TRALI - An acute transfusion reaction mechanism that continues to elude

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Case Study

- 48 year old male
- Past history of alcoholic liver disease and recent history of drinking in excess, now massive hematemesis
- Transfused one unit RCC in ED and admitted to ICU
- O Rh(D) Negative, Antibody Screen: NAD, INR 2.6, APTT 32s Hb 78g/L, Platelet count 51 x10⁹/L and BP 150/100
- he was transfused 1 RCC, 4 FFP, 2 PLTS, PTX, Vitamin K prior to gastroscopy for banding of oesophageal varices
Case Study (continued)

- 5 hours post transfusion the patient became feverish, hypotensive and hypoxic, with breathing difficulties and needed oxygen support
- Temp: 38.2, Hb 89 g/L BP: 114/86, O2 Sat: 74%
- Transfusion reaction investigation: negative
- chest x-rays returned an acute respiratory distress syndrome picture so TRALI / TACO were considered
In summary

- multiple blood products were transfused
- the patient became feverish and hard to ventilate
- improved on mechanical ventilation and diuretics
- blood cultures showed no growth
- TRALI-like symptoms resolved after 3 days
- the patient recovered and was discharged on day 11
- awaiting HLA & HNA antibody results from donors
Transfusion-related acute lung injury

TRALI is a serious, often life threatening, pulmonary transfusion reaction characterised by non-cardiogenic lung oedema, hypoxemia and respiratory distress in association with blood transfusion.

Currently the number one cause of transfusion-related fatality in the US but rarely reported in Australia and UK.
FDA USA Fatalities 2009-13

Number of fatalities

TRALI
HTR (non ABO)
HTR (ABO)
Microbial Infection
TACO

Number of fatalities

2006
2007
2008
2009
2010
2011
2012
2013
STIR notifications of adverse events 2009-11

- ATR
- WBIT
- Near-Miss
- ICBT
- Bacterial
- TACO
- TRALI
- DTR
- PTP
TRALI has been defined by international consensus as:

- new acute lung injury within 6 hours of transfusion
- oxygen saturation <90% when on room air
- chest x-ray displaying bilateral infiltrates
- with no pre-existing ALI
TRALI Diagnosis

- a clinical diagnosis of new acute lung injury
- usually associated with fevers, chills and transient hypotension
- sometimes with transient neutropenia and thrombocytopenia
- because it is a clinical diagnosis many cases go unreported
Differential Diagnosis

- **ARDS:** TRALI like ARDS but resolves in 24-48 hrs
- **TACO:** clinically like TRALI, but no fever. TRALI does not usually respond to diuretics
- **Anaphylactic reaction:** usually afebrile, a negative chest x-ray is diagnostic
- **Septic transfusion reaction:** shows bacterial contamination
Treatment

- Once TRALI is implicated treatment is fairly straightforward
- Involves respiratory support with oxygen and intubation (mechanical ventilation) if needed
Prognosis

- generally good if diagnosed and treated
- mortality higher in critically ill and surgical patients
Prevention

- male-only donor plasma
- universal leucodepletion of RCC
- test multi-parous platelet donor women for anti-HLA class I and II as well as anti-HNA
- these strategies have been a major break-through for reduction of TRALI but have not eradicated the problem
Mechanisms of TRALI

• TRALI is thought to be mediated by neutrophils
• Under normal circumstances there are plenty of neutrophils in the lungs. Neutrophils may be directly or indirectly activated by pro-inflammatory mediators present in all transfused products
• Primed neutrophils become rigid and damage pulmonary endothelial cells and capillaries, which lead to alveolar leakage, pulmonary oedema and TRALI
• Two mechanisms have been proposed
Immune modulation model

- Donor antibodies (HLA or HNA) bind to recipient antigens on neutrophils.
- These complexes deposit and activate a microbicidal response.
- Secretion of toxic oxygen radicals or reactive oxygen species (ROS) and microbicidal enzymes cause damage to the pulmonary endothelial cells lining the capillaries and thus leakage of fluids into the alveolar spaces.
- Demonstrated by donor and recipient WBC cross matching
BUT

• This immune modulated mechanism does not explain why TRALI still occurs even with leucodepletion of red cells and the use of male-only plasma donors
A two-hit event model proposed

- The first event could be a pre-transfusion condition that primes neutrophils and activates lung endothelial cells. E.g. sepsis, major surgery, massive transfusion or inflammation.

- The second hit is blood product transfusion that stimulates capillary damage and pulmonary oedema. Possibly caused by biological response markers (BRM) in stored blood.
Current TRALI research

• Washing red cells to reduce the stimulus
• Platelet involvement has been studied, with platelet depletion and treatment with aspirin shown to prevent TRALI
• Solvent/detergent treatment of plasma has been trialled overseas and recently FDA approved Octaplas © a solvent/detergent treated plasma product for routine replacement of coagulation factors and therapeutic plasma exchange in TTP
• Transfusion of old vs new red cells with possible causes of TRALI - BRMs in stored blood (CD40L and lipids). Maybe it is not so much the age of the blood product but the amount of BRMs present
Conclusion

• TRALI is under-diagnosed, under-reported and thus underestimated

• As TRALI incidence is much higher in critically ill patients a restrictive transfusion policy is advocated at least until the acute inflammation has subsided
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Further reading


