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Evaluation of the Implementation of an Anemia Algorithm in Chronic Hemodialysis Patients

by

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Abstract

Although anemia is a common complication of chronic kidney disease, demanding much resource in its management, practice variability in its management continues to exist. In an effort to standardize management, the Northern Alberta Renal Program developed and implemented an anemia algorithm, the "Anemia Protocol". A retrospective, cohort design was used to evaluate the effectiveness of the "Anemia Protocol" by following patients 3 months pre-implementation, and 3 and 6-months post- implementation. Clinical outcomes of hemoglobin levels, iron indices, erythropoietin and iron dosages, and its associated costs, were compared pre and post implementation. The study did not show any significant change in clinical outcomes pre versus post the "Anemia Protocol" algorithm implementation.

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CHAPTER ONE

Introduction

Chronic Kidney Disease (CKD) is an insidious, progressive disease leading to irreversible loss of kidney function. The National Kidney Foundation (2001) defines CKD as kidney damage of greater than three months that is manifested by either pathological abnormalities and/or abnormal kidney function with a glomerular filtration rate less than 60 ml/minute/1.73m^2. Declining kidney function progresses to end-stage renal disease (ESRD), rendering patients to be permanently dependent on renal replacement therapy such as dialysis or transplantation.

There are a host of disorders that can lead to CKD. For example, diabetes mellitus, hypertensive nephrosclerosis, and chronic glomerulonephritis (GN) can result in CKD [Hsu, Vittinghoff, Lin, & Shlipak, 2004; Obrador, Pereira, & Kausz, 2002; Canadian Organ Replacement Register (CORR), 2002]. In the past 10 years, diabetes mellitus and GN are the two leading causes of new cases of ESRD, accounting for 33% and 14%, respectively (CORR, 2002). According to the Canadian Organ Replacement Register (2002), a not-for-profit organization that records, analyzes and reports renal activities in Canada, the number of new patients starting on renal replacement therapy has more than doubled in the past 10 years. As of December 31, 2000, there are more than 14, 000 patients on various modalities of dialysis and this number does not include the countless number of pre-dialysis patients who are being managed conservatively and medically (CORR, Preliminary Report for Dialysis and Transplantation, 2002).

The prevalence of patients with CKD may be attributable to better health management, where patients are surviving longer; it may be attributable to improved

diagnostic and screening tools, where more diagnoses are being made; or it may be attributable to a more sedentary lifestyle, leading to the prevalence of diabetes mellitus (Hsu et al., 2004; Obrador et al., 2002). Regardless of the reasons for this alarming trend, one cannot deny the challenge and strain this puts on the health care system. CKD does not only involve the kidneys but it also affects almost every organ system. Because patients often present with many co-morbidities and complications, management is challenging and sometimes problematic.

CORR (2002) reported that the leading cause of death in CKD patients is attributed to cardiac etiologies (30.3%). This is not surprising, as more and more patients are presenting with cardiac risk factors: 25.8% with angina, 21.8% with myocardial infarction, 12.8% with cerebral vascular accident, 19.6% with peripheral vascular disease, and 82.2% on medications for hypertension by the time they develop kidney impairment (CORR, 2002). This is further complicated by other ailments that are common to kidney failure.

A wide range of complications develops as a consequence of kidney failure. Disorders related to fluid and electrolyte imbalance may include hypervolemia, hyperkalemia, nausea and vomiting, hyperparathyroidism, bone disease, and hypertension (Mitch, 2005; Snively, 2004). One of the most common complications associated with CKD is anemia (Pendse & Singh, 2005). Anemia itself can be disruptive in that it can cause weakness, fatigue, and tachycardia, but it can also further potentiate other existing complications, such as left ventricular hypertrophy and arrhythmias (Eckardt, 2005; Levin, 2004; Levin, 2002).

Managing anemia is essential in optimizing quality of life, in enhancing well-being, and in reducing hospitalizations and morbidities. Because of practice variability and inconsistencies in patient care delivery, national guidelines were established by the National Kidney Foundation to help guide anemia management (NKF-K/DOQI, 2001). The Northern Alberta Renal Program (NARP) in Edmonton, Alberta has adopted these guidelines and created an anemia algorithm, the "Anemia Protocol" (Appendix A) to assist health professionals to assess, treat, and monitor anemia in patients with chronic kidney disease. The "Anemia Protocol" was adopted in 2004 in three satellite dialysis units of NARP, Edmonton General Hospital (EGH), Aberhart Center (ABC), and the Royal Alexandra Hospital (RAH) in NARP. Since the implementation of the "Anemia Protocol", there has not been any formal evaluation as to the overall effectiveness of the algorithm.

Purpose of the Study

The purpose of this study was to evaluate the effectiveness of the "Anemia Protocol" algorithm (Appendix A) that was adopted by the Northern Alberta Renal Program. The algorithm was implemented at the EGH and ABC dialysis units in April 2004 and in July 2004 at the RAH dialysis unit. The outcomes of hemaglobin level, iron indices (ferritin and transferrin saturation), recombinant human erythropoietin (r-HuEpo) and iron use, and cost related to r-HuEpo and iron use were examined monthly for the period between January to September 2004 for the EGH and ABC dialysis units, and April to December 2004 for the RAH dialysis unit. Effectiveness reflects an increase in hemoglobin level and a reduction in use and subsequent cost of r-HuEpo and iron supplements. The following questions were addressed:

1. Is there a significant difference in hemoglobin levels pre and post implementation of the "Anemia Protocol" algorithm?
2. Is there a significant reduction in anemia pre and post implementation of the "Anemia Protocol" algorithm?
3. Is there a significant difference in iron indices level pre and post implementation of the "Anemia Protocol" algorithm
4. Is there a significant difference in use of r-HuEpo and iron supplements pre and post implementation of the "Anemia Protocol" algorithm?
5. Is there a significant difference in cost of r-HuEpo and iron supplements pre and post implementation of the "Anemia Protocol" algorithm?

Definition of Terms

Hemoglobin (Hgb) is the iron-containing protein in red blood cells that transports oxygen from the lungs to the body's tissues. In adult males, the average Hgb level is 15.7 ±1.7 g/dL, compared to 13.8 ±1.5 g/dL in adult females.

Anemia in patients with CKD is defined as Hgb level below 110 g/L in both adult males and females.

Iron indices are serum ferritin and transferrin saturation. Ferritin is the available iron stores in the body, whereas transferrin saturation is the available iron for usage. In patients with CKD, target values for ferritin and transferrin saturation are ≥100 ng/mL and ≥20%, respectively.

Iron supplements are medications, such as Ferrous Sulphate, Ferrous Fumarate, Iron Dextran, or Iron Sucrose, which are given for the treatment and/or prevention of iron deficiencies.

Recombinant human erythropoietin (r-HuEpo) is a recombinant version of naturally occurring Epo in the body. It is a glycoprotein that mimics the action of natural Epo. It acts on the bone marrow to increase the production of red blood cells. The two available versions of r-HuEpo are Eprex® and Aranesp®. Aranesp® is the more common r-HuEpo used in NARP, with an average dosage between 60-100 mcg every two weeks.

Costs related to Aranesp® and iron use are calculated on dosage price by University of Alberta Hospital Pharmacy Pricing Guideline.

Hypo-responsiveness is the failure to achieve and maintain target hemoglobin levels, despite adequate iron stores and maximum r-HuEpo dosage (Aranesp® 150 mcg every two weeks).

Significance of the Study

Anemia of CKD is a common complication, affecting more than 75% of patients who are dialysis-dependent. Management of anemia is important as it may improve physiologic and clinical parameters, and quality of life. Treatment of anemia has been reported to improve muscle strength and function, cardiac function, and cognitive function because of improved peripheral oxygen supply. The use of r-HuEpo, since its introduction in 1986, has revolutionalized the management of anemia. Its use has steadily increased over the past years. Currently, there are over 90% of American dialysis patients and over 75% of Canadian dialysis patients receiving r-HuEpo [United States Renal Data System (USRDS), 2003; CORR, 2002].

Despite the routine use of r-HuEpo and its associated costs, variations in anemia management practices continue to exist. This can be attributed to differences in target

range and action threshold among healthcare providers. Since the National Kidney Foundation released its recommendations on the management of anemia in 1997, many centers have developed and implemented anemia algorithms. Algorithms provide standardized approaches for assessing anemia, for initiating treatment, and for monitoring progression.

The "Anemia Protocol" algorithm, initiated at the three satellite dialysis units, may provide consistencies in anemia management by having a set target range for hemoglobin level and iron indices, and the necessary actions to achieve these targets. This was the first study to evaluate the effectiveness of an algorithm, using Aranesp® as the r-HuEpo of choice. Use of the algorithm should result in an increase in hemoglobin level and iron indices, and a reduction in associated costs in r-HuEpo and iron supplement use. With these outcomes, the use of algorithms will have a significant impact on how anemia is being managed.

CHAPTER TWO

Literature Review

Anemia

The World Health Organization defines anemia as hemoglobin (Hgb) concentration below 130 g/L for adult males and post-menopausal women, and Hgb below 120 g/L for pre-menopausal women. The body maintains this balance by constantly producing red blood cells (RBC) and removing destructed cells. Under ideal physiological conditions, the rate of RBC production equals the rate of RBC destruction (Richmond, Chohan, & Barber, 2005; Tefferi, 2003). Mature RBCs normally survive in circulation for 120 days and when they are destroyed, mature RBCs are removed and replaced with reticulocytes (immature RBCs).

When there is a disruption in this balance, anemia develops. Anemia can result from inadequate production of RBCs, increased RBC destruction and/or excessive loss of RBCs. Hypoproliferative anemia is a condition where there is decreased RBC production. This can stem from lack of essential nutrients, like iron, folate, or vitamin B_{12}, from inadequate levels of endocrine hormone, erythropoietin, or from suppression of bone marrow function, either from drugs or by infiltration of a tumor (Ly, Marticorena, & Donelly, 2004; Sargent & Acchiardo, 2004). Hemolytic anemia occurs when there is an accelerated RBC destruction that can be caused by hereditary disorders such as sickle cell anemia or hemolysis from chemicals or physical trauma (Garratty, 2005; Semple & Freedman, 2005; Vaziri, 2004). Anemia due to excessive loss of RBCs is most commonly from gastrointestinal bleeding (National Kidney Foundation, 2001).

Decreased amount of circulating RBCs results in decreased oxygen carrying capacity of the blood, which affects almost every organ system. Initially, anemia can be so mild it goes unnoticed. But signs and symptoms increase as the condition progresses. The symptoms related to anemia arise from a reduction in oxygen delivery to tissues. Fatigue is the most common sign and symptom of anemia, but it can also be associated with dizziness, weakness, pallor, tachycardia, shortness of breath, and headaches (Odden, Wholley, & Shlipak, 2004; Strippoli, Craig, Manno, & Schena, 2004).

Anemia of Chronic Kidney Disease

The pathogenesis of anemia of CKD, like anemia in general, can develop from decreased RBC production, from accelerated and premature RBC destruction, or from acute or chronic blood loss. The primary cause of anemia seen in patients with CKD is from hypoproliferative anemia (Ly et al., 2004; Barrett, Fenton, Ferguson, Halligan, Langlois, McCready, Muirhead, & Weir, 1999). As outlined by Bahlmann, De Groot, Duckert, Niemczyk, Bahlmann, Boehm, Haller, and Fliser (2003), the pathogenesis of hypoproliferative anemia is usually multifactorial, but the primary cause is from insufficient production of erythropoietin (Epo). In advanced kidney failure, the number of functioning renal tubular cells is decreased, resulting in decreased stimulation of hematopoiesis. Epo is an erythroid specific growth factor that binds with erythroid progenitors to enhance the proliferation and differentiation of erythroblasts into reticulocytes. After two to three days, reticulocytes are then released into the blood stream where the mature RBCs normally survive for 120 days (Pfeilschifter & Huwiler, 2004; Bahlmann, De Groot, Spandau, Landry, Hertel, Duckert, Boehm, Menne, Haller, & Fisher, 2003). The lifespan of RBCs in patients with CKD is decreased to 60-90 days.

The pathogenesis of shortened lifespan of RBCs is not clear, but it is thought that the uremic environment may alter the cell physiology (Ly et al., 2004). Along with reduced Epo, shortened RBC lifespan contributes to the development of anemia of CKD.

Like anemia in general, patients with anemia of CKD may also experience fatigue, weakness, headaches, and tachycardia (Odden et al., 2004; Beusterien, Ross, Fahrbach, Frame, Scheve, Connelly, & Glaspy, 2003). In the long term, if untreated, anemia is associated with a number of physiological abnormalities, including the development of left ventricular hypertrophy, congestive heart failure or angina, increased cardiac output, impaired cognitive and mental function, decreased exercise tolerance and quality of life, and it may also weaken an already altered immune system (Eckardt, 2005; Weiner, Tighiouart, Vlagopoulos, Griffith, Salem, Levey, & Sarnak, 2005; Levin, 2004; Roman, Lobo, Taylor, Goodkin, LaBrecque, Powers, & Bolton, 2004).

Many authors report a link between anemia and cardiovascular disease (Eckardt, 2005; Kausz, Solid, Pereira, Collins, & St. Peter, 2005; Strippoli et al., 2004; Snively, 2004; Silverberg, Wexler, Blum, Wollman, Schwartz, Sheps, Keren, & Iaina, 2004; Pereira, & Sarnak, 2003; Levin, 2002). Anemia has been implicated to contribute to the worsening of cardiac function as well as having a role in increasing left ventricular mass (Wexler, Silverberg, Blum, Sheps, Keren, Wollman, Schwartz, & Iaina, 2005; Silverberg, Wexler, & Ianina, 2004). It is an independent risk factor for cardiovascular disease in patients with CKD. In order to maintain tissue oxygen supply, adaptive cardiovascular mechanisms are induced. Stroke volume and heart rate are increased, resulting in cardiac stress and the development of left ventricular dilation and hypertrophy and cardiomyopathy (Snively, 2004). As of December 2000, of all the new patients

presenting with CKD, 60.4% also have cardiovascular risk factors (angina, myocardial infarction and/or cerebral vascular accident) (CORR, 2002). It is estimated that by the time patients need to start dialysis, three-quarters of patients already have left ventricular hypertrophy, and left ventricular hypertrophy, in itself, is a strong predictor of mortality (Ayus, Go, Valderrabano, Verde, de Vinuesa, Achinger, Lorenzo, Arieff, & Luno, 2005; Jones, Schenkel, & Just, 2005; Weiner, Tighiouart, Vlagopoulos, Griffith, Salem, Levey, & Sarnak, 2005).

Cardiac disease and anemia have been referenced to decrease physical capacity and exercise tolerance, in turn affecting the well-being of patients with CKD (Odden et al., 2004). The mechanism by which physical capacity is reduced in patients with CKD is unclear, but it has been postulated that it may be due to patients' cardiac status, nutritional status, or anemic state (Odden et al., 2004). Odden et al. (2004) studied a cohort of 954 hemodialysis patients from the San Francisco area to examine the influence of psychosocial factors on cardiac outcomes in participants with known coronary disease. They found that both CKD and anemia were independently associated with reduced self-assessed physical function and exercise capacity. Self-perception of physical function was assessed by Seattle Angina Questionnaire, which measures how daily activities are limited by symptoms of coronary disease. Scores are from 0-100, with higher scores being associated with better physical function. Exercise capacity was assessed on graded exercise treadmill test using the standard Bruce Protocol, score <5 being associated with low exercise capacity. The authors reported that patients with CKD, as well as coronary disease, had a physical function score of 67.6 ± 24.2 and exercise capacity of 5.5 ± 2.8, compared to 74.9 ± 22.9 and 7.9 ± 3.3 ($p < 0.001$) in patients with only coronary disease.

In patients with anemia, physical function score was 62.6 ± 22.7 and exercise capacity of 5.7 ± 2.3, compared to 74.3 ± 23.2 and 7.5 ± 3.4 (p <0.001) in patients with only coronary disease. However, the presence of both conditions was associated with a further reduction in self-assessed or measured physical function. The authors concluded that patients with CKD already have lowered physical capacity that is further reduced in the presence of anemia.

Anemia is also associated with increased hospitalizations, health care costs, and mortality due to various complications. Kausz et al. (2005) looked at a national cohort of more than 130,000 American hemodialysis patients from 1996 to 2000. They compared the differences between patients who were able to achieve Hgb >110 g/L and patients who were not able to achieve this level. Patients who were not able to achieve Hgb >110 g/L had more co-morbid conditions, had more hospital admissions, and had more blood transfusions. Patients with Hgb <110 g/L were 8% more likely to receive blood transfusions, compared to 3% in patients with Hgb >110 g/L (p <0.0001). They were also more likely to be hospitalized, 1.63 compared to 0.99 (p <0.0001), and had longer hospital duration, 11.2 days compared to 6.5 days (p <0.0001). Patients with Hgb <110 g/L also had more infections, 1.16 compared to 0.61 (p <0.0001) than patients with Hgb >110 g/L.

Benefits of Managing Anemia of Chronic Kidney Disease

There has been tremendous amount of literature on anemia of CKD and the clinical benefits of treatment are well documented (Odden et al. 2004; Collins, Li, St. Peter, Ebben, Roberts, Ma, & Manning, 2001; Ma, Ebben, Xia, & Collins, 1995). Supporting literature reports improved survival, decreased morbidity, improved cardiac

function, and enhanced cognitive acuity (Furuland, Linde, Ahlmen, Christensson, Strombom, & Danielson, 2003; National Kidney Foundation, 2001). Because effective treatment of anemia is associated with improved clinical outcomes and quality of life, and reduced hospitalizations and mortality, anemia management is a major goal of CKD management.

Levin (1992) showed that once anemia is alleviated, maximal oxygen uptake was increased by 50% from baseline, leading to increased exercise capacity. Although McMahon, McKenna, Sangkabutra, Mason, Sostaric, Skinner, Burge, Murphy, and Cranshaw (1999) did not show as much of an increase, they did find that there was an 18% greater maximum oxygen consumption in CKD patients without anemia. Odden, Whooley, and Shlipak (2004), Silverberg, Wexler, Blum, and Iaina (2003), Mayer, Thum, Cada, Stummvoll, and Graf (1998), and Marsh, Brown, Wolcott, Carr, Harper, Schweitzer, and Nissenson (1991), also reported that once anemia is treated, there is a reflective improvement in exercise capacity, physical performance, and work capacity.

Whether it is improved exercise capacity or general well-being, erythropoietin has a role in the functional well-being of patients with CKD (McCullough & Lepor, 2005; Furuland, Linde, Ahlmen, Christensson, Strombom, & Danielson, 2003). Correcting anemia in CKD patients has consistently shown that it improves quality of life (Jones, Ibels, Schenkel, & Zagari, 2004; Thomas, 2004; Ross, Fahrbach, Frame, Scheve, Connelly, & Glaspy, 2003; Silverberg, et al., 2003; Moreno, Aracil, Perez, & Valderrabano, 1996). Moreno et al. (1996) assessed quality of life of a group of hemodialysis patients at baseline before r-HuEpo treatment, and after 3 and 6 months of follow-up, using the Karnofsky sale (KS) and the Sickness Impact Profile (SIP)

questionairre. A high KS score and a low SIP score indicate better quality of life. They reported that patients with r-HuEpo treatment had a rise in Hct from 21 to 29% at the end of six months. Mean KS scores increased from 68 ±1.8 to 81 ±1.5 (p <0.0001) and the mean SIP score decreased from 19.8 ±1.6 to 13.5 ±1.2 (p <0.0001).

Other studies reported decreased hospitalizations and mortality rates as beneficial consequences of treating anemia (Jones et al., 2004; Furuland et al., 2003; Collins et al., 2001; Collins, Ma, & Ebben, 2000; Xia, Ebben, Ma, & Collins, 1999). Collins et al. (2001) looked at a cohort of hemodialysis patients and found that there was a 16-22% lower hospitalization rate in patients who were able to achieve target Hct levels above 36%. Similarly, Xia et al. (1999) demonstrated that patients with Hct levels in the range of 33-36% exhibited less risks of hospitalization (7-22% reduction), compared with patients with Hct values in the range of 30-33%. They concluded that patients with Hct <30%, compared to baseline of 30-33%, had a 14-30% increased risk of hospitalization (p =0.0001) and patients at the 33-36% range, had the lowest risk at 0.93 (p =0.0001). Ma, Ebben, Xia, and Collins (1999) also reported improved patient survival and a 4-25% lower mortality rate in patients with a higher hematocrit level.

Management of Anemia of Chronic Kidney Disease

Historically, management and treatment options for anemia of chronic kidney disease have been limited. Administering blood transfusions was the common treatment option for managing and treating anemia. But the adverse consequences of blood transfusions can be problematic. Blood administration carry the risks of transmitting infectious agents, as well as potentially increasing antibodies in patients, making transplantation a challenge, and it may suppress production of Epo in some patients

(Raghavan & Marik, 2005; Jones, et al., 2004). The body has a strict feedback mechanism for Epo synthesis. The primary stimulus for increased Epo synthesis is tissue hypoxia, from decreased blood oxygen availability. When the kidneys sense a reduction in oxygen supply (renal hypoxia), it increases Epo secretion to stimulate erythrocyte production (Pfeilschifter & Muhlfelder, 2004). Consequently, with blood transfusions, the stimulus for Epo synthesis is suppressed. It is now recommended that blood transfusions be reserved for severely anemic patients who are symptomatic or for erythropoietin-resistant patients who have chronic blood loss (National Kidney Foundation, 2001).

Since the introduction of exogenous erythropoiesis-stimulating agents in Canada in 1986, the management and treatment of anemia of CKD was revolutionized. The gene encoding Epo was cloned in 1985, leading to the production of recombinant human erythropoietin (r-HuEPO). Since its introduction, many patients are spared from transfusion dependency (Eschbach, 1995; Adamson & Eschbach, 1989). R-HuEPO is a recombinant version of Epo. They are glycoproteins that mimic natural Epo to stimulate the bone marrow to produce RBCs, which in turn, increase oxygen availability to tissues (Debska-Slizien, Owczarzak, Lysiak-Szydlowska, & Ruthkowski, 2004; Graf, Lacombe, & Braun, 2000; Macdougall, 2000). Currently, there are two agents available in Canada: epoetin alpha (Eprex®) and darbepoietin alpha (Aranesp®).

Although both Aranesp® and Eprex® stimulate erythropoiesis by binding to the same Epo receptors and have the same mechanisms of intracellular signaling, they are structurally distinct from each other. Aranesp® is made up of 22 sialic acid molecules (compared to 14 in Eprex®), rendering it more potent and having a longer half-life. The

prolonged half-life makes it possible to extend dosing intervals, thus making administration more convenient. Rather than administering Eprex® thrice weekly, Aranesp® may be given once weekly to biweekly (Deicher & Horl, 2004; Nissenson, 2001; Egrie & Browne, 2001; MacDougall, 2000; Graf et al., 2000).

Since the introduction of Eprex® in 1986, the drug has been known to be relatively safe for the treatment of anemia. But in December 2001, Johnson and Johnson, the company that markets Eprex®, reported that at least 40 patients have developed pure red cell aplasia. Pure red cell aplasia is an immune response that causes the shut down of red blood cell production (Rossert, Casadevall, & Eckardt, 2004; Casadevall, Nataf, Viron, Kolta, Kiladijan, Martin-Dupont, Michaud, Papo, Ugo, Teyssandier, Varet, & Mayeux, 2002; Bunn, 2002). The condition was thought to be a consequence of the manufacturing techniques of Eprex® and since then, different manufacturing techniques have been implemented by the company (Sibbald, 2004; Macdougall, 2004). Although the risk of developing pure red cell aplasia is rare (1 in 10,000), many centers opted to use Aranesp®. To date, Aranesp® has not reported any cases of pure red cell aplasia.

The cost associated with the use of r-HuEpo is high. It is estimated that the average cost of 80 micrograms of Aranesp® is $225.12. As of December 2000, over 75% of hemodialysis patients are on r-HuEpo, compared to 10.3% in 1989 (CORR, 2002). Although there is growing resources devoted to managing anemia of chronic kidney disease, variations in anemia management practices continue to exist. In an effort to limit practice variability, the National Kidney Foundation formed a work group to specifically look at the management of anemia of CKD. In 1997, the group released recommendations for anemia management, including screening criteria, target

hemoglobin/hematocrit levels, initiation parameters and ongoing management issues. These guidelines are known as the NKF-K/DOQI (National Kidney Foundation – Dialysis Outcomes Quality Initiative) Guidelines for anemia management.

The NKF-K/DOQI guidelines define anemia in patients with CKD as Hgb <110 g/L or Hct <33% in pre-menopausal females and pre-pubertal patients, or when Hgb <120 g/L or Hct <37% in adult males and post-menopausal females. NKF-K/DOQI recommendation for target Hgb level to be >110 g/L is consistent with other national guidelines, such as the European Best Practice Guidelines on Anemia Management (Cameron, 1999) and the Clinical Practice Guidelines of the Canadian Society of Nephrology (CSN). When Hgb falls below 110 g/L or Hct <33%, r-HuEpo is to be initiated, to maintain Hgb between 110-120 g/L or Hct between 33-36% (National Kidney Foundation, 2001).

Besides having guidelines for r-HuEpo initiation, NKF-K/DOQI also has recommendations for iron indices management and therapy. It recommends that transferrin saturation be maintained between 20-50% and that ferritin level is between 100-800 ng/mL. Transferrin saturation reflects the available iron for usage, whereas ferritin is a good indicator of available iron stores in the body. Iron supplementation is initiated when transferrin saturation is below 20% or ferritin is below 100 ng/mL. Conversely, iron supplementation is halted when transferrin saturation is above 50% or ferritin is above 800 ng/mL (National Kidney Foundation, 2001). Ferritin level as an indicator of iron adequacy needs to be used with caution because ferritin level also reflects "acute phase" conditions. Ferritin levels may be falsely elevated in conditions of inflammation, infection or malignancies (Slotki, 2005; Pagana et al., 2003) and may not

be a true reflection of iron stores. Thus, understanding its limitations and having a more detailed history of co-morbidities of patients are important in assessing iron adequacy.

Iron supplementation is predominantly given intravenously because iron absorption by the oral route is limited. Poor absorption through the oral route may be due to concomitant use of other drugs such as proton pump inhibitors, phosphate binders or antacids and it can be very upsetting to the gastrointestinal system (Charytan, Qunibi, & Bailie, 2005; Barrett et al., 1999).

Hyporesponsiveness of Epoietin therapy

The NKF-K/DOQI guidelines define hypo-responsiveness "as a failure to achieve and maintain target hemoglobin level", despite adequate iron stores and maximum dosage of r-HuEpo. There are many possible causes for this inadequate response. Causes such as iron deficiency, infection and inflammation, hyperparathyroidism, inadequate dialysis, aluminum toxicity, or deficiencies in vitamin B_{12} and folic acid (Del Vecchio, Pozzoni, Andrulli, & Locatelli, 2005; Dar Santos, Shalansky, & Jastrzebski, 2003; Drueke, 2001) are factors that may interfere with hematopoiesis.

Iron deficiency is the most common cause of inadequate response to r-HuEpo (Dar Santos et al., 2003; Drueke, 2001; Wians, Urban, Keffer, & Kroft, 2001; Barret et al., 1999). In order for r-HuEpo to be beneficial, patients must be iron replete. It is estimated that among American CKD patients who are receiving r-HuEpo, more than 50% of the patients are also iron deplete. Iron depletion may result from increased iron demand due to increased rate of erythropoiesis or it may be from blood loss, such as frequent blood tests, residual loss to the dialysis process, or from gastrointestinal bleeding (Sargent & Acchiardo, 2004; National Kidney Foundation, 2001; Beserab et al., 2000).

Besides iron adequacy, responsiveness of r-HuEpo is also affected by inflammatory states. Infection and inflammation influence responsiveness by interfering with iron metabolism and eliciting the release of cytokines (Kalantar-Zadeh, McAllister, Lehn, Lee, Nissenson, & Kopple, 2003; Bowawski, Pawlak, & Mysliwiec, 2002). Macrophages release cytokines such as tumor necrosis factor-α, interleukin-1 and interferon-γ, which in turn inhibits erythropoiesis (Smizova, Balla, & Barany, 2005; Nemeth, Valore, Territo, Schiller, Lichtenstein, & Ganz, 2003; Drueke, 2001). Aluminum overload also can interfere with iron metabolism (Drueke, 2001; Caramelo, Cannata, Rodeles, Fernandez-Martin, Mosquera, Monzu, Outeirino, Blum, Andrea, & Lopez-Farre, 1995) but this is not commonly seen in patients today because of the limited use of aluminum-based medications and better water filtering system.

Adequate nutrition and dialysis are also associated with r-HuEpo responsiveness. Poor nutrition may result in inadequate amounts of essential nutrients for hematopoiesis, such as folate, vitamin B_6, and vitamin B_{12} (Del Vecchio et al., 2005; Kalantar-Zadeh, Block, McAllister, Humphreys, & Kopple, 2004; Locatelli & Del Vecchio, 2003; Kalantar-Zadeh, 2003; Kalantar-Zadeh, McAllister, Lehn, Lee, Nissenson, & Kopple, 2003). Quality of dialysis has also been linked to hematopoiesis process. It is theorized that uremia may shorten the lifespan of RBCs, thus better dialysis adequacy will result in prolonged RBC life. McLennan, Frankenfield, and Johnson (2000) and Movilli, Cacarini, Zani, Camerini, Sandrini, and Maiorca (2001) showed that dosages of r-HuEpo do decrease with improved dialysis adequacies. Movilli et al. concluded that patients with KT/V >1.4 required lower r-HuEpo dose than patients with KT/V ≤1.2, 86 ±33 U/kg compared to 183 ±95 U/kg ($p < 0.0001$), respectively. Ifudu et al. (2000) reported that

patients with PRU >70% were 2.6 times more likely to have Hct >33% (odds ratio 2.6; 95% confidence interval [CI], 1.3 to 5.3; $p = 0.009$). Similarly, Panagoutsos, Yannatos, Passadakis, Thodis, Galtsidopoulos, and Vargemezis (2002) reported a rise in Hgb from 10.4 ±1.7 to 11.0 ±1.3 g/dL ($p < 0.05$) when KT/V was increased from 0.93 ±0.19 to 1.55 ±0.29 ($p < 0.001$).

Other causes of r-HuEpo hypo-responsiveness include hyperparathyroidism. Secondary hyperparathyroidism is a common complication in patients with end-stage renal disease (Stevens, Djurdjev, Cardew, Cameron, & Levin, 2004; Yasunaga, Matsuo, Yanagida, Matsuo, Nakamoto, & Goya, 2002), resulting from phosphate retention, hypocalcemia, and low levels of vitamin D, which trigger the hyperparathyroid gland to secrete parathyroid hormone. Hyperparathyroidism and other types of bone disease reduce the number of erythroid progenitor cells, resulting in a reduction in the proliferation and differentiation of erythroblasts into reticulocytes (Yasunaga et al., 2002; Drueke, 2001).

Anemia Managed Algorithm

Practice variability and inconsistencies in patient care delivery are evident in the management of patients with CKD. Adoption of an anemia-managed algorithm would be a "valuable tool for standardizing and optimizing the treatment of anemia in patients with end-stage renal disease" (Senger, Trenkle, & St. John, 1998, p.235). Algorithms provide a systematic approach for assessing Hgb and iron indices, for providing safe and effective iron supplementation, for initiation and maintenance of erythropoietin, and for monitoring patient outcomes.

Many centers, especially in the United States, have created and implemented anemia algorithms as part of their anemia management (Kimura, Arai, Masuda, & Kawabat, 2004; Brimble, Rabbat, McKenna, Lambert, & Carlisle, 2003; Aiello, 2002; To, Stoner, Stolley, Buenvaje, & Ziegler, 2001; DeOreo & Eschbach, 1999; Patterson & Allon, 1998; Senger et al., 1998; Hossli, 1997; Macdougall et al., 1990). Based on recommendations from the NKF-K/DOQI anemia work-group, anemia algorithms were developed to standardize care and limit practice variability. Algorithms provide a step-by-step approach for healthcare workers to systematically review the pathogenesis of anemia, the appropriateness of interventions, and the possible factors that may be associated with hypo-responsiveness.

A search of the literature was conducted to identify anemia management algorithms in CKD. Although there were many reports on the development and implementation of anemia algorithms, there were few studies that evaluated the effectiveness of the algorithm in anemia management (Appendix B). Patterson and Allon (1998) reported that with the use of an anemia algorithm, the number of patients who were able to achieve target Hct levels (31 - 35%), increased from 27 to 61% during months 4 to 6 of the algorithm use. During the same period, the proportion of patients whose transferrin saturation was <18%, decreased from 47 to 20% ($p = 0.04$). Weekly Eprex® dose also decreased from 11, 200 ± 1, 200 units/week to 9, 400 ± 1, 200 units/week in month 6 of the algorithm use ($p = 0.06$).

To et al. (2001), in a retrospective cohort study, compared the management of anemia (without an algorithm) by physicians to the management of anemia by pharmacists (with an anemia algorithm based on recommendations from NKF-K/DOQI

guidelines). Patients who were managed with an anemia algorithm had equivalent outcomes to patients who were managed by physicians. The Hct level for the period without an algorithm was 32 - 38.7%, compared to 32.8 - 39.7% for the period with an algorithm. Although not statistically significant, the authors did report a reduction in the total number of units of Eprex® used; 7.7 million units with an algorithm compared to 8.5 million units without an algorithm ($p = 0.37$) but at the same time, there was an increase in oral iron use of 85, 605 mg without algorithm to 95, 550 mg with algorithm ($p = 0.64$), and also an increase in intravenous iron use from 13, 600 mg without algorithm to 33, 025 mg with algorithm ($p < 0.001$).

Brimble et al. (2003) conducted a randomized controlled trial of 215 hemodialysis patients over an 8-month period. Patients were either grouped into the control group (without anemia algorithm) or the protocol group (with an anemia algorithm). They found that the use of an algorithm does not result in more patients achieving target Hgb levels. At the end of the study, 62.8% of all patients were able to achieve target Hgb levels (11 – 12.5 g/dL), compared to 47.4% at the start of the study ($p = 0.001$). In the control group, there was an increase from 49.1 to 62.0% ($p = 0.05$) who achieved target Hgb levels, and in the protocol group, an increase from 45.8 to 63.6% ($p = 0.02$) was noted. The authors also reported that there was a non-significant difference in total Eprex® dose between the two groups but when they analyze only patients who were able to complete at least 5 months of the study, they found that there was a decrease in Eprex® dose in the algorithm group of 2788 units/wk ($p < 0.05$), which would result in savings of $1245.98 per patient. The study demonstrated that use of an algorithm can safely achieve target Hgb values, but it does not offer any advantage over not using an

algorithm because of the substantial improvement in the control group during the study. However, there was a substantial cost savings in the protocol group.

Kimura et al. (2004), similar to the earlier study by To et al. (2001), compared the management of anemia (without an algorithm) by physicians to the management of anemia by pharmacists (with an anemia algorithm). In the pre-study survey, the authors found that out of 45 patients, 41 of the patients were on Eprex®. But despite the high proportion of patients on r-HuEpo, 34 of the 41 patients did not achieve Hct >30%. On further investigation, they found that 23 of those patients were iron deficient, with ferritin <100 ng/mL. As a result of the use of algorithm, the number of patients who were able to achieve target Hct (>30%) increase from 17 to 78%, and the monthly Eprex® use decreased from 915, 000 to 642, 000 units.

CHAPTER THREE

Methods

The purpose of this study was to evaluate the effectiveness of the implementation of the "Anemia Protocol" (Appendix A) in anemia management. All hemodialysis patients who dialyzed at either the Aberhart dialysis unit (ABC), Edmonton General Hospital dialysis unit (EGH), or the Royal Alexandra Hospital dialysis unit (RAH) were eligible for the study.

Design

A retrospective cohort design was used to evaluate the effectiveness of the "Anemia Protocol" (Appendix A) algorithm in chronic hemodialysis patients. This study followed a cohort of patients who received maintenance hemodialysis for a 9-month period, from January to September 2004 at the EGH and ABC dialysis units, and from April to December 2004 at the RAH dialysis unit. From patient health records, outcome variables of hemoglobin level, iron indices, r-HuEpo dose, iron supplement dose, and factors related to hypo-responsiveness were reviewed monthly. Data were collected in three time periods: pre-implementation (T1), intra-implementation (T2), and post-implementation (T3). T1 is the timeframe of 3 months before the implementation of the "Anemia Protocol" algorithm. After the introduction of the algorithm, a period of 3 months (T2) was included for staff to familiarize with the use of the algorithm; T3 is the 3 months following the implementation of the "Anemia Protocol" algorithm.

Blood work, including hemoglobin levels and iron indices (serum ferritin and transferrin saturation) were measured in patients at the beginning of each month at the dialysis units, either Wednesday or Thursday, dependent on the patient's dialysis

schedule. As standard protocol in the dialysis units, if there was a 15-20 g/L discrepancy in hemoglobin level from the previous value, the result was reported to the responsible nephrologists. The following week, r-HuEpo and iron dosages were then adjusted according to the "Anemia Protocol" algorithm.

Sample/Setting

The sample included health records of persons with end-stage renal disease who received maintenance hemodialysis either at the EGH dialysis unit, ABC dialysis unit, or RAH dialysis unit. Patients eligible for the study were 18 years of age or older and had received hemodialysis treatments at each of the respective dialysis units for the 9-month study period.

Patients excluded from the study were those who did not complete their maintenance hemodialysis at the respective dialysis units, those who were transplanted or switched to peritoneal dialysis, those who were hospitalized, those who received Eprex® as the r-HuEpo of choice, and those who received blood transfusions during the study period. There were a total of 242 patients who were eligible for the study.

Data Collection Protocol

The investigator reviewed health records of all patients who dialyzed at each of the dialysis units 3-months prior to the initiation of the algorithm. Health records of patients were assessed monthly for a period of 9 months to ensure that the following inclusion criteria were met: remain dialyzing at each of the dialysis units, have not been transplanted, have not switched to peritoneal dialysis, and have not deceased. The investigator then recorded demographic information (age, gender) and clinical information (etiology of chronic kidney disease, co-morbidities, and time on dialysis) on

all eligible patients (Appendix C). Patient health records were then reviewed to document any hospital admissions or blood transfusions received. Patients who received Eprex® or blood transfusions, or were admitted during the 9-month period at each of the satellite units were excluded from the study. Hemoglobin, ferritin and transferrin saturation levels, and values that may affect hypo-responsiveness to r-HuEpo (parathyroid hormone and albumin levels, and dialysis adequacy parameters: PRU and KT/V) were also documented for the study periods of T1, T2, and T3. Health records were also screened for any documentation of infection and/or gastrointestinal bleeding. Finally, costs related to r-HuEpo and iron use were calculated based on the University of Alberta Pharmacy Pricing Guideline.

Data Analysis

Data were analyzed by using SPSS (version 13.0, SPSS, Inc., Chicago, IL) software. Descriptive statistics were performed on the demographic and clinical variables to provide an overview of the subjects involved in the study. Repeated measures ANOVA was used to compare the hemaglobin levels, iron indices, r-HuEpo and iron dosages, and costs related to r-HuEpo and iron use, to determine if there was a significant difference pre, during, and post implementation of the "Anemia Protocol". The presence/absence of anemia, pre and post-implementation, was compared using Chi-square. A $p < 0.05$ was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Health Research Ethics Board, University of Alberta. Director of Nursing and Medical Lead of NARP were also approached for approval to review patient health records. All patient information was kept confidential

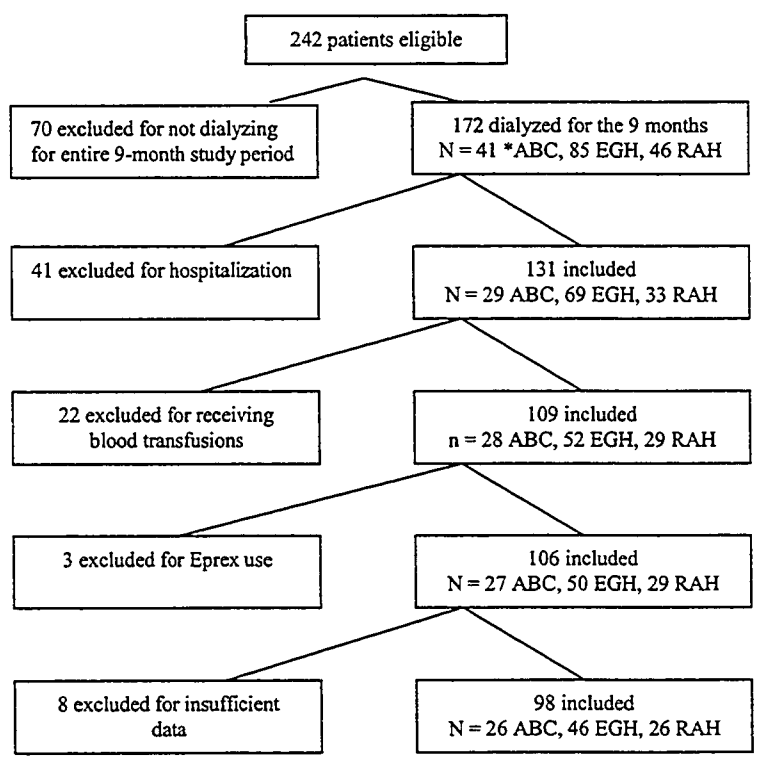
and used only for the purpose of this study. Data were organized by code numbers only, and will be kept in a locked filing cabinet for seven years.

CHAPTER FOUR

Findings

Characteristics of Study Cohort

There were 242 patients eligible for the study. Of the 242 patients, 70 patients were excluded because they did not dialyze for the entire 9 months at their respective dialysis unit. Further 74 patients were excluded from the study for the following reasons: 41 for hospitalization, 22 for receiving blood transfusions, 3 for using Eprex®, and 8 for having incomplete data. Total number of patients enrolled in the study was 98, 26 from Aberhart dialysis unit (ABC), 46 from Edmonton General Hospital (EGH), and 26 from Royal Alexandra Hospital (RAH) (Figure 1).



*ABC: Aberhart Dialysis Unit

EGH: Edmonton General Dialysis Unit

RAH: Royal Alexandra Dialysis Unit

Figure 1. Patient Enrollment

Patients (n =98) had a mean age of 64.5 ± 16.5 years, with a range of 21 to 91 years. There were a total of 54 men (55%). The causes of chronic kidney disease included diabetes (31.6%), glomerulonephritis (25.5%), hypertension (13.2%), renal/vascular disease (2%), pyelonephritis (4%), polycystic kidney disease (2%), and other/unknown (21.4%), such as drug toxicities and amyloidosis. Baseline patient characteristics are summarized in Table 1. There were no significant differences in age, duration of dialysis, or incidence of diabetes, hypertension, coronary artery disease, cerebral vascular accident, peripheral vascular disease, malignancies, lung disease, or other diseases, such as liver disease, gallbladder disease or gastrointestinal diseases associated with bleeding among the 3 satellite dialysis units.

Table 1

Baseline Characteristics of Patients

Variable	ABC* (n=26)	EGH* (n=46)	RAH* (n=26)	*P* value
Gender, *n (%)*				0.518
Men	12 (46.2)	26 (56.5)	16 (61.5)	
Women	14 (53.8)	20 (43.5)	10 (38.5)	
Age				0.568
Mean ± SD *(years)*	60.6 ± 15.2	67.1 ± 16.6	63.4 ± 17.3	
Range	27 - 83	21 - 91	25 - 87	
Duration of dialysis				0.135
Mean ± SD *(years)*	5.2 ± 2.9	4.4 ± 2.5	3.9 ± 4.1	
Diagnosis, *n (%)*				0.075
Diabetes	6 (23.1)	13 (28.2)	12 (46.1)	
Glomerulonephritis	9 (34.6)	13 (28.2)	3 (11.5)	
Hypertension	2 (7.7)	5 (10.9)	6 (23.1)	
Renal/Vascular	0	2 (4.3)	0	
Pyelonephritis	1 (3.8)	3 (6.5)	0	
Polycystic Kidney	2 (7.7)	0	0	
Unknown/Other	6 (23.1)	10 (21.7)	5 (19.2)	
Co- morbidities, *n (%)*				
Diabetes	8 (30.8)	18 (39.1)	13 (50.0)	0.364
Hypertension	18 (69.2)	38 (82.6)	16 (34.8)	0.128
°CAD	14 (53.8)	20 (43.5)	12 (46.2)	0.696
°CVA	4 (15.4)	6 (13.0)	1 (3.8)	0.363
°PVD	4 (15.4)	2 (4.3)	5 (19.2)	0.116
Malignancies	4 (15.4)	1 (2.2)	4 (15.4)	0.078
Lung Disease	3 (11.5)	3 (6.5)	3 (11.5)	0.692
Other	13 (50.0)	19 (41.3)	7 (26.9)	0.226

*ABC = Aberhart Dialysis Unit
EGH = Edmonton General Hospital Dialysis Unit
RAH = Royal Alexandra Hospital Dialysis Unit

°CAD = coronary artery disease
CVA = cerebral vascular accident
PVD = peripheral vascular disease

Hemoglobin Levels and Incidence of Anemia

Over the 9-month study period, there was no significant change in hemoglobin (Hgb) levels (F =2.075, df =5, p =0.075). Furthermore, there was no significant difference in Hgb levels and site of dialysis (F =0.243, df =2, p =0.785). Pre-implementation of the anemia algorithm Hgb levels were 116 ±13 g/L, 117 ±13 g/L, and 117 ±12 g/L, at 1, 2, and 3 months, respectively. Intra-implementation Hgb values were 115 ±11 g/L, 114 ±11 g/L, and 112 ±12 g/L at 4, 5, and 6 months, respectively. Post-implementation Hgb levels were 114 ±13 g/L, 113 ±11 g/L, and 114 ±12 g/L at 7, 8, and 9 months, respectively (Table 2).

Anemia in the study was defined as hemoglobin <110 g/L. The presence/absence of anemia, pre and post-implementation, was compared using Chi-square. There was no significant difference in the incidence of anemia throughout the study period (χ^2 =6, p =0.429). Incidence of anemia was 28% pre-implementation, 34% intra-implementation, and 32% post-implementation of the anemia algorithm (Table 2).

Iron Indices

Similar to Hgb levels, there was no significant change in ferritin levels over the 9-month study period (F =1.205, df =4, p =0.309). There was also no significant difference in ferritin levels and site of dialysis (F =2.937, df =2, p =0.058). Ferritin levels in the pre-implementation phase were 516 ±334 g/L, 517 ±329 g/L, and 453 ±294 g/L at 1, 2, and 3 months, respectively. Intra-implementation ferritin levels were 482 ±338 g/L, 498 ±546 g/L, and 491 ±303 g/L at 4, 5, and 6 months, respectively. Post-implementation ferritin levels were 517 ±310 g/L, 491 ±308 g/L, and 468 ±286 g/L at 7, 8, and 9 months, respectively (Table 2).

Table 2
Laboratory Values Pre-, Intra-, and Post Algorithm Implementation

	T1 (Pre-Implementation)			T2 (Intra-Implementation)			T3 (Post-Implementation)		
	1	2	3	4	5	6	7	8	9
*Hgb, *g/L* Mean ± SD Median (range)	116 ± 13 117 (86-158)	117 ± 13 118 (83-153)	117 ± 12 118.5 (88-144)	115 ± 11 116 (86-140)	114 ± 11 113 (85-141)	112 ± 12 113 (72-146)	114 ± 13 114 (80-149)	113 ± 11 114 (89-139)	114 ± 12 114 (89-140)
Anemia (Hgb <110 g/L), *n*	28	25	29	30	35	35	29	33	33
Ferritin, *g/L* Mean ± SD Median (range)	516 ± 334 449 (13-432)	517 ± 329 429 (27-1432)	453 ± 294 400 (24-1129)	482 ± 338 423 (48-1650)	498 ± 346 438 (32-1650)	491 ± 305 453 (29-1408)	517 ± 310 456 (61-1233)	491 ± 308 465 (39-1535)	468 ± 286 434 (52 – 1591)
∞TSat, % Mean ± SD Median (range)	35 ± 13 33 (10 – 92)	35 ± 15 32 (10 – 85)	33 ± 15 29 (8 – 97)	34 ± 16 32 (13 – 97)	32 ± 13 29 (8 – 91)	34 ± 15 31 (13 – 84)	37 ± 16 33 (15 – 96)	32 ± 12 31 (9 – 77)	33 ± 12 31 (11 – 79)
Serum albumin, *g/L* Mean ± SD Median (range)	38.7 ± 3 39 (30 – 47)	38.9 ± 3 39 (31 – 46)	39.1 ± 3 39 (31 – 45)	38.8 ± 3.6 39 (28 – 47)	38.6 ± 3.4 39 (28 – 47)	38.9 ± 3.6 39 (25 – 46)	38.9 ± 3.2 39 (32 – 46)	38.9 ± 3.1 39 (31 – 46)	38.0 ± 4.1 38 (21 – 46)
°PTH, *pmol/L* Mean ± SD Median (range)							27.1 ± 34.3 15.7 (1.3-193)		
•PRU, % Mean ± SD Median (range)	75.1 ± 5.3 75.5 (57.4 – 84.7)	75.2 ± 5.6 76.1 (54.0 – 86.0)	75.6 ± 5.0 75.5 (52.6 – 86.4)	76.0 ± 5.3 76.3 (50.2 – 85.6)	75.1 ± 5.6 75.1 (49.8 – 90.1)	75.8 ± 5.1 76.5 (50.6 – 85.3)	75.4 ± 5.4 75.7 (54.5 – 84.9)	75.5 ± 5.4 76.0 (49.6 – 84.3)	75.4 ± 4.9 75.9 (53.6 – 83.0)
•KT/V Mean ± SD Median (range)	1.6 ± 0.2 1.63 (0.98 – 2.23)	1.6 ± 0.3 1.64 (0.81 – 2.26)	1.7 ± 0.2 1.63 (0.83 – 2.34)	1.7 ± 0.3 1.68 (0.80 – 2.31)	1.6 ± 0.2 1.61 (0.77 – 2.35)	1.7 ± 0.2 1.68 (0.99 – 2.29)	1.7 ± 0.2 1.64 (0.91 – 2.13)	1.6 ± 0.3 1.63 (0.78 – 2.23)	1.7 ± 0.3 1.63 (0.83 – 2.85)
◊Tested for GIB, *n*	1	1	1	0	0	0	1	0	1
Presence of infection, *n*	1	1	2	1	2	1	1	0	1

*Hgb: hemoglobin
∞TSat: transferrin saturation
°PTH: parathyroid hormone
•PRU, KT/V: dialysis adequacy
◊GIB: tested for gastrointestinal bleeding, but negative

However, there was a significant increase in the transferrin saturation (TSat) level over the 9-month study period ($F = 2.146$, $df = 7$, $p = 0.041$). TSat levels pre-implementation were 35 ±13%, 35 ±15%, and 33 ±15% at months 1, 2, and 3, respectively. Intra-implementation TSat levels were 34 ±16%, 32 ±13%, and 34 ±15% at months 4, 5, and 6, respectively. TSat levels post-implementation of the anemia algorithm were 37 ±16%, 33 ±12%, and 33 ±12%. There was no significant difference between TSat levels and site of dialysis ($F = 1.052$, $df = 2$, $p = 0.354$) (Table 2).

Doses of Aranesp and Iron Supplements

As summarized in Table 3, doses of Aranesp® and iron supplement remained constant from pre-implementation to post-implementation of the anemia algorithm ($F = 0.445$, $df = 3$, $p = 0.745$). Doses of Aranesp® pre-implementation were 159 ±138 mcg, 159 ± 144 mcg, and 154 ±121 mcg at 1, 2, and 3 months, respectively. Intra-implementation doses of Aranesp® were 152 ±120 mcg, 151 ±114 mcg, and 165 ±129 mcg at months 4, 5, and 6, respectively. Doses of Aranesp® post-implementation were 162 ±124 mcg, 167 ±127 mcg, and 162 ±129 mcg at months 7, 8, and 9, respectively. There was also no significant difference between Aranesp® dose and site of dialysis ($F = 0.815$, $df = 2$, $p = 0.446$).

There were a total of 19 oral iron pills (Palafer®) that were used pre-implementation of the anemia algorithm, compared to 18 pills intra-implementation, and 13 pills post-implementation of the anemia algorithm ($F = 1.401$, $df = 1$, $p = 0.243$). Intravenous Iron Dextran dose for pre-implementation were 80.61 ±140.44 mg, 84.59 ±142.97 mg, and 97.45 ±142,97 mg at 1, 2, and 3 months, respectively.

Table 3
Aranesp and Iron Dose and Its Associated Costs

	T1 (Pre-Implementation)			T2 (Intra-Implementation)			T3 (Post-Implementation)		
	1	2	3	1	2	3	1	2	3
*Epo, *mcg*									
Mean ± SD	159 ± 138	159 ± 144	154 ± 121	152 ± 120	151 ± 114	165 ± 129	162 ± 124	167 ± 127	162 ± 129
Median	120	120	120	120	120	140	140	160	140
(range)	(0-640)	(0-640)	(0-640)	(0-640)	(0-600)	(0-600)	(0-600)	(0-600)	(0-640)
Cost of Epo, $									
Mean ± SD	452.82 ± 387.21	452.54 ± 403.74	435.88 ± 343.03	431.86 ± 339.76	428.70 ± 325.34	466.61 ± 364.62	461.44 ± 348.73	477.23 ± 354.22	464.60 ± 359.74
Median	337.68	337.68	337.68	337.68	337.68	393.96	450.24	450.24	450.24
(range)	(0 – 1800.96)	(0 -1800.96)	(0 – 1800.96)	(0 – 1800.96)	(0 – 1688.40)	(0 – 1688.40)	(0 – 1688.40)	(0 – 1800.96)	(0 – 1800.96)
Iron dextran, *mg*									
Mean ± SD	80.61 ± 140.44	84.59 ± 142.97	97.45 ± 146.50	102.04 ± 170.49	118.37 ± 158.18	93.88 ± 136.08	79.59 ± 128.40	104.08 ± 189.98	103.06 ± 176.71
(range)	(0 – 400)	(0 – 400)	(0 – 400)	(0 – 1000)	(0 – 400)	(0 – 400)	(0 – 400)	(0 – 1200)	(0 – 1200)
Venofer, *mg*									
Mean ± SD	19.39 ± 82.06	15.31 ± 72.30	31.63 ± 129.71	39.8 ± 136.78	21.43 ± 78.98	28.57 ± 121.84	13.27 ± 48.99	23.47 ± 99.28	15.31 ± 59.81
(range)	(0 - 400)	(0 – 400)	(0 – 1000)	(0 – 1000)	(0 – 400)	(0 – 1000)	(0 – 200)	(0 – 800)	(0 – 400)
Oral iron, *n*	5	6	8	8	5	5	5	5	3
Cost of Iron, $									
Mean ± SD	19.37 ± 34.71	18.91 ± 32.52	26.64 ± 49.89	30.15 ± 53.07	25.54 ± 33.79	24.44 ± 46.90	16.88 ± 24.52	21.65 ± 33.48	21.71 ± 32.07
(range)	(0 – 150)	(0-150)	(0 – 375)	(0 – 375)	(0 – 150)	(0 – 375)	(0 – 178.80)	(0 – 178.80)	(0 – 178.80)

*Epo: Aranesp dose

Intra-implementation doses of intravenous Iron Dextran were 102.04 ±170.49 mg, 118.37 ±158.18 mg, and 93.88 ±136.08 mg at 4, 5, and 6 months, respectively. Post-implementation doses of intravenous Iron Dextran were 79.59 ±128.40 mg, 104.08 ±189.98 mg, and 103.06 ±176.71 mg at 7, 8, and 9 months, respectively ($F = 0.899$, $df = 4$, $p = 0.469$). There was also no significant difference between doses of intravenous Iron Dextran and site of dialysis ($F = 1.055$, $df = 2$, $p = 0.3520$). Pre-implementation doses for intravenous Venofer® were 19.39 ±82.06 mg, 15.31 ±72.3 mg, and 31.63 ± 129.71 mg at 1, 2, and 3 months, respectively; intra-implementation doses were 39.8 ±136.78 mg, 21.43 ± 79.98 mg, and 38.57 ±121.84 mg at 4, 5, and 6 months, respectively; post-implementation were 13.27 ±48.99 mg, 23.47 ±99.28 mg, and 15.31 ±59.81 mg at 7, 8, and 9 months, respectively ($F = 1.71$, $df = 5$, $p = 0.139$). There was also no significant difference between intravenous Venofer® dose and site of dialysis (($F = 2.676$, $df = 2$, $p = 0.074$).

Costs associated with Aranesp and Iron Supplements

The cost of Aranesp over the 9-month study period did not show any significant change ($F = 0.494$, $df = 3$, $p = 0.707$). There was also no overall significant difference in Aranesp costs and site of dialysis ($F = 0.751$, $df = 2$, $p = 0.475$). Costs of Aranesp pre-implementation were $452.84 ±387.21, $452.54 ±403.74, and $435.88 ±343.03 at 1, 2, and 3 months, respectively. Intra-implementation costs were $431.86 ±339.76, 428.70 ±325.34, and 466.61 ±364.62 at 4, 5, and 6 months, respectively; post-implementation costs of Aranesp were $461.44 ±348.73, 477.23 ±354.22, and 464.70 ±359.74 at 7, 8, and 9 months, respectively (Table 3).

Over the 9-month study period, there was no significant change in cost of iron supplements ($F = 1.973$, $df = 4$, $p = 0.090$), nor was there a significant difference in costs of iron supplements and site of dialysis ($F = 1.52$, $df = 2$, $p = 0.223$). Cost of iron supplements pre-implementation were $19.37 ±34.72, $18.91 ±32.52, and $26.64 ±49.89 at 1, 2, and 3 months, respectively; intra-implementation costs were $30.15 ±53.07, $25.54 ±33.79, and $24.44 ±46.90 at 4, 5, and 6 months, respectively; post-implementation costs were $16.88 ±24.52, $21.65 ±33.48, and $21.71 ±32.07 for 7, 8, and 9 months, respectively (Table 3).

CHAPTER FIVE

Discussion

Managing anemia is essential in optimizing quality of life, in enhancing well-being, and in reducing hospitalizations and morbidities. Because of practice variability and inconsistencies in patient care delivery, national guidelines were established by the National Kidney Foundation to help guide anemia management (NKF-K/DOQI, 2001). Anemia guidelines are intended to provide standardized approaches in assessing, treating, and monitoring anemia in patients with chronic kidney disease.

Many centers, especially in the United States, have created and implemented anemia algorithms as part of their anemia management (Kimura, Arai, Masuda, & Kawabat, 2004; Brimble, Rabbat, McKenna, Lambert, & Carlisle, 2003; Aiello, 2002; To, Stoner, Stolley, Buenvaje, & Ziegler, 2001; DeOreo & Eschbach, 1999; Patterson & Allon, 1998; Senger, Trenkle, & St. John, 1998; Hossli, 1997; MacDougall, Hutton, Cavil, Coles, & Williams, 1990). The intended outcome of any anemia algorithm is to improve anemia management, either by decreasing the incidence of anemia, by increasing iron indices levels, or by reducing costs associated with anemia management.

The purpose of this study was to evaluate the effectiveness of the implementation of the "Anemia Protocol" in 3 satellite dialysis units in the Northern Alberta Renal Program. Effectiveness of the "Anemia Protocol" in this study was defined as a reduction in anemia (hemoglobin <110 g/L), an increase in hemoglobin and iron indices levels, and a reduction in r-HuEpo and iron dose and its associated costs, over the 9-monthstudy period.

Effectiveness of the "Anemia Protocol" Algorithm

This retrospective, cohort study showed no significant change in incidence of anemia, hemoglobin and iron indices levels, doses of r-HuEpo and iron supplements and its associated costs, pre versus post-implementation of the "Anemia Protocol" algorithm. Results of this study are comparable to findings by To et al. (2001) and Brimble et al. (2003).

To et al. (2001) compared management of anemia (without an algorithm) by physicians to the management of anemia (with an algorithm) by pharmacists, and found no significant change in hematocrit (Hct) or transferrin saturation levels between groups (p =0.20 and p =0.66, respectively), no significant difference with Eprex® use over the 6-month study period (p =0.37), and no significant difference in the use of oral iron supplement (p =0.64). However, there was a significant difference in intravenous iron use in the group being managed by an anemia algorithm (p <0.001). The authors concluded that the algorithm was effective, in that there was no reduction in Hct or transferrin saturation level, and there was no increase in the amount of Eprex® used.

Similarly, Brimble et al. (2003) compared management of anemia without an algorithm (control group) to the management of anemia with an algorithm (protocol group). Despite group membership, there was an overall increase in hemoglobin (Hgb) levels (p =0.001). The authors also reported that there was a non-significant difference in total Eprex® dose between the groups but when they analyzed only patients who were able to complete at least 5 months of the study, they found that there was a decreased Eprex® dose in the algorithm group of 2788 units/week (p <0.05). Brimble et al. concluded that the use of an algorithm offered no advantage over not using an algorithm.

In contrast to To et al. and Brimble et al.'s findings, Patterson and Allon (1998) reported significant changes in Hct and transferrin saturation (TSat) levels, and doses of Eprex used, with the use of an algorithm (p =0.004, p =0.04, and p =0.06, respectively). Patterson and Allon found that 44-50% of patients had TSat level <18%. By correcting iron deficiency, the proportion of patients with TSat level <18% decreased to 17 to 25% by the end of the study. Patterson and Allon did not report the difference in the use of iron supplements throughout the study. They did however recognize that improvements in Hct levels and Eprex® use were due, in part, to the correction of iron deficiency.

Kimura et al. (2004) also compared management of anemia (without an algorithm) by physicians to the management of anemia (with an algorithm) by pharmacists and found that out of 45 hemodialysis patients, 41 (91.1%) were receiving Eprex® but only 7 (17.1%) patients achieved Hct >30%. They found that by having an algorithm in place, they were able to improve the number of patients with therapeutic target value (Hct >30%) from 7 (17.1%) to 32 (78%). However, they also showed that more than 60% of patients who did not achieve Hct >30% were also iron deficient. Whether the increase in Hct or the decrease in Eprex® consumption, is attributable to iron deficiency, is unclear.

There are several reasons why this study did not find significant differences in incidence of anemia, levels of Hgb or iron indices, doses of r-HuEpo and iron supplement use and its associated costs, pre versus post-implementation of the "Anemia Protocol" algorithm. Some of these reasons may be attributed to how anemia was managed pre-implementation of the algorithm, the baseline characteristics of study patients and sample size, or the "Anemia Protocol" algorithm.

Anemia Management Pre- "Anemia Protocol" Implementation

In this study, the percentage of patients below target Hgb/Hct levels pre-implementation of the "Anemia Protocol" algorithm was relatively low at 28%, compared to 46% in Patterson and Allon's (1998) study, and 82.9% in Kimura et al.'s (2004) study. Unfortunately there is no large scale population data available on the prevalence and acceptable level of anemia in hemodialysis patients. The large number of patients below therapeutic level may explain the significant change in Hct levels, with the use of an algorithm, in the latter two studies. Because anemia was already relatively well managed in the Northern Alberta Renal Program (NARP), there was no significant difference in Hgb levels, pre versus post-implementation of the algorithm.

Patient Characteristics and Sample Size

Unlike studies by Patterson and Allon (1998) and Kimura et al. (2004), this study did not reveal significant iron deficiencies in the study patients (9%). Iron indices levels and iron supplement use were constant throughout the 9-month study period. As iron deficiency is known to be one of the most common causes of inadequate response to r-HuEpo (Dar Santos, Shalansky, & Jastrzebski, 2003; Drueke, 2001; Wians, Urban, Keffer, & Koft, 2001; Barret, Fenton, Ferguson, Halligan, Langlois, McCready, Muirhead, & Weir, 1999), it is not surprising that correcting iron deficiency will result in improved hemoglobin/hematocrit levels, increased iron indices level, and reduced r-HuEpo use. In Patterson and Allon's study, 47% of the study patients were found to be iron-deficient. By correcting the iron deficiency, they also found a reduction in Eprex® used. Similarly, Kimura et al. reported that 67.6% of their study patients were iron-

deficient and by correcting the iron deficiency, they also found a reduction in Eprex® used.

Furthermore, parameters of hypo-responsiveness in this study (dialysis adequacy: PRU and KT/V, albumin, and presence of gastrointestinal bleeding and/or infection) were constant throughout the study. There was inadequate data from the other studies to determine whether hypo-responsive factors were corrected to explain the increase in Hct levels and reduction in r-HuEpo use.

Sample size in this study was dependent on the inclusion and exclusion criteria, resulting in 98 eligible patients. Although the sample size was relatively small, patients were used as their own control group, having measurements done over a 9-month study period.

Anemia Algorithm

The "Anemia Protocol" algorithm itself may be the reason why this study did not find significant differences in clinical outcomes, pre versus post-implementation of the algorithm. Successful implementation is dependent on many factors, including the clinical context and the methods of dissemination and implementation of the algorithm (Cluzeau, Littlejohns, Grimshaw, Feder, & Moran, 1999). Unfortunately, the process and methods of algorithm development is unclear. Even though the algorithm was adopted from another program, Southern Alberta Renal Program, the processes/strategies that were used for reviewing the evidence to support this algorithm were unavailable for evaluation.

Furthermore, it is ambiguous as to how well the algorithm was disseminated. Inservices were provided to staff but the level of comprehension/understanding of the use of the algorithm is unknown. Differences in staff's knowledge/familiarity with the algorithm may affect the interpretation of the algorithm itself, which in turn, may hinder the effectiveness of the algorithm.

There also must be outcome indicators on which to judge effectiveness. Because there was no defined clinical outcomes of the "Anemia Protocol", evaluating the quality and validity of the implementation of the algorithm is difficult. Consequently, clinical impact of the algorithm cannot be assessed. As outlined by American Psychological Association (2002) on evaluating treatment guidelines/algorithms, a common assumption with guidelines/algorithms is that they are beneficial to standardizing treatments. Standardizing treatments may limit practice variability; however, they may be insensitive to the needs of individual patients and their treatment responses. Results of this study did not show improvement in the incidence of anemia. There was a reported 28% incidence of anemia pre-implementation of the algorithm, compared to 34% intra-implementation, and 32% post-implementation. This leads to the conclusion that by standardizing treatments, individual needs of some patients may be overlooked. The "Anemia Protocol" algorithm may need to be revised to target this select group of anemic patients.

Critical evaluation of the algorithm is important to improve clinical outcomes for patients. Effectiveness of the algorithm needs to be monitored on an ongoing basis. Since the implementation of the "Anemia Protocol" in Northern Alberta Renal Program, review of the algorithm is limited. There must be set guidelines to periodically review and revise the algorithm.

Limitations of the Study

Because this was a retrospective study, it had several limitations. Poor documentation and missing data hindered adequate collection of information. In fact, 8 patients had to be excluded from the study due to missing data. Documentation of the presence of gastrointestinal bleeding and /or infection was only dependent on the accuracy of nurses or physicians' documentation of events/symptoms. Furthermore, adjustments of the doses of Aranesp® and iron supplements were under the discretion of two nurses; there was no system in place to review the accuracy of their interpretation. It is also unclear as to the compliance/adherence of nurses to the algorithm throughout the study.

Implications of the Findings

Although not statistically significant, there were noted differences in incidence of anemia, hemoglobin and ferritin levels, Aranesp® and iron dose and its associated costs, pre versus post-implementation of the "Anemia Protocol" algorithm (Table 4). Incidence of anemia had increased, with a reflective decrease in Hgb levels after the implementation of the algorithm. The amount and cost of Aranesp® used have also increased in the post-implementation timeframe. Although transferrin saturation level remained constant pre versus post-implementation of the anemia algorithm, ferritin levels were increased.

Table 4

Clinical Outcomes

	Intra-implementation	Post-implementation	
	Compared to Pre	Compared to Pre	Compared to Intra
Hemoglobin	↓	↓	same
Incidence of Anemia	↑	↑	↓
Ferritin	↑	↑	↑
Transferrin saturation	same	same	same
Aranesp dose & cost	↑	↑	↑
Iron dose & cost			
Oral iron	↓	↓	↓
Iron Dextran	↑	↑	↓
Venofer	↑	↓	↓

Findings indicate that even though the 3 satellite dialysis units in the Northern Alberta Renal Program were able to achieve NKF-K/DOQI recommended Hgb levels, between 112 ±12 g/L to 117 ±12 g/L, there still remains patients with Hgb levels as low as 72 g/L. Similarly, transferrin saturation levels throughout the study were from 32 ±13% to37 ±16%. The lowest range of transferrin saturation was between 8 to 10%. As alluded to earlier, algorithms need to be periodically reviewed and may need revision to target this group of patients with sub-optimal levels.

Although this study did not show significant differences in costs of Aranesp® and iron supplements, it may be of interest to also measure the indirect and long-term costs associated with the implementation of the algorithm. This will include the time that has been allotted to managing the algorithm. It may also be of interest to look at r-HuEpo-resistance. Some patients in the study were receiving Aranesp® 150 mcg IV weekly and

others every 2 weeks. Would there be a significant difference in clinical outcomes if doses were decreased to every 2-week dosing?

Conclusions

Since the release of recommendations from the NKF-K/DOQI anemia work-group, many dialysis units adopted these guidelines and created and implemented algorithms as part of their anemia management. Although it is useful to have standardized approaches in anemia management, as they may limit practice variability, effectiveness of the algorithm itself needs to be regularly evaluated to ensure that intended clinical outcomes are achieved.

This study did not show significant change in anemia or anemia management pre versus post implementation of the "Anemia Protocol" algorithm in the Northern Alberta Renal Program. However, this is not to imply that algorithms are not useful/valuable in clinical settings. Review/revision of the algorithm is warranted.

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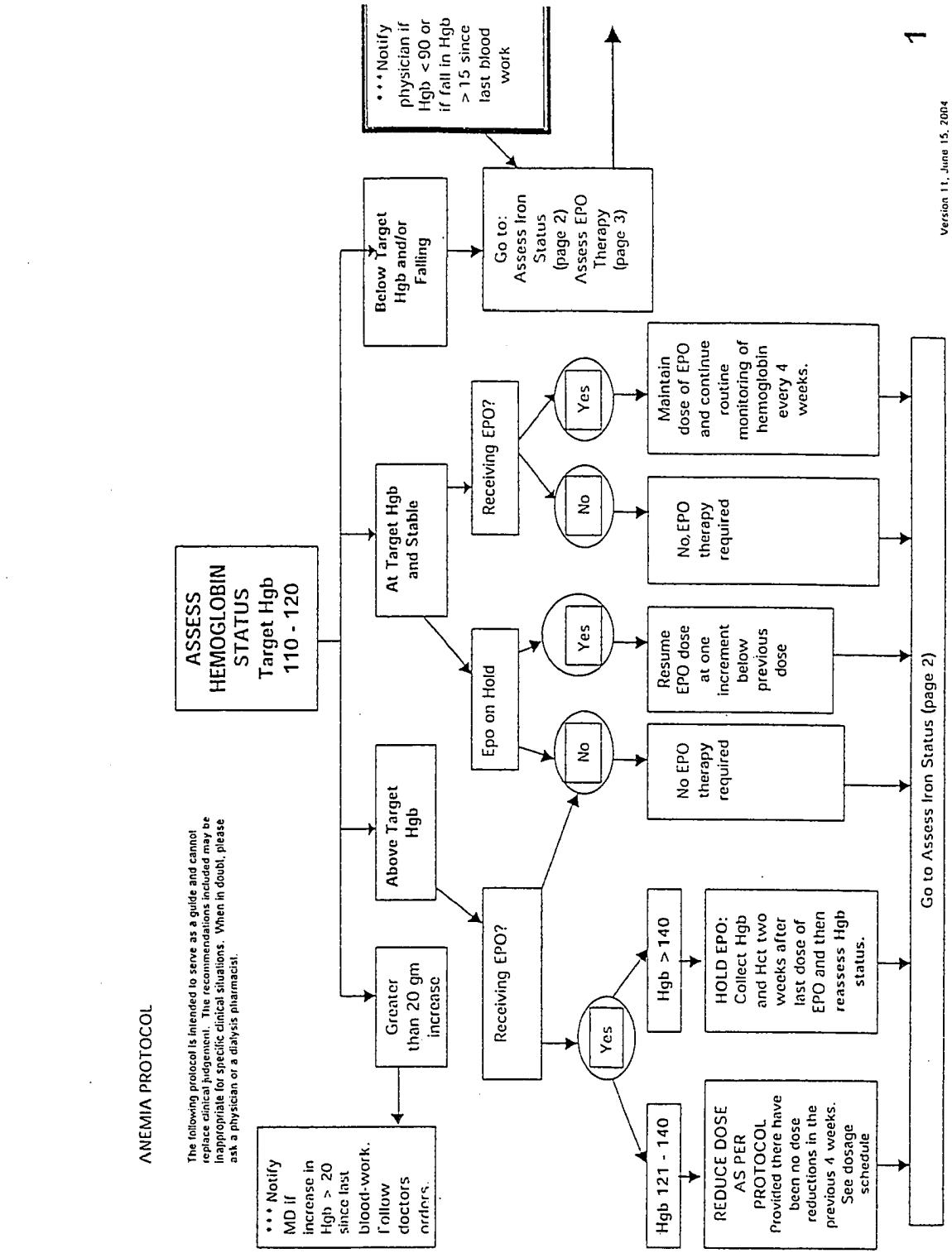
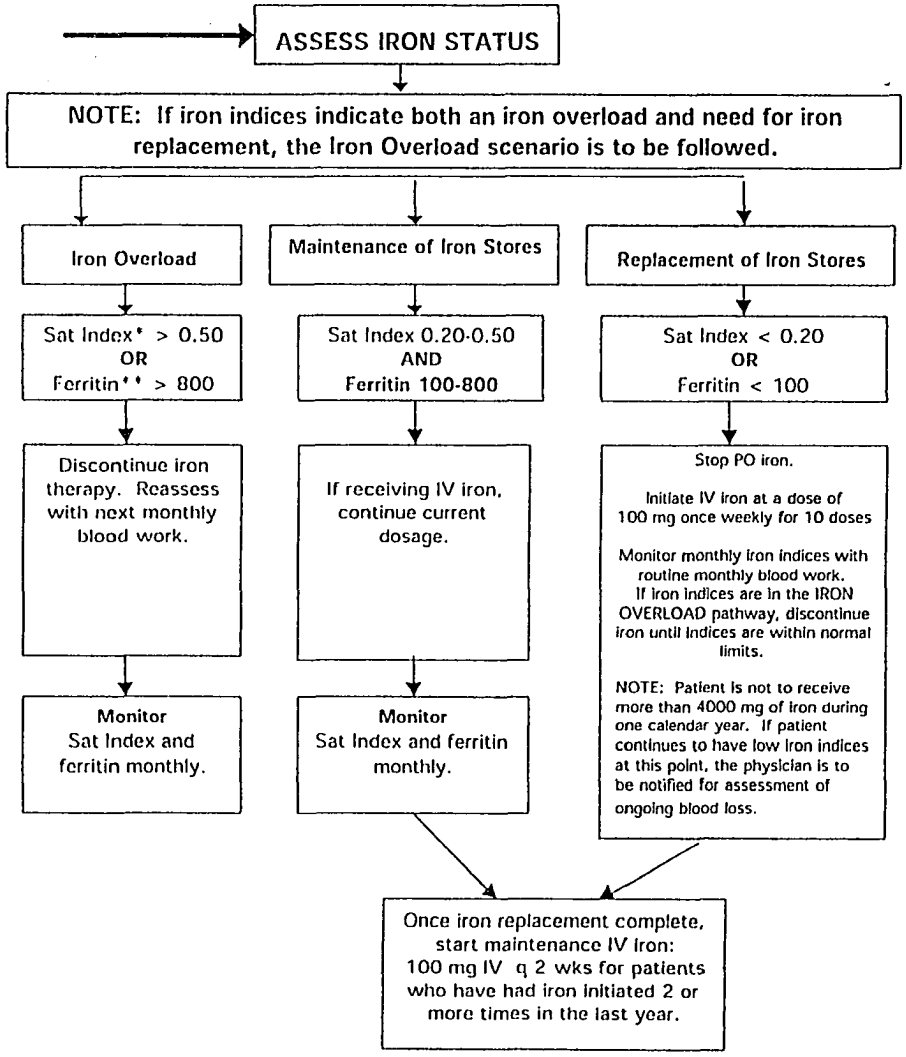
Appendix A: Anemia





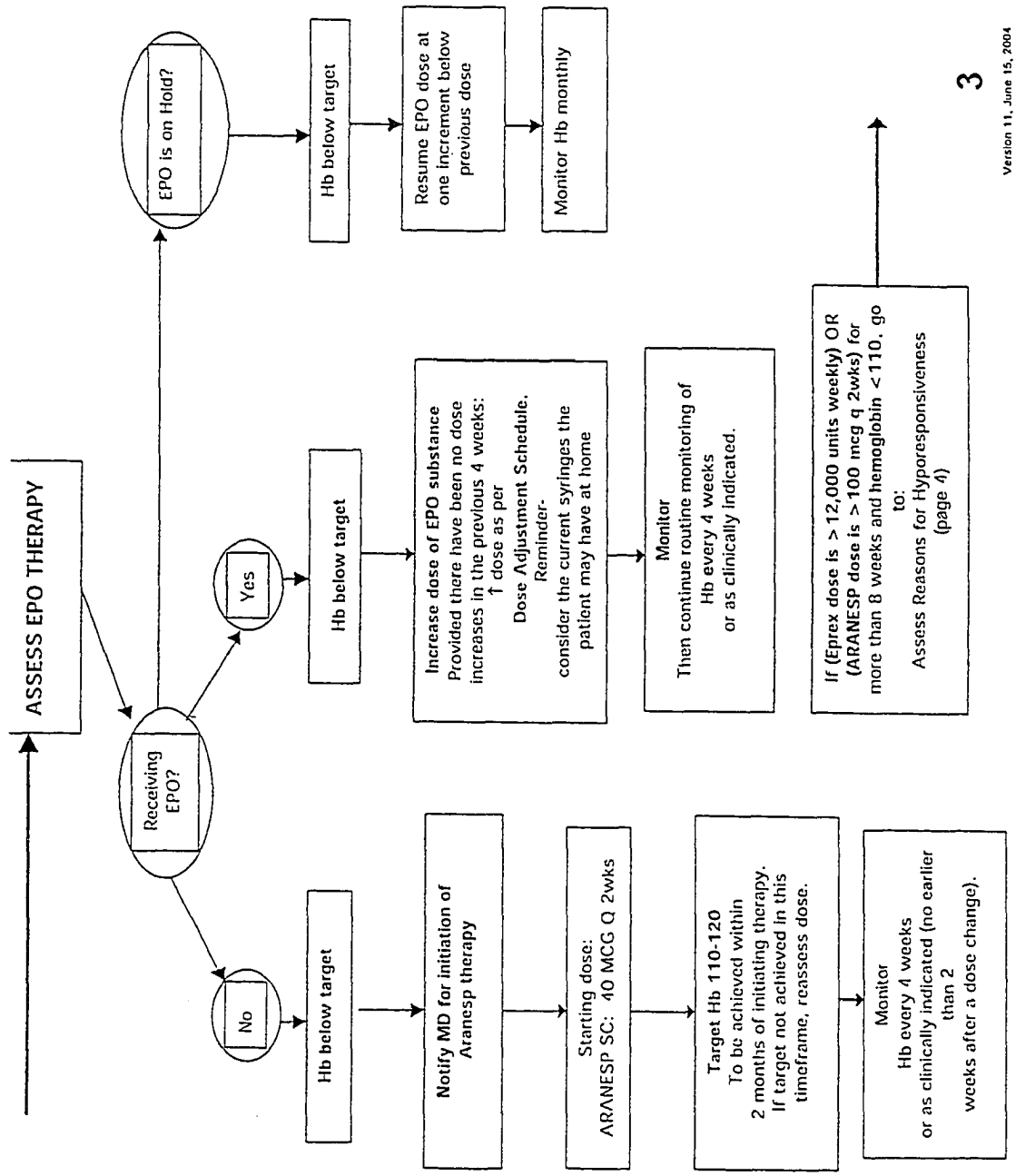
IV IRON CAN BE EITHER DEXIRON OR VENOFER

*Sat Index – saturation index is an indicator of circulating serum iron available to the bone marrow for erythropoiesis.

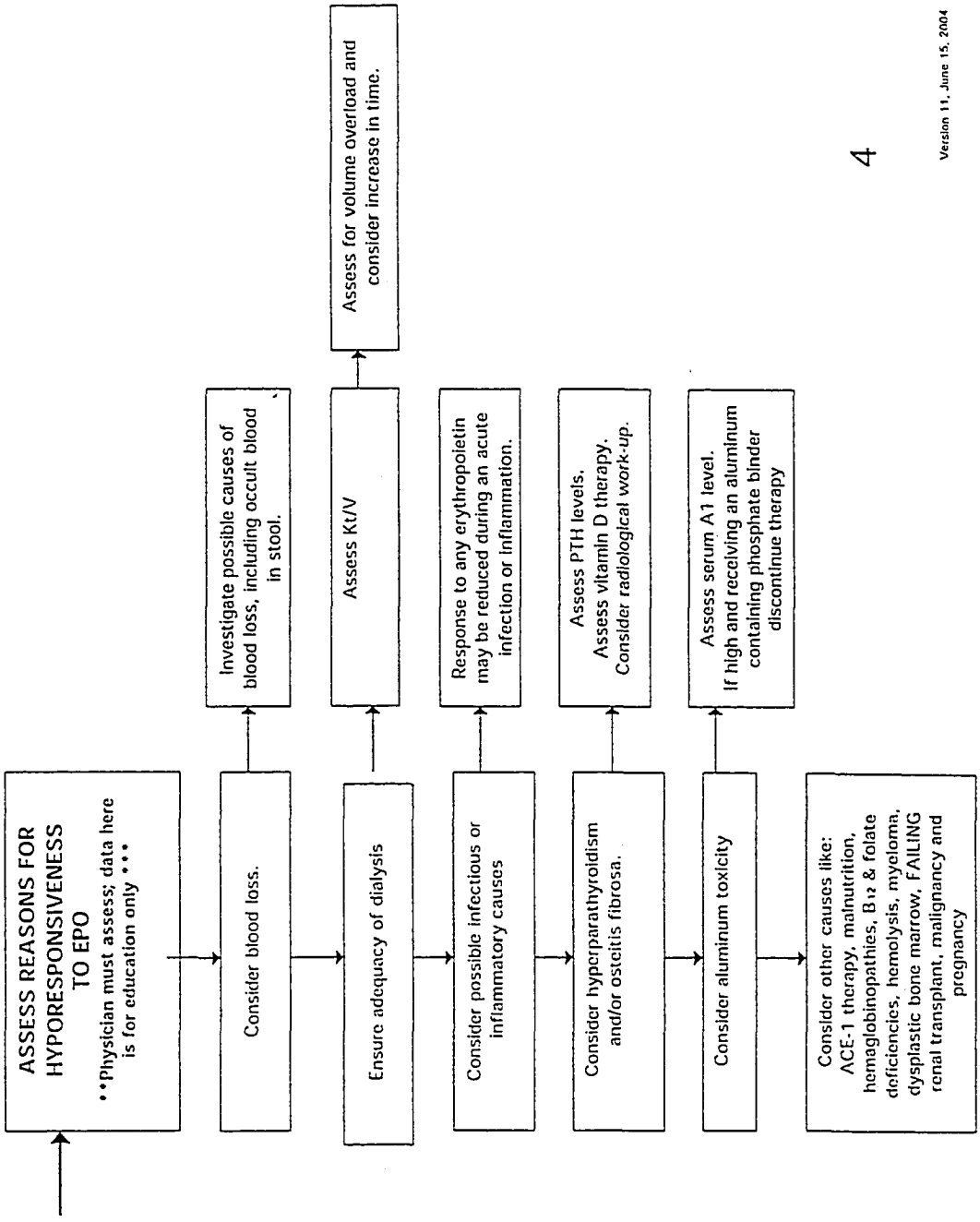
**Ferritin – an indicator to quantify iron stores. Serum ferritin levels may also be elevated as an acute phase reactant, in patients with liver disease, malignancy or inflammation. The ferritin cutpoint is based on the 2001 DOQI Guidelines.

IV IRON SHOULD BE HELD IF THE PATIENT IS RECEIVING ANTIBIOTICS

Appendix A: Anemia Protocol



Appendix A: Anemia Protocol



Appendix B: Studies of Anemia Algorithms

Authors	Measurement	Sample	Method	Outcomes
Patterson & Allon (1998)	-Hct: 32-34% -TSat >17% -ferritin >500	30 HD patients (satellite) -57 ± 16 years -16 men, 14 women -DM (40%), HTN (33%), GN (13%), PCKD (3%), unknown (7%) -KT/V: 1.46 ±0.21	Prospective, cohort study over 6 months	With use of algorithm: -# of patients with target Hct ↑ from 27-61% -# of patients below target Hct ↓ from 46% to 18% (p =0.004) -# of patients above target did not ↑ -# of patients with TSat 18%, ↓ from 47% to 20% (p =0.04) -weekly Epo dose ↓ from 11, 200 ±1, 400 to 9, 400 ±1, 200 (p = 0.06)
To et al. (2001)	Based on K/DOQI guidelines: -Hct: 33-36% -TSat: 20-50% -ferritin: 100-800	49 HD patients -60 ± 12 years -48 men, 1 woman -DM (47%), GN (20%), HTN (18%), other (14%)	Retrospective, cohort study over 6 months	-Hct without algorithm: 35.36% ±3.33 vs. 36.21% ± 3.46 with algorithm (p = 0.2), not statistically significant -total Epo used without algorithm: 8.5 million units compared to 7.7 million units with algorithm (p = 0.37) -total oral iron used without algorithm: 85, 605mg compared to 95, 550mg with algorithm (p =0.64) -total IV iron used without algorithm: 13, 600mg vs. 33, 025mg with algorithm (p <0.001)
Brimble et al. (2003)	Based on K/DOQI guidelines: -Hgb: 11–12.5 -TSat: 20-50% -ferritin: 100-800	215 HD patients -control group: 65.8 years with 37% women, 44.4% with DM -protocol group: 65.7 years with 42.1% women, 30.8% with DM	Randomized, controlled trial (algorithm vs. no algorithm) over 8 months	-42.8% of all patients were able to achieve target Hgb levels (11–12.5 g/dL), compared to 47.4% at the start of the study (p =0.001) -without algorithm: 49.1-62.0% (p = 0.05) -with algorithm: 45.8-63.6% (p = 0.02) -use of algorithm >5 months, reduction of Eprex® by 2788 units/wk (p <0.05)
Kimura et al. (2004)	-Hct >30% -ferritin >100	45 HD patients -66.1 years -22 men, 23 women	Prospective, cohort study over 9 months	-# of patients with Hct >30%, ↑ from 17.1-78% at end of study -monthly Eprex® used, ↓ from 91, 500 units to 64, 200 units with use of algorithm

Appendix C: Data Collection Sheet

Demographic and Relevant Dialysis Information Study ID

UAH ID:	Time on dialysis (in years):
Age (in years): _____ ☐ <44 ☐ 45-64 ☐ 65-74 ☐ >75	Gender: ☐ male ☐ female
Causes of CKD: ☐ DM ☐ GN ☐ HTN ☐ renal/vascular ☐ pyelonephritis ☐ PKD ☐ unknown ☐ other:	
Co-morbidities: ☐ diabetes ☐ HTN ☐ CAD ☐ CVA ☐ PVD ☐ malignancies ☐ lung disease ☐ other:	

Laboratory Data, r-HuEpo & Iron Supplement (January to September 2004)

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept
Hgb									
Ferritin									
TSat									
r-uEpo									
Iron									
Albumin									
PTH									
PRU									
KT/V									
GIB	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Infection	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐