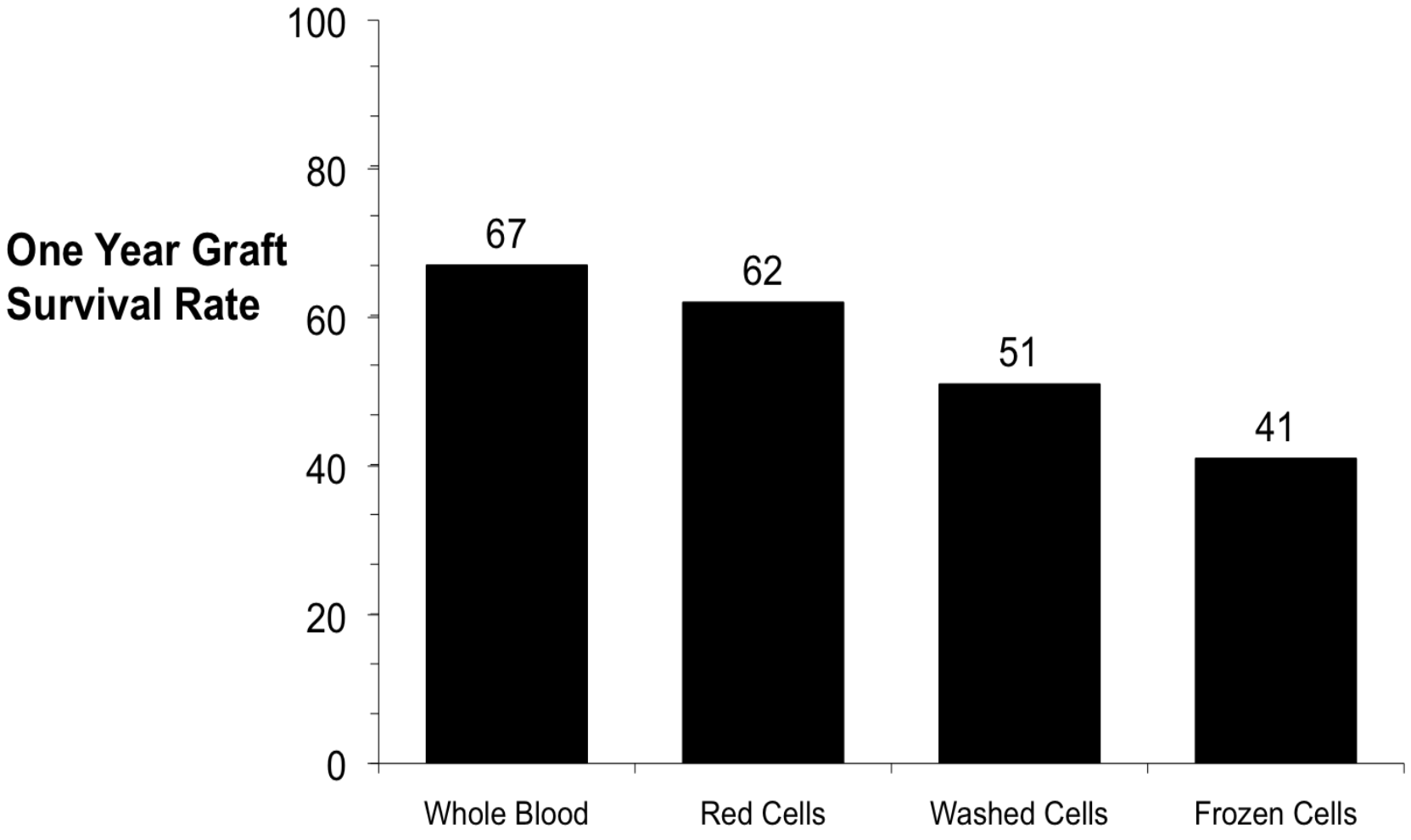
- 7 – 10 fold increase in postoperative infection rates leading to increased LOS, resource consumption, total hospital costs

- Increased cancer recurrence rates in transfused patients, increased 5 year mortality in CABG

Kidney Graft Survival Versus Transfusion Dose, 1978-1982, UCLA Registry

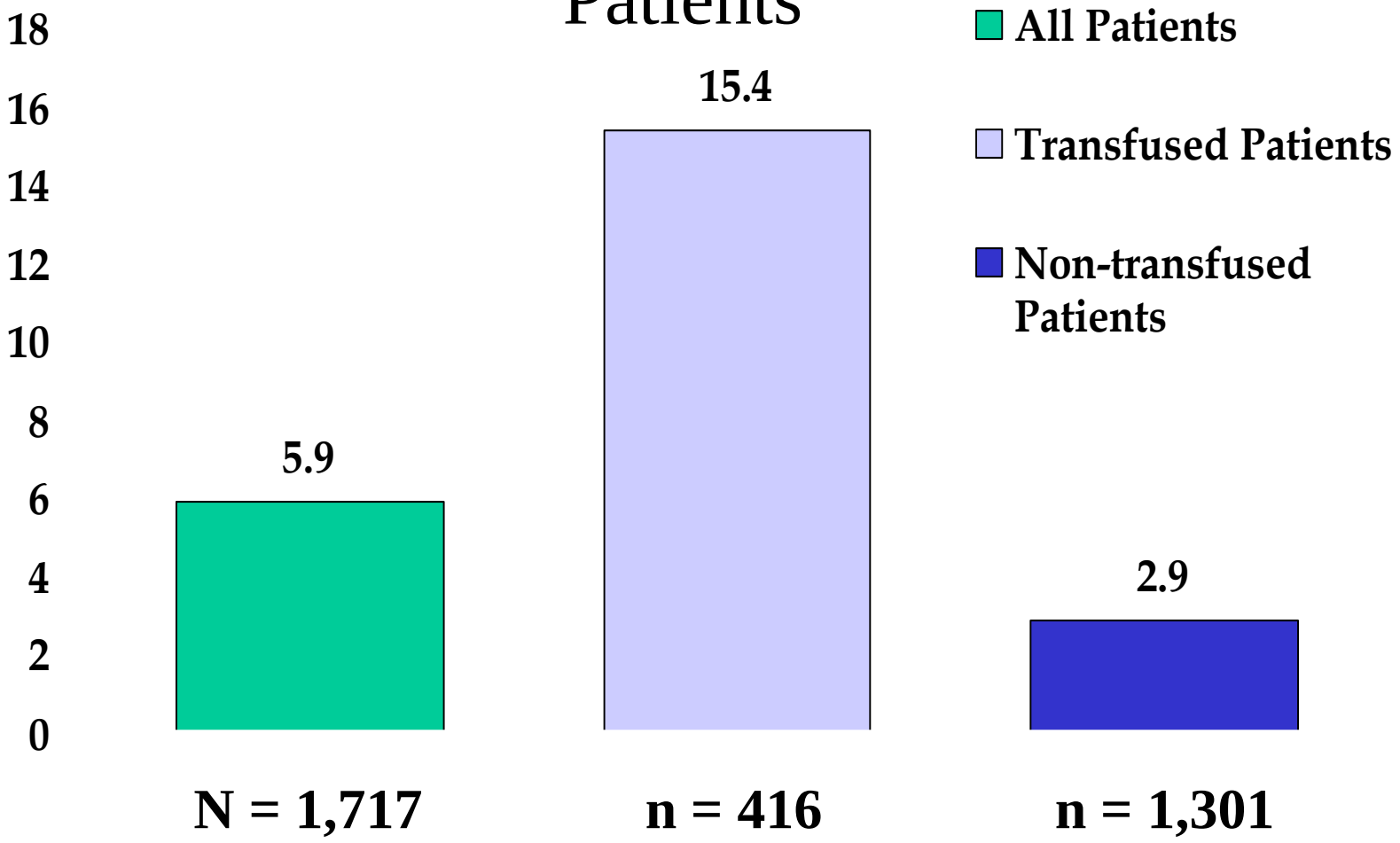


Kidney Graft Survival in Recipients of 1-5 Units of Blood



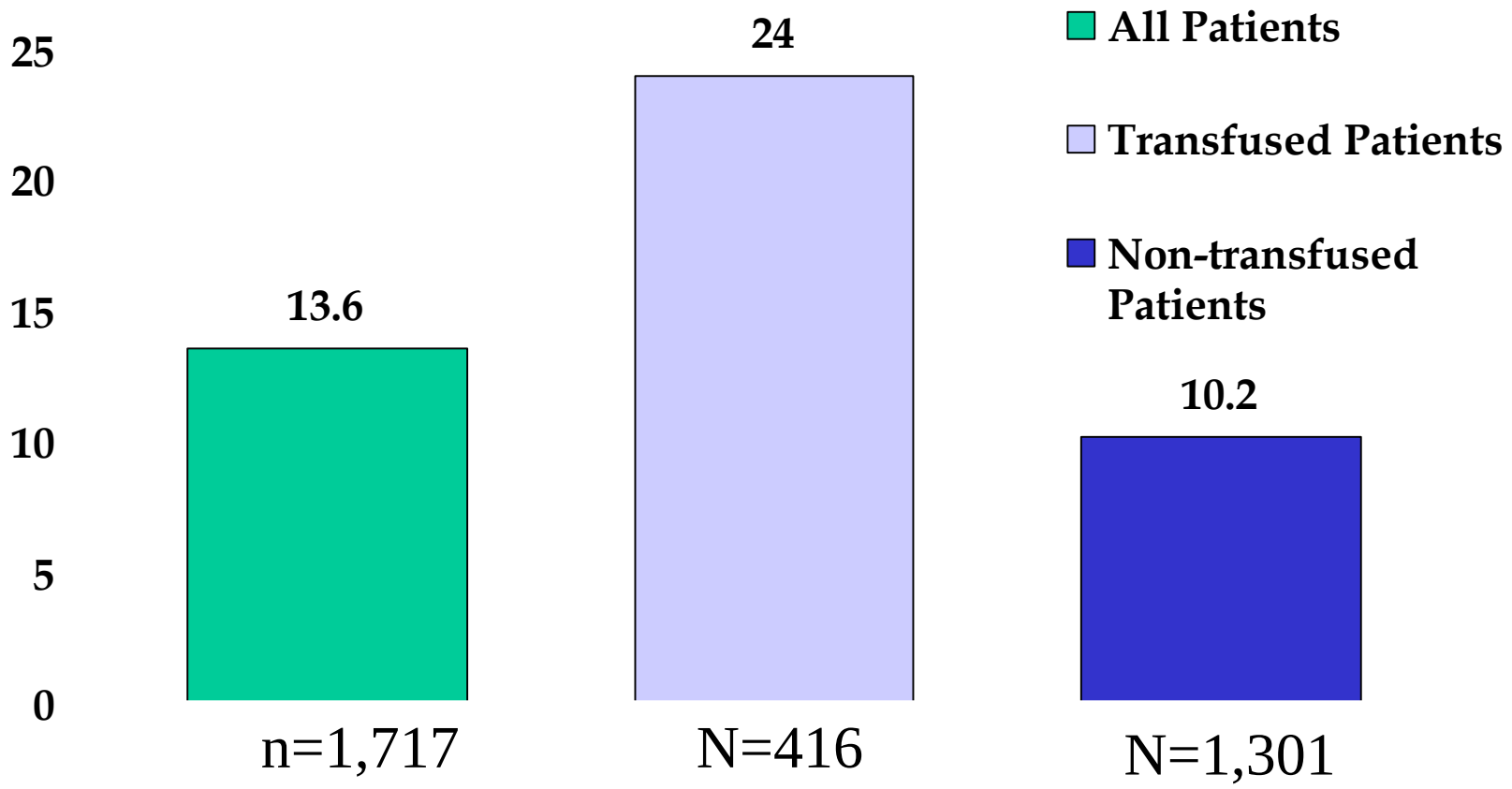
(Transplantation 35: 320 (1983)

Nosocomial Infection Rates in Critically Ill Patients



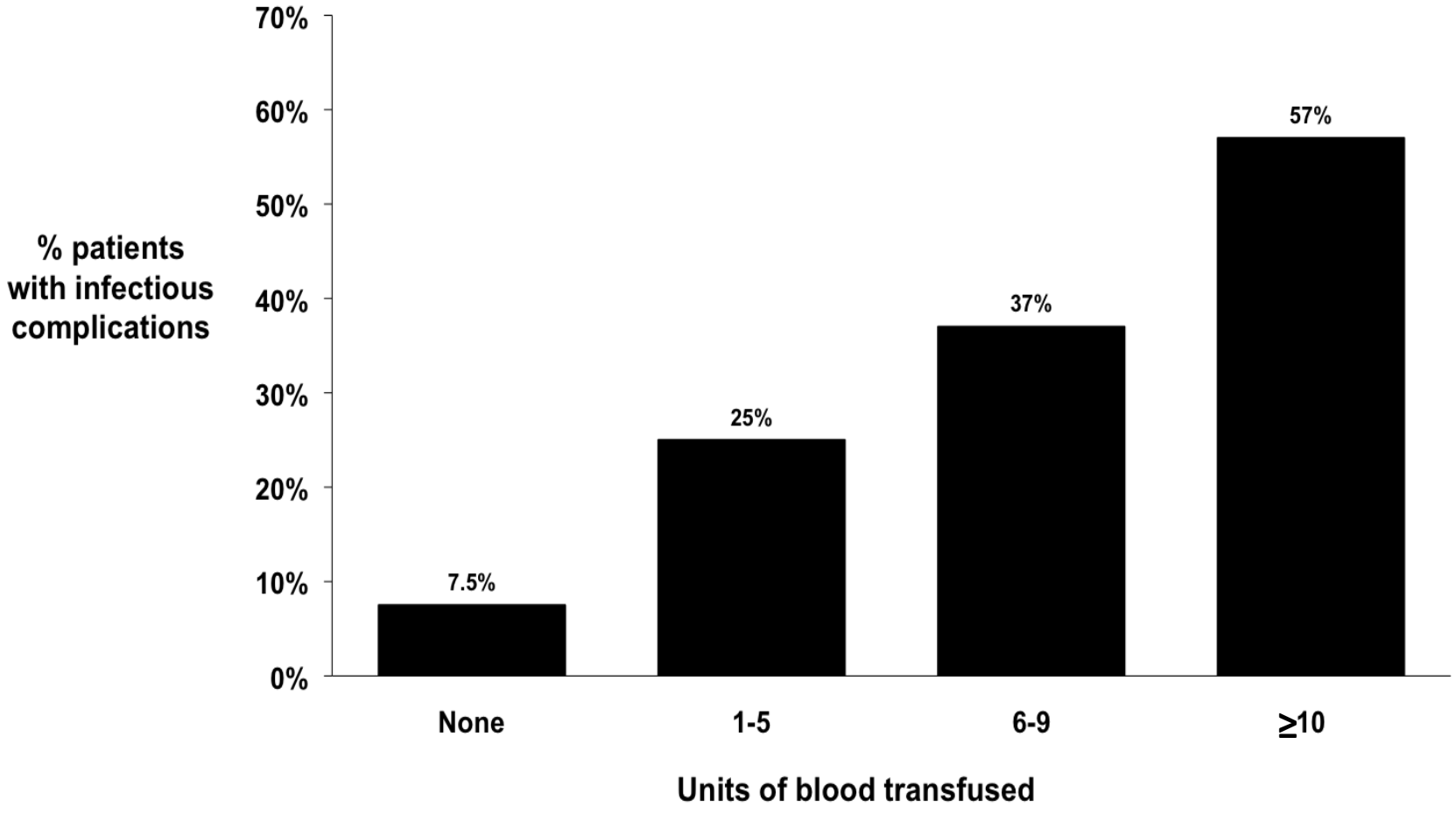
Taylor RW, et al. *Crit Care Med*. 2002;30:1-6.

Mortality Rates in Critically Ill Patients



Taylor RW, et al. *Crit Care Med*. 2002;30:2249-54.

The Relationship between Post-operative Infectious Complications and Number of Blood Transfusions



Surgery. 1986 Oct;100(4):796-803.

Transfusion and Cancer

Association between red blood cell transfusions and development of non-Hodgkin lymphoma: a meta-analysis of observational studies

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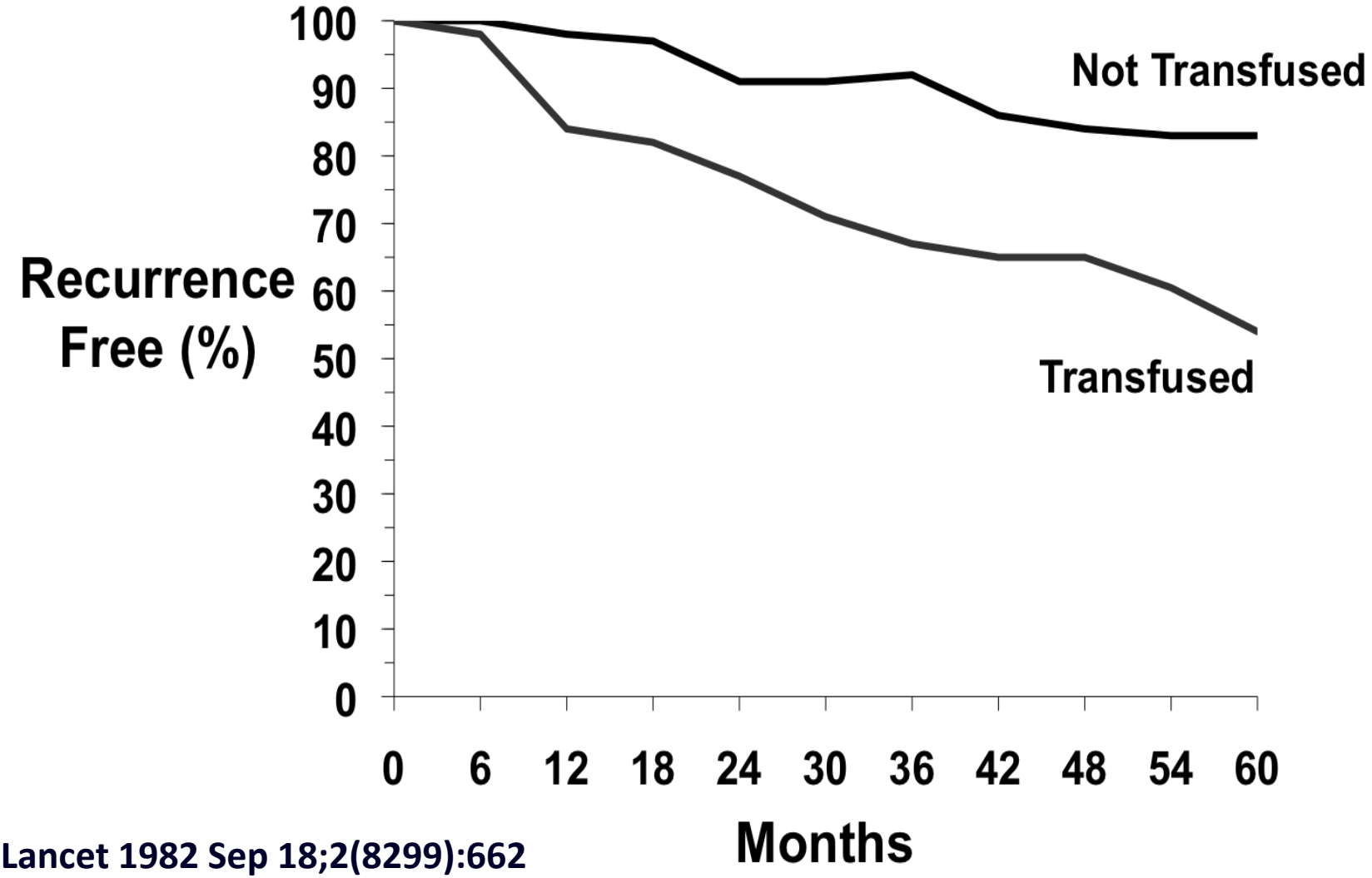
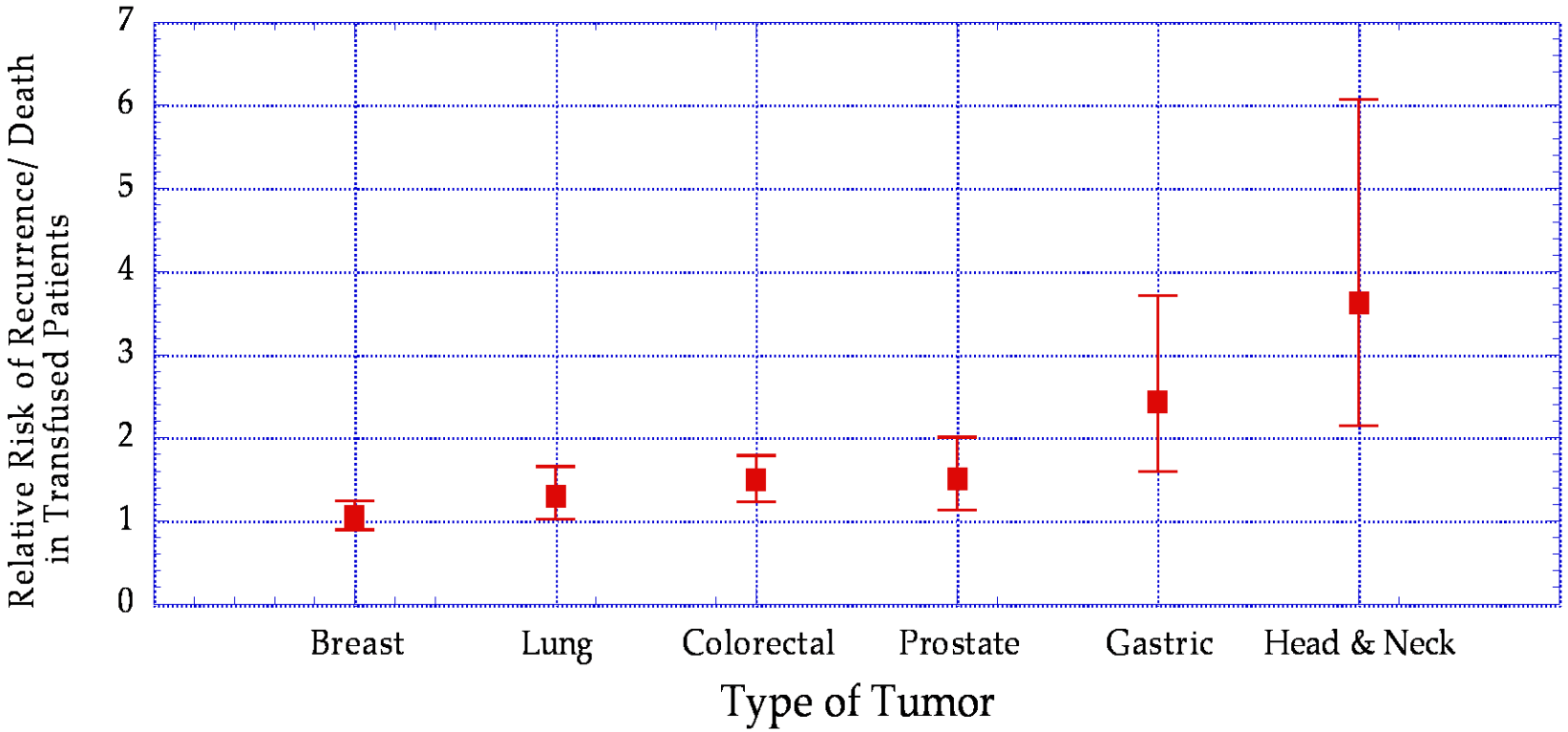
The incidence of non-Hodgkin lymphoma (NHL) has increased steadily for the past few decades. Previous studies have suggested an association between blood transfusions and NHL. The main objective of this study was to evaluate this relationship with a meta-analysis of observational studies. A literature search was undertaken, looking for case-control and cohort studies evaluating the risk of developing NHL in persons who received allogeneic blood transfusions; 14 studies were included. Outcome was calculated and reported as relative risk (RR). Heterogeneity was assessed with Cochrane Q and I^2 statistics. Dissemination bias was evaluated by funnel plot visualization and trim-and-fill analysis. Quality assessment was performed with the Newcastle-Ottawa scale. Our analysis showed a RR of developing NHL of 1.05 (95% CI, 0.89-1.25; $P = .42$) and 1.34 (95% CI, 1.15-1.55; $P < .01$) in case-control and cohort studies, respectively. When pooling all studies, RR was 1.2 (95% CI, 1.07-1.35; $P < .01$). In subset analysis, RR of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was 1.66 (95% CI, 1.08-2.56; $P = .02$). The RR of NHL was elevated in both men and women and in persons receiving transfusions either before or after 1992. Blood transfusions appear to increase the risk of developing NHL; however, the risk of CLL/SLL appears higher than for other NHL subtypes. (*Blood*. 2010;116(16):2897-2907)

Percentage of Colorectal Cancer Patients Surviving Recurrence Free



Lancet 1982 Sep 18;2(8299):662

Meta-Analysis: Association of Cancer Recurrence & Transfusion



Vamvakas, Transfusion 1995; 35:760-768

TRIM Mitigation

Leukocyte Reduction

Leukoreduction decreases post-operative mortality in cardiac surgery

- Death rate reduced from 7.8% to 3.5% (van de Watering 1998), and 10.1% to 5.5% (Bilgin 2001) in randomized trials of leukoreduced transfusions
- Death rate reduced from 5.3% to 3.2% in our implementation trial with LR blood (p= NS)
- Post-operative infection has a mortality of 8-15% and is the leading cause of multiorgan failure syndromes

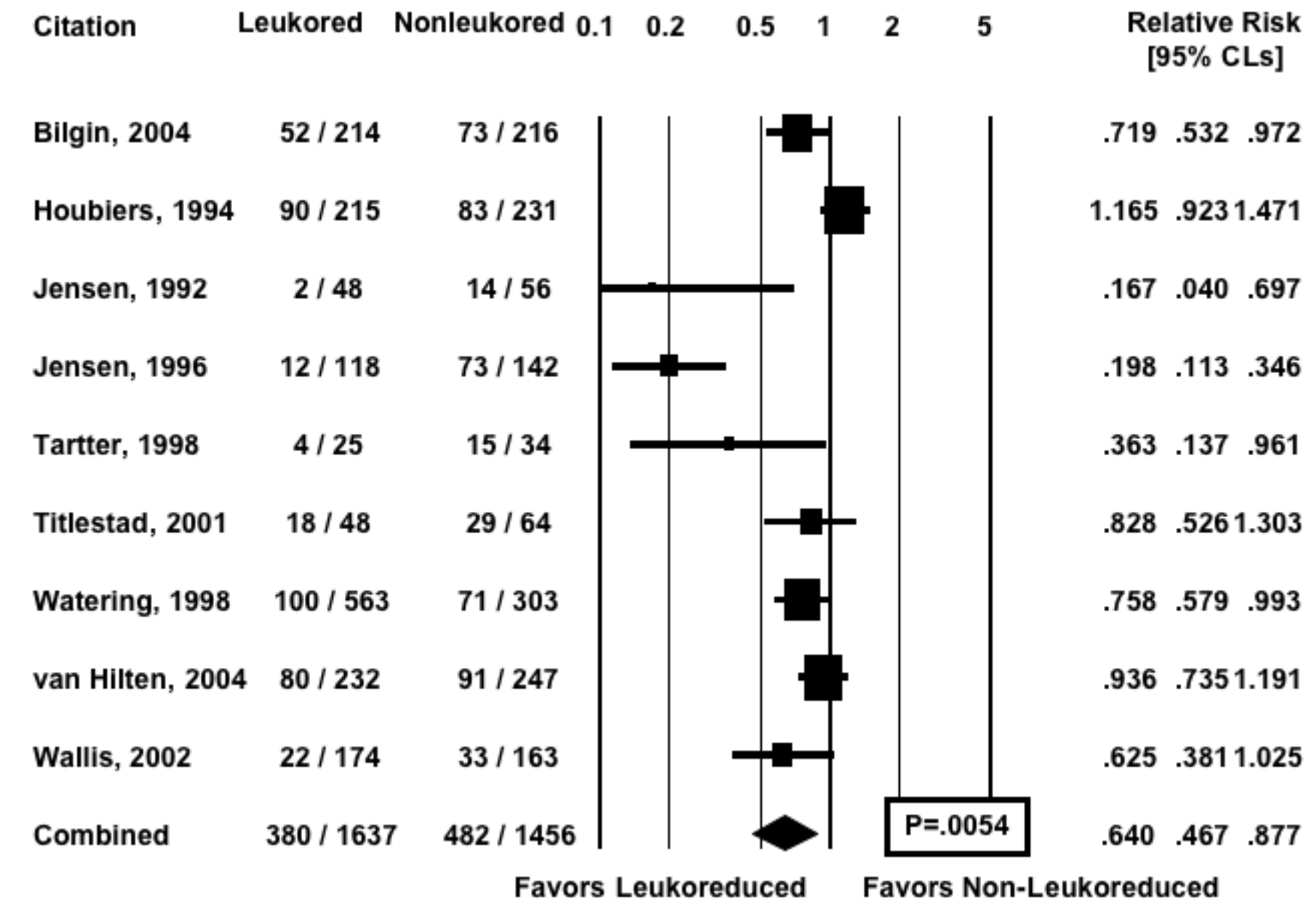
Misapplication of the intention to treat principle in meta-analyses of LR

- The published meta-analyses arbitrarily assigned hundreds of non-transfused patients and their infections, in equal numbers, to each arm of the study.
  - These patients had been excluded by the original authors.
  - This rendered the results non-significant in some cases

- Evidence based medicine cannot consist of adding back to the analysis patients for whom you have no data whatever.
  - Fictional data cannot be used to draw scientific conclusions

Postoperative Infection Risk

Transfusion 47: 573-581(2007)



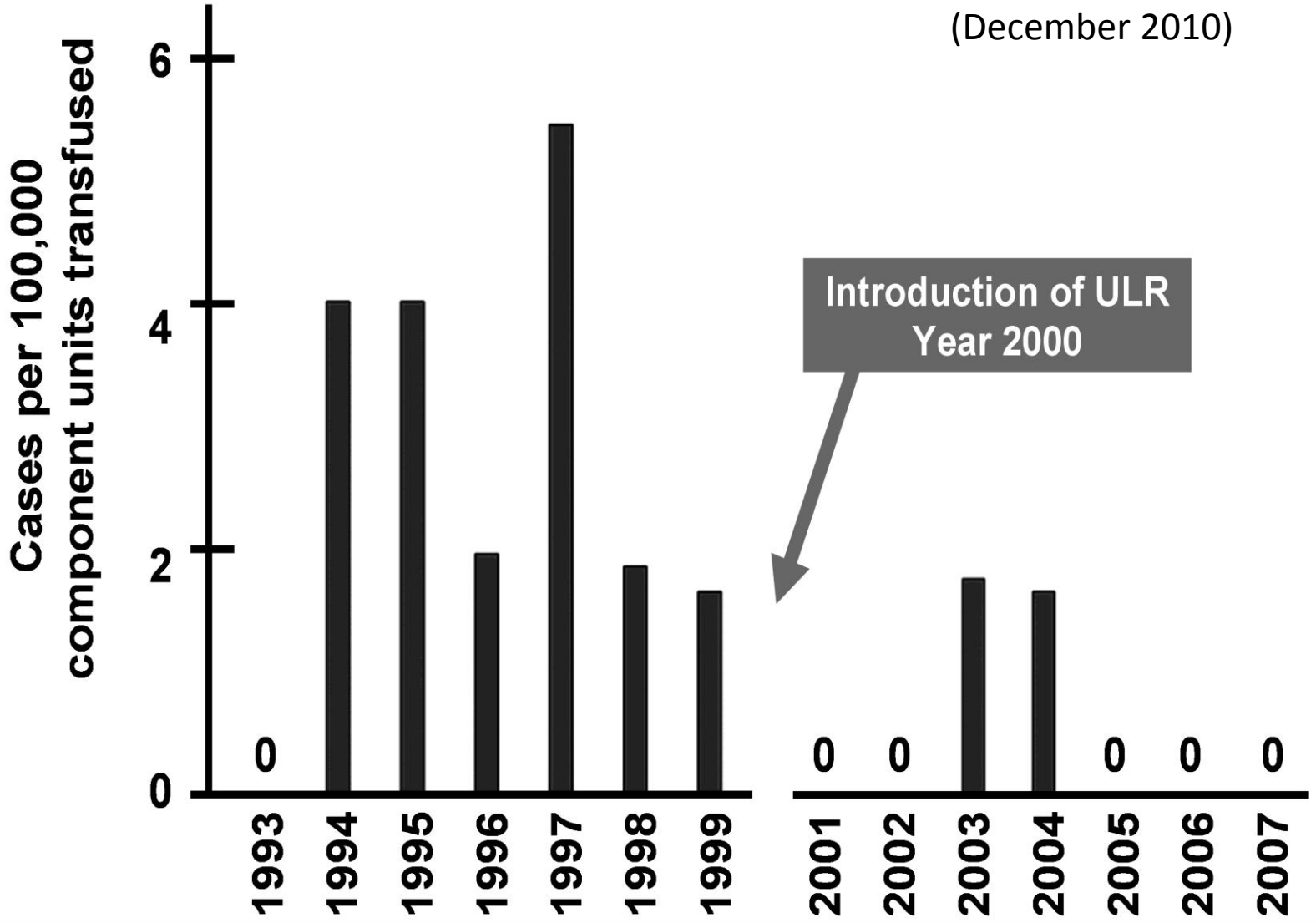
Limitations of the Existing Trial of ULR--Transfusion 42:1114 (2002)

- More than one in eight patients in the LR arm received some non-LR blood (12.6%)

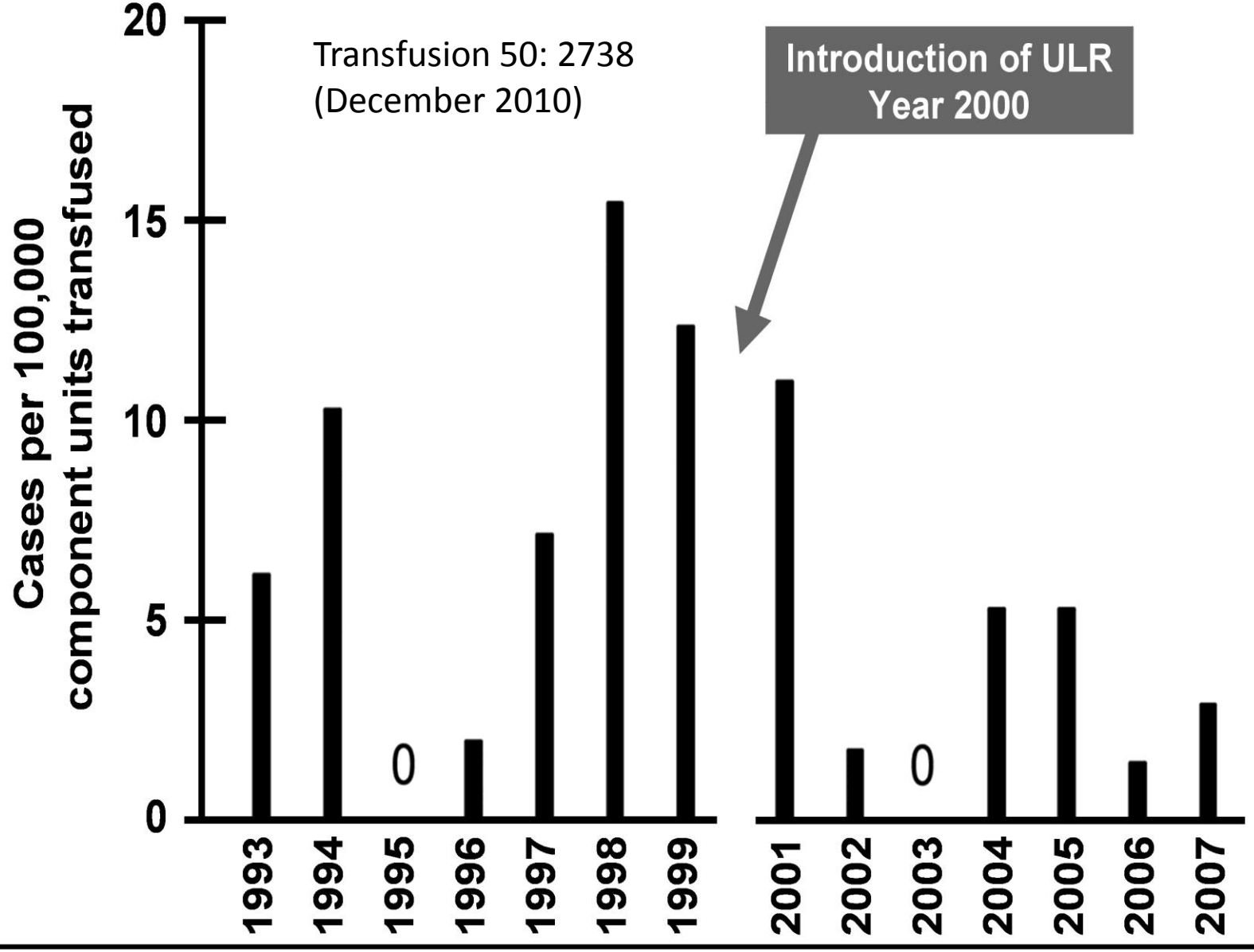
- Patients in the LR arm were significantly more likely to receive non-LR blood than patients in the non-LR were to receive LR blood (p=0.0055)

Annual Incidence of TRALI Before (1993-99) and After (2001-07) Universal Leukoreduction

Transfusion 50: 2738
(December 2010)



Annual Incidence of TACO Before (1993-99) and After (2001-07) Universal Leukoreduction



Proven Benefits of Leukoreduction

- Reduced febrile transfusion reactions
- Reduced HLA alloimmunization/reduced platelet refractoriness
- Reduced CMV transmission
- Reduced post-operative infections
- Reduced cardiac surgery mortality

Cost Savings with Leukoreduction

- Cardiac surgery implementation trial (Am J Clin Path 118: 376-381, 2002)
  - Leukoreduction: cost per hospitalization DECREASED $1,700
  - Non-transfused patients: cost per hospitalization INCREASED $4,000
  - 750,000 cases nationwide x $1,700 = $1.3 billion/year
    - Enough to pay for universal leukoreduction 2-3 times over

Estimated deaths potentially averted in surgical patients by leukoreduced transfusions

- 2 million surgeries with transfusion
  - ↗10% fewer infections = 200,000 fewer infections
  - ↗8-15% of infections lead to death
  - ↗16,000 to 30,000 fewer deaths per year
- Cardiac Surgery: 750,000 cases per year
  - ↗ 2-4% fewer deaths
  - ↗15,000 to 30,000 fewer deaths per year

Number to treat to save one life (NNT)

- Nucleic Acid Testing (NAT) for HIV/HCV
  - 500,000 to 1,000,000
    - Cost per life saved = $2.5-5,000,000
- Leukoreduction of allogeneic transfusions in cardiac surgery
  - 20
    - Cost per life saved = $400-600

Immunomodulation and Leukoreduction

- **Surgery for Colorectal Ca & GI Diseases**
  Reduced: post-op infection, Hospital costs

- **Cardiac Surgery**
  Reduced:post-operative mortality, MOF

- **Acute leukemia**
  Reduced: blood use, infections, hospital costs, mortality

- **BMT for Lymphoma**
  Reduced: blood use, infections, costs

Evidence that immunologic mechanisms underlie the clinical evidence

- **In patients with Crohn's disease, perioperative allogeneic transfusion is associated with increases in post-operative infection, but decreases in inflammatory bowel disease recurrence**
- **In patients undergoing solid organ transplants, perioperative allogeneic transfusion is associated with increases in post-operative infection, but decreases in allograft rejection**
- **The suggestion that transfusion is merely a measure of unfavorable pre-existing morbidity is thus implausible**

Effects of Allogeneic Transfusions on Recipient Immunologic Functions Arch Path Lab Med 118: 371(1994)

1. Decreased Th1 and increased Th2 cytokine production in vitro

2. Reduced responses in mixed lymphocyte culture

3. Decreased proliferative response to mitogens or soluble antigens in vitro; impaired delayed type hypersensitivity skin responses

4. Increased CD8 T cell number or suppressor function in vitro

5. Decreased natural killer cell number and activity in vitro

6. Decreased CD4 helper T cells number

7. Decreased monocyte/macrophage function in vitro and in vivo

8. Enhanced production of anti-idiotypic antibodies suppressive of mixed lymphocyte response in vitro

9. Decreased cell mediated cytotoxicity (LAK) against certain target cells in vitro

10. Humoral alloimmunization to cell associated and soluble antigens

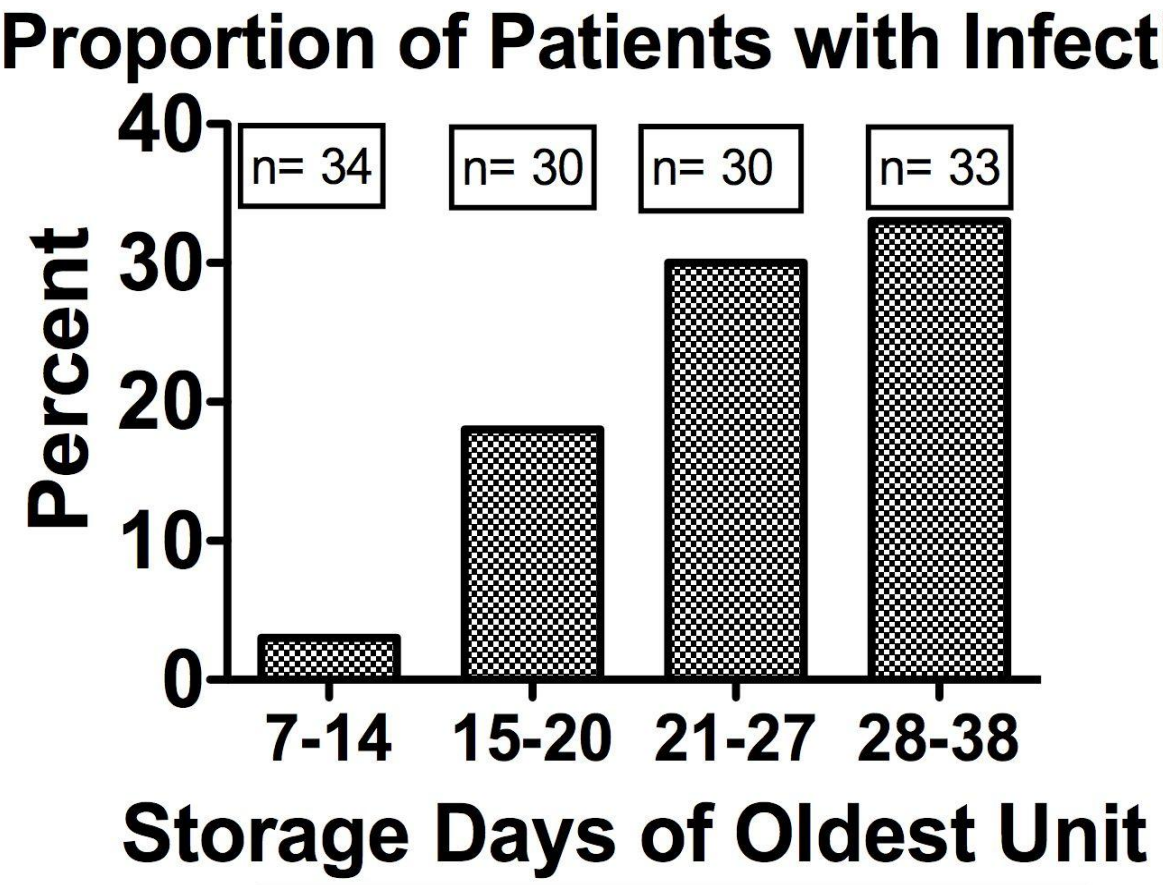
So what about the supernatant of stored blood components?

- During 14 years the incidence of TACO and TRALI due to leukoreduced PLTS and RBC was 11 of 319,161
- During that same period, the incidence of TACO and TRALI due to washed leukoreduced PLTS and RBC was **ZERO** of 97,445(p = 0.049)
  - Transfusion 50: 2738 (December 2010)

Clinical Outcome data

Variable	Washed Group N=64	Unwashed Group N = 64
Mechanical ventilation duration (median hours)	45	50
Inotropic/vasopressor duration (median hours)	72	72
Antibiotics (number)	18	18
Infection (number)	14	14
Thrombosis (number)	7	9
ICU length of stay (median days)	4.5	5
Total stay (median days)	8	8.5
ECMO (number)	0	2
Death (number [%])	2 [3.1%]	6 [9.4%]

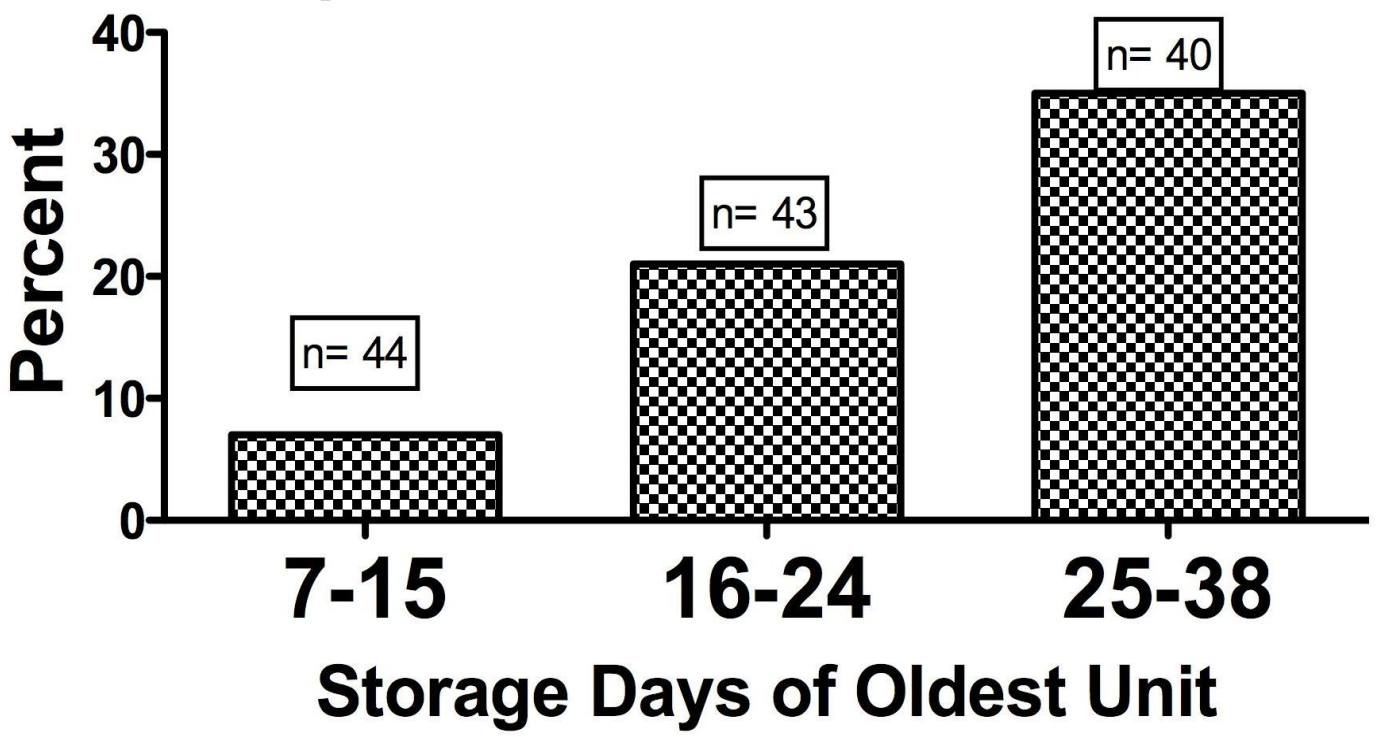
No statistically significant differences Washed v. Unwashed



Includes all patients
p = 0.004 by Chi square

Transfusion 52[Supplement]: 51A (2012)

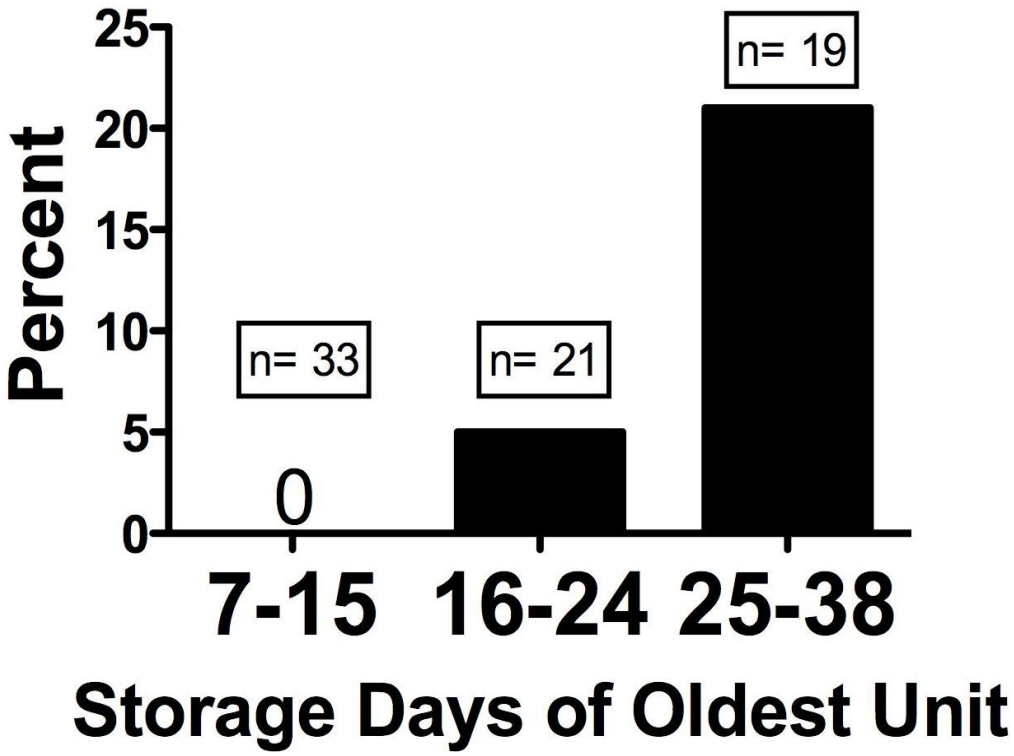
Proportion of Patients with Infection



Includes all patients; p = 0.004 by Chi square

Transfusion 52[Supplement]: 51A (2012)

Proportion of Patients with Infection



Restricted to maximum of 1-2 transfusions, given only on the day of surgery; p = 0.01 by Chi square

Transfusion 52[Supplement]: 51A (2012)

Effect of washing when the oldest red cell transfused is ≤15 days of storage

	Unwashed (n=22)	Washed (n=22)	P value
Transfusions	**2.4 ± 0.33**	**1.5 ± 0.33**	**0.06**
IL-6 at 6 hrs	**180 ± 25**	**92 ± 25**	**0.006**
Hours Intubated	**104 ± 21**	**41 ± 21**	**0.008**
Hours Inotropes	**94 ± 17**	**58 ± 17**	**0.028**
Thrombosis	9%	4.5%	0.50
Infection	**14**%	**0**%	0.23

- ***Washed is superior to unwashed when ≤15 day storage blood is transfused***

Transfusion 52[Supplement]: 51A (201

Effect of washing when the oldest red cell transfused is ≥28 days of storage

	Unwashed (n=17)	Washed (n=14)	P value
Transfusions	**3.1 ± 0.88**	**5.6± 0.97**	**0.11**
IL-6 at 6 hrs	200 ± 64	230 ± 71	0.92
Hours Intubated	**128 ± 58**	**239 ± 66**	**0.054**
Hours Inotropes	**83 ± 37**	**234 ± 43**	**0.01**
Thrombosis	18%	29%	0.89
Infection	**18%**	**57%**	**0.056**

- ***Washed is inferior to unwashed when ≥28 day storage blood is transfused***

Transfusion 52[Supplement]: 51A (20

Summary

Older stored red cells at doses equivalent to massive transfusion in adults dramatically predispose to post-operative infection in infants

- **In pediatric cardiac surgery, washed red cells should be selected to be <21 and ideally <15 days of storage**
- **Washed red cells of shorter storage duration (<15-21 days) may reduce morbidity and perhaps mortality in pediatric cardiac surgery**
- **Older red cells (>15 days) are associated with increases in infection quantitatively similar to those seen with steroid use**

Conclusions

- **Transfusions strikingly predispose to infection, cancer recurrence, lung injury, inflammation, multi-organ failure and possibly thrombosis**

- **More restrictive transfusion practices are associated with reduced morbidity and mortality**

- **Leukoreduction strikingly reduces the risks of post-operative infection, multi-organ failure and death in cardiac surgery, and may reduce the risk of lung injury, inflammation, and thrombosis**
  - **Leukoreduction also reduces CMV transmission, febrile reactions, HLA alloimmunization**

Conclusions

- **Washing may reduce the risk of death in younger patients with acute leukemia and reduces inflammatory markers in pediatric cardiac surgery**
  - **Reduces allergic & febrile reactions to leukoreduced platelets**
  - **Washing may increase the post-operative infection rate in pediatric cardiac surgery when units >27 days of storage are transfused, yet decrease morbidity and mortality when units <15 days of storage are transfused**

- **Receipt of an oldest unit >27 days of storage is associated with a ten fold increase in post-operative infections in pediatric cardiac surgery**