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

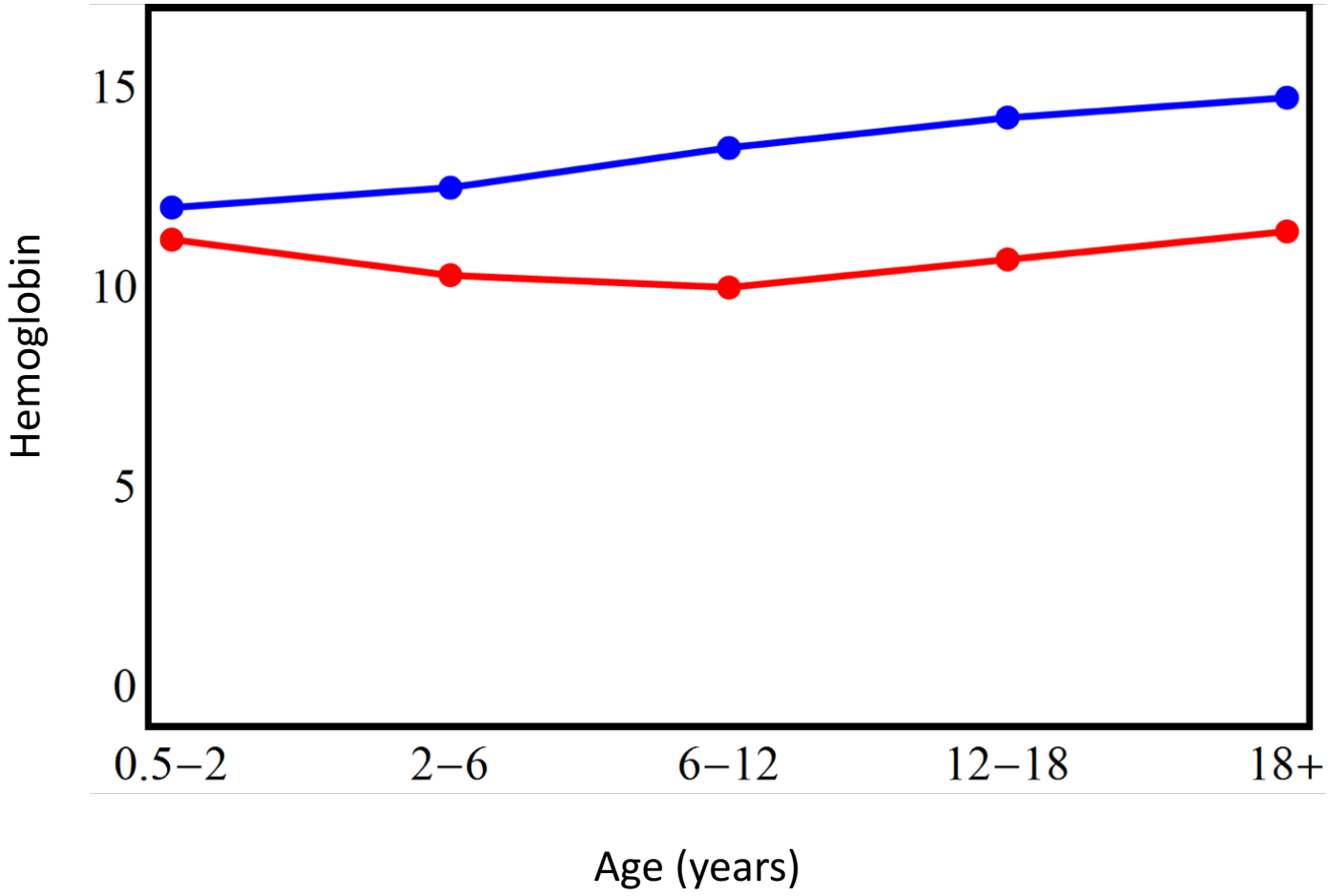
- The average age of onset and prevalence of anemia have not been studied, but anemia tends to be more common in older children

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

Fine JD and Mellerio JE, J Am Acad Dermatol 2009;61:387-402
Hwang SJE et al, Int J Womens Dermatol 2015:1:37-40

Cincinnati Children's

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

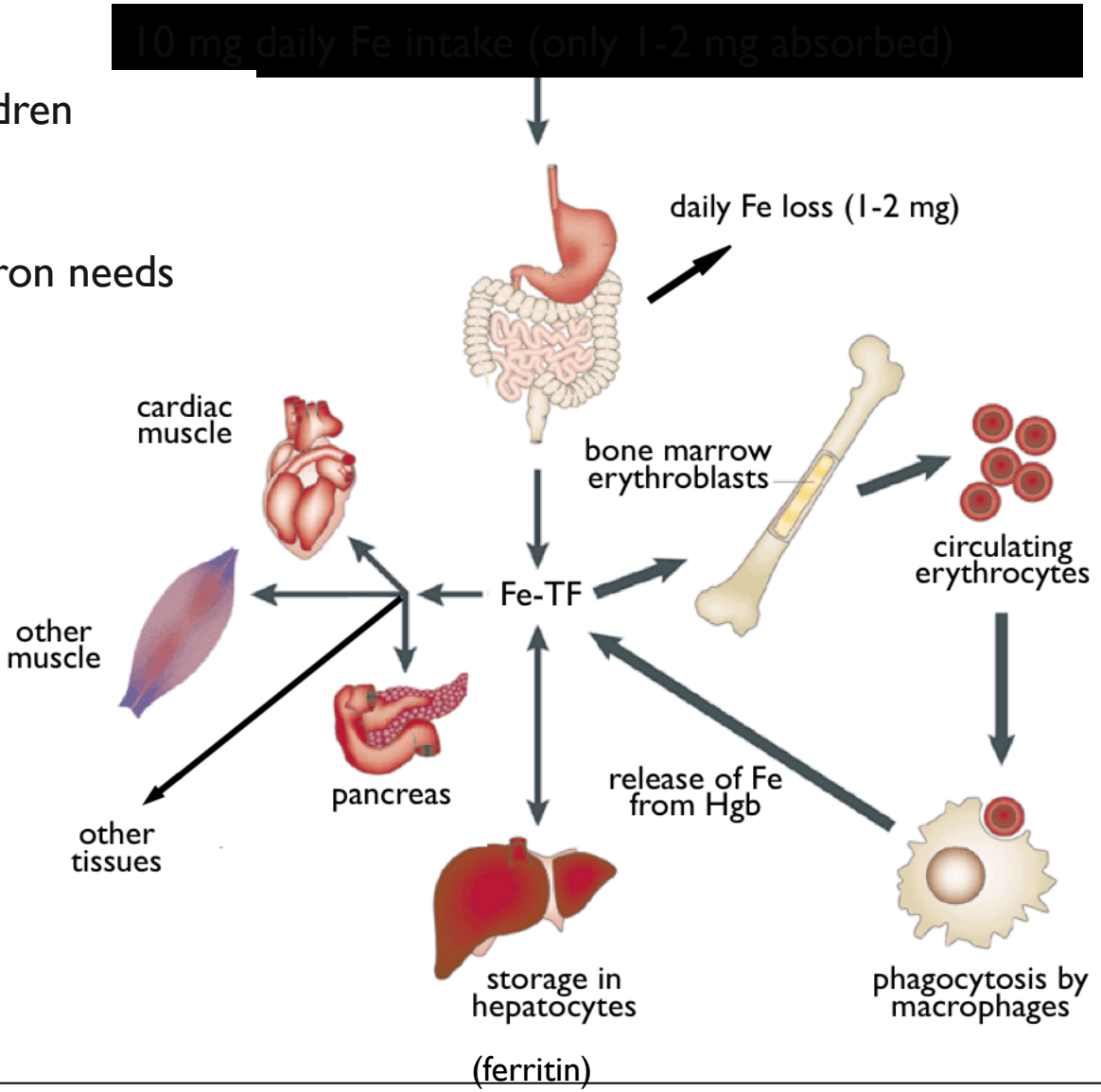
- Anemia of Inflammation
  - Also Known As: Anemia of Chronic Disease

The Normal Iron Cycle

Total body iron in children
Is ~75mg/kg

Children have higher iron needs

No natural mechanism of eliminating excess iron from the body



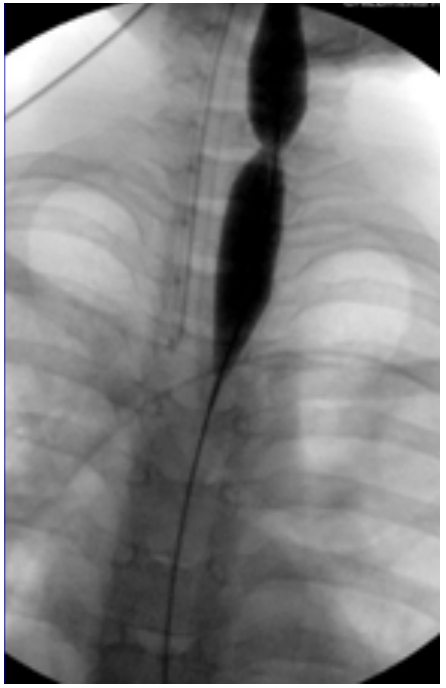
Andrews NC. Nat Rev Genet. 2000; 1:208-217

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

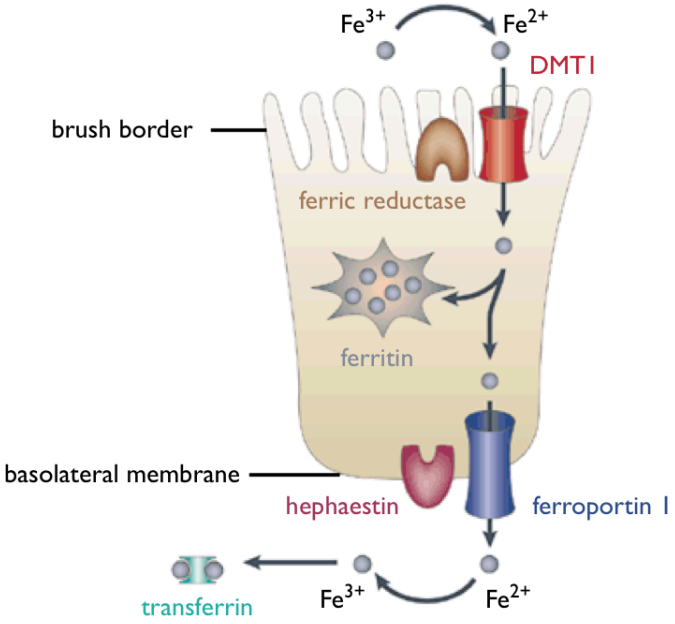


Iron Deficiency: Poor Absorption

- There is often generally poor nutrition in patients with EB

- It is believed that poor nutrition can result in intestinal malabsorption of iron

The Duodenal Enterocyte



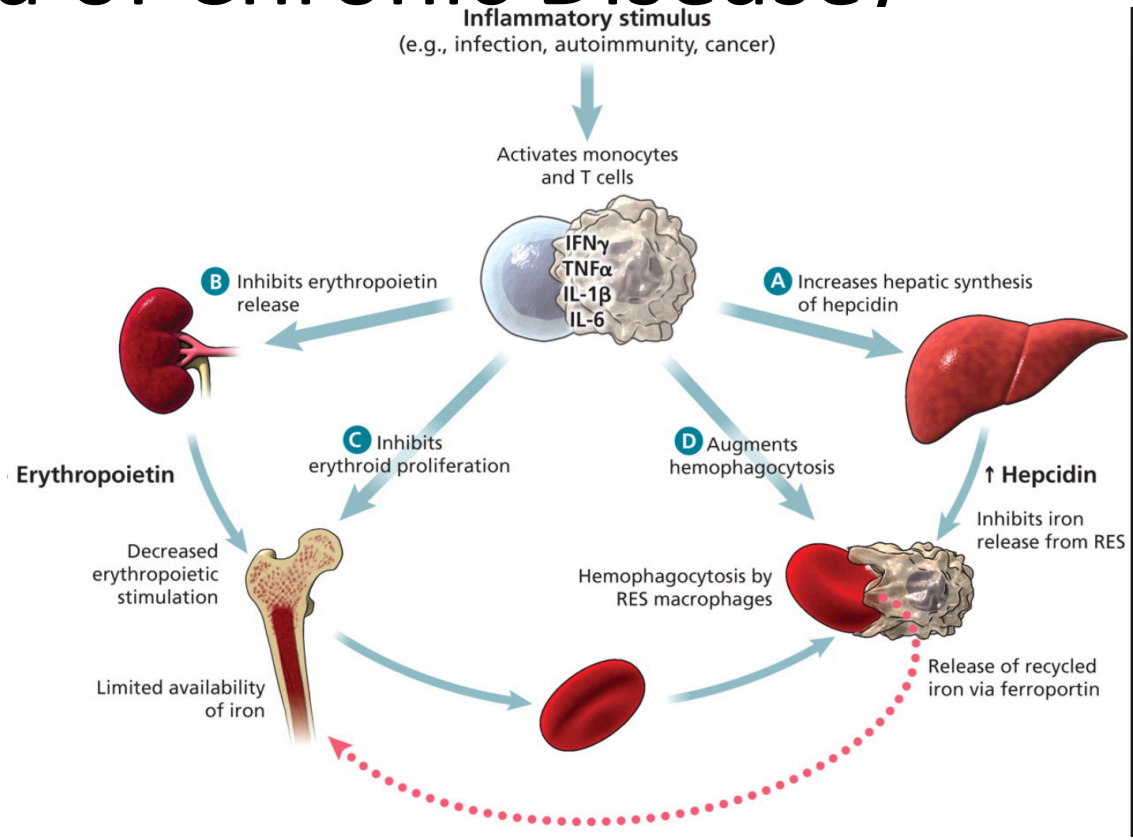
Andrews NC. Nat Rev Genet. 2000; 1:208-217

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



Andrews NC. Nat Rev Genet. 2000; 1:208-217

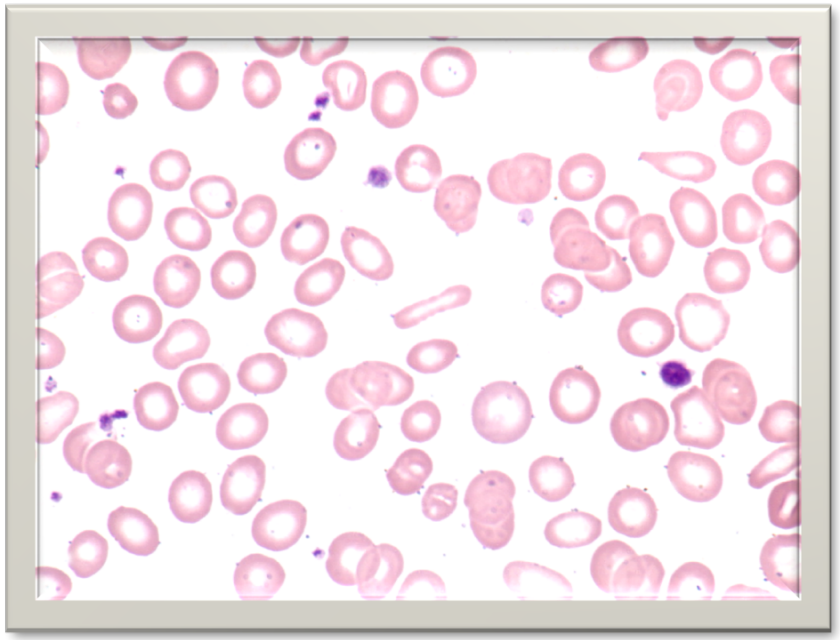
Chronic Inflammation (aka Anemia of Chronic Disease)

- Many patients with EB have wounds that are 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



Blood Smear in Iron Deficiency

Hypochromia ↓ MCH

Microcytosis ↓ MCV

Anisopoiklocytosis ↑ RDW

Courtesy of Cristina Tarango, MD

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 D_3
- 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
Akenami FOT et al. 1997 Br. J. Nutr. 77: 39 –397

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?

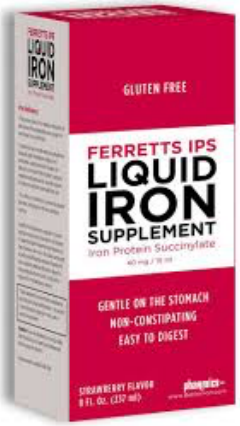
Treatment of Anemia in EB: Enteral (Oral or Gastrostomy) Iron

- 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, polysa 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

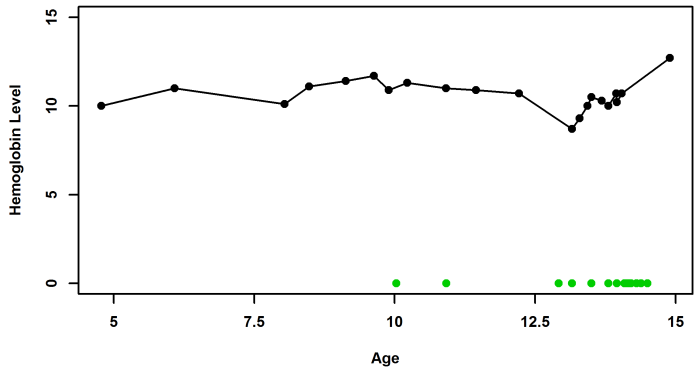
- Check fasting serum iron level i.e. nothing by mouth nor gastrostomy for at least 6 hours
- Give liquid ferrous sulfate, 2 mg elemental Fe/kg orally or through gastrostomy
- Check serum iron levels prior to iron and in 2 hours after iron
- Positive response is 2x to 3x over baseline and Fe level > 100 mcg/dl

Gross SJ et al. J Peds. 1974; 88(5): 795-799

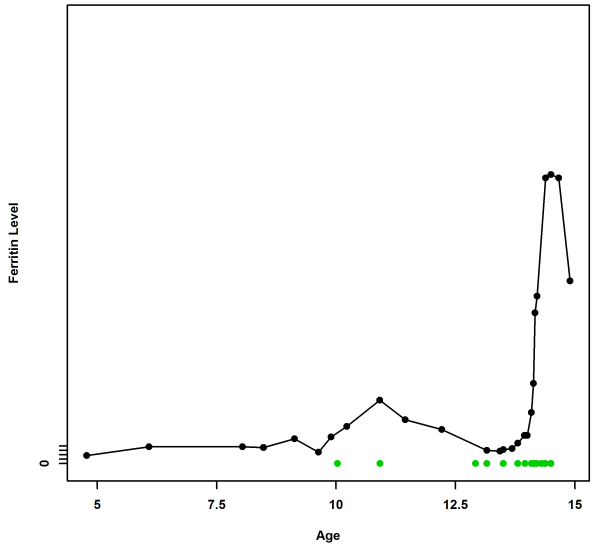
Treatment of Anemia in EB: Iron Infusion

- 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)

Hemoglobin



Ferritin



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

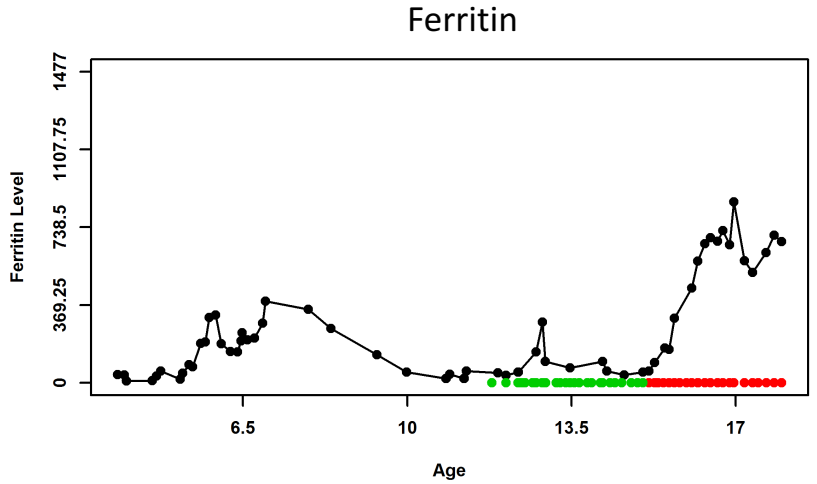
Treatment of Anemia in EB: Transfusion

- 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?

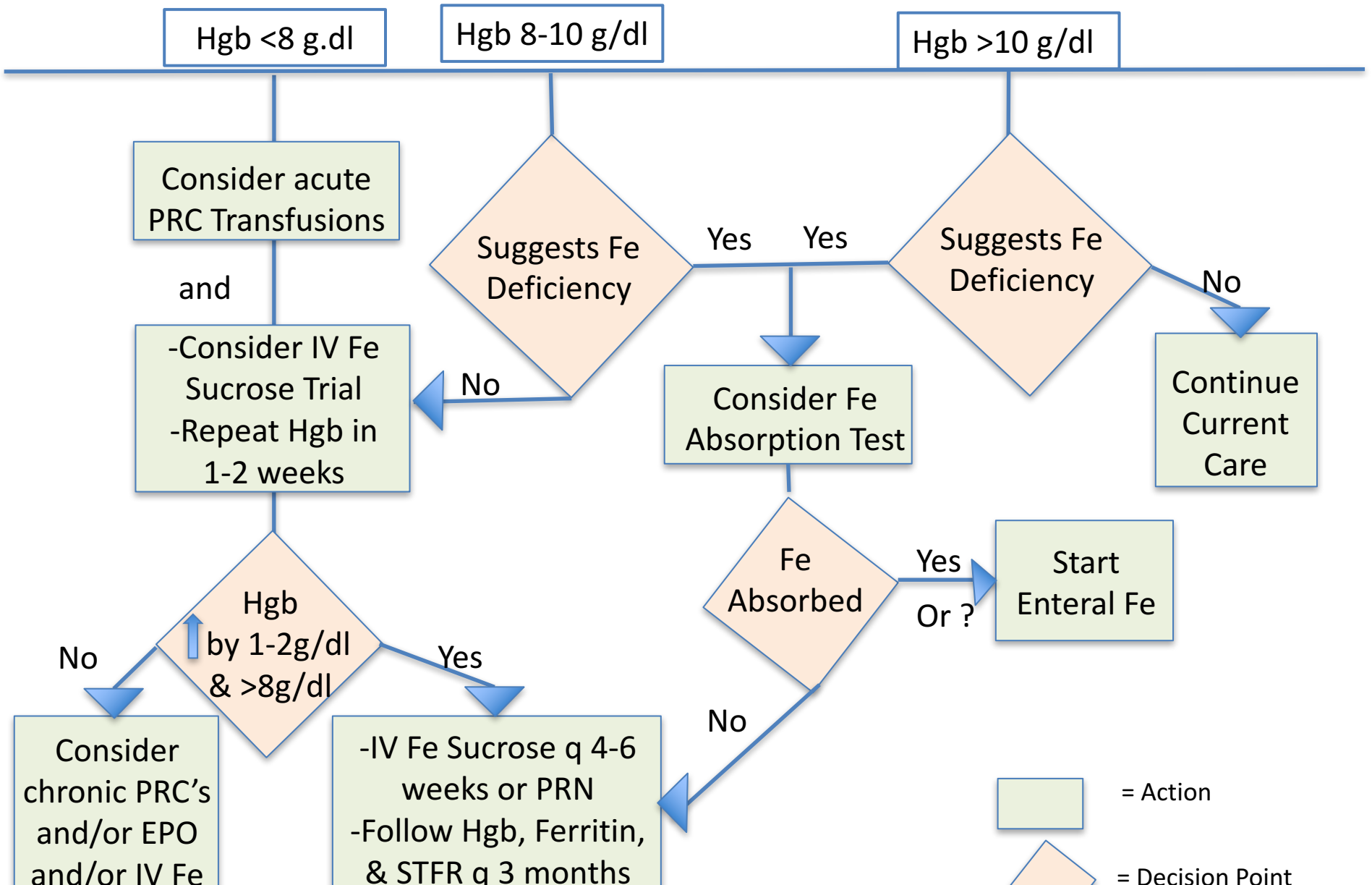
- Three small series showed improvement in Hemoglobin with infusions of iron plus subcutaneous erythropoietin

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

- Worth future clinical trials

- Kuo (2006), Fridge (2004), Antunes (1999)

EB Anemia Flowchart



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

Acknowledgements

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Thank You!