UCSF Benioff Children's Hospital Oakland

Hematology Program

CLINICAL PRACTICE MANUAL

Iron Deficiency Anemia—Disposition and Management

PRINCIPLE:
Severe iron deficiency anemia (IDA) is common and therefore requires an agreed upon management plan across hospital settings.

OBJECTIVES:
To provide a standardized approach for pediatric patients with IDA presenting to the ED.

SCOPE:
Management of IDA in the ED and inpatient settings for the general pediatric population. This protocol does not apply to patients with underlying complex congenital heart disease or heart failure.

BACKGROUND
Iron deficiency anemia (IDA) is the most common cause of anemia in the pediatric population, with the highest prevalence in early childhood and adolescence. Infants and toddlers most often develop IDA due to insufficient iron supplementation while breastfeeding or with excessive consumption of cow's milk (>16-24 oz per 24 hours). Adolescents who menstruate may develop iron deficiency in the setting of heavy menstrual bleeding (HMB). As part of the work-up, it is important to consider diseases of the GI tract that may cause blood loss and/or iron malabsorption (e.g., IBD, celiac disease, H. pylori, Meckel's diverticulum or history of GI surgery/tract alteration). For patients who present with IDA of unknown etiology and/or with respiratory symptoms, it is vital to consider idiopathic pulmonary hemosiderosis, a rare condition that can present with or without symptoms and result in a varying degree of complications. Patients who present with IDA without any of the above findings may require additional workup to determine an underlying cause.

Symptoms of IDA may include lethargy/fatigue, pallor, irritability, cardiomegaly, tachypnea, and/or pica, though many children are asymptomatic. Iron plays an important role in neurocognitive development and cardiac function. Long-term neurocognitive deficits, growth delay, immunologic deficiencies, and exercise intolerance may be seen. Cardiac literature suggests iron deficiency may contribute to or worsen cardiomyopathy, possibly related to the role of iron in cardiomyocyte cytochrome activity. IDA may also be a risk factor for lead poisoning. Additional rare, but life-threatening complications of severe IDA include cerebral sinus venous thrombosis and high output heart failure. Furthermore, iron deficiency (with or without anemia) is common in children with heart failure and is associated with impaired health related quality of life. *It is important to recognize that some patients with subclinical symptoms or organ injury may present with mild or no symptoms.*

While this protocol focuses on IDA, iron deficiency without anemia can also lead to impairment of cognitive performance, behavior and development. Therefore, a comprehensive management plan must include both inpatient and outpatient management to fully investigate causation and ensure treatment through iron repletion.

Oral iron remains the mainstay of treatment for iron deficiency. While most children will respond appropriately to oral iron therapy, many have incomplete response due to failure to complete an oral iron course, often due to side effects and poor adherence. Ongoing blood loss, such as in individuals with HMB, or impaired absorption, such as in children with IBD, may also prevent complete response to oral iron therapy. In addition, patients who present with chronic, severe IDA may have additional social barriers to care that prevent adequate PCP follow-up.

Increasingly, intravenous (IV) iron is being utilized as first-line therapy for severe IDA in lieu of PRBC transfusion and, potentially, oral iron. The American Society of Hematology (ASH)–American Society of Pediatric Hematology Oncology (ASPHO) and American Association of Blood Banks (AABB) Choosing Wisely Campaigns recommend avoiding red cell transfusion in hemodynamically stable individuals with IDA and no active bleeding, regardless of the hemoglobin level (with no minimum cutoff level). While allergic or anaphylactic reactions were seen with older IV iron formulations, newer formulations have well established safety with very infrequent adverse reactions (<1 per 250,000 doses). Established indications for IV iron include malabsorption in the setting of GI disorders and high hepcidin levels in the setting of systemic inflammation. In patients with active IBD, IV iron also avoids further oxidative damage to intestinal mucosa. In children with heart failure, IV iron repletion is associated with improved likelihood of receiving heart transplant and decreased mortality. Finally, for those with chronic blood loss (such as HMB) IV iron may allow for more consistent repletion. Upfront administration of IV iron can mitigate prolonged anemia due to nonadherence and intolerance.

While red blood cell transfusion does produce an immediate increase in hemoglobin concentration, with approximately 200-250 mg of iron per unit of blood, it is a temporizing solution that may be overutilized and with well-documented risks. Blood transfusion does not ensure complete treatment as the form of iron obtained from PRBCs is not immediately bioavailable for erythropoiesis and does not replenish iron stores. Essentially, transfusion effectively treats anemia, but not iron deficiency.

Note that this protocol does not apply to patients with complex congenital heart disease or heart failure. There is growing evidence that intravenous iron therapy, in particular with ferric carboxymaltose, is indicated for management of iron deficiency in these children. For patients with underlying cardiac conditions presenting with iron deficiency, please consult with the pediatric cardiology service for recommendations on management.

RESPONSIBLE PERSONNEL:
Providers in the ED, infusion center, and inpatient including pediatric hospital medicine/general pediatric teams, hematology, PICU, pharmacy and nursing staff.

GUIDELINES FOR MANAGEMENT

Initial Workup

<u>History and Physical</u>

For patients with presumed IDA, a thorough history, including consideration of age, sex, dietary patterns, current symptoms including history of blood loss, as well as barriers to access to care are important factors in determining underlying etiology and guiding additional work-up, short- and long-term management:

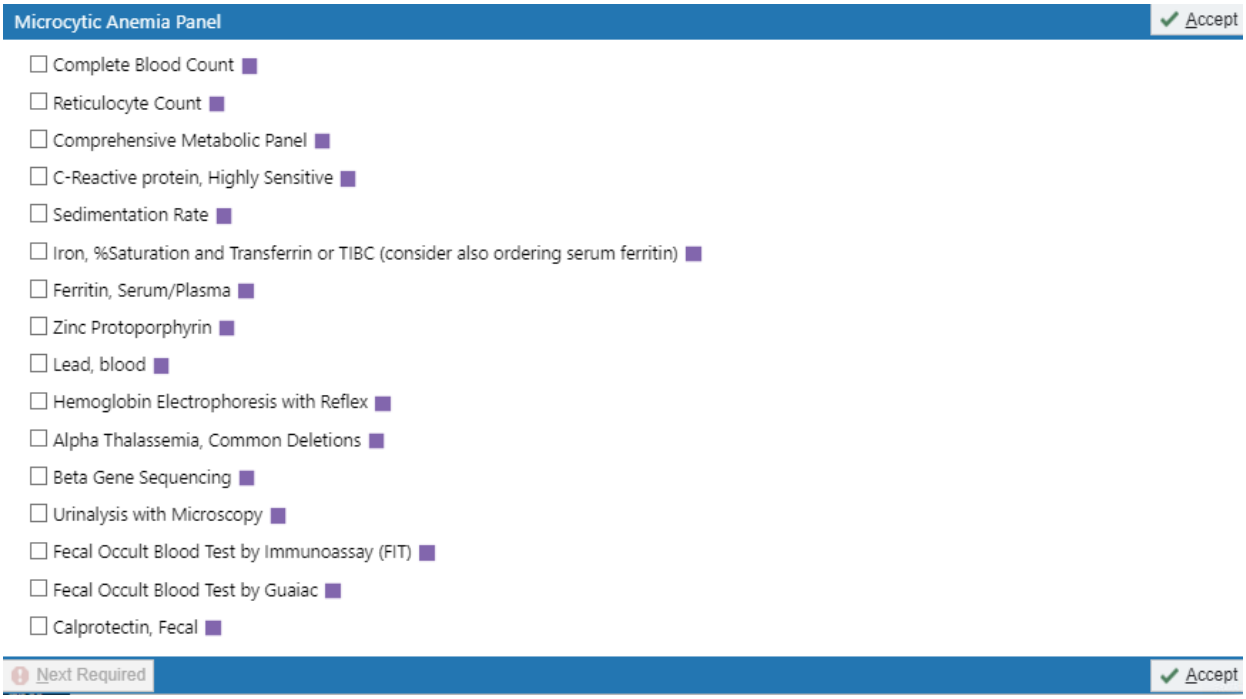
- Diet: focus on milk consumption (>24 oz/24 hours), bottle-feeding habits, introduction of solid foods, intake of iron-rich foods, vegetarianism/veganism
- Pica
- Lead exposure, or history of elevated lead levels
- Bleeding symptoms, heavy menses, hematuria, easy bruising, epistaxis and trauma
- Chronic, or recurrent abdominal pain, chronic diarrhea, hematochezia
- History of iron prescriptions, multivitamin use, home iron supplementation and adherence
- Current or recent illness (to identify possible acute inflammatory state or transient erythroblastopenia of childhood, TEC)
- Exposure to medications or new foods (i.e. fava beans) if concern for bone marrow suppression or hemolysis.
- Behavioral concerns, developmental delay, aversion to solid foods
- Social determinants of health:
    - Where does the patient live?
    - Do they have reliable access to care, including PCP follow-up?
- Birth and perinatal history including history of prematurity, neonatal jaundice and newborn screen if concern for hemolysis and thalassemia.
- Family history: thalassemia, bleeding disorders (e.g. von Willebrand disease), IBD, heavy menses, family members who have needed iron supplementation or blood transfusions, G6PD deficiency
- Drugs: chronic use of NSAIDs, corticosteroids, salicylates, antiplatelet agents, anticoagulants, PPI/H2-blockers

If evaluation is not consistent with iron deficiency, proceed with additional workup to identify other underlying cause of anemia (e.g., hemolysis, acute bleed).

<u>Laboratory studies</u>

Many patients will present to the acute care setting after recent labs show severe anemia with low MCV and MCH. For these patients, a CBC, reticulocyte count, CMP, iron panel, ferritin and type & screen should be done at a minimum. For patients who present with no recent lab evaluation but symptoms of anemia, additional laboratory work up may be done to evaluate for other causes of anemia (bone marrow failure, hemolysis, etc.) History and initial labs (Hemoglobin, MCV, MCH) may be highly suggestive of iron deficiency, so often additional lab evaluation is not required, however ferritin is very to quantify the degree of iron deficiency (assuming no underlying inflammation that would falsely elevate ferritin). Serum iron is not a useful marker unless measuring for response to oral iron.

Please use the Microcytic Anemia Panel on Epic to help you order the appropriate studies:



<u>For symptomatic patients (i.e., hemodynamic instability, syncope, respiratory symptoms, severe neurological symptoms such as seizures or AMS), additional workup is recommended:</u>

- For CNS symptoms, obtain stat head CT or MRI/MRV to rule out cerebral venous sinus thrombosis in consultation with radiology and PICU
- For respiratory symptoms, obtain CXR, EKG and consider ECHO

Additional considerations include:

- Iron Deficiency – the below lab values are suggestive but not diagnostic of IDA
  - Elevated RDW
  - Low ferritin (Also check ESR as ferritin may be normal with inflammation)
  - Elevated TIBC (also check CMP, as TIBC will be normal with low albumin)*
  - Low transferrin % saturation
- Thalassemia trait
  - Normal RDW, or MCV/RBC < 13 (Mentzer Index)
  - Hgb electrophoresis (HEP):
    - Beta thalassemia trait: elevated HbF/A2
    - Alpha thalassemia trait: normal HEP
  - Alpha and beta globin gene analysis (HEP w/reflex)
- Lead toxicity**
  - Elevated lead level (lead level should be checked in all children <5y)
- Anemia of chronic disease
  - Normal to elevated ferritin, low iron saturation, elevated CRP/ESR
  - High hepcidin level (hepcidin level not routinely sent. May be sent in consultation with hematology)
- GI/GU conditions
  - FOBT
  - Fecal calprotectin
  - Celiac studies

  - UA and urine culture
- Type and Screen

*Hypoalbuminemia/periorbital edema seen with cow's milk protein allergy)
** BCHO lead program: if elevated, please consult PNH and BCHO lead program (Allison.Matsunaga@ucsf.edu). See separate lead toxicity protocol for management.

Disposition

Disposition from the ED depends on clinical status, hgb level and assessment of underlying etiology. All patients with-severe anemia (i.e., hgb < 7 g/dL) should be discussed with hematology on call to determine most appropriate disposition (see IDA management algorithm). For children with asymptomatic iron deficiency anemia ≥5 g/dL who may be able to replete iron stores completely with oral iron, admission is not always necessary, however it is imperative that the family establishes a clear follow up plan to manage iron deficiency with oral iron in partnership with the PCP or the outpatient hematology team.

Asymptomatic patients with mild-moderate IDA with hemoglobin <7g/dL could benefit from a single dose of IV iron (iron sucrose) in the emergency room prior to discharge to facilitate rapid resolution of iron deficiency, though may also be appropriately managed with oral iron alone. Shared decision making with family is helpful to guide this disposition.

Goals of admission:

- Initiate work up for underlying cause of IDA, especially if reliable PCP or hematology follow up has not been established
- Initiate acute treatment for IDA
- Resolve acute clinical symptoms of anemia
- Initiate iron supplementation (IV and/or oral)
- Social support and education including identification and mitigation of barriers to care
- Nutrition consultation and education for IDA
- Establish outpatient plan for full correction of iron deficiency and to consider further work up to determine etiology if not clear on presentation

Triage

Disposition from the ED depends on clinical status, hemoglobin level and assessment of underlying etiology. All patients with severe anemia (hb <7g/dL) should be discussed with hematology on call to determine most appropriate disposition.

Criteria for PICU admission

Patients with hemodynamic instability, severe symptoms (e.g., AMS/seizures, respiratory distress, hypoxia) and/or hemoglobin ≤3g/dL regardless of symptoms should be admitted to the PICU for urgent transfusion and hemodynamic support. Hematology should be called at presentation regardless of where patient is admitted. Only in the event no critical care beds are available, PICU, hematology and ED providers must agree that the patient is clinically stable to be admitted to the ward (Red Team). Note, 5E/S has an established protocol for safe transfusion of children with Hb 3-5 that can be cautiously adapted for children with Hb ≤3. Once hemoglobin and symptoms have improved, patients can be

transferred to Red team for ongoing management. *We are still determining appropriate place of care when no PICU beds/staffing is available.

Criteria for Red team admission
Patients with a hemoglobin >3 g/dL and <5 g/dL should be admitted to Red team for management which may include pRBC transfusion and/or IV iron repletion. Clear outpatient follow up plans will be established prior to discharge. Patients with anemia without a clear diagnosis should be admitted to Red team.

Criteria for PHM team admission
Patients with hgb ≥ 5g/dL deemed inappropriate for ED discharge (due to symptomatic anemia, concomitant diagnoses, family discomfort with discharge, concern for outpatient nonadherence to oral iron, and/or inability to follow up outpatient) should be admitted to PMH in consultation with hematology on call. Patients with underlying causative GI etiology should be admitted directly to the GI service for further management and workup of their GI condition and concomitant IDA. Patients with HMB who require transfusion may also be admitted to PHM regardless of hemoglobin.

Special populations

Jehovah's Witnesses
Due to the religious conviction that Jehovah will turn his back on anyone who receives blood, Jehovah's Witnesses should be given every opportunity to avoid PRBC transfusion. For a patient with hemodynamic instability deemed unsafe to withhold transfusion, emergency PRBCs can be given with or without consent from the family. The Jehovah's Witnesses advocate should be involved as well as the family's particular congregation leader, as possible. For hemodynamically stable patients with hgb ≤3 g/dL, IV iron should be utilized in lieu of transfusion

Neonates/Infants
The AAP and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommend that all infants born before 37 weeks' gestation who are breastfed should receive at least 2-3 mg/kg/d supplemental elemental iron through 12 months of age. The AAP and ESPGHAN recommend supplementation with iron up to age 6 months at a dose of 2-3 mg/kg/d for term infants with a birthweight less than 2,000 kg and a dose of 1-2 mg/kg/d for term infants with a birthweight between 2,000 and 2,500 g, especially if exclusively breastfeeding. In otherwise healthy exclusively breastfed term infants, the AAP recommends supplements of 1 mg/kg/d elemental iron starting at age 4 months and continuing until the infant is receiving sufficient iron from iron-containing complementary foods. For children <1 year of age, FCM is not an approved option and therefore PRBCs may be a more reasonable approach if with hgb <5 g/dL with subsequent IV iron sucrose, depending on the clinical scenario.

Who benefits from IV iron?
Most patients with IDA will respond well to oral iron supplementation. However, patients admitted to the hospital with hgb ≤ 5 g/dL have likely either not responded to oral iron therapy or have ongoing dietary behaviors or bleeding symptoms that contributed to the severity of IDA. IV iron should therefore be utilized for all patients who are admitted with IDA and hgb ≤5 g/dL or who have significant ongoing or recent blood loss.

The most commonly used IV iron formulations are ferric carboxymaltose (FCM, Injectafer) and iron sucrose (venofer). FCM, usually dosed at 15mg/kg, can be given in doses up to 750-1000mg at once whereas iron sucrose, usually dosed at 7mg/kg, has a maximum dose of 300mg per dose. Less commonly in children, iron dextran complex (INFeD) is also be used. FCM is preferred as it allows a larger dose to be given at one time, though most children do not need full correction in the acute setting since they may continue oral iron after discharge.

It is important to distinguish which children require full IV iron repletion versus those who can transition to oral iron to fully replete iron stores after initial IV supplementation. Children with hgb ≤5 g/dL who have been assessed to have exclusively nutritional IDA, low suspicion for poor iron absorption or poor adherence to oral iron due to side effects/intolerance would benefit from single dose of IV iron sucrose (i.e., incomplete iron repletion) followed by outpatient oral iron therapy. An oral iron challenge is not typically indicated unless a patient has prior failed oral iron therapy with clear adherence and/or concerns for oral iron absorption. For patients with ongoing blood loss (e.g., GI bleeds/IBD, heavy menstrual bleeding), impaired absorption (short gut syndrome, systemic inflammation, etc.), or heart failure, FCM is preferred to reduce the total number of infusions required. Repletion may also be started inpatient with IV iron sucrose with plans to fully replete post-discharge in the infusion center. Cost is an important consideration for inpatient utilization of FCM as it is significantly more expensive for inpatient use than iron sucrose (even when comparing multiple doses of iron sucrose versus less doses of FCM).

Calculating Iron Deficit:
Ganzoni Equation*:

$$\text{Total dose (mg)} = ([\text{Target Hgb} - \text{Actual Hgb}] \times \text{weight (kg)} \times 2.4) + [15 \times \text{weight (kg)}]$$

- Target Hb should be normal range for patient's age
- The dose to replete assumes that there is no ongoing blood loss.
- Different IV iron formulations have more specific calculations for the deficit replaced. Please refer to Lexicomp for the precise calculations.

*Online calculators may facilitate this calculation (i.e., MDcalc)

Dosing of IV iron

- **Ferric Carboxymaltose:** 15mg/kg IV, max dose 750mg. May be dosed weekly (usually 1-2 doses for full iron repletion, assuming no ongoing blood loss)
- **Iron Sucrose:** 3-7 mg/kg/dose (max dose 300 mg), can be given every 3-7 days until repletion goal has been met.
- **Iron Dextran Complex** (INFeD): Dose (mL) =0.0442 (Desired Hb – Observed Hb) x W + (0.26 x W). A test dose is usually given first.

Criteria for Transfusion
There is no specific consensus hgb threshold in the literature for asymptomatic pediatric patients with IDA to receive PRBC transfusion. To minimize transfusion, we uniformly recommend PRBCs only for children with hgb ≤3 g/dL, those with ongoing blood loss and/or those who are deemed unstable. The decision to transfuse followed by utilization of iron supplementation (IV and/or oral) should be

discussed with the family as there may be situations where the family does not want PRBCs even if hgb ≤3 g/dL (i.e., Jehovah's Witnesses) or prefer PRBCs in a stable patient with hgb > 3 g/dL (and <5 g/dL). Given the lack of guidelines, these different treatment options and the risks/benefits, should be discussed with the family, in accordance with our institutional guidelines here.

IV iron sucrose followed by outpatient oral iron should be utilized after PRBC transfusion.

Historically, there has been concern about clinical volume overload (i.e., TACO, transfusion associated circulatory overload) with rapid transfusion of severe IDA patients due to expansion of the plasma volume. Published data from BCH Oakland suggest that it is safe to transfuse children with severe chronic anemia if no evidence of cardiopulmonary compromise (i.e., 10 mL/kg over 4 hours). Patients to receive PRBCs should have CXR to assess for cardiomegaly, pleural effusions/pulmonary edema and any evidence of pulmonary hemorrhage which may predispose patients to respiratory distress when transfused.

Volume of blood to transfuse may be calculated using the following formula:

$$\text{Volume of blood (mL)} = (\text{Goal Hgb} - \text{Current Hgb}) \times 4 \times \text{weight(kg)}$$

With this formula, 4mL/kg will raise hemoglobin by 1g/dL. We recommend 10-15mL/kg to be run over 4 hours with close monitoring for fluid overload (generally limiting to 10 mL/kg over 4 hours for baseline hgb <3 g/dL). Suggested goal hemoglobin: If no ongoing bleeding, then 6-7 g/dL, if bleeding then >9 g/dL.

Ongoing management during admission and discharge follow up

Patients with nutritional iron deficiency should be placed on a milk-restricted diet and receive education about nutritional iron sources, appropriate intake of cow's milk, and establishment of appropriate follow-up care. Discuss with families any behavioral concerns or social determinants that may prevent adherence to oral iron maintenance therapy post-discharge. In cases without active bleeding, reticulocyte increase will occur within 1 week, hemoglobin correction in 2-3 months and ferritin repletion by 3-4 months. Note that ferritin may increase rapidly after IV iron repletion before iron has been utilized for erythropoiesis. Be cautious about checking ferritin too soon after IV iron (at least 4-6 weeks). Iron repletion should continue until hemoglobin and ferritin are corrected (normal ferritin >30-50 ng/mL). Finally, the underlying cause of iron deficiency (nutrition, bleeding, etc) must be addressed in order to stop iron supplementation.

Patients should have a planned follow up with hematology in 2-4 weeks (in person or via telehealth) with labs prior to ensure adherence with oral iron and improvement in hgb. There should be communication with the PCP to ensure hematology referral has been placed. If there is intolerance or nonadherence with inappropriate hgb increase, patients can be scheduled for IV iron in the infusion center. Patients with AUB should have adolescent and/or adolescent gynecology follow up scheduled. Patients with an underlying GI etiology should have GI follow up in place. These patients may also benefit from ongoing IV iron supplementation in the infusion center.

Patients should be discharged on **once daily oral iron, 3-4 mg/kg elemental iron**. Iron can be given with orange juice for palatability and absorption but avoid giving iron with milk. The family may also consider Novaferrum which is more palatable but must be purchased. Families should be advised on the

potential for constipation as well as staining of the teeth and having black stools while on iron. MiraLAX should be prescribed as needed.

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