

Reducing the Risk of TRALI Options for the Blood Service

Dr Peter Flanagan
National Medical Director
New Zealand Blood Service

Initial Observations

- Data from haemovigilance schemes indicates that TRALI is a significant cause of transfusion related morbidity and mortality.
- Frequency estimated as 1 in 5000 transfusions
- 80% of cases are associated with leucocyte antibodies in the donor directed against a leucocyte antigen present in the recipient.
- 70 % of cases require mechanical ventilation
- Mortality estimated at between 6-8% but possibly higher depending on case mix.

Toward an Understanding of TRALI

- Canadian Consensus Conference held in 2004.
- Panel asked to consider whether sufficient evidence exists to justify implementation of donor screening strategies to reduce risk.
- Panel recommended investigation of feasibility of introducing possible restrictions on donors '*having or at risk of having WBC antibodies*'.

UK SHOT

- Identified TRALI as major cause of transfusion morbidity and mortality.
- Donor antibodies recognising recipient antigens identified in 65% of cases.
- Relative TRALI risk per component of 6.9 for FFP and 8.2 for platelets compared to RBC.
- All implicated donors in FFP/Platelet cases were female.
- In late 2003 UKBTS implemented preferential 'male only FFP' policy resulting in 80-90% of FFP being derived from male donors.

AABB Guidance on TRALI

Date	Bulletin	Requirement
June 05	05-06	Donors implicated in TRALI or associated with multiple events of TRALI shall be evaluated regarding their continued eligibility to donate (Final Interim Standard 5.4.2.1)
August 05	05-09	Guidance on possible means of complying with revised standard
November 06	06-07	<ul style="list-style-type: none"> - Blood collecting facilities required to implement interventions to minimise preparation of high plasma-volume components from donors <ul style="list-style-type: none"> • known to be leucocyte allo-immunised, or • at increased risk of leucocyte allo-immunisation - Complete full implementation of measures relating to <ul style="list-style-type: none"> • platelet components by November 2008 • plasma components by November 2007
November 07	07-03	<ul style="list-style-type: none"> - Revised implementation date for platelet components - Recognises potential adverse impact on supply of apheresis platelet components - Acknowledge possibility of only partial implementation by November 2008

Approaches to Risk Reduction (1)

- Promote appropriate use of blood components
- Appropriate investigation of case reports and management of implicated donors
- Effective monitoring systems to assess impact of any interventions

Approaches to Risk Reduction (2)

- Donor selection/exclusion
- Testing of donors and/or donations
- Blood component manufacturing strategies
 - Removal of plasma or neutralisation/inactivation of antibodies

Development of a Risk Framework

- Identification of high risk components
- Development of a framework to assess donor risk status
 - Gender
 - History of transfusion
 - History of pregnancy in females
 - Presence or absence of WBC antibodies
 - Which antibodies are most important?
 - How sensitive should the test be?
- What will be the impact of any intervention on ability to supply?

English National Blood Service

Implicated components/total issues

HIGH PLASMA (300 MLS)

FFP /CSP 45/ 2.6 million = 1: 58,000

Platelets 27/ 1.7 million = 1: 63,000

LOW PLASMA (30 MLS)

Cryoppt 2/ 0.6 million = 1: 300,000

Red cells 34/17.8 million = 1: 523,000

Risk from 'high plasma' components was 5-8 times higher than from 'low plasma' components.

High Plasma–Volume Components

AABB Bulletin 06-07

- FFP obtained from whole blood
- FFP obtained from apheresis
- Plasma frozen within 24 hours after phlebotomy
- Plasma, cryoprecipitate reduced from either whole blood or apheresis
- Apheresis platelets
- Buffy coat derived platelets in plasma from one of the donors in the pool
- Whole blood

Targets for Risk Reduction

- Fresh Frozen Plasma
- Apheresis platelets
- Buffy coat derived platelets resuspended in plasma from one of the donors in the pool
- *Apheresis Cryoprecipitate*

ORIGINAL ARTICLE

How much residual plasma may cause TRALI?

N. Win,* C. E. Chapman,† K. M. Bowles,‡ A. Green,§ S. Bradley,¶ D. Edmondson§ & J. P. Wallis**
**Red Cell Immunology Department, National Blood Service, Tooting Centre, London, †Red Cell Immunology Department, National Blood Service, Newcastle Centre, Newcastle-Upon-Tyne, ‡Department of Haematology, Norwich and Norfolk Hospital, Norwich, §Histocompatibility & Immunogenetics Department, National Blood Service, Bristol Centre, Bristol, ¶Department of Haematology, Hemel Hempstead General Hospital, Hemel Hempstead, and **Department of Haematology, Freeman Hospital, Newcastle-Upon-Tyne, UK*

Received 1 April 2008; accepted for publication 12 July 2008

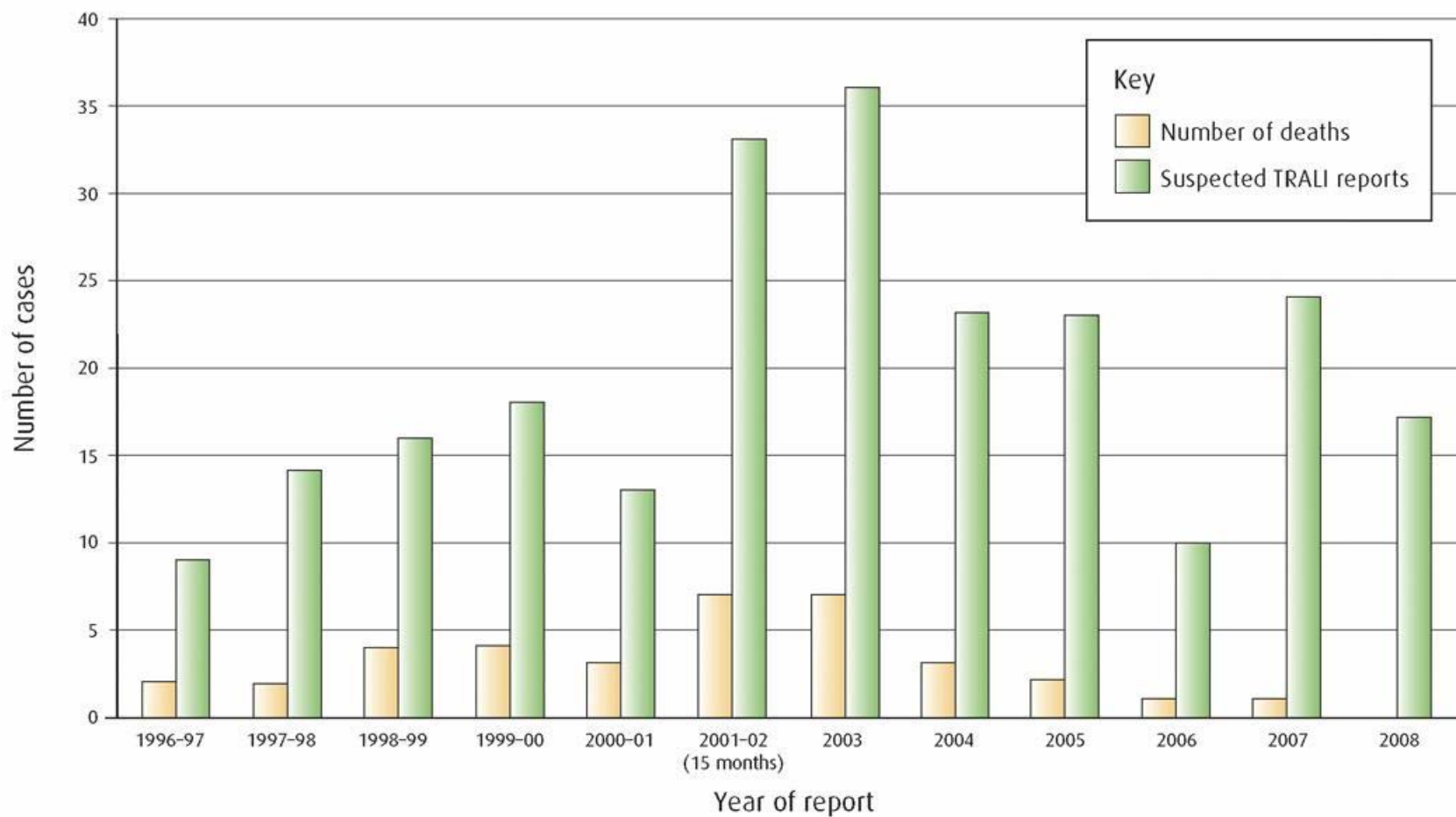
- 3 cases involving TRALI and low volume blood components.
- 2 cases related to RBC in optimal additive solution and one to buffy coat platelet pool (implicated donor contributed buffy coat).
- All cases involved cognate antibody/antigens
 - All involved the presence of HLA class II antibodies and/or HLA A2 in female donors.
- Concluded that 10-20ml of plasma might be sufficient to cause TRALI.

Preferential 'Male Only' FFP

- Policy developed initially by English National Blood Service:
 - Involves preferential selection of donations given by male donors for manufacture of FFP
 - Female donations are used where necessary to ensure continuity of supply
 - In practice NBS reports 80-90% male FFP
- Noteworthy that 2008 SHOT report includes 3 cases of TRALI associated with use of female FFP in NBS.
- In 2007 NZBS implemented male only FFP based on apheresis plasma. Male source of FFP is guaranteed.

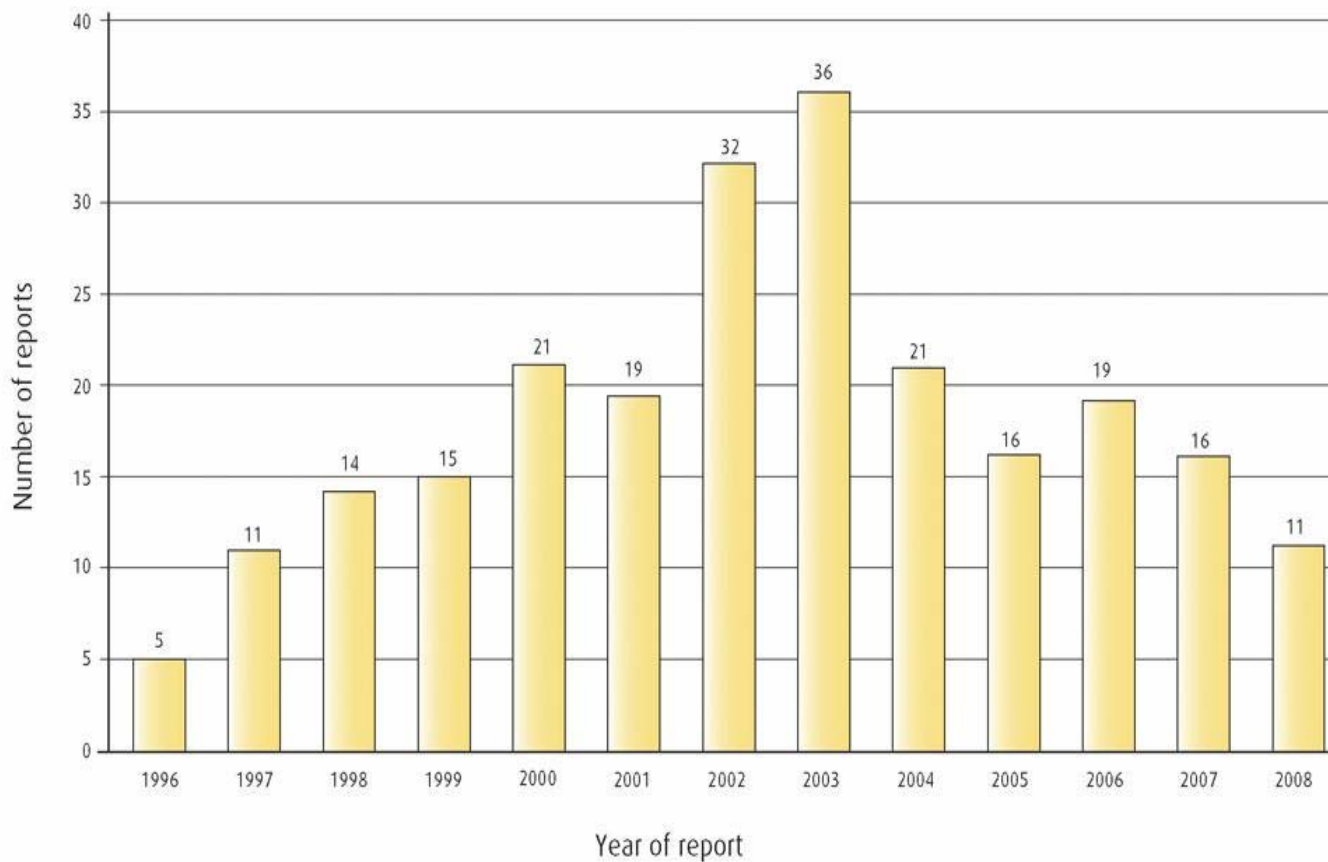
UK SHOT Report 2008

Deaths at least possibly due to TRALI and number of suspected TRALI reports by year



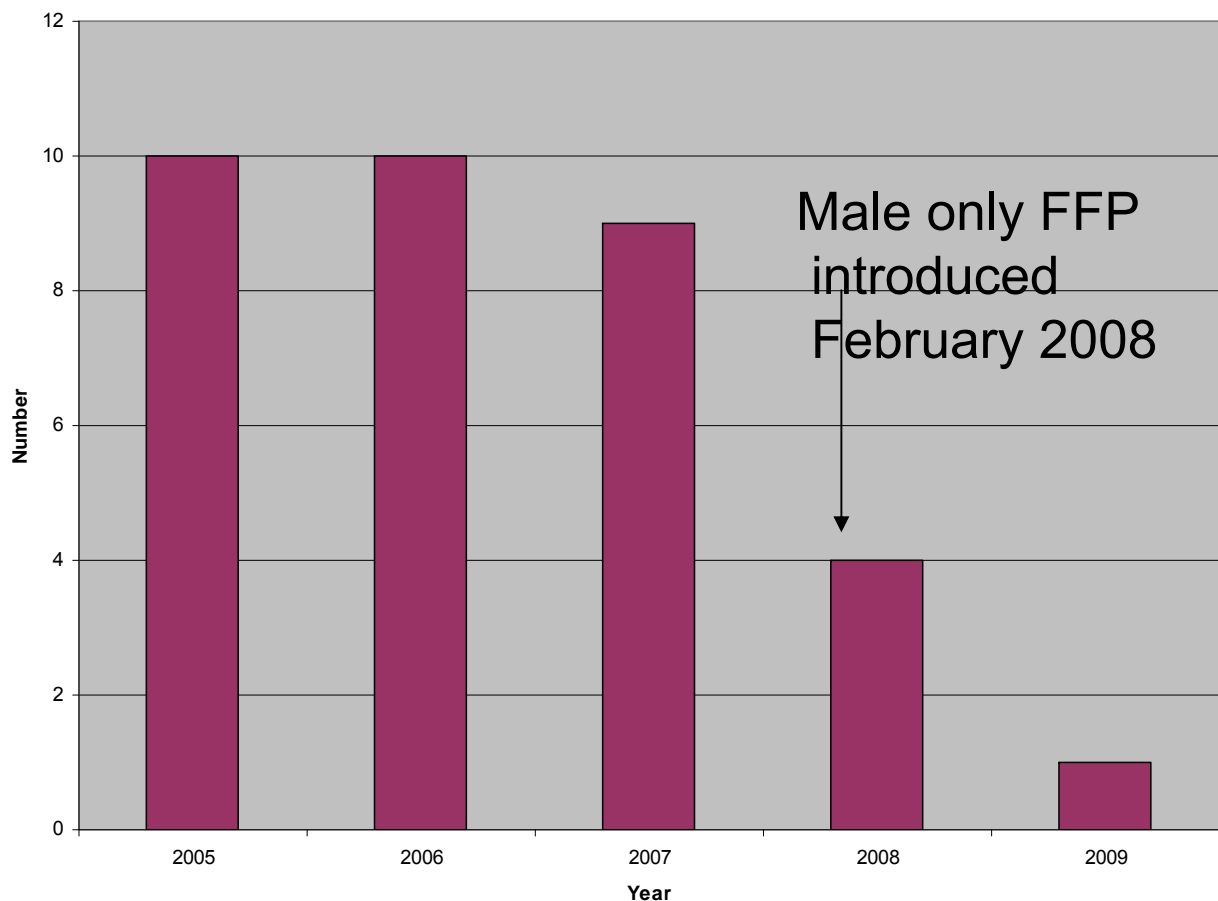
UK SHOT Report 2008

TRALI by year of transfusion $n = 236$



Impact of Male only FFP in New Zealand

Number TRALI reports by year in NZ



Does History of Transfusion Matter?

- Transfusion is a recognised source of WBC alloimmunisation.
- The use of leucocyte-depleted components in most developed countries will have reduced the frequency of sensitisation.
- A number of studies have demonstrated that there is no significant difference in the frequency of WBC antibodies in transfused versus non transfused male donors.

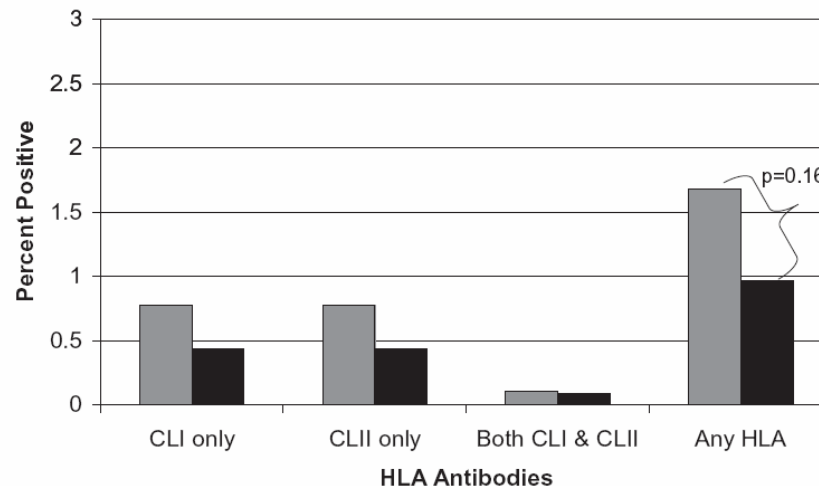
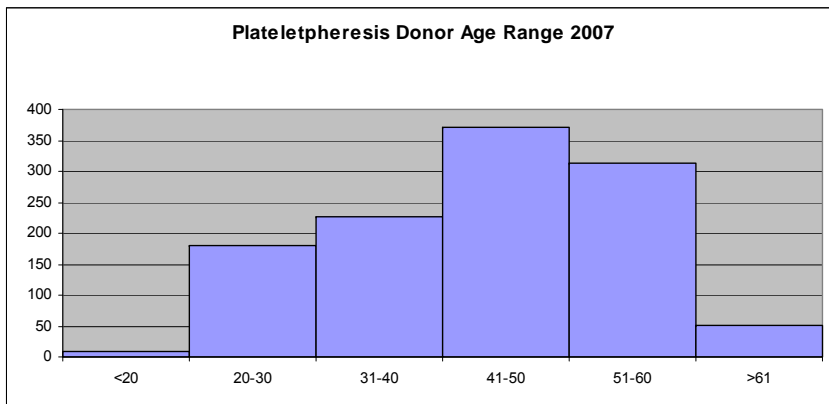


Fig. 2. HLA antibody prevalence for Class I (CLI), Class II (CLII), Class I and II, and any HLA antibody at a 3SD cutoff in transfused (■) and nontransfused (■) males. The difference in HLA antibody prevalence was not significant ($p = 0.16$).

NZBS Plateletpheresis Panel

GENDER	NUMBER
Female	724 (63%)
Male	427 (27%)
Total	1151

- High proportion of female plateletpheresis donors.
- Donors are predominantly older.
- This profile of older female donors is the one most likely to have WBC antibodies.



Reducing the Risk Associated with Female Donors

- Impractical to exclude all female donors from platelet pheresis panels.
- Three possible approaches to manage risk
 - History of pregnancies
 - Screening for WBC screening
 - Combination of history and testing
- The combination approach is being increasingly utilised.

Not all WBC Antibodies are Equal

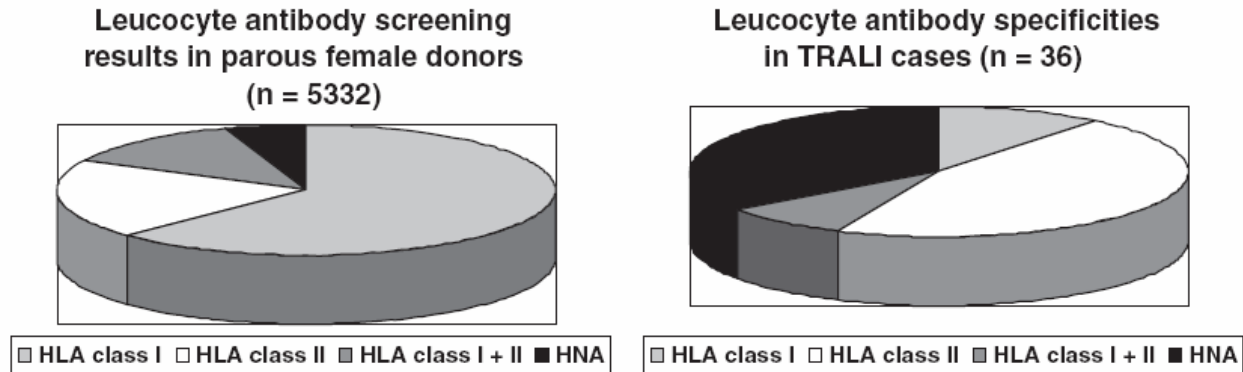


Fig. 1 Specificities of leucocyte antibodies in donor screening programme and TRALI cases.

- HLA class I antibodies predominate in donor population but are an infrequent cause of TRALI.
- Important to ensure that testing strategies identifies the 'high risk' donors to maximise risk reduction and avoid unnecessary loss of donors from panel.

Antibody Specificity and TRALI

Report	Antibody class specificity (%)			
	HNA	HLA Class I	HLA Class II	Mixed
Keller-Stanislawski et al(1)	20	10	37.5	32.5
Reil et al (2)	33	11 2/4 HLA A2	47	8
Chapman et al (3)	14	20 5/12 HLA A2	41	3

1. Vox Sanguinis (2010) 98, 70-77
2. Vox Sanguinis (2008) 95, 313-317
3. Transfusion (2009) 49, 440-452

50% of cases had a Leucoagglutinin (GAT positive)

HLA A2 high risk

ISBT Working Party on Granulocyte Immunobiology

- Recommendations on leucocyte antibody screening for TRALI reported in 2009.
- Apply to both investigation of suspected cases and donor screening.
- Recommend that high plasma volume components should not be prepared from donors with leucocyte antibodies.
- Raise possibility that donors with HNA-3a antibodies should be permanently deferred.
- Caution the use of highly sensitive antibody screening systems particularly for HLA class I.

Why might HLA Class I Antibodies not be Important?

- Transfused HLA Class I antibodies are primarily absorbed to platelets and soluble class I molecules that represent 90% of HLA class I antigens in blood.
- It is unlikely that an antibody directed against a low frequency HLA Class I antigen will be transfused into a patient who carries the cognate antigen and who is susceptible to TRALI.
- Based on the above they conclude that the clinical relevance of weakly reactive antibodies detected in assays with increased sensitivity is questionable.

ISBT Working Party on Granulocyte Immunobiology

ANTIBODY CLASS SPECIFICITY	RECOMMENDED TECHNIQUES	COMMENTS
HNA	(i) Granulocyte immunofluorescence test (GIFT) (ii) Granulocyte agglutination test (GAT) (iii) Granulocyte Chemiluminescence test (iv) Any other validated test	<ul style="list-style-type: none"> • Important to detect HNA 1a, 1b, 3a • GAT has enhanced ability to detect granulocyte agglutinins
HLA Class I	(i) Enzyme immunoassay (ii) Flow cytometry with microbeads (iii) Lymphocytotoxicity (iv) Lymphocyte immunofluorescence (v) Any other validated test	<ul style="list-style-type: none"> • Detection of HLA A2 particularly important • Question relevance of detecting weak and low frequency antibodies
HLA Class II	(i) Enzyme immunoassay (ii) Flow cytometry with microbeads (iii) Any other validated test	

HLA Immunisation in Platelet Donors

STUDY	NUMBER OF DONORS	RESULTS
<p>Densmore et al. Transfusion 1999: 39: 103-106</p>	<p>332 female platelet donors</p>	<p>17% had HLA antibodies Clear relationship between risk of HLA antibodies and number of pregnancies Donor with HLA antibodies had average 2.9 pregnancies</p> <ul style="list-style-type: none"> ▪ 0 pregnancies 7.8% ▪ 1-2 pregnancies 14.6% ▪ 3+ pregnancies 26.3% <p>Donors without antibodies had average 1.8 pregnancies</p>
<p>McLennan et al Vox Sanguinis 2004: 87 suppl 3 S2-S16</p>	<p>1416 platelet donors –1166 female –250 male</p>	<p>75% of female donors had been pregnant 15% female donors had HLA antibodies HLA Antibody prevalence increased with parity</p> <ul style="list-style-type: none"> ▪ 0 pregnancies 1.6% ▪ 1 pregnancy 10.5% ▪ 2 pregnancies 15.8 % ▪ 3 pregnancies 25% ▪ 4+ pregnancies 17%

Leukocyte Antibody Prevalence Study (LADS)

- Study managed by Retrovirus Epidemiology Donor Study Group (REDSII).
- Assessed prevalence of HLA antibodies and their relationship to previous transfusion or pregnancy.
- Tested for HLA Class I and II antibodies using multi-antigen bead flow analysis (One Lambda using Luminex).
- Utilised a desensitised assay based on mean plus 3SD cut off.
- A total of 8171 donors enrolled of which 7841 had both history and test results for analysis.

Leukocyte Antibody Prevalence Study (LADS)

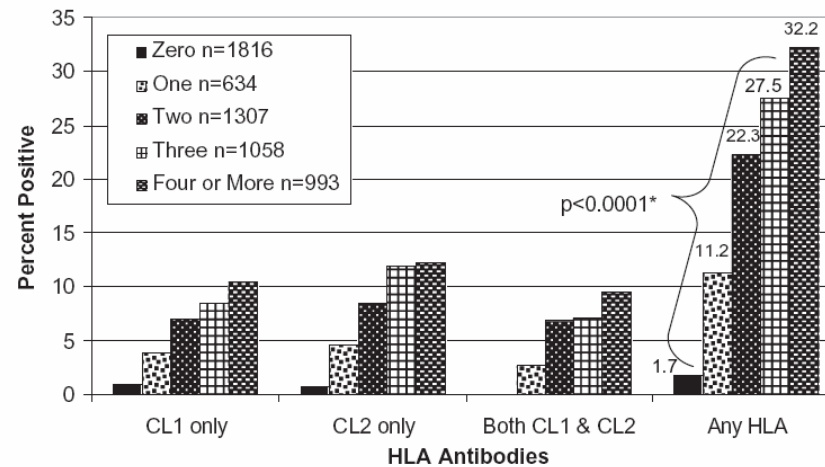


Fig. 3. HLA antibody prevalence for Class I, Class II, Class I and II, and any HLA antibody at a 3SD cutoff in never pregnant women and women with one or more pregnancies is shown. There is a significant increase in the prevalence of Class I, Class II, or any HLA antibody with an increasing number of pregnancies, from one to four or more (*overall difference comparing all groups,

- Frequency of HLA antibodies increases with successive pregnancies.
- The first two pregnancies are associated with the greatest increase in prevalence.
- Estimate that implementation of HLA antibody screening would lead to the loss of 6% of apheresis platelet donations based on donor panel profile in participating centres.

Personal Observations

- Most studies assessing prevalence of WBC antibodies in donors have focussed on HLA class I and II antigens.
- Limited data is available in relation to prevalence of HNA antibodies.
- This reflects the absence of high throughput screening systems capable of detection HNA antibodies.
- The efficacy of antibody based risk reduction systems is currently unproven.
- Further work is required to refine antibody screening protocols. This should probably be undertaken in parallel with the implementation of screening of female donors.

Broader Benefits of Reducing WBC Antibody Content of Blood Components

A randomized controlled trial of
transfusion-related acute lung injury:
is plasma from multiparous blood donors dangerous?

Miodrag Palfi, Sören Berg, Jan Ernerudh, and Gösta Berlin

Transfusion (2001) 41:317-322

The transfusion of neutrophil-specific antibodies causes
leukopenia and a broad spectrum of pulmonary reactions

*Emmanuel A. Fadeyi, Maria De Los Angeles Muniz, Alan S. Wayne, Harvey G. Klein,
Susan F. Leitman, and David F. Stroncek*

Transfusion (2007) 47 545-550

Impact of fresh-frozen plasma from male-only donors versus
mixed-sex donors on postoperative respiratory function in
surgical patients: a prospective case-controlled study

*Harumasa Nakazawa, Hiroaki Ohnishi, Hitoshi Okazaki, Shiho Hashimoto, Hajime Hotta,
Takashi Watanabe, Ryunosuke Ohkawa, Yutaka Yatomi, Kazunori Nakajima,
Yasuhide Iwao, Shigeru Takamoto, Masaru Shimizu, and Takehiko Iijima*

Transfusion (2009) 49 2434-2441

A series of publications that suggest that TRALI
might represent the severe end of a spectrum of
adverse reactions associated attributable to WBC
antibodies present in donor plasma.

What is NZBS Doing?

- Study currently being undertaken by NZBS.
- Designed by Krishna Badami:
 - Ethics Approval obtained mid 2009
 - Assesses history of pregnancy and transfusion
 - Testing by National Tissue Typing laboratory using novel assay that detects HLA Class I and II plus HNA antibodies
- Study outline:
 - Test all current female platelet donors
 - 100 male platelet donors (>50 years & no h/o transfusion)
 - 50 male platelet donors (<50 years & no h/o transfusion)
 - 20 male platelet donors with h/o transfusion

What is NZBS Doing?

- Results of study will be used to develop a risk reduction framework.
- Study recruitment now complete.
- Testing had commenced but has been delayed by kit access issues.
- Anticipate that testing will be completed within this financial year.
- Resstructuring of platelet pheresis panel will then follow in 2010/11 financial year.

Blood Component Manufacture

INTERVENTION	IMPACT
Leucocyte Depletion	No significant impact.
Washing of components	Will reduce risk but not practical as a mainstream measure.
Pathogen Reduction	No significant impact. Antibodies in plasma should be unaffected.
Platelet Additive Solution	Extent of risk reduction unclear.
Pooling	Convincing data that solvent detergent treated pooled FFP eliminates the risk of TRALI.
Plasma Fractionation	Rare case reports of TRALI associated with IVIG.

Platelet Additive Solutions

- A balanced nutrient solution specifically designed to support preservation of platelets.
- Used in a number of countries:
 - Maintains platelet metabolism well
 - Reduces frequency of febrile reactions to platelets
 - Potentially will reduce risk of TRALI
- Mixture of plasma and PAS required (30% plasma).

Composol™ PS



Platelet Additive Solution

- Platelet pools suspended in plasma comprise 4-5 buffy coats and one unit of plasma.
- Risk can be reduced by using only plasma from a male donor (NBS approach).
- Platelet pools in PAS require 4-5 buffy coats and one bag of PAS.
- The use of Pooled platelets in PAS thus moves this component from a high to a low plasma volume component.



Apheresis Platelets and PAS

- Platelets suspended in PAS require a minimum of 30% plasma.
- This significantly reduces the volume of plasma in the component.
- There is little data on whether this is sufficient to eliminate the risk of TRALI.
- It seems likely that PAS will compliment the impact of WBC antibody screening of female donors.

Solvent Detergent FFP

- TRALI has not been reported with the use of S/D FFP
 - Evident from Finnish and Irish Haemovigilance data
- WBC antibodies are not detected in S/D FFP (Sachs et al 2005)
 - Tested 20 batches for HNA and HLA I & II antibodies. All were negative.
 - Attributable to either dilution effect or impact of soluble antigens in plasma.
 - S/D treatment does not affect immunoglobulin content or composition.

Cost Effectiveness of Solvent Detergent FFP

- Time series analytic model used to estimate the incremental cost/life year saved for S/D FFP compared to untreated FFP.
- Various infective and non infective transfusion related complications considered.
- Concluded that previous analyses greatly underestimated the cost effectiveness of S/D FFP. Inclusion of non infectious complications, including TRALI, suggests that S/D FFP is cost-effective in patients ≤ 48 years and in older patients with good clinical prognosis.
- Model did not take impact of preferential male only FFP into account.

Concluding Comments

- TRALI is recognised as a significant cause of transfusion morbidity and mortality.
- Introduction of preferential ‘male only FFP’ in the UK was associated with a significant reduction in case reports. Similar approaches have been adopted by other Blood Services.
- Strategies to further reduce the risk of antibody associated TRALI utilising WBC screening of female donors are being developed.
- Further work is required to optimise the sensitivity and range of antibody targets in order to maximise the effectiveness of these interventions.