

Updates in Neonatal Anemia and Thrombocytopenia: Causes, Risk Factors, and Management

Maged Naser¹, Mohamed MN² and Lamia H. Shehata³

¹Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of ob/gyn

²King Fahd Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of Surgery

³Care National hospital, Department of Radiology



Abstract – There is no worldwide agreement with respect to red cell and platelets transfusion thresholds, bringing about generally changing practices.

The distinguishing proof of appropriate biomarkers for red cell and platelets transfusion may add to a more individualized and viable transfusion practice.

Restrictive platelet transfusion might be desirable over liberal rules in preterm neonates with thrombocytopenia.

Prevention of neonatal anemia can be partly prevented by delayed cord clamping and iatrogenic blood loss.

Keywords – Anemia, Thrombocytopenia, Erythrocytes, Platelets, Transfusion.

I. INTRODUCTION

An anemia and thrombocytopenia are regular hematologic issues in neonates, especially in (very) preterm neonates. Blood products, either red blood cells (RBC) or platelets to correct anemia and thrombocytopenia, separately, are as often as possible controlled in neonates admitted to neonatal intensive care units (NICU). With the advances in neonatal care and related increment of survival of neonates and particularly of preterm neonates, the overall rate of transfusions has increased expanded in the course of the last years. (1)

Up to 90% of (extremely) low-birth-weight as well as (very) preterm neonates require in any event one RBC transfusion during admission due to anemia, (1, 2) while thrombocytopenia is accounted for to happen in 20% to 35% of neonates admitted to a NICU, with again much higher frequencies in the more delicate subpopulations of preterm

neonates. (2–4) Anemia and thrombocytopenia are generally treated with transfusions. In any case, current transfusion rehearses are vigorously talked about, less due to wellbeing issues (blood items in developed countries are these days when all is said in done thought about safe), however generally concerning adequacy and the ideal bonding limits. Transfusion edges are generally founded on master sentiment instead of logical proof, and the extraordinary change in accessible transfusion rules mirrors the absence of agreement on this subject.

This review plans to give a concise overview of the causes, hazard factors, and management of neonatal pallor and thrombocytopenia, focusing chiefly on the ongoing advancements in transfusion practices and sketching out a few anticipated future turns of events.

II. ANEMIA

A. Causes and Risk Factors

Anemia is characterized as a hemoglobin level below the lower limit reaches of the reference go balanced for age and is a typical finding in neonatal population. All neonates show a physiologic postnatal decrease in hemoglobin in the first weeks after birth, bringing about shifting degrees of (relative) anemia. In term newborn neonates, hemoglobin levels decline from 14.6 to 22.5 g/dL during childbirth to 10.0 to 12.0 g/dL by 8 to 10 weeks old enough, the physiologic nadir. From that point, hemoglobin levels step by step increment toward adult hemoglobin values within the first 2 years of life. This physiologic anemia, or "early iron deficiency of infancy," is more articulated in preterm and low-birth-weight neonates than in term neonates. It is a reflection of the progress from fetal hemoglobin with a high oxygen affinity, on the grounds that the fetal circulation is moderately hypoxic, to adult hemoglobin after birth and a transitional decrease in plasma erythropoietin (EPO).(5)

Nevertheless, the physiologic hemoglobin decrease after birth isn't the fundamental driver of iron deficiency in hospitalized neonates. Its impact is exceeded by non-physiologic factors, for example, obstetric complications,

clinical conditions, for example, sepsis, insufficient nutrition, and cardiorespiratory infection, and specifically, iatrogenic blood loss accompanying frequent laboratory testing. Estimates of iatrogenic blood loss because of laboratory testing in the NICU in the initial 6wks of life differ, however may sum up to 15% to 30% of a newborn infant's total blood volume. Neonatal anemia can likewise be brought about by conditions, for example, HDFN (hemolytic disease of fetus and newborn) brought about by maternal erythrocyte antibodies against the various blood group systems. (5, 6)

B. Treatment: Erythrocyte Transfusion Thresholds

There is no global agreement with respect to ideal hemoglobin threshold for RBC transfusions. A summary of guidelines is appeared in Table 1, focusing on the incredible between public variety in transfusion hemoglobin limits. Suggestive indications of anemia, for example, apnea, bradycardia, and increased oxygen need, frequently happen when there is an imbalance between oxygen utilization and delivery. (7)

These side effects are nonspecific, and synchronous conditions, including sepsis and lung conditions, may obscure the indicative course of anemia.

Table-1 International guidelines for red blood cell transfusion

	British Committee for Standers in Hematology 2016 ⁵⁰		Australian National Blood Authority 2016 ⁵¹		Canadian Blood Services 2017 ⁵²	
	Respiratory support	No respiratory support	Respiratory support	No Respiratory support	Respiratory support	No Respiratory support
Week1	10–12g/dL	<10g/dL	11–13g/dL	10–12g/dL	<11.5g/dL	<10g/dL
Week2	9.5–10g/dL	<7.5g/dL	10- 12.5g/dL	8.5–11g/dL	<10g/dL	<8.5g/dL
Week3	8.5–10g/dL	<7.5g/dL	8.5–11g/dL	7–10g/dL	<8.5g/dL	<7.5g/dL

As For example, supplemental oxygen, high-flow nasal cannula, CPAP (continuous positive airway pressure), positive-pressure ventilation

The decision to transfuse is made based on clinical judgment of the care giver and national or local guidelines. reviews have given an account of the variety in guidelines and proposed hemoglobin thresholds between and inside countries and geographic areas.(8,9) To date, just a couple of randomized controlled preliminaries looked at changed transfusion hemoglobin thresholds in extremely low-birth-

weight children (<1000 g) concerning wellbeing and adequacy. As appeared in the most recent Cochrane review,(10) no critical differences were found among liberal and restrictive transfusion groups, on both short-and long term outcome parameters, this would support a prohibitive mentality toward transfusion in clinically stable patients, yet ends must be drawn mindfully. Correlation of these preliminaries and sufficient understanding of their outcomes are muddled on the grounds that these preliminaries didn't utilize similar meanings of "liberal" and "prohibitive" regarding RBC transfusion, which brought about an

assortment of hemoglobin limits. Two progressing preliminaries in this field may reveal further insight sooner rather than later on the wellbeing and adequacy of liberal versus prohibitive edges for RBC transfusions.

C. Transfusion markers

A significant advance toward arriving at agreement on obviously characterized transfusion threshold might be the Identification of better markers for anemia and the need of transfusion.(11) Currently, choices depend on a mix of clinical signs, research center discoveries, for example, hemoglobin levels, and cardiorespiratory or ventilation status. The connection between pretransfusion fringe hemoglobin esteems and real tissue perfusion and oxygenation has been questioned, (12, 13) though different markers of oxygenation and perfusion have increased a lot of interest. Serum lactate, for instance, is a final result of anaerobic metabolism and diminishes fundamentally after transfusion. (14) However, lactate is likewise raised in conditions, for example, sepsis and asphyxia, and may subsequently be excessively nonspecific for clinical use. A tool of specific interest because of its noninvasive nature is close infrared spectroscopy (NIRS), which measures local tissue oxygen immersion by utilizing the distinction in light saturation of oxygenated and deoxygenated hemoglobin. NIRS has generally been assessed in neonates for cerebral estimations with empowering results,(15) yet the gut and splanchnic oxygenation has increased expanded interest and, it is trusted, will distinguish an ideal trigger for transfusion.(11) Despite its promising highlights, NIRS presently can't seem to be approved for neonates of various gestational age groups. As an optional report in the previously mentioned TOP preliminary, the distinctions in cerebral oxygenation and partial tissue oxygen extraction with NIRS will be resolved among high-and low-hemoglobin value threshold during RBC transfusions, which will help to evaluate the function of NIRS in Transfusion practice.

D. Type of product

RBC products in the neonatal population are regularly leukocyte depleted and irradiated for infants weighing under 1200 g, and the RBC transfusion volumes fluctuate between 10 and 20 mL/kg. A few concerns were raised over the period of RBC products at the time of transfusion, however a preliminary tending to whether more established old stored RBCs are unsafe to neonates indicated no advantage of fresher RBC items. In this examination, 377 preterm neonates were randomized to RBC items put away not exactly or equivalent to 7 days, contrasted and standard RBC items (stockpiling time 2–42 days). No distinctions were found in

death or neonatal morbidities, for example, intra ventricular discharge (IVH), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP).(16)

E. Complications

All blood component transfusion accompanies comparative risks, for example, clinical errors in administration and incorrect blood component transfusion. When all is said in done, transfusions is safe as protected. Transmission of infectious agents is uncommon in developed countries with broad screening and preparing conventions of human blood items, however a few entanglements may be under recognized in the neonatal population and especially in (very) preterm neonates. It is hazy unclear different risks revealed in adults undergoing transfusion mean a neonatal population. For instance, conditions, for example, transfusion related lung injury (TRALI) and transfusion related circulatory over-load (TACO) might be hard to separate in the sick neonates with prematurity related respiratory failure.(17) However, the typical neonatal conditions might be related with transfusion, as a few studies have proposed relationship with RBC transfusions and IVH,(18) NEC (purported TANEC, transfusion related necrotizing enterocolitis),(19) ROP(retinopathy of prematurity),(20) and iron overload.(21) The pathophysiologic clarifications for these associations are unknown and are likely multifactorial. Also, the proof for a causal relationship between RBC transfusions and different neonatal complications is lacking and stays theoretical. Last, different transfusions may hypothetically suppress the endogenous erythropoiesis and cause a delay in natural recovery of iron deficiency.

F. Erythropoietin administration

The physiologic decline of hemoglobin after birth is joined by a transient deficiency of endogenous EPO, a hormone that stimulates erythropoiesis. Administration of synthetic EPO or darbepoetin, a long-acting type of EPO, may hypothetically lessen neonatal anemia.(6) Many studies have researched the function of EPO in the counteraction of anemia and the decrease RBC transfusions in preterm or potentially low-birth-weight neonates just as assessed its part as a neuro protective agent. Two isolated, as of late refreshed Cochrane studies evaluated the adequacy and security of early EPO administration (at or before 7 days after birth, 34 randomized controlled preliminaries, enlisting 3643 preterm infants)(22) and late EPO administration (following 7 days, 30 randomized controlled trials, selecting 1591 preterm newborn infants), respectively.(23) Overall, EPO treatment caused a decrease in RBC transfusions and the volume of RBCs transfused, in spite of the fact that the results shift and

the general impact is accounted for to be of restricted clinical significance. In ongoing trials, the rate of ROP was not, at this point a subject of concern and didn't vary between treatment groups, albeit late administration of EPO still indicated a pattern in expanded risk for ROP. A meta-investigation specifically tending to the issue of ROP in EPO treatment demonstrated no expanded risk for any stage of ROP. (24, 25) Furthermore, early EPO treatment essentially diminished risks of IVH and NEC, despite the fact that these impacts were not seen after late EPO treatment. The impact of EPO on neurodevelopment is harder to evaluate, on the grounds that long term follow-up is restricted. Until this point, the neuroformative results at 18 to 22 months shift enormously, and in spite of the fact that outcomes appear to be encouraging and recommend a neuroprotective impact of EPO, further long term assessment of these infants is vital. (26)

In the particular instance of hemolytic disease of the fetus and newborn (HDFN), EPO treatment may be advantageous to treat the anemia, which can be continuous for a while after birth. HDFN is certainly not an enlisted sign for EPO treatment, yet off-mark use has been reported.(27,28) The likely impact of EPO in neonates with HDFN was appeared in little studies and case reports, demonstrating by and large an expanded hemoglobin level and diminished transfusion need.

G. Reduction of iatrogenic phlebotomy

Neonatal iron deficiency is, in hospitalized infants, generally brought about by iatrogenic blood loss going with regular lab testing. (29) Neonates with arterial lines or central venous lines are at most elevated risk, because collecting blood is more convenient and accessible. Tests drawn from central venous catheters likewise have more prominent over-draw volumes contrasted and peripheral venous catheters. (30) Iatrogenic blood loss ought to be decreased to a minimum, and critical assessment of the requirement for lab testing is one of the major steps toward prevention of neonatal anemia. Noteworthy reductions in anemia by phlebotomy can additionally be accomplished by micro technique laboratory procedures, which take into account small sampling volumes, the improvement of noninvasive monitoring systems, and ensuing utilization of fetal blood from the placenta for all NICUbaseline lab blood tests. (30) Mathematical modeling has been utilized to create calculations to anticipate when blood levels are important dependent on clinical findings. (31)

H. Delayed umbilical cord clamping

As of late, the impact of Delayed umbilical cord clamping has recovered much interest concerning the anticipation of neonatal anemia. Delayed umbilical cord clamping by at any rate 30 to 60 seconds after birth considers a drawn out placental transfusion and is presently suggested in preterm and full-term neonates, as expressed in a rule by the World Health Organization. (32) In preterm neonates, it is related with less RBC transfusions, better circulatory stability, and conceivably a lower risk for IVH and NEC compared with early or direct cord clamping. (33) In full-term neonates, the useful impact is less clear. Overall, delayed clamping is related with higher hemoglobin levels after birth, however not with altogether less RBC transfusion, with an increase in iron stores at 4 to 6 months of age, (34) and improved neurodevelopmental results at 12 months (35) and 4 years of age. (36) In full-term neonates, delayed umbilical cord may cause an increase in hyperbilirubinemia and phototherapy. (34)

III. THROMBOCYTOPENIA

A. Causes and Risk Factors

In the late fetal and neonatal period, megakaryocytes are smaller and create less platelet per megakaryocyte compared with adult megakaryocytes. (37) To compensate, the fetal megakaryocytes have a higher multiplication rate and are more sensitive to thrombopoietin, the strongest stimulating agent of megakaryocyte production and differentiation. (38)

From the finish of the primary trimester, the mean platelet count is viewed as more prominent than $150 \times 10^9/L$, regardless of gestational age. Be that as it may, reference levels for ordinary platelet count are discussed. In neonates, "reference levels" are restricted in light of the fact that sound neonates by and large don't go through blood sampling, and there is a wide typical scope of platelet means neonates of various gestational ages.(39) There is no clear connection between platelet cutoff levels and individual bleeding risk,(40,41) as was likewise the determination of an ongoing methodical review on this matter.(42) Platelets levels under $20 \times 10^9/L$ are still commonly thought to be high risk for bleeding, in spite of the fact that the clinical significance of platelet count cutoff levels stays dubious.

The thrombocytopenia in neonates can be divided into the decreased production, increased platelet consumption, increased Extravascular loss or a combination of these factors. The reasons for thrombocytopenia in neonates fluctuate as indicated by the hidden sickness and can be ordered by the period of beginning in ahead of schedule

(inside 3 days after birth) and late-beginning (over 3 days after birth) thrombocytopenia. Beginning stage thrombocytopenia is for the most part connected with pre-birth factors, for example, maternal disease (pre-eclampsia), intrauterine development restriction, perinatal asphyxia, or fetal/neonatal alloimmune thrombocytopenia, while late-beginning thrombocytopenia is frequently brought about by bacterial sepsis or NEC, or thrombotic occasions related with the utilization of central lines.(2,43)

B. Treatment: Platelet Transfusions Thresholds

Thrombocytopenia is commonly treated with transfusions to prevent or treat significant hemorrhages, for example, IVH or lung bleeding. In spite of the fact that bleeding in relationship with marked thrombocytopenia is a clear indication for platelet transfusion, the connection between the seriousness of thrombocytopenia and the event of

hemorrhages isn't obvious. An imminent observational investigation demonstrated that 81% of platelet transfusion in neonates are given prophylactically (i.e., when transfusions are shown by a predefined platelet threshold and not by bleeding signs). Of the 194 neonates in this investigation with platelet checks under $60 \times 10^9/L$, 73% were reported to have minor hemorrhages, yet just 9% created extreme hemorrhage. Among the most severe thrombocytopenic neonates in this examination, with a platelet count under $20 \times 10^9/L$ (n 5 58), just 9% created major hemorrhage.4 only one randomized preliminary looked at higher ($<150 \times 10^9/L$) versus a lower ($<50 \times 10^9/L$) platelet include limit for prophylactic transfusion in preterm thrombocytopenic neonates. The essential result was the frequency of intracranial hemorrhage, which didn't altogether differ between the 2 treatment groups (26 versus 28%). (44) Several national guidelines on platelet transfusion levels are summed up in Table 2.

Table 2. International guidelines for platelets transfusion

	British Committee for Standards in Hematology 2016 ⁵⁴	Australian National blood authority 2016 ⁵¹	Canadian Blood Services 2017 ⁵²	Dutch Guidelines Quality Council (concept) 2018 ⁵³
Prophylactic in stable infant	$25 \times 10^9/L$	$10-20 \times 10^9 /L$	$<20 \times 10^9 /L$	$<25 \times 10^9 /L$
Bleeding or invasive procedure	$50-100 \times 10^9/L$	$50 \times 10^9 /L$	$<50 \times 10^9 /L$	$<50 \times 10^9 /L$

In a recently distributed global randomized preliminary, 660 preterm neonates with severe thrombocytopenia were randomized to get platelet transfusion at platelet count limits of $50 \times 10^9/L$ or $25 \times 10^9/L$. Mortality of significant bleeding inside 28 days of randomization was altogether higher in the under $50 \times 10^9/L$ bunch contrasted and the under $25 \times 10^9/L$ group , separately, 26% (85/324) versus 19% (61/329) (chances proportion 1.57, 95% certainty stretch 1.06–2.32, P 5 .02). This examination proposes that platelet transfusion may cause hurt in preterm neonates. Prohibitive platelet transfusion guidelines may in this way be ideal contrasted and liberal transfusion guidelines. (45)

1. Transfusion markers

A novel laboratory parameter might be useful in the clinical evaluation of neonatal thrombocytopenia, immature platelet fraction (IPF). Platelets, when recently delivered from the liver or bone marrow, are reticulated (i.e., contain RNA that can be recognized by indispensable stains or thiazole orange) and can be measured in this immature precursor state. The evaluation of these reticulated platelets is known as the IPF and might be a solid proportion of the

platelet production rate, equivalent to the reticulocyte include in the appraisal of anemia. An expansion in IPF goes before rising platelet counts and could give extra data about the thrombocytopenia in the neonate. Notwithstanding, as of now there are not yet characterized reference ranges for neonates of various gestational ages and clinical conditions. (46)

2. Complications

Like RBC transfusions, platelet transfusions likewise have the risk of "human" errors in practical administration of transfusion just as a risk of transmission of bacterial or viral diseases, risks of hypersensitive response, and a risk of causing TACO(transfusion related overload) or TRALI(transfusion related acute lung injury).(17)

In an examination by Baer and colleagues, (47) in 1600 thrombocytopenic neonates admitted to the NICU, a study was found between various platelet transfusions and mortality in neonates. Nonetheless, a portion of this association was credited to unmeasured factors, for example, level of illness. It is along these lines unclear whether

expanded neonatal deaths were a result or a reason for thrombocytopenia and platelet transfusions.

C. Treatment: Alternatives Thrombopoietic Agents

Exogenous organization of recombinant human thrombopoietin was tried in solid volunteers yet prompted development of antithrombopoietin antibodies and extreme hyporegenerative thrombocytopenia. (48) Currently, research has changed concentration to thrombopoietin receptor agonists, for example, eltrombopag and romiplostim. These agonists act through binding to the thrombopoietin receptor, simulating the impact of thrombopoietin. Albeit endorsed for use in children, these agents have not been tried in children. The pharmacodynamics and pharmacokinetics properties of these agents in children are hazy and need further examination, particularly on the grounds that thrombopoietin receptors have additionally been recognized on nonhematopoietic cells, including the brain. (49)

IV. FUTURE PERSPECTIVES

Despite the fact that anemia and thrombocytopenia are frequent neonatal complications, there is extraordinary vulnerability in transfusion practice. Appraisal of transfusion need could be improved by biomarkers integral to the serum hemoglobin level and platelet check, for example, NIRS measures or the IPF. Moreover, global agreement rules would assist with diminishing the changeability in transfusion practice. To upgrade transfusion rules, the consequences of continuous randomized controlled preliminaries should be deliberately assessed, and further examination is required in specific neonatal subpopulations to ascertain appropriate thresholds...

The best advances in transfusion practice are preventive and steady measures. Further decrease of iatrogenic phlebotomy, delayed cord clamping, and opportune acknowledgment and treatment of fundamental conditions, for example, infection, may forestall a critical number of transfusions. Moreover, strong measures, for example, the administration of EPO in anemia and thrombopoietin receptor agonists in thrombocytopenia, may demonstrate of extraordinary future worth and should be examined in the neonatal population.

V. CONCLUSION

Anemia and thrombocytopenia are regular in (very) preterm youngsters. Up to 90% of low-birth-weight and additionally (very) preterm youngsters require at any rate one RBC transfusion because of iron deficiency, and thrombocytopenia is accounted for to happen in 20% to 35% of neonates admitted to the NICU.

There is no worldwide agreement with respect to optimal hemoglobin thresholds for RBC transfusion, and studies contrasting liberal and restrictive hemoglobin levels are not decisive. Prevention of neonatal anemia in preterm neonates can incompletely be accomplished by actualizing reasonable measures, for example, postponed cord clipping and minimization of iatrogenic blood loss. RBC transfusions are commonly viewed as safe; however, a few confusions of transfusions might be underreported in neonatal populations.

Thrombocytopenia can be brought about by perinatal factors, for example, intrauterine growth retardation, yet is most regularly found in sepsis or NEC. There is no reasonable connection between platelet cutoff levels and individual bleeding, and most platelet transfusions are given as prophylactic treatment. Nonetheless, the advantage of these prophylactic transfusions is unclear in nonbleeding neonates, and ongoing randomized controlled preliminary shows a higher rate of mortality or significant bleeding if a higher platelet level limit is utilized contrasted and a lower threshold.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Authors have equally participated and shared every item of the work.

REFERENCES

- [1] 1-Keir AK, Yang J, Harrison A, et al. Temporal changes in blood product usage in preterm neonates born at less than 30 weeks gestation in Canada. *Transfusion* 2015; 55(6); 1340-6.
- [2] 2-Christensen RD, Henry E, Wiedmeier SE, et al. Thrombocytopenia among extremely low birth weight neonates: data from multihospital health care system. *J Perinatal* 2006; 26(6):348-53.
- [3] 3-Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the neonate. *Blood Rev* 2008; 22(4); 173-86.
- [4] 4-Staworth SJ, Clarke P, Watts T, et al., Prospective, observational study of outcomes in neonates with severe thrombocytopenia. *Pediatrics* 2009; 124(5):e826-34.
- [5] 5-Widness JA. Pathophysiology of anemia during neonatal period, including anaemia of prematurity. *Neoreviews* 2008; 9(11); e520.
- [6] 6-Widness JA, Madan, Grindeanu LA, et al., Reduction in red blood cell transfusions among preterm infants; results of randomized trials with an in-line as and chemistry monitor. *Pediatrics* 2005; 115 (5); 1299-306.

- [7] 7-Alverson DC. The physiologic impact of anemia in the neonate. *Clin Perinatol* 1995; 22(3):609-25.
- [8] 8-Murray NA, Howarth LJ, McCloy MP, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. *Transfus Med* 2002; 12(1):35-41.
- [9] 9- Von Linder JS, Lopriore E. Management and prevention of neonatal anemia; current evidence and guidelines. *Expert Rev Haematol* 2014; 7(2):195-202.
- [10] 10-Whyte R, Kirplani H. Low versus high hemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev* 2011; (11): CD000512.
- [11] 11-Banerjee J, Aladangady N. Biomarkers to decide red blood cell transfusion in newborn. *Transfusion* 2014; 54(10):2574-82.
- [12] 12-Baily SM, Hendricks -Munoz KD, Wells JT, et al. Packed red blood cells transfusion increases cerebral and splanchnic tissue oxygen saturation in anemic symptomatic preterm infants. *Am J Perinatol* 2010; 27(6):445-53.
- [13] 13-Seidel D, Blaser A, Gabauer C, et al. Changes in regional tissue oxygenation saturation and desaturation after red blood cell transfusion in preterm infants. *J Perinatol* 2013; 33(4):282-7.
- [14] 14-Takahashi D, Matsui M, Shigematsu R, et al. Effect of transfusion on the venous blood acetate level in very low birth weight infants. *Pediatr Int* 2009; 51(3):321-5.
- [15] 15-Van Hoften JC, Verhagen EA, Keating P, et al. Cerebral tissue oxygen saturation and extraction in preterm infants before and after blood transfusion. *Arch Dis Child Fetal Neonat Ed* 2010; 95(5):F352-8.
- [16] 16-Furgess DA, Hebert P, Hogan DL, et al. Effect of fresh blood cell transfusions on clinical outcome in premature, very low birth weight infants: The ARIPI randomized trial. *JAMA* 2012; 308(14):1443-51.
- [17] 17-Stainsby D, Jones H, Wells AW, et al. Adverse outcomes of blood transfusion in children: UK reports to the serious hazards of transfusion scheme 1996-2005. *Br J Haematol* 2008; 141(1):73-9.
- [18] 18-Baer VR, Lambert DK, Henry E, et al. Among very low birth weight neonates is red blood cell transfusion an independent risk factor for subsequently developing a severe intra ventricular hemorrhage? *Transfusion* 2011; 51(6):1170-8.
- [19] 19-Mohamed A, Shahps, Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. *Pediatrics* 2012; 129(3):529-40.
- [20] 20-Hesse L, Eberl W, Sschlaud M, et al. Blood transfusion iron load and retinopathy of prematurity. *Eur J Pediatr* 1997; 156(6):465-70.
- [21] 21-Hirano K, Morino T, Kim H, et al. Blood transfusion increases radical promoting non-transferrin bound iron in preterm infants. *Arch Dis Child Fetal Neonat Ed* 2001; 84(3):F188-93.
- [22] 22-Ohlsson A, Asher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. *Cochrane Database Syst Rev* 2017; (11):CD004863.
- [23] 23-Aher SM, Ohlsson A. Late erythropoietin for preventing red cell transfusion in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2014; (4):CD004868.
- [24] 24-Xu XJ, Huang HY, Chen HL. Erythropoietin and retinopathy of prematurity: a meta-analysis. *Eur J Pediatr* 2014; 173(10):1355-64.
- [25] 25-Chou HH, Chung MY, Zhou XG, et al. Early erythropoietin administration does not increase the risk of retinopathy on preterm infants. *Pediatr Neonatol* 2017; 58(1):48-56.
- [26] 26-Ohls RK, Kamath-Rayne BD, Christensen RD, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. *Pediatrics* 2014; 133(6):1023-30.
- [27] 27-Zuppa AA, Alighieri G, Calabrese V, et al. Recombinant human erythropoietin in the prevention of late anemia in intrauterine transfused neonates with Rh-immunization. *J Pediatr Hematol Oncol* 2010; 32(3):e95-101.
- [28] 28-Nicaise C, Gire C, Casha P, et al. Erythropoietin as treatment for late hypo regenerative anemia in neonates with Rh hemolytic disease after in utero exchange transfusion. *Fetal Diagn Ther* 2002; 17(1):22-4.
- [29] 29-Bateman ST, Lacroix J, Boven K, et al. Anaemia, blood loss, and blood transfusion in North American Children in the intensive care unit. *Am J Respir Crit Care Med* 2008; 178(1):26-33.
- [30] 30-Valentine SL, Bateman ST. Identifying factors to minimize phlebotomy-induced blood loss in the pediatric intensive care unit. *Pediatr Crit Care Med* 2012; 13(1):22-7.
- [31] 31-Rosenbraugh MR, Widness JA, Nalbant D, et al. A mathematical modeling approach to quantify the role of phlebotomy losses and need for transfusions in neonatal anemia. *Transfusion* 2013; 53(6):1353-60.
- [32] 32-World Health Organization. WHO guidelines delayed umbilical cord clamping for improved maternal

- and infant health and nutrition outcomes. Geneva (Switzerland): World Health Organization; 2014.
- [33] 33-Rabe H, Diaz-Rossello JL, et al. Effect of timing umbilical cord clamping and strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012 ;(8):CD003248.
- [34] 34-McDonald SJ, Middleton P, Dowswell T, et al. Effect of timing umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2013 ;(7) CD004074.
- [35] 35- Rana N, Kc A, Malqvist M, et al. Effect of delayed cord clamping of term babies on neurodevelopment at 12 months: a randomized controlled trial. *Neonatology* 2018; 115(1):36-42.
- [36] 36-Andersson Lindquist B, Lindegren M, et al. Effect of delayed cord clamping on neurodevelopment at 4 years of age: a randomized clinical trial. *JAMA Pediatr* 2015; 169(7):631-8.
- [37] 37-Mattia G, Vulcano F, Milazzo L, et al. Different ploidy levels of megakaryocytes generated from peripheral or cord blood CD341 cells are correlated with different levels of platelets release. *Blood* 2002;99(3):888-97.
- [38] 38-Debili N, Wendling F, Katz A, et al. The Mpl-ligand or thrombopoietin or megakaryocyte growth and differentiative factor has both direct proliferative activities on human megakaryocyte progenitors. *Blood* 1995;86(7):2516-25.
- [39] 39-Widmeier SE, Henry E, Sola-Visner MC, et al. Platelet reference ranges for neonates using data from over 47,000 patients in multihospital health care system. *J Perinatol* 2009; 29(2):130-6.
- [40] 40-Bonifacio L, Petrov A, Nanjundaswamy S, et al. Thrombocytopenia related neonatal outcome in preterms. *Indian J PEDIATR* 2007; 74(3):269-74.
- [41] 41-Von Lindern JS, Van den Bruele T, Lopriore E, et al. Thrombocytopenia in neonates and the risk of intra ventricular hemorrhage: a retrospective cohort study. *BMC Pediatr* 2011; 11:16.
- [42] 42-Fustolo-Gunnink SF, Huijssen-Huisman E J, van der Bom JG, et al. Temporary removal: are thrombocytopenia and platelet transfusion associated with major bleeding in preterm neonates? A Systematic review. *Blood Rev* 2018.
- [43] 43-Sola-Visner M, Saxonhouse MA, Brown RE. Neonatal thrombocytopenia: What we do and don't know. *Early Human Dev* 2008; 84(8):499-506.
- [44] 44-Andrew M, Vegh P, Caco C, et al. Randomized, controlled trial of platelet transfusions in thrombocytopenic premature infants. *J Pediatr* 1993; 123(2):285-91.
- [45] 45-Cremer A, Stanworth SJ, Willoghby K, et al. Randomized trial of platelet transfusion threshold in neonates. *N Engl J Med* 2019;380(3):242-51.
- [46] 46-Cremer M, Paetzold J, Schemalish G, et al. Immature platelet fraction as novel laboratory parameter predicting the course of fraction as novel laboratory parameter predicting the course of neonatal thrombocytopenia. *Br J Haematol* 2009;144(4):619-21.
- [47] 47-Baer VL, Lambert DK, Henry E, et al. Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopenic neonates in multi-hospital health care system. *J Perinatol* 2007; 27(12):790-6.
- [48] 48-Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of anti-bodies to thrombopoietin. *Blood* 2001;98(12):3241-8.
- [49] 49-Sallmon H, Gutti RK, Ferrer-Marin F, et al. Increasing platelets without transfusion: is it time to introduce novel thrombopoietic agents in neonatal care? *J Perinatol* 2010; 30(12):765-9.
- [50] 50-New HV, Berryman J, Bolton-Maggs PH, et al, British Committee for Standards in Haematology. Guidelines on transfusion for Standards in Hematology. Guidelines on transfusion for fetuses, neonates and older children. *Br J Haematol* 2016;175(5):784-828.
- [51] 51-Australian National Blood Authority. Patient blood management guidelines: module 6 neonatal and pediatrics. Available at: <https://blood.gov.au/pbm-module6>. Accessed October 23, 2018.
- [52] 52-Lau W. Chapter 13: neonatal and pediatric transfusion. blood.ca/en/transfusion/clinical-guide/neonatal-and-pediatric-transfusion.
- [53] 53-Dutch Guidelines Quality Council, 3RD revision, 2018.
- [54] 54-Estcourt LJ, Birchall J, Allard S, et al, British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *Br Haematol* 2017; 176(3):365-94.