
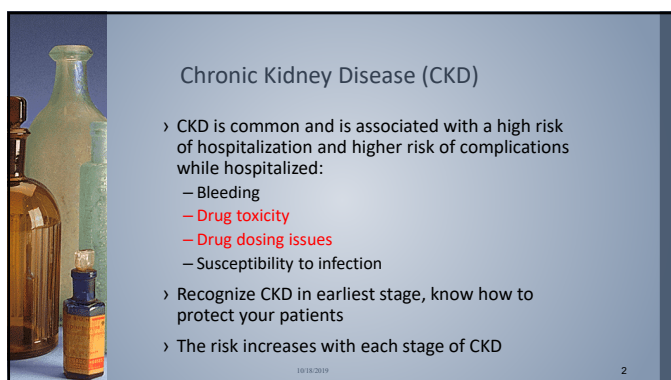


Renal Red Flags



Focus on pharmacology and drug safety

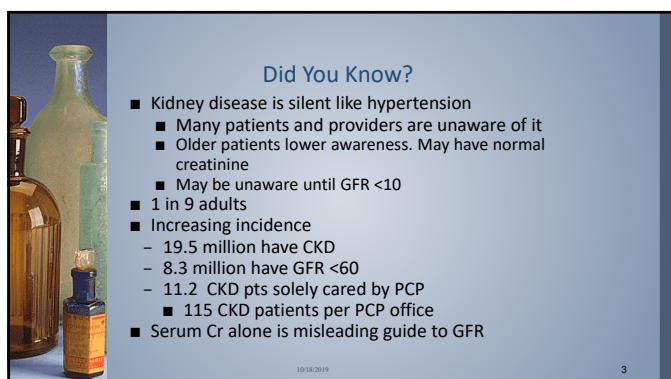
Susan Busch MSN, CNP
October 25, 2019



Chronic Kidney Disease (CKD)

- › CKD is common and is associated with a high risk of hospitalization and higher risk of complications while hospitalized:
 - Bleeding
 - Drug toxicity
 - Drug dosing issues
 - Susceptibility to infection
- › Recognize CKD in earliest stage, know how to protect your patients
- › The risk increases with each stage of CKD


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Did You Know?

- Kidney disease is silent like hypertension
 - Many patients and providers are unaware of it
 - Older patients lower awareness. May have normal creatinine
 - May be unaware until GFR <10
- 1 in 9 adults
- Increasing incidence
 - 19.5 million have CKD
 - 8.3 million have GFR <60
 - 11.2 CKD pts solely cared by PCP
 - 115 CKD patients per PCP office
- Serum Cr alone is misleading guide to GFR


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High Risk CKD

- Diabetes mellitus
- Hypertension
- Obesity
- Family members with CKD
- US ethnic minority status, Black, Am Indian, Hispanic, Asian, or Pacific Is.
- Cardiovascular disease
 - CHD
 - CHF
 - PVD
 - Stroke


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Glomerular Filtration Rate

- › Can measure using an exogenous substance like inulin, iothalamate, iothexol, or radioisotopes
 - Expensive and require administration to the patient
- › 24-hour urine for creatinine clearance
 - Often incomplete
- › Cystatin C
- › Equations
 - Cockcroft-Gault (possibly more accurate and would lend to lower medication dosages)
 - MDRD
 - CKD-EPI

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When you lose 50% of function pharmacokinetic properties become altered:

Unsafe medication doses in kidney patients have been reported at rates of:

- 44% in long-term facilities
- 69% in outpatient settings
- 19% in inpatient settings.

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Pharmacokinetics Alterations at 50% Function

Absorption

- Alterations in pH (alter amount and rate being absorbed)
- Drug interactions
 - Ex. Ca binders/Drug binds with Ca (don't give Ca binders with quinolones, cipro)
- Gut motility (delayed emptying in DM)
 - Drugs broken down in stomach and absorbed in small intestine)
- Gut edema
 - Ex. Lasix sensitive to gut edema

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Pharmacokinetics

Distribution: volume

- › Vd- Volume of distribution
 - Apparent volume into which a drug distributes
 - If a patient is fluid overloaded, may need increased loading doses

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Pharmacokinetics

Distribution: protein binding

- › Decreased protein binding secondary to decreased albumin and uremia.
 - Means more free (active drug is floating around)
 - Increased “free” drug, will see increased effects at ‘normal drug levels’
 - › Ex-Dilantin
 - › Too much drug hanging around
 - › Always check free level
- Common protein bound drugs include:
 - › Doxycycline, dicloxacillin, digitoxin, furosemide, glyburide, glipizide, diphenhydramine

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Pharmacokinetics

Elimination

- Non Renal elimination
 - Ex. Liver
- Some decrease in hepatic enzyme activity in liver with kidney disease
- Accumulation of metabolic by-products (active and toxic)
 - Ex. Acetaminophen(liver fail), allopurinol(hypersensitive rxn), glyburide(hypoglycemia), meperidine(seizure activity), procainamide


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Pharmacokinetics: Elimination

- › Renal Excretion
 - Renal clearance significantly decreased
 - Impacts elimination of renally excreted drugs
 - 1/2 life will be prolonged
 - › Ex aminoglycoside (1/2 life extended 4-5days) e.g gentamycin and vancomycin
 - Accumulation of drug, risk toxicity
 - **Dose adjust if >30% renal eliminated and if GFR <50ml/min**


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Renally Eliminated Drugs

■ Aminoglycosides	■ Vancomycin
– Gent, amikacin, tobra	■ Bactrim
■ Penicillins	■ Imipenem
– Ampicillin, Pip, Amoxi, Unasyn, Zosyn	■ Others
■ Cephalosporins	■ Fluconazole
■ Cefazolin, cefoxitin, cefuroxime, cefepime, ceftazidime	■ digoxin
■ Quinolones	
– Cipro, levofloxacin	


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Renally Eliminated Drugs

- › Antihypertensives
 - ACEI's, atenolol, clonidine, sotalol
- › H2 antagonists
 - Ranitidine, cimetidine, famotidine
- › Acyclovir and other antivirals (neurotoxicity)
- › Others
 - Lorazepam
 - Gabapentin (mental status changes)
 - Lyrica
 - Metformin
 - › Contraindicated in GFR <30
 - › Lactic acidosis


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The Dilemma with ACE-I or ARB

- › The intraglomerular pressure drops
- › The post glomerular arteriole (efferent) dilates more than the preglomerular arteriole (afferent)
- › If someone has renal artery stenosis, the glomerular filtration pressure, GFR, renal function drop and lead to ARF
- › ARF may be a clue that person has RAS
- › ACE may also cause direct interstitial nephritis.
- › The **dilemma** is that ACE's can reduce proteinuria and slow progression of kidney disease. Recommended that all diabetics who can tolerate it are placed on an ACE

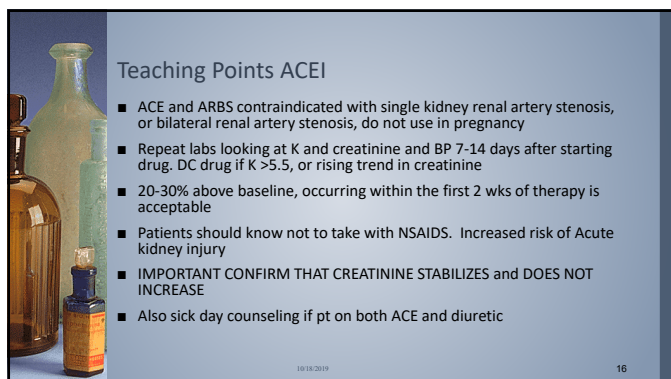
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Can ACE-I or ARB Cause ARF?

- Yes, in pts with Bilateral RAS or in solitary kidney with RAS
 - RAS kidney produces excess renin
 - This increases Angiotensin II via Angiotensin converting enzyme
 - Angiotensin II elevates BP to increase blood flow thru stenosis and increase renal perfusion
 - It increases intraglomerular pressure by constricting post glomerular (efferent) arteriole more than preglomerular (afferent) arteriole
 - It can also independently cause interstitial nephritis

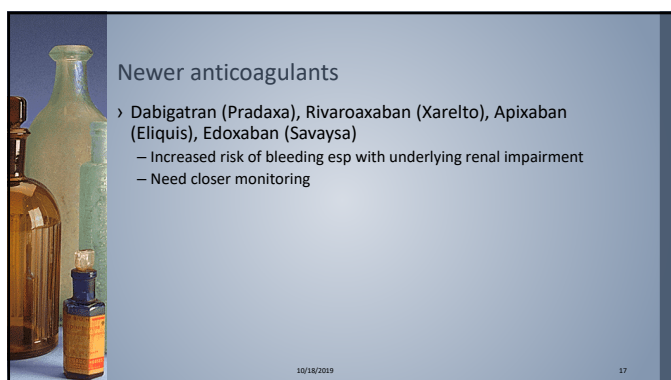
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Teaching Points ACEI

- ACE and ARBS contraindicated with single kidney renal artery stenosis, or bilateral renal artery stenosis, do not use in pregnancy
- Repeat labs looking at K and creatinine and BP 7-14 days after starting drug. DC drug if K >5.5, or rising trend in creatinine
- 20-30% above baseline, occurring within the first 2 wks of therapy is acceptable
- Patients should know not to take with NSAIDS. Increased risk of Acute kidney injury
- IMPORTANT CONFIRM THAT CREATININE STABILIZES and DOES NOT INCREASE
- Also sick day counseling if pt on both ACE and diuretic

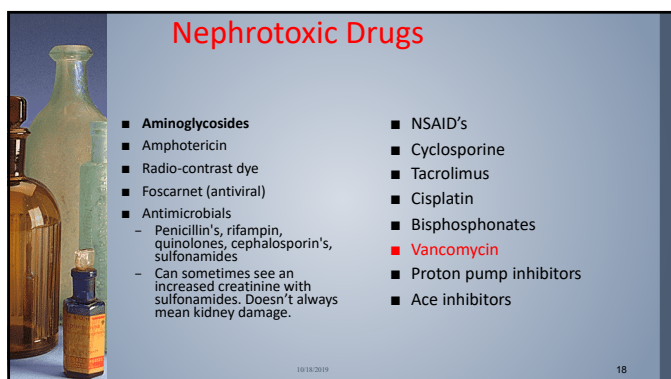
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Newer anticoagulants

- › Dabigatran (Pradaxa), Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (Savaysa)
 - Increased risk of bleeding esp with underlying renal impairment
 - Need closer monitoring


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Nephrotoxic Drugs


■ Aminoglycosides	■ NSAID's
■ Amphotericin	■ Cyclosporine
■ Radio-contrast dye	■ Tacrolimus
■ Foscarnet (antiviral)	■ Cisplatin
■ Antimicrobials	■ Bisphosphonates
– Penicillin's, rifampin, quinolones, cephalosporin's, sulfonamides	■ Vancomycin
– Can sometimes see an increased creatinine with sulfonamides. Doesn't always mean kidney damage.	■ Proton pump inhibitors
	■ Ace inhibitors

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Drugs causing interstitial nephritis (AIN)


- › Antibiotics
 - B-lactams, sulfonamides, fluoroquinolones, rifampin, vancomycin, erythromycin, ethambutol, chloramphenicol
- › Antivirals
 - Acyclovir, atazanavir, abacavir, idinavir
- › Analgesics
 - NSAIDs, COX-2 inhibitors,
- › Anticonvulsants
 - Phenytoin, carbamazepine, phenobarbital,
- › GI meds
 - PPIs (most common cause of AIN worldwide—mean time 11 weeks can also occur months after therapy)
 - H2 receptor blockers
- › Diuretics
 - HCTZ, furosemide, triamterene, chlorthalidone
- › Anti cancer agents




Causes of Acute interstitial Nephritis

- › A study of 133 cases of biopsy-proven nephritis
 - 49% caused by antibiotics
 - 14% proton pump inhibitors
 - 11% NSAIDs
- › People with previously documented kidney disease had more severe AKI at the time of biopsy and were less likely to recover kidney function

Murthi, AK., Leung, N., Valeri AM. et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. *Am J Kidney Dis* 2014;64:558-566 . 10/18/2019




› No drug is above suspicion and every agent must be considered in the evaluation



Nephrotoxins

- › Non-Steroidal Anti-Inflammatory Drugs (NSAID)
 - Ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, celebrex
 - Decrease renal vasodilatory prostaglandins resulting in decreased renal blood flow
 - Risk factors -preexisting disease, volume depletion, age, combination with ACEI's or cyclosporine
 - Also cause acute interstitial nephritis


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Nephrotoxins

- › Aminoglycosides: Gent, tobra, amikacin
- › Glycopeptide: vancomycin
 - Direct nephrotoxicity (tubular cell damage)
 - Risk factors
 - › Prolonged therapy, trough>2mg/L, prolonged hi peak, combo with other nephrotoxins, preexisting CKD, age, dehydration


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Nephrotoxins

- **Lithium Carbonate**
 - Can cause:
 - Nephrogenic Diabetes Insipidus, Nephrotic syndrome, Renal tubular acidosis, Interstitial fibrosis
 - Acute toxicity when levels>1.2. Serum levels measure periodically 12 hrs after dose
 - 1/2 life does not reflect tissue accumulation
 - Plasma levels rebound after dialysis
 - Toxicity enhanced by volume depletion, NSAIDS and Diuretics


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Nephrotoxins

- Cyclosporine (neoral) and tacrolimus (prograf)
 - Vasoconstriction to renal arteriole, decreased renal blood flow
- Risk factors
 - Elevated drug concentrations (dose related)
 - Advanced age
 - Renal graft rejection
 - Hypotension
- Combination with other nephrotoxins

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Nephrotoxins

Radiocontrast dye

Causes Radiocontrast Induced Nephropathy

Direct tubular toxicity; renal ischemia


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Nephrotoxins

- › Radiocontrast Nephropathy
 - Rise in serum creatinine within 48hrs after contrast exposure
 - Or an increase of 25% over baseline
 - Or an absolute increase of 0.5mg/dl
 - Scr peaks in 4-5 days and returns to baseline over next week
 - Sometimes damage is permanent and the person ends up on dialysis


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Risk Factors for RCIN

- CKD stage 3 or greater. Risk is higher with higher stages, and proteinuria
- Diabetes Mellitus (With Renal Insufficiency)
- High dose Contrast medium (125-200cc)
- CHF, volume depletion, cirrhosis, loop diuretics)
- Nephrotoxic Meds (ACE/ARB/NSAIDS)
- Age > 70 years
- Female gender
- High osmolar contrast agents (two fold risk)
- Multiple myeloma (only if hypercalcemic or volume depleted)


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Precontrast Considerations

- Limit use of dye (clear indication)
- Identify risk factors for RCIN (at risk pts) caution use of absolute serum creatinine alone (ie old female)
- Use nonionic contrast dye in high risk pts (iodixanol)
- Space out repeat dye exposure
- Use least amount of dye
- Hold metformin 48 hours before
- Avoid NSAIDS
- **Keep well hydrated**
- The risk of RCIN is 10 x the creatinine

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Drug-induced Nephrotoxicity

› Summary Prevention/Treatment

- Recognize risk factors
- Discontinue/avoid medication
- Drug concentration monitoring
- Adequate hydration
- Blood pressure control (high or low)


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Common Drugs Removed by Hemodialysis (>30%)


- Antimicrobials
- Aminoglycosides
- Ampicillin/amoxicillin
- Cephalosporin's (not ceftriaxone)
- Fluconazole
- Ganciclovir
- Imipenem
- Metronidazole
- sulfamethoxazole
- Penicillin
- Antihypertensives
 - Captopril, enalapril, lisinopril, atenolol, metoprolol, sotalol, minoxidil
- Others
 - ASA, acetaminophen, allopurinol, azathioprine, gabapentin, theophylline

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Medication prescribing for dialysis patients

- › Medications still need dialysis doses
- › If cleared by dialysis may need a dose after or mid-dialysis
 - Antibiotics
 - Gabapentin
 - Lyrica
 - Acetaminophen
 - Anti-hypertensives (usually have pt hold antihypertensives before dialysis)



The end

