RMMG
Revista Médica de Minas Gerais

REVIEW ARTICLE

Crystalluria in older people may require more attention

Cristalúria em idosos pode demandar maior atenção

Glísia Mendes Tavares Gomes[1]

ABSTRACT

Chronic kidney disease (CKD) is a major public health problem that tends to get worse with population aging, which is inevitable, considering that the elderly generally have comorbidities that can impact kidney health. The objective of this study was to emphasize the importance of observing crystalluria in geriatric patients, in addition to renal lithiasis, the possible triggering factors of this condition, and its renal impact. For the narrative review, related articles were searched in databases such as PubMed, BIREME, Web of Science, and Google Scholar with the themes: "Crystalluria in elderly people"; "Drugs induced crystalluria in elderly people". It can be observed that the geriatric population often presents, concomitantly, comorbidities that may contribute to the occurrence of crystalluria, which may be a factor to be considered among the criteria related to kidney injury in this group. Since in addition to encompassing already known causes of kidney damage, the elderly may suffer the negative effect of environmental, dietary, dehydration, and medication. Such variables can culminate in the formation of urinary crystals, which, secondary to their deposition in the renal parenchyma, can cause intratubular obstructive events, direct and indirect renal lesions, and urolithiasis. It is concluded that urinary crystals may be related to more common conditions, such as renal lithiasis, and to more complex diagnostic episodes that require a more refined investigation, as in crystallopathies.

Keywords: Acute kidney injury; Comorbidity; Metabolic syndrome; Nephrolithiasis.

[1] Centro de Saúde Escola Germano Sinval Faria/ENSP-Fiocruz, Rio de Janeiro, RJ, Brasil.

Responsible Editor:
Dr. Enio Roberto Pedroso
Faculty of Medicine of the Federal University of Minas Gerais
Belo Horizonte/MG, Brazil.

Corresponding Author:
Glísia Mendes Tavares Gomes
E-mail: glisiagomes@gmail.com

Supporting sources:
There were no supporting sources.

Conflict of interests:
The author declares that she has no conflicts of interest.

Ethics Committee (if applicable):
Not applicable

Clinical Trial Registration (if applicable):
Not applicable.

Preprint URL (If applicable):
Not applicable.

Received on: September 02, 2022
Approved on: December 26, 2022
Publication Date: May 3, 2023.

DOI: 10.5935/2238-3182.2023e33204

RESUMO

A doença renal crônica (DRC) é um grande problema de saúde pública e isso tende a se agravar com o envelhecimento populacional que é inevitável, considerando que idosos, geralmente, apresentam comorbidades que podem impactar na saúde renal. O objetivo desse trabalho foi ressaltar a importância da observação da cristalúria em pacientes geriátricos, para além da litíase renal, os possíveis fatores desencadeadores dessa condição e seu impacto renal. Para a revisão narrativa, artigos relacionados foram pesquisados em base de dados como PubMed, BIREME, Web of Science e Google Acadêmico com os temas: "*Crystalluria in elderly people*"; "*Drugs induced crystalluria in elderly people*". Pode-se observar que, a população geriátrica, muitas vezes apresenta, concomitantemente, comorbidades que podem contribuir para a ocorrência de cristalúria, podendo esta ser um fator a ser considerado entre os critérios relacionados à lesão renal nesse grupo. Visto que, além de englobar causas já conhecidas de lesão renal, idosos podem sofrer o efeito negativo de fatores ambientais, alimentares, de desidratação e medicamentosos. Tais variáveis podem culminar na formação de cristais urinários que, secundários à deposição destes no parênquima renal, podem ocasionar eventos obstrutivos intratubulares, lesões renais diretas e indiretas e urolitíase. Conclui-se que os cristais urinários podem estar relacionados a quadros mais comuns, como litíases renais, e a episódios de diagnóstico mais complexos e que requerem uma investigação mais aprimorada como nos casos das cristalopatias.

Palavras-chave: Injúria renal aguda; Comorbidade; Síndrome metabólica; Nefrolitíase.

Introduction

The lack of data on the prevalence of chronic kidney disease (CKD) in Brazil, especially in geriatric patients, is alarming, considering that the prevalence of chronic dialysis in 2012 in individuals aged ≥ 65 years was 31.9%[1].

Elderly, obese patients with metabolic syndrome have an increased rate of urinary acidification, promoting the formation of uric acid stones (UA)[2]. There is evidence that the formation of these stones is favored by high temperatures, which cause an increase in fluid loss through the skin, with a consequent reduction in urinary volume and in urinary pH, both disorders promoting UA crystallization[3]. Some studies have shown that chronic diseases such as kidney disease, chronic heart failure, and metabolic abnormalities such as obesity and metabolic syndrome can lead to low urinary pH[4].

Substantial changes in water metabolism, primarily related to decreased total body water, reduced osmotic thirst stimulation, and inadequate renal function, are associated with aging, factors that increase the risk of dehydration, especially in the most fragile elderly[5]. Dehydration due to water loss or hypertonic is the most frequently found water disturbance, having several adverse effects such as urolithiasis, urinary tract infection, colorectal cancer, bladder cancer, and venous thromboembolism. Furthermore, it seems to be an underestimated event in hospitalized elderly[6].

A marker of urinary supersaturation, crystalluria derives from metabolic disorders, hereditary diseases or drugs, and the imbalance between crystallization promoters and inhibitors. However, as urine is an environment with constant supersaturation of one or more crystalline species, some authors consider evaluating urinary crystals an unnecessary test[7].

However, opposing the idea that the evaluation of urinary crystals is unnecessary, evaluations of repeated urine samples for crystalluria show that certain characteristics of the crystals (larger, aggregated crystals) are strongly related to the occurrence of calculus. In addition, a recent study evaluating 188 patients with more than 3 years of follow-up with multiple collections of urine samples demonstrated that having 50% or more urine samples with crystals was

predictive of stone recurrence with a sensitivity of 88% and an 84% specificity[8].

Thus, analyzing some aspects that raise questions about the importance of this finding is the objective of this work.

Methods

Searches were carried out in databases such as PubMed, BIREME, Web of Science, and Google Scholar with the themes Crystalluria in elderly people; Drugs induced crystalluria in elderly people. Searches were carried out from April 2021 to June 2022. Due to the small volume of articles available in the databases on crystalluria in the elderly and drugs that induce crystalluria in the elderly, related terms were also searched for, the elderly (sarcopenia) and crystalluria (dehydration and urinary tract infection), and 180 articles were found. Articles that contained some correlation with crystalluria in the elderly and possible associated factors were chosen, resulting in a total of 34 works. The excluded articles were not related to the central terms for the elaboration of this work.

Crystalluria, kidney damage, and aggravating factors

Regarding the pathogenesis of crystal-associated renal injury, this exhibits intrarenal deposition, which occurs mainly due to the high concentration of ions and molecules that cross the tubules, increasing the likelihood of substrate supersaturation and crystal nucleation. Even if precipitated out, the crystals are deposited in the kidneys due to innate characteristics and can lead to tubular obstruction and direct and indirect renal damage[9].

Pietro et al. (2019)[10], in a cohort of overweight or obese older adults with metabolic syndrome, had a higher prevalence of lithogenic urine.[10] Urinary calculi are always preceded by crystalluria, although the occurrence of crystalluria will not necessarily result in renal lithiasis. However, studies have proposed crystalluria as a factor for the disorder, leading into account the hypothesis that the recurrence of crystals in the urine may reflect the propensity to form stones, with potential clinical relevance in association with the nature of urinary acidity or alkalinity[11]. Older individuals often have atypical calculi or no pain, and the increased prevalence may be confounded, in part, by the greater use of abdominal imaging[2].

Unlike developed countries, in the tropics, AKI is underestimated due to the lack of centralization of these data, and the pattern and incidence differ between countries. Furthermore, such numbers seem to be just the tip of the iceberg. Furthermore, infections and exposure to nephrotoxins remain the main cause despite the etiological variations. In acute kidney injury (AKI), the mechanism induced by nephrotoxins induces a direct toxic effect on the renal tubules, with precipitation of substances such as oxalic acid (crystalluria) and intratubular obstruction[12]. The elderly are particularly more sensitive to the action of nephrotoxins[13].

The geriatric population is one of the fastest growing in many parts of the world, and although age is not a disease, physiological changes can be aggravated by special situations such as perioperative periods, bleeding, or medical complications. On the other hand, the increased incidence and considerable recurrence, with serious consequences for renal function, make urolithiasis a medical and surgical problem requiring prompt diagnosis and adequate management of the elderly population. Older patients, in previous studies, had more comorbidities than younger individuals. Metabolic syndrome, for example, seems more common among the elderly, having been linked in some studies with the formation of stones. Diabetes mellitus is also another aggravating factor in the formation of stones and, together with cardiovascular diseases, are among the most frequent comorbidities in this population[14].

Even though crystalluria also positively correlates with age, body mass index, duration of diabetes, and urinary specific gravity, this is not significant. However, the presence of crystals in the urine showed a significant correlation with fasting glucose; the higher the blood glucose levels, the greater the number of crystals observed, and vice versa[15]. Chao et al. (2020)[16], emphasize that, despite all the known complications of diabetes, it has recently been reported that this is also an important risk for the development of urolithiasis. The relationship between diabetes and the increased risk for calculi has been previously attributed to the acidification of the urine related to insulin resistance, hypercalciuria induced by high levels of insulin, followed by an exaggerated carbohydrate diet, the coexistence of morbidities (e.g.: SAH or hyperuricemia) and high-sodium diets[16]. In a study carried out with an elderly population in Rio Branco, Acre, diabetes had the highest prevalence, 41.5% and metabolic syndrome was present in 30.3% of subjects classified as having CKD[17].

Crystalluria and obstructive nephropathy

In the last decade, recent data have shown an increase in the rate of older people with AKI requiring hospitalization. Some factors are known to predispose to AKI in the elderly, including exposure to nephrotoxic drugs[18], reaching a rate of up to 66%[19]. Drug-induced AKI exhibits four different phenotypes representing distinct clinical and pathological characteristics presentations: acute kidney injury, glomerular disorder, tubular disorders, or nephrolithiasis/crystalluria. Each phenotype shows a change in its biomarkers; serum creatinine (acute kidney injury), proteinuria and/or hematuria (glomerular injury), electrolyte abnormalities (tubular disorders), and sonographic findings (nephrolithiasis)[20]. A fact to be highlighted is that drug precipitation can range from isolated, asymptomatic crystalluria to obstructive calculi. Renal ultrasound or computed tomography may not be the best diagnostic method for detecting crystals or a microscopic tubular obstruction[18].

As predicted, HIV-infected adults on successful antiretroviral (ARV) therapy have near-normal life expectancies and are increasingly subject to age-related

comorbidities[21]. This reduction in the mortality rate has been accompanied by an increase in other related diseases, such as CKD, which is increasingly common among HIV-infected patients and can occur at any stage of the disease, even before seroconversion[22].

AKI may result from urinary obstruction and, among the causes, include nephrolithiasis and crystalluria induced by drugs. Although its use has been reduced in developed countries, due to its high potential for crystalluria (67%) and kidney stones (3%), Indinavir has been used in other countries with few resources. Among the risks of urinary crystals, we can also mention high drug administration and co-administration of another nephrotoxic drug. The presence of crystalluria may point to potential nephrotoxicity, although its evaluation to predict the development of chronic kidney disease (CKD) has not yet been tested[23].

Another important type of crystallopathies, atheroembolic renal disease (AERD), is a multisystemic complication that involves several organs such as the kidneys, skin, gastrointestinal tract, eyes, muscles, central nervous system, and extremities. They can be iatrogenic events secondary to surgical or invasive endovascular manipulation; however, they can also result from spontaneous episodes. Autopsy studies indicated that the kidneys were involved in 74% of AERD cases, making it a common cause of renal failure in adults over 60 years of age and advanced atherosclerosis[24].

In a study by Chávez-Iñiguez et al. (2020)[25], in patients with acute kidney injury due to obstructive nephropathy, those treated in an emergency setting had twice the incidence rate of AKI concerning what received elective treatments; in addition, they were older, male, had more severe AKI and their probability of death within 30 days was three times higher and renal recovery was less frequent[25].

The presence of AKI in critically ill patients is common, especially in the presence of sepsis. Although with different pathophysiology, it is possible to distinguish septic AKI from Ischemic or toxic AKI, showing a worse prognosis for the former than the latter. Although previous literature has raised interest in urinary microscopy to predict or detect AKI in critically ill patients, none has described urinary crystals. However, crystals may favor renal damage through an intratubular obstruction or reflect disturbed renal metabolism in the early stages, which leads to poor urine solubility and extreme urinary pH values. Aiming to evaluate the prevalence and determinants of urinary crystals among 103 critically ill patients admitted to the surgical Intensive Care Unit, the study by Tabibzadeh et al. (2021)[26] found the following characteristics in this group: the median age of 57 (45-69), 34% of patients had sepsis and 43% had a brain injury. Of these patients, 7% had CKD, and 39% had AKI. In urine sent for microscopy, crystalluria was observed in 53 (51%) patients, with the majority of uric acid crystals (51%) and calcium oxalate crystals present in 12 (23%) of the patients. It is important to highlight that osmolality and creatinine levels were not significantly higher in these patients, suggesting that the presence of crystals was not directly related to urinary concentration[26].

Demotier et al. (2022)[27], emphasize the benefits of investigating, for example, amoxicillin crystalluria in patients receiving high intravenous dosages of the drug, as the phenomenon is frequent in 1/4 of patients and that it seems to be associated with angiotensin-converting enzyme inhibitors and the decrease in urinary pH, with the occurrence of both factors being the main predictor of the development of in-hospital AKI. In the univariate analysis, the factors associated with the presence of amoxicillin crystalluria were the presence of hematuria in the cytobacteriological examination, acidification of the urinary pH, advanced age, and the use of angiotensin-converting enzyme inhibitors. Hematuria seems to be caused by more than one consequence, such as tubular damage and medullary congestion, secondary to the precipitation of intrarenal crystals[27]. Garnier et al. (2020)[28], report that crystalline nephropathy induced by amoxicillin may be underestimated in patients treated with high doses; in addition, data suggest that the prognosis may be less favorable than previously thought, recommending careful monitoring of the renal function of patients exposed to these conditions, even considering an early change to another class of antibiotics[28].

Foscarnet is the standard treatment in cytomegalovirus infections, resistant to ganciclovir, and in cases where its administration is not possible. Some reports of renal crystal damage from Foscarnet use involve, for example, tubulointerstitial damage. However, crystal deposition in tubular cells or lumens and glomerular capillaries has been reported repeatedly, suggesting that a form of nephropathy crystalline may be another mechanism causing kidney damage. Of the 6 drug-treated study patients, 5 developed kidney disease, and 4 were aged ≥ 63[29].

The literature has also described cases of AKI, such as tubulointerstitial nephritis secondary to the administration of ciprofloxacin. However, even though crystalluria is a rare event related to this drug, the elderly patient in the cited case report developed an oliguric AKI 48 hours after oral and intravenous administration of ciprofloxacin, treatment to overcome an infectious process installed, with its sediment urine exhibited star-shaped, birefringent crystals under polarized light, with high suspicion of ciprofloxacin crystals[30].

A 66-year-old patient from another case report had a history of urolithiasis due to calcium oxalate crystals, with afebrile back pain associated with dysuria and milky urine. Urinalysis findings: pH: 7.5; specific gravity: 1.010; 20 to 30 leukocytes per high power field and numerous crystals of triple magnesium phosphate, these crystals representing 10 to 15% of renal lithiasis. The conversion of excess urea by bacterial urease (in this case, *Pseudomonas aeruginosa*) into ammonia alkalizes the urine and promotes the crystallization of magnesium ammonium phosphate, insoluble in alkaline urine. Such crystals can block the urethra and warrant investigation for stones. However, this was not the case for this patient,

who had clear and symptomatic crystalluria but without calculus[31].

A study involving crystalluria in patients with active lithiasis based its methodology on criteria such as stone composition, serum uric acid level, serum calcium level, urinalysis results (including urinary pH, hematuria, and leukocyturia), and demographic data that included age, body mass index (BMI) and gender. There was an association between active cases of urolithiasis and parameters related to the type of crystal found, urine pH, and patient characteristics such as age and BMI. The likelihood of uric acid crystals decreased as the patient's age decreased, while the likelihood of calcium oxalate crystals increased. The neural network model demonstrated that, although there was a greater presence of calcium oxalate crystals, there was a greater possibility of uric acid stones[32].

Throughout life, epidemiological evidence on the prevalence and incidence of urolithiasis seems to vary geographically. However, this disorder is known to be associated with ethnicity, lifestyle problems (dietary pattern, fluid intake, sedentary lifestyle), comorbidity status, and age; recent data have indicated an increasing incidence of urolithiasis, probably explained by the increase in the geriatric population[33].

Results and Discussion

Dehydrated elderly, assisted in emergencies and referred for hospitalization, usually have serious illnesses, high mortality rates, and a higher risk of functional impairment after discharge[6].

Furthermore, the literature has corroborated the wide variation in the prevalence and incidence of urolithiasis. In more fragile individuals, especially older ones, diabetes mellitus itself predisposes to fluid loss by osmotic diuresis, increasing the risk of dehydration[16].

Another important factor to note is that, due to sarcopenia, older adults are often encouraged to increase their intake of dietary products rich in animal protein, which increases the risk of hyperoxaluria and hypercalciuria[33].

Even though the urine harbors urinary sediment with normal crystals, in some pathological conditions, the alteration and sudden change from normal to abnormal crystals showed the pathogenesis, stage, and severity of the kidney problem[11].

In addition to easy sample collection, urinalysis is a cost-effective screening tool. A well-executed analysis of the urinary sediment can indicate the conditions of the lower urinary tract and nephrons. Furthermore, although automation has reduced time and costs in carrying out urinary sedimentoscopy, this methodology still has limitations in diagnosing several kidney diseases, such as ATN, glomerulonephritis, vasculitis, and crystalline nephropathy[34].

Much more than a simple marker of severity, AKI is a complex syndrome that affects all systems and can lead to multiple organ failure. Obstructive nephropathy is a frequent cause of AKI, being related to 5 to 10% of all AKI cases; however, among the elderly, this percentage can reach 22% of cases[25]. Intratubular crystal deposition has been thought to be the primary cause of AKI due to urinary obstruction (obstruction of the tubular lumens), and the frequent observation of acute tubular injury in biopsies may play a contributory role in AKI[9].

Conclusion

Because of the imminent aging of the world population, aggravated by the repercussions of this reality for public health, it is of the utmost importance to explore all possibilities for screening, diagnosis, and follow-up related to this population, paying attention to the impact factors, in most cases, negative, such as environmental, social, economic, nutritional, cultural and political ones in the lives of these individuals, which have profound consequences, mainly on kidney health, including the formation of crystalluria and possible crystallopathies. Accurate laboratory diagnostic support plays an enormous role in this process, helping the physician and the prognosis of this patient.

There is an urgent need for a healthcare structure that adapts to all these possibilities and fights against weaknesses, to reduce the effect of this serious, silent, and gradual disorder, which is renal failure, in the personal, family, and social life of the elderly.

Copyright

References

1. 1. Abdulkader RCRM, Burdmann EA, Lebrão ML, Duarte YAO, Zanetta DMT. Aging and decreased glomerular filtration rate: an elderly population-based study. PLoS One. 2017 Dec;12(12):e0189935. DOI: https://doi.org/10.1371/journal.pone.0189935

2. Youssef RF, Martin JW, Sakhaee K, Poindexter J, Dianatnejad S, Scales CD, et al. Rising occurrence of hypocitraturia and hyperoxaluria associated with increasing prevalence of stone disease in calcium kidney stone formers. Scand J Urol. 2020;54(5):426-30. DOI: https://doi.org/10.1080/21681805.2020.1794955

3. Trinchieri A, Maletta A, Simonelli G, Boeri L, De Lorenzis E, Montanari E. Time changes in the spectrum of urinary

stone composition: a role for climate variations? BMC Nephrol. 2020;21(1):535. DOI: https://doi.org/10.1186/s12882-020-02193-x

4. Saitsu A, Iwazu Y, Matsushita H, Hayashi H, Mizuhashi Y, Kotani K. Low urine pH associated with sarcopenia in the elderly: a multi-center observational study. Medicine. 2021;100(21):e26114. DOI: https://doi.org./10.1097/md.0000000000026114

5. Betomvuko P, Saint-Hubert M, Schoevaerdts D, Jamart J, Devuyst O, Swine C. Early diagnosis of dehydration in hospitalized geriatric patients using clinical and laboratory criteria. Eur Geriatr Med. 2018 Set;9(5):589-95. DOI: https://doi.org/10.1007/s41999-018-0100-0

6. Buaprasert P, Piyapaisarn S, Vanichkulbodee A, Kamsom A, Sri-on J. Prevalence and risk factors of hypertonic dehydration among older patients admitted to the emergency department: a prospective cross-sectional study. Geriatr Gerontol Int. 2021;21(6):485-91. DOI: https://doi.org/10.1111/ggi.14168

7. Frochot V, Daudon M. Clinical value of crystalluria and quantitative morphoconstitutional analysis of urinary calculi. Int J Surg. 2016 Dec;36(Pt D):624-32. DOI: https://doi.org/10.1016/j.ijsu.2016.11.023

8. Williams JC, Gambaro G, Rodgers A, Asplin J, Bonny O, Costa-Bauzá A, et al. Urine and stone analysis for the investigation of the renal stone former: a consensus conference. Urolithiasis. 2021;49(1):1-16. DOI: https://doi.org/10.1007/s00240-020-01217-3

9. Perazella MA, Herlitz LC. The crystalline nephropathies. Kidney Int Rep. 2021 Dec;6(12):2942-57. DOI: https://doi.org/10.1016/j.ekir.2021.09.003

10. Prieto RM, Rodriguez A, Sanchis P, Morey M, Fiol M, Grases F, et al. Association of adherence to the mediterranean diet with urinary factors favoring renal lithiasis: cross-sectional study of overweight individuals with metabolic syndrome. Nutrients. 2019;11(8):1708. DOI: https://doi.org/10.3390/nu11081708

11. Prabhu N, Bandhavi SP, Marzuk SM, Uma A, Sarada V. Comparative analysis of bacterial pathogens and crystalluria in cases enrolled in a tertiary care teaching hospital, Tiruchirapalli, India. Med Res Chron [Internet]. 2015; [cited 2022 May 28]; 2(3):342-52. Available from: https://medrech.com/index.php/medrech/article/view/92

12. Arogundade FA, Omotoso BA, Sanusi AA, Balogun RA. Burden and etiopathogenesis of acute kidney injury in the tropics. Clin Nephrol. 2020;93(1):8-16. DOI: https://doi.org/10.5414/cnp92s102

13. Coca SG. Acute kidney injury in elderly persons. Am J Kidney Dis. 2010 Jul;56(1):122-31. DOI: https://doi.org/10.1053/j.ajkd.2009.12.034

14. Dursun M, Ozbek E, Otunctemur A, Sahin S, Cakir SS. Clinical presentation of urolithiasis in older and younger population. Arch Ital Urol Androl. 2014;86(4):249-52. DOI: https://doi.org/10.4081/aiua.2014.4.249

15. Ephraim RKD, Anoff KA, Brenyah RC, Osakunor DNM, Sakyi SA, Osei-Yeboah J, et al. Determinants of crystalluria among type 2 diabetes patients; a case-control study of the Agona West Municipality, Ghana. Niger Med J. 2017;58(3):114-8. DOI: https://doi.org/10.4103/nmj.NMJ_121_16

16. Chao CT, Wang J, Huang JW, Hung KY, Chien KL. Frailty predicts a higher risk of incident urolithiasis in 525 368 patients with diabetes mellitus: a population-based study. BMJ Open Diabetes Res Care. 2020;8(1):e000755. DOI: http://dx.doi.org/10.1136/bmjdrc-2019-000755

17. Amaral TLM, Amaral CA, Vasconcellos MTL, Monteiro GTR, Amaral TLM, Amaral CA, et al. Prevalence and factors associated to chronic kidney disease in older adults. Rev Saude Publica. 2019;53:44. DOI: https://doi.org/10.11606/S1518-8787.2019053000727

18. Khan S, Loi V, Rosner MH. Drug-induced kidney injury in the elderly. Drugs Aging. 2017;34(10):729-41. DOI: https://doi.org/10.1007/s40266-017-0484-4

19. Kane-Gill SL, Goldstein SL. Drug-induced acute kidney injury: a focus on risk assessment for prevention. Crit Care Clin. 2015 Oct;31(4):675-84. DOI: http://dx.doi.org/10.1016/j.ccc.2015.06.005

20. Mehta RL, Awdishu L, Davenport A, Murray PT, Macedo E, Cerda J, et al. Phenotype standardization for drug-induced kidney disease. Kidney Int. 2015 Aug;88(2):226-34. DOI: http://dx.doi.org/doi:10.1038/ki.2015.115

21. Allavena C, Hanf M, Rey D, Duvivier C, BaniSadr F, Poizot-Martin I, et al. Antiretroviral exposure and comorbidities in an aging HIV-infected population: the challenge of geriatric patients. PLoS One. 2018 Sep;13(9):e0203895. DOI: https://doi.org/10.1371/journal.pone.0203895

22. Reghine ÉL, Foresto RD, Kirsztajn GM, Reghine ÉL, Foresto RD, Kirsztajn GM. HIV-related nephropathy: new aspects of an old paradigm. Rev Assoc Med Bras. 2020;66(Suppl 1):S75-S81. DOI: http://dx.doi.org/10.1590/1806-9282.66.S1.75

23. Campos P, Ortiz A, Soto K. HIV and kidney diseases: 35 years of history and consequences. Clin Kidney J. 2016 Dec;9(6):772-81. DOI: https://doi.org/10.1093/ckj/sfw104

24. Li X, Bayliss G, Zhuang S. Cholesterol crystal embolism and chronic kidney disease. Int J Mol Sci. 2017;18(6):2-12. DOI: https://doi.org/10.3390/ijms18061120

25. Chávez-Iñiguez JS, Navarro-Gallardo GJ, Medina-González R, Alcantar-Vallin L, García-García G. Acute kidney injury caused by obstructive nephropathy. Int J Nephrol. 2020;2020:e8846622. DOI: https://doi.org/10.1155/2020/8846622

26. Tabibzadeh N, Zalc M, Michel T, Letavernier E, Mebazaa A, Borouchaki A, et al. Prevalence and identification of crystalluria in critically ill patients: association between uric acid crystals and sepsis. Clin Kidney J. 2021 Apr;14(4):1291-3. DOI: https://doi.org/10.1093/ckj/sfaa187

27. Demotier S, Limelette A, Charmillon A, Baux E, Parent X, Mestrallet S, et al. Incidence, associated factors, and effect on renal function of amoxicillin crystalluria in patients receiving high doses of intravenous amoxicillin (The CRISTAMOX Study): a cohort study. eClinicalMed.

2022 Mar;45:101340. DOI: https://doi.org/10.1016/j.eclinm.2022.101340

28. Garnier AS, Dellamaggiore J, Brilland B, Lagarce L, Abgueguen P, Furber A, et al. High incidence of amoxicillin-induced crystal nephropathy in patients receiving high dose of intravenous amoxicillin. J Clin Med. 2020;9(7):2022. DOI: https://doi.org/doi:10.3390/jcm9072022

29. Deffert C, Stoermann C, Ernandez T, Nabergoj M, Chalandon Y, Jaeger P. Phosphonoformate crystalluria, a warning signal of foscarnet-induced kidney injury. Kidney Int Rep. 2020 Nov;5(11):2102-8. DOI: https://doi.org/10.1016/j.ekir.2020.08.019

30. Khan M, Ortega LM, Bagwan N, Nayer A. Crystal-induced acute kidney injury due to ciprofloxacin. J Nephropathol. 2015;4(1):29-31. DOI: https://doi.org/10.12860/jnp.2015.06

31. Trimarchi H, Young P, Lombi F. Milky urine and struvite crystals. Kidney Int. 2015;88(1):205. DOI: https://doi.org/10.1038/ki.2014.314

32. Almannie RM, Alsufyani AK, Alturki AU, Almuhaideb M, Binsaleh S, Althunayan AM, et al. Neural network analysis of crystalluria content to predict urinary stone type. Res Rep Urol. 2021;13:867-76. DOI: https://doi.org/10.2147/RRU.S322580

33. Wu HHL, Chinnadurai R. To what extent does frailty influence the risk of developing urolithiasis? Urol. 2022;2(1):1-5. DOI: https://doi.org/10.3390/uro2010001

34. Cavanaugh C, Perazella MA. Urine sediment examination in the diagnosis and management of kidney disease: core curriculum 2019. Am J Kidney Dis. 2019;73(2):258-72.