Amoxicillin Crystalluria, an Emerging Complication with an Old and Well-Known Antibiotic

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As described by Hentzien et al. recently, amoxicillin is a drug that can crystallize in the urinary tract as amoxicillin trihydrate and lead to macroscopic hematuria and acute renal insufficiency through tubular obstruction (1). However, amoxicillin crystalluria is a rare event (2–4) whose incidence remains unknown.

For 10 years (September 2004 to September 2014), we managed a cohort of 2,348 patients with osteoarticular infections. Among 228 patients who received high-dose intravenous (i.v.) amoxicillin (6 to 16 g/24 h), fewer than 1/year developed amoxicillin crystalluria with renal insufficiency.

During the past year (1 September 2014 to 31 October 2015), we observed an important increase in this complication. Among 285 patients hospitalized for osteoarticular infections, 56 received i.v. amoxicillin at a dose of ≥ 8 g/24 h for at least 48 h. Ten (18%) developed acute renal insufficiency associated with signs of amoxicillin crystallization. The median age of these seven women and three men was 70 (range, 47 to 86) years, their median weight was 71 (range, 57 to 90) kg, and their median initial creatinine level was 58 (range, 45 to 116) $\mu\text{mol/liter}$. Eight patients received 12 g, one received 9 g, and one received 15 g of i.v. amoxicillin per 24 h. Amoxicillin was administered i.v. in three, four, or six infusions of 60 to 120 min, in unit doses of 4, 3, 2, and 2.5 g, to four patients, four patients, three patients, and one patient, respectively. Three different amoxicillin generics were used. The first clinical manifestations of amoxicillin crystalluria (macroscopic hematuria in all of the patients, oliguria in seven, intense burning during urination in three, and abdominal or lumbar pain in two) appeared within 15 (range, 1 to 27) days after starting amoxicillin. Acute renal insufficiency became manifest a median of 2 (range, 0 to 3) days after the first clinical signs. The median maximum creatinine level was 411 (range, 153 to 728) $\mu\text{mol/liter}$. For all patients, treatment consisted of amoxicillin withdrawal, i.v. hydra-

tion, and urine alkalinization. A JJ ureteral stent was inserted to treat renal pelvis dilatation in two patients. All patients achieved complete recovery of previous renal function within a median of 13 (range, 1 to 24) days.

The sharp rise in this complication over the past year, while our prescription modalities have not changed, leads us to think that it is related to an increase in urinary amoxicillin concentrations, e.g., by another drug or infusion solution, or to the manufacture of the drug. Further studies are warranted to answer that question.

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