



**American  
Red Cross**

# PLUS

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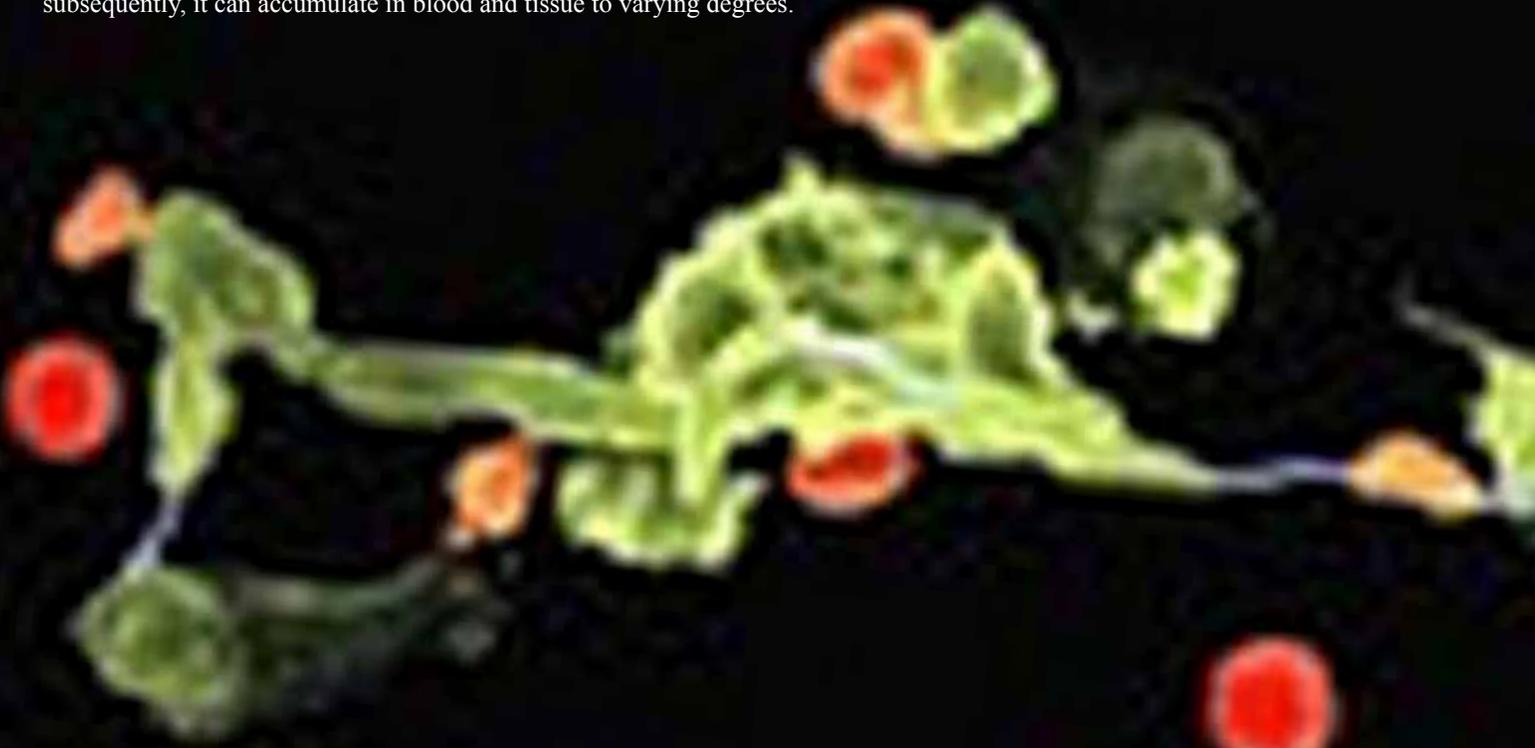
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# STUDIES EXAMINE THE PARADOX OF NEUTROPHIL'S ROLE

The neutrophil is an essential component of the innate immune system, and its function is vital to human life. Its production increases in response to virtually all forms of inflammation, and subsequently, it can accumulate in blood and tissue to varying degrees.



## TISSUE INJURY

Although its participation in the inflammatory response is often salutary by nature of its normal interaction with vascular endothelium and its capability to enter tissues and respond to chemotactic gradients and to phagocytize and kill microorganisms, it can contribute to processes that impair vascular integrity and blood flow.

The mechanisms that the neutrophil uses to kill microorganisms also have the potential to injure normal tissue under special circumstances. Its paradoxical role in the pathophysiology of disease is particularly, but not exclusively, notable in seven circumstances:

- 1) diabetic retinopathy,
- 2) sickle cell disease,
- 3) TRALI,
- 4) ARDS,
- 5) renal microvasculopathy,
- 6) stroke, and
- 7) acute coronary artery syndrome.

The activated neutrophil's capability to become adhesive to endothelium, to generate highly reactive oxygen species (ROS), and to secrete proteases gives it the potential to induce local vascular and tissue injury.

In this review, University of Rochester researchers summarize the evidence for its role as a mediator of tissue injury in these seven conditions, making it or its products potential therapeutic targets

**Segel GB, Halterman MW, Lichtman MA.** The paradox of the neutrophil's role in tissue injury: *J Leukoc Biol.* 2011;89:359-72

## ENDOTOXEMIA

**N**eutrophils play an important role in host defense. However, deregulation of neutrophils contributes to tissue damage in severe systemic inflammation.

In contrast to complications mediated by an overactive neutrophil compartment, severe systemic inflammation is a risk factor for development of immune suppression and as a result, infectious complications. Since the role of neutrophils in this clinical paradox is poorly understood, Dutch researchers tested whether this paradox could be explained by distinct neutrophil subsets and their functionality.

They studied the circulating neutrophil compartment immediately after induction of systemic inflammation by administering 2 ng/kg *Escherichia coli* LPS i.v. to healthy volunteers. Neutrophils were phenotyped by expression of membrane receptors visualized by flow cytometry, capacity to interact with fluorescently labeled microbes, and activation of the NADPH-oxidase by oxidation of Amplex Red and dihydrorhodamine. After induction of systemic inflammation, expression of membrane receptors on neutrophils, such as CXCR1 and -2 (IL-8Rs), C5aR, FcγRII, and TLR4, was decreased.

Neutrophils were also refractory to MLF-induced up-regulation of membrane receptors, and suppression of antimicrobial function was shown by decreased interaction with *Staphylococcus epidermidis*. Simultaneously, activation of circulating neutrophils was demonstrated by a threefold increase in release of ROS.

The researchers concluded that this paradoxical phenotype can be explained by the selective priming of the respiratory burst. In contrast, newly released, CD16(dim) banded neutrophils display decreased antimicrobial function. They found that systemic inflammation leads to a functionally heterogeneous neutrophil compartment, in which newly released refractory neutrophils can cause susceptibility to infections, and activated, differentiated neutrophils can mediate tissue damage.

**Pillay J, Ramakers BP, Kamp VM, Loi AL, Lam SW, Hietbrink F, Leenen LP, Tool AT, Pickkers P, Koenderman L.** Functional heterogeneity and differential priming of circulating neutrophils in human experimental endotoxemia. *J Leukoc Biol.* 2010;88:211-20.

## CANCER

**H**uman cancers are comprised of numerous cell types including neutrophils. Although often ignored, neutrophils are frequently present at sites of tumorigenesis including the kidney, breast, colon and lung. These cells possess substances such as reactive oxygen species and proteinases that are capable of modifying tumor growth and invasiveness.

This review addresses recent reports describing both pro-host and pro-tumor roles for neutrophils and neutrophil-derived substances and examines the alterations in neutrophil behavior that explain this apparent biological discrepancy.

Unfortunately, with the exception of investigator driven manipulation of neutrophil function, these cells function overwhelmingly

against the host in the setting of cancer. Many cancers are capable of recruiting neutrophils to sites of tumorigenesis where they enhance tumor growth.

Identification of the neutrophil-derived substances that promote tumor growth may yield novel therapeutic approaches to inhibit cancer progression. Alternatively, strategies designed to generate highly activated and cytotoxic neutrophils within the tumor microenvironment may provide a means to unleash the tumoricidal potential of the host's innate immune response.

**Houghton AM.** The paradox of tumor-associated neutrophils: fueling tumor growth with cytotoxic substances. *Cell Cycle.* 2010 9:1732-7.

## NEONATAL HEMOSTASIS: COMPARING THE EFFECTS OF IN VITRO ADULT PLATELET TRANSFUSIONS



**T**hrombocytopenia is frequent among neonates, and 20-25% of affected infants are treated with platelet transfusions.

These are frequently given for mild thrombocytopenia (platelets  $50-100 \times 10^9 / L$ ), largely due to the known hyporeactivity of neonatal platelets. In tests of primary hemostasis, however, neonates have shorter bleeding and closure times (CTs) than adults. This has been attributed to their higher hematocrits, higher von Willebrand factor (VWF) concentrations, and predominance of longer VWF polymers.

In this study, Children's Hospital, Boston and Harvard Medical School researchers sought to determine whether the "transfusion" of adult (relatively hyper-reactive) platelets into neonatal blood results in a hypercoagulable profile.

Cord blood (CB) and adult peripheral blood (PB) were separated (using a modified buffy-coat method) to generate miniaturized platelet concentrates (PCs) and thrombocytopenic blood. PB- and CB-derived PCs ( $n=7$  per group) were then "transfused" in vitro into thrombocytopenic CB and PB. The effects of autologous vs. allogeneic (developmentally mismatched) "transfusions" were evaluated using whole blood aggregometry, platelet function analyzer (PFA-100), and thromboelastography (TEG).

Adult platelets aggregated significantly better than neonatal platelets in response to TRAP, ADP and collagen, regardless of the blood into which they were transfused. The "transfusion" of adult platelets into thrombocytopenic CB resulted in shorter CTs-Epi (PFA-100) and higher clot strength and firmness (TEG), compared to "transfusion" of neonatal autologous platelets.

The researchers concluded that in vitro "transfusion" of adult platelets into neonatal blood results in shorter CTs than "transfusion" with neonatal platelets, and that their findings should raise awareness of the differences between the neonatal and adult hemostatic system and the potential "developmental mismatch" associated with platelet transfusions on neonatal hemostasis.

**Ferrer-Marin F, Chavda C, Lampa M, Michelson AD, Frelinger III AL, Sola-Visner M.** Effects of in-vitro adult platelet transfusions on neonatal hemostasis. *J Thromb Haemost.* 2011 [Ahead of print]

## IS THERE A RELATIONSHIP BETWEEN CHRONIC TRANSFUSION THERAPY AND BODY COMPOSITION IN THALASSEMIA PATIENTS?

**I**n order to measure body composition in patients with thalassemia and explore its relationship to abnormal growth and bone mass, researchers at the Children's Hospital & Research Center in Oakland, California conducted a cross-sectional, multicenter study.

Fat, lean, and bone mineral density (BMD) were assessed with dual-energy x-ray absorptiometry. Medical history, food frequency, and physical activity questionnaires were conducted in 257 transfused patients with thalassemia (age,  $23.7 \pm 11$  years [mean $\pm$ -SD]; 51% male) compared with 113 non-transfused patients ( $21.3 \pm 13$  years; 44% male).

Subjects with thalassemia were leaner compared with healthy American subjects from National Health and Nutrition Examination Survey III data. Transfused subjects had a higher percentage of body fat compared with non-transfused subjects after controlling for age, sex, and ethnicity; 11.8% of non-transfused pediatric subjects were considered underweight, significantly lower

than National Health and Nutrition Examination Survey data ( $P=.03$ ). Hemoglobin level was positively related to lean mass ( $P=.008$ ). Body fat and lean mass were positive predictors for both height and BMD z-scores after adjustment for transfusion status, age, sex, ethnicity, calcium intake, and physical activity (all  $P<.001$ ).

Although most adult patients with thalassemia had healthy body composition with rare obesity, young non-transfused patients appear at risk for being underweight. Optimizing physical activity and appropriate use of transfusion therapy may improve growth and bone health in these patients who are at-risk for being underweight.

**Fung EB, Xu Y, Kwiatkowski JL, Vogiatzi MG, Neufeld E, Olivieri N, Vichinsky EP, Giardina PJ, Neufeld E, Holm I, Cohen AR, Kwiatkowski JL, Manno CS, Martin M, Hillman D, Jackson GM, Vichinsky E, Fung EB, Foote D, Pang EH, Holden S, Higa A, Olivieri N, Quinn CT, Boger D, Giardina PJ, Grady RW, Mait JE, Kleinert D, Chaikhoutdinov I, Cintron G, Holm S, Peterson C, McKinlay S, Trachtenberg F.** Relationship between chronic transfusion therapy and body composition in subjects with thalassemia. *J Pediatr.* 2010 157:641-7.

# STUDY LOOKS AT BLOOD TRANSFUSION AMONG OLDER ADULTS IN THE UNITED STATES



## AGING IN AMERICA : A LOOK AT THE FUTURE

2004

**36.3**  
Americans are 65 or older

**12%**  
of population  
65 or older

2050

**86.7**  
Americans projected to be  
65 or older

**21%**  
of population  
65 or older

2000-2050

**49%**  
projected growth rate of  
entire U.S. population

**147%**  
projected growth  
rate of Americans 65  
and older

Source: U.S. census

While there have been epidemiologic studies of blood donors, the characteristics of individuals who receive transfusions have not been well described for the US population. In this study, subjects were from the nationally representative Health and Retirement Study whose data were linked to Medicare files from 1991 through 2007 (n= 16,377). A cohort study was conducted to assess the frequency of transfusion in older Americans over time and to describe the characteristics of blood recipients.

The researchers found that 31 percent (95% confidence interval [CI], 30%-33%) of older Americans received at least one transfusion within a 10-year period and 5.8% (95% CI, 5.4%-6.2%) experienced repeated transfusion-related visits within 30 days.

“31 percent of older Americans received at least one transfusion within a ten year period.”

The mean number of transfusion-related visits was 2.3 over a 10-year period (95% CI, 2.2-2.4). Older Americans who lived in the South were most likely to receive a transfusion (34%), independent of demographic and health-related factors, while those who lived in the western United States were the least likely (26%).

Predictors of transfusion included smoking, low body mass index, and a history of cancer, diabetes mellitus, end-stage renal disease, and heart disease. African-Americans and Mexican-Americans had greater rates of blood utilization than other races and other Hispanics (respectively). There were also differences in transfusion utilization by education, marital status, religion, and alcohol use.

Rogers MA, Blumberg N, Heal JM, Langa KM. Utilization of blood transfusion among older adults in the United States. *Transfusion*. 2010. [Ahead of print]

## WHAT IS THE EFFECT OF PSYCHOACTIVE DRUGS ON IN VITRO PLATELET FUNCTION?

Neuro-hormonal and hemostatic mechanisms are important in a wide range of psychological and cardiovascular diseases. The use of psychoactive drugs in mental illnesses is often involved with hematologic side effects including impaired platelet function. Subsequently, the risk for the development of cardiovascular diseases may be higher in these patients. Interestingly, platelets that play a key role in cardiovascular complications contain quite a number of neuronal receptors which are involved in psychotic disorders. It has been widely discussed whether psychoactive drugs used in the therapy of psychotic disorders have a direct effect on platelet function and whether the effects are transmitted through the corresponding receptors on the platelet surface.

In this study, German researchers tested several psychoactive drugs regarding their impact on whole blood platelet aggregation. Antidopaminergics preferentially inhibited ADP-induced aggregation whereas anticholinergics mainly inhibited U46619-induced aggregation. Because platelets respond selectively to different psychoactive drugs, the researchers assumed that corresponding receptors have a functional aspect on platelets and that receptor blockade affects platelet aggregation through different mechanisms. They concluded that learning about the effects of psychoactive drugs on platelet function may help to characterize neuronal receptors on platelets and may contribute to a better understanding of altered platelet function during therapy with psychoactive drugs.

## DEFERRAL OF FEMALE PLATELET DONORS HELPS MITIGATE TRALI

**T**ransfusion-related acute lung injury (TRALI) mitigation strategies include the deferral of female donors from apheresis platelet (PLT) donations and the distribution of plasma for transfusion from male donors only. Researchers from the American Red Cross and other community blood centers studied the implications of these policies in terms of component loss at six blood centers in the United States.

Researchers collected data from allogeneic blood donors making whole blood and blood component donations during calendar years 2006 through 2008. They analyzed the distribution of donations in terms of the sex, transfusion and pregnancy histories, and blood type.

The researchers found that a TRALI mitigation policy that would not allow plasma from female whole blood donors to be prepared into transfusable plasma components would result in nearly a 50% reduction in the units of whole blood available for plasma manufacturing and would decrease the number of type AB plasma units that could be made from whole blood donations by the same amount.

Deferral of all female apheresis PLT donors, all female apheresis PLT donors with histories of prior pregnancies, or all female apheresis PLT donors with histories of prior pregnancies and positive screening test results for antibodies to human leukocyte antigens (HLAs) will result in a loss of 37.1, 22.5, and 5.4% of all apheresis PLT donations, respectively. The study concluded that a TRALI mitigation policy that only defers female apheresis PLT donors with previous pregnancies and HLAs would result in an approximately 5% decrease in the inventory of apheresis PLTs, but would eliminate a large proportion of components that are associated with TRALI.

**Rios JA, Schlumpf KS, Kakaiya RM, Triulzi DJ, Roback JD, Kleinman SH, Murphy EL, Gottschall JL, Carey PM.** Blood donations from previously transfused or pregnant donors: a multicenter study to determine the frequency of alloexposure. *Transfusion*. 2010. [Ahead of print]

## TRALI HOST FACTOR EXAMINED

**R**ecent insights from models of transfusion-related acute lung injury (TRALI), and from clinical reports reveal that host factors are important in TRALI pathogenesis.

Predisposing factors with lung neutrophil-priming capacity, such as sepsis and mechanical ventilation, increase susceptibility for a TRALI reaction, and can aggravate the course of disease. These findings may explain the higher incidence of TRALI in the critically ill compared with general hospital populations.

The emerging importance of host factors may have implications for TRALI management. Suspected TRALI cases in which another acute lung injury risk factor is present (termed 'possible TRALI' in the consensus definition) should be reported to the blood bank, including patients suffering from an underlying condition. In reporting of TRALI cases, use of the international TRALI consensus definition should be used, rather than national TRALI scoring systems, to ensure a uniform approach, which may decrease variance in estimations of incidence. In terms of treatment of TRALI patients, there is a rationale to apply therapeutic strategies, which have proven to be beneficial in acute lung injury.

**Juffermans NP.** Transfusion-related acute lung injury: emerging importance of host factors and implications for management. *Expert Rev Hematol*. 2010. 3:459-467.



An anatomical illustration of a human torso, showing the lungs, spine, and ribcage. The lungs are depicted in a light pinkish-purple hue, and the spine is shown in a darker purple. The ribcage is visible as a series of curved lines. The illustration is positioned on the left side of the page, partially overlapping the text.

## RESEARCHERS INVESTIGATE TRALI AFTER MATERNAL BLOOD TRANSFUSIONS

University of California San Francisco, researchers conducted a single-center retrospective case-control study of 7 transfusion-related acute lung injury (TRALI) cases and 28 controls (4 controls per case) in the pediatric spinal surgery population to determine the association between maternal transfusion and risk of TRALI in pediatric spinal surgery patients.

Previous studies support a “2-hit” model for the pathogenesis of TRALI-activation and sequestration of neutrophils in the pulmonary vasculature followed by transfusion of a biologic response modifier such as anti-leukocyte antibodies. Maternal donation of blood products is a potential risk factor for TRALI because of the development of antileukocyte antibodies during pregnancy. Until now there have been no studies specifically addressing the risk of TRALI following maternal transfusions.

In this study, cases were matched by strata for volume of plasma transfused. All cases were also identified by the Transfusion Biology and Medicine Specialized Center of Clinically Oriented Research with a TRALI diagnosis to be eligible for inclusion. Electronic medical records and operative notes were reviewed to obtain demographic data, diagnosis, surgical approach, and number of spine levels for each operation.

The researchers found an increased prevalence of maternal blood transfusion among the TRALI cases compared with the control cases: 43% (3 of 7) versus 7% (2 of 28),  $P = 0.044$ . There were otherwise no statistical differences between the groups, including age, gender, surgical approach, number of spinal levels, or type of blood product transfused.

The researchers concluded that pediatric patients undergoing spinal surgery may be at increased risk for the development of TRALI following the transfusion of maternal blood products. Accordingly, they recommend that directed donation of maternal blood products be avoided in this population. This study also found that TRALI may be underrecognized and underreported.

**Dunbar N, Cooke M, Diab M, Toy P.** Transfusion-Related Acute Lung Injury After Transfusion of Maternal Blood: A Case-Control Study. *Spine* 2010;35:E1322-7.

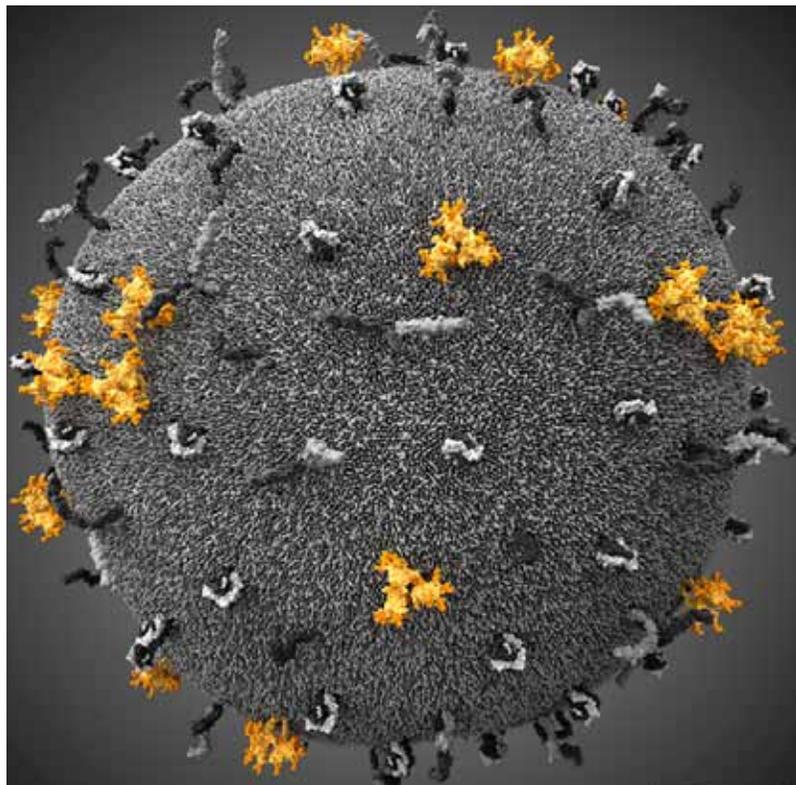
## UNIQUE BIOCHEMICAL LANDSCAPE OF HIV-1 REPLICATION IN MACROPHAGES REVEALED

University of Rochester researchers biochemically simulated HIV-1 DNA polymerization in physiological nucleotide pools found in two HIV-1 target cell types: terminally differentiated/non-dividing macrophages and activated/dividing CD4(+) T cells.

Quantitative tandem mass spectrometry shows that macrophages harbor 22-320-fold lower Deoxy-ribonucleotide triphosphate concentrations and a greater disparity between ribonucleoside triphosphate (rNTP) and dNTP concentrations than dividing target cells. A biochemical simulation of HIV-1 reverse transcription revealed that rNTPs are efficiently incorporated into DNA in the macrophage but not in the T cell environment. This implies that HIV-1 incorporates rNTPs during viral replication in macrophages and also predicts that rNTP chain terminators lacking a 3'-OH should inhibit HIV-1 reverse transcription in macrophages. Indeed, 3'-deoxyadenosine inhibits HIV-1 proviral DNA synthesis in human macrophages more efficiently than in CD4(+) T cells.

The researchers concluded that this study reveals that the biochemical landscape of HIV-1 replication in macrophages is unique and that ribonucleoside chain terminators may be a new class of anti-HIV-1 agents specifically targeting viral macrophage infection

**Kennedy EM, Gavegnano C, Nguyen L, Slater R, Lucas A, Fromentin E, Schinazi RF, Kim B.** Ribonucleoside triphosphates as substrate of human immunodeficiency virus type 1 reverse transcriptase in human macrophages. *J Biol Chem.* 2010 285:39380-91.



**HIV Virus.** Ivan Konstantinov and his team from Visual Science have created the most-detailed 3D model of the virus to date. The image won first place in the 2010 International Science and Engineering Visualization Challenge, sponsored jointly by the journal *Science* and the National Science Foundation (NSF).

The model contains 17 different viral and cellular proteins and the membrane incorporates 160 thousand lipid molecules, of 8 different types, in the same proportions as in an actual HIV particle. It denotes the parts encoded by the virus's own genome in orange, while grey shades indicate structures taken into the virus when it interacts with a human cell.

## PROGRAM DEvised TO MINIMIZE PLATELET OUTDATING

Platelet (PLT) transfusions are essential for patients who are bleeding or have an increased risk of bleeding due to a decreased number or abnormal function of circulating PLTs. A shelf life of 5 days for PLT products presents an inventory challenge for many hospitals. In 2006, greater than 10% of apheresis PLTs made in the United States outdated. It is imperative to have a sufficient number of products for patients requiring transfusion, but outdated PLTs is a financial burden and a waste of a resource.

In this article, Johns Hopkins Medical Institutions researchers present the approach used in their institution to anticipate inventory needs based on current patient census and usage. Strategies to predict usage and to identify changes in anticipated usage are examined. Annual outdated is reviewed for a 10-year period from 2000 through 2009.

From January 1, 2000, through December 2009, there were 128,207 PLT transfusions given to 15,265 patients.

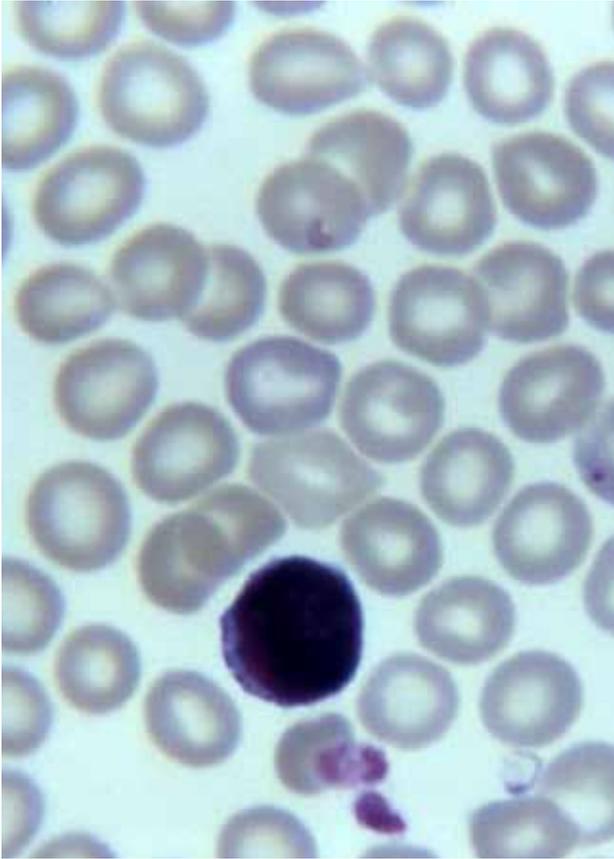
The methods used to anticipate usage and adjust inventory resulted in an annual outdate rate of approximately 1% for the 10-year period reviewed. In addition, they have not faced situations where inventory was inadequate to meet the needs of the patients requiring transfusions.

The researchers identified three elements of their transfusion service that can minimize outdate: a knowledgeable proactive staff dedicated to PLT management, a comprehensive computer-based transfusion history for each patient, and a strong two-way relationship with the primary product supplier.

Johns Hopkins claims that through this comprehensive program, based on the principles of providing optimal patient care, they have minimized PLT outdated for more than 10 years.

**Fuller AK, Uglik KM, Braine HG, King KE.** A comprehensive program to minimize platelet outdated. *Transfusion.* 2011 [Ahead of print]

# RED CROSS SCIENTIST DISCUSSES TRANSFUSION-TRANSMITTED *BABESIA*



This blood smear micrograph revealed the presence of *Babesia* sp. ring formations inside the host erythrocytes. Photo: CDC

**B***abesia* spp. are intraerythrocytic protozoan parasites of animals and humans that cause babesiosis, a zoonotic disease transmitted primarily by tick vectors. Although a variety of species or types of *Babesia* have been described in the literature as causing infection in humans, the rodent parasite *Babesia microti* has emerged as the focal point of human disease, especially in the United States. Not only has *B. microti* become established as a public health concern, this agent is increasingly being transmitted by blood transfusion: estimates suggest that between 70 and 100 cases of transfusion-transmitted *Babesia* (TTB) have occurred over the last 30 years. A recent upsurge in TTB cases attributable to *B. microti*, coupled with at least 12 fatalities in transfusion recipients diagnosed with babesiosis, has elevated TTB to a key policy issue in transfusion medicine. Despite clarity on a need to mitigate transmission risk, few options are currently available to prevent the transmission of *B. microti* by blood transfusion.

In this article, David Leiby, of the American Red Cross Holland Laboratory, discusses how future mitigation efforts may stress serological screening of blood donors in regionalized areas of endemicity, with adjunct nucleic acid testing during the summer months, when acute infections are prevalent. However, several hurdles remain, including the absence of a licensed blood screening assay and a thorough cost-benefit analysis of proposed interventions.

Leiby contends that despite current obstacles, continued discussion of TTB without proactive intervention is no longer a viable alternative.

**Leiby DA.** Transfusion-Transmitted *Babesia* spp.: Bull's-Eye on *Babesia microti*. *Clin Microbiol Rev.* 2011 24:14-28.

## CASE STUDY:

# AUTOIMMUNITY IN TRANSFUSION BABESIOSIS A SPECTRUM OF CLINICAL PRESENTATIONS

**T**ransfusion-acquired babesiosis can be an asymptomatic or self-limited febrile hemolytic illness in a healthy host. A persistent, relapsing, and/or fulminant course with the development of life-threatening complications may be seen in immunocompromised or splenectomized patients.

As in malaria, erythrocyte parasitemia is often associated with nonimmune hemolysis, and can be treated with erythrocytapheresis. Just as warm autoantibodies have been reported in malaria infection, the development of autoantibody-mediated immune hemolysis has been reported in babesiosis.

In Philadelphia, Thomas Jefferson University Hospital physicians treated a previously healthy male with multiple injuries from a motor vehicle accident necessitating massive transfusion. Late in the hospitalization, his blood smear revealed *Babesia microti*, confirmed by PCR study and serology. This was eventually traced

to a unit of blood from an asymptomatic blood donor that was transfused during his initial trauma care. Specific antibiotic therapy was begun, and severe hemolysis from a high parasite burden required red blood cell exchange which led to rapid abatement of the hemolysis. He had a positive DAT (IgG with a pan-reactive eluate) but no serum autoantibody. This persisted for 10 days following cessation of hemolysis, and became negative while still on antibiotics while his parasite burden became undetectable.

Reports of autoimmunity associated with community acquired babesiosis often have severe hemolysis from their autoantibodies, but this case shows that autoantibodies may also follow transfusion-acquired babesiosis. The nature of the autoantigen is unknown.

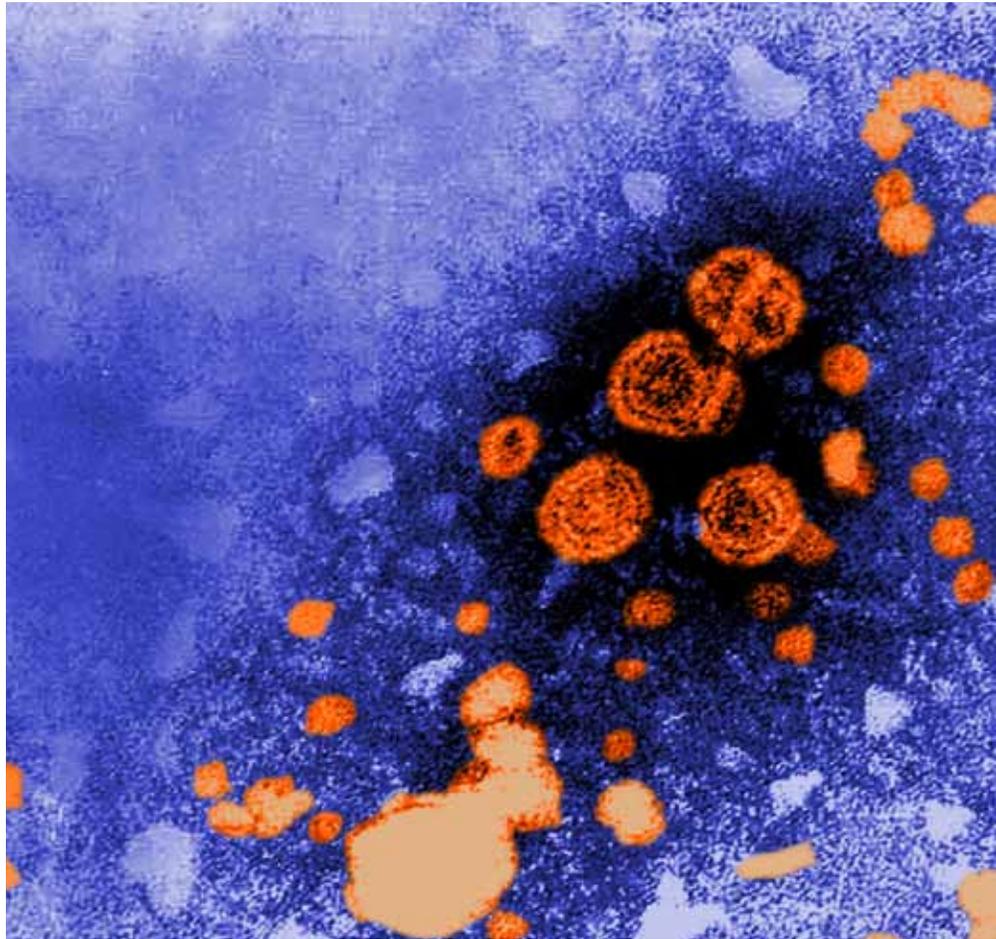
**Herman JH, Ayache S, Oikowska D.** Autoimmunity in transfusion babesiosis: a spectrum of clinical presentations. *J Clin Apher.* 2010 25:358-61.

# NUCLEIC ACID TESTING USED TO DETECT HBV INFECTION IN BLOOD DONORS

The detection of hepatitis B virus (HBV) in blood donors is achieved by screening for hepatitis B surface antigen (HBsAg) and for antibodies against hepatitis B core antigen (anti-HBc). However, donors who are positive for HBV DNA are currently not identified during the window period before seroconversion. The current use of nucleic acid testing for detection of the human immunodeficiency virus (HIV), RNA, hepatitis C virus (HCV) RNA and HBV DNA in a single triplex assay may provide additional safety.

American Red Cross scientists performed nucleic acid testing on 3.7 million blood donations and further evaluated those that were HBV DNA-positive but negative for HBsAg and anti-HBc. They determined the serologic, biochemical, and molecular features of samples that were found to contain only HBV DNA and performed similar analyses of follow-up samples and samples from sexual partners of infected donors. Seronegative HIV and HCV-positive donors were also studied.

“1 in 410,540 blood donations were positive for HBV DNA.”



Hepatitis B virus (HBV)

Photo: E. Palmer/CDC

American Red Cross researchers identified 9 donors who were positive for HBV DNA (1 in 410,540 donations), including 6 samples from donors who had received the HBV vaccine, in whom subclinical infection had developed and resolved. Of the HBV DNA-positive donors, 4 probably acquired HBV infection from a chronically infected sexual partner. Clinically significant liver injury developed in 2 unvaccinated donors. In 5 of the 6 vaccinated donors, a non-A genotype was identified as the dominant strain, whereas subgenotype A2 (represented in the HBV vaccine) was the dominant strain in unvaccinated donors. Of 75 reactive nucleic acid test results identified in seronegative blood donations, 26 (9 HBV, 15 HCV, and 2 HIV) were confirmed as positive.

Triplex nucleic acid testing detected potentially infectious HBV, along with HIV and HCV, during the window period before seroconversion. HBV vaccination appeared to be protective, with a breakthrough subclinical infection occurring with non-A2 HBV subgenotypes and causing clinically inconsequential outcomes.

**Stramer SL, Wend U, Candotti D, Foster GA, Hollinger FB, Dodd RY, Allain JP, Gerlich W.** Nucleic Acid Testing to Detect HBV Infection in Blood Donors *N Engl J Med* 2011. 364:236-247

## HEPATITIS B: USA AND WORLD

### WORLD

2 billion

1 in 3

400 million

1 million

### UNITED STATES

12 million

1 in 20

1 million

5,000

people or  
are infected with HBV

are chronically infected

die from HBV and related complications.

Source: Hepatitis B Foundation

# STUDY FINDS IONIZED CALCIUM LEVELS PREDICT THE NEED FOR MULTIPLE TRANSFUSIONS

**D**eaths from uncontrolled exsanguinating hemorrhage occur rapidly post-injury. Any successful resuscitation strategy must also occur early, underscoring the importance of rapid identification of patients at risk for multiple transfusions. Previous studies have shown low ionized calcium (iCa) levels to be associated with hypotension and function as a predictor of mortality. In this study, University of Tennessee researchers hypothesized that admission iCa levels could potentially predict the need for multiple transfusions in critically ill trauma patients.

Admission iCa was collected prospectively on all trauma activations during a 9-month period. Youden's index was used to determine the appropriate cutpoint for iCa. Outcomes (mortality, multiple transfusions [ $\geq 5$  units packed red blood cells in 24 hours] and massive transfusion [ $\geq 10$  units packed red blood cells in 24 hours]) were compared using Wilcoxon rank-sum and  $\chi^2$  tests where appropriate. Multivariable logistic regression was performed to determine whether iCa was an independent predictor of multiple transfusions.

A total of 591 patients were identified: 461 (78%) men and 130 (22%) women. Cutpoint was identified as 1.00. iCa was  $<1.00$

(lo-Cal) in 332 patients and  $\geq 1.00$  (hi-Cal) in 259 patients. Mortality was significantly increased in the lo-Cal group (15.5% vs. 8.7%,  $p = 0.036$ ). In addition, both multiple transfusions (17.1% vs. 7.1%,  $p = 0.005$ ) and massive transfusion (8.2% vs. 2.2%,  $p = 0.017$ ) were significantly increased in the lo-Cal group. Multivariable logistic regression analysis identified iCa  $<1$  as an independent predictor of the need for multiple transfusions after adjusting for age and injury severity (odds ratio = 2.294, 95% confidence interval = 1.053-4.996).

The study concluded that low iCa levels at admission were associated with increased mortality as well as an increased need for both multiple transfusions and massive transfusion. Multivariable logistic regression analysis identified low iCa levels as an independent predictor of multiple transfusions. Admission iCa levels may facilitate the rapid identification of patients requiring massive transfusion, allowing for earlier preparation and administration of appropriate blood products.

**Magnotti LJ, Bradburn EH, Webb DL, Berry SD, Fischer PE, Zarzaur BL, Schroepfel TJ, Fabian TC, Croce MA.** Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patients. *J Trauma.* 2011 70:391-7.

# PACKED RED BLOOD CELL TRANSFUSION DECREASES MORTALITY IN INTRACEREBRAL HEMORRHAGE

**A**ccumulating data suggest that anemia worsens outcomes in critically ill patients, including those with subarachnoid and intracerebral hemorrhage (ICH). Although packed red blood cell (PRBC) transfusion appears to increase brain tissue oxygen, it is unknown whether these transfusions, which are commonly administered in patients with intracranial hemorrhage, alter outcome.

Following up on their observation that anemia is associated with poor outcome in patients with ICH, University of Maryland, Massachusetts General Hospital, Thomas Jefferson University Hospital, and University of Calgary researchers investigated whether RBC transfusion was associated with any benefit.

In this study, 546 consecutive subjects were identified from an ongoing single center prospective cohort study of non-traumatic ICH over a six-year period. Clinical and radiographic characteristics, laboratory values including admission and daily mean hemoglobin values as well as all instances of packed RBC

transfusion were recorded. Aggressiveness of care was assessed by whether or not the patient had a "do not resuscitate" (DNR) order activated during hospitalization. The primary endpoint was 30-day survival.

Anemia was present in 144/546 (26%) patients on admission and developed subsequently in an additional 250, leaving just 152/546 (28%) patients who never developed anemia. Packed RBC transfusion was administered to 100 (18%) patients during their hospital stay, 98% of whom were anemic. In multivariable analysis, packed RBC transfusion was associated with improved survival at 30 days (O.R. = 2.76; 95% C.I. 1.45-5.26;  $p = .002$ ).

The majority of patients with ICH develop anemia at some point during their hospitalization. The study found packed RBC transfusion was associated with improved outcome in these patients.

**Sheth KN, Gilson AJ, Chang Y, Kumar MA, Rahman RM, Rost NS, Schwab K, Cortellini L, Goldstein JN, Smith EE, Greenberg SM, Rosand J.** Packed Red Blood Cell Transfusion and Decreased Mortality in Intracerebral Hemorrhage *Neurosurgery.* 2011 [Ahead of print]

# THORACIC SURGEONS AND CARDIOVASCULAR ANESTHESIOLOGISTS BLOOD CONSERVATION GUIDELINES UPDATED

The Society of Thoracic Surgeons (STS) recommends review and possible update of previously published guidelines at least every three years. This summary is an update of the blood conservation guideline published in 2007.

In this 2011 guideline update, areas of major revision include:

- 1) management of dual anti-platelet therapy before operation,
- 2) use of drugs that augment red blood cell volume or limit blood loss,
- 3) use of blood derivatives including fresh frozen plasma, Factor XIII, leukoreduced red blood cells, platelet plasma pheresis, recombinant Factor VII, antithrombin III, and Factor IX concentrates,
- 4) changes in management of blood salvage,
- 5) use of minimally invasive procedures to limit perioperative bleeding and blood transfusion,
- 6) recommendations for blood conservation related to extracorporeal membrane oxygenation and cardiopulmonary perfusion,
- 7) use of topical hemostatic agents, and
- 8) new insights into the value of team interventions in blood management.

This document contains new and revised recommendations.

**Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J, Baker RA, Dickinson TA, Fitzgerald DJ, Likosky DS, Shann KG.** 2011 update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg.* 2011 91:944-82.

## PUBLICATIONS CORNER

American Red Cross scientists and physicians invite you to explore some of their recent publications:

**Lebedeva TV, Mastromarino SA, Lee E, Ohashi M, Alosco SM, Yu N.** Resolution of HLA class I sequence-based typing ambiguities by group-specific sequencing primers. *Tissue Antigens.* 2011 77:247-50.

**Leiby DA.** Transfusion-transmitted Babesia spp.: bull's-eye on Babesia microti. *Clin Microbiol Rev.* 2011 24:14-28.

**Moroff G, AuBuchon JP, Pickard C, Whitley PH, Heaton WA, Holme S.** Evaluation of the properties of components prepared and stored after holding of whole blood units for 8 and 24 hours at ambient temperature. *Transfusion.* 2011 51 Suppl 1:7S-14S.

**Stramer SL, Wend U, Candotti D, Foster GA, Hollinger FB, Dodd RY, Allain JP, Gerlich W.** Nucleic acid testing to detect HBV infection in blood donors. *N Engl J Med.* 2011 364:236-47.

**Vassallo RR, Adamson JW, Gottschall JL, Snyder EL, Lee W, Houghton J, Eifath MD.** In vitro and in vivo evaluation of apheresis platelets stored for 5 days in 65% platelet additive solution/35% plasma. *Transfusion.* 2010 50:2376-85.



# RED CROSS OFFERS A SERIES OF UNIQUE, CREATIVE CONTINUING EDUCATION SELF-STUDIES ON-LINE



The American Red Cross Blood Services is pleased to announce SUCCESS, an online educational resource available exclusively to Red Cross hospital customers. Developed by experts, this site offers you access to courses in the fields of immunohematology, blood banking and transfusion medicine at [success.redcross.org](http://success.redcross.org).

Through SUCCESS, you enjoy easy, no-cost access to courses developed by nationally and internationally recognized transfusion medicine physicians and blood banking experts.

SUCCESS programs are self-study, online courses available from any computer with internet access which offer the opportunity to earn Continuing Education Unit (CEU) credits, recognized for recertification and licensure for laboratory professionals, or AMA PRA Category 1 credits for physician Continuing Medical Education (CME) requirements.

The Red Cross is excited to offer this online resource to you, our valued hospital partners.

## RESOURCES



**A Compendium of Practice Guidelines for Transfusion** is an essential resource-- 112 pages of vital information aligned with the AABB Circular of Information. Copies are available through your Red Cross representative.

**2011 Blood Product & Donor Eligibility Dating Calendar** is popular with hospitals, and clinicians to determine the age of blood units at a glance. Blood donor eligibility dates, the Julian date for quick reference to the ISBT expiration date, and the 21, 35, 42, 56, and 112 red cell dates are also incorporated. Ask your Red Cross representative for a copy.



## REMEMBER THESE WEBSITES

**Immunohematology Journal**  
[redcross.org/immunohematology](http://redcross.org/immunohematology)  
**Reimbursement**  
[redcrossblood.org/reimbursement](http://redcrossblood.org/reimbursement)  
**SUCCESS**  
[success.redcross.org](http://success.redcross.org)

PLUS  
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