Chronic Kidney Disease and Anemia

A Practical Approach to Management for the Consultant Pharmacist

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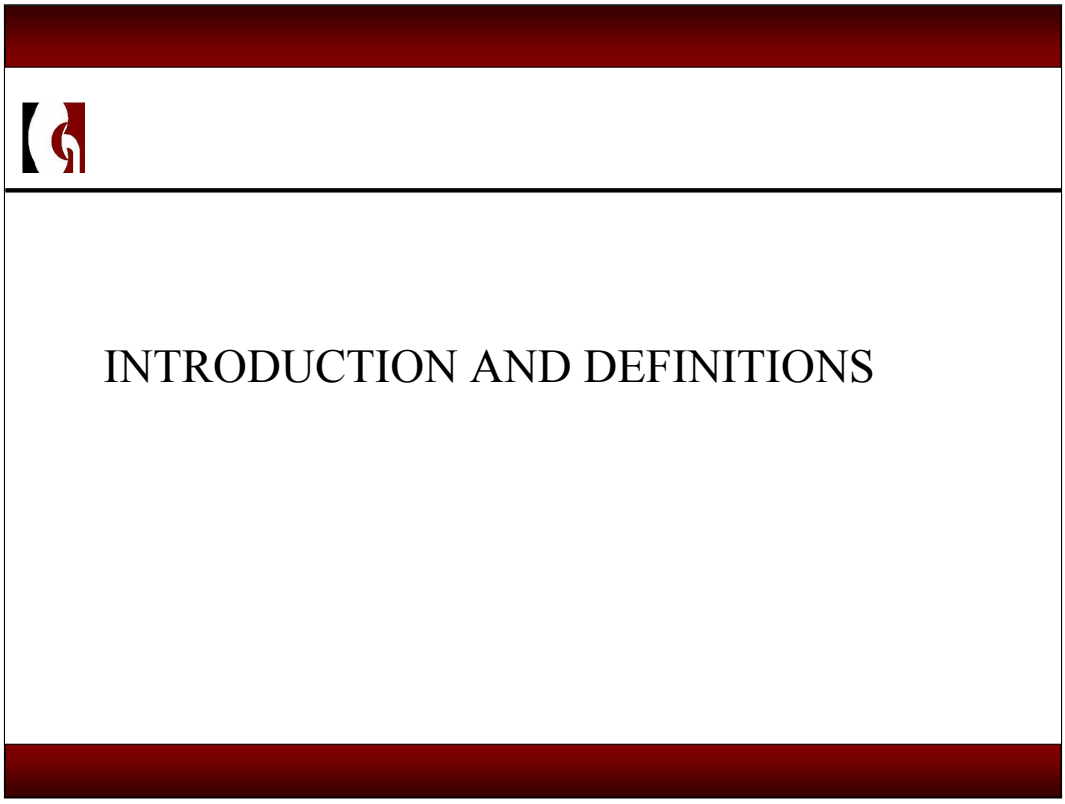
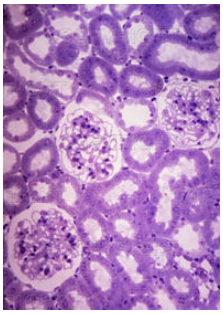
Learning Objectives

1. To define chronic kidney disease (CKD)
2. To discuss the prevalence of CKD and anemia in older patients
3. To review the impact of anemia in the LTC settting
4. To review the pathophysiology of chronic kidney disease and the development of anemia
5. To review the differences in RBC production in healthy individuals vs individuals with CKD
6. To review how to assess for CKD-related anemia in geriatric patients
7. To review treatments available for CKD-related anemia


INTRODUCTION AND DEFINITIONS

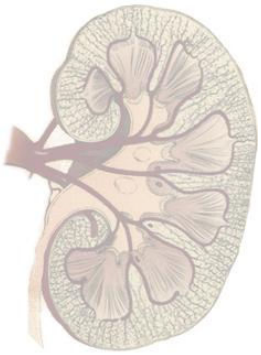
What is GFR?

- Glomerular Filtration Rate (GFR)
  - *The rate at which fluid containing metabolic waste products is filtered by the glomerulus of the kidney*



Chronic Kidney Disease

- A condition which occurs when the kidneys can not do their job of cleaning blood of toxins and waste products.
- Kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests
- GFR < 60 mL per minute per 1.73 m2 for three months or more, with or without kidney damage



http://www.google.com/search?hl=en&lr=&oi=definer&q=define:chronic+kidney+disease&defl=en

How do we estimate GFR?

- GFR should be estimated using age, creatinine, gender, race and body size
- Creatinine Clearance
  - Cockcroft Gault and other formulas
  - 24 hour urine creatinine determination
  - **Modification of Diet in Renal Disease (MDRD)**

Estimated GFR (mL/min/1.73 m^2) =

186 x $(SCr)^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

Staging and Prevalence

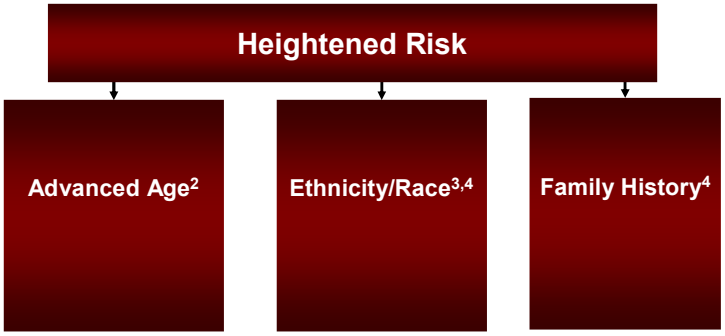
NKF Kidney Disease Outcomes Quality Initiative (K/DOQI): CKD Stages[1]

	Stage	Description	GFR (mL/min/1.73 m^2)
5,900,000	1	Kidney damage with normal or ↑ GFR	≥90
5,300,000	2	Kidney damage with mild ↓ GFR	60-89
7,600,000	3	Moderate ↓ GFR	30-59
400,000	4	Severe ↓ GFR	15-29
300,000	5	Kidney failure	<15 (or dialysis)

National Kidney Foundation. *Am J Kidney Dis 2002;39(suppl 1): S1-S266.*

RISK FACTORS AND PREVALENCE

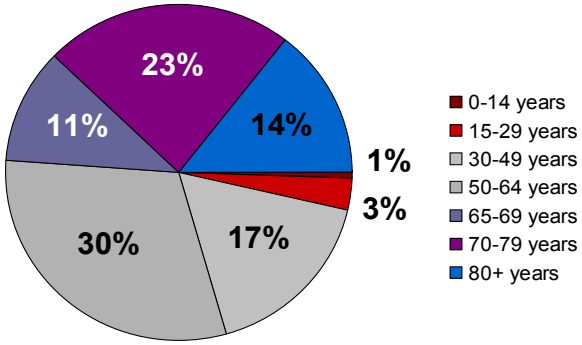
Risk Factors for CKD



References: 1. United States Renal Data System. *2006 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States*. Bethesda, Md: National Institutes of Health, National Institute of Diabetes & Digestive & Kidney Diseases, Division of Kidney, Urologic, & Hematologic Diseases; 2006. **2.** Hansberry et al. *Adv Chronic Kidney Dis*. 2005;12:71-77. **3.** Levey et al. *Ann Intern Med*. 2003;139: 137-147. **4.** National Kidney Foundation. *Am J Kidney Dis*. 2005;46(suppl 3):S1-S158.

The Effect of Age On CKD Prevalence

Patients >64 years of age make up 48% of patients with CKD

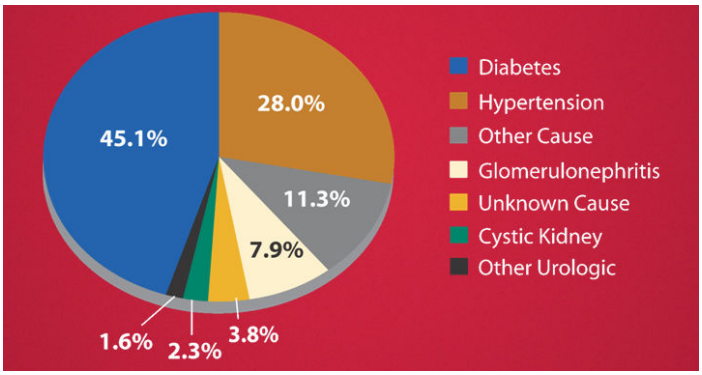


Adapted from the United States Renal Data System (USRDS).[1]

Reference: 1. United States Renal Data System. 2007 annual data report reference tables: incidence. Available at: http://www.usrds.org/2007/ref/A_incidence_07.pdf. Accessed February 6, 2008.

Causes of CKD

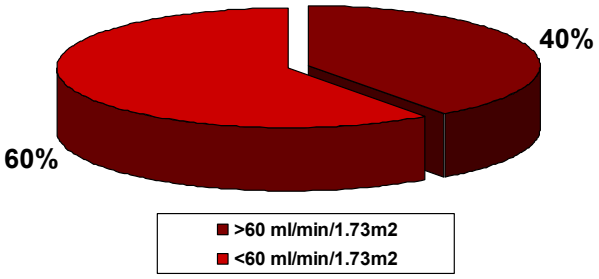
Diabetes and Hypertension are the most common causes of CKD



United States Renal Data System. 2004 Annual Data Report Atlas of End-Stage Renal Disease in the United States. Bethesda, Mo. National Institutes of Health

Prevalence of CKD in the LTC Facilities

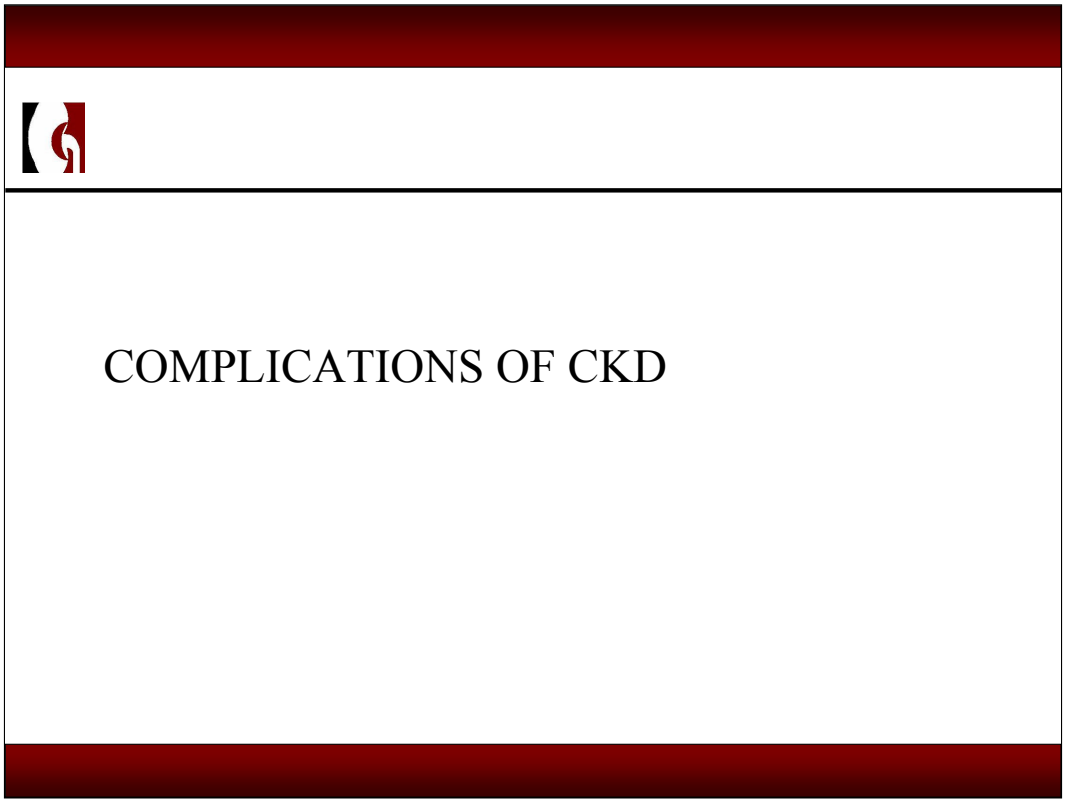
- Based on a retrospective, cross-sectional analysis of 9931 LTC residents age 65 years or older[1]
  - **Approximately 40% of LTC patients had CKD, with a GFR of <60 mL/min/1.73 m^2 [1]**



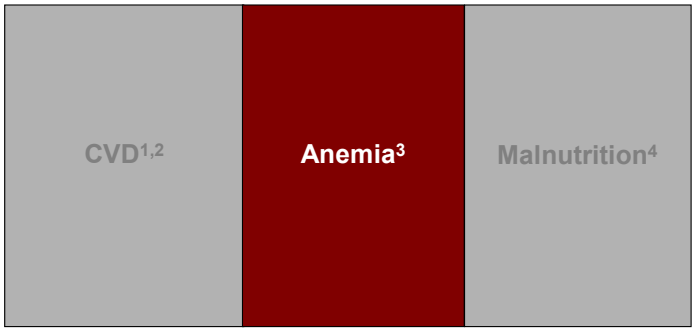
Reference: 1. Garg et al. *Kidney Int.* 2004;65:649-653.

Prevalence Summary

- Anemia and CKD occur commonly in LTC facility patients
- Anemia is often ignored when recognized due to the thought process of, “anemia is a consequence of aging”
- It is difficult to discern the underlying cause of anemia without the appropriate workup. Iron and B12 are not the “cure-alls”
- **Anemia directly impacts QOL and quality indicators**
- **The treatment of anemia is not just a preventative treatment. Patients feel better immediately**


COMPLICATIONS OF CKD

COMPLICATIONS ASSOCIATED WITH CKD



References: 1. Collins et al. *Kidney Int.* 2003;64(suppl 87):S24-S31. **2.** Go et al. *N Engl J Med.* 2004;351:1296-1305. **3.** National Kidney Foundation. *Am J Kidney Dis.* 2006;47(suppl 3):S1-S145. **4.** Pupim et al. *Semin Nephrol*. 2006;26:134-157.

CKD and Anemia

- Anemia is a common complication of chronic kidney disease because the kidneys are unable to manufacture enough erythropoietin, a hormone that regulates the production of red blood cells.

Anemia Defined

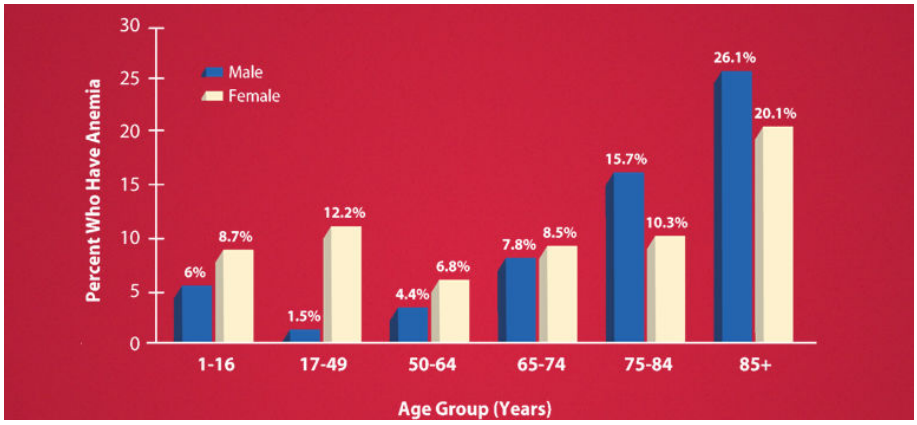
NKF Definition of CKD-related Anemia[1]	WHO Definition of Anemia in the General Population[2]
Men: Hb level <13.5 g/dL Women: Hb level <12.0 g/dL	Men: Hb level <13.0 g/dL Women: Hb level <12.0 g/dL

Hb=hemoglobin.

References: 1. National Kidney Foundation. *Am J Kidney Dis.* 2006;47(suppl 3):S1-S145.
2. Guralnik et al. *Hematology.* 2005:528-532.

The Prevalence of Anemia Increases with Age[1,2]

- The highest rates of anemia occurs in the very old[3]

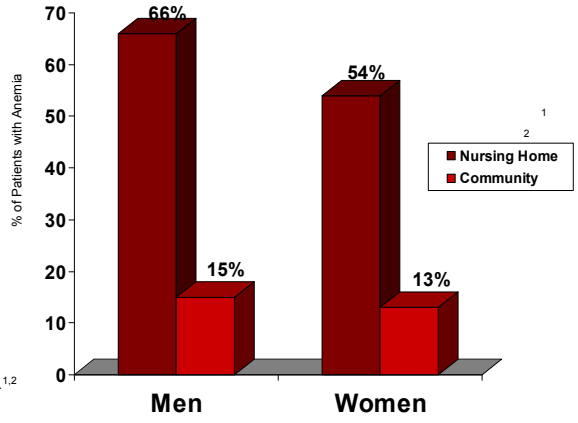


1. Carmel R. *Blood Rev*. 2001;15:9-18. **2.** Salive et al. *J Am Geriatr Soc*. 1992;40:489-496. **3.** Guralnik et al. *Blood*. 2004;104:2263-2268.

Anemia Prevalence Higher in LTC Versus Community Setting

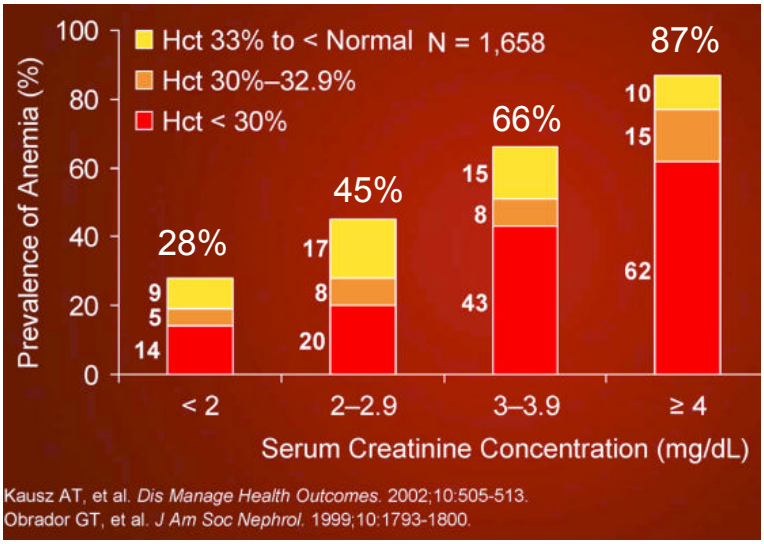
- Based on index Hb in the SALT study, 56% (n=317) of all residents evaluated were anemic*[1]
- 4-fold higher rate of anemia found in nursing home residents over 70 years of age in the SALT study versus community rates found by Salive, 1992[1,2]

*WHO definition: Hb <12 g/dL in women, <13 g/dL in men.[1,2]



References: 1. Pandya et al. Study of Anemia in Long-Term Care (SALT)–Prevalence of anemia in nursing home residents: relationship with resident characteristics and comorbidities. Poster presented at: Annual Symposium of the American Medical Directors Association; March 29-April 1, 2007; Hollywood, Fla. **2.** Salive et al. *J Am Geriatr Soc.* 1992;40:489-496.

The Prevalence of Anemia Increases with Decreased Renal Function



Kausz AT, et al. *Dis Manage Health Outcomes.* 2002;10:505-513.
Obrador GT, et al. *J Am Soc Nephrol.* 1999;10:1793-1800.

Why Treat CKD Anemia?

- Cardiac complications
  - Worsening CHF
  - LVH
- **Depression**
- **Insomnia**
- **Impaired cognition**
- **Loss of appetite**
- **Functional dependence**
- **Hospitalization**
- **Falls/ Fracture?**
- Muscle weakness

MDS

Anemia Directly Impacts QOL for Residents in LTC

References: 1. Penninx et al. *J Am Geriatr Soc*. 2004;52:719-724. **2.** Penninx et al. *Am J Med*. 2003;115:104-110. **3.** Beard et al. *Ann Epidemiol*. 1997;7:219-224. **4.** Dharmarajan et al. *J Am Med Dir Assoc*. 2004;5:395-400. **5.** Salive et al. *J Am Geriatr Soc*. 1992;40:489-496. **6.** Izaks et al. *JAMA*. 1999;281:1714-1717. **7.** Artz et al. *J Am Geriatr Soc*. 2004;52:423-427. **8.** Penninx et al. *Blood*. 2003;102(11, pt 1):251a. Abstract 881. **9.** Kikuchi et al. *J Am Geriatr Soc*. 2001;49:1226-1228.

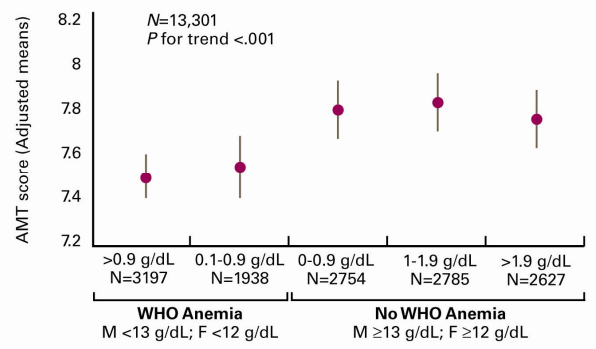
Anemia and Impaired Cognition?

- Zamboni et al1
- Objective
  - To evaluate the **association between Hb levels/anemia and cognitive function** in hospitalized older patients
- Study Design
  - Data from the **Italian Group** of Pharmacosurveillance in the Elderly (GIFA) study
  - Collaborative, **observational study**
- Methods
  - Cognitive performance was assessed by the **Hodkinson's Abbreviated Mental Test (AMT). Scores <7 defined cognitive impairment**
  - Anemia was defined by WHO criteria: Hb <12 g/dL in women; Hb <13 g/dL in men
- Patients
  - **13,301 patients; mean age was 72 years**

Reference: 1. Zamboni et al. *Int J Geriatr Psychiatry.* 2006;21:529-534.

Anemia and Impaired Cognition?

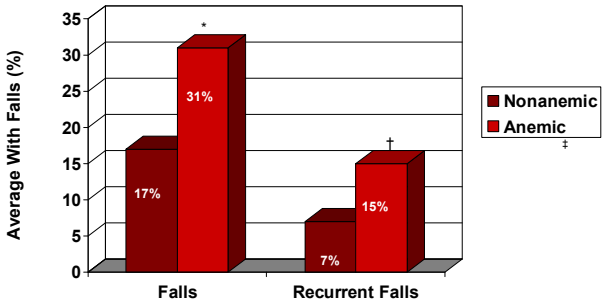
- **Patients without anemia had significantly higher AMT scores versus those with anemia (*P*<.001)1**



Reference: 1. Zamboni et al. *Int J Geriatr Psychiatry.* 2006;21:529-534.

Anemia and Falls?

Patients With Anemia Had More Falls and More Recurrent Falls[1]



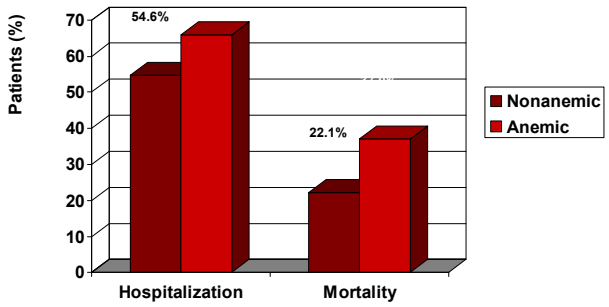
- Based on the regression model developed for the **SALT study, anemia‡ and use of psychoactive medication were found to be associated with 4 times the risk of experiencing a fall[1]**
- Another retrospective study by **Philpot et al (2007) found a 68% higher likelihood of falling in patients with anemia‡** compared to nonanemic patients (OR: 1.68; 95% confidence interval: 1.20-2.36) (N=804)[2]

*P<.001.
†P=.003.
‡Anemia defined by the WHO criteria: Hb <13 g/dL men, Hb <12 g/dL women.[1]

References: 1. Pandya et al. Study of anemia in long-term care (SALT): relationship between anemia and falls in the nursing home setting. Poster presented at: Annual International Meeting of the International Society of Pharmacoeconomics and Outcomes Research; May 19-23, 2007; Arlington, Va. **2.** Philpot et al. Anemia in long-term care patients: prevalence and relationship to falls. Poster presented at: Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research; May 19-23, 2007; Arlington, Va.

Anemia and Hospitalization?

Patients With Anemia Had Increased Hospitalization and an Increased Risk of Death (*P*<.001)[1]



- N=3607 patients aged 71 years or older

Reference: 1. Penninx et al. *Blood*. 2003;102(11, pt 1):251a. Abstract 881.

PATHOPHYSIOLOGY OF CKD ANEMIA

Pathophysiology

- Red Blood Cell
  - Healthy adults have between 4 and 6 million
  - Carries oxygen to tissues and organs
  - Removes CO2 from tissues and organs and returns to the lungs fro re-oxygenation
  - The formation of red blood cells is known as erthyropoiesis, and the kidney plays a vital role in this process.

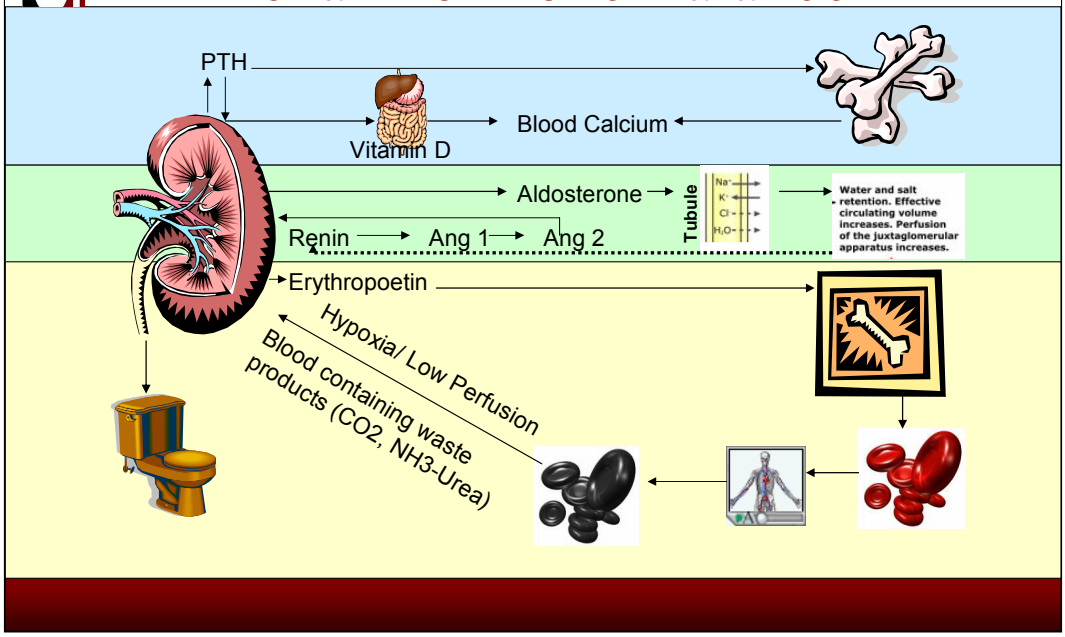
Pathophysiology

- Kidney Funtion
  - Fluid regulation and ADH secretion
  - Acid-base regulation through hydrogen ions and bicarbonate control
  - Secretes renin and aldosterone as part of the RAAS (Blood pressure)
  - Metabolizaton of insulin
  - Nitrogenous waste products

Pathophysiology

- Kidney Function
  - Hormone regulation
    - Calicitriol and parathyroid hormone
      - Vitamin D allows for calcium reabsorption from the intestines
      - Turns the parathyroid gland on and off
    - Erythropoesis
      - Stimulates the division and differentiation of erythroid progenitor cells in the bone marrow leading to RBC production

Renal Hormone Balance



The Vicious Cycle of CKD and Anemia

- Hypertension (RAAS)
- Weak, fibrous, mushy bone (PTH) leading to a reduction in bone marrow and progenitor cell response
- Inadequate EPO response and less RBC production
- Increased circulating ammonia/urea leading to decreased RBC lifespan

ASSESSMENT OF CKD ANEMIA

What Are the Signs and Symptoms of Anemia in General?

Physical Signs	Symptoms
Pallor of skin, nail beds, mucous membranes	Fatigue/drowsiness
Mild pedal edema	Dyspnea
Tachycardia, systolic ejection murmur, cervical venous hum, left ventricular stroke volume	Palpitations
Gallop rhythm may be present	Ankle swelling
Decreased exercise capacity	Anorexia
Cognitive impairment	Headache

References: 1. Varat et al. *Am Heart J*. 1972;83:415-426. **2.** Bunn HF. Anemia. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. 13th ed. New York, NY: McGraw-Hill, Inc; 1994:313-317.

NKF Guidelines: Assessment of Anemia in CKD

Monitor and Measure Hb in Patients With CKD[1]

- **Test Hb at least annually in all patients, regardless of stage or cause of CKD**

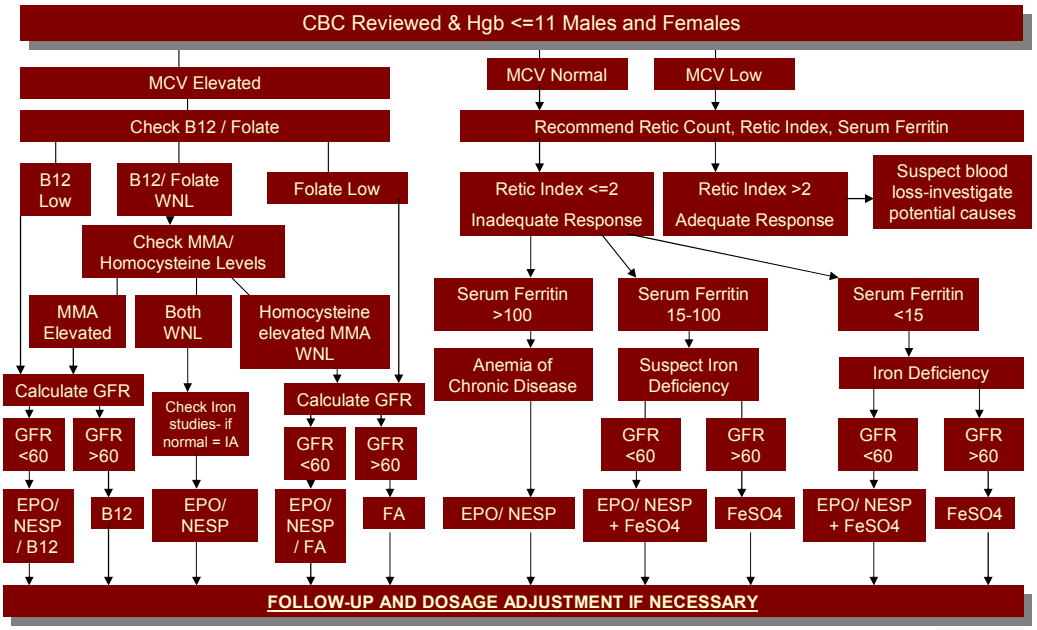
- **Assessment should include the following tests:**
  - A complete blood count (initial iron status with MCV)
  - Absolute reticulocyte count (is the bone marrow producing RBCs?)
  - Serum ferritin to assess iron stores (>100 ng)
  - Serum transferrin saturation (TSAT) or content of Hb in reticulocytes to assess adequacy of iron for erythropoiesis (>20%)
  - Stool for occult blood (R/O GI bleeding due to other causes such as medications)

1. National Kidney Foundation. *Am J Kidney Dis*. 2006;47(suppl 3):S1-S145.

Interpreting the CBC

- CBC interpretation when evaluating anemia
  - ↓ Hb, ↓MCV, ↓MCHC
    - General interpretation
      - Iron deficiency
      - Chronic blood loss
  - ↓ Hb, ↑MCV, Normal MCHC
    - General interpretation
      - B12/ folate deficiency
      - Hypothyroidism
      - Myelodysplastic syndrome
  - ↓ Hb, Normal MCV, Normal MCHC
    - General Interpretation
      - Acute blood loss (within weeks)
      - Possible hemolytic anemia (drug-induced?)
  - RDW
    - General interpretation
      - High value = variation in cell size

CKD & Anemia Management Algorithm

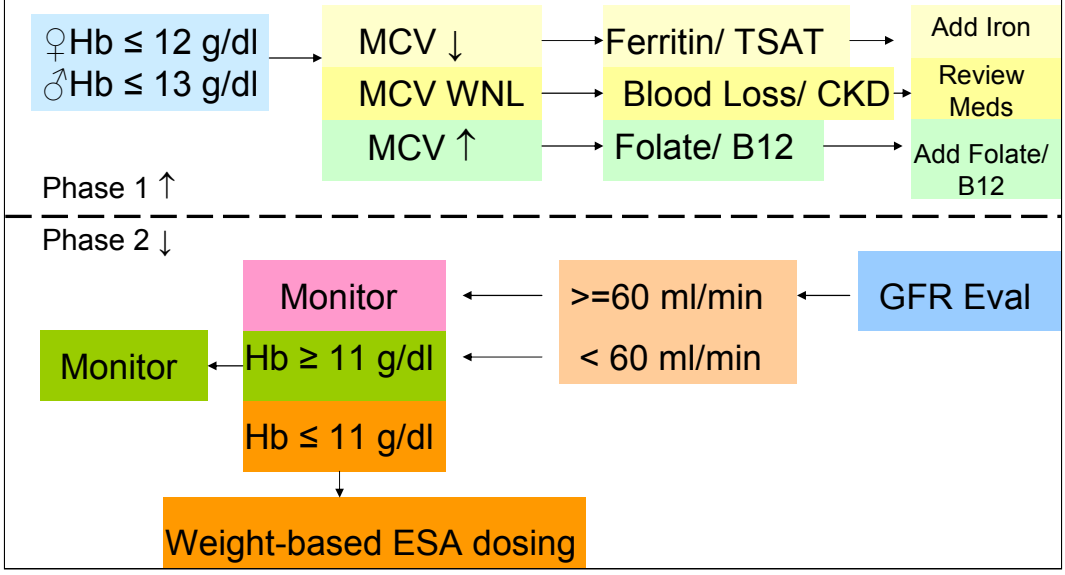


Adapted from:

1. Smith DL. Anemia in the Elderly. Am Fam Phys. Vol.62/No. 7 (October 1,2000)
2. National Kidney Foundation. Am J Kidney Dis. 2002;39(suppl 1):S1-S266.

GeriMed

Quick Anemia Management Algorithm for the Consultant Pharmacist



ESA Weight-based Dosing

Suggested Blood Modifier Dosing		
	epoetin (Procrit®)	**darbepoetin (Aranesp®)**
Anemia of chronic kidney disease	50 units/kg, SQ three times a week or 150 u/kg once weekly; individualize to target Hgb 10-12 gm/dl	0.75 mcg/kg Q2WK (non-dialysis), 0.45 mcg/kg (dialysis) (Hgb </= 12g/dl)
Weight-based dose for this patient:	**units SQ weekly**	**mcg SQ weekly (dialysis)**
	units SQ Q2 weeks (for comparison)	**mcg SQ Q2 weeks (non-dialysis)**
Chemotherapy related anemia	150 units/kg, SQ one to three times a week, or 40,000 units SQ once a week, 8 week duration	2.25 mcg/kg SQ weekly; individualize to maintain target Hgb
Weight-based dose for this patient:	**units SQ weekly**	**mcg SQ weekly**
AZT-related anemia	100 units/kg, SQ one to three times a week; 8 week duration	
Weight-based dose for this patient:	**units SQ weekly**	
End-stage renal disease	50 to 100 units/kg SQ three times a week; indefinite duration (*if given at dialysis center EPO is dispensed by dialysis center)	
Weight-based dose for this patient:	**units SQ TIW**	
Depressed EPO (based on EP/ Hgb)	100 units/kg SQ weekly	0.45 mcg/kg SQ weekly
Weight-based dose for this patient:	**units SQ weekly**	**mcg SQ weekly**
Blood transfusion	300 units/kg for 10 days before surgery, the surgical day, and 4 days after surgery	
Weight-based dose for this patient:	**units SQ**	

Iron Replacement

- **K/DOQI sets forth recommendations for dosing of oral iron at a daily dose of at least 200 mg of elemental iron for adult patients**
  - ***Percent Elemental Iron for Iron Salts/Formulations***
  - NOTE: Different iron formulations are not directly exchangeable on a mg per mg basis; the different salts contain roughly the following amounts of elemental iron:
    - *Ferrous sulfate:* 20% elemental iron
    - *Ferrous sulfate*: exsiccated (dried): 30% elemental iron
    - *Ferrous gluconate:* 12% elemental iron
    - *Ferrous fumarate:* 33% elemental iron
    - *Carbonyl iron (Feosol):* 100% elemental iron
    - *Polysaccharide-iron complex (Nu-Iron):* 100% elemental iron
    - *Ferrochel® (ferrous bis-glycinate chelate):* 75% elemental iron
    - Combinations
      - Niferex- Polysaccharide-iron complex + ferrous bis-glycinate chelate: 100% elemental iron
      - Chromagen- ferrous bis-glycinate chelate + B12: 75% elemental iron (Folic acid in Chromagen FA)

Clinical Pharmacology. Drug Information Database 2006

Iron Replacement

- Chromagen/ Ferrochel has better than ½ the GI upset as compared with FeSO4 per package insert studies
- Ferrochel® / Niferex have been deemed to have a bioavailability that is 4-7 times greater than ferrous sulfate, while still being regulated by the iron stores in the body
- Niferex, Nu-Iron, Chromagen products may be better options for elderly patients if covered by Part-D plans

1 Coplin MS, et al. Tolerability of iron: a comparison of bis-glycino iron II and ferrous sulfate. Clin Ther 1991;31:606-12.
2 Pineda O. Effectiveness of treatment of iron-deficiency anemia in infants and young children with ferrous bis-glycinate chelate. Nutrition. 2001;17:381-84.
3 Ashmead SD. The chemistry of ferrous bis-glycinate chelate. *Archivos Latinoamericanos De Nutricion*. 2001;51(1):7-12.

Other Treatments

- B12 1000mcg IM q month
- Oral B12 1000 to 2000 ug daily
- Folate 1mg q day
- Epoetin Alfa- 150 units/kg/SC weekly
- Darbepoetin Alfa- 0.45mcg/kg SC weekly
- Darbepoetin Alfa- Non-dialysis CKD- 0.75mcg/kg SC q2 weeks

Erythropoetic Considerations

- Dosage adjustments should occur every 2-6 weeks in 25% increments
- The target Hgb is 12 g/dl due to the potential for cardiac side effects
- Do not D/C and restart
- Check Hgb weekly during initiation and monthly once stable on a dose
- Watch Blood Pressure
- Make sure the patient has adequate iron
- Consider developing a weight-based dosing and monitoring protocol.

Points to Ponder

- Are you including an anemia assessment when you review patients that have fallen?
- Do you consider anemia as a possible contributor to mental changes (mood, cognition, etc)?
- “Would treating anemia make a difference in my patients’ quality of life?”
- “Is it worth the effort due to the prior authorization process?”
- “It is extremely expensive, and I am trying to work on reducing Medicare A costs.”

Q & A