

Update in Hematology: Anemia, Iron & Monocytes

“The Irony of it all”

with a dash of screening

- ▣ **ALBERT M. BRADY. MD, FACP, FACOI**
- ▣ **The Pacific Northwest University, COM**
- ▣ **Spring 2026**

The Irony of it all

▣ Objectives:

- Listeners will gain a new understanding of “normal” iron levels.
- Listeners will recognize the importance of iron beyond oxygen carrying capacity.
- Listeners will know how to identify and address deficiencies in pregnancy.
- Listeners will develop an understanding of the anemia of older patients.
- Listeners will understand the complexity of a macrocytic anemia.
- Listeners will be aware that iron deficiency always has a cause that must be searched for
- Listeners will be aware of the challenges of mammography screening.

ANEMIA AND IRON, AN UPDATE

- Dr. Brady attended medical school at the University of Los Angeles (UCLA) before entering Internal Medicine Residency at Oregon Health Sciences University (OHSU). He served two years as a Commander in the Navy at the National Institute of Health. Following his fellowship in Oncology at University of Minnesota, he partnered in private practice in Portland, Oregon for 12 years.
- Dr. Brady worked to establish multidisciplinary Oncology Programs. The programs sought to better serve cancer patients by bringing together all physicians involved in the patient's care to develop a single, cohesive, coordinated plan of care for the patient. This pursuit led him to hospital systems in Denver, Fort Worth, and suburban Detroit. Following the high school graduation of his youngest daughter (of four), he and his wife returned to the Pacific Northwest to be near family. He headed a private practice in hematology/oncology in Yakima from 2005-2015, while continuing his passion for teaching by counseling medical, nursing, and physician assistant students throughout his career.
- Professional societies include: American Society of Clinical Oncology, American Society of Hematology, American College of Physicians, American Medical Association and Washington State Medical Society. He is a Fellow in the American College of Physicians and the American College of Osteopathic Internists.

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- ▣ **Conflicts: An intimate and ongoing relationship with chocolate.**



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- ▣ Janice is a 34 year old who comes to you at week six. US shows a viable pregnancy.
- ▣ Lab: Hgb 11.4, Ferritin 33,
- ▣ Remember, our first step is to classify the anemia according to the MCV. This is helpful to narrow our diagnostic possibilities but is by no means diagnostic in itself.
- ▣ Furthermore,

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- ▣ It is critical not to confuse iron deficiency and anemia.
- ▣ This is an area of considerable unknowns but consider:
- ▣ A ferritin of 50 corresponds to no stainable marrow iron.
- ▣ Iron is important to many functions in the body and brain—its only purpose is not to carry oxygen.
- ▣ You can be iron deficient and have a normal hemoglobin.

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- ▣ Consider Jeffery, a 47 year old male hop farmer who has atrophic gastritis.
- ▣ HGB 15.1, B 12 0, Ferritin 34, MCV 108
- ▣ He is endoscoped, no malignancy is found, and he is placed on oral B 12.
- ▣ At 6 weeks his HGB is 14.8, B-12 is normal, ferritin is 24 and MCV is 100. He continues to complain of fatigue which he states is getting worse.

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- ▣ Oral iron, one tablet a day is added,
- ▣ 6 weeks later his HGB is down to 14 and his MCV is 91. Recheck of the ferritin is 18.
- ▣ Unsurprisingly, he cannot absorb oral iron either. He receives an infusion of iron and states he feels better walking out of the infusion center. Ferritin goes to 280 and then begins to fall.
- ▣ He now requires iron infusions every 16 months to keep his ferritin above 80.

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- ▣ **Returning to Janice whose ferritin was 33, it is important to note:**
 - She is not anemic by conventional standards for pregnancy.
 - A ferritin of 50 corresponds to no stainable marrow iron
 - The cognitive function of children is related to maternal iron stores (among other things)
 - Current thinking is that a woman should start pregnancy with a ferritin of 60, AND take oral iron throughout the pregnancy, or receive an iron infusion close to conception.
 - Intolerance of oral iron is treated with an iron infusion.
 - Lower limit of FERRITIN?

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- ▣ We all know folate supplementation is important during pregnancy.
- ▣ Of course, those anticipating a pregnancy should be on folate.
- ▣ Serum folate levels reflect your last meal.
- ▣ RBC folate reflects folate stores.
- ▣ While normal RBC folate is roughly 150-850ng/ml, the incidence of neurotube defects AND cardiac defects decreases in a linear fashion up to 950ng/ml.
- ▣ There are gains thereafter but at a very low rate.

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- ▣ Janice's RBC folate is 258 ng/ml. A perfectly normal level.
- ▣ For Janice I would recommend an iron infusion and folate supplementation beyond what is in a usual OTC prenatal vitamin.
- ▣ There is no data, but I would recommend 1 mg twice a day. Allergic reactions, nausea and bloating are rare.

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- ▣ Returning to Jeffery, at 1 year his ferritin is 112 (down from 280); at 15 months it is 92; at 18 months it is 77 and he is noticing increased fatigue.
- ▣ Infuse?
- ▣ Wait until ferritin is 50?
- ▣ Wait until 35?

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- ▣ **What do we know about iron supplementation and status?**
- ▣ **In a meta analysis published in the Canadian Medical Association Journal in 2023, iron supplements improved global cognitive scores and in 7,089 students.**
- ▣ **If the student was anemic, the IQ score improved and the student gained height and weight.**

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- ▣ In health and high performance: 33-80 % of female athletes and 10-17 % of male athletes are iron deficient defined as ferritin below 50.
- ▣ Supplementation improves maximal exercise ability, endurance, strength and interestingly, cold tolerance.
- ▣ Innumerable studies demonstrate low or absent iron stores in women in childbearing years:

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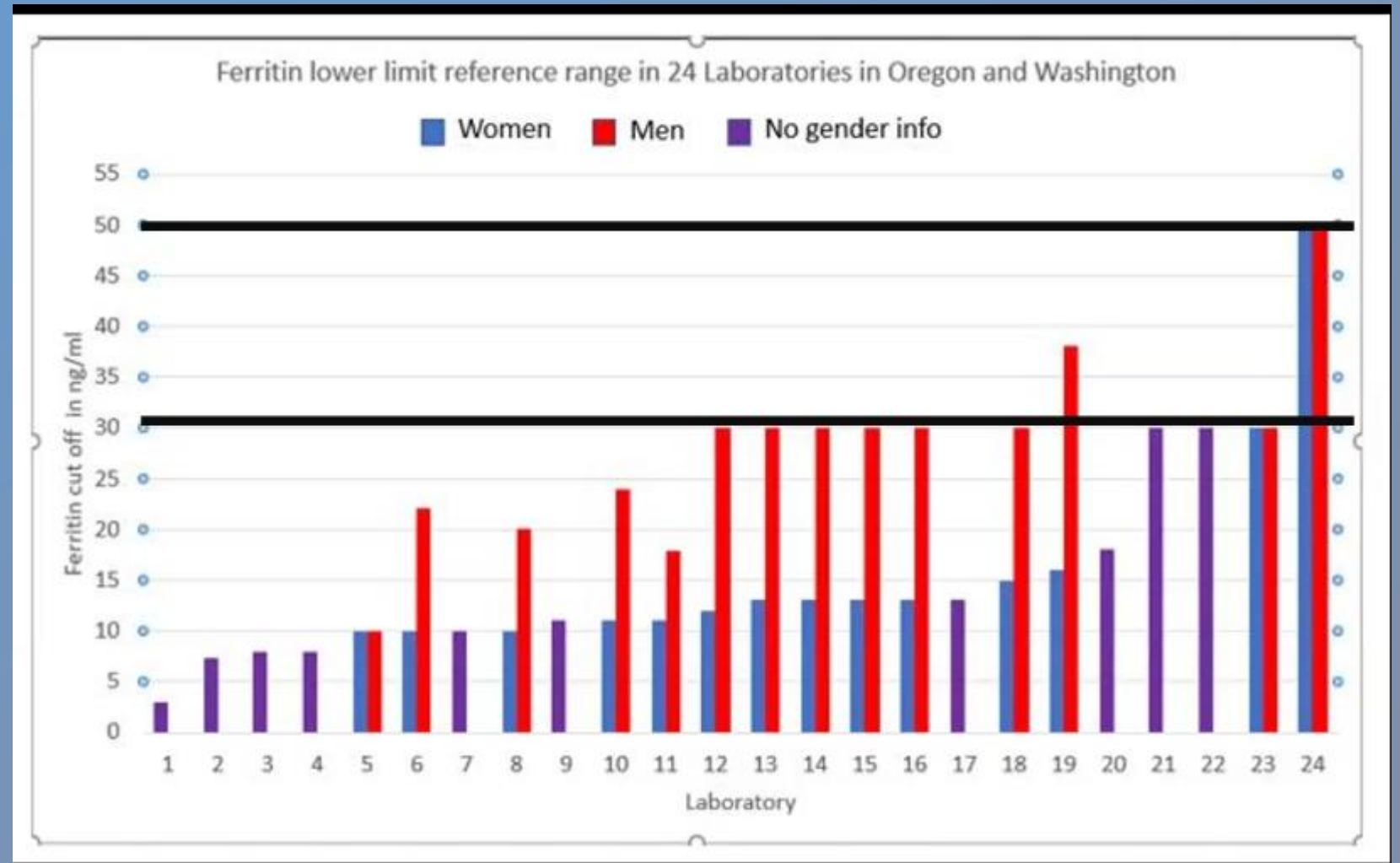
- ▣ Puolakka: 50 % had absent iron stores and 15% had scant stores
- ▣ Hallberg: 34% had absent stores
- ▣ Rybo: 32% had absent stores and 15% had scant stores
- ▣ In a study of blood donors 66% of the women were deemed iron deficient based on a ferritin of 35; and 50% of the men were deficient.
- ▣ In a separate study of pregnant women (who had been instructed to take supplemental iron) 84% were deficient (ferritin 35) at the START of the third trimester.

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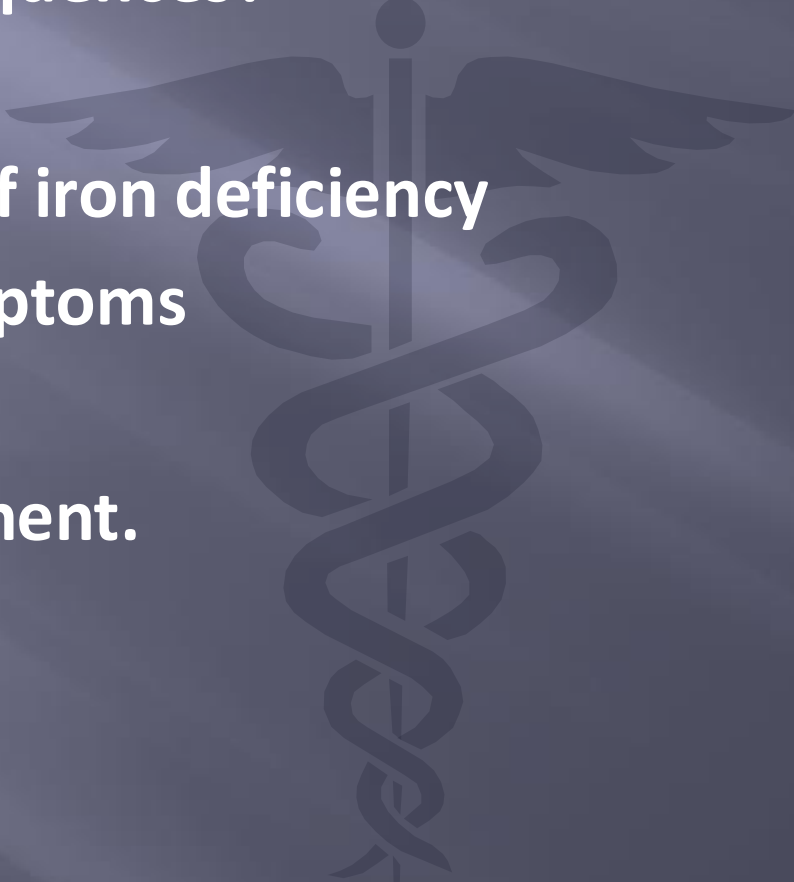
- ▣ There are two randomized controlled trials that show treatment of a ferritin that is less than 50 improves symptoms/outcomes.
- ▣ I believe that 50ng/ml is the natural cutoff.

THE ONLY LAB WITH A “NORMAL” FERRITIN LEVEL OF 50 OR HIGHER IS THE

U OF W.



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- ▣ **What are the consequences?**
 - ▣ **Under recognition of iron deficiency**
 - ▣ **Trivialization of symptoms**
 - ▣ **Undertreatment**
 - ▣ **And denial of treatment.**
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- ▣ **How about the tests:**
 - **Iron levels vary widely and are affected by many variables**
 - **MCV: lacks sensitivity AND specificity**
 - **RDW: do you even look at it? I find it to be of little value.**
 - **Saturation: can be confusing. Level varies with things that impact transferrin level. It is low in Fe deficiency and the anemic of chronic disease/inflammation.**

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- ▣ Consider Harry: His ferritin is 60. He requires iron infusions about once a year, he is 11 months out and symptomatic. HGB 14.8, MCV 91. Sats are 29% (20-50). His TIBC is 251 at the very lower limits of normal and his iron is modest at 80. His saturation is 32%, “normal”; but if the TIBC was midrange at 350, saturation is now borderline at 22%. Furthermore, he is symptomatic.
- ▣ I would infuse him, with?

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Formulation	Recommended Dose
LMW Iron Dextran	1000 mg over 1 hour
Ferumoxytol (Feraheme)	510 x 2 or 1020 over 15 minutes
Ferric carboxymaltose (injectafer) (hypophosphatemia)	1000 mg over 15 minutes
Iron isomaltoside (monofer)	1-2000 mg over 15 minutes

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- ▣ Rashid is a 68 y/o Algerian AMAB who sees you for osteoarthritis, hypertension and COPD. He has a 52 pack year smoking history and was hospitalized 10 months ago for pneumonia (CAP) from which he has recovered completely.
- ▣ At a 3 month follow up physical and lab including a CBC were normal.

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- ▣ He has no new complaints today. He has a chronic cough productive of small amounts of mucoid sputum. Vital signs are unremarkable, and physical exam is consistent with COPD.
- ▣ Lab today: HGB 9.9, MCV 108, WBC 3.7, plts 156K.

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- ▣ **B 12 or folate right? Chronic inflammation (unlikely)?**
- ▣ **Certainly B 12, folate and CRP will be checked but remember, folate deficiency is rare in patients. It is primarily a disease of the malnourished.**
- ▣ **B 12 deficiency is a frequent cause of anemia of the elderly (terrible term).**
- ▣ **With a normal B 12 one must think of myelodysplasia or Copper deficiency and evaluate the stomach.**

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- ▣ Myelodysplasia frequently presents with monocytosis and a macrocytic anemia.
- ▣ Macrocytic anemia or undiagnosed macrocytosis with normal B 12 and folate should see a hematologist.
- ▣ Copper deficiency is seen in the setting of dentures or gastric surgery/disease. In addition to a macrocytic anemia one often sees leukopenia and neurologic symptoms similar to subacute combined degeneration of the spinal cord can develop.

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- ▣ **B 12 deficiency and neurologic symptoms:**
 - There are many strategies. Certainly one starts with injected B12 to quickly reverse the neuro-symptoms and prevent permanent disability. Probably daily for a week or so. One can quickly migrate to 2/3 times a week for about a month.
 - With improvement injections can go to weekly then monthly. Once the patient stabilizes daily oral B-12 should be sufficient to maintain levels.
 - The stomach must be evaluated. Also, intrinsic factor blocking antibodies and anti-parietal cell antibodies.

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- ▣ **Anemia in the elderly:**
 - This a common and complex problem.
 - An estimated 17% of individuals over 65 have anemia.
 - One third of these, after careful investigation, are the unexplained anemia of aging.
 - Why do we care? Even a mild anemia causes poor physical performance, decreased strength, increased falls, decreased QOL, and perhaps most importantly, increased mortality.

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- ▣ **Anemia in the elderly:**
 - **Even in physically high-functioning older adults, anemia is associated with a four-fold increase in the risk of impaired executive function.**
 - **Often patients have more than one cause of anemia and therapy for one cause will not result in resolution of the anemia.**
 - **Nutrient deficiencies are common and result from surgery, failure of nutrient sensing, GI disease including blood loss which can be compounded by antiplatelet therapy.**

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- ▣ **Anemia in the elderly:**
 - **Chronic inflammatory conditions are common and range from the metabolic syndrome and type II diabetes to classic rheumatologic disorders like rheumatoid arthritis.**
 - **Ergo: any chronic illness: COPD, CHF, CRF**
 - **A decline in nephron size and number reduces erythropoietin production (CKD).**
 - **A decline in testosterone.**
 - **Myelodysplasia and myeloid precursor conditions like clonal cytopenia of unknown significance (CCUS).**

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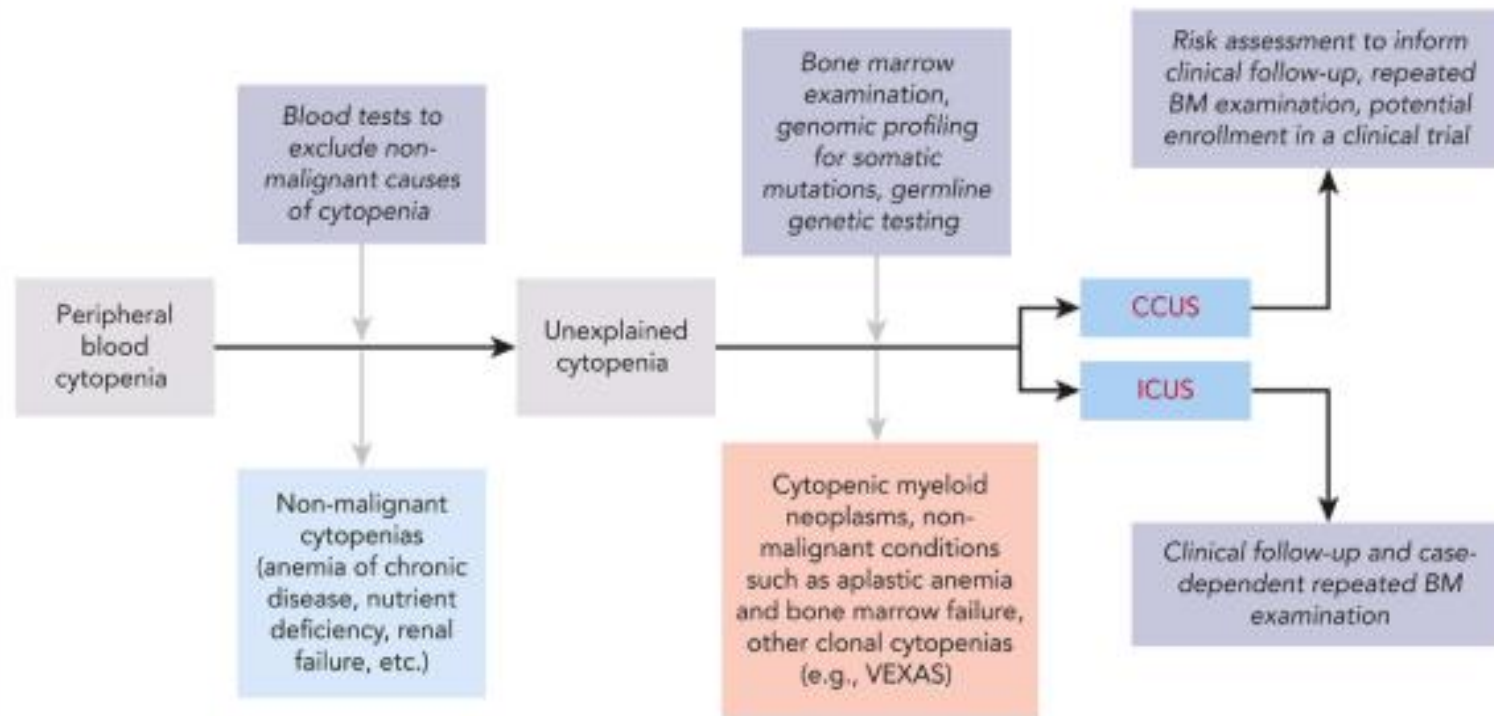
- ▣ Polypharmacy must be considered.
- ▣ The “anemia of aging” is characterized by stem cell exhaustion and cellular senescence.
- ▣ The approach to such a patient is to have the peripheral smear reviewed and start with renal function, CRP, ferritin, B12, folate and copper.
- ▣ In addition, a careful history may reveal an underlying condition or polypharmacy.

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- ▣ If there is an unexplained cytopenia (persistent low blood count in one or more lineage over 4-6 months and your workup has ruled out a common or identifiable cause), a hematology consult is in order.

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How I Manage Patients with Unexplained Cytopenia



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Conclusions: Somatic mutation analysis may serve as a valuable complement to the diagnostic work-up and clinical management of unexplained cytopenia, enabling the identification of patients with unmutated (idiopathic) cytopenia of undetermined significance (ICUS) or with clonal cytopenia of undetermined significance (CCUS). CCUS is a condition with an elevated risk of progression to a myeloid neoplasm, and recently developed prognostic models represent valuable tools for personalizing clinical follow-up and designing clinical trials for these patients.

Malcovati and Cazzola. DOI: 10.1182/blood.2024025771

 blood
Visual
Abstract

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- ▣ The anemia of chronic inflammation is an interesting condition. Inflammatory cytokines increase a hormone called hepcidin. High hepcidin levels impair iron mobility, it cannot be absorbed, nor can it get out of storage. Ferritins are often normal, but the marrow is deprived of iron, consequently, erythropoiesis is impaired.
- ▣ Initially the anemia is NCNC but with time the anemia becomes microcytic.
- ▣ If there is confusion about the ACI vs another cause a hepcidin can be ordered, it will be high.

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- ▣ What about treatment?
- ▣ This will depend on what you find.
- ▣ For example, there is evidence that patients with CHF_rEF do better if their ferritin is greater than 100 even with a normal hemoglobin. This can only be obtained by infusions of iron.
- ▣ CKD is managed with erythropoietin and iron infusions if needed.
- ▣ Restless legs keep ferritin 2-300.

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- ▣ Rex is a previously healthy 63 year old, AMAB, who is complaining of fatigue and weakness but otherwise feels well. He has assumed this is his age but routine testing demonstrates a microcytic anemia.
- ▣ His ferritin is 37 and he responds nicely to oral iron with minimal side effects.
- ▣ And so?

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- ▣ This is not the anemia of chronic inflammation as he has no risk factors and responded to oral iron.
- ▣ In spite of the fact that symptoms have improved with the rising hemoglobin his bowel must be checked if that has not been done. Even if he had a colonoscopy at age sixty, stool should be checked for blood and we should be sure he is not hemolyzing.
- ▣ The tests for hemolysis include:

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- ▣ Medication history
- ▣ Jaundice, splenomegaly
- ▣ Smear of course, (schistocytes) reticulocytes (also a test for marrow failure), LDH, Bilirubin, Bili in urine, “blood” in urine (dipstick positive, no RBC on micro), Coombs’.

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- ▣ A word about screening:
- ▣ While I am passionate about screening and I think guidelines for colon and lung are clear, I want to offer some food for thought about breast.
- ▣ Screening is done in patients with no complaints whose family history does not suggest increased risk.
- ▣ Note that BRCA is not the only gene conferring increased risk, therefore, in patients who are BRCA negative and with a suggestive history more detailed testing is in order.

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- ▣ There is good agreement that BREAST screening should be established by age 50.
- ▣ Annual as opposed to biennale imparts a very small advantage.
- ▣ Remember that mammography reduces breast cancer mortality but does not reduce all cause mortality.
- ▣ Newer treatments account for most of the improvement in breast cancer mortality.
- ▣ 30% of mammographically discovered tumors are interval tumors, that is tumors that developed between mammograms and are therefore MORE AGGRESASIVE.

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- ▣ The USPSTF decision is based on low quality modeling data.
- ▣ Most studies date to the last ½ of the previous century (recruiting 1963-1991). Technology and therapy have changed (30 new drugs from 2010-20 alone).
- ▣ The model suggests that for every 1.5 deaths averted per 1000 women there are 2 overdiagnoses.
- ▣ My reading of the data is that most of the benefit that accrues to the 40-49 age group happens in the 45-49 group.

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- ▣ We are all concerned about the harms of false positives and false negatives as well as the apparent increase in cancer in younger patients, presumable due to lifestyle and environmental changes.
- ▣ BC incidence has increases 2% per year from 2015-19 (most recent data).
- ▣ Harms include overdiagnosis (and a lot of research is being done on determining which cancers will not impact a patient's life), anxiety, discomfort, fear, unnecessary biopsies, unnecessary treatment treatment, and, of course, death.

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- ▣ {Data for example: annual screening for 2000 women saves 4.2 BC deaths and 102 life-years gained vs 3.0 and 88 for biennial screening. However, there are an additional 30,000 mammograms, 1400 false-positives, 174 benign biopsies and 14 over diagnosed cases (are there lost life-years here?)}.
- ▣ (the data are actually for 1000 women I just doubled everything to make it all come out even.)

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- ▣ Given all these vagaries, what should be done?
- ▣ Have a strategy and stick to it.
- ▣ Certainly, women 40-45 are best served by an informed discussion that must respect their values and preferences.
- ▣ Numbers should be absolute and not relative.
- ▣ Be aware that women overestimate their risk by a factor of 20 and the effectiveness of screening by a factor of 30.
- ▣ Beliefs are important.
- ▣ **Family history or known genetic risk changes all this.**
- ▣ **WISDOM TRIAL**

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- ▣ Breast cancer is big business, a common disease, most women survive to advocate for their disease.
- ▣ I urge you to proceed, but with caution.
- ▣ You must document patient's preferences.
- ▣ Note that an invitation to screen does not equal a screening.

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