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Darbepoetin Use in the Management of Anemia of Prematurity Clinical Pathway

Johns Hopkins All Children's Hospital

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patient based on the patient's individualized circumstances and the practitioner's professional judgment.

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Rationale

Darbepoetin is utilized in the neonatal populations as an approach to the management of anemia of prematurity. There is no strong published data available for or against its use and different institutions across the country have come up with their own recommendations for patient selection, age at first administration, dosage and duration of treatment. This clinical pathway was proposed as a consensus amongst neonatal experts and JHACH neonatology physicians as how to best approach dosing, supplementation and initiation/discontinuation in the neonatal population given the available evidence-based medical literature for its usage.

Background / Published Data and Levels of Evidence

Anemia of prematurity is a known entity in premature neonates resulting from the impaired ability of neonate to increase serum erythropoietin appropriately in the setting of anemia and decreases tissue availability of oxygen (15,16,17). Management of anemia of prematurity consists of iron supplementation, laboratory monitoring, red blood cell transfusion and erythropoiesis stimulating agents.

Administration of erythropoiesis stimulating agents (ESAs) (namely Erythropoietin (EPO) and Darbepoetin) has been proposed as a strategy for treating anemia of prematurity while decreasing the number of RBC transfusions and potential number of blood donors to which the infant is exposed. The major focus of this guideline is to address the usage of Darbepoetin for anemia of prematurity.

a. Early ESA use (less than or equal to 7 days of life)- grade 1B

- Early administration of EPO has been shown to reduce the number of transfusions required in preterm infants, though the small reduction is thought to be of limited clinical importance. This is because, although the total number of transfusions was decreased in these studies, the use of EPO did not decrease the number of donor exposures.
- There are potential neuroprotective effects with administration of early EPO but this is this was not substantiated with the results of the PENUT trial (1).
- Given that erythropoietin is a vascular growth factor, known to play a role in the developing human eye, concerns have been raised that administration of EPO may increase both the risk and severity of retinopathy of prematurity (ROP). This risk was observed in initial studies with use of early EPO but not replicated in subsequent studies (2,3).

- A systematic 2020 Cochrane review and meta-analysis was performed which confirmed these findings, comparing the use of EPO to both placebo and no intervention. The findings are as listed below (4):
 - Early ESAs reduced the risk of 'use of one or more [red blood cell] RBC transfusions' (typical risk ratio (RR) 0.79, 95% confidence interval (CI) 0.74 to 0.85; typical risk difference (RD) -0.14, 95% CI -0.18 to -0.10; I² = 69% for RR and 62% for RD (moderate heterogeneity); number needed to treat for an additional beneficial outcome (NNTB) 7, 95% CI 6 to 10; 19 studies, 1750 infants). The quality of the evidence was low.
 - Necrotizing enterocolitis was significantly reduced in the ESA group compared with the placebo group (typical RR 0.69, 95% CI 0.52 to 0.91; typical RD -0.03, 95% CI -0.05 to -0.01; I² = 0% for RR and 22% for RD (low heterogeneity); NNTB 33, 95% CI 20 to 100; 15 studies, 2639 infants). The quality of the evidence was moderate.
 - Data show a reduction in 'Any neurodevelopmental impairment at 18 to 22 months' corrected age in the ESA group (typical RR 0.62, 95% CI 0.48 to 0.80; typical RD -0.08, 95% CI -0.12 to -0.04; NNTB 13, 95% CI 8 to 25. I² = 76% for RR (high heterogeneity) and 66% for RD (moderate); 4 studies, 1130 infants). The quality of the evidence was low.
 - Results reveal increased scores on the Bayley-II Mental Development Index (MDI) at 18 to 24 months in the ESA group (weighted mean difference (WMD) 8.22, 95% CI 6.52 to 9.92; I² = 97% (high heterogeneity); 3 studies, 981 children). The quality of the evidence was low.
 - The total volume of RBCs transfused per infant was reduced by **7 mL/kg**. The number of RBC transfusions per infant was minimally reduced, but the number of donors to whom infants who were transfused were exposed was not significantly reduced.
 - Data show no significant difference in risk of stage ≥ 3 retinopathy of prematurity (ROP) with early EPO (typical RR 1.24, 95% CI 0.81 to 1.90; typical RD 0.01, 95% CI -0.02 to 0.04; I² = 0% (no heterogeneity) for RR; I² = 34% (low heterogeneity) for RD; 8 studies, 1283 infants).
 - Mortality was not affected, but results show significant reductions in the incidence of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).
- Per the 2020 Cochrane systematic review and meta-analysis and subsequent literature/reviews, it was published: "Early administration of ESAs reduces the use of red blood cell (RBC) transfusions, the volume of RBCs transfused, and donor exposure after study entry. Small reductions are likely to be of limited clinical importance. Donor exposure probably is not avoided, given that all but one study included infants who had received RBC transfusions before trial entry. This update found no significant difference in the rate of ROP (stage ≥ 3) for studies that initiated EPO treatment at less than eight days of age, which has been a topic of concern in earlier versions of this review. Early EPO treatment significantly decreased rates of IVH, PVL, and NEC. Neurodevelopmental outcomes at 18 to 22 months and later varied in published studies. Ongoing research should evaluate current clinical practices that will limit donor

exposure. Promising but conflicting results related to the neuro protective effect of early EPO require further study. Very different results from the two largest published trials and high heterogeneity in the analyses indicate that we should wait for the results of two ongoing large trials before drawing firm conclusions. Administration of EPO is not currently recommended because limited benefits have been identified to date.”

- Recent publications have shown overall safety of the erythropoiesis stimulating agents and no differences in the incidence of any stage of ROP or visual impairment at 18-22 months' corrected age (5,6,7,8,9).
- These conclusions were further substantiated as the results of the Preterm Erythropoietin Neuroprotection Trial were published in 2020, finding no difference in ROP between the EPO and placebo groups (18).

b. Late ESA use (between 8 and 28 days of life) - grade 1B

- The late use of ESAs, defined as between 8 and 28 days of life, namely EPO, has also been proposed with the goal of reducing the use of RBC transfusions in preterm and/or low birth weight infants. Studies overall have shown that late administration of EPO does in fact reduce the number of RBC transfusions administered but this was found to be of “limited benefit.” (10)
- An additional Cochrane systematic review and meta-analysis was performed in 2014 which evaluated the effects of late EPO administration (at or later than 8 days of age) late EPO administration (at or later than eight days of age up to 28 days of age) compared with placebo or no intervention. (10) Of note, the majority of the infants in the analyzed studies had previously received at least 1 blood transfusion prior to enrollment. The following findings were noted (10):
 - EPO reduced the risk of receiving one or more red blood cell transfusions (RR 0.71, 95% CI 0.64-0.79).
 - EPO reduced the number of red blood cell transfusions (weighted mean difference of -0.22, 95% CI -0.38 to -0.06).
 - There was no difference in the volume of blood transfused (mean difference -1.6 mL/kg, 95% CI -5.8 to 2.6).
 - EPO had no effect on the rates for ROP, mortality, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), hypertension, length of hospital stay, or long term neurodevelopmental outcome. However, there was a trend towards an increased risk of ROP associated with EPO administration (RR 1.27, 95% CI 0.99-1.64).
 - Late administration of EPO reduced the mean number of transfusions by a little less than one transfusion per infant. This small benefit of EPO was diminished due to the exposure of previous blood transfusions before eight days of life, and the use of satellite packs that would mitigate against additional donor exposure in the control group.
- The 2014 Cochrane systematic review and meta-analysis concluded that if cost is an issue, “, we recommend NOT to routinely administer EPO after eight days because its limited benefit of limiting exposure to blood donors does not justify its cost.” (10)

c. Use of ESAs after 28 days (“late-late use”)

- There is no published data about the use of ESAs after 28 days of life.
- Darbepoetin was utilized at our institution prior to publishing this clinical practice guideline in 2018. Its use was not standardized, with no clear guidance or thresholds when determining initiation, discontinuation, nutritional supplementation or laboratory monitoring.
- This clinical practice guideline was first approved and adopted into practice in 2018, as a consensus for usage at JHACH. We have utilized the phrase “late-late darbepoetin” when discussing our usage. Our data from this time period has shown efficacy in treating anemia of prematurity, without changes in rates of ROP, severe ROP, mortality, and NEC, similar to the data seen on the various published studies of both early and late utilization of ESAs. When comparing rate of ROP and severe ROP from this time period to historical rates of ROP at our institution both pre-guideline and pre-usage in our neonatal ICU, no differences have been appreciated.

d. Erythropoietin versus darbepoetin alfa- grade 1B

- If EPO is given, it can be administered intravenously three times a week as a once daily infusion of 200 units/kg per dose or as a continuous infusion over 24 hours of 300 units/kg; or subcutaneously (400 units/kg per dose, three times per week). (11)
- Darbepoetin alfa is a longer acting ESA, has been used in preterm infants using a weekly dose of 10 mcg/kg (12). Overall, fewer injections are required when administered in Darbepoetin as an ESA when compared to Erythropoietin.

e. Dosing of Darbepoetin, nutrition and laboratory monitoring- grade 1B

- Infants treated with EPO require additional iron supplementation. A proposed regimen is a daily elemental iron dose of 6 mg/kg for infants on full enteral feedings, and 3 mg/kg for those taking at least 60 mL/kg per day (6). For infants receiving total parental nutrition, iron dextran be added to the solution (3 to 5 mg/kg weekly or 0.5 mg/kg qd) (11).
- The reticulocyte count, central hematocrit or hemoglobin concentration, and absolute neutrophil count are measured before as well as one to two weeks after starting EPO treatment. EPO is withheld if the absolute neutrophil count is less than 1000/microL. Serum ferritin levels may be useful in evaluating those infants who are not responding to therapy to detect iron deficiency (11).

Clinical Management

Based on the known evidence utilizing erythropoiesis stimulating agents (ESAs) in the

management of anemia of prematurity, its proven safety and the benefits that infants have experienced in our institutions over the past 4 years since implementing a clinical pathway for its routine use, we have performed a thorough review of the recent literature and revised our recommendations as proposed:

The clinical practice guideline addresses the late (defined as 8 to 28 days of age) to late-late (defined as greater than 28 days of age) use of ESAs in order to reduce the need for red blood cell transfusions and overall donor exposure.

1. Darbepoetin administration could be considered in the following scenarios:
 - a. Infants with a hematocrit ≤ 30 mg/dL, who do NOT require an acute red blood cell transfusion.
 - i. If the premature infant was born at ≤ 28 0/7 weeks of age and is less than 28 days of age a packed red blood cell transfusion should be considered depending on clinical status.
 - ii. If the premature infant was born at ≤ 28 0/7 weeks of age and is greater than 28 days old administration of Darbepoetin could be considered *.
 1. Dosing:
 - a. 10 μ g/kg subcutaneous injection once weekly
 2. Nutrition:
 - a. If receiving enteral nutrition:
 - i. At ≥ 60 ml/kg/day, begin supplemental Fe at 3 mg/kg/day
 - ii. At ≥ 120 ml/kg/day, increase the supplemental Fe to 6 mg/kg/day
 - iii. FeSO₄ dosing/information
 1. *Poly-vi-sol with iron includes 11 mg of iron per ml, Fer-in-sol provides 15 mg iron per ml*
 2. Example: for a 1.5 kg baby
 - a. *Total iron needed: 1.5 kg x 6 mg/kg of elemental iron= 9 mg total iron needed*
 - b. *Subtract the 5.5 mg of iron from PVS at 0.5 ml/day = 3.5 mg iron needed*
 - c. *Would be 2.3 mg/kg iron needed in this example: 3.5 mg iron/1.5 kg) . Pharmacy would prefer it to be ordered total per day (not per kg)*
 - b. If NPO:
 - i. Consider stopping Darbepoetin based on clinical status

- ii. If continuing, consider IV iron sucrose at the discretion of the team (IV iron sucrose 1 mg/kg per day in TPN OR 6 mg/kg once weekly)
 - c. Laboratory Monitoring:
 - i. Weekly hematocrit and reticulocyte count to start 1 week after initiation
 - ii. ANC prior to initiation and q2 weeks after initiation
 - iii. Ferritin
 - 1. Check serum ferritin for patients who do not appear to respond adequately after 4 doses, to determine adequacy of iron supplementation.
 - 2. Obtain CRP at same time as ferritin
 - d. Discontinuation of darbepoetin:
 - i. When hematocrit is ≥ 35 mg/dL, if the patient receives blood transfusion or when patient is clinically ready for discharge
- iii. If the premature infant was born at ≥ 28 0/7 weeks of age, but less than 21 days of life a packed red blood cell transfusion should be considered depending on clinical status.
- iv. If the infant was born at ≥ 28 0/7 weeks of age and is greater than 21 days old, administration of darbepoetin could be considered *.
 - 1. Dosing:
 - a. 10 μ g/kg subcutaneous injection once weekly
 - 2. Nutrition:
 - a. If receiving enteral nutrition:
 - i. At ≥ 60 ml/kg/day, begin supplemental Fe at 3 mg/kg/day
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 - c. *Would be 2.3 mg/kg iron needed in this example: 3.5 mg iron/1.5 kg) . Pharmacy would prefer it to be ordered total per day (not per kg)*

- b. If NPO:
 - i. Consider stopping Darbepoetin based on clinical status
 - ii. If continuing, consider IV iron sucrose at the discretion of the team (IV iron sucrose 1 mg/kg per day in TPN OR 6 mg/kg once weekly)
- c. Laboratory Monitoring:
 - i. Weekly hematocrit and reticulocyte count to start 1 week after initiation
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- d. Discontinuation of darbepoetin:
 - i. When hematocrit is ≥ 35 mg/dL, if the patient receives blood transfusion or when patient is clinically ready for discharge

**: In certain circumstances applicable to the premature infant individual needs and at the discretion of the treating neonatologist, Darbepoetin could be initiated as early as one week prior to the recommended age above*

Summary

Anemia of prematurity is a known entity in premature neonates resulting from the impaired ability of neonate to increase serum erythropoietin appropriately in the setting of anemia and decreases tissue availability of oxygen. Management of anemia of prematurity consists of iron supplementation, laboratory monitoring, red blood cell transfusion and erythropoiesis stimulating agents. Administration of erythropoiesis stimulating agents (ESAs) (namely Erythropoietin (EPO) and Darbepoetin) has been proposed as a strategy for treating anemia of prematurity while decreasing the number of RBC transfusions and potential number of blood donors to which the infant is exposed. The major focus of this guideline is to address the usage of Darbepoetin for anemia of prematurity.

Both early administration of ESAs, defined as initiation at ≤ 7 days of age, and late administration of ESAs, defined as initiation between 8 and 28 days of age, appear to avoid the need to red blood cell transfusions, though with limited efficacy in decreasing the number of donors to which the infant is exposed. Many questions have been raised about the cost of such a therapy when the overall benefits appear limited.

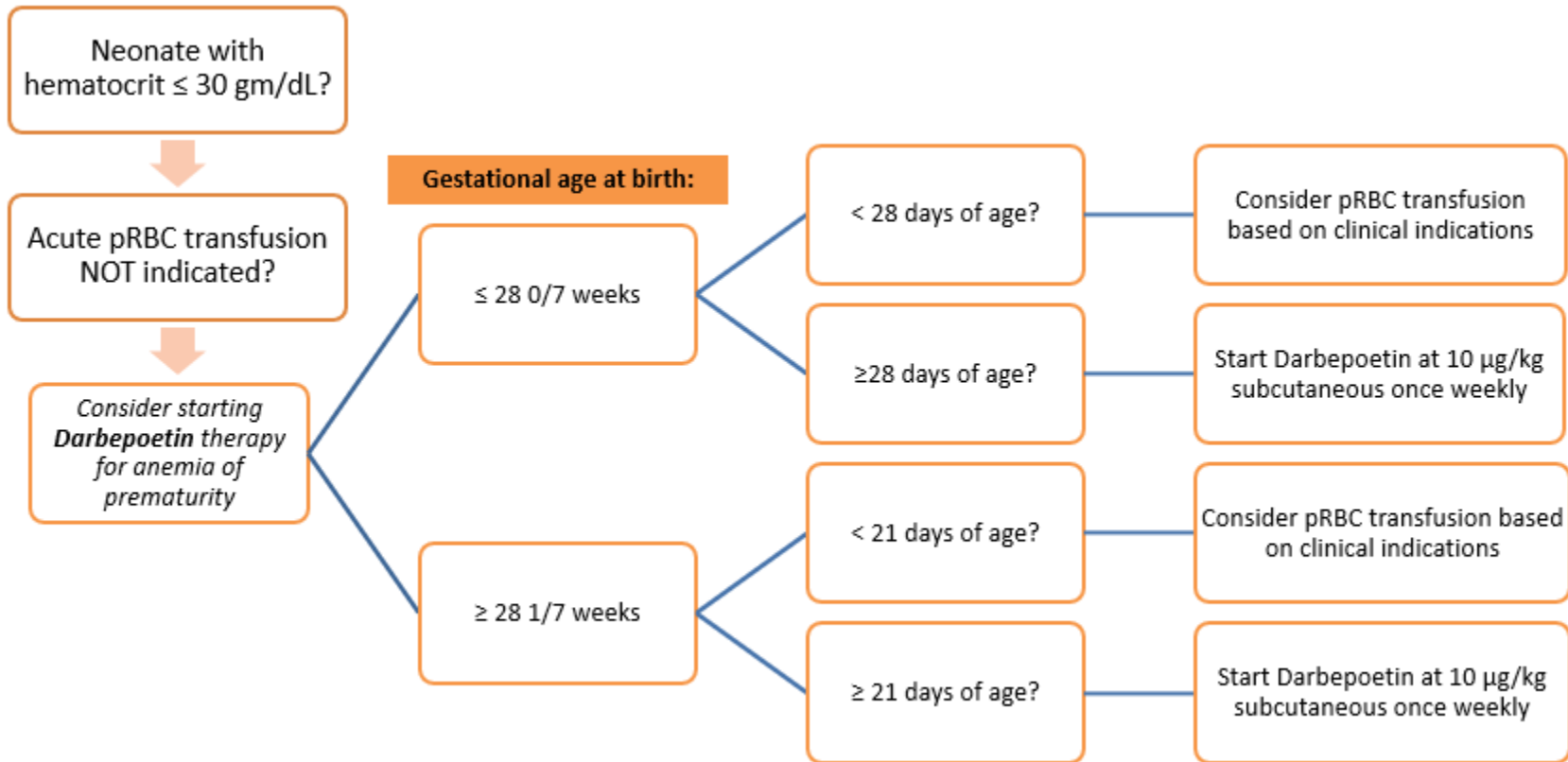
The current usage at Johns Hopkins All Children's Hospital is that of "late-late" administration of ESAs, namely Darbepoetin at >28 days of age. The side effects of therapy with Darbepoetin,

both transient neutropenia and iron deficiency, have been found to be minimal and easily detected with routine laboratory monitoring as well as adequate iron supplementation. In combination with the limiting and monitoring of blood drawn, a restrictive policy for red blood cell transfusions, and the use of satellite packs, which would allow for repeated transfusions from the same donor to the individual infant, the use of Darbepoetin in the management of anemia of prematurity can be useful to limit the need for RBC transfusions.

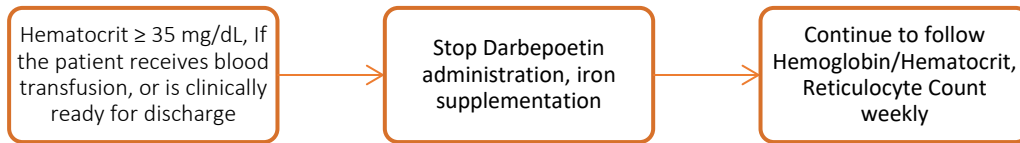
This clinical practice guideline aims to integrate our current approach to the use of Darbepoetin in the management and treatment of anemia of prematurity, namely dosing, nutritional supplementation, laboratory monitoring, initiation and discontinuation, so that the appropriate patients receive this medication in the safest and most consistent manner.

Darbepoetin Use in the Management of Anemia of Prematurity/ Pathway

Algorithm: initiation of Darbepoetin (Appendix A)



Algorithm: Discontinuation of Darbepoetin (Appendix B)



Darbepoetin: dosing, nutrition, laboratory monitoring (Appendix C)

Darbepoetin Dosing	Nutrition	Laboratory monitoring
<ul style="list-style-type: none">• 10 µg/kg subcutaneous injection once weekly	<ul style="list-style-type: none">• <u>If receiving enteral nutrition:</u><ul style="list-style-type: none">• At ≥ 60 ml/kg/day begin supplemental Fe at 3 mg/kg/day• At ≥ 120 ml/kg/day, increase the supplemental Fe to 6 mg/kg/day• <u>If NPO:</u><ul style="list-style-type: none">• Consider stopping Darbepoetin based on clinical status• If continuing Darbepoetin, consider providing IV iron sucrose at the discretion of the team.• 1 mg/kg per day in TPN OR 6 mg/kg once weekly	<ul style="list-style-type: none">• Weekly hematocrit, reticulocyte count to start 1 week after initiation• ANC prior to initiation and q2 weeks after initiation• Ferritin<ul style="list-style-type: none">• Check serum ferritin for patients who do <u>not</u> appear to respond adequately after 4 doses, to determine adequacy of iron supplementation.• Obtain CRP at same time as ferritin• <i>Avoid unnecessary lab draws!</i>

Glossary

- ESAs (erythropoiesis stimulating agent)
- AOP (anemia of prematurity)
- EPO (erythropoietin)
- ROP (retinopathy of prematurity)
- RBC transfusion (red blood cell transfusion)

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Appendix

- a. Darbepoetin administration algorithm
- b. Discontinuation of darbepoetin
- c. Dosing/Nutrition/laboratory monitoring recommendations

Clinical Pathway Team

Darbepoetin Use in the Management of Anemia of Prematurity Clinical Pathway

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Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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