Published in final edited form as:
Arch Dis Child Fetal Neonatal Ed. 2008 November ; 93(6): F469–F473. doi:10.1136/adc.2007.128819.

When to transfuse preterm babies

EF Bell

Abstract

The physiological anaemia experienced by preterm babies is exacerbated by common care practices such as early clamping of the umbilical cord at birth and gradual exsanguination by phlebotomy for laboratory monitoring. The need for subsequent transfusion with red blood cells can be reduced by delaying cord clamping for 30–60 s in infants who do not require immediate resuscitation. The need for transfusions can be further reduced by limiting phlebotomy losses, providing good nutrition, and using standard guidelines for transfusion based on haemoglobin or haematocrit. What those guidelines should be is not clear. Analysis of two recent large clinical trials comparing restrictive and liberal transfusion guidelines leads to several conclusions. Restrictive transfusion guidelines may reduce the number of transfusions given, but there is no reduction in donor exposures if a single-donor transfusion programme is used. There is some evidence that more liberal transfusion guidelines may help to prevent brain injury, but information on the impact of transfusion practice on long-term outcome is lacking. Until further guidance emerges, transfusion thresholds lower than those used in the two trials should not be used, as there is no evidence that lower thresholds are safe.

"Should I transfuse this baby today, or would it be better to wait?" This question has perplexed neonatologists for decades. The anaemia experienced by small preterm infants depends on the blood volume at birth, the baby's rate of erythropoiesis, and the rate of red blood cell (RBC) loss by phlebotomy, haemorrhage or haemolysis. The decision to transfuse should arise only after reasonable efforts have been made to provide a larger initial blood volume, optimise erythropoiesis, and limit blood loss by all means, but especially by phlebotomy. The decision must be viewed in the context of what is known about the benefits and risks of RBC transfusion for preterm babies.

SINGLE-DONOR TRANSFUSION PROGRAMMES

Donor screening, testing for infection, leukoreduction and irradiation have led to very low risks from blood transfusion.[1] The risks of multiple transfusions to a single infant can be reduced even further by providing most or all transfusions from a single uninfected donor. Modern storage media enable RBCs to be stored for up to 6 weeks and safely transfused into preterm infants without harm.[2–6] If a unit of RBCs is dedicated to one or two preterm infants, a single donor can often provide all the RBCs needed by an infant in the first 6 weeks of life. Such single-donor programmes should be the standard practice in blood banks that serve preterm infants. So, in units with a single-donor transfusion programme, the question of transfusion is more important for babies who have not been transfused previously. The question then becomes, "Can we safely avoid transfusion altogether for this baby?"

Correspondence to: Dr E F Bell, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, USA; edward-bell@uiowa.edu.

Competing interests: None.

STRATEGIES FOR AVOIDING TRANSFUSION

Delayed clamping of the umbilical cord at birth

The first answer to the dilemma posed by the title of this article, "When to transfuse preterm babies," is "at birth." Delaying the umbilical cord clamping for 30 –120 s in the preterm infant increases the infant's blood volume,[7–9] improves circulatory and respiratory function,[10] reduces the need for blood transfusion,[8 10 11] and reduces the risk of intraventricular haemorrhage[8 10 11] and necrotising enterocolitis.[11] Studies to date suggest that this practice is beneficial, and no adverse effects have been identified consistently except higher peak serum bilirubin concentration.[11] The impact of delayed cord clamping on neurodevelopmental outcome has not yet been reported. A large trial of delayed cord clamping with long-term outcome would be an important step to guide practice. Even without this important information, it seems reasonable on balance, given what we know so far, to recommend delaying cord clamping for 30–60 s for infants who do not require immediate resuscitation. An alternative approach that shows promise and would avoid the dilemma of delayed resuscitation is milking the umbilical cord at birth.[12] Several cautions apply regarding the practice of delayed cord clamping. Data are sparse for extremely preterm infants, those for whom blood conservation is most important. Moreover, there may be groups of infants, for example those with poor cardiac function from hypoxia, for whom volume loading at birth would be harmful. A third approach that has been used is to collect blood from the placenta at birth for later transfusion into preterm infants.[9 13–16] This approach has been limited by the practical challenge of collecting adequate volumes of sterile, anticoagulated, non-haemolysed blood of sufficient quality from the placentas of infants born before 29 weeks' gestation, the group most likely to need transfusion later.[9 16–18]

When viewed in the context of RBC transfusions for preterm infants, delayed cord clamping is a form of autologous transfusion; as such, it avoids some of the risks associated with allogeneic transfusion. The hope is that providing the baby with a larger blood volume from the beginning would give him or her a better chance of withstanding the blood loss by phlebotomy for laboratory monitoring without the need for allogeneic transfusion.

Limiting blood loss by phlebotomy

Perhaps the most important single factor contributing to the magnitude of anaemia in preterm infants is the volume of blood taken by phlebotomy for laboratory monitoring. Reports of the mean volume of blood lost by phlebotomy range from 1.1 to 3.5 ml/kg/day.[19–23] It is common for the cumulative phlebotomy loss for laboratory analysis during the first weeks of life to equal or exceed the infant's total circulating blood volume.[24] Efforts should be made to limit phlebotomy loss by using micro-methods for laboratory analysis wherever possible and avoiding the common practice of "overdraw", collecting more blood than is needed for the analyses requested.[25] The need for transfusion can be reduced by limiting phlebotomy blood loss.[26]

Erythropoietin

Administration of recombinant human erythropoietin has been extensively evaluated as a means of avoiding RBC transfusion in preterm babies. Systematic reviews of published studies show that erythropoietin treatment, whether started in the first week of life ("early") or later ("late"), increased the chance that an infant would not require transfusion while enrolled in the study, from 33% to 49% in 15 studies of early erythropoietin and from 39% to 60% in 19 studies of late erythropoietin.[27 28] However, complete avoidance of transfusions has been elusive, in part because many infants in nearly all studies, both early and late, were transfused before enrolment. The number of transfusions was reduced with both early and late erythropoietin; however, the mean reduction was less than one transfusion per infant for both

early and late erythropoietin treatment. Similarly, the number of donor exposures was reduced with both early and late erythropoietin treatment but by an average of less than one donor per infant. If the transfusions before enrolment had been included in the analysis, the relative reductions in number of transfusions and donor exposures would have been even smaller. The risk of severe retinopathy of prematurity—stage 3 or higher—was increased with early erythropoietin treatment compared with placebo.[27] No other adverse effect of erythropoietin was found in the systematic reviews.

The benefits of erythropoietin for preterm babies in general are so small as to be of little clinical significance. However, further investigation may help to define a group of babies with more significant benefit and acceptably low risk from erythropoietin therapy.[29] It is also possible that other doses and regimens of erythropoietin will be found that are both safe and efficacious for selected groups of infants.

Nutrition

Adequate intakes of iron, folate, vitamin B12, vitamin E and protein are important to support erythropoiesis in preterm babies.[30–33] Ensuring an adequate intake of each of these essential nutrients will help to optimise erythropoiesis and may help to avoid RBC transfusions.

Use of standardised transfusion guidelines

Transfusion practices vary widely among and even within centres that treat preterm babies.[2 3 34 35] Several analyses have shown that the introduction of standardised transfusion guidelines reduces the frequency of transfusions given to preterm babies.[2 22 36–39]

BENEFITS OF TRANSFUSION

Transfusions can be life-saving when given to replace blood lost by internal or external haemorrhage—including fetomaternal haemorrhage—or by extensive haemolysis. When given to anaemic preterm infants to replace the blood lost by natural attrition and phlebotomy, the benefits are not so clear. The benefits of transfusion, documented or putative, derive from enhanced systemic oxygen transport and, in the case of acute blood loss, replenishment of low circulating blood volume. The anticipated benefit would be greatest in the most severely anaemic or hypovolaemic infant. The challenge is to transfuse whenever benefit outweighs risk and not otherwise. Potential benefits of RBC transfusion suggested by small trials of transfusion for anaemic preterm infants include prevention of apnoea[40] and promotion of weight gain.[41]

RISKS OF TRANSFUSION

Transfusion reactions, both immune-mediated and non-immune, are very rare in neonates, especially those born prematurely. Also, the risk of transmitting infection through blood transfusion is extremely low given modern methods of donor screening and testing and blood processing.[1 42] The estimated risks of transmitting infection range from 1 in 1.8 million for HIV to 1 in 171 000 for hepatitis B.[1] The risks of infection are further reduced by using a single-donor transfusion programme for preterm babies who require multiple transfusions. Although transfusion reaction and transfusion-related infection are very uncommon, transfusion of blood products can never be completely free of risk. Errors related to cross-matching and identification of patient or blood product are also very rare. Several retrospective and cohort analyses have found transfusions to be linked to retinopathy of prematurity in preterm babies,[43–48] but no causal link has been established. The smallest, sickest babies are the most heavily transfused and also the group at highest risk of retinopathy. Moreover, randomised clinical trials have shown no impact of transfusion practice on retinopathy.[49–51]

WHEN IS TRANSFUSION ADVISABLE?

What information from clinical trials do we have to guide transfusion decisions? Several small clinical trials have compared restrictive and liberal criteria for transfusing preterm babies with RBCs.[40 41 49 52 53] The findings of these studies have been inconsistent. Most of these trials showed no important difference in outcome between restrictive and liberal transfusion practices. However, more liberal transfusion was associated with less frequent apnoea in one study[40] and faster weight gain in another.[41] The ongoing need for a better understanding of appropriate indications for RBC transfusion for preterm infants led to two larger randomised clinical trials of restrictive versus liberal transfusion criteria, the Iowa trial[50] and the PINT (Premature Infants in Need of Transfusion) trial.[51]

Iowa and PINT trials

Both the Iowa trial and the PINT trial were randomised clinical trials comparing restrictive and liberal transfusion criteria, but there were important differences in study design and results.[54] The Iowa trial was conducted in a single centre; the PINT trial was a multicentre trial with 10 participating centres. The PINT trial was larger, with 451 subjects versus 100 in the Iowa trial. The babies in the PINT trial were smaller (mean birth weight 0.77 vs 0.95 kg) and more premature (mean gestational age 26 vs 28 weeks). Both trials used transfusion thresholds (haematocrits or haemoglobins) that varied with patient status, respiratory support needed and, in the PINT trial, postnatal age. The transfusion thresholds in the restrictive groups were similar in the two trials, but the transfusion thresholds for the liberal groups were considerably higher in the Iowa trial than in the PINT trial. The transfusion threshold for the youngest, sickest babies in the Iowa trial was a haemoglobin concentration of 15.3 g/dl (haematocrit 46%), whereas in the PINT trial, it was 13.5 g/dl (capillary). In contrast, the transfusion thresholds for the oldest, most stable babies were similar, 7.3 g/dl in the Iowa trial versus 7.5 g/dl (capillary) in the PINT trial. As a result, the difference in mean haemoglobin between the restrictive and liberal groups was higher in the Iowa trial, 2.7 versus 1.1 g/dl in the PINT trial.[54]

The primary outcomes were also different. The Iowa trial was designed to test whether using more restrictive transfusion criteria (lower transfusion thresholds) would reduce the number of transfusions received by preterm infants with birth weight of 500–1300 g. The PINT trial was designed to examine the impact of transfusion strategy on the incidence of a composite outcome—death, retinopathy of prematurity, bronchopulmonary dysplasia, or abnormal brain ultrasound—in infants with birth weight below 1000 g.

In the Iowa trial, the restrictive transfusion group received fewer transfusions, but the number of donor exposures was not reduced, presumably because a single-donor transfusion programme was used. In the PINT trial, the number of transfusions given according to study criteria was reduced in the restrictive transfusion group, but the total number of transfusions was not significantly different because there were more transfusions outside the study protocol in the restrictive group than in the liberal group. In the PINT trial, the number of donor exposures from RBC transfusions alone was not reduced by restrictive transfusion criteria, but the total number of donors, including platelet and plasma transfusions, was reduced.

Perhaps the most important measure of success in limiting transfusions is the number of infants who receive no transfusions at all. In the Iowa trial, the restrictive transfusion guidelines did not allow a greater number of infants to avoid transfusion altogether. In the restrictive transfusion group, 10% of infants received no transfusions, and in the liberal group, 12% received none. In the PINT trial, in contrast, the restrictive transfusion guidelines allowed more infants to avoid transfusion, 11% vs 5%.

In the Iowa trial, several adverse outcomes were more common among the restrictive transfusion babies than among their liberally transfused counterparts. Of particular interest and concern, major abnormalities on cranial ultrasound scans were more common in the restrictive transfusion group in the Iowa trial. Six infants (12%) in the restrictive transfusion group had parenchymal brain haemorrhage or periventricular leucomalacia (or both) versus none in the liberal transfusion group. This finding must be viewed with caution; whereas each of the outcomes, parenchymal brain haemorrhage and periventricular leucomalacia, was a planned secondary outcome, analysis of the composite outcome of parenchymal brain haemorrhage or periventricular leucomalacia was not planned from the beginning of the trial but was done only after non-significant trends were seen in both of the two component outcomes. Nevertheless, if this finding is to be believed, the number needed to treat using the Iowa liberal transfusion thresholds to prevent one case of severe brain injury is only eight. The composite outcome of severe brain injury or death was also significantly greater in the restrictive transfusion group, 16% vs 2%. In contrast, the PINT trial found no effect of transfusion practice on the rate of abnormal ultrasound scans or on the composite outcome of brain injury or death, which was 31% in each group.[54]

The Iowa trial found that the babies in the restrictive transfusion group had more frequent apnoea, both total and severe. Although the difference in apnoea frequency was statistically significant, the difference in mean events per day was so small as to be of questionable clinical significance. The PINT trial found no difference between the restrictive and liberal transfusion groups in the frequency of apnoea requiring treatment, but the analysis of apnoea in this trial was limited to this single question.

What might be the mechanism of brain protection by transfusing preterm infants more liberally? One would surmise that the higher blood oxygen content that accompanies higher haemoglobin concentration would allow better oxygen transport to the brain at times of low perfusion. Some practitioners might be concerned about increased risk of hyperviscosity with the Iowa liberal transfusion guidelines. The transfusion threshold used for ventilated babies in the Iowa liberal transfusion group was haematocrit 46%. The infants were transfused with 15 ml/kg packed RBCs whenever their haematocrit fell below 46%. Transfusing this volume of RBCs with this pretransfusion haematocrit would typically raise the haematocrit to about 58%, which is not enough to cause hyperviscosity,[55] especially in preterm infants, whose plasma protein concentrations are lower than those of term infants. A second potential mechanism by which more liberal transfusion guidelines might help to ensure adequate brain oxygen delivery is by reducing the frequency and severity of apnoea.

CONCLUSIONS

What are we left to conclude from the Iowa and PINT trials? Restrictive transfusion guidelines based on haemoglobin or haematocrit transfusion thresholds may reduce the need for RBC transfusions in preterm babies. However, if a single-donor programme is used, the number of donor exposures is not significantly reduced by restrictive transfusion guidelines. The Iowa trial suggests that liberal transfusion practices, as used in this study, may protect against brain injury; but this conclusion depends on a composite outcome that was not originally planned as part of the analysis. Based on the Iowa trial, higher transfusion thresholds may reduce apnoea frequency and severity, but the magnitude of the reduction is of marginal clinical significance.

Are there better indicators of transfusion than haemoglobin or haematocrit? More accurate yet practical transfusion triggers have eluded investigators. Potential triggers examined have included circulating RBC volume,[56] blood lactate[57] and fractional oxygen extraction.[58] So far, there is insufficient evidence that any of these is better than haematocrit or haemoglobin

as a guide to the need for transfusion. Moreover, RBC volume and fractional oxygen extraction are not easily applied in the clinical arena.

The information provided in the original reports of the Iowa trial and the PINT trial is limited to outcomes during hospitalisation. It will be very important to re-examine the subjects of these trials later in infancy and childhood to provide additional data on their neurodevelopmental outcomes. Abnormalities of brain imaging studies are of less concern if they are not accompanied by adverse long-term effects on brain function.

In the meantime, as we await more information, efforts should focus on limiting the anaemia of prematurity by allowing the baby to begin extrauterine life with a larger blood volume and minimising the blood loss by phlebotomy for laboratory analyses. Some guidelines for transfusion should be used, but how the guidelines should be constructed is still up for discussion. Until we know more about the impact of liberal and restrictive transfusion practices on long-term outcome, it would seem prudent to avoid pushing too hard to avoid transfusing preterm babies. As the restrictive transfusion guidelines were similar in the Iowa and PINT trials, these should be considered the lower limit of safe transfusion thresholds, at least until more is known about the long-term impact of maintaining lower haemoglobin concentrations. For young, mechanically ventilated preterm infants, the capillary haemoglobin should not be less than 11.5 g/dl; for older, stable infants, the haemoglobin should not be allowed to fall below 7.5 g/dl. The burden of proving safety falls to anyone who proposes to use even more restrictive transfusion practices.

Acknowledgements

This review and some of the research described herein were supported by grants p01 HL46925 and m01 RR00059 from the National Institutes of Health.

References

1. Galel SA, Fontaine MJ. Hazards of neonatal blood transfusion. NeoReviews 2006;7:e69–74.
2. Liu EA, Mannino FL, Lane TA. Prospective, randomized trial of the safety and efficacy of a limited donor exposure transfusion program for premature neonates. J Pediatr 1994;125:92–6. [PubMed: 8021796]
3. Wood A, Wilson N, Skacel P, et al. Reducing donor exposure in preterm infants requiring multiple blood transfusions. Arch Dis Child Fetal Neonatal Ed 1995;72:F29–33. [PubMed: 7743280]
4. Lee DA, Slagle TA, Jackson TM, et al. Reducing blood donor exposures in low birth weight infants by the use of older, unwashed packed red blood cells. J Pediatr 1995;126:280–6. [PubMed: 7844679]
5. Strauss RG, Burmeister LF, Johnson K, et al. AS-1 red cells for neonatal transfusions: a randomized trial assessing donor exposure and safety. Transfusion 1996;36:873–8. [PubMed: 8863773]
6. Strauss RG. Controversies in the management of the anemia of prematurity using single-donor red blood cell transfusions and/or recombinant human erythropoietin. Transfus Med Rev 2006;20:34–44. [PubMed: 16373186]
7. Aladangady N, McHugh S, Aitchison TC, et al. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. Pediatrics 2006;117:93–8. [PubMed: 16396865]
8. Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology 2008;93:138–44. [PubMed: 17890882]
9. Strauss RG, Mock DM, Johnson KJ, et al. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. Transfusion 2008;48:658–65. [PubMed: 18194383]
10. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev 2004;(4):CD003248. [PubMed: 15495045]
11. Reynolds GJ. Beyond sweetness and warmth: transition of the preterm infant. Arch Dis Child Fetal Neonatal Ed 2008;93:F2–3. [PubMed: 18156444]

12. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F14–19. [PubMed: 17234653]
13. Ballin A, Arbel E, Kenet G, et al. Autologous umbilical cord blood transfusion. Arch Dis Child Fetal Neonatal Ed 1995;73:F181–3. [PubMed: 8535878]
14. Surbek DV, Glanzmann R, Senn HP, et al. Can cord blood be used for autologous transfusion in preterm neonates? Eur J Pediatr 2000;159:790–1. [PubMed: 11039140]
15. Brune T, Garritsen H, Hentschel R, et al. Efficacy, recovery, and safety of RBCs from autologous placental blood: clinical experience in 52 newborns. Transfusion 2003;43:1210–15. [PubMed: 12919422]
16. Jansen M, Brand A, von Lindern JS, et al. Potential use of autologous umbilical cord blood red blood cells for early transfusion needs of premature infants. Transfusion 2006;46:1049–56. [PubMed: 16734824]
17. Anderson S, Fangman J, Wager G, et al. Retrieval of placental blood from the umbilical vein to determine volume, sterility, and presence of clot formation. Am J Dis Child 1992;146:36–9. [PubMed: 1736646]
18. Bifano EM, Dracker RA, Lorah K, et al. Collection and 28-day storage of human placental blood. Pediatr Res 1994;36:90–4. [PubMed: 7936844]
19. Kakaiya RM, Morrison FS, Rawson JE, et al. Pedi-Pack transfusion in a newborn intensive care unit. Transfusion 1979;19:19–24. [PubMed: 432909]
20. Nexø E, Christensen NC, Olesen H. Volume of blood removed for analytical purposes during hospitalization of low-birthweight infants. Clin Chem 1981;27:759–61. [PubMed: 7226502]
21. Obladen M, Sachsenweger M, Stahnke M. Blood sampling in very low birth weight infants receiving different levels of intensive care. Eur J Pediatr 1988;147:399–404. [PubMed: 3396595]
22. Alagappan A, Shattuck KE, Malloy MH. Impact of transfusion guidelines on neonatal transfusions. J Perinatol 1998;18:92–7. [PubMed: 9605296]
23. Ringer SA, Richardson DK, Sacher RA, et al. Variations in transfusion practice in neonatal intensive care. Pediatrics 1998;101:194–200. [PubMed: 9445491]
24. Widness JA, Madan A, Grindeanu LA, et al. Reduction in red blood cell transfusions among preterm infants: results of a randomized trial with in-line blood gas and chemistry monitor. Pediatrics 2005;115:1299–1306. [PubMed: 15867038]
25. Lin, JC.; Strauss, RG.; Kulhavy, JC., et al. Phlebotomy overdraw in the neonatal intensive care nursery; Pediatrics. 2000. p. 106http://pediatrics.publications.org.cgi/content/full/106/2/e19
26. Madan A, Kumar R, Adams MM, et al. Reduction in red blood cell transfusions using a bedside analyzer in extremely low birth weight infants. J Perinatol 2005;25:21–5. [PubMed: 15496875]
27. Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2006;(3):CD004863. [PubMed: 16856062]
28. Aher S, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2006;(3):CD004868. [PubMed: 16856064]
29. Meyer MP, Sharma E, Carsons M. Recombinant erythropoietin and blood transfusion in selected preterm infants. Arch Dis Child Fetal Neonatal Ed 2003;88:F41–5. [PubMed: 12496225]
30. Bechensteen AG, Håga P, Halvorsen S, et al. Erythropoietin, protein, and iron supplementation and the prevention of anaemia of prematurity. Arch Dis Child 1993;69:19–23. [PubMed: 8346946]
31. Worthington-White DA, Behnke M, Gross S. Premature infants require additional folate and vitamin B-12 to reduce the severity of anemia of prematurity. Am J Clin Nutr 1994;60:930–5. [PubMed: 7985636]
32. Franz AR, Mihatsch WA, Sander S, et al. Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. Pediatrics 2000;106:700–6. [PubMed: 11015511]
33. Haiden N, Klebermass K, Cardona F, et al. A randomized, controlled trial of the effects of adding vitamin B_{12} and folate to erythropoietin for the treatment of anemia of prematurity. Pediatrics 2006;118:180–8. [PubMed: 16818564]

34. Maier RF, Obladen M, Messinger D, et al. Factors related to transfusion in very low birthweight infants treated with erythropoietin. Arch Dis Child Fetal Neonatal Ed 1996;74:F182–6. [PubMed: 8777681]
35. Bednarek FJ, Weisberger S, Richardson DK, et al. Variations in blood transfusions among newborn intensive care units. J Pediatr 1998;133:601–7. [PubMed: 9821414]
36. Widness JA, Seward VJ, Kromer IJ, et al. Changing patterns of red blood cell transfusion in very low birth weight infants. J Pediatr 1996;129:680–7. [PubMed: 8917234]
37. Maier RF, Sonntag J, Walka MM, et al. Changing practices of red blood cell transfusions in infants with birth weights less than 1000 g. J Pediatr 2000;136:220–4. [PubMed: 10657829]
38. Franz AR, Pohlandt F. Red blood cell transfusions in very and extremely low birthweight infants under restrictive transfusion guidelines: is exogenous erythropoietin necessary? Arch Dis Child Fetal Neonatal Ed 2001;84:F96–100. [PubMed: 11207224]
39. Myashiro AM, dos Santos N, Guinsburg R, et al. Strict red blood cell transfusion guideline reduces the need for transfusions in very-low-birthweight infants in the first 4 weeks of life: a multicentre trial. Vox Sanguinis 2005;88:107–13. [PubMed: 15720608]
40. Ross MP, Christensen RD, Rothstein G, et al. A randomized trial to develop criteria for administering erythrocyte transfusions to anemic preterm infants 1 to 3 months of age. J Perinatol 1989;9:246–53. [PubMed: 2681578]
41. Meyer J, Sive A, Jacobs P. Empiric red cell transfusion in asymptomatic preterm infants. Acta Paediatr 1993;82:30–4. [PubMed: 8453217]
42. Bell MD. Red blood cell transfusions. Pediatr Rev 2007;28:299–304. [PubMed: 17670954]
43. Clark C, Gibbs JA, Maniello R, et al. Blood transfusion: a possible risk factor in retrolental fibroplasia. Acta Paediatr Scand 1981;70:537–9. [PubMed: 6895573]
44. Sacks LM, Schaffer DB, Anday EK, et al. Retrolental fibroplasia and blood transfusion in very low-birth-weight infants. Pediatrics 1981;68:770–4. [PubMed: 6895663]
45. Cooke RWI, Clark D, Hickey-Dwyer M, et al. The apparent role of blood transfusions in the development of retinopathy of prematurity. Eur J Pediatr 1993;152:833–6. [PubMed: 8223786]
46. Hesse L, Eberl W, Schlaud M, et al. Blood transfusion: iron load and retinopathy of prematurity. Eur J Pediatr 1997;156:465–70. [PubMed: 9208245]
47. Inder TE, Clemett RS, Austin NC, et al. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. J Pediatr 1997;131:541–4. [PubMed: 9386655]
48. Dani C, Reali MF, Bertini G, et al. The role of blood transfusions and iron intake on retinopathy of prematurity. Early Hum Dev 2001;62:57–63. [PubMed: 11245995]
49. Brooks SE, Marcus DM, Gillis D, et al. The effect of blood transfusion protocol on retinopathy of prematurity: a prospective, randomized study. Pediatrics 1993;82:30–4.
50. Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005;115:1685–91. [PubMed: 15930233]
51. Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301–7. [PubMed: 16939737]
52. Blank JP, Sheargren TC, Vajaria J, et al. The role of RBC transfusion in the premature infant. Am J Dis Child 1984;138:831–3. [PubMed: 6206718]
53. Ransome OJ, Moosa EA, Mothebe FM, et al. Are regular “top-up” tranfusions necessary in otherwise well, growing premature infants? S Afr Med J 1989;75:165–6. [PubMed: 2645662]
54. Bell EF. Transfusion thresholds for preterm infants: how low should we go? J Pediatr 2006;149:287–9. [PubMed: 16939732]
55. Rosenkrantz TF. Polycythemia and hyperviscosity in the newborn. Semin Thromb Hemost 2003;29:515–27. [PubMed: 14631551]
56. Strauss RG, Mock DM, Johnson K, et al. Circulating RBC volume, measured with biotinylated RBCs, is superior to the Hct to document the hematologic effects of delayed versus immediate umbilical cord clamping in preterm neonates. Transfusion 2003;43:1168–72. [PubMed: 12869126]
57. Frey B, Losa M. The value of capillary whole blood lactate for blood transfusion requirements in anaemia of prematurity. Intens Care Med 2001;27:222–7.

58. Wardle SP, Garr R, Yoxall CW, et al. A pilot randomised controlled trial of peripheral fractional oxygen extraction to guide blood transfusions in preterm infants. Arch Dis Child Fetal Neonatal Ed 2002;86:F22–7. [PubMed: 11815543]