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Anemia in the elderly: clinical implications and new therapeutic concepts

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Anemia in the elderly (defined as people aged > 65 years) is common and increasing as the population ages. In older patients, anemia of any degree contributes significantly to morbidity and mortality and has a significant effect on the quality of life. Despite its clinical importance, anemia in the elderly is under-recognized and evidence-based guidelines on its management are lacking.

Part of the problem here relates to its definition, which is based on WHO-criteria established in 1968.[1] The WHO definition of anemia is hemoglobin (Hb) less than 130 g/L in men, Hb less than 120 g/L in non-pregnant women, and less than 110 g/L in pregnant women. Hemoglobin levels decline with age, and there has been a debate as to whether these values are applicable to older people, although there is no accepted alternative definition of anemia in this age group. Most clinicians, however, accept this definition and are of the opinion that the normal hemoglobin range should not be lowered for older people because of its association with morbidity, mortality and hospitalization. The challenge of defining a normal hemoglobin range lies in part in finding a cohort of 'healthy' elderly subjects confounded by the high prevalence of comorbidities and impairments in parallel with advancing age. In the analysis of Cheng *et al.*,[2] an important proportion (60%) of the older adults were excluded due to frequent diseases including obesity, arterial hypertension, diabetes, recent treatment for anemia, or recent surgery or hospitalization. Thus, the introduction of selection bias limits the practical applicability of this approach. Another approach is based on the definition of Hb concentrations that are optimal for the clinical outcome of elderly subjects. Based on the distribution of Hb levels, the elderly can be grouped into quartiles or quintiles, revealing inverse J-shaped correlations with unfavorable outcome. An increased mortality was found in the lower quintile (<137 g/L for men; <126 g/L for women) as defined in the Cardiovascular Health Study cohort.[3] Similarly, anemia correlated with increased hospitalization[4] and mortality.[4,5] Thus, a suggested optimal

Hb value to avoid hospitalization and mortality was 130-150 g/L for women and 140-170 g/L for men, suggesting a redefinition of cut-off points for anemia.

Nonetheless, based on the WHO definition, studies have estimated that, in people over 65 years, the prevalence of anemia is 12% in those living in the community, 40% in those admitted to the hospital, and as high as 47% in nursing home residents. All in all, an estimated 17% of those over 65 has been found to be anemic (Table 1).[6-14] Based on this proportion, the current number of anemic elderly persons in the European Union is estimated to be as many as 15 million. This number is likely to increase dramatically in the coming years due to an aging population in Western societies.[8,13]

Anemia in the elderly is particularly relevant as it has a number of serious consequences. Anemia has been associated with a higher incidence of cardiovascular disease,[4] cognitive impairment,[15] decreased physical performance and quality of life,[16-18] and increased risk of falls and fractures.[16] Furthermore, presence of anemia is significantly associated with longer hospital stays[4,19] and with an increased risk of mortality, in particular, mortality related

Table 1. Prevalence and subtypes of anemia in the elderly in selected studies.

Study population	N.	Age (years)	Prevalance (%)	Iron deficiency anemia (IDA) (%)	B12/ folate deficiency (%)	Anemia of chronic disease (ACD) (%)	Renal insufficiency (%)	Unexplained anemia (UA) (%)	Comments
NHANES III-Study[6] Non-institutionalized US population from 3rd National Health & Nutrition Examination Survey (1988-1994).	2096	≥ 65	10.6	16.6	B_{12}: 5.9 B_6: 6.4 both: 2.0	19.7	8.2	33.6	
NHANES III-Study[7] Cohort constituted as described in Guralnik *et al.*[6]	7171	≥ 50	12	24		26	11	39	Relevant negative impact of anemia on survival is shown (RR of 1.8; P<0.001)
Health / Anemia Study (Salute e Anemia)[8] Prospective, population-based study in all residents (including nursing or residential homes) in Biella, Italy	8744	≥ 65	14.2	16	10.1	17.4	15	26.4	Thalassemia trait in 14.4% Possible MDS in 8.5%
Community-dwelling older outpatients from hematology clinics at Stanford Hospital and Clinics (SHC) and Veterans Affairs Palo Alto Health Care System (VAPAHCS), USA[9] A comprehensive hematologic evaluation was performed	190	≥ 65	not applicable	12	nd	6	4	35	MDS 4% Suspected for MDS 16%
Cohort from Chicago, USA[10] *Racially diverse cohort (African Americans 69%)* from a single-institutional university referral anemia clinic; primarily community-dwelling adults aged 65 years. A comprehensive hematologic evaluation was performed	174	≥ 65	not applicable	25.3	4.6	9.8	3.4	43.7	Thalassemia trait in 4.6% Hematologic malignancy in 7.5%
InCHIANTI (Invecchiare in Chianti, "Aging in the Chianti Area") Population based study, Tuscany Region, Italy[11]	582	≥ 65	9.6	17.4	10.5	24.4	10.5	37.2	Patients with potentially associated bleeding source were excluded
Leiden 85+-Study[12] Population–based prospective study; Leiden, The Netherlands	490	≥ 85	23.3	11.4	5.3	20.2	7.0	25.4	
Innsbruck Medical University cohort, Austria[13] Cross-sectional, retrospective analysis of in- and outpatients	4117	≥ 64	21.1	AID: 14.4 FID: 28.2	B_{12}: 2.0 B_6: 6.7	62.1	11.3	-	Large proportion of multifactorial anemias detected; MDS is suspected in a substantial proportion

The defintion of anemia in all studies cited is based on WHO-criteria.[1] The classification of the different types of anemia varies between the different studies particularly in ACD and in UA. RR: relative risk; AID: absolute iron deficiency; FID: functional iron deficiency.

to cardiovascular disease.[4] More importantly, anemia might be an early sign of a previously undiagnosed malignant disease.[20]

Causes of anemia in the elderly are divided into three broad groups: nutritional deficiency, anemia of chronic disease (ACD) and unexplained anemia (UA). These groups are not, however, mutually exclusive. In any given patient, several causes may co-exist and may each contribute independently to the anemia. Nutritional deficiencies represent a treatable subgroup and include lack of iron, vitamin B_{12} or folate. The most frequent nutritional anemia is due to iron deficiency, which is characterized by low serum ferritin levels and transferrin saturation (Table 1). However, normal / high serum ferritin levels do not rule out iron deficiency, as ferritin represents an acute phase protein, which might be elevated in inflammatory processes and with advanced age. Thus, the diagnosis should be mainly based on decreased transferrin saturation. Diagnosis of iron deficiency should not be an end in itself but should rather be the initiation of a search for its cause, including looking for a possible site of blood loss and for possible underlying malignancy. The pathophysiology of ACD is multifactorial and relates to a reduced efficiency of iron recycling from red blood cells resulting in a functional iron deficiency. There is enhanced apoptosis of erythroid progenitor cells in the marrow, an inadequate production of erythropoietin (EPO) and impaired response to EPO. It has been proposed that elevated pro-inflammatory cytokines such as TNFα, IL-6, IL-1 and macrophage migration inhibitory factor (MIF) underlie ACD and a key mediator is the induction of hepcidin synthesis by IL-6. Hepcidin inhibits iron absorption in the intestine and the release of recycled iron from the macrophages, resulting in an iron-restrictive anemia (reviewed by Weiss and Goodnough[21]). Unexplained anemia (UA) accounts for approximately one-third of all anemias in the elderly and represents primarily a diagnosis of exclusion, unclassifiable by currently available methods. The pathophysiology is complex and poorly understood. Although undiagnosed malignancy including myelodysplasia,[13] previously unrecognized chronic kidney disease, and other uncommon causes may explain a proportion of the UAs, their combined contribution is relatively small. In populations where thalassemia is prevalent, thalassemia trait may account for another proportion of the UAs.[8,10] Dissecting the causes of UA is confounded by the high frequency of co-morbidities in the elderly, age-associated increases in levels of pro-inflammatory cytokines such as IL-6 that may reduce sensitivity of stem cells and progenitors to growth factors and induce hepcidin synthesis in an environment of reduced pluripotent hemopoietic stem cell reserve. Elevated hepcidin levels have been detected in UA, suggesting that inflammatory processes might contribute to anemia in the elderly, involving mechanisms similar to those encountered in ACD.[12] Thus, a cause for a large proportion of the UAs remains unclear despite comprehensive hematologic evaluation (Table 1).[9,10]

Our great challenge now is to refine the pathological classification of anemia based on the integration of currently routinely available parameters, e.g. ferritin, transferrin saturation (TSAT), reticulocyte hemoglobin content (CHr), pre-inflammation markers and new parameters including plasma hepcidin, erythroferron and soluble hemojuvelin. This should lead to a better understanding of its pathophysiology and the role of hepcidin-targeted therapeutics.

Considering the central role of hepcidin in the pathophysiology of anemia in the elderly, it is not surprising that a plethora of drugs manipulating the hepcidin pathway for therapeutic purposes have been developed[22] with some of these agents already being applied in clinical studies.

It is envisaged that a combination of these biochemical and genetic tests could refine classification of anemia in the elderly, leading to the development of individualized treatment algorithms that would facilitate the appropriation of therapeutic options, including ESAs with a target Hb 100-120 g/L, intravenous iron and novel oral iron formulations, as well as drugs directed at hepcidin or ferroportin.[22] Blood transfusions should be kept to a minimum.

Anemia of the elderly represents a challenge and a burden for the individual, the community and health care providers. All healthcare providers, including hematologists, should be aware that anemia impacts a significant group within our societies. It is an entity that lies within our ability to diagnose and treat.

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How we diagnose neutropenia in the adult and elderly patient

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Neutropenias (NP) comprise a wide spectrum of disorders with varying clinical significance. At one end of the spectrum are the severely neutropenic patients, where the NP, being either acute (such as the unexpected, idiosyncratic drug-induced agranulocytosis or the chemotherapy-induced agranulocytosis) or chronic (e.g. the severe congenital NP), represent serious conditions that, if not appropriately treated, lead to considerable mortality, primarily due to bacterial and fungal infections. Experience from chemotherapy-induced NP over the last 50 years has been valuable in order to develop strategies for severely neutropenic patients. At the opposite end of the spectrum are patients with mild NP, often detected during evaluation for other conditions. These subjects are rarely prone to infections, yet they might suffer from other disorders where NP might be a key part of another underlying disease. The HIV-associated NP is an example in this category. The levels of NP and the risk for infections are given in Table 1.

Against this background, most NP patients are in need of evaluation in order to determine the causes, risks and prognosis. Since non-chemotherapy-induced NP is a relatively rare condition, many hematologists may need support in approaching the NP patient workup. The Scientific Working Group on Granulocyte and Monocyte Disorders of the EHA has promoted science and education in this area since 2004. The approach to chemotherapy-induced NP is discussed elsewhere.[1]

Reviews on the diagnosis and treatment of the neutropenic child have been published recently.[2,3] However, the spectrum of diseases causing NP is different in children compared to adults, mainly because congenital disorders predominate in pediatric clinical experience, whereas other hematologic disorders, autoimmune and chronic viral diseases, and drug-induced agranulocytosis constitute the majority of cases in adults.

This review will focus on how we diagnose and treat acute and chronic NP in the adult patient, particularly in the elderly, through discussing one case.

The case

A 68-year old Swedish female, with a history of hypertension and lower back pain since approximately ten years, presented with a sore throat, fever (40°C) and chills since four days. She was clearly ill; blood pressure was 100/70 mm Hg. Physical examina-

Table 1. Stratification of neutropenia by severity and clinical context.

Neutropenia stratification	ANC (x10^9/L)	Clinical context	Risk of infection
Mild	1.0-1.5	General good health	Usually none
		Associated disease, debilitated, malnourished.	Minimal to severe*
Moderate	0.5-1.0	General good health	Usually minimal
		Associated disease, debilitated, malnourished.	Moderate to severe*
Severe	< 0.5	*All clinical settings*	Moderate to severe

**Often because of co-existent acquired immunodeficiency.*