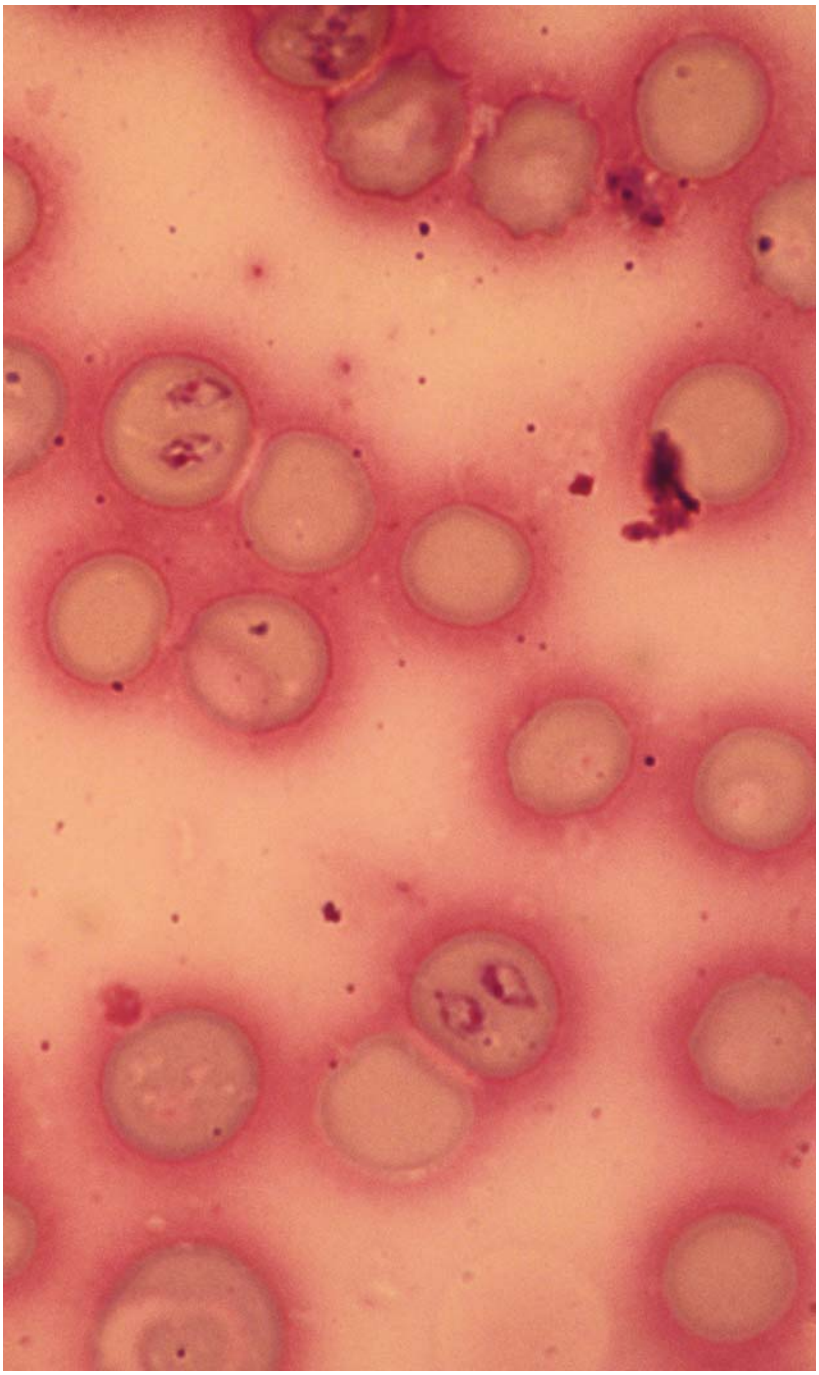
American Red Cross

PLUS

YOUR PARTNER IN PATIENT CARE

AN EDUCATIONAL RESOURCE PUBLISHED BY AMERICAN RED CROSS BLOOD SERVICES | SPRING 2009



Babesia bigemina Protozoa in red blood cells. LM X400.

TRANSFUSION-TRANSMITTED BABESIOSIS INFECTION UP IN U.S.

During January 2009, the US Food and Drug Administration reported that the agency had received nine reports of deaths due to a parasitic infection called babesiosis transmitted by blood transfusions, following nearly a decade in which no cases were reported.

Babesiosis, caused by the parasite *Babesia*, is usually transmitted through the bite of a tick, the same tick responsible for Lyme disease. Transmission via blood transfusion has also been reported. The disease is hardest on the elderly and people with compromised immune systems.

Physicians should consider babesiosis in immunocompromised patients with fever and a history of recent transfusion, Diane M. Gubernot, MD, at the FDA in Rockville, Maryland, and colleagues advised in a report published in *Clinical Infectious Diseases*.

Most patients developed altered mental status, kidney failure, or respiratory distress, with symptoms appearing from 2.5 to 7 weeks following blood transfusion. Once symptoms developed, death followed within five to 17 days. Implicated blood donations were identified, and all donors tested positive for the infection. In addition to the nine fatal cases, the number of reports of potential transfusion-transmitted *Babesia* infection and post-donation babesiosis rose from zero in 1999 to 25 in 2007.

The FDA team noted that *Babesia* can survive blood banking procedures, including freezing. There are currently no laboratory tests available to detect *Babesia* infection in blood donors.

Gubernot DM, Lucey CT, Lee KC, Conley GB, Holness LG, Wise RP. Babesia Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997–2007. *Clin Inf Dis* 2009; 48:25-30.

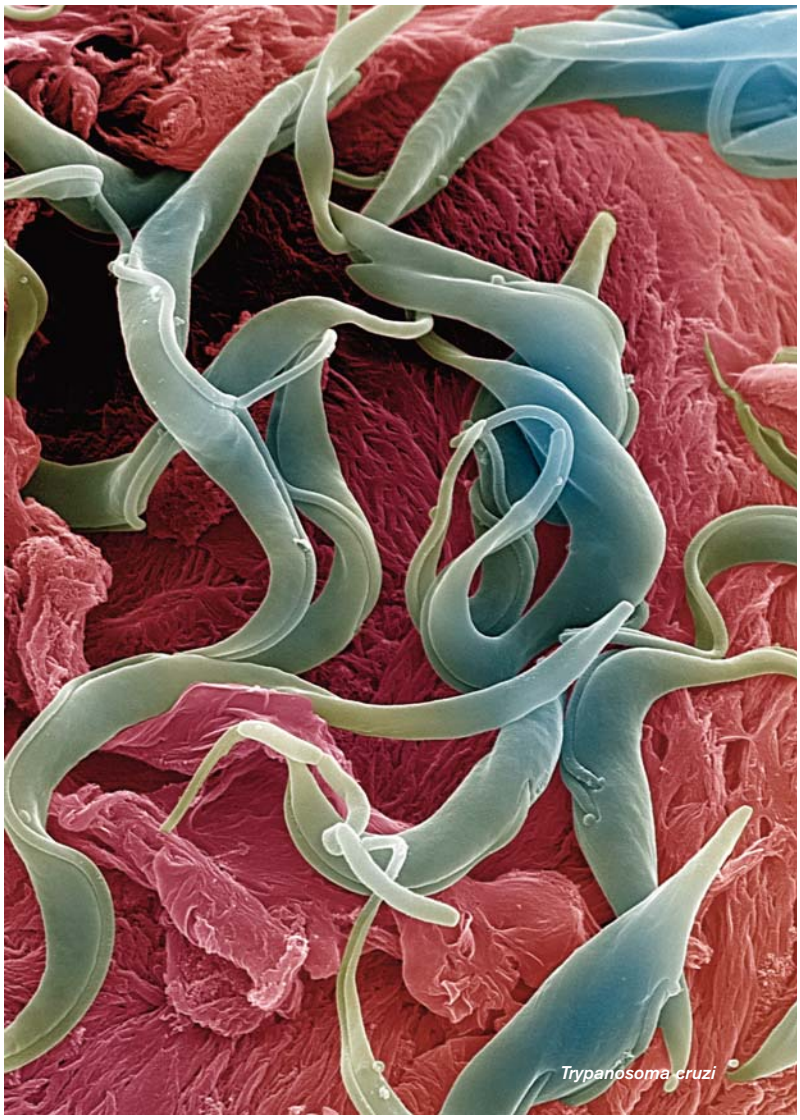
RESEARCHERS DISCUSS PROGNOSTIC IMPACT OF CHAGAS DISEASE IN THE UNITED STATES

A group of Argentinian researchers, who previously reported that Chagas disease was underdiagnosed, have written a new review that summarizes several aspects of Chagas disease in the United States, including modes of transmission, and why clinicians should be more aware of the disease and its consequences.

Trypanosoma cruzi is present in many animal species throughout most of the United States. Chagas disease also reaches the North American continent through immigration, making it more frequent than expected. Apart from immigration, non-endemic countries should be aware of transmissions through blood transfusions, organ transplantations, or mother-to-child infections.

The authors concluded it is possible that many chagasic cardiomyopathies are being misdiagnosed as primary dilated idiopathic cardiomyopathies. Recognizing that there is an evident threat of Chagas disease present in the United States allows an increase in a clinicians' awareness and permits them to correctly diagnose and treat this cardiomyopathy. They support a generalized screening of *T. cruzi* of blood donors, before organ donations, and of pregnant women who were born or have lived in endemic areas.

Milei, J, Guerri-Guttenberg RA, Grana, DR; Storino, R. Prognostic impact of Chagas disease in the United States. *American Heart Journal* 2009; 157:22-29.



Trypanosoma cruzi

STUDY CONTENDS PEPTIDE SECRETION NOT INFALLIBLE FOR TELLING TACO FROM TRALI

The secretion of brain natriuretic peptides (BNP) and N-terminal pro-brain natriuretic peptides (NT-pro-BNP) has been thought to reliably indicate transfusion-associated circulatory overload (TACO).

However, a recent study found natriuretic peptides were of limited diagnostic value in determining TACO from transfusion-related acute lung injury (TRALI) and possible TRALI in a cohort of 115 transfused critically ill patients. The researchers found the positive predictive value of the tests to be in the range of 74-78%.

The authors assert, high levels of BNP and NT-pro BNP cannot be used to obviate the need for diagnostic workup of TRALI.

G Li, Daniels CE, Kojicic M, Krpata T, Wilson GA, Winter JL, Moore SB, Gajic O. The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic peptide) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill. *Transfusion* 2009;49:13-20.

STUDY ANALYZES IMPACT OF BLOOD TRANSFUSION ON ALCOHOL-POSITIVE TRAUMA PATIENTS

Blood transfusion is a common therapy for multiple trauma patients, and it is often performed soon after hospital admission. In this study, researchers evaluated the role of blood transfusion in the treatment of blood alcohol concentration (BAC)-positive multiple trauma patients. In a three-year period, 164 patients at a single trauma center were presented with a positive BAC, and 145 met the inclusion criteria for further evaluation and regression analysis.

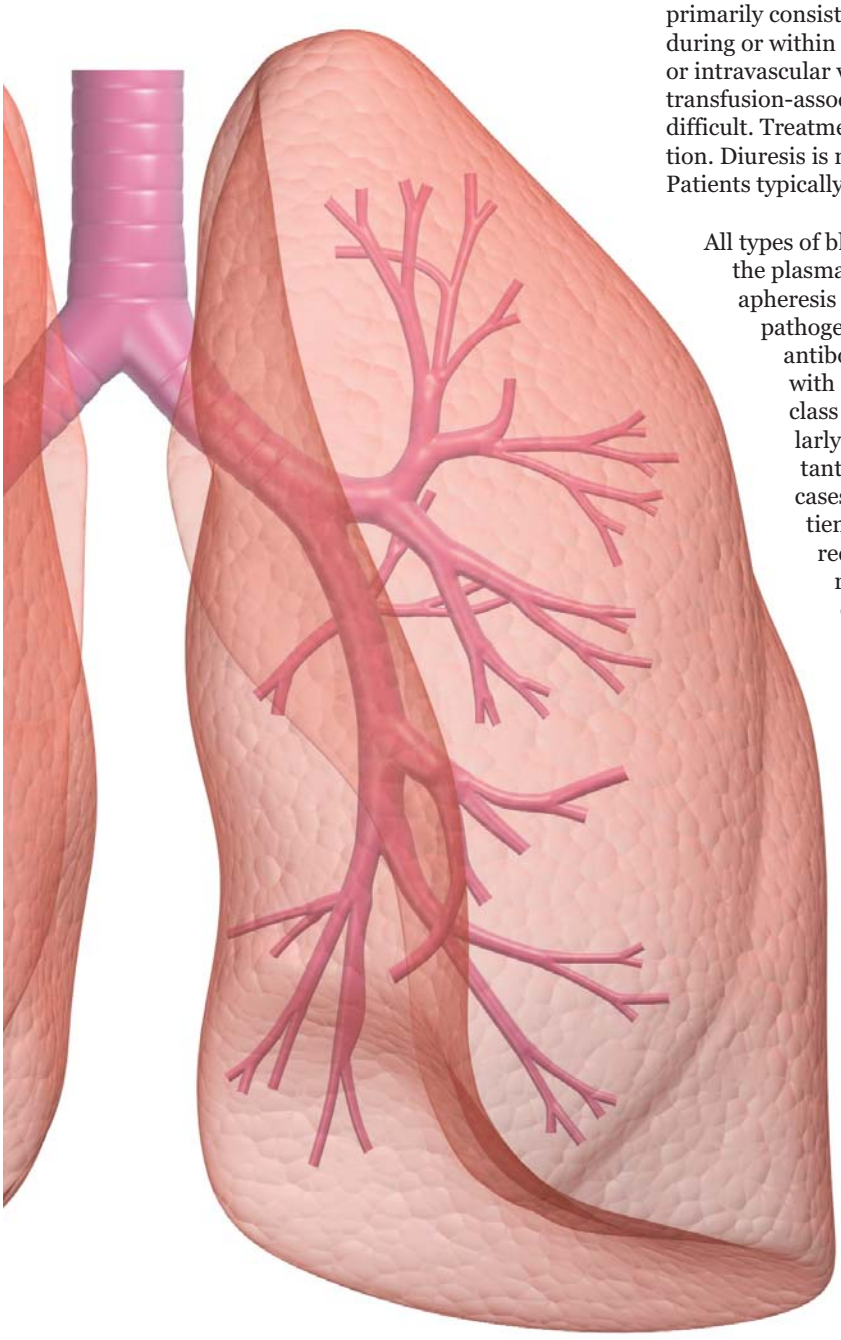
The study compared patients who were transfused (n=76) with those who were not transfused (n=69). In both groups, the most common causes of trauma were traffic accidents and falls. Most patients were admitted to the hospital from the scene of the accident (77.2%) and were male (89.0%).

Transfused patients had lower Glascow coma scale (GCS) ($p <$ or $=$ .001), had higher Injury Severity Scores (ISS) ($p <$ or $=$ to 0.001), were more likely to have severe head injuries ($p <$ or $=$ to 0.001), tended to have higher BACs ($p = 0.053$), had lower hemoglobin levels and prothrombin times in the first 24 hours ($p <$ or $=$ to .001), had lower lactate levels, had higher rates of intubation ($p <$ or $=$ to .001) and ICU admission, and had longer ICU stays and artificial ventilation times ($p <$ or $= .001$). Mortality was significantly higher in transfused patients (n=15 vs.n=3, $p <$ or $= .001$). Non-survivors were more likely to have severe head injuries; be intubated and ventilated; be older; have higher ISS scores, lactate levels, and numbers of transfusions in the first 24 hours; and have lower GCS scores, hemoglobin measurements, and prothrombin levels. In a binary logistic regression model, only age ($p = 0.009$) and ISS ($p = 0.004$) independently predicted mortality.

This single-center study concluded that the BAC of multiple trauma patients and the number of blood transfusions they received did not predict mortality in multiple trauma patients if used as independent predictors. Prospective studies with greater sample sizes should be performed to clarify the role of blood transfusions in the outcome of this sub-population.

Struck MF, Schmidt T, Stuttmann R, Hilbert P. Alcohol-positive multiple trauma patients with and without blood transfusion: an outcome analysis. *Journal of Trauma Management & Outcomes*. 2009; 3:3.

REVIEW PROBES CURRENT TRALI CONCEPTS FOR THE CLINICIAN



The leading cause of transfusion-related morbidity and mortality in the United States is transfusion-related acute lung injury (TRALI). Diagnostic criteria for TRALI have recently been developed and primarily consist of hypoxia and bilateral pulmonary edema occurring during or within 6 hours of a transfusion in the absence of cardiac failure or intravascular volume overload. The primary differential diagnosis is transfusion-associated circulatory overload and differentiation can be difficult. Treatment is supportive with oxygen and mechanical ventilation. Diuresis is not indicated and the role of steroids is unproven. Patients typically recover within a few days.

All types of blood products have been associated with TRALI; however, the plasma-rich components, such as fresh frozen plasma and apheresis platelets, have been most frequently implicated. The pathogenesis of TRALI is not completely understood. Leukocyte antibodies in donor plasma have been implicated in most cases with antibodies directed at human leukocyte antigen (HLA) class I, HLA class II or neutrophil-specific antigens, particularly HNA-3a. Activation of pulmonary endothelium is important in the development of TRALI and may account for most cases being observed in surgical or intensive care unit patients. Transfused leukoagglutinating antibodies bind to recipients' neutrophils localized to pulmonary endothelium, resulting in activation and release of oxidases and other damaging biologic response modifiers that cause capillary leak.

In a minority of TRALI cases, no antibodies were identified and it is postulated that neutrophil priming factors in the transfused component can mediate TRALI in a patient with pulmonary endothelial activation, the so called "two-hit" mechanism.

Recognition of the role of anti-leukocyte antibodies has led to new strategies to reduce the risk of TRALI. Female blood donors with a previous pregnancy frequently have HLA antibodies, with an overall prevalence of 24% and increasing prevalence related to the number of previous pregnancies. Since HLA antibodies have been implicated in TRALI, blood centers have adopted policies to produce plasma components primarily from male donors. Strategies to reduce the risk from apheresis platelets are problematic and are likely to involve testing female apheresis platelet donors for HLA antibodies. Much more research is needed to understand the blood component and patient risk factors for TRALI so novel strategies for treatment and additional measures to reduce the risk of TRALI can be developed.

Triulzi, DJ. Transfusion-Related Acute Lung Injury: Current Concepts for the Clinician. *Anesth Analg* 2009; 108:770-776.

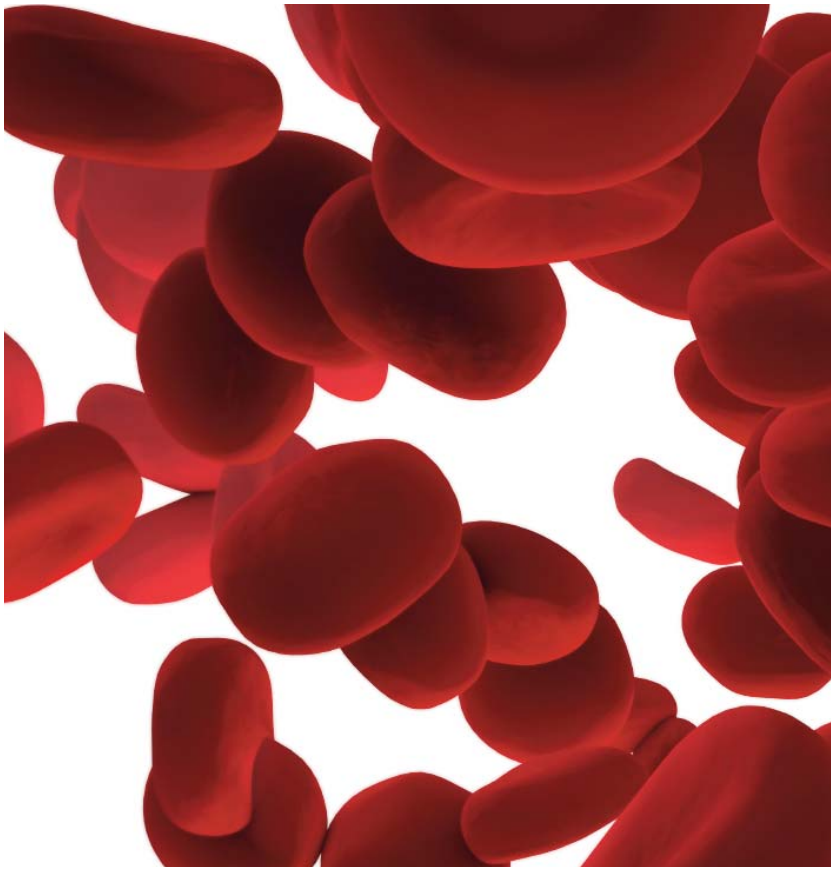
ALLOIMMUNE RESPONSE AFTER ADDITIONAL RED BLOOD CELL ANTIGEN CHALLENGE

After initial alloimmunization, 20 to 25% of immunized nonhematoncology patients develop additional red blood cell (RBC) antibodies after subsequent transfusions, but the percentage is unknown for hematoncology patients.

A 24-year retrospective study was conducted in the Netherlands to determine whether RBC-immunized hematoncology patients differ from other patient cohorts regarding this strong immune response toward additional RBC challenges within clinically relevant Rh, KEL, FY, Jk, and MNS antigens.

Overall, 25 of 115 immunized patients (21.7%) formed 30 additional antibodies after a median number of 7 RBC units were transfused. The median interval between primary and additional antibody detection was 4 months. Diagnosis or treatment intensity did not significantly influence additional antibody development.

The researchers found additional antibody formation occurences in more than 20% of RBC-alloimmunized hematoncology patients after subsequent transfusions which is comparable with the frequency in other immunized patients. To avoid extensive RBC alloimmunization, preventive extended antigen matching may be considered in hematoncology patients, who have shown to be capable of antibody formation.



Schonewille H, de Vries RR, Brand A. Alloimmune response after additional red blood cell antigen challenge in immunized hematooncology patients. *Transfusion*. 2009 ;49:453-7.

STUDY LOOKS AT THE PERSISTENCE AND EVANESCENCE OF BLOOD GROUP ALLOANTIBODIES IN MEN

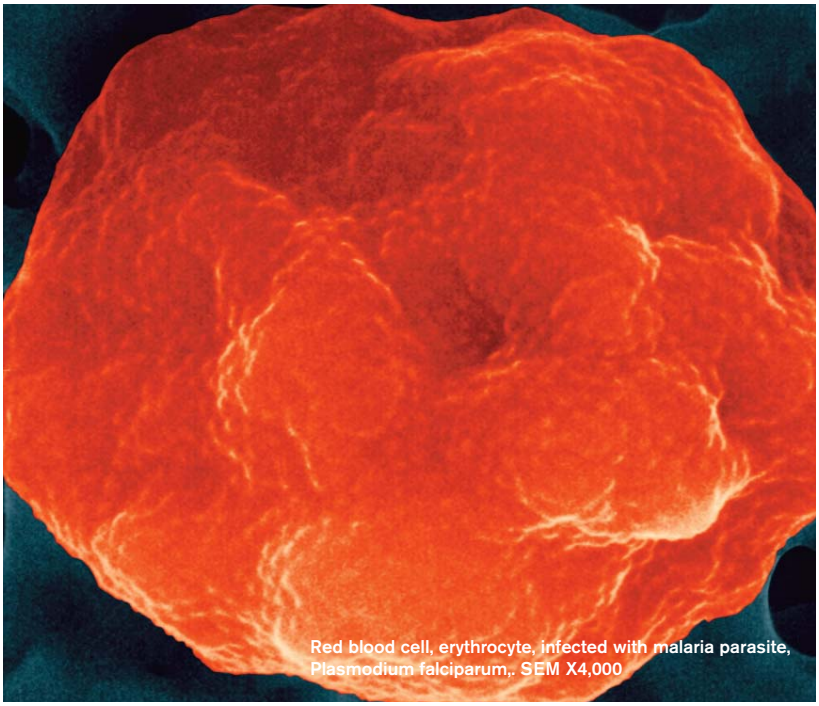
Non-ABO blood group (BG) alloantibodies can disappear over time, confounding compatibility testing and predisposing patients to delayed hemolytic transfusion reactions. The goal of this study was to analyze BG antibody disappearance after transfusion-related alloimmunization in men.The transfusion service records of 18,750 military veterans at a Department of Veterans Affairs (VA) medical center were screened to identify male patients with one or more BG alloantibodies and who had at least one type and screen performed after initial antibody detection (n = 304). Antibodies were categorized as to whether they were present at a patient's first antibody screening test ("preexisting") or after initial negative testing ("hospital-acquired").

Researchers found that overall, the evanescence of hospital-acquired antibodies (108/222; 48.6%) was significantly higher ($p < 0.0001$) than that of preexisting antibodies (36/185; 19.5%). Half (54/108) of evanescent, hospital-acquired alloantibodies disappeared within 6 months of detection, and all disappeared by 10 years. Evanescence of hospital-acquired antibodies was dependent on duration of follow-up testing, because antibodies tested 5 or more years after initial development demonstrated the highest evanescence rate (35/55; 64%; $p < 0.01$). Some evanescent antibodies (9/407; 2.2% of total antibodies) disappeared and reappeared one or more times without known antigenic reexposure ("multiple evanescence"). Among commonly observed alloantibodies, disappearance varied with antigenic specificity. The study found that approximately two-thirds of BG alloantibodies disappeared within 5 years of induction, a rate higher than previously reported in mixed-sex populations. Evanescence did not appear to be a random, first-order decay process, as evidenced by the lower evanescence rate of preexisting antibodies.

Tormey CA, Stack G. The persistence and evanescence of blood group alloantibodies in men. *Transfusion* 2009; 49:505-12.

STUDY FINDS PLATELETS KILL INTRAERYTHROCYTIC MALARIAL PARASITES

Platelets play a critical role in the pathogenesis of malarial infections by encouraging the sequestration of infected red blood cells within the cerebral vasculature. However, platelets also have well-established roles in innate protection against microbial infections. Researchers found that purified human platelets killed *Plasmodium falciparum* parasites cultured in red blood cells. Inhibition of platelet function by aspirin and other platelet inhibitors abrogated the lethal effect human platelets exert on *P. falciparum* parasites. Likewise, platelet-deficient and aspirin-treated mice were more susceptible to death during erythrocytic infection with *Plasmodium chabaudi*. Both mouse and human platelets bind malarial-infected red cells and kill the parasite within. These results indicate a protective function for platelets in the early stages of erythrocytic infection, distinct from their role in cerebral malaria.



Red blood cell, erythrocyte, infected with malaria parasite, Plasmodium falciparum,. SEM X4,000

Increased mortality in platelet-deficient mice and direct killing of *P. falciparum* by human platelets indicate that platelets are important in controlling malarial infection. Thrombocytopenia occurs early in infection in both humans and mice, before severe forms of the disease develop. Therefore, the study found the major protective effect of platelets was early in infection. Modulation of parasite growth by platelets would buffer the parasite growth rate and allow the engagement of the adaptive immune response. The researchers also found that inhibition of platelet activation abrogates the protective effect, which may explain the deleterious effect aspirin may have on malarial outcome.

McMorran BJ, Marshall VM, de Graaf C, Drysdale KE, Shabbar M, Smyth GK, Corbin JE, Alexander WS, Foote SJ. Platelets Kill Intraerythrocytic Malarial Parasites and Mediate Survival to Infection. *Science* 2009; 323: 797-800.

BRITISH STUDY FINDS FFP-RELATED TRALI CASES DECREASING

British researchers found that from 1996 through 2006, 195 cases of transfusion-related acute lung injury (TRALI) were reported. From 1999 onward, these cases were classified by probability, using clinical features and HLA and/or HNA typing. Since late 2003, the United Kingdom National Blood Service provided 80 to 90% of fresh-frozen plasma (FFP) and plasma for platelet (PLT) pools from male donors.The study found 49% of reports were highly likely/probable to contain TRALI, and 51% possible/unlikely. Of 96 investigations, donor antibodies recognizing recipient antigens were found in 73 cases (65%), with HLA Class I in 25 of those (40%), HLA Class II antibodies in 38 (62%), and granulocyte antibodies in 12 (17%). A review in 2003 revealed that the TRALI risk/component was 6.9 times higher for FFP and 8.2 times higher for PLTs than for red blood cells, and that in donors of implicated FFP/PLTs, white blood cell antibodies were found 3.6 times more often than by chance ($p <or= 0.0001$), with all implicated donors being female. Provision of male plasma was associated with a reduction in TRALI reports from 36 in 2003 to 23 in each of 2004 and 2005 and 10 in 2006. Highly likely/probable cases reduced from 23 in 2003 to 10, 6, and 4 in the 3 subsequent years, with cases implicating FFP or PLTs falling from 16 to 9, 3, and 1 respectively.

The researchers concluded that the risk of highly likely/probable TRALI due to FFP has fallen from 15.5 per million units issued during 1999 through 2004 to 3.2 per million during 2005 through 2006 ($p = 0.0079$) and from 14.0 per million to 5.8 per million for PLTs.

Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, Navarrete C, Lucas G, Soni N, Morgan C, Choo L, Cohen H, Williamson LM; Serious Hazards of Transfusion Steering Group. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009; 49:440-452.

STUDY EVALUATES ADVERSE REACTIONS TO BLOOD DONATION BY 16 AND 17-YEAR OLDS

Blood donations by minors (16-and 17-year-olds) now account for approximately 8% of the whole blood collected by the American Red Cross, but young age and first-time donation status are known to be independent risk factors for donation-related complications.

Red Cross scientists evaluated adverse reactions to allogeneic whole blood donation by 16-and 17-year-olds compared with older donors in American Red Cross blood centers using standardized collection protocols, definitions, and reporting methods in 2006. Data were from nine American Red Cross blood centers that routinely collect from 16-and 17-year-olds, a population that provides 80% of its donations at high school blood drives.

The American Red Cross hemovigilance program prospectively evaluates reports of complications and injuries, including cases referred for outside medical care, after allogeneic whole blood and automated (apheresis) collection procedures in 35 blood services regions. Collection staff in all American Red Cross regions receive standardized training, follow standard collection procedures, and use common definitions to recognize, manage, and document adverse reactions following blood collection. All major reactions that occur at collection sites and any reaction reported back to the centers are reviewed by a physician serving that center's region and are tracked by the American Red Cross hemovigilance program; all cases involving outside medical care are also reviewed by the national medical director of the program.

The researchers found that in 2006, nine American Red Cross regions collected 145,678 whole blood donations from 16-and 17-year-olds, 113,307 from 18-and 19-year-olds, and 1, 517, 460 from donors aged 20 years or older. Complications were recorded in 15,632 (10.7%), 9,359 (8.3%), and 42,987 (2.8%) donations in each corresponding age group. In a multivariate logistic regression model, young age had the strongest association with complications (odds ratio [OR], 3.05; 95% confidence interval [CI], 2.52-3.69; P < 0.001), followed by first-time donation status (OR, 2.63; 95% CI, 2.24-3.09; P < .001) and female sex (OR, 1.87; 95% CI, 1.62-2.16; P < .001). Infrequent but medically relevant complications, in particular physical injury from syncope-related falls, were significantly more likely in 16- and 17-year-old donors (86 events; 5.9/10 000 collections) compared with 18- and 19-year-old donors (27 events; 2.4/10, 000 collections; OR, 2.48; 95% CI, 1.61-3.82) or adults aged 20 years or older (62 events; 0.4/10, 000 collections; OR, 14.46; 95% CI, 10.43 -20.04). Sixteen-year-old donors who experienced even a minor complication were less likely to return to donate within 12 months than were 16-year-olds who experienced uncomplicated donations (52% vs 73% return rate; OR, 0.40; 95% CI, 0.36-0.44).

The study found a higher incidence of donation-related complications and injury occurs among 16-and 17-year-old blood donors compared with older donors. The increasing dependence on recruiting and retaining young blood donors requires a committed approach to donor safety, especially at high school blood drives.

Eder AF, Hillyer CD; Dy BA, Notari EP, Benjamin, RJ. Adverse Reactions to Allogeneic Whole Blood Donation by 16-and 17-Year-Olds. *JAMA* 2008; 299: 2279-2286.

FDA REPORTS BLOOD SUPPLY CONTINUES TO BE SAFEST IN HISTORY

The FDA continues to report that the blood supply is safer than at any time in history. Due to advances in donor screening, improved viral marker tests, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions.

During FY2008 (October 1, 2007, through September 30, 2008), the FDA received a total of 82 fatality reports. Of these reports, 72 were transfusion recipient fatalities and 10 were post-donation fatalities.

In combined FY2005, FY2006, FY2007, and FY2008, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (51%), followed by hemolytic transfusion reactions (25%) due to non-ABO (15%) and ABO (10%) incompatibilities. Complications of microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities.

Transfusion-Related Fatalities by Complication, FY2005 through FY2008

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	total	total
	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56	34*	65%	16*	35%	114	51%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	34	15%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	28	13%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	22	10%
TACO	1	2%	8	13%	5	10%	3	7%	17	8%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	6	3%
Other	2**	3%	0	0%	0	0%	0	0	2	1%
Totals	62	100%	63	100%	52	100%	46	100%	223	100%

*In FY2007, the FDA review committee began using the Canadian Consensus Conference criteria[1],[2] for evaluating TRALI cases – these numbers includes both "TRALI" and "possible TRALI" cases**Other: Includes one case of Graft vs. Host Disease (GVHD) and one therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

US Food and Drug Administration (FDA). Fatalities reported to FDA following blood collection and transfusion. Annual summary for fiscal year 2008. March 4, 2009. Available online at www.fda.gov/cber/blood/fatal08.htm

REMEMBER THESE WEBSITES

***Immunohematology* Journal**
www.redcross.org/en/immunohematology

Reimbursement
www.redcross.org/hospitals/reimbursement

PLUS

Spring 2009, Volume Three, Issue Two

American Red Cross

SEROLOGIC FINDINGS IN AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH IMMUNOGLOBIN M WARM AUTOANTIBODIES

Autoimmune hemolytic anemia (AIHA) associated with immunoglobulin M (IgM) warm autoantibodies is unusual but often severe, with more fatalities than other types of AIHA. Diagnosing this type of AIHA can be difficult because routine serologic data are not always informative.

American Red Cross researchers conducted research in which 49 cases of IgM warm AIHA in 25 years were studied by serologic methods. Routine direct antiglobulin tests (DATs) detected red blood cell (RBC)-bound C3 in 90% of cases (65% had C3 but no immunoglobulin G [IgG] on their RBCs) and IgG in 24%. IgM was detected on 29 of 47 (62%) patients' RBCs; RBC-bound IgM was detected in 14 of 47 cases by a tube DAT method and in an additional 15 of 21 (71%) cases using fluorescein isothiocyanate anti-IgM and flow cytometry. 81% of eluates from patients' RBCs reacted. Warm autoagglutinins were present in 94% of serum samples; untreated and enzyme-treated RBCs were hemolyzed at 37 degrees C by 13 and 65% of serum samples, respectively. Most agglutinins were optimally reactive at 30 to 37 degrees C. Patients' RBCs were spontaneously agglutinated in 78% of cases; washing with 37 degrees C saline or treating RBCs with dithiothreitol resolved this problem. Clear specificity of autoantibody was defined in 35% of serum samples. The researchers concluded that IgM warm AIHA can be confused with cold agglutinin syndrome and "mixed/combined"-type AIHA; a serologic workup by a specialist reference laboratory can help with the diagnosis.

Arndt PA, Leger RM, Garratty G. Serologic findings in autoimmune hemolytic anemia associated with immunoglobulin M warm autoantibodies. *Transfusion* 2009; 49:235-242.