Chapter 2

Anemia and Aging or Anemia of Aging?

Lodovico Balducci and Matti Aapro

The Western population is aging. Currently, individuals aged 65 and older represent 12% of the US population and by the year 2030 they are expected to represent 20% (1). The segment of the population increasing more rapidly than any other involves individuals over 85, the so called "oldest old." The mean life expectancy of the population was around 60 years in 1900, is currently 80 for women and 76 for man and is expected to rise to 84 and 80, respectively, in 2030 (1).

This epidemic presents medical and social implications. Aging is associated with increased prevalence of chronic diseases, disabilities and functional dependence, that in turn lead to increased demand for medical services as well as for social services and care-giving (2, 3). While aging cannot be prevented, the complications of aging may be preventable or at least delayed. Compression of morbidity may prolong the independence and improve the quality of life of the older aged person and at the same time it may minimize the management-related costs (4, 5).

This chapter explores the interactions of anemia and aging that are of interest for at least three reasons. First, incidence and prevalence of anemia increase with aging (6–8). Second anemia may represent the early sign of an underlying serious disease such as cancer, hypothyroidism or malabsorption (6). Third, anemia itself is associated with increased mortality and disability (7). It is reasonable to expect that prompt and effective management of anemia may help compress the aging-related morbidity.

The causes and the management of anemia in the older aged person will be studied after reviewing the biology of aging.

Biology of Aging and its Clinical Implications

Aging has been defined as loss of entropy and of fractality (9, 10). Loss of entropy implies loss of the functional reserve of multiple organ systems, that involves reduced ability to cope with stress. Loss of fractality entails loss of important physiologic functions. Fractals are repetitive, albeit unpredictable subdivisions of a single unit, such as the bronchi or the neurons. Thus loss of fractality involves decline in the arteriolar alveolar interface in the lung and reduction in the number of neurosynapsis, which in turn leads to reduced ability to perform complex activities. Ultimately, loss of fractality entails decline of one's functional independence, and social and environmental interactions.

Underlying loss of entropy and fractality is a chronic and progressive inflammation that represents the biologic hallmark of aging (11). Seemingly, this inflammation originates from the interaction of individual genetics, diseases, and environment. Increased concentrations of inflammatory cytokines, especially interleukin-6 (IL-6) have been associated with increased mortality, functional dependence, and with a number of geriatric syndromes including dementia and osteoporosis (10, 11). In this perspective, it is not far-fetched to hypothesize that anemia may be both a consequence and a cause of aging (Fig. 2.1). Correction of anemia may break this vicious circle and delay the complications of aging.

Loss of entropy and fractality is reflected in the declining function of several organ systems (12). Of clinical relevance are:

- A progressive decline in glomerular filtration rate (GFR) that is almost universal and may be associated with reduced production of erythrpopoietin;

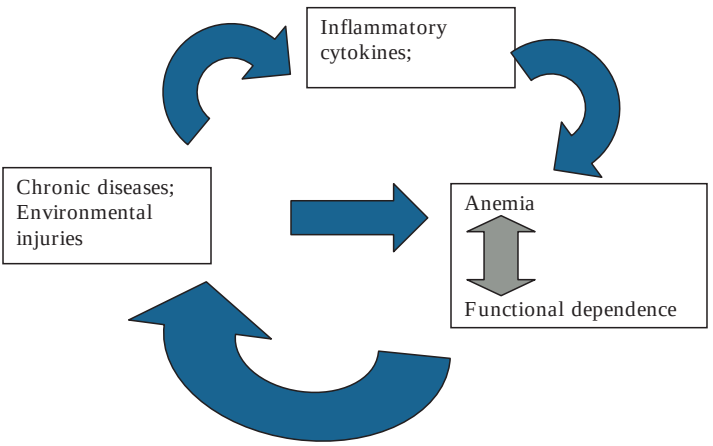

Fig. 2.1. Anemia and aging: a vicious circle

- A progressive decline in the digestion and absorption of nutrients due to reduced gastro-intestinal secretions, gastric motility, splanchnic circulation and absorbing surface. The absorption of iron, that my lead to iron deficiency may be hampered by hepcidine, a glycoprotein synthesized in the liver whose production is stimulated by IL-6 (13). The absorption of B12 may be reduced in older individuals due to inability to digest food bound cobalamaine;
- A number of endocrine changes, including decreased concentration of testosterone and dehydroepiandrotestosterone (DHEA), growth hormone, insulin, and thyroxine, while the concentration of corticosteroids in the circulation may be increased (14);
- Progressive reduction in marrow cellularity, associated with reduced ability to withstand hemopoietic stress (15). This has become particularly evident with cytotoxic chemotherapy of cancer that causes more frequent and severe neutropenia and thrombocytopenia in older individuals.

Aging is universal, albeit highly individualized and is poorly reflected in chronologic age, as it can be seen by the fact that individuals of similar age have different risks of mortality and functional dependence (Fig. 2.2) (16). The management of the older aged person involves an assessment of the physiologic age of each individual. While it is common practice to screen individuals 70 and older for age-related problem, it would be a disservice to consider everybody in this age group as "elderly." Age 70 is just a landmark beyond which the risk of being old increases: by no means it is by itself a sign of old age.

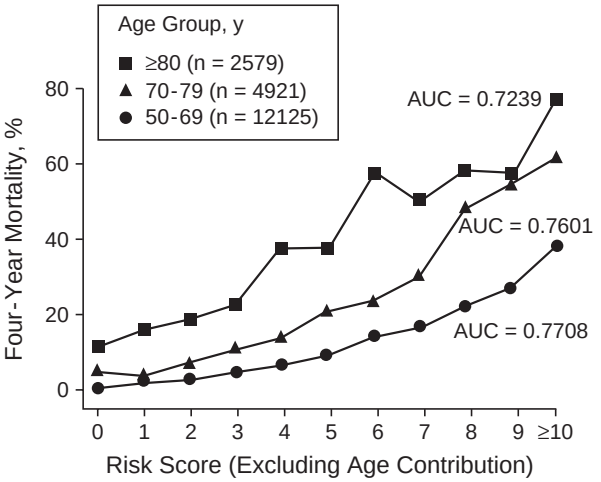

Fig. 2.2. Risk of 4 year mortality based on age and a score computed from function and comorbidity (16)

Clinical Evaluation of Aging

In the absence of reliable measurements of entropy and fractality, the clinical assessment of age relies mainly on the clinical evaluation of the patient. A comprehensive geriatric assessment (CGA) is a time honored assessment of aging and involves the evaluation of function, comorbidy, presence or absence of ageriatric syndromes, as well as of polipharmacy, social support, and nutrition. An example of CGA utilized by the Senior Adult Oncology Program (SAOP) at the H. Lee Moffitt Cancer Center and Research Institute is illustrated in Table 2.1 (17).

In addition to the ADLs and IADLs, the assessment of the advanced activities of daily living (AADL), that is the ability to perform enjoyable activities (such as playing golf or dancing) is also part of the assessment of the functional status (17), as an indirect assessment of one's quality of life.

The comorbid conditions of major interest, because they have been associated with increased risk of mortality include cardiovascular diseases, renal insufficiency, and cancer (16). Comorbidity scales assess both the number and the seriousness of comorbid conditions. Scales of common use include the Charlson scale (17), that is particularly useful in epidemiological studies, and the CIRS-G that proved the most sensitive in our experience (17).

Geriatric syndromes are conditions that are typical, albeit not unique, of aging. Approximately 20% of cancer patients aged 70 and older had some form of early dementia or sub-clinical depression when screened for these conditions (18). Early detection of dementia may allow prompt institution of medications that delay memory loss, and appropriate social arrangements to prevent a person from being hurt. In rare cases, a reversible cause of memory disorder, such as cobalamine deficiency, hypothyroidism, or normal pressure hydrocephalus may be identified (19, 20). Sub-clinical depression is associated with increased mortality in older people (21) and is reversible in the majority of cases. Screening women over 65 for osteoporosis is a recommended intervention, as proper treatment may reverse this condition. There are no clear guidelines for screening man, though they too may experience osteoporosis with aging, especially when hypogonadic (22). Neglect and abuse suggest at least inadequate caregiving, but may also be a sign of deeper problems, including criminal activities in the elder's home. Failure to thrive is a poorly defined but well-recognized condition, in which a person undergoes progressive weight loss and functional decline despite adequate food intake (23). This condition is generally terminal, may involve different causes. Seemingly, inflammatory cytokines are the main mechanism of failure to thrive.

Table 2.1. The CGA at the SAOP: clinical implications

Domain	Assessment	Clinical implication
Functional status	Performance status (PS) Activities of daily living (ADL): • Transferring • Feeding • Grooming • Dressing • Use of the bathroom Instrumental activities of daily living (IADL): • Use of transportations • Use of telephone • Ability to take medications • Financial management • Shopping • Ability to provide to one's nutrition	Dependence in ADL and IADLs: Increased risk of mortality Increased vulnerability to stress Dependence in ADLs: need for a home caregiver Dependence in IADL: need for a caregiver Explore possibility of functional rehabilitation
Comorbidity	Number of comorbid conditions Comorbidity scales	Risk of mortality and vulnerability to stress increases with the number and severity of comorbid conditions Optimal management of diseases may improve patient health and prevent functional decline
Geriatric syndromes	Dementia (screen) Depression (screen) Delirium Falls (screen for risk of falls) Osteoporosis Dizziness Neglect and abuse Failure to thrive	Increased risk of mortality and functional dependence Increased vulnerability to stress Medication may delay dementia, reverse depression and osteoporosis Fall prevention
Nutrition	Assessment of malnutrition and of risk of malnutrition	Malnutrition is associated with increased vulnerability to stress
Polypharmacy	Number of medications Risk of drug interactions	Complications and cost
Social support	Personal resources Social resources	

Approximately 20% of individuals 70 and older have some degree of malnutrition (18), and many more are at risk for malnutrition, due to lack of appetite, depression, isolation, and inadequate access to food. Most of the risk factors for malnutrition are reversible.

The CGA is time consuming and may not be necessary for all individuals who appear healthy and independent. For this purpose a number of screening tests have been proposed to identify individuals in need of more "in depth" assessment. Of these, the five-item screening instrument of the cardiovascular health study (CSH) had gained almost universal acceptance, because it is very simple to perform and has been validated in 8500 individuals followed for an average of 11 years (24) (Table 2.2). This instrument is capable to identify three groups of otherwise independent individuals: fit, pre-frail, and frail, with different risk of mortality, hospitalization, and admission to an assisted living facility.

As aging is associated with a chronic and progressive inflammation, it is reasonable to explore the possibility that the concentration of inflammatory cytokines and other markers of inflammation in the circulation may reflect a person's chronologic age. While definitive studies of the subject have not been produced as yet, Cohen et al. demonstrated that increased concentrations of IL-6 and D-Dimer in the circulation of home-dwelling individuals aged 70 and over were associated with increased risk of mortality and functional decline (25).

Thus, a reasonable approach to a person 70 and older that is independent, may involve the CHS assessment first, followed by a more "in depth" evaluation of individuals who score as pre-frail and frail. The concentration of inflammatory cytokines in the circulation may become important in the near future.

Table 2.2. The CHS assessment

A. Variables of interest
- Involuntary weight loss of ≥10% of the original body weight over 1 year or less;
- Decreased grip strength
- Early exhaustion
- Slow walk
- Difficulty in starting movements.

B. Clinical groups:
- Fit: negative assessment
- Pre-frail: 1–2 abnormal parameters
- Frail: 3 or more abnormal parameters

Frailty and its Implications

The CHS calls pre-frail and frail individuals with one or more abnormalities in the five evaluation parameters. The term frailty has been considered for long time germane to if not synonymous of old age, and it recurs in the geriatric jargon. At a recent consensus conference on frailty (10), agreement was reached on two basic points:

- Frailty implies a condition of increased vulnerability to stress;
- Frailty is a syndrome characterized by sarcopenia, malnutrition, reduced strength and endurance, and reduced neuromuscular adaptability.

Frailty overlaps to some extent with comorbidity and loss of function, but comorbidity and loss of function by themselves cannot account for all cases of frailty.

While the definition and the understanding of frailty is evolving, the practitioner should be aware of the fact that a group of elderly individuals present increased vulnerability to stress, increased risk of functional dependence, and decreased life expectancy. These individuals may be identified by a number of signs, including reduction of sight and hearing, polipharmacy, uncertain gait, episodes of memory loss and of delirium, falls, etc. (26, 27). Identification of frail individuals is important for at least two reasons. The Assessment and Care of Vulnerable Elderly (ACOVE) study clearly demonstrated that management focused on areas of vulnerability may improve the survival and the autonomy of frail individuals (28). Also, any treatment plan for a specific disease involving a frail person must take into account that the benefits of treatment may be lessened by reduced life-expectancy and increased risk of therapeutic complications.

Clearly, the term frailty embraces a wide array of conditions, from that of a person with reduced exercisa endurance to that of a person unable to walk. A so called "frailty index" proposed in 2004 by Mitnitski et al., may provide a quantitative measurement of frailty (29). This index, that is based on the assessment of 70 conditions including function, activities, and disease has been correlated in different patient cohorts with the risk of mortality and hospitalization (29). According to the authors, this index may provide an estimate of a person's physiologic age. While it has been used so far for population studies, the frailty index may become a useful assay of individual life expectancy and functional reserve.

Assessment of Treatment Outcome

In the following discussion, we will explore the effects of anemia on the older aged person and the potential benefits of managing anemia. Together

with life prolongation, "compression of morbidity" is a major goal of managing older people (4, 5). This involves delay of the manifestations of disease and preservation of function until the latest times of life.

Preservation of function may be assessed as:

- Functional independence, that implies independence of all ADLs and IADLs essential for living alone;
- Reduction, reversal or delay of impairments, disabilities and handicaps. Impairment involves the progressive loss of a function, such as the movement of a lower extremity; impairment may lead to disability, such as inability to climb stairs; an uncompensated disability is a handicap; for example, inability to climb stairs becomes a handicap if the building does not provide an elevator or an escalator.
- Proves of physical performance, including strength of upper and lower extremities.

Epidemiology and Causes of Anemia in Older Age

The incidence and prevalence of anemia increase with age. The NHANES III study (6) found that the prevalence of anemia was approximately 9.5% in individuals aged 65 and older, increased with age, and it was higher for African-Americans, when compared with Caucasians, non black Hispanic and Asian-Americans. Anemia was more common in older man than in older women, a finding that needs qualification. The NHANES III adopted the definition of anemia of the World Health Organization (WHO), that normal hemoglobin values are ≥12 gm/dl for women and ≥13.0 gm/dl for man. The accuracy of these values has been questioned since the publications of the Woman Health and Aging studies (WHAS), demonstrating that in women 65 and older hemoglobin levels <13.5 gm/dl were associated with increased risk of mortality (30) and of functional impairment (31). If there is no reason to expect that the average hemoglobin levels should be lower in older women than in older men, as suggested by the WHAS, the prevalence of anemia in the NHANES III is similar for both sexes.

The NHANES III data are consistent with the studies of Olmstead county that demonstrated an age-related increase in incidence and prevalence of anemia. The prevalence of anemia was somehow higher in Olmsted county, as this was a survey of the full population, including the sickest and oldest individuals (8). The data are also consistent with the Italian cross-sectional study that showed a prevalence of anemia of 9.2% for individuals aged 65 and over (32). The Italian study showed that the

average hemoglobin levels did not change with age, whereas the prevalence of anemia increased with age, suggesting that anemia, even mild anemia, is not a consequence of age by itself. This suggestion has been challenged by a Japanese cohort study, showing that in the absence of any disease or impairment the values of hemoglobin decreased by 0.036 gm/dl/year for women and by 0.04 gm/dl for men between age 70 and 80 (33). Irrespective of whether there is a modest drop in average hemoglobin levels with age, this appears negligible and unable to explain the increased incidence of anemia in the elderly.

The most common causes of anemia in older individuals in the NHANES III and the Olmstead county study are shown in Table 2.2. It is possible that with more investigations a specific cause might have been found for the so called anemias of unknown causes, including early myelodysplasia, and anemia of renal insufficiency, as the GFR declines with age in the majority of cases, and this decline has not been associated with increase in the concentration of serum creatinine (12). A number of studies indicated that the secretion of erythropoietin by the kidney may decrease when the GFR drops below 60 ml/dl (34).

Recent findings are germane to the discussion of the causes of anemia in older individuals:

- Incidence and prevalence of B12 deficiency increase with age (35, 36). The most common cause of B12 deficiency is the inability to digest food B12 due to decreased gastric secretion of hydrochloric acid and of pepsin, and may be responsive to oral crystalline B12. In addition to anemia, B12 deficiency may be a cause of neurologic disorders including dementia, and posterior column lesions.
- Seemingly, the main cause of iron deficiency is chronic bleeding, from cancer, diverticuli, or angiodysplasia. In older age iron deficiency may have other causes, including decreased absorption of iron, due to gastric achylia, and to increased circulating concentrations of hepcidin. Hepcidin prevents the absorption of iron from the duodenum, and is a protein synthesized in the liver, whose production is stimulated by IL-6 (37) A recently recognized cause of iron deficiency is H Pylori gastritis (38).
- In some older individuals the secretion of erythropoietin and the erythropoietic response to erythropoietin may be impaired, as a result of increased circulating concentrations of IL-6 and other inflammatory cytokines (39, 40). In elderly patients from Chianti, Ferrucci et al. demonstrated that increased concentration of inflammatory cytokines in the circulation is associated with increased concentrations of erythropoietin initially, followed by reduced response of erythropoietin to anemia

(Fig. 2.3) (39). Similar findings were reported in a sample of patients from the Baltimore Longitudinal Study by Ershler et al. (40). These studies suggest a biphasic response of erythropoietin to inflammatory cytokines: an initial increased production of erythropoietin even for normal hemoglobin levels, followed by a reduced response of erythropoietin to the drop of hemoglobin concentration. This condition of relative erythropoietin deficiency, similar to relative insulin deficiency in type II diabetes, is exacerbated by increased resistance of erythropoietic progenitors to erythropoietin, also mediated by IL-6, and increased circulating levels of hepcidine, that prevent mobilization of iron from iron stores. Is there a difference between anemia of aging and anemia of chronic inflammation (ACI) (41)? Certainly there is almost complete overlap in the pathogenesis of the two forms of anemia, and aging may be considered a chronic progressive inflammation. At present there is not good reason to distinguish the two entities.

- In the INCHIANTI study Ferrucci et al. found that anemia was associated with low testosterone levels both in men and women and that low testosterone levels predicted the development of anemia in non anemic

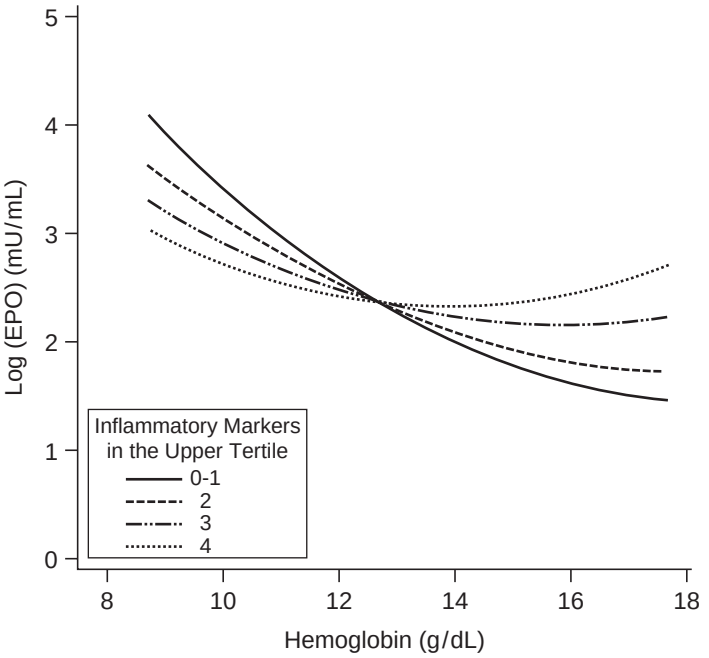

Fig. 2.3. Recommended diagnostic investigations of anemia

individuals over the next 3 years (42). The role of hypogonadism in the development of anemia deserves further exploration especially in view of the current trend to treat older men with testosterone replacement.

- Recent studies show that lenalidomide may induce a complete cytogenetic response in patients with refractory anemia and q (–) cytogenetic abnormalities (43) and may prolong the survival of these patients. Thus, work up for myelodysplasia in older individuals with mild anemia of unknown causes may avert to some extent the mortality and morbidity from this condition. This hypothesis should be tested in randomized controlled studies.

Consequences of Anemia

The clinical consequences of anemia are listed in Table 2.3.

At least seven cohort studies demonstrated that anemia is an independent risk factor for mortality in older individuals (8, 30, 44–48). Of these, the most provocative are the WHAS and the study by Zakai et al. The WHAS reported an increased risk of mortality for hemoglobin levels <13.4 gm/dl home dwelling women aged 65 and over followed for an average of 11 years, and may mandate a revision of the WHO definition of anemia in older women (30). The study by Zakai found that mortality was increased for hemoglobin levels lower than 12.7 gm/dl for women and 13.5 gm/dl for men (47).

Table 2.3. Consequences of anemia

Increased risk of mortality
Increased risk of functional dependence
Increased risk of dementia
Increased risk of delirium
Increased risk of chemotherapy-related toxicity
Increased risk of congestive heart failure and coronary death
Increased risk of falls

Development of functional dependence represents the failure of one of the major goals in the management of older individuals: compression of morbidity. Clearly, functional dependence is one of the most serious consequences of anemia in older individuals (31, 49–51). In the WHAS, the EPESE, and the Chianti studies anemia after age 65 was associated with increased risk of dependence in instrumental activities of daily livings (IADLs) and with mobility impairments. The risk of functional dependence and of mobility impairment was inversely related to the levels of hemoglobin, when these dropped below 13.5 gm/dl. This finding was constant in all studies and suggests that even mild anemia may have serious consequences for the independence of older individuals.

Anemia is associated with increased risk of therapeutic complications from medications and from surgery. Anemia was an independent risk factor for the complications of cytotoxic chemotherapy in at least five studies (52–56). The majority of antineoplastic agents are bound to red blood cells, so that the concentration of free drug in the circulation and the risk of toxicity are increased in the presence of anemia. It is also possible that chronic hypoxia of normal tissue may enhance the susceptibility of these tissues to treatment complications. Seemingly, hypoxia of the brain increases the risk of delirium from medications in older individuals with anemia (57).

The association of chronic anemia and congestive heart failure is well known (58–61). A review of Medicare record showed that individuals 65 and older with myocardial infarction and hematocrit lower than 30% were more likely to die if they did not receive any blood transfusions (62).

Studies in patients with chronic renal failure suggested that anemia might have been a cause of dementia, as the risk of dementia was significantly increased among patients whose anemia had not been corrected with erythropoietin (63). A recent study by Atti et al. demonstrated that the risk of dementia was higher in the presence of anemia among older patients, and anemic individuals with normal mental status were more likely than non-anemia patients of the same age to develop dementia over 5 years (65). Other authors reported increased risk of cognitive dysfunctions in older individuals even with mild anemia (65, 66).

According to a recent study anemia was also associated with increased risk of falls, both in institutions and in the community (67). Falls are a geriatric syndrome, associated with increased mortality and morbidity, including hip fractures.

At this point it should be emphasized that currently there is no proof that correction of mild anemia in older patients will avert the complications of anemia. Anemia of a specific cause of course should be corrected. Correction of ACI with erythropoietic growth factors improves the fatigue of cancer patients, but so far no other benefits of this approach have been demonstrated (68).

Diagnosis and Management of Anemia

Diagnosis of Anemia

As the WHO criteria for the diagnosis of anemia have been challenged in recent studies, it appears reasonable to institute a work up for anemia when hemoglobin levels are lower than 13 gm/dl both in man and women. Seemingly for some individuals, especially woman and African-Americans, hemoglobin levels between 12 and 13 gm/dl are normal, and they should be considered normal if no cause of anemia becomes apparent and the hemoglobin does not drop for one year or longer.

The basic work up of anemia is illustrated in Fig. 2.4. Only rarely a hyper-proliferative anemia may present as chronic anemia. This is the case with micro-angiopathic anemia in individuals with artificial heart valves or severe vascular diseases. Though the mean cellular volume (MCV) may direct the diagnosis, it is prudent to investigate all common causes of anemia in older individuals irrespective of the MCV, as the simultaneous presence of multiple deficiencies may influence the MCV in opposite directions.

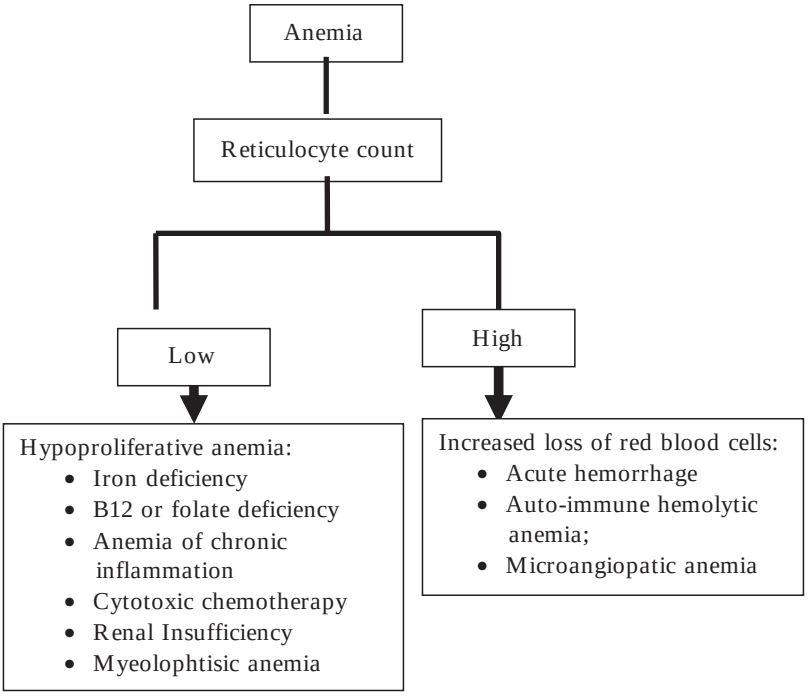

Fig. 2.4. Anemia work-up

An examination of the bone marrow should be performed when there is pancytopenia, suggesting myelophtysis. Examination of the bone marrow with cytogenetics may also be necessary for the diagnosis of MDS.

Iron deficiency is characterized by low serum iron, increased serum iron capacity, low ferritine levels and high concentrations of soluble transferrin receptors, while the ACI is characterized by low serum iron and iron binding capacity, high levels of ferritine and low concentrations of soluble transferrin receptors (41). A diagnosis of iron deficiency mandates investigations of blood loss through the digestive tract. More rarely iron deficiency may be due to loss of iron in the urine from chronic intravascular hemolytic anemia, suggested by hemosiderin in the urines.

Though the lowest levels of cobalamine in the blood are listed as 180 pg/ml, about 15% of individuals with values between 180 and 300 pg/ml have increased levels of methyl malonic acid (MMA) in the circulation suggesting functional cobalamine deficiency (69).

Anemia from chronic renal insufficiency should be suspected in all individuals whose creatinine clearance is lower than 60 ml/min and can be confirmed by levels of erythropoietin inadequate for the degree of anemia (34).

Treatment of Anemia

The treatment consists in elimination of the cause (ex. gastro-intestinal bleeding) and replacement of the missing nutrient (example iron).

Older individuals may be unable to absorb oral iron due to stomach achilia and to increased concentration of hepcidine, so they may need IV replacement.

B12 deficiency may be corrected orally, as most older people can absorb crystalline B12.

Erythropoietic growth factors should be used only for anemia of renal insufficiency and for cancer-chemotherapy related anemia. In the case of anemia of aging or other forms of ACI the benefits of erythropoietin should be explored in randomized controlled study having as end-points survival, compression of morbidity, and preservation of independence.

Conclusions

Anemia becomes more common with age and is associated with decreased survival, functional dependence, coronary deaths, congestive heart failure, and a number of geriatric syndromes, including dementia delirium, depression and falls.

In approximately one third of cases, the cause of anemia was not apparent. A number of these cases may be due to early myelodysplasia or undetected kidney insufficiency. A number of cases may be due to relative erythropoietin insufficiency, due to the pro-inflammatory status of aging.

Investigations of anemia should be initiated for hemoglobin levels lower than 13 both in man and women. In some individuals, especially women and African-Americans levels of hemoglobin between 12 and 13 gm/dl should be considered normal, if no cause of anemia is detected and the hemoglobin levels do not change for one year or longer.

The management of anemia consists in eliminating its causes and replenishing the missing factors. Currently there is no proof that management of anemia of aging with erythopoietic growth factors is beneficial. This issue should be tested in randomized controlled trials.

References

1. US life tables
2. Pitsenberger DH: Juggling work and elder caregiving: work-life balance for aging American workers. AAOHN J. 2006 Apr;54(4):181–5
3. Chapman DP, Williams SN, Strine TW et al: Dementia and its implications for public health. Prev Chronic Dis. 2006 Apr;3(2):A34. Epub 2006
4. Liao I, McGee DL, Cao G et al: Quality of the last year of life of older adults: 1986 vs 1993. JAMA. 2000;283:512–8
5. Fries GF: Aging, natural death, and the compression of morbidity. 1980. Bull W Health Org. 2002;80:245–50
6. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC: Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004 Oct 15;104(8):2263–8
7. Beghe C, Wilson A, Ershler WB: Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. Am J Med. 2004 Apr 5;116 Suppl 7A:3S–10S
8. Anía BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton LJ 3rd: Incidence of anemia in older people: an epidemiologic study in a well defined population. J Am Geriatr Soc. 1997 Jul;45:825–31
9. Lipsitz LA: Physiological complexity, aging, and the path to frailty. Sci Aging Knowledge Environ. 2004 Apr 21;2004(16):pe16. Review
10. Walston A, Headley EC, Ferrucci L et al: Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006 Jun;54(6):991–1001
11. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, Guralnik JM, Longo DL: The origin of age-related proinflammatory state. Blood. 2005 A March 15;105(6):2294–9A
12. Duthie et al: In: Balducci L; Lyman GH, Ershler WB, Extermann M: Comprehensive Geriatric Oncology 2nd edition, Taylor & Francis, London, 2004
13. Ganz T: Regulation of iron metabolism. In: Balducci L, Ershler WB, DeGaetano G: Blood Disorders in the Elderly. Cambridge Academic Press, Cambridge 2006

14. Maggio, Cappola AR, Ceda GP et al: The hormonal pathway to frailty in older men. J Endocrinol Invest. 2005;28(11 Suppl Proceedings):15–9
15. Balducci L, Hardy CL, Lyman GH: Hemopoiesis and aging. Cancer Treat Res. 2005;124:109–31
16. Lee SJ, Lindquist K, Segal MR et al: Development and validation of a prognostic index for 4-year mortality in older adults. JAMA. 2006 Feb 15;295(7):801–8. Erratum in: JAMA. 2006 Apr 26;295(16):1900
17. Balducci L, Extermann M: The assessment of the older cancer patient. In: Balducci L, Lyman GH, Ershler WB, Extermann M: Comprehensive Geriatric Oncology 2nd edition, Taylor and Francis, London, 2004
18. Extermann M, Overcash J, Lyman GH et al: Comorbidity and functional status are independent in older cancer patients J Clin Oncol. 1998;16:1582–7
19. Anerbo S, Wahlund LO, Lokk J: The significance of thyroid-stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year follow-up study. Am J Alzheimers Dis Other Demen. 2006 Jun–Jul;21(3):182–8
20. Clarfield AM: The decreasing prevalence of reversible dementias: an updated meta-analysis. Arch Intern Med. 2003 Oct 13;163(18):2219–29
21. Lyness JM, Ling DA, Cox C et al: The importance of subsyndromal depression in older primary care patients. Prevalence and associated functional disability. J Am Ger Soc. 1999;47:647–52
22. Shaininan VB, Kuo YF, Freeman: Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005;352:154–64
23. Verdery RB: Failure to thrive in old age: follow-up on a workshop. J Gerontol Biol Scie Med.1997;52:M333–6
24. Fried LP, Tangen CM, Walston J et al: Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci. 2001;56A:M146–56
25. Cohen HJ, Harris T, Pieper CF: Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. Am J Med. 2003;114:180–7
26. Rockwood K, Mitnitski A, Song X et al: Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc. 2006 Jun;54(6):975–9
27. Mitnitski A, Song X, Skoog I et al: Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc. 2005 Dec;53(12):2184–9
28. Ruben DB, Roth C, Kamberg D et al: Restructuring primary care practices to manage geriatric syndromes: the ACOVE-2 intervention. J Am Geriatr Soc. 2003 Dec;51(12):1787–93
29. Mitnitski A, Song X, Rockwood K: The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. J Gerontol A Biol Sci Med Sci. 2004 Jun;59(6):M627–32.G
30. Chaves PH, Ashar B, Guralnik J et al: 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 Jul;50(7):1257–64
31. Chaves PH, Sumba RD, Leng SX et al: Impact of anemia and cardiovascular diseases on frailty status of community dwelling women. The Women Health and Aging Studies I and II. J Gerontol A Biol Sci Med Sci. 2005;60:729–35

32. Inelmen EM, Alessio MD, Gatto MRA, et al: Descriptive analysis of the prevalence of anemia in a randomly selected sample of elderly people at home: some results of an Italian multicentric study. Aging Clin Exp Res. 1994;6:81–9
33. Yamada M, Wong FL, Suzuki G et al: Longitudinal trends of hemoglobin levels in a Japanese population-RERF's Adult Health Study Project. Eur J Haematol. 2003;70:129–35
34. Ble A, Fink J, Woodman R et al: Renal function, erythropoietin and anemia of Older Persons: The In Chianti study. Arch Intern Med. 2005;165:2222–7
35. Sipponen P, Laxen F, Huotari K et al: Prevalence of low vitamin B12 and high homocysteine in serum of an elderly male population: association with atrophic gastritis and Helicobacter Pylori Infection. Scand J Gastroenterol. 2003;38:1209–216
36. Slhub J, Jacques PF, Roenberg IH et al: Serum total homocysteine concentrations in the third National Health and nutrition Examination Survey (1991–1994): population references ranges and contribution of vitamin status to high serum concentrations. Ann Intern Med. 1999;131:331–9
37. Nemeth E, Tuttle MS, Powelson J et al: Hepcidin regulates iron efflux by binding to ferroportin and inducing its internalization. Science. 2004
38. Choi JW: Serum-soluble transferrin receptor concentrations in Helicobacter pylori-associated iron-deficiency anemia. Ann Hematol. 2006 Oct;85(10):735–7
39. Ferrucci L, Guralnik L, Woodman RC et al: Proinflammatory state and circulating erythropoietin in persons with and without anemia. Am J Med. 2005;118:1288–96B
40. Ershler WB, Sheng S, McKelvey J et al: Serum erythropoietin and aging: a longitudinal analysis. J Am Ger Soc. 2005;53:1360–65 A
41. Weiss G, Goodnough LT: Anemia of chronic disease NEJM. 2005;352:1011–23
42. Ferrucci L, Maggio M, Brandinelli S et al: Low testosterone levels and risk of anemia in older men and women. Arch Int Med. 2006;166:1380–8
43. List A, Dewald G, Bennett J et al: Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006 Oct 5;355(14):1456–65
44. Kikuchi M, Inagaki T, Shinagawa N: Five-year survival of older people with anemia: variation with hemoglobin concentration. J Am Ger Soc. 2001;49:1226–8
45. Izaks GJ, Westendorp RGJ, Knook DL: The definition of anemia in older persons. JAMA. 1999;281(18):1714–1719
46. Penninx BW, Pahor M, Woodman RC et al: Anemia in old age is associated with increased mortality and hospitalization. J Gerontol Med Sci. 2006;61:474–9
47. Zakai NA, Katz R, Hirsch C et al: A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovasccular Health Study. Arch Intern Med. 2005;165:2214–20
48. Culleton BF, Manns BJ, Zhang J et al: Impact of anemia on hospitalization and mortality in older adults. Blood. 2006 May 15;107:3841–6
49. 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;52:719–24
50. Penninx BW, Guralnik JM, Onder G et al: Anemia and decline in physical performance among older persons. Am J Med. 2003;115:104–10
51. Cesari M, Penninx BW, Lauretani F et al: Hemoglobin levels and skeletal muscle: results from the INCHIANTI study. J Gerontol A Biol Med Sci. 2004;59:238–41
52. Extermann M, Chen A, Cantor AB, Corcoran MB, Meyer J, Grendys E, Cavanaugh D, Antonek S, Camarata A, Haley WE, Balducci L: Predictors of tolerance from chemotherapy in older patients: a prospective pilot study. Eur J Cancer. 2002 Jul;38(11):1466–73

53. Schrijvers D, Highley M, DeBruyn E, Van Oosterom AT, Vermorken JB: Role of red blood cell in pharmacokinetics of chemotherapeutic agents. Anticancer Drugs 1999;10:147–53
54. Ratain MJ, Schilsky RL, Choi KE et al: Adaptive control of etoposide administration: impact of interpatient pharmacodynamic variability. Clin Pharmacol Ther. 1989;45:226–33
55. Silber JH, Fridman M, Di Paola RS et al: First-cycle blood counts and subsequent neutropenia, dose reduction or delay in early stage breast cancer therapy. J Clin Oncol. 1998;16:2392–400
56. Wolff D, Culakova E, Poniewierski MS et al: Predictors of chemotherapy-induced neutropenia and its complications: results from a prospective nationwide Registry. J Support Oncol. 2005;3(6 suppl 4):24–25
57. Joosten E, Lemiengre J, Nelis T et al: Is aneamia a risk factor for delirium in acute geriatric population? Gerontology. 2006;52:382–5
58. Maraldi C, Volpato S, Cesari M et al: Anemia, physical disability and survival in older patients with heart failure. J Card Fail. 2006;12:533–9
59. Lewis BS, Karkabi B, Jaffe R et al: Anemia and heart failure: statement of the problem. Nephrol Dial Transplant. 2005;20(suppl 7):3–6
60. Phillips S, Olimann H, Schink T et al: The impact of anaemia and kidney function in congestive heart failure and preserved systolic function. Nephrol Dial Tranplant. 2005;20:915–9
61. Elabassi W, Fraser M, Williams K et al: Prevalence and clinical complications of anemia in congestive heart failure patients followed at a specialized heart function clinic. Congest Heart Fail. 2006;12:258–64
62. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM: Blood transfusions in elderly patients with acute myocardial infarction. N Engl J Med. 2001 Oct 25;345(17):1230–36
63. Pickett JL, Theberge DC, Brown WS, Schweitzer SU, Nissenson AR: Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis 1999;33(6):1122–30
64. Atti AR, Palmer K, Volpato S et al: Anemia increases the risk of dementia in cognitively intact elderly. Neurobiol Aging. 2006;27:278–84
65. Zamboni V, Cesari M, Zuccala G et al: Anemia and cognitive performance in hospitalized older patients: results from the GIFA study. Int J Geriatr Psychiatry. 2006;21:529–34
66. Chaves PH, Carlson MC, Ferrucci L et al: Association between mild anemia and executive function impairment in community dwelling older women: The women health and aging study II. J Am Ger Soc. 2006;54:1429–35
67. Penninx BW, Pluijm SM, Lips P et al: Late life anemia is associated with increased risk of recurrent falls. J Am Geriatr Soc. 2005;53:2106–111
68. Bohlius J, Langersiepen S, Schwarzer G et al: Recombinant human erythropoietin and overall survival in cancer patients. Results of a comprehensive meta-analysis. J Natl Cancer Inst. 2005;97:489–98
69. Norman EJ, Morrison JA: Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry. Am J Med. 1993 Jun;94(6):589–94