بسم الله الرحمن الرحيم

Drugs and the kidney

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Drugs & renal disease

- Renal disease alters the pharmacokinetics of renally excreted drugs and affects pharmacodynamics of many drugs, when the active drug moieties are renally formed or cleared.
- Drug doses should usually be reduced in renal disease in proportion to the predicted reduction in clearance of the active drug moiety; both patient and drug factors should be considered

1- patient factor: to consider in adjusting drug doses include the degree of renal impairment and patient size.

2- Drug factors to consider in adjusting doses include: the fraction of the drug excreted unchanged in urine and the drug's therapeutic index.

- Estimates of renal function are useful to guide dosing of renally cleared drugs with medium therapeutic indices but are not precise enough to guide dosing of drugs with narrow therapeutic indices.

Dose adjustment according to therapeutic index

- ❑ For drugs with narrow therapeutic indices (**aminoglycosides, warfarin, lithium, digoxin, vancomycin, cyclosporin, and phenytoin**), even small changes in drug concentration can cause toxicity or loss of efficacy.
- ❑ Narrow therapeutic index drugs should be dosed using robust biomarkers (clinical response, INR for warfarin, therapeutic drug monitoring, etc.) as estimates or empirical calculations of dose are not reliable enough to be safe.
- ✓ Conversely, for drugs with a wide therapeutic index (e.g., beta lactams), even large changes in drug clearance may have only a modest impact on response, and therefore dose adjustments are less important.
- ✓ For example, Amoxicillin is usually used acutely (short-term) and most dosing guidelines do not discriminate based on renal clearance except for patients with end-stage renal disease.

- an intermediate therapeutic index: an estimate of renal function as an estimate of drug clearance provides useful guidance to dosing and can be used together with clinical and biochemical measures of effects (e.g. serum uric acid for the anti-gout drug allopurinol).

Dose adjustment according to renal functions

- For chronic kidney disease, estimates of renal function are used to predict disease outcome.
- However, for drug dosing estimates of renal function are used to estimate the renal clearance of the drug which is used for further calculation of doses.

For dose adjustment:

1- Calculate the drug clearance based on renal functions.

2- Consider oral bioavailability for oral drugs

Both CL and F determine steady state conc.

$$\text{Dose} = \text{Desired plasma conc.} \times \frac{Clearance}{Bioavilability}$$

- Thus, if a drug is 100% renally cleared and renal function is half-normal, the drug dose should be halved, all other things being equal.
- However, many drugs are inactivated by metabolism (in the liver predominantly), and hence doses of metabolized drugs do not usually require changing in renal disease.

Drug-induced nephrotoxicity

Drug-induced nephrotoxicity is defined by the presence of any kidney injury (acute or chronic) caused directly or indirectly by medication.

Drugs can cause acute renal injury, intrarenal obstruction, interstitial nephritis, nephrotic syndrome, and acid-base and fluid electrolytes disorders.

- Drugs like ACEI, ARBs, NSAID, cyclosporine, and tacrolimus can cause nephrotoxicity by altering intraglomeular hemodynamics and decreasing glomerular filtration rate (GFR)
- Ampicillin, ciprofloxacin, sulfonamides, acyclovir, ganciclovir, methotrexate and triamterene are associated with crystal nephropathy.
- Drugs associated with tubular cell toxicity and acute interstitial nephropathy include aminoglycosides, amphotericin B, cisplatin, beta lactams, quinolones, rifampin, sulfonamides, vancomycin, acyclovir, and contrast agents .These agents induce renal tubular cell injury
- Chronic use of **acetaminophen**, **aspirin**, **diuretics and lithium** is associated with **chronic interstitial nephritis** leading to fibrosis and renal scarring

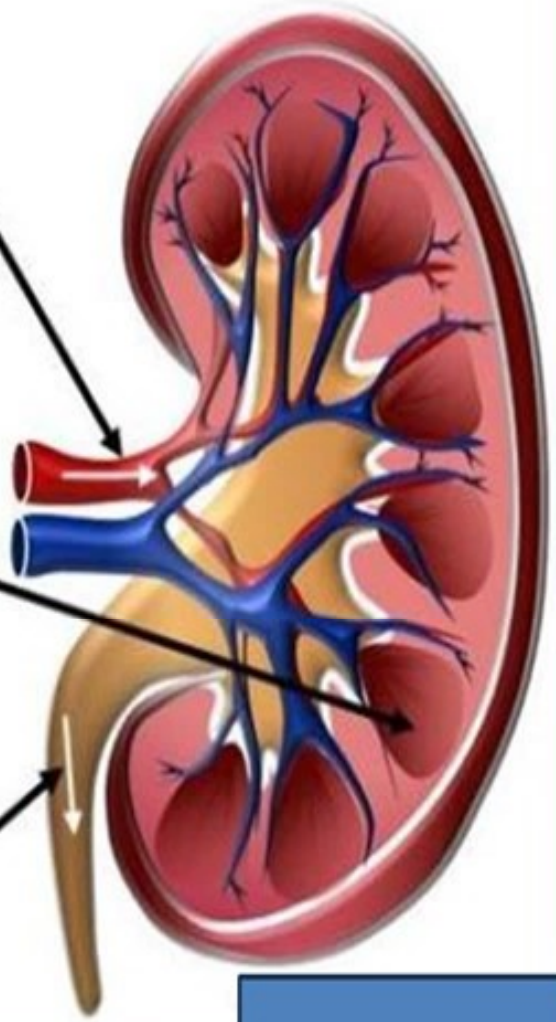
Acute kidney injury (AKI) induced by drugs

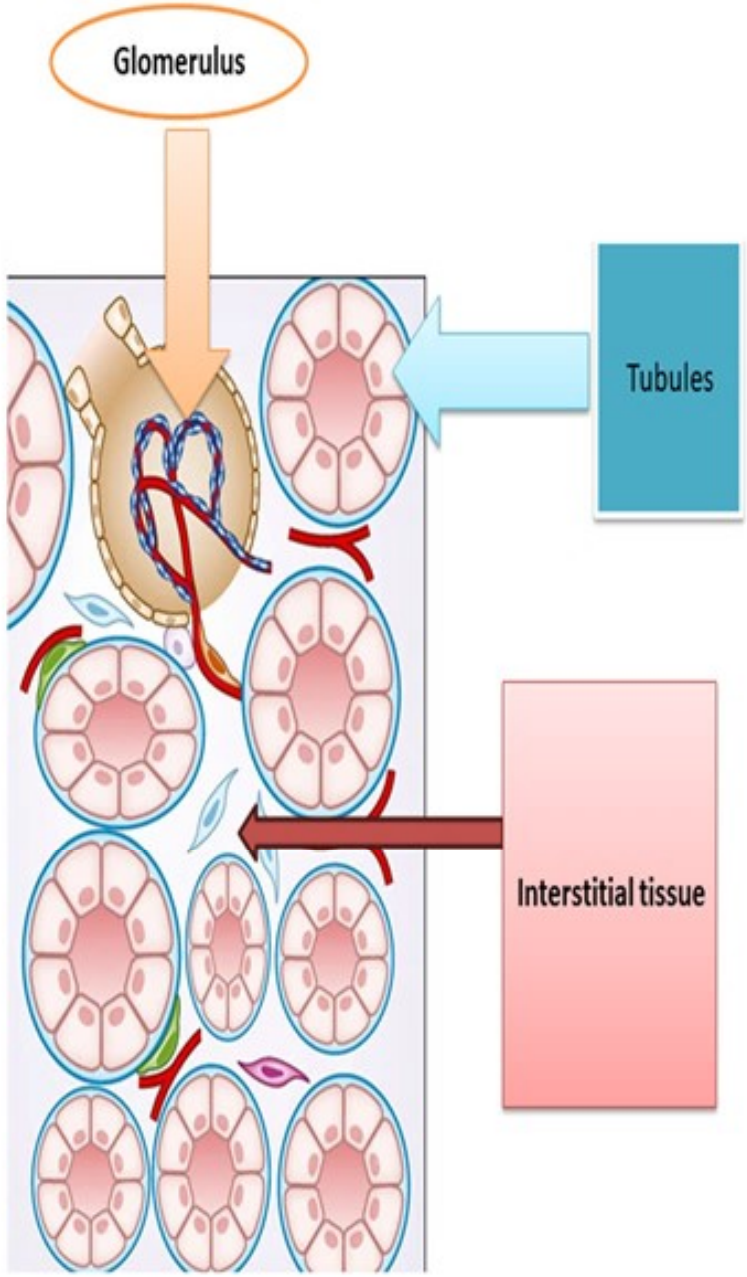
Acute Kidney Injury (AKI)

Prerenal: marked decrease in renal blood flow

Renal: damage within the kidney structures

Postrenal: obstruction of urine outflow





Pre-renal injury		NSAIDs, ACEIs, ARBs, calcineurin inhibitors (cyclosporine, tacrolimus), diuretics
Renal	1-Acute Tubular Necrosis	Aminoglycosides, Amphotericin B, rifampicin, radiocontrast agents, cisplatin, NSAIDs, Loop diuretics, Acyclovir, Cephalosporins, calcineurin inhibitors, **Paracetamol**, **vancomycin**, mannitol
	2- Acute Interstitial Nephritis	Antimicrobials (**β-lactams**, sulfonamides, quinolones, vancomycin, others), NSAIDs, PPIs, phenytoin, carbamazepine, **allopurinol**, thiazide diuretics, Calcium channel blockers, lithium, Aminoglycosides.
	3-Glomerulonephritis	Interferon, **Pamidronate**, Hydralazine, NSAIDs, penicillin and ampicillin, lithium, Rifampin Thiazides, Dapsone
Post-renal injury		Acyclovir, **methotrexate**, **sulfonamides**, **triamterene**, sulfadiazine, antiretrovirals (indinavir, **tenofovir**), large doses of vitamin C & probenecid

NSAIDs, nonsteroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; PPIs, proton pump inhibitors

Acute kidney injury (AKI) induced by drugs

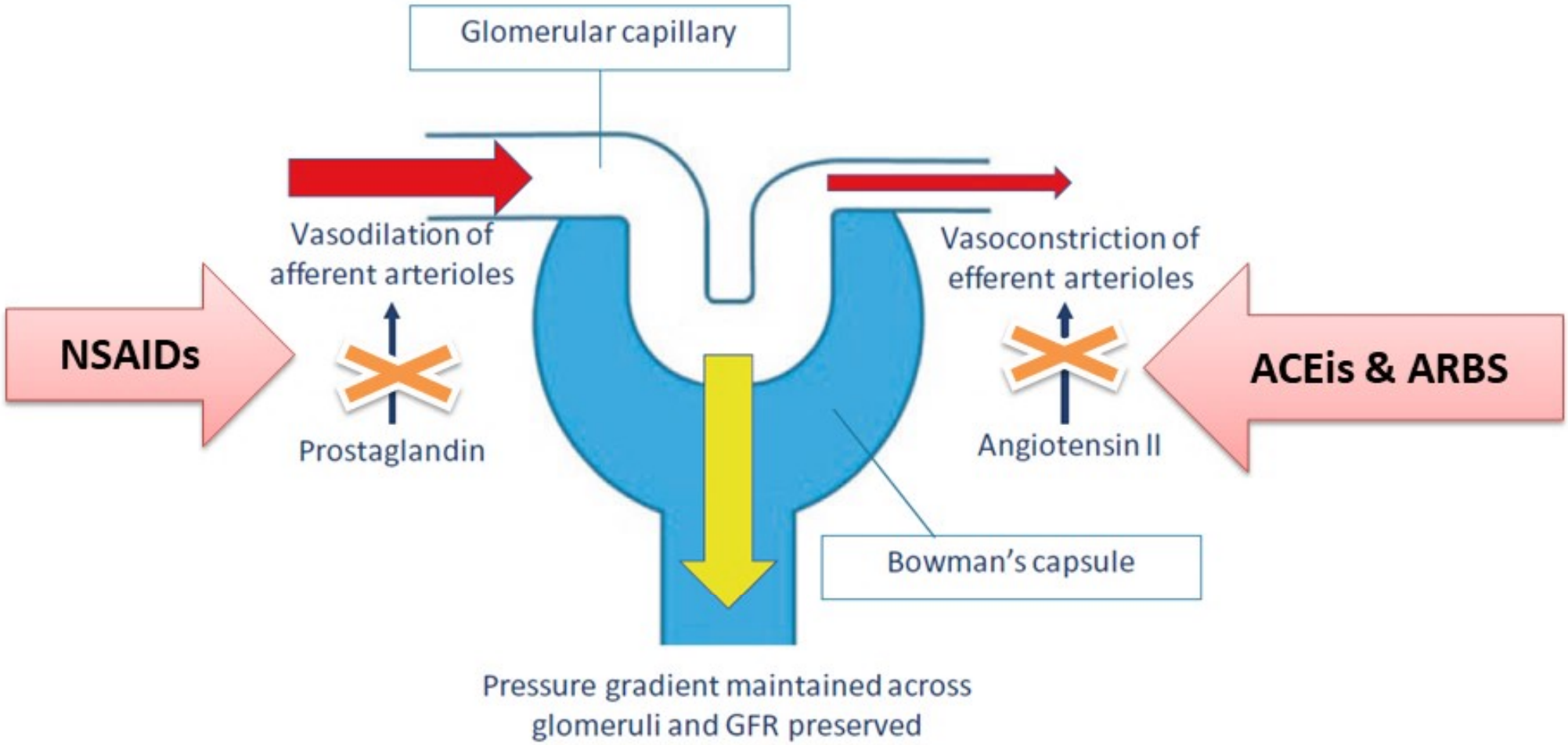
1-Drug induced pre-renal AKI

1- Reduced circulating volume (e.g., Diuretics).

2- Selective reduction in renal perfusion (Drugs that affect glomerular blood flow) like:

- NSAIDs/COX2 inhibitors – inhibit synthesis of vasodilatory prostaglandins.
- ACE inhibitors/ARB – block vasoconstrictor effects of angiotensin II.
- Calcineurin inhibitors (cyclosporin and tacrolimus) which increase vasoconstriction.

- Treatment include maintain vascular volume, Using Vasopressors if necessary.


Glomerular capillary
Vasodilation of afferent arterioles
Vasoconstriction of efferent arterioles
NSAIDs
ACEis & ARBS
Prostaglandin
Angiotensin II
Bowman's capsule
Pressure gradient maintained across glomeruli and GFR preserved

2- Intra-renal AKI induced by drugs

Intra-renal refer to intrinsic damage to the structure of the kidney (apoptosis or necrosis) by ischemia or other cellular mechanisms by impairing mitochondrial function and interfering with tubular transport and increasing oxidative stress.

Mechanisms of intra-renal acute kidney injury:

1- Drugs causing **Acute Tubular Necrosis** or injury.

2-Drugs causing **Acute Interstitial Nephritis**

3-Drugs causing **Glomerulonephritis**

1- Acute tubular injury (ATI) or tubular necrosis

Examples: Aminoglycosides, Amphotericin B, rifampicin, radiocontrast agents, cisplatin, NSAIDs, Loop diuretics, Acyclovir, Cephalosporins, calcineurin inhibitors, **Paracetamol**, **vancomycin**, mannitol.

The important risk factors for acute tubular injury:

1. Exposure to multiple nephrotoxic drugs.
2. A disease that increase the tubular injury (e.g., diabetes, and hypertension).
3. Very young or very old age.
4. Pre-existing chronic kidney disease.
5. Intravascular volume depletion.

2- Acute interstitial nephritis (ANI)

Acute interstitial nephritis (AIN) is an immune-mediated form of kidney injury that is characterized histologically by infiltration of immune cells in the tubulo-interstitium .

- Medications are the most common cause of AIN.
- AIN can cause **permanent kidney damage** from fibrosis formation.
- In drug-induced AIN, drug discontinuation is critical.
- Given the immune-mediated nature of kidney damage, **corticosteroids are often prescribed**. However, corticosteroid dosing regimens are not standardized and vary widely.
- Examples of drug induced AIN: Antimicrobials (**β-lactams**, sulfonamides, quinolones, vancomycin, others), NSAIDs, PPIs, phenytoin, carbamazepine, **allopurinol**, thiazide diuretics, Calcium channel blockers, lithium, Aminoglycosides.

3- Drug induced glomerulonephritis

- Although medications are a widely known cause of tubulointerstitial damage, **drug-related glomerular injury is not well appreciated** but nonetheless, **important**.
- Glomerular damage that occurs after exposure to medications can be caused by **direct cellular injury** involving the **mesangial, endothelial, or visceral epithelial cells (podocytes)**.

Drug-induced podocytopathy can occur in several situations:

1- **IFN causes podocyte injury and nephrotic syndrome may occur.**

2- **Pamidronate** in high doses can cause **direct podocyte injury.**

3- Chronic **lithium** exposure.

4- **Minimal change disease** (MCD) is the most common glomerular lesion observed with **NSAIDs**, which may be because of shunting of Arachidonic A metabolites into pathways that alter immune function and promote podocyte injury.

Post renal injury by drugs

- Crystalline nephropathies are characterized primarily by the histologic finding of intratubular crystal deposition (crystalluria).
- Medications are a well-described cause of this entity and can cause AKI, although less commonly than ATI and AIN.
- Urine sediment examination showing crystal-containing casts is a helpful noninvasive diagnostic test and may eliminate need for biopsy.

Intrarenal crystal deposition occurs when:

1-The kidney is the major route of a drug/metabolite excretion.

2- Increased excretion of the drug (e.g., excessive drug dosing).

3- Supersaturation of the drug & precipitation within urine due to :

- Circulatory volume depletion/dehydration.
- Urine pH also influences supersaturation depending on the pK of the drug. Examples include acid pH for methotrexate and sulfadiazine and alkaline pH for ciprofloxacin.

4-The presence of underlying kidney disease may further enhance risk for drug-induced crystalline nephropathy.

Culprit Medication	Clinical Kidney Syndromes	Preventive and Therapeutic Strategies
Methotrexate	Crystalluria, AKI, and chronic kidney disease (CKD)	IV fluids before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarbidase (<60 h after methotrexate); high-flux hemodialysis in certain circumstances
Sulfadiazine, sulfamethoxazole	Crystalluria, AKI, CKD, and nephrolithiasis	Alkalinize urine, adjust dose for kidney function, assure euvolemia before drug exposure
Indinavir, atazanavir, darunavir	Crystalluria, AKI, CKD, and nephrolithiasis	No role for urine acidification, assure euvolemia during drug therapy; switch to different medication
Acyclovir	Crystalluria, AKI, and CKD	Avoid rapid iv bolus, adjust drug dose for kidney function, assure euvolemia during drug therapy

Ciprofloxacin, levofloxacin	Crystalluria and AKI	Assure euvolemia during drug therapy and avoid alkaline urine (if possible)
iv ascorbic acid, orlistat (by causing enteric hyperoxaluria)	Crystalluria, AKI, and CKD	assure euvolemia during drug therapy,
Triamterene	Crystalluria, AKI, CKD, and nephrolithiasis	Alkalinize urine, assure euvolemia during drug therapy
Amoxicillin	Crystalluria and AKI	Assure euvolemia, adjust drug dose for kidney function
Foscarnet	AKI, hematuria, proteinuria, and CKD	Assure euvolemia during drug therapy and adjust drug dose for kidney function.
Cyclophosphamide	Hemorrhagic cystitis	Adequate hydration, continuous bladder irrigation, and prophylactic dosing of mesna.

Indirect drug induced postrenal AKI:

Here, **AKI is NOT caused by precipitation of the drug** itself or its metabolites in urine. Instead, different mechanisms are involved.

Examples:

1- Crystal nephropathy may also result from the use of anticancer chemotherapy due to uric acid and calcium phosphate crystal deposition (due to death of many malignant cells).

2- Drug induced **rhabdomyolysis** and **myoglobnuria** (postrenal AKI). **Statins** , alcohol, **Benzodiazepines, methadone and Methamphetamine** can cause rhabdomyolysis and AKI.

3- Drugs most often associated with thrombotic microangiopathy include antiplatelet agents including **aspirin**, **cyclosporine**, **mitomycin- C** (anticancer), and **quinine**.

Drug induced nephrotic syndrome

Certain drugs can induce nephrotic syndrome, including nonsteroidal anti-inflammatory drugs (NSAIDs), gold therapy, probenecid, penicillamine, Tolbutamide heroin, interferon-alfa, lithium, and pamidronate

Drug induced renal Acid base disturbances

- **Phenformin** (antidiabetic) and to lesser extent metformin may cause lactic acidosis
- Proximal renal tubular acidosis (by acetazolamide)

Drug induced renal water imbalance

- Hyponatremia, syndrome inappropriate ADH secretion by Chlorpropamide (antidiabetic).
- Nephrogenic diabetes insipidus by lithium.

- Aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), contrast agents, and angiotensin converting enzyme inhibitors (ACEIs) are the most common cause of AKI in hospitalized patients .
- The risk of contrast-induced nephropathy is highest in diabetics and chronic kidney disease diabetes.

Management of drug induced AKI

Individual Medications	Preventative Strategies
Aminoglycosides (gentamicin, neomycin, amikacin)	• Once daily dosing & Adjust dose for underlying eGFR and Consider TDM • Use tobramycin if possible
Vancomycin (+/− piperacillin-tazobactam)	• Adjust dose for underlying eGFR • Therapeutic drug monitoring • Avoid combination with piperacillin-tazobactam • Use alternative agents (teicoplanin)
Amphotericin B	• Use lipid or liposomal forms • iv isotonic crystalloid hydration
Cidofovir, tenofovir, adefovir	• Adjust dose for underlying eGFR • Screen for tubular toxicity to identify early injury • Use alternative agents
Foscarnet	• Use alternative agents

Individual Medications	Preventative Strategies
NSAIDs including COX-2 inhibitors	• **Avoid use in high-risk patients**
Acetaminophen overdose	• Avoid excessive dosing especially in liver disease
Cisplatin (less common with other platin analogs)	• Adjust dose or Use of cisplatin analogs • iv isotonic crystalloid–induced diuresis • Consider **sodium thiosulfate** in high-risk patients
Ifosfamide	• Limit dose & Adjust dose for underlying eGFR • Mesna and N-acetylcysteine of unproven efficacy
Iodinated radiocontrast agents	• iv isotonic crystalloid hydration
Cyclosporine, tacrolimus	• Reduce dose and follow drug levels (TDM) • Consider alternative agents such as mTOR inhibitors


THANK YOU