Current Risks of Transfusion--What has Changed: Immunomodulation & TRALI

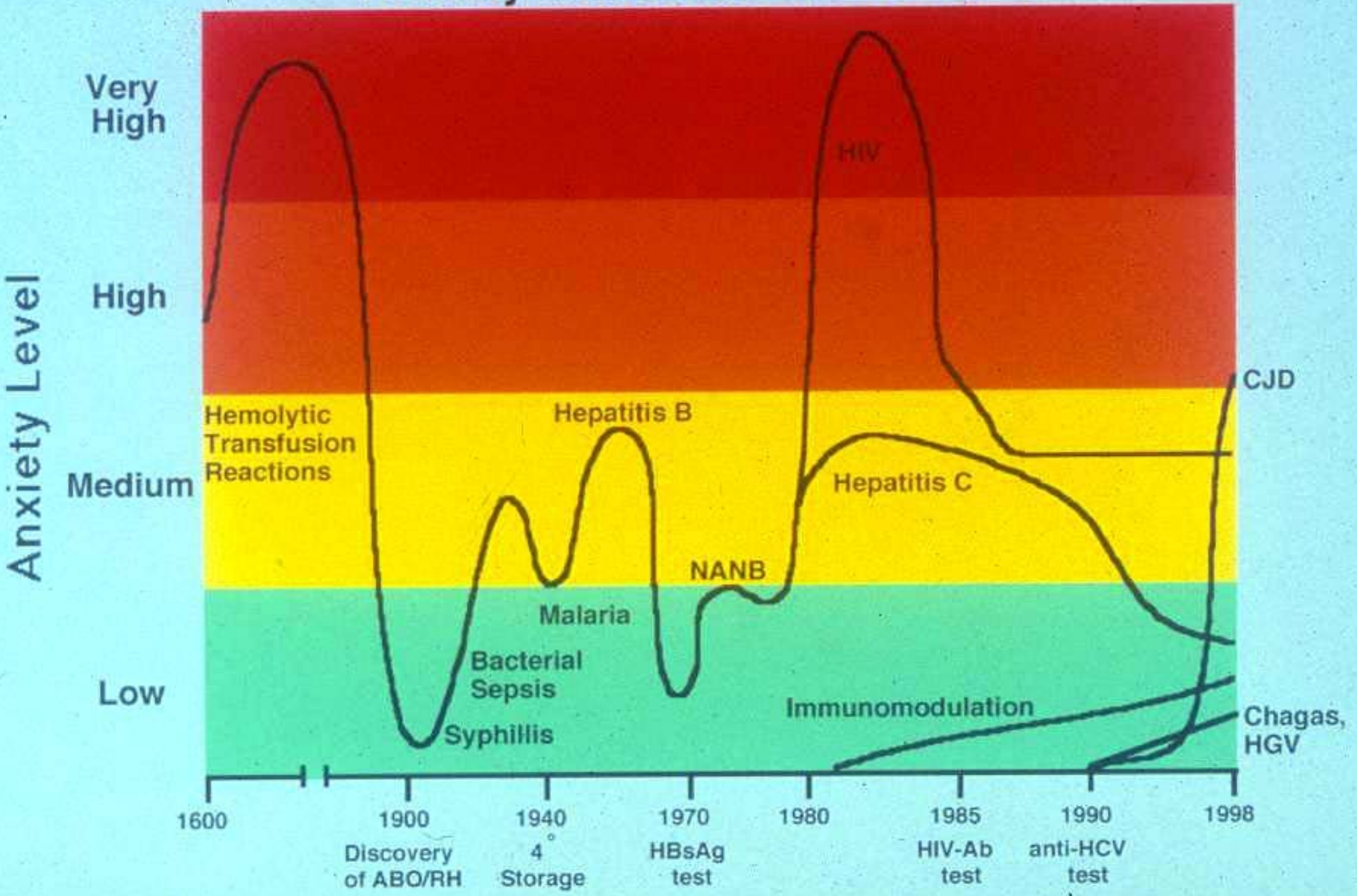
Neil Blumberg MD*, Susan Roseff MD# & Joanna Heal MRCP†

*Prof. of Pathology and Laboratory Medicine and Director, Transfusion Medicine, †Assoc. Prof., Medicine, University of Rochester, Rochester, NY

#Associate Professor, Pathology, MCV

Anxiety and Blood Transfusion

J.M. HEAL MRCP



Blood Donor Testing Chronology

1938:	Syphilis
1971/2:	Hepatitis B
1985:	Anti-HIV
1986/7:	**ALT**, anti-HBc
1989:	Anti-HTLV I-II
1990:	Anti-HCV
1992:	Anti-HIV 1,2; Anti-HCV 2.0
1995:	Syphilis – treponemal test
1996:	**HIV antigen;** Anti-HCV 3.0
1999:	NAT:HCV,HIV
2003:	NAT:WNV
2004:	Bacterial detection - platelets

Viral Pathogens

- HIV 1,2, variant strains
- Hepatitis A*,B,C...X
- HTLV I,II
- HHV: CMV, EBV
- Parvovirus B-19*

**Transmissions occur*

Viral Pathogens: Risk of Disease per Screened Unit

	Serology	Nucleic Acid Test (NAT)
HIV	1:493,000	1:1,900,000
HBV	1:205,000	Not yet available
HCV	1:103,000	1:1,600,000
HTLV I,II	1:641,000	Not applicable

What is TRALI?

- First recognized as a discrete **clinical syndrome** about 20 years ago. 36 cases of TRALI over 29 months at Mayo Clinic
- **Sudden onset of:**

  1. Acute respiratory distress

  2. Progressive hypoxia (severe)

  3. Hypotension (moderate)

  4. Fever (1-2F)

  5. Bilateral diffuse pulmonary infiltrates on Chest X-ray

  6. With no signs of CCF or fluid overload

Within 4 hours of transfusion of blood component

- Indistinguishable from ALI/ARDS
- Anti-HLA (72%) or anti-Granulocyte Abs (89%) in 1 or more donors

Popovsky MA & Moore SB Transfusion 1985: 25; 573-577

TRALI: Implicated Blood Products

Most frequent with

Highest volume plasma

- FFP
- Apheresis platelets
- Random Platelet Concentrates
- RBC

Also reported with:

- Granulocytes
- Cryoprecipitate
- Whole blood

- **Rare reports with:**
  - Allogeneic Bone marrow
  - Peripheral blood stem cells
  - IV gammaglobulin
  - Directed donations
    - Child to Mother
    - Mother to child
    - Sister in law to patient

Never reported with:

-washed products or

-pooled SD plasma

TRALI: Special Clinical Features-I

- **Onset of Symptoms**
  - Dramatic & often fulminant
  - **< 6 hours of transfusion**
  - 90% occur within 1-2 hours of onset of transfusion
  - Sometimes within 5-30 mins
  - Reports of mild symptoms < 6 hours with rapid resolution and reappearance of severe symptoms at 24 hours

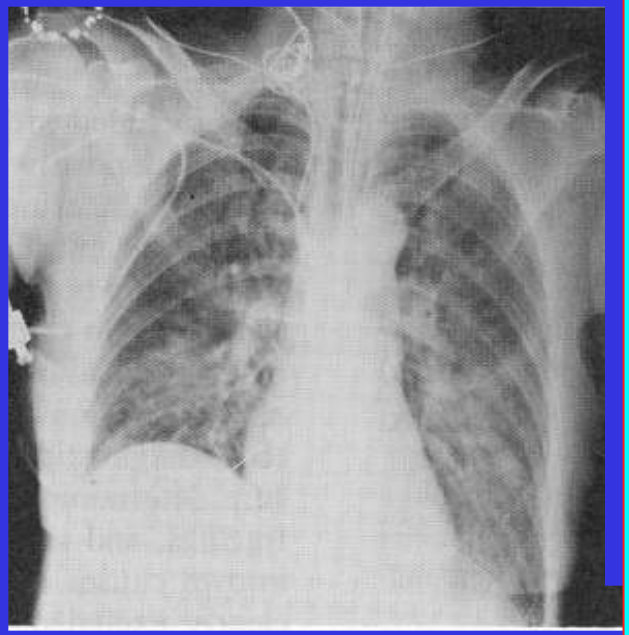
- **Usually due to transfusions that contain plasma**
  - Generally volume of plasma infused is ≥ 60ml
  - Can occur 10ml

TRALI: Chest X-Ray Post transfusion

Non- specific

HEART

- Heart is normal in size & outline
- No pleural effusions



LUNGS

Classic:

- Bilateral pulmonary infiltrates
- Interstitial & alveolar
- At time of reaction

Early:

- Patchy & mild
- May be dependant & unilat in decubitus

Late:

- White out

CXR is indistinguishable from ARDS

TRALI: A Diagnosis of Exclusion

- High Index of suspicion
- No rapid or conclusive test
- Rule out:
  1. **Cardiogenic Pulmonary edema due:**
     - **Heart Disease (Left ventricular failure)**
     - **Fluid overload**
  2. Pulmonary infection, or embolus
  3. Transfusion reactions (11% have dyspnoea)

     Hemolytic TR, FNHTR
     Allergic, anaphylactic
     Bacterial contamination
  4. Other causes ARDS

Expanded Two-event Hypothesis
Immune & Non-Immune TRALI

1st event

A clinical condition which causes **activation of pulmonary endothelium** (due to release of pro-inflammatory mediators intravascularly) leading to **sequestration, adhesion & priming of PMN**

e.g. Sepsis, Trauma

Recent Surgery

Massive transfusion

Cytokine administration

Hematological malignancies

Cardiac disease- Bypass surgery

DIC

2nd event

Transfusion of biologic response modifiers:

1. WBC antibodies (Plasma)
2. Biologically active lipids &/or cytokines released during storage of blood components (RBC & plt, but not FFP)
3. CD 40L (PLT,WB, Non-LR RBC)
4. Immune complexes

These activate

- adherent primed PMN to
- undergo respiratory burst
- release granule content
- causing endothelial damage, capillary leak, ALI

Treatment of TRALI - I

- Make correct diagnosis
- Prompt, vigorous & based on pathophysiology
- Increased endothelial cell permeability results in:
    - Fluid and protein leak into the alveolar spaces;
    - Pulmonary edema
    - Large fluid loss- severe hypovolemia
    - Lungs become stiff
- Stop the transfusion of blood product
- Patients with severe TRALI should be transferred to ICU
- Consider monitoring LA pressure (Swann- Ganz) to:
  - exclude cardiogenic edema
  - guide fluid management

General Approach is Supportive - II

- Supplemental Oxygen & Ventilatory support
  - Mild: supplement O_2 only and supportive care
  - Mod: Intubation, Mechanical ventilation, PEEP
    - Low tidal volume with low plateau pressures as for ARDS
- IV fluids to restore circulatory volume
  - often unresponsive to fluids, require pressor agents
- Avoid diuretics

TRALI: Clinical Outcome

- Rapid improvement: 80%
  - Often clinical improvement before CXR clears
    - Symptoms and oxygenation < 48 hours
    - clearing of infiltrates on CXR in < 96 hours
  - no permanent sequelae in survivors
- Slow resolution: 20%
  - Hypoxemia & infiltrates persists > 7 days
- Mortality 5-10% of cases cf 30-50% in ARDS
  - May occur acutely
  - During mechanical ventilation
  - Multi-organ failure

Summary

- TRALI- family of Acute Lung Injury syndromes, is the leading cause of transfusion associated deaths reported to FDA
- Under-recognized & under-reported
- Best evidence suggests a “two-hit” pathogenesis
- Complex interplay between WBCs, endothelial cells, & transfused donor antibodies, PMN-priming lipids & cytokines results in pulmonary endothelial injury & edema
- Prevention remains controvertial
- Treatment is supportive with O_2, ventilation and fluids
- Recovery is expected in 90% of patients

Immunomodulation by Transfusion and Leukocyte Reduction in 2006

Three Persisting Questions

1. Are there enough indications to go to 100% leukoreduction?

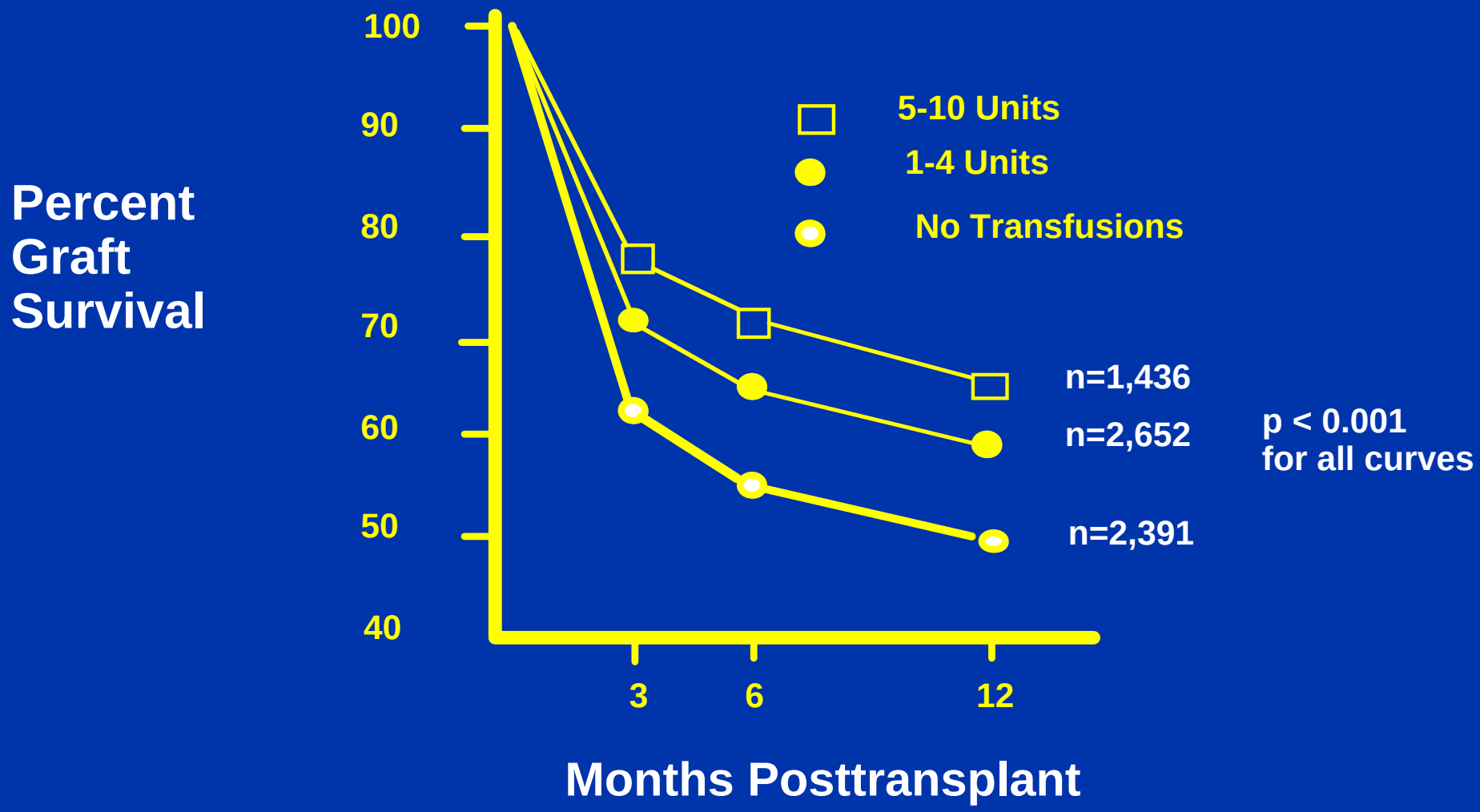
2. Is the immunomodulation that follows blood transfusion clinically important and can it be abrogated by leukoreduction?

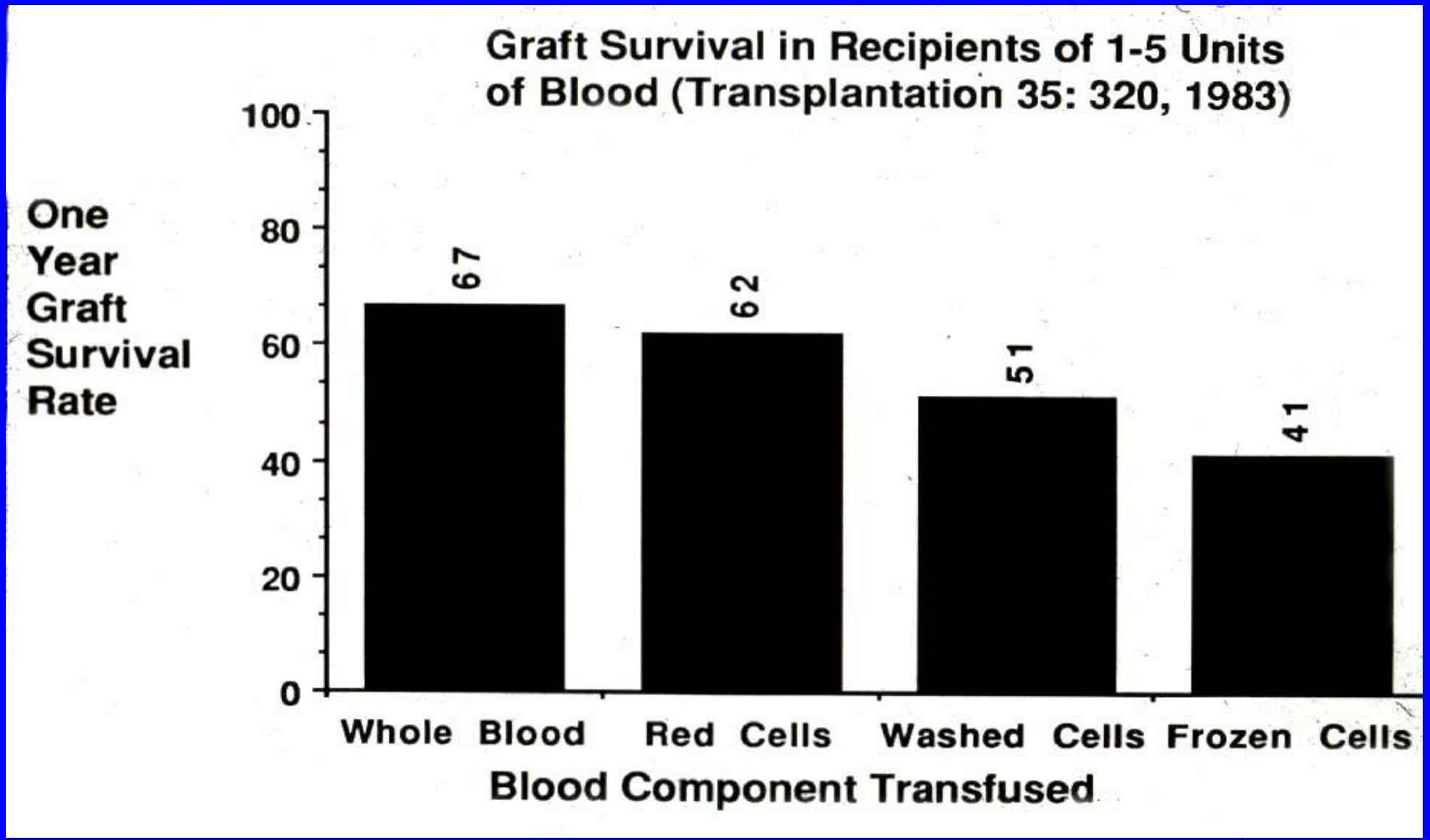
3. Is it cost effective?

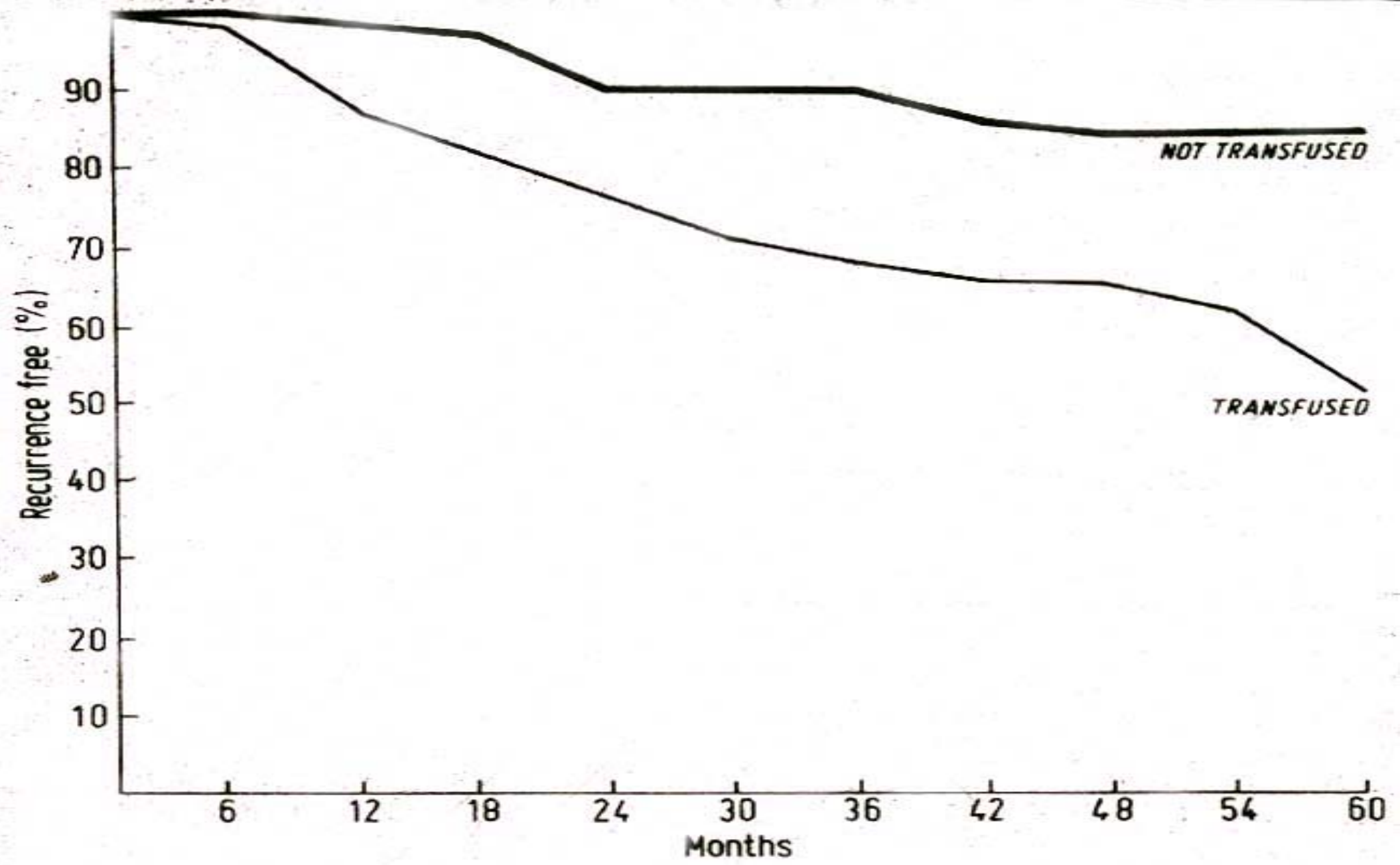
Proven Benefits of Leukoreduction

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

Graft Survival Versus Transfusion Dose, 1978-82, UCLA Registry




Graft Survival in Recipients of 1-5 Units of Blood (Transplantation 35: 320, 1983)
One Year Graft Survival Rate
100
80
60
40
20
0
67
62
51
41
Whole Blood
Red Cells
Washed Cells
Frozen Cells
Blood Component Transfused



Percentage of patients surviving recurrence free.

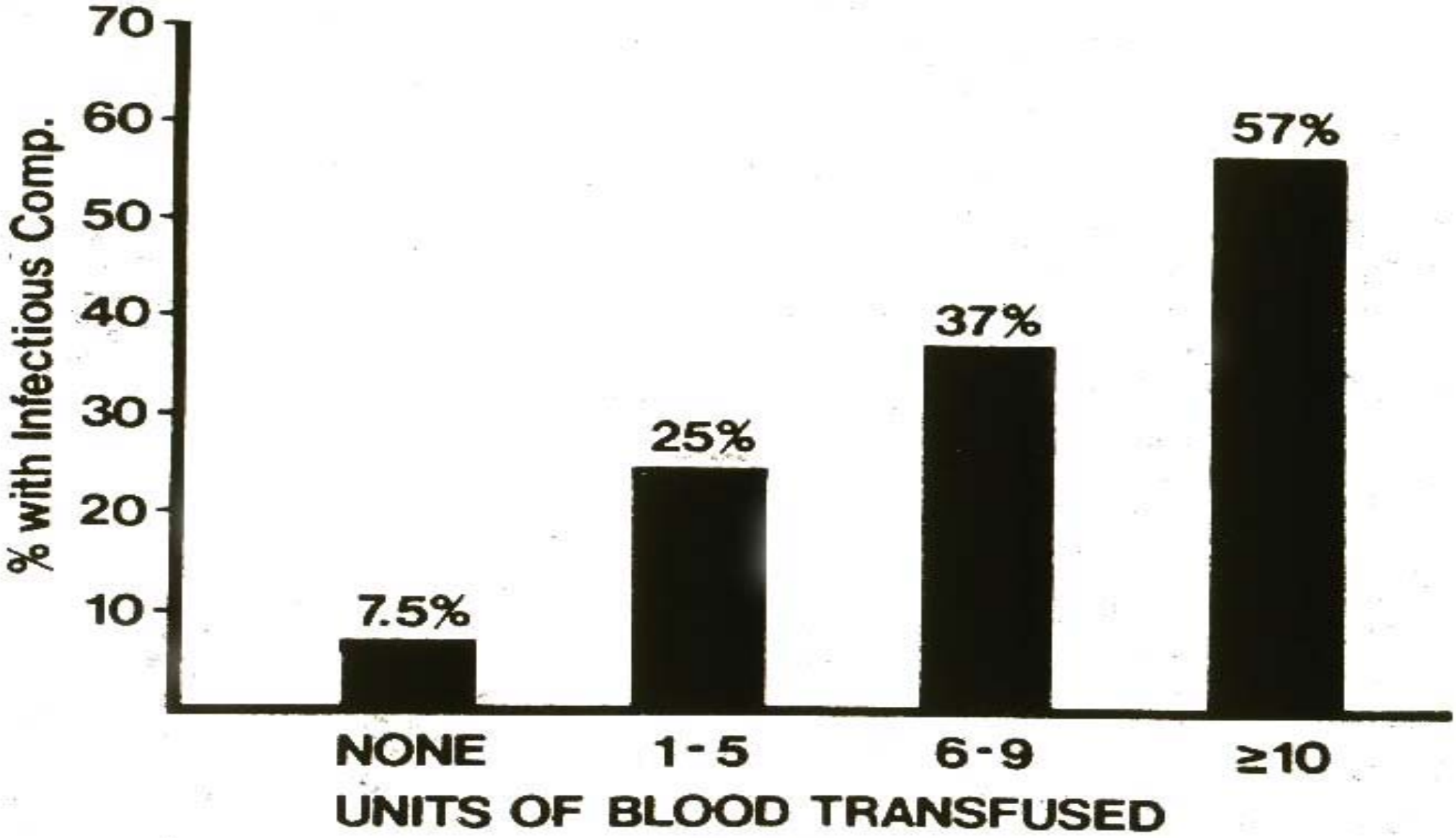
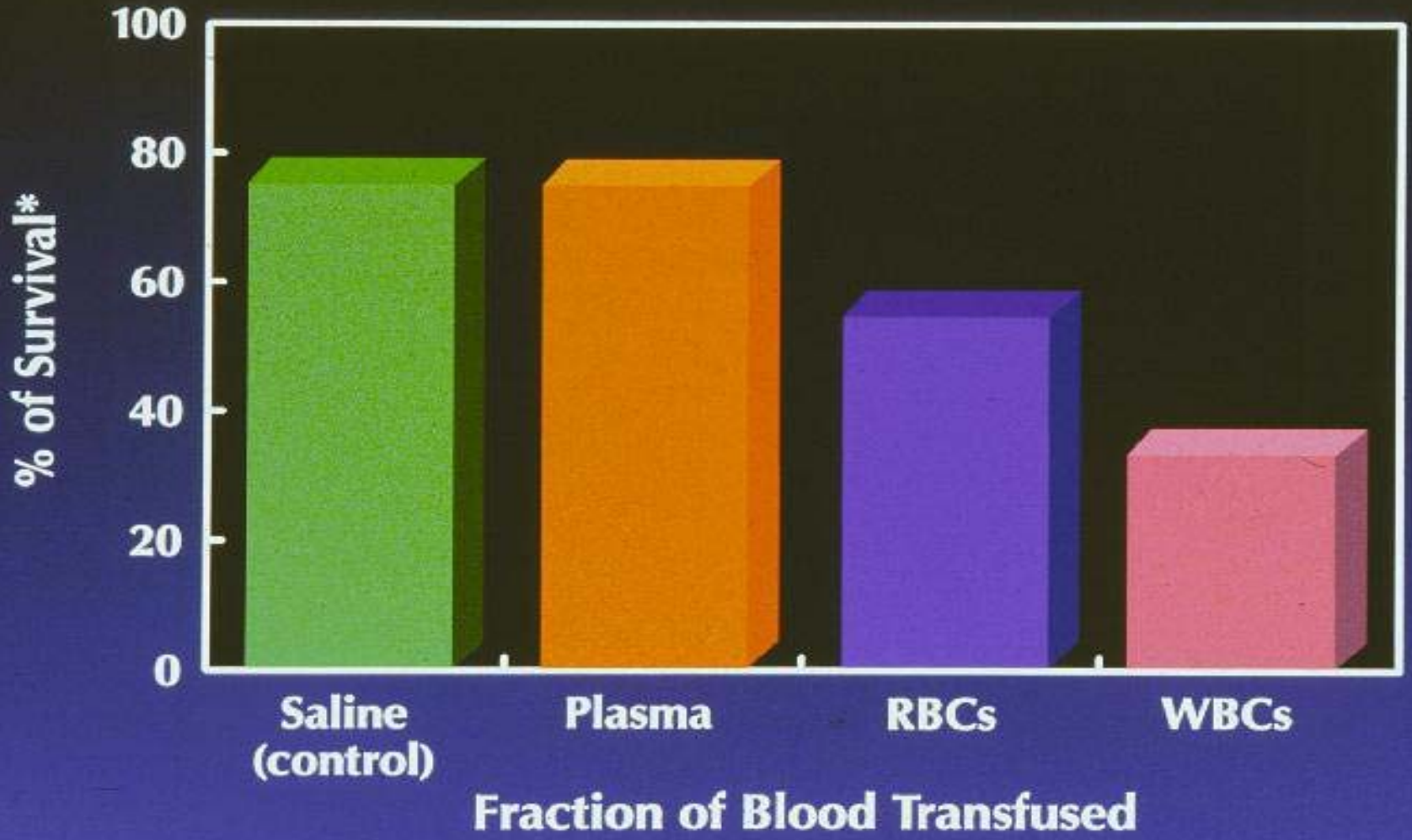


Fig. 2. The relationship between infectious complications and blood transfusion requirements.

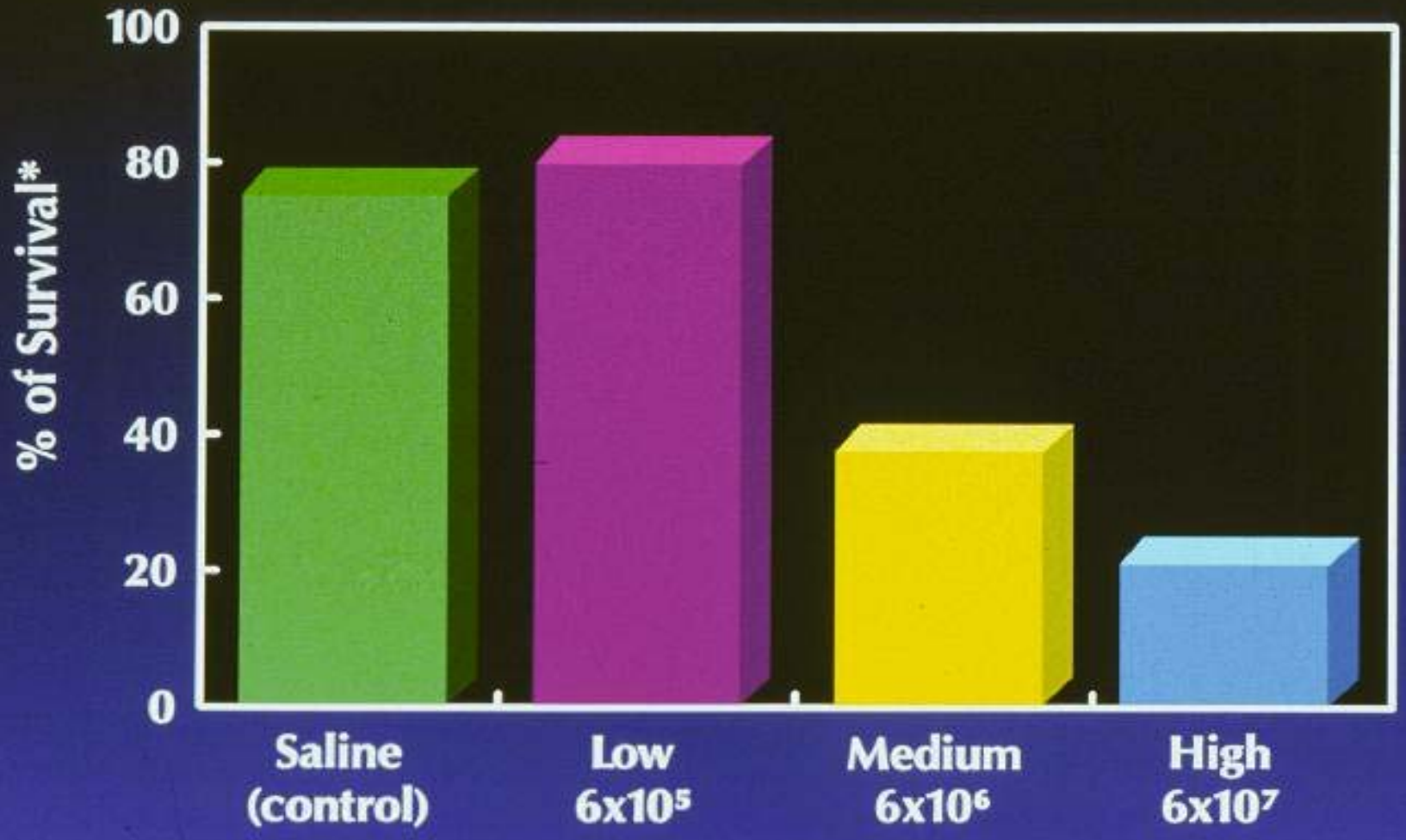
Survival Rates of Balb/c Mice Undergoing Transfusion With Different Fractions of Blood



*Subjects used were undergoing burn injury and bacterial gavage at the time of transfusion.

Transfusion. 1993;33:458.

Survival Rates of Balb/c Mice Undergoing Transfusion With Three Different Doses of Allogeneic WBCs



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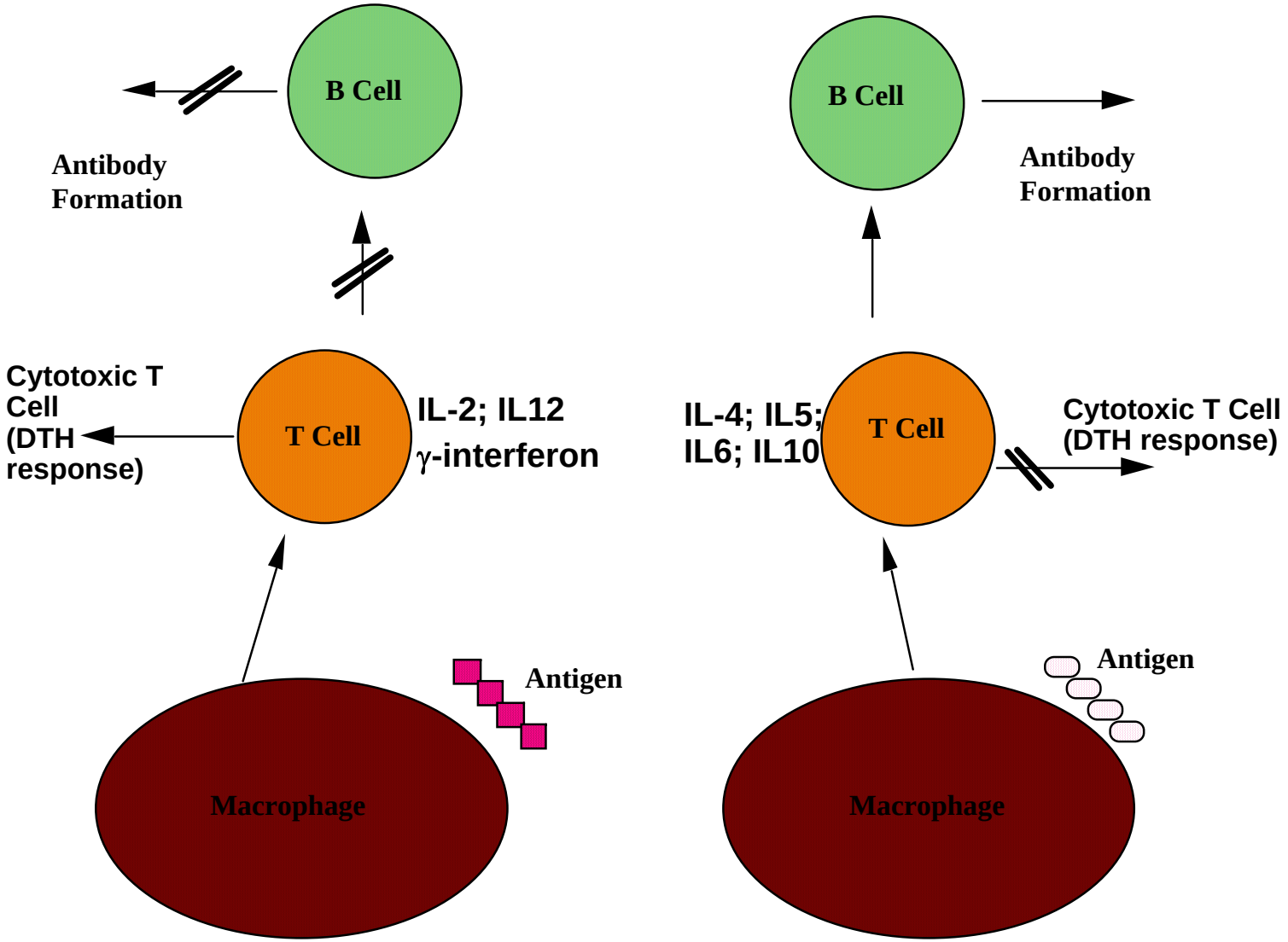
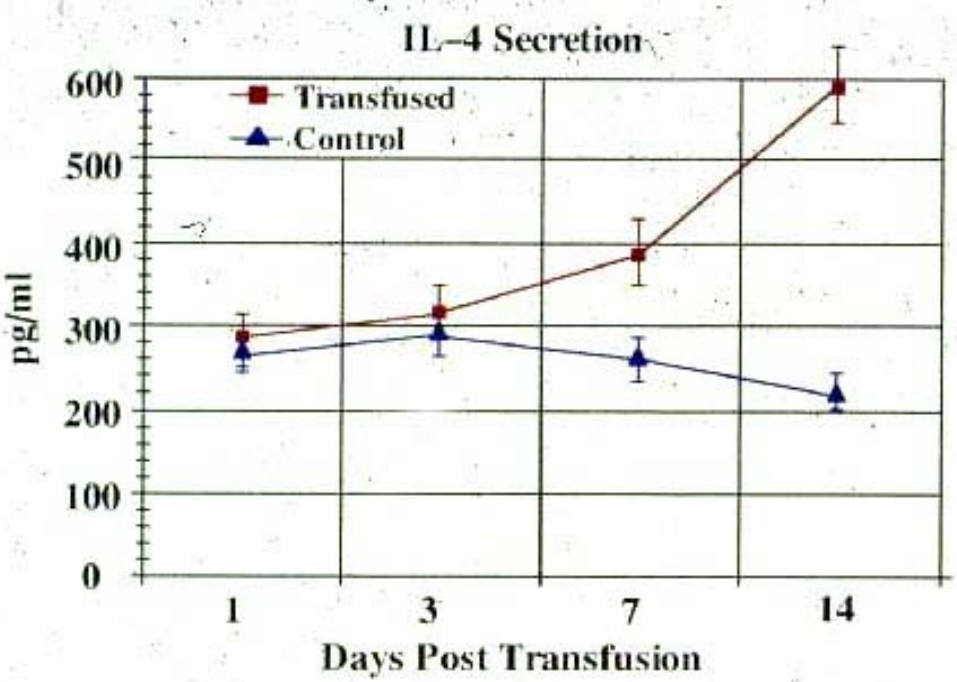
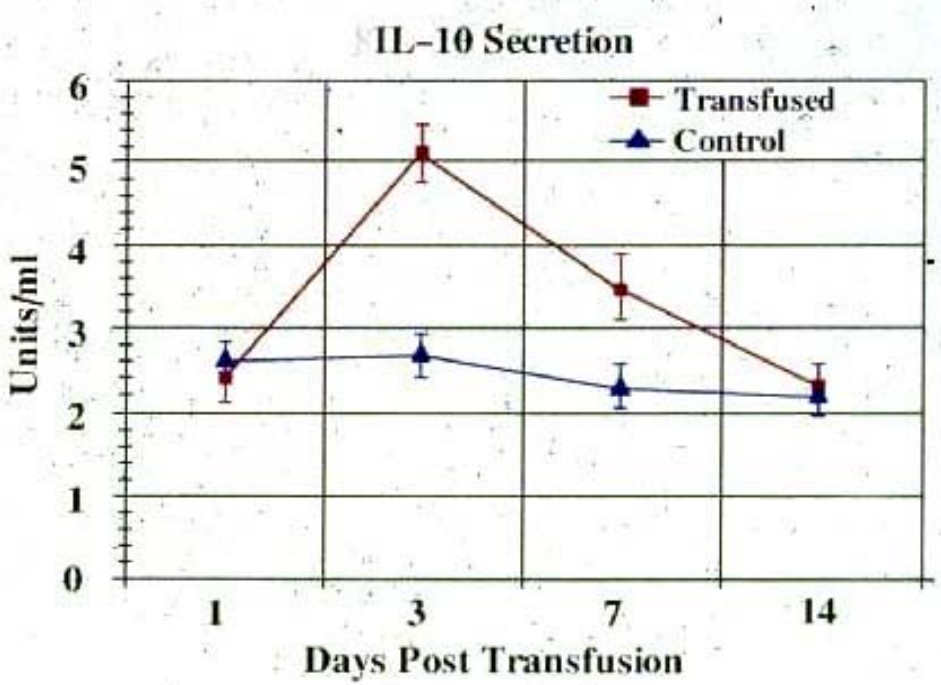
Transfusion. 1993;33:458.



T helper type 1 response

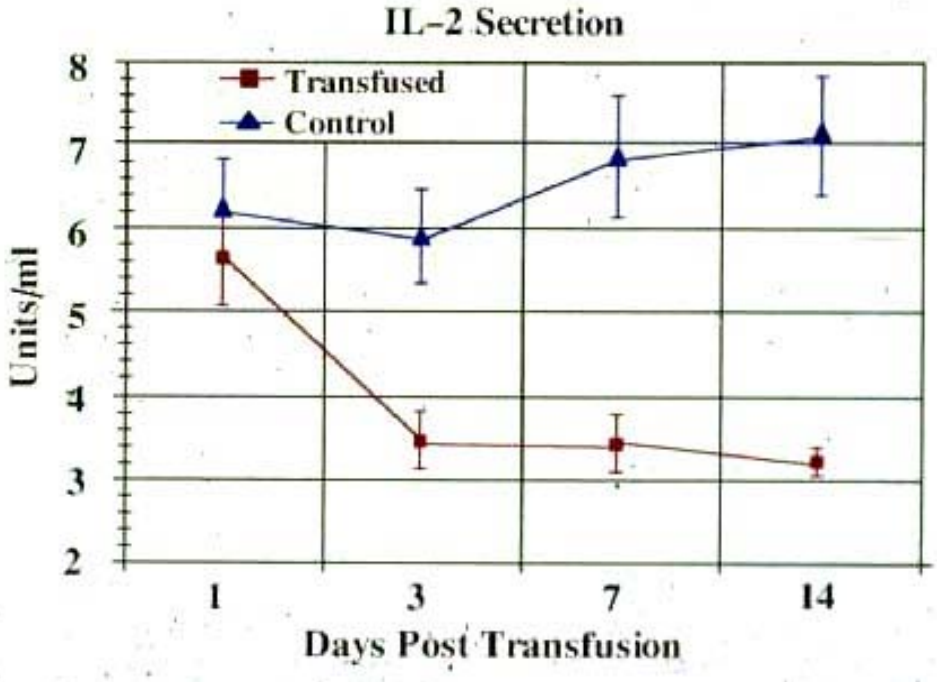
T helper type 2 response





Effect of donor specific transfusions, in mice, on the production of IL-4, IL-10, and IL-2 from mitogen stimulated spleen cultures over time

Babcock and Alexander,
Transplantation 61:465-468, 1996

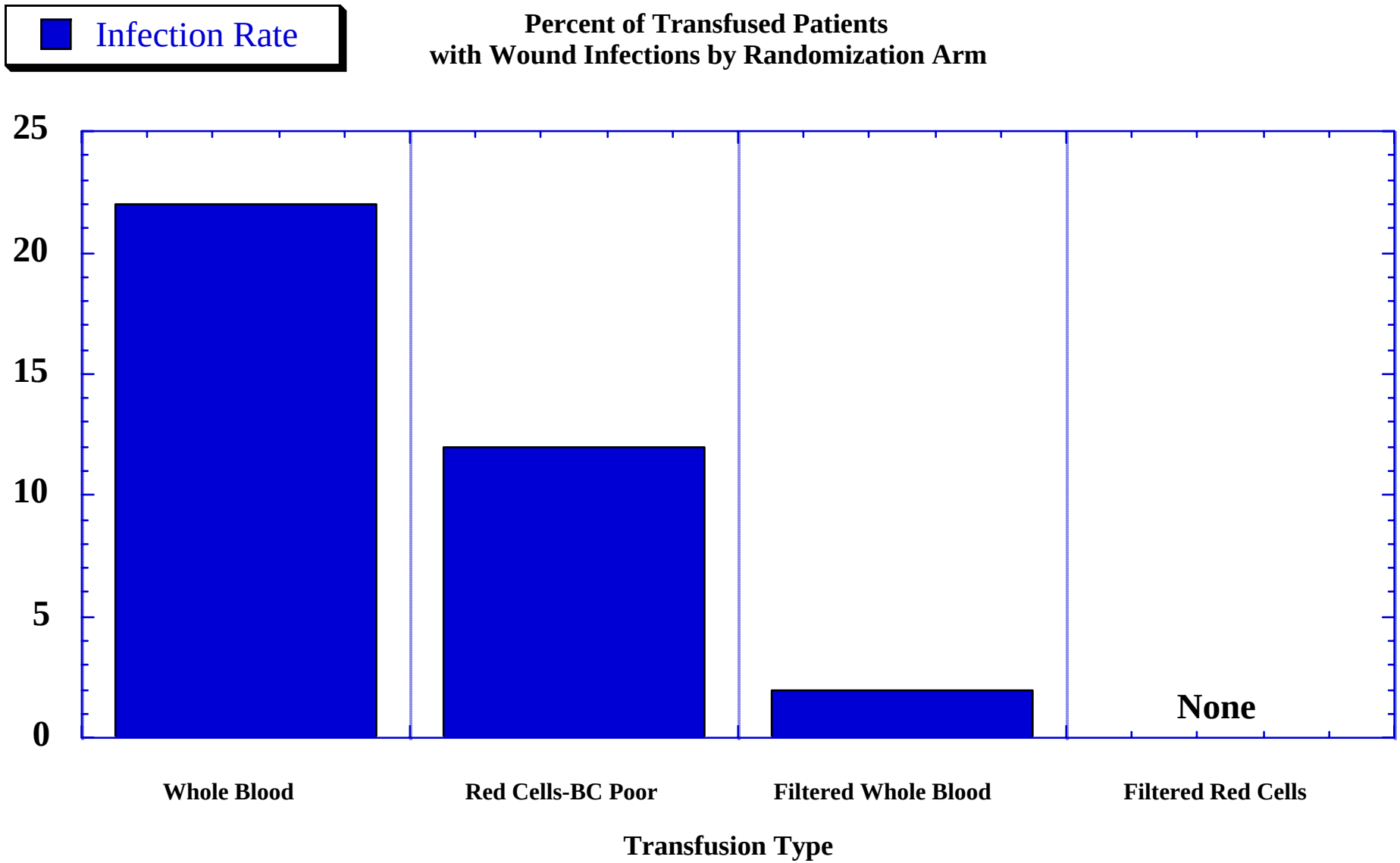


“Good” Th1 processes antagonized by allogeneic transfusion

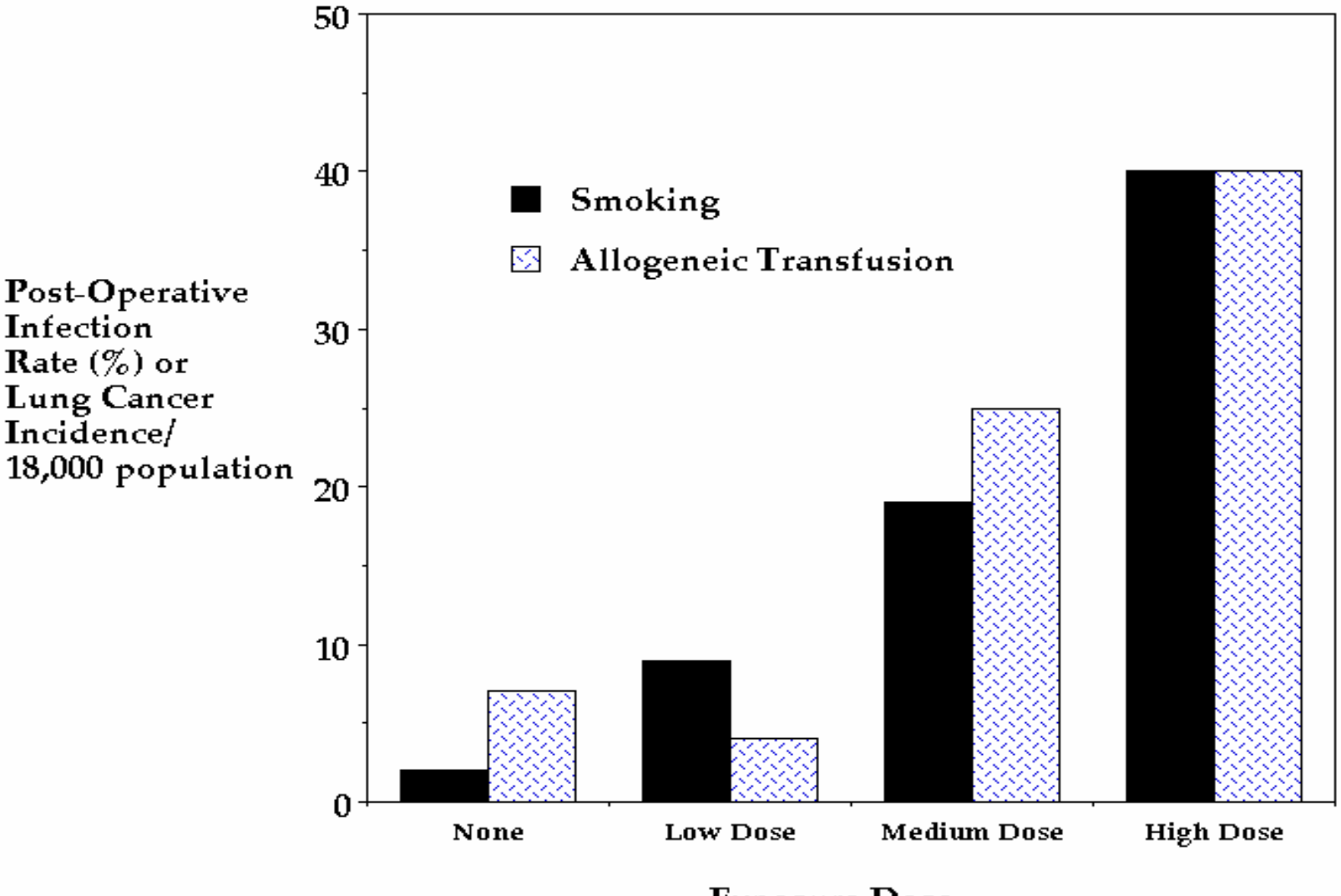
- Antibacterial immunity
- Antitumor immunity
- Antiviral immunity

“Bad” Th1 processes antagonized by allogeneic transfusion

- Allograft rejection
- Rejection of the fetus as an allograft
- Inflammatory diseases such as Crohn’s, Rheumatoid Arthritis, Type I Diabetes



Data from the studies of Lone Jensen, et al.



0, 1-14, 15-24 and 25+ cigarettes per day [BMJ 2: 1525, 1976]

0, 1, 2, 3 units in orthopedic surgery [Transfusion 31: 212, 1991 and 32: 517, 1992]

Clinical Trials of Immunomodulation

- 7 of 9 fully published randomized trials of leukoreduction found evidence of benefit
- 4 of 6 randomized trials of autologous transfusion found evidence of benefit
- 7 of 9 implementation trials of leukoreduction found evidence of benefit
  - Thus 18 of 24 trials (75%) found evidence for abrogation of transfusion immunomodulation by leukoreduction or autologous techniques

Caveats in Interpreting Randomized Trials of Transfusion Immunomodulation

- In the European trials 70-80% leukoreduced transfusions (BC poor) are compared with 99.9% leukoreduced transfusions
- In the autologous predonation trials 30% of patients in the autologous arm received allogeneic blood
- In multicenter studies there was no standardization of surgical, anesthetic and postoperative management

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

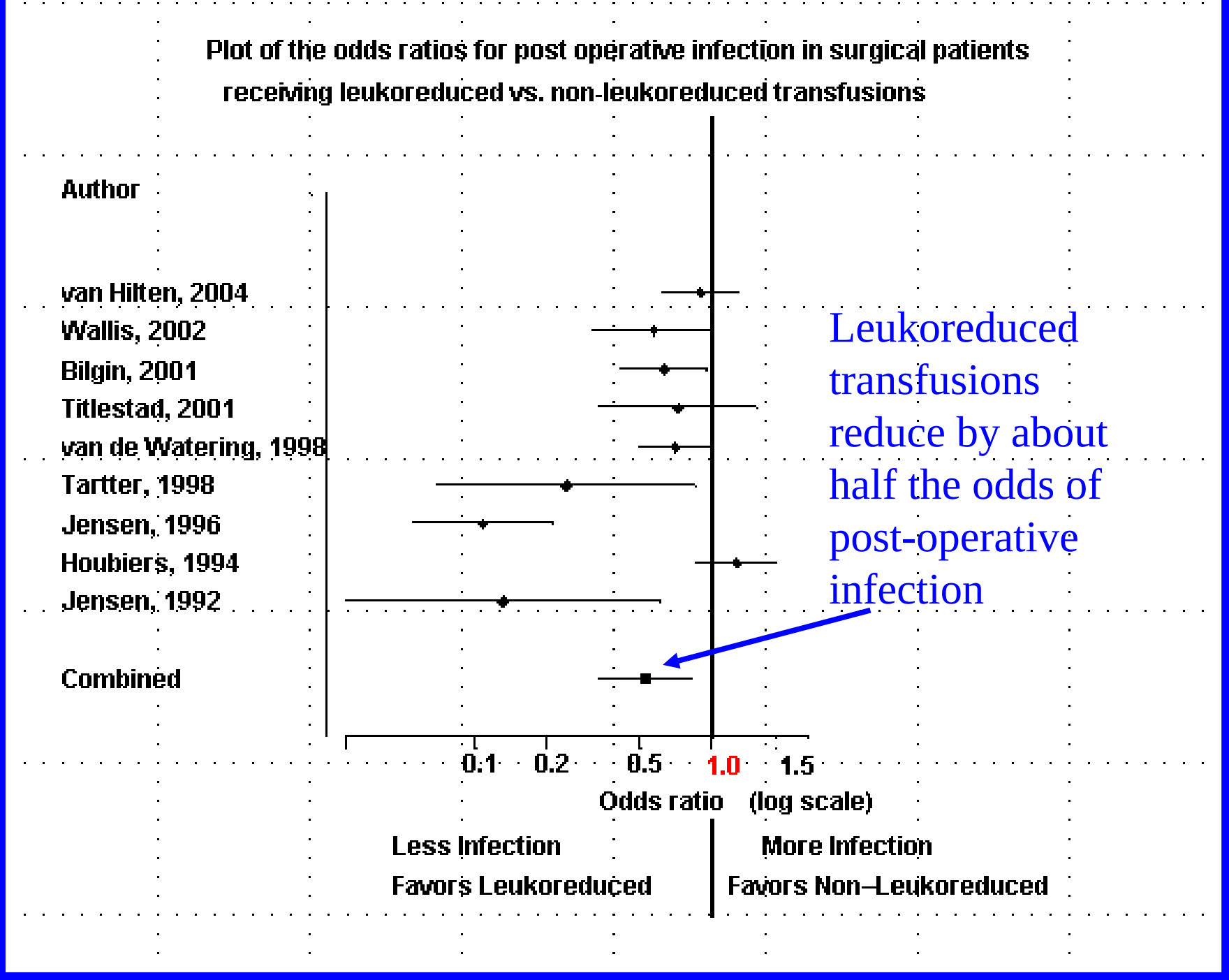
- Patients randomized but not transfused should not be included in the data analysis--all meta-analyses have included such patients, as did three of the nine trials

- Conclusions about the efficacy of LR in preventing post-operative infections cannot be drawn from data on patients receiving no transfusions

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


Plot of the odds ratios for post operative infection in surgical patients receiving leukoreduced vs. non-leukoreduced transfusions
Author
van Hilten, 2004
Wallis, 2002
Bilgin, 2001
Titlestad, 2001
van de Watering, 1998
Tartter, 1998
Jensen, 1996
Houbiers, 1994
Jensen, 1992
Combined
0.1
0.2
0.5
1.0
1.5
Odds ratio (log scale)
Less Infection
Favors Leukoreduced
More Infection
Favors Non–Leukoreduced
Leukoreduced transfusions reduce by about half the odds of post-operative infection

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)

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

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

Estimates of Cost Reduction with Leukoreduction/Autologous Transfusions in Surgery

- Jensen (Transfusion 35: 719, 1995) [Leukoreduction]
  - $2,000 decrease in costs per unit transfused
- Blumberg (Amer J Surg 171: 324, 1996) [Autologous]
  - $1,000 to $1,500 decrease in costs per unit transfused
- Leveque (Orthoped Transactions JBJS 20: 114, 1996) [Autologous]
  - $1,100 decrease in costs per unit transfused
- Blumberg (Transfusion 40[Suppl.]: 130S, 2000) [Leukoreduction]
  - $700 decrease in costs per unit transfused

- Nationwide: 6 million units x $1,000-2,000 = $6-12 billion saved

N Blumberg MD &
JM Heal MRCP

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

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Top Ten Transfusion Risks 2006*

- Multi-organ failure in surgery/critical care
- Increased post-operative infection
- Increased tumor recurrence
- Increased lung injury
- Increased severity of existing infections
- Increased incidence of thrombosis
- Viral infections we don't know about yet
- ABO mismatched transfusions
- Bacterial contamination of platelets
- Transmission of odd-ball organisms (mycoplasma, chlamydia, etc.)

*Developed world

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