Laboratory Diagnostics:
A focus on assessing renal insufficiency

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Disclosure

• No real or potential conflict of interest to disclose
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives

• Upon completion of the learning activity the participant will be able to:
  – Identify the appropriate use of laboratory testing as part of the clinical evaluation process of the person with or at risk for renal impairment.
  – Discuss the clinical utility of select renal laboratory parameters in renal impairment.

Objectives (continued)

• Upon completion of the learning activity the participant will be able to: (cont.)
  – Identify the impact of renal impairment on prescribing select medications.

First Rule:
Preserve Renal Function!

Select References

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQITM)
Available at
http://www.renal.org/information-resources/the-uk-ckd-guide/ckd-stages#sthash.a27Q0iV7.7BnpoGJK.dpbs

Anaizi, N, The Drug Monitor-
Review Renal Pharmacology
Available at
http://www.thedrugmonitor.com/RIT97.html
Renal Anatomy and Physiology
Urine Formation

• Each kidney with ~1 million nephrons
• Involves 3 main processes
  – Filtration at glomerular level
  – Selective reabsorption from filtrate passing along renal tubules
  – Secretion by cells of tubules into filtrate

Factors Influencing Nephron Destruction and Renal Failure

- Nephrons in the fetal kidney are formed up to the 36th week of gestation.
- The range of nephrons in individuals within a given healthy populations can range from 200,000 to more than 2 million per kidney.
Risk Factors That You Probably Did Not Consider...

- Increase HTN risk=Potential risk for CRF
  - Low birth weight
  - Gestational age at birth
  - Maternal HTN during pregnancy
  - Low maternal calcium intake during pregnancy
  - Low nephron number

Source: http://www.rmmj.org.il/userimages/83/1/PublishFiles/125Article.pdf

Impact of Aging on the Kidney

- Glomeruli changes
  - Sclerotic glomeruli=1% to 2% age 30 to 40 y to >12% age >70 y
- Renal blood flow
  - Decreases related to reduction in cardiac output
- Result
  - Less reserve, increased risk of drug-induced nephrotoxicity


Defining the Terms

(continued)

- Creatinine
  - Breakdown product of muscle creatine phosphate and is usually produced at a fairly constant rate by the body (depending on muscle mass)

Defining the Terms

(continued)

- Blood urea nitrogen
  - Evaluation of the amount of nitrogen in the blood in urea form
    - Urea=Metabolism by-product of proteins by liver, removed from the blood by kidneys

- BUN to creatinine ratio (BUN:Cr)
  - Usually ≤20:1 in the presence of appropriate hydration
    - Reduced in over hydration
  - Often elevated in renal disease
    - In absence of renal disease, can be transiently elevated in dehydration, ingestion of extreme amounts of protein, upper, lower GI bleed
Altered BUN:Cr Ratio in Absence of Significant Renal Disease

- 45 yo otherwise well woman of European ancestry with severe dehydration due to gastroenteritis
  - BUN=55 mg/dL (19.6 mmol/L)
  - Cr=0.8 mg/dL (70.7 µmol/L)
  - BUN:Cr ratio>20:1=68.75
  - GFR=89 mL/min/1.73 m²

Altered BUN:Cr Ratio in Absence of Significant Renal Disease (continued)

- Upper GI bleed in 50 yo AA man
  - Appropriate hydration
  - Hemoglobin=11.2 g/dL (112 g/L), hematocrit=33% (0.33 proportion)
  - BUN=36 mg/dL (12.85 mmol/L), Cr=0.9 mg/dL (79.6 µmol/L)
  - BUN:Cr ratio>20:1=36
  - GFR=115 mL/min/1.73 m²

Altered BUN:Cr Ratio in Absence of Significant Renal Disease (continued)

- Lower GI bleed in a 50 yo male
  - Appropriate hydration
  - Hemoglobin=10.2 g/dL (102 g/L), hematocrit=30.5% (0.305 proportion)
  - BUN=24 mg/dL (8.6 mmol/L), Cr=0.9 mg/dL (79.6 µmol/L)
  - BUN:Cr ratio>24

Altered BUN:Cr Ratio in Absence of Significant Renal Disease (continued)

- BUN, Cr in Late Pregnancy
  - 28 yo woman, 34-weeks pregnant, normotensive, healthy
    - Normative up to 50% or greater increase in blood volume
    - Hemoglobin=12.5 g/dL (125 g/L), HCT=34% (0.34 proportion)
    - BUN=9 mg/dL (3.2 mmol/L), Cr=0.5 mg/dL (44.2 µmol/L)
    - Source: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4089195/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4089195/)

Defining the Terms

(continued)

- Proteinuria
  - Presence of abnormal amount of protein in the urine
    - Adult urinary protein excretion in health ≤150 mg/day
    - "Negative" dip UA for protein accounts for this level

Defining the Terms (continued)

- Proteinuria
  - Most commonly wasted protein=Albumin
  - Most common type=Glomerular proteinuria
    - Due to increased filtration of macromolecules including albumin across glomerular capillary wall
    - Seen in DM nephropathy, other glomerular disease
    - Also in absence of renal disease such as exercise-induced or orthostatic proteinuria
Defining the Terms (continued)

- **Microalbuminuria**
  - Excretion of small amount of albumin that would escape detection by standard urine dip test
  - Normal albumin excretion rate <30 mg/day (20 mcg/min)
  - Microalbuminuria = Persistent albumin excretion = 30–300 mg/day (20 to 200 mcg/min)

- **Glomerular filtration rate (GFR)**
  - Volume of fluid filtered from the renal glomerular capillaries into Bowman's capsule per unit time

- **Creatinine clearance**
  - A comparison of the level of urine creatinine in with blood creatinine. Because creatinine is found in stable plasma concentrations, is freely filtered and not reabsorbed, and is minimally secreted by the kidneys, creatinine clearance is used to estimate the glomerular filtration rate (GFR).

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Cr Cl vs. GFR

- Cr Cl approximates GFR but might overestimate due to
  - Creatinine secreted by proximal tubule
  - Filtered by the glomerulus

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GFR>60 mL/min/1.73 m² vs. <60 mL/min/1.73 m²?

- Equation less accurate at GFR estimates greater than 60 mL/min/1.73 m²
  - Most labs with NL or near normal Cr simply report GFR>60 mL/min/1.73 m²
- W/estimated GFR<60 mL/min/1.73 m²
  - Equation accurate for most of average body size and muscle mass
    - Source: https://www.kidney.org/professionals/KDOQI/gfr
### Factors Affecting Serum Creatinine Concentration

- **Muscular bulk**
  - Increased muscle generation due to increased muscle mass ± increased protein intake
- **Malnutrition, muscle wasting, amputation**
  - Reduced creatinine generation due to reduced muscle mass ± reduced protein intake

### Vegetarian diet
- Decrease in creatinine generation

### Ingestion of cooked meats
- Transient increase in creatinine generation; however, might be blunted by transient increase in GFR

### Older age
- Reduction in creatinine generation due to age-related decline in muscle mass

### Female sex
- Reduced creatinine generation due to reduced muscle mass

### Obesity
- No change, excess mass is fat, not muscle mass and does not contribute to increased creatinine generation

### Does age, gender, race or lifestyle influence serum Cr?

- **Aging**
  - Less muscle mass = Lower creatinine produced
- **Male vs. female**
  - Men with greater muscle mass = High creatinine

### African ancestry
- ~15% higher AST
- ~10% higher Cr
  - Due to greater muscle mass
- Possible influence of increased physical activity

Source: [https://www.kidney.org/professionals/KDOQI/gfr](https://www.kidney.org/professionals/KDOQI/gfr)
GFR: True or false?

- The normal mean GFR in young adults is approximately 120 to 130 (20 to 25) mL/min/1.73 m².
- Children reach adult values for mean GFR by approximately age 2 years.

Two Patients

- 70 yo man who weighs 75 kg and is at ideal body weight
  - Cr=1.4 mg/dL (123.76 µmol/L)
- 70 yo woman who weighs 75 kg and is at ideal body weight
  - Cr=1.4 mg/dL (123.76 µmol/L)

Cockcroft-Gault Equation

Use IBW

- To calculate Cr Cl in men
  - \((140 - \text{age}) \times \text{wt in kg}/(72 \times s\text{Cr})\)
    - 70 yo man, weighs 75 kg, sCr=1.4 mg/dL (123.76 µmol/L)
    - \((140 - 70 = 70) \times 75/(72 \times 1.4=100.8) = 70 \times 0.744=52.08 \text{ mL/min}\)

Another Formula

Modification of Diet in Renal Disease Formula

- Needed patient information
  - Age
  - Gender
  - Serum creatinine
  - Ethnicity
    - Black vs. non black
- Source: www.kidney.org/professionals/kdoqi/gfr_calculator.cfm

With Identical Parameters, Calculated GFR

- GFR=51 mL/min/1.73 m², non African American male
- GFR=58 mL/min/1.73 m², African American male

Cockcroft-Gault Equation

Use IBW

- To calculate Cr Cl in women
  - 70 yo, weighs 75 kg, sCr=1.4 mg/dL (123.76 µmol/L)
    - \((140 - \text{age}) \times \text{wt in kg}/(72 \times s\text{Cr}) \times 0.85\)
    - \((140 - 70 = 70) \times 75/(72 \times 1.4=100.8) = 70 \times 0.744=52.08 \times 0.85=44.26 \text{ mL/min}\)
With Identical Parameters, Calculated GFR

- GFR=38 mL/min/1.73 m², non-African American female
- GFR=44 mL/min/1.73 m², African American female


What is the significance in clinical practice?

- 70 yo woman
  - Cr Cl=44 mL/min (0.74 mL/s)
  - Lisinopril=50–75% of typical dose

- 70 yo man
  - Cr Cl=52 mL/min (0.87 mL/s)
  - No dose adjustment for lisinopril at current Cr Cl

CKD (Chronic Kidney Disease) Stages Based On GFR (Glomerular Filtration Rate)

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<th>Stage</th>
<th>GFR*</th>
<th>Description</th>
<th>Treatment</th>
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<td>1</td>
<td>90+</td>
<td>Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease</td>
<td>Observation, control of blood pressure.</td>
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<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease</td>
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<td>3B</td>
<td>30-44</td>
<td>Severe reduced kidney function</td>
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<td>15-29</td>
<td>Severely reduced kidney function</td>
<td>Planning for endstage renal failure.</td>
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*All GFR values are normalized to an average surface area (size) of 1.73 m²

Stages of Chronic Renal Failure

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQITM)
Available at http://www.renal.org/information-resources/the-uk-eckd-guide/ckd-stages#sthash.a27QOVI.7BnpoGJK.dpbs

Anaizi, N, The Drug Monitor Review Renal Pharmacology
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Based On GFR (Glomerular Filtration Rate)

Stage GFR* Description Treatment

3A 45–59 Moderately reduced kidney function
3B 30–44

4 15–29 Severely reduced kidney function Planning for endstage renal failure.
5 <15 or on dialysis Very severe, or endstage kidney failure (sometimes called established renal failure) Treatment choices.

*All GFR values are normalized to an average surface area (size) of 1.73 m²
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**Hematologic Changes in CKD**

- **Erythropoietin supply**
  - Diminished in advancing renal failure
  - Usually beginning when glomerular filtration rate (GFR)<49 mL/min/1.73 m²
- **Resulting anemia of chronic disease (ACD)**
  - Treatment- Treat underlying cause, erythropoietin replacement

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**52-year-old Woman with Stage 3 CKD**

- Hg=10.1 g/dL (12–14)
  (101 g/L [120–140 g/L])
- Hct=32% (36–43)
  (0.32 proportion [0.36–0.43 proportion])
- RBC=3.2 million/mm³ (4.2–5.4)

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**52-year-old Woman with Stage 3 CKD (continued)**

- MCV=82 fL (81–96) NL
- MCHC=34.8 g/dL (31–37) NL
  (348 g/L [310–370])
- RDW=12.1% (11.5–15) NL
  (0.121 proportion [0.115–0.15 proportion])

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**Michael 58-year-old Man w/o Complaint**

- Known to be hypertensive>18 y
- No therapy>3 years, feeling well
  - Gr II HTN retinopathy
  - S4, Gr II/VI systolic murmur
  - PMI @ 6th ICS, MCL
  - BP=170/110 mm Hg
- Renal issues likely acute or chronic?
HTN Retinopathy

Michael

- FPG=180 mg/dL
  - 9.99 mmol/L
- HgA1c=8%
  - 0.08 proportion
- HDL=32 mg/dL
  - 0.83 mmol/L
- LDL=170 mg/dL
  - 4.4 mmol/L
- TG=280 mg/dL
  - 3.16 mmol/L
- Cr=1.6 mg/dL
  - 122 µmol/L
- UA=Protein 30 mg/dL
  - 300 g/L

GFR per NKF Calculator
African Ancestry or Otherwise
- If Michael has African ancestry
  - GFR=54 per mL/min/1.73 m²
- If any other ethnic group
  - GFR=45 per mL/min/1.73 m²
- If female and African ancestry
  - GFR=45 per mL/min/1.73 m²
- If female and other ethnic group
  - GFR=33 per mL/min/1.73 m²

Intervention in Proteinuria/Albuminuria with T2DM
- Is adding an ACEI/ARB enough?
  - Improved glycemic control
  - Improved lipid control
  - Improved HTN control

65 kg, 80-year-old with HTN, on ACEI, Thiazide Diuretic
- With a 3-day history increasing confusion, new onset urinary incontinence
  - H/H=11 g/dL /38%
    (110 g/L /0.38 proportion)
  - H:H ratio>1:3
  - WBC=2,600 mm³
  - Neuts=35% (AMNC=910)
  - Bands=48% (ABC=1248)
  - Metas=2%

65 kg, 80-year-old with HTN, on ACEI, Thiazide Diuretic (continued)
- BUN=55 mg/dL (19.6 mmol/L)
- Cr=2.1 mg/dL (185.6 µmol/L)
- BUN:Cr ratio≥20, C/W volume depletion
- GFR per NKF calculator=
  - 24 mL/min/1.73 m²
65 kg, 80-year-old with HTN, on ACEI, Thiazide Diuretic (continued)

- Previous Cr 2 months ago
  - Cr=1.1 mg/dL (97.24 µmol/L)
- GFR per NKF calculator= 51 mL/min/1.73 m²

True or false?
- If the prescribing information about a given medication includes a warning about the need for dose adjustment in the presence of renal impairment, then that product is likely nephrotoxic.

What type of renal failure?
- Prerenal?
- Intrarenal?
- Post renal?

Ciprofloxacin PI
- Cr Cl>50 mL/min (0.84 mL/s)
  - See usual dosage
- Cr Cl 30–50 mL/min (0.50–0.84 mL/s)
  - 250–500 mg q 12 h
- Cr Cl 5–29 mL/min (0.08–0.48 mL/s)
  - 250–500 mg q 18 h
- Hemodialysis or peritoneal dialysis
  - 250–500 mg q 24 h (after dialysis)

Antimicrobial Dose Adjustment in Renal Impairment: Nitrofurantoin (from PI)
- If Cr Cl≥50 mL/min (0.84 mL/s)
  - Standard dosing according to indication
- If Cr Cl<50 mL/min (0.84 mL/s)
  - Avoid use

Antimicrobial Dose Adjustment in Renal Impairment
- No dose adjustment required
  - Ceftriaxone
  - Azithromycin

Metformin Use in Renal Impairment

- Rational for possible metformin in renal impairment
  - Decrease lactic acidosis risk
    - 90% renally eliminated
  - National Institute for Health – Discontinue at eGFR below 45 mL/min per 1.73 m², absolute metformin discontinuation at eGFR<30 mL/min per 1.73 m².

Resources for Dosing

Source: http://www.globalrph.com/quicksearch_renal_dosing.htm

Janita

- 35-year-old woman
  - Dysuria, right flank pain × 2 d
  - 1 episode of gross hematuria reported by patient
  - BP=140/92 mm Hg
    - 3 months ago=110/72 mm Hg

Janita (continued)

- 3+ proteinuria
  - 300 mg/dL (3000 g/L)
    - Albumin most commonly wasted protein
- 2+ RBC
  - Intact RBC, found in infection, stones, bladder cancer
- Neg hemoglobin
  - Released by hemolyzed RBC
    - Found in hemolytic anemia

Janita (continued)

- + Leukocytes
  - Primarily neutrophil
- + Nitrites
  - Surrogate marker for Gram-negative organism in urine
    - Held for at least 30 mins, neg if recent void, indwelling cath, Gram-positive or viral pathogen

So Right Now You Know...

Likely Gram-negative UTI

- But you do not know why her BP is up?
- Why such profound proteinuria?
Later You Know...

- BUN=32 mg/dL (11.42 mmol/L)
- Cr=1.8 mg/dL (159.12 µmol/L)
  - BUN: Cr ratio<20:1
    - Unlikely to be volume depleted
    - Volume depletion BUN:Cr ratio>20:1
  - GFR=34 mL/min/1.73 m²
- Urine C and S ≥100K colonies *E. coli*

Janita

- Spiral CT results
  - Thinning of renal cortex
  - Dilatation of renal pelvis
  - Large calculus

Post-renal Azotemia

- Impediment of urine flow
  - BUN:Cr ≤20:1
    - Stones
    - Crystals
    - Tumor
    - Stricture
    - Prostate

Risk for Drug-induced Post Renal Failure

- Acyclovir
- Sulfonamides
- Methotrexate
- Indinavir
- Triamterene
- Vitamin C
- Guaifenesin
- Ephedrine
- Particularly with altered volume, cardiac output
  - Hypovolemia
  - Diuretic use
  - CHF

Conclusion

Additional References and Resources

Additional References and Resources (continued)


End of Presentation
Thanks for your time and attention.
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Components of the Normal Nephron

- Bowman's Capsule
- Proximal Convoluted Tubule
- Adventitial Mast Cell/Macrophage
- Renal Sympathetic Nerves
- Juxtaglomerular Cells
- Distal Convoluted Tubule
- Macula Densa
- Efferent Renal Artery
- Glomerulus
- Mesangial Matrix
- Mesangial Cells
- Vascular Smooth Muscle Cells

Factors Influencing Nephron Destruction and Renal Failure

- Constrictors/Growth Promoters
  - Angiotensin II
  - Catecholamines
  - Endothelin-1
  - ROS
  - Cytokines
  - EDCF

- Dilators/Growth Inhibitors
  - Nitric Oxide
  - Prostacyclin
  - Bradykinin
  - EDHF

- Vascular tone and structure

EDHF=Endothelium-derived hyperpolarizing factors
ROS=Reactive oxygen species
EDCF=Endothelium-derived constricting factors

Nephron destruction and renal failure

www.hypertension-online.org