Amoxicillin crystalluria and amoxicillin-induced crystal nephropathy

- Amoxicillin, an antibiotic widely used for treating and preventing infection,
- was first introduced in the 1980s
- usually administered orally
- can also be given i.v. for preoperative prophylaxis or for such as bone and joint infections, meningitis, and endocarditis

- In these cases, high-dose i.v. amoxicillin (HDIVA; >150 mg/kg or 8 g/d) is recommended at the start of treatment

- (AKI) occurs

through 2 primary mechanisms.

- first : a cellmediated immune response directed against nephritogenic antigens, specifically targeting amoxicillin or its metabolites inthat context, resulting in acute interstitial nephritis

- The second consists of the: precipitation of soluble amoxicillin into amoxicillin trihydrate crystals in the urine, to as amoxicillin crystalluria (AC).
- is shared with other b-lactams, notably ampicillin

and third-generation cephalosporins

- AC can lead to AKI and is known as amoxicillin-induced crystalline nephropathy(AICN) when the kidney injury is attributed to thetubular precipitation of amoxicillin into amoxicillin trihydrate crystals.

- amoxicillin excreted unchanged in the urine by glomerular filtration (93%) and tubular secretion (7%), the latter being reduced when probenecidis administered.

- The renal excretion rate of amoxicillin follows the same trend as amoxicillin blood levels (peak and then a slow decrease)

- it culminates at the amoxicillin blood level peak whose determinants are the administered dose, the duration of i.v. infusion, and the residual amoxicillin blood level.

- oral absorption of amoxicillin is nonlinear and saturable in adults,cases of AC occur after HDIVA administration (typically 12 g/d or more in adults)

- 1 mg/ml increase in amoxicillin blood level in patients treated with HDIVA for endocarditis was associated with the onset of AC in this population

- AC has been described after a single administration of low doses (2 g) of i.v. amoxicillin for surgical prophylaxis

- In those cases, i.v. amoxicillin was administered instantaneously, while it is recommended to administer it over a 30- to 60-minute period, leading to a very rapid and high rise in amoxicillin blood levels and in renal excretion

- other factor can increase the urinary amoxicillin level.
- absolute hypovolemia—which may also contribute to increased amoxicillin blood level—or
- Relative hypovolemia, such as sepsis and fasting before surgery

- In chronic heart failure, in addition to relative hypovolemia, prescription of urine-acidifying drugs such as furosemide can be an additional contributing factor.

- patients receivingHDIVA, increased urine density tended to increase the risk of AC

- factor may be the augmented

renal clearance of amoxicillin.

- Augmented renal clearance is observed in critically ill patients, particularly during sepsis.
- defined by increased creatinine clearance and

increased elimination of substances including drugs excreted by the kidney.

- solubility in urine is also altered by its ionization state, driven by changes in urinary pH,.
- The solubility is divided by 2 when the urinary pH drops from 7 to 6.

- association between decreased urine pH and the onset of AC

- prescription of angiotensin-converting enzyme (ACE) inhibitors was associated with the onset of AC in univariate analysis.
- no evidence to suggest that ACE inhibitors directly alter urinary pH.

- onset of AC is not always associated with the onset of AKI

- In case reports or
- retrospective case series, the diagnosis of AICN was based on the simultaneous onset of AC and AKI, with no other apparent cause of AKI identified.

- 2 prospective studies with the same design and statistical analysis:

  demonstrated a statistical association between the onset of AC and AKI

- associated factors:septic shock and treatment by vancomycin

- 7 patients underwent kidney biopsy:6 displaying acute tubular necrosis and 1 patient showing tubular vacuolization

- first histologic evidence of amoxicillin crystallizationin the tubular lumen was recently documented.

- as amoxicillin trihydrate crystals using infrared spectroscopy
- electron microscopy direct visualization of tubule obstruction by amoxicillin crystals

- Kidney biopsy is rarely performed in AKI, when the clinical and paraclinical findings suggest acute tubular necrosis

- When the diagnosis of AICN was not considered, the AKI might have been attributed to sepsis,is not an indication for kidney biopsy,

- when the diagnosis of AICN was considered, the AKI was attributed to the nephrotoxicity of amoxicillin, is not an indication for kidney biopsy

- Some patients who developed AICN were not admitted to a nephrology department or were treated in hospitals without a nephrology department

- Concerning the biopsies performed, the crystals probably dissolved during the preparation of the paraffinembedded kidney sections, resulting in missed crystal detections.

- in AICN, AKI usually resolves quickly once amoxicillin is discontinued, reducing the benefit/risk ratio for biopsy.

Diagnosis of AC:

- typically described as the sudden onset of macroscopic hematuria associated with cloudy urine exhibiting a fine granular appearance.

- Amoxicillin crystals :rarely be observed with the naked eye in urine

- associated with other nonspecific symptoms :dysuria, cystitis-like symptoms, back pain, or hypogastric pain.
- Back pain :suspicion of amoxicillin crystals trapped in the ureters and prompt anultrasound scan

- AC is usually :

  asymptomatic; notably macroscopic hematuria is not always observed.

- Microscopic hematuria : difficult to interpret in patients with urinary catheters.

- more than one-quarter of documented AC :did not develop hematuria.

- Non-nephrotic proteinuria and leukocyturia are frequently reported but were not statistically associated with AC.

- In all cases, the final diagnosis :

  phase-contrast microscope with a polarized light device ,the birefringence of crystals

- identification of amoxicillin crystals:

  fresh urine (first-morning urine in

  ambulatory patients or, in hospitalized patients, urine collected within 2 hours of emptying the bladder or urine bag)
- stored at room temperature and sent to the laboratory as soon as possible.

- If crystals are not clearly identified by the microscopic study:infrared spectroscopic analysis

- Amoxicillin trihydrate crystals :
- fine,nonpolarizing needles with pointed ends, or as thicker,monochromatically polarized rods, isolated or aggregated,forming “broom bush”–like structures

- crystals may be associated with amoxicillin crystals : 10% of cases (uric acid and/or calcium oxalate crystals)

Diagnosis of AICN

- No validated criteria exist for diagnosing AICN.
- First: coincidence between i.v. amoxicillin administration and the onset of AKI is of limited diagnostic utility.

- delay betweenamoxicillin exposure and the diagnosis of AICN ranging from 3.0 to 5.5 days.

- Second, hematuria is not systematically found in AICN
- cannot be used as an indirect marker of AC and thus a criterion for AICN diagnosis

- identification of amoxicillin trihydrate crystals are limited because the technique is not routinely implemented within most hospitals, and when urine samples are collected outside of normal working hours.

- Third:differential

  diagnoses are easy to rule out
- 2 remain difficult exclude:
- First:sepsis-induced AKI. Diagnosing is challenging ,lack of functional stress-related, and tissue-damage biomarkers

- Simultaneous development of at least 1 new organ dysfunction :suggest the diagnosis of sepsis-induced AKI

- the onset of AKI more than 7 days after theonset of sepsis:

  rules out the diagnosis of sepsis-induced

  AKI

- The second: acute interstitial
- sometimes occur without extranephrological

symptoms or laboratory markers, indicating hypersensitivity,difficult to distinguish from AICN

- itsonset after the initiation of amoxicillin therapy is often longer than that of AICN (within 10 days), and it is notassociated with HDIVA (not dose-dependent)

- In addition,the recovery time of kidney function after amoxicillin discontinuation in AICN is probably shorter than that observed in acute interstitial nephritis

- the recovery time of kidney function after amoxicillin discontinuation in AICN : probably shorter than that observed in acute interstitial nephritis

- the diagnosis of AICN remains largely presumptive:clinical context and clinical and biological parameters , include acidic urine pH, AC, and high amoxicillin blood levels

- is probably strengthened in the event of rapid improvement (within 7 days) after the discontinuation of amoxicillin

Epidemiology of AC and AICN

- prevalence of AC ranging between 24.1% and 41.0%
- prevalence of AKI (not AICN) of between 17.9% and 47%,

- the onset of AC and AICN may be related to individual Susceptibilities
- Amoxicillin pharmacokinetics involve organic anion transporters 1 and 3, located on the basolateral membrane of kidney proximal tubular cells.

- Some patients have single nucleotide polymorphisms in these Transporters
- individuals with polymorphisms in the organic anion transporter genes may be more prone to develop AICN.

Treatment

- mainly based on stopping/reducing the dose of amoxicillin.
- Alkalinization of the urine may be suggested.
- onset of AC is statistically associated with the onset of AICN, and its prospective monitoring in patients treated with HDIVA could enable preventive strategies to be implemented to prevent AICN.