

Reducing the risk of TRALI.

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TRALI

- Cause not fully understood
- Incidence largely unknown
- No diagnostic test
- No specific treatment
- Commonest cause of transfusion related mortality SHOT and FDA

Today's Talk

- Describe TRALI and its aetiology
- Describe reduction measures
- Paper by G Lucas re NHSBT donor antibody screening
- IBTS donor panel and our approach to TRALI reduction

Eras in transfusion medicine

- Compatibility procedures established
- Detection of known TTIs
- Now the attention is on enhancing blood safety

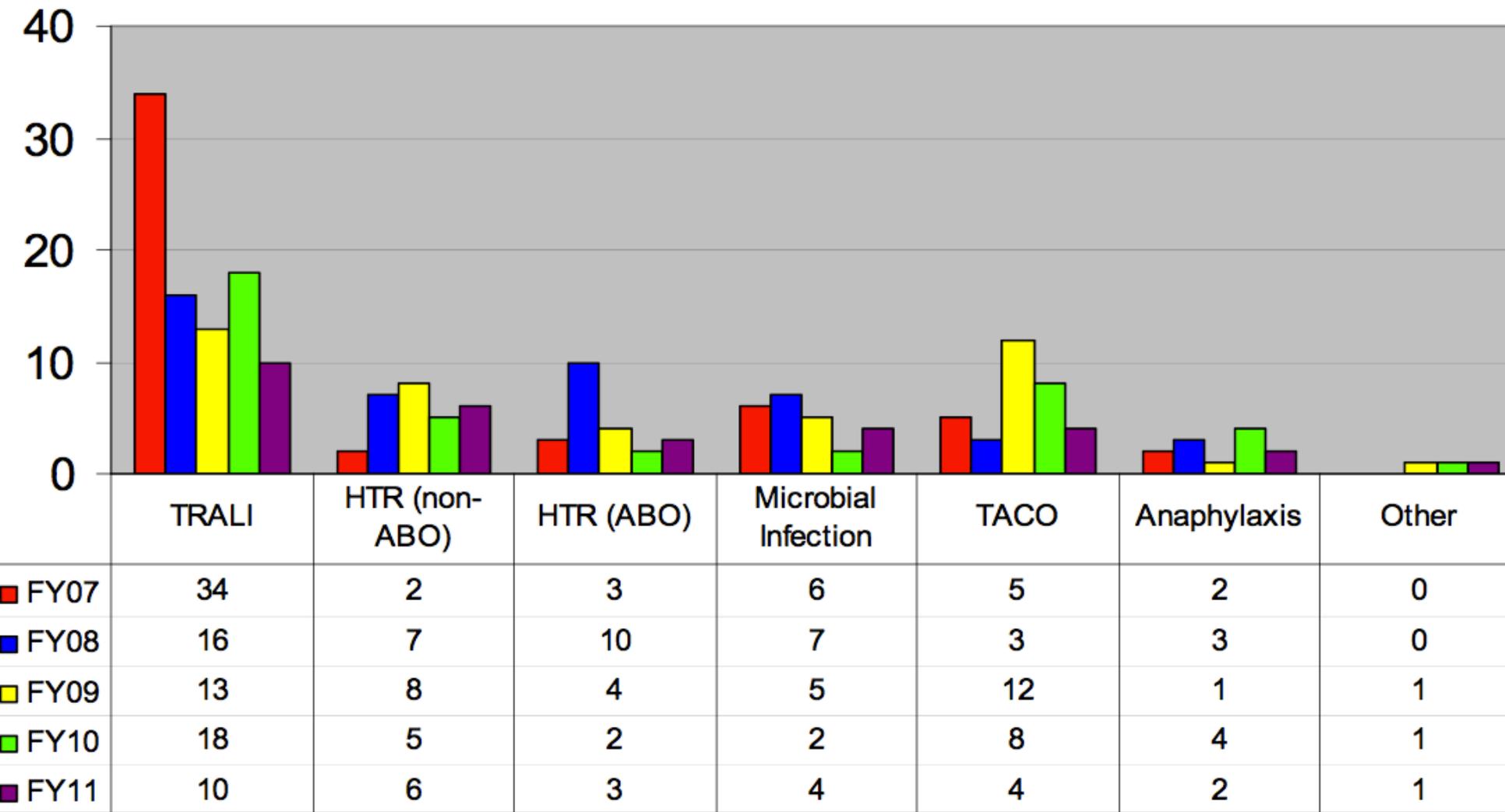
Adapted from Emily Cooley lecture 2009

Mark A Popovsky

Incidence

- TRALI is the number one cause of acute mortality from transfusion (SHOT and FDA)
- TRALI is both under-recognised and under reported.
Kopko et al JAMA 2002
- Incidence unclear lack of common definitions US v UK
- Overall risk of approx 1:5000 transfused units.
- ICU patients have a quoted risk of 1:1300 when monitored closely.

The Blood Bank Guy 2012



Complication

Single Hit Hypothesis

- Result of immunological response between antibodies contained in the plasma of transfused blood components and the recipients white cells or endothelial cells.
- The resulting inflammatory response traps the recipients white cells in the small blood vessels of the lung
Damages the pulmonary endothelium
Causes leakage of fluid and inflammatory cells into the lung
- Implicated antibodies are directed against HLA class 1 and 2 and /or HNA antibodies of the recipient

The two hit hypothesis

- **Antibody mediated**
- **The first hit** damages the pulmonary vascular endothelium (PVE), recruiting neutrophils to the area where they become activated and adhere to the PVE
eg surgery, sepsis, trauma and liver disease
- **The second hit** is infusion of white cell antibodies or bioactive substances in stored blood components which stimulate neutrophils to produce an oxidative burst damaging the pulmonary endothelium

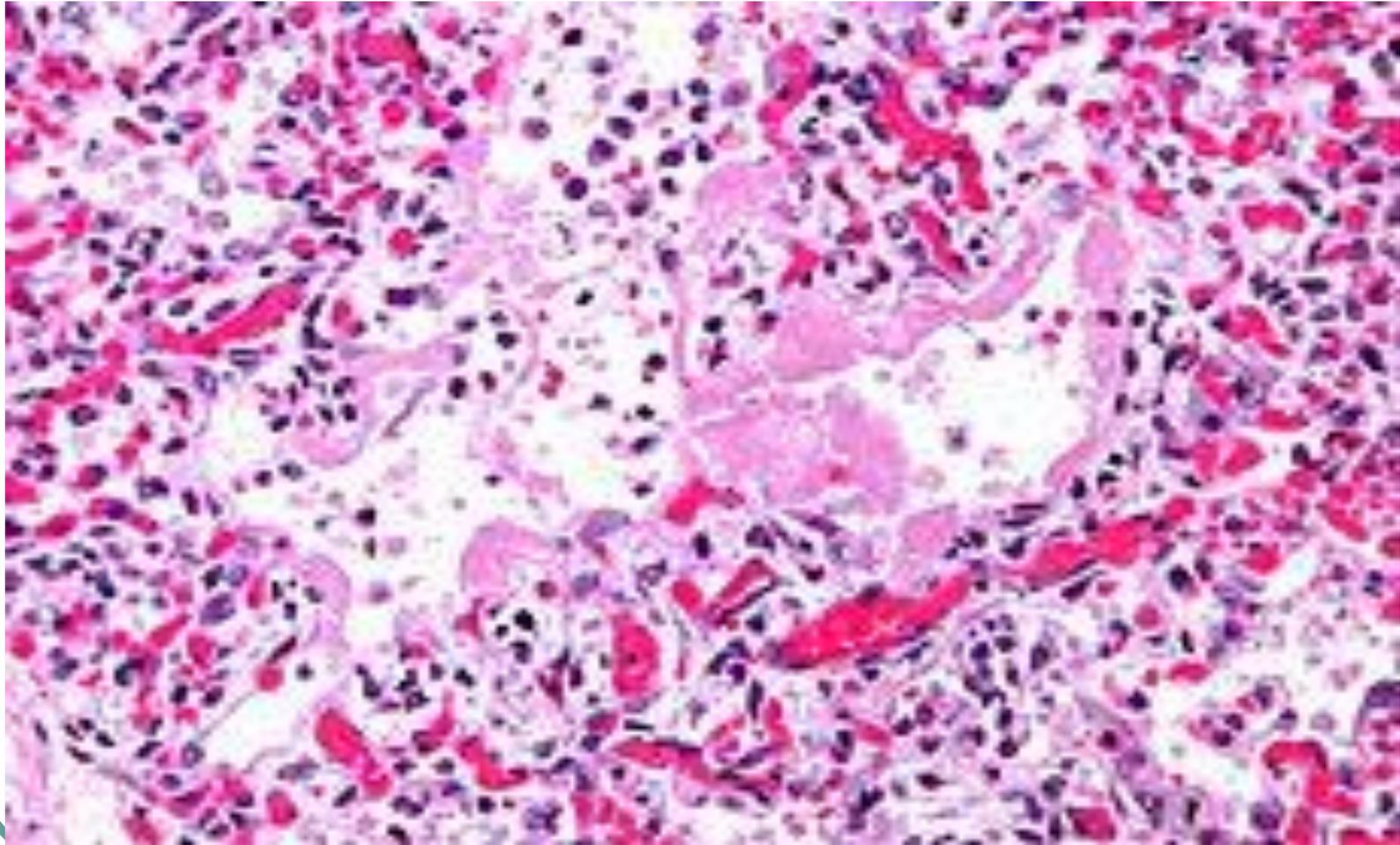
Transfusion Related Acute Lung Injury (TRALI)

- First described by Popovsky and Moore.
Acute onset respiratory distress during or within 2- 6 hours of transfusion
- Associated with
 - Hypoxaemia
 - Bilateral lung infiltratesWithout evidence of Left atrial hypertension or circulatory overload.
- In 90% of the cases the patient recovers within 96 hours. The other are slower to recover or are fatal. 5% to 10% mortality

Pathology

- Limited to post mortem case reports
- Grossly oedematous lungs
- Granulocytes in the microvasculature
- Evidence of capillary damage
- Adherent activated granulocytes

Lung H and E



2004 Canadian Consensus Definition

- Acute onset within 6 hours
- Bilateral pulmonary infiltrates
- No evidence of overload

Clinical manifestations

- Male =Female
- Dramatic onset of symptoms.
- Acute respiratory distress/non cardiogenic pulmonary oedema
- Tachycardia and O² desaturation. Requires mechanical ventilation in 70% of cases.
- Some patients experience a low grade fever for several hours.
- Bilateral rales or creps
- Transient fall in white cell count in some patients
- Symptoms and signs may be muted under general anaesthesia.

Differential Diagnosis

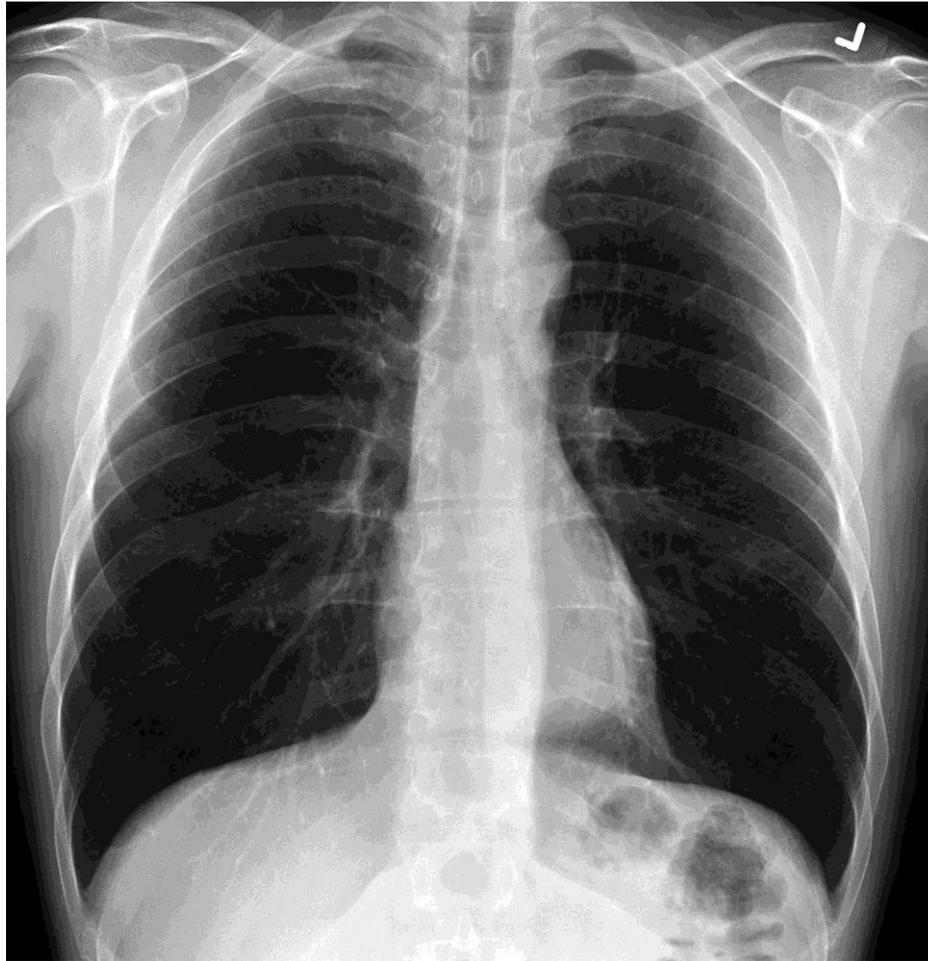
- TACO
- ARDS
- Severe HTR
- Anaphylaxis
- Sepsis
- Distress

- No specific diagnostic test for TRALI

Investigations of Patient

- CxR
- HLA genotype
- Leukocyte antibody investigation
- Pre and post B type Natriuretic Peptide (BNP)
Not thought useful in distinguishing TACO
from TRALI
Guangxi L et al Transfusion 2009

Normal Chest X-ray



Chest X-ray in TRALI



Management of patient TRALI

- Supportive
- No role for steroids
 - Supplemental O₂ mechanical ventilation +/- intubation
 - Fluid management
 - IV fluids to correct low BP
 - Diuretics if element of CCF present or if TACO can't be excluded

Subsequent Transfusion

- No extra precautions required in subsequent transfusions as recurrent TRALI very rare.
- No chronic sequelae

Implicated blood components

- All types of blood components RCC, Cryo, FFP and Plt most common and most severe with products containing large amounts of **plasma**.
- SHOT incidence of TRALI per blood component issued prior to 2004
 - RCC 1:556 000
 - Cryo 1:317 000
 - FFP 1:81 000
 - Plt 1:68 000
- **SD plasma has not been shown to cause TRALI**

IBTS protocol following report of a suspected TRALI

- Case review
- Rapid alert
- Recall any implicated product
- Female donors code 6072
- Male donors not investigated further unless
- Female donors contacted and investigated
- If positive crossmatch and permanent exclusion from donating
- If negative reinstate as active donor

Implicated antibodies

- 80- 85% of cases are due to donor leukocyte antibodies directed at neutrophil-specific or HLA antigens of the patient.
- Reverse TRALI
- Implicated antibodies are HLA class 1, HLA class 2 and anti HNA antibodies (anti-HNA 3 is the most severe and is associated with fatalities)
- From 1996 to 2014 195 cases of TRALI fully investigated by SHOT
 - 58% had concordant antibody.
 - Majority HLA ; 11% HNA +/- HLA

- Reducing the incidence of TRALI in the UK: the results of screening for donor leukocyte antibodies and the development of national guidelines.

Lucas G et al Vox Sanguinis (2012) 103,10-17

Strategies to reduce the risk of TRALI (UK)

- 2004 Canadian Consensus Panel make recommendations
- Universal leukodepletion introduced in 1999 as vCJD risk reduction
- Policy of producing FFP from predominantly male donors introduced in late 2003 and 100% target met in Feb 2010
- Re-suspension of plt concentrates in plasma from male donors leaving <30 mL plasma per female donor in pool. Initiated in late 2003
- The amount of plasma in RCC reduced to approx 20 mL early 2004

Comparison IBTS vs NHSBT

Product	NHSBT	IBTS
Universal Leukodepletion	1999	1999
Male FFP	2003--2010	SD plasma 2001
Pooled Plts male plasma	2003	2002
Pools in PAS	2008	2007

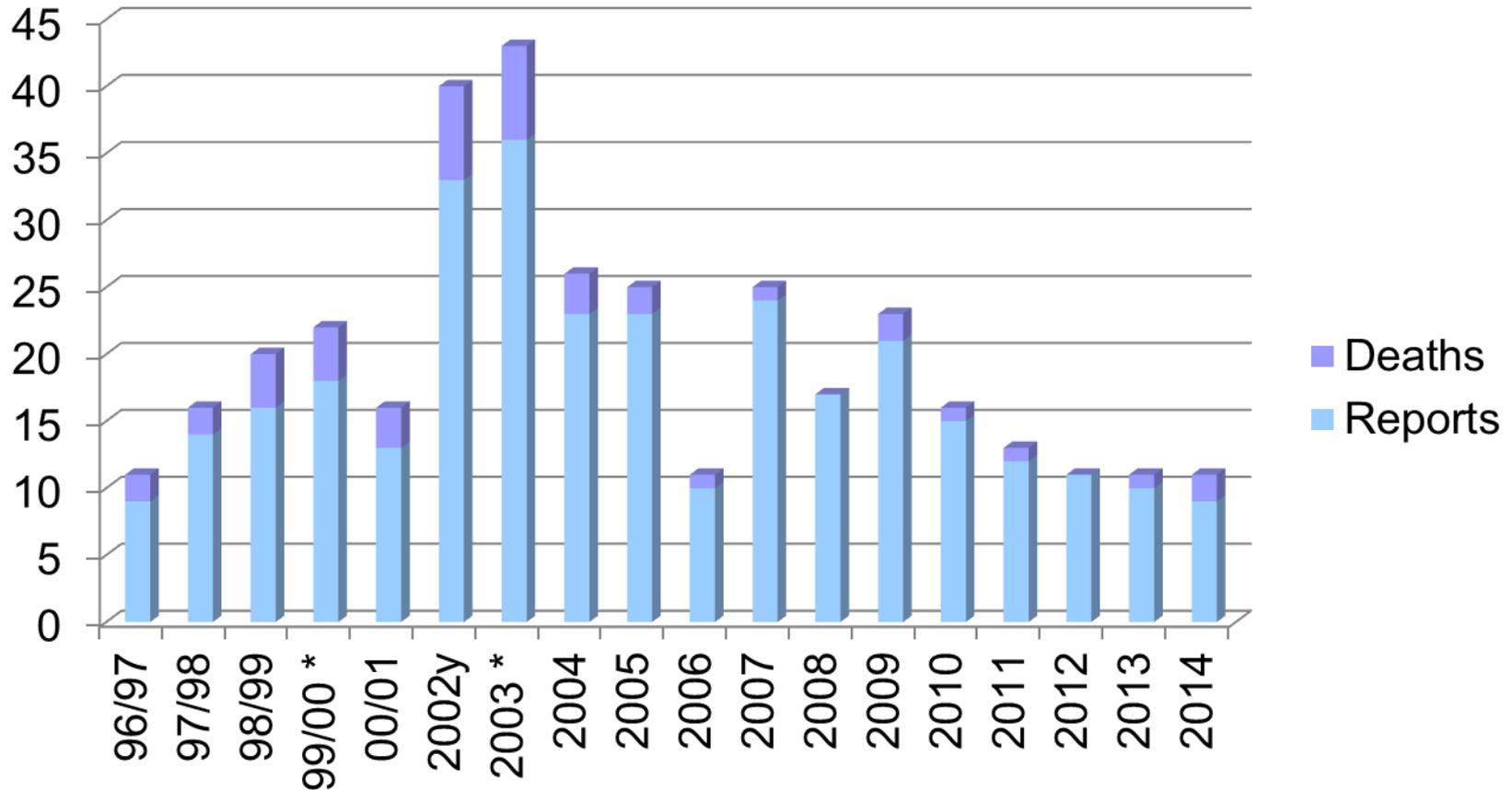
Results of these measures

- The annual number cases of TRALI as reported in SHOT fell dramatically against an overall background of increased reporting
- 36 in 2003
- 23 in 2004-2005
- 10 2006
- 24 2007
- 21 2009
- 15 2010
- Also fall in cases classified as highly likely or probable from 23 in 2003 to 3 in 2010
- Mortality associated with TRALI as reported in SHOT has decreased with no deaths in 2008. In 2009 2 deaths assoc with female FFP and 2010 saw death following massive transfusion where pt had other causes for respiratory compromise.

SHOT Imputibility

- Highly likely: clinic picture and positive serology
- Probable: less convincing story and positive serology or vice versa
- Possible: clinic picture or serology compatible with TRALI but other clinic causes not excluded
- Unlikely: picture or serology not supportive of diagnosis

SHOT Report 2015



- Following slides from Vox sanguinis 2012
- Lucas G et al
- Reducing the risk of TRALI in the UK

Further risk reduction measure

- Following the measures outlined above the main residual risk of TRALI lay in apheresis female donors which comprised only 10% of donor panel in UK
- In April 2009 NHSBT began screening all female recruits to apheresis panel for leukocyte antibodies.

Donor screening for leukocyte antibodies

1,157 female donors

New recruits to panel

Non transfused

No history taken in relation to possible previous pregnancies

Results

- 315 positive for HLA antibodies
Specificities not determined
Returned to red cell component donation
- 57 of remaining 842 donors negative for HLA had *granulocyte-specific antibodies*
 - 33 IgM Okay to donate plt
 - 21 non specific or HNA 1a or 2a return to blood panel
 - 3 HNA 3a excluded from donation

Discussion

- Considerable variation in antibody levels of both HLA class 1 and 2 between studies ranging from 8.25% to 68.75%
- Reflects the greater sensitivity of the microbead assay vs the ELISA assay for the detection of HLA antibodies.
- 8171 blood donors including 1138 non transfused males.
 - HLA antibodies in 17.3% parous females with increasing rates as the number of pregnancies increased (11.2% for one to 32% for four plus)
Triulzi et al.
(Similar results from Middleburg from Holland)
- Transfusion alone does not result in significant increase in prevalence of HLA antibodies.
- Non transfused males /non parous females with antibodies may be false pos or “naturally occurring” and their significance is uncertain.

Guidelines for TRALI Reduction

Drawn up by UK Standing Advisory Committee for immunohaematology

- All female plt donors with a history of pregnancy tested for HLA 1 and 2 antibodies
- Those negative for HLA antibodies are screened for HNA 1, 2 and 3 antibodies
- Donors with negative results for leukocyte antibodies should only be screened again if they have a potentially sensitising event
- Donors testing positive for HLA/HNA antibodies are returned to blood donation of OAS red cells with the exception of **Donors with anti-HNA 3a who are permanently excluded from donation**

Conclusion

- The reported incidence of TRALI has decreased significantly since 2003 with the introduction of various strategies .
- Screening new and in the future existing female plt donors should further reduce this risk.
- The assay for HLA antibodies is highly sensitive and the authors query if a higher cut off point might be considered if this is being used as a tool to screen plt donors and thus retain more precious apheresis donors on the panel

NHO Statistics 2007 onwards

- 16 cases reported
- 6 reclassified
 - 2 anaphylaxis
 - 4 TACO
- 5 unlikely

NHO figures 2006 to Present

Case	Age	Gender	Imputability	Component	SAR	Comment
Case 1 (2008)	Elderly (70+)	Female	Possible	Red Cells Solvent Detergent (SD) Plasma	Transfusion related acute lung injury (TRALI)	
Case 2 (2012)	Elderly (70+)	Female	Likely / Probable	Red Cells	Transfusion related acute lung injury (TRALI)	
Case 3 (2014)	Adult (51 - 70 years)	Female	Possible	Red Cells	Transfusion related acute lung injury (TRALI)	Remains under review
Case 4 (2014)	Adult (51 - 70 years)	Female	Possible	Solvent Detergent (SD) Plasma Red Cells	Transfusion related acute lung injury (TRALI)	
Case 5 (2015)	Adult (51 - 70 years)	Male	Possible	Red Cells	Transfusion related acute lung injury (TRALI)	Remains under review

IBTS story

- Universal leukodepletion 1999
- SD plasma 2001
- Male only plasma for component use December 2002
- Recruitment of parous female apheresis donors ceased
- November 2003
- Pooled plt in PAS 100% by August 2007
- Male only donors for “X” packs 2012
- Screening female plt donors 2012/2013

IBTS Apheresis Panel 2012

	Total donors	Female
NBC	1753	217
MRTC	679	69
Total	2432	286 (11.8%)

Our experience

- From October 2003 only nulliparous donors recruited and existing donors who became pregnant were returned to the blood panel.
- It was felt that donors who had a history of pregnancy but to our knowledge had not caused adverse events in patients could safely remain on the active donor panel.
- In November 2012 it was decided to test all parous donors for HLA and HNA antibodies.
- The IBTS would largely follow the algorithm used by the NHSBT

All female donors asked re history of pregnancy 28 Nov - 07 January '13

- If “no” may donate without restriction
- If “yes” allowed to donate on that attendance
- Donor counselled re antibodies and made aware that she cannot donate again until she is screened and asked not to make an appointment.
- Temporary deferral code applied to donor

2003 - 2013

- October 2003 IBTS no longer accepted women with a history of pregnancy as plt donors.
- Existing donors were permitted to continue to donate

From 07 January 2013

- No further donations taken from female donors with a history of pregnancy
- From 14/01/2013 code 6090 replaced code 6052 on donor profile.
- Letters posted to all 82 donors; followed up by a telephone call from an RGN
- Donor screening appointments made for the following weeks with approx 10 donors attending per week.

Results of testing

Nulliparous	37 (incl 1 MRTC)
Confirmed Pregnancy	39 + (3 off panel)
Samples taken	37
Samples outstanding	2
Pos HLA 1or 2	23
Negative HLA	17
Samples to Bristol	17
HNA pos	2
Donors re-instatable	11 neg/neg
Return to blood (letter)	23
Inconclusive	5

Number of pregnancies in negative screened donors

- 6 donors reinstated so far
 - 1 had 7 pregnancies
 - 2 had 4 pregnancies
 - 1 had 3 pregnancy
 - 2 had 2 pregnancies

IBTS Results

Never had a pregnancy of any duration	37 (inc 1 MRTC)
Confirmed pregnancy	39 (3 donors although confirmed pregnancy, were off the Panel)
No of donors screened	37
Samples not taken	1:No sample and 1: unknown
Confirmed <u>positive</u> for HLA or HNA antibodies	23 (16 pos for HLA, 2 pos for HNA and 5 inconclusive)
Inconclusive result	5 inconclusive and treated as pos Code 60903
Confirmed Negative for HLA antibodies	17
Donors removed from the panel	23

Conclusion

- The IBTS now has a Plt apheresis panel consisting of males, untested nuliparous females and females with a history of pregnancy who are negative for anti neutrophil antibodies and HLA class 1 and 2 antibodies.
- We have not detected any donor with an anti-HNA 3a antibody.
- We have returned the “positive” donors to the blood panel
- Before so doing we put a procedure in place to ensure that they will not be part of a plt pool
- Whole blood for ET or IUT is from male donors only

- Passive transfer of leukocyte antibodies in blood products
- Introduction of strategies by different blood services (antibody screening of donors)
- Partially successful
- Not eliminated