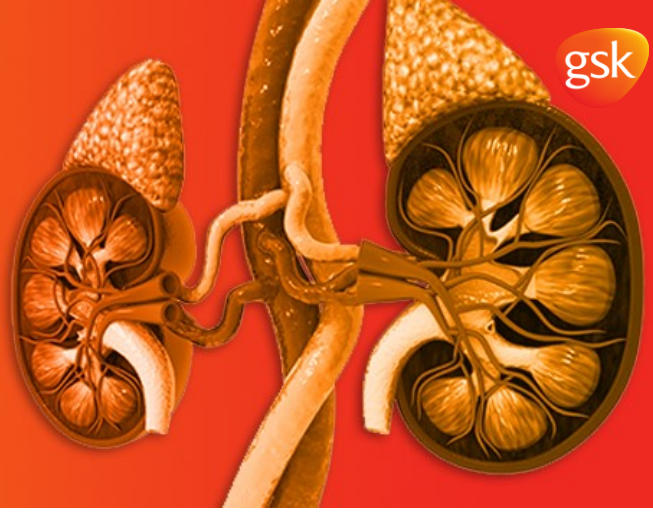
Anemia of CKD: Standard of Care



This document provides an overview of **iron supplementation and erythropoietin-stimulating agents** for the treatment of anemia of chronic kidney disease.

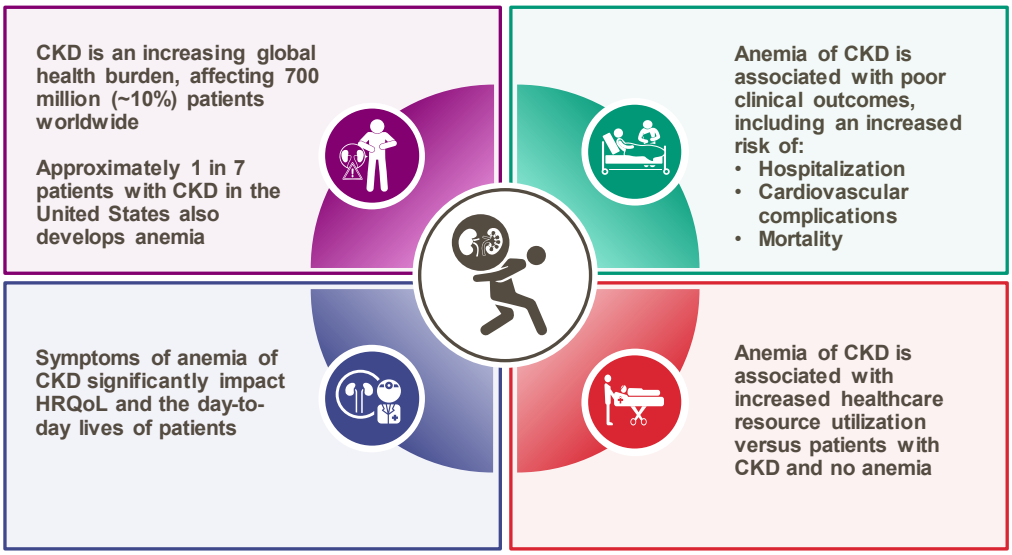
Overview of Anemia of CKD

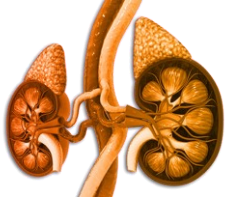
Anemia is a common feature in patients with chronic kidney disease (CKD).[1] KDIGO (Kidney Disease: Improving Global Outcomes) recommends diagnosing anemia in adults with CKD when hemoglobin concentrations are <13.0 g/dL in men and <12.0 g/dL in women.[2] Untreated anemia of CKD is associated with several signs and symptoms, as shown below.[1,3]

Signs and Symptoms of Anemia of CKD[4]

The signs and symptoms of anemia have a significant impact on health-related quality of life (HRQoL), with the majority of patients assessed through interviews reporting that their daily life activities are affected.[5] Unmet needs in the current standard of care (SoC) of anemia of CKD lead to a substantial burden on patients and healthcare systems.[1,3]

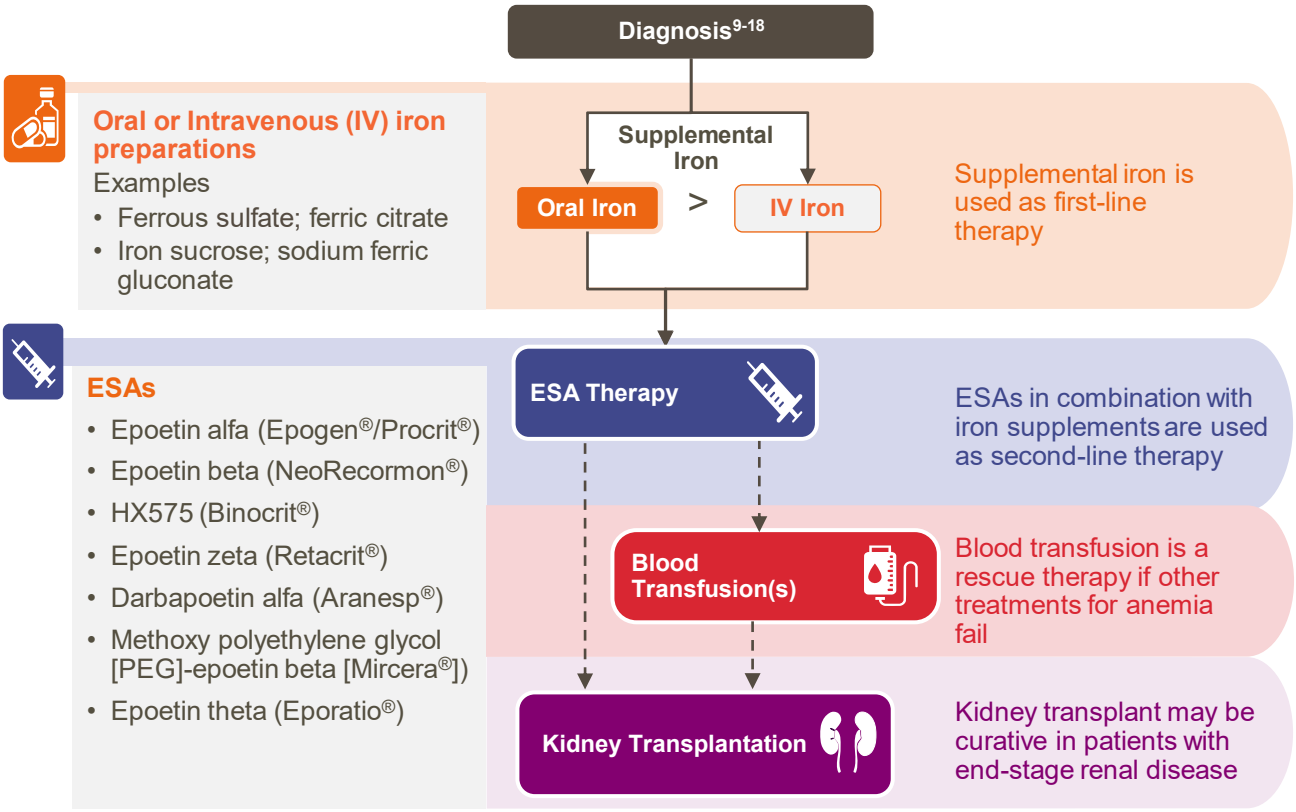
Burden of Anemia of CKD[3,5-8]



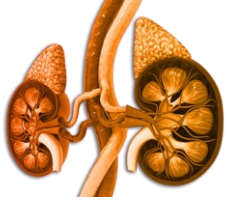


Current Standard of Care in Anemia of CKD

Two of the most common SoC treatments for anemia of CKD are iron preparations and erythropoietin-stimulating agents (ESAs).[1]



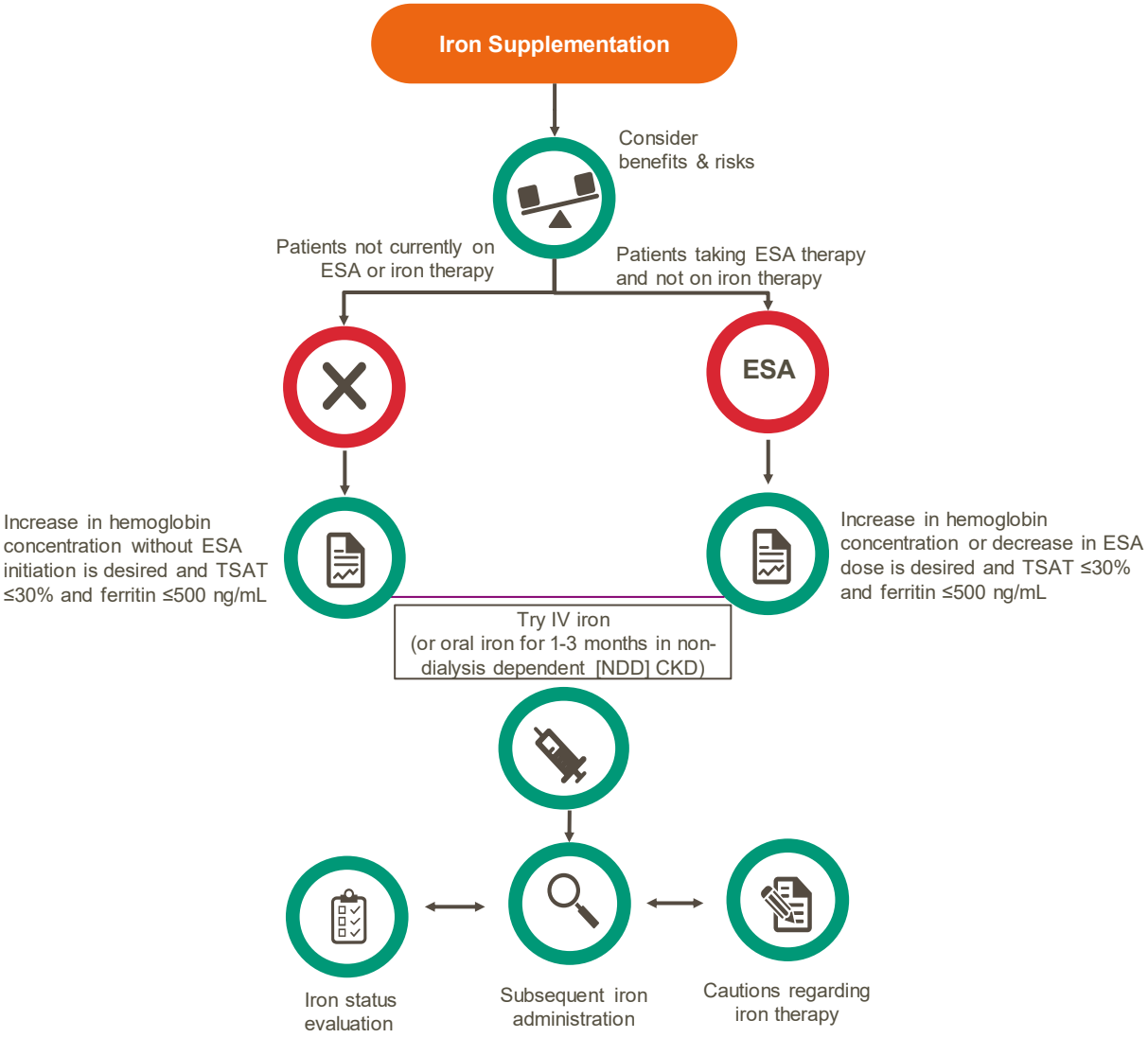
Note that this document will present information on iron supplementation and ESA therapy. Information regarding blood transfusions and kidney transplantation as treatment for anemia of CKD will be provided in a separate document.



First-Line Therapy: Iron Supplementation

KDIGO provides guidelines and recommendations for the treatment of anemia in CKD.[19] Among patients with CKD, iron therapy has the potential to increase hemoglobin concentration or decrease ESA dose when serum transferrin saturation (TSAT) is ≤30% and should be considered as first-line therapy.[19] The following section summarizes the KDIGO recommendations for iron therapy for the treatment of anemia in CKD in adults and is followed by a closer look at the recommendations, with additional comments and cautions.

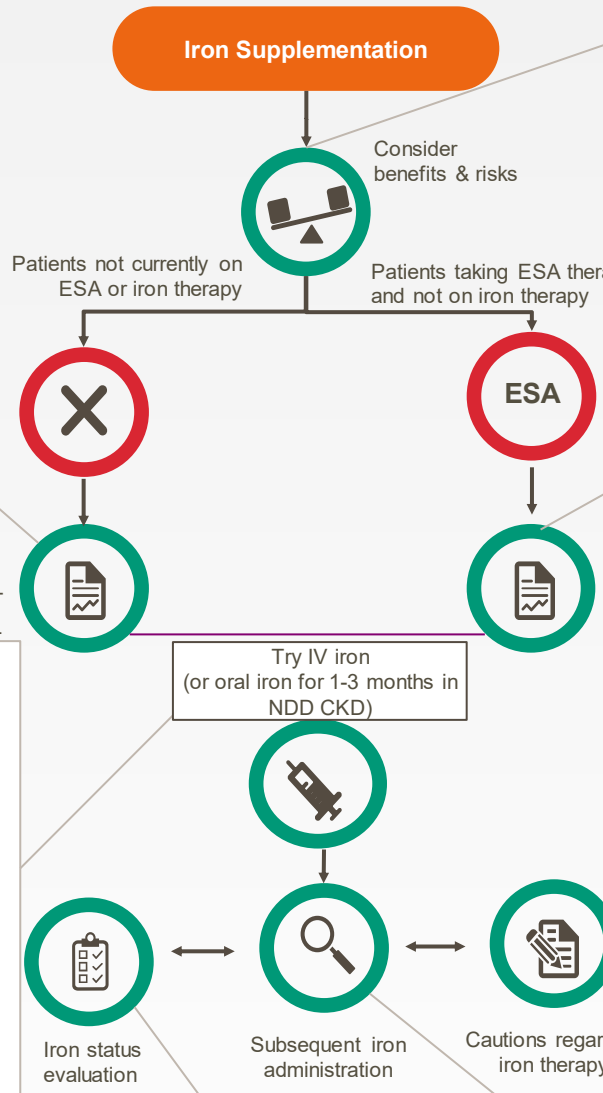
KDIGO Recommendations for Iron Therapy in Adults[20]



KDIGO Considerations and Cautions for Iron Supplementation[20]

KDIGO Guideline 2.1.1 (Not graded)
When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risk of harm in individual patients (eg, anaphylactoid and other acute reactions, unknown long-term risks)

KDIGO Guideline 2.1.2 (Grade 2C)
For adult CKD patients with anemia not on iron or ESA therapy, we suggest a trial of IV iron (or in NDD CKD patients, alternatively a 1-3–month trial of oral iron therapy) if an increase in hemoglobin concentration without starting ESA treatment is desired AND if TSAT ≤30% and ferritin ≤500 ng/mL



KDIGO Guideline 2.1.3 (Grade 2C)
For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in NDD CKD patients, alternatively, a 1-3–month trial of oral iron therapy) if an increase in hemoglobin concentration or a decrease in ESA dose is desired AND if TSAT ≤30% and ferritin ≤500 ng/mL

KDIGO Guideline 2.1.4 (Not graded)
For NDD CKD patients who require iron supplementation, select the best route of iron administration based on:

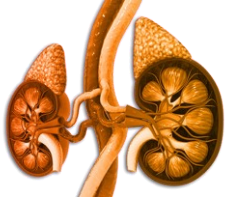
- Severity of iron deficiency
- Availability of venous access
- Response to prior oral iron therapy
- Side effects with prior oral or IV iron therapy
- Patient compliance
- Cost

KDIGO Guidelines 2.4 (Not graded)
Avoid administering IV iron to patients with active systemic infections

KDIGO Guideline 2.2.1 (Not graded)
Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy

KDIGO Guideline 2.2.2 (Not graded)
Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may be depleted

KDIGO Guideline 2.1.5 (Not graded)
Subsequent iron administration in CKD patients should be based on hemoglobin responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), hemoglobin concentration, ESA responsiveness and ESA dose in ESA-treated patients, trends in each parameter, and the patient's clinical status



Available Oral and IV Iron Agents

There are several oral and IV iron agents available. Available agents, their recommended dosages, and the pros and cons of oral and IV iron are discussed below.

Oral Iron Agents[9,21]

Iron (oral)	Recommended Dosage
Ferric citrate (Auryxia®)	630 mg/day elemental iron in divided doses (3 tablets/day) with meals for iron deficiency anemia (IDA) in CKD
Ferric maltol (Accrufer®)	30 mg twice daily
Ferrous sulfate (generic)	1000 mg/day (200 mg/day elemental iron) for IDA in CKD
Ferrous fumarate (Ferro-Sequels®; Slow FE®; Apo-Ferrous Gluconate)	600 mg/day (200 mg/day elemental iron) for IDA in CKD
Ferrous gluconate (Fergon®)	1600 mg/day (200 mg/day elemental iron) for IDA in CKD

Pros

- Convenient
- Inexpensive

Cons

- Limited daily intestinal absorption results in slower iron replacement than IV iron
- Dose-dependent gastrointestinal side effects
- Impaired uptake in certain conditions (eg, celiac disease, anemia of CKD, autoimmune gastritis)
- Mucosal injury and/or potential exacerbation of disease activity may occur in irritable bowel disease
- Alteration of microbiota

IV Iron Agents[10,11,21-25]

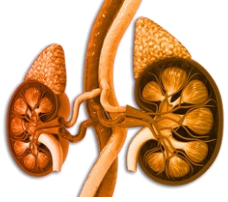
Iron (IV)	Recommended Dosage
Iron dextran (CosmoFer®; INFeD®; Dexferrum®)	100-200 mg iron (2-4 mL) slow IV, 2 or 3 times a week depending on the hemoglobin level
Iron sucrose (Venofer®)	• DD CKD: 100 mg slow IV injection over 2 to 5 minutes, per consecutive dialysis session. Total treatment dose of 1000 mg • NDD CKD: 200 mg slow IV injection × 5 doses over 14-day period • Peritoneal DD CKD: 2 slow IV infusions (diluted in 250 mL 0.9% NaCl) – each 300 mg over 1.5 hours 14 days apart followed by one 400-mg infusion over 2.5 hours 14 days later
Sodium ferric gluconate (Ferrlecit®)	DD CKD: 125 mg over 60 minutes; a cumulative dose of 1000 mg of elemental iron administered over 8 dialysis sessions
Ferric carboxymaltose (Injectafer®)	750 mg of iron IV at 100 mg/min or infusion over 15 minutes. For patients weighing <50 kg (110 lb), maximum of 15 mg of iron/kg body weight
Ferric derisomaltose (Monoferric®)	Weight ≥50 kg: 1000 mg as an IV infusion over at least 20 minutes Weight <50 kg: 20 mg/kg body weight as an IV infusion over at least 20 minutes
Ferumoxytol (Feraheme®)	510 mg of iron IV at 30 mg/s or infusion over 15 minutes

Pros

- Fast repletion of iron stores
- Effective even when intestinal absorption is impaired

Cons

- Requires administration by a healthcare professional, with associated increased costs
- Potential for iron overload and transient increase in oxidative stress
- Potential for anaphylactic reactions



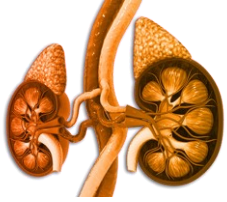
Second-Line Therapy: ESAs

The first ESA (Epogen® [epoetin alfa], Amgen) was developed in 1989 and revolutionized the clinical management of anemia of CKD.[18] There are 2 types of ESAs: short-acting agents (shorter half-life) and long-acting agents (longer half-life).[18] ESAs with a shorter half-life require frequent dosing (1 to 3 times weekly), while those with a longer half-life can be administered once weekly or once every 2 weeks.[18]

Currently Used ESAs[12-14,17,18]

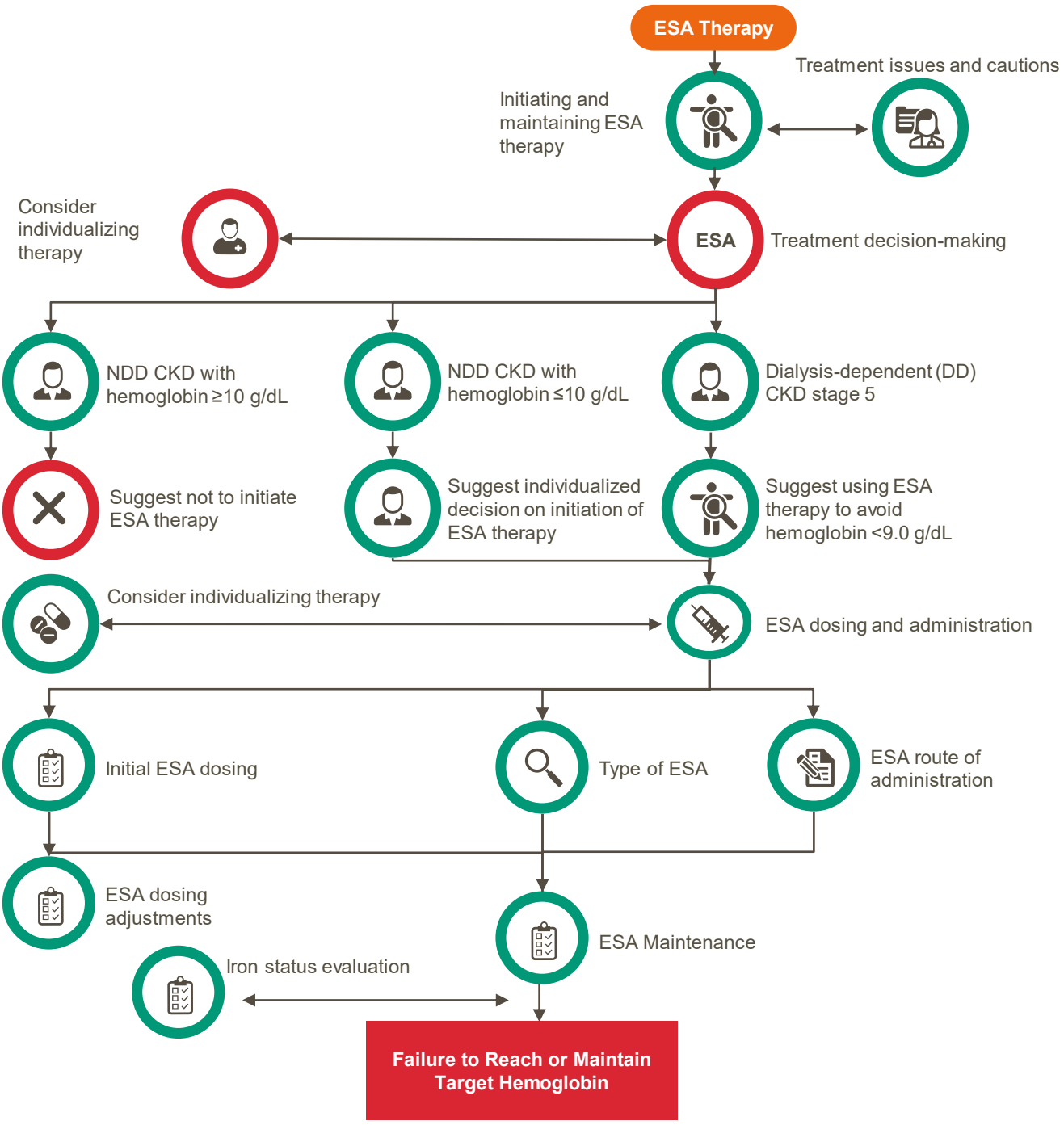
Short-acting Agent	Type	Route	Dose
• Epoetin alfa (Epogen®[a]/Procrit®[a]) • Epoetin beta (NeoRecormon®) • HX575 (Binocrit®) • Epoetin zeta (Retacrit®[a,b]) • Epoetin theta (Eporatio®)	Human erythropoietin	IV/ Subcutaneous (SC)	1-3 times weekly
Long-acting Agent	**Type**	**Route**	**Dose**
Darbepoetin alfa (Aranesp®[a])	Hyperglycosylated epoetin alpha	IV/SC	Every 1-4 weeks
Methoxy polyethylene glycol-epoetin beta (Mircera®[a])	Pegylated epoetin beta	IV/SC	2 weeks-once monthly

[a] Available in the United States.
[b] Biosimilar.



The following figure summarizes the KDIGO recommendations for ESA therapy for the treatment of anemia in CKD in adults and is followed by a closer look at the recommendations, with additional comments and cautions.

KDIGO Recommendations for ESA Therapy in Adults[20]

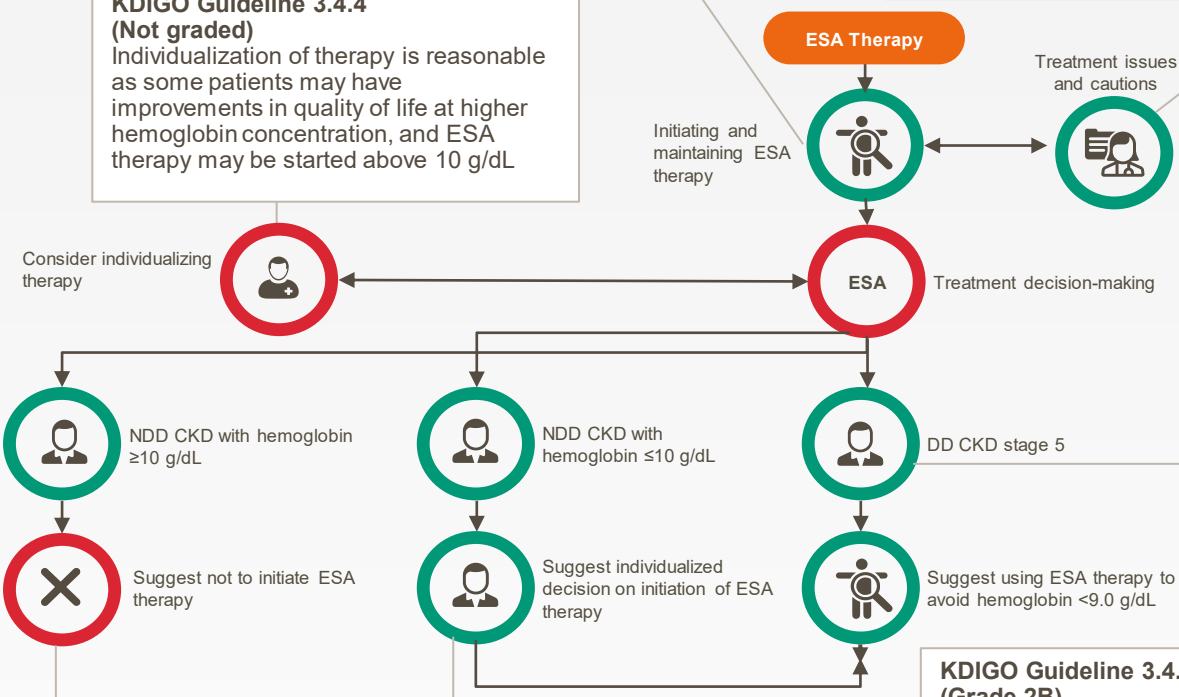


KDIGO Considerations and Cautions for ESA Initiation and in Different Populations[20]

KDIGO Guideline 3.1
(Not graded)
Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy
KDIGO Guidelines 3.2
(Grade 1B)
In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (eg, stroke, vascular access loss, hypertension)

KDIGO Guideline 3.3
We recommend using ESA therapy with GREAT CAUTION, if at all, in CKD patients with the following:
- ACTIVE MALIGNANCY, in particular, when cure is the anticipated outcome (EVIDENCE GRADE 1B)
- HISTORY OF STROKE (EVIDENCE GRADE 1B)
- HISTORY OF MALIGNANCY (EVIDENCE GRADE 2C)

KDIGO Guideline 3.4.4
(Not graded)
Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher hemoglobin concentration, and ESA therapy may be started above 10 g/dL



KDIGO Guideline 3.4.1
(Grade 2D)
For adult NDD CKD patients with hemoglobin concentration ≥10 g/dL, we suggest that ESA therapy not be initiated

KDIGO Guideline 3.4.2
(Grade 2D)
For adult NDD CKD patients with hemoglobin concentration <10.0 g/dL, we suggest that the decision to initiate ESA therapy be individualized based on:
- Rate of fall of hemoglobin concentration
- Prior response to iron therapy
- Risk of needing a transfusion
- Risks related to ESA therapy
- Presence of symptoms attributable to anemia

KDIGO Guideline 3.4.3
(Grade 2B)
For adult DD CKD stage 5 patients, we suggest that ESA therapy be used to avoid having the hemoglobin concentration fall below 9.0 g/dL by starting ESA therapy when the hemoglobin is between 9.0-10.0 g/dL

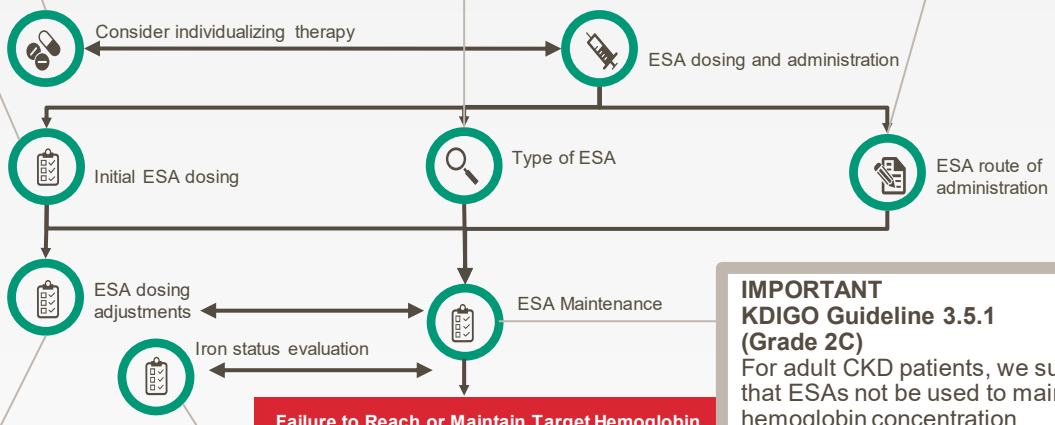
KDIGO Considerations and Cautions for ESA Therapy Dosing and Administration[20]

KDIGO Guideline 3.4.4 (Not graded)
Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher hemoglobin concentration, and ESA therapy may be started above 10 g/dL

KDIGO Guideline 3.11.1 (Grade 1D)
We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability
KDIGO Guideline 3.10 (Grade 2C)
We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA

KDIGO Guideline 3.9.1 (Grade 2C)
For DD CKD stage 5 patients and those on hemofiltration or hemodiafiltration therapy, we suggest either IV or SC administration of ESA
KDIGO Guideline 3.9.2 (Grade 2C)
For NDD CKD and DD CKD stage 5 patients, we suggest SC administration of ESA

KDIGO Guideline 3.8.1 (Grade 1D)
We recommend determining the INITIAL ESA DOSE using:
- Hemoglobin concentration
- Body weight
- Clinical circumstances



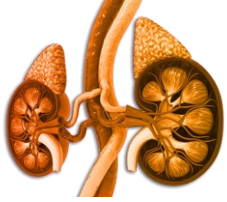
KDIGO Guideline 3.8.2 (Grade 1B)
We recommend that ESA DOSE ADJUSTMENTS be made based on:
- Hemoglobin concentration
- Rate of change of hemoglobin concentration
- Current ESA dose
- Clinical circumstances

KDIGO Guideline 3.8.3 (Grade 2C)
We suggest decreasing ESA dose in preference to withholding ESA when a downward adjustment of hemoglobin concentration is needed
KDIGO Guideline 3.8.4 (Not graded)
Re-evaluate ESA dose if:
- Patient suffers an ESA-related adverse event
- Patient has an acute or progressive illness that may cause ESA hyporesponsiveness

KDIGO Guideline 2.2.1 (Not graded)
Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy
KDIGO Guideline 2.2.2 (Not graded)
Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted

IMPORTANT
KDIGO Guideline 3.5.1 (Grade 2C)
For adult CKD patients, we suggest that ESAs not be used to maintain hemoglobin concentration >11.5 g/dL
KDIGO Guideline 3.6 (Grade 1A)
In all adult patients, we recommend that ESAs not be used to intentionally increase the hemoglobin concentration above 13 g/dL

KDIGO Guideline 3.5.2 (Not graded)
Individualization of therapy will be necessary as some patients may have improvements in quality of life at hemoglobin concentrations >11.5 g/dL



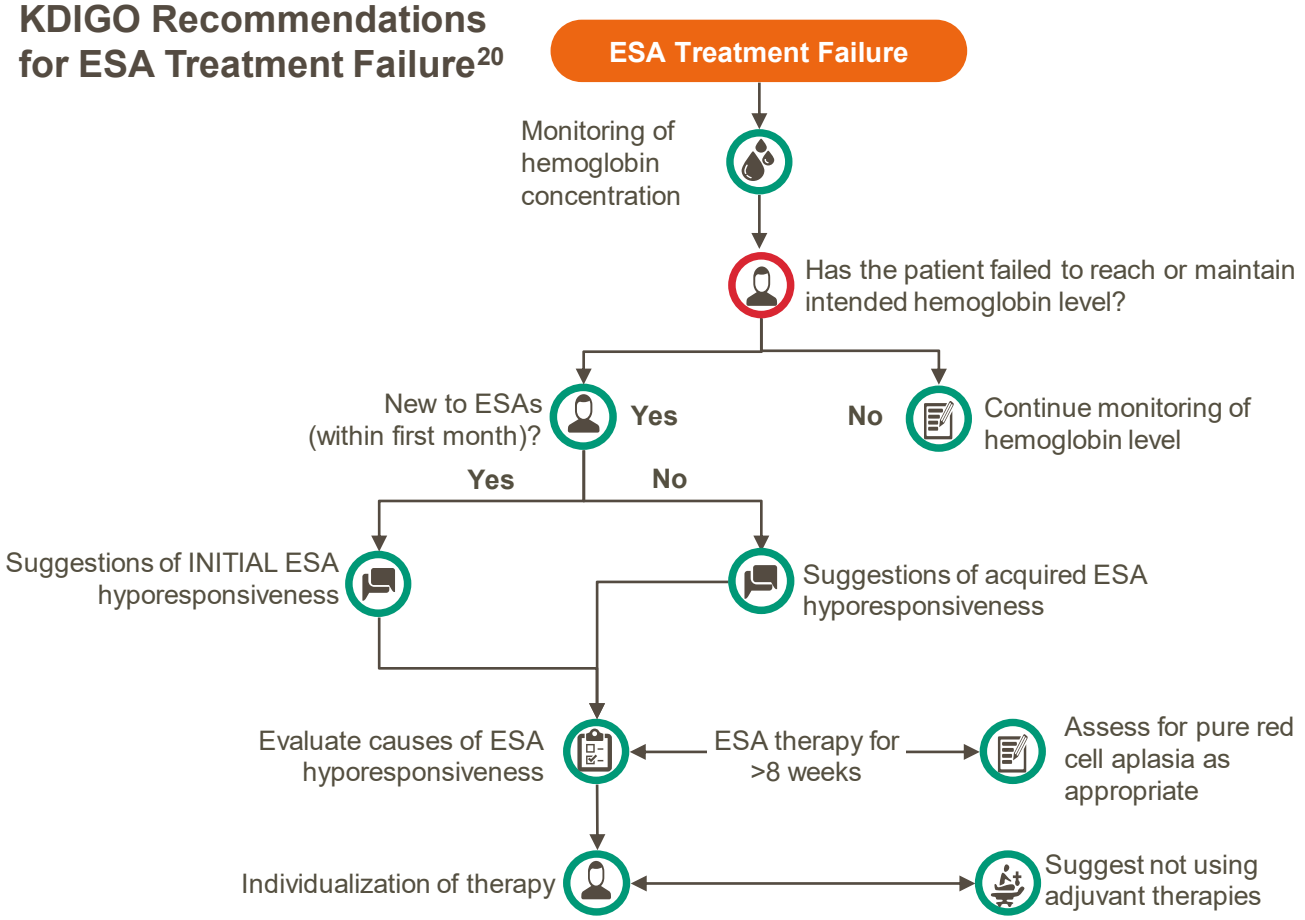
ESA Hyporesponsiveness

Although 90% of patients with anemia of CKD respond to ESAs in a dose-dependent manner, the remaining 10% show resistance to ESAs and exhibit hyporesponsiveness.[26] ESA hyporesponsiveness refers to patients who need high doses of ESAs (25% to 100% higher than what is recommended) to increase and/or maintain their hemoglobin levels within the acceptable range.[27] More specifically, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines define patients as ESA hyporesponsive if they do not experience an increase in hemoglobin levels within the first month of ESA treatment using an appropriate weight-based dosing (not graded).[27] Resistance to ESAs can be experienced as acute, short-term episodes or as longer, more chronic episodes.[26] Four months of continuous ESA hyporesponsiveness can be used to differentiate acute from chronic forms, but there is no standard definition.[26]

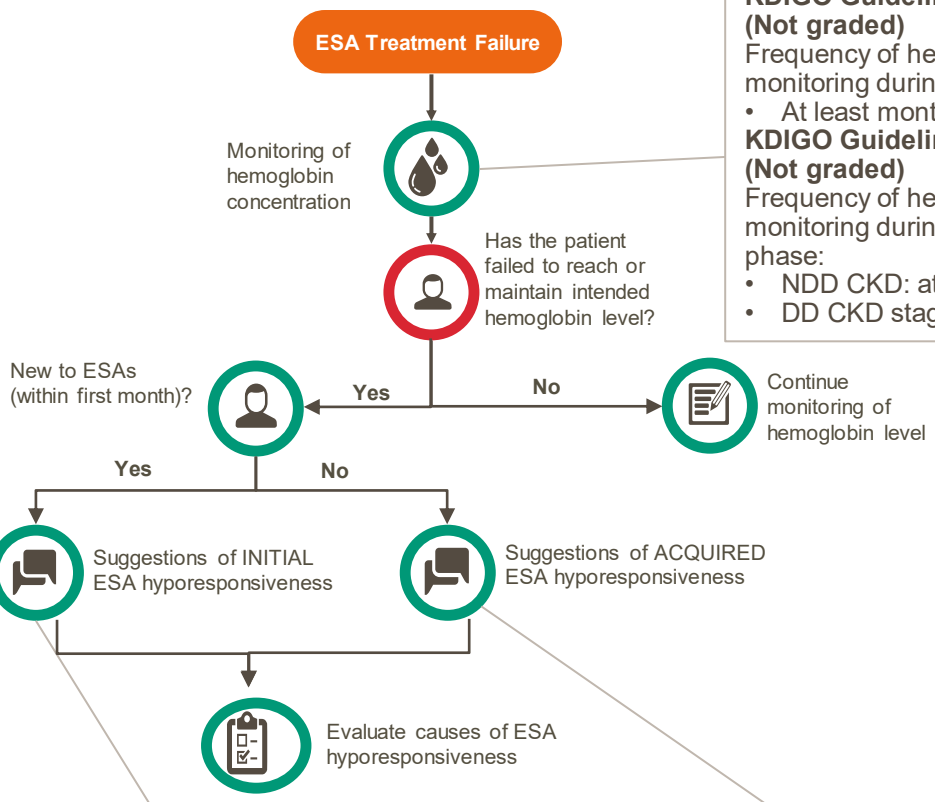
Although ESA-resistant anemia persists in some DD patients even after sufficient iron supplementation, iron deficiency (either absolute or functional) is considered a major cause of ESA resistance.[26] Patients receiving high doses of ESA relative to hemoglobin response experience poorer outcomes, including an increased risk of cardiovascular events and increased rates of morbidity and mortality, calling for more efficient treatments in ESA-hyporesponsive patients.[26] KDIGO provides treatment recommendation for patients who experience ESA treatment failure.

The following section summarizes the KDIGO recommendations for ESA treatment failure followed by a closer look at the recommendations, with additional comments and cautions.

KDIGO Recommendations for ESA Treatment Failure[20]



KDIGO Considerations and Cautions for ESA Treatment Failure[20]



KDIGO Guideline 3.12.1
(Not graded)
Frequency of hemoglobin concentration monitoring during INITIATION phase:
- At least monthly

KDIGO Guideline 3.12.2 and 3.12.3
(Not graded)
Frequency of hemoglobin concentration monitoring during MAINTENANCE phase:
- NDD CKD: at least every 3 months
- DD CKD stage 5: at least monthly

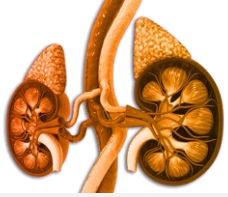
KDIGO Guideline 3.13.1
(Not graded)
Classify patients as having ESA hyporesponsiveness if they have no increase in hemoglobin concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing

KDIGO Guideline 3.13.2
(Not graded)
In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose

KDIGO Guideline 3.14.1
(Not graded)
Classify patients as having ACQUIRED ESA hyporesponsiveness 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 the stable hemoglobin concentration

KDIGO Guideline 3.14.2
(Grade 2D)
In patients with ACQUIRED ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable

NOTE: This algorithm continues on the next page.



NOTE: This algorithm is continued from the previous page

KDIGO Considerations and Cautions for ESA Treatment Failure (cont)[20]

KDIGO Guideline 3.15.1
(Not graded)
Evaluate patients with either INITIAL or ACQUIRED ESA hyporesponsiveness and treat for specific causes of poor response

Evaluate causes of ESA hypo-responsiveness

ESA therapy for >8 weeks

Assess for pure red cell aplasia as appropriate

Individualization of therapy

Suggest not using adjuvant therapies

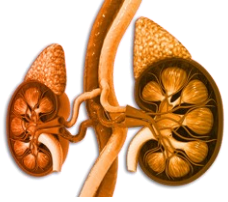
KDIGO Guideline 3.17.1
(Not graded)
Investigate for possible antibody-mediated pure red cell aplasia when a patient receiving ESA therapy for more than 8 weeks develops the following:
- Sudden, rapid decrease in hemoglobin concentration at the rate of 0.5 to 1.0 g/dL per week OR requirement of transfusions at the rate of approximately 1 to 2 per week AND
- Normal platelet and white cell counts, AND
- Absolute reticulocyte count less than 10,000/μL

KDIGO Guideline 3.17.2
(Grade 1A)
We recommend that ESA therapy be stopped in patients who develop antibody-mediated pure red cell aplasia

KDIGO Guideline 3.15.2
(Grade 2D)
For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, according for relative risks and benefits of:
- Decline in hemoglobin concentration
- Continuing ESA, if needed to maintain hemoglobin concentration, with due consideration of the doses required
- Blood transfusions

KDIGO Guideline 3.16.1
(Grade 1B)
We recommend not using androgens as an adjuvant to ESA treatment

KDIGO Guideline 3.16.2
(Grade 2D)
We suggest not using adjuvants to ESA treatment, including:
- Vitamin C
- Vitamin D
- Vitamin E
- Folic acid
- L-carnitine
- Pentoxifylline



Limitations of Iron Supplementation and ESA Therapy

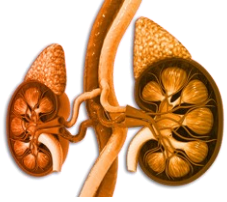
There are some limitations to keep in mind with iron and ESA therapy.[1] IV iron supplementation should not be given to patients with active infections.[2] ESAs have been linked to a possible increased risk of adverse cardiovascular events when treatment is targeting a normal hemoglobin range; therefore, cautious correction of anemia is recommended.[1] It is important to note that this is only an association and not a causative finding.[1]

Other Concerns Regarding IV Iron Therapy

- High ferritin levels have been related to poor survival in in both NDD and DD patients, but the ferritin levels at which risk of iron overload and mortality increase is still a matter of debate.[28] When IV iron is given despite oversaturation of iron-binding proteins, free iron may enhance bacterial growth, which may lead to infection in patients with CKD.[28]
- An international prospective cohort study of hemodialysis patients (the DOPPS study) showed a trend toward an increase in infection-related mortality in hemodialysis patients treated with >300 mg IV iron.[28] Similarly, a meta-analysis of 24 clinical trials also found an increased risk of infection with IV iron compared with oral or no iron treatment.[28]

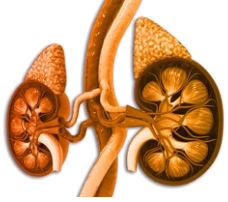
Other Concerns Regarding ESA Therapy

- High-dose ESA therapy for anemia of CKD and end-stage renal disease can result in erythropoietin (EPO) levels as high as 700 mU/mL, which is suspected to account for at least some of the harm observed in randomized trials.[29]
- Current renal anemia therapy poses several clinical challenges, including increase in cardiovascular risk that is associated with supraphysiologic ESA plasma levels, EPO resistance caused by inflammation, and hypertension.[30]
- ESA therapy poses concern in the treatment of patients with ESA hyporesponsiveness/resistance or anti-EPO antibodies.[1]



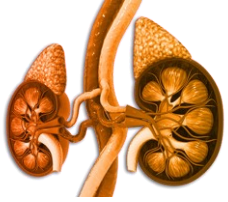
Conclusions

- Anemia is a common feature in patients with CKD.[1]
- Iron supplementation and ESAs are the current SoC for treatment of anemia of CKD.[1]
- Iron supplementation should not be given to patients with active infections.[2]
- Use of ESAs requires IV or SC injections and regular hemoglobin monitoring to ensure stable and reliable hemoglobin levels throughout treatment.[14]
- Effective treatment options with convenient administration and monitoring are needed to improve the HRQoL in patients with CKD.[3,5]



References

1. Kaplan JM, Sharma N, Dikdan S. Hypoxia-inducible factor and its role in the management of anemia in chronic kidney disease. *Int J Mol Sci*. 2018;19(2):389. doi:10.3390/ijms19020389
2. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl (2012)*. 2012;2(4):279-335.
3. Kutuby F, Wang S, Desai C, Lerma EV. Anemia of chronic kidney disease. *Dis Mon*. 2015;61(10):421-424. doi:10.1016/j.disamonth.2015.08.002
4. National Institute of Diabetes and Digestive and Kidney Diseases. Anemia in Chronic Kidney Disease. Available at: https://www.niddk.nih.gov/health-information/kidney-disease/anemia. Accessed January 13, 2022.
5. Mathias SD, Blum SI, Sikirica V, Johansen KL, Colwell HH, Okoro T. Symptoms and impacts in anemia of chronic kidney disease. *J Patient Rep Outcomes*. 2020;4(1):64. doi:10.1186/s41687-020-00215-8
6. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9(1):e84943. doi:10.1371/journal.pone.0084943.
7. Bibkov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3
8. St. Peter WL, Guo H, Kabadi S, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. *BMC Nephrol*. 2018;19(1):67. doi:10.1186/s12882-018-0861-1
9. Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. *Adv Chronic Kidney Dis*. 2019;26(4):272-291. doi:10.1053/j.ackd.2019.05.002
10. Venofer (iron sucrose) injection, for intravenous use [package insert]. Shirley, NY: American Regent, Inc; October 2020.
11. Ferrlecit (sodium ferric gluconate complex in sucrose injection), for intravenous use [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; December 2020.
12. Goldsmith D, Dellanna F, Schiestl M, Krendyukov A, Combe C. Epoietin biosimilars in the treatment of renal anemia: what have we learned from a decade of European experience? *Clin Drug Investig*. 2018;38(6):481-490. doi:10.1007/s40261-018-0637-1
13. Aranesp® (darbopoetin alfa) injection, for intravenous use or subcutaneous use [package insert]. Thousand Oaks, CA: Amgen Inc; January 2019.
14. Mircera® (methoxy polyethylene glycol-epoetin beta) injection, for intravenous or subcutaneous use [package insert]. St. Gallen, Switzerland: Vifor (International) Inc; June 2018.
15. Locatelli F, Barany P, Covic A, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*. 2013;28(6):1346-1359. doi:10.1093/ndt/gft033
16. Aimaretti LA, Arze S. Preemptive renal transplantation – the best treatment option for terminal chronic renal failure. *Transplant Proc*. 2016;48(2):609-611. doi:10.1016/j.transproceed.2016.02.047



17. National Institute for Health and Care Excellence. Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta; and, darbepoetin alfa) for treating cancer-treatment induced anemia (including review of TA142). 2013. Available at: https://www.nice.org.uk/guidance/ta323/documents/anaemia-cancertreatment-induced-erythropoiesisstimulating-agents-epoetin-and-darbepoetin-protocol2. Accessed 12-8-2021.

18. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. *Patient Prefer Adherence*. 2008;2:195-200. doi:10.2147/ppa.s2356

19. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guidelines for Anemia in CKD. *Am J Kidney Dis*. 2013;62(5):849-859. doi:10.1053/j.ajkd.2013.06.008

20. Kidney Disease: Improving Global Outcomes (KDIGO). Anemia in CKD: visual guidelines. Available at: http://www.treatalgo.com/kdigo-anemia/. Accessed December 31, 2021.

21. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of iron deficiency anemia. Gastroenterol Hepatol (NY). 2015;11(4):241-250. PMID:27099596

22. Summary of Product Characteristics – CosmoFer. Pharmacosmos A/S. Accessed via: https://www.medicines.org.uk/emc/files/pil.48.pdf on 12/31/21 [date of revision of the text Jan 2020].

23. Monoferric (ferric derosomaltose) injection, for intravenous use [package insert]. Morristown, NJ: Pharmacosmos Therapeutics Inc; September 2020.

24. Wu M, Sun D, Tyner K, Jiang W, Rouse R. Comparative evaluation of U.S. brand and generic intravenous sodium ferric gluconate complex in sucrose injection: in vitro cellular uptake. *Nanomaterials (Basel)*. 2018;7(12):451. doi:10.3390/nano7120451

25. Injectafer® (ferric carboxymaltose injection), for intravenous use [package insert]. Shirley, NY: American Regent Inc; November 2021.

26. Cizman B, Sykes AP, Paul G, Zeig S, Cobitz AR. An exploratory study of daprodustat in erythropoietin-hyporesponsive subjects. *Kidney Int Rep*. 2018;3(4):841-850.

27. Ingrasciotta Y, Lacava V, Marciano I, et al. In search of potential predictors of erythropoiesis-stimulating agents (ESAs) hyporesponsiveness: a population-based study. *BMC Nephrol*. 2019;20(1):359. doi:10.1186/s12882-019-1554-0

28. Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. *Clin Kidney J*. 2016;9(2):260-267. doi:10.1093/ckj/sfv142

29. Coyne DW, Goldsmith D, Macdougall IC. New options for anemia of chronic kidney disease. *Kidney Int Suppl* (2011). 2017;7(3):157-163. doi:10.1016/j.kisu.2017.09.002

30. Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv Chronic Kidney Dis*. 2019;26(4):253-266. doi:10.1053/j.ackd.2019.04.004