Anemia

Not Just an Innocent Bystander?

ANEMIA HAS traditionally been identified through abnormal laboratory values, with a focus on whether or not it should be treated, rather than perceived as a serious clinical condition. For example, the decision to manage anemia with blood transfusions is based on the evaluation of relative risks and benefits, in which the estimated risks of a blood transfusion are quantifiable[1] and can be communicated to patients. But the magnitude of the risks associated with untreated anemia has largely remained unknown, and therefore has not been effectively conveyed to patients. In contrast to treatment strategies for other diseases, guidelines[2,3] for the management of anemia have only occasionally been developed for patients with specific conditions.

For too long, anemia has been viewed as an "innocent bystander," accepted as normal in certain groups (eg, menstruating women), or accepted as an abnormality associated with chronic illnesses. However, the evidence is becoming clearer that the bystander is not completely innocent. In this commentary, we will review the growing body of evidence indicating that (1) anemia occurs commonly, (2) anemia is frequently overlooked and considered merely secondary to other underlying illnesses, and (3) anemia has an independent impact on both length and quality of life (QOL). The evidence is highly suggestive, if not compelling, and mandates a call to action, the initial elements of which we propose herein.

ANEMIA OCCURS COMMONLY

Anemia is more common than is generally realized (for purposes of this review, anemia is defined as hemoglobin levels <13 g/dL in men or <12 g/dL in women, as recommended by the World Health Organization [WHO]).[4] Self-report data from the National Center for Health Statistics, which likely underestimates the frequency of anemia, reveal that approximately 3.4 million Americans have anemia, and that the groups with the highest prevalence are women, African Americans, the elderly, and those with the lowest incomes.[5] Using laboratory data from the general US population, the second National Health and Nutrition Survey (NHANES) reported anemia to be the most prevalent in infants (5.7%), teenage girls (5.9%), young women (5.8%), and elderly men (4.4%).[6] Importantly, iron deficiency has been found in 18% to 50% of menstruant women who are regular blood donors.[7] This has led to debate whether young women should be recruited into blood donor programs in the absence of iron status screening and supplemental iron therapy.[8] The prevalence of anemia in both the general population and ill persons is confounded by the lack of a standardized definition of anemia.

The likelihood of anemia is even greater in the elderly. The prevalence of anemia (hemoglobin levels <12 g/dL) studied in a general elderly population (>65 years old) was 7.5% for men (4% when <75 years old and 12% when >75 years old) and 20% for women (15% when <75 years old and 25% when >75 years old).[9] In another general population survey,[10] the prevalence of anemia (hemoglobin levels <12.5 g/dL) for men aged between 65 and 75 years was 7.2%, and it was 20.8% for men older than 75 years. In the same survey, 11.1% of women aged between 65 and 75 years had anemia (hemoglobin levels <12 g/dL), as did 23.3% of women older than 75 years. One study found that 24% of the hospitalized elderly had anemia (hemoglobin levels <11.5 g/dL), 35% had anemia of chronic disease, and 15% had iron deficiency.[11] Another study[12] of the elderly (>65 years old) found anemia in 475 (75%) of hospitalized patients, but admission was due to anemia in only 57 (12%) of these patients. The authors concluded that the incidence of anemia among the elderly is 4 to 6 times greater than generally suspected. Moreover, survival among elderly patients with anemia is significantly less than that expected for an age- and sex-matched US population.[12] While the association of anemia and adverse outcomes in the elderly is generally acknowledged, it is noteworthy that no guidelines or recommendations for screening and identifying anemia in the elderly exist.

Data for the prevalence of anemia associated with disease has been studied in more depth. Anemia of chronic disease has been identified in 30% to 70% of patients with chronic liver disease,[13] 27% of patients with rheumatoid arthritis,[14] and 28% to 55% (depending on the extent of disease) of patients with human immunodeficiency virus infection.[15] Anemia associated with

cancer or cancer treatment varies widely with stage of disease and/or treatment. In small cell carcinoma of the lung, anemia was identified in 30% to 60% of patients, depending on treatment.[16] In an analysis of a 5% sampling of Medicare patients, the percentage of patients with a diagnosis of anemia in addition to a primary diagnosis was 20% for acquired immunodeficiency syndrome, 17% for rheumatoid arthritis, 21% for inflammatory bowel disease, 27% for chemotherapy, 27% for radiation therapy, and 30% for congestive heart failure(CHF) (A. Collins, oral communication, February 2, 2002). These studies suggest that anemia occurs commonly, either alone or in conjunction with a chronic illness. If anemia had no independent consequences, then these statistics would only represent abnormal laboratory values. However, a growing body of evidence underscores the independent impact of anemia on a variety of clinical, functional, and economic indicators, and suggests that treatment of anemia can improve patient outcomes.

ANEMIA IMPACTS MORTALITY

Higher mortality rates are almost always observed in patients with anemia. Does anemia merely reflect a sicker patient, or does anemia itself have an incremental impact on these rates? This relationship has been explored in patients undergoing maintenance hemodialysis. In a retrospective review[17] of nearly 20000 of these patients, 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[18] of nearly 100000 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. Moreover, patients who entered the study with a hematocrit less than

30%, and were treated to achieve a hematocrit above 30% after 1 year of follow-up, had an odds ratio for death that was not different from that of patients who began and finished the study with a hematocrit higher than 30%. Subsequent analyses have determined that hematocrit levels maintained between 33% and 36% were associated with the lowest risk of death.[19] These studies provided the first evidence that management of anemia, independent of other risk factors, improves mortality rates. These are retrospective administrative database analyses, which makes cause-and-effect relationships difficult to prove. However, after correcting for many important patient characteristics known to affect mortality, such as age and presence of diabetes, these studies identified anemia as an independent factor impacting mortality.

Data on the impact of anemia on survival rates are also available for patients with medical conditions other than renal failure. A growing body of evidence suggests that anemia influences the mortality rates of patients with CHF or with ischemic heart disease. Almost 20 years ago, hemoglobin was identified as 1 of 8 significant factors predicting prognosis and response to treatment in patients with CHF.[20] Two large observational studies noted an association between levels of hemoglobin below 9.5 or 10 g/dL and increased mortality rates for patients with cardiovascular disease, and suggested that these patients did not tolerate anemia as well as patients with other diseases.[21,22] A more recent study of Medicare patients with CHF reported that anemia was an independent predictor of subsequent death.[23] For every 1% decrease in hematocrit, the mortality rate increased by 1.6%.

A prospective, randomized trial in patients with CHF explored whether the treatment of anemia influenced outcomes. Patients enrolled in the study had moderate to severe CHF (New York Heart Association class III to IV), a left ventricular ejection fraction of 40% or less despite maximally tolerated doses of CHF medications, and hemoglobin levels that were persistently between 10.0 and 11.5 g/dL.[24]

Over a mean ± SD of 8.2 ± 2.6 months, the hemoglobin levels in the treatment cohort increased from 10.3 g/dL to 12.9 g/dL, compared with 10.9 g/dL to 10.8 g/dL in the control group. Twenty-five percent of patients in the control group died of CHF-related illnesses during the study, compared with no one in the treatment group.

A recent retrospective observational analysis[25] of 78974 elderly patients hospitalized because of acute myocardial infarction in the United States found that blood transfusions in patients with hematocrits of less than 33% upon admission were associated with significantly lower 30-day mortality rates. The positive transfusion effect disappeared, however, for patients with hematocrits higher than 33% upon admission. For these patients, in whom underlying comorbidities may have overridden any positive transfusion effect, transfusions were associated with a higher odds ratio for death. Both advanced age[26,27] and the presence of flow-limiting coronary stenosis[28] 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.[29] In the absence of prospective data or other data to the contrary, it may be assumed that a substantial number of lives may be saved when the hematocrit values of patients who present with acute myocardial infarction are maintained above 33%. On the other hand, blood transfusion in elderly patients with acute myocardial infarction presenting with higher hematocrit values, even if anemia is present, cannot be recommended for blood transfusion.[30]

ANEMIA IMPACTS MORBIDITY

In addition to its impact upon mortality, anemia also significantly in-

fluences morbidity. In patients with end-stage renal disease, multiple studies support this assertion. One 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%.[31] Prospective clinical trials of patients with end-stage renal disease have demonstrated a relationship among hematocrit, left ventricular dilatation,[32] and left ventricular hypertrophy (LVH).[33-36] Management of anemia led to improvement in LVH, which supports the existence of a cause-and-effect relationship between anemia and LVH.[36] In other studies, patients with end-stage renal disease who underwent treatment for anemia had increased cognitive function, increased exercise tolerance, and increased QOL.[37-39]

In patients with chronic kidney disease and CHF, treatment of anemia improves many of the abnormalities seen in CHF: it reduces LVH[40-42]; prevents left ventricular dilatation[43]; and increases left ventricular ejection fraction,[41-43] stroke volume, and cardiac output.[44] Despite the association between anemia and CHF, anemia is not mentioned in guidelines for the diagnosis and treatment of CHF.[45] As discussed in the "Mortality" section above, 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%.[24] 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.

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.

Two thirds of women with cervical carcinoma are anemic at baseline, and 82% are anemic during radiotherapy.[46] Correlations between anemia, tumor tissue oxygenation, local recurrence, and survival have been demonstrated.[47,48] The Gynecology Oncology Group is currently conducting a prospective, randomized clinical trial on the effect of anemia management on disease recurrence and survival in patients with cervical carcinoma. In cases of head and neck cancer, 75% of patients undergoing combined chemotherapy and radiotherapy become anemic (with hemoglobin levels <8 g/dL)[49] and anemia has been associated with worse local regional control and survival rates.[50,51] On the basis of these observations, the Radiation Therapy Oncology Group has initiated a prospective, randomized study of the effect of anemia management on the rates of disease recurrence and length of survival in patients with head and neck cancer undergoing combined modality therapy. While the former studies suggest that a high red blood cell number may be the mediator of a beneficial response to radiotherapy,[47,48] the latter study should provide more definitive evidence on the actual mechanism. There is presently little evidence that anemia treatment per se impacts the tumor response to chemotherapy alone.

ANEMIA IMPACTS QOL

In addition to reducing length of life, patients with anemia have a significantly impaired QOL—although this field is complicated by the large number of available instruments to measure QOL, and by the lack of adequate guidance for a comparison of results across instruments. Multiple studies have examined this issue in patients with kidney failure receiving hemodialysis. For example, in one study, patients underwent interventions to increase their hematocrits from an average of 30.9% to 38.4% (a hemoglobin level between 10.2 and 12.5 g/dL). Treatment of anemia was associated with improvements in QOL based on both the Karnofsky score and the Sickness Impact Profile.[52]

For patients with cancer who undergo chemotherapy, two[53,54] large, community-based unblinded and noncontrolled prospective studies of patients with solid, nonmyeloid malignancies used a patient self-assessment tool and found significant improvements in QOL over 4 months with anemia management. Incremental analysis determined that significant QOL changes were associated when hemoglobin levels reached the range of 8 to 14 g/dL, and that the largest improvement in QOL occurred between 11 to 12 g/dL.[55] This relationship was maintained after controlling for tumor type and status, transfusions, and extent of chemotherapy or radiotherapy. These findings have been corroborated by 2 prospective randomized and double-blind studies,[56,57] and both of them showed significant improvement in QOL with anemia management. The American Society of Hematology and the American Society of Clinical Oncology have jointly developed guidelines regarding the management of anemia in cancer patients.[58]

ANEMIA MANAGEMENT NEEDS IMPROVEMENT

Despite the mounting evidence that anemia independently contributes to poor outcomes, it is frequently overlooked and untreated. In a study of 200 000 patients enrolled in a health maintenance organization between 1994 and 1997,[59] 23% of the patients with chronic kidney disease (defined as sex-specific, elevated creatinine concentrations) had hematocrits less than 30%, but only 30% of them were receiving treatment for anemia.

Anemia has been identified as a risk factor for the development of LVH in chronic kidney disease[35,36] and LVH has been identified as a risk factor for death.[60] Yet, the mean hematocrit in patients starting maintenance dialysis between April 1, 1995, and December 31, 1999, was only 29.3%. Once the relationship between anemia and morbidity and mortality in patients undergoing maintenance hemodialysis was established, the National Kidney Foundation Kidney Disease Outcomes Quality Ini-

tiatives Guidelines recommended that their hemoglobin levels be maintained between 11 g/dL and 12 g/dL.[61] Yet, in a study of patients undergoing peritoneal dialysis, 11% of them had hemoglobin levels below 10 g/dL.[62]

In patients with cancer, one review reported an extremely high incidence of anemia.[15] Depending on the definition used, the incidence in some patients with cancer who underwent chemotherapy ranged from 55% (WHO grade 3, hemoglobin levels <8.0 g/dL) to 100% (WHO grade 1, hemoglobin levels <11.0 g/dL). Yet, fewer than 30% of patients with hemoglobin levels less than 10 g/dL were treated for their anemia.

CONCLUSIONS

The evidence leads to an undeniable conclusion: anemia is not an innocent bystander. Although the picture is only partially complete, mounting evidence suggests that anemia impacts the length and QOL of patients with diverse conditions. A significant number of patients who have anemia remain untreated or even undiagnosed. The lack of a widely disseminated coherent picture of the prevalence and consequences of anemia may be one of the chief barriers preventing practicing clinicians from adequately recognizing and treating anemia. In the absence of a clear-cut understanding of the independent impact of anemia, the status quo will remain. Anemia will continue to be viewed as secondary to a traditionally "more important" illness, the consequences and treatment benefits of which are immediately apparent.

On the positive side, a greater awareness of the importance of anemia is slowly beginning to arise. As an example, *Healthy People 2010*[63] raises the issue of anemia, but identifies iron deficiency in only a narrow population that includes pregnant women. We believe that this is only a first step, and that a much broader opportunity exists to address anemia in the many patients who experience it in the context of a chronic illness.

To translate awareness into action, guidelines related to anemia should be reexamined and modified within the medical subspecialties. Guidelines for transfusion in perisurgical anemias exist; yet they suggest a hemoglobin level of 6 to 8 g/dL as a threshold for treatment, and no benefit beyond 10 g/dL.[64-66] A recent study, however, suggests that even a mild anemia (hematocrit <35%) may be an independent risk factor for death following general surgery.[67] Based upon the data presented above, these recommendations may misguide clinicians and underserve patients with anemia who are at risk. For example, despite strong evidence for the benefit of identifying and treating anemia in conditions such as CHF, guidelines for management of CHF do not address the danger of anemia.

Although strong evidence supports the relationship between anemia and adverse outcomes, more data are needed to isolate the independent impact of anemia on outcomes across disease states and patient populations. In addition, a better understanding of treatment patterns is needed. What is the burden of anemia in certain populations? What are the direct medical costs associated with anemia and how often does anemia remain untreated? The request for applications by the National Institutes of Health to establish a clinical trials network in transfusion medicine is one opportunity for clinical studies to answer these and other important questions.[68]

Anemia can be caused by nutritional deficiency, blood loss, hemolysis, or chronic disease. Although this consideration is beyond the scope of this review, it is clear that the cause must be ascertained before the condition can be properly treated. Once the cause of anemia is determined, appropriate therapy can be initiated. Additional research is needed to assess the costs and benefits of these therapies in individual patients and patient groups, particularly as outcome data drive a move toward treatment of mild anemia.

In summary, the time has come for a structured public and professional dialogue and an educational approach that addresses anemia as a serious public health condition warranting high-quality care to achieve optimal health outcomes.

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REFERENCES

1. Goodnough LT, Brecher ME, Kanter MH, Aubuchon JP. Transfusion medicine, part I: blood transfusion. *N Engl J Med*. 1999;340:438-444.
2. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for red blood cell transfusion. *Ann Intern Med*. 1992;116:393-402.
3. American College of Physicians. Practice strategies for elective red blood cell transfusion. *Ann Intern Med*. 1992;116:403-406.
4. DeMaeyer E, Adiels-Yagman M. The prevalence of anaemia in the world. *World Health Stat Q*. 1985;38:302-316.
5. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. *Vital Health Stat*. 1999;10(200). Available at: http://www.cdc.gov/nchs/data/series/sr_10/sr10_200.pdf. Accessed March 4, 2003.
6. Dallman PR, Yi PR, Johnson C. Prevalence and causes of anemia in the United States, 1976 to 1980. *Am J Clin Nutr*. 1984;39:437-445.
7. Gordeuk VR, Brittenhamn GM, Bravo J, Hughes MA, Keating LJ. Prevention of iron deficiency with carbonyl iron in female blood donors. *Transfusion*. 1990;30:239-245.
8. Conrad ME. The Hippocratic principle of primum nil nocere demands that the metabolic state of a donor should be normalized prior to a subsequent donation of blood or plasma: how much blood, relative to his body weight, can a donor give over a certain period, without a continuous deviation of iron metabolism in the direction of iron deficiency? *Vox Sang*. 1981;41:336-343.
9. McLennan WJ, Andrews GR, Macleod C, Caird FI. Anemia in the elderly. *Q J Med*. 1973;165:1-13.
10. Parsons PL, Withey JL, Kilpatrick GS. The prevalence of anemia in the elderly. *Practitioner*. 1965;195:656-660.
11. Joosten E, Pelemans W, Hiele M, Noyen J, Uerhaeghe R, Boogaerts MA. Prevalence and causes of anemia in a geriatric hospitalized population. *Gerontology*. 1992;38:111-117.
12. Ania BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton LJ. Incidence of anemia in older people: an epidemiologic study in a well-defined population. *J Am Geriatr Soc*. 1997;45:825-831.
13. Siciliano M, Tomasella D, Milani A, Ricerca BM, Storti S, Rossi L. Reduced serum levels of immunoreactive erythropoietin in patients with cirrhosis and chronic anemia. *Hepatology*. 1995;22:1132-1135.
14. Baer AN, Dessypris EN, Krantz SB. The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis. *Semin Arthritis Rheum*. 1990;19:209-223.

15. Zon LI, Arkin C, Groopman JE. Hematologic manifestations of the human immune deficiency virus (HIV). *Semin Hematol*. 1988;25:208-212.

16. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst*. 1999;91:1616-1634.

17. Ma J, Ebben J, Xia H, et al. Hematocrit levels and associated mortality in hemodialysis patients. *J Am Soc Nephrol*. 1999;10:610-619.

18. Collins A, Xia H, Ebben J, et al. Change in hematocrit and risk of mortality. *J Am Soc Nephrol*. 1998; 9(suppl A):204A.

19. Collins AJ, Li S, St. Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*. 2001;12: 2465-2473.

20. Maeda K, Tanaka Y, Tsukano Y, et al. Multivariate analysis using a linear discriminate function for predicting the prognosis of congestive heart failure. *Jpn Circ J*. 1982;46:137-142.

21. Carson JL, Duff A, Poses RM, et al. Effect of anemia and cardiovascular disease on surgical mortality and morbidity. *Lancet*. 1996;348:1055-1060.

22. Hebert PC, Wells G, Sweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? *Am J Respir Crit Care Med*. 1997;155: 1618-1623.

23. McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol*. 2002;13:1928-1936.

24. Silverberg OS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001;37:1776-1779.

25. Wu WC, Rathmore SS, Wang Y, Radford MJ, Krumholz HM. Effectiveness of blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345:1230-1236.

26. Duke M, Abelman WH. The hemodynamic response to chronic anemia. *Circulation*. 1969;39: 503-515.

27. Ogawa T, Spina RJ, Martin WH III, et al. Effects of aging, sex and physical training on cardiovascular responses to exercise. *Circulation*. 1992; 86:494-503.

28. Levy PS, Song-Jung K, Eckel PK, et al. Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. *Am J Physiol*. 1993;265:H340-H349.

29. Maggioni AA, Meseri A, Fresco C, et al, for the Investigators of the Gruppo Italiano por lo Studio della Sopravvivenza nell'Infartoo Miocardico (GISSI-2). Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. *N Engl J Med*. 1993;329:1442-1448.

30. Goodnough LT, Bach RG. Anemia, transfusion, and mortality. *N Engl J Med*. 2001;345:1272-1273.

31. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-590.

32. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in end stage renal disease. *Am J Kidney Dis*. 1996;28:53-61.

33. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*. 1999;34:125-134.

34. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis*. 1996;27:347-354.

35. Silverberg JS, Rahal DP, Patton R, Sniderman AD. Role of anemia in the pathogenesis of left ventricular hypertrophy in end-stage renal disease. *Am J Cardiol*. 1989;64:222-224.

36. Canella G, LaCanna G, Sandrini M, et al. Reversal of left ventricular hypertrophy following recombinant human erythropoietin treatment of anaemic dialysed uraemic patients. *Nephrol Dial Transplant*. 1991;6:31-37.

37. Collins A, Ma JZ, Ebben J, et al. Impact of hematocrit on morbidity and mortality. *Semin Nephrol*. 2000;20:345-349.

38. Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. *Am J Kidney Dis*. 1999;33: 1122-1130.

39. Valderrabano F, Jofre R, Lopez-Gomez JM. Quality of life in end-stage renal disease patients. *Am J Kidney Dis*. 2001;38:443-464.

40. Low I, Grutzmacher P, Bergmann M, Schoeppe W. Echocardiographic findings in patients on maintenance hemodialysis substituted with recombinant human erythropoietin. *Clin Nephrol*. 1989; 31:26-30.

41. Low-Friedrich I, Grutzmacher P, Marz W, Bergmann M, Schoeppe W. Therapy with recombinant human erythropoietin reduces cardiac size and improves heart function in chronic hemodialysis patients. *Am J Nephrol*. 1991;11:54-60.

42. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. *Am Heart J*. 1992;124:424-427.

43. Foley RN, Parfrey PS, Morgan J, et al. A randomized controlled trial of complete vs partial correction of anemia in hemodialysis patients with asymptomatic concentric LV hypertrophy or LV dilatation. *J Am Soc Nephrol*. 1998;9:208.

44. Linde T, Wikstrom B, Andersson LG, Danielson BG. Renal anaemia treatment with recombinant human erythropoietin increases cardiac output in patients with ischemic heart disease. *Scand J Urol Nephrol*. 1996;30:115-120.

45. Packer M, Cohn JN. Consensus recommendations for the management of chronic heart failure. *Am J Cardiol*. 1999;83(suppl):1A-38A.

46. Harrison LB, Shasha D, White C, Ramdeen B. Radiotherapy-associated anemia: the scope of the problem. *Oncologist*. 2000;5(suppl 2):1-7.

47. Bush RS. The significance of anemia in clinical radiation therapy. *Int J Radiat Oncol Biol Phys*. 1986; 12:2047-2050.

48. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer*. 1999; 86:1528-1536.

49. Lee JS, Scott C, Komaki R, et al. Concurrent chemoradiation therapy with oral etoposide for locally advanced inoperable non-small-cell lung cancer: radiation therapy oncology group protocol 91-06. *J Clin Oncol*. 1996;14:1055-1064.

50. Fein DA, Lee WR, Hanlon L, et al. Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. *J Clin Oncol*. 1995;13:2077-2083.

51. Lee WR, Berkey B, Marcial V, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. *Int J Radiat Oncol Biol Phys*. 1998;42:1069-1075.

52. Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F, for the Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. *J Am Soc Nephrol*. 2000;11:335-342.

53. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol*. 1997;15:1218-1234.

54. Demetri GD, Kris M, Wade J, Degos L, Cela D. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol*. 1998;16:3412-3425.

55. Cleveland CS, Demetri GD, Glaspy J, et al. Identifying hemoglobin level for optimal quality of life: results on an incremental analysis. *Proc Am Soc Clin Oncol*. 1999;18:574a.

56. Abels R. Erythropoietin for anaemia in cancer patients. *Eur J Cancer*. 1993;29A(suppl 2):S2-S8.

57. Littlewood TJ, Bajetta E, Nortier JWR, Vercammen E, Rapoport B. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2001;19:2865-2874.

58. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol*. 2002;20:4083-4107.

59. Nissenson AR, Collins AJ, Hurley J, Peterson H, Pereira BJG, Steinberg EP. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. *J Am Soc Nephrol*. 2001;12:1713-1720.

60. Parfrey PS, Griffiths SM, Harnett JD, Taylor R, King A, Hand J. Outcome of congestive heart failure, dilated cardiomyopathy, hypertrophic hyperkinetic disease, and ischemic heart disease in dialysis patients. *Am J Nephrol*. 1990;10:213-221.

61. National Kidney Foundation. NFK-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure: National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis*. 1997;30(4 suppl 3):S192-S240.

62. Flanigan MJ, Rocco MV, Prowant B, Frederick PR, Frankenfield DL. Clinical performance measures: the changing status of peritoneal dialysis. *Kidney Int*. 2001;60:2377-2384.

63. US Department of Health and Human Services. *Healthy People 2010: Understanding and Improving Health*. 2nd ed. Washington, DC: US Government Printing Office; November 2000.

64. Consensus conference: perioperative red blood transfusion. *JAMA*. 1988;260:2700-2703.

65. Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology*. 1996;84:732-747.

66. Expert Working Group. Guidelines for red blood cell and plasma transfusions for adults and children. *CMAJ*. 1997;156(suppl 11):S1-S25.

67. O'Brien MM, Gonzales R, Shroyer AL, et al. Modest serum creatinine elevation affects adverse outcome after general surgery. *Kidney Int*. 2002;62: 585-592.

68. Transfusion Medicine/Hemostasis Clinical Research Network. Available at: http://grants.nih.gov /grants/guide/rfa-files/rfa-HL-02-001.html. Accessed March 4, 2003.