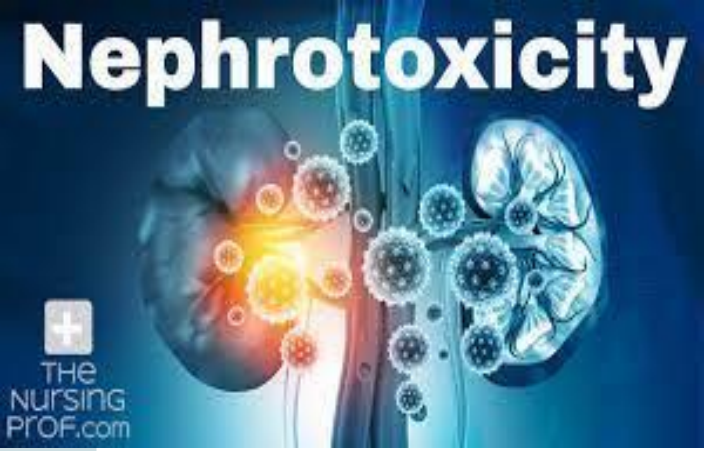

Antibacterial and Antifungal

Dr. F. Ahmadi

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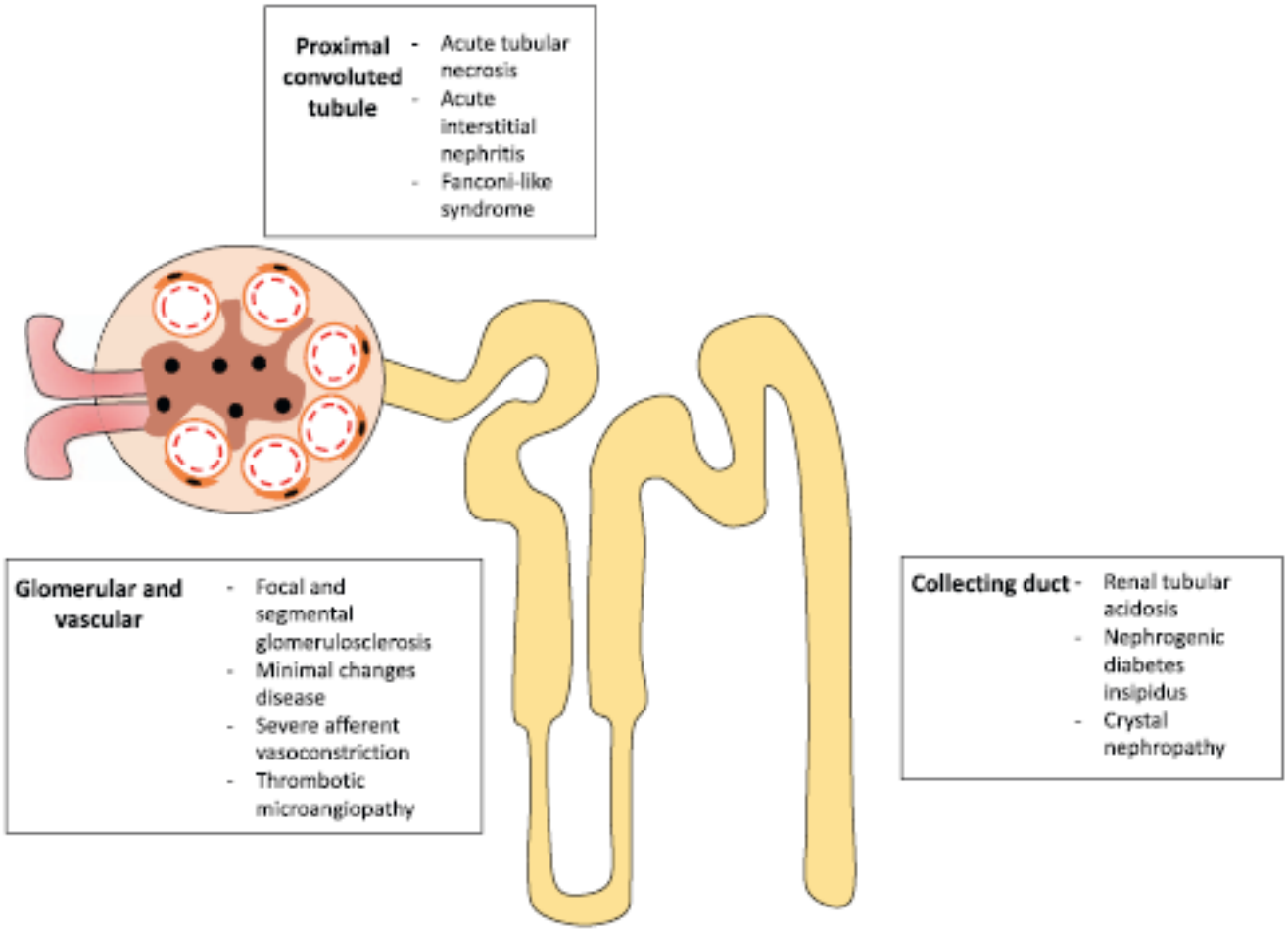
- Drugs cause approximately 20%-40% of acute kidney injury (AKI), perhaps as high as 60% of AKI in the elderly population.
- Aminoglycosides and beta-lactams are considered the most common antimicrobials causing AKI mainly due to acute tubular necrosis (ATN) and acute interstitial nephritis (AIN), respectively

Summary of Antimicrobial-Induced Nephrotoxicity: Mechanisms and Clinical Manifestations

Antibiotics	Aminoglycosides	Direct proximal tubule cytotoxicity	Fanconi-like syndrome
		Direct distal tubule cytotoxicity	ATN
			Electrolyte wasting tubulopathy
	Beta-lactams	Direct proximal tubule cytotoxicity	ATN
		Glomerular injury	Acute glomerulonephritis
	Trimethoprim/Sulfamethoxazole	Impaired creatinine secretion	AIN
		ENaC inhibition	Falsely elevated creatinine
			Hyperkalemia
	Fluoroquinolones	Tubular damage	AIN
		Enhanced cellular immunity/structural similarity to quinine	TMA
	Vancomycin	Direct proximal tubule cytotoxicity	ATN
			AIN
	Daptomycin	Rhabdomyolysis	Myoglobin-induced tubulopathy
			Mild ATN
	Polymyxins	Direct proximal tubule cytotoxicity	ATN
Antifungal	Amphotericin B	Direct distal tubule cytotoxicity	Renal distal tubular acidosis
	Caspofungin	Direct distal tubule cytotoxicity	Mild distal tubulopathy

Adv Chronic Kidney Dis. 2020;27(1):31-37

Structural and clinical manifestation of antimicrobial-induced nephrotoxicity

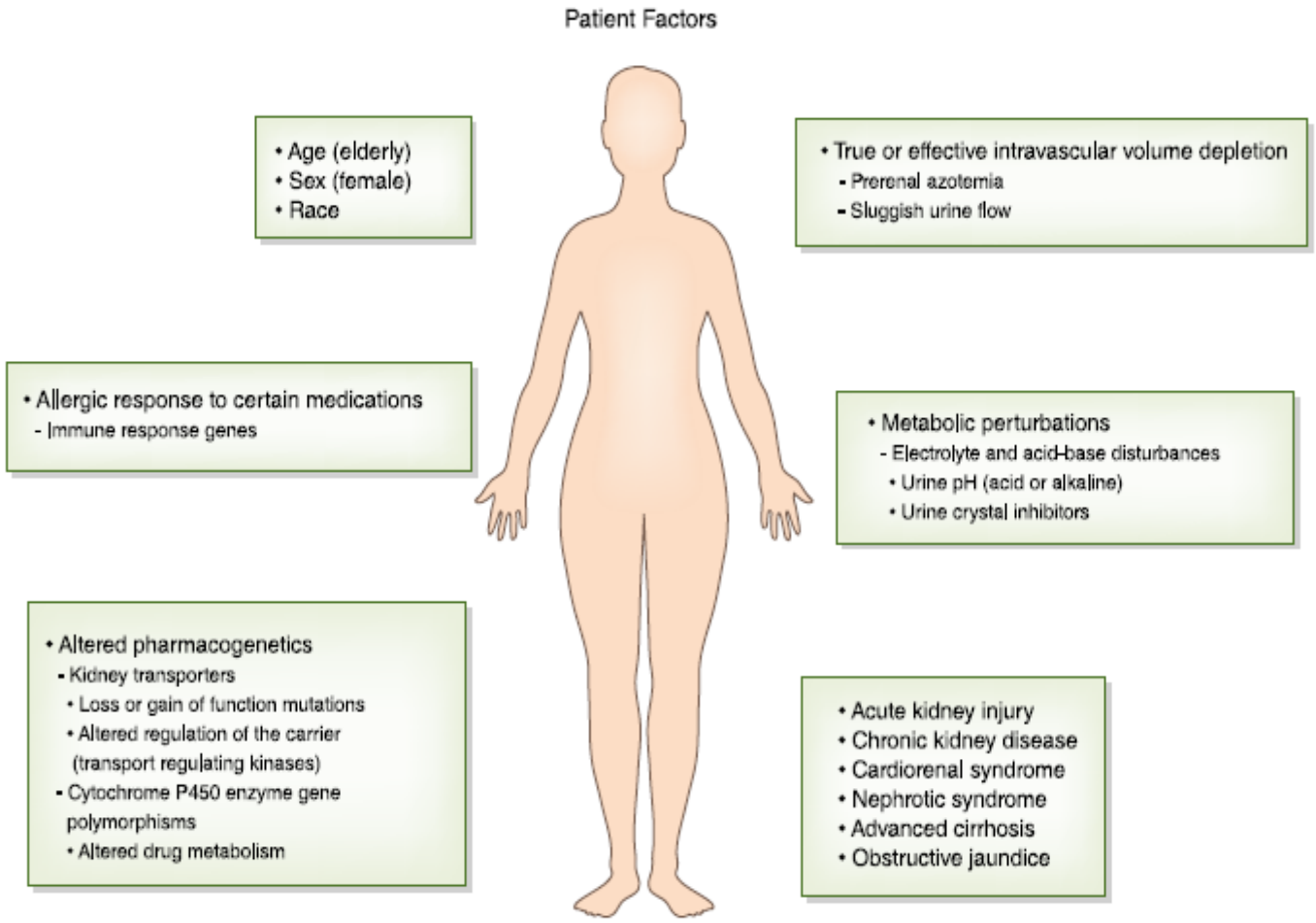


Adv Chronic Kidney Dis. 2020;27(1):31-37

Risk factors for drug nephrotoxicity

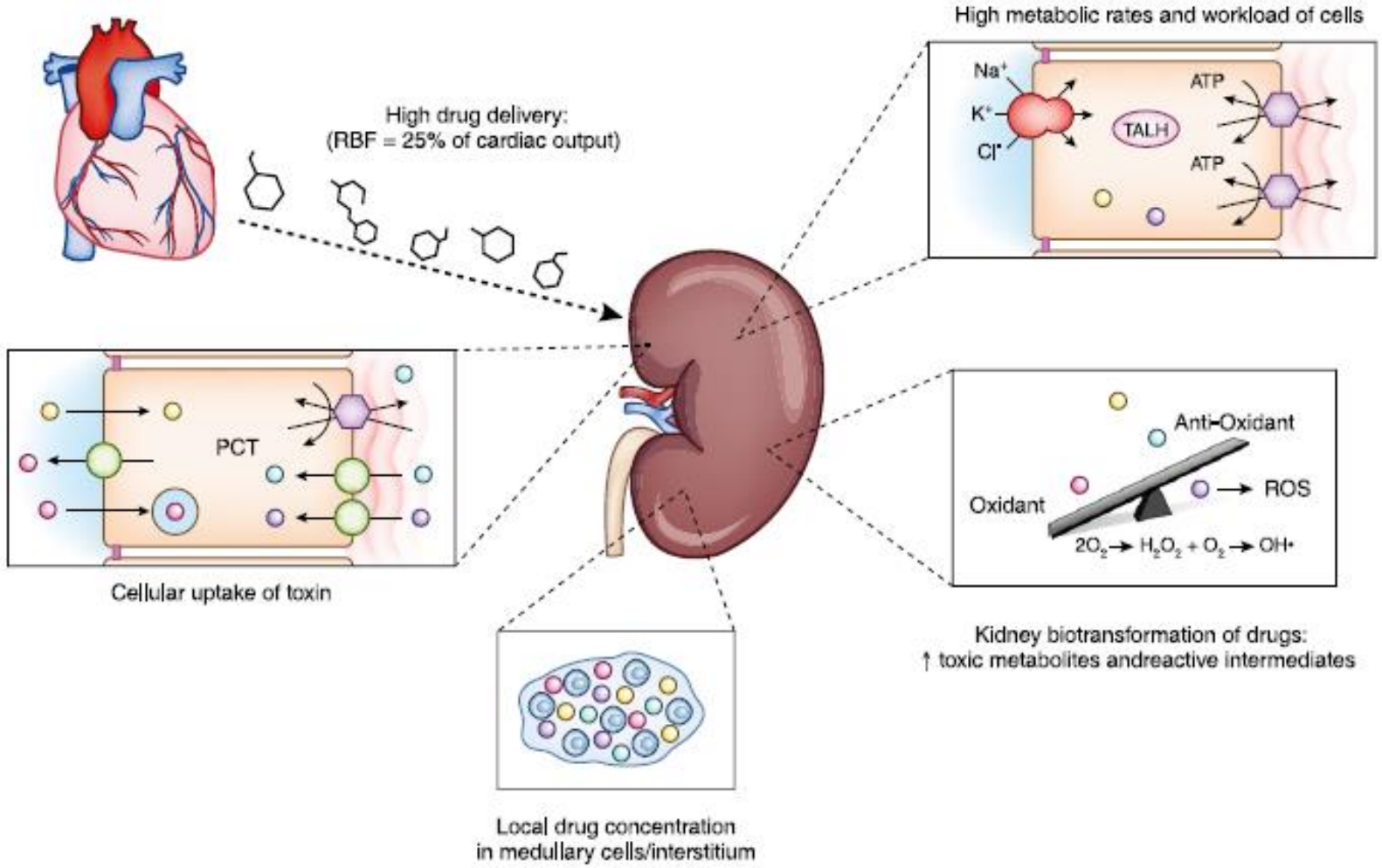
- Drug factors
- Patient factors
- Kidney factors

Patient factors that increase risk for drug-induced nephrotoxicity



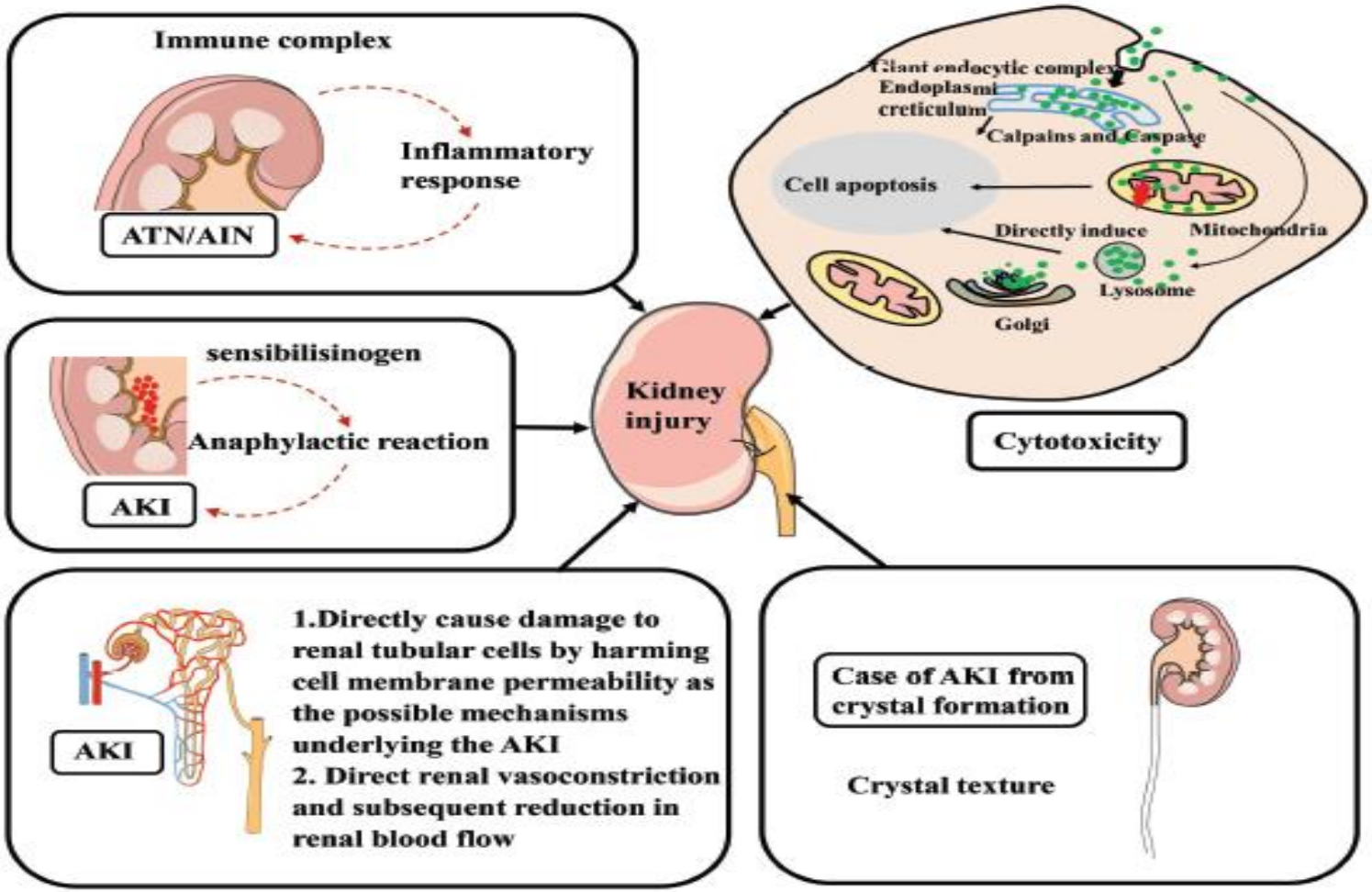
Clin J Am Soc Nephrol 13: 1897–1908, December, 2018

Kidney factors that enhance risk for drug-induced nephrotoxicity



Clin J Am Soc Nephrol 13: 1897–1908, December, 2018

The pathogenic mechanisms of antibiotic-induced nephrotoxicity



Aminoglycosides

- Despite rigorous patient monitoring, nephrotoxicity appears in 10–25% of therapeutic courses
- Phospholipidosis correlates tightly with the level of toxicity of aminoglycosides.
- Tubular regeneration and recovery of kidney function are typically complete after approximately 20 days post discontinuation of the medication

Aminoglycosides

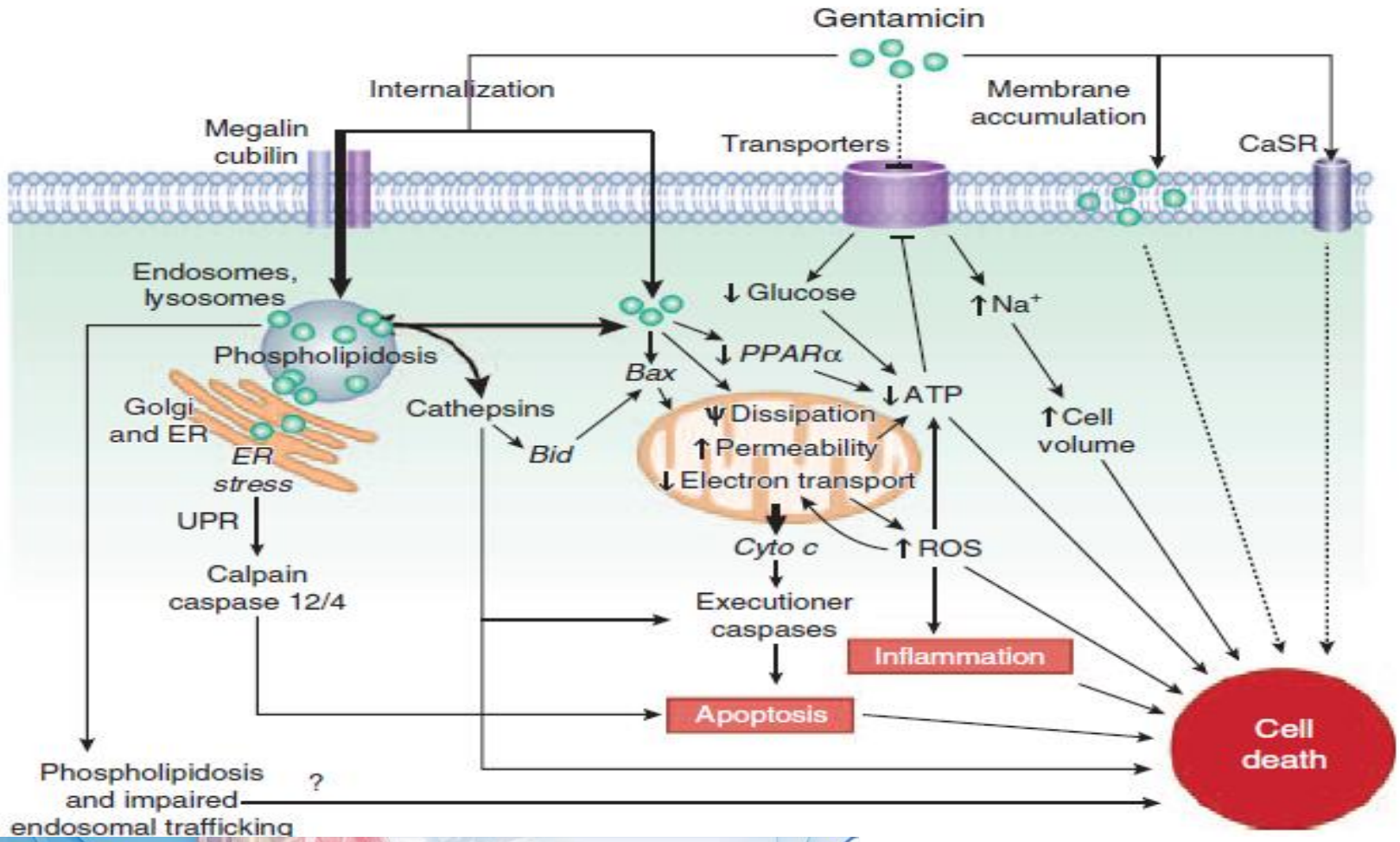
- The typical clinical manifestation of aminoglycoside toxicity is nonoliguric or even polyuric renal excretion dysfunction accompanied by an increase in plasma creatinine, urea and other metabolic products of the organism, proteinuria, enzymuria, aminoaciduria, glycosuria, and electrolyte alterations (hypercalciuria, hypermagnesuria, hypocalcemia, and hypomagnesemia).

Risk factors of aminoglycoside antibiotics related to patient and treatment characteristics, and to the concomitant administration of other drugs

Patient	Treatment	Other drugs
Older age	Longer treatment	NSAIDs
Reduced renal function	Higher dosage	Diuretics
Pregnancy	Split dosage	Amphotericin
Dehydration	—	Cisplatin
Renal mass reduction	—	Cyclosporin
Hypothyroidism	—	Iodide contrast media
Hepatic dysfunction	—	Vancomycin
Metabolic acidosis	—	Cephalosporin
Sodium depletion	—	—

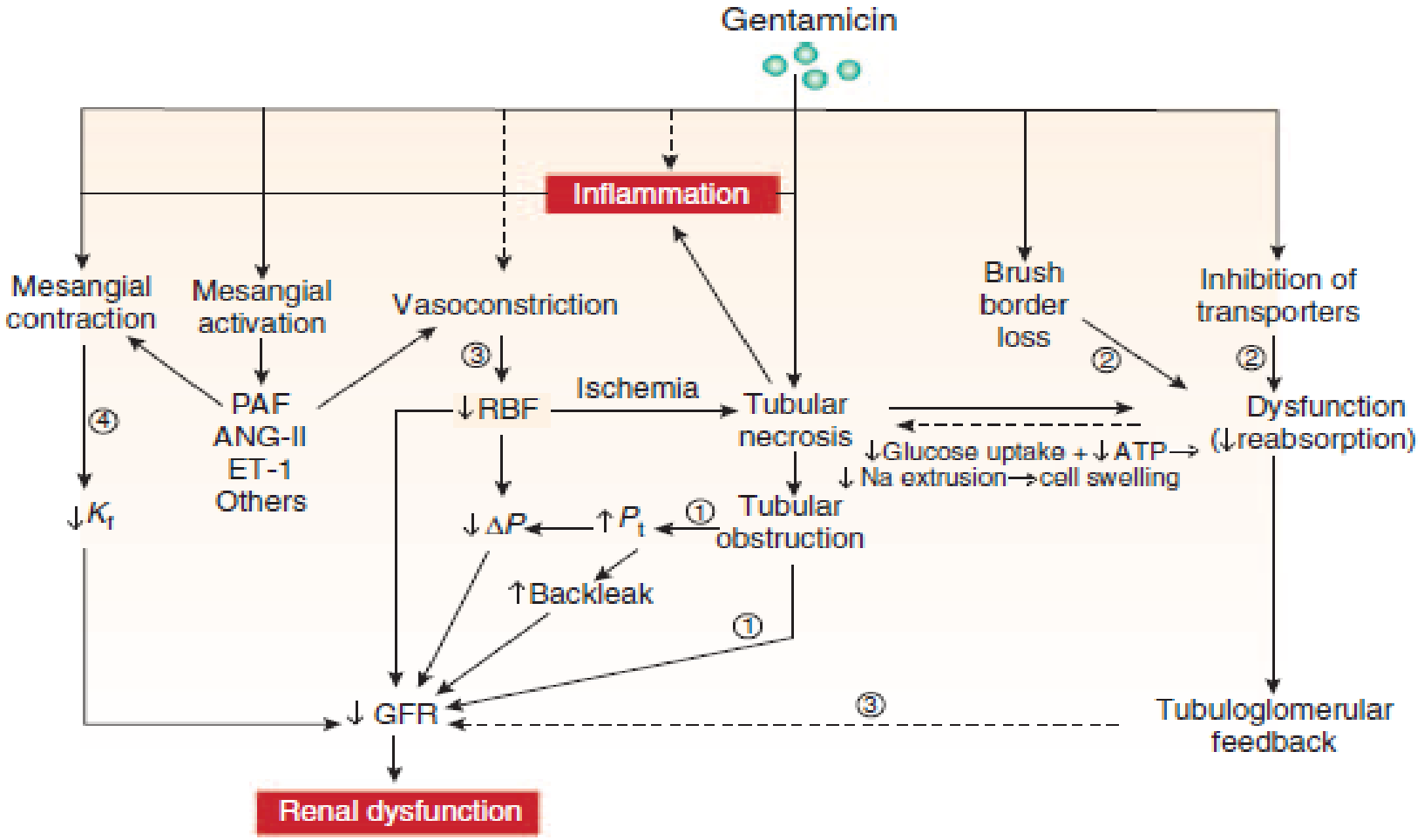
Kidney International (2011) 79, 33–45

Mechanisms and cell signaling pathways underlying the cytotoxic effect of gentamicin



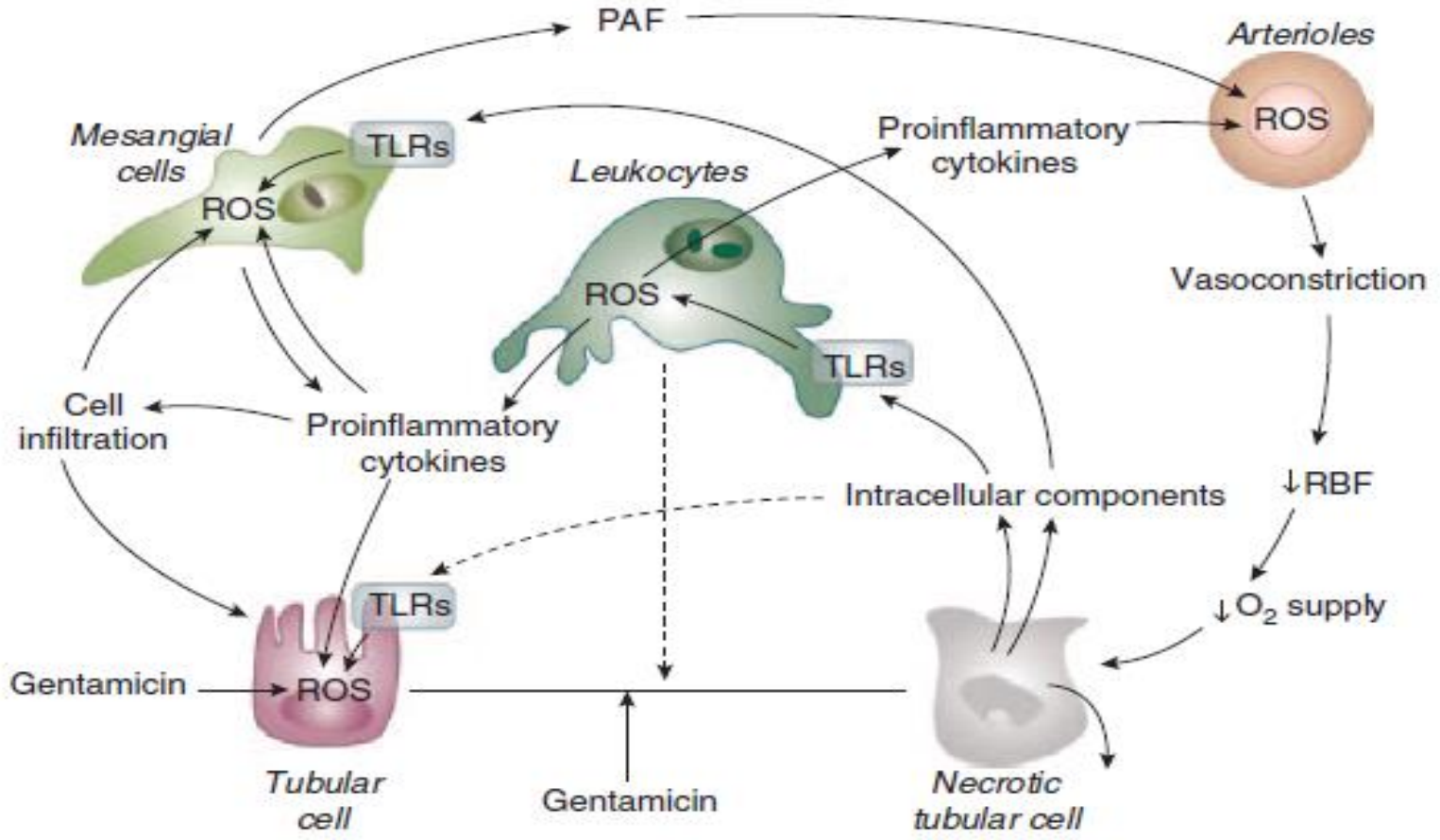
Kidney International (2011) 79, 33–45

Integrative view of the mechanisms leading to gentamicin nephrotoxicity



Kidney International (2011) 79, 33–45

Role of inflammation in the amplification of tubular, glomerular, and vascular effects of gentamicin

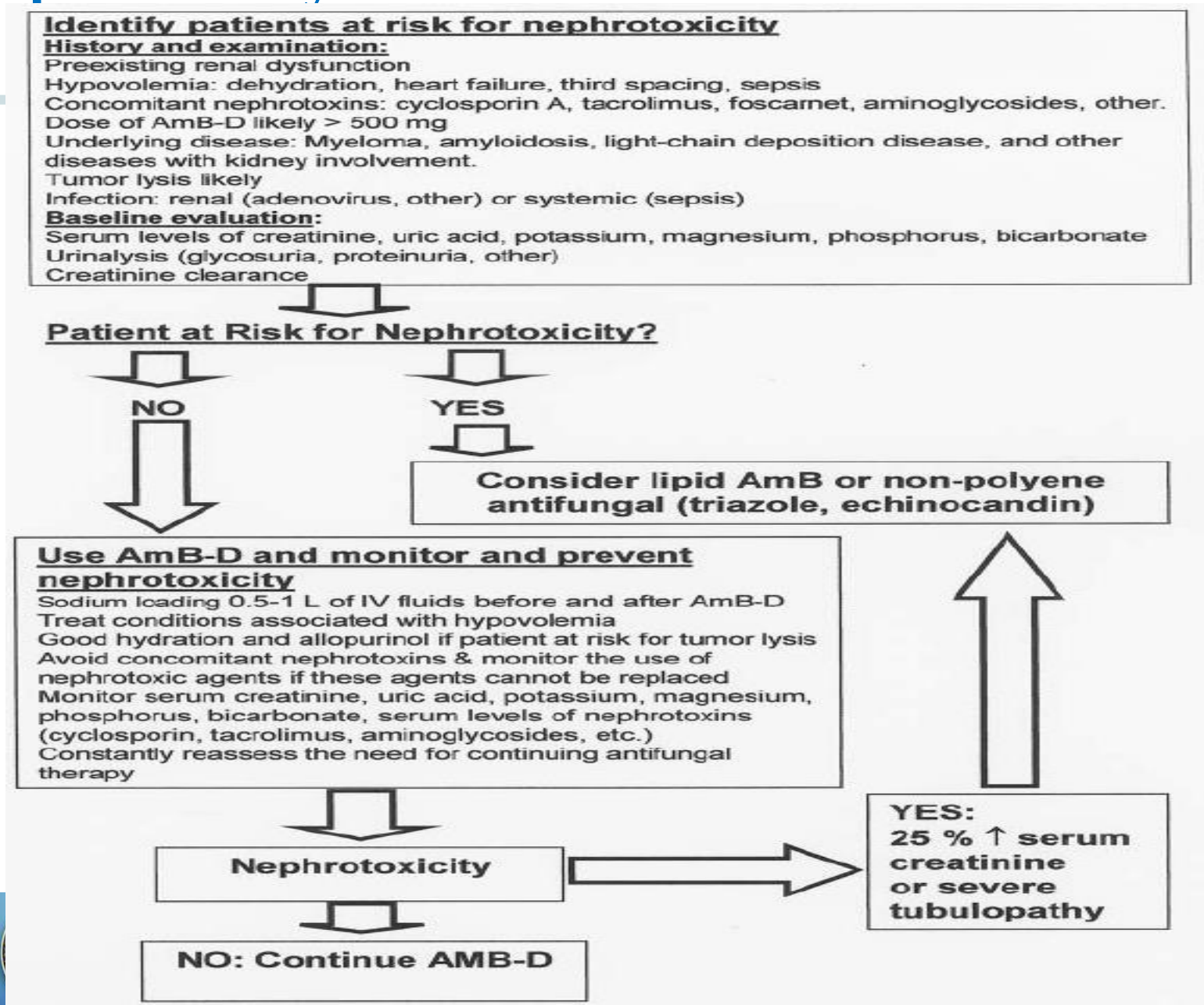


Kidney International (2011) 79, 33–45

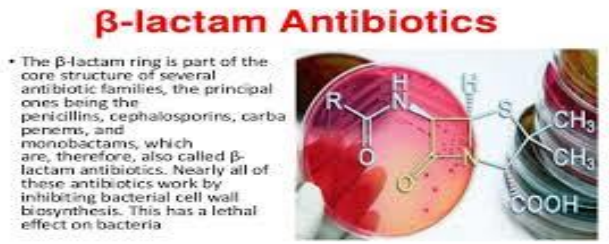
Amphotericin B

- Amphotericin B-induced nephrotoxicity results in tubular dysfunction due to cell swelling driven by increased cation permeability in disrupted tubular cell membranes.
- Renal distal tubular acidosis
- Increased permeability of NaCl in the macula densa cells causes severe afferent vasoconstriction and decreased GFR
- The most important specific risk factor of kidney injury is the total amphotericin cumulative dose (>600 mg).
- Lipid-based amphotericin formulations, including amphotericin B lipid complex and liposomal amphotericin B, achieve considerably less plasma and renal concentration, nephrotoxicity

Managing amphotericin B-deoxycholate (AmB-D) nephrotoxicity



Beta-Lactams



- Acute glomerulonephritis,ATN, and AIN.
- penicillins and cephalosporins are associated with significantly less renal toxicity compared with carbapenems.
- The combination of some penicillins such as piperacillin-tazobactam with vancomycin significantly increases the incidence of AKI, 2-3 times higher than with vancomycin alone

Beta-Lactams

- Some reports state lower nephrotoxic potential of aztreonam compared with cephalosporins and penicillins
- cephalosporins cefoxitin and cefazolin, interfere with the assay and can increase apparent creatinine concentration without causing kidney injury

Trimethoprim/Sulfamethoxazole

- Trimethoprim/Sulfamethoxazole increasing creatinine concentration without causing significant kidney injury
- Bactrim-induced hyperkalemia may progress to flaccid paralysis, cardiac conduction disturbances,and life-threatening arrhythmia (complete heart block, ventricular fibrillation).

Fluoroquinolones

- Ciprofloxacin carries the highest estimated risk for AKI (risk ratio [RR] 2.76, followed by moxifloxacin and levofloxacin.
- AIN, with some cases showing granulomatous interstitial nephritis or crystal deposition when urine pH is greater than 6.8
- A few cases of TMA after levofloxacin use have been reported.

Vancomycin

- Nephrotoxicity has been a major concern for the use of vancomycin since its approval in 1958
- Significantly lower AKI than aminoglycosides or amphotericin B but higher than daptomycin or linezolid.
- The onset of AKI occurs after 4-8 days of therapy with subsequent improvement after discontinuation of the medication.

Vancomycin

- The underlying mechanisms supported by several studies is proinflammatory oxidation, mitochondrial dysfunction,and cellular apoptosis leading to proximal tubular injury and, when extensive, also ATN.

KI REPORTS
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CLINICAL RESEARCH

Vancomycin-Associated Tubular Casts and Vancomycin Nephrotoxicity

Ngoentra Tantranont[1,2], Yosu Luque[3,4], Mary Hsiao[1], Claire Haute[1], Lillian Gaber[1], Roberto Barrios[1], Horacio E. Adrogue[5], Aïssata Niasse[4] and Luan D. Truong[1]

- VTC displays a characteristic morphologic profile amenable to ready recognition in biopsy specimens. It results from coprecipitation of vancomycin and uromodulin
- It may have a nephrotoxic effect superimposing on and independent from the ATN or interstitial nephritis in the pathogenesis of vancomycin nephrotoxicity.

Kidney Int Rep (2021) 6, 1912–1922

KI REPORTS
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CLINICAL RESEARCH

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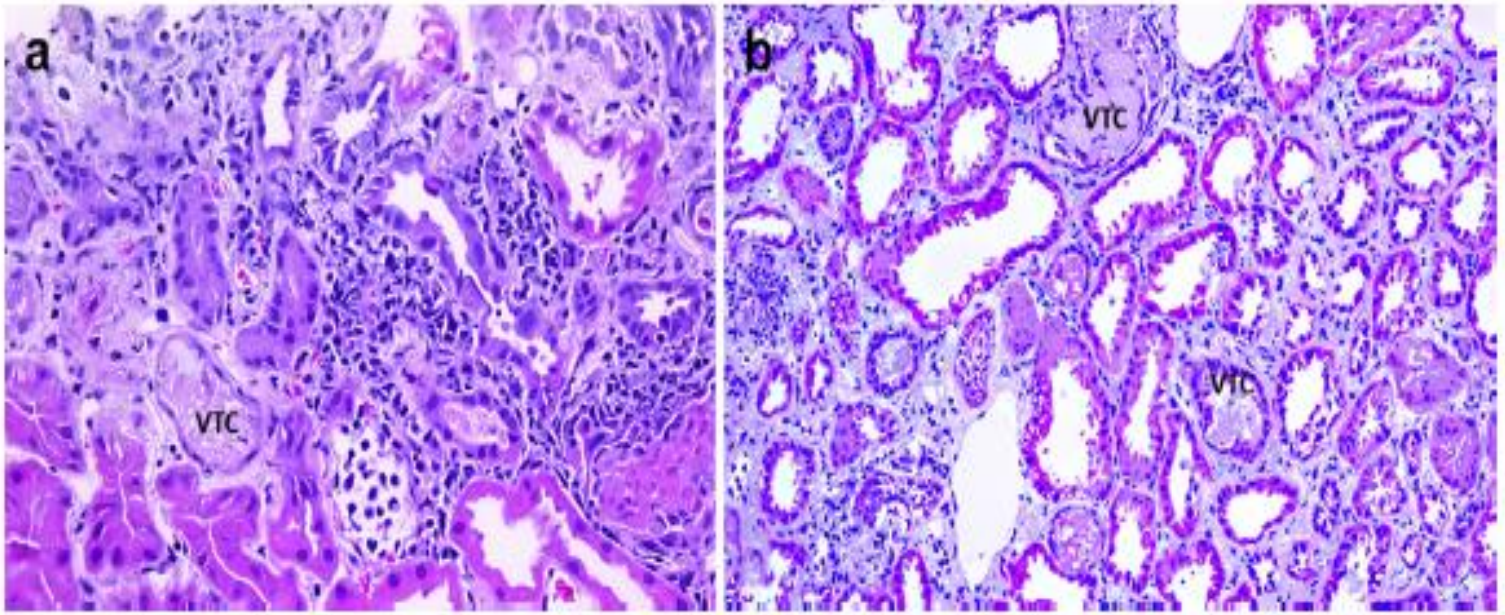

The background changes include acute tubulointerstitial nephritis (a), or acute tubular necrosis with a minor interstitial inflammation
(b). Vancomycin-associated tubular casts (VTCs) are noted in each biopsy

Risk factors for vancomycin nephrotoxicity

- Pre-existent kidney disease
- Severity of illness
- Concomitant nephrotoxic
- Medications (primarily aminoglycosides or piperacillin/tazobactam)
- Total daily dose
- Area under the curve
- Method of administration

Potential risk factors associated with VA-AKI

	Potential Risk Factors
Modifiable	• Effective intravascular volume depletion • Concurrent acute illness: acute kidney injury or acute kidney disease, systemic infection/inflammation, hypotension, immunosuppression state, increased disease severity, electrolyte, and acid–base disturbances
Non-modifiable	• Older age • Female gender • Race • Allergic response to drugs • Altered pharmacogenetics (kidney drug transporters, cytochrome P450 enzyme gene polymorphisms) • Pre-existing systemic comorbidities: chronic kidney disease, nephrotic syndrome, advanced liver cirrhosis, obstructive jaundice, cardiovascular comorbidities (including heart failure), diabetes mellitus, obesity, immunosuppression state

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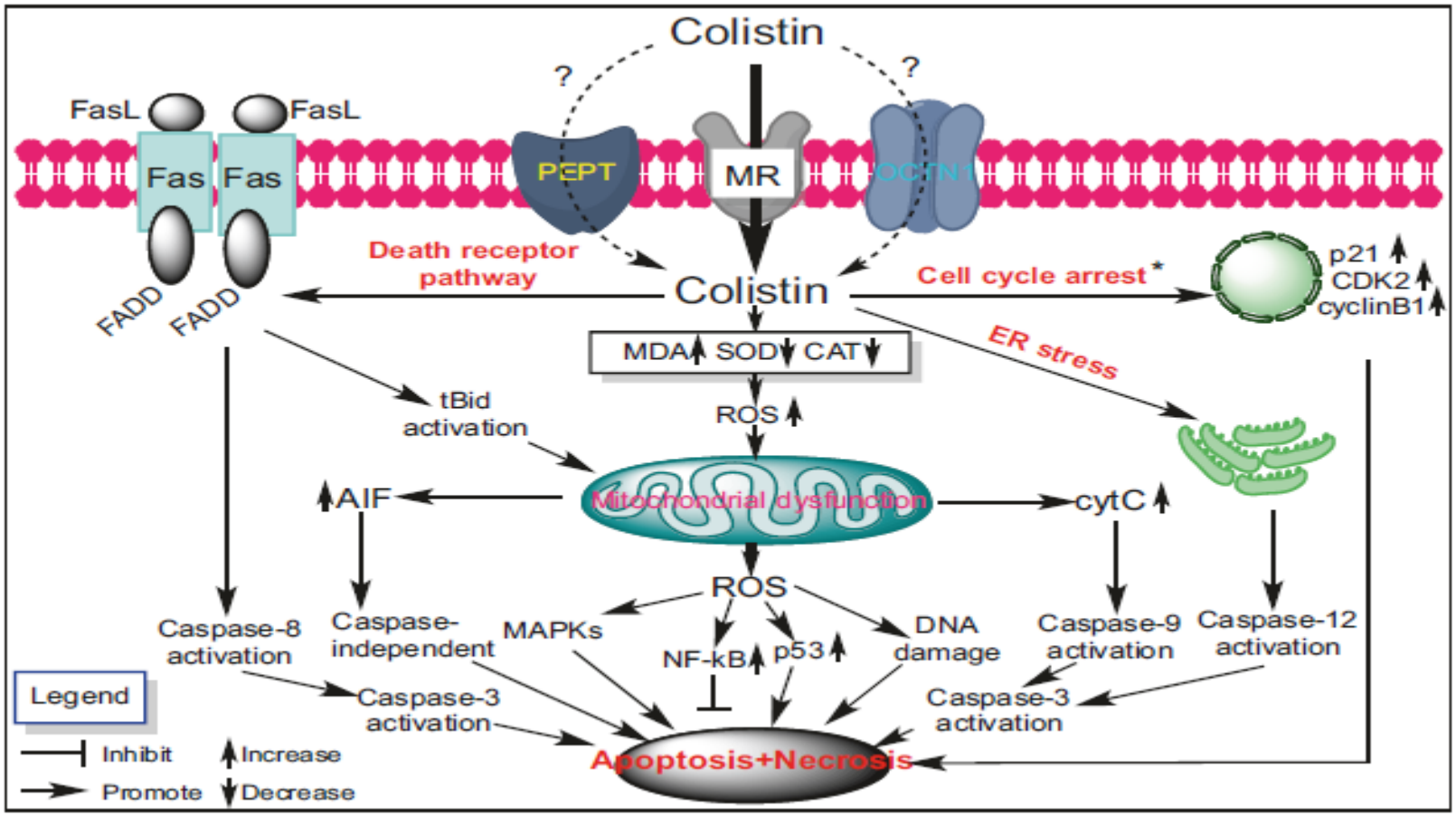
Polymyxins (Colistin and Polymyxin B)

- The estimated prevalence of nephrotoxicity ranges from 0% to 50%.
- Some of the clinical manifestations of polymyxin-induced nephrotoxicity are ATN, proteinuria,and cylindruria.
- Polymyxins promote ion and water influx through increased permeability of tubular epithelial cell membranes, leading to cellular swelling and cell death.
- Another antimicrobial in this class, colistin (polymyxin E), has also been associated with increased risk of AKI with a few cases displaying features of AIN.

Schematic diagram of the proposed mechanisms of polymyxin-induced apoptosis



Experimental Medicine and Biology 1145, https://doi.org/10.1007/978-3-030-16373-0_18

Amelioration of Polymyxin-Induced Nephrotoxicity

- N-acetylcysteine (NAC)
- Ascorbic acid (50 or 200 mg/kg)
- Melatonin, 100 or 400 mg/kg
- Polyaspartic acid
- Grape seed extract
- Methionine

Strategies Prevention of Antimicrobials AKI

- Creatinine clearance or estimated GFR-based dose adjustment
- Assay and adjustment based on trough or random levels
- Adequate and appropriate hydration
- Avoidance of concomitant nephrotoxins
- Daily assessment of antibiotic indications, and use of short antibiotic courses,
- If long-term antibiotic is required, regular assessment of kidney function
- Use vitamin E, vitamin C, N-acetylcysteine, erythropoietin, a-lipoic acid, curcumin,or statins to prevent antimicrobial-induced AKI

Mechanisms and Prevention of Acute Kidney Injury Induced by Different Types of Antibiotics

Antibiotics	Related drugs	Mechanisms	Preventions	Hemodialysis
Aminoglycosides	Gentamicin, Amikacin, Streptomycin	Cytotoxicity, Decrease in kidney perfusion pressure	Statins, Prolonged interval dosing, Nebulised aminoglycosides	Effective clearance[37]
Antituberculous	Isoniazid, Rifampicin, Ethambutol	Hypersensitive reactions	...	Effective clearance (pyrazinamide) Poor clearance (large molecularweight, wide distribution, high protein binding, rapid hepatic clearance or adherence to the dialyzer membrane of isoniazid, rifampicin and ethambutol)[41-45]
Amphotericin B	Amphotericin B	Cytotoxicity, Decrease in kidney perfusion pressure	Liposomal amphotericin B, Nacetylcysteine, Saline loading, Slowing infusion speed	Poor clearance (widely volume of distribution, lipophilicity, large size 924 daltons, and highly protein bound > 90%)[54]
Beta-lactams	Carbapenems, Cephalosporins, Penicillins	Cytotoxicity, Hypersensitive reactions	Reduce the combination with Vancomycin	Effective clearance[61]
Macrolides	Azithromycin, Clarithromycin, Roxithromycin	Hypersensitive reactions	...	Poor clearance (widely volumes of distribution, high molecular weights 700 Da to 1100 Da).[69]
Quinolones	Levofloxacin , Ciprofloxacin, Norfloxacin	Hypersensitive reactions, Crystalline nephropathy	Appropriate hydration	Effective clearance[75]
Vancomycin	Vancomycin	Cytotoxicity	Cilastatin, Antioxidants	Effective clearance[83,84]

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نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳-۱۵ مهر