Anemia in Chronic Renal Disease

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Abbreviations

ACE-I	Angiotensin converting enzyme inhibitor
CKD	Chronic kidney disease
CRP	C-reactive protein
ESA	Erythropoiesis stimulating agent
GFR	Glomerular filtration rate
Hb	Hemoglobin
HD	Hemodialysis
IL-6	Interleukin-6
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
Kg	Kilogram
LVH	Left ventricular hypertrophy
MCV	Mean corpuscular volume
PD	Peritoneal dialysis
PEG	Polyethylene glycol
rHuEPO	Recombinant human erythropoietin
SLE	Systemic lupus erythematosus
TIBC	Total iron binding capacity
TSAT	Transferrin saturation

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Introduction

Anemia is one of the most common problems in children with chronic kidney disease (CKD); it is almost universal in children with stage 5 CKD. The development of recombinant human erythropoietin (rHuEPO) revolutionized the treatment of anemia in CKD, but anemia management remains challenging. Many management issues remain uncertain, including the ideal target hemoglobin (Hb). There are guidelines for the management of anemia in CKD [1, 2].

Pathophysiology of Anemia

A variety of factors contribute to anemia in CKD (Table 57.1). The principal etiology is decreased production of EPO by the kidneys. However, many children are still anemic despite administration of erythropoiesis stimulating agents (ESAs) [3], emphasizing the multifactorial etiology of anemia in children with CKD.

Erythropoietin Deficiency

The kidneys produce EPO and kidney damage leads to decreased EPO production. In children with CKD, EPO levels are inappropriately low for the degree of anemia [4]. The degree of EPO deficiency generally worsens as the glomerular filtration rate (GFR) decreases, but the level of

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Table 57.1 Causes of anemia in CKD

Erythropoietin deficiency
Blood loss
Hemolysis
Bone marrow suppression
Iron deficiency
Inadequate dialysis
Malnutrition
Chronic or acute inflammation
Infection
Hyperparathyroidism
B12 or folate deficiency
Aluminum toxicity
Carnitine deficiency
Medications (e.g., ACE-inhibitors)
Systemic disease
Hemoglobinopathy
Hypothyroidism
Systemic lupus erythematosus
Malignancy

ACE angiotensin converting enzyme

GFR at which inadequate EPO causes anemia varies between patients, partially due to the nature of the underlying kidney disease [5]. A GFR below 43 mL/min/1.73 m^2 is associated with a decline in Hb in children with CKD [6].

Blood Loss

Excessive blood loss may directly cause anemia, or it may lead to iron deficiency (see below). Causes of blood loss in children with CKD include phlebotomy, blood lost in the dialyzer and tubing during hemodialysis (HD) [7], gastrointestinal losses [7], and increased menstrual bleeding due to the acquired platelet function defect of CKD. Children receiving HD have increased intestinal blood loss when compared to other children with CKD [7]. Increased blood loss is associated with rHuEPO resistance in pediatric HD patients [8].

Decreased Red Blood Cell Survival

Red blood cells in children with CKD have a decreased lifespan [7]. This may be partially due to carnitine deficiency (see below) [9], and a direct consequence of EPO deficiency, since red cell survival increases in CKD patients after starting rHuEPO [10]. Red blood cells in patients receiving HD have an increased osmotic fragility. Hemolytic anemia may occur due to a child's primary disease [e.g., systemic lupus erythematosus (SLE)].

Bone Marrow Suppression

In an in vitro assay, serum from children with CKD directly suppresses red blood cell production [4]. The specific inhibitory substances have not been identified, but dialysis appears to effectively remove some of these molecules, allowing for decreased doses of rHuEPO [11]. In a study of teenagers receiving HD, the children with Hb less than 11 g/dL had a slightly lower Kt/V (1.53 vs 1.46), but dialysis adequacy did not predict anemia in the multiple regression analysis, perhaps due to the high overall Kt/V in this patient population [12]. Severe bone marrow suppression may occur in children after renal transplantation due to medications [13] or infections, especially parvovirus B19 [14].

Iron Deficiency

Iron deficiency is a significant cause of anemia in patients with CKD; it is multifactorial (Table 57.2). In a study of older children, a serum transferrin saturation (TSAT) less than 20 % was an independent predictor of anemia [12]. However, serum ferritin was not predictive of anemia, perhaps because ferritin is often elevated in CKD patients with concurrent inflammation, which may inhibit red cell synthesis (see below).

Iron deficiency often develops after initiation of an ESA because the increase in red blood cell synthesis depletes iron stores. In some patients, there is a functional iron deficiency following ESA treatment; there are adequate supplies of iron, but the transfer of iron from ferritin is not fast enough to meet the high demand for red blood cell synthesis.

Table 57.2 Causes of iron deficiency in children with CKD

Blood loss
Phlebotomy
Hemodialysis
Menses
Gastrointestinal
Surgical procedures
Dietary iron deficiency
Poor absorption of enteral iron
Inflammation
Medications (phosphate binders, gastric acid inhibitors)
Iron depletion during ESA therapy

ESA erythropoiesis-stimulating agent

Inadequate Dialysis

In adults receiving dialysis, there is evidence that anemia is associated with inadequate dialysis. An increase in dialysis dose leads to an improvement in Hb. In addition, there is an inverse relationship between Kt/V and ESA dose. Resistance to ESAs was associated with a lower Kt/V in a study of pediatric HD patients [8]. Dialysis is effective at removing hepcidin (see below) [15], suggesting a possible mechanism for the relationship between dialysis dose and anemia.

Malnutrition

Malnutrition may be another factor contributing to anemia in CKD. In one pediatric study, low albumin was one predictor of anemia [12]. There are many possible explanations for the relationship between malnutrition and anemia. Generalized malnutrition may be a marker for nutritional iron deficiency or for deficiency of other nutrients that influence red cell production or survival. Another possible explanation for this observation is the relationship between markers of malnutrition and markers of inflammation [16]. As described below, inflammation is another mechanism of resistance to rHuEPO. It is possible that inflammation causes malnutrition, and this directly causes resistance to ESAs. An alternative explanation is that inflammation directly causes rHuEPO resistance, and that malnutrition is a surrogate marker of inflammation. A malnutrition inflammation score predicted ESA resistance in a study of pediatric HD patients [8].

Inflammation

Acute inflammation and chronic inflammation are well-known causes of decreased red blood cell synthesis. Inflammation is one of the mechanisms of the anemia of chronic disease and of the decreased erythropoiesis that occurs during infections. Markers of inflammation are commonly increased in CKD patients. There are a variety of putative mechanisms. Surgical procedures and acute infections are more common in CKD patients, especially those who are receiving dialysis or have a kidney transplant. The impaired immune system in uremia may lead to an increase in non-specific inflammation [17]. CKD patients may have underlying systemic diseases, such as SLE or Wegener's granulomatosis. HD may induce inflammation via complement activation, direct activation of inflammatory cells by the dialysis membrane, and diffusion of endotoxin into the patient from the dialysate. Use of ultrapure dialysis in HD patients decreases inflammatory markers, increases Hb levels, and decreases ESA use [18].

Hepcidin is an important mediator of ESA resistance [19]. Hepcidin, which is produced in the liver, inhibits intestinal absorption of iron and release of iron stores from the reticuloendothelial system. This is accomplished through down-regulation of ferroprotein, the principal transmembrane transporter of iron. Hepcidin is normally down-regulated in anemia, increasing absorption of iron and release of iron stores. In contrast, hepcidin increases when iron stores are adequate. Hepcidin is also up-regulated by inflammation. Interleukin 6 (IL-6) induces production of hepcidin and is risk factor for ESA resistance [20, 21]. Hepcidin's effect on release of iron stores explains inflammatory block, a condition where body stores of iron are adequate, but there is ineffective delivery of iron to the bone marrow. Findings in patients with inflammatory blockade

may include elevated C-reactive protein (CRP) levels, resistance to ESAs, high serum ferritin levels, and low levels of serum iron and TSAT [22]. This mechanism is common to the anemia of many chronic diseases.

Hyperparathyroidism

Hyperparathyroidism may decrease bone marrow production of red blood cells [23] and rarely causes pancytopenia [24]. Elevated PTH levels are associated with ESA resistance in pediatric HD patients [8]. Treatment of hyperparathyroidism via parathyroidectomy may lead to an increase in Hb.

B12 or Folate Deficiency

Patients with CKD may rarely develop a megaloblastic anemia due to folate or vitamin B12 deficiency. Poor nutritional intake combined with dialytic losses may predispose CKD patients to deficiencies of these water-soluble vitamins. There is some evidence that routine folate supplementation improves the response to rHuEPO, even in the absence of low serum levels of folic acid [25].

Aluminum Toxicity

Aluminum overload may cause a microcytic anemia in patients with CKD [26]. Currently, aluminum overload is an uncommon cause of anemia due to the recognition of the dangers of aluminum-containing phosphate binders.

Carnitine Deficiency

Carnitine deficiency may occur in CKD, principally due to removal of carnitine by dialysis, although decreased dietary intake and endogenous synthesis may also contribute [9]. Renal losses of carnitine are significant in children with Fanconi syndrome. Carnitine deficiency may decrease red blood cell survival by reducing the strength of the red cell membrane [9]. Intravenous (IV) carnitine may reduce rHuEPO dose requirements in adults receiving HD, but there is disagreement regarding the strength of the evidence; carnitine should not be used routinely, if at all, outside of a research setting [2, 9, 27, 28]. Oral carnitine should not be used in patients receiving hemodialysis [9].

Medications

A variety of medications can inhibit erythropoiesis, especially certain medications used in renal transplant recipients [13, 29]. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers are especially pertinent in CKD patients because of their widespread use [30].

Summary

Erythropoietin deficiency and iron deficiency are the most common causes of anemia in children with CKD. Inflammation is an important mediator of ESA resistance.

Epidemiology of Anemia in Pediatric CKD

Anemia is common in children with CKD, even in patients with stage 3 CKD [31]. In one study, anemia was more common in children greater than 2 years old, males, and patients receiving antihypertensive medications [31]. In another cohort, African American race was associated with an increased risk of anemia in children with CKD [3].

In children receiving peritoneal dialysis (PD), anemia is quite common and varies by region [32]. Risk factors for anemia include inflammation, decreased residual urine output and hyperparathyroidism [32]. In another study of children receiving HD or PD in the USA, risk factors for anemia included increasing age, dialysis for less than 6 months, and treatment with PD. Adolescents receiving PD were especially likely to be anemic, suggesting a possible role of non-adherence [33].

Anemia is common in children after kidney transplantation [34]. The principal cause of anemia is allograft dysfunction, although current immunosuppressive medications appear to be responsible for the increased prevalence of anemia in these patients. Iron deficiency is common in children who are anemic after renal transplantation.

Clinical Effects of Anemia

There are a variety of clinical effects of anemia (Table 57.3). The clinical consequences of anemia in patients with CKD are difficult to discern because anemia identifies patients with co-morbidities such as inflammation and malnutrition. A variety of studies demonstrated an association between anemia and morbidity and mortality, but these conclusions may be biased by co-morbidities.

Studies in adult CKD patients have shown an association between anemia and increased mortality and hospitalization rates [35–38]. In a pediatric analysis, anemia 30 days after initiation of dialysis was associated with a significant increase in mortality and hospitalization rate [39]. In analysis of children receiving PD, anemia was associated with increased mortality, hypertension, and left ventricular hypertrophy (LVH) [32]. In children with CKD, anemia was associated with an increased risk of hospitalization [40].

In a group of children receiving dialysis, treatment of anemia with rHuEPO was associated with an elevated cardiac index in 6 months and a significant reduction in left ventricular mass index by 12 months [41]. In a study by Mitsnefes and coworkers [42], children with severe LVH had significantly lower Hb values than children without LVH. However, anemia did not predict LVH in the final multiple regression model.

There is uncertainty regarding the direct deleterious consequences of a lower Hb in adults with CKD. These include observational studies that have corrected for a variety of co-morbidities [43]. More importantly, randomized studies using ESAs to target different Hb levels have failed to demonstrate a benefit of higher Hb targets on morbidity or mortality [44, 45]. In fact, a higher Hb target has resulted in a significant increase in morbidity and mortality in randomized studies [46, 47].

In randomized studies in adults, a higher Hb improves quality of life [45], although this is not a consistent finding [46]. In a placebo-controlled trial, randomization to rHuEPO resulted in less fatigue, improved exercise tolerance and improved scores of physical symptoms and depression [48]. There is evidence of the deleterious effects of anemia on child development. There is an association in children with CKD between anemia and lower scores of health-related quality of life [49]. Studies of the effect of rHuEPO in children with CKD have shown improvement in quality of life, exercise tolerance, appetite, peak oxygen consumption and treadmill time during exercise testing, Wechsler intelligence score, and ventilatory aerobic threshold [50–52]. There does not appear to be a beneficial effect of anemia correction on the growth retardation associated with CKD [53].

Table 57.3 Clinical effects of anemia

Cardiovascular
Left ventricular hypertrophy
Systemic
Fatigue
Depression
Decreased quality of life
Sleep disturbances
Decreased exercise tolerance
Impaired cognitive function
Loss of appetite

Clinical Evaluation of Anemia

Initial Evaluation

Alternative causes of anemia should be evaluated prior to treating patients with an ESA (Table 57.4). The diagnosis of anemia in children should be based on age and gender specific normal ranges.

The initial evaluation of children with CKD and anemia should include a complete blood

Table 57.4 Indications for additional evaluation in children with chronic kidney disease and anemia

Indication	Response
Macrocytosis	Consider B12 or folate deficiency, unless due to brisk reticulocytosis
Decreased platelets and/or white blood cells	Consider malignancy, acute infection, SLE, severe hyperparathyroidism or medications
History of using aluminum-containing phosphate binders or other symptoms of aluminum overload	Consider aluminum toxicity
Anemia despite adequate reticulocytosis	Consider excessive blood loss or hemolysis
Microcytosis	Consider iron deficiency, hemoglobinopathy, or inflammation
Iron deficiency prior to starting an ESA	Evaluate for causes of iron deficiency (see Table 57.2)
Low reticulocyte count and falling hemoglobin in a patient being treated with an ESA	Consider non-adherence, anti-erythropoietin antibodies, parvovirus B19 infection

ESA human erythropoiesis stimulating agent, *SLE* systemic lupus erythematosus

count, reticulocyte count, ferritin, iron, total iron binding capacity (TIBC) and a TSAT. The TSAT is calculated by dividing the serum iron by the TIBC. Measurement of EPO levels generally does not have clinical utility. A cost-effectiveness analysis in adults argues against routine screening for aluminum overload or deficiencies of folate or B12 [54]. EPO deficiency causes a normocytic anemia; macrocytosis or microcytosis should lead to consideration of other etiologies (Table 57.4).

A low mean corpuscular volume (MCV) occurs with iron deficiency, thalassemia and in up to 50 % of patients with anemia of chronic disease. A high MCV suggests the possibility of B12 or folate deficiency. Measurement of serum levels of B12 and folate is indicated if there is an elevated MCV or if there is anemia without an alternative explanation. RBC folate is useful when a serum folate level is inconclusive or if recent intake of folate may lead to a falsely normal serum folate level.

Concomitant depression of white cells or platelets raises the specter of malignancy, although an isolated low white blood cell count may be due to a transient viral infection or a medication. SLE may cause depression of the white blood cell count, platelet count and an autoimmune Coombs positive hemolytic anemia. EPO deficiency causes an inappropriately low reticulocyte count, and the presence of an adequate reticulocytosis suggests alternative explanations, such as blood loss or hemolysis. An elevated CRP, indicating inflammation, may provide an explanation for anemia refractory to ESAs.

Iron deficiency is common in children with CKD, even prior to starting an ESA. There are a variety of explanations for iron deficiency in children with CKD (Table 57.2). All children with CKD should be queried about gastrointestinal blood loss and, when appropriate, menstrual losses. A more aggressive work-up (e.g., testing stool for occult blood or endoscopy) is appropriate in children with significant, unexplained iron deficiency prior to receiving ESA therapy. Along with low serum ferritin and TSAT, children with iron deficiency typically have a low MCV. Because it is a marker of inflammation, serum ferritin may be misleadingly normal in children with CKD despite iron deficiency.

Evaluation of the ferritin and TSAT establishes a baseline, since iron deficiency is likely to develop during ESA treatment. In addition, while all patients starting an ESA should receive oral iron supplementation unless iron overload is present, iron deficiency prior to starting ESA therapy may significantly attenuate the response to therapy. Such patients are candidates for IV iron.

Chronic Monitoring

Routine monitoring in children with anemia due to CKD includes periodic assessment of Hb, MCV, and iron stores. The development of macrocytosis in a patient after starting an ESA is usually due to the expected reticulocytosis; an increasing Hb, arguing against a nutritional deficiency anemia, supports this explanation. Iron overload may also cause an increased MCV [55]. Microcytosis is usually due to iron deficiency.

A decrease in Hb is expected during acute infections [56] or after surgical procedures [57]. ESA dose requirements increase following blood loss that causes a fall in Hb; this persists until the Hb returns to the target range. Depleted iron stores are the usual explanation for a poor response to ESA therapy. Some children have a functional iron deficiency, and may respond to IV iron, even though the ferritin levels are adequate. Additional evaluation is indicated in children who have an unexplained increase in ESA dose requirement, need unexpectedly large doses of ESA, or have a decreasing Hb (Table 57.4).

A reticulocyte count is the usual first step in evaluating unexplained anemia or an excessive ESA requirement. An appropriately elevated reticulocyte count (corrected for the degree of anemia) argues that the patient is anemic due to blood loss or hemolysis. Blood loss is also suggested by a minimal increase in ferritin and TSAT despite the use of multiple doses of IV iron. The child should then have stool tested for occult blood; an evaluation for hemolysis may also be appropriate. Inadequate reticulocytosis suggests that there is a defect in red cell production. This may be due to poor adherence or technique failure in a patient receiving home ESA. There may be a readily identifiable explanation, such as severe secondary hyperparathyroidism. Alternatively, additional testing may be necessary. A serum aluminum level is an appropriate test in the child with a history of using aluminum-containing phosphate binders. One of the most common causes of a poor response to ESA is an inflammatory block due to acute or chronic inflammation. An elevated CRP supports this diagnosis [17]. Other testing, depending on the patient, may include screening for anti-EPO antibodies (see below), and serum levels of folate and B12. A hematologist should evaluate refractory anemia with no identifiable explanation [28, 58].

Treatment of Anemia

Treatment with an ESA is necessary in many children with CKD, including children with chronic allograft dysfunction [59]. Almost all children receiving dialysis are treated with an ESA. In addition, almost all treated patients require oral or IV iron. Other underlying causes of anemia should be corrected (Table 57.1). Blood transfusions should be reserved for children with symptomatic anemia or with worsening anemia due to blood loss, hemolysis, or unresponsiveness to ESAs [2].

Target Hemoglobin

A number of randomized studies in adult patients with CKD have demonstrated that targeting higher Hb levels leads to increased morbidity and mortality [44, 46, 47, 60]. In one study, targeting a higher Hb led to a decrease in dialysis adequacy and a higher use of IV iron [44]. The TREAT trial compared placebo and darbepoetin alpha in adults with CKD. The risk of stroke was almost doubled in the patients randomized to receive darbepoetin alpha to achieve a Hb of 13 g/dL, although there was a modest improvement in fatigue in the darbepoetin alpha group [47]. Stroke was also increased when adult HD patients were randomized to a higher Hb target [60]. In the CREATE trial, the group randomized to a higher Hb had more episodes of hypertension and headache [45]. In the CHOIR trial, the group randomized to a higher Hb had an increased risk of death or cardiovascular event and there was no difference in quality of life between the groups [46]. In a retrospective cohort study of adult kidney transplant recipients, patients receiving an ESA with a Hb level above 12.5 g/dL had an increase in mortality [61].

The reason for the increased morbidity and mortality associated with a higher Hb target is unresolved. It could be attributed to a higher Hb level or to the need for higher doses of ESAs, which have been postulated to have untoward effects beyond increasing the Hb. High ESA dose is associated with increased morbidity and mortality, but this appears to be partially related to resistance to ESAs due to co-morbidities [62–64]. However, in studies that randomized CKD patients to ESA or placebo, the groups receiving ESAs had an increased risk of stroke [47] and access clotting [48]. Moreover, in a randomized study of rHuEPO in patients with ischemic stroke, the group receiving rHuEPO had

significantly increased mortality [65]. Dialysis patients who have high Hb levels without the use of ESAs do not have increased mortality [66]. A higher Hb target could lead to more variation in Hb levels, which has been associated with increased mortality [67].

The negative consequences of targeting higher Hb concentrations in the trials of ESAs has led the United States Food and Drug Administration to recommend that ESAs be given at the lowest dose possible to avoid blood transfusions and that ESAs should be reduced or withheld if the Hb exceeds 11 g/dL and withheld if the Hb exceeds 12 g/dL. Moreover, all ESAs have a black box warning and patients must receive education regarding the possible adverse effects of ESAs. A combination of these concerns, and possibly a change in the payment structure for ESAs, has led to a decrease in the dose of ESAs and Hb levels in United States dialysis patients [68].

There are no data on the ideal target Hb in children or whether the target should be adjusted based on age and gender. KDIGO recommends an upper limit Hb of 11.5 g/dL in adults, but recommends targeting pediatric CKD patients between 11 and 12 g/dL. The British NICE guidelines recommend a target of 10–12 g/dL for all patient 2 years and older, with a target of 9.5–11.5 g/dL in children less than 2 years [1]. The Canadian Society of Nephrology recommends a target of 10–11 g/dL for adults, but considers 9.5–11.5 g/dL an acceptable range [69]. The United States KDOQI commentary on KDIGO advocates the FDA-recommended upper cutoff of 11 g/dL for adults, but a range of 11–13 g/dL for children [70]. There are clearly clinical situations that require different target Hb values. For example, specific children may require a higher target Hb (e.g., a child with underlying cyanotic heart disease) or a lower target (e.g., a child with sickle cell disease).

Some patients remain anemic or develop refractory anemia despite ESA therapy and correction of other etiologies of anemia. This is especially common in patients who have inflammation. Ongoing escalation of ESA dose in these patients has been associated with adverse outcomes in adults [47], suggesting that ESA dose should not be increased without limit in patients who are hyporesponsive. Patients who do not respond to an ESA or stop responding to an ESA should have an evaluation of possible etiologies of anemia (Tables 57.1 and 57.4).

Hemoglobin Monitoring

Hb monitoring is preferred over hematocrit because Hb measurements are more standardized and consistent. For patients receiving HD, blood samples should be taken immediately prior to dialysis. This may lead to a falsely low Hb value due to hemodilution from fluid gain between dialysis sessions. Hence, this should be considered in children with significant interdialytic weight gain. It is reasonable to measure Hb prior to a HD session after a short interdialytic period (2 days) since the effect of hemodilution on Hb is generally less significant [28].

The frequency of monitoring varies depending on the patient. Children who are being given a stable dose of ESA and within their target Hb can have a Hb level performed as infrequently as monthly in a dialysis patient, and even less often in a predialysis patient (minimum of every 3 months). After the initiation of ESA or after a dosing change, a Hb should generally be obtained at least monthly until the Hb has stabilized within the target range. Protocols that use less frequent monitoring and dose adjustments may reduce costs and minimize Hb cycling, large variations in Hb values that are associated with increased morbidity in adults [71, 72].

Erythropoiesis Stimulating Agents

rHuEPO was the first ESA, but a number of other preparations are now available. Two preparations, darbepoetin alpha and methoxy polyethylene glycol-epoetin beta, are modified forms of EPO. Peginesatide is a dimeric pegylated peptide. The main advantage of other preparations is a longer half-life, which permits less frequent dosing. This is especially advantageous in children who require subcutaneous dosing given the

discomfort and fear associated with injections. Less frequent dosing may also decrease provider burden in a dialysis unit and provide cost savings [73]. There are no studies directly comparing different ESAs in children, and limited studies in adults. Availability of the different preparations varies by country.

Table 57.5 Factors influencing erythropoietin dosing

Route of administration
Mode of dialysis
Initial and target hemoglobin
Endogenous erythropoietin
Patient age
Dosing frequency
Presence of other causes of anemia (see Table 57.1)

Recombinant Human Erythropoietin

Multiple studies in adult patients demonstrated the efficacy of IV and subcutaneously administered rHuEPO for correcting the anemia of CKD. A placebo controlled trial demonstrated that rHuEPO is effective in children with CKD [52], and studies in adults demonstrate that use of ESAs decreases the need for transfusions [47, 48, 74].

Pharmacokinetics

The pharmacokinetics of rHuEPO in CKD has been studied in children and adults. There are clear differences based on the route of administration, with less complete absorption of subcutaneous rHuEPO, but a significantly longer half-life when compared to IV administration. In studies of children with CKD, the measured mean half-life of rHuEPO is 5.6–7.5 h for IV dosing and 14.2–25.2 h for subcutaneous dosing. For iv dosing, there is evidence in adults that the half-life of rHuEPO increases as the dose increases.

Dosing

There are dramatic differences in the dosing needs of children with CKD who are receiving rHuEPO, even when adjusted for patient size [75, 76]. Some have recommended dosing children independent of weight and utilizing "adult" dosing [77]. A variety of variables influence the dosing needs of patients (Table 57.5), but it remains difficult to predict the dosing needs of an individual patient. Factors affecting the necessary dose per kilogram (kg) of rHuEPO in children with CKD include the stage of CKD (higher in stage 5), the mode of dialysis (higher in HD due to increased blood loss) [78, 79], the age of the patient (higher in younger patients) [75, 76, 79], the route of administration (higher with IV versus subcutaneous) [76], and the dosing frequency (higher with less frequent dosing regimens). Concurrent causes of poor response to rHuEPO, such as iron deficiency, inflammation, or hyperparathyroidism, often result in higher doses. Blood loss, due to HD, blood draws, and other sources, increase the need for rHuEPO. Blood draws can be especially problematic in the youngest patients, because they often need more frequent monitoring and the relative losses per kilogram of body weight tend to be higher. Finally, residual renal production of EPO can decrease the need for rHuEPO.

In children receiving PD or predialysis patients, an appropriate starting dose for subcutaneous rHuEPO is 100 units/kg/week divided into two doses, although once weekly dosing may be appropriate in a child with mild anemia. Children less than 5 years are likely to need a higher dose, and a starting dose of 150 units/kg/week may be appropriate in such patients, especially if severe anemia (Hb <8 g/dL) is present. For children receiving HD and IV rHuEPO dosing, a starting dose of 150 units/kg/week divided into three doses is reasonable, again with the caveat that higher doses are likely necessary in children less than 5 years. A starting dose of 200–300 units/kg/week may be more appropriate in such patients, especially if there is concomitant severe anemia.

In children receiving chronic subcutaneous dosing of rHuEPO, the majority can be maintained on weekly dosing to minimize the number of painful injections. However, some patients require more frequent injections. Less frequent dosing regimens of rHuEPO are effective in adults with pre-dialysis CKD [80].

When children receive IV dosing during HD, it is important to inject rHuEPO via the bloodlines. Use of the venous drip chamber may result

in reduced drug delivery due to "trapping" of rHuEPO, although this appears to be somewhat machine dependent.

For children receiving subcutaneous dosing, the site of injection should be rotated. The discomfort of subcutaneous dosing can be reduced by utilizing the multidose vial, which contains the local anesthetic benzyl alcohol as a preservative. In children who are using a single use vial, adding bacteriostatic saline that contains benzyl alcohol to the rHuEPO in a 1:1 ratio can decrease injection site pain.

Frequent dose adjustments are typically necessary in patients receiving rHuEPO. This is probably due to variations in the factors that cause anemia (Table 57.1) and that influence rHuEPO dosing (Table 57.5). In addition, more active erythropoiesis is needed to increase a patient's Hb. Hence, the dose that patients need to increase their Hb level into the target range is often more than the dose needed to maintain a stable Hb. Patients may need higher doses of rHuEPO at the start of therapy or after a decrease in Hb due to blood loss or a transient illness.

Most children, when they initiate HD, are converted to IV dosing of rHuEPO, which should then almost always be given thrice weekly. Based on adult studies, the total weekly dose of rHuEPO should be increased by 50 % when a patient changes from subcutaneous to IV dosing. Similarly, patients changing from IV dosing to subcutaneous dosing should have their weekly dose decreased by 33 %. However, most pediatric patients who convert between IV and subcutaneous dosing are also changing dialysis modality. Given the higher needs for rHuEPO in children on HD [75], patients changing to IV dosing because they are initiating HD may need an additional increase in their dose. In children less than 10 years and certainly those less than 5 years, rHuEPO dosing requirements during HD are very high [76]. This suggests that these patients may need an increase in their rHuEPO dose after beginning HD, irrespective of any change in route of administration. Young children should have careful monitoring of the Hb when initiating HD, increasing the dose of rHuEPO further if necessary. Even in older children, there is extreme variability in the dose requirements when converting to IV dosing; dose requirements may increase or decrease. The ability to more aggressively treat iron deficiency in children receiving HD (see below) may result in a decrease in rHuEPO requirements.

The goal of rHuEPO therapy is to maintain patient Hb within a desired target range. Overly rapid increases in Hb can be associated with hypertension, and should be avoided. In patients with a Hb below the target, the goal is to increase the Hb by 1–2 g/dL per month. The dose of rHuEPO should be increased by 25 % if the patient is below the target Hb and has not increased at least 1 g/dL over the last month. The dose should be reduced by 25 % if the Hb is greater than the target Hb or the Hb has increased by more than 2 g/dL over the last month. The rHuEPO should be temporarily held if the Hb is more than 1 g/dL over the target Hb or the Hb has increased by more than 2 g/dL over the last month and is above the target Hb.

Complications

An increase in blood pressure after starting rHuEPO therapy may occur in children [52, 81]. This appears to be more common in children who receive higher doses of rHuEPO, and have a consequent more rapid increase in Hb [82]. Hence, rapid increases in Hb should be avoided. While the increase in red cell mass appears to be one mechanism of the hypertension, there also appears to be a direct effect of rHuEPO on the vasculature.

An increase in vascular access clotting following rHuEPO treatment has been attributed to the increase in Hb. There may also be a small negative effect on dialytic clearance, but this is not clinically significant.

Iron deficiency may develop in children treated with rHuEPO [52, 81]. This is secondary to iron utilization for red blood cell synthesis. Consequently, unless iron overload is present, all patients treated with rHuEPO should receive iron supplementation and be screened for iron deficiency before and during therapy.

A rare complication of rHuEPO is the development of anti-EPO antibodies [83]. These

antibodies neutralize both endogenous EPO and rHuEPO, resulting in red cell aplasia. Immunosuppressive therapy, including after renal transplantation, results in hematologic recovery in many patients [84]. Patients with undetectable anti-EPO antibodies may subsequently respond to rHuEPO [84]. As described below, peginesatide is an effective option for patients with anti-EPO antibodies [85].

Darbepoetin Alpha

Darbepoetin alpha (Aranesp™, Thousand Oaks, CA, USA) is a genetically engineered molecule with a longer half-life than rHuEPO, permitting less frequent administration. The longer half-life of darbepoetin alpha is due two additional N-glycosylation sites.

Efficacy

Studies in adults demonstrate comparable efficacy of rHuEPO and darbepoetin alpha, despite less frequent dosing of darbepoetin alpha [86, 87]. One study demonstrated that many CKD patients do well when receiving darbepoetin alpha subcutaneously as infrequently as once every 3–4 weeks [88].

In a prospective study, children receiving rHuEPO were randomized to rHuEPO or darbepoetin alpha at a less frequent dosing interval (0.42 μg of darbepoetin alpha per week for each 100 units/week of rHuEPO). There was no significant difference in Hb or side effects between the groups at the end of the 20-week study; the median weekly dose of darbepoetin alfa was 0.41 mcg/kg, with 25th and 75th percentiles of 0.25 and 0.82 mcg/kg, respectively [89]. A small prospective study evaluated the response to converting seven children receiving HD from thrice weekly rHuEPO to weekly darbepoetin alpha (1 mcg of darbepoetin alpha per week for each 200 units/week of rHuEPO). Especially in the younger children who were receiving high doses of rHuEPO, there were problems initially with elevated Hb levels and associated hypertension. This was corrected by reducing the dose of darbepoetin alpha, suggesting that this dose conversion ratio may be inappropriate in younger children, and that careful monitoring of the initial response is necessary when converting to darbepoetin alpha. The mean steady-state dose of darbepoetin alpha after 3 months was 0.51 mcg/kg/week [90].

In a large prospective study, children with CKD and anemia were given darbepoetin alpha at a starting dose of 0.45 μg/kg/week. There was a significant improvement in Hb and it was sustained during the 28 weeks of the study. By the end of the study, slightly more than half the patients were receiving darbepoetin alpha at dosing intervals of at least 2 weeks [91]. A small study has described the successful use of darbepoetin alpha in infants, with a starting dose of 0.5 μg/kg/week [92]. The dose was able to be reduced and the dosing interval was increased to 3–4 weeks in some of the infants [92]. In another study in children, the initial dose in naïve patients was 0.45 mcg/kg and patients previously treated with rHuEPO were converted using a dose of 1 mcg of darbepoetin alpha per 200 IU of rHuEPO [93]. The final dose was higher in the patients converted from rHuEPO, perhaps because most of these patients were receiving dialysis and none of the naïve patients were dialysis patients [93].

Pharmacokinetics

One study evaluated the half-life of darbepoetin alpha in 12 pediatric patients with CKD [94]. Most of the patients were receiving HD [n = 9], but other patients were receiving PD [n = 1] or not yet receiving dialysis [n = 2]. Each patient received one dose of darbepoetin alpha (0.5 mcg/kg) intravenously and subcutaneously. The half-life of darbepoetin alpha with IV administration was 22.1 h (SD = 4.5 h). The half-life was 42.8 h (SD = 4.8 h) with subcutaneous administration. The pharmacokinetics were comparable to a similarly designed study in adults except for increased bioavailability (54 % vs. 37 %) and an earlier T_{max} (36 h vs. 54 h) in the pediatric patients when darbepoetin alpha was administered subcutaneously [94, 95]. Hence, darbepoetin alpha may be absorbed more rapidly in pediatric patients [94]. More rapid absorption was also seen in pediatric studies of rHuEPO [96].

Dosing

Based on protein mass, 1 mcg of darbepoetin alpha is equivalent to 200 units of rHuEPO. Nevertheless, the recommended darbepoetin alpha dose by the manufacturer when converting patients from rHuEPO to darbepoetin alpha is not a direct conversion based on the 1 mcg of darbepoetin alpha to 200 units rHuEPO ratio (Table 57.6). The recommended conversion ratios are based on an analysis of the dose conversion clinical trials [97]. This analysis indicates that proportionally less darbepoetin alpha was needed in patients who began the trial on higher doses of rHuEPO [97]. The explanation for this observation is unclear. It is possible that the efficacy of darbepoetin alpha increases at higher doses. Alternatively, there may simply be a "regression to the mean" in those patients who were on very high doses of rHuEPO. These patients may have had a transient reason (e.g., inflammation) that led to high ESA dose requirements that subsequently resolved, allowing lowering of the darbepoetin alpha dose during the study.

One challenge with darbepoetin alpha administration in children is the lack of a multidose vial. First, many small pediatric patients are likely to need less than 25 μg, the smallest available single-dose vial. This results in wasting of the unused medication. Second, pediatric patients may not tolerate the discomfort of 1 mL injections or may require multiple injections in order to tolerate the full 1 mL volume of the single-dose vials. A useful alternative is to utilize darbepoetin alpha in more concentrated single-dose prefilled syringes. Thus, dosing of darbepoetin alpha necessitates knowledge of the available preparations (Table 57.7), and requires creative adjustments of doses and dosing intervals to minimize wasting of medication.

Recommendations for converting patients from rHuEPO to darbepoetin alpha based on adult data are available (Table 57.6). Patients who are receiving rHuEPO twice or thrice weekly should receive darbepoetin alpha weekly, and patients who are receiving weekly rHuEPO should receive darbepoetin alpha every other week.

Based on the pediatric literature, a reasonable starting dose of darbepoetin alpha in ESA naïve patients is approximately 0.5 mcg/kg given weekly. Alternatively, the same total dose could be given every 2 weeks (i.e., 1 mcg/kg every 2 weeks). Every 2-week dosing at initiation should be reserved for patients with a Hb that is only mildly below target. Close monitoring of the Hb is essential for all patients due to the variable response to darbepoetin alpha.

As occurs with rHuEPO, frequent dose adjustments of darbepoetin alpha are often necessary [86]. Since darbepoetin alpha has a long half-life, it is important not to increase the dose too quickly to avoid overshooting the target Hb. Many patients require lower doses after their Hb reaches the target range. When adjusting darbepoetin alpha dosing, it is desirable to round doses based on the available preparations (Table 57.7) to avoid excessive wasting of the medication. Nevertheless, excessive rounding is not appropriate; some patients will need to discard some of their medication. Table 57.8 presents one system for dose adjustment. It is unclear whether the dar-

Table 57.6 Starting dose of darbepoetin alpha based on previous dosing of rHuEPO

Previous weekly rHuEPO dose (units/week)	Weekly darbepoetin alpha dose (mcg/week)
<2500	6.25
2500–4999	12.5
5000–10,999	25
11,000–17,999	40
18,000–33,999	60
34,000–89,999	100
≥90,000	200

Table based on manufacturer's recommendations
rHuEPO recombinant human erythropoietin

Table 57.7 Available preparations of darbepoetin alpha (single use vials)

25 mcg*	40 mcg*	60 mcg[a]	100 mcg[a]	150 mcg[a]	200 mcg[a]	300 mcg[a]	500 mcg

[a]Preparations that are available in low volume prefilled syringes (0.3–0.6 mL, depending on the dose)

Table 57.8 Dose adjustment table for darbepoetin alpha

6.25	10	15	20	30	40	50	60	80	100	130	150	200

Doses are in micrograms. The dose to the left of the current dose should be used for dose decreases and the dose to the right of the current dose for dose increases

bepoetin alpha is evenly distributed in the prefilled syringes. Hence, gentle mixing of the medication and transfer to a 1 mL syringe has been recommended for patients who do not need a full dose [92].

Dose frequency of darbepoetin alpha can be gradually reduced from weekly to every other week to every 3 weeks to every 4 weeks [98]. Not all patients will tolerate decreased dose frequency, especially beyond every 3 weeks. The dose frequency can be reduced whenever the patient has a Hb level that would normally mandate decreasing the dose. Alternatively, the dose frequency can be reduced in patients who are on a stable darbepoetin alpha dose and have a Hb in the target range. The total weekly dose should remain the same. For patients receiving darbepoetin alpha less often than weekly, consideration should be given to increasing the dose frequency if a patient requires more than 1 dose increase, especially if the total weekly dose is relatively high.

Complications

Side effect profiles have been similar in studies comparing IV darbepoetin alpha with IV rHuEPO [86, 87]. In one study, there was a statistically significant increase in pruritus in the darbepoetin alpha group [87]. Injection site pain is more severe in children with subcutaneous darbepoetin alpha than with rHuEPO [99]. There have been cases of antibodies developing to darbepoetin alpha leading to pure red cell aplasia.

Methoxy Polyethylene Glycol-Epoetin Beta

Methoxy polyethylene glycol (PEG)-epoetin beta is made by linking EPO with a large polymer chain via amide bonds between amino acids and methoxy polyethylene glycol butanoic acid. Methoxy PEG-epoetin beta is also called Continuous Erythropoietin Receptor Activator (C.E.R.A.). A long half-life permits less frequent dosing [100].

Efficacy

A number of studies have demonstrated the effectiveness of methoxy PEG-epoetin beta in adult patients with CKD [101–107]. In a direct comparison with darbepoetin alpha in adult HD patients, methoxy PEG-epoetin beta was superior at maintaining Hb at the prescribed target [108]. Methoxy PEG-epoetin beta given either every 2 weeks or every 4 weeks was comparable to rHuEPO in adult dialysis patients [103, 105].

Methoxy PEG-epoetin beta is effective in adult kidney transplant recipients [109, 110]. In a randomized study, once-monthly methoxy PEG-epoetin beta was compared with every 1–2 weeks darbepoetin alpha, with similar efficacy and side effect profiles [111].

Pharmacokinetics

The half-life of methoxy PEG-epoetin beta was 134 h and 139 h in adult PD patients following IV and subcutaneous dosing, respectively [112]. The peak reticulocyte count occurred at a mean of 8 days in both groups. Injection site location does not influence the pharmacokinetics, with half-lives between 160 and 164 h [100].

Dosing

For adults, the starting dose is 0.6 mcg/kg every 2 weeks initially, with conversion to monthly dosing once the Hb is within the target range. The every 2 week dose is doubled to calculate the monthly dose. An initial dose of 1.2 mcg/kg every 4 weeks was effective and comparable to darbepoetin alpha every 1–2 weeks in a randomized clinical trial in ESA naïve non-dialysis patients [106]. There are recommendations for conversion from another ESA to monthly

Table 57.9 Conversion from rHuEPO or darbepoetin alpha to methoxy PEG-epoetin beta

rHuEPO dose (units/week)	Darbepoetin dose	Monthly methoxy PEG-epoetin beta
<8000 units/week	<40 mcg/week	120 mcg/month
8000–16,000 units/week	40–80 mcg/week	200 mcg/month
>16,000 units/week	80 mcg/week	360 mcg/month

methoxy PEG-epoetin beta (Table 57.9). In one study the dose conversion ratio for HD patients converted from darbepoetin alpha to methoxy PEG-epoetin beta was 1.21 mcg of methoxy PEG-epoetin beta for each 1 mcg of darbepoetin alpha [113]. In a small study of pediatric kidney transplant recipients, the patients received a median dose of 2.5 mcg/kg every 4 weeks [114].

Methoxy PEG-epoetin beta is available in single use vials and single use prefilled syringes in a variety of doses. The prefilled syringes are more concentrated and hence preferable in patients who require subcutaneous injection.

Complications

In adult HD patients, conversion from darbepoetin alpha to methoxy PEG-epoetin beta led to more transfusions [113].

Peginesatide

Peginesatide is a synthetic peptide that is attached to polyethylene glycol and is thus pegylated. It mimics the structure of EPO and binds the EPO receptor, but it has no sequence amino acid homology to EPO. Its major advantage is a long half-life that permits monthly dosing [115]. In addition, it may be effective in patients with anti-EPO antibodies and pure red cell aplasia [85]. Peginesatide may be administered subcutaneously or intravenously.

Efficacy

In a randomized study of adults receiving HD, monthly peginesatide was as effective as EPO (one to three times per week) at maintaining Hb levels [116]. In non-dialysis patients, monthly peginesatide had similar efficacy to every 2 week administration of darbepoetin alpha [117]. However, the patients receiving peginesatide had an increased risk of cardiovascular events and mortality [117]. In another study, adults with CKD, with approximately 50 % receiving dialysis, were converted from darbepoetin alpha to peginesatide, which was administered once monthly. The patients receiving HD had a slight decrease in Hb and there was a small increase in Hb in the patients not receiving dialysis [118]. Peginesatide is an effective option for patients who develop pure red cell aplasia due anti-EPO antibodies [85]. There is limited information on the use of peginesatide in pediatric patients.

Pharmacokinetics

The half-life in healthy adult subjects is 25 h and 53 h following IV and subcutaneous administration, respectively. In dialysis patients, the half-life in adult dialysis patient is 48 h after IV administration, suggesting decreased clearance with reduced kidney function [119].

Dosing

The recommended starting dose for adults not currently receiving an ESA is 0.04 mg/kg once monthly. There are specific recommendations for converting patients from another ESA to peginesatide, with the first dose 1 week after the last dose of rHuEPO or when the next scheduled darbepoetin alpha dose would have been given. Peginesatide is available in 1 ml or 2 ml vials, each at a concentration of 10 mg/ml.

Complications

Antibodies to peginesatide have been described [116] and one patient with red cell aplasia due to anti-EPO antibodies subsequently developed antibodies to peginesatide that led recurrence of red cell aplasia [85]. In the United States, peginesatide was only approved for use in dialysis patients due to the increased risk of cardiovascular complications in the randomized study of

peginesatide in non-dialysis patients [117]. In addition, there was an increased rate of back pain and acute kidney injury in the non-dialysis patient receiving peginesatide [117]. Peginesatide was withdrawn from the United States market in 2013 due to serious hypersensitivity reactions, including anaphylaxis.

Monitoring Iron Stores

Serum ferritin and TSAT are currently the most widely used tests for monitoring iron stores. A variety of other tests, such as soluble transferrin receptor, percentage of hypochromic red blood cells, and erythrocyte zinc protoporphyrin, have been evaluated, but none of these are readily available or well-studied in pediatric patients. In all children with CKD, TSAT and serum ferritin should be measured at initiation of ESA therapy [2]. Subsequent monitoring should be at least every 3 months [2]. More frequent monitoring is appropriate in a variety of clinical situations, including after initiation of ESA therapy, when there is a poor response to ESA therapy, after a course of IV iron, or during administration of chronic IV iron therapy. Children receiving IV iron doses of more than 1.5 mg/kg or more than 100 mg should have a delay of at least 1 week before checking serum iron parameters.

Diagnosis of Iron Deficiency

The gold standard for diagnosing iron deficiency in patients with CKD is bone marrow assessment of iron stores, a test that is impractical on a routine basis. An alternative definition is the response to IV iron. An increase in Hb or a decrease in ESA dose after receiving IV iron suggests that the patient was iron deficient. This definition is not perfect—the "response" to IV iron may be coincidental or the patient may not respond for other reasons—but it has been widely used in clinical research and clinical practice.

The traditional criterion for iron deficiency, the combination of a low serum ferritin and a low TSAT, are not applicable in patients with CKD. The serum ferritin is especially problematic because ferritin is an acute phase reactant, and it is therefore often elevated in CKD patients because of infection and non-specific inflammation. Moreover, treatment with an ESA can induce functional iron deficiency. This occurs because the high rate of red blood cell synthesis depletes the readily available iron, even though total body iron stores may be adequate. Patients with functional iron deficiency due to rapid erythropoiesis may have a normal ferritin, but a low TSAT. Often the ferritin level decreases in these patients, yet it remains in the normal range, and it is therefore not as useful a predictor of iron deficiency as the TSAT.

A TSAT below 20 % and a serum ferritin above 100 ng/mL suggests a functional iron deficiency. This same scenario can also occur with an inflammatory block, a condition where inflammation prevents effective delivery of iron for erythropoiesis. Clinical signs of infection, a low serum iron, an elevated CRP, and an increasing ferritin support a diagnosis of an inflammatory block.

KDIGO recommends treating adult CKD patients with IV iron when the TSAT is <30 % and the ferritin is <500 ng/mL, assuming there is an indication (desire to increase the Hb or decrease the ESA dose). It is clear that some patients respond to IV iron despite an elevated ferritin [120]. This has led to controversy regarding the upper limit of ferritin in the KDIGO guidelines, with some suggesting that there is no evidence-based upper limit for ferritin of 500 ng/mL [69, 70]. There has been an increase in the use of IV iron worldwide [121], and in the United States the mean serum ferritin in HD patients has increased to close to 800 ng/ml [68].

The KDIGO cutoffs for initiating IV iron in pediatric patients are a TSAT <20 % and a ferritin <100 ng/ml. This is quite conservative and many pediatric nephrologists treat patients with TSATs <20–30 % despite ferritin values >100 ng/ml. The upper limit of ferritin for holding IV iron for pediatric patients varies among clinicians, with some practitioners using cutoffs of 500–800 ng/ml. This variation is due to the lack of evidence supporting a specific cutoff.

Iron Therapy

After EPO deficiency, iron deficiency is the leading cause of anemia in children with CKD. Treatment of iron deficiency often allows achievement of the target Hb with a lower dose of ESA. Iron therapy should not be given to patients who have iron overload, which is commonly defined as a ferritin greater than 800 ng/mL or a TSAT >50 %.

Oral Iron

Only a small percentage of oral iron is absorbed, limiting its efficacy in patients who have high iron requirements due to blood loss, such as children receiving HD [7]. Adherence to therapy may be problematic due to problems with gastric irritation and constipation. In HD patients, oral iron appears to be of limited benefit and is poorly tolerated [122].

There is an up-regulation in oral iron absorption in patients who have a low serum ferritin or decreased marrow iron stores. However, HD patients have decreased absorption of oral iron when compared to normal controls; inflammation, which is common in HD patients, decreases iron absorption. This is partially mediated by hepcidin, which inhibits iron absorption from the intestines, and is increased by inflammation [19].

Oral iron absorption is decreased when given with food; hence, iron should be given either 1 h before or 2 h after a meal. Calcium carbonate and calcium acetate decrease iron absorption; oral iron should not be given at the same time as these phosphate binders. Sevelamer seems to have little effect on oral iron absorption [123]. H2-receptor antagonists and proton pump inhibitors may also adversely affect iron absorption.

Children should receive a dose of 3–6 mg/kg/day of elemental iron (maximum dose: 150–300 mg/day). Oral iron may be adequate therapy in children who are not receiving HD. In children receiving HD, oral iron is often not sufficient to correct absolute or functional iron deficiency [124, 125]. Children receiving IV iron should not receive oral iron given the limited benefits and high rate of side effects of oral iron.

Intravenous Iron

IV iron is more effective than oral iron in correcting anemia in adult patients with CKD, although the benefit is relatively small in pre-dialysis patients [126, 127]. IV iron is believed to be cost effective in HD patients [128, 129] and its use has been increasing [130]. Studies in children, including a meta-analysis [131], have shown the efficacy of IV iron in correcting iron deficiency, improving Hb levels, and reducing rHuEPO dose requirements [124, 125, 132–135]. There is limited experience using IV iron in pediatric kidney transplant recipients [136].

Acute dosing of IV iron is used for patients who have evidence of iron deficiency, which is most commonly defined based on measures of iron stores. The dose given is relatively large. Chronic dosing utilizes smaller doses to maintain iron stores and provide a regular source of iron for erythropoiesis. Acute dosing results in a more significant change in Hb and iron stores [137]. For children receiving PD or who are predialysis, the goal is usually to minimize the need for IV line placement by maximizing the dose given during a single infusion. A chronic dosing strategy is generally only utilized in patients receiving HD due to the burden of IV placement.

Preparations

There are a variety of IV iron preparations available in the United States: iron dextran (INFeD®, Actavis, Dublin, Ireland), sodium ferric gluconate conjugate in sucrose, hence referred to as ferric gluconate (Ferrlecit®, Sanofi-Aventis US, Bridegewater, NJ, USA), iron sucrose (Venofer®, American Regent, Shirley, NY, USA), ferric carboxymaltose (Injectafer® American Regent, Shirley, NY, USA) and ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Waltham, MA, USA). The European Pediatric PD Working Group recommended not using iron dextran due to concerns about life-threatening anaphylactic reactions [27]. These preparations have different side effect profiles. In addition, there is no preparation that is ideal in every situation. Iron sucrose and ferric gluconate have limitations on individual doses and must be given over an extended

period when higher doses are utilized. This somewhat limits their utility in patients who are not receiving HD. In contrast, ferric carboxymaltose and ferumoxytol can be given more rapidly at higher doses. However, ferric carboxymaltose and ferumoxytol are not designed to be given in a chronic dosing strategy due to product packaging in very high doses.

Ferric gluconate is generally well-tolerated [138, 139], and an effective treatment for CKD patients with iron deficiency [120, 140–143]. Ferric gluconate is available in 62.5 mg vials. Acute dosing in adult HD patients is typically 125 mg administered over 10 min given over eight consecutive HD sessions (total dose = 1000 mg). The recommended acute dose in children receiving HD is a maximum of 1.5 mg/kg over 10 min. In adults, ferric gluconate doses of 250 mg, over 60 or 90 min, were well tolerated [144], as were infusions over 1–4 h [145]. In children, one study reported administration of doses ranging from 1.5 to 8.8 mg/kg, with the child receiving the highest dose having a significant adverse event [132]. Thus, acute doses of ferric gluconate in patients not receiving HD should not exceed 4 mg/kg (250 mg if >60 kg), which should be given over at least 90 min.

Iron sucrose is generally well-tolerated [146, 147] and effective in correcting iron deficiency in patients with CKD [148–150]. Iron sucrose is available in 50 mg vials. Adult HD patients are usually given 50 or 100 mg over 5 min [146]. Infusions of 100 mg over ten consecutive dialysis sessions is used for acute dosing to provide a total of 1000 mg. For chronic dosing in adult HD patients, doses of 50 or 100 mg avoids wasting medication and can be given weekly or every other week [146].

In adult PD or predialysis patients, 200 mg of iron sucrose can be given over 2 min, although there is a small risk of symptoms of acute iron overload (see "complications below), especially in smaller patients [151]. This is not convenient for outpatients since it would need to be repeated four additional times to provide 1000 mg. In adults, iron sucrose doses of 300 mg, given over 1.5–2 h, appear to be well tolerated. Doses of iron sucrose as high as 500 mg have been given, but the infusion time must be extended to avoid side effects, and this dose may not be tolerated in smaller adults [149, 152, 153]. In children, a dose of 2 mg/kg (maximum 100 mg) over 3 min or 5 mg/kg (maximum 300 mg) over 90 min is well-tolerated [154]. The 5 mg/kg dose can be repeated the next day [154].

Ferric carboxymaltose is effective in treating iron deficiency and is approved for use in non-dialysis CKD patients [155–157]. There are recommendations for acute dosing in adults: 15 mg/kg (maximum 750 mg) with a second dose at least 1 week later. It is administered over 15 min. There is limited pediatric experience and there are no recommendations for dosing in children <50 kg. Ferric carboxymaltose is available in 750 mg vials, precluding its use in a chronic dosing strategy (see below) or in small children without wasting medication.

Ferumoxytol, approved for use in all CKD patients, is effective when given to adults at a dose of 510 mg, followed by a second dose 3–8 days later [158, 159]. The infusion rate should not exceed 30 mg of iron/s. Pediatric dosing experience is limited [160], and there are no recommendations for dosing in children <50 kg. The large vial size (510 mg) limits its utility in small children or for use in a chronic dosing strategy.

Acute Dosing

Acute doses of IV iron are given when the patient has evidence of iron deficiency (see criteria above). The goal of acute IV iron dosing is to normalize the serum ferritin and the TSAT. In some cases, an acute dose may be used as a trial of IV iron in a patient with normal iron studies, but a poor response to an ESA. In these patients, the goal of acute IV iron is a reduction in ESA dose or correction of resistant anemia.

In adult HD patients, studies suggest that a total dose of 1000 mg of iron, divided over multiple consecutive dialysis sessions, is appropriate, since smaller doses are not as effective [142]. A total dose of 1000 mg has been used in older children with good results [125]. A randomized study of children receiving HD compared two acute dosing regimens of ferric gluconate (1.5 mg/kg/

dose and 3.0 mg/kg/dose; maximum dose, 125 mg/dose) given during eight consecutive HD sessions. The patients had a TSAT <20 % and/or a ferritin less than 100 ng/mL at baseline. Both doses led to an increase in Hb and normalization of iron indices. Since there was no difference in the response, the authors recommended a dose of 1.5 mg/kg/dose (maximum of 125 mg/dose) for eight consecutive HD sessions [134]. This provides a total dose of 12 mg/kg (maximum dose of 1000 mg). Based on the available evidence, the total dose for acute pediatric dosing should be between 12 and 25 mg/kg (1000 mg maximum) divided over up to12 HD sessions, depending on the dose and iron preparation (see above discussion of specific preparations).

Chronic Dosing

Acute dosing is effective in correcting iron deficiency, but especially in HD patients there is a risk of ongoing episodes of iron deficiency due to continued blood loss. Transient iron deficiency may lead to decreased red blood cell synthesis. This has led to more frequent chronic IV iron use. Observational studies in adults suggests that maintenance therapy may be associated with better outcomes than an acute dosing strategy [161, 162].

In one pediatric study, 1 mg/kg of ferric gluconate for 12 weeks led to a significant increase in Hb [124]. In another pediatric study, chronic IV iron sucrose (2 mg/kg [max = 200 mg] weekly) produced a reduction in rHuEPO dose [133]. A randomized 16-week study in children receiving HD compared maintenance IV iron dextran (doses of 25, 50 or 100 mg/week based on weight; doses therefore ranged from 1.25 to 2.5 mg/kg/week) with oral iron (4–6 mg/kg/day). The patients receiving IV iron had a significant increase in ferritin when compared to the oral iron group. There was a trend toward a reduction in rHuEPO dose in the IV iron group when compared to the oral iron group [135].

Another study randomized children receiving HD to intermittent IV iron versus maintenance IV iron. There was a higher rate of iron overload in the children receiving intermittent IV iron [163]. This observation may be secondary to a decreased ability to utilize stored iron in children receiving HD due to an inflammatory block. The low doses of maintenance IV iron are immediately employed for red cell synthesis, avoiding an excessive accumulation of stored iron. This contrasts with intermittent IV iron; the high doses cannot all be utilized immediately, increasing the risk of eventual iron overload.

One pediatric study prospectively followed children who were started on a maintenance dose of 1 mg/kg/week of ferric gluconate and then adjusted the dose of ferric gluconate based on iron studies. The majority of the patients completing the study required a dose of 1.5 mg/kg to maintain adequate iron stores [164].

Maintenance IV iron in children receiving HD should be started at about 1 mg/kg/week, usually given as a once/week dose. The maintenance dose is titrated to keep the TSAT above 20 % and the ferritin above 100 ng/mL; IV iron should be held if the TSAT is greater than 50 % or the ferritin is greater than 500 ng/mL.

Complications

There are some complications of IV iron that are specific to the particular preparation. Iron dextran may cause an acute anaphylactic reaction, which is potentially fatal [165]. Iron sucrose [139] and ferric gluconate [142] have a safer side effect profile, although all IV iron preparations have the potential to cause serious adverse reactions. Children and adults who have had anaphylactic reactions to iron dextran have tolerated other iron preparations [132, 166, 167]. High doses of iron dextran may cause patients to develop arthralgias and myalgias [168].

There are reports of laboratory findings and clinical symptoms that may be due to acute iron toxicity during the use of iron sucrose and ferric gluconate. This effect is related to the dose and infusion rate and is presumably secondary to rapid release of free iron. Symptoms with ferric gluconate have included loin pain, hypotension, emesis and paresthesias [169]. Iron sucrose side effects have included rash, flushing, and hypotension, which were rapidly reversible [170]. These side effects limit the maximum single dose of these compounds when compared to iron dextran, which releases free iron at a slower rate.

Ferumoxytol is associated with higher rates of adverse events than iron sucrose or ferric gluconate [147]. Adverse reactions include injection site reactions, hypersensitivity reactions and hypotension that can be severe [171]. Patients should be observed for at least 30 min after receiving ferumoxytol. Its use may also transiently affect MRI interpretation since it is also used as a contrast agent for MRIs [171].

Iron overload is a potential complication of IV iron therapy, and may occur in CKD patients receiving IV iron [172–174]. There is concern that current IV iron protocols may lead to more problems with iron overload, which has been seen in children receiving acute or maintenance IV iron [133, 163]. Use of IV iron may increase generation of reactive oxidative species, which has the potential to impair endothelial cell function, promote atherosclerosis, cause inflammation, and decrease immune function [175–178]. IV iron may cause hypophosphatemia, which appears to be mediated by increased levels of FGF-23 and urinary phosphate wasting [179]. This complication would not be expected in most CKD patients.

IV iron may increase the risk of infection [180]. A multivariate analysis did not find a relationship between IV iron and infection, although there was a trend toward more infections among those patients who received large amounts of IV iron versus those who received lower doses [181]. Given this potential complication, IV iron should be held in patients with acute infections.

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