Update on Transfusion Related Acute Lung Injury (TRALI)

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Issue for the Blood Products Advisory Committee (BPAC)

FDA seeks to be advised whether available scientific data support the development of FDA policies on methods to reduce the incidence of TRALI

Presentations

Introduction

Alan Williams, Ph.D., DBA, OBRR, FDA

Clinical and Laboratory Aspects of TRALI,

David Stroncek, M.D., National Institutes of Health

Current Use of Transfusable Plasma

Ravi Sarode, M.D., University of Texas Southwestern Medical Center

Presentations

Review of REDS-II LAPS Study on HLA and Granulocyte Antibody Prevalence in Blood Donors

Steven Kleinman, M.D., University of British Columbia

American Red Cross Experience with TRALI

Richard Benjamin, M.D., American Red Cross

America's Blood Centers Experience with TRALI,

Celso Bianco, M.D., America's Blood Centers

TRALI Recipient Fatality Reports to FDA
FY 2004 – FY 2006

CATEGORIES	FY-04		FY-05		FY-06	
TRALI	21	30.9%	30	36.6%	35	50.7%

Components Associated with Reported Fatalities Due to TRALI FY 06

FFP	24
RBC	6
Platelets, Pheresis	2
RBC & FFP	2
RBC & Cryo-poor Plasma	1

TRALI: Incidence and Products

Incidence:

- From 1 in 1,000 to 1 in 10,000 units transfused

Products implicated :

- Fresh Frozen plasma, platelets, and red cell concentrates
- More likely to be associated with FFP and platelets

SD plasma is not thought to cause TRALI

Sachs UJ et al. Transfusion 2005;45:1628-31

Transfusion Related Acute Lung Injury (TRALI): What is it?

- Severe shortness of breath within 4 to 6 hours of a transfusion
- No signs of fluid overload
- Pulmonary infiltrates on chest x-ray

TRALI: Clinical Features

- Dyspnea and hypoxemia
- Fever
- Hypotension or hypertension
- Chest x-ray: bilateral infiltrates, “white out”

TRALI: Treatment

Hypoxemia

- Supplemental oxygen
- Intubation and mechanical ventilation

Hypotension

- Intravenous fluids
- Agents to increase blood pressure

Corticosteroids

Moore SB. Critical Care Medicine 2006; 34: S114-117

TRALI: Clinical Course

- Symptoms generally resolve in 24 to 48 hours
- Symptoms may resolve before diagnosis is made
- Mortality 10% to 50%

Moore SB. Critical Care Medicine 2006; 34: S114-117

Rana R et al. Transfusion 2006;46:1478-1483

Mechanisms of TRALI

- 45-60% of TRALI cases associated with neutrophil-specific antibodies (NSA) in donor
- Donor antibodies to HLA Class I or Class II antigens also implicated
- Allotypic leukocyte antibodies known to be stimulated by pregnancy and transfusion

Prior FDA Public Discussions Regarding TRALI

- Blood Products Advisory Committee - June 15, 2001

Should FDA consider regulatory interventions at this time to identify donors and/or donations with an increased risk for producing TRALI in a recipient?

1 – Yes

13 - No

- The committee recommended more research
- October 2001 FDA Physician Letter to Improve TRALI Recognition
  - *Increase in fatality reports to FDA*

Recent Observations Regarding TRALI

- Serious Hazards of Transfusion (SHOT) analysis and UK intervention study
  - TRALI incidence 5 – 7 fold higher following administration of high volume plasma units
  - UK Minimized use of FFP and buffy coat-derived platelets from female donors in October 2003. TRALI incidence in the UK subsequently declined dramatically.

- 2004 Canadian TRALI Consensus Conference
  - Introduced standardized TRALI definitions based on clinical and radiologic criteria. Recommended that blood collection agencies assess the value and cost of TRALI interventions

UK NBS (SHOT) data
Change in TRALI profile since 2003

Reporting Year	1999-2002	2003	2004	2005
TRALI Cases analyzed	64	36	23	23
Highly likely	16	20	10	3
Probable	16	2	3	3
Possible	25	6	4	3
Unlikely	7	8	6	14

Recent Observations Regarding TRALI

American Red Cross (ARC) objectively assessed 550 system wide suspected TRALI cases including 72 fatalities (2003-2005)

- Plasma transfusion was associated with 24/38 (63%) of probable TRALI fatalities
  ($4.93/10^6$ distributed components)
- Platelets, Pheresis were associated with 5/38 (13%) of probable TRALI fatalities
  ($3.12/10^6$ distributed components)
- Female donors & high plasma volume components were disproportionately implicated in TRALI
- Limiting plasma from female donors might reduce as many as six recipient deaths annually in the ARC system

Voluntary Industry Recommendations
AABB Association Bulletin #06-07

- Blood collecting facilities should implement interventions to minimize the preparation of high plasma volume components from donors known to be leukocyte-alloimunized or at increased risk of leukocyte Alloimmunization.
- Blood transfusion facilities should work toward implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion
- Blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality (using the Canadian Conference Definition)

Voluntary Interventions (Discussed or Implemented) by the Blood Collection Community

- Deferral of donors implicated in previous TRALI cases
- Preferential Use of Male Plasma for Transfusion
- Selected Donor questioning or Testing for NSA and HLA antibodies
  (e.g. female donors of Platelets, Pheresis)
- Review of Evidence Supporting Appropriate Use of Plasma
- Research
  - Mechanisms of TRALI pathogenesis
  - Prevalence of associated antibodies and other factors
  - Role of previous transfusion in WBC alloimmunization of donors

Reds II Leukocyte Antibody Prevalence (LAPS) Study

A five year study funded by NIH in 2004 in multiple project areas across the U.S.

LAPS-1 Determine HLA class I and II prevalence, antibody specificities & correlate with pregnancy, history of transfusion, and immune status. (compare with baseline group)

Determine prevalence of neutrophil antibodies in those with HLA antibodies and controls (limited in scope)

LAPS-2 Clinical Lookback study of TRALI

The incidence of TRALI in recipients of high plasma volume components from donors with leukocyte antibodies

(planning stage)

TRALI :Take Home Messages

- Significant misuse of plasma
- Overuse by a factor of 10 (NIH 1984)
- Current evidence does not support prophylactic plasma transfusion to correct mild or moderate abnormal coagulation tests in patients with no history of excessive bleeding
- Blood banks should practice transfusion medicine rather than function simply as dispensing units
- Greater need for clinicians' and medical students' education in transfusion medicine and hemostasis
  - The clinicians respond to education

TRALI Appropriate Products

- The practice of plasma transfusion to 1.5 X normal clotting time should be revised:
- Cryoprecipitate
- Antifibrinolytic agents
- Protamine for heparin-induced bleeding
  - FFP may make bleeding worse
- Prothrombin complex concentrates for reversal of coumadin effect

Ravi Sarode U of Texas Med Center

BPAC votes & comments

- Unanimous **YES** for the use of predominantly male plasma for transfusion.
- Unanimous **NO** for the non-use of plasma from donors with a history of prior transfusion.
- Unanimous **Yes** that more data is needed for selective donor screening for anti-neutrophil or anti-HLA antibodies which could be beneficial but the technology is lacking for anti-neutrophil screening and anti-HLA screening is less beneficial
- Little or no effect on U. S. plasma supply if predominantly male plasma is used for transfusion

Comments from BPAC

Females with no history of pregnancy or transfusion should be allowed to donate plasma

Non-specified Female plasma could be used in critical shortages.

Guidance on appropriate clinical use of plasma should be distributed

(AABB –CTMC is working on guidance)