Transfusion Rationalization on Pediatric Ventricular Assist Devices

**BACKGROUND**

Iron deficiency and anemia are extremely common comorbidities in patients with heart and/or kidney failure, inflammatory states as well as childhood growth and blood loss. These factors are common denominators in children supported with ventricular assist devices. Clinically, despite already known effects on oxygen carrying capacity, iron depletion can reduce exercise capacity and quality of life and should be treated even in absence of anemia. Iron deficiency and anemia in hospitalized children are further affected by poor nutritional balance and blood loss. For example, frequent phlebotomy for laboratory sampling can significantly impact neonates and infant’s hemoglobin levels. Studies suggest that children can tolerate 0.25ml·kg−1·day−1 of blood sampling without a fall in hematocrit, hence sampling should be tailored to child needs balancing the net result of multiple samples and blood wasted daily.

Transfusion thresholds and the impact of excessive blood transfusions are becoming a more frequent topic of debate. Data is lacking on optimal transfusion thresholds, as are strategies for blood sparing in children with ventricular assist devices, where viscosity and shear stress can affect pump function and risk of thrombosis. Patient blood management programs and early establishment of transfusion thresholds, although well recognized and appreciated in the adult setting, are yet to become a standard of care in the pediatric patient population.

**ACTION REVISED DATE:** 01/06/21

**OBJECTIVES**

To review strategies for minimizing blood loss, while optimizing transfusion thresholds in pediatric patients supported with VADs in a broad but yet individualized approach.

**PROTOCOL**

**1. Establish lower thresholds for transfusion** (first 1-2 weeks post implant):

If patients’ clinical markers of oxygen delivery and extraction are preserved in the context of adequate hemostasis, hematocrit is targeted based on patients’ individual needs, using laboratory and clinical context such as: mixed venous saturation with an appropriate extraction ratio obtained from an upper extremity central venous line (if feasible), near-infrared spectroscopy (NIRS), arterial saturation and oxygen requirements, adequate end-organ function, or signs of exacerbated heart failure.

1. Biventricular physiology: Hematocrit of 25 or greater (suggested)
2. Univentricular physiology: Hematocrit of 30 or greater (suggested)
3. Multidisciplinary approach to establish transfusion thresholds for other blood products in the context of individual needs and according to hemostasis management algorithm used.

**2. Micro-nutrient supplementation** (1-2 weeks post implant, if not yet initiated):

* 1. Iron, reticulocytes and hemoglobin studies:
		1. If iron storages inadequate, it is suggested to start iron supplementation at 6 mg/kg/day of **elemental** iron. Iron absorption is best in the acidic gastric environment and although iron can cause gastrointestinal discomfort, administration of antacids, milk and calcium can impair its absorption and should ideally be withheld until 1 hour before or 2 hours after an iron dose. Some of the pediatric formulas have iron and vitamin supplementation, and additional supplemental iron dosing should be adjusted to the total daily dose target. Careful attention should be given to iron storage tests in the setting of hemolysis, as iron supplementation can lead to iron overload and hepatic dysfunction. In severe cases of iron deficiency and GI intolerance, iron infusions can be administered according to patient needs.
		2. Intravenous Iron:

Contraindications: Significant active infection, history of anaphylaxis with IV iron.

There are superior results when used with lower baseline ferritin & with use of concurrent erythropoietins as marrow stimulatingagents (ESA).

Total replacement dose (mg of iron) =

$$0.6\*Wt (kg)\left.\left(100- \frac{Hg (actual)}{Hg (ideal, e.g. 12)}\right.\*100\right)^{}$$

Usual preparations include Venofer™ (iron sucrose) and Injectafer™ 9(Ferric carboxymaltose), but may be institution-specific.

Routine pre-medication is not required (consider pre-medication if atopic history). Slower infusion rates decrease adverse event risk.

Even with the use of the formula, most studies have used IV iron sucrose (maximum dose of 200 mg per setting) or ferric carboxymaltose (maximum dose of 1000 mg per week).

Monitoring: HR, BP, O2 Sat every 15 minutes. Less than 1/200,000 infusions will result in serious adverse event. Common issues with administration include muscle cramps, nausea/vomiting, headache, dyspnea, extravasation, fever, blood pressure changes. Risk of anaphylaxis is low.

Follow CBC, reticulocyte count, ferritin, iron panel pre-dose and at a minimum of 1 and 4 weeks after administration.

* 1. Folic acid level, B12, and B6 levels: Folic acid is essential for DNA synthesis and erythrocyte membrane stability. It is sometimes supplemented to facilitate erythropoiesis. Folic acid and Vitamin B12 also aid in the treatment and balance of hyperhomocysteinemia together with other B vitamins.
	2. Other vitamin levels, along with an assessment of micronutrient status, can aid in absorption of iron (example Vitamin C).

Follow up studies should be drawn monthly post initiation of above supplementation.

**3. Erythropoietin (EPO) supplementation** (1-2 weeks post implant):

Erythropoietin is produced by the kidney and can be affected by renal dysfunction/injury, inflammatory states and other medications (especially chemotherapy and theophylline). Consider starting in accompaniment with iron and folic acid supplementation and, ideally, after ensuring iron storage levels adequate. Studies have shown potential increase for thrombotic events in adult population, thought to be secondary to increased viscosity and to non-specific thrombopoietin effect sometimes causing an increase in platelet count. Anecdotally, several pediatric VAD centers have implemented regular use of erythropoietin stimulating agents (ESA) without clear evidence of increased thromboembolic events. More data is needed to analyze the effect of blood product sparing and thromboembolic episodes in relationship to use of ESAs.

Some centers measure erythropoietin level prior to supplementation. These steps can be done in conjunction with hematology team. If levels are low for the Hemoglobin level, then supplementation is started. Other centers start them empirically based on the assumption of ongoing baseline hemolysis and need for transfusions. Once ESA started, one should carefully verify ESA dose-response potentially using rate of hemoglobin (Hgb) increase over time. If rapid increase in Hgb (ex: greater than 1g/dL in any 2-week period), one may decrease ESA dosing by 40-50%.

Suggested ESAs and dosing:

* 1. Epogen 50-100 Units/kg IV two to three times per week (MWF)
	2. Darbopoetin 0.45-0.8 mcg/kg/dose IV weekly

Caution: Please monitor for thrombosis in the context of ESA supplementation when platelet counts increase over 450,000. Consider stopping ESA and resume once platelet counts below 300,000. Monitor for hemolysis:

**4. Hemolysis tests: CBC, direct and indirect bilirubin, LDH, plasma free hemoglobin:**

These tests can be done periodically to monitor for hemolysis. Most patient hemolyze down to a nadir and then stop, which is usually in the range of a hematocrit of 25-35. Anecdotally, hemolysis complications have been more significant with single ventricle physiology patients. Interventions may include:

* Decrease diuresis and prevent hemoconcentration
* Check for possibility of transfusion reaction
* Check for immune mediated or cold-agglutin-mediated hemolysis due to medications or infections
* Rule out pump thrombosis
* Trial of pulse steroids in inflammatory states and to treat suspected clots (please refer to ACTION steroids harmonization document)
* Ensure adequate afterload reduction to minimize turbulent flow and shear stress
* If paracorporeal support: exchange pump to a larger pulsatile device, maintaining cardiac index with a lower ejection rate
* Change to continuous flow VAD
* Review cannulation technique and sites.

**5. Judicious laboratory frequency** (2 weeks post implant):

When patient is stable, laboratory frequency can be adjusted to minimize blood loss by phlebotomy.

* 1. Cohort extended blood sampling to once or twice a week if possible to minimize blood draws, with exception of your chosen method of anticoagulation (at discretion of institutional preference), such as monitoring for bivalirudin, heparin, or enoxaparin effect.
	2. Blood sampling techniques: if feasible, minimize waste of blood sampling by considering revising techniques, such as waste-free “push and pull” technique or point-of-care tests with nursing leadership.
	3. Explore using pediatric minimum sample volumes per institutional practice and batch sampling to optimize sample usage
	4. In case of “out of range goals” anticoagulation test results, institute a guideline practice with your local team (for example: early warning of established “out of range” results, repeat sample with adequate technique, prevention of sampling contamination, STAT laboratory test execution) in the context of clinical assessment of the patient at bedside (ex: addition of hepzyme test to verify aPTT contamination by heparinized lines, reminders of timely testing for bivalirudin aPTT samples ).

**6. Surveillance and treatment of bleeding:**

Please refer to *ACTION Bleeding protocol*.

If significant or major bleeding, consider investigation for innate or acquired factor related deficiencies and conditions, such as Factor V, Factor VII, von-Willebrand family, angiodysplasia, or arterio-venous malformations.

Tests: consider more frequent surveillance of diagnostic studies and adequate anticoagulation accordingly. TEG or ROTEM could be a valuable surveillance tools for propensity of bleeding

(TEG: R>20 or 25 min and MA<40 mm; ROTEM INTEM CT >300, HEPTEM CT >210 sec, EXTEM A10 <35 mm, FIBTEM A10 <9 mm) and should be correlated in the context of other tests of heparin or bivalirudin effect and other clinical scenarios (example sepsis and DIC).

As per previous published literature TEG platelet mapping (TEG/PM) is not recommended to be used to guide antiplatelet therapy. Baseline TEG is only used to assess baseline values such as R and MA to give a more general guidance for anticoagulation and initiation of antiplatelet use. Once initiated antiplatelet are increased by protocol.

Treatment: consider revisiting anticoagulation goals and anti-platelets. Establish temporary transfusion thresholds during bleeding events according to severity.

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***Disclaimer:*** *The ACTION network is focused on quality improvement efforts such as harmonizing best practice protocols, disseminating them among institutions, and helping centers to improve care practices at the local level. This protocol was developed as a consensus tool for pediatric VAD programs. The information in the protocols are based on center practices, individual opinions, experiences, and, where available, published literature. Centers may choose to adapt this protocol to include in their center-specific protocols with reference to ACTION with the understanding that these are meant as guidelines and not standard of care. (Revised: 01/06/2021)*

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