How do we transfuse children in Italy? Results of a national survey

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Arrived: 21 June 2024
Revision accepted: 10 October 2024
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Background - Adherence to optimal practices in the preparation and issuance of pediatric blood components can significantly influence patient care outcomes. This study aims to examine the blood banking procedures across prominent Italian children's hospitals, with the goal of identifying both consistent and potentially divergent standards within this field.

Materials and methods - A survey was conducted among the blood banks affiliated with the Italian Association of Pediatric Hospitals. Modeled after the AABB Neonatal and Pediatric Blood Bank Practices Survey, the questionnaire comprised 25 questions covering hospital characteristics, definitions of the neonatal period, pre-transfusion tests, blood component availability, and irradiation protocols.

Results - Fourteen out of the sixteen invited blood banks participated in the survey. The findings revealed a wide range of practices among the surveyed hospitals. Major differences were noted in the neonatal period definition, pre-transfusion compatibility procedures, and platelet transfusion protocols. All hospitals provided leukodepleted packed red blood cells (pRBCs), with differences in availability of autologous blood and reconstituted whole blood. Irradiated blood components were universally accessible, with differences in post-irradiation acceptable storage time. Additionally, differences in dosages for packed red blood cells (pRBCs) and platelet concentrates (PCs) were observed across hospitals.

Conclusions - Standardized guidelines for pediatric transfusion practices within Italian blood banks are of paramount importance. The observed variability underscores the necessity for sharing best practices among centers supplying blood components to pediatric patients.

Keywords: *pediatric transfusion, neonatal transfusion, red blood cells, platelets, survey.*

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INTRODUCTION

Blood is a critical resource in healthcare, and its appropriate utilization can significantly enhance patient outcomes[1]. Recognizing this, the World Health Organization has included blood and its products in the Model List of Essential Medicines[2]. However, inappropriate blood use not only wastes a limited resource but also exposes patients to unjustifiable risks associated with transfusions[3].

Blood Transfus. 2025; 23(2): 128-136 doi: 10.2450/BloodTransfus.838
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In pediatric patients, the administration of packed red blood cells (pRBCs), platelet concentrates (PCs), or plasma (FFP) transfusions is a crucial aspect of treatment in several clinical settings. Pediatric intensive care units (PICUs) frequently administer blood component transfusions during patient hospitalization[4]. In oncological and hematological contexts, transfusion support therapy, particularly prophylactic platelet transfusion, improves patients' tolerance to aggressive therapeutic regimens, leading to enhanced life expectancy and treatment outcomes in both pediatric and adult populations[5,6].

Neonatal transfusions represent a particular field in transfusion medicine, which have been specifically addressed in few clinical randomized studies[7-10], and by specific clinical guidelines[11-13].

However, regarding the processing of specific blood products and blood bank procedures, the limited availability of randomized controlled trials (RCTs) in pediatric settings, combined with the wide range of clinical situations across different contexts, has limited the widespread adoption of standardized blood bank practices in pediatric transfusion[14,15].

In Italy, data from the National Blood Center revealed that in 2022, more than 12,000 pediatric patients received approximately 38,000 blood component transfusions[16]. The absence of specific national guidelines tailored to the pediatric population has highlighted the need to gather further information on current transfusion blood bank practices throughout the country. This study presents the findings of a survey conducted among major Italian children's hospitals.

MATERIALS AND METHODS

Questionnaire development involved members of the promoting children hospital blood banks, who collaborated through remote meetings held between November 2022 and January 2023 (**Table I**). The questionnaire was modelled after the 2021 Association for the Advancement of Blood & Biotherapies (AABB) Neonatal and Pediatric Blood Bank Practices Survey[14]. It comprised 25 multiple-choice and open-ended questions on various aspects, including hospital characteristics, definition of the neonatal period, pre-transfusion tests, repertoire of blood components, methods for preventing transfusion transmitted infections, and formulas for blood component pediatric doses calculation. In January 2023 the questionnaire was electronically submitted (via Google Forms [Google, Mountain View, CA, USA]) to directors of the 16 blood banks supplying children's hospitals affiliated with the Italian Association of Pediatric Hospitals (AOPI). Descriptive statistical analysis was conducted using Microsoft Excel Suite 365 (Redmond, WA, USA), presenting results as numbers or percentages (%) relative to the specific question analyzed.

RESULTS

By late February 2023, 14 out the 16 blood banks managers of the hospital belonging to the Italian Association of Pediatric Hospitals completed the questionnaire with a participation rate of 88%. These facilities were located across 12 regions, including 9 of Italy's most densely populated regions.

Hospital characteristics

Out of the 14 hospitals surveyed, 11 (78.6%) were exclusively dedicated to neonatal and pediatric care. All participating hospitals have a neonatal intensive care unit (NICU). Additionally, 11 hospitals (78.6%) have departments for pediatric oncology, hematology, and hematopoietic stem cell transplantation. Eight hospitals (57.1%) serve as trauma center hubs, while 10 hospitals (71.4%) provide Extracorporeal Membrane Oxygenation (ECMO) services (**Figure 1**). In 6 cases (42.9%), these services were all available in the same hospital. The number of pediatric transfusions conducted annually (in the reference year 2022) varied widely, ranging from 50 to 12,269, with a median value of 1,300 transfusions.

Definition of the neonatal period

Ten centers (71.4%) defined the neonatal period as <28 days after birth, three centers (21.4%) as <4 months after birth, and one center (7.1%) as between 28 days and 4 months after birth according to gestational age at birth (**Figure 2**).

Pre-transfusion compatibility procedures

Type and screen (T&S) with electronic cross-match was utilized at least for some patients in eleven facilities (78.6%); among these, it was exclusively reserved for surgical patients in six hospitals (42.9%). Coombs' crossmatch was the sole pre-transfusion test in three hospitals (21.4%), while in the remaining eleven (78.6%) facilities, cross-matching was reserved for one or more specific patient categories: those with hemoglobinopathies on chronic transfusion regimens (three hospitals, 21.4%),

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Table I - *Survey questionnaire*

1. Which of the following characteristics does your hospital have?

(multiple choice, more than one answer possible)
a. Pediatric-only hospital
b. Presence of neonatal intensive care unit (NICU)
c. Presence of hematology and stem cell transplant unit
d. ECMO service available (Extracorporeal Membrane Oxygenation)
e. Trauma Hub

2. How many pediatric/neonatal red blood cell transfusions are performed annually?

(open answer)

3. What is the definition of the "neonatal period"?

(multiple choice, one answer only)
a. < 28 days from birth
b. Between 28 days and 4 months from birth
c. < 4 months from birth

4. What is the definition of "pediatric age"?

(multiple choice, one answer only)
a. 0-14 years
b. 28 days - 15 years
c. 28 days - 18 years
d. 4 months - 16 years
e. 4 months - 18 years

5. What types of red blood cells are available?

(multiple choice, more than one answer possible)
a. Leukodepleted pre-storage red blood cells suspended in SAG-M
b. Leukodepleted pre-storage red blood cells without SAG-M
c. Autologous whole blood
d. Reconstituted whole blood

6. What processing options are available for red blood cells?

(multiple choice, more than one answer possible)
a. Red blood cell washing in an open system
b. Red blood cell washing in a closed system
c. SAG-M removal from red blood cell units
d. Irradiation

7. What are the main indications for red blood cell washing and SAG-M removal from red blood cell units?

(open answer)

8. Are potassium levels assessed in the periodic quality checks of red blood cell units?

(multiple choice, one answer only)
a. Yes
b. No, never
c. No, but it can be done if needed

9. What types of platelet concentrates are available?

(multiple choice, more than one answer possible)
a. Apheresis platelets
b. Buffy coat pool platelets
c. Pathogen-inactivated platelets

10. What processing options are available for platelet concentrates?

(multiple choice, more than one answer possible)
a. Washed platelets
b. Volume-reduced platelets
c. Deplasmated platelets resuspended in additive solution (T-Sol, InterSol)
d. Irradiation

11. In which cases are washed or volume-reduced platelets requested?

(open answer)

12. Are blood component fractions prepared?

(multiple choice, one answer only)
a. At the time of production (standardized pediatric units)
b. Tailored, case by case
c. Both standardized and tailored
d. Not fractionated

13. In the case of tailored fractions, what dose is used for red blood cells?

(multiple choice, one answer only)
a. 10 mL/kg
b. 15 mL/kg
c. 20 mL/kg
d. Dose requested by the clinician
e. Dose agreed upon between clinician and blood bank physician

14. In the case of tailored fractions, what dose is used for platelet concentrates?

(multiple choice, one answer only)
a. 5-10 mL/kg
b. 0.5×10^{11} platelets/10 kg
c. $1.1\text{-}2.2\times10^{11}$ platelets/m^2 of body surface area
d. Units are divided into two aliquots of equal volume

15. What strategy is used to prevent CMV infection?

(multiple choice, one answer only)
a. Leukodepleted units are considered CMV-safe
b. Red blood cell and platelet units are considered CMV-safe only from CMV-negative donors

16. Is an irradiator available at your center?

(multiple choice, one answer only)
a. Yes
b. No, but irradiation can be performed at another center if necessary
c. No, but irradiation can only be performed at another center if scheduled in advance

17. Are blood component irradiation requests always compliant with guideline recommendations?

(multiple choice, open answer, one answer only)
a. Yes
b. Yes, but additional indications exist (please specify)
c. No

18. After irradiation, within what time frame can red blood cells be transfused?

(multiple choice, one answer only)
a. Within 6 hours
b. Within 24 hours
c. Within 48 hours
d. Within 5-7 days
e. Until the unit's expiration date

19. Is the Type and Screen (T&S) with electronic cross-match adopted for assigning red blood cell units?

(multiple choice, one answer only)
a. Yes
b. No
c. Yes, only for surgical patients
d. Yes, except for specific categories (specified in the next question)

20. In which patient categories is the Type and Screen (T&S) with electronic cross-match not adopted for assigning red blood cell units?

(open answer)

21. In neonatal transfusions, is maternal plasma/serum used for irregular antibody screening?

(multiple choice, one answer only)
a. Yes, always
b. Yes, if available
c. No

22. Are ABO-incompatible platelet concentrates assigned if necessary?

(multiple choice, one answer only)
a. Yes, without isoagglutinin titration
b. Yes, but only if the isoagglutinin titer is below a certain value (specified in the next question)
c. No

23. What isoagglutinin titer allows for the assignment of ABO-incompatible platelet concentrates?

(open answer)

24. Are RhD-positive platelet concentrates assigned to RhD-negative patients?

(multiple choice, one answer only)
a. Yes, with Rh-Ig prophylaxis
b. Yes, without Rh-Ig prophylaxis
c. No

25. In case of massive transfusion, how is the ratio of transfused blood components (red blood cells, plasma, platelets) determined?

(multiple choice, one answer only)
a. A massive transfusion protocol is available
b. Based on viscoelastic test results
c. Fixed 1:1:1 ratio of red blood cells, platelets, and plasma
d. Ratio is determined case by case

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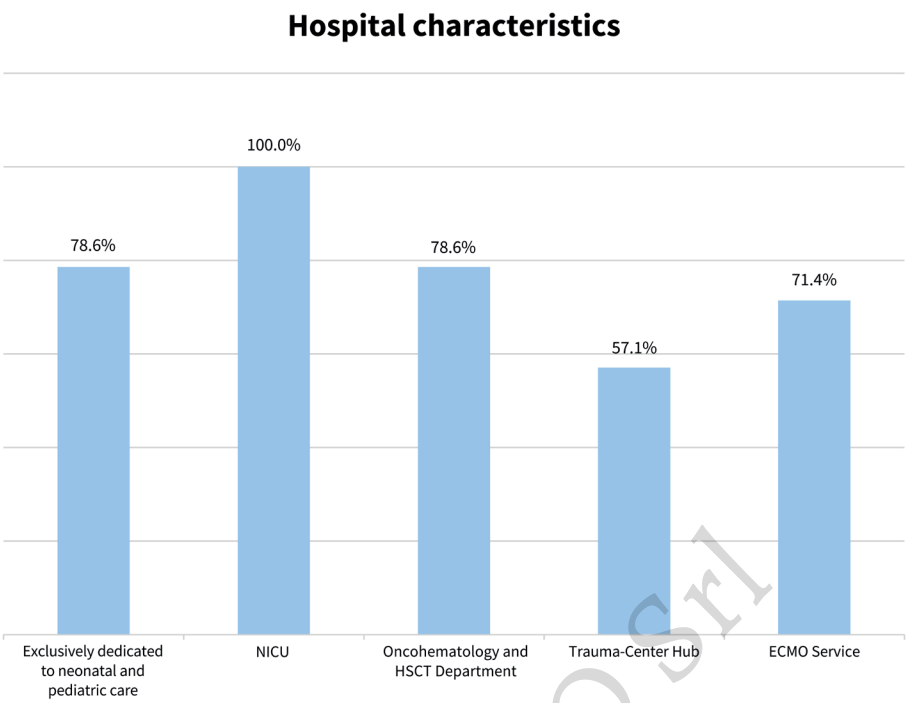


Figure 1 - Hospital characteristics: description of the characteristics of the Hospitals involved in the survey
Of the 14 hospitals, 11 (78.6%) are exclusively dedicated to neonatal and pediatric care, all 14 (100%) have Neonatal Intensive Care Units (NICU), 11 hospitals (78.6%) have Oncohematology and Hematopoietic Stem Cell Transplantation (HSCT) Departments, 8 hospitals (57.1%) serve as Trauma-Center hubs, and 10 hospitals (71.4%) provide Extracorporeal Membrane Oxygenation (ECMO) services.

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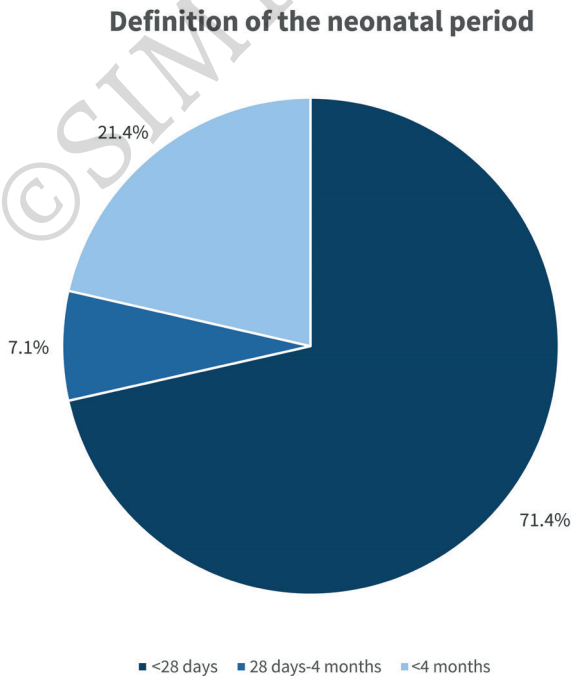


Figure 2 - Definition of the neonatal period
Description of the definition of the neonatal period: “within 28 days from birth” (<28 days) *vs* “between 28 days and 4 months from birth” (28 days-4 months) *vs* “within 4 months from birth” (<4 months).

patients under one year of age (two hospitals, 14.3%), patients undergoing stem cell transplantation (two hospitals, 14.3%), non-surgical patients (five hospitals, 35.7%), polytransfused patients (one hospital), patients with ABO-incompatible solid tumors (one hospital), and cases of maternal alloimmunization (one hospital). Additionally, pre-transfusion tests for newborns were also conducted on maternal plasma/serum in ten hospitals (71.4%) (**Figure 3**).

Regarding platelet transfusion, the principle of ABO plasma-compatibility was applied in all facilities. If ABO-compatible PCs were unavailable, plasma-incompatible PCs were transfused anyway in 3 hospitals (21.4%), while in 4 hospitals (28.6%), incompatible PLTs were transfused only if the isoagglutinin titer was below a predetermined cut-off (1:64 in 3 cases, 1:100 in 1 case). In 7 hospitals (50%) ABO plasma-incompatible PCs were never transfused. In the case of RhD-negative recipients, in 2 hospitals (14.3%), only RhD-negative PCs were assigned, in 4 hospitals (28.6%), RhD-positive units were assigned to female patients associated with prophylaxis with anti-RhD Ig, in all other cases (57.1%), RhD-positive units can be assigned to all Rh-negative patients without the adoption of additional measures (**Figure 4**).

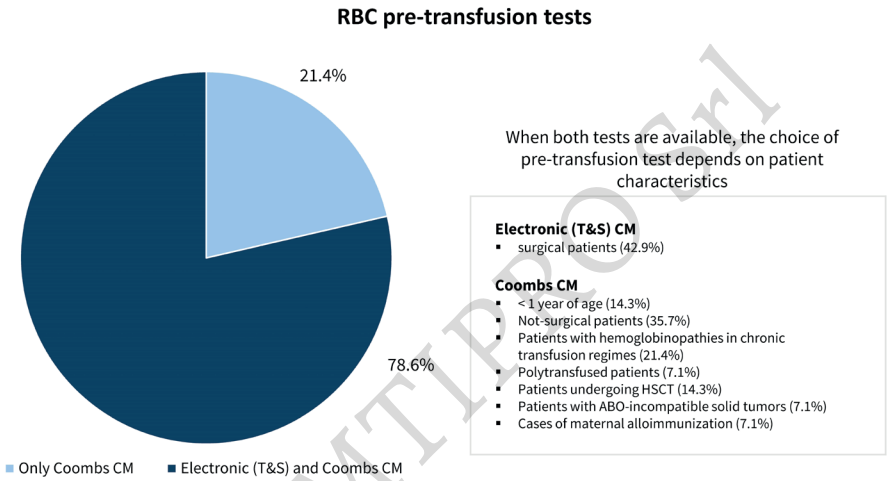


Figure 3 - RBC pre-transfusion tests
Representation of transfusion policy in relation to red blood cells (RBC). Use of electronic cross-match (Type and Screen [T&S]) and Coombs cross-match, and characteristics of the patients in whom these tests are used.

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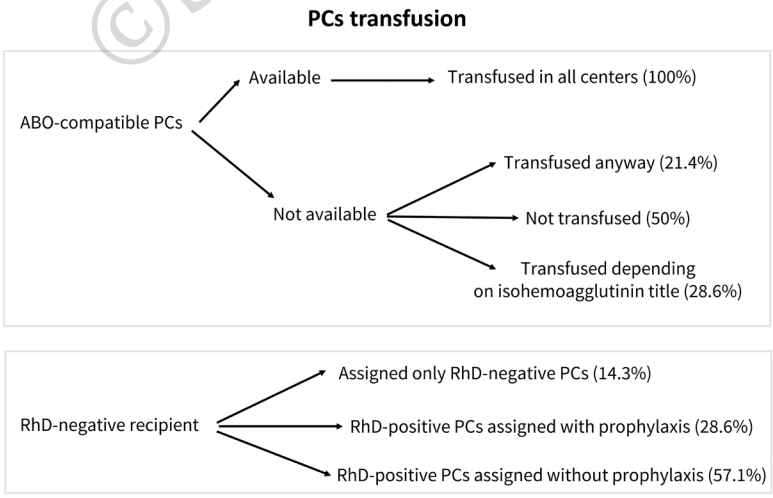


Figure 4 - PCs transfusion
Representation of the transfusion policy for platelet concentrates (PCs) in relation to ABO compatibility and RhD-negative recipients.

Available blood products

All facilities supply leukodepleted pRBCs. Autologous blood was collected and distributed in 5 centers (42.9%). Reconstituted whole blood, prepared from RBCs suspended in plasma, was available on demand in 9 hospitals (64.3%).

Regarding second-level processing, open-circuit RBC washing was available in 8 centers (57.1%), while closed-circuit RBC washing was available in the remaining 6 centers (42.9%). The primary indication for RBC washing was a history of allergic/anaphylactic reactions or IgA deficiency.

Platelet concentrates (PCs) from apheresis or buffy coat pools were available in all facilities. Pathogen-inactivated PCs were available in 2 hospitals (14.3%). Additionally, PC volume reduction was available in 3 hospitals (21.4%), with one hospital plasma-reducing all PCs in case of pediatric transfusion, regardless of patient age or clinical condition. PC washing was available in 7 hospitals (50%). The main indication for PCs washing was a history of allergic/anaphylactic reactions, IgA deficiency, or ABO incompatibility between donor and recipient.

Irradiated blood components

Irradiated blood components were available in all participating facilities. Nine hospitals had an on-site irradiator operational 24 hours a day. In the remaining hospitals, irradiation was conducted by other facilities: in two cases, irradiated blood components can be obtained as needed, while in three hospitals, the treatment must be scheduled.

All hospitals adhere to current national and international indications for blood component irradiation. In addition to current indications, some institutions required irradiation for all oncohematology patients, irrespective of the underlying disease or current therapies, and in one case blood component irradiation was required for patients with Down syndrome.

Following irradiation, blood products were transfused within varying timeframes based on patient age and weight: in one hospital (7.1%) all irradiated blood products were transfused within 6 hours; in six hospitals (42.9%) within 24 hours; in one hospital within 48 hours; and in one hospital, within 5-7 days after irradiation. In the remaining centers (35.7%), a general limit of 28 days after collection was applied.

Prevention of CMV infection

Regarding the prevention of CMV infection transmission, leukodepleted products were considered CMV-safe in 11 hospitals (78.6%). In 3 hospitals (21.4%), blood units were screened for CMV antibodies. Out of these, in two cases (14.3%), both pRBCs and PCs from CMV-negative donors (IgG/IgM negative) were available, and in 1 (7.1%) hospital only pRBCs from CMV-negative donors were available (**Figure 5**).

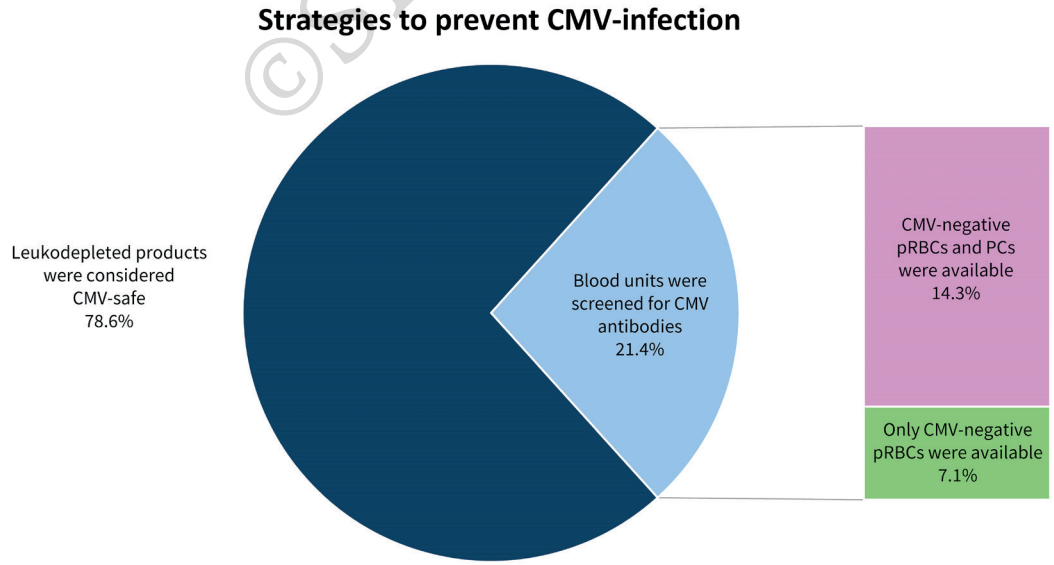


Figure 5 - CMV-infection prevention strategies
Representation of strategies aimed at preventing CMV infection transmission.

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Prevention of hyperkalemia

In all centers adverse events related to hyperkalemia were minimized by transfusing units collected from less than 5 to 7 days in patients weighing <10 kg.

Transfusion dose of RBCs and PLTs

The dose of pRBCs to be transfused was calculated based on the patient's weight, and aliquots were prepared as required by the transfusion service. Except when a specific dose is requested by the ward physician, the dose is determined by the blood bank physician.

In 4 hospitals (28.6%), the pRBC dose was 10 mL/kg, in 2 hospitals (14.3%) it was 15 mL/kg, and in 1 hospital it was 20 mL/kg. In 6 hospitals (42.9%), the volume to be transfused was always calculated and requested by the ward physician. In the remaining hospital, no aliquots were prepared, and the entire unit was given to the requesting ward regardless of the patient's weight.

The dose of platelet PCs was calculated based on the patient's weight in 10 hospitals (71.4%): in 6 hospitals (42.9%) the dose was 5-10 mL/kg, in 4 hospitals (28.6%) it was 0.5×10^{11} platelets/10 kg. In 1 hospital, the platelet dose was calculated according to body surface area and varies depending on whether the patient was hospitalized or not: if patients were hospitalized the dose was 1.1×10^{11} platelets/m^2, while for outpatients, the dose was 2.2×10^{11} platelets/m^2. In the remaining hospitals, PCs units were always aliquoted as 50% of the volume of a standard apheresis PC regardless of the patient's weight and correct dose was calculated in the ward.

Massive transfusion

The protocol for massive transfusion of blood components was available in 8 centers (57.1%). In 4 hospitals (28.6%) it was applied a fixed ratio of RBCs, PLTs and FFP of 1:1:1. In 4 hospitals (28.6%) transfusion was guided by the outcomes of viscoelastic results. In the remaining hospitals (42.9%), the ratio of blood components to be transfused was evaluated on a case-by-case basis, with no specific protocol in place.

DISCUSSION

All hospital blood banks that participated in the survey provide specific blood components for children. This demonstrates a general awareness of the unique aspects of pediatric transfusion. However, different rules and requirements were applied, both in blood component preparation and processing, as well as in the immunohematology aspects of transfusion practice. This is evident in the case of neonatal age definition, blood component dosage, particularly for platelets, indications for blood component irradiation, and platelet compatibility rules. The use of type and screen as a compatibility method for RBCs varies among different blood banks. In some cases, practices do not appear to be evidence-based but rather based on local customs, such as the indication of irradiated products for children with Down syndrome or the universal volume depletion for platelets.

The survey findings share some similarities and differences with those of the AABB survey[14], thus confirming the variability in blood bank practices regarding pediatric transfusions. Similarities with the AABB survey include the prevention of CMV transmission and practices related to irradiated blood component. Ant-CMV IgG/IgM antibody screening in donors is today applied by a minority of center, while the majority rely on CMV safe leucoreduced products. As far as irradiated RBC components are concerned, variability in the maximum storage times after such treatment were highlighted in both surveys. Although available in both regions, the washing treatment of RBCs is primarily intended to prevent hyperkalemia in the AABB survey, while in the Italian survey, it is aimed at preventing allergic reactions and in cases of IgA deficiency. In Italy hyperkalemia prevention for low-weight patients is obtained mainly transfusing RBCs collected within <5-7 days, without further processing. Policies regarding platelet concentrates ABO and Rh compatibility rules were not consistent among participating centers. Pathogen-reduced platelet concentrates are available in a minority of blood banks as emerged in both surveys. Although not directly addressed by the surveys in US a FDA guidance[17] recommends additional measures, including bacteria testing, to minimise the risk of bacterial contamination of platelet concentrates, while in Italy, apart from the limited utilization of pathogen reduced products, none of such strategies are known to be implemented[18].

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A major strength of the present survey is a high response rate of hospitals involved that provides a good representation of pediatric transfusion practices in the country. The response rate was significantly higher than that observed in the AABB survey (78.5 *vs* 15.8%), although it was primarily limited to the Italian Association of Pediatric Hospitals network, that includes the majority of metropolitan centers, the survey did not encompass all hospitals performing pediatric transfusions, and especially the peripheral ones were not included in this survey.

CONCLUSIONS

Pediatric patients cannot be regarded as "miniature adults", and a thorough comprehension of the unique aspects of blood component transfusion in children is crucial in contemporary medicine[19]. Many of the blood bank practices investigated in the survey, both in the communicable disease transmission prevention and in the immunohematology and biochemical risks reduction strategies, may impact on blood safety for pediatric patients[20-25], and especially for the most vulnerable ones. Further future high-quality studies are needed to clarify some of the most controversial issues in pediatric blood bank transfusion practice. In the meantime, enhancing the exchange and sharing of information and results among blood bank professionals and pediatricians, could facilitate the identification and dissemination of best practices among the diverse transfusion centers that supply blood components to Italian pediatric hospitals.

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ACKNOWLEDGMENTS

We wish to thank all the Institutions for responding to the survey.

FUNDING AND RESOURCES

This work was supported by the Italian Ministry of Health with Current Research funds.

AUTHORS' CONTRIBUTIONS

PB, MV, FB, VA, NB, MVM, GT, LC, and MLR designed the study, acquired, and analyzed the data. PB and MV also drafted the initial manuscript, while MLR critically reviewed it for important intellectual content. RA, MDV, MM, BC, AO, SP, FP, EP, CA, TT, SV, and OP collected data, critically reviewed the manuscript, and approved the submitted version.

The Authors declare no conflict of interest.

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