Erythropoietin-Stimulating Agent Hyporesponsiveness in Patients Living with Chronic Kidney Disease

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Abstract

Background: Erythropoietin-stimulating agent (ESA) hyporesponsiveness is commonly observed in patients with anemia secondary to chronic kidney disease (CKD). Because of its complexity, a global consensus on how we should define ESA hyporesponsiveness remains unavailable. The reported prevalence and demographic information on ESA hyporesponsiveness within the CKD population are variable with no consensus definition. **Summary:** ESA hyporesponsiveness is defined as having no increase in hemoglobin concentration from baseline after the first month of treatment on appropriate weight-based dosing. The important factors associated with ESA hyporesponsiveness include absolute or functional iron deficiency, inflammation, and uremia. Hepcidin has been demonstrated to play an important role in this process. Mineral bone disease secondary to CKD and non-iron malnutrition among other factors are also associated with ESA hyporesponsiveness. There is continued debate toward determining a gold-standard treatment pathway to manage ESA

hyporesponsiveness. The development of hypoxia-inducing factor-stabilizers brings new insights and opportunities in the management of ESA hyporesponsiveness. **Key Message:** Management of ESA hyporesponsiveness involves a comprehensive multidisciplinary team approach to address its risk factors. The progression of basic and clinical research on identifying risk factors and management of ESA hyporesponsiveness brings greater hope on finding solutions to eventually tackling one of the most difficult problems in the topic of anemia in CKD.

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Introduction

Anemia is frequently observed in patients living with advanced chronic kidney disease (CKD) and associated with adverse outcomes [1]. Since approval for use by the US FDA in 1989, erythropoietin-stimulating agents (ESAs) represent an important therapeutic agent in anemia management for advanced CKD patients. USRDS 2020 Annual Data report highlighted more than 85% of hemodialysis (HD) patients received ESA treatment [2].

ESA hyporesponsiveness remains a difficult problem in clinical practice. Currently, there is no standardized global definition to define ESA hyporesponsiveness. Since no unified definition is determined, reported prevalence of ESA hyporesponsiveness varies according to the definition applied. ESA hyporesponsiveness portrays worsened prognosis [3]. Escalating ESA doses to achieve hemoglobin (Hgb) targets may elevate cardiovascular, thrombotic, and subsequently mortality risks [4]. The complex relationship between ESA dose and Hgb levels is increasingly appreciated. Research continues to expand on the numerous factors which influence this dynamic and nonlinear relationship. Iron deficiency, inflammation, and the role of hepcidin in these processes is a recent topic of interest from the literature relating to ESA hyporesponsiveness [5, 6]. Other factors such as uremia, CKD-mineral bone disease (CKD-MBD), and non-iron malnutrition are also increasingly studied [7, 8].

Identifying factors and treating reversible causes should be initially pursued when managing ESA hyporesponsiveness [9]. Decision whether to continue ESA treatment hinges on symptom control of anemia, morbidity, quality of life status, and future opportunities of kidney transplantation [9]. The past decade has gone by with new innovations to manage anemia in CKD including achieving dialysis adequacy in HD patients through convective HD, vitamin E-bonded dialysis membrane application, and other methods to improve membrane permeability [10–12]. Progressive development of hypoxia inducible factor (HIF) prolyl-hydroxylase inhibitors (HIF-stabilizers), now in phase III clinical trials, allows for endogenous production of erythropoietin [13–15]. Administered orally, cost-effective benefits of HIF-stabilizers to manage anemia in CKD are evident [16]. There are concerns regarding carcinogenic effects of HIF-stabilizers however, and it remains to be seen whether they are the optimal solution over long term [17].

In this review, we will recap the updated definitions and prevalence of ESA hyporesponsiveness in CKD and the surrounding debate. Recent evidence relating to clinical outcomes of ESA hyporesponsiveness will be reviewed. Our latest understanding of factors contributing to ESA hyporesponsiveness will be discussed, and mechanisms of these factors will be explored. We will evaluate pathways to treat anemia in CKD and how ESA hyporesponsiveness could be minimized. Based on current evidence, we aim to conject a practical approach to address ESA hyporesponsiveness in renal anemia management and identify remaining gaps in our knowledge base which may provide future avenues of research.

Defining ESA Hyporesponsiveness in CKD

There is no consensus definition for ESA hyporesponsiveness internationally. In the revised European Best Practice Guidelines (ERBG) 2004, evaluation of ESA hyporesponsiveness in CKD patients is recommended if there is increase in erythropoietin dose $\geq 25\%$ to maintain the same Hgb level or <1 mg/dL gain in Hgb after 2–4 weeks [18]. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines defined initial ESA hyporesponsiveness as having no increase in Hgb concentration from baseline after the first month of treatment on appropriate weight-based dosing [19]. For CKD patients receiving consistent doses of ESA treatment initially, subsequent ESA hyporesponsiveness is defined as those requiring 2 instances of increased ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain similar Hgb concentration levels [19]. The Kidney Disease Outcomes Quality Initiative/National Kidney Foundation and Kidney Health Australia-Caring for Australasians with Renal Impairment guidelines currently recommend KDIGO 2012 definition for ESA unresponsiveness [20, 21]. Updated definitions of ESA hyporesponsiveness in select guidelines are summarized in Table 1 [18–23].

One quantitative measure of ESA hyporesponsiveness developed in the past 15 years is the ESA resistance index (ERI). ERI is based on a ratio between ESA dose per kilogram and Hgb level based on weekly averages [24]. It is suggested to play a role in outcome prediction and ESA dosage guidance [3, 25]. However, the validity of ERI remains controversial, and ERI is not yet advocated for use in the clinical setting by most guidelines [24].

Prevalence of ESA Hyporesponsiveness in CKD

National registry data reporting the prevalence of ESA hyporesponsiveness are currently unavailable. Anemia is expected to be more frequently observed in dialysis than in nondialysis CKD patients. In an observational study encompassing both HD and peritoneal dialysis patients, Bae et al. [26] divided ERI into tertiles to represent the degree of ESA responsiveness and noted 33% of HD or peritoneal dialysis patients were classified into the highest tertile, where the highest tertile represents patients with poorest ESA responsiveness. From other cohort studies primarily focusing in HD groups, ESA hyporesponsiveness varied between 5 and 20% in the HD population [27, 28]. Minutolo et al. [29]

Table 1. Selected definitions of ESA hyporesponsiveness in patients living with CKD

Guideline	Definition of ESA resistance
ERBG 2004 [22]	Increase in erythropoietin dose $\geq 25\%$ to maintain the same HgB level or < 1 mg/dL gain in HgB after 2–4 weeks
KDIGO 2012 [23]	Initial ESA resistance: No increase in Hgb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing Subsequent ESA resistance: If after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable HgB concentration
KDOQI/NKF guidelines on anemia in CKD [24]	As per KDIGO 2012 (refer to KDOQI US commentary on KDIGO 2012 Clinical Practice Guideline for Anemia in CKD)
KHA-CARI 2013 [25]	As per KDIGO 2012
NICE 2021 [26] and BRA 2017 [27]	An aspirational HgB range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5 μ g/kg/week of darbepoetin Or There is a continued need for the administration of high doses of ESAs to maintain the aspirational HgB range

ERBG, European Best Practice Guidelines; KDOQI, Kidney Disease Outcomes Quality Initiative; NKF, National Kidney Foundation; KDIGO, Kidney Disease Improving Global Outcome; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NICE, National Institute of Clinical Excellence; BRA, British Renal Association; HgB, hemoglobin; CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent.

conducted a prospective observational study to evaluate ESA hyporesponsiveness in nondialysis CKD patients over a 4-year period by dividing ESA responsiveness into good, intermediate, and poor categories, and observed 34% of the study cohorts were placed in the poor ESA responsiveness group.

Race was noted as a risk factor for ESA unresponsiveness in an observational study on 20,516 patients receiving HD by Okoro et al. [30] though this association is not significant when taking age, gender, and dialysis vintage into account in a multivariate model. Further work is required to evaluate ESA hyporesponsiveness across various health systems internationally and the impact of socioeconomic factors on this.

Clinical Significance of ESA Hyporesponsiveness in CKD

Over the past decade, clinical outcomes of ESA hyporesponsiveness were investigated with greater frequency. Outcomes in HD patients attracted most research attention [3, 31, 32]. In a study assessing ESA dosing and responsiveness against composite events as defined by car-

diovascular events, infection, hospitalization, and mortality, Kuragano et al. [31] have shown that elevated ESA dosage and hyporesponsiveness are correlated to increased occurrence of adverse clinical events, among 1,095 maintenance HD patients followed up over 2 years. The “RISchio Cardiovascolare nei pazienti afferenti all’Area Vasta In Dialisi” (RISCAVID) study followed up 753 patients on maintenance HD over a 36-month period in which demographic, clinical, and laboratory data; comorbidity conditions; administered drugs; all-cause mortality; and fatal and nonfatal cardiovascular events were recorded [33]. The investigators measured ERI, C-reactive protein (CRP), and interleukin-6 (IL-6) in study patients. With ERI values categorized in quartiles (quartile I < 5.6 , quartile II 5.7–9.6, quartile III 9.7–15.4, and quartile IV > 15.4), ERI demonstrated a significant correlation with all-cause mortality as well as fatal and nonfatal cardiovascular events (RR 1.97, 95% CI 1.39–2.79 and RR 1.62, 95% CI 1.12–2.33, respectively) in the RISCAVID study [33]. Furthermore, CRP levels were higher in patients with the highest quartile of ESA hyporesponsiveness, i.e., quartile IV ($p < 0.001$), and predicted all-cause mortality and cardiovascular events [33]. In the RISCAVID study, IL-6 was shown to be a strong predictor of ESA

Table 2. Potential factors of ESA hyporesponsiveness and responding treatment

Risk factor	Responding treatment
Iron deficiency <ul style="list-style-type: none"> • Absolute • Functional 	Iron supplementation, treat cause of blood loss. Address other factors, i.e., inflammation and uremia, which may have led to functional iron deficiency. IV iron required for functional iron deficiency
Inflammation and hepcidin accumulation	Address likely cause of inflammation, i.e., antibiotics for acute infection and steroid treatment for systemic inflammation. To lower serum hepcidin production and accumulation, rule out sources of infection from catheter and graft access
Uremia	Increased uremic clearance; adequate dialysis delivery – increased dialysis intensity and dialysate flow, e.g., convective HD; and improved membrane permeability
CKD-MBD <ul style="list-style-type: none"> • Vitamin D deficiency • Secondary hyperparathyroidism • Other CKD-MBD factors – elevated FGF-23, ALP 	Vitamin D supplementation (native and activated), calcimimetics, low-phosphate diet, and phosphate binders. Consider parathyroidectomy if refractory to medical treatment
Non-iron malnutrition <ul style="list-style-type: none"> • Folic acid deficiency • Vitamin C deficiency • Copper deficiency • α-Lipoic acid deficiency • L-Carnitine deficiency • Other non-iron malnutrition factors – PEW, vitamin B₆ deficiency, vitamin B₁₂ deficiency 	Nutritional supplementation to address the cause of non-iron nutritional deficiency
Other factors of ESA hyporesponsiveness <ul style="list-style-type: none"> • Drug-induced factors – ACEi, ARB • Malignancy • Primary bone marrow and myelosuppressive disorders • Antibody-mediated pure red cell aplasia • Aluminum overload 	Reduce dose or hold ACE inhibitor and ARBs Treat underlying oncological or hematological cause, and reduce its associated complications Anti-ESA treatment if indicated Supportive treatment for aluminum overload

CKD-MBD, chronic kidney disease-mineral bone disease; FGF-23: fibroblast growth factor-23; ALP, alkaline phosphatase; PEW, protein energy wasting; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent; HD, hemodialysis.

hyporesponsiveness; however, this was not the case for CRP [33].

Associations between ESA hyporesponsiveness and first-time thrombotic events are extensively validated in HD patients [3, 32, 34]. Recent data have also highlighted an increased healthcare cost associated with poorer clinical outcomes in ESA hyporesponsiveness [35].

Observational studies discussing adverse outcomes in ESA hyporesponsiveness for non-HD CKD groups remain limited [36]. Hard evidence showing associations between ESA hyporesponsiveness and other outcome parameters, such as renal function trajectory, is scarce. Future aims to address these research gaps should involve a wider population of CKD patients receiving different forms of renal replacement therapy.

Factors Associated with ESA Hyporesponsiveness in CKD

A summary of currently known factors associated with ESA hyporesponsiveness in CKD and their responding treatments is shown in Table 2.

Iron Deficiency

Iron deficiency is the most common cause of ESA hyporesponsiveness in CKD, with erythropoiesis being the primary consumer of iron in the human body. Major biomarkers of iron status are serum ferritin and transferrin. Ferritin reflects the body's iron storage, but may not be entirely accurate in an inflammatory state due to its acute phase protein profile. It may be raised in patients with iron deficiency anemia when there is concurrent liver disease or malignancy [37]. Transferrin is a plasma protein

which transports iron across the bloodstream for utilization and is an indicator of functional iron availability. Transferrin levels fall in iron deficiency [37].

Absolute iron deficiency is defined by a reduced transferrin saturation (TSAT) level of $\leq 20\%$, and serum ferritin concentration of ≤ 100 ng/mL for pre-dialysis and peritoneal dialysis patients or ≤ 200 ng/mL for HD patients [37, 38]. Blood loss, such as gastrointestinal bleeding and excess menstruation, leads to increased iron demands [39]. Absolute iron deficiency is caused by inadequate gastrointestinal absorption relating to disorders such as inflammatory bowel disease and celiac disease [39]. Inadequate dietary intake is frequently observed in CKD. Poor nutritional balance and chronic alcoholism are also contributing factors toward absolute iron deficiency [40].

Functional iron deficiency is currently defined by ferritin concentration >100 ng/mL with TSAT $<20\%$ [37, 38]. Despite adequate iron stores overall, anemia develops because of inefficient iron utilization [37]. Anemia of chronic disease is the most well-known cause [37, 38]. Erythrocytes may appear normocytic or microcytic [38]. Inflammation and the role of hepcidin in functional iron deficiency will be discussed in the next subsections.

Inflammation

Inflammation is an important factor of ESA hyporesponsiveness and associated clinical outcomes [41]. Between 30 and 50% of HD patients are found to have elevated CRP and IL-6 levels, even in the absence of identifiable sources of inflammation or infection. Inflammation in uremia could be episodic or chronic, but nonetheless associated with elevated all-cause mortality [42]. Causes of inflammation tend to be multifactorial. The stresses of chronic renal impairment are compounded by comorbidities, increased oxidative stress and infection risk, obesity, and genetic and immunological factors [6, 42, 43]. For patients receiving dialysis, dialysis inadequacy accumulates inflammatory cytokines [44]. Catheter and graft access infections add inflammatory risks [45]. The mechanism of how inflammation occurs in CKD likely relates to decreased renal clearance of tumor necrosis factor- α , interleukin-1, and IL-6, among other pro-inflammatory cytokines [6, 46]. Increased production of these cytokines is expected [6, 46]. The activation of pro-inflammatory cytokines in uremia is mainly triggered by reduced activity of antioxidant enzymes, superoxide dismutase, and glutathione peroxidase [47]. The pathophysiological mechanism of this process is not fully clear and warrants further investigation. What is known is that inflamma-

tory cytokines directly inhibit erythropoiesis and promote apoptosis of erythroid precursors [6, 46].

Hepcidin

Hepcidin is a cysteine-rich, 25-amino acid peptide hormone [48]. Its main action is to inhibit iron entry into plasma from the cellular environment [49, 50]. Hepcidin reduces circulating iron in the human body by binding to ferroportin, a cellular iron transporter which exports absorbed iron from duodenal enterocytes, recycled iron from splenic and hepatic macrophages, and stored iron from hepatocytes to plasma [49, 50]. Increased serum hepcidin heightens the frequency of hepcidin-ferroportin binding, and therefore greater inhibition of iron efflux [49, 50]. Direct hepcidin-ferroportin binding triggers endocytosis in both molecules, consequently leading to lysosomal degradation [49, 50].

Hepatocytes are the main location of hepcidin production though other cell types such as macrophages and adipocytes also express hepcidin mRNA [51]. Ongoing research continues to explore sources of extrahepatic hepcidin production. Hepcidin synthesis is stimulated by differing plasma transferrin and stored iron within hepatocytes [50]. Hepcidin production is mainly regulated by feedback signals reflecting systemic iron concentration and storage in the human body, as well as the body's erythropoiesis activity and host defense function [50]. When iron levels are abundant, more hepcidin is produced, while hepatocytes produce less hepcidin in iron deficiency [50]. To a lesser extent, hepcidin production is regulated by erythropoietic demands for iron in the body [50]. Hepcidin production is suppressed during active erythropoiesis, allowing higher iron availability for Hgb synthesis [50]. Although not yet comprehensively explained, suppression of hepcidin production occurs in this context through the erythroid factor, a circulating factor produced by bone marrow erythroid precursors [52]. A summary diagram of hepcidin regulation and action in iron homeostasis is shown in Figure 1 [53].

In CKD, 2 major mechanisms – impaired renal clearance and increased inflammatory status – contribute to elevated serum hepcidin levels [52]. For the well-functioning kidney, hepcidin comfortably passes through the glomerular membrane where it is taken up and degraded in the proximal tubule, similarly to other small-sized proteins. Small fractions of filtered hepcidin will pass intact into urine where it is readily detectable [54]. CKD impairs hepcidin clearance and leads to its accumulation in plasma [54]. Though there are suggestions that serum hepcidin may circulate in association with $\alpha 2$ -microglobulin,

Fig. 1. Hepcidin regulation and action in iron homeostasis (Obtained from Locatelli F., Fishbane S., Block G.A., Macdougall I.C. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *Am J Nephrol.* 2017 Mar; 45(3):187–99. Permission obtained from S. Karger AG, Basel).

its affinity for hepcidin is low, and a significant proportion of serum hepcidin will be unbounded [55]. Elevated serum hepcidin limits iron availability for erythropoiesis, contributing to ESA hyporesponsiveness.

The transcriptional phase of hepcidin synthesis by hepatocytes is regulated by IL-6 through the STAT-3 signaling pathway [56]. Because of this, increased hepcidin production is observed during acute phases of infection and systemic inflammation. Compared to other hepcidin-inducing mechanisms which reduce iron availability, acute infection and inflammation decrease iron levels at the fastest rate [52]. The host defense mechanism involving the multiplication process of iron-dependent extracellular microbes is being limited by the body's functional iron stores [52]. Downside of this mechanism is increased iron sequestration in response. The activation of the reticulo-endothelial system and increased hepcidin production will limit the potential of erythropoiesis [52]. Anemia of inflammation (chronic disease) leads to functional iron deficiency and ESA hyporesponsiveness in CKD.

Multiple studies have demonstrated the diagnostic ability of serum hepcidin for ESA hyporesponsiveness in both dialysis and nondialysis CKD patients [5, 6]. The instantaneous relationship between serum hepcidin levels and ESA hyporesponsiveness still requires further evaluation, and future research is warranted to address this.

CKD-Mineral Bone Disease

CKD-MBD is a common manifestation in CKD and a recognized factor of ESA hyporesponsiveness. Links

among vitamin D deficiency, secondary hyperparathyroidism, and ESA hyporesponsiveness are well-established [57].

The inability to synthesize active vitamin D (1,25(OH)₂D₃) from its inactive form 25(OH)₂D₃ is the major cause of vitamin D deficiency in CKD [58]. This is exacerbated by inadequate dietary intake, poor sunlight exposure, and nephrotic urinary loss [58]. The pleiotropic functions of vitamin D involve the hematopoietic system, which explains for the role of vitamin D deficiency in ESA hyporesponsiveness [8, 58]. 1,25(OH)₂D₃ binds to the vitamin D receptor to exercise its effects on erythropoiesis [8].

Elevated parathyroid hormone (PTH) circulation from secondary hyperparathyroidism is a factor of ESA hyporesponsiveness [57, 59]. PTH directly inhibits early erythroid progenitors, and reduces endogenous erythropoiesis and red cell survival [59]. Metabolic acidosis and hyperphosphatemia associated with secondary hyperparathyroidism encourage rightward shift of the oxygen-HgB dissociation curve and downregulation of erythropoietin receptors [59]. Excess uremic and inflammatory load exacerbates the hyperparathyroid state through calcium-dependent and calcium-independent mechanisms [59]. Transforming growth factor- β and insulin-like growth factor-1 receptor downregulation is exacerbated with secondary hyperparathyroidism in patients with severe uremic states, thereby increasing the burden of ESA hyporesponsiveness [59]. Bone marrow fibrosis, a complication of secondary hyperparathyroidism, has reported associations with ESA hyporesponsiveness [57, 59].

In recent years, fibroblast growth factor-23 (FGF-23) and alkaline phosphatase have been advocated as biomarkers to reflect ESA hyporesponsiveness status; however, more extensive evaluation is needed [60, 61]. FGF-23 has previously been demonstrated to be a negative regulator of erythropoiesis in mice [60]. Whether iron-restricted erythropoiesis consistently improves with lowering of FGF-23 levels in CKD requires further validation [62].

Non-Iron Malnutrition

The impact of non-iron nutrition on ESA hyporesponsiveness should not be underestimated. Folic acid is vital to support processes involved in erythroid proliferation, such as nucleotide synthesis, DNA repair, and homocysteine re-methylation [63]. Vitamin C promotes iron absorption and utilization from tissue stores and downregulates cytokine synthesis from hepatocytes through its role as an antioxidative free oxygen scavenger [64]. Copper encourages iron absorption from the intestinal tract [65]. Both α -lipoic acid and L-carnitine play roles to suppress inflammation [66, 67]. α -Lipoic acid, required for ATP synthesis, reduces oxidative stress by lowering serum concentration of symmetric-dimethyl arginine [66]. L-Carnitine stimulates heme-oxygenase 1, which has antioxidant effects, and shares the same metabolic pathway with erythropoietin [67]. Protein-energy wasting and vitamin B12 deficiency have previously been shown to display associations with anemia and ESA hyporesponsiveness [42, 68]. There are conflicting results describing the relationship between vitamin B6 and ESA hyporesponsiveness [69]. The mechanism of these associations requires further investigation.

Other Factors

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers promote ESA hyporesponsiveness through several mechanisms, of which inhibition of angiotensin-II-induced erythropoietin release and augmentation of N-acetyl-seryl-aspartyl-lysyl-proline to prevent recruitment of pluripotent hematopoietic stem cells are the major mechanisms [70]. Patients with cancer, with or without CKD, frequently demonstrate ESA hyporesponsiveness [71]. This is most commonly observed in patients with hematological malignancies such as multiple myeloma and chronic lymphocytic leukemia [71]. ESA hyporesponsiveness has been shown to associate with primary bone marrow disorders and secondary to myelosuppressive agents; however, this is uncommon [72]. Antibody-mediated pure red cell aplasia from the production

of neutralizing anti-ESA antibodies during ESA administration is rare [73]. ESA hyporesponsiveness stemming from aluminum overload because of distortion in processes involved in heme synthesis is seldom reported [74].

Management of ESA Hyporesponsiveness and Anemia in CKD

Iron Supplementation

There is no clear guidance for an optimal iron supplementation regime in CKD. KDIGO 2012 recommends iron repletion if TSAT $\leq 30\%$ and serum ferritin ≤ 500 ng/mL [19]. ERBG 2013 recommended iron repletion only if TSAT $< 20\%$ and serum ferritin < 100 ng/mL, with aims to remain TSAT $\leq 30\%$ and serum ferritin ≤ 500 ng/mL [1]. More recent results show high proportions of CKD patients with ferritin ≥ 500 ng/mL [75]. NICE 2015 and BRA 2017 advised ferritin cutoffs of 800 ng/mL for patients receiving iron supplementation [22, 23].

Ferrous preparations of orally administered iron are more frequently used because of cost and availability [76]. For CKD patients requiring IV iron, smaller doses and increased frequencies of administration are recommended to improve the cost-effectiveness of iron-restricted erythropoiesis [76].

Ferritin levels in iron supplementation are tightly monitored because of fears regarding iron overload [76]. Concerns relate to damage from oxidative stress, increased risks of infection, atherosclerosis, and tissue-iron deposition [76]. There is increasing evidence to support more liberal regimes of iron supplementation, as demonstrated from results in the PIVOTAL randomized-controlled trial comparing high-dose versus reactive low-dose IV iron supplementation in HD patients [77]. With a ceiling of ferritin < 700 ng/mL and TSAT $< 40\%$, the high-dose arm demonstrated lower mortality, cardiovascular events, and hospitalization after 2 years of follow-up, with lower ESA and transfusion requirements [77].

Absolute iron deficiency could be managed with either oral or IV iron, while functional iron deficiency will require IV iron supplementation because of poor intestinal uptake and utilization of iron stores [37, 38]. Numerous trials such as REVOKE and FIND-CKD evaluated the risk-benefit balance for IV iron compared to oral iron use, in which mixed results are seen [78, 79].

HIF-Stabilizers

Since the discovery of the HIF for the EPO gene in 1992, development of drugs, known as HIF-stabilizers or prolyl-

hydroxylase domain (PHD) inhibitors, acting through the HIF-PHD pathway has brought novel opportunities for renal anemia management. Erythropoiesis in HIF-PHD is dependent on hypoxic status within the cellular environment because oxygen-dependent degradation of HIF controls its levels [16]. In advanced CKD, decreased oxygen diffusion into renal cells occurs because of increased fibrosis, with increased transformation of erythropoietin-producing cells into renal myofibroblasts [80]. Hypoxia is exacerbated by other factors such as destruction of peritubular capillary networks, increased metabolic demands by the renal tubule, and reduced peritubular capillary blood flow [80].

HIF is a heterodimer made up by α and β subunits [80]. There are 3 isoforms of the α subunit: HIF-1 α , HIF-2 α , and HIF-3 α of which all can combine with the β subunit to induce expression of different target gene combinations [80]. HIF activity regulation occurs with the HIF- α subunit, synthesized continuously in cells, undergoing hydroxylation at specific proline residues [80]. This process is executed by PHD, and the hydroxylated HIF- α is then ubiquitinated by the von Hippel Lindau-E3 ligase complex before degradation by the proteasome [81]. When PHD activity decreases in hypoxia, reduced hydroxylation of HIF- α allows it to stabilize and translocate into the nucleus, where dimerization occurs with HIF- β [80, 81]. Activation of the EPO gene takes place in the nucleus after binding to the hypoxia response element (HRE) at target gene regulatory regions among other genes [80, 81]. In a hypoxic state, increased stabilization of HIF- α will elevate erythropoiesis activity initially [80, 81]. Eventually, HIF function and expression is insufficient to manage demands of erythropoiesis in the hypoxic environment, exacerbated by excess oxidative stress, uremia, and inflammatory cytokine production.

HIF-stabilizers have brought hope to this issue through restoring erythropoiesis in a consistent rate and address factors of ESA hyporesponsiveness. Regulating iron homeostasis to meet iron demands is a key effect. Mechanisms involved in this process increase transferrin, transferrin receptor concentration, duodenal cytochrome B, divalent metal transporter-1, and ceruloplasmin levels [82]. Effects of HIF-stabilizers in suppressing hepcidin and other pro-inflammatory cytokine production have been well-validated [16, 83]. Associations with improved nutritional status and bone health are observed in trials relating to HIF-stabilizers [83]. Development and integration of HIF-stabilizers into clinical practice has gone from strength to strength with the majority having completed, or in ongoing phase III trials currently [15, 84–87]. They are under close monitoring in the post-market sur-

veillance phase throughout the next decade, with approval for clinical use in Asia-Pacific countries such as China and Japan currently [88]. It remains to be seen whether HIF-stabilizers would be approved by the United States Food and Drug Administration, following the unsuccessful application for roxadustat in July 2021.

Although there are multiple advantages of HIF-stabilizers, concerns regarding these drugs are associated with their potential malignancy risks. Transcription of the VEGF gene is regulated by HIF-1 α and HIF-2 α binding to hypoxia response elements [17]. The risk of neoplasia and diabetic retinopathy from HIF-stabilizer use should be recognized as VEGF promotes angiogenesis, vascular permeability, and tumor growth [17]. Phase II studies for vadadustat and daprodustat did not demonstrate change in VEGF levels over the dose range arranged for phase III clinical trials [89, 90]. Other adverse effects such as metabolic acidosis, hyperkalemia, and upper respiratory tract infections were reported in the world's first HIF-stabilizer phase III clinical trial for roxadustat in the treatment arm [15, 86]. Going forward, we await more substantive conclusions to determine if HIF-stabilizers is the viable solution to address for ESA hyporesponsiveness in anemia in CKD over long-term.

Management of Inflammatory Factors

Traditional approach to manage inflammation in CKD is to treat the causative source, whether that is antibiotics for acute infection or steroid treatment for chronic systemic inflammation. Iron supplementation and sufficient dialysis address anemia of inflammation and reduce hepcidin levels. Newer therapies targeted to inhibit hepcidin production are being evaluated. Anti-IL-6 and IL-6 monoclonal antibody treatment such as tocilizumab and siltuximab are touted as potential options [91, 92]. Atorvastatin use in CKD has been discussed to lower serum hepcidin levels [93]. Recent research also proposed the use of pentoxifylline, a methylxanthine derivative, may have anti-inflammatory effects and improve ESA responsiveness for CKD patients with anemia [94]. Within an optimal concentration range, pentoxifylline suppresses the production of various pro-inflammatory cytokines, such as interleukin-2 and interferon-gamma [94].

Dialysis Adequacy

Increasing the intensity of dialysis and dialysate flow to reduce ESA hyporesponsiveness could be achieved via numerous mechanisms. Availability of convective HD allows more efficient clearance of middle-weight molecules, such as inflammatory cytokines, and peptides such

Fig. 2. Proposed pragmatic approach to CKD patients with ESA hyporesponsiveness.

as hepcidin [10]. The REDERT study is a randomized cross-over trial comparing outcomes in patients who underwent high-volume online hemodiafiltration with high-flux polysulfone membranes and exchange volume 20L/session versus standard bicarbonate dialysis with low-flux polysulfone membranes [10]. Improved ESA responsiveness and reduced serum hepcidin levels were observed in the online hemodiafiltration group in 3- and 6-month follow-ups, respectively [10].

Options to alter membrane permeability during dialysis have broadened in recent times. Due to antioxidant effects of vitamin E, the application of synthetic vitamin E-bonded dialysis membrane during dialysis has been considered. A multicenter, randomized, controlled trial by Locatelli et al. [11] has illustrated improved ESA responsiveness for patients receiving HD with vitamin E-coated polysulfone versus a low-flux synthetic dialyzer. Evidence evaluating the impact of membrane permeability on ESA responsiveness remains generally premature, and further validation of these measures is required.

CKD-MBD Management

Optimizing CKD-MBD treatment may improve ESA responsiveness for patients living with CKD. Vitamin D administered as daily, weekly, or monthly supplements is important as an anti-inflammatory treatment [95]. Use of various vitamin D analogs and vitamin D receptor activators has demonstrated increases in ESA responsiveness, particularly for HD groups [96]. Vitamin D supplementation has direct suppressive effects on PTH and serum hepcidin levels [97].

KDIGO 2017 guidelines on CKD-MBD recommend medical management of secondary hyperparathyroidism initially and to consider parathyroidectomy if medical treatment is refractory [98]. Published evidence note improved ESA responsiveness after parathyroidectomy or calcimimetic treatment [99, 100]. Despite its potential benefits, increased risks of acute mortality from surgical complications should be acknowledged for those undergoing parathyroidectomy [99]. Hyperphosphatemia from secondary hyperparathyroidism is shown to be associated with ESA hyporesponsiveness; however, the mechanism requires more evaluation [101].

Non-Iron Malnutrition Management

Replenishments to correct non-iron nutrient deficiencies may improve anemia in CKD and ESA responsiveness. Current guidelines do not advocate adjuvant supplementation of these nutrients for nondeficient CKD patients, due to concerns regarding safety levels and risk-benefit balance. An optimal regime for folic acid, vitamin C, copper, α -lipoic acid, L-carnitine, and vitamin B6 and B12 supplementation remains desirable. Larger sampled randomized, controlled trials should be conducted to establish this.

Conclusion

Our understanding of the issues surrounding ESA hyporesponsiveness and potential solutions has certainly expanded over recent years. Despite remaining concerns regarding some of its adverse effects, HIF-stabilizers may

indeed be the formula to eradicate our concerns over ESA hyporesponsiveness in renal anemia management. Figure 2 illustrates our proposed approach to the assessment and management of ESA hyporesponsiveness based on current evidence. Nonetheless, there are still many gaps in our knowledge base relating to this topic. The nephrology community should endeavor to reach a wider consensus regarding definition, assessment, and management of ESA hyporesponsiveness through continued research efforts to determine a gold-standard pathway. An exciting future awaits to unlock this conundrum.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.H.L.W. wrote the initial draft. R.C. reviewed the paper and revised it critically. All authors read and approved the final manuscript.

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