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Neonatal thrombocytopenia: A review. II. Non-immune thrombocytopenia; platelet transfusion

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ABSTRACT
Non-immune thrombocytopenia is caused by multiple pathologies; the most common causes are extra- or intrauterine infections, whereas secondary cases result from other pathologies involved in the fetal-placental-maternal interface. This second article lists its causes and provides details of the different pathologies. Platelet transfusion is widely used in neonatology, both as treatment and as bleeding prophylaxis. However, there is no general consensus about the platelet count threshold that is convenient to indicate a transfusion or actual indications. Recent articles are commented regarding the different proposed strategies. The emphasis is on discussing the multiple adverse effects of platelet transfusions because knowledge about them is changing the paradigm for indications, suggesting that a much more restrictive policy is required.

Key words: *thrombocytopenia, newborn infant, infections, platelet transfusion, bleeding.*

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NON-IMMUNE THROMBOCYTOPENIA

Non-immune thrombocytopenia may be the result of increased platelet destruction, decreased platelet production or a mixed mechanism. In some cases, the causative mechanism is still unknown.

Perinatal infections

These are the most common cause of thrombocytopenia in newborn infants. Any bacterial, viral or fungal infection may lead to a reduction in platelet count (PC).[1] It is estimated that 54-80 % of infected neonates develop thrombocytopenia, with no evidence of disseminated intravascular coagulation (DIC) in more than half of cases.[2-4] This is basically due to an increased platelet destruction that may coexist with decreased synthesis (*Figure 1*).[1,5,6]

The reduction in PC occurs early; it may even precede the onset of infection symptoms and, in general, it lasts for approximately one week.[2-4] If thrombocytopenia occurs alone and not in association with DIC, it is usually not severe and bleeding manifestations are minimal.[1]

Necrotizing enterocolitis

Thrombocytopenia is almost always present in this clinical condition; it is observed in 80-90 % of affected neonates, without associated DIC. PCs usually range between 30 and 60 x 10^9/L, and may cause moderate to severe bleeding manifestations.[1]

Thrombocytopenia is considered a predictor of poor prognosis.[9] It is due to increased destruction with an unknown cause, although a suppressed production may also be involved.[10,11] Routine treatment implies platelet transfusions (PT) to maintain a safe PC, although some studies have questioned its indication in this pathology.[12-14]

Intrauterine infections

These are one of the most common

causes of thrombocytopenia, in general associated with anemia and/or neutropenia, and, other times, they are part of DIC.[5] Thrombocytopenia may be caused by increased destruction, decreased synthesis or both mechanisms together. Typically, petechiae occur since the first day of life and may last for weeks or months.

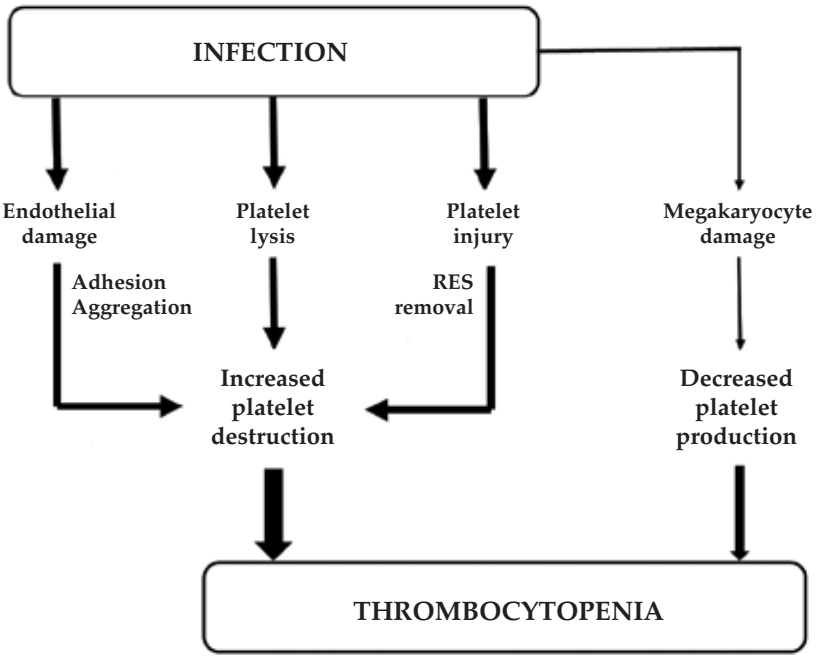
Cytomegalovirus is the most common intrauterine infection, occurring in 0.2-25 % of fetuses.[16-18] Thrombocytopenia is observed in 36-70 % of cases.[19-21] Sometimes, it is the only manifestation of congenital cytomegalovirus infection. Petechiae are rarely present at birth; in general, they appear a few hours after and disappear within weeks. Any petechial rash that may be observed may not necessarily be associated with thrombocytopenia.

It is typical to note an almost total lack of megakaryocytes in the bone marrow due to the direct action of cytomegalovirus on them, so the main mechanism involved is decreased platelet production.[19,22,23] There is also plenty evidence of an increased platelet destruction, either secondary to DIC, antibodies or hypersplenism.[16,24-26]

Between 40 % and 80 % of neonates with **rubella** develop thrombocytopenia.[27-34] At birth, the PC is usually below 50 x 10^9/L and, in general, it goes back to normal spontaneously towards the end of the second week, although it may last up to 2 months.[19,29,35] Its clinical manifestations include purpura, which is more severe in the first hours of life; severe bleeding is very rare.[19] A noticeable reduction in megakaryocytes is observed in the bone marrow, which evidences that synthesis suppression is the main mechanism involved.[15,33]

In other infections, the causative mechanism is increased destruction. In the case of **syphilis**, anemia is the most common hematologic manifestation, but associated thrombocytopenia is observed in 28-45 % of patients.[36,37] In the case of **toxoplasmosis**, thrombocytopenia is also less frequent than anemia, and it is observed in approximately 10 % of neonates.[19,38] In **enterovirus** infection, DIC is the most common

FIGURE 1. *Causative mechanisms of thrombocytopenia in infections*



RES: reticuloendothelial system.
Production mechanisms are multiple. The main one is increased platelet destruction, which is mediated by several pathways. Platelets may be directly destroyed by the microorganism or damaged for the subsequent removal by the reticuloendothelial system. The endothelium may also be damaged, leading to endothelial adhesion and platelet aggregation. In addition, decreased platelet synthesis may occur due to the direct damage of the microorganism on megakaryocytes, which is evidenced by the decreased number of megakaryocytes and/or increased circulating thrombopoietin levels.
Source: Developed by the author.

manifestation, and bleedings secondary to DIC are one of the most important causes of death.[39-42] Isolated thrombocytopenia may be observed in approximately 17 % of patients.[40] In **herpes virus** infection, thrombocytopenia caused by DIC is also the most common hematological alteration, present in 40-50 % of cases, and is an indicator of poor prognosis.[19,43-46] Approximately 86 % of neonates with hydrops fetalis secondary to severe anemia due to **parvovirus B19** infection have thrombocytopenia.[47]

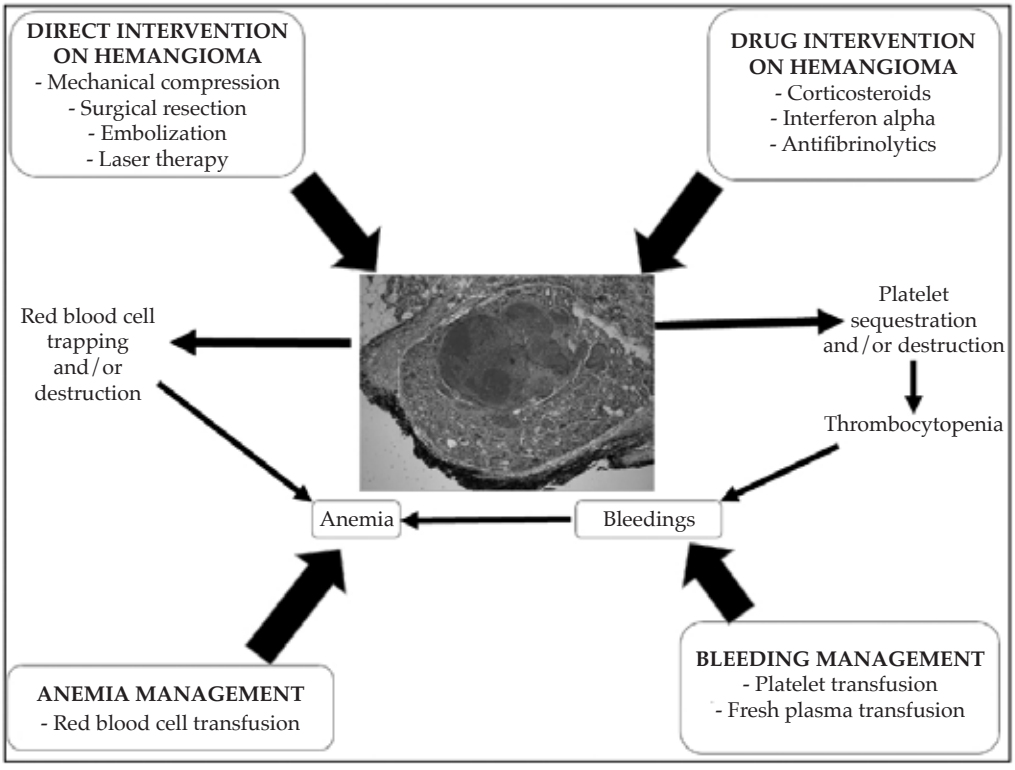
Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) syndromes are characterized by thrombocytopenia, hemolytic anemia, and fragmented red cells. The most common cause is **DIC**, which may be triggered by multiple pathologies associated with acidosis, hypoxia and/or shock.[48-50] Congenital **thrombotic thrombocytopenic purpura** caused by partial or total deficiency in ADAMTS13, a protease that cleaves von Willebrand factor,[51] and **atypical hemolytic uremic syndrome**, caused by complement deregulation, are two rare, but very severe, conditions that should be considered in any neonate with TMA without evident cause.[52-54]

Giant hemangioma

Thrombocytopenia secondary to giant hemangioma (Kasabach-Merritt syndrome) may or may not be accompanied by bleeding. These cases correspond to congenital hemangioendotheliomas evident since birth. In

FIGURE 2. *Potential therapeutic interventions in Kasabach-Merritt syndrome*



When, due to location or severity, an active drug management for hemangioma is decided, corticosteroids are the first option, although their usefulness is doubtful. Interferon alpha, which has an inhibitory effect on angiogenesis, has shown good results, although it is not always effective and may cause major adverse reactions. It is indicated if corticosteroid therapy has failed. Direct intervention on the hemangioma may be through surgical resection, embolization or laser therapy, with varying results and probable development of complications resulting from these procedures. Replacement therapy with platelet, plasma or packed red blood cell transfusion should be individualized for each patient.
Source: Developed by the author.

general, they are large and occur alone, and may be located in any site, although rarely in organs such as the liver or spleen.[55-57]

Thrombocytopenia takes place through platelet sequestration or destruction inside the tumor mass, and the presence of a DIC process is common.[58,59] It may coexist with anemia, as a result of bleeding or red blood cell trapping and destruction inside the tumor mass.[60] Treatment should consider that hemangiomas tend to solve spontaneously, so potential risks should be assessed. *Figure 2* shows potential therapeutic interventions.[60-68]

Thrombocytopenia secondary to other neonatal pathologies

Thrombocytopenia has been observed in some cases of **severe hyperbilirubinemia after phototherapy** for several days, as well as in some neonates with **severe Rh-hemolytic disease**.[69-71] This is due to the platelet damage caused by phototherapy.[72,73] In Rh-hemolytic disease there is probably some additional mechanism related to immune reaction.[74] Thrombocytopenia is almost never severe. PC is generally between 50 and 150 x 10^9/L and goes back to normal levels within 48 hours after stopping phototherapy.[1]

Some studies have reported that 20-30 % of neonates with **polycythemia-hyperviscosity syndrome** develop thrombocytopenia, probably in relation to an increase in platelet adhesion and aggregation and a reduced average lifespan.[75-77] **Perinatal respiratory disorders** may be associated with thrombocytopenia of varying severity. It is more common in perinatal aspiration syndrome (approximately, 13 % of cases) than in hyaline membrane disease or neonatal asphyxia.[78] In neonates with **intrauterine growth restriction**, thrombocytopenia may be present.[79] It is much more common in preterm than in term newborn infants.[1,79,80] It is basically caused by a decreased platelet production, but may also result from increased destruction secondary to intrauterine hypoxia or anti-human leukocyte antigen (anti-HLA) antibodies.[5,81-84] Thrombocytopenia develops in the first days; it is moderate and generally does not last more than 2 weeks.[84]

Thrombocytopenia due to bone marrow occupation

Thrombocytopenia is the result of a disease occupying the medullary canal and gradually replacing normal bone marrow tissue. It is observed in congenital leukemia, transient myeloproliferative disorder, neuroblastoma, Langerhans cell histiocytosis, and osteopetrosis. It is very uncommon.

Amegakaryocytic thrombocytopenias

This is a rare disease characterized by the total or partial absence of megakaryocytes in the bone marrow. **Congenital amegakaryocytic thrombocytopenia** is an autosomal recessive disease characterized by severe thrombocytopenia since birth.[85,86] It may be caused by mutations in the *MPL* or *THPO* genes.[87,88]

Most patients do not have associated physical abnormalities, although micrognathia, microcephaly, congenital heart disease, growth retardation, and maturation disorders have been described.[86,89] The association with such physical alterations may confound the condition with Fanconi anemia, so a chromosomal fragility test must be performed. Thrombocytopenia develops in the first week of life in more than 50 % of cases.[86,90]

Mortality is high, in general secondary to intracranial hemorrhage. These patients tend to progress to aplastic anemia (50 % of cases), leukemia or myelodysplasia,[85,86,89,91] so the treatment of choice is hematopoietic stem cell transplantation, which should be done as early as possible; transplantation achieves a survival of more than 90 %.[92,93] Until the procedure is performed, the patient should be managed with PTs.[89,91] Treatment with romiplostim, which has proven to be highly effective in 3 children from an affected family, is under study.[88]

Thrombocytopenia with absent radii (TAR) is an autosomal recessive syndrome characterized by the absence of both radii.[86] It may be associated with other skeletal malformations, especially in the upper limbs, and other organ malformations; the most common ones are congenital heart disease (22-33 %), facial hemangioma (24 %), and kidney abnormalities (23 %).[86,94-96] Thrombocytopenia is severe and develops in the first week of life in 59 % of cases and before 4 months old in 90 %.[86,96] The mortality rate is approximately 25 %, usually due to intracranial hemorrhage, and death occurs in the first months of life.[86,90,95] As of 1 year old, thrombocytopenia tends to resolve, and remission is achieved by 4 years old in 70 % of cases.[91] These patients do not progress to pancytopenia and generally do not tend to a malignant change,[74,85,86,89,97] although isolated cases of leukemia have been reported.[98-100] Treatment includes periodic PTs to maintain the

PC above 30 x 10^9/L.[1,74,89,91,93]

Amegakaryocytic thrombocytopenia with radio-ulnar synostosis is an autosomal dominant disease behaving similarly to congenital amegakaryocytic thrombocytopenia. It is characterized by the presence of proximal radio-ulnar synostosis and may be associated with clinodactyly, syndactyly, hip dysplasia, and hearing loss.[85,91,93]

Neonatal thrombocytopenia may sometimes account for the initial manifestation of **Fanconi anemia** and may persist for several years as the only symptom, until pancytopenia, typical of this condition, becomes established.[89]

Inherited hrombocytopenias

These are syndromes caused by structural platelet alterations. In many cases, platelets also present functional abnormalities.[85,101] Thrombocytopenia may be associated with the involvement of other hematopoietic lineages or other organs (kidney, ear, eyes, skin, etc.) or progression to a malignancy. This is a group of multiple pathologies, some better known than others, and new syndromes are still being described.[85,102]

Table 1 shows their classifications based on platelet size, which is one of the most practical options.[102] In general, thrombocytopenia is mild to moderate; only a few cases become severe. Most cases develop after 1 year old and are rare in the neonatal period. The number of megakaryocytes in the bone marrow is normal.

A case of severe neonatal thrombocytopenia has been recently described, initially diagnosed as neonatal alloimmune thrombocytopenia, in a child with a novel mutation related to the *MYH-9* gene.[103] Macrothrombocytopenia is the most frequent type, especially when caused by mutations in the *MYH-9* gene, which codes the non-muscle myosin heavy chain IIA. It may be accompanied by other clinical and laboratory manifestations, and it is part of different syndromes that were previously described as different entities, but are currently considered an unique, clinically heterogeneous disease.[85,102] A typical characteristic of this disease, observed in most cases, is the presence of azurophilic inclusions, similar to Döhle bodies, corresponding to ribosome clusters in the cytoplasm of neutrophils, eosinophils, and monocytes (*Figure 3*).

Inherited metabolic disorders

These are exceptionally rare pathologies that may develop with thrombocytopenia since birth. Reported cases included methylmalonic acidemia, ketotic glycinemia, isovaleric acidemia, and acidemia due to holocarboxylase synthetase deficiency.[60,104-106]

Chromosomal abnormalities

Several alterations, mainly trisomies 13, 18, and 21 and Turner syndrome may cause neonatal thrombocytopenia.[107] In a study with 5194 samples of fetal blood, thrombocytopenia was observed in 247 (4.8 %); of these, 43 (17 %) corresponded to fetuses carrying chromosomal disorders. Thrombocytopenia was observed in 26/30 cases of trisomy 18; in 6/11 cases of trisomy 13; in 5/16 cases of Turner syndrome; in 3/4 cases of triploidy; and in 3/44 cases of trisomy 21.[20] Thrombocytopenia is usually mild to moderate and does not cause major bleedings.[1,20]

Thrombocytopenias secondary to maternal conditions

Arterial hypertension (AHT) is observed in 12 % of pregnancies, and is severe in 3 % of them. It is one of the most common causes of neonatal thrombocytopenia.[108-111] In a review of 1414 pregnancies with severe HTN, 130 neonates developed thrombocytopenia, but only 5 of them (0.4 % of the total) had a PC below 50 x 10^9/L.[112] In general, neonates do not develop bleeding and

TABLE 1. *Classification of inherited thrombocytopenias*

Large platelets (macrothrombocytopenia)
• *MYH9* gene-related conditions
• Bernard-Soulier syndrome
• Gray platelet syndrome
• Platelet-type von Willebrand disease
• *GATA1* gene-related conditions
• Paris-Trousseau thrombocytopenia
• Jacobsen syndrome
• Thrombocytopenia associated with sitosterolemia
• *FLNA* gene-related thrombocytopenia
• *TUBB1* gene-related macrothrombocytopenia
Normal platelets
• Familial platelet disorder with predisposition to acute myeloblastic leukemia
• *ANKRD26* gene-related thrombocytopenia
• *CYCS* gene-related thrombocytopenia
Small platelets
• Wiskott-Aldrich syndrome
• X-linked thrombocytopenia

the PC returns to normal in 5-7 days.[74] Maternal **hyperthyroidism** may rarely lead to neonatal thrombocytopenia.[113]

PLATELET TRANSFUSIONS

Although a PT is a useful procedure in the management of platelet disorders, it is worth noting that there is no direct relationship between severe thrombocytopenia and the onset of bleeding.[114-120] Some prospective, observational studies showed that bleeding was present in only 9-10 % of neonates with severe thrombocytopenia.[115,121] In a review of six studies, with the aim of determining if prophylactic transfusion would reduce the risk for bleeding, no evidence of a cause-and-effect relationship between PC and bleeding was observed.[122]

The severity of thrombocytopenia itself is not currently considered the most accurate predictor of the risk for bleeding. There are other parameters to determine both the occurrence and severity of thrombocytopenia, including gestational age, chronological age, the cause of thrombocytopenia, coexistence with other clotting defects, vascular endothelium integrity, metabolic conditions associated with oxidative stress, medications, platelet volume, etc.[123]

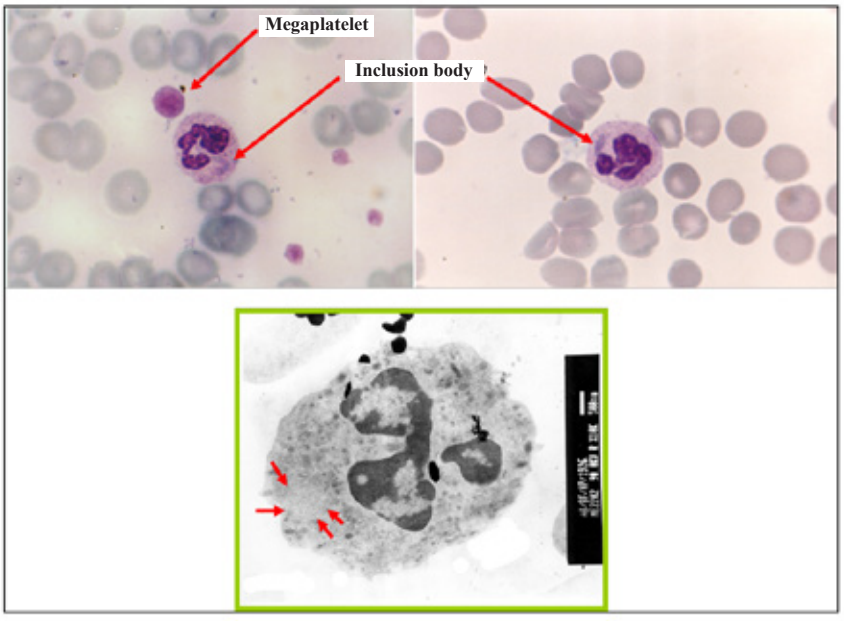
Different publications have established that, in case of active bleeding, the decision to indicate a PT is basically determined by the clinical condition, not the PC.[124-127] Several authors have suggested different indication schedules (*Table 2*), but there is no general consensus.[121,128-132]

A 10-15 mL/kg bank platelet dose or 1 unit of platelets obtained by apheresis is enough to increase the PC by 50-100 x 10^9/L.[74,123,133] Its effectiveness depends especially on the cause and production mechanism of thrombocytopenia. The duration of platelet infusion does not modify the response.[134]

Currently, the main controversy is not related to the management of bleeding but to its prevention, in an attempt to establish the PC threshold below which bleeding would be highly probable and would warrant a prophylactic PT. Such decision is basically based on dogmas and expert opinions, with a minimal support from conclusive scientific data.

In recent years, some studies have provided interesting data. Borges et al. reported a similar incidence of intraventricular hemorrhage comparing 50 x 10^9/L or 100 x 10^9/L thresholds

FIGURE 3. *MYH-9-related disease*



The upper pictures (light microscopy) show a megaplatelet and inclusion bodies in two neutrophils. The lower picture (electron microscopy) shows the ribosome cluster making up the body.
Source: Developed by the author.

to indicate a PT and suggested that a restrictive guideline was preferable to liberal criteria.[135] Recently, in an excellent prospective, multicenter study, 660 preterm newborn infants with less than 34 weeks of gestation who had severe thrombocytopenia were randomized to receive a PT with a PC below 50 x 10^9/L (liberal) or 25 x 10^9/L (restrictive).[136] The results related to the primary objective (death or major bleeding within 28 days) showed a greater mortality or severe bleeding incidence in the group that received the PT based on liberal criteria than in the restrictive guideline group (26% versus 19%, respectively; $p = 0.02$). Based on these results, the 25 x 10^9/L platelet threshold seems to be adequate for a prophylactic PT, although it should be taken into account that some authors consider that using this threshold in the first week of life, when the risk for bleeding is at its peak, is arguable.[137]

As a secondary objective, a significantly higher incidence of bronchopulmonary dysplasia (BPD) was also observed in the liberal group. These findings focus the attention on an aspect that has caught the eye of several authors: PTs are not harmless and may cause severe adverse effects.[123,138] The association between the number of PTs administered and a worse course has been suggested in several prior studies.[139-142] In 2007, Baer et al., in a retrospective study with 1600 hospitalized neonates, found an association between multiple PTs and a higher mortality rate.[13] Du Pont-Thibodeau et al. observed in pediatric patients in the intensive care unit that a prophylactic PT was associated with a higher risk for multiple organ failure, sepsis, nosocomial infections, and mortality.[14] Similar findings have been reported in adults.

An association has been described between prophylactic PTs in invasive procedures and an increased risk for thrombosis and mortality, between prophylactic PTs in patients with intracranial hemorrhage and a greater mortality and worsening of the neurological condition, between PTs and an increased risk for respiratory distress in patients with major trauma, and between PTs and an increased risk for mortality and complications in patients undergoing myocardial revascularization surgery.[143-146] However, other studies in adults reported that a prophylactic PT is not associated with a greater risk.[147-149] A recent systematic review failed to draw conclusive conclusions in this regard.[150]

There is also strong evidence that newborn infants are much more susceptible to experience adverse effects from transfusions. An analysis of the Serious Hazards of Transfusion (SHOT), the United Kingdom's hemovigilance scheme, reported that, over a 10-year period, there was a disproportionately higher number of adverse effects among neonates compared to pediatric or adult patients receiving transfusions.[151] In the case of red blood cell transfusions, the number of adverse events in patients younger than 1 year was 37:100 000, whereas in older children it was 18:100 000, and in adults, 13:100 000. Unfortunately, there are still no reliable data specifically related to PTs. Similar findings were reported by the hemovigilance system in Norway.[152,153]

Some mechanisms may help to explain the harmful effects of PTs. The high transfusion volume associated with PT in neonates, especially preterm babies (15 mL/kg), is 3-5 times higher than that administered to adults. Such volume, which in a preterm newborn infant with a weight of 1 kg accounts for approximately 17 % of their blood volume, may theoretically cause adverse hemodynamic effects, including increased cerebral blood flow and cerebral arterial pressure, associated with a greater risk for intracranial hemorrhage.[154-156] It may also cause complications in neonates with concomitant cardiac involvement.[115]

TABLE 2. *Recommended platelet count for platelet transfusion indication, according to different authors*

Author	PNBI No bleeding Sick	PNBI No bleeding Stable	TNBI No bleeding Sick	TNBI No bleeding Stable	NBI Active bleeding
Blanchette et al.	< 50	< 30	< 30	< 20	< 50
Calhoun et al.	< 50	< 25	< 50	< 50	< 50
Murray et al.	< 50	< 30	< 30	< 30	< 100
Gibson et al.	< 30	< 20	< 30	< 30	< 50

NBI: newborn infant; PNBI: preterm newborn infant; TNBI: term newborn infant. Platelet counts are indicated as platelets x 10^9/L.

Another factor to consider is the potential harmful effect of adult platelets transfused to newborn infants given that their platelets are less responsive to platelet agonists, have less alpha-adrenergic receptors on their surface, a reduced calcium mobilization, and differences in thromboxane receptor signaling.[157] In preterm newborn infants, such platelet hyporeactivity is even more pronounced.[158,159] It is still unknown to what extent such differences may lead to greater microthrombosis or other adverse effects.[155,160,161]

The transmission of infectious agents should also be taken into consideration because platelets are the blood component most susceptible to contamination given that concentrates are stored at room temperature.[162] The potential severe adverse effects of transfusions should not be ruled out either (transfusion-related acute lung injury [TRALI], among others), which, given their characteristics, are not easily recognizable in severely-ill newborn infants, so they may be under-recorded.[151,155,162] In addition to their hemostatic role, platelets have important proinflammatory and immunomodulatory effects.[163,164] Considering that the inflammatory component is fundamental in BPD pathophysiology, it is valid to speculate that the proinflammatory effect of PTs may be a mechanism leading to a greater occurrence of BPD. To what extent such proinflammatory activity facilitates the development of other pathologies (short bowel syndrome, liver damage, etc.) is still to be elucidated.[12,165]

To conclude, the data obtained in recent years have demonstrated that many indicated PTs provide no benefit, are unnecessary, and imply risks; this leads to a drastic paradigm shift in relation to transfusions and supports the decision to adopt a 25 x 10^9/L threshold for platelets as prophylaxis. In addition, in the future, the decision to perform a prophylactic PT should be individualized, after assessing the different risk factors, rather than based on an arbitrary PC limit.[142] To this end, it would be necessary to have an algorithm based on a score that measured the bleeding risk, as for adults. ■

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