Néphropathies aux bêta-lactamines

Pr Maxime Hentzien

DUACAI – 20/11/2024

Conflits d’intérêts

- Pas de conflit d’intérêt en lien avec cette présentation

Tout part d’un cas

- 62 ans, pas d’antécédents significatifs
- Fièvre dyspnée arthralgies depuis 6 jours
- DFGe à l’entrée : 82 mL/min/1.73m²
- Arthrite sternoclaviculaire
- Hémocultures positives à *S. agalactiae*
- ETT: Endocardite infectieuses
- TTT: Amoxicilline 200 mg/kg/j + gentamicine 3 mg/kg/j

Tout part d’un cas (un peu modifié pour les besoins de l’exercice)

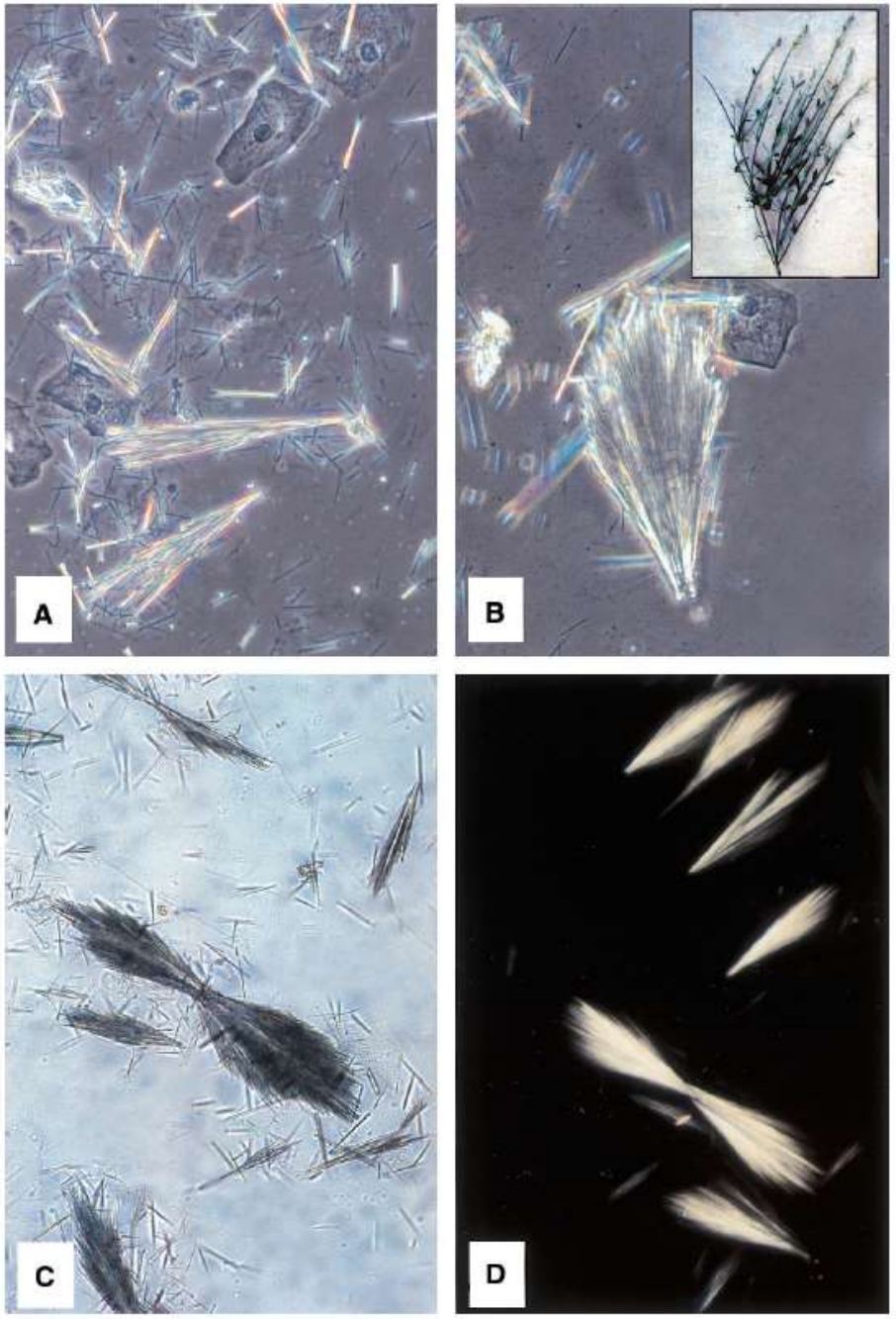
- Elle développe des douleurs lombaires, des signes de cystite, et une hématurie vers J4 de traitement.
  - Que faites-vous?

Tout part d’un cas

- Le lendemain elle est en oligurique, en OAP, créatinine 373 µmol/l, va nécessiter une dialyse.

Tout part d’un cas

Hentzien M et al. The Lancet 2015



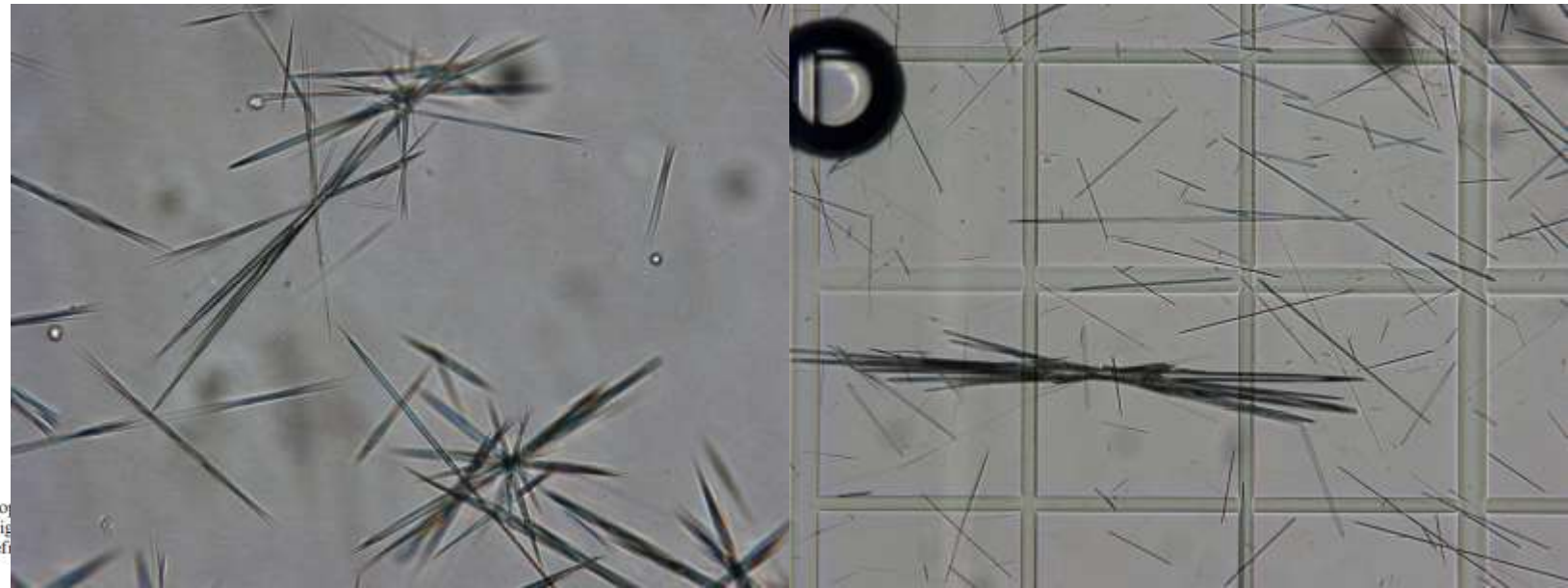


Fig. 1. (A) Large numbers of needle-shaped amoxycillin crystals and a few 'bunches' (phase-contrast microscop
400×). (B) An amoxycillin crystal resembling the branch of a broom bush (inset) (phase-contrast microscopy, orig
(C) An amoxycillin 'sheaf' as seen under bright-field microscopy (original magnification 400×). (D) The birefri
'sheaves' under polarized light (original magnification 400×).

Introduction

- Cristallurie médicamenteuse
  - Définie comme la présence de cristaux, microscopiques ou macroscopique, d'origine médicamenteuse, à l'examen direct des urines fraiches.
  - Généralement demi-vie courte et élimination rénale
- Nombreux anti-infectieux impliqués
  - Certains bien connus
  - D'autres moins

Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010
Daudon M. Nephrol ther 2015

Introduction

- Expression clinique variée
  - Asymptomatique
  - Cristallurie macroscopique
  - Lithiase
  - Hématurie
  - Signes d’irritation vésicale
  - Insuffisance rénale aiguë
    - Précipitation intratubulaire ou obstructive
    - Parfois sévère

Figure 6 Calcul d’amoxicilline.

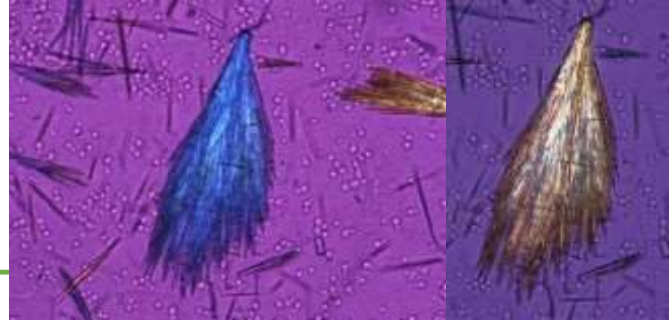
Facteurs favorisant

- Favorisant la sursaturation urinaire
  - Facteurs augmentant la concentration médicamenteuse urinaire
    - Hypoalbuminémie
    - Surdosage / doses élevées / bolus
    - Déshydratation/faible diurèse
    - Insuffisance rénale
  - Facteurs physicochimique
    - pH urinaire (bas ou élevé selon le médicament)
  - Déficit en inhibiteurs

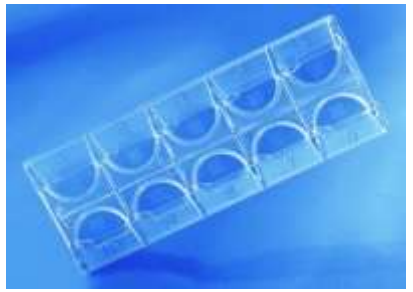
Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010

Comment la rechercher ?

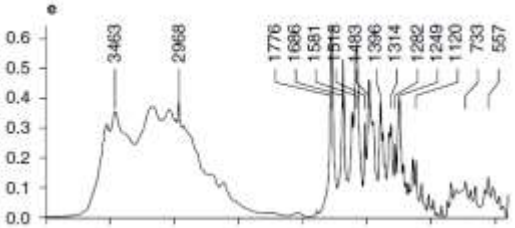
Comment la rechercher ?



- Prélèvement urinaire
  - Sur les premières urines du matin
  - Pot envoyé (Pas de mise en tube)
  - Acheminé en moins de 2h au laboratoire
  - pHmètre + densité urinaire
  - Homogénéisation par retournement



Possibilité d'envoi du culot sec pour spectrophotométrie infrarouge après centrifugation de la totalité de l'urine disponible



Principaux médicaments pourvoyeurs de cristallurie médicamenteuse?

Principaux médicaments pourvoyeurs de cristallurie médicamenteuse

- Anti-infectieux
  - Sulfadiazine
  - Sulfamethoxazole
  - Indinavir
  - Atazanavir
  - Darunavir?
  - Amoxicilline
  - ceftriaxone
  - Ciprofloxacine
  - Norfloxacine
  - Aciclovir
- Autres
  - Triamterene
  - Piridoxylate
  - Primidone
  - Naftidrofuryl
  - Vitamine C
  - Orlistat
  - Felbamate
  - Methotrexate

Daudon M et al. Drugs 2004
Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010
De Lastours V. JAC 2013
Daudon M. Nephrol ther 2015

Drug	Crystal	Clinical manifestations
Sulfadiazine	Birefringent "shocks of wheat" or "shells" with radial striations and amber colour	Asymptomatic crystalluria, haematuria, acute renal failure, obstructive uropathy
Amoxicillin	Birefringent needles, "shocks of wheat", "broom bush-like"	Isolated crystalluria, haematuria, acute renal failure, obstructive uropathy
Ciprofloxacin	Birefringent needles, "stars", "sheaves", "fans", "butterflies", etc.	Isolated crystalluria, acute renal failure, obstructive uropathy
Acyclovir	Birefringent needles with sharp or blunt extremities	Asymptomatic crystalluria, acute renal failure, haematuria and leukocyturia
Indinavir	Birefringent irregular plates, "crosses", "stars", "fans", etc.	Asymptomatic crystalluria, acute renal failure, obstructive uropathy, sterile leucocyturia, interstitial nephritis
Triamterene	Birefringent coloured spheres (brown, green, orange, red)	Asymptomatic crystalluria, ?acute renal failure
Piridoxylate	Asymmetrical hexagons	Urinary stones
Primidone	Birefringent hexagons	Asymptomatic crystalluria, transient haematuria
Naftidrofuryl oxalate	Birefringent monohydrated calcium oxalate	Asymptomatic crystalluria, acute renal failure
Vitamin C	Birefringent monohydrated calcium oxalate	Crystalluria, haematuria, acute renal failure
Orlistat	Calcium oxalate (?mono- or ?bi-hydrated)	Acute renal failure
Felbamate	(?Birefringent) sharp needles isolated or in clumps	Haematuria, acute renal failure

Daudon M et al. Drugs 2004
Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010
De Lastours V. JAC 2013
Daudon M. Nephrol ther 2015

Quelle incidence ? Quel impact ?

Amoxicillin crystalluria in patients receiving high doses of intravenous amoxicillin: incidence, associated factors and impact on renal function, the CRISTAMOX study

The CRISTAMOX Study Group

Presenter: Dr Maxime Hentzien

UNIVERSITÉ DE REIMS CHAMPAGNE-ARDENNE

CRISTAMOX

CHU DE REIMS

Lisbon, Portugal
23–26 April 2022

32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Introduction - objectives

- Amoxicillin crystalluria (AC)
  - is a potentially severe side-effect of a very frequently prescribed antibiotic
    - Symptoms: asymptomatic, hematuria, lumbar pain, lithiasis, sludge with ureteral obstruction, macroscopic crystalluria, acute kidney injury (AKI)
  - Occurs typically in low pH – high density urines
  - Its incidence was unknown
    - But it was increasingly reported in Europe and the U.S.

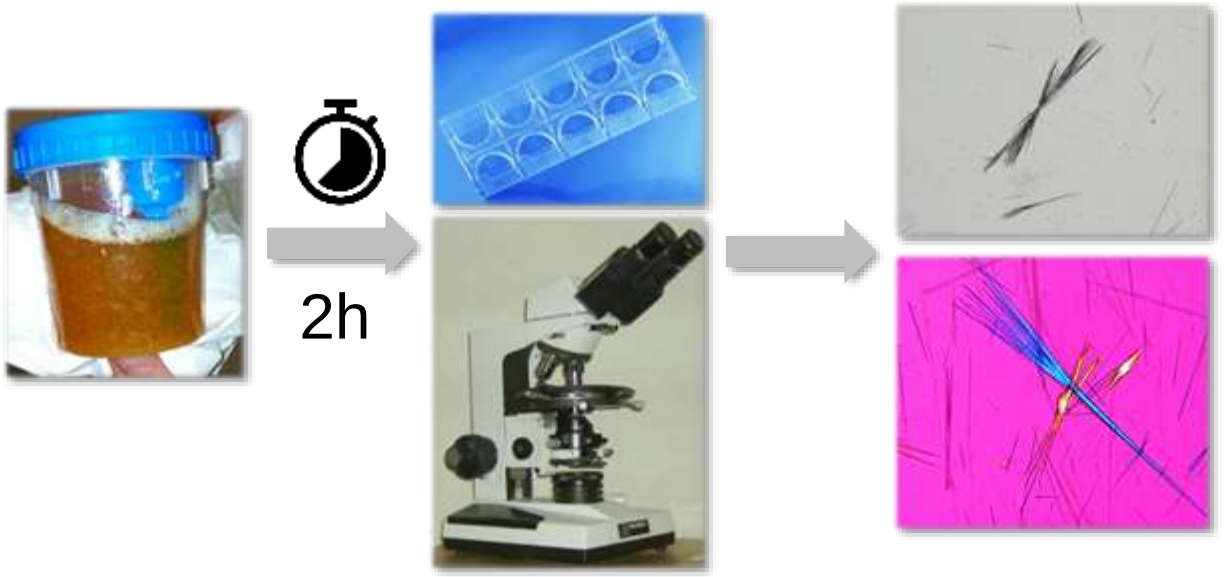
Amoxicillin calculus

- Objectives:
  - Main: To evaluate AC incidence in patients treated with high-dose intravenous amoxicillin (HDIVA)
  - Secondary: To identify factors associated with AC and to evaluate its impact on the risk of AKI

Hentzien M et al. The Lancet 2015
Daudon M. Nephrol ther 2015, Daudon M. Drugs 2004, Gatti M et al. J Nephrol 2021, Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010

Methods

- Study design
  - multicentre, observational cohort study (2014 – 2019)
- Study population:
  - Adults treated with high-dose IV amoxicillin (>150 mg/kg/d)
    - Initiated at most 48 hours before the admission in a study center
    - In North-East of France
  - And who had at least one AC search



- AC search
  - Participating centers had progressively implemented since 2014 routine AC search at day 3, 7 and 14 and in case of hematuria or AKI after high-dose IV amoxicillin initiation

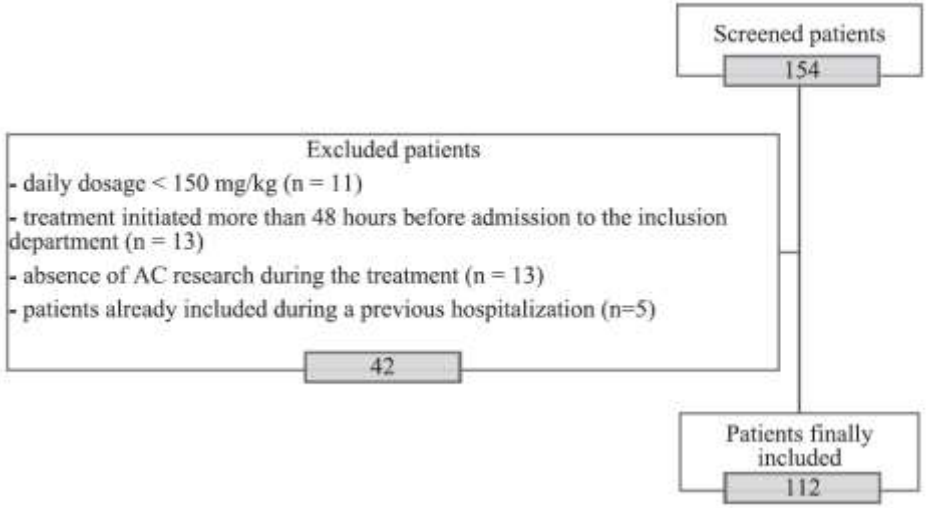
Methods

- Analysis of factors associated with the occurrence of amoxicillin crystalluria:
  - repeated measures univariable logistic regression model

- Factors associated with the occurrence of AKI:
  - AKI defined as KDIGO ≥1 (>50% increase in serum creatinine)
  - Cox model (with AC as a time-varying covariate)

Study population

- Screened: 154
- Included: 112



	Characteristics	
	N	(%)
Age (years) (mean±sd)	66.9	±16.0
Male gender	73	(65.2)
BMI (kg/m²) (mean±sd)	28.0	±6.9
Chronic renal insufficiency	25	(22.3)
Indications for high-dose amoxicillin	112	(100.0)
Infectious endocarditis	92	(75.4)
Osteoarticular infections	26	(23.2)
Initial amoxicillin daily dosage (g per day) (mean±sd)	14.0	±3.2
Number of injections per day (mean±sd)	5.0	±1.4
Intravenous treatment duration (days) (mean±sd)	22.5	±21.0
Associated antibiotics during amoxicillin course		
Aminoglycosides	71	(63.4)
Ceftriaxone	20	(17.9)
Other	32	(28.6)
Other treatments received at amoxicillin initiation		
ACE inhibitors	23	(20.5)

Results - Incidence

	Crystalluria		Missing data
	N	% [95%CI]	
At least one positive crystalluria	**27**	**24.1 [16.2-32.0]**	0
Positive crystalluria at D3 ± 1d	**18**	**21.7 [12.8-30.6]**	29
Positive crystalluria at D7 ± 2d	6	9.4 [2.2-16.5]	48
Positive crystalluria at D14 ± 2d	4	12.9 [1.1-24.7]	81
Positive crystalluria in other searches	1	12.5 [0.0-35.4]	104

- AC occured early, within a mean time of 5 days

Results –factors associated with AC

- Factors associated with AC by univariable analysis
  - **ACE inhibitor intake:**
    - **OR= 4.6; 95%CI [2.2-9.3], p<0.0001**
  - Age (per 1-year increase):
    - OR= 1.04; 95%CI [1.01-1.06], p=0.01
  - Urinary pH (urinary dipstick - per decrease of 1 point of pH)
    - OR=2.13; 95%CI [1.21-3.74], p=0.009
  - (Hematuria)
- No protective factors were found

Results – impact on renal function

AKI occured in **18%** of patients

after a mean time of **10 days** after treatment initiation (5 days after AC)

	Univariable analysis		Multivariable analysis	
	HR [95%CI]	p value	HR [95%CI]	p value
Female gender	0.49 [0.14-1.73]	0.26		
Age (per increase of 1 year)	**1.05 [1.00-1.10]**	**0.04**		
BMI (per increase of 1 kg/m²)	**1.08 [1.01-1.16]**	**0.03**		
Chronic renal insufficiency	1.81 [0.62-5.30]	0.28		
Diabetes mellitus	2.20 [0.79-6.07]	0.13		
Hypertension	**4.41 [1.25-15.65]**	**0.02**	3.43 [0.96-12.28]	0.06
Infectious endocarditis	2.50 [0.33-19.11]	0.38		
Aminoglycosides	1.73 [0.48-6.19]	0.40		
Vancomycin	3.80 [0.50-29.07]	0.20		
Diuretics	2.22 [0.79-6.24]	0.13		
Loop diuretics	1.39 [0.49-3.90]	0.53		
ACE inhibitors	1.46 [0.50-4.29]	0.49		
Angiotensin II receptor blockers	0.91 [0.21-4.03]	0.90		
NSAIDs	2.09 [0.27-15.99]	0.48		
Initial amoxicillin daily dosage (per 1 g/day)	1.09 [0.95-1.25]	0.23		
Initial plasma creatinine value (per 1 µmol/L)	1.00 [0.99-1.01]	0.98		
Amoxicillin crystalluria	**8.65 [2.91-25.67]**	**0.0001**	**7.41 [2.48-22.16]**	**0.0003**

Discussion

- AC incidence was 24% in *Cristamox*
  - Other cohorts
    - 44% (n=34, infective endocarditis) *Jamme M et al. Nephrol Dial Transplant 2021*
    - 22% (n=32, infective endocarditis) *Tamisier N et al. Med Mal Infect 2019*
- Only one other study assessed the impact of AC on AKI (n=34)
  - Cause-specific hazard = 7.4, p = 0.005 *Jamme M et al. Nephrol Dial Transplant 2021*
- No study to date has assessed the association between ACE inhibitors and AC

Strengths and limits

Strengths

- Systematic AC search, regardless of the presence of symptoms
- Multicenter
- Largest number of patients to date
- All HDIVA indications

Limits

- Some patients did not have AC search at all timepoints
- Observational design, with some data was collected retrospectively
- No reliable data on amoxicillin plasma levels
- Lack of power for predictive factors

Conclusion and perspectives

- **AC, when searched systematically, occured in about one quarter of patients and was highly predictive of AKI**

→ This advocates for a systematic repeated AC search at the beginning of HDIVA.

→ The effect of preventive measures remains to be determined by a randomized clinical trial using urine alkalinization or using an antibiotic alternative in case of AC

- The role of ACE inhibitors has to be confirmed

Incidence, associated factors, and effect on renal function of amoxicillin crystalluria in patients receiving high doses of intravenous amoxicillin (The CRISTAMOX Study): A cohort study

Sophie Demotier, MD,[a] Anne Limelette, MD,[b] Alexandre Charmillon, MD,[c] Elisabeth Baux, MD,[c] Xavier Parent, PharmD,[d] Stéphanie Mestrallet, MD,[e] Simona Pavel, MD,[f] Amélie Servettaz, MD PhD,[a] Moustapha Dramé, MD PhD,[g] Anaelle Muggeo, PharmD PhD,[b] Alain Wynckel, MD,[h] Claire Gozalo, PharmD,[i] Malak Abou Taam, PharmD,[j] Aurélie Fillion, MD,[k] Roland Jaussaud, MD PhD,[l] Thierry Trenque, MD PhD,[m] Lionel Piroth, MD PhD,[n] Firouze Bani-Sadr, MD PhD,[a] and Maxime Hentzien, MD PhD[a], and the CRISTAMOX Study group*

Amoxicillin crystalluria and amoxicillin-induced crystal nephropathy: a narrative review

Dominique Vodovar[1,2,3], Cyril Mousseaux[4,5,6], Michel Daudon[6,7], Matthieu Jamme[8,9] and Emmanuel Letavernier[5,6,7]

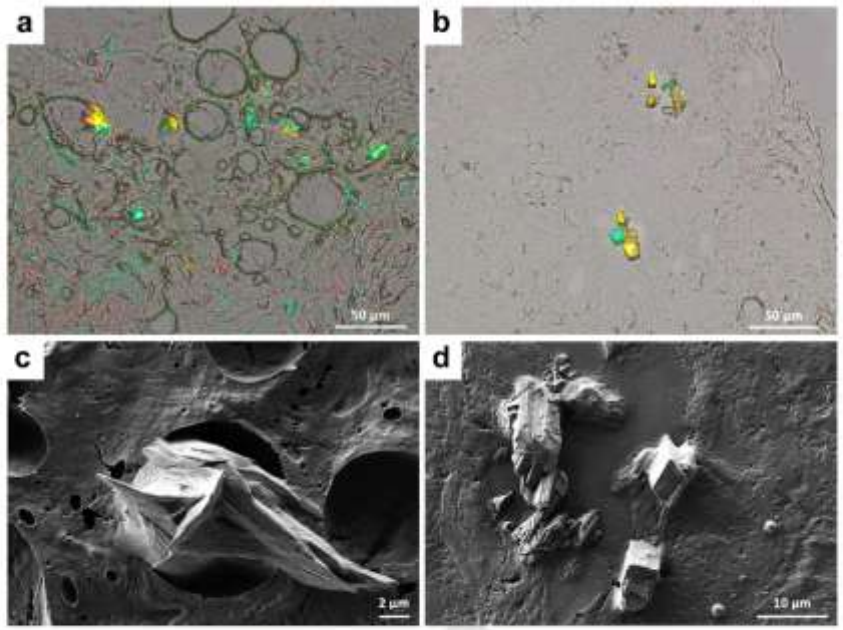


Figure 2 | Kidney biopsy of a patient with amoxicillin-induced crystalline nephropathy. (**a**,**b**) Aspect of amoxicillin trihydrate crystallites in polarized light, on a frozen section of a biopsy from a patient with amoxicillin-induced crystalline nephropathy. Some crystalline aggregates have a broom-like or egret-like appearance (**a**), while others have a square or rectangular appearance (**b**). (**c**,**d**) Electron microscopy appearance of amoxicillin trihydrate crystallites on the same biopsy, revealing asymmetric aggregation of sometimes striated and truncated crystallites (**c**), and parallelepipeds (**d**).

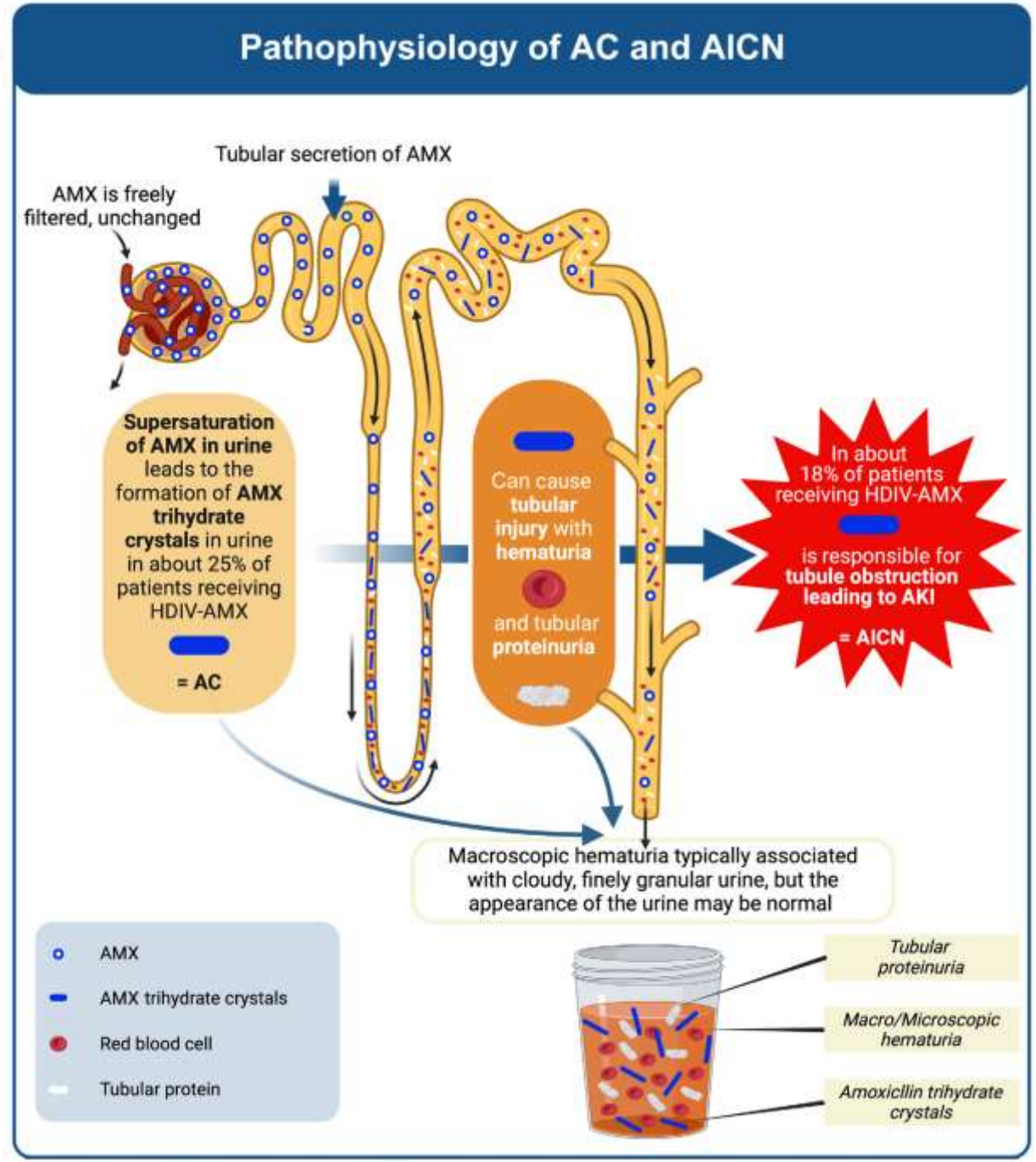
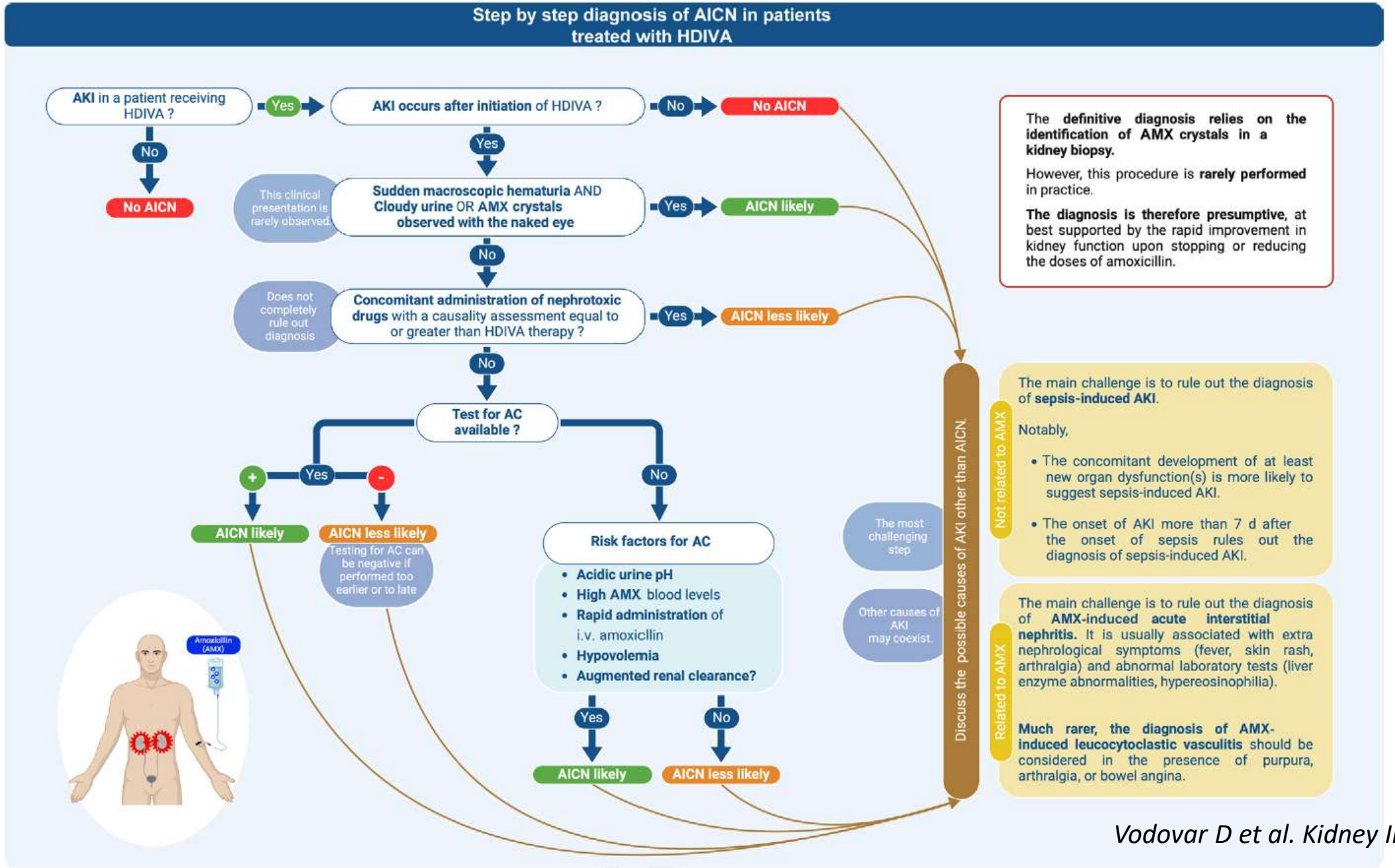


Figure 1 | Pathophysiology of amoxicillin-induced crystal nephropathy (AICN). AC, amoxicillin crystalluria; AKI, acute kidney injury; AMX, amoxicillin; HDIV-AMX, high-dose i.v. amoxicillin. Created with BioRender.com.



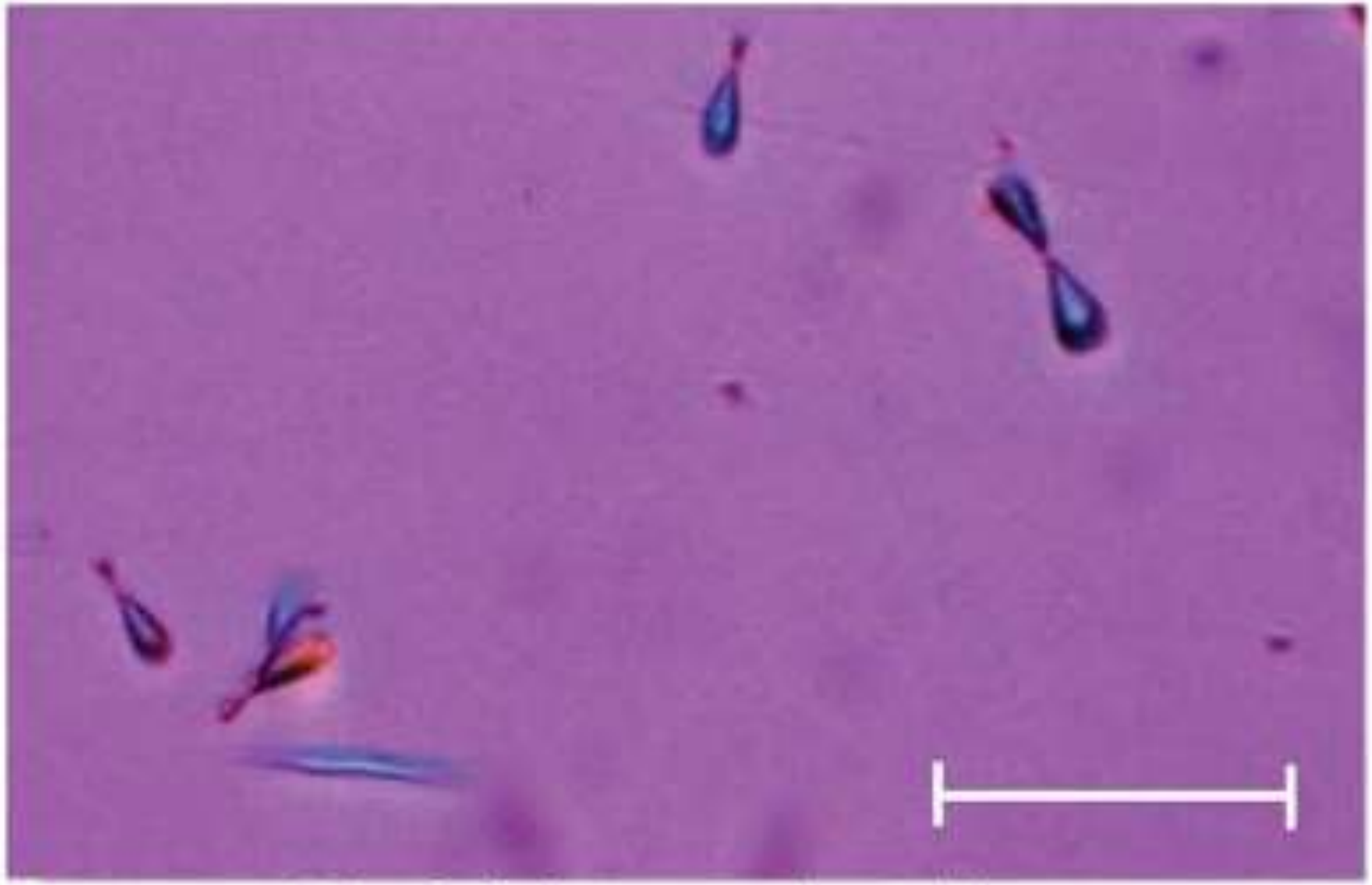
Vodovar D et al. Kidney Int 2024

Figure 4 | Step-by-step diagnosis of amoxicillin-induced acute kidney injury (AICN) in patients treated with high-dose i.v. amoxicillin (HDIVA). AC, amoxicillin crystalluria; AICN, amoxicillin-induced crystal nephropathy; AKI, acute kidney injury. Created with BioRender.com.

Considérations pratiques

- Quelle est la fréquence optimale de recherche d'une cristallurie en dépistage ?
- Comment prévenir une cristallurie ?
  - Posologies adaptées, administration sur une heure, pas plus de 2g à la fois.
  - Arrêt des IEC?
  - Majoration des apports hydrosodés?
  - Alcalinisation systématique?
- Mais surtout, si cristallurie, quelles mesures à prendre?
  - Relais par un antibiotique moins néphrotoxique ? Ceftriaxone ? (mais impact écologique)
  - Diminution de la posologie d'amoxicilline ?
  - Alcalinisation des urines ?
  - Majoration des apports hydrosodés?
- Apports et alcalinisation : pas facile au cours des infections sévères… et pas de bénéfice prouvé à ce jour

Autres cristalluries au cours des anti-infectieux



26 - Ceftriaxonate de calcium
(aiguilles agrégées en massues)
pH 6,0 à 7,5

Sulfadiazine

- pH<5,5

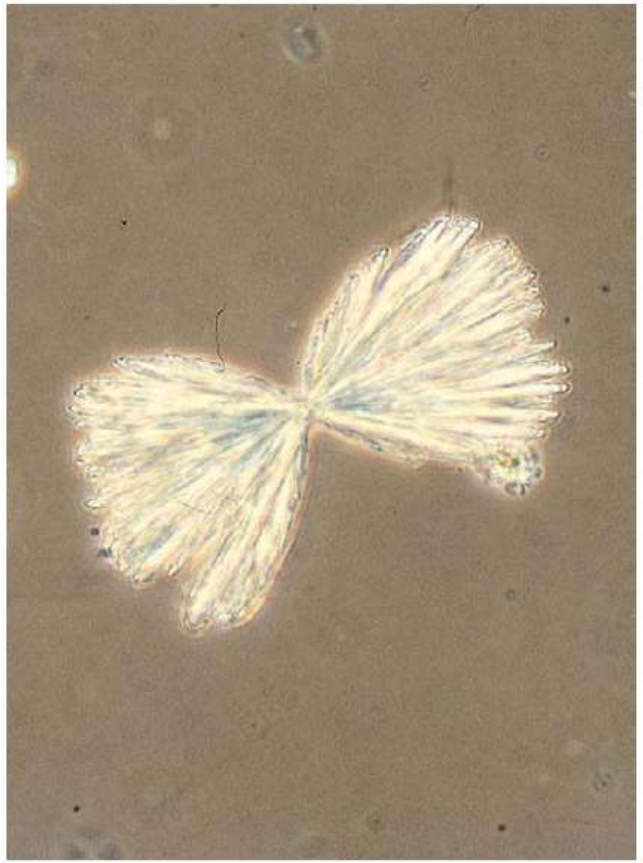


FIGURE 3.1 A crystal of sulfadiazine with typical shape ("shock of wheat") and striations (phase contrast, × 400).

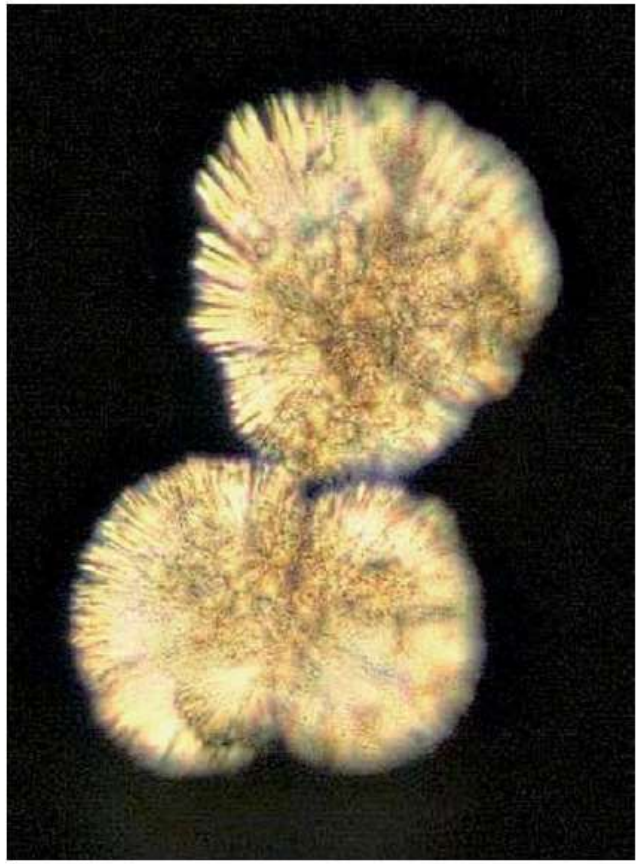


FIGURE 3.2 Strongly birefringent sulfadiazine crystals (polarized light, x 256).

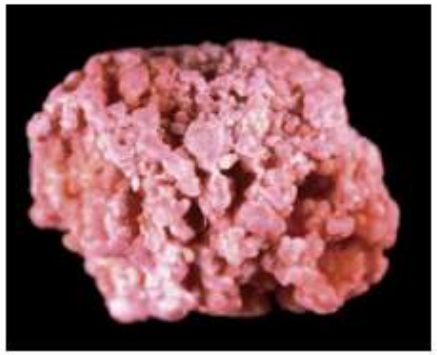
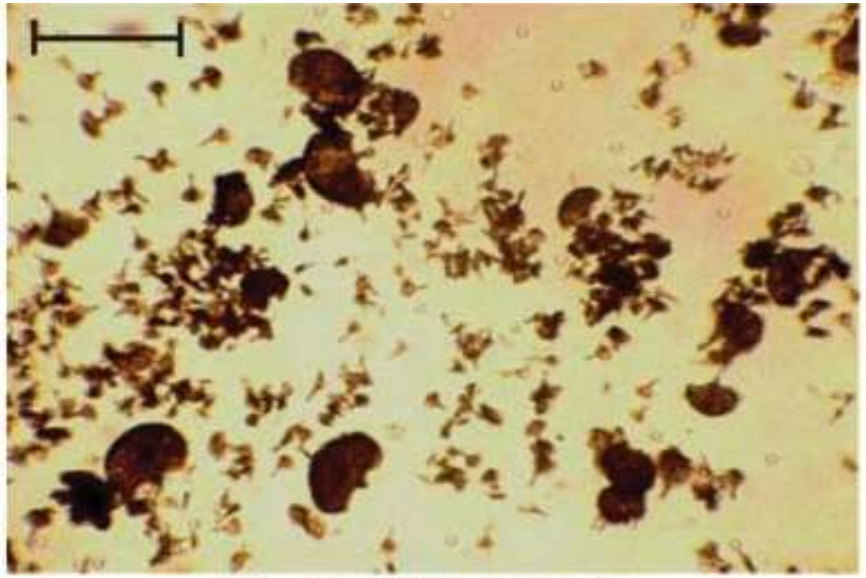


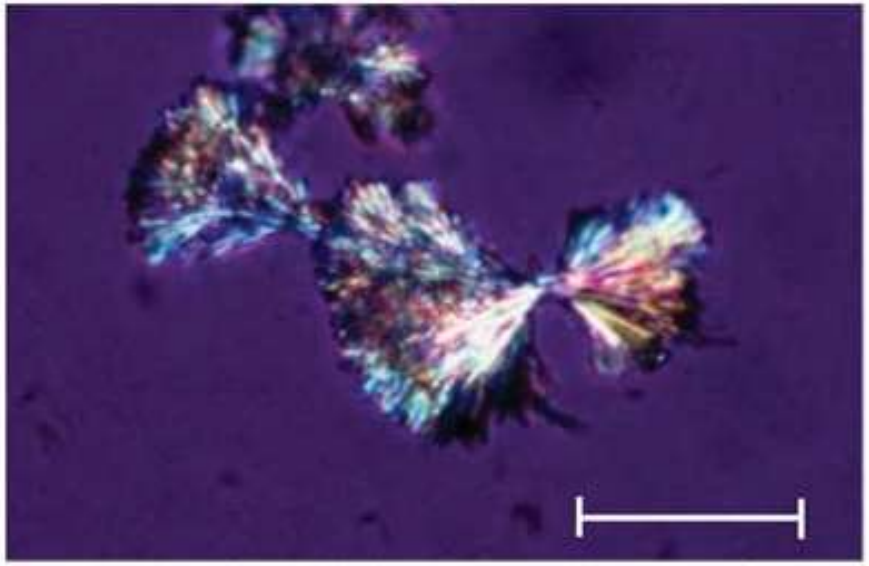
Figure 4 Calcul pur de N-acétylsulfadiazine de morphologie et de couleur caractéristiques.

Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010

Sulfadiazine



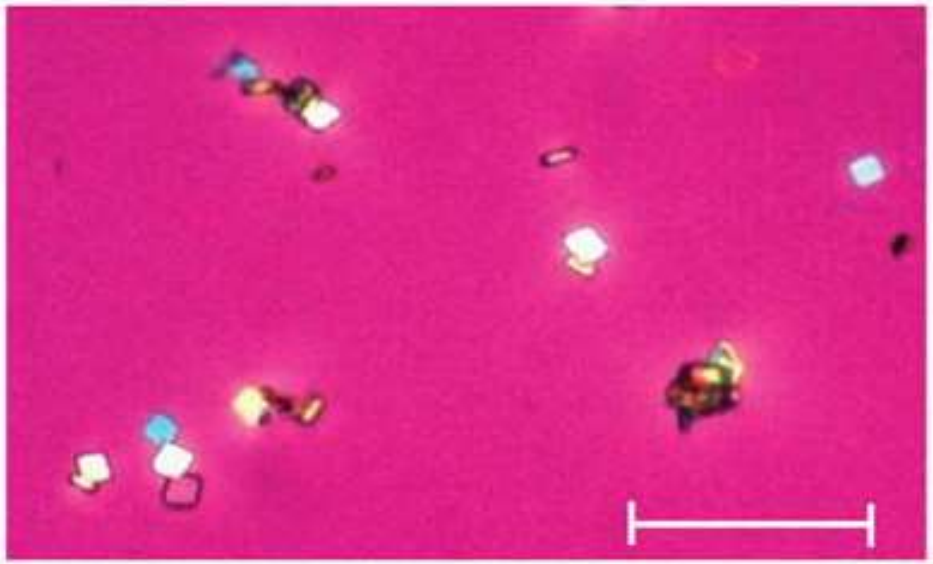
29 - N-acétylsulfadiazine
(aiguilles agrégées en éventails)
pH 5,8 à 6,8



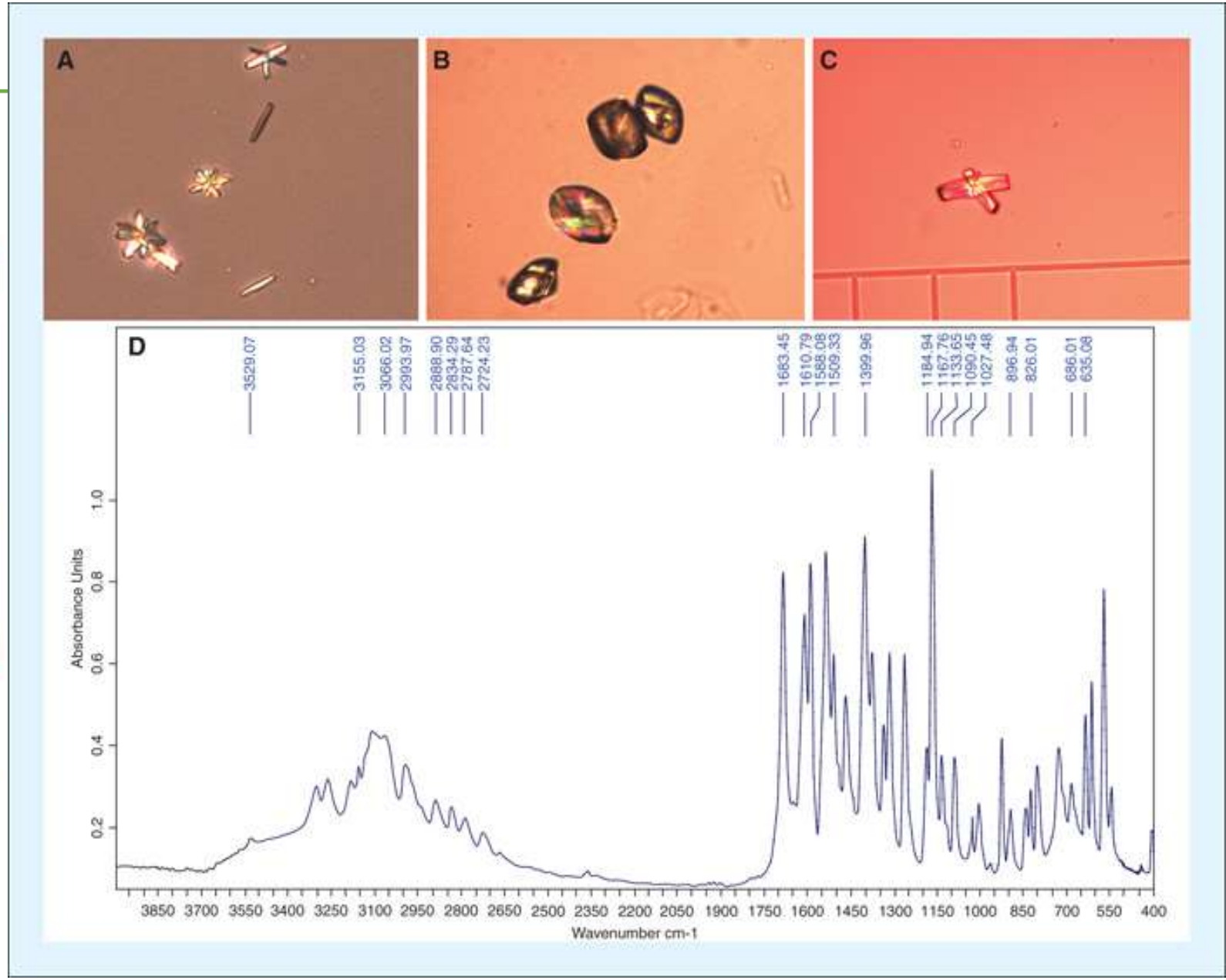
30 - N-acétylsulfadiazine (aiguilles agrégées)
pH 5,8 à 6,8

Sulfamethoxazole

- pH<5,9

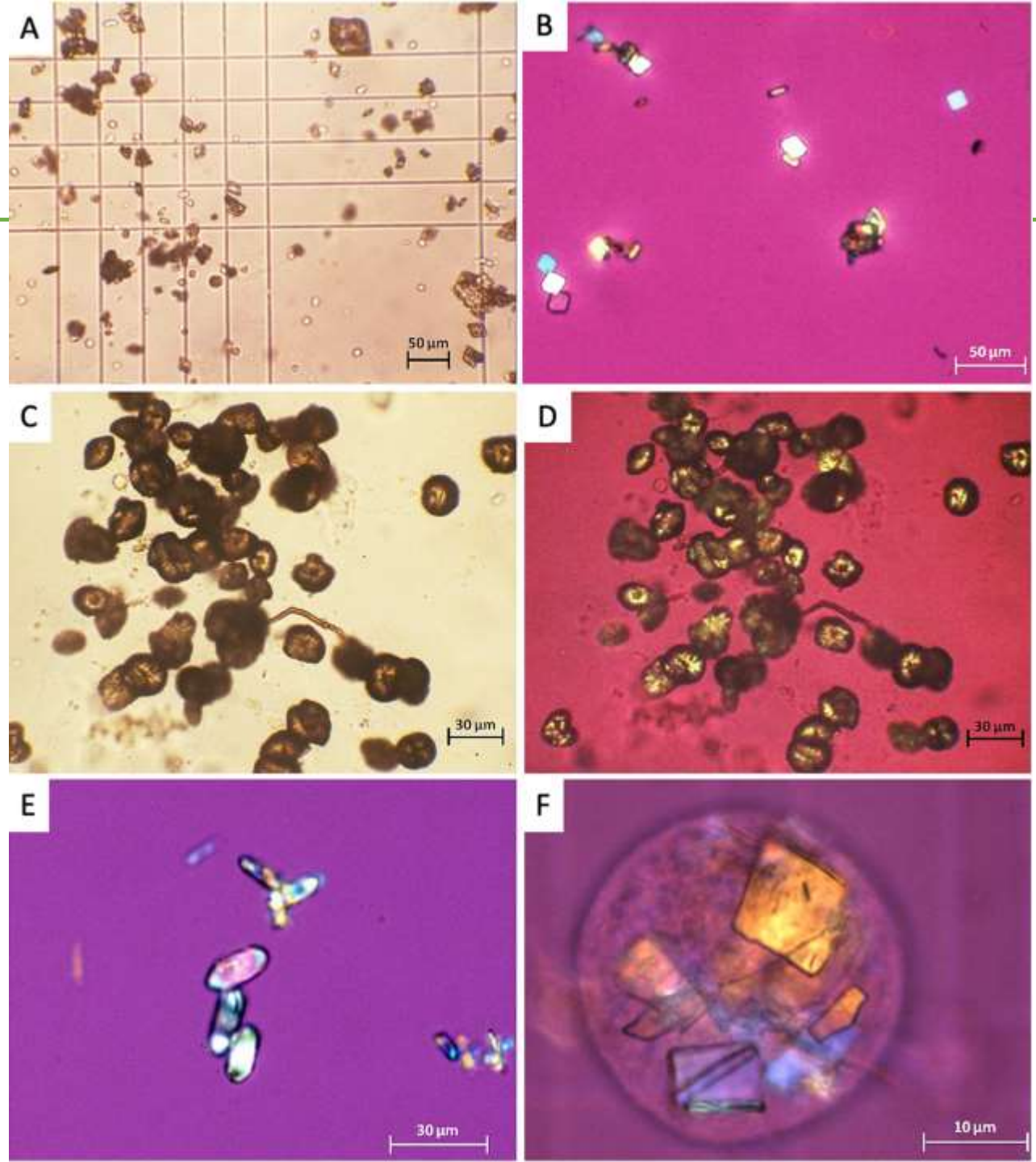


27 - N-acétylsulfaméthoxazole, HCl (losanges)
pH 5,2 à 6,2



Daudon M et al. Ann Biol Clin 2004.
Capaldo C et al. Ann Biol Clin 2021
Azencot R et al. Sci Rep 2024

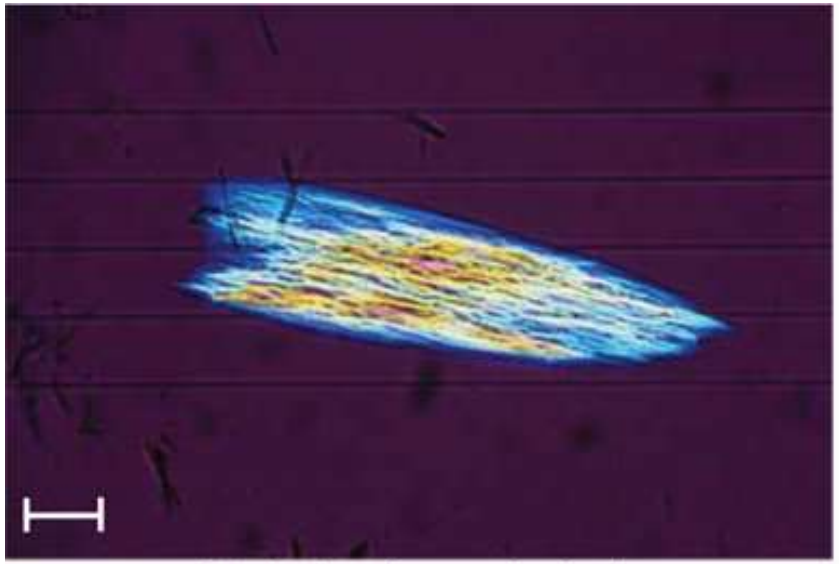
Sulfamethoxazole



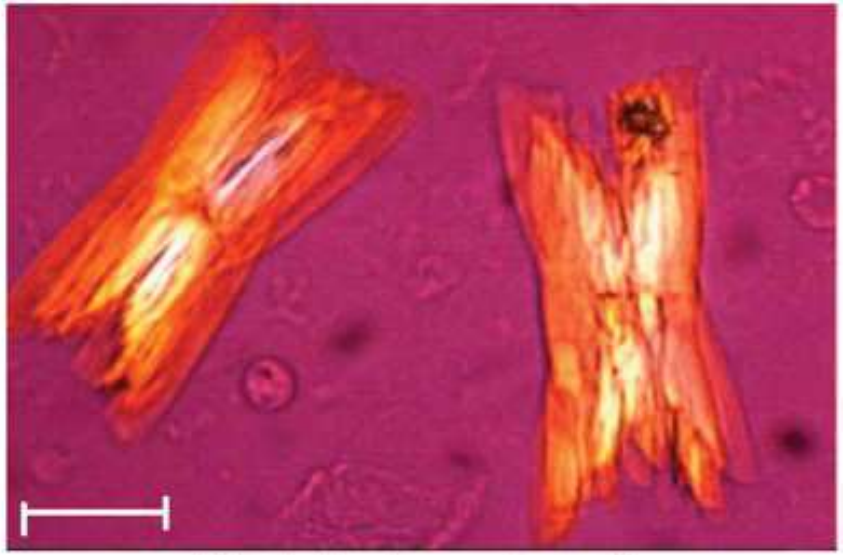
Azencot R et al. Sci Rep 2024

Indinavir

- pH>6
- Prévalence
  - 60% à pH>7,5
  - 12,7% à pH=5,0



31 - Indinavir monohydraté
(aiguilles agrégées en plaques striées)
pH 5,5 à 8,0



32 - Indinavir monohydraté
(lamelles agrégées en larges plaques)
pH 5,5 à 8,0

Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010

Gagnon RF et al. Clin nephrol 2006

Indinavir

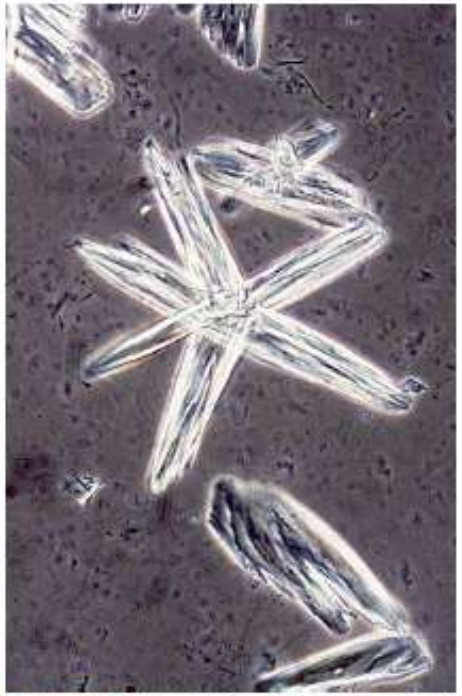


FIGURE 3.13 A "star-like" crystal and plates of indinavir (phase contrast, x 400).

FIGURE 3.14 The same crystals by polarized light (x 400).

FIGURE 3.17 Indinavir crystal with the shape of irregular plates (phase contrast, x 160).

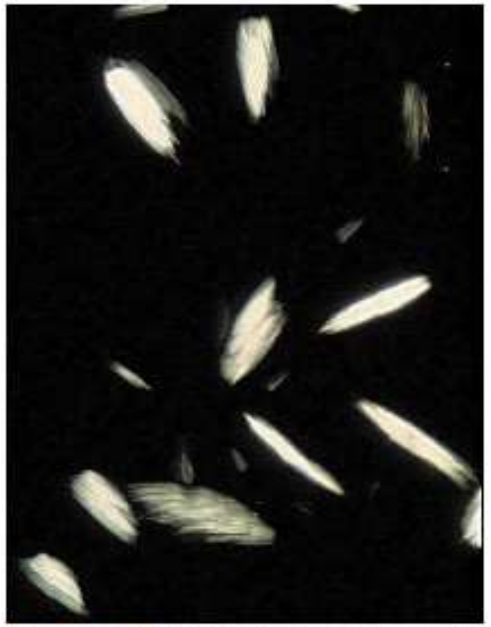


FIGURE 3.18 The same crystals by polarized light (x 160).

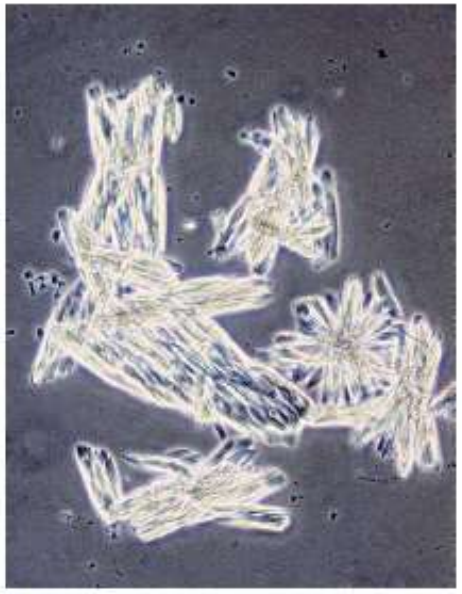


FIGURE 3.15 Several crystals of indinavir with different shapes and sizes (phase contrast, x 160).

FIGURE 3.16 The same crystals by polarized light (x 160).

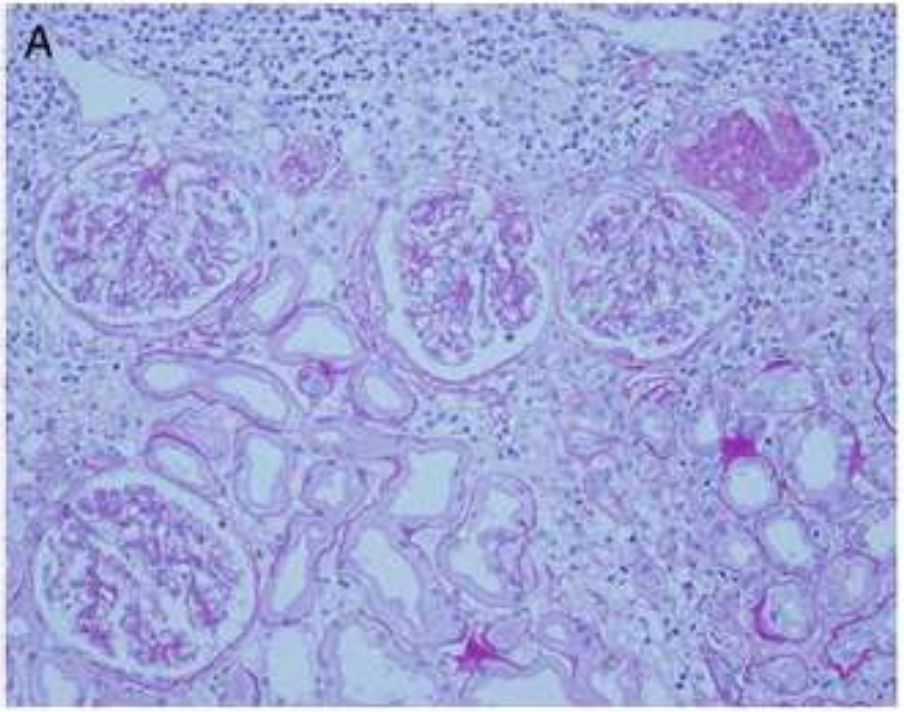
Figure 2 Calcul d'indinavir.

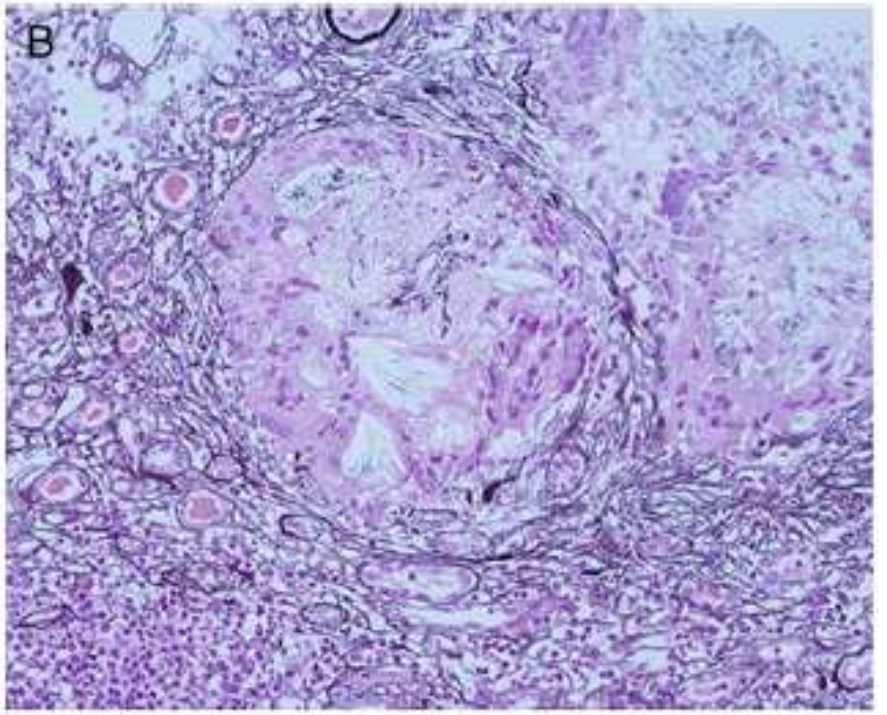
Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010
Servais A et al. An urol 2004

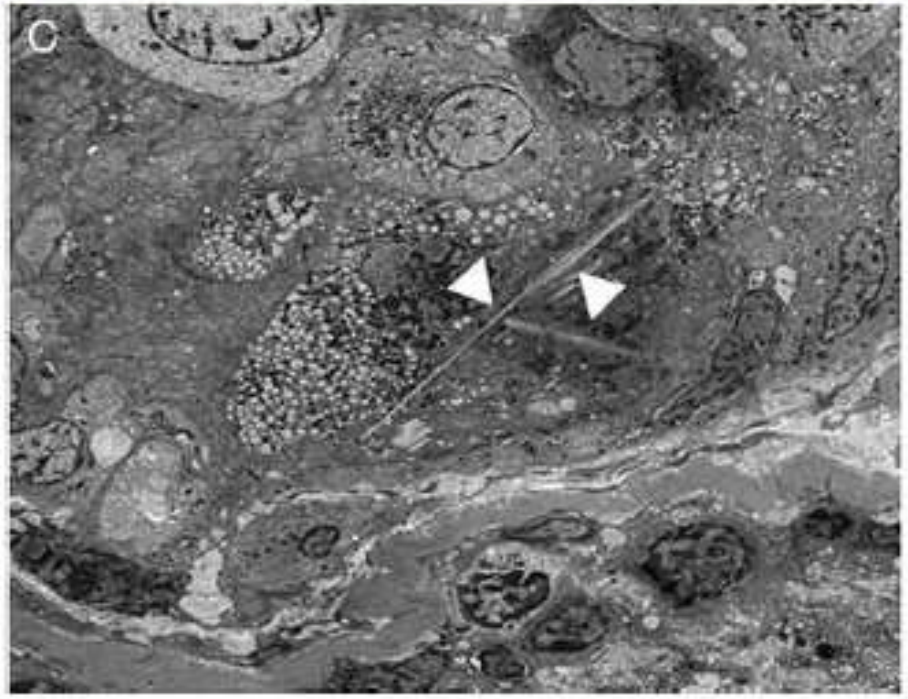
Atazanavir

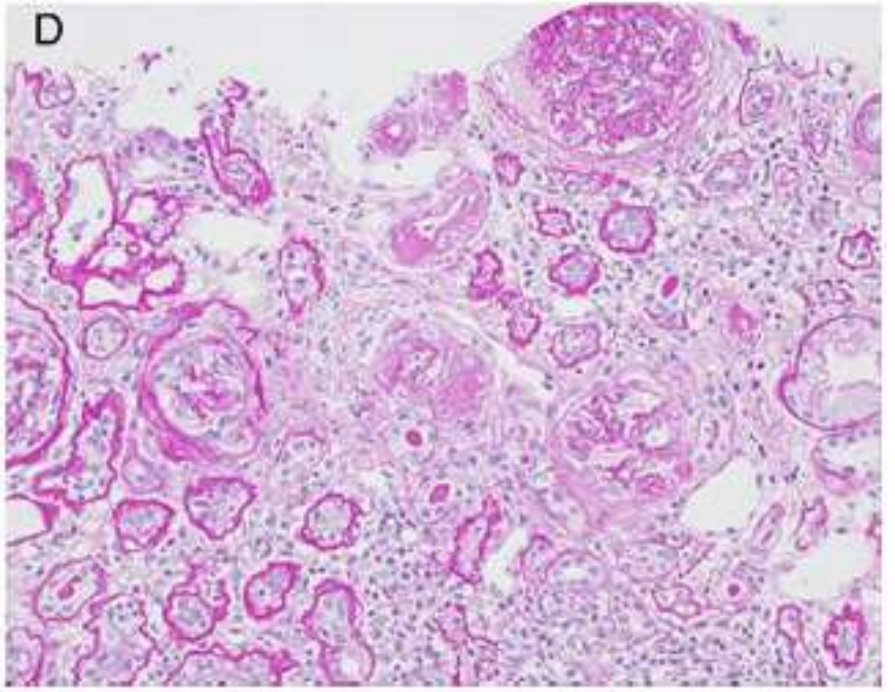
Atazanavir

- *Hara M et al. Clin Kidney J 2015*









Atazanavir

	OR	95% CI	p
MAIN MODEL WITH 3 VARIABLES			
Duration of ATV (per year)	1.32	0.95–1.84	0.10
Serum free bilirubin level (per 2-fold increase)	2.31	1.18–4.52	<0.02
Previous history of urolithiasis	3.66	0.88–15.2	0.07
ALTERNATIVE MODELS WITH 2 VARIABLES			
Serum free bilirubin level (per 2-fold increase)	1.94	1.12–3.36	<0.02
Previous history of urolithiasis	4.79	1.44–15.98	<0.02
Duration of ATV (per year)	1.42	1.04–1.93	<0.03
Serum free bilirubin level (per 2-fold increase)	2.66	1.35–5.21	<0.01

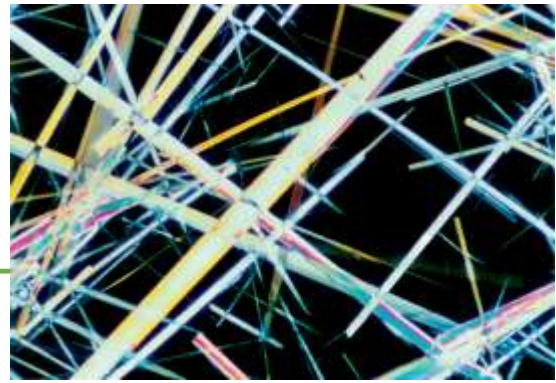
doi:10.1371/journal.pone.0112836.t004

- pH alcalin

- Lafaurie M et al. Plos one 2014
- Marinescu et al. AIDS Res Treat 2015
- Daudon M. Nephrol ther 2015

Aciclovir

Fogazzi GB et al. The urinary sediment –an integrated view. 3rd Edition. 2010
Mason WJ et al. NEJM 2014



- pH acide, rôle des bolus

Ciprofloxacine

- Urines alcalines (pH>7,3)

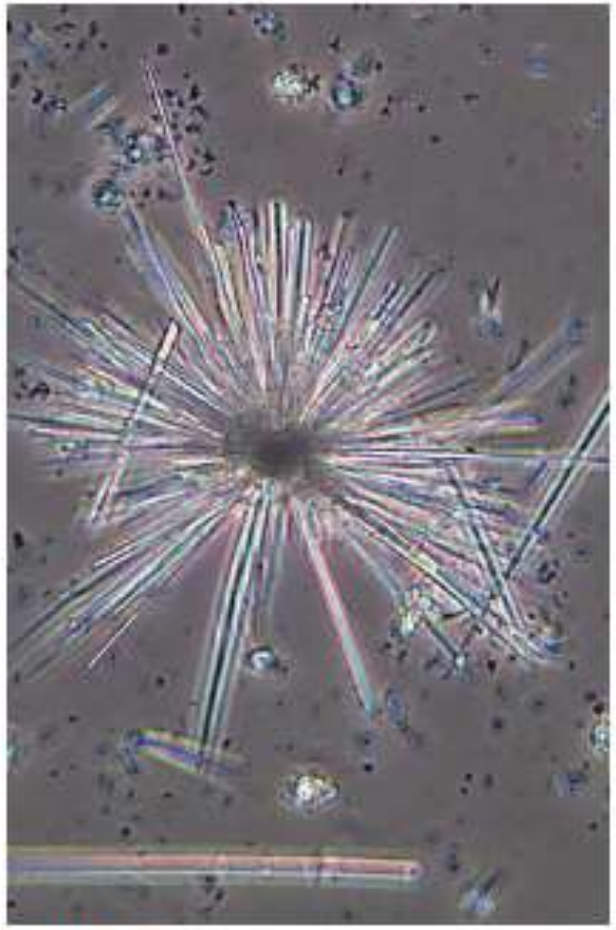


FIGURE 3.7 A "star-like" crystal and "needles" of ciprofloxacin (phase contrast, x 256).

FIGURE 3.8 The same crystals by polarized light (x 256).

FIGURE 3.9 Many "needles" of ciprofloxacin (phase contrast, x 160).

FIGURE 3.10 The same crystals by polarized light (x 160).

FIGURE 3.11 A clump of ciprofloxacin crystals with different shapes (phase contrast, x 400).

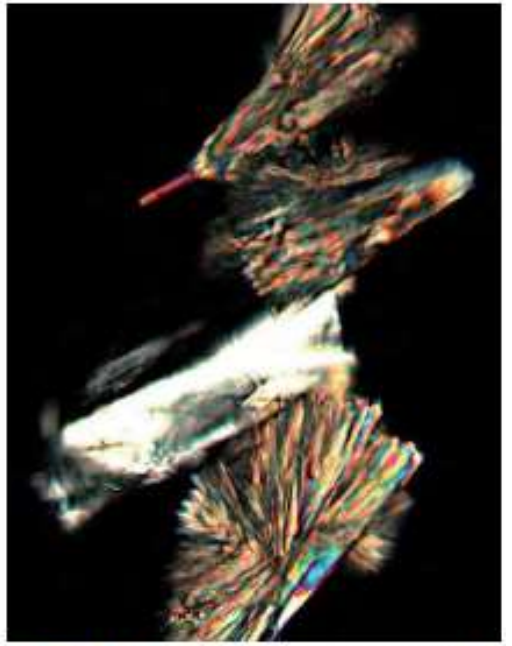


FIGURE 3.12 The same crystals by polarized light (x 400).

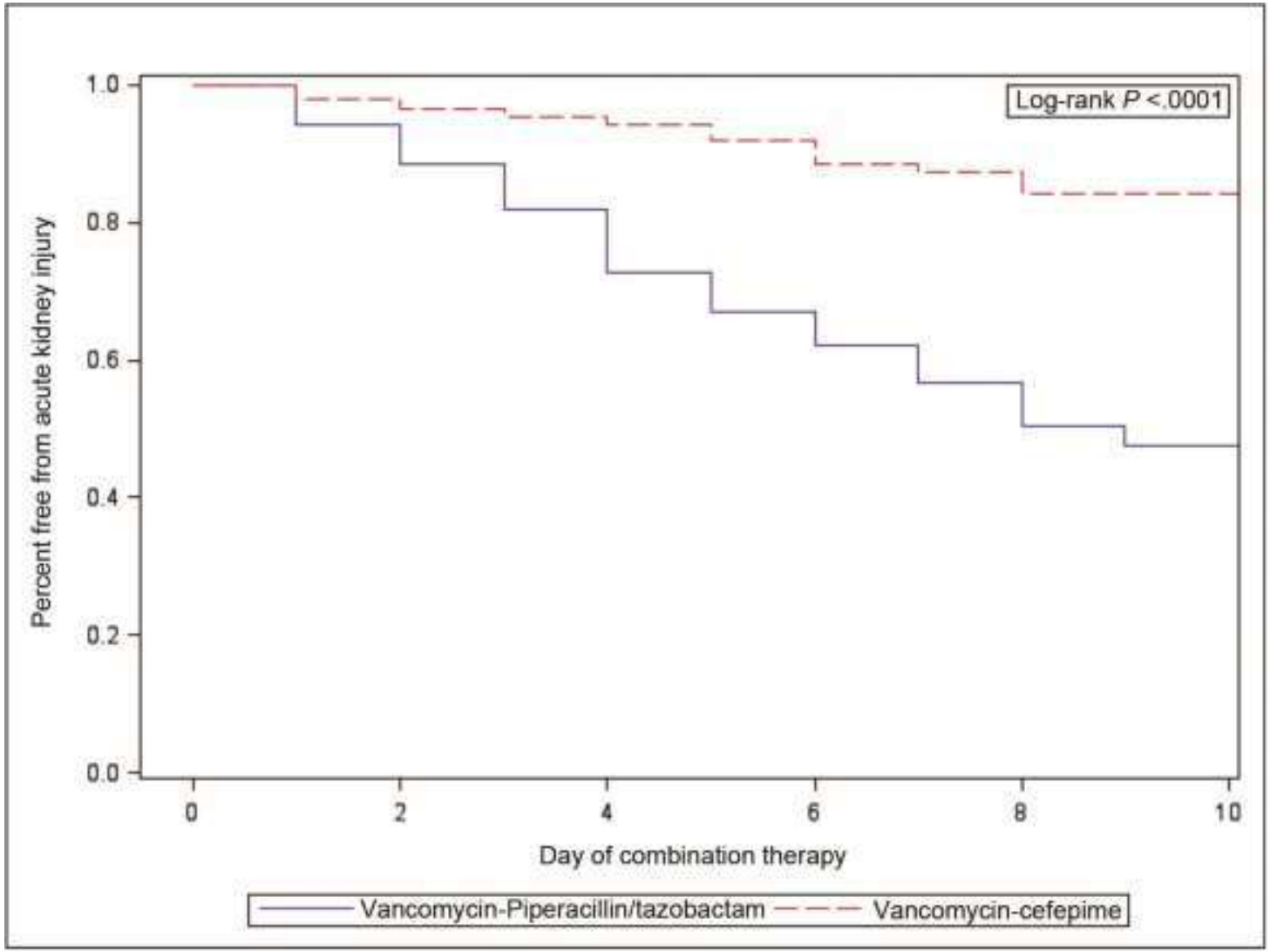
Tosufloxacine

Table 2. Clinical data of cases with crystalluria attributable to TFLX

Case No.	WBC (/μL)	Neutro (%)	BUN (mg/dL)	Cre (mg/dL)	eGFR (mL/min/1.73m^2)	UA (mg/dL)	pH	pCO2 (mmHg)	HCO_3^- (mEq/L)	base excess (mEq/L)	Urine test						Infusion	Duration of infusion (days)	Other complications
											pH	Gravity	Protein	Hematuria	Ketone	Tubular epithelial cells			
1	8670	15	6.9	0.18	119.2	3.9	-	-	-	-	6	1.015	−	−	−	10–19	-	-	-
2	10,450	31	3.2	0.18	119.9	4.9	7.415	34	21.8	−1.5	6	1.020	±	-	2+	1–4	+	7	-
3	10,470	28	12	0.28	84.5	5.4	7.310	45.8	23	−3.1	6	1.013	-	-	-	<1	+	2	-
4	17,060	46	9.9	0.19	123.5	3.4	7.470	29	21.1	−1.5	6	1.006	-	-	-	<1	+	1	-
5	14,280	17	10.1	0.22	104.8	4.9	7.331	39.5	20.8	−4.3	5.5	1.015	-	-	1+	<1	+	2	-
6	12,290	33	5	0.18	131.6	4.3	7.408	41.1	25.9	1.8	6	1.017	−	−	−	1–4	+	4	-
7	12,140	71	9.9	0.40	88.9	-	-	-	-	-	5.5	1.005	-	-	-	<1	-	-	-
8	11,390	85	26.5	0.48	79.5	6.5	7.400	28	17.3	−6.1	5.5	1.011	-	1+	2+	<1	+	4	+
9	10,950	27	14.5	0.39	104.1	6.2	7.405	45.6	28.5	3.8	5.5	1.020	-	-	-	<1	-	-	-
10	1960	48	8.6	0.41	101.5	2.9	7.475	29.1	21.4	−0.3	6	1.024	1+	-	1+	1–4	+	2	-
11	7720	77	15.5	0.89	*	5.3	7.476	33.4	24.6	1.1	6.5	1.008	-	-	-	<1	+	5	-
12	8280	75	12.1	0.71	87.2	5.6	7.335	48.3	25.8	−0.4	6	1.015	-	-	2+	<1	+	3	-
13	6450	60	13.2	0.72	89.9	-	-	-	-	-	5.5	1.015	-	-	-	1–4	-	-	-

- Atsumi Y et al. Pediatr int 2022

Néphrotoxicité indirecte des β-lactamines?



- Navalkele et al. CID 2017

Understanding vancomy
β-lactams: a synthesis of
tubule mitochondrial me

Sara Alosaimy, Michael J Rybak, George Sakoulas

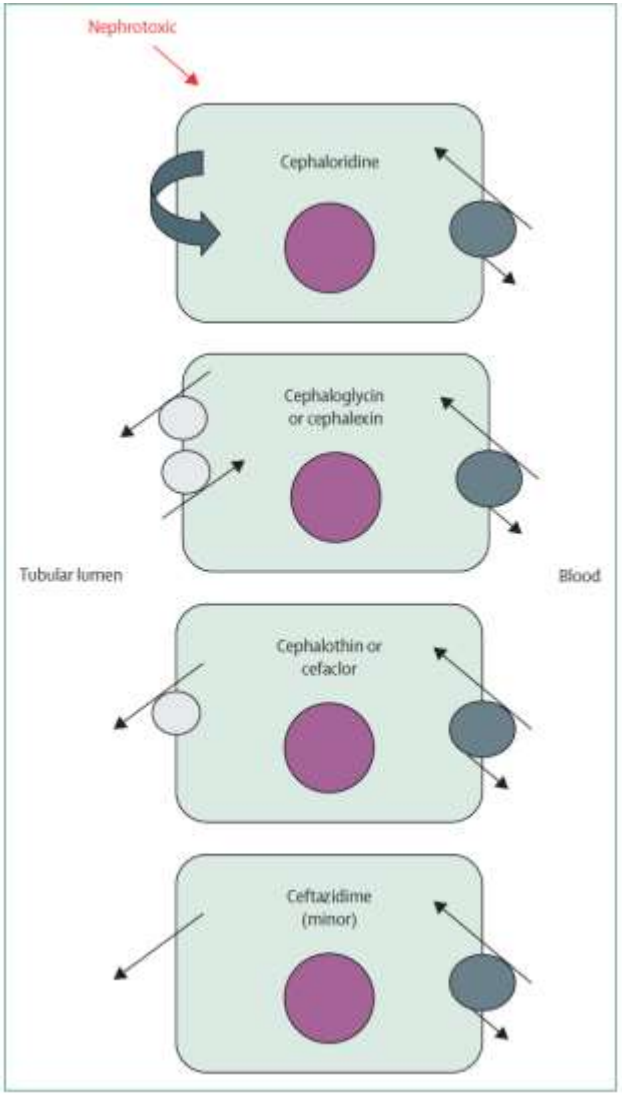
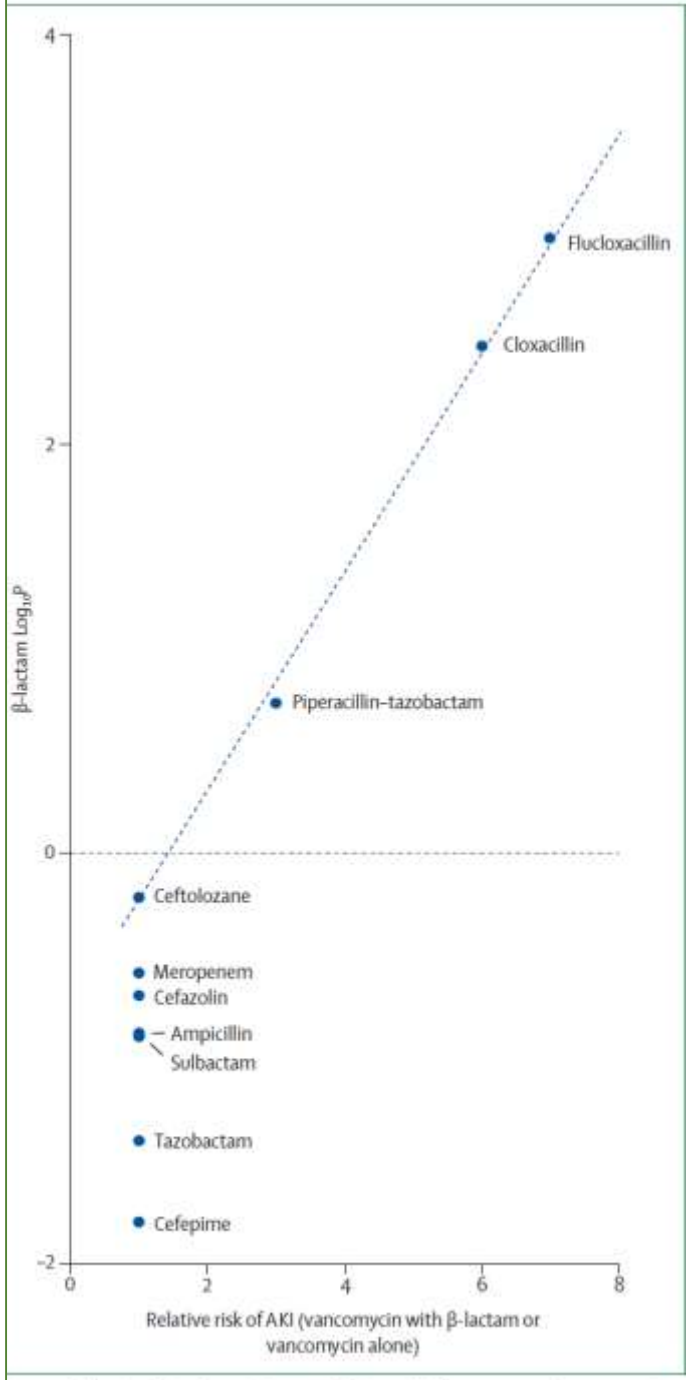


Table 2. Physiochemical properties of clinically significant β-lactams

	Partition coefficient ($Log_{10}P$)	Predictive added nephrotoxicity
Penicillin		
Penicillin G	1·83	++
Penicillin V	2·09	++
Ampicillin	1·35	+
Nafcillin	3·3	+++
Oxacillin	2·4	++
Flucloxacillin	3·2	+++
Cloxacillin	2·48	++
Dicloxacillin	3·7	+++
Piperacillin	0·3	+
Cephalosporins		
Cefazolin	−0·58	−
Cephalexin	0·65	−
Cefaclor	0·4	−
Cefiderocol	−2·265	−
Cefodroxil	−0·4	−
Cefoperazone	−0·74	−
Cefuroxime	−0·16	−
Ceftriaxone	−1·7	−
Cefotaxime	−0·5	−



gure 3: Relationship of partition coefficient of β-lactams and vancomycin
KI

Néphropathies interstitielles

- Multiples étiologies:
  - Ischémique, médicamenteuse et toxique, toxique endogène, infectieuse, immunologique, néoplasique
- Tableau:
  - Clinique pauvre
    - Signes extrarénaux selon l'étiologie
  - Pas de chute du débit urinaire (sauf NTA ischémique)
  - IRA souvent nue, protéinurie à faible débit (<1g/l, <50% albumine), protéinurie tubulaire, leucocyturie aseptique, +/- discrète hématurie

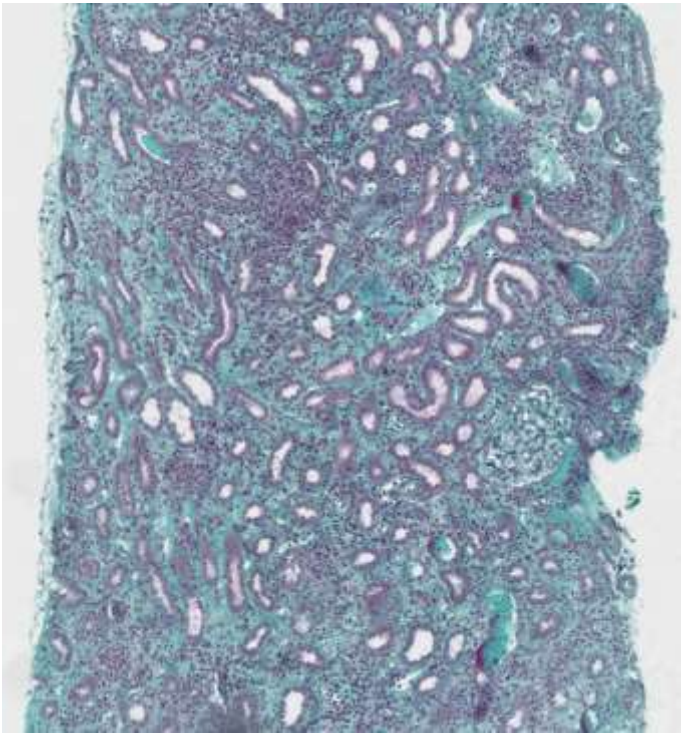
- Karras A et al. EMC 2021

NTIA médicamenteuses

- Tubulopathies / Nécroses tubulaires aigües
  - Anti-infectieux: concerne surtout les aminosides, antiviraux (ténofovir, cidofovir, adéfovir), amphotéricine B
- Précipitations intratubulaires de médicaments (cf. cristalluries)
- Néphropathies immuno-allergiques
  - Anti-infectieux: beta-lactamines +++, mais également Q2G et rifampicine
  - Arguments pour une hypersensibilité de type IV
    - l'absence de dose-dépendance ;
    - la rechute à la réexposition ;
    - les manifestations extrarénales d'hypersensibilité ;
    - la faible incidence de la NIA par rapport au nombre de personnes exposées ;
    - la prédominance de lymphocytes T (LT) dans l'infiltrat interstitiel ;
    - la mise en évidence dans le sang et le tissu rénal de LT reconnaissant spécifiquement le médicament imputé
- Karras A et al. EMC 2021

Néphropathies immuno-allergiques

- Fièvre (30%)
- Éruption cutanée (21%)
- Arthralgies (45%)
- Hépatite aiguë
- Hyperéosinophilie (25-35%)
- Douleur lombaire (20%)
- Intervalle en générale de l'ordre de 8-10 jours
- Diagnostic
  - Clinique, contexte, éosinophilurie
  - Biopsie rénale: infiltrat inflammatoire mononucléé (habituellement LT CD4+ et monocytes), œdème local et parfois une fibrose interstitielle associée à une atrophie tubulaire. Modifications glomérulaires sont rarement présentes
- TTT: éviction + corticoïdes 0,5 à 1 mg/kg/j avec diminution rapide 6-8 sem



- Karras A. et al. EMC 2021

Take home messages

- Avoir l'esprit ouvert en cas d'IRA sous β-lactamines (vrai pour d'autres classes)
  - Eliminer les causes « standard » : fonctionnelle, obstructive, sepsis, néphrotoxicité…
  - Mais toujours évoquer des causes spécifiques
    - Cristallurie médicamenteuse → pH urinaire, recherche de cristallurie, dosages médicamenteux (?)
      - Amoxicilline +++, ceftriaxone
    - Atteinte immuno-allergique → signes extra-rénaux, hyperéosinophilie, recherche d'éosinophilurie
    - Associations de malfaiteurs

Take home messages

- Cristallurie fréquente dans des situations cliniques spécifiques
  - Peu connue
  - Sous-diagnostiquée
    - Connaitre les modalités de recherche
  - Devrait-être recherchée systématiquement dans certaines situations cliniques?
- Méthodes de prévention et de prise en charge non consensuelles
  - Prévention: alcalinisation? TDM? Diminuer les posologies? Fractionner les doses? Augmenter la durée d'injection? Éviter certaines associations?
  - Traitement: Suspension/diminution des doses? Relais par autre ATB/antiviral? Alcalinisation? + PEC de l'IRA

Acknowledgements

Thanks to the *Cristamox* study investigators

- S. Demotier, A. Limelette, A. Charmillon, E. Baux, X. Parent, S. Mestrallet, S. Pavel, A. Servettaz, M. Dramé, A. Muggeo, A. Wynckel, C. Gozalo, M. Abou Taam, A. Fillion, R. Jaussaud, T. Trenque, L. Piroth, F. Bani-Sadr

- All study participants
- Everyone involved in the study

Full study results:

- Demotier S et al. Eclinicalmedicine 2022

Merci de votre attention