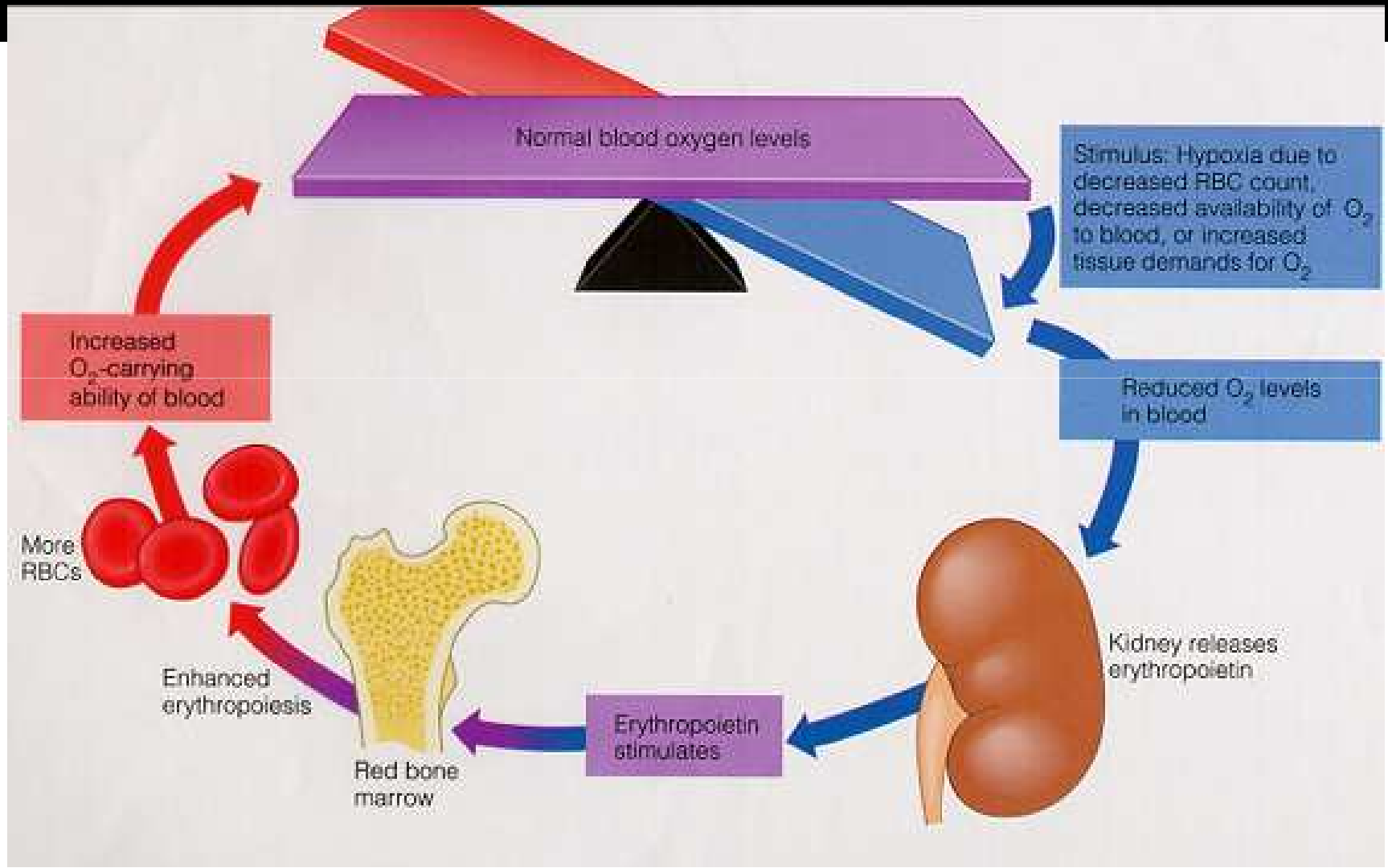

بسم الله الرحمن الرحیم

Anemia in Chronic Kidney Disease and ESRD Patients

Objectives

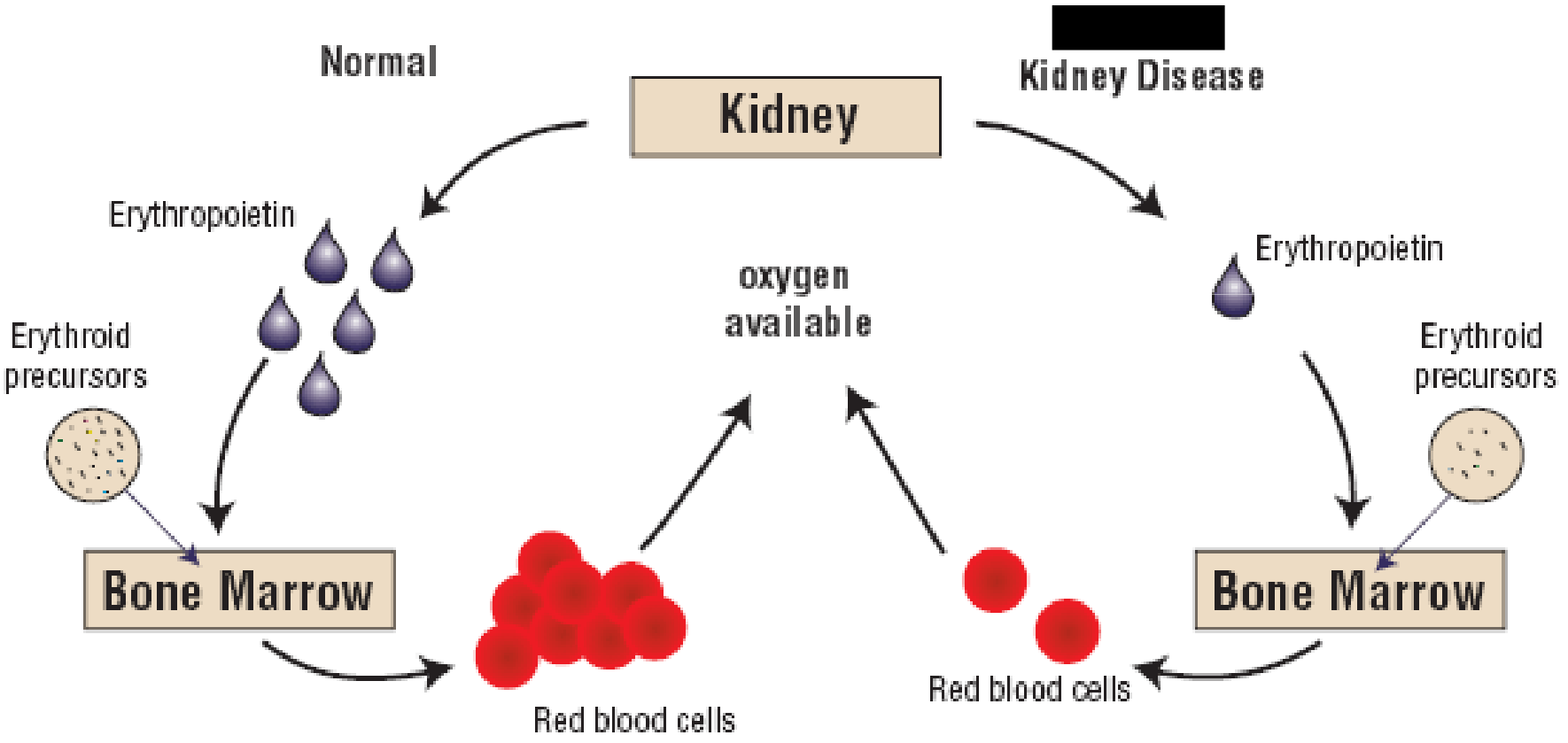
- Review the role of the kidney in RBC production and the factors influencing onset of anemia in CKD.
- Review the treatment of anemia in CKD
- Understand the importance of blood avoidance in patients with CKD

Erythropoiesis



www.tarleton.edu/Departments/anatomy/erythro.jpg

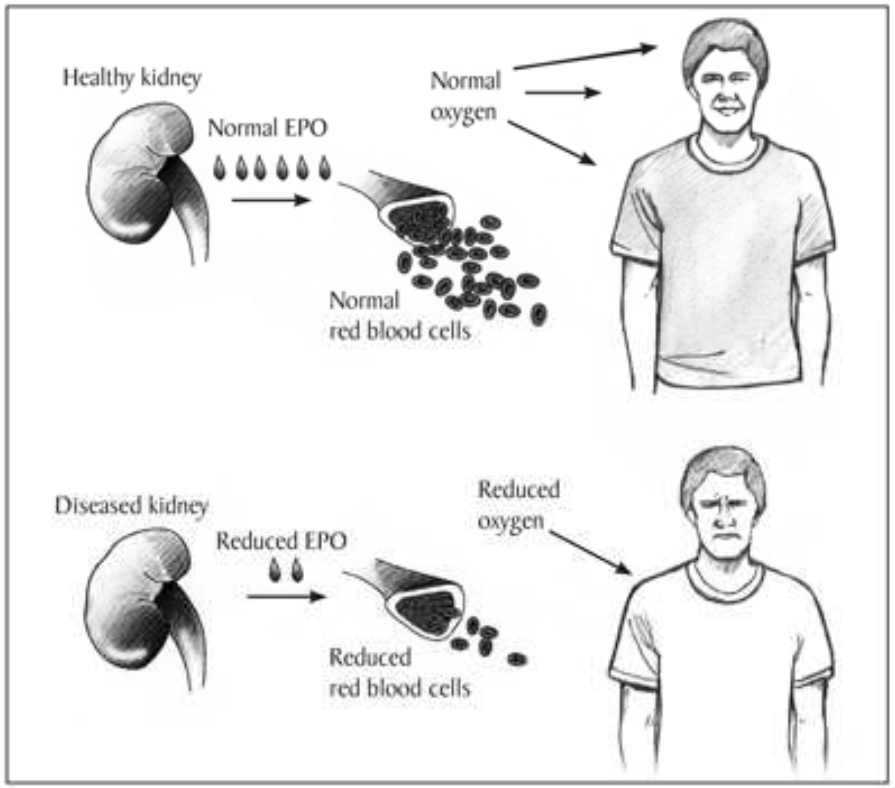
Erythropoiesis Failure in Renal Disease



Adapted from http://www.anemia.org/professionals/monograph/images/diabetes_kidney.gif

What are the implications of anemia in CKD patients?

- Fatigue
- Diminished quality of life
- Impaired cognitive function
- Cardiovascular effects:
  - Leading cause of death in adult population.
  - Anemia correction has shown to decrease LV mass index.
  - However, no studies have shown treatment of anemia to prevent LVH in children.



Increased Morbidity

Probability of Being Hospitalized for More Than 30 Days Within 1 Year Post-Dialysis Initiation

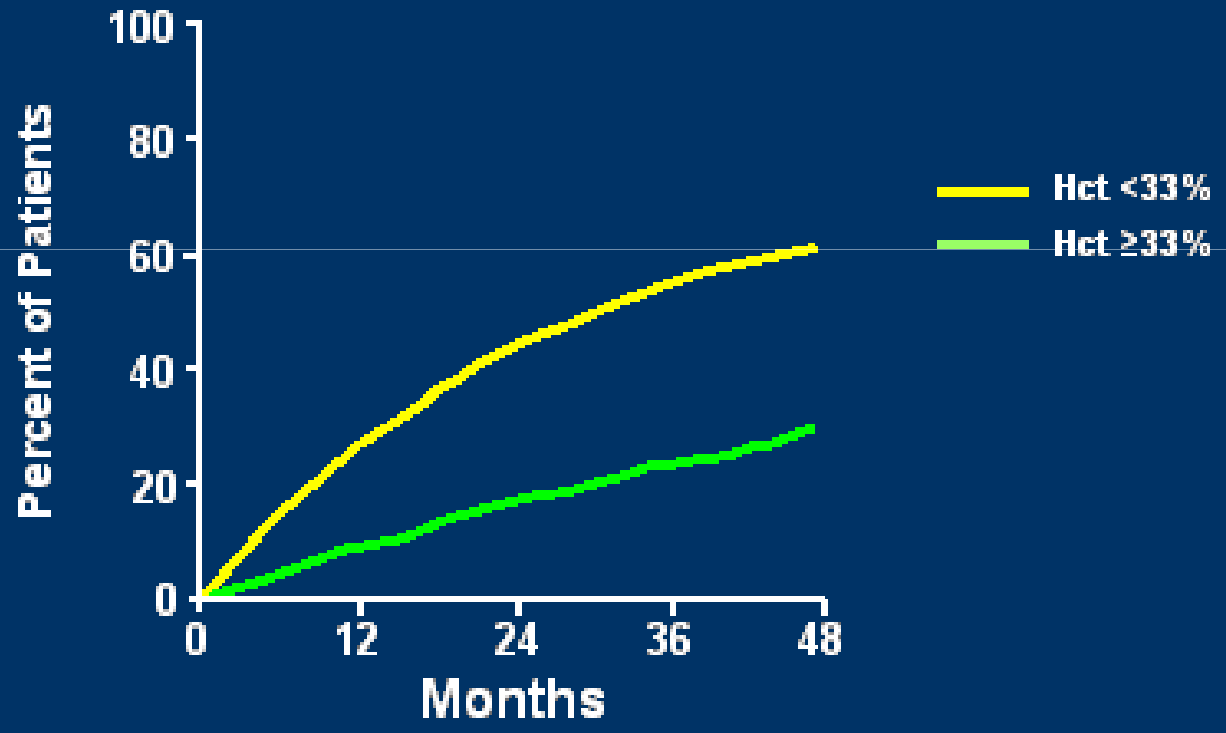
PD	Probability,% (SE)	*P*
Hct ≥33%	12.3 (2.1)	
Hct <33%	17.2 (1.8)	<0.001

HD	Probability,% (SE)	*P*
Hct ≥33%	2.0 (1.7)	
Hct <33%	11.1 (2.2)	<0.001

Warady et al. *Pediatr Nephrol*. 2003;18:1055-1062.

Increase in the ESRD Population

Progression to ESRD



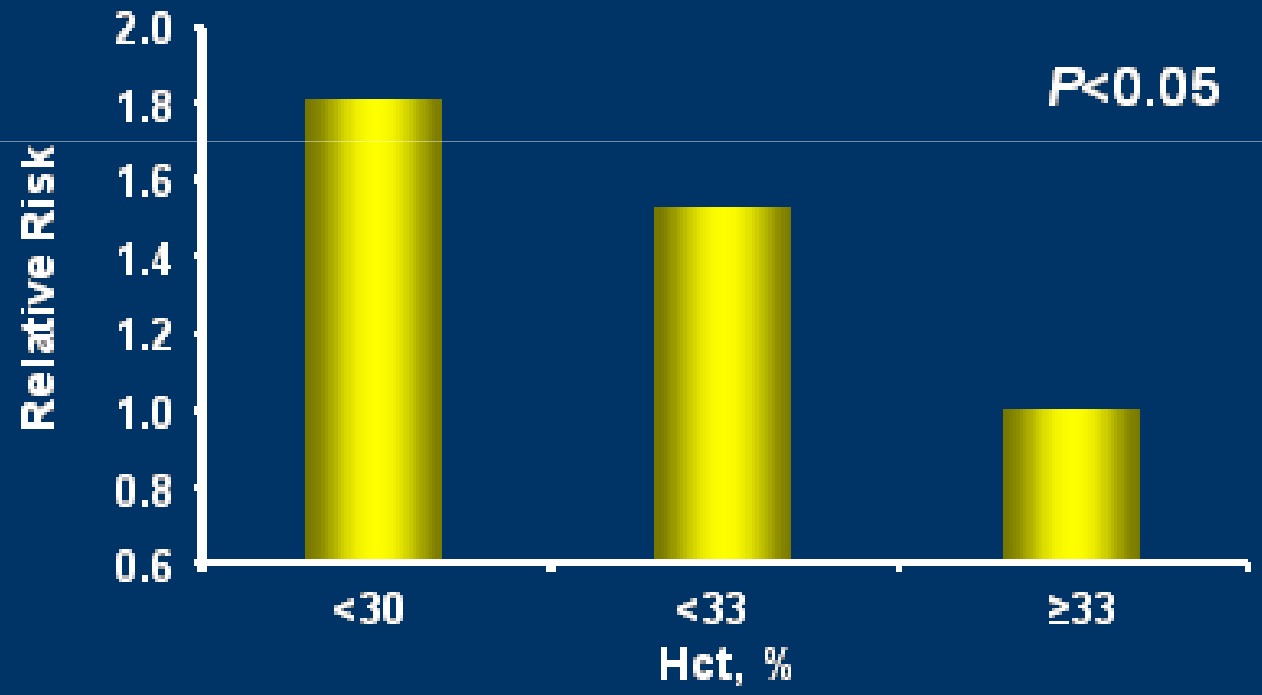
North American Pediatric Renal Transplant Cooperative Study (NAPRTCS).
2004 Annual Report: Renal Transplantation, Dialysis, Chronic Renal Insufficiency.

Increased Mortality

- North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database from 1992 to 2001:
  - Children with an Hgb level < 9.9 g/dL *versus* those with an Hgb level > 9.9 g/dL showed an elevated risk for mortality: adjusted RR 1.52 (95% CI, 1.03 to 2.26; P < 0.05).

Mortality

Relative Risk of All-Cause Death



Waradγ et al. *Pediatr Nephrol*. 2003;18:1055-1062.

Review of NAPRTCS database

When does anemia occur in CKD patients?

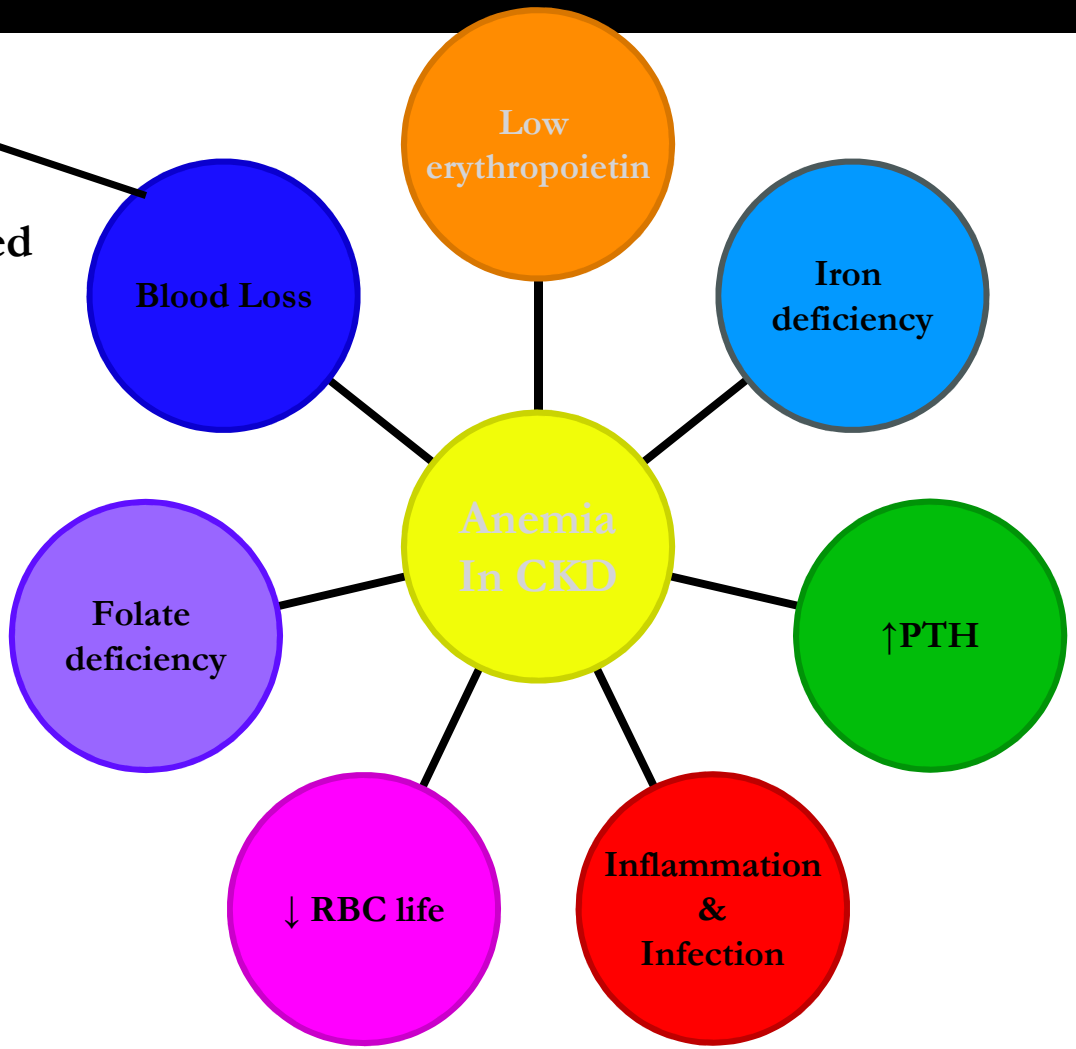
Stage	Description	GFR (mL/min/1.73m^2)
I	Kidney damage with normal or increased GFR	≥90
II	Mild ↓GFR	60-89
III	Moderate ↓GFR	30-59
IV	Severe ↓GFR	15-29
V/ESRD	Kidney failure	<15 or dialysis

Most agree on 20-35 ml/min/1.73m2

From National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis 39(suppl 1):S1–S266, 2002.

Contributing Factors in Anemia

1. Phlebotomy
2. Dialyzer loss
3. GI loss
4. Uremic acquired platelet dysfunction

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Blood Loss

- For pediatric hemodialysis patients
  - Mean GI blood loss is 11 mL/m^2/d
  - Dialyzer losses of 8 mL/m^2 per treatment
  - Translates to a yearly cumulative loss of approximately 1.6 g/1.73 m^2.

Other Potential Contributing Factors

- Folate or B12
- Carnitine
- Malnutrition ↔ surrogate marker of inflammation or caused by?
- Medications
- Increased inhibitory molecules: lead, aluminum toxicity
- Bone marrow suppression or myelofibrosis

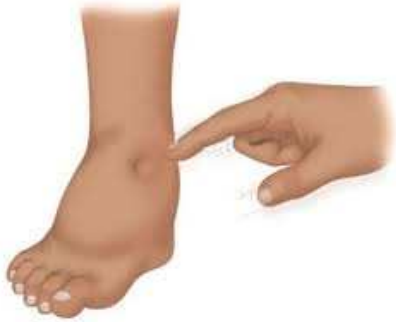
KDOQI

- Anemia in patients with CKD is not always caused by erythropoietin deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to ESA hyporesponsiveness.

AJKD, VOL 47, NO 5, SUPPL 3, MAY 2006

Avoid of unnecessary transfusion

- Given the relationship between Hb level and interdialytic weight gain in patients with HD
  - Consideration must be given to potential dilutional effect of interdialytic weight gain.



AJKD, VOL 47, NO 5, SUPPL 3, MAY 2006

Plenty of reasons nephrologists want to avoid transfusion

- Sensitization

Indications for blood transfusion

- For clinically symptomatic anemia
- In the setting of acute bleeding or blood loss
- Goal is to prevent inadequate tissue oxygenation or heart failure.

- K/DOQI guidelines:
  - **In the opinion of the Work Group, no single Hgb concentration justifies or requires transfusion. In particular, the target Hgb recommended for chronic anemia management *should not* serve as a transfusion trigger.**

AJKD, VOL 47, NO 5, SUPPL 3, MAY 2006

Indications for blood transfusion

- Typically anemia of CKD is not acute and there is time to consider alternatives to transfusion.

- K/DOQI guidelines:
  - Before considering transfusion of red blood cells for the treatment of chronic anemia, it is essential to assess signs and symptoms and determine the cause of the anemia so that, when appropriate, treatment other than red blood cell transfusions may be used

AJKD, VOL 47, NO 5, SUPPL 3, MAY 2006

Indications for blood transfusion

- In the presence of severe chronic anemia, transfusion may lead to CHF, particularly in the elderly.
- In patients with HD-CKD, transfusion during hemofiltration may be required.
- The administration of many red blood cell transfusions over a prolonged period can eventually lead to iron overload.

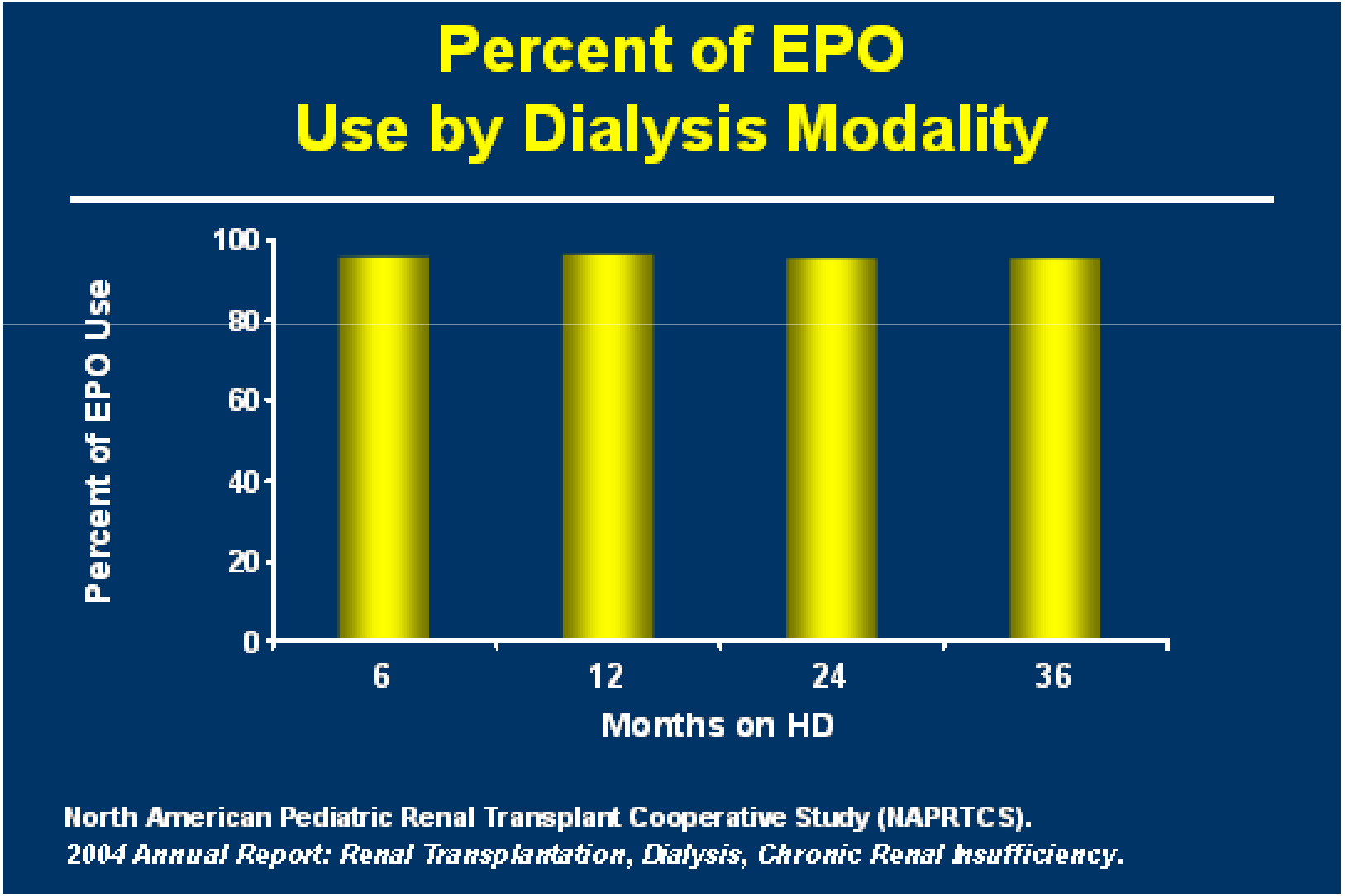
Treatment: K/DOQI Target Hgb/Hct for Epoetin Therapy

The target range for Hgb (Hct) =
11 g/dL (33%) - 12 g/dL (36%)
In dialysis and non-dialysis patients with CKD receiving ESA therapy

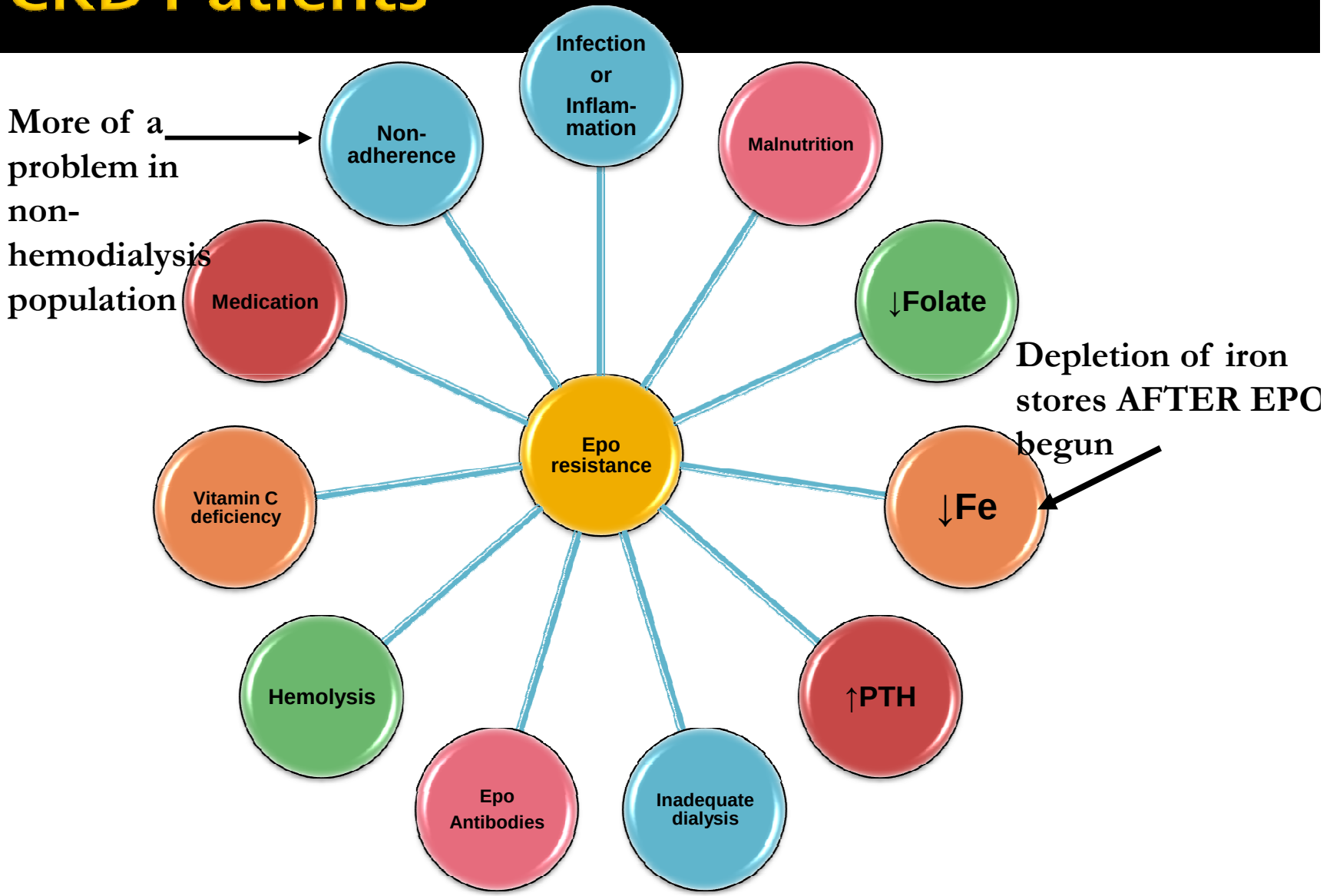
Hgb target should not be greater than 13.0 g/dL.

K/DOQI. Am J Kidney Dis. VOL 47, NO 5, SUPPL 3, MAY 2006

Why do some patients have persistent anemia despite erythropoietin therapy?



Contributing Factors to EPO Failure In CKD Patients

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Why does rHuEPO Treatment Fail?

- Consider OTHER causes other than EPO deficiency especially when:
  - Anemia is out of proportion to level of CKD
    - Concurrent inflammation despite adequate rHuEPO doses and iron stores
    - Blood loss or hemolysis
  - Evidence of leukopenia or thrombocytopenia
  - Evidence of iron deficiency (or folate or B12)
    - Iron deficiency AFTER rHuEPO therapy begun→ depletion of stores.

- 1394 pediatric patients undergoing peritoneal dialysis (PD) who were prospectively followed in 30 countries:
  - ESA sensitivity was positively associated with residual diuresis and serum albumin and inversely associated with serum parathyroid hormone and ferritin.
  - The prevalence of hypertension and left ventricular hypertrophy increased with the degree of anemia.
  - Patient survival was positively associated with achieved hemoglobin and serum albumin and was inversely associated with ESA dose
  - ESA resistance is associated with inflammation, fluid retention, and hyperparathyroidism. Anemia and high ESA dose requirements independently predict mortality.
    - International Pediatric Peritoneal Dialysis Network (IPPN) Registry, J Am Soc Nephrol. 2013 Mar;24(4):665-76

Anemia Evaluation

- Labs:
  - Initial evaluation: CBC, reticulocyte count, iron level, TSAT (=total iron/TIBC), ferritin.

- Does the patient have the following?
  - Reticulocystosis or lack thereof?
  - Low or high iron levels?
  - Macrocytosis or microcystosis?
  - Additional considerations:
    - Elevated CRP?
    - Hemodilution?

Monitoring

- Monitor Hgb every 1-2 weeks until stabilized after therapy begun.
- Maintenance after rHuEPO begun:
  - Monthly Hgb and iron levels for dialysis patients.
  - Every 3 months for stable non-dialysis outpatients

rHuEPO Dosing Influences

- Mode of dialysis.
- Endogenous EPO.
- Patient age.
- Dosing frequency.
- Presence of inhibitory factors on EPO effectiveness.
- Route of administration.

Route of administration

- IV rHuEPO:
  - Increased bioavailability with IV rHuEPO
  - Preferred in HD patients
- Subcutaneous
  - Longer half-life (SQ 14-25 hrs *vs.* IV 5-7.5 hrs)
  - Preferred in PD and non-dialysis CKD patients.

Side Effects

- Hypertension
  - Rapid rise in Hgb
  - Direct effect on vasculature
- Vascular access clotting
- Antierythropoietin antibodies→ red cell aplasia
- Injection site pain and pruritis

Iron Deficiency

- Determine functional versus absolute iron deficiency.
- KDOQI Guidelines:
  - Functional:
    - Transferrin saturation (TSAT) <20%
    - Ferritin >100 ng/ml
  - Absolute:
    - TSAT <20%
    - Ferritin <100 ng/ml

Iron Influence

- Ferritin alone is not reliable → acute phase reactant.
- TSAT of <20% was found to be an independent predictor of anemia in 435 children, ages 12-18, maintained on chronic HD (Frankenfield, et al, *Kidney Int*, 64:1120-24, 2003).

Iron Influence

- IV iron therapy with Ferric Gluconate (Ferrlecit) has been found to be safe and effective in the pediatric HD population.
  - Safer than iron dextran.
  - Dosing recommended at 1.5 mg/kg [max 125 mg/dose] or 12-25 mg/kg divided over 8-12 sessions.
  - Side effects related to rapid release of free iron: rash, loin pain, hypotension, emesis and paresthesias.
  - Contraindicated in patients with acute infections.

K/DOQI Goals of Iron Therapy

- HD CKD patients:
  - Serum ferritin >200 ng/mL
    AND
  - TSAT >20%
  - Preferred route: IV

- Non-HD or PD-CKD patients:
  - Serum ferritin >100 ng/mL
    AND
  - TSAT >20%
  - Preferred route: oral or IV

K/DOQI Guidelines:

PHARMACOLOGICAL AND NONPHARMACOLOGICAL ADJUVANTS

- L-Carnitine: In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.
- Vitamin C: In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.
- Androgens: Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD.

Are renal patients missing potential benefits of Vitamin C?

- Vitamin C deficiency → Lack of response to iron administration
- CKD and dialysis patients at high risk of deficiency
  - Restriction of potassium rich foods (citrus and juices)
  - Concern of oxalate toxicity
  - Vitamin C is water soluble, non-protein bound and LMW = ↑Dialytic removal
    - 1 dialysis treatment→50% or more decreased plasma levels


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