TACO vs. TRALI:

Recognition, Differentiation, and Investigation of Pulmonary Transfusion Reactions

Shealynn Harris, M.D.
Assistant Medical Director
American Red Cross Blood Services
Southern Region

Case Presentation

- 74 year-old female with GI bleed
- Transfused
  - 1 unit Apheresis Platelets
  - 4 units RBCs
- During transfusion
  - Difficulty breathing
  - Hypoxia
  - Increased respiratory rate

Considerations: Transfusion Reaction

- **Pulmonary Transfusion Reaction**
  - Transfusion-associated circulatory overload (TACO)
  - Transfusion-related acute lung injury (TRALI)
- **Transfusion Reaction with Pulmonary Symptoms**
  - Allergic (anaphylaxis)
  - Septic Transfusion Reaction

Other Considerations

- **Myocardial infarction**
- **Acute respiratory distress syndrome (ARDS)**
- **Sepsis**
- **Drug reaction**
- **Pneumonia**

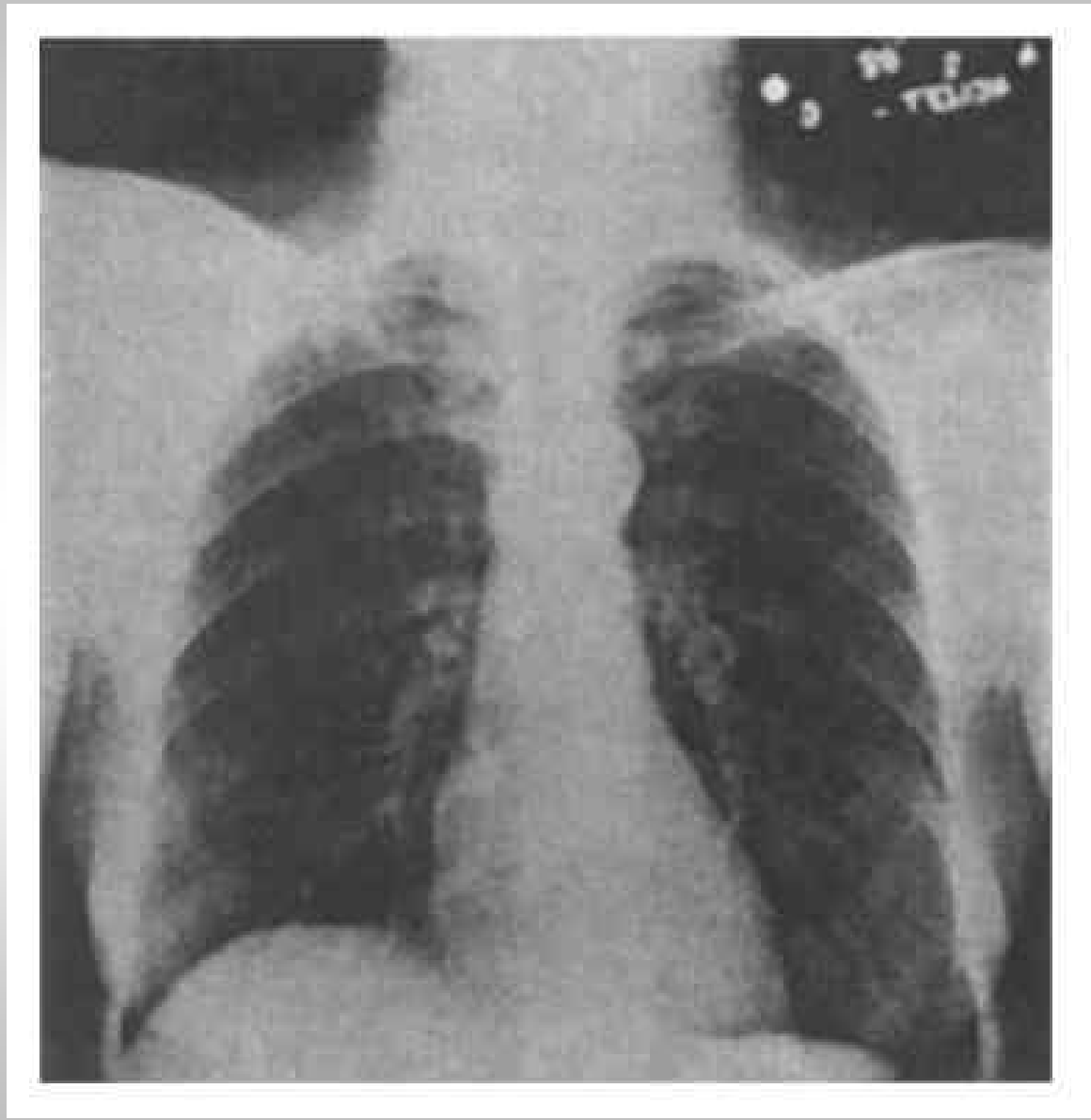
Challenges in Characterizing Pulmonary Symptoms Associated with Transfusion

- Recognizing a transfusion reaction
- Differentiating between possible etiologies
  - Criteria for diagnosis
  - Diagnostic tools
- Contributing factors (e.g., underlying disease)
- Obtaining complete clinical and laboratory information
- Investigating donors and understanding results of investigation

Case Presentation

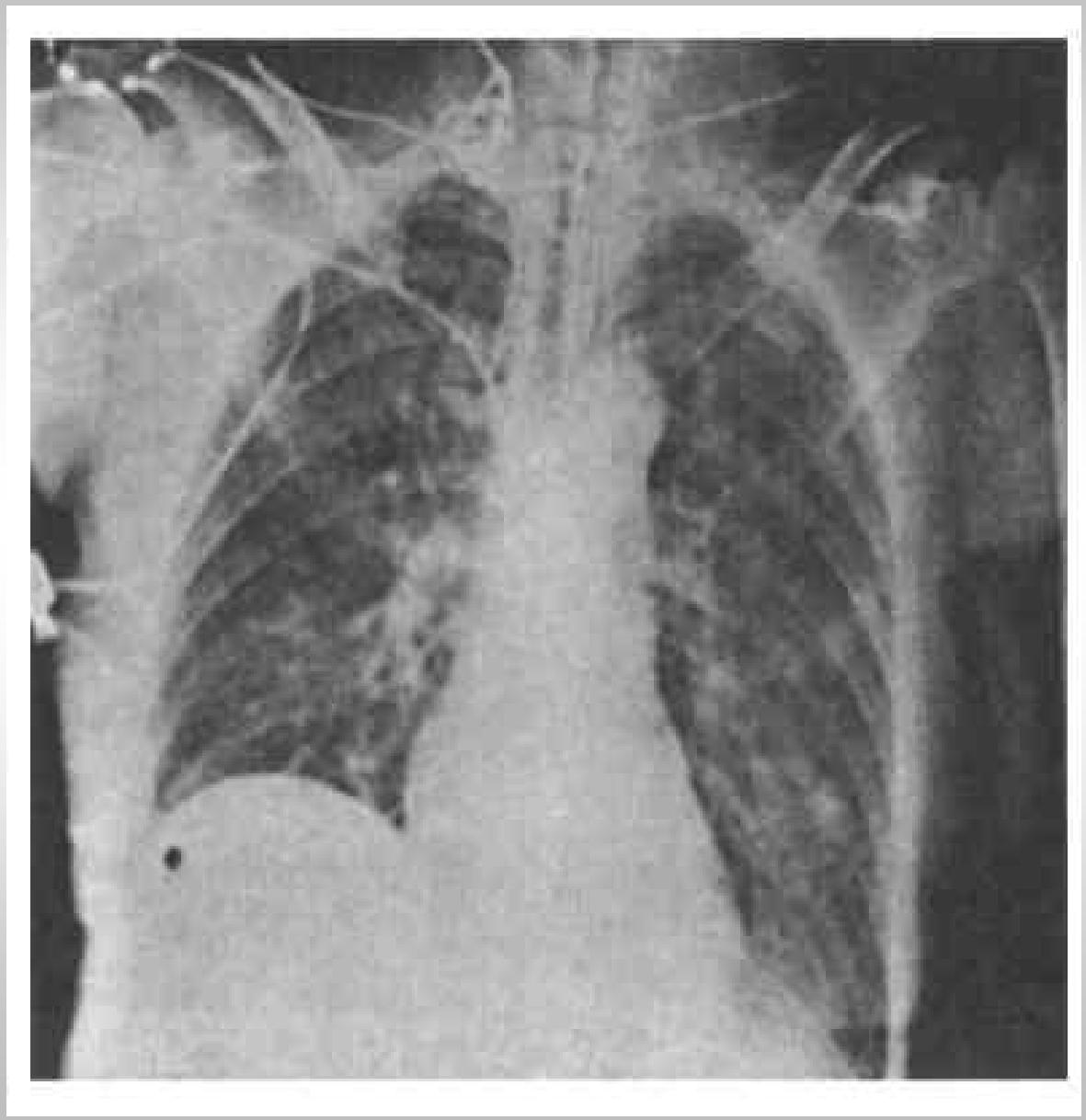
- 74 year-old female with GI bleed
- Transfused
  - 1 unit Apheresis Platelets
  - 4 units RBCs
- During transfusion
  - Difficulty breathing
  - Hypoxia
  - Increased respiratory rate

Pre-Transfusion



Kopko PM, Holland PV. *Br J Haematol*. 1999;105:322-329.

Post-Transfusion

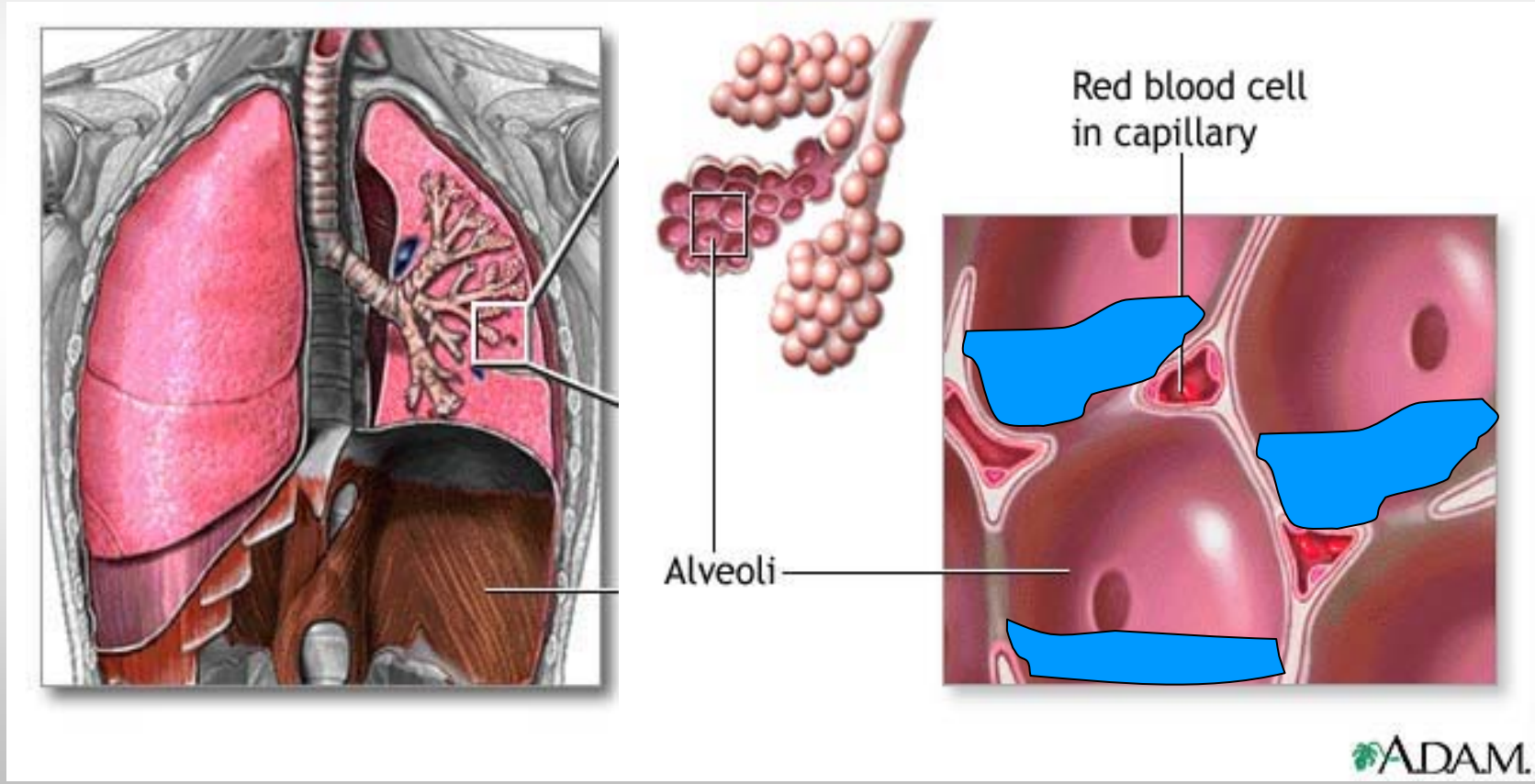


Kopko PM, Holland PV. *Br J Haematol*. 1999;105:322-329.

Transfusion-Associated Pulmonary Edema: TACO vs TRALI

Pulmonary Edema

Abnormal accumulation of fluid in the lung

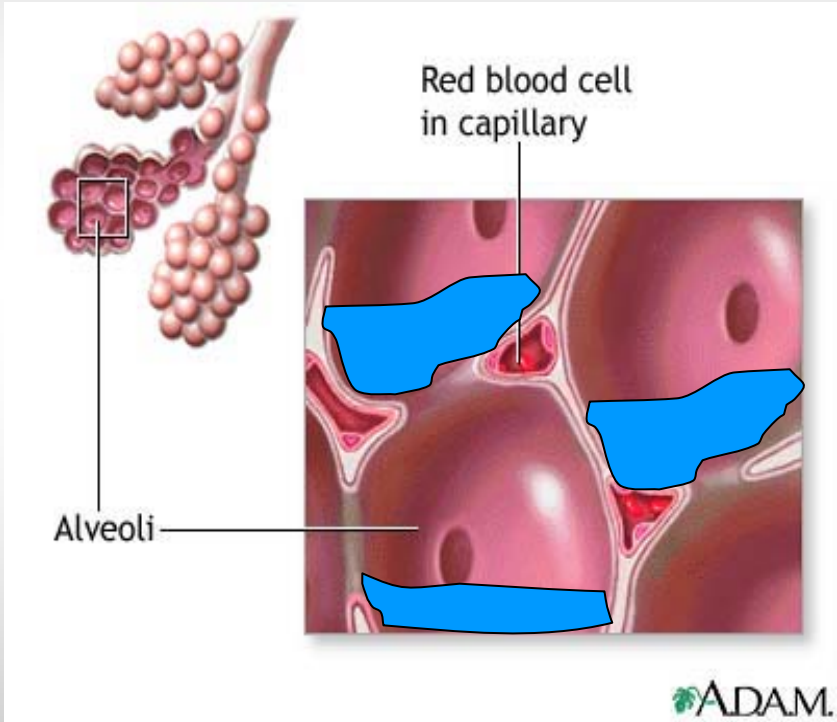


Pulmonary Edema

- **Cardiogenic (hydrostatic)**
  - TACO
  - Myocardial Infarction
- **Non-cardiogenic (permeability)**
  - TRALI
  - ARDS

Transfusion-Associated Circulatory Overload (TACO)

- Volume overload temporally associated with transfusion
- **Signs and Symptoms**
  - Shortness of breath
  - Increased respiratory rate
  - Hypoxemia
  - Increased left atrial pressure
  - Jugular venous distension
  - Elevated systolic blood pressure



Transfusion-Associated Circulatory Overload (TACO)

- **Incidence**
  - Overall: 0.1% - 1%
  - Elderly: up to 8%
  - Critical Care: 2% - 11%

- **Mortality**
  - Estimated 5 - 15%

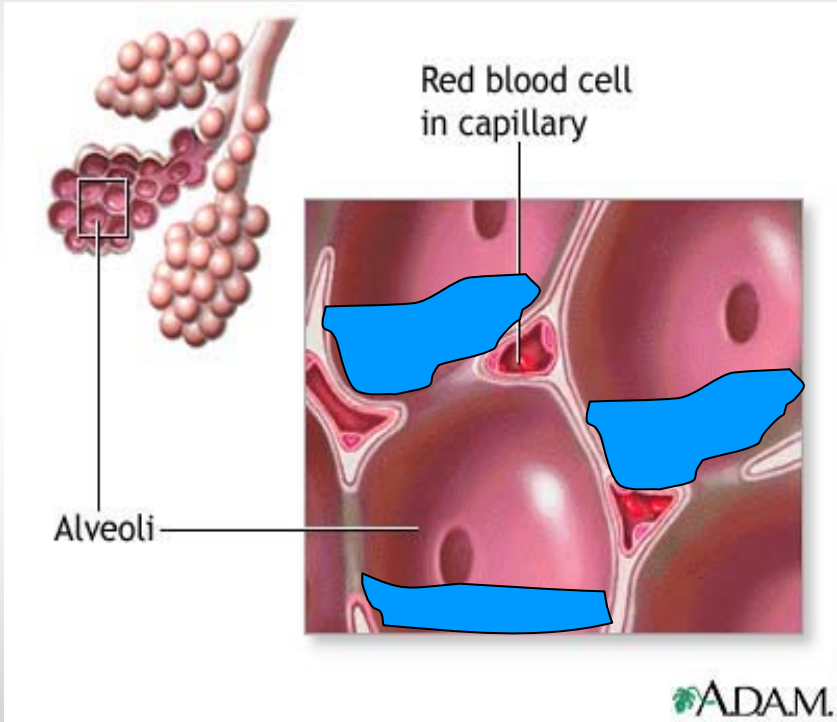
Transfusion-Associated Circulatory Overload (TACO)

- **Treatment**
  - Oxygen
  - Possible intubation and mechanical ventilation
  - Diuresis to reduce volume

- **Also consider Myocardial Infarction**

Transfusion-Related Acute Lung Injury (TRALI)

- Leakage of fluid into alveolar space due to diffuse alveolar capillary damage
- **Signs and Symptoms**
  - Shortness of breath
  - Increased respiratory rate
  - Hypoxemia
  - Hypotension
  - Occasionally fever



Transfusion-Related Acute Lung Injury (TRALI)

- **Incidence**
  - Overall: 0.16% per patient
  - Critical Care: 0.08% per unit transfused
  - Tertiary Care: 0.04% per unit transfused

- **Mortality**
  - Estimated 5% - 10%

Transfusion-Related Acute Lung Injury (TRALI)

- **Treatment**
  - Oxygen
  - Possible intubation and mechanical ventilation
  - Possible fluids to treat hypotension

- **Also consider ARDS**

Transfusion-Related Acute Lung Injury (TRALI)

NHLBI Definition

"**TRALI is defined as new acute lung injury occurring during or within 6 hrs after a transfusion, with a clear temporal relationship to the transfusion**…."

Crit Care Med. 2005 Apr;33(4):721-6.

Transfusion-Related Acute Lung Injury (TRALI)

Canadian TRALI Consensus Conference Definition

- TRALI
  - New occurrence of acute onset acute lung injury (with hypoxemia and bilateral infiltrates on chest x-ray but no evidence of left atrial hypertension
  - Not preexisting BUT
  - Emerging during or within 6 hours of the end of transfusion AND
  - Having no temporal relationship to an alternative acute lung injury risk factor

Transfusion-Related Acute Lung Injury (TRALI)

Canadian TRALI Consensus Conference Definition

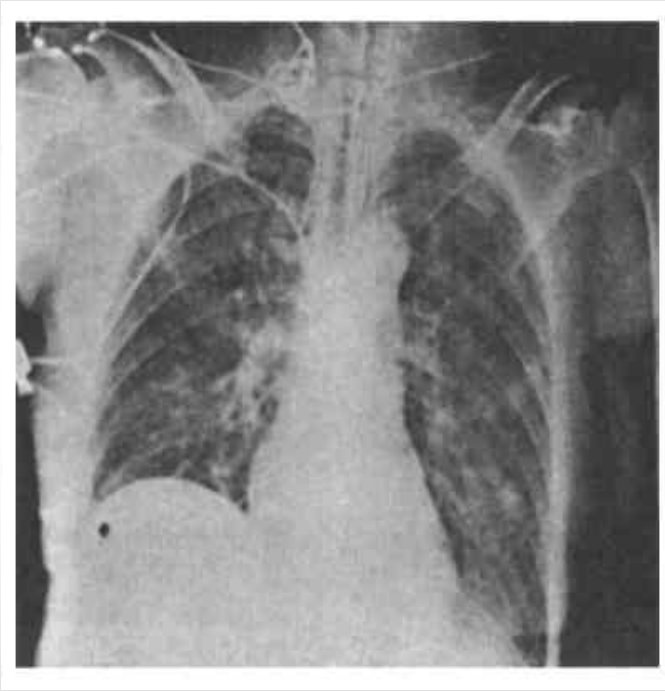
- Possible TRALI
  - Cases in which there was a temporal association with an alternative risk factor

TRALI is a Diagnosis of Exclusion

We must rule out all other possible etiologies before rendering a diagnosis of TRALI

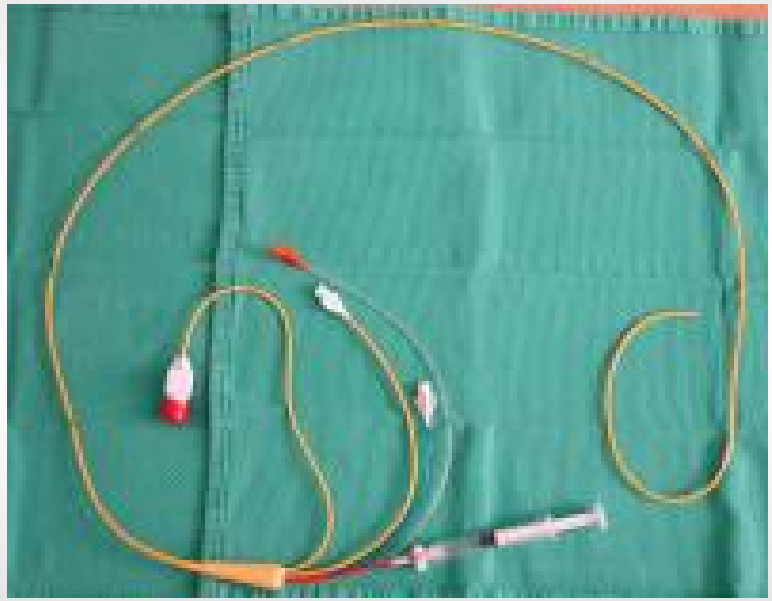
TACO vs. TRALI
Diagnostic Tools: Chest X-ray

- Pros:
  - Identify pulmonary edema
  - Identify pleural effusions (more consistent with TACO)
  - See evidence of other pulmonary disease
- Cons:
  - Does not show specific mechanism of edema
  - Radiology reports are often vague
- Suggested to measure vascular pedicle width and cardiothoracic ratio to improve specificity (never seen this)



TACO vs. TRALI
Diagnostic Tools:
Pulmonary Artery Occlusion Pressure

- Insertion of catheter into pulmonary artery to measure back pressure from heart
- Pros
  - Definitive measurement
- Cons
  - Invasive
  - Increased morbidity and mortality
  - Interobserver variability
  - Lacks sensitivity and specificity



www.emedicine.com

TACO vs. TRALI
Diagnostic Tools: Pulmonary Edema Fluid Protein Concentration

- Small catheter inserted into the alveoli to measure lung fluid protein concentration
- Blood sample to measure plasma protein concentration
- Calculate ratio pulmonary edema/plasma protein concentration
- Pros:
  - Sensitive measurement
- Cons:
  - Mostly used in research
  - Not very feasible in clinical setting
  - Must sample as soon as patient is intubated (difficult timing)

TACO vs. TRALI
Diagnostic Tools:Echocardiography

- Sound waves used to measure heart function
- Pros
  - Not invasive
  - Sensitive and specific for measuring left heart function (ejection fraction)
- Cons
  - Normal test DOES NOT rule out cardiogenic pulmonary edema

TACO vs. TRALI
B-type Natriuretic Peptide (BNP)

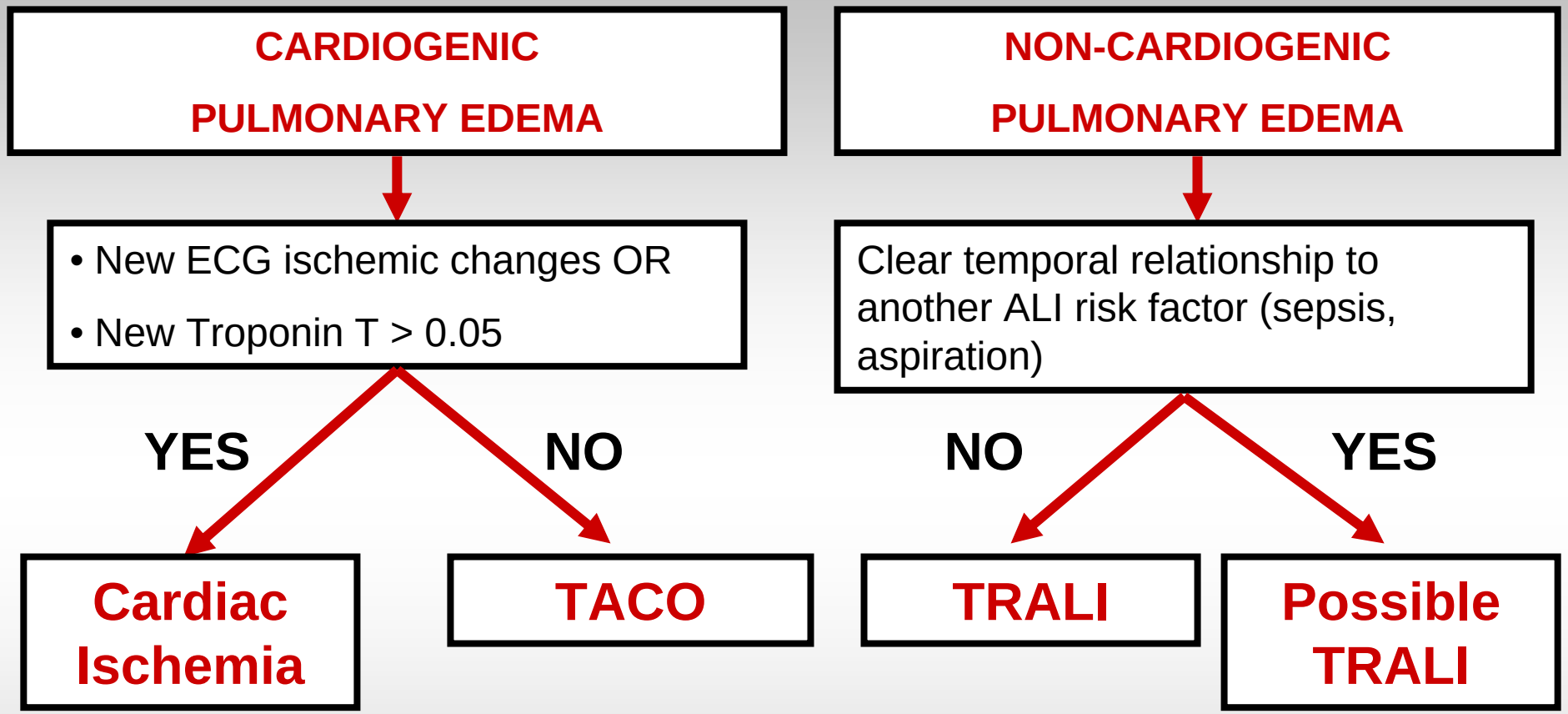
- Hormone released from heart with volume expansion in ventricles from pressure overload
- BNP <250 pg/mL more consistent with TRALI
- Pros:
  - Easy to measure
  - Sensitive and specific indicator of cardiogenic pulmonary symptoms
  - Pre-transfusion to post-transfusion ratio has relatively good sens and spec
  - Can be used to rule out TACO
- Cons:
  - Biological variability
  - Who measures BNP before transfusion?

- New onset hypoxemia: $PaO_2/FIO_2 < 300$ or Arterial Oxygen Saturation <90% on room air
- Chest x-ray: new or worsening bilateral infiltrates consistent with pulmonary edema
- Symptoms started within 6h of transfusion

- Edema/plasma protein concentration >0.65
- Pulmonary artery occlusion pressure <18 mmHg
- BNP < 250 or pre/post transfusion BNP ratio < 1.5
- Absence of rapid improvement with volume reduction (diuretics)
- Two of the following:
  - Systolic ejection fraction >45 and no sever valvular heart disease
  - Systolic BP <160
  - Vascular Pedicle Width <65 mm and Cardio-thoracic ratio <0.55

NO → **CARDIOGENIC PULMONARY EDEMA**

YES → **NON-CARDIOGENIC PULMONARY EDEMA**



Gajic O et al. Crit Care Med 2006;34(5) Suppl: 109-113.

	TRALI	TACO
Dyspnea	YES	YES
Arterial blood gas	Hypoxemia	Hypoxemia
Blood Pressure	Low to Normal	Normal to High
Temperature	Normal to Elevated	Normal
Chest X-ray	White out. Normal heart size. No vascular congestion.	White out. Normal to increased heart size. Vascular congestion. Pleural effusions.
BNP	Low (<250 pg/mL)	High
Pulm artery occlusion pressure	Low to Normal	High
Echocardiogram	Normal heart function	Abnormal heart function
Response to Diuretics	Worsens	Improves
Reponse to Fluids	Improves	Worsens

What about Testing for Donor Leukocyte Antibodies?

Anti-HLA

Anti-Granulocyte (anti-HNA)

TRALI and Leukocyte Antibodies

- Pathogenesis of TRALI is not clear
- Few controlled experimental studies of TRALI
- Lack of in vivo animal model
- Two Hypotheses
  - Donor leukocyte antibodies bind to recipient neutrophils which cause acute lung injury
  - Bioactive lipids in stored blood “prime” neutrophils which cause acute lung injury

Popovsky *et al. Transfusion*; 1985. 25:573-577.

Test	n	%
Granulocyte antibodies		
Patient	2	6
Donor	32	89
Lymphocytotoxic antibodies (donor)	26	72
HLA-specific antibodies	11*	65
HLA-antigen (patient)/antibody correspondence	10*	59

Densmore *et al.* Prevalence of HLA sensitization in female apheresis donors. *Transfusion.* 1999;39:103-106.

Pregnancies	Number Tested	Number Sensitized	Percentage of Women Sensitized
0	103	8	7.8
1	33	5	15.2
2	70	10	14.3
3	58	15	25.9
4	33	10	30.3
>5	27	6	22.2
All women	324	54	16.6

UK SHOT Data

- TRALI risk is 5 to 7 fold greater in components containing high volume of plasma
- Majority of TRALI cases involved leukocyte-antibody positive female donors
- Oct 2003: UK moved to male-only plasma
- Significant reduction in TRALI cases in UK since Jan. 2004

MacLennan S et al. Vox Sang 2004;87(Suppl 3):227.

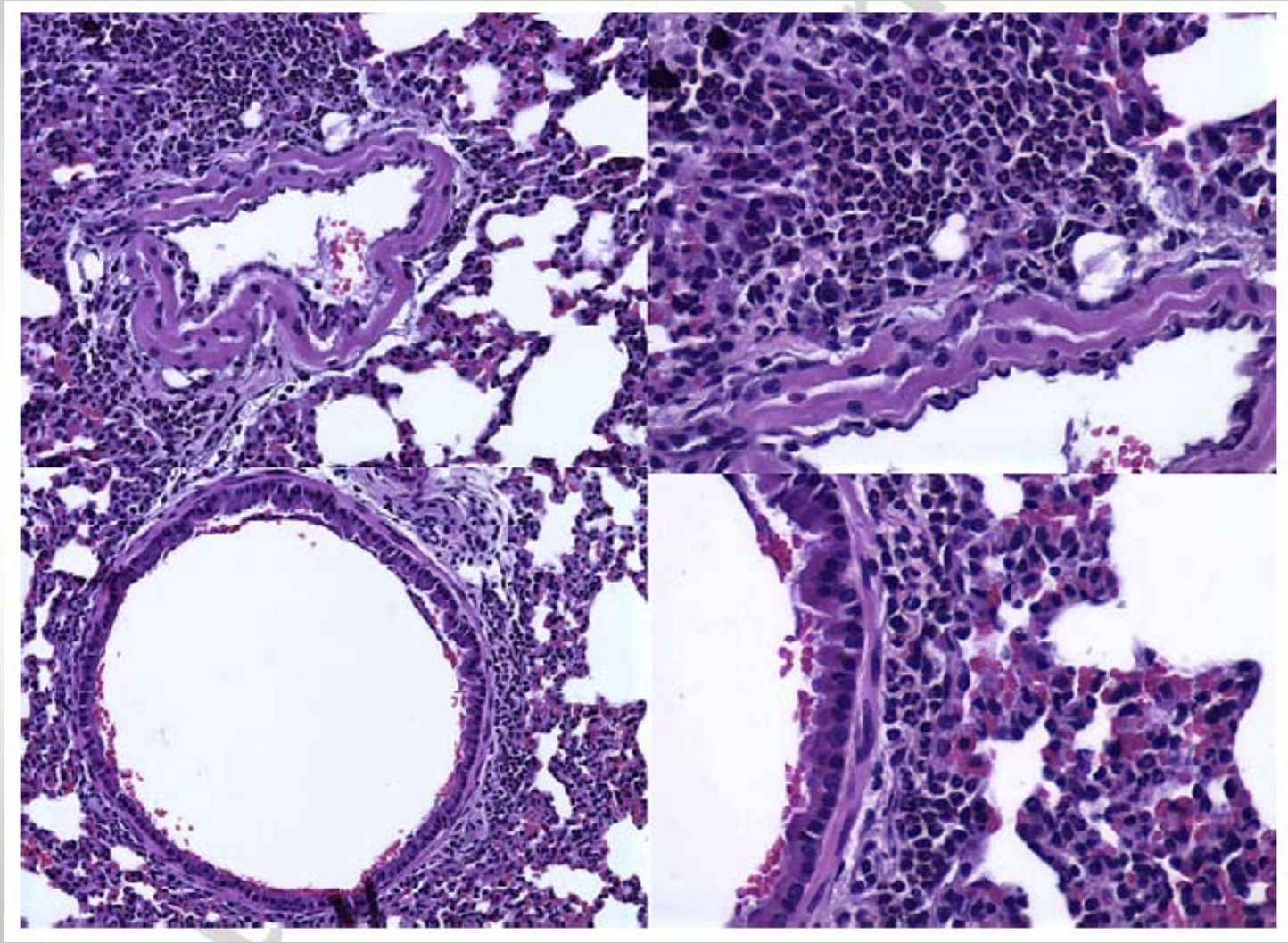
Stainsby D et al. Serious Hazards of Transfusion (SHOT) Annual Report 2004. www.shot-uk.org

ARC Data

- TRALI reports 2003-2005 (n = 550)
- 38 cases of probable TRALI
  - 24 related to plasma transfusion
  - 75% cases involved plasma from leukocyte-antibody positive female donors

Eder A et al. Transfusion 2007 in press.

TRALI: In Vivo Mouse Model



Sheppard CA et al. Hematol Oncol Clin N Am 2007;27:163-176.

Bray RA, Harris SB, Josephson CD, et al. Unappreciated risk factors for transplant patients: HLA antibodies in blood components. Hum Immunol 2004;65(3):240-4.

Components (n)	Class I n (%)	Class II n (%)	Class I & Class II n (%)	Total n (%)
RBCs (106)	7 (7)	8 (8)	3 (3)	18 (17)
Cryo (66)	3 (5)	3 (5)	10 (15)	16 (24)
Plts (59)	7 (12)	5 (9)	1 (2)	13 (22)
FFP (77)	9 (12)	4 (5)	9 (12)	22 (29)
All Components (308)	26 (8)	20 (7)	23 (8)	69 (22)

Challenges

- No clear test for TRALI
- Leukocyte antibody positive donor DOES NOT equal TRALI diagnosis
- Incidence of HLA antibodies in donors is very high relative to number of TRALI cases
- Many TRALI cases are not associated with leukocyte antibodies
- Massive transfusion: odds are high that at least one donor will be positive

Case Presentation

- 74 year-old female with GI bleed
- Transfused
  - 1 unit Apheresis Platelets
  - 4 units RBCs
- During transfusion
  - Difficulty breathing
  - Hypoxia
  - Increased respiratory rate

Investigation of Pulmonary Transfusion Reactions

- Rule out EVERYTHING before diagnosing TRALI
- Clinical Presentation: Need as much information as possible
- Timeline of Events: Temporal relationship of transfusion to symptoms
- Diagnostic Studies: Chest x-ray, BNP, Echocardiogram, Blood cultures
- Donor Testing: only if highly suspicious for TRALI
  - Male donor: no testing unless transfusion hx
  - Female donor: if test positive, then defer
  - HLA crossmatch positive: more supportive of TRALI

Summary

- Several etiologies to consider with pulmonary symptoms during transfusion
- Pulmonary edema within 6 hrs of transfusion consider TACO and TRALI
- Consider clinical presentation and all diagnostic studies
- No specific diagnostic study
- TRALI is a DIAGNOSIS OF EXCLUSION
- TRALI is not diagnosed by positive leukocyte antibody test alone