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REPORT

Summary of the Caribbean subregional workshop on quality in immunohematology, a collaborative effort to improve international blood transfusion services

J.R. CRUZ, D.M. HARMENING, AND S.J. NANCE

In 1999, the Pan American Health Organization (PAHO), after consulting with the Directors of the Blood Banks in the Caribbean countries and with the Coordinators of the National Blood Programs of the Latin American countries, prepared an action plan for improving the safety of blood transfusion in the region of the Americas. It clearly expressed (1) the need to assure the quality of blood bank services in all sectors, (2) the requirement for blood banks to participate in programs of external evaluation of performance, and (3) a subregional approach that was warranted in the Caribbean countries because of the small number of blood banks. The plan of action was approved by the Directing Council of PAHO in October 1999.[1] As part of the initiative to strengthen blood services, the Caribbean Epidemiology Center (CAREC), with technical and financial support from PAHO and the collaboration of the AABB, prepared the Caribbean Regional Standards for Blood Banks and Transfusion Services.[2] These standards have specific sections that detail the requirements for compatibility testing and external quality assessments.

To bring the plan of action into operation and to facilitate compliance with the Caribbean Regional Standards, PAHO requested that the United Kingdom National External Quality Assessment Scheme (UK NEQAS) for Blood Transfusion Laboratory Practice

Table 1. Participation in external evaluation of performance

Country	Centers participating in external evaluation
Anguilla	1
Antigua and Barbuda	1
Aruba	1
Bahamas	2
Barbados	1
Belize	1
British Virgin Islands	1
Cayman Islands	1
Curacao	0
Dominica	1
Grenada	1
Guyana	1
Haiti*	1
Jamaica	2
Montserrat	1
St. Kitts and Nevis	2
St. Lucia	1
St. Vincent and the Grenadines	1
Suriname	1
Trinidad and Tobago	3
Turks and Caicos Islands	1

*Haiti started participating in 2005.

Table 2. Error rates (%) among participating centers, 2002–2005

Test	2002–03	2003–04	2004–05
ABO	2.5	0.0	0.5
D	4.3	2.3	0.6

organize a program to assess the performance in ABO grouping, D typing, crossmatching, antibody screening, and antibody identification of 25 Caribbean blood services in 20 countries (Table 1). UK NEQAS sends the panels of unknown samples four times each year to CAREC, which, in turn, ships the materials to each country.

The results of the surveys from 2002 to 2005[3] showed improvement in ABO grouping and D typing by participating centers (Table 2). Nevertheless, in 2005, antibody identification results were returned for only 49.5 percent of potential cases, and there were persistent unsatisfactory reports for antibody screening (four) and for crossmatching (seven). These prompted the UK NEQAS to conclude that "follow-up of problems identified by the external quality assessments is required, in the form of education and training."[3]

PAHO took on the recommendation of the UK NEQAS to organize a hands-on, wet workshop to address the more prevalent weaknesses among the Caribbean blood services. The workshop was a collaboration of the University of Maryland School of Medicine and the American Red Cross. Reagents were donated by Ortho-Clinical Diagnostics, Inc., Raritan, New Jersey, and Immucor, Inc., Norcross, Georgia.

The Workshop

Participants represented countries shown in Table 1. The workshop included both lectures and practical sessions. The topics were designed to address external proficiency program failures with emphasis on the most important issues of ABO and D testing, compatibility testing, antibody screening and crossmatching, and antibody identification. Additional topics included errors in transfusion medicine, a discussion on the overall safety of transfusion in the Americas, and technology recently developed for the blood transfusion service. The number of workshop participants was 17 and the number of contact hours was 14.

Baselining

At the start of the workshop, the participants were surveyed using electronic ResponseCard keypads (courtesy of Turning Technologies LLC, Youngstown, OH) to ascertain: (1) how many laboratories participate in the UK NEQAS, (2) the type of testing performed, and (3) the technology, procedures, and reagents used in their laboratories. The responses were used to adjust the program to meet the needs of the audience.

The responses indicated that 64.7 percent of the attendees participated in the UK NEQAS. In terms of technology, 37.5 percent reported using gel technology, 12.5 percent tube testing, 12.5 percent column technology, and 37.5 percent a combination of technologies. Only 27 percent of the laboratories routinely perform all of the following tests: ABO grouping and D typing, crossmatching, antibody screening, and antibody identification. In terms of antibody screening, 43 percent of the laboratories use a three-vial set (not pooled) of reagent screening RBCs, and 14 percent use one vial of pooled group O reagent screening RBCs. The enhancement reagents used with the antibody screen were LISS in 42 percent of the laboratories, albumin in 25 percent, PEG in 25 percent, and other reagents in 8 percent. When asked what type of crossmatches they performed, 50 percent of the laboratories reported immediate spin (IS) if the patient has no history of an alloantibody and a negative antibody screen, and 50 percent reported a complete crossmatch (IS, 37°C, and anti-human globulin).

For the practical sessions, clinical histories, samples, standard operating procedures, and worksheets were given to each participant for individual work. Because the results of the proficiency survey indicated testing failures, the participants were individually proctored at a ratio of one proctor for four participants. Results were tabulated using the anonymous vote-in electronic technology (TurningPoint, Turning Technologies; Table 3). The response cards allowed instant tabulation of results. Root causes of the problems were shared by proctors, and the rationale for the tests, results, and interpretations were discussed collectively. During the first practical session there were 64 reporting opportunities, 48 (75%) of which were correct, with 9 nonresponses (Table 3).

As further preventive action and future education, a copy of the book *Modern Blood Banking and Transfusion Practices,*[4] D.M. Harmening, editor, was given to each participant. To facilitate mentoring and problem solving, e-mail addresses of the primary faculty were distributed.

Evaluation

Eleven (65%) of 17 participants graded the overall quality of the workshop as Excellent. All the comments

Table 3. Results of ABO and D determination by participants in the workshop

Expected result	No response	Incorrect	Correct
Group A_2 RBCs with anti-A1	5	5	6
Group B, D+ with anti-A1 (<4+)	1	0	15
Group O, D–	2	1	13
Group AB, D+	1	1	14
Total	9	7	48 (75%)

for improvement were suggestions to extend the duration of the workshop to allow for more discussion and interaction with the professors. As indicated by participant responses, we believe that the workshop achieved the objective of improving knowledge and competencies among the participants; it also renovated their motivation for the work they do. Furthermore, opportunities for future clinical discussions, consultations, and referrals were also established.

Discussion

The need for this workshop was precipitated by the scores in the external quality assessment using proficiency samples. Although the scores had improved somewhat over time, the failure rate was too large to depend solely on time to improve it. As a result of the scores in the different areas, lectures, surveys, and wet workshop samples were developed to directly impact the problems.

Once the workshop was designed and approved, the participants were invited and supported in travel accommodations.

Survey data obtained at the beginning of the workshop indicated further areas for concentration and confirmed the topics were appropriate. Interim evaluations as to topic area development and the directives were used to allow course correction during the workshop.

The proof of the value of the workshop and the applicability to the participants will be unknown until better scores in the external evaluation are observed. Success will also rely on the participants sharing their knowledge and training with other staff. Sixty-five percent of the participants evaluated the workshop as excellent, with thirty-five percent rating the program as good.

Acknowledgments

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REVIEW

Technical issues in neonatal transfusions

S.R. SLOAN

Neonatal transfusions provide challenges at several steps in the process. Neonates are often transfused with relatively small volumes at slow flow rates from syringes, whereas at other times they require relatively massive transfusions or exchange transfusions. To facilitate these specialized transfusions, blood banks often modify their procedures to provide small volumes of blood components that are sometimes dispensed in syringes or to reconstitute whole blood for exchange transfusions. Hospitals must implement policies and procedures to ensure that the blood components are transfused safely when using these specialized techniques for infants. Nevertheless, some issues remain in many hospitals, such as the difficulty in safely warming blood components for neonatal transfusions and the difficulties in using approved labels for small containers that are sometimes prepared at the bedside. ***Immunohematology* 2008;24:4–9.**

Key Words: neonatal transfusions, syringes, aliquots, exchange transfusions, concentrating blood components, washing blood components

Neonatal Transfusion Volumes

The large variation in volumes transfused to neonates impacts the processes for preparing blood components in the blood bank and for transfusing the patient at the bedside. Neonates can receive very small simple transfusions or larger transfusions, some of which are considered massive.

Large transfusions including massive transfusions can occur in one of several settings. Exchange transfusions, which are most frequently performed for neonatal hyperbilirubinemia, usually consist of exchanging two blood volumes with reconstituted whole blood. Some surgical procedures result in substantial hemorrhage, necessitating large and sometimes massive transfusions. Other scenarios in which neonates commonly receive massive transfusions include those when the patient is placed on an extracorporeal circuit such as a cardiopulmonary bypass circuit or an extracorporeal membrane oxygenation circuit.

An entire massive transfusion for a neonate may be obtained from 1 unit because the volume in 1 RBC unit may be more than the blood volume of the neonate. Very small premature infants have blood volumes of up to 100 mL/kg, which means, for example that a 1500-g premature infant has a blood volume of up to 150 mL, which is less than the volume of 1 RBC unit.

Although "massive transfusions" for an infant are relatively small and may be less than 1 unit of RBCs, standard simple transfusions can be extremely small. Indeed, an entire simple transfusion usually consists of less than 50 mL. A standard transfusion of RBCs or plasma or platelets usually consists of 5 to 15 mL/kg. For example, in the 1500-g premature infant, an entire simple transfusion would be approximately 10 mL.

Venous Access

Transfusions can be performed via a large-bore central catheter, a small-bore central catheter, or a peripheral venous catheter. A large-bore central catheter is used for extracorporeal circuits in which the "transfusion" is an integral part of the circuit. Other neonates sometimes have small-bore central catheters. However, some people prefer to reserve these catheters for nutrient solutions or drugs because of concerns about clogging a small-bore central catheter with a blood transfusion.[1] Hence, small peripheral needles are often used for transfusions.

Rapid transfusion through narrow peripheral needles can cause small amounts of hemolysis in some situations.[2,3] Although the resulting hemolysis may be measurable and even cause hemoglobinuria in rare circumstances, it is rarely if ever clinically significant. The most potentially dangerous effect of hemolysis at the needle would be the effect of transfusing free potassium. However, more potassium is liberated from RBCs during storage than is released via hemolysis at the needle, and it would be extremely unlikely that enough potassium would be transfused through a small-bore needle to induce dangerous hyperkalemia.[2]

Blood Warmers

Unfortunately, no blood warmers available in the United States are specifically designed for neonatal transfusions. There are some disadvantages associated with using blood warmers designed for adult transfusions for neonatal transfusions. One disadvantage is that the volume of fluid required for the blood warmer is often larger than the volume to be transfused, which means that some of the blood component will often be wasted. Another disadvantage associated with some blood warmers is that because the flow rate for neonatal transfusions is relatively slow, the blood may reequilibrate to ambient room temperature after passing through the blood warmer but before entering the patient's circulation. However, most simple neonatal transfusions do not need to be warmed.

Transfusion Techniques—Controlling Flow Rate

Except for transfusions that are an integral part of a circuit, most neonatal transfusions are administered from a syringe. Although the syringe plunger may be manually pressed, most simple transfusions are administered using a syringe pump to control the transfusion rate, which is usually approximately 5 to 15 mL/kg per hour.

Syringes

Unlike most transfusions, neonatal transfusions usually require transfer of a blood component into a syringe before the actual transfusion. This step often occurs at the patient's bedside, but some hospital blood banks transfer blood components into syringes for select neonatal transfusions.

When a relatively large volume of a unit (approximately one half) might be transfused, the blood bank often prepares the unit using procedures identical to those used for most transfusions of larger patients; blood is dispensed in a standard blood bag. The transfusionist might then transfer aliquots of the unit into a syringe at the patient's bedside so that the transfusion rate and volume can be controlled. The transfusionist can connect the blood bag to a syringe through a three-way stopcock, with the other port on the stopcock connected to a catheter that enters the patient's circulation. Using this setup, the blood component can be filtered while it is transferred from the bag to the syringe using a blood administration set; then the stopcock is readjusted, and the blood component is then transfused from the syringe. One risk associated with this approach is that RBCs could hemolyze if forced through an improperly adjusted stopcock, but this rarely causes clinically significant problems.

Some blood banks transfer blood components into syringes for clinical areas such as the neonatal intensive care unit. The blood bank may simply transfer the blood into a syringe using the same connection devices that would be used by the clinical area. The disadvantage of this approach is that the remainder of the blood component will have a reduced shelf life because the system has been opened and is susceptible to contamination. AABB Standards limits the shelf life of such a unit to 24 hours from the time the unit is entered.[4]

If the blood bank has a sterile docking device, it can connect a blood administration set to the tubing that is part of the blood unit. The blood bank then transfers a portion of the blood component into a syringe, seals off the tubing, and disconnects the blood administration set from the blood bag. This allows the remainder of the blood component to be stored and used at a later date.[5]

It is advisable to minimize the time that platelets are stored in syringes, which, unlike platelet storage bags, are made of gas-impermeable plastic. Platelets are metabolically active, and platelets stored in syringes become depleted of oxygen and use anaerobic metabolism.[6,7] This results in the generation of lactic acid and decreases the pH of the platelet component.[6–8] This effect happens more rapidly in conditions that favor greater metabolic activity, including storage at 37°C and storage of volume-reduced platelets.[6,7] Although storage in syringes for up to 6 hours results in platelets that are generally acceptable by FDA standards and that appear acceptable after passage through a syringe, it is advisable to avoid storage at 37°C and to minimize storage times and storage of volume-reduced platelets.[7,8]

Satellite Bags

Some hospital transfusion services dispense blood components in satellite bags instead of, or in addition to, syringes. Syringe aliquoting is most useful when the transfusion service has a sterile connection device to attach the blood administration set to a blood component unit. Without a sterile connection device, the blood administration set must be spiked into the blood component unit, which opens the system, increasing the risk of contamination and limiting the shelf life of the remaining unit to no more than an additional 24 hours by AABB Standards.[4]

A variety of satellite bag systems are available, all of which are designed to provide aliquots of the original blood component units in smaller bags. These systems, such as some "pediatric packs" provided by some blood centers, contain several (usually six) satellite blood bags containing aliquots of the original RBC unit. When they are prepared by a blood center, sterility of the system is maintained and the RBC units have the same outdate as a nonaliquoted RBC unit. Similar systems, such as the Pedi-Pak (Genesis BPS, Hackensack, NJ) are available to hospital transfusion services. With these systems, staff in the transfusion service can aliquot a unit into smaller bags, either with or without a sterile connection device. Without the sterile connection device, the shelf life of the unit is decreased, but this may still be useful because it allows 1 unit to be used for several babies in 1 day or several aliquots of 1 unit to be used for one baby who requires multiple transfusions during 1 day.

Satellite bag systems are also available for plasma. Most commonly, a unit of plasma is divided into 4 to 6 smaller subunits before freezing, and blood suppliers can often provide this. The transfusion service then thaws a small dose of plasma when needed. The unit can be thawed in the same warmers used for standard units, but the thawing times differ and each laboratory should determine the thawing times for the different types of frozen plasma units that are used. When using a standard plasma warmer device, the thawing time depends on the dimensions of the unit and is especially dependent on the unit's thickness. Hence, smaller units sometimes take more time to thaw than larger units.

Alternatively, a plasma unit can be aliquoted into satellite bags after thawing, using a sterile connection device. This might be useful if no small frozen plasma units are available and several pediatric doses are needed. Additionally, if one infant is expected to need several plasma doses, donor exposure can be limited by transfusing with aliquots from the same thawed unit.

Filtering

All blood components should be filtered near the time of transfusion, as required by accrediting organizations such as the AABB.[9] This filtering step, which is in addition to optional filtering to reduce leukocyte concentration, is designed to remove any aggregates that may develop during storage of blood components. Although this filtering is generally performed when the blood component is transfused, the most common exception occurs with neonatal transfusions, in which the blood component is often filtered when it is transferred into a syringe. This exception is allowed because it is extremely difficult to appropriately prime a catheter and blood filter and then precisely control the transfusion volume flow rate when the syringe is connected to a filter during the transfusion. Because filtering is often most conveniently performed when the blood component is transferred into a syringe, the blood bank may filter the blood component.

Some facilities use blood administration sets especially designed for neonatal transfusions. These sets are designed to minimize the priming volume and blood losses that occur in standard blood administration sets. Indeed, it is not unusual for up to 40 mL to be lost in the standard blood administration set. Neonatal blood administration sets have smaller filters and narrower catheters that are often shorter to minimize these volumes. Additionally, manufacturers such as Charter Medical, Ltd., Winston-Salem, North Carolina, sell sets with various configurations, such as sets with a syringe or syringes preattached to facilitate transfer into syringes within a sterile closed system.[5] With these systems, volume losses can be minimized to 1 to 3 mL for each aliquot that is prepared from a unit, and some blood banks have reported preparing more than 20 aliquots from 1 unit of a blood component.

Irradiation

Cellular blood components, including RBCs, whole blood, and platelets, may be irradiated to prevent transfusion-associated GVHD. The shelf life and function of platelets is not affected by irradiation.[10–13] However, RBC units are affected by irradiation, which should be considered in blood bank policies and procedures.

Potassium is released from RBCs during storage, and this process is substantially hastened by irradiation.[14] To minimize exposure to extracellular potassium, the unit should be irradiated as close to the time of transfusion as possible if the unit will be used for a large and rapid transfusion.[15,16] This is recommended because case reports suggest that neonates are particularly susceptible to transfusion-associated hyperkalemia, which occurs, although rarely, when they are transfused with RBC units or whole blood that contains elevated potassium concentrations in the supernatant.[17] If it is not possible to provide freshly irradiated units, either because of a lack of inventory of appropriate units or because the hospital transfusion service lacks an irradiator, then the units used for large transfusions can be washed to remove most of the extracellular potassium.

Washing and Concentrating Blood Components

Although the methods used to wash blood components for neonates are the same as those used to wash blood components for older patients, a few possible indications for washing are more common in neonates. Case reports suggest that transfusion of plasma-containing components increases hemolysis owing to T-cell activation in neonates, and hence washing may be indicated for these patients.[18] Although transfused potassium is not problematic for standard simple transfusions, it may be problematic for large transfusions for very young patients, and RBC units are sometimes washed to reduce extracellular potassium. Although this is effective for the first 2 to 3 hours after washing, potassium can rapidly rise after washing, and 18 hours after washing irradiated RBC units, the extracellular potassium concentration can exceed 15 mEq/L.[19]

Although there is little evidence that concentrated RBCs or platelets are beneficial for neonatal transfusions, some transfusion services provide concentrated RBCs and platelets. A dose of RBCs concentrated to a hematocrit of approximately 68% can be obtained by removing the aliquot from an RBC unit that has been hanging upside down in the refrigerator for 72 hours.[20] Alternatively, some have developed methods to concentrate RBCs to more than 80 percent by centrifuging the unit at 4000 × g for 4 minutes and transferring a portion of the concentrated RBCs to a satellite bag.[21,22]

Platelets can be concentrated by centrifugation, removal of some supernatant, and resuspending the remaining platelets.[23] However, the additional manipulation of platelets required to wash or volume-reduce platelets causes platelet loss, can cause clumping, and may induce some platelet dysfunction.

Exchange Transfusions

Special considerations apply to a neonatal exchange transfusion, which involves a massive transfusion for an infant. The methods used to prepare the blood component and perform the exchange are designed to minimize the risk involved with the procedure.

Two blood volumes are usually exchanged, with a neonate's blood volume ranging from 85 mL/kg for full term infants to 100 mL/kg for very low birth weight infants. Most frequently, the neonate's blood is exchanged with reconstituted whole blood with a hematocrit of 40 to 60% that is prepared from RBC units and plasma.[24,25] Often the first step in preparing reconstituted whole blood is to remove the supernatant from the RBC unit, especially if the RBC unit contains an additive. Although this can be accomplished by washing the unit in an automated blood washer, a modified method in which normal saline solution is added, the unit is centrifuged, and most of the supernatant is removed removes sufficient amounts of supernatant for this purpose. When the RBC unit is ready for reconstitution, the hematocrit of the unit is measured, and the amount of plasma needed to dilute the RBC unit to the desired final hematocrit is calculated.

The exchange transfusion is sometimes performed through simultaneous withdrawal and transfusion through two sites of vascular access.[26,27] However, the discontinuous method is more frequently used. With the discontinuous method, a stopcock is used to alternate transfusion and withdrawal of blood through one site.[28] With the discontinuous method, usually no more than 5 mL/kg of blood is withdrawn and replaced during each replacement cycle. With either method, a blood warmer is usually recommended, and the unit should be kept well mixed throughout the procedure.

Labels

Bags and syringes of blood used for transfusion need to be labeled, and all FDA-licensed and registered facilities and all AABB-accredited facilities will soon need to be in full compliance with ISBT standards.[29,30] These regulations apply regardless of where the aliquot is prepared. In most cases, the labels for aliquots will need to be provided by the hospital transfusion service even if the aliquot is prepared at the bedside. Because labels need to be in compliance with specific size requirements, facilities are developing labels and techniques that permit the labels to be used with syringes and syringe pumps. For example, some labels may need to be folded back to permit visualization of the blood component in a syringe.

Summary

Two issues result in the use of special techniques when preparing and transfusing blood components for neonates. First, neonates can be especially susceptible to some transfusion risks such as metabolic abnormalities and fluid shifts. Hence, blood banks and clinical areas avoid transfusing fluids containing nonphysiologic electrolyte concentrations and using rapid transfusion rates whenever possible. Second, standard supplies and equipment are designed for transfusion of larger

patients. In some cases, hospitals need to use equipment that is not well designed for neonatal transfusions, such as blood warmers. In other cases, equipment and supplies for neonatal transfusions are available, such as satellite bags, pediatric filters, syringe pumps, and syringes. In these cases, hospitals must consider the impact that these systems have on workflow and the potency and purity of transfused blood components.

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REVIEW

Neonatal red cell transfusions

C.A. LITTY

This review discusses RBC transfusion in the neonatal age group and explores how one institution arrived at current common practice. Special considerations such as CMV infectious risk and GVHD are discussed. ***Immunohematology* 2008;24:10–14.**

The neonatal intensive care unit (NICU) patient population is one of the patient groups in the hospital most heavily transfused with RBCs. All infants experience a normal decline in hemoglobin concentration during the first weeks of life; however, this is problematic in premature infants because of a diminished output of erythropoietin in response to anemia. In addition, these patients, who often have low birth weights, need close monitoring of blood gases, electrolytes, and other laboratory variables, which contributes substantially to the transfusion requirement as a result of the small circulating RBC volume. Although these tests are often impossible to do without, there is some help that can be provided to the phlebotomists to relieve the blood loss volume from being even greater. The infant younger than 4 months of age is immunologically immature, which makes RBC alloimmunization exceedingly rare, so some of the serologic testing performed in the blood bank for other age groups can be abbreviated. This 4-month period is often defined in the blood bank as the neonatal period because of this distinction. In other medical subspecialties the term neonate may describe different age ranges. For this patient population the reverse grouping and the crossmatch that are seen in routine blood bank practice can be waived. This saves the repeated drawing of a crossmatch specimen every 3 days. Initial testing must determine ABO group and D type and include a screen of the serum (infant's or mother's) for unexpected antibodies. If there are antibodies present in the serum, blood that tests negative for the corresponding antigen can be provided without crossmatch.[1]

In the start of the 1990s the sick infant who underwent multiple transfusions was typically exposed to 9 or 10 different donors.[2] These transfusions were dispensed in small amounts or "aliquots" of the original unit because of the small size of the patient, but even so the number of donors increased the risk of certain transfusion-related complications, such as infectious risks, which are proportional to donor exposure. Neonatal transfusion practices have changed since then, not in reducing the total volume of blood transfused, but in decreasing the number of donor exposures. At the outset of the decade the rise in potassium that was seen in RBC units stored for any length of time was feared by neonatologists because of the risk that a posttransfusion rise in serum potassium to abnormal levels would cause fatal arrhythmias. Studies of small-volume transfusions in neonates that compared units of RBCs stored until their expiration date with fresher units showed that posttransfusion potassium concentrations did not rise to abnormal levels and were not a clinical issue.[3–5] It is important to note that the transfusions being discussed were small-volume (15 mL/kg), slow transfusions. Large-volume, rapid transfusions performed in this age group can occur in surgery, exchange transfusion, and extracorporeal membrane oxygenation. When the potassium load cannot distribute itself throughout the total blood volume quickly enough, it may result in arrhythmia. This was described in 1993 in a neonate who received older RBCs as a rapid transfusion in cardiac surgery, and died of cardiac arrest.[6] The RBCs were stored in CPDA-1; today more commonly used additive solutions have a better potassium profile. However, it is still prudent in a rapid or large-volume transfusion setting to use the freshest RBCs possible as opposed to units that are close to their expiration date, although in a small-volume, slow transfusion setting, minimizing donor exposures is more important than age of the RBCs.

Another change in practice occurring at the same time, as alluded to previously, was the use of additive solutions, which were new to transfusion services. These solutions increased RBC storage to 42 days because they were better for RBC metabolism and decreased hemolysis. The first additive solution in widespread use was AS-1 (Adsol), which contained additional dextrose

and mannitol. Mannitol may cause an osmotic diuresis, which again was worrisome to neonatologists because of the potential consequences. This was a theoretical risk, and in 1991 before controlled studies appeared Luban et al.[7] addressed this eloquently by calculating the amount of supernatant fluid present in a small-volume transfusion and the volume of these additives actually transfused to the infant. In fact the concentration of mannitol actually transfused per kilogram was substantially less than would be needed to cause an osmotic diuresis.[7] Indeed, this was borne out when controlled studies began to appear. A study comparing AS-1 units with CPDA-1 units showed that the patients receiving AS-1 actually had an improved glucose homeostasis in that the amount of hypoglycemia seen after neonatal transfusions was reduced. (Hypoglycemia seen with neonatal transfusions is usually a function of high-glucose fluids being discontinued during a transfusion to use the current intravenous access owing to the difficulty of obtaining multiple access sites in this patient group.) Also, urine output, pH, and serum electrolytes were not significantly different.[8]

With time many centers accepted the use of AS-1 units with no negative consequences; however, blood centers began to purchase bag sets from manufacturers who used AS-3 (Nutricel). This product differed from AS-1 in the presence of phosphate rather than mannitol. Again, a study confirmed that in clinical use the additive solution did not cause harm to the neonates transfused.[9]

Use of all group O, D– or only group O, D– and group O D+ for neonates stemmed from the practice of using only fresh RBCs for transfusion. This way the unit could be used for many neonates before it reached its 5- or 7-day expiration date. The problem with this method is that it depletes group O units from the blood supply, when they are already used excessively (i.e., trauma patients). When the practice changed to using dedicated units many centers switched to ABO-specific RBCs. The changeover was not complete, unfortunately, and this exacerbates group O shortages in many regions. Some blood bank workers advocate not switching to ABO-specific units in a patient of any age until a second sample is drawn for confirmation as a safety measure. Whether this will become the practice in neonates, in whom blood draws should be kept at a minimum, is unknown, but obligating this entire group of patients to receive only group O RBC units will certainly have an impact on the supply in the community at large.

A consideration in the choice of blood in the NICU is that the multiply transfused preterm infant of a CMV-seronegative mother is at an increased risk of transfusion-transmitted CMV infection. CMV infection has a highly variable clinical picture and can be asymptomatic, severe, or fatal. There is often sepsis associated with hepatosplenomegaly, abnormal blood counts, and pneumonitis.

Blood products can be tested for CMV antibodies, and seronegative products can then be provided for use. Because CMV is an organism that is associated with WBCs, providing WBC-reduced cellular blood components is an appropriate way to reduce the risk.[10–13] With the increasing use of leukoreduction this method has become well accepted as a CMV safe alternative, but there are some physicians who will still insist on CMV-seronegative blood. Because most communities have high rates of seropositivity in the donor population, it is unacceptable to waste seronegative blood on seropositive patients in a situation in which only CMV-tested blood products are requested. Many hospitals find it easier to provide leukoreduced blood to all than to test all mothers and provide selective blood products.

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when an immunocompromised patient is transfused with blood from an immunologically competent donor. The donor T lymphocytes can then proliferate unimpeded and engraft. Fever follows at about 4 weeks (versus 10 days in an adult) and rash at about 30 days (versus 12 days in an adult);[14] liver and gastrointestinal involvement and severe cytopenia ensue. The pancytopenia differs from the GVHD seen after bone marrow transplant because in TA-GVHD the bone marrow is part of the host, thus it is affected also. This accounts for the very high fatality rate seen in the latter, attributable to hemorrhage and infection. There is also a longer course of infection from transfusion to death in neonates than adults. Several theories as to the mechanism of these differences are discussed in the thorough literature review from Japan of Ohto and Anderson.[14]

Irradiation of blood components is the only method to render the T lymphocyte nonmitogenic and prevent the reaction. Although leukoreduction reduces the number of WBC greatly, there is no known threshold below which TA-GVHD will not occur; therefore, it is not an adequate method for prevention.

The infants who are at risk for TA-GVHD have specific risks other than being an infant. These include immunodeficiency disorder, intrauterine transfusion followed by postnatal exchange transfusion, severe prematurity and low birth weight, and family members

providing directed donations.[13] Therefore a blanket policy of irradiating blood for all infants or NICU patients is not required. Some hospitals, however, may opt to do this. A number of factors should go into this consideration. A hospital with a high-level NICU, with very premature or sick infants, and a blood bank that has its own irradiator and can easily irradiate before transfusion for infants who are at sufficient risk is most likely to find a policy to irradiate RBCs for all neonates useful. This is more efficient than expecting clinical staff to provide birth weight and clinical history so that each patient's risk can be determined and will avoid missing the one patient who falls through the cracks. Hospitals without this high-risk population or an irradiator of their own will have to wait for irradiated components to be sent specially from the blood center. If they are not used as originally planned then the issue of storage lesion comes into play. (Irradiated RBCs have a shorter shelf life, 28 days, because of increased storage lesion.) Considering the wait time and the decreased shelf life of units, it would be more efficient to determine the actual risk of each patient than to set a broad policy.

RBCs are supplied to replace oxygen carrying capacity, but the improvement in oxygen offloading at the tissue level and its effects on patient outcome cannot be measured. Therefore we do not actually know whether we are improving the patient's condition. It is important for clinicians to believe there is a benefit before transfusing and not just have a knee-jerk reaction to a number on a lab report, which is all too common. However, conflicting evidence provides reason for debate among clinicians.

Iatrogenic losses were discussed earlier; however, to quantify, these losses should be replaced when 10 percent of the blood volume has been phlebotomized. Anemia is harder to define in this age group because of the changing normal values. At this institution, the hemoglobin range on the first day of life is 16.5 to 21.5 g/dL. This declines throughout the next few months, and at 3 months of age a hemoglobin of 10.4 g/dL is the lower limit of normal. This is called the physiologic anemia of infancy. As this change takes place HbF is replaced by HbA, which has a lower affinity for oxygen, and thus releases it for tissue consumption more efficiently. In preterm infants the hemoglobin levels are lower at any given point and the decline is more pronounced, and the switch over to HbA is affected by the degree of prematurity. There is even controversy over defining the signs of anemia in this age group, with tachycardia, tachypnea, bradycardia, recurrent apnea, and poor weight gain being used.[15,16]

Table 1. RBC indications for infants younger than 4 months of age[15,16]

Hb < 13 g/dL	Severe pulmonary or cyanotic heart disease, heart failure
Acute loss of 10% blood volume	Phlebotomy or other cause
Hb < 8 g/dL	Stable neonate with clinical manifestations of anemia

Table 2. RBC transfusion thresholds for infants younger than 4 months of age[17]

Anemia in the first 24 hours	Hb = 12 g/dL
Cumulative blood loss in 1 week NICU	10% blood volume
Neonate receiving intensive care	Hb = 12 g/dL
Acute blood loss	10% blood volume
Chronic oxygen dependency	Hb = 11 g/dL
Late anemia, stable patient	Hb = 7 g/dL

Table 1 summarizes guidelines by the AABB Pediatric Hemotherapy Committee. It is interesting to note that these are from the mid-1990s; more recent, more restrictive guidelines are available from Britain and are summarized in Table 2.[17]

Two recent studies provide a glimpse of the conflicting opinions. A study from 2005 that randomized 100 preterm infants to a restrictive or liberal transfusion group showed there may be harm to patients in the restrictive group.[18] The liberal group received transfusions for hematocrits less than 46%, and the restrictive group used 34% as the cutoff for transfusion. However, these thresholds were adjusted lower as patients progressed through three stages of clinical condition. Infants in the restrictive group had more intraparenchymal brain hemorrhage, periventricular leukomalacia, and apnea. In 2006, a larger study was published.[19] It was called the PINT study for premature infants in need of transfusion. It also used a low and high threshold for hemoglobin, which changed for clinical condition, starting with 10 to 11.5 g/dL versus 12 to 13.5 g/dL. Differences in each group depended on whether or not there was respiratory support. There were 451 infants enrolled in this study, and there was no significant evidence of benefit to the high transfusion threshold.

An exception to using hemoglobin values as an aid to determining transfusion threshold is seen when a newborn suffers from HDN. In HDN the mother has formed IgG antibodies to an antigen on the fetal RBCs. It can be the D of the Rh system or another RBC antigen. There is immune-mediated hemolysis resulting in anemia, but a further problem exists related to the bilirubin levels. This is because at birth the newborn's liver is not mature enough to conjugate the large

amounts of bilirubin produced by the hemolysis. Unconjugated bilirubin presents a great danger to the developing central nervous system. Exchange transfusions are performed with reconstituted whole blood created by removing the additive solution from RBCs and combining with thawed FFP. The infant's blood is removed in aliquots followed by transfusion of aliquots of reconstituted whole blood. It is best to use a reconstituted product with a hematocrit of 45 ± 5%.The plasma portion of this product is necessary to replace the infant's plasma, which has high levels of unconjugated bilirubin and maternal antibody. In addition the process removes IgG-coated RBCs before they have been hemolyzed, and the RBCs treat the anemia. The RBCs chosen must be compatible with the mother's serum, which means they lack the antigen corresponding to the maternal antibody. Typically group AB FFP is used to reconstitute. The need for irradiation should be evaluated as discussed in a previous section.

The levels of bilirubin that lead to this procedure will vary from hospital to hospital based on differing normal ranges, usually more than 25 mg/dL, but the rate of rise of bilirubin is used along with the level to decide when an exchange transfusion is appropriate. When HDN is not severe enough to necessitate exchange transfusion, treatment consists of phototherapy, which exposes the skin to a specific wavelength of light that converts the bilirubin into a more soluble form that can be excreted without conjugation.

The transfusing physician should always be aware that the well-defined risks that are documented in the textbooks are not the only risks to transfusion. There may be consequences to transfusion that are hard to show because of the complexities of the illness of the sick, transfused population. There also may be donor characteristics specific to one region that are not widely seen. One example is lead in the environment. A donor exposed to lead may be a source of lead exposure to a transfusion recipient. This was shown in a study from 1991 to 1992.[20] Posttransfusion increases of lead were seen in 19 premature infants in relation to the amount of blood they received in Oakland, California. Whether this would be seen in other locations or in the present decade is unknown.

Another interesting and more recent study looked at the association of RBC transfusions and necrotizing enterocolitis (NEC).[21] This is a serious acquired gastrointestinal disorder seen in low birthweight neonates. A small group of stable, growing premature neonates developed NEC within 48 hours of transfusion. Whether there are host-specific or RBC storage characteristics that influence this risk is unknown.

HCV look-back is a good example of future consequences to what seems like a life-saving intervention today. The first tests for HCV appeared in 1990, and a second-generation test came out in 1992. In 1998 the FDA recommended HCV look-back to all blood establishments. This meant that donors who tested positive for HCV had previously negative or untested donations traced so that recipients could be found and tested in case the virus had been transmitted by the earlier transfusion. Among patients whose donors were later found to be HCV-positive, children represented 10 to 20 percent of those who acquired posttransfusion hepatitis C.[22] A recent study from Alaska looked at all patients who were transfused while in the NICU as opposed to the FDA-recommended look-back described here, which only tested recipients whose donors later were tested positive.[23] In this study of 216 screened patients, 7 (3%) were hepatitis C antibody–positive; 6 of which were also hepatitis C virus-RNA positive.

Some of their lives may very well have been saved by the transfusions, but it is certainly something the transfusing physician should be thinking about when considering whether or not to transfuse. The risk of serious consequences that may manifest themselves many years in the future is only worth taking if there is a real benefit from the transfusion.

Those in the transfusion medicine community can help patients even though they are not the professionals writing orders at the bedside. From the technologists in the blood bank to the medical directors, every chance to educate the clinicians should be seized. Much of what we know about risks of transfusion has been described in the last 15 to 20 years. This is not covered in the medical school curriculum.

This can be said for all patients, but it is especially true in the infant who has the most years of life ahead of all transfused patients. Although the current healthcare team of transfusing physicians and blood bank workers will probably not be involved in the patient's care after 15 years, the patient may be dealing with a transfusion-transmitted illness we cannot even imagine today.

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Neonatal and infant platelet transfusions

D.A. SESOK-PIZZINI AND D. FRIEDMAN

Neonates are defined as infants younger than 28 days old, and in general many transfusion protocols are standardized to represent infants younger than 4 months of age. Often the distinction is made between premature neonates and term neonates, and institutional protocols may be established on the basis of age or birth weight. When this is important in terms of transfusion protocols, premature neonates, neonates, and infants will be described separately.

Indications for Neonatal and Infant Platelet Transfusions

Healthy term infants are born with the same platelet count as adults, whereas premature infants may have platelet counts that are on the lower end of the adult normal range (150×10^9/L to 450×10^9/L). When the platelet count is less than normal, this is an indication for investigation and possibly treatment that may include platelet transfusions. Many disorders are associated with thrombocytopenia in neonates, and an investigation for infections, drug exposures, autoimmunity or alloimmunity, thromboses, neoplasms, and genetic conditions is important for the evaluation of the need for treatment or transfusion.

The degree of thrombocytopenia in newborns varies, although thrombocytopenia is the most commonly reported hematologic abnormality in neonatal intensive care units (NICU). According to Castle et al.,[1] 75 percent of sick neonates will have a transient thrombocytopenia by day 2 of life, which will nadir by day 4 and return to normal counts by day 10 of life in 86 percent of neonates. These neonates may not require a transfusion. However, approximately 50 percent of hospitalized neonates will have a platelet count decrease to less than 100×10^9/L, and 20 percent will have a decrease to less than 50×10^9/L.[1,2] These neonates may require platelet transfusion. There is ongoing controversy over the indications, trigger, and dosing for platelet transfusions in these patients, and this presents a clinical challenge owing to the limited data from controlled clinical trials.

Platelet Transfusion Guidelines

The decision to transfuse is often considered in terms of treatment of severe bleeding in an unstable neonate or prophylaxis to prevent bleeding in a more stable neonate. The AABB Pediatric Hemotherapy Committee, by developing a practice consensus, was one of the first groups to develop guidelines for neonatal platelet transfusion for the purposes of auditing.[3] AABB members who were surveyed for the study noted that the platelet transfusion criteria for sick premature infants was too liberal at 100×10^9/L in contrast to the medical practice at many institutions to transfuse at less than 50×10^9/L. After that consensus survey, other published guidelines emerged for infants. These guidelines recommended that stable neonates with a platelet count of less than 50×10^9/L with active bleeding or an invasive procedure with production failure may require platelet transfusion. Neonates with platelet counts less than 30×10^9/L as a result of failure of platelet production, but no identified bleeding or risk of bleeding, may also require platelet transfusion. In rare instances, guidelines for neonates may more closely resemble guidelines for older children and adults, in whom transfusions are recommended for platelet counts of 5 to 10×10^9/L. A sick unstable neonate may be transfused if the platelet count drops below 100×10^9/L with active bleeding or when an invasive procedure is anticipated in patients with sepsis, disseminated intravascular coagulation, or other mechanism of platelet consumption.[4,5]

The sick premature infant is at especially high risk for an intracranial hemorrhage (ICH) from a low platelet count or poor platelet function. These infants (younger than 37 weeks) have decreased plasma coagulation

proteins and poor platelet function compared with older children and adults. In addition, these premature neonates have an underdeveloped subependymal matrix that puts them at increased risk for an ICH, particularly in the first 3 to 5 days after birth.[6] A multicenter prospective, randomized controlled trial investigated whether early use of platelet concentrates reduced the incidence or extension of ICH in sick neonates.[2] This study concluded that neonates who were transfused when their platelet count decreased to less than 150×10^9/L did not show a significant difference in a new, or extension of an, ICH compared with the untransfused control group. Infants in the control group received a transfusion when their platelet counts were less than 50×10^9/L or the infant was bleeding. However, the study group did show an overall reduction in the use of plasma and RBCs compared with the controls. This study would suggest that prophylactic transfusion at a higher trigger value does not impact clinical outcome for risk of ICH.

More recent guidelines for platelet transfusion recommended a lower trigger value of less than 20×10^9/L or 30×10^9/L for platelet transfusions in term infants.[7,8] The rationale for the lower trigger value is that most serious bleeding caused by thrombocytopenia occurs in the first days of life. Therefore, patients severely thrombocytopenic from sepsis or necrotizing enterocolitis beyond the first few days of life rarely have major hemorrhage. Other recommendations given are a higher trigger level of less than 50×10^9/L for patients who are at highest risk for hemorrhage caused by clinical instability or very low birth weight (less than 1000 g). Lastly, a trigger value of less than 50×10^9/L would be indicated for neonates with major bleeding from a pulmonary, gastrointestinal, or renal source. In reviewing studies of contemporary platelet transfusion practice in neonates, Murray and Roberts[9] noted that there were a variety of platelet triggers used in different neonatal intensive care units and that thrombocytopenic neonates were 10 times more likely to die than neonates who did not receive transfusions. Del Vecchio et al.[10] also concluded that neonates who receive more than four platelet transfusions had a risk of death 29.9 times that of neonates who did not receive a transfusion. This is most likely attributable to the underlying disease and severity of the clinical condition resulting in the thrombocytopenia. The lack of definitive criteria for prophylactic platelet transfusions in this population caused the authors to conclude that alternative treatments for thrombocytopenia are needed. These treatments may include hemopoietic growth factors. Clinical trials are needed to investigate the use of recombinant thrombopoietin to increase platelet production in thrombocytopenic neonates.

Selection of Platelet Components

Platelet components may be platelet pheresis (single-donor platelets or apheresis platelets) or platelets (whole blood–derived platelets). Both platelet components are currently stored for 5 days, but they differ with respect to their platelet counts and risk for adverse effects. Apheresis platelets are prepared using an automated collection device from a single donor and collected in volumes of 200 to 400 mL, which includes platelets, donor plasma, anticoagulants, leukocytes, and a few RBCs. Apheresis platelets that are leukocyte reduced should contain less than 5×10^6 WBCs and greater than 3×10^{11} platelets. In contrast, whole blood–derived platelets are prepared from centrifuged whole blood to a final concentrated volume of about 50 mL. Whole blood–derived platelets also contain donor plasma, anticoagulant, leukocytes, and RBCs. Whole blood–derived platelets that are leukocyte reduced have less than 5×10^6 WBCs and greater than 5.5×10^{10} platelets.[11,12]

The standard dose for neonates is based on body weight and is the same for either apheresis platelets or whole blood–derived platelets at 5 to 10 mL/kg for an increase of 50,000/ L in the platelet count. Some centers calculate doses based on random donor units or their equivalents.[13] In some institutions, dose is based on the platelet count from the component, and the aliquot given to the neonate is adjusted accordingly. If apheresis platelets are used for platelet transfusions, the platelets may be separated into smaller aliquots to decrease donor exposures and platelet wastage. The aliquot or platelet syringe is considered an open system, and the platelets will expire within 4 hours. As long as the separation into a syringe is done with a sterile connecting device, the expiration time of the "mother unit" should not change.[11,12] However, the viability of the platelets may be affected by altering the volume within the storage bag. Transfusion services preparing aliquots from apheresis platelets should be aware of the manufacturer requirements for platelet storage. This practice of providing platelet aliquots from apheresis platelets is controversial because of the accuracy of the platelet component in volume only and not in final platelet concentration.

Both platelets and apheresis platelets require the same storage conditions, but the testing for bacterial contamination remains disparate between the two components. Platelet pheresis components routinely undergo sampling for bacterial contamination via culture methods. In the case of whole blood–derived platelets, bacterial testing is often done by pH testing or other methods less sensitive than those used for apheresis platelets. In the future, changes in standard pooling practices for whole blood–derived platelets and improved testing methods may provide the most sensitive and specific bacterial testing for both platelet components.

Risk of Platelet Transfusion in the Neonate and Infant

The infectious risk for each component may be perceived as different for neonatal transfusions because of the ability to transfuse many more aliquots from apheresis platelets compared with whole blood–derived platelets. This provides a mechanism for donor limitation with regard to platelet transfusion and therefore exposes the neonatal patient to less infectious risk. Strict adherence to sterile technique for the aliquot preparation is necessary to avoid bacterial contamination during the aliquot manufacturing process.

In addition to infectious risk, the neonate is exposed to other risks of transfusion with the use of either whole blood–derived platelets or apheresis platelets. Hemolytic risks from ABO-incompatible plasma may be significant in the neonate owing to small blood volumes, although a precise risk estimate for neonates is not available. Accrediting agencies such as the College of American Pathologists and AABB require protocols to ensure safety of ABO-incompatible transfusions.[11,14] If possible, infants should receive only platelets that are ABO-group specific or compatible with the infant's plasma. When ABO-group specific or compatible platelets are not available, the institution may elect to modify the component to remove plasma and reduce the risk for hemolysis. These modifications include saline replacement, volume reduction, and washing.[12] Depending on the institution, all or some of these modifications may be available. With each modification, less platelets are recovered and some will become activated, which can adversely affect the efficacy of the transfusion. Until the platelet supply is sufficient for demand, these modifications are necessary for platelet transfusion support in the neonate.

Neonates may require additional special components as a result of the underlying disease causing the thrombocytopenia. Neonates with neonatal alloimmune thrombocytopenia will require special platelets that lack the platelet-specific antigen implicated in the disease. These antigen-negative platelets may be available from a maternal source or another allogeneic donor. It is also conceivable that maternal HLA antibodies passively acquired in the neonate may impact response to platelet transfusions. Transfusion-transmitted CMV is of concern in the premature neonate because of the risk of serious CMV disease in premature infants. Components with reduced risk for CMV transmission are either negative when tested for CMV antibodies or leukocyte reduced. Patients at risk for severe CMV infection include those with congenital immunodeficiency disorders or AIDS, hematopoietic progenitor cell transplant recipients, organ allograft transplant recipients, premature infants during infancy, cancer patients undergoing intense chemotherapy, and recipients of intrauterine transfusion.[5] Irradiation of platelet components to prevent transfusion-associated GVHD is also indicated for premature infants. The requirement for CMV-negative and irradiated platelets in the term neonate is more controversial.

Protocols for Neonatal and Infant Platelet Transfusion at The Children's Hospital of Philadelphia

At The Children's Hospital of Philadelphia (CHOP), we support a very large infant intensive care unit with 60 NICU and 15 cardiac intensive care unit (CICU) beds. Our NICU and CICU neonates and infants receive irradiated, "CMV-safe" leukocyte-reduced apheresis platelets when a transfusion is required. ABO and D type-specific or compatible apheresis platelet aliquots are selected. If ABO group-specific or compatible is not available, saline replacement is performed to remove ABO-incompatible plasma. Saline suspension requires centrifugation to remove plasma followed by the sterile addition of 0.9% normal saline, usually back to the starting volume. These components are placed back on the rotator for approximately 1 hour to ensure proper mixing. Aliquots are manufactured in the blood bank with the use of a sterile connecting device. The syringe aliquots expire within 4 hours as an open system, and the remaining platelets are stored in the original container with no change in expiration time. During blood shortages, whole blood–derived platelets are used for transfusion. Our present policy calls for irradiation

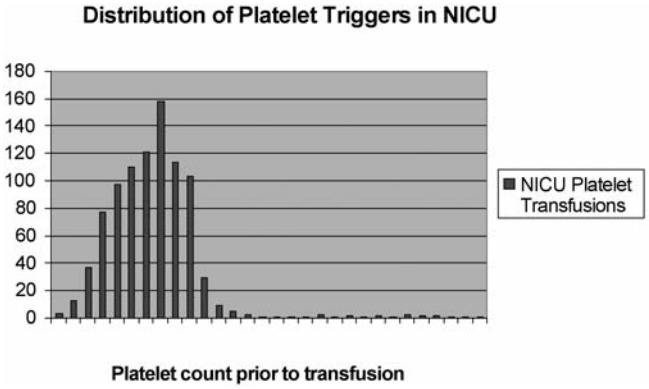

Fig. 1. Frequency distribution of 909 pretransfusion platelet counts in infants who received platelet transfusions while admitted to The Children's Hospital of Philadelphia NICU between July 1, 2006, and June 30, 2007.

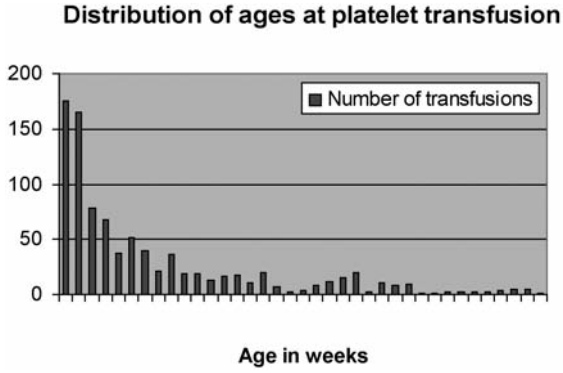

Fig. 2. Frequency distribution of patient ages at the time of platelet transfusion (N = 909) in infants who received platelet transfusions while admitted to The Children's Hospital of Philadelphia NICU between July 1, 2006, and June 30, 2007.

of all platelet products in inventory, but it excludes irradiation of RBC components for term neonates in surgery unless there is a specific medical indication for irradiation.

CHOP provides D type–specific or compatible platelets and would recommend RhIG administration in the event a female neonate with D– RBCs received D+ components. Our policy reinforces concerns raised with the reported case from Brigham and Women's Hospital where an infant, at 17 weeks of age, developed anti-D from a platelet transfusion. This case report suggests that only a small amount of D+ RBCs may cause antibody formation in an infant just beyond 4 months of age.[15] Further data need to be collected to determine the sensitization risk of D+ platelet transfusion in D– infants around 4 months of age.

At CHOP, we have surveyed our institutional platelet triggers in the NICU, and our data are similar to those published by Del Vecchio et al.,[10] who noted a range of platelet transfusion triggers. Figure 1 displays the platelet count that immediately preceded the transfusion in 909 platelet transfusion events in our NICU. A trigger platelet count value of less than 100×10^9/L would account for about 90 percent of the platelet transfusions administered in the CHOP NICU. However, according to published guidelines, a more stringent trigger value of less than 50×10^9/L may have been considered in some of these patients. Figure 2 shows that the majority of platelet transfusions in neonates occurred in the first week of life. It appears that the majority of the platelet transfusions were given in accordance with published guidelines. As we begin to look at our institutional data and outcomes, we may better understand the risks and outcomes of our NICU trigger values, and our guidelines may change accordingly.

Neonates and infants on extracorporeal membrane oxygenation (ECMO) are at considerable risk for thrombocytopenia. Platelets are given at startup and at circuit change to avoid the thrombocytopenia generally associated with the procedure as a result of platelets binding to the tubing or activated within the ECMO circuit. Additional dilutional effects from the massive transfusion of RBCs and plasma also factor into the risk for thrombocytopenia. Approximately 10 to 35 percent of neonates receiving ECMO will have a hemorrhagic event.[16] Patient platelet counts need to be closely monitored during ECMO. Adjustments are required to allow a higher transfusion of platelet dose based on weight. At CHOP, ECMO infants and neonates are transfused platelets to a maximum volume of 40 mL/kg.

Conclusions

Neonatal and infant platelet transfusions are given in a prophylactic or therapeutic setting to thrombocytopenic neonates and infants, either to reduce the risk of bleeding or for active bleeding. Because thrombocytopenia in a neonate can be caused by a variety of factors, it is important for the hospital to develop indications, guidelines, and thresholds for platelet transfusions. Neonates and infants receiving transfusions are at additional risk for other adverse reactions to blood products, including infection, immunologic effects, transfusion-related acute lung injury, and fluid overload, among others. Institutional protocols should define the need for irradiation and CMV-negative components in infants, neonates, and premature neonates. Standardization of practice, when possible, allows for better process control and patient management.

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REVIEW

Neonatal plasma transfusions

P.T. PISCIOTTO

Sick neonates are among the more heavily transfused groups of patients in the hospital setting.[1] Transfusion therapy for neonates began early in the 20th century. One of the first controlled trials compared the use of intravenous versus intramuscular administration of whole blood in infants with hemorrhagic disease of the newborn (vitamin K deficiency bleeding).[2] The use of plasma components in neonates for hemostatic abnormalities coincided with the availability of these blood components for all patients in the 1950s. In general, plasma transfusions are administered less frequently to neonates than RBC transfusions.[3,4] Inasmuch as the physiologic state of the hemostatic system in newborns is different compared with that in older children and adults, it is important to have a good understanding of the developmentally unique aspect of this system to appreciate the therapeutic goals of plasma replacement therapy.[5] Although there are guidelines for neonatal transfusion as well as recommendations to assess transfusion criteria, most of these are derived from consensus opinion because there are limited evidence-based data from controlled clinical trials.[6,7]

Developmental Hemostasis

Normal hemostasis is the physiologic mechanism by which the body controls bleeding and prevents thrombotic events. This results from a dynamic balance between the formation of thrombin, fibrin deposition, thrombin inhibition, and fibrinolysis. The process can be viewed in three overlapping stages, starting with the formation of a platelet plug, which involves the endothelial layer of the vessel wall and platelets, followed by the interaction of platelets and plasma procoagulant proteins (coagulation factors) to form a stable fibrin clot limited to the area of vascular injury (by action of anticoagulant proteins). The final stage results in the breakdown of the fibrin clot and repair of the vascular damage (fibrinolytic system).

Plasma coagulation proteins do not cross the placenta. Synthesis of these proteins begins in the first trimester of pregnancy. Although the basic coagulation, anticoagulation, and fibrinolytic pathways are the same in neonates as in older children and adults, the concentration of many of the coagulation proteins varies greatly. Concentrations are selectively and significantly different and dependent on both the gestational and postnatal age of the infant.[5] Several factors, including fibrinogen; factors VIII, V, and XIII; and von Willebrand factor, achieve adult levels at birth, but most other hemostatic proteins are decreased. The altered state is the result of multiple mechanisms including decreased production as a result of the immature nature of the neonatal liver, increased clearance of the proteins, consumption at the time of birth, and synthesis of proteins that have decreased functional activity.[5] In full-term infants these factors are approximately 50 percent of adult levels and even lower in healthy premature infants.[8,9] As a result of the decreased production of these factors, the generation of thrombin, which is the key enzyme in the formation of fibrin, may be decreased or delayed.[10] Despite these findings, healthy infants are hemostatically stable. The standard laboratory tests of coagulation function, however—the prothrombin time and activated partial thromboplastin time—are greater than the adult reference ranges, reflecting the reduction of these multiple procoagulant proteins. Therefore, it is important to refer to established reference ranges for age when evaluating hemostatic integrity and potential need for transfusion in the neonate. The newborn hemostatic system matures rapidly, with variables reaching adult levels usually by 6 months. This process is accelerated in premature infants, who show similar levels of coagulation proteins to term infants by 6 months after birth. As this is a dynamic maturing system multiple reference ranges, reflecting the gestational and postnatal age of the infant, are necessary. The ranges published by Andrew et al.[5] are the most comprehensive and often are used as guidelines.[11] It is important to remember, however, that these ranges were established using different reagents and assay systems for measuring coagulation function than are available today.

The plasma concentration of the anticoagulants, which include anti-thrombin III; heparin cofactor II; and the vitamin K–dependent factors, protein C and protein S, are also decreased. This appears to be compensated in part by the enhanced thrombin inhibition via the increased levels of α_2-macroglobulin (α_2-M). In terms of the fibrinolytic system in the newborn there is a decrease in the concentration of plasminogen and therefore the generation of plasmin, which is the key enzyme responsible for breakdown of fibrin.[5] Despite these developmental differences, the hemostatic system in the healthy infant is largely physiologic, providing protection from both bleeding and thrombosis because the balance between procoagulants, anticoagulants, and the fibrinolytic system is maintained. The concern, however, is that there is very little reserve capacity and any additional pathologic insult, such as birth asphyxia, which is associated with disseminated intravascular coagulation (DIC) in the neonate, may contribute to morbidity in the sick and premature infant.

Bleeding in the Neonatal Period

Bleeding complications from coagulation abnormalities in the newborn are usually the result of an acquired defect in hemostasis, although congenital disorders may be present, particularly in association with an iatrogenic challenge.[11] The clinical presentation of bleeding in the neonate may present at various sites, and the consequences are different compared with those of older children and adults. Oozing from the umbilicus or peripheral blood sampling sites, bleeding into the scalp resulting in large cephalohematomas, or bleeding from circumcision are some of the typical ways bleeding may present in the neonate. Often, however, the first sign is an intracranial hemorrhage (ICH), and even a minor bleed can result in shock.

Disseminated Intravascular Coagulation

The incidence of DIC is high in the neonate, particularly the premature infant. DIC is an acquired coagulation disorder in which both the coagulation and fibrinolytic systems are activated, resulting in the formation of microthrombi and a bleeding tendency owing to the consumption of certain coagulation factors. This occurs as a secondary event to another disease entity. In the neonate this can include many conditions such as sepsis, birth asphyxia, acidosis, respiratory distress syndrome (RDS), necrotizing enterocolitis, infection, and shock.[12] Because these infants are already starting with lower levels of procoagulant proteins, the increased consumption of these proteins, in conjunction with consumption of platelets, can result in a profound coagulopathy early in the disease process. The clinical spectrum of DIC in the neonate can range from an asymptomatic low-grade compensated DIC to fulminant DIC characterized by bleeding requiring replacement therapy. Although there are no randomized studies looking at the efficacy of replacement therapy for bleeding associated with DIC, its use in this clinical situation is generally recommended in guideline documents.[6,7,11] The latter may necessitate not only replacement of procoagulant proteins and naturally occurring inhibitors with plasma transfusion but also platelet transfusions. Cryoprecipitate, which contains a higher concentration of factor VIII and fibrinogen per unit volume of FFP, may be particularly useful in the presence of hypofibrinogenemia. There has been some evidence of beneficial effects with the use of antithrombin and protein C concentrates in adults with DIC associated with multiorgan failure.[13] There has been limited clinical experience with their use in neonates, and therefore further clinical trials would be warranted for definitive recommendation regarding their use as treatment. It is important to remember, however, that if the underlying condition is not corrected the hemostatic improvement will only be temporary. Therefore one of the most important aspects of managing DIC is taking aggressive measures to reverse the underlying disease process.

Vitamin K Deficiency

Hemorrhagic disease of the newborn was described in 1894,[14] but was not linked to vitamin K deficiency until the mid-1900s. The vitamin K–dependent factors as mentioned previously are physiologically low at birth and functionally inactive in the presence of vitamin K deficiency. Vitamin K is required for modifying the coagulation proteins II, VII, IX, and X and the anticoagulant proteins C and S. Placental transfer of the vitamin is poor, and neonates have limited stores of vitamin K at birth. Because intestinal bacteria produce vitamin K_2, a contributing factor for decreased vitamin K in neonates may be the presence of a sterile gut in the first few days of life. This can be further aggravated in infants who are breast-fed, because vitamin K content is also limited in breast milk. In most countries prophylactic vitamin K_1 (phytonadione, which is present in green leafy vegetables) is given after birth to reduce the risk of hemorrhagic disease. There are actually three classifications of hemorrhagic disease of the newborn,

which are based on the clinical presentation and risk factors.[15] Early hemorrhagic disease is the rarest, with the onset of bleeding occurring within the first 24 hours. Bleeding is variable, but can be serious, including ICH. Early onset is usually associated with medications, such as anticonvulsants, taken during pregnancy that can cross the placenta and interfere with vitamin K metabolism.[16] In an attempt to reduce early hemorrhagic disease, strategies for the prophylactic use of antenatal vitamin K have been suggested.[17] Classic hemorrhagic disease of the newborn presents between 2 and 5 days of life with purpura, mucosal membrane bleeding, bleeding from the umbilicus, or gastrointestinal bleeding in an infant who otherwise appears well. Presentation with ICH appears to be relatively less common. The classic form of hemorrhagic disease is usually associated with infants who are being breast-fed, but may also occur if there are feeding problems. A late form of hemorrhagic disease may also occur in the newborn, in which the onset of bleeding occurs after the first week of life, peaking between 2 and 8 weeks of life. Although breast-feeding and inadequate prophylaxis with vitamin K are frequently documented, there are a variety of diseases that can compromise the supply of vitamin K that must be considered. Unlike those with classic hemorrhagic disease of the newborn, these infants often present with ICH, which can be associated with significant morbidity (neurologic) and mortality. The treatment of vitamin K deficiency will be dictated by the clinical situation. The vitamin K–dependent proteins increase within a few hours after the administration of a parenteral dose of vitamin K. In the presence of significant bleeding that may be life threatening, plasma in addition to vitamin K can be given to correct the hemostatic defect.[6,7,11]

Liver Disease

Although some degree of hepatic impairment is not uncommon in the neonatal period and may occur in conjunction with sepsis, hypoxia, and total parenteral nutrition, fulminant hepatic failure is an uncommon event. Viral infections, metabolic disorders, storage disorder, and shock are some recognized causes of neonatal hepatic failure.[18] The coagulopathy of liver failure is the result of several processes, but reduced synthesis of procoagulant proteins plays an important role in a setting in which there already are physiologically reduced levels of many coagulation proteins. Other contributing factors are decreased clearance of activated coagulation factors by the liver, activation of fibrinolysis, impaired utilization of vitamin K, and thrombocytopenia. In the presence of clinical bleeding some temporary benefit may be achieved by the replacement of coagulation proteins with plasma and cryoprecipitate. Management of the coagulopathy, however, would essentially be supportive until recovery of hepatic function could be achieved. If there is evidence of cholestasis, the administration of vitamin K supplements may be helpful.

Coagulopathy Associated With Cardiopulmonary Bypass and Extracorporeal Membrane Oxygenation

A substantial coagulopathy occurs during cardiopulmonary bypass (CPB), which is the result of several different contributing factors. Neonates are at higher risk for increased bleeding, related in part to the immature nature of their coagulation system. In addition the often complex repairs that are needed can require longer CPB time or deeper hypothermia.[19–22] Hypothermia (a means of cerebral protection), which is often induced during CPB, can alter hemostasis by negatively affecting platelet function as well as inhibiting serine protease activity. During CPB a hemodilution occurs, which is more pronounced in the neonate than in larger pediatric and adult patients. This is the result of the small intravascular volume of the neonate relative to the volume of the bypass circuit. After the onset of CPB mean plasma concentrations of procoagulant proteins and inhibitors are reduced by approximately 50 percent of pre-CPB values.[19] There is a similar reduction in the fibrinolytic proteins. All of these changes have a significant effect on the generation of thrombin. In addition to the hemodilution, and despite systemic heparinization, there is evidence that both the coagulation and fibrinolytic systems are activated by the CPB circuit, which may result in a low-grade consumptive coagulopathy. A dilutional thrombocytopenia also occurs, and platelet function is impaired. Various strategies have been used to decrease the morbidity of CPB and transfusion requirements. Some of these have included minimizing the amount of exposure to the CPB circuit by keeping the duration of CPB as short as possible and miniaturizing the circuit to limit the artificial surface area to which the blood is exposed.[21,22] This miniaturization also results in smaller priming volumes and less hemodilution. The use of ultrafiltration during or immediately after CPB to remove excess fluid has helped to maintain the patient's hemoglobin through hemoconcentration, attenuate the dilutional coagulopathy, and

reduce postoperative bleeding.[22,23] The use of aprotinin, which is a serine protease inhibitor used to prevent fibrinolysis as well as contact activation, has not shown consistent results in the pediatric setting and warrants further investigation as to its risk-benefit ratio.[21] A recent prospective randomized controlled trial in 200 infants less than 1 year of age compared the use of fresh whole blood (less than 48 hours) with reconstituted blood consisting of one unit of RBCs in additive solution and one unit of thawed FFP for priming the bypass circuit and for adding to the bypass circuit when the patients were rewarmed at the end of surgery.[24] Fresh whole blood did not confer a clinical or biochemical advantage over reconstituted blood. However, an increased length of stay in the intensive care unit and increased perioperative fluid overload were associated with priming the circuit with fresh whole blood.

Extracorporeal membrane oxygenation (ECMO) is a modified heart-lung machine, which provides gas exchange to support patients who have severe but potentially reversible respiratory or cardiac failure. Some of the differences from patients requiring CPB are that these patients are maintained at normal body temperature, undergo extrathoracic cannulation from relatively accessible vessels, and because there is no large venous reservoir in the circuit, require only partial anticoagulation with heparin.[25] The time course for ECMO support, however, can be days to weeks. As with CPB, coagulation complications of ECMO can be significant as the patient is heparinized, and the associated activation and consumption of procoagulant factors and platelets related to the exposure of blood to artificial surfaces is also present. If ECMO is initiated after open heart surgery, the coagulation effects are additive. The number of transfusions required varies considerably based on individual patient characteristics as well as variation related to the institutional protocol and ECMO technique. There have been no clinical trials looking at the influence of transfusion protocols on clinical outcome. Approximately 15 percent of neonates on ECMO sustain an ICH.[25]

Intracranial Hemorrhage

The commonest form of ICH in the premature infant is a periventricular-intraventricular hemorrhage (IVH). The incidence is around 15 to 20 percent for infants less than 32 weeks' gestation.[26] The majority occur within the first 72 hours of life. Although low birth weight and increasing prematurity are associated with IVH, additional risk factors are RDS, intrapartum asphyxia, and vaginal delivery. The etiology is incompletely understood. Some of the factors believed to contribute to IVH include alterations in cerebral blood flow, fragility of the immature germinal matrix vessels, and hypoxia-induced endothelial damage. These appear to be more significant than impaired hemostasis. A randomized control trial of prophylactic FFP carried out in the 1980s did show a reduced risk of IVH documented by cranial ultrasound.[27] However, there was no substantial change in the coagulation profile after the administration of FFP, which suggested that the benefit seen might have been secondary to circulatory stabilization after volume expansion. A subsequent large prospective randomized control study undertaken by the Northern Neonatal Nursing Initiative Trial Group, comparing the infusion of FFP, gelatin, or glucose in 776 preterm infants less than 32 weeks' gestation within 2 hours of birth, showed no evidence that any of the interventions had any effect on death or disability, followed out 2 years.[28,29] Current evidence therefore does not support the routine use of prophylactic FFP in preterm infants at risk for IVH.[7]

Indications and Contraindications

FFP has been transfused to neonates for a variety of reasons that may not have had any proven benefit. National surveys of transfusion practice have shown that although neonates receive relatively few FFP transfusions as compared with RBC transfusions, a percentage of hospitals responded that some of the frequent uses of FFP were either to treat hypovolemia, as fluid replacement during partial exchange transfusion, or as adjuvant therapy for sepsis.[3,4] Hypovolemia as the most frequent indication for transfusion of plasma was reported by 11 percent of respondents in one survey and 41 percent in another. These surveys reflect practice in the late 1980s and early 1990s. There have been no recent surveys to determine whether there has been a shift in transfusion practice. A more recent report of transfusion practice in a single institution showed that a significant shift toward appropriate use of plasma occurred only after implementation of a computer-based audit system that included an educational component as follow-up.[30] Before the initiation of the audit system approximately 8 percent of the plasma transfusions administered to neonates would have been classified as not being appropriate because there was no evidence of a coagulopathy. This was reduced to approximately 1 percent after an educational effort.

The underlying principle that should govern the appropriateness of plasma transfusion in the neonate is

the same as that in older patients: plasma transfusion should be given for the treatment of clinically significant bleeding, or to prevent bleeding before an invasive procedure, when there is a decrease in one or more coagulation factors, and a safer more appropriate alternative to treatment does not exist.[6,7] Some of the difficulty in the neonate is trying to determine what role an immature hemostatic system plays in the etiology of a bleed. This is the case with IVH in which randomized clinical trials have been helpful.

Plasma Components

There are several plasma components available that are used for coagulation factor replacement. Plasma from whole blood collected in either CPDA-1, CPD, or CP2D that is separated by centrifugation and frozen within 8 hours is labeled as FFP and if frozen within 24 hours as "Plasma Frozen Within 24 Hours After Phlebotomy" (FP24). Frozen plasma is thawed usually in a water bath and should be either transfused immediately or stored at 1 to 6°C for up to 24 hours. If these frozen products are thawed and not used within 24 hours they are relabeled as "Thawed Plasma" and need to be transfused within 5 days. The processing of FP24 may result in slightly lower concentration of factors V and VIII. However, based on in vitro data of the functional activity of these factors, they still are within the normal reference ranges, supporting the use of these products for the accepted indications for plasma transfusion.[31–33] The concentrations of coagulation factors in thawed plasma from FFP which is stored at 1 to 6°C until expiration (day 5) are stable with the exception of factor VIII activity, which is reduced by 35 to 41 percent.[34] FFP can also be collected by apheresis technology. In this case the anticoagulant is either ACD or sodium citrate, and the plasma is frozen within 6 to 8 hours.

Dose and Administration

No specific compatibility testing is required before transfusion of frozen plasma components. However, because plasma contains isohemagglutinins, the component must be ABO compatible with the recipient's RBCs. Hemolytic reactions attributable to incompatible plasma transfusions have been reported in the neonate.[35] If the recipient's ABO type is not available, then group AB plasma can be administered. Because Rh-alloimmunization rarely occurs as a result of Rh(D) mismatch of frozen plasma components, Rh(D) compatibility is not essential. After the frozen plasma is thawed, aliquots can be prepared using a sterile connecting device and transfer bags if multiple doses are needed.

A guide for replacement therapy is to achieve a "minimal hemostatic level" based on gestational and postnatal age of the infant.[36] There have been no studies looking at the recovery of coagulation factors or clearance time after FFP administration in a sick neonate. A common dosing regimen has been 10 to 20 mL/kg. This theoretically should result in a rise in coagulation factors of approximately 20 percent immediately after infusion. The dose and frequency, however, will depend on the clinical situation and plasma concentration that is being targeted. Posttransfusion monitoring of the coagulation status is important to determine optimal therapy.

Summary

Although there has been an overall trend toward reduction of transfusions in neonates, limited data from randomized clinical trials to guide practice exist. The neonatal hemostatic system is immature at birth, placing sick premature infants, who may have minimal reserve capacity, at potential increased risk for bleeding complications. In general, there is agreement that plasma should be transfused to correct deficiencies in the face of bleeding. What is needed, however, is a better understanding of when these deficiencies do or do not affect bleeding risk and outcome to further provide more evidence-based approaches to transfusion practice.

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Letter to the Editors

Prevalence of Yt(a–) in Hispanic blood donors

The Yt blood group system consists of a high-prevalence antigen (Yt^a) and a low-prevalence antigen (Yt^b), which give rise to three phenotypes: Yt(a+b–), Yt(a+b+), and Yt(a–b+).[1] The Yt(a–) phenotype is more prevalent in Israeli Jews (1 in 69), Arabs (1 in 45), and Druse (1 in 40)[2] than it is in Northern Europeans, Canadians, and African Americans (1 in 500), or in Japanese (none in 5000).[3] This phenotype has not been found in testing cohorts of Japanese, Inuits, Thais, and Native Americans.[3] The Yt^a antigen is quite immunogenic, and anti-Yt^a is not infrequently made by Yt(a–) persons exposed to Yt(a+) RBCs. Sometimes, but not always, anti-Yt^a causes reduced in vivo survival of transfused Yt(a+) RBCs. For this reason, physicians often request Yt(a–) blood components for transfusion to their patients with anti-Yt^a.[3] In spite of our ongoing testing of African American and Caucasian donors with anti-Yt^a, in our region there is still a relative shortage of Yt(a–) blood donors. Thus, we extended our testing to include Hispanic donors, and the results are presented here.

RBCs from blood donors who self-identified as being African American, Caucasian, or Hispanic were screened with anti-Yt^a in IgG gel cards (Micro Typing Systems, Inc., Ortho-Clinical Diagnostics, Raritan, NJ). Nonreactive RBCs were retested by the same technologist using the same anti-Yt^a but by IAT in test tubes. Repeat nonreactive samples were then tested by a second technologist using a different source of anti-Yt^a by the IAT in test tubes. The results of our testing are shown in Table 1.

The prevalence of Yt(a–) in Hispanic donors was similar to that in Caucasian donors. The prevalence in Caucasians was similar to published figures. Hispanics are, therefore, a valuable ethnicity to screen for this rare phenotype. We identified nearly three times as many Yt(a–) donors in the Hispanic and Caucasian donors as in African American donors. The number of Yt(a–) African American donors we found was about a quarter of that expected from reports in the literature.

Table 1. Results of screening donors with anti-Yt^a

Donors	Number tested	Number Yt(a–)	Prevalence
Hispanic	9933	13	1 in 764 (0.13%)
Caucasian	2077	3	1 in 692 (0.14%)
African American	10,622	5	1 in 2124 (0.05%)

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References

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2. Levene C, Bar-Shany S, Manny N, et al. The Yt blood groups in Israeli Jews, Arabs, and Druse. Transfusion 1987;27:471–4.
3. Issitt PD, Anstee DJ. Applied blood group serology, 4th ed. Durham, NC: Montgomery Scientific Publications, 1998.

ERRATUM

Vol. 23, No. 1, 2007; page 39

Differences in ABO antibody levels among blood donors: a comparison between past and present Japanese, Laotian, and Thai populations.

The author has informed the editors of *Immunohematology* that there is an error on page 39, Table 2. The column headings for Anti-A titer should read as such:

Table 2. Distribution of anti-A and anti-B IgG titers in three populations

Anti-A titer	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**1024**	**2048**	**4096**	**Total (n)**
Laos 2001*	–	–	–	–	–	13	15	**16**	6	2	52
Thailand 2005*	1	8	8	9	**23**	15	5	3	3	–	75
Japan 1986*	–	–	–	1	3	**39**	21	20	2	–	86
Japan 2001*	–	2	16	**51**	8	1	1	–	–	–	79
Japan 2005*	2	22	**24**	21	6	–	–	–	–	–	75
Japan (group O)											
16–29 male	2	14	**33**	28	14	11	–	–	–	–	102
16–29 female	2	22	23	**34**	9	11	1	–	–	–	102
51–69 male	–	6	18	**35**	32	3	–	–	–	–	94
51–69 female	–	2	**18**	14	4	6	2	3	–	–	49
Anti-B titer	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**1024**	**2048**	**4096**	**Total (n)**
Laos 2001*	–	–	–	–	–	1	**23**	11	3	2	40
Thailand 2005*	1	1	1	7	12	**19**	15	5	1	–	62
Japan 1986*	–	–	–	–	1	2	28	**32**	22	3	88
Japan 2001*	–	11	**69**	9	2	2	–	–	–	–	93
Japan 2005*	–	17	**20**	16	8	1	–	–	–	–	62
Japan (group O)											
16–29 male	3	28	**37**	27	5	2	–	–	–	–	102
16–29 female	1	26	**39**	17	6	4	4	5	–	–	102
51–69 male	2	15	**40**	29	8	–	–	–	–	–	94
51–69 female	–	4	**15**	4	3	5	10	8	–	–	49

* Data include group O and nongroup O donors

ANNOUNCEMENTS

Monoclonal antibodies available at no charge:

The New York Blood Center has developed a wide range of monoclonal antibodies (both murine and humanized) that are useful for donor screening and for typing RBCs with a positive DAT. These include anti-A1, -M, -s, -U, -D, -Rh17, -K, -k, -Kp^a, -Js^b, -Fy^a, -Fy3, -Fy6, -Wr^b, -Xg^a, -CD99, -Do^b, -H, -Ge2, -Ge3, -CD55 (both SCR2/3 and SCR4), -Ok^a, -I, and anti-CD59. Most of the antibodies are murine IgG and require the use of anti-mouse IgG for detection (Anti-K, -k, and -Kp^a). Some are directly agglutinating (Anti-A1, -M, -Wr^b and -Rh17) and a few have been humanized into the IgM isoform (Anti-Js^b). The antibodies are available at no charge to anyone who requests them. Please visit our Web site for a complete list of available monoclonal antibodies and the procedure for obtaining them.

For additional information, contact: Gregory Halverson, New York Blood Center, 310 East 67th Street, New York, NY 10021 / e-mail: ghalverson@nybloodcenter.org (phone 212-570-3026, FAX: 212-737-4935) or visit the Web site at http://www.nybloodcenter.org >research >immunochemistry >current list of monoclonal antibodies available.

Specialist in Blood Bank (SBB) Program

The Department of Transfusion Medicine, National Institutes of Health, is accepting applications for its 1-year Specialist in Blood Bank Technology Program. Students are federal employees who work 32 hours/week. This program introduces students to all areas of transfusion medicine including reference serology, cell processing, HLA, and infectious disease testing. Students also design and conduct a research project. NIH is an Equal Opportunity Organization. Application deadline is December 31, 2008 for the July 2009 class. See www.cc.nih.gov/dtm > education for brochure and application. For further information contact Karen M. Byrne at (301) 451-8645 or KByrne@mail.cc.nih.gov

Meetings!

April 11–13 American Red Cross Immunohematology Reference Laboratory (IRL) Conference 2008

The American Red Cross Immunohematology Reference Laboratory (IRL) Conference 2008 will be held April 11 through 13, 2008, at the Chaparral Suites Resort, in Scottsdale, Arizona. For more information, **contact** Cindy Flickinger at (215) 451-4909 or flickingerc@usa.redcross.org.

May 8–9 Heart of America Association of Blood Banks (HAABB)

The spring meeting of the Heart of America Association of Blood Banks (HAABB) will be held May 8 and 9, 2008, at the Embassy Suites on the Country Club Plaza in Kansas City, Missouri. For more information, refer to the Web site at http://www.haabb.org.

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The course is accredited by The Institute of Biomedical Sciences and directed by Professor David Anstee and Dr Tricia Denning-Kendall.

For further details visit:

http://www.blood.co.uk/ibgrl/MSc/MScHome.htm
or contact:
Dr Tricia Denning-Kendall,
University of Bristol, Geoffrey Tovey Suite,
National Blood Service, Southmead Rd Bristol, BS10 5ND, England.
TEL 0117 9912093, E-MAIL P.A.Denning-Kendall@bristol.ac.uk

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Faculty Position

The Department of Clinical Laboratory Sciences at Virginia Commonwealth University invites applications for a full-time, 12 month, tenure-track faculty position. The Department, located on the MCV Campus of VCU, is one of nine departments in the School of Allied Health Professions. VCU is a large urban, research-extensive institution with a richly diverse university community and commitment to multicultural opportunities. The Department offers both B.S. and M.S. degree programs in Clinical Laboratory Sciences and provides the CLS specialty track in the Ph.D. program in Health Related Sciences.

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Review of applications will begin immediately and continue until the position is filled. Send a letter of interest, curriculum vitae, and the names of three references to:

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Immunohematology

JOURNAL OF BLOOD GROUP SEROLOGY AND EDUCATION

Instructions to the Authors

I. GENERAL INSTRUCTIONS

Before submitting a manuscript, consult current issues of *Immunohematology* for style. Double-space throughout the manuscript. Number the pages consecutively in the upper right-hand corner, beginning with the title page.

II. SCIENTIFIC ARTICLE, REVIEW, OR CASE REPORT WITH LITERATURE REVIEW

A. Each component of the manuscript must start on a new page in the following order:

1. Title page
2. Abstract
3. Text
4. Acknowledgments
5. References
6. Author information
7. Tables
8. Figures

B. Preparation of manuscript

1. Title page
   a. Full title of manuscript with only first letter of first word capitalized (bold title)
   b. Initials and last name of each author (no degrees; all CAPS), e.g., M.T. JONES, J.H. BROWN, AND S.R. SMITH
   c. Running title of ≤40 characters, including spaces
   d. Three to ten key words
2. Abstract
   a. One paragraph, no longer than 300 words
   b. Purpose, methods, findings, and conclusion of study
3. Key words
   a. List under abstract
4. Text (serial pages): *Most manuscripts can usually, but not necessarily, be divided into sections (as described below). Survey results and review papers may need individualized sections*
   a. Introduction
      Purpose and rationale for study, including pertinent background references
   b. Case Report (if indicated by study)
      Clinical and/or hematologic data and background serology/molecular
   c. Materials and Methods
      Selection and number of subjects, samples, items, etc. studied and description of appropriate controls, procedures, methods, equipment, reagents, etc. Equipment and reagents should be identified in parentheses by model or lot and manufacturer's name, city, and state. Do not use patient's names or hospital numbers.
   d. Results
      Presentation of concise and sequential results, referring to pertinent tables and/or figures, if applicable
   e. Discussion
      Implication and limitations of the study, links to other studies; if appropriate, link conclusions to purpose of study as stated in introduction
5. Acknowledgments: *Acknowledge those who have made substantial contributions to the study, including secretarial assistance; list any grants.*
6. References
   a. In text, use superscript, Arabic numbers.
   b. Number references consecutively in the order they occur in the text.
7. Tables
   a. Head each with a brief title; capitalize the first letter of first word (e.g., Table 1. Results of . . .) use no punctuation at the end of the title.
   b. Use short headings for each column needed and capitalize first letter of first word. Omit vertical lines.
   c. Place explanation in footnotes (sequence: *, †, ‡, §, ¶, **, ††).
8. Figures
   a. Figures can be submitted either by e-mail or as photographs (5″ × 7″ glossy).
   b. Place caption for a figure on a separate page (e.g. Fig. 1 Results of…), ending with a period. If figure is submitted as a glossy, place first author's name and figure number on back of each glossy submitted.
   c. When plotting points on a figure, use the following symbols if possible: ○ ● △ ▲ □ ■.
9. Author information
   a. List first name, middle initial, last name, highest degree, position held, institution and department, and **complete** address (including ZIP code) for **all** authors. List country when applicable.

III. EDUCATIONAL FORUM

A. All submitted manuscripts should be approximately 2000 to 2500 words with pertinent references. Submissions may include:

1. An immunohematologic case that illustrates a sound investigative approach with clinical correlation, reflecting appropriate collaboration to sharpen problem solving skills
2. Annotated conference proceedings

B. Preparation of manuscript

1. Title page
   a. Capitalize first word of title.
   b. Initials and last name of each author (no degrees; all CAPs)
2. Text
   a. Case should be written as progressive disclosure and may include the following headings, as appropriate
      i. Clinical Case Presentation: *Clinical information and differential diagnosis*
      ii. Immunohematologic Evaluation and Results: *Serology and molecular testing*
      iii. Interpretation: *Include interpretation of laboratory results, correlating with clinical findings*
      iv. Recommended Therapy: *Include both transfusion and nontransfusion-based therapies*
      v. Discussion: *Brief review of literature with unique features of this case*
      vi. Reference: *Limited to those directly pertinent*
      vii. Author information (see II.B.9.)
      viii. Tables (see II.B.7.)

IV. LETTER TO THE EDITOR

A. Preparation

1. Heading (To the Editor)
2. Title (first word capitalized)
3. Text (written in letter [paragraph] format)
4. Author(s) (type flush right; for first author: name, degree, institution, address [including city, state, Zip code and country]; for other authors: name, degree, institution, city and state)
5. References (limited to ten)
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Send all manuscripts by e-mail to immuno@usa.redcross.org

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Contact the following programs for more information:

Program	Contact Name	Phone Contact	Email Contact	Website	On site or or On line Program
Walter Reed Army Medical Center	William Turcan	202-782-6210	William.Turcan@NA.AMEDD.ARMY.MIL	www.militaryblood.dod.mil	On site
American Red Cross, Southern CA Region	Michael Coover	909-859-7496	CooverM@usa.redcross.org	none	On site
ARC-Central OH Region	Joanne Kosanke	614-253-2740 x2270	kosankej@usa.redcross.org	none	On site
Blood Center of Southeastern Wisconsin	Lynne LeMense	414-937-6403	Lynne.Lemense@bcw.edu	www.bcw.edu	On site
Community Blood Center/CTS Dayton, OH	Nancy Lang	937-461-3293	nlang@cbccts.org	http://www.cbccts.org/education/sbb.htm	On line
Gulf Coast School of Blood Bank Technology	Clare Wong	713-791-6201	cwong@giveblood.org	www.giveblood.org/education/distance/htm	On line
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Medical Center of Louisiana	Karen Kirkley	504-903-3954	kkirkl@lsuhsc.edu	none	On site
NIH Clinical Center Department of Transfusion Medicine	Karen Byrne	301-496-8335	Kbyrne@mail.cc.nih.gov	www.cc.nih.gov/dtm	On site
Rush University	Veronica Lewis	312-942-2402	Veronica_Lewis@rush.edu	www.rushu.rush.edu/health/dept.html	On line
Transfusion Medicine Center at Florida Blood Services	Marjorie Doty	727-568-5433 x 1514	mdoty@fbsblood.org	www.fbsblood.org	On line
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University of Texas Medical Branch at Galveston	Janet Vincent	409-772-3055	jvincent@utmb.edu	www.utmb.edu/sbb	On line
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Additional Information can be found by visiting the following websites: www.ascp.org, www.caahep.org and www.aabb.org

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