New Advances in Understanding Iron Deficiency, Treatment and Relationship to Fatigue

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Objectives

1. Recognize causes of iron deficiency anemia in the pediatric age group, including new understanding of iron deficiency in young athletes.

2. Discuss controversy concerning low ferritin levels and relationship to fatigue.

3. Review possible uses of the new, safer IV iron preparations.
Normal Iron Metabolism

- meticulous balance between dietary uptake and loss
- average adult has 4-5 grams of iron
- 1 mg lost each day from sloughing of cells
- menstruating females lose an additional 1 mg daily
- absorption primary means of regulating iron stores
Iron Absorption

• primarily in proximal duodenum
• increased iron uptake with ascorbate and citrate
• phytates, bran and tannins inhibit iron absorption
Importance of Iron

• indispensible for DNA synthesis and host of metabolic processes
• deficiency arrests cell proliferation
• most iron ultimately incorporated into hemoglobin
• deficiency impairs neurologic function perhaps by effect on neurotransmitters, dopamine receptors, myelination or cytochromes
Storage Sites

1. Ferritin – tissue stores correlates with total body iron stores
2. Transferrin – small amount of iron circulates in plasma bound to transferrin. TIBC is sum of iron binding sites on transferrin
3. Hemoglobin – contains 60-80% of total body iron stores
Three Stages of Iron Deficiency

1. Prelatent – tissue stores depleted without change in serum iron or hemoglobin. Manifest by low ferritin.

2. Latent iron deficiency – RE macrophage iron stores are depleted. Ferritin low, serum iron low, TIBC high, Hgb and MCV normal

3. Frank iron deficiency – low ferritin, low serum iron, high TIBC, low MCV, low Hgb
   - 1 & 2 – iron deficiency without anemia (IDWA)
   - 3 – iron deficiency with anemia (IDA)
Caution About Ferritin

- altered by liver disease, infection, tumor or chronic inflammation
- in absence of above, serum ferritin roughly proportional to total body iron stores
Causes of Iron Deficiency Anemia

INADEQUATE ABSORPTION
Poor bioavailability (absorption of heme Fe > Fe^{2+} > Fe^{3+})
Antacid therapy/high gastric pH
Bran, tannins, phytates, starch
Other metals (Co, Pb)
Loss/dysfunction of absorptive enterocytes

INSUFFICIENT/INACCESSIBLE IRON STORES
**Gastrointestinal Blood Loss**
Epistaxis
Gastritis
Ulcer
Meckel’s diverticulum
Milk-induced enteropathy
Parasitosis
Varices
Tumor or polyps
Inflammatory bowel disease
Arteriovenous malformation
Colonic diverticula
Hemorrhoids
Causes of Iron Deficiency Anemia (cont.)

**Vaginal Blood Loss**
Increased menstrual flow
Tumor

**Urinary Blood Loss**
Chronic infection
Tumor

**Pulmonary Blood Loss**
Pulmonary hemosiderosis
Tuberculosis
Bronchiectasis

**Inflammation/Infection**
Focus on Five Important Causes

1. Cow’s milk-induced enteropathy
2. Menstrual bleeding
3. GI losses
4. Prematurity
5. Adolescent athletes
Cow’s Milk-Induced Enteropathy: Mechanisms

- low iron content, low bioavailability
- replaces iron rich foods in diet
- calcium and casein peptides interfere with iron absorption
- proteins irritate lining of GI tract, causes chronic hemorrhage
- neonatal growth spurt requires tremendous quantities of iron
Neurocognitive Consequences of IDA

• association between IDA and impaired neurocognitive function is well established, even when potential cofounders taken into account
• infants and toddlers, undergoing critical neurocognitive development may be at particular risk
• specific impairments include mental and motor (Pediatrics, 1987, 79, 981-995) psychomotor development (Pediatrics, 1989, 84, 7-17), motor and verbal skills (Pediatrics, 2001, 107, 1381-1386)
• not clear whether dietary iron supplementation can reverse this cognitive dysfunction; several studies show it cannot (J Pediatr, 1996, 129, 382-389)
Neurocognitive Consequences of Iron Deficiency

• IDWA associated with impaired mental and motor functioning (Pediatrics, 1983, 71, 877-80)

• iron deficiency may increase risk for lead exposure through PICA or increased absorption

• actual mechanism by which iron deficiency impairs neurologic function is unknown
AAP Recommendations

1. Breast milk for at least 5-6 months if possible. If exclusively breast fed after 6 months, supplement with iron.

2. If not breast fed, nourish with iron supplemented formula until end of first year of life.

3. Iron enriched cereals should be among first foods introduced.

4. Cow’s milk should be avoided in first year of life.

5. My recommendation: limit to 16 oz per day of cow’s milk.
Menstrual Bleeding

• most common cause of iron deficiency in teenage girls
• if IDA from heavy periods, think underlying bleeding disorder. Up to 40% of women with heavy periods have underlying bleeding disorder, only 5% are diagnosed
• consider hormone therapy such as birth control pills
GI Blood Loss

• leading cause of iron deficiency world wide
• anatomic defects such as Meckel’s diverticulum
• parasites
• IDA can be presenting symptom of inflammatory bowel disease
Prematurity

• fetus accumulates iron at mother’s expense in third trimester
• preterm infants deplete iron stores by 3-4 months of age
• preterm infants require iron supplementation
Iron Deficiency in Young Athletes
Case Report 1

17-year-old female twins, both avid, elite cross country runners.

  - Started on iron at dose of 60 mg elemental iron t.i.d.
  - 8/2011 Hgb down to 10.6
  - 10/2011 – First seen by me
  - PMH – Amenorrhea, required hormonal stimulation. Borderline diet with little red meat
  - Rec: restart iron t.i.d.
Twin A

- Spring 2012 – decreased iron to 1 tablet per day. (GI complaints)
- Oct 2012 – poor running times, fatigue, Hgb 16.5, ferritin 8
- Dec 2012 – Hgb 15.6, ferritin 24
- May 2013 – Hgb 13.7, ferritin 10.5, intermittent fatigue
- Received IV iron prior to State Track finals – reaction to IV iron (unclear) but afterwards less fatigue, ferritin 46. Finished 5th in State 2-mile run.
Twin B
(similar story)

• Oct 2012 – fatigue, poor racing performance, Hgb 14, ferritin 6. Started on iron t.i.d., much better
• May 2013 – Hgb 12.5, ferritin 13
• Received IV iron, some type of reaction (unclear) but afterwards fatigue better, ferritin 61. Finished 3rd in State 2-mile run
Causes of Iron Deficiency in Adolescent Athletes

• Studied 72 high school runners
• ID defined as ferritin $\leq 12$, and saturation $\leq 16$ simultaneously
• ID in 34% of female cross country runners, 8% of male
• ID from GI bleeding and low dietary iron (menstrual loss – insignificant)
• Higher doses of oral iron (180 mg/day) necessary to correct ID
Key Points from Case Report 1

1. ID common in female cross country runners
2. ID persists as long as they run extreme mileage
3. ID seems to be associated with perceived fatigue and poor performance
4. Higher doses of oral iron needed to correct ID
5. IV iron may be of benefit in this situation
Iron Deficiency (low ferritin) Associated with Fatigue
Effect of Iron Supplementation on Fatigue in Non-Anemic, Menstruating Women with Low Ferritin
(Vaucher et al. CMAJ, 2012, 184 (11) 1247-54)

- Multicentric, parallel, randomized, controlled, closed label, observer blinded trial
- 198 French women, aged 18-53, fatigue and ferritin $\leq 50$. Hgb $\geq 12$
- Randomized to receive oral iron supplementation (80 mg daily) or placebo for 12 weeks
- Primary outcome was fatigue (Current & Post Psychological Scale) and biologic markers
1. Mean score for fatigue decreased by 48% in iron group by 29% in placebo group (p = .02)
2. No difference in quality of life, depression or anxiety
3. Iron supplementation significantly increased Hgb (1.32, p = .002) and ferritin (11.4; p < .001)
4. Consider iron supplementation in women with unexplained fatigue who have ferritin levels < 50.

- Compared 233 university women, divided into iron replete and iron depleted, using standardized fatigue and well-being questionnaires
- No significant difference in self perceived health and well-being or fatigue (once other factors taken into account)
Intravenous Iron For the Treatment of Fatigue in Non-Anemic, Premenopausal Women with Low Serum Ferritin Concentration

(Kravenbuehl et al. Blood 2011, 118, 3222-7)

• Randomized, double blind placebo controlled study, 90 premenopausal women with fatigue, ferritin < 50 and Hgb > 12
• 800 mg of IV iron -vs- IV placebo
• Borderline significant decrease in fatigue in all patients (p = .07)
• Very significant decrease in fatigue in those with ferritin < 15 (p = .005)
Iron Supplementation For Unexplained Fatigue in Non-Anemic Women

(Verdon et al. BMJ, 2003, 326, 1124)

- 144 Swiss women, unexplained fatigue, normal Hgb, ferritin < 50 (most < 20)
- Randomized to either oral iron (80 mg/day) or placebo
- Level of fatigue decreased by 29% in iron group versus 13% in placebo group (p = .004)
- Non-anemic women with unexplained fatigue and ferritin < 50 may benefit from iron supplementation
Case Report 2

Fatigue in the Adolescent Female:

- Nov 2012 – 17 y/o female, fatigued (but 6 hrs of sleep with job and school)
- heavy periods, spontaneous bruising, wisdom teeth removal with oozing for 1 day
- older sister has heavy periods
- Hgb 8.6, MCV 68, iron saturation < 10, ferritin 6
Case Report 2
Recommendations

1. Bleeding evaluation – negative
2. OCPs – normalized periods
3. Thyroid, EBV normal
4. Denies depression
5. Regulate lifestyle, i.e. more sleep
6. Start oral iron
Case Report 2 (cont.)

• could not tolerate oral iron
• IV iron x3 in Dec 2012
• 1/7/13 – energy better, back to school, good grades, Hgb 13.4, ferritin 94
Case Report 2 (cont.)

• did well for 6 weeks
• 2/28/13 – fatigue worsening, missing school, ? depression, Hgb 12.7, MCV 86, ferritin 25
• options of observation, oral iron, IV iron
• tried observation but fatigue persisted
• 3/10/13 – IV iron once, energy significantly improved, mood better, sleeping 7-8 hours/night, better in school, ferritin 142
• has done well since
Conclusions

- some evidence in literature that iron supplementation in fatigued women with low ferritin (< 50 or < 15) helps decrease fatigue
- US Olympic team recommends female athletes keep ferritin > 50
- fatigue in adolescent teens a common but difficult problem, often with no clear etiology. My observation – seems reasonable to check ferritin and if < 50, trial of iron supplementation
- role of IV iron unclear
Intravenous Iron

• older forms of IV iron (high molecular weight, iron dextran) associated with significant rate of anaphylaxis, required test dose
• in past, IV iron reserved for those in extreme clinical situations when oral iron could not be used
• newer forms of IV iron (low molecular weight, iron sucrose) much safer
Intravenous Iron Sucrose for Children with Iron Deficiency Failing to Respond to Oral Iron Therapy

• 38 children (< 18 years) received iron sucrose for non-renal indications
• 510 total infusions, six adverse reactions (all mild), no test doses
• IV iron safe and effective means to treat iron deficiency
Accompanying Editorial by Auerbach (adult hematologist)

- Current IV iron safe and effective in many clinical situations in adults.
- Useful in treating restless leg.
- Pediatricians reluctant to use IV iron (almost to point of calling us wimps).
Intravenous Low Molecular Weight Iron Dextran in Children With Iron Deficiency Anemia Unresponsive to Oral Iron
(Plummer et al, Pediatr Blood Cancer, 2013, 60, 1747-1752)

- 31 children (11 mos – 18 years)
- IDA, poorly responsive to oral iron
- LMWID administered in 1 dose over 60 min as outpatient
- 2/3 complete hematologic response
- 29% mild nonspecific adverse reactions
Conclusions

• LMWID well tolerated and effective when given as total dose infusion in IDA refractory to oral iron therapy

• Transient reactions common but not serious
Accompanying Editorial by Forman

• “considerable weight to argument for giving IV iron to children unresponsive to oral iron”
• Diminishes cost (compared to multiple infusions), time and general burden for child and family
• Raises question of whether IV iron might be used as initial therapy for child with IDA
• Until randomized study done, standard oral iron therapy seems best for toddlers
What is role of IV iron in pediatrics?

Is 1-2 doses of IV iron easier than three months of difficult to administer oral iron?
Dose of IV Iron

- calculate total iron deficit
- total cumulative dose = \([\text{target Hgb} - \text{Actual Hgb}] \times \text{weight (kg)} \times .24 + [15 \times \text{weight (kg)}]\)
- maximum dose is 300 mg or 7 mg/kg
- can give every 3-7 days until total dose administered
Conclusions

1. Iron is important in many functions of the body.
2. Iron deficiency with anemia and iron deficiency without anemia may be harmful.
3. Always ask about cow’s milk ingestion.
4. Iron deficiency anemia associated with heavy periods mandates a bleeding workup.
Conclusions (cont.)

5. Consider iron deficiency in “aggressive” high school athletes, especially women.
6. Fatigue may be associated with ID even without anemia (ferritin < 50). Iron supplementation may help.
7. Consider low ferritin ID as cause of fatigue.
8. Consider use of IV iron early in therapy.
Contact the Center for Cancer and Blood Disorders (CCBD) at Children’s Hospital Colorado

- Hematology and Sickle Cell Clinic (720) 777-6672
- Bone Marrow Transplant (720) 777-6892
- Oncology (720) 777-6688
- Neuro-Oncology (720) 777-6772
- Experimental Therapeutics Program (720) 777-4159
- Helping Oncology Patients Excel (H.O.P.E.) Clinic (720) 777-5441
- Fertility Team Consults (720) 777-6686
- Wellness/Psychosocial Support (720) 777-8857

- One Call 24/7 Provider Dedicated Line (720) 777-3999 or (800) 525-4871

Thank you, Thomas Smith, MD
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