Published in final edited form as:

Curr Opin Nephrol Hypertens. 2014 July ; 23(4): 385–390. doi:10.1097/01.mnh.0000447017.28852.52.

Acute and chronic kidney injury in nephrolithiasis

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Abstract

Purpose of review—Nephrolithiasis is a common systemic disease associated with both acute kidney injury (AKI) and chronic kidney disease (CKD). The purpose of this review is to discuss recent publications on nephrolithiasis-associated kidney damage, with an emphasis on AKI.

Recent findings—Nephrolithiasis is not a common cause of adult AKI (1–2% of cases), although it may be a more important factor in young children (up to 30%). The primary mechanism of nephrolithiasis-associated AKI is obstructive nephropathy, and factors at presentation with obstructive uropathy predict the likelihood of long-term renal recovery. Crystalline nephropathy is another potential pathway in certain circumstances that is often associated with a worse outcome. Recent studies have elucidated additional pathways whereby calcium oxalate crystals can cause acute injury, implicating innate immunity and intracellular inflammasome pathways. Several large cohort studies have demonstrated an independent association of nephrolithiasis with CKD and ESRD, although the effect size is modest. Urologic comorbidities, urinary infection, and shared underlying risk factors (e.g., diabetes, hypertension) all impact nephrolithiasis-associated CKD risk.

Summary—Obstructive nephropathy and crystalline nephropathy both contribute to nephrolithiasis-associated AKI, although the latter appears to have a worse prognosis. Nephrolithiasis is an independent albeit small risk factor for CKD. Further study is needed to clarify the incidence and mechanisms of nephrolithiasis-associated AKI, and the relationship between nephrolithiasis-associated AKI and CKD.

Keywords

acute kidney injury; chronic kidney disease; crystalline nephropathy; end-stage renal disease; nephrolithiasis; urolithiasis

Introduction

Kidney stone disease (nephrolithiasis) is extremely common, causing substantial pain and a large economic cost. It is well known that nephrolithiasis can cause post-renal acute kidney injury (AKI) via obstruction of urinary outflow, often associated with rapid deterioration in renal function. Irreversible kidney damage can result if urinary drainage is not corrected in a timely fashion. Recent studies also suggest that patients with nephrolithiasis are more likely to develop chronic kidney disease (CKD). In this review, we will discuss recent advances in our understanding of the interrelationships between nephrolithiasis, AKI, and CKD. Since there are several excellent and recent reviews regarding the association between CKD and nephrolithiasis [1–3], we will place more emphasis on the mechanisms and treatment of nephrolithiasis-related AKI.

Nephrolithiasis as a cause of obstructive AKI

Few epidemiological studies have defined the incidence and prevalence of nephrolithiasis-associated AKI. Kaufman and colleagues characterized 100 patients with community-acquired AKI, among whom 17% had an obstructive cause [4]. Similarly, a multi-center in Spain suggested that the incidence of obstructive nephropathy was 23 cases per million population per year, accounting for 10% of community-acquired AKI [5]. Therefore, obstruction is a relatively common cause of community-acquired AKI. However, only 10–12% of obstructive AKI cases were caused by urolithiasis, and these accounted for only about 1–2% of all AKI events [4–6]. Looked at another way, a retrospective Chinese series of 2,073 adult ureteral stones similarly revealed a prevalence of AKI on presentation of only 0.72% [7]. In this Chinese series stone patients that presented with AKI were more likely to have larger stones (1.05 ± 0.34 cm vs. 0.82 ± 0.40 cm), bilateral ureteral stones, presence of a solitary kidney, and preexisting CKD. Urolithiasis may be a more common factor in pediatric AKI, since in a series of children aged 2–12 obstructing stones were cited as a cause of AKI in up to 30% [8].

Signs of obstructive nephropathy are often nonspecific. Although a decrease in urine output is frequently observed, normal or even elevated urine output does not rule out partial obstruction [7]. Therefore, imaging studies play a crucial diagnostic role. Recent studies report that a discrepancy between serum cystatin C and creatinine levels can also be a clue that suggests a post-renal cause [9, 10]. In a rodent study that compared post-renal obstruction and bilateral nephrectomy, Tsuda and colleagues found that the increment in serum cystatin C and β_2 microglobulin were much smaller in the post-renal group, while increases in serum creatinine were similar in both groups. The ratio of serum creatinine to cystatin C and serum β_2 microglobulin in the post-renal group were higher than in the nephrectomy group (20.6 and 8.3 versus 18.5 and 5.3, respectively) [9]. Similarly, Fujisawa reported no or only a minimal serum cystatin C increase in three patients with post-renal obstruction, compared to a marked increase of serum creatinine [10]. These studies suggest that some amount of low molecular weight protein glomerular filtration followed by tubular re-uptake still occurs even in the face of obstructive uropathy. However, clinical investigation in a larger number of patients is needed to confirm the role of these newer biomarkers in the diagnosis of post-renal AKI.

Surgical treatment of nephrolithiasis and long-term renal outcome

Once obstructive uropathy from a kidney stone has been identified, prompt and appropriate urologic intervention is necessary to avoid irreversible renal damage. Nevertheless, most nephrolithiasis-associated AKI has a reasonably good prognosis. In a multicenter study of 93 children with anuria caused by stones, kidney function fully recovered in 57% and improved in 37.6%, with significant improvement occurring promptly over the first 72h after intervention in 84% [11].

The ultimate degree of renal recovery depends primarily on the extent and duration of the obstruction together with the presence or absence of infection [12, 13]. In a rodent ureteral obstruction model, the severity of tubular atrophy and interstitial fibrosis linearly increased as the duration of obstruction was extended [12]. Recently Lucarelli and colleagues evaluated long-term renal outcome (mean 60.8 months) among 76 patients with iatrogenic renal injury caused by ureteral obstruction [13]**. In multivariable logistic modeling, time elapsed before relief of the obstruction was the only significant predictor of outcome, and if outflow was restored in less than 2 weeks no evidence of long-term renal damage was observed. However, when repair was delayed greater than 2 weeks, renal outcome became progressively worse. The urinary epidermal growth factor (EGF)/ monocyte chemotactic peptide-1 (MCP-1) ratio measured 4 weeks after relief of obstruction correlated with long term outcome, suggesting pathways that favor long term fibrosis are activated quite early. In case series up to 15–23% of patients that present with AKI and obstruction may require short-term dialysis [11, 14], although early relief of obstruction and prompt correction of electrolyte and acid-base imbalances can minimize this risk [15].

Open nephrolithotomy was previously an important contributor to nephrolithiasis-associated CKD. However, there is little evidence that currently-employed and less invasive treatments are associated with permanent renal injury. Although many studies in both animal models and patients have clearly demonstrated short-term structural and functional injury after shock wave lithotripsy (SWL), including the development of hematomas [16, 17], these changes appear to be temporary and largely resolve within 1 to 3 months [16, 18]. Previous studies connected SWL with new-onset hypertension, exacerbation of stones, or the development of diabetes [19], however more recent population based cohort studies did not confirm these associations [20, 21]. Indeed, there is currently no clear evidence of long-term detrimental effects from SWL, even among patients with pre-existing CKD [22]. Likewise, studies suggest percutaneous nephrolithotomy (PCNL) is not associated with adverse renal outcome in the short or long-term [3]. However, baseline CKD appears to influence the course of recovery since operative time, length of hospital stay and complication rates were all increased among those with CKD stages 4 and 5 [23].

Occasionally, patients with kidney stones require nephrectomy for large stones. There has always been concern about the fate of the remaining kidney in these circumstances, especially were the stone disease to remain active after nephrectomy. Carvalho and colleagues recently reported that the creatinine clearance among 30 nephrolithiasis patients who underwent nephrectomy was 52.5 ± 18.8 ml/min, significantly lower than matched nephrolithiasis controls with two intact kidneys (92.9 ± 24.2 ml/min, $p < 0.001$) [24]*. This

study did not have data regarding long-term outcome after the nephrectomy, however three decades worth of follow-up in a tertiary kidney stone clinic did not suggest that those stone patients with a solitary kidney inexorably lost function [25]. Indeed, in a study such as Carvalho's it is difficult to determine the exact role the nephrectomy played in the reduced kidney function since only patients with extensive and complicated stones are likely to be offered this procedure. Women represented the vast majority (17/20) of the nephrectomy patients in the Carvalho cohort, perhaps because concurrent infection is a frequent indication for nephrectomy in association with stone disease, [24]. Women have been similarly overrepresented in other series of stone patients requiring nephrectomy [25].

Mishra and colleagues recently developed a model to predict chance of renal function recovery among patients who presented with bilateral obstructive uropathy due to stones [26]**. Stones were treated with ureteroscopy or PCNL in a cohort of 167 patients with a mean age 48 ± 14 yrs and serum creatinine of 7.26 ± 4.42 mg/dl at presentation. Twenty-eight percent progressed to CKD stage 5 by the end of the first year. In a multiple logistic stepwise regression model, combined renal cortical width, proteinuria, nadir GFR 5 days after relief of obstruction, and a positive urine culture, were used to develop a one-year renal deterioration index (RDI). The RDI had good predicting value (Receiver Operating Area Under the Curve = 0.90; Table 1). Those with an RDI > 12 at presentation had markedly increased odds ratio (11.2) of being at CKD stage 5 one year later.

Crystal induced AKI in nephrolithiasis

Although nephrolithiasis-related AKI is usually associated with mechanical obstruction, crystalline nephropathy may be a factor in certain cases. Distal tubular solute supersaturation is a well-known kidney stone risk factor. Factors that favor supersaturation include dehydration (or inadequate oral fluid intake), over excretion of lithogenic substances such as calcium or oxalate, or an abnormally high (calcium phosphate) or low (uric acid) urine pH. Ingestion of poorly soluble drugs or toxins that are renally excreted, or over excretion of metabolic intermediaries among patients with specific genetic diseases (e.g., cystinuria, dihydroxyadenuria, primary hyperoxaluria), can also produce intratubular plugging and renal damage [27].

Acute oxalate nephropathy is observed in association with genetic disorders characterized by intrinsic overproduction of oxalate (primary hyperoxaluria), acquired gastrointestinal disorders characterized by fat malabsorption (enteric hyperoxaluria), or after excessive ingestion of vitamin C, oxalate-rich foods, or ethylene glycol [28]. Patients with pre-existing CKD may be particularly susceptible to oxalate nephropathy [29]. Renal injury in association with calcium oxalate-induced crystalline nephropathy is often not reversible, since in one series only 27% of patients experienced functional recovery [29].

Acute uric acid nephropathy (UAN) can occur when uric acid is massively over produced after chemotherapy for lymphoma or leukemia. UAN has also been reported in association with rare inherited syndromes such as hypoxanthineguanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome), as a result of impaired proximal tubular urate reabsorption (Fanconi-like syndrome), or among patients with familial renal hypouricemia,

in the latter circumstance especially after vigorous exercise [30]. Because uric acid is predominately eliminated via the kidney, it is occasionally difficult to determine if an increased blood uric acid level is the cause or result of AKI. In such cases a ratio of urinary uric acid to creatinine of >1.0 or a uric acid excretion rate greater than 0.57 mg per 100 ml of glomerular filtration rate (GFR) support the diagnosis of UAN [30]. Numerous uric acid crystals in the urinalysis also support this possibility. Acute UAN appears to have a better outcome than oxalate nephropathy, and often resolves with a combination of aggressive volume expansion, urinary alkalization, oral allopurinol, and early initiation of dialysis (as indicated). It is important to keep in mind that excessive administration of allopurinol can have the unintended consequence of increased xanthine production, which can also crystallize in the kidney [31].

Certain medications and toxins that have relatively low solubility can also crystallize in the kidney and collecting system including acyclovir, sulfonamide antibiotics, methotrexate, and the protease inhibitor indinavir. Melamine-induced acute kidney injury was observed in association with tainted baby formula during 2008 in China [32]. The mean time from initiation of the suspect milk powder to the onset of disease was 9.4 months. Low urinary pH appeared to be an important cofactor that favored melamine crystal deposition and AKI [32]. Fortunately, melamine-induced renal damage appeared to be reversible, and affected children have been reported to have a satisfactory short and long-term renal prognosis [33].

Mechanisms of nephrolithiasis-associated kidney injury

The mechanism of post obstructive AKI has been well-studied in animal models. Unilateral ureteral obstruction produces increased intratubular pressure, which is followed by intense renal vasoconstriction and a rapid fall in renal blood flow and GFR [34]. If the obstruction is prolonged interstitial fibrosis and nephron dropout ensue, eventually leading to CKD [35].

Another potential mediator of nephrolithiasis-associated kidney damage is direct cellular toxicity caused by crystals. The interaction of renal cells and calcium oxalate (CaOx) crystals, the major crystal in human kidney stones, has been extensively studied in animal and cell culture models. Multiple biological effects of CaOx crystals as well as soluble oxalate ion on renal epithelial cells have been characterized (Figure 1) [36]. Apoptosis and cell death, perhaps triggered by mitochondrial dysfunction and release of reactive oxygen species, has been observed [37]. Two very recent studies demonstrated that CaOx crystals can also activate innate immunity via the intracellular inflammasome [38, 39]. In a series of elegant experiments performed in a mouse model of acute oxalate toxicity, Mulay and colleagues demonstrated that intratubular and interstitial CaOx deposition was associated with diffuse interstitial neutrophilic infiltration and tubular necrosis [39]**. Activation of the NLPR3 inflammasome by CaOx crystals triggered intrarenal secretion of a diverse array of inflammatory cytokines and chemokines including IL-1 β and IL-18, thus perpetuating further damage. After blockade with an IL-1 agonist, tubular injury and neutrophil recruitment was reduced and kidney function improved.

Risk of CKD among those with nephrolithiasis

Although 0.8 to 17.5% of nephrolithiasis patients have CKD stage 2 or greater [3], only a relatively small percentage (0.8–3.2%) of ESRD has been attributed to stone disease [40, 41]. Nevertheless, several recent reports suggest that nephrolithiasis is indeed a small yet independent risk factor for both CKD and ESRD. The mechanism(s) remain unclear. In a study that took advantage of a large health care database in Taiwan, 21,474 individuals with newly diagnosed CKD were found 1.91 times more likely to have a prior diagnosis of urinary calculi than matched controls lacking CKD, after adjusting for socioeconomic factors and medical co-morbidities [42]. A population-based cohort study in Olmsted County found that stone formers were at a similar 2.1-fold higher risk of developing ESRD over 25 years of follow up, independent of baseline CKD and cardiovascular risk factors [43]. A third population-based epidemiological study of over 3 million Canadian adults without ESRD at baseline found that one or more stone episodes during follow-up was associated with increased risk of both CKD and ESRD [41].

There is little doubt that traditional CKD risk factors such as hypertension, diabetes, obesity and albuminuria are enriched among patients with kidney stones, which is probably an important contributor to the relationship between stones and CKD.

Certain patient-specific factors also likely increase the risk of nephrolithiasis CKD. Population-based studies in Olmsted County, MN suggested that stone formers who developed ESRD were more likely to have specific urological diagnoses including hydronephrosis, recurrent urinary tract infection, a solitary kidney, neurogenic bladder and an ideal conduit [43]. Other studies suggest that stone type impacts the risk of kidney failure. In a cross sectional study of 1918 patients with kidney stones, patients with calcium-containing stones (calcium oxalate and calcium phosphate) had a much higher GFR than those with non-calcium containing stones (struvite and uric acid) [44]. Similarly, Worcester and colleagues found that struvite and calcium phosphate stones were more common in nephrolithiasis patients with single kidney [25]. In a European cohort Jungers and colleagues observed that infection stones accounted for 42.2% of the patients with ESRD due to nephrolithiasis, while calcium and uric acid stones contributed 26.7% and 17.8%, respectively [40]. Finally, CKD and ESRD risk are increased among patients with certain hereditary stones such as primary hyperoxaluria, cystinuria, Dent disease, and adenine phosphoribosyltransferase deficiency, although the absolute number of such cases is small [45].

Conclusions

Recent reports demonstrate that nephrolithiasis is not a common cause of adult AKI, but may be a relatively major cause in younger children. Obstructive nephropathy is the main feature of nephrolithiasis-associated AKI. Recovery of renal function depends primarily on the extent and the duration of the obstruction. Crystalline nephropathy is another recently-recognized mechanism of nephrolithiasis-associated AKI that appears to impart a worse renal prognosis than obstruction alone, especially in hyperoxaluric states. Although several large epidemiological studies have identified an increased CKD risk among those with

nephrolithiasis, relatively few have focused on the epidemiology of AKI. Do prior AKI episodes have adverse impact on the kidney function? What cellular mechanisms contribute to the development and resolution of crystal-induced AKI? More research is clearly needed to define the characteristics and mechanisms of nephrolithiasis-associated AKI.

Acknowledgments

This study was supported by the Mayo Clinic O'Brien Urology Research Center (U54 DK100227), the Rare Kidney Stone Consortium (U54KD083908), a member of the NIH Rare Diseases Clinical Research Network (RDCRN), funded by the NIDDK and the National Center For Advancing Translational Sciences (NCATS), the Mayo Hyperoxaluria Center, the Mayo Foundation, and by Shanghai Top Priority Key Clinical Disciplines Construction Project (XT).

REFERENCES

- [1]. Keddiss MT, Rule AD. Nephrolithiasis and loss of kidney function. *Curr Opin Nephrol Hypertens*. 2013; 22:390–396. [PubMed: 23736840]
- [2]. Rule AD, Krambeck AE, Lieske JC. Chronic kidney disease in kidney stone formers. *Clin J Am Soc Nephrol*. 2011; 6:2069–2075. [PubMed: 21784825]
- [3]. Kartha G, Calle JC, Marchini GS, Monga M. Impact of stone disease: chronic kidney disease and quality of life. *Urol Clin North Am*. 2013; 40:135–147. [PubMed: 23177641]
- [4]. Kaufman J, Dhakal M, Patel B, Hamburger R. Community-acquired acute renal failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 1991; 17:191–198. [PubMed: 1992662]
- [5]. Liano F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. *Madrid Acute Renal Failure Study Group. Kidney international*. 1996; 50:811–818.
- [6]. Organ M, Norman RW. Acute reversible kidney injury secondary to bilateral ureteric obstruction. *Can Urol Assoc J*. 2011; 5:392–396. [PubMed: 22154632]
- [7]. Wang SJ, Mu XN, Zhang LY, et al. The incidence and clinical features of acute kidney injury secondary to ureteral calculi. *Urol Res*. 2012; 40:345–348. [PubMed: 21853241]
- [8]. Jamal A, Ramzan A. Renal and post-renal causes of acute renal failure in children. *J Coll Physicians Surg Pak*. 2004; 14:411–415. [PubMed: 15279743]
- [9]. Tsuda H, Isaka Y, Takahara S, Horio M. Discrepancy between serum levels of low molecular weight proteins in acute kidney injury model rats with bilateral ureteral obstruction and bilateral nephrectomy. *Clin Exp Nephrol*. 2009; 13:567–570. [PubMed: 19536607]
- [10]. Fujisawa N, Yashiro M, Segawa H, et al. Discrepancy between cystatin C and creatinine points leading to a diagnosis of postrenal acute kidney injury and its reversibility: three case reports. *Clin Exp Nephrol*. 2010; 14:608–613. [PubMed: 20607577]
- [11]. Ziada AM, Sarhan OM, Habib EI, et al. Assessment of recoverability of kidney function in children with obstructive calcular anuria: multicenter study. *J Pediatr Urol*. 2011; 7:252–256. [PubMed: 21527220]
- [12]. Chevalier RL, Thornhill BA, Chang AY. Unilateral ureteral obstruction in neonatal rats leads to renal insufficiency in adulthood. *Kidney international*. 2000; 58:1987–1995. [PubMed: 11044219]
- [13]. Lucarelli G, Ditunno P, Bettocchi C, et al. Delayed relief of ureteral obstruction is implicated in the long-term development of renal damage and arterial hypertension in patients with unilateral ureteral injury. *The Journal of urology*. 2013; 189:960–965. [PubMed: 23017525] ** This retrospective study evaluated the relationship between long-term renal outcome and time to relief of bilateral iatrogenic ureteral obstruction of diverse causes. A delay of more than 2 weeks before uri drainage was restored was associated with poorer renal outcome; the longer the time the worse the outcome.
- [14]. Rabbani M, Habib H, Siddiqui B. Etiology of acute renal failure in a tertiary center. *Saudi J. Kidney Dis*. 2008; 19:1009–1014.

- [15]. Nalcacioglu H, Ozden E, Genc G, et al. An uncommon cause of acute kidney injury in young children: cystinuria. *J Pediatr Urol.* 2013; 9:e58–63. [PubMed: 23099233]
- [16]. Fahmy N, Sener A, Sabbiseti V, et al. Urinary expression of novel tissue markers of kidney injury after ureteroscopy, shockwave lithotripsy, and in normal healthy controls. *Journal of endourology / Endourological Society.* 2013; 27:1455–1462. [PubMed: 24180435]
- [17]. McAteer JA, Evan AP, Williams JC Jr, Lingeman JE. Treatment protocols to reduce renal injury during shock wave lithotripsy. *Curr Opin Urol.* 2009; 19:192–195. [PubMed: 19195131]
- [18]. Sheir KZ, Gad HM. Prospective study of the effects of shock wave lithotripsy on renal function: role of post-shock wave lithotripsy obstruction. *Urology.* 2003; 61:1102–1106. [PubMed: 12809870]
- [19]. Krambeck AE, Gettman MT, Rohlinger AL, et al. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup. *J Urol.* 2006; 175:1742–1747. [PubMed: 16600747]
- [20]. Krambeck AE, Rule AD, Li X, et al. Shock wave lithotripsy is not predictive of hypertension among community stone formers at long-term followup. *The Journal of urology.* 2011; 185:164–169. [PubMed: 21074794]
- [21]. de Cogain M, Krambeck AE, Rule AD, et al. Shock wave lithotripsy and diabetes mellitus: a population-based cohort study. *Urology.* 2012; 79:298–302. [PubMed: 22088569]
- [22]. Yoo DE, Han SH, Oh HJ, et al. Removal of kidney stones by extracorporeal shock wave lithotripsy is associated with delayed progression of chronic kidney disease. *Yonsei Med J.* 2012; 53:708–714. [PubMed: 22665335]
- [23]. Sairam K, Scoffone CM, Alken P, et al. Percutaneous nephrolithotomy and chronic kidney disease: results from the CROES PCNL Global Study. *J Urol.* 2012; 188:1195–1200. [PubMed: 22901573]
- [24]. Carvalho M, Martin RL, Passos RC, Riella MC. Nephrectomy as a cause of chronic kidney disease in the treatment of urolithiasis: a case-control study. *World J Urol.* 2013; 31:1141–1145. [PubMed: 22373698] * A study of urolithiasis patients who required nephrectomy demonstrated a lower creatinine clearance compared to matched stone patients without nephrectomy. However, no long term outcome data regarding these patients was presented.
- [25]. Worcester E, Parks JH, Josephson MA, et al. Causes and consequences of kidney loss in patients with nephrolithiasis. *Kidney Int.* 2003; 64:2204–2213. [PubMed: 14633144]
- [26]. Mishra S, Sinha L, Ganesamoni R, et al. Renal deterioration index: preoperative prognostic model for renal functional outcome after treatment of bilateral obstructive urolithiasis in patients with chronic kidney disease. *J Endourol.* 2013; 27:1405–1410. [PubMed: 23537205] ** In this prospective study risk factors for irreversible renal failure one year later were assessed in a cohort of patients with bilateral obstructive uropathy caused by kidney stones. A renal deterioration index was developed that can be used to estimate long-term renal prognosis and the potential benefit of intervention when a patient presents with obstructing stones.
- [27]. Evan AP, Coe FL, Lingeman JE, et al. Renal crystal deposits and histopathology in patients with cystine stones. *Kidney Int.* 2006; 69:2227–2235. [PubMed: 16710357]
- [28]. Getting JE, Gregoire JR, Phul A, Kasten MJ. Oxalate nephropathy due to 'juicing': case report and review. *The American journal of medicine.* 2013; 126:768–772. [PubMed: 23830537]
- [29]. Nasr SH, D'Agati VD, Said SM, et al. Oxalate nephropathy complicating Roux-en-Y Gastric Bypass: an underrecognized cause of irreversible renal failure. *Clin J Am Soc Nephrol.* 2008; 3:1676–1683. [PubMed: 18701613]
- [30]. Fathallah-Shaykh SA, Cramer MT. Uric acid and the kidney. *Pediatr Nephrol.* 2013
- [31]. Sikora P, Pijanowska M, Majewski M, et al. Acute renal failure due to bilateral xanthine urolithiasis in a boy with Lesch-Nyhan syndrome. *Pediatr Nephrol.* 2006; 21:1045–1047. [PubMed: 16773422]
- [32]. Bhalla V, Grimm PC, Chertow GM, Pao AC. Melamine nephrotoxicity: an emerging epidemic in an era of globalization. *Kidney Int.* 2009; 75:774–779. [PubMed: 19212415]
- [33]. Shang P, Chang H, Yue ZJ, et al. Acute kidney injury caused by consumption of melamine-contaminated infant formula in 47 children: a multi-institutional experience in diagnosis, treatment and follow-up. *Urol Res.* 2012; 40:293–298. [PubMed: 21877125]

- [34]. Hsu CH, Kurtz TW, Rosenzweig J, Weller JM. Intrarenal hemodynamics and renal function in postobstructive uropathy. *Invest Urol.* 1978; 15:348–351. [PubMed: 627479]
- [35]. Tanner GA, Evan AP. Glomerular and proximal tubular morphology after single nephron obstruction. *Kidney international.* 1989; 36:1050–1060. [PubMed: 2601255]
- [36]. Mulay SR, Evan A, Anders HJ. Molecular mechanisms of crystal-related kidney inflammation and injury. Implications for cholesterol embolism, crystalline nephropathies and kidney stone disease. *Nephrol Dial Transplant.* 2013
- [37]. Joshi S, Peck AB, Khan SR. NADPH oxidase as a therapeutic target for oxalate induced injury in kidneys. *Oxid Med Cell Longev.* 2013; 2013:462361. [PubMed: 23840917]
- [38]. Knauf F, Asplin JR, Granja I, et al. NALP3-mediated inflammation is a principal cause of progressive renal failure in oxalate nephropathy. *Kidney international.* 2013
- [39]. Mulay SR, Kulkarni OP, Rupanagudi KV, et al. Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1beta secretion. *J Clin Invest.* 2013; 123:236–246. [PubMed: 23221343] ** An elegant series of experiments in hyperoxaluric mice model demonstrated that calcium oxalate crystals induced acute kidney injury the activation of innate immunity and the intracellular inflammsome pathway.
- [40]. Jungers P, Joly D, Barbey F, et al. ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. *Am J Kidney Dis.* 2004; 44:799–805. [PubMed: 15492945]
- [41]. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. *Bmj.* 2012; 345:e5287. [PubMed: 22936784]
- [42]. Keller JJ, Chen YK, Lin HC. Association between chronic kidney disease and urinary calculus by stone location: a population-based study. *BJU Int.* 2012; 110:E1074–1078. [PubMed: 22934937]
- [43]. El-Zoghby ZM, Lieske JC, Foley RN, et al. Urolithiasis and the risk of ESRD. *Clin J Am Soc Nephrol.* 2012; 7:1409–1415. [PubMed: 22745275]
- [44]. Chou YH, Li CC, Hsu H, et al. Renal function in patients with urinary stones of varying compositions. *Kaohsiung J Med Sci.* 2011; 27:264–267. [PubMed: 21757143]
- [45]. Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. *Pediatric nephrology.* 2013

Key points

- Nephrolithiasis is not a common cause of AKI in adults, but may be a relatively major one in younger children.
- The primary feature of nephrolithiasis-associated AKI is obstructive nephropathy; odds of recovery depend primarily on the extent and the duration of the obstruction.
- Crystalline nephropathy is another important pathogenetic mechanism in nephrolithiasis-associated AKI, and can be associated with direct cellular toxicity mediated by some combination of oxidative stress, innate immunity, and the intracellular inflammasome.
- Nephrolithiasis is a small and independent risk factor for subsequent CKD and ESRD.

Figure 1. Possible mechanisms of nephrolithiasis related acute kidney injury

Acute kidney injury can occur in patients with nephrolithiasis via several different pathways.

If a stone is dislodged and blocks the collecting system this can cause an obstructive uropathy associated with secondary vasoconstriction and renal hypoperfusion. Intratubular crystallization events can lead to an obstructive uropathy on a microscopic level, for example in uric acid nephropathy. The interaction of individual tubular epithelial cells with urinary crystals is also associated with cellular responses that include apoptosis and cell death. Oxidative stress pathways and innate immune system/inflammasome pathways also appeared to be activated by the interaction of tubular epithelial cells with specific urinary crystals such as calcium oxalate.

Table 1

Factors that predict lack of renal recovery after relief of bilateral obstructing stones (Adapted from [26])

Individual Factor	AUC	Renal Deterioration Index Value [*]		
		1	2	5
Combined cortical width (mm)	0.85	>20	10–20	<10
GFR at 5 th day (ml/min)	0.83	>60	30–60	<30
Proteinuria	0.75	0	+1	>+1
Urine culture	0.59	Negative	Positive	
Combined Renal Deterioration Index [*]	0.90			

* Renal recovery unlikely for Renal Deterioration Index values >12