YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 3 - Pharmacology

Lec. Title : Drug & The Kidney

Written By : Emad A Alzoubi

Lojain Dawood

If you come by any mistake , please kindly report it to
shaghafbatch@gmail.com

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.

Many drugs cause real nephrotoxicity to kidney by direct or indirect mechanism

we have 4 mechanisms in drug induce nephrotoxicity

As a doctor , the prevention is more important to avoid irreversible

cases of nephrotoxicity

Drug-Induced Acute Renal Dysfunction

- Acute Renal Failure → Four Mechanisms of how drugs act on the renal

  - Prerenal: reduction of renal perfusion

    NSAIDs, Cyclosporine, ACEI/ARB,

    Diuretics, amphotiricine B

  - Intrinsic: direct tubular toxicity –

    ATN – Aminoglycosides, Amphotericin + Vancomycin

    Radiocontrast Media

  - Allergic interstitial nephritis: Penicillins and cephalosporines

  - Obstructive: by precipitation

    Sulfonamide, Methotrexate, Acyclovir, Indinavir,

Sheet# 1

if the mechanism is out side the glomerulus (either in afferent or efferent arterioles)
so affect intraglomerular pressure (vasodilation or vasoconstriction for afferent or efferent) it is called prerenal mechanism

- afferent arteriole it is controlled by vasodilation by prostaglandin
- efferent arteriole it should be vasoconstricted by angiotensin
    why it should be vasoconstricted?
    to maintain the intraglomerular pressure in the correct range → hydrostatic pressure in glomerulus → Filtration toward the lumen
- any change in these (example : inhibition in prostaglandin so vasocontraction → ↓filtration → acute renal failure
- also long use of drugs that inhibit angiotensin so it inhibit vasoconstriction in efferent arteriole and make vasodilation in it → ↓filtration of urine in glomerulus → acute renal failure

Drugs in this group will be divided to :

1 - Drugs affect afferent arterioles
2 - Drugs affect efferent arterioles

Sheet# 2

Second mechanisms : (intrinsic / direct tubular toxicity)
- these drugs directly cause nephritis → directly affect lumen cells
→ direct nephritis and bulging → ↓urine output
- these drugs are dose related (accumulative dose related)
* accumulative means → (you should follow up the patient)
At the beginning of take aminoglycosides you have to write down in the drug chart (the first dose , the second , …etc) when the all dose reach certain amount , patient should stop taking the drug

Sheet# 3

third mechanism - Allergic interstitial nephritis
- many patients are sensitive to beta lactam rings
- beta lactam ring → allergic reactions (drugs and antibody reaction affects nephrotic cells) → interstitial nephritis

fourth mechanism : Obstructive by precipitation (crystal urea formation)
these group contain certain drugs like acidic or basic drugs
- But acidic drug are more involve in this mechanism than basic drugs

also depend on the PH of urine
(acid will be in non-ionized form in acidic media)
(Base will be in non-ionized form in Basic media)

most of crystals are acidic (due to acidity of urine → acid drug will precipitate) → stones → obstruction → ↓urine output → acute renal failure

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:

بعض الأدوية مش ضروري يكون إلها (Risk Factor)
و ممكن تأثر فجأة مثل الـ(Penicillin)

- 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.

some drugs like ACEIs + NSAID are contraindicated in patient with preexisting renal artery stenosis or in patient with dehydration

CLASSIFICATIONS

- **Anuric:** **< 50ml/day urine output**

  In this case acute renal failure will occur

- **Oliguric:** **50-400ml/day urine output**

- **Non-oliguric:** **>400ml/day urine output**

  Still less than normal range (1 L)

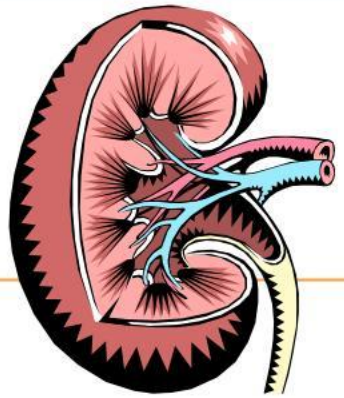
Kidney Function Tests

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) راح نعتمد عليها في الحسابات mg/dL	</= 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

Sheet# 4

- Urea Nitrogen blood used to know the source of damage in kidney (either inside the renal or outside the renal)

→ As creatinine in serum increase it will decrease the creatinine clearance



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

ESTIMATION OF RENAL FUNCTION

- Cockcroft and Gault Equation:

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

Serum Creatinine

اذا زاد الSerum Creatinine
للضعف رح يقل ال Creatinine
للنصف clearance

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

Serum Creatinine

- **Creatinine 1.0 mg/dL** — **Normal GFR**
- **Creatinine 2.0 mg/dL in GFR** — **50% reduction**
  Creatinine (Serum) Increase — Creatinine clearance Decrease
- **Creatinine 4.0 mg/dL reduction in GFR** — **70–85%**
- **Creatinine 8.0 mg/dL reduction in GFR** — **90–95%**

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

Sheet #5

Major

-monitoring parameters:

1. Serum creatinine
2. Serum blood urea nitrogen (BUN)
3. Creatinine clearance

Sheet #6

- Pre-renal mechanism

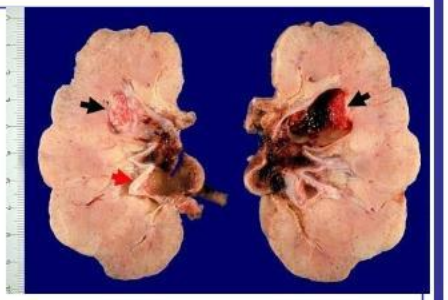
  Both afferent and efferent arterioles are affected

  1. Any drug that decreases cardiac output and decreases stroke volume decreases renal blood flow like Beta blockers

     -Beta blockers indirectly decrease cardiac output this decreases renal blood flow which causes acute renal failure (specially if patients had previous MI or CHF (already have low blood flow))
  2. All vasodilation drugs (such as Hydralazine, nitrates and calcium channel blockers) decrease renal blood flow and cause prerenal acute failure.
  3. Patients who suffer from dehydration + loss of blood and take diuretics will suffer from hypovolemia and decrease in renal blood flow.
  4. Vascular obstruction means (vasoconstriction)
     example: when a patient takes NSAIDs/ACEI/ARB/vasopressors this causes vasoconstriction that causes a decrease in renal blood flow.

Pre-renal nephropathy

(Analgesic 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.

These drugs inhibit prostaglandin and cause vasoconstriction in afferent arteriole.

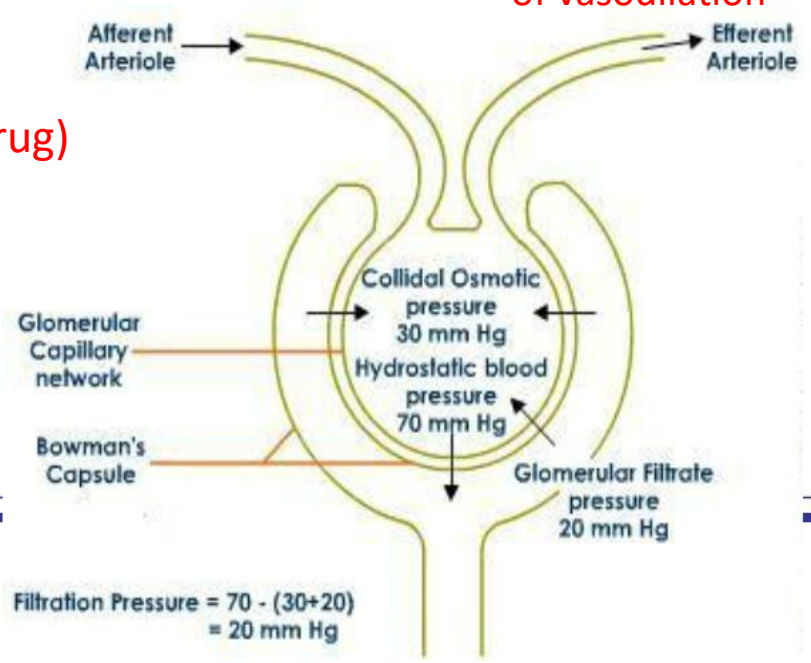
- About 6 or more pills per day for 3 years increases the risk some for this problem. This frequently occurs as a result of self-medicating, often for some type of chronic pain.

This risk factor will increase if patients use other drugs that cause nephrotoxicity

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

Afferent Arteriolar vasoconstrictors

- Vasodilatory Prostaglandin Inhibitors (**Inhibits** vasodilation by inhibiting prostaglandins)
  - NSAIDs
  - COX-2 Inhibitors Protective for the stomach
- Direct Afferent Arteriolar Vasoconstrictors → Do not inhibit the mechanism of vasodilation
  - *Cyclosporine*
  - Amphotericin-B (Anti-fungal drug)
  - Radiocontrast Media
  - Vasopressors



Anything that inhibits vasoconstriction causes vasodilation and decreases interglomerular pressure, filtration and renal output

Efferent Arteriolar vasodilators

Efferent arteriole is controlled by Angiotensin that causes vasoconstriction

- Renin-Angiotensin-Aldosterone
  - ACEIs
  - ARBs Angiotensin receptor blockers
- Direct Efferent Arteriolar Vasodilators

- CCBs (calcium channel blockers)non-dihydropyridine: Diltiazem,Verapamil + CCBCs dihydropyridines: Istradipine, Nifedipine.

ACEI/ARB

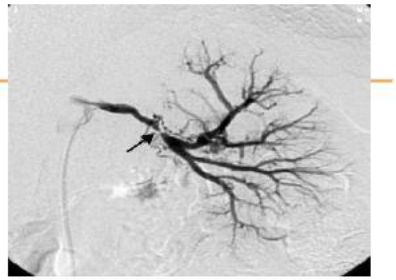
- At the start of the treatment a decrease of urine volume and increase of creatinine by 30% indicates
  - Damage is reversible
  - Rehydration of patient is advisable
  - Initiate treatment with short acting (captopril) and titrate later with long acting

How to prevent acute renal failure

1. **Slow titration** (start with small dose then titrate up)
   start from 12.5 or 5 in captopril then rise to 10.. 15... Etc..
2. **Monitoring** (potassium, serum creatinine and urine output)
3. **Rehydration** (in case of acute renal failure give the patient IV normal saline)
4. **Always initiate with captopril** (Ramipril contraindication or take with caution if the creatinine clearance is less than 40)

ACE Inhibitors & ARBs

What are signs of acute renal failure?



- 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 → Or make dose adjustments ربع الجرعة
- Losartan: avoid if GFR < 30

Sheet #7

The most important parameter is creatinine (serum)
-in some cases, it reaches 3.5 or 4 ⟶ 75% reduction in creatinine clearance (creatinine clearance =20 ml/min
So, we must stop the medication and replace ACEI with another drug.

<u>Strategy:</u>

1. Monitor blood pressure/ potassium and creatinine
   -increase in potassium is a bad indicator
2. Diuretic holiday (days before start)
   بحكيله الدكتور مثلا بكرة ما تاخد المدر او حتى يومين تلاتة

This is important to maintain the hydration of the body

لانه هو لما ياخد ال diuretic و بده يبدأ ب captopril ⟵ شغله على ال aldosterone
و باقي السيستم حيكون أسوأ

This causes faster acute renal failure

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

Directly acting on tubular epithelium ⟶ cell damage ⟶ obstruction of tubular lumen

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

Sheet #8

Aminoglycosides and vancomycin are dose related ; they depend on accumulative dose.
Aminoglycoside depend on trough level and peak level

Trough level and peak level:

When we give the patient aminoglycosides, we should apply drug monitoring or total drug monitoring (TDM)
So, before the second dose we take pre-dose sample (trough level) and after-dose sample (peak level) to make sure that aminoglycoside within the therapeutic range

Example:

If the second dose is at **8:00 am** half an hour before and 2 hours after.
-**7:30 am** pre-dose sample (trough level) normally (1-2 mg/L)
If value is > 2 this indicates a previous problem in previous dose which means higher risk to make nephrotoxicity.
(pharmacologist recalculates and adjusts the dose to the right one)
-**10:00 am** after-dose sample (peak level)
if this reading is higher than normal this means there is a higher risk to make ototoxicity.

Sheet #9

When is the risk of the aminoglycosides increased?

1. If it is taken with another drug that may cause nephrotoxicity

   example: aminoglycoside-vancomycin / aminoglycoside-cephalosporin / aminoglycoside-methotrexate / aminoglycoside- nonsteroidal
2. If we use the aminoglycoside for long therapy (more than 10 days)
3. If patients are dehydrated

Antibiotics

We have 2 protocols to administer aminoglycosides:

1) High once daily dose is less nephrotoxic than multiple doses
2) As creatinine clearance decreases, the drug dose should be taken less frequently

- Aminoglycosides
  - Trough >2mg/L, repeated course in months ⟵ ***nonoliguric*** ATN
  - Recommendations:
    - High OD (once daily) dose (5-7mg/kg/24h x 2-3wks) is less nephrotoxic and equally effective
    - CrCl > 60, 1-2.5mg/kg Q8H → If creatinine clearance is more than 60, we give the patients dose per 8 hours
    - CrCl 40-60, Q12H
    - CrCl 20-40, Q24H
    - CrCl <20, loading dose then monitor levels → كونه ممكن يكون contraindication
  - **Neomycin> Gentamicin,Tobramycin > Netilmicin,Streptomycin**

Neomycin is more nephrotoxic than other aminoglycosides (but is taken locally (not absorbed))

Risk factor for Aminoglycoside Nephrotoxicity

Increase if:

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 بس احيانا ما بكون في بدائل
- 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 functionand electrolytes
- Discontinue AMG if changes are seen.

Because it may lead to irreversible damage

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

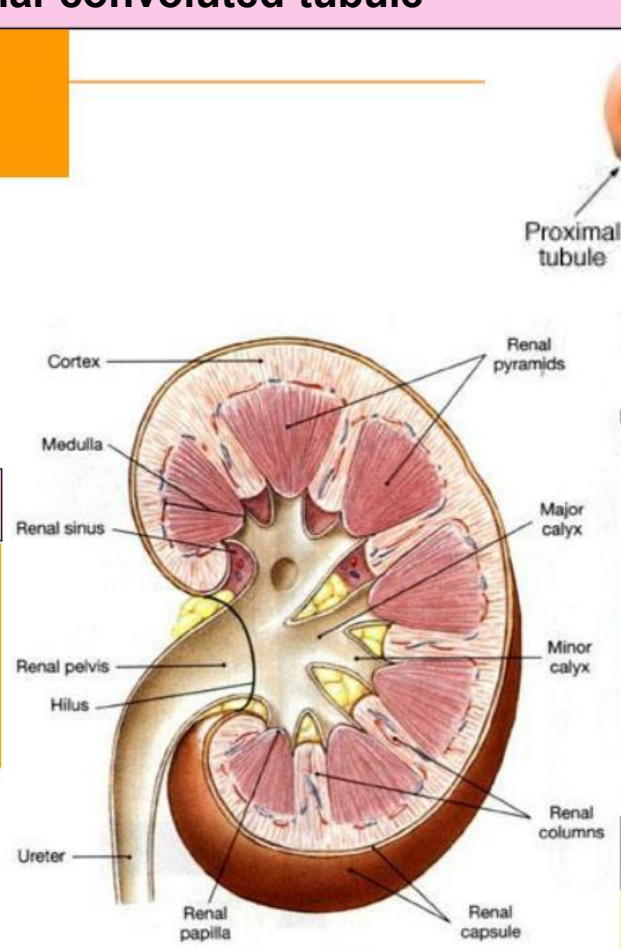
Cephaloridine

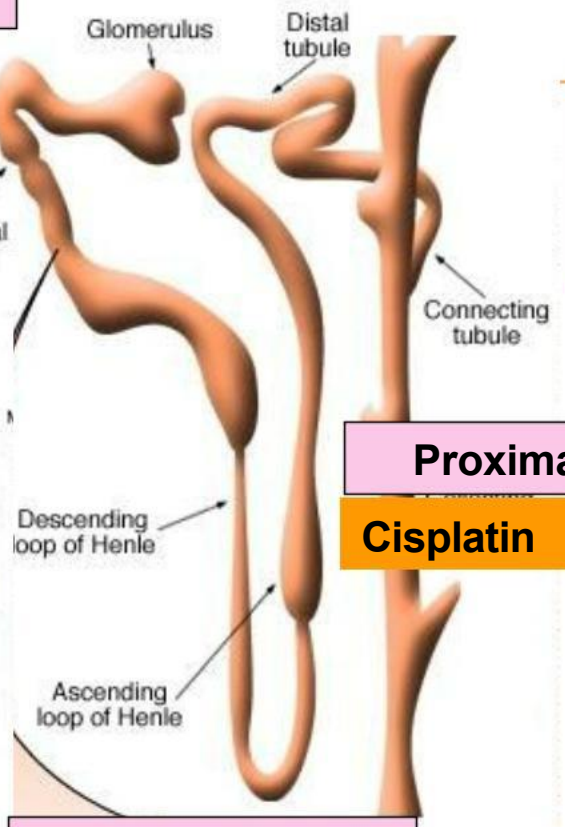
Glomeruli

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 Like using beta blocker or diuretic
    - 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 (rehydration)
  - Urinary alkalinization (for weak acids) And vise versa
- Full Renal Recovery expected

Sheet #10

Risk factor :
prolonged intratubular transit time
Example:
Using probenecid with methotrexate → precipitation
Methotrexate stays longer in the kidneys
or sulfonamide

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** (Moderate)
  - 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 → "normal saline"
  - Pre-existing renal failure – adjust dose
  - Other nephrotoxins

Sheet #11

Why is the acidosis responsible for stone?

Weak acid does not dissolve in acidic media, so it is precipitated, and urine is an acidic media.

Example:

Methotrexate is a weak acid and found in two forms :

1) ionized

2) Non-Ionized

كل ما كان ال acidity of urine اكتر رح يكون نسبة ال non-ionized أعلى و بالتالي رح يترسب و على فترة بتجمع و بعمل ال crystals

Methotrexate metabolitis may also precipitate in the kidney

Methotrexate should be given with hydration (like normal saline)

2) After high dose of methotrexate, we should give diuretic like thiazide to help the kidney get rid of methotrexate

3)Urinary alkalinization

(give IV sodium bicarbonate with normal saline to increase PH of urine and prevent precipitation and crystal formation. (preventive method)

Urine becomes alkaline if a patients is administered a drug that increases the PH of the urine.

ARF: Drug-Induced Crystalluria

- **Indinavir** (weak base)
  - 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

Risk :

Prevention:

- **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)

Prevention ←

Patient should use vitamin C to increase acidity of urine

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 **Requires dose adjustments during acute renal failure**
Allopurinol	Dosage adjustment; 100mg/day max in Stage 5 (dialysis)