# Risks of TRALI and TA-GvHD related to the use of Fresh Whole Blood.

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# Transfusion related acute lung injury – TRALI

- **Definition:**
  - Acute lung injury occurring **within 6 hours after transfusion**, without the presence of circulatory overload or any other evident cause
- **Etiology and pathogenesis:**
  - **Immune mechanism** – (little significance for FWB from fellow military personel)
    - Reaction between **anti-HLA** (anti-leukocyte antibodies) or **anti-HNA** (anti-neutrophil granulocyte antibodies) **in a blood component** (plasma unit or plasma remaining in an erythrocyte- or thrombocyte unit) and their antigens **in the recipient**
    - A **prerequisite** is the **pretransfusion presence of lung pathology** implying **accumulation of leukocytes / granulocytes**. The antigen-antibody reaction induces an **acute local inflammatory reaction.**
  - **Alternative, non-immune mechanism:** Activation of locally accumulated neutrophile granulocytes in otherwise caused lung pathology, by **bioactive lipids** released from

# Transfusion related acute lung injury – TRALI



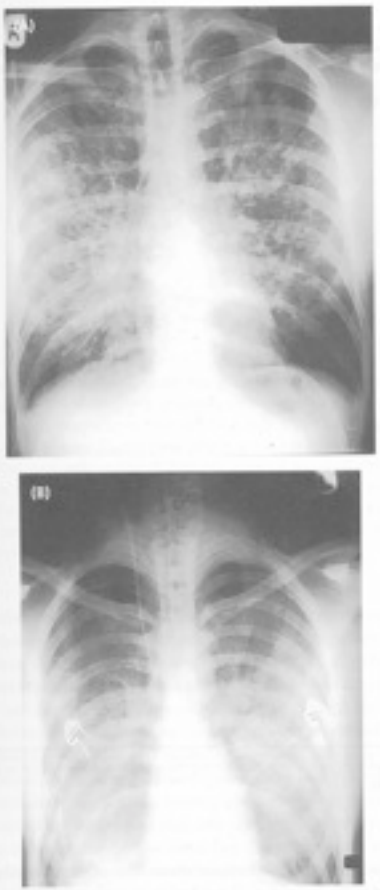


**Figure 56-1.** Chest x-rays from a 33-year-old man with severe TRALI, taken 2 hours (A) and 24 hours (B) after onset of symptoms, following transfusion of FFP containing HLA Class II antibodies. Note the "bat's wing" pattern of edema with sparing of the lung bases, and the air bronchograms clearly visible on the first radiograph, and the more confluent airspace shadowing but still with basal sparing in the second x-ray.

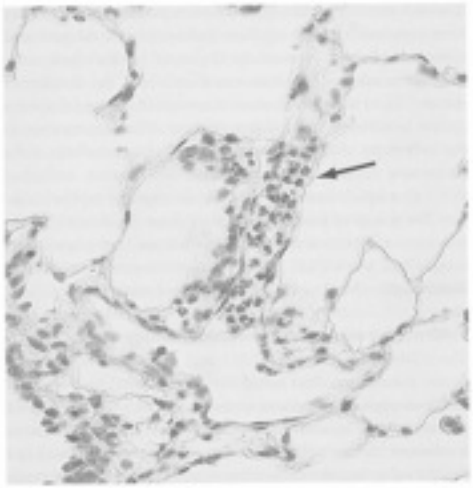


**Figure 56-2.** Sections of lung from a fatal case of TRALI. Note the presence of granulocytes in the capillaries (arrow indicates neutrophils).

## Pathophysiology

### Acute Lung Injury

ALI is the result of a capillary endothelial leak that allows fluid to pass from the pulmonary vessels, initially into the interstitial space and subsequently into the alveolar space. Because this edema is distinct from hydrostatic edema caused by cardiac failure or volume overload, it is sometimes known as nonhydrostatic edema. Numerous stimuli have been suggested to contribute to the likelihood of developing nonhydrostatic pulmonary edema including sepsis, trauma, aspiration of gastric contents, disseminated intravascular coagulation, and high tidal volume ventilation. In some cases of TRALI the transfusion appears to be the only probable cause of the lung injury, whereas in other cases it may be only one of several possible factors present. Histopathology, clinical findings, and experimental work have helped elucidate the nature of the stimulus from the transfused blood and the mechanism of the lung damage.

# Degree of seriousness (UK) (Haemovigilance system "SHOT")

**Mortality: 16.3%**

**Mortality: 100%; all patients immunocompromised; all cases reported 1996–2001**

Table 10
Cumulative mortality/morbidity data 1996–2009
*NB TACO, TAD and autologous are new since 2008, and HSE and I&U were separated from IBCT in 2008*

| | Total | IBCT | I&U | HSE | ANTI-D[†] | ATR | HTR | TRALI | TACO | TAD | PTP | TA-GvHD | TTI | AUTOL-OGOUS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Death in which transfusion reaction was causal or contributory | 138 | 27 | 4 | 0 | 0 | 19 | 11 | 42 | 5 | 0 | 2 | 13 | 15 | 0 |
| Major morbidity probably or definitely attributed to transfusion reaction (imputability 2/3) | 495 | 116 | 3 | 0 | 25 | 58 | 48 | 165 | 18 | 1 | 13 | 0 | 48 | 0 |
| Minor or no morbidity as a result of transfusion reaction | 5998 | 3439 | 161 | 335 | 361 | 1154 | 383 | 50 | 29 | 4 | 34 | 0 | 6 | 42 |
| Outcome unknown | 15 | 11 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **TOTAL*** | **6646** | **3593** | **168** | **335** | **386** | **1234** | **443** | **257** | **52** | **5** | **49** | **13** | **69** | **42** |

**Total excludes 7 cases from 1998–1999 that were not classified*
*[†]Cases with potential for major morbidity included in the Anti-D data are excluded from this table*

No consistent use of leukocyte filtered components until 2000

**3.9% of all reports**

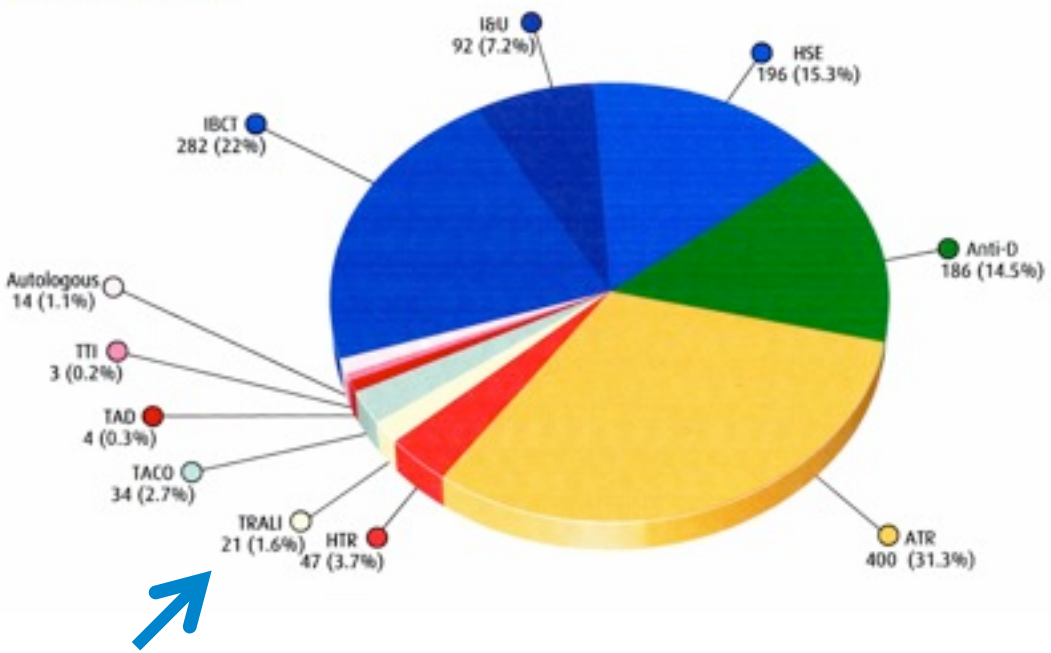
**0.2% of all reports**

# Recorded transfusion complications UK 2009 ("SHOT")

Table 7
Summary of reports reviewed 2009

| IBCT | I&U | HSE | ANTI-D | ATR | HTR | TRALI | TACO | TAD | PTP | TA-GvHD | TTI | AUTO-LOGOUS | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 282 | 92 | 196 | 186 | 400 | 47 | 21 | 34 | 4 | 0 | 0 | 3 | 14 | 1279 |

Figure 4
Cases reviewed *n* = 1279




13/21 TRALI without detected antibodies; no FWB used

Introduction of prestorage leukocyte filtered blood components has reduced TRALI by >60% and prevented GVHD completely

# TRALI diagnostics

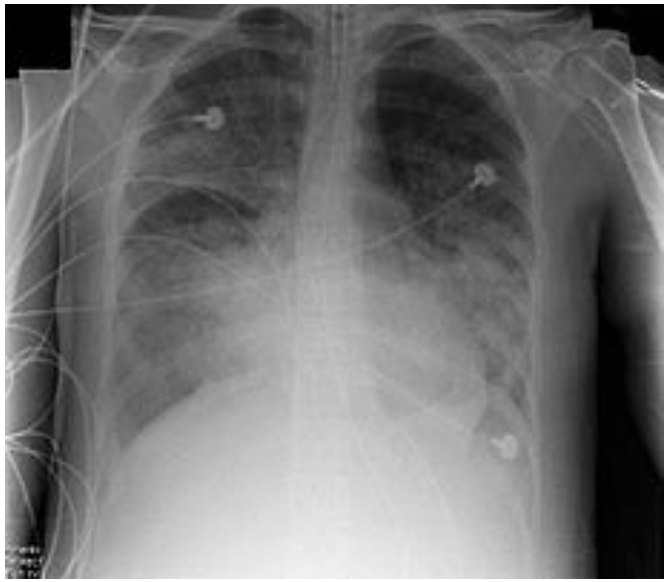
- **Diagnosis:**
  - Purely clinical, there is no diagnostic test
  - Underdiagnosed?

- **Differential diagnosis:**
  - **Acute respiratory distress syndrome (ARDS)**
  - ARDS can occur within 24 to 48 hours of an injury (trauma, burns, aspiration, massive blood transfusion, drug/alcohol abuse) or an acute illness (infectious pneumonia, sepsis, acute pancreatitis).
  - Acute onset
  - Bilateral infiltrates on chest radiograph sparing costophrenic angles
  - Pulmonary artery wedge pressure < 18 mmHg (obtained by pulmonary artery catheterization), if this information is available; if unavailable, then lack of clinical evidence of left ventricular failure suffices

# ARDS (Acute Respiratory Distress Syndrome)

ARDS can occur within 24 to 48 hours of an injury (trauma, burns, aspiration, **massive blood transfusion**, drug/alcohol abuse) or an acute illness (infectious pneumonia, sepsis, acute pancreatitis). ARDS patients usually presents with shortness of breath, tachypnea and occasionally confusion.

Long term illnesses, such as malaria, can also trigger ARDS, which may then occur sometime after the onset of a particularly acute case of the infection.



ARDS is characterized by:[1][3]

Acute onset
Bilateral infiltrates on chest radiograph sparing costophrenic angles
Pulmonary artery wedge pressure < 18 mmHg (obtained by pulmonary artery catheterization), if this information is available; if unavailable, then lack of clinical evidence of left ventricular failure suffices
if $PaO_2$:$FiO_2$ < 300 mmHg (40 kPa) acute lung injury (ALI) is considered to be present
if $PaO_2$:$FiO_2$ < 200 mmHg (26.7 kPa) acute respiratory distress syndrome (ARDS) is considered to be present

**To summarize and simplify, ARDS is an acute (rapid onset) syndrome (collection of symptoms) that**

# Lung Injury Score and transfusion

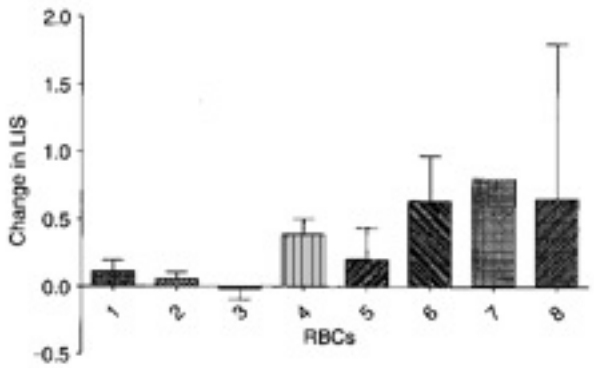



**Fig. 1.** Relationship (199 RBC transfusions in 83 patients) between number of RBC units given per transfusion and mean change in LIS between prior to and within 24 h after transfusion ($r = 0{\cdot}869$, $P = 0{\cdot}0051$). Whiskers represent SEM.

NB! Only leukocyte filtered, but stored, components applied!

Popovsky et al. Transfusion Medicine 2010; 20 (4): 221-6

No report found on TRALI or on frequency of lung complications in relation to FWB transfusion – i.e. **TRALI or other lung complications have never been reported as induced by FWB transfusion**

# TRALI, bioactive substances and FWB transfusion

- **Hypothesis:** There is a gradual and dose-related connection between amount of bioactive substances transfused and lung complications.
  - **TRALI** is a **hyperacute ARDS,** induced by local antigen-antibody reactions or by large amounts of previously released bioactive substances (See also Wallis J, Sachs UJH. Transfusion-related acute lung injury. In Rossi's Principles of Transfusion Medicine 4th Ed., pp 870-884)

- No report found on TRALI or on frequency of lung complications in relation to FWB transfusion – i.e. **TRALI or other lung complications have never been reported as induced by FWB transfusion**
  - Underdiagnosed?
  - Viable leukocytes do not induce TRALI??

# FWB and graft-versus-host disease (GVHD) I

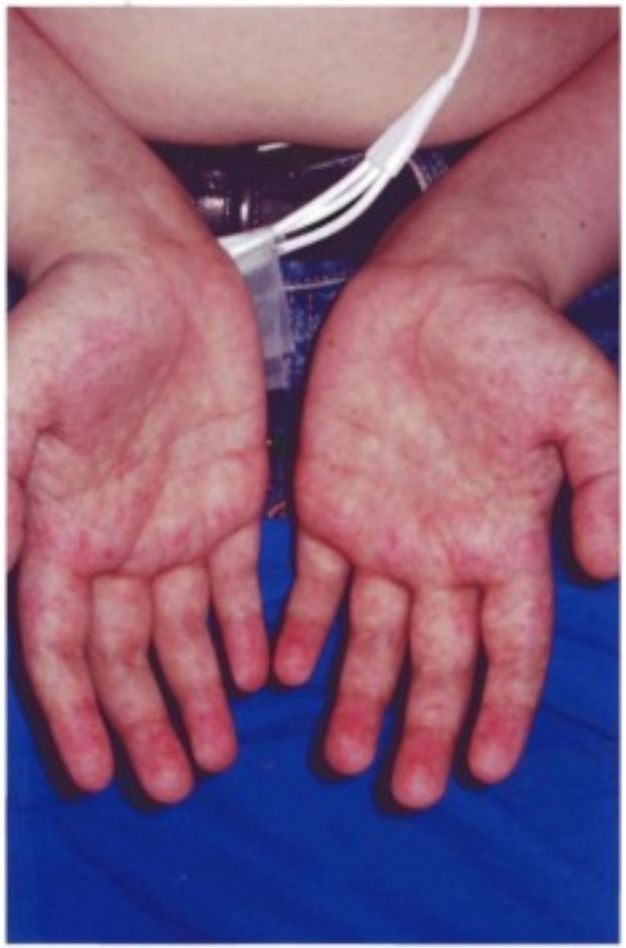
- FWB contains leukocytes, **including immunocompetent T lymphocytes**, which may survive up to ~100 hrs after donation

- Leukocytes transfused with FWB are usually recognised as foreign by the recipient's immune competent T lymphocytes and eliminated

- The transfused immuncompentent T lymphocytes may establish themselves in the recipient and elicit their own immune response against the recipient's histocompatibliity antigens **in two main situations**:
  - **Immunocompromised recipient:**
    - Immunocompromising disease
    - Immunocompromising treatment

# Graft versus host disease (GvHD)

Typical skin rash, acute phase



Mortality: >80% in all reported patient groups

# FWB and graft-versus-host disease

- GVHD after FWB transfusion in immunocompetent individuals described **predominantly in Japan** and **predominantly in cardiovascular surgery**
- GVHD not described in relation to military use (Kauvar DS et al. Fresh whole blood transfusion: A controversial military practice. J Trauma 2006; 61: 181-4)

- Risk of homozygous donor in Japan: 1:874
- Risk of homozygous donor **in family donor** in Japan: 8-30-fold increase
- Risk of homozygous donor in USA: 1: 7174
- Risk of homozygous donor **in first-degree relative donor** in USA: 1:475 (Ohto H et al. Risk of transfusion-associated GVHD as a result of directed donation from relatives. Transfusion 1992; 32: 691-3)

- Risk in Norwegian general population not known; i.e. risk from "walking blood bank" by Norwegian personel not calculated. Risk in e.g. Afghani population not known.

# GVHD prophylaxis

- All FWB applied for civilian use in Norway (~100 units / yr at OUS/RH in Oslo; Haukeland??) are **gamma irradiated before transfusion.** This efficient GVHD prophylaxis reduces survival of transfused erythrocytes; effect on thrombocyte function not known

- In using FWB in the military setting, irradiation cannot be applied. GVHD prophylaxis is principally insufficient, but should imply:
  - Minimal use of FWB – only in case of uncontrolled bleeding
  - Avoid family donors

# Summing up

- **There is an apparently dose related connection between transfused bioactive substances and degree of non-immune transfusion-related lung complications, including clinical ARDS and TRALI.**
  - It is not clear if this applies also to the transfusion of FWB; in fact TRALI seems not to have been reported as induced by FWB, and notably in military personel
  - TRALI therefore does not seem to afford a strong contraindication to the transfusion of FWB
  - However, TRALI may be underdiagnosed
  - Accordingly, **TRALI should be kept in mind as a possible and significant side effect of FWB transfusion**

- **GVHD has not been described as induced by FWB in the US / NATO military setting**
  - This may be because recipients are usually immunocompetent and donors are not relatives
  - Avoid family donors – both for military personel and local civilians!!!

# Conclusion

- On the basis of currently available knowledge, **neither TRALI nor GVHD can be considered strong contraindications to the use of FWB to achieve control of bleeding in the military setting.**

- However, the risk of these complications must be considered significant and not = 0.

- The risk of both complications may be dose-related and, for GVHD, much increased if relatives are used as donors.

- **FWB should only be used in case of uncontrolled, life threatening bleeding**