Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics

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Objectives: To describe the total and unbound plasma concentration–time profiles for highly protein-bound flucloxacillin (95%–97% protein binding) in critically ill patients with hypoalbuminaemia and without severe renal dysfunction, and to use population pharmacokinetic modelling and Monte Carlo simulations to assess the probability of target attainment against an MIC distribution.

Patients and methods: Ten patients with hypoalbuminaemia and receiving flucloxacillin as part of therapy were enrolled. Sixty-seven total, 67 unbound plasma and 10 urine samples were collected and analysed. Population pharmacokinetic modelling of unbound plasma data and Monte Carlo simulations were then undertaken with NONMEM®. Non-compartmental pharmacokinetic analysis was performed for total plasma concentrations.

Results: Total flucloxacillin V was increased in critically ill patients with hypoalbuminaemia 2-fold compared with healthy volunteer data. Unbound flucloxacillin concentrations after 2 g bolus fell below 1 mg/L 4 h after the end of the infusion, providing evidence that standard dosing would be insufficient for the treatment of methicillin-susceptible Staphylococcus aureus (MSSA) (MIC = 2 mg/L). Monte Carlo simulations suggest that continuous infusion of 8 g/24 h flucloxacillin would enable 100% successful attainment of the pharmacodynamic target, 50% fT MIC. For more aggressive targets (4–5× MIC for 100% fT MIC), continuous infusion of higher doses (i.e. 12 g/24 h) would be required.

Conclusions: Administration of standard doses by intermittent bolus is likely to result in underdosing, and continuous infusion of higher doses is more likely to achieve pharmacokinetic–pharmacodynamic targets for the treatment of infections caused by the most common wild type of MSSA. Our data emphasize the importance of using unbound concentrations for determining dosage regimens for highly bound antibiotics.

Keywords: β-lactams, protein binding, albumin, population pharmacokinetics, pharmacodynamics, intensive care units

Introduction

Flucloxacillin is an isoxazolyl penicillin frequently prescribed for treatment of many infections caused by Gram-positive species, such as streptococci and penicillinase-producing staphylococci including methicillin-susceptible Staphylococcus aureus (MSSA).1 Flucloxacillin has shown more rapid killing activity against MSSA and much less toxicity than vancomycin,2 and is therefore considered the preferred option for the treatment of severe infections produced by non-resistant bacteria. The pharmacokinetic–pharmacodynamic behaviour of flucloxacillin is time dependent, where antibacterial activity is related to the time for which the unbound (pharmacologically active) concentration is maintained above the MIC during a dosing interval (fT > MIC).3 The fT > MIC required for optimal bactericidal activity for penicillins has been reported to be 50%–60% from in vitro and in vivo animal models.4

In vitro and healthy volunteer studies have shown that flucloxacillin is 95%–97% bound to plasma albumin.5–7 The extent of binding to plasma proteins is highly relevant, as it is the unbound fraction of drug that produces the pharmacological effect.5 The unbound fraction would typically correspond to...
3%–5% of the total flucloxacillin concentration in patients with normal plasma albumin levels (>42 g/L). However, in critically ill patients, hypoalbuminaemia is frequently observed. Data from the SAFE study indicated that between 40% and 50% of patients in the intensive care unit (ICU) had low albumin plasma concentrations (<25 g/L). Lower albumin concentrations might alter the extent to which flucloxacillin is bound to this protein and, therefore, lead to variations in the unbound fraction of antibiotic that may consequently affect its pharmacokinetics and pharmacodynamics. That effect may be additive to the significant variations in pharmacokinetics observed in critically ill patients due to several factors such as the presence of a systemic inflammatory response syndrome (SIRS), fluid resuscitation or the use of inotropes.

The effects of hypoalbuminaemia on the pharmacokinetics of other highly bound antibiotics have been reported previously, and suggest a potential risk for inappropriate antibiotic therapy in patients with hypoalbuminaemia. Studying this concept, Joyn et al. observed a substantial decrease in the \( T_{1/2} \text{MIC} \) of total ceftriaxone concentrations in critically ill patients with hypoalbuminaemia that led to failure to attain pharmacokinetic–pharmacodynamic targets. However, a dearth of data exists providing pharmacokinetic–pharmacodynamic simulations for unbound concentrations of highly protein-bound drugs. It follows that where such analyses are conducted on total concentrations without accurate knowledge of the free fraction of antibiotic, misinterpretation of the ability of particular dosing schedules to achieve target antibiotic exposures is highly likely.

Similar to ceftriaxone, flucloxacillin binds significantly to plasma albumin and we hypothesize that altered pharmacokinetics may also occur with this antibiotic. However, despite its use in the ICU, no data are available on the pharmacokinetic variability of the unbound fraction of flucloxacillin in critically ill patients with hypoalbuminaemia, or the ability of empirical dosing schedules to achieve pharmacokinetic–pharmacodynamic targets likely to be associated with maximal efficacy.

The aims of this study were: (i) to describe the concentration–time profiles for total and unbound flucloxacillin administered to critically ill patients with hypoalbuminaemia and without severe renal dysfunction; (ii) to describe the pharmacokinetic variability of unbound flucloxacillin concentrations in this cohort using a population pharmacokinetic model; and (iii) to assess the plasma pharmacokinetic–pharmacodynamic profile of various flucloxacillin dosing regimens and to assess the expected probability of target attainment (PTA) by MIC against MSSA.

**Drug administration and dosage**

All patients received flucloxacillin (Flucil IV; Aspen, Sydney, Australia). Dosing was at the discretion of the treating intensivist. Flucloxacillin was administered over 30 min through a separate lumen of a central venous catheter using a volumetric infusion pump controller (Gemini PC2, Imed; Alaris Medical Systems, San Diego, CA, USA).

**Blood and urine sampling**

Five millilitres of blood was collected using the indwelling arterial catheter for each blood sample for determination of total and unbound plasma flucloxacillin concentrations at apparent steady state. Steady state was assumed to have been achieved after five drug half-lives, or five doses, in this constant multiple-dosing schedule. In this study, we assumed steady state had been reached after the first 24 h of treatment (half-life in healthy volunteers reported to be 1.6 h). Timed samples were collected at 0, 15, 30, 60, 90 and 120 min after the 30 min infusion. For patients who were prescribed flucloxacillin every 4 h, a trough sample at 180 min after the infusion was collected (30 min prior to the following dose); while for patients prescribed flucloxacillin every 6 h this sample was taken at 300 min after the infusion (30 min prior to the following dose). Specimens were put directly on ice after sampling. Within 1 h of collection, samples were centrifuged at 3000 rpm at 4 °C for 10 min and the plasma was frozen at −80 °C. All samples were assayed individually.

**Drug assay**

Total and unbound concentrations in plasma and urine were measured using a validated analytical method.

**Sample preparation**

For determination of the total concentration of flucloxacillin in plasma, a 100 μL aliquot of plasma with buffered internal standard (dicloxacillin; Diclocil®; Bristol-Myers Squibb, Australia) was precipitated with acetonitrile, washed thereafter with dichloromethane and injected. The unbound concentration was measured by direct injection of the filtrate obtained after filtering 400 μL of plasma heated at 37 °C in a water bath (to reproduce body temperature and avoid variations in albumin binding due to temperature) at 12 000 rpm for 5 min using a Microcon® centrifugal filter device with Ultracel YM-10 membrane (Millipore Corporation, Billerica, MA, USA). Urine concentration was measured by direct injection of the urine samples diluted 1:10 with blank urine.

**Sample bioanalysis**

Total and unbound flucloxacillin concentrations in plasma and urine were measured using HPLC (Shimadzu Prominance HPLC system). The stationary phase was a 2.5 mm Waters XBridge C18 (30×4.6 mm) 2.5 μm column. The mobile phase was composed of 25% acetonitrile/75% phosphate buffer pH 3 with isotropic flow at a rate of 1 mL/min. Flucloxacillin and the internal standard (dicloxacillin) were detected by UV detection at \( \lambda = 220 \) nm.

**Method validation**

The precision and accuracy were determined by replicate injections of quality controls, and were within 10% for all matrices. The concentration...
function was linear in the range 0.5–500 mg/L for total flucloxacillin, 0.1–500 mg/L for unbound flucloxacillin and 5–10 000 mg/L for urine. The lower limits of quantification were 0.1 mg/L for unbound, 0.5 mg/L for total and 5 mg/L for urine concentration.

Pharmacokinetic and pharmacodynamic analysis

The unbound concentration versus time data for flucloxacillin in plasma were analysed using a non-linear mixed effects modelling approach using NONMEM (Version 6.1; GloboMax LLC, Hanover, MD, USA) with double precision with the COMPAQ VISUAL FORTRAN compiler. The NONMEM runs were executed using Wings for NONMEM (WFN 6.1.3). Data were analysed using the first-order conditional estimation (FOCE) method with INTERACTION.

For the population pharmacokinetic analysis, one-, two- or three-compartment linear and non-linear models were fitted to unbound plasma flucloxacillin concentrations using subroutines from the NONMEM library. The concentration–time profile can be described as (Eqn 1):

\[ y_{ij} = f_i(\theta, x_{ij}) + e_{ij} \]  

where \( y_{ij} \) is the \( j \)th observed concentration at timepoints \( x_{ij} \) for the \( i \)th subject. Also, \( \theta \) represents fixed effects parameter of the structural model to be estimated. \( f_i \) is the function for the prediction of the \( j \)th response for the \( i \)th subject. Finally, \( e_{ij} \) denotes the \( j \)th measurement error for the \( i \)th subject. In other words, \( e_{ij} \) is the difference of the observed concentration from the predicted concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance \( \sigma^2 \).

### Between-subject variability (BSV)

BSV was modelled using an exponential variability model (Eqn 2):

\[ \theta_i = \theta \cdot e^{h_i} \]

where \( \theta_i \) is the value of the parameter for the \( i \)th subject, \( \theta \) is the typical value of the parameter in the population and finally \( h_i \) is a random vector with normal distribution, zero mean and variance–covariance matrix of BSV \( \Omega \) to be estimated. Between-occasion variability was not included as sampling occurred on only one occasion for each patient.

Model diagnostics

Statistical comparison of nested models was based on a \( \chi^2 \) test of the difference in the objective function value (OFV). A decrease in the OFV of 3.84 units (\( P < 0.05 \)) was considered significant.

Goodness-of-fit was evaluated by visual inspection of graphs of the predicted versus observed concentration values and a visual predictive check.

Bootstrap

A non-parametric bootstrap method (\( n = 1000 \)) was used to study the uncertainty of all pharmacokinetic parameter estimates. From the bootstrap empirical posterior distribution we have been able to obtain the 95% confidence interval (CI) (2.5%–97.5% percentile) for the parameters, as described previously.

Covariate screening

The covariates analysed were age, weight, body mass index (BMI), lean body weight, plasma albumin, Sepsis Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, plasma creatinine concentration, creatinine clearance (Cl_{cre}) measured by 4 or 6 h urine collection and plasma bilirubin concentration. The individual covariates were centred by the median or standard values. Individual empirical Bayesian (POSTHOC) parameters were plotted against covariate values to assess relationships. If a trend between covariates and pharmacokinetic parameters was observed, then it was considered for inclusion in the population model. Possible covariates were added in a stepwise fashion into the model. Covariates were kept in the model if there was a significant improvement in the fit over the base model, i.e. decrease in OFV and/or decrease in the BSV of the parameter of at least 10%.

Dosing simulations

Dosing simulations of unbound concentration data were performed. Four extended infusion and three continuous infusion dosing regimens were simulated using Monte Carlo simulations. The four intermittent bolus infusion dose regimens (infusion over 30 min) evaluated were 1000 mg every 6 h, 1000 mg every 4 h, 2000 mg every 6 h and 2000 mg every 4 h. The three continuous infusion regimens evaluated were 8000 mg, 12 000 mg and 16 000 mg of flucloxacillin every 24 h (including a loading dose of 1000 mg). Each Monte Carlo simulation generated unbound concentration–time profiles for 1000 subjects per dosing regimen using the parameters from the final covariate model. From this data the \( T_{\text{MIC}} \) was calculated for each simulated subject using linear interpolation. The PTA was obtained by counting the subjects who achieved 50% \( T_{\text{MIC}} \).

Results

### Patient demographics

Ten patients who were administered flucloxacillin for the treatment of confirmed MSSA infections were enrolled. Dosing was undertaken at the discretion of the clinician and varied between each of the patients. Five patients were prescribed flucloxacillin 2 g every 4 h, three patients were prescribed 1 g every 6 h and two patients were prescribed 2 g every 6 h. All patients were ventilated and fulfilled the criteria for hypoalbuminaemia and absence of severe renal dysfunction (see Table 1). After the first four samples were taken, one of the patients refused to continue in the study and no further samples were collected. The mean duration of flucloxacillin therapy was 17.7 ± 17.3 days (mean ± SD).

Drug concentrations

In total, 67 total plasma, 67 unbound plasma and 10 urine samples were analysed. The observed concentration–time profiles for all patients are shown in Figure 1 (total and unbound concentration). The mean clearance (CL), volume of distribution (V) and half-life (\( t_{1/2} \)) for total flucloxacillin concentrations calculated by non-compartmental analysis are described in Table 2. The values for these parameters in other populations are also included in the table for comparative purposes. The relationship between percentage protein binding and plasma albumin levels was found to be linear, with \( r^2 \) values of 0.5691.

No relationship was found between flucloxacillin total CL and creatinine CL measured by 4 or 6 h urinary creatinine CL (\( r^2 = 0.002 \)).
Pharmacokinetic modelling was performed using the data from the 67 unbound plasma concentration samples. The OFV for the one-compartment model was 305.638 and for the two-compartment model was 213.716 (statistically significant change required is 3.84). The best base model, based on the model building criteria, consisted of a two-compartment linear model with exponential residual unexplained variability (RUV). Other linear or non-linear models could not be supported, as they did not result in an improvement in the OFV or BSV. The model supported between-subject variability on clearance (CL) and inter-compartmental clearance (Q) only. The final OFV for this model was 156.935.

The covariate that most significantly influenced flucloxacillin CL was BMI normalized to 22.5 kg/m². The addition of this parameter resulted in a non-significant reduction in the OFV but reduced BSV for CL by 12% and was thus deemed appropriate for inclusion. Total body weight normalized to 70 kg improved BSV by 10%, which was smaller than the improvement resulting from addition of normalized BMI, and therefore normalized BMI was deemed more appropriate for inclusion. The addition of any other covariates in the model could not be statistically supported. The final model was represented by Eqn 3:

\[ TVCL = CL \cdot \left(\frac{BMI}{22.5}\right) \]

where TVCL is the typical value of CL.

Goodness-of-fit plots for the final model were evaluated and showed no unacceptable results in terms of visual or statistical biases for the prediction. These plots show that the final pharmacokinetic model describes the measured flucloxacillin unbound concentrations adequately (Figure 2). The values of the parameters and 95% CIs from the bootstrap runs for the final covariate model are given in Table 3. It should be noted that the population pharmacokinetic model did not accurately describe the unbound concentration–time profile for patient 8. Patient 8 was an older patient, and had a moderate degree of organ dysfunction, which may affect drug metabolism and elimination. All subsequent flucloxacillin Monte Carlo dosing simulations were then based on this model.

### Dosing simulations and PTA

PTA versus MIC profiles for dosing simulations for seven different dose regimens (four intermittent bolus infusion and three continuous infusion administration) of different doses of flucloxacillin are represented in Figure 3. These results suggest that continuous infusion achieved higher pharmacokinetic–pharmacodynamic targets (100% success) against strains of MSSA than intermittent dosing. Low doses such as 1 g 6 hourly and

<table>
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<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Dose</th>
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<th>SOFA score at time of sampling</th>
<th>Diagnosis</th>
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<th>CLCR (mL/min)</th>
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<td>—</td>
<td>16.8–21</td>
<td>5.3–10.3</td>
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<td>50.5–86.3</td>
<td>109–148.5</td>
<td>19.3–22.8</td>
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M, male; F, female; V AP, ventilator-associated pneumonia; IQR, interquartile range; q6h, every 6 h; q4h, every 4 h.

![Figure 1. Observed unbound concentrations for 2 g (n=7; filled squares, continuous line) and 1 g (n=3; open circles, broken line) of flucloxacillin administered to critically ill patients with hypoalbuminaemia and without renal dysfunction.](https://academic.oup.com/jac/article-abstract/65/8/1771/740193/1774)

![Table 1. Demographic and clinical data](https://academic.oup.com/jac/article-abstract/65/8/1771/740193/1774)
1 g 4 hourly were sufficient for the treatment of pathogens with low MIC (0.0625–0.5 mg/L), but failed in the attainment of the pharmacokinetic–pharmacodynamic target against those with intermediate MIC (1–4 mg/L). For pathogens with intermediate MIC (2–4 mg/L), administration of high doses (≥ 8 g/24 h) by continuous infusion was required to achieve optimal pharmacodynamic targets.

**Discussion**

The data presented in this study provide support for previous studies on altered pharmacokinetics of highly protein-bound antibiotics in critically ill patients with hypoalbuminaemia.\(^\text{12–18}\)

Total flucloxacillin V was significantly larger in our cohort of patients compared with healthy volunteers\(^\text{20}\) and other hospitalized, non-critically ill patients,\(^\text{24}\) as shown in Table 2. This increase in V may be related, in part, to an increased unbound fraction of flucloxacillin resulting from low plasma albumin levels. It follows that because unbound drug is the fraction available for distribution and clearance, the higher fraction of unbound flucloxacillin will be able to distribute to peripheral tissues to a greater extent and explain the larger V.\(^\text{25–27}\)

Interestingly, we did not observe any significant variation between total flucloxacillin CL in hypoalbuminaemic critically ill patients compared with previous data from healthy volunteers.\(^\text{20}\) This is despite data from other antibiotics that suggest that...
a higher unbound fraction will lead to increased CL because only the unbound molecule is glomerularly filtered.\(^2\) We have attributed this curious finding to the multiple excretion pathways of flucloxacillin. Flucloxacillin is eliminated by renal (glomerular filtration and tubular secretion, \(~\sim 40\%\) recovery in urine)\(^2\) and non-renal mechanisms (where hepatic metabolism accounts for \(30\%–40\%\) of total CL).\(^3\) Therefore, an increase in the glomerular filtration rate resulting from a higher unbound fraction of flucloxacillin might not be significant enough to alter the total CL, as observed in these patients. However, clarification of this observation can only be achieved by comparison of unbound concentrations between hypoalbuminaemic critically ill patients and healthy volunteers. Our results are in agreement with a previous study in patients with severe renal failure (CL\(_{\text{CR}}\) \(=\) 10–15 mL/min) that compared flucloxacillin pharmacokinetics with a patient with normal renal function and demonstrated that dose reduction is not required in renal failure.\(^4\)

This study is the first to describe the pharmacokinetics of unbound flucloxacillin in critically ill patients with hypoalbuminaemia. There are no equivalent data available in healthy volunteers or other patient populations to compare with our results. However, Figure 1 shows that \(<\) 4 h after administration of flucloxacillin the unbound concentrations of 6/10 patients have fallen below 1 mg/L, which is lower than the defined MIC for wild-type MSSA (2 mg/L) reported by both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the CLSI.\(^3\) Therefore, the achievement of the pharmacokinetic–pharmacodynamic target of 50% \(f_{T_{>\text{MIC}}\text{MIC}}\) is likely to be compromised in 6-hourly dosing regimens in this patient population. Furthermore, we chose 50% \(f_{T_{>\text{MIC}}\text{MIC}}\) as a conservative pharmacokinetic–pharmacodynamic breakpoint, but recent retrospective data from McKinnon et al\(^3\) of other \(\beta\)-lactam antibiotics in critically ill patients suggest that a pharmacokinetic–pharmacodynamic target of 100% \(f_{T_{>\text{MIC}}\text{MIC}}\) for \(\beta\)-lactam antibiotics is associated with better clinical and bacteriological outcomes. It follows that both 1 and 2 g dosing would be suboptimal for the treatment of MSSA with MIC \(\geq 2\) mg/L when aiming for more aggressive pharmacokinetic–pharmacodynamic targets. The results of the Monte Carlo simulations and PTA suggest that a 1 g loading dose followed by continuous infusion of 8 g/24 h flucloxacillin would be sufficient for 100% success in attainment of 50% \(f_{T_{>\text{MIC}}\text{MIC}}\) for the treatment of MSSA for which the MIC = 2 mg/L. Furthermore, for intermediately susceptible MSSA strains (MIC 2–4 mg/L), the probability of pharmacodynamic target attainment dramatically falls with administration of the highest bolus doses (2 g every 4 h), while continuous infusion of lower doses (i.e. 8 g/24 h) maintains 100% (Figure 3) achievement of pharmacodynamic targets. These data suggest that if flucloxacillin is prescribed for the treatment of intermediately susceptible MSSA, administration by continuous infusion would be advisable. In addition, the results of other in vitro and clinical studies with \(\beta\)-lactams suggest that maintaining sustained antibiotic concentrations of 4–5× MIC for extended

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<th>Parameter</th>
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<td>RUV (additive)</td>
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CV, coefficient of variation.

Figure 3. Probability of target attainment for unbound flucloxacillin administered by intermittent bolus infusion (infused over 30 min) or continuous infusion. All continuous infusion doses initially received a 1000 mg loading dose. The chosen target for analysis was 50% \(f_{T_{>\text{MIC}}\text{MIC}}\) for plasma concentrations. Please note that the 12 000 mg/24 h and the 16 000 mg/24 h lines overlap.

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periods of the dosing interval is associated with optimal bacterial killing, for which reason, concentrations higher than the MIC should be targeted. For the treatment of MSSA with an MIC of 2 mg/L, maintenance of a trough level (100% \( f_{T > MIC} \)) of 8–10 mg/L is suggested. Therefore, loading doses followed by higher doses administered in continuous infusion (i.e. 12 g/24 h) might be necessary for the attainment of this combined pharmacokinetic–pharmacodynamic target for less susceptible MSSA strains. Unlike other \( \beta \)-lactams, such as meropenem, where stability is problematic, flucloxacillin is suitably stable in saline solution for up to 24 h at room temperature. Due to the relationship between underdosing and development of antibiotic resistance, optimization of flucloxacillin dosing in this cohort of patients is strongly recommended. This may be facilitated using therapeutic drug monitoring of unbound flucloxacillin trough levels and titrating dose thereafter as a strategy to achieve the pharmacokinetic–pharmacodynamic breakpoints.

**Limitations of the study**

The small cohort of 10 patients could be considered a limitation of this study given the variability of different levels of patient sickness severity and the constellation of clinical interventions that can affect patient pharmacokinetics. The small cohort may have also prevented other covariates from being shown to be significant and predictive of the variability of pharmacokinetic parameters. Due to the inclusion criteria of the study, the dose recommendations derived from the data analysis cannot be extrapolated to other critically ill patient populations such as patients with renal replacement therapy or albumin plasma levels >32 g/L. Finally, the increased \( V \) cannot be completely attributed to the effect of hypoalbuminaemia on the unbound concentration, as it is well known that increases in drug \( V \) in critically ill patients can be produced due to capillary leakage and fluid shifts due to the SIRS.

**Conclusions**

Contemporary clinical investigations highlight the importance of optimizing antibiotic dosing to further reduce morbidity and mortality in critically ill patients. Our study provides new information on the pharmacokinetics of highly protein-bound flucloxacillin in a homogeneous group of critically ill patients with hypoalbuminaemia. Important considerations include the use of data from pharmacologically active, unbound concentration, to assess flucloxacillin dosing in this patient population. The results of Monte Carlo dosing simulations using unbound plasma concentrations show that administration of high standard doses (i.e. 2 g 6 hourly) by intermittent bolus administration is likely to result in underdosing, whereas continuous infusion at a loading dose is more likely to achieve pharmacokinetic–pharmacodynamic targets for the treatment of infections caused by the most common wild-type MSSA (MIC = 2 mg/L). Furthermore, when choosing more aggressive pharmacokinetic–pharmacodynamic targets (4−5 × MIC for 100% \( f_{T > MIC} \)), administration of loading doses followed by high doses by continuous infusion may be even more clinically advantageous for flucloxacillin. Our data emphasize the importance of using unbound concentrations for determining dosage regimens for highly bound antibiotics in any patient population.

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**Transparency declarations**

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