



Kentucky Association of Blood Banks

CHANNELS

Spring 2009

The Editor's Corner:

Hello again, we hope when you receive this issue of Channels you are enjoying the wonderful weather of the early summer.

This issue is very special to us. Our main article features Dr. William B. Lockwood. Dr. Lockwood is retiring this fall. We wanted to acknowledge his many contributions to Transfusion Medicine, both nationally and locally. Dr. Lockwood has been a major supporter of KABB for many years and we all are better blood bankers because of it.

Dr. Lockwood has been a friend, leader and mentor to so many of us over the years, it's impossible to put all his attributes into one article. We would like to thank Faye Kugele for agreeing to write this article to highlight some of Dr. Lockwood's accomplishments.

We have given a lot of thought to our second issue and as you will notice almost every article is about or related to the Rh system. Rh is a fascinating system: it is comprised of more than fifty specificities and contains one of the most immunogenic red blood cell antigens-the D antigen. It also contains the compound antigen "F" and the "G" antigen. This is without mentioning the complexities of the weak D's and the partial D's.

We have a very interesting article on the Rh blood group and weak D testing. To keep it in clinical perspective Dr. Duncan MacIvor has written a review on Hemolytic Disease of the Newborn. We are also publishing an article on pediatric red blood cells transfusions.

We hope this issue of Channels is as interesting to read as it was interesting to put it together. As we said in the winter issue we hope that this newsletter is useful for you daily practice.

We want to hear your comments and suggestions and most of all we want your collaboration. Let your voices and thoughts be heard through the Channels pages.

Channels is a channel of communication for all blood bankers in our beautiful Commonwealth of Kentucky.

Contact us at channels@kabb.org. Submissions are accepted year round.

In this edition:

Page 2: Featured article: Dr. Lockwood

Page 3: Featured article, continued

Page 4: Rh System, Weak D Testing

Page 5: Pediatric Red Blood Cell Transfusion

Page 6: HDFN: A Brief Review

Page 7: HDFN, continued

Page 8: Ask Miss Blood Bank

President's Message

Hello All,

On April 18th, 2009 KABB held a Spring meeting at Somerset Community College in Somerset, KY. The meeting was attended by 40+ members and students. Four speakers shared their knowledge and expertise with the audience.

KABB will be offering a Summer meeting on July 18th at Buckhorn State Park in Buckhorn, KY. Plans are underway. Look for more information in the near future and please check our website at www.kabb.org.

KABB hopes to have a fall meeting in the Louisville area; however dates and locations have not been set for this meeting.

If you have any suggestions, ideas for future educational topic, comment, or would like to become more active in KABB, please contact me at jprice@kybloodcenter.org.

I'd also like to thank Karla Smith and Dr. Elpidio Pena from Kentucky Blood Center. It is with their support and assistance; this issue of Channels has been published.

Sincerely,

Jami M. Price, MT(ASCP)

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William Byron Lockwood, PhD, MD

Born in Knoxville, Tennessee, Dr. William "Bill" Lockwood has been a friend and co-worker to so many of us. With his upcoming retirement in October, this year marks his final year working in transfusion medicine. Upon hearing that he was retiring, many of us felt that Dr. Lockwood should be honored for his body of work and decided to nominate him for the 2009 AABB Hemphill-Jordan Leadership award. The Hemphill-Jordan Leadership award recognizes an individual who made significant contributions in the areas of administration, quality programs, law and/or government affairs while demonstrating leadership qualities and a consistent willingness to lend his/her expertise to his/her peers. When the time came to ask for letters of recommendation to nominate him for this award, many stepped forward and offered praises and thanks for all he has accomplished over the past years. This article attempts to touch on some of those accomplishments and contains words of tribute taken from some of those letters.

In 1978, Dr. Lockwood accepted the position of pathologist and Director of Laboratory at the VA Medical Center. In 1988, he became the Medical Director of the American Red Cross Blood Services, River Valley Region. During this time, he conducted research on blood storage and its affect on blood products. He worked closely with David Jenkins, Jr., MD, to bring the River Valley Region to a thriving, fiscally solvent and self supporting blood center with a strong regulatory compliance record.

Dr. Lockwood's expertise in Compliance and Quality Assurance also received recognition well beyond the boundaries of Louisville. From November of 1994 until December of 1995, Dr. Lockwood was on full time special assignment to National Headquarters of the American Red Cross Biomedical Services in Washington, D.C. to participate in the Manufacturing and Computer Standardization (MACS) Project. The recommendations of that Task Force provided major input into the development of a fully integrated national computer system for the entire Red Cross Blood Services as

well as to the development of system wide standardized manufacturing SOP's fully compatible with the integrated computer system.

In 1999, Dr. Lockwood left the Red Cross and went to work full time with the University of Louisville Hospital. In early 2000, he became Medical Director of the Transfusion Services, University of Louisville Hospital and later in that year assumed the responsibilities as Medical Director of the Transfusion Services and Coagulation Laboratory at Norton/Kosair Children's Hospitals. Each of these Transfusion Services is a large, active and complex operation providing irreplaceable support to a major tertiary care hospital. He met these new challenges with distinction. He was able to bring his expertise in regulatory compliance and process control to the clinical arena in these new positions. He oversaw a major upgrade of the SOP's and quality programs of these two large Transfusion Services. This is another example of how programs have performed with distinction under Dr. Lockwood's leadership. In his various jobs over the years, he has earned high esteem and respect by the staff he has supervised and this has been a key factor in the excellence achieved by these programs.

Dr. Lockwood's outstanding achievements in service duties and the dedication he devoted to these duties were complimented by a continuing commitment to research, scholarship and education. Since 1992, he has maintained an ongoing research program in the important field of blood component viability using both chemical and cell labeling techniques to evaluate the recovery and yield of blood products under varying conditions of preparation and storage. This field of research has provided invaluable data to facilitate the development of new and improved methods for preparing high quality blood components. He has managed to maintain funding for this research throughout this period even though funding for research in general has been very scarce and he had to compete for funding as a solo investigator against much larger, established programs, especially in the early days. In addition to his funded

research, he has maintained a continuing scientific interest in collaborative studies with other laboratory medicine professionals resulting in a number of publications related to Transfusion Medicine.

Dr. Lockwood is an excellent teacher and maintains a strong commitment to teaching medical technologists, medical students, residents and fellows in pathology and laboratory medicine. Despite his many service duties, he has continued to be active in teaching second year medical students over the years. He has always maintained a strong commitment to teaching residents. Together, Dr. Lockwood and Dr. Jenkins secured approval by the American Board of Pathology for a Blood Banking/Transfusion Medicine Fellowship Program in 1993. Afterward, Dr. Lockwood secured funding to sustain that fellowship.

Dr. Lockwood's zest for research and teaching does not stop there. He has been very active in educational and advisory programs of the Jefferson County Medical Society and the Kentucky Medical Association. He has maintained a strong commitment to the continuing education and training of health care professionals of all disciplines involved in Transfusion Medicine and other fields of Laboratory Medicine. He has actively participated in training programs for medical technologists and technicians. He was a key contributor in the re-establishment of the Kentucky Association of Blood Banks (KABB) in 1988. He has been a major force in sustaining that organization since then and has served on a variety of committees to assure the provision of high quality programs for their biannual meetings. He served as president of the KABB in 1993-94. In 1999, he received the KABB Colonel Frank Camp award in recognition of his sustained high quality contributions to the association. He has also been active in the AABB (formerly known as the American Association of Blood Banks) and has frequently presented workshops and lectures at the national AABB meetings. He is a recognized expert in the very important area of coding and

reimbursement. He has chaired a number of workshops on this topic at annual AABB meetings and has been Chairman of the AABB Coding and Reimbursement Committee since 2002. In this capacity he has served as the AABB liaison to the American Society of Hematology Coding Committee since 2004. Despite his busy schedule Dr. Lockwood has been an Assessor for the AABB Inspection and Accreditation Program since 1996, once again reflecting his well established expertise in the area of compliance and quality assurance.

Dr. Lockwood has had a positive impact upon every organization and institution he has served. He is very dedicated to his professional duties and has always achieved a high level of performance in his work. He is a relentless worker with a strong commitment to excellence, and has worked tirelessly to maintain his own professional excellence. He has maintained a similar commitment to enhance and promote the training and development of health care colleagues of all disciplines. We, like so many others who have worked closely with him, hold him in the highest regard as a colleague and fellow health care professional.

As a final note to his illustrious career, Dr. Lockwood will speak at the 2009 AABB Annual Meeting in New Orleans as the very deserving recipient of the Hemphill-Jordan Leadership Award!

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Rh System

History:

The Rh System is the second most important Blood Group System after ABO. Two genes (RHD and RHCE) located on chromosome 1 compose the Rh system. RHD gene encodes the D antigen. RHCE gene encodes the CE antigens. These genes encode the 416 Rh system proteins. Over 100 distinctive RHD alleles have been identified. This has resulted in changes in the amino acid chains for the D antigen and varying expressions of the D antigen. These variations may be classified as weak D, partial D, or D_{el}. The incidence and inheritance of the RHD gene also varies in different populations. This complexity attributes to the D antigen being the most immunogenic within the Rh System¹. The D antigen has been attributed to the most severe cases of HDFN (Hemolytic disease of the fetus and newborn). By the 1960s, Rh Immune Globulin (RhoGam) was introduced and decreased the incidence of HDFN due to Anti-D.

Weak D:

Historically, weak D was defined as having a weakened amount of D antigen on the red cells. This weakened expression is a result from a series of nucleotide mutations encoded from the RHD gene. These weak D cells were only identified using an indirect antiglobulin test. Since weak D people are considered to have a normal D antigen, it is thought weak D individuals should not produce Anti-D. There is still much debate as to the possibility of some weak D people having the ability to produce an allo-Anti-D.

Partial D:

Partial D (D variant) phenotypes result from hybrid genes in which part of the RHD gene is replaced with a portion of the RHCE gene. This results in missing D epitopes. Individuals of this type may form Anti-D to the missing portion of their D antigen. Further information about D variants and their categories may be found in the references.

D_{el}:

D_{el} is commonly seen in populations in the Far East. This is a weakened expression of the D antigen caused from gene mutations. This class of antigen types Rh Negative through conventional serologic methods. It is only detectable through adsorption and elution studies.

For further reading:

1. Mollison, PL, Klein, HG, Anstee, DJ. *Blood Transfusion in Clinical Medicine*. 11th edition, Ch. 5, pp163-202.
2. Westhoff, CM. The Rh System. *AABB Technical Manual* 16th edition, Ch. 13, pp 387-409.

Weak D Testing – When is it necessary?

Commercially available Anti-D reagents have changed significantly over the years. The first available reagents were based on human sources of antibody. With the introduction of monoclonal antibodies, reagents now contain a mix of IgM and IgG antibodies. These reagents may detect the D antigen as it reacts at room temperature or at IAT (indirect antiglobulin phase). This modification increased reagent sensitivity and the ability to detect varying forms of the D antigen. While all licensed commercially available reagents must meet FDA regulations, it's important to note reagents from different manufacturers may detect different portions of the D antigen. Also, these reagents do not detect all forms of the D antigen. With the newer combination reagents and the differences between reagent manufacturers, people that were previously thought to be Rh Negative began testing as Rh Positive.

Due to the immunogenic capability of the D antigen, it is important to have strict testing and transfusion guidelines for both patients and donors. Policies for patient testing may vary between facilities. Some facilities test all patients for weak D, where as, others only test a select patient population. These differences in testing often create Rh discrepancies in individuals. A patient may

type Rh Negative at one hospital, but that same individual may test Rh Positive when they are at a different facility. These discrepancies should be investigated¹. Investigations should include finding out the type of testing each facility uses and which manufacturer reagent was used for testing.

Regulations for weak D testing have also changed over the years. Requirements are aimed to prevent unnecessary exposure to the D antigen; thus, reducing the risk of allo-anti-D formation. Currently, weak D testing is required for newborns of Rh Negative woman. It's important to detect any weakly expressed D antigen in the newborns. This is to ensure the mothers are correctly identified as Rh Immune Globulin candidates.

For blood recipients or pregnant women, weak D testing is no longer required². By omitting this testing and calling these patients Rh Negative, we decrease exposure to the D antigen; thus, decreasing the incidence of allo-anti-D.

For blood centers, it's important to detect even the weakest form of D. Weak D testing is required for all donations². This is to ensure blood components that have any expression of the D antigen are appropriately labeled as Rh Positive.

For further reading:

1. Westhoff, CM. The Rh System. *AABB Technical Manual*. 16th edition, Ch. 13, pp 387-409.
2. Price, TH, ed. *Standards for Blood Banks and Transfusion Services*. 25th edition.

Pediatric Red Blood Cell Transfusions

For transfusion purposes there are two distinct pediatric populations:

1. Neonates up to four months of age
2. Infants (more than four months) and children.

The transfusion of neonates requires that the blood bank should be able to prepare small aliquots depending on the size of the neonate. The blood volume of a term neonate is about 85 ml/kg and the blood volume of a preterm neonate is 100 ml/kg. The usual dose of red blood cells for neonates is 10-15 ml/kg.

The most common indication for red blood cell transfusion at this age is symptomatic anemia. It is worth noting the hemoglobin/hematocrit values in this age group are higher than in older children or adults. The hemoglobin value of a term neonate varies between 11 and 17 g/dl.

There are many causes of anemia in neonates, including hemolytic disease of the fetus and newborn (see Dr. MacIvor's article in this issue of Channels), hemoglobinopathies, sepsis, acute blood loss and others. One preventable cause of anemia in these patients is the blood loss due to multiple phlebotomies for testing.

Transfusions are very safe, but there is always the risk of a transfusion transmitted infection. For that reason, it is recommended to limit the exposure of these patients to the lowest number of donors possible. Many hospitals allocate a single unit of blood to two or three neonates so that these little patients will be exposed to only one or two donors.

In most pediatric hospitals, neonates are transfused only with group "O" red blood cells. This is done for safety. It is also preferred to transfuse these patients with leukocyte-reduced units to prevent the transmission of CMV. Premature neonates of CMV seronegative mothers should receive CMV seronegative units.

It is recommended to assign units that are less than five days old to these patients. The rationale for this is that with time, the potassium will increase in these units, the pH falls and the 2, 3 DPG will decline. Many centers transfuse only CPDA-1 units, but studies have shown that for small volume transfusions, units with additive solution (AS) are fine. A transfusion of 10 ml of blood preserved in AS could increase the hemoglobin approximately 3g/dl. The usual dose of red blood cells for this age group of patients is 10-15 ml/kg.

The pretransfusion testing of neonates must include ABO, Rh(D) typing and antibody screen. Some hospitals include an IgG DAT on all neonates up to thirty days. Only forward typing is done in the ABO typing because neonates do not developed anti-A and anti-B until later on.

Neonates usually do not form antibodies, but if the mother has an antibody, the red cells for the neonate should be negative for that particular antigen.

There are special circumstances in neonates that are worth mentioning. One of them is exchange transfusion and the other

is extra-corporeal membrane oxygenation (ECMO). In exchange transfusion, reconstituted blood should be used ("O" red cell and AB plasma).

Transfusion reactions can occur in neonates including hemolytic, allergic, febrile and even TRALI. Of particular importance for this group are the metabolic reactions which include hyperkalemia, hypoglycemia, hypothermia and hypocalcemia. All of these are related to the age of the red cells as well as the type of preservative used.

The transfusion of older infants (more than four months of age) is essentially similar to transfusion of adults, of course the blood volumes are different and the hemoglobin values to achieve need to be in accordance to the age.

For those who want a detailed discussion on this issue, please read:

1. Josephson, C: Neonatal and Pediatric Transfusion Practice, *Technical Manual* 16th edition, Ch. 23, pp 639-663.
2. Hillyer C, Strauss R, Luban N (editors): *Handbook of Pediatric Transfusion Medicine*, Elsevier 2004.

HDFN: A Brief Review

Dr. Duncan MacIvor, MD is a Professor in the Department of Pathology at the University of Kentucky and Associate Medical Director of Kentucky Blood Center.

Rh immune globulin (RhIG) treatment reduces the incidence but not the importance of hemolytic disease of the fetus and newborn (HDFN). Blood bankers and pregnancy caregivers must understand its causes, treatment, and prevention.

IgG crosses the placenta; other immunoglobulins do not. Maternal IgG bound to fetal RBC antigens provokes extravascular hemolysis. Classically, these are alloantibodies formed following transfusion or pregnancy, but the most common cause of HDFN is actually the IgG fraction of naturally occurring anti-A and anti-B found in type O mothers carrying non-O babies. This form of HDFN causes neonatal jaundice, but rarely anemia.

Severe HDFN is due to maternal alloantibodies directed against many possible fetal RBC antigens; by definition, "clinically significant" RBC antigens can cause HDFN. Some antigens are unlikely culprits; e.g., Lewis antigens are poorly expressed in the fetus, and M provokes mainly IgM antibodies. HDFN due to allo-anti-D is the prototype and most frequent cause of severe HDFN, and the only one that can be prevented.

85% of Caucasians (more in other races) are Rh positive, possessing at least one D gene. Children of Rh Negative women are thus likely to inherit a paternal D gene. D is the most immunogenic RBC antigen. While

seroconversion is less likely in immunocompromised patients, healthy Rh Negative people stand an 80% chance of forming anti-D if exposed in pregnancy or transfusion. For comparison, about 30% of healthy K negative individuals would form anti-K; the rate is less for other antigens.

While fetal red cells may cross the placenta early on, this seldom happens before delivery. Antibody formation takes about three months following initial exposure to paternal RBC antigens; thus, HDFN seldom occurs in first pregnancies with antigen-

positive infants. Feto-maternal bleeding may occur early in spontaneous or induced abortion, ectopic pregnancy, amniocentesis, or abdominal trauma during pregnancy. If the pregnancy continues long enough afterward, initial sensitization and HDFN could occur in the same pregnancy. However, the first *affected* pregnancy usually begins after antibody formation. Re-exposure to the alloantigen may provoke a high-titer anamnestic response.

As fetal RBCs coated with maternal IgG are cleared from the circulation, the baby suffers progressive anemia. Plasma volume increases as viscosity declines. In response, cardiac output, intra-arterial flow velocity, and extramedullary hematopoiesis increase, compensating temporarily until high output congestive failure supervenes. The combination of heart failure, increased intravascular volume, portal hypertension, and reduced plasma protein content lead to fetal hydrops. If this spiraling process is not interrupted by delivery or intrauterine transfusion with antigen-negative RBCs (type O, washed, irradiated), the baby will die *in utero*.

Free hemoglobin breaks down to bilirubin. *In utero*, excess bilirubin is cleared via the placenta, and does not threaten the fetus. In a living, affected newborn, however, continued hemolysis may push bilirubin across the immature blood-brain barrier to cause a devastating neurological complication called *kernicterus*. Jaundiced newborns are treated with phototherapy, but in severe cases, exchange transfusion with

group O antigen-negative blood removes both antibody and hemolyzing native cells.

Clearly, it is better to prevent or interrupt HDFN early on. Antibody screens are routine in prenatal lab work. If positive for a significant antibody, clinicians measure serial titers and Doppler flow velocity in the fetal middle cerebral artery. Flow velocity varies inversely with viscosity, providing a useful non-invasive measure of fetal anemia due to hemolysis (which has supplanted the older method of following the optical density of bilirubin in amniotic fluid obtained by serial amniocentesis). An affected fetus can be transfused *in utero* when necessary, delivered when viable, and exchange transfused if kernicterus threatens.

In antibody-negative Rh negative mothers carrying fetuses whose Rh type is positive or unknown, fetomaternal bleeding must be assumed even if the fetal screen (rosette test) is negative. RhoGam should be administered at the conclusion of each such pregnancy; if the fetal screen is positive, follow-up Kleihauer-Betke quantitation determines the dose. Details of RhoGam dosing are supplied in the references.

For further reading:

1. Kennedy MS. Perinatal issues in transfusion practice. *AABB Technical Manual* 16th edition, Ch. 22, pp 625-33.
2. Callum J, Barrett J. Obstetric and intrauterine transfusion. Hillyer, et al. editors, *Blood Banking and Transfusion Medicine*, 2nd edition, Ch. 36, pp 498-505.

Summer 2009 Edition:

- Ethical Issues in Transfusion Medicine
- Product Recalls
- Case Studies

Ask Miss Blood Bank

Is it ever appropriate to give Rh(D) Positive red blood cells to an Rh(D) Negative patient? What about recommendations for plasma products?

John

John,

There is much to consider when thinking about switching Rh(D) Negative patients to Rh(D) Positive blood products. Let's look at each situation individually.

1. Is it ever appropriate to give Rh(D) Positive red blood cells to an Rh(D) Negative patient?

We should always try to give Rh(D) identical red blood cells. Only in cases of desperate need and when no Rh(D) Negative units are available should we consider transfusing Rh(D) Positive units to an Rh(D) Negative patient. In those cases we need to consider the following:

- A. Notify your blood supplier of your need of Rh(D) Negative red cells.
- B. Notify your clinician, so (s)he is aware of the situation and can approve the switch or decide to wait.
- C. Make sure that the patient has no anti-D.
- D. Take in consideration the characteristic of the patient: is not a good idea to give an Rh(D) Negative child or woman of reproductive age Rh(D) Positive red cells.

2. If we give a unit of Rh(D) Positive cells to an Rh(D) Negative patient should we given RhIG?

No, The amount of RhIG needed to "neutralize" that amount of red cells is too large and can cause hemolysis.

3. How about the same situation, but with platelets and plasma products?

The amount of red blood cells in platelets is minimal, but even with that low number of red cells there is the possibility of Sensitization and developing of anti-D. If you have to transfuse platelets from an Rh(D) Positive donor to an Rh(D) Negative recipient, notify the clinician. In these cases, if clinically indicated, RhIG can be given.

FFP and Cryoprecipitate do not have to be Rh(D) identical.