RENAL FAILURE IN ELDERLY

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- There is a high prevalence of CKD in the elderly.
- This is attributable mainly to increasing prevalence of traditional risk factors for CKD such as diabetes, hypertension and cardiovascular disease (CVD)
- These new definitions for CKD are kidney damage evidenced by abnormal renal markers or a reduction of the absolute eGFR to less than 60 ml/min/1.73 m^2 for at least 3 months.
- Abnormal renal markers are proteinuria, abnormal radiology, abnormal cells in the urine or renal pathology on biopsy.

- Multiple medications
- Accumulation of drugs/toxic metabolites
- Pharmacokinetic
- Pharmacodynamic
- Uremia :
  - drug disposition
  - protein binding
  - distribution and elimination
  - increase sensitivity to drugs

Definitions

- Renal Insufficiency
- Azotemia
- Uremia
- CKD
- ESRD

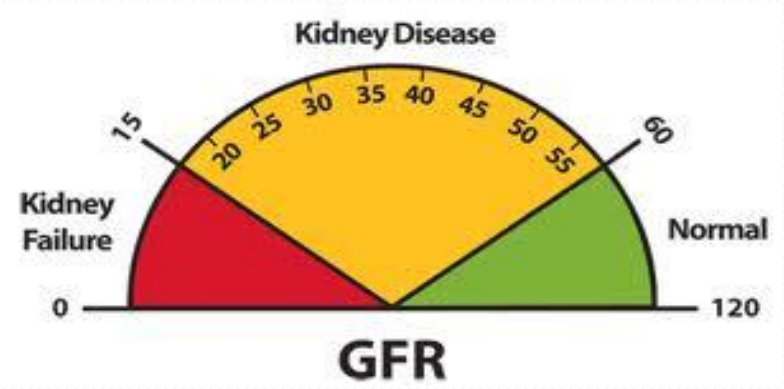
ESRD

- Définition
- Staging chronic kidney disease based-on GFR

Stage	Description	GFR (ml/min/1.73)
-	At ↑risk	≥ 90 with CKD risk factor
1	Damage with normal/↑ eGFR	≥90
2	Damage with mild ↓ eGFR	60-89
3	Moderate ↓ eGFR	30-59
4	Severe ↓ eGFR	15-29
5	Kidney failure	<15/ need for transplant

National Kidney Foundation K/DOQI Staging System for Chronic Kidney Disease

Stage	Description	GFR (mL per minute per 1.7m21
1	Kidney damage with normal or increased GFR	>= 90
2	Kidney damage with a mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	< 15



Risk factors for CKD in the elderly

Modifable traditional risk factors

- Hypertension
- Diabetes
- Obesity
- Proteinuria
- Hyperlipidemia
- Cardiovascular disease
- Glomerular and tubulointerstitial disease
- Metabolic acidosis
- Smoking
- High-protein diet

Modifable nontraditional risk factors

- Anemia
- Hyperuricemia
- Radiological contrast
- Nephrotoxic herbs
- NSAIDs
- Interstitial calcium phosphate deposition
- Hyperphosphatemia
- Hypercalcemia
- Polycystic Renal

Nonmodifable risk factors

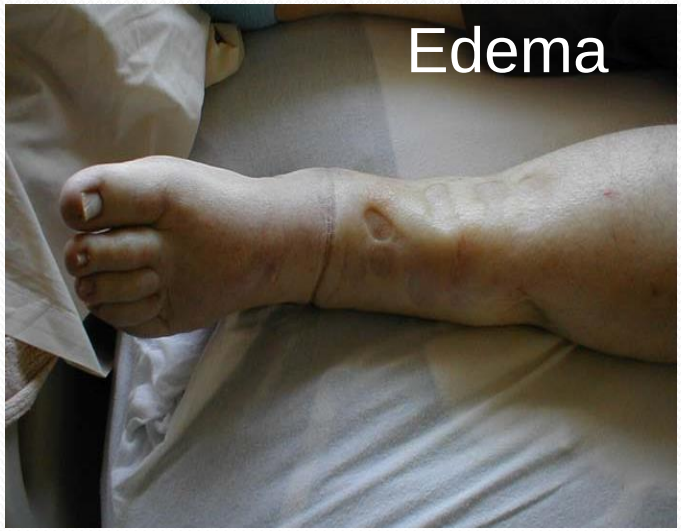
- Old age
- Race/ethnicity
- Gender
- Low birth weight
- Family history

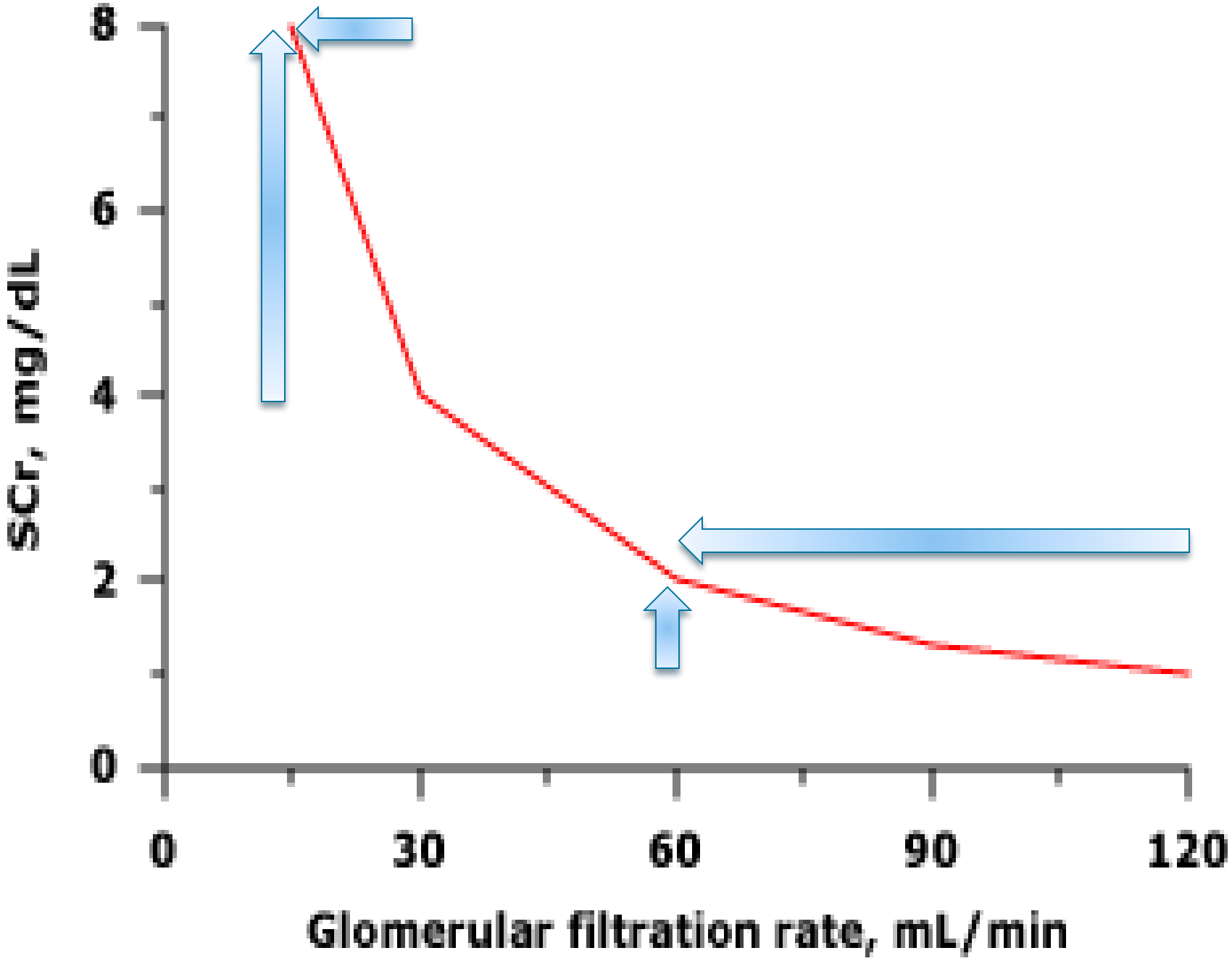
- Microvascular disease resulting from diabetes can cause CKD in about 40–50% of patients with diabetes, a process called diabetic nephropathy.

Nephrotic Syndrom Diagnosis:

Pro ++++

- Proteinuria: >3.5g/d
- Hypoalbuminemia: SAlb <30g/L
- Edema;
- Hyperlipidemia.




8
6
4
2
0
SCr, mg/dL
0
30
60
90
120
Glomerular filtration rate, mL/min

KEY RECOMMENDATIONS FOR PRACTICE

- Over-the-counter and herbal medicine
- Medications with toxic metabolites
- Nephrotoxic agents
- Active metabolites
- Dosages of drugs cleared renally

ARF

Traditionally, ARF has been defined as an increase in scrum creatinine (SrCr) of >0.5 mg/dL when the baseline SrCr is <2.5 mg/dL, and an increase in SrCr of > 1.0 mg/dL when he baseline SrCr is >2.5 mg/dL.

RIFLE criteria

Risk : decrease (>25% in GFR, or serum creatinine × 1.5 Sustained) UO <0.5 mg/kg/h × 6 h

Injury : Adjust creatinine or GFR decrease > 50% serum creatinine × 2 or urine output <0.5 mg/kg/h × 12 h

Failure : Adjust creatinine or GFR decrease > 75% serum creatinine × 3 or UO <0.5 mg/kg/h × 24 h or anuria × 12 h

Loss : Irreversible AKI or persistent AKI > 4 weeks

ESRD : ESRD >3 months

AKI versus ARF

- AKI is used to describe acute injuries that has not progressed to overt organ failure → AKI is more representative of the full spectrum of acute kidney dysfunction
- So the term AKI to replace the older terminology of ARF is highly appropriate

The commonest risk factor for AKI is:

- 1 Age
- 2 Co-morbidity
- 3 Medication
- 4 Previous chronic kidney disease
- 5 Hypovolaemia

Pre-renal causes

- Diuretics
- Laxatives – can exacerbate dehydration
- NSAIDs - remember COX-2 inhibitors
- ACEis
- Low BP – stop antihypertensives!
- Lithium toxicity can cause intravascular depletion

Intra-renal causes

- Drugs :
  - Gentamicin, furosemide ,iodine contrast
  - Analgesic nephropathy
  - Immunosuppressants can cause ATN – do not stop!
  - Obstructive uropathy – blockage of tubules
  - Statins – rhabdomyolysis causing myoglobinuria
  - Allergic/hypersensitivity reactions – lots of drugs

Post-renal causes

- Anti-muscarinics – may cause retention of urine leading to hydronephrosis

Estimating GFR and Creatinine Clearance

- The most common equations used are the Cockcroft-Gault (CG) & Modification of Diet in Renal Disease (MDRD) equations
- Stable SrCr

$$\text{CrCL (CG equation)} = \frac{(140 - \text{Age}) \times \text{IBW (kg)} \times [\ 0.85 \text{ if female}]}{72 \times \text{SrCr (mg/dl)}}$$

- MDRD Equation:
  - GFR (mL/min/1.73 m^2) = 186.3 x $(SrCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.21 if black)

Dosing Adjustments

- Loading doses

- Maintenance dosing adjustments:
  - Dose reduction
  - Lengthening the dosing interval, or both.

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- Dose reduction :
  - normal dosing interval
  - more constant drug concentrations
  - higher risk of toxicities
- The dosing interval Lengthening :
  - lower risk of toxicities
  - higher risk of subtherapeutic drug concentrations

Antihypertensives

- Thiazide diuretics
  - if the serum creatinine level is higher than 2.5 mg per dL?
- Loop diuretics
- No adjustment needed：
  - Metolazone (Zaroxolyn)
  - Furosemide (Lasix)
  - Bumetanide (Bumex)

Antihypertensives

- potassium-sparing diuretics and aldosterone blockers

- ACE inhibitors and ARBs :
  - efferent arteriolar dilation
  - Acute ↓ GFR
  - Can be continued safely if the rise in serum creatinine is less than 30 %
  - return to baseline in four to six weeks

Beta blockers

- Hydrophilic beta blockers (e.g., atenolol, bisoprolol , nadolol)
- Metoprolol ,propranolol and labetalol are metabolized by the liver and adjustments are not required.
- Other antihypertensive :
  - calcium channel blockers, clonidine and alpha blockers.

Beta blockers

Drug	> 50	50-30	<10
Acebutolol	100%	50%	30 to 50 %
Atenolol	100%	50%	25%
Bisoprolol	100%	75%	50%
Nadolol	100%	50%	25%

Adverse renal effects of NSAIDs include

- Acute renal failure
- Nephrotic syndrome with interstitial nephritis.
- Chronic renal failure with or without glomerulopathy,
- decreased potassium excretion, which can cause hyperkalemia
- decreased sodium excretion, which can cause peripheral edema, elevated blood pressure, and decompensation of heart failure.
- The risk of acute renal failure is three times higher in NSAID users than in non-NSAID users
- NSAIDs can blunt antihypertensive treatment, especially if beta blockers, ACE inhibitors, or ARBs are used.

Hypoglycemic agents

- Metformin
- Sulfonylureas
- Acarbose

Aminoglycosides

- medical team decides that the addition of an aminoglycoside antibiotic is now necessary to treat her infection.
- Considering that her renal function has remained stable, how should the gentamicin be dosed?
- Is it best to alter the dose or the dosing interval for this drug?

Treatment of CKD Include

- Specific therapy based on Dx
- Evaluation & management of comorbid conditions
- Slowing the loss of kidney function
- Prevention and Rx of CVD
- Prevention and Rx of CKD complications
- Preparation for kidney failure & kidney replacement therapy
- Dialysis or transplantation if uremic signs are present

Review medication at all visits to:

- Dose adjustment based on kidney function
- ADRs detection
- Drug interactions detection
- TDM, if possible

Interventions proven to be effective to slow the progression of CKD

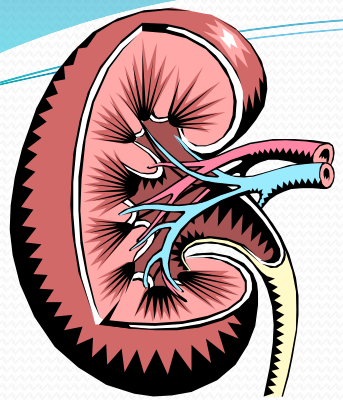
- Strict glucose control
- Strict BP control
- ACEIs or ARBs

Interventions studied to slow the progression of CKD but results are inconclusive

- Pro restriction
- Lipid-lowering therapy
- Partial correction of anemia

Complications of CKD

- anemia
- renal osteodystrophy (hypo Ca, hyper P, sHPT)
- GI complications, bleeding
- neurological complications
- dermal complications
- leg cramps
- homeostatic complications
- cardiovascular complications (HTN, hyperlipidemia)



- نارسایی کلیوی

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

Drug-Induced Acute Renal Dysfunction

- Acute Renal Failure
  - Prerenal

    NSAIDs, CyA/Tacrolimus, ACEI/ARB, Diuretics
  - Intrinsic – ATN vs AIN

    ATN – Aminoglycosides, Amphotericin B, Radiocontrast Media
  - Obstructive

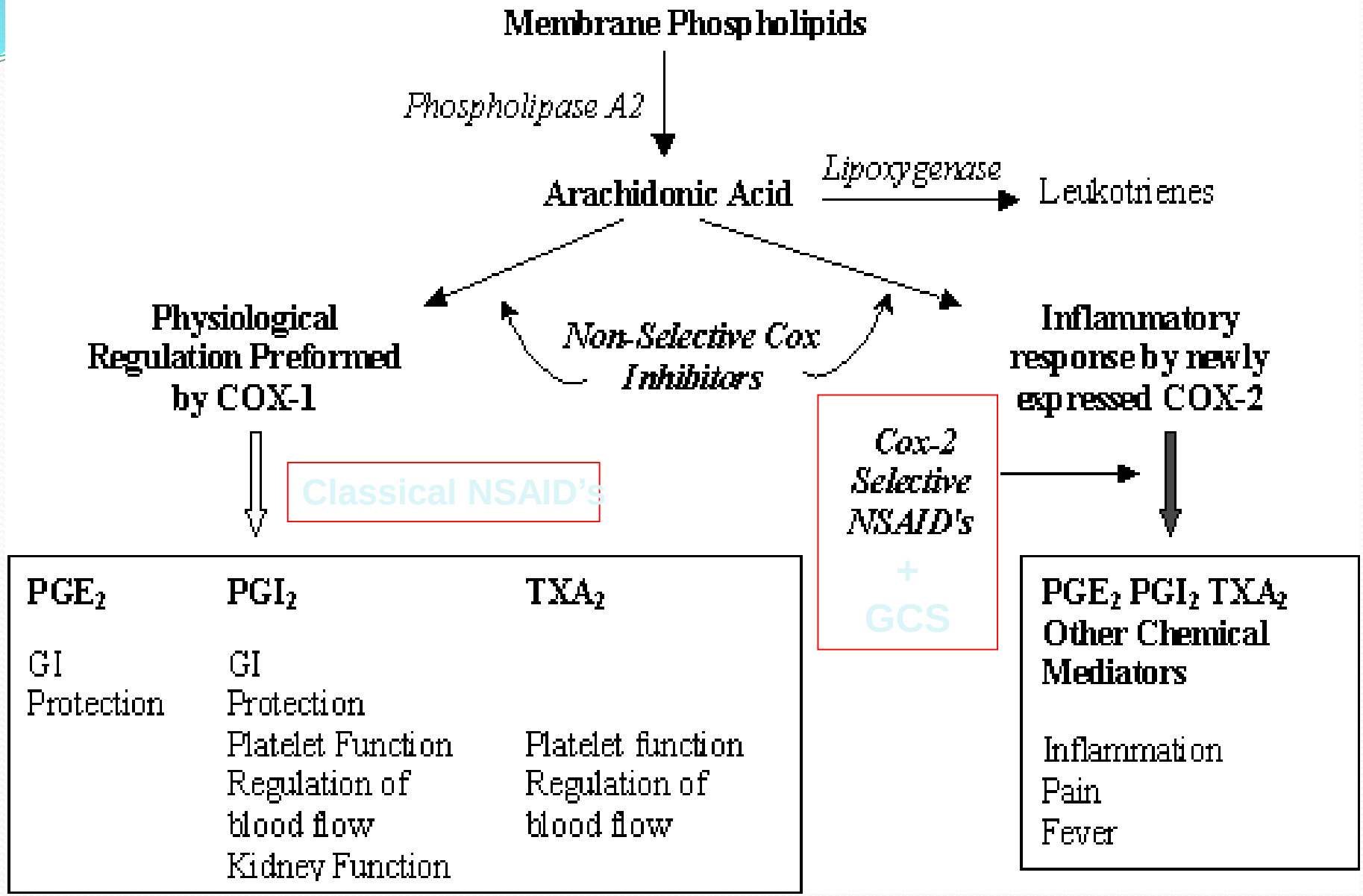
    Methotrexate, Acyclovir, Indinavir, Rhabdomyolysis (Statins)

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, diuresis(diuretics)
- ***Vascular Obstruction:*** NSAIDS, ACE-I, Vasopressors, renal artery occlusion

Table 1. Classification of NSAIDs

Salicylates	Arylalkanoic acids	2-Arylpropionic acids (profens)	N-Arylanthranilic acids (fenamic acids)
• Acetylsalicylic acid (aspirin) • Amoxiprin • Benorylate/Benorilate • Choline magnesium salicylate • Diflunisal • Ethenzamide • Faislamine • Methyl salicylate • Magnesium salicylate • Salicyl salicylate • Salicylamide	• Diclofenac • Aceclofenac • Acemethacin • Alclofenac • Bromfenac • Etodolac • Indomethacin • Nabumetone • Oxametacin • Proglumetacin • Sulindac • Tolmetin	• Ibuprofen • Alminoprofen • Carprofen • Dexibuprofen • Dexketoprofen • Fenbufen • Fenoprofen • Flunoxaprofen • Flurbiprofen • Indoprofen • Ketorolac • Loxoprofen • Naproxen • Oxaprozin • Pirprofen • Suprofen • Tiaprofenic acid	• Mefenamic acid • Flufenamic acid • Meclofenamic acid • Tolfenamic acid
Pyrazolidine derivatives	**Oxicams**	**[COX]-2 inhibitors**	
• Phenylbutazone • Ampyrone • Azapropazone • Clofezone • Kebuzone • Metamizole • Mofebutazone • Oxyphenbutazone • Phenazone • Sulfinpyrazone	• Piroxicam • Droxicam • Lornoxicam • Meloxicam • Tenoxicam	• Celecoxib (FDA alert) • Etoricoxib (FDA withdrawn) • Lumiracoxib TGA cancelled registration • Parecoxib FDA withdrawn • Rofecoxib (withdrawn from market) • Valdecoxib (withdrawn from market)	



N.B.: COX-2 also in :
- **Endothelium, brain, spinal cord**
- **Kidney (Macula densa), ovaries, uterus**

Angiotensin II Receptor Antagonists

Candesartan (Atacand)

Eprosartan (Tevetan)

Irbesartan (Avapro)

Losartan (Cozaar)

Olmesartan (Benicar)

Telmisartan (Micardis)

Valsartan (Diovan)

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

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)

ATN: Radiographic Contrast Media

- Incidence: 40-50% in high risk pts (CKD, DM)
- Onset: within 12-24 hrs, SCr peaks 2-5 days after exposure, recovery usually after 4-10 days
- Pathogenesis
  - Direct tubular necrosis, renal ischemia
- Presentation
  - Typically non-oliguric (high risk may require HD)
  - Urinalysis – hyaline and granular casts, low F_ENa
- Risk Factors: DM, CKD, prestudy dehydration
- Management – Low-osmolality nonionic contrast agents (eg. Iohexol), smallest dose, Hydration

ARF: Obstructive Nephropathy

- **Rhabdomyolysis**
  - Intratubular precipitation of myoglobulin
  - Reddish-brown urine
  - Statins: simvastain, atorvastatin – risk ↑'ed with Cyp 3A4 inhibitors (clarithromycin, erythro, itraconazole) **or** combination fibrate
- **Prevention**
  - **Hold Statin** while on clarithro/erythro or itraconazole therapy (alternative azithromycin OK)
  - Pravastatin, Rosuvastatin not metabolized by CYP 3A4

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)

Thanks for your Attention