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REVIEW ARTICLE

Unexplained anemia of aging: Etiology, health consequences, and diagnostic criteria

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Abstract

Background: Up to 15% of people aged 60 and over are anemic, and the prevalence of anemia increases with age. In older men and women, anemia is associated with increases in the risk of death and all-cause hospitalization, poor functional capacity, quality of life, and depression.

Methods and Results: We reviewed the literature describing anemia in aging populations, focusing on the specific diagnostic criteria of anemia and potential causes in older men and women. Even after extensive etiologic workup that involves careful medical history, physical examination, laboratory measurements, and additional studies such as bone marrow biopsy, anemia of aging is unexplained in up to 40% of older patients with anemia. As a result, treatment options remain limited.

Conclusions: The prevalence of unexplained anemia of aging (UAA; also called unexplained anemia of the elderly, UAE), its deleterious impacts on health, physical function, and quality of life, and the lack of effective treatment or therapy guidelines represent a compelling unmet clinical need. In this review and consensus document, we discuss the scope of the problem, possible causes of UAA, diagnostic criteria, and potential treatment options. Because even mild anemia is strongly linked to poor clinical outcomes, it should receive clinical attention rather than simply being considered a normal part of aging.

KEYWORDS
erythropoietin, hemoglobin, physical function

UNEXPLAINED ANEMIA IS PREVALENT IN AGING POPULATIONS

Key points

- The prevalence of unexplained anemia of aging (UAA) increases with age.
- UAA is diagnosed by exclusion of known causes of anemia.
- UAA is associated with decreased quality of life and increased mortality.

Why does this paper matter?

Because of detrimental effects on health and lack of therapeutic guidelines, UAA represents an unmet clinical need.

Anemia, defined by the World Health Organization criteria as circulating hemoglobin (Hb) <12 g/dl in women and <13 g/dl in men, is common among individuals over the age of 60.[1–3] The prevalence of anemia increases with age and is particularly common among the oldest and most frail: in a retrospective study of more than 19,000 hospital patients, the incidence of anemia rose from 15% at the ages of 64–69 to 37% in those over aged 90 (Figure 1). Many anemia cases have no clear underlying cause, a population that we will refer to as unexplained anemia of aging (UAA).

In one of the first population-based studies to describe UAA, Guralnik et al. examined the third National Health and Nutrition Examination Survey (NHANES) of 4199 community-dwelling men and women over the age of 65 years.[4] One third of cases of anemia could be attributed to nutritional causes, and another third were associated with inflammation or chronic kidney disease (CKD). This left one third of cases without a clear etiology. A comparable proportion of mild anemia (defined as a Hb concentration of 10.0–11.9 g/dl in women and 10.0–12.9 g/dl in men) is unexplained: in an Italian cohort of 8744 individuals between aged 65–84, mild anemia had no identifiable cause in 26.4% of cases.[5]

In a wide range of population-based studies of anemia, 25%–44% of cases could be classified as UAA (Table 1). This holds true whether the study population is community-based, hospital inpatient, or long-term care residents. Importantly, the prevalence of UAA remains high even when the potential cause of anemia is rigorously examined. In study populations consisting of hematology clinic outpatients and patients referred to anemia referral clinics, in which cohorts were subjected to comprehensive examinations, the frequency of UAA is 35%–44%. For example, Artz et al.[6] examined a community-dwelling, predominantly African-American (69%) group of patients over the age of 65 who had been referred to an anemia clinic and even after intensive evaluations of causes, UAA was the most common category in both white and African-American patients. Michalak et al.[7]

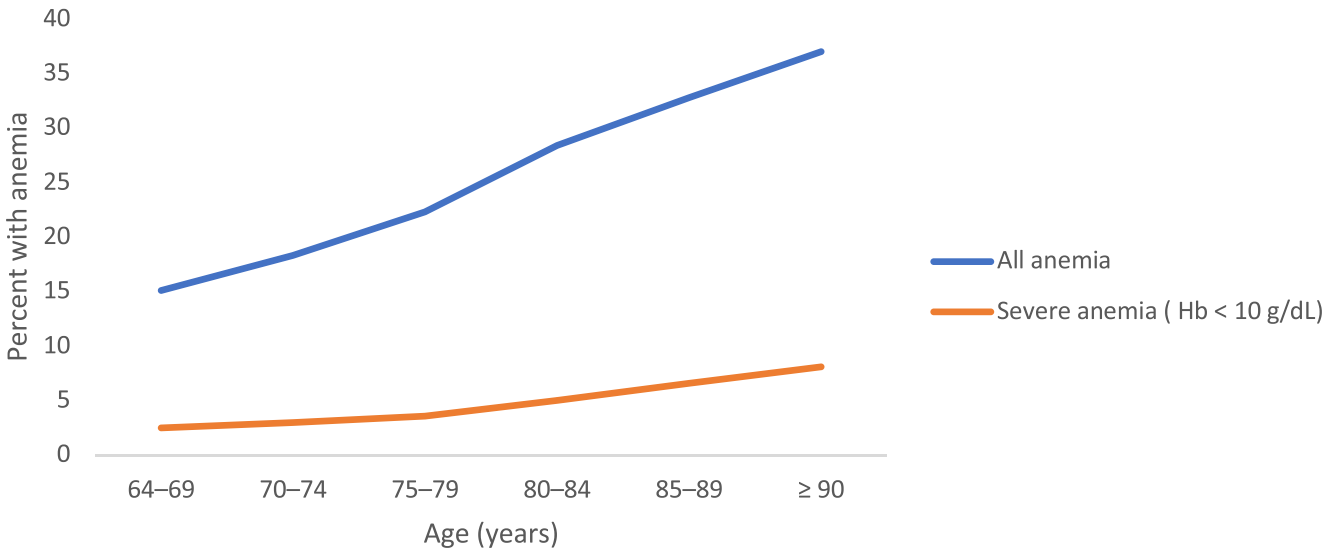

FIGURE 1 Prevalence of anemia increases with age. Prevalence of anemia (WHO criteria: Hb < 12 g/dl in women and <13 g/dl in men) and severe anemia (Hb < 10 g/dl) in a cohort of 19,758 inpatients and outpatients aged ≥64 years with complete blood counts treated at Innsbruck Medical University Hospital between October 1, 2004 and September 29, 2005. *Source*: Data from Reference 8

TABLE 1 Prevalence of diagnostic causes of anemia in older patients, including UAA

Source	N	Age	%CKD	%IDA	%ACI/ACD	%B_{12}/folate deficiency	%UAA
NHANES III[4]	2096	≥65	8.2	16.6	19.7	B_{12}: 5.9 B_6: 6.4 Both: 2.0	33.6
Health and Anemia[5]	8744	≥65	15.0	16.0	17.4	10.1	26.4
Community dwelling outpatients[64]	190	≥65	4.0	12.0	6.0	NA	35
InChianti[65]	582	≥65	10.4	17.6	24.5	10.5	37.2
Leiden (≥ 85y)[66]	490	≥85 years	7.0	32.4	20.1	8.7	25.4
Polish Clinic patients[7]	981	≥60	NA	NA	NA	NA	28.4
Innsbruck Medical University cohort[8]	4117	≥64	11.3	14.4	62.1	B_{12}: 2.0 B_6: 6.7	-
Community dwelling[6]	174	≥65	9.8	25	9.8	1	44

Abbreviations: ACD, anemia of chronic disease; ACI, anemia of chronic inflammation; CKD, chronic kidney disease; IDA, iron deficiency anemia; UAA, unexplained anemia of aging.

retrospectively examined medical records of 981 patients over the age of 60 and found that anemia was unexplained in 48 of 169 patients, with a UAA prevalence of 4.9%. The prevalence of UAA increased from 2.9% in those between 60 and 69 to 12.3% in patients ≥80 years of age.

DIAGNOSTIC CRITERIA AND ETIOLOGY FOR UAA

The etiology of anemia in older patients is complex and falls into four often overlapping categories: (1) deficiencies of nutrients, including iron, vitamin B12, and folic acid; (2) anemia of inflammation or chronic disease, congestive heart failure (CHF), malignancy, auto-immune disease or infections; (3) chronic kidney disease (CKD); (4) hematologic malignancies[6]; and (5) UAA, which is diagnosed mainly by exclusion. Although there is not yet a consensus regarding its etiology, UAA is a recognized disease among older patients with anemia who do not meet the standard criteria for anemia subclassification.[8–10]

The causes of UAA are likely multifactorial, with variable contributions from renal disease, endocrine deficiency (blunted erythropoietin response), chronic inflammation, androgen deficiency, nascent myelodysplasia, and other underlying conditions. Ferrucci et al.[11] reported a significant correlation between low circulating testosterone and anemia in community-dwelling men and women over the age of 65 from the InChianti study, a relationship that was independent of circulating erythropoietin levels.[12] Tettamanti et al.[5] suggested a number of potential causes for low Hb in people over 65 years, including undiagnosed myelodysplastic syndrome, hypogonadism (testosterone <275 ng/ml), impaired bone marrow response to EPO (decreased responsiveness), low-grade chronic inflammation (elevated IL-6, TNF-α, or hepcidin), vitamin D deficiency [25(OH) < 20 ng/ml], and unrecognized iron deficiency. Aging is also associated with dysfunction of hematopoiesis, evidenced by an age-related decrease in the number of hematopoietic stem cells in the bone marrow and the circulation[13.14] Many men and women with anemia have elevated inflammatory markers in the absence of a diagnosed acute or chronic disease,[11] and should be considered and treated similarly to patients with UAA.

Although not unexplained, perioperative bleeding represents a significant cause of anemia for many older patients undergoing hip fracture repair.[15] Preoperative anemia in older patients is also common (up to 20% of patients) with limited treatment options. For example, intravenous iron is relatively save but not effective in raising hemoglobin levels in this patient group.[16] The drop in hemoglobin resulting from a hip fracture prior to surgery is substantial,[17] and the drop is exacerbated during the surgery. In the early postoperative period after hip fracture repair surgery, uncorrected anemia (Hb <100 g/L) was an independent risk factor for inability to walk on the third postoperative day, independent of the type of surgery or prefracture function.

Guralnik et al.[4,18] used the criteria established for the NHANES study to identify potential causes of anemia (left column, Table 2). In cases of anemia (Hb < 13 g/dl), UAA could be ruled out if a patient meets any these criteria. The right column of Table 2 contains our proposed expansion of the exclusion criteria used by Guralnik et al.

ANEMIA IS ASSOCIATED WITH MORBIDITY AND MORTALITY

Anemia is not only more common in older people but is also more likely to be associated with harm. A recent study[19] in a large cohort of 138,670 subjects demonstrated that in individuals older than 60 years, anemia was associated with elevated mortality and poorer quality of life (QOL), whereas in individuals aged 60 or younger, anemia had no effect on mortality and a very limited impact on health-related quality of life. In that study, lower QOL resulted from lower physical function subscales. After adjusting for age, sex, type II diabetes, and comorbidity in a population of 17,030 community-dwelling men and women over 66 years of age, anemia was associated with increased risks of all-cause hospitalization (HR = 2.16, confidence interval [CI] 1.88–2.48) and death (HR: 4.29, CI 3.55–5.12).[20] Consistent with this, in men and women over the age of 65, anemia is associated with a higher risk of various poor health outcomes, including poor functional capacity, poor QOL,[21] depression,[22] sarcopenia, and poor muscle quality.[23] Similarly, data from the EPESE cohort[24] of older Americans demonstrated that after controlling for age, sex, cognitive status, blood creatinine, and comorbid conditions, individuals with anemia had more disabilities, and poorer functional status than people without anemia. Decline in performance with lower hemoglobin was also observed in people with hemoglobin levels above the WHO clinical threshold for anemia. Of course, factors other than age can exacerbate the risk of anemia; prevalence in older black men and women is substantially greater than that of the general population,[25] with black women 80–85 years old having a prevalence that is 6.4 times greater than the population average.

For older individuals with comorbid disease, the deleterious effects associated with anemia are similarly clear. For example, among patients >75 years old with stable angina, anemia is associated with elevated rates of death (34% increase for every 1 g/dl decrease in Hb, $p < 0.01$), increased cardiac death (28% increase for every 1 g/dl decrease in Hb, $p < 0.01$), and increased major adverse clinical events (23% increase for Hb <13.3 g/dl).[2]

TABLE 2 Diagnostic exclusion criteria for unexplained anemia of aging

Potential cause	Guralnik et al. criteria	Expanded criteria
Diagnosis of anemia	World Health Organization criteria: Men <13 g/dl Women <12 g/dl	men and postmenopausal women <13 g/dl
Iron Status	Ferritin <12 ng/ml Transferrin saturation < 15%	Ferritin <40 ng/ml[67] Transferrin saturation < 15%
B12	< 200 pg/ml	< 200 pg/ml
Folate	red blood cell folate <102.6 ng/ml Home exam: serum folate <2.6 ng/ml	Red blood cell folate <102.6 ng/ml Alternative: serum folate <2.6 ng/ml
Chronic kidney disease	Creatinine clearance <30 ml/m	Creatinine clearance <30 ml/m
Chronic inflammation	Serum iron <60 μg/dl	Diagnosed inflammatory disease and serum iron <60 μg/dl[10]
Thyrotropin/TSH		<0.1 mU/ml or >10 mU/ml (except in cases of corrective thyroid therapy without erythroid response)
Other		No history of evidence of hematologic malignancy or myelodysplastic syndrome

THE NEGATIVE EFFECTS OF ANEMIA ON PHYSICAL FUNCTION IN OLDER PEOPLE ARE UNDER-ASCERTAINED AND UNDER-REPORTED

Progressive, age-associated decreases in functional capacity, strength, and physical activity are well-described consequences of aging with multiple etiologies. Reduced hemoglobin is associated with low aerobic capacity, strength, and endurance in all adults, including older men and women.[26] Slower walking speed, an important biomarker of aging and prognostic of mortality and other adverse outcomes, is strongly associated with maximal aerobic capacity in older people.[27]

Functional capacity, in turn, is strongly associated with health-related outcomes in older men and women. In particular, the short physical performance battery (SPPB), a combined functional measurement of usual walking speed, time to stand up and sit down from a chair five times, and standing balance, is a powerful predictor of disability, institutionalization, and death.[28,29] Usual walking speed, one of the components of the SPPB, is strongly and

independently associated with health-related outcomes and mortality risk.[30] This simple assessment is so strongly linked to health-related outcomes in geriatric patients that it has been termed the "sixth vital sign."[31] The SPPB (or usual walking speed) can be easily measured in a limited amount of space with no requirement for specialized equipment. In addition, the Functional Assessment of Chronic Illness Therapy (FACIT) is a brief, standardized set of 13 questions[32] that can identify functional differences between patients with or without anemia.

Although these measurements are strongly linked to outcomes, they are not commonly assessed in geriatric patients. Perhaps because these functional tests are not a routine component of a geriatric assessment by most health care providers, decreases in function are not often recognized and, as a result, lower Hb levels in geriatric patients may be considered inconsequential, with little effect on functional status or quality of life. We strongly recommend the routine use of a standardized assessment of functional capacity and fatigue during routine office visits so that such deficits may be quickly identified, and appropriate therapies may be implemented. However, current treatment options for UAA are extremely limited. By definition, the etiology of UAA is not understood and traditional treatment options such as iron, folate, B_{12}, or improved nutrition often have little or no effect on resolving the anemia. The use of erythropoietin stimulating agents may be effective, but are generally used only for severe anemia, and even then only rarely.

PHARMACOECONOMICS: ANEMIA LEADS TO HIGH HEALTHCARE COSTS IN OLDER PEOPLE

Use of healthcare resources and overall medical costs are significantly higher among patients with anemia. Anemia accounts for 2.8 million physician office visits and 890,000 emergency department visits per year in the United States.[33] One-quarter of patients admitted to the hospital for anemia are readmitted to the emergency department within 30 days,[34] with the likelihood of unplanned readmission increasing with the severity of anemia at first discharge.[35] Following admission, anemia is associated with elevated in-hospital mortality and longer stays.[36,37]

These trends are exacerbated in the older people, in whom anemia is associated with up to fourfold greater risk of overall mortality and twofold greater risk of hospitalization.[20,38] Hospital stays are longer among older patients with anemia[37,39]: average length of stay increases 4–5 days in patients with moderate anemia and 7–10 days in the most severe cases.[40] As a consequence of the combined increases in hospitalization, readmission, length of stay, morbidity, and mortality, patients with anemia experience medical costs more than twice as high as those of patients without anemia of comparable age, sex, comorbidities, and insurance status.[41] This holds true for patients overall, as well as for populations with specific comorbidities: greater costs have been reported for patients with anemia and chronic kidney disease,[42] chronic obstructive pulmonary disease[43] or colorectal disease requiring surgery.[44] Anemia is also strongly associated with frailty in older men and women[45]: an increase in one point of hemoglobin concentration is associated with a 14% risk reduction of being frail (OR = 0.86, 95% IC = 0.79–0.94).

Anemia drives up healthcare costs in the older people by increasing the risk of falls. Individuals with anemia over the age of 65 years are twice as likely to experience recurrent falling[46] and are 3-fold more likely to have a history of falls when controlling for age, gender, arthritis, and residence type.[40] Anemia is associated with a 66% increase in the incidence of injurious falls among people 65 years and older[47] (10% of all injurious falls in this age group). Risk rises as Hb level decreases, but importantly, even individuals with the mildest anemia (Hb 12–12.9 g/dl) are significantly more likely to experience falls.[40,47]

Fall injuries are the fifth largest category of personal health care spending in the United States. People over 65 sustain more than 3.2 million injurious falls per year[48] and the ensuing care is responsible for up to $48–49 billion in costs.[49,50] A retrospective analysis of claims for injurious falls from more than 30 health plans (mean patient age, 76 years) performed in 2005 found that anemia increased costs by $1855 per patient per month, and $2811 for falls causing hip fracture.[51] Between 1996 and 2013, spending on falls increased 25%–50%, depending on the category of care,[49] and expenditures are predicted to continue rising.[50] Among older nursing home residents with a hip fracture, anemia is associated with an increased mortality risk (HR = 1.6, 95% CI 1.1–2.5).[52] Anemia is 4-fold more prevalent among nursing home residents in the US than in community-dwelling older people (56% overall; 64% for males and 53% for females) and was associated with a 2-fold increase in risk of falling.[53]

CLINICAL CONSEQUENCES OF MILD ANEMIA

These studies demonstrate that anemia is associated with elevated morbidity and mortality in older men and women. It is important to note that these risks are also present for patients on the mild end of the anemia spectrum. Awareness of these clinical consequences is particularly important because of the high prevalence of mild

anemia among patients with anemia. The vast majority of UAA cases (91.7%) are classified as mild (Hb ≥ 10 g/dl),[7] with most patients presenting with hypoproliferative anemia with normocytic indices.[5] Moreover, the proportion of patients with anemia that can be classified as mild (Hb ≥ 10 g/dl) increases with age (Figure 1).

Relative to age-matched nonanemic people, patients with mild anemia experience declines in mobility and physical performance.[4] Moreover, mild anemia is prospectively associated with clinically relevant outcomes such as risk of hospitalization and all-cause mortality[38] (Table 3). Mortality increases steadily as Hb declines: in women over 65, Hb of 11 g/dl is associated with significantly greater mortality than the low-normal WHO cutoff of 12 g/dl; conversely, women with Hb of 14 g/dl experienced a 24% reduction in mortality relative to patients below the cutoff.[54] The significant differences in mortality risk among people near the threshold for anemia diagnosis strongly implies that the overall health consequences of anemia cannot be attributed to individuals with severely low Hb.

Among both male and female participants in the Cardiovascular Health Study, baseline Hb status was strongly associated with health-related outcomes, and a decrease in Hb over 3 years was associated with decline in cognitive function.[3] The authors concluded that reduced blood Hb was present in many older patients who were at elevated risk for adverse outcomes but who would not have been identified as anemic according to the WHO criteria.

Together, these associations with poor clinical outcomes indicate that mild anemia should receive clinical attention rather than simply being considered a normal part of aging.[4]

DEFINING ANEMIA THRESHOLDS IN MEN AND WOMEN

The WHO definition of anemia uses different Hb thresholds for men and women, but these differences are based largely on population averages for all adults, rather than on specific clinical outcomes related to Hb values <12 g/dl for women and <13 g/dl for men. According to the WHO criteria, the prevalence of anemia increases with advancing age to a greater extent in men than in women[4] as a result of different sex-related thresholds for diagnosis. However, there is little metabolic or physiological rationale for a different threshold between postmenopausal women and older men. Importantly, women with a Hb concentration between 12.0 and 13.0 g/dl (anemic in men but not in women, according to the WHO definition) experienced a significantly lower QOL than women with Hb > 13 g/dl. Mild anemia, estimated to affect 11.1% in the population over the age of 65,[5] is defined by WHO criteria as Hb levels of 11.0–11.9 in women and 11.0–12.9 g/dl in men. The differences in these ranges (0.9 g/dl in women vs 1.9 g/dl in men) result in different therapeutic guidelines, potentially leading to undertreatment of older women with anemia. Recently, Simonsick et al.[55] examined fatigue and anemia in a cohort of older men and women from the Baltimore Longitudinal Study on Aging. They reported that even subclinical anemia, defined as Hb of 12–12.9 g/dl for women and 13–13.9 g/dl for men, was associated with fatigability. They also demonstrated that fatigability was predictive of subsequent clinical anemia. The observation that reduced QOL is observed in older women with Hb values up to 13 g/dl implies that the threshold for anemia in postmenopausal women should be similar to that in men. Such a change in diagnostic criteria would allow mild anemia in older people to be defined in the same range, and to be treated according to the same guidelines, in both sexes.

THERAPIES FOR UAA

At the present time, there is no consensus optimal therapy for UAA,[56] in large part because a single targetable deficit has not been characterized. Currently, erythropoietin-stimulating agents (ESA) such as epoetin alfa and darbepoetin alfa are used to treat anemia in

TABLE 3 Mild anemia increases hospitalization and mortality

		Percent hospitalized				Percent deceased			
Years of follow-up		**0.5**	**1.0**	**1.5**	**2.0**	**0.5**	**1.0**	**1.5**	**2.0**
Women	Nonanemic	5	11	16	21	0.5	2	2.5	5
	Mildly anemic	13	20	26	29	3	7.5	10	13
Men	Nonanemic	10	18	24	30	1	2	4	10
	Mildly anemic	17	28	35	42	5	9	14	17

Note: Percent of patients experiencing one or more hospitalizations or deceased, stratified by sex and mild anemia status, over a 2-year follow-up in the Health and Anemia population-based study (2003–2007). Mild anemia was defined as Hb concentration between 10.0 and 11.9 g/dl in women and between 10.0 and 12.9 g/dl in men. *Source*: From Reference 38.

patients with chronic kidney disease (CKD), patients receiving dialysis, or in patients with nonmyeloid malignancies where anemia is due to effect of concomitant myelosuppressive chemotherapy.[57] A retrospective analysis[58] of patients with anemia over aged 60 revealed that those with UAA had inappropriately low EPO levels after adjusting for Hb, eGFR, and comorbidities. Gowanlock et al.[59] performed a retrospective analysis of the use of epoetin alfa to treat UAA in 570 patients with anemia over aged 60. They observed a larger increase in Hb in UAA (47%) and CKD (54%) relative to other etiologies (22%) and found that a baseline EPO level < 200 IU/L independently predicted treatment response. Agnihotri et al.[60] conducted a randomized controlled trial to examine the effects of epoetin alfa versus placebo in older (≥65 years; mean age 76.1 ± 7.2 years) women with anemia (Hb ≤ 11.5 g/dl). Patients randomized to epoetin alfa had improved fatigue and QOL relative to the placebo group, and achieved Hb was directly related to improvements in fatigue and QOL. These data imply that patients over the age of 65 years are quite responsive to ESAs.

Idiopathic cytopenia of unknown significance with anemia has been proposed to be synonymous with UAA,[10] and Maggio et al.[61] suggested that UAA is a result of the cumulative effects of age-associated changes in androgen production, low insulin like growth factor 1, and low thyroid hormone levels. At present, however, there is no consensus on the definitive etiology for UAA. Consequently, the diagnosis of UAA is one of exclusion, according to the criteria enumerated in Table 2. The criteria in this table have been somewhat expanded using data published after the paper by Guralnik et al. Moreover, despite strong evidence that even mild anemia is associated with fatigue and reduced quality of life, there is no consensus for treatment options.

Guralnik et al.[18] suggested that patients with UAA may have age-associated deficiencies in the ability to sense hypoxia or erythropoietin (EPO), and consequently require higher rates of erythropoietin production to maintain normal erythrocyte production, a finding supported by data from the Baltimore Longitudinal Study of Aging.[62] Ferrucci et al.[11] separately hypothesized that in many anemic older people, elevated inflammation may prevent EPO from being upregulated sufficiently to meet the need for red cell production.

Several potential treatment options for UAA have been suggested[56] or are in development, including hepcidin antagonists, hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitors (PHIs), the transforming growth factor beta superfamily ligands, and androgens. The HIF-PHIs are of particular importance. The HIF pathway is a critical component of the cellular response to lower oxygen, and accordingly plays a major role in the regulation of iron metabolism and erythropoiesis. HIF prolyl hydroxylases (PHDs) post-translationally modify HIF, targeting it for degradation by the proteasome; HIF-PHIs prevent this degradation and increase HIF activity under normoxia.[63] Unlike ESAs, which are delivered via injection, this class of drugs is orally delivered small molecules that stimulate production of EPO at physiologic levels. Because a HIF-PHI has been approved for a chronic indication (CKD) in multiple nations, it is reasonable to consider this class of drugs as candidate treatments for UAA.

CONCLUSIONS

Anemia is prevalent in men and women over the age of 65 years and becomes progressively more common with age. Anemia is associated with reductions in functional capacity and quality of life, as well an increased risk of death from all causes. Roughly one third of anemia in older patients is unexplained (UAA). Although the WHO diagnostic thresholds for anemia are most frequently used, evidence supports the use of a single criterion of Hb < 13 g/dl in both older men and postmenopausal women. Even mild anemia (Hb 11.0–12.9) is associated with poor clinical outcomes, lower QOL, and elevated mortality. Although UAA is currently diagnosed by exclusion of identifiable causes for anemia, the diagnostic criteria for UAA are clearly defined, and the UAA patient population experiences significant functional decline, morbidity, and mortality. In part due to the lack of consensus on the etiology of UAA, treatment options are extremely limited at present. Novel therapies are currently in development for the treatment of this highly prevalent condition. Finally, we strongly recommend routine assessment of functional capacity and quality of life in all older patients by healthcare providers, particularly those suffering from anemia, using standardized tools that will help to identify functional deficits and changes in functional capacity in older patients with anemia.

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CONFLICT OF INTEREST

No other conflicts are reported.

AUTHOR CONTRIBUTIONS

William Evans is a consultant for BioAge Labs, Inc. All authors contributed equally to the writing and editing of this manuscript.

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