

COMMITTEE UPDATES

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Transfusion Related Acute Lung Injury (TRALI)
The FDA Current View
BPAC – July 22-23, 2004

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REPORTED FATALITIES

CATEGORIES	FY - 01	FY - 02	FY - 03
TRALI	12 15.8%	16 16.8%	21 22.3%
ABO HEMOLYTIC TRANSFUSION RX	10 13.2%	14 14.7%	11 11.7%
BACTERIAL CONTAMINATION	8 10.5%	17 17.9%	11 11.7%
OTHER TRANSFUSION RELATED CAUSES	27 35.5%	24 25.3%	26 27.7%
TRANSFUSION RELATION NOT RULED OUT	11 14.5%	9 9.5%	13 13.8%
NOT TRANSFUSION RELATED	4 5.3%	5 5.3%	4 4.3%
DONOR FATALITIES	4 5.3%	10 10.5%	8 8.5%
TOTAL	76	95	94

AVERAGE OF KEY CAUSES FY-01 THROUGH FY-03

- TRALI 16.3%
- ABO/Hemolytic Transfusion Reactions 14.3%
- Bacterial Contamination 14.1%

TRALI

FDA Fatality Program reports:

- TRALI implicated in 16 - 22% of total fatalities reported in each of the last three years
- The most common cause of transfusion related fatalities reported to FDA in 2003
- Majority of deaths associated with FFP followed by RBCs and apheresis platelets

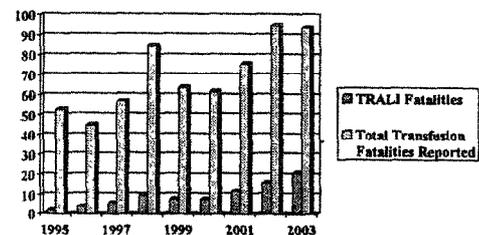
TRALI

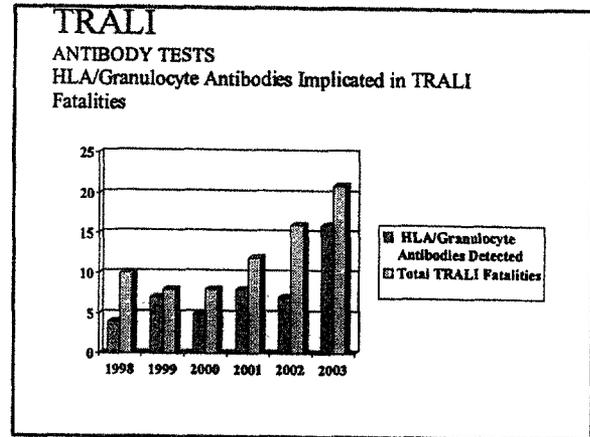
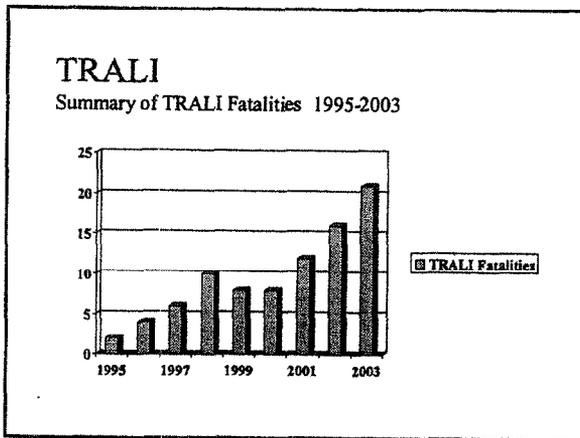
- Review of all FDA reported transfusion-associated fatalities from 1976-1995, found respiratory deaths as a percentage of total reported deaths = 15%

K.Sazama, MD, UT MD Anderson
FDA workshop on Transfusion Errors 2/2002

TRALI

TRALI Fatalities vs. Total Transfusion Fatalities Reported





TRALI- Toronto Consensus Conference

- Magnitude of the risk is unknown
- Estimates 1 in 5000 to 1 in 100,000
- Evidence for two mechanisms
- Insufficient evidence for screening tests and/ or other donor exclusion measures at this time

TRALI

FDA Actions Taken in 2001

- Issue presented to BPAC June 15, 2001
- CBER Health Alert to blood community October 13, 2001 www.cber.fda.gov
- Recommend pre-storage leukoreduction
May reduce recipient antibodies
- Recommended voluntary MED WATCH reporting of non-fatal TRALI cases
- Several poster presentations to raise clinician awareness

TRALI

Question to the Committee:

- BPAC June 15, 2001
- Should the FDA consider *Regulatory* action at this time to identify donors and donations at increased risk for producing TRALI in a recipient?

Votes 1, Yes; 13, No; 0, abstentions

TRALI,

BPAC Recommendations

- 1 member thought it prudent to identify and defer donors implicated in multiple TRALI cases.
- BPAC agreed that this should be the responsibility of each establishment
- Research to define the scope of the syndrome, and a prospective epidemiologic study to establish incidence, donor & recipient risks

TRALI

**BPAC Recommendations
Research**

- ? Role of HLA, Leukocyte antibodies & other potential causative mechanisms
- Careful evaluation of cases in which the donor can be linked with the reaction
- A multi-center study to assess & evaluate acute pulmonary reactions & lung problems in the transfusion setting using a standardized protocol
- Surveillance of recipients of IVIG for TRALI reactions

TRALI

**Possible future regulatory
strategies:**

1. Diversion of plasma from female donors to components other than FFP
Does not involve a new question
FFP most often involved in TRALI

Plasma in other components ignored
Shortages of FFP may occur

TRALI

**Possible future regulatory
strategies:**

2. Preventive antibody testing, and/ or questioning of donors on parity followed by plasma product diversion & RBC wash from donors with risk

Samples & testing not standardized
All WBC antibodies may not be equal in their ability to cause TRALI other recipients

TRALI

**Possible future regulatory
strategies:**

3. Defer donors implicated in a single unit or in more than one multiple unit TRALI case regardless of antibody status

Allows first case of TRALI to occur
Depends on accurate case reports & donor tracing

**Statement of
The American Association of Blood Banks**

Before the Blood Products Advisory Committee

July 22, 2004

Transfusion-related Acute Lung Injury (TRALI)

**Presented by Kay R. Gregory, MS, MT(ASCP)SBB
Director, Regulatory Affairs**

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

The American Association of Blood Banks (AABB) believes that transfusion-related acute lung injury (TRALI) is a significant transfusion safety concern that merits increased awareness and research. In an effort to educate our members about the clinical and laboratory features of TRALI, AABB has issued guidelines for the management of TRALI and our association considers this a priority transfusion safety matter. We commend the Food and Drug Administration (FDA) for alerting physicians to the risk of TRALI from transfusion of plasma-containing blood products in 2001. However, we are disappointed that the federal government has not done more to advance needed research regarding this important transfusion safety issue since the Blood Products Advisory Committee (BPAC) last addressed TRALI in 2001.

Definitions

In order to allow for the most effective and meaningful research and clinical understanding of this condition, the AABB proposes that a uniform definition of TRALI be established and adopted by the medical community and policy makers, including the FDA. Earlier this year, Canadian Blood Services and Hema-Quebec hosted a valuable consensus conference, bringing together the leading experts to discuss the current state of knowledge regarding TRALI. At the end of this conference, the group recommended definitions of TRALI, and "possible TRALI" (see attached definitions).

In general, the group recommended that TRALI should be diagnosed in patients with no acute lung injury (ALI) prior to transfusion who, during or within six hours after transfusion, experienced certain specific criteria. They distinguished "possible TRALI" cases, which would involve patients with the same criteria who also had one or more temporally associated ALI risk factors.

The AABB endorses the definitions set forth during the consensus conference and urges the FDA to adopt these definitions as well. Emerging data and research regarding TRALI should be carefully monitored to determine if refinements to these definitions are necessary over time.

Research

Using the uniform definitions, AABB recommends that additional research be conducted to define the scope of the problem and its mechanisms or pathophysiology. As we proposed to BPAC in 2001, AABB continues to advocate a prospective epidemiologic study to establish the incidence of TRALI. For example, we propose a multi-center study of acute lung problems in the transfusion setting to assess, evaluate, and analyze all pulmonary reactions using a standardized protocol.

The AABB also continues to recommend that the National Heart, Lung and Blood Institute (NHLBI) establish a multi-center study to lead to a better understanding of the mechanisms that cause TRALI. Once the mechanisms of TRALI are better understood, the risk factors in donors and recipients may become apparent.

Donor Deferrals

The AABB continues to believe that more data are needed before establishing donor deferral criteria for TRALI. When a severe clinical reaction has occurred, an antibody has been identified in the donor and the recipient has the corresponding antigen, the preventive measure is relatively clear. In such cases, it is generally agreed that blood from that donor should not ever again be transfused to the same recipient. However, it is not so clear that such a donor should be permanently deferred from donating all blood components. The appropriate preventive measures are even less obvious for the majority of pulmonary reactions that occur in the transfusion setting.

It is important to understand what proportion of the donor population would be affected by proposed deferral criteria, so that the potential impact on the blood supply can be evaluated. These data are especially critical, as we already too frequently face blood shortages in regions across the country. A careful and thorough analysis of the risks and benefits of any donor deferrals must be completed before taking steps that could unnecessarily hinder patient access to life-saving blood components.

Consensus Conference Definitions

TRALI:

For patients with no Acute Lung Injury (ALI) prior to transfusion, the diagnosis of TRALI is made if, during or within six hours after completion of transfusion, there is:

- *Acute onset of respiratory distress*
- *Hypoxemia, as defined by one of the following:*
 - *PaO₂/FI_O₂ < 300 mm Hg or*
 - *Oxygen saturation is < 90% on room air or*
 - *Other clinical evidence*
- *Bilateral lung infiltration in the chest radiograph*
- *No evidence of circulatory overload*
- *No other temporally associated ALI risk factor(s)*

“Possible TRALI:”

For patients with no ALI prior to transfusion, the diagnosis of POSSIBLE TRALI is made if, during or within six hours after completion of transfusion, there is:

- *Acute onset of respiratory distress*
- *Hypoxemia, as defined by one of the following:*
 - *PaO₂/FI_O₂ < 300 mm Hg or*
 - *Oxygen saturation is < 90% on room air or*
 - *Other clinical evidence*
- *Bilateral lung infiltration in the chest radiograph*
- *No evidence of circulatory overload*
- *One or more temporally associated ALI risk factor(s)*

The risk factors for ALI which if pre-existing prior to transfusion distinguish TRALI from “possible TRALI” include:

- *Septic shock*
- *Sepsis*
- *Aspiration*
- *Lung contusion*
- *Pneumonia ICU*
- *Multiple trauma*
- *Drug overdose*
- *Burn injury*
- *CP bypass*
- *Inhalation injury*
- *Acute pancreatitis*

Issue Summary
Blood Products Advisory Committee
July 22-23, 2004

Committee Update II: Blood Pressure Standards

Issue:

Recently, questions have been raised regarding the requirements for lower limits for blood pressure in donors. This update will review the current regulations that apply to blood pressure determination in donors, and the evidence for relevance of normal blood pressure to safety of donation.

Background:

Blood pressure determinations have been performed routinely for many years as part of screening for both Whole Blood and Source Plasma donors. However, the value of these determinations has been questioned, especially regarding any need to set lower limits. More generally, it is uncertain whether blood pressure screening adds measurably to donor safety.

Blood pressure determinations are required under *21 CFR 640.3 (b) (1)* which states that the donor's systolic and diastolic blood pressure are within normal limits, unless a physician, after examining the donor, is satisfied the donor is otherwise qualified to donate blood despite having pressures outside these limits.

The criteria for an upper and lower limit is required under *21 CFR 606.100 (b) (2)* which states that a blood collection facility include in its Standard Operating Procedure (SOPs) methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or a procedure when a factor in determining acceptability.

CBER's interpretation of 21 CFR 640.3(b)(1) and 606.100(b)(2) is that a blood collection center should have a range of acceptance for the donor's systolic and diastolic blood pressures. CBER has not made recommendation as to what these limits should be but has accepted the limits set by industry. Donors whose blood pressure does not fall within the established values are ineligible to donate unless evaluated by a qualified physician who can make determination that the collection of a unit of Whole Blood or Source Plasma will not present a risk to the donor's health

In the U. S., the American Association of Blood Banks (AABB) in its Technical Manual published a range of 90-180 mm of mercury and a diastolic not to exceed 100 mm in 1974. Medical evaluation is not addressed. It was changed in 1977, when a range of 90-180 mm of mercury for systolic blood pressure and 50 – 100 mm of mercury for diastolic blood pressure replaced the original recommendations. Medical evaluation was advised for determinations outside these limits. A further change occurred in 1990 edition of the

Technical Manual when a systolic blood pressure no higher than 180mm of mercury and a diastolic pressure no higher than 100 mm of mercury was recommended, deleting the lower limits. Medical evaluation was advised for blood pressure values above the limits. This standard continued to be published until the present.

A random sampling by the Food & Drug Administration (FDA) of the Standard Operating Procedures (SOP) of 18 licensed blood and plasma establishments found they all had upper and lower limits for both systolic and diastolic blood pressures with recommendations for medical evaluation of blood pressures outside of the stated ranges. However, FDA inspections at some registered, unlicensed facilities have found an absence of lower limits for donor blood pressure.

Discussion:

A recent review of medical textbooks and relevant literature suggests that there is no uniform agreement on the lower limit of normal blood pressure. Moreover, there is a question as to whether an isolated blood pressure reading truly is indicative of a donor's health. Furthermore, the evidence is not convincing that blood or plasma donation causes harm either to persons who are hypertensive or hypotensive.

Donor policies in Europe are noteworthy in this debate. The Council of Europe recommendations state: "It is recognized that recording the blood pressure may be subject to several variables but as a guide the systolic blood pressure should not exceed 180 mm of mercury and the diastolic pressure 100 mm." Within the German guidelines, the systolic blood pressure has to be between 100 and 180 mm of mercury and the diastolic blood pressure below 100 mm of mercury. In contrast, the U.K. blood services have no requirement for routine blood pressure determinations of donors. However, equipment for measuring blood pressure is provided at each center for use if there is a history of hypertension in a potential donor or of fainting occurred after previous donations. The rationale as stated by a Committee of Quality Assurance Experts in 2003 was the following: the conditions at the donor sessions render a good quality BP determination unreliable because of poor staff competence, "white coat hypertension", the hastiness of many blood drives, etc. Blood pressure determination may represent an added attraction to donate and increase attendance by otherwise unqualified donors.

The following articles concerning blood pressure are of interest:

Trouern –Trend et al, in a case controlled multicenter study of vasovagal reactions in blood donors found that 3.5 donors per 1,000 with blood pressures less than 100/60 fainted, while the rate for donors with blood pressure readings of 129-149/70-90 was significantly less (1.02 per 1,000). The authors summarize their findings with the following statement, "Female donors, young donors, low weight donors and donors with lower pressure had higher absolute donation reaction rates than did other donors. When adjusted for other variables by regression analysis, age weight and donation status were

significant (regression coefficient $p < 0.0001$), while sex, predonation blood pressure were not. The variables that contributed most to predictions, in descending order were age, weight, and donation status".

Kaspirin DO et al in a study of moderate and severe reactions in blood donors compared 217 donors with reactions with 5,630 control donors Those with reactions had an average systolic blood pressure of 116.2 vs. 119.4 in controls; the reactors had an average diastolic blood pressure of 73.3 vs. 75.5 in the controls. These differences in blood pressure were statistically significant at $p < 0.0001$, and donors with systolic blood pressure of 80 – 100 had 70 % more reactions than those with a systolic blood pressure of 120-140, The authors state, "The observation that the systolic and diastolic blood pressures are significantly lower in donors with reactions than donors without reactions has been studied previously. However, as in earlier studies, differences in blood pressure were too small to be of clinical value."

Tomita T et al in reviewing 28,189 apheresis donors in Japan found that a particular pattern of blood pressure could not be used for prediction of vasovagal reaction occurrence. However, by averaging the values obtained from five women donors, the authors found that systolic blood pressure gradually decreased by about 15 mm of mercury in 10 – 15 minutes after starting apheresis donors and then became more or less steady. Diastolic pressure also decreased with time at the beginning but its degree was less than systolic.

In summary, current FDA regulations require that blood and plasma collection centers should establish both upper and lower acceptance limits for blood pressure in a donor. However, FDA is aware of conflicting reports on the value of blood pressure as a predictor of donor reactions to phlebotomy and will consider whether any change in current policy should be pursued.

References

- 1- Title 21 Code of Federal Regulations, Part 600 to 799, Revised as of April 1, 2003
- 2- Determination of blood pressure of blood donors at blood collection sessions
Summary Report of the 26th meeting of The Select Committee of Experts on Quality Assurance in Blood Transfusion Services, February 2003
- 3- Personal Communication with Dr Peter Hellstern, Head of the Institute of Hemostaseology & Transfusion Medicine (IHT) Academic City Hospital Ludwigshafen, Germany
- 4- Guide to the preparation, use and quality assurance of blood components
(8th edition, 2001) pp 32. Council of Europe

5- Standards for Blood Banks and Transfusion Services, American Association of Blood Banks. 1991

7- Technical Manual, American Association of Blood Banks, 6th, 7th, 9th and 10th editions

8- Trouren-Trend JJ, Cable RG, Baden SJ, Newman BH, Popovsky MA. A case-controlled multicenter study of vasovagal reactions in blood donors: Influence of gender, age, donation status, weight, blood pressure, and pulse. *Transfusion* 1999;39:316-20

9- Kasprisin DO, Glynn SH, Taylor F, et al. Moderate and severe reactions in blood donors. *Transfusion* 1992;32:23-6

10- Tomita T, Takayanagi M, Kiwada K et al. Vasovagal reactions in apheresis donors. *Transfusion* 2002:1561 - 1556

**Statement of
The American Association of Blood Banks
Before the Blood Products Advisory Committee**

July 22, 2004

Blood Pressure Lower Limit

**Presented by Kay R. Gregory, MS, MT(ASCP)SBB
Director, Regulatory Affairs**

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

The AABB does not support the need for a lower limit for blood pressure for blood donors. Blood collection facilities have had only upper limits for blood pressure in place for many years.

- The AABB “Standards for Blood Banks and Transfusion Services” requires that blood pressure be ≤ 180 mm Hg systolic and ≤ 100 mm Hg diastolic. These levels have been the requirement since 1987. This particular standard was reviewed in 2002 and again in 2003, and the BBTS [Blood Banks and Transfusion Services] Standards Program Unit found no scientific evidence to warrant changing the standard.
- Blood pressure is not a requirement for donor qualification in the latest European Union Commission Directive 2004/33/EC.
- The Council of Europe Guide states: “If pulse and blood pressure is tested then the pulse should be regular and between 50 and 100 beats per minute. It is recognised that recording the blood pressure may be subject to several variables but as a guide the systolic blood pressure should not exceed 180 mm of mercury and the diastolic pressure 100 mm.”
- A review of medical textbooks revealed that there is no consistency about what is considered to be hypotension in asymptomatic individuals, and that a low blood pressure

is not a matter of great interest or concern outside of the emergency room or intensive care settings.

- A number of researchers have published articles in peer-reviewed journals showing a lack of correlation between low pre-donation systolic or diastolic blood pressure and adverse donor reactions.
- A 2002 study of 72,059 whole blood donations at the American Red Cross (ARC) showed no statistical association between low pre-donation systolic or diastolic blood pressure and adverse reaction. In addition, ARC reviewed pre-donation blood pressure on all donors with adverse reactions that resulted in hospitalization from January 1999 to December 2002. This review showed no over-representation of low blood pressure in those donors.
- A review of donor fatality reports obtained under FOIA shows no low pre-donation donor blood pressure.

There are two Code of Federal Regulations (CFR) requirements that FDA has quoted as the rationale for adding a lower limit for blood pressure: 21 CFR 640.3(b)(2), which states that systolic and diastolic blood pressure must be within normal limits, and 606.100(b)(2), which states that the standard operating procedures for donor-qualifying tests and measurements must specify maximum and minimum values. It is unclear why FDA has recently chosen to selectively enforce this particular requirement. There are other donor-qualifying tests and measurements that do not have both upper and lower limits. For example, temperature has only an upper limit, and weight, hemoglobin and age only a lower limit. We have already noted the lack of uniform agreement as to what constitutes a low blood pressure in asymptomatic individuals. In short, while there may be a regulation that can be cited as justification for this change in policy, the regulation has not been enforced in the past and a change in policy is unnecessary.

A key element of the FDA's 2004 strategic action plan is "efficient risk management." This plan states that in all of its major policies and regulations, FDA is seeking to use the best biomedical science, the best risk management science, and the best economic science to achieve health policy goals as efficiently as possible. A change to the requirement for donor blood pressure does not meet these criteria.

References:

Poles, FC, Boycott M. Syncope in blood donors. *Lancet* 1943;2: 531-5

Graham, DT. Prediction of fainting in blood donors. *Circulation* 1961;23:901-6

Callahan R et al. Study of the incidence and characteristics of blood donor "reactors."
Transfusion 1963;3:7-82

Tomasulo PA et al. A study of criteria for blood donor deferral. *Transfusion* 1980;20:511-8

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Newman BH. Donor reactions and injuries from whole blood donation. *Transfusion Medicine Reviews*; 1997;11:64-75

Trouern-Trend JJ et al. A case-controlled multicenter study of vasovagal reactions in blood donors: influence of sex, age, donation status, weight, blood pressure, and pulse, *Transfusion* 1999;39:316-20

Newman BH. Vasovagal reactions in high school students: findings relative to race, risk factors, synergism, female sex, and non-high school participants *Transfusion* 2002;42:1557-60

Tomita T et al. Vasovagal reactions in apheresis donors. *Transfusion* 2002;42:1561-6

