Acute kidney injury during treatment with high-dose cloxacillin A report of 23 cases and literature review

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HIGHLIGHTS

- We report a case series of 23 patients who developed acute kidney injury (AKI) during treatment with high doses cloxacillin, as recommended for endocarditis or osteomyelitis due to meticillin-susceptible staphylococci
- Most cases occurred during the first week of treatment, in elderly patients with cofactors for AKI, including hemodynamic instability, and nephrotoxic agents
- Therapeutic drug monitoring of cloxacillin may allow early recognition of trough plasma concentrations >50 ng/mL, and reduce the risk of AKI

Acute kidney injury during treatment with high-dose cloxacillin: a report of 23 cases and literature review

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Running title: Acute kidney injury and high-dose cloxacillin

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ABSTRACT

Background International guidelines recommend high-dose cloxacillin for endocarditis or osteoarticular infections due to meticillin-susceptible staphylococci. However, data on the tolerability of these regimens are scarce.

Methods We used the computerized registry of suspected drug-related adverse events in our institution. Cases of acute kidney injury (AKI), as defined by KDIGO, in patients receiving high-dose cloxacillin, were retrospectively reviewed. Data were collected from medical charts on a standardized questionnaire.

Results From 2009 to 2015, 23 consecutive patients (16 men, 7 women), with a median age of 75 years (interquartile range, IQR 66-80), fulfilled inclusion criteria. By the time of AKI diagnosis, patients were treated with a median cloxacillin dose of 12 g/day (IQR, 10-12), after a median duration of 7 days (IQR, 4-10). Most patients fulfilled RIFLE criteria for failure (n=20), with a median peak serum creatinine concentration of 339 µmol/L (IQR, 249-503). Urinalysis was suggestive of tubular disease in 7 patients, 3 had hypereosinophilia, and 8 had abnormal liver function tests. All patients presented at least one risk factor for AKI, including concomitant nephrotoxic drugs: gentamicin (n=19), diuretics (n=15), angiotensin-converting enzyme inhibitors (n=8), and angiotensin II receptor-blockers (n=6). Thirteen patients (57%) had cloxacilllin plasma concentrations >50 µg/mL. Thirteen patients (57%) had complete recovery of renal function.

Conclusions AKI during high-dose cloxacillin treatment mostly occurs in elderly patients, with concomitant nephrotoxic drugs. The outcome is usually favorable after cloxacillin discontinuation. Therapeutic drug monitoring may decrease the risk of AKI in patients treated with high-dose cloxacillin.

Key words: acute kidney injury; nephrotoxicity; cloxacillin; high-dose; therapeutic drug monitoring

1. INTRODUCTION

Cloxacillin, a member of the isoxazolyl penicillin group with oxacillin, dicloxacillin, and flucloxacillin, is a major anti-staphylococcal agent, recommended as first line treatment for a broad range of severe infections due to meticillin-susceptible *Staphylococcus aureus* (MSSA), and included on the World Health Organization (WHO) list of essential medicines. According to the cloxacillin prescribing information, the maximum dose is 6 g/day, but doses recommended by the European Society of Cardiology for infective endocarditis [1], or the French Society of Infectious Diseases for osteoarticular infections [2] are 8-12 g/day, intravenously, for 2-6 weeks. These higher doses are justified by the need to reach effective concentrations within difficult-to-reach infected foci (e.g. bone, cardiac valves and vegetations, brain), and their acceptable tolerability. Accordingly, no dose adjustment is recommended for patients with renal impairment if estimated glomerular filtration rate (eGFR) is >30 mL/min, while daily dose must be reduced by 50% for patients with eGFR<30 mL/min.

Although few cases of acute kidney injury (AKI) imputable to cloxacillin have been reported following its approval in the early 1980's, increasing use of high doses, in an ageing population, with comorbidities, and concomitant use of potentially nephrotoxic drugs, may change the overall good tolerability of this old drug. Recent reports have suggested an emergence of AKI with different extended-spectrum penicillins [3]. However, little is known about the respective nephrotoxicity of currently recommended antistaphylococcal agents (penicillinase-resistant penicillins, or cefazolin), and the risk factors for AKI associated with these treatments. We report a contemporary case series of 23 consecutive patients with AKI associated with high-dose cloxacillin, to better define the characteristics, the mechanisms, and the outcome of this emerging severe adverse event.

2. METHODS

2.1. Patients

The study was conducted in Pontchaillou, a university-affiliated hospital that serves as a referral center for the area of Rennes, Bretagne, in western France. All suspicion of cloxacillin-induced AKI registered by the pharmacovigilance center in Pontchaillou hospital between January 1st, 2009 and December 31st, 2015 were retrieved. Cases were identified through passive surveillance (voluntary notification), and through systematic queries in biomedical data warehouse, using ICD-10 (International Classification of Diseases 10th Revision) codes or codes combinations suggestive of drug-induced kidney injury, described elsewhere [4].

2.2. Clinical and biological data

Data were collected on a standardized questionnaire from medical files, including: age, sex, comorbidities, treatment received within two weeks before AKI onset, including iodinated contrast media. Doses, duration, and indication for cloxacillin were collected. Clinical data recorded included: hemodynamic instability (defined as systolic blood pressure <90 mmHg requiring volume expansion and/or vasopressive drugs), hypersensitivity signs (cutaneous eruption, fever of acute onset more than 48 h after cloxacillin start, arthralgia). Cloxacillin plasma concentration was determined by high-performance liquid chromatography method with UV detection, as previously described [5]. The target range of trough concentration (or steady-state concentration, in case of continuous administration), was 20-50 µg/mL, as previously described [6].

We systematically recorded serum creatinine (SCr, µmol/L) before cloxacillin start and 1, 3 and 6 months after cloxacillin treatment, as well as white blood cells count (including

eosinophil count), platelets, and hemoglobin level by the time of AKI. Serum levels of aspartate and alanine aminotransferases (AST, ALT), alkaline phosphatases, and bilirubin were collected. Urinalysis with urine dipstick, proteinuria by 24-h collection or on sample and estimated in g/g of urinary creatinine, and crystalluria were recorded when available. For dipstick analysis, thresholds were 5 erythrocytes/µL for microscopic hematuria, 5 white blood cells/µL for leukocyturia, and 1 +, or 25 mg/dL for proteinuria.

2.3. Definitions

AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, through increase in SCr by 26.5 µmol/L, or 1.5 times baseline [7]. The Risk, Injury, Failure, Loss of function, End stage renal disease (RIFLE) score was used for AKI classification [7]. Because urine output was not available for each patient, only SCr maximal value was used to determine the RIFLE score. An increase of SCr by a factor of 1.5, 2 or 3, was used to classify AKI as, respectively, stage Risk, Injury, or Failure. eGFR using the Cockcroft and Gault formula was calculated only once before cloxacillin start. Chronic kidney disease (CKD) stage was determined for each value at baseline, as well as 3 and 6 months after AKI. Cases were classified as complete recovery if CKD stage after AKI was 1 or 2, or if CKD stage after AKI was equal to baseline CKD stage. Recovery was analyzed 3 months after AKI or as soon as creatinine returned to baseline level. Anemia was defined as Hb <12 g/dL, thrombocytopenia as platelets count <150 G/L, and hypereosinophilia as eosinophils count >0.6 G/L. Hepatic cytolysis was defined as AST or ALT >2 upper normal values (N); cholestasis as alkaline phosphatases >2 N. When performed, results of renal biopsy were collected, as was the number of renal replacement therapy sessions.

2.4. Statistics

Statistical analyses were descriptive. Categorical variables were presented as number and percentages. Continuous variables were presented as medians with first and third quartile (interquartile range, IQR). Statistical analyses were performed using EXCEL 2016 software (Microsoft®, Mountain view, USA). To estimate the incidence of AKI in patients receiving cloxacillin treatment, we extracted data on cloxacillin use in our institution from the pharmacy computerized database (SAP BusinessObjects®, Paris, France). The number of patients who received cloxacillin was estimated by dividing the total amount of intravenous cloxacillin purchased during the study period for the whole institution, by the mean total dose received by each patient (i.e., mean daily dose times mean duration of cloxacillin treatment, in days).

2.5. Ethics/regulatory issues

In France, any suspicion of severe adverse events must be reported to the drug safety surveillance department (pharmacovigilance). Cases are investigated by the local department, anonymized, and recorded in a national database that ensures data privacy. This study has been approved by the institutional review board of Rennes University hospital. An information letter was sent to each patient, who was offered the opportunity to decline participation in this study.

3. RESULTS

3.1. Patients characteristics

Twenty-five cases of AKI suspected to be related to high-dose cloxacillin were registered by the drug safety surveillance system during the study period. Two were excluded, because review of medical records found that AKI started before cloxacillin was introduced. Hence,

23 cases were enrolled (16 men, 7 women), with a median age of 75 years (IQR, 66-80). Patients characteristics are detailed in Table 1. Of note, no patient should have received reduced cloxacillin dose according to current guidelines, as all had eGFR >30 mL/min when cloxacillin was started, whatever the method used to estimate GFR. All cases were classified as 'AKI possibly or probably related to cloxacillin' by the drug safety surveillance department.

3.2. Acute kidney injury

AKI occurred after a median cloxacillin treatment duration of 4 days (IQR, 3-7 days). According to RIFLE criteria, 3 patients (13%) were scored 'Injury', and 20 patients (87%) 'Failure'. The median SCr at peak was 339 µmol/L (IQR, 249-503). Five patients required renal replacement therapy, with a median number of 4 (IQR, 3-5) sessions of intermittent hemodialysis, over a maximum duration of three weeks. No patient presented clinical signs of hypersensitivity, with the possible exception of one patient with unexplained back pain of acute onset, that resolved when cloxacillin dose was reduced.

Urinalysis was available for 19 patients (83%): 16 patients (70%) had microscopic hematuria, 3 (13%) had aseptic leukocyturia, and 10 (44%) had proteinuria on dipstick. Proteinuria was quantified in 12 patients, with a median of 0.825 g/g (IQR 0.75-0.97). Only one patient had proteinuria >3 g/g, with normal serum albumin level. Seven patients presented urinalysis compatible with tubular disease, with proteinuria dosage on sample higher than by the dipstick. Crystalluria was investigated in four patients, and positive for one. One patient underwent renal biopsy that revealed acute tubulointerstitial nephritis, with lymphocytic infiltrate and acute tubular necrosis (figure 1).

3.3. Cofactors for AKI

Most patients were receiving drugs with potential immuno-allergic side effects, including proton pump inhibitors (15/23), and non-steroidal anti-inflammatory drugs (NSAID, 2/23), long before cloxacillin was introduced. Hence, the contribution of these drugs is unlikely. In addition, 18 patients were receiving drugs known to reduce renal perfusion and function, mostly diuretics (15/23), angiotensin-converting enzyme (ACE) inhibitors (8/23), and/or angiotensin II receptor blockers (ARB, 6/23). Although they were well tolerated before cloxacillin start, these drugs may have contributed to AKI through their pharmacodynamic properties.

Noteworthy, most patients (19/23) were receiving gentamicin in addition to cloxacillin when AKI occurred, either once (n=13), twice (n=4), or thrice (n=2) daily. Of these, only one had documented gentamicin trough plasma concentration >1 µg/mL. Lastly, three patients (13%) underwent CT-scan with iodinated contrast media injection within 48 h before AKI onset, and 9 (39%) presented hemodynamic instability. Overall, only one case of AKI associated with high dose cloxacillin had neither hemodynamic instability, nor concomitant use of gentamicin, or iodinated contrast media injection.

3.4. Cloxacillin treatment

Twenty-two patients received intravenous cloxacillin, and one patient received oral cloxacillin. Median duration of cloxacillin treatment when AKI developed was 4 days (IQR, 3-7 days), and median daily dose was 11 g (IQR, 10-12). One patient erroneously received 31.5 g during one day. Cloxacillin plasma concentration was measured before or during AKI onset in 18 patients. The first measure was performed after a median delay of 3.5 days (IQR, 2-4). Thirteen patients (57%) had plasma concentration >50 µg/mL (range 51.4-135.0), including 10 (43% of total), with trough plasma concentration >100 µg/mL. Only 2 patients (9%) had plasma concentrations within the therapeutic target (i.e. 20-50 µg/mL). Among the

13 patients with cloxacillin trough plasma concentration >50 µg/mL, 7 were documented at the same time as AKI onset, 3 were observed before AKI, and 3 were observed after AKI.

3.5. Outcome

Only the patient with AIN biopsy-proven received steroids. AKI improved in all patients: for 21 (91%), SCr decreased after cloxacillin was discontinued, with a median delay of 5 days (IQR, 1-7) between last dose of cloxacillin and the beginning of renal function improvement. In 2 patients with simultaneous cloxacillin plasma concentration >50 µg/mL and AKI, cloxacillin daily dose reduction led to a stabilization of kidney function in one patient, and significant improvement for the other. Evolution of kidney function is detailed on Table 2. Finally, considering the last SCr value available, complete recovery was observed for 13 patients (57%). The infectious diseases that motivated high-dose cloxacillin were finally controlled in all patients initially, and all patients could be discharged. However, one patient had a recurrence of endocarditis and died 3 months later.

3.6. Estimates of AKI incidence in patients treated with high-dose cloxacillin

During the study period (2009-2015), 137,675 defined daily doses (275,350 g) of cloxacillin were administered in our institution. With a mean daily dose of 9.7 g, and a mean duration of treatment of 10.5 days, the number of patients who received intravenous cloxacillin during the study period is estimated at 676. Hence, these 23 cases of AKI would translate into a cumulative risk of AKI of 3.4% per patient treated with cloxacillin, and an incidence rate of 0.3% per treatment-day.

4. DISCUSSION

To the best of our knowledge, this is the first case series of AKI associated with cloxacillin. AKI occurred early after cloxacillin start (i.e. median, 4 days (IQR, 3-7), primarily in elderlies (median age 75 years, IQR, 66-80), and was often serious: 20 cases were classified as 'failure' according to RIFLE, and 5 patients required renal replacement therapy. Renal function had returned to baseline value at the end of follow-up for 57% of patients.

Renal toxicity of cloxacillin has been rarely reported: In 1989, 7 years after cloxacillin was approved for use, Grimm et al. reported the first case of acute renal failure with eosinophiliuria in a four-year-old child after 10 days of oral cloxacillin [8]. Renal function totally recovered following cloxacillin discontinuation, and a three-day course of corticosteroids. Although no renal biopsy was performed, this observation was highly suggestive of acute interstitial nephritis (AIN). Three other cases of cloxacillin-induced AIN were reported in 1991-1992 [9-11], including one case of AIN documented by biopsy in a 15-year-old child, after a three-month course of oral cloxacillin [9]. This child required 4 sessions of peritoneal dialysis, and recovered normal renal function 21 days after cloxacillin discontinuation, without corticosteroids. Lastly, an observational study on the risk of AKI associated with antimicrobial agents found that among 40 patients treated with cloxacillin, one developed AKI [12], with an estimated risk of 2.5% in patients treated with cloxacillin, quite similar to the 3.4% estimated in our study. Of note, similar incidence rates have been reported with the other isoxazolyl penicillins currently licensed (i.e. oxacillin, dicloxacillin, and flucloxacillin), and the primary mechanism suspected or documented was AIN [13].

Although most cases of cloxacillin-induced nephropathy reported to date were suspected or documented to be immuno-allergic [8-11], the cases reported herein suggest that other mechanisms may be involved. Although AIN was documented for the only patient who underwent kidney biopsy, several points argue against a primarily immuno-allergic pathway,

and suggest other possible mechanisms for cloxacillin-induced AKI. Firstly, all patients except one were receiving high-dose cloxacillin, and more than half had cloxacillin plasma concentration >50 µg/mL. Secondly, for 2 patients, renal function improved or stabilized while cloxacillin was continued, at a lower dose. These two facts are suggestive of dose-related, direct tubular toxicity. Thirdly, few patients had clinical or biological signs of hypersensitivity (e.g. only three had hypereosinophilia). Fourthly, crystalluria was documented in one patient, suggesting that tubular precipitation of cloxacillin may occur, as reported with other penicillins [14-16]. Similar hypothesis were raised regarding nephrotoxicity of flucloxacillin, an isoxazolyl penicillin structurally close to cloxacillin [17]. For the latter, a dose effect was recently demonstrated, with an higher risk of AKI in patients who received high-dose flucloxacillin prophylaxis before knee surgery, as compared to standard dose [18].

Whatever the mechanism, our case series underlines that almost all patients who developed AKI during cloxacillin treatment had other risk factors for AKI, including hemodynamic instability and concomitant use of nephrotoxic drugs or iodinated contrast media. More than half were receiving ACE inhibitors, ARB, or diuretics. As intravenous cloxacillin is mainly eliminated by urinary route, and actively excreted by renal tubules [19], drugs that modify renal hemodynamic, may increase the risk of AKI during cloxacillin treatment. In addition, 19 patients (83%) were also receiving gentamicin, and 3 received at least one bolus of iodinated contrast media, both products with direct toxicity on renal tubules [20-22], that may increase the tubular toxicity of high-dose cloxacillin. These data have two major clinical implications for the management of patients who require high dose cloxacillin: i) patients with cofactors for AKI, including hemodynamic instability and concomitant use of nephrotoxic agents, should be closely monitored; ii) whenever possible, these cofactors must

be addressed (e.g. discontinuation of nephrotoxic agents, and early correction of hemodynamic instability).

Several questions arise regarding cloxacillin dose adaptation to avoid trough plasma concentrations >50 µg/mL. We found that, despite patients were prescribed the cloxacillin dose recommended by guidelines, taking into account their eGFR, 57% had trough plasma concentration > 50 µg/mL. This result is consistent with a recent study that reported trough plasma concentration > 50 µg/mL in 83.9% of 62 patients treated by oxacillin or cloxacillin in intensive care unit [6]. Of note, intravenous cloxacillin is mainly bound to plasma proteins (>90%) [23], and the active metabolite is the unbound fraction. In case of hypoalbuminemia (e.g. malnutrition or inflammation), this unbound fraction increases [24]. In addition, tubular excretion is a saturable mechanism, with interindividual variations [25]. Target cloxacillin plasma concentration can be achieved with much lower doses than 12 g/d [26], which suggests that doses currently recommended are probably too high, especially for the contemporary population of patients with severe staphylococcal infections (i.e. elderly, with comorbidities, and sepsis).

These data suggest that therapeutic drug monitoring of cloxacillin should be developed, as for vancomycin or gentamicin, which would allow early adaptation of daily doses. Individualized treatment is probably necessary for this population of elderly patients with major comorbidities, and multiple comedications. A recent study showed that cloxacillin monitoring was routinely available only in 16.5% of cases in France [27], although the impact of therapeutic drug monitoring has been demonstrated for this betalactam agent as well as others, when prescribed at high doses [28]. One of the major caveats of therapeutic drug monitoring for cloxacillin is that the therapeutic target has not been validated. In France [6], we routinely use a target of 20-50 µg/mL for cloxacillin trough plasma concentrations (or steady-state concentrations, in case of continuous administration), for difficult-to-treat MSSA

infections (e.g. cardiovascular or osteoarticular infections), based on the following points: i) the activity of this drug, as for most betalactam agents, is time-dependent, which means that there won't be major gain in terms of efficacy once you reach the MIC; ii) for the main indication of cloxacillin use (i.e. MSSA), MIC90 is at 0.5 µg/mL; iii) tissue diffusion of cloxacillin, although not thoroughly investigated, is probably moderate, at best; and iv) for most betalactam antibiotics, dose-related toxicity is observed above plasma concentrations of 50 µg/mL.

This study has limitations: Firstly, as it was retrospective, investigation of cases was not standardized, hence missing data may have introduced bias. Secondly, no active surveillance of cloxacillin tolerability was in place during the study period. Hence, we had to rely on passive surveillance and voluntary notification, so that cases may have been missed. Thirdly, only one case underwent kidney biopsy, so that the underlying mechanism of AKI remained unproven in most cases. Lastly, the lack of a control group of patients who received high-dose cloxacillin, but did not develop AKI, precluded identification of risk factors for AKI associated with high-dose cloxacillin. Strengths of this study includes its relatively large sample size, as compared to literature data available to date, and the investigation of each case while patients where still admitted, with the expertise of trained staff from the drug safety monitoring department, and the support of nephrologists and infectious diseases physicians whenever required.

In conclusion, this first case series of 23 patients who developed AKI associated with high dose cloxacillin suggests that direct tubular toxicity and/or tubular precipitation may play a major role. This study advocates for systematic therapeutic drug monitoring when cloxacillin is prescribed at high doses, with a first determination early after introduction (e.g. 48 to 96 hours after cloxacillin start), even when baseline renal function is normal. eGFR must be monitored at least twice a week, and dose of cloxacillin should be reduced as soon as

AKI develops. Finally, monitoring of cloxacillin plasma concentration should be particularly tight in patients with cofactors for AKI, including age, comorbidities, concomitant medication with antihypertensive agents or aminoglycosides, hemodynamic instability and injection of iodinated contrast media.

Conflicts of Interest: None.

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Ethical Approval: This study has been approved by the ethical committee of Rennes University hospital (reference number n° 16.99).

Figure legend

Fig. 1: Masson's trichrome staining showing acute tubulointerstitial nephritis with lymphocytic infiltrate (arrows to the left), and acute tubular necrosis (arrow to the right), magnification x 200

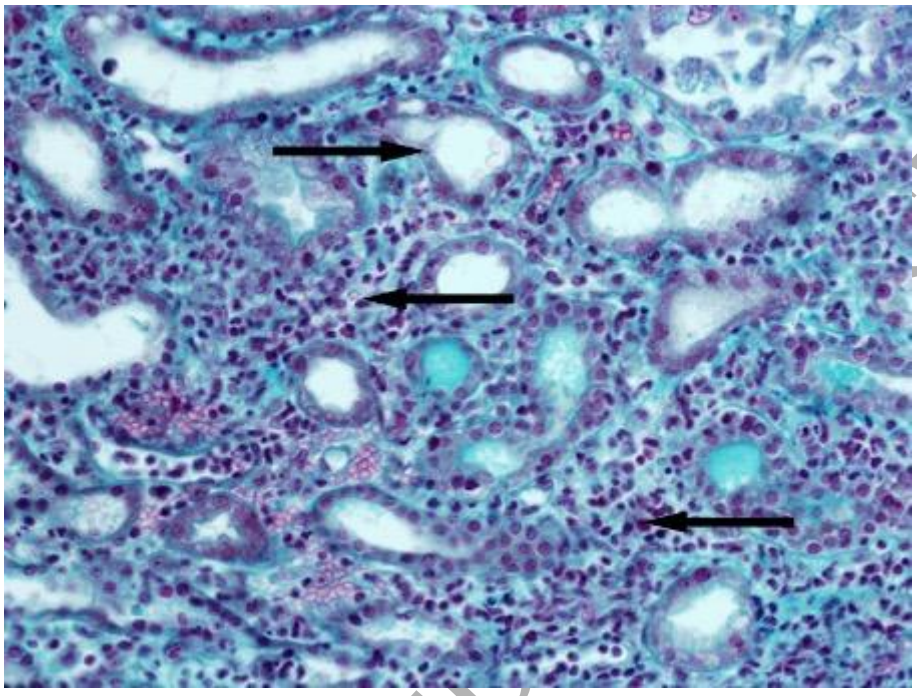

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Table 1. Patients characteristics before cloxacillin start (*n* = 23)

Demographics	
Median age, years (interquartile range)	75 (66-80)
Male/Female, n	16/7
Comorbidities n (%)	
Cancer	2 (4)
Diabetes	8 (35)
Cardiopathy	13 (57)
High blood pressure	12 (25)
Kidney function	
Median serum creatinin, µmol/L (IQR)	79 (59-92)
Median eGFR, mL/min (IQR)	86 (64-110)
CKD stage ≤ 2, n (%)	20 (87)
CKD stage 3, n (%)	3 (13)
CKD stage 4, n (%)	0
Associated drugs, n (%)	
PPI	15 (65)
NSAID	2 (9)
Diuretic	15 (65)
ACE inhibitor or ARB	14 (61)
Main indication for cloxacillin, n (%)	
Osteoarthritis infection	9 (39)
Cardiovascular	7 (30)
Bacteremia	11 (48)
Microbiology, n (%)	
MSSA	17 (74)
Coagulase-negative staphylococci	3 (13)
Not documented	3 (13)

eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; PPIs: proton pump inhibitor; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; MSSA: meticillin-susceptible *Staphylococcus aureus*

Table 2. Outcome

	At AKI	1 month after	3 months after	6 months after
Number	23	20	15	15
Median SCr μmol/L, (IQR)	339 (249-503)	135 (112-179)	113 (107-122)	114 (90-123)
Median eGFR mL/min, (IQR)			53 (47-55)	52 (40-63)
CKD stage ≤ 2, n (%)			3 (13)	5 (22)
CKD stage 3, n (%)			12 (52)	9 (39)
3A			9 (39)	5 (22)
3B			3 (13)	4 (17)
CKD stage 4			0	1 (4)
CKD stage 5			0	0
Death		0	0	2 (9)
Data not available		3 (13)	8 (35)	6 (26)

AKI: acute kidney injury, IQR : interquartile range, SCr: serum creatinine, eGFR: estimated glomerular ion rate, CKD: chronic kidney disease