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ORIGINAL ARTICLE

# Evaluation of the use of blood components in non-critical pediatric patients

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child,
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## Abstract

**Objective:** This retrospective descriptive study aimed to portray the epidemiological characteristics of blood component recipients and the technical characteristics of the products offered to non-critical patients of a pediatric tertiary care hospital, and to assess the appropriateness of blood transfusions relative to the guidelines published by the British Committee for Standards in Haematology. **Methods:** The study included all transfusions performed in 2015 at IFF/Fiocruz and screened the corresponding patient records for epidemiological data. Transfusion procedures were subsequently categorized as appropriate or inappropriate based on clinical indication and the aforementioned guidelines. **Results:** A total of 49 transfusions took place during the study period in the non-critical clinical and surgical care units of the hospital; 63.3% were transfusions of packed red blood cells, followed by platelet concentrates (32.6%), and fresh frozen plasma (4.1%). Subsequent evaluation found that 55.1% of the transfusion indications were inappropriate, a proportion higher than the rates published in the literature. **Conclusion:** The results described in this study call for prompt intervention and implementation of measures to ensure the adoption of the guidelines published by the BCSH and the consequent improvement of the transfusion practices in effect for this group of patients.

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## INTRODUCTION

Blood and blood component transfusions - potentially life-saving procedures - are commonly performed in medical practice despite their inherent risks and possible acute and late complications.[1]

In pediatric populations, the long-term effects of transfusions become even more relevant given the significant life expectancy after transfusion observed in this population in relation to the general population. Studies indicated that the general population survives on average for 51 months after transfusion.[2]

Brazilian reality forces one to consider the costs of the procedure, since blood and blood component transfusions require expensive high-technology equipment and well-trained personnel, in addition to relying on voluntary blood donors.

In Brazil, 3,657,756 blood donations were made from 2012 to 2014, with 2014 outnumbering 2013 by 162,446 donations. Public centers accounted for 90.94% of the blood collected, while the remaining 9.06% were collected at private centers.[3]

These numbers amount to 18.49 donations per 1,000 population in 2014, an increase of 0.65 donation per 1,000 population in relation to 2013.[3]

Most of the numerous protocols devised for blood and blood component transfusions in pediatric populations were adapted from procedures developed originally for adults, often inadequate for children and adolescents.[4]

For these and other reasons, prescriptions of blood and blood components must take a number of factors into account, including donor and recipient safety and access to the procedure.

A study enrolling physicians of a pediatric intensive care unit and an oncology-hematology unit in Canada revealed that the symbolism attributed to blood in matters of identity, lineage, ethnicity, and race, in addition to its representations of strength and regeneration, affect the perception and acceptance of blood transfusions by individuals of different beliefs. These factors have contributed for blood transfusion to be imbued with subjectivity, albeit ruled by protocols and scientific evidence. The study also indicated that most physicians did not receive training on blood transfusions at medical school, but acquired knowledge on the subject during their years in residency or as they started to practice. Most physicians tended toward adopting minimum hemoglobin levels to trigger transfusion, adding however that the decision was made based on each patient's health status, thus generating significant variability in blood transfusion indications. Some claimed to have prescribed transfusion to improve patient quality of life.[5]

While there is no equivalent Brazilian data, studies carried out in the United States estimated that about 5% of all whole blood and packed red blood cell (PRBC) transfusions performed in 2013 involved patients under 18 years of age, 58.3% of which were administered irradiated components.[6]

According to US data, the conditions more frequently associated with blood transfusions in childhood are low birth weight, hemoglobinopathies, heart diseases that require surgery, spinal fusion surgery, and chemotherapy to treat cancer.[7]

Few studies have looked into the indications, complications, and clinical use of blood component transfusion in pediatric patients. Additionally, the specificities of each age and the stages of physiological development increase the risk of pediatric patients suffering with adverse events, including human error, adverse immune reactions, and transmission of infectious diseases.[7]

Exposure of immunocompetent recipients to donor blood may result in alloimmunization - immune response to donor antigens. In blood transfusions, the most commonly involved antigens are the ones related to platelet and lymphocyte HLA, in addition to granulocyte-, platelet-, and erythrocyte-specific antigens. When this paper was written, 308 blood group antigens had been identified on the surface of human red blood cells.[8]

This phenomenon, albeit rare in neonatal life, becomes clinically relevant for pediatric patients and children needing repeated blood transfusions in particular. These patients have good long-term survival after blood transfusion, which makes it harder to find bags with compatible blood as time goes by.

In the general pediatric population, 1-5% of transfusion patients develop alloimmunization. This number, however, is much higher in individuals with hemoglobinopathies - 7.7% in patients with thalassemia and 29% in patients with sickle-cell anemia. On the other hand, alloimmunization occurs in 0-2% of cancer patients on chemotherapy.[9-11]

The long-term effects in female patients include complicated pregnancy and possibly hemolytic disease of the newborn (HDN), death of the fetus, and miscarriage.

The Brazilian Ministry of Health's ordinance 158 issued on February 4, 2016 recommends that screening for irregular red cell antibodies be performed in all transfusions and that phenotype-matched components be used particularly in the more immunogenic systems (Rh, Kell, Duffy, Kidd, and MNS) on patients alloimmunized against erythrocyte antigens and current/potential candidates for chronic transfusion in order to help identify possible irregular red cell antibodies.

In regards to the risk of infection, the Ministry of Health advises that all bags with collected blood be tested and used only after the workup for the following diseases has been completed: hepatitis B, hepatitis C, HIV I and II, Chagas disease, syphilis, and infection by HTLV I and II. Screening for CMV is performed in specific cases. Leukoreduced blood components may be used as a replacement for CMV seronegative components.

In endemic areas where there is active transmission of malaria, blood components should also be tested for plasmodium or plasmodium antigens.

The risk of transfusion reactions is another important factor to consider in the prescription of blood components. Although adults are more likely to receive transfusions than children, pediatric populations are at increased risk of long-term

adverse outcomes on account of several physiological factors, including the immaturity of their immune system and blood-brain barrier, and the longer post-transfusion life expectancy they have.[4]

A study conducted in the United States reported an incidence rate of 6.2 reactions per 1,000 transfusions in pediatric patients versus 2.4 per 1,000 transfusions in adult subjects. In the pediatric population, age was not associated with risk of transfusion reaction, while male individuals had increased incidence of reactions. The occurrence of life-threatening events seemed not to be significantly different when pediatric and adult patients were compared.[12]

Despite significant underreporting, the Brazilian Risk Monitoring Authority hypothesized that the incidence rate of transfusion reactions is close to five per 1,000 transfusions, predominantly comprised of cases of immediate reaction (more than 96%). Febrile non-hemolytic transfusion reaction and allergic transfusion reaction were more prevalent. Mild reactions accounted for approximately 82% of the cases.[13]

Some adverse events require special attention in pediatric populations. For example, one unit of blood accounts for a larger proportion of the total fluid volume of a child when compared to an adult. Additionally, at the end of shelf life or when stored after irradiation, packed red blood cell units present potassium levels high enough to cause severe hyperkalemia when they are transfused at fast rates into small children or when volumes greater than 25mL/kg are transfused.[14-15]

The longer survival of pediatric patients also puts them at greater risk of developing long-term clinical complications. Patients on chronic transfusion therapy suffer from clinically relevant iron overload that may progress to liver failure and cardiac toxicity. Studies have indicated that donor leukocytes may persist in the recipient's blood, causing a condition referred to as transfusion-associated microchimerism. The consequences of this condition include autoimmune disease and chronic transfusion-associated graft-versus-host disease (TA-GVHD).[4,16]

In spite of these factors, data from the United Kingdom show that incorrect blood component transfusions are still highly prevalent in neonatal and pediatric transfusion incidence reports, particularly the failure to prescribe irradiated or CMV-negative components. Lack of training and poor knowledge on the subject are possible causes, since transfusion rates are lower among pediatric patients when compared to their adult counterparts.[14]

Primary measures adopted to adjust blood components to the needs of recipients include filtering and removing white blood cells from blood before transfusion (leukoreduction), thus decreasing the incidence of HLA-mediated reaction, TA-GVHD, and immunosuppression secondary to immunomodulation following transfusion; irradiation, thus preventing the proliferation of donor lymphocytes in the patient, decreasing the risk of TA-GVHD and the use of washed components that decrease the levels of blood protein and potassium levels, indicated to patients presenting anaphylactic reaction caused by IgA deficiency, severe allergic reaction to blood proteins, and newborns with neonatal alloimmune thrombocytopenia set to receive platelets from their mothers.[17]

This study aimed to describe non-critical pediatric patients submitted to blood transfusions and the technical features of the procedures carried out at the Pediatrics Service of the Fernandes Figueira Institute (IFF, Brazilian acronym) for Children's, Women's, and Adolescents' Health in 2014, and to assess the appropriateness of blood component transfusion prescriptions vis-à-vis the evidence-based guidelines regulating the use of blood components.

Multiple guidelines on the prescription and use of blood components have been published, the more relevant of which in Brazilian practice are the guidelines published by the American Association of Blood Banks (AABB), the Guide issued by the Brazilian Ministry of Health, and the guidelines of the British Committee for Standards in Haematology (BCSH)[1,18,19]. After a meeting with the heads of the Pediatrics Service, we opted to use the guidelines of the BCSH, since it considers patients in the pediatric age range, covers thrombocytopenia alone or with active bleeding, and encompasses a greater diversity of surgical procedures.

## METHODS

This retrospective descriptive study was based on the data collected from the charts of patients aged between 28 days and 18 years diagnosed with clinical or surgical conditions and staying in pediatric and pediatric surgery wards and outpatient units at IFF in the year of 2015, who received blood and blood component transfusions. The Institute offers tertiary care in the areas of Pediatrics and Pediatric Surgery, but does not offer hematology, oncology, or heart surgery services - a factor that significantly affects the number of transfusions performed and the profile of transfusion recipients. Additionally, the IFF is a teaching hospital with medical and multidisciplinary residency programs in the areas of Pediatrics, Pediatric Surgery, and Women's Health. The study attained the approval of the Ethics Committee of the institution and was assigned permit 1.676.030 on August 12, 2016.

A search was made in the epidemiology registry of the Hemotherapy Service for transfusions performed in 2015. The charts of the children who underwent transfusion in the given period were analyzed and data concerning patient age, sex, blood group, clinical diagnosis, indication for transfusion, ordering center, ordered blood component, and component age were extracted.

The performed transfusions were assessed and categorized as appropriate or inappropriate as a function of clinical indication. After reviewing the literature on the subject, the guidelines of the British Committee for Standards in Haematology (BCSH) were chosen as the reference against which the performed transfusions were analyzed. The BCSH guidelines are summarized in Chart 1.

## RESULTS

Table 1 presents the epidemiological characteristics of the included blood component recipients and the technical features of the utilized blood products.

Nearly two thirds (63.3%) of the recipients were administered packed red blood cells, followed by platelet concentrate (32.6%), and fresh frozen plasma (4.1%). Cryoprecipitate and plasma frozen within 24 hours after phlebotomy were not administered in the studied period.

The mean blood component storage time - or the time between blood collection and transfusion - was 14.65 days for packed red blood cells (PRBC), 3.36 days for platelet concentrate (PC), and 11.65 days for fresh frozen plasma (FFP).

More than half of the patients (53%) were females. In terms of age range, the majority of the patients given blood components were aged between 0-2 years (42.8%), followed by adolescents (28.6%). The mean age and weight of the patients was 2.08 years and 14.58 Kg, respectively.

Forty percent of the transfusions were performed in surgical units (operating room and pediatric surgery ward), while 59.2% were carried out in the Pediatric Ward, in the Intermediate Care Unit, or in the Pediatric Outpatient Clinic.

On average, recipients of PRBC were given 14.91 mL per kilogram of body weight of the blood component, versus 6.05 mL/Kg of body weight for recipients of PC, and 11.96 mL/Kg of body weight for FFP recipients.

The assessment of transfusion indications based on the clinical and workup parameters described in Chart 1 found that 55.1% of the procedures were inappropriately indicated, as shown in Table 2.

Platelet concentrate transfusions had the poorest level of clinical appropriateness as a proportion, with 56.3% of the procedures deemed inappropriate, followed by PRBC with 54.8% and FFP with 50%.

In the case of platelet concentrates, inappropriateness occurred on account of lack of pre-transfusion testing in one case and unnecessary transfusion based on levels found in lab tests and amount of bleeding as per the BSCH criteria (Table 3).

PRBC was inappropriately prescribed to patients with serum Hb > 7g/dL without the risk factors described in Chart 1.

Patients with evidence of intraoperative bleeding and normal coagulation tests were given FFP nonetheless.

Greater proportions of error were seen in blood component transfusion indications to infants (51.8%) - the age group with the largest number of transfusions (Table 4).

## DISCUSSION

No discrepancy was seen in the studied population in relation to sex. In terms of age, however, most of the patients given transfusions were infants (42.8%), a finding concerned with the potential long-term effects of transfusion. The longer survival of pediatric patients puts them at greater risk for future transfusion and possible transfusion-related complications.

Nearly two thirds (63.3%) of the transfusions were performed with PRBC, followed by PC, and FFP. Bahadur et al. also reported predominance of PRBC in a similar study, although the authors described significant use of whole blood and more transfusions with FFP than PC, differently from our study.[20]

The mean volume of transfusion was 11.96 mL/kg of body weight. Cases of transfusion-associated circulatory overload were not mentioned in the patient charts. However, our study did not look into the occurrence and reporting of transfusion reactions.

About three fifths (59.2%) of the transfusions were performed in clinical settings and 40.8% in surgical units. These proportions probably relate to the number of patients coming into each type of unit and the clinical characteristics of these patients, and cannot be used to support inferences on the prevalence of transfusion in each service at this point.

The assessment based on the BCSH criteria described in Chart 1 showed that 44.9% of the transfusions were prescribed appropriately, revealing a marked difference against the 59.65% reported by Bahadur et al. in a study also conducted at a teaching hospital.

A multicenter study involving 15 neonatal care units in Brazil indicated that the level of knowledge of health providers, their attitudes and preferences toward using old practices and abiding by patient preferences, the working environment, and lack of adequate infrastructure were among the factors more significantly connected with trouble implementing clinical guidelines in care centers.[21]

Our study found a large proportion of inappropriate indications for transfusion when compared to a similar study. Interventions are required to fully implement the guidelines of the BCSH and enhance the use of blood components at IFF/Fiocruz and improve the overall performance of transfusion services.

A number of strategies based fundamentally on providing ongoing education to health providers and conducting frequent hearings and studies to assess the quality of transfusions and the efficacy of implemented measures may be adopted.

From the standpoint of education, health providers must be encouraged to use means other than blood to treat stable patients with vitamin- or iron-deficiency anemia, such as iron and vitamin supplementation. Medical personnel should be trained on the indications of blood component transfusion to judiciously assess the clinical need for each transfusion despite isolated lab test results, and identify patients at risk of suffering from complications secondary to severe anemia or blood component deficiency. Additionally, health providers must be trained to monitor and report complications and transfusion reactions. Another strategy described in the literature revolves around embedding the key points and indications described in the guidelines in the forms used to order blood components, thereby encouraging a careful review of the indications at the time of prescription.

**Chart 1.** Criteria adopted in the assessment of transfusions.

| Packed red blood cells |
|---|
| Use restrictive transfusion thresholds for patients not presenting severe bleeding, acute coronary syndrome, or not needing transfusion to treat chronic anemia. In these cases, the transfusion threshold is 7g/dL with a post-transfusion target of 7-9 g/dL. |
| The transfusion threshold for patients with acute coronary syndrome is 8 g/dL and the post-transfusion target is 8-10g/dL |
| Individualized reference values apply to patients with chronic anemia. |
| Prioritize the transfusion of one unit of PRBC to adults or the equivalent volume based on the body weight to children and low weight patients when there is no evidence of active bleeding. |
| After the transfusion of each PRBC unit or equivalent volume based on the body weight of the patient, check hemoglobin levels before ordering additional units. |
| Platelet concentrates |
| Offer transfusion to patients with evidence of Grade 2 bleeding in the WHO scale and platelet counts < 30.000/mm³ |
| Use higher thresholds (as high as 100,000/mm³) if there is evidence of severe bleeding (WHO scale Grades 3 and 4) or bleeding in critical sites such as the eyes or central nervous system (CNS) |
| If there is no evidence of bleeding, set the platelet threshold at 10,000/mm³, as long as the patient is free from chronic bone marrow failure, autoimmune thrombocytopenia, heparin-induced thrombocytopenia, or thrombotic thrombocytopenic purpura. |
| Set the threshold at 50,000 platelets/mm³ to indicate transfusion to patients scheduled to undergo invasive procedures. The threshold may be increased (up to 75,000/mm³) considering the procedure to be performed, the cause of thrombocytopenia, tendency of decreasing platelet counts, and other causes of coexisting blood dyscrasia. |
| In surgery in critical sites (such as the CNS and the eyes), set the post-transfusion target to 100,000 platelets/mm³. |
| Platelet concentrates must not be prescribed to patients with chronic bone marrow failure, autoimmune thrombocytopenia, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, or individuals scheduled to undergo low risk procedures such as bone marrow biopsies or implantation of a deep venous access. |
| Avoid transfusing more than one PC unit or the equivalent volume based on the body weight of the patient; after transfusion, check for platelet levels before ordering another unit. |
| Fresh frozen plasma |
| FFP transfusions should only be performed in patients with clinically significant, yet not severe, hemorrhage, if they present with abnormal coagulation test results. |
| FFP should not be prescribed to patients not presenting bleeding or needing reversal of vitamin K antagonists. |
| Consider prophylactic FFP transfusion to patients with abnormal coagulation scheduled to undergo invasive procedures carrying risk of clinically significant bleeding. |

**Table 1.** Characteristics of blood component recipients at IFF/Fiocruz in 2015.

| Variable | PRBC (n=31) | PC (n =16) | FFP (n =2) | Total (n =49) |
|---|---|---|---|---|
| Sex | | | | |
| Female (%) | 13 (41,9) | 12 (75) | 1 (50) | 26(53) |
| Male (%) | 18 (58,1) | 4 (25) | 1 (50) | 23 (47) |
| Age | | | | |
| Infants (%) | 12 (38,7) | 8 (50) | 1 (50) | 21 (42,8) |
| Preschoolers (%) | 6 (19,3) | 5 (31,2) | 0 | 11 (22,4) |
| School-age children (%) | 2 (6,4) | 0 | 1 (50) | 3 (6,1) |
| Adolescents (%) | 11 (35,5) | 3 (18,8) | 0 | 14 (28,6) |
| Median age a (range) | 2,17 (0,08-18) | 2 (1,83- 14) | 3,79 (1,83-5,75) | 2,08 (0,08-18) |
| Weight | | | | |
| Mean weight b (range) | 15,36 (3,6-40) | 13,53 (7,8-30) | 11,3 (7,6-15) | 14,58 (3,6-40) |
| Transfusion volume | | | | |
| Mean transfusion volume c (range) | 14,91 (8,5-21,4) | 6,05 (5,5-7,86) | 16,4 (13-19,7) | 11,96 (5,5-21,4) |
| Blood component age | | | | |
| Mean time between collection and transfusion d (range) | 14,65 (3-32) | 3,36 (2-5) | 116,5 (103-130) | 21,17 (2-130) |
| Specialty | | | | |
| IMCU (%) | 15 (48,4) | 4 (25) | 1 (50) | 20 (40,8) |
| Pediatric Care (%) | 16 (51,6) | 12 (75) | 1 (50) | 29 (59,2) |

[a] Median, years.

[b] Kg.

[c] Values calculated as mL of blood component/kg. For PRBC, a ratio of 1U = 300mL was adopted. For PC, a ratio of 1U = 55 mL and 5.5 x 1010 platelets was adopted.

[d] Days.

**Table 2.** Appropriate and inappropriate transfusions of blood components performed at IFF/Fiocruz in 2015.

| Component | Transfusions | Appropriate transfusions (%) | Inappropriate transfusions (%) |
|---|---|---|---|
| CH | 31 | 14 (45,2) | 17 (54,8) |
| CP | 16 | 7 (43,7) | 9 (56,3) |
| PFC | 2 | 1 (50) | 1 (50) |
| Total | 49 | 22 (44,9) | 27 (55,1) |

**Table 3.** Bleeding Scale of the World Health Organization.[15]

| | |
|---|---|
| Grade 1 | Petechiae (ruptured capillary blood vessels). |
| Grade 2 | Mild blood loss (clinically significant). |
| Grade 3 | Gross blood loss requiring transfusion (severe). |
| Grade 4 | Debilitating blood loss; cerebral or retinal bleeding; bleeding associated with death. |

**Table 4.** Appropriate and inappropriate transfusions per age range at IFF/Fiocruz in 2015.

| Age range | Transfusions | Appropriate transfusions (%) | Inappropriate transfusions (%) |
|---|---|---|---|
| Infants | 21 | 7 (31,8) | 14 (51,8) |
| Preschoolers | 11 | 5 (22,7) | 6 (22,2) |
| School-age children | 3 | 2 (9) | 1 (3,7) |
| Adolescents | 14 | 8 (36,4) | 6 (22,2) |
| Total | 49 | 22 (44,9) | 27 (55,1) |

Retrospective studies based on patient chart analysis pose well-known limitations and technical barriers, including the lack of clear clinical reports and the loss of data not entered in patient charts. Besides, additional investigations are not possible, thus limiting the scope of the study. In this study, the absence of data on the outcomes arising from inappropriate blood transfusions and the possible impacts on patients, along with the size of the sample, imposed limitations to the analysis of our results.

However, studies such as ours are of paramount importance to assess the quality of medical practice and the level of awareness health providers have of adopted practices.

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