Transfusion-Related Acute Lung Injury: An Update

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Transfusion Complications & Lung

- Lung not typically viewed as a target of injury

- Pulmonary complications include

  - Anaphylactic and allergic reactions

  - Circulatory overload

  - Hemolytic transfusion reactions (infrequent)

  - Bacterial contamination (rare)

  - Transfusion-related acute lung injury

TRALI: Clinical/Laboratory Features

Symptom/Sign	Frequently
Dyspnea/respiratory distress	Very common
Hypoxemia	Very common
Pulmonary edema	Very common
Hypotension	Very common
Fever (1-2° increase)	Very common
Tachycardia	Common
Cyanosis	Common
Hypertension	Uncommon
Leucopenia	?
Hypocomplementemia	?
Monocytopenia	?

Adapted from Webert K & Blajchman. TMR 2003;17

What is TRALI?

Predominant presenting symptoms (N=46)

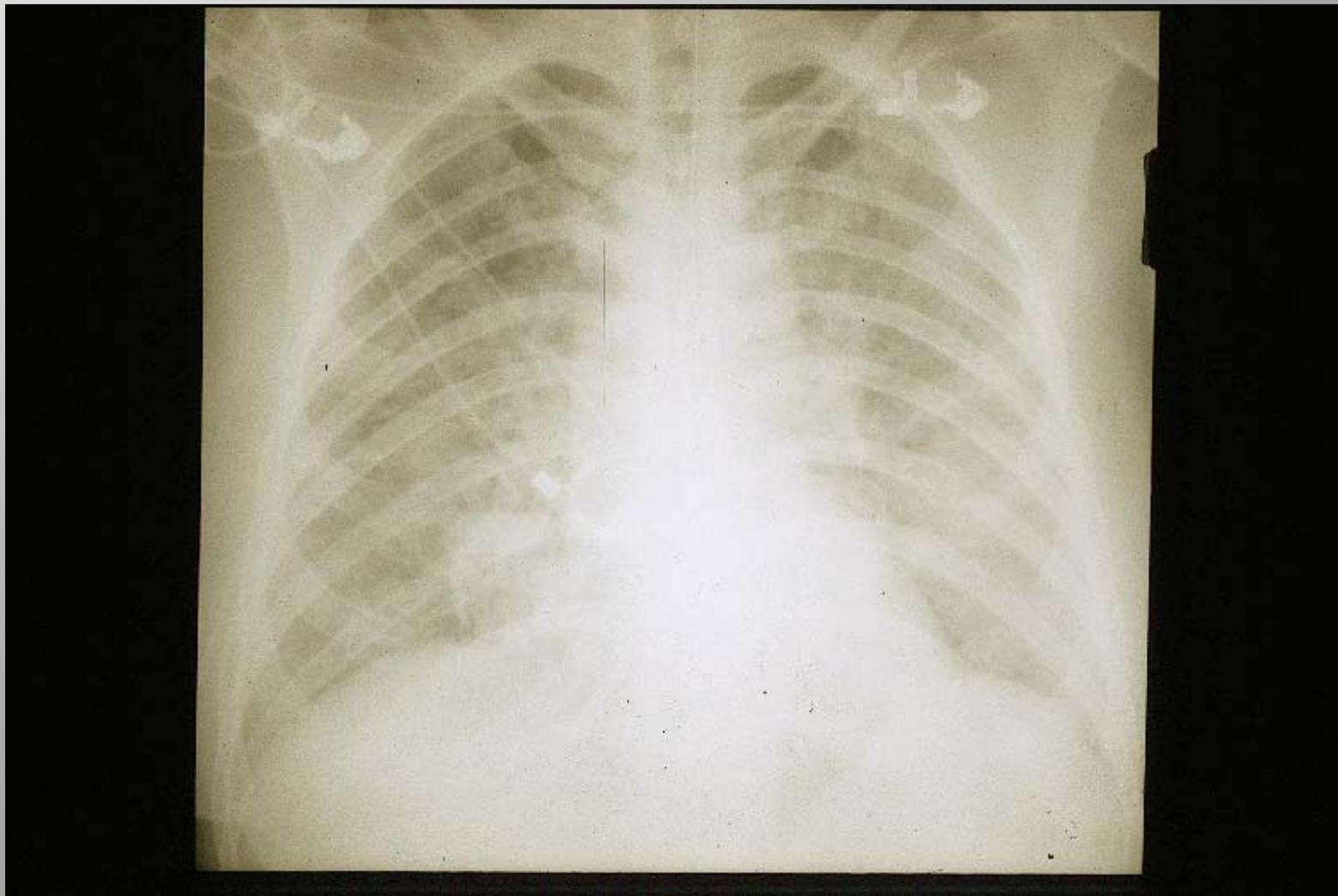| Sign/Symptoms	%
Respiratory distress	76
Hypotension	15
Hypertension	15

[Popovsky & Haley, Immunohematology 2000;16]

Clinical Features

- Timeline: Symptoms from onset of transfusion

  ➢ >90% of cases within 1-2 hours

  ➢ 100% of cases within 6 hours

- Plasma-containing transfusions

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

Chest X-ray

Clinical Features (cont.)

- Hypotension does not respond to intravenous fluids

- Rales and diminished breath sounds

No fluid overload

- Normal jugular venous pressure

- Absent S3

- Normal/low pulmonary wedge pressure

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Implicated Blood Products

- Whole blood

- FFP

- RBC (all anticoagulant/preservatives)

- Granulocytes (by apheresis)

- Cryoprecipitate (rare)

- Platelet concentrate

- Plateletpheresis

- IVIG (rare)

Most Frequent Implicated Blood Products

- Red Blood Cells

- Fresh Frozen Plasma

- Apheresis platelets

- Platelet concentrates

TRALI: The Earliest Definition

- Acute respiratory distress

- Hypoxemia: PaO_2 of 30-50 torr

- Bilateral pulmonary edema: rapid onset

- Hypotension: moderate

- Fever

- Within 6 hours of a plasma-containing transfusion

- Exclusions: Underlying cardiac failure/respiratory disease

Popovsky & Moore: 1983 & 1985 (Transfusion & Amer Rev Resp Disease)

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Clinical Course

Morbidity	N	%
Required oxygen support	36	100
Required mechanical ventilation	26	72
Pulmonary infiltrates		
Rapid resolution (≤ 96 hrs)	29	81
Slow resolution (> 7 days)	6	17
Mortality	2	6
Long-term sequelae	0	

Popovsky & Moore, Transfusion 1985;25:573-577

FDA: Average of Key Causes of Death FY01 – FY03

- TRALI

  ✓ 16.3%

- ABO/Hemolytic Transfusion Reactions

  ✓ 14.3%

- Bacterial Contamination

  ✓ 14.1%

Mortality Rate

- Popovsky
- Silliman
- Holness
- Wallis
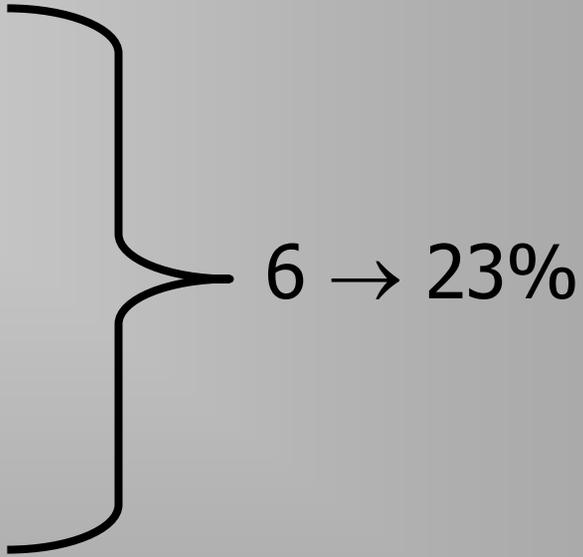
$6 \rightarrow 23\%$

TRALI: Incidence

- 1982 -1985: 1:5,000 plasma-containing transfusions

    - Mayo Clinic: "Educated" Medical Center

    - Specially trained nurses administer non-operating room transfusions

- Current incidence unknown

TRALI: Incidence

Risks per 100,000 Units & Patients for TRALI				
Study	Years	# cases	Risk per 100,000 units	Per 100,000 Patients
Popovsky	1982-1985	36	20	160
Weber	1985-1993	8	----	42
Clarke	1991-1993	46	320	----
French Hemovigilance	1995-2000	7	----	1.4
SHOT	2000-2001	RBC 6	0.25	----
		PLT 3	1.38	

Adapted from Kleinman S. TMR 2003;17:120-162

Under-reported

➤ Retrospective chart review of 50 patients receiving blood from a donor linked to fatal TRALI

➤ Outcome measure:

- Mild/moderate: dyspnea/hypotension, +/- hypoxemia

- Severe: Acute pulmonary edema/mechanical ventilation

Kopko et al. JAMA 2002;287:1968

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Under-reported (cont.)

- ➢ 36 chart reviews included

- ➢ 7 mild/moderate reactions (16.7%)

- ➢ 8 severe reactions (22.2%)

- ➢ 2 had 2 reactions

- ➢ Only 2 of 8 severe reactions reported to transfusion service

Kopko et al. JAMA 2002;287:1968

Who is at Risk?

- Male: Female = 1:1
- No age predilection
- No disease or diagnosis predilection
- No medication pattern
- Multiple transfusions?
- Transfusion?

Admitting Diagnosis of 58 TRALI Fatalities

Diagnoses (n = 58)	Number	Percent
Cardiopulmonary	20	36
Hematological disorder	19	32
Diabetes and end-stage renal disease	5	9
Cancer	4	7
Other (fever, gastrointestinal bleeding, AIDS)	6	10
Diagnosis not provided	4	7

L Holness et al. Transfusion Medicine Reviews 2004;18:184-188

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Spectrum of Clinical Presentation

Mild	Severe
Dyspnea Fever	Dyspnea Hypoxemia Pulmonary Edema Hypotension Fever

Laboratory Findings

Pre-Mayo Studies (before 1983 – 1985)

	Leukoagglutinating Antibodies	Lymphocytotoxic
Donor	+	+
Recipient	+	+

Laboratory Findings (cont.)

1980's Mayo Clinic Studies

Reference	Findings
1983 (N = 5)	•Donor Class I •HLA antibodies in 4/5 •Leukoagglutinating Antibodies in 5/5 • Antibody/Antigen correspondence in 3/5
1985 (N = 36)	•Donor Class I •HLA/leukoagglutinating in 89% •Aby/Ag correspondence in 59% •Recipient antibody in 6%

TRALI: Pathogenesis

Increased Microvascular Permeability

Leukocyte Antibodies

**Bioactive Lipids
(2 "hit" model)**

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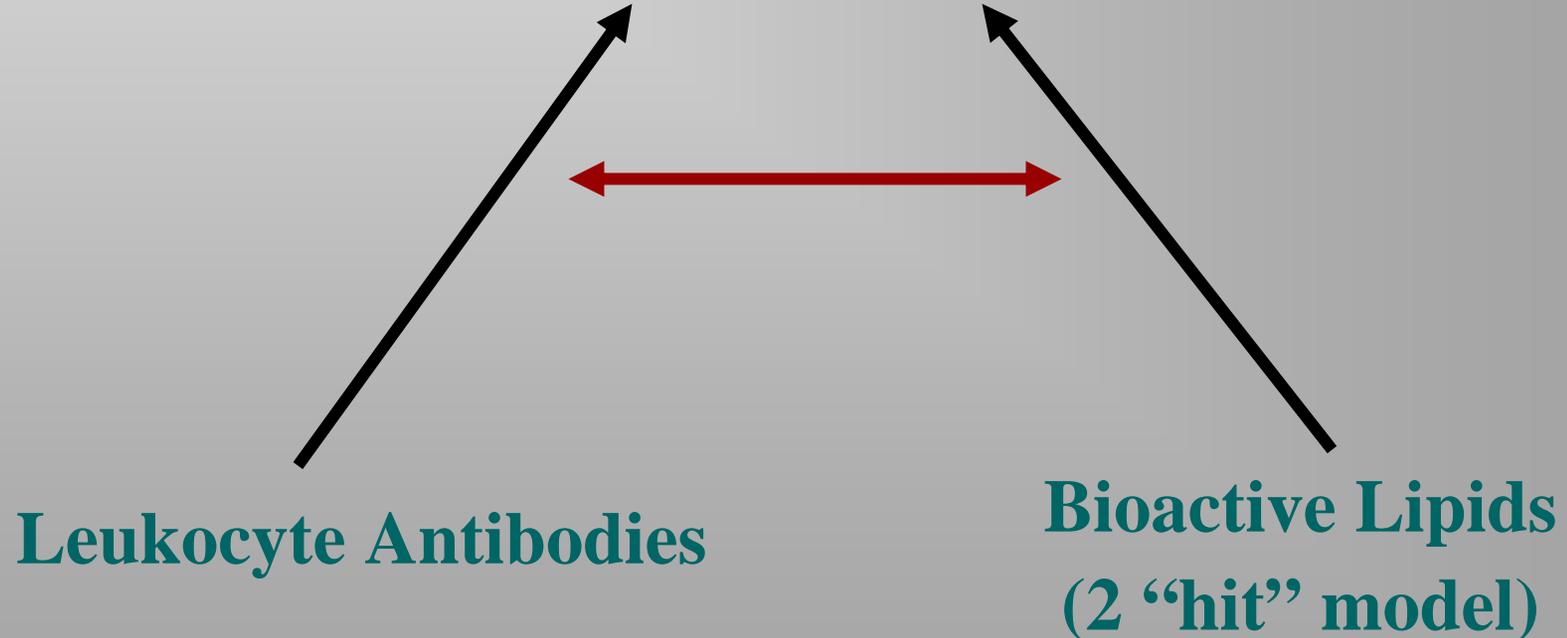
Pathogenesis

HLA Class I/Granulocyte Antibodies

- Precise mechanism is unknown

- Donor HLA or granulocyte-specific antibodies (anti-NB2, -NA2, -5b): 60-85% of cases

- HLA antibody/antigen correspondence: 50% of cases

- Antibodies activate complement

24

Pathogenesis (1)

HLA Class I/Granulocyte Antibodies

- C5a promotes neutrophil aggregation/sequestration in microvasculature of lung

- There is margination of neutrophils in pulmonary microvasculature

- Activated neutrophils release proteases, superoxide radicals: results in endothelial cell injury $\rightarrow$ pulmonary edema
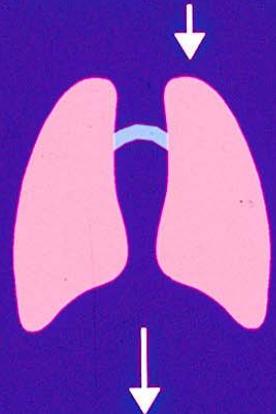
Pathogenesis (2)

TRALI EX VIVO LUNG MODEL

Perfusate

Exp. Protocol

Evaluation of Lung injury

5b pos PMN + Anti-5b + Complement
(human)   (human)   (rabbit)

Rabbit lungs perfused for a 6 hrs

Repetitive hydrostatic challenges performed at timed intervals

Measurements of:

Pulmonary Artery Pressure

Lung weight gain

Seeger et al, Blood:76, 1990

Clay

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Pathogenesis (3)

Pathogenesis (4)

- 14 of 16 cases (87.5%) demonstrated antigen-antibody correlation (class I or II)

- In 6 cases TRALI monocytes incubated with <u>implicated</u> TRALI serum, expressed significantly greater cytokine and tissue factor

(Transfusion 2003;43:177-184)

Pathogenesis (5)

Role of Multiparous donor plasma

- Prospective, randomized study

- 102 ICU patients receiving $\geq$ 2 units FFP

- Multiparous ($\geq$ 3 pregnancies) donors vs. controls

- 5 patients had clinical reactions $\rightarrow$ 1 TRALI

    - Donor was multiparous

- $\downarrow$ PaO_2/FiO_2 (p< 0.05) in multiparous-donor vs. control plasma

(Palfi et al, Transfusion 2001:41)

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TRALI: Antibody & Severity

	% with Antibody
Recovered without ventilation	45%
Recovered with ventilation	69%
Death	77%

J Freedman (Hema Quebec): Personal correspondence

Pathogenesis: 2-Hit Model

1st Event   Pulmonary endothelial
                             activation (underlying
                             condition)

                                    ↓

2nd Event   Infusion of BRM from
                             stored blood

                                    ↓

                             Acute Lung Injury

U.K. Developments

- 89% of investigated TRALI cases associated with leukocyted antibodies

- Excess of cases attributed to FFP or platelets (47%) compared to total units issued (25%)

- Of FFP & platelet cases, 91% included leukocyte antibody-positive female donors

- Now "diverting" female plasma away from FFP production

- "Male only" FFP

What Needs To Be Done?

- Identify patients at risk

- Identify donors at risk

  - Screen multiparous donors (for platelet/FFP products) for HLA/granulocyte antibodies?

  - Screen transfused donors?

- Develop a product management scheme

  - Defer implicated donors

  - Wash/freeze RBC from implicated donors

  - Divert plasma from females or antibody-positives?

Conclusion

➢ TRALI is an under-diagnosed, under-reported serious problem

➢ Represents a spectrum of lung injury (NCPE → ARDS)

➢ Antibody-mediated injury is primary mechanism of injury

➢ Several pathogenic models may be operative

➢ Prospective, multicenter studies needed

➢ Proactive steps are needed to reduce risk