Pharmacokinetic-pharmacodynamic target attainment and clinical outcomes in patients treated with oral flucloxacillin plus probenecid

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Running head: Flucloxacillin plus probenecid oral regimens

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What is already known about this subject?

- Probenecid, an inhibitor of organic anion transporters, can be used to increase half-life of penicillins such as flucloxacillin, in order to improve the attainment of pharmacokinetic-pharmacodynamic targets.
- There are limited data in the literature regarding the tolerability and efficacy of oral flucloxacillin and probenecid regimens outside of healthy volunteer studies.

What this study adds

- Flucloxacillin plus probenecid was well-tolerated in a cohort of patients treated for proven or probable staphylococcal infections.
- Through population pharmacokinetic modelling we have identified optimal dose regimens, which vary according to fat free mass and renal function.
- Dose regimens demonstrating high probability of target attainment may increase the applicability of oral antibiotic regimens for moderate-severe staphylococcal infections, but require confirmation in larger prospective studies.
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Abstract

Aim

Oral flucloxacillin may be co-administered with probenecid to increase flucloxacillin concentrations and increase attainment of pharmacokinetic-pharmacodynamic (PK-PD) targets. The aims of this study were to describe outcomes of patients treated with oral flucloxacillin plus probenecid as follow-on therapy from initial intravenous treatment, and to identify optimal dosing regimens when treating infections caused by susceptible Gram-positive organisms.

Methods

We performed a prospective observational study of adults treated with oral flucloxacillin 1000 mg and probenecid 500 mg 8-hourly (with food) for proven or probable staphylococcal infections. We developed a population pharmacokinetic model of free flucloxacillin concentrations within Monolix, in order to estimate probability of PK-PD target attainment (fT>MIC), and used Monte Carlo simulation to explore optimal dosing regimens.

Results

The 45 patients (73% male) had a median (range) age of 49 years (20 – 74), weight of 90 kg (59 – 167), fat free mass (Janmahasatian) of 65 kg (38 – 89) and eGFR (CKD-EPI) of 89 mL/min/1.73m2 (41 – 124). The most common infections were osteomyelitis (n=18, 40%) and septic arthritis (n=12, 27%). Forty patients (89%) were cured 30 days after completion of therapy. 10 (22%) experienced nausea which did not require treatment alternation. Free flucloxacillin clearance depended on allometrically-scaled fat free mass, and increased by 1% for each unit increase in eGFR.

Conclusion

Oral flucloxacillin and probenecid was well-tolerated and efficacious. Patients with higher fat free mass and eGFR may require four times daily dosing and/or therapeutic drug monitoring to ensure PK-PD target attainment.

1. Introduction

The treatment of soft tissue, bone, and joint infection attributable to *Staphylococcus aureus* constitutes a large proportion of the work performed by Infectious Diseases physicians in secondary care. In the post-acute phase of many severe infections, this treatment often takes the form of outpatient continuously administered intravenous (IV) therapy with antimicrobial agents like flucloxacillin or cefazolin.(1) Intermittent parenteral antimicrobial therapy (e.g., once or twice daily dosing of cefazolin, often with probenecid) for acute moderate *S. aureus* skin and soft tissue infection is often given in community-based facilities.(2,3) Outpatient IV approaches are cheaper than inpatient care but are nevertheless associated with considerable expense. In the 12 months to November 2019, Canterbury District Health Board, which provides publically-funded hospital services to a population of approximately 570,000 people in Canterbury (New Zealand), spent approximately NZD200,000 on flucloxacillin infuser devices (approximately NZD110 per device) for continuous home IV administration. This figure excludes costs associated with nursing, medical and pharmacy time, and the necessary equipment and overheads. Moreover, there are patient risks associated with the IV route, including thrombosis and infection.(1) In contrast, oral flucloxacillin is cheap (approximately NZD1 per day) but oral dosing introduces additional therapeutic uncertainty, due to pharmacokinetic variability of the oral route of administration, and potentially incomplete adherence.(4) A recent study suggested that it is not necessary to dose oral flucloxacillin on an empty stomach, which may improve adherence and tolerability.(5) Further study is required to establish reliable oral dose regimens (with or without probenecid), and the role of therapeutic drug monitoring in the outpatient setting, which may allow safe and effective application of this antimicrobial agent more widely.

Flucloxacillin is an isoxozolyl penicillin with activity against Gram-positive cocci, including methicillin-susceptible *S. aureus* and coagulase-negative staphylococci, and *Streptococcus pyogenes*.(6) As with other penicillins, it exhibits time-dependent bacterial killing. Flucloxacillin is highly protein bound and only unbound ('free') drug has antimicrobial activity.(7) For the treatment of *S. aureus* infection, it is suggested that free flucloxacillin concentrations should be above the minimum inhibitory concentration (MIC) for at least 30% of the dosing interval in stable, mildly ill, non-neutropenic patients, and at least 50% of the dosing interval for neutropenic or moderately ill patients.(8,9) The MIC_{90} of flucloxacillin for *S. aureus* is 0.5 mg/L.(10,11) Recent studies suggested that these targets would be difficult to achieve with oral dosing of up to 1000 mg four times daily.(5,12)

Probenecid competes with many β-lactam antimicrobials for renal tubular secretion (and other transport pathways) resulting in delayed β-lactam excretion and elevated blood concentrations.(13) Two studies have investigated the effect of probenecid on flucloxacillin concentrations in patients. In one small clinical study (n=6), the addition of probenecid 1000 mg twice daily to flucloxacillin 1000 mg twice daily was associated with a doubling of total flucloxacillin area under the concentration-time curve (AUC).(14) The addition of probenecid resulted in an average increase in free drug time above MIC_{90} ($fT>MIC_{90}$) from approximately 5.1 to 10.8 hours per 24 hours, based on an MIC_{90} of 0.5mg/L.(10) Free flucloxacillin concentrations were not measured directly, but were estimated from total flucloxacillin concentrations and an assumed protein binding of 0.95.(15,16) This study indicated that the addition of probenecid to this modest flucloxacillin dose will get closer to achieving a >50% free drug time above MIC_{90} PK-PD target. In our single-dose study in healthy volunteers (n=11) the addition of probenecid 500 mg to flucloxacillin 1000 mg resulted in an increase in the probability of target attainment of 0.5 mg/L for 30% of a 6-hour dose interval from ~70% to >95% and of 0.5 mg/L for 50% of a 6-hour dose interval from ~20% to ~90%.(12) When probenecid 500 mg and flucloxacillin 1000 mg were co-administered to these volunteers the probabilities of target attainment for 30% and 50% of 8-hour dose intervals were ~90% and ~60% respectively. [12] Collectively, these data suggest that moderate skin, soft tissue and bone infections due to *S. aureus* could be treated with an oral flucloxacillin plus probenecid combination at 8-hour or 6-hour dose intervals, thereby avoiding prolonged parenteral therapy, and that therapeutic drug monitoring could be used to assist clinical decision making.

The aims of this study were therefore to describe the tolerability and clinical outcomes associated with oral flucloxacillin and probenecid regimens for confirmed or suspected staphylococcal infection, and to explore PK-PD target attainment according to accepted targets associated with efficacy.

2. Materials and methods

2.1 Subjects

We prospectively recruited 45 patients who were treated with oral flucloxacillin plus probenecid for confirmed or suspected staphylococcal infections. An Infectious Diseases registrar or physician assessed each patient at enrolment and at subsequent outpatient clinic visits until completion of the treatment course.

Male or female patients were eligible for this study if they were:

1. Willing and able to provide informed written consent, AND

2. >18 years of age, AND

3. Appropriate to receive combined treatment with oral flucloxacillin plus probenecid (Infectious Diseases physician discretion) for one of the following indications:

   a. Primary treatment of mild to moderate skin or soft tissue infection (e.g. cellulitis, wound infection, abscess) or bone infection, OR

   b. Oral follow-on after initial IV treatment of severe skin, soft tissue, bone or joint infection, OR

   c. Oral follow-on after initial IV treatment of complicated *S. aureus* bacteraemia, OR

   d. Oral follow-on after initial IV treatment or primary treatment of diabetic foot infection suitable for management with flucloxacillin as the sole antimicrobial (*S. aureus* isolated from a wound)

   TOGETHER WITH

   a. Confirmed or suspected *S. aureus* or methicillin-sensitive coagulase-negative staphylococcus infection based on culture of pus, tissue, or blood, OR

   b. Clinical improvement with IV flucloxacillin in patients with suspected *S. aureus* infection without positive microbiology.

Patients were not eligible for recruitment if they had any of the following:

1. Likely inability to comply with the oral dosing regimen
2. Calculated creatinine clearance (CrCl; Cockcroft and Gault) of < 30 mL/min
3. Pregnancy or breastfeeding
4. A likely pathogenic isolate resistant to flucloxacillin (e.g., methicillin-resistant *S. aureus*)
5. Allergy to a penicillin or to probenecid
6. Requirement for long-term IV therapy e.g., to treat complicated S. aureus bacteraemia
7. Hepatic cirrhosis with impaired synthetic function
8. Recent gout (flare within 30 days) or gout requiring allopurinol
9. Severe immunocompromise, e.g., severe neutropenia
10. Concomitant medicines with a risk of adverse drug-drug interactions (e.g. methotrexate).

2.2 Dosing regimen

All patients were prescribed flucloxacillin 1000 mg plus probenecid 500 mg orally three times daily. Patients were advised to take the two drugs together with food, and as close as possible to 8-hourly.

2.3 Blood sampling

Blood samples (2 x 4.5 mL EDTA tubes) were taken via peripheral venepuncture for determination of total and free serum flucloxacillin concentrations at approximately 4 hours post-dose (mid-dosing-interval) on the day of a clinic appointment, and at least three days after commencement of oral combination therapy to ensure steady state. The exact timing of the preceding dose and the blood sample was recorded.

2.4 Flucloxacillin assay

Total and free serum flucloxacillin concentrations were determined using a validated liquid chromatography tandem mass-spectroscopy (LC-MS/MS) method with ultrafiltration used for separation of free (unbound) and bound flucloxacillin, as previously described.(17) Briefly, for the total flucloxacillin range of 0.2–100 mg/L, the intra– and inter-day bias and coefficient of variation (CV) were ≤6.8% and ≤7.8%, respectively. Similarly, for the free flucloxacillin range of 0.005–10 mg/L, the intra– and inter-day bias and CV were ≤7.6% and ≤7.3%, respectively. The total serum flucloxacillin concentration was determined contemporaneously, to assist with clinical decision making (described below), while the second tube of blood was centrifuged and plasma stored for batched analysis of free flucloxacillin concentration, as the free flucloxacillin assay was not routinely performed at the time the study was conducted.

2.5 Clinical management

To promote compliance with dosing and blood sampling, we contacted patients via telephone one or two days prior to their outpatient appointment to remind them to take their doses on time, and to ask them to record the dose time prior to the blood draw in a patient diary. The ideal dose times in the 24 hours prior to blood sampling were 8-hourly e.g. 0700, 1500 and 2300 h; this translated to a study day dose time of 0700 h (after the participant's usual breakfast) and a 4-hour blood sampling time of 1100 h. Patients were cared for according to standard clinical practice by the treating physicians, with emphasis on clinical review. Total flucloxacillin concentrations were used to support but not dictate clinical decision making. Patients with a total flucloxacillin concentration less than 10 mg/L were recalled for clinical reassessment and consideration of a change in regimen, although this was not mandated if the patient was clinically improving. Total flucloxacillin concentrations of 10 mg/L were expected to equate to a free concentration of 0.5 mg/L assuming protein binding of 0.95.(15,16) This pragmatic therapeutic drug monitoring approach should achieve approximately 50% fT>MIC_{90} of *S. aureus*.

2.6 Data collection

We collected baseline patient data including ethnicity, age, weight, height, estimated creatinine clearance using Cockcroft and Gault formula (18) and eGFR using the CKD-EPI equation,(19) concurrent drug therapy, and indication for flucloxacillin. When possible, data on the infecting organism were collected.

2.7 Outcomes

The primary clinical outcome was clinical cure at 30 days post completion of oral antimicrobial therapy. Secondary outcomes included clinical cure at completion of oral therapy and at 90 days after completion of oral therapy, and the occurrence of treatment-emergent adverse events. Clinical cure was judged by the treating physician, and required the absence of infective signs or symptoms, lack of need for a change in antimicrobial therapy (IV, or alternative oral antimicrobial agents), and absence of treatment-emergent adverse events requiring a change in therapy. The primary PK-PD outcome was the percentage of patients achieving 30% and 50% fT>MIC_{90} of *S. aureus* (0.5mg/L).

2.8 Statistical analysis and population pharmacokinetic modelling and simulation

We performed statistical summaries using R (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) implemented in the RStudio environment (version 1.0.136, RStudio Team (2016), RStudio, Inc., Boston, MA). We assessed PK-PD target attainment using population pharmacokinetic modelling of free flucloxacillin concentrations in Monolix (version 2019R1; Lixoft SAS, 2019, Antony, France), in order to estimate concentration time profiles for each patient. Due to the sparse nature of the sampling (one mid-dose-interval sample per patient), we augmented these data with that of the intensively-sampled pharmacokinetic study of healthy volunteers previously described.(12) This combined population pharmacokinetic modelling approach allowed estimation of PK-PD target attainment, which would not have been possible by simply examining the mid-dose concentrations directly, due to variation in timing of blood sampling and the concentration-time profile of the oral route of administration. Using the population pharmacokinetic model we then used Monte Carlo simulation within the RxODE package for R to elucidate the association between patient covariates and PK-PD target attainment for different dose regimens.(20) A detailed description of the population pharmacokinetic modelling strategy is given in the supplementary material.

3. Results

Table 1 shows the patient demographics and clinical outcomes. The 45 patients (73% male) had a median (range) age of 49 years (20 – 74), weight of 90 kg (59 – 167), fat free mass of 65 kg (38 – 89), BMI of 28 kg/m^2 (19 – 69) and eGFR of 89 mL/min (41 – 124). The most common infections were osteomyelitis (n=18, 40%) and septic arthritis (n=12, 27%). Thirty-one patients (69%) had confirmed *S. aureus* infection. Patients were admitted to hospital for a median of 6 days (range 0 – 43). IV antimicrobial treatment was given for a median (range) of 26 days (1 – 73), and oral treatment for a median of 28 days (8 – 362), with a total (IV plus oral) median duration of 45 days (9 – 416). Blood samples for flucloxacillin concentrations were taken at a median (range) of 4 h (2.8 – 4.5) post-dose. The median (range) concentrations for total and free flucloxacillin respectively were 18.8 mg/L (7.9 – 93.9) and 0.7 mg/L (0.3 – 5.4), corresponding to a fraction unbound of 0.04 (0.02 – 0.09).

Forty-two patients (93%) were assessed as cured at the completion of oral antimicrobial therapy, with one patient relapsing within 30 days, and another patient relapsing between 30 and 90 days after completion of oral therapy. One patient assessed as cured at the completion of therapy did not attend subsequent follow-up appointments, which precluded formal outcome assessment at later time points. The three patients who had evidence of ongoing infection at the end of oral therapy are described below. One patient had chronic lymphoedema, previous surgery to the limb, and raised BMI (44 kg/m^2), had received multiple courses of IV and oral antimicrobial therapy over the two years prior to enrolment, and suffered a recurrence of lower limb cellulitis 12 weeks after starting oral flucloxacillin plus probenecid (50% fT>MIC$_{90}$). Another patient had tibial osteomyelitis without implanted metal ware and relapsed following treatment with six weeks of IV flucloxacillin and 20 weeks after starting oral flucloxacillin plus probenecid (80% fT>MIC$_{90}$). The third patient had tibial osteomyelitis without implanted metal ware and relapsed following treatment with three weeks of IV flucloxacillin and five weeks after starting oral flucloxacillin plus probenecid (45% T>MIC$_{90}$). One patient with native knee septic arthritis relapsed within 30 days of completion of four weeks of IV flucloxacillin and two weeks of flucloxacillin plus probenecid, had a raised BMI (31 mg/kg^2) and eGFR (149 mL/min), and achieved only 25% fT>MIC$_{90}$ on the oral regimen. The patient who relapsed between 30 and 90 days after completion of oral therapy had a diabetic foot infection with osteomyelitis, and had completed a 10-week course of oral flucloxacillin plus probenecid (96% fT>MIC$_{90}$). Gastrointestinal disturbance was reported in 6 patients (13%), and nausea was reported in 10 (22%). No patient had treatment-emergent adverse events necessitating a change in therapy or clinical review.

A free flucloxacillin concentration above 0.5 mg/L for 30% and 50% of the dosing interval was achieved by 84% and 56% of the patients, respectively, while a lower target, 0.25 mg/L, was achieved by 100% and 98% of the patients, respectively. There was a wide range of modelled mean steady-state free flucloxacillin serum concentrations observed between patients, with a median of 0.52 mg/L, and a range of 0.30-3.75 mg/L.

In the final population pharmacokinetic model, fasting was identified as a significant covariate of absorption lag time (t_{lag}), where the fasting condition was associated with a mean decrease in t_{lag} from 0.47 h to 0.24 h. Fat-free mass and fasting status were covariates for V/F in the final model. For CL/F, eGFR, fat-free mass, and the use of probenecid were identified as significant covariates in the final model. Consequently each 1 mL/min increase in eGFR was associated with an increase in free flucloxacillin CL of 1%. Note that the effects of fasting and probenecid use in the final population pharmacokinetic model were determined entirely by the healthy volunteer data, because all of the patients were treated with probenecid and were advised to take their medication with food. Based on the healthy volunteer data incorporated into the model, the co-administration of probenecid was estimated to decrease flucloxacillin CL by approximately 50% compared with flucloxacillin alone.

Monte Carlo simulation of dose regimens for different values of significant covariates demonstrated the importance of probenecid, fat free mass, and eGFR on PTA (figures 1-4). Fed versus fasting status had minimal effects on PTAs (results not shown), thus results displayed are for flucloxacillin plus probenecid with food. For a target of 0.5mg/L for 30% of the dosing interval, regimens without probenecid were associated with a low PTA in patients with typical renal function and body size. For example, a patient with a fat free mass of 60kg and eGFR of 90 (typical values for patients in this study) has a PTA of 0.43 for 1000mg flucloxacillin every 8 hours, compared to a PTA of 0.99 with the addition of probenecid at the same dosing frequency. For a target of 0.5mg/L for 50% of the dosing interval, the same patient would have a low PTA with flucloxacillin alone, but could achieve PTAs of 0.74 and 0.98 with flucloxacillin 1000mg plus probenecid 500mg every 8 hours and every 6 hours respectively.

4. Discussion and conclusions

We observed high rates of clinical success in this cohort of patients receiving oral flucloxacillin plus probenecid for probable or confirmed staphylococcal infection. The combination of flucloxacillin and probenecid was well-tolerated by patients. Nausea was the most commonly observed side effect (22%),

but did not necessitate alteration of therapy in any patient. Despite this clinical success, not all patients achieved the pre-specified PK-PD end-points: 84% of the patients achieved fT> 0.5 mg/L for 30% of the dosing interval, and only 56% achieved the target concentration for 50% of the dosing interval. This study suggests that flucloxacillin 1000 mg plus probenecid 500 mg three times daily may not be sufficient to achieve the nominated PK-PD targets for *S. aureus* in some patients, and that four times daily dosing may result in more robust target attainment in larger patients with normal renal function. The simulations exploring dosing regimens for a range of patient covariates provide a straightforward means for clinicians to select an appropriate dose regimen for an individual patients based on their fat free mass and eGFR, and a nominated PK-PD target. Fat free mass can be calculated based on the patient's sex, weight, and height, using online tools or using the contour plot provided in figure 5, based on Janmasatian et al.(21) In particular, it may identify patients and dosing regimens with high PTAs and hence may allow a more proactive oral dosing strategy in these patients. Conversely, these simulations can identify those with more marginal PTAs, who may benefit from therapeutic drug monitoring or alternative antimicrobial strategies. It should be noted that the population pharmacokinetic model, and the formula estimating fat free mass were developed with data from predominantly Caucasian populations. Prescribers should use caution when applying these to patients of other ethnicities, where systematic differences in body composition can lead to bias in fat free mass estimation.(22,23) The granular presentation of PTAs in this study allow prescribers to consider the potential effect of such bias, and adjust their dosing and monitoring decisions accordingly.

A key limitation of this study is that it was not possible to directly evaluate the association between target attainment and clinical outcome. There are many reasons for this, including the small number of treatment failure cases, and the likelihood of non-antimicrobial factors contributing to clinical outcome. In addition, initial IV treatment was frequently given for a prolonged duration prior to oral follow-on, thus it is possible that some patients would have been cured regardless of oral regimen. Flucloxacillin MICs were not measured directly in this study, and thus the nominated concentration target of 0.5 mg/L used may have been higher than required in individual patients. The importance of this is uncertain, given the imprecision of MIC estimation in clinical practice, and thus the difficulty of relating a measured MIC of an isolate to an individualised therapeutic target.(24) Further research is required to validate PK-PD targets in different clinical scenarios, given the increasing interest in the use of oral antimicrobials for serious infections such as endocarditis, osteomyelitis, prosthetic joint infection, and *Staphylococcus aureus* bacteraemia.(25–29) The population pharmacokinetic model and dose simulations developed in

this study would benefit from external validation, and may serve as a basis for an optimal dose regimen for further prospective trials of the safety and efficacy of flucloxacillin plus probenecid.

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6. Supplementary materials

Supplementary material associated with this article, including detailed population pharmacokinetic modelling and simulation strategy and results, can be found in the online version.

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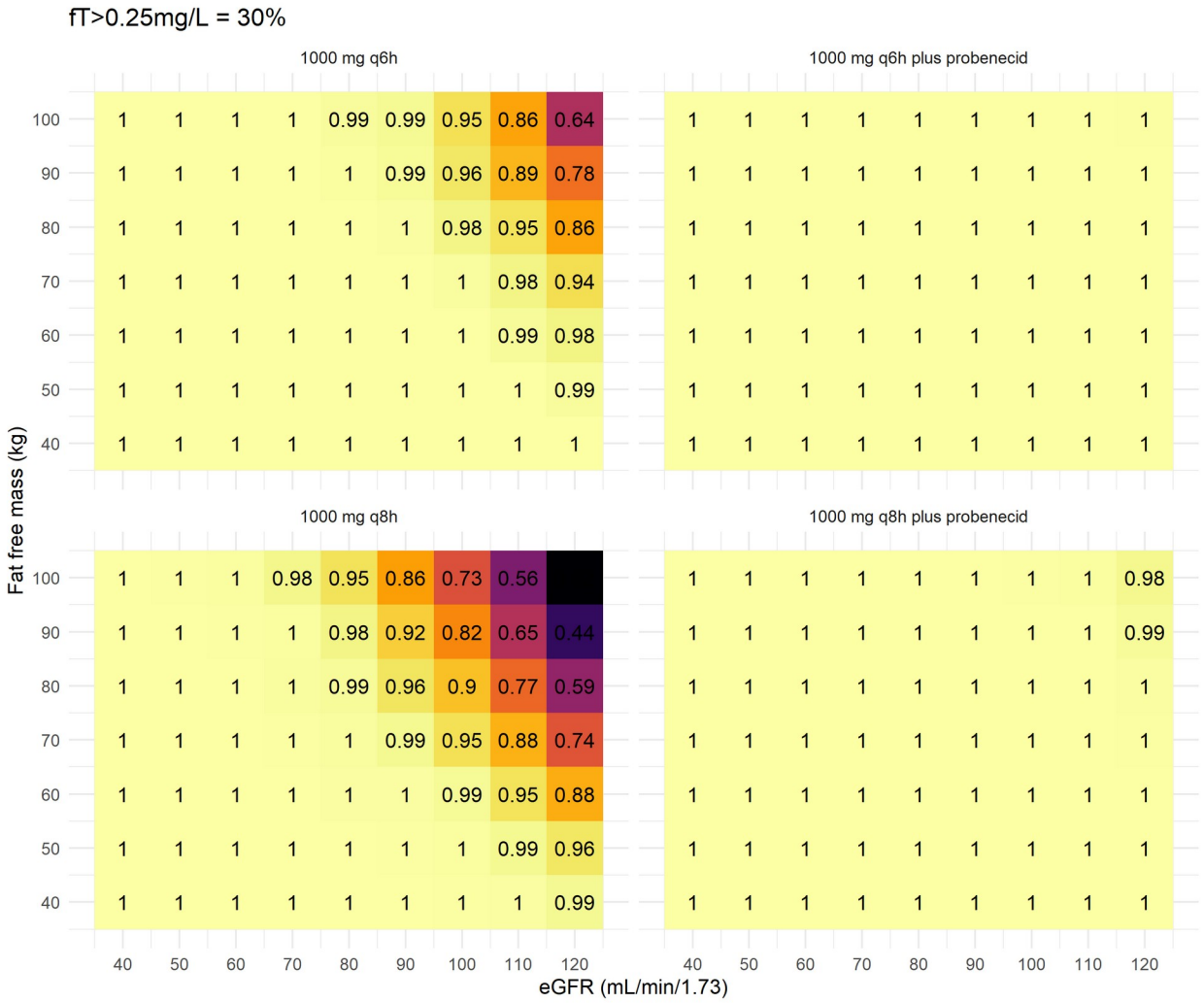

Figure 1: Probability of target attainment for different flucloxacillin dose regimens (left: flucloxacillin alone, right: flucloxacillin with probenecid) according to eGFR and fat free mass for a target of 30% time above free flucloxacillin concentration of 0.25 mg/L

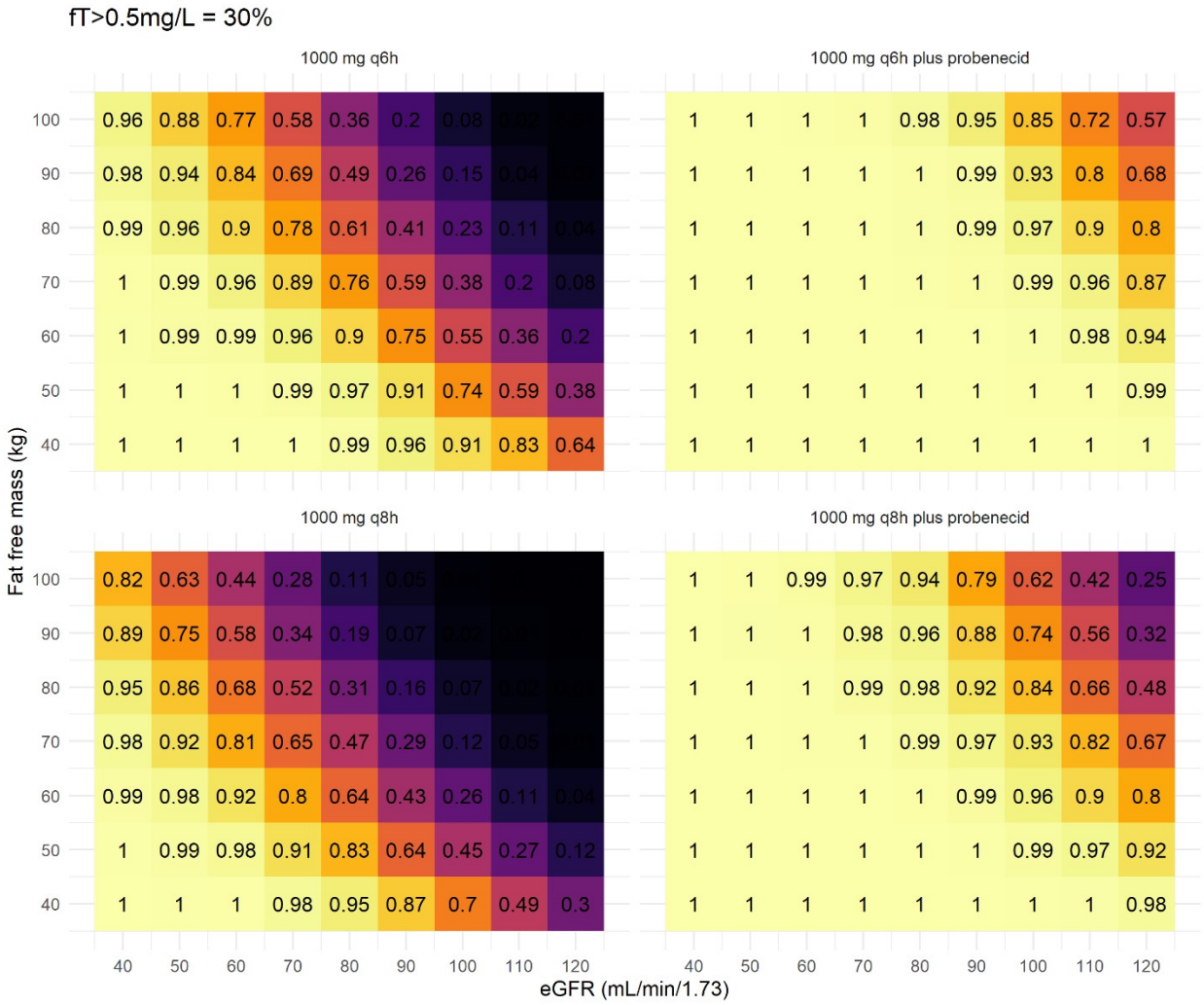

Figure 2: Probability of target attainment regimens (left: flucloxacillin alone, right: flucloxacillin with probenecid) according to eGFR and fat free mass for a target of 30% time above free flucloxacillin concentration of 0.5 mg/L

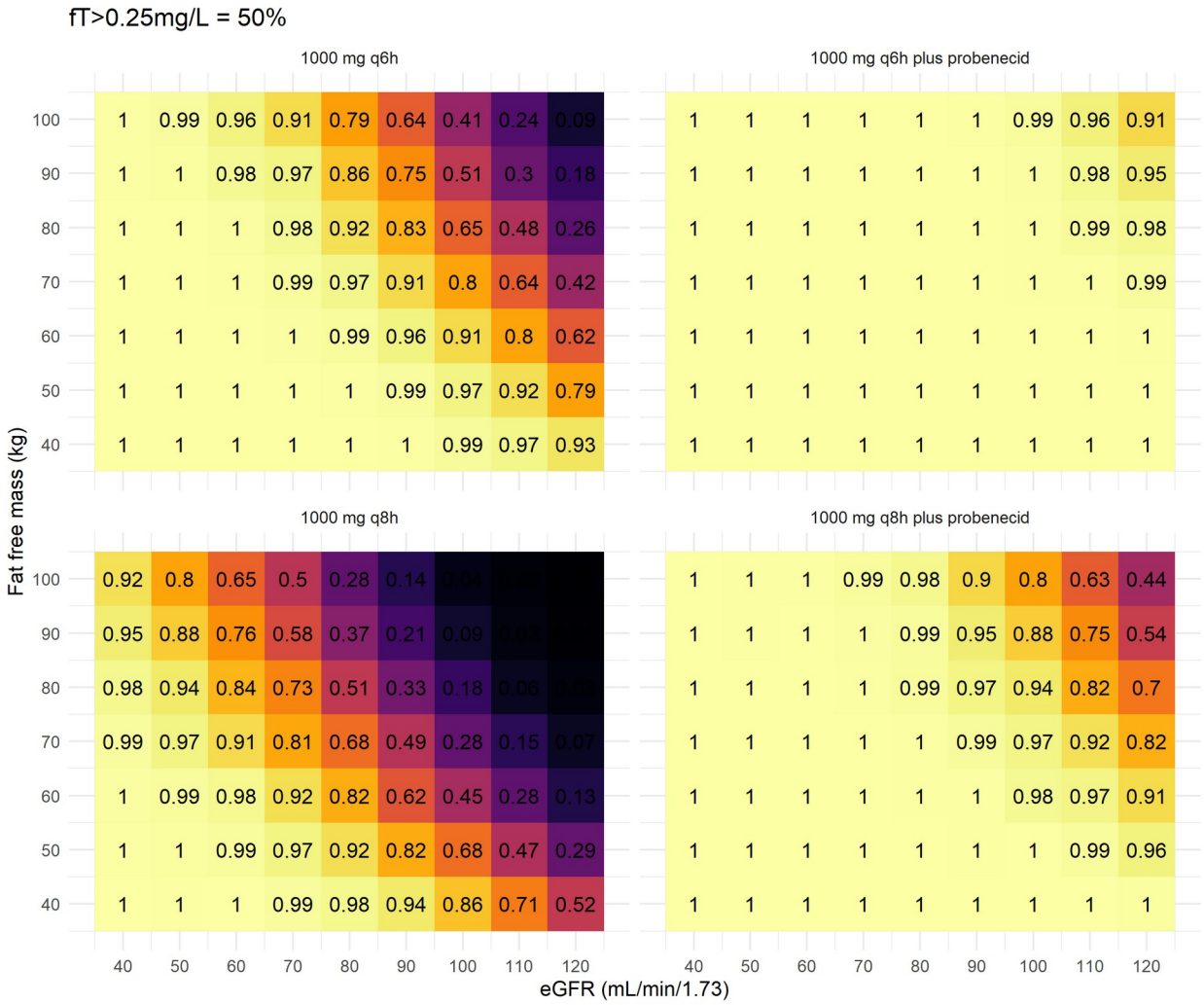

Figure 3: Probability of target attainment regimens (left: flucloxacillin alone, right: flucloxacillin with probenecid) according to eGFR and fat free mass for a target of 50% time above free flucloxacillin concentration of 0.25 mg/L

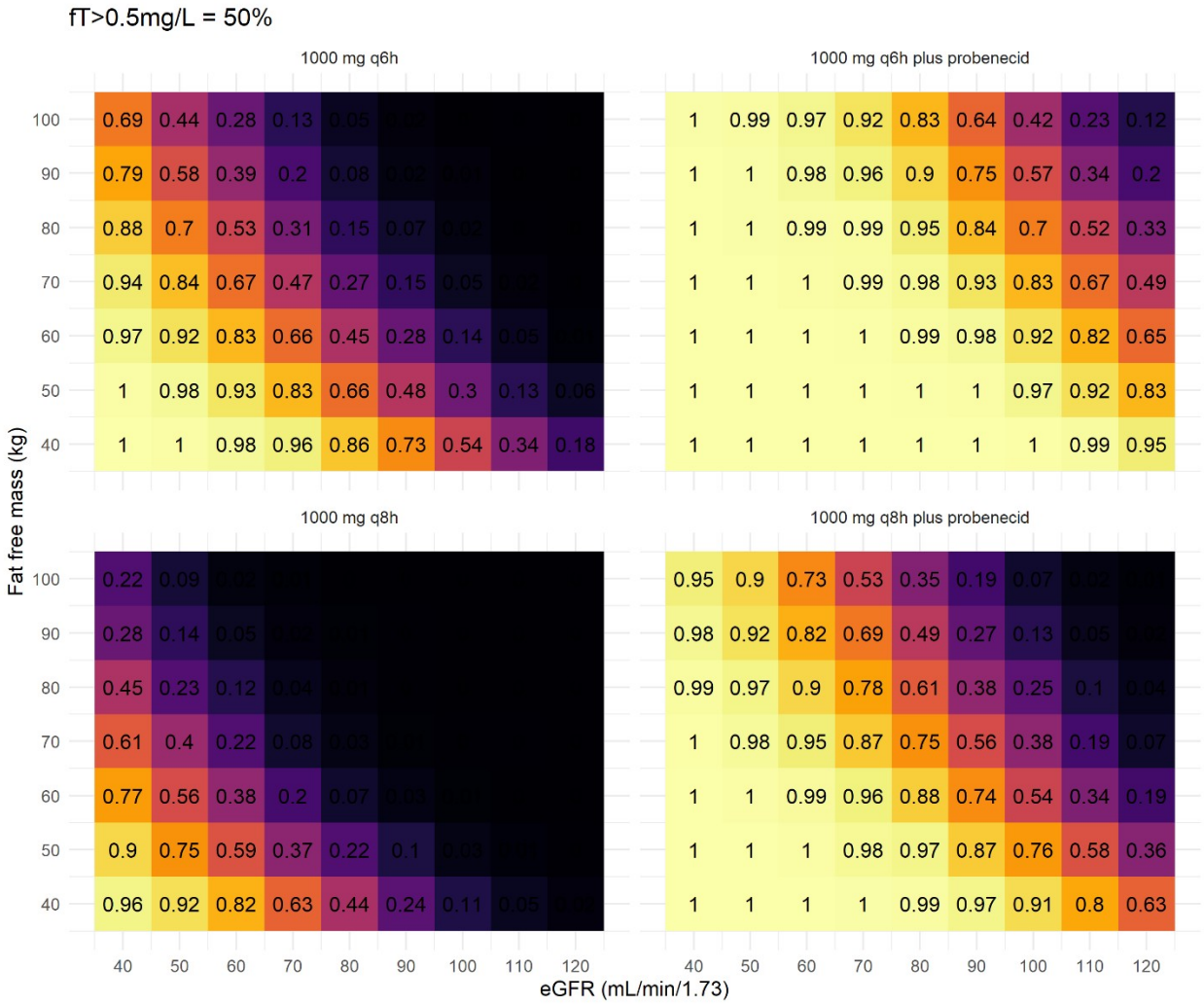

Figure 4: Probability of target attainment regimens (left: flucloxacillin alone, right: flucloxacillin with probenecid) according to eGFR and fat free mass for a target of 50% time above free flucloxacillin concentration of 0.5 mg/L

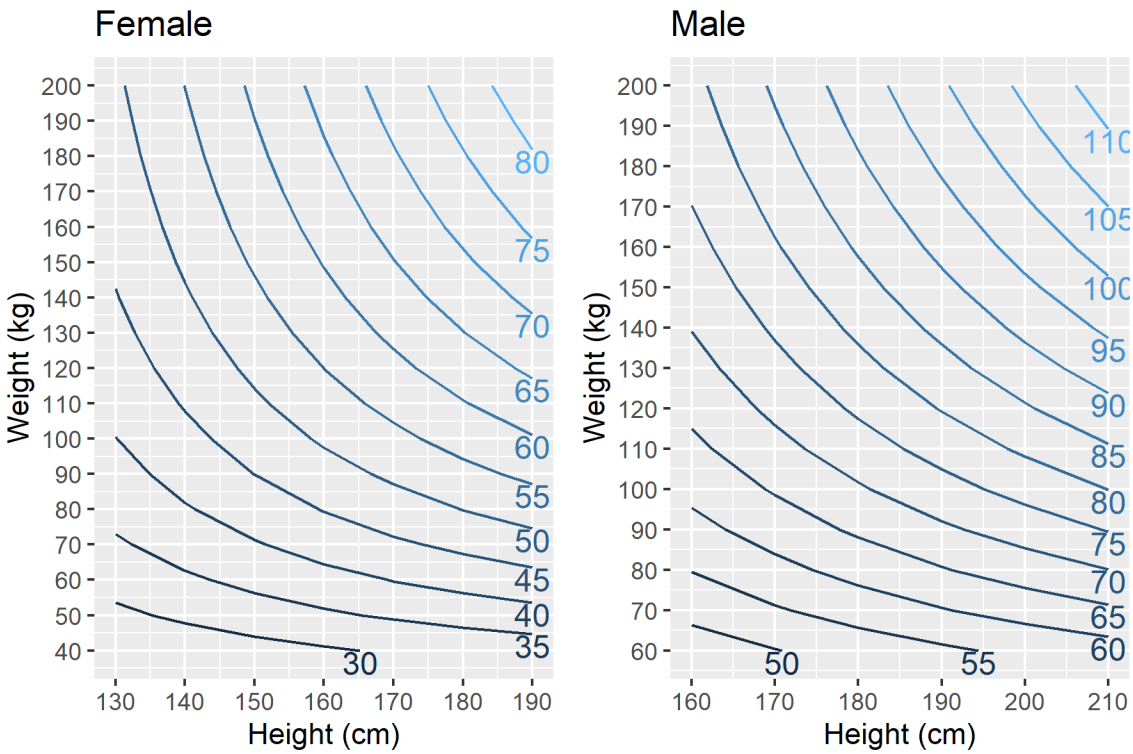

Figure 5: Fat free mass according to height, weight, and sex, using the formula of Janmahasatian et. al.

Table 1: Demographic characteristics, diagnoses, flucloxacillin concentrations, and treatment outcomes in patients (n=45) treated with oral flucloxacillin plus probenecid

Demographic characteristics	Median [range], or n (%)
Age, years	48.8 [19.8 – 73.7]
Male	33 (73.3)
Ethnicity	
European	40 (88.9)
Maori	3 (6.7)
Pacific Island	2 (4.4)
Weight, kg	90.0 [59.1 – 166.9]
Height, cm	178 [156 – 195]
Fat free mass, kg	64.8 [38.4 – 89.1]
BMI, kg/m^2	28.4 [18.9 –68.6]
eGFR, mL/min/1.73m2	89 [41 – 124]
Comorbidities	
Diabetes	8 (17.8)
Malignancy	5 (11.1)
Diagnosis	
Deep abscess	1 (2)
Osteomyelitis	16 (36)
Osteomyelitis - prosthetic material retained	2 (4)
Septic arthritis	12 (27)
Septic bursitis	3 (7)
Septic thrombophlebitis	2 (4)
Skin / soft tissue infection	5 (11)
Spinal infection	4 (9)
Organism	
Coagulase-negative staphylococci	3 (7)
S. aureus	31 (69)
Nil isolated	11 (23)
Flucloxacillin concentrations	
Time of sample, hours post dose	4.00 [2.83 – 4.50]
Total concentration, mg/L	18.79 [7.89 – 93.90]
Free concentration, mg/L	0.72 [0.27 – 5.44]
Fraction unbound	0.04 [0.02 – 0.09]
Achieved 30% $fT>MIC_{90}$	38 (84)
Achieved 50% $fT>MIC_{90}$	25 (56)
Mean steady state free concentration	0.52 [0.30 – 3.75]
Treatment outcomes	
Duration of admission, days	6 [0 – 43]
Duration of IV antimicrobials, days	26 [1 – 73]
Duration of oral antimicrobials, days	28 [8 – 362]
Total duration of antimicrobials, days	45 [9 – 416]
Success at cessation of oral therapy	42 (93)
Success 30 days post cessation	40 (89)
Success 90 days post cessation	39 (87)
Treatment-emergent adverse events	
Gastrointestinal disturbance	6 (13)
Nausea	10 (22)

425 **Table 2: Parameter estimates for final population pharmacokinetic model**

	Stochastic approximation			Bootstrap		
	Value	**S.E.**	**R.S.E. (%)**	**Median**	**5th centile**	**95th centile**
Fixed Effects						
$T_{lag_{pop}}$ (h)	0.464*					
$\beta_{Tlag_{fastina}}$	-0.656*					
$k_{a_{pop}}$ (h^{-1})	0.469*					
V_{pop} (L)	371	53.7	14.5	406	322	552
$\beta_{V_{fastina}}$	-1.28*					
$\beta_{V_{ffm}}$	1*					
CL_{pop} ($L.h^{-1}$)	402	45	11.2	406	319	496
$\beta_{CL_{eGFR}}$	0.0128	0.0026	20.1	0.014	0.008	0.019
$\beta_{CL_{ffm}}$	0.75*					
$\beta_{CL_{probenecid}}$	-0.627	0.109	17.4	-0.633	-0.840	-0.394
Standard deviation of the random effects						
$\omega_{t_{laa}}$	0.292	0.18	61.7	0.27	0.081	0.787
ω_{k_a}	0.064	0.138	216	0.129	0.023	0.447
ω_V	0.328	0.147	44.9	0.256	0.114	0.612
ω_{Cl}	0.243	0.0703	28.9	0.228	0.080	0.337
$\gamma_{t_{laa}}$	0.522	0.149	28.5	0.411	0.195	0.628
γ_{k_a}	0.294	0.0548	18.7	0.226	0.094	0.373
γ_V	0.321	0.122	38	0.417	0.123	0.716
γ_{Cl}	0.29	0.0481	16.6	0.276	0.202	0.337
Error model parameters						
a (mg/L)	0.060	0.0038	6.44	0.051	0.002	0.089
b	0.196	0.0138	7.02	0.209	0.174	0.269

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