Introduction to Blood Products for the Medical Resident

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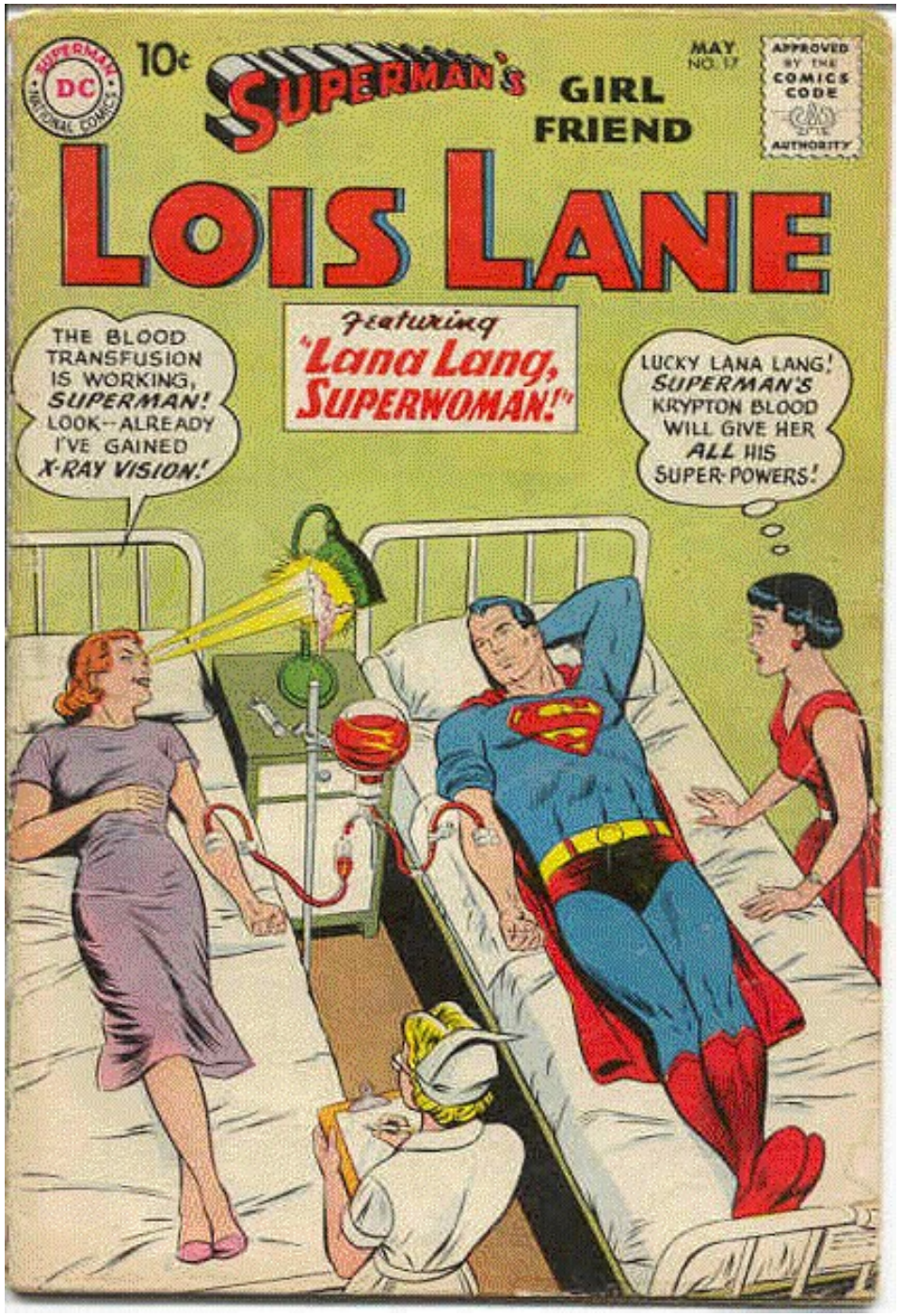
Blood Transfusion Service



Transfusion Medicine Series

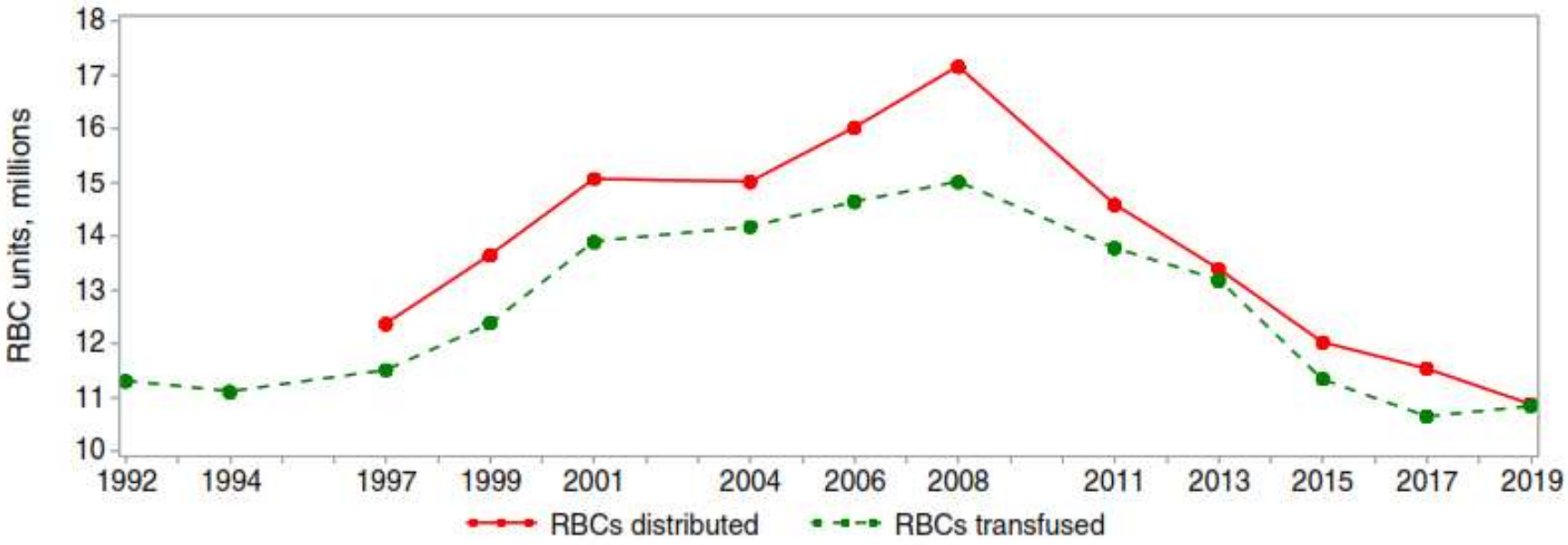
1. Basics of transfusion medicine and blood banking
2. TMA/MAHA and therapeutic apheresis
3. Hemolytic anemias

What is Transfusion Medicine?

- Blood product collection, storage, and use
- Clinical hemostasis
- Hemolytic disease of the fetus and newborn
- Laboratory medicine
- Apheresis
  - Plasmapheresis, plasma exchange
  - Leukapheresis
  - RBC exchange
  - Stem cell collection

The US Blood Supply

- Blood is transfused in 10-15% of all hospitalizations
- 35,000 units are drawn daily
- Blood products 2015 cost per unit
  - Leukoreduced pRBCs: $211
  - Platelets: $524
  - FFP: $54



Jones, et al. *Transfusion* 2021
Klein, et al. *NEJM* 2017

Part 1: Finding Your Match

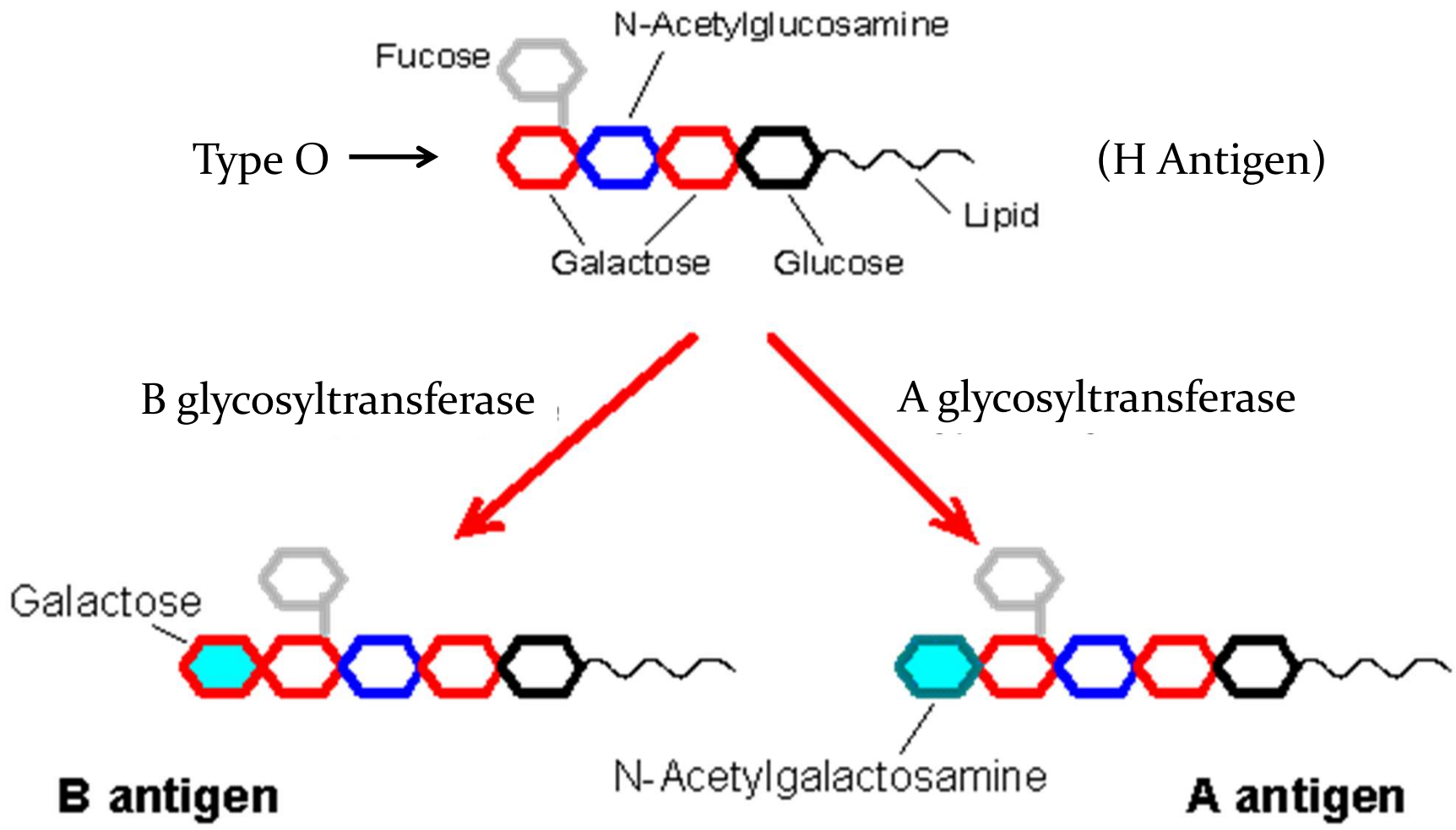
Part 2: Blood Component Therapy

Part 3: Red Blood Cells

Part 4: Platelets

Part 5: Transfusion Reactions

What Are ABO Antigens?



Origin of ABO Antibodies

A antigen mimetic ⟶ Influenza virus (α-D-N-galactosamine)

B antigen mimetic ⟶ E. coli (α-D-galactose)

- *Neonates usually don't develop isohemagglutinins until 6-9 months of age*
- *Animals raised in sterile environments don't develop isohemagglutinins*

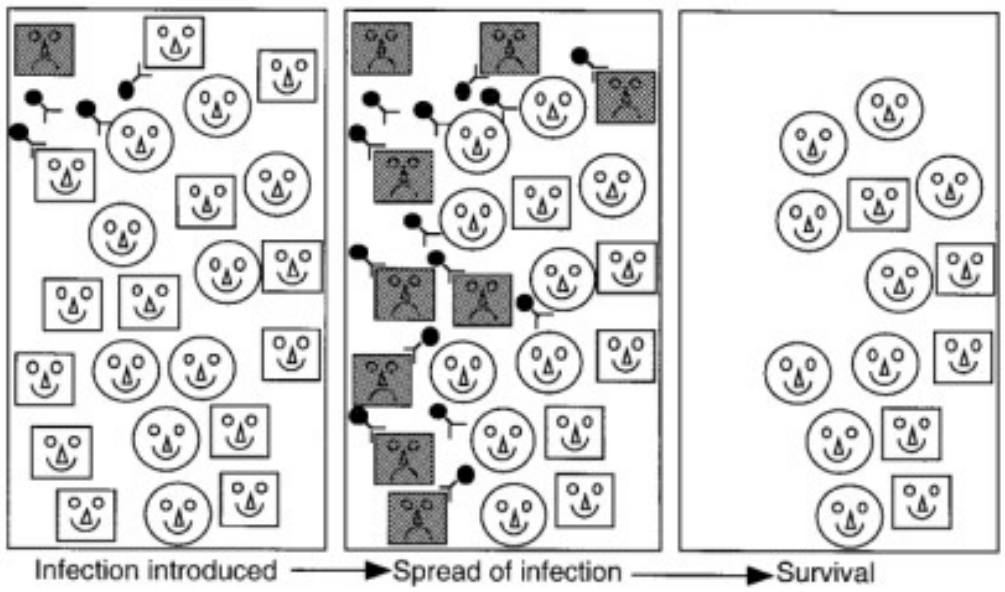
Evolution of ABO Blood Groups

Theory 1: Protection from Malaria

Theory 2: "Viral Sink"

- Viruses utilize cell surface carbohydrate receptors to gain entry
- RBCs lack nuclei and can't support viral replication
- Surface carbohydrates on 25 trillion RBCs help "sop up" invading virus

Theory 3: Herd Immunity



Gagneux, et al. *Glycobiology* 1999

Other Blood Group Antigens

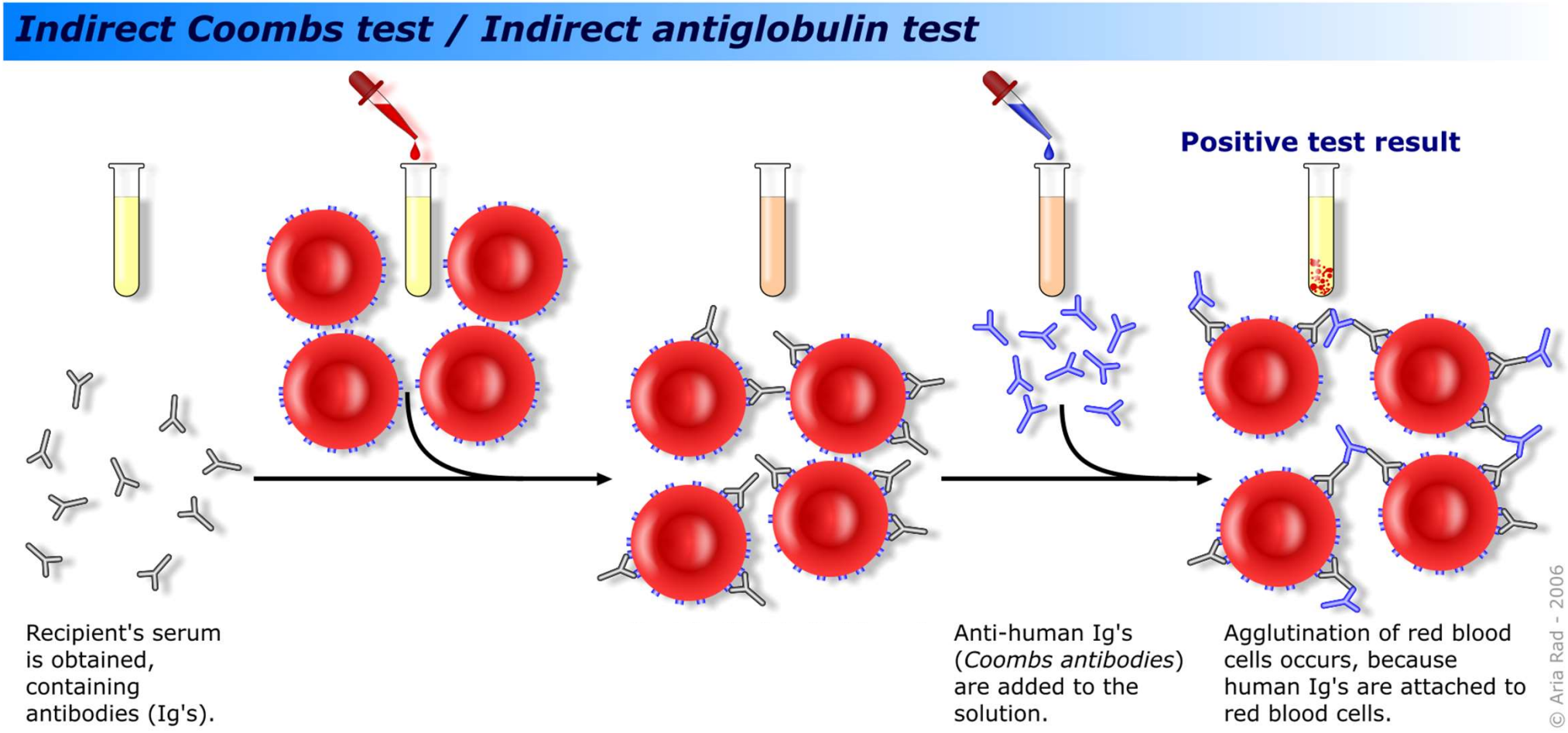
- ABO Antigens (“Major Antigens”)
  - Probably stimulated by molecular mimicry
  - First exposure hemolysis

“TYPE”

- “Minor” Blood Group Antigens (Rh, Duffy,Kell, etc.)
  - No antibodies unless exposed (“allo-antibodies”)
  - Prior exposure required for hemolysis (i.e. hemolytic disease of the newborn)

“SCREEN”

The “Blood Bank Specimen”



BLOOD “TYPING”: Check for ABO using serum and cells
BLOOD “SCREENING”: Check for allo-antibodies (recipient serum, reagent cells)
“CROSSMATCH”: Check donor cells directly against recipient serum

Part 1: Finding Your Match

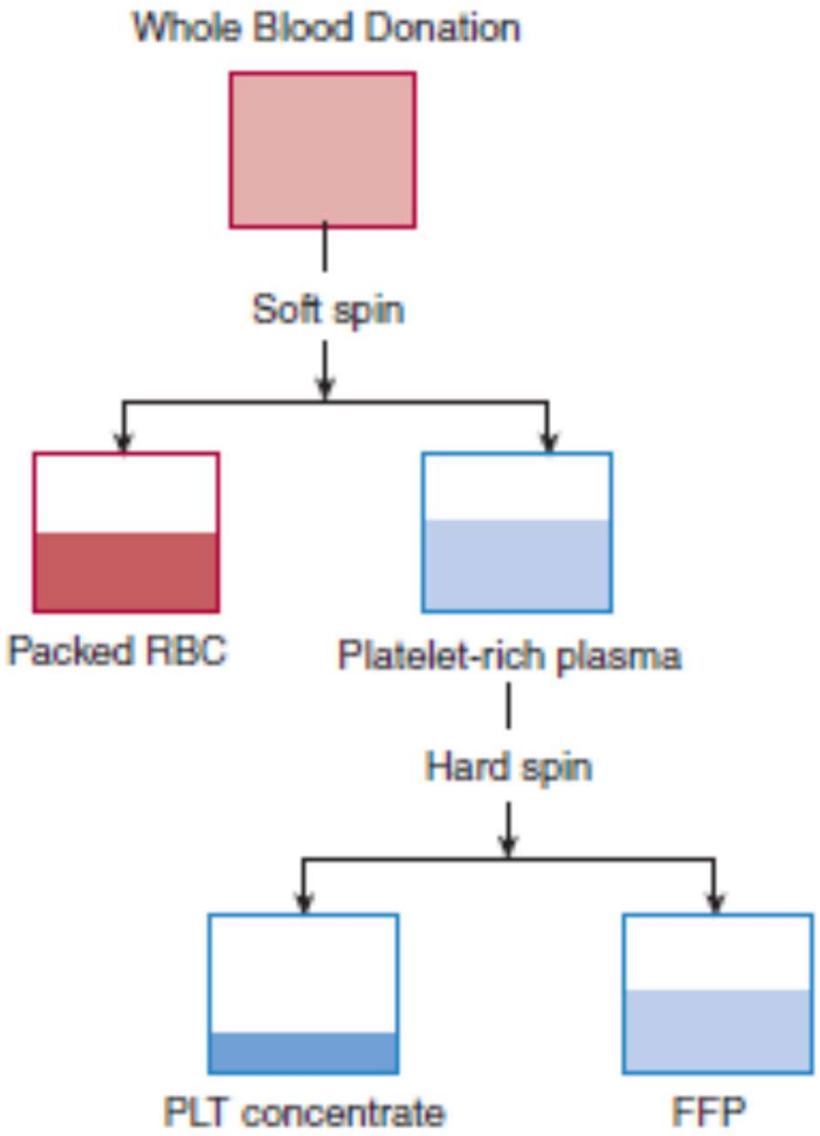
Part 2: Blood Component Therapy

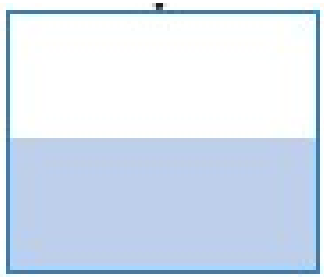
Part 3: Red Blood Cells

Part 4: Platelets

Part 5: Transfusion Reactions

Why Do Component Therapy?





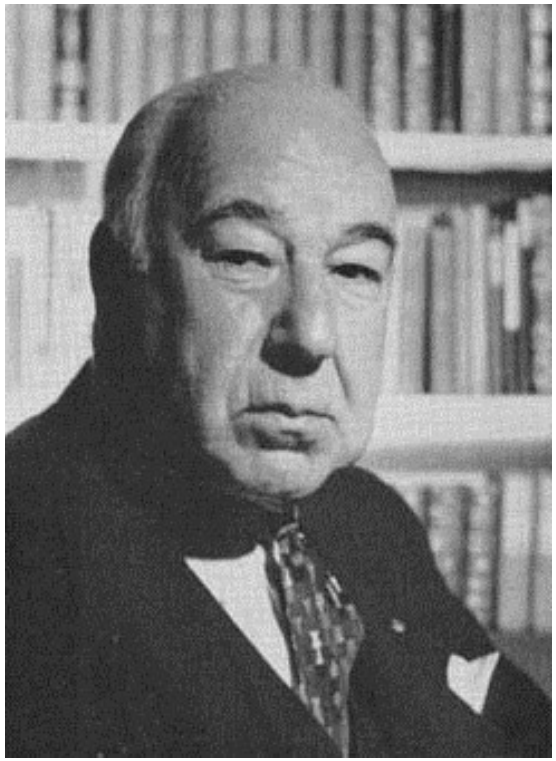
FFP

- Albumin
- Cryoprecipitate
- IVIg
- Coagulation Factors

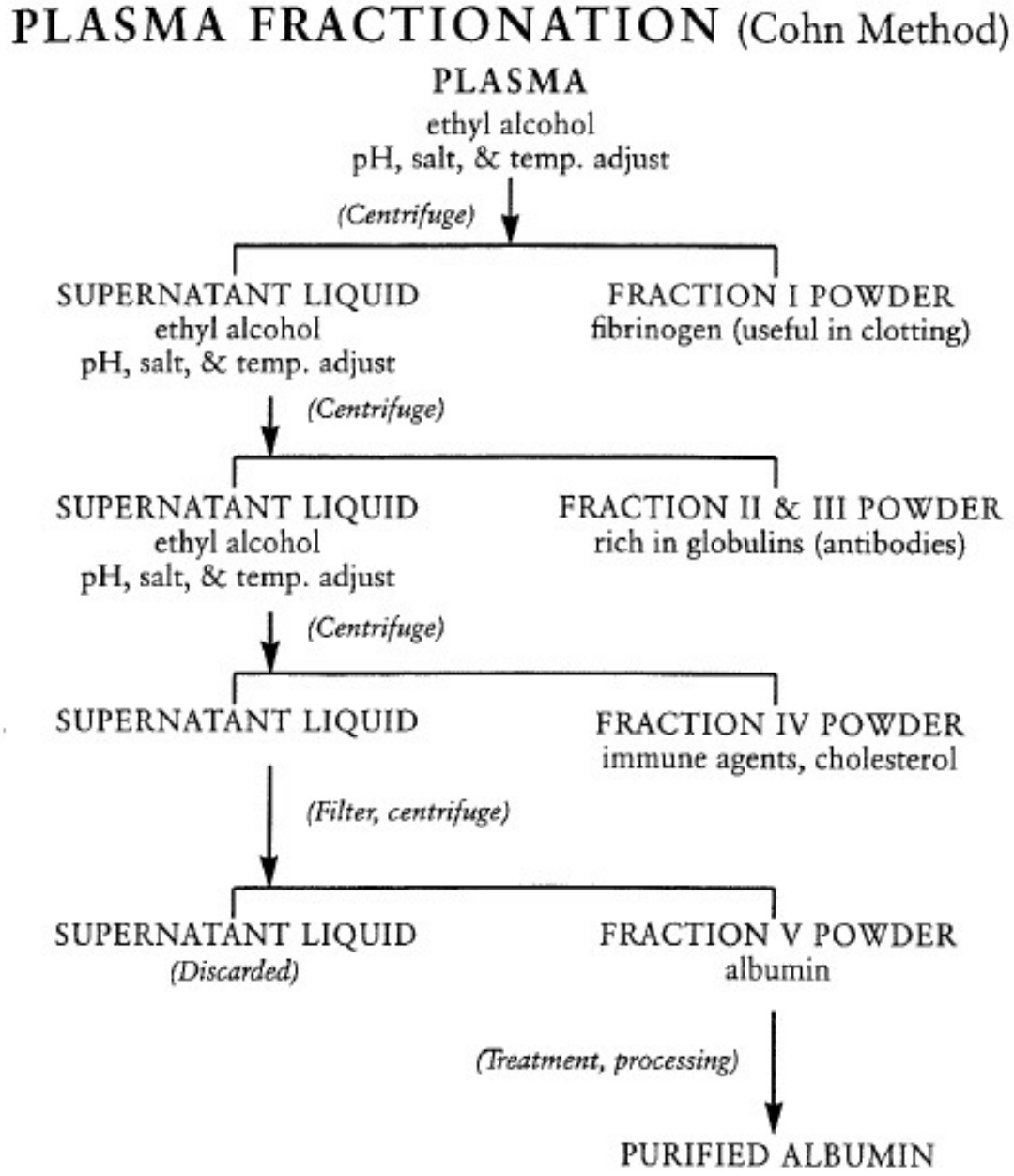
Fresh Frozen Plasma

- Donor plasma frozen within 8 hrs of collection
- By definition, 1 ml of plasma has 1 unit of clotting factor
- FFP cannot correct INR below 1.6, FV and FVIII have worst recovery from FFP
- Store at -80°C for up to 7 years, -20°C for 1 year
- Must be thawed prior to use (takes up to 30 min)
- ABO match all units
- Volume ~250 ml

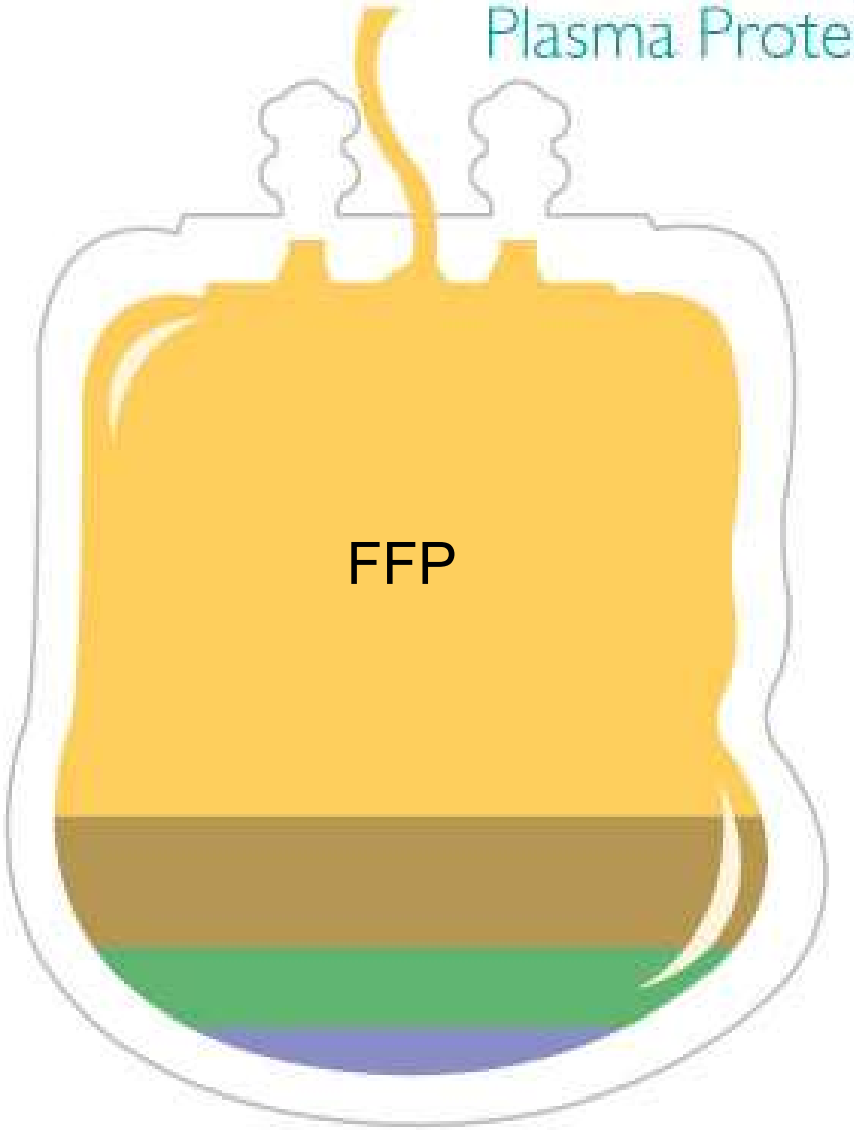
Plasma Fractionation



Edwin Cohn (1892-1953)



Why are some products so expensive?



Plasma Proteins and the Diseases They Treat

Albumin (25 grams*)

Shock, Burns, Adult Respiratory Distress Syndrome, Cardiopulmonary Bypass Surgery

IVIG (Intravenous Immunoglobulin) (4 grams*)

Primary Immunodeficiency Diseases, Autoimmune Diseases, Chronic Inflammatory Demyelinating Polyneuropathy, Idiopathic Thrombocytopenic Purpura

Alpha-1 Antitrypsin (.15 to .30 grams*)

Alpha-1 Antitrypsin Deficiency (Genetic COPD)

Coagulation Factors
(Factor VIII: 300 to 450 IUs, Factor IX: 180 to 200 IUs*)

Hemophilia A & B, von Willebrand Disease, Bleeding Disorders

** Plasma Protein Yields Per Liter of Plasma*

- 1 bottle of albumin = 12.5g, 1/2 L of plasma, 2U of blood
- IVIg dosed at 2g/kg, 140g for 70kg pt, 35L plasma, 140U of blood

What is Cryoprecipitate?

- Solid layer formed when plasma is thawed at 4°C
- Originally discovered in Judith Graham Pool in 1964
- Contains FVIII, VWF, FXIII, and fibrinogen
- Given as pools from 10 donors' FFP ("10-pack" or "10 units"), not ABO-matched
- One 10-pk raises fibrinogen ~85 mg/dL

Part 1: Finding Your Match

Part 2: Blood Component Therapy

Part 3: Red Blood Cells

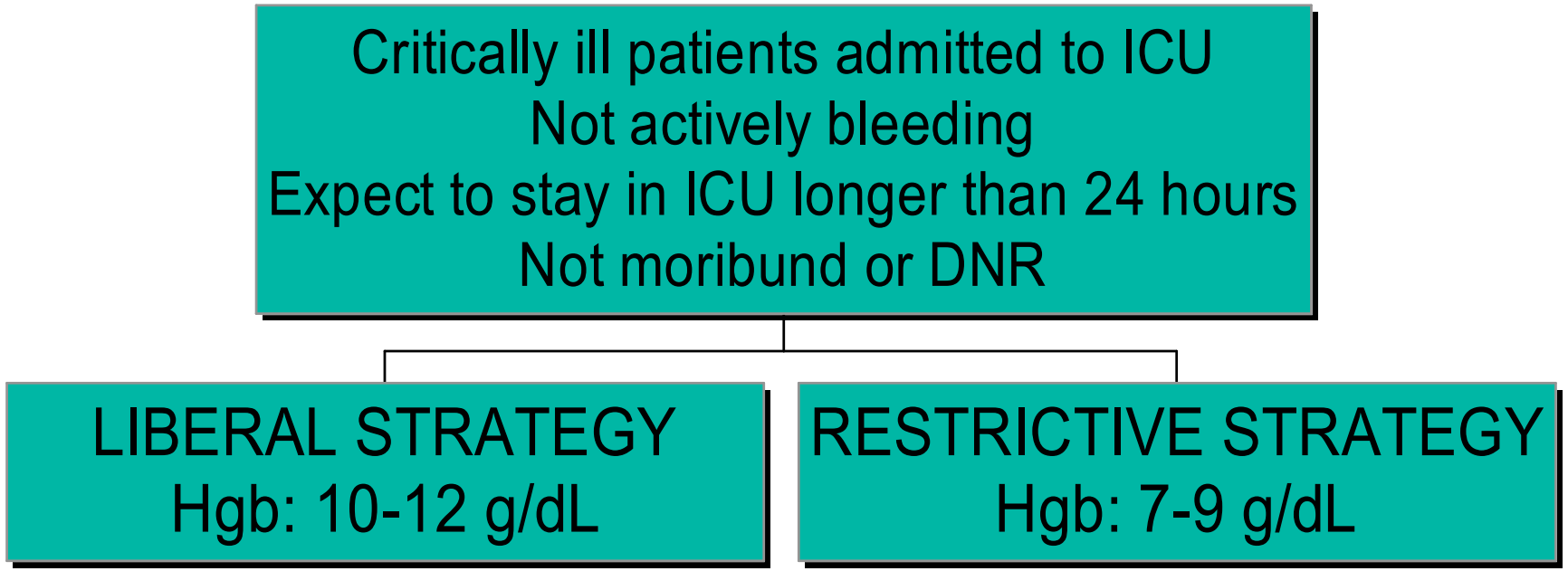
Part 4: Platelets

Part 5: Transfusion Reactions

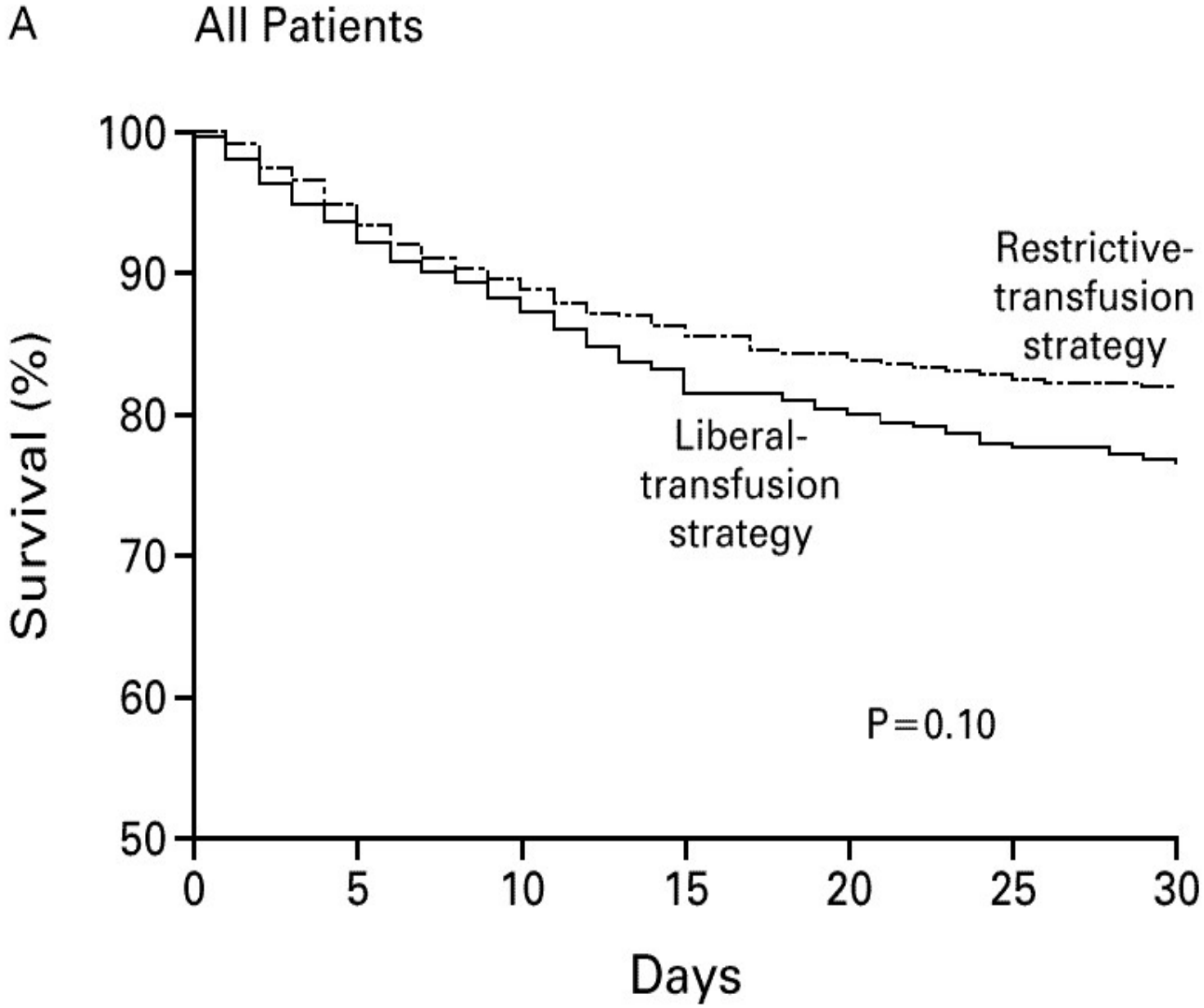
Packed RBC

- **Hct < 60% (average 55%), low in plasma**
- **Approximately 300 cc total volume**
- **1 mg iron per cc of pRBCs**

RBC Transfusion in the ICU: The TRICC Trial



Hébert et al. *NEJM* 1999;340:409-17



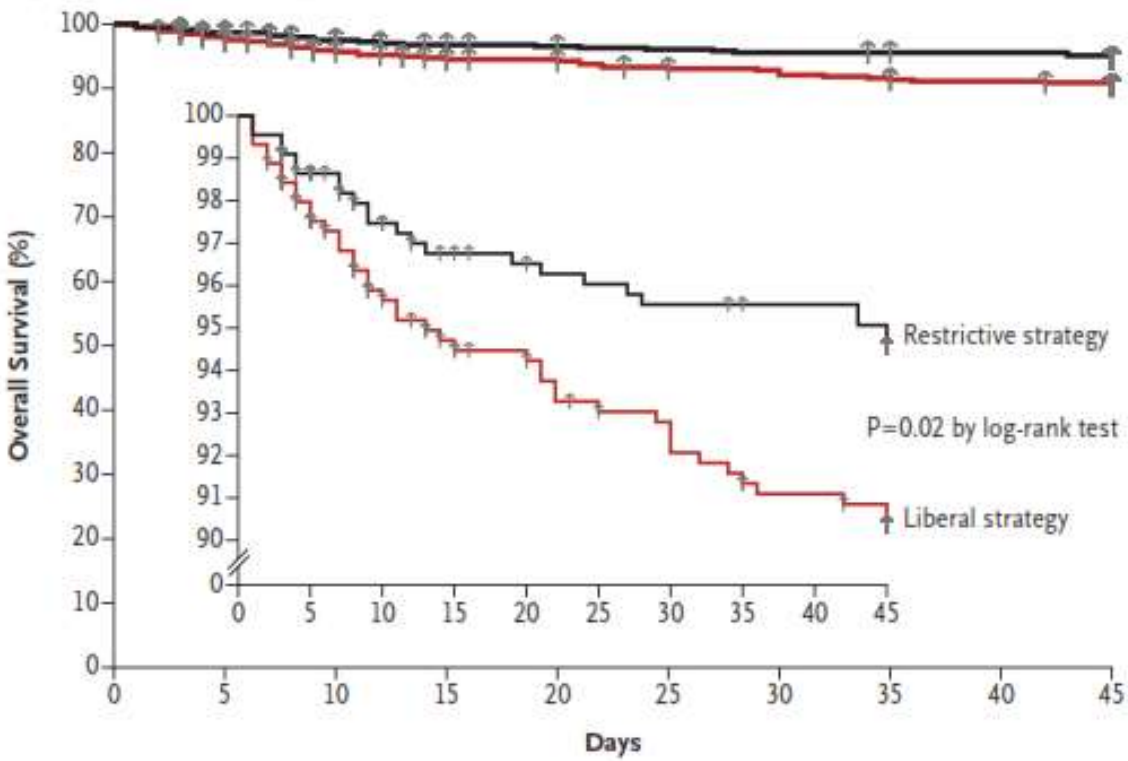
Hébert et al. *NEJM* 1999;340:409-17

Transfusion "Trigger" Trials

- **ICU Patients (7 vs. 10)**
  - *TRICC Trial* *(NEJM 1999)*
- **Cardiac Surgery Patients**
  - *TRACS Trial* (8 vs. 10) *(JAMA 2010)*
  - *TITRe2 Trial (7.5 vs. 9)* *(NEJM 2015)*
- **Patients with Acute MI (8 vs. 10)**
  - *REALITY* Trial (JAMA 2021)
- **Orthopedic Surgery Patients (8 vs. 10)**
  - *FOCUS Trial* *(NEJM 2012)*
- **Patients with Upper GI Bleed (7 vs. 10)**
  - *Villanueva, et al.* *(NEJM 2013)*
- **Patients in Septic Shock (7 vs. 9)**
  - *TRISS Trial* *(NEJM 2014)*

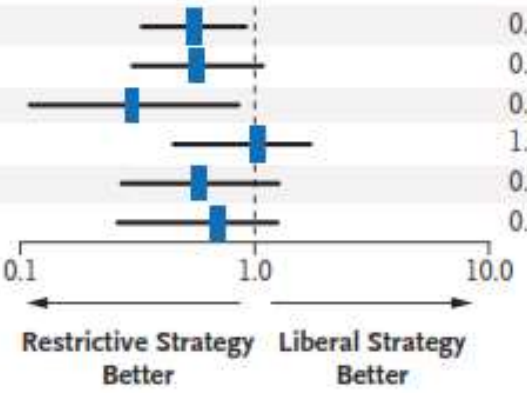
Special Case 1: Actively Bleeding Patients

- 921 patients with non-exanguinating UGIB
- Randomized to Hct >7 vs. >9 g/dL
- Looked at rebleeding and overall survival
- Looked at portal venous pressures



B Death by 6 Weeks, According to Subgroup

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26

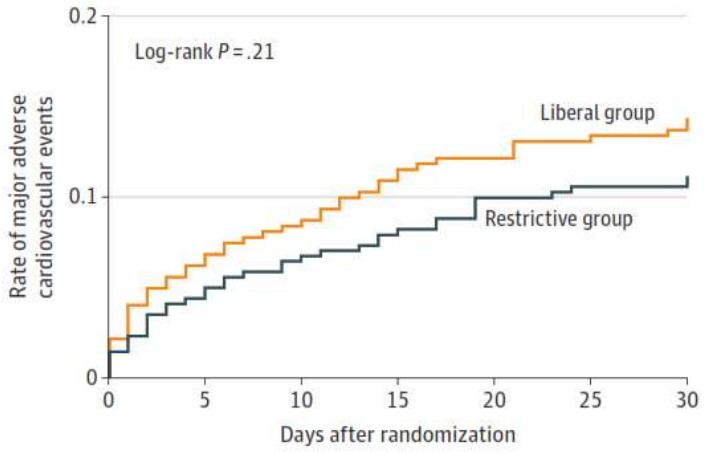


Villanueva, et al. (NEJM 2013)

Special Case 2: Cardiac Ischemia

- TRICC trial subgroup analysis: patients with “ischemic heart disease” trended towards better OS if liberally transfused (p=0.3)
- “REALITY” RCT
  - 666 patients with acute STEMI (~30%) or NSTEMI (~70%) and Hgb <10
  - Randomized to Hgb >10 vs. Hgb >8
  - Primary outcome: MACE at 30 days
- Conclusion: Hgb 8 noninferior to Hgb 10 but not superior

Figure 2. Rate of Major Adverse Cardiovascular Events in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy Among Patients With Acute Myocardial Infarction and Anemia



No. of patients at risk

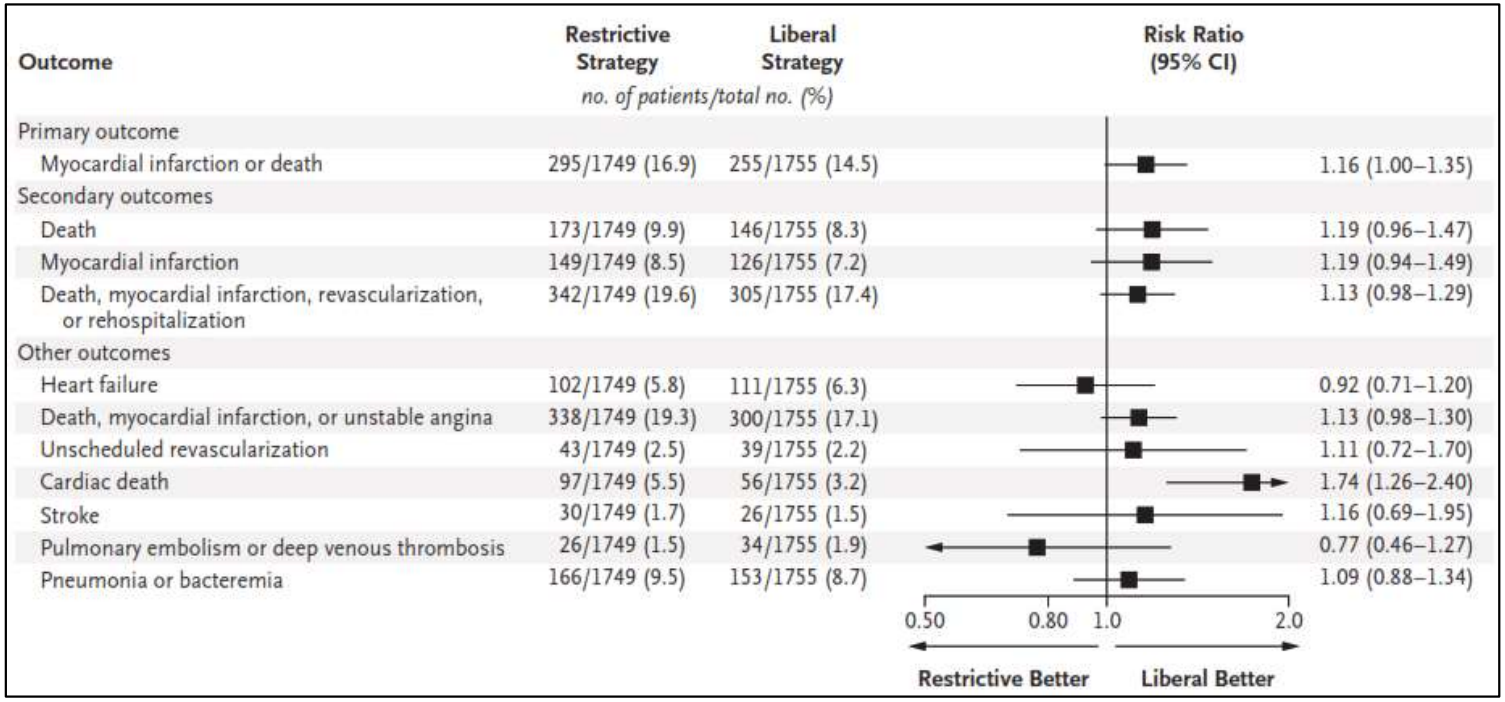
Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305

Table 4. Adverse Events Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

	No. (%)	
Adverse event	Restrictive (n = 342)	Liberal (n = 324)
At least 1 adverse event	40 (11.7)	36 (11.1)
Acute kidney injury[a]	33 (9.7)	23 (7.1)
Acute heart failure[b]	11 (3.2)	12 (3.7)
Severe allergic reaction[a]	3 (0.9)	0
Acute lung injury/ARDS[a]	1 (0.3)	7 (2.2)
Multiorgan system dysfunction[a]	1 (0.3)	3 (0.9)
Infection[a,c]	0	5 (1.5)

Ducrocq, et al. *JAMA* (2021)

- MINT Trial
  - 3504 patients with active MI and Hgb <10 g/dL
  - 80% NSTEMI, 20% STEMI
  - Randomized to Hgb >10 vs Hgb >7-8
  - Outcome: MI or death from any cause at 30 days
- Primary outcome with restrictive strategy: OR = 1.15 (P=0.07)
- Conclusion: liberal strategy "probably" beneficial in MI patients, but effect is likely small → evaluate on case-by-case basis



Outcome	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
Primary outcome			
Myocardial infarction or death	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Secondary outcomes			
Death	173/1749 (9.9)	146/1755 (8.3)	1.19 (0.96–1.47)
Myocardial infarction	149/1749 (8.5)	126/1755 (7.2)	1.19 (0.94–1.49)
Death, myocardial infarction, revascularization, or rehospitalization	342/1749 (19.6)	305/1755 (17.4)	1.13 (0.98–1.29)
Other outcomes			
Heart failure	102/1749 (5.8)	111/1755 (6.3)	0.92 (0.71–1.20)
Death, myocardial infarction, or unstable angina	338/1749 (19.3)	300/1755 (17.1)	1.13 (0.98–1.30)
Unscheduled revascularization	43/1749 (2.5)	39/1755 (2.2)	1.11 (0.72–1.70)
Cardiac death	97/1749 (5.5)	56/1755 (3.2)	1.74 (1.26–2.40)
Stroke	30/1749 (1.7)	26/1755 (1.5)	1.16 (0.69–1.95)
Pulmonary embolism or deep venous thrombosis	26/1749 (1.5)	34/1755 (1.9)	0.77 (0.46–1.27)
Pneumonia or bacteremia	166/1749 (9.5)	153/1755 (8.7)	1.09 (0.88–1.34)

Carson, et al. *NEJM* (2023)

Part 1: Finding Your Match

Part 2: Blood Component Therapy

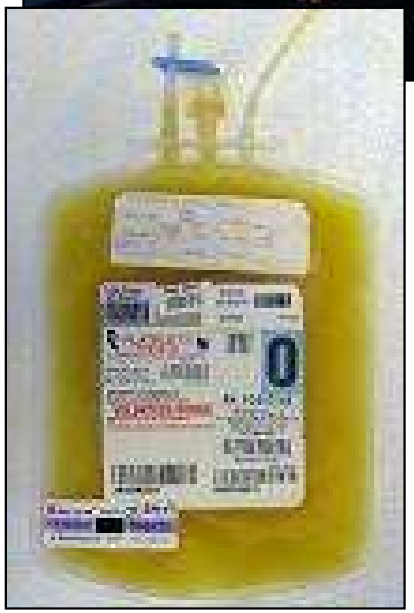
Part 3: Red Blood Cells

Part 4: Platelets

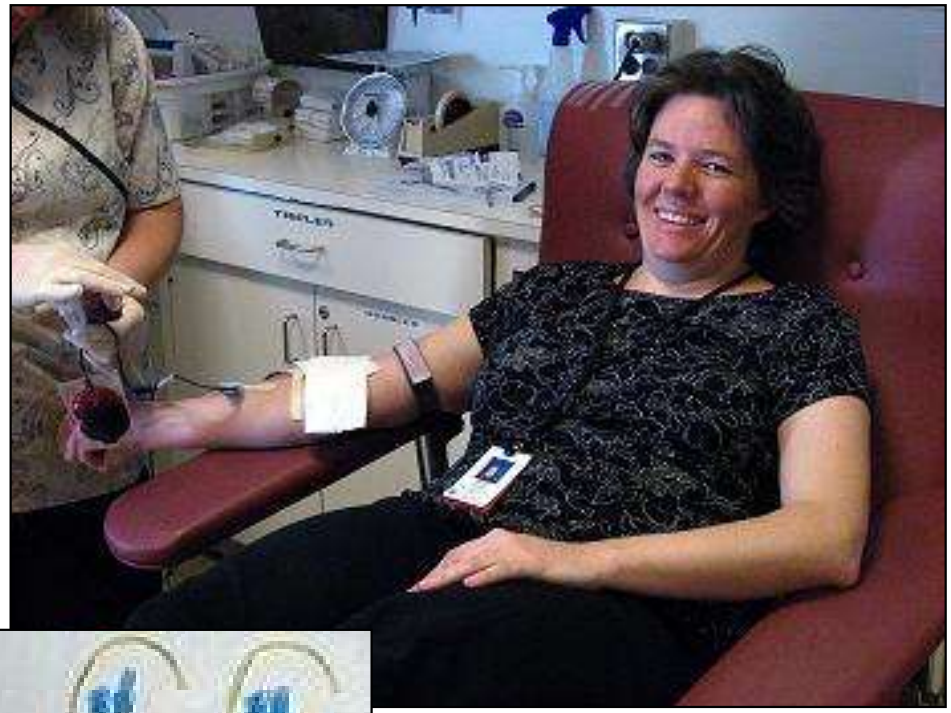
Part 5: Transfusion Reactions

Platelet Donation

Apheresis



Whole Blood



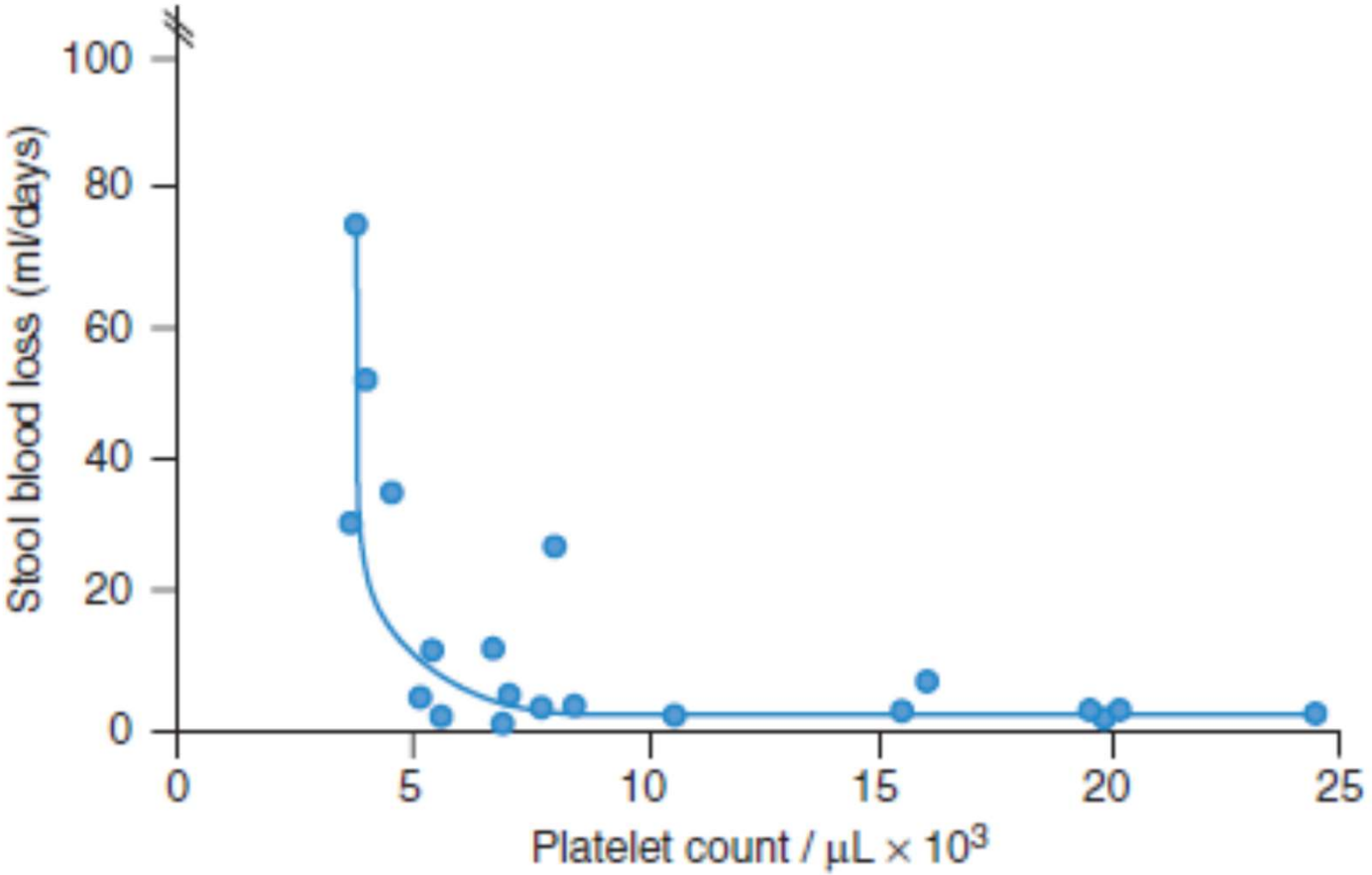
Blood Product Use

	Doses Issued Per Year (2017-2018)	
	MGH	**Heme-Onc (% Total)**
RBCs	30,448	8,258 (27.1)
FFP	6,278	99 (1.6)
Platelets	8,682	4,757 (54.8) ←
Cryo	734	85 (11.6)

A Prophylactic Platelet Transfusion Trigger of 10,000/μL is Safe in Clinically Stable AML and Transplant Patients

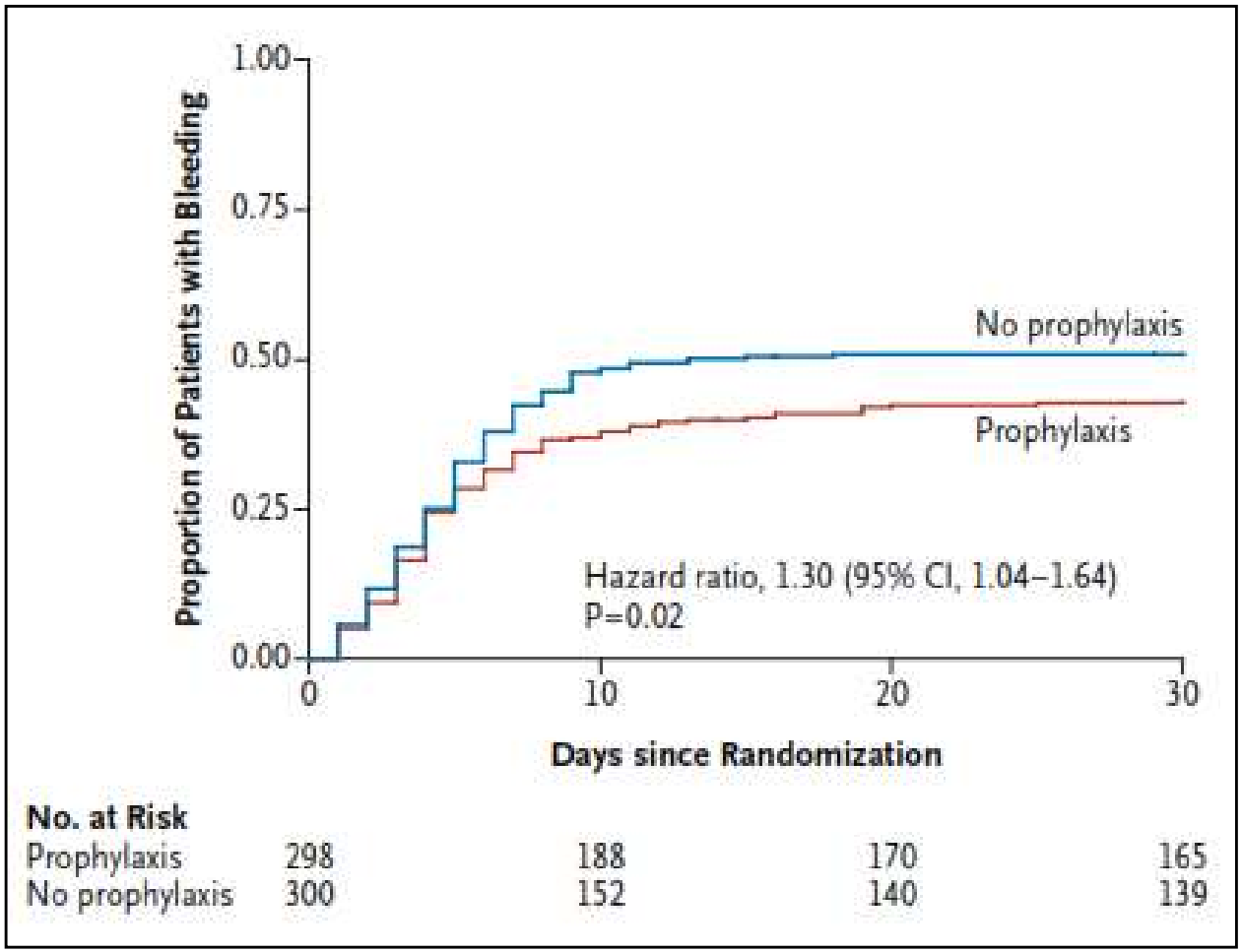
Study	Setting	10,000/μL Limb			Control Limb		
		N	Major Bleeding	Deaths	N	Major Bleeding	Deaths
Bone Marrow Transplant 1996;8:931	BMT	103	13%	3	87	14%	4
J Clin Oncol 1997; 15:1143	AML	37	-	0	41	-	0
NEJM 1997;337:1870	AML	135	21%	1	120	20%	0
Blood 1998;91:3601	AML	58	33%	0	47	28%	0
Biol Blood Marrow Transplant 2002;8:569	HSCT	78	14%	0	81	17%	0
Transfusion 2005;45:1064	AlloHSCT	79	18%	0	87	15%	0

Bleeding Risk with Thrombocytopenia



Slichter, et al., *Clinics in Haematology* 1978

Do We Need Prophylaxis At All?



- Plts maintained > 10K or only xfused when bleeding
- 7% absolute RR in grades 1 and 2 bleeding
- No mortality benefit to ppx
- No benefit seen in auto BMT pts

Stanworth, et al. *NEJM* 2013

Platelets Prior to Procedures

ORIGINAL ARTICLE

Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia

F.L.F. van Baarle, E.K. van de Weerdt, W.J.F.M. van der Velden, R.A. Ruiterkamp, P.R. Tuinman, P.F. Ypma, W.M. van den Bergh, A.M.P. Demandt, E.D. Kerver, A.J.G. Jansen, P.E. Westerweel, S.M. Arbous, R.M. Determann, W.N.K.A. van Mook, M. Koeman, A.B.U. Mäkelburg, K.P. van Lienden, J.M. Binnekade, B.J. Biemond, and A.P.J. Vlaar

Table 1. CVC-Related Bleeding.*

Bleeding Grade	Definition
Grade 0	No bleeding
Grade 1	Oozing; hematoma; bleeding that results in <20 min of manual compression to stop
Grade 2	Bleeding that results in minor interventions to stop, such as prolonged manual compression (>20 min)
Grade 3	Bleeding that results in radiologic or elective operative intervention or red-cell transfusion without hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability (hypotension, defined as a decrease of >50 mm Hg or >50% in either systolic or diastolic blood pressure), with associated tachycardia (heart rate increase, >20% for 20 min) and resulting in increased red-cell transfusion or fatal bleeding

- Very common clinical question, very few studies
- Studied 338 patients with plt count 10K-50K who needed CVC
- 50/50 heme or heme malignancy vs. ICU
- Tunneled and 3 non-tunneled CVC sites
- Patients randomized to receive 1U plts or nothing (not blinded)
- Outcome was graded CVC-related bleeding

Van Baarle, et al. *NEJM* 2023

Table 3. Primary and Secondary Outcomes.*

Outcome	Transfusion (N=188)	No Transfusion (N=185)	Effect Size (90% or 95% CI)
Primary outcome			
Grade 2–4 catheter-related bleeding — no./total no. (%)	9/188 (4.8)	22/185 (11.9)	2.45 (1.27 to 4.70)†
Bleeding-related secondary outcomes			
Catheter-related bleeding — no./total no. (%)			
Grade 3–4	4/188 (2.1)	9/185 (4.9)	2.43 (0.75 to 7.93)†
Grade 1	88/188 (46.8)	106/185 (57.3)	1.22 (0.91 to 1.61)†
Hematoma — no./total no. (%)	23/188 (12.2)	35/185 (18.9)	1.62 (0.94 to 2.80)†
Median hematoma size (IQR) — cm	4.0 (2.2–5.9)	2.1 (1.8–4.3)	1.34 (0.96 to 1.86)‡
Rate of red-cell transfusion in ≤24 hr	0.48±0.76	0.49±0.75	1.02 (0.76 to 1.37)§
Hemoglobin level after CVC placement — g/dl			
After 1 hr	8.1±1.4	8.5±1.3	0.34 (0.06 to 0.62)¶
After 24 hr	8.4±1.4	8.5±1.2	0.09 (−0.17 to 0.35)¶

- Take homes
  - Plt transfusion increased counts by 28K at 1 hr and 10K at 24 hrs
  - Transfusion led to fewer episodes of Grade 2-4 and Grade 3-4 bleeding, but no difference in mortality
  - Bleeding clustered among pts with lower platelet counts
  - Slightly higher allergy and ALI rates in transfused pts
  - Authors' suggestion: give prophylactic platelets to pts at lower end of platelet count and those with downward trend

Van Baarle, et al. *NEJM* 2023

Platelet Refractoriness

- Repeated failure to generate an appropriate therapeutic "bump" following platelet transfusion
- Myriad causes
  - Med effect (e.g. vancomycin)
  - Splenic sequestration
  - Non-immune consumption (fever, sepsis, liver disease, DIC, etc.)
  - Immune-mediated consumption (e.g. HLA or platelet allo antibodies)
- HLA-alloimmunization is a common cause of refractoriness in hematologic malignancies: call BTS for a PRA

Part 1: Finding Your Match

Part 2: Blood Component Therapy

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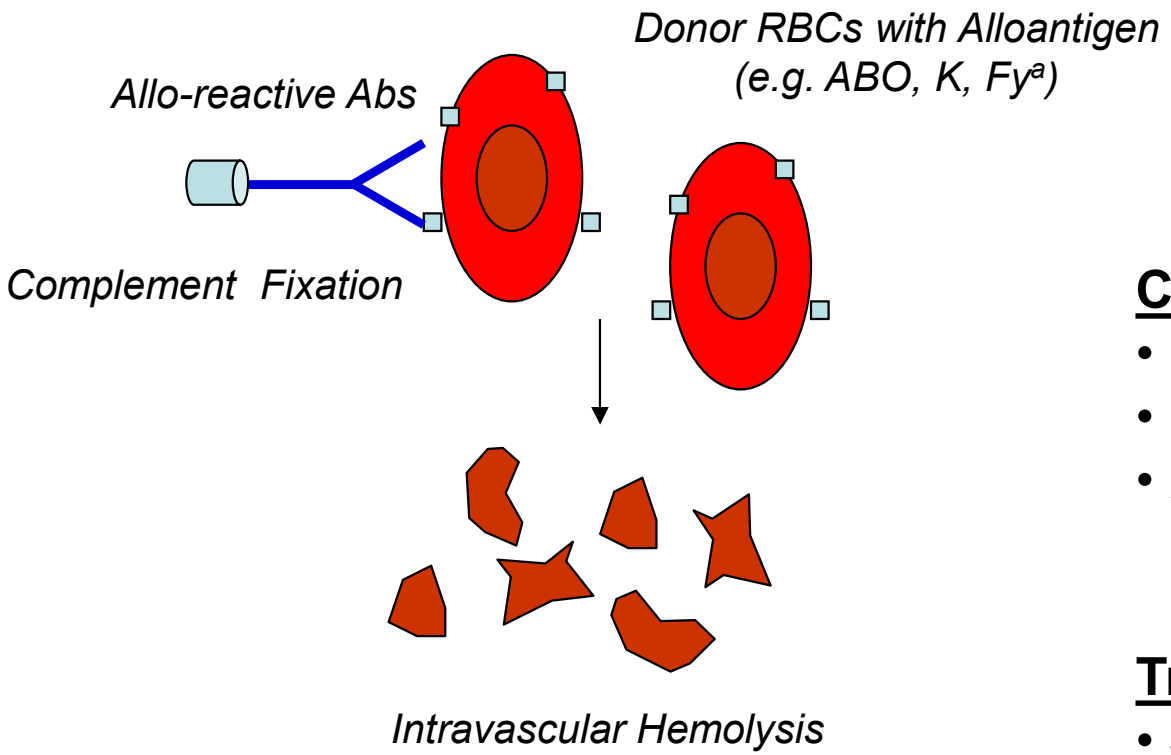
Types of transfusion reactions

- **Not serious (common)**
  - Simple allergic
  - Febrile non-hemolytic transfusion reaction (FNHTR)

- **Serious (rare)**
  - Acute hemolytic
  - Septic
  - TRALI
  - Anaphylaxis

Acute hemolytic reaction



Incidence

- 1:12,000 to 1:76,000

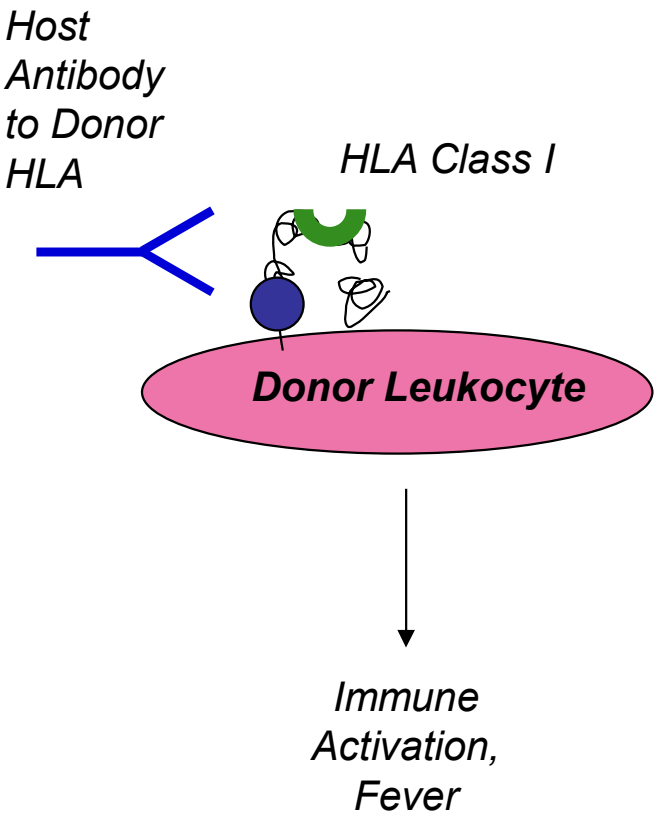
Clinical presentation

- Fever, chill, n/v, flank pain
- Urine discoloration
- *May result in DIC, shock, AKI*

Treatment

- Stop transfusion
- Alkalinize urine
- Start NS 100-200mL/hr
- *Get DAT*

Febrile non-hemolytic transfusion reaction (FNHTR)



Incidence

- 1:200-2,500 for RBCs
- 1:50-1:600 for platelets

Setup

- Multiparous female recipient
- Extensive transfusion hx
- Non-LR product

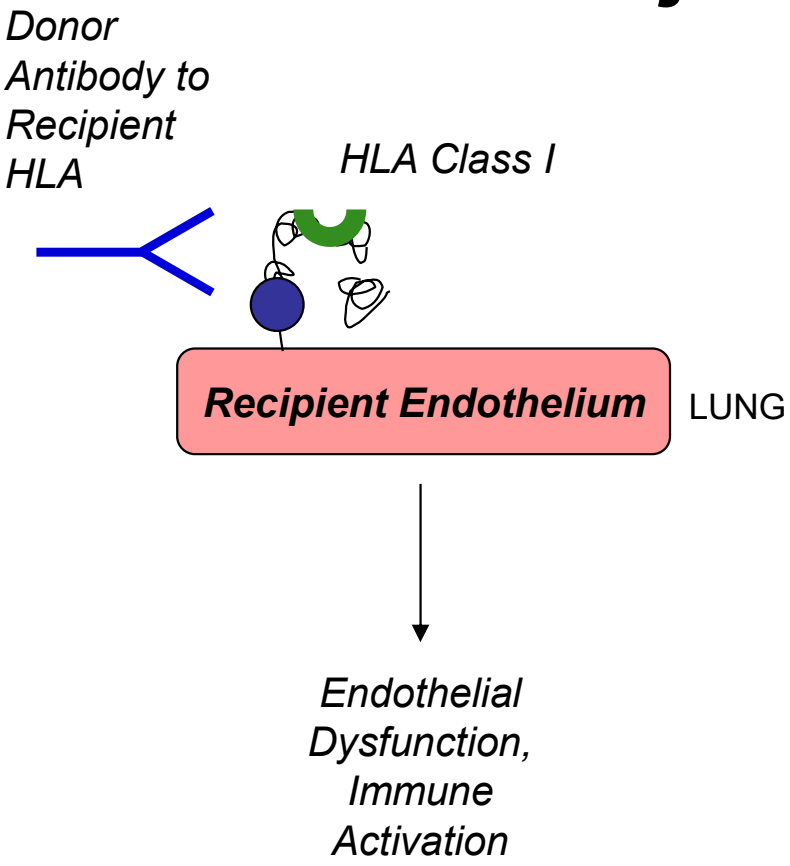
Clinical presentation

- Fever/Chills
- Tachycardia/hypertension
- +/- mild dyspnea

Treatment

- Stop transfusion, contact BTS
- Give Tylenol for fever, meperidine for rigors
- Ask for leukoreduced products in the future

Transfusion related acute lung injury (TRALI)



Setup
- Product from multiparous female
- High plasma content product

Clinical presentation
- Hypoxemia within 6 hrs
- Hypotension
- Fever
- Non cardiogenic pulmonary edema

Treatment
- Stop transfusion, contact BTS
- Respiratory support

Incidence
- 1:5000
- Death in 10%
- Donor is invariably parous woman

Product Restrictions for Select Patients

Restriction	Indication
Leukoreduction	Prior history of FNHTR Prevent HLA alloimmunization Reduce risk of TT-CMV disease
FNHTR, heme malignancies, transplant pts (not liver)	
Irradiation	Prevent TA-GvHD
BMT pts, heme malignancies (not solids) and AA, congenital T cell deficiency, SCIDS, WAS, DiGeorge, neonates, other peds pts	
CMV Seronegative	Reduce risk of TT-CMV disease
CMV (-) pregnant women, transplant pts, neonates	

When to Call BTS

- TTP and other urgent pheresis
- Red cell exchange
- Platelet refractoriness requiring PRA
- IVIG questions
- Severe transfusion reaction
- Whenever you're not sure

Thank You

- MGH
  - Sunny Dzik
  - Rob Makar
  - Chris Stowell
- BWH
  - Rick Kaufman
- BIDMC
  - Lynne Uhl
  - Rich Haspel