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Akebia THERAPEUTICS

Anemia in Chronic Kidney Disease

Jay Wish, MD

Thanks to our speaker!

- Jay B. Wish, MD
  - Professor of Clinical Medicine at Indiana University School of Medicine in Indianapolis
  - Chief Medical Officer of dialysis services at Indiana University Health
  - Numerous publications on anemia management

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Objectives

- What is anemia?
- What are the symptoms of anemia?
- Why does chronic kidney disease cause anemia?
- How is anemia treated?

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What is Anemia?

- Anemia happens when there are not enough red blood cells in your body
- Red blood cells carry oxygen through your bloodstream, giving you energy and helping your muscles, heart, brain and other organs work properly
- A decreased number of red blood cells results in less oxygen being delivered to these organs

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How is Anemia Diagnosed?

- Hemoglobin is the molecule in red blood cells that carries oxygen
- Fewer red blood cells means less hemoglobin in the blood
- The major blood test used to diagnose anemia is the hemoglobin level

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Hemoglobin Level

- The normal hemoglobin level for men is around 14-17 and the normal hemoglobin level for women is around 12-15
- Men have higher hemoglobin levels than women because male sex hormones stimulate red blood cell production and because women lose blood with menstruation
- Anemia is defined as hemoglobin level less than 13 in men and less than 12 in women

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Why Does Anemia Cause Symptoms?

- The symptoms of anemia are mainly due to less oxygen going to the organs
- The lower the hemoglobin level the more likely symptoms are to occur
- Patients are more likely to have symptoms from anemia if they have many medical conditions
- Most patients with anemia do not develop symptoms until the hemoglobin is less than 11

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What are the Symptoms of Anemia?


Tiredness, weakness, low energy level


Shortness of breath, especially with exercise


Feeling cold all the time


Dizziness, lightheadedness, loss of concentration


Chest pain, especially with exercise


Pale skin

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If I have these symptoms does it always mean I have anemia?

- No, the symptoms of anemia are non-specific and can be seen in other diseases
- The only way to make the diagnosis of anemia for sure is with a blood test showing a lower hemoglobin level than normal
- Even if anemia is present, it does not always mean the symptoms are due to the anemia
- Discuss each symptom with your doctor who will determine if additional evaluation is needed

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Chronic Kidney Disease (CKD) and Anemia

- Anemia is very common in patients with CKD
- Anemia may happen in patients with stage 2 CKD and it usually gets worse in more advanced stages of CKD
- It is recommended that patients with stage 3 or greater CKD have a hemoglobin test at least once a year to screen for anemia

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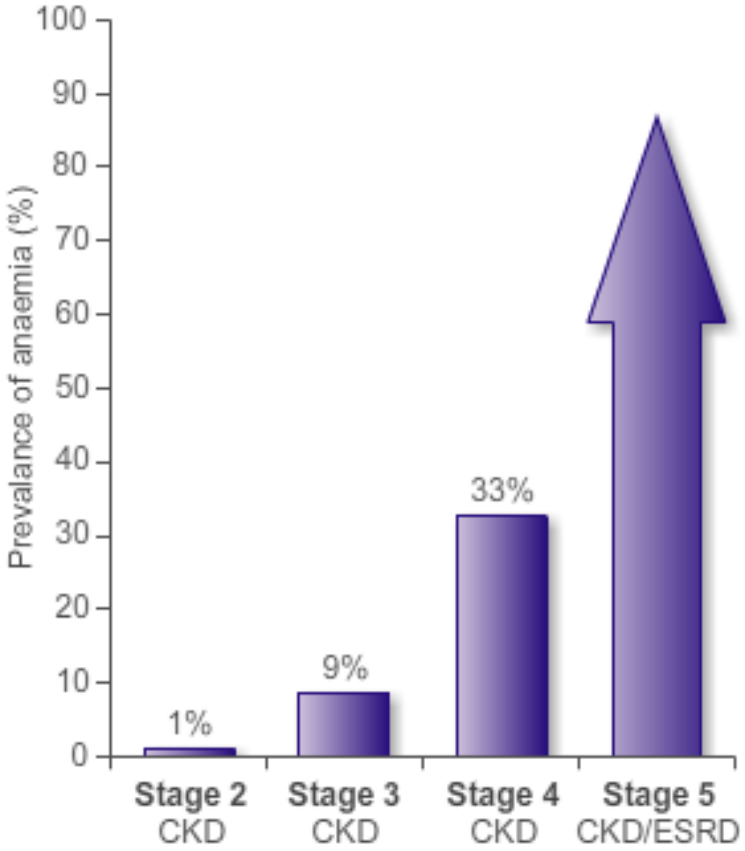
Increasing prevalence of anemia as CKD progresses[1]



[1] Mikhail, *et al*. Clinical Practice Guidelines – Anaemia of CKD: UK Renal Association. 2010:1-40.

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Anemia is more common in CKD if you

- Have diabetes
- Have heart disease
- Have high blood pressure
- Are African American
- Are over 75 years old

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How Does CKD Cause Anemia?

- There are two major causes by which patients with CKD develop anemia
  - Erythropoietin deficiency
  - Iron deficiency
- These two causes of anemia are often both present in the same patient at the same time

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What is Erythropoietin (EPO)?

- EPO is a hormone made by normal kidneys that signals the bone marrow to make more red blood cells
- In patients with normal kidney function, a decrease in hemoglobin level is sensed by the kidneys which leads to more EPO production
- This causes the bone marrow to make more red blood cells to return the hemoglobin level to normal

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Normal Red Blood Cell Lifespan

- Normal red blood cells live around 115 days
- In patients with CKD, the red blood cell life span is less than normal
- The body always needs to make new red blood cells to make up for those that have died or have been lost due to bleeding
- EPO is essential to send the appropriate signal to the bone marrow to make new red blood cells based on the hemoglobin level

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What Happens to EPO in Patients with CKD?

- Patients with CKD are unable to make sufficient EPO to stimulate the bone marrow to make enough red blood cells to keep the hemoglobin level normal
- The ability of the kidneys to make EPO declines as the kidney function decreases
- Without EPO, your body doesn’t know how to make enough red blood cells
- Fewer red blood cells are available to carry oxygen throughout your body

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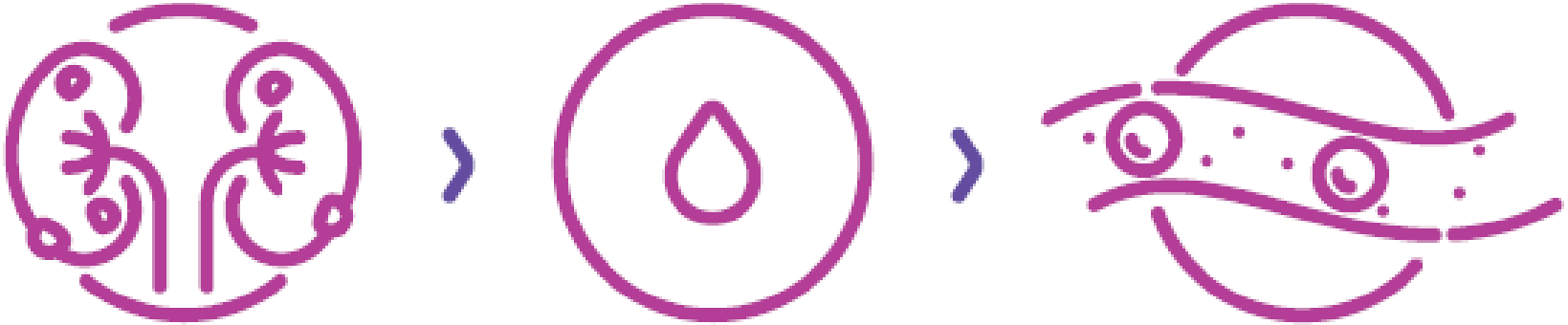

Chronic kidney disease

Reduced EPO

Reduced number of red blood cells

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Iron Deficiency in CKD

- Iron is a mineral in many foods
- Iron is an essential component of hemoglobin
- Without enough iron your bone marrow cannot make red blood cells even if EPO is present
- Iron deficiency is common in patients with CKD and can be due to not enough dietary iron intake and blood loss

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Inadequate Dietary Iron Intake in CKD

- Major dietary sources of iron are red meats and leafy green vegetables
- Many CKD patients eat less of these foods due to loss of appetite, dietary restrictions, and inadequate financial resources
- Even with adequate or proper iron intake there may be decreased intestinal absorption of dietary iron in CKD patients due to inflammation (redness and swelling)
- This may also affect the intestinal absorption of oral iron supplements that are taken by mouth

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Blood Loss Leading to Iron Deficiency

- Patients on hemodialysis have considerable blood losses due to
  - Blood remaining in the dialyzer circuit
  - Frequent blood testing
  - Oozing from needle sites following dialysis
  - Vascular access procedures

- It is estimated that the average hemodialysis patient loses more than 4 pints of blood per year

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Blood Loss Leading to Iron Deficiency

- Patients with CKD may have increased blood losses due to
  - Blood clotting abnormalities
  - Increased incidence of gastrointestinal ulcers and other abnormalities
  - Surgical procedures

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How is Anemia in CKD Treated?

- Once the diagnosis of anemia is made by a low hemoglobin level, the first step is to evaluate for iron deficiency which is common and treatable
- The tests for iron deficiency are
  - Transferrin saturation which is a measure of iron circulating in the blood
  - Ferritin which is a measure of iron stored in the body

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Treating Iron Deficiency: CKD Patients Not on Hemodialysis

- A diagnosis of iron deficiency is made in an anemic patient with CKD if
  - The transferrin saturation is less than 20% OR
  - The ferritin is less than 100
- For CKD patients with iron deficiency the first treatment is usually an oral iron supplement unless
  - The iron deficiency is severe
  - The patient has had an adverse reaction to oral iron supplements in the past

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Treating Iron Deficiency: CKD Patients Not on Hemodialysis

- Many patients with CKD and iron deficiency anemia will not respond to oral iron supplements
  - Absorption of oral iron is impaired in patients with CKD due to systemic inflammation
  - There is a high incidence of adverse reactions to the doses of oral iron required (3 tablets per day of ferrous sulfate), mostly nausea and constipation
  - The iron deficiency is too severe

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Treating Iron Deficiency: CKD Patients Not on Hemodialysis

- The goal of iron therapy is to increase the transferrin saturation to 20-30%, not to normalize the hemoglobin level
- A new oral iron product, ferric citrate, appears to be more effective and have fewer side effects than current oral iron agents, but it is more expensive and requires a prescription
- Patients who fail a 1-3 month trial of oral iron therapy may be candidates for intravenous (IV) iron

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Intravenous Iron in CKD Patients Not on Hemodialysis

- Generally given in an infusion center, over about 30 minutes
- Number of treatments depends upon agent used
  - May require 4-5 infusions with older iron agents
  - Newer iron agents require 1-2 infusions
- Total iron dose usually will raise hemoglobin level by 1 point (ex: from 10 to 11)

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Intravenous Iron in CKD Patients on Hemodialysis

- Oral iron agents are not effective in patients on hemodialysis due to decreased absorption and ongoing iron losses
- Intravenous iron is administered or given during the hemodialysis treatment through the blood circuit
- About 80% of hemodialysis patients require regular intravenous iron treatments

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Intravenous Iron in CKD Patients on Hemodialysis

- Intravenous iron is given to correct iron deficiency (repletion) and to prevent iron deficiency due to ongoing iron losses (maintenance)
- Repletion usually requires 8-10 larger doses of intravenous iron during consecutive hemodialysis treatments
- Maintenance usually requires a smaller dose of intravenous iron given every 1-2 weeks

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Side Effects of Intravenous Iron

- The major side effects of the forms of intravenous iron usually used in patients not on hemodialysis are allergic reactions
- The major side effects of the forms of intravenous iron usually used in patients on hemodialysis are nausea, vomiting and low blood pressure
- Side effects are usually decreased with lower doses of iron given more slowly

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Erythropoietin (EPO) Treatment (ESAs)

- If an anemic patient with CKD does not have iron deficiency or another identifiable cause of anemia then the anemia can be assumed to be due to EPO deficiency
- There are several forms of EPO on the market that can be used to replace the deficient hormone in patients with CKD
- Since EPO is a protein, it cannot be administered by mouth and must be given by injection into under the skin or into the bloodstream

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Erythropoietin (EPO) Treatment (ESAs)

- High doses of EPO have been associated with negative cardiovascular events, especially stroke
- The Food & Drug Administration recommends that EPO be initiated only in patients with hemoglobin less than 10 and the drug be decreased or discontinued when the hemoglobin goes above 10 in non-dialysis patients and 11 in dialysis patients

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Types of EPO

- Epoetin alfa (Epogen®, Procrit®, Retacrit®) – identical to the hormone made by the kidneys. Given every treatment in hemodialysis patients and every 1-2 weeks in non-hemodialysis patients
- Darbepoetin alfa (Aranesp®) – given every week in hemodialysis patients and every 2-4 weeks in non-hemodialysis patients
- Methoyx polyethylene glycol-epoetin beta (Mircera®) - given every 4 weeks in hemodialysis patients (starting dose every 2 weeks)

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Administration of EPO in CKD Patients Not on In-Center Hemodialysis

- Given by injection under the skin
- Frequency of injection depends on the agent used
- Medicare does not allow for self-administration of EPO at home for non-dialysis patients, so patient must go to a clinic to get the injection
- Other forms of insurance allow for EPO injection at home by patient or helper

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Administration of EPO in CKD Patients on In-Center Hemodialysis

- EPO is usually administered into the hemodialysis blood circuit, but can be given subcutaneously which decreases the dose required
- The dose of EPO is adjusted as needed on a monthly basis to keep the hemoglobin in the 10-12 range
- A small percentage of patients will not be able to achieve the target hemoglobin level despite enough EPO and iron therapy

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Red Blood Cell Transfusions

- Transfusion of red blood cells is a last resort for patients who fail EPO and iron therapy or whose hemoglobin level has fallen due to acute illness
- The trigger hemoglobin level for red blood cell transfusion depends on a number of factors, but is generally around 7
- Red blood cell transfusions can sensitize the patient to other people's proteins, which may limit options for future kidney transplant

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New Treatments for Anemia in CKD

- A number of new orally administered drugs are being developed which can prompt the body to make more EPO even in the presence of kidney failure
- The EPO then stimulates the bone marrow to make new red blood cells to increase the hemoglobin to the target range of 10-12
- It is hoped that the first of these new drugs will be approved in 2020

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Summary and Conclusions

- Anemia is very common in patients with CKD; and its frequency and severity increase with the severity (stage) of the CKD.
- Anemia causes many symptoms including fatigue, loss of stamina, shortness of breath and dizziness.
- The cause of anemia in most patients with CKD is iron deficiency and EPO deficiency.

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Summary and Conclusions

- Iron and EPO replacement are effective in most patients with CKD, but there are side effects associated with high doses of both agents.
- New agents for anemia being developed can be taken orally and may offer greater convenience and patient access.

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Live Q&A

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