Hôpitaux Universitaires Paris Est
TENON

FILFOIE
FILIÈRE DE SANTÉ MALADIES RARES DU FOIE DE L'ADULTE ET DE L'ENFANT

FILFOIE

Filière de Santé Maladies Rares du Foie de l'Adulte et de l'Enfant

Lésions rénales induites par la cholestase « Néphropathie par cristaux biliaires/ néphropathie cholémique»

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Hôpital TENON

Conflits d’intérêts

- Travel grant : Fresenius
- Lecture grant : Alexion

Lésions rénales induites par la cholestase

Vignette clinique

Tableau néphrologique & circonstances de découverte

Physiopathologie : la bilirubine un « coupable vraiment idéal ? »

Un cas clinique

- Un patient de 69 ans
- Retraité, ancien chauffeur-livreur.
- Ethylisme chronique non sevré 80 g/j
- Tabagisme actif 30 PA non sevré.
- Fracture du pied gauche en 2010

HdM

- Découverte d'une **cirrhose alcoolique** **en mars 2014** devant cytolyse hépatique

- **Mi-février 2015** : ictère, OMI, ascite motivant une consultation aux urgences de Bichat le 03/03/2015.

- **Hépatologie de SAT :** 1er épisode de décompensation oedémato-ascitique :

  - **hépatite OH aigue** confirmée à la PBH du **07/03/2015**.

  - Score de Maddrey 57,

HdM

- Traitement par **Cortancyl**

✓ 40mg pendant 7 jours sans effet motivant l'arrêt des corticoïdes.

- **Aggravation du bilan hépatique** :
  - TP 45 %
  - ASAT 260, ALAT 356,
  - PAL 778, GGT 1607, Bilirubine c/t : 789/988 µmol/L

- **Bilan étiologique :** négatif en dehors de l'exogénose.
  - Echographie hépatique : flux porte hépatopète. Pas de CHC visible. VO grade I.
  - **LA : 12 éléments**, culture négative
  - Candidose oesophagienne traitée par Fluconazole.
  - Apparition d'une **encéphalopathie hépatique** traitée par Duphalac associé à un **ictère ++**
  - Hypertendu sous Loxen

Apparition d'une IRA (1)

Créatinine à **66** µmol/L à l'arrivée le **03/03/2015**

IRA

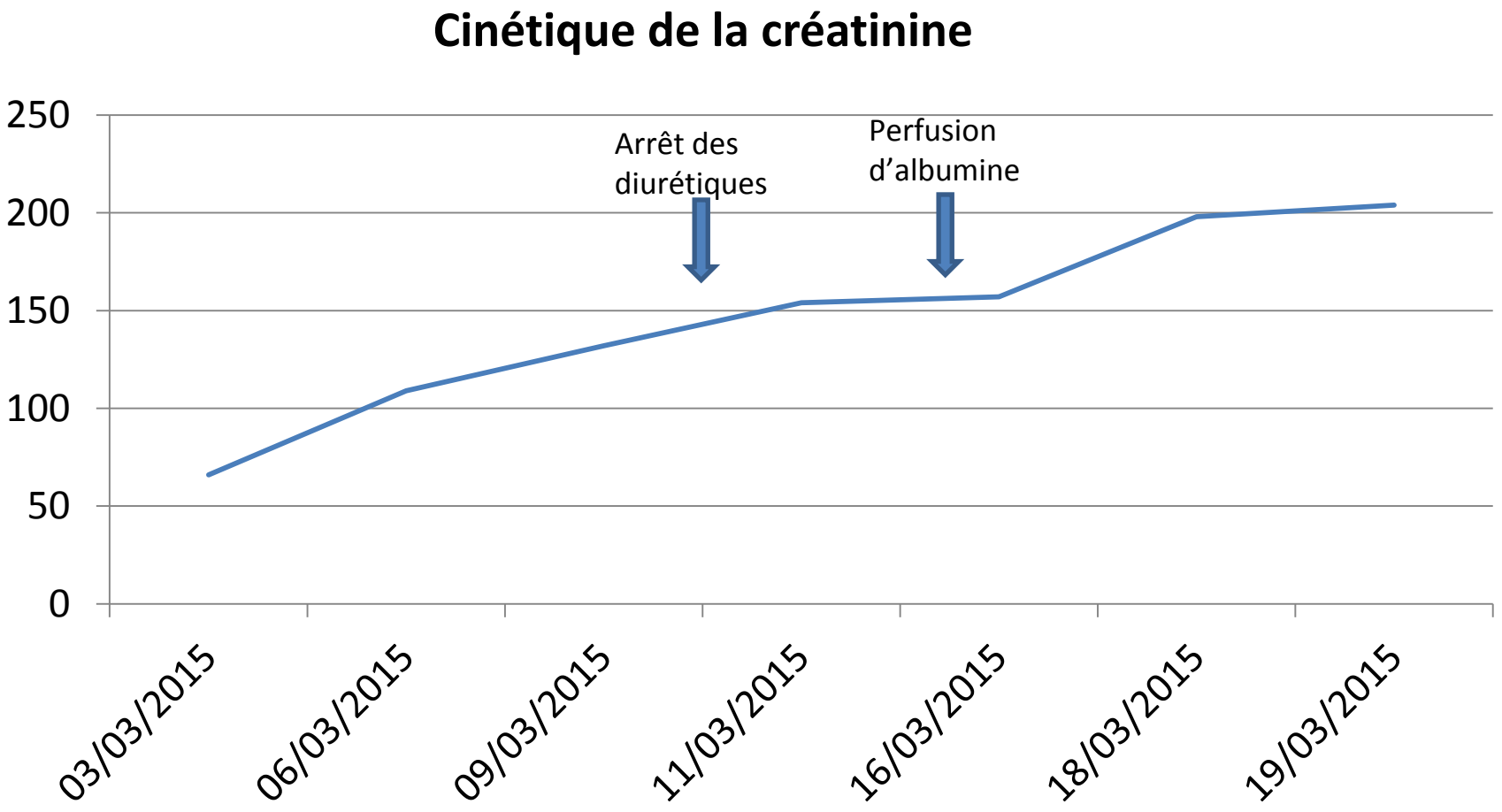
IRA d'aggravation progressive/J2 post PBH : avec une créat à **134 -> 380** µmol/L entre le **09/03/2015 et le 19/03**

Pas de dilatation des cavités pyélocalicielles et doppler hépatique perméable le **11/03/2015**

Iono U **17/03** : Nau 46mmol/L, Ku 26mmol/L, FeUrée 50%.

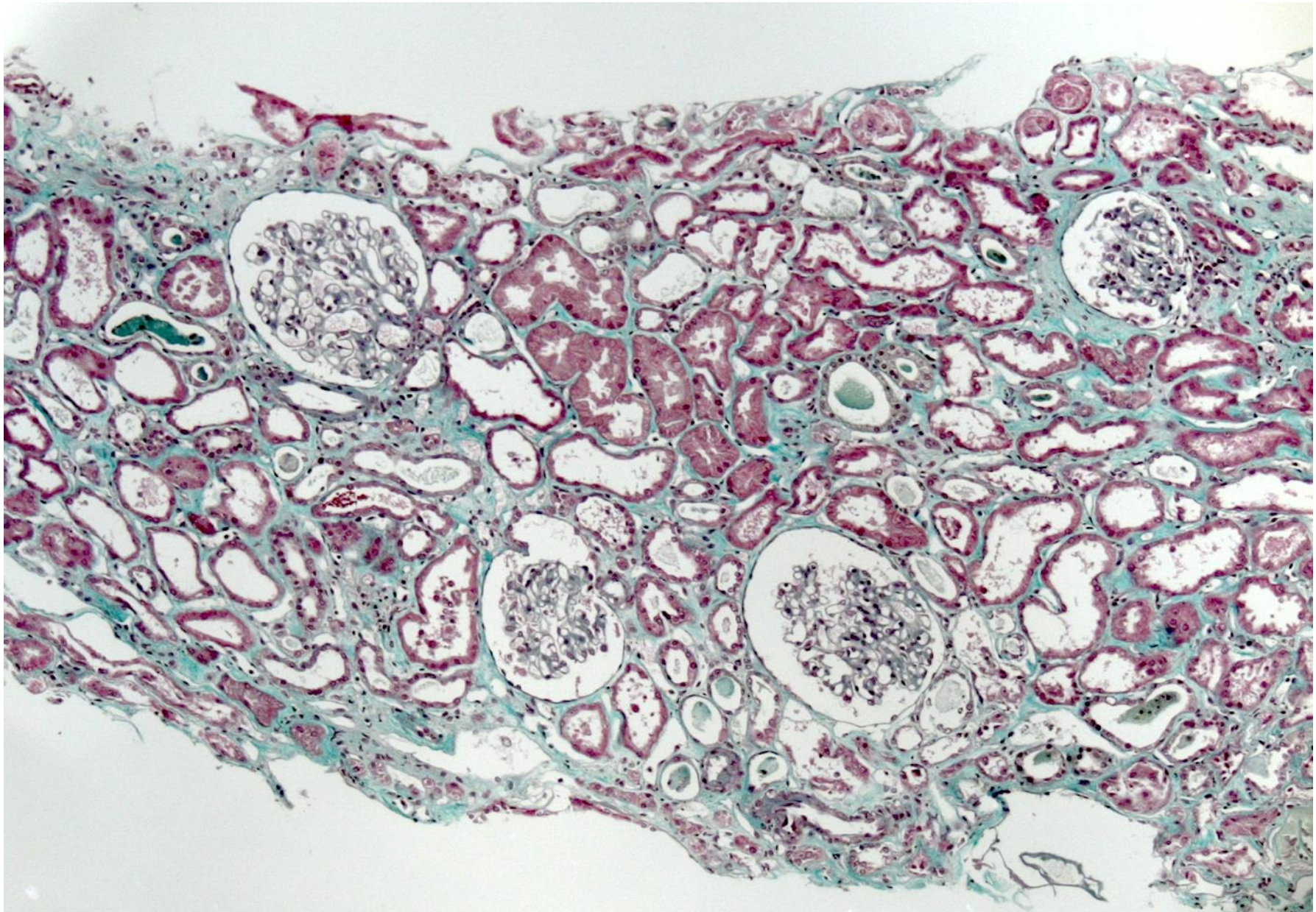
Protéinurie/créatininurie sur échantillon : 0.04 g/mmol, sédiment inactif, acanthocytes absents

Apparition d'une IRA (2)

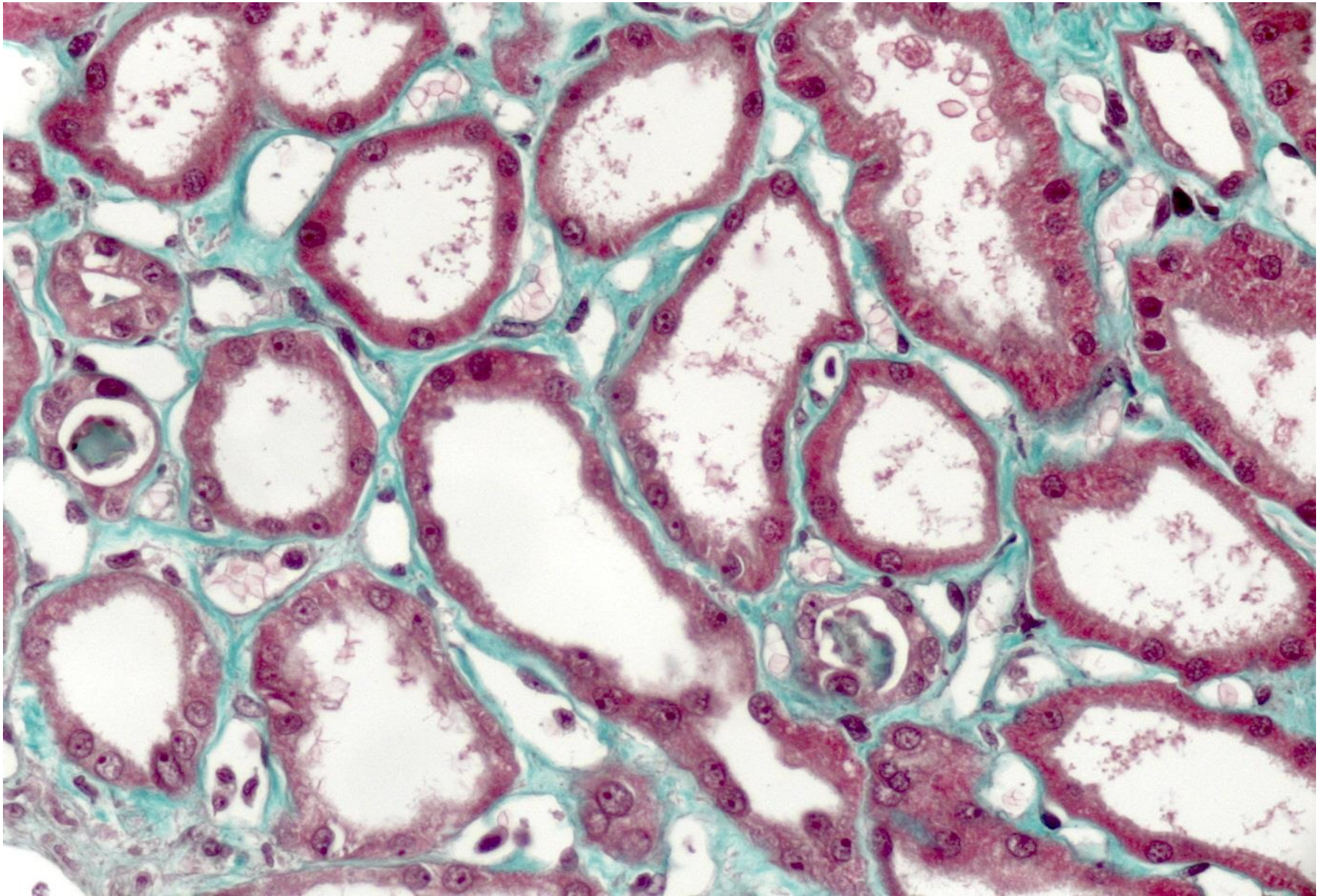


Devant la poursuite de la dégradation de la fonction rénale, **Admission en UNTR**

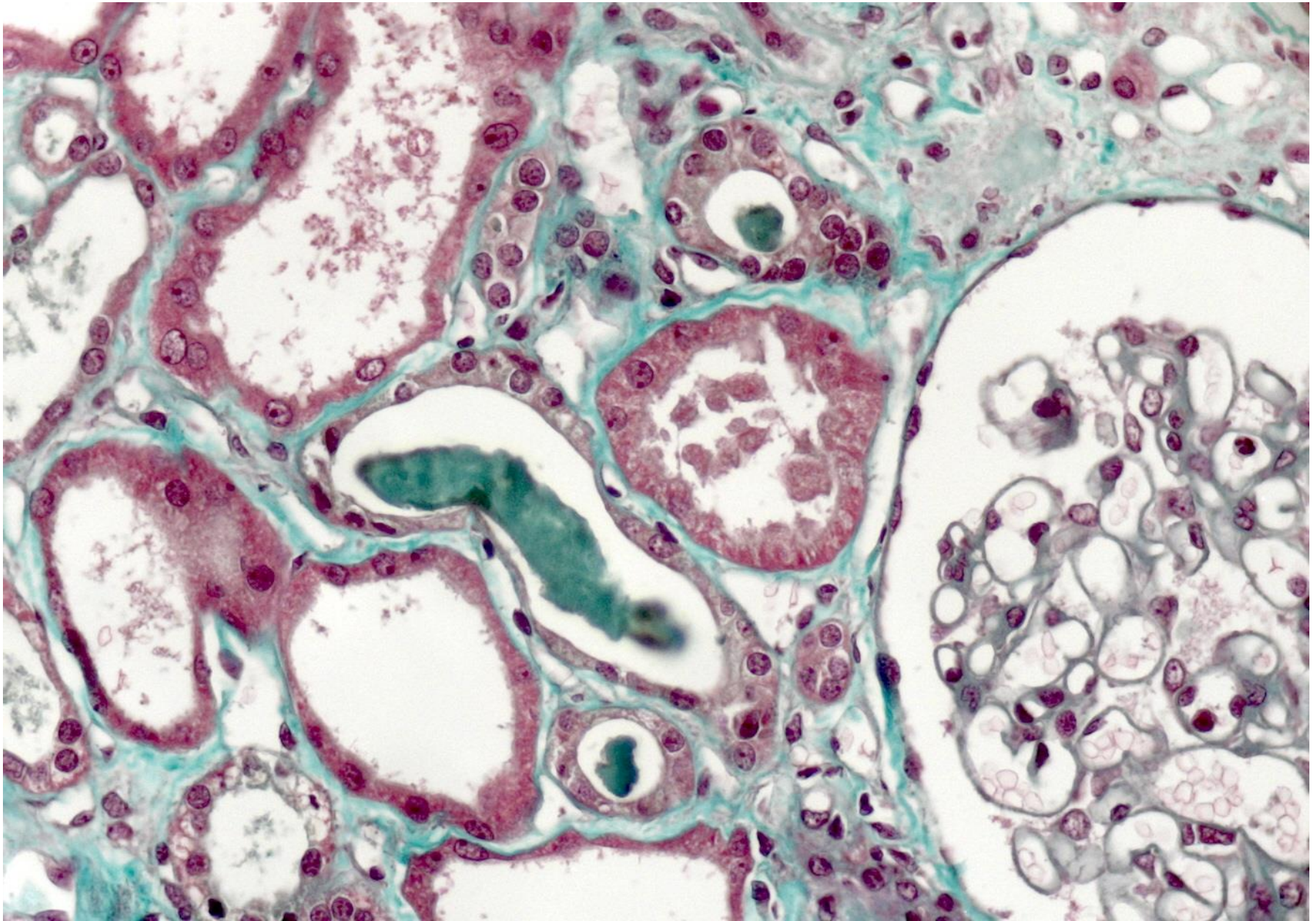
Résultats de la PBR



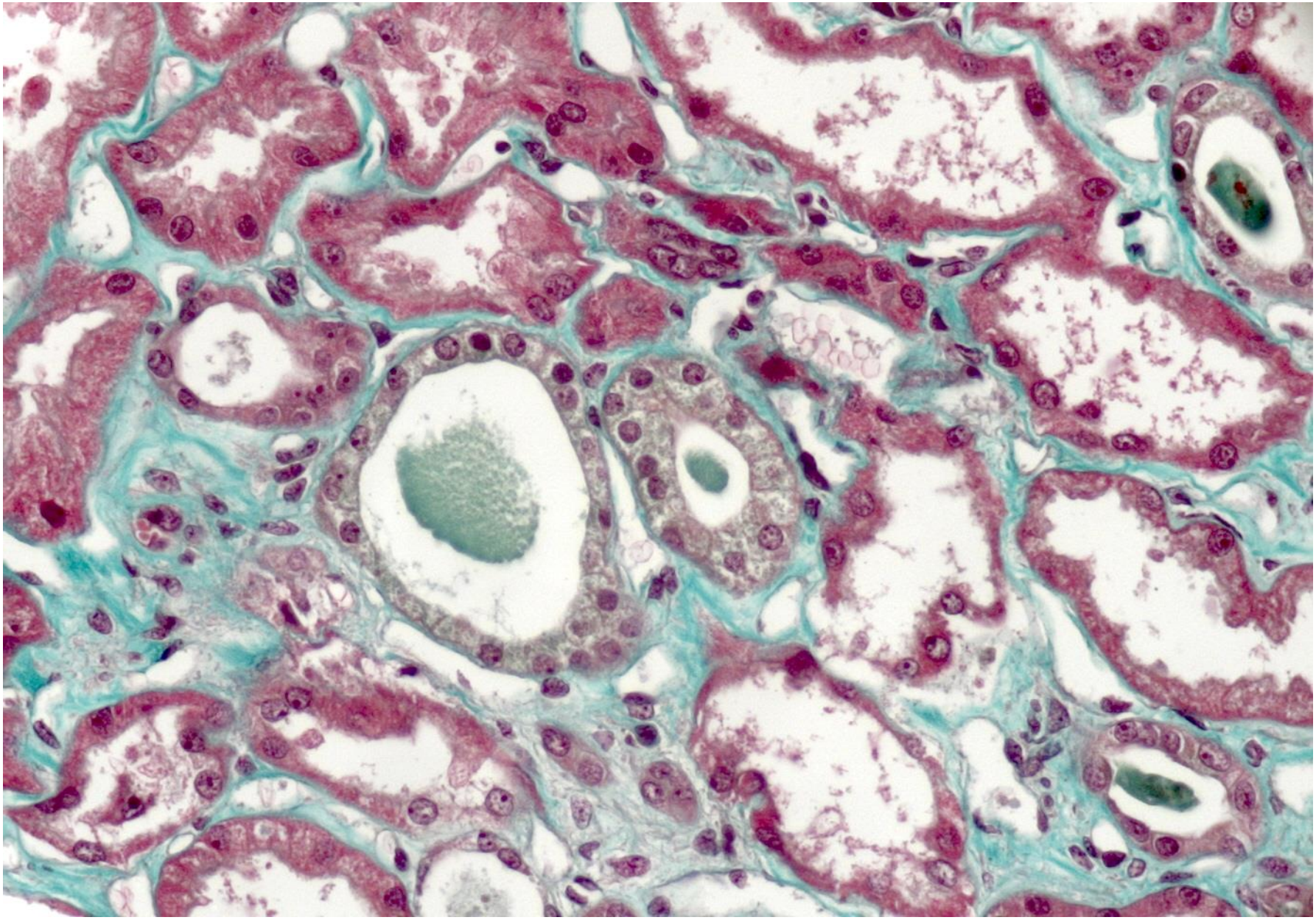
Résultats de la PBR



Résultats de la PBR

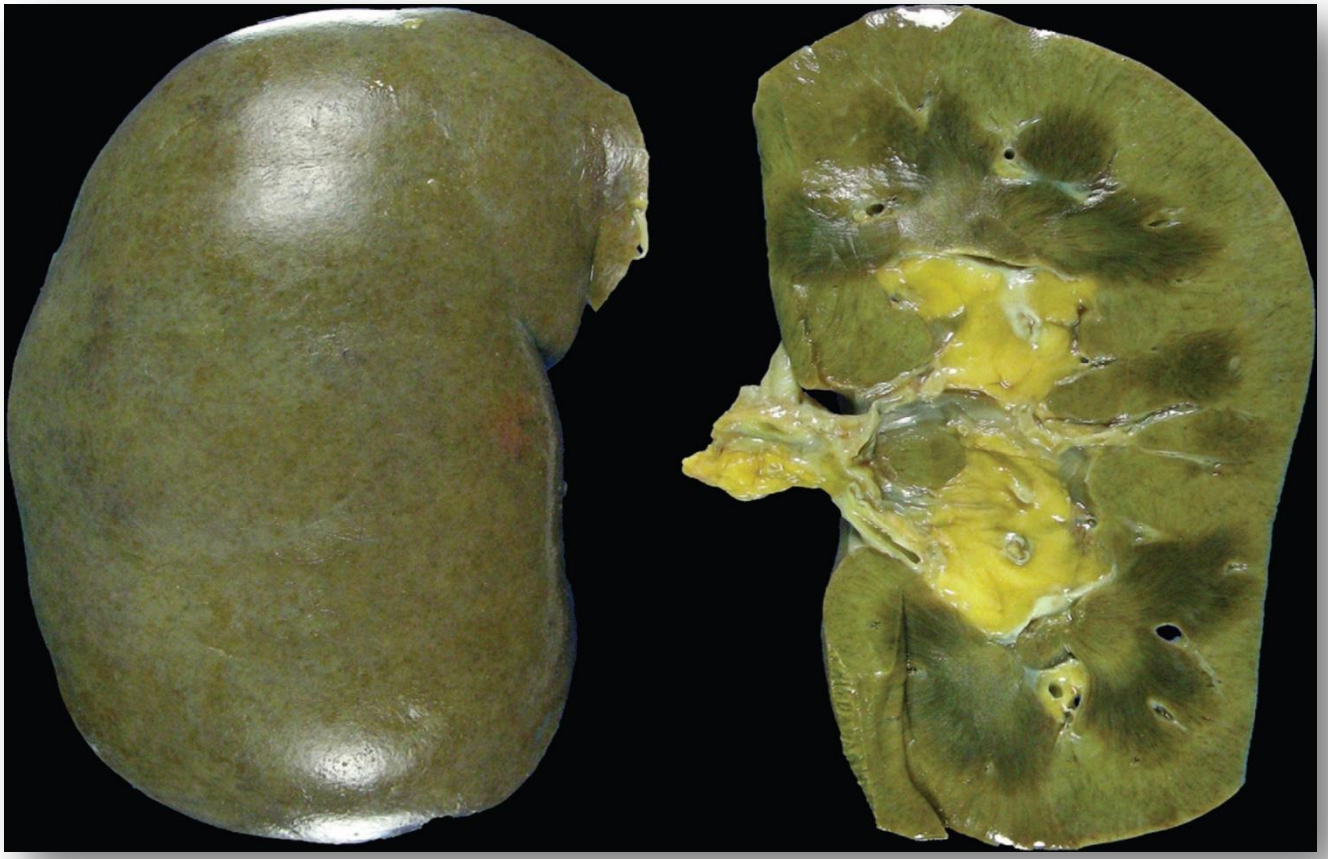


Résultats de la PBR



NÉPHROPATHIE CHOLÉMIQUE : CARACTÉRISATION CLINICO-HISTOLOGIQUE

Quand le rein est vert, vous pensez à quoi ?



Historiquement : **cholestase obstructive**

Clairmont et von Haberer, 1911

Un regain d'intérêt récent

Author	Source of data	Subjects, n	Etiology of jaundice	Clinical/histological features	
van Slambrouck et al. [33]	Autopsy Biopsy	44	Cirrhotic jaundice Cholestasis/obstructive jaundice Acute cholestatic hepatitis	Bile casts predominantly at distal nephron segments Variable degree of acute tubular injury Mononuclear inflammatory cells in vasa recta	2013
Uslu et al. [73]	Biopsy	20	Obstructive jaundice	Acute tubular necrosis Dilatation of peritubular venules	2010
Betjes and Bajema [29]	Biopsy	2	Obstructive jaundice	Bilirubin pigment in tubules Acute tubular necrosis Granular casts upon urine sediment	2006
Luciano et al. [32]	Clinical Urine microscopy Biopsy	1	Anabolic steroid-induced severe cholestatic liver injury	AKI Bile-stained granular casts and renal tubular epithelial cells upon urine microscopy Acute tubular injury with greenish-brown casts in distal tubular lumina	2014
Rafat et al. [77]	Biopsy	1	Obstructive jaundice (cholangiocarcinoma)	Deterioration of kidney function Bile thrombi in dilated tubules Bile granules in cytoplasm of tubular epithelial cells	2013
van der Wijngaart et al. [75]	Biopsy	1	Obstructive jaundice	Bile casts in tubules Reactive changes of tubular epithelial cells	2014
Song [78]	Autopsy	1	Severe liver dysfunction	Numerous pigmented casts in distal tubules or collecting ducts	2009

Krones Dig Dis 2015

Une pathologie sous-estimée ?

paramètre	Hall + n=52 (55%)	Hall - n=42 (45%)	p
Total bilirubin, mg/dL	**10.4 +/- 12.0 (170 µmol/L)**	3.5 +/- 4.3	<.001
Conjugated bilirubin, mg/dL	6.3 +/- 9.4 (100 µmol/L)	1.5 +/- 3.4	0.02
Ictère	30/51 (59.0)	6/41 (15.0)	<.01
Creatinine (┼ -7J)	2.8 +/- 2.1	1.8 +/- 1.4	0.02
Tubular atrophy	43/52 (82.7)	24/42 (57.0)	<.01
Interstitial fibrosis	41/52 (78.8)	21/42 (50.0)	<.01

Foshat Am J Pathol 2017

Pourquoi une réémergence actuelle ?

- **difficultés de documentation histologique**
- Troubles de l'hémostase et/ou de la coagulation
- Localisation préférentielle dans la medulla
- Physiopathologie ?

Des variantes en terme de présentation clinique

Rein et ictère	Sdre de Fanconi
	Tubulopathie proximale incomplète
	NTA

Bairaktari hepatology 2001, Mairiang KI 1990, Betjes J Nephrol 2006

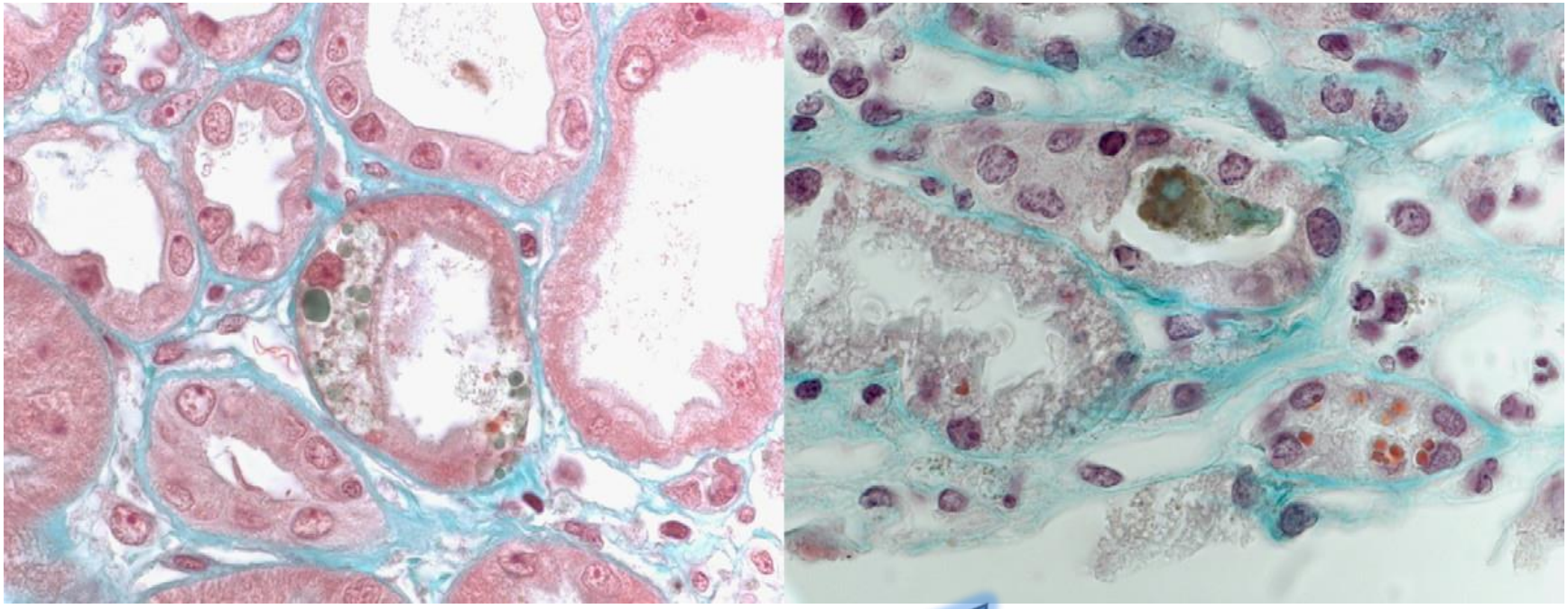
Tubulopathie au cours de l'ictère

Fonction rénale et tubulaire chez des patients ictèriques vs sujets contrôle

Renal Function Studies	Jaundiced Patients (n = 35)	Normal Subjects (n = 40)	*P*
Creatinine clearance (mL/min)	92 ± 21	97 ± 16	NS
$TmPO_4/GFR$ (mg/dL)	3.3 ± 0.6 (8/23%)	3.6 ± 0.5	.01
Fractional excretions (%)			
Uric acid	35.6 ± 19.4 (27/77%)	8.0 ± 2.4	.001
Sodium	0.9 ± 0.3	0.8 ± 0.1	NS
Potassium	10.5 ± 3 (2/5.7%)	8.6 ± 1.6	NS
Magnesium	3.4 ± 1.2 (5/14.3%)	3.2 ± 0.8 (2/5%)	NS
Phosphate	18.3 ± 15 (12/34.3%)	14 ± 4.0	.01
Calcium	2.0 ± 0.8	1.8 ± 1.0	NS
Percent reabsorption of glucose	98.9 ± 0.06 (27/77%)	99.8 ± 0.05	.05
Excretion of α_1-microglobulin (mg/g creatinine)	78 ± 65 (27/77%)	7 ± 4	
Urinalysis			
Volume (L/24 h)	1.4 ± 0.5	1.5 ± 0.4	NS
Osmolality (mosmol/Kg)	690 ± 190	640 ± 175	NS
Fasting pH	5.2 ± 0.5	5.4 ± 0.8	NS

Bairaktari hepatology 2001

La « marque » histologique : présence de cylindres de bilirubine



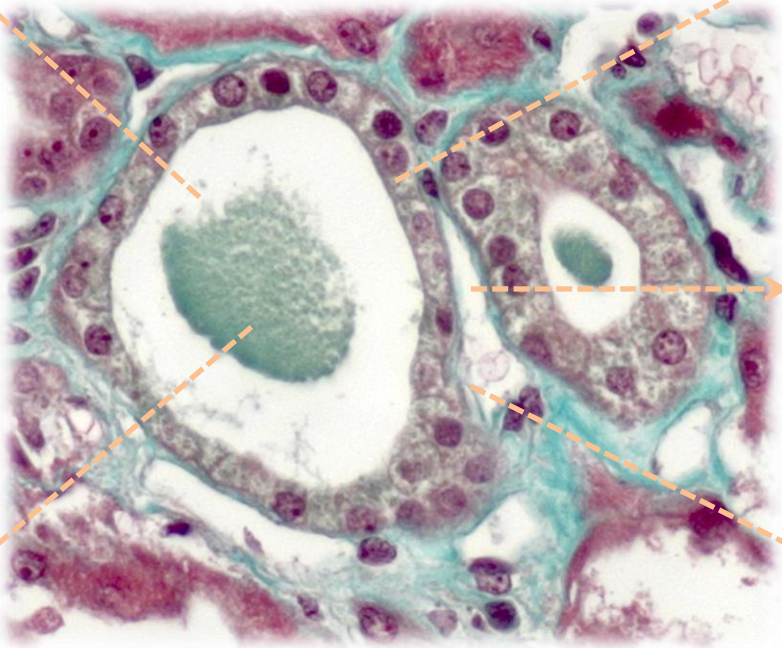
Cholestase majeure

Rafat et al AJKD 2013, Mairiang KI 1990, Shet Ind J Pathol

Diagnostic différentiel anatomopathologique ?

Cylindre myélomateux
polychromatophile et fracturé

Cylindre myoglobine
Rouge et granulaire

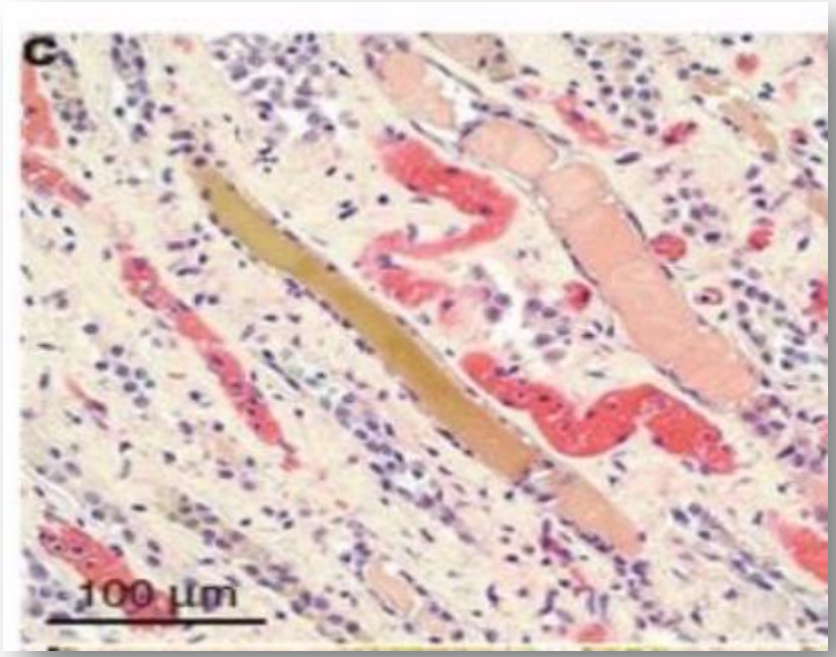


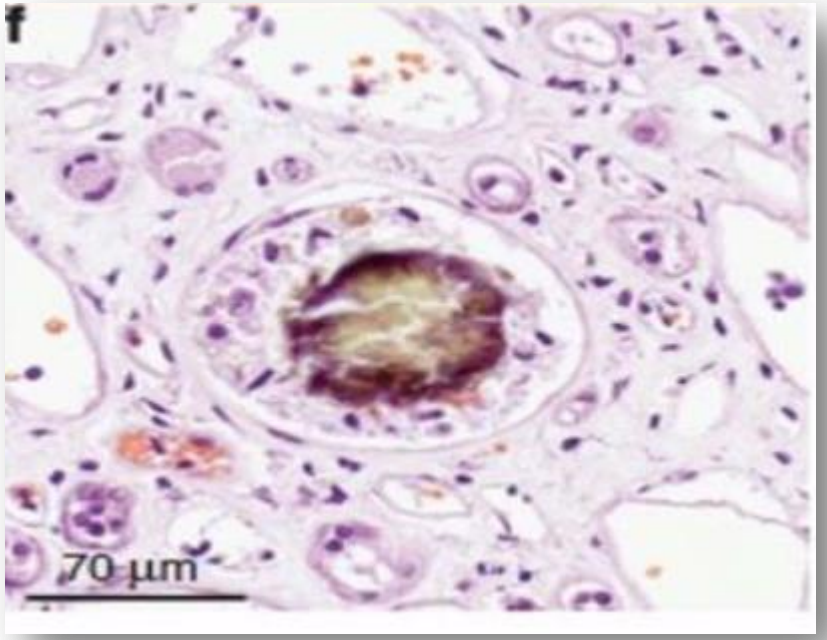
Cylindre lysozyme
Sombre et contexte de LMNC

Cylindre hémoglobine
Rouge et granulaire

Cylindre de bilirubine
Vert/marron avec des contours rugueux

D’autres présentations histologiques

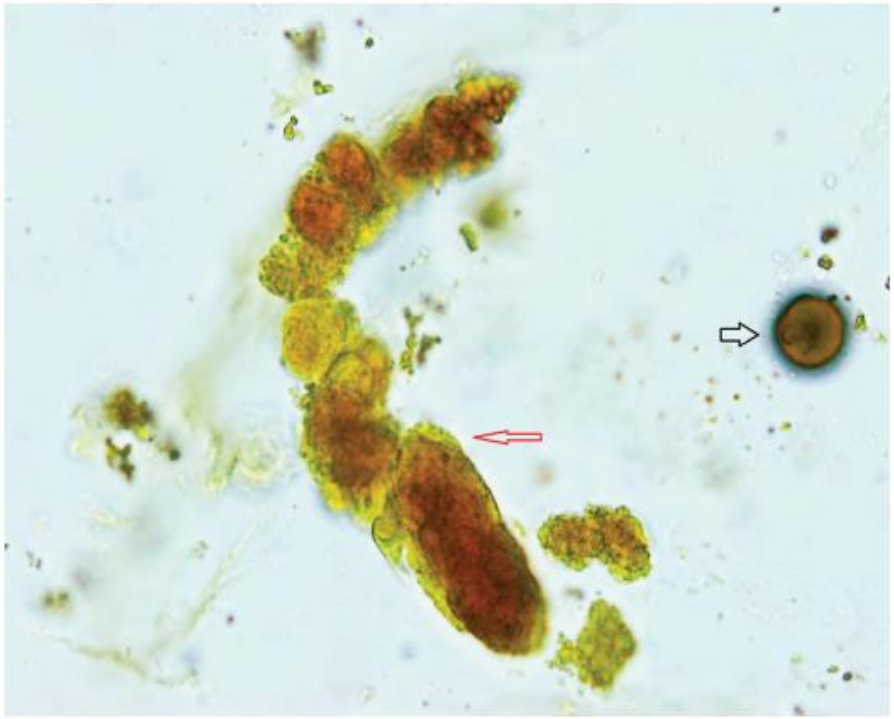


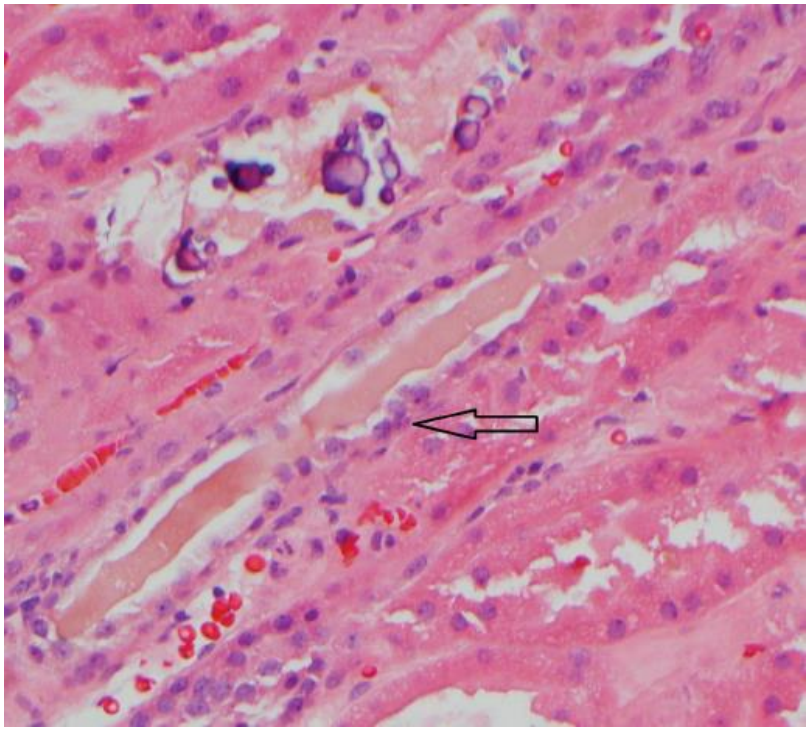


pH urinaire acide ?

van Slambouck KI 2013

Penser aux urines……





Jain kidney international 2015

QUELS SONT LES PATIENTS A RISQUE ?

clinical investigation http://www.kidney-international.org

Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

Charles M. van Slambrouck[1], Fadi Salem[2], Shane M. Meehan[1] and Anthony Chang[1]

[1]Department of Pathology, University of Chicago Medical Center, Chicago, Illinois, USA and [2]Department of Pathology, Mount Sinai School of Medicine, New York, New York, USA

Ictère

Clinique et biologique

Bilirubine

Pre mortem

> 34 µmol/L

Histologie

44 cas

--24 cylindres bilirubine/

--20 SANS cylindre

van Slambouck KI 2013

clinical investigation http://www.kidney-international.org

Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

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Table 2 | Clinical data for 44 cases

	SCr (mg/dl)	BUN (mg/dl)	Total Bili (mg/dl)	Direct Bili (mg/dl)	AST (U/l)	ALT (U/l)	ALK (U/l)	Albumin (g/dl)
Bile casts present ($n = 24$)	2.3	35.5	26.2	16.3	302	148	159	3.1
Bile casts absent ($n = 20$)	1.8	39.2	15.1	9.2	252.8	85	178	3
P-value	0.12	0.11	**0.001**	**0.003**	0.14	0.1	0.11	0.2

http://www.kidney-international.org

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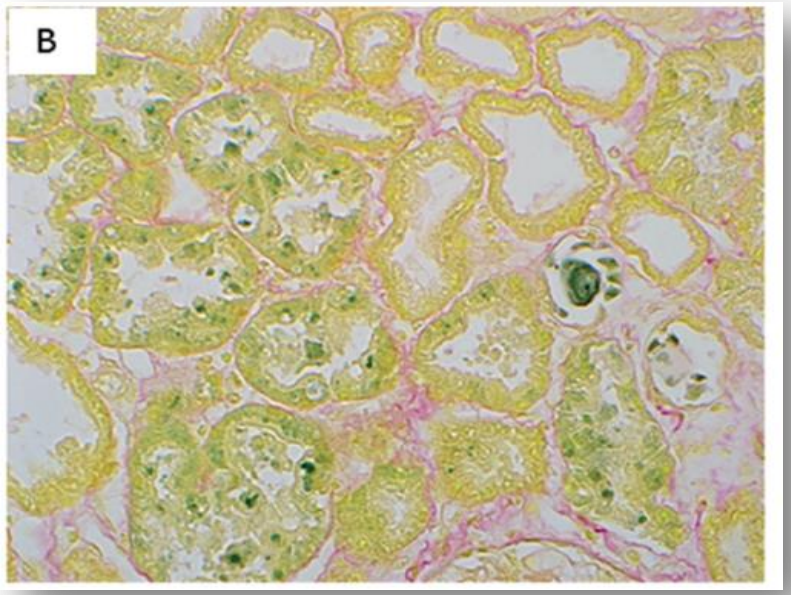
	Patients (% of total)	Bile casts present	Bile casts absent
Total	44	24 (55%)	20 (45%)
Males	25 (57%)	15 (60%)	10 (40%)
Females	19 (43%)	9 (47%)	10 (53%)
African American	22 (50%)	12 (55%)	10 (45%)
Caucasian	15 (34%)	8 (53%)	7 (47%)
Hispanic	4 (9%)	1 (25%)	3 (75%)
Unknown ethnicity	3 (7%)	3 (100%)	0
Hepatorenal syndrome, present	13 (30%)	11 (85%)	2 (15%)
Hepatorenal syndrome, absent	31 (70%)	13 (42%)	18 (58%)
Acute tubular injury, present	32 (73%)	21 (66%)	11 (34%)
Acute tubular injury, absent	5 (11%)	1 (20%)	4 (80%)
Acute tubular injury, indeterminate	7 (16%)	2 (29%)	5 (71%)
Gross jaundice, present	7 (17%)	7 (100%)	0
Gross jaundice, absent	34 (83%)	14 (41%)	20 (59%)
Cirrhotic jaundice	23 (52%)	14 (61%)	9 (39%)
Cirrhosis due to HCV	5 (11%)	0	5 (100%)
Cirrhosis due to EtOH	10 (23%)	10 (100%)	0
Cirrhosis due to HCV and EtOH	4 (9%)	2 (50%)	2 (50%)
Cirrhosis due to NASH	1 (2%)	0	1 (100%)
Cirrhosis due to drug (TPN)	1 (2%)	1 (100%)	0
Cirrhosis (cryptogenic)	2 (5%)	1 (50%)	1 (50%)
Cholestatic/obstructive jaundice	14 (32%)	6 (43%)	8 (57%)
Hepatic jaundice	5 (11%)	4 (80%)	1 (20%)
Hemolytic jaundice	2 (5%)	0	2 (100%)

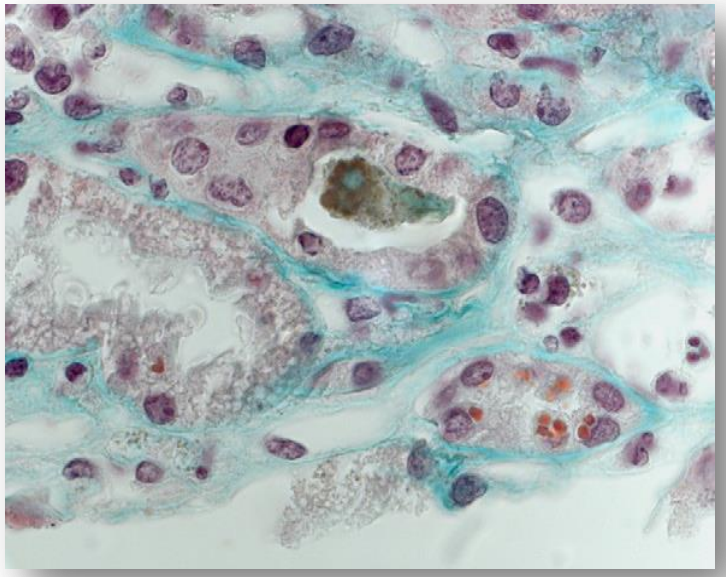
Abbreviations: EtOH, alcohol; HCV, hepatitis C virus; NASH, nonalcoholic

Mais aussi dans d'autres causes de cholestase aiguë



- ✓ 28 ans **Prise d'anabolisants**
- ✓ ASAT 39 UI/L ALAT 46 UI/L
- ✓ PAL 211 UI
- ✓ bilirubine tot/conj :44/29 mg/L **(x 400!!)**
- ✓ TP : 60%
- ✓ Creat 190 µmol/L Pu < 0 BU neg

- ✓ 46 ans, transplanté rénal
- ✓ **Chiolangiocarcinome**
- ✓ bilirubine tot/conj :31/29 mg/L **(x 280 !)**
- ✓ TP : 88%
- ✓ Creat 450 µmol/L Pu < 0 BU neg



Alkhunaizi Clin Nephrol 2017
Rafat AJKD 2013

UNE TUBULOPATHIE SECONDAIRE A LA BILIRUBINE, VRAIMENT ?

Physiopathologie ??

« hémodynamique systémique et régionale »

« tubulaire »

Toxicité des acides biliaires ??

Bile cast nephropathy ou cholemic nephrosis ?

Betjes J Nephrol 2006

…..Un effet néphrotoxique de la bilirubine ???

Pro-toxique

Table 1. Summary of the Main Studies With Evidence of Pro-Toxic Effects of Bilirubin in the Kidneys

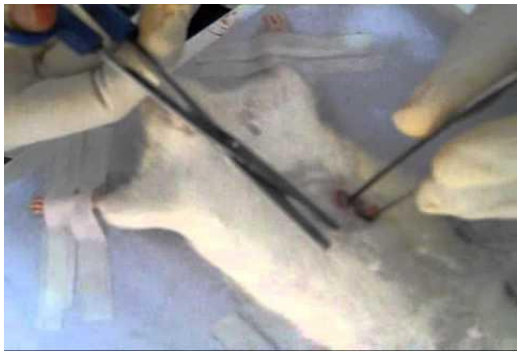
Authors/year	Methods	Results	Conclusion
Padillo et al, 2009 [15]	Experimental study. Animals submitted to common bile duct ligation had their renin, aldosterone, endothelin-1 and prostaglandine E2 studied and compared to control group.	Both groups had the same values for diuresis, renin and creatinine clearance at 24 h. Animals with obstructive jaundice had lower sodium concentration and an increase in aldosterone levels ($P < 0.03$), endothelin-1 ($P < 0.001$) and prostaglandine E2 ($P < 0.001$) in urine.	Vasoactive hormones may play a role in renal complications during obstructive jaundice.
Fickert et al, 2013 [13]	Experimental study. Animals submitted to 3-day common bile duct ligation, with a group of receptor knockout (para que?) mice for bile acids and (?) renal histology analyzed.	Bile common duct ligation induced renal tubular epithelial injury predominantly at the level of collecting ducts, followed by progressive interstitial nephritis and tubulointerstitial fibrosis. Knockout mices were completely protected from renal fibrosis.	Urinary excretion of bile acids represents a trigger for renal tubular epithelial injury leading to cholemic nephropathy.
Van Slambrouck et al 2013 [9]	Clinicopathologic study of 44 subjects (41 autopsies and three biopsies) from jaundice patients.	24 patients had bile casts with involvement of distal nephron tubules for?? six severe cases. Eleven of 13 patients with hepatorenal syndrome and all 10 with cirrhosis had tubular bile casts.	Bile cast nephropathy is an appropriate term for severe form of renal injury observed in cirrhotic patients.
Pereira et al, 2008 [23] Esse parece mais table 2	Experimental study. Male Wistar rats were submitted to sham surgery or bile duct ligation. Determination of renal function and histology samples were obtained after 6 weeks.	At 6 weeks the group with bile duct ligation showed features of hepatorenal syndrome including increase in serum creatinine and reduction of creatinine clearance, water excretion and urinary sodium concentration. Histological analysis has shown no alterations.	Bile duct ligation produced progressive renal dysfunction, although without structural changes in the kidneys, characterizing functional HRS.
Bal et al, 2000 [10]	Post-mortem histological analysis from patients died from subacute hepatic failure.	Bile cast nephropathy was observed in three of the patients.	Bile cast nephropathy is an important finding in the kidneys of icteric patients.

Neutre/ protecteur

Table 2. Summary of the Main Studies With Evidence Against Toxic Effects of Bilirubin in the Kidneys

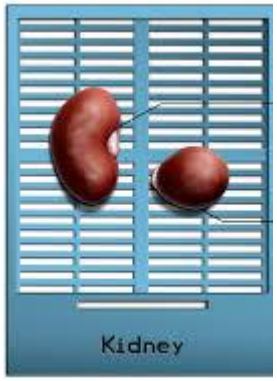
Authors/year	Methods	Results	Conclusion
Leung et al, 2001 [24]	Experimental study. Animals were submitted to common bile duct ligation and hypertonic glycerol was used to induce acute tubular necrosis (ATN). Renal injury was assessed by plasma creatinine concentration and histology.	Ligation of the common bile duct markedly reduced acute renal injury evidenced by less severe ATN and lower plasma creatinine. Ligation of the bile duct induced heme oxygenase-1 expression in the kidneys.	Ligation of bile common duct confers resistance to glycerol-induced acute renal injury which may be related to the expression of heme oxygenase-1 in the kidneys.
Guo et al, 2011 [30]	Experimental study. Animals divided into groups with biliary cirrhosis induced by bile duct ligation and sham. Expression of heme oxygenase-1 in kidneys was analyzed as serum creatinine and renal blood flow.	Heme oxygenase-1 expression, serum creatinine levels and renal blood flow were lower in the cirrhotic group ($P < 0.05$).	Intervention to increase the expression of heme oxygenase-1 in kidneys played a role in bilirubin protective effect in renal failure.
Deetman et al, 2012 [21]	Prospective data collected from August 2001 and July 2003 from non-icteric renal transplant recipients patients with a functioning graft for > 1 year.	Median data follow up to 7.1 years. Circulating levels of bilirubin were inversely associated with late graft failure, independently of urinary protein excretion, calcineurin inhibitors and gender.	Findings consistent with a protective effect of increased endogenous bilirubin against development of late graft failure in renal transplant recipients.
Oh et al, 2013 [22]	Experimental study. Male rats were submitted to intraperitoneal injection of bilirubin three times daily for 1 week before the administration of ciclosporine and a control group only with ciclosporine administration.	Ciclosporine induced increase in urine kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Bilirubin reduced KIM-1 ($P < 0.05$) while NGAL exhibited a downregulation trend. The protein expression of NOX4 and p22phox was reduced by bilirubin and also apoptosis evaluated by TUNEL assay was ameliorated by bilirubin injection ($P < 0.01$).	The direct administration of bilirubin protected against ciclosporine induced tubular injury via inhibition of oxidative stress and apoptosis.

Effets protecteurs de la bilirubine ?

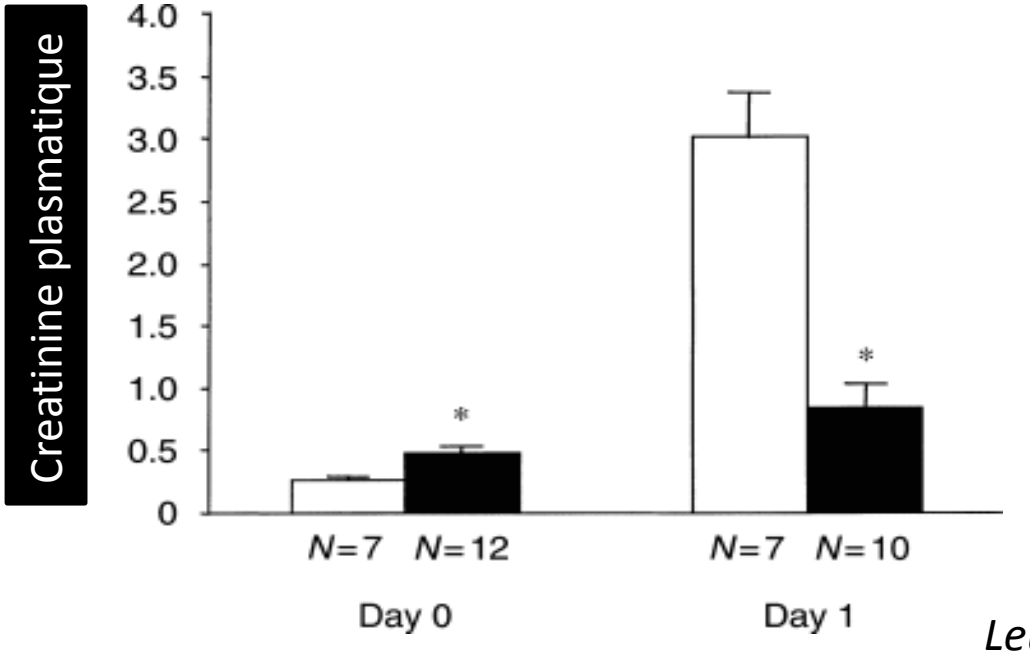


J6

J8

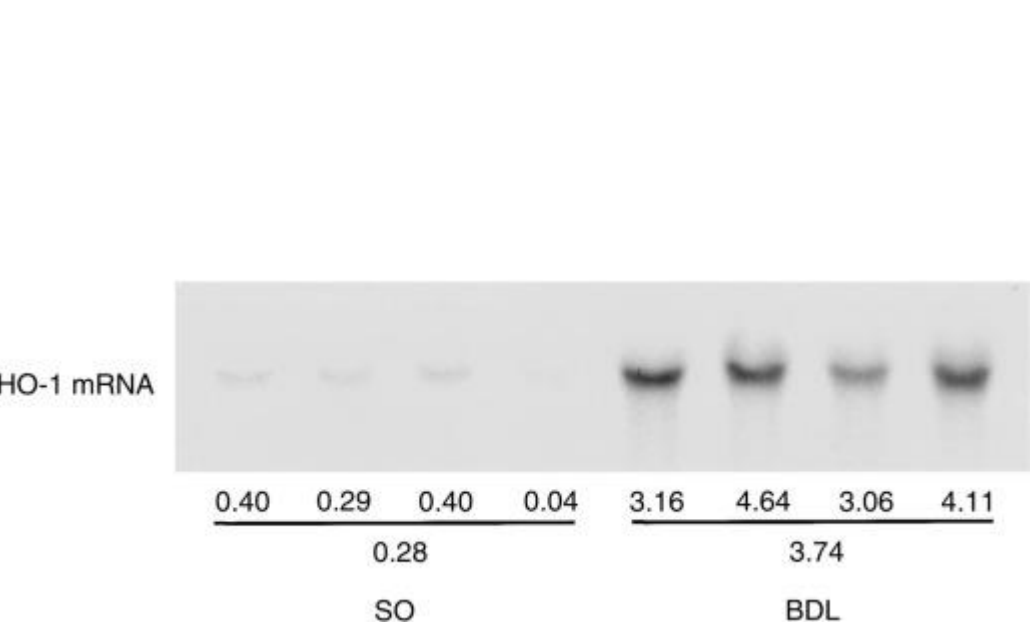


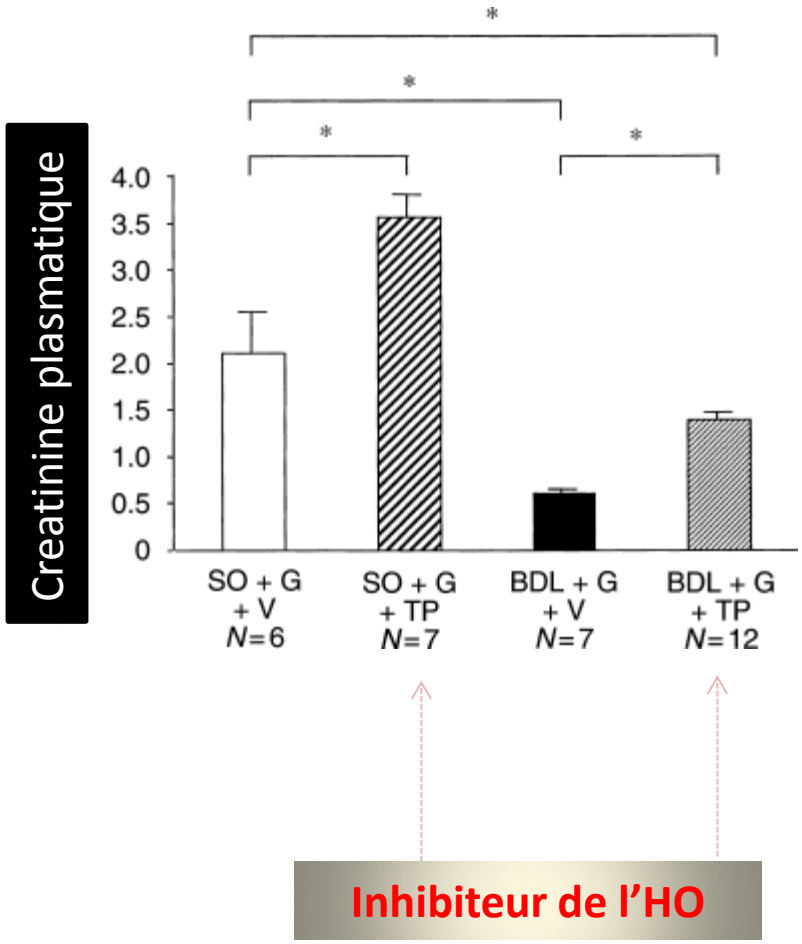
Injection de glycerol



Leung kidney international 2001

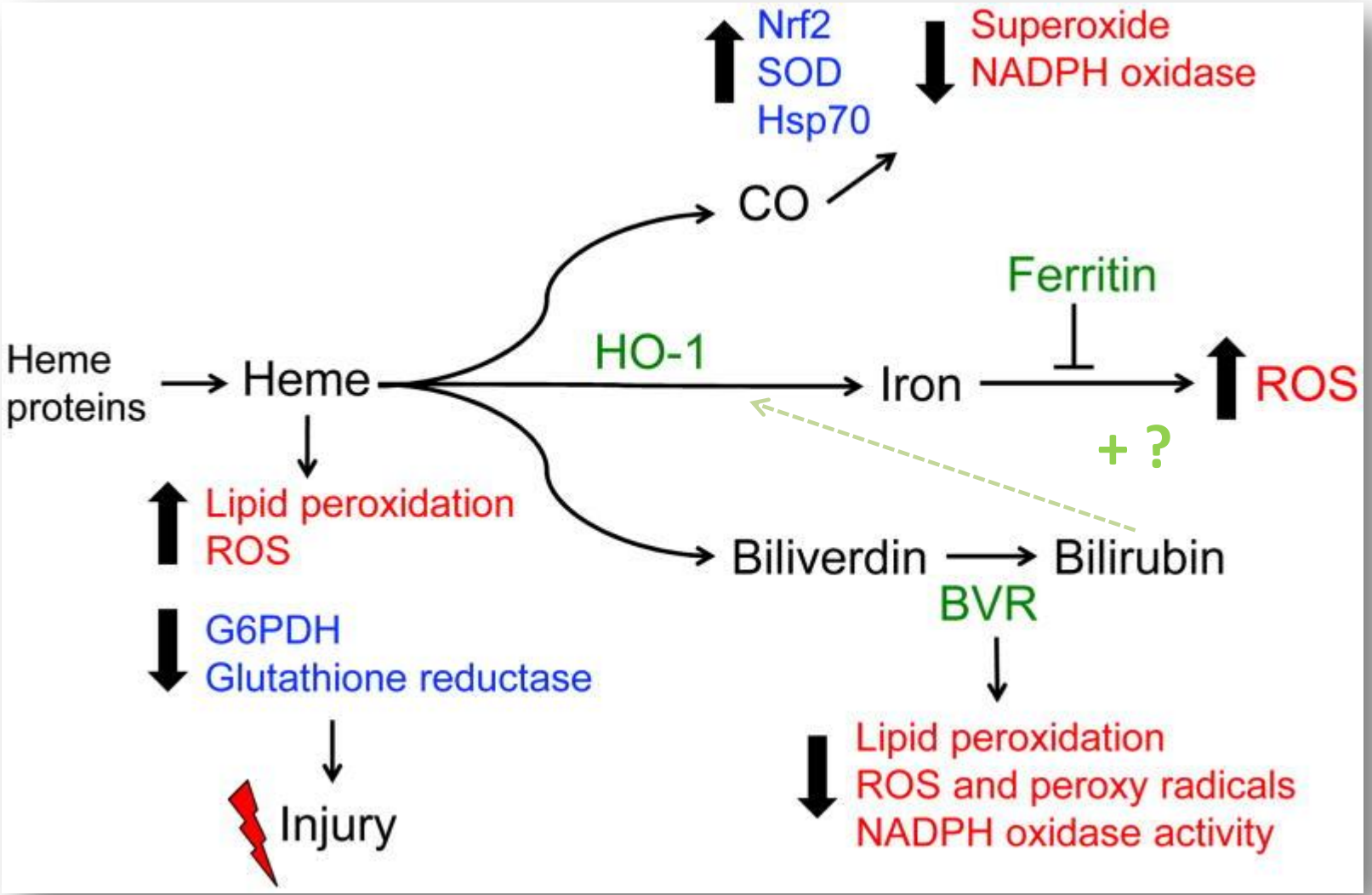
Un effet médié par l'induction de l'hème oxygénase 1





Leung kidney international 2001

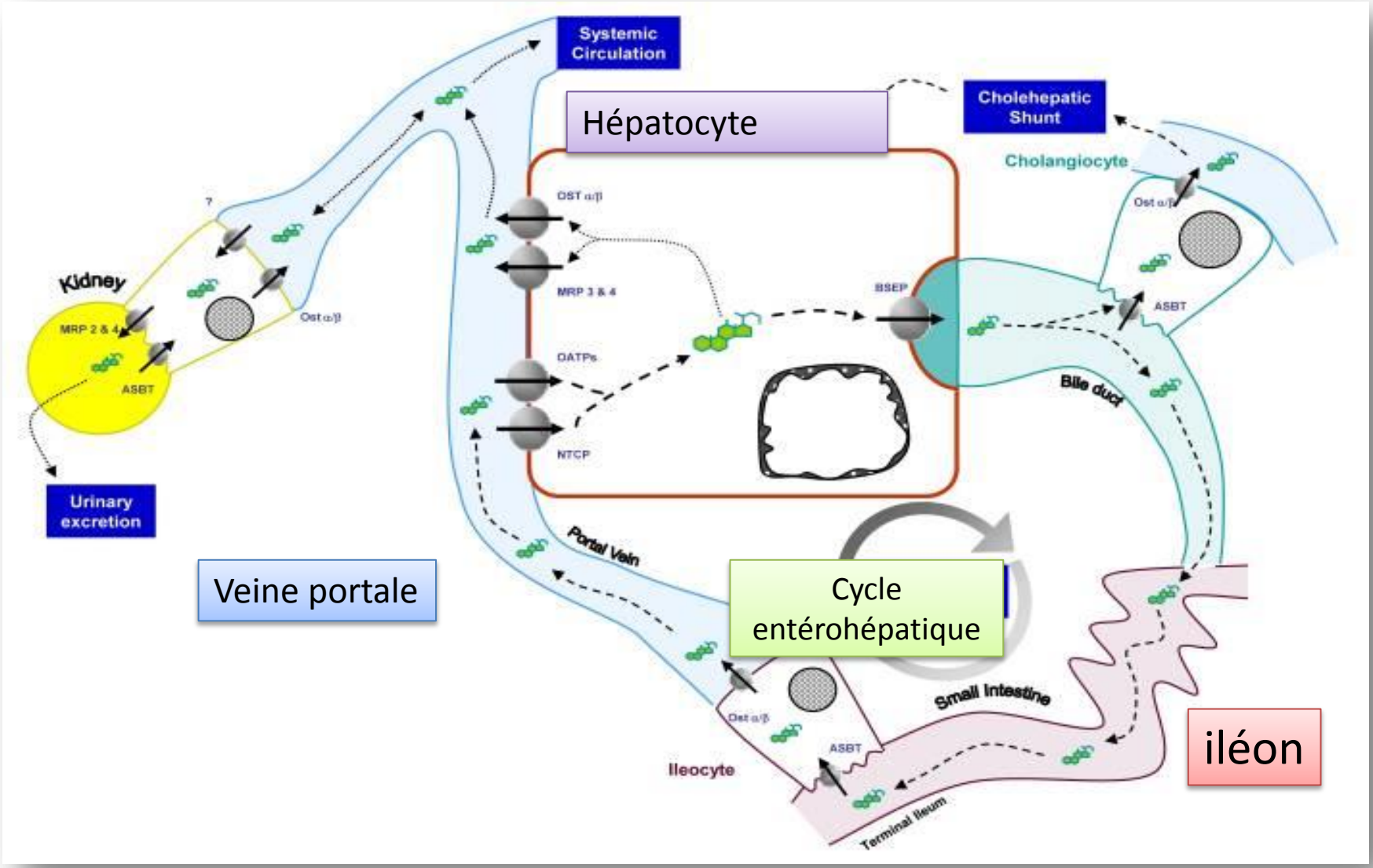
La bilirubine comme témoin des effets protecteurs de l'HO-1?



Subashini AJKD 2017

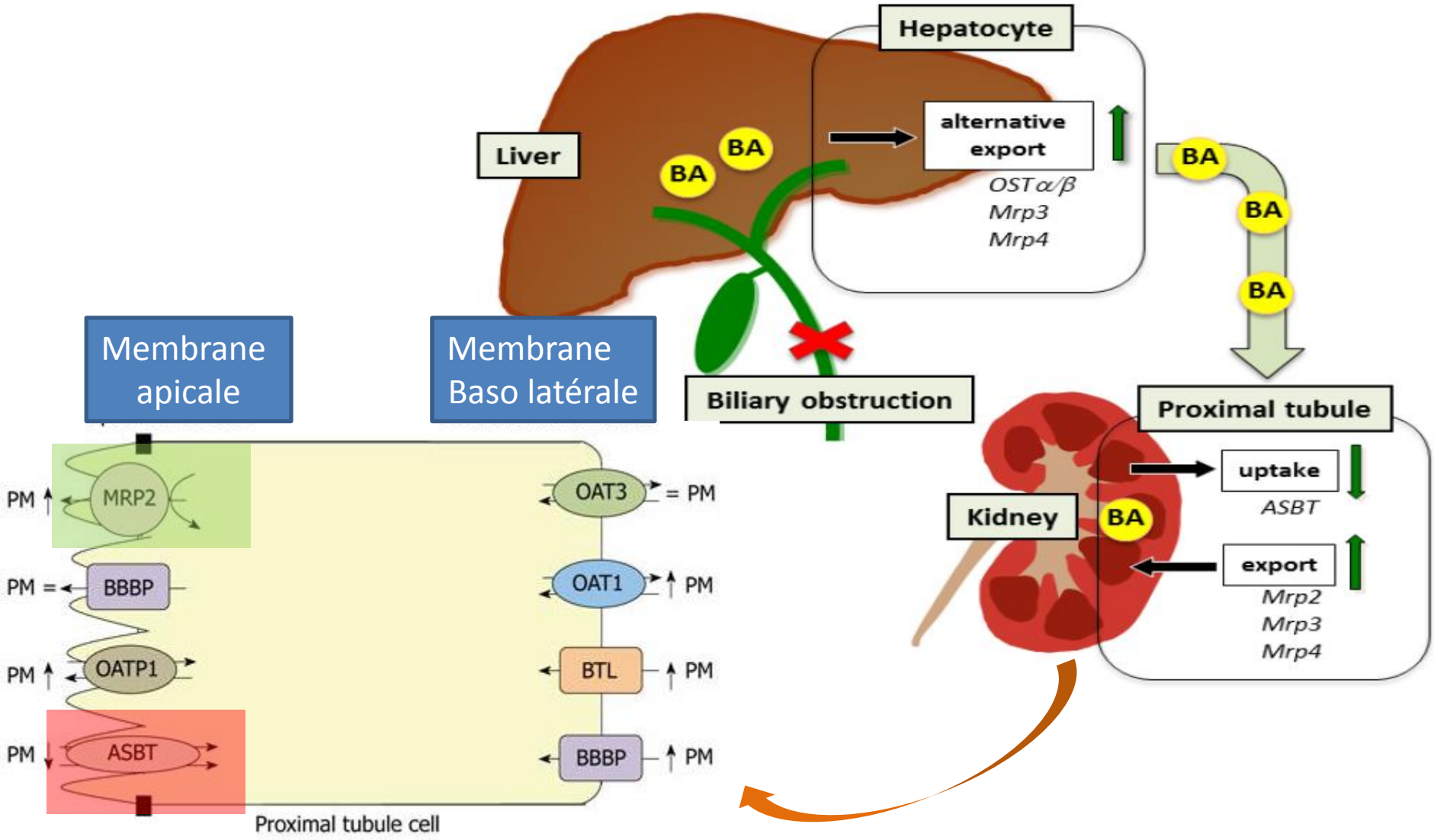
DE LA TUBULOPATHIE SECONDAIRE A LA BILIRUBINE A LA NÉPHROPATHIE CHOLÉMIQUE

Système rénal & homéostasie des acides biliaires
(1) Physiologie



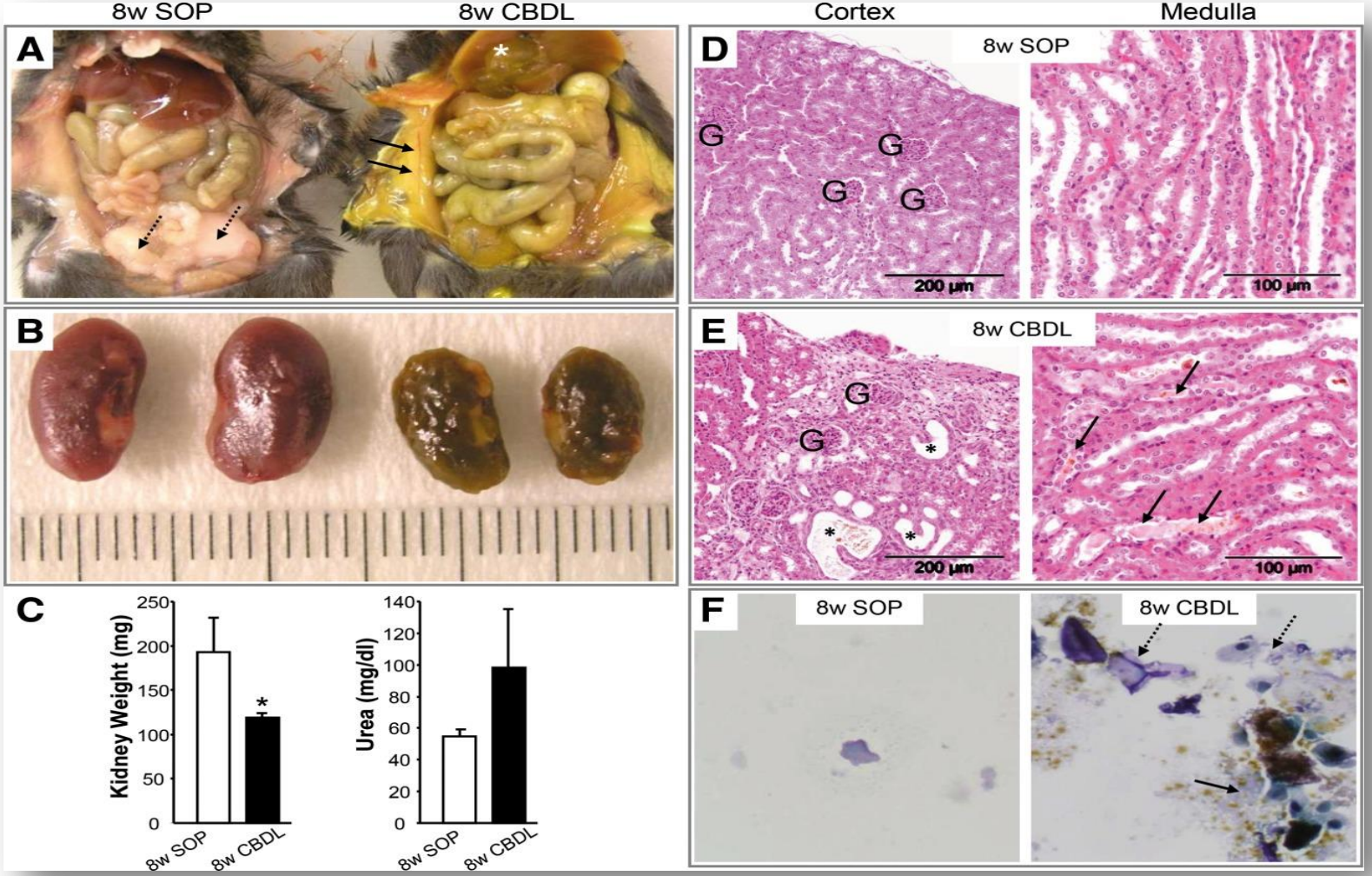
Kosters Xenobiotica 2008

Système rénal & homéostasie des acides biliaires (2) Physiopathologie



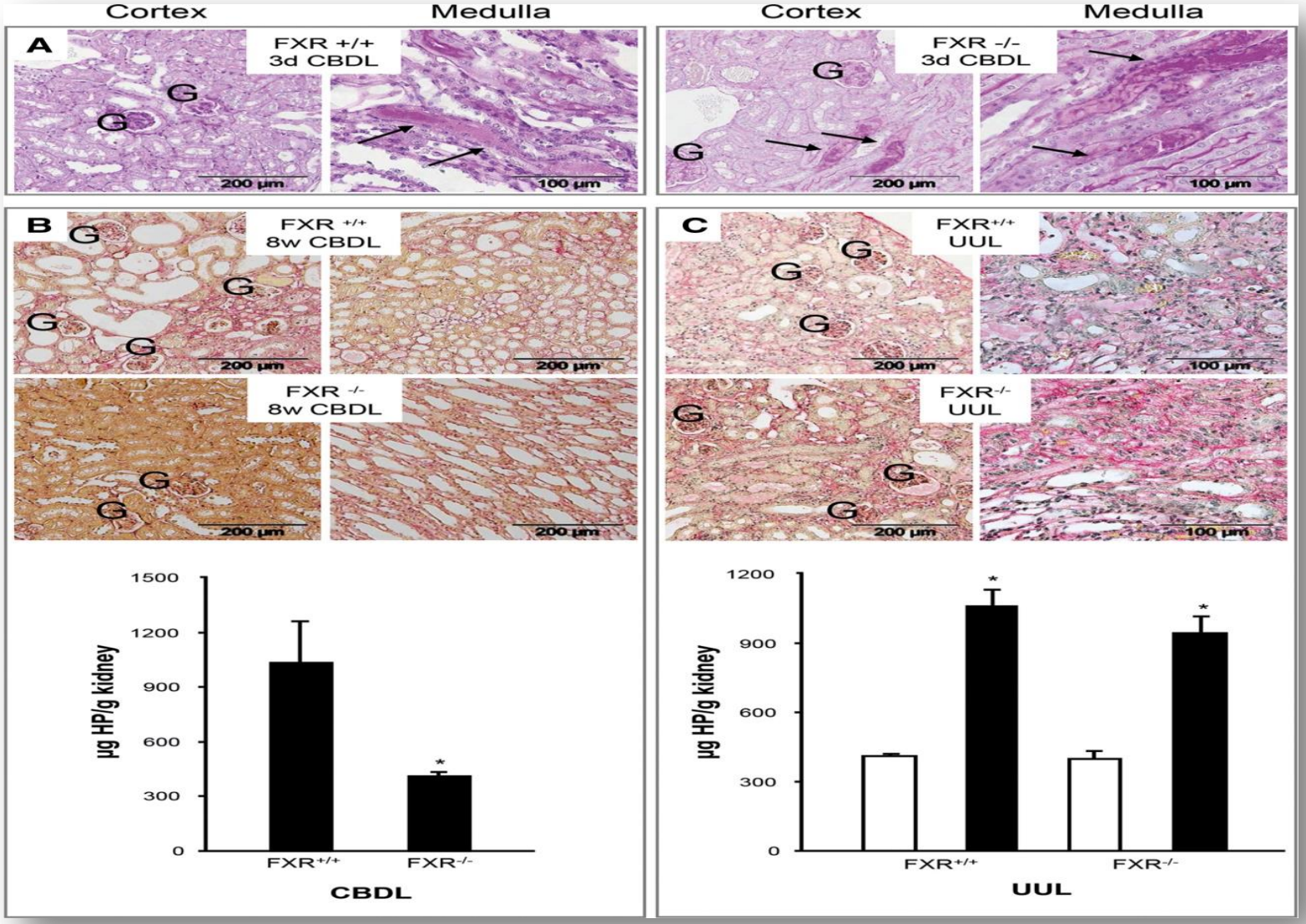
Krones Biochem Biophys Acta 2017

La ligature de la voie biliaire principale : un modèle d'insuffisance rénale



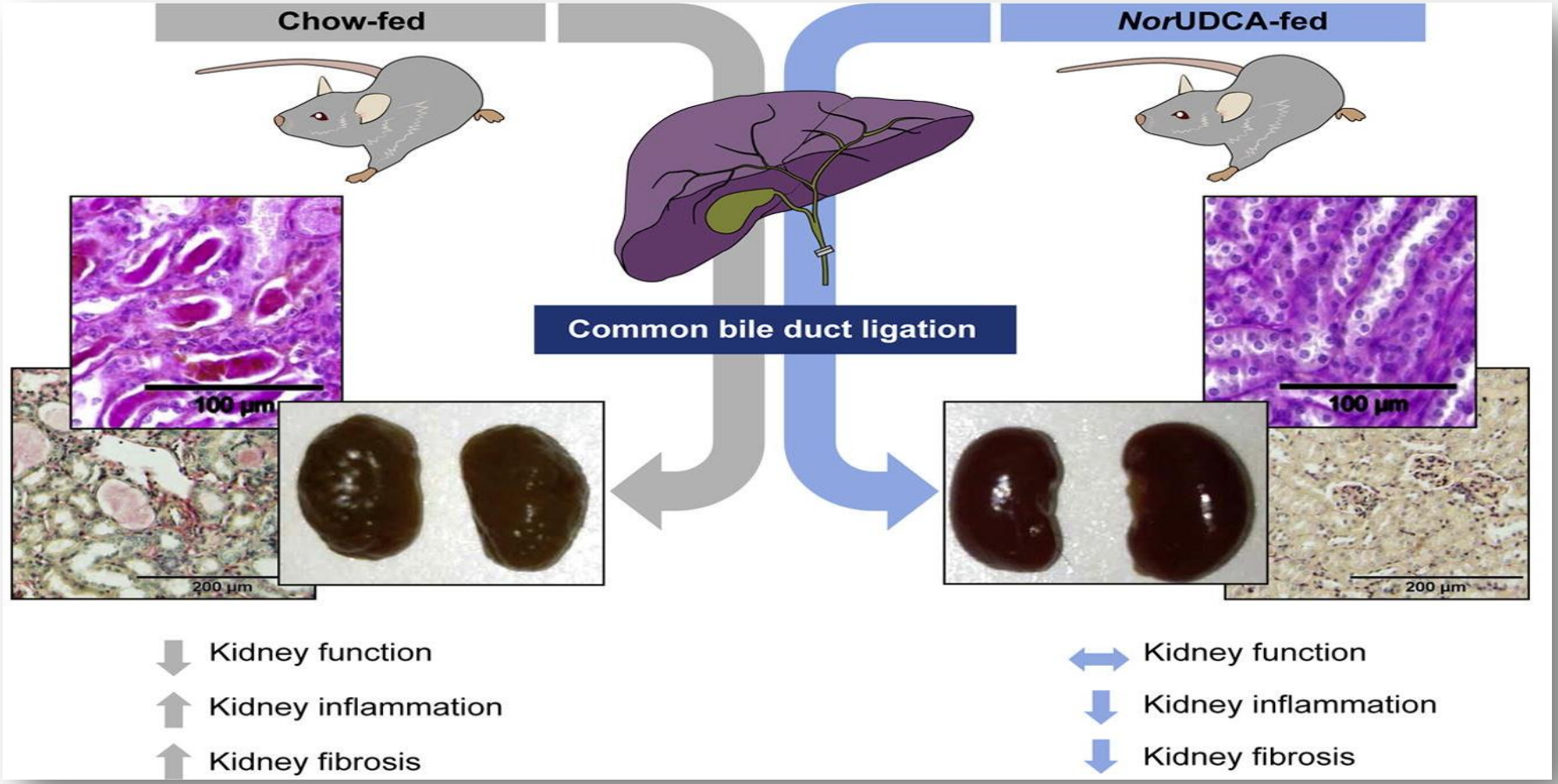
Fickert Hepatology 2013

Et si ce n'était pas la bilirubine qui était en cause ?



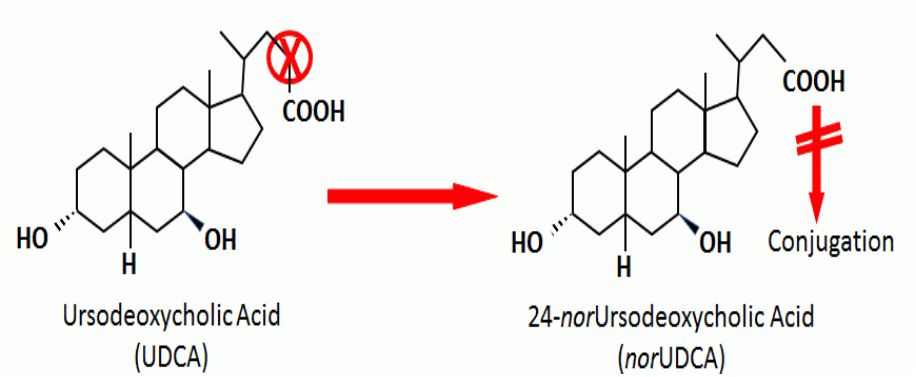
Fickert Hepatology 2013

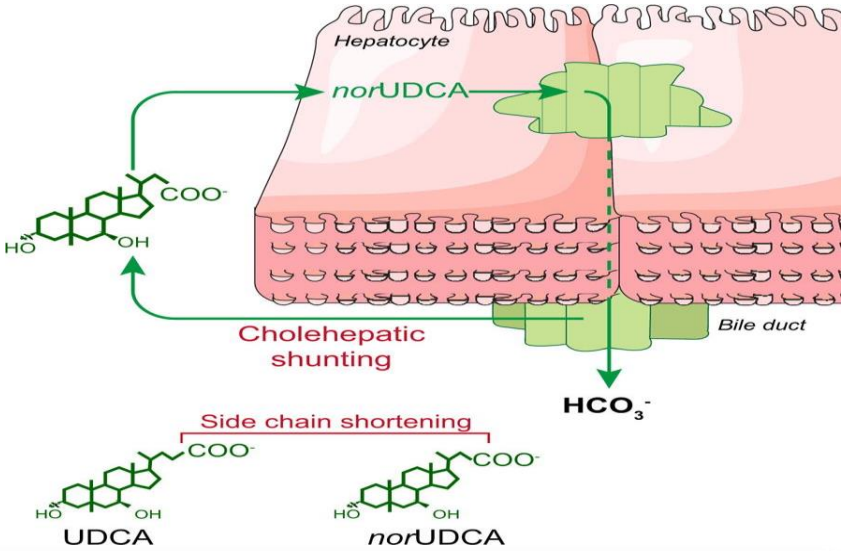
Réversion de l'atteinte rénale en cas de résolution de l'ictère cholestatique



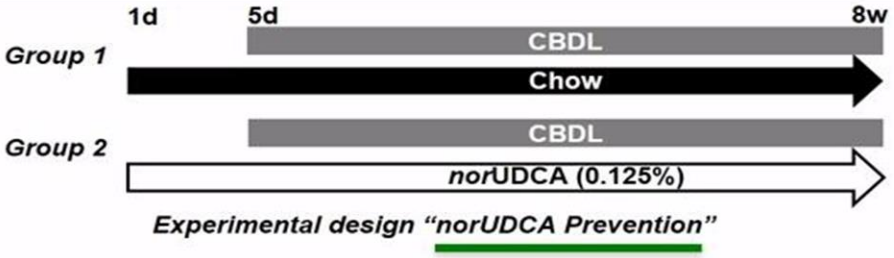
Krones J hepatology 2017

Impact du *nor*UDCA sur la néphropathie cholémique

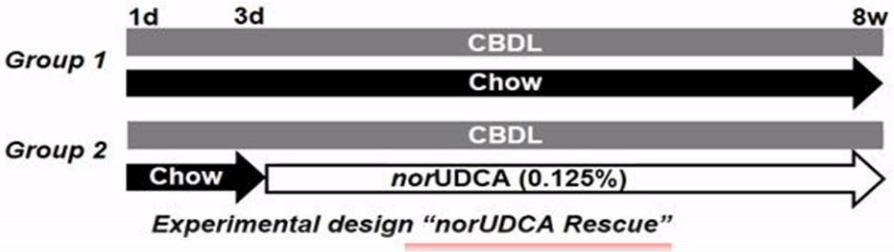




*nor*UDCA 5d **prior** CBDL

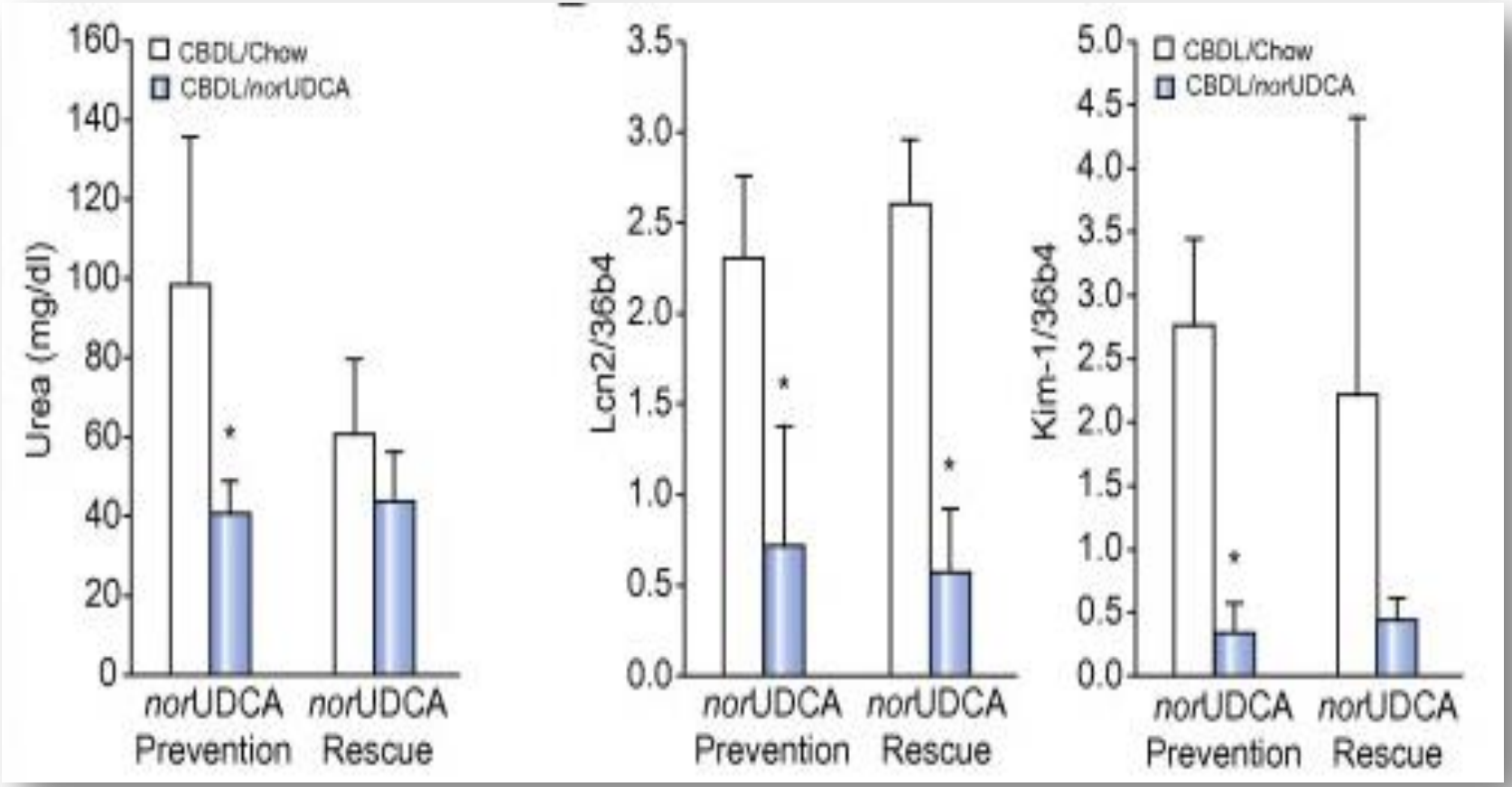


*nor*UDCA 3d **post** CBDL



Fickert, Krones J hepatology 2017

*nor*UDCA améliore les paramètres **fonctionnels rénaux**



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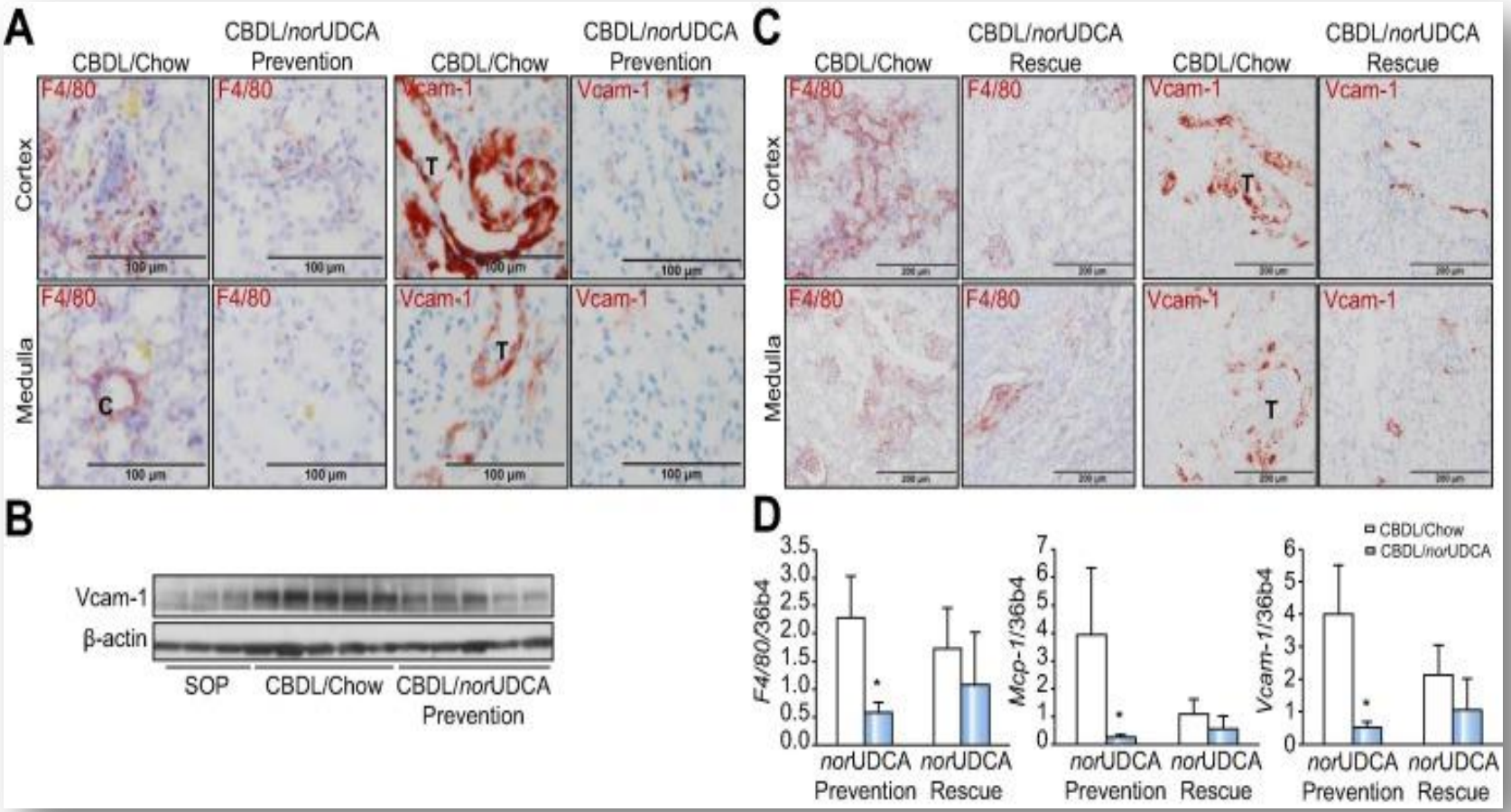
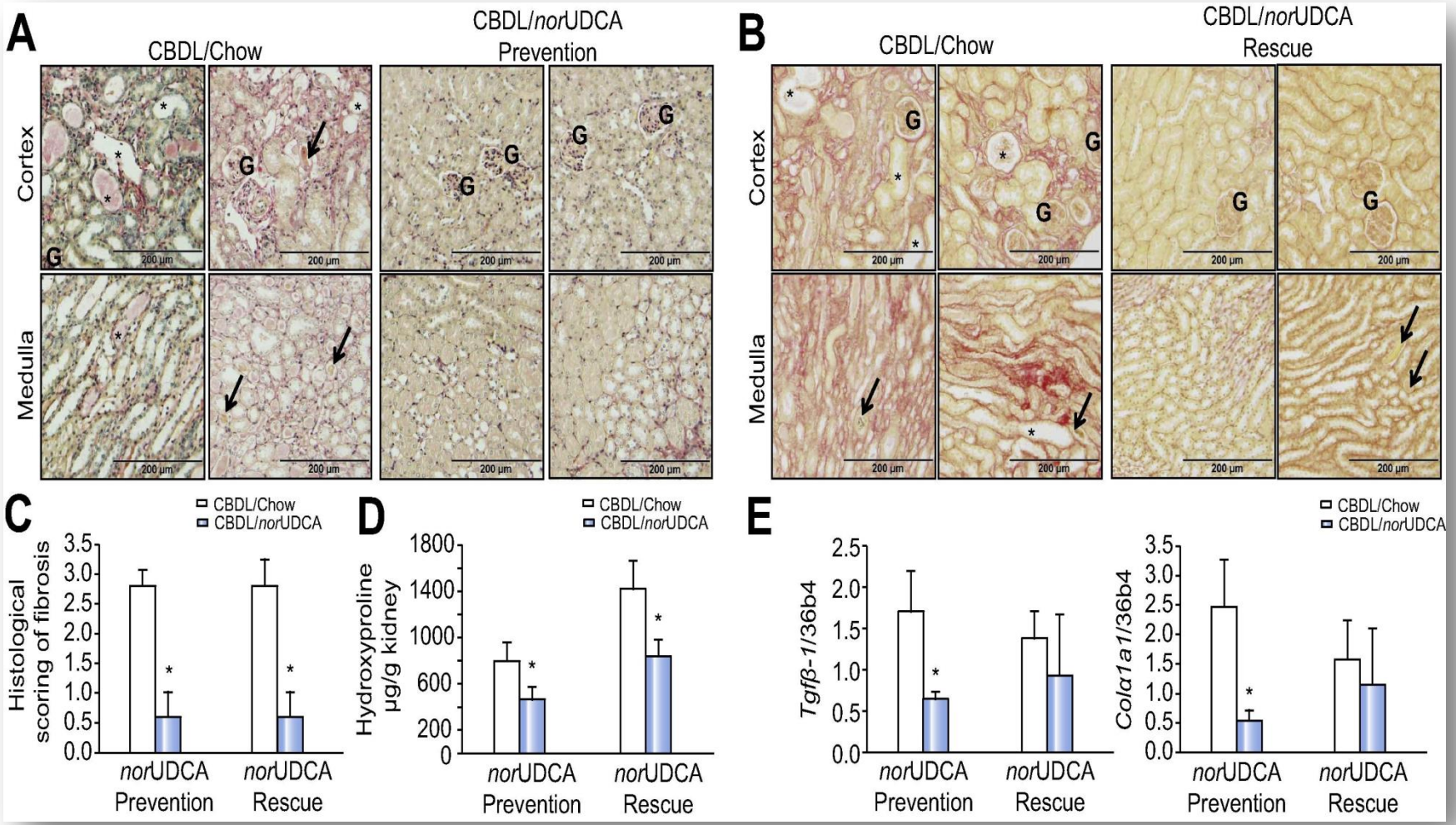
*nor*UDCA améliore les paramètres **de l'inflammation rénale**



Fickert, Krones J hepatology 2017

*nor*UDCA réduit la constitution de **fibrose rénale**



Fickert, Krones J hepatology 2017

« Take home messages »

- ✓ Le syndrome hépato-rénal n'est pas la seule cause d'IRA au cours de la cirrhose décompensée
- ✓ Les cylindres intra-tubulaires de bilirubine sont des marqueurs d'une néphropathie de physiopathologie complexe
- ✓ Les preuves expérimentales font actuellement la part belle à la cytotoxicité des sels biliaires…a
- ✓ …Avec possiblement des conséquences thérapeutiques (à l'essai)
- ✓ Les deux entités ne sont pas mutuellement exclusives