CHAPTER 26

Anaemia in the elderly

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1. Definition of anaemia in the elderly

Available data suggest that anaemia in the elderly is a common problem. However, this depends in part on the definition of anaemia. Most commonly, World Health Organisation (WHO) criteria of a haemoglobin less than 13 g/dL in men and less than 12 g/dL in women are used. These criteria were initially put forth in a 1968 WHO technical report on nutritional anaemias (1), and were developed based on data in populations that did not include individuals above 65 years of age (2-5) (aside possibly from cited unpublished observations not currently available (1)). Thus, an argument has been made that these criteria are not applicable to the older individual (6). There is additional debate as to whether modifications should be made for different racial and ethnic groups, particularly persons of African descent. Approximately 30% of African-Americans have the 3.7kb deletion form of alpha thalassaemia (7). In the much more common heterozygous state (one of four alpha genes affected), this can lead to low-normal and occasionally mildly low haemoglobin and mean corpuscular volume (MCV) values, whereas homozygotes (two of four alpha genes affected) have a mild, microcytic anaemia (7). Thus, thalassaemia may contribute to lowering of the haemoglobin in the appropriate racial groups (7). There may also be additional underlying genomic and/or environmental factors which contribute to lowering of haemoglobin values. When all those with the alpha thalassaemia -3.7 kb allele, iron deficiency, renal insufficiency and sickle trait were removed from a (largely non-elderly) African-American population, the African-American group still had significantly lower haemoglobin values compared to a corresponding white population (7). Additional data bolstering this hypothesis is that the prevalence of anaemia, using WHO criteria, is three-fold higher in elderly African-Americans relative to elderly Caucasians (8).

More recently, Beutler et al. analysed two large databases, the third US National Health and Nutrition Examination Survey (NHANES III), a nationally representative sampling of community-dwellers, and the Scripps-Kaiser database, collected in the San Diego area between 1998 and 2002, in an attempt to more accurately determine normal ranges in the elderly (6). Older subjects (59 years and older in men and 49 years and older in women) with laboratory-based evidence of increased inflammation or renal insufficiency were excluded, which, importantly, led to the elimination from the analysis of up to 50% of older black men and 40% of black women from the NHANES database. Using the fifth percentile value of haemoglobin concentration, new lower limits of normal were proposed, and were slightly higher for older white men and women (13.2 and 12.2 g/dL, respectively) and lower for older black men and women (12.7 and 11.5, respectively) compared to current WHO criteria. Further

data are needed to confirm or refute the necessity for more precise age and race-based definitions of anaemia before they can be put into widespread use.

2. Prevalence of anaemia in the elderly

Given the absence of a uniform definition of anaemia, and the likely importance of both genetic and environmental influences, it is not surprising that the reported prevalence of anaemia in the elderly has wide variability in the literature. In a systematic literature review, prevalence rates of anaemia in older adults were found to vary between 2.9% and 61% in men and 3.3% and 41% in women (9). The highest prevalence rates were in hospitalised elderly (9); nursing home residents are also at high risk for anaemia (10, 11). However, anaemia is also quite prevalent in non-institutionalised elderly: in large studies of community-dwelling older adults from the United States and Europe, prevalence rates range from 8 to 25% (12). In the community-dwelling NHANES III population, 10.2% of women and 11% of men 65 and older were anaemic (8). Prevalence of anaemia also increased with increasing age, such that 26% of men and 20% of women aged 85 and above were anaemic (8), a pattern also seen in other studies (9, 13, 14). This is particularly important in light of the aging global population. In 2008 the world population was estimated to be 6.7 billion with 98 million people aged 80 and above (15). By 2030 this is estimated to grow to 8.4 billion total population, and 216 million aged 80 and above (15), in this age bracket, extrapolating from data obtained in the developed world. This number is likely to be substantially increased, however if one takes into account the much higher prevalence rates of anaemia found in areas in the developing world (16).

Importantly, the anaemia reported in these studies tends to be mild, with haemoglobin values generally remaining above 10 g/dL. In NHANES III, less than 10% of anaemic men and women aged 65 and older had haemoglobin levels less than 10 g/dL (and thus less than 1% of the total population of men and women aged 65 and older) (8). This proportion as might be expected has been found to be somewhat higher in institutionalised elderly subjects, ranging from 11 to 19% (10, 17).

3. Anaemia in the elderly: Functional outcomes

A key question is whether even this relatively mild anaemia has a negative impact on the functional status of elderly patients. Decreased functioning can radically impact an older person's life and ultimately lead to loss of independent living in the community (18). Measures of physical function are important both in assessing current status and in predicting more severe disablement, such as mobility, difficulty

predicting subsequent nursing home admission (18, 19). Recent studies have highlighted the association between mild anaemia and even low-normal haemoglobin values and impaired performance-based mobility function (20-22). Anaemia in the elderly has also been found to be associated with other markers of impaired physical function, including increased frailty (23), muscle weakness (22) and falls (24). Beyond physical measures, anaemia in the elderly is associated with impaired cognitive performance (25, 26), and decline in cognitive function over time (27).

Perhaps most importantly, multiple studies have shown an association between anaemia in the elderly and increased mortality. In a Dutch study of community-dwelling men and women aged 85 and older, anaemia was associated with an increased mortality rate over a 10-years period, even after adjustments for functional impairment and associated diseases (28). Anaemia in Japanese nursing home residents was associated with increased mortality over 4 years (29). In the Framingham study, there was increased mortality in men with a haematocrit of less than 42% and less than 39% in women compared to those with higher values (30). The risk of mortality may be related to the aetiology of the anaemia; in one study, elderly female subjects with anaemia due to renal insufficiency or anaemia of chronic inflammation had an increased risk of death compared to non-anaemic controls, whereas those with anaemia due to nutrient deficiencies or unexplained anaemia did not (31).

The impact of anaemia on morbidity and/or mortality may also be influenced by race, although data are conflicting. In the Health, Aging, and Body Composition (Health ABC) Study, which included 3,075 community-dwelling adults aged 70-79 years old, anaemia in whites but not blacks was significantly associated with increased mortality over 6 years of follow-up (32). Conversely, in a prospective cohort study including 1,744 men and women aged 71 years or older from North Carolina, anaemia was significantly associated with mortality in African-Americans but not Caucasians over 8 years of follow-up when adjusted for demographic and other variables (27). And finally, in the Chicago Health and Aging Project (CHAP) study, which included 1,806 elderly men and women, anaemia was associated with increased mortality in both African-Americans and Caucasians after 3.5 years of follow-up (33). These discrepant results may be due to different sampling strategies (34) or disproportionately missing follow-up data in the different races (35). However, these studies further the debate regarding the validity of using race-specific normal values, and the potential disparate impact of anaemia within different racial groups.

Interestingly, many of the studies showing an association between anaemia and morbidity and/or mortality replicate a reversed J-shaped curve, with worse outcomes at both the lower and upper extremes of haemoglobin level (36). Possible

explanations for increased morbidity and/or mortality at the upper extreme include the affects of underlying cardiac or pulmonary disease which may cause a relative polycythaemia, or increased blood viscosity and consequent thrombotic events. Importantly, none of these studies investigating anaemia in the elderly and poor outcomes have been designed to establish causality. It is unknown whether anaemia itself leads to increased morbidity and/or mortality or it is the underlying aetiology of the anaemia or associated co-morbidities which do so. Nonetheless, it is plausible to suggest that anaemia, potentially leading to increased cardiac output or local tissue hypoxia, could aggravate functional decline.

4. Aetiologies of anaemia in the elderly

In NHANES III, a third of the anaemia in the elderly was attributed to "nutrient" deficiencies, 20% to anaemia of chronic inflammation, 8% to renal insufficiency alone, and a third was "unexplained" (8). Importantly, these determinations were made based on laboratory data only. However, reliance on biochemical data alone, without an accompanying clinical evaluation, may lead to the faulty presumption that a subclinical biochemical abnormality has caused the anaemia. This is particularly important for the "nutrient" deficiency category. In this study anaemia was attributed to cobalamin deficiency when the cobalamin level was less than 200 pg/mL, which occurred in 11.3% of anaemic patients (either as the sole diagnosis or in combination with other abnormalities) (8). This is consistent with other studies, in which low cobalamin levels have been found to occur in 10-20% of older adults (37, 38). However, while low cobalamin levels are frequently found, for the most part the deficiency tends to be subclinical, without haematologic or neurologic manifestations (38-40). Thus the NHANES III data are likely to overestimate the prevalence of anaemia due to cobalamin deficiency.

5. Diagnostic evaluation of anaemia in the elderly

In general, diagnostic algorithms for anaemia in the elderly are similar to those for anaemia found in any adult patient. In addition to the usual history and examination, the evaluation must, when the information is available, take into account the rate of fall of haemoglobin as well as any accompanying changes in red cell indices and other cell counts. The absolute reticulocyte count or reticulocyte production index is crucial in determining if the anaemia is hypo or hyperproliferative. The MCV will allow for further narrowing of diagnostic possibilities (41). The peripheral smear should be carefully reviewed for abnormalities of all cell lines. It is important to note that patients can have mixed disorders, for example underlying renal insufficiency may blunt the erythropoietic response to typically hyperproliferative disorders

such as haemolysis. Particular attention should be paid to abnormalities that warrant more aggressive diagnostic manoeuvres, including the findings of additional cytopenias, macrocytosis without an attributable cause, or dysplasia on the peripheral smear, suggestive of an underlying myelodysplastic syndrome (MDS) (42) or leukaemia. An abnormal serum or urine protein electrophoresis raises the possibility of multiple myeloma. A very low or undetectable reticulocyte count suggests pure red cell aplasia (43). The evaluation may take several visits, including monitoring a response to nutrient supplementation or possible bone marrow evaluation.

There are several clinical areas that warrant particular attention in the elderly population and are discussed more fully here.

5.1 Iron deficiency anaemia in the elderly

Diagnosing iron deficiency anaemia in the elderly can be problematic. Iron deficiency anaemia is typically a microcytic, hypochromic anaemia, however may be normocytic in the early stages (44) or in combination with other disorders (17, 45). The diagnostic gold standard is demonstration of absent stainable iron on bone marrow aspirate; however, the invasiveness of this procedure limits its usefulness in everyday practice. Peripheral blood measurements include iron indices (serum iron, transferrin, transferrin saturation, and ferritin); as well as other tests such as free erythrocyte protoporphyrin and reticulocyte haemoglobin content, each with strengths and weaknesses. The serum ferritin is perhaps the most frequently used peripheral blood measurement to assess iron deficiency anaemia. Iron stores are reliably depleted when ferritin is less than 12 μg/L (41, 46). However, whereas a low serum ferritin dependably indicates iron deficiency (44), a normal level in an elderly patient does not necessarily rule out iron deficiency, as serum ferritin rises with aging (47). Thus, a higher serum ferritin cut-off may more accurately diagnose iron deficiency in the elderly. In one study in elderly outpatients and inpatients over the age of 65, either a serum ferritin ≤ 18 μg/L or a serum ferritin ≤ 45 μg/L combined with a transferrin saturation index below 0.08 were found to be the best indicators of iron deficiency (48). In another study also in elderly inpatients, a serum ferritin less than or equal to 50 μg/L was the single best laboratory test to diagnose iron deficiency anaemia (49).

Iron indices may also be influenced by the presence of inflammation, in which the transferrin is normal or low, and the ferritin is normal or elevated (50). The serum soluble transferrin receptor (sTfR) divided by the log of the ferritin can be particularly useful to diagnose iron deficiency anaemia in the setting of concomitant inflammation (45, 50). The sTfR rises in parallel with the tissue soluble transferrin

receptor mass (51) and thus will be elevated in states of increased erythropoiesis (erythroid hyperplasia) or increased transferrin receptor density (as is seen in iron deficiency) (52). In one study in the elderly, the sTfR/log ferritin was found to be much more sensitive than standard iron indices in diagnosing iron deficiency anaemia (88 versus 16%) (53). However, in another study, a serum ferritin cut-off of 60 µg/L was found to have comparable sensitivity (76%) and specificity (97%) in a group of inpatients compared to the sTfR/log ferritin (sensitivity 81%, specificity 97%); the mean age was 52 years in the iron deficient patients and 60 years in the control subjects (54). The authors suggested that while the serum ferritin is the most cost-effective diagnostic measurement of iron deficiency, the sTfR/log ferritin may be useful for indeterminate cases (55). However, the lack of standardised reagents for the sTfR assay (56, 57) complicates local interpretation of the sTfR/ferritin ratio. A carefully monitored trial of iron supplementation may be needed to confirm the diagnosis. Constipation can be a major side effect for elderly patients on oral supplementation and may require initiation of low dose with dose escalation over several weeks, or, occasionally, the use of intravenous iron.

Importantly, the diagnosis of iron deficiency anaemia in the elderly requires, in addition to iron repletion, a search for a source of blood loss. In the industrialised world this generally leads to evaluation of the gastrointestinal tract due to the high frequency of occult upper and lower gastrointestinal lesions found in these patients (58, 59). In one study in 111 hospitalised patients 75 years and older found to have iron deficiency anaemia, 92% of whom underwent endoscopy and 82% of whom underwent colonoscopy, 68% were found to have a bleeding source, and 11% had synchronous lesions (60). Of the 43 patients found to have a colorectal source of bleeding, 31 (72%) had colon cancer; of the 44 patient found to have an upper gastrointestinal (GI) source of bleeding, 6 (14%) had an upper GI cancer. At 2 years of follow-up, those with cancer treated curatively (28/102) had a survival rate (68%) similar to those with benign lesions (80%) or those in whom no cause of the anaemia was found (66%), whereas none of the 10 patients with cancer treated palliatively were alive (61). Even iron deficiency in the absence of anaemia may require an evaluation for a bleeding source. In one study, 151 elderly hospitalised patients with serum ferritin levels less than 50 µg/L on two occasions underwent upper endoscopy and either barium enema or colonoscopy, regardless of haemoglobin level (62). A potential upper GI lesion was found in approximately half of both anaemic and non-anaemic patients, and a lower GI lesion was found in 32% of anemic patients and 16% of non-anaemic patients. Six percent of the non-anaemic patients were found to have cancer in the upper gastrointestinal tract and 9% of the non-anaemic patients were found to have colon cancer.

5.2 The impact of renal disease/hypoxia-sensing abnormalities in relation to anaemia in the elderly

In adults, erythropoietin is produced primarily by the peri-tubular interstitial cells in the kidney (63) and prevents apoptosis of erythroid progenitors (64). Basal erythropoietin levels are approximately 10-20 U/mL (65), and the normal response to decreased oxygen tension in the blood is a logarithmic increase in erythropoietin levels corresponding to the severity of the anaemia (66). This response is blunted in patients with renal disease, and worsening renal excretory function corresponds with lower erythropoietin levels (67, 68). This is of particular importance in the elderly given the known decline in renal excretory function that occurs with aging (69). However, the degree of renal impairment necessary and sufficient to cause anaemia in the elderly, and how to measure it, is a matter of ongoing debate. Varying degrees of impairment in renal excretory function have been found to correlate with anaemia in the elderly (70, 71). In a study by Ble et al. of 1,005 community-dwelling men and women 65 years and older living in Italy, a creatinine clearance (calculated from a 24 hour urine collection) of ≤ 30 mL/min was associated with a significantly increased risk of anaemia, and significantly decreased age-and-haemoglobin-adjusted serum erythropoietin levels (72), suggesting that this might be the inflection point below which anaemia is most likely to be due to renal disease in elderly patients. The measurement of serum erythropoietin is not generally useful in diagnosing anaemia due to kidney disease, first because erythropoietin levels do not rise dramatically until the anaemia is more severe than is typically seen in the elderly anaemic patient (68), and secondly because there is substantial overlap of erythropoietin levels in those with and without chronic kidney disease (68).

Interestingly, although there is data to the contrary (73, 74), several studies have shown a rise in erythropoietin with increasing age (75, 76). This elevation suggests the need for relatively more erythropoietin in order to maintain physiologic erythropoiesis in the elderly, possibly secondary to a relative resistance to erythropoietin. Alternatively, elevated erythropoietin levels might reflect decreased utilisation of erythropoietin in a hypoplastic marrow, increased local hypoxia, or a perturbation in the hypoxia sensing pathway.

5.3 Unexplained anaemia in the elderly

Unexplained anaemia (also called "idiopathic anaemia of aging") occurs in approximately 20-30% of community-dwelling elderly anaemic subjects in cross-sectional epidemiologic studies (8, 77), and in up to half of anaemic nursing home residents (10, 17). Even with a thorough clinical and laboratory evaluation, 17% of elderly hospitalised patients with a haemoglobin < 11.5 g/dL had unexplained

anaemia (78). Recent interest has focused on the importance of this group and potential mechanisms underlying the anaemia, including hypogonadism (79), alterations in haematopoietic stem and erythroid progenitor cell number and/or function, and the presence of "early" or overt myelodysplastic syndrome (MDS) (80). Preliminary observations indicate that erythropoietin levels are significantly lower in this group compared to those in whom the aetiology of the anaemia is found (81), suggesting possible impairment either in hypoxia sensing or erythropoietin production. Although increased inflammation leading to otherwise unexplained anaemia in the elderly is also an attractive hypothesis, given the increase in interleukin (IL)-6 seen with advancing age (82) and the known effects of the IL-6/hepcidin axis on erythropoiesis (83), two recent studies argue against this supposition. In the first, elderly patients with unexplained anaemia were found to have no elevation in inflammatory markers (IL-6, tumour necrosis factor alpha, C-reactive protein) compared to non-anaemic elderly controls (77). In the second study, 18 patients with unexplained anaemia were compared to age- and sex-matched controls, as well as a control group with anaemia of inflammation; there were no significant differences in hepcidin levels between the groups. Plasma hepcidin levels were measured using a recently described immunoassay (84) which has not yet been validated in large numbers of elderly individuals. Although these two studies suggest that unexplained anaemia is not driven by inflammation, it remains possible that there is a subset within this group with anaemia of chronic inflammation-type pathophysiology driving the anaemia.

5.4 Myelodysplastic syndrome as a cause of anaemia in the elderly

A percentage of those with otherwise unexplained anaemia is likely to have MDS. MDS is a disease of the elderly, with the median age of diagnosis in the late 60s to 70s (85). Several small studies have investigated the prevalence of MDS in elderly patients with otherwise unexplained anaemia. In the first study, 124 patients over the age of 75 underwent evaluation for macrocytosis (defined as an MCV > 95 fL). A diagnosis was established in 60% by non-invasive techniques, and the remaining 49 patients underwent bone marrow examination. Six of 124 (5%) were diagnosed with MDS; an additional 19 (15%) had some dysplastic features but did not fit diagnostic criteria for MDS by the French-American-British (FAB) classification and were felt to have "pre-MDS"; the remaining 24 had no morphological abnormalities (86). There was no follow-up information regarding evolution of the "pre-MDS" group to frank MDS or leukaemia. In a second study, 37 of 245 (15%) hospitalised geriatric patients who underwent evaluation for unexplained haematologic abnormalities were diagnosed with MDS, also using the FAB classification (87). Thirty-four patients had refractory anaemia, 2 had refractory

anaemia with ringed sideroblasts, and one had refractory anaemia with excess blasts. Seven additional patients had dysplastic features in only one lineage, and were considered to have "early MDS"; 5 of these 7 had only dysmegakaryopoiesis (87). Follow-up ranged from 1 to 70 months, and there was no survival difference between those with MDS and "early MDS". In a third study, 178 of 732 (24%) patients admitted to an acute geriatric ward (ages 65 to 81 years) were found to be anaemic (78). One hundred and nine underwent bone marrow evaluation, and 9 patients of the 178 (5%) were diagnosed with MDS by FAB criteria. Thus, approximately 5 to 15% of elderly patients with unexplained anaemia are likely to have MDS using FAB criteria, and an additional minority may have abnormalities which are suspicious but not confirmatory of MDS. This "pre-MDS" category is particularly intriguing, and more data are needed to better categorise these patients and better understand their long-term prognosis. Emerging molecular techniques to detect clonal haematopoiesis (88) will likely play an important role in this area.

6. Management of anaemia in the elderly

Therapy for anaemia in the elderly most importantly and effectively requires correction of any treatable underlying aetiology. In the individual with unexplained anaemia, treatment requires individual management, and depends on a multiplicity of factors, including functional status, co-morbidities, and patient wishes. There is no single threshold at which therapy should be initiated. In some patients, a haemoglobin less than 10 g/dL may be well tolerated, whereas in others, particularly those with cardiac or renal disease, intervening to maintain a haemoglobin above 10 g/dL is likely to benefit the patient. Given the generally mild nature of anaemia in this population, the majority of patients will not require therapy. Current therapeutic interventions are limited to the use of packed red cell transfusions or erythropoiesis stimulating agents (ESAs).

6.1 Transfusion in the treatment of unexplained anaemia in the elderly

Risks of red blood cell transfusion include the more common and less serious febrile or cutaneous reactions, as well as the more rare and more serious risks such as infection, anaphylaxis, volume overload, transfusion-related acute lung injury and fatal haemolytic reactions (89). In addition, given the transient effects of red cell transfusion, committing those with chronic anaemia to a chronic transfusion program brings with it the attendant risks of iron overload. Organ toxicity secondary to iron overload is disease-specific to some extent; although it is clear that transfusional iron overload in thalassaemia major leads to severe cardiac and hepatic iron overload and eventual death (90) which can be prevented by effective

iron chelation (91), there is debate about whether iron overload leads to the same degree of organ toxicity in other diseases (92, 93), including MDS (94). However, current guidelines recommend consideration of iron chelation therapy in patients with lower-risk MDS in whom 20 to 30 units of packed red blood cells have been transfused and who have ongoing transfusion requirements and a serum ferritin greater than 2500 µg/L (95). It is unknown if similar recommendations are warranted in elderly patients with unexplained anaemia on chronic transfusion therapy.

6.2 ESA therapy in the treatment of unexplained anaemia in the elderly

The currently available alternative to packed red blood cell transfusion is the use of ESAs. Three ESAs are currently in use: epoetin alfa, epoetin beta and darbepoetin. All are recombinant human erythropoietins and bind to the erythropoietin receptor (64, 96). Most data related to the use of ESAs exist in patients with renal disease (both dialysis-dependent and non-dialysis dependent) or those with cancer. Data from patients in renal disease are most likely to be relevant to elderly patients with unexplained anaemia, given the decline in renal function with aging and low erythropoietin levels seen in these patients. Two recent trials suggest that ESAs can be harmful in those with renal disease, particularly with aggressive correction of anaemia (97, 98). Based in part on these data, the US Food and Drug Administration (FDA) has issued a black box warning related to the use of ESAs in renal disease, and the package inserts recommend maintaining haemoglobin levels between 10 and 12 g/dL (99-101). Few studies have been carried out specifically in elderly patients with unexplained anaemia. In one randomised, blinded placebo-controlled crossover trial in elderly predominately African-American women with unexplained anaemia or anaemia of inflammation (defined by iron indices), increasing the haemoglobin by 2 g/dL led to improvements in quality of life as measured by the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system (102). Importantly, the target haemoglobin in this study was 13.0-13.9 g/dL, a target which would no longer be acceptable in today's climate. No serious adverse events were felt to be treatment related. The one reported thrombotic event was a pulmonary embolism occurring during epoetin alfa administration with a last study haemoglobin of 14.3 g/dL. However, the patient had been diagnosed with a lower leg deep vein thrombosis during the prior placebo portion of the study and was subsequently inadequately anticoagulated with an international normalised ratio of 0.9. Additional data are needed to determine whether correction of mild anaemia in the elderly patient with unexplained anaemia will lead to improvements in functional outcomes without accompanying toxicity, as well as to determine the optimal therapeutic target.

7. Conclusions

Anaemia in the elderly is common, and, although typically mild, is associated with substantial morbidity and even mortality. Elderly anaemic patients should undergo a standard evaluation for anaemia, including careful review of the peripheral smear. A diagnosis of iron deficiency anaemia requires a search for a source of blood loss. In elderly patients with unexplained anaemia, neither the optimal threshold for initiating therapy nor the optimal therapeutic target is established.

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Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/iron-handbook2009answers.htm

1. The prevalence of anaemia in independently living outpatients 65 and older is:

a) 2% ☐
b) 10% ☐
c) 50% ☐
d) 75% ☐

2. Anaemia in the elderly is associated with:

a) No functional impairments ☐
b) Increased rate of blindness ☐
c) Increased mortality ☐

d) Urinary incontinence ☐

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3. If iron deficiency anaemia is found in an elderly patient, in addition to iron repletion, evaluation and/or treatment must include:

a) Bone marrow aspirate and biopsy to assess iron stores ☐
b) Evaluation for the source of blood loss ☐
c) Folic acid supplementation ☐
d) Assessment of intrinsic factor antibodies ☐

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4. Possible contributors to "unexplained anaemia" of aging include all of the following except:

a) Haematopoietic stem cell or erythroid progenitor cell dysfunction ☐
b) Myelodysplastic syndrome ☐
c) Renal insufficiency ☐
d) Hyperoestrogenism ☐

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5. Peripheral smear findings suggestive of underlying myelodysplastic syndrome include all of the following except:

a) Additional cytopenias ☐
b) Dysplasia ☐
c) Rouleaux formation ☐
d) Macrocytosis ☐