Kidney Disease

Acute and Chronic

Definitions

- Acute Kidney Injury (AKI), also know as acute kidney failure (AKF) or acute renal failure (ARF)
  - Sudden onset with ongoing loss of function due to infection, injury, blockage, poor perfusion, etc. but may be reversible if diagnosed in a timely manner
- Chronic Renal Disease (CKD)
  - GFR less than 60 ml/minute/1.73 m^2, abnormalities of kidney structure or function, present for >3 months
  - https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

SOURCE OF CONCERN

- 26 million Americans - 1 in 9 US adults - have chronic kidney disease (CKD) and another 20 million more are at increased risk.
- The incidence of acute kidney injury (AKI) increasing as patients present with comorbidities and population ages.
  - AKI difficult to diagnose
  - Early detection can help prevent the progression of kidney disease to kidney failure

– National Kidney Foundation
www.kidney.org

SOURCE OF CONCERN

- AKI affects millions of people in the US, increasing morbidity, and mortality
  - Available laboratory tests for early and accurate diagnosis of AKI have significant limitations
    - JALM. 386–399. 02:03. November 2017
    - AKI can progress to CKD and end-stage renal disease
    - Mortality rates 40-80% because of diagnoses delays
- Individuals with CKD more likely to die from heart disease
  - Heart disease also "injures" kidneys leading to impaired renal function
  - Hypertension causes CKD and CKD causes hypertension.

Acute Kidney Injury (AKI)

- Criteria to identify AKI not uniform
- RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria:
  - Risk: Increase in serum creatinine of 50%–99% or urine output of <0.5 mL/kg/h for 6 to 12 hours
  - Injury: Increase in serum creatinine of 100%–199% or urine output of <0.5 mL/kg/h for 12 to 24 hours
  - Failure: Increase in serum creatinine of ≥200% or increase in serum creatinine by >0.5 mg/dL to >4.0 mg/dL or urine output of <0.3 mL/kg/h for >24 h or anuria for >12 hours

Acute Kidney Injury (AKI)

- Acute Kidney Injury Network (AKIN) criteria:
  - Stage 1: Increase in serum creatinine of ≥0.3 mg/dL or 50%–100% or urine output of <0.5 mL/kg/h for 6 to 12 hours
  - Stage 2: Increase in serum creatinine of >100%–200% or urine output of <0.5 mL/kg/h for 12 to 24 hours
  - Stage 3: Increase in serum creatinine of ≥200% or increase in serum creatinine by >0.5 mg/dL to >4.0 mg/dL or urine output of <0.3 mL/kg/h for >24 h or anuria for >12 hours

Acute Kidney Injury (AKI)

- Kidney Disease: Improving Global Outcomes (KDIGO) criteria very similar to RIFLE and AKIN
  - Slight differences in numbers really do not change how/when a patient should be identified and treated
- At issue is need for more sensitive tests/biomarkers to prevent delays in diagnosis and treatment

Other Markers

- Neutrophil gelatinase-associated lipocalin
- Kidney Injury Molecule 1
- Translational Research Investigating Biomarker Endpoints – Acute Kidney Injury (TRIBE-AKI) Consortium Study
  - IL-18 in one study shown to increase on the first day of acute kidney injury
  - KIM-1 increased on day 2
  - Creatinine did not increase till day 3

NATIONAL KIDNEY FOUNDATION

- CKD is classified based on cause, GFR category, and albuminuria category (CGA)
  - Persistent proteinuria means CKD
- High risk groups include those with diabetes, hypertension and family history of kidney disease.
- African Americans, Hispanics, Pacific Islanders, Native Americans and seniors of all races and ethnicities are at increased risk.
- Three tests can be helpful in detecting CKD: blood pressure, urine albumin and serum creatinine.

NKDEP GOALS

- **Health care providers**
  - Increase identification of people at risk.
  - Increase use of strategies to delay or prevent kidney failure in people with CKD.
  - Adequately prepare patients who are unable to delay kidney failure, for dialysis.
  - Promote a multi-disciplinary, coordinated and integrated approach to care.

DEFINITION OF CKD

- NKF's Kidney Disease Outcomes Quality, NIH and NKDEP collaborated on definition for chronic kidney disease (CKD)
- http://www.medscape.com/viewarticle/503813_3

Symptoms of Kidney Disease

- Feel more tired and have less energy
- Have trouble concentrating
- Poor appetite
- Have trouble sleeping
- Muscle cramping at night
- Swollen feet and ankles
- Puffiness around eyes, especially in the morning
- Dry, itchy skin
- Need to urinate more often, especially at night.
  - https://www.kidney.org/atoz/content/about-chronic-kidney-disease#symptoms

GFR DEFINITION

- Glomerular filtration rate is a measure of kidney function
  - The rate refers to the amount of blood that is filtered per minute by the kidneys.
  - Measuring GFR directly difficult
    - Exogenous materials such as inulin best but not simple to use in typical clinical settings
    - Creatinine and Cystatin C best substitutes to date

K/DOQI

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
GFR >90	GFR 60-89	GFR 30-59	GFR 15-29	GFR <15
Kidney damage with normal function	Kidney damage with mild decrease in function*	Moderate decrease in GFR	Severe decrease in GFR	Kidney failure

EVALUATION OF KIDNEY DISEASE

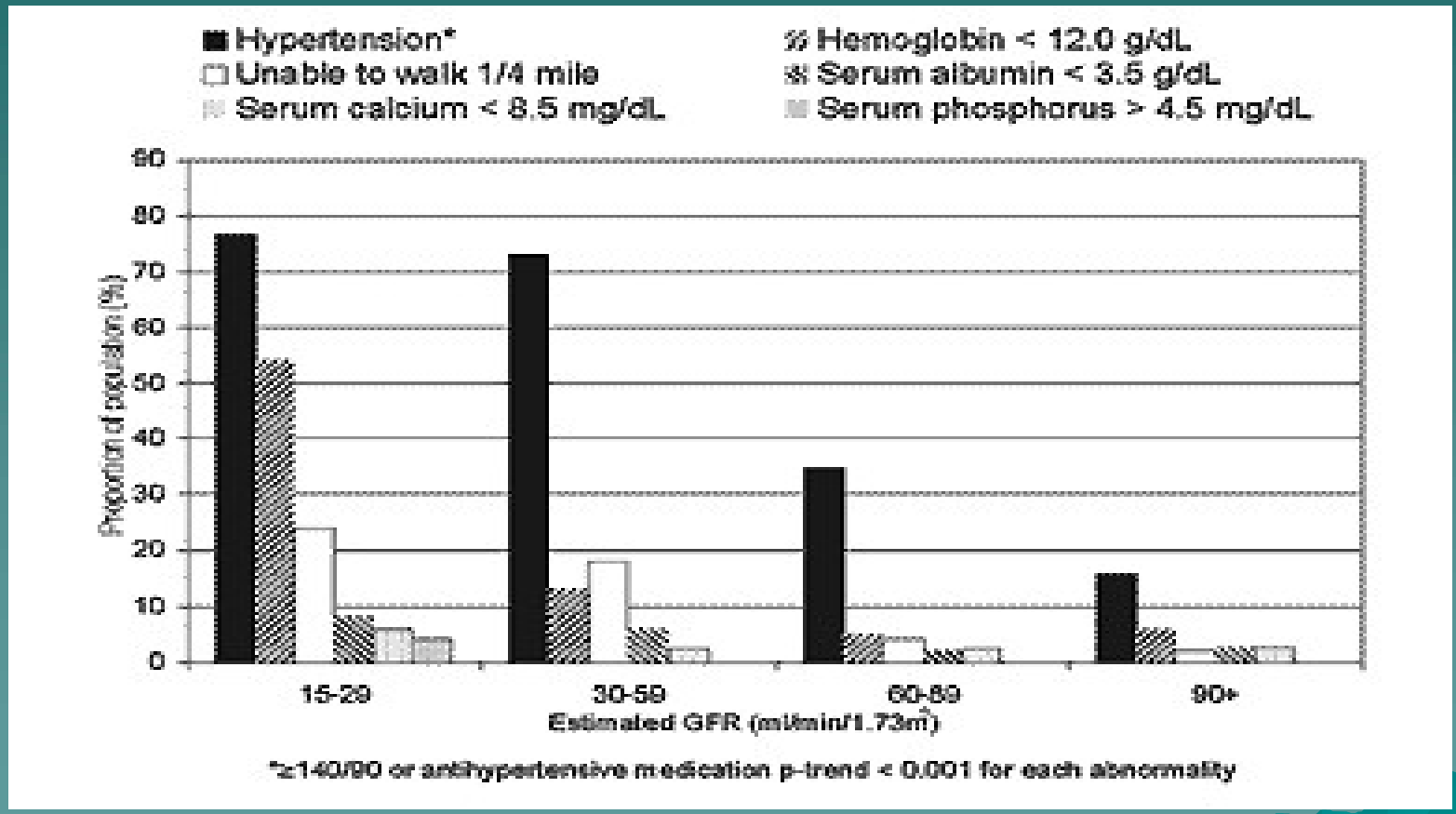
- Estimate GFR from serum creatinine
- Calculate GFR from creatinine clearance
  - 24 hour urine plus serum creatinine
- "Spot"urine albumin to creatinine ratio
  - https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate/estimating

- In adults, the normal GFR number is more than 90. GFR declines with age; decline occurs faster in males than females
- Age (years) Average estimated GFR):
  - 20–29 - 116
  - 30–39 - 107
  - 40–49 - 99
  - 50–59 - 93
  - 60–69 - 85
  - 70+ - 75

Complications of CKD

- Hypertension
- Malnutrition, anemia
  - Decrease in hemoglobin, albumin and calcium
  - Increase in phosphorous
- Decreased ability to ambulate
  - Clinical measure is ability to walk ¼ mile

Complications of CKD



K/DOQI GUIDELINES

- Clinicians should evaluate patients at risk with three laboratory tests:
  - eGFR
    - Laboratories now routinely report for everyone over 18 years of age
  - Albumin-Creatinine ratio
  - Urinalysis looking for protein, red cells and leukocytes

RECOMMENDATIONS

- Laboratories originally were told to use the Cockcroft-Gault or the Modification of Diet in Renal Disease study (MDRD) equation (preferred)
  - MDRD uses serum creatinine, sex, gender, and race
  - GFR=186* X $(S_{cr})^{-1.154}$ X $(Age)^{-0.203}$
    - *Use 175 if using a traceable method
  - x 0.742 (If Female)
  - x 1.212 (If African-American)

K/DOQI GUIDELINES

- Traditional creatinine clearance not recommended
  - Creatinine is secreted by kidneys so clearance overestimated
  - Secretion also not uniform from patient to patient
  - Urine collection not always complete

RECOMMENDATIONS

- Most current for laboratorians
  - Report estimated GFR using the MDRD or CKD-EPI equation
  - Report eGFR results above 60mL/min as >60 rather than an exact number
  - Report eGFR results less than 60 to the nearest whole number
  - Report serum creatinine results to 2 decimal places and in mg/dL

RECOMMENDATIONS

- For laboratorians:
  - Recalibrate your serum creatinine method to an isotope dilution mass spectrometry (IDMS) method
  - All laboratories should use an IDMS traceable equation when estimating and reporting GFR
  - https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate/estimating

LWG RECOMMENDATIONS

- Improved accuracy in measurement of creatinine in the 1-2 mg/dL range
  - Important because a creatinine of 1 mg/dL in an 80 year old Caucasian woman would indicate Stage 3 disease

CREATININE ASSAY

- Results effected by:
  - Age
  - Sex
  - Muscle mass
  - Race
  - Drugs
  - Diet
  - Day-to-day variation

CREATININE ASSAY

- Method interferences:
  - False elevations
    - Protein
    - Glucose
    - Ketones
    - Some cephalosporins
  - False decreases
    - Hemolysis
    - Lipemia
    - Bilirubin

CREATININE ASSAY

- Interference by glucose and ketones of major concern since diabetes patients make up a large number of the patients seen with CKD

CREATININE ASSAY

- The goal of the creatinine standardization program was to reduce the bias among methods at the low levels to improve the accuracy of estimated GFR.
  - These measurement limitations are part of the reason NKDEP recommends not to report eGFR values >60 mL/min/1.73m^2.

CREATININE STANDARDIZATION PROGRAM

- The purpose was to reduce inter-laboratory variation in creatinine assay calibration and provide more accurate estimated GFRs
- The efforts to calibrate serum creatinine methods to a isotope dilution mass spectrometry (IDMS) have been completed

CREATININE STANDARDIZATION

- Now that methods have been standardized the eGFR equation had to be recalculated
  - It was thought that the reference values for eGFR could be changed over time.
- Creatinine methods with calibration traceable to IDMS may have large enough changes in creatinine values that drug dose algorithms will be affected.

CREATININE STANDARDIZATION

- Manufacturers have provided detailed descriptions (including mathematical conversion factors, equations, or functions) of the impact of their calibration changes, for both serum and urine creatinine values
  - With emphasis on the serum 0.5 to 2.5 mg/dL (45 to 220 µmol/L) range of interest.

- This ensures that customers or labs using any of the pharmacy drug dosing approaches can adjust IDMS-traceable creatinine values for use with appropriate legacy dosing reference tables and algorithms (such as serum creatinine value, eGFR or creatinine clearance based on estimating equations from serum creatinine, or traditional measured creatinine clearance from serum and urine values).

CREATININE STANDARDIZATION

- For most patients, an eGFR using the MDRD Study equation is more accurate than a creatinine clearance calculated from serum and urine measurements.
- Therefore, NKDEP recommends not performing a measured creatinine clearance procedure for adults except when the patient's basal creatinine production is very abnormal.
  - This may be the case with patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases) or with unusual dietary intake (e.g., vegetarian, creatine supplements).

MDRD EQUATION

- Used for patients >18 years
- Not accurate in:
  - Elderly >85 years old
  - Patients in acute renal failure
  - Inpatients
  - Normal renal function
- Was not tested in the healthy population

- What are you doing for the pediatric and elderly population?
  - For pediatrics the Bedside Schwartz should be used
  - https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate/estimating
- Are you reporting the eGFR with caveats for these groups or just for the difference between Caucasian and African populations?

- GFR estimates from the MDRD Study equation can be used in patients who are in the hospital; however, it is important to pay attention to potential inaccuracies due to:
  - the non-steady state of serum creatinine,
  - comorbid conditions that cause malnutrition, and
  - use of medications that interfere with the measurement of serum creatinine.

MDRD EQUATION

- 2004 study at Mayo Clinic showed that the MDRD equation underestimated GFR in healthy patients by 26-29%
  - Underestimated the GFR of patients with CKD by 6.2%
- Using this equation on the general population may lead to an overestimation of CKD

Annals of Internal Medicine. Vol 141 #12, p930-937

MDRD EQUATION

- Mayo suggested recalculations of this equation for healthy population at least
- Example
  - 50y/female with creatinine of 1.1 mg/dL
  - With current MDRD, her eGFR is 56 mL/min/1.73m^2
  - With Mayo modification, her eGFR is 90 mL/min/1.73m^2

CKD-EPI EQUATION

- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (adults >18)
  - Females, creat </= 0.7 mg/dL:
    - $=144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
  - African-American Females, creat </= 0.7 mg/dL
    - $=166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
  - Males, creat </=0.9mg/dL:
    - $=141 \times (Scr/0.7)^{-0.411} \times (0.993)^{Age}$
    - African-American Males multiplier =163

- CKD-EPI
  - Females, creat >0.7 mg/dL:
    - $=144x(Scr/0.7)^{-1.209}\ x(0.993)^{Age}$
  - African-American Females, creat >0.7 mg/dL
    - $=166x(Scr/0.7)^{-1.209}\ x(0.993)^{Age}$
  - Males, creat >0.9 mg/dL:
    - $=141x(Scr/0.7)^{-1.209}\ x(0.993)^{Age}$
    - African American Males multiplier=163

CKD-EPI

- As a single equation:
- GFR=141 x min(Scr/κ, 1)$^{\alpha}$ x max(Scr/κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Afr Amer]
  - Scr = serum creatinine
  - κ = 0.7 for females and -0.411 for males
  - α = -0.329 for females and -0.411 for males
  - min is the minimum of Scr/κ or 1
  - max is the maximum of Scr/κ or 1
    - http://nkdep.nih.gov/lab-evaluation/gfr/estimating.shtml

CKD-EPI

- Equation developed with larger population than MDRD
- Included the healthy and patients with disease
  - Still not a lot of elderly
- Accuracy better between 60 and 120 so might be able to report numbers when GFR >60

OTHER EQUATIONS

- Bedside Schwartz
  - Developed by Chronic Kidney Disease in Children (CKiD) group
  - 0.41 x (height/serum creat)
  - Height in cm
  - For children <18 years
  - Old equations give falsely elevated results with standardized creatinine methods
    - Miller. GW. Glomerular Filtration Rate. Clinical Laboratory News. Dec 2011

LIMITATIONS

- Relationship between eGFR and creatinine only valid for individuals in a metabolic steady state.
  - Therefore not reliable for inpatients, during pregnancy or in individuals with chronic illnesses
- Muscle mass/metabolism changes reliability
  - Important in elderly, obese, amputees, body builders, those who exercise a lot or not at all

CAVEATS

- eGFR is an estimate – it is inaccurate in people of extreme body types, i.e. grossly obese, malnourished, etc.
  - Also not valid during pregnancy or in children under 18 years of age
- Not been validated in some racial and ethnic groups, especially Hispanics. Therefore they do not fit the MDRD equation; racial mix may not be evident

CAVEATS

- The MDRD equation underestimates normal or near-normal function so slightly low values should not be over-interpreted.
- Stage 1 & 2 CKD should not be diagnosed based solely on the eGFR; there should be other signs and symptoms of renal disease.

2012 Guidance

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150.

STAGING KIDNEY DISEASE

- Serum creatinine is not enough
  - Values of patients with CKD many times fall within reference intervals
- Serum creatinine levels would not indicate kidney disease until Stage 3
  - At the upper limit of reference interval already 50% of the kidney function is usually lost

Other Markers

- Cystatin C
  - Protein whose level in serum is a marker of kidney function
  - Concentration in blood directly correlates with glomerular filtration rate; filtered freely by glomeruli
  - Levels are independent of weight, height, muscle mass, age (after 1 year of age), and sex
  - Considered by many to be a better marker of GFR than creatinine and therefore a better indicator of kidney function
  - Appears to be better at detecting small changes in kidney function
    - http://www.medterms.com/script/main/art.asp?articlekey=39781

Cystatin C

- Research has clearly demonstrated that Cystatin C is a better predictor of adverse events in the elderly, including mortality, heart failure, bone loss, peripheral arterial disease and cognitive impairment, than either serum creatinine or estimated GFR.
  - Sarnak MJ, Katz R, Stehman-Breen CO, et al.: Cystatin C concentration as a risk factor for heart failure in older adults. Ann Intern Med 142: 497-505, 2005
  - Shlipak MG, Sarnak MJ, Katz R, et al.: Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 352: 2049-2060, 2005
- Need for a reference method cystatin C being addressed.
  - Certified reference material has been developed by IFCC/IRMM http://nkdep.nih.gov/lab-evaluation/cystatin-c.shtml

- Serum cystatin C is sensitive to detect mild GFR reduction between 60 and 90 mL/min/1.73 m^2.
  - Limitations: effect of thyroid dysfunction, high corticosteroid doses, rapid cell turnover and inflammation, obesity, smoking and potentially the presence of cardiovascular diseases on cystatin C levels.
  - Therefore a panel of GFR markers to facilitate the detection of reduced GFR at various stages and in different populations may be more useful

2012 CKD-EPI Equations

- With Cystatin: $133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [0.932 if female], where SCysC is serum cystatin C (in mg/l), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.
- With Cystatin and Creatinine: $135 \times \min(SCr/\kappa, 1)^{-\partial} \times \max(SCr/\kappa, 1)^{-0.001} \times \min(SCysC/0.8, 1)^{-.375} \times \max(SCysC/0.8, 1)^{-.711} \times 0.995^{age}$ [x 0.969 if female][x 1.08 if black]
  - If female: $\kappa = 0.7$, $\partial = -0.248$
  - If male: $\kappa = 0.9$, $\partial = 0.207$

- All equations are improved by including cystatin C and creatinine N Engl J Med 2012;367:20-9.
- http://www.medscape.com/viewarticle/811362_3
- "For many years, cystatin C level has been known to have a higher correlation with measured GFR and much stronger associations with adverse outcomes compared with creatinine level. Recent advances have facilitated the use of cystatin C as a clinical measure of kidney function: an international reference standard, broadly applicable GFR equations, and a guideline-endorsed indication for confirming CKD in persons with eGFR of 45–59 mL/min/1.73 m2. Future work must develop strategies for implementing cystatin C into clinical care with the goal of optimizing the diagnosis, staging, and treatment of CKD."

Other Markers

- **Neutrophril gelatinase-associated lipocalin** is expressed early after injury and has value in predicting acute kidney injury after kidney transplant and cardiopulmonary bypass.
- **Interleukin-18** has been detected early in acute kidney injury after kidney transplant, cardiopulmonary bypass and sepsis.
- **Kidney injury molecule-1** is increased after ischemic/toxic injury and has the ability to predict the need for renal replacement therapy and mortality.
- These biomarkers may have value as a sequential 'panel' to aid in detecting, classifying and predicting the clinical course of acute kidney injury.
  - Curr Opin Crit Care. 2007 Dec;13(6):638-44.
  - http://www.aacc.org/publications/cln/2014/january/Pages/Kidney-Injury.aspx#

Other Markers

- Promising novel biomarkers for **acute kidney injury** include a plasma panel (neutrophil gelatinase-associated lipocalin and cystatin C) and a urine panel (neutrophil gelatinase-associated lipocalin, interleukin-18, and kidney injury molecule-1).
- For chronic kidney disease, a similar plasma panel and a urine panel (neutrophil gelatinase-associated lipocalin, asymetric dimethylarginine, and liver-type fatty acid-binding protein).
- The biomarker panels will probably be useful for assessing the duration and severity of kidney disease, and for predicting progression and adverse clinical outcomes.
- It is also likely that the biomarker panels will help to distinguish between the various etiologies of acute kidney injury or chronic kidney disease.

Symmetric Dimethyl-arginine

- SDMA: thought to be an early biomarker for CKD – in animals
- Researchers at Yale are running studies to determine if this marker would be as effective in humans (CAP TODAY. Oct. 27,2016)
- https://www.ncbi.nlm.nih.gov/pubmed/29101459

- In principle, clinicians should be aware of the limitations of and cautioned not to overrate, estimated GFR results that are based on a single marker or calculated by equations and should not rely only on GFR estimates to make precise clinical decisions.
  - Clinical Biochemistry Volume 40, Issues 3-4, February 2007, Pages 153-161

- eGFR may be of limited benefit according to the results of a study reported Jan 2009 in Clinical Journal of Nephrology

And When to Measure GFR

- Persons with known kidney damage (for example as reflected by albumin or protein in the urine)
- Patients of extreme age (very old or very young)
- Patients of extreme body mass (obese, malnourished, with muscle wasting diseases)
  (creatinine are not appropriate measure in the group)
- Persons with unusual dietary intakes, including vegetarians
- Persons with rapidly changing renal function (includes acute renal disease)
- When drug dose adjustments are necessary (persons taking drugs with significant renal toxicity and renal clearance)

Questions?

Elissa Passiment
elissap17@gmail.com