

# Cholemic Nephropathy Reloaded

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## Abstract

Acute kidney injury (AKI) is a dreaded complication in patients with liver disease and jaundice, since it is associated with significant morbidity and mortality. Cholemic nephropathy (CN) is thought to represent a widely underestimated important cause of AKI in advanced liver diseases with jaundice. The umbrella term CN describes impaired renal function along with histomorphological changes consisting of intratubular cast formation and tubular epithelial cell injury directed primarily toward distal nephron segments. In cholestasis, biliary constituents may be excreted via the kidney and bilirubin or bile acids may trigger tubular injury and cast formation, but as we begin to understand the underlying pathophysiologic mechanisms, we become increasingly aware of the urgent need for clearly defined diagnostic criteria. In the following, we aim to summarize current knowledge of clinical and morphological characteristics of CN, discuss potential pathomechanisms, and raise key questions to stimulate evolution of a research strategy for CN.

## Keywords

- ▶ acute kidney injury
- ▶ cholestasis
- ▶ hepatorenal syndrome
- ▶ advanced liver disease
- ▶ jaundice

It is a reliable sign of uncertainty in medicine whenever we use a considerable number of names for what is most likely one single entity as is the case with cholemic nephropathy (CN), bile cast nephropathy, icteric nephrosis, and bile acid nephropathy.<sup>1</sup> It is, however, a clinical truism that jaundiced patients are at significantly increased risk for renal failure and patients with jaundice and renal failure have a dismal prognosis, as shown in former studies and recently confirmed by the sound results of the landmark CANONIC study.<sup>2–5</sup> Consequently, we have to ask ourselves whether the resurrection of CN we currently observe is (1) the end of the hibernation of an important disease, (2) the reinvention of the emperor's new clothes, or (3) the slow emergence of a black box in clinical hepatology and nephrology that is now hidden in the mixed bag of acute kidney injury-hepatorenal syndrome (AKI-HRS)?

“A rose of any other name would smell as sweet” (William Shakespeare): Cholemic nephropathy (CN) – What is in a name and does the name matter?

The concept that bile constituents, and more specifically bile pigments, might harm the kidney dates back to 1899

when Quincke noted bile pigments staining the glomeruli in autopsies of patients with acute onset of jaundice<sup>6,7</sup>; our short historical note on that has appeared elsewhere.<sup>1</sup> On its journey through medical literature, kidney injury in cholestatic patients, animals, and corresponding experimental animal models was referred to with numerous names as mentioned earlier. Some terms found in literature, such as the currently widely used bile cast nephropathy, result from description of presumably characteristic morphological alterations or still unproven pathophysiological concepts.<sup>8</sup> We think that “bile cast” is a misnomer, since bile can be found either in bile ducts, the gall bladder, or in the intestine but never in the kidney, and consequently also not in renal tubular casts. Nevertheless, this term suggests that we know that tubular casts observed in patients with CN primarily consist of bile or biliary constituents, most likely bilirubin, while there is no information on other important biliary constituents such as phospholipids and bile acids. Other names, such as bile acid nephropathy, suggest a clarified etiopathogenesis<sup>9–12</sup>; however, such an assumption would currently appear constricting and premature even in the light of some experimental evidence showing a central role

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for bile acids in CN.<sup>13–15</sup> In contrast, we find that the term CN is more neutral in that it indicates spill-over of biliary constituents such as bile acids and bilirubin into blood (i.e., cholemia) leading to renal dysfunction and histological changes in jaundiced patients. Based on findings in longitudinal studies in common bile duct ligated mice, CN starts with tubular epithelial injury in distal nephron segments, accompanied by intraluminal cast formation (the composition of which remains to be determined in detail), leading to obstruction and dilatation of the tubules.<sup>13</sup>

We find that harmonizing the nomenclature by using CN might be most advantageous,<sup>1</sup> since CN neither restricts to a specific histology (which may well not exist) nor to a specific and so far unproven pathogenetic mechanism (e.g., the highly controversial issue of whether tubular casts are the cause or consequence of CN, and the overall impact of bile acids in CN).

“Cause and effect are two sides of one fact” (Ralph Waldo Emerson): What causes cholemic nephropathy (CN)?

Although intuitive, as outlined above, the focus on biliary constituents such as bilirubin and bile acids as potentially causative for CN<sup>1,9</sup> may conceptually be misleading as it neglects inflammatory processes that may also contribute to CN (► Fig. 1).<sup>16</sup> However, what we know so far on the pathogenesis of CN still circles around these two molecules.

## Bilirubin

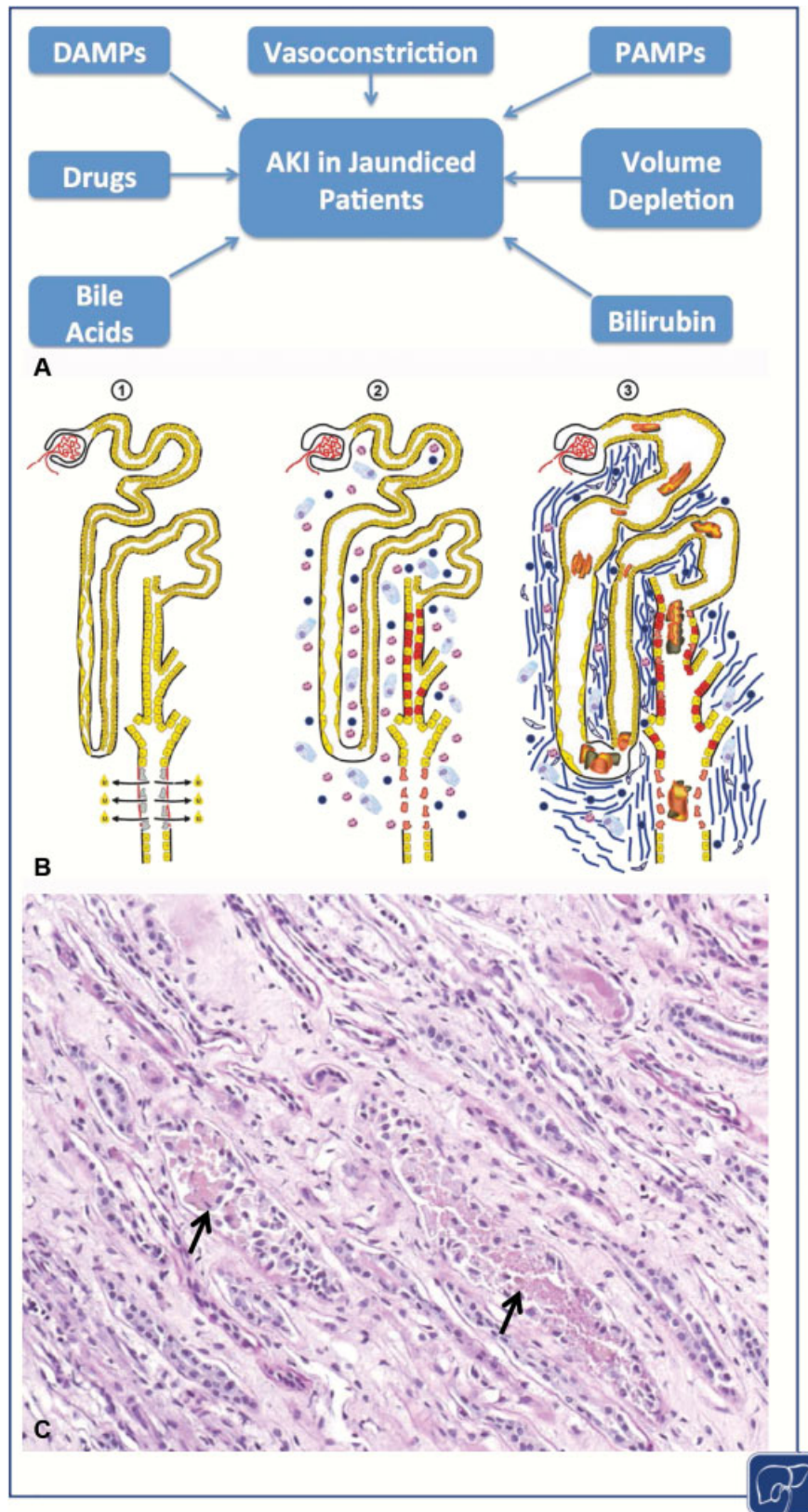
Bilirubinuria means that in cholestasis, when less bile reaches the duodenum, conjugated bilirubin is alternatively excreted via the urine. The potential nephrotoxicity of unconjugated bilirubin was ascribed to its accumulation in mitochondria with subsequent inhibition of oxidative phosphorylation with decreased adenosine triphosphatase activity. This was associated with mitochondrial defects and led to increased permeability of cell membranes, resulting in modified electrolyte content and cell volume.<sup>17–21</sup> However, currently there is no direct proof for the concept that bilirubin may be causative for tubular epithelial injury, cast formation, or more generally speaking CN. Renal bilirubin accumulation in CN may therefore just be an innocent bystander caused by accumulation through alternative renal excretion in cholestasis hampered through cast formation and tubular injury. Interestingly, there seems to be a certain threshold for serum bilirubin levels (> 15 mg/dL) in patients with CN. However, this does not necessarily mean that high bilirubin levels are causative; rather, it might reflect the degree of cholestasis and liver disease. Indeed, bilirubin may even have renoprotective effects, which were attributed to an increased expression of heme oxygenase-1 and increased activity of this enzyme in kidneys of common bile duct ligated rodents.<sup>22–27</sup> In addition, bilirubin was shown to improve vascular resistance, tubular function, mitochondrial integrity, and inhibition of nicotinamide adenine dinucleotide phosphate hydrogen oxidase and nitric oxide synthase 2 expression, which all together would be assumed to be beneficial for stressed kidneys.<sup>24–26</sup> There is also increasing clinical evidence

that elevated serum bilirubin levels may be renoprotective. In line with that assumption, late graft failure in kidney transplant patients was significantly lower in those with higher bilirubin.<sup>27</sup> Moreover, a large-sized cohort study showed slower chronic kidney disease progression in individuals with only mild elevations of serum bilirubin levels beyond the upper limit of normal (ULN).<sup>28</sup> In essence, there is currently no strong experimental evidence supporting a causative role for bilirubin in the pathogenesis of CN. Nevertheless, increased urinary excretion of bilirubin may still be an attractive cause of tubular casts and virtually nothing is known about the physicochemistry of bilirubin within casts or the tubular lumen in CN. Consequently, several intriguing questions remain such as whether there is bilirubin crystal formation or cross-reaction with proteins or alternative molecules in CN.

## Bile Acids

Under physiological conditions, glomerular-filtered bile acids are reuptaken in the distal part of Henle's loop via active transport systems, apical sodium-dependent transporter and organic solute transporter  $\alpha/\beta$ ,<sup>29</sup> similar to the quantitatively much more important reuptake of bile acids in the terminal ileum during their enterohepatic circulation that starts with the excretion of hepatic bile acids with bile into the duodenum.<sup>30</sup> In cholestatic patients, less bile reaches the duodenum and bile acids spill over from the liver and accumulate in serum. Alternative renal excretion of bile acids is currently seen as a mechanism of compensation under this condition.<sup>31–35</sup> It is therefore tempting to speculate that this mechanism may exceed the kidneys' capability for alternative bile acid excretion at certain levels of cholestasis, resulting in CN.<sup>36</sup>

The most compelling evidence that bile acids may trigger CN derives from experimental animal models. In response to common bile duct ligation (CBDL), serum bile acids peak around day 3.<sup>13,31,36</sup> Notably, this coincides with discrete alterations in proximal tubule architecture, which may easily be missed on hematoxylin and eosin stained kidney sections but may be more easily seen on periodic acid-Schiff (PAS)-stained sections.<sup>13,36</sup> We showed epithelial injury in collecting ducts in CBDL mice at day 3 that will hardly be detected in patients.<sup>13</sup> Besides tubular epithelial injury, basement membrane defects leading to leaky tubuli and obstruction of collecting ducts due to sloughed cells, tubular casts, and increased urinary neutrophil gelatinase-associated lipocalin levels were found.<sup>13–15</sup> There is no evidence in this model that tubular casts contain plentiful bilirubin; however, CBDL mouse liver, intriguingly, shows neither bilirubinostasis nor bile plugs and the species differences remain unexplained. Time course studies revealed that these early lesions were followed by interstitial nephritis and tubulointerstitial fibrosis later on. With long-term CBDL (up to 8 weeks), we were able to model the typical human histomorphological and functional alterations with CN.<sup>13</sup> These findings suggest that full-blown CN in CBDL mice requires a long-standing and severe form of cholestasis. Evidence that bile acid toxicity is key in this model is based on two main experimental findings and key experiments: (1) increasing the hydrophilicity of the bile acid pool



**Fig. 1** (A) Potential triggers of acute kidney injury (AKI) in jaundiced patients. (B) Conceptual model for the pathogenesis of cholemic nephropathy (CN). (1) CN in common bile duct ligated mice starts at the level of collecting ducts with injury to aquaporin 2 (AQP2)-positive tubular epithelial cells and basement membrane disintegrating leading to leaky collecting ducts. (2) Tubules cell injury and cast formation increase pressure within the tubular part of the nephron with dilatation and tubulointerstitial nephritis. (3) Progressive tubular dilatation and interstitial nephritis trigger interstitial fibrosis (adapted from Fickert et al)<sup>13</sup> (C) *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 (magnification 10 $\times$ ).

with the aid of hydrophilic and nontoxic norursodeoxycholic acid (*norUDCA*) significantly ameliorated the renal phenotype<sup>14</sup> and (2) CBDL in FXR<sup>-/-</sup> mice (with a much more hydrophilic bile acid pool in comparison to the wild-type controls) were protected against CN but showed similar renal fibrosis in response to unilateral ureteral ligation.<sup>13</sup> Accordingly, bile acids might represent a key determinant of CN in CBDL mice. High concentrations of cholephiles such as bile acids in the renal tubules (probably in concert with alternative danger signals or inflammatory mediators) may be toxic to tubular epithelial cells and consequently trigger inflammation. Detailed mechanisms, however, still have to be determined and most importantly currently there is no human evidence that bile acids have a major role in CN. This is of critical importance and likely based on the numerous species differences in bile acid biology between rodents and humans that have to be considered.<sup>37,38</sup>

There is a lively discussion on the issue whether tubular casts in CN may be the cause or rather the consequence of a decreased glomerular filtration rate (please see *AJKD* blog; #NephMadness 2019: Hepatorenal Region). Currently, known cast ingredients in CN include desquamated epithelial cells, protein precipitates, and bilirubin as evidenced by positive PAS and Hall's stain. However, this has to be referred to as indirect evidence from unspecific staining methods, since a detailed biochemical analysis of casts in CN is still unavailable. The enigma also remains as to whether casts themselves are tubulotoxic or may trigger CN. Such a mechanism could hypothetically be analogous to cast nephropathies by myeloma or myoglobin release from crushed muscles.<sup>39-42</sup> Interestingly, tubular casts in CN are predominantly found in aquaporin 2-positive collecting ducts in CBDL mice.<sup>13</sup> This key finding was recently confirmed in kidney biopsies of patients with CN.<sup>43</sup> Tubular cast formation at the level of collecting ducts originate not only from a higher urinary concentration due to water reabsorption in this part of the nephron but also from lower pH, both of which may promote cast formation.<sup>44,45</sup> Consequently, the formation of tubular casts in CN could be due to the poor water solubility of cholephiles such as bilirubin and specific bile acids and/or limited proximal tubular reabsorption. Again, detailed biochemical analysis of tubular casts should provide important results and answers.

## Inflammation

Cholestasis and jaundice are frequently seen in patients with decompensated cirrhosis. CN may in fact be more frequent as suggested so far in such patients, since several studies showed that there may actually be renal pathology comparable to CN, even when patients were clinically classified as having HRS. Thus, our current diagnostic criteria for HRS do not rule out CN.<sup>8,46</sup> In recent years, evidence has accumulated indicating that decompensated cirrhosis is associated with persistent systemic inflammation, which may play an important part in the progression of cirrhosis and the development of complications, including not only HRS but also CN.<sup>16,47-49</sup> Patients with advanced cirrhosis show bacterial translocation from the

gut to mesenteric lymph nodes, which is associated with increased levels of proinflammatory cytokines. In addition, pathogen-associated molecular patterns (PAMPs) deriving from bacterial translocation or bacterial infections and damage-associated molecular patterns (DAMPs, e.g., high-mobility group protein B1) may come into play. It is consequently attractive to speculate that such inflammatory cascades may also trigger CN, again analogues as to the pathogenesis of myoglobin nephropathy underscoring the importance of macrophages and activated platelets in this disease.<sup>50</sup>

Figuring out the pathogenesis of CN will be demanding indeed and will require a multidisciplinary approach including clinical and experimental nephrologists, hepatologists, and pathologists.

“The proof of the pudding is in the eating” (English saying): What is the clinical evidence for cholemic nephropathy?

The clinical literature on CN published since the early 20th century was more or less anecdotal, constituting mainly of case reports or case series and CN did not attract much attention either in the hepatologists' or the nephrologists' camps (→ **Table 1**). This may be related to its overlap with different medical disciplines and their respective interests, and general problems with research funding for CN; even a lack of clinical appeal due to the generally poor prognosis of jaundiced patients with AKI may be a reason. The pathology series published by van Slambrouck et al including analysis of 44 patients (classified as 23 cirrhotic jaundice, 14 obstructive jaundice, 5 hepatic jaundice, 2 hemolytic jaundice) had a game changing effect, at least with the invention of the new name “bile cast nephropathy” and suddenly raised considerable interest in the cause and consequences of kidney disease in jaundiced patients.<sup>8,46</sup> In essence, the findings of this interesting study can be summarized in that the presence of tubular casts (positive for Hall's stain indicating bilirubin content) correlated with higher serum bilirubin levels and showed a trend toward higher creatinine levels. However, as we discussed above, changing the name from CN to bile cast nephropathy may harbor significant disadvantages, but most importantly, this paper substantially stimulated nephrologists' and hepatologists' imaginations and interest in this most likely underestimated and probably important disease and stimulated recent research and discussions.<sup>8,46</sup>

Subsequently, Bräsen et al investigated the frequency and clinical course of CN in their tertiary care hospital over a period of more than 15 years (from 2000 to 2016) when a total of 79 patients with liver disease underwent kidney biopsy due to deteriorating renal function.<sup>43</sup> It is important to note that this retrospective analysis was based on the presumed histomorphological characteristics of CN, specifically the presence of Hall's stain-positive bilirubin casts. Out of 79 patients, 45 presented with AKI and in this study the diagnosis of CN was exclusively observed in patients with AKI (8 of 45, 18%). All patients with histological findings compatible with CN were positive for bilirubin in the urine, whereas only 22% of non-CN

**Table 1** Common clinical features in case reports/case series on cholemic nephropathy published since 2000 (adapted from Kroneš et al<sup>1</sup>)

Author	Year	No. of cases	Etiology of jaundice	Peak total bilirubin or mean levels $\pm$ SEM	Diagnosis of CN	Histological findings	Outcome
Bal et al <sup>54</sup>	2000	3 out of 40	Subacute hepatic failure	20 $\pm$ 10.2 mg/dL	Postmortem biopsy in 3 patients	Meningeal proliferation and thickening, basement membrane thickening, presence of hyaline, granular, and bile casts	N/A
Kiewe et al <sup>55</sup>	2004	1	Hodgkin's lymphoma with liver involvement and jaundice	1.7 mg/dL	Biopsy	Multiple intratubular greenish bile casts	Improvement of renal function along with restoration of cholestasis and liver function
Betjes and Bajema <sup>56</sup>	2006	2	Obstructive jaundice in patient A, autoimmune hepatitis in patient B	36.2 mg/dL 33.2 mg/dL	Biopsy	Bilirubin pigment in the tubules Tubular cell necrosis	Improvement of renal function along with decrease of bilirubin in patient A, patient B died
Uslu et al <sup>57</sup>	2010	20	Obstructive jaundice (mean duration 15.5 $\pm$ 1.4 d)	10.1 $\pm$ 1.0 mg/dL	Biopsy	Dilatation of peritubular venules, acute tubular necrosis	Absolute recovery of renal function in all patients after biliary drainage
Bredewold et al <sup>58</sup>	2011	1	Progressive jaundice due to mononucleosis infectiosa	36.1 mg/dL	Biopsy	Acute tubular necrosis, casts consisting of bilirubin pigment	Patient fully recovered
van Slambrouck et al <sup>8</sup>	2013	24	Obstructive cholestasis	24.9 mg/dL	Autopsy Biopsy	Bile casts with involvement of distal nephron segments	N/A
Rafat et al <sup>59</sup>	2013	1	Jaundice due to malignant cholangiocarcinoma	30 mg/dL	Biopsy	Bile thrombi in dilated tubules Bile granules in cytoplasm of tubular epithelial cells	Patient died due to cholangiocarcinoma
Luciano et al <sup>12</sup>	2014	1	Cholestatic jaundice related to ingestion of anabolic steroids	47.9 mg/dL	Urine microscopy Biopsy	Pigmented granular casts and heavily pigmented renal tubular epithelial cell casts upon urine microscopy Dilated tubules containing heavily pigmented granular casts upon histology	Serum creatinine levels remained mildly elevated
van der Wijngaart et al <sup>60</sup>	2014	1	Obstructive jaundice with multiple gallstones in the common bile duct	39.6 mg/dL	Biopsy	Bile casts, reactive changes of tubular epithelial cells	Improvement of kidney function after biliary drainage and hemodialysis for 5 wk
Jain et al <sup>61</sup>	2015	1	Jaundice following wedge resection of liver	42.5 mg/dL	Urine microscopy Biopsy	Bile casts and leucine crystals upon urine microscopy Intratubular bile casts upon kidney biopsy	N/A
Sequeira and Gu <sup>62</sup>	2015	1	Alcoholic steatohepatitis	23.1 mg/dL	Biopsy	Acute tubular injury, bile casts	Hemodialysis
Tabatabaee et al <sup>63</sup>	2015	2	Cholestatic jaundice related to ingestion of anabolic steroids	50 mg/dL	Biopsy	Acute tubular epithelial cell damage, bile cast deposition	Improvement of serum creatinine along with decrease of bilirubin
Patel et al <sup>64</sup>	2016	1	Drug-induced liver injury secondary to antibiotic use	19.3 mg/dL	Biopsy	Pigmented bilirubin casts and droplets in proximal and distal tubules, tubular atrophy, and interstitial fibrosis	Combined liver and kidney transplant

(Continued)

Table 1 (Continued)

Author	Year	No. of cases	Etiology of jaundice	Peak total bilirubin or mean levels $\pm$ SEM	Diagnosis of CN	Histological findings	Outcome
Sens et al <sup>65</sup>	2016	1	Episode of cholestasis in a patient with Maturity Onset Diabetes of the Youth (MODY) type 5	20.1 mg/dL	Biopsy	Bile casts, marked tubular necrosis	Improvement of serum creatinine along with decrease of bilirubin
Werner et al <sup>66</sup>	2016	1	Painless jaundice due to cholangiocellular carcinoma	N/A	Biopsy	Dilated tubules, bile casts	Resolution of renal function after restoration of cholestasis
Alkhunazi et al <sup>67</sup>	2016	1	Cholestatic jaundice related to ingestion of anabolic steroids	44 mg/dL	Biopsy	Bile casts within distal tubular lumina, filamentous bile inclusions within tubular cells, signs of acute tubular injury	Improvement of serum creatinine along with decrease of bilirubin
Alnasrallah et al <sup>68</sup>	2016	1	Flucloxacillin-induced liver dysfunction	51.5 mg/dL	Biopsy	Dilated tubules, bile casts, tubular epithelial injury	Decline of serum creatinine after improvement of jaundice
Mohapatra et al <sup>69</sup>	2016	20	Severe falciparum malaria complicated with jaundice	26.5 $\pm$ 4.1 mg/dL	Urine microscopy Biopsy	Bile-stained casts upon urine Numerous tubular casts, acute tubular Necrosis but maintained glomerular architecture upon kidney histology	Recovery time of renal dysfunction 15.1 $\pm$ 6.5 d
Leclerc et al <sup>10</sup>	2016	1	Drug-induced hepatic jaundice	30.9 mg/dL	Biopsy	Brown casts clogging the tubular lumen, brown deposits in the cytoplasm of tubular epithelial cells	Improvement of kidney function after normalization of bilirubin and hemodialysis
Aniort et al <sup>70</sup>	2017	1	Obstructive cholestasis caused by stones in the common bile duct	32.6 mg/dL	Biopsy	Intraluminal green casts, tubular injury	Complete recovery following removal of the bile duct obstruction
Nayak et al <sup>46</sup>	2017	57	42 ACLF, 25 decompensated cirrhosis	Median (range) 27.0 mg/dL (1.5–72.8)	Postmortem biopsy	Hall's stain-positive casts in 57 from 127 autopsy kidney specimens. Interstitial edema 11/57, interstitial fibrosis 6/57, tubular atrophy 1/57	Postmortem biopsy study
Bräsen et al <sup>43</sup>	2019	8	3 viral hepatitis, 1 AIH, 4 others	45.5 $\pm$ 17.8 mg/dL	Biopsy	Hall's stain-positive tubular casts, pigment inclusions in tubular epithelial cells	5/8 required renal replacement therapy

Abbreviations: ACLF, acute on chronic liver failure; AIH, autoimmune hepatitis; CN, cholemic nephropathy; SEM, standard error of the mean.

patients had detectable urinary bilirubin. An additional univariate logistic regression analysis identified bilirubin > 5 times the ULN and alkaline phosphatase > 3 times the ULN as independent risk factors. Importantly, this study calls the specificity of histological findings in CN into question. To further characterize the histomorphology of CN and to determine the specificity of these findings, the authors developed a questionnaire and included some CN cases in a group of 20 acute tubular injury cases (7 CN, 7 cases with liver disease and elevated bilirubin but no CN, and 6 cases with pigment deposits for different reasons such as lipofuscin, iron, or porphyria). The authors invited six highly experienced nephropathologists from three different pathology departments to participate and answer the questionnaire. Neither the evaluation of all six raters nor a subgroup analysis based on their level of experience (nephropathologists with > 10 vs. > 15 years of experience) identified discriminating histopathological features among the chosen entities indicating that the histopathological findings in CN may be less specific than initially suggested. Moreover, Hall's stain is known to have a low sensitivity.<sup>8</sup> Of note, this important study confirmed that kidney biopsy carried a significant risk of bleeding (6 of 79 patients, 8%; 4 underwent surgery or vascular coiling). Therefore, kidney biopsy/histology may not represent the ideal diagnostic test and the findings of the Bräsen et al study reinforce the need for noninvasive and alternative diagnostic methods.

Both studies raise the pivotal question about the estimated number of unreported cases of CN within the group of patients currently referred to as AKI-HRS, since they may also fulfill the revised modern criteria for this syndrome.<sup>51,52</sup> It is attractive to hypothesize that AKI-HRS patients with insufficient response to terlipressin or noradrenalin may be most likely to have CN.

## Diagnostic Challenges in Cholemic Nephropathy

A consensus on diagnostic criteria for CN is sorely missed. From the clinicians' point of view, the differential diagnosis of CN arises in cases with (prolonged) deep jaundice and concomitant impairment of renal function which may not be primarily related to or explained by clinical significant portal hypertension (i.e., the situation with only minimal or lack of ascites). Currently, the diagnosis of CN is solely based upon kidney histology with Hall's stain-positive bilirubin casts as the diagnostic corner stone, which are frequently considered as disease specific. The tubular casts in CN may significantly differ in color (e.g., greenish yellow, light to dark red), composition (variable degree of cellular debris), and localization (primarily in the distal nephron segments, also in the proximal segments in severe cases). Pathologists use the Hall's stain (i.e., using Fouchet's reagent which converts bilirubin to green biliverdin) to confirm bilirubin in the casts and Perls' Prussian blue stain to rule out ferric iron deposits. It again has to be mentioned that Hall's histochemical stain is insensitive. In addition, kidney biopsy in patients with advanced liver disease may involve a significant risk of bleeding, as also observed in the Bräsen et al

study.<sup>43</sup> Consequently, the benefit–risk ratio for kidney biopsy in such cases is complicated, especially in the light of the current lack of therapeutic consequences. Together with the current evidence that kidney histology in CN might not be as specific as has been suggested,<sup>43</sup> this also raises the critical question of whether CN is indeed a specific entity in each individual case. Alternatively, CN may also represent a part of the spectrum of AKI in jaundiced patients also including those with advanced chronic liver disease, acute on chronic liver failure (ACLF), or inflammatory-driven AKI. At least what is known from published autopsy studies argues for such an assumption, since there are numerous patients reported showing morphological characteristics of CN in kidney histology but were clinically classified as AKI-HRS.<sup>8,46</sup> A *postmortem* kidney biopsy study by Nayak et al included 127 renal biopsies for analysis obtained from 84 patients with decompensated cirrhosis and 43 patients with ACLF.<sup>46</sup> Fifty-seven of the total 127 (45%) biopsies showed CN with Hall's stain-positive and Perls' stain-negative tubular casts. Patients with CN had significantly higher levels of serum total bilirubin, total leukocyte count, and Model of End-stage Liver Disease score than those without CN. The authors concluded that CN was found in 72% of patients with ACLF and 27% patients with decompensated cirrhosis hospitalized with HRS-AKI. This indicates that a so far undefined percentage of patients fulfilling current AKI-HRS criteria will show kidney histology compatible with the findings in CN. Such a concept is further supported by the finding in Bräsen et al's study that patients with a unalterable liver problem did not recover from CN in contrast to those with a treatable liver disease (e.g., chronic hepatitis B).<sup>43</sup> It is attractive to speculate that the percentage of CN in terlipressin nonresponder AKI-HRS patients will be high. However, all these intriguing questions have to be resolved in future prospective clinical trials, since *postmortem* analysis and retrospective analysis of kidney biopsies in AKI-HRS patients have several flaws and weaknesses ranging from the problem of potential *postmortem* artifacts to the important issue of selection bias. Still, the studies discussed above are relevant, since they challenge our current concepts of definition and classification of AKI-HRS on one hand and those of CN on the other and will stimulate further essential research in this area.

The fact that kidney biopsy is risky especially in AKI patients with advanced liver disease raises the critical issue of alternative and noninvasive diagnostic methods. One rather simple method could be urine cytospin and cellblock analysis,<sup>53</sup> but this still has to be evaluated in prospective trials. In the Nayak et al study, there was no difference in the (routine) urinary analysis between patients with and without CN; however, they did not use adequate protocols to detect casts (e.g., centrifugation of 10 mL of urine at 2,000 revolutions per minute for 20 minutes) and the authors critically discuss this interesting issue in detail.<sup>46</sup> Future prospective studies should therefore evaluate such protocols for potential noninvasive detection of Fouchet's or Hall's stain-positive casts in CN patients. Moreover, urinary biomarkers such as NGAL, interleukin-18, kidney injury molecule-1, and liver-type fatty acid binding protein should be studied in CN as discussed in detail earlier.<sup>1</sup>

## Management of Patients with Cholemic Nephropathy

Currently, there is no specific treatment or management recommendation for CN available. The published evidence on that issue still has to be referred to as anecdotal and publication bias is additionally very likely (→ **Table 1**). Since jaundiced patients are known to be at significantly increased risk for AKI, potentially nephrotoxic agents should be omitted to minimize tubular stress and volume status of patients has to be checked and corrected carefully. In some patients, however, complete recovery of renal function after successful biliary drainage was observed, which is again a strong argument for cholephiles as causing factors of CN. There is currently no single published prospective clinical trial on the therapeutic management of CN, which may originate in the ambiguity of the diagnostic criteria and standards of CN, the discussed differential diagnostic problems (especially clear discrimination from AKI-HRS), and the mixed patients population. Animal experiments suggest that bile acids such as *norUDCA* may represent attractive candidates for medical treatment.<sup>14</sup>

## Task List for Cholemic Nephropathy

- We need diagnostic criteria and standards for CN.
- One of the most critical issues in the area is the widely unknown clinical impact of CN in patients with and without concomitant liver disease and the undefined but likely overlap with AKI-HRS. For that aim, we urgently need carefully designed prospective large cohort studies, which should be performed by powerful study groups.
- Careful retrospective histological analysis of explanted kidneys from patients with refractory AKI-HRS undergoing combined liver and kidney transplantation should be most informative.
- Clinical studies should especially aim on the identification of triggers, risk factors, and noninvasive diagnostic tests for CN.
- Animal models with cholestatic liver diseases should be screened for CN, since CBDL in rodents comprises several limitations.<sup>1</sup>
- Mechanisms of renal tubular cell injury, impact of bile acid signaling molecules such as FXR and TGR5 on renal bile acid transport, and mediators of inflammation in CN have to be determined.
- Since CN may have numerous parallels to myoglobin nephropathy where platelets were just recently shown to play a major role,<sup>50</sup> the influence of platelets should be clarified.
- Impact of activation of inflammatory cells, of DAMPs or PAMPs, as well as of different cytokines and chemokines has to be determined and such studies should specifically focus on the identification of novel potential therapeutic targets.

## Main Concepts and Learning Points

- The term cholemic nephropathy (CN) refers to renal dysfunction with tubular epithelial injury primarily in

distal nephron segments accompanied by intraluminal cast formation in patients with deep jaundice.

- The mechanisms of tubular cell injury remain elusive and whether tubular casts in CN are cause or consequence of the disease is unclear; the role of bilirubin is controversial, but the role of bile acids is likely pivotal.
- Lack of clear diagnostic criteria and standards as well as the need for invasive and potentially risky kidney biopsy currently hinders accurate but exact diagnosis and consequently a clear picture of the clinical impact of CN in the absence of prospective clinical trials.
- CN frequently resolves if cholestasis can be resolved, but there is no specific therapy to achieve this.
- Research in CN should focus on its pathophysiology, identification of noninvasive diagnostic tests, determination of its prognosis and clinical importance, and on the development of specific treatment strategies.

### Conflict of Interest

P.F. reports grants from Dr. Falk Pharma GmbH, other from Medical University of Graz, grants from Austrian Science Foundation, during the conduct of the study; grants from Dr. Falk Pharma GmbH, other from Medical University of Graz, outside the submitted work. P.F. has a patent WO2006119803 licensed to Medical University of Graz, and a patent WO20099013334 licensed to Medical University of Graz.

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