Idaho Society of Health-System Pharmacists

Acute Kidney Injury: Drug-Induced Unless Proven Otherwise

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Disclosures

- I do not have any disclosures or conflicts of interest in regards to my presentation
- I will not discuss off-label uses of any medications

Learning Objectives

- Summarize definition and staging criteria for acute kidney injury (AKI)
- Outline etiology and diagnosis of acute kidney injury
- Review management of acute kidney injury
- Discuss preventive strategies for drug-induced kidney injury
- Summarize the job description for a Pharmacist-Ninja

80 y/o female admitted with AMS and ® foot surgical wound infection

- PMH: s/p recent Charcot foot repair, anemia, HTN, T2DM, peripheral neuropathy, COPD, hypothyroidism, OA, depression
- Dry mucous membranes noted on physical exam
- VS: T 98.6F, BP 141/67, P 84, T 98.6F, RR 20
- Height: 5'1'', weight 105 kg
- Labs: glucose 113, Na 135, K 5.2, Cl 98, Bicarb 27, BUN 53, SCr 1.5 (baseline 0.9), eGFR 33, CRP 26, wbc 8,200, Hgb 9.5/Hct 29, plt 219
- Wound culture: MRSA – sensitive to Vancomycin (MIC of 1)
- Blood culture – no growth x 48 hrs

- Is this patient experiencing AKI?
- What is the most likely underlying cause for her AKI?

80 y/o female admitted with AMS and ® foot surgical wound infection

- Discharged 5 days later to LTCF on Vancomycin 1.5 gm IV every 24 hrs, last trough prior to 3rd dose was 15.2
- SCr 0.9 at discharge

	8/21/18	8/22/18	8/23/18	8/24/18	8/25/18
SCr (mg/dL)	0.9	0.8	0.9	1.0	0.9
Total Intake (ml)	2,319	2,773	3,610	3,003	1,356
Total Output (ml)	3,950	1,900	1,125	850	450

- What is your assessment of this patient's renal function?
- Should this patient continue on vancomycin therapy?

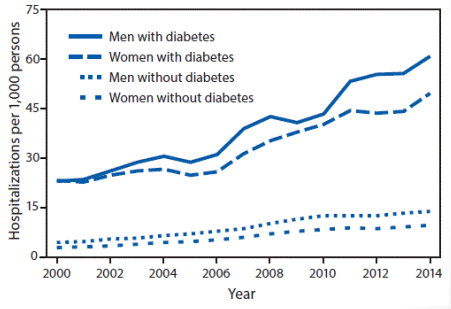
Acute kidney injury (AKI) increases the risk of subsequent AKI, the risk of progression to chronic kidney disease (CKD) and mortality

Background

- Formerly known as acute renal failure or acute renal insufficiency
- Syndrome characterized by an abrupt decline of renal function manifested by an accumulation of creatinine, urea, and other waste products with/without reduced urine output
- Global public health concern associated with high morbidity, mortality and healthcare costs
- AKI affects ~5-10% of hospitalized patients & up to 60% of patients admitted to ICU
- AKI is associated with higher incidence of CKD
- 18-27% of AKI in hospitalized patients is drug-induced

Pavkov ME, Harding JL, Burrows NR. Trends in Hospitalizations for Acute Kidney Injury — United States, 2000–2014. MMWR Morb Mortal Weekly Rep 2018;67:289–293.

Incidence of hospitalizations with AKI among men and women ≥ 20 years of age with and w/o diabetes: United States - 2000 - 2014



Pavkov ME et al. Trends in Hospitalizations for Acute Kidney Injury – Unites States, 2000-2014. Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Reports 2018;67(10):289-293.

Trends in Hospitalization for AKI Among Men and Women Aged ≥ 20 Years with and with Diabetes

Characteristic	2000	2006	2014	Absolute change (95% CI)	Percent change (95% CI)
All persons with diagnosed diabetes					
Weighted No.	11,863,011	17,109,522	21,871,994		
All AKI No.	364,527	666,060	1,571,265		
Hospitalization Rate (95% CI)	23.1 (21.5–24.8)	28.5 (27.0–29.9)	55.3 (54.1-56.6)	32.2 (30.1-34.3)	139.2 (121.1-157.3)
All persons without diagnosed diabetes					
Weighted No.	189,675,970	202,950,590	217,677095		
All AKI No.	589,399	1,156,994	2,388,295		
Hospitalization Rate (95% CI)	3.5 (2.4-3.7)	6.5 (6.3-6.7)	11.7 (11.5-11.8)	8.1 (7.9-8.3)	230.4 (216.1-244.7)

Pavkov ME et al. Trends in Hospitalizations for Acute Kidney Injury – Unites States, 2000-2014. Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Reports 2018;67(10):289-293.

AKI Definition

- According to 2012 KDIGO guidelines, AKI is defined by any of the following:
  - Increase in SCr by ≥ 0.3 mg/dL within 48 hrs OR
  - SCr increase to ≥ 1.5 times baseline which is known or presumed to have occurred within the previous 7 days OR
  - Urine volume < 0.5 ml/kg/hr for 6 hours

Staging of AKI

RIFLE CRITERIA			COMMON CRITERIA	AKIN CRITERIA	
	Classification	**SCr or GFR Criteria**	**Urine Output**	**Stage**	**SCr or GFR Criteria**
R	Risk of renal dysfunction	SCr ↑ 1.5 X baseline OR GFR ↓ > 25%	< 0.5 ml/kg/hr for 6-12 hrs	1	SCr ↑ ≥ 0.3 mg/dL OR 1.5-1.9 X baseline in 48 hrs
I	Injury to kidney	SCr ↑ 2 X baseline OR GFR ↓ by > 50%	< 0.5 ml/kg/hr for ≥ 12 hrs	2	SCr ↑ to 2-2.9 X baseline
F	Failure of kidney function	SCr ↑ to 3 X baseline OR GFR ↓ by > 75% OR SCr ≥ 4 mg/dL with acute ↑ of ≥ 0.5 mg/dL	< 0.3 ml/kg/hr for ≥ 24 hrs OR anuria for ≥ 12 hrs	3	SCr ↑ to ≥ 3 X baseline; OR SCr ≥ 4 mg/dL OR initiation of RRT
L	Loss of kidney function	Complete loss of kidney fxn for > 4 wks			
E	End-stage kidney disease	Complete loss of fxn for > 3 mo			

Risk Factors for AKI

- Advanced age
- Sepsis
- Diabetes Mellitus
- Volume depletion
  - Vomiting, diarrhea, poor fluid intake, fever, diuretic use
  - Heart failure, hepatic failure with ascites
- Pre-existing CKD (GFR < 60)
- Nephrotoxins
  - Aminoglycosides and amphotericin
  - NSAIDs
  - ACEIs/ARBs
  - Cyclosporine and tacrolimus
  - Iodinated contrast media
  - Cysplatin
  - Amphotericin

46 y/o M presents to ED with generalized weakness x 2 wks and N/V

- HPI: Pt. also reports chronic blurred vision and polyuria, although his UO has been low recently
- PMH: T2DM, dyslipidemia, hypertension, occasional aches & pain (treated with ibuprofen)
- VS: T 101.5F, BP 66/42, HR 140, RR 32, 95% on RA
- Home medications:
  - Lisinopril 20 mg po daily
  - Ibuprofen 200-400 mg po prn pain
  - Rosuvastatin 20 mg po daily
- What are this patient's risk factors for AKI?

Classification of AKI

	Prerenal/Functional	Intrinsic (ATN & AIN)	Postrenal
History & clinical presentation	Volume depletion RAS, HF, Hypercalcemia NSAID, ACEI/ARB use Cyclosporine	Long-standing renal hypoperfusion Nephrotoxins (contrast, antibiotics) Vasculitis Glomerulonephritis	Kidney stones BPH Cancers
Physical exam	Hypotension Dehydration, Ascites Petechia if thrombotic	Rash, fever (with AIN)	Distended bladder Large prostate
Serum BUN/SCr	> 20:1	15:1	15:1
Urine sodium	< 20 mEq/L	> 40 mEq/L	> 40 mEq/L
FENa	< 1%	> 2%	> 2%
Urine osmolality	High	Low	Low
Urine sediment	Normal	Muddy, brown granular or tubular epithelial casts	Variable
Urine WBC	Negative	2-4+	Variable
Urine RBC	Negative	2-4+	1+
Proteinuria	Negative	Positive	Negative

Fractional Excretion of Sodium Calculation

FENa = (Urine Na/Serum Na)/(Urine Cr/Serum Cr) x 100

Urine Output Classifications

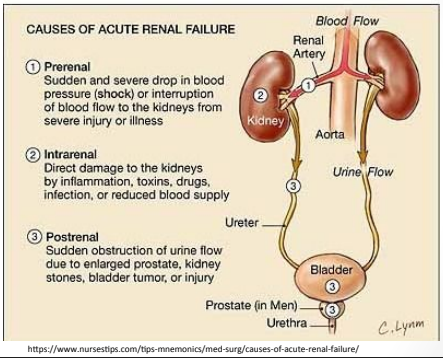
- Anuric: < 50 ml/24 hrs
  - Associated with worse outcomes
- Oliguric: 50 – 500 ml/24 hrs
- Nonoliguric: > 500 ml/24 hrs
  - Associated with better patient outcomes
  - Easier to manage – fewer problems with volume overload

46 y/o male presents to ED with generalized weakness x 2 wks and intractable N/V

- CBC: wbc 17,400, Hgb 11.0, Hct 33.5, plt 298
- CMP: glucose 566, Na 130 (corrected), K 4.7, SCr 5.4, BUN 47, Alb 1.6, Mag 1.7, Phos 0.7, lactate 5.2, CRP 21, procalcitonin 28
- UA: SG 1.020, protein 500 mg/dL, glucose 250 mg/dL, nitrite (+), leukocyte esterase 500/ul, rbc > 100, wbc – packed field, 2-5 granular casts
- Urine: random Na 91, random creatinine 25
- Urinary output: initial 150 ml after 8 L of fluids; 400 ml in the first 24 hrs
- Four days later: SCr 5.6
- Urine culture: > 100,000 CFU/ml of *Enterobacter cloacae*
- Blood culture: *Enterobacter cloacae* in 2 of 2 bottles

- According to AKIN criteria, which stage of AKI is this patient experiencing?
- What is this patient's AKI classification based on available laboratory data?

Acute renal failure



https://www.nursestips.com/tips-mnemonics/med-surg/causes-of-acute-renal-failure/

Etiology of AKI

- Among the most common causes of AKI in hospitalized patients is exposure to nephrotoxins
- Prerenal
  - Characterized by renal hypoperfusion
    - Decrease in effective intravascular volume (HF, cirrhosis with ascites)
    - Dehydration, hemorrhage
    - Medications (NSAIDs, ACEIs/ARBs)
- Intrinsic renal
  - Most common cause is acute tubular necrosis (ATN)
  - Other causes: acute interstitial nephritis (AIN), acute glomerulonephritis, vasculitis
- Postrenal
  - Inadequate drainage of urine distal to the kidneys
  - Bladder outlet obstruction is the most common cause

Diagnosis

- Early diagnosis is critical for improving outcomes
  - Once AKI is recognized, a critical next step is prompt evaluation for the cause of AKI
- Careful history taking
  - Exposure to nephrotoxins
- Physical exam & vital signs
  - Careful assessment of hemodynamic and volume status
- Laboratory tests
  - Urinalysis: granular casts on microscopy indicate ATN
  - Renal panel, CBC, uric acid
  - Urine studies: osmolality, sodium, creatinine
- Renal ultrasound
  - Used to rule out obstruction
- CT KUB (without iodinated contrast)
  - Used for suspected urolithiasis
- Renal biopsy
  - Definite way to establish diagnosis for AIN and ATN

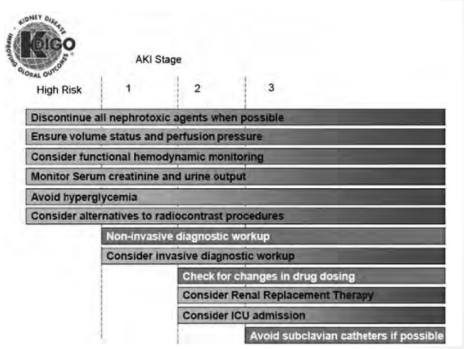
Monitoring of Renal Function

- In most clinical settings renal function is monitored via measurement of serum creatinine
  - Not a sensitive marker
- Creatinine as a product of muscle metabolism
  - Proportional to muscle mass
- Glomerular filtration rate (GFR) must decline by ~50% to 60 ml/min before SCr rises to 1.5 mg/dL
  - By the time SCr becomes abnormal, significant renal dysfunction may already be present
- GFR is an optimal way to measure kidney function
  - Creatinine clearance is a cumbersome test (24-hour urine collection) thus not routinely performed
- Estimated GFR (eGFR) – surrogate marker
  - Calculated using MDRD (Modification of Diet in Renal Disease) calculation (age, gender, SCr, race), Cockcroft-Gault or CKD-EPI
  - More accurate predictor of GFR than serum creatinine alone

Novel Biomarkers for AKI

- Being studies as more sensitive markers for detection of AKI
- May be able to detect presently undetectable mild to moderate renal dysfunction
- Have the potential to describe mechanisms and predict anatomical sites of acute kidney injury
- CysC (Cystatin C) has been used for GFR estimation
  - Thought to be more accurate at higher GFRs and in those with reduced muscle mass
  - Limitations: not accurate if not at steady-state, impact of volume of distribution has not been studied
- Tubular injury biomarkers: NGAL (neutrophil gelatinase-associated lipocalin), KIM-1 (kidney injury molecule 1), interleukin 18 (IL-18), liver-type fatty acid binding protein (L-FABP)
- Biomarkers that reflect kidney stress: TIMP-2, IGFBP-7
  - Recently approved by FDA to ID patients at high risk for developing stage 2 and 3 AKI during the next 12-24 hrs
  - Marketed as NephroCheck Test

Management of AKI



Management of Established AKI

- **General measures**
  - Fluid resuscitation (balanced crystalloids)
    - Assess fluid responsiveness
  - Discontinuation and future avoidance of nephrotoxic medications
  - Adjust medications based on renal function
  - Avoidance of contrast media exposure
  - Correction of electrolyte imbalance
  - Renal replacement therapy (CRRT, IHD)
- **Prerenal azotemia**: goal is to correct hemodynamics
  - Fluid resuscitation if volume depleted (LR vs. NS)
    - Preference is for balanced crystalloids (Lactated Ringer's solution or Plasma-Lyte A)
  - Blood pressure management
  - Blood products if needed
  - Hold or D/C medications which affect renal hemodynamics
    - ACEIs/ARBs, NSAIDs

Management of Established AKI

- **Intrinsic AKI**
  - No specific treatment found to be universally effective
  - Eliminate the hemodynamic instability
  - Discontinue the causative toxin
  - Avoid additional insults
  - Manage fluid and electrolytes
  - Avoid/treat hyperglycemia
    - NICE-SUGAR: no difference in rates of RRT between groups, higher mortality in intensive glycemic control group
  - Nutrition support
    - AKI is a catabolic state; pts may need enteral/parenteral nutrition
  - Medication management
    - Loop diuretics – lack of evidence for their benefit in AKI except in the setting of volume overload
- **Postrenal AKI**
  - Early identification is critical
  - Relieve the obstruction
  - Consult urology or radiology

Box 2. Key Medications Requiring Dose Adjustment (or Cessation) in AKI

- Analgesics (morphine, meperidine, gabapentin, pregabalin)
- Antiepileptics (lamotrigine)
- Antivirals (acyclovir, gancyclovir, valgancyclovir)
- Antifungals (fluconazole)
- Antimicrobials (almost all antimicrobials need dose adjustment in AKI, with important exceptions of azithromycin, ceftriaxone, doxycycline, linezolid, moxifloxacin, nafcillin, rifampin)
- Diabetic agents (sulfonylureas, metformin)
- Allopurinol
- Baclofen
- Colchicine
- Digoxin
- Lithium
- Low-molecular-weight heparin
- NOACs

Moore PK et al. Management of Acute Kidney Injury: Core Curriculum 2018. Am J Kidney Dis. 72(1): 136-148.

Fluid Resuscitation for AKI: An Empty Promise

- Mainstay of prevention and treatment of AKI has been IV fluid therapy
  - Rationale: augments CO, maintains urinary flow, dilutes nephrotoxins, thus minimizing ischemic and toxic insults to the kidneys
- IV fluids are potent drugs with complex pharmacologic actions
  - Only ~20% of fluids remains in intravascular space after 90 min
- Positive fluid balance of 5-10% of body weight has been associated with organ dysfunction and poor clinical outcomes in critically ill and after routine surgery
  - Fluid overload is associated with AKI, prolonged ICU stay, worsening organ function and excess mortality
  - Fluid overload appears to cause endothelial dysfunction
- Benefits of fluids are short-lived and limited only to early stages of select disease states

Watkins SC and Shaw AD. Fluid resuscitation for acute kidney injury: an empty promise. Curr Opin Crit Care 2016;22:527-532.

Fluid Resuscitation for AKI

- Evidence suggests that avoidance of fluid overload may be associated with reduced need for RRT, lower incidence of AKI, increased survival from septic shock
- Certain fluids impair renal function independent of the quantity administered
- Isotonic saline (0.9% NaCl) has been linked to greater risk of AKI, morbidity and mortality when compared with other balanced electrolyte solutions
  - Harm due to hyperchloremia and metabolic acidosis
  - High chloride causes vasocontraction of the afferent arteriole leading to decreases renal cortical perfusion
- Composition, quantity and timing of fluids should be personalized to each patient based on his/her response to fluids

Watkins SC and Shaw AD. Fluid resuscitation for acute kidney injury: an empty promise. Curr Opin Crit Care 2016;22:527-532.

46 y/o male presents to ED with generalized weakness x 2 wks and N/V

- How would you manage acute tubular necrosis in this patient?
- What is your plan regarding his home medications?

Indications for RRT

- Life-threatening/refractory hyperkalemia (K > 6.5)
- BUN > 100 mg/dL
- Refractory fluid overload (pulmonary edema)
- Signs of uremia: pericarditis, pleuritis, uremic encephalopathy
- Refractory metabolic acidosis (pH < 7.1)

Preventive Strategies

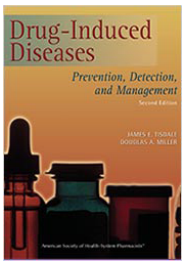
- Prevention is the key: team-based, standardized approach
- Avoidance of nephrotoxic medications whenever possible
- Ensuring adequate hydration
- Patient education
- Use of drug therapies to decrease incidence of contrast-induced nephropathy

KDIGO Recommendations for Practice

- Low-dose dopamine is not recommended for the prevention or treatment of AKI (Level of Evidence 1A)
- Diuretics do not improve morbidity, mortality or renal outcomes and should not be used to prevent or treat AKI in the absence of volume overload (2C)
- KDIGO suggests not using aminoglycosides for treatment of infections unless no suitable, less nephrotoxic therapeutic alternatives are available (2A)
- Aminoglycosides are to be administered as single daily dose rather than multiple-dose daily regimens in patients with normal renal function (2B)
- NAC not recommended for the prevention of AKI in critically-ill patients with hypotension (2D)
- NAC not recommended for the prevention of postsurgical AKI (1A)

DRUG-INDUCED ACUTE KIDNEY INJURY (DI-AKI)

Best Reference for Drug-Induced Diseases



Background

- Exposure to nephrotoxins represents a nearly ubiquitous event in the course of hospitalization
- DI-AKI accounts for ~7% of all drug toxicities
- 18-27% of AKI cases in hospitalized patients are drug-induced
- True incidence has not been well characterized because of lack of consistency in defining the condition
- Most implicated medications: NSAIDs, ACEIs/ARBs, aminoglycosides, amphotericin, iodinated contrast media
- Kidneys are at risk of toxic injury:
  - Receive 25% of cardiac output
  - Concentration of toxins in tubules
  - High intra-renal drug metabolism
  - Autoregulation/specialized blood flow through glomerulus

Risk Factors for DI-AKI

- Concomitant administration of nephrotoxins
- Pre-existing CKD
- Advanced age
- Diabetes
- Dose/duration of therapy
  - Prolonged treatment with nephrotoxins
- Renin-dependent disease states
  - Cirrhosis
  - Heart failure
  - Over-diuresis
  - Hypovolemia

Pseudonephrotoxicity

- Medications that inhibit tubular secretion of creatinine
  - Trimethoprim, cimetidine
- Medications that increase BUN
  - Tetracyclines, corticosteroids
- Medications that interfere with serum creatinine assay
  - Cefoxitin and other cephalosporins

Agents Implicated in DI-AKI

Hemodynamic-mediated
- Diuretics
- ACEIs/ARBs
- Cyclosporine
- NSAIDs/COX-2 inhibitors

Glomerulonephritis
- Allopurinol
- Hydralazine
- Lithium
- NSAIDs
- Phenytoin
- PTU
- Rifampin

Nephrolithiasis
- Acyclovir
- Allopurinol
- Topiramate
- Zonisimide
- Sulfonamides
- Furosemide
- Indinavir
- Foscarnet

Acute Tubular Necrosis
- Aminoglycosides
- Amphotericin B
- Radiocontrast media
- Cisplatin
- Ifosfamide

Acute Interstitial Nephritis
- Allopurinol
- Antibiotics
- H2 blockers/PPIs
- Phenytoin, valproic acid
- Diuretics
- NSAIDs

TABLE 43–2 Mechanisms of Drug-Induced Acute Kidney Injury

Drug	Mechanism
ACE inhibitors and ARBs[7-9]	Efferent arteriole vasodilation especially when renin–angiotensin–aldosterone system–dependent vasoconstriction is present
NSAIDs and COX-2 inhibitors[11-17]	Hemodynamic: Inhibition of prostaglandin-dependent afferent arteriole vasoconstriction Acute interstitial nephritis: T cells infiltrate the kidney interstitium, imitating an immunologic response
Aminoglycosides[18-22]	Saturable accumulation of aminoglycosides in the S1 and S2 segments of the proximal tubule, leading to inhibition of phospholipases and tubular cell death
Amphotericin B[18,23-27]	Afferent arteriole vasoconstriction and altered tubule cell permeability leading to cell lysis
Radiocontrast media[30-40]	Afferent arteriole vasoconstriction and reactive oxygen species–mediated tubular toxicity
Cisplatin[48-50]	Tubular cell toxicity secondary to binding to mitochondrial DNA, impairing cellular function and inducing apoptosis
Acyclovir,[63] sulfadiazine,[70] indinavir[67,68]	Supersaturation of the urine with solute, resulting in crystal formation
Lithium[59]	Development of minimal-change disease and focal segmental glomerulosclerosis

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; COX-2 = cyclooxygenase-2; DNA = Deoxyribonucleic acid; NSAIDs = nonsteroidal antiinflammatory drugs.

Tisdale et al. Drug-induced Diseases, 2nd edition.

Clinical Presentation

General Signs and Symptoms	Acute Tubular Necrosis
• CVA tenderness • Edema • Elevated SCr • Rapid weight gain • Fever • Malaise • Hypertension	• Oliguria • Magnesium wasting **Nephrolithiasis** • Renal colic • Hematuria
Acute Interstitial Nephritis	**Glomerulonephritis**
• Eosinophilia • Eosinophiluria • Proteinuria • Pyuria • Skin rash • Arthralgias	• Foamy urine • Facial and LE pitting edema • Oliguria • Proteinuria • Skin rash

Tisdale et al. Drug-induced Diseases, 2nd edition.

Aminoglycosides: ATN

- Typically cause acute tubular necrosis
- Incidence of nephrotoxicity: 1.7-58% of patients
- Presentation
  - Gradual increase in SCr concentration and a decrease in GFR
  - Onset: 6-10 days
  - Nonoliguric AKI
  - Hypokalemia and hypomagnesemia
- Risk factors
  - Large total cumulative dose
  - Prolonged therapy
  - Trough concentrations > 2 mg/L
  - Recent, previous aminoglycoside therapy
  - Concurrent use of nephrotoxins
  - Patient-related: CKD, advanced age, gram – bacteremia, liver disease, hypoalbuminemia, dehydration, K and Mag deficiencies, shock, poor nutrition

Aminoglycosides: ATN

- Prevention
  - Avoid in high risk patients
  - Maintain adequate hydration
  - Use once-daily dosing
  - Avoid use of other nephrotoxins
  - Limit the total cumulative dose

Intravenous Contrast Media

- Third leading cause of AKI among hospitalized patients
- Incidence: 2-50% of patients depending on risk factors
- Associated with high in-hospital mortality risk (34%)
- Iodine-containing contrast media
  - Used for CT, angiography, coronary angiography, arthrography, myelography, GI fluoroscopic studies
  - Cause CI-AKI, specifically ATN
- Gadolinium-based contrast agents (GBCAs)
  - Used for MRI studies
  - Cause nephrogenic systemic fibrosis (NSF)

Intravenous Contrast Media: ATN

- Osmolality of contrast agents
  - High-osmolar contrast media (HOCM): ~1500-2000 mOsm/kg
    - Oldest agents
    - Relatively inexpensive
  - Low-osmolar contrast media (LOCM): 500-800 mOsm/kg
    - Non-ionic → do not dissociate in water → fewer particles in solution
    - Examples: iohexanol 240, iohexanol 300 (Omnipaque), iopamidol (Isovue-200, -300, -370)
  - Iso-osmolar contrast media (IOCM): 290 mOsm/kg
    - Non-ionic dimers
    - Newest class of agents
    - Examples: iodixanol 320 (Visipaque)

Contrast-induced AKI (CI-AKI)

- As osmolality of contrast agents approaches that of serum, the toxicity decreases
- Half life: 1-2 hours, assuming normal renal function
- Pathogenesis
  - Clearance of contract agents is entirely by glomerular filtration
  - Renal ischemia
    - Osmotic diuresis – higher risk with high-osmolar contrast media
    - Systemic hypotension on injection and renal vasoconstriction
  - Direct tubular toxicity caused by reactive oxygen species
    - Directly influenced by duration of exposure of tubules

Contrast-induced AKI

- Clinical presentation
  - Initial transient osmotic diuresis, then tubular proteinuria
  - SCr rise within 24 hrs with a peak 2-5 days after procedure
  - 50% of patients experience oliguria and some may need dialysis
- Risk factors
  - CKD
  - Diabetes mellitus
  - Age ≥ 75 years
  - Anemia
  - Volume depletion/dehydration
  - Hypotension
  - Other nephrotoxins
  - Concomitant use of diuretics
  - Repeated and/or large volume of contrast (>140 ml)
  - Hyperosmolar contrast agents
  - HF, liver failure

Contrast-induced AKI (CI-AKI)

- Uncommon event in patients with normal renal function and no additional risk factors
  - No significant advantage with regard to AKI has been demonstrated by using LOCM over HOCM
- For patients with renal impairment, several studies have demonstrated that LOCM are less nephrotoxic
- Adverse effects of contrast are intensified in dehydrated patients
- Diabetes increases CI-AKI even when SCr is normal
- Among all predisposing factors, patients with diabetes with preexisting CKD are at highest risk for CI-AKI

Contrast-Induced AKI

- Prevention
  - CIN Risk Calculator
  - Volume expansion with IV NS at 1ml/kg/h for 12 h before and 12 h after contrast exposure or 3ml/kg/h x 1 hour and 1.5 ml/kg/h x 4-6 h
    - No benefit to using bicarbonate in high risk patients undergoing angiography with respect to composite end point of death, RRT and 50% reduction in GFR at 90 days
  - Use alternative non-contrast imaging studies whenever possible
  - Discontinue nephrotoxic agents at least 24 hrs prior to procedure
  - Avoid laxatives and diuretics
  - Use low-osmolar or iso-osmolar contrast agents
  - Use the lowest necessary dose in patients with renal impairment
  - N-Acetylcysteine (NAC): antioxidant and vasodilatory effects
    - Widely used, conflicting evidence, generally considered safe
    - May use oral NAC in combination with IV hydration (KDIGO, 2D)

Gadolinium-based Contrast Agents (GBCAs)

- Used for MRI studies
- Gadolinium is retained for months to years in brain, bone, skin, kidney, liver, spleen
- Linear GBCAs
  - Examples: gadobenate dimeglumine, gadopentetate dimeglumine (Magnevist), gadoxetate disodium
  - Result in greater retention of gadolinium than macrocyclic GBCAs
- Macrocyclic GBCAs
  - Examples: gadobutrol, gadoterate meglumine, gadoteridol
- Increase risk of nephrogenic systemic fibrosis (NSF)

Nephrogenic Systemic Fibrosis

- Onset: 2-18 days after exposure
- Presentation: burning, itching, swelling, hardening of skin, joint stiffness, muscle weakness
- NSF may result in fatal or debilitating systemic fibrosis affecting skin, muscle and internal organs
- Risk of NSF is highest among CKD stage 4 and 5 (GFR < 30) and those with AKI
  - Use of Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), OptiMARK (gadoversetamide) is considered inappropriate for use in patients with CKD and AKI

Gadolinium-based Contrast Agents

- Prevention of NSF
  - Screen all patients for AKI or other conditions which may reduce renal function
  - Obtain baseline SCr and calculate estimated GFR prior to contrast-enhanced imaging
  - Do not exceed the recommended dose
  - Allow sufficient period of time for elimination of drug from the body prior to re-administration
  - In hemodialysis patients, consider prompt initiation of hemodialysis following administration

Cisplatin & Carboplatin: ATN

- Incidence: 6-13%
- Direct tubular toxins
- Presentation
  - SCr peaks 10-12 days after therapy is initiated
  - Renal magnesium wasting is common; may be accompanied by hypokalemia and hypocalcemia
  - May cause irreversible kidney damage
- Risk factors: multiple courses of cisplatin, advanced age, dehydration, concurrent nephrotoxins, alcohol abuse
- Prevention
  - Avoid concurrent nephrotoxins
  - Use smallest dose possible, decrease frequency of administration
  - Aggressive hydration: 1-4 L within 24 hrs of high-doses to maintain UO of 125 ml/h
  - Amifostine 910 mg/m2 may be administered 30 min prior to cisplatin to avoid nephrotoxicity in high risk patients

Amphotericin B: ATN

- Drug of choice for initial treatment of Mucormycosis
- Incidence of AKI increases as cumulative dose increases
  - ~80% with cumulative dose ≥ 4 grams
- Causes direct proximal and distal tubular toxicity and afferent arteriole vasoconstriction
- Presentation
  - Median onset is 7 days
  - Manifests after administration of 2-3 grams
  - Electrolyte wasting (K, Na, Mg)
  - SCr increases and GFR decreases due to vasoconstriction and decrease in kidney blood flow
- Risk factors: existing CKD, high average daily dose, diuretic use, concomitant nephrotoxins, rapid infusion, dehydration
- Prevention: avoid nephrotoxins, limit total cumulative dose, IV hydration with 0.9% NaCl, use of liposomal products

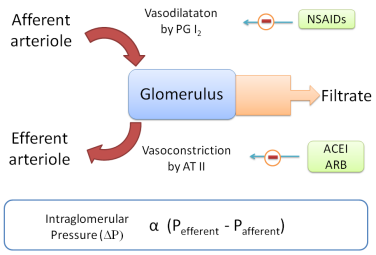
Hemodynamically-mediated AKI

- Mechanism: decreased intraglomerular pressure secondary to vasoconstriction of afferent arterioles or vasodilation of efferent arterioles
- ACEIs/ARBs
  - Cause decrease in glomerular hydrostatic pressure and a decrease in GFR
  - SCr is typically expected to rise up to 30%
  - Onset: 2-5 days, should stabilize in 2-3 weeks
  - Increases > 30% may be detrimental
  - Usually reversible upon discontinuation of the drug
  - Risk factors: bilateral RAS, decreased effective blood flow to kidneys (HF, liver failure), preexisting CKD, dehydration
  - Prevention: start with low doses, titrate slowly, switch to long-acting agents, monitor SCr daily on inpatient and weekly for outpatients, avoid concomitant diuretics and NSAIDs

Hemodynamically-mediated AKI

- NSAIDs
  - Incidence: 500,000 – 2.5 million people develop NSAID-induced nephrotoxicity in US annually
  - Cause vasoconstriction of afferent arteriole and reduced glomerular blood flow
  - Presentation: onset within days of starting therapy; low urine volume, edema, weight gain; increase in SCr, BUN, and serum K
  - Risk factors: preexisting CKD, high plasma renin activity, concomitant diuretics, advanced age
  - Prevention: avoid NSAIDs
  - Treatment: Discontinue drug, provide supportive care, avoid concomitant medications affecting RAAS, recovery is typically rapid

Hemodynamically-mediated AKI



Acute Interstitial Nephritis

- AIN is responsible for up to 3% of all AKI cases
- Caused by allergic hypersensitivity reaction
- Common culprits: β-lactam antibiotics and NSAIDs
- Presentation for β-lactam abx:
  - Onset: 1-2 weeks after therapy initiation
  - Fever, maculopapular rash, eosinophilia, pyuria, hematuria, proteinuria, eosinophiluria
- Presentation for NSAIDs:
  - Delayed onset: after 6 months of therapy
  - No systemic symptoms
- Kidney biopsy may be needed to confirm diagnosis
- Treatment: discontinue the offending agent, consider corticosteroids

Postrenal AKI

- Obstruction of urine flow after glomerular filtration
- Renal tubular obstruction
  - Caused by intratubular precipitation of tissue degradation products
    - Uric acid precipitation associated with tumor lysis syndrome
    - Drug-induced rhabdomyolysis (precipitation of myoglobin)
    - Rapid decline in renal function
    - Oliguric or anuric AKI
  - Caused by precipitation of drugs
    - Sulfonamides, methotrexate, acyclovir, others
    - Needle-like crystals seen in leukocytes on urinalysis
  - Prevention: pre-treatment hydration, maintenance of high urinary volume, alkalinization of urine

Postrenal AKI

- Extra-renal urinary tract obstruction
  - BHP
  - Tumors
  - Anticholinergic agents
- Nephrolithiasis
  - Medications which contribute to formation of kidney stones: triamterene, indinavir, sulfadiazine, others

Vancomycin-induced AKI

- Nephrotoxicity associated with vancomycin is a long-standing, yet highly debated adverse effect
- Known as Mississippi mud in 1950s due to brown color of early formulations (70% pure)
  - Increased incidence of adverse drug reactions
  - In 1985 purity increased to 95%
- Frequency of nephrotoxicity due to vancomycin monotherapy following purification was considered infrequent at 5-7%
- Mechanism of injury
  - Vancomycin is not metabolized; excreted unchanged in the urine via glomerular filtration
  - Decreased GFR from any cause will result in increased vancomycin concentrations
  - Vancomycin has oxidative effects on cells of the proximal renal tubule and causes renal tubular ischemia

Elyasi et al. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations: A literature review. Eur J Clin Pharmacol 2012;68:1243-1255.

Vancomycin-induced AKI

- Guideline-driven more intense vancomycin dosing with goal troughs between 15-20 has been associated with increasing reports of vancomycin-induced AKI
- Rates reported as 5-43% in a recent meta-analysis of 15 studies (1996-2012) – dependent on population
- OR = 2.67 for nephrotoxicity for troughs ≥ 15 vs troughs < 15
  - Highest rates with troughs > 20
- OR = 3.3 for patients receiving concomitant nephrotoxins
- Time of onset : on average 4-17 days after initiation
- Up to 75% of cases resolved within ≤ 7 days
  - Short-term dialysis required in 3% of pts
  - None reported to require long-term dialysis

Van Hal, SJ et al. Systemic Review and Meta-Analysis of Vancomycin-Induced Nephrotoxicity Associated with Dosing Schedules that Maintain Troughs between 15 and 20 mg/L. Antimicrobial Agents and Chemotherapy. 2013;57(2): 734-744.

Vancomycin-induced AKI

- Nephrotoxicity risk correlates with troughs > 15 and duration of treatment > 7-14 days
- Other risk factors: doses ≥ 4 gm/day, weight > 100 kg, critically ill in ICU, concomitant nephrotoxic drugs, preexisting CKD
- Concomitant nephrotoxins can increase incidence of vancomycin-induced AKI by up to 35%
  - Tobramycin, vasopressors, IV contrast media, amphotericin B, loop diuretics, some cephalosporins and PCNs
- Although vancomycin-induced nephrotoxicity is usually reversible, it is associated with poorer outcomes
  - Nephrotoxicity is associated with increased overall mortality, prolonged hospital and ICU lengths of stay

Vancomycin-induced AKI

- Avoid total daily doses > 4 grams
- Avoid duration of therapy > 7 days
  - Order nasal MRSA swab for patients admitted with MDRO pneumonia and D/C MRSA-coverage if negative
    - 95-98% negative predictive value
- Limit exposure to concomitant nephrotoxins
- Monitor renal function very carefully
  - Both urinary output and SCr
- Consider alternative anti-MRSA agents for patients with risk factors for nephrotoxicity requiring prolonged treatment with vancomycin
- Obtain a thorough allergy history in patients claiming allergy to penicillin in order to avoid unnecessary vancomycin prescribing
- Treat patients with MSSA infections with nafcillin or cefazolin over vancomycin (decreased mortality over vanco)

Vancomycin + Piperacillin/Tazobactam AKI

- Package insert for Piperacillin/Tazobactam lists incidence of nephrotoxicity at < 1%
- Recent retrospective cohort study comparing 99 pts on vancomycin alone with 92 pts on combo therapy observed nephrotoxicity in 8.1% and 16.3% of pts, respectively (p = 0.041)
- Consider alternatives to piperacillin/tazobactam (e.g.. cefepime) for antipseudomal coverage in patients already on vancomycin

Burgess LD, et al. Comparison of the Incidence of Vancomycin-Induced Nephrotoxicity in Hospitalized Patients with and without Concomitant Piperacillin-Tazobactam. Pharmacotherapy 2014;34(7): 670-676.

80 y/o female admitted due to increased confusion

- Admission diagnosis: uremic encephalopathy secondary to AKI
- VS: T 36.6, BP 161/79, P 67, RR 14
- Labs: wbc 7,800, Hgb 8.5/Hct 27 , platelets 384, glucose 170, Na 135, K 5.9, Cl 105, Bicarb 22, BUN 28, SCr 2.0, eGFR 24, CRP 16
- Home medications: lisinopril 20 mg daily, vancomycin 1.5 gm IV every 24 hrs (held x 3 days), aspirin 81 mg po BID…
- UA: SG 1.011, protein 30 mg/dL, rbc > 182/hpf, wbc 71/hpf, glucose (-)
- SCr on discharge: 2.3 (max while hospitalized 2.6)

- What is the stage of her AKI?
- What is the underlying cause of her AKI?

Help Prevent DI-AKI

- Avoid use of medications associated with AKI in patients with risk factors
- Avoid concurrent use of agents which affect renal hemodynamics
- Avoid over-diuresis
- Consider once-daily dosing of aminoglycosides
- Avoid concomitant exposure to nephrotoxins
- Counsel patients about risks of volume depletion and a need to maintain adequate fluid intake
- Preferential use of non-ionic, iso-osmolar contrast agents
- Limit duration of therapy with medications associated with AKI
- Maintain adequate fluid status
- Start at lowest doses (medications with hemodynamic effects)
- Preferential use of lipid-based products

Tisdale et al. Drug-induced Diseases, 2nd edition.

NINJA Project

- NINJA: Nephrotoxic Injury Negated by Just-in-Time Action
- Prospective quality-improvement project utilizing EHR screening and decision support process at Cincinnati Children's Hospital Medical Center
- Population:
  - Children at high risk for DI-AKI admitted to non-critical care units
  - Pediatric patients receiving aminoglycosides for ≥ 3 days or ≥ 3 nephrotoxins simultaneously
- Intervention:
  - Pharmacists recommended daily SCr monitoring in exposed patients
  - AKI was defined by modified criteria of ≥ 25% decrease in estimated creatinine clearance

Goldstein SL et al. Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury. Pediatrics 2013;132:e756-e767.

NINJA Results

- In the first year, AKI occurred in 25% of exposed patients
- In 3 years, EHR-driven, pharmacy-led notification process resulted in 38% decrease in the rate of 3 nephrotoxic medication exposure and 64% decrease in AKI rates

Goldstein SL et al. Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury. Pediatrics 2013;132:e756-e767.

Healthy People 2020

- One of the goals for 2020 focuses on decreasing the burden of Chronic Kidney Disease (CKD)
- Objective #3 for CKD goal focuses on AKI follow-up
- Patients hospitalized for AKI should be evaluated 6 months after discharge to monitor kidney function and prevent or delay onset of CKD
  - Per KDIGO guidelines, all pts who experience AKI should have their kidney function re-evaluated 3 months after AKI to identify new or worsening CKD

www.healthypeople.gov

New Nomenclature

- Traditional taxonomy of AKI based on anatomic locations (pre, intra, and post-renal) is overly simplistic
- New specific AKI syndromes:
  - Hepatorenal
  - Cardiorenal
  - Nephrotoxic
  - Sepsis-associated

Kellum JA. Why are patients still getting and dying from acute kidney injury? Curr Opin Crit Care 2016;22:513-519.

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Idaho Society of Health-System Pharmacists

Acute Kidney Injury: Drug-Induced Unless Proven Otherwise

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