The Frequency and Significance of Iron-Deficiency Anemia in Patients with Selected Concurrent Illness

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Citation
J Huang, R Means. The Frequency and Significance of Iron-Deficiency Anemia in Patients with Selected Concurrent Illness. The Internet Journal of Internal Medicine. 2008 Volume 8 Number 1.

Abstract
Approximately 30% of the world’s population is anemic, of which 50% is iron deficiency anemia (IDA). The extent to which IDA affects patients with concomitant illness has not been described. A systematic review was conducted on the prevalence of IDA and its relationship to clinical outcomes in selected concurrent illness. After pooling the results of eligible studies, we found considerable disparities in the prevalence for IDA, which varied by the diagnostic tools employed. When bone marrow aspirates were used, the prevalence of IDA was: 52% for rheumatoid arthritis, 53% for inflammatory bowel disease, 54% for HIV, and 73% for heart failure. However, when serum ferritin was used, the estimates were: 39%, 22%, 38%, and 32%, respectively. Decreased survival and peak VO\textsubscript{2} were also reported in heart failure patients with IDA. IDA is prevalent in concomitant illness and can be underestimated. It may also be an important indicator of adverse prognosis.

SOURCE OF SUPPORT
This review article was funded by Beckman Coulter, Inc.

INTRODUCTION
Iron deficiency anemia (IDA) is an important public health concern that affects every population. The World Health Organization estimates that over 30% of the world’s population is anemic, of which 50% is attributable to IDA(1). In the United States, the prevalence of IDA has been found to be 2% in adult males, 9-12% in adult white females, and up to 20% in females of African and Hispanic origin(2). In the non-institutionalized elderly population, IDA also contributed to 20% of all anemic cases(3). Due to the negative impacts on human health, productivity, and the socioeconomic development of both industrialized and non-industrialized countries, IDA significantly adds to the global burden of disease.

A growing body of evidence suggests that anemia reflects poor health and increases risks of adverse outcomes. For instance, anemia alone is an established prognostic indicator in a variety of clinical circumstances. In the elderly, anemia is an independent predictor of fragility, function, and mortality(4,5). Patients with gastrointestinal malignancies who present with anemia have 5-year survival approximately half that predicted for the general population of patients with such malignancies(6).

As one of the primary etiologies of anemia, iron deficiency (ID) and consequent anemia (IDA) may have unique prognostic implications as well. In one recent report, the presence of ID predicted a six-fold increase in in-hospital mortality in patients undergoing carotid endarterectomy(7). In addition, in patients with cystic fibrosis, ID is also associated with more severe supplicative lung disease indicated by increased sputum volume and decreased FEV\textsubscript{1}(8).

Detecting IDA in patients with concomitant illness has significant implications in management; however, the extent to which this disorder affects the population has not been described to the best of our knowledge. Therefore, this study was undertaken to review the reported prevalence of IDA in selected concurrent illnesses, and its impact on clinical outcomes in these disorders.

METHODS
The study goal was to systematically identify and review articles on the prevalence of IDA and its impact on clinical outcomes in selected concurrent illness. In addition, the effect of diagnostic tools on the prevalence measures of IDA was compared. Clinical outcomes of interest included mortality and survival rates.

LITERATURE SEARCH
The eligibility of articles was determined prospectively. We
conducted a systematic search of English-language literature (1950-Sept 2008) in Medline and Cochrane database, using the key words iron deficiency anemia in combination with one of the following: cancer, malignancy, neoplasm, HIV, heart failure, rheumatoid arthritis, and inflammatory bowel disease. Crohn’s disease and ulcerative colitis were also included as search terms. The search was limited to English-language and human studies, and bibliographies of included articles were also reviewed. (Table 1)

Figure 1
Table 1. Literature search terms and number included

REVIEW METHODS (STUDY SELECTION AND DATA EXTRACTION)

Study selection was prioritized to identify randomized controlled trials and observational studies over meta-analyses. Abstracts, letters, narrative reviews, editorials, or commentaries were excluded from the search. Articles met our inclusion criteria if they were (1) randomized clinical trials, (2) observational or epidemiological studies, (3) assessments of the prevalence of IDA in selected disease populations, and (4) studies that correlated IDA with quantitative outcome measures, including morbidity, mortality, survival rate, healthcare utilization, or cost. A total of 433 studies were identified, and 18 studies met our inclusion criteria after the authors completed the review. (Figure 1)

RESULTS

DESCRIPTION OF STUDIES

As shown in Figure 1, the initial literature search yielded 433 articles, of which 18 met the inclusion criteria for the systematic review. Excluded studies mostly either failed to report the diagnostic strategies used for detecting IDA, or did not specify the cut-off for anemia or IDA. The distribution of concurrent diseases among the studies reviewed is shown in Table 1. Of the 18 studies eligible, three were studies on rheumatoid arthritis (RA), three on patients with inflammatory bowel disease (IBD), three on HIV, five on heart failure, three on GI malignancy, and one on geriatric patients presented for acute care with signs of anemia. Six studies were retrospective reviews, while the rest were prospective observational or interventional studies which included details on the status of anemia. With regard to outcome measures, only “survival” and “mortality rates” yielded results. No studies were found on “healthcare utilization” or “cost”. Sample sizes of these studies range from 21 to 20,862 with a median of 131.

Four studies identified used cytochemical staining of bone marrow aspirates for the evaluation of iron stores(9-12). Of the eight articles that reported using serum ferritin levels for
the diagnosis of IDA, two articles(13;14) employed gender-specific lower thresholds of 10-13 ng/ml for females and 13-33 ng/ml for males. Six studies employed age-specific cutoffs at 30 ng/mL for adults, 10 ng/mL for children, and 50 ng/mL for the elderly(15-20). Vijverman et al did not specify the threshold of serum ferritin in the IDA cohort(21), while Agrawal et al appeared to have raised the ferritin cutoff to 50 ng/mL to account for the inflammatory state of their patient cohort(22).

Two studies used recorded diagnoses to identify IDA, with one population-based cohort study using International Classification of Diseases [ICD]-9 codes(23), and another utilized retrospective chart review not otherwise described(6).

**FREQUENCY OF ANEMIA**

Since anemia commonly affects patients with chronic illness, it is of interest to know the size of the anemic population in particular medical conditions. The criteria used for the diagnosis of anemia in the reviewed articles were age- and gender-specific hemoglobin cutoff. We found that in patients with rheumatoid arthritis, the proportion of anemia ranged between 55% and 69%, and the pooled average was 65%. The proportion of patients with inflammatory bowel disease who were also affected by anemia was between 34% and 81%, with the pooled average being 30%. In HIV patients-pediatric and adult- the proportion of anemia ranged from 44% to 83%, and the average was 60%. In patients with heart failure, the proportion of anemia was estimated to be between 17% and 33%. The pooled average was 18%. (Table 2 and Figure 2)

**Figure 3**

Table 2. Proportion of anemia in selected concurrent illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease state</th>
<th>Total patients (N)</th>
<th>Patients with anemia** (%)</th>
<th>Proportion of anemia (%)</th>
<th>Pooled estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngrenholz, 1989</td>
<td>Rheumatoid Arthritis (RA)</td>
<td>36</td>
<td>28</td>
<td>66.0%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Agrawal, 2006</td>
<td>RA</td>
<td>214</td>
<td>151</td>
<td>70.0%</td>
<td></td>
</tr>
<tr>
<td>Remshatkh, 1992</td>
<td>RA</td>
<td>139</td>
<td>75</td>
<td>55.3%</td>
<td></td>
</tr>
<tr>
<td>Child 1979</td>
<td>Inflammatory Bowel Disease (IBD)</td>
<td>21</td>
<td>17</td>
<td>81.0%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Vaglan, 2007</td>
<td>IBD</td>
<td>120</td>
<td>50</td>
<td>40.0%</td>
<td></td>
</tr>
<tr>
<td>Vijverman, 2006</td>
<td>IBD (1993 diagnosis)</td>
<td>86</td>
<td>27</td>
<td>31.3%</td>
<td></td>
</tr>
<tr>
<td>Vijverman, 2008</td>
<td>IBD (1993 diagnosis)</td>
<td>59</td>
<td>55</td>
<td>18.7%</td>
<td></td>
</tr>
<tr>
<td>Mardillos, 1995</td>
<td>PEV, children</td>
<td>60</td>
<td>50</td>
<td>83.3%</td>
<td>69.2%</td>
</tr>
<tr>
<td>Elk, 2002</td>
<td>HIV, children</td>
<td>60</td>
<td>44</td>
<td>73.3%</td>
<td></td>
</tr>
<tr>
<td>Semb, 2002</td>
<td>HIV, female injection drug users</td>
<td>136</td>
<td>60</td>
<td>44.1%</td>
<td></td>
</tr>
<tr>
<td>Witte, 2004</td>
<td>Heart failure</td>
<td>17</td>
<td>17</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td>De Silva, 2008</td>
<td>Heart failure</td>
<td>955</td>
<td>205</td>
<td>21.4%</td>
<td></td>
</tr>
<tr>
<td>Zarkowski, 2003</td>
<td>Heart failure</td>
<td>12,005</td>
<td>2091</td>
<td>17.0%</td>
<td></td>
</tr>
</tbody>
</table>

*Not defined in paper
**Defined by age- and gender-specific [high] cutoff

**Figure 4**

Figure 2. Distribution of anemia in selected medical conditions

Diagnosis of anemia is based on age- and gender-specific hemoglobin cutoff

**IRON DEFICIENCY IN THE ANEMIC POPULATION WITH CONCURRENT ILLNESS**

IDA and anemia of chronic disease make up the two most common anemia syndromes. Therefore, it was of interest to review those anemic patients who subsequently underwent iron evaluation, and establish the prevalence of IDA in the context of multiple anemic etiologies. And we found considerable disparities in these findings even among the same disease population, and this was apparently associated with the tools used for diagnosis. (Table 3)
In geriatric patients, Rimon and colleagues reported as many as 77% of anemic cases were also iron-deficient, as determined by bone marrow biopsy(24). However, when a gender-specific ferritin cutoff (<15 ng/mL for women, <24 ng/mL for men) was used, only about 13% of this cohort was found to have IDA.

Among patients with rheumatoid arthritis, approximately 52% were found to have IDA, ascertained by bone marrow biopsy(11). However, when standard ferritin cutoff (<13 ng/mL for women, <33 ng/mL for men) were applied as the diagnostic criteria, the proportion of patients with IDA was reduced to 20%. This proportion was increased to 48%, resembling the findings of bone marrow biopsy, when a higher ferritin cutoff was used (<50 ng/mL).

Patients affected with inflammatory bowel disease (IBD), either Crohn’s Disease or ulcerative colitis, also exhibited varied distributions of IDA according to the diagnostic strategies used. Child et al found that 53% of IBD patients were also affected with IDA, based on bone marrow aspirates(9). Studies using ferritin, however, found IDA in only 19% to 24% of the disease population(15;21). One of these studies defined the ferritin cutoff for ID at < 20ng/ml(15).

In the HIV infected population, 54% of the patients were found to have decreased iron stores in the bone marrow(10), while only about 25-47% of the patients were iron deficient when the diagnosis was made with ferritin assays(16;17).

The prevalence of IDA in congestive heart failure (CHF) patients also varied widely, depending on the tools used for evaluation. In the study by Nanas and colleagues, up to 73% of advanced CHF patients with anemia were found to be iron deficient, ascertained by bone marrow examination(12). Yet when ferritin assay was used, approximately 5% to 43% of the anemic CHF patients had IDA, at the cutoff of <15 ng/mL and 30 ng/mL, respectively(14;18;19). In one large cohort study which examined hospital discharge data for 12,065 patients using ICD-9 codes, around 21% of the anemic cohort was found to have IDA(25).

Figure 3 shows the pooled prevalence of IDA in selected concurrent illness, as determined by different diagnostic tools.

**RELATIONSHIP OF IDA TO CLINICAL OUTCOMES**

The significance of IDA to concurrent illness has been examined in terms of clinical outcomes such as survival rate, mortality, and functional status in CHF patients. In a study of advanced heart failure patients, a trend suggesting that IDA may have a negative impact on disease outcomes was also noted. The short-term survival rates for this cohort, with IDA or without IDA, were 44% and 50%, respectively(12). Okonko and colleagues gave intravenous iron to CHF patients with ID, whether anemic or not(26). All subjects showed improved exercise tolerance, although the effect was
more pronounced in the anemic patients.

**DISCUSSION**

Anemia is a frequent complication of various chronic diseases. In the studies reviewed in this current paper, anemia was reported in the majority of patients with rheumatoid arthritis (RA) or HIV infection and in significant minorities of CHF and inflammatory bowel disease (IBD) patients (Table 2). The presence of concurrent anemia is a significant indicator of adverse prognosis in these disorders. In CHF patients, concurrent anemia significantly decreases the probability of survival(27). Similar, though less striking, associations have been reported for HIV disease(28).

Anemia in RA and IBD patients is less clearly associated with survival, since these disorders have a comparatively long survival: however, correction of anemia appears to improve quality of life(29;30).

The literature analysis reported in the paper was undertaken to attempt to identify the frequency with which iron deficiency (ID) is a component of the anemia in these disorders, and to identify the prognostic implications of concurrent ID. This is significant because it emphasizes that the etiology of anemia in patients with these syndromes is complex, but it is of greater significance because ID is a treatable disorder and also requires specific evaluation to identify an etiology of blood loss(31). The anemia of RA is often cited as the classic example of the anemia of chronic disease (ACD): a syndrome in which anemia results from a varying combination of hypoferremia despite adequate iron stores, impaired erythropoietin production, and a decreased response of erythroid progenitors to erythropoietin. All of these mechanisms can be linked to the cytokines which mediate the immune and inflammatory response, and factors induced by them, such as the iron-regulatory protein hepcidin(32;33). We found that 20-53% of anemic RA patients have evidence of ID, which is generally higher than the frequency reported by Baer and coworkers(34). The anemia of HIV infection is also generally attributed to ACD mechanisms(35), but a similar proportion of anemic patients with HIV show evidence of ID. Anemia in CHF patients is often attributed to erythropoietin deficiency associated with renal underperfusion (the cardio-renal syndrome)(36). In contrast, the anemia of IBD has usually been attributed to gastrointestinal blood loss: recent research on anemia in IBD has focused primarily on emphasizing the importance of these other mechanisms(37). Interestingly, the frequency of ID among anemic patients with these diverse syndromes is relatively similar, ranging between 20% and 50%.

This study also serves as a reminder that the frequency of ID varies depending upon how it is identified. When based upon a low serum ferritin concentration, which is highly specific but insensitive, the observed frequency of ID is lower than it would appear by the gold standard definition of absent iron on a Prussian blue-stained marrow specimen. The frequency also decreases when the target serum ferritin concentration is set to a more specific (i.e., lower) level. The diagnosis of ID is difficult in patients with underlying disorders associated with cytokine activity, like those in this study. Serum ferritin concentration, the best single chemical parameter for assessing iron stores, is an acute phase reactant which may be elevated out of proportion in inflammation(38). Serum iron and transferrin/total iron binding capacity (TIBC), in contrast, tend to be depressed by inflammation(39), again decreasing their utility as indicators of iron deficiency. Bone marrow examination, while the definitive standard, is resource-intensive, and inconvenient as well as expensive. It is also dependent upon specimen quality(40). In 2002, Ioannou et al. proposed a diagnostic algorithm for IDA in which patients with low serum ferritin concentration were defined as ID, patients with serum ferritin greater than 100 ng/mL were defined as iron replete, and individuals with values in between underwent bone marrow examination(41). In 2007, Killip and colleagues updated this algorithm, replacing bone marrow examination by a combination of tests, including the serum soluble transferrin receptor (sTfR) concentration(2). A similar algorithm based on the sequential combination of serum ferritin and serum sTfR concentrations had been proposed by Means et al., based on a study assessing the ability of serum sTfR concentration to predict bone marrow iron results(40). As an isolated, stand-alone test, sTfR concentration is highly sensitive to ID(40;42); however, sTfR concentration also is increased by marrow erythroid activity, which may reduces its specificity(43). For this reason, it is necessary to use it in association with another parameter, such as serum ferritin concentration. One way to combine these two parameters is to calculate the ratio of the serum sTfR concentration to the logarithm of the serum ferritin concentration(44). This ratio has been suggested as an effective way to exclude iron deficiency in patients with underlying IBD(45). Thomas and colleagues have proposed that serum sTfR concentration can be combined in a graph with an automated red cell indices of iron deficiency such as reticulocyte hemoglobin concentration (46) to both diagnose iron deficiency and to predict which patients are most likely to respond to iron and/or erythropoiesis stimulating agents(47).
Analysis of CHF patients for whom iron parameters are available indicates that ID identifies a poor prognosis subset. It also appears to predict functional status in CHF patients. Correction of ID improves functional status, although it is unclear whether the same would be true for survival. This raises a clinically important issue for CHF and other syndromes: will correcting ID alter the prognosis of these patients, or is ID a marker for underlying pathology – for CHF patients, an indicator of mesenteric hypoperfusion, for example?

In summary, ID is a frequent complication of a variety of chronic illnesses. The frequency with which it is detected varies depending upon the diagnostic studies employed. If, as studies of CHF suggest, ID has specific functional implications which respond to iron repletion, the utilization of the most effective diagnostic approach to ID is imperative.

ACKNOWLEDGEMENTS

Robert T. Means, Jr., M.D. is a consultant for Beckman Coulter, Inc.

The authors acknowledge Melissa Martinson, Ph.D., for assistance with literature search, selection, and review.

References

exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency
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