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EDUCATIONAL REVIEW

Anemia in chronic kidney disease

Meredith A. Atkinson[1] · **Bradley A. Warady**[2]

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Abstract Anemia is common and associated with adverse outcomes in children with chronic kidney disease (CKD). Many factors contribute to declining hemoglobin as CKD progresses, but impaired production of erythropoietin by failing kidneys is a central cause. Hepcidin-mediated iron restriction also contributes to anemia by downregulating both intestinal iron absorption and release of stored iron for erythropoiesis. The core components of anemia management remain erythropoiesis-stimulating agents (ESA) and iron supplementation, but despite these therapies, a substantial number of children remain anemic. Although escalating ESA dose to target higher hemoglobin has been associated with adverse outcomes in adults, no trials have investigated this association in children, and maintaining hemoglobin levels in a narrow range with conservative ESA dosing is challenging. Judicious use of iron supplementation can enhance the response to ESAs, but the iron storage markers most commonly used in clinical practice have limitations in distinguishing which patients will benefit most from additional iron. Several novel anemia therapies, including hypoxia-inducible factor stabilizers, prolyl hydroxylase inhibitors, and dialysate-delivered iron supplements, have been developed and may offer options for alternative anemia management. However, the safety and efficacy of these agents in children with CKD has yet to be assessed.

Keywords Hemoglobin · Anemia · Iron-restricted erythropoiesis · Erythropoiesis-stimulating agent · Hepcidin

✉ Meredith A. Atkinson
matkins3@jhmi.edu

[1] Division of Pediatric Nephrology, Johns Hopkins University School of Medicine, 200 N. Wolfe St, Baltimore, MD 21287, USA

[2] Division of Pediatric Nephrology, Children's Mercy Kansas City, Kansas City, MO, USA

Introduction

Among the many comorbidities associated with chronic kidney disease (CKD) in children, anemia and its management remains a challenging endeavor for clinicians. The emergence of recombinant human erythropoietin (rHuEPO) >30 years ago revolutionized the treatment of anemia for CKD patients, but since that time, the mainstays of therapy have remained erythropoiesis-stimulating agents (ESA) and iron supplementation, with a significant number of patients demonstrating persistent anemia despite these interventions. Scientific advances in the understanding molecular regulation of EPO production and the role of the iron-regulatory protein hepcidin in iron metabolism have opened the door for the development of novel ESAs and renal anemia therapies. We review definition, risk factors for, and pathophysiology of anemia in children with CKD with specific attention to current therapeutic strategies, insights into mechanisms of novel therapies, and ongoing challenges in patient management.

Epidemiology, risk factors, and adverse associations

Anemia is one of the most common and clinically significant complications of CKD in children and is associated with a variety of adverse clinical consequences, including an increased risk for hospitalization and mortality, and the development and progression of cardiovascular disease (CD) risk factors, including left ventricular hypertrophy (LVH) [1–3]. The severity of CKD is a primary risk factor for the development of anemia in this population of patients. Data from the

North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) cohort has consistently shown that the risk for anemia increases as CKD stage advances, with a prevalence of 73% at stage 3, 87% at stage 4, and >93% at stage 5 [4, 5]. Furthermore, of children prescribed an ESA, >20% at stage 4 and >40% at stage 5 CKD demonstrate persistently low hemoglobin (Hb) levels [4]. Within the Chronic Kidney Disease in Children (CKiD) cohort study, the median Hb declined as the measured glomerular filtration rate (GFR) decreased to <43 ml/min/1.73m^2 [6, 7]. A variety of other risk factors for anemia have been identified, including the use of angiotensin-converting enzyme (ACE) inhibitors, which may predispose to anemia via inhibition of erythropoiesis [8]. In the International Pediatric Peritoneal Dialysis Network (IPPN) registry, low serum albumin, increased parathyroid hormone (PTH) levels, high serum ferritin, and the use of bioincompatible dialysate were associated with low Hb levels [9]. The inverse relationship between Hb and ferritin may reflect its limited utility as a marker of available stored iron, in contrast to its capacity to reflect active inflammation. Patients with less residual urine output and clinically judged as having fluid overloaded also demonstrated lower Hb levels, suggesting that some portion of treatment-resistant anemia may in fact be due to the dilution of the red cell mass in an expanded extracellular volume [9]. Race is also a recognized risk factor for anemia. Among children enrolled in the CKiD study, African Americans have consistently demonstrated lower levels than white children, even after adjusting for the level of kidney function [10]. Normal Hb levels also vary in healthy children by race, and whereas differences in the prevalence of hemoglobinopathy traits, iron deficiency, or socioeconomic status do not fully explain this disparity, genetic polymorphisms may contribute to these differences [11]. Current anemia management guidelines do not recommend varying Hb targets or the approach to treatment by race [11].

Among children on dialysis, a low Hb value is a strong and independent predictor of mortality and is associated with an increased frequency of hospitalization [1, 9, 12]. Even in the predialysis population, anemia is an independent risk factor for accelerated decline in GFR compared with those without anemia and is associated with an almost 40% increased risk for all-cause hospitalization in children with stage 2–5 CKD [5]. Anemia is also an important cardiovascular risk factor in children, increasing the risk for the development of LVH independent of an elevation in blood pressure, even in the setting of mild to moderate CKD [2, 13, 14]. Parents or caregivers of anemic adolescents with CKD report greater limitations in physical functioning, exercise capacity, schoolwork, and activities with friends and family than caregivers of their peers who do not have anemia—all of which may adversely impact patient quality of life (QoL) in patients [15]. Finally, patients with treatment-resistant anemia are more likely to require escalation of ESA dosing, with its attendant risks, and red blood cell (RBC) transfusions, which are associated with an increased risk for the development of human leukocyte antigen (HLA) antibodies. Leukoreduction of blood products is an ineffective means to decrease HLA sensitization, and RBC transfusions lead to clinically significant increases in HLA antibody strength and breadth, which is a barrier to future transplantation and may adversely affect graft outcomes [16, 17].

Definition of anemia and hemoglobin monitoring

The application of adult normative Hb thresholds substantially underestimates the prevalence of anemia in CKD patients under the age of 18 years, as normal Hb levels vary by age and sex [10, 18–20]. For this reason, Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia uses World Health Organization (WHO) age-specific Hb values to define the level at which an evaluation for the cause of anemia in patients with CKD should be initiated (Table 1) [21]. An alternative source for normative Hb thresholds in children aged 1–19 years is the National Health and Nutrition Examination Survey (NHANES) III data from 1988 to 1994, which reports age- and sex-specific fifth percentile values (Table 2) [18]. KDIGO also recommends that for children with CKD but without an established diagnosis of anemia, Hb should be measured at least annually in those with stage 3 CKD, at least twice annually in those with stage 4–5 CKD, at least every 3 months in those on dialysis. It should be measured more frequently for clinical indications and in patients already determined to be anemic [21].

Etiology/pathophysiology

Erythropoietin deficiency and dysregulation

Although a complex interaction of factors is responsible for the decrease in Hb seen with progressive CKD (Table 3), impaired EPO production by failing kidneys is a decisive cause. EPO, the product of the *EPO* gene on chromosome 7, is a glycoprotein hormone that serves as a signaling molecule for erythrocyte precursors and is unique among hematopoietic

Table 1 World Health Organization age-specific hemoglobin thresholds for defining anemia in children [21]

Age (years)	Hemoglobin (g/dl)
0.5–5	< 11.0
5–12	< 11.5
12–15	< 12.0
> 15 Male	< 13.0
> 15 Female	< 12.0

Table 2 Age- and sex-specific fifth percentile hemoglobin values for children 1–19 years of age derived from population-based data in the National Health and Nutrition Examination Survey 1988–1994 [18]

Age (years)	Hemoglobin (g/dl)	
	Male	Female
1–2	10.7	10.8
3–5	11.2	11.1
6–8	11.5	11.5
9–11	12.0	11.9
12–14	12.4	11.7
15–19	13.5	11.5

growth factors in being produced outside the bone marrow [22–24]. Prenatally, the liver is the primary site of EPO production, but this shifts to the kidney after birth, with a small additional amount continually produced in the liver [23]. Circulating EPO binds to specific transmembrane receptors on erythroblasts to regulate erythroid proliferation and survival via an antiapoptotic mechanism and serves as a growth factor to enhance RBC maturation [23]. EPO is synthesized by interstitial cells in the peritubular capillary bed of the renal cortex, but under conditions of injury, these cells transdifferentiate into myofibroblasts that synthesize collagen and lose their ability to produce EPO [23].

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor regulating EPO production through its binding to the hypoxia response element on the *EPO* gene [22]. In the absence of hypoxia, the oxygen-sensitive HIF-1α subunit is hydroxylated by prolyl hydroxylase, targeting it for rapid degradation in the proteasome and preventing its binding to the *EPO* gene [22, 25]. Hypoxic stress associated with anemia reduces the activity of prolyl hydroxylase, which stabilizes HIF-1 and leads to upregulation of *EPO* gene transcription [22, 25]. In CKD, diminished oxygen consumption by renal tissue leads to dysregulation of EPO production by increasing tissue oxygen pressure, which subsequently leads to decreased HIF stability and transcriptional activity, independent of damage to EPO-producing cells [24]. EPO levels in CKD patients may, in turn, be normal to slightly increased overall but are inappropriately low for the degree of anemia and are 10–100× lower than in anemic patients with normal renal function [23].

Table 3 Etiology of the anemia of chronic kidney disease in children

- Erythropoietin deficiency and/or dysregulation
- Iron-restricted erythropoiesis
  - Absolute iron deficiency
  - Functional iron deficiency
  - Impaired iron trafficking
- Inflammation and hepcidin up-regulation
- Chronic blood loss
  - Frequent phlebotomy
  - Hemodialysis circuit losses
  - Gastrointestinal losses
  - Menstrual losses
- Uremia and oxidative stress
- Hyperparathyroidism and myelofibrosis
- Nutritional deficiencies
  - B12, folate, carnitine, vitamin C
- Medications
  - ACE inhibitors
  - Nonadherence with anemia therapies
  - Drug toxicity
  - Pure red-cell aplasia associated with ESA

Iron restriction

Iron availability is a rate-limiting step in the maturation of RBCs, which requires incorporation of iron into erythroblasts in the bone marrow. Hb consists of four heme groups, each of which requires incorporation of one Fe^{2+} ion for oxygen binding [26]. Each mature RBC contains ~300 million Hb molecules, and two thirds of total body iron is located in the erythroid compartment [26]. Iron transported into the circulation bound to transferrin is released to erythroblasts via the interaction of transferrin with the transferrin receptor and receptor-mediated endocytosis [27]. Concurrent with EPO dysregulation, deficiency of accessible iron stores can exacerbate the degree of anemia and reduce responsiveness to ESA therapy [23]. Thus, iron-restricted erythropoiesis is also a critical contributor to anemia in CKD. Iron restriction may be secondary to absolute iron deficiency, to functional iron deficiency in which accessible iron stores are depleted by an ESA-stimulated bone marrow, or to impaired iron trafficking in the setting of inflammation [28]. Children with CKD are at risk for absolute iron deficiency due to multiple factors, including decreased nutritional intake, poor enteral absorption, blood loss via the gastrointestinal (GI) tract, menstruation, frequent phlebotomy, and hemodialysis [29, 30].

Hepcidin as a mediator of iron blockade

The iron-regulatory protein, hepcidin, a 25-amino acid antimicrobial peptide encoded by the *HAMP* gene and produced by hepatocytes, has emerged as the key mediator of iron-restricted erythropoiesis in the setting of inflammation and in CKD [31]. Hepcidin regulates both intestinal iron absorption and bodily iron distribution via posttranslational suppression of cell-membrane expression of ferroportin, which is the sole cellular iron exporter. Hepcidin binding to ferroportin causes internalization and lysosomal degradation of ferroportin, which results in downregulation of dietary iron absorption via intestinal enterocytes and inhibits the release of stored iron from reticuloendothelial cells (Fig. 1) [32]. In this way, hepcidin prevents the use of absorbed or stored iron for erythropoiesis by the bone marrow, a process that in the short term may serve as a host-defense mechanism intended to sequester iron from invading pathogens or malignant cells [33].

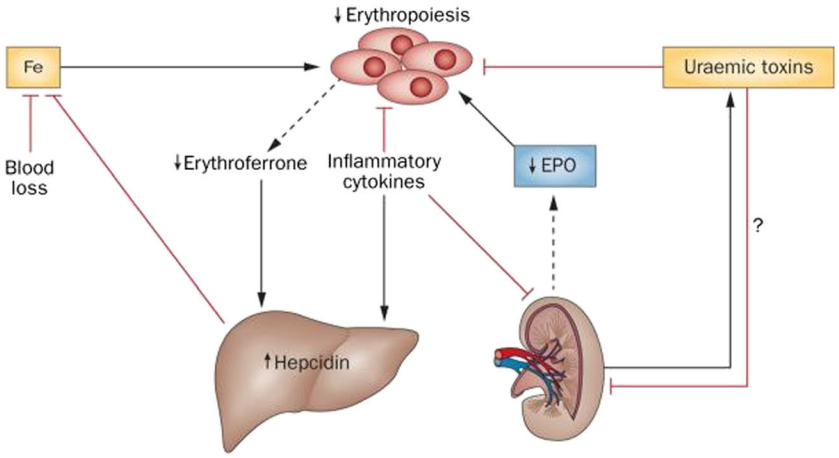

Fig. 1 In renal anemia, the kidney's ability to produce EPO is impaired. Inflammatory cytokines suppress erythropoiesis in the bone marrow and EPO production in the kidney and stimulates hepcidin production in the liver, which negatively affects iron absorption and mobilization. Hepcidin is also maintained at higher levels by decreased erythroferrone production, which is secondary to reduction in erythroblast numbers due to EPO deficiency. In patients with advanced CKD, the liver contributes significantly to plasma EPO levels. The contribution of uremic toxins to the pathogenesis of renal anemia is only poorly understood. Uremic toxins have been shown to suppress erythroid colony formation in vitro as well as *EPO* transcription in hepatoma cells, the latter indicating possible suppressive effects on hepatic and renal EPO production in vivo [23]. *CKD* chronic kidney disease; *EPO*, erythropoietin; *Fe*, iron. With permission [23]

A number of pathways regulate hepcidin (*HAMP*) gene expression via mechanisms involving iron status, erythropoiesis, and inflammation. Iron loading increases production of hepcidin, and hepcidin expression is modulated based on circulating levels of transferrin-bound iron via a bone morphologic protein (BMP)/mothers against DPP homolog 1 (SMAD) signaling pathway [23, 26]. Erythropoietin-stimulated erythroblasts produce erythroferrone, a hormone that acts directly on hepatocytes to suppress *HAMP* messenger RNA (mRNA) and decrease hepcidin production, with a resultant increased iron acquisition from absorption and storage sites [23, 26, 27]. In CKD, reduction in erythroblast number resulting from EPO deficiency diminishes the production of erythroferrone and prevents it from checking hepcidin production [23]. Finally, hepcidin expression is induced by inflammation in general and in particular by the inflammatory cytokine interleukin (IL)-6 and is cleared from circulation by glomerular filtration, leading to increased levels in the setting of decreased renal function [34]. Hepcidin is elevated in adults and children with CKD and those on dialysis, and levels are positively correlated with serum ferritin levels [35, 36]. A study in the CKiD cohort found that in children with mild to moderate CKD, higher hepcidin levels were associated with lower Hb values and an increased risk for incident anemia [34]. The potential role of nutritional vitamin D supplementation in reducing hepcidin production is under active investigation, and vitamin D decreases hepcidin mRNA expression in vitro [37]. A study in healthy adults showed that a single dose of vitamin D orally decreased circulating hepcidin levels within 24 h [37], but a small trial in children with early-stage CKD did not demonstrate a significant change over 3 months with daily cholecalciferol supplementation [38].

Other mechanisms of anemia in CKD

Accumulated uremic toxins and associated oxidative stress can induce changes in erythrocyte cell membranes and cytoskeletons that promote hemolysis and shorten cell lifespan, with RBC survival time decreased by as much as 50% compared with healthy controls [39]. Hyperparathyroidism can also contribute to anemia and ESA hyporesponsiveness due to decreased bone marrow production of RBCs in the setting of myelofibrosis [40–42]. Beyond iron deficiency, nutritional deficiencies of B_{12}, folate, carnitine, vitamin C, and copper may also contribute to anemia in CKD. Folate is required for DNA synthesis during erythropoiesis; when a deficiency in folate was corrected in 15 children on dialysis, their mean Hb level increased by 8% and ESA dose requirements decreased [30, 43, 44]. CKD, and especially chronic hemodialysis, is a leading cause of secondary carnitine deficiency due to its ready dialyzability [45]. Some studies suggested that L-carnitine supplementation can prolong RBC lifespan and stimulate erythropoiesis by inhibiting apoptosis, but there have been no large-scale randomized clinical trials evaluating whether supplementation is effective as an adjunctive treatment [45]. Vitamin C enhances absorption of dietary iron, contributes to mobilization of intracellular stored iron, and increases carnitine synthesis, but no clinical trial has assessed effects of vitamin C supplementation on anemia in dialysis patients [46]. Caution should also be used, as excessive vitamin C ingestion can be associated with renal oxalate deposition and acute kidney injury [47]. Copper deficiency is relatively rare but can arise from excessive zinc intake and be associated with a microcytic anemia resembling iron deficiency and leukopenia; it is correctable with supplementation [48].

Because anemia in children with CKD, particularly those with mildly impaired function, may not be associated solely with EPO deficiency, incident anemia should prompt an initial laboratory evaluation to include assessment of RBC indices and iron stores and other correctable nutritional deficiencies, such as B_{12} and folate [21]. Anemia with concurrent lymphopenia or thrombocytopenia should prompt evaluation for malignancy, autoimmune disease, or drug toxicity.

Treatment strategies

Erythropoiesis-stimulating agents (ESA)

The human *EPO* gene was isolated in 1985, with commercial production of rHuEPO beginning soon thereafter. In 1987, a seminal paper was published in the *New England Journal of Medicine* reporting that rHuEPO was effective in raising Hb and eliminating the need for chronic transfusions in 25 adult patients on hemodialysis [49]. Epogen was subsequently approved by the US Food and Drug Administration (FDA) for treating anemia in CKD in 1989 and remains a cornerstone for management to this day. The development and widespread use of rHuEPO in adults and children eliminated dependence on RBC transfusions, which was complicated by transfusion-associated viral infections, iron overload, and allosensitization. However, treatment with an ESA alone is usually not sufficient; as noted above, up to 40% of children with advanced CKD demonstrate persistently low Hb levels while being treated with an ESA [4]. Contributing factors for persistent anemia despite ESA therapy include iron deficiency/restriction, inadequate ESA dosing, and chronic inflammation.

Agents and dosing schemes

Prior to initiating treatment with an ESA in patients with CKD, other correctable (e.g., iron deficiency), non-CKD-specific causes of anemia should be ruled out. Once the need for an ESA is established, there are several types of both short- and long-acting ESAs available worldwide, and new formulations continue to emerge requiring ongoing attention to the relative safety and efficacy in children compared with adults. There is currently no definitive evidence of superiority in patient outcomes for any particular ESA brand [21]. Among rHuEPO types, epoetin alfa is commonly used in the US, with epoetin beta more commonly used in Europe [50]. Short-acting epoetin formulations generally achieve maximum efficacy when dosed 1–3 times weekly and are more effective when given SC (SC) (half-life 19–24 h) rather than IV (half-life 6–8 h) [51].

Darbepoetin alfa, an EPO analog with two additional sialic-acid-containing carbohydrates resulting in extended in vivo biological activity, shows equivalent efficacy as rHuEPO for maintaining Hb when dosed weekly or every other week [21, 30, 51, 52]. Darbepoetin alfa may be administered IV or SC, and while drug clearance, half-life, and bioavailability are similar in adults and children regardless administration route, in children, absorption when given SC may be more rapid [53]. The longer dosing interval inherent to treatment with darbepoetin compared with rHuEPO has made darbepoetin alfa SC an attractive alternative in younger children, with the potential for improving adherence because if less frequent administration. A randomized clinical trial in children with CKD stages 4 and 5 demonstrated it is as safe and effective as rHuEPO for correcting anemia [52]. A recent longitudinal European registry study similarly demonstrated no increased rates of adverse events, such as infection or severe hypertension [54]. A potential limitation is the reported discomfort associated with injection. One blinded randomized controlled trial demonstrated higher levels of postinjection pain on the visual analog scale (VAS) compared with those receiving epoetin beta, consistent with an increased impression of pain as reported by their parents and nurses [55]. A potential explanation is the greater physiological pH of the buffer in epoetin beta preparation [49]. Other pediatric studies did not report pain to be more frequent or severe in patients receiving darbepoetin [52].

Alternative ESAs continue to emerge, and rHuEPO biosimilar agents show only minor differences in clinically inactive components to those of licensed products. Over the last 10+ years, several have been approved in Europe, and the FDA has developed a process for approving these agents, which will likely result in their wider entry into the US market [56]. Immunogenicity is a potential safety concern regarding biosimilar agents, and additional studies are required to examine safety and efficacy in children. In 2012, the FDA approved peginesatide, a synthetic pegylated peptide with no structural similarity to rHuEPO, for use in adults on dialysis. However, the agent was subsequently recalled after reports of fatal anaphylactic reactions [56]. An additional EPO analog is the continuous EPO receptor activator (CERA) that integrates a large methoxy polyethylene glycol polymer chain into the EPO molecule, resulting in a higher molecular weight and extended circulating half-life of up to 130 h [57]. A study in children on peritoneal dialysis (PD) demonstrated that CERA safely and effectively maintained Hb levels when dosed once or twice monthly, although doses required to meet goal Hb levels were higher than those required in published adult studies [57].

The KDIGO clinical practice guideline for anemia recommends that Hb concentration at which to begin ESA therapy must consider the benefits and risks for the individual patient. KDIGO recommends that ESA initiation in adults be considered for Hb levels persistently <10 g/dl and that Hb levels <9 g/dl in dialysis patients should be avoided [21]. A specific Hb level to trigger ESA initiation in children is not provided, as the guideline recommends considering the potential benefits vs. harms of starting the therapy. However, in clinical practice, the 10-g/dl threshold is often applied to children as

well [21]. The goal after ESA initiation is for a rate of increase in Hb concentration of no more than 1–2 g/dl per month [21]. In children on ESA therapy, the target Hb level should be 11–12 g/dl, largely based on results of observational data demonstrating a relationship between lower Hb values and poorer patient outcomes [1, 21, 58]. The starting dose for epoetin alfa or beta is generally 20–50 IU/kg three times weekly (SC or IV), whereas the initial recommended darbepoetin alfa dose is 0.45 μg/kg IV or SC once weekly or 0.75 μg/kg every 2 weeks SC [21]. The dosing requirements of rHuEPO may differ substantially between children and adults. Based on registry data, young children require higher weight-related rHuEPO doses than adults, ranging from 275 to 350 U/kg/week for infants to 200–250 U/kg/week for older children [40]. Children and adolescents on chronic hemodialysis also require higher absolute doses than adults to maintain target Hb levels despite lower body weight [59, 60]. In contrast to typical drug dosing in children, which is based on body size to account for a decreased volume of distribution, rHuEPO dose requirements appear to be independent of weight [60, 61]. The potential mechanisms for increased dose requirement in children are not clear but may include increased presence of nonhematopoietic EPO binding sites (e.g., endothelial, kidney, brain, skeletal muscle cells) resulting in increased drug clearance, or increased EPO demand during periods of accelerated body growth [40, 61]. Data from the IPPN showed that the weekly ESA dose scaled to body weight was inversely correlated with age, but when normalized to body surface area (BSA), dose was independent of age, with a median [interquartile range (IQR)] weekly ESA dose of 4208 (2582–6863) U/m^2 [9]. An absolute rHuEPO dose of 1000 U given IV to both adults and children can increase Hb by 0.4 g/dl, suggesting that dosing schemes based on Hb deficit rather than weight may be useful [61]. Finally, studies in adults with nondialysis CKD have shown epoetin alfa administered SC at higher doses but extended intervals (20,000–80,000 U every 2 or 4 weeks) to be as effective as weekly dosing regimens [62, 63]. This could be an attractive option for allowing less frequent ESA dosing in regions where darbepoetin alfa is not readily available, although extended-interval epoetin alfa dosing has not yet been systematically assessed in children.

ESA dose adjustments after treatment initiation should generally be done after the first 4 weeks of therapy and no more often than every 2 weeks—in the outpatient setting—as the effects of therapy are not likely to be seen after shorter intervals [21]. Decisions on dosing adjustments should be made based on the rate of Hb increase after initiation and the stability of Hb during maintenance therapy [21]. When a decrease in Hb is necessary, ESA dose should be decreased but not necessarily held, as a pattern of holding and reinitiating ESA therapy can lead to Hb cycling around the desired target range [64]. Long-acting ESAs like darbepoetin alfa, with its increased half-life and lower binding affinity for the EPO receptor, stimulate erythropoiesis for longer periods and thus may increase Hb levels higher than intended. This can be avoided by using lower starting doses and making less frequent dose adjustments than in children treated with short-acting ESAs [51].

Safety of ESA therapy

Although ESA use is associated with multiple benefits, including a decreased need for RBC transfusions in patients with CKD and end-stage renal disease (ESRD), clinical trials conducted in adults have raised concerns about the safety of using escalating ESA doses to normalize Hb levels. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) trial, for example, performed in adults with nondialysis CKD, found that treatment with epoetin alfa to a target Hb 13.5 g/dl vs. 11.3 g/dl was associated with an increased risk for the composite primary outcome of death, myocardial infarction, stroke, or hospitalization for congestive heart failure [65]. In 2009, results of the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) were published in which >4000 adults with diabetes and CKD were randomized to receive either darbepoetin alfa to achieve Hb levels >13 g/dl or placebo; the treatment demonstrated an increased risk for stroke [66]. Based on evidence from these and other trials, the US FDA changed the ESA product labeling in 2011 to recommend use of the lowest possible ESA dose to prevent transfusions in contrast to attaining any target Hb level and that the dose should be reduced or interrupted for Hb levels >11 g/dl [67]. The label change did not distinguish between pediatric and adult CKD patients. No clinical trials in adults have clarified whether a higher Hb level or a higher ESA dose specifically contributes to adverse outcomes, although it is interesting that a prospective study in adults on hemodialysis found that patients with naturally occurring higher Hb levels (>12 g/dl) were not at increased risk for mortality [68, 69]. The precise mechanisms for the adverse cardiovascular outcomes observed with ESA use have not been defined but may include trophic effects on vascular endothelial or smooth muscle cells [70].

Observational studies in pediatric dialysis patients have demonstrated associations between higher ESA doses and an increased risk for all-cause mortality. In the IPPN registry, patient survival was inversely correlated with ESA dose, and survival was significantly decreased in patients receiving cumulative weekly ESA doses >6000 IU/m^2 compared with those receiving less [9]. In another analysis performed in 829 prevalent pediatric US chronic dialysis patients, including patients on both hemodialysis and peritoneal dialysis <18 years, those receiving rHuEPO doses ≥350 U/kg/week or darbepoetin ≥1.5 U/kg week had more than a three times higher risk for mortality over 18 months compared with those receiving lower doses [71]. In both studies, the link between

higher ESA doses and mortality was independent of achieved Hb level, which could be taken to suggest that higher ESA doses may carry increased risks even in young patients without pre-existing cardiovascular disease. However, no randomized controlled trials examining the effects of ESA administration or achieved Hb level on clinical outcomes, including mortality, have been performed in children with CKD; given results from adult trials, this is unlikely to occur. Thus, current recommendations regarding safe target Hb levels in children treated with ESA are extrapolated from adult trials.

ESA-induced pure RBC aplasia (PRCA) is an increasingly rare hematologic disorder first described in the late 1990s. PRCA is characterized by severe and progressive normocytic anemia, reticulocytopenia, and almost complete absence of erythroid precursors in bone marrow, with affected patients becoming transfusion dependent [72]. ESA-induced PRCA is secondary to the development of neutralizing antibodies, which block the interaction between an ESA (including epoetin alfa or beta, darbepoetin alfa, anf endogenous EPO) and its receptor [72]. Most initial cases of ESA-induced PRCA were seen in countries in which epoetin alfa formulated with a polysorbate 80 stabilizer was administered to CKD patients SC, and regulatory advisories have subsequently discouraged this practice [73].

Iron therapy

Assessment of iron stores (challenges)

In clinical practice, the most commonly used biomarkers of stored iron are ferritin, serum iron, and transferrin saturation (TSAT). Distinguishing hepcidin-mediated impaired iron trafficking from absolute iron deficiency anemia can present a clinical challenge, as both disorders can be characterized by anemia that may be microcytic, with low reticulocyte counts, decreased serum iron concentration, and low transferrin saturation. Serum ferritin levels can be helpful in distinguishing the disorders; absolute iron deficiency is associated with a low ferritin concentration, while impaired trafficking is characterized by normal or elevated serum ferritin, reflecting iron sequestration in the reticuloendothelial system. In contrast, in patients with functional iron deficiency on ESA therapy, the rate of enteral iron absorption or release from reticuloendothelial cells is inadequate to meet the demands for erythropoiesis; these patients often have low TSAT values with normal or high levels of ferritin, and selected patients may benefit from IV iron administration [28, 74]. The limitations of serum ferritin as a marker of accessible stored iron are, however, well established in the literature, including higher ferritin levels being associated with lower Hb values and ferritin serving as an acute-phase reactant [9, 75]. Although we measure ferritin in serum, its function is as an intracellular iron-storage protein, and though we assume that serum concentrations reflect some steady-state "leakage" of intracellular ferritin, the process by which ferritin enters the circulation is not well understood [76]. TSAT has recognized limitations also, including diurnal fluctuations, and reduction in the setting of malnutrition and chronic disease [77]. There is, in turn, a need for diagnostic tests that could more accurately predict the need for or response to iron therapy. A recent study in pediatric dialysis patients found that the reticulocyte hemoglobin content (Ret-He), which is not an acute-phase reactant and reflects iron availability for incorporation into reticulocytes over the previous 2–4 days, performed better than either ferritin or TSAT to distinguish between iron deficiency and suboptimal ESA dosing [77]. Thus, Ret-He may be an attractive alternative indicator of iron status in clinical practice.

Iron supplementation

Iron can be supplemented enterally or IV. The usual dosing range for iron orally is 3–6 mg/kg day of elemental iron divided into two daily doses; coadministration of iron supplements with phosphate binders or antacids can limit absorption due to changes in gastric pH [43]. While enteral iron supplementation is relatively inexpensive, highly available, safe, and is efficacious in many children with CKD, those with more advanced disease or especially those on hemodialysis often benefit from iron preparations administered IV due to poor enteral absorption or poor tolerance for the oral administration. There in an increasing number of available choices for clinicians opting for IV therapy (Table 4). Early compounds were formulated as inorganic iron oxyhydroxide complexes, which could result in the release of labile iron directly into plasma and formation of highly reactive free radicals associated with potentially severe toxicity, including hypotension. Currently available formulations surround the iron oxyhydroxide core with carbohydrate shells of different sizes and polysaccharide branch characteristics [78]. The shell characteristics determine how long the iron remains circulating, with larger molecular weight formulations such as iron dextran resulting in longer residence in plasma [79]. IV treatment can be delivered as a loading phase, using consecutive doses to replace a patient's iron stores, or as smaller maintenance doses given weekly.

Safety of iron supplementation

Given trial evidence in adults that higher ESA doses are associated with adverse cardiovascular outcomes, using iron administered IV to reduce ESA dose requirements is an attractive treatment option. However, there is a shortage of clinical studies to evaluate the effect of differences in formulation and pharmacokinetics of such agents and to determine whether repeated induction of oxidative stress has longer-term sequelae in terms of inflammation and cellular and tissue iron deposition. A study in adults with CKD found an increased

Table 4 Physiochemical characteristics and pharmacokinetics of iron formulations for intravenous administration

Properties	Ferumoxytol	Ferric carboxy maltose	Iron dextran	Iron sucrose	Ferric gluconate
Molecular mass (D)	731,000	150,000	410,000	252,000	200,000
Carbohydrate shell	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Dextran polysaccha-ride	Sucrose	Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)	26.3	23.1	12.2	8.3	8.6
Relative catalytic iron release	+	+	++	+++	+++
Relative stability of elemental iron within the carbohydrate shell	High	High	High	Medium	Low
Relative osmolality	Isotonic	Isotonic	Isotonic	Hypertonic	Hypertonic
Administration (IV push) rates	30 mg/s	Bolus push	50 mg (1 ml)/min	~20 mg/min	12.5 mg/min
$t_{1/2}$ (h)	~15	7–12	5–20	6	~1

With permission [76]

incidence of anaphylactoid reactions in those treated with iron dextran IV compared with those receiving sodium ferric gluconate complex or iron sucrose, but this has not been evaluated in children [79]. In clinical practice, administration of iron therapy IV is often avoided during acute infections due to concern that it may increase patient risk. There is biologic plausibility for this practice, as iron may impair neutrophil and T-cell function and serve as a growth factor for pathogens [80]. However, few studies have tested this association. One retrospective cohort study based on data from 23,000 adult hemodialysis patients in the US Renal Data System registry and who had been hospitalized for bacterial infections and received iron therapy IV prior to admission, found that continuation of after admission was not associated with longer length of stay, readmission or death related to infection within 30 days, or increased risk for all-cause mortality compared with those who were discontinued [80]. Although fewer studies have been conducted in children than in adults, short-term clinical trials in children demonstrate the safety and efficacy of iron therapy IV when used to increase ferritin and TSAT levels (as biomarkers of iron status) and Hb and thus reduce the required ESA dose [81–83].

Emerging therapies

Given the limitations of ESAs and conventional iron supplementation for treating CKD-related anemia, a number of novel therapies are in varying stages of development. Small-molecule HIF stabilizers/prolyl hydroxylase domain inhibitors modulate HIF-controlled gene products, including EPO, and are capable of inducing endogenous EPO production [84]. Inhibitors of HIF prolyl hydroxylases can be administered orally via highly bioavailable preparations and have been shown in clinical trials conducted in adults to increase endogenous EPO production, increase Hb, and decrease hepcidin [84–86]. Investigational strategies for direct hepcidin modulation include monoclonal antibodies aimed directly at hepcidin or at the inflammatory stimuli that induce its production, including IL-6 [86]. Fully human antihepcidin antibodies have been successfully developed and applied in animal models [87]. Also under investigation are other bioavailable iron preparations delivered IV or in dialysate. Ferric pyrophosphate citrate, a novel, carbohydrate-free, water-soluble, complex iron salt that can be administered via the dialysate was approved by the FDA in 2015 and has shown good efficacy and safety in adults on hemodialysis [88]. This mode of iron delivery provides smaller amounts of iron over hours compared with supplementation IV, which may help avoid oxidative toxicity [88]. Ferric citrate is a novel phosphate binder available orally that also supplies elemental iron and has the potential benefit of providing therapy for at least two CKD comorbidities in a single agent—a potentially adherence-enhancing strategy. The ferric ion in ferric citrate combines with dietary phosphorus in the GI tract, but excess ferric ions are reduced by the bowel mucosa to ferrous iron and absorbed into the systemic circulation [89]. Although ferric pyrophosphate citrate and ferric citrate orally are approved for adults, their safety and efficacy have yet to be systematically assessed in children.

Treatment-resistant anemia/ESA hyporesponsiveness

There are patients who, despite iron supplementation combined with escalating ESA therapy, do not reach even a minimum Hb goal. KDIGO defines initial ESA hyporesponsiveness as no increase in Hb concentration from baseline after the first month of appropriate weight-based dosing and acquired ESA hyporesponsiveness as a requirement for two increases in ESA doses up to 50% beyond the dose at which they had previously remained stable to maintain a stable Hb

concentration [21]. An alternative definition is a persistent Hb deficit after 3 months of high-dose ESA treatment (rHuEPO >400 U/kg weekly or darbepoetin alfa >1 μg/kg weekly [90, 91]). In the IPPN registry, ESA resistance and escalated ESA dosing was associated with inflammation, fluid retention, and hyperparathyroidism [9]. The observational association between higher ESA doses and mortality in pediatric patients may, in turn, reflect the impact of chronic inflammatory processes that negatively impact patient survival, rather than a direct ESA effect on the risk for death. While ESA hyporesponsiveness may be chronic, it can also be seen in the context of shorter-term clinical events, such as infections or surgical procedures, which may negatively impact response to ESA therapy. Thus, the potential risks and benefits of escalation in ESA dose vs. iv administration of iron vs. RBC transfusion in this setting must be assessed for individual patients [21].

Posttransplant anemia

Although the endogenous production of EPO increases after successful renal transplantation, posttransplant anemia (PTA) remains an active clinical problem for many children. Anemia in the early period (< 3 months) can be secondary to surgical blood loss and associated iron deficiency, treatment-resistant anemia pretransplant, delayed graft function, OR high-intensity immunosuppression [92, 93]. Estimates of the prevalence of late PTA, occurring ≥3–6 months following transplant, vary but have been reported in as many as 50–70% of children [93, 94]. Late PTA has been associated with impaired graft function, iron deficiency, and drug-site effects [93]. Transplant patients may be more susceptible to the effects of ACE inhibitors when on RBC synthesis, and immunosuppressive drugs also contribute to the risk for anemia [93]. Mycophenolate mofetil (MMF) has direct antiproliferative effects on the bone marrow and its use has specifically been associated with an increased risk for PTA. The wide variability in reported rates of PTA may be due in part to variations is dosing [93, 94]. Genetic factors may also play a role in MMF-related anemia; single-nucleotide polymorphisms (SNPs) in the genes producing IL-12A and cytochrome P450 (CYP) 2C8 are associated with increased risk after kidney transplant [94]. Given that anemic transplant recipients are at risk for adverse consequences in terms of QoL, cardiovascular morbidity, and, by some reports, graft survival, their anemia should be evaluated and treated [93].

Key summary points

1. The primary causes of the anemia in CKD are impaired erythropoietin production and hepcidin-mediated iron-restricted erythropoiesis.
2. Current therapeutic challenges include dosing ESAs conservatively to maintain Hb levels in the narrow range of 11–12 g/dl and the limitations of using serum ferritin and TSAT as accurate indicators of accessible stored iron.
3. HIF stabilizers, antihepcidin monoclonal antibodies, and dialysate-based iron supplements are under investigation and may provide future therapeutic alternatives.
4. Anemia resistant to ESA treatment is common, and the risks and benefits of ESA dose escalation vs. iron IV vs. RBC transfusion must be determined based on the individual patient's needs.

Multiple choice questions (answers are provided following the reference list)

1. The primary site of endogenous EPO production in children is:

   a. Hepatocytes
   b. Peritubular interstitial cells
   c. Renal tubular epithelial cells
   d. Bone marrow erythroid progenitors
2. HIF-1 regulates EPO production by binding to:

   a. *HAMP* mRNA
   b. Ferroportin channels
   c. Hypoxia response element on the *EPO* gene
   d. BMP-SMAD
3. Iron-restricted erythropoiesis includes:

   a. Absolute iron deficiency
   b. Depletion of iron stores by ESA-stimulated bone marrow
   c. Impaired iron trafficking with inflammation
   d. All of the above
4. Short-acting rHuEPO formulations have longer half-lives and are more effective when administered:

   a. SC
   b. IV
   c. Enterally
   d. In dialysate
5. Which is NOT associated with anemia after renal transplant?

   a. Iron deficiency
   b. Immunosuppressive medications
   c. Persistent acidosis
   d. Surgical blood loss

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Compliance with ethical standards

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References

1. Amaral S, Hwang W, Fivush B, Neu A, Frankenfield D, Furth S (2006) Association of mortality and hospitalization with achievement of adult hemoglobin targets in adolescents maintained on hemodialysis. J Am Soc Nephrol 17(10):2878–2885
2. Schaefer F (2008) Cardiac disease in children with mild-to-moderate chronic kidney disease. Curr Opin Nephrol Hypertens 17(3):292–297
3. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascock BJ, Khoury PR, Daniels SR (2006) Progression of left ventricular hypertrophy in children with early chronic kidney disease: 2-year follow-up study. J Pediatr 149(5):671–675
4. Atkinson MA, Martz K, Warady BA, Neu AM (2010) Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS. Pediatr Nephrol 25(9):1699–1706
5. Staples AO, Wong CS, Smith JM, Gipson DS, Filler G, Warady BA, Martz K, Greenbaum LA (2009) Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol 4(1):48–56
6. Fadrowski JJ, Pierce CB, Cole SR, Moxey-Mims M, Warady BA, Furth SL (2008) Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. Clin J Am Soc Nephrol 3(2): 457–462
7. Warady BA, Abraham AG, Schwartz GJ, Wong CS, Muñoz A, Betoko A, Mitsnefes M, Kaskel F, Greenbaum LA, Mak RH, Flynn J, Moxey-Mims MM, Furth S (2015) Predictors of rapid progression of glomerular and Nonglomerular kidney disease in children and adolescents: the chronic kidney disease in children (CKiD) cohort. Am J Kidney Dis 65(6):878–888
8. Naito M, Kawashima A, Akiba T, Takanashi M, Nihei H (2003) Effects of an angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitors on burst forming U-erythroid in chronic hemodialysis patients. Am J Nephrol 23(5):287–293
9. Borzych-Duzalka D, Bilginer Y, Ha IS, Bak M, Rees L, Cano F, Munarriz RL, Chua A, Pesle S, Emre S, Urzykowska A, Quiroz L, Ruscasso JD, White C, Pape L, Ramela V, Printza N, Vogel A, Kuzmanovska D, Simkova E, Müller-Wiefel DE, Sander A, Warady BA, Schaefer F, International Pediatric Peritoneal Dialysis Network (IPPN) Registry (2013) Management of anemia in children receiving chronic peritoneal dialysis. J Am Soc Nephrol 24(4):665–676
10. Atkinson MA, Pierce CB, Zack RM, Barletta GM, Yadin O, Mentser M, Warady BA, Furth SL (2010) Hemoglobin differences by race in children with CKD. Am J Kidney Dis 55(6):1009–1017
11. Robins EB, Blum S (2007) Hematologic reference values for african american children and adolescents. Am J Hematol 82(7):611–614
12. Warady BA, Ho M (2003) Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 18(10):1055–1062
13. Mitsnefes M, Flynn J, Cohn S, Samuels J, Blydt-Hansen T, Saland J, Kimball T, Furth S, Warady B, CKiD Study Group (2010) Masked hypertension associates with left ventricular hypertrophy in children with CKD. J Am Soc Nephrol 21(1):137–144
14. Matteucci MC, Wühl E, Picca S, Mastrostefano A, Rinelli G, Romano C, Rizzoni G, Mehls O, de Simone G, Schaefer F, ESCAPE Trial Group (2006) Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol 17(1):218–226
15. Gerson A, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush B, Furth S (2004) Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 44(6):1017–1023
16. Yabu JM, Anderson MW, Kim D, Bradbury BD, Lou CD, Petersen J, Rossert J, Chertow GM, Tyan DB (2013) Sensitization from transfusion in patients awaiting primary kidney transplant. Nephrol Dial Transplant 28(11):2908–2918
17. Obrador GT, Macdougall IC (2013) Effect of red cell transfusions on future kidney transplantation. Clin J Am Soc Nephrol 8(5):852–860
18. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C, Centers for Disease Control and Prevention, National Center for Health Statistics (2005) Hematological and iron-related analytes–reference data for persons aged 1 year and over: United states, 1988-94. Vital Health Stat 11(247):1–156
19. Jackson RT (1990) Separate hemoglobin standards for blacks and whites: a critical review of the case for separate and unequal hemoglobin standards. Med Hypotheses 32(3):181–189
20. Filler G, Mylrea K, Feber J, Wong H (2007) How to define anemia in children with chronic kidney disease? Pediatr Nephrol 22(5): 702–707
21. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group (2012) KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2:279–335
22. Foley RN (2008) Erythropoietin: physiology and molecular mechanisms. Heart Fail Rev 13:405–414
23. Koury MJ, Haase VH (2015) Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol 11: 394–410
24. Donnelly S (2001) Why is erythropoietin made in the kidney? The kidney functions as a *Critmeter*. Am J Kid Dis 38(2):415–425
25. Locatelli F, Fishbane S, Block GA, Macdougall IC (2017) Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease Pateints. Am J Nephrol 45(3):187–199
26. Sangkhae V, Nemeth E (2017) Regulation of the iron homeostatic hormone Hepcidin. Adv Nutr 8(1):126–136
27. Camaschella C, Pagani A, Nai A, Silvestri L (2016) The mutual control of iron and erythropoiesis. Int J Lab Hematol 38S1:20–26
28. Goodnough LT, Nemeth E, Ganz T (2010) Detection, evaluation, and management of iron-restricted erythropoiesis. Blood 116(23): 4754–4761
29. Greenbaum LA (2005) Anemia in children with chronic kidney disease. Adv Chronic Kidney Dis 12(4):385–396
30. Atkinson MA, Furth SL (2011) Anemia in children with chronic kidney disease. Nat Rev Nephrol 7(11):635–641
31. Poli M, Asperti M, Ruzzenenti P, Regoni M, Arosio P (2014) Hepcidin antagonists for potential treatments of disorders with hepcidin excess. Front Pharmacol 5:86
32. Atkinson MA, White CT (2012) Hepcidin in anemia of chronic kidney disease: review for the pediatric nephrologist. Pediatr Nephrol 27(1):33–40
33. Ganz T (2003) Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 102(3):783–788
34. Atkinson MA, Kim JY, Roy CN, Warady BA, White CT, Furth SL (2015) Hepcidin and risk of anemia in CKD: a cross-sectional and longitudinal analysis in the CKiD cohort. Pediatr Nephrol 30(4): 635–643
35. Zaritsky J, Young B, Wang HJ, Westerman M, Olbina G, Nemeth E, Ganz T, Rivera S, Nissenson AR, Salusky IB (2009) Hepcidin–a

potential novel biomarker for iron status in chronic kidney disease. Clin J Am Soc Nephrol 4(6):1051–1056
36. Zaritsky J, Young B, Gales B, Wang HJ, Rastogi A, Westerman M, Nemeth E, Ganz T, Salusky IB (2010) Reduction of serum hepcidin by hemodialysis in pediatric and adult patients. Clin J Am Soc Nephrol 5(6):1010–1014
37. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, Nayak A, Wesseling-Perry K, Westerman M, Hollis BW, Saluskt IB, Hewison M (2014) J Am Soc Nephrol 25(3):564–572
38. Atkinson MA, Juraschek SP, Bertenthal MS, Detrick B, Furth SL, Miller ER 3rd (2016) Pilot study of the effect of cholecalciferol supplementation on hepcidin in children with chronic kidney disease. Pediatr Nephrol. doi:10.1007/s00467-016-3563-6
39. Nangaku M, Eckardt KU (2006) Pathogenesis of renal anemia. Semin Nephrol 26(4):261–268
40. Koshy SM, Geary DF (2008) Anemia in children with chronic kidney disease. Pediatr Nephrol 23(2):209–219
41. Rao DS, Shih MS, Mohini R (1993) Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. N Engl J Med 328(3):171–175
42. Chutia H, Ruram AA, Bhattacharyya H, Boruah P, Nath C (2013) Association of secondary hyperparathyroidism with hemoglobin level in patients with chronic kidney disease. J Lab Phys 5(1):51–54
43. Yorgin PD, Zaritsky J (2012) Management of Renal Anemia in children with chronic kidney disease. In: Warady BA, Schaefer F, Alexander SA (eds) Pediatric dialysis, 2nd edn. Springer, New York, pp 531–568
44. Bamgbola O, Kaskel F (2005) Role of folate deficiency on erythropoietin resistance in pediatric and adolescent patients on chronic dialysis. Pediatr Nephrol 20(11):1622–1629
45. Calo LA, Vertolli U, Davis PA, Savica V (2012) L carnitine in hemodialysis patients. Hemodial Int 16(3):428–434
46. Raimann JG, Levin NW, Craig RG, Sirover W, Kotanko P, Handelman G (2013) Is vitamin C intake too low in dialysis patients? Semin Dial 26(1):1–5
47. Nasr SH, Kashtanova Y, Levchuk V, Markowitz GS (2006) Secondary oxalosis due to excessive vitamin C intake. Kidney Int 70(10):1672
48. Lazarchick J (2012) Update on anemia and neutropenia in copper deficiency. Curr Opin Hematol 19(1):58–60
49. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW (1987) Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. N Engl J Med 316(2):73–78
50. Covic A, Cannata-Andia J, Cancarini G, Coppo R, Frazão JM, Goldsmith D, Ronco P, Spasovski GB, Stenvinkel P, Utas C, Wiecek A, Zoccali C, London G (2008) Biosimilars and biopharmaceuticals: what the nephrologists need to know–a position paper by the ERA-EDTA council. Nephrol Dial Transplant 23(12):3731–3737
51. Horl WH (2013) Differentiating factors between erythropoiesis-stimulating agents: an update to selection for anaemia of chronic kidney disease. Drugs 73(2):117–130
52. Warady BA, Arar MY, Lerner G, Nakaniski AM, Stehman-Breen C (2006) Darbepoetin alfa for the treatment of anemia in pediatric patients with chronic kidney disease. Pediatr Nephrol 21(8):1144–1152
53. Anemia in Chronic Kidney Disease Work Group (2006) KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 47(Supplement 3):S1–S146
54. Schaefer F, Hoppe B, Jungraithmayr T, Klaus G, Pape L, Farouk M, Addison J, Manamley N, Vondrak K (2016) Safety and usage of darbepoetin alfa in children with chronic kidney disease: prospective registry study. Pediatr Nephrol 31:443–453
55. Schmitt CP, Nau B, Brummer C, Rosenkranz J, Schaefer F (2006) Increased injection pain with darbepoetin-alpha compared with epoetin-beta in paediatric dialysis patients. Nephrol Dial Transplant 21(12):3520–3524
56. Wish JB, Charytan C, Chertow GM, Kalantar-Zadeh K, Kliger AS, Rubin RJ, Yee J, Fishbane S (2016) Introduction of biosimilar therapeutics into Nephrology practice in the United States: report of a scientific workshop sponsored by the National Kidney Foundation. Am J Kidney Dis 68(6):843–852
57. Cano F, Alarcon C, Azocar M, Lizama C, Lillo AM, Delucchi A, Gonzalez M, Arellano P, Delgado I, Droguett MT (2011) Continuous EPO receptor activator therapy of anemia in children under peritoneal dialysis. Pediatr Nephrol 26(8):1303–1310
58. Warady MA, Ho M (2003) Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 18(10):1055–1062
59. Bamgbola OF, Kaskel FJ, Coco M (2009) Analyses of age, gender and other risk factors of erythropoietin resistance in pediatric and adult dialysis cohorts. Pediatr Nephrol 24(3):571–579
60. Port RE, Kiepe D, Van Guilder M, Jelliffe RW, Mehls O (2004) Recombinant human erythropoietin for the treatment of renal anaemia in children: no justification for bodyweight-adjusted dosage. Clin Pharmacokinet 43(1):57–70
61. Port RE, Mehls O (2009) Erythropoietin dosing in children with chronic kidney disease: based on body size or on hemoglobin deficit? Pediatr Nephrol 24(3):435–437
62. McGowan T, Vaccaro NM, Beaver JS, Massarella J, Wolfson M (2008) Pharmacokinetic and Pharmacodynamic profiles of extended dosing of Epoetin alfa in anemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol 3: 1006–1014
63. Pergola PE, Gartenberg G, Fu M, Sun S, Wolfson M, Bowers P (2010) A randomized controlled study comparing once-weekly to every-2-week and every-4-week dosing of Epoetin alfa in CKD patients with anemia. Clin J Am Soc Nephrol 5:598–606
64. Fishbane S, Berns JS (2005) Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 68(3):1337–1343
65. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, Investigators CHOIR (2006) Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 355:2085–2098
66. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R, Investigators TREAT (2009) A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 361(21):2019–2032
67. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, Szczech L (2013) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. Am J Kidney Dis 62(5):849–859
68. Badve SV, Hawley CM, Johnson DW (2011) Is the problem with the vehicle or the destination? Does high-dose ESA or high haemoglobin contribute to poor outcomes in CKD? Nephrology (Carlton) 16(2):144–153
69. Goodkin DA, Fuller DS, Robinson BM, Combe C, Fluck R, Mendelssohn D, Akizawa T, Pisoni RL, Port FK (2011) Naturally occurring higher hemoglobin concentration does not increase mortality among hemodialysis patients. J Am Soc Nephrol 22(2):358–365
70. Unger EF, Thompson AM, Blank MJ, Temple R (2010) Erythropoiesis-stimulating agents–time for a reevaluation. N Engl J Med 362(3):189–192
71. Lestz RM, Fivush BA, Atkinson MA (2014) Association of higher erythropoiesis stimulating agent dose and mortality in children on dialysis. Pediatr Nephrol 29(10):2021–2028
72. Pollock C, Johnson DW, Horl WH, Rossert J, Casadevall N, Schellenkens H, Delage R, De Francisco A, Macdougall I,

Thorpe R, Toffelmire E (2008) Pure red cell aplasia induced by erythropoiesis-stimulating agents. Clin J Am Soc Nephrol 3(1): 193–199
73. Bennett CL, Starko KM, Thomsen HS, Cowper S, Sartor O, Macdougall IC, Qureshi ZP, Bookstaver PB, Miller AD, Norris LB, Xirasagar S, Trenery A, Lopez I, Kahn A, Murday A, Luminari S, Cournoyer D, Locatelli F, Ray P, Mattison DR (2012) Linking drugs to obscure illnesses: lessons from pure red cell aplasia, nephrogenic systemic fibrosis, and reye's syndrome. A report from the southern network on adverse reactions (SONAR). J Gen Intern Med 27(12):1697–1703
74. Babitt JL, Lin HY (2012) Mechanisms of anemia in CKD. J Am Soc Nephrol 23(10):1631–1634
75. Atkinson MA, Pierce CB, Fadrowski JJ, Benador NM, White CT, Turman MA, Pan CG, Abraham AG, Warady BA, Furth SL (2012) Association between common iron store markers and hemoglobin in children with chronic kidney disease. Pediatr Nephrol 27(12): 2275–2283
76. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH (2006) The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? Clin J Am Soc Nephrol Suppl 1:9–18
77. Davidkova S, Prestidge TD, Reed PW, Kara T, Wong W, Prestidge C (2016) Comparison of reticulocyte hemoglobin equivalent with traditional markers of iron and erythropoiesis in pediatric dialysis. Pediatr Nephrol 31(5):819–826
78. Charytan DM, Pai AB, Chan CT, Coyne DW, Hung AM, Kovesdy CP, Fishbane S, Dialysis Advisory Group of the American Society of Nephrology (2015) Considerations and challenges in defining optimal iron utilization in hemodialysis. J Am Soc Nephrol 26(6): 1238–1247
79. Anirban G, Kohli HS, Jha V, Gupta KL, Sakhuja V (2008) The comparative safety of various intravenous iron preparations in chronic kidney disease patients. Ren Fail 30(6):629–638
80. Ishida JH, Marafino MJ, McCulloch CE, Dalrymple LS, Dudley RA, Grimes BA, Johansen KL (2015) Receipt of intravenous iron and clinical outcomes among hemodialysis patients hospitalized for infection. Clin J Am Soc Nephrol 10(10):1799–1805
81. Warady BA, Kausz A, Lerner G, Brewer ED, Chadha V, Brugnara C, Dahl NV, Watkins SL (2004) Iron therapy in the pediatric hemodialysis population. Pediatr Nephrol 19(6):655–661
82. Warady BA, Zobrist RH, Wu J, Finan E, Ferrlecit Pediatric Study Group (2005) Sodium ferric gluconate complex therapy in anemic children on hemodialysis. Pediatr Nephrol 20(9):1320–1327
83. Goldstein SL, Morris D, Warady BA (2013) Comparison of the safety and efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young adults with CKD: a randomized controlled trial. Am J Kidney Dis 61(4):588–597
84. Brigandi RA, Johnson B, Oei C, Westerman M, Olbina G, de Zoysa J, Roger SD, Sahay M, Cross N, McMahon L, Guptha V, Smolyarchuk EA, Singh N, Russ SF, Kumar S on behalf of the PHI112844 Investigators (2016) A novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: a 28-day, phase 2A randomized trial. Am J Kidney Dis 67(6):861–871
85. Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, Chan DTM, Leong R, Poole L, Zhong M, Saikali KG, Franco M, Hemmerich S, Yu K-HP, Neff TB (2016) Roxadustat (FG-4592): correction of anemia in incident dialysis patients. J Am Soc Nephrol 27:1225–1233
86. Schmid H, Jelkmann W (2016) Investigational therapies for renal disease-induced anemia. Expert Opin Investig Drugs 25(8):901–916
87. Cooke KS, Hinkle B, Salimi-Moosavi H, Foltz I, King C, Rathanaswami P, Winters A, Steavenson S, Begley CG, Molineux G, Sasu BJ (2013) A fully human antihepcidin antibody modulates iron metabolism in both mice and nonhuman primates. Blood 122(17):3054–3061
88. Shah HH, Hazzan AD, Fishbane S (2016) Ferric pyrophosphate citrate: a novel iron replacement agent in patients undergoing hemodialysis. Semin Nephrol 36(2):124–129
89. Yagil Y, Fadem SZ, Kant KS, Bhatt U, Sika M, Lewis JB, Negoi D, for the Collaborative Study Group (2015) Managing hyperphosphatemia in patients with chronic kidney disease on dialysis with ferric citrate: latest evidence and clinical usefulness. Ther Adv Chronic Dis 6(5):252–263
90. Gilbertson DT, Peng Y, Arneson TJ, Dunning S, Collins AJ (2013) Comparison of methodologies to define hemodialysis patients hyporesponsive to epoetin and impact on counts and characteristics. BMC Nephrol 14:44
91. Bamgbola O (2012) Resistance to erythropoietin-stimulating agents: etiology, evaluation, and therapeutic considerations. Pediatr Nephrol 27(2):195–205
92. Bamgbola O (2016) Spectrum of anemia after kidney transplantation: pathophysiology and therapeutic implications. Clin Transpl 30:1185–1194
93. Krause I, Davodovits M, Tamary H, Yutcis M, Dagan A (2016) Anemia and markers of erythropoiesis in pediatric kidney transplant recipients compared with children with chronic renal failure 2016. Pediatr Transplant 0:1–5
94. Jacobson PA, Schladt D, Oetting WS, Leduc R, Guan W, Matas AJ, Lamba V, Mannon RB, Julian BA, Israni A, Investigators DKAF (2011) Genetic determinants of mycophenolate-related anemia and leukopenia after transplantation. Transplantation 91(3):309–316

Answers to questions:

1. b
2. c
3. d
4. a
5. c