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HEMATOLOGIC DISEASE AT OLDER AGE

Anemia at older age: etiologies, clinical implications, and management

Reinhard Stauder,[1] Peter Valent,[2,3] and Igor Theurl[4]

[1]Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University, Innsbruck, Austria; [2]Division of Hematology & Hemostaseology, Department of Internal Medicine I, and [3]Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Vienna, Austria; and [4]Department of Internal Medicine II (Infectious Diseases, Immunology, Rheumatology, Pneumology), Innsbruck Medical University, Innsbruck, Austria

Anemia is quite frequently diagnosed in older individuals and is a key indicator of various reactive and clonal conditions. Many underlying diseases, like myelodysplastic syndrome (MDS), develop preferentially in elderly individuals. The prevalence of anemia at older age is increasing, and this is mainly attributable to more frequently applied diagnostics and demographic changes in our societies. The etiology of anemia at older age is complex and ranges from bone marrow failure syndromes to chronic kidney disease, and from nutritional deficiencies to inflammatory processes including inflammaging in immunosenescence. In a smaller number of cases, no clear-cut etiology is identified. These patients are referred to as unexplained anemia or idiopathic cytopenia of unknown significance. In others, somatic mutations in leukocytes are found, but diagnostic criteria for MDS or other hematologic diseases are not fulfilled, a condition termed clonal cytopenia of undetermined significance. Management of anemias at older age depends on (1) the severity of the anemia, (2) underlying condition(s), and (3) patient-related factors, including comorbidities. Even a mild anemia may substantially affect physical and cognitive capacities and quality of life. An underestimated aspect is that because of age-related changes, organ function such as erythropoietin production in the kidney may become suboptimal. Management and treatment of anemia in older patients often require a multidisciplinary approach and detailed investigations of organ function. In this article, we review current concepts around anemias at older age, with special emphasis on etiologies, clinical implications, and innovative concepts in the management of these patients. (*Blood*. 2018;131(5):505-514)

Introduction

Anemia is most frequent at older age, reaching a prevalence of ~17% in the cohort of older persons >65 years of age.[1] Improved diagnostics and demographic changes in our societies have resulted in an increase in the incidence and prevalence of anemia in past decades. In fact, many underlying disorders, such as myelodysplastic syndrome (MDS), other blood cell disorders, cancer, chronic kidney disease (CKD), or certain gastrointestinal (GI) diseases develop more frequently at advanced age. In many patients, different etiologies may act together and thereby contribute to the development of anemias at older age.[2,3]

Based on the etiology, anemias can be divided into nutritional deficiency anemias, bleeding anemias, anemias developing in the context of chronic inflammation and in CKD, and clonal anemias. In a small number of cases, however, no etiology is found. These patients may initially be diagnosed as unexplained anemia (UA).[4] However, when applying recent classifications and a thorough workup including bone marrow (BM) studies, these cases are diagnosed as idiopathic cytopenia of unknown significance (ICUS) with isolated anemia (ICUS-A).[5-7] In some cytopenic patients, somatic mutations are detected in blood leukocytes, but diagnostic criteria for MDS or other BM neoplasms are not fulfilled, a condition termed clonal cytopenia of undetermined significance (CCUS).[7,8]

The management of anemias in older individuals is a clinical challenge, especially when the etiology remains uncertain and/or (multiple) comorbidities are present. An underestimated aspect is that because of age-related changes, organ function such as erythropoietin (EPO) production in the kidney or red cell production in the BM may be too low to prevent anemia under certain pathologic conditions. Management and treatment of anemia in older patients usually require a multidisciplinary approach as well as detailed investigations of organ function. In many cases, supplementation therapy or elimination of the underlying etiology can correct the anemia. In other cases, long-term treatment with interventional drugs, continuous therapy with EPO, or transfusions are required to control the anemia. With all these therapies, efficacy and benefit have to be balanced against safety and quality of life (QoL).[9] In this article, we review current concepts surrounding clinical relevance, pathogenesis, and management of anemia in older patients.

Definition of anemia at older age

World Health Organization (WHO) thresholds were established in 1968 in a cohort of persons <65 years old, defining anemia as

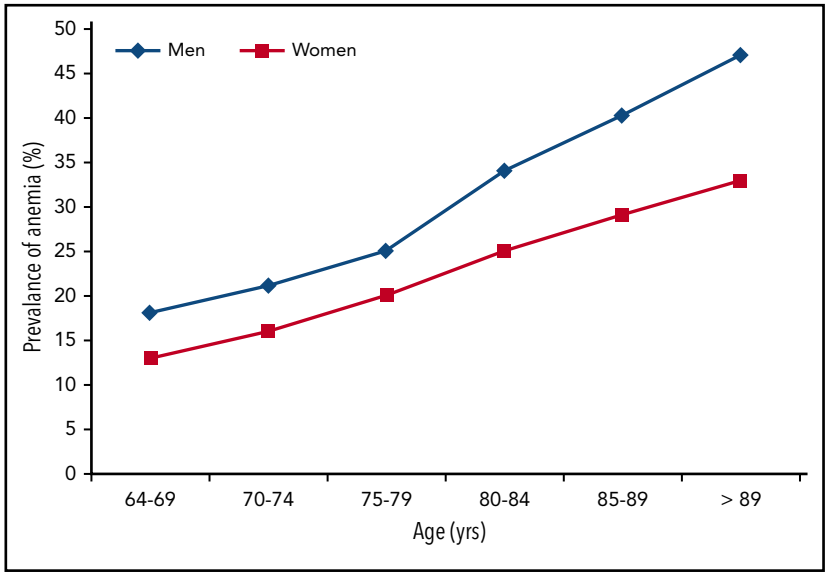

Figure 1. Increase in prevalence of late-life anemia. Increase in prevalence of anemia as defined by WHO (Hb <12 g/dL in women and <13 g/dL in men) with advanced age; cohort of 19 758 university hospital inpatients and outpatients (based on Bach et al[16]).

a hemoglobin (Hb) level of <130 g/L in men and <120 g/L in women.[10] However, Hb levels decline with age and are distinct in different ethnic groups. So far, the WHO definition[10] of anemia has been applied in the majority of studies at older age. Analyses of the American databases National Health and Nutrition Examination Survey (NHANES) III[11] and the Scripps-Kaiser database[12] have suggested higher reference values to define anemia for white men but have in general supported the validity of the WHO thresholds on the prevalence of anemia.[13]

A relevant approach might be to base the definition of anemia on Hb concentrations relevant to clinical outcomes in older persons. In fact, correlations between unfavorable outcome and Hb levels have been demonstrated. For example, "optimal" Hb concentrations of ≥137 g/L for men and ≥126 g/L for women have been described in connection with better survival in the Cardiovascular Health Study (CHS).[14] Similarly, the optimal Hb value to avoid hospitalization and mortality was 130 to 150 g/L for women and 140 to 170 g/L for men.[15]

In summary, the authors believe that the WHO definition should be used in general for the classification of anemia in older persons. However, Hb ranges associated with best possible outcome parameters might be discussed and considered in daily practice and in clinical studies to optimize clinical benefit.

Epidemiology of anemia in senior adults

Anemia in older persons is common and relevant, thus posing new challenges to health care systems worldwide. Large prospective registry studies have revealed an overall prevalence of anemia ranging from 10% to 24% in older individuals.[3] Senior adults admitted to the hospital are more frequently affected by anemia (40%), and the prevalence is even higher (47%) in nursing home residents. Considering the global prevalence of 17%,[1] as many as 15 million older persons may suffer from anemia in the European Union, and the same may hold true for North America. Prevalence increases with age, reaching nearly 50% in men older than 80 years in both hospital inpatients and outpatients (Figure 1).[16] Moreover, the number of anemic patients is likely to increase dramatically in the coming years because of an aging population in Western societies.[2,16,17]

Clinical relevance of anemia at older age

Anemia has been associated with a number of clinically relevant conditions in many epidemiological studies (Table 1).[2] Low Hb levels are a risk factor for cardiovascular diseases,[15] cognitive impairment,[18-20] insomnia,[21] impaired mood,[19,22] and restricted QoL.[23-26] Moreover, anemia is associated with reduced executive function[27] and physical performance.[23,28] Low Hb levels are associated with an increased risk for falls and fractures.[25,26] In addition, the presence of anemia is significantly associated with more frequent hospitalization[29] and longer hospital stays.[15,30] Whereas these studies highlight the relevance of prevalent Hb levels at diagnosis, future analyses should address and consider the clinical impact of the Hb decline and thus the dynamics of anemia development.[24,31]

Importantly, accumulating evidence suggests that anemia is a marker for mortality[14,24,30,32] (Table 1). The essential question is whether anemia per se determines unfavorable outcome or whether anemia is a surrogate marker for underlying processes such as inflammation or CKD. To investigate the complex interplay between anemia and confounding factors, epidemiological studies have been performed.[11,14,19,20,22-24,31] In particular, these studies analyzed a possible association between anemia and mortality, adjusted for confounding factors including markers of inflammation or CKD.[11,14,19,20,22-24,31] In support of the concept of the additive adverse effect of anemia and underlying disorders, the highest mortality has been found for nutritional disorders, chronic renal disease, and chronic inflammation as compared with UA (Table 1).[11] However, epidemiological studies cannot figure out what causal role anemia plays in the restrictions and declines mentioned previously. Moreover, the underlying cause of anemia was not explicitly determined in many studies. Studies have often focused on inflammation and

Table 1. Association between anemia in older adults and adverse clinical outcome based on large prospective studies

Study name	Study population	Reference	Finding/comments
NHANES III Study (National Health & Nutrition Examination Survey)	Noninstitutionalized US population ≥65 y from third NHANES (1988-1994)	11	Significant negative impact of anemia on OS (RR of 1.8; $P < .001$). Differential impact of subtypes of anemia: nutritional (RR of 2.34, $P < .0001$), CKD (1.70, $P < .0001$), chronic inflammation (1.48, $P < .0001$), UA (1.26, $P < .01$).
Health and Anemia Study (Salute e Anemia)	Observational study of all 65- to 84-y-old residents (N = 10 110); Biella, Piedmont, Italy	19	Mild-grade anemia (F: 10.0-11.9 g/dL; M: 10.0-12.9 g/dL) independently associated with poorer cognition, function, mood, and QoL (uni- and multivariate analysis adjusted for comorbidities, age, and sex).
InCHIANTI (Invecchiare in Chianti, "Aging in the Chianti Area")	Population-based study; Tuscany region, Italy	23 22	Anemia is associated with disability, poorer physical performance, and lower muscle strength (even in adjusted analyses including comorbidities, renal function, and inflammatory markers). Anemia is associated with a significantly higher risk of depressive symptoms after adjusting with potential confounders (OR = 1.93; 95% confidence interval [CI], 1.19-3.13).
Leiden 85-Plus Study	Population-based prospective study; Leiden, The Netherlands	24	Prevalent anemia and incident anemia were both associated with an increased mortality, even after adjustment (hazard ratio [HR] for prevalent anemia, 1.41; 95% CI, 1.13-1.76; HR for incident anemia, 2.08; 95% CI, 1.60-2.70).
Health, Aging, and Body Composition Study (Health ABC)	Prospective cohort 3075 community-dwelling white and black older adults 70-79 y from Memphis, Tennessee, or Pittsburgh, Pennsylvania; beginning in 1997	20	Baseline anemia had an increased risk for dementia (23% vs 17%; HR, 1.64; 95% CI, 1.30-2.07) in unadjusted analysis. Remains significant in adjusted analyses (for comorbidities, MCV, renal function, CRP, etc).
Cardiovascular Health Study	Prospective cohort study with 11.2 y of follow-up of 5888 community-dwelling men and women 65 y or older, enrolled in 1989-1990 or 1992-1993 in 4 US communities	14 31	Anemia as per WHO criteria was independently associated with increased mortality. After multivariate adjustment, HR for mortality was 1.33 (95% CI, 1.15-1.54). Hb decline was associated with subsequently poorer cognitive function in men and anemia development with poorer cognitive function in women. Both anemia development (HR, 1.39; 95% CI, 1.15-1.69) and Hb decline (HR, 1.11; 95% CI, 1.04-1.18 per 1 g/dL decrease) predicted subsequent mortality.

CRP, C-reactive protein; F, female; M, male; MCV, mean corpuscular volume; OR, odds ratio; OS, overall survival; RR, relative risk.

on CKD but might have missed other confounding factors (Table 1).

In summary, even mild anemia is a relevant prognostic parameter. Moreover, in most cases anemia is considered to be a surrogate marker for underlying overt or subclinical diseases. Therefore, anemia in older individuals should definitely be taken seriously and worked up.

Pathogenesis and basic mechanisms of anemia at older age

A wide range of causes and underlying diseases are known to result in anemia at older age (Table 2; Figure 2). In a given disease, often >1 factor may contribute to the development of anemia. Based on pathophysiological concepts, underlying diseases may be divided into the following 3 groups.

Anemias based on iron, folate, and/or vitamin B_{12} deficiency

Lack of iron is by far the most frequent nutritional deficiency anemia. Similar to folate deficiency, iron depletion is often associated with malnutrition. Age-dependent alterations in function of GI tract, polypharmacy, and social isolation may lead to malnutrition and subsequent anemia.[33] However, in our clinical routine we experienced several times how important it is to consider that bleeding because of a variety of medications (eg, acetylsalicylic acid, standard or direct oral anticoagulants) or GI diseases, including cancer, is the most frequent cause of iron-deficient anemia in older patients. Thus, apart from iron replacement therapy, a careful GI diagnostic workup is mandatory to define a possible site of blood loss in these patients.[34]

Malnutrition, particularly in association with alcohol abuse, may result in folate deficiency. In addition, drugs like anticonvulsants and methotrexate are further causes. Pernicious anemia, the classic vitamin B_{12}-deficient anemia, is relatively rare based on data from the literature and our clinical experience. By contrast, *Helicobacter pylori* infections, acid-reducing agents, or atrophic gastritis may cause hypochlorhydria, more frequently leading to a food-cobalamin malabsorption syndrome.[35]

Importantly, for these subtypes of anemia effective medication is available. For example, in vitamin B_{12} deficiency anemia, neurologic symptoms are often detected and usually resolve immediately on initiation of vitamin B_{12} supplementation.

Thus, early and correct diagnosis is essential. Therefore, we always include folate and vitamin B_{12} measurement in our basic laboratory screening in elderly anemic patients.

Anemias developing in the context of chronic inflammation and in CKD

At least one-third of anemic patients older than 65 years show a hyperinflammatory state typical for CKD or for AI (cancer, autoimmune disease, and chronic infection). Underlying pathophysiological mechanisms in AI are manifold, are overlapping, and show differences in extent between patients.

Table 2. Diseases frequently associated with anemia in the elderly

Category and subtypes	Specific examples
Chronic inflammatory diseases	
Rheumatologic diseases	Rheumatoid arthritis, polymyalgia rheumatica
Chronic infectious diseases	Chronic hepatitis, osteomyelitis
Inflammaging	Frailty, cachexia, geriatric syndromes
Miscellaneous	Chronic leg ulcers
Nonhematopoietic neoplasms	
Gastrointestinal tumors	Colorectal cancer, gastric cancer, etc
Multiorgan metastasis	End-stage carcinomas
BM metastasis	Various cancer types including breast and prostate
Endocrinologic and metabolic causes	
Low production of EPO	Renal anemia or pure EPO deficiency*
Thyroid dysfunction	Hypothyroidism or hyperthyroidism
Insulin deficiency	Diabetes mellitus
Blood loss	
Gastrointestinal tract bleeding	Peptic ulcer, ulcerative colitis, etc
Diffuse GI tract bleeding	Anticoagulant-mediated bleeding
Surgical procedures	Multiple abdominal surgeries
Different locations	Epistaxis, hematuria
Increased consumption or destruction of erythrocytes	
Chronic nonmechanical hemolysis	Autoimmune hemolytic anemia
Mechanical destruction of red cells	Heart valve–mediated red cell lysis
Hypersplenism	Hepato-/splenomegaly
Lack of nutrients	
Vitamin deficiency	Vitamin B_{12} and/or folate deficiency
Trace element deficiency	Copper deficiency†
Iron deficiency	Blood loss
Drug-induced anemia	
Chemotherapy	Chemotherapy-induced pancytopenia
Antimetabolites, anticonvulsants	Folate deficiency
Toxic drug reactions	Drug-induced hemolysis

Typical and more common causes of anemia in the elderly are listed. Many more underlying disorders may be identified. In addition, in many elderly individuals, >1 disease is present and may substantially aggravate the anemia.

*Insufficiently low EPO production in response to anemia is typically seen in patients with CKD but is sometimes also seen in elderly patients without impaired excretory renal function. This pure form of impaired EPO production is typically seen in elderly patients with mild anemia and may be an underestimated cause of anemia at older age or ICUS-A.

†Copper deficiency may be associated with marked BM dysplasia and may even mimic MDS.

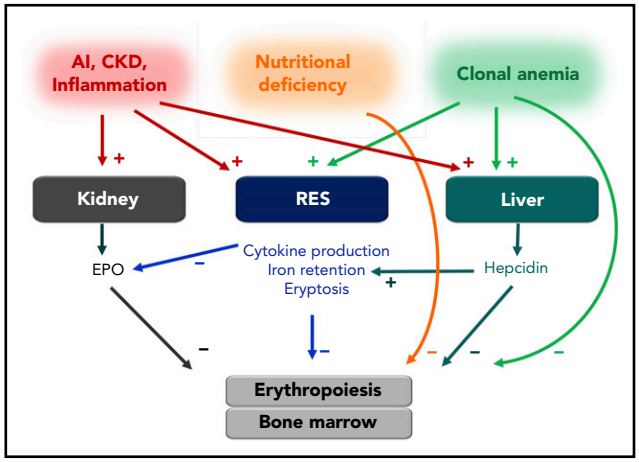

Figure 2. Possible mechanisms of anemia in older adults. A hyperinflammatory state is typical in anemia of inflammation (AI), CKD, and inflammaging. This state is characterized by increased hepcidin production in the liver, resulting in a direct negative impact on erythropoiesis and increased iron retention in the reticuloendothelial system (RES). Moreover, production of EPO is insufficient in response to anemia, and EPO response in the erythropoiesis is blunted. A further hallmark in the pathogenesis of AI is the increased phagocytosis of aging erythrocytes (eryptosis). Clonal disorders in leukocytes increase the risk of developing cardiovascular complications and anemia. This association may be caused by the promotion of inflammatory processes. Plus signs symbolize stimulation, and minus signs inhibition.

First, reduced EPO production that is too low to counteract anemia and a blunted response of erythroid progenitors to EPO represent essential underlying mechanisms.[36]

A direct negative effect of different cytokines, like tumor necrosis factor α, interleukin-1 (IL-1), and transforming growth factor β, on proliferation and differentiation of erythroid progenitor cells has also been reported[37] and is at least partly because of a down-regulation of EPO receptor expression on erythroid progenitors. In addition, these cytokines promote myelopoiesis with the overall net effect of reduced erythropoiesis.[38] Alterations in energy metabolism and body composition have also been reported to potentially regulate erythropoiesis in the elderly.[39]

Second, an essential mechanism driving the development of AI is an increased uptake and retention of iron (in the form of senescent/damaged erythrocytes) within the reticuloendothelial system leading to an iron-restricted erythropoiesis.[40]

Hepcidin, a mainly liver-derived antimicrobial acute phase protein, reduces both duodenal iron absorption and iron release from macrophages.[41] These effects can be explained by the interaction of hepcidin and the transmembrane protein ferroportin, the only so far known iron exporter in mammalians.[42] In macrophages, which have a general turnover of ~20 to 25 mg of iron per day as a result of being recycled from senescent red blood cells (RBCs), this produces iron restriction with an accompanying increase in ferritin levels and decrease in transferrin saturation (TSAT), resulting in a relative iron-deficient erythropoiesis.

Increased hepcidin levels have been reported in cancer patients and patients suffering from autoimmune disease and CKD.[43] Remarkably, elevated hepcidin levels have also been reported in older patients, with an age-related increase.[44] As hepcidin seems to be the central player in iron metabolism, several mechanisms are involved in tightly controlling hepcidin. Hepcidin expression is upregulated by inflammatory cytokines like IL-6 and different bone morphogenic proteins (BMPs), mainly BMP6 and BMP2.[45] Moreover, endoplasmic reticulum stress[46] and reactive oxygen species (ROS),[47] as well as reduced levels of estrogen and testosterone,[48,49] seem to directly increase hepcidin expression. This helps in understanding why endocrine changes at menopause or andropause result not only in a constitutively increased presence of inflammatory mediators,[50] but also in increased hepcidin levels.[48,49]

Third, eryptosis, the phagocytosis of aging erythrocytes triggered by changes in their plasma membrane, is often discussed as a further hallmark in the development of AI. Recycling of aged and/or damaged RBCs occurs under physiological conditions mainly in the spleen. It is well known that in distinct situations including inflammation, RBC numbers and Hb levels drop much faster than can be explained by a pure reduction in RBC production and Hb synthesis. In fact, translocation of phosphatidylserine to the membrane surface is a first step in this process.[51] It enables macrophages to engulf erythrocytes and ultimately eliminate them from circulation. Lupescu et al showed that ROS production leads to a much higher frequency of phosphatidylserine-presenting erythrocytes in older than in younger patients.[52] Other reports have shown that disorders that are quite common at advanced age, including dehydration, diabetes mellitus, or chronic heart disease, might also affect RBC stability.[53]

In addition, the concept of a proinflammatory state or "inflammaging," offers a potential model to explain the high prevalence of anemia and age-associated disorders including sarcopenia, asthenia, weight loss, and frailty. The term inflammaging was first used in 2000 by Franceschi et al[54] to describe a low-grade proinflammatory state associated with the aging process and immunosenescence. This condition is characterized by an age-associated chronic upregulation of the inflammatory immune response with increased levels of proinflammatory cytokines like IL-1, IL-6, and tumor necrosis factor.[55-57] In addition, activation of NF-κB signaling has been reported in older patients.[58] It is known and well described that a reduction in autophagy, as found in senior persons, leads to NF-κB activation, which in turn is known to be a potent inducer of NLRP3 inflammasome activation. The same holds true for ROS.[59] Thus, both pathways seem to activate the inflammasome response.

However, whether this state of chronic proinflammation reflects a primary age-related immune response or a systemic response to an unrecognized comorbid condition is not clear. More recent data suggest that age-related clonal hematopoiesis of indeterminate potential (CHIP) mutations in macrophages may lead to proinflammatory responses.[60] It would be plausible that mildly elevated IL-6 levels caused by age alone, body composition change, or smoldering inflammatory disease result in inhibition of EPO production and/or activation of hepcidin, both of which cause anemia.[55,56] Yet, one of the biggest limitations of this concept is the lack of methods that can be used to determine the suggested subclinical and often local inflammation in a clinical setting.

In fact, the cause of anemia for a relatively large proportion of UAs remains obscure, despite extended hematologic evaluation.[61]

Table 3. Classification of UA, ICUS-A, and pre-MDS conditions

Condition	UA	ICUS-A	CCUS	IDUS	CHIP	MDS	
						Low risk	High risk
Cytopenia*	+	+	+	−	−	+	+
Dysplasia	nd	−	−	+	−	+	+
BM blasts, %	nd	<5%	<5%	<5%	<5%	<5%	>20%
Cytogenetic abnormalities	nd	−/+	−	−/+	+/−	+	++
Molecular aberrations	nd	−	+	−	+	+	+++
Comment	Workup needed	Cytopenic patients		Noncytopenic patients		Classification of MDS is based on WHO definition	

"Unexplained anemia" (UA) is the term used in the literature so far. In these patients, a thorough workup including BM and molecular analyses is recommended. These investigations will enable classification of the diagnosis ICUS-A, CCUS, or MDS or will help exclude other malignant hematologic disorders. Based on Valent et al.[7]

IDUS, idiopathic dysplasia of undetermined significance; nd, not detected or not done.

*The definition of anemia in cytopenia is based on WHO criteria: Hb <130 g/L in men and Hb <120 g/L in women.[10]

Namely, iron deficiency (ID), borderline CKD, and low-grade local inflammation may go unrecognized in a number of patients because of inappropriate cutoff levels or technical limits of laboratory tests.

UAs and clonal anemias

Clonal leukocytes are detectable in a considerable proportion of older individuals. Such clonal hematopoiesis is associated with increased mortality and an augmented prevalence of hematologic malignancies, such as MDS. Remarkably, numbers of somatic mutations in blood leukocytes increase with age.[8,60,62,63] In otherwise healthy individuals without cytopenia, this condition is termed CHIP.[8] However, as soon as mild anemia develops, the diagnosis changes to CCUS[8] or to overt MDS when criteria for MDS are fulfilled.[7] Indeed, the clinical features and the course of CCUS patients and MDS patients are quite similar. In addition, most CCUS patients may progress to overt MDS over time. However, CHIP and CCUS patients may also develop another hematologic neoplasm, such as acute myeloid leukemia. Based on the obvious clinical implications, we recommend that leukocytes be screened for the presence of somatic mutations in all patients with unexplained cytopenia. In addition, BM cells should be examined for the presence of cytogenetic abnormalities and flow cytometric abnormalities (Table 3).

Cytopenic patients lacking molecular aberrations and not fulfilling the criteria of MDS or of any other underlying disease (causing cytopenia) are termed ICUS. ICUS presenting with anemia is termed ICUS-A.[7] As ICUS-A is often detected in older individuals,[6,64,65] it has been hypothesized that ICUS-A may be regarded as the classical prototype of an "anemia at older age."[5]

As outlined previously, a clue to the etiology of ICUS-A may be the observation that endogenous EPO levels are often quite low, suggesting insufficient EPO production in response to anemia.[5] Because low EPO production is found in ICUS-A independent of the excretory kidney function, one hypothesis is that an endocrine defect in EPO production because of an aged kidney or a decrease in testosterone or estrogen synthesis in elderly individuals is causative in the development of ICUS-A.[5,66] In this regard, it is also noteworthy that such a decrease in EPO production may also be found in MDS patients, namely, those who respond to treatment with recombinant EPO.[67,68] In other words, individuals with CHIP or IDUS may convert to overt MDS as soon as they also develop ICUS-A during aging. This concept is supported by the Nordic score that predicts responsiveness to EPO therapy in those MDS patients who have an inadequately low EPO level.[67] Whether these EPO thresholds might be applied in other subgroups of anemia remains to be determined. A remaining question is whether true cases of ICUS-A with adequate EPO production really exist. An interesting point worth noting is that the age-related decrease in EPO production can contribute to the manifestation of an overt neoplasm, namely, MDS from a preexisting CHIP or IDUS.[65,69]

Diagnostic aspects

Primary laboratory evaluation in older anemic patients should include basic parameters including Hb, differential blood count, MCV, mean corpuscular hemoglobin, reticulocyte count, ferritin, reticulocyte Hb, TSAT, EPO level, CRP, fibrinogen, creatinine/glomerular filtration rate, vitamin B_{12}, serum folate, copper, thyrotropin, lactate dehydrogenase, haptoglobin, alanine aminotransferase/aspartate aminotransferase, and serum electrophoresis. In quite a number of cases, this profile will help identify and classify nutritional deficiency including iron-deficient anemia, AI, and CKD. Depending on the clinical evaluation, more detailed investigations may be needed including gastro- and colonoscopy and ultrasound of the abdomen and kidney. BM aspiration and biopsy are mandatory to exclude hematologic disorders including MDS and to make an appropriate diagnosis, especially when additional blood count abnormalities or other signs of a clonal hematologic disease are found.

These diagnostic procedures including BM evaluation should, however, be discussed in light of the burden of the procedure and weighed against the possible therapeutic consequences of the suspected diagnosis as well as life expectancy and burden of anemia. The authors feel the patient should have a life expectancy of minimum 3 months in order to justify BM aspiration in an anemic elderly patient.

Table 4. New targeted drugs that may counteract anemia in older patients

Drug	Lexaptepid-pegol NOX-94H	PRS-080	RO62	CSJ137	H5F9-AM8
Target	Hepcidin	Hepcidin	BMP6	BMP6?	HJV (RGMc)
Modality	PEGylated Spiegelmer	Anticalin scaffold	Engineered heparins	IgG1	Unclear
Mechanism	Hepcidin binding	Hepcidin binding	BMP6 binding	BMP6 binding (?)	Unclear
Indications	MM, CKD, cancer	CKD	Unknown	Functional iron deficiency by CKD	CKD likely
Phase	Phase 2	Phase 1	Discovery	Phase 1/2	Phase 1 (?)
Company	Noxxon	Pieris	Glycolsplit heparins	Novartis	AbbVie

IgG1, immunoglobulin G1; MM, multiple myeloma; PEG, polyethylene glycol.

In those with unclear results molecular, cytogenetic, and/or flow cytometry studies may help reach the conclusion that the patient is suffering from a clonal BM disorder such as MDS. In such studies, detection of clonality of myeloid cells may cause a change in the diagnosis, for example from ICUS to CCUS or even to MDS.[7]

There are a number of other complex conditions and pitfalls that may pose diagnostic problems in elderly patients, especially those who suffer from comorbidities. For example, it may be difficult to assess the extent of iron deficiency in patients suffering from inflammatory bowel disease and pronounced inflammatory bowel disease–related inflammation. In these cases, soluble transferrin receptor (sTfR), the sTfR/log ferritin index, and serum hepcidin may assist in estimating the degree of iron deficiency. An index above a certain cutoff level indicates the presence of a true iron deficiency that may be overseen in an inflammatory state when using ferritin and TSAT levels only.[41] Specific cutoff levels have been published. A ratio of <1 suggests AI, whereas a ratio of >2 suggests absolute iron deficiency coexisting with AI.[41] Yet, it is important to understand that sTfR assays are not standardized, and therefore, a cutoff level for the sTfR/log ferritin index has to be established by each laboratory individually, depending on the sTfR assay.[70]

Other parameters like reticulocyte Hb content and percentage of hypochromic erythrocytes have proved to be informative to predict the response rate to iron therapy in CKD patients.[71,72]

Therapeutic options

Before establishing a treatment plan, the primary diagnosis and accompanying diseases with emphasis on treatable disorders should be properly defined. As mentioned before, often several causes contribute to anemia in the elderly. Then, optimal age-adjusted therapy is introduced, with recognition of potential side effects and impact on QoL. Even a weekly referral (transport burden) for injections may already interfere with QoL in frail patients. Whenever possible, the primary goal is to treat and thus eliminate the underlying disease and thereby the etiology of anemia.

In most patients suffering from true ID, oral iron substitution seems to be sufficient.[73] Moreover, in recent years new oral iron formulations like ferric maltol[74] and Sucrosomial Iron[75] showing higher efficacy and fewer side effects have been approved, thus further reducing the need for intravenous iron. Yet, sometimes oral application in the elderly is not effective because of reduced uptake in the GI tract, impaired compliance, and/or an inflammatory state leading to decreased iron utilization.[76,77]

In this situation, when oral iron does not ameliorate anemia, IV iron therapy may be a valuable alternative. Actually, a number of IV iron formulations are available including iron sucrose, ferric gluconate, and ferumoxytol. In recent years, new and safer formulations have been approved with mainly ferric carboxymaltose and iron isomaltoside being prescribed. Still, especially ferric carboxymaltose, but also to some extent iron isomaltoside, may rarely lead to severe hypophosphatemia with subsequent osteomalacia and bone fractures,[78] especially when high doses are needed in patients with severe ID and relatively normal kidney function. This is of special concern in elderly patients already presenting with metabolic bone diseases. Therefore, we are of the opinion that IV iron supplementation should be recommended when oral iron preparations are not tolerated, in patients nonadherent to oral iron substitution, in case of ongoing blood loss, or if iron uptake in the GI tract is insufficient.

Erythropoiesis-stimulating agents (ESAs) are so far registered for the treatment of anemia in CKD and in European Union countries in patients with MDS. Data on application of ESAs in other subtypes of anemia are limited. Nevertheless, 1 study suggested that EPO may be beneficial in a patient cohort of age 65 and older African American women with no obvious explanation for the existing anemia.[79] In that study, ESAs significantly increased Hb levels and also patients' QoL. Yet, considering studies reporting a reduced EPO response in a large portion of UA patients, larger studies are definitely needed to support the idea of ESA therapy in UA patients.[80] In general, the risk for thromboembolic complications increases at higher Hb levels, so that the current recommendation is to maintain Hb levels between 9 and 11.5 g/dL.

Blood transfusions are the first and most effective option for the treatment of elderly patients with severe, symptomatic anemia.

Although no specific cutoff level is available for Hb, elderly anemic patients should always be transfused with recognition of

comorbidities and an adequate oxygen supply that needs to be maintained. Transfusion numbers and frequency in the individual patient have to be based on many different factors and the overall situation in each case. In those with severe cardiovascular disorders, blood should be transfused more slowly and on a unit-by-unit basis, and Hb levels should be kept above 9 or even 10 g/dL in these patients.[81]

Thanks to a better understanding of mechanisms regulating erythropoiesis, new drugs are currently being developed such as hepcidin inhibitors (Table 4). Currently, these drugs are mainly developed for anemia in CKD and cancer patients. However, they may be a future therapeutic approach for a defined group of elderly patients. Another group of agents are the hypoxia inducible factor (HIF)–prolyl hydroxylase inhibitors. Especially older patients with low endogenous EPO levels may benefit from these drugs. Yet, persons at advanced age may be more vulnerable to HIF stabilization. Finally, activin type II receptor agonists are currently being investigated in patients with MDS and CKD and might present a future option for the treatment of anemia at advanced age. As sufficient clinical data are not yet available, these drugs still await final approval.

Concluding remarks and future perspectives

Anemia in older persons poses a clinical challenge in daily practice as the population ages. In many cases, 1 or more etiologies are detected, and a thorough investigation immediately leads to the correct diagnosis. In these patients, management is largely dependent on the underlying etiology, and in many cases, anemia can be corrected by interventional therapy independent of age. Good examples are iron, vitamin B_{12}, or folate deficiency. EPO deficiency with or without overt exocrine kidney insufficiency can be detected quite often in older persons. A large number of patients turn out to have an underlying (chronic) inflammatory disease. The concept of a subclinical proinflammatory state called inflammaging may be a good explanation for the development of anemia in senior persons. In other cases, a clonal myeloid or other neoplasm is detected. In a relevant proportion of patients, no underlying cause of anemia is found after a first examination, resulting in the provisional diagnosis of UA. However, in many cases no underlying etiology is found even after a thorough diagnostic workup that includes an examination of all organ systems including the BM and also cytogenetic and molecular studies. These patients may have a pre-MDS condition and are often diagnosed as ICUS-A or CCUS.

The definition of the underlying mechanisms of anemia at older age will form the basis for individualized treatment algorithms including iron supplementation, application of ESAs, and promising new drugs directed at regulation of hepcidin or HIF.

Acknowledgments

The manuscript was edited by Mary Heaney Margreiter, native-speaker translator/interpreter/editor. In addition, Bojana Borjan edited the references, and Karin Koinig edited the tables and designed Figure 2.

This work was supported by Verein Senioren-Krebshilfe (R.S.) and Horizon 2020 research and innovation program (grant 634789), MDS-RIGHT, within Personalising Health and Care program PHC-2014-634789 (R.S.). Additionally, this work was supported by Translational Implementation of Genetic Evidence in the Management of MDS (TRIAGE-MDS, Austrian Science Found I 1576) within the TRANSCAN–Primary and secondary prevention of cancer call (ERA Net) (R.S.) and by the Austrian Science Fund (SFB grant F4704-B20 [P.V.] and project P 28302-B30 [I.T.]).

Authorship

Contribution: R.S., P.V., and I.T. were responsible for conception and design, manuscript writing, and final approval of the manuscript.

Conflict-of-interest disclosure: R.S. received research funding and honoraria from Celgene, Teva, and Novartis. P.V. received honoraria from Celgene, Teva, and Novartis. I.T. received research funding and honoraria from Gilead, Novartis, and Kymab.

Correspondence: Reinhard Stauder, Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University, Anichstr 35, 6020 Innsbruck, Austria; e-mail: reinhard.stauder@i-med.ac.at.

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Submitted 6 July 2017; accepted 5 October 2017. Prepublished online as *Blood* First Edition paper, 15 November 2017; DOI 10.1182/blood-2017-07-746446.

REFERENCES

1. Gaskell H, Derry S, Andrew Moore R, McQuay HJ. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr*. 2008;8:1.
2. Merchant AA, Roy CN. Not so benign haematology: anaemia of the elderly. *Br J Haematol*. 2012;156(2):173-185.
3. Stauder R, Thein SL. Anemia in the elderly: clinical implications and new therapeutic concepts. *Haematologica*. 2014;99(7):1127-1130.
4. Artz AS, Thirman MJ. Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. *J Gerontol A Biol Sci Med Sci*. 2011;66A(8):925-932.
5. Valent P. Anaemia of the elderly (AOE): does it exist and does it matter in clinical practice? *Eur J Clin Invest*. 2008;38(10):782-783.
6. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference. *Leuk Res*. 2007;31(6):727-736.
7. Valent P, Orazi A, Steensma DP, et al. Proposed minimal diagnostic criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. *Oncotarget*. 2017;8(43):73483-73500.
8. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood*. 2015;126(1):9-16.
9. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. *Am J Hematol*. 2014;89(1):88-96.
10. Blanc B, Finch CA, Hallberg L, et al. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
11. Shavelle RM, MacKenzie R, Paculdo DR. Anemia and mortality in older persons: does the type of anemia affect survival? *Int J Hematol*. 2012;95(3):248-256.
12. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747-1750.
13. Steensma DP, Tefferi A. Anemia in the elderly: how should we define it, when does it matter, and what can be done? *Mayo Clin Proc*. 2007;82(8):958-966.
14. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch Intern Med*. 2005;165(19):2214-2220.

15. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107(10):3841-3846.

16. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. *Clin Interv Aging*. 2014;9:1187-1196.

17. Tettamanti M, Lucca U, Gandini F, et al. Prevalence, incidence and types of mild anemia in the elderly: the "Health and Anemia" population-based study. *Haematologica*. 2010;95(11):1849-1856.

18. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *Am J Med*. 2006;119(4):327-334.

19. Lucca U, Tettamanti M, Mosconi P, et al. Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: the "Health and Anemia" study. *PLoS One*. 2008;3(4):e1920.

20. Hong CH, Falvey C, Harris TB, et al. Anemia and risk of dementia in older adults: findings from the Health ABC study [published correction appears in *Neurology*. 2013;81(10):939]. *Neurology*. 2013;81(6):528-533.

21. Chen-Edinboro LP, Murray-Kolb LE, Simonsick EM, et al. Association between non-iron-deficient anemia and insomnia symptoms in community-dwelling older adults: the Baltimore Longitudinal Study of Aging [published online ahead of print 20 January 2017]. *J Gerontol A Biol Sci Med Sci*. doi:10.1093/gerona/glw332.

22. Onder G, Penninx BW, Cesari M, et al. Anemia is associated with depression in older adults: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2005;60(9):1168-1172.

23. Penninx BW, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc*. 2004;52(5):719-724.

24. den Elzen WP, Willems JM, Westendorp RG, de Craen AJ, Assendelft WJ, Gussekloo J. Effect of anemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. *CMAJ*. 2009;181(3-4):151-157.

25. Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. *Am J Med*. 2004;116(7, suppl 1):3-10.

26. Balducci L. Anemia, fatigue and aging. *Transfus Clin Biol*. 2010;17(5-6):375-381.

27. Chaves PH, Semba RD, Leng SX, et al. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci*. 2005;60(6):729-735.

28. Chaves PH, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? *J Am Geriatr Soc*. 2002;50(7):1257-1264.

29. Riva E, Tettamanti M, Mosconi P, et al. Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. *Haematologica*. 2009;94(1):22-28.

30. Penninx BW, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci*. 2006;61(5):474-479.

31. Zakai NA, French B, Arnold AM, et al. Hemoglobin decline, function, and mortality in the elderly: the Cardiovascular Health Study. *Am J Hematol*. 2013;88(1):5-9.

32. Patel KV, Longo DL, Ershler WB, et al. Haemoglobin concentration and the risk of death in older adults: differences by race/ethnicity in the NHANES III follow-up. *Br J Haematol*. 2009;145(4):514-523.

33. Ahmed T, Haboubi N. Assessment and management of nutrition in older people and its importance to health. *Clin Interv Aging*. 2010;5:207-216.

34. Gordon SR, Smith RE, Power GC. The role of endoscopy in the evaluation of iron deficiency anemia in patients over the age of 50. *Am J Gastroenterol*. 1994;89(11):1963-1967.

35. Loikas S, Koskinen P, Irjala K, et al. Vitamin B12 deficiency in the aged: a population-based study. *Age Ageing*. 2007;36(2):177-183.

36. Means RT Jr, Krantz SB. Inhibition of human erythroid colony-forming units by gamma interferon can be corrected by recombinant human erythropoietin. *Blood*. 1991;78(10):2564-2567.

37. Wang CQ, Udupa KB, Lipschitz DA. Interferon-gamma exerts its negative regulatory effect primarily on the earliest stages of murine erythroid progenitor cell development. *J Cell Physiol*. 1995;162(1):134-138.

38. Gomes AC, Gomes MS. Hematopoietic niches, erythropoiesis and anemia of chronic infection. *Exp Hematol*. 2016;44(2):85-91.

39. Takeda A, Toda T, Shinohara S, Mogi Y, Matsui N. Factors contributing to higher hematocrit levels in hemodialysis patients not receiving recombinant human erythropoietin. *Am J Kidney Dis*. 2002;40(1):104-109.

40. Theurl I, Aigner E, Theurl M, et al. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. *Blood*. 2009;113(21):5277-5286.

41. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352(10):1011-1023.

42. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004;306(5704):2090-2093.

43. Nemeth E, Ganz T. Anemia of inflammation. *Hematol Oncol Clin North Am*. 2014;28(4):671-681.

44. den Elzen WP, de Craen AJ, Wiegerinck ET, Westendorp RG, Swinkels DW, Gussekloo J. Plasma hepcidin levels and anemia in old age. The Leiden 85-Plus Study. *Haematologica*. 2013;98(3):448-454.

45. Verga Falzacappa MV, Vujic Spasic M, Kessler R, Stolte J, Hentze MW, Muckenthaler MU. STAT3 mediates hepatic hepcidin expression and its inflammatory stimulation. *Blood*. 2007;109(1):353-358.

46. Vecchi C, Montosi G, Zhang K, et al. ER stress controls iron metabolism through induction of hepcidin. *Science*. 2009;325(5942):877-880.

47. Choi SO, Cho YS, Kim HL, Park JW. ROS mediate the hypoxic repression of the hepcidin gene by inhibiting C/EBPalpha and STAT-3. *Biochem Biophys Res Commun*. 2007;356(1):312-317.

48. Bachman E, Feng R, Travison T, et al. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. *J Clin Endocrinol Metab*. 2010;95(10):4743-4747.

49. Hou Y, Zhang S, Wang L, et al. Estrogen regulates iron homeostasis through governing hepatic hepcidin expression via an estrogen response element. *Gene*. 2012;511(2):398-403.

50. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med*. 2000;51:245-270.

51. Theurl I, Hilgendorf I, Nairz M, et al. On-demand erythrocyte disposal and iron recycling requires transient macrophages in the liver. *Nat Med*. 2016;22(8):945-951.

52. Lupescu A, Bissinger R, Goebel T, et al. Enhanced suicidal erythrocyte death contributing to anemia in the elderly. *Cell Physiol Biochem*. 2015;36(2):773-783.

53. Pretorius E, du Plooy JN, Bester J. A comprehensive review on eryptosis. *Cell Physiol Biochem*. 2016;39(5):1977-2000.

54. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244-254.

55. Baylis D, Bartlett DB, Patel HP, Roberts HC. Understanding how we age: insights into inflammaging. *Longev Healthspan*. 2013;2:8.

56. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc*. 2002;50(7):1268-1271.

57. Bloomer SA, Kregel KC, Brown KE. Heat stress stimulates hepcidin mRNA expression and C/EBPα protein expression in aged rodent liver. *Arch Gerontol Geriatr*. 2014;58(1):145-152.

58. Salminen A, Huuskonen J, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T. Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. *Ageing Res Rev*. 2008;7(2):83-105.

59. Gross O, Thomas CJ, Guarda G, Tschopp J. The inflammasome: an integrated view. *Immunol Rev*. 2011;243(1):136-151.

60. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science*. 2017;355(6327):842-847.

61. Artz AS, Xue QL, Wickrema A, et al. Unexplained anaemia in the elderly is characterised by features of low grade inflammation. *Br J Haematol*. 2014;167(2):286-289.

62. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. *Nat Genet*. 2012;44(11):1179-1181.

63. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498.

64. Wimazal F, Fonatsch C, Thalhammer R, et al. Idiopathic cytopenia of undetermined significance (ICUS) versus low risk MDS: the diagnostic interface. *Leuk Res*. 2007;31(11):1461-1468.

65. Valent P, Bain BJ, Bennett JM, et al. Idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of uncertain significance (IDUS), and their distinction from low risk MDS. *Leuk Res*. 2012;36(1):1-5.

66. Valent P. Low erythropoietin production as non-oncogenic co-factor contributing to disease-manifestation in low-risk MDS: a hypothesis supported by unique case reports. *Leuk Res*. 2008;32(9):1333-1337.

67. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, et al; Scandinavian MDS Group. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol*. 2003;120(6):1037-1046.

68. Valent P. Low blood counts: immune mediated, idiopathic, or myelodysplasia. *Hematology Am Soc Hematol Educ Program*. 2012;2012:485-491.

69. Valent P, Jäger E, Mitterbauer-Hohendanner G, et al. Idiopathic bone marrow dysplasia of unknown significance (IDUS): definition, pathogenesis, follow up, and prognosis. *Am J Cancer Res*. 2011;1(4):531-541.

70. Punnonen K, Irjala K, Rajamäki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. *Blood*. 1997;89(3):1052-1057.

71. Fishbane S, Galgano C, Langley RC Jr, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int*. 1997;52(1):217-222.

72. Mittman N, Sreedhara R, Mushnick R, et al. Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. *Am J Kidney Dis*. 1997;30(6):912-922.

73. Tay HS, Soiza RL. Systematic review and meta-analysis: what is the evidence for oral iron supplementation in treating anaemia in elderly people? *Drugs Aging*. 2015;32(2):149-158.

74. Gasche C, Ahmad T, Tulassay Z, et al; AEGIS Study Group. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis*. 2015;21(3):579-588.

75. Tarantino G, Brilli E, Zambito Y, Giordano G, Equitani F. Sucrosomial Iron®: a new highly bioavailable oral iron supplement [abstract]. *Blood*. 2015;126(23). Abstract 4561.

76. Silay K, Akinci S, Yalcin A, et al. The status of iron absorption in older patients with iron deficiency anemia. *Eur Rev Med Pharmacol Sci*. 2015;19(17):3142-3145.

77. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(suppl 1):S4-S9.

78. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens*. 2017;26(4):266-275.

79. Agnihotri P, Telfer M, Butt Z, et al. Chronic anemia and fatigue in elderly patients: results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. *J Am Geriatr Soc*. 2007;55(10):1557-1565.

80. Ferrucci L, Guralnik JM, Bandinelli S, et al. Unexplained anaemia in older persons is characterised by low erythropoietin and low levels of pro-inflammatory markers. *Br J Haematol*. 2007;136(6):849-855.

81. ABIM Foundation. Choosing Wisely: lists—American Society of Hematology. http://www.choosingwisely.org/clinician-lists/american-society-hematology-red-blood-cell-transfusions-for-anemia/. Accessed 22 September 2017.