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Acute Kidney Injury After High Doses of Amoxicillin



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Amoxicillin (AMX) has been associated with acute kidney injury (AKI). Two distinct mechanisms have been described: acute interstitial nephritis and crystal nephropathy, the latter of which has been the primary focus of anecdotal reports.^{1,2} Clinical presentation of crystal nephropathy seems to be stereotypical: gross hematuria and rapidly resolving AKI with evidence of crystals in the urine following prescribed AMX. High doses of AMX, acid urine pH, low diuresis, and hypovolemia have been suggested as risk factors for AMX crystallization. However, published studies do not systematically identify crystalluria and provide no histologic evidence of parenchymal AMX crystal deposits. Reports of amoxicillin-induced crystal nephropathy (AICN) appear to be on the rise in France, suggesting an increased incidence.^{3–5}

In 2016, Zeller *et al.*⁶ published a preliminary report highlighting an increased incidence of AICN among a population of patients treated for an osteoarticular infection. In the present study, we analyze the risk factors and the prognosis of AICN in these patients exposed to high doses of intravenous AMX. We retrospectively analyzed patients who received high doses of intravenous AMX (>8 g/day) for osteoarticular infections in the Department of Internal Medicine and Rheumatology of the Diaconesses-Croix Saint-Simon Hospital in Paris, France, over a 1-year period. Of these, we identified patients with AKI (based on creatinine variation of Kidney Disease: Improving Global Outcomes staging⁷) after AMX prescription and defined as AICN ([Supplementary Material](#)).

From September 2014 to October 2015, 76 patients were admitted to the center with a diagnosis of

osteoarticular infection. Of these, 53 were included in the study because they required high doses of AMX ([Figure 1](#)). Baseline patient characteristics are detailed in [Table 1](#). The main indication of AMX was hip arthroplasty infection. The median dose was 12 g/day (interquartile ratio [IQR] 12–12.75 g/day), or 181.5 mg/kg/day (IQR 137–202 mg/kg/day). AMX alone (3 different brands) was given as a discontinuous intravenous infusion. All clinical features are summarized in [Table 2](#).

Ten patients (18.8%) developed AICN. AKI was often severe (8 patients with Kidney Disease: Improving Global Outcomes stage 3) with serum creatinine median peak of 3.9 mg/dl (IQR 2.7–6.7 mg/dl). The median delay between AMX introduction and AKI was 14 days (IQR 3–17.25 days). Most of the cases were preceded by hematuria of acute onset (9 patients). Renal ultrasound revealed urinary tract dilatation in 3 patients. Urinalysis showed leukocyturia in 6 patients. Proteinuria was available for 4 patients (median level 0.04 g/mmol [IQR 0.02–0.49 g/mmol]). Urinary pH was acid (<6) in 3 patients of 6 tested. Only 1 patient tested positive for crystals in his urine (the other 9 patients were not tested). No other cause of AKI was noted (no clinical indication of acute interstitial nephritis or circulatory failure). No kidney biopsy specimens were obtained.

Treatments and outcomes are summarized in [Table 3](#). AMX was stopped in all patients with a median delay of 1 day after AKI detection. Seven patients were treated with volume expansion and 2 patients needed a double J catheterization because of obstruction of the urinary tract. Only 1 patient received renal

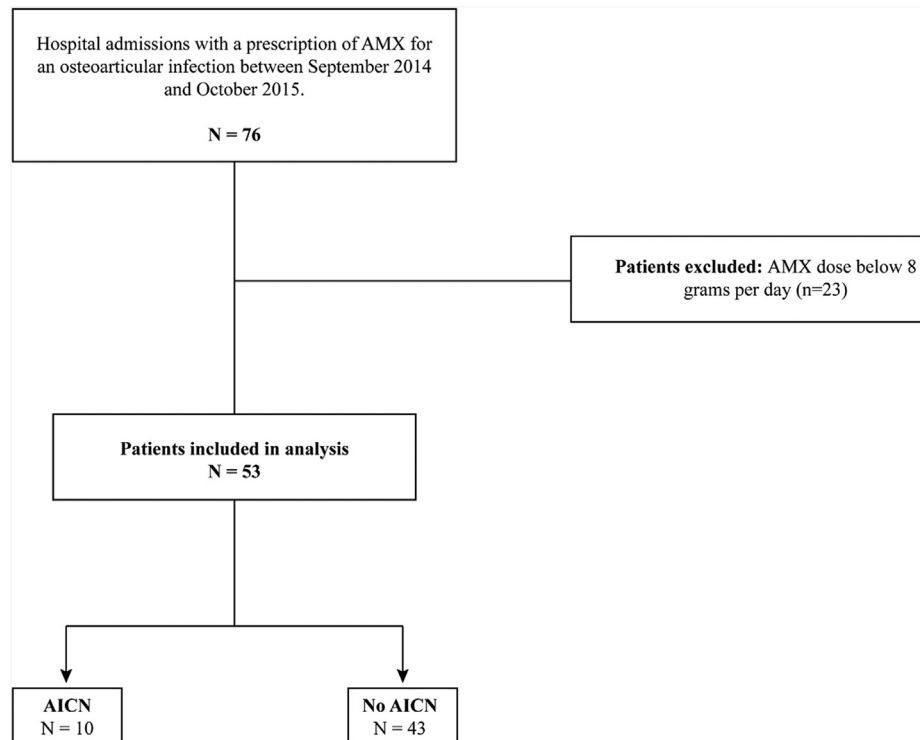


Figure 1. Flow chart of the study. AICN, amoxicillin-induced crystal nephropathy; AMX, amoxicillin.

replacement therapy after anuria and pulmonary edema. At discharge, 8 patients had regained their previous creatinine levels. AMX was reintroduced at a

reduced dose in 4 patients. The median time to renal recovery after AMX discontinuation was 8 days (IQR 2.5–16 days). At last follow-up, the median estimated glomerular filtration rate (eGFR) was 97.5 ml/min/1.73 m² (IQR 66.75–130 ml/min/1.73 m²), with only 1 patient <60 ml/min/1.73 m² (follow-up duration of only 3 days).

We compared patients who developed AICN ($n = 10$) and those who did not ($n = 43$; Table 4). No difference was noted in terms of age, sex, comorbidities (diabetes mellitus, hypertension, chronic kidney disease), or body mass index. There was a significantly lower level of baseline serum creatinine for patients with AICN (0.68 mg/dl [IQR 0.58–0.76 mg/dl] vs. 0.84 mg/dl [IQR 0.69–1 mg/dl], $P = 0.03$). However, there were similar levels of baseline eGFR (93 ml/min/1.73 m² [IQR 77–123 ml/min/1.73 m²] in patients with AICN vs. 85 ml/min/1.73 m² [IQR 67–110 ml/min/1.73 m²] for patients without AICN; $P = 0.49$).

The daily dose of AMX did not differ between the 2 groups, with a median dose of 12 g/day (IQR 12–12.75 mg/kg/day), even when based on patient weight (181.5 mg/kg/day [IQR 137–202 mg/kg/day] in AICN vs. 163 mg/kg/day [IQR 146–182 mg/kg/day] in patients without AICN, $P = 0.21$). The median duration of AMX was shorter in patients with AICN (12 days [IQR 4.5–18.5 days] vs. 27 days [IQR 10–33 days] in the patients without AICN; $P = 0.03$). No statistical differences were found for associated drugs (Table 4).

Table 1. Clinical characteristics of the study cohort

Variables	Overall, $n = 53$
Age, yr, median (IQR)	71 (66–82)
Women, n (%)	26 (49)
Comorbid conditions	
Weight, kg, median (IQR)	74 (64–90)
BMI, kg/m ² , median (IQR)	27.1 (24.7–30)
Chronic kidney disease, n (%)	8 (16)
Hypertension, n (%)	31 (55)
Diabetes mellitus, n (%)	11 (21)
eGFR, ml/min/1.73 m ² , median (IQR)	86 (70–110)
Creatinine at baseline, mg/dl, median (IQR)	0.77 (0.67–0.99)
Amoxicillin treatment	
Duration, days, median (IQR)	22 (10–31)
Daily dose, mg/kg/day, median (IQR)	167 (146–186)
Daily dose, g/day, median (IQR)	12 (12–12)
Discontinuous administration, n (%)	52 (98)
Medications, n (%)	
Vancomycin	8 (15)
Gentamicin	11 (21)
Piperacillin-tazobactam	4 (8)
Iodinated contrast agents	1 (2)
ACEs/ARBs	12 (23)
NSAIDs	4 (8)
Diuretics	15 (28)
Vasopressor	1 (2)

ACE/ARB, angiotensin-converting enzyme/angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Clinical characteristics of patients with AICN

Patient no.	Age, yr	Gender	BMI, kg/m ²	Baseline creatinine, mg/dl	Baseline eGFR, ml/min/1.73 m ²	Indication for AMX	AMX dose, g/day	AMX dose, mg/kg/day	Time from amoxicillin to AKI, days	KDIGO stage	Gross hematuria		Proteinuria, g/mol		Urinary tract obstruction	Confirmed crystalluria	
											Leukocyturia UFS	pHu	mmol	g			
1	67	F	22.3	0.75	81	Hip arthroplasty infection	12	211	17	3	1	1	1	0.02	5.5	0	0
2	71	F	32	0.6	105	Hip arthroplasty infection	12	171	17	3	1	1	1	0.63	7	1	0
3	85	F	27	0.69	90	Hip arthroplasty infection	12	187	3	2	0	0	0	NA	7	0	0
4	66	M	23.7	0.79	69	Hip arthroplasty infection	9	128	13	2	1	0	1	NA	NA	0	0
5	74	M	26	0.78	124	Spondylodiscitis	15	200	3	3	1	1	0	NA	NA	0	1
6	64	F	28.5	0.53	123	Septic arthritis	15	208	18	3	1	1	1	NA	NA	0	0
7	47	F	30.1	0.51	138	Osteo-arthritis	12	138	15	3	1	1	1	NA	NA	1	0
8	83	F	28	0.63	96	Hip arthroplasty infection	12	188	4	3	1	0	1	0.07	5.5	0	0
9	86	M	31.9	1.2	52	Hip arthroplasty infection	12	133	3	3	1	1	0	0.02	6	0	0
10	70	F	23	0.7	79.8	Hip arthroplasty infection	12	176	27	3	1	0	1	NA	7	1	0

AKI, acute kidney injury; AMX, amoxicillin; BMI, body mass index; eGFR, estimated glomerular filtration rate by modification of diet in renal disease equation; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not available; pHu, urinary pH; UFS, urinary functional symptoms, including urinary burns, back, and hypogastric pain.

DISCUSSION

Our work sought to precisely describe AICN and to identify risk factors for its occurrence in a homogeneous population study with osteoarticular infection. We confirmed the typical clinical presentation of AICN of gross hematuria of abrupt onset after high doses of AMX and AKI. In line with most of the literature describing AMX crystal nephropathy,^{3,5} prognosis was mostly favorable. Our study shows that this complication may occur in the late stages of AMX therapy (≤ 27 days after treatment initiation). A cumulative dose effect could explain this delay. Even though discontinuation of AMX and volume expansion is sufficient for most cases, we confirmed that AKI may be severe enough to require renal replacement therapy and double J catheterization in selected cases.

Despite being known for several decades,⁸ AICN cases seem to have increased recently in France without a definitive cause.³⁻⁶ The first pharmacovigilance study, restricted to the Paris region, identified an increase of AICN reports after 2010 and 2 patterns of patients (surgical vs. medical).³ These data were confirmed by a nationwide pharmacovigilance study.⁵ The last study confirmed the increase of AICN after adjustment for AMX sales. These studies ruled out a change in the drug formulation. The authors of these 2 studies hypothesized that previous underreporting of this complication, together with a growing awareness among clinicians, could explain the recent increase in reports of AICN.^{3,5} Higher AMX dosing recommendations in France may have underpinned the heightened incidence of AICN compared with that of other European countries.⁹ In our center, 3 different brands of AMX were used, ruling out a specific brand effect.

The pathophysiology of AICN is not completely elucidated. It is thought to be linked to AMX concentration-dependent oversaturation and consequently crystallization in the urine after AMX glomerular filtration and tubular secretion (via the organic anion transporter family). Apart from drug dosing, the only proven risk factor of AMX crystallization is an acid urinary pH < 6 .¹⁰ Although this remains to be proven, it could suggest a role for urine alkalization as a preventive measure. Unlike other crystallopathies, no evidence for AMX crystal deposits in renal parenchyma has been described and, in any case, crystalluria is not consistently performed.

Pending nephropathologic and *in vivo* experimental investigations, cast formation inside the distal convoluted tubule via AMX–uromodulin interactions, intracellular AMX accumulation, or increased AMX concentrations inside tubular proximal cells via organic

Table 3. Treatments and outcomes of patients with AICN

Patient no.	AMX arrest	Volume expansion	Solutes	Double J catheterization	AMX rechallenge	Delay of reintroduction, days	RRT	Return of baseline sCr before discharge	Delay between recovery and AMX arrest, days	sCr on discharge, mg/dl	Length of follow-up, days	Last sCr, mg/dl	Last eGFR, ml/min/1.73 m ²
1	1	0		0	0		0	1	8	0.73	184	0.9	66
2	1	1	Crystalloids	1	0		0	0	23	1.46	287	0.6	103
3	1	1	Crystalloids/oral sodium bicarbonate intake	0	1	7	0	1	3	0.86	0	0.86	67
4	1	1	Oral sodium bicarbonate intake	0	1	7	0	1	1	NA	3	1.1	51
5	1	1	Crystalloids	0	1	0	1	0		3.4	68	0.86	92
6	1	NA	NA	0	0		0	1	5	NA	128	0.48	136
7	1	NA	NA	1	0		0	1	8	NA	602	0.58	119
8	1	1	Crystalloids/HCO ₃ Na 1.4%	0	0		0	1	14	2.14	305	0.71	83
9	1	1	Ringer lactate	0	1	19	0	1	18	0.97	171	0.62	130
10	1	1	Crystalloids/HCO ₃ Na 1.4%	0	0		0	1	2	0.53	0	0.53	130

AICN, amoxicillin-induced crystal nephropathy; AMX, amoxicillin; sCr, serum creatinine; eGFR, estimated glomerular filtration rate by modification of diet in renal disease equation; NA, not available; RRT, renal replacement therapy.

anion transporter competition represent other plausible mechanisms.¹¹ In the latter case, we hypothesize that a genetic polymorphism of organic anion transporters

Table 4. Baseline characteristics of study cohort based on AICN status

Variables	AICN, n = 10	No AICN, n = 43	P value ^a
Age, yr, median (IQR)	71 (66–81)	71 (65–82)	0.94 ^b
Women, n (%)	7 (70)	19 (44)	0.17
Comorbid conditions			
Weight, kg, median (IQR)	70 (65–74)	80 (64–90)	0.34
BMI, kg/m ² , median (IQR)	27.5 (23.5–30.5)	27.1 (24.75–30)	0.91
Chronic kidney disease, n (%)	1 (10)	7 (16)	1
Hypertension, n (%)	7 (70)	22 (51)	0.3
Diabetes mellitus, n (%)	1 (10)	10 (23)	0.66
eGFR, ml/min/1.73 m ² , median (IQR)	93 (77–123)	85 (67–110)	0.49
Creatinine at baseline, mg/dl, median (IQR)	0.68 (0.58–0.76)	0.84 (0.69–1)	0.03 ^{b,c}
Amoxicillin treatment, median (IQR)			
Duration, days	12 (4.5–18.5)	27 (10–33)	0.03 ^c
Daily dose, mg/kg/day	181.5 (137–202)	163 (146–182)	0.21
Daily dose, g/day	12 (12–12.75)	12 (12–12)	0.53 ^b
Medications, n (%)			
Vancomycin	3 (30)	5 (12)	0.34
Gentamicin	1 (10)	19 (44)	0.07
Piperacillin-tazobactam	2 (20)	2 (5)	0.18
Iodinated contrast agents	0	1 (2)	1
ACEs/ARBs	2 (20)	10 (24)	0.7
NSAIDs	1 (10)	3 (7)	0.57
Diuretics	3 (30)	12 (28)	1
Vasopressor	0	1 (2)	1

ACE/ARB, angiotensin-converting enzyme/angiotensin II receptor blocker; AICN, amoxicillin-induced crystal nephropathy; BMI, body mass index; eGFR, estimated glomerular filtration rate by modification of diet in renal disease equation; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

^aComparisons are made between AICN and no AICN using the Fisher exact test for qualitative variables. For quantitative variables, we tested the normality of the distribution using the Shapiro-Wilk test. In case of a Gaussian distribution, an unpaired Student test was used. Otherwise, a Mann-Whitney test was used.

^bData compared using the Mann-Whitney test.

^cStatistically significant.

may serve as a physiopathologic basis in the absence of clinical risk factors for AICN.

We observed a lower baseline level of serum creatinine in patients who developed AKI. Because our study patients are elderly, it is possible they have a lower genuine GFR despite an apparently normal serum creatinine and eGFR. Indeed, older patients have a decreased lean body mass and reduced total body water. As a result, they are more exposed to excess drug dosing, so clinicians should exercise caution when adapting AMX doses in malnourished elderly patients. It may also suggest that hyperfiltration is associated with an increased risk for AMX urine/tubular saturation via a faster AMX urine excretion.

In line with the published literature,^{4,5} patients in our cohort were exposed to high dose of intravenous AMX (median dose 12 g/day). This is in accordance with the fact that urinary excretion of AMX is correlated with its plasmatic concentration (the higher the plasma concentration of AMX, the higher its urinary excretion)¹⁰. Thus, high dose and/or rapid administration of AMX may lead to oversaturation of AMX in the primitive urine. This hypothesis, in addition to being predicated on a sound pharmacokinetic model, is further reinforced by the decreased incidence of AICN because of the study center changing from discontinuous to continuous intravenous administration of AMX.

Our study has several limitations. First, crystalluria was not routinely performed, thus precluding a definite diagnosis despite a clinical presentation highly suggestive of AMX crystallization. Second, because of the retrospective nature of the study, some data such as urinary pH values are missing. Indeed, it is possible that the lack of differences observed in the 2 groups is

related to differences in pH values. Third, the study size is small, potentially leading to a lack of statistical power. However, our population study is homogeneous with the same indications for AMX.

Overall, the clinical presentation of AICN is mostly typical, suggesting a micro-obstructive mechanism and a mainly straightforward prognosis. The lack of availability of crystal urinalysis and paucity of experimental models make the diagnosis uncertain. Our study suggests clinicians should be cautious when prescribing high doses of AMX, especially in elderly patients. Prospective studies, including nephropathologic and genetic investigations, are urgently required to understand the mechanisms underpinning this reemerging complication.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Materials and Methods.

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