CORE CURRICULUM IN NEPHROLOGY

Toxic Nephropathies: Core Curriculum 2010

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INTRODUCTION

Toxic nephropathies are an important and relatively common category of kidney damage. Although they generally are reversible when detected early, they may be permanent, leading to chronic kidney disease (CKD). Toxic nephropathies are defined primarily as kidney injury caused by any number of medications, diagnostic agents, alternative products, herbal adulterants, or other toxin exposures, which includes environmental agents and chemicals. Because the kidney performs a number of essential bodily functions, including clearance of endogenous waste products, control of volume status, maintenance of electrolyte and acid-base balance, and modulation of endocrine activity, loss of kidney function leads to a number of clinical problems. Furthermore, metabolism and excretion of exogenously administered medications and environmental exposures is a critically important function. In its role as the primary eliminator of exogenous drugs and toxins, the kidney is vulnerable to develop various forms of injury.

General Categories of Toxic Nephropathies

- Therapeutic and diagnostic agents
- Alternative and complementary products
- Environmental compounds and chemicals

Drug and Toxicant Handling by the Kidney

- Metabolism and excretion of medications, environmental compounds/chemicals, and other toxins
  - Metabolism by cytochrome P450 (CYP450) enzymes, conjugation with glutathione and cysteine, and other metabolic pathways
  - Clearance through glomerular filtration and/or tubular secretion

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RISK FACTORS FOR RENAL TOXICITY

Vulnerability of a patient to nephrotoxicity from medications or toxicant exposure is related to a number of factors. Included are the actual kidney handling of drugs and toxins, underlying host characteristics and comorbid conditions, and the innate nephrotoxicity of the offending agent (especially certain drug combinations). Older age, female sex, diabetes mellitus, underlying kidney disease, hypertension, and congestive heart failure are a few examples of factors that have significant influence on the patient's ability to tolerate and/or recover from the toxic injury.

Classification of risk factors that enhance renal vulnerability to drug toxicity is accomplished best by dividing them into 3 major categories (Box 1). Each risk factor contributes to the increased development of nephrotoxicity. Generally, $\geq$ 1 risk factor is acting to cause various forms of kidney disease. These factors explain the variability and heterogeneity with drug- or toxin-induced nephrotoxicity.

Major Categories of Risk Factors

- Kidney-specific factors
- Patient-specific factors
- Drug/toxin-related factors

Kidney-Specific Factors

High Blood Flow to Kidneys

- Blood flow is ~20%-25% of cardiac output
- Increased delivery of drug/toxin to the kidneys increases renal exposure to potential nephrotoxins

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Box 1. Risk Factors for Toxic Nephropathy

Kidney-Specific Factors
- High blood (and drug) delivery rate to the kidneys
- Relatively hypoxic renal environment
- Increased drug/toxin concentration in renal medulla & interstitium
- Biotransformation of substances to ROS, causing oxidative stress
- High metabolic rate of tubular cells in the loop of Henle
- Proximal tubular uptake of toxins
  - Apical tubular uptake through endocytosis or other pathway
  - Basolateral tubular transport through OAT and OCT pathways

Patient-Specific Factors
- Older age and female sex
- Nephrotic syndrome, cirrhosis, obstructive jaundice
- Acute or chronic kidney disease
- True or effective circulating blood volume depletion
  - Diminished glomerular filtration rate
  - Increased proximal tubular toxin reabsorption
  - Sluggish distal tubular urine flow rates
- Metabolic disturbances
  - Hypokalemia, hypomagnesemia, hypocalcemia
  - Hypercalcemia
  - Alkaline or acid urine pH
- Immune response genes
  - Increased allergic reactions to drugs
- Pharmacogenetics favoring drug/toxin toxicity
  - Gene mutations in hepatic and renal cytochrome P450 enzyme systems
  - Gene mutations in transport proteins and renal transporters

Drug-Specific Factors
- High-dose drug/toxin exposure and prolonged course of therapy
- Insoluble drug or metabolite forms crystals within intratubular lumens
- Potent direct nephrotoxic effects of the drug or toxin
- Drug combinations enhance nephrotoxicity
- Competition between endogenous and exogenous toxins for renal tubular excretory transporters increase intracellular toxin accumulation

Abbreviations: OAT, organic anion transporters; OCT, organic cation transporters; ROS, reactive oxygen species.

Relatively Hypoxic Renal Environment

- High metabolic rate of cells in the loop of Henle in the medulla (from active transport of solutes through the adenosine triphosphatase sodium-potassium pump [Na^+-K^+-ATPase])
- Excess cellular workload and hypoxic environment increase sensitivity to renal injury to potentially nephrotoxic substances

Concentrating Ability of the Kidneys

- Occurs through countercurrent flow
- Results in high concentration of nephrotoxins and metabolites in the renal medulla and interstitium
- Increased tissue concentrations of toxins cause injury through 2 mechanisms
  - Direct renal toxicity and oxidative stress
  - Ischemic damage from reduced medullary prostaglandin synthesis and increased thromboxane production

Biotransformation Leading to Oxidative Stress

- Conversion of medications, xenobiotics, and other toxins to toxic metabolites and reactive oxygen species (ROS)
- Multiple renal enzyme systems involved
  - Renal CYP450 enzyme system
  - Flavin-containing monooxygenases
- Toxic metabolites and ROS promote oxidative stress that outstrips local antioxidants, thereby increasing renal injury through:
  - Nucleic acid alkylation or oxidation
  - Protein damage
  - Lipid peroxidation
  - DNA strand breaks

Cellular Uptake of Drugs and Toxins

- Overview
  - Occurs through apical and basolateral transport pathways
  - Cellular uptake increases intracellular concentrations, which increase cellular injury (damage to lysosomes, mitochondria, phospholipid membranes, and other intracellular organelles/targets)
  - Extensive trafficking of potentially nephrotoxic substances increases renal tubular exposure and risk of increased concentration of toxin when other risk factors supervene
- Apical uptake of drug/toxin through endocytosis and other transport pathways increases intracellular concentrations
  - Aminoglycoside uptake through negative phospholipid interactions and megalin binding (Fig 1)
  - Sucrose, hydroxyethyl starch (HES), dextran, mannitol, and radiocontrast through pinocytosis/endocytosis (Fig 2)
  - Heavy metals and other toxins

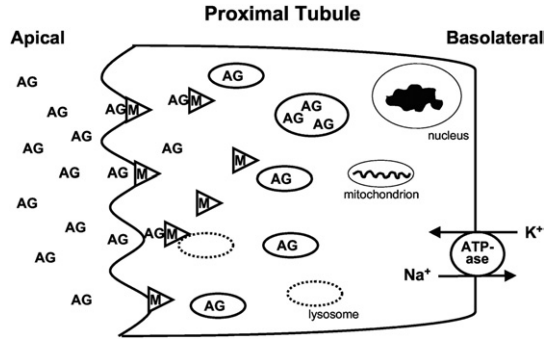

Figure 1. Aminoglycoside (AG) antibiotics are filtered freely at the glomerulus. Because of their cationic charge, they are attracted to the proximal tubular apical membrane brush border, which is rich in anionic phospholipids. At this site, they bind the cationic drug receptor megalin (M; encoded by the *LRP2* gene) located deep at the base of the brush border villi. The receptor-AG complex is internalized by pinocytosis and taken up by lysosomes (denoted with dotted lines). The adenosine triphosphatase sodium-potassium pump (Na^+-K^+-ATPase) is shown at the basolateral surface.

- Basolateral drug/toxin uptake, after delivery by the peritubular capillaries, through multiple transport systems, including organic anion transporters, organic cation transporters, and other transport pathways, increases intracellular concentrations
  - Examples of drugs using the organic anion transporter pathway are tenofovir, cidofovir, adefovir, nonsteroidal anti-inflammatory drugs (NSAIDs), β-lactams, salicylates, and diuretics (Fig 3)

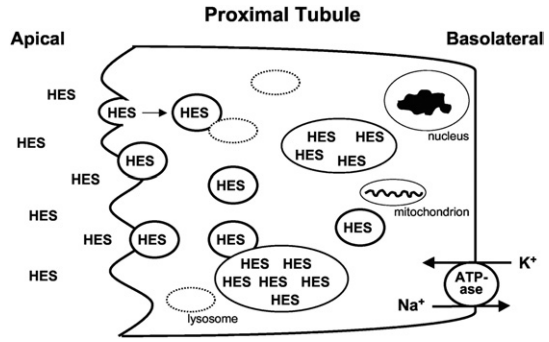

Figure 2. Hydroxyethyl starch (HES) uptake by the apical membrane of proximal tubular cells occurs by pinocytosis. When these pinocytotic vesicles are internalized within the cell, the vesicles fuse with each other and lysosomes. The cytoplasm becomes packed with the lysosomal vacuoles (denoted with HES-containing lysosomes), causing cell swelling and dysfunction. The adenosine triphosphatase sodium-potassium pump (Na^+-K^+-ATPase) is shown at the basolateral surface.

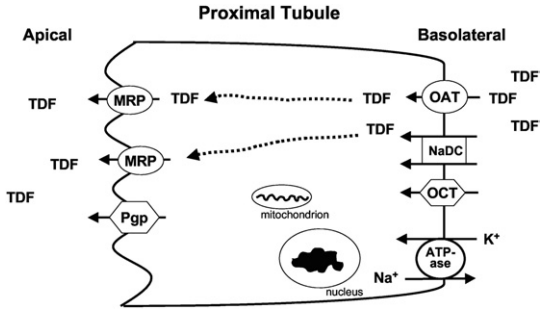

Figure 3. Organic anion drugs, such as tenofovir (TDF), are delivered to the basolateral membrane of proximal tubular cells. At this site, they are transported from the blood into the cell by the human organic anion transporter (OAT; encoded by the *SLC22A6* gene). When within the cell, they are transported through carrier proteins. Eventually, the organic anion drugs are secreted into the urinary space by apical efflux transporters. In the case of drugs such as tenofovir, multidrug resistance–associated protein (MRP) family members MRP2 and MRP4 (encoded by the *ABCC2* and *ABCC4* genes, respectively) are the major transporters. Abbreviations: OCT, organic cation transporter; NaDC, sodium dicarboxylate symporter; Pgp, P-glycoprotein.

  - Examples of drugs using the organic cation transporter pathway are cisplatin, acyclovir, protease inhibitors, cimetidine, quinidine, and trimethoprim
- Transport of drugs/toxins through the intracellular space occurs through various regulated carrier proteins
- Exit of drugs/toxins from tubular cells into urine occurs through apical transport proteins, such as multidrug resistance–associated protein (MRP; encoded by the *ABCC1* gene), P-glycoprotein (encoded by the *ABCB1* gene), and other efflux transporters
  - Loss-of-function mutations in and competition for apical secretory transporters decreases toxin efflux from the cell into urine and may promote accumulation of toxic substances within proximal tubular cells and cause cellular injury through apoptosis or necrosis

Patient-Specific Factors

Nonmodifiable Patient Characteristics

- Older age, typically > 65 years
- Female sex
- Decreased total-body water, which is associated with drug excess/overdose
- Lower glomerular filtration rate (GFR) that is unrecognized because of lower serum

creatinine concentrations associated with decreased muscle mass and lower protein intake
- Decreased drug binding from hypoalbuminemia with associated increased free concentrations
- In the elderly, renal vasoconstriction from excessive angiotensin II and endothelin (kidney ischemia) and higher concentrations of oxidatively modified biomarkers are present and increase risk of drug nephrotoxicity

Underlying Kidney Disease (acute kidney injury and/or CKD)

- Excessive drug dosing from incorrect dose adjustment
- Ischemia-preconditioned tubular cells
- Increased kidney oxidative injury response to drugs and toxins

Nephrotic Syndrome, Cirrhosis, Obstructive Jaundice

- Altered kidney perfusion from decreased effective circulating blood volume
- Hypoalbuminemia with increased free drug
- Excessive drug dosing from unrecognized decreased kidney function
- Direct tubular injury from bile salts (obstructive jaundice)

True or Effective Circulating Blood Volume Depletion

- Renal hypoperfusion; prerenal azotemia to frank renal ischemia increase drug toxicity through:
  - Decreased GFR (excessive drug dose)
  - Increased proximal tubular reabsorption
  - Sluggish distal tubular flow with crystal precipitation with certain drugs

Metabolic Disturbances

- Hypokalemia, hypomagnesemia, and hypocalcemia increase aminoglycoside nephrotoxicity
- Hypercalcemia causes direct afferent arteriolar vasoconstriction, nephrogenic diabetes insipidus, and salt wasting, which all decrease GFR (prerenal physiology) and increase drug nephrotoxicity
- Acidic urine (systemic acidosis) with pH $<$ 5.5 increases crystal precipitation within tubules from sulfa drugs, methotrexate, and triamterene
- Alkaline urine with pH $>$ 6.0 increases crystal precipitation from drugs such as oral sodium phosphate solution, indinavir, and ciprofloxacin

Genetic Makeup

- Adduct formation from drugs/metabolites may be immunogenic in certain patients who are hyperallergic
  - T-Cell–driven process may result in acute interstitial nephritis (AIN)
- Drug- and toxin-metabolizing enzyme gene polymorphisms
  - CYP450 (both hepatic and renal) enzyme gene polymorphisms may be present that decrease metabolism of drugs/toxins and increase nephrotoxic risk
  - Loss-of-function mutations in tubular apical efflux transporters can increase intracellular drug concentrations and toxicity
    - Single-nucleotide polymorphism (G→A change at nucleotide 1249) in the gene encoding the MRP2 efflux transporter is associated with Fanconi syndrome in human immunodeficiency virus (HIV)-infected patients treated with tenofovir, which normally is secreted into urine by this pathway
  - Mutations in kinases that regulate drug carrier proteins within cells can impair drug and toxin excretion

Drug/Toxin-Related Factors

High Doses/Prolonged Course of Therapy

- Increased exposure of tubules or other kidney compartments

Insoluble Drug or Metabolite

- Precipitation of drug or metabolite within distal tubular lumens
- Exacerbated by low tubular flow and urinary pH

Cationic Charge of Aminoglycosides

- Aminoglycosides that are more cationic (neomycin $>$ gentamicin $>$ amikacin) are more nephrotoxic
- Increased interaction with negatively charged membrane phospholipids (increase interac-

tion with megalin binding and tubular uptake)
- Toxicity: neomycin > gentamicin > tobramycin ~ amikacin ~ netilmicin > streptomycin

Drug Combinations

- Certain combinations more nephrotoxic; examples include:
  - NSAIDs and radiocontrast
  - Cisplatin and aminoglycosides
  - Ifosfamide and cisplatin

High Toxicity Profile

- Nephrotoxic even with brief or low-dose exposure
  - Colistin and polymyxin
    - Cell swelling and injury caused by increased membrane permeability to cations
  - Amphotericin B
    - Cell swelling and injury from disrupted cell membranes and increased influx of cations
  - Adefovir and cidofovir
    - Adefovir causes mitochondrial injury through inhibition of DNA polymerase γ, which is the sole DNA polymerase in mitochondria
    - Cidofovir causes tubular injury by formation of cidofovir-phosphocholine, an analog of cytidine 5-diphosphocholine within cells that interferes with synthesis and/or degradation of membrane phospholipids

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NEPHROTOXINS

Exposure to an offending agent with potential for inducing kidney injury is critical for the development of toxic nephropathy. On average, humans are exposed to a variety of potential nephrotoxic substances on a rather frequent basis. Therapeutic agents, which include prescribed and over-the-counter drugs and medications, as well as diagnostic agents, are a rich source of potential nephrotoxic agents. Alternative and complementary products are an over-the-counter source of unregulated potentially kidney-toxic drugs and toxins (adulterants). Environmental compounds and chemicals are yet another problematic source of nephrotoxins. These 3 general categories of nephrotoxins are reviewed.

Therapeutic and Diagnostic Agents

Prescribed Therapeutic Agents

- Antimicrobial agents (including antiviral and antifungal)
  - Aminoglycosides cause dose-related tubular toxicity in the proximal tubule loop of

Henle and distal tubules through phospholipid injury, oxidative stress, and mitochondrial dysfunction
  - Amphotericin B causes afferent arteriolar vasoconstriction and distal tubular injury through cell membrane disruption
  - Tenofovir, cidofovir, and adefovir primarily injure the proximal tubule through mitochondrial disruption; distal tubular injury also occurs
  - Polymyxins, such as colistin and polymyxin B, are highly nephrotoxic and injure proximal tubules
  - Sulfadiazine, and other sulfonamides to a lesser degree, precipitate within renal tubules, whereas AIN also can occur
  - Acyclovir given in high doses with rapid intravenous infusion precipitates within renal tubules
  - Indinavir and atazanavir are protease inhibitors that precipitate within renal tubules
  - Ciprofloxacin causes AIN and, rarely, crystal precipitation within renal tubules when dosed excessively and in alkaline urine; other quinolones can cause AIN
  - β-Lactam antibiotics primarily cause AIN with rare tubular toxicity
- Cancer therapies
  - Platinum drugs (cisplatin $>$ carboplatin $>$ oxaliplatin $\sim$ nedaplatin) cause dose-related tubular toxicity in proximal, loop of Henle, and distal tubules
  - Ifosfamide targets the proximal tubule with nephrotoxic metabolites, such as chloracetaldehyde, in a dose-related fashion
  - Mitomycin C primarily causes thrombotic microangiopathy by promoting endothelial injury in a dose-related fashion
  - Azacitidine causes asymptomatic or clinical tubular damage
  - Gemcitabine causes thrombotic microangiopathy through endothelial injury in a dose-related fashion
  - Pentostatin causes dose-related nephrotoxicity and impaired GFR
  - Methotrexate causes kidney injury through formation of insoluble methotrexate and 7-hydroxymethotrexate crystals within renal tubules
  - Interleukin 2 induces prerenal azotemia due to the induction of a capillary leak syndrome
  - Bisphosphonates injure visceral and tubular epithelial cells in a dose-related fashion; pamidronate causes collapsing focal segmental glomerulosclerosis (FSGS) and minimal change lesions, whereas zoledronate causes tubular injury
  - Antiangiogenesis therapies, such as bevacizumab, sorafenib, and sunitinib, target the vascular endothelial growth factor (VEGF) pathway and injure glomerular endothelium, causing primarily endotheliosis and thrombotic microangiopathy; rare cases of AIN described
- Analgesics
  - NSAIDs of all classes decrease renal prostaglandin production and cause decreased GFR and impaired sodium, water, potassium, and hydrogen excretion; AIN and minimal change/membranous glomerulopathy also can occur
  - Selective cyclooxygenase 2 (COX-2) inhibitors cause renal problems similar to traditional NSAIDs through decreased renal prostaglandin production
  - Analgesic combinations cause chronic tubulointerstitial and papillary injury through both direct toxic and ischemic effects
- Immunosuppressive agents
  - Calcineurin inhibitors, such as cyclosporine and tacrolimus, cause ischemic and direct renal injury known as calcineurin toxicity
  - Sirolimus has been shown to injure the glomerulus, causing an FSGS lesion
- Other agents
  - Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers cause hemodynamic kidney injury in at-risk patients with impaired renal perfusion
  - Sucrose and HES cause proximal tubular injury and impair kidney function through cellular swelling and lysosomal damage
  - Orlistat induces enteric hyperoxaluria with calcium oxalate deposition in renal tubules with high doses
  - Oral sodium phosphate solution causes calcium phosphate deposition within renal tubules in at-risk patients

- Topiramate and zonisamide cause a type 2 renal tubular acidosis (RTA) with formation of calcium phosphate stones
- Mesalamine and other salicylates used to treat inflammatory bowel disease cause both AIN and chronic tubulointerstitial injury
- Methoxyflurane and high-dose ascorbic acid are associated with calcium oxalate deposition in renal tubules
- Quinine causes thrombotic microangiopathy
- Proton pump inhibitors are associated with AIN and less commonly with hyponatremia and hypomagnesemia

Diagnostic Agents

- Radiocontrast agents cause kidney injury through ischemia, direct tubular toxicity, and perhaps hyperosmolar effects on tubules
  - High osmolar is most nephrotoxic
  - Low osmolar is less nephrotoxic, but still a problem in high-risk patients
  - Iso-osmolar appears similar to low-osmolar agents, perhaps related to hyperviscosity
- Gadolinium-based contrast agents rarely cause kidney impairment, except in high-risk patients exposed to high doses and intra-arterial administration
  - Linear and macrocyclic chelates are available with varying osmolarities
  - Modest nephrotoxicity that is much less common than radiocontrast

Alternative and Complementary Products

- Numerous substances are included in this category of unregulated products, including herbal remedies, natural products, and nutritional supplements available at most health food stores
  - Aristolochic acid was found in a slimming product and causes tubulointerstitial injury by CYP450 enzyme–derived intermediates that form DNA adducts that cause DNA alkylation
  - *Ephedra* species cause stone formation with high doses
  - Glycyrrhiza causes apparent mineralocorticoid excess (hypertension and hypokalemia) by inhibiting the enzyme 11β-hydroxysteroid dehydrogenase, which metabolizes cortisol to cortisone
  - *Datura* species cause tubular injury
  - *Taxus celebica* is a tubular toxin and also causes hemolysis with hemoglobinuria
  - *Capes aloe* is a known renal tubular toxin and hepatotoxin
  - *Uno degatta* causes proximal tubulopathy and acute kidney injury (AKI)
- A major concern is that although many of the substances are innocuous, even those that are safe may contain harmful contaminants and chemicals
  - Dichromate causes direct toxic tubular injury, as well as renal injury from hemoglobinuria
  - Cadmium is a heavy metal that causes proximal tubular injury
  - Phenylbutazone is an NSAID and causes similar renal injury
  - Melamine causes tubular injury and stones through melamine crystal formation in infants exposed to contaminated formula

Environmental Compounds and Chemicals

- Heavy metals primarily cause kidney injury through proximal tubular toxicity with reduced GFR and proximal tubulopathy
  - Lead
    - At high doses causes classic lead nephropathy
    - Even with low exposures (considered normal levels), increases rate of CKD progression
  - Cadmium
  - Mercury
  - Uranium
  - Copper
  - Bismuth
- Solvents
  - Hydrocarbons, such as trichloroethylene, chloroform, and bromobenzene, target proximal tubules and cause injury through formation of toxic metabolites and oxidative stress
  - The organic solvent ethylene glycol causes tubular injury through calcium oxalate crystal formation in renal tubules

Other Toxins

- Herbicides, such as paraquat and diquat, cause proximal tubular injury after entry

through organic cationic transporters, whereupon they form ROS and induce oxidative stress
- Germanium causes renal injury through direct tubular effects and is associated with chronic tubulointerstitial injury
- Silicon is rarely described to cause renal injury with massive intoxication

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KIDNEY COMPARTMENTS TARGETED BY NEPHROTOXINS

As shown, kidney damage induced by nephrotoxins can be caused by several different mechanisms. Importantly, different kidney compartments, including the renal vasculature, various nephron segments, the interstitium, and the collecting system, may be drug and toxin targets. They can be divided simply into the following kidney compartments: (1) hemodynamic, (2) renal parenchyma, and (3) collecting system.

Hemodynamic Injury

- Occurs in those with other risk and often is associated with other disease associated with poor renal perfusion, such as hypotension, renal arterial disease, and other processes
  - Increased afferent arteriolar vasoconstriction from NSAIDs and direct vasoconstrictors, such as vasopressors, calcineurin inhibitors, and amphotericin B
  - Decreased efferent arteriolar vasoconstriction from ACE inhibitors and angiotensin receptor blockers

Renal Parenchyma

- Vasculature, in particular medium and small vessels, may be involved by drugs that induce thrombotic microangiopathy or a hypercoagulable state
- Glomerular injury by numerous drug-induced toxicities, including
  - Direct damage to glomerular endothelial cells and visceral epithelial cells
  - Immune-complex deposition within glomerular capillary basement membranes from a drug-induced antibody formation

- Tubules all along the nephron are damaged by
  - Direct nephrotoxic injury
  - Generation of toxic intermediates
  - Ischemia in areas with high metabolic activity
  - Oxidative stress
  - Crystal deposition within renal tubules
- Interstitial disease
  - Occurs acutely from allergic drug reactions
  - Occurs chronically from persistent inflammation complicated by fibrosis
  - Direct toxicity and chronic ischemia from certain drugs, such as combination analgesics, heavy metals, mesalamine, and alternative products

Collecting System

- Renal pelvis and ureters
  - Drug-induced stone formation from medications such as sulfadiazine, indinavir, atazanavir, melamine, topiramate, and others
  - Ureteral encasement from retroperitoneal fibrosis from drugs, such as methysergide and pergolide
- Bladder
  - Dysfunction induced by drugs such as anticholinergics, opioids, α_1-receptor agonists, and benzodiazepines

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CLINICAL SYNDROMES INDUCED BY NEPHROTOXINS

Injury to these specific areas of the kidney results in ≥ 1 of the following clinical renal patterns. AKI, various tubulopathies, vascular and glomerular pathologic states, and CKD are a simple categorization of clinical renal syndromes (Box 2). Diagnostic workup includes assessment of kidney function, including thorough evaluation of GFR, proximal and distal tubular function, and structural evaluation of the renal parenchyma and collecting system. A kidney biopsy may be indicated to establish the diagnosis.

Box 2. Clinical Renal Syndromes Caused by Nephrotoxins

Acute Kidney Injury
- Prerenal azotemia
- Acute tubular necrosis
- Acute interstitial nephritis
- Acute glomerulonephritis
- Crystal nephropathy
- Obstructive nephropathy

Tubulopathies
- Renal tubular acidosis/Fanconi syndrome
- Sodium wasting (Bartter-like syndrome)
- Potassium wasting
- Distal renal tubular acidosis
- Nephrogenic diabetes insipidus

Proteinuria
- Nephrotic syndrome
  - Minimal change glomerulonephritis
  - Membranous glomerulonephritis
  - Focal segmental glomerulosclerosis
  - Other
- Nephritic syndrome
  - Thrombotic microangiopathy
  - Vasculitis and hypersensitivity angiitis

Chronic Kidney Disease
- Secondary progression of toxin-induced kidney disease
- Chronic tubulointerstitial nephritis

Acute Kidney Injury

- Numerous drugs and toxins cause AKI; common types of AKI and classic nephrotoxic agents are noted

Prerenal Azotemia

- NSAIDS, selective COX-2 inhibitors
- Renal vasoconstrictors
- ACE inhibitors and angiotensin receptor blockers

Acute Tubular Necrosis

- Aminoglycosides and other antimicrobial agents
- Cancer therapies, such as cisplatin, ifosfamide, and zoledronate
- Radiocontrast agents
- Osmotic agents, such as sucrose and HES

Acute Interstitial Nephritis

- β-Lactam and sulfa-based antibiotics, as well as other antibiotics
- NSAIDs and selective COX-2 inhibitors
- Proton pump inhibitors and H_2 blockers

Crystal Nephropathy

- Indinavir, atazanavir, acyclovir, ciprofloxacin, and sulfadiazine
- Methotrexate
- Oral sodium phosphate solution
- Orlistat, high-dose ascorbic acid

Obstructive Nephropathy

- Drug-induced nephrolithiasis
  - Sulfadiazine, indinavir, atazanavir, melamine, and topiramate
- Retroperitoneal fibrosis from methysergide and other drugs
- Urinary retention from anticholinergics and several other medications

Tubulopathies

- Tubular dysfunction at various nephron segments leads to a number of clinical findings, depending on the segment involved
- Proximal RTA and Fanconi syndrome occur with drugs that cause proximal tubulopathy (sometimes associated with concomitant AKI)
  - Tenofovir, adefovir, and cidofovir
  - Aminoglycosides and outdated tetracycline
  - Ifosfamide and cisplatin
  - Heavy metals, aristolochic acid, and *Akebia* species
- Salt wasting and acquired Bartter syndrome from disturbed loop of Henle tubular cell function
  - Aminoglycosides
  - Cisplatin
- Nephrogenic diabetes insipidus from drug-induced disruption of distal nephron water handling
  - Lithium
  - Tenofovir
  - Heavy metals

Proteinuria

Nephrotic Syndrome

- Minimal change lesion
  - NSAIDs
  - Interferon alfa
  - Pamidronate and lithium
- Membranous glomerulopathy
  - Gold and penicillamine
  - NSAIDs and selective COX-2 inhibitors
  - Captopril
- FSGS
  - Pamidronate
  - Sirolimus
  - Heroin
  - Lithium
  - Interferon

Nephritic Syndrome

- Thrombotic microangiopathy
  - Gemcitabine and mitomycin C
  - Antiangiogenesis drugs, such as bevacizumab, sorafenib, and sunitinib
  - Quinine, ticlopidine, and other drugs
- Vasculitis and hypersensitivity angiitis
  - Ciprofloxacin, allopurinol, and others
  - Hydralazine
  - Propylthiouracyl

Chronic Kidney Disease

- Many forms of drug-induced AKI and subacute kidney injury, as discussed, can progress to CKD
- Chronic tubulointerstitial nephritis can lead to CKD; induced by drugs and toxins
  - Combination analgesics
  - Mesalamine and other salicylates
  - Aristolochic acid–containing herbal remedies
  - Other alternative and complementary product adulterants
- Low-level lead exposure, even within accepted "normal" ranges, has been shown to promote more rapid progression of diabetic and nondiabetic forms of CKD

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