

How to Review for *American Family Physician*
Sample reviews can be found following instructions.

NOTE: If you have a financial relationship with a drug or device maker relevant to the topic of the manuscript, please check with our editorial office at afpjournal@aafp.org before doing your review. [Example: you are on the speakers' bureau for a company that makes drugs for diabetes, and the manuscript is about diabetes].

We ask for your help in making this manuscript a current, high-quality presentation on the topic.

- Look for any errors of commission: are any of the facts incorrect?
- Look for any errors of omission: is there important information missing?
- Are there any new developments, references, or tables/figures that should be added?
- Is the presentation adequately balanced?
- You need not correct misspellings or grammar, unless you think it's necessary to ensure clarity.

You will be asked to provide detailed comments to the authors.

- Make these as specific as possible, rather than speaking in generalities.
- Tell them what they can do to improve the presentation.
- Comment on any weaknesses, but mention strengths of the paper as well.
- If desired, you can provide separate comments to the editor (but do not repeat your comments to the authors). For example, please say if you feel there is any inappropriate bias, or whether the manuscript does not seem authoritative.

We also ask that you rate key aspects of the manuscript on a rating scale in Editorial Manager, our online peer review system. We use these ratings to get a composite, semi-quantitative sense of the external reviews.

To give you an idea of what reviews for *AFP* look like, here is a set of five reviews on a manuscript on iron deficiency anemia (two from *AFP* medical editors, and three external reviewers). For the sake of completeness, we also include the author's responses to the reviews, as outlined in the resubmission letter. [The reviewers and author involved have given us permission to post these reviews and responses, which in *AFP* are done anonymously.]

REVIEWER #1

General comments-

This is a well written review of a very common clinical issue. However, I think there are some additional references/observations that the authors should strongly consider in adding in making their paper a more practical a guide for the clinician as outlined below.

Specific comments-

Pg 3, last para- thalassemia is misspelled; also, specifically would refer to chronic disease states as chronic inflammatory states

Pg 4, first para- authors may want to reiterate that the low cutoff of ferritin <15 reflects pre-menopausal menstruating women in the "pool" that "drives down" the ferritin; authors may want to point out that bone marrow aspirate and biopsy for assessment of iron stores is the gold standard particularly when the ferritin in > 50>100 ng/ml in the setting of inflammation

Pg 5- IDA in pregnancy- it would be nice for the authors to state at what hemoglobin is there increased risk for poor fetal outcomes....perhaps this will be discussed later but its practical issue in terms of when to transfuse an iron deficient pregnant women or when to give IV iron.

Pg 7, para 1- the authors should also acknowledge that failure of Hb rise by 1 gram/dl in pregnant women does not necessarily further investigation but rather parenteral therapy if there is any suspicion for poor compliance or intolerance.

Pg 7, last para- pagophagia and other cravings (pica) should be mentioned as a symptom

Pg 8, para 1- where it's stated that "If gynecologic workup is negative..", I suggest it be added that "If gynecologic workup is negative and patient does not have evidence for ongoing increased menstrual loss (e.g. changing protection < 2 hrs., passing clots size of a quarter, staining underclothes).

Pg 8, para 2- ACOG states that VWF testing should be done in cases of idiopathic menorrhagia in women with a positive bleeding history (i.e. normal gyn exam excluding fibroids). I suggest adding that- ACOG Committee opinion 451, December 2009

Pg 9, para 3- Are the authors implying with their suggestion that celiac serology should be considered at presentation without doing GI endoscopy if serological testing is positive?; they should follow up that statement with a sentence that the finding of seropositivity does not trump the need for endoscopies in males and post-menopausal women.

Pg 10, para 1- the authors may want to cite the classic NEJM paper by Cello and Rockey who in 1993 (Volume 329:1691-1695) reported that up to third of a 100 consecutive IDA patients referred for upper and lower endoscopy had negative endoscopies

Pg 10, para 2- I disagree that SI evaluation is unnecessary if there is adequate response to iron therapy as that could mask a SB lesion like a AVM or tumor.

Pg 11, last para- I take issue with the assertion that amount of elemental iron is 120 mg as the erythron cannot incorporate more than 20 mcg of elemental iron a day!!!

Pg 12, para 2- another possible indication for parenteral therapy may be the amelioration of fatigue in non-anemic but iron deficient premenopausal females (Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration, Krayenbuehl A-H et al- BLOOD, 22 SEPTEMBER 2011 _ VOLUME 118, NUMBER 12)

Pg. 13, at top- the authors should cite the observation by Walter (Sunny) Dzik in Blood (Is iron gluconate really safer than iron dextran? Blood, 1 May 2003, 101 (9)) that iron gluconate (and by extrapolation, iron sucrose) is probably not less immunogenic than IV iron dextran i.e. side effect profile is not truly less severe than iron dextran. Furthermore, the main advantage of dextran over sucrose and gluconate is that the total dose can be given at one sitting while a calculated iron deficit of 1400 mg will require four infusions of IV iron (200 mg over 2 hrs the first time; 400 mg the next three times each one over 4 hrs.). The authors should also update this manuscript and include the relatively recently approved iron formulation Feraheme (ferumoxytol) which can be given over 5 minutes at a higher dose than IV sucrose (510 mg for Feraheme).

REVIEWER #2

Introduction: Last sentence, page 3, either expand or delete. How does it affect child development? What type of prognosis with what co-morbid states? Overall mortality in which population group?

Diagnosis Section: Page 3:

I think you need to re-work this section. I would focus on the AFP article in 2007 by Dr. Killip, Iron Deficiency Anemia. They did a very nice job with the diagnosis section. Your approach utilizes from a standpoint of microcytosis. However, IDA can appear without microcytosis. And the LR using microcytosis < 80 is 1, which is basically flipping a coin. Only when it's less than 70fL is it useful. Using ferritin less than 45, however, is 1.8 and if less than 24, LR=8.8. In any case, all the guidelines, from the British guidelines (http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf), the Canadian guidelines (http://www.bcguidelines.ca/pdf/iron_deficiency.pdf) recommend FERRITIN as first line test for evaluation for IDA (even with or without microcytosis).

Table 2 focuses on Microcytosis and again, should be focused on IDA evaluation as IDA does not necessarily have to have concomitant microcytosis. I would eliminate Table 2 and start by reviewing the Killip AFP article as your basis for diagnosis.

STFR paragraph on page 4: Technically, the STFR index is more sensitive and specific and is useful for those patients whose ferritin is between 45-100 and has concomitant anemia of chronic disease. Please see the article: <http://www.ncbi.nlm.nih.gov/pubmed/21812017>; Am J Hematol. 2011 Nov;86(11):923-7. doi: 10.1002/ajh.22108. Epub 2011 Aug 2.

Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. Skikne et al.

Should add a figure on diagnosis of IDA, again you could utilize Killip's article and modify if needed.

PREGNANCY paragraph on Page 5:

Can you provide the trimester cutoffs provided in the ACOG bulletin or the USPSTF recommendation. It is different for different trimester.

CHILDREN; end of page 5 and start of page 6:

Might consider adding the very good evidence re: delayed cord clamping and prevention of iron deficiency anemia in infants.

SORT TABLE: PAGE 22

Would add use of ferritin to dx IDA as the first line test.

Table 2: would remove (as focus is on diagnosis of IDA, not dx of microcytosis)

Add FIGURE on Diagnosis

TABLE 4: Can you put in the bottom of the table something regarding recommended treatment dosing (i.e. 120mg/day for 3 months for adults and 3mg/kg/day, up to 60mg/day for children?) That will help physicians figure out the dosing properly.

Also, since you mention the fatality and adverse reactions utilizing IV Iron Dextran, is there any reason to use it? One of the hematologists told me there should be no reason to use it since we have Iron Sucrose.

FIGURE 1: Needs to be FIXED. Your figure at the end of the Pre-menopausal pathway, no abnormal uterine bleeding--> treat with iron--> states "BEGIN POST-MENOPAUSAL WORKUP" makes no sense. Do you mean if no improvement, then begin work up for occult GI losses??

Also what happens after capsule and there isn't anything? Also what if there's a good reason, i.e. a vegan or lack of dietary intake? How far do you go in the GI workup? Is there any evidence from the hematology literature vs. the GI literature? I'd assume the GI literature would be heavily focused on the occult GI blood loss. How about in hematology literature/textbooks?

FIGURE 2: TREATMENT

You mention very little guidelines re: follow up for IDA treatment. Therefore I'd consider after treatment, "continue therapy 3 months after hematocrit normalization then discontinue iron" add something about if ferritin stores are restored (i.e. > 45) . After that the screening every 3 months, then 12 months is pretty impractical in the primary care setting. I would lump the left side to "check CBC periodically, and if any concerns, then go to the RIGHT side of the algorithm.

REVIEWER #3

Overall, this is a very well written manuscript on an important clinical topic which will prove very useful for a busy general practitioner. I suggest the following changes:

Page 3, para 2 change "as well as signs of low iron stores" to "as well as evidence of low iron store"

Page 9, last para change "in patients whom" to "in patients in whom"

Page 12, para 2- include conditions like gastrectomy, gastrojejunostomy, bariatric surgery or other small bowel surgeries in this

Page 13, para 1, last sentence - Delete "Only". 35% of patients experiencing side effects is a significant number.

Page 13, Last para - the statement regarding indication for blood transfusion for hemoglobin below 7 needs to be modified. Hemoglobin below 7 is not an absolute indication for blood transfusion. Transfusion needs should be assessed clinically depending on how well the anemia is being tolerated. Many patients with chronic anemia that developed slowly tolerate very low hemoglobins extremely well and do not need blood transfusion.

Page 14, para 1 Last sentence should be modified. It can be argued that transfusion is not necessary in "stable patient". Please also see comments above.

Page 14, last sentence of last para - the beneficial effect of iron in patients with heart failure is irrespective of whether they also have anemia. Additionally, the effect is not specific for iron sucrose. Other intravenous iron preparations have similar beneficial effect. Consider adding another reference of a randomized clinical trial published in NEJM 2009, 361:2436-2448.

Page 22, level of evidence for use of parenteral iron treatment to improve functional class in patients with CHF is better than "C" since there are 2 randomized trials supporting this recommendation. Also "parenteral" is spelled incorrectly in the table

AUTHOR'S RESPONSE TO THE REVIEWS

Comments from Dr. Wellbery (AFP deputy editor):

Many thanks for this well-written informative paper. I think the other comments on our reviewers' part cover the issues you need to address. Of note, I suspect our senior medical editor's question about parenteral therapy in part has to do with the fact that once a patient undergoes iron transfusions, their anemia is usually no longer within the purview of the Family Physician. You might wish to emphasize this along with reviewing the evidence for the efficacy of parenteral therapy for its various indications. One reviewer asks about the "hematology perspective." This is a bit puzzling to me

Response: Thank you. I have addressed the individual responses outlined below. In regard to the "hematology perspective" I have drawn from several resources to include the British Society of Hematology for the recommendations and information provided in the review.

p. 6. I would put the negative recommendations at the end of the paragraph, because the way it is stated now, it lacks a context. Although we believe the USPSTF recommendations should be given priority in presenting guidelines, it just sounds odd to start the paragraph this way. I would also add "and does not make recommendations for other ages"

Response: I agree with your recommendation and have placed the statement at the end of the paragraph along with the addition of "and do not make recommendations for other ages."

p. 8 "Endometrial biopsy should be considered for women under age 35 with unopposed estrogen exposure" I am confused by this statement. Under what circumstance would a premenopausal female with a uterus have 'unopposed estrogen exposure'?

Response. : Unopposed estrogen exposure occurs in this age group when anovulation occurs during which the corpus luteum fails to develop and the ovary does not secrete progesterone. Conditions such as PCOS, hypothyroidism and hyperprolactinemia can cause anovulation to occur. This has been inserted in the text to clarify.

p. 10. Define Cameron lesion

Response: Cameron lesions are erosions that develop in large hiatal hernias. This definition has been added to the text

p. 10 "if the patient has obscure gastrointestinal bleeding not discovered on initial or repeat endoscopy" how is it known they have obscure GI bleeding that is not discovered? Or do you mean "if the patient is suspected to have obscure.."

Response: I have corrected the statement to reflect if the patient is suspected of having obscure GI bleeding.

Comments from Dr. Siwek (AFP editor):

Overall, this is a well-written, professionally prepared manuscript. Many thanks for writing it for our readers. I think you did a good job using the Q&A format.

RESPONSE: Thank you.

Abstract: "The underlying cause of the IDA should be treated and oral or parental iron therapy can be initiated to replenish iron stores. In patients with heart failure, parenteral treatment of IDA with iron sucrose results in improved exercise capacity and functional class." I question the emphasis on parenteral iron therapy. In the first sentence, it's unqualified, as if it's an equally acceptable choice, whereas oral therapy is standard. In the second sentence, I wonder about the strength of the evidence regarding parenteral therapy. I checked reference 33, and it's a study of 35 patients randomized (meaning, only half received parenteral iron), and there was no comparison with oral iron. And reference 32 was a randomized study of only 40 patients, with a focus on changes in blood tests. [There's a typo in ref 32: "adrenal insufficiency" in place of "and renal insufficiency" Big difference!]. So, I think this is insufficient evidence to make blanket statements that seem to imply that millions of patients with heart failure should start receiving parenteral iron therapy. Please omit or downplay this point in the text (page 14) and omit it entirely from the abstract (it just doesn't rise to a level of significance compared with the other key facts that should be in the abstract).

Response: The wording of the abstract has been modified to reflect oral iron as standard treatment and to indicate circumstances in which parenteral iron may be used for therapy. Based on overall feedback and accurate statements reflecting the limitations of the studies on parenteral iron therapy in patients with CHF this aspect of the article has been removed and as such removed from statements in the Abstract and SORT table. As such references 32 and 33 have been removed.

Page 9: "Upper endoscopy with duodenal biopsies should be performed if serology is not available, or to confirm the diagnosis after positive testing." I can't imagine endoscopes being available but not simple blood tests that can be shipped anywhere if needed. Please revise to: "Upper endoscopy with duodenal biopsies should be performed to confirm the diagnosis after positive testing."

Response: Done

Page 10: please spell out VCE (don't abbreviate).

Response: Done

SORT table ratings:

Screening for Gastrointestinal malignancy should be performed on all adult men and postmenopausal women with IDA. Please change to "C" (disease oriented, expert opinion).

Response: Done

Screening serology for Celiac Disease should be performed on all adults with IDA. Please change to "C" (disease oriented, expert opinion).

Response: Done

The use of parental iron treatment may improve functional status in patients with CHF and IDA. This should be "B" (patient oriented, limited evidence), but I think this is too narrow and premature for a Key Clinical Recommendation. I wouldn't see this as one of the four most important things docs should know about IDA. For this reason, please omit from the SORT

table. (If there's another important diagnosis or treatment recommendation to add, please do so).

Response: Done. See above. I have omitted the comments on iron therapy in patients with CHF based on the feedback of limited data.

Table 3: Two concerns:

1. Laundry lists like this, while common, aren't very clinically useful. Better would be listing these in order of frequency, or according to signs/symptoms (which is probably too cumbersome for such a long list).
2. Grouping by mechanism/pathophysiology also isn't very clinically useful. Patients don't present saying, I have a problem with decreased iron absorption, or increased iron demand.

If ultimately you aren't able to organize this in some other way, then please alphabetize the lists within groups, rather than presenting them randomly, which might mistakenly imply some order of priority.

*Table organization: Think of this as an educational opportunity, to help readers put this information into perspective, by virtue of listing items in order of frequency, clinical importance, and so forth. A conventional pathophysiologic listing is good as a taxonomy for anatomists, but it doesn't help physicians sort through the differential diagnosis or diagnostic evaluation. It would be more helpful if items were grouped by similar presentation, or in a problem oriented, rather than disease oriented fashion.

Response: I have reorganized the table reflecting order of frequency based on a table found in reference 6. If this is not adequate I will prepare a table in alphabetical order as requested.

Algorithms: thanks for developing these. Were you able to find any validated algorithms in the literature, or ones endorsed by a major medical organization? If so, please review, cite, and incorporate as relevant.

Response: We were unable to find any validated algorithms in review of the literature that evaluates such a broad spectrum of patients (men as well as pre and post menopausal women). Our algorithm best reflects the work up presented in reference 11 published in the World Journal of Gastroenterology. As such it has been cited as the first reference for the algorithm.

"Pediatric": Our style is to use "childhood" or "in children" in place of "pediatric," unless referring to the specialty, such as "pediatric cardiologist." Please change this throughout the manuscript. [Used at least twice in the manuscript].

So, "In pediatric and pregnant patients" becomes: "In children and pregnant patients?"

Response: Done.

Essential Evidence Plus: I'm just checking to see if you received an Evidence Summary from our deputy editor, Dr. Mark Ebell, before starting to write your manuscript. If you did, and used it, please add it to the Literature Search/Data Sources paragraph (referring to it as "Essential Evidence Plus"). If you didn't receive it, or received it but didn't use it, please let me know, as a check on our processes.

Response: We did receive the Evidence Summary and used it. We accidentally omitted it from the Search/Data Sources paragraph and have corrected this.

* Patient Education: To help our readers and their patients, I'd like to ask you to develop a patient education handout to accompany your article. If you'd like to do so, please prepare a handout of two to four double-spaced pages in length. What would complement your article nicely is a piece on "Iron deficiency anemia---causes and treatment." Please highlight the important points, such as the need for a GI eval in men and post-menopausal women, and the fact that in adult, IDA is rarely nutritional, but almost always a sign of blood loss that needs to be investigated or explained.

You can find instructions on writing simplified patient handouts for a lay audience, as well as sample handouts, in our Authors Guide at:

http://www.aafp.org/online/etc/medialib/aaafp_org/documents/news_pubs/afp/authors_form/patienthandoutinstructions.Par.0001.File.tmp/PatientHandoutInstructions.pdf

As another example, you can review a handout on anemia from our sister publication, FamilyDoctor.org:

<http://familydoctor.org/familydoctor/en/diseases-conditions/anemia.html>

This handout is on anemia in general with a some discussion on iron, but yours could focus solely on iron deficiency anemia.

Response: I appreciate this opportunity to address our patients on this important topic and have developed the requested patient handout.

In your resubmission, please incorporate all tables into the document (so that everything that's supposed to go into the article is in the article).

Response: Done

COMMENTS FROM REVIEWER #1:

General comments-

This is a well written review of a very common clinical issue. However, I think there are some additional references/observations that the authors should strongly consider in adding in making their paper a more practical a guide for the clinician as outlined below.

RESPONSE: Thank you.

Pg. 3,last para- thalassemia is misspelled; also, specifically would refer to chronic disease states as chronic inflammatory states

Response: Done

Pg. 4, first para- authors may want to reiterate that the low cutoff of ferritin <15 reflects pre-menopausal menstruating women in the "pool" that "drives down" the ferritin; authors may want to point out that bone marrow aspirate and biopsy for assessment of iron stores is the gold standard particularly when the ferritin in > 50>100 ng/ml in the setting of inflammation

Response: Bone marrow biopsy as gold standard was placed at the end of the paragraph on page 5. Not sure if the comments regarding pre-menopausal women and low ferritin adds much to this section.

Pg. 5- IDA in pregnancy- it would be nice for the authors to state at what hemoglobin is there increased risk for poor fetal outcomes. Perhaps this will be discussed later but its practical issue in terms of when to transfuse an iron deficient pregnant women or when to give IV iron.

Response: This is mentioned under treatments, but has been recorded in this area as well to emphasize the ramifications of untreated or undiagnosed severe IDA.

Pg. 7, para 1- the authors should also acknowledge that failure of Hb rise by 1 gram/dl in pregnant women does not necessarily further investigation but rather parenteral therapy if there is any suspicion for poor compliance or intolerance.

Response: I agree with this statement and have made the necessary corrections.

Pg. 7, last para- pagophagia and other cravings (pica) should be mentioned as a symptom

Response: Done

Pg. 8, para 1- where it's stated that "If gynecologic workup is negative..", I suggest it be added that "If gynecologic workup is negative and patient does not have evidence for ongoing increased menstrual loss (e.g. changing protection < 2 hrs., passing clots size of a quarter, staining underclothes).

Response: Done

Pg. 8, para 2- ACOG states that VWF testing should be done in cases of idiopathic menorrhagia in women with a positive bleeding history (i.e. normal gyn exam excluding fibroids). I suggest adding that-ACOG Committee opinion 451, December 2009

Response: This has been added

Pg. 9, para 3- Are the authors implying with their suggestion that celiac serology should be considered at presentation without doing GI endoscopy if serological testing is positive?; they should follow up that statement with a sentence that the finding of seropositivity does not trump the need for endoscopies in males and post-menopausal women.

Response: This has been modified to state that upper endoscopy should be performed to confirm diagnosis as well as to rule out additional etiologies

Pg. 10, para 1- the authors may want to cite the classic NEJM paper by Cello and Rockey who in 1993 (Volume 329:1691-1695) reported that up to third of a 100 consecutive IDA patients referred for upper and lower endoscopy had negative endoscopies

Response: After review of the article I did not feel that it added to the point of this paragraph which was to emphasize the importance of missed etiologies on initial testing in patients with unimproved anemia. Of the 38 patients in Rockey and Cellos study that did not have findings 32 of the 38 improved with iron supplementation and those that did not had findings of underlying co morbidities which may be contributing. I do not feel this would fit in this part of the article.

Pg. 10, para 2- I disagree that SI evaluation is unnecessary if there is adequate response to iron therapy as that could mask a SB lesion like a AVM or tumor.

Response: Interestingly, the same source cited above states, “Although theoretically appealing, small-bowel enteroscopy is expensive and time consuming, requires special equipment, and has not been rigorously studied.” In addition it states, “The role of enteroscopy in identifying abnormalities in the small bowel is controversial” Multiple references recommended avoiding small bowel investigation unless initial evaluation with traditional upper and lower endoscopy was negative and patients did not respond to conservative therapies.

Pg. 11, last para- I take issue with the assertion that amount of elemental iron is 120 mg as the erythron cannot incorporate more than 20 mcg of elemental iron a day!!!

Response: This is the recommended dose put out by the WHO and also supported by recommendations of the CDC which recommend 50-60mg bid of elemental iron for adults with iron deficient anemia. As stated in the CDC recommendations of 1998 “The percentage of iron absorbed (i.e., iron bioavailability) can vary from less than 1% to greater than 50% (19). The main factor controlling iron absorption is the amount of iron stored in the body. The gastrointestinal tract increases iron absorption when the body's iron stores are low and decreases absorption when stores are sufficient. An increased rate of red blood cell production can also stimulate iron uptake several fold. So while an existent erythron may only incorporate 20mcg/d new cells would assume to require more.

Pg. 12, para 2- another possible indication for parenteral therapy may be the amelioration of fatigue in non-anemic but iron deficient premenopausal females (Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration, Krayenbuehl A-H et al- BLOOD, 22 SEPTEMBER 2011 _ VOLUME 118, NUMBER 12)

Response: Agreed that this may be another valid use of parenteral iron but as the article is focused on Iron Deficient anemia and not the entire spectrum of Iron deficiency, I feel this would add little to the focus of the article and if added would require removing something more pertinent.

Pg. 13, at top- the authors should cite the observation by Walter (Sunny) Dzik in Blood (Is iron gluconate really safer than iron dextran? Blood, 1 May 2003, 101 (9)) that iron gluconate (and by extrapolation, iron sucrose) is probably not less immunogenic than IV iron dextran i.e. side effect profile is not truly less severe than iron dextran. Furthermore, the main advantage of dextran over sucrose and gluconate is that the total dose can be given at one sitting while a calculated iron deficit of 1400 mg will require four infusions of IV iron (200 mg over 2 hrs. the first time; 400 mg the next three times each one over 4 hrs.). The authors should also update this manuscript and include the relatively recently approved iron formulation Feraheme (ferumoxytol) which can be given over 5 minutes at a higher dose than IV sucrose (510 mg for Feraheme).

Response: I have added your suggested reference as a possible argument for iron dextran, but based on the small size of the study, I emphasized the need for larger

studies with duplicated results before making this recommendation. Also I have added the manuscript with Feraheme and its dosing.

COMMENTS FROM REVIEWER #2:

Introduction: Last sentence, page 3, either expand or delete. How does it affect child development? What type of prognosis with what co-morbid states? Overall mortality in which population group?

Response: Based on limited word count this has been replaced with a statement of the important need to identify underlying causes and administer appropriate treatments for management.

Diagnosis Section: Page 3:

I think you need to re-work this section. I would focus on the AFP article in 2007 by Dr. Killip, Iron Deficiency Anemia. They did a very nice job with the diagnosis section. Your approach utilizes from a standpoint of microcytosis. However, IDA can appear without microcytosis. And the LR using microcytosis < 80 is 1, which is basically flipping a coin. Only when it's less than 70fL is it useful. Using ferritin less than 45, however, is 1.8 and if less than 24, LR=8.8. In any case, all the guidelines, from the British guidelines (http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf), the Canadian guidelines (http://www.bcguidelines.ca/pdf/iron_deficiency.pdf) recommend FERRITIN as first line test for evaluation for IDA (even with or without microcytosis).

Response: Further review of my references as well as those you provided allowed me to modify this section with mention that 40% of patients with IDA have normocytic erythrocytes and utilized the cut off value of MCV from the Killip article. I also updated this section ferritin as the first step as requested but utilized cut off values from other resources highlighting the fact that patients with chronic inflammatory states may have higher values.

Table 2 focuses on Microcytosis and again, should be focused on IDA evaluation as IDA does not necessarily have to have concomitant microcytosis. I would eliminate Table 2 and start by reviewing the Killip AFP article as your basis for diagnosis.

Response: Table 2 has been removed and I have modified this section based on my review of the Killip article and my references.

STFR paragraph on page 4: Technically, the STFR index is more sensitive and specific and is useful for those patients whose ferritin is between 45-100 and has concomitant anemia of chronic disease. Please see the article: <http://www.ncbi.nlm.nih.gov/pubmed/21812017>; Am J Hematol. 2011 Nov;86(11):923-7. doi: 10.1002/ajh.22108. Epub 2011 Aug 2.

Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. Skikne et al.

Response: I have added this reference as suggested as well as indicating the usefulness of the test in the patient with concomitant anemia of chronic disease.

Should add a figure on diagnosis of IDA, again you could utilize Killip's article and modify if needed.

Response: I have developed a similar figure while incorporating different cut off values for ferritin and utilization of erythrocyte protoporphyrin.

PREGNANCY paragraph on Page 5:

Can you provide the trimester cutoffs provided in the ACOG bulletin or the USPSTF recommendation. It is different for different trimester.

Response: These have been added

CHILDREN; end of page 5 and start of page 6:

Might consider adding the very good evidence re: delayed cord clamping and prevention of iron deficiency anemia in infants.

Response: This has been added as a suggestion with a comment on need for larger studies with maternal outcomes prior to making this a generalized recommendation.

SORT TABLE: PAGE 22

Would add use of ferritin to dx IDA as the first line test.

Response: Done

Table 2: would remove (as focus is on diagnosis of IDA, not dx of microcytosis)

Response: Done

Add FIGURE on Diagnosis

Response: Done, see above comment.

TABLE 4: Can you put in the bottom of the table something regarding recommended treatment dosing (i.e. 120mg/day for 3 months for adults and 3mg/kg/day, up to 60mg/day for children?) That will help physicians figure out the dosing properly.

Response: This has been added

Also, since you mention the fatality and adverse reactions utilizing IV Iron Dextran, is there any reason to use it? One of the hematologists told me there should be no reason to use it since we have Iron Sucrose.

Response: See Page 14 paragraph 2, Iron Dextran does have a higher risk of anaphylactic reaction, however carries the advantage of administering the entire amount of required iron in one dose as oppose to iron gluconate or iron sucrose and based on this smaller study may have a similar adverse effect profile to iron gluconate.

FIGURE 1: Needs to be FIXED. Your figure at the end of the Pre-menopausal pathway, no abnormal uterine bleeding--> treat with iron--> states "BEGIN POST-MENOPAUSAL WORKUP" makes no sense. Do you mean if no improvement, then begin work up for occult GI losses??

Response: Yes, if no improvement then a work up for occult GI losses should be initiated

Also what happens after capsule and there isn't anything? Also what if there's a good reason,

i.e. a vegan or lack of dietary intake? How far do you go in the GI workup? Is there any evidence from the hematology literature vs. the GI literature? I'd assume the GI literature would be heavily focused on the occult GI blood loss. How about in hematology literature/textbooks?

Response: As suggested in the algorithm if the patient does not respond to therapy and suspicion still persist a secondary small bowel evaluation could be performed with yet another capsule study or enteroscopy. Obviously if the patient is a vegan or lacks dietary intake it would be expected that these individuals would respond to supplementation as outlined in the algorithm. As far as hematology literature, I have reviewed several resources and incorporated recommendations from the British Society of Hematology in reference to therapies. I did not see any different recommendations or suggestions for approach to patients with this condition in review of hematology literature.

FIGURE 2: TREATMENT

You mention very little guidelines re: follow up for IDA treatment. Therefore I'd consider after treatment, "continue therapy 3 months after hematocrit normalization then discontinue iron" add something about if ferritin stores are restored (i.e. > 45) . After that the screening every 3 months, then 12 months is pretty impractical in the primary care setting. I would lump the left side to "check CBC periodically, and if any concerns, then go to the RIGHT side of the algorithm.

Response: This has been modified.

COMMENTS FROM REVIEWER #3:

Overall, this is a very well written manuscript on an important clinical topic which will prove very useful for a busy general practitioner.

RESPONSE: Thank you.

Page 3, para 2 change "as well as signs of low iron stores" to "as well as evidence of low iron store"

Response: Done

Page 9, last para change "in patients whom" to "in patients in whom"

Response: Done

Page 12, para 2- include conditions like gastrectomy, gastrojejunostomy, bariatric surgery or other small bowel surgeries in this

Response: Done

Page 13, para 1, last sentence - Delete "Only". 35% of patients experiencing side effects is a significant number.

Response: This has been changed to approximately

Page 13, Last para - the statement regarding indication for blood transfusion for hemoglobin

below 7 needs to be modified. Hemoglobin below 7 is not an absolute indication for blood transfusion. Transfusion needs should be assessed clinically depending on how well the anemia is being tolerated. Many patients with chronic anemia that developed slowly tolerate very low hemoglobins extremely well and do not need blood transfusion.

Response: I reviewed the recommendations of the British Society of Hematology and have corrected the transfusion section to reflect that ultimately the decision to transfuse is based on clinical judgment and should not be based solely on a lab value.

Page 14, para 1 Last sentence should be modified. It can be argued that transfusion is not necessary in "stable patient". Please also see comments above.

Response: Agreed and has been modified.

Page 14, last sentence of last para - the beneficial effect of iron in patients with heart failure is irrespective of whether they also have anemia. Additionally, the effect is not specific for iron sucrose. Other intravenous iron preparations have similar beneficial effect. Consider adding another reference of a randomized clinical trial published in NEJM 2009, 361:2436-2448.

Response: This section has been removed due to limited data. See above comments

Page 22, level of evidence for use of parenteral iron treatment to improve functional class in patients with CHF is better than "C" since there are 2 randomized trials supporting this recommendation. Also "parenteral" is spelled incorrectly in the table

Response: This section has been removed due to limited supporting data. Although 2 RCTs support the evidence they were of small patient populations. See above comments