

CLINICAL HEMATOLOGY/ONCOLOGY NEWSLETTER

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RE: Common (Overlooked) Answers In Patients Referred To Hematology.

Office practices are busier than ever and office staffs expend a great amount of time trying to manage office records and paperwork, the volume of which was never present in the past. Laboratory tests that are ordered cause in an incalculable amount of paper. Some reports are labeled “preliminary,” and they turn up repetitively. Other reports are entitled “complete,” but they may still lacking some of requested tests. Laboratory data arrive by computer screens, by FAX, and by regular mail. Government and insurance companies add additional layers of requests, photocopies, authorizations, etc. Laboratory tests must comply with “guidelines” for the routine follow-up of patients or for the assessment of new patients’ problems. The bottom line is that the office burden is excessive and it may interfere with the expected activities of being a doctor.

Sometimes, an abnormal laboratory test per se results in a referral for a consultation. The more appropriate approach to a laboratory abnormality should be a personal review by the referring physician, either in the presence of the patient or with the patient’s chart. Some offices have created a system for laboratory review by nurse practitioners, physician assistants, or some combination of the above before the data arrive at the physician’s desk. Laboratory abnormalities should result in a clinical assessment rather than a referral. In some instances, the patients who are sent to hematologists have answers for those problems which were not addressed or were overlooked by the referring physicians.

The types of hematologic problems referred to me within one calendar year are shown in Table 1. Anemia is predominant.

Table 1: Referring “Diagnosis” to the Hematologist

	<u>Percent</u>
Anemia	40
Thrombocytopenia	13
Leukopenia	11
Leukocytosis	10
Hypercoagulability	9
Hypergammaglobulinemia	8
Erythrocytosis	7
Abnormal PT+/-PTT	1
Thrombocytosis	1

Let us review an actual case and look for information that could be sought in a clinical assessment and consider what might have been overlooked.

A 71 year old African American female complains of tiredness and is referred for “anemia.” Her history also included degenerative and rheumatoid arthritis for which she takes aspirin. The laboratory data were as follows:

<i>Hemoglobin – 11.6 G/dL</i>	<i>(normal 12-14.5)</i>
<i>Serum iron - 28 ug/dL</i>	<i>(normal 50-170)</i>
<i>Total iron binding capacity (TIBC) - 360 ug/dL</i>	<i>(normal 200-400)</i>
<i>Percent iron saturation – 7.8%</i>	<i>(normal 15-45%)</i>

She was started on iron by her physician and referred for “iron deficiency anemia.”

A repeat testing of the hemoglobin is always reasonable to document the accuracy of the result. The next step is to decide if the patient is, in fact, anemic. The range of normal values that are provided on the standard laboratory report form indicated that this patient’s hemoglobin fell below “normal.” However, this “normal range” does not represent an accurate sampling of a healthy population of individuals. These “normal” values are often derived from old textbooks or outdated WHO data. Many of the ranges that are used have no consistency from one laboratory report to another, especially in regards to the lower limits of normal. Additionally, they usually provide no determination as to the number of people with values that are below the lower limits who are truly normal; Gaussian distribution or standard deviations are not given. Clinical hematologists have already recognized that there are variations in the so-called “normal” population and that it may depend on ethnic and racial origin.

Recently, the data bank of the 3rd US National Health and Nutrition Examination Survey (NHANES-III) and the Scripps-Kaiser database were evaluated for a definition of “normal hemoglobin.” Beutler et. al. deleted those individuals with laboratory evidence of iron deficiency, thalassemia and renal disease from the “normal” population[1]. As shown in Table 2, the mean lower limit of hemoglobin (5th percentile or 95% accuracy) for Whites is higher than for African Americans. The lower limit of hemoglobin for African American females is the lowest of the groups reviewed. There was no significant difference within each group based on age.

Table 2. Lower Limit of Normal (based on 5th percentile)

<u>Group</u>	<u>Hemoglobin, g/dL</u>
White men, yrs	
20-59	13.7
60+	13.2
White women, yrs	
20-49	12.2
50+	12.2
Black men, yrs	
20-59	12.9
60+	12.7
Black women, yrs	
20-49	11.5
50+	11.5

Based on the Scripps-Kaiser data, the above patient who was referred for anemia was not anemic. However, if previous hemoglobins documented a higher value, then indeed, her hemoglobin of 11.6 would be new and a referral might be appropriate. Unfortunately, when previous data are sought, they are often unavailable, as was the case with this woman. She complained of “tiredness.” If the hemoglobin value of 11.6 was a new finding, then “tiredness” may relate to it. However, if the hemoglobin value was previously at this level, then adaptations to “anemia” might have been made and “tiredness” should not be a symptom.

The remaining comments will focus on the iron laboratory results that led to a presumed diagnosis of iron deficiency: a) low level of the serum iron and b) low percent iron saturation. If the referring physician was correct with the diagnosis of iron deficiency, a referral to hematology would not be needed. What would have been necessary was a determination of blood loss and, if present, referral to appropriate physicians depending on the site of blood loss. The treatment of iron deficiency and the correction of anemia are less important than is the identification (and correction, if possible) of the site of blood loss.

Before referral to any specialist, a complete history is needed. In addition to questions about previous anemia and blood loss, a family history might identify thalassemia, sickle cell or other chronic anemias. Other important points of the history include comorbid illnesses beyond her arthritis, and the identification of drugs that she is taking other than aspirin. On physical examination, if koilonychia were present, iron deficiency would be very likely. An enlarged spleen may be seen in iron deficiency, but it may be an important clue to other illnesses, as well.

The peripheral blood smear is essential for review[2]. Referring physicians usually do not have an opportunity to see peripheral smears, but the laboratory report may describe the size and shape of red cells. Unfortunately, the MCV is used as a replacement by referring physicians. When the MCV is low, it is erroneously presumed that it is caused by iron deficiency. An MCV is an average of the size of all red cells. It does not describe the actual cells that are displayed on the smear. Confusion with the MCV may occur in the following instances:

1. A low MCV may indicate iron deficiency, but it is also seen in thalassemia, anemia of renal disease, and anemia of chronic disease. Some of these disorders have characteristic abnormal cells on the peripheral smear.
2. A normal value for the MCV may not mean that the red cells are all of normal size. A normal MCV may represent microcytes and macrocytes of megaloblastic anemia or myelodysplasia, or the presence of microcytosis with reticulocytosis. Reticulocytes are large-sized cells that may offset the microcytic size estimate and cause the average cell size to appear normal.

When this patient arrived at the hematologist’s office, she described no bleeding, no family history of anemia, and no use of drugs other than aspirin. She had no telltale signs on physical examination other than mild ulnar deviation of the wrists, seen in rheumatoid arthritis and distal phalangeal changes of degenerative joint disease. Her nails were normal and her spleen was not palpable. The gynecologic and rectal examinations were negative as was the stool for blood. The repeat laboratory data affirmed the low serum iron, normal transferrin level (TIBC) and low percent iron saturation. In addition, other iron tests were ordered and will be discussed below.

Does she have iron deficiency? A misreading of textbook information could give this conclusion, but other possibilities have similar laboratory results. Indeed, low serum iron

values are seen in iron deficiency, but the serum iron is a negative acute phase reactant. Therefore, acute and chronic inflammatory diseases, infections, and renal disease all lower the serum iron in spite of normal iron stores. The TIBC might be more helpful. When it is normal, it is of little value, but when it is elevated, it occurs only with iron deficiency and/or with increased estrogen levels (pregnancy or the use of estrogen therapy). If this woman's TIBC had been high, then it would have been likely that she had iron deficiency, especially since she was not on estrogens and not pregnant. The percent iron saturation (serum iron/TIBC X 100) is usually of limited use. As noted above, many different illnesses will lower the serum iron; consequently, all of these illnesses also cause a lowered percent iron saturation.

In this woman's case, the history of rheumatoid arthritis suggested the anemia of chronic disease with or without concomitant iron deficiency. Aspirin was a consideration but she had no history of bleeding, a negative stool for blood, and a negative rectal and pelvic examination. A look at the bilirubin value in the automated chemistry test can sometimes be helpful. The serum level of bilirubin is derived from the catabolism of hemoglobin. Normal red cell destruction *in vivo* is responsible for the bilirubin that is in the normal range (0.3-1.2 ug/dL). When red cells are destroyed *ex vivo* (blood loss), the bilirubin value may be low (< 0.2 ug/dL). Her bilirubin was normal at 0.6 ug/dL.

Finally, two new laboratory tests are helpful for the diagnosis of iron deficiency: ferritin, and soluble transferrin receptor activity (STRA). Ferritin represents storage iron and a serum level of ferritin is usually a good indicator of marrow and liver iron. Her ferritin value was 35 ng/mL (normal is 22-300). The STRA was normal as well. Elevated levels of STRA are found in iron deficiency. As a final note, hepcidin is a new laboratory test that very closely correlates with iron deficiency. Hepcidin is associated with the transfer of iron through the intestinal mucosa as well as the transport of iron from macrophages to red cell precursors. It is also probably responsible for the observation that serum iron levels are negative acute phase reactants. The routine testing of hepcidin is not yet readily available. Hepcidin was reviewed in the January 2006 Newsletter and is obtainable, if requested.

This woman had a normal blood smear with no abnormalities to suggest thalassemia or other inherited anemias. In addition, the bilirubin, ferritin and STRA were normal. Therefore, it was very unlikely that she had iron deficiency. By exclusion, she may have the anemia of chronic disease (arthritis) or no anemia at all.

In summary, the commonest referral to hematology is anemia. Often, a presumption of iron deficiency is made, iron is started, and the patient is sent to hematology and/or gastroenterology (for endoscopies). Iron therapy is wrong and may cause added iron uptake or overload. Unnecessary endoscopic procedures can result in complications and will add to the costs of health care. The referring physician should first clinically assess the (?) newly discovered low hemoglobin. Is anemia truly present? If it is present, are there clues and pieces of information that are overlooked?

Keywords: *anemia, iron deficiency, serum iron, ferritin, STRA, hepcidin.*

References:

1. Beutler, E. and J. Waalen, *The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration?* Blood, 2006. **107**(5): p. 1747-50.
2. Shattil, S.J., *A (blood) smear campaign.* Blood, 2003. **101**(7): p. 2453.