

Anemia Institute Review

ANEMIA INSTITUTE FOR RESEARCH AND EDUCATION

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A letter from the editor:

The Anemia Institute for Research and Education is pleased to provide you with the inaugural issue of the Anemia Institute Review. The review is intended to give you an overview of leading-edge research on anemia. This issue includes a review of the consequences of anemia on cardiac functions and other body systems; of the benefits of anemia treatment in patients with congestive heart failure, cancer, kidney disease and critical illness; and of the additional benefits of treating anemia, such as neuroprotective functions. Future issues will further investigate inherited anemias, and anemia and nutrition.

Editor

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CONSEQUENCES OF ANEMIA

The pathological consequences of anaemia

SILVERBERG DS, IAINA A, WEXLER D, BLUM M.

CLIN LAB HAEM 2001 23: 1 – 6.

Anemia of chronic disease (ACD) results in a blunted erythropoietin (EPO) response and reduced release of stored iron due to cytokines and leukotrienes. ACD has been associated with renal failure, cancer, rheumatoid arthritis, chronic inflammation, and, more recently, congestive heart failure (CHF). This paper discusses the mutually causative relationships between anemia and CHF and chronic renal failure, and the benefits of EPO therapy and intravenous iron in improving organ, tissue, and cellular functions.

The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study

SILVERBERG DS, WEXLER D, SHEPS D, BLUM M, KEREN G, BARUCH R,

SCHWARTZ D, YACHNIN T, STEINBRUCH S, SHAPIRA I, LANIADO S,

IAINA A. *J AM COLL CARDIOL* 2001 37(7): 1775 – 80.

Mild anemia occurs frequently in patients with congestive heart failure (CHF). Patients with moderate to severe CHF and mild anemia were randomized to receive either subcutaneous erythropoietin (EPO) and intravenous (IV) iron along with CHF medications, or CHF medications alone. Those who were treated for anemia with EPO and IV iron showed marked improvement in cardiac function and demonstrated less deterioration of renal function, need for diuretics, and hospitalization.

Symptomatology of anemia

LUDWIG H, STRASSER K. *SEMINARS IN ONCOLOGY* 2001 28(2)

[SUPPL 8]: 7 – 14.

While the body attempts to compensate for decreased oxygen delivery, for example, by decreasing oxygen affinity in the hemoglobin, increasing respiratory rate, and increasing erythropoietin release, anemia can affect every body system. A review of studies evaluating the administration of epoetin alfa to anemia patients concludes that raising hemoglobin levels ameliorates patient symptoms and may improve treatment efficacy and overall survival for cancer patients.

ANEMIA AND MYOCARDIAL INFARCTION

Blood transfusion in elderly patients with acute myocardial infarction

WU WC, RATHORE SS, WANG Y, RADFORD MJ, KRUMHOLZ HM. *N ENGL*

J MED 2001 345(17): 1230 – 1236.

A retrospective study of data on 78,974 elderly patients hospitalized with acute myocardial infarction (MI) found that those with hematocrit lower than 30 who were treated for anemia with blood transfusion had a lower 30-day mortality than those not treated. There was no added benefit for patients with higher hematocrits.

Anemia, transfusion, and mortality

GOODNOUGH LT, BACH RG. *N ENGL J MED* 2001 345(17): 1272 – 74.

Current guidelines for blood transfusion have favoured a restrictive strategy (Hgb = 60 – 80g/L) than a more liberal strategy (Hgb < 10 g/L). However, this evidence seemingly does not hold for patients with impaired cardiovascular function. Those with ischemic heart disease showed lower survival if treated according to a restricted transfusion strategy. New data suggest that patients with anemia and myocardial infarction who were treated to raise hematocrit survived longer than those who were not treated for anemia. This suggests that the elderly may not have a sufficient physiologic reserve to draw on when red blood cell level low and are less able to tolerate anemia with acute myocardial infarction, placing them at higher risk for death. The evidence suggests that the underuse of transfusion may be as serious as its overuse, especially for patients with cardiovascular disease.

ERYTHROPOIETIN AND NEUROPROTECTION

Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades

DIGICAYLIOGLU M, LIPTON SA. *NATURE* 2001 412(6847): 641 – 647.

Erythropoietin (EPO) is a naturally occurring kidney cytokine regulating hematopoiesis that is also produced in the brain after oxidative or nitrosative stress. Following hypoxic stimuli, the transcription factor hypoxia-inducible factor-1 (HIF-1) upregulates EPO. In models of ischemia, preconditioning with EPO protects neurons and prevents degenerative damage.

EPO AND COGNITIVE FUNCTIONING

Benefits of recombinant human erythropoietin on cognitive function

EHRENREICH H, SIRÉN A-L. *ERYTHROPOIESIS: NEW DIMENSIONS IN THE TREATMENT OF ANAEMIA*. VOL. II 2001: 35 – 40.

Patients with anemia resulting from various chronic diseases (renal failure, cancer, AIDS and inflammation) demonstrate decreased cognitive function; anemia may also be associated with vascular dementia and the dementia of Alzheimer's disease and AIDS. The improvement in cognitive function with recombinant erythropoietin (EPO) may be attributed to increased hematocrit, but may also be a direct result of the neuroprotective function of EPO. This review discusses the mechanisms of EPO-induced neuroprotection and concludes that treatment with EPO may be both prophylactic and therapeutic with respect to cognitive dysfunction.

ANEMIA AND CANCER

Anemia as an independent prognostic factor for survival in patients with cancer

CARO JJ, SALAS M, WARD A, GOSS G. *CANCER* 2001 91(12): 2214 – 2221.

Anemia has been associated with reduced survival times in patients with various malignancies. A literature review of 60 papers found that relative risk of death increased by 19% in anemic patients with lung cancer, by 75% in anemic patients with head and neck cancer, by 47% in anemic patients with prostate cancer, and by 67% in anemic patients with lymphoma, for an overall increase in risk of 65%. While additional study is needed to determine whether treatment of anemia improves survival, these findings suggest the need for correction of anemia.

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

LITTLEWOOD TJ, BAJETTA E, NORTIER JWR, VERCAMMEN E, RAPOPORT B. *J CLIN ONC* 2001 19(11): 2865 – 2874.

Anemia occurs frequently in cancer patients, especially those receiving chemotherapy. Previous studies have demonstrated that increased hemoglobin improves quality of life (QOL); similarly, various trials have shown that recombinant erythropoietin (EPO) safely increases hemoglobin and reduces the need for blood transfusions. In an international study, anemic patients with a variety of malignancies were randomized to receive epoetin alfa or a placebo. Those treated with EPO demonstrated significantly higher hemoglobin, decreased transfusion requirements, and improved QOL. In addition, post hoc analyses indicated potential survival benefits with increased hemoglobin.

The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix

GROGAN M, THOMAS GM, MELAMED I, WONG FLW, PEARCEY RG, JOSEPH PK, PORTELANCE L, CROOK J, JONES KD. *CANCER* 1999 86(8): 1528 – 1536.

Anemia is assumed to be a causative factor for poor local control and survival among cancer patients receiving radiotherapy (RT). Anemia appears to increase tumour hypoxic fraction and subsequently increase relative radioresistance. Increased hemoglobin level through blood transfusion was associated with increased local control, disease-free survival, and overall survival in a multicentre, retrospective study of 605 patients with carcinoma of the cervix treated with RT. The survival rate of transfused patients who maintained a higher Hgb level was not significantly different from that of patients who had the same level spontaneously. The five-year

survival rate was 74% for patients with an average weekly nadir Hgb (AWN) during RT ≥ 120 g/L as compared with 45% for patients with AWN levels ≤ 110 g/L.

ANEMIA AND RENAL FUNCTION (PRE-DIALYSIS)

Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients

CODY J, DALY C, CAMPBELL M, DONALDSON C, GRANT A, KHAN I, PENNINGTON S, VALE L, WALLACE S, MACLEOD A. *COCHRANE REV ABSTRACT* 2000. THE COCHRANE COLLABORATION.

A review of 12 studies involving 232 patients showed that treatment of anemia with recombinant human erythropoietin (rHuEPO) corrects anemia and avoids the need for blood transfusion. Quality of life and exercise capacity improved, but most trials were not long enough to clearly measure the impact on residual renal function or progression of renal disease.

Epoetin therapy in chronic kidney disease: cardiovascular benefits

LEVIN A. *ERYTHROPOIESIS: NEW DIMENSIONS IN THE TREATMENT OF ANAEMIA*. VOL. II. 2001: 41 – 46.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Anemia is the major contributing factor because the heart compensates for the anemic condition by increasing heart rate, left ventricular stroke volume and thus cardiac output. This paper reviews current evidence supporting the need for early identification of anemia in patients with kidney disease and treatment with epoetin therapy, which reduces the cardiovascular consequences of anemia. Normalization of Hgb does not promote hypertension if blood pressure is controlled.

Use of erythropoietin before the initiation of dialysis and its impact on mortality

FINK JC, BLAHUT SA, REDDY M, LIGHT PD. *A J KIDNEY DISEASES* 2001 37(2): 348 – 355.

A retrospective analysis of 4,866 patients progressing toward end-stage renal disease (ESRD) showed that pre-ESRD patients treated with recombinant erythropoietin (EPO) had a lower risk of death than those not started on EPO before dialysis. Patients with an adequate hematocrit response before initiation of dialysis showed the most survival benefit.

Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure

HAYASHI T, SUZUKI A, SHOJI T, TOGAWA M, OKADA N, TSUBAKIHARA Y, IMAI E, HORI M. *AM J KIDNEY DISEASES* 2000 35(2): 250 – 256.

A progressive study of nine predialysis patients with chronic renal failure (CRF) found that total correction of anemia (normalization of hematocrit to 40) with recombinant human erythropoietin (rHuEPO) led to a significant decrease in left ventricular mass index (LVMI). This strategy was much more effective than partial correction of anemia (target hematocrit 30). There was no difference in progression of renal failure.

The beneficial effects of intervention in early renal disease

PORTELÉS J. *NEPHROL DIAL TRANSPLANT* 2001 16 [SUPPL 2]: 12 – 15.

A decrease in hemoglobin has been associated with an increase in left ventricular hypertrophy (LVH) and mortality among end-stage renal disease (ESRD) patients on dialysis. This paper summarizes recent evidence of the benefits of correcting anemia using epoetin alfa (EPO) with predialysis patients, including the observation in one study that, in patients without basal LVH, the left ventricular mass

index remained stable during epoetin therapy but increased in the absence of EPO. This suggests that aggressive identification and treatment of anemia before dialysis may reduce long-term cardiovascular morbidity and mortality.

INDUCED RED CELL ANEMIA

Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin

CASADEVALL N, NATAF J, VIRON B, KOLTA A, KILADJIAN JJ, MARTIN-DUPONT P, MICHAUD P, PAPO T, UGO V, TEYSSANDIER I, VARET B, MAYEUX P. *N ENGL J MED* 2002 346(7): 469 – 475

Serum samples from 13 patients diagnosed with pure red-cell aplasia who were receiving epoetin (recombinant human erythropoietin) as treatment for anemia of chronic renal failure were found to have antierythropoietin antibodies. There was a decline in antibody titers following discontinuation of treatment. It is recommended that patients receiving epoetin who develop unexplained anemia be tested for the presence of neutralizing antibodies as soon as possible.

Drug-induced autoimmune red-cell aplasia

BUNN HF. *N ENGL J MED* 2002 346(7): 522 – 523

The majority of cases of drug-induced red-cell aplasia have occurred recently in Europe and much less frequently in the United States, raising the question of whether the antigenicity of the European product has been slightly enhanced by the manufacturing process. Since the recombinant erythropoietin polypeptide is identical to the endogenous erythropoietin, it is possible that a subtle difference in their carbohydrate structures may create an epitope on the epoetin polypeptide to which an antibody binds. Given that darbepoetin alfa differs more markedly from the endogenous erythropoietin than does epoetin, it will be important to determine whether it engenders cross-reacting antibodies.

ANEMIA AND CRITICAL ILLNESS (INTENSIVE CARE)

Anaemia in the critically ill – the optimal haematocrit

TAN JKS, LIM JMJ. *ANNALS ACADEMY OF MEDICINE* 2001 30(3): 293 – 299.

Anemia in critically ill patients may result from frequent blood sampling, gastrointestinal bleeding, surgical blood loss, impaired erythropoietic response, and nutritional deficiencies. Data suggest a linear relationship between Hct and cerebral oxygen delivery. There is evidence that anemia increases morbidity and mortality in critical care patients, but red blood cell transfusions have been linked to lower survival and higher care costs. Therefore, it is important to minimize blood loss, prevent anemia through nutritional supplements, and consider blood alternative strategies such as the administration of erythropoietin and blood substitutes.

Nutritional deficiencies and blunted erythropoietin responses as causes of the anemia of critical illness

RODRIGUEZ RM, CORWIN HL, GETTINGER A, CORWIN MJ, GUBLER D, PEAR RG. *J CRITICAL CARE* 2001 16(1): 36 – 41.

Patients in intensive care units (ICUs) were screened for iron, B₁₂, folate, and EPO levels. About 13% of those patients had correctable nutritional deficiencies associated with anemia and iron studies consistent with anemia of chronic disease, as well as a blunted-EPO response.

ANEMIA AND HIV/HCV

Consensus statement: anemia in HIV infection – current trends, treatment options and practice strategies

VOLBERDING P. *CLINICAL THERAPEUTICS* 2000 22(9): 1004 – 1020.

Anemia is a common complication of HIV infection, although the

prevalence and incidence varies in different groups. Anemia may be a result of HIV infection itself; of complications of the disease, such as opportunistic infections and malignancies; and of treatment agents. Other causes are malnutrition and malabsorption of nutrients, erythropoietic insufficiency, and ineffective hematopoiesis. A growing body of evidence suggests that anemia is independently associated with increased mortality risk and disease progression. Transfusions are essential for patients with severe or symptomatic anemia; however, allogeneic transfusions may cause further immunosuppression. In this era of highly active antiretroviral therapy (HAART), patients with chronic anemia and endogenous erythropoietin levels < 500 mU/mL are candidates for recombinant human erythropoietin therapy. Studies that better delineate the effects of treatment – and the best options in particular patient groups – should be performed.

Update on the management of HIV and hepatitis C virus coinfection

PETERS MG, LOUIE K, TERRAULT N. *MEDSCAPE HIV/AIDS E JOURNAL* 8(1), 2002. MEDSCAPE PORTALS, INC.

Individuals coinfecting with HIV and hepatitis C virus (HCV) in an era of highly active antiretroviral therapy (HAART) may be ineligible for standard HCV therapies because of concomitant hepatotoxicity, steatosis, and cytopenias. Early studies suggest that similar proportions of HIV-infected and HIV/HCV-coinfecting individuals achieve sustained virologic responses to combination anti-HCV therapy with interferon plus ribavirin. Anemia is the most common side effect of ribavirin therapy. Hemoglobin concentrations start to drop after the first week of therapy, with a mean decrease from baseline of 29 g/L. Erythropoietin is being used to treat anemia in mono- and coinfecting individuals, and larger randomized controlled studies are being performed.

ANEMIA AND NUTRITION

Treatments for iron deficiency anaemia in pregnancy

CUERVO LG, MAHOMED K. *COCHRANE REV ABSTRACT* 2002.

THE COCHRANE COLLABORATION.

Iron deficiency is the most common cause of anemia in pregnancy worldwide. This review assessed the effectiveness of different treatments: oral, intramuscular or intravenous injection, blood transfusions, and recombinant erythropoietin. It concluded that there were insufficient high-quality studies with outcome data.

Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of residual iron-deficiency during pregnancy

BREYMANN C, VISCA E, HUCH R, HUCH A. *AM J OBST GYNAEC* 2001 184: 662 – 667.

In severe cases of iron-deficiency anemia during pregnancy, there is increased risk to mother and fetus. High-dose oral iron has a high incidence of side effects and therefore noncompliance. Two groups of pregnant women with Hgb < 10 g/L were randomized to receive either recombinant human erythropoietin (rHuEPO) and iron sucrose or iron sucrose alone. The group treated with rHuEPO had higher reticulocyte counts and greater increases in hematocrit. Only one patient in the EPO-treated group failed to achieve target Hgb, while five in the iron sucrose group failed. The results show that EPO with iron sucrose is more effective in correcting pregnancy-related anemia than iron sucrose alone.

ANEMIA AND SURGERY

Transfusion practices for elective orthopedic surgery

FEAGAN BG, WONG C, JOHNSTON WC, ARELLANO R, COLTERJOHN N, KARKOUTI K, TURNER K. *CMAJ* 2002 166(3): 310 – 314.

Use of blood conservation techniques in elective surgery reduces the risk of infection and transfusion reactions that result from using allogeneic blood products. A review of 4,535 medical records of patients in 19 hospitals who underwent total hip or knee joint arthroplasty between June 1998 and January 1999 found that 2,561 (57.9%) were eligible to participate in an autologous blood donation program. Only 842 (18.6%) of the patients predated blood. Patients who did not predate blood were older and were more likely to have concomitant medical conditions. Of the patients who did not predate blood, 30.6% received allogeneic transfusions compared with 14.1% for those who predated. The frequency with which blood conservation techniques other than autologous blood donation were used was minimal (2.4%).

CHRONIC ANEMIAS

Peripheral blood stem cell transplantation in children with beta-thalassemia

YESILPEK MA, HAZAR V, KUPESIZ A, KIZILORS A, UGUZ A, YEGIN O. *BONE MARROW TRANSPLANT* 2001 28(11): 1037 – 1040.

This study followed 15 children (ages 1–15 years) with beta-thalassemia who received allogeneic peripheral blood stem cell transplant (PSCT) from human leukocyte group A (HLA) phenotypically identical donors. Two patients died. The 13 surviving patients were transfusion-independent at follow-up (2–30 months after PSCT). The researchers conclude that PSCT can be considered a safe and effective treatment for children with beta-thalassemia.

Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia

MILLER ST, WRIGHT E, ABOUD M, BERMAN B, FILES B, SCHER CD, STYLES L, ADAMMS RJ. *J PEDIATR* 2001 139(6): 785 – 789.

The Stroke Prevention Trial (STOP) had demonstrated that chronic transfusion is highly effective in reducing the risk of stroke in children with sickle-cell disease and abnormal transcranial Doppler ultrasonography examination result. This randomized, controlled study examined the impact of chronic transfusion on incidence of pain and acute chest syndrome. Results demonstrated lower hospitalization rates for acute chest syndrome and for pain in the transfusion-treated group as compared with the observation control group.

Correction of sickle cell disease in transgenic mouse models by gene therapy

PAWLIUK R, WESTERMAN KA, FABRY ME, PAYEN E, TIGHE R, BOUHASSIRA EE, ACHARYA SA, ELLIS J, LONDON IM, EAVES CJ, HUMPHRIES RK, BEUZARD Y, NAGEL RL, LEBOULCH P. *SCIENCE* 2001 294(5550): 2368 – 2371.

Sickle cell disease (SCD) is caused by a single point mutation in the human betaA globin gene that results in the formation of an abnormal hemoglobin. A betaA globin gene variant that prevents HbS polymerization was inserted into mouse models using a lentiviral vector optimized for transfer to hematopoietic stem cells. All transplanted mice demonstrated long-term expression of antisickling protein in up to 52% of total hemoglobin and 99% of circulating red blood cells. In two mouse models, inhibition of red blood cell dehydration and sickling was achieved with correction of hematological parameters, splenomegaly, and prevention of urine concentration defect.

Celiac sprue

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FARRELL RJ, KELLY, CP. *N ENGL J MED* 2002 346(3): 180 – 188.

Iron-deficiency anemia is the most common clinical presentation in adults with celiac sprue. Celiac sprue results from inappropriate T-cell-mediated immune response against ingested gluten in genetically predisposed individuals. Celiac sprue is relatively common, affecting an estimated one of every 120 to 300 persons in both Europe and North America. Diagnosis is based on gastrointestinal symptoms, family history, steatorrhea, and unexplained iron-deficiency anemia, as well as serological tests for IgA endomysial or tissue transglutaminase antibody with small-bowel biopsy. Treatment includes a gluten-free diet. Additionally, newly diagnosed patients should receive appropriate supplements to correct iron or folate deficiency. Approximately 70% of patients have symptomatic improvement within two weeks.

Quebecers with celiac disease: analysis of dietary problems

LAMONTAGNE P, WEST GE, GALIBOIS I. *CAN J DIET PRACT RES* 2001 62(4): 175 – 181

It is difficult for many celiac sufferers to achieve a lifelong avoidance of dietary gluten. A survey of members of the Quebec Celiac Foundation found that 36% reported difficulties in compliance with a gluten-free diet. Over 35% experienced intestinal discomfort at least twice a week. Only 44% said they had received sufficient information about celiac disease treatment from dietitians.

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