Anemia: When Is it Not Iron Deficiency?

Marcela Popescu
Pediatric Hematology/Oncology

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Perceptions of Iron Deficiency

Koilonychia

“From Stettin in the Baltic to Trieste in the Adriatic an iron curtain has descended across the Continent”
Iron is 4th most abundant element in the earth’s crust

Iron deficiency is the most common nutritional deficiency that affects more than 3.5 billion people globally - Project IDEA (Iron Deficiency Elimination Action)®, CDC

It is estimated that iron deficiency is the cause of 726,000 childhood deaths each year
Consequences of Iron Deficiency

- Anemia
- Increased susceptibility to infection
- Neurological problems in young children
- Delayed mental and psychomotor development
- Increases lead absorption
  (NHANES data show elevated lead levels in 1.5% of children 12-36 months, with 7.1% having concomitant ID)
- IDA during pregnancy has been associated with increased risk for LBW, preterm delivery, perinatal mortality

Lozoff et al. - Pediatrics 2000;105:e51
Screening for Iron Deficiency (AAP Recommendations)

- Universal Hb screening at 9-12 months
- Additional screening between the ages of 1 and 5 years for high risk children

<table>
<thead>
<tr>
<th>Population Sampled (n)</th>
<th>Estimates Adjusted for Sampling Weightings, % (95% CI)</th>
<th>Proportion of US Toddlers Population</th>
<th>Prevalence of ID</th>
<th>Prevalence of Anemia (All types)</th>
<th>PPV of Hb &lt; 110 g/L for ID</th>
<th>Sensitivity of Hb &lt; 110 g/L for ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>General US population (389)</td>
<td>—</td>
<td>9 (7-11)</td>
<td>5 (12-6)</td>
<td>9 (7-11)</td>
<td>28 (20-36)</td>
<td>30 (20-46)</td>
</tr>
<tr>
<td>Above poverty line (185)</td>
<td>72 (64-76)</td>
<td>8 (5-10)</td>
<td>3 (11-7)</td>
<td>6 (4-8)</td>
<td>21 (10-36)</td>
<td>16 (5-31)</td>
</tr>
<tr>
<td>Below poverty line (127)</td>
<td>28 (24-33)</td>
<td>12 (7-15)</td>
<td>7 (7-12)</td>
<td>15 (8-20)</td>
<td>22 (12-43)</td>
<td>18 (7-50)</td>
</tr>
<tr>
<td>Enrolled in WIC (242)</td>
<td>18 (14-21)</td>
<td>7 (7-15)</td>
<td>7 (7-14)</td>
<td>10 (6-14)</td>
<td>30 (15-51)</td>
<td>48 (25-77)</td>
</tr>
<tr>
<td>Non-Hispanic white (432)</td>
<td>6 (4-8)</td>
<td>7 (7-12)</td>
<td>6 (4-8)</td>
<td>19 (12-31)</td>
<td>20 (12-31)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black (379)</td>
<td>17 (15-19)</td>
<td>10 (6-13)</td>
<td>9 (7-12)</td>
<td>15 (12-24)</td>
<td>15 (12-40)</td>
<td>35 (12-71)</td>
</tr>
<tr>
<td>Mexican American (299)</td>
<td>11 (9-12)</td>
<td>18 (13-24)</td>
<td>9 (7-12)</td>
<td>11 (7-13)</td>
<td>23 (15-32)</td>
<td>29 (25-35)</td>
</tr>
<tr>
<td>Other/ethnicities (517)</td>
<td>10 (7-13)</td>
<td>18 (13-25)</td>
<td>4 (6-8)</td>
<td>12 (6-20)</td>
<td>30 (13-60)</td>
<td>29 (13-56)</td>
</tr>
</tbody>
</table>

Fig 4. Venn diagram illustrating overlap of groups with ID and anemia


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Fig 1. Comparisons of distributions of [Hb] of toddlers in US NHANES III

Fig 2. PPV vs (Hb) threshold: estimates and 95% CIs.

Fig 3. Sensitivity vs (Hb) threshold: estimates and 95% CIs

Clinical Bottom Lines

- Most anemic toddlers are not iron deficient, and most ID toddlers in the US are not anemic
- Screening for ID cannot be adequately performed by obtaining only a Hb level
- Many ID children will be missed and many anemic children will be treated inappropriately

Alternative Screening Test for Iron Deficiency


- CHr of less than 27.5 pg is a more accurate hematological indicator of iron deficiency compared with hemoglobin of less than 11 g/dL in healthy 9- to 12-month-old infants
Receiver Operating Characteristic Curves for Reticulocyte Hemoglobin Content and Hemoglobin for the Detection of Iron Deficiency at Initial Screening


Timing of Screening

- Reasons for universal screening of toddlers at a later time
  - Weaning off the iron-fortified milk at 12 mo
  - Toddler dietary fads; switch to adult type cereal
  - Evaluation of tolerance of cow’s milk protein

Risks and Benefits of Iron Supplementation


- Reviewed 26 randomized controlled trials of preventive, oral iron supplementation in young children (aged 0-59 mo)
- Outcomes: anemia, development, growth, morbidity, and mortality
- Among ID or IDA children, Hb concentrations improved with iron
- Reductions in cognitive & motor deficits were observed in ID or IDA children, particularly with longer-duration regimens
- With iron supplementation, weight gains were adversely affected in iron-replete children; the effects on height were inconclusive
- Most studies found no effect on morbidity, although few had sample sizes or study designs that were adequate for drawing conclusions
- In a malaria-endemic population of Zanzibar, significant increases in serious adverse events were associated with iron supplementation, whereas, in Nepal, no effects on mortality were found

Iron Supplementation (AAP)

- Iron intake
  - LBW (1500-2500 g) - 2 mg/kg/day
  - LBW (<1500 g) - 4 mg/kg/day
  - FT and < 4 y - 1 mg/kg/day
  - 4-10 y - 10 mg/day
  - > 11 y - 18 mg/day

- 2005 AAP breastfeeding guidelines
  - Continuing breastfeeding for at least the first year
  - Complementary foods rich in iron beginning at 6 mo
  - Breastfed infants weaned before 12 months of age should receive iron-fortified infant formula
  - Preterm & LBW infants receive iron supplementation before 6 months of age
Iron Metabolism

Iron Transfer Between Cells and Tissues: Mediated by Hepcidin

The Best Marker for Iron Deficiency?

• Ferritin – Ali et al. CMA Journal - 118:945 (1978) showed that serum ferritin correlates with bone marrow iron stores - 248 cases
• 58 patients with Ferritin < 10 ug/l = absent BM iron
Serum Transferrin Receptor (sTfR)

- TfR is located on the bone marrow erythroid progenitors & small amounts are circulating in the blood
- sTfR is increased in IDA
- When Ferritin is normal may help differentiate between IDA (high sTfR) and ACD (normal sTfR)

Increased Risk for Iron Deficiency

- Decreased iron stores
  - Premature infants, perinatal blood loss
- Rapid growth
  - Adolescent growth spurt, infants
- Low dietary intake
- Impaired iron absorption
  - Celiac disease, H.pylori
- Chronic blood loss
  - Cow’s milk intake, Meckel’s, menstruation
Development of Iron Deficiency Anemia (IDA)

- IDA
- Compromised Delivery
- Depleted Stores
- Anemia
- Low Fe/High TIBC
- Low Ferritin

Iron Status

Definition of ID Used in the NHANES II and III Studies

- * A measure of significant inflammation (CRP) was normal

Laboratory Diagnosis of Iron Deficiency

- MCV: low (<70 fl + age in years)
- RDW: high
- Reticulocyte: low
- Serum iron: low (<65 μg/dl)
- Transferrin Saturation: low (<20%)
- TIBC: high (> 385)
- Ferritin: low (<12 μg/L)
- sTFR and EPP: high

Key point: there is no single indicator for the evaluation of iron-deficiency that is ideal

Oral Iron Therapy – General Principles

- Ferrous salts are absorbed better than ferric
- All ferrous salts are absorbed to the same extent
- Iron polysaccharide complex (Niferex) is better tolerated than iron salts
- Ascorbic acid increases absorption and toxicity
- Iron should not be given with antacids, milk, tea;
"What is food to one man may be fierce poison to others."

Everything I eat has been proved by some doctor or other to be a deadly poison, and everything I don't eat has been proved to be indispensable for life. But I go marching on. - George Bernard Shaw

### Causes of Anemia in 56 Patients Referred to St Jude (Dec,08-Nov,09)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency (unrecognized or refractory)</td>
<td>26</td>
</tr>
<tr>
<td>ACD -infection -malignancy -inflammation</td>
<td>8</td>
</tr>
<tr>
<td>Iron Deficiency and Anemia of Inflammation</td>
<td>5</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>2</td>
</tr>
<tr>
<td>RBC Membrane Defect</td>
<td>3</td>
</tr>
<tr>
<td>TEC</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3</td>
</tr>
<tr>
<td>Spurious (no evidence of anemia was found)</td>
<td>4</td>
</tr>
</tbody>
</table>

### Reasons for Refractory IDA Referrals

- Non compliance with dietary changes
- Oral iron intolerance
- Poor response to therapy because of continued blood loss
- Suboptimal use of iron supplements

### Parenteral Iron Therapy

- Iron dextran – high anaphylaxis risk (NOT USED)
- Iron polysaccharide (1/1000 anaphylaxis risk)
- Indicated when non-compliance/ toxicity / malabsorption with oral therapy
- Rapid increase in Hb synthesis and iron stores
Over Diagnosed Iron Deficiency

- RBC membrane defect - 1 case
- Beta Thalassemia Minor - 2 cases
- Spurious - 3 cases
- TEC - 1 case
- ACD - 1 case

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Case # 1

- 2 ½ y boy with moderate anemia
- PMHx of refractory dermatitis, wheezing, staph aureus abscess
- Diet: 56-60 oz of 2% milk/day
- On exam: pallor; generalized eczema
- CBC: Hb 8.1; MCV 55; RDW 18.4; Retic 1.2%
- Plt: 324; WBC 18.9 with 4900 eosinophils
- Ferritin 5.5; iron 20; TIBC 502; TS 4%
- IgE = 6717 (normal 0-352)

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Case # 1

- Dx. IDA - excessive cow’s milk intake
- Hyper IgE Syndrome?
- Management: Oral Iron therapy
  Dietary changes
  Immunology referral
- Follow-up after 2 months of therapy:
  Hb 12.7 g/dl, MCV 74.6, Plt 285 k, Ferritin 92

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Case # 2

- 17 y girl referred for anemia x 6 months
- She tried 3 different oral iron preparation, but not tolerated due to N/V
- PMHx: Appendectomy in 2008 – no ↑ bleeding
- ROS: - menometrorrhagia since menarche at age 11; on OCPs for last 4 months with improvement
  - recurrent epistaxis and easy bruising; pagophagia
- FHx: mother and maternal aunt underwent hysterectomy for uterine bleeding; maternal uncle with prolonged bleeding after minor trauma
Case # 2

- Wt 91 kg, pallor, HR 120
- Hb 7.4, retic 3%, MCV 59, RDW 18, ferritin < 1
- WVD panel – slightly low, but nondiagnostic

Case # 2

- Dx. IDA - menorrhagia; ? obesity
  Underlying VWD – very likely
- Oral Niferex –well tolerated
- Stimate challenge with good response
- Follow-up: Hb 9.7, MCV 64, Ferritin 1.9
  Further tests: Hemoccult – positive
  H.Pylori stool antigen +

Case # 3

- 7 y girl with refractory IDA x 4 months despite compliance with oral iron
- Hemoccult +
- FHx: 1st cousin with Celiac Disease
- ROS: no diarrhea, no abdominal pain, no bloating
- Anti-gliadin and anti-endomysial antibodies +
- Responded to gluten-free diet and IV iron

Iron Deficiency in Celiac Disease

- 1026 cases of biopsy-proven celiac disease (644 children; 382 adults)
- Extra-intestinal symptoms
  - Iron deficiency anemia ~46%
  - Dermatitis herpetiformis
  - Diabetes mellitus
  - Short-stature in children

*Schrier, S. ASH Image Bank 2002;2002:103325*

*Am J Gastroenterology 1999;94:691*
### Case # 3 Take Home Messages

- Celiac disease should be considered as a possible cause of anemia in patients with unexplained or refractory iron deficiency anemia
- Iron deficiency is common in celiac disease
- Both, gluten-free diet and iron supplementation, will replete the iron stores

### Case # 4

- 16 y boy referred for recurrent fever, abdominal pain & anemia in the context of recent EBV
- ROS: nausea, abdominal pain, wt loss (12 lb)
- Exam: very thin, epigastric tenderness, no HSM
- CBC: Hb 12.3, MCV 71; Retic 1.4%; Ferritin 96
- Abs lymph 1764; some reactive; LFTs-wnl;
- Hemoccult positive; H. pylori atg – negative
- TIBC 222 (218-385);Fe 13 (>65); TS 5.9% (>20%)
- ESR 44; CRP 96; Serum PCR for EBV DNA – positive

### Case # 4

- Dx. ACD; likely Iron Deficiency; Acute Gastritis
- Management: Rx: Prilosec & Sucralfate
  - GI referral
- Gastric bx + H pylori - triple therapy given
- Follow-up: clinical improvement; inflammatory tests improved; still low Hb & MCV; Ferritin 24; normal Hb electrophoresis
- Started oral iron therapy and tolerated

### Helicobacter Pylori Infection

- Prevalence 20-50% in industrialized countries
- Prevalence inversely related to socioeconomic conditions
- May be inadvertently cured by antibiotics treatment for other reasons
- Causes continuous gastric inflammation in all infected subjects
**H. pylori Infection and IDA**

![Table 1. Response of iron-deficiency anemia (IDA) to H. pylori eradication.](image)

**H. pylori Infection: Mechanism of ID**

- Occult GI bleeding
- Competition for dietary iron - would expect more patients to be iron deficient
- Possible cause of ID in *H. pylori* infection mediated by achlorhydria
  - High intragastric pH
  - Low gastric juice ascorbic acid
  

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**Case # 5**

- 10 y girl referred for anemia and thrombocytosis
- Fever/exanthema/ left upper abdominal pain/chest pain 6 weeks prior; treated empirically for Strep with Amoxicillin x 10 days
- ROS: persistent fevers, fatigue, wt loss (10 lb)
- Exam: unremarkable
- CBC: Hb 10.7; normocytic; plt 815,000
- Low iron & TS, normal TIBC ; Ferritin 156; ESR 74
- U/A - no hematuria

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**Case # 5**

- Dx. ACD; Reactive thrombocytosis
- ASO > 400
- CXR- left pleural effusion and lung abscess

Admitted to General Pediatrics for iv antibiotics
Anemia of Chronic Disease (ACD)

- ACD is related to decreased RBC production
  - Impairment in the transport of iron from iron storage
  - Poor response to or a relative decrease in EPO production
- Unexplained slightly shortened RBC survival

Characteristics of ACD

- Anemia of variable severity (mild-severe)
- Usually normocytic
- Low reticulocyte count
- Decreases serum Iron, TS and TIBC
- Relative low erythropoietin level
Case # 6
- 22 mo girl with refractory IDA x 9 months
  Mostly noncompliant with oral iron due to GI toxicity
- Diet - 25oz cow’s milk + toddler foods; no tea. She was switched to whole milk at 9 mo and she was taking ½ gallon/day between 9-15 mo
- ROS: PICA (pebbles, dirt); poor weight gain; recurrent hives
- Exam: pallor; tachycardia, flow murmur

Case # 6
- Hb 6.6; MCV 52.7; Plt 681,000; eosinophils 7600
  Iron 23; TS 6.7%; TIBC 343; Ferritin 152
  Lead and Hb electrophoresis- wnl
  Hemoccult, O&P, H.Pylori atg - negative
- Dx. ACD + IDA
- Management:
  - Attempted oral iron absorption test; IV iron x 4
  - Plt 313 k, Hb 11.3, MCV 76;
  - ID consult – Toxocara serology + ; Albendazole x 2
  Ferritin decreased to 14; eos= 1500

Case # 7
- 18 mo boy referred for worsening IDA despite compliance with oral iron x 1 month
- PMH: recent OM and Pneumonia
- Diet- 20 oz cow's milk/day after 12 mo of age
- FH: mother with hx of IDA
- Exam: pallor, L eye with periorbital swelling and yellowish discoloration
- Hb 7.2; MCV 73; Plt 129 K, normal WBC and diff
- Smear – few tear drops

Dacryocytes

Blood 2006;108:2892
Case # 7

- Ferritin 204; Iron 30; TS 8.2%
  - LDH 2134; uric acid – normal
- CT orbits/chest/abdomen – L retroperitoneal mass with orbital bone metastasis
- Elevated urine VMA and HVA
- Dx. Stage IV Neuroblastoma
  
  Started chemotherapy 3 days after initial consult

Case # 8

- 15 mo hispanic/caucasian girl referred for refractory iron deficiency x 4 months, dx. by low Hb.
  
  Poor compliance with iron therapy due to GI upset
  - Diet - 18oz of whole milk/day; toddler foods
  - No recent illness; negative ROS
  - PMHx- born FT, hospitalized 5 days for hyperbilirubinemia
  - Exam: pallor, oral thrush
  - CBC: Hb 9.6; MCV 59; RBC 4.9; TIBC 356; Ferritin 45

Case # 8 - Take Home Message

- Although the laboratory data of thalassemia minor may resemble those of iron deficiency anemia, iron therapy is unnecessary and potentially harmful
  
  - Do not start Iron therapy based on Hb screen
Case #9

- 18 y girl referred for refractory anemia x 8 months;
- Diet: balanced, but also drinking a lot of tea
- ROS: fatigue; regular, moderate flow menses
- Exam: looks tired, otherwise negative
- CBC: Hb 11.1; MCV 86.6; Retic 0.6%; few spherocytes; Coombs -, OF-nl; ESR 5; ANA-negative
- TIBC nl; Iron nl; TS 8%; Ferritin 24
- Dx. Normochromic, normocytic anemia, likely ACD
- Next visit with PMD found to have high BUN & creatinine

Case #10

- Toddler with typical dietary hx for IDA;
- Exam: signs of severe anemia; no HSM
- Hb 4.3; MCV 56; Plt 52,000; WBC & diff-normal
- Normal uric acid and LDH
- Ferritin <1
- Dx. Severe IDA with associated thrombocytopenia

Summary

- Neurologic effect of correction of iron-deficient anemia in infancy remains controversial
- Prognosis of severe iron deficiency, despite treatment in infancy, is poor
- Screening for iron deficiency cannot be adequately performed by obtaining only a Hb level
Summary

- Consider GI losses in patients with anemia resistant to therapy: Celiac disease, H. pylori
- Consider ACD when Iron studies don’t fit with IDA
- Iron therapy is unnecessary and potentially harmful in thalassemia

References

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