Drugs and the kidney

Dr. Laila M Matalqah

UGS

Faculty of Medicine

Objectives

- Discuss the mechanisms by which drugs and chemicals damage the kidney
- Understand how to select and prescribe drugs for patients with renal impairment.

Drug-Induced Acute Renal Dysfunction

- Acute Renal Failure
  - Prerenal: reduction of renal perfusion

    NSAIDs, Cyclosporine, ACEI/ARB,

    Diuretics, amphotiricine B
  - Intrinsic: direct tubular toxicity –

    ATN – Aminoglycosides, Amphotericin

    Radiocontrast Media
  - Allergic interstitial nephritis: Penicillins and cephalosporines
  - Obstructive: by precipitation

    Sulfonamide, Methotrexate, Acyclovir, Indinavir,

DRUG-INDUCED RENAL FAILURE

Mechanism	Drug(s)
Reduction of renal perfusion	NSAIDs, ACE-inhibitors,cyclosporine, tacrolimus, amphotericin B
Direct tubular toxicity	Aminoglycosides, radiocontrast agents, cyclosporine, tacrolimus, amphotericin B, pentamidine, cisplatin
Allergic interstitial nephritis	Penicillins, cephalosporins, sulfonamides, NSAIDs
Intratubular obstruction by precipitation	Acyclovir, sulfonamides, chemotherapeutics

Risk factors:

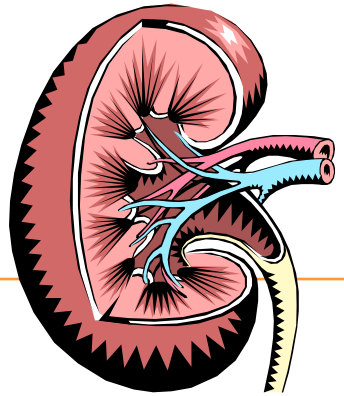
- Idiosyncratic
- Direct cumulative toxicity
- No generalizable risk factors are applicable to all drug classes and patient situation ,Exception: ARF due to NSAIDs & ACEIs
- The risk factors are: Preexisting renal insufficiency & decrease effective renal blood flow from volume depletion and HF, liver disease.

CLASSIFICATIONS

- **Anuric: < 50ml/day urine output**
- **Oliguric: 50-400ml/day urine output**
- **Non-oliguric: >400ml/day urine output**

Kidney Function Tests

Urea Nitrogen blood (BUN) (serum)	7 - 30 mg/dL Alternative source: 8-25 mg/dL	2.5 - 10.7 mmol urea /L Alternative source: 2.9-8.9 mmol/L
Creatinine (Serum)	0.7 - 1.4 mg/dl (<1.2)	</= 106 µmol/L
Creatinine (Urine)	Male: 0.8 - 2.4 g/day Female: 0.6 - 1.8 g/day	Male: 7.1 - 21.2 mmol/day Female: 5.3 - 15.9 mmol/day
Creatinine Clearance (CrCL) Note: Creatinine clearance reference intervals are based on a body surface area of 1.73 square meters.	Male: <12 yr: 50-90 mL/minute, >12 yr: 97-137 mL/minute	Female: < 12 yr: 50-90 mL/minute, > 12 yr: 88-128 mL/minute



- Pre Renal: ↑ BUN/ ↑ Cr >20
- Post Renal: ↑ BUN/ ↑ Cr 10 – 20
- Renal: ↑ BUN/ ↑ Cr < 10

ESTIMATION OF RENAL FUNCTION

- Cockcroft and Gault Equation:

$$CL_{Cr}(ml/min) = \frac{(140-Age)\times(Wt.)}{72(Scr)}$$

$$= \times\ 0.85\ (female)$$

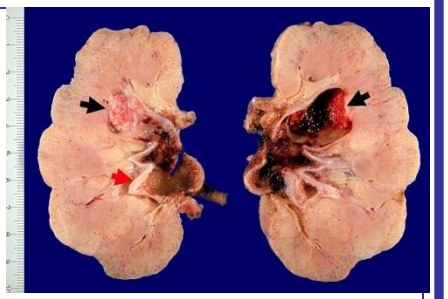
Serum Creatinine

- **Creatinine 1.0 mg/dL** — **Normal GFR**
- **Creatinine 2.0 mg/dL** — **50% reduction in GFR**
- **Creatinine 4.0 mg/dL** — **70–85% reduction in GFR**
- **Creatinine 8.0 mg/dL** — **90–95% reduction in GFR**

ETIOLOGY: pre-renal

- ***Decreased cardiac output:*** CHF,MI,PE, Beta-blockers
- ***Peripheral vasodilation:*** bacterial sepsis, vasodilators (nitrates, hydralazine,etc.)
- ***Hypovolemia:*** blood loss, Severe dehydration, diarrhea, burns, third-spacing, diuretics
- ***Vascular Obstruction:*** NSAIDS, ACE-I, Vasopressors, renal artery occlusion

Pre-renal nephropathy



- **Causes and risk factors**

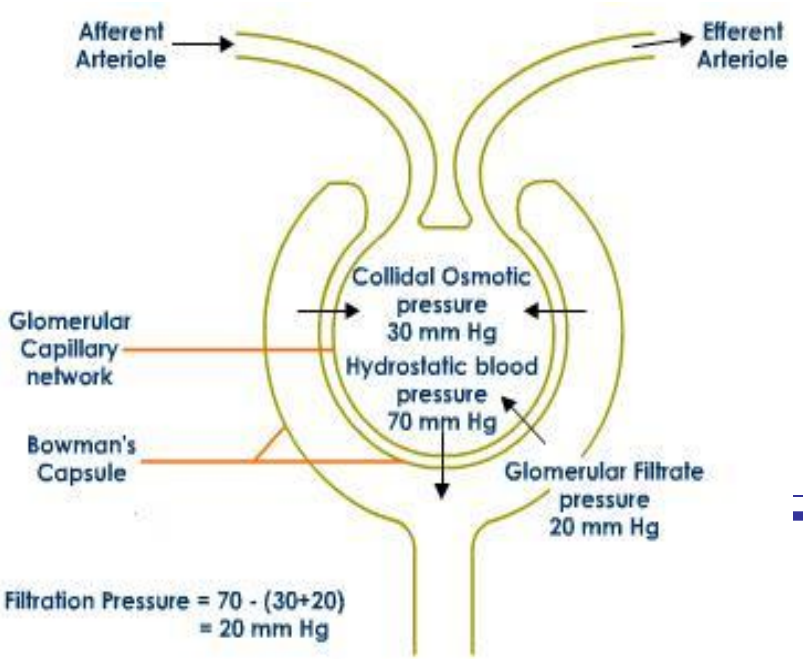
  - Analgesic nephropathy involves damage within the internal structures of the kidney. It is caused by long-term use of analgesics, especially over-the-counter (OTC) medications that contain phenacetin or acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen.

  - About 6 or more pills per day for 3 years increases the risk some for this problem. This frequently occurs as a result of self-medicating, often for some type of chronic pain.

- **Injuries: renal necrosis and chronic interstitial nephritis.**

Afferent Arteriolar vasoconstrictors

- Vasodilatory Prostaglandin Inhibitors
  - NSAIDs
  - COX-2 Inhibitors
- Direct Afferent Arteriolar Vasoconstrictors
  - *Cyclosporine*
  - Amphotericin-B
  - Radiocontrast Media
  - Vasopressors

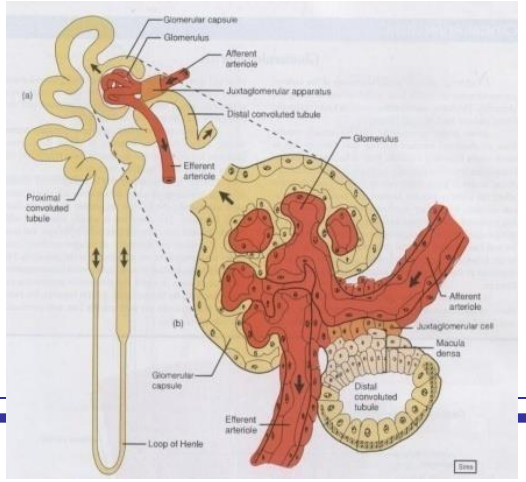


Efferent Arteriolar vasodilators

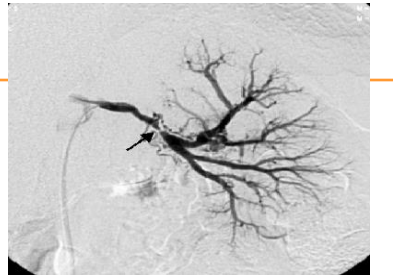
- Renin-Angiotensin-Aldosterone
  - ACEIs
  - ARBs
- Direct Efferent Arteriolar Vasodilators
  - CCBs dihydropyridine: Diltiazem, Verapamil

ACEI/ARB

- At the start of the treatment a decrease of urine volume and increase of creatinine by 30% indicates
  - Damage is reversible
  - Rehydration of patient is advisable
  - Initiate treatment with short acting (captopril) and titrate later with long acting



ACE Inhibitors & ARBs



- Uremia, hyper K+
- Cr > 3.5 → consult nephrology!
- Avoid in bilateral renal artery stenosis
  - ARB causes less renal failure than ACE Inhibitor
- Strategy:
- monitor: BP, K, Cr
- "diuretic holiday" x days before start
- start captopril 1st, then long-acting
- Ramipril: CrCl < 40, give 25% of normal dose
- Losartan: avoid if GFR < 30

Guidelines into Practice

— ACE INHIBITORS —

ACE Inhibitors

Worsening renal function

- If K^+ rises to >6.0 mmol/L, or creatinine increases to above 4 mg/dL (354 µmol/L), the dose of ACE inhibitor should be stopped and specialist advice sought
- Blood chemistry should be monitored serially until K^+ and creatinine have plateaued

Direct Tubular toxicity

ATN: Aminoglycosides

- Incidence 5-20%
- Onset
  - Gradual ↑ SCr after 5-10 days
- Pathogenesis
  - Tubular epithelial cell damage leading to obstruction of tubular lumen
- Presentation
  - Non-oliguria > 500mL/day; granular casts in urine
- Risk Factors
  - Combination therapy with other nephrotoxic drugs
  - Total cumulative dose; trough levels > 2 mg/L; repeated courses of A/G therapy; prolonged therapy > 10 days
  - Dehydration
- Management – Reversible if D/C drug, adequate hydration, monitor levels

Antibiotics

- Aminoglycosides
  - Trough >2mg/L, repeated course in months → ***nonoliguric*** ATN
  - Recommendations:
    - High OD dose (5-7mg/kg/24h x 2-3wks) is less nephrotoxic and equally effective
    - CrCl > 60, 1-2.5mg/kg Q8H
    - CrCl 40-60, Q12H
    - CrCl 20-40, Q24H
    - CrCl <20, loading dose then monitor levels
  - **Neomycin > Gentamicin,Tobramycin > Netilmicin,Streptomycin**

Risk factor for Aminoglycoside Nephrotoxicity

Related to AMG dosing

- Large total cummulative dose
- Prolong therapy
- High peak or trough conc.
- Recent previous AMG therapy

Related to synergistic nephrotoxicity

AMG combination with

- Cyclosporin
- Amphotericin B
- Vancomycin
- Diuretics

Related to Predisposing condition in the patient

- Preexisting renal insufficiency
- Increased age
- Poor nutrition
- Shock
- Gram-negative bactermia
- Liver disease
- Hypoalbuminemis
- Obstructive jaundice
- K+ or Mg++ deficiency

Irreversible Damage!

Aminoglycoside Nephrotoxicity

Prevention

- Switching to alternative antibiotics
- Avoid volume depletion, concomitant therapy with other nephrotoxic drugs
- Limit total dose
- Decreasing the frequency of AMG dosing to at least daily (as direct by renal clearance)

Management

- Monitor Scr, concentration, renal function and electrolytes
- Discontinue AMG if changes are seen.

Aminoglycoside

- Drug interactions with other nephrotoxic medications:
  - Cephalothin and other Cephalosporins
  - Cyclosporin A
  - Cisplatin
  - NSAIDs
  - ACE Inhibitors
  - Loop Diuretics
  - Amino acids

ATN: Amphotericin B

- Incidence: ~80% when cumulative dose reaches 2 g
- Pathogenesis
  - Direct tubular epithelial cell damage; binds to cell wall resulting in ↑ tubular permeability and necrosis
- Presentation
  - ↑ SCr, BUN, ↓ Mg, K (urinary wasting) – monitor q1-2d
  - Distal RTA, polyuria (nephrogenic DI)
- Risk Factors
  - Combination therapy with other nephrotoxic drugs
  - Total cumulative dose; daily dose > 0.5mg/kg/day
  - Dehydration
- Management – Reversible if D/C drug, Hydration (1L NS daily)

Drug-induce renal structural-functional changes

Proximal convoluted tubule

Aminoglycoside

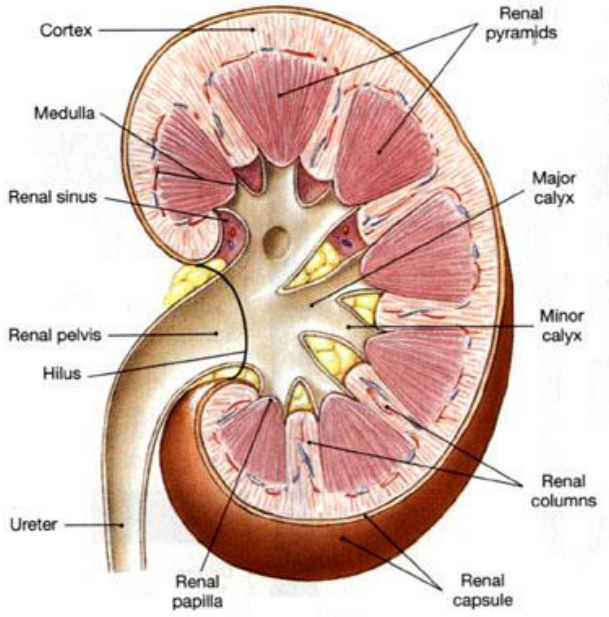
Cephaloridine

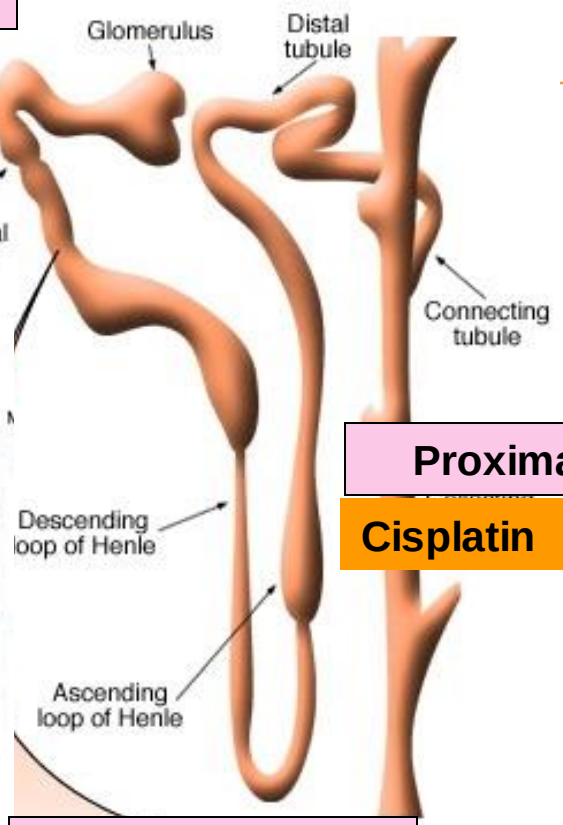
Glomeruli

Interferon-α

Gold

Penicillamine





Proximal tubule

Cisplatin

Renal vessel

NSAIDs

ACE Inhibitor

Cyclosporin A

Interstitium

Cephalosporin

NSAIDs

Drug-Induced Crystalluria

- Drug insoluble in urine and crystallizes in distal tubule
- Risk Factors:
  - Decreased circulating volume
    - High concentration of drug in tubular fluid
    - Prolonged intratubular transit time
  - Renal dysfunction
    - ↑ amount of drug excreted per functioning nephron
  - Acid or alkaline urine pH
- Prevention:
  - Dosage adjustment for underlying renal failure
  - Volume expansion to enhance urinary output
  - Urinary alkalinization (for weak acids)
- Full Renal Recovery expected

ARF: Drug-Induced Crystalluria

(Drug insoluble in urine and crystallizes in distal tubule)

- **Methotrexate**
  - Weak Acid – precipitates in acidic urine (pH < 7)
  - Precipitation of MTX and its metabolite in renal tubules
  - High dose MTX (12-15g/m^2)
- **Prevention**
  - Diuresis – U/O 100-200mL/h x 24h post-high dose MTX
  - Urinary alkalinization (sodium bicarb 25-50 mEq/L hydration fluid)

- **Acyclovir**
  - Weak acid and weak base
  - Intratubular precipitation of acyclovir in dehydrated oliguric patients
  - Needle-shaped crystals
- **Risks/Prevention**
  - IV – too fast infusion rate
    - Infuse over 1 hour
  - High dose > 500mg/m^2
  - Dehydration – IV NS
  - Pre-existing renal failure – adjust dose
  - Other nephrotoxins

ARF: Drug-Induced Crystalluria

- **Indinavir**
  - Protease inhibitor for HIV
  - Weak base - precipitates in alkaline urine
  - Crystal nephropathy (8%) dysuria, urinary freq
  - Rectangular crystals
- **Risk/Prevention**
  - Severe volume depletion
  - Precipitation prevented by consumption of ~2 L fluid per day

- **Sulphonamides**
  - Weak Acid – precipitates in acidic urine
  - Higher doses
  - More common with sulfadiazine
- **Risk/Prevention**
  - Volume depletion - maintain good fluid intake
  - Renal dysfunction - adjust dose
  - Urinary alkalinization (treatment)

Tips: Reducing Drug-Induced Toxicities

Opioids	**Meperidine** metabolite (normeperidine) is neurotoxic and may cause seizures – C/I GFR < 50 mL/min **Fentanyl and Methadone** preferred for chronic pain management as no active metabolites **Hydromorphone** preferred over Morphine (less 3-glucuronide metabolite - myoclonus, hallucinations)
NSAIDs	Caution if GFR < 30-60 mL/minute → ARF, ↑ K, hypertension esp if patient on ACEI or diuretics
Sulfonylureas	**Chlorpropamide** –↑'ed half-life, prolongs hypoglycemia **Glyburide** has active metabolite - ↑ t1/2 → hypoglycemia **Gliclazide** preferred agent – no active metabolite (needs SA) (glyburide 5mg = gliclazide 80mg = gliclazide MR 30mg)
Metformin	Do not use if GFR < 30-60 mL/min → lactic acidosis
Insulin	↓ renal clearance – potential for hypoglycemia
Allopurinol	Dosage adjustment; 100mg/day max in Stage 5 (dialysis)