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ABSTRACT

CLINICAL DECISION-MAKING IN THE INVESTIGATION OF ANEMIAS IN HOSPITALIZED PATIENTS.

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The present study was designed to determine the prevalence of various causes of anemia in hospitalized patients, and to examine the clinical decision-making of the medical team in evaluating those patients. Knowledge of the actual prevalence of different kinds of anemias should make work-up more efficient. We identified 99 consecutive anemic inpatients being evaluated for new anemias, defined as having one of several laboratory investigations performed to workup their anemia: serum iron, TIBC, serum ferritin, reticulocyte count, serum haptoglobin, serum folate, RBC folate, vitamin B12, or serum erythropoietin. We then followed their evaluation as documented in the medical record, assessing factors such as the clinical context of their anemia, the result of Hemoccult™ stool testing and other ancillary testing, and the major diagnoses made during their hospitalization.

The most common causes of anemia were the anemia of chronic disease (37%), iron deficiency (14%), renal insufficiency (14%), and acute gastrointestinal bleeding (13%). The most commonly ordered tests were ferritin, serum iron, and TIBC in 89%, 84% and 83% of patients, respectively. Vitamin B12 and folate assays were performed in half of patients. The least commonly ordered test was serum erythropoietin in 12% of patients.

While the anemia-related diagnoses in these patients were not surprising, the contribution of renal disease was often underestimated and underinvestigated. ACD and iron deficiency were generally appropriately investigated, while vitamin B12 and folate deficiency may have been overinvestigated. The pervasiveness of anemia in the hospital may lead to complacency and the misconception that anemia is normal in this population.

Table of Contents

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I must also thank the Department of Laboratory Medicine and the staff of the clinical hematology, chemistry, and immunology laboratories for facilitating my research and answering my myriad questions. And I thank Laboratory Administrator Denise Fiore and her secretary, Debbie Hoffman, for supplying me with information on lab costs. I must also thank Sue Roberts and the Office of Medical Records for their constant assistance during this project.

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INTRODUCTION

Anemia is a common disorder among both inpatients and outpatients at Yale-New Haven Hospital. In fact, more than two-thirds of blood specimens submitted to the Clinical Hematology Laboratory for complete blood counts (CBCs) reflect anemia. For most of these patients, the cause of the anemia is known, but for some, the cause is not known. It is this latter population that the current study aims to investigate.

In 1989, a prospective evaluation was done of anemic patients tested in hospital laboratories at Yale-New Haven Hospital (Hall, R. and McPhedran, P. 1989. Anemia in the hospital. Unpublished data.). Among 202 adult, non-pregnant patients identified as having newly diagnosed anemia, the most common etiologic groups, from most frequent to least frequent, were patients with inflammatory diseases, active bleeding, iron deficiency, renal insufficiency, and liver disease, each present in more than 10% of new anemias. Other causes were less common, including those often featured in the "standard" workup: B12 and folate deficiency totaled 1.5%, and hemolytic anemias totaled 2%.

A few published studies have examined populations of anemic inpatients and the diagnostic pathways chosen by their physicians. In 1974, Paine et al. performed a prospective study of 500 consecutive patients admitted to the medical service of a large general hospital (1). Their goal was to determine both the various types of anemia represented and the prevalence of these types within their cohort. Of the admitted patients, 114 (23%) were found to be anemic (Hgb < 13 gm/dL for men or < 11 gm/dL for women), and all of these patients had various laboratory studies as well as bone marrow aspiration and hemoglobin electrophoresis. Patients with hematologic

malignancies and hemoglobinopathies were not excluded. Patients were classified into physiologic diagnostic groups, the largest being hypoproliferative anemias (59 patients, 52%). Infection, inflammation, uremia, and non-hematologic malignancy made up 38 of the 59 patients in the hypoproliferative group (64%). The other major diagnostic group was iron deficiency, which included 26 of the anemic patients (23%). Still, iron deficiency made up less than half as many patients as did hypoproliferative states, but iron therapy remains a common empiric therapy initiated in anemic patients. Other "deficiency states," namely folate and vitamin B12 deficiencies were uncommon: folate deficiency existed in four patients while pernicious anemia existed in two patients.

The authors also observed that mild anemias often went unnoticed or disregarded, and the cause of this was, in part, the misconception that anemia is the "norm" for elderly, hospitalized patients, and therefore is often without significance. The above study is unique in that the authors had the benefit of bone marrow examination in all their patients to assist them in definitive physiologic categorization. It still represents perhaps the largest prevalence study of anemic inpatients that also examines housestaff behaviors, but having been performed more than 25 years ago, this study may not reflect current prevalences, or current diagnostic and therapeutic practices.

In a study by Carmel et al., the authors surveyed attendings, house officers, and medical students on their knowledge of anemia (2). For instance, they asked respondents to define anemia and to give a hemoglobin level below which they would act in various clinical situations. Using the textbook definition of anemia as Hgb <14 gm/dL for men, and <12 gm/dL for women, only 54% of respondents could define anemia for women, and a dismal 30% could define anemia for men. Futhermore, between 35 and 60% of

respondents would not initiate a workup until the hemoglobin was between 1 and 4 gm/dL below the lower limit of normal range. Interestingly, respondents at all levels of medical training performed equivalently. The observations made by the authors included that a disparity exists between what is taught and what is done in practice, and there also seems to exist a lack of knowledge about anemia, from medical students to attendings. One hypothesis was that "[physicians] may 'expect' older patients, poor patients, and others to be anemic," which may be further influenced by the fact that house officers in municipal hospitals have a skewed experience with so many admitted patients being anemic.

Many other authors have examined various facets of the diagnosis, treatment, and prevalence of anemia in hospitalized patients (3,4,5,6), but no prevalence study exists that looks at the overall workup performed by house officers and the diagnoses that are found without intervention by the researching group. In other words, there is a lack of a "real world" look at the investigation of anemias of unknown origin (AUOs), without the benefit of bone marrow examination and an all-inclusive panel of tests in all patients. Such an approach is, of course, neither feasible, nor appropriate, nor cost-effective for all patients admitted to the hospital with anemia. Yet, ". . . the 'burden of proof' is on the physician to show that disease is absent in every patient in whom the hemoglobin or hematocrit falls below the limits of normal" (5).

Statement of Purpose and Hypothesis

We have hypothesized that the common laboratory tests and procedures used in the diagnosis of anemia do not necessarily reflect the diagnoses commonly represented in anemic inpatients. Furthermore, inappropriate workups and inappropriate diagnostic conclusions may reflect a lack of physician education about the significance of anemia and its various causes.

Based on our hypothesis, the aims of this study point to improving diagnosis and treatment of patients whose anemias are most likely to be missed, misdiagnosed, or mistreated:

1. We aim to determine the prevalence of various causes of anemias in hospitalized adult patients.
2. We aim to investigate the clinical context in which the anemia was recognized by thorough review of the medical record, and this includes evaluation of the tests and procedures chosen by the physician(s) to investigate the anemia.
3. From these data, we aim to formulate clinical guidelines for investigating newly diagnosed anemias in the inpatient setting and perhaps to impact teaching on this common workup.

METHODS

Patient Selection

The study group was comprised of 99 consecutive adult patients identified as anemic who were admitted to the medical service at Yale-New Haven Hospital during a two-month period from June to August of 1997. Anemia was defined as a hemoglobin of less than 12 gm/dL for men, or less than 11 gm/dL for women; or a hematocrit of less than 36% for men, or less than 33% for women. We used only the admission value of hemoglobin and hematocrit in defining patients as anemic to avoid patients appearing to be anemic because of dilution caused by intravenous hydration after admission, and to avoid patients who have actually been made anemic by blood-drawing which *can* be significant.

The patients were identified from the clinical laboratory computer that was programmed to produce a daily printout of patients who had orders for various tests used in the workup of anemia. These printouts were reviewed daily by this author, and all further data collection and medical record review were also performed by this author. Patients had to have one of the following tests ordered by their physician(s) to qualify as being evaluated for their anemia: serum iron, total iron binding capacity (TIBC), serum ferritin, serum folate, RBC folate, serum vitamin B12, haptoglobin, reticulocyte count, or serum erythropoietin. Patients were excluded if they were younger than 18 years old, pregnant, had a known hemoglobinopathy or hematologic malignancy, had recent or ongoing chemotherapy within one year of admission, had previously begun renal dialysis, or had recent surgery within six weeks of admission.

The intended study group was patients with new or previously unidentified anemia, so patients were further excluded if they had been previously diagnosed with a cause of anemia that was thought to be the same as the cause of their current anemia, *and* were being treated for that anemia. Patients were *not* excluded if they were not currently receiving treatment for a previously diagnosed anemia, and the housestaff involved in the patient's care initiated a workup without knowledge of that previous diagnosis. One major problem with previous studies, including the unpublished study from Yale-New Haven Hospital, is that there was no satisfactory definition of what constituted a new or newly perceived case of anemia. Our recruitment methods and inclusion criteria therefore attempt to use the clinician's decision to work up a patient's anemia as evidence that the anemia is new.

Data Collection

The data collected came from the patients' hospital charts. All laboratory and diagnostic studies were initiated by the primary medical team. We reviewed the initial peripheral blood smear of all patients as well as recording the laboratory's reading. We reviewed hospital charts both during the admission, and again after discharge. Data collected on every patient included the complete blood count (CBC) on admission including the mean corpuscular volume (MCV); the blood urea nitrogen (BUN) and serum creatinine on admission; and results of any of the anemia workup tests ordered (serum iron, TIBC, ferritin, serum or RBC folate, B12, haptoglobin, reticulocyte count, or erythropoietin level). Additionally, charts and laboratory results were examined for results of erythrocyte sedimentation rate (ESR), fecal occult blood testing, presence of

further workup for a source of gastrointestinal bleeding, and bone marrow aspiration and/or biopsy. We made note of any other miscellaneous testing that may have contributed to the final diagnosis (eg. osmotic fragility test).

Diagnostic Categorization

Upon reviewing the medical charts after discharge, we attempted independently to assign a diagnosis to all study patients based on the workup that had been performed. Based on experience, knowledge of the literature, and knowledge of the previous Yale-New Haven Hospital study, we expected to encounter many anemias caused by chronic inflammatory disease, iron deficiency, bleeding, and renal failure. We therefore developed a set of criteria for diagnosis of each of these entities (Table 1).

The most straightforward categories were the deficiency states including uncomplicated iron deficiency (ie., not coexistent with ACD), folate deficiency, and B12 deficiency. Laboratory evidence of iron deficiency was defined as a ferritin level less than 20 mg/mL and/or a TIBC greater than 400 μg/dL . While a serum iron less than 60 μg/dL added evidence, the TIBC has a more reliable correlation to ferritin and total body iron stores (7), and it was therefore a more important definer of iron deficiency in patients without serum ferritin levels.

The normal ranges for the serum and RBC folate and vitamin B12 assays at Yale-New Haven Hospital were used to define folate and vitamin B12 deficiencies. A serum folate less than 2.7 ng/mL or an RBC folate less than 140 ng/mL was consistent with folate deficiency. If both serum and RBC folate levels were obtained, the RBC folate was used preferentially to assess body folate stores (see DISCUSSION for further elaboration).

ANEMIA DIAGNOSES	LABORATORY CRITERIA FOR CATEGORIZATION
IRON DEFICIENCY (SIMPLE)	▪ Ferritin < 20 and/or TIBC > 400
FOLATE DEFICIENCY	▪ RBC Folate < 140 ng/mL, *or* ▪ Serum Folate < 2.7 ng/mL if no RBC Folate
VITAMIN B12 DEFICIENCY	▪ B12 < 200 pg/mL
RENAL INSUFFICIENCY	▪ Creatinine persistently > 2 mg/dL, *and/or* ▪ Serum Erythropoietin < 25 mU/mL with anemia ▪ *And* exclusion of other causes
ANEMIA OF CHRONIC DISEASE	▪ Ferritin > 100 with normal or low Iron/TIBC ▪ *And*, presence of one of the following: ACUTE/SUBACUTE INFECTION ▪ Sepsis, fever > 48 hrs, WBC >10,000/μL, or significant local inflammation INFLAMMATORY DISEASE ▪ Local or multifocal inflammatory state (eg. arthritis or cellulitis) persisting > 1 week ▪ ESR > 20 mm/hr, if available MALIGNANCY: DISSEMINATED LIVER DISEASE ABLE TO CAUSE ANEMIA ▪ Active hepatitis (viral or alcoholic) with characteristically elevated LFTs, *or* ▪ Chronic liver disease temporally associated with anemia and not explained by hydremia alone HIV DISEASE ABLE TO CAUSE ANEMIA ▪ A CD4+ cell count of < 100, *and/or* ▪ A systemically active opportunistic infection with/without wasting sydrome

TABLE 1. LABORATORY CRITERIA FOR DIAGNOSTIC CLASSIFICATION OF ANEMIAS.

A vitamin B12 level of less than 200 pg/mL was considered to be consistent with vitamin B12 deficiency, though confirmatory studies would be required to make a diagnosis of pernicious anemia and/or vitamin B12-deficient neuropathy.

In assigning the diagnosis of the anemia of chronic disease, we attempted to combine both laboratory data with an implicated disease state. The "anemia of chronic disease" is generally caused by an infectious or inflammatory state, with fever or prominent local inflammation; or by widely disseminated cancer, with or without fever. The primary laboratory evidence we used was an elevated ferritin (>100 mg/mL) with low or normal serum iron and TIBC. Additional laboratory evidence might include and elevated ESR (>20 mm/hr) or WBC greater than 10,000/μL. We further classified patients as having ACD due to acute/subacute infection, inflammatory disease (eg. chronic sterile inflammation or rheumatoid arthritis), or malignancy.

Within the category of ACD, we also thought it appropriate to include advanced human immunodeficiency virus (HIV) disease with wasting and/or history of recently or currently active opportunistic infections (OIs). We considered this to fall under the category of ACD if the CD4+ count was <100, or if the patient had active systemic opportunistic infections leading to the hospitalization. In the case of liver disease, we assigned the diagnosis of ACD when the liver disease was active, as in acute viral or alcoholic hepatitis with characteristically elevated LFTs. We also assigned the diagnosis of ACD when the patient had chronic liver disease corresponding historically to their anemia (as best as could be determined with available records), and when the anemia could not be explained by hydremia alone. Additionally, the diagnosis of ACD due to

liver disease was *not* assigned if other specific liver-related diagnoses could be assigned, for instance, spur cell hemolysis or hypersplenism/sequestration.

In the case of renal disease, the diagnosis was often somewhat presumptive due to the lack of serum erythropoietin levels ordered in the cohort as discussed later. The overall clinical context combined with any available indices of renal function were taken into consideration as well as the trend of serum creatinine and BUN throughout admission to screen out patients with simple dehydration. We assigned the diagnosis of renal insufficiency in patients with serum creatinine levels persistently greater than 2.0 mg/dL in whom other diagnoses did not seem likely, or when other diagnoses did not seem to account for the degree of anemia. If an erythropoietin level was obtained, a result of less than or equal to 25 mU/mL was considered inappropriately low in the face of anemia. Certainly, all patients with elevated serum creatinine levels were not assigned to the category of renal disease-related anemia, although perhaps all such patients deserve serum erythropoietin levels as part of their workup as will be discussed later.

Obviously, the diagnosis of acute gastrointestinal bleed sufficient to cause anemia was made based on both history (eg. substantial hematemesis, hematochezia, and/or melena) and physical examination as well as any endoscopy or other studies performed. Positive stool for occult blood, alone, did not justify assigning anemia to gastrointestinal blood loss. An elevated reticulocyte added to the overall clinical picture, but a normal reticulocyte count did not exclude the diagnosis of acute bleeding.

Two or more diagnoses were assigned to patients who had clear laboratory or clinical evidence of more than one cause of anemia, for instance chronic iron deficiency anemia with an acute bleed (eg. melena).Patients with documented multiple likely causes of

anemia were counted by each diagnosis; in other words, a patient with two diagnoses was counted twice leading to more diagnoses than cohort patients in our results.

RESULTS

Subjects and Demographics

Of all inpatients identified as anemic during our two-month period of enrollment, 99 patients met our inclusion criteria for new or previously unidentified anemias being actively evaluated by their primary medical team. This cohort included 57 men and 42 women. The demographics of our patient population, shown in Table 2, shows an overall average age of 63.3 ± 18.8 years with the male cohort having an average age of 64.3 ± 17.7 years, and the female cohort averaging 61.8 ± 20.3 years. The range of ages was 30 to 95 overall, and 33 to 92 for men. The ethnic makeup of our cohort was predominantly Caucasian, with Black (African- or Caribbean-American), Hispanic, East Asian, and Indian/Pakistani groups all represented. The female population had a slightly larger

	ALL PATIENTS (99; 100%)	MEN (57, 57.6%)	WOMEN (42, 42.4%)
AVERAGE AGE (YRS)	63.3 ± 18.8	64.3 ± 17.7	61.8 ± 20.3
CAUCASIAN	58 (58.6%)	35 (61.4%)	23 (54.7%)
BLACK	28 (28.3%)	17 (29.8%)	11 (26.3%)
HISPANIC	7 (7.1%)	1 (1.8%)	6 (14.3%)
ASIAN	2 (2.0%)	1 (1.8%)	1 (2.4%)
INDIAN/PAKISTANI	3 (3.0%)	2 (3.5%)	1 (2.4%)
UNIDENTIFIED	1 (1.0%)	1 (1.8%)	0 (0.0%)

TABLE 2. DEMOGRAPHIC CHARACTERISTICS OF PATIENT COHORT.

proportion of Hispanic patients, making up 14.3% of the female cohort while Hispanic patients made up only 7.1% of the cohort overall. The male cohort in fact included only one Hispanic patient. We did not have information available on the socioeconomic status of the cohort.

Laboratory Data

The average admission laboratory values, shown in Table 3, show that our patient population had mean hemoglobin and hematocrit levels well below our inclusion criteria. This is, of course, in part due to the fact that there were a handful of patients with extreme, "panic value" anemia, most often caused, at least in part, by a source of hemorrhage. The average MCV of our population fell within normal range (88.5 fl ± 12.2) with the average in the male population being 91.3 ± 11.3, and the average in the female population being 84.7 ± 12.4, both still falling within normal range. Indeed, the male cohort had a higher percentage of macrocytosis (MCV > 94) while the women had a higher percentage of microcytosis (MCV < 78). Of the 57 men in the study, 31.6% were macrocytic, 59.6% were normocytic, and 8.8% were microcytic. Of the 42 women, 21.4% were macrocytic, 40.5% were normocytic, and 38.1% were microcytic.

Our population also showed a significant amount of renal insufficiency on admission with average BUN and creatinine levels of 29.5 mg/dL and 1.6 mg/dL respectively. Again, this was in part accounted for by a handful of extreme cases of acute renal failure requiring emergent dialysis, but 50 patients (50.5%) had admission serum creatinine

values above laboratory normals.* Subsequent renal function testing often normalized or improved with hydration, as commonly found in hospitalized patients. The male cohort demonstrated a higher degree of renal insufficiency with admission BUN and creatinine levels averaging 33.6 mg/dL and 1.9 mg/dL compared to the female patients' average BUN and creatinine of 23.7 mg/dL and 1.2 mg/dL, respectively.

	ALL PATIENTS (99; 100%)	MEN (57, 57.6%)	WOMEN (42, 42.4%)
HEMOGLOBIN (GM/DL)	9.6 ± 1.7	9.8 ± 1.9	9.4 ± 1.4
HEMATOCRIT (%)	29.0 ± 4.9	29.4 ± 5.6	28.4 ± 3.8
MCV (FL)	88.5 ± 12.2	91.3 ± 11.3	84.7 ± 12.4
WHITE CELL COUNT (1000/μL)	8.0 ± 4.1	8.5 ± 4.7	7.4 ± 3.0
PLATELET COUNT (1000/μL)	218.5 ± 106.9	210.8 ± 111.0	229.9 ± 101.0
BUN (MG/DL)	29.5 ± 20.7	33.6 ± 20.9	23.7 ± 19.2
SERUM CREATININE (MG/DL)	1.6 ± 1.2	1.9 ± 1.4	1.2 ± 0.8

TABLE 3. MEAN LABORATORY VALUES IN STUDY PATIENTS ON ADMISSION.

The Anemia Workup

To be included in the study, patients had to have at least one of the following tests ordered by their physician: serum iron, TIBC, ferritin, reticulocyte count, serum or RBC folate, vitamin B12, haptoglobin, or serum erythropoietin. The average number of these tests ordered per patient was 4.6 overall, 4.8 for the men, and 4.2 for the women. The

* The Clinical Chemistry Laboratory at Yale-New Haven Hospital uses 1.2 mg/dL as the upper limit of

most commonly ordered test was serum ferritin ordered in 88 patients (88.9%), followed by TIBC and serum iron, ordered in 82 patients (82.8%) and 83 patients (83.8%), respectively, as shown in Table 4. The least commonly ordered test was serum erythropoietin ordered in only 12 patients (12.1%), despite the high proportion of renal insufficiency in the cohort as a whole. Only one woman had an erythropoietin level performed, while 11 patients in the male cohort (19.3%) had erythropoietin levels drawn. This follows the discrepancy in renal function between the male and female cohorts reflected in the admission laboratory values.

Anemia Workup Tests	Tests Ordered in 99 Patients
Serum Ferritin	88
TIBC	83
Serum Iron	82
Reticulocyte Count	61
Vitamin B12 Assay	56
RBC Folate	36
Serum Folate	19
Serum Haptoglobin	14
Serum Erythropoietin	12

Table 4. Anemia Tests Ordered in the Ninety-Nine Study Patients.

normal for serum creatinine, not accounting for gender or body mass.

Vitamin B12 levels were obtained in 56 patients (56.6%). Similarly, 51 patients (51.5%) had either serum folate or RBC folate determinations. Of these, 19 patients (19.2%) had serum folate levels, and 36 patients (36.4%) had RBC folate levels. Four of these patients had both serum and RBC folate measurements. The tests ordered in the male and female cohorts closely approximated the overall study population.

Reticulocyte counts were obtained in 61 patients (61.6%) including 71.9% of men (41 patients) and 47.6% of women (20 patients). Haptoglobin levels were much less commonly ordered with only 14 patients (14.1%) having this test. Ordering of haptoglobin levels in men and women were similar. Erythrocyte sedimentation rates (ESRs) were ordered to augment the anemia workup in 14 patients (14.1%), but this laboratory test was not among the tests used to identify patients for inclusion in the study group.

Rectal exams with Hemoccult™ results were documented in the charts of 72 patients (72.7%) including 43 men (75.4%) and 29 women (69.0%). Additionally, three patients had Hemoccult™ results documented by nursing staff only. Twenty-three patients (23.2%) had neither documentation of a rectal exam nor Hemoccult™ results recorded by nursing staff at any time during their admission. Hemoccult™ positivity was documented in 28 of the 75 patients tested (37.3%). One additional patient was documented as persistently refusing rectal examination. We attempted to record reported stool color in all patients, but a large number of patients had no such documentation in their charts.

A gastrointestinal workup (eg., esophagogastro-duodenoscopy, sigmoidoscopy, or colonoscopy) in search of a source of acute bleeding or iron deficiency was performed in 28 patients (28.3%) (16 men and 12 women). Of course, there were some patients in

whom an invasive workup was not pursued based on the clinical condition of the patient. While this was documented in at least two charts, the entire decision-making process of the clinical team cannot be known for certain in all patients.

Bone marrow exam was not a prominent feature in the workup of this cohort. This procedure may also have been avoided in some fragile patients although not necessarily documented in their charts. Only four patients received aspiration and/or biopsy, and in each case, important diagnostic information was obtained. One patient had documented myelodysplasia, one patient had erythroid hyperplasia without evidence of myelodysplastic processes or malignancy, and one patient had erythroid aplasia secondary to Parvovirus B19 infection. The fourth patient had a bone marrow examination reported to be consistent with erythropoietin deficiency secondary to renal insufficiency. This last result we believed likely to be an "over-reading" by the morphologist.

We independently reviewed the peripheral blood smears of all patients and, if possible, used that information in assigning diagnoses to patients. When assessing the clinical context known to the primary team, however, we assumed that the laboratory reading of the admission blood smear was all the information available to them. In a study by Self et al., the authors kept track of whether anyone on the medical team came to see the smear of patients they were evaluating for anemia (8), but we did not collect such data. While most textbooks recommend viewing the smears of anemic patients, Jen and colleagues, in their study of the role of a physician's smear reading versus the laboratory reading, found that in no cases did the physician's reading provide "unique

diagnostic abnormalities that were not already provided by the laboratory's smear reading" (9). Still, the laboratory reading was not without value.

Anemia Diagnoses

In the study cohort of 99 patients, a total of 131 diagnoses were assigned as significantly contributing to patients' anemias. A total of 69 patients (69.7%) had one diagnosis to explain their anemia, while 27 patients (27.3%) had two diagnoses, and 3 patients (3.0%) had three diagnoses thought to explain their anemia. The majority of patients were assigned one of the following diagnoses: anemia of chronic disease, iron deficiency, renal insufficiency, acute gastrointestinal bleeding, hypersplenism/

Figure 1. Causes of Anemia in the Study Population.

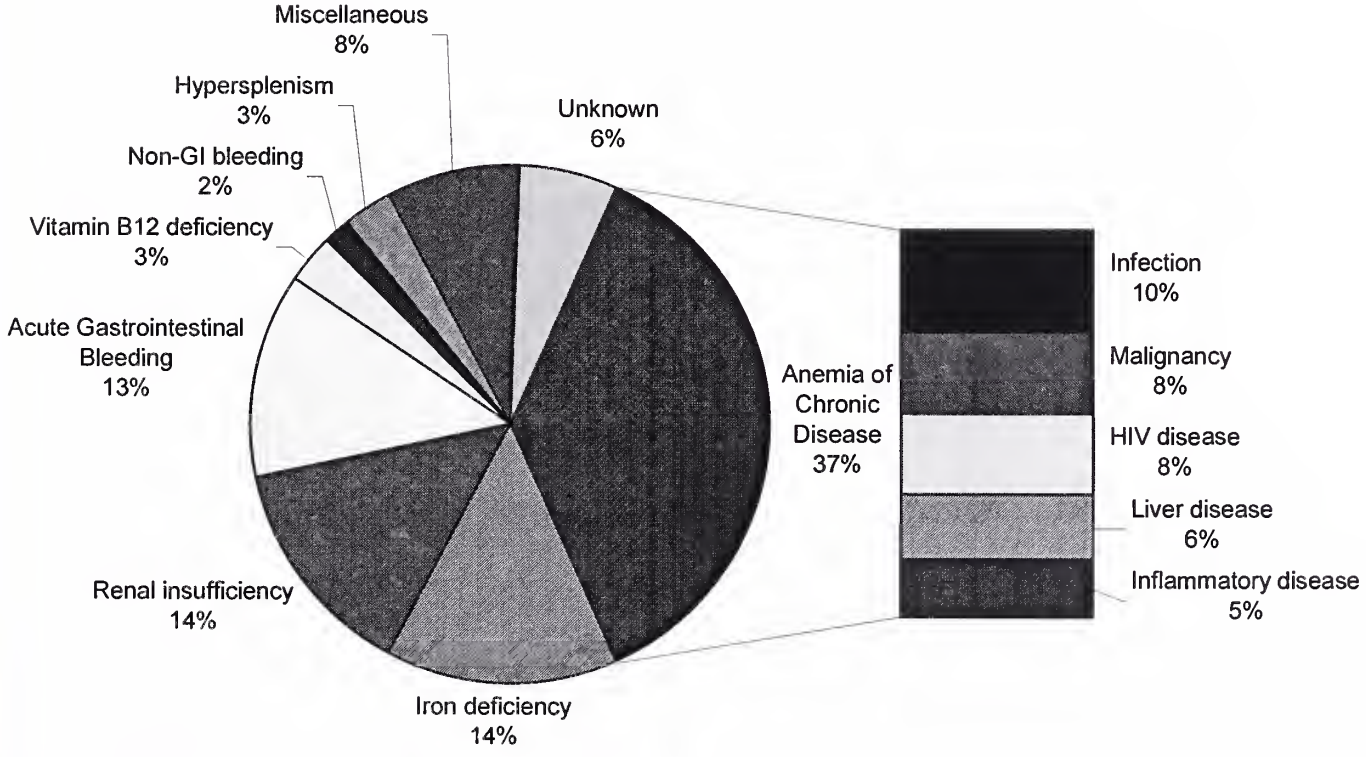


Figure 2. Causes of Anemia in the Male Cohort.

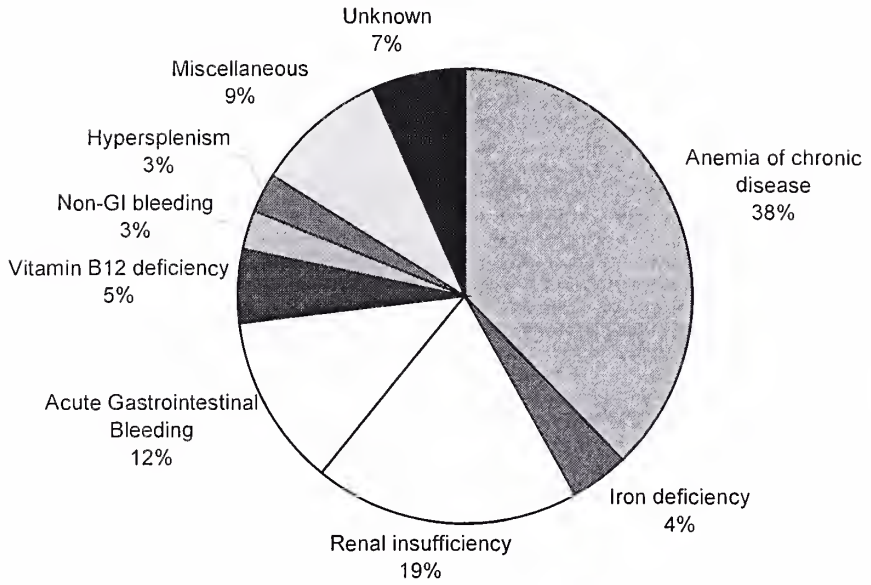
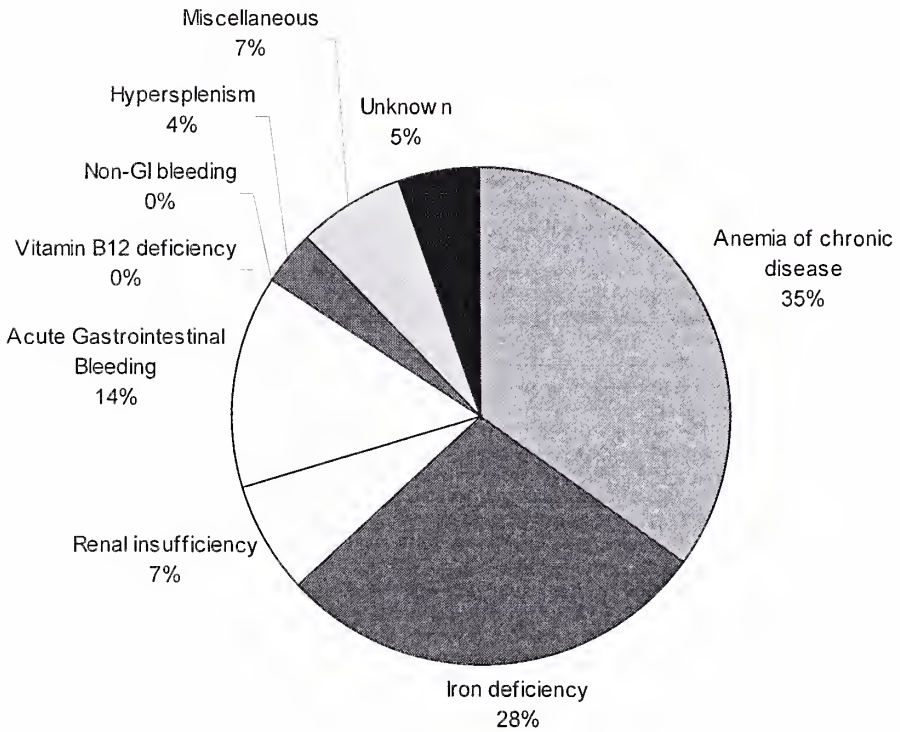


Figure 3. Causes of Anemia in the Female Cohort.



sequestration, vitamin B12 deficiency, or non-GI bleeding (Figures 1-3). A small group of patients fell into either a "miscellaneous" category, or an "unknown" category in which the cause of their anemia could not be clearly decided. No patients had folate deficiency. The percentages in the figures represent the 131 diagnoses rather than the 99 individual patients. Refer to Table 1 for definitions of our diagnostic categories.

The largest diagnostic group was anemia of chronic disease (ACD) which included 48 of the 131 diagnoses (36%). Under the heading of ACD, we assigned five possible categories: ACD associated with disseminated malignancy, acute/subacute infection, inflammatory disease, liver disease, or HIV disease (Figure 1; Table 1). The largest group of ACD patients had acute/subacute infections; in all, 13 patients (8 men and 5 women) had various infections including pneumonia, osteomyelitis, and endocarditis (Table 5). Disseminated malignancy and HIV disease each accounted for 10 patients; cancer was present in 6 men and 4 women, while HIV disease/AIDS was present in 8 men and 2 women. Active liver disease was present in 8 patients (4 men and 4 women), while inflammatory disease accounted for the smallest portion of ACD (Table 5) with only 7 patients affected (2 men and 5 women).

The second largest diagnostic category was iron deficiency found in 19 patients (3 men and 16 women), followed by renal insufficiency (18 patients; 14 men, and 4 women), and acute gastrointestinal bleeding (17 patients; 9 men and 8 women). Vitamin B12 deficiency and hypersplenism were each diagnosed in 4 patients; all four B12-deficient patients were men, while 2 men and 2 women had splenic sequestration. Non-GI bleeding was present in 2 patients, both men. One of these patients was coagulopathic with gingival bleeding over a week's time, eventually requiring surgical suturing. The

	Specific Diagnoses	Total Patients
Anemia of Chronic Disease		48
Acute/Subacute Infection		13
	Pneumonia	6
	Osteomyelitis with sepsis	3
	Cellulitis with sepsis	1
	Urosepsis	1
	Ascending cholangitis	1
	Staph. aureus endocarditis	1
Malignancy (disseminated)		10
	Non-small cell lung cancer	4
	Signet cell adenocarcinoma of the stomach	2
	Adenocarcinoma of the colon	2
	Adenocarcinoma of the esophagus	1
	Squamous cell carcinoma of the head/neck	1
HIV Disease/AIDS		8
Inflammatory Disease		7
	Inflammatory Bowel Disease	3
	Rheumatoid Arthritis	1
	Cutaneous T-Cell Lymphoma	1
	Febrile diarrheal illness	1
	Chronic cellulitis/Diabetic foot ulcers	1
Liver Disease		4
Miscellaneous		11
	Myelodysplastic Syndrome	1
	β-Thalassemia Trait	1
	Parvovirus B19 Infection	1
	Spherocytic AIHA	1
	Malnutrition	1
	Thyrotoxicosis	2
	Drug Effects (eg. AZT)	4

Table 4. Specific Diagnoses Represented Among Patients With the Anemia of Chronic Disease or Miscellaneous Anemia-Related Diagnoses.

other patient had a substantial rectus hematoma verified on CT scan related to subcutaneous heparin administration on a previous recent hospitalization.

Eleven patients had various miscellaneous diagnoses including myelodysplastic syndrome (1 patient), parvoviral infection (1 patient), spherocytic autoimmune hemolytic anemia (AIHA) (1 patient), thyrotoxicosis (2 patients, discussed in detail below), and β-thalassemia trait (1 patient). The diagnosis of β-thalassemia in this last patient was actually made presumptively. The team had ordered a hemoglobin electrophoresis, but at the time of the test, the laboratory was not using technology that allowed for a quantitative measure of hemoglobin A2 as part of the screening test ordered. The patient's other tests, however, showed that he was not iron deficient, yet he had an MCV of 64 and a disproportionately high hematocrit of 35.8%. Thus, we assigned what we believed to be the most likely diagnosis without benefit of a hemoglobin A2 level.

One additional patient in the miscellaneous category had global malnutrition not easily assigned to specific "deficiency state" anemias. The effects of the antiretroviral medications (eg., AZT) were thought to be contributing factors in the anemia of four patients. No clear diagnosis could be assigned in 8 patients.

As mentioned above, two patients, both women, were given the anemia-related diagnosis of thyrotoxicosis. Anemia is generally thought to be a result of *hypo*thyroidism since thyroid hormones have a trophic effect on erythropoiesis (10). Hyperthyroidism should thus cause erythrocytosis, but generally, both plasma volume and red cell mass increase together, so the net result is no change in the hematocrit (10). There exist several studies, however, that show roughly a 20% incidence of anemia in hyperthyroid patients, and the anemia resolves with treatment of the hyperthyroidism alone (11, 12). One

proposed mechanism is that thyroxine is directly toxic to bone marrow in excess quantities; red cell survival may also decrease (11, 12). Evidence also exists implicating impaired iron utilization (11, 13) placing anemia from thyrotoxicosis in the physiologic category of ACD. One study has shown increased ferritin levels in patients with hyperthyroidism; "[t]his hyperferritinemia. . . may reflect an expansion of the iron storage induced by ineffective erythropoiesis, and escape of ferritin from damaged reticuloendothelial cells, or an impaired clearance of ferritin from the plasma" (13). The two patients in our study with thyrotoxicosis and anemia had no other clear cause of anemia other than severe hyperthyroidism. Based on the evidence above, we chose to classify their anemia as being due to the thyrotoxicosis rather than leaving them in the category of "unknown."

In the 29 patients who had more than one diagnosis, several combinations existed. The most common pairs inlcuded an acute gastrointestinal bleed and iron deficiency in four patients, and an acute gastrointestinal bleed and a GI malignancy in two patients, and iron deficiency and GI malignancy in two patients. Furthermore, all three patients with inflammatory bowel disease provoking ACD had either coexisting iron deficiency or acute GI bleeding. The one patient with rheumatoid arthritis also had iron deficiency.

Three patients had coexisting cancers and serious subacute infections; in two cases, this was disseminated lung cancer with postobstructive pneumonia, and in the third case, the patient had a stomach cancer metastatic to the ampulla with ascending cholangitis. One patient had an acute variceal bleed in addition to chronic anemia due to liver disease.

Renal disease also coexisted with a variety of other anemia-related diagnoses in six patients, for instance myelodysplasia, cutaneous T-cell lymphoma, liver disease, and iron deficiency. HIV nephropathy with erythropoietin depression coexisted with HIV-related anemia of chronic disease in two patients. Coincidentally, both of these patients had a third diagnosis which in one case was related to retroviral medication, and in the other case was end-stage liver disease. HIV most commonly coexisted with the macrocytic states of AZT or d4T use, present in four patients.

DISCUSSION

Patient Selection

The laboratory definition of anemia used for inclusion in this study, (Hgb < 12 mg/dL for men or < 11 m/dL for women, or Hct < 36% for men or < 33% for women) is one full mg/dL hemoglobin and 4% hematocrit below the Yale-New Haven Hospital laboratory cutoff for normal range. This reflects our intention to examine a population of patients with significant anemia that should be indisputably in need of evaluation and less confounded by analytical variability. The *admission* values were used for deciding inclusion in the study to avoid the confounders of iatrogenic anemias caused by phlebotomy or intravenous hydration ("dilutional" anemia). Some researchers have also used the admission CBC as their inclusion criterion (1), but other groups have chosen to look at several hemoglobin or hematocrit values. Self and colleagues, in their study of the diagnosis and treatment of anemia in medical inpatients (8), identified their cohort based on the admission CBC, but they further recorded the hemoglobin levels of the patients 24 hours after admission. They used the lower of the two for their data analysis in an attempt to control for rehydration. Some authors have included all patients who were anemic at any point in their hospitalization (4, 9). While false elevations in hemoglobin due to dehydration may have led to the exclusion of some patients, we still aimed to focus on the patients who would be recognized by housestaff as anemic on admission causing them to initiate a workup.

Furthermore, several studies of anemic inpatients have excluded patients with acute bleeding, usually from a gastrointestinal source, because those patients were not considered to have an anemia of unknown origin (4, 5, 9). We decided to include such

cases, however, because it may not be immediately evident that an acute bleed is sufficient to cause anemia, and an acute gastrointestinal bleed may coexist with chronic bleeding or with a malignancy. A lack of workup of the anemia may thus result in either misdiagnosis or a missed additional diagnosis. Also, a low hematocrit may be the sentinel sign of an occult bleeding source (eg. retroperitoneal hemorrhage) in anticoagulated or coagulopathic patients. Indeed, the results of the present study showed several instances of coexistance of iron deficiency, acute gastrointestinal bleeding, and gastrointestinal malignancy in various combinations.

The Anemia Workup Vs. the Diagnoses

As with any other disease entity, the first steps in narrowing the differential diagnosis are the history and physical exam. A review of systems covering symptoms of infection, inflammation, or malignancy; gastrointestinal disease, nutritional history, medications, ethnic background, and other information might elucidate a probable cause of anemia. The most important aspect of the physical exam in the workup of anemia is the rectal exam. All patients with anemia should undergo this noninvasive, inexpensive screening test. It certainly is not a perfect screen for gastrointestinal blood loss, but the information supplied by a positive Hemoccult™ test can shape the appropriate evaluation pathway. Only 73% of the patients in this study had rectal exams documented in their charts which, by our standards, is 27% too few. Furthermore, in the review of patients' admission physical examinations, the information provided was generally limited to the result of the Hemoccult™ test. It infrequently included the color of the stool which can provide important diagnostic information, for instance, differentiating melenic stool secondary to

a bleeding ulcer from brown stool coated with bright red blood due to hemorrhoids, both of which would be positive for blood.

As mentioned previously, between 83 and 89% of patients had laboratory determination of iron stores using serum ferritin, serum iron, and/or TIBC making these the most common tests ordered. This triad of tests is of course used to distinguish iron deficiency from the anemia of chronic disease, which together made up 51% of the diagnoses in our cohort. While ferritin is considered the best estimation of iron stores, it is also an acute phase reactant and can thus be somewhat difficult to interpret when it falls between 20 and 100 mg/mL. In patients with coexisting iron deficiency and anemia of chronic disease, the ferritin will generally still fall below 50 mg/mL (14), and a ferritin of greater than 100 mg/mL makes the diagnosis of iron deficiency very unlikely (10). In cases of indeterminate ferritin levels, TIBC can become the next best indicator of iron deficiency short of bone marrow examination; a high TIBC (> 400 μg/dL) is quite specific for iron deficiency (7). The high number of iron tests ordered in the study patients matches the high prevalence of diseases in which these tests are diagnostic, and serum ferritin is thus certainly an appropriate first screening test.

What is less clear is the role of vitamin B12 and folate levels as a screen in all patients. Folate and vitamin B12 deficiency continue to be diagnoses commonly sought after in the workup of anemias, and in our study were second only to iron studies in frequency of use. While the yield is low, these causes are easily treatable, and therefore missing the diagnosis would be unacceptable, especially in the case of vitamin B12 deficiency which may lead to irreversible neurologic sequelae. In our cohort, 57% of patients had B12 assays, and 52% had folate assays (RBC or serum), and yet only 3% of

patients had B12 deficiency (all men), and zero patients had folate deficiency. While the B12 and folate assays are only in the intermediate cost range for anemia workup tests (Table 6), perhaps they are not necessary for all anemic patients. Certainly, macrocytic and alcoholic patients deserve testing, and the normocytic population can obviously include both early micro- or macryocytic anemias, or combination anemias with both micro- and macrocytic red cell populations. Purely microcytic patients, however, probably do not need to be screened as a first-line evaluation. Among our patients, this was generally the practice of housestaff, although a handful of microcytic patients did get tested including one severely iron deficient woman with an MCV of 64.

Anemia Workup Tests	Effective Cost[A]	Turn-Around Time for Test Results[B]
Serum Ferritin	$7.50	1-3 days
TIBC	$2.11	up to 12 hours
Serum Iron	$2.77	up to 12 hours
Reticulocyte Count	$6.63	up to 12 hours
Vitamin B12 Assay	$5.45	up to 4 days
RBC Folate	$10.68	up to 4 days
Serum Folate	$7.02	up to 4 days
Serum Haptoglobin	$19.80	4-8 days
Serum Erythropoietin	$40.82	up to 8 days

[A]The effective cost accounts for labor. (Source: Laboratory Administrator, YNHH)
[B]Turn-around time is based on the times/week the laboratory runs the test.

Table 6. The Cost and Turn-Around Time of Laboratory Tests Used in the Workup of Anemia.

Another problem does exist in the workup of folate deficiency. The choice between serum and RBC folic acid assays among the study group often appeared haphazard, and this is most likely due to misconceptions about the purpose of each test. In the evaluation of anemia due to folate deficiency, the RBC folic acid assay gives a better estimate of tissue folate stores over greater than one month. The serum folate level, on the other hand, gives more information about recent folic acid intake as it tends to fluctuate with diet over the past one to three weeks (15). In this study, four patients had both serum and RBC folate levels ordered. This could either reflect a desire to assess short- and long-term nutritional status, or it could reflect a lack of knowledge as to which of the two tests is appropriate. Similarly, nineteen patients (19.2%) had only a serum folate level drawn, a test that would unlikely give a conclusive answer regarding the presence or absence of true folate deficiency. And since every patient who had a serum folate level drawn also had a vitamin B12 level drawn, the medical team clearly seemed to be in search of a "deficiency-state" anemia.

As is obvious by the admission laboratory values (Table 3), the patient population represented in this study has a high incidence of renal insufficiency. The one reliable laboratory test available for assessing the kidney's impact on red cell production is the serum erythropoietin level. "The erythropoietin feedback loop ensures that the hemoglobin mass for oxygen delivery matches the body's needs and that production equals destruction of red cells under stable conditions" (16). Thus, a patient with anemia should have an elevated erythropoietin level as a response to decreased red cell mass. In our cohort, only 12 patients had erythropoietin levels drawn even though more than half had abnormal renal function tests on admission in concordance with anemia. The

diagnosis of renal disease-related anemia was made in 14% of patients overall, and among men it made up 19% of diagnoses. Erythropoietin testing is expensive (Table 6) which may serve as a deterrent for physicians in this cost-conscious era of health care. What may be more discouraging is the long turn-around time for getting results (Table 6). As this is a labor-intensive test, a batch is run once a week, and this means that the medical team may not get the result for more than a week. While the result may not be available to the treating physician(s) during a short hospital stay, and while the cost of the test may be high, the result may allow an intervention, namely recombinant erythropoietin administration, that might benefit the patient immensely. The mindset of the hospital team must certainly extend beyond the date of discharge. Perhaps a goal needs to be set to enact a mechanism by which any delayed testing results aiding in diagnosis should be delivered to both the primary care provider *and* the patient when those results become available after discharge.

Another more expensive test with a longer turn-around time is serum haptoglobin. It is difficult to assess the use of this test in the present study, however, because hemolysis was not a prominent diagnosis in this study population. Other useful tests such as bilirubin levels and lactate dehydrogenase (LDH) are, of course, not specific to hemolysis, and thus their role in the workup of hemolytic anemia could not be determined for all patients in this study. Hemolysis is a diagnosis in which the peripheral blood smear may be extremely helpful, but again, assessing the medical team's use of the smear reading was not possible in this study.

The role of the bone marrow examination in anemic inpatients is also difficult to determine since it is both invasive, although minimally, and because it can be pursued on

an outpatient basis. In the present study, only four patients had bone marrow aspiration and biopsy, but in at least three cases, a conclusive diagnosis was made. This is in contrast to a study by Elis and colleagues examining the role of bone marrow aspiration and biopsy in the evaluation of patients with "idiopathic" normocytic-normochromic anemia (17). They looked at inpatients receiving consultations from Hematology as well as outpatients seen in Hematology clinic. For each patient with normocytic-normochromic anemia who had normal leukocytes and platelets, they launched an exhaustive workup which included standard testing as well as Coombs' testing, rheumatoid factor (RF), antinuclear factor (ANF), and serum protein electrophoresis (SPEP). If no cause was found, patients proceeded to bone marrow examination. In all, 29 patients had aspirations and 21 patients had biopsies. Of these, one patient was diagnosed with myelofibrosis, and one patient was diagnosed with iron deficiency. All other patients had bone marrow samples read as normal. The extensive workup performed for each patient in this study does not simulate a realistic inpatient evaluation. Furthermore, this study may not be widely applicable for a couple of reasons. First, the authors only looked at normocytic-normochromic anemia. Second, the exclusion criteria were extensive including any patient with a "chronic disorder," an organic mental syndrome, or a life-threatening disease. These categorizations were not further explained, and clearly, many diagnosable anemias would be present among a wider population of patients.

Iron Therapy

The topic of anemia diagnosis and management cannot be discussed without mentioning iron therapy. It is an easy intervention to make, but empiric iron administration is often used indiscriminately as a panacea for anemia. In one series, anemic inpatients frequently received iron regardless of the cause of their anemia, often with no formal anemia evaluation (3). Furthermore, the iron therapy was usually stopped at the time of discharge, and patients left the hospital untreated, not even having been told that they were anemic.

It seems that not only does "uncertainty about diagnostic workup. . . underlie reluctance to respond to some abnormal hemoglobin results" (2), but ignorance about therapeutic options results in practitioners falling back on iron therapy as the sole treatment. In the present series, house officers generally seemed thoughtful in their choice to institute iron therapy, but certainly some glaring errors existed. In fact, in some cases, the error was failure to institute iron therapy. For instance, one 51-year-old woman thought to be iron deficient was *not* started on iron therapy in the hospital, nor was she discharged on iron. Furthermore, there was no mention in her chart of a workup to find the cause of her iron deficiency. She did not have a rectal exam or stool testing by nursing staff, but she was sent home with Hemoccult™ cards to test herself. She may have refused rectal examination, but this was not documented. Another woman who presented with a CHF exacerbation was found on admission to have a hematocrit of 28% and an MCV of 76. Her smear showed hypochromia. The only anemia test ordered by the primary team, ironically, was a serum erythropoietin in this patient with a creatinine of 1.1.

In some patients, the label of iron deficiency was applied despite the laboratory evidence to the contrary. For instance, one patient with a ferritin level of 115 mg/mL, iron and TIBC levels of 24 and 242 μg/dL, and an MCV of 94 was labeled as iron deficient and discharged on ferrous sulfate. House officers are often taught that "iron saturation," or serum iron/TIBC, of less than 10% is indicative of iron deficiency. While this formula may not be devoid of value, it ignores the fact that the serum ferritin is much more predictive of actual iron stores. The "saturation" may be falsely low in the presence of low iron and low TIBC, as in this patient whose indices and history of fever for two weeks make anemia of chronic disease the more likely diagnosis. Several patients with ferritin levels well above 100 mg/mL received iron therapy including one patient with a ferritin of 401 mg/mL.

Several patients were started on iron therapy after GI bleeding despite the fact that their bleeding had ceased and their iron stores were normal. This seems to be the practice of some physicians although the body should be able to recover from an acute bleeding episode without the need for exogenous iron, assuming iron stores are normal.

Clinical Challenges of the Anemia of Chronic Disease

The anemia of chronic disease is an entity provoking much frustration among medical practitioners. First, it can rarely be diagnosed with complete certainty since laboratory testing only provides indirect evidence of its presence. Second, it is not always obvious what diseases can be blamed for the ACD phenomenon. There are a variety of diseases commonly implicated in ACD, however "many patients have an anemia with the characteristics of ACD but do not have one of the infectious, inflammatory, or neoplastic

disorders usually associated with ACD" (5). Such was the topic of a study by Cash and Sears in which they looked at anemic inpatients with an ACD diagnosis made on laboratory evidence alone (5). They then scrutinized the patients' underlying diseases to find the anemia-provoking process. Similar to the present study, they found that 35.6% of the ACD patients had an infectious cause (eg., pneumonia, cellulitis, or endocarditis), 18.9% had a neoplastic cause, and 5.6% had an inflammatory cause (eg. systemic lupus erythematosus or scleroderma). Cash and Sears actually included renal disease in their causes of ACD, rationalizing that if laboratory data showed a low serum iron, renal failure alone would not account for this impaired iron utilization. In all, 15.6% of their patients had renal insufficiency implicated in their anemia, again similar to the present study.

Perhaps the most interesting finding in Cash and Sears' study were the "other" diagnoses that did not fit into the traditional categories of ACD diseases. One-quarter of the patients fell into this category which included diseases *not* thought to be causally associated with anemia. The diagnoses included: brittle diabetes mellitus, ischemic heart disease, congestive heart failure (with anemia *not* explained by hypervolemia), thrombophlebitis and/or deep venous thrombosis, chronic obstructive pulmonary disease (COPD) without apparent infection, and alcoholic liver disease. The conclusion the authors arrived at was, "Until etiologic and pathogenetic mechanisms are better understood, a broad inclusive view of ACD seems prudent."

A word of caution might also be advisable, however, in that a more inclusive view is only useful as long as it does not encourage practitioners to conduct incomplete evaluations of patients' anemias with the mindset that ACD must be responsible for

anemia in anyone with a complicated medical history. Still, our own cohort had eight patients in whom a clear anemia-related diagnosis could not be elucidated. Four of these patients had brittle, poorly-controlled diabetes *without* clear evidence of 1) nephropathy, 2) chronic ulcers, or 3) other inflammatory states. This raises the question as to what is the significance of anemia in a diabetic patients. While anemia related to renal dysfunction and ACD related to chronic infections and inflammation in diabetics are commonly recognized, there may exist an ACD-like anemia as the result of the diabetes itself. There are in vitro studies giving some evidence that erythropoiesis is impaired in diabetic patients (18, 19). Red cell mass and function may also be affected by hyperglycemia itself (10) which would support the presence of anemia in poorly-controlled diabetes. Clearly, more research and in vivo studies are necessary to sort out the significance of anemia in diabetic patients.

Of the four remaining "unknown" patients in our study, one simply had an inadequate anemia evaluation; his only anemia test was a serum haptoglobin which was negative for hemolysis. Another patient had several chronic conditions such as COPD, CHF, and coronary artery disease, but no obvious infectious, inflammatory, or neoplastic process. Another patient had a history of severe depression and anorexia nervosa, but her weight had been stably within normal range for four months, and laboratory testing found no clear nutritional deficiencies. One final patient had an unrevealing basic workup which included panendoscopy, and his MCV was 70 with normal iron indices and a normal hemoglobin A2 level. Further investigation was planned as an oupatient.

Cash and Sears did not include liver disease among their chronic disease diagnoses except in the case of one patient with non-active alcoholic liver disease. The category of

liver disease is perhaps the most challenging under the heading of anemia of chronic disease because anemia in cirrhotic or other liver failure patients can arise from so many mechanisms. In fact, one classic article implicates seven distinct causes of anemia in chronic liver disease (20). Blood loss can be a major contributor in patients with esophageal varices or ulcers from chronic alcohol use. Impaired production of clotting factors, impaired platelet function, and shortened platelet survival can all be significant in liver disease, and thus other sources of blood loss such as severe epistaxis can be problematic. Iron deficiency is not uncommon, usually as a result of chronic blood loss. Vitamin B12 deficiency generally occurs because of physiologic impairment of absorption. Folate deficiency, on the other hand, is usually due to poor nutrition among alcoholic liver patients. Hydremia, or an expanded plasma volume, can cause a dilutional anemia or pancytopenia. Hemolysis can arise in liver patients as autoimmune hemolytic anemia, spur cell anemia, or microangiopathic anemia secondary to splenomegaly. Finally, patients with chronic liver disease can show evidence of impaired iron utilization consistent with the anemia of chronic disease.

It can be impossible to decide if one of these seven diagnoses applies to a patient with liver disease, especially since many liver failure patients have multiple medical problems. In some cases, several mechanisms are certainly interacting. It was equally difficult for us to sort out these mechanisms in the study patients, and the diagnosis of ACD due to liver disease is one of the softer categorizations in our study.

Another challenge of evaluating the anemic patient with liver disease is how much emphasis to put on the MCV. Most of the liver disease patients encountered in large urban hospitals have chronic heavy alcohol use as the cause of their liver disease. It has

been shown that ethanol use itself leads to macrocytosis regardless of anemia, and in the study of the seven causes of anemia in liver disease mentioned above, the authors found that macrocytosis (MCV > 98) was present in 56.5% of patients studied, often in the absence of anemia (20). In a classic article by Wu et al. examining red cell indices in alcoholics, 89% of patients were found to be macrocytic (defined as MCV > 90 by these authors). Only 17% of the alcoholics studied were anemic, but all the anemic patients were macrocytic. Interestingly, the authors showed that the "macrocytosis disappeared on alcohol withdrawal alone, but persisted, despite folate supplement, when alcohol intake was not curtailed" (21). This study implicated a direct toxic effect of alcohol on developing erythroblasts in the bone marrow. All patients had bone marrow examination, and only one-third showed any megaloblastic changes; the remaining two-thirds were normoblastic. The relatively low MCV used in defining macrocytosis here may falsely elevate the number of macrocytic patients, but clearly there is an overrepresentation of macrocytosis in the alcoholic cohort. This phenomenon of macrocytosis in alcoholics may be another factor contributing to the overzealous search for B12 and folate deficiency anemias which are usually heralded by macrocytosis.

Anemia in the Elderly

Another common diagnostic challenge is how aggressive to be in working up the geriatric anemic patient. One of the most prolific authors on this topic has been D. A. Lipschitz, both a geriatrician and a hematologist. In one of his studies, he looked at 196 ambulatory, apparently healthy elderly patients (> 65 years old) to determine the prevalence of anemia in that population (22). He found that 21.4% of women and 34% of

men studied were anemic (Hct < 36% in women, < 40% in men). Iron deficiency was diagnosed in three patients, and ACD was diagnosed in two, but in the remaining 46 anemic subjects, a clear cause was not recognized. Lipschitz and colleagues hypothesized that "it is possible that the fall in hemoglobin that occurs with age represents a direct effect of senescence and may be a normal physiological response to aging." Among the mechanisms that might be responsible are the decrease in lean body mass leading to a decrease in oxygen requirement, and a decrease in testosterone circulation, especially in men. Androgens are known to enhance erythropoietin production (16). Finally, there may be "an overall reduction in hematopoietic reserve," or loss of stem cells, as evidenced by the relative leukopenia also observed by Lipschitz et al. (22).

In contrast to this concept of the anemia of senescence, some authors have contradicted the idea that anemia might be normal in older people (17, 23). While "[physicians] may 'expect' older patients, poor patients, and others to be anemic" (17), what impact does this attitude ultimately have on patients? In a study that argues against changing normal hemoglobin and hematocrit values in the elderly, the authors note that "since anemia is often the first sign of a severe underlying illness, it is necessary to feel confident that the values assigned for a certain age group accurately reflect the normal range and do not include data on patients with anemia" (23). In their cohort of 292 unselected geriatric outpatients, they found a statistically significant mean decrease in hemoglobin and hematocrit compared to the normal range. But, when they excluded a subgroup of 17 patients who had hemoglobin levels less than 10 gm/mL or hematocrits less than 35%, the mean values of the cohort fell within the normal range. In 71% of the anemic subgroup, a clear etiology for the anemia was documented. The authors therefore

concluded that their study population did not represent all normal patients but rather included pathologically anemic patients thus falsely lowering the mean values of hemoglobin and hematocrit. They therefore recommended the following:

> Evaluation of an anemia usually is a noninvasive procedure requiring a thorough history and physical examination, a search for blood loss, and a few additional blood tests to determine the etiology. Thus, the assignment of new geriatric hematologic norms at present would risk the exclusion of many patients from the opportunity to have a life-threatening illness diagnosed at a correctable stage. [Therefore] establishment of new hematologic norms is premature and should not be a substitute for good medical judgment and practice. (23)

The anemia of senescence may have a real physiologic basis, but in the clinical setting, this concept could become a rationale for complacency in the evaluation of the anemic elderly. In other words, this diagnosis of exclusion may be made without making the effort to exclude other causes first.

Elderly inpatients often pose another diagnostic challenge. How aggressively should fragile patients be worked up for their anemia? Of course, there is no simple answer to this question, but a thorough knowledge of the most prevalent causes of anemia may help guide the clinician in the decision. Diagnosing ACD can be unsatisfying since the only treatment is treating the underlying disease. The search for the underlying disease is often the limiting step in the fragile patient, for instance, in the case of malignancy when further treatment is not likely to be pursued. Diagnosing iron, B12, or folate deficiency, on the other hand, is easy to do with blood work, and easily treatable. Similarly, anemia related to renal insufficiency can be treated with recombinant erythropoietin. Finding a treatable cause of anemia in an elderly patient may in fact be *more* important than in a younger patient since the elderly patient will generally not tolerate the physiologic effects of the anemia as well (eg., in the presence of ischemic heart disease). Rectal examination

remains an easy screening test for blood loss which, while it might lead to a diagnosis unlikely to be treated in a fragile patient (eg. malignancy), might also lead to the diagnosis of iron deficiency which would be easily treated. A certain amount of vigilance must thus be maintained to avoid missing treatable causes which may improve the overall health of an elderly patient.

Clinical Implications

This study set out to examine what causes of anemia are commonly seen in hospitalized patients, and how physicians search for these causes. As might have been expected, patients were most often found to have anemia of chronic disease, iron deficiency, renal insufficiency, or acute bleeding. Iron deficiency was particularly prominent among women while renal insufficiency was pervasive among men. Based on the data presented in this study, the two most pertinent first-line tests in the anemic inpatient are the serum ferritin and the serum creatinine (Figure 4). The suggestion of using ferritin to sort out causes of anemia is certainly not novel. Creatinine, on the other hand, is not generally thought of as a test for anemia. The large proportion of patients with renal disease supports the notion, however, that assessing kidney function is no less important than assessing iron stores. Watching a patient's creatinine level over time to establish a sense of their baseline will guide the clinician as to the appropriateness of proceeding to a serum erythropoietin level. The interpretation of this level may be confusing to some clinicians since it effectively has no absolute normal or abnormal numerical value, but rather must be interpreted as normal or abnormal relative to the hemoglobin or hematocrit. The measurement of erythropoietin in the present study was

greatly underutilized compared to the number of patients with renal insufficiency. It can thus be inferred that an unknown number of patients were denied appropriate treatment.

And to reiterate, the vitamin B12 and folate levels are perhaps overutilized, but the possibility of intervention and the prevention of neurologic sequelae probably justify the common use of these tests. Still, remembering the value of the physical examination is always warranted, and the workup of anemia is no different. The rectal exam is the cheapest and easiest test to perform in the evaluation of anemia and should therefore not go undone. Based on the observations above, we propose a decision tree for the workup of the anemic inpatient (Figure 4).

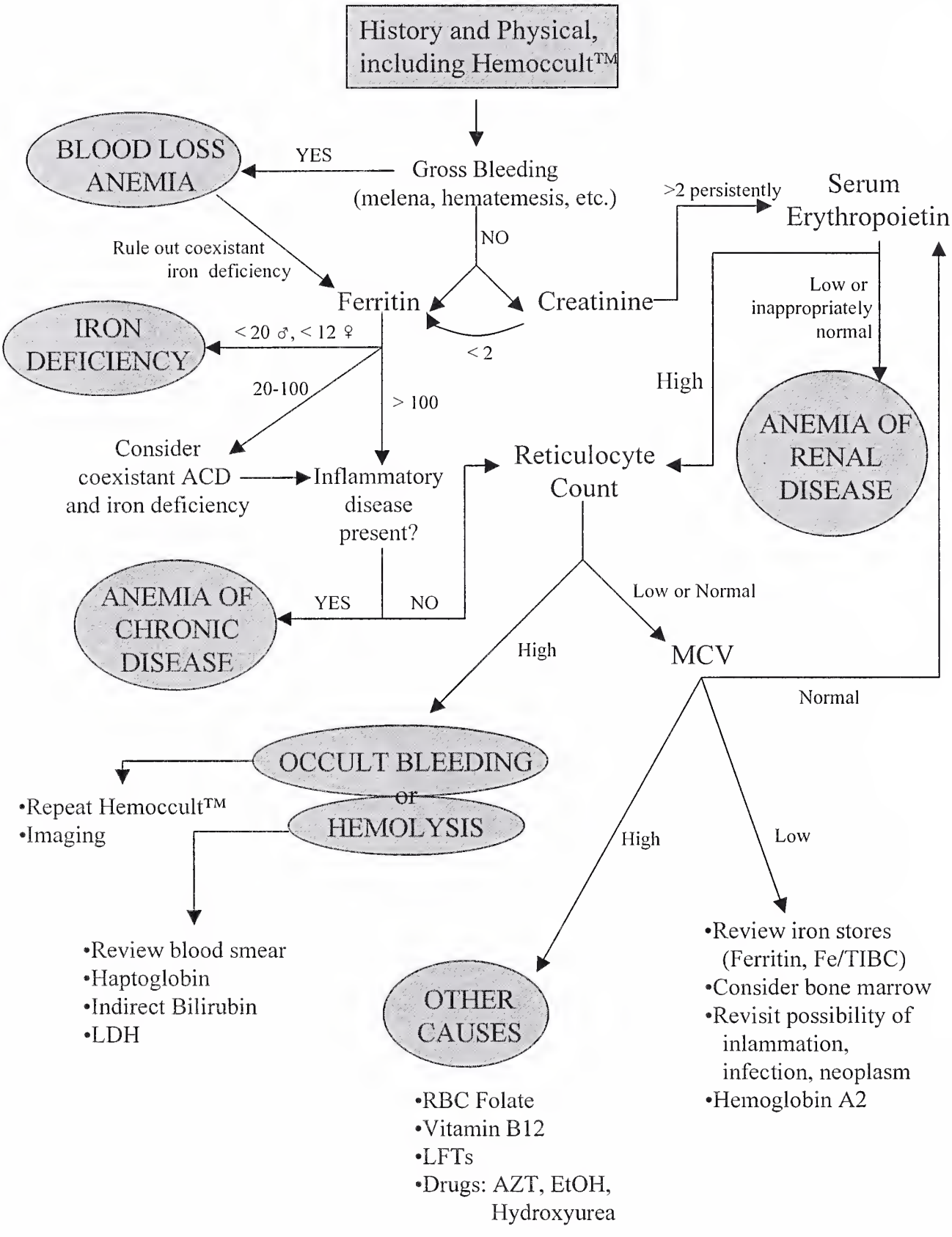
It is commonly taught in the field of Medicine that several diagnoses should not be given when one will do. This tenet, known as Ockham's Razor, is a pearl of wisdom in the evaluation of medical patients. In the case of anemia, however, it may not be as appropriate. Our study included a large proportion of patients in whom one diagnosis alone could not be assigned as the causal entity of the anemia. It appears, from our data, that certain causes of anemia tend to "keep company" with each other. This was most clear in the case of iron deficiency, acute gastrointestinal bleeding, and gastrointestinal malignancy, three diagnoses that commonly occur in pairs because of the mechanisms behind each. Similarly, inflammatory bowel disease occurred together with gastrointestinal bleeding and iron deficiency in our patients. Renal disease coexisted with several causes of anemia, but this was probably more a function of the pervasiveness of renal insufficiency rather than the physiology of the disease. It is important to recognize these diagnostic pairs for a couple of reasons. First, in most cases, at least one of the

diagnoses is easily treatable. Second, an additional diagnosis may be missed with serious consequences. For instance, iron deficiency might be easily treated with oral iron, but if a gastrointestinal malignancy is missed, a chance for cure might be lost.

Certainly, there is much room for further research to create laboratory testing that easily identifies various causes of anemia. The search for a test to differentiate iron deficiency from anemia of chronic disease has been ongoing for many years. Serum values of various inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-1β, serum amyloid A (SAA) protein and C-reactive protein (CRP) have all been examined as diagnostic markers (24, 25, 26). Furthermore, various studies have been performed looking at serum measurement of soluble transferrin receptors, membrane-bound transferrin receptors, and the ratio of serum ferritin to transferrin to differentiate iron deficiency from ACD (27, 28, 29, 30, 31, 32). While some studies have been promising, results have generally been mixed, and no laboratory test has yet become widely accepted for use in clinical practice.

Anemia is so common among medical inpatients that it can be easy to become complacent about its evaluation. Especially in the context of tertiary care hospitals, house officers and physicians see a disproportionate number of anemic patients. We find ourselves forgetting what is normal when we encounter it so rarely. And in the chaotic role of house officer, ordering the same battery of tests in every patient is certainly easier than agonizing over the appropriate workup for each. Diagnoses are missed or made erroneously, and therapeutic options are thus unnecessarily sacrificed. In the end, this "autopilot" phenomenon does not serve the patient's best interest.

Figure 4. A Decision Tree for Evaluating the Anemic Inpatient



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