Incidence and determinants of flucloxacillin-induced hypokalaemia

Intravenous flucloxacillin is used to treat severe infections in hospitalized patients. Treatment with high dose intravenous flucloxacillin can lead to potentially life threatening hypokalaemia as adverse event. In this single-centre retrospective observational cohort study, we investigated the incidence and severity of hypokalaemia in patients treated with intravenous flucloxacillin. Furthermore, risk factors for flucloxacillin-induced hypokalaemia were identified.

All patients treated for at least 48 hours with ceftriaxone or intravenous flucloxacillin and a normal baseline serum potassium level were included. The primary endpoint of the study was the incidence of hypokalaemia presented as the percentage of patients with a serum potassium measurement <3.5 mmol/L two to five days after initiation of antibiotic treatment. Logistic regression modelling was used to investigate the influence of sex and other risk factors on the development of flucloxacillin-induced hypokalaemia.

In total 2290 patients treated with ceftriaxone and 452 patients treated with flucloxacillin were included. The incidence of hypokalaemia was 13.1% in patients receiving flucloxacillin. The incidence of moderate and severe hypokalaemia were respectively 1.3% and 0.2%. Identified risk factors for the development of hypokalaemia in patients treated with flucloxacillin were lower baseline potassium levels, older age and lower BMI.

The incidence of hypokalaemia is increased in patients receiving flucloxacillin compared to patients receiving ceftriaxone. Healthcare providers should be aware of the risk for developing hypokalaemia in patients treated with intravenous flucloxacillin, especially in patients with risk factors.

1 | INTRODUCTION

Flucloxacillin is a narrow-spectrum penicillin antibiotic used to treat infections caused by gram positive bacteria. It is a bactericidal antibiotic that works by inhibiting crosslinking of peptidoglycans in the cell wall leading to lysis and finally cell death. In the Netherlands flucloxacillin is frequently used, with more than 300.000 patients treated with any form of this drug each year (1). It is available as capsule or as powder for suspension or injection. High-dose flucloxacillin is used intravenously in hospitals to treat severe infections such as sepsis caused by *Staphylococcus aureus*.

A small cohort study showed that treatment with intravenous flucloxacillin may provoke hypokalaemia, and that female sex and the use of diuretics are risk factors (2). Another previously conducted study identified lower baseline potassium, older age, lower bodyweight, use of concomitant antibiotics and a longer treatment duration with flucloxacillin as risk factors for flucloxacillin-induced hypokalaemia. Moreover, this study showed that females receiving >8 gram of intravenous flucloxacillin per day are more prone to develop hypokalaemia compared to males (3). Hypokalaemia is defined as a serum potassium level below 3.5 mmol/L. Severe hypokalaemia (serum potassium level <2.5 mmol/L) can lead to rhabdomyolysis and cardiac arrhythmias and may be potentially fatal. There is little knowledge about the incidence and severity of flucloxacillin-induced hypokalaemia. In the European summary of product characteristics (SmPC) of flucloxacillin, hypokalaemia is reported as a potentially life treating adverse event with an unknown incidence (4).

The primary aim of this retrospective cohort study was to investigate the incidence and severity of hypokalaemia in patients who receive intravenous flucloxacillin. Furthermore, the influence of other risk factors, especially sex, on flucloxacillin-induced hypokalaemia was evaluated. This study might identify a specific patient group who benefits from frequent serum potassium measurements during the use of intravenous flucloxacillin, thus improving future patient care in hospitals.

2 | METHODS

2.1 | Design and study population

This single-centre retrospective observational cohort study was conducted at Erasmus MC, Rotterdam, the Netherlands. All adult patients admitted to this hospital between 2017 (initiation of Electronic Patient Files program HiX) and July 2021 who received ceftriaxone or intravenous flucloxacillin were screened for eligibility. Patients receiving ceftriaxone were included as control group. A non-WMO statement was issued by the institutional Medical Ethics Review Committee (METC). The need for patient informed consent was waived, because the aim of the project was to improve patient care locally.

Patients were included if they were treated with ceftriaxone or intravenous flucloxacillin for at least 48 hours. Moreover, a normokalemic (3.5 – 4.8 mmol/L) baseline serum potassium measurement at the start of the antibiotic therapy, and no serum potassium levels below or above this range in the 24 hours before to 24 hours after start of the antibiotic therapy had to be documented. Finally, at least one follow-up serum potassium measurement during treatment documented at 48-120 hours after start of the antibiotic therapy had to be available. Patients were excluded if they received both ceftriaxone and flucloxacillin at the time of baseline or follow-up serum potassium measurement and if the antibiotic treatment regime was interrupted for more than 1 day.

2.2 | Outcomes

The primary outcome of the study was the incidence and severity of hypokalaemia during antibiotic therapy. Hypokalaemia was

defined as ≥1 serum potassium level of <3.5 mmol/L measured at 48-120 hours after initiation of antibiotic therapy. The incidence of mild hypokalaemia (≥3.0-<3.5 mmol/L), moderate hypokalaemia (≥2.5-<3.0 mmol/L) and severe hypokalaemia (<2.5 mmol/L) was also documented. For this endpoint, differences between males and females were presented to investigate the effect of sex on the incidence of hypokalaemia. To investigate whether the expected effect of sex on hypokalaemia is restricted to patients receiving flucloxacillin, the incidence of hypokalaemia was also presented for patients receiving ceftriaxone. Because a previous conducted study showed that only females receiving a high daily dose of >8 gram of intravenous flucloxacillin were more prone to flucloxacillin-induced hypokalaemia than men, the incidence of hypokalaemia was presented separately for three different flucloxacillin dosing regimens.

Secondary outcomes were the number of days from initiation of treatment until the patient developed hypokalaemia and patient factors associated with flucloxacillin-induced hypokalaemia.

2.3 | Data collection

The study parameters were retrospectively extracted from the Electronic Patient Files (Chipsoft HiX version 6.2). In order to identify risk factors for flucloxacillin-induced hypokalaemia the following data was extracted: sex, age, bodyweight, length, body mass index (BMI), use of concomitant diuretics and kidney function (using the chronic kidney disease epidemiology collaboration formula (CKD-EPI). The indication for the antibiotic use was also registered.

Length and bodyweight were documented as close as possible to the starting date of the antibiotic therapy, but at last 7 days after initiation of the therapy. Estimated glomerular filtration rate (eGFR) was documented as close as possible to the starting date of the antibiotic therapy. At the start of the antibiotic treatment the dose of the antibiotic and use of concomitant diuretics were documented. The use of diuretics was divided into loop, potassium-sparring and thiazide diuretics and coded as dichotomous variables. Flucloxacillin dose was divided into three categories (≤4 gram, >4-<12 gram, and 12 gram).

2.4 | Statistical analysis

Categorical variables were reported as counts and percentages, linear normally distributed variables as mean ± SD and non-normally distributed variables as medians with 25th to 75th percentiles. Statistical analysis of differences in characteristics between patients receiving ceftriaxone or flucloxacillin was performed with an independent samples t-test for normally distributed data, a Mann-Whitney U test for non-normally distributed data or a Chi-square test for categorical data.

Incidence of hypokalaemia was presented as percentage of patients with hypokalaemia during antibiotic treatment. Differences between males and females or ceftriaxone and flucloxacillin in incidence of hypokalaemia were tested for significance using the Chi-square test or Fisher's exact test as appropriate.

Because hypokalaemia is considered a multifactorial condition, stepwise logistic regression was used to investigate the influence of sex and other risk factors on hypokalaemia in the flucloxacillin group. Multiple variables that are biologically likely to affect serum potassium levels were tested independently in an univariate analysis. Variables associated with a low serum potassium level in the univariate analysis (potential confounders) were added to a multivariable model. Forward selection was used to delete variables in the multivariable model. Missing data was replaced by medians. Variables were omitted from the analysis if more than 50% of the values were missing.

All analyses were carried out with SPSS version 28.0.1

3 | RESULTS

3.1 | Study sample

In total 4217 patients receiving either ceftriaxone or intravenous flucloxacillin were found. For 1201 patients normokalemic baseline serum potassium levels 24 hours before to 24 hours after start of the antibiotic therapy were absent, 161 patients had fewer than 48 hours of antibiotic treatment, 61 patients received both ceftriaxone and flucloxacillin and in 52 patients antibiotic treatment has been interrupted for more than 1 day. Thus, in total 2742 patients were included (figure 1). 2290 patients were treated with ceftriaxone and 452 patients were treated with flucloxacillin.

3.2 | Characteristics of the population

Characteristics of the included patients are displayed in table 1. In the flucloxacillin group more men than women were included (65.9%), the median age was 62.0 years (IQR 21.0) and the median eGFR was 83.0 ml/min/1.73 m^2 (IQR 33.0). Most common indications for flucloxacillin therapy were bloodstream infections (sepsis) (27.7%), pneumonia (15.7%) and skin or soft tissue infections (13.7%). Most patients (54.4%) used a high dose of 12 gram intravenous flucloxacillin per day, 14.8% used more than 4 gram but less than 12 gram per day and 30.8% used 4 gram or less per day. 19.9% of patients receiving flucloxacillin used loop diuretics, 12.2% used potassium-sparing diuretics and 5.1% used thiazide diuretics.

The following data was missing in the flucloxacillin group: bodyweight in 23.2%, length in 26.5%, BMI in 26.5% and eGFR in 64.6%. In the ceftriaxone group also slightly more men than women were included (63.4%), the median age was 62.0 years (interquartile range [IQR] 20.0) and the median eGFR was 81.0 ml/min/1.73 m^2 (IQR 39.0).

Ceftriaxone was mostly prescribed for pneumonia (15.2%), skin or soft tissue infections (13.7%) and urinary tract infections (7.2%).

Loop diuretics were used most frequently (21.9%), followed by potassium-sparing diuretics (4.5%) and thiazide diuretics (2.0%). The following data was missing in the ceftriaxone group: bodyweight in 27.4%, length in 29.4%, BMI in 29.6% and eGFR in 50.9%. Baseline potassium levels were similar in both groups (mean 4.1, standard deviation [SD] 0.34).

Both flucloxacillin and ceftriaxone groups were comparable in most baseline characteristics. Potassium- sparing diuretics were used more frequently by patients receiving flucloxacillin (12.2% vs 4.5%, P = <0.001). This also applies to thiazide diuretics (flucloxacillin 5.1% vs ceftriaxone 2.0%, P = <0.001).

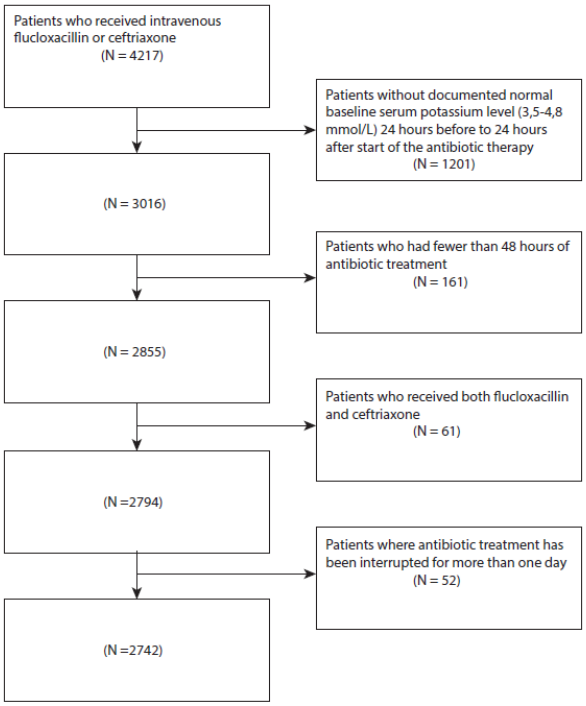

Figure 1 Flowchart for the study population

3.2 | Incidence of hypokalaemia

In patients treated with flucloxacillin the incidence of hypokalaemia was 13.1%. This is higher than in patients treated with ceftriaxone (8.0%) ($P < 0.001$) (table 2). In both groups the incidence was increased in females compared to males (and flucloxacillin: 16.9% vs 11.1%, $P = 0.082$ ceftriaxone: 11.6% vs 6.5%, $P < 0.001$), which indicates that female sex is associated with an increased risk of developing hypokalaemia. The incidence of moderate hypokalaemia was comparable in both groups (ceftriaxone: 1.0% and flucloxacillin 1.3%). Severe hypokalaemia only occurred in four patients. The mean number of days from start until hypokalaemia occurred was 3.8 (SD ± 0.83) in the flucloxacillin group and 3.3 (SD ± 0.9) in the ceftriaxone group.

The incidence of hypokalaemia for different flucloxacillin dosing regimens is displayed in table 3. The highest incidence of hypokalaemia (20.5%) was found in females receiving a high daily flucloxacillin dose (12 g).

3.3 | Risk factors for hypokalaemia

Sex, age, BMI, baseline potassium level, the use of diuretics and three dosing regimens (≤4 g, >4-<12 g and >12 g) were tested in an univariate logistic regression analysis. eGFR was omitted, because an eGFR measurement was only available in 35.4%. The final multiple regression model after forward selection (Wald) contained age, BMI and baseline potassium level (variables entered: sex, age, BMI, baseline potassium level, and use of loop diuretics) as independent risk factors for hypokalaemia (table 4).

The model showed that in patients receiving flucloxacillin, a 1 point higher BMI decreases the risk of developing hypokalaemia by 6.7%, a 1 mmol/L higher baseline potassium level decreased the risk by 83.9% and age increased the risk by 2.2% per year. Sex appeared to be no independent risk factor for hypokalaemia in this analysis.

4 | DISCUSSION

In this retrospective cohort study, the incidence and severity of flucloxacillin-induced hypokalaemia was investigated. In the included population the incidence of hypokalaemia was 13.1% (16.9% in females vs 11.1% in males) in patients treated with intravenous flucloxacillin. A previous similar study conducted at the Haga hospital in the Hague in the Netherlands by Leegwater et al. revealed an incidence of hypokalaemia of 23.7% in patients treated with flucloxacillin (28.4% in females vs 20.4% in males) (3). A possible explanation for this difference in incidence, is the narrow time frame for detecting hypokalaemia of 48-120 hours after initiation of antibiotic therapy that has been chosen in this study. Another explanation could be that in this study a relatively large part of the patients receiving flucloxacillin also used potassium-sparing diuretics, lowering the risk of developing hypokalaemia (12.2% in this study vs 4.4% in the previous study conducted by Leegwater et al.). The incidence of hypokalaemia in the general outpatient population is estimated around 2.0% to 3.0% (5)(6). For the general inpatient population estimates vary widely, ranging from 3.5% up to 23.0% (7, 8). A large Swedish study found an incidence of hypokalaemia of 13.6% for the general inpatient population (9). This is deviant from the incidence of 8.0% found in patients treated with ceftriaxone in this stud y.The incidence of hypokalaemia found in patients treated with ceftriaxone, was as expected lower than compared to patients receiving flucloxacillin.

In previous studies female sex, presence of comorbidities like hypertension, older age, higher eGFR and use of loop or thiazide diuretics were associated with an increased risk of developing hypokalaemia (6, 9). Identified risk factors for the development of hypokalaemia in flucloxacillin users in this study were: lower BMI, lower baseline potassium level and older age.

TABLE 1 Characteristics of patients included in the study

	Flucloxacillin (n = 452)	Ceftriaxone (n = 2290)	Statistical analysis (ceftriaxone vs flucloxacillin)
Sex is male (%)	298 (65.9)	1452 (63.4)	Ns (*P* = 0.308)
Age (median [IQR]), years	62.0 [50.0, 71.0]	62.0 [50.0, 70.0]	Ns (*P* = 0.769)
Bodyweight (median [IQR]), kg	81.0 [70.0, 93.0]	80.4 [70.0, 93.5]	Ns (*P* = 0.972)
Length (median [IQR]), cm	175.0 [169.0, 182.0]	175.0 [167.2, 180	Ns (*P* = 0.111)
BMI (median [IQR]), kg/m^2	25.8 [23.2, 29.7]	26.6 [23.7, 30.1]	Ns (*P* = 0.131)
eGFR (CKD-EPI) (median [IQR]), ml/min/1.73 m^2	83.0 [57.0, 90.0]	81.0 [51.0, 90.0]	Ns (*P* = 0.337)
eGFR (CKD-EPI) < 60 (%), ml/min/1.73 m^2	43 (9.5)	344 (15.0)	Ns (*P* = 0.838)
eGFR (CKD-EPI) < 30 (%), ml/min/1.73 m^2	14 (3.1)	93 (4.1)	Ns (*P* = 0.336)
Baseline serum K^+ level (mean ± SD), mmol/L	4.1 ± 0.34	4.1 ± 0.34	Ns (*P* = 0.541)
Dose per day (%)			
• ≤4 g	139 (30.8)	2290 (100.0)	
• >4-<12 g	67 (14.8)		
• ≥12 g	246 (54.4)		
Diuretics (%)			
• No diuretics	334 (73.9)	1730 (75.5)	Ns (*P* = 0.445)
• Loop diuretics	90 (19.9)	502 (21.9)	Ns (*P* = 0.343)
• Potassium-sparing diuretics	55 (12.2)	102 (4.5)	*P* = <0.001
• Thiazide diuretics	23 (5.1)	5 (2.0)	*P* = <0.001
Indication for antibiotic use (%)			
• Bloodstream infections (sepsis)	125 (27.7)	95 (4.1)	
• Pneumonia	71 (15.7)	348 (15.2)	
• Bone and joint infections	57 (12.6)	23 (1.0)	
• Skin or soft tissue infections	62 (13.7)	104 (4.5)	
• Urinary tract infections	7 (1.5)	166 (7.2)	
• Endocarditis	29 (6.4)	55 (2.4)	
• Unknown	10 (2.2)	105 (4.6)	
• Other/not documented	91 (20.1)	1394 (60.9)	

Abbreviations: BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; K^+, potassium; Ns, nonsignificant; SD, standard deviation.

TABLE 2 Incidence of hypokalaemia in patients treated with ceftriaxone and flucloxacillin

	Flucloxacillin				Ceftriaxone			
	Total (n = 452)	Male (n = 298)	Female (n = 154)	Statistical analysis (male vs female)	Total (n = 2290)	Male (n = 1452)	Female (n = 838)	Statistical analysis (male vs female)
Hypokalaemia (< 3.5 mmol/L) (%)	59 (13.1)	33 (11.1)	26 (16.9)	Ns (*P* = 0.082)	191 (8.0)	94 (6.5)	97 (11.6)	*P* = <0.001
Mild hypokalaemia (≥3.0-<3.5 mmol/L) (%)	52 (11.5)	31 (10.4)	21 (13.6)	Ns (*P* = 0.192)	165 (7.2)	86 (5.9)	79 (9.4)	*P* = <0.001
Moderate hypokalaemia (≥2.5-<3.0 mmol/L) (%)	6 (1.3)	2 (0.7)	4 (2.6)	Ns (*P* = 0.106)	23 (1.0)	7 (0.5)	16 (1.9)	*P* = <0.001
Severe hypokalaemia (<2.5 mmol/L) (%)	1 (0.2)	0 (0.0)	1 (0.6)		3 (0.1)	1 (0.1)	2 (0.2)	Ns (*P* = 0.558)
Number of days from start of treatment until event (mean ± SD), days	3.8 ± 0.82	3.8 ± 0.83	3.7 ± 0.83	Ns (*P* = 0.451)	3.3 ± 0.90	3.4 ± 0.90	3.1 ± 0.90	*P* = 0.010

Abbreviations: Ns, nonsignificant; SD, standard deviation.

TABLE 3 Incidence of hypokalaemia for different flucloxacillin dosing regimens

Dose	Population size			Incidence of hypokalaemia			
	Total (n = 452)	Male (n = 298)	Female (n = 154)	Total	Male	Female	Statistical analysis (male vs female)
≤4 - 12 g	452 (100.0)	298 (100.0)	154 (100.0)	59 (13.1)	33 (11.1)	26 (16.9)	Ns (*P* = 0.082)
≤4 g	139 (30.8)	89 (29.9)	50 (32.5)	17 (12.2)	9 (10.1)	8 (16.0)	Ns (*P* = 0.309)
>4-<12 g	67 (14.8)	46 (15.4)	21 (13.6)	5 (7.5)	4 (8.7)	1 (4.8)	Ns (*P* = 0.570)
12 g	246 (54.4)	163 (54.7)	83 (53.9)	37 (15.0)	20 (12.3)	17 (20.5)	Ns (*P* = 0.088)

TABLE 4 Logistic regression analysis for the development of hypokalaemia in the flucloxacillin group (N = 452)

	Univariate analysis			Multivariable analysis		
Variable	**OR**	**CI**	***P***	**OR**	**CI**	***P***
Sex						
• Male	1.000 (reference)					
• Female	1.631	(0.936-2.843)	Ns (*P* = 0.084)			
Age (years)	1.018	(1.000-1.037)	Ns (*P* = 0.051)	1.022	(1.003-1.041)	0.025
BMI (kg/m^2)	0.939	(0.882-1.000)	Ns (*P* = 0.050)	0.933	(0.873-0.998)	0.044
Baseline K^+ level (mmol/L)	0.159	(0.065-0.385)	< 0.001	0.161	(0.067-0.385)	< 0.001
Diuretics						
• No diuretics	1.000 (reference)					
• Loop diuretics	3.107	(1.469-6.571)	0.003			
• Potassium sparing diuretics	1.047	(0.419-2.619)	Ns (*P* = 0.922)			
• Thiazide diuretics	1.690	(0.545-5.237)	Ns (*P* = 0.363)			
Dose						
• ≤4 g	1.000 (reference)					
• 6-8 g	0.579	(0.204-1.642)	Ns (*P* = 0.304)			
• 12 g	1.270	(0.686-2.353)	Ns (*P* = 0.446)			

Abbreviations: BMI, body mass index; CI, confidence interval; K^+, potassium; Ns, nonsignificant; OR, odds ratio

This is partly in line with the study of Leegwater et al. that identified lower baseline potassium, older age, lower bodyweight, use of concomitant antibiotics and a longer treatment duration with flucloxacillin as risk factors for flucloxacillin-induced hypokalaemia.

The total amount of potassium in the body is determined by the intake of potassium from food and the excretion of potassium through the intestines, kidneys and skin (by transpiration). Normally the concentration of electrolytes in the extracellular fluid is tightly regulated by the kidneys. Hypokalaemia is caused by abnormal potassium loss, transcellular shifts or insufficient potassium intake and may sometimes be attributed to drug use. Loop and thiazide diuretics may cause hypokalaemia via increased renal potassium excretion.

Penicillins that are excreted through the kidneys can disrupt the potassium balance by acting as non-reabsorbable anions in the cortical collecting duct. The negatively charged particles attract positively charged potassium ions and cause a transmembrane potential gradient leading to increased renal potassium excretion. The increased potassium excretion may finally result in hypokalaemia. We found the highest incidence of hypokalaemia in females receiving a high daily dose (12 g) of flucloxacillin. This is in line with the results of the cohort study conducted by Leegwater et al. The authors of that study hypothesized that in patients receiving high dose intravenous flucloxacillin, the body is unable to correct serum potassium levels because the amount of renal excreted anions exceeds a threshold (3, 10).

In both patients receiving ceftriaxone and flucloxacillin the incidence of hypokalaemia was increased in females compared to males (ceftriaxone: 11.6% vs 6.5%, P < 0.001 and flucloxacillin: 16.9% vs 11.1%, P = 0.082). Females have a relatively lower amount of total body potassium compared to males (11, 12). This could be explained by a different body composition with relatively more fat and less muscle tissue. This results in lower baseline potassium levels (13). Previous studies and this study showed that a higher baseline potassium level reduces the chance of developing hypokalaemia. Females are thus more prone to flucloxacillin-induced hypokalaemia, because they have lower baseline potassium levels (3). Older aged patients also have lower baseline potassium levels and are thus more vulnerable for hypokalaemia. Age-related reduction of muscle mass leads to a lower total body potassium and thus to lower baseline potassium levels (14). Patients with a higher BMI have a lower chance of developing hypokalaemia, because the relative exposure to flucloxacillin (dose/kg) is lower and due to the higher weight the body is better able to correct the potassium levels (12).

There are several limitations to this study. First, because the data was extracted retrospectively from the Electronic Patient Files program, for some patients data was unavailable. The amount of missing data was comparable between the patients receiving

ceftriaxone and flucloxacillin. Second, patients could be referred from a regional hospital where they may have already been treated with antibiotics but this is not registered in the database. The baseline risk of developing hypokalaemia might be different in these patients leading to selection bias. Third, the likelihood of detecting hypokalaemia depends on the frequency of serum potassium monitoring. Even though serum potassium measurements are common under hospitalized patients, it is not standard procedure for patients receiving ceftriaxone or flucloxacillin. Thus, it is possible that patients with hypokalaemia have been missed due to detection bias. Finally, data regarding comorbidities is missing in this study. Some comorbidities are associated with an increased or decreased risk of developing hypokalaemia and could be a potential confounder not included in the logistic regression analysis.

In conclusion, the incidence of flucloxacillin-induced hypokalaemia measured 48-120 hours after initiation of the antibiotic therapy was 13.1%. Moderate and severe hypokalaemia were rare in patients treated with flucloxacillin. The highest incidence of hypokalaemia was found in females receiving high daily dose (12 g) of flucloxacillin, but sex was not an individual risk factor for hypokalaemia. Identified risk factors for flucloxacillin-induced hypokalaemia were lower BMI, lower baseline potassium level and older age. This study highlights the importance of awareness by clinicians of the risk for developing hypokalaemia in patients treated with flucloxacillin. Patients treated with intravenous flucloxacillin, especially patients with risk factors, should undergo frequent potassium measurements. Future prospective studies should verify the results found in this study.

5 | REFERENCES

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