# Cyclosporine and tacrolimus nephrotoxicity

***Professor of nephrology***

***Isfahan kidney diseases research center***

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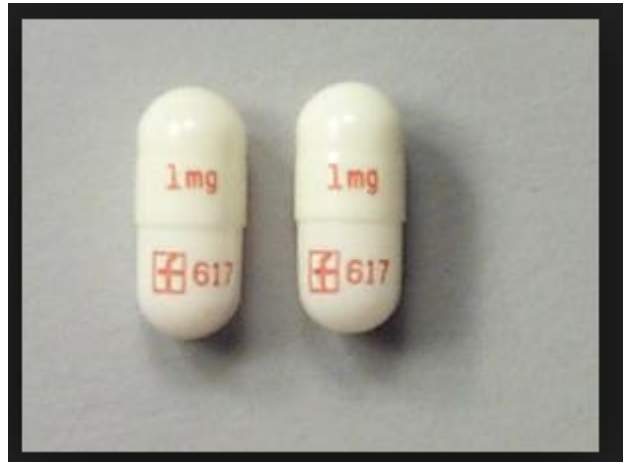


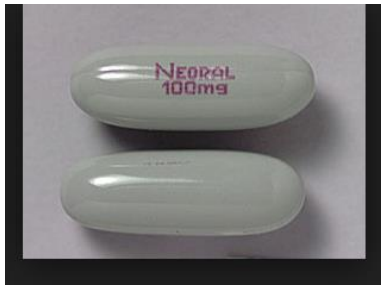

- **RISK FACTORS**
- **Acute calcineurin inhibitor nephrotoxicity**
- **Chronic calcineurin inhibitor nephrotoxicity**
- **Thrombotic microangiopathy**
- **Electrolyte and acid-base disturbances**
- **PREVENTION OF CHRONIC CALCINEURIN INHIBITOR NEPHROTOXICITY**
- **Therapies with unclear benefit**
- **Therapies with no benefit**
- **SUMMARY AND RECOMMENDATIONS**

# INTRODUCTION

- CNI nephrotoxicity clinically presented as the abrupt increase in serum creatinine (Scr) disturbed homeostasis and nodular arteriolar hyalinosis (as histologic hallmark) without morphologic changes, resulting in reversible acute/irreversible chronic allograft lesions.
- Other renal effects of the calcineurin inhibitors include tubular dysfunction and, rarely, a hemolytic uremic syndrome (HUS) that can lead to acute graft loss
- The immunosuppressive properties of cyclosporine and tacrolimus result from inhibition of calcineurin, a calcium- and camodlulin-dependent phosphatase (protein phosphatase 3)

# INCIDENCE

- there was considerable variability in the incidence of AKI in various centers.
- the risk was greatest with prolonged ischemia time of the donated kidney prior to transplantation
- Subsequent trials using lower doses of cyclosporine showed that these problems were dose related
- The best data on the overall incidence of chronic kidney disease (CKD) with CNIs come from a cohort study of non-kidney transplant recipients (mostly liver, heart, and lung) in the United States
- Cyclosporine was given to 60 percent and tacrolimus to 28 percent.
- At a median follow-up of 36 months, 17 percent developed CKD

:Risk factors for CKD included calcineurin therapy, older age, lower pretransplant GFR, female sex, postoperative AKI, baseline diabetes and hypertension, and hepatitis C virus infection.

REVIEW

# Risk factors for calcineurin inhibitor nephrotoxicity after renal transplantation: a systematic review and meta-analysis

Abstract | **Fulltext** | Metrics | Get Permission | Cite this article

**Authors** Xia T, Zhu S, Wen Y, Gao S, Li M, Tao X, Zhang F, Chen W

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Altmetric 1

- CNI nephrotoxicity is multifactorial with demographic, environmental, and pharmacogenetic flexibility, whereas studies indicating risk factors for CNI nephrotoxicity obtained incomplete or conflicting results.

- Twelve observational studies containing a total of 2,849 cases were identified.
- Donor age (odds ratio [OR], 1.01; 95% CI, 1.01–1.03; *p*=0.02), recipient zero-time arteriosclerosis (OR, 1.44; 95% CI, 1.04–1.99; *p*=0.03), and *CYP3A5*3/*3* genotype (OR, 2.80; 95% CI, 2.63–2.98; *p*=0.00) were confirmed as risk factors for CNI nephrotoxicity..

# RISK FACTORS

- High doses of cyclosporine [24,25] or tacrolimus [26]
- Older age of donated kidney [27]
- Concomitant use of nephrotoxic drugs, particularly nonsteroidal antiinflammatory drugs (NSAIDs) [28,29]
- Salt depletion and diuretic use
- Drugs that inhibit cytochrome P-450 3A4/5 (CYP3A4/5), thereby increasing exposure to CNI metabolites ( table 1)
- Drugs that inhibit P-glycoprotein-mediated efflux of CNIs from tubular epithelial cells, thereby increasing local renal exposure to CNIs ( table 2)
- Genetic polymorphisms in the genes encoding CYP3A4/5 *(CYP3A4/5)* and P-glycoprotein (*ABCB1*) [30-35]

# Acute calcineurin inhibitor nephrotoxicity

# *Acute CNI Nephrotoxicity*

**Vascular Effects:“Acute Arteriolopathy.”**

**Tubular Effects: “Toxic Tubulopathy.”**

# Vascular Effects:"Acute Arteriolopathy."

- Studies have demonstrated that cyclosporine causes vasoconstriction of the afferent and efferent glomerular arterioles and reductions in renal blood flow and glomerular filtration rate (GFR).
- The exact mechanism of vasoconstriction is unclear, but there appears to be substantial impairment of endothelial cell function, leading to reduced production of vasodilators (prostaglandins and nitric oxide) and enhanced release of vasoconstrictors (endothelin and thromboxane)
- Increased sympathetic tone also may be present ,although renal vasoconstriction occurs even in denervated kidneys.
- In addition, transforming growth factor beta-1, endothelin-1, and the production of reactive oxygen and nitrogen species have also been implicated.

*Up to date*

## TABLE 5.8 Approximate Therapeutic Ranges for Cyclosporine

| Post-transplantation Month | HPLC and EMIT (ng/mL) | FPIA (ng/mL) | C2 levels* (µg/mL) |
|---|---|---|---|
| 0-2† | 150-350 | 250-450 | 1.2-1.5 |
| 2-6 | 100-250 | 175-350 | 0.8-1.2 |
| >6 | ~100 | ~150 | 0.5-0.8 |

EMIT, enzyme-multiplied immunoassay technique; FPIA, fluorescent polarization immunoassay; HPLC, high-performance liquid chromatography.

*Drawn within 15 minutes of 2 hours postdose. For C2 levels, no change in target levels is required for different assay types.

†In the first few days after transplantation, the trough cyclosporine level should not fall below 300 ng/mL by HPLC.

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/mL. It is necessary to consider the clinical condition of the patient when interpreting whole blood concentrations.

In clinical practice during the **early post-transplant period**, whole blood trough levels have generally been in the following range:

| | **Early post-transplant period** |
|---|---|
| Liver | 5-20ng/ml |
| Kidney | 10-20ng/ml |
| Heart | 10-20ng/ml |

Subsequently, during **maintenance therapy**, blood concentrations have generally been in the range of **5 - 15 ng/ml in liver, kidney and heart transplant recipients**

| | **Maintenance therapy** |
|---|---|
| Liver | 5-15ng/ml |
| Kidney | 5-15ng/ml |
| Heart | 5-15ng/ml |

Blood level

Do Adjustme

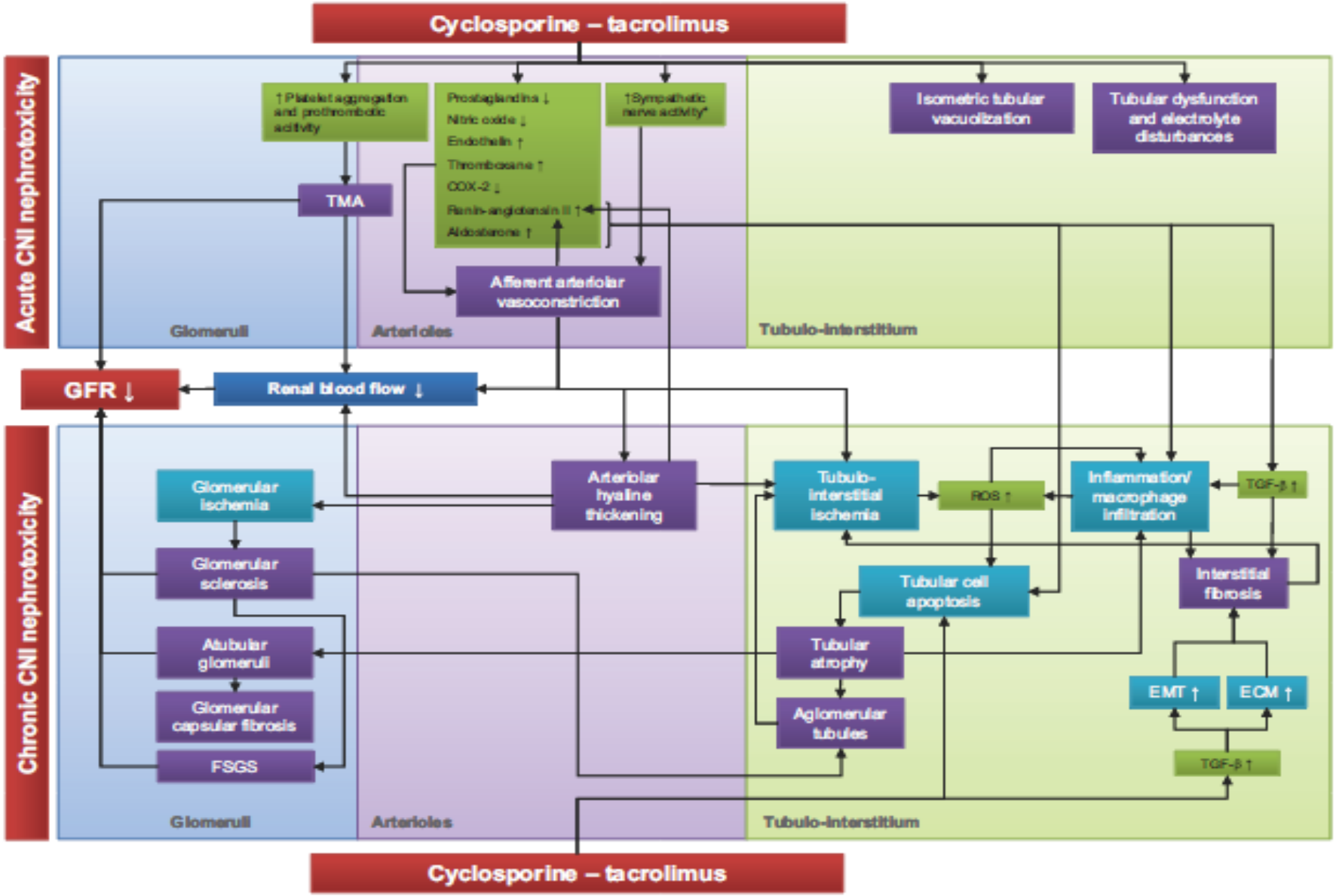
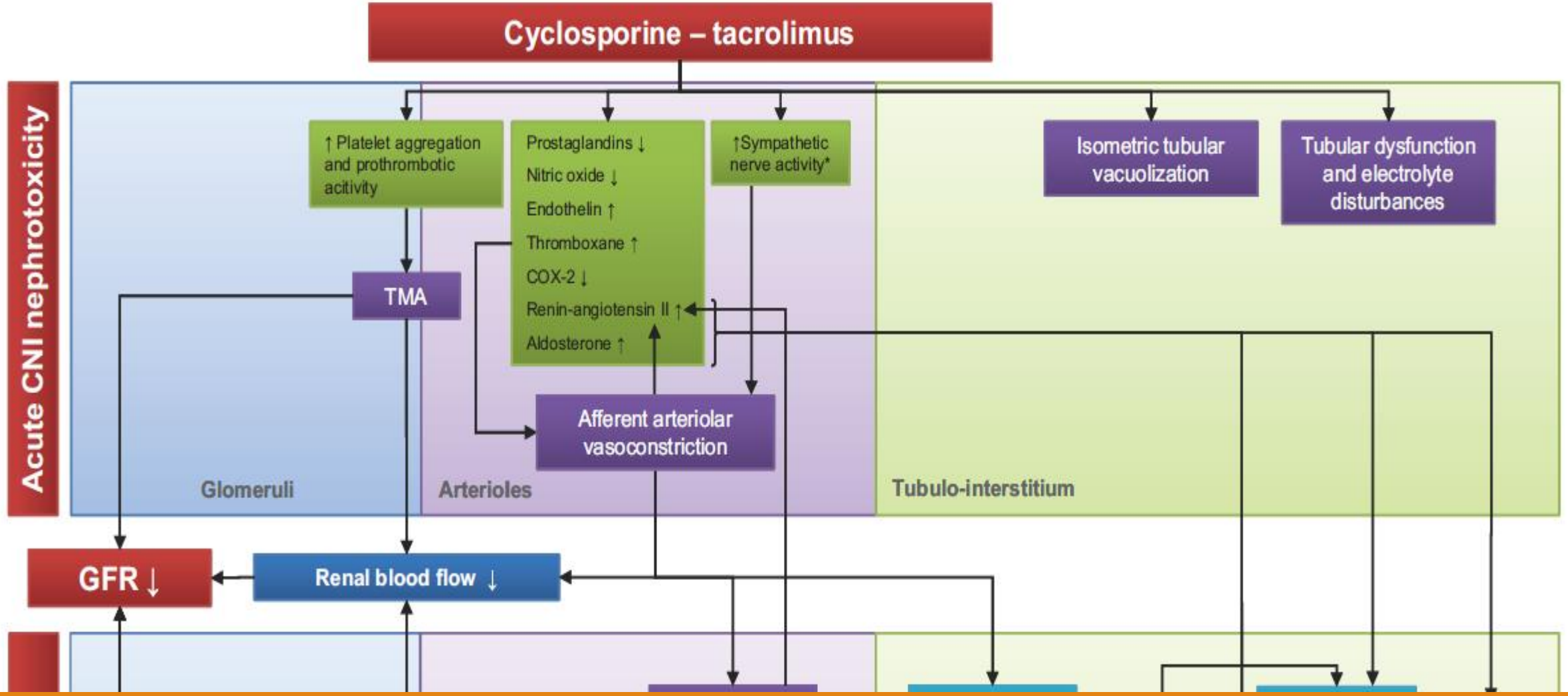
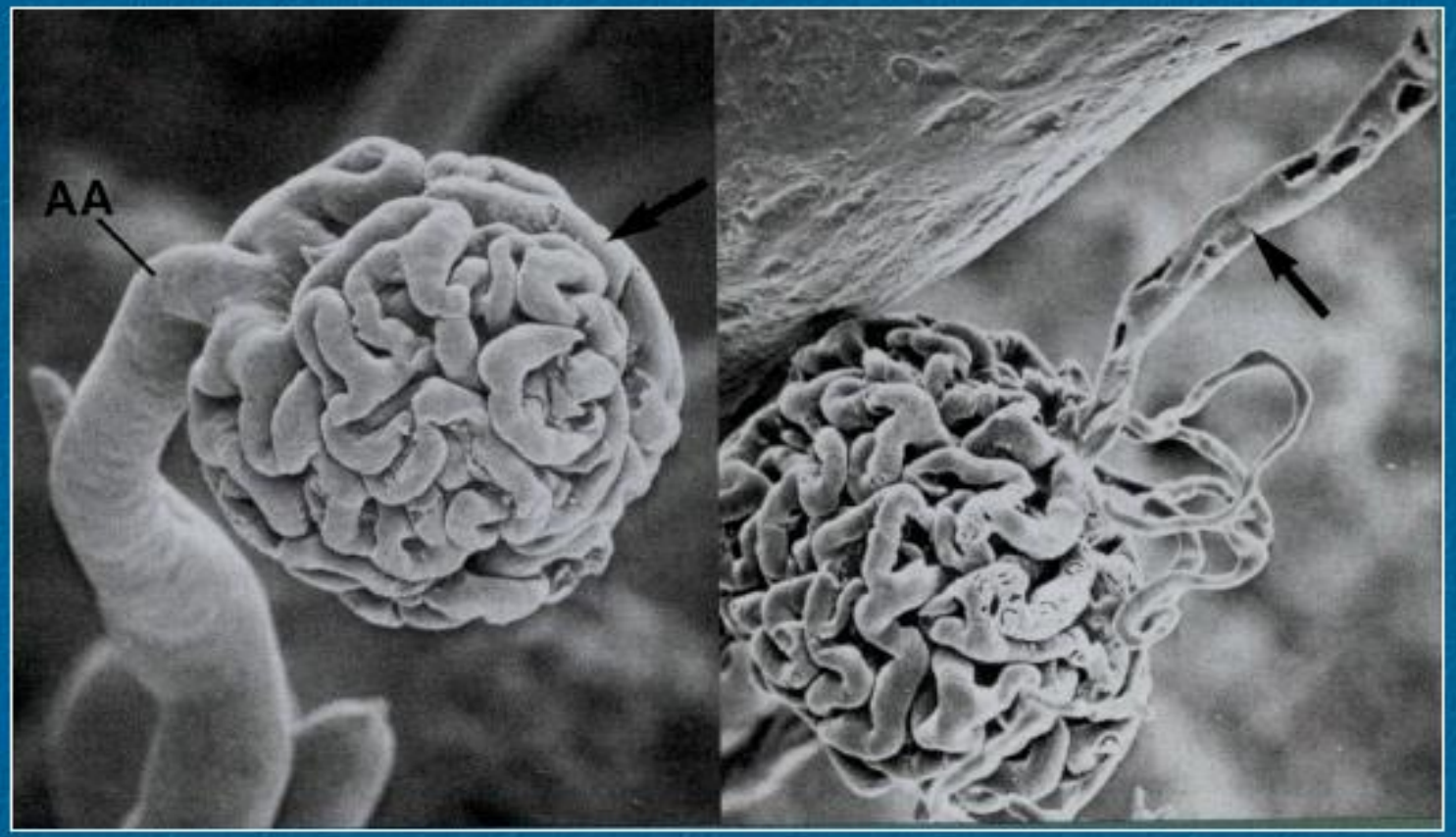



*Figure 1.* Schematic representation of the etiology of calcineurin inhibitor nephrotoxicity. CNI, calcineurin inhibitor; TMA, thrombotic microangiopathy; EMT, epithelial mesenchymal transition; ECM, extracellular matrix; GFR, glomerular filtration rate; FSFS, focal segmental glomerulosclerosis; ROS, reactive oxygen species. *Only in native kidneys.


Cyclosporine – tacrolimus
Acute CNI nephrotoxicity
↑ Platelet aggregation and prothrombotic acitivity
Prostaglandins ↓
Nitric oxide ↓
Endothelin ↑
Thromboxane ↑
COX-2 ↓
Renin-angiotensin II ↑
Aldosterone ↑
↑Sympathetic nerve activity*
Isometric tubular vacuolization
Tubular dysfunction and electrolyte disturbances
TMA
Afferent arteriolar vasoconstriction
Glomeruli
Arterioles
Tubulo-interstitium
GFR ↓
Renal blood flow ↓

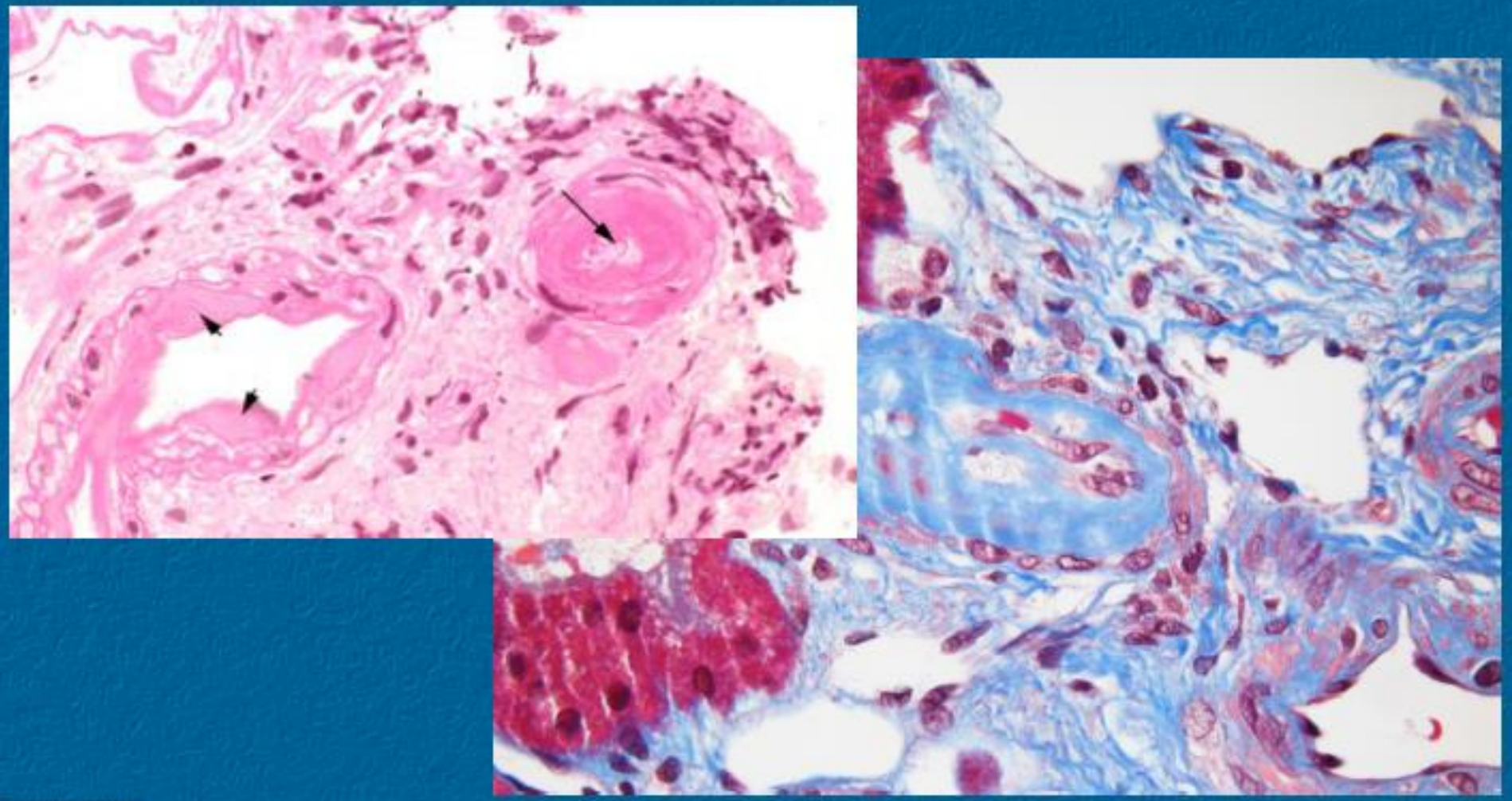



# Diffuse vasoconstriction within the kidney In sodium-depleted, cyclosporine treated model

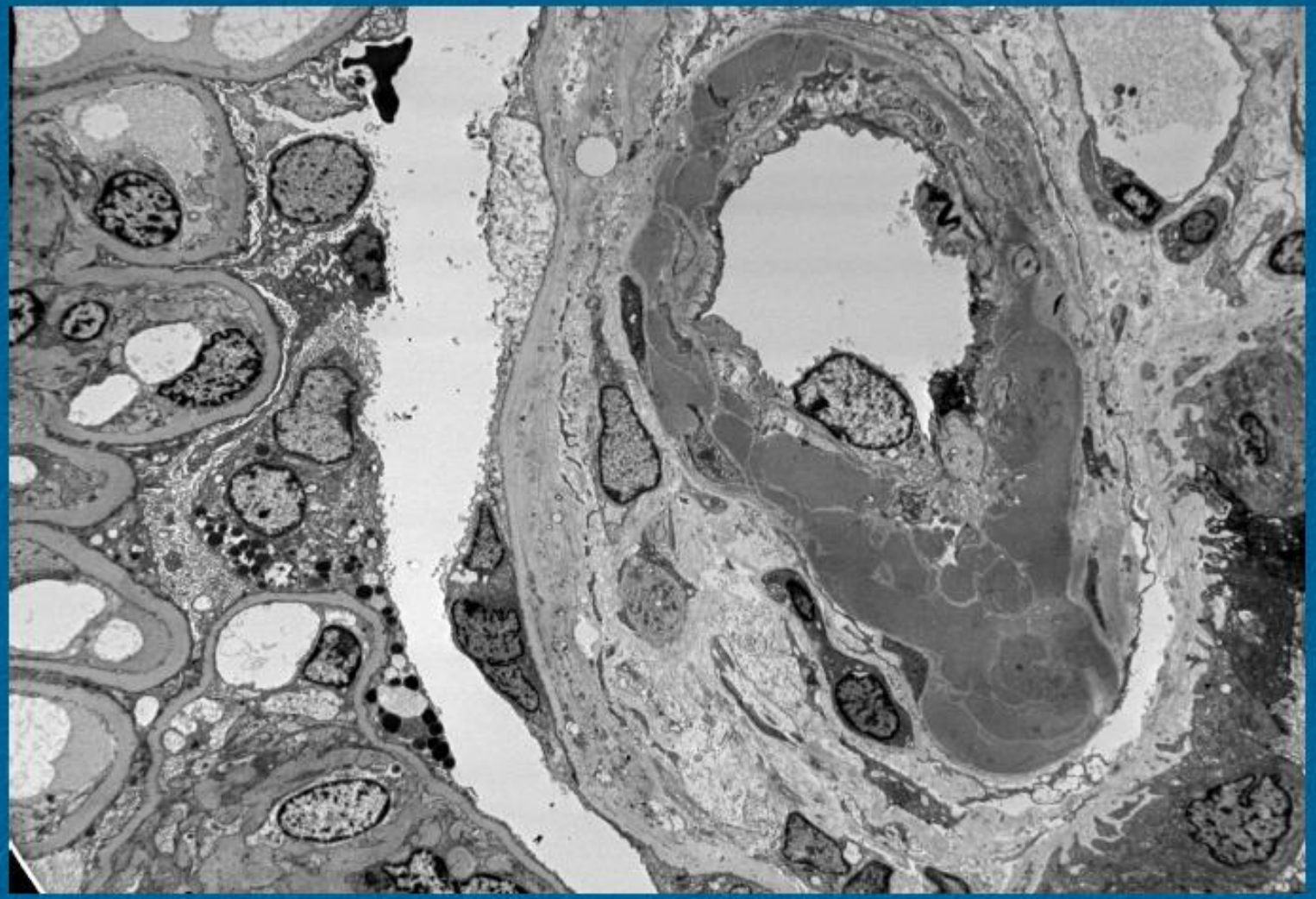
# Calcineurin-Inhibitor Nephrotoxicity: Clinical Course

| Early: 1-6 mos | Late: Beyond 6 mos |
|---|---|
| Suppressed RAS | Late increase in RAS activity |
| Reversible vasoconstriction | ?reversible / Onset fibrosis |
| Decline in GFR transient | Little recovery of GFR with transition |
| Dose Dependent | ?Dose and duration dependent |

# Arteriolar Hyalinosis during Calcineurin Inhibitor Rx

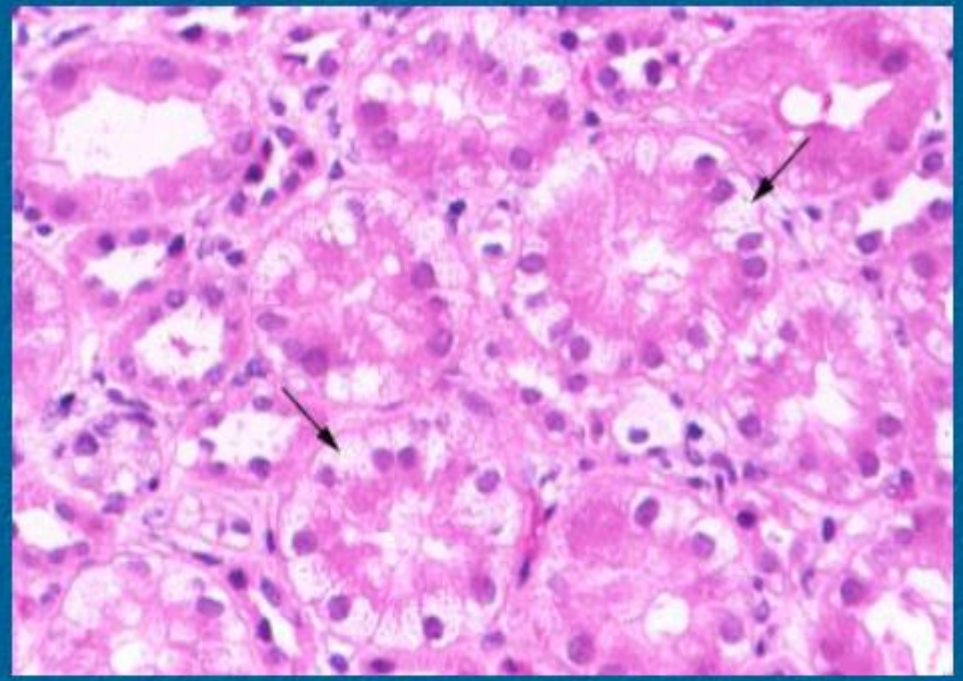


# Arteriolar Hyalinosis: CNI induced

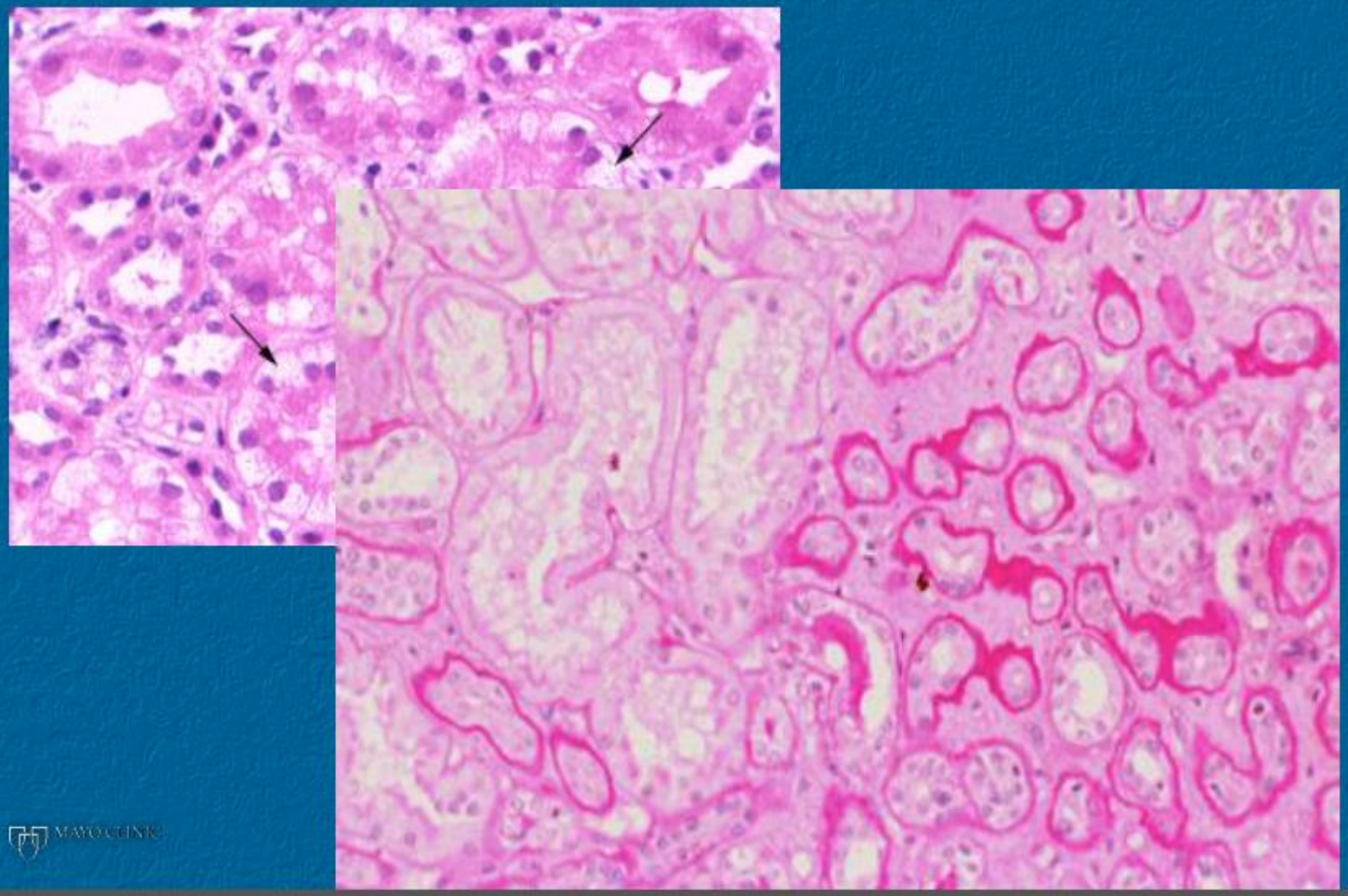


*EM courtesy of D. Lager, M.D., Mayo Clinic.*

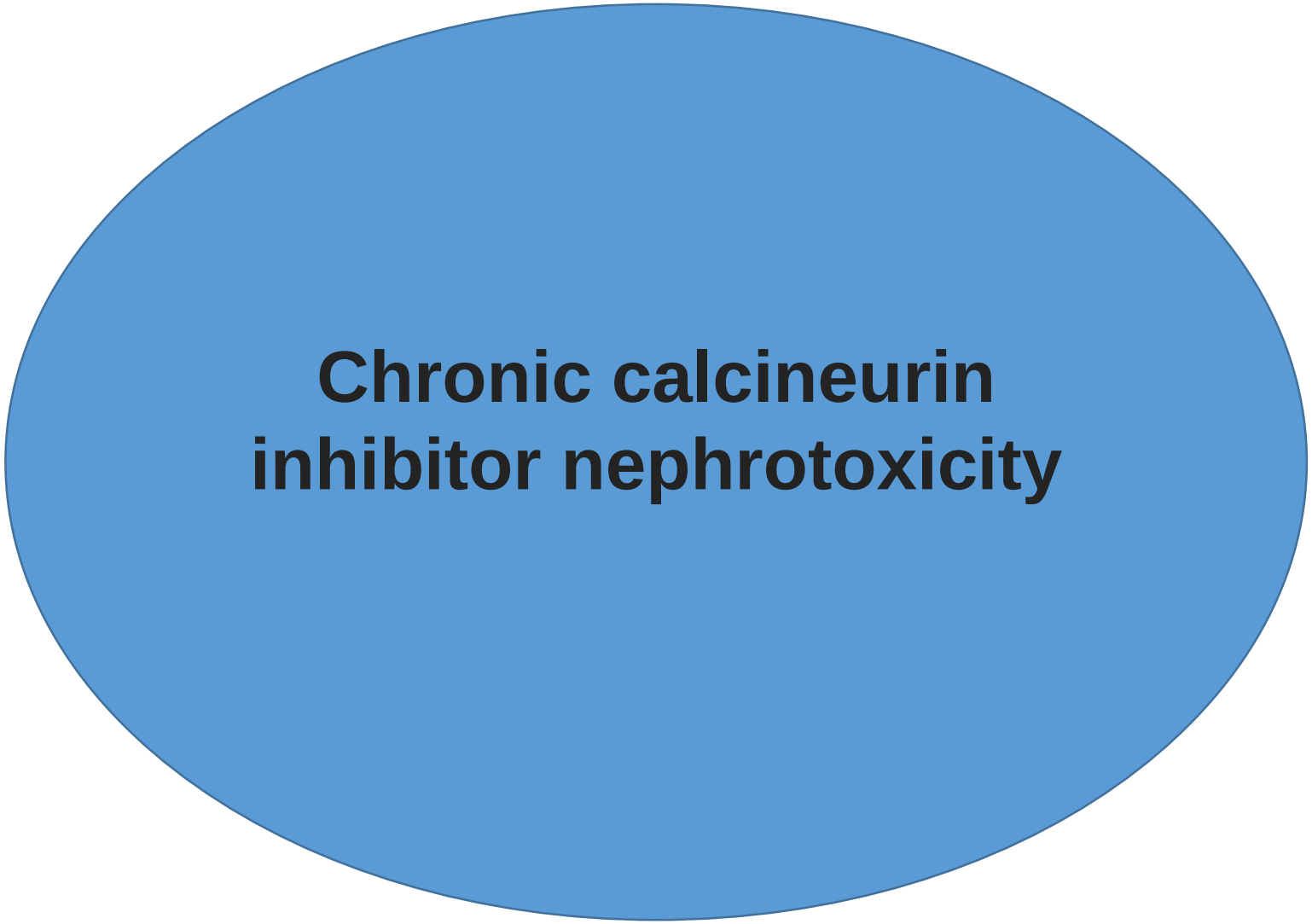
# Tubular abnormalities during Calcineurin inhibitor Rx



# Tubular abnormalities during Calcineurin inhibitor Rx



however, even patients with therapeutic trough levels may show signs of nephrotoxicity.


Chronic calcineurin
inhibitor nephrotoxicity

# *Chronic CNI Nephrotoxicity*

- **Vascular Effects**
- **Tubular-Interstitial Effects**

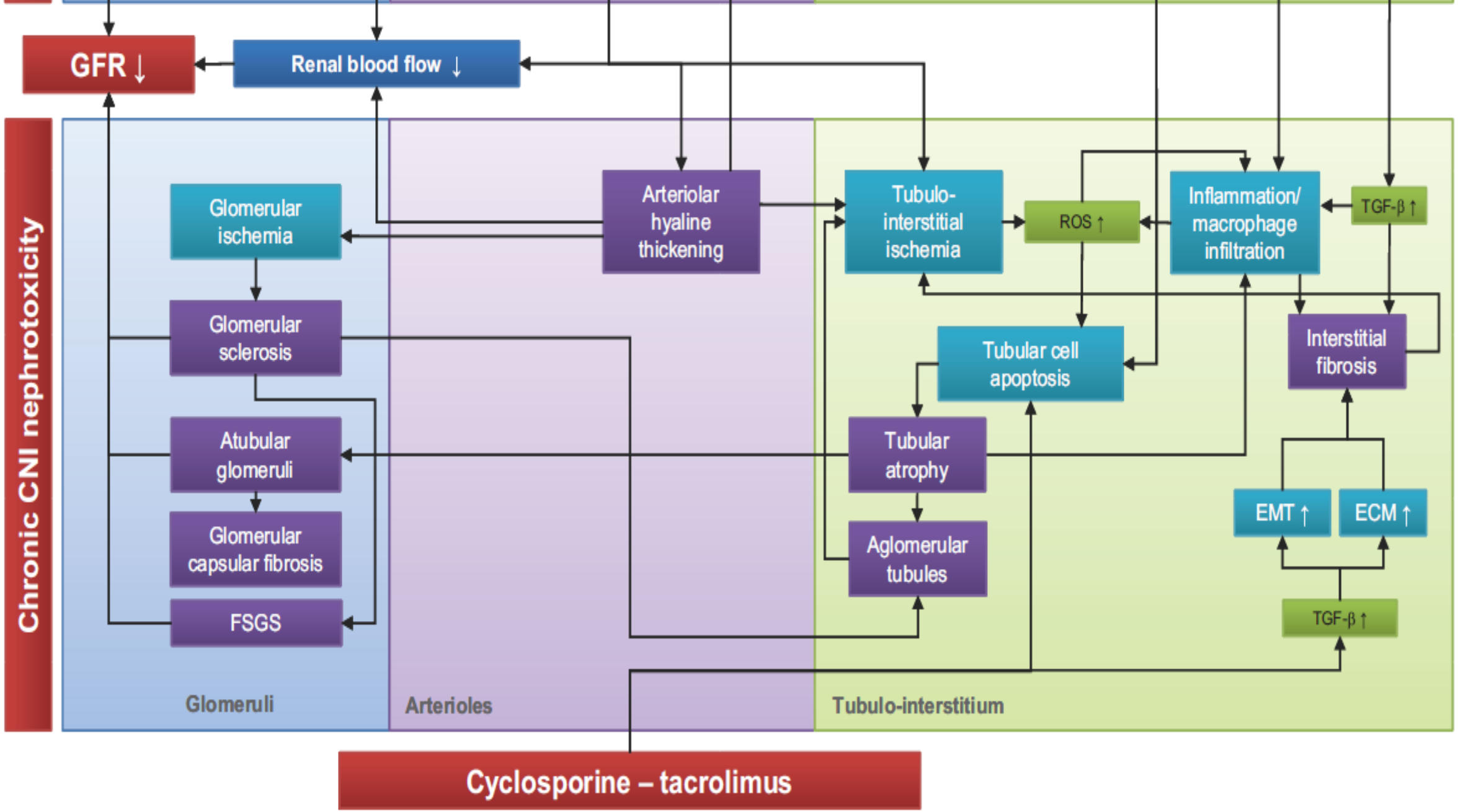
| | |
|---|---|
| **Chronic CNI nephrotoxicity** | |
| Interstitial fibrosis and tubular atrophy (typically striped) | Pre-existing donor injury, aging, ischemia-reperfusion injury, tubulo-interstitial rejection, infection (*e.g.*, UTI, polyomavirus, CMV), chronic ischemia (*e.g.*, renal artery stenosis, size discrepancy in pediatric transplantation), chronic postrenal obstruction, diabetes mellitus |
| Medial arteriolar hyalinosis | Pre-existing donor injury, aging, diabetes mellitus, hypertension (in these cases more subendothelial deposition) |
| Glomerular capsular fibrosis | Glomerular ischemia (*e.g.*, renal artery stenosis, chronic arteriolar vasoconstriction, or arteriolar hyalinosis) and other causes of atubular glomeruli (*i.e.*, causes of tubular atrophy) |
| Global glomerulosclerosis | Pre-existing donor injury, aging, chronic glomerular ischemia (*e.g.*, renal artery stenosis, arteriolar vasoconstriction, or hyalinosis), recurrent primary disease, *de novo* glomerular disease, hypertension secondary to tubular atrophy in a late stage |
| Focal segmental glomerulosclerosis (FSGS) | Recurrent primary disease; donor–recipient size discrepancy with hyperfiltration injury; FSGS secondary to other causes of glomerulosclerosis |
| Juxtaglomerular apparatus hyperplasia | Not well established, but likely other causes of hyperreninemia (*e.g.*, transplant renal artery stenosis) |
| Tubular microcalcifications | Pre-existing donor injury, ischemic tubular injury and acute tubular necrosis, bone and mineral metabolism imbalance, proteinuria |

HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy; CNI, calcineurin inhibitor; UTI, urinary tract infection; CMV, cytomegalovirus; FSGS, focal segmental glomerulosclerosis.

# اولین ابنرمالیتی در مصرف داروهای مهار کننده کلسینورین کدام است؟

- 1- اسیب عروقی
- 2-اسیب توبولی

It has been proposed that the arterial lesions are the primary abnormality, with secondary ischemia being responsible for the tubular and interstitial lesions.


GFR ↓
Renal blood flow ↓
Chronic CNI nephrotoxicity
Glomerular ischemia
Glomerular sclerosis
Atubular glomeruli
Glomerular capsular fibrosis
FSGS
Arteriolar hyaline thickening
Tubulo-interstitial ischemia
ROS ↑
Inflammation/ macrophage infiltration
TGF-β ↑
Tubular cell apoptosis
Interstitial fibrosis
Tubular atrophy
Aglomerular tubules
EMT ↑
ECM ↑
TGF-β ↑
Glomeruli
Arterioles
Tubulo-interstitium
Cyclosporine – tacrolimus

# *Chronic CNI Nephrotoxicity*

- Increased apoptosis (ie, programmed cell death) occurs in kidneys exposed to cyclosporine
- This finding may help explain the interstitial abnormalities associated with cyclosporine toxicity: the loss of cells and renal tubules accompanied by fibrosis.

# CLINICAL PRESENTATIONS

# CLINICAL PRESENTATIONS

- Acute CNI nephrotoxicity commonly presents as an acute but typically reversible functional renal impairment and rarely as a thrombotic microangiopathy (TMA)

- Chronic CNI nephrotoxicity manifests as a chronic progressive deterioration in kidney function

# Chronic kidney disease

- Chronic CNI nephrotoxicity commonly presents as a chronic and progressive renal insufficiency due to glomerular and vascular disease, abnormalities in tubular function, and an increase in blood pressure

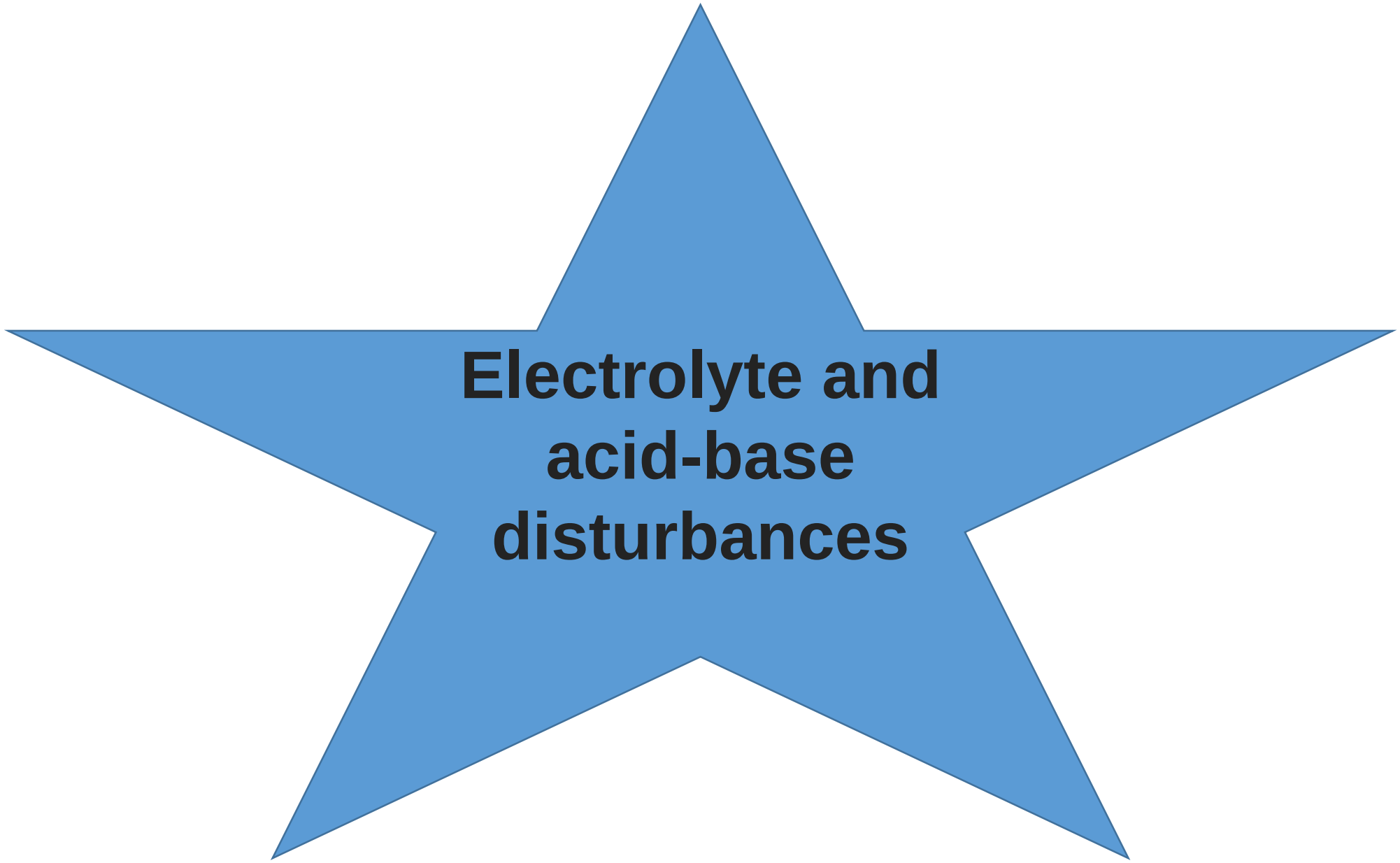
- **It is usually irreversible**

- Chronic CNI nephrotoxicity is thought to be caused by a combination of CNI-induced hemodynamic changes and toxic effects of CNIs on renal tubular epithelial cells.

# Thrombotic microangiopathy

- The TMA associated with CNIs is presumably initiated by CNI-induced injury to the vascular endothelial cells.

- Concurrent use of cyclosporine with mammalian (mechanistic) target of rapamycin (mTOR) inhibitors has been shown to increase the risk of TMA


Electrolyte and
acid-base
disturbances

# *Electrolyte Disturbances*

- Some of the effects of cyclosporine and tacrolimus on tubular function can be explained by reduced expression of the Na-K-2Cl--cotransporter (NKCC2) at the apical membrane of tubular epithelial cells
- The hyperkalemia seen with calcineurin inhibition is likely multifactorial and relates to inhibitory effects on Na-K-ATPase in collecting ducts and possibly to distal tubular acidosis
- In addition, there is evidence that decreased numbers of mineralocorticoid receptors, which are detected in 75% of patients who are treated with cyclosporine, lead to hyperkalemia and metabolic acidosis as a result of aldosterone resistance

# داروهای مهار کننده کلسینورین باعث اختلال کدام کانال یونی در توبول کلیه میشوند؟

1-کاهش کانال سدیم – پتاسیم –دو کلر

2-اثر مهاری روی سدیم –پتاسیم توبول جمع کننده

3-کاهش گیرنده های مبنرالوکورتیکوویید

4- همه موارد

# کدام اختلال الکترولیتی در مصرف مهار کننده های کلسی نورین دیده میشود؟

1- هیپرکالمی

2-هیپر کلسمی

3-هیپرناترمی

4-هیپرمنیزمی

# Hyperkalemia

- An elevation in the plasma potassium concentration due to reduced efficiency of urinary potassium excretion

- CNIs may reduce potassium excretion both by decreasing the activity of the renin-angiotensin-aldosterone system and by impairing tubular responsiveness to aldosterone

# Metabolic acidosis

- Tubular injury induced by cyclosporine can also impair acid excretion.
- This may be manifested as a normal anion gap (hyperchloremic) metabolic acidosis that may also reflect decreased aldosterone activity and suppression of ammonium excretion by hyperkalemia

# Hypophosphatemia

- Some patients treated with cyclosporine develop hypophosphatemia due to urinary phosphate wasting

# Hypomagnesemia

- Renal magnesium wasting is common in cyclosporine- and tacrolimus treated recipients, presumably due to drug effects on magnesium reabsorption
- Hypomagnesemia has been implicated as a contributor to the nephrotoxicity associated with cyclosporine

# Hypercalciuria

- Both cyclosporine and tacrolimus are associated with hypercalciuria

# Hyperuricemia and gout

- Cyclosporine and tacrolimus, via glomerular and tubular effects, can decrease urinary uric acid excretion, leading to hyperuricemia in most patients and occasionally symptomatic gout

# Cyclosporine versus tacrolimus

# Comparison Between Cyclosporine and Tacrolimus

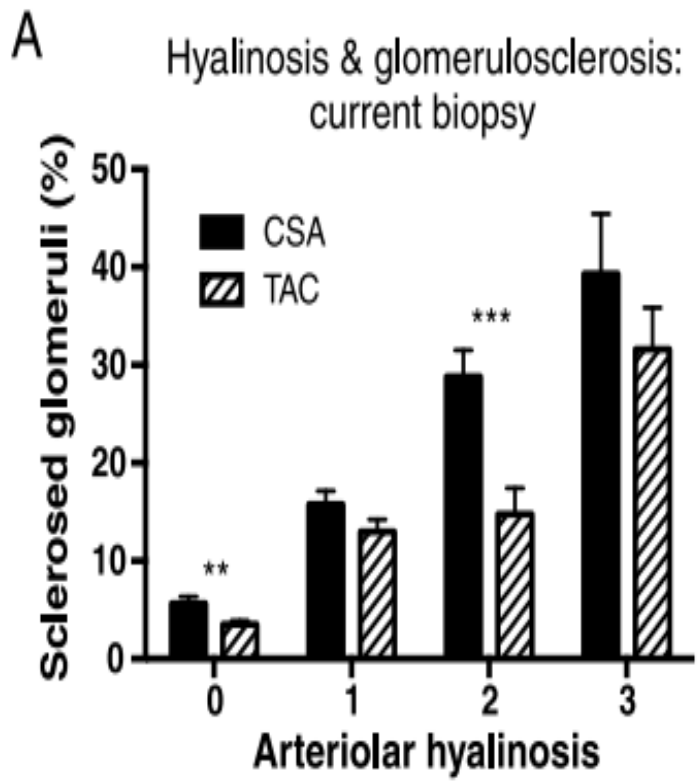
- Acute and chronic nephrotoxicity is generally similar with both cyclosporine and tacrolimus
- tacrolimus has less nephrotoxicity with lower doses without compromising overall outcomes
- Tacrolimus can also cause hyperkalemia, hyperuricemia, gout, and rarely the hemolytic-uremic syndrome
- The mechanism of potassium retention is similar to that described above for cyclosporine : relatively selective inhibition of Na-K-ATPase in the cortical collecting tubule

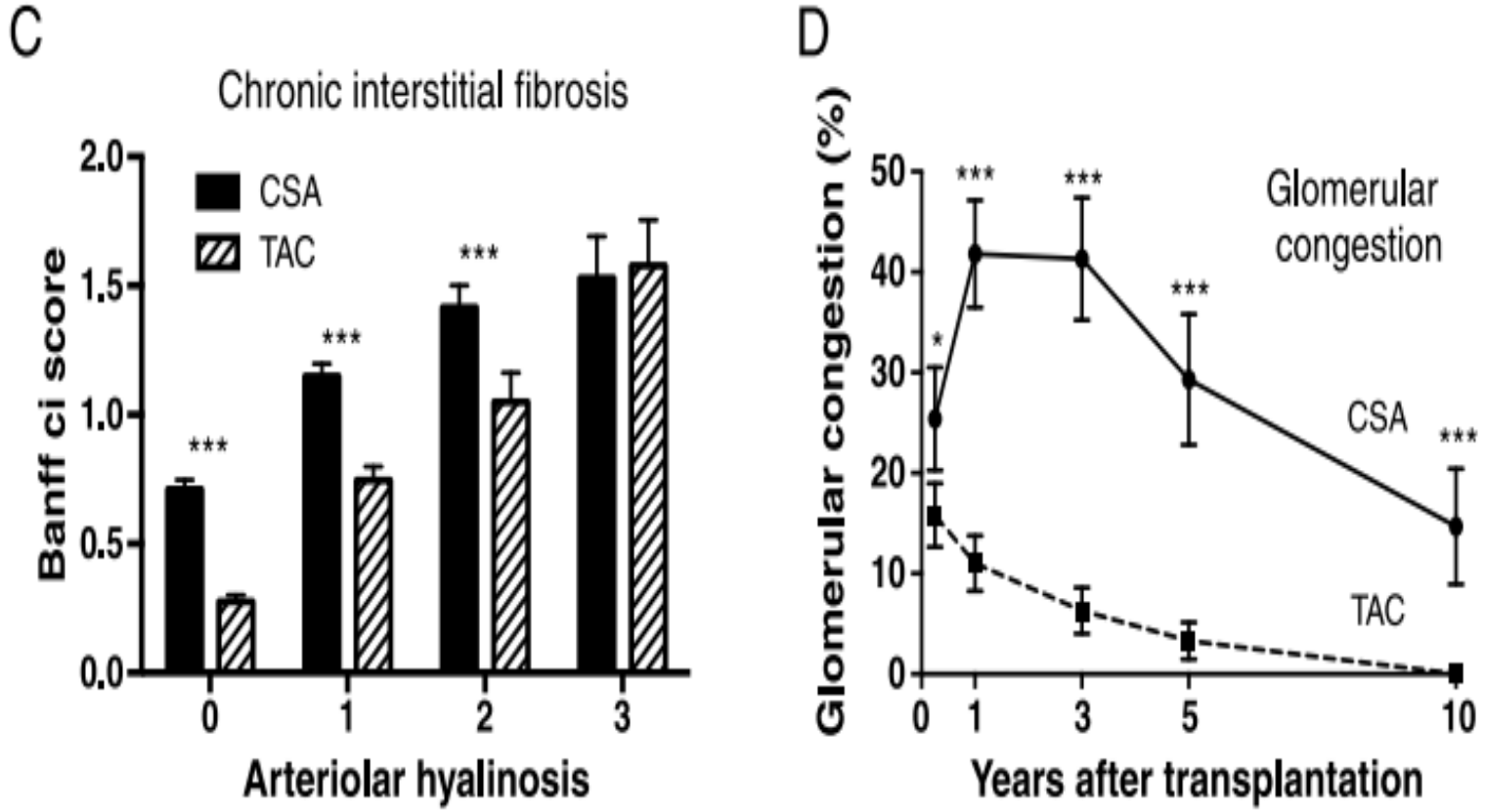
Original Clinical Science—General

# Calcineurin Inhibitor Nephrotoxicity Through the Lens of Longitudinal Histology: Comparison of Cyclosporine and Tacrolimus Eras

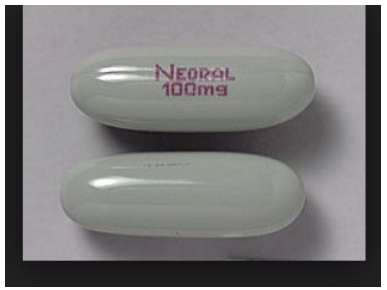
Brian J. Nankivell, MD, MSc, PhD, MRCP (UK), FRACP,[1] Chow H. P'Ng, FRCPA,[2] Philip J. O'Connell, FRACP,[1] and Jeremy R. Chapman, FRACP[1]

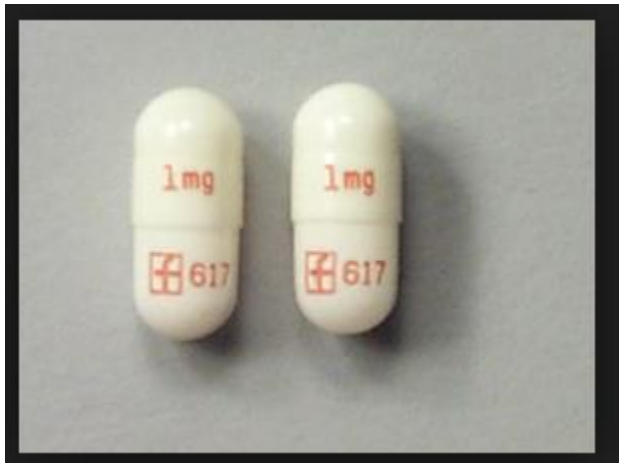
Transplantation ■ August 2016 ■
Volume 100 ■ Number 8


A
Hyalinosis & glomerulosclerosis:
current biopsy
Sclerosed glomeruli (%)
50
40
30
20
10
0
CSA
TAC
**
***
0
1
2
3
Arteriolar hyalinosis


C
Chronic interstitial fibrosis
Banff ci score
2.0
1.5
1.0
0.5
0.0
CSA
TAC
***
***
***
0
1
2
3
Arteriolar hyalinosis
D
Glomerular congestion (%)
50
40
30
20
10
0
Glomerular congestion
*
***
***
***
***
CSA
TAC
0
1
3
5
10
Years after transplantation

# Prevention and Treatment of CNI Nephrotoxicity



# Reduced exposure to calcineurin inhibitors

frontiers in Medicine

MINI REVIEW
published: 24 November 2017
doi: 10.3389/fmed.2017.00210

Check for updates

# Does Mineralocorticoid Receptor Antagonism Prevent Calcineurin Inhibitor-Induced Nephrotoxicity?

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[1] *Department of Nephrology, Odense University Hospital, Odense, Denmark,* [2] *Department of Clinical Research, University of Southern Denmark, Odense, Denmark*

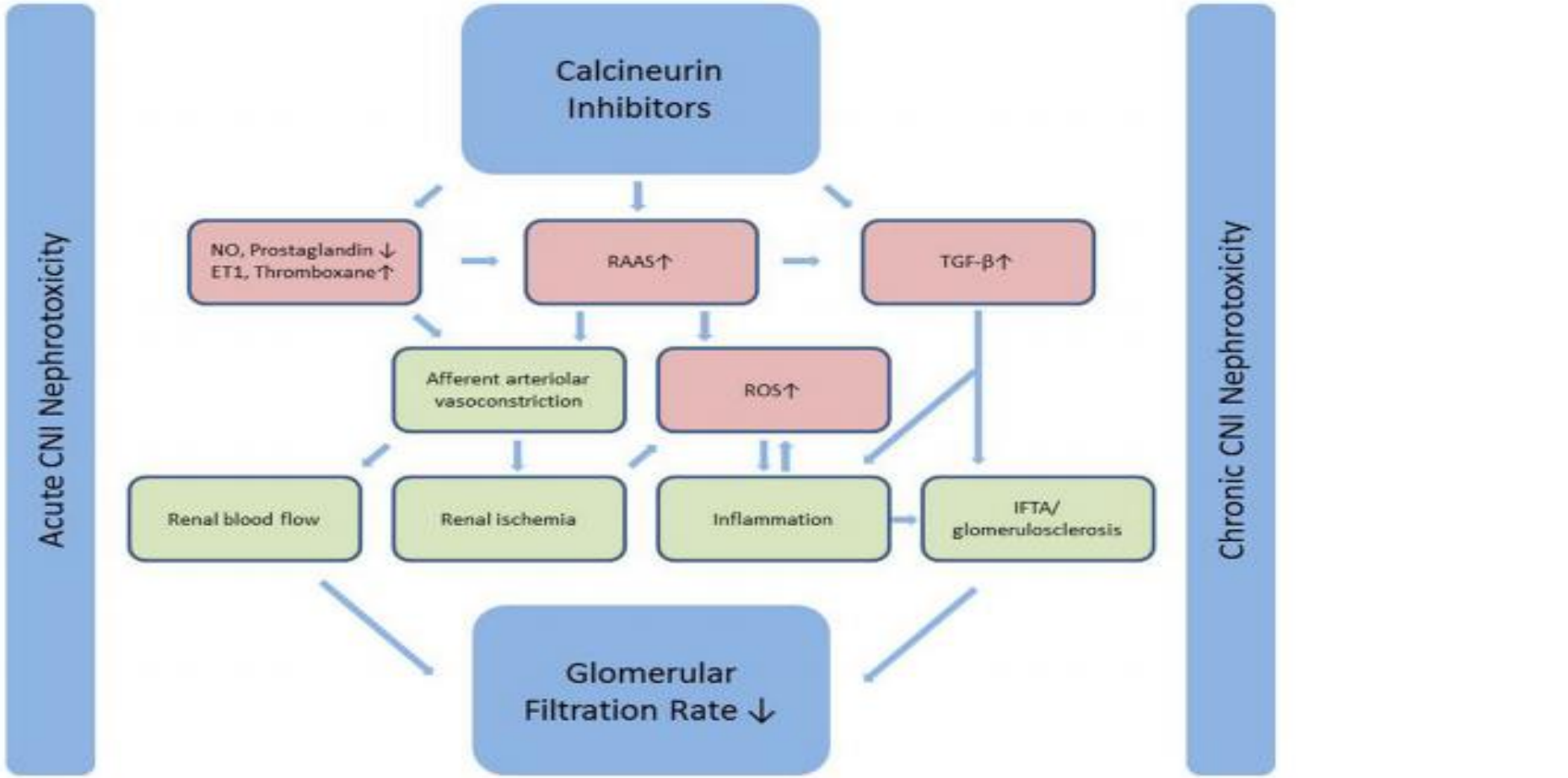


**FIGURE 1** | Calcineurin inhibitors induce afferent arteriolar vasoconstriction through an effect on both mediators of endothelial dysfunction and a direct stimulator

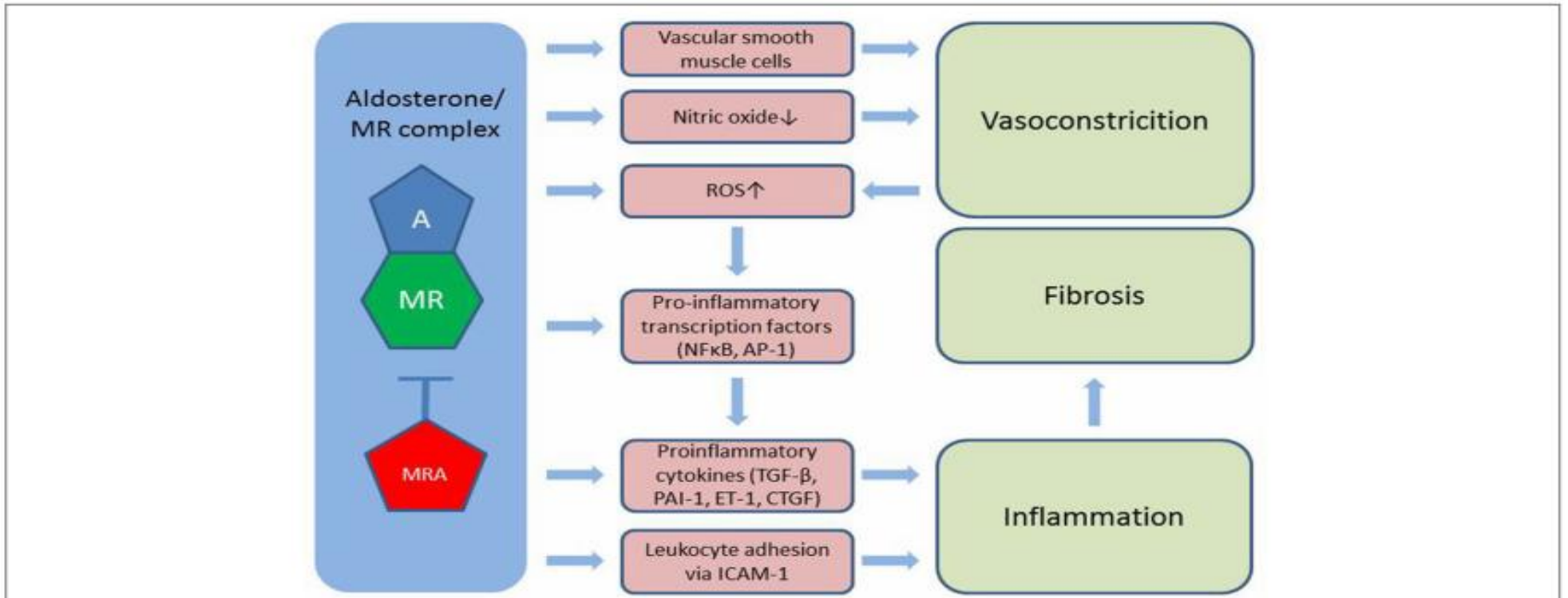


**FIGURE 2 |** Aldosterone induces vasoconstriction *via* MR in vascular smooth muscle cells and through reduced bioavailability of nitric oxide. Also, aldosterone stimulates the formation of ROS further worsened by vasoconstriction. Activation of pro-inflammatory transcription factors as well as the direct stimulation of cytokines and leukocyte adhesion to the vessel wall leads to inflammation, which contributes to tissue fibrosis. A, aldosterone; MR, mineralocorticoid receptor; MRA, MR antagonist; ROS, reactive oxygen species; TGF-β, transforming growth factor β; PAI-1, plasminogen activator inhibitor 1; ET-1, endothelin 1; CTFG, colony transforming growth factor; ICAM-1, intercellular adhesion molecule 1; NFκβ, nuclear factor κβ; AP-1, activator protein 1.

- This review summarizes current evidence of mineralocorticoid receptor antagonism in animal models of calcineurin inhibitor-induced nephrotoxicity and the results from studies of mineralocorticoid antagonism in renal transplant patients


Therapies with unclear benefit

# PREVENTION OF CHRONIC CALCINEURIN INHIBITOR NEPHROTOXICITY

- Fish oil
- Calcium channel blockers
- Pentoxifylline
- Other

## Fish oil

- The fish oils, which contain omega-3 fatty acids, may act by competitively reducing thromboxane synthesis, thereby diminishing cyclosporine-induced vasoconstriction and hypertension, and by direct immunosuppressive actions, such as decreasing the generation of cytokines

# Calcium channel blockers

- Animal and human data suggest that concurrent administration of calcium channel blockers may be protective against cyclosporine nephrotoxicity, at least in part by minimizing renal vasoconstriction

# Renin-angiotensin system inhibitors

- Although studies in animals have shown that ACE inhibitors and angiotensin receptor blockers (ARBs) can prevent cyclosporine-induced interstitial fibrosis and improve kidney function , studies in humans have not demonstrated a clear benefit

# Therapies with no benefit

- **Pentoxifylline**
- **Thromboxane synthesis inhibitor**

*Biomedical Research and Therapy, 5(12):2888-2897*

*Original Research*

# Cyclosporine-A induced nephrotoxicity in male and female rats: Is zinc a suitable protective supplement?

Samira Choopani[1], Sayyedehnikta Kasaei[1], Ardeshir Talebi[1,2], Mojgan Mortazavi[3], Yousef Gheisari[4], Mohammad Matinfar[3], Mehdi Nematbakhsh[1,5,6,*]

# Methods

- Male and female rats were treated with 10, 50 or 100 mg/kg/day of CYC alone or accompanied with 10 mg /kg/day of Zn sulfate for 10 days.
- The parameters related to renal function were determined and the kidney tissues were subjected to histological evaluation.

# *CONCLUSIONS*

- The high dose of CYC (100 mg/kg) demonstrated the highly toxic effect.
- No animals survived on the last day of experiment, and the other dose of CYC induced nephrotoxicity gender dependently.
- However, the 10 mg/kg of Zn sulphate as a supplement may prevent induced nephrotoxicity in males, possibly due to its antioxidant effects

# SUMMARY AND RECOMMENDATIONS

- Several factors may contribute to the risk of CNI nephrotoxicity, including high doses of cyclosporine or tacrolimus; older age of donated kidney; concomitant use of nephrotoxic drugs, particularly nonsteroidal antiinflammatory drugs (NSAIDs); salt depletion and diuretic use; drugs that inhibit cytochrome P-450 3A4/5 (CYP3A/5) or P-glycoprotein; and genetic polymorphisms in the genes encoding CYP3A4/5 (*CYP3A4/5*) and P-glycoprotein (*ABCB1*).

# SUMMARY AND RECOMMENDATIONS

- Acute CNI nephrotoxicity commonly presents as an acute but typically reversible functional renal impairment and rarely as a thrombotic microangiopathy
- Chronic CNI nephrotoxicity manifests as a chronic progressive deterioration in kidney function