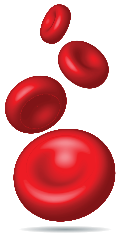


Evaluation and management of anemia in the elderly

Lawrence Tim Goodnough^{1,2,3*} and Stanley L. Schrier^{2,3*}

Anemia is now recognized as a risk factor for a number of adverse outcomes in the elderly, including hospitalization, morbidity, and mortality. What constitutes appropriate evaluation and management for an elderly patient with anemia, and when to initiate a referral to a hematologist, are significant issues. Attempts to identify suggested hemoglobin levels for blood transfusion therapy have been confounded for elderly patients with their co-morbidities. Since no specific recommended hemoglobin threshold has stood the test of time, prudent transfusion practices to maintain hemoglobin thresholds of 9–10 g/dL in the elderly are indicated, unless or until evidence emerges to indicate otherwise.

Am. J. Hematol. 89:88–96, 2014. © 2013 Wiley Periodicals, Inc.



■ Introduction

Anemia is now recognized as a risk factor for a number of adverse outcomes in older adults, including hospitalization, morbidity, and mortality [1–7]. The elderly is an important demographic population that is growing rapidly (<http://www.census.gov/ipc/www/idb/worldpopgraph.html>) in the context of increasing prevalence of anemia with age [8]. An analysis of two databases (NHANES-III, Third U.S. National Health and Nutrition Examination Survey; and SCRIPPS-Kaiser Data, 1998–2002) found that normal ranges for hemoglobin values are unchanged for aging populations, with the exceptions of minor adjustments for males (Table I) [9]. More than 10% of community-dwelling adult ≥ 65 years of age have a World Health Organization (WHO)—defined anemia (hemoglobin < 12 g/dL in women and < 13 g/dL in men). After 50 years of age, prevalence of anemia increases with advancing age and exceeds 20% in those ≥ 85 years of age [10]. As illustrated in Fig. 1 [11], there is a J-shaped correlation of anemia with mortality in older men and women. A recent study has analyzed the impact of declines (rather than an absolute level) in hemoglobin in 3,759 non-anemic elderly participants from the Cardiovascular Health Study [12], a prospective randomized cohort of community-dwelling elderly patients ≥ 65 years of age followed for up to 16 years. The authors found that hemoglobin decreases identified a large group of elderly individuals at risk for subsequent adverse outcomes (worse cognitive function) who would not be identified using the WHO anemia criteria.

With increasing recognition of the importance of anemia in the general population, guidelines have been published for the detection, evaluation, and management of anemia in medical [13] and surgical [14] patients. However, for elderly patients, attempts to identify suggested hemoglobin levels for management of anemia, including blood transfusion therapy, have been confounded by increased risks from anemia, along with additional co-morbidities. What constitutes an appropriate work-up for an elderly patient with anemia; and when to refer the patient to a hematologist, given the potentially large number of subjects involved, are significant costs-benefit issues [15]. In this review, we summarize our approach for management of anemia in the elderly, with a focus on transfusion therapy.

■ Characterization of Anemia in the Elderly

An important contribution was made by the NHANES III investigators who did a laboratory evaluation of over 5,000 community-dwelling elderly subjects, 10% of whom had anemia according to the WHO criteria. For the most part the anemia is mild, with hemoglobin levels infrequently < 10 g/dL [8]. Nevertheless, this mild anemia has been associated with significant negative outcomes, including decreased physical performance [16], increased number of falls [17], increased frailty [18], decreased cognition [18], increased dementia [19], increased hospitalization [1], and increased mortality [7]. The NHANES III investigators used fixed laboratory measures to determine that about one-third of these anemic patients have evidence of a nutritional deficiency, primarily that of iron; one-third have chronic inflammation or chronic kidney disease (CKD); and one-third have unexplained anemia [8].

Unexplained anemia of the elderly (UAE) is a real entity characterized by a hypoproliferative normocytic anemia that is not due to the nutritional deficiency, CKD or inflammatory disease; and in which the erythropoietin response to anemia appears to be blunted. In a study of 124 anemic elderly (≥ 65 years) persons, 42 (37%) had UAE [20]. These patients had significantly lower C-reactive protein (CRP) levels than non-anemic

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Disclosures: LTG: consultant for Amgen, Venofor, Luitpold, CSL Behring; SLS: is a recipient of NIH funding: RO1 AG029124; UO1 AG034661

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Contract grant sponsor: NIH funding; Contract grant numbers: RO1 AG029124, UO1 AG034661.

Received for publication: 10 September 2013; **Accepted:** 21 September 2013

Am. J. Hematol. 89:88–96, 2014.

Published online: 20 September 2014 in Wiley Online Library (wileyonlinelibrary.com).

DOI: 10.1002/ajh.23598

controls. Additionally, hepcidin levels do not seem to increase with age in the general population. Hepcidin levels in the anemia of aging change with comorbid conditions (low in iron-deficiency anemia and higher in inflammatory conditions); however, in patients with UAE, who have no identifiable comorbidities, hepcidin levels remain in the normal range [20–22]. These observations could be because UAE is heterogeneous, in which diverse underlying causes such as impaired erythropoietin response to anemia and or an underlying stem cell disorder, may confound an effect from hepcidin [21]. The role of testosterone deficiency in males is currently being studied by an National Institute of Aging (NIA) funded consortium.

Typically, in persons 65 years of age or older there is an underlying etiology for the anemia such as chronic disease, iron deficiency, or myelodysplastic syndromes that can be identified by further investigation [23]. In a study of 232 patients aged 65 to 98 (median 81) years of age, 24% were found to be anemic [24]. Of these, after a comprehensive work-up 17% did not have an identifiable underlying cause. The major causes of anemia and their prevalence in the elderly are illustrated in Fig. 2 [25]: prevalence ranges from three studies [8,26,27] are for UAE (34%–44%); iron deficiency (12%–25%); CKD (4%–8%); MDS (9%–16%); malignant hematologic (e.g., chronic lymphocytic leukemia) disorder (2%); or inflammation (6%–20%). Interestingly, folic acid deficiency has disappeared in the U.S. population, probably as a result of fortification of flour [26,27]. While 10%–20% of elderly patients have been described as Vitamin B₁₂ deficient (defined by reduced serum levels of Vitamin B₁₂) [28,29], clinically significant Vitamin B₁₂ deficiency is uncommon, diagnosed in only 1/190 [26] and 1/174 subjects [27] in two studies, respectively. For emphasis that means that as a cause of macrocytosis, Vitamin B₁₂ deficiency is much less common than MDS or ethanol abuse.

Studies at two academic institutions using comprehensive clinical and hematologic analyses have refined the prevalence and causes of anemia in the elderly [26,27]. Iron deficiency anemia represented the most common cause of anemia in the elderly, at 25.3% [27]. Iron deficiency may be due to the nutritional deficiency or blood loss; in the relatively affluent Western world, blood loss is the major issue. The cause of blood loss must be identified since in this patient group, iron deficiency could be a sign of a serious disorder such as colon cancer [30–33]. Furthermore, in this patient group one cannot use simple laboratory tests based on transferrin saturation and ferritin levels to readily differentiate between iron deficiency and inflammation as a cause of anemia.

A number of studies have demonstrated that IL-6 levels increase with aging, and are correlated with the development of anemia in the elderly [23], including healthy women [34], such as the Framingham Heart Study [35], and the Established Populations for Epidemiologic

Studies of the Elderly (EPESE) [36]. More recently, studies of IL-6 and hepcidin levels have not been found these to be elevated in elderly patients who do not have comorbid diseases [20–22]. There may be several reasons for these discrepant results. First, if aging is associated with only small increases in IL-6, one would need a large sample size for detection. Additionally, currently these assays measure the monomeric form of IL-6, which also exists as a multimer complicating the analysis.

Evaluation of Anemia

Commonly identified when the elderly are scheduled for elective surgical procedures. Anemia is a common condition in surgical patients and is independently associated with increased perioperative mortality [37]. When pre-admission testing prior to elective surgery reveals anemia, it should therefore be viewed as a significant and treatable medical condition, rather than as simply an abnormal laboratory value [38]. The diagnosis of an unexpected anemia in patients scheduled for elective surgery in which significant blood loss is anticipated, should be considered an indication for rescheduling elective surgery until evaluation and management of anemia is accomplished.

In traditionally taught approaches to evaluating a patient with anemia, the mean corpuscular volume (MCV) typically has been used as a starting indice [39], followed by biochemical analysis. The MCV has been shown to add value to the red cell distribution width (RDW) for evaluation of macrocytosis [40]. However, for microcytic anemias, MCV is of less value, particularly for patients with iron deficiency who have comorbidities. Twenty-two percent of elderly patients can be identified as having iron deficiency anemia by their response to a course of ORAL iron therapy, despite not having the typical laboratory findings of transferrin saturation <16% and ferritin <30 ng/mL [25]. When transferrin saturation is low (<16%) and the ferritin level is high (>200 ng/mL), the diagnosis of anemia of inflammation is generally considered [41]. However, the MCV is normal in 70% of patients with anemia of inflammation [42], despite

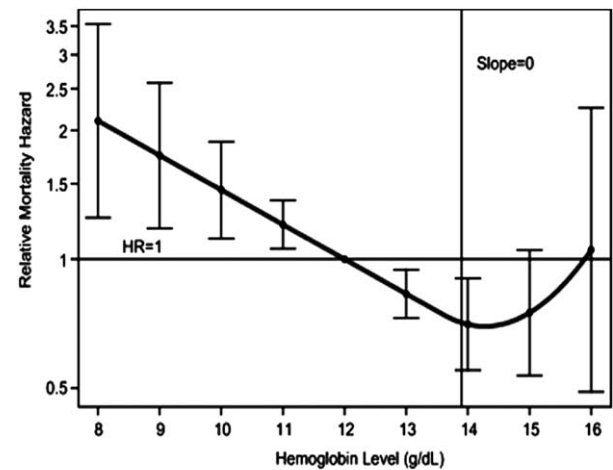


Figure 1. Relationship between hemoglobin (Hb) concentration and 5-year all-cause mortality in community-dwelling, disabled older women. Graphical display of relative risk estimates for the mortality linked to specific Hb concentrations compared with the risk linked to Hb of 12 g/dL. The curve represents smoothed relative mortality hazards across Hb concentrations, and the bars indicate their 95% confidence intervals. Indicated also is the 13.9 g/dL Hb threshold at which the slope of mortality risk decline was no longer statistically significant (i.e., the 95% confidence interval for the slope of the tangent included 0). The y-axis was transformed so that, for example, the graphical display of an increase in risk of the magnitude of two (hazard ratio [HR] 52) would be equivalent to that of a decrease in risk of the same magnitude (HR 50.5) in terms of scale size. Reproduced from Chaves et al. [11].

TABLE I. Lower Limits of Normal for Hemoglobin Concentration for White and Black Adults

Group	Hemoglobin (g/dL)
White men (yr)	
20–59	13.7
60+	13.2
White women (yr)	
20–49	12.2
50+	12.2
Black men (yr)	
20–59	12.9
60+	12.7
Black women (yr)	
20–49	11.5
50+	11.5

From Beutler et al. [9].

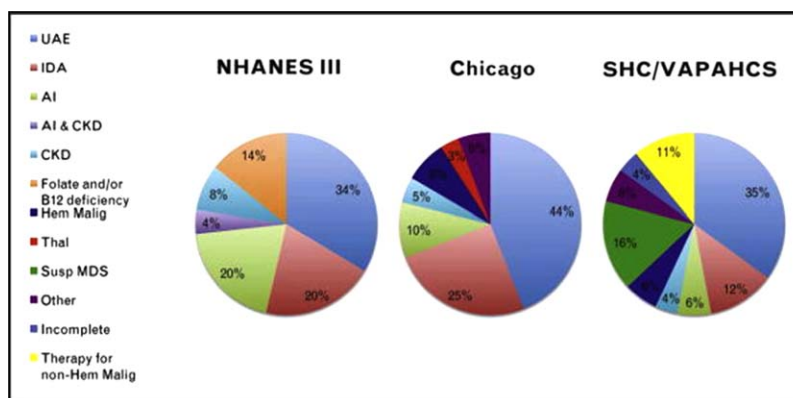


Figure 2. Prevalence of anemia in the elderly. Prevalence of anemia in the elderly by cause identified in three studies. Studies shown are National Health and Nutrition Survey (NHANES) III [8], Chicago [27], and Stanford Hospital & Clinics, VA Palo Alto Health Care System (SHC/VAPAHCS) [26]. AI, anemia of inflammation; CKD, anemia secondary to renal disease; Hem Malig, hematologic malignancy; IDA, iron-deficiency anemia; Susp MDS, suspicious for myelodysplastic syndrome; Thal, thalassemia; UAE, UAE. Reproduced, From Pang, Schrier [25]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

limited iron delivery to red cell precursors as indicated by the low transferrin saturation. This overlap of these two common causalities of anemia (iron deficiency and inflammation) has made the use of the traditional markers: MCV, transferrin saturation, and ferritin, difficult to interpret in routine practice [43].

An algorithm for the evaluation and management of anemia in the elderly is presented in Fig. 3. Iron-restricted erythropoiesis can cause anemia due to an absolute iron deficiency, iron sequestration which is mediated by hepcidin [44], and/or a functional iron deficiency due to the erythropoietin-stimulated erythropoiesis [45]. The evaluation of anemia must also consider unexpected diagnoses including CKD [46] or occult malignancy [30,31]. If absolute iron deficiency is diagnosed, in the elderly postmenopausal population it is mandatory to rule out gastrointestinal (GI) pathology, including malignancy as a source of chronic blood loss. Referral to a gastroenterologist may be the most effective way to proceed. However, in one-third to two-thirds of such patients, work-up of the GI tract is negative [30–33,47]. Serum creatinine and GFR must be determined in order to evaluate for CKD, in which case referral to a nephrologist may be appropriate. The suggested cut-off of glomerular filtration rate (GFR) <60 mL/min for consideration that the anemia is secondary to end stage renal disease (ESRD), follows CMS guidelines on reimbursement for erythropoietic stimulating agent (ESA) therapy in patients with ESRD; but between 30 and 60 mL/min GFR, other causes for anemia may be possible.

When serum ferritin and transferrin saturation values are inconclusive, further evaluation is necessary to rule out absolute iron deficiency or inflammation/chronic disease. As noted above, a response to a therapeutic trial of oral iron confirms absolute iron deficiency. However, lack of response to oral iron therapy may require a trial of intravenous (IV) iron, since in the presence of hepcidin, absorption of iron from the intestinal tract is impaired [13]. In a study of patients with a clinical diagnosis of iron deficiency anemia based on ferritin and transferrin saturation assays, only 21% responded to 4 weeks of oral iron therapy compared with 65% of patients given IV iron therapy [48].

A lack of response to iron therapy suggests a diagnosis of the anemia of inflammation or UAE. At this point, clinical evaluation for inflammatory conditions as well as measurement of CRP, fibrinogen, erythrocyte sedimentation rate (ESR), IL6, and hepcidin levels (if clinically available) may be useful [44]. If abnormal, management of the underlying condition supplemented with an erythropoiesis stimulating agent (ESA) may be appropriate for further management [49]. A

careful history for alcohol use/abuse particularly in patients with an MCV > 100 may be in order contributing either to poor marrow reserve or folate deficiency in the elderly. An early study by Cash and Sears of 90 patients (mean age 50.9 ± 16.5 , not confined to elderly individuals) with anemia of chronic disease observed that there was a broader spectrum of associated diseases with ACD than had previously been recognized [50]. A more recent study by Waalen et al. [21] compared a large cohort of UAE cases in the elderly with a matched, non-anemic control group and found that IL-6 and hepcidin levels did not differ significantly; whereas testosterone levels were lower in men and erythropoietin levels were inappropriately low for the degree of anemia.

The diagnosis of UAE is usually considered when other causes of anemia in the elderly have been eliminated. The diagnosis of UAE is based on the findings of a hypoproliferative anemia: a low reticulocyte index and an inadequate erythropoietin level for the degree of anemia. The management of these patients is a serious and recurrent issue, since in the absence of an etiology there is no proven efficacious intervention. When such patients are symptomatic, when they find themselves in clinical situations involving blood loss, or when surgical intervention is required, consideration of transfusion therapy is necessary, as described below.

Management of Anemia

As detailed above, management of anemia is determined by results of the evaluation. While folate deficiency is increasingly being made a non-entity with folate supplementation in flour, particular attention needs to be paid in certain settings, for example, poor diet combined with alcoholism, or compliance failure with folate supplementation in a dialysis patient. Similarly, Vitamin B₁₂ deficiency may be infrequently diagnosed, but a diagnostic trial of Vitamin B₁₂ therapy may be necessary if the constellation of symptoms and signs are consistent with Vitamin B₁₂ deficiency. Further assays for, methylmalonic acid and homocysteine may be helpful but can also be inconclusive [51].

As indicated above, a diagnostic or therapeutic trial including IV iron therapy may be necessary to rule out absolute iron deficiency [49,52,53]. Even the “gold standard” diagnostic bone marrow aspirate indicating the presence of some stainable iron may obscure a deficiency of storage iron, since in some of these cases the patients’ anemia has been shown to be responsive to iron therapy [49,54].

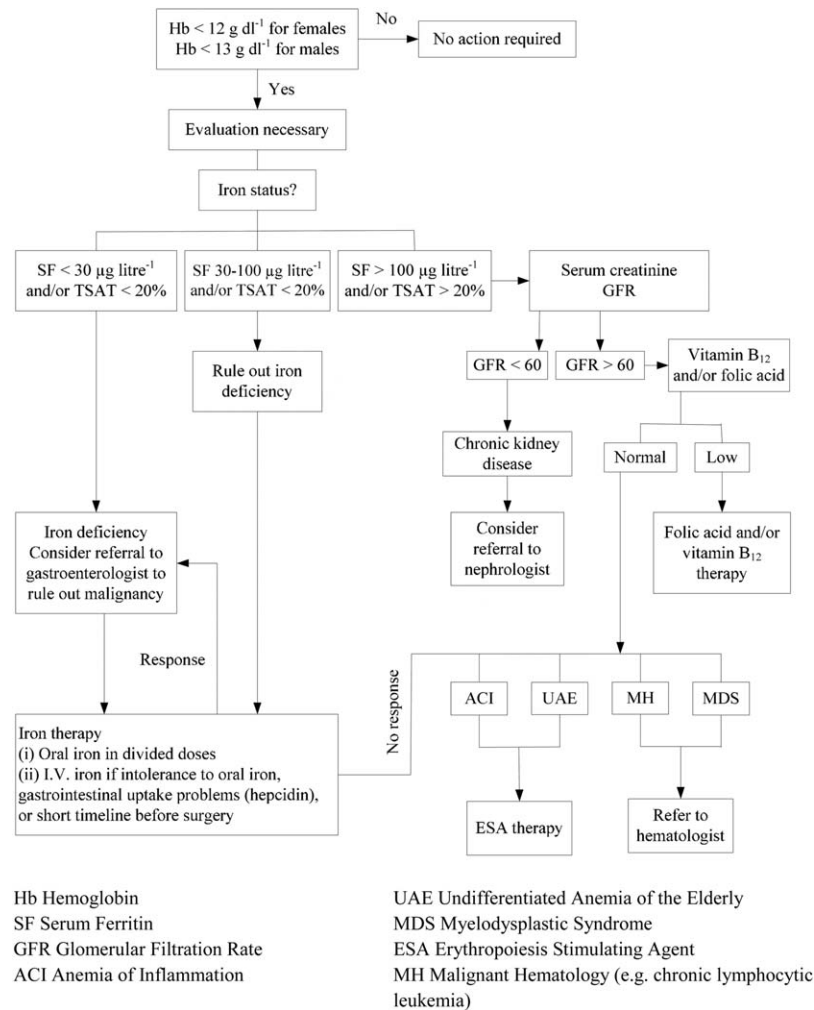


Figure 3. Evaluation and management of anemia in the elderly. Once the screening blood count demonstrates anemia, an evaluation is necessary and begins with an assessment of iron status. When ferritin and/or iron saturation levels indicate absolute iron deficiency, referral to a gastroenterologist to rule out a GI malignancy as a source of chronic blood loss may be indicated. When ferritin and/or iron saturation values rule out absolute iron deficiency, serum creatinine and GFR determination may indicate CKD and the need for referral to a nephrologist. When ferritin and/or iron saturation values are in determinant, further evaluation to rule out absolute iron deficiency versus inflammation/chronic disease is necessary. A therapeutic trial of iron would confirm absolute iron deficiency. No response to iron therapy would indicate the anemia of chronic disease, suggesting that ESA therapy be initiated.

Thirdly, therapy with an ESA may be indicated for treatment of one of several causes of anemia in the elderly. ESA's can be useful in treating the anemia in patients with end stage kidney disease [55], anemia in patients with inflammation/chronic disease who are scheduled for elective surgery [49], and in patients with MDS [56] who have moderate to severe anemia, in which the only other alternative may be chronic blood transfusions.

ESAs were first demonstrated and approved for use to increase the hemoglobin levels in patients with end-stage CKD undergoing dialysis [57] and subsequently in such subjects who did not require dialysis [58]. Based on prospective randomized trials that demonstrated reduced allogeneic blood transfusion [59], ESAs have subsequently been approved in patients undergoing elective surgery [60] and in oncology patients with chemotherapy-induced anemia.

Subsequent to FDA approval, clinical trials were undertaken in an attempt to demonstrate long-term improved patient outcomes with ESA therapy [61–67]. Table II lists five such clinical trials in patients undergoing elective spine surgery [61], patients with CKD (pre-dialysis) [62–66], and in patients with stage II–IV (New York Heart Association) congestive heart failure (CHF) [67]. Each of these studies

were designed to evaluate aggressive anemia management (to a target Hgb within normal range) versus conservative Hgb correction. In patients scheduled for elective spine surgery, outcomes were compared for ESA and placebo-treated cohorts who did not receive anticoagulation prophylaxis. In this study a higher incidence of deep vein thrombosis was found in patients receiving epoetin alfa compared with placebo. According to the subsequently revised prescribing information for ESA therapy, antithrombotic prophylaxis should be considered when ESA's are used in elective surgical patients who do not receive perioperative anticoagulation. In anemic patients with CHF a large, randomized trial [67] of patients whose median age was 72.0 (range 63–78), long-term ESA therapy was successful in correcting anemia and reducing blood transfusions, but did not improve long-term clinical outcomes (composite outcome of death or any cause of hospitalization from worsening CHF). The American Society of Hematology/American Society of Clinical Oncology Clinical Practice guideline update [68] has recommended use of ESAs in patients with low-risk MDS, in order to avoid blood transfusions. In clinical practice, the potential for increased risks of death and thromboembolic events should be balanced against the benefits of treatment with ESAs, including avoidance of allogeneic blood transfusions [69].

TABLE II. Selected Post-Approval Clinical Trials of ESA

Trial	Age (yrs)	Target vs. control (Hgb)	Reference (yr)	Clinical outcomes
I. Surgery				
SPINE	60 ± 14	<13	Stowell 2009 [61]	Inc Thromb
II. CKD^a				
CHOIR	66 ± 14	13.5 vs. 11.3	Singh 2006 [62]	Dec OS
CREATE	59 ± 14	13–15 vs. 10.5–11.5	Drueke 2006 [63]	Dec OS
TREAT	68 (60–75) ^b	13 vs. 9	Pfeffer 2006 [64–66]	Dec OS
III. CHF				
	71.5 (63–78) ^b	≥13	Swedberg 2013 [67]	Dec OS

ESA, erythropoiesis stimulating agents; CHF, congestive heart failure; Inc, Increase; Dec, decreased; OS, overall survival; CHOIR, Correction of Hemoglobin and Outcomes in Renal; CREATE, Cardiovascular Risk Reduction by Early Treatment with Epoetin beta; TREAT, Trial to Reduce Cardiovascular Events with Aranesp Therapy.

^a CKD, Chronic Kidney Disease pre-dialysis.

^b Median (interquartile range).

■ Blood Transfusion Therapy

Patients with moderate anemia have few associated symptoms, due to the significant compensatory mechanisms that preserve oxygen transport in the setting of a reduced hemoglobin. These compensatory mechanisms include increased blood flow due to the decreased blood viscosity, increased oxygen unloading to tissues due to the increased red cell bisphosphoglycerate (2,3 BPG), increased plasma volume, and redistribution of blood flow [70]. Generally, symptomatic manifestations occur only when the hemoglobin is below two-thirds of normal (i.e., <9–10 g/dL) as basal cardiac output increases in the anemic patient and is manifested clinically by symptoms of fatigue, dyspnea, and tachycardia [71]. However, the normal compensatory mechanisms of tachycardia and increased stroke volume may be impaired in the elderly, particularly in those with cardiovascular disease (CVD).

The recognition that transmission of non-A, non-B–hepatitis was one of the complications for patients undergoing cardiac bypass surgery, along with the advent of HIV transmission by blood transfusion, led to the realization that rather than reacting to the cardiovascular compensatory response to anemia with blood transfusion therapy [72,73], a more appropriate response for stable patients would be to allow the normal compensatory cardiovascular response to anemia to preserve oxygen transport in patients who were otherwise stable and did not have risk factors [74]. Based on Level 1 evidence it is now generally agreed that a more restrictive transfusion practice is safe, with equivalent patient outcomes compared with transfusion practice to maintain hemoglobin levels above 10 g/dL.

Blood transfusion strategies to treat anemia in the elderly and patients with CVD, are poorly understood [75]. For patients known to have risk factors such as age or CVD, the odds adjusted ratio of postoperative mortality has been observed to increase significantly when compared with patients not known to have CVD (Fig. 4) [76], illustrating that the management of anemia, including blood transfusion therapy, should be different for patients known to have CVD. In this study of 1,958 Jehovah's Witness patients undergoing surgery without blood transfusions, overall mortality was 3.2%. Five hundred forty-seven (28%) patients had Hgb < 12 g/dL preoperatively. Ten deaths (16.1%) occurred within 1 day of surgery and 25 (40.3%) occurred within 1 week. Patients with CVD had a 10.0% death rate, which was 4.3 times (95% CI, 2.6–7.1) higher than in patients without CVD. This assessment echoes a clinical practice guideline that concluded that “the presence of coronary artery disease likely constitutes an important factor in determining a patient's tolerance to low hemoglobin [77].”

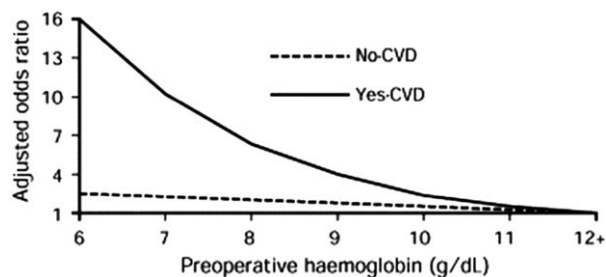


Figure 4. Adjusted odds ratio for mortality in patients undergoing surgery. Overall 30 day mortality for 1,958 Jehovah's Witness patients undergoing surgery without blood transfusions was 3.2% ($n = 62$; 95% CI 2.4–4.0). Patients with CVD had a 10.0% death rate, which was 4.3 times (95% CI 2.6–7.1) higher than in patients without CVD, according to preoperative hemoglobin. Reproduced with permission from Carson et al. [76].

Acute coronary syndromes (ACS)

Perioperative myocardial ischemic episodes are associated with hematocrit levels <28% in patients undergoing radical prostatectomy [78]. A retrospective analysis of Center for Medicare Services (CMS) data on 79,000 elderly patients (>65 years of age) hospitalized with acute myocardial infarction (MI) in the United States, found that blood transfusion in patients whose admission hematocrit values were <33%, were associated with significantly lower mortality rates [79]. Anemia (defined as a hematocrit of <39%) was present on admission to the hospital in nearly half of the patients (43.4%) and was clinically significant (i.e., 33% or lower) in 10.4% of the patients. It was concluded that a more proactive management of anemia in elderly patients including blood transfusion therapy, was warranted [80].

There is substantial variation in the use of blood transfusions in patients with ACS. An analysis of 24,000 patients in 27 countries found an association between non-ST segment ACS and a lower likelihood of blood transfusion [81]. Rates of 30 and 60 day clinical outcomes did not correspond to rates of transfusion, suggesting that the geographic variability in transfusion practices represented either underuse or the overuse of transfusions. A study of 44,000 patients with ACS in 400 U.S. hospitals found that 22.2% of patients were anemic and 10.4% received transfusions [82]; of those with a nadir hematocrit $\leq 24\%$, transfusions had a beneficial impact on mortality; and for patients with hematocrit levels between 24% and 27%, transfusions had a neutral impact on mortality. However, more recently a systemic review [83] of 10 published studies of blood transfusion strategies in patients with anemia associated with MI, found that patients receiving blood transfusions had a higher all-cause mortality rate associated with blood transfusion versus no blood transfusion (18.2% vs. 10.2%, risk ratio 2.9, $P < 0.001$). The difficulty in interpreting these retrospective, observational studies is that any conclusion that blood transfusions are causative, is confounded by both the underlying anemia and the underlying cause of the anemia as driving causes of the poor outcomes [84].

A small pilot trial randomized 45 patients with acute MI and hematocrit level $\leq 30\%$ to a liberal cohort receiving transfusions to maintain hematocrit $\geq 30\%$ or a conservative cohort (transfusions to maintain 24%–27%) [85]. The primary clinical safety measurement of in-hospital death, recurrent MI or worsening CHF occurred in 8 (38%) of the liberal cohort versus 3 (13%) in the conservative cohort ($P = 0.046$). These results suggested that more liberal transfusion practices in patients with AMI was associated with worse clinical outcomes. An addendum to the British Committee for Standards in Haematology (BCSH) guidelines [86] dealt with measures to avoid over-transfusion, particularly transfusion-associated circulatory overload (TACO) in vulnerable patients such as

TABLE III. Five Key Clinical Trials of Blood Transfusion in Adults

Clinical setting (Ref)	Hemoglobin threshold (g/dL)	Age (yrs)	Patients transfused (%)	Deviation from transfusion protocol (%)	Mean hemoglobin at transfusion (g/dL)	Participation of eligible patients (%)
Intensive care [89]	7 vs.	57.1 ± 18.1	67	1.4	8.5 ± 0.7 ^a	41
	10	58.1 ± 18.3	99	4.3	10.7 ± 0.7 ^a	
CT surgery [90]	8 vs.	58.6 ± 12.5 vs.	78	1.6	9.1 (9.0–9.2)	75
	10	60.7 ± 12.5	78	0.0	10.5 (10.4–10.6)	
Hip fracture repair [91]	8 vs.	81.5 ± 9.0 vs.	41	9.0	7.9 ± 0.6	56
	10	81.8 ± 8.8	97	5.6	9.2 ± 0.5	
Acute upper GI bleeding [92]	7 vs.	NA	49	9.0	7.3 ± 1.4	93
	9	NA	86	3.0	8.0 ± 1.5	
Symptomatic coronary artery disease [93]	8 vs.	74.3 ± 11.1 vs.	28.3	1.8	7.9 ± 0.8	12.2
	10	67.3 ± 13.6	NA ^b	9.1	9.3 ± 7.9	

^a Average daily hemoglobin.

^b NA, not available.

the elderly. It was noted that there were complex issues including lack of attention to fluid balance and prescription of diuretics.

■ Clinical Trials

There is limited but emerging Level I evidence to guide blood transfusion practices. A Cochrane systematic review of prospective randomized trials up to 2011 [87] compared “high” versus “low” hemoglobin thresholds of 19 trials involving a total of 6,264 patients. The authors found that (a) “low” hemoglobin thresholds were well tolerated; (b) blood transfusions were reduced by 34% (CI 24%–45%) in the “low” hemoglobin cohorts; and (c) blood transfusions were reduced by 1.2 units (CI 0.5–1.8 units) in the “low” hemoglobin cohorts. However, the authors have subsequently concluded that there are insufficient data available regarding transfusion thresholds for high-risk patients, such as patient with ACS or brain injury [88].

There are currently five Level I evidence clinical trials of liberal versus restrictive transfusion strategies (Table III). These prospective, randomized trials include patients in the intensive care setting [89], patients undergoing cardiothoracic surgery [90], elderly patients (mean >80 years of age) undergoing repair of hip fracture [91], medical patients with GI bleeds [92], and patients with symptomatic CVD undergoing cardiac catheterization [93]. Each trial investigated whether patients could tolerate a restrictive transfusion strategy with hemoglobin thresholds for blood transfusion between 7 and 8 g/dL, compared with a liberal strategy to maintain hemoglobin levels above 9 to 10 g/dL. As noted in Table III, except for the FOCUS trial [91], eligibility for trial participation was not centered on the elderly; nevertheless, the mean ages approximate the lower end of the range for the elderly, particularly in the trial for patients with symptomatic coronary artery disease [93].

The Transfusion Requirements in Critical Care (TRICC) trial [89] found that intensive care patients could tolerate a restrictive transfusion strategy (hemoglobin range 7–9 g/dL, 8.2 g/dL on average) as well as patients transfused more liberally (10–12 g/dL, 10.5 g/dL on average), with no differences in 30 day mortality rates. In contrast, a retrospective study of 2,393 patients consecutively admitted to the intensive care unit (ICU) has found that an admission hematocrit <25%, in the absence of transfusion, was associated with long-term mortality, suggesting that there may be hematocrit levels below which, the risk to benefit imbalance reverses [94].

The Transfusion Requirements after Cardiac Surgery (TRACS) trial [90] was a large, single center study of patients randomized to receive either restrictive (hematocrit >24%) or liberal (hematocrit >30%) red blood cell transfusions postoperatively. Thirty day all-cause mortality

was not different (10% vs. 11%, respectively) between the two cohorts. The FOCUS trial found that elderly, high risk (co-factors for CVD) patients who underwent repair of hip fracture surgery, tolerated a hemoglobin trigger without red blood cell transfusions postoperatively to as low as 8 g/dL (or higher with transfusions, if symptomatic) [91]. Of the four large trials, only the FOCUS trial targeted a clinical setting that specifically evaluated elderly patients (mean age ~81 years of age). The age of the patients in the clinical trial of patients with acute GI bleeds [92] was not specified.

The MINT trial [93] was a pilot, feasibility study of liberal (hemoglobin ≥10 g/dL) versus restrictive (hemoglobin <8 g/dL) transfusion thresholds was initiated for a planned enrollment of 200 patients with symptomatic coronary artery disease (ACS or stable angina undergoing cardiac catheterization), but was terminated at the end of 18 months after enrollment of only 110 patients; of eligible screened patients, only 12% were enrolled (Table III). The primary, composite outcome (death, MI, or revascularization) occurred in 10.9% of the liberal transfusion cohort, compared with 25.9% of the restrictive cohort ($P=0.054$); and mortality occurred in 1.8% and 13.0%, respectively ($P=0.032$). The MINT trial [93] provides evidence that a more liberal transfusion practice to maintain hemoglobin thresholds above 10 g/dL, represents prudent management of high-risk patients with symptomatic coronary artery disease.

It is noteworthy that one of the limitations of prospectively, randomized clinical trials is that patients who are eligible and who agree to participate in the study may not be particularly reflective of all patients in these clinical settings. Only 30% of the TRACS trial and 41% of the TRICC trial patients [89] who were eligible, actually enrolled in the study. This leads to a concern over a selection bias; did the treating physicians accurately predict prior to enrollment, which patients would survive the study, thereby insuring that survival outcomes would be equivalent between treatment groups? It is reassuring that the patients who did participate were treated according to the clinical trial design in more than 90% of cases (defined according to authors' published criteria), as indicated in Table III.

Another limitation is the interpretation of the “transfusion trigger” in these studies. While the target hemoglobin level in the restrictive group in the TRACS trial was 8.0 g/dL, the mean pretransfusion hemoglobin for these patients was 9.1 g/dL (Table III). Yet a clinical practice guideline [95] has interpreted this study to conclude that a hemoglobin level of 8 g/dL is appropriate for use as the “transfusion trigger” in coronary care patients. Similarly, while the target hemoglobin level in the restrictive group for the TRICC trial was 7.0 g/dL, the mean pretransfusion hemoglobin for these patients was 8.5 g/dL; yet

TABLE IV. Published Clinical Practice Guidelines for Blood Transfusion

Red blood cell transfusion			
Year	Society	Recommendations	Reference
1988	NIH Consensus Conference	<7 g/dL (acute) ^a	[98]
1992	Am Coll Physicians (ACP)	No number	[99]
1996/2006	AmerSocAnesth (ASA)	<6 g/dL (acute) ^a	[109] [102]
1997/1998	Can Med Assoc (CMA)	No number	[77] [100]
1998	Coll Amer Path (CAP)	6 g/dL (acute) ^a	[107]
2001/2012	Br Com Stand Haematol	No number 7–8 g/dL ^a	http://www.bcsghguidelines.com/documents/BCSH_Blood_Admin_-_addendum_August_2012.pdf [101]
2001	Australasian Soc Blood Trans	7 g/dL	http://www.nhmrc.health.gov.au
2007/2011	Soc Thor Surg (STS)/SocCardvasc Anesth (CVA)	7 or 8 g/dL ^a	[103] [112]
2009	ACCM/SCCM	7 g/dL 7 g/dL	[104] [105]
2011	SABM	8 g/dL	[108]
2012	National Blood Authority, Australia	No number	http://www.nba.gov.au/guidelines/review.html [111]
2012	AABB	7–8 g/dL or 8 g/dL ^b	[95]
2012	KDIGO ^c	No number	[55]
2012	National Cancer Center Network (NCCN)	7 g/dL	[106]

^a For patients with acute blood loss.

^b For patients with symptoms of end-organ ischemia.

^c KDIGO: Kidney Disease: Improving Global Outcomes.

Modified from Goodnough et al. [75].

the authors interpreted this study to recommend a hemoglobin of 7 g/dL as appropriate for use as the transfusion trigger in critical care patients [96]. The authors of the FOCUS trials concluded that “it is reasonable to withhold transfusion in patients who have undergone surgery in the absence of symptoms of anemia, or a decline in the hemoglobin level below 8 g/dL, even in elderly patients with underlying CVD or other risk factors” [91]. However, during the FOCUS study, mean hemoglobin values were 9.0–9.5 g/dL for the restrictive cohort, about 1.5 g/dL higher than the suggested thresholds during the study. An accompanying editorial [97] to the FOCUS trial concluded that no specific hemoglobin level could be recommended for blood transfusion; rather, the constellation of patient symptoms, signs, clinical variables, and co-morbidities should be considered. This kind of scrutiny needs to be taken into account in interpreting results of clinical trials, and in management of the acute postsurgical care of elderly patients who have increased cardiovascular risks.

Clinical practice guidelines

The number of clinical practice guidelines for blood transfusions [55,77,86,95,98–111] by professional societies (listed in Table IV) attests to the increasing interest in appropriate blood utilization. The published guidelines acknowledge the consideration of patient co-variables (including age) or other patient-specific criteria for making transfusion decisions. Among these guidelines, it is generally agreed that transfusion is not of benefit when the hemoglobin is >10 g/dL, but may be beneficial when the hemoglobin is <6–7 g/dL. However, the selection of a discrete hemoglobin as a “trigger” for transfusion has been controversial. For example, the initial guidelines by The American Society of Anesthesiology (ASA) in 1996 [109] identified hemoglobin <6 g/dL as a transfusion trigger for acute blood loss, whereas the updated ASA guidelines in 2006 [102] noted that “although multiple trials have evaluated transfusion thresholds on

patient outcome, the literature is insufficient to define a transfusion trigger in surgical patients with substantial blood loss.” Five guidelines [98,101,107,109,112] have specified a hemoglobin threshold for patients only in those with acute bleeding. The attempt to define an empiric hemoglobin concentration as a transfusion trigger for patients who are stable clinically, has been contested by seven published clinical practice guidelines [55,77,86,99,102,110,111] that do not recommend a specific hemoglobin threshold for transfusion. A recent study of elderly population with hip fracture found that while blood transfusion was not associated with changes in mortality, blood transfusion was associated with an increased rate of postoperative infection [113]. The authors concluded that these data add to the wider literature about adverse clinical outcomes in patient receiving blood transfusions, and emphasizes the need for prospective trials to evaluate the role of transfusion in the elderly.

Conclusion

Arbitrary laboratory values are inadequate to define when red blood cell transfusions are appropriate. Each patient must be evaluated individually, and patient-specific anemia management strategies be employed [75]. This dilemma is illustrated by serial recommendations for a variety of integers for hemoglobin levels recommended as transfusion triggers, based on the Level 1 evidence-based literature over time: no number [55,77,86,99,102,110,111]; 7–8 g/dL [95]; and 6–8 g/dL [87,88]. This conflict between guideline-based medicine and a more personalized approach to elderly patients, predominantly occurs when considering withholding or providing a therapy that is not addressed by the guidelines, but may be beneficial for an individual patient group [114]. For elderly patients, prudent transfusion practices to maintain hemoglobin thresholds of 9–10 g/dL are indicated, unless or until evidence emerges to indicate otherwise.

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