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[Some] Adverse Effects of Blood Transfusion

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Kermanshah blood transfusion conference - 4/feb/2019

Blood Transfusion is "*Unavoidably Unsafe*"

- High volume
- High cost
- High Risk
- Problem prone

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The Risk Side of the Transfusion Equation

- Blood transfusions are the *most common procedure* performed on inpatients in the US.
- Over **21 million** blood components are transfused annually in the US to more than 5 million patients
- Blood transfusions remain the #1 most common *allogeneic tissue transplant* in medicine
- Blood transfusions expose patients to allogeneic antigens much more commonly than the sum of all other tissues and organs transplanted worldwide.

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The Risk Side of the Transfusion Equation

- **Infectious disease risks have been vastly reduced over the last 35 years**
  - The viral risks remain "***non-zero***"
  - Bacteria are the *most common* pathogens
  - Constant concerns for *emerging* pathogens
- **Acute adverse effects remain common**
  - *Irreducible* human errors
  - *Irreducible* immunologic risks due to use of allogeneic tissue donors

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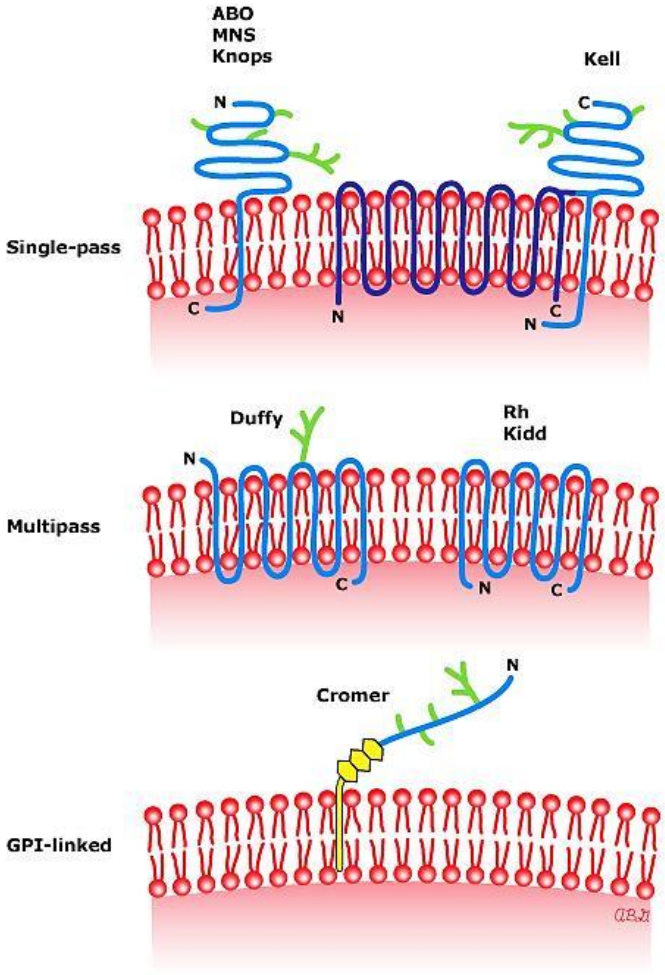
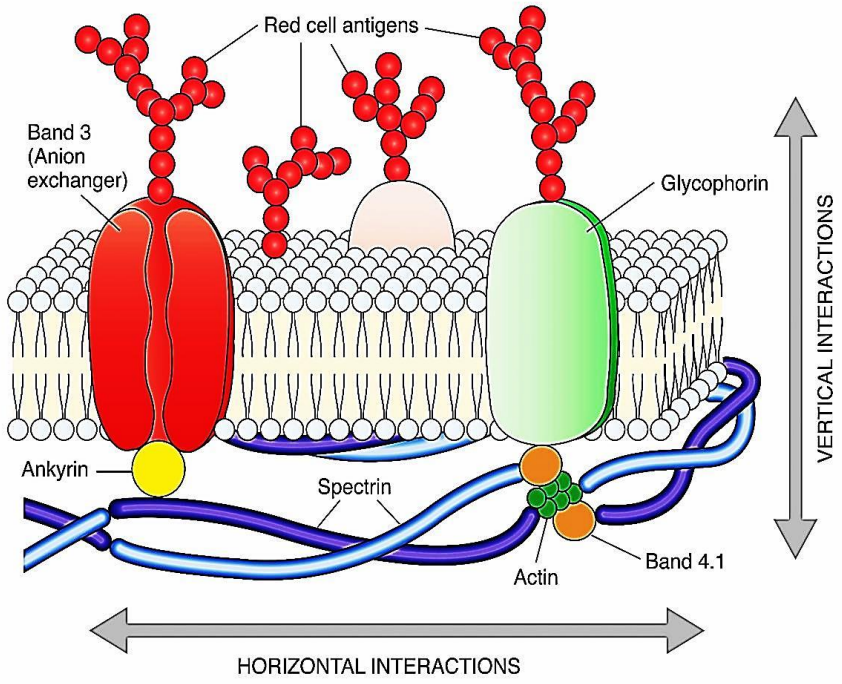
There are 35 Blood Group Systems & ~ 350 *authenticated Blood Group* Antigens





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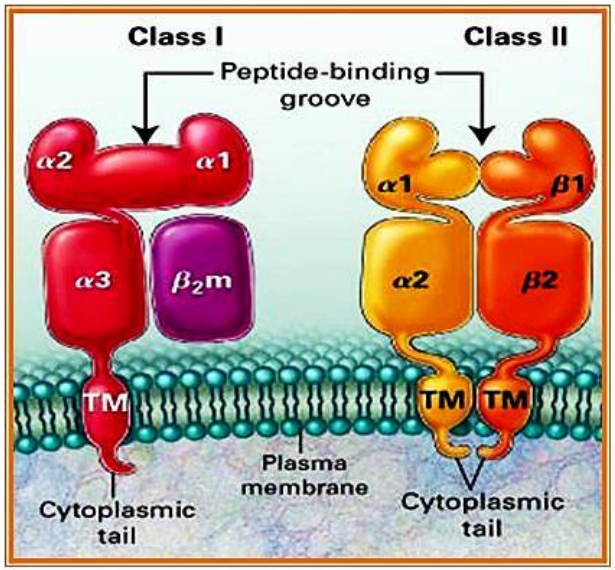
HLA Antigens – Expressed on WBC's - are

- *THE* Tissue-Typing Antigens
- Are the most polymorphic in man
- Basis of Immune-mediated platelet refractoriness

HLA class I and class II antigens

- Monomer with non-covalently associated subunit (β2m)
- Presents antigenic peptides to CD8+ T cells
- Expressed by all nucleated cells



- Heterodimer
- Presents antigenic peptides to CD4+ T cells
- Restricted expression on antigen presenting cells (dendritic cells, B cells, macrophages)
- Inducible on other cells (endothelium and epithelium)

Platelet-Specific Alloantigens

- 24 platelet-specific alloantigens defined by immune anti-sera
- 16 are grouped into 8 bi-allelic systems
- The alleles differ by a SNP
- The molecular basis of 22 of 24 have been resolved
- **Platelet-specific antibodies are the pathophysiological basis of**
  - Posttransfusion purpura (PTP)
  - Neonatal alloimmune thrombocytopenia (NAIT)

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Platelet-Specific Alloantigen *Families*: "Human Platelet Antigens" [HPA's]

Antigen Family, Allelic Pairs	Epitopes on Specific Membrane Glycoproteins
HPA-1a/1b	GP IIb/IIIa
HPA-2a/2b	GP-Ib-IX
HPA-3a/3b	GP IIb/IIIa
HPA-4a/4b	GP IIb/IIIa
HPA-5a/5b	GP IIb/IIIa
HPA-6a/6b	GP IIb/IIIa
HPA-9a/9b	GP IIb/IIIa
HPA-15a/15b	CD 109

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RESIDUAL INFECTIOUS DISEASE RISKS in TRANSFUSION

Disease Transmitted by Blood	Estimated Frequency per Unit
Hepatitis B virus	1 : 843,000 – 1,280,00
Hepatitis C virus	1 : 1,149,000
HIV- 1 / 2	1 : 1,470,00
HTLV – I / II	< 1 : ~ 3,000,000
WNV	<< 1 : ~ 4,000,000
Bacterial contamination (platelets)	1 : ~ 2000 – 3000 platelet transfusions

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Next *Diseases of Concern* for Testing in the Blood Supply

- Arboviruses
  - **Zika**, Dengue, Chikungunya
- *Babesia* species
- Parvovirus B19
- Human v-CJD

Emerging Infectious Diseases and their potential threat to transfusion safety, *Transfusion* 2009;49, 1S-29S.

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Critical & Fundamental Process Defects

- Blood transfusion is "***unavoidably unsafe***"
- Transfusions = allogeneic tissue transplants
- The complex series of processes to deliver transfusions are performed by imperfect humans
- Process control is often lacking

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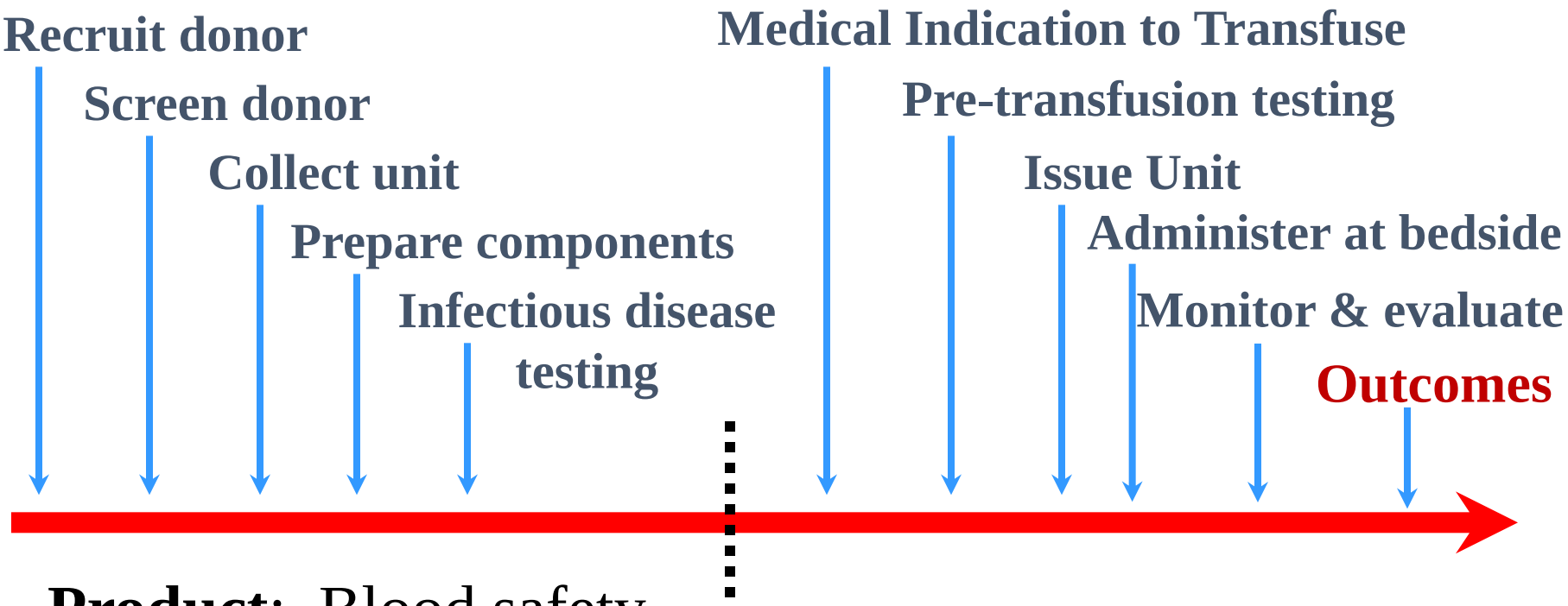
Transfusion Therapy is a Set of Processes, not just *a Product* or a *Lab Result*



Product: Blood safety

Entire process: *Safe* Blood Transfusion

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Systematic Review of RBC Transfusion in the Critically Ill

- 45 studies with a median of 687 patients per study
- Outcome measures, attributed to "***immunomodulation***"
  - Mortality
  - Infection
  - MOF Syndrome
  - ARDS
- **Risks of RBC transfusion outweighed benefits in 42 of 45 studies!!**

Marik & Corwin, ***Crit Care Med* 2008**;36(9):2667-74.

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Association of Transfusion & Risk of Death

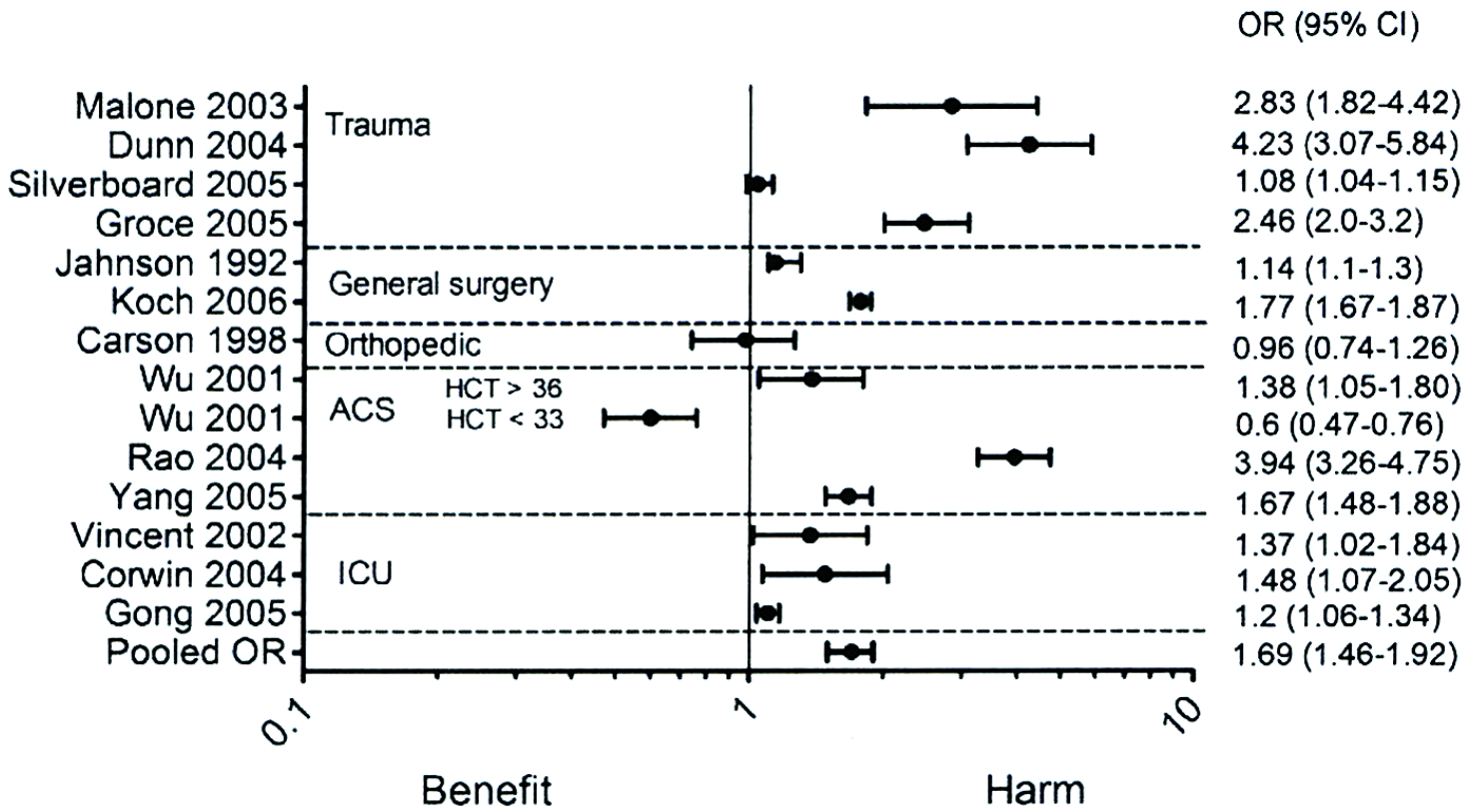

Figure 2. Association between blood transfusion and the risk of death (odds ratio [*OR*] and 95% confidence interval [*CI*]). *ACS*, abdominal compartment syndrome; *ICU*, intensive care unit.

Marik & Corwin, ***Crit Care Med* 2008**;36(9):2667-74.

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Transfusion Reactions

- Acute (intravascular) hemolytic reaction
- Delayed (extravascular) hemolytic reaction
- Febrile non-hemolytic reaction
- Allergic (urticarial) reaction
- Bacterial contamination
- Transfusion-related acute lung injury
- Transfusion-associated circulatory overload
- Post-transfusion purpura
- Graft-vs.-host disease

Acute Adverse Effects

- **Immune-Mediated**
  - **Acute hemolytic TR's**
  - **Fever without hemolysis: FNHTR's**
  - **Simple *allergic* reactions**
  - **TRALI**
  - **Anaphylactoid / anaphylactic reactions**

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Acute Adverse Effects

- **Nonimmunologic**

  - **Transfusional hypervolemia** (circulatory overload), *aka* **TACO**
  - **Bacterial septic reaction**
  - **Isolated Hypotensive TR's**
  - **Citrate toxicity**
  - **Nonimmune hemolysis (often asymptomatic)**

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Acute Transfusion Reactions by Systemic Manifestations

- **Fever and/or chills** (including rigors), no hemolysis
  - R/o acute, immune-mediated hemolysis
    - Work-up required by laboratory Standards
  - **FNHTRs**
  - Bacterial contamination
- **Allergic (Type I hypersensitivity reactions)**
  - Mucocutaneous (pruritus / urticaria) *vs*. more generalized, involving other organ systems
- **Respiratory Distress**
  - **TACO**
  - **TRALI**
  - May be part of anaphylactoid or anaphylaxis
- **Isolated Hypotensive TR's**

  (without cardiovascular collapse)

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Estimated Frequencies of Some Adverse Effects of Transfusion

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TYPE of Reaction	Reported Frequency
TACO	1 : 68 to 1 : 356 (ICU patients) [Mortality 1 to 3%]
TRALI	1 : 1200 to 1 : 190,000 [Leading reported cause of transfusion-related mortality]
WBC alloimmunization	1 : 20 to 1 : 100
FNHTR's	1 : 100 – 200
Cutaneous allergic	1 : 100 – 300
Delayed serologic	1 : 1500
Delayed hemolytic	1 : 4000
Anaphylactoid	1 : 20,000
Acute hemolysis	1 : 6,000 – 33,000
Anaphylactic	1 : 20,00 to 1 : 50,000
Hypotensive TR's	1 : 18,500

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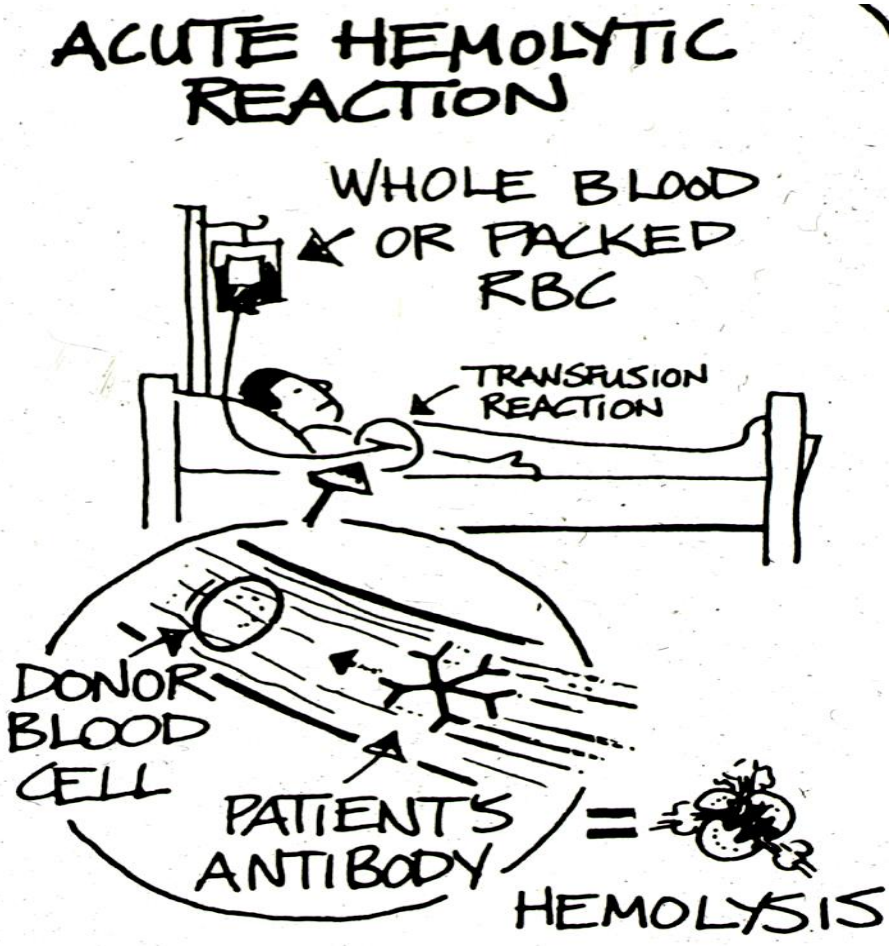
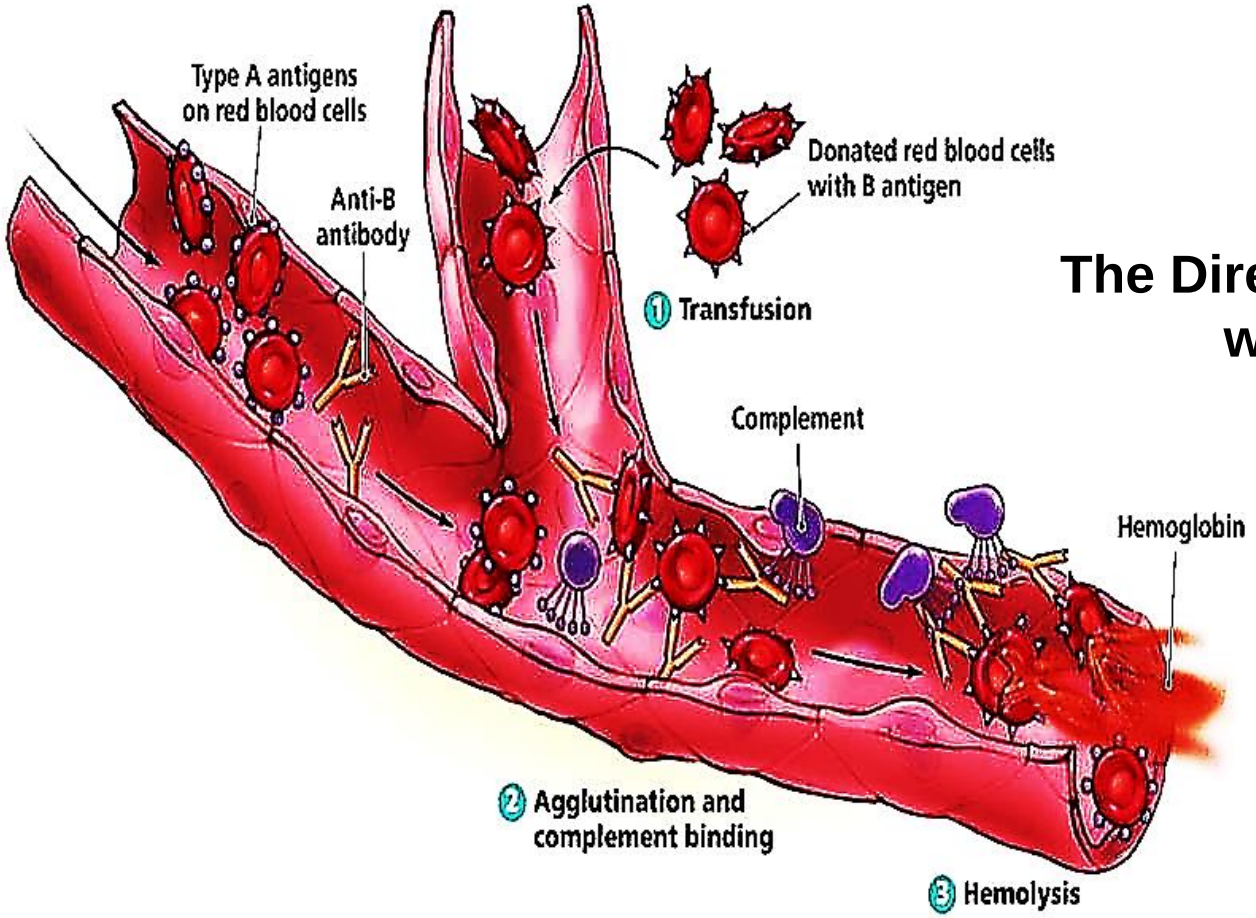
Preventing Acute Hemolysis due to Pre-formed IgM, as seen in ABO-incompatibility

- **All steps in specimen & patient identification are aimed at prevention!**
- **All pretransfusion testing is done to prevent acute intravascular hemolysis**
  - **Blood typing & confirmation**
  - **Antibody screening**
  - **Crossmatching**



Acute Complement-Mediated, Immediate Hemolysis



The Direct Antiglobulin Test will be positive

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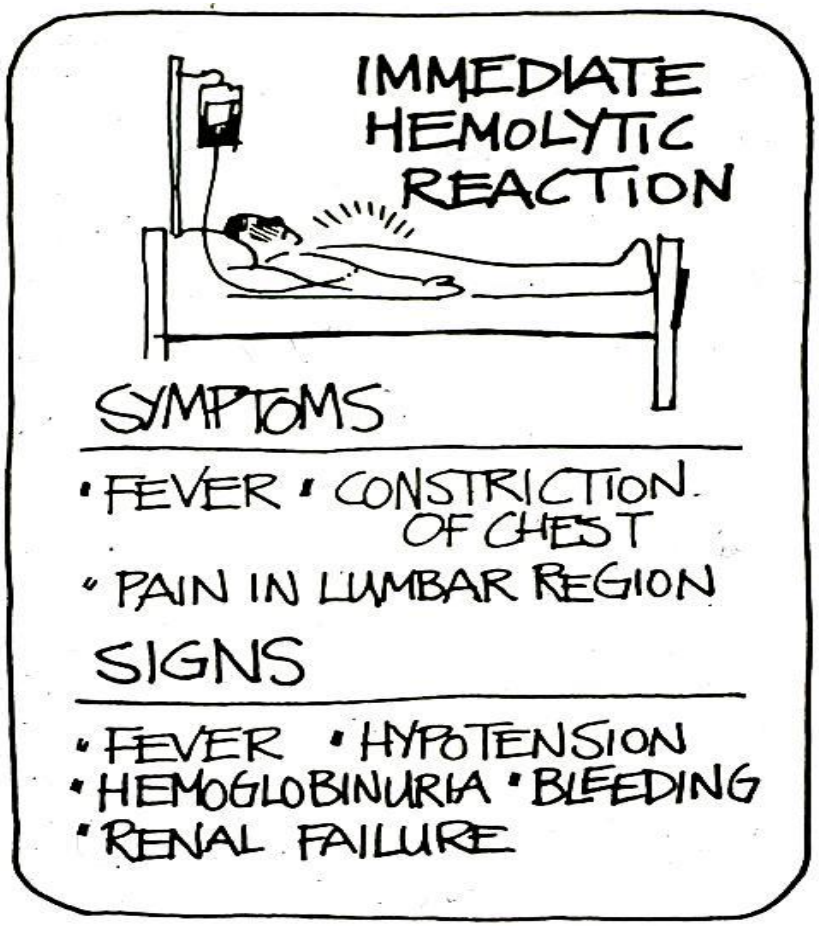
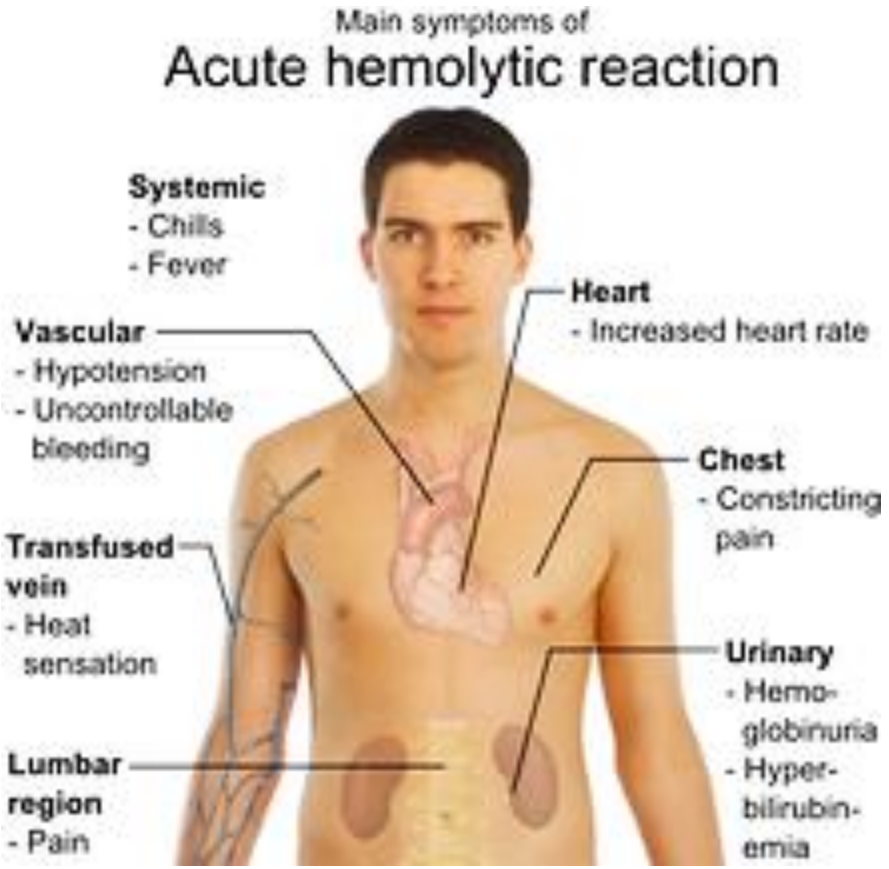
Acute Intravascular Hemolytic Transfusion Reaction





Freshly Hemolyzed Plasma (Actual Case from an OR)

Dr. DeChristopher's gloved fingers

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Febrile Nonhemolytic Transfusion Reactions

- **<u>Cardinal Signs & Symptoms</u> (near end of transfusion or up to 2 hours posttransfusion)**
  - **Fever**
  - **Chills / *cold feeling* are more common than frank *fever***
  - **General discomfort**
  - **Less commonly rigors, nausea/vomiting, dyspnea**
  - **Not associated with clinical hemolysis (by laboratory testing)**

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FNTRs

- **Common Etiologies**
  - Pre-formed recipient WBC antibodies
    - Chronically, heavily transfused recipients
    - Multi-gravid females
    - Solid-organ transplant recipients
  - *Storage lesion* cytokines, termed a "*Cytokine Storm*"
    - Proinflammatory cytokines, such as IL-1, IL-2, IL-6, IL-8, TNF-α, in the blood components

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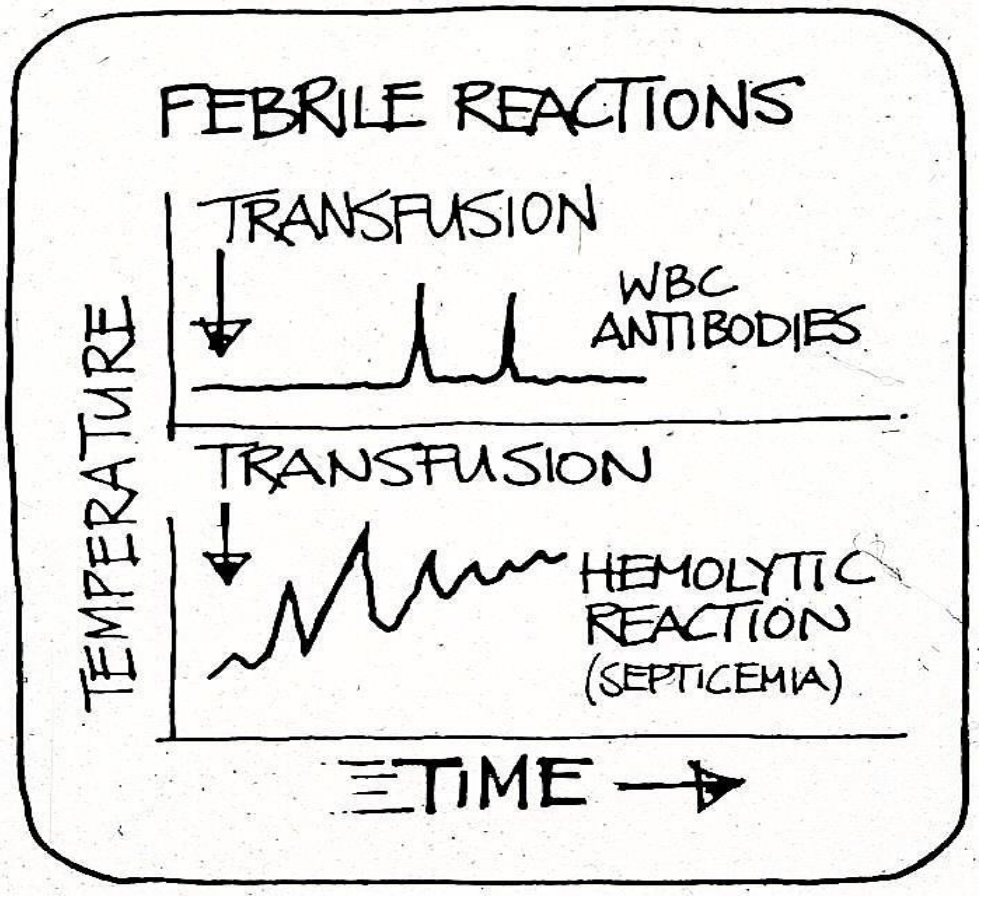
Febrile Reactions: Rule Out Hemolysis & Acute Bacterial Sepsis



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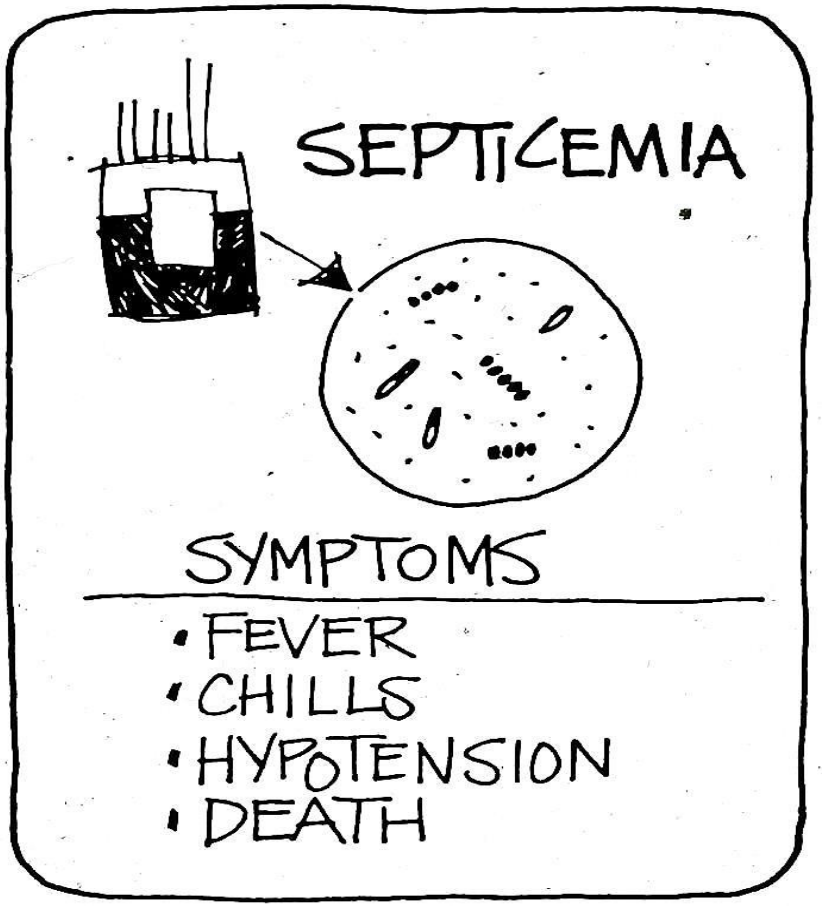
Bacterial Contamination and/or Endotoxemia



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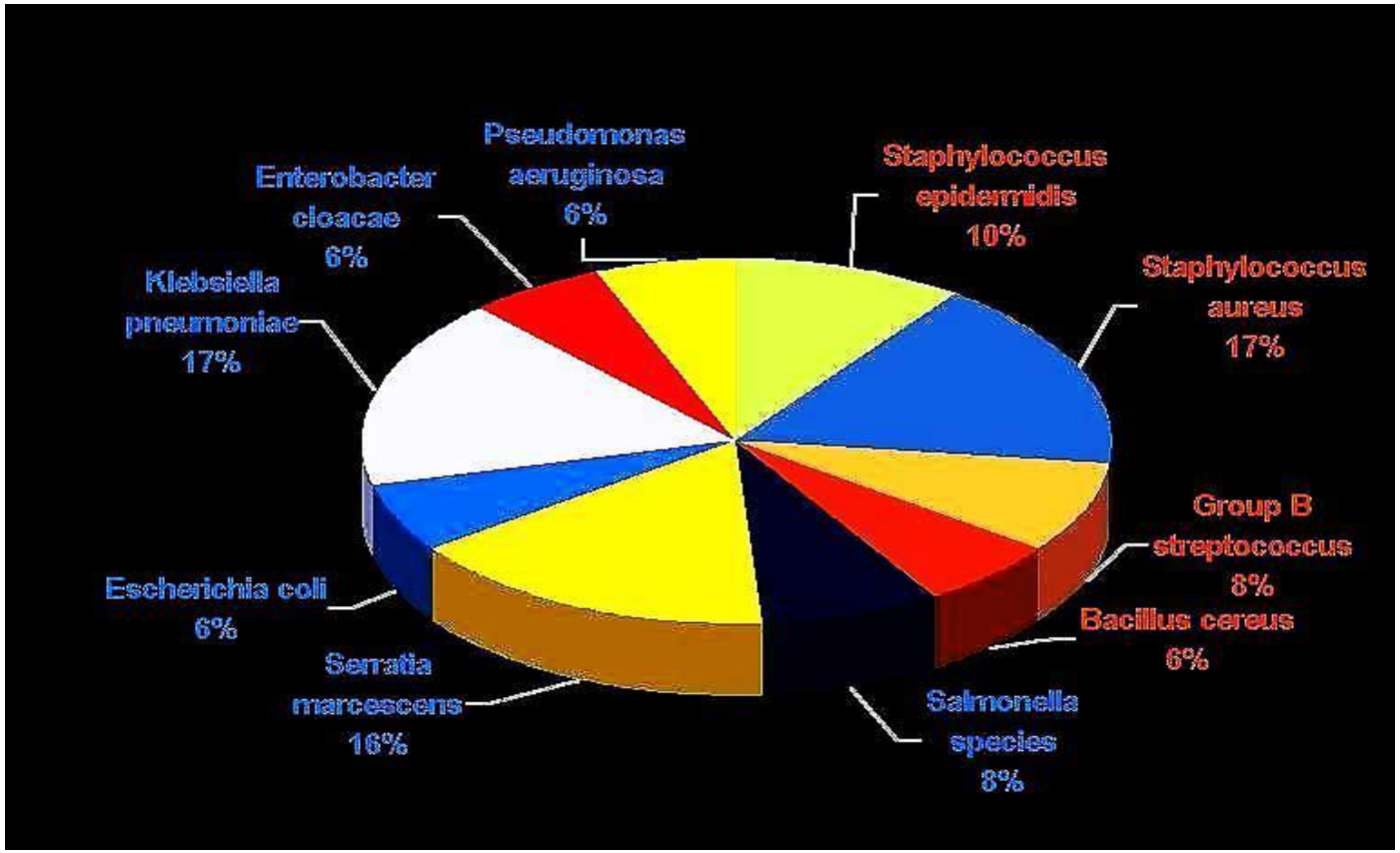
The Cavalcade of Bacterial *Stars* Implicated in Transfusion-transmitted Septic Deaths



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Simple Cutaneous Hypersensitivity

- Usually involves the skin and is limited anatomically
- Common, but usually mild / self-limited
- More common in recipients of large volumes of **plasma**
- The transfusion can temporarily be halted
- Consider administration of antihistaminic medications
- Can restart the transfusion if non-progressive
- Not required by AABB *Standards* to be reported as a "*transfusion reaction*"

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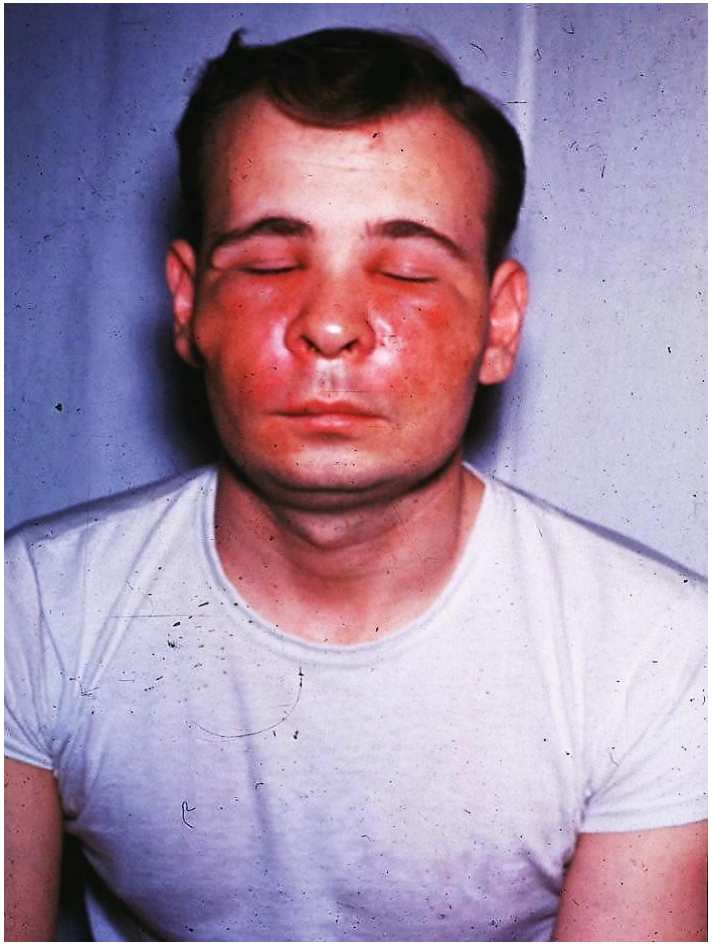
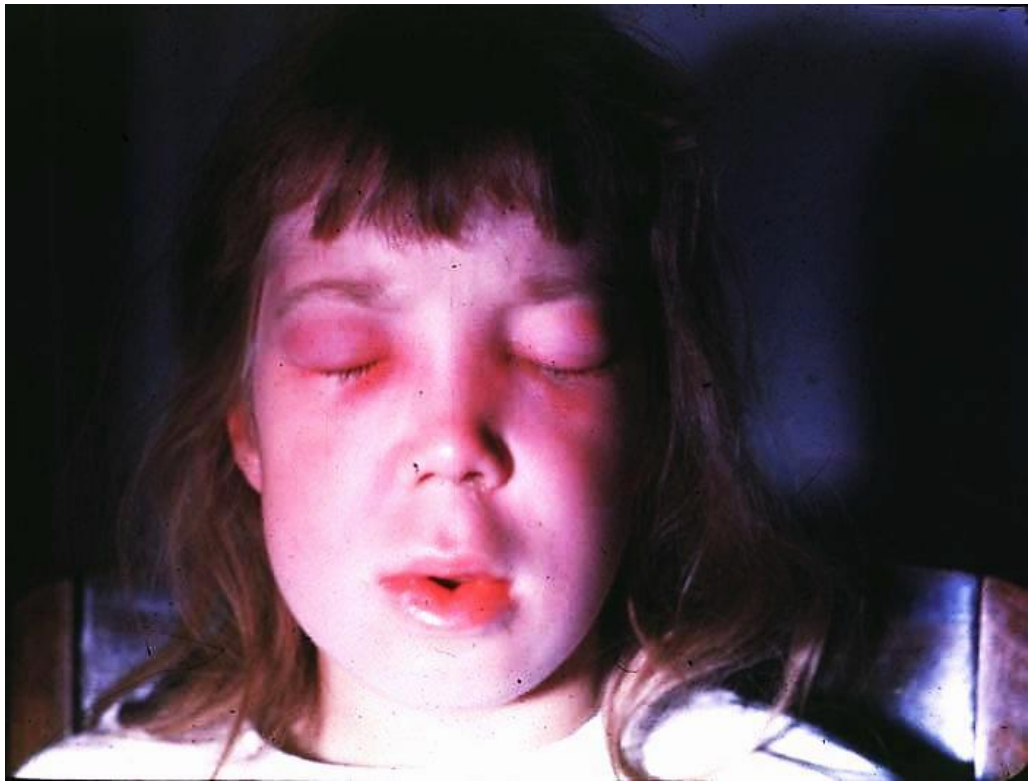
Allergic Transfusion Reactions: Hives and Itching





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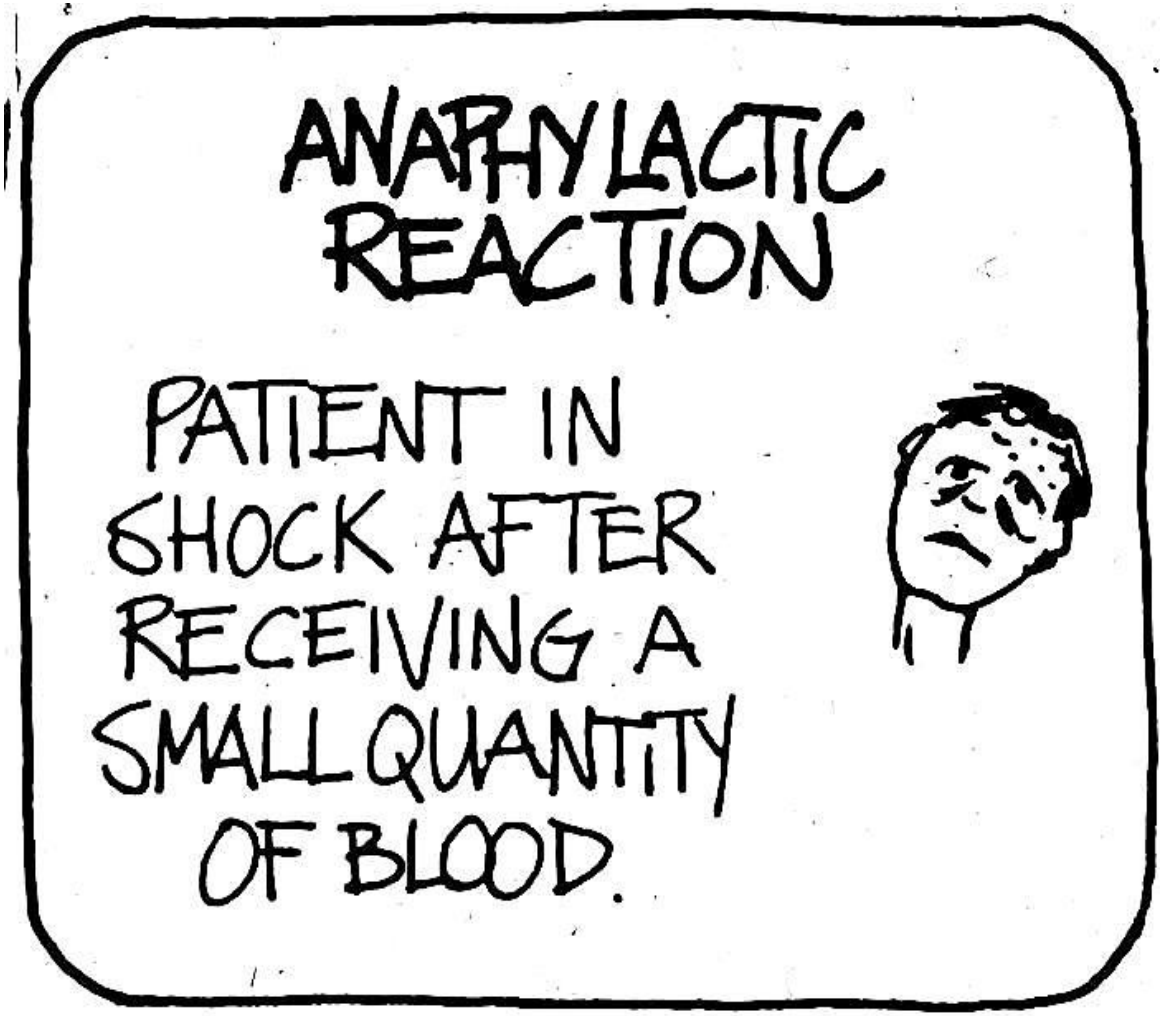
Acute Anaphylactic Shock



- Acute cardiopulmonary collapse
- Evolves **RAPIDLY**
- **Plasma proteins** are etiologic
- **Cannot be predicted or prevented**
- “Reactions” occur after exposure to only small quantities of blood
- Will likely require ACLS

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Consensus Definition of TRALI

- **A new ALI within 6 hours of a completed transfusion**
- **No other temporally-associated ALI risk factors**
- **TRALI is a *clinical syndrome* rather than a disease with a single etiology**
- **It is a clinical and radiographic diagnosis**
- **TRALI is NOT diagnosed based on laboratory test results**

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Canadian Consensus Conference Panel on TRALI

- Acute onset
- Hypoxemia
  - Research setting
    - PaO_2 / FiO_2 ratio ≤ 300mm Hg or
    - SpO_2 < 90% on room air
  - Non-research setting
    - As above or other clinical evidence of **hypoxemia**
- Bilateral infiltrates on frontal CXR
- No evidence of left atrial hypertension (circulatory overload)

Kleinman S, *et al.*, Transfusion 2004;44:1774-89.

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Transfusion-Related Acute Lung Injury (TRALI)

- **Very common signs / symptoms**
  - **Dyspnea, respiratory distress, hypoxia, bilateral pulmonary edema, fever (1 – 2 degree increase)**
- **Common signs / symptoms**
  - **Tachycardia, hypotension, cyanosis**
- Diagnosis includes ruling out cardiogenic causes of pulmonary edema
- **A clinical diagnosis of exclusion**

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1st Basic Mechanism Proposed for TRALI Pathogenesis

- **1st Mechanism (antibody-mediated)**:
  - Specific antibodies
    - Usually HLA Class I or anti-granulocyte
  - PMN's with cognate antigens
  - Pulmonary leukostasis and PMN activation
  - (Positive complement activation)
  - **Endothelial injury, capillary leak, ALI**

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2nd Basic Mechanism Proposed

- *Two-Hit*, two independent events:
  - Systemic inflammation (patient *primed* by underlying clinical condition)
  - Release of proinflammatory mediators
    - Inflammatory cytokines
    - *Storage lesion* lysophosphatidylcholines & neutral lipids
  - Pulmonary leukostasis, PMN activation and release of “reactive oxygen species”
  - **Endothelial injury, capillary leak, ALI**

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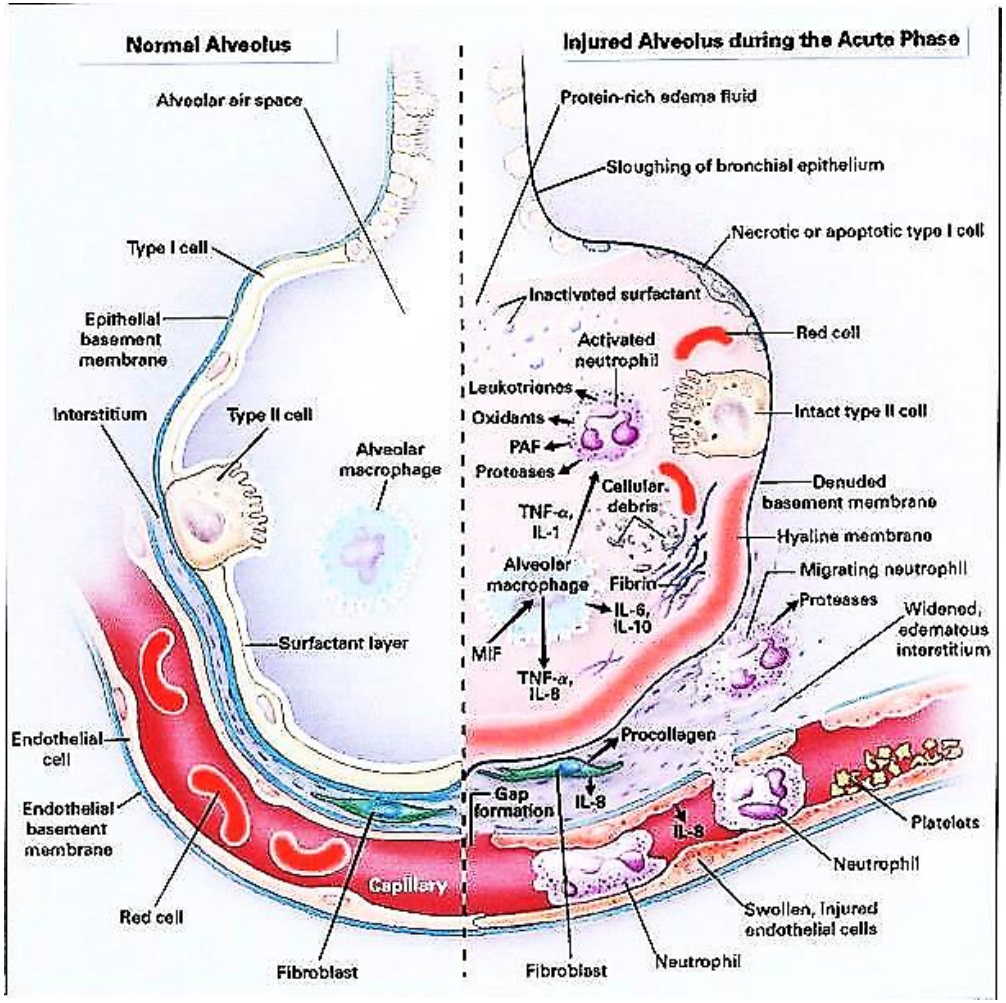
The Business End of Respiration and of TRALI



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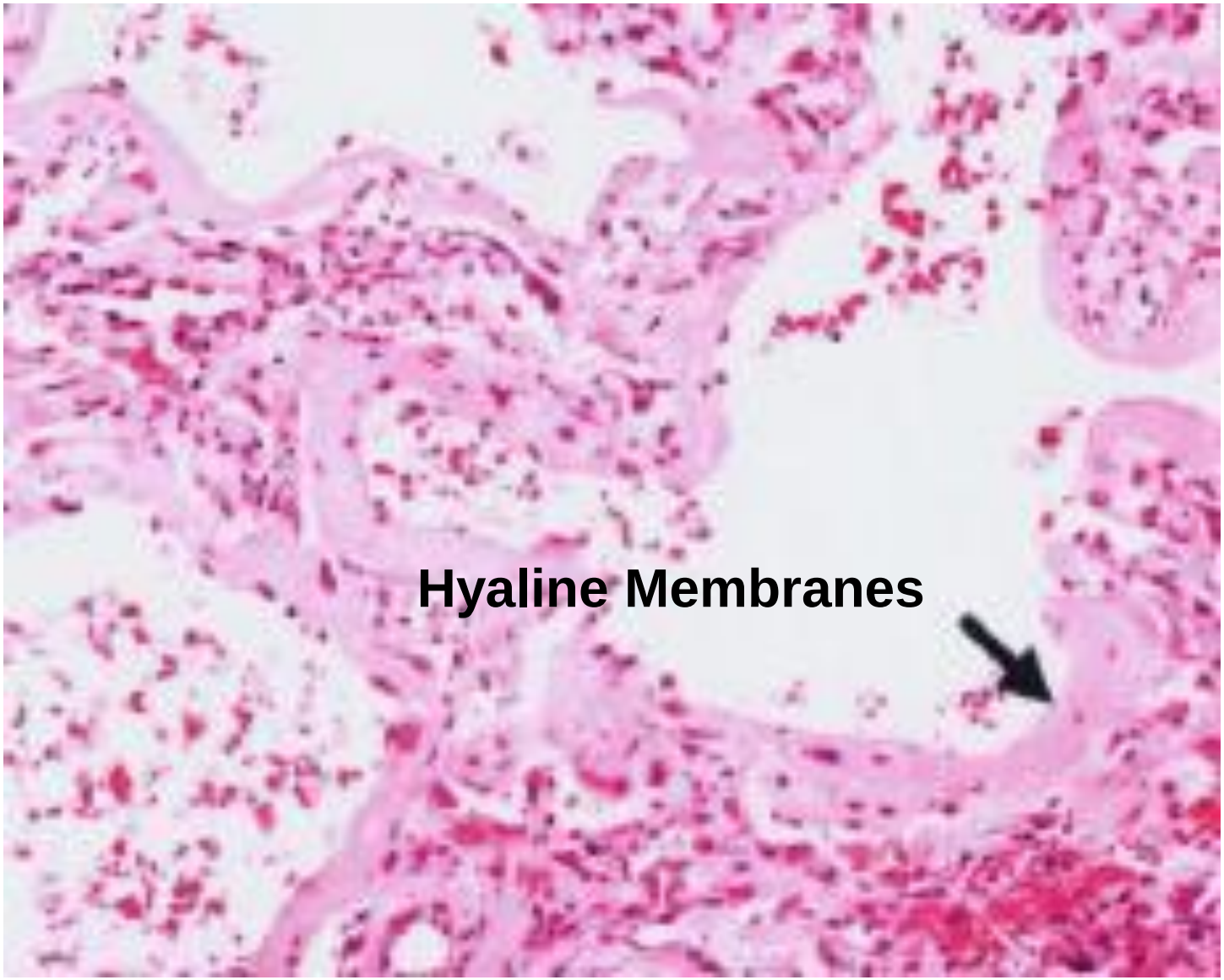
Diffuse Alveolar Damage



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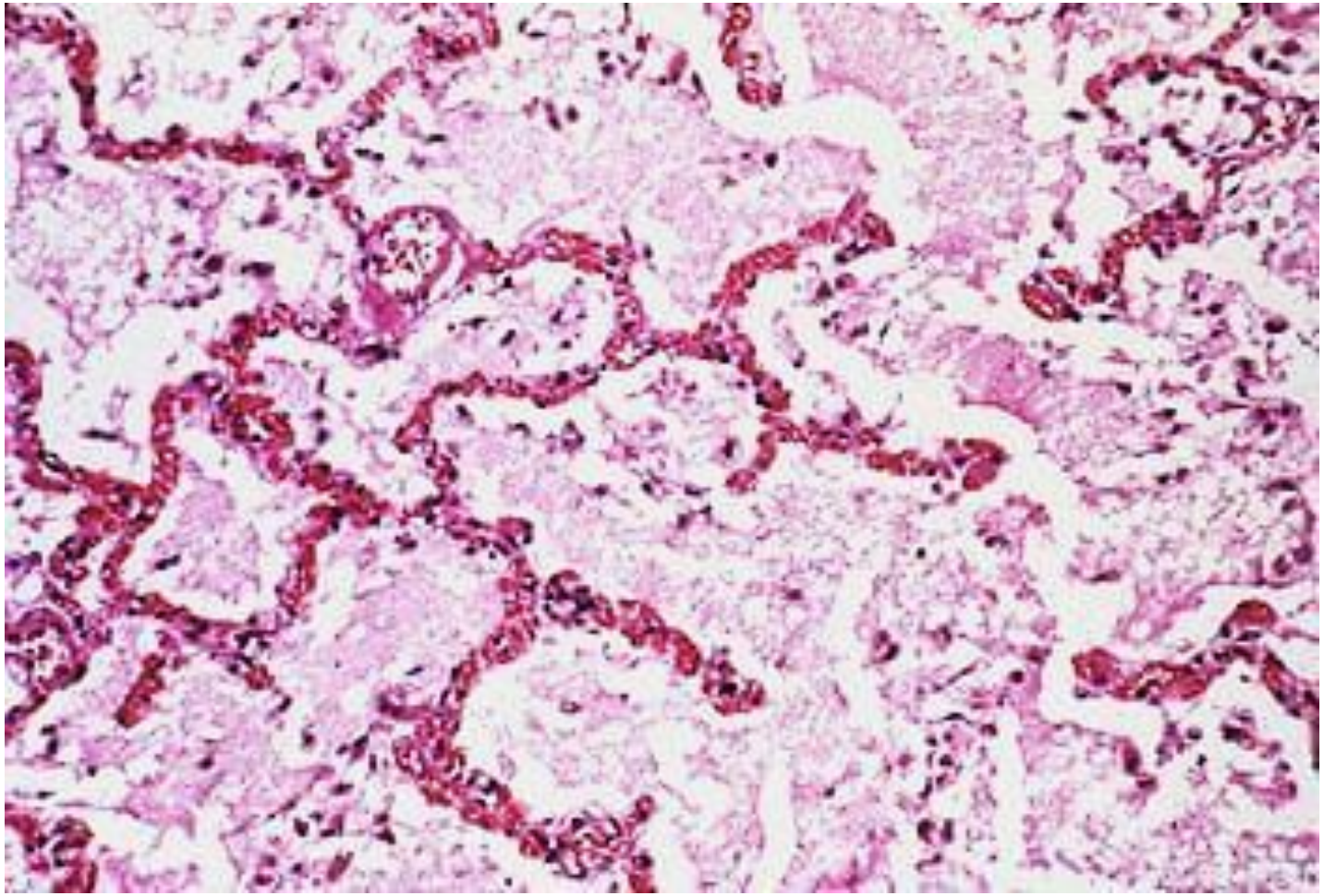
Pulmonary Congestion and Edema



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Transfusion Reactions with Respiratory Symptoms: TRALI

Risk Factors

- Higher odds among specific groups
  - Age 65 – 79 vs. older than 79 years
  - Rates higher for platelet and plasma-containing transfusions
  - Females vs. males
  - White vs. nonwhite
  - (Incidence 0.02%)
- Post-inflammatory pulmonary fibrosis
- Cancers of blood forming tissues
- Pulmonary insufficiency following trauma or surgery
- Tobacco use
- Blood transfusion

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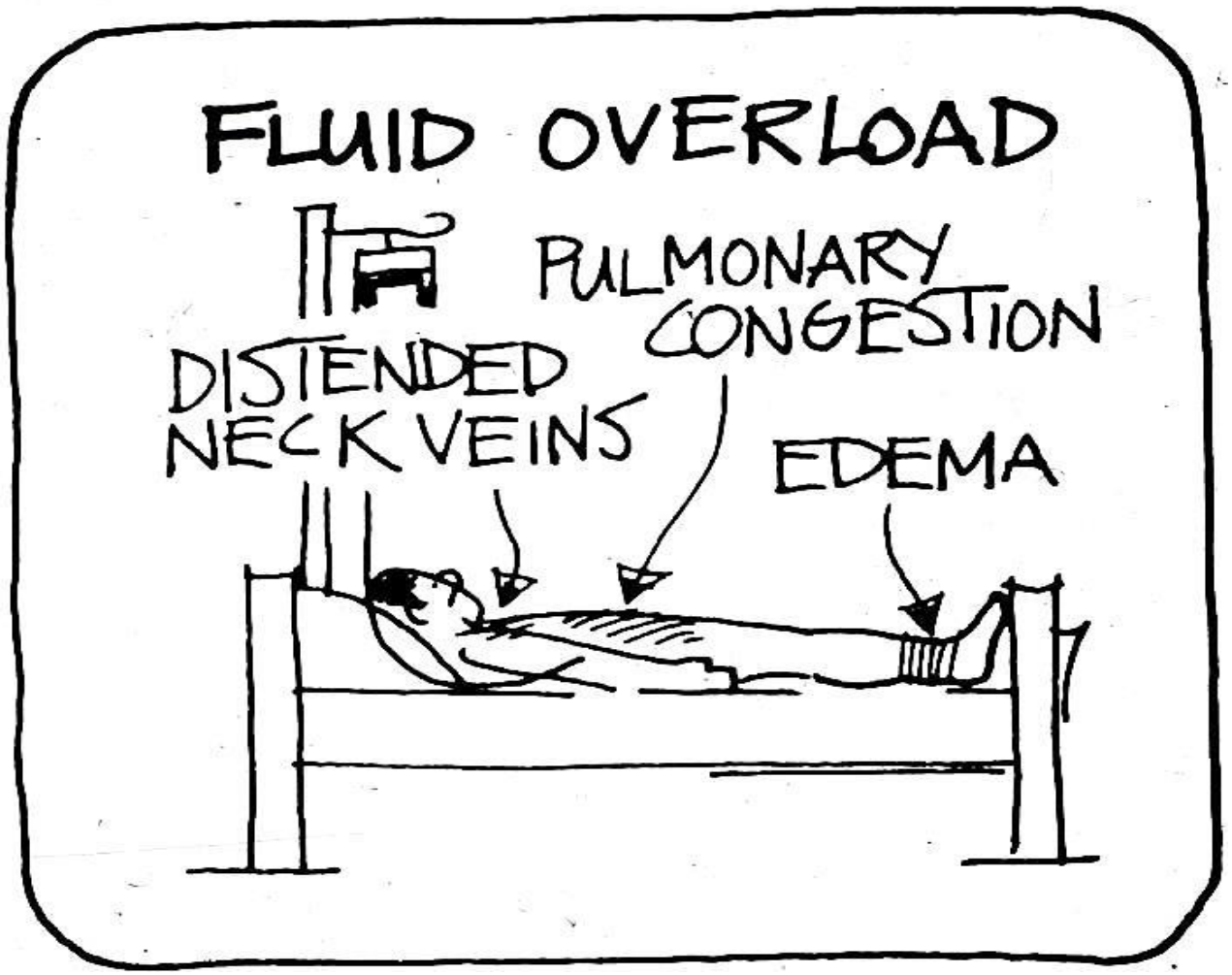
Transfusional Hypervolemia, *aka* TACO



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Transfusion Reactions with Respiratory Symptoms: TACO

Risk Factors

- Patient demographics
  - Age (60% ≥ 70 years of age)
  - ≥ 80 years, **4-fold higher** rate (7.4% vs. 2.0%)
  - 1 : 68 – 1 : 1566 risk in **plasma recipients**
  - 1 : 356 transfused ICU patients
- Medical Conditions (critically ill vulnerable)
  - Chronic renal failure (OR **27.0**)
  - Left ventricular dysfunction (OR **8.23**)
  - Congestive heart failure (OR **6.6**)
  - Blood transfusion (OR **1.11** / unit)
- Perioperative setting (4.3% incidence)
  - Vascular, transplant & thoracic surgeries highest rates
  - Increasing transfusion volumes
  - Positive fluid balance

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Transfusional Hypervolemia, *aka* TACO

- **Must Be Distinguished from TRALI**
- **TACO Kills!!**
- **<u>Some Distinguishing Characteristics</u>**
  - **Usually affects patients at the age extremes**
  - **Evaluate fluid status (I's & O's)**
  - **Evaluate BNP**
  - **SOB, pulmonary congestion, distended neck veins, cyanosis, peripheral edema**
- **<u>Preventive Measures</u>**
  - **Avoid transfusions!**
  - **Slower transfusion rates**
  - **Aliquoting components**
  - **Concomitant diuresis / volume reduction**

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Comparing TRALI & TACO

	TRALI	TACO
Similar Features		
• Chest X-ray	Diffuse bilateral infiltrates	Diffuse bilateral infiltrates
• Respiratory Symptoms	Acute dyspnea	Acute dyspnea
• Auscultation	Rales	Rales

TRALI = transfusion-related acute lung injury;
TACO = transfusion-associated circulatory overload

Skeate RC, Eastlund T, Distinguishing between transfusion-related acute lung injury and transfusion-associated circulatory overload, *Curr Opin Hematol* **2007**;14: 682-87.

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Comparing TRALI & TACO

	TRALI	TACO
Disparate Features		
• Temperature	Often elevated	Often unchanged
• Blood pressure	Hypotension	**Hypertension**
• Pulmonary artery occlusion pressure	≤ 18 mm Hg	> 18 mm Hg
• Response to diuretic	Minimal	Significant
• WBC count	May have transient leukopenia	Unchanged
• Pulmonary edema fluid	Exudate	Transudate
• Fluid balance	Positive, even, negative	**Positive**

- **Patients with either may lack *typical* features**
- **Patients with TRALI may have TACO features**
- **TRALI & TACI may present concurrently**

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TRALI *vs.* TACO

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TRALI	TACO
Signs & Symptoms • Respiratory distress • Tachypnea • Hypoxemia • Hypotension • **Noncardiogenic** pulmonary edema • Fever • Onset within 6 hours of transfusion **Supporting Data** • B/L pulmonary infiltrates on CXR • Decreased WBC count • *Associated with* HLA and/or Neutrophil Antibodies	**Signs & Symptoms** • Respiratory distress • Tachypnea • Hypoxemia • **Hypertension** • **Cardiogenic** pulmonary edema • Improves with diuretics **Supporting Data** • B/L pulmonary infiltrates on CXR • Pretransfusion **fluid overload** • **Elevated BNP** • Increased heart size • Vascular congestion • Pulmonary wedge P > 18 mm Hg

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Admission Parameters

- 77-y/o female with PMH of invasive ductal breast carcinoma and SLL / CLL, both 4 years PTA
- CBC showed: H & H of 5.8 g/dL & 17.4%; WBC 119 K / µL (98% lymphs); platelets 25 K / µL
- The CLL was "*end-stage*", refractory to all prior treatment attempts
- Patient refused further oncologic therapy!!
- Admitted for evaluation and treatment of cytopenias, specifically the anemia
- Plan was to provide RBC transfusion, then d/c to home or other hospice care.

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Admission Parameters

- Patient had a chronic UTI x 3 months, sinus congestion and a productive cough (no evidence of pneumonia), aFib with RVR
- Transfusion support (cellular components):
  - Irradiation
  - Leukoreduction
  - CMV-seronegative
  - XM-compatible
- Three units of RBC were ordered
- The patient was pre-medicated with 375 mg of acetaminophen

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Three RBC Transfusions Given over an Elapsed 10-Hour Period

#1: Begun 00:45, Completed 03:35		
Vital Signs	**Pre-Txn**	**Post-Txn**
Temp (ºC)	36.3	36.6
Pulse	66	80
BP	**108/53**	**119/55**
Respirations	20	20

#2: Begun 04:10, Completed 07:00		
Vital Signs	**Pre-Txn**	**Post-Txn**
Temp (ºC)	36.6	36.5
Pulse	70	64
BP	**108/54**	**144/80**
Respirations	20	20

#3: Begun 08:00, Completed 10:00		
Vital Signs	**Pre-Txn**	**Post-Txn**
Temp (ºC)	36.5	36.9
Pulse	64	87
BP	**144/80**	**196/84**
Respirations	20	20

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Unintended Consequences

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- 12:00: Anxiety & agitation set in, but breathing normal
- 14:00: Dyspnea & increased WOB began
- 18:00: Cough developed with frothy, bloody sputum, AMS, lethargy, a/w desaturations → intubated & MICU transfer
- New-onset symptoms, associated abnormalities:
  - **Positive** fluid balance - Net I's / O's **+ 2600** mL
  - CXR with cardiomegaly new B/L lower lobe opacities
  - EKG with atrial flutter & new RBBB
  - Troponin I level at **0.69 ng/mL**
  - BNP **743 pg/mL**
- Worsening, refractory hypotension. DNR status & comfort care elected. Patient expired 12 hours posttransfusion.

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And Your Diagnosis Is?

- Narrow Differential
  - **TACO vs. TRALI**
- Reportabilities?
  - To whom would YOU report this event?
    - The Blood Bank, order a "*Transfusion Reaction Work-up*"
    - Your immediate superiors
- To whom is such events required to be reported?
  - Institutional Patient Safety / Risk Management
  - Regional Blood Center (why?)
  - The FDA!!
- One of 3 RBC donors was a female with broad HLA alloimmunization!! (Possible TRALI!)

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What's Being Done to Mitigate Risks of Transfusion?

- Blood Center Donor Qualification, Unit Disease and other Testing:
  - ABO, Rh, antibody screen
  - Serologic tests
    - Syphilis (RPR or VDRL)
    - HBsAg, anti-HBc and anti-HCV
    - Retroviruses: Anti-HIV-1/2, anti-HTLV-I/II
    - Anti-*trypanosoma cruzi* (Chagas' disease)
  - Genomic amplification methods
    - HIV-1
    - HCV
    - HBV
    - WNV
    - Zika virus

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TRALI Mitigation Strategies

- **Provision & transfusion of "*all-male*" plasma**
  - Successful in Europe since 2003
  - Difficult to meet AB plasma demands from *male-only donors*
  - The US incidence of FDA-reported TRALI deaths from plasma has significantly decreased since FY07
  - TRALI deaths still occur with RBC transfusion
- Qualify female platelet donors by testing for HLA and neutrophil antibodies

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Other Risk Mitigation Strategies

- "*Universal*" leukoreduction
  - Reduces FNHTRs
  - Reduces alloimmunization to HLA antigens
  - Reduces platelet refractoriness
  - Reduces risk of CMV transmission
  - Reduces mediastinitis in CT surgery
- "*All male*" plasma selection (reduces TRALI risks)
- HLA / neutrophil Ab screening, female platelet donors
- Supplemental bacteriologic testing of platelets
- Repeat ABO / Rh testing to confirm recipient typing
- Selective recipients protections (e.g. CMV, irradiation)
- Application of pathogen inactivation techniques / products

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What are YOU Prepared to Do to Mitigate Risks of Transfusion?

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- Employ robust specimen & patient identification know-how
- *Discover* the literature: IDENTIFY the evolving evidence base & indications for transfusion therapy!
- Informed consent for transfusion: Describe & weigh risks!
- Limit or avoid transfusion (one element of *Patient Blood Management*)
  - **Don't order 2 when 1 will do!**
- Learn how to appropriately order blood in Epic
- Recognize requirements for surgical blood ordering
- **Report *suspected* Transfusion Reactions to Blood Bank**
- Identify & use our institutional urgent agent reversal strategies in life-threatening bleeding
- *The Pharmacy is your friend*! (Alternatives to transfusion)

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8 Rights of Transfusion Administration

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Transfusion Complications that Kill

- Acute intravascular hemolysis
- **TACO**
- **TRALI**
- Bacterial contamination
- Other microorganism contamination
- Anaphylaxis
- (Hyperhemolytic syndrome)
- Complications of Immunomodulation
- Acute TR graft-vs-host disease

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The Risk Side of the Transfusion Equation

- Blood transfusion is a "*liquid transplant*"
- Blood transfusion risks can be mitigated, but not eliminated (*"**unavoidably unsafe**"*)
- There is always another "*microorganism of the month*" waiting in the wings
- Blood transfusions are the only tissues casually transplanted with the stroke of a *mouse* click
- **The safest transfusion is the one you don't give**

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