

# Treatment Decision for Anemia in Chronic Kidney Disease



## Learning Objectives

- ❑ Explain the pathophysiology mechanism of anemia in Chronic kidney disease (CKD)
- ❑ Assess current treatment strategies along with clinical challenges
- ❑ Evaluate the clinical data of a new investigational drug, Hypoxia-induced factors prolyl hydroxylase inhibitors (HIF-PHI)
- ❑ Develop a personalized treatment plan for a patient with stage-3 CKD and Hb levels  $<10$  g/dl

# Background

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Anemia is a frequent complication of chronic kidney disease (CKD). Its prevalence increases as CKD progresses, with over 50% of stage 5 CKD patients develop anemia.<sup>1</sup> Despite the higher prevalence, anemia is often undertreated in CKD, with only 2% of patients eligible for erythropoiesis-stimulating agent (ESA) therapy. The multifactorial nature of anemia makes identification of its cause and treatment challenging.

1. Kovesdy CP, Davis JR, Duling I, Little DJ. Prevalence of anaemia in adults with chronic kidney disease in a representative sample of the United States population: analysis of the 1999-2018 National Health and Nutrition Examination Survey. *Clin Kidney J.* 2022;16(2):303-311. Published 2022 Nov 12. doi:10.1093/ckj/sfac240

# Case Introduction



Mr. Smith, a 65-year-old retired accountant, has stage 3a-Chronic Kidney Disease (CKD). His CKD was diagnosed a year ago. He is visiting you today for his first follow-up visit after diagnosis. When you asked him about his physical well-being, he said that even after his diagnosis, he was able to manage his active lifestyle, including weekly hiking trips. But lately, he has noticed that he gets tired quickly and finds it challenging to maintain his active lifestyle, including hiking trips. He adds that he is also unable to help his wife maintain their garden. When you inquire how long this has been going on, he says about 2-3 months. He asked you worryingly, is my condition worsening?

You take his blood pressure and order a blood test for him. He takes high blood pressure medications daily. He had a family history of cardiovascular disease; his mother had hypertension and his father died of a heart attack.

He visits you in a week to discuss his results. You tell him that his CKD is stable because his estimated glomerular filtration rate (eGFR), a measure of his kidney health, has decreased only by a point from his last visit. You explain to him that his tiredness could be due to anemia. His Hb level is 9.5 g/dl, down from 12.5 g/dl six months ago. You tell him that you need to do more tests to determine the cause of his anemia.

**Table 1 Mr. Smith lab results**

|   |                               |
|---|-------------------------------|
| Blood pressure  | 135/90 mm/Hg                  |
| Hb levels   | 9.5 g/dl                      |
| eGFR  | 54 ml/min/1.73 m <sup>2</sup> |
| Albumin to creatinine ratio (ACR)<br>Albumin excretion rate (AER) | 2.7 mg/mmol<br>28 mg/24 hours |
| HbA1C levels  | 7%                            |
| Height  | 5 ft 7 in                     |
| Weight  | 160 lb                        |
| Body Mass Index (BMI)   | 25 kg/m <sup>2</sup>          |

In addition to measuring complete blood count (CBC) and absolute reticulocyte count, which other tests would you perform to diagnose the cause of Mr.

Smith's anemia? (Select all that apply)

A: Serum levels of vitamin B12 and folate

B: Bone marrow examination

C: Serum levels of ferritin and transferrin saturation (TSAT)

D: Erythropoietin (EPO) levels

### Correct choices

A & C: Kidney Disease Improving Global Outcomes (KDIGO) guidelines<sup>2</sup> recommends measuring both the red blood cells (RBCs) status and iron levels because of the multifactorial nature of anemia in CKD. CBC measures white and RBCs, and absolute reticulocyte count measures the number of immature RBCs. Serum levels of ferritin, transferrin saturation (TSAT), vitamin B12, and folate levels determine the iron status.

### Incorrect choices

B: Although bone marrow examination provides valuable information about bone marrow functions and blood cells, it is usually performed when blood test results are non-specific.

D: Anemia in CKD is characterized by low EPO levels. Thus, its measurement is not recommended in CKD.<sup>2</sup>

2. Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. 2016;2(4). <https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf>

Mr. Smith's lab results showed decreased iron levels, with ferritin levels at 465 ng/ml and TSAT levels at 24%. Which treatment option would you choose for Mr. Smith? (Select all that apply)

- A: Erythropoiesis-stimulating agent (ESA) therapy
- B: Oral Iron (Fe) therapy
- C: Intravenous (IV) Fe therapy
- D: HIF-PHI inhibitors

### Correct choices

B: KDIGO guidelines<sup>2</sup> suggest initiating an oral Fe therapy trial (65-200mg) for 1-3 months for non-dialysis (ND) patients not on IV Fe or ESA therapy.

C: Per KDIGO guidelines, a trial of IV Fe therapy can be a first-line treatment for non-dialysis (ND) patients not on iron supplementation or for whom oral Fe therapy is ineffective. But consider access, cost, and side effects, including hypotension and anaphylactic reactions, when recommending this therapy.

### Incorrect choices

A: ESA therapy can be initiated when Fe therapy is ineffective in increasing Hb concentration. However, consider the treatment-related cardiovascular events, hypertension, and stroke when recommending it for a patient at risk of cardiovascular disease.<sup>2</sup>

D HIF-PHI is an investigational drug and meets non-inferiority criteria. However, treatment-related cardiovascular events of HIF-PHI are similar to standard ESA therapy.<sup>3,4</sup>

3. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. *N Engl J Med.* 2021;385(25):2325-2335. doi:10.1056/NEJMoa2113379

4. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, open-label, active-controlled study (DOLOMITES). *Nephrol Dial Transplant.* 2021;36(9):1616- 1628. doi:10.1093/ndt/gfab191

You initiated oral Fe treatment for Mr. Smith because he met the eligibility criteria of not being on dialysis and Fe or ESA therapy. You agreed to see him in 2 months. When he came for his follow-up visit, he expressed concerns about his energy levels. He said, "This medication is not working for me. I'm always lethargic. Is this a new normal for me?" Although he tolerated oral iron therapy, his serum ferritin (465 ng/ml) and TSAT levels (24%) remained unchanged. His Hb levels only increased by 0.2 g/dl. Which treatment option would you choose for Mr. Smith to help him increase his Hb levels? (Select all that apply)

A: Continue oral Fe therapy

B: IV Fe therapy

C: Oral Fe therapy + low dose ESA

D: IV Fe therapy + high dose ESA

### Correct choices

B: Correct. IV Fe therapy can be a second line of treatment. KDIGO guidelines<sup>2</sup> recommends a single large dose of 1000mg or repeated small doses.

C: Correct. ESA therapy can be initiated along with Fe therapy for patients who may show improvement in their quality of life at higher Hb concentration. KDIGO guidelines<sup>2</sup> recommends checking Hb concentration every month with ESA therapy.

### Incorrect choices

A: Although Hb concentration slightly improved with oral Fe, the patient's quality of life and iron status didn't improve much.

D: Choose this option if oral Fe therapy and low-dose ESA therapy are ineffective for a patient. But weigh the benefits and side effects per patient's clinical status.

# Case Conclusion

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Since oral Fe was ineffective in increasing his Hb, TSAT, and ferritin levels, you initiated IV Fe therapy for Mr. Smith. You administered a single dose of 1000 mg and agreed to see him in a week. When he came for his follow-up visit, he reported having back pain and diarrhea for a few days after the treatment. His blood pressure was high, 140/92 mm/Hg. You advised him to measure his blood pressure daily and contact you if readings are 140/92 mm/Hg or higher. You ask him to come after a month for a follow-up visit.

In a follow-up visit, he said his energy levels were slightly better. He added that he can now to maintain his lawn without exhaustion and looks forward to resuming his hiking trips. His lab values indicated that IV Fe therapy was effective in increasing his Hb, TSAT, and ferritin levels. His c-reactive protein levels were in the normal range, indicating no active infection. Overall, he tolerated IV Fe therapy well. You decided to continue IV Fe therapy but with a low dose.

**Table 2 Mr. Smith lab results**

|                    |              |
|--------------------|--------------|
| Blood pressure     | 136/90 mm/Hg |
| Hb levels          | 10.9 g/dl    |
| TSAT               | 28 %         |
| Ferritin           | 480 ng/ml    |
| C-reactive protein | 3.5 mg/L     |
| HbA1C levels       | 7.1 %        |