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Although most common in tropical regions, population migration has meant that sickle cell disease (SCD) is now one of the most prevalent genetic diseases worldwide. The issues and challenges faced by physicians and patients were discussed recently by an international group of experts representing four key regions: the USA, Europe, Latin America, and the Middle East/Africa.

Conclusive evidence to support the use of transfusion therapy for the prevention of stroke has resulted in key changes to patient management in all regions, and increasing numbers of patients are benefiting from this approach. However, it is apparent that transfusion therapy is still under-utilized, largely due to concerns over iron overload, alloimmunization, limited blood supplies, and, sometimes, parental refusal. Once transfused, assessment and
“Evidence suggests more patients could benefit from regular transfusion therapy.”

management of body iron levels can be poor, particularly in patients who are intermittently transfused. Compliance with chelation therapy regimens is a significant challenge, but new therapeutic options are likely to overcome some of the current barriers.

In another study to gain an insight into current transfusion and chelation practice in patients with SCD, Researchers at Children’s Hospital & Research Center (Oakland, California) conducted a survey of international experts. The findings demonstrate that general utilization of transfusion therapy is low, the primary barrier to treatment being concerns over resultant iron overload and a subsequent need for iron chelation therapy. Where patients were transfused, many physicians indicated that a high proportion of patients had hemosiderosis. As evidence suggests more patients with SCD could benefit from regular transfusion therapy, it is apparent that greater awareness of the need to monitor and treat iron overload in transfused patients is required.


**RED CROSS ASKS BLACKS TO GIVE MORE BLOOD FOR SICKLE CELL PATIENTS**

The American Red Cross has a program to encourage more black people to donate blood to help treat sickle cell disease (SCD).

Since SCD is prevalent in blacks and up to 80,000 black people in the United States suffer from it, the Red Cross has developed a program to encourage donors -- specifically blacks -- to give blood for SCD patients.

SCD distorts the shape of blood cells and causes a multitude of problems. The symptoms of SCD are painful, dangerous and sometimes lead to death. The most effective treatment to prevent symptoms is frequent blood transfusions.

Blood transfusions are most beneficial when the blood transfused is the closest match possible to that of the recipient. Blood type is a genetic factor like skin color, hair color, eye color. The closest match is when blood is transfused between people of the same ethnic group.

Blood specifically donated for SCD patients will be marked by the Red Cross, and if it can’t be used for a SCD patient, the unit will be made available for general transfusion.

**SICKLE CELL DISEASE AT A GLANCE**

- **70,000 to 100,000** Americans have Sickle Cell Disease
- **1 out of every 500** African Americans is born with Sickle Cell Disease
- **1 out of every 36,000** Hispanic Americans is born with Sickle Cell Disease
- **1 in 12** African Americans has sickle cell trait

Born with Sickle Cell anemia, Elise (left) relies on the support of generous blood donors and her family to help her get through her monthly blood transfusions.
Transfusion of blood components is common in patients admitted to the intensive care unit (ICU) for gastrointestinal (GI) bleeding, yet the incidence and risk factors for development of transfusion-related acute lung injury (TRALI) in these patients are unknown.

Patients admitted to a medical ICU for GI bleeding (n = 225) were analyzed for patient- and transfusion-specific risk factors for development of TRALI.

University of Colorado Denver researchers found that the incidence of TRALI was 15% in transfused patients (n = 150) [95% confidence interval (CI), 10-21%], and accounted for 76% (22/29) of all acute lung injury (ALI) cases. Transfused patients with end-stage liver disease (ESLD) (n = 72) developed TRALI more frequently than those without ESLD (29% versus 1%, p < 0.01). Fresh frozen plasma (FFP) was temporally associated with TRALI in 86% of cases. Transfusion-specific risk factors for development of TRALI included number of transfused units of FFP and nonleukoreduced red blood cells. Patient-specific risk factors included Model for End-Stage Liver Disease (MELD) score, admission serum albumin level, and presence of ALI risk factors.

The researchers concluded that since TRALI is common in critically ill ESLD patients with gastrointestinal bleeding, nonleukoreduced red blood cells and FFP are significant transfusion-specific risk factors and their use should be re-evaluated in bleeding patients with ESLD.


### STUDY EXAMINES TACO INCIDENCE AND RISK FACTORS AMONG ICU PATIENTS

Transfusion-associated circulatory overload (TACO) is a complication of blood transfusion. Since investigations identifying risk factors for TACO in critically ill patients are lacking, researchers from the Mayo Clinic, the Guang An Men Hospital, China Academy of Chinese Medical Science, and The Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia performed a 2-year prospective cohort study of consecutive patients receiving blood product transfusion in the medical intensive care unit (ICU) of the tertiary care institution.

Patients were followed for development of transfusion-related complications. TACO was defined as acute hydrostatic pulmonary edema occurring within 6 hours of transfusion. In a nested case-control design, transfusion characteristics were compared between cases (TACO) and controls after matching by age, sex, and ICU admission diagnostic category. In a secondary analysis, patient characteristics before transfusion were compared between cases (TACO) and randomly selected controls.

The study found 51 of 901 (6%) transfused patients developed TACO. Compared with matched controls, TACO cases had a more positive fluid balance (1.4 L vs. 0.8 L, p = 0.003), larger amount of plasma transfused (0.4 L vs. 0.07 L, p = 0.007), and faster rate of blood component transfusion (225 mL/hr vs. 168 mL/hr, p = 0.031). In a secondary analysis comparing TACO cases and random controls, left ventricular dysfunction before transfusion (odds ratio [OR], 8.23; 95% confidence interval [CI], 3.36-21.97) and plasma ordered for the reversal of anticoagulant (OR, 4.31; 95% CI, 1.45-14.30) were significantly related to the development of TACO.

The researchers identified the volume of transfused plasma and the rate of transfusion as transfusion-specific risk factors for TACO. They also found that left ventricular dysfunction and fresh-frozen plasma ordered for the reversal of anticoagulant were strong predictors of TACO before the onset of transfusion.

In this review, University of California, San Francisco researchers summarize the recent experimental and clinical literature on the pathogenesis of transfusion-related acute lung injury (TRALI).

In both experimental and clinical TRALI, an immune priming step is generally necessary to produce lung injury. Experimental studies have used mainly lipopolysaccharide (LPS) as the priming step, whereas in clinical TRALI the specific priming events are currently being defined and include recent surgery and active infections. Experimental studies have modeled TRALI by using major histocompatibility complex antibodies, neutrophil antibodies, and also bioactive lipids isolated from stored human blood. A common theme among the experimental TRALI models is the central importance of neutrophils in mediating the early immune response and lung vascular injury. New work has focused on the interplay between neutrophils and platelets in the lung microcirculation. Finally, plasma mitigation strategies implemented in several countries are showing early promise in decreasing the incidence of TRALI from high plasma volume blood products.

TRALI requires an immune priming step followed by transfusion of a blood product with either leukocyte allo-antibodies or biological response modifiers. TRALI invokes an acute immune response dominated by neutrophils interacting with platelets and the lung endothelium.

Erythrocyte in capillary.
Dutch researchers found that a PubMed query using the word "erythrocyte" resulted in 198,013 scientific articles of which 162 are red blood cell proteomics studies, indicating that this new technique has been only recently applied to the red blood cell and related fields.

Standard and comparative proteomics have been widely used to study different blood components. A growing body of proteomics literature has since developed, which deals with the characterization of red blood cells in health and disease. The possibility offered by proteomics to obtain a global snapshot of the whole red blood cell protein make-up, has provided unique insights to many fields including transfusion medicine, anemia studies, intra-red blood cell parasite biology and translational research.

The researchers found that, a full red blood cell understanding will ultimately require, in addition to proteomics, lipidomics, glycomics, and study of post-translational modifications. In this review, they discuss the methodology and limitations of proteomics, the contribution it made to the understanding of the erythrocyte and the advances in red blood cell-related fields brought about by comparative proteomics.


A burn injury represents one of the most severe forms of human trauma and is responsible for significant mortality worldwide. In this article, scientists from the Biological Sciences Division and Environmental Molecular Sciences Laboratory, Stanford University, the University of Texas, the University of Florida, Massachusetts General Hospital, and Shriners Burn Hospitals present the first quantitative proteomics investigation of the blood plasma proteome response to severe burn injury by comparing the plasma protein concentrations of 10 healthy control subjects with those of 15 severe burn patients at two time-points following the injury.

The overall analytical strategy for this work integrated immunoaffinity depletion of the 12 most abundant plasma proteins with cysteinyl-peptide enrichment-based fractionation prior to LC-MS analyses of individual patient samples. Incorporation of an (18)O-labeled "universal" reference among the sample sets enabled precise relative quantification across the samples. In total, 313 plasma proteins confidently identified were with two or more unique peptides quantified.

Following statistical analysis, 110 proteins exhibited significant abundance changes in response to the burn injury. The observed changes in protein concentrations suggest significant inflammatory and hypermetabolic response to the injury, which is supported by the fact that many of the identified proteins are associated with acute phase response signaling, the complement system, and coagulation system pathways.

The regulation of approximately 35 proteins observed in this study was in agreement with previous results reported for inflammatory or burn response, but approximately 50 potentially novel proteins previously not known to be associated with burn response or inflammation were also found. Elucidating proteins involved in the response to severe burn injury may reveal novel targets for therapeutic interventions as well as potential predictive biomarkers for patient outcomes such as multiple organ failure.

Group O RBCs are typically issued for urgent transfusions to avoid ABO-incompatible hemolytic transfusion reactions (HTRs). Identification of other clinically significant alloantibodies requires an antibody detection test, and emergency release (ER) of RBCs before its completion carries a risk of non-ABO alloantibody-mediated HTRs.

Beth Israel Deaconess Medical Center researchers performed a retrospective review of 1,002 ER RBC transfusions involving 265 ER episodes (262 recipients) in a tertiary medical center, 2006-2008, to determine the risk of non-ABO alloantibody-mediated HTRs.

A positive antibody detection test was found in 29 (10.9%) of 265 ER episodes, with clinically significant alloantibodies in 17 (6.4%) of 265 ER episodes. Fifteen antigen-incompatible RBC units were transfused to 7 recipients with clinically significant alloantibodies; 1 transfusion was followed by an HTR.

The study concluded that transfusing ER RBCs before completion of routine blood bank testing carries a low risk of non-ABO alloantibody-mediated HTRs (1/265 [0.4% ER episodes]) and receipt of antigen-incompatible RBCs (7/265 [2.6% ER episodes]).

Several studies have described predictive models to identify trauma patients who require massive transfusion (MT). Early identification of lethal exsanguination may improve survival in this patient population. The purpose of this study was to validate a simplified score to predict MT at multiple Level I trauma centers.

All adult trauma patients treated at three Level I trauma centers from July 2006 to June 2007 who:

(1) were transported directly from the scene,
(2) were trauma activations, and
(3) received any blood transfusions during admission were included.

An assessment of Blood Consumption (ABC) score was developed using the same inclusion criteria for patients admitted to a single trauma center (Vanderbilt University Medical Center [VUMC]-1) between July 2005 and June 2006. The ABC score calculated by assigning a value (0 or 1) to each of the four Wdssparameters: penetrating mechanism, positive focused assessment with sonography for trauma for fluid, arrival blood pressure <90 mm Hg, and arrival pulse >120 bpm. A score of 2 was used as "positive" to predict MT. Area under receiver-operating characteristic curve was calculated to compare the predictive ability of the score at each institution.

There were 586 patients in the developmental population (VUMC-1), 513 patients at trauma center 1 (VUMC-2), 372 at trauma center 2 Parkland Memorial Hospital (PMH), and 133 at trauma center 3 (Johns Hopkins Hospital). MT rate was similar among the centers: 14% to 15%. Sensitivity and specificity for the ABC score predicting MT ranged from 75% to 90% and 67% to 88%, respectively. Correctly classified patients and area under receiver-operating characteristic curve, however, were 84% to 87% and 0.83 to 0.90, respectively.

This study concluded that the ABC score is a valid instrument to predict MT early in the patient's care and across various demographically diverse trauma centers. Future research should focus on this score's ability to prospectively identify patients who will receive MT.


Previous reports have emphasized the importance of humoral immunity in heart failure in humans, primarily determined by the presence of circulating antibodies. However, there is little or no information about the frequency of anticardiac antibodies present in failing human myocardium.

Researchers from the Methodist Hospital in Houston, Texas, analyzed clinical data and myocardial tissue samples to determine the role of humoral immunity in patients with chronic heart failure (CHF) in different settings. They found anticardiac antibodies to be present in failing hearts, but not in normal control hearts. They also found that the level of expression of these anticardiac antibodies changed with the severity of the disease state; and in patients with acute heart failure, they saw selective activation of B cells. The treatment of CHF patients with therapeutic plasma exchange, a strategy that removes circulating antibodies, also resulted in a reduction in anticardiac antibody deposition and improvements in cardiac function.

The researchers concluded that these data collectively suggest a role of humoral immunity in the progression of heart failure.

Blood platelets are involved in primary and secondary hemostasis and thus maintain the integrity of the vasculature. They circulate with an average lifespan of 5-9 days in humans. Thus, the body must generate and clear platelets daily to maintain normal physiological blood platelet counts. Known platelet clearance mechanisms include antibody-mediated clearance by spleen macrophages, as in immune thrombocytopenia, and platelet consumption due to massive blood loss.

New concepts in the clearance mechanisms of platelets have recently emerged. New evidence shows that platelets desialyted due to chilling or sepsis are cleared in the liver by macrophages, that is Kupffer cells, as well as hepatocytes, through lectin-mediated recognition of platelet glycans. On the contrary, platelet-associated antibodies normalize the clearance of platelets in a mouse model for Wiskott-Aldrich syndrome.

In this review, researchers from Brigham and Women’s Hospital and Harvard Medical School summarize the latest findings in platelet clearance mechanisms with a focus on lectin-mediated recognition of platelet glycans. Transfusion medicine and treatments of hematopoietic disorders associated with severe thrombocytopenia may benefit from a better understanding of these mechanisms.


IS ALLOGENEIC RED-BLOOD CELL TRANSFUSION ASSOCIATED WITH SURGEON CASE-VOLUME?

Surgeon case-volume predicts a variety of patient outcomes. In this article, Johns Hopkins University School of Medicine researchers hypothesize that surgeon case-volume predicts RBC transfusion across different surgical procedures.

They performed a cohort study of 372,670 in-patient surgical cases in the 52 non-federal hospitals in Maryland between 2004 and 2005. The main outcome measure was relative risk of receiving a transfusion.

Overall, 13.9% of patients received a transfusion. Patients seen by the highest case-volume surgeons (>161 cases/y) were more likely to receive a transfusion (16% versus 11%, P < 0.01) compared with middle case-volume surgeons (89-161 cases/y). After adjusting for confounders. Patients of the highest case-volume surgeons were still at increased risk of transfusion [relative risk (RR) 1.10, 1.07-1.14]. This result was true across many surgery types.

The study concluded that surgeon case-volume is independently associated with the likelihood of RBC transfusion across a broad range of surgical procedures. Future efforts should be directed towards studying and standardization of transfusion practices.

Prion diseases are a family of rare, progressive, neurodegenerative disorders that affect humans and animals. The most common form of human prion disease, Creutzfeldt-Jakob disease (CJD), occurs worldwide. Variant CJD (vCJD), a recently emerged human prion disease, is a zoonotic foodborne disorder that occurs almost exclusively in countries with outbreaks of bovine spongiform encephalopathy. This Centers for Disease Control and Prevention (CDC) study describes the occurrence and epidemiology of CJD and vCJD in the United States.

Analysis of CJD and vCJD deaths using death certificates of US residents for 1979-2006, and those identified through other surveillance mechanisms during 1996-2008. Since CJD is invariably fatal and illness duration is usually less than one year, the CJD incidence is estimated as the death rate. During 1979 through 2006, an estimated 6,917 deaths with CJD as a cause of death were reported in the United States, an annual average of approximately 247 deaths (range 172-304 deaths). The average annual age-adjusted incidence for CJD was 0.97 per 1,000,000 persons. Most (61.8%) of the CJD deaths occurred among persons > or = 65 years of age for an average annual incidence of 4.8 per 1,000,000 persons in this population. Most deaths were among whites (94.6%); the age-adjusted incidence for whites was 2.7 times higher than that for blacks (1.04 and 0.40, respectively).

Three patients who died since 2004 were reported with vCJD; epidemiologic evidence indicated that their infection was acquired outside of the United States.

Surveillance continues to show an annual CJD incidence rate of about 1 case per 1,000,000 persons and marked differences in CJD rates by age and race in the United States.

Ongoing surveillance remains important for monitoring the stability of the CJD incidence rates, and detecting occurrences of vCJD and possibly other novel prion diseases in the United States.


STUDY FINDS THE EXPRESSION OF CELLULAR PRION PROTEIN IS UNDERESTIMATED ON HUMAN RED BLOOD CELLS

The recent transmissions of variant Creutzfeldt-Jakob disease by blood transfusion emphasize the need for the development of prion screening tests. The detection of prions in blood is complicated by the presence of poorly characterized cellular prion protein (PrP(C)) in both plasma and blood cells. According to published studies, most of PrP(C) in blood cells resides in platelets (PLTs) and white blood cells.

To clarify conflicting reports about the quantity of PrP(C) associated with human red blood cells (RBCs), quantitative flow cytometry, Western blot (WB), and enzyme-linked immunosorbent assay (ELISA) were used to measure protein levels in healthy donors.

In this study, researchers found RBCs expressed 290 ± 140 molecules of PrP(C) per cell, assuming equimolar binding of monoclonal antibody (MoAb) 6H4 to PrP(C). Binding of alternate PrP(C) MoAbs, FH11 and 3F4, was substantially lower. WB estimated the level of PrP(C) per cell on RBCs to be just four times lower than in PLTs. A similar level of PrP(C) was detected using ELISA. The weak binding of commonly used MoAb 3F4 was not caused by PrP(C) conformation, truncation, or glycosylation, suggesting a covalent modification, likely glycation, of the 3F4 epitope.

Taken together, human RBCs express low but significant amounts of PrP(C)/cell, which makes them, due to high RBC numbers, major contributors to the pool of cell-associated PrP(C) in blood. Previous reports utilizing MoAb 3F4 may have underestimated the amount of PrP(C) in RBCs. Likewise, screening tests for the presence of the abnormal prion protein in blood may be difficult if the abnormal protein is modified similar to RBC PrP(C).

RED CROSS OFFERS UNIQUE, CREATIVE CONTINUING EDUCATION SELF-STUDY PROGRAMS

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.

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

SUCCESS courses 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, as we work toward better patient outcomes by sharing expertise.

PUBLICATIONS CORNER

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


American Society for Apheresis Updates Guidelines on the Use of Therapeutic Apheresis

The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (fourth edition), the subcommittee has incorporated systematic review and evidence-based approach in the grading and categorization of indications.

The Fifth ASFA Special Issue has further improved the process of using evidence-based medicine in the recommendations by refining the category definitions and by adding a grade of recommendation based on the widely accepted GRADE system. The concept of a fact sheet was introduced in the Fourth edition and is only slightly modified in this current edition. The fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis. The article consists of 59 fact sheets devoted to each disease entity currently categorized by ASFA as category I through III. Category IV indications are also listed.


RESOURCES

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

2011 Blood Product & Donor Eligibility Dating Calendar is popular with hospitals, clinicians and others 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 day red cell date with 35, 42, 56, and 112 dates are also incorporated. Ask your Red Cross representative for a copy.

REMEMBER THESE WEBSITES

Immunohematology Journal
redcross.org/immunohematology

Reimbursement
redcrossblood.org/reimbursement

SUCCESS
success.redcross.org

PLUS
Winter 2011, Volume Five, Issue One