Use of blood and blood components and derivatives in newborn infants

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Abstract

Objective: to describe the current rationale for the transfusion of blood, blood components, and plasma derivatives in term and preterm infants.

Sources: selection of relevant medical articles published within the last ten years.

Summary of the findings: peculiar characteristics and special care concerning exchange transfusion, transfusion of red blood cells, platelets, granulocytes, and fresh frozen plasma were described. The recommendations for the use of hematopoietic growth factors, and plasma derivatives such as fibronectin, immunoglobulins, and albumin were also evaluated.

Conclusions: the authors comment on the recommendations and contraindication of blood transfusions, and warn against the limitations and hazards involved.


Introduction

Transfusion of blood, blood components or derivatives is part of the therapeutic arsenal that provides advanced support to babies at risk in neonatal intensive care units, especially in the treatment of hemolytic disease of the newborn (HDN).

newborns constitute the group of patients that take up most of the supply of blood and blood components in children’s hospitals. The smaller their weight and gestational age, the bigger their needs for transfusion.1

Whole blood for exchange transfusion

Exchange transfusion (EXT) is the replacement of the blood of the newborn, through removal of multiple aliquots, with the same amount of blood from a homologous donor.2

EXT can be carried out early based on previous history of kernicterus in other newborns from the same mother, and on hydrops of the fetus diagnosed by prenatal exams.

The objective of EXT in HDN is to correct anemia, reduce titer of circulating maternal antibodies, remove sensitized erythrocytes and replace them for nonsensitized erythrocytes, and remove nonconjugated bilirubin before diffusion to the tissues.

EXT is indicated for newborns in cases of HDN due to maternal-fetal erythrocytic antigen incompatibility; neonatal hyperbilirubinemia caused by hereditary erythroenzymopathy (G-6PD and pyruvate kinase deficiency); congenital structural defects of the erythrocytic membrane (hereditary spherocytosis and elliptocytosis); disseminated intravascular coagulation and severe septicemia, as an adjuvant; and, in neonatal alloimmune thrombocytopenia,
Whole blood or EC used in composition of RWB must have been collected within less than 5 days (several services use blood between 3 and 7 days of collection), must not contain hemoglobin S (Hb S), and must be submitted to gamma irradiation (2,500 rads) a few hours before the procedure.

Two basic principles guide the specific choice of products according to the presence of antigens/antibodies of erythrocytic systems:

1. Erythrocytes to be used in transfusion must be compatible with the mother’s serum.
2. FFP must be compatible with the erythrocytes of the newborn.

These principles are valid for choosing products in each and every situation of maternal-fetal incompatibility.

- **ABO antigen incompatibility**: occurs frequently when the mother is “O” and the newborn is “A”, but other combinations are also possible. In this case, the EXT should be carried out with RWB with EC “O”, Rh equal to that of the newborn with low titer or washed anti-A, and reconstituted with FFP “A”.

- **Rh antigen incompatibility**: EXT should be carried out with ABO-compatible whole blood, negative for the Rh antigen against which the antibody reacts; or with RWB with ABO-compatible erythrocytes negative for the Rh antigen against which the antibody reacts, and with isogroup FFP - preferably all from the same donor.

A sample should be collected from the unit of whole blood (WB) or reconstituted whole blood (RWB), preferably without opening the system. Quality control procedures should be observed. Table 1 presents laboratory indices for safe EXT.

<table>
<thead>
<tr>
<th>Newborn category</th>
<th>Bilirubin levels (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-term newborn</td>
<td>18-22</td>
</tr>
<tr>
<td>With hemolysis</td>
<td></td>
</tr>
<tr>
<td>With risk factors for bilirubin encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Healthy full-term newborn</td>
<td>&gt;22</td>
</tr>
<tr>
<td>Pre-term and/or low-weight newborn</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>With hemolysis</td>
</tr>
<tr>
<td>&lt;1,500</td>
<td>13</td>
</tr>
<tr>
<td>1,500–1,999</td>
<td>16</td>
</tr>
<tr>
<td>2,000–2,499</td>
<td>18</td>
</tr>
</tbody>
</table>

**Note**: Hemolysis = Hb < 13 mg/dl, reticulocytes > 5%, reduction in Hb level.

**Figure 1** - Indirect bilirubin levels suggested for the recommendation of exchange transfusion.

During EXT, with the removal of bilirubin there is a redistribution of bilirubin from the extravascular to the intravascular space. This balance occurs simultaneously with EXT so that at the end of the procedure, despite the fact that 87% of the erythrocytic mass was replaced, the serum level of bilirubin is reduced only 40 to 50%. In this sense, the slower the procedure, the greater the decrease in bilirubin (5 ml/kg/3 min).
A second EXT is usually necessary in 44% of cases of HDN due to Rh incompatibility, and in 17% of cases due to ABO incompatibility.4

The main complications of EXT are embolism; thrombosis; arrhythmia due to volume overload; cardiac arrest; acid-base disorders (metabolic acidosis soon after the procedure, and metabolic alkalosis 3 hours later) and hydroelectrolytic disorders (hyperkalemia, hypocalcemia, hypocalcemia and hypomagnesemia).6 Mortality attributed to the procedure decreased from 4.4% in the 1960s to between 0.3 and 1.3% in the 1990s. Thrombocytopenia caused by pathology affecting the newborns, or by the EXT itself, requires transfusion of platelet concentrates after EXT is carried out.

**Transfusion of erythrocyte concentrates (EC)**

The high frequency of anemia among newborns is mainly due to iatrogenic causes,5,7 such as excessive collection of samples for laboratory tests.

Other causes of anemia in the neonatal period are late-onset anemia of the premature infant, occult bleeding, insufficient erythrocyte production (Blackfan-Diamond and Shwachman-Diamond syndromes).

Newborns with respiratory failure, bronchopulmonary dysplasia, apnea or irregular respiratory rhythm, or those on oxygen therapy or mechanical ventilation, may benefit from small-volume transfusions of EC.

The requirements of erythrocyte transfusion of preterm newborn infants are greater than those of term newborns. Hemoglobin levels used for indication of transfusion for preterm newborns are higher than those for term newborns.1

Indication8 of transfusion of EC is carried out according to presence or absence of risk factors associated with anemia, such as respiratory failure and infectious and hemorrhagic processes. Newborns with associated risks receive transfusion of higher serum levels of hemoglobin than newborns without risks. The age and maturity of the newborn are also parameters used to indicate transfusion of red blood cells.1 Figure 2 presents the experience reported at several services.9 This figure can be used as a helpful guideline for indication of EC transfusion according to serum hemoglobin and other parameters often involved in the decision, such as: associated risk, gestational age at birth, and postnatal age.

**Selection of blood group**

The determination of the ABO human phenotype depends on the presence of antigens and antibodies (isoagglutinins). At up to 4 months of age, the expression of these antigens can be incomplete and the antibodies detected are usually originated by the mother.

In these first four months, what guides red blood cell transfusion in children is the compatibility with maternal serum. The use of a blood sample from the mother can replace the need for collecting a sample from the baby for compatibility tests. Only antibodies of IgG class can cross the placental barrier; in this sense, if a sample from the mother is not available, reverse typing on the child’s sample should be carried out using antiglobulin (Coombs’ serum) to increase test sensitivity.

However, when the child expresses antigens “A” and/or “B”, and there is no maternal-fetal incompatibility, transfusion of erythrocytes of the same type than that of forward typing (isogroup transfusion) is recommended (Table 2).

The choice of isogroup transfusion is based on the fact that approximately 40% of type “O” blood donors have very high titers of isohemagglutinins. These titers present the risk of causing hemolysis due to lower incompatibility in children, even after extraction of plasma for production of EC. If the hemotherapy service does not determine the titers of antibodies of type “O” donors (not required in Brazil), the indiscriminate transfusion of “O” erythrocytes is not recommended, even in the case of adults.10

Children younger than 16 weeks do not have the ability to develop irregular antibodies against erythrocytic antigens. Hence, the American Association of Blood Banks (AABB) has considered unnecessary the repeated screening for irregular antibodies in children younger than 16 weeks of age and who have previous negative screening results, even if the child has received transfusion of globules in the period.11 This recommendation, together with the use of micromethods in blood banks that use a smaller number of samples, constitute efforts to save the newborn from the

<table>
<thead>
<tr>
<th>Associated risk</th>
<th>Gestational age at delivery</th>
<th>Age (days of life)</th>
<th>Hb (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>≤37 weeks</td>
<td>≤7</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;37 weeks</td>
<td>≤7</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;7</td>
<td>11.0</td>
</tr>
<tr>
<td>Absent</td>
<td>≤37 weeks</td>
<td>≤7</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;37 weeks</td>
<td>≤7</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;7</td>
<td>9.0</td>
</tr>
</tbody>
</table>

**Figure 2** - Parameters used for the recommendation of blood transfusion in newborns
spoliation due to phlebotomy and, consequently, to reduce transfusion requirements.

**Posology and administration**

The volume of the concentrate of globules to be transfused depends on the desired results (difference between desired and preexisting serum hemoglobin), on the child’s volemia (in relation to weight), and on the characteristics of the available products. For example, whole blood and concentrates with additive solutions present lower concentrations of hemoglobin per ml than CPDA-1 concentrates. The performance of products with lower concentrations of hemoglobin per ml is proportionally lower.

**EC in CPDA-1:** the most frequently used volume is of 10 ml per kg of weight. This volume should provide 3.3 g/dl of hemoglobin. For a 1.0 g/dl increase in hemoglobin, it is necessary to transfuse 3 ml of EC in CPDA-1 per kg of weight.

**Concentrates in additive solution:** additive solutions conserve blood components for a longer period of time with fewer storage lesions than those in CPDA-1. The use of these solutions has been increasing in newborns. For results similar to those with concentrates in CPDA-1, a volume of 15 to 20 ml per kg of weight is suggested due to lower hemoglobin concentration in these products.

Special attention should be paid to volume since there are considerable risks for overload, especially in children with cardiac or renal failure. Volumes should be used between 10 and 20% of the child’s volemia, approximately.

Children with respiratory failure may present decrease in oxygen saturation during transfusion. In these cases, the speed of transfusion should be reduced or transfusion should be interrupted.

The infusion of other fluids simultaneously with transfusion is not allowed. This is a strong recommendation based on the fact that certain drugs can operate as agonists to the anticoagulant solution (e.g.: solutions rich in Ca++. This recommendation is also useful as a prophylaxis for the risk of volume overload. Glucosed serum at 5% is hypotonic and can cause hemolysis to some extent in the blood that is being transfused. Adverse effects of the transfusion can be masked by simultaneous use of certain drugs (e.g.: corticoids, antihistaminics). Other drugs can also cause adverse effects that may be mistakenly attributed to transfusion (e.g.: urticarial reactions to vancomycin, amphotericin fever).

However, in certain occasions it is impossible to follow these recommendations. Examples include cases of transfusion during use of vasoactive drugs (Ex.: dopamin, nitroprusside), antiepileptics, and other drugs whose administration cannot be interrupted. In these cases, the transfusion should be carried out at least through a different pathway.

In order to avoid volume overload, alternative resources can be used, such as: administration of diuretics and slower infusion of smaller aliquots.

Children on the brink of volume overload will be, at least, normovolemic; thus, there is no reason for transfusion of large volumes in shorter periods of time. In these situations, anemia can be corrected slowly.

<table>
<thead>
<tr>
<th>Mother</th>
<th>Newborn</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Forward typing</td>
<td>Reverse typing/ Coombs’ test (antibodies)</td>
</tr>
<tr>
<td>O</td>
<td>A</td>
<td>anti-A, anti-B</td>
</tr>
<tr>
<td>B</td>
<td>anti-A, anti-B</td>
<td>O</td>
</tr>
<tr>
<td>O</td>
<td>anti-A, anti-B</td>
<td>O</td>
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<tr>
<td>A</td>
<td>A</td>
<td>anti-B</td>
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<tr>
<td>B</td>
<td>anti-B</td>
<td>O</td>
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<tr>
<td>AB</td>
<td>anti-B</td>
<td>A</td>
</tr>
<tr>
<td>O</td>
<td>anti-B</td>
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</tr>
<tr>
<td>B</td>
<td>B</td>
<td>anti-A</td>
</tr>
<tr>
<td>A</td>
<td>anti-A</td>
<td>O</td>
</tr>
<tr>
<td>AB</td>
<td>anti-A</td>
<td>B</td>
</tr>
<tr>
<td>O</td>
<td>anti-A</td>
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<tr>
<td>AB</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>-</td>
<td>AB</td>
</tr>
</tbody>
</table>
The alternative use of smaller aliquots is justified by the limitation of 4 hours for infusion of a transfusion after the system is open, independently of the volume of the system. This period was determined according to the risk for spontaneous contamination with bacteria.

There are no minimum time limits for transfusion of one unit of EC. In the case of children, the limit is usually determined by the capacity of the pathway, which is often scalp.23 The ideal flow is of approximately 2.5 ml/min.

If the flow of is highly limited by the pathway, it is possible to increase the original volume with 20% saline solution for dilution purposes. This procedure can be carried out by the nursing staff, at bedside, and following normal asepsis procedures - especially if the transfusion equipment uses a burette attached to the system (ideal for transfusion with newborns). Diluting the concentrate may allow for easier infusion.

Under no circumstances can the bag of blood components be perforated outside the appropriate place for connection to the equipment.

In case the equipment does not employ a burette, additional volume for dilution can be added using Y-shaped equipment. Ideally, the additional fluid should be handled using laminar flow or transfusion bags with sterilized connections.

In the absence of the above resources, after 4 hours of the system being open at bedside, transfusion should be interrupted and the blood bank informed. It is then possible to evaluate the residual volume and prepare another unit of EC.

Every transfusion must be supervised by the nursing staff, who must check vital signs before starting transfusion. Though abrupt changes in vital signs during transfusions are not common in newborns, they can be an indication of a reaction to the transfusion.

The use of equipment with filters for macroaggregates (140 to 170 micrograms) is mandatory due to the risk for embolism and obstruction of the system by small clots and debris of the unit.

EC can be used for transfusion at room temperature. However, it is important to mind places where the room temperature is very low or very high without control of temperature variation in the hospital. EC stored at 4 degrees Celsius will reach its balance at room temperature (between 20 and 30 degrees Celsius) in 20 minutes (which allows time for pretransfusion tests). In the case of small-volume transfusions, EC at room temperature will reach body temperatures very rapidly.

The heating of units of EC or whole blood for transfusion is justified when using EXT or when submitting the child to massive transfusion. That is because rapid infusion at low temperatures may lead to cardiac arrhythmias such as sinus bradycardia and other complex ventricular arrhythmias. There are heaters especially designed for this purpose, which interpose the system and maintain a constant temperature at 37 degrees Celsius in the line of infusion.

In newborns, the ability to maintain body temperature is compromised. Blood components at low temperatures, when infused, may cause deep metabolic alterations with significant morbidity (apnea, hypotension, hypoglycemia).

Transfusion of platelet concentrates (PC)

Platelet concentrates (PC) are the second most used type of blood component in Neonatology,13,14 PC are used for treatment of hemorrhages caused or in combination with numeric and/or functional reduction of platelets. Transfusion of PC can also be indicated prophylactically before the hemorrhage occurs.15

Prophylactic transfusion of platelets is indicated when clinical and laboratory findings suggest high risk for spontaneous bleeding. Spontaneous bleeding in the central nervous system caused by disturbance in homeostasis are related to high mortality and morbidity rates.16

Thrombocytopenia in the neonatal period can affect 25 to 40% of newborn infants in neonatal ICUs and 0.2% of “normal” newborn infants in nurseries.

The transfusion of PC should be indicated every time there is active bleeding due to qualitative and/or numeric platelet deficiencies, independently of the etiology. In this sense, it is important that blood banks offer the adequate conditions in order to meet the demands of patients, and the appropriate products for each case. In turn, there is still a lot to be said as to what concerns the matter of prophylactic transfusion of platelets.14

The factors associated to platelet deficiency that can affect the homeostasis of newborn infants are: immature coagulation system, physiological deficiency of vitamin-K-dependent factors, significant reduction in the ability to produce thrombin, natural difficulty in mobilization of intraplatelet Ca++, increased vascular fragility, and natural maternal anticoagulant that traverses through the placental barrier.

These risk factors contribute to the fact that most preterm infants with platelet monitoring below 60,000 platelets/mm³ present intracranial bleeding in the first 72 hours of life. In this sense, prophylactic transfusion of platelets in stable, preterm newborns is indicated when platelets are less than 50,000 platelets/mm³ and for risk, preterm newborns, when less than 100,000 platelets/mm³.17

Healthy term newborns rarely bleed spontaneously, even when platelets are 10,000/mm³. Others14 have shown that most North American hospitals indicate prophylactic transfusion of platelets in term newborns without associated risk at approximately 20,000 platelets/mm³, and in preterm newborns at 30,000 to 50,000 platelets/mm³.

The presence of disturbance of secondary homeostasis (coagulopathy) associated with platelet deficiency is an additional factor for increasing indication of prophylactic transfusion of platelets. In cases of surgery or other invasive procedures, the platelet count should be maintained above 50,000 platelets/mm³. Moreover, in cases of cardiac or
neurological surgery, it should be above 100,000 platelets/mm³.

Another important situation is dilutional platelet deficiency after EXT. The transfusion of PC is indicated if platelet count is below 50,000 platelets/mm³ following EXT.

ABO compatibility in platelet transfusion for newborns should be observed whenever possible. ABO system antigens can be found in platelets; thus, the transfusion of incompatible platelets (greater incompatibility) can affect transfusion results. In cases of smaller ABO incompatibility, there is incompatibility of the plasma in which platelets are in suspension and the titers of isohemagglutinins can result in risk for hemolysis for the newborn.

Rh compatibility can be ignored for PC transfusions in the neonatal period. Despite the indication for transfusion of ABO-identical platelets in detriment of the Rh factor, there is the possibility that blood banks may not have the necessary products. In these cases, we suggest the use of ABO-incompatible plasma PC with lower titers of isohemagglutinins (upper limit = 512).

The calculation of the volume for PC transfusion depends on the difference between current and desired platelet monitoring, on the child’s volemia, on the platelet concentration of the product used, and on the standard platelet results after one hour (0.80).

The calculation of the volemia of newborns accounts for birth weight and gestational age at birth. Preterm infants present a different relation between weight and volemia, which can reach 110 ml/kg.\(^{16}\)

The time of PC infusion depends on circulatory overload, on cardiac and renal functions, and on relation between blood component volume and the child’s volemia. In general, the time of infusion varies from 20 to 30 minutes, but never more than 4 hours after opening of the system.

The risk for bacterial contamination in PC is much higher than in EC since storage between 22 and 24 degrees Celsius favors spontaneous proliferation of bacteria in the earlier. Transfusion of platelets contaminated with bacteria can result in shock and disturbance of coagulation. In case of units suspected with contamination, samples should be sent for bacterioscopy and culture. Hemoculture should be carried out on the child as well.

**Transfusion de fresh frozen plasma (FFP)**

Transfusion of fresh frozen plasma (FFP) is uncommon for newborns. FFP is indicated\(^{18}\) especially in the replacement of vitamin-k-dependent factors (II, VII, IX, X, protein C, and protein S) in newborns with prolonged prothrombin time and active bleeding; or in those requiring emergency surgical procedures. It is also indicated for reverting alterations of homeostasis caused by EXT in which deficiency of the factor is the main alteration. In disseminated intravascular coagulation (DIC), the treatment should be aimed at the baseline disease, and replacement therapy is indicated in cases of hemorrhage.

In cases of C1 esterase deficiency, FFP is indicated as a prophylactic therapy. It should be administered before surgery to prevent laryngeal edema in newborns with hereditary angioedema. In these cases, it is used when there is no availability of the specific concentrate and when carrying out surgery with extracorporeal circulation, for example, in newborns being submitted to surgical correction of congenital cardiac malformations.

FFP is not indicated for use as volume expander and as nutritional supplement. It is also not indicated for neutralization of the effect of heparin in extracorporeal circulation. In this case, the use of protamine is indicated.

**Transfusion of granulocyte concentrates (GC)**

Despite the continuous augmentation of the arsenal of antimicrobials and of the increasing development of colony stimulating factors (G-CSF and GM-CSF), infection is still a common and frequently fatal complication in neutropenic newborns.

Due to rapid deterioration of the function of granulocytes during storage, GC should be infused as soon as possible after collection; preferably after a maximum 6 hours. It is suggested that the product be submitted to gamma radiation for transfusion-associated graft-versus-host disease (TA-GVHD) prophylaxis. GC should be slowly infused at 1-2 x 10\(^{10}\) cells/hour. Premedication with antihistaminics and/or antipyretics is recommended.

Due to the large number of erythrocytes in GC, transfusion should be ABO-compatible. In case of ABO incompatibility between donor and receptor, the erythrocytes should be removed from the component by sedimentation before infusion.

Once granulocyte transfusion is indicated, it ought to be effectively administered. The recommended dosage for children is of 1.0-2.0 x 10\(^9\)/kg or 15 ml/kg/day of CG. Infusion should continue until endogenous recovery of the granulocytes or until the infection is cured. In turn, the infusion should be interrupted in case of noticeable worsening of the infection (despite transfusion of granulocytes using adequate doses) or of severe reaction to the transfusion.

The use of granulocyte therapy should be considered carefully before it is applied to neutropic newborns with severe bacterial or fungal infection; especially if the infection is refractory to combined, wide spectrum antimicrobial treatment, and chiefly if the newborn has congenital granulocyte dysfunction.

Newborns with polymorphonuclear count below 3.0 x 10\(^9\)/l can already be considered for granulocyte transfusion. Sepsis procedures should be assessed in all cases of newborns presenting infections and polymorphonuclear count below 3.0 x 10\(^9\)/l during the first week of life.
Several authors have reported the use of granulocyte transfusion in the treatment of neonatal septicemia. Out of six controlled studies aimed at assessing efficacy of granulocyte transfusion in the treatment of neonatal infections, four showed a higher survival rate in the group who received granulocyte transfusion in comparison to controls. However, these studies were carried out with a reduced number of patients and with heterogeneous populations and quality of transfused GC. Thus, the use of granulocyte transfusion in the treatment of neonatal septicemia is still controversial. Several neonatologists prefer using intravenous immunoglobulin or administration of G-CSF in adjunct treatment of neonatal infections.

It is still necessary that further controlled studies be carried out in order to determine the real potential of granulocyte transfusion in the treatment of infection of the newborn.

Hematopoietic growth factors are a family of glycoproteins with defined biologic specificity and with ability to stimulate proliferation and differentiation of hematopoietic cells of several lineages. These factors are increasingly being used in clinical practice and with all age ranges. Their use follows these objectives: restore adequate factor production, as in erythropoietin of anemia of prematurity; and increase factor concentration to levels above those of physiological conditions - this strategy is used to reduce periods of post-chemotherapy neutropenia.

In newborns with bacterial infections, the referred objectives would be desirable in the therapeutics.

Use of G-CSF and GM-CSF

G-CSF: the human G-CSF was purified in 1985; in 1987, it was first observed that the gene that codifies this factor is located in the chromosome 17 long arm. G-CSF is a protein which is consisted of 207 amino acids. It is naturally produced by monocytes, macrophages, endothelial cells, and fibroblasts. The recombinant form is made by the Escherichia coli from human gene DNA, and it plays the same role as the natural factor. This factor stimulates maturation and specific proliferation of cells that generate neutrophil granulocytes (CFU-G), and releases neutrophils from neutrophil storage pools into peripheral blood.

GM-CSF: known as Granulocyte-Macrophage Colony Stimulating Factor, the GM-CSF is of great help in the treatment of cancer patients who have been submitted to chemotherapy; it is also helpful after marrow transplant, aplastic anemia, and myelodysplastic syndromes - clinical conditions in which neutropenia requires that therapeutic dosages be reduced and, thus, of increased risk for infection. This factor stimulates proliferation of myeloid progenitor cells (colony forming unit-granulocyte and monocyte (CFU-GM) and colony forming unit- eosinophil (CFU-Eo)); and causes maturation and release of marrow neutrophil pools into peripheral blood. This is observed from 2 to 6 hours after administration of GM-CSF. Both factors - in addition to acting on the bone marrow - also have been reported to improve in vitro neonatal neutrophil physiologic activity; i.e. increasing chemotaxis, opsonization, phagocytosis, bacterial killing, and oxidative metabolism.

These two factors can be applied to newborns with neutropenia caused by pregnancy toxemia (48% to 50% of newborns born from hypertensive mothers present neutropenia soon after birth; out of which 14% develop sepsis during the course of neutropenia); with congenital neutropenias ( though rare, when present are difficult to be treated); and with infections associated with neutropenia. They can also be applied in improvement of neutrophilic function.

As to the use of stimulating factors in neutropenic babies from hypertensive mothers, a study was carried out with 9 neutropenic newborns (total number of neutrophils less than 1750/mm³) of mothers with preeclampsia (systolic pressure levels greater than 14 mmHg and diastolic levels greater than 9 mmHg). Patients were administered endovenous G-CSF at 10 µg/kg in 15-minute infusions for the first 24 hours of life. Next, babies received additional doses at 24-hour intervals in case neutropenia persisted. The authors observed that 8 out of the 9 newborns presented an increase in neutrophils count 6 hours after the first dose; this finding was statistically significant in comparison to initial values. The difference remained statistically significant for 72 hours, as indicated in Table 3.

Another study also reported the increase in neutrophils count after administration of G-CSF for preeclampsia-associated neonatal neutropenia. The study reported the increase in neutrophils in four newborns, three males and one female. Absolute neutrophil counts increased nearly fourfold within 48 hours; maximal values were recorded 7 to 10 days after treatment. The initial increase, according to the authors, is more due to a rapid release of circulating neutrophils than to cellular mitosis. The delayed increase in neutrophil count is more due to an increase in the pool of progenitor cells and to a facilitated mitosis. Thus, use of stimulating factors is responsible for a statistically significant increase.

<table>
<thead>
<tr>
<th>Time elapsed after G-CSF (hours)</th>
<th>Neutrophil count (x 10⁹/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.81 ± 0.77</td>
</tr>
<tr>
<td>6</td>
<td>6.47 ± 2.70*</td>
</tr>
<tr>
<td>24</td>
<td>7.77 ± 3.35*</td>
</tr>
<tr>
<td>48</td>
<td>5.85 ± 1.61*</td>
</tr>
<tr>
<td>72</td>
<td>4.10 ± 1.60*</td>
</tr>
<tr>
<td>120</td>
<td>4.19 ± 2.53</td>
</tr>
</tbody>
</table>

Count: mean and standard deviation.
* P< 0.001 compared to the count at 25 hours
increase in neutrophils count that occurs hours and days after administration to babies of hypertensive mothers. This is an important indication of use of these factors.

Stimulating factors are widely indicated for newborns presenting characteristics of congenital neutropenia (patients with Kostmann Syndrome, an autosomal recessive disease that causes important neutropenia); of neutrophils count always lower than 0.2 x 10/l; and of bone marrow examination indicating a halt in the development of these cells in the stages of promyelocyte or myelocyte. Most of these patients develop bacterial infections with severe outcome, including death. We had the opportunity to administer G-CSF to a neutropenic newborn female patient at the Neonatal ICU of the Children’s Institute at the Hospital das Clínicas. The patient presented severe neutropenia and sepsis caused by Pseudomonas aeruginosa with ecthyma (characteristic of this type of bacteria). After administering the stimulating factor at 5 µg/kg subcutaneously and on a daily basis, we observed an improvement of neutropenia and of the infection.

In relation to the use of stimulating factors in infections that occur together with neutropenia, such as neonatal sepsis, Ceccon et al. carried out a randomized, double-blind, placebo-controlled study at the Neonatal ICU of the Children’s Institute at the Hospital DAs Clínicas. The authors administered GM-CSF and placebo to 11 newborns with sepsis who had neutrophils count lower than 1,750/mm³. The study showed that there was a significant increase in neutrophils count after the use of 5 µg/kg of stimulating factor, subcutaneously, on a daily basis. The dose was administered until a count of 3,000 neutrophils/mm³ was attained in the experimental group, with a growth curve similar to that found in the literature; in other words, rapid growth in the first 24 hours and peak value on the eighth and ninth days of evolution. The authors observed a good tolerance to the stimulating factor, without adverse effects; however, the authors did not observe a statistically significant difference in the comparison of mortality and neutrophils count of the experimental and control groups. We understand that stimulating factors can contribute to treatment of newborns with sepsis and neutropenia, not only due to the reported increase in neutrophils count, but especially due to the increase in their function.

Miura et al. carried out a randomized, double-masked, parallel-groups, placebo-controlled trial of recombinant granulocyte colony-stimulating factor (rG-CSF) administration to 44 preterm neonates who had diagnosis of early-onset sepsis. In the study, patients received 10 microgram/kg/day of intravenous rG-CSF once daily for 3 days or placebo. The objective was to assess mortality and nosocomial infections up to two weeks after administration of the last dosage. Results indicated that administration of rhGM-CSF (5 microgram/kg/day) was administered to 30 of the patients for 7 consecutive days; whereas the other 30 patients received conventional treatment (controls). The objective of the study was to assess mortality rates and safety of the use of this colony-stimulating factor. The comparison of results of the experimental and control groups indicated that newborns presented good tolerance to GM-CSF without adverse effects; the mortality rate for the experimental group was 10%, which was statistically different from that of the control group (30%). We believe that further studies should be carried out before colony-stimulating factors are included in routine treatments of newborns with sepsis.

Early and late transfusion complications: prophylaxis and procedures

The transfusion of blood components can cause early and late-onset complications in newborns; however, there are ways to reduce risks. Though early posttransfusion reactions such as nonhemolytic and urticarial fever reactions are not common in newborns, these patients can present reactional hyperinsulinism and hypoglycemia. Surveillance of glycemia with reagent strips is recommended up to three hours after beginning the transfusion of erythrocytes. Frequent replacement of the glucose solution is also necessary.

In 1982, posttransfusion syndrome of the newborn exposed to multiple transfusions (including IT and EXT) was described. It is a benign syndrome that is not very frequently reported in the literature. The syndrome is characterized by transient maculopapular rash that can occur together with eosinophilia and trombocytopenia. It is equivalent to allergic reactions against homologous antigens.

The filtration of cell products (erythrocyte and platelet concentrates) with reduction filters greater than or equal to 3 log can protect the newborn against sensitivity to HLA antigens.

Severe hemolytic transfusion reactions due to ABO incompatibility are not frequent. In addition to fever, shivering, shaking, hyperemia, paleness, tachycardia, tachypnea and cyanosis, there can also be cases of discomfort and psychomotor agitation. All reactions to transfusion should be considered potentially severe. There are also examples of hemoglobinuria (due to intravascular hemolysis), coagulation disorders, disseminated intravascular coagulation (DIC), hypotension, shock, and acute renal failure. Treatment of these complications requires intensive care for the patient since mortality related to ABO-incompatible transfusions is high. Most posttransfusion hemolytic reactions occur during mixtures of units administered to different patients, and mistakes in identification of the receptor.
Precautions to avoid these types of mistakes rely on paying full attention to correct identification of samples, of erythrocyte concentrates, and of newborns. In this sense, it is recommended that the latter always be wearing an identification bracelet.

Newborns do not present late-onset hemolytic reactions (anamnestic reactions) because these reactions are mediated by performed immune antibodies. The titers of these antibodies increase after transfusion of globules with incompatible antigens.

Among the late-onset complications there is the transmission of well-known infectious and contagious agents, such as: human hepatitis B and C viruses, TTV, CMV, HTLV1 and 2, HIV, parvovirus, Treponema pallidum (syphilis), Borrelia sp (lyme disease); and also of parasitosis, such as: malaria, Chagas’ disease, babesiosis, Kala azar, and toxoplasmosis. Creutzfeld-Jacob disease, which is caused by a prion, can also be transmitted through transfusion. An alternative to reduce the use of homologous blood transfusion in newborns is the use of human recombinant erythropoietin (rHuEPO), which is recommended in the prophylaxis of late-onset anemia of the newborn.

The use of products with poor concentrations of leukocytes or without leukocytes reduces the risk for transmission of infectious agents such as the cytomegalovirus (CMV). The risk for complications due to CMV infection in newborns is high, especially in premature newborn infants. The blood components of donors with CMV-negative serology should be separated for use with newborns weighing less than 1,200 g or when mother and child present CMV-negative serology. Cell products filtered up to 24 hours after collection (reduction filters greater than or equal to 3 log) offer protection against CMV that is equivalent to use of products with negative serology.

New preservative solutions and sterilized connection devices allow for repeated use of aliquots from the same blood component for the same receptor. The advantages of less exposure to different homologous donors (smaller immunological and infection risks) surpass the disadvantages of the use of the same unit of blood with longer duration of storage. Storage lesions are negligible. Thus, especially in the case of newborns, whose average required volume for each transfusion is around 25 ml, the use of multiple aliquots of the same unit is extremely advantageous.

### Blood derivatives

**Fibronectin**

Fibronectin is a glycoprotein with high molecular weight (440 kD) found in insoluble form on the cellular surface of neutrophils, and in soluble form in plasma at 220 µg/ml in the neonatal period; in adults, it is found at 350 µg/ml.

It presents important immunological properties since it stimulates endothelial adherence, increasing fagocytosis of the opsonized material in stimulated neutrophils; facilitates neutrophil activation at the site of the inflammatory process; stimulates the reticuloendothelial depuration of bacteria and immune complexes.

Purified human fibronectin is removed from cryoprecipitates of human plasma. This is a promising therapeutic approach for the treatment of newborns with sepsis; however, it is still in the initial stages of clinical evaluation.

### Immunoglobulin

The number of premature newborns who survive in Neonatal ICUs is increasing. However, these infants are also being increasingly exposed to hospital microorganisms and invasive procedures, which make them more susceptible to severe infections. In this sense, sepsis is the main type of infection and is responsible for high mortality and morbidity rates of these children.

It is known that the greater part of immunoglobulin G (IgG) is acquired by the fetus in the second half of the third semester of gestation. This immunoglobulin is acquired through placental transfer. Premature newborn infants miss the opportunity to receive IgG from their mothers; thus, they can present severe hypogammaglobulinemia, which results not only from low IgG levels in the first days of life, but also from the deterioration of IgG acquired from the mother and delay in production of IgG after birth. Several studies have been carried out with the objective of assessing the ability of endovenous gammaglobulin to prevent nosocomial infections in premature newborns. Moreover, several reviews, including metaanalyses of published material, suggest that infections caused by microorganisms in hospitals can be reduced by the prophylactic use of IgG.

Baker et al. (1992) carried out a multicenter, double-blind study with 588 newborns with birth weight of 500 to 1,735g; the authors assessed mortality, morbidity, and nosocomial infection. They concluded that the use of IgG EV was efficient in reducing incidence of nosocomial infections.

Nosocomial infections are the most important cause of morbidity and mortality among premature newborns. The prophylactic use of immunoglobulin could contribute to reduce infection rates in these children. In this aspect, a prospective, controlled, multicenter study was carried out with 2,416 newborns, stratified according to birth weight (501 to 1,000 g and 1,001 to 1,500 g) and randomly assigned to an intravenous immune globulin group (n = 1,204) or a control group (n = 1,212). Infants weighing 501 to 1,000 g at birth were given 900 mg of immune globulin per kilogram of body weight, and infants weighing 1,001 to 1,500 g at birth were given a dose of 700 mg per kilogram. The immune globulin infusions were repeated every 14 days until the infants weighed 1,800 g. The authors observed Nosocomial infections of the blood, meninges, or urinary tract occurred in 439 of the 2,416 infants (18.2%): 208...
(17.3%) in the immune globulin group and 231 (19.1%) in the control group. Septicemia occurred in 15.5% of the immune globulin recipients and 17.2% of controls. The authors also observed that use of immune globulin therapy had no effect on respiratory distress syndrome, bronchopulmonary dysplasia, intracranial hemorrhage, the duration of hospitalization, or mortality. The incidence of necrotizing enterocolitis was 12.0% in the experimental group and 9.5% in the control group. The authors concluded that prophylactic use of intravenous IgG failed to reduce the incidence of hospital-acquired infections in very-low-birth-weight infants.

Lacy and Ohlson published, in 1995, the results of metaanalyses on the administration of intravenous immunoglobulin for prophylaxis or treatment of infection. Their objective was to verify the effectiveness of intravenous immunoglobulin administration to premature infants in the prevention and/or treatment of bacterial infection. After comprehensive analysis of the literature, the authors observed that the use of immunoglobulin for premature newborns did not interfere in mortality (death from all causes), in death rates due to neonatal infection, in the occurrence of sepsis or of necrotizing enterocolitis. Their conclusion was that routine administration of intravenous immunoglobulin to preterm infants is not recommended.

Ceconno et al. carried out a study with premature newborns presenting risk factors for infection. The study showed a statistically significant difference on the serum levels of IgG of infected and noninfected newborns with the same gestational age. Infected newborns presented serum levels of IgG at birth lower than 500 mg/dl (less than 5g/l). Recently, Sandenberg et al. evaluated the prophylactic use of intravenous immunoglobulin G (IVIgG) in the prevention of neonatal infections for preterm infants (gestational age less than 33 weeks) with umbilical cord blood IgG levels less than or equal to 4 g/L. Intravenous IgG or placebo (albumin), 1 g/kg body weight, was given on days 0, 3, 7, 14, and 21 to 81 infants, out of which those in the IVIgG group (n=40) had mean gestational age 27.7 weeks and birth weight 1.130 kg; infants with umbilical cord blood IgG levels greater than or equal to 4 g/L were used as controls. Infections were monitored until 28 days of life. The authors observed that infants who received IVIgG had no significant reduction in infectious episodes or mortality rate when compared with those given placebo. However, they observed that infants with a serum concentration of IgG greater than 4 g/L at birth had significantly fewer infectious episodes than infants with low serum concentrations of IgG (< or =4 g/L) at birth. The authors concluded that prophylactic use of IVIgG did not improve the immune competence in preterm infants with low serum IgG concentrations at birth. They also suggested that a spontaneously high serum IgG concentration at birth reflects placenta function and is an indicator of a more mature immune system capable of protecting the preterm infant against severe neonatal infections.

Thus, despite the controversy found in the literature, the group of newborns who can benefit from this therapeutic are those with birth weight less than 1,500g and/or younger than 34 weeks of gestational age with clinical status of infection; in these patients, the objective would be to attain serum levels similar to those of term newborns, in other words, around 700 mg/dl. Usually, the dosage administered is of 500 mg/kg (endovenously) in a 6-hour infusion, once a week, for 3 to 4 weeks. Serum levels should be checked before administration of the dosage.

Other uses for endovenous gammaglobulin are those against hematological autoimmune diseases, such as idiopathic and isoimmune thrombocytopenic purpura, hemolytic anemia, neutropenia, and other platelet deficiencies refractory to the treatment with platelet transfusion. The dose used for these diseases is 400 mg/kg/day for two to five consecutive days.

**Albumin**

Albumin is a protein that can be extracted from whole blood, plasma, serum or human placenta. At least 96% of the total protein of the final product is albumin, which is available in concentrations of 5.0%, 20%, and 25%, and contains 130 to 160 mEq/l of sodium.

Albumin is prepared from Cohn fraction V; and it is heated for at least 10 hours at 60°C in order inactivate the contaminating viruses.

- Its main uses in neonatology are:
  - in severe hypoalbuminemia;
  - as a volume expander in the treatment of newborns in shock after correction of hydration;
  - in volume replacement of newborns submitted to partial exchange transfusion due to blood hyperviscosity;
  - in diseases with extensive cutaneous damage with loss of protein through the skin, such as in burns and in patients with epidermolysis bullosa hereditaria.

The commonly used dose is of 1 g per kg through endovenous infusion. When used at 20% to 25% concentration, it should be infused for over 2 hours due to the risk for congestive cardiac failure.

**References**

Use of blood and blood components... - Diniz EMA et alii


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