Cholemic Nephropathy

Abbas Etminan

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Article

Cholemic Nephropathy as Cause of Acute and Chronic Kidney Disease. Update on an Under-Diagnosed Disease

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Cholemic Nephropathy Reloaded

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Renal Replacement Therapy

REVIEW **Open Access**

Bile cast nephropathy: when the kidneys turn yellow

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ELSEVIER

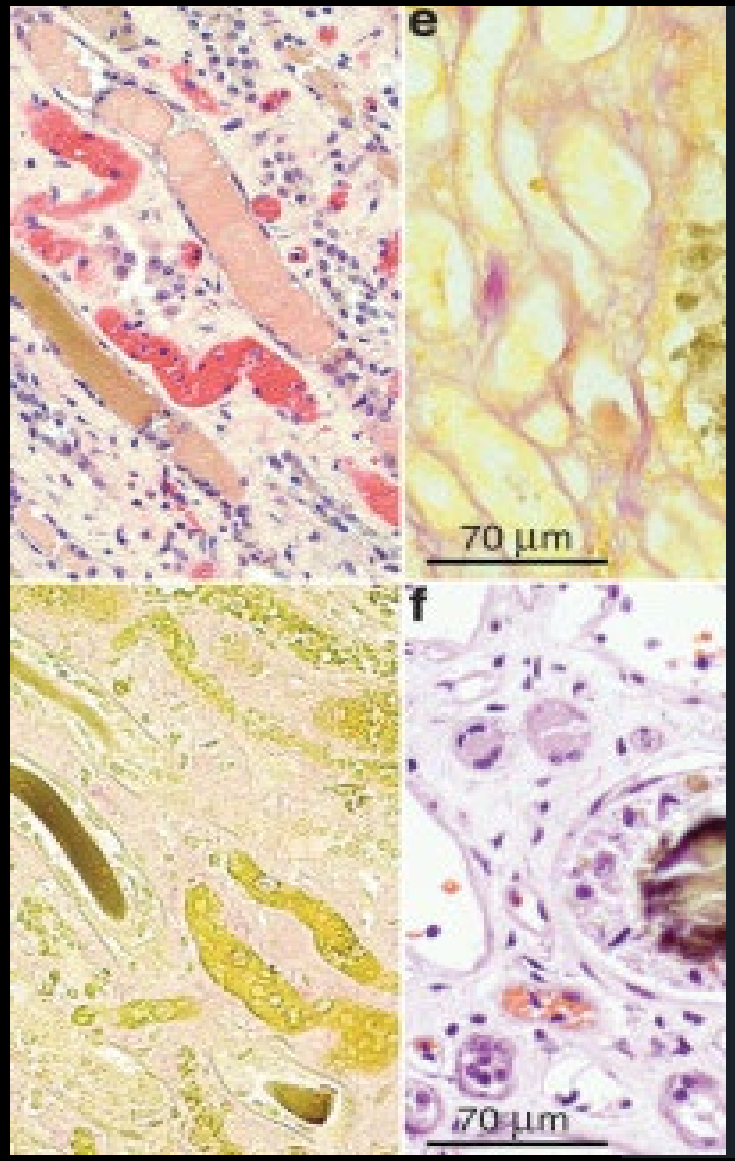
Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease

Volume 1864, Issue 4, Part B, April 2018, Pages 1356-1366

Review

Cholemic nephropathy – Historical notes and novel perspectives

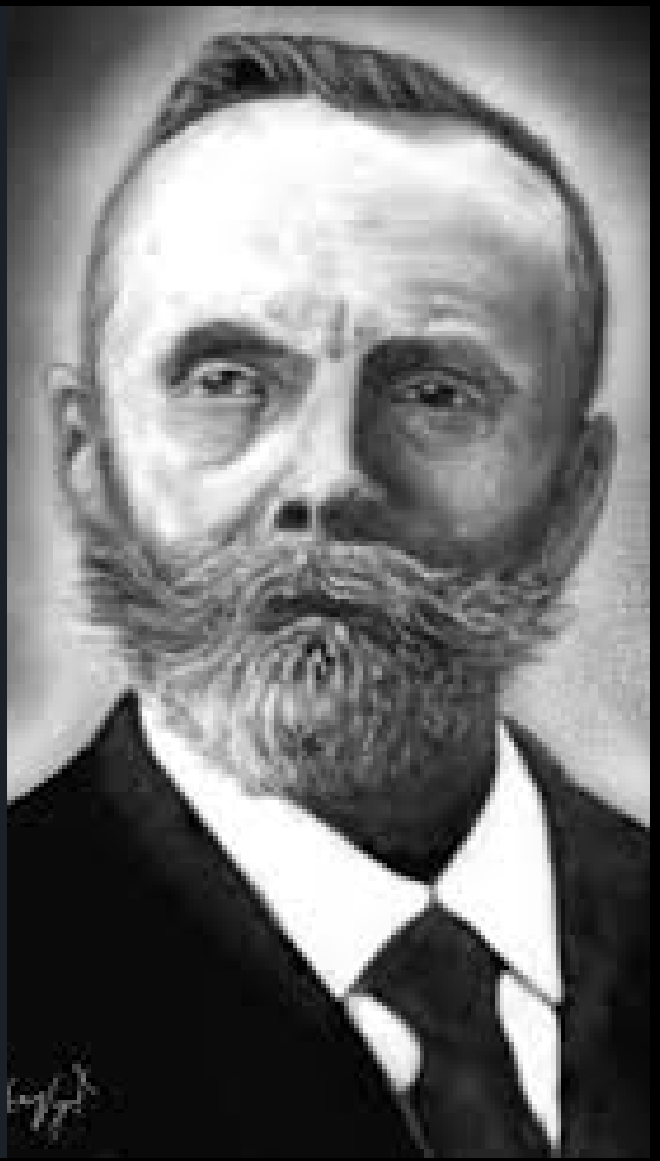
Elisabeth Krones [a], Marion J. Pollheimer [b], Alexander R. Rosenkranz [c], Peter Fickert [a]



Cholemic Nephropathy

The Cause of acute kidney injury (AKI) in patients with severe hyperbilirubinemia (sHyb) and jaundice

First described in 1899 by Quincke and Nothnagel in patients with jaundice, kidney injury and evidence of bile casts in their kidney biopsies



Cholemic Nephrosis

“Bile or Biliary nephrosis”

“Jaundice related nephropathy”

“Bile acid nephropathy”

“Bile cast Nephropathy”

Cholemic nephropathy

In patients with hyperbilirubinemia caused by:

Obstructive jaundice

Malignancy

Drug-induced liver injury

Acute hepatitis

Advanced liver diseases such as decompensated cirrhosis or end stage liver disease

Cholemic nephropathy

Acute kidney injury developing in cholemic nephropathy is secondary to sHyb; its early recognition may lead to improved diagnosis, management and enhanced outcome of renal function

sHyb: Sever Hyperbilirubinemia

Cholemic Nephropathy **Pathophysiology**

- Hepatocytes in cholestasis (e.g. biliary obstruction) limit increased hepatocellular levels of bile acids via upregulation of basolateral adaptive transporters (Mrp3, Mrp4, OSTα/β) facilitating their alternative renal elimination via glomerular filtration, transporter mediated active tubular secretion (Mrp2, Mrp3, Mrp4) and reduced tubular bile acid re-uptake via reduced expression of ASBT

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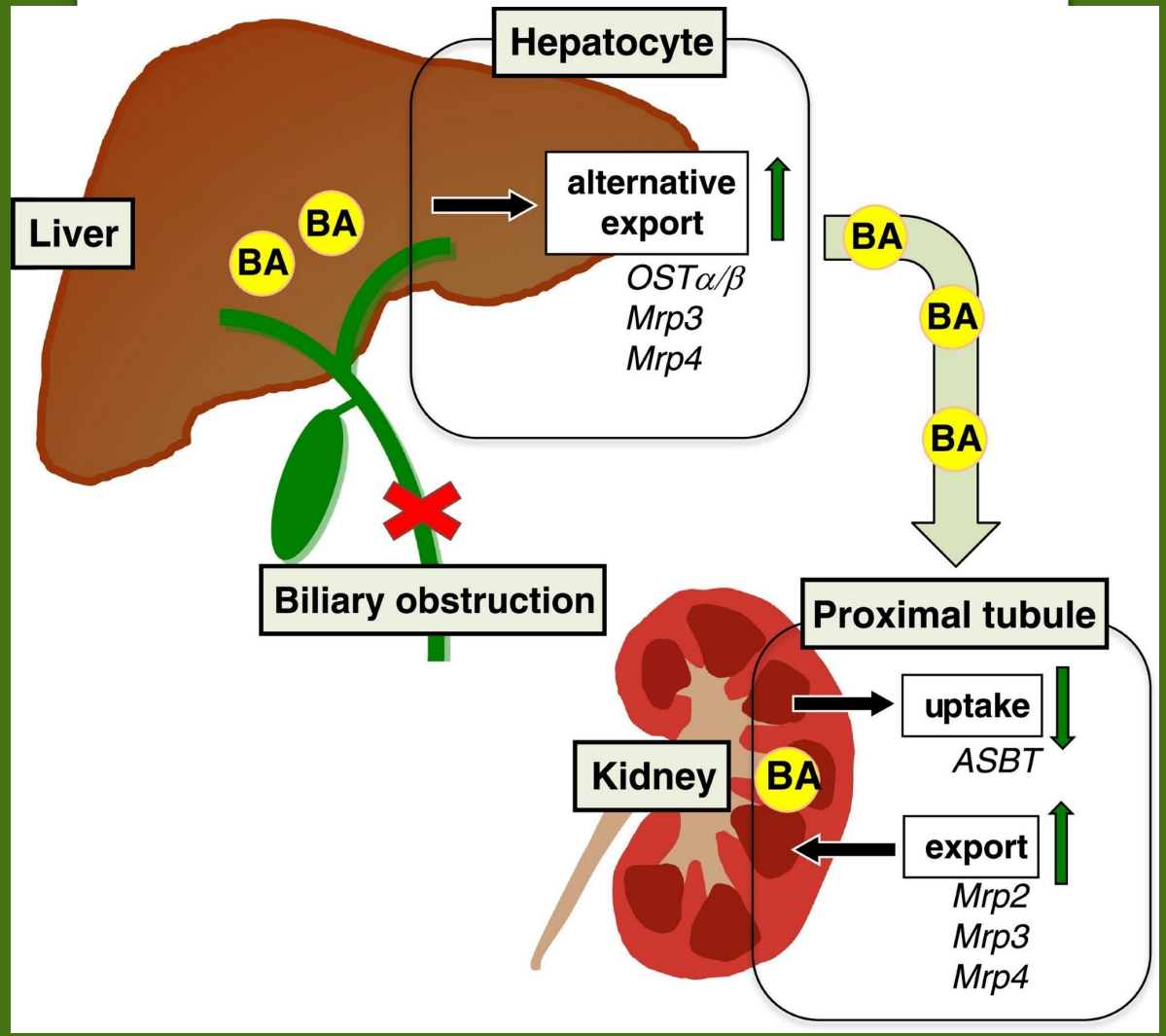
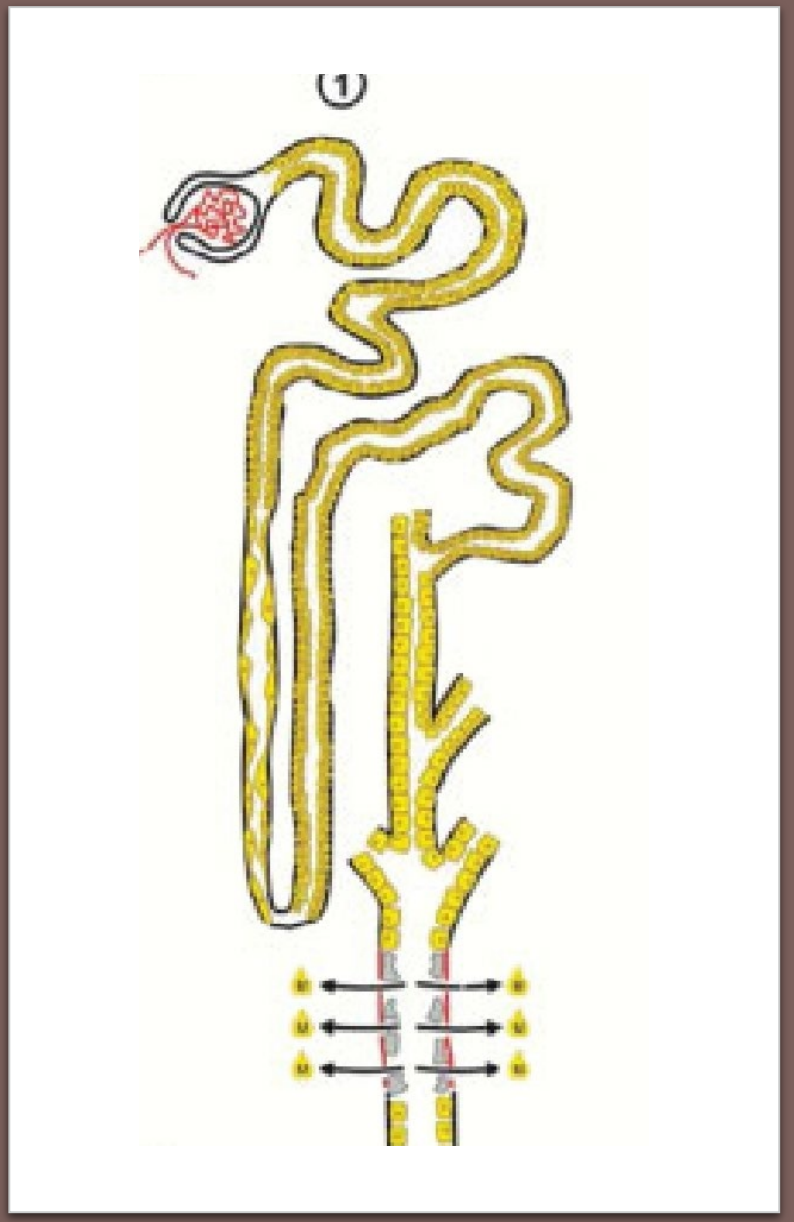


Cholemic Nephropathy

Pathophysiology

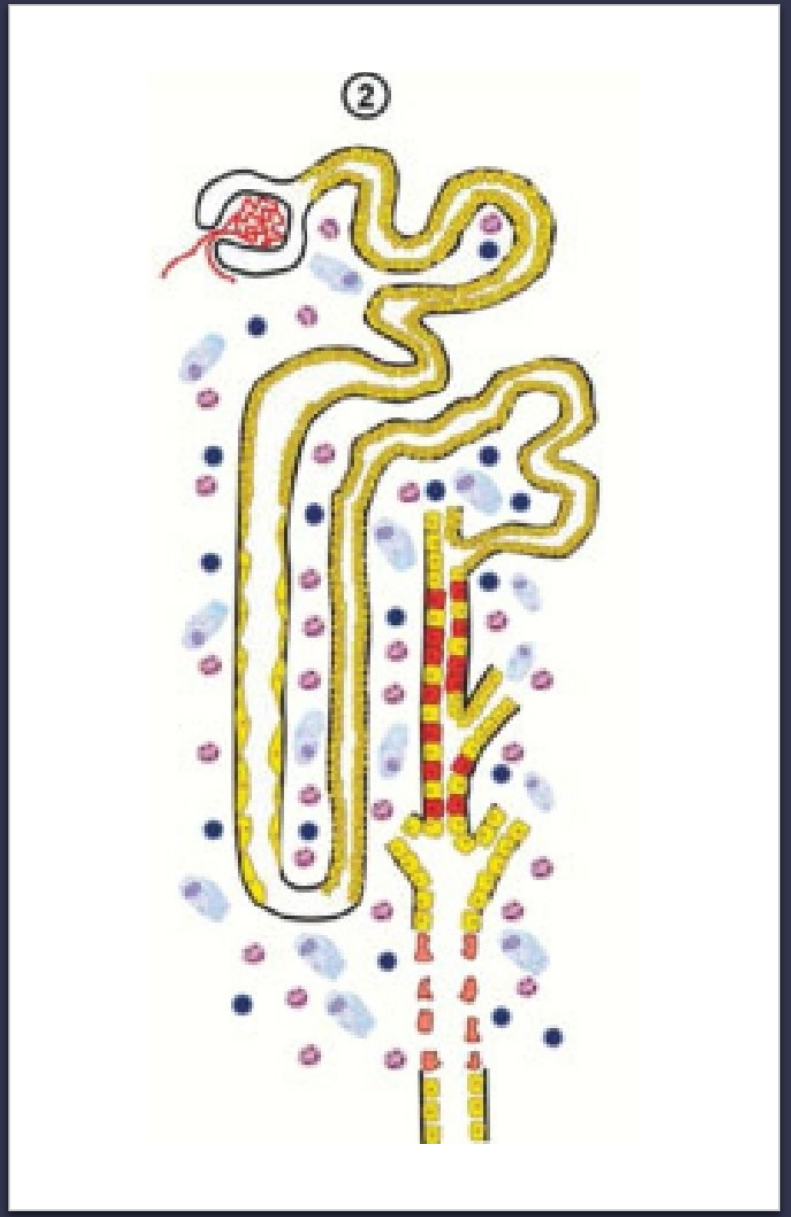
- CN in *common bile duct ligated (CBDL) mice* starts at the level of collecting ducts with injury to aquaporin 2 (AQP2)-positive tubular epithelial cells and basement membrane disintegrity leading to leaky collecting ducts



Cholemic Nephropathy

Pathophysiology

- (2) Tubules cell injury and cast formation increase pressure within the tubular part of the nephron with dilatation and tubulointerstitial nephritis

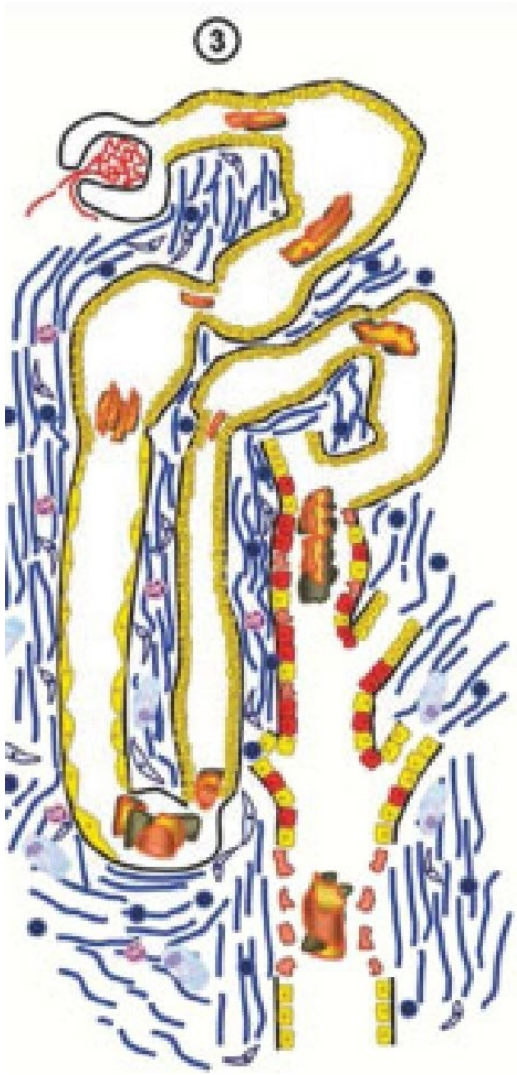


Cholemic Nephropathy

Pathophysiology

- (3) Progressive tubular dilatation and interstitial nephritis trigger interstitial fibrosis

- *(adapted from Fickert et al)*



Cholemic Nephropathy **Pathophysiology**

Direct toxicity of cholephiles

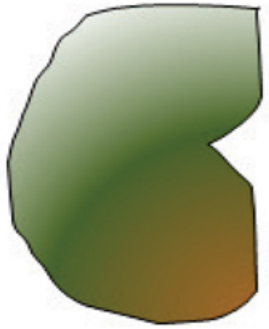
Bile casts formation in nephrons: *Prolonged exposure to severe hyperbilirubinemia ≥20 mg/dL (sHyb), enhances bile casts formation and direct kidney injury, especially in presence of bile casts promoting factors (BCPFs) such as metabolic acidosis and hypoalbuminemia*

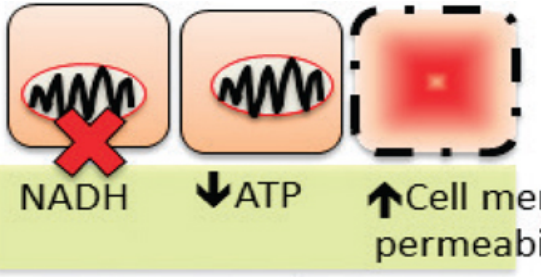
Tubular obstruction

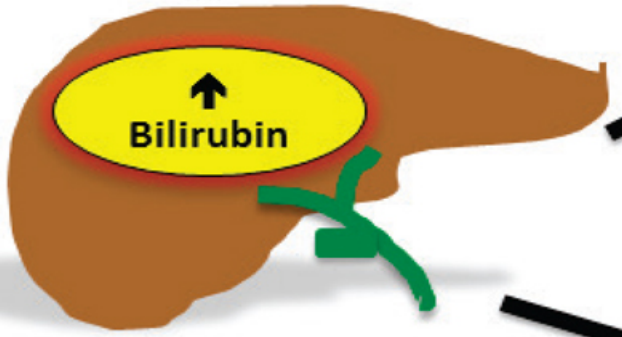
Interstitial nephritis

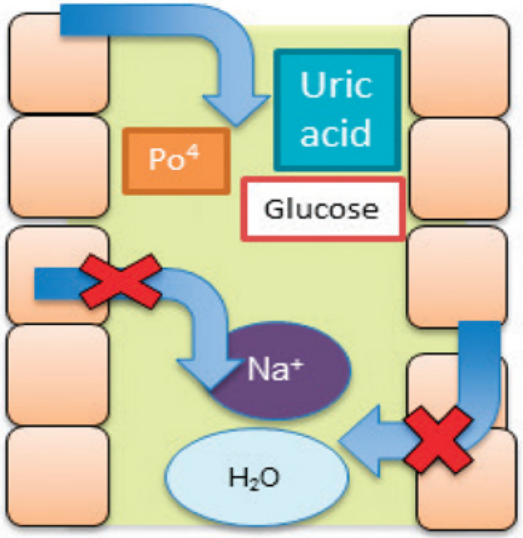
Hemodynamic changes induced by portal and systemic endotoxemia

Kidney looks brownish and green



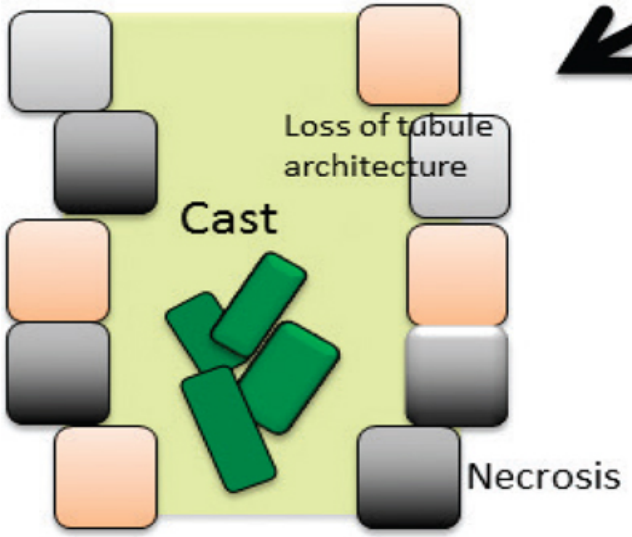






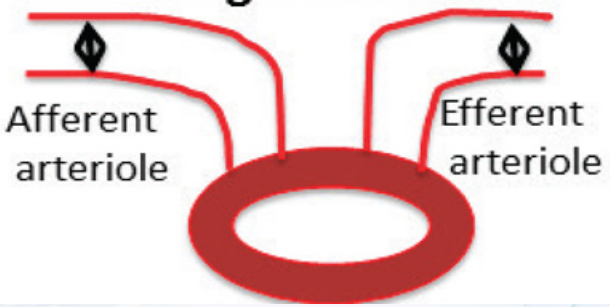
Tubular dysfunction:
Uricosuria , phosphaturia, impair natriuresis and diuresis

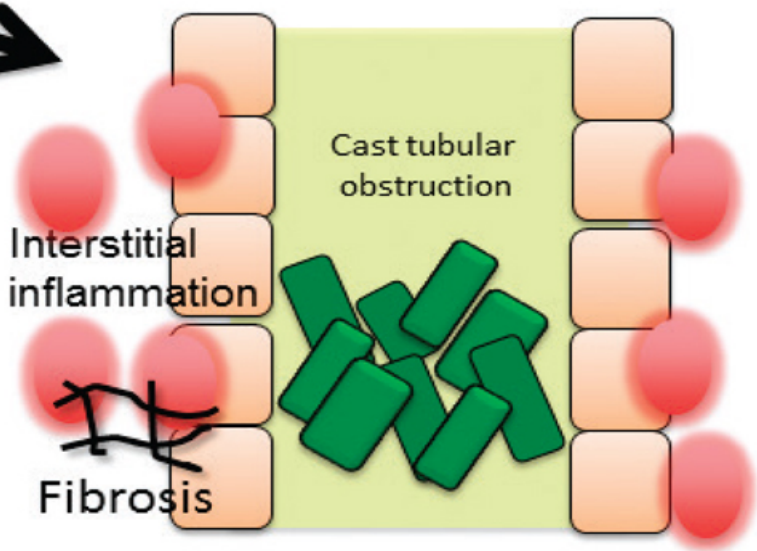
Cast: desquamated epithelial cells, proteins and bilirubin



Impaired intraglomerular hemodynamics

Angiotensin II





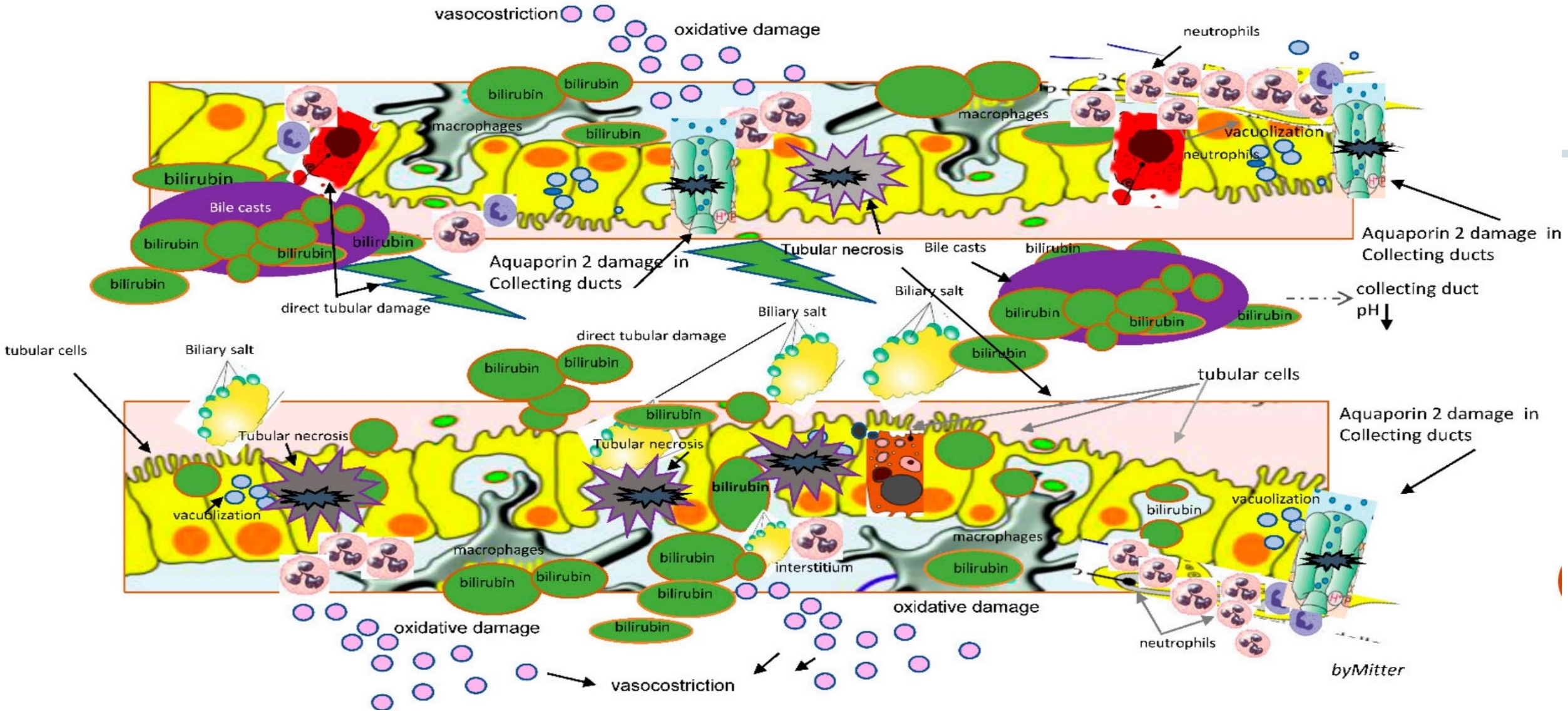
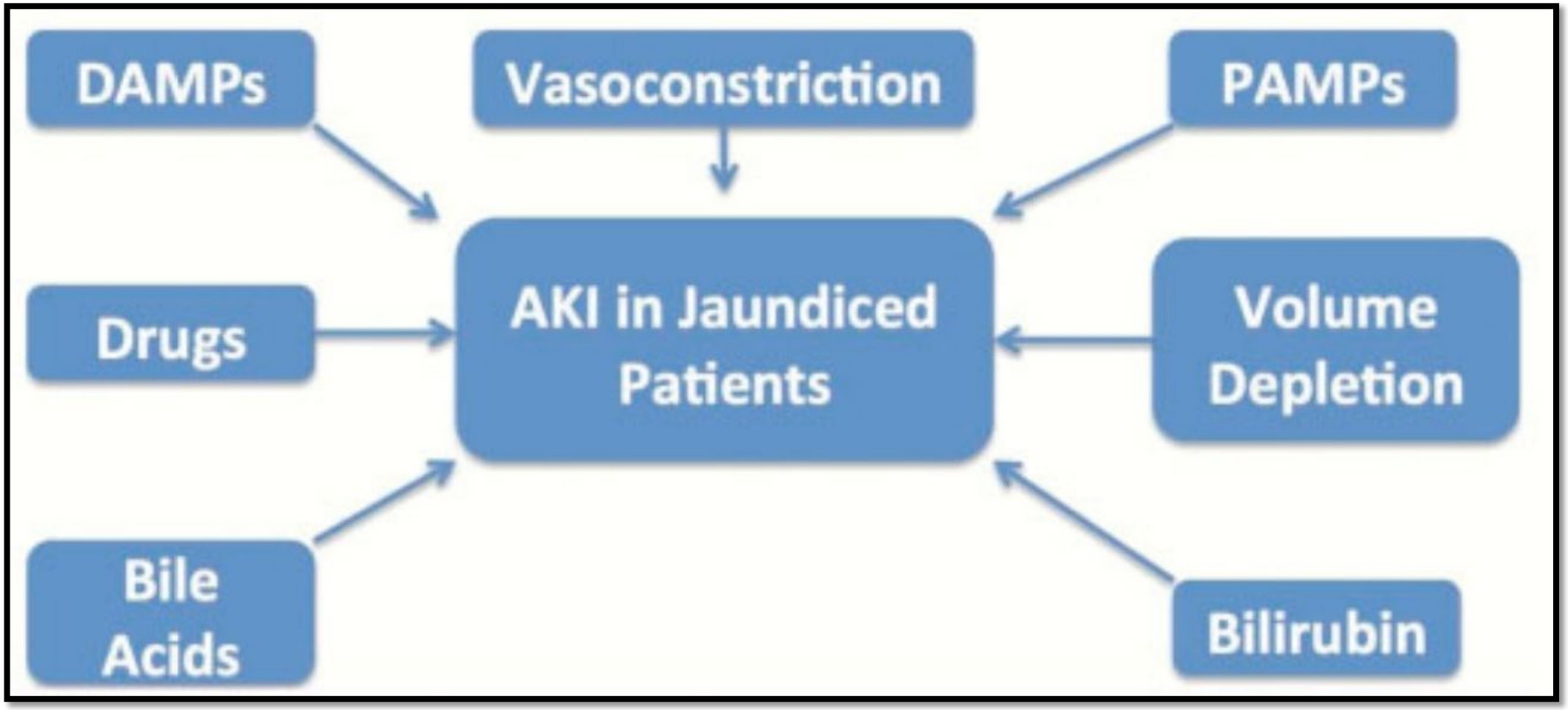


Figure 1. Schematic description of features characterizing cholemic nephropathy: renal tubular, interstitial and epithelial damage with bile casts formation, direct tubular toxicity damage, bile interstitial nephropathy, bile casts formation and direct kidney injury, oxidative stress, direct renal epithelial cells apoptosis and necrosis, reduced production of nitric oxide; tubular toxicity with tubular cells necrosis and exfoliation, interstitial nephritis, impaired M2 macrophages most involved in wound healing and fibrosis.

Cholemic Nephropathy **Pathophysiology**



DAMPs: Damage-associated molecular patterns
PAMPs: Pathogen-associated molecular patterns

Histologic changes

Glomerular congestion

Proximal and distal tubule vacuolization and necrosis

Interstitial edema and cellular infiltration

In some cases, profound biliary pigment and casts in the kidneys

Tubular epithelial injury

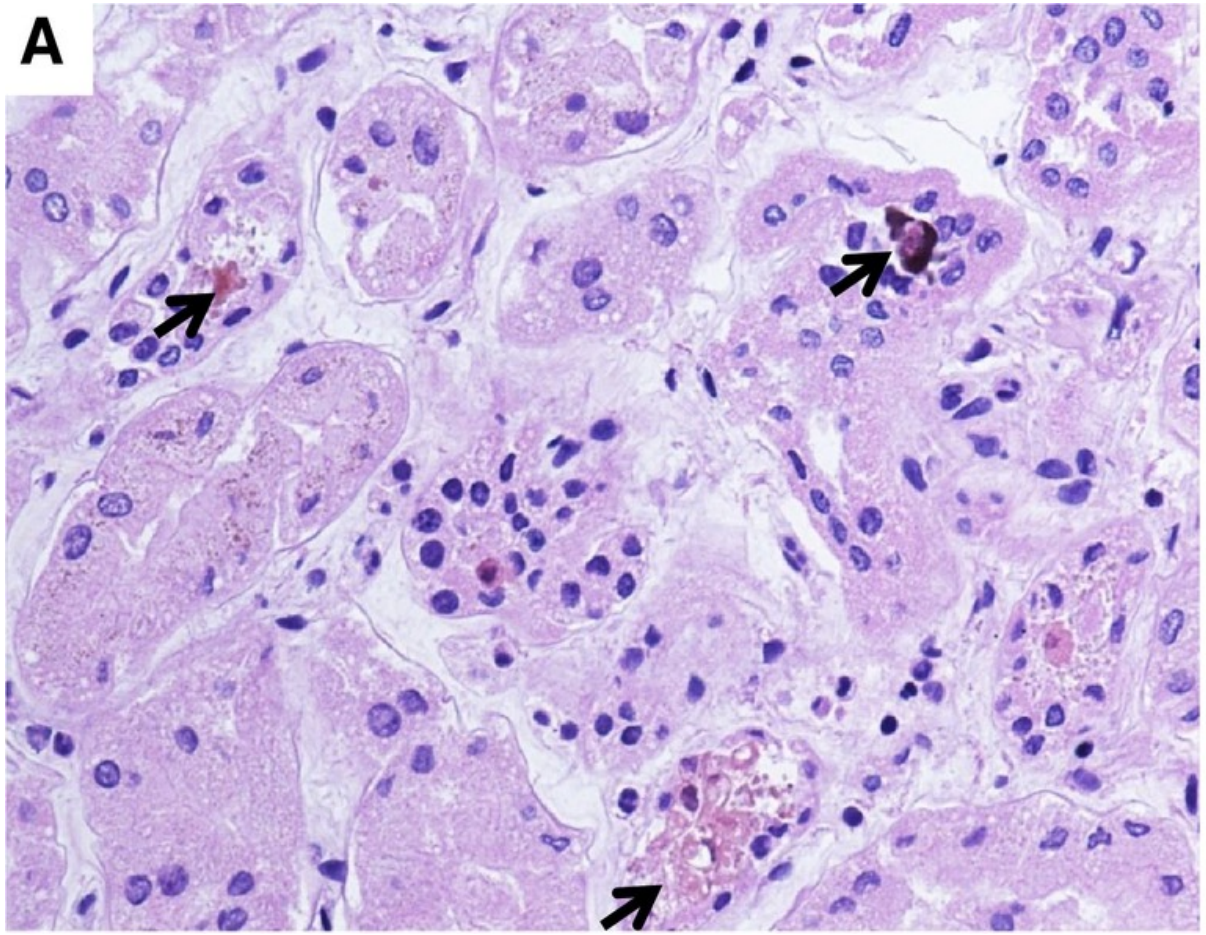
Basement membrane defects leading to leaky tubules

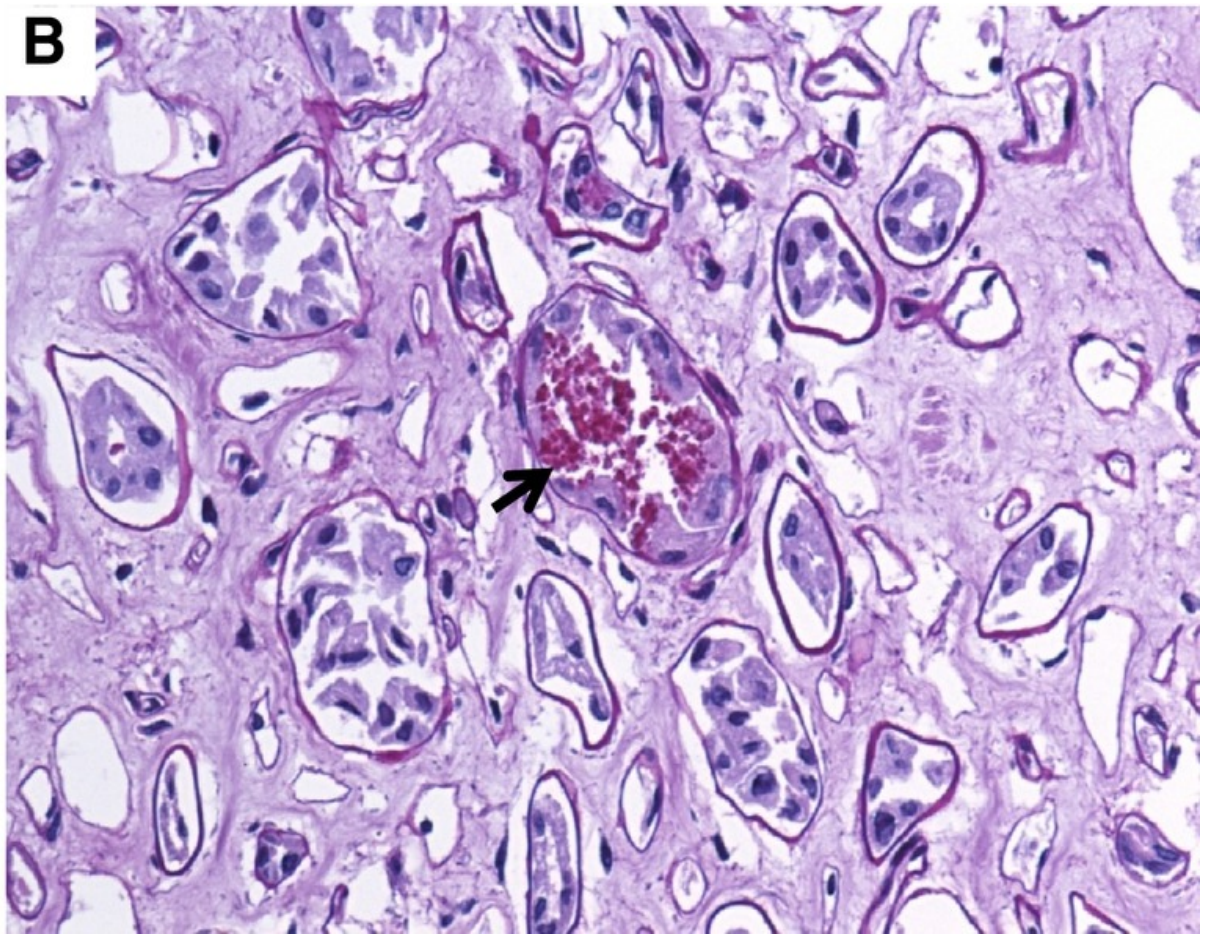
Obstruction of collecting ducts due to sloughed cells and bile casts

Damage to Aqaporin-2 channels

Histologic changes

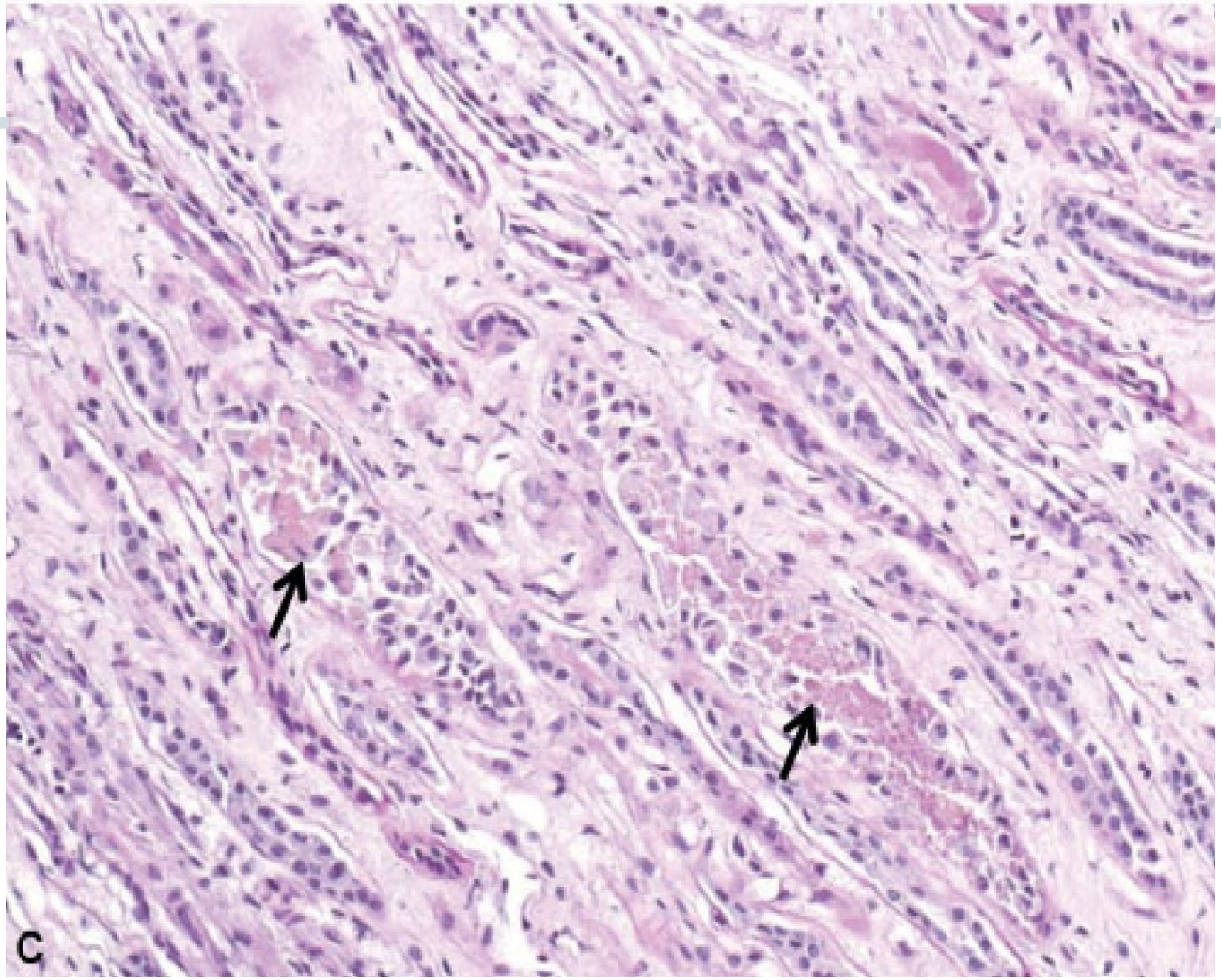
(A) Hematoxylin & eosin stain shows dark-red to brownish casts within the distal tubules (arrows) of the renal medulla in a patient with end-stage liver disease. (B) Periodic-acid Schiff (PAS) stain shows PAS-positive (dark red colored) tubular protein casts (arrows)

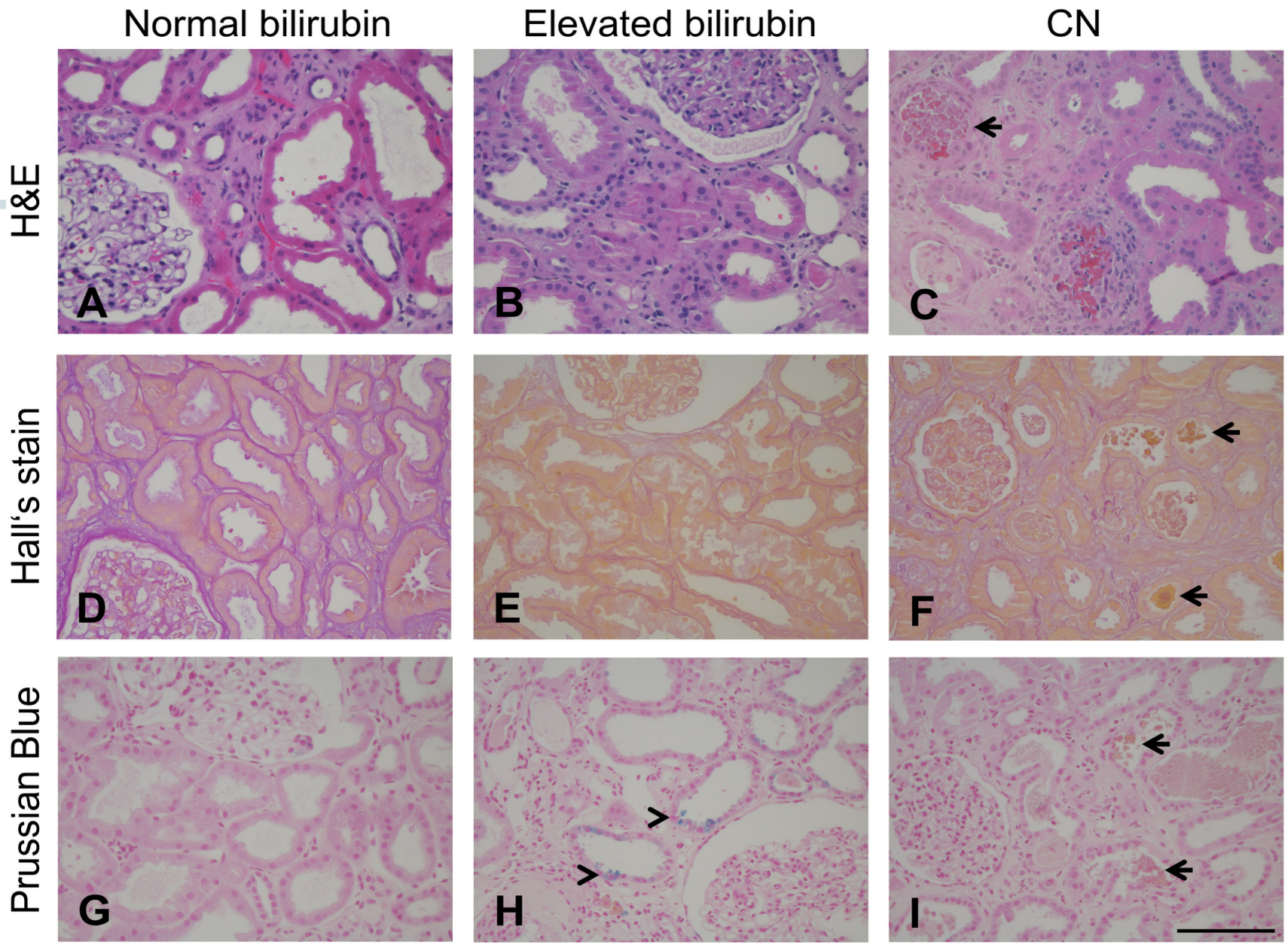




Histologic changes

Postmortem kidney histology in a patient with CN. Periodic acid-Schiff (PAS)-stained section showing granular (partially PAS-positive) intratubular casts with cellular debris in the tubulus lumina (as highlighted by arrows).Note also a mixed-cell inflammatory infiltrate in the tubulus lumina and the interstitium




Normal bilirubin
Elevated bilirubin
CN
H&E
Hall's stain
Prussian Blue
A
B
C
D
E
F
G
H
I

Cholemic nephropathy

- AKI or AKI on CKD
- Bile casts in urine
- Biliary nephropathy in kidney biopsy

Diagnosis

Renal biopsy is not easily performed in patients with liver disease due to impaired coagulation

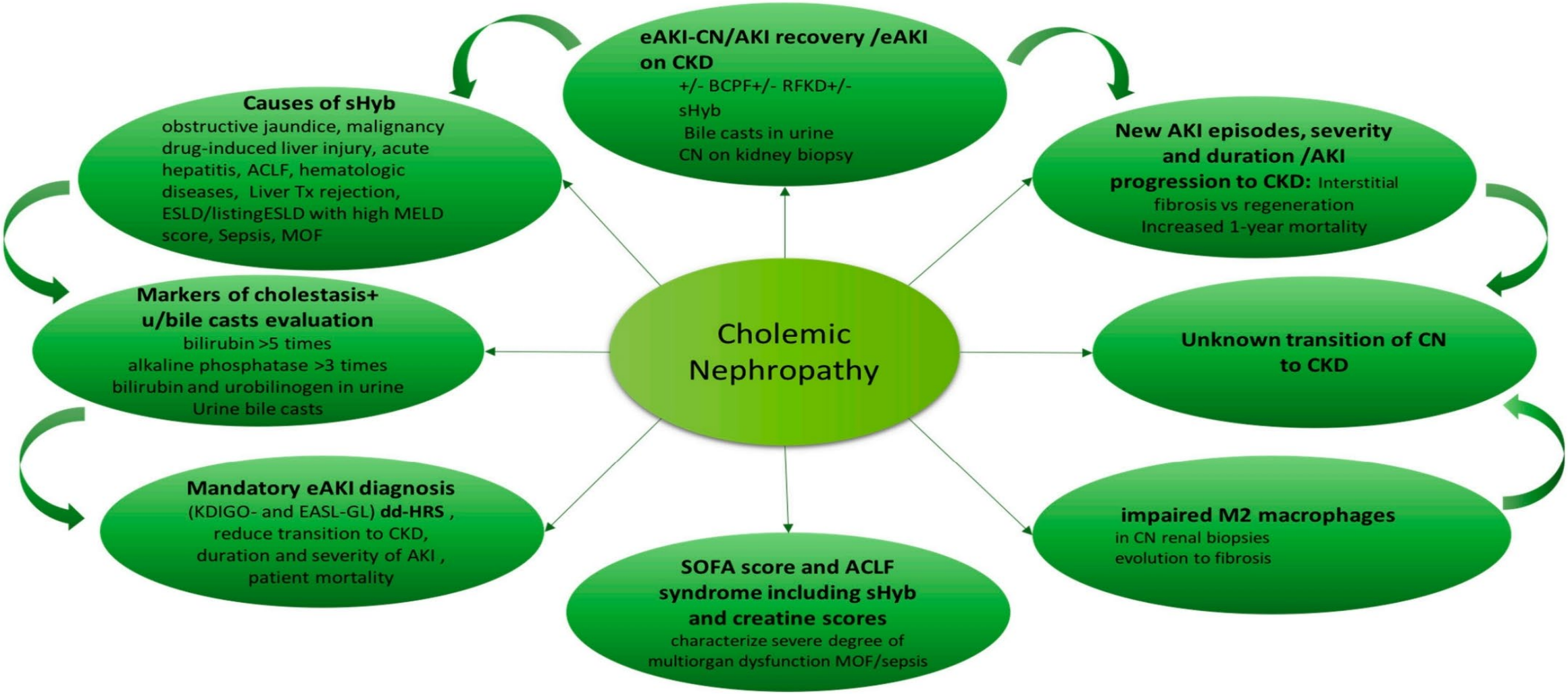


Figure 2. Cholemic nephropathy, AKI and CKD: Diagnosis of AKI related to CN and potential evolution of CN to CKD. Abbreviations: ACLF: Acute-on-Chronic Liver Failure; AKI: acute kidney injury; BCPF: bile cast promoting factors; CKD: chronic kidney disease; CN: cholemic nephropathy; dd-HRS: differential diagnosis with hepato-renal syndrome; eAKI: early AKI diagnosis; EASL: European Association for the Study of the Liver; ESLD: end-stage liver disease; listing ESLD: patients on the waiting list for liver transplantation; GL: guidelines; KDIGO: kidney disease: improving global outcome; M2 macrophages: macrophages most involved in wound healing; MELD score: Model for End Stage Liver disease score; MOF: multiorgan failure; sHyb: severe hyperbilirubinemia (>20 mg/dL); SOFA: sequential organ failure assessment.

Causes for AKI in end-stage liver disease (ESLD) or in acute decompensated liver disease

Hypovolemia due to gastrointestinal bleeding

Aggressive diuretic treatment

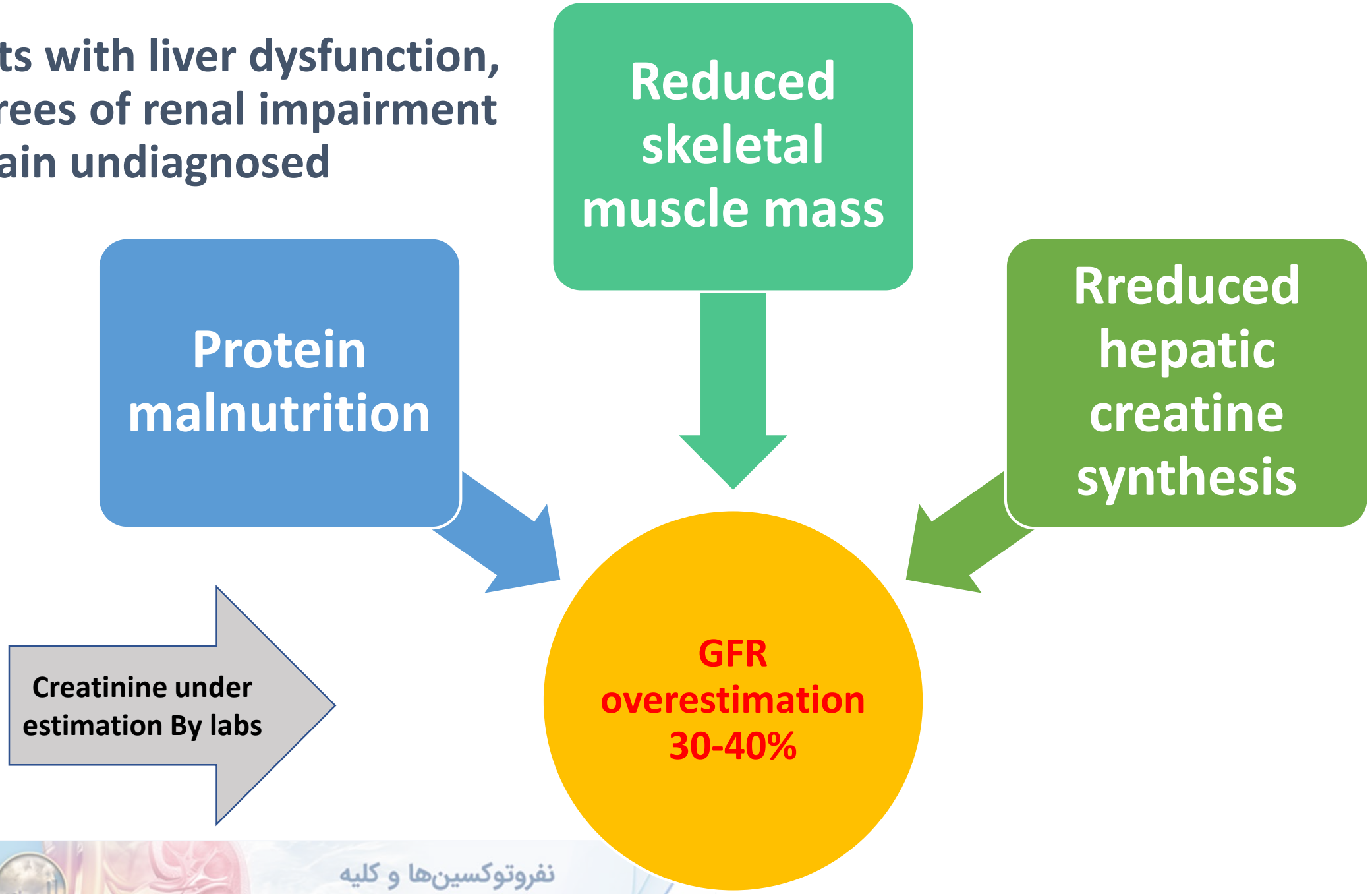
Diarrhea

Hypotensive state

Infections

The differential diagnosis with hepatorenal syndrome (HRS) is mandatory

In patients with liver dysfunction, mild degrees of renal impairment may remain undiagnosed



Cholemic Nephropathy

Treatment

Bilirubin level reduction <20 mg/dL

- Reduce bilirubin, bile acids in plasma and urine (treating the underlying cause of sHyb)
  - Vascular expansion with isotonic solutions or saline
  - Albumin
- Early recognition and treatment of AKI
- Limit factors involved with bilirubin or bile acid tubular precipitation and toxicity (bile cast promoting factors)
  - Bicarbonate
  - norursodeoxycholic acid norUDCA

In severe cases:

extracorporeal albumin dialysis (ECAD), including molecular adsorbent recirculating system (MARS) or single-pass albumin dialysis (SPAD) systems

Clinical Management of CN

Treatment

Resolving the cause of hyperbilirubinemia

Early recognition and treatment of AKI

- The study of biomarkers of early AKI damage, such as urine neutrophil gelatinase-associated lipocalin and interleukin-1β, is also proposed
- Monitoring of renal function and evaluation of bile cast in the urine sediment

Chediak et al. Renal Replacement Therapy (2020) 6:15
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REVIEW Open Access

Bile cast nephropathy: when the kidneys turn yellow

Alissar El Chediak[1†], Khaled Janom[2†] and Sahar H. Koubar[3*]

cases of persistent intractable sHyb, as a bridge to resolution

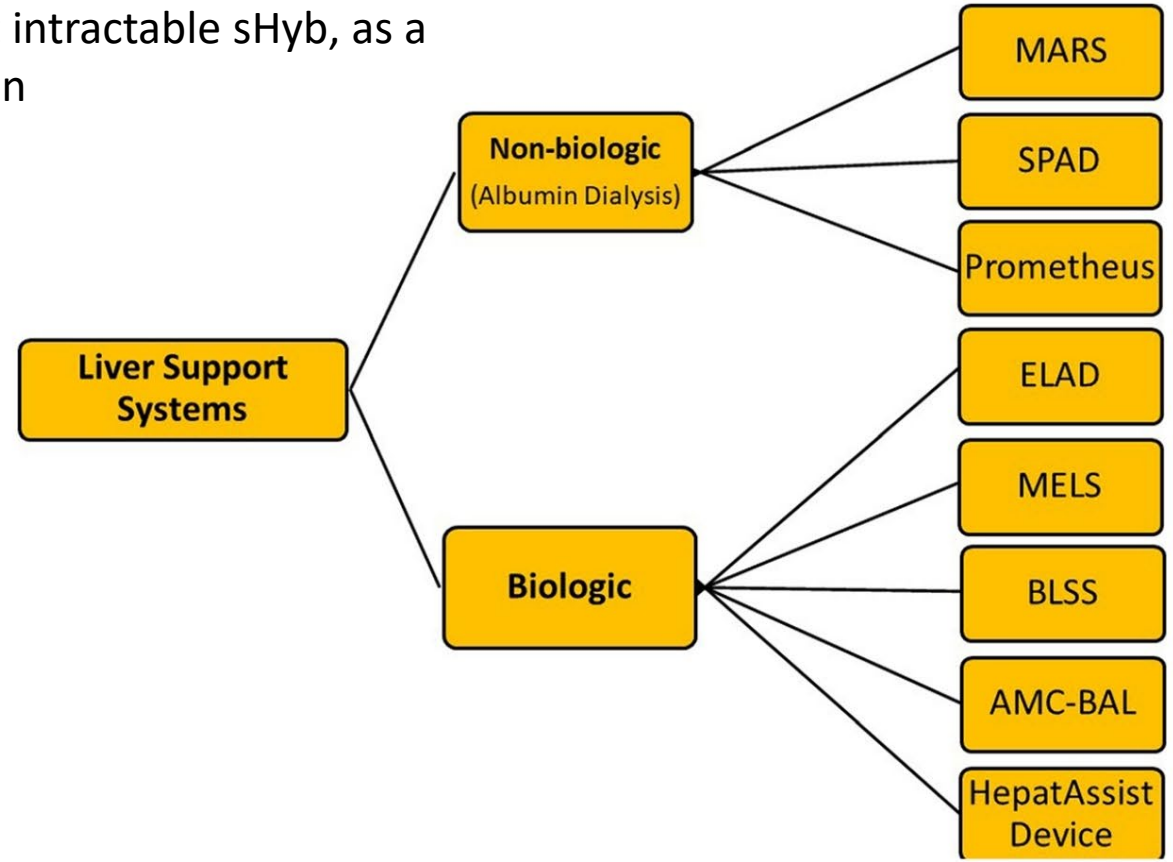

Fig. 2 Extracorporeal therapies