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Vox Sanguinis International Forum on Pediatric Indications for Blood Component Transfusion

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Introduction

Blood transfusions have in recent years become increasingly evidence based, at least for adult patients.

Implementing transfusion strategies based on the most recent evidence, and utilizing other principles of Patient

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Blood Management such as using pharmaceuticals to optimize the hemoglobin concentration of pre-operative patients, and to enhance coagulation, are now commonplace in many hospitals worldwide [1-3]. Most of the research on transfusion strategies has been undertaken in adult patients, however several randomized studies during the past decades have also investigated red blood cell (RBC) transfusion thresholds for pediatric patients[4-6], and evidence that a restrictive hemoglobin threshold for RBC transfusion is safe for different groups of pediatric patients is growing [6, 7]. Another reason to employ restrictive RBC transfusion thresholds is that fewer transfusions will necessarily lead to a lower number of adverse reactions, which in children has been shown to be high [8, 9]. Additionally, a recent review concluded that transfusion decisions for pediatric patients should involve consideration of the potential risks, benefits, and strategies that might serve to reduce transfusion requirements[10]. The optimal transfusion strategy for different pediatric patients with different diseases still needs to be confirmed in high-quality studies.

Given the increasing attention being paid to pediatric transfusion issues, the time is now propitious to conduct a Vox Sanguinis International Forum on current pediatric transfusion practice. The main aim of this International Forum was to assess the variability in the current pediatric transfusion practices around the world. The insight gained from this survey can be used as a basis to implement pediatric transfusion guidelines and for benchmarking between comparable hospitals. The participants in the survey were selected from diverse parts of the world in an attempt to reflect a wide variety of practices.

Summary of responses

Hospital and transfusion service demographics:

Sixteen hospitals and one blood center (that responded on behalf of three different hospitals) from fifteen different countries participated in the survey (table 1). Countries from North America, South America, Asia, Australia and Europe were represented. Some of the demographics of the hospitals and transfusion services blood center are listed in table 1. Except for one of the Russian hospitals, all hospitals were academic hospitals and the blood center served academic hospitals. Approximately half of the participants had a hospital based blood collection facility while half of the hospitals received blood from a blood collector that was not located at the hospital. Eight hospitals were pediatric specialty hospitals and nine treated both pediatric and adult patients. Most hospitals defined the neonatal period as being less than 28 days/one month old, while The American and Canadian hospitals defined neonates as less than 4 months old. Pediatrics was defined as below 18 years old in most places, while the Indian and Japanese participants defined pediatric patients as below 13 or 15 years old, respectively. The number of pediatric inpatient beds ranged from 20 to 574 beds. Eleven hospitals provided the fullest range of pediatric specialties including Allergy, Immunology and Rheumatology, Cardiology,

Emergency Medicine, Endocrinology, Gastroenterology, Genetics and Metabolism, General Pediatrics and Adolescent Medicine, Hematology-Oncology, Infectious Diseases, Intensive care (neonatal and/or pediatric), Nephrology, Pulmonology, Surgery of any kind, Trauma care, Otolaryngology, and Palliative Care. Four hospitals provided twelve to fourteen of these specialties, and the *Russian National Centre for Pediatric Hematology, Oncology and Immunology* provided only Hematology-Oncology, Immunology, Genetics, Intensive care and surgery. The number of pediatric RBC transfusions ranged from 12,144 units that were administered at the Indian participant's hospital (286 beds) to 651 units that were administered at one of the Moscow participant's hospital (574 beds). In all but two of the sixteen hospitals that provided the number of pediatric transfusions, most of the components that were transfused were RBCs, followed by platelets, and then plasma units. In the *Children's City Clinical Hospital of St. Vladimir of the Department* in Moscow (this hospital does not provide hematology and oncology services) almost three times as many plasma units compared to RBC units were transfused, and very few platelets were transfused. The *Russian National Centre for Pediatric Hematology, Oncology and Immunology* transfused mainly platelets. Some of these differences are probably explained by the nature of the hospitals since hematology and oncology patients consume more platelets than other pediatric groups[5, 11]. Eight hospitals were able to determine the number of RBCs transfused according to pediatric age categories including < 1 months old, 1-4 months old and older than 4 months (table 2). All of these hospitals transfused most components to patients who were older than 4 months, but there were large differences in the proportion of RBCs transfused to those patients who were < 4 months old. At the Indian hospital almost half of RBCs (3894/8250, 47.2%) were transfused to patients who were less than 4 months old, and one third (2754, 33,4%) were transfused to neonates (defined locally as < one month old), while at the *Russian National Centre for Pediatric Hematology, Oncology and Immunology* only 5 percent (308/5692) of RBCs were transfused to patients who were less than 4 months old. Also plasma and platelet components were primarily transfused to children who were more than 4 months, except in Brazil where 45/86 (52.3%) of the plasma components were transfused to patients who were less than 4 months old.

Transfusion Indications for pediatric and neonatal patients.

- 1) *Does your country have national guidelines or policies specific for neonatal and/or pediatric transfusions? If yes – do they differ from adult guidelines and if so, how do they differ?*

National guidelines or policies specific for neonatal and/or pediatric transfusions existed in nine of the fifteen countries. With the exception of the hospitals in those nine countries, the hospital in Israel had national guidelines for pediatric platelet transfusions and in the hospital in the Czech Republic followed the recommendations in their national guidelines about intrauterine or intrauterine transfusions and doses for children.

- 2) *Does your hospital have local guidelines or policies specific for neonatal and/or pediatric transfusions? If yes – do they differ from adult guidelines and if so, how do they differ?*

Sixteen hospitals have local guidelines or policies specific for neonatal and/or pediatric transfusions. The hospitals in Russia-III, Japan and the Netherlands follow the national guidelines.

- 3) *Does your hospital have a list of indications for ordering RBC/plasma/platelets? If yes – list the indications for these products for both pediatrics and neonates, if applicable*

Fifteen of the nineteen hospitals (including the three hospitals in Singapore) have a list of indications for ordering blood products. The respondents from the Czech Republic, one of the Russian hospitals, Japan and Sweden did not have indications for ordering blood products.

- 4) *Is it mandatory for the person ordering the transfusion to provide the indication for the transfusion at the time that the blood products are ordered? If yes – is the indication entered electronically?*

At thirteen hospitals it is mandatory for the person ordering the transfusion to provide the indication for the transfusion at the time that the blood products are ordered, and in ten of these hospitals it is entered electronically.

- 5) *Is it mandatory for the person ordering the transfusion to provide the patient's diagnosis when blood products are ordered?*

It is mandatory for the person ordering the transfusion to provide the patient's diagnosis at seven hospitals.

- 6) *Does your hospital have thresholds for RBC transfusion? If yes, please list the thresholds for both pediatrics and neonates, if applicable.*

Most hospitals transfuse hemodynamically stable pediatric patients at hemoglobin less than 7 g/dl or 7.5 g/dl. Only the participants at three hospitals (the Netherlands, Israel and Brazil) employed lower thresholds and no hospitals had higher thresholds for this group of patients. In the hospital in the Netherlands a hemoglobin transfusion threshold of 5.6-6.4 g/dl (3.5-4.0 mmol/L) for stable children is used. Thresholds for non-stable patients or patients who are experiencing symptoms from their anemia are in general higher and differ according to indication and diagnosis. For example the hospital in Spain used a threshold of less than 13 g/dl for children with severe pulmonary disease, cyanotic cardiopathy or oxygenation with extracorporeal membrane with descent of oxygen saturation. Hemoglobin thresholds for neonatal patients are in general higher than thresholds for the general pediatric patients, and also differ according to indication and between locations. The hospital in Sweden's thresholds for neonates differs from less than 120 g/dl to 85 g/dl according to patient's age and respiratory status.

- 7) *Does your hospital have thresholds for platelet transfusion? If yes, please list the thresholds for both pediatrics and neonates, if applicable*

A platelet count of less than $10 \times 10^9/L$ is an absolute indication for platelet transfusion for pediatric patients at most of the participating hospitals, while less than $20 \times 10^9/L$ is an absolute indication for most neonates. For patients with other indications for platelet transfusions, for instance sepsis, active bleedings, planned surgery or CNS bleedings, the thresholds were higher. Some examples include the recommendation to transfuse at a threshold of less than $50 \times 10^9/L$ before an invasive procedure at the hospitals in Spain, Brazil, the Netherlands, Italy and Australia, and a threshold of less than $100 \times 10^9/L$ before a neurosurgical procedure are specified at ten of the hospitals.

- 8) *Does your hospital have thresholds for plasma transfusion? If yes, please list the thresholds for both pediatrics and neonates, if applicable*

Plasma transfusions in general seem to be more dependent on the diagnosis than on INR or clotting factor thresholds, although some hospitals, especially the hospitals in Brazil, Italy, India and Singapore do have several coagulation factor based thresholds for plasma transfusions. For example at the hospital in Brazil a fibrinogen level of less than 1g/L before surgery with a significant risk of bleeding is an indication for plasma transfusion, and at the hospital in India plasma transfusion is indicated for critically ill patients with coagulopathy associated with active bleed and International Normalized Ratio (INR) greater than 1.5.

Product manipulations for pediatric and neonatal patients.

- 1) *Does your transfusion department offer irradiated products? If yes, what are the indications for irradiation?*

All of the respondents, except one of the hospitals in Russia (Russia-I), offer irradiated products. At the participating hospitals in USA, Russia-II and Japan all RBCs and platelets are irradiated. The Australian participant uses universal blood product irradiation for patients admitted to specific units (intensive care, neonatal, oncology). All other hospitals offer irradiated products for specific clinical indications, typically intrauterine and exchange transfusions, preterm/neonatal patients, HLA-compatible transfusions, and immune-compromised patients (immune deficiencies, transplantations, medication).

- 2) *Does your transfusion department offer leukodepleted RBCs? If yes, what are the indications for leukodepletion?*

Universal leukodepletion of all blood components is done at all centers except at the participating hospitals in Brazil, Singapore, Israel, and India. At these hospitals leukodepletion is done by clinical indication, especially where CMV negative components are required and for patients who previously experienced a febrile non-hemolytic transfusion reaction.

- 3) *Does your transfusion department offer washed RBCs? If yes, what are the indications for washing RBCs?*

All but one of the Russian hospitals offer washed RBCs. Typically this manipulation is performed for patients with IgA deficiency and patients with severe allergic reactions to previous red cell transfusions.

- 4) *Does your transfusion department maintain a stock of thawed plasma units for immediate issue? If yes, how many units are kept thawed and what is their ABO group?*

Sweden (4 AB units in blood bank, 4 in trauma), UK (1 unit AB plasma), Israel (2 units of all ABO types) and Australia (2 AB units) maintain a stock of thawed plasma units for immediate issue from their hospital's blood bank. All of the other centers do not maintain thawed plasma.

- 5) *Does your transfusion department offer pathogen inactivated blood products? If yes, which pathogen inactivated products are offered and which pathogen inactivation technologies are employed?*

Six hospitals offer pathogen inactivated plasma products; two of the Russian hospitals, and the hospitals in Sweden and Spain, also offer pathogen inactivated platelets. The hospitals in Sweden, Italy and United Kingdom uses solvent/detergent treated plasma for transfusions, the hospitals in Spain and Russia-III uses methylene blue treatment and the hospital in Russia-II uses riboflavin. Platelets at the hospitals in Spain and Russia-III are inactivated by amotosalen.

- 6) *Does your transfusion department prophylactically match RBC blood group antigens other than ABO and RhD for pediatric patients? If yes – which antigens and for which patient categories?*

Besides Japan and Singapore all transfusion departments prophylactically match RBC blood group antigens other than ABO and RhD for specific groups of pediatric patients (table 3). At some locations all RBCs are matched and some places match RBCs for all girls. For example in the hospital in Italy, all RBCs for neonates and pediatric patients are matched for the C,c,E,e, and K antigens. At most places the degree of matching depends on the patient's diagnosis. Patients who usually get matched RBCs include patients with chronic transfusion needs, for example patients with hemoglobinopathies and hematological diseases, and patients who have formed a red cell alloantibody. Most places match for Rh and K, while others include Jk, Fy and MNS antigens in their matching strategy. As another example, RBCs for children with hemoglobinopathies at the hospitals in the Netherlands and Brazil are matched for the Rh, K, Jk, Fy and MNS antigens.

- 7) *Does your transfusion department provide other specific tests for pediatric patients (for example CMV-testing)?*

Eight of the hospitals provide CMV negative cellular blood components on specific (rare) indications. Most hospitals consider leukodepletion sufficient for CMV prophylaxis.

- 8) *Does your transfusion department have procedures to minimize the number of donors the patients are exposed to? If yes, please elaborate the procedures?*

Eleven of the participating hospitals have procedures to minimize the number of donors to which patients are exposed. All of these hospitals use small-volume splits of large RBC units and store them for the same

patient. Four hospitals also preferably use apheresis platelets instead of pools of whole blood derived platelets.

- 9) *Does your hospital have a policy to minimize the volume and frequency of the samples drawn for laboratory testing such as using small volume test tubes for collecting samples?*

Fifteen hospitals also have a strategy to minimize the volume and frequency of the samples drawn from each patient for laboratory testing, by using small test tubes and only taking the minimum volume needed to perform the test. Many hospitals also focus on minimizing the frequency of obtaining blood samples, and one of the hospitals in Singapore also focuses on transcutaneous measurements of blood gases and bilirubin to avoid drawing blood samples.

- 10) *Does your transfusion department have a policy for the maximum storage age of RBCs that can be issued to specific patients? If yes, please state the policy*

The maximum storage age of RBCs varies (table 3). Many centers use the freshest RBCs for intrauterine transfusions, exchange transfusions and pre-term/neonatal transfusions. The maximum storage times for these patients varies from 3 days at one of the hospitals in Singapore to 5, 7 or 10 days at many centers. Three hospitals also keep a maximum storage time of 24 hours post irradiation for specific groups, inclusive liver transplanted patients, exchange transfusions, intrauterine transfusions, prime blood and neonatal cardiac patients.

Blood product dosing:

- 1) *What dose of RBCs/platelets/plasma is usually prescribed for stable pediatric and/or neonatal patients (milliliters/kg or dose of unit)?*

The doses vary between 5 to 20 ml/kg for RBC and platelets and between 10 to 20 ml/kg for plasma.

Discussion

With the exception of one respondent, the hospitals that participated in this international forum provided a similar range of pediatric services, which makes it meaningful to compare practices at the hospitals. The survey found that current pediatric transfusion practices varies around the world, and highlights areas of variability. All of the hospitals had some guidelines for pediatric transfusions, some were very detailed and some more general. All hospitals had employed restrictive transfusion triggers of 7.5 g/dl or less for stable patients, and in the Netherlands the thresholds for some stable patients were as low as 5.6 g/dl (3.5 mmol/L). Interesting differences in the manipulation of blood products included universal irradiation of all RBCs and platelets in USA, Russia-II and Japan, while some hospitals only irradiated their products for limited indications. Thawed plasma for immediate issue were only offered at four the hospitals, and pathogen inactivation at six hospitals.

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Table 1. Demographics and details of the survey responses from the participants.

Country	United States of America	Czech Republic	Russia-I	Russia-II	Russia-III	Netherlands	Brazil	Spain	Japan	Italy	India	Sweden	Singapore	United Kingdom	Israel	Australia	Canada
City	Washington D.C.	Brno	Moscow	Moscow	Moscow	Rotterdam	São Paulo	Madrid	Tokyo	Torino	Chandigarh	Stockholm	Singapore (3 hospitals)	London	Petah Tiqva	Parkville	Toronto
Is the hospital a teaching/academic hospital	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do the hospital receive blood components from the blood center or are they collected and prepared in your own facility?	Both	In our own facility	In our own facility	Hospital based blood bank	Blood Center	Blood Center	In our own facility	Blood Center	Blood Center	In our own facility	Hospital based blood bank	Hospital based blood bank	Blood Center	Blood Center	Prepared in a neighboring facility	Blood Center	Blood Center
Neonate definition	< 4 months	30 days old		< 28 days old	< 30 days old	< 28 days old. For transfusion < 3 months	< 28 days old	< 30 days old	< 30 days old	< 30 days old	< 30 days old	< 1 month, corrected for GA	< 1 month	< 28 days old	< 30 days old	< 28 days old	< 4 months
Pediatric definition	< 18 years old	< 19 years old		< 18 years old	< 18 years old	< 18 years old	< 18 years old	< 18 years old	< 15 years old	< 18 years old	< 13years old	< 18 years old	< 16 years old in KKH*, < 18 years old in NUH*	< 18 years old	< 18 years old	< 18 years old	< 18 years old
Does the hospital primarily treat pediatric patients?	Yes	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
Number of pediatric inpatient beds	313	400	574	220	N/A	N/A	106	180	20	300	283	212	SGH* : 48, NUH*: 100	350	300	357	350
RBC units transfused to pediatric and neonatal patients per year	8057	1671	651	6000	N/A	1468	708	1800-2000	1260	3000	12144	3683	4394 (all of Singapore)	5250	> 5000	4700	8000-8700
Plasma units transfused to pediatric and neonatal patients per year	1760	182	1896	1700	N/A	551	86	150-250	406	1300	3322	1339	1063	1700	> 700	2350	1500
Platelet units transfused to pediatric and neonatal patients per year	3525 (Full size units, aliquoted to smaller doses)	921	64	6300	N/A	816	504	1300-1500	8067	2000	8282	1876	2241	4457	>2150	3200	3500-3800

Table 2. The number of blood products transfused to pediatric patients at the hospitals where these data were available.

Country	Czech Republic	Russia-II	Netherlands	Brazil	Japan	Italy	India	Singapore
City	Brno	Moscow	Rotterdam	São Paulo	Tokyo	Torino	Chandigarh	Singapore
Total number of RBC units transfused to pediatric patients per year	1671	6000	1468	708	1260.24	3000	12144	4394
• Younger than 1 month	216	30	31	114	240.74	300	2754	794
• 1-4 months	231	278	50	98	79.5	180	1140	530
• Older than 4 months	1224	5692	1387	496	940	2500	8250	3070
Total plasma units for pediatric patients per year	182	1700	551	86	406	1300	3322	1063
• Younger than 1	24	10	21	28	134	240	715	320

<i>month</i>								
• 1-4 months	29	104	21	17	40	90	212	106
• Older than 4 months	129	1586	509	41	232	1000	2395	637
Total platelet units for pediatric patients per year	921	6300	816	504	8067	2000	8282	2241
• Younger than 1 month	40	29	26	58	647	50	2402	310
• 1-4 months	24	69	19	39	90	15	328	274
• Older than 4 months	857	6202	771	407	7330	1900	5552	1656

The number of RBC, plasma and platelet units transfused for pediatric patients in total, patients younger than 1 month, 1-4 months and older than 4 months. Note: Units are defined differently at the various hospitals, hence the relationship between the transfusions for the different categories is the most comparable parameter.

Table 3. Description of RBC antigen matching strategies.

Country	Does your transfusion department prophylactically match RBC blood group antigens other than ABO and RhD for pediatric patients? If yes – which antigens and for which patient categories?	Does your transfusion department have a policy for the maximum storage age of RBCs that can be issued to specific patients? If yes, please state the policy
United States of America	SCD: Rh/K matched. Antigen matched cells when a patient has certain serological findings, on the case-by-case basis.	Neonates, ECMO and cardiac surgery pump prime units: Maximum 10 days storage (preferable < 7 days storage for cardiac surgery pump prime units). Specific storage time allowed after irradiation.
Czech Republic	Oncology patients	Polytraumatic patients: Maximum 14 days storage. Neonates: Maximum 5 days storage. Pediatric: Maximum 14 days storage.
Russia-1	Since 1999, we have been selecting erythrocytes with antigens - A, B, C, Cw, c, E, e, K, k.	Children < 1 month: Maximum 10 days storage. Exchange transfusion: Maximum 5 days storage.
Russia-2	All patients: k and Cw matched.	Neonatal patients: Maximum 5 days storage.
Russia-3	N/A	No
Netherlands	All girls, patients with MDS and auto-antibodies against red blood cells: cEK matched. Hemoglobinopathies: cEK, Fy a/b, Jk a/b, MNSs matched.	N/A
Brazil	Chronically transfused patients with hereditary hemoglobinopathies and myelodysplastic syndrome: Rh, K, Fy, Jk, and MNS matched.	Massive transfusion, exchange transfusions, intrauterine transfusion: Maximum 5 days storage.
Spain	All girls: Rh and K matched.	No
Japan	No	No

Italy	All neonates and pediatric patients: C,c,E,e, and K matched.	Patients <6 months old: Maximum 5 days storage post-irradiation. Liver transplant, exchange transfusions, intrauterine transfusions and neonatal cardiac surgery: Maximum 5 days storage and 24 hours post-irradiation.
India	Thalassemia patients: E,e,C,c and K matched.	Department of transfusion medicine has a policy to reserve RBCs for maximum of 72 hours for a particular patient after which it can be released for other patients for optimum usage of the product .
Sweden	Chronic transfusion requirements: Rh, K, Jk, Fy matched.	Pediatric patients and all who requires chronic transfusions: Maximum 14 days storage. Exchange transfusions and prime blood: < 5 days storage, maximum 24 hours post-irradiation.
Singapore	No	SGH: For neonates: Preference < 3 days storage. BSG: Intrauterine transfusion and exchange transfusion: < 5 days storage. Pediatric ECMO and neonates < 5kg undergoing cardiac surgery: < 7 days storage.
United Kingdom	Transfusion dependent patients: Rh matched. Clinically significant antibodies: Rh matched.	Patients < 1 year requiring large volume neonatal pack transfusions: < 5 days storage. Cardiac surgery and SCD: < 14 days storage. Irradiated units: < 14 days storage (<24 hours for specific groups)
Israel	Hemoglobinopathies, AIHA patients	Exchange transfusion and pre term: < 7 days storage. Thalassemia and SCD patients: < 10 days storage (up to 14 if multiple antibodies).
Australia	All patients: K neg. Hemoglobinopathies: C, D, E and K matched. Exchange transfusions, WAIHA: Rh/K, Jka, Fy and Ss matched. Alloantibodies: Extended red cell matching. Intrauterine transfusions, HDFN: Fya, Jk, M, N and Ss matched.	Exchange transfusion and intrauterine transfusion: < 5 days storage. Cardiac surgery: < 7 days storage. Massive transfusion: Aim < 10 days storage. Chronically transfused: Aim < 14 days storage.
Canada	All girls: K neg. SCD and WAIHA: Rh and K matched. SCD with clinically significant antibodies: Fya, Jka, Jkb, S matched.	Infants < 3-6 months: < 7 days storage. 6 months to 4 years: < 14 days storage. Patients over 4 years: < 28 days storage. Hemoglobinopathy patients: < 21 days storage. Fresher units for cardiac surgery.

SGH: Singapore General Hospital, NUH: National University Hospital. AIHA: Autoimmune hemolytic anemia, ECMO: Extracorporeal membrane oxygenation, SCD: Sickle cell disease, WAIHA: Warm autoimmune hemolytic anemia

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