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Morbidity and Mortality in Anemia

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1. Introduction

A growing body of research suggests that anemia is independently associated with morbidity and mortality in the general population as well as in patients with chronic diseases where the prevalence of anemia is high (1-4). Anemia prognosis depends on the underlying cause of the anemia. However, the severity of the anemia, its etiology, and the rapidity with which it develops can each play a significant role in the prognosis. Similarly, the age of the patient and the existence of other co-morbid conditions influence outcome. Higher mortality rates are almost always observed in patients with anemia. Many studies (5-11) identified anemia as an independent factor impacting mortality and provided the evidence that management of anemia, independent of other risk factors, improves mortality rates. In one study (3), independent of the underlying disease, anemia was associated with increased mortality in chronic kidney disease, congestive heart failure and acute myocardial infarction patients; increased morbidity in chronic kidney disease, congestive heart failure and cancer radiotherapy patients; and decreased quality of life in chronic kidney disease and cancer patients. In addition to its impact upon mortality, anemia also significantly influences morbidity. Multiple studies support this assertion especially in patients with chronic kidney disease and heart failure (12-17).

2. Morbidity and mortality among patients with certain types of anemia

2.1 Aplastic anemia

In the early 1930s aplastic anemia was considered almost inevitably fatal. However, the morbidity and mortality of this disease have decreased dramatically since the introduction of bone marrow transplantation and immunosuppressive therapy. Survival figures in aplastic anemia from several studies have shown biphasic curves, with the highest mortality rates within the first 6 months after diagnosis. Five-year survival rates have been described to range from 70% to 90% and to be similar among patients treated with either bone marrow transplantation or immunosuppression (18). Patients who undergo bone marrow transplantation have additional issues related to toxicity from the conditioning regimen and graft versus host disease (19). With immunosuppression, approximately one third of patients does not respond. For the responders, relapse and late-onset clonal disease, such as paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, and leukemia, are risks (20). In one retrospective institutional analysis, predictors for response to immmunosuppresion at 6 months were younger age, higher baseline absolute reticulocyte, lymphocyte, and neutrophil counts with the five-year survivals ranging from 92 in the

responders to 53% in the non responders (21). Two factors determines the clinical outcome in aplastic anemia, the severity of the pancytopenia and patient age. In a retrospective review from the European Group for Blood and Marrow Transplantation (EBMT), the relative risk for a poor outcome following immunosuppressive treatment was 3.4 for patients with very severe anemia and 1.5 in those with severe anemia compared with less severe cases. In the EBMT, the 5-year survival rate varied inversely and significantly with age. Also, at any degree of severity, the outcome was worse in older patients. The increase in mortality in the older patients was mainly due to infection or bleeding. Most infections were acquired from endogenous microbial flora of the skin and gastrointestinal tract (22).

2.2 Vitamin B12 deficiency anemia

Pernicious anemia is associated with a two- to threefold excess risk of intestinal-type gastric cancer but, the actual degree of risk varies with the duration of disease and geographic location. Pernicious anemia is also associated with an increased risk of gastric carcinoid tumors, presumably due to prolonged achlorhydria with compensatory hypergastrinemia, and argyrophilic cell hyperplasia. There is also a suggested excess of oesophageal cancer among these patients (23). In the analysis of the Oxford Vegetarian Study (24), low vitamin B12 intake could explain the increased death rate (2.2 times) from mental and neurological diseases among vegetarians compared to non-vegetarians. Specific neurologic problems associated with vitamin B12 deficiency consist of subacute combined degeneration of the dorsal (posterior) and lateral spinal columns, axonal degeneration of peripheral nerves and central nervous system symptoms including memory loss, irritability, and dementia (25).

In some cases, B12-deficient dementia may be misdiagnosed as Alzheimer's disease (26). The cognitive decline in older subjects associated with subclinical vitamin B12 deficiency is difficult to explain but a role for increased homocysteine level is possible. People with Alzheimer's disease were found to have elevated homocysteine, reduced B12, or reduced folate levels (27). On the other hand studies found elevated homocysteine to be associated with risk of Alzheimer's disease (26). Selhub et al. (27) analyzed data from 8,083 people, including whites, blacks, and Hispanics. They found that elevated homocysteine levels (> 11.4 µmol/l for men, > 10.4 µmol/l for women) were associated with B12 levels less than 338 pg/ml. A level of 430 pg/ml provides a safety factor for homocysteine and other potential problems. Elevated homocysteine is associated with increased mortality, with an increased risk of 33% per 5 µmol/l increase in homocysteine (28,29) with increased risk for coronary artery, cerebrovascular, and peripheral vascular diseases and venous thrombosis (30). A 2008 meta-analysis of vitamin supplementation and cognitive function found little benefit to people already diagnosed with dementia, but did improve cognition in elderly people with elevated homocysteine but who were not diagnosed with dementia (31). Another 2008 study found that vitamin supplementation did not slow cognitive decline in people with mild to moderate Alzheimer's disease (32).

Vitamin B12 deficiency appears to be associated with an increased risk of osteoporosis (33,34), and hip and spine fractures (35), possibly due to suppression of osteoblast activity (36,37). Even subtle degrees of B12 deficiency may be associated with bone loss (38), although this has not been shown in all studies (39). Supplementation with vitamin B12 and folate has been shown to reduce hip fractures in a group of elderly Japanese patients with residual hemiplegia after an ischemic stroke. However, there is insufficient data to recommend this therapeutic approach in other populations at high risk for fracture.

2.3 Folic acid deficiency anemia

Studies found that both maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects (40). In a literature review, Ray et al examined 8 studies that demonstrated that folate deficiency was a risk factor for placental abruption/infarction (41). Several observational and controlled trials have shown that neural tube defects can be reduced by 80% or more when folic acid supplementation is started before conception (42). In countries like the United States and Canada, the policy of widespread fortification of flour with folic acid has proved effective in reducing the number of neural tube defects (43). Although the exact mechanism is not understood, a relative folate shortage may exacerbate an underlying genetic predisposition to neural tube defects. Diminished folate status is associated with enhanced carcinogenesis. A number of epidemiologic and case-control studies have shown that folic acid intake is inversely related to colon cancer risk (44). With regard to the underlying mechanism, Blount et al showed that folate deficiency can cause a massive incorporation of uracil into human DNA leading to chromosome breaks (45). Another study by Kim et al suggested that folate deficiency induces DNA strand breaks and hypomethylation within the *p53* gene (46). Low folate and high homocysteine levels are a risk factor for cognitive decline in high-functioning older adults (47) and high homocysteine level is an independent predictor of cognitive impairment among long-term stay geriatric patients (48). Despite the association of high homocysteine level and poor cognitive function, homocysteine-lowering therapy using supplementation with vitamins B-12 and B-6 was not associated with improved cognitive performance after two years in a double-blind, randomized trial in healthy older adults with elevated homocysteine levels (49).

2.4 Thalassemia

Iron excess in patients with thalassemia is associated with early death if untreated. Several publications provide evidence that the heart is unquestionably the most critical organ affected by iron jeopardizing survival of thalassemia patients. In a study of 97 thalassemia patients (50), 36% of patients between the ages of 15 and 18 showed detectable cardiac iron, the risk of cardiac disease increases as patient's age increases. For the full cohort, the estimated survival without cardiac disease was 80% after 5 years of chelation therapy, 65% after 10 years and only 55% after 15 years. At the New York Academy of Sciences, Seventh Symposium on Thalassemia (51), the causes of death reported in 240 thalassemia major patients in Italy born between 1960-1984 were cardiac disease (71%), infections (12%), liver (6%) and other causes (11%). Another review of information available to the Cooley's Anemia Foundation shows that 11% of its 724 registered patients (77 total) died over the time period January 1999 – July 31, 2008. The data demonstrate that heart disease in these young patients remains the leading cause by far.

Since 1999, there has been a marked improvement in survival in thalassaemia major in the UK (52), similar change with improved survival has been reported from Italy (53,54) and Cyprus (55). This improvement has been mainly driven by a reduction in deaths due to cardiac iron overload. The most likely causes for this include the introduction of T2* cardiac magnetic resonance imaging technique to quantify myocardial iron overload and appropriate intensification of iron chelation treatment, alongside other improvements in clinical care. With a reduction in deaths from iron overload, infection may become a leading cause of death in thalassaemia in the future. Splenectomy increases risk of infection with Pneumococcus and Haemophilus influenzae and deferoxamine therapy increases risk of infection with Yersinia enterocolitica, and there have been at least 3 deaths from these

infections. However, the most frequently isolated organism was Klebsiella. An increased risk of Klebsiella infection in thalassaemia has previously been reported from South East Asia (56,57), and some forms of Klebsiella can use deferoxamine as an iron source (58), but it remains to be clarified whether Klebsiella infection is related to iron chelation therapy. Hepatocarcinoma is also a growing problem for hepatitis C positive patients, and improved antiviral treatments are needed. Fortunately, transmission of hepatitis C by blood transfusion is now very rare, so this risk may be limited to older patients (52).

2.5 Sickle cell anemia

The greatest burden of sickle cell anemia (SCA) is in sub-Saharan Africa (SSA), and estimates suggest that 50–80% of these patients will die before adulthood (59). Identification of risk factors has led to improved survival through targeted interventions. In the West, reported risk factors for death include infections, low hemoglobin and fetal hemoglobin (HbF), high white blood cell count and hemolysis (60-62). Comprehensive care includes prompt treatment of acute events and prophylaxis against infections, mainly with oral penicillin and vaccination against *Streptococcus pneumoniae.* Countries that have introduced these interventions have achieved significant reductions in mortality; with up to 94% surviving to 18 years in the USA (63) and 99% to 20 years in the UK (64). In most African countries, the lack of an evidence-base has led to inertia in terms of implementation of these interventions, such as penicillin prophylaxis. In Africa, available mortality data are sporadic and incomplete. Many children are not diagnosed, especially in rural areas, and death is often attributed to malaria or other comorbid conditions (65). The mortality rates in SCA amongst a hospital-based cohort in Tanzania (66) was 1.9 per 100 PYO which is similar to 3 per 100 PYO reported from the USA before use of penicillin prophylaxis (67), with the highest incidence of death was in the first 5 years of life. Evidence from previous research suggests that infection is the most likely cause of death in this period, with the proportion of deaths from infection reported to be 50% in the USA (60, 68), 28% in Jamaica (69) and 20% in Dallas (63). The prevention of pneumococcal infection with penicillin and the introduction of pneumococcal conjugate vaccine has been shown to be effective in reducing mortality (70) with improved survival rates of 84% in Jamaica (69), 86% by 18 years in Dallas (64) and 99% in London (65). One review reported 42% reduction in mortality in SCA in USA, 0 to 3 years old, between two eras, 1995–1998 and 1999–2002 (71). There is compelling justification for implementation of these interventions in Africa to prevent deaths due to infections (65,66).

Sudden death is not uncommon among SCA patients. A retrospective/prospective review of 21 autopsy cases from sickle cell patients who died suddenly between 1990 and 2004 demonstrated higher-than-expected percentages of acute and chronic sickle cell-related lung injury such as fat embolism (33.3%) and pulmonary hypertension (33.3%), with right ventricular hypertrophy (33.3%) (72). In Sickle cell trait (SCT) under unusual circumstances serious morbidity or mortality can result from complications related to polymerization of deoxy-hemoglobin S. Although rare, sudden death is the most serious complication of sickle cell trait. SCT has a substantially increased age-dependent risk of exercise-related sudden death as in military basic training and civilian organized sports. A retrospective review of all soldiers in basic training found that those with SCT had a 40-fold increased risk of sudden exertional death (73). Sudden death may occur in susceptible persons when poor

physical conditioning, dehydration, heat stresses or hypoxic states precipitate sickling of the abnormal erythrocytes. Most of the death mechanisms are related to the biological consequences of diffuse microvascular occlusion due to sickling, although a significant number of such sudden deaths remain unexplained after thorough autopsy. Rare mechanisms encountered include acute splenic sequestration (74). Other problems may also be encountered in SCT patients including increased urinary tract infection in women, gross hematuria, complications of hyphema, splenic infarction with altitude hypoxia or exercise and life-threatening complications of exertional heat illness (exertional rhabdomyolysis, heat stroke, or renal failure). In addition, some disease associations have been noted with sickle cell trait which might not result from polymerization of hemoglobin S but from linkage to a different gene mutation. There is an association with renal medullary carcinoma, early end stage renal failure in autosomal dominant polycystic kidney disease, and surrogate end points for pulmonary embolism (75).

2.6 Paroxysmal nocturnal hemoglobinuria

Most patients with paroxysmal nocturnal hemoglobinuria (PNH) die from venous thrombotic events. Stroke is a common cause of morbidity and mortality in PNH and it is almost exclusively a result of cerebral venous thrombosis. Case reports of ischemic stroke complicating PNH have implicated a similar propensity for arterial events caused by the disease. PNH is a rare cause of arterial stroke with reported 9 cases but it should be considered in young stroke patients with abnormal blood findings (76).

3. Morbidity and mortality of anemia in high risk groups

3.1 Effect of anemia on maternal mortality and morbidity

Maternal anemia is a ubiquitous pregnancy complication, and has been associated with an array of adverse perinatal and reproductive outcomes. It is estimated that 20% of maternal deaths in Africa can be attributed to anemia. In combination with obstetric hemorrhage, anemia is estimated to be responsible for 17–46% of cases of maternal death (77). A review of symptoms associated with maternal deaths in Bangladesh led researchers to conclude that anemia had played a secondary role in nearly all cases (78). Estimates of maternal mortality resulting from anemia range from 34/100,000 live births in Nigeria to as high as 194/100,000 in Pakistan (79). The risk of death is greatly increased with severe anemia. There is little evidence of increased risk associated with mild or moderate anemia. Viteri (80) reported that anemic pregnant women are at greater risk of death during the perinatal period and that anemia is the major contributory or sole cause of death in 20–40% of the 500 000 maternal deaths/year. A study from Indonesia illustrated the much higher risk of maternal death in anemic women from rural areas than from urban areas, possibly as a result of problems with timely access to obstetric care (81). On the basis of the evidence available, it seems reasonable to assume that the risk of maternal mortality is greatly increased with severe anemia. The data available only confirm an associative—not a causal—relationship. Nevertheless, the strength of this relationship makes it appropriate to presume that it is causal. It must also be noted that there are currently no agreed international standards or sets of criteria for attributing death to anemia (82). Except in South Asia and Papua New Guinea, the reported rates of severe anemia do not appear to exceed 10% of pregnant women (79). In a large Indonesian study, the maternal mortality rate for women with a

hemoglobin concentration <100 g/L was 70.0/10000 deliveries compared with 19.7/10000 deliveries for non-anemic women (81). However, the authors believed that the relation of maternal mortality with anemia reflected a greater extent of hemorrhage and late arrival at admission rather than the effect of a prenatal anemic condition. In another study, approximately one-third of the anemic women had megaloblastic anemia due to folic acid deficiency and two-thirds had hookworm. The cutoff for anemia was extremely low (<65 g hemoglobin/L), and the authors stated that although anemia may have contributed to mortality, it was not the sole cause of death in many of the women (83). It has been suggested that maternal deaths in the puerperium may be related to a poor ability to withstand the adverse effects of excessive blood loss, an increased risk of infection, and maternal fatigue; however, these potential causes of mortality have not been evaluated systematically (84).

Maternal morbidity resulting from anemia includes diminished work capacity and physical performance have been reported as a result mostly of iron deficiency anemia. Anemia leads to abnormalities in host defense and neurological dysfunction. Increased risks of premature labor and low birth weight have also been reported in association with anemia in pregnancy (80).

3.2 Effect of anemia on infant mortality and morbidity

There is substantial evidence that maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight, and accumulating information suggests an association between maternal iron status in pregnancy and the iron status of infants postpartum. Preterm infants are likely to have more perinatal complications, to be growth-stunted, and to have low stores of iron and other nutrients. Lower birth weights in anemic women have been reported in several studies (85-87). In one study, the odds for low birth weight were increased across the range of anemia, increasing with lower hemoglobin in an approximately dose-related manner (88). Welsh women who were first diagnosed with anemia (hemoglobin <104 g/L) at 13–24 wk of gestation had a 1.18–1.75-fold higher relative risk of preterm birth, low birth weight, and prenatal mortality (89). After controlling for many other variables in a large Californian study, Klebanoff et al., (90) showed a doubled risk of preterm delivery with anemia during the second trimester but not during the third trimester. In Alabama, low hematocrit concentrations in the first half of pregnancy but higher hematocrit concentrations in the third trimester were associated with a significantly increased risk of preterm delivery (91). When numerous potentially confounding factors were taken into consideration, analysis of data from low-income, predominantly young black women in the United States showed a risk of premature delivery (<37 wk) and subsequently of having a low-birth-weight infant that was 3 times higher in mothers with iron deficiency anemia on entry to care (92). Similar relations were observed in women from rural Nepal, in whom anemia with iron deficiency in the first or second trimester was associated with a 1.87-fold higher risk of preterm birth, but anemia alone was not (88). In an analysis of 3728 deliveries in Singapore, 571 women who were anemic at the time of delivery had a higher incidence of preterm delivery than did those who were not anemic (93). An association between maternal anemia and lower infant Apgar scores was reported in some studies. In 102 Indian women in the first stage of labor, higher maternal hemoglobin concentrations were correlated with better Apgar scores and with a lower risk of birth asphyxia (94). In the Jamaican Perinatal Mortality Survey of >10000 infants in 1986, there was an ≈50% greater chance of mortality in the first year of life for those infants whose

mothers had not been given iron supplements during pregnancy (95). Trials that included large numbers of iron-deficient women showed that iron supplementation improved birth weight (86,96) and Apgar scores (97). In rural populations in China antenatal supplementation with iron-folic acid was associated with longer gestation and a reduction in early neonatal mortality compared with folic acid. Multiple micronutrients were associated with modestly increased birth weight compared with folic acid, but, despite this weight gain, there was no significant reduction in early neonatal mortality (98).

3.3 Effect of anemia on children and adolescents mortality and morbidity

Apart from previously mentioned morbidity and mortality from hereditary anemia among children, by far the most common cause of anemia in this age group is chronic iron deficiency anemia (IDA). There is reasonably good evidence that mental and motor developmental test scores are lower among infants with IDA. Although some aspects of cognitive function seem to change with iron therapy, lower developmental IQ and achievement test scores have still been noted after treatment. A variety of non-cognitive alterations during infant developmental testing has also been observed, including failure to respond to test stimuli, short attention span, unhappiness, increased fearfulness, withdrawal from the examiner, and increased body tension. Exploratory analyses suggest that such behavioral abnormalities may account for poor developmental test performance in infants with IDA. There has been a steady accumulation of evidence that IDA limits maximal physical performance, sub-maximal endurance, and spontaneous activity in the adult, resulting in diminished work productivity with attendant economic losses. However, it is important to consider that studies that attempt to separate indicators of malnutrition, such as iron deficiency, from other types of environmental deprivation may be inappropriately separating factors that occur together naturally and that therefore cannot be differentiated (99). The behavioral effects of IDA may be due to changes in neurotransmission. In a recent review that focuses on human studies, short- and long-term alterations associated with iron deficiency in infancy can be related to major dopamine pathways (100). It is widely accepted that long-term consequences of iron deficiency are often irreversible. Several studies have found that reversal of the anemia did not improve standardized test scores (101,102). One study (103) examined a group of Costa Rican children at five years of age. Children who had moderately severe IDA (hemoglobin less than 10 g per dL [100 g per L]) in infancy scored significantly lower on standardized tests at five years of age, despite a return to normal hematologic status and growth.

However, there is accumulating evidence for the potential benefits of preventing iron deficiency in infancy and treating it before it becomes chronic or severe. A recent study (104) of the preschool-aged Chinese children found that children who had chronic IDA in infancy displayed less positive social and emotional development. In contrast, the behavior and affect of children whose anemia was corrected before the age of 24 months were comparable to those of children who were non-anemic throughout infancy. The persistence of poorer cognitive, motor, affective, and sensory system functioning during childhood highlights the need to prevent iron deficiency in infancy and to find interventions that lessen the long-term effects of this widespread nutrient disorder.

Iron deficiency is also implicated in such neurologic sequelae as irritability, lethargy, headaches, and infrequently papilledema, pseudotumor cerebri, and cranial nerve

abnormalities. Although only a few cases (30 cases) in the literature support the association between IDA and increased intracranial tension, it may be more common than previously thought. The underlying mechanisms remain unknown, but cerebral venous thrombosis should be carefully excluded (105). Rarely has iron deficiency been recognized as a significant cause of stroke in the adult or pediatric populations (106,107). One case series reported 6 children, 6 to 18 months of age, who presented with an ischemic stroke or venous thrombosis after a viral prodrome. All patients had iron deficiency as a consistent finding among the group, and other known etiologies of childhood stroke were excluded (108)

3.4 Effect of anemia on mortality and morbidity in elderly people

In the past decade, anemia has been associated with a number of negative outcomes in elderly people. In a report from the Netherlands, community-dwelling subjects older than 85 years with anemia had higher 5-year mortality rates than subjects with normal hemoglobin levels (109,110). In a cohort of older women with mild-to-moderate physical disability, Chaves et al noted an increase in mortality associated with hemoglobin levels less than 110 g/L (111). In a study of 1744 community-dwelling persons aged 71 years or older, anemia is independently associated with increased mortality over 8 years for both races and sex. Anemia also is a risk factor for functional and cognitive decrease (1).

In an analysis of 5888 community-dwelling older adults enrolled in the Cardiovascular Health Study (2), anemia was associated with increased risk for hospitalization and mortality in older adults. In another community-based study of more than 17 000 older adults more than 66 years (4), anemia was significantly associated with risk for all-cause hospitalization, hospitalization secondary to cardiovascular disease, and all-cause mortality. In both studies, the association between hemoglobin and mortality was not linear; with the risk for death increased at both extremes of hemoglobin. As this risk occurs at hemoglobin levels that are currently considered normal, consideration should be given to refining the current definition of anemia in older adults to reflect this continuum of risk (2, 4).

Not only anemia in elderly is a strong predictor of death, it has also been associated with various conditions such as decreased physical performance, disability in daily living, mobility disabilities, cognitive impairment, depression, falls and fractures, frailty, admission to hospital and diminished quality of life (112-114). However in the presence of common comorbidities among elderly, anemia could be considered as a risk marker rather than a risk factor. In the Leiden 85-plus Study (115), a population-based prospective follow-up study of 562 people aged 85 years, anemia in very elderly people was found to be associated with an increased risk of death, independent of comorbidity. However, the associated functional decline appears to be attributed mainly to comorbidity.

3.5 Effect of anemia on mortality and morbidity in patients with cancer

Anemia is common in cancer patients, although the prevalence is influenced both by the type of malignancy and the choice of treatment. Individual studies have compared the survival of patients with and without anemia and have shown reduced survival times in patients with various malignancies associated with anemia including carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. A systemic, quantitative review in 2001 (116) estimated the overall increase in risk of death with anemia to 65% (CI: 54-77%). In addition, an intriguing association has also been observed between anemia and disease progression among patients undergoing radiotherapy, particularly in those with

cervical carcinoma or with squamous cell carcinoma of the head and neck. Harrison et al found that two thirds of women with cervical carcinoma are anemic at baseline, and 82% are anemic during radiotherapy (117). Correlations between anemia, tumor tissue oxygenation, local recurrence, and survival have been demonstrated in other studies (118,119). In one study including cases of head and neck cancer, 75% of patients undergoing combined chemotherapy and radiotherapy become anemic (120) and anemia has been associated with worse local regional control and survival rates (121). However, there is presently little evidence that anemia treatment per se impacts the tumor response to chemotherapy alone.

3.6 Effect of anemia on mortality and morbidity in patients with cardiac diseases

Substantial evidence suggests that anemia is an independent risk factor for worse outcomes in patients with heart failure (CHF) and ischemia heart disease including myocardial infarction. Anemia is a common comorbidity in CHF. Compared with nonanemic patients the presence of anemia also is associated with worse cardiac clinical status, more severe systolic and diastolic dysfunction, a higher beta natriuretic peptide level, increased extracellular and plasma volume, a more rapid deterioration of renal function, a lower quality of life, and increased medical costs (122-129).

In a systematic review and meta-analysis published in 2008, after a minimal follow-up of 6 months, 46.8% of anemic patients died compared with 29.5% of non-anemic patients irrespective to the cause of CHF. In studies that analyzed hemoglobin as a continuous variable, a 1-g/dL decrease in hemoglobin was independently associated with significantly increased mortality risk (130).

The associations between hemoglobin and outcomes was studied in 2653 patients randomized in the CHARM Program in the United States and Canada. Anemia was common in heart failure, regardless of left ventricular ejection fraction (LVEF). Lower hemoglobin was associated with higher LVEF yet was an independent predictor of adverse mortality and morbidity outcomes (131). On the contrary, a large nationally representative study of older patients in the United States hospitalized with HF demonstrated no graded relationship between lower hematocrit values and increased mortality and suggest that although anemia is an independent predictor of hospital readmission, its relationship with increased mortality in HF patients is largely explained by the severity of comorbid illness. The authors suggest that anemia may be predominantly a marker rather than a mediator of increased mortality risk in older patients with HF (132).

In heart failure, the causes of anemia and the associations between anemia and outcomes are probably multiple and complex. The anemia in CHF mainly is caused by a combination of renal failure and CHF-induced increased cytokine production, and these can both lead to reduced production of erythropoietin (EPO), resistance of the bone marrow to EPO stimulation, and to cytokine-induced iron-deficiency anemia caused by reduced intestinal absorption of iron and reduced release of iron from iron stores. The use of angiotensin-converting enzyme inhibitor and angiotensin receptor blockers also may inhibit the bone marrow response to EPO. Hemodilution caused by CHF also may cause a low hemoglobin level (129). The potential mechanisms linking anemia to increased mortality risk in CHF have not been characterized but may be related to changes in ventricular loading conditions and cardiac structure, altered neurohormonal activation, or reduced free radical scavenging capacity. It is also possible that anemia is a marker of more severe underlying myocardial disease (133).

In several controlled and uncontrolled studies, correction of the anemia with subcutaneous erythropoietin (EPO) or darbepoetin in conjunction with oral and intravenous iron has been

associated with an improvement in clinical status, number of hospitalizations, cardiac and renal function, and quality of life. However, larger, randomized, double-blind, controlled studies still are needed to verify these initial observations. The effect of EPO may be related partly to its nonhematologic functions including neovascularization; prevention of apoptosis of endothelial, myocardial, cerebral, and renal cells; increase in endothelial progenitor cells; and anti-inflammatory and antioxidant effects (129).

In ischemic heart disease, both advanced age and the presence of flow-limiting coronary stenosis markedly impaired cardiac compensatory response to anemia, even without concomitant acute myocardial injury. These conditions, among other limits to the patients' physiologic reserve, may explain why levels of hemoglobin tolerated by younger individuals would not be tolerated by the elderly. They may also explain why elderly patients with acute myocardial infarction represent a group at extremely high risk for death, despite infarct sizes similar to those of younger patients (3).

The clinical utility of blood transfusion in anemic cardiovascular disease populations is controversial. According to the guidelines from the American College of Physicians and the American Society of Anesthesiology, the "transfusion threshold" for patients without known risk factors for cardiac disease is a hemoglobin level in the range of 6 to 8 g/dL. In one study, patients hospitalized with acute myocardial infarction, blood transfusion was associated with a significantly lower 30-day mortality rate among patients with a hematocrit <30% on admission (134). But in 838 critically ill patients (26% with cardiovascular disease), maintaining hemoglobin at 10 to 12 g/dL did not provide additional benefits on 30-day mortality compared with maintaining hemoglobin at 7 to 9 g/dL (135). Blood transfusion may be associated with other adverse effects including immunosuppression with increased risk of infection, sensitization to HLA antigens, and iron overload. Given this profile of risks and benefits, transfusion may be considered as an acute treatment for severe anemia on an individualized basis but does not appear to be a viable therapeutic strategy for the long-term management of chronic anemia in CHF (135,136).

Pilot studies have found that in a large number of HF patients it's safe to raise hemoglobin with erythropoietin-stimulating therapies and there is a suggestion that raising hemoglobin in anemic HF patients may lead to improved outcomes (136). A prospective, randomized trial studied the treatment of anemia in patients with moderate-to-severe CHF (NYHA class III to IV) whose left ventricular ejection fraction was less than 40% of normal. Patients who received treatment had a 42.1% improvement in NYHA class, compared with the control cohort who had a decrease of 11.4%. Number of hospital days, need for diuretic therapy, and renal function impairment were all significantly greater in the control group than in the treated group (137).

The Study of Anemia in Heart Failure Trial (STAMINA-HeFT) is a large multicenter, randomized, double-blind, placebo-controlled trial. In this study treatment of anemia with erythropoiesis-stimulating agents (ESAs) (darbepoetin alfa) was not associated with significant clinical benefits. But in the post hoc analysis of outcomes among the treated group, an increase of 1.0 g/dL or more in hemoglobin is required to achieve benefit in reduction of all-cause mortality or heart failure-related hospitalization (138). However, further observational and experimental studies are needed to help identify optimal treatment algorithms for both ESAs and iron that maximize clinical benefit while minimizing adverse outcomes. A pragmatic approach to the care of patients with HF needs definitive anemia treatment goals that are dynamic and disease specific, rather than those that adopt a more simplistic hemoglobin-specific approach.

3.7 Effect of anemia on mortality and morbidity in patients with end stage renal diseases

Anemia is associated with higher mortality rates and possibly heart disease in patients with kidney disease. However, the available evidence is limited as concluded in a systematic literature review published in 2006 (139). In a retrospective review (140) of nearly 20 000 of patients undergoing maintenance hemodialysis, hemoglobin levels of 8.0 g/dL or less were associated with a 2-fold increase in odds of death when compared with hemoglobin levels ranging between 10.0 and 11.0 g/dL. A similar study (141) of nearly 100 000 hemodialysis patients confirmed that a hematocrit higher than 30% was associated with a lower mortality. Compared with patients with a hematocrit higher than 30%, the overall relative risk of death was between 33% and 51% higher for the group with a hematocrit less than 27%, and between 12% and 20% higher for the group with a hematocrit of 27% to 30%, with and without adjustments for severity of disease. Subsequent analyses have determined that hematocrit levels maintained between 33% and 36% were associated with the lowest risk of death (142). Another study showed that in patients undergoing maintenance hemodialysis, the risk of hospitalization declines with hematocrit improvement, with a 16% to 22% lower hospitalization rate for patients with hematocrit values between 36% and 39% compared with patients with hematocrits between 33% and 36% (12). Also, prospective clinical trials of patients with end-stage renal disease have demonstrated a relationship among hematocrit, left ventricular dilatation, and left ventricular hypertrophy (LVH) (13-17,143).

The optimal management of anemia in patients with end-stage renal disease is controversial. Appropriate use of ESAs and intravenous iron can effectively manage the anemia of chronic kidney disease and end-stage renal disease (ESRD) (144-146), several randomized trials have reported an increased risk of mortality and cardiovascular events in patients treated to achieve higher hematocrit levels (145-147). A large cohort of incident US hemodialysis patients found that dialysis units that treated severe anemia more aggressively with ESAs and intravenous iron had a one-year mortality rate that was 5 percent lower than in units that treated more conservatively. But the same aggressive treatment for milder anemia brought a 10 percent increase in the rate of mortality (147).

3.8 Effect of anemia on mortality and morbidity in patients with end stage renal diseases and heart failure

Anemia also may play a role in increasing cardiovascular morbidity in chronic kidney insufficiency, diabetes, renal transplantation, asymptomatic left ventricular dysfunction, left ventricular hypertrophy, acute coronary syndromes including myocardial infarction and chronic coronary heart disease, and in cardiac surgery. Renal failure, cardiac failure, and anemia therefore all interact to cause or worsen each other--the so-called cardio-renal-anemia syndrome (129). The reciprocal relationships among these 3 components of cardiorenal anemia have been the subject of a number of trials with inconsistent and sometimes paradoxic results (148). Cardiovascular disease (CVD) is a significant complication in chronic kidney disease (CKD) and a major cause of death in dialysis patients. Clinical studies have shown that anemia is associated with reduced survival in patients with renal disease, heart failure or both. Low haemoglobin (Hb) has been identified as an independent risk factor for LV growth in CKD patients, suggesting that there is a direct link between anemia and adverse cardiac outcomes. This suggests that correction of anemia may improve prognosis. In patients with chronic kidney disease and CHF, treatment of anemia improves many of the abnormalities seen in CHF: it reduces LVH (149-151);

prevents left ventricular dilatation (152); and increases left ventricular ejection fraction, (153-154), stroke volume, and cardiac output (153).

The evidence for an association between anemia and an increased risk of adverse cardiovascular outcomes in patients with CKD is strong. The relationship between anemia and adverse outcomes is complex. While it is likely to be indirect to some extent, evidence also suggests that there may be a causal link between low hemoglobin levels and the development of CVD. Treatment of anemia with epoetin has been shown to improve cardiac function and to produce regression of LVH in CKD patients, whether or not they are receiving dialysis. Furthermore, consistent treatment with epoetin before the initiation of dialysis is associated with a reduced risk of developing cardiac disease in patients with CKD. Normalizing Hb levels in patients with advanced CVD has a limited effect on changes in LV geometry, however, and – at least under certain circumstances –may increase their risk of death. The degree of CVD could affect other factors, such as vascular reactivity, which may determine whether partial or full correction of anemia is appropriate for a particular individual (154).

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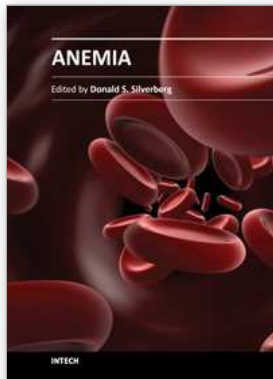
This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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