Anemia in Epidermolysis Bullosa 2017

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Anemia in EB: Introduction

• Anemia can be a severe and even life-threatening problem in many patients with EB

• Causes are multifactorial

• Early detection and treatment are necessary to maintain good health
Anemia in EB: Introduction

• There are very few guidelines and even fewer studies concerning prevalence, etiology, best diagnostic tools, or best treatment

• The average age of onset and prevalence of anemia have not been studied, but anemia tends to be more common in older children

• It is more likely to be a problem in severely affected individuals

Average Hemoglobin in 108 Untreated Patients with RDEB (---) Compared to Normal Values (---)
Causes of Anemia in EB:

• Iron Deficiency
  – Blood loss from wounds
  – Decreased intake of nutritional iron
  – Decreased intestinal absorption of iron

• Anemia of Inflammation
  – Also Known As: Anemia of Chronic Disease
The Normal Iron Cycle

10 mg daily Fe intake (only 1-2 mg absorbed)

daily Fe loss (1-2 mg)

Total body iron in children is ~75 mg/kg

Children have higher iron needs

No natural mechanism of eliminating excess iron from the body

Iron Deficiency: Blood Loss

• Bleeding from wounds is the most frequent cause of blood loss

• In girls menstrual loss can also contribute

• Rarely
  – GI bleeding secondary to medication etc.
  – Renal loss secondary to glomerulonephritis
Iron Deficiency: Poor Intake

- Difficult oral intake due to
  - Mucosal blistering
  - Poor dentition and microstomia
  - Esophageal strictures
Iron Deficiency: Poor Absorption

- There is often generally poor nutrition in patients with EB
- It is believed that poor nutrition can result in intestinal malabsorption of iron

Anemia of Inflammation
(AKA: Anemia of Chronic Disease)

Inflammation:
- Limits availability of iron to invading microbes
- Erythropoietin
- RBC from bone marrow
- Hemophagocytosis
- Hepcidin from liver: inhibits iron release from reticuloendothelial system

Chronic Inflammation
(aka Anemia of Chronic Disease)

• Many patients with EB have wounds that are chronically colonized and/or infected

• Markers of inflammation are elevated in EB
  – ESR
  – CRP
  – Ferritin
  – Platelet count
Diagnosis of Anemia in EB: Iron deficiency

- Complete Blood Count and Differential
- Reticulocyte count (will be low)
- Peripheral blood smear
Routine Tests Every 6-12 Months
Cincinnati Children’s EB Center

- Complete Blood Count (CBC)
- Iron
- TIBC
- Ferritin
- Erythropoietin
- Soluble Transferrin Receptor (STfR)
- C Reactive Protein (CRP)
- Erythrocyte Sedimentation Rate (ESR)
- Zinc
- Selenium
- Carnitine
- 25 –OH Vit D3
- Calcium
- Liver Function Tests (including albumin)
- Renal Panel (BUN, Creatinine, Electrolytes)
- Free T4 and TSH
- Urinalysis
Diagnosis of Iron Deficiency in EB

• More difficult in EB because:

  – Serum **ferritin** is elevated because of inflammation

  – Serum **iron** is not reliable because of low albumin

  – **MCV** may be high if red cells are clumped
Diagnosis of Iron Deficiency in EB

• Elevated soluble transferrin receptor (STfR) may be an indicator of iron deficiency

• STfR/log ferritin >1 may be best indicator of iron deficiency in patients who also have anemia of inflammation

• But… STfR may be reduced in severe malnutrition

Punnonen K et al. Blood. 1997; 89(3):1052-1057
Other Hematologic Parameters

• Hepcidin
  – Reflects inflammation
  – Not routinely available

• Enteral iron absorption test
  – Determines whether to give iron orally or by gastrostomy (enterally)

• MRI of liver and heart
  – Diagnoses iron overload
  – Suspect when ferritin is >1,000
Treatment of Anemia in EB
Treatment of Anemia in EB

- Improve nutrition
- Decrease inflammation
- Enteral iron supplements
- Intravenous Iron
- Blood Transfusions
- Erythropoietin?
Treatment of Anemia in EB: Enteral (Oral or Gastrostomy) Iron

• Replacement:

  – Consider 1-3mg/kg/d of elemental iron initially to assess tolerability

  – If tolerated, increase to 4-6 mg/kg/d of elemental iron
Treatment of Anemia in EB: Enteral (Oral or Gastrostomy) Iron

• Many preparations
  – Capsules, tablets, liquid,
  – gummies, chewables

– Ferrous sulfate, ferrous gluconate, polysaccharide iron complex, etc.
Treatment of Anemia in EB: Enteral iron

• However enteral iron may cause
  – Abdominal distress
  – Constipation

• And it tastes terrible
Treatment of Anemia in EB: Iron Absorption Test

- Check fasting serum iron level i.e. nothing by mouth nor gastrostomy for at least 6 hours

- Give liquid ferrous sulfate, 2 mg elemental Fe/kg orally or through gastrostomy

- Check serum iron levels prior to iron and in 2 hours after iron

- Positive response is 2x to 3x over baseline and Fe level > 100 mcg/dl

Treatment of Anemia in EB: Iron Infusion

- If intolerant to enteral iron or poorly absorbing it
- Requires IV access and hospital visits
- May need multiple infusions at regular intervals
- Monitor for iron overload (keep ferritin <1,000)
Treatment of Anemia in EB: Iron Infusion

- Several preparations available:
  - Iron Sucrose (Venofer)
  - Iron Dextran (Cosmofer)
  - Ferric carboxymaltose (Ferinject)
  - Low molecular weight dextran

- Potential risks include allergy, edema, anaphylaxis, myagias, tachycardia,

- Consult hematologist for doses and choice of product
Treatment of Anemia in EB: Iron Infusion

• Caveat in patients with significant active infection:
  
  – Invading microbes need iron

  – Inflammation decreases the available iron

  – Thus we do not give enteral iron when a patient is actively infected
Treatment of Anemia in EB: Transfusion

• Use packed red blood cells (PRBC)

• Usually 5-10 ml/kg/hr

• Be aware of fluid overload if reduced cardiac function or severe dehydration
Treatment of Anemia in EB: Transfusion

- Risks include
  - Transfusion reactions
  - Infections
  - Alloimmunization
  - Iron overload
    - Liver
    - Heart
- Follow Hgb, ferritin and clinical response
Treatment of Anemia in EB: Erythropoietin?

- Three small series showed improvement in Hemoglobin with infusions of iron plus subcutaneous erythropoietin

- However, no good controls and no levels of erythropoietin measured

- Worth future clinical trials
EB Anemia Flowchart

- **Hgb <8 g.dl**
  - Consider acute PRC Transfusions
  - Consider IV Fe Sucrose Trial
  - Repeat Hgb in 1-2 weeks

- **Hgb 8-10 g/dl**
  - Suggests Fe Deficiency
  - Yes: Consider Fe Absorption Test
  - No: Hgb by 1-2 g/dl & >8 g/dl

- **Hgb >10 g/dl**
  - Suggests Fe Deficiency
  - Yes: Start Enteral Fe
  - No: Continue Current Care

Consider chronic PRC's and/or EPO and/or IV Fe Sucrose q 4-6 weeks or PRN
-Follow Hgb, Ferritin, & STFR q 3 months

F = Action
D = Decision Point
Conclusions

• Anemia in EB is a result of both iron deficiency and anemia of chronic inflammation

• Starting around 2 years of age, the average hemoglobin of RDEB patients is 2-3.5 points lower than normal for age

• Regular monitoring after age 2 is recommended
Conclusions

• Treatment of iron deficiency anemia in EB consists of replacement of iron enterally, intravenously or by transfusion

• Difficulties include
  – poor adherence
  – poor intravenous access
  – cost
  – side effects
  – risk of iron overload
  – concurrent anemia of inflammation
Conclusion

• Prevention and treatment of the anemia of EB should maintain and improve the quality of life of patients with EB
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