Published in final edited form as:
Semin Hematol. 2008 October ; 45(4): 250–254. doi:10.1053/j.seminhematol.2008.06.003.

Unexplained Anemia in the Elderly

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Abstract

Among the elderly, anemia occurs with increasing frequency with each advancing decade. Unlike when anemia occurs in younger adults, the cause of anemia in the elderly is oftentimes not readily apparent or attributable to a single cause. However, this commonly observed form of anemia in the elderly (termed unexplained anemia [UA]) can generally be dissected to its root causes, which include renal insufficiency, inflammation, testosterone deficiency, and stem cell proliferative decline. Myelodysplasia (MDS) occurs commonly in this age group but can and should, for both diagnostic and therapeutic considerations, be distinguished from UA.

Guralnik and colleagues reported that approximately one third of anemias occurring in community-dwelling men and women over the age of 65 years were not attributable to nutritional deficiency, inflammatory disease, or renal insufficiency and used the term "unexplained anemia" (UA) to identify this group.[1] For their analysis, the World Health Organization (WHO) criteria for anemia (<13 g/dL in men and <12 g/dL in women) were applied to registrants in the National Health and Nutrition Examination Survey (NHANES III) database and the cause of anemia was estimated, as possible, based on existing laboratory values in that dataset. Although certain measures, such as reticulocyte count, haptoglobin level, and serum lactate dehydrogenase (LDH) may have offered additional precision, their findings are in line with other reports of anemia in the elderly that have acknowledged a similar subset of undefined anemia, the prevalence of which appears to increase with advancing age and frailty (Table 1).

Defining Unexplained Anemia

UA is most commonly mild, with hemoglobin levels approximately 1 g/dL lower than the WHO standard. The red blood cells are typically of normal size and examination of the peripheral smear reveals no evidence for intravascular destruction or morphological features suggestive of myelodysplasia (Table 2). Because UA is typically mild, it is likely to be overlooked. In fact, in one population-based cohort that included elderly patients with even more significant anemia, the medical records of affected individuals did not mention anemia as a problem in 75% of the cases.[2] For reasons detailed elsewhere in this issue of *Seminars* and in other recent publications,[3] this casual acceptance in older populations may not be advisable. Not only can a decline in important functional measures be related to mild anemia,[4–7] but longitudinal studies have demonstrated increased mortality among individuals with even mild anemia.[8–10] Furthermore, a retrospective cohort study of Veterans Affairs National Surgical Quality Improvement database, indicated that of 310,311 subjects 65 years and older who underwent non-cardiac surgery, the 30-day mortality and cardiac event rates increased by 1.6% for each 1% change in hematocrit below the level of 39%.[11] Thus, although in younger

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individuals mild anemia may be well tolerated, in many older individuals it is associated with important negative consequences.

Mechanisms of UA: Contributing Factors

For a hematologist, "unexplained anemia" is an unfortunate term, perhaps reflecting negatively on our capacity to understand erythropoiesis. However, UA is not so much unexplained as it is multi-factorial (Table 3). Several age-related physiological changes may contribute to either a decline in red blood cell production or shortened red blood cell survival and these in composite are likely to be at the root of UA (Table 4). Included in these physiological changes are age-associated renal insufficiency, stem cell aging, androgen insufficiency, chronic inflammation, and myelodysplasia (MDS).

Age-Associated Renal Insufficiency

Renal function declines with age even in the absence of clinically recognized disease.[12] In persons with underlying conditions, such as diabetes mellitus[13] or hypertension,[14] the decline may be more pronounced. In addition to the exocrine function, the kidney is the major source of erythropoietin, and although not directly linear, erythropoietin production is known to be less than adequate in patients with renal insufficiency,[15] accounting in large part for the anemia associated with kidney failure. Under normal circumstances, erythropoietin levels increase with advancing age.[16] However, for subjects with a history of diabetes mellitus and/or hypertension, the age-associated rise in erythropoietin is either significantly less, or not existent, and hemoglobin levels for these individuals decline in later years.[16] In fact, erythropoietin levels have been shown to be less than expected in the larger group of elderly individuals who meet criteria for UA, and this occurs even in the absence of clinically evident renal exocrine insufficiency.[17–20] Among the very oldest, particularly those who meet criteria for frailty, anemia occurs in 50% to 85%[21–23] and in this group renal insufficiency is more apparent. For example, in a recently reported survey of 6,220 nursing home residents, 43% were found to have an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, supporting the notion that chronic renal insufficiency is a major contributor to the high prevalence of anemia in that setting.[23]

Stem Cell Aging

Currently an active domain for investigation, there is now ample evidence that hematopoietic stem cells undergo qualitative changes with age, resulting in reduced proliferative and regenerative capacity.[24–27] In the absence of stress, disease, or an unusual homeostatic demand (eg, erythroid reconstitution after systemic chemotherapy), whether these age-associated changes account for cytopenias in general, or specifically anemia, remains unknown.

Androgen Insufficiency

Androgens have been known to have a stimulatory effect on erythropoiesis for over three decades[28] and hormonal treatment remains effective for some patients with hypoplastic or aplastic anemia.[29] Patients with androgen deficiency, such as observed after orchiectomy or pharmacologic androgen ablation for prostate cancer, typically have a drop in hemoglobin level of 1 g/dL,[30–32] but this can be as high as 2.5 g/dL in patients who have had complete hormonal ablation and radiotherapy.[33] Thus, it is likely that an age-associated decline in androgen contributes to some extent to a decline in erythroid mass and may thus be a contributing factor to unexplained anemia. In support of this, Ferrucci and colleagues measured total and bioavailable testosterone levels in 905 participants in the "Invecchiare in Chianti" (InCHIANTI) epidemiological cohort of men and women 65 years and older.[34] For both sexes there was a significant linear relationship between testosterone and hemoglobin levels. Furthermore, for subjects who had low testosterone levels but not anemia at the time of

initial evaluation, there was an increased risk of anemia being discovered when tested 3 years later. However, it is notable that not all individuals in the study with low testosterone had, or developed, anemia. Thus, an age-associated decline in serum testosterone is likely to be a contributing factor in some cases of unexplained anemia.

Chronic Inflammation

Anemia is common in patients with both acute and chronic inflammatory disease and it has long been held that inflammatory cytokines have an inhibitory role in erythropoiesis.[35–38] The mechanism whereby inflammatory cytokines, or for that matter the process of inflammation, produces anemia is incompletely understood. Inflammation-associated hypoproliferative anemia has much overlap with iron deficiency, but typically iron stores are within normal limits or elevated.[39,40] Inflammatory cytokines stimulate liver production of hepcidin, which in turn reduces intestinal iron absorption and decreases iron release from macrophages.[41–44] Thus, the underlying mechanism for inflammation-associated anemia is coming to light.

The prevalence of chronic inflammatory diseases increases dramatically with advancing age. In addition to cancer and arthritis, atherosclerosis,[45] diabetes,[46] and other common disease processes are associated with elevated serum pro-inflammatory cytokines, suggesting that inflammatory processes are common in the pathogenesis of many age-associated diseases. Furthermore, pro-inflammatory cytokine levels increase with increasing adiposity, and it has been speculated that the age-associated changes in relative body composition account for much of the observed rise in these inflammatory markers with advancing age.[47,48]

It is true, however, that serum levels of inflammatory cytokines increase with age in the absence of clinically recognized inflammatory disease or obesity. Because both estrogen[49,50] and testosterone[51] are inhibitors of nuclear factor kappa B (NFκB) activity and thereby the transcription of several inflammatory mediators, including interleukin-6, it has been suggested that those endocrine changes that occur at menopause or andropause result in a constitutively increased presence of inflammatory mediators.

That cytokines may be involved in the pathogenesis of late life anemia is suggested by a number of experimental observations. T cells from poor responders to erythropoietin therapy were found to produce increased interferon gamma and tumor necrosis factor alpha (TNFα) when compared with those patients with excellent erythroid response to treatment or to normal controls.[52] Furthermore, bone marrow cell cultures treated with serum from patients with inflammation exhibited suppression of erythroid colony-forming units (CFU-E) and this effect was reversed by using antibodies against TNFα and or interferon gamma (IFNγ).[53]

Although by no means proven, it is quite possible that the presence of even mildly elevated IL-6 present on the basis of age alone, body composition change, or smoldering inflammatory disease results in inhibition of erythropoietin production and/or activation of hepcidin, both of which would result in anemia.

Myelodysplasia

MDS occurs most often in older age groups.[54,55] Anemia is a common feature, and early in the disease may be difficult to classify. The red blood cells are typically macrocytic and examination of the peripheral blood smear may indicate qualitative or quantitative abnormalities in white blood cells or platelets. However, bone marrow examination including cytogenetic studies may be required for accurate diagnosis. Thus, although the anemia associated with MDS should not be considered a component of UA, some cases of MDS will present with anemia alone. Because the anemia in these circumstances may have other features of UA (ie, no iron, B_{12}, or folate deficiency; adequate renal exocrine function; no obvious

inflammatory disease), it might be considered UA for some time. However, in the majority of patients with MDS, the anemia will become more severe and ultimately there will be evidence of a trilineage disorder distinct from UA.

Treatment of UA

Patients with UA, by definition, do not have a well-characterized anemia resulting from a single cause, such as iron or B_{12} deficiency. Because many will have evidence for mild or moderate renal insufficiency, there is a temptation to proceed with recombinant erythropoietin or other erythroid-stimulating agent (ESA). Recently, Agnihotri et al reported on 62 elderly anemia patients, most of whom had multiple comorbidities, who were enrolled in a randomized controlled trial of epoetin alfa or placebo.[56] Treated patients had a rise in hemoglobin of 2 g/dL and this was associated with a reduction in fatigue and improvement in other quality-of-life indicators. Although the protocol was not designed for the treatment of UA, it was encouraging to note the improvement in quality of life among these elderly participants. However, there remains no published report of the effect of anemia treatment in elderly patients with UA in terms of physical function or disability. With the current appreciation of the risks inherent in ESA treatment, it is critical that appropriate and well-designed studies be undertaken to assure both safety and efficacy of such an approach in this vulnerable population.

Summary

We believe UA is not as mysterious as it is complex. We suggest that a composite of five age-associated contributing factors account for the bulk of the phenotype of UA. The relative contributions of these factors will vary, accounting for the observed clinical heterogeneity. These are:

1. Age-associated decline in renal endocrine function resulting in a reduced erythropoietin response.
2. Age-associated reduction in androgen levels in both males and females, accounting for a decline in hemoglobin level of up to 1 g/dL.
3. Anemia attributable to age-associated cytokine dys-regulation. Pro-inflammatory cytokines, most notably IL-6, have been shown to increase in tissue and in serum with advancing age and this may occur in the absence of known inflammatory disease. The presence of these pro-inflammatory cytokines correlates with the advent of several features of frailty, including anemia, and has a negative prognostic importance with regard to symptoms, comorbidities, and survival. Elevated cytokine levels may contribute to UA by mechanisms noted above for inflammation (inhibition of erythropoietin and induction of hepcidin).
4. An age-associated (but yet to be defined) contribution of hematopoietic stem cell proliferative capacity.
5. Early MDS presenting as anemia without associated white blood cell or platelet features.

These factors (with the exception of MDS) might be considered typical features of aging and do not require or even imply the presence of concurrent disease. Certainly, the presence of comorbidities, the use of multiple prescription and over-the-counter medications (polypharmacy), inadequate nutrition, and alcohol abuse, which are not the result of aging per se but which occur more frequently in older people, may also have a negative effect on erythropoiesis. To the extent that these contribute to the observed anemia, the UA picture becomes that much more complicated.

Thus, UA is both directly and indirectly related to aging. As such, it is most common in the oldest old and virtually not existent in healthy individuals under the age of 50 years. UA is associated with important functional declines, more prominent manifestations of age-associated diseases, and shortened survival. Yet, it remains to be determined whether interventions to improve hemoglobin concentration will be associated with improved function or survival.

Acknowledgments

Supported by the Intramural Research Program, National Institute on Aging, National Institutes of Health.

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Table 1

Prevalence of Anemia and Unexplained Anemia in the Elderly

	Population	% Anemic	% UA*
Joosten et al[55]	Geriatrics inpatient unit	24%	17%
Ania et al[2]	Community	7–9%	16%
Guralnik et al[1]	Community (NHANES III)	11%	33%
Ble et al[57]	Community (InCHIANTI)	10%	37%
Tecson J, IASIA, unpublished data	Community, internal medicine practices	21%	N/A
Artz et al[17,21]	Nursing home (NGRC)	49%	43%

Abbreviations: IASIA, Institute for Advanced Studies in Aging; NGRC, National Geriatrics Research Consortium; N/A, not available.

* Percent of anemic patients who fit UA criteria (see text).

Table 2

Features of Unexplained Anemia

Hemoglobin	10.5–12 g/dL
Reticulocyte index	Low
Mean corpuscular volume (MCV)	80–95 fL
Platelet and white blood cell counts	Normal
Peripheral smear	No dysplastic features
Serum iron	Mildly low or normal
Total iron binding capacity (TIBC)	Normal
% Iron saturation	Mildly low or normal
Serum levels of vitamin B_{12} and folic acid	Normal
Serum level of thyroid-stimulating hormone (TSH)	Normal
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	Normal
Serum erythropoietin level	Not elevated
Creatinine clearance	>30 to <90 mL/min

Table 3

Component Factors of Unexplained Anemia: Aging Versus Disease

	Aging	Disease
Erythropoietin insufficiency	There is an age-associated decline in GFR and presumably a corresponding reduction in erythropoietin response.	Diabetes, hypertension, and chronic inflammation have been associated with reduction in erythropoietin response and anemia.
Cytokine inhibition of erythropoiesis	Certain proinflammatory cytokines, most notably IL-6, are elevated in serum and tissue sections with advancing age.	Inflammatory diseases, including atherosclerosis and cancer, are associated with the presence of increased pro-inflammatory cytokines.
Androgen decline (both males and females)	Androgens support erythropoiesis and declining levels with advancing age.	Certain diseases are associated with decline in testosterone. Furthermore, anti-androgen therapy as treatment for prostate cancer is associated with a drop in hemoglobin of 1 g/dL.
Stem cell function	Hematopoietic stem cells decline in both replicative and proliferative capacity with age.	Certain diseases and/or treatments will inhibit the proliferative capacity of stem cells.
Myelodysplasia		A disease process and NOT a component of normal aging. To the extent that it may present with anemia (without the other features such as neutropenia or thrombocytopenia) it will account for some component of UA.

Table 4

Explaining Unexplained Anemia

Age (yr)	Marrow Reserve	Renal Endocrine (EPO) Function	IL-6	Hepcidin	Iron Utilization	HSC Proliferative Capacity	EPO Level	? Anemia
<70	OK	OK	↑	↑	↓	↓	↑	No
≥70 frailty-resistant	OK	↓	↑	↑	↓	↓	↓	Mild
≥70 frailty-prone	OK	↓↓	↑↑	↑↑	↓↓	↓↓	↓	Moderate
MDS-prone		OK	↑	↑	↓	↓↓↓	↑	Moderate to severe

Abbreviations: EPO, erythropoietin; IL-6, interleukin-6; HSC, hematopoietic stem cell; MDS, myelodysplastic syndrome.