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Letter to the Editor

LETTER TO THE EDITOR

Prevalence and identification of crystalluria in critically ill patients: association between uric acid crystals and sepsis

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Acute kidney injury (AKI) is common among critically ill patients, especially in the presence of sepsis. Both AKI and sepsis are recognized as major prognostic factors during critical care [1]. Differences in their pathophysiology might distinguish septic AKI from ischaemic or toxic AKI, explaining the poorer prognosis of the former compared with the latter. Previous literature has raised the interest of urine microscopy examination in order to detect or predict AKI and/or sepsis in critically ill patients [2], but none has described urinary crystals. Yet, crystals might either contribute to kidney damage through intratubular obstruction, or reflect disturbed kidney metabolism at early stages, resulting in poor urine solubility or extreme urine pH values [3]. We thus aimed at evaluating the prevalence and the determinants of urinary crystals among 103 consecutive critically ill patients admitted in the Surgical Intensive Care Unit of Hôpital Lariboisière, Paris, France. Characteristics of the population are described in Table 1. Median (interquartile range) age was 57 (45–69) years; 34% of patients were admitted for sepsis and 43% for brain injury. The median simplified acute physiology score II was 37 (21–52), 7% had underlying chronic kidney disease and AKI occurred in 39%. Urine was sent for analysis within the first 24 h after admission. Polarized light microscopy analyses were performed in a renal stone centre by skilled lab technicians and validated by specialized biologists, within 2 h after voiding. Crystals were identified according to their morphology or their infrared spectrum (IRS) when identification was doubtful. Crystalluria was detected in 53 (51%) patients with a majority of uric acid crystals (51%) (Table 1). Calcium oxalate crystals were present in 12 (23%) patients. Two patients had drug-induced crystals, one with amoxicillin crystals and one with IRS-confirmed vancomycin nanospheres, allowing clinicians to discontinue these potentially nephrotoxic drugs [4]. Patients with uric acid crystals had more frequently ongoing AKI and ongoing bacterial infection, and displayed higher plasma uric acid levels, higher urine uric acid levels, lower urinary pH and lower urinary citrate levels (Table 2). Of note, urine osmolality and creatinine levels were not significantly higher in these patients, suggesting that the presence of urinary crystals was not primarily due to higher urine concentration. Serum creatinine at discharge and maximal serum creatinine during hospital stay were higher in patients with uric acid crystalluria. Multivariable linear regression analysis showed that the

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Table 1. Main characteristics of patients and urinary crystals

Characteristics	$n = 103$
Age, years	57 (45–69)
Female, *n* (%)	42 (41)
Admission diagnosis, *n* (%)	
Sepsis/infection	35 (34)
Brain injury	44 (43)
Haemorrhagic shock	2 (2)
Polytraumatism	1 (1)
Major abdominal surgery	8 (8)
Other causes	12 (12)
Charlson comorbidity index	4 (2–5)
Diabetes mellitus, *n* (%)	18 (17.5)
Chronic kidney disease, *n* (%)	7 (7)
SAPS II	37 (21–52)
In-hospital mortality, *n* (%)	22 (21)
Length of hospital stay, days	23 (14–36)
Serum creatinine at ICU admission, μmol/L	71 (59–100)
Serum creatinine at discharge, μmol/L	63.5 (51–93)
Maximal serum creatinine during hospital stay, μmol/L	92.5 (67–166)
Delay between admission and crystalluria study, days	1 (1–3)
Ongoing infection at the time of crystalluria study, *n* (%)	42 (41)
AKI, *n* (%)	40 (39)
Positive crystalluria, *n* (%)	53 (51)
Type of crystals, *n* (%)	
Uric acid	27 (51)
Calcium oxalate	12 (23)
Amoxicilline	1 (2)
Vancomycine	1 (2)
Other (struvite, brushite, ACP)	12 (21)

Values are median (interquartile range) and number (percentage).
SAPS II, simplified acute physiology score II; ICU, intensive care unit; ACP, amorphous calcium phosphate.

determinants of uric acid crystals were higher urine uric acid level [adjusted B = 0.06, 95% CI (0.02–0.09), P = 0.001] and the presence of a bacterial infection [adjusted B = 0.38, 95% CI (0.22–0.53), P < 0.001], but not urine pH (P = 0.14) (Supplementary data, Table S1).

Our study showed that among critically ill patients, crystalluria prevalence was substantially higher compared with the general population (estimated between 2% and 22%) [5, 6]. The proportion of uric acid crystals was also surprisingly high, representing 51% of positive crystalluria, compared with 18–26% in the literature [5, 6]. Acidic urinary pH and hyperuricosuria are the main known risk factors of uric acid crystals and stones, and primarily occur in patients with diabetes or metabolic syndrome [7]. Noteworthy, neither of these conditions was associated with uric acid crystals in our study. In multivariable analysis, the major determinant of uric acid crystals was the existence of an ongoing bacterial infection and a higher uricosuria, fading away the classical association between uric acid crystals and urinary pH. Interestingly, fractional excretion of uric acid was not significantly higher in patients with uric acid crystals, suggesting that these crystals did result from metabolic changes associated with sepsis, rather than from proximal tubular injury.

Patients with uric acid crystals also more frequently displayed AKI. This result might give insights regarding the pathophysiological role of renal tubular crystals on kidney damage, especially uric acid crystals [8, 9]. These are known to induce local inflammatory response that might trigger and/or aggravate renal tissue injury [10]. Intratubular crystal formation might also be promoted in these haemodynamically unstable patients, due to a decreased tubular fluid flow rate. Whether uric acid crystals directly promote septic AKI or reflect metabolic changes associated with sepsis remains to be evaluated in experimental and interventional clinical studies.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

FUNDING

None.

CONFLICT OF INTEREST STATEMENT

All authors have declared that they have no potential conflicts of interest. All authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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Table 2. Characteristics of patients according to the presence of urine crystals and according to the presence of uric acid crystals

Variable	No urine crystals ($n=50$)	Urine crystals ($n=53$)	P-value	No UA crystals ($n=76$)	UA crystals ($n=27$)	P-value
Age, years	57 (40–70)	57 (49–66)	0.30	56 (42–66)	61 (51–74)	0.07
Female sex, *n* (%)	25 (50)	17 (32)	0.07	36 (47)	7 (26)	0.09
Admission diagnosis			**0.03***			**0.02***
Neurological	28 (56)	16 (30)		36 (47)	8 (30)	
Infection	13 (26)	22 (41)		20 (26)	15 (55)	
Others	9 (18)	15 (28)		20 (26)	4 (15)	
SAPS II	42 (25–54)	32 (20–46)	0.11	36 (19–52)	41 (25–50)	0.39
Diabetes, *n* (%)	6 (12)	12 (23)	0.15	12 (16)	6 (22)	0.62
AKI, *n* (%)	14 (28)	24 (45)	0.07	21 (28)	17 (63)	**<0.01***
Infection/sepsis, *n* (%)	14 (28)	28 (53)	**0.01***	20 (26)	22 (81)	**<0.01***
CKD, *n* (%)	4 (8)	3 (6)	0.94	4 (5)	3 (11)	0.55
Uricaemia, μmol/L	232 (170–360)	298 (144–441)	0.67	216 (152–357)	425 (230–458)	**<0.01***
Leukocytes, 10^9/L	13 (10–17)	13.3 (6.6–21.5)	0.13	12.5 (9.7–16.6)	11.1 (8.9–18.4)	0.61
Blood pH	7.39 (7.36–7.45)	7.40 (7.35–7.44)	0.87	7.41 (7.36–7.45)	7.40 (7.32–7.42)	0.13
Serum HCO_3^-, mmol/L	22 (20–24)	23 (20–25)	0.33	22 (20–25)	23 (20–25)	0.72
BUN, mmol/L	5.4 (3.3–7.9)	7.3 (4.9–10.4)	**0.04***	5.6 (3.5–7.9)	8.8 (6.1–11.5)	**<0.01***
SCreat, μmol/L	69 (50–93)	82 (61–124)	0.17	67 (50–94)	96 (70–145)	**<0.01***
SCreat-admission, μmol/L	68 (55–88)	78 (62–108)	0.12	68 (57–86)	98 (68–120)	**<0.01***
Na-U, mmol/L	61 (32–112)	59 (31–106)	0.87	73 (33–120)	39 (22–68)	**<0.01***
K-U, mmol/L	40 (28–55)	35 (24–49)	0.33	39 (25–53)	37 (30–50)	0.87
Creat-U, mmol/L	7.7 (5.5–12.4)	7.9 (4.9–12.3)	0.99	7.7 (5.5–11.3)	11.5 (5.1–15.6)	0.13
PO_4-U, mmol/L	19.3 (7.6–34.2)	21.2 (12.8–32.7)	0.26	17.9 (8.8–29.3)	31.8 (18.0–41.2)	**<0.01***
Uric acid-U, mmol/L	2.7 (1.3–3.7)	2.8 (1.7–4.4)	0.27	2.7 (1.3–3.7)	3.0 (2.5–6.3)	**0.02***
FeAU, %	11.5 (8.2–17.2)	13.4 (6.6–21.5)	0.77	12.1 (8.4–17.4)	10.7 (5.5–23.1)	0.83
Urea-U, mmol/L	201 (113–264)	239 (127–314)	0.10	198 (107–266)	258 (172–367)	**0.02***
Prot-U, mg/mL	22 (8–35)	21 (10–65)	0.22	22 (8–38)	23 (14–76)	0.05
sCa-U, mmol/L	87 (24–164)	93 (24–289)	0.43	106 (35–273)	40 (15–117)	**0.01***
Mg-U, mmol/L	2.5 (1.0–4.9)	2.4 (1.1–4.9)	0.99	2.3 (1.1–5.0)	3.2 (0.8–4.9)	0.96
Citrate-U, mmol/L	1.00 (0.18–2.40)	0.92 (0.15–1.69)	0.55	1.02 (0.24–2.30)	0.42 (0.07–1.45)	**0.03***
Osmolality-U, mOsm/kgH_2O	586 (421–761)	573 (429–761)	0.85	565 (408–759)	599 (466–189)	0.37
Urine pH	5.9 (5.3–6.0)	5.9 (5.3–6.6)	0.14	5.9 (5.3–6.5)	5.6 (5.3–5.9)	**0.02***
LOS, days	20 (12–36)	24 (15–39)	0.38	20 (12–42)	26 (17–34)	0.29
SCreat-discharge, μmol/L	60 (49–90)	70 (52–105)	0.22	60 (50–82)	88 (55–135)	**0.03***
Maximal SCreat, μmol/L	86 (66–150)	105 (70–175)	0.18	84 (65–147)	131 (94–199)	**0.02***
In-hospital mortality, *n* (%)	10 (20)	11 (21)	1	14 (18)	7 (26)	0.58

Values are median (interquartile range) and number (percentage).
SAPS II, simplified acute physiology score II; UA, uric acid; CKD, chronic kidney disease; BUN, blood urea nitrogen; SCreat, serum creatinine concentration; FeAU, fractional excretion of uric acid; U, urinary; LOS, length of hospital stay. P-values in bold and with asterisk are considered significant (<0.05).

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