Anemia in elderly people: Risk marker or risk factor?

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The association between old age and anemia has been recognized for decades. But does it occur because aging causes anemia or because specific age-related diseases bring it on? Recent population-based surveys have renewed the debate and have even referred to the high prevalence of anemia among elderly people as a "public health crisis."[1] Many of us, schooled before the availability of erythropoiesis-stimulating agents, were taught that anemia is often a concomitant of chronic disease and perhaps aging. Thus, we were admonished not to try to correct anemia but rather to treat the underlying cause.

Recent studies have called into question the role of anemia in cognitive and physical dysfunction and mortality among elderly patients, independent of the underlying cause. The study by den Elzen and colleagues adds further information about the role of anemia in their carefully designed and executed analysis of data from the Leiden 85-plus Study.[2] Their study appears to confirm that mortality is associated with anemia, even after adjustment for important covariables, despite the fact that adjustment for comorbidity largely neutralized the deleterious effects of anemia on both cognitive and physical function. Furthermore, they showed a clear dose–response relation between increasing severity of anemia and risk of death. In other words, anemia appeared to be an independent predictor of mortality. However, with respect to functional decline over time, the authors could not discern whether anemia constituted an intermediate step in the causal pathway from chronic disease to decline in function.

Although the mortality rates were similar among people without anemia and among those whose anemia was corrected during the study period, we have no information as to whether the correction was obtained by treating the underlying disease or by raising the hemoglobin level. If the hemoglobin level was increased, the possibility of intervening via transfusion or erythropoeisis-stimulating agents becomes pertinent in elderly patients.

Anemia in elderly people appears to have multiple etiologies, including nutritional deficiencies and chronic disease.[3] Nevertheless, the cause of about one-third of cases remain unexplained, and there is usually only a mild decrease in the hemoglobin level.[4] Possible mechanisms of unexplained anemia of aging include a blunted erythropoetic response in the setting of iron deficiency, higher circulating levels of proinflammatory cytokines (e.g. IL6, which may reduce erythropoietin levels), decreased androgen levels, and decreased proliferative and regenerative capacity of bone marrow stem cells.[4] Furthermore, although not a concomitant of normal aging, myelodysplasia, which is more common in elderly people, is associated with reduced life-expectancy and is often included in the group of "unexplained" anemias.

Key points

- Anemia in the elderly is associated with decreased function and increased mortality.
- It is not yet known if this association indicates causality.
- Randomized trials of anemia correction should demonstrate that treatment does more good than harm by examining clinically important outcomes.

Three decades ago, the possibility of a benign form of so-called "senile anemia," unexplained by other known causes, was raised. Because elderly people have less need for oxygen transport than do active younger people, the authors argue that there was little urgency in treating this type of anemia.[5] However, the question of whether aging (as opposed to disease) causes anemia has recently become more relevant, given the possibility of treatment without blood transfusion.

If anemia is due to a lack of iron, B_{12} or folate, we can correct the deficiency and, if possible, treat the underlying cause. In the current study, excluding people taking B_{12}, folate and iron supplementation did not change the overall rate of mortality, suggesting that nutritional causes do not necessarily contribute to the excess mortality observed.

Clinical studies in both chronic kidney disease[6] and cancer[7] have shown improvement in health-related quality of life following treatment of anemia with erythropoeisis-stimulating agents.[8] However, this benefit comes at a cost, because hemoglobin correction to nonanemic levels may be associated with increased mortality.[9,10] Moreover, it has even been argued that anemia of chronic disease is an adaptive response and that efforts to correct the hemoglobin level may be futile at best or harmful at worst.[11]

For unexplained anemia in elderly patients, we may never be able to disentangle whether the underlying cause or the anemia is responsible for death. In their study, den Elzen and colleagues corrected for as many factors as possible, but the risk of residual confounding by underlying disease remains. A randomized clinical trial involving elderly people showed that subcutaneous epoetin alfa was associated with a rise in hemoglobin and a statistically significant improvement in fatigue and anemia (on subscales of the FACIT questionnaire).[12] However, this small trial, despite showing benefits in quality of life, was seriously underpowered to detect any effect on risk of death. Subsequent studies will need to address this question, especially among patients aged 85 or more years, among who, as shown in the

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Leiden study, have a high risk of death (> 8% per year).

Unexplained anemia in elderly people is usually characterized by a mild decrease in hemoglobin.[4] As such, a helpful finding in the study by den Elzen and colleagues is that the risk of death was significantly elevated in the adjusted models only when anemia was severe (hemoglobin < 100 g/L for women and < 110 g/L for men). This finding implies that the causes of anemia in this group are primary bone marrow failure or severe disease and not the "unexplained" anemias of the elderly. It also suggests that trials of hemoglobin correction should focus on this group.

Elderly people may also want a voice in their treatment, given the competing risks and benefits. It is possible that some patients might choose the quality of life and functional improvements despite the increased risk of death.

Physicians should be alert to the possible role of interested parties, including industry, who push for unexplained anemia to be considered a treatable condition. Elderly people constitute a large and growing target for those seeking new markets. Let us first insist on proof that correction of anemia in elderly patients (beyond the treatment of underlying causes) does more good than harm.

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