Exploration de l'insuffisance rénale aiguë survenant sous antibiothérapie : imputabilité

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Journée Régionale
de Pathologie Infectieuse 2025

Conflits d’intérêt

Une problématique importante

- IRA chez les patients hospitalisés = 60% d'origine médicamenteuse
- Antibiotiques +++
- Surrisque de morbi-mortalité et surrisque de MRC

Mécanismes de l’IRA

1) Néphrite interstitielle aiguë

2) Atteinte tubulaire

- Toxicité tubulaire directe
- Néphropathies cristallines

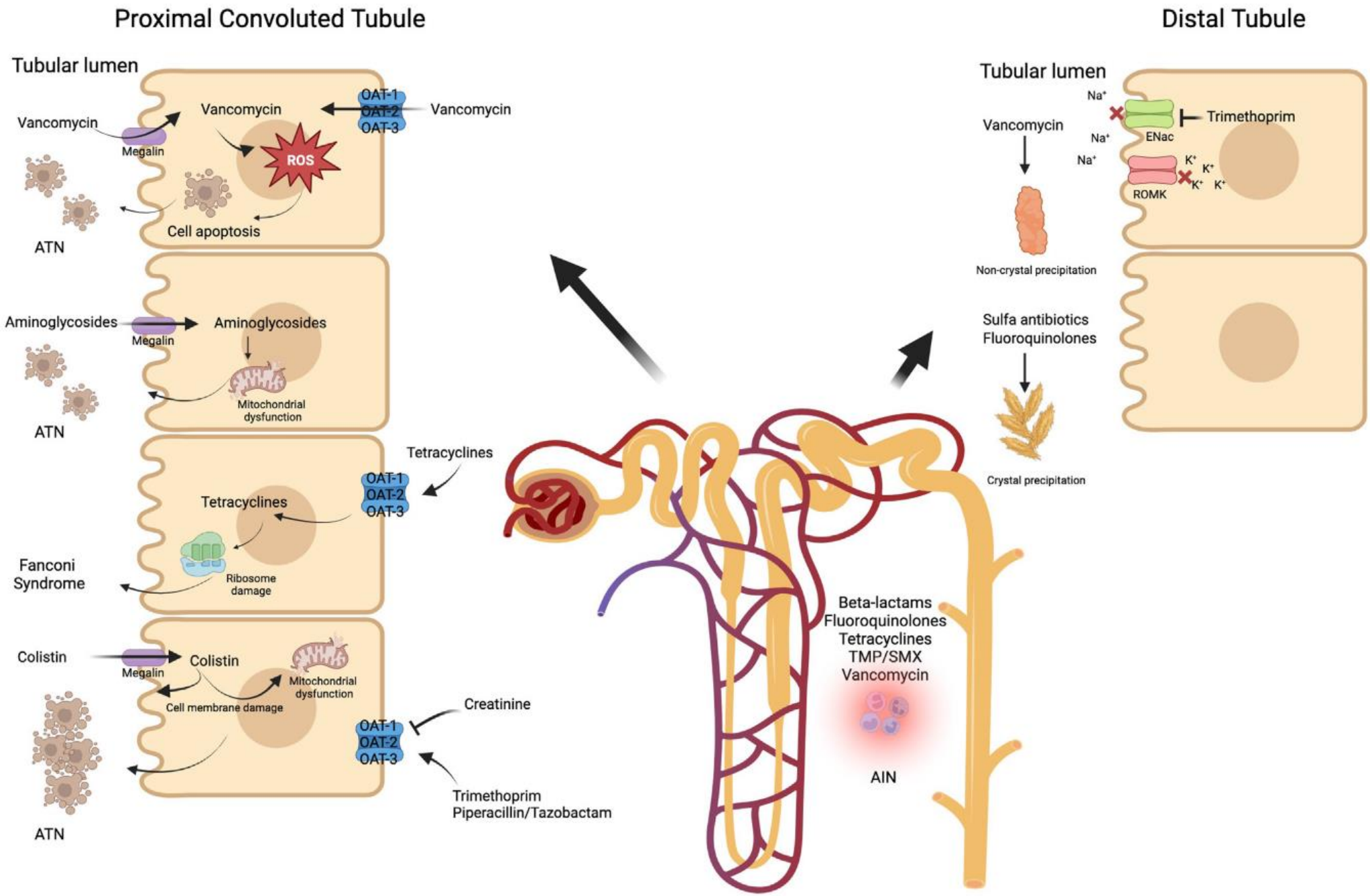

Figure 1. Mechanisms of antibiotic-induced nephrotoxicity. ATN, acute tubular necrosis.

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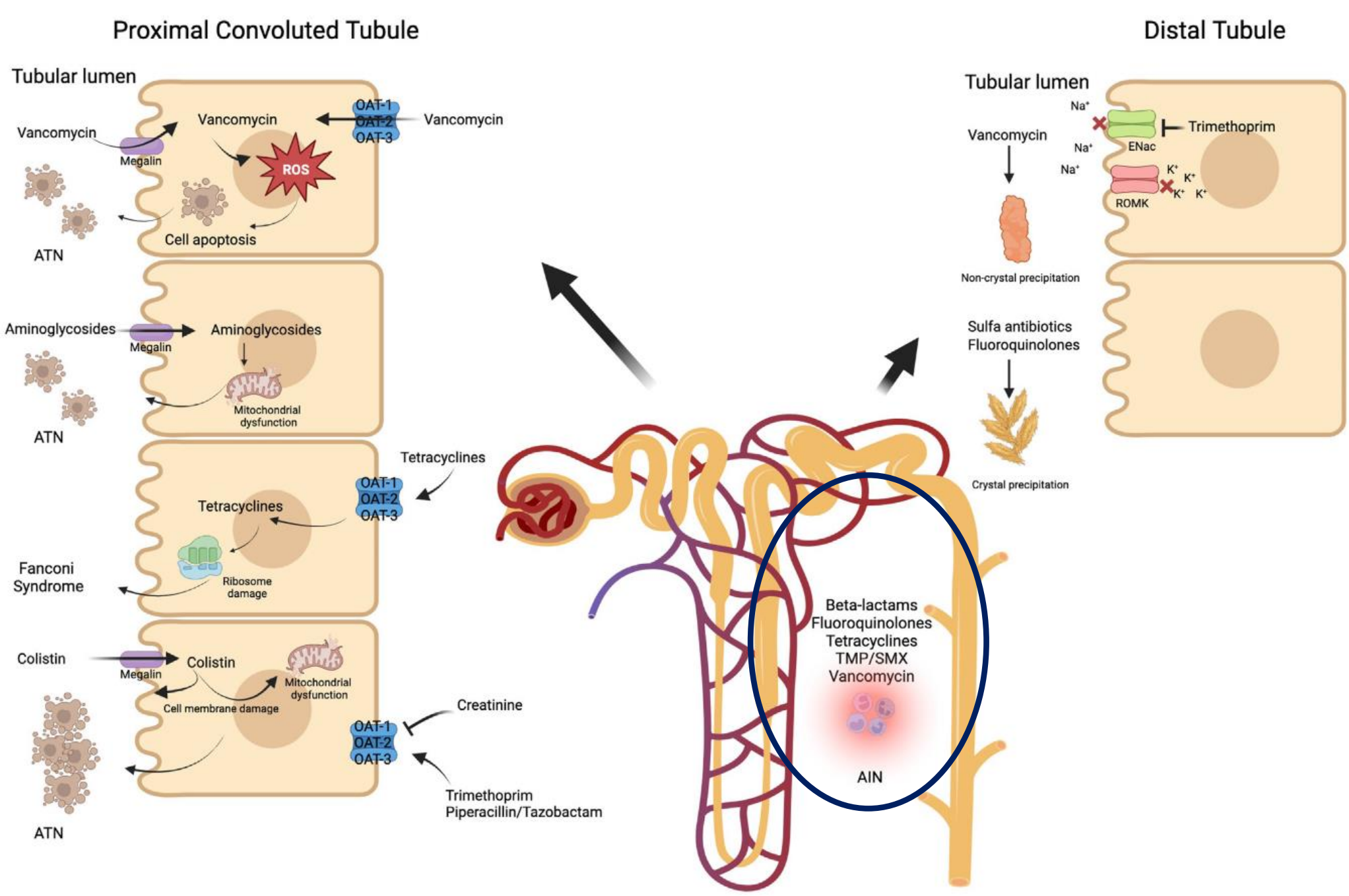

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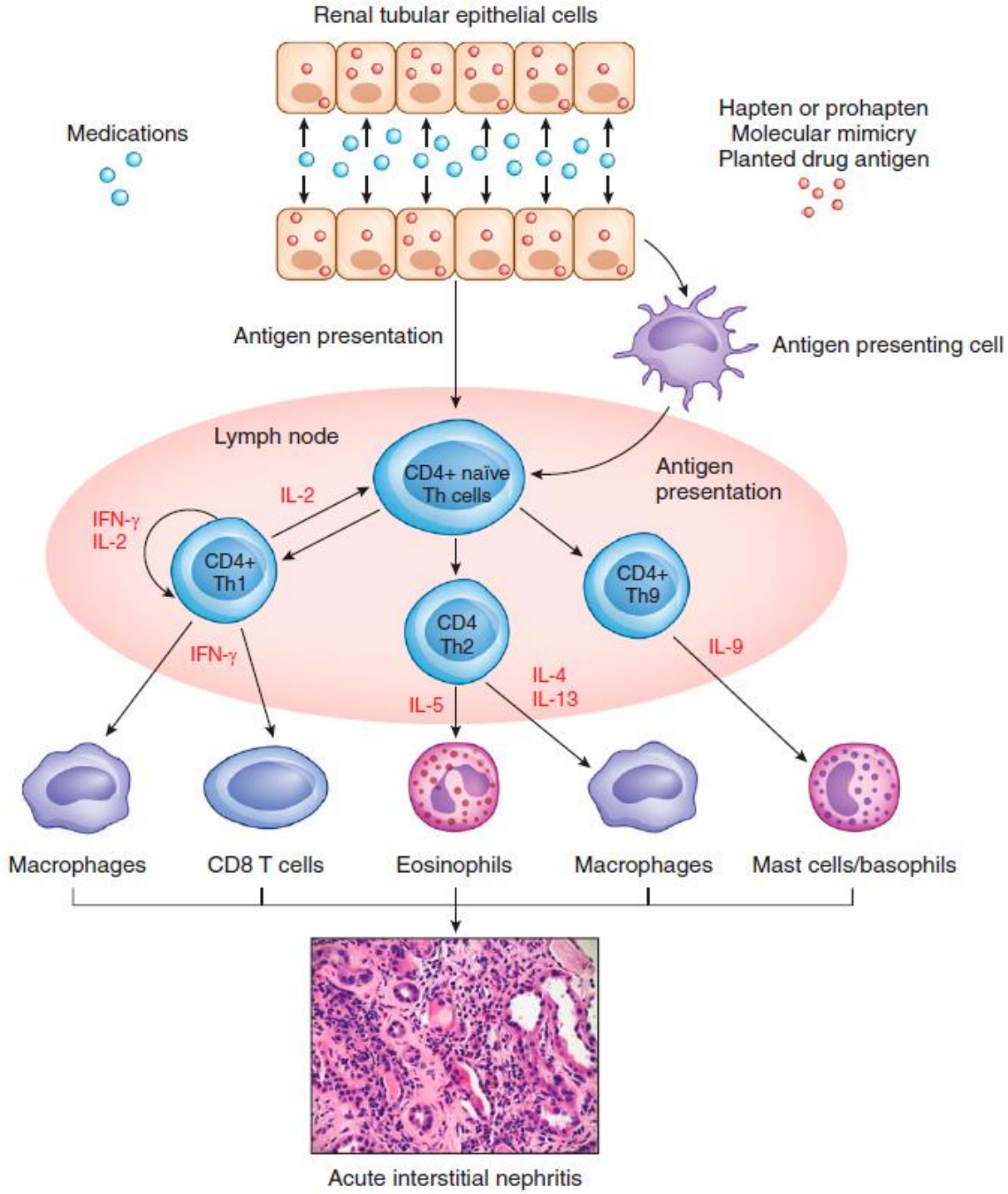
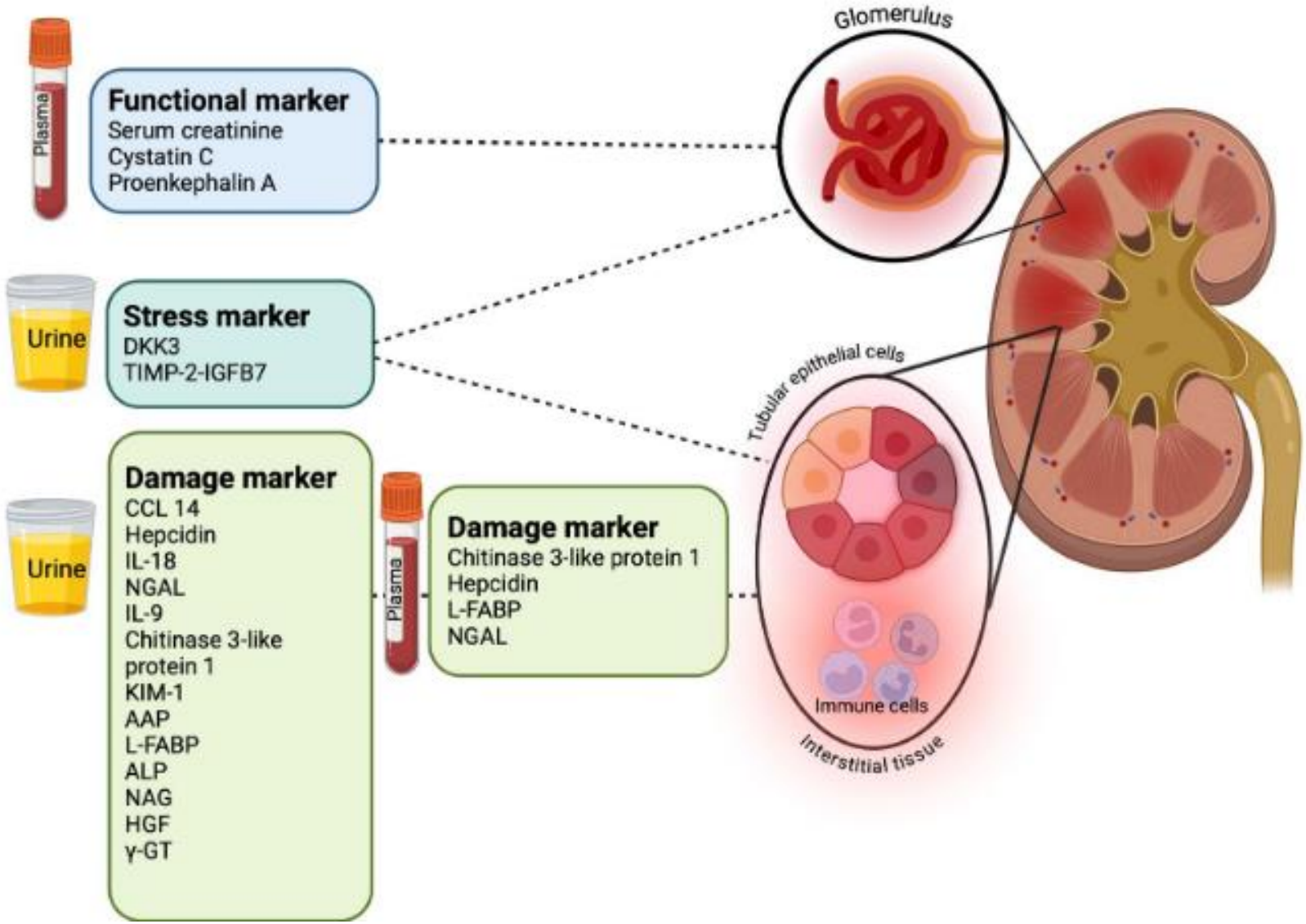
- AIN = delayed T cell-mediated (type IV) hypersensitivity reaction that occurs after exposure to a culprit drug
- Antibiotiques = 50% des AIN
- Classic but rare : allergic features such as rash, fever, and eosinophilia
- Leucocyturie fréquente (>50%), éosinophilurie finalement peu discriminante
- Diagnostic = Biopsie rénale
- Arrêt médicament en cause, corticothérapie discutée





Ostermann et al. Annals of Intensive Care

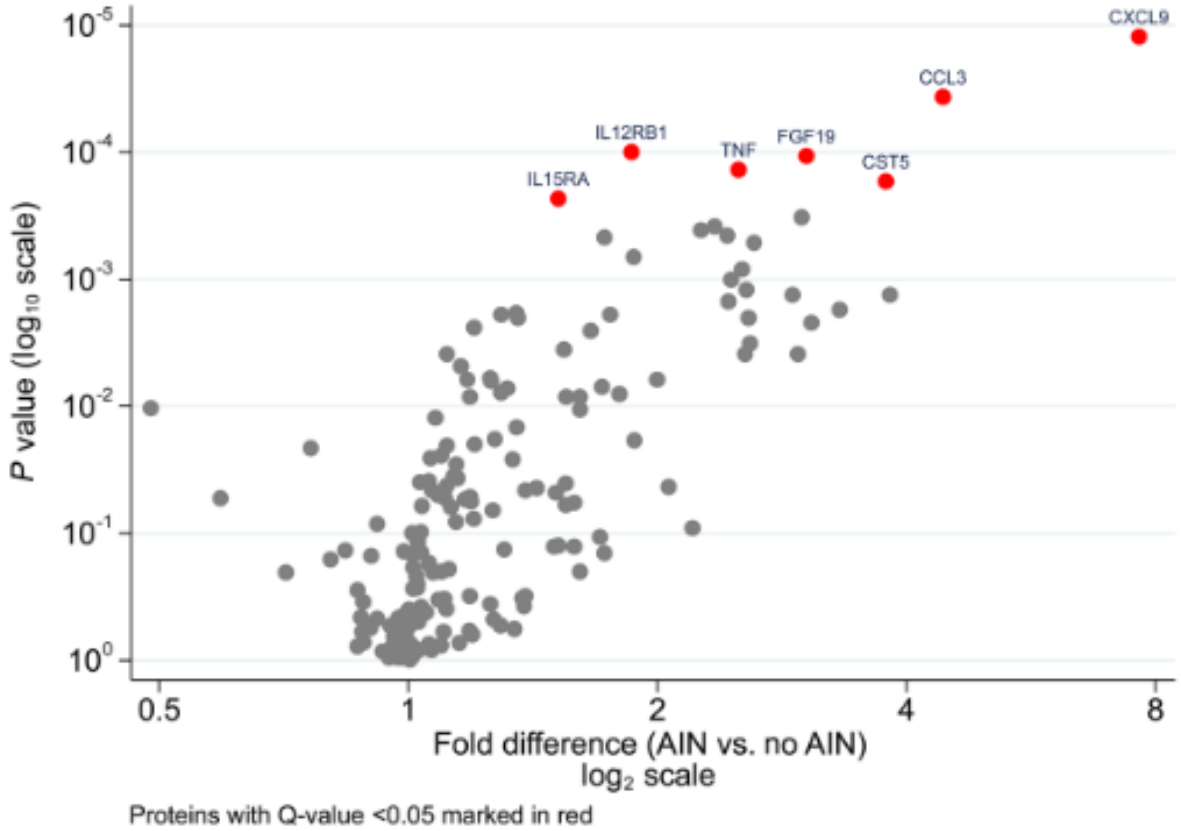


Figure 1. Volcano plot demonstrating associations of proximity extension measurement of urine proteins with acute interstitial nephritis diagnosis. Proteins with Q values of less than 0.05 using the Benjamini-Hochberg procedure are highlighted in red.

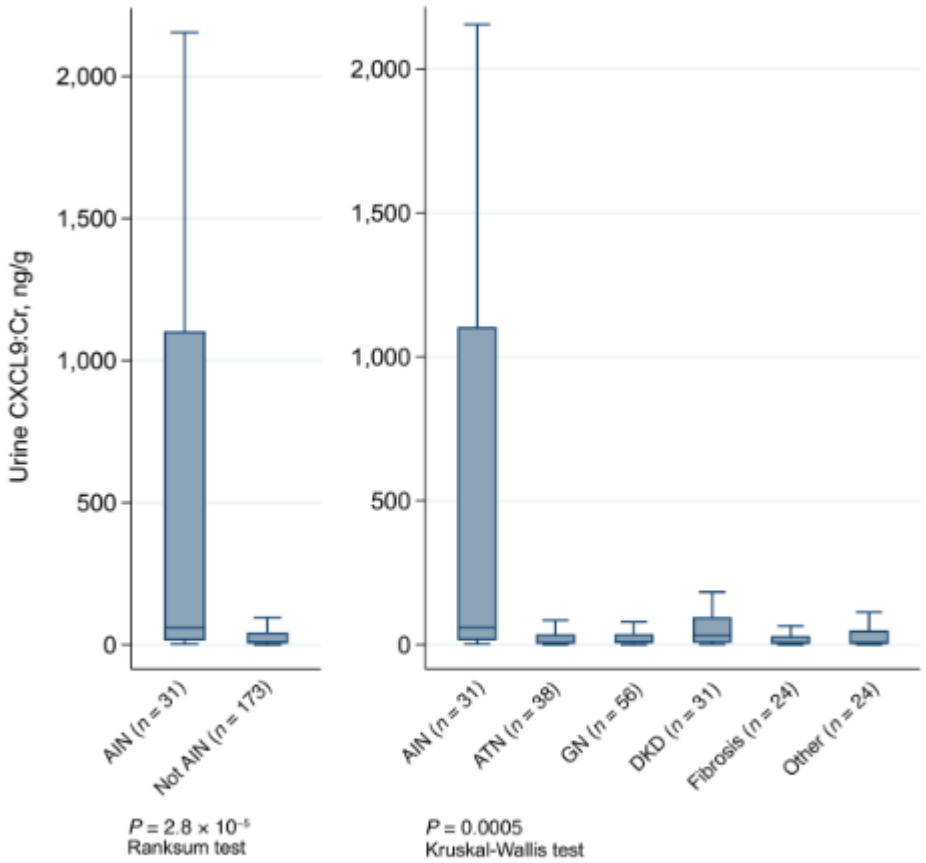


Figure 2. Urine CXCL9 levels are higher in acute interstitial nephritis compared with controls in the discovery cohort. Box and whisker plots of CXCL9 by presence or absence of AIN (left panel) and by histological diagnosis in the discovery cohort (right panel). Boxes represent interquartile range and horizontal line within box represents median. Median and interquartile range values are presented in Table 2.

Moledina et al. JCI

ORIGINAL ARTICLE

The use of gallium-67 scintigraphy in the diagnosis of acute interstitial nephritis

François Graham[1,2], Martin Lord[3], Daniel Froment[2], Héloise Cardinal[2], and Guillaume Bollée[2]

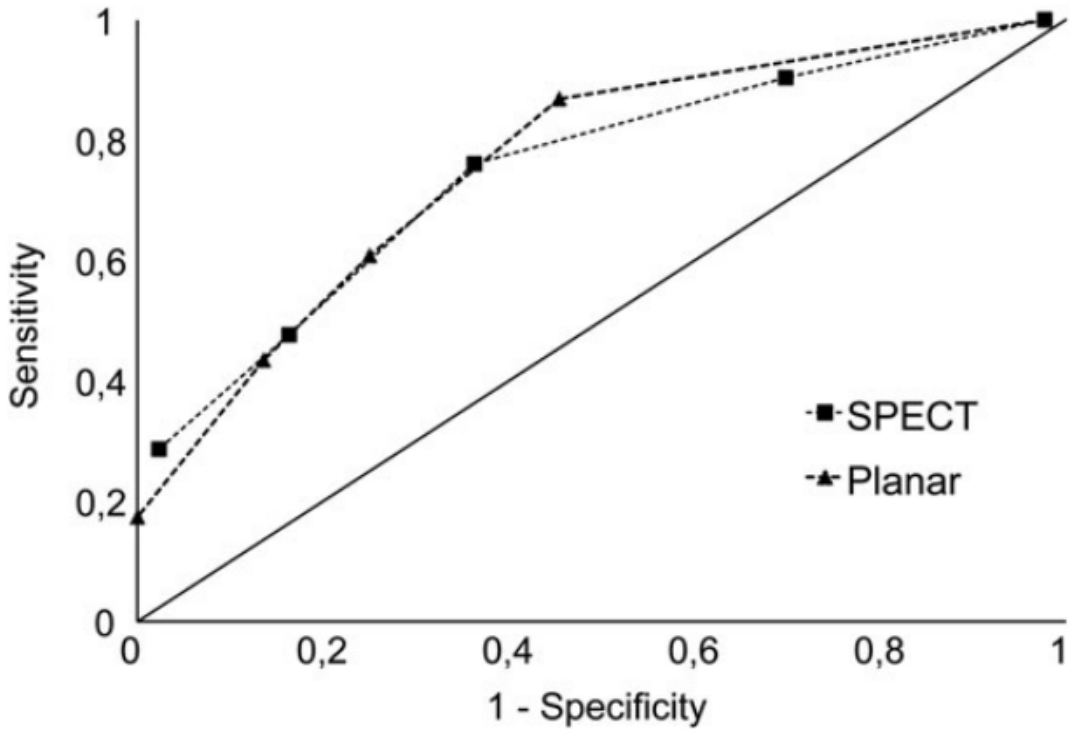
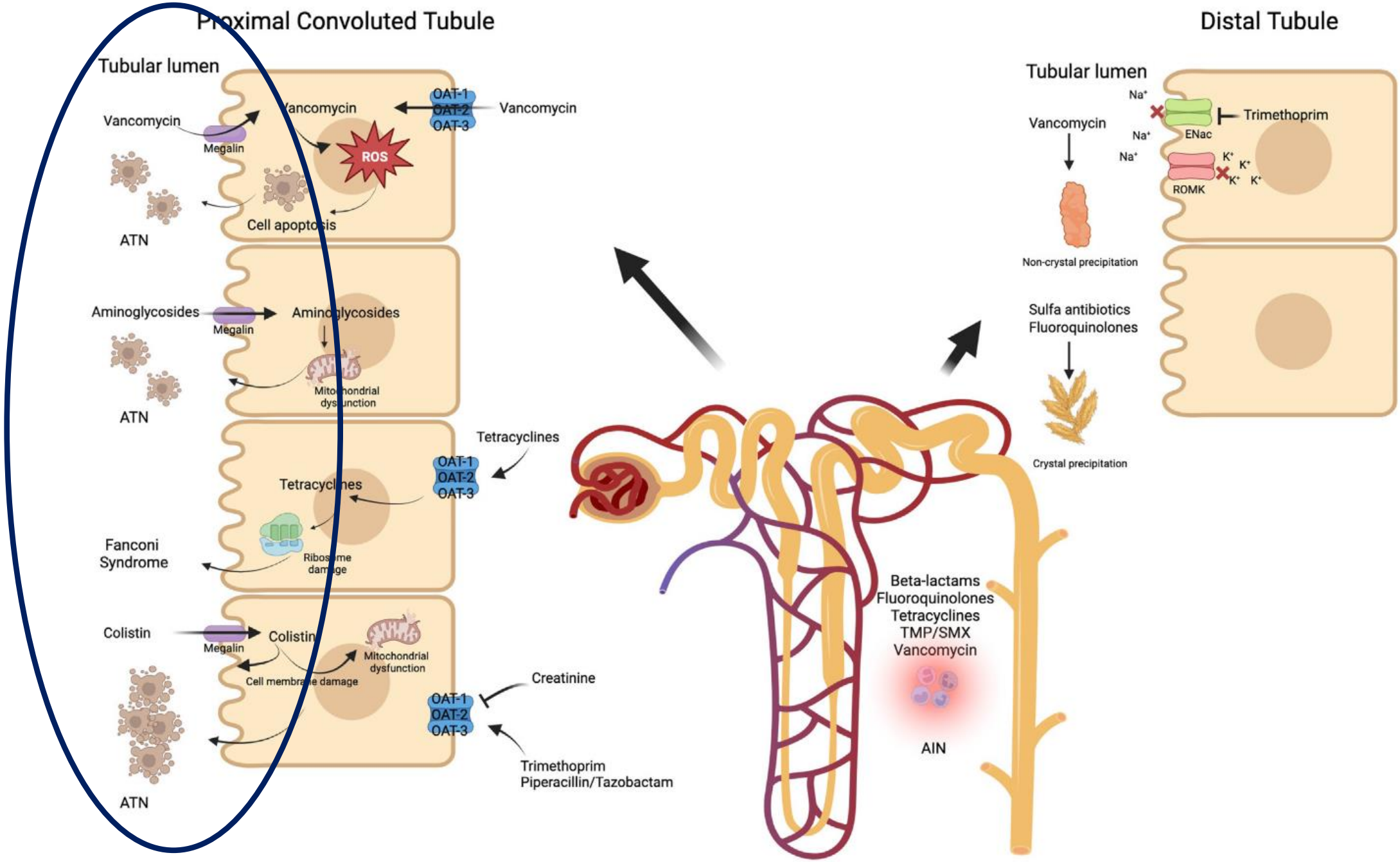


Fig. 2. ROC illustrating the diagnostic performance of posterior planar and SPECT imaging for the assessment of AIN.



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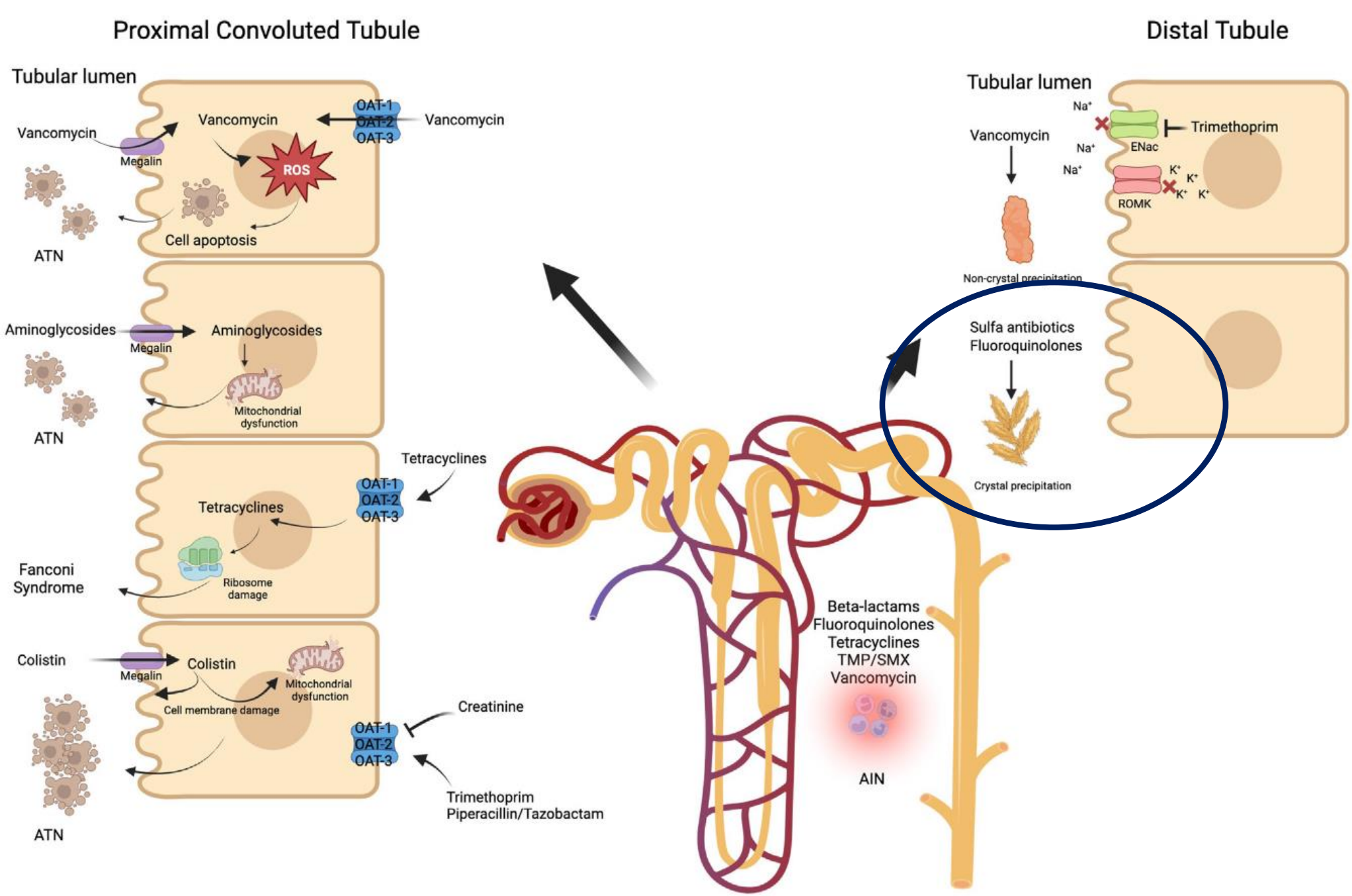
NTA – l'exemple des aminoglycosides

- Nephrotoxicity occurs with frequent repeat dosing, which leads to increased accumulation of the antibiotic in the renal parenchyma
- Endocytose médiée par la Megaline
- Perturbe la synthèse protéique et la fonction mitochondriale
- Relation directe entre les concentrations plasmatiques et au niveau du cortex rénal
- NTA, vers J5-J7, parfois tubulopathie proximale



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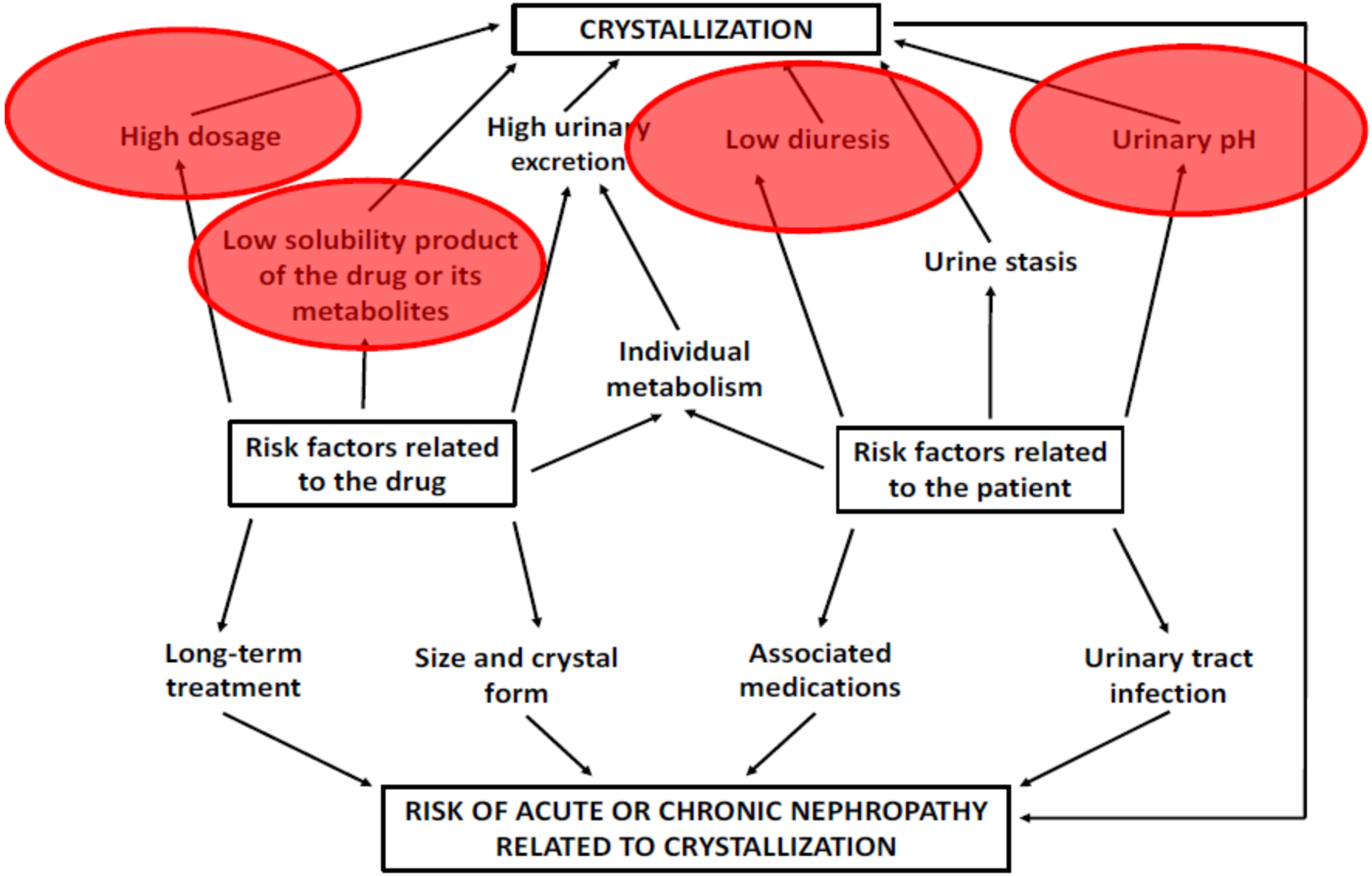

Frochot et al, 2016

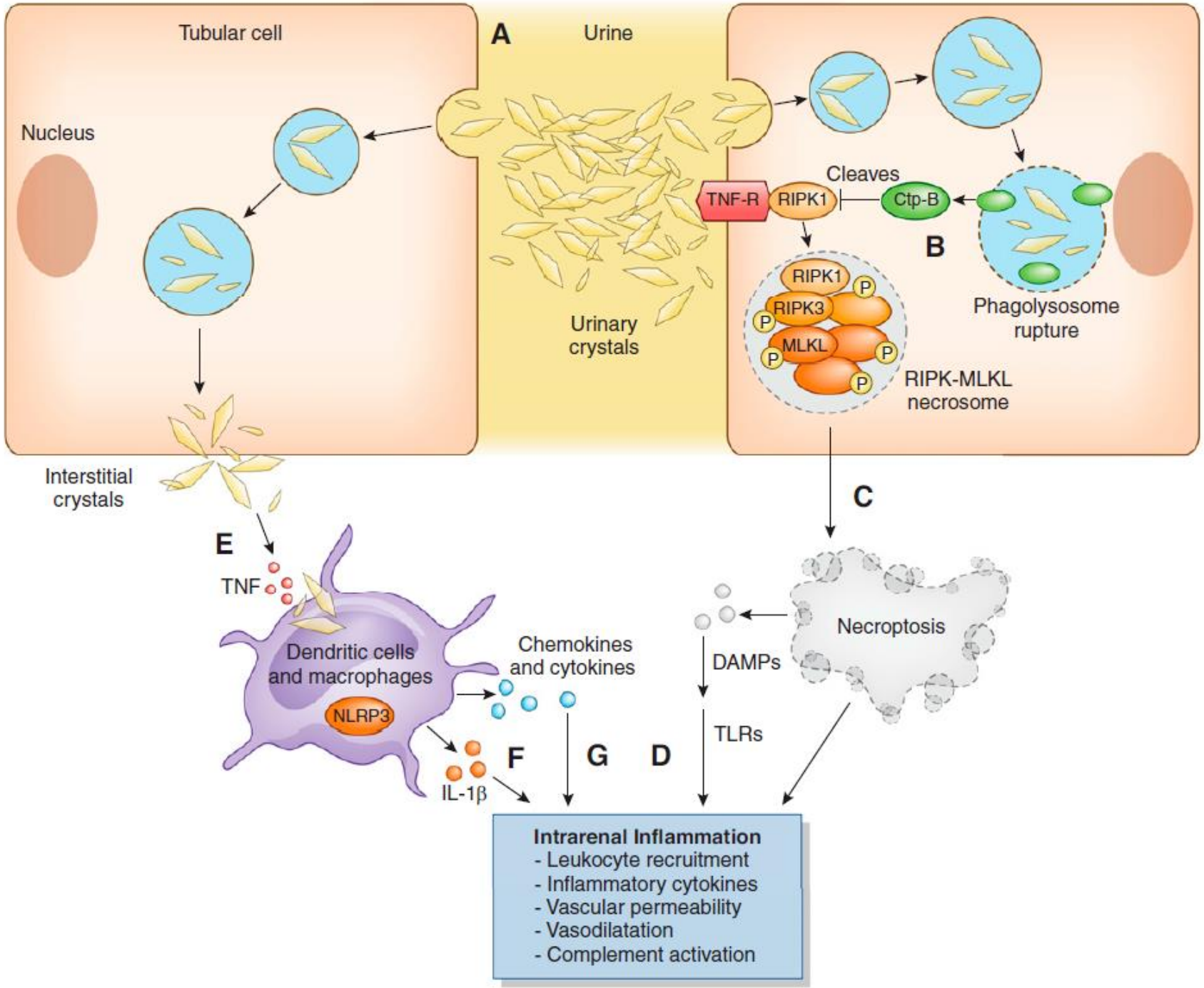

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Table 1. Crystalline nephropathies associated with various medications

Medication	Urinary crystal morphology	Clinical renal findings	Histologic findings of the kidney	Preventive measures[a]
Sulfadiazine, sulfamethoxazole	Shocks or sheaves of wheat, shells, or dumbbells Positively birefringent on polarization	Crystalluria, nephrolithiasis, AKI, and CKD	Mild mononuclear inflammation and interstitial fibrosis noted without sulfa crystals present within tubules or interstitium	Alkalinize urine; adjust dose for kidney function; assure euvolemia before drug exposure
Methotrexate	Annular shapes, yellow, golden, or brown Positively birefringent on polarization	Crystalluria, AKI, and CKD	Annular structures consisting of small needle-shaped crystals that stain yellow, golden, or brown on H&E stain, weak rim staining on PAS, black staining on JS Positively birefringent on polarization	IVFs before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarpidase if toxic level (<60 h after methotrexate exposure)
Indinavir, atazanavir, darunavir	Needle, rectangle, fan-shaped or starburst aggregates Positively birefringent on polarization	Crystalluria, nephrolithiasis, AKI, and CKD	Needle-shaped (translucent) indinavir, atazanavir, or darunavir crystals within tubules with an associated monocytic infiltrate and giant-cell reaction	No role for urine acidification; assure euvolemia during drug therapy; switch to different medication
Acyclovir	Thin needles with sharp or blunt ends Positively birefringent on polarization	Crystalluria, leukocyturia, AKI, and CKD	Needle-shaped crystals within tubules ± peritubular inflammation Positively birefringent on polarization	Avoid rapid i.v. bolus; adjust drug dose for kidney function; assure euvolemia during drug therapy
Triamterene	Brown, green, orange, and red spheres Positive birefringence and Maltese cross	Crystalluria, nephrolithiasis, AKI, and CKD	Crystals stain yellow/brown on H&E and PAS, silver positive on JS Strongly birefringent on polarization	Alkalinize urine; assure euvolemia during drug therapy
Ciprofloxacin, levofloxacin	Needles, stars, fans, or sheaves Positively birefringent on polarization	Crystalluria and AKI	Needle-shaped crystals within tubules Strongly birefringent on polarization	Assure euvolemia during drug therapy and avoid alkaline urine (if possible)
Amoxicillin	Thin needles, broom/brush-like Positively birefringent on polarization	Crystalluria and AKI	No histologic evidence of intrarenal deposits of amoxicillin crystals has been described on kidney biopsy findings	Assure euvolemia; adjust drug dose for kidney function
I.v. ascorbic acid, orlistat (by causing enteric hyperoxaluria), ethylene glycol	Calcium oxalate -Monohydrated: ovoid, dumbbells, or rods -Bihydrated: bipyramidal shapes Positively birefringent on polarization	Crystalluria, AKI, and CKD	Crystals are translucent to pale blue fan-like or sunburst shapes within tubules and interstitium with interstitial inflammation Positively birefringent on polarization	Ascorbic acid and orlistat: assure euvolemia during drug therapy, avoid other nephrotoxins; fomepizole ± HD for ethylene glycol
Foscarnet	Crystals as plates and geometric shapes Positively birefringent on polarization	Hematuria, proteinuria, AKI, and CKD	Plates and geometric shapes in dilated capillary loops and tubular lumens Positively birefringent on polarization	Assure euvolemia during drug therapy and adjust drug dose for kidney function
Sodium phosphate purgative (oral rather than enema)	Calcium phosphate; white, amorphous, granular structures	AKI and CKD	Granular bluish-purplish crystal deposits with positive von Kossa staining Negative birefringence on polarization	Assure euvolemia before exposure; avoid concomitant NSAIDs, diuretics, and RAS blockers

AKI, acute kidney injury; CKD, chronic kidney disease; H&E, hematoxylin and eosin; HD, hemodialysis; IVF, i.v. fluid; JS, Jones methenamine silver; NSAID, nonsteroidal anti-inflammatory drug; PAS, periodic acid–Schiff; RAS, renin-angiotensin system.
[a]Therapy includes medication discontinuation, administration of i.v. fluids for hypovolemia, and provision of supportive care, including hemodialysis.

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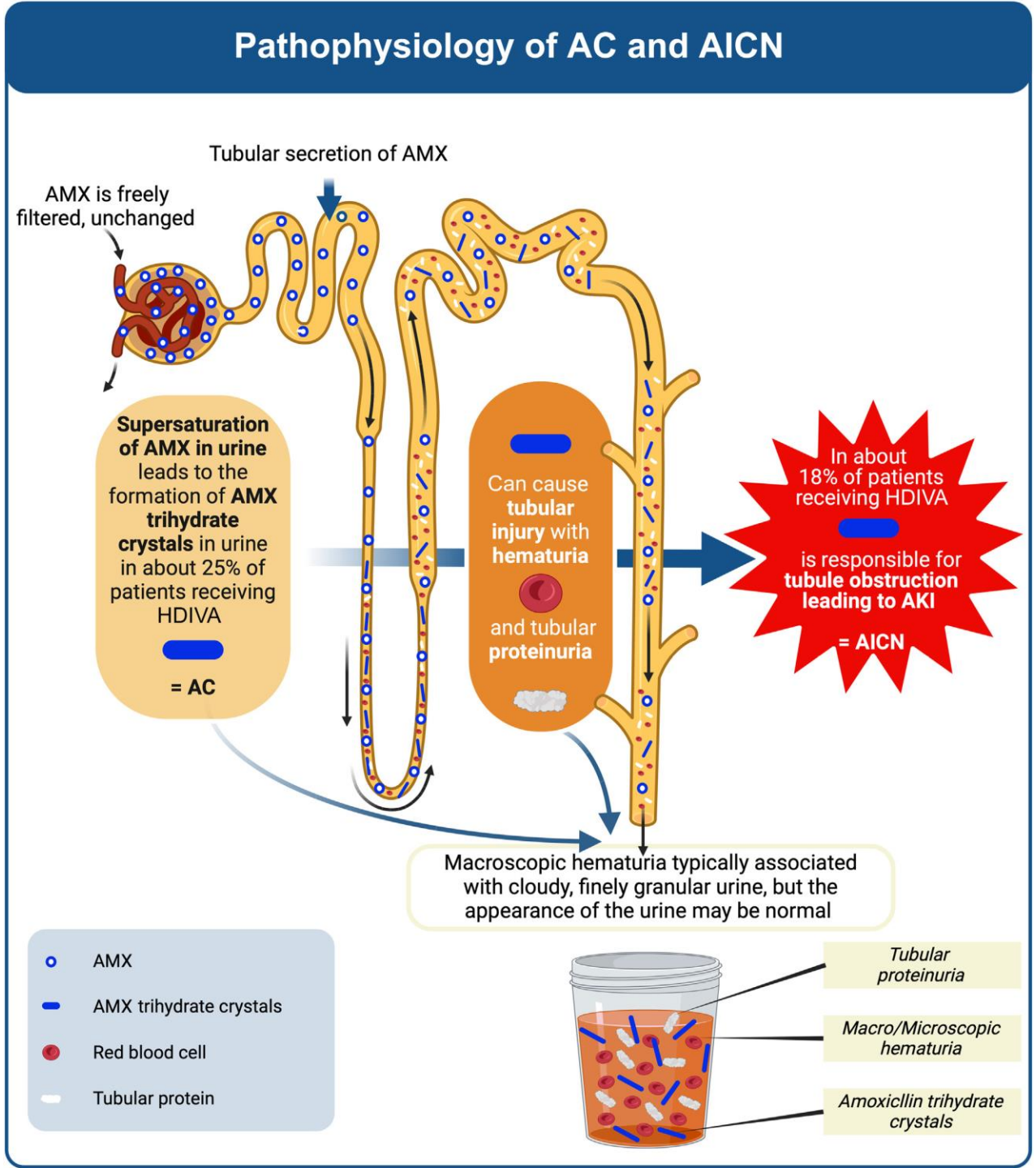
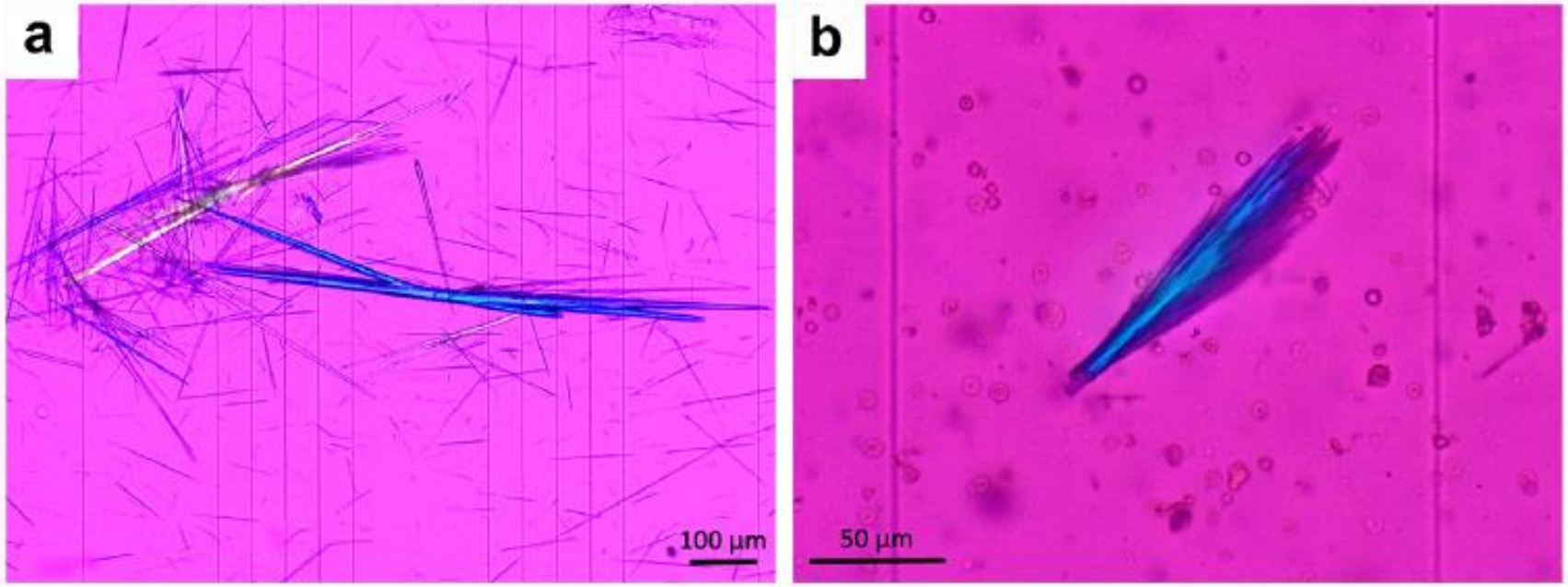


Vodovar et al. KI 2025



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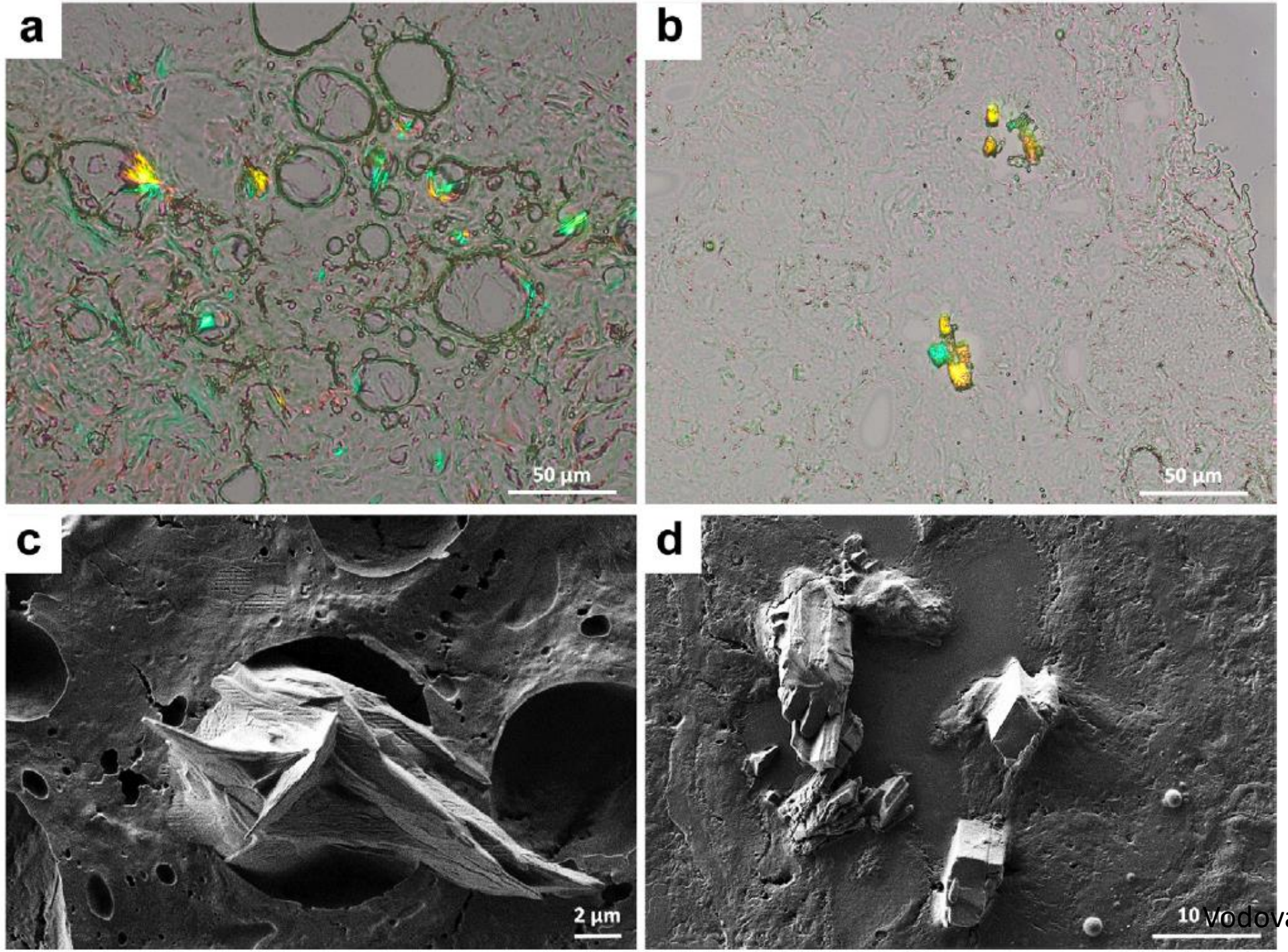


Vodovar et al. KI 2025

Step by step diagnosis of AICN in patients treated with HDIVA

AKI in a patient receiving HDIVA ?

- No → **No AICN**
- Yes → **AKI occurs after initiation** of HDIVA ?
  - No → **No AICN**
  - Yes → **Sudden macroscopic hematuria** AND **Cloudy urine** OR **AMX crystals observed with the naked eye**
    - This clinical presentation is rarely observed.
    - Yes → **AICN likely**
    - No → **Concomitant administration of nephrotoxic drugs** with a causality assessment equal to or greater than HDIVA therapy ?
      - Does not completely rule out diagnosis
      - Yes → **AICN less likely**
      - No → **Test for AC available ?**
        - Yes
          - \+ → **AICN likely**
          - \- → **AICN less likely**
            - Testing for AC can be negative if performed too earlier or to late
        - No → **Risk factors for AMX AC**
          - **Acidic urine pH**
          - **High AMX** blood levels
          - **Rapid administration** of i.v. amoxicllin
          - **Hypovolemia**
          - **Augmented renal clearance?**
          - Yes → **AICN likely**
          - No → **AICN less likely**

The most challenging step

Other causes of AKI may coexist.

Discuss the possible causes of AKI other than AICN

The **definitive diagnosis relies on the identification of AMX crystals in a kidney biopsy.**

However, this procedure is **rarely performed** in practice.

The diagnosis is therefore presumptive, at best supported by the rapid improvement in kidney function upon stopping or reducing the doses of amoxicillin.

Not related to AMX

The main challenge is to rule out the diagnosis of **sepsis-induced AKI**.

Notably,

- The concomitant development of at least new organ dysfunction(s) is more likely to suggest sepsis-induced AKI.
- The onset of AKI more than 7 d after the onset of sepsis rules out the diagnosis of sepsis-induced AKI.

Related to AMX

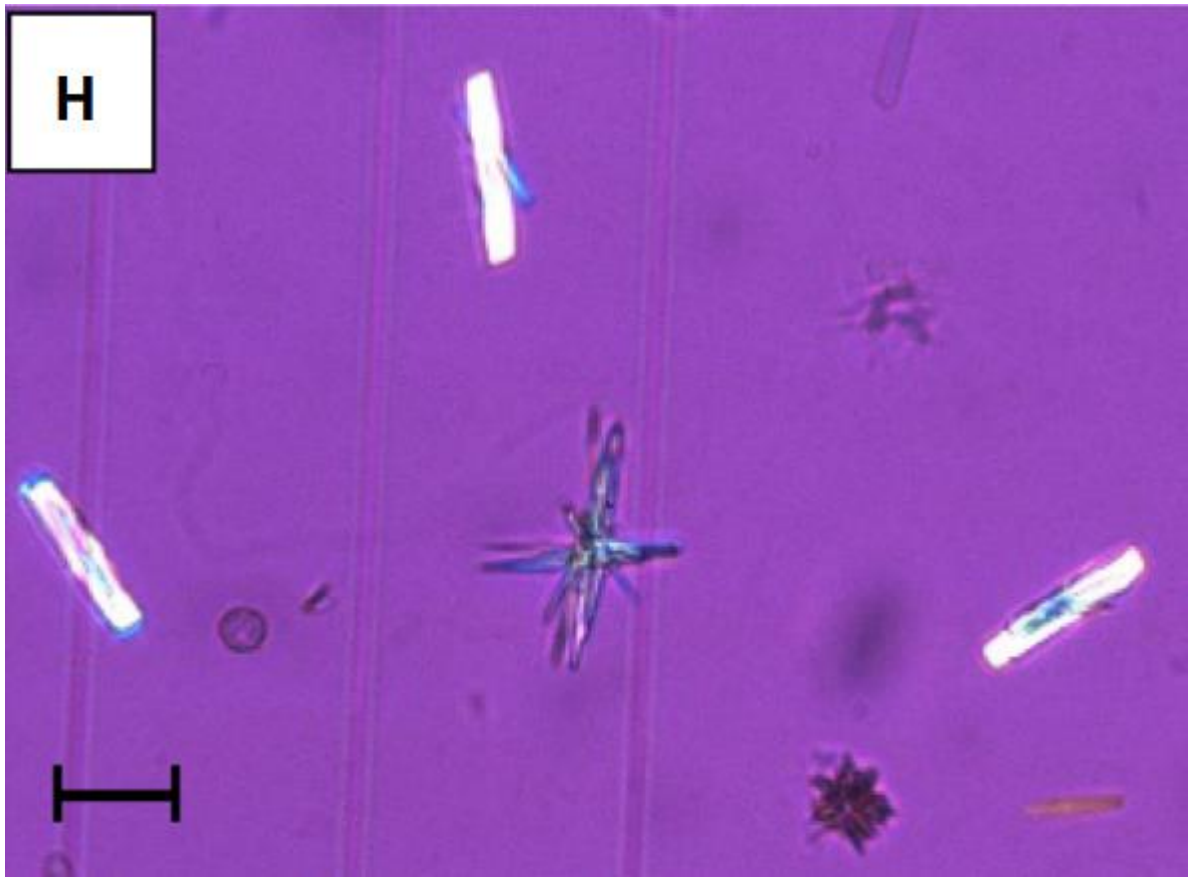
The main challenge is to rule out the diagnosis of **AMX-induced acute interstitial nephritis.** It is usually associated with extra nephrological symptoms (fever, skin rash, arthralgia) and abnormal laboratory tests (liver enzyme abnormalities, hypereosinophilia).

Much rarer, the diagnosis of AMX-induced leucocytoclastic vasculitis should be considered in the presence of purpura, arthralgia, or bowel angina.

Vodovar et al. KI 2025

Cristallurie et Quinolones

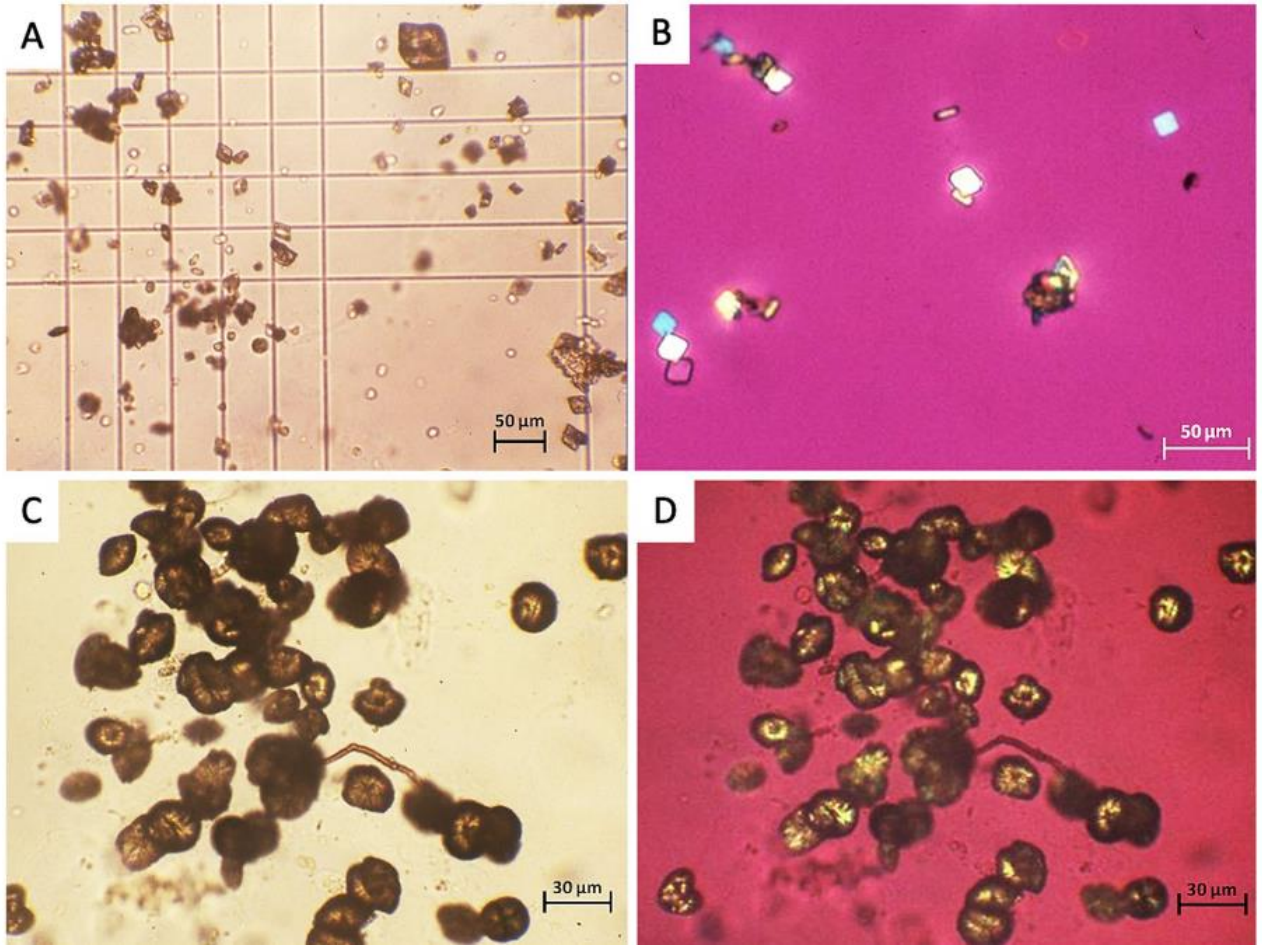
- précipite à pH alcalin
- surtout à des fortes doses
- Biréfringent en lumière polarisée



Daudon Drugs 2018

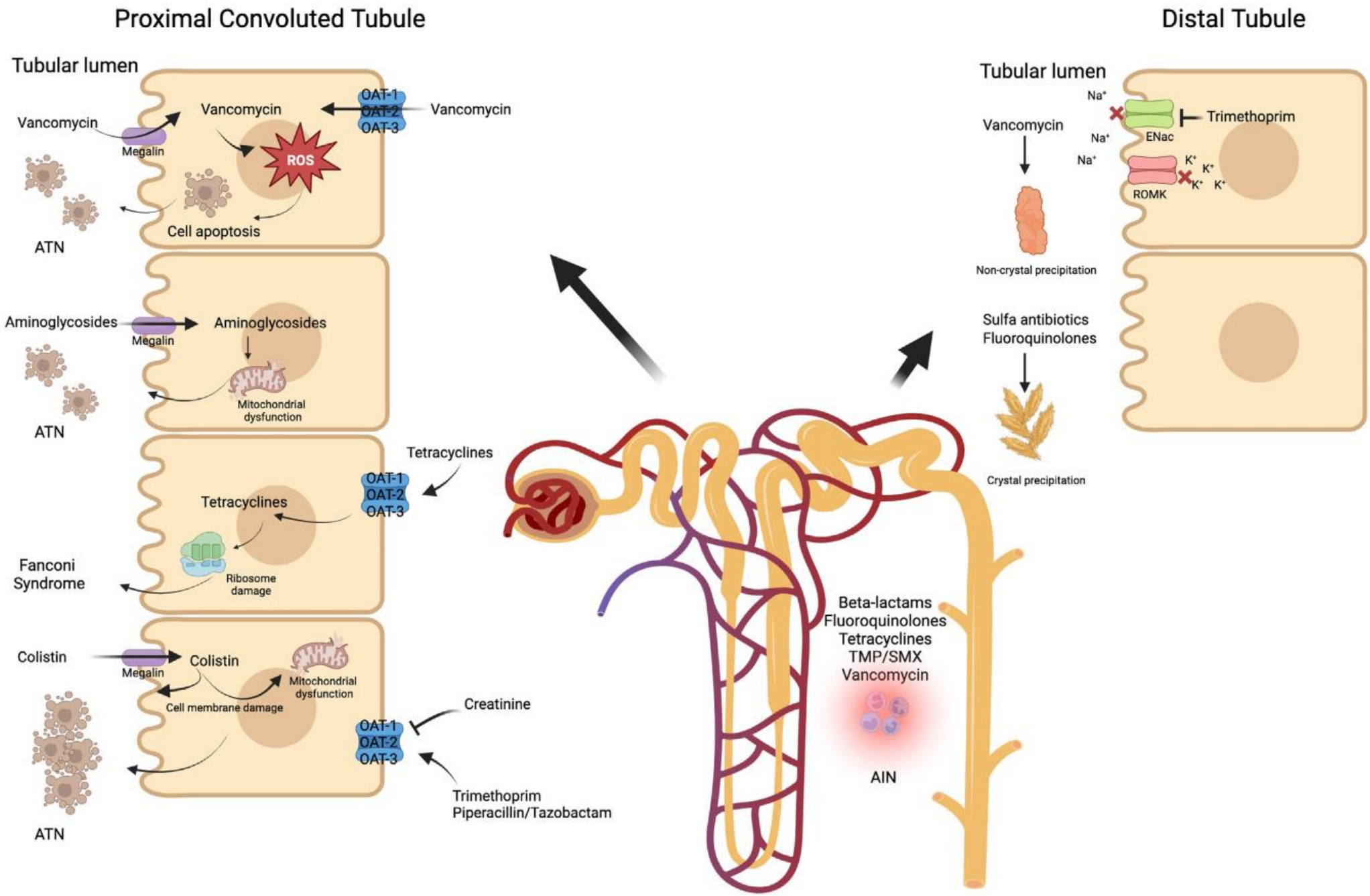
Cristallurie et Bactrim

- SMX converti en N-acetyl-sulfamethoxazole (NASM) par le foie
- Elimination rénale
- FdR d'IRA = MRC préexistante



Azencot et al, Sci Rep 2024

≠ Trimethoprime qui inhibe sécrétion tubulaire



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IRA et Antibiotique
= 1 molécule 1 infection 1 contexte

<u>Mesures communes à toutes les IRA</u>

1) ECHOGRAPHIE RENALE
2) PROTEINURIE / ALBUMINURIE
3) ECBU et IONO URINAIRE

<u>Mesures de néphroprotection</u> = optimisation de la volémie, arrêt des néphrotoxiques, adaptation des doses de ttt au DFG

Elimine les DD = cause obstructive, IRA fonctionnelle, protéinurie glomérulaire (GNA, GNC3, MRC sous-jacente)

IRA et Antibiotique
= 1 molécule 1 infection 1 contexte

<u>En faveur d'une néphropathie cristalline</u>
= Amoxicilline++, fortes doses IV, caractère brutal, résolution rapide
Intérêt de la cristallurie

<u>En faveur d'une NTIA</u>
= signes extra-rénaux (rash, cytolyse hépatique), leucocyturie aseptique, hyperéosinophilie
Intérêt de marqueurs non invasifs (CXCL9, Scinti gallium) voire PBR

Perspectives

- Diagnostiques :

- Quelle sensibilité et spécificité d'une cristallurie positive en cas d'IRA?
- Outils automatisés d'analyse et lecture de cristallurie
- Biomarqueurs non invasifs

- Thérapeutiques:

- Inflammation tissulaire induite par les cristaux ?
- Voies d'inflammation spécifique dans la NTIA ?

- Merci de votre attention