Hypokalaemia in patients treated with intravenous flucloxacillin: incidence and risk factors

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ORIGINAL ARTICLE

Hypokalaemia in patients treated with intravenous flucloxacillin: Incidence and risk factors

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Introduction: Hypokalaemia is a potentially life-threatening adverse event of flucloxacillin with unknown incidence. The risk of flucloxacillin-induced hypokalaemia has recently been suggested to be increased among females compared to males. The aim of this study is to describe the incidence and to determine the influence of sex and other risk factors on flucloxacillin-induced hypokalaemia.

Methods: A retrospective single-centre cohort study was performed. Patients treated with intravenous flucloxacillin for >24 hours between January 2017 and October 2020, a baseline potassium level of ≥3.5 mmol/L and potassium measurement during treatment were included. The primary endpoint was incidence of hypokalaemia defined as the percentage of patients with a potassium measurement <3.5 mmol/L during flucloxacillin treatment. Logistic regression modelling was used to establish risk factors for hypokalaemia.

Results: A total of 835 patients were included, 58.2% male and median age 71.0 years (interquartile range 61.0-81.0). The incidence of hypokalaemia was 23.7% (28.4% in females *vs* 20.4% in males). A dose-dependent relation between sex and the incidence of hypokalaemia was found. The risk of hypokalaemia was 4.41 (95% confidence interval 1.47-13.24) times higher in females compared to males when receiving a flucloxacillin dose of >8 g/24 h. No sex differences were found for lower daily doses. Other risk factors for hypokalaemia were older age, concomitant antibiotic use, lower bodyweight, lower baseline plasma potassium concentration and longer treatment duration.

Conclusion: Hypokalaemia is a frequent complication in patients treated with intravenous flucloxacillin. Females receiving >8 g intravenous flucloxacillin per day are more prone to develop hypokalaemia compared to males.

KEYWORDS
flucloxacillin, hypokalaemia, risk factors, sex-differences

1 | INTRODUCTION

Hypokalaemia is one of the most common electrolyte imbalances in clinical practice.[1] Although mostly mild and predominantly identified on routine screening only, hypokalaemia can lead to potentially life-threatening events (eg, cardiac dysrhythmias, paralysis).[2–4] In most cases, if observed, hypokalaemia is easily treated by potassium supplementation. Patients at risk for hypokalaemia should have their potassium concentrations monitored frequently to identify hypokalaemia early and avoid the potentially life-threatening complications.

The authors confirm that the Principal Investigator for this study is Dr Loes Visser.

A population which might benefit from frequent potassium measurements and subsequent interventions are patients treated with intravenous flucloxacillin. Flucloxacillin is a key drug in the treatment of *Staphylococcus aureus* infections and has been associated with an increased risk of hypokalemia.[5–7] The exact mechanism of flucloxacillin-induced hypokalaemia has not been elucidated, but it is assumed to be a class effect of penicillins. Being a non-reabsorbable anion, flucloxacillin causes a negative gradient on the luminal side of the cortical collecting duct, which increases renal potassium excretion and subsequent hypokalemia.[8,9]

Data on the incidence and risk factors for hypokalaemia in patients receiving intravenous flucloxacillin is scarce. The European summary of product characteristics (SmPC) describes hypokalaemia as an adverse event with an unknown incidence.[10] In a small cohort study, the cumulative incidence of hypokalaemia was 42% in patients receiving high-dose (≥ 6 g/24 h) intravenous flucloxacillin.[5] Female sex and the use of diuretics were associated with an increased risk of hypokalaemia in this study. Other studies showed that in general the incidence of hypokalaemia and associated hospitalization is higher among females.[1,11–14] Females are also more at risk for other flucloxacillin-induced adverse events, including drug-induced liver injury and metabolic acidosis.[15,16]

Considering the limited knowledge about the incidence, risk factors and potential influence of sex on flucloxacillin-induced hypokalaemia, a retrospective cohort study was performed. The primary aim of this study was to determine the incidence of flucloxacillin-induced hypokalaemia. Secondarily, the influence of sex and other risk factors for flucloxacillin-induced hypokalaemia was evaluated.

What is already known about this subject

- High-dose flucloxacillin has been associated with hypokalaemia in a single-cohort study with limited sample size.
- Female sex might be a risk factor for flucloxacillin-induced hypokalaemia.

What this study adds

- This study describes the incidence and risk factors of flucloxacillin-induced hypokalaemia.
- Females are more prone to develop flucloxacillin-induced hypokalaemia when receiving more than 8 g/24 h.
- Frequent potassium monitoring is especially important during the first week of flucloxacillin therapy and in patients with concomitant antibiotic use, older age, low bodyweight and low baseline plasma potassium concentration.

2 | METHODS

2.1 | Design and study population

A single-centre, retrospective cohort study was conducted in the Haga Teaching Hospital (700 beds) in the Netherlands. All adult hospitalized non-ICU patients receiving intravenous flucloxacillin between January 2017 and October 2020 were screened for eligibility. Inclusion criteria were treatment with intravenous flucloxacillin for at least 24 hours, baseline potassium concentration ≥3.5 mmol/L and at least one follow-up potassium measurement during treatment.

2.2 | Outcomes

The main study outcome was the incidence of hypokalaemia, defined as a plasma potassium concentration <3.5 mmol/L at any point during flucloxacillin therapy. Secondary outcomes were the incidence of moderate hypokalaemia (<3.0 mmol/L) and severe hypokalaemia (<2.5 mmol/L), patient factors associated with flucloxacillin-induced hypokalaemia, and the relation between flucloxacillin concentration and hypokalaemia. All outcomes were separately explored for possible differences between sexes.

2.3 | Variables and data collection

Clinical data and laboratory variables were extracted from the hospital electronic patient records using CTcue datamining software (CTcue B.V., Amsterdam, The Netherlands). Data on demographics and laboratory values were extracted ≤1 day prior to initiation of flucloxacillin and included sex, age, bodyweight, body mass index (BMI), estimated glomerular filtration rate (eGFR) calculated using the chronic kidney disease epidemiology collaboration formula and treatment indication. Last plasma potassium concentration prior to flucloxacillin therapy and all measurements during therapy were documented. Baseline potassium was defined as the last potassium concentration measured ≤1 day prior to the first flucloxacillin administration. During treatment, the following variables were collected: duration of treatment, dose, number of potassium measurements, use of concomitant diuretics, other antibiotics, acetaminophen, beta-blockers, corticosteroids or laxatives, time to hypokalaemia development and flucloxacillin serum concentration. Flucloxacillin dose was divided into three categories based on the different clinical dosing regimens (≤4, 4-8 and >8 g per day). The use of diuretics was divided into loop, thiazide and potassium saving diuretics and used as dichotomous variables. The number of potassium measurements divided by the number of days until an event occurred was calculated to investigate potential detection bias. For flucloxacillin serum concentration, the first concentration measurement after initiation of flucloxacillin treatment was used.

2.4 | Statistical analysis

Categorical variables were reported as counts and percentages, and continuous variables as medians with 25th to 75th percentiles.

Incidence of hypokalaemia is presented as percentage of patients with hypokalaemia during flucloxacillin treatment. The lowest potassium measurement during flucloxacillin treatment was used to calculate the incidence. Differences between males and females were calculated using Fishers exact test or the Mann-Whitney U test as appropriate.

Multivariable logistic regression modelling with backwards deletion was used to establish risk factors for hypokalaemia. Variables were omitted from analysis if more than 50% of the values were missing. Variables were included in the multivariable logistic regression model if there was a biological plausible explanation or if a variable was considered a potential confounder and were deleted using a backward deletion procedure ($P > .10$ for removal) to create the final model. To investigate potential interaction between sex and other risk factors, an interaction term was added to the multivariable logistic regression. The following interactions were tested: sex*age, sex*dose sex*weight and sex*diuretics use. The interaction term remained in the final model if the fit significantly improved ($P < .05$). The final model was used to calculate odds ratios (ORs) of the risk factors for flucloxacillin-induced hypokalaemia. The ORs for variables included in interaction terms were calculated on the multiplicative scale. To further explore the relation between flucloxacillin exposure and hypokalaemia, dose divided by bodyweight was used as an alternative measure of exposure in a sensitivity analysis using the final model.

The Mann-Whitney U test was used to compare the relation between flucloxacillin concentration and sex as well as hypokalaemia.

All analyses were carried out using R, version 4.0.3.

2.5 | Ethics statement

The study was approved by the Institutional Scientific Review Board. As the data were collected anonymously, the need for patient informed consent was waived.

3 | RESULTS

3.1 | Characteristics of the population

In total, 2012 patients were found with a prescription for intravenous flucloxacillin during the study period. For 761 patients the baseline or follow-up potassium measurements were unavailable, in 260 patients intravenous treatment was discontinued within 24 hours, and 156 patients were not included because the baseline potassium concentration was below 3.5 mmol/L.

Thus, 835 patients were included in the study involving 3855 potassium measurements. The following data was missing: BMI in 12.3%, body weight in 8.6% and height in 6.0%. Patient characteristics are listed in Table 1: 58.2% of patients were male and the median age was 71.0 years (interquartile range [IQR] 61.0-81.0). The median treatment duration was 5.3 days (IQR 2.6-12.2). Most common indications for flucloxacillin therapy were skin or soft tissue infections (54.2%), bone and joint infections (13.4%), bloodstream infections (10.7%), endocarditis (6.8%) and pneumonia (6.8%). Females were slightly older (median 73.0 *vs* 70.0 years, $P = .001$) and had a lower bodyweight (median 73.0 *vs* 85.3 kg, $P = <.001$) and a slightly higher baseline potassium concentration (median 4.2 *vs* 4.1 mmol/L, $P = .043$) compared to males. There were no differences between males and females in the number of potassium measurements per day of treatment or other variables. The median time to first potassium measurement after initiation of flucloxacillin was 1.4 days (IQR 0.6-2.6) and the median number of potassium measurements per day of treatment was 0.5 (IQR 0.27-0.80).

TABLE 1 Patient characteristics

n	835
Sex is male (%)	486 (58.2)
Age (median [IQR]), years	71.0 [61.0, 81.0]
Bodyweight (median [IQR]), kg	81.7 [69.9, 95.0]
BMI (median [IQR]) kg/m^2	27.0 [24.0, 31.7]
eGFR (CKD-EPI) (median [IQR])	72.0 [45.0, 92.5]
Baseline potassium (median [IQR]), mmol/l	4.2 [3.9, 4.5]
Duration of treatment (median [IQR]), days	5.3 [2.6, 12.2]
Potassium measurements per day (median [IQR])	0.50 [0.27, 0.80]
Indication for flucloxacillin use (%)	
Skin or soft tissue infections	453 (54.2)
Bone and joint infections	112 (13.4)
Bloodstream infections	89 (10.7)
Endocarditis	57 (6.8)
Pneumonia	57 (6.8)
Other	50 (6.0)
Unknown	17 (2.0)
Dose per day (%)	
≤4 g	383 (45.9)
4-8 g	360 (43.1)
>8 g	92 (11.0)
Diuretics (%)	
No diuretics	526 (63.0)
Thiazide diuretics	218 (26.1)
Loop diuretics	54 (6.5)
Potassium-saving diuretics	37 (4.4)
Other antibiotics (%)	476 (57.0)
Acetaminophen (%)	670 (80.2)
Beta-blockers (%)	350 (41.9)
Corticosteroids (%)	127 (15.2)
Laxatives (%)	551 (66.0)
Potassium supplements (%)	38 (4.6)

Abbreviations: BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

3.2 | Incidence of hypokalaemia and sex differences

The incidence of hypokalaemia was 23.7% in the total population and higher in females (28.4% *vs* 20.4%, $P = .009$; Table 2). The incidences of moderate and severe hypokalaemia were 8.6% and 1.3% and incidence was also increased in females compared to males (11.5% *vs* 6.6%, $P = .019$ and 2.3% *vs* 0.6%, $P = .074$, respectively). The median time to hypokalaemia was 3.0 days (IQR 1.8-6.0) and 83% of cases of hypokalaemia occurred within 7 days after the initiation of flucloxacillin.

3.3 | Risk factors

Sex, age, bodyweight, eGFR, duration of treatment, baseline potassium, concomitant antibiotics, diuretics, corticosteroids, beta-blockers, laxatives or potassium supplementation and flucloxacillin dose were included in the multivariable logistic regression analysis (Table 3). Flucloxacillin serum concentration was omitted because a flucloxacillin measurement was only available in 16% of patients. The final model after backwards deletion contained age, bodyweight, baseline potassium, treatment duration, concomitant antibiotics use, concomitant beta-blocker use, average number of potassium measurements per day of treatment and an interaction between sex and flucloxacillin dose. The calculated ORs revealed that age increased the risk of hypokalaemia by 2% per year, longer duration of therapy increased the risk by 4% per day, a decrease of 1 kg bodyweight increased the risk by 1% and a 1 mmol/L higher baseline potassium concentration decreased the risk by 61%. Concomitant use of other antibiotics increased the risk of hypokalaemia by 65% (Table 3).

Female sex was not an independent risk factor for flucloxacillin-induced hypokalaemia. However, a statistical interaction between dose and sex explained the differences in incidence of flucloxacillin-induced hypokalaemia between sexes. A higher flucloxacillin dose combined with female sex was associated with an increased incidence of hypokalaemia. In females receiving a flucloxacillin dose of more than 8 g/24 h the OR for hypokalaemia was 8.46 (3.00-23.89) compared to males receiving 0-4 g/24 h and 4.41 (1.47-13.24) compared to males receiving >8 g/24 h. No sex differences were found in patients receiving 0-8 g/24 h (Table 4). In the sensitivity analysis with dose divided by weight as alternative measure of flucloxacillin exposure (see **Supporting Information File**), there was no interaction between female sex and dose divided by weight ($P = .126$). However, there was an association between female sex and hypokalaemia (OR 1.79, confidence interval 1.22-2.64, $P = .003$).

3.4 | Flucloxacillin concentrations

Flucloxacillin concentrations were available in 16% of patients. The different concentrations for patients with and without hypokalaemia as well as for males and females are shown in Figure 1A,B. Increased flucloxacillin concentrations were found both in patients with hypokalaemia and in females.

4 | DISCUSSION

In this retrospective cohort study, we investigated the incidence, sex differences and risk factors for hypokalaemia in 835 patients receiving intravenous flucloxacillin in a large teaching hospital in the Netherlands. To our knowledge, this is the largest study investigating hypokalaemia in flucloxacillin-treated patients and the first that focuses on establishing risk factors. We found that the incidence of hypokalaemia was 23.7%. As this is notably higher than previous reports (approximately 13.5%), our study confirms that intravenous flucloxacillin treatment is associated with an increased risk of developing hypokalaemia.[1,5] The incidence of hypokalaemia in our study was lower compared to the cohort study from Van der Heijden et al (23.7% *vs* 42%).[5] As flucloxacillin-induced hypokalaemia is considered to develop dose-dependently, this difference is likely explained by the inclusion of patients with high-dose flucloxacillin only (≥6 g/24 h) in the study by Van der Heijden et al.[5] This assumption is confirmed by the incidence of 50% in the subgroup with high-dose flucloxacillin (>8 g/24 h) in our study.

Flucloxacillin-induced hypokalaemia was more prevalent in females when receiving a high daily dose (>8 g). Being a non-reabsorbable anion, flucloxacillin causes a potential gradient in the collecting duct of the nephron, leading to increased renal potassium excretion and exhausting the bodies exchangeable potassium storage. Based on the pathophysiological mechanism of this adverse event, it is most likely a dose-dependent effect. Several studies investigating total body potassium concentration have found that other than bodyweight, both increasing age and female sex are associated with a lower total body potassium level.[17–19] This may be explained by an absolute and relative increase in fat and a reduced muscle mass.[19,20] We hypothesize that the amount of renal excreted anions in high-dose flucloxacillin therapy exceeds a threshold, causing potassium excretion to an extent where the body is unable to correct the plasma potassium concentration and resulting in hypokalaemia. In females this threshold is lower compared to males because of differences in bodyweight and body composition. This

TABLE 2 Incidence of hypokalaemia in patients treated with intravenous flucloxacillin (%)

n	Total 835	Male 486	Female 349	*P*
Hypokalaemia (<3.5 mmol/L)	198 (23.7)	99 (20.4)	99 (28.4)	.009
Moderate hypokalaemia (<3.0 mmol/L)	72 (8.6)	32 (6.6)	40 (11.5)	.019
Severe hypokalaemia (<2.5 mmol/L)	11 (1.3)	3 (0.6)	8 (2.3)	.074

TABLE 3 Logistic regression analysis to investigate the association between variables and hypokalaemia

	Univariate analysis			Multivariable analysis		
	OR	CI	*P*	OR	CI	*P*
Sex						
Male	1 (ref.)			1 (ref.)		
Female	1.55	(1.12-2.13)	.008	1.03	(0.57-1.86)	.928
Age (years)	1.03	(1.01-1.04)	<.001	1.02	(1.01-1.04)	<.001
Weight (kg)	0.98	(0.97-0.99)	<.001	0.99	(0.98-1.00)	.018
BMI (kg/m^2)	0.96	(0.93-0.99)	.007			
Baseline potassium (mmol/L)	0.51	(0.38-0.73)	<.001	0.39	(0.26-0.60)	<.001
eGFR (ml/min/1.73m^2)	0.99	(0.99-1.00)	.027			
Treatment duration (days)	1.04	(1.03-1.06)	<.001	1.04	(1.03-1.06)	<.001
Potassium measurements per day of flucloxacillin	1.20	(0.95-1.50)	.117	1.59	(1.16-2.18)	.004
Daily dose						
≤4 g	1 (ref.)			1 (ref.)		
4-8 g	1.36	(0.95-1.95)	.089	0.88	(0.50-1.56)	.660
>8 g	4.55	(2.81-7.41)	<.001	1.92	(0.96-3.83)	.0
Other antibiotics						
No antibiotics	1 (ref.)			1 (ref.)		
Other antibiotics	2.16	(1.54-3.07)	<.001	1.65	(1.11-2.44)	.013
Paracetamol						
No paracetamol use	1 (ref.)					
Paracetamol use	0.79	(0.54-1.17)	.231			
Diuretics						
No diuretics	1 (ref.)					
Loop diuretics	2.05	(1.40-2.86)	<.001			
Thiazide diuretics	1.32	(0.66-2.49)	.412			
Potassium saving diuretics	2.00	(0.94-4.03)	.061			
Beta-blockers						
No beta-blocker use	1 (ref.)			1 (ref.)		
Beta-blocker use	1.46	(1.06-2.01)	.021	1.42	(0.96-2.09)	0.076
Corticosteroid						
No corticosteroid use	1 (ref.)					
Corticosteroid use	1.27	(0.82-1.93)	.269			
Laxatives						
No laxatives use	1 (ref.)					
Laxatives use	1.41	(1.00-2.02)	.052			
Potassium supplementation						
No potassium supplementation	1 (ref.)					
Potassium supplementation	1.16	(0.53-2.35)	.700			
Additional						
Interaction female sex*dose = 4-8 g[a]				1.58	(0.71-3.54)	.265
Interaction female sex*dose = >8 g[a]				4.29	(1.23-14.91)	.022

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
[a]Statistical interaction: the effect of one variable on the outcome is dependent on the value of another variable.

results in a relatively lower amount of total body potassium, and thus females are more prone to flucloxacillin-induced hypokalaemia, as found in this study.

Three factors could have contributed to the observed sex differences in patients receiving >8 g/24 h flucloxacillin. First, sex-dependent reduced potassium intake and/or gastrointestinal

TABLE 4 Multivariate odds ratios for hypokalaemia stratified by sex and dose[a]

	Male	Female	OR F to M within strata of dose
≤4 g	1 (reference)	1.03 (0.57-1.86)	1.03 (0.57-1.86)
4-8 g	0.88 (0.50-1.56)	1.43 (0.81-2.53)	1.62 (0.92-2.88)
>8 g	1.92 (0.96-3.83)	8.46 (3.00-23.89)	4.41 (1.47-13.24)

Abbreviations: F, female; M, male; OR, odds ratio.

[a]Corrected for age, bodyweight, baseline potassium concentration, treatment duration and stratified over the use of other antibiotics and beta blockers.

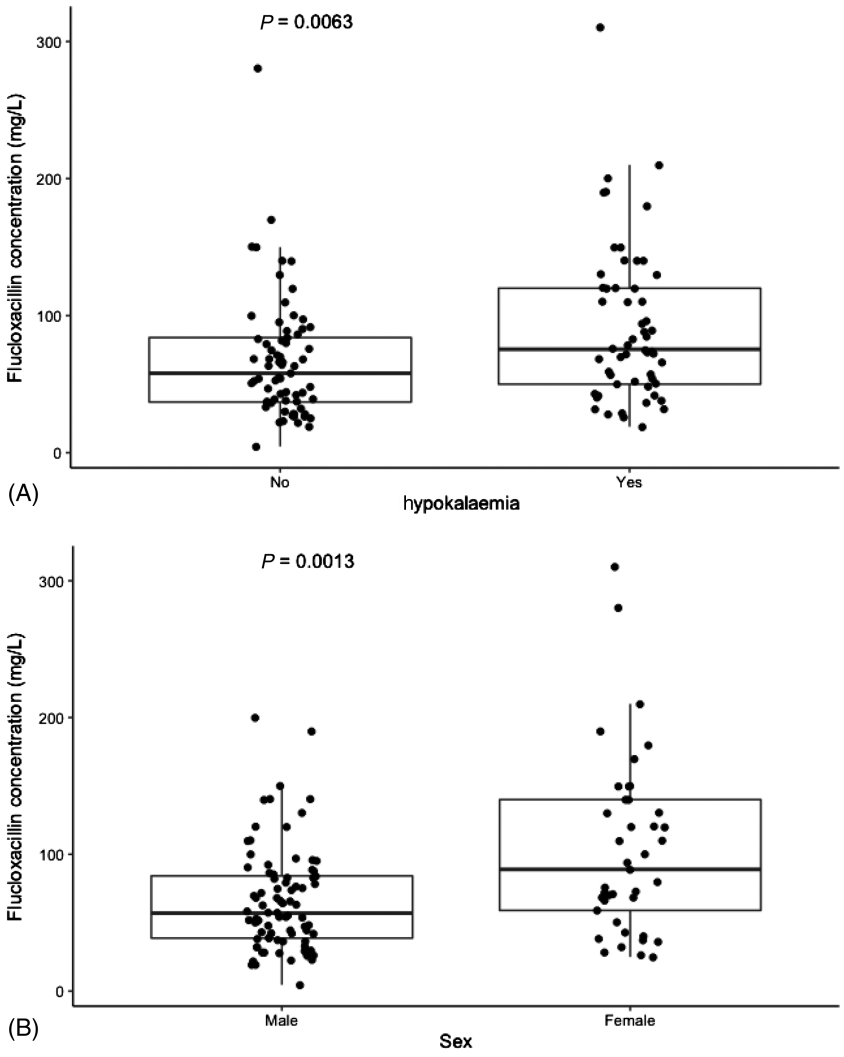

FIGURE 1 (A) The first serum flucloxacillin concentration after initiation of therapy in patients with or without hypokalaemia. (B) The first serum flucloxacillin concentration after initiation of therapy in males compared to females

potassium loss in case of vomiting or diarrhoea and/or intolerance of high dose flucloxacillin may also have led to hypokalaemia.[21] Second, animal studies investigating the influence of oestrogen and progesterone on plasma potassium found sex differences related to aldosterone-initiated renin-angiotensin-aldosterone system (RAAS) activation which could have influenced the compensation mechanisms following flucloxacillin-induced potassium excretion.[22] Third, sex-related differences in metabolism, protein binding and transporter affinity have been documented for several drugs.[20] For flucloxacillin this could lead to an alternative distribution, and differences in the free fraction and ratio between flucloxacillin and metabolites. As a result, this may alter the amount of renal excreted nonreabsorbable anion and thereby the amount of excessive potassium excretion.

Other identified risk factors for hypokalaemia in our study were lower baseline potassium, older age, lower bodyweight, use of concomitant antibiotics and longer treatment duration. Older age is a known risk factor for hypokalaemia and caused by the age-related reduction of muscle mass and as such total body potassium.[14,17,18] Lower bodyweight leads to a relative increased flucloxacillin exposure (dose/kg) and reduced capacity to correct potassium imbalances.[17] Several classes of antibiotics (eg, penicillins, glycopeptides and

aminoglycosides) have also been associated with an increased risk of hypokalemia.[2,23,24] Even though both thiazide and loop diuretics are known risk factors for hypokalaemia, the use of any type of diuretics was not an independent risk factor for flucloxacillin-induced hypokalaemia in our study.[25]

Recent pharmacologic studies showed that in a majority of patients, a reduction of the flucloxacillin dose would still lead to attainment of the optimal pharmacodynamic endpoint.[26,27] Also, our study and other reports suggest an increased risk of adverse events with a higher flucloxacillin dose and flucloxacillin concentration.[27,28] Although the flucloxacillin concentration measurements in our study were limited, Figure 1A suggests that higher flucloxacillin concentration is associated with hypokalaemia. Future studies investigating the optimal individualized, bodyweight adjusted or sex-specific flucloxacillin dose are needed. This knowledge could help to avoid dose-dependent side effects, which are a result of historically accepted and potentially unnecessarily high flucloxacillin dosing regimens.

This study has several limitations First, hypokalaemia is a surrogate endpoint that might be a subclinical phenomenon. Data on clinical outcomes of patients who developed flucloxacillin-induced hypokalaemia were not available and should therefore be collected in future studies. Second, data collection with CTcue was limited as data from ICU patients or patients treated in the outpatient setting could not be collected. Third, the retrospective design and the selection of patients with baseline and follow-up potassium measurements made it impossible to prevent detection bias and potentially missed cases of hypokalaemia. Prospective studies are needed to verify the incidence rate found in this study.

5 | CONCLUSION

The incidence of hypokalaemia in patients treated with intravenous flucloxacillin is high and mostly occurs during the first week of flucloxacillin therapy. This study has identified older age, lower bodyweight, lower baseline potassium, longer treatment duration and concomitant antibiotic use as independent risk factors, and discovered a dose-dependent association between sex and the incidence of hypokalaemia. Among females the risk of developing flucloxacillin-induced hypokalaemia was increased compared to males when a daily dose of >8 g/24 h was administered. Clinicians should therefore closely monitor patients at risk of flucloxacillin-induced hypokalaemia, especially during the first week of treatment.

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COMPETING INTERESTS

None to declare.

CONTRIBUTORS

L.E.V. conceived the study. L.E.V., E.L., A.C.W., E.F.S. and C.vN. designed the study. E.L. collected and analysed the data. E.L. and A.C.W. wrote the manuscript. All authors critically read and adjusted the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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