Nephrotoxicity

Pierre Cochat, MD PhD
Professor of Pediatrics
Head, Center for Rare Renal Diseases Néphrogones
Hospices Civils de Lyon & University Claude-Bernard, Lyon, France

www.conepmt.com.br

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IPNA TEACHING COURSE

Introduction

- An underestimated problem
  - > 200 drugs may lead to AKI
  - Risk of AKI x 3 under NSAIDs compared to controls
- Mainly for drugs with renal clearance
  - Role of parent molecule
  - Role of metabolites
- Background
  - Dose-dependent or dose-independent phenomenon
  - Possible with any kind of administration route

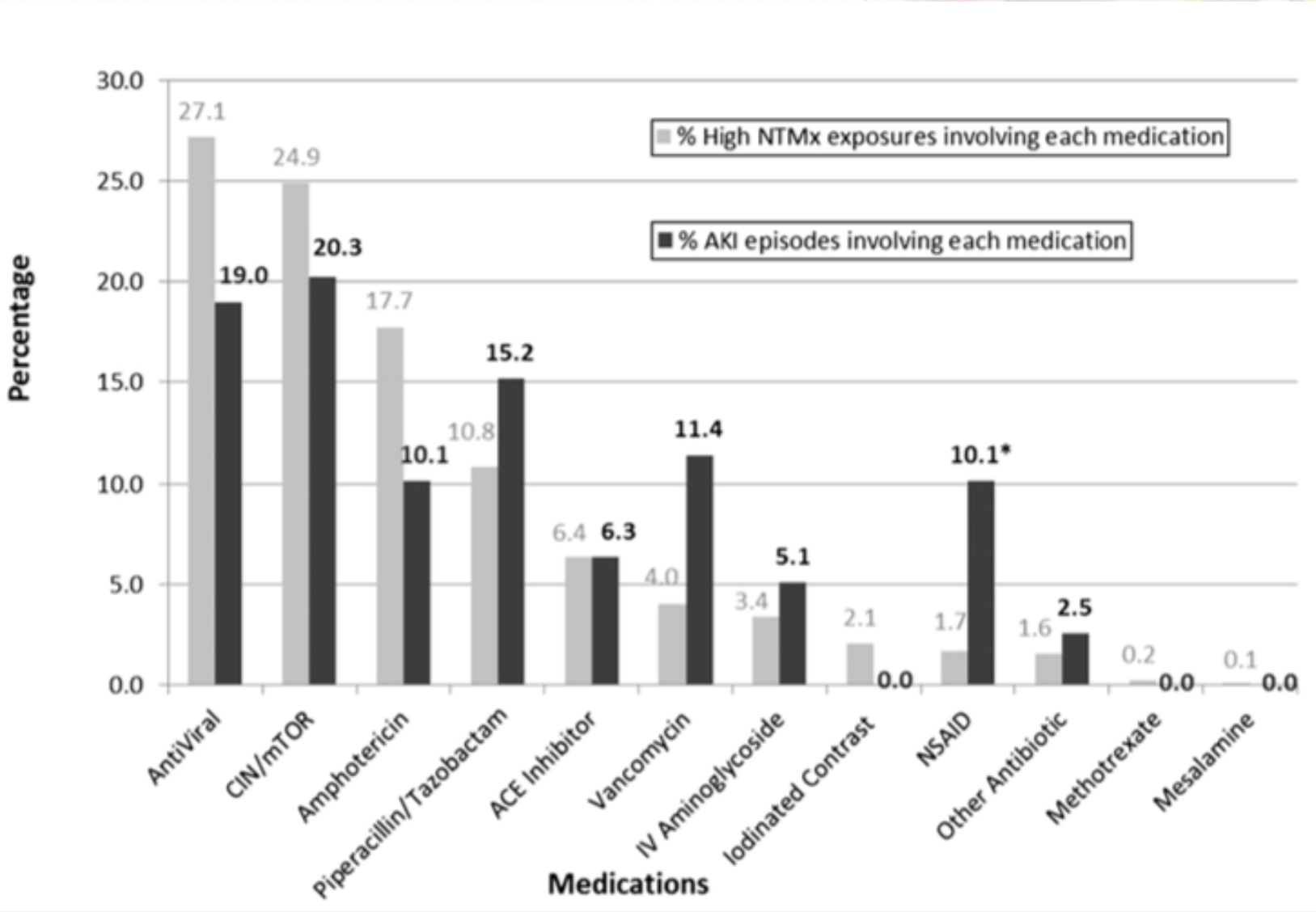
Spectrum of nephrotoxicity

- Prerenal ARF
- Acute tubular necrosis
- Immune-mediated acute tubulointerstitial nephritis
- Renal vasculitis
- Syndrome of proteinuria + ARF
- Microangiopathy
- CKD
- Others

Risk factors

Related to patient	*Related to treatment*
First weeks of life	Additional nephrotoxicity (HIV, cancer)
RAS stimulation (volume/Na depletion) ▪ Nephrotic syndrome ▪ Liver cirrhosis	Drug interactions/addition ▪ Loop diuretics ▪ ACEi & ARB ▪ NSAIDs
Preexisting renal damage ▪ Acute pyelonephritis ▪ Reduced nephron mass ▪ Previous nephrotoxicity ▪ Concurrent renal disease ▪ Urinary obstruction	Reduced nephron mass
Fever and sepsis	Irradiation
Acidosis, hyperuricemia	Drug dosing
	Duration of drug exposure
	Route of administration

AKI is the most common presentation



PNA TEACHING COURSE

Goldstein *Pediatrics* 2013

NSAIDs-associated AKI

Table I. Demographic and clinical characteristics of patients with NSAID-associated AKI (n = 27)

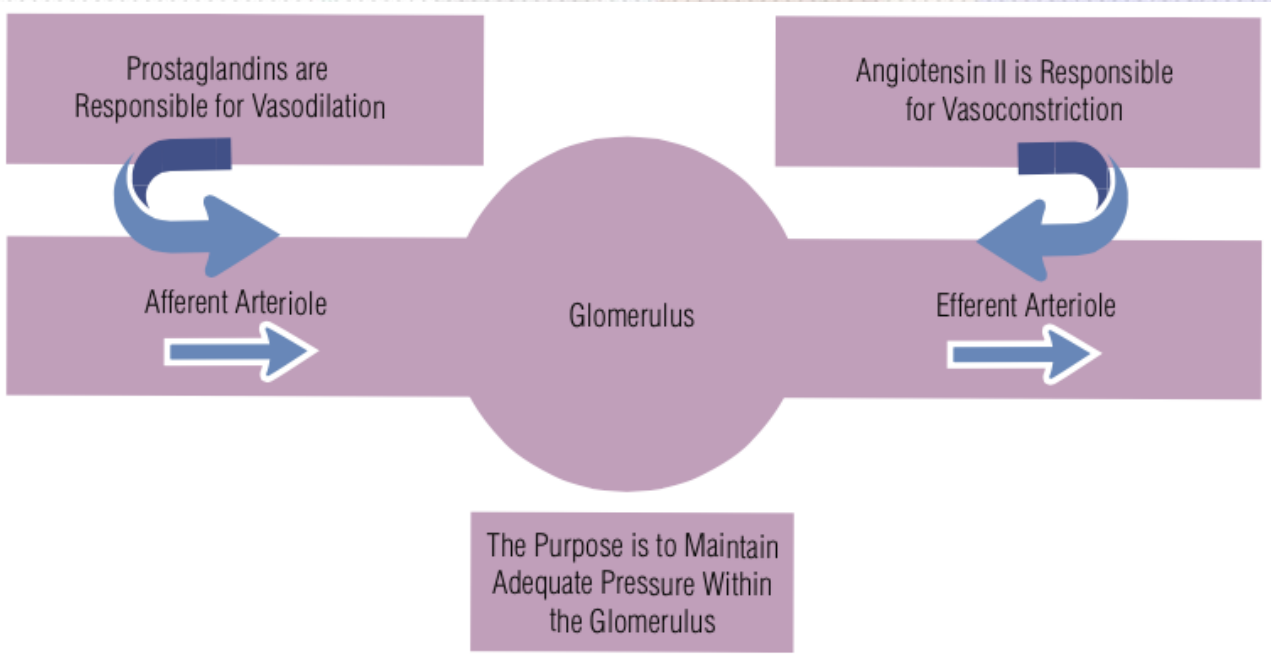
Age, y*	14.7 (0.5-17.7)
Weight, kg†	63.9 (8.3-154.2, SD 37.3)
Age- and sex-specific body mass index percentile*‡	83 (6.8-99.9)
Male patient, No.	12 (44%)
White, No.	24 (89%)
NSAID used, No.	
Ibuprofen	18 (67%)
Naproxen	3 (11%)
Ketorolac	2 (7%)
Ibuprofen and naproxen	2 (7%)
Ibuprofen and ketorolac	2 (7%)
History of volume depletion, No.	18 (67%)
History of decreased urine output, No.	15 (56%)
Duration of NSAID use, d*	4 (1-729)
History of exceeding recommended dose§	25% (5 of 20)
Median eGFR at presentation, mL/min/1.73 m^2*	21 (7-65)
Length of stay, d*	8 (1-24)
Patients requiring ICU stay, No.	5 (18%)
Patients requiring dialysis, No.	4 (15%)
Time to recovery of GFR >75 mL/min/1.73 m^2, d*	15 (1-180)

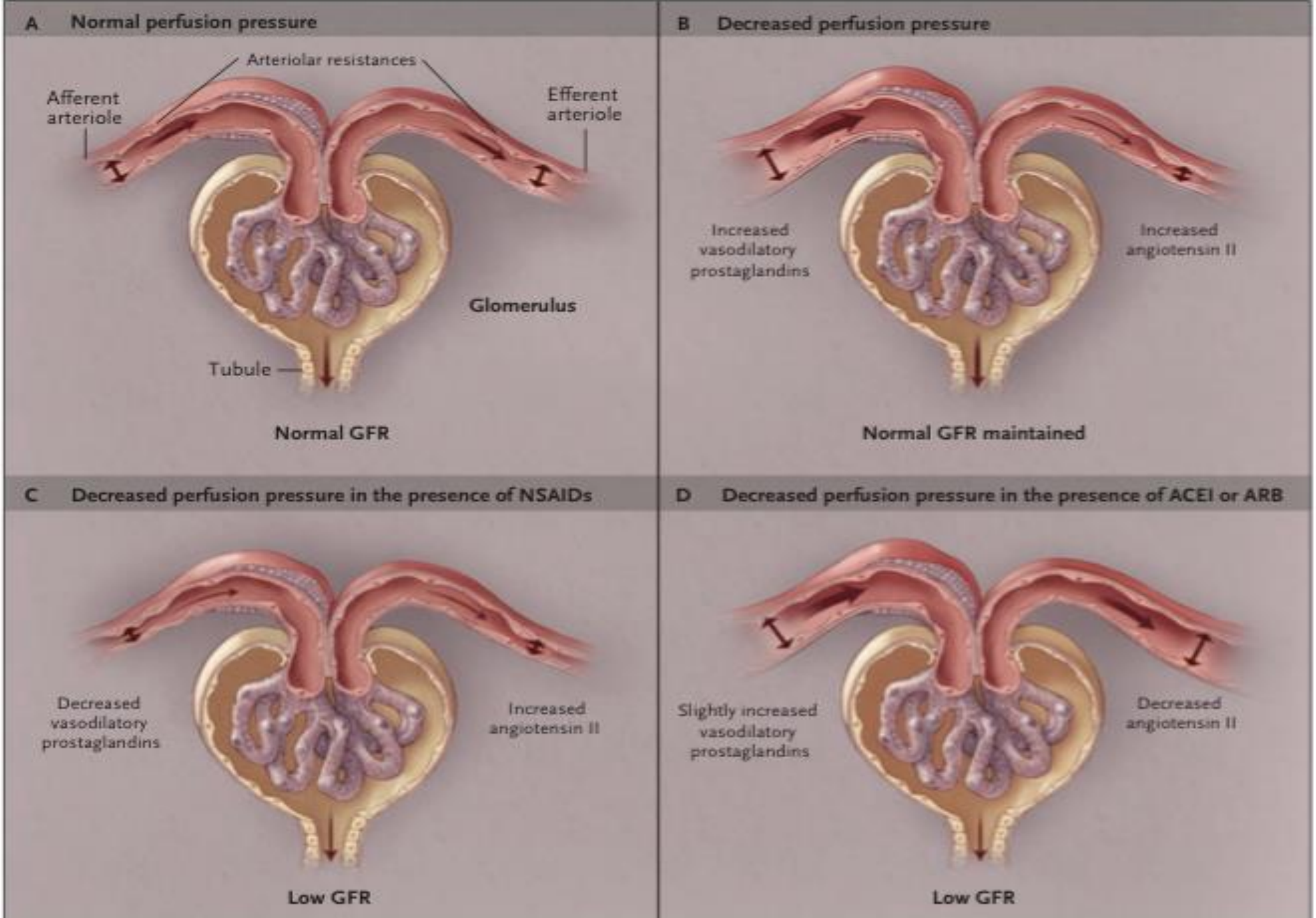
Misurac *J Pediatr* 2013

Prerenal/vasomotor ARF - Pathophysiology

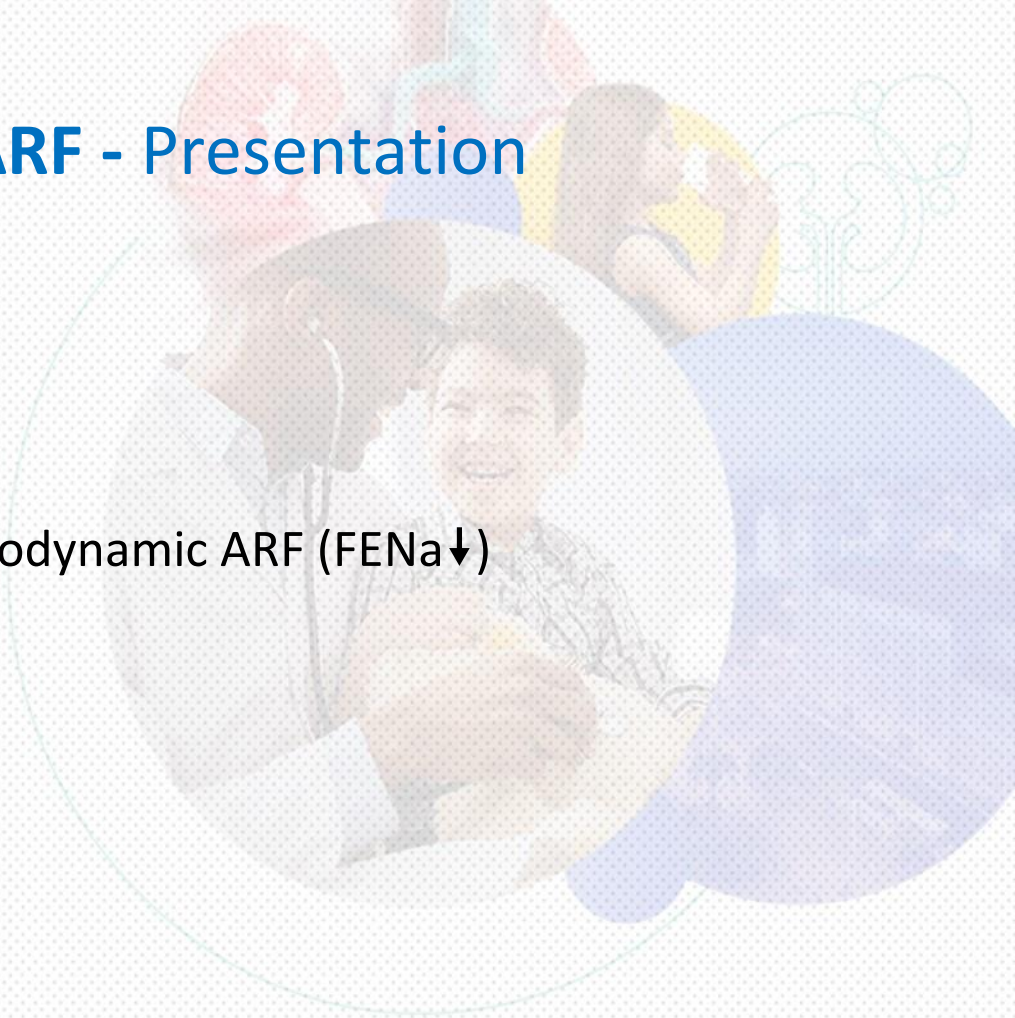
- Early and transient phenomenon
- NSAIDs, ACEi, ARB, contrasts, cisplatin, calcineurin inhibitors, etc.

- Combined action of
  - Angiotensin-2
  - Prostaglandins
  - Nitric oxide
  - Endothelin
  - Adenosin




A Normal perfusion pressure
Arteriolar resistances
Afferent arteriole
Efferent arteriole
Glomerulus
Tubule
Normal GFR
B Decreased perfusion pressure
Increased vasodilatory prostaglandins
Increased angiotensin II
Normal GFR maintained
C Decreased perfusion pressure in the presence of NSAIDs
Decreased vasodilatory prostaglandins
Increased angiotensin II
Low GFR
D Decreased perfusion pressure in the presence of ACEI or ARB
Slightly increased vasodilatory prostaglandins
Decreased angiotensin II
Low GFR

Prerenal/vasomotor ARF - Presentation



- In the short/mean term
  1. Transient oliguric prerenal/hemodynamic ARF (FENa↓)
  2. Acute tubular necrosis
  3. Isolated tubular dysfunction

- In the long term
  1. Papillary necrosis
  2. Interstitial fibrosis
  3. Glomerulosclerosis

Acute tubular necrosis – 2 main mechanisms

1. Final lesion following long-lasting prerenal/vasomotor ARF++
2. Direct toxicity
   - Action on membrane phospholipids
   - Formation of free radicals
   - Impairment of mitochondrial metabolism
   - Inhibition and inactivation of protein transports
   - Induction of apoptosis

Proximal tubule as the main target (Fanconi syndrome)

- High-energy segment (mitochondrial density)
- Many binding sites for toxic compounds

Acute tubular necrosis - Presentation

- Clinical presentation
  - ARF with maintained urine output
  - Delayed onset after drug exposure

- Pathology
  1. Sometimes, minimal change
  2. Damaged brush border of epithelial cells
  3. Giant lysosomes and mitochondria
  4. Tubular cell necrosis

Acute tubular necrosis

Diagnosis

- Drug dosage
- Urine sediment
- Kidney biopsy

Management

- Drug discontinuation
- Sometimes, renal hemodynamics management

Acute tubular necrosis – Prevention

- Hydration — 150 to 200 mL/h per 1.73m²
- Sodium — Increases urine outflow
  Inhibits RAS activity
- Diuretics — Mannitol: decreases tubular cell edema

- Adaptation of drug dosage and intervals
- Progressive increase in drug dosage in at-risk patients
- Limited exposure to drug
- Identification and et control of at-risk situations

Immune-mediated acute interstitial nephritis - Presentation

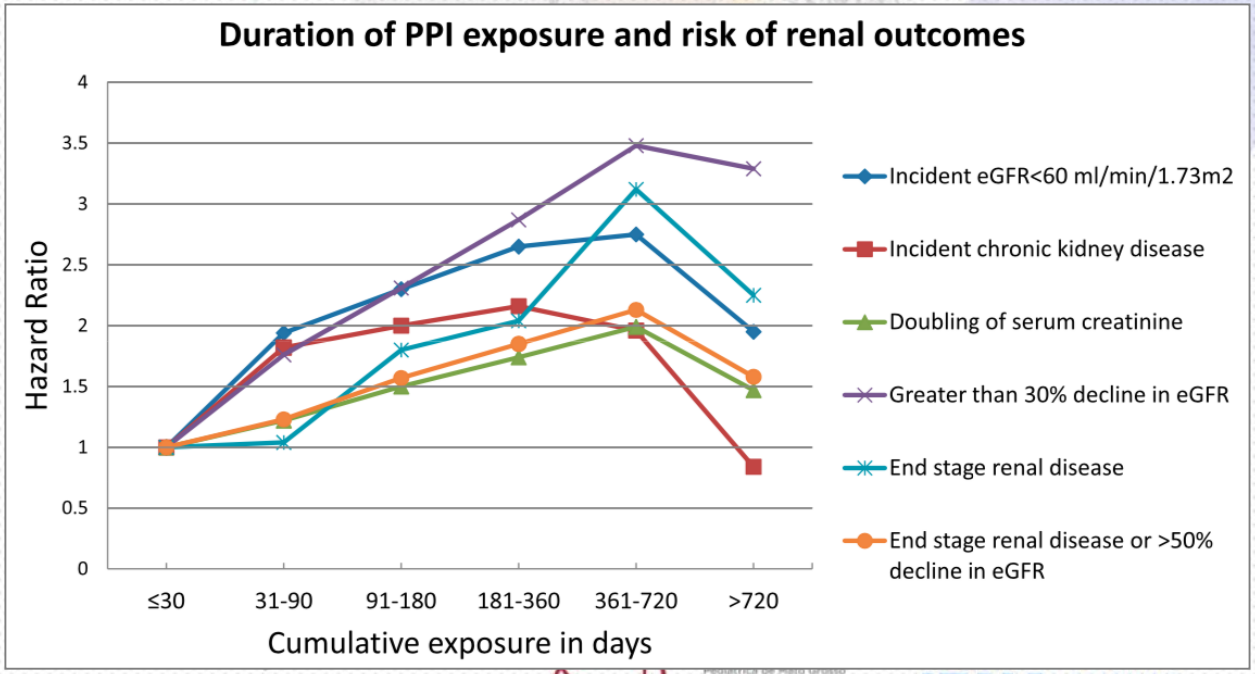
Renal signs	*Extra-renal signs*
ARF	Fever
Hematuria	Skin rash
Proteinuria	Arthralgias
Leukocyturia	Eosinophilia
Eosinophiluria	Hemolysis
Natriuresis	Liver cytolysis

Sometimes: DRESS syndrome [*Drug Reaction with Eosinophilia and Systemic Symptoms*]

Immune-mediated acute interstitial nephritis – Which drugs?

- Antibiotics (β-lactamines, cotrimoxazole, rifampicin, ciprofloxacin)
- Phenytoin, phenobarbital
- NSAIDs
- Allopurinol
- Azathioprin
- Frusemide, thiazides
- Proton pump inhibitors
- Interferons

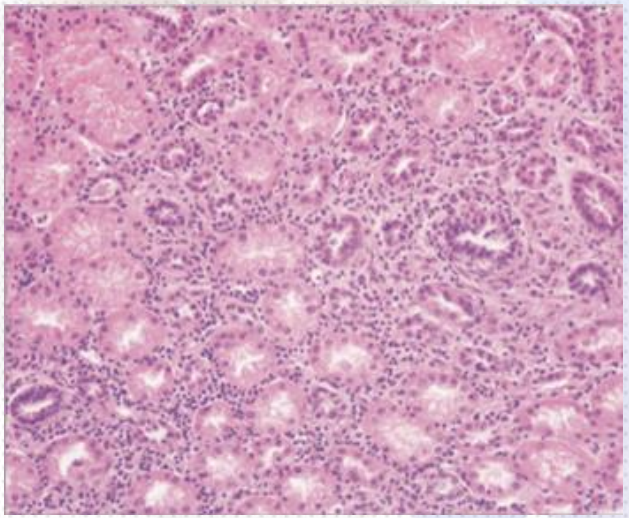
- Many other drugs



Xie Y, Am Soc Nephrol 2016

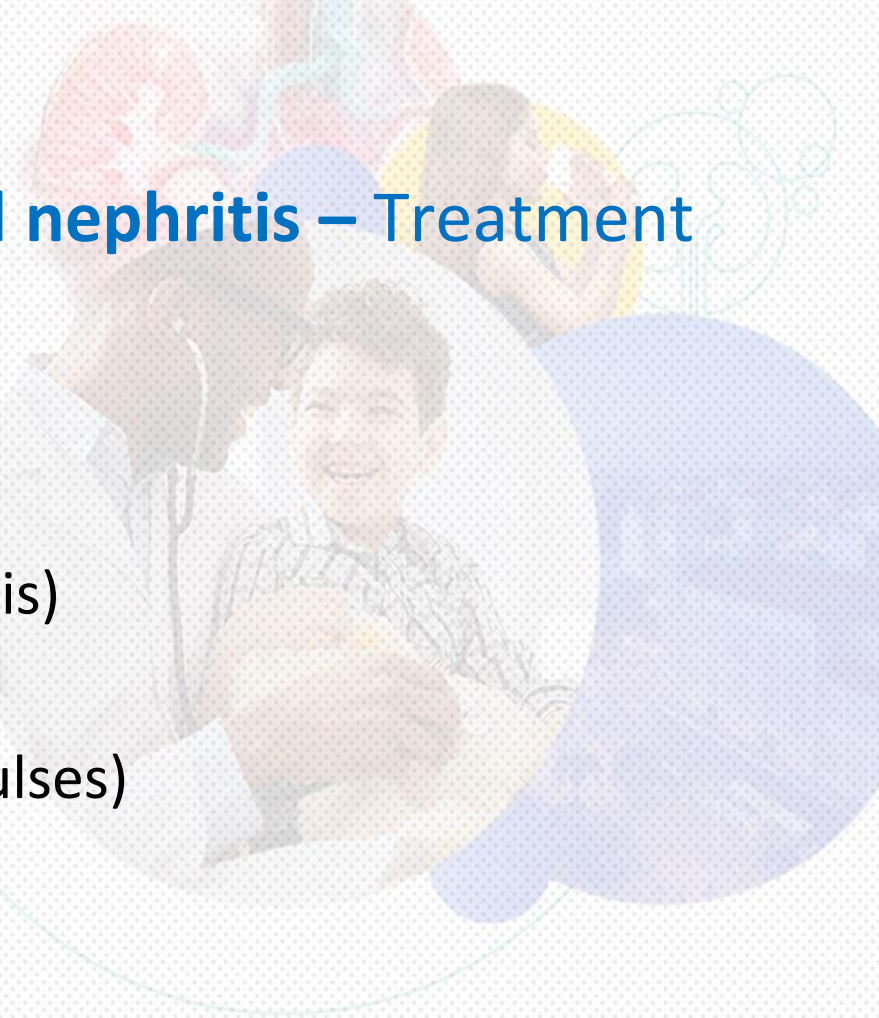
Immune-mediated acute interstitial nephritis – Diagnosis

- Kidney biopsy
  - Prognosis value
  - Interstitial infiltrate
  - Immunofluorescence: no deposit



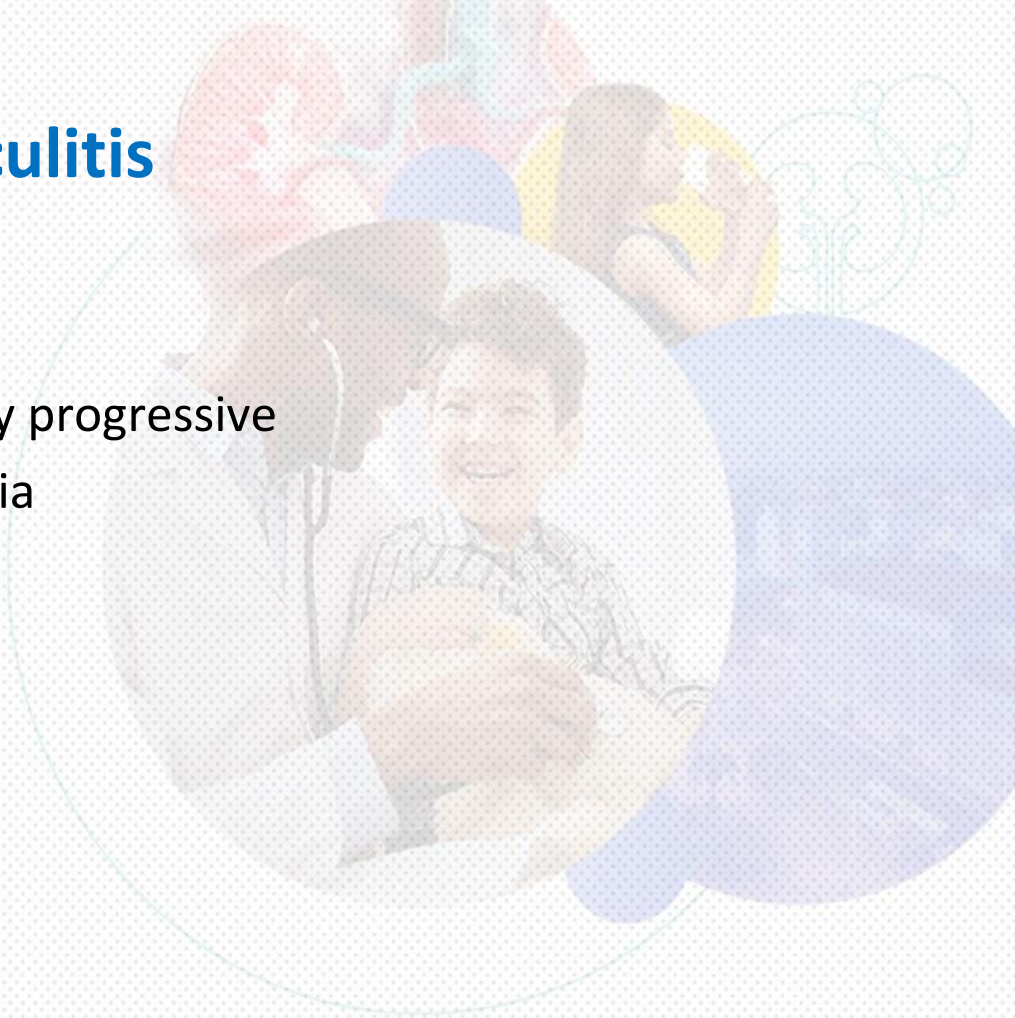
- Biological tests: anti-drug Ab, lymphocyte transformation test, etc.

Immune-mediated acute interstitial nephritis – Treatment



- Supportive measures (sometimes dialysis)
- Glucocorticoids (methylprednisolone pulses)
- No prevention - Avoid re-exposure!

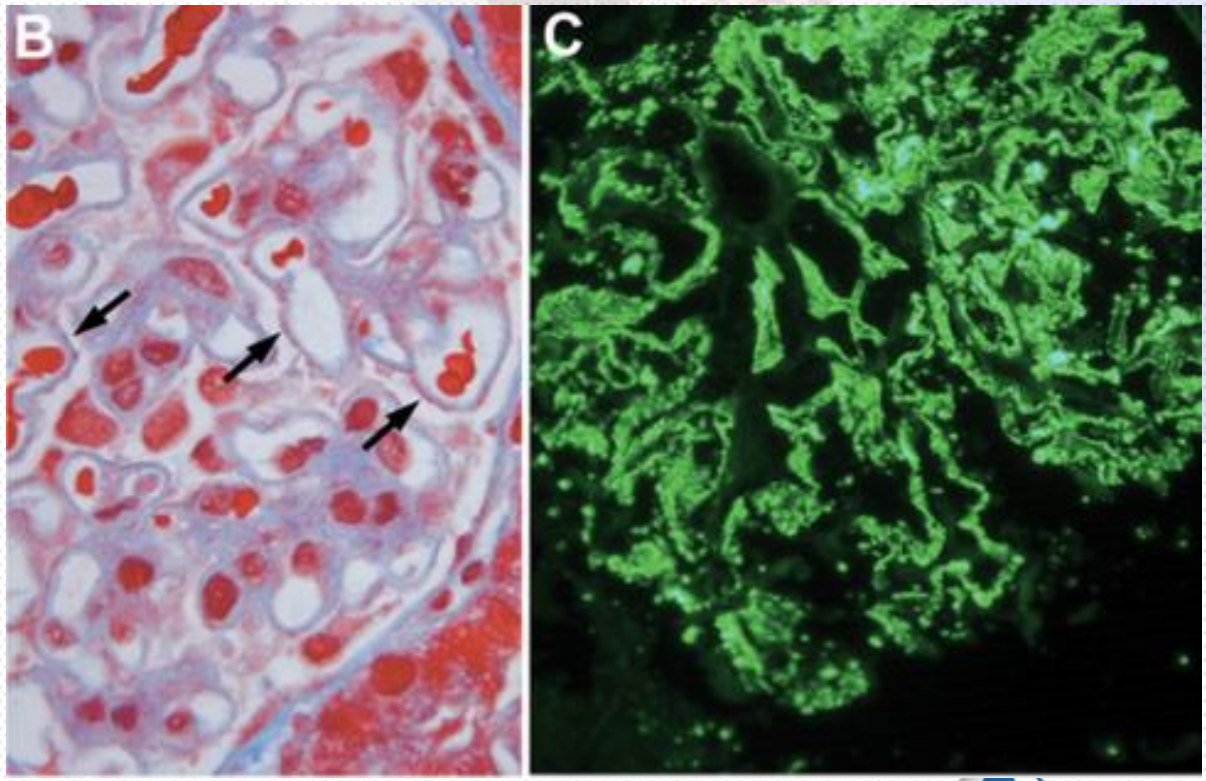
Renal vasculitis



- Presentation
  - Glomerulonephritis, sometimes rapidly progressive
  - Hypertension – Proteinuria – Hematuria
  - Extrarenal signs
  - Sometimes +ANCA
- Which drugs?
  - Penicillin
  - NSAIDs
  - Cyclins
  - Propylthiouracil
- Diagnosis: Renal biopsy
- Treatment: Glucocorticoids

Membranous nephropathy

Drugs
Penicillamine
Bucillamine
Gold salts
Captopril
Lithium
Nonsteroidal anti-inflammatory drugs
Anti–tumor necrosis factor
2-Mercaptoprioprionyl glycine
Trimethadione
Tiopronin
Chronic formaldehyde exposure
Mercury



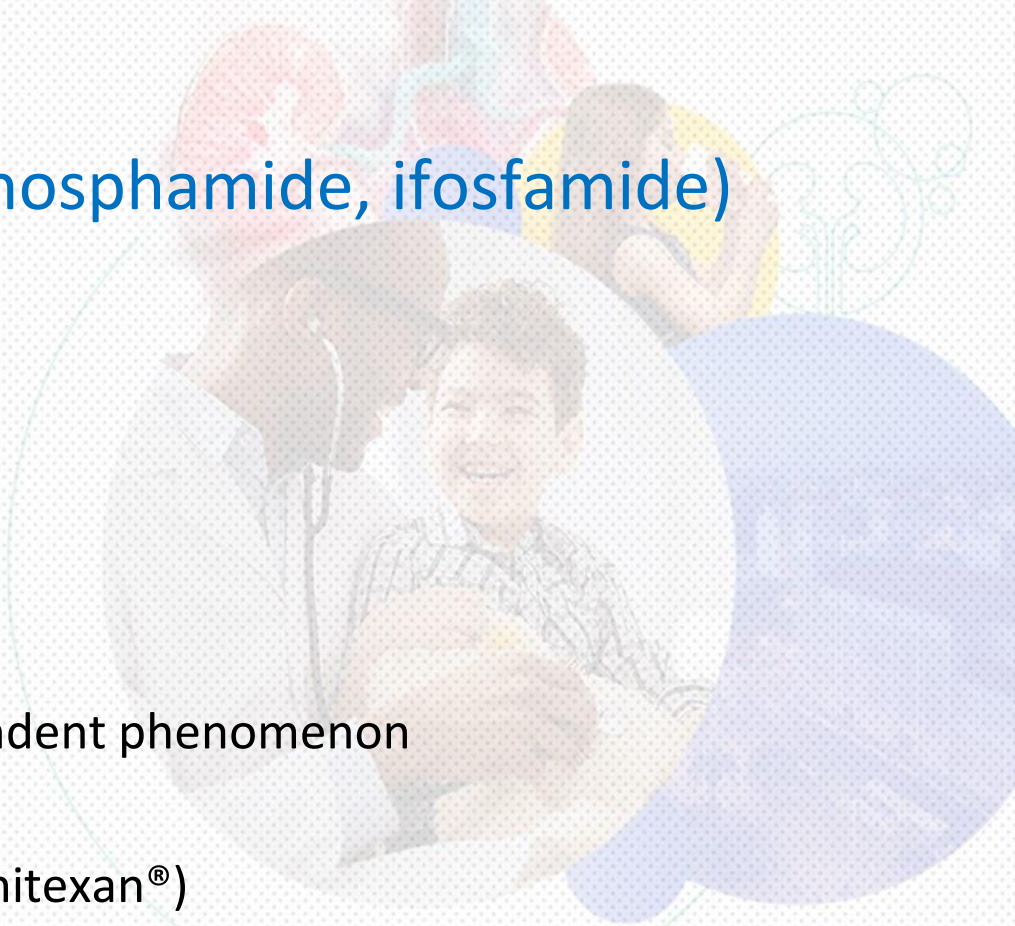
Nawas *Am J Kidney Dis* 2013

Syndrome of proteinuria + ARF

- Delayed feature
  - From microalbuminuria to nephrotic syndrome
  - Concommittent ARF
- Renal biopsy
  - From minimal change
  - To acute interstitial nephritis
- Which drugs?
  - NSAIDs
  - Lithium, phenytoin, ampicillin, rifampicin, interféron-α
- Return to normal after drug withdrawal

Focus on specific drug-induced nephrotoxicity

Oxazaphosphorines (cyclophosphamide, ifosfamide)



- Toxicity of metabolites

- Urothelial toxicity
  - Common to both drugs – Dose-dependent phenomenon
  - Due to acrolein production
  - Prevention: hydration + mesna (Uromitexan®)

- Proximal tubular damage (Fanconi syndrome ± rickets)
  - Only with ifosfamide
  - Due to chloroacetaldehyde production

Methotrexate

- Folate antagonist (dihydrofolate-reductase inhibitor)
- Two different uses
  - Oncology: IV high-dose
  - Rheumatology: IM/SC low-dose
- ARF due to intratubular crystal formation
  - Specific treatment: carboxypeptidase G2
  - MTX + CPDG2 → [hydrolysis] → DAMPA + glutamate (inactive)
- At risk in case of repeated injections if GFR is impaired (te be checked)

Cochrane Library

Cochrane Database of Systematic Reviews

2019 Prevalence of CKD (eGFR < 90 mL/min per 1.73 m^2)

Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer (Review)

Kooijmans ECM, Bökenkamp A, Tjahjadi NS, Tettero JM, van Dulmen-den Broeder E, van der Pal HJH, Veening MA

Risk factors for cisplatin-induced kidney injury

Increasing cumulative dose

Shorter administration time

Concurrent treatment with other nephrotoxins (e.g. ifosfamide/loop diuretics/aminoglycosides)

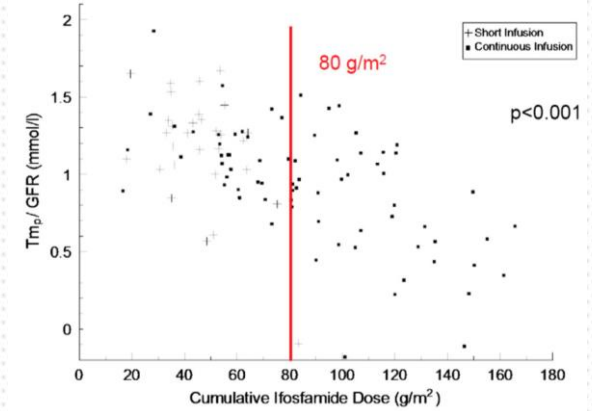
Increased peak serum/urine platinum concentrations (interindividual differences in pharmacokinetics)

Increasing patient age

Barton *Pediatr Nephrol* 2018

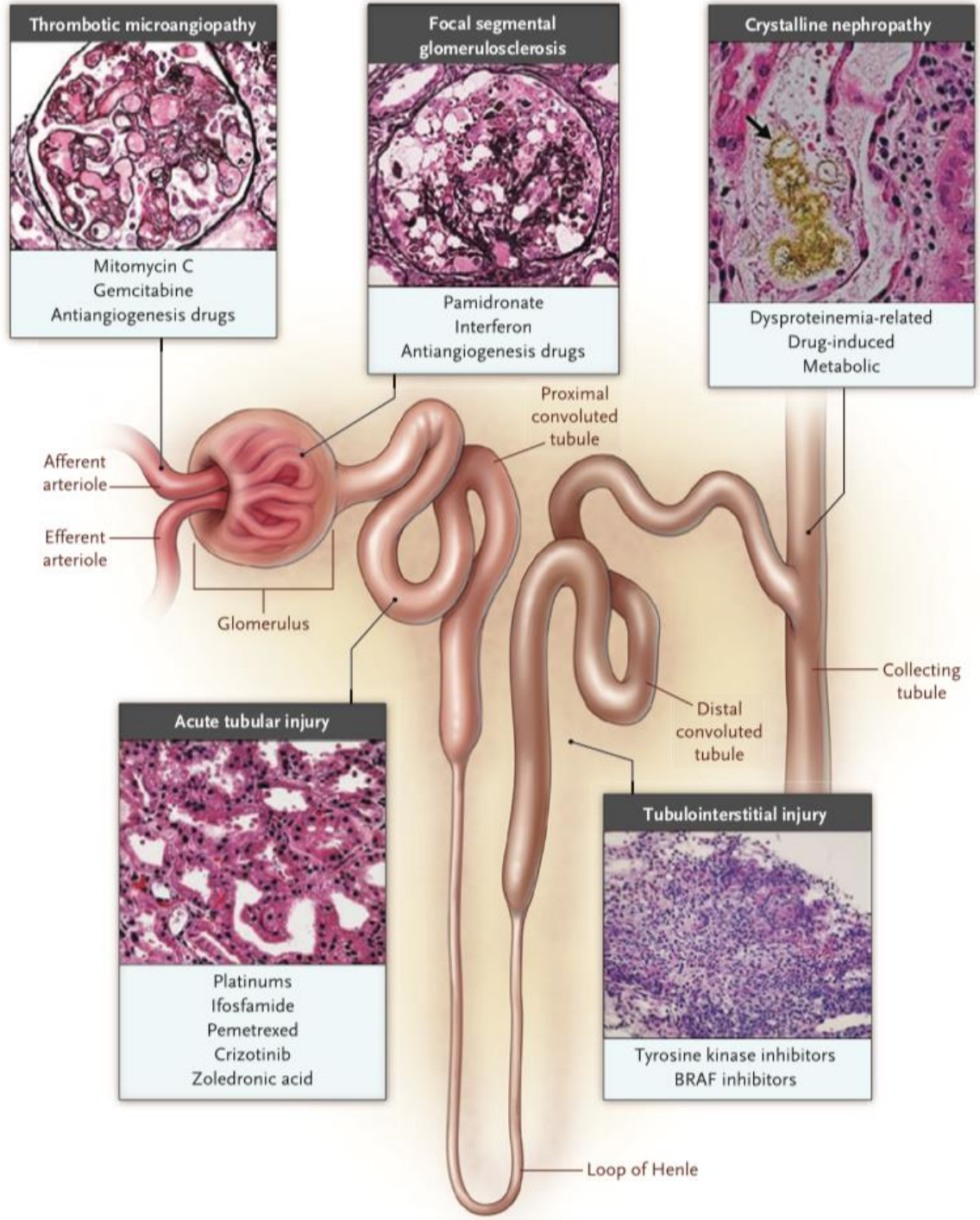
Cumulative dose of Ifosfamide and renal tubular threshold of phosphate

Skinner *Pediatr Nephrol* 2018



Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV,Random,95% CI	Prevalence IV,Random,95% CI
1 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	73.68 (7.14)		73.68 [59.69, 87.67]
2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Stefanowicz 2012	30	0	1.67 (2.33)		1.67 [-2.90, 6.24]
Davidoff 2015	36	0	36.11 (8.01)		36.11 [20.41, 51.81]
Schiavetti 2015a	35	0	40 (8.28)		40.00 [23.77, 56.23]
Stefanowicz 2011	32	0	43.75 (8.77)		43.75 [26.56, 60.94]
Interiano 2017	25	0	44 (9.93)		44.00 [24.54, 63.46]
3 Carboplatin and/or nephrectomy					
Cozzi 2012	25	0	36 (9.6)		36.00 [17.18, 54.82]
4 Ifosfamide, radiotherapy and/or nephrectomy					
Kubiak 2004	22	0	27.27 (9.5)		27.27 [8.65, 45.89]
5 Radiotherapy and/or nephrectomy					
Kostel Bal 2016	50	0	0 (0)		Not estimable
Stefanowicz 2010	26	0	3.85 (3.77)		3.85 [-3.54, 11.24]
Bailey 2002	40	0	22.5 (6.6)		22.50 [9.56, 35.44]
6 Nephrectomy					
Interiano 2015	73	0	21.92 (4.84)		21.92 [12.43, 31.41]

Anticancer therapies and their site of action leading to AKI



Rosner *N Engl J Med* 2018

Calcineurin inhibitors

- Ciclosporine and tacrolimus
- Acute nephrotoxicity
  - Hemodynamic ARF
  - Acute tubular necrosis due to direct toxicity
- Chronic nephrotoxicity
  - Vasculopathy (arterial hypertension)
  - Interstitial fibrosis (CKD)

Anti-TNFα

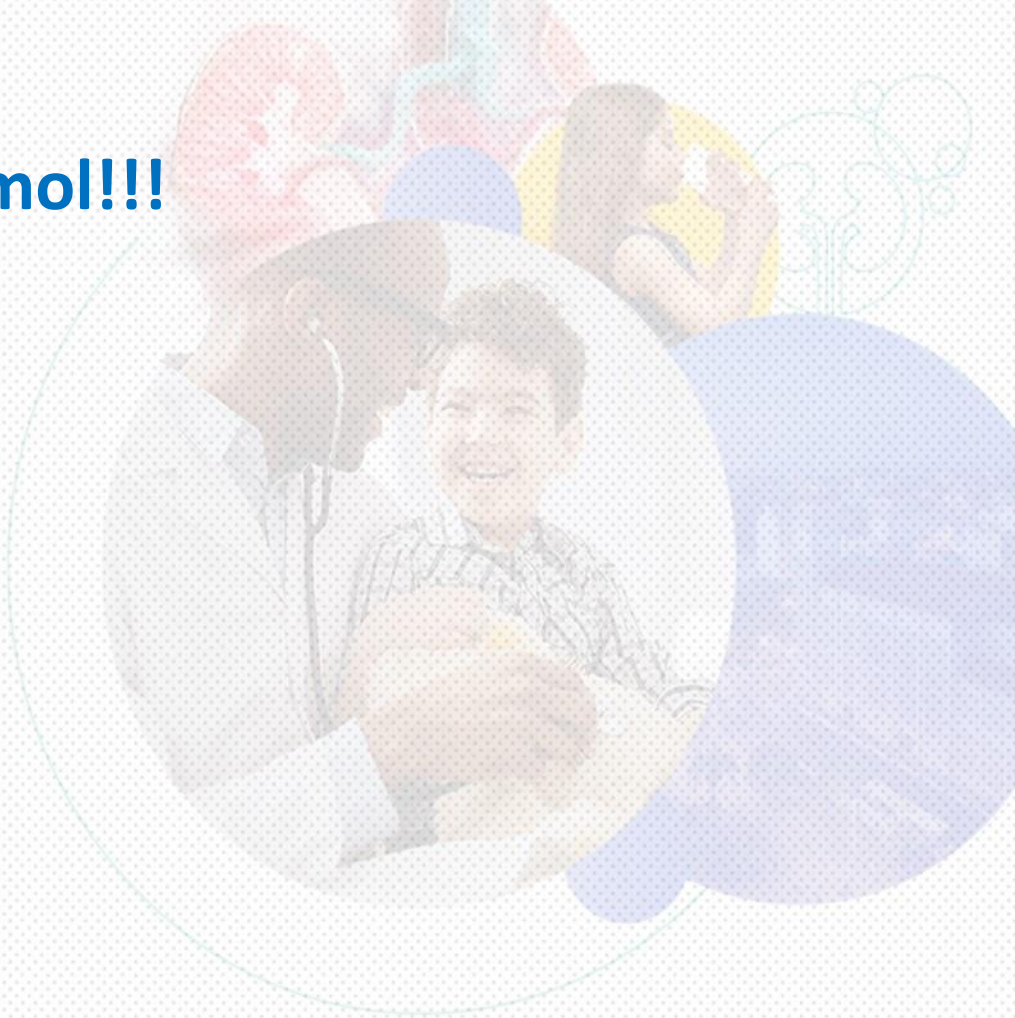
Etanercept - Adalimumab - Infliximab

- Nephrotic syndrome (minimal change or membranous nephropathy)
- Lupus-like syndrome
- Necrotizing crescentic glomerulonephritis
- Renal vasculitis
- (IgA) mesangial nephropathy
- Granulomatous interstitial nephritis

- Disappearance after drug withdrawal

Piga *Autoimmunity Rev* 2014 – Sokumbi *Mayo Clin Proc* 2012

Paracetamol!!!



- Risk of acute tubular necrosis
- Depending on drug dosage

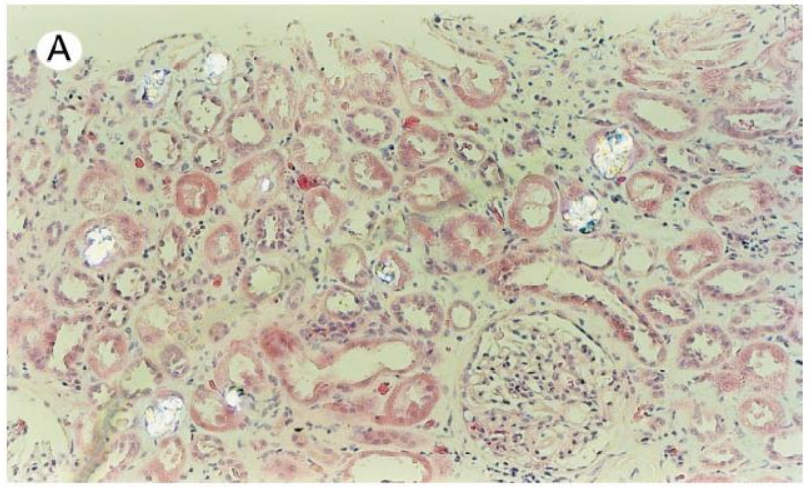
Non drug-induced nephrotoxicity

Industrial procedures: melamine

- Chinese children, September 11th, 2008
  - 294 000 children, 5 000 hospitalizations, 6 deaths
  - Melamine in powdered milk formulas: 1000x higher than the USFDA tolerable daily intake
- Clinical picture
  - 80 % of patients <2 years
  - AKI + radiolucent nephrolithiasis: melamine + uric acid
  - Unexplained crying, vomiting, hematuria, acute urinary obstruction, stones, fever, HTN
- Outcomes
  - 7933 children < 36 months living in an exposed area, US screening
  - N= 48 (0.61 %) : US abnormalities
  - Follow-up 6 months: 41 resolution of stones

Liu JM CMAJ *2010* - *Langman* Pediatr Nephrol *2009* - *Langman* N Engl J Med *2009*

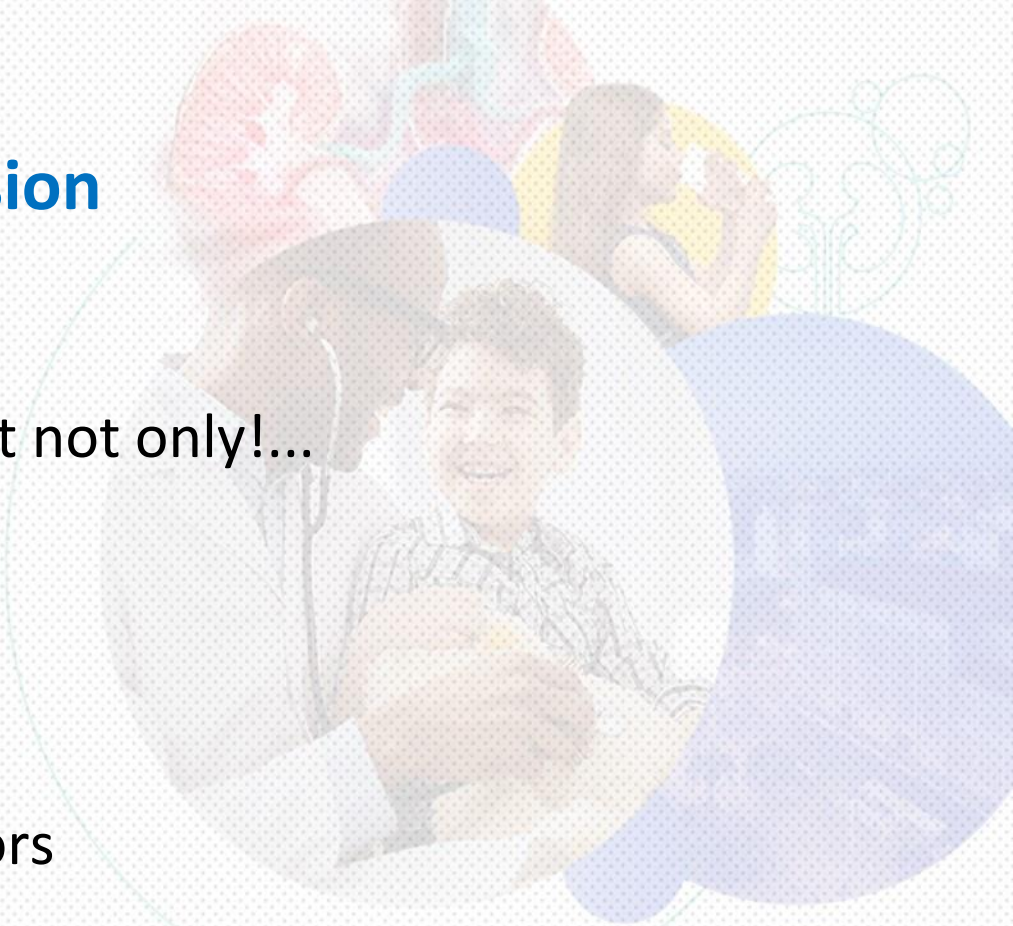
Other unusual nephrotoxicity



- Star fruit intoxication: acute oxalosis
- Chinese herbs: chronic interstitial nephritis
- Cadmium: chronic tubulointerstitial nephritis
- Snake bite: AKI in many developing countries
- Diethylene glycol: AKI (wine, toothpaste, topical medications, etc.)
- Ochratoxin (mycotoxin): CKD (oat, dried fruit, pork, nuts, etc.)

Chen Am J Kidney Dis *2001 / Isnard Bagnis* Am J Kidney Dis *2004*

Conclusion



- NSAIDs, NSAIDs and still NSAIDs, but not only!...
- Importance of risk-to-benefit ratio
- Give priority to identifying risk factors
- Simple investigation of renal function in at-risk conditions
- Collaboration with nephrologist

Thank you for your attention!