Drug Metabolism and Disposition

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Electronic supplementary material to

Predictive Performance of Physiologically Based Pharmacokinetic Modelling of Beta-Lactam Antibiotic Concentrations in Adipose, Bone and Muscle Tissues

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Extended methodology

Calculating unbound interstitial fluid concentration from total tissue concentrations

At distribution equilibrium (steady-state between blood and tissue concentration), the total tissue to plasma partition coefficient (Kp_{total}) can be defined as the ratio of the total tissue concentration ($C_{total\ tissue,SS}$) to the (total) plasma concentration ($C_{plasma,SS}$):

$$Kp_{total} = \frac{C_{total\ tissue,SS}}{C_{plasma,SS}} \quad \text{Eq. S1}$$

Similarly, an unbound interstitial fluid to plasma partition coefficient ($Kp_{ISF,u}$) can be defined based on the unbound interstitial fluid concentration ($C_{ISF,u,SS}$) and total plasma concentrations at distribution equilibrium:

$$Kp_{ISF,u} = \frac{C_{ISF,u,SS}}{C_{plasma,SS}} \quad \text{Eq. S2}$$

Based on the free drug hypothesis, an equilibrium between the unbound plasma concentration ($C_{plasma,u,SS}$) and the unbound interstitial fluid concentration can be assumed, giving:

$$C_{plasma,u,SS} = C_{ISF,u,SS} \quad \text{Eq. S3}$$

Substituting Eq. S3 in Eq. S2 gives:

$$Kp_{ISF,u} = \frac{C_{plasma,u,SS}}{C_{plasma,SS}} = fu_{plasma} \quad \text{Eq. S4}$$

where fu_{plasma} is the free fraction in plasma. Using Eq. S1, Eq. S2 and Eq. S4, the unbound interstitial fluid concentration at distribution equilibrium can be expressed in terms of the total tissue concentration at distribution equilibrium as follows:

Re-arranging Eq. S1 and Eq. S2 in terms of $C_{plasma,SS}$ gives:

$$C_{plasma,SS} = \frac{C_{total\ tissue,SS}}{Kp_{total}} = \frac{C_{ISF,u,SS}}{Kp_{ISF,u}} \quad \text{Eq. S5}$$

Re-arranging Eq. S5 in terms of $C_{ISF,u,SS}$ and substituting $Kp_{ISF,u}$ for fu_{plasma} (Eq. S4) gives:

$$C_{ISF,u,SS} = \frac{Kp_{ISF,u}}{Kp_{total}} C_{total\ tissue,SS} = \frac{fu_{plasma}}{Kp_{total}} C_{total\ tissue,SS} \quad \text{Eq. S6}$$

When an instant equilibrium between interstitial and intracellular tissue compartments is assumed, the relative differences between total tissue and unbound interstitial fluid concentrations are constant as a function of time. Eq. S6 can be generalized to non-steady-state timepoints as:

$$\frac{dC_{ISF,u}}{dt} = \frac{fu_{plasma}}{Kp_{total}} \frac{dC_{total\ tissue}}{dt} \quad \text{Eq. S7}$$

Using Eq. S7 (Eq. 2 in main manuscript), PBPK total tissue profiles of perfusion limited tissues can be converted to unbound interstitial fluid concentration profiles by multiplying them with a factor equal to the ratio of fu_{plasma} to Kp_{total}.

Extended results

Supplementary Figures S1-9

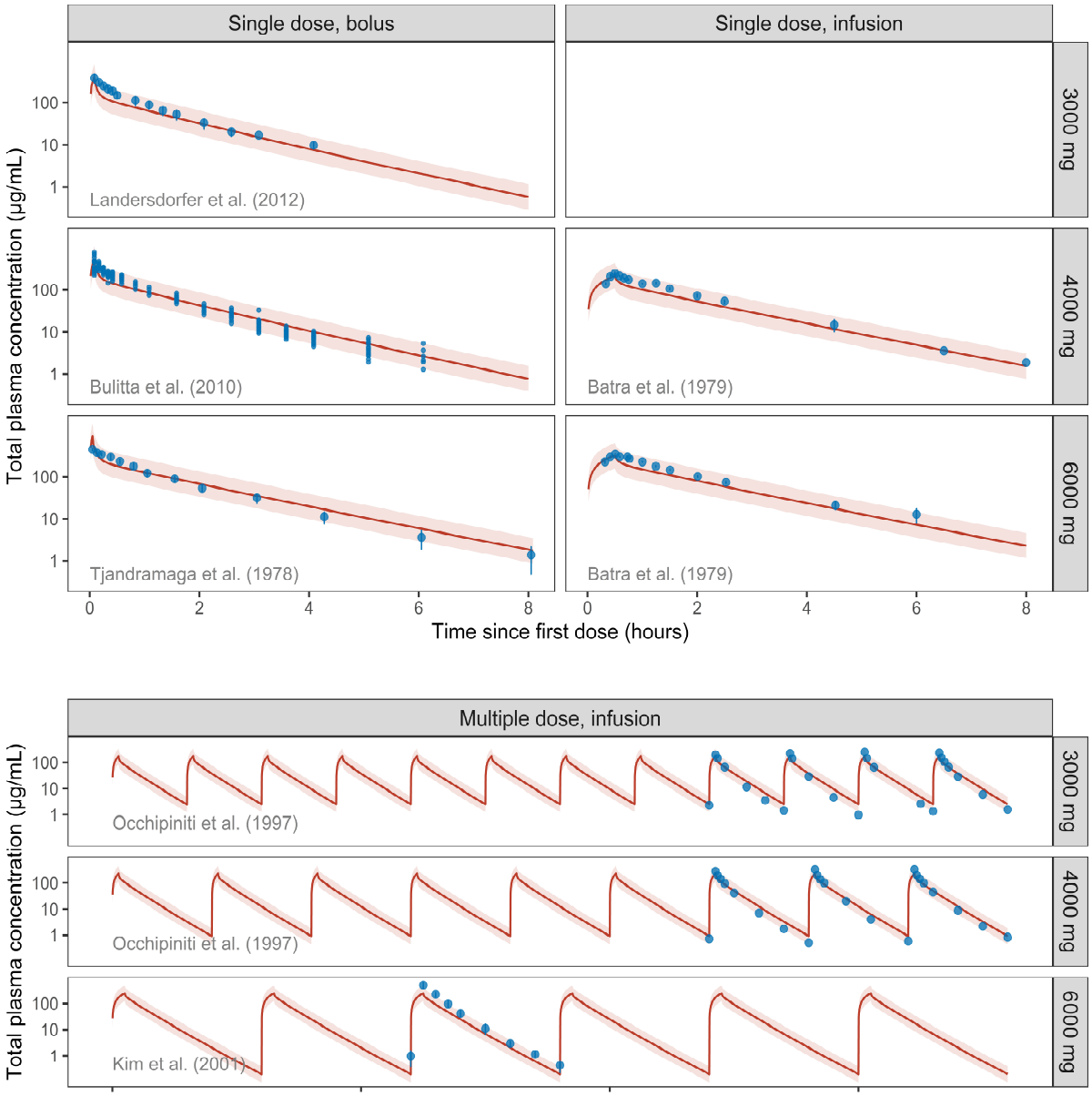

Figure S1: Model verification of the piperacillin model in plasma. Mean PBPK predicted (red lines) versus observed total plasma concentrations (blue dots). Smaller dots denote individual concentrations whereas larger symbols denote mean data (with or without error bars signifying standard deviations). The shaded red area represents a two-fold interval around the median PBPK predicted profile. See Table S2 for simulation settings.

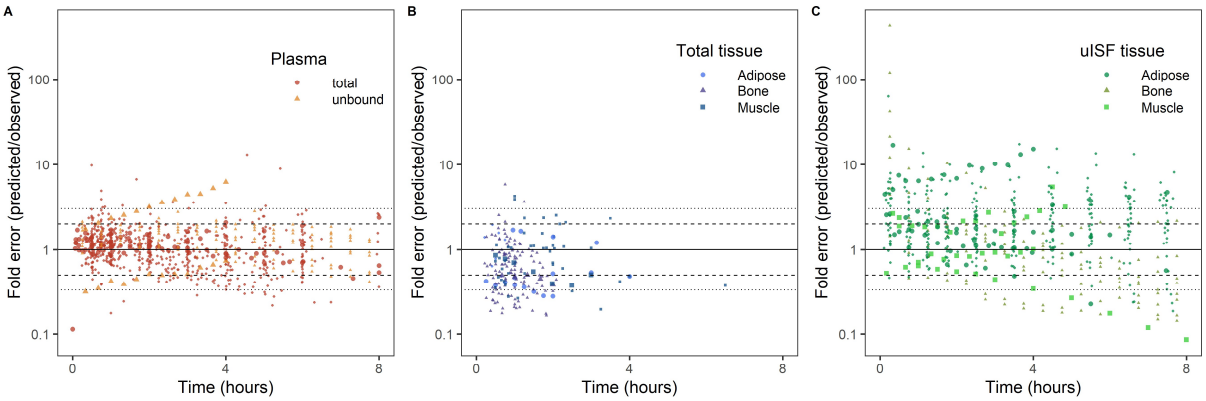

Figure S2: Fold errors of physiologically based pharmacokinetic (PBPK) predicted concentrations versus time of the five beta-lactams in plasma (A), total tissue biopsy homogenates (B) and unbound interstitial fluid (uISF) probed by microdialysis (C). Dashed and dotted lines denote two- and threefold deviations from the line of unity, respectively. Smaller squares or circles represent individual datapoints whereas larger symbols denote mean data.

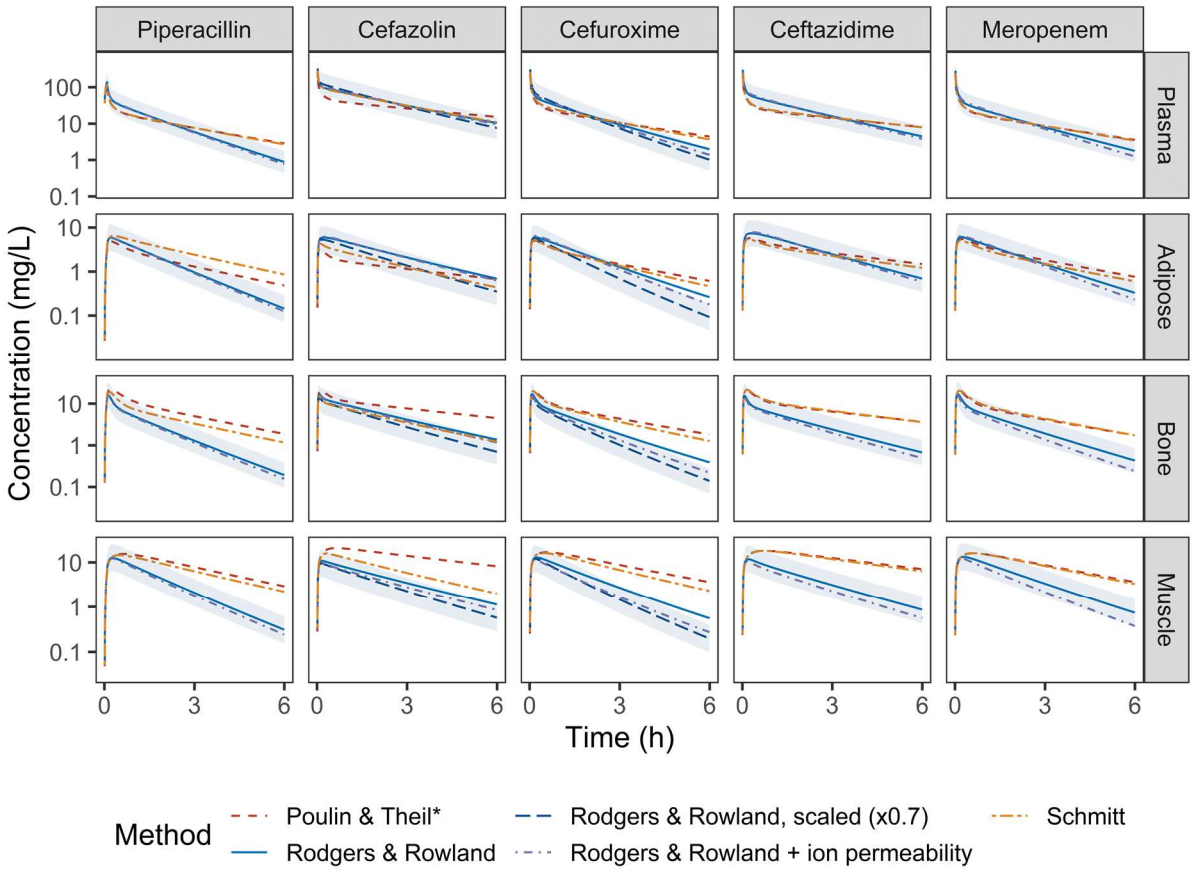

Figure S3: PBPK predicted concentrations of the five beta-lactams in plasma and adipose-, bone- and muscle tissues, using four different Kp estimation methods. All concentrations are total concentrations. For each antibiotic, a 1g intravenous bolus dose was simulated in 100 virtual subjects between 20 and 50 years old. The applied Kp estimation methods are: Poulin and Theil*: Poulin and Theil method with a Breshkovsky correction (Method 1 in Simcyp), Rodgers & Rowland (Method 2 in Simcyp), Rodgers & Rowland + ion permeability (Method 3 in Simcyp) and Schmitt: after Schmitt (Schmitt, 2008), using the uniform tissue composition proposed by Utsey *et al*. (Utsey *et al.*, 2020). The shaded area signifies a twofold interval around the prediction with the original Kp estimation method (Rodgers and Rowland for piperacillin, ceftazidime and meropenem, and Rodgers and Rowland scaled by a factor 0.7 for cefazolin and cefuroxime). Corresponding tissue-to-plasma partition coefficients can be found in supplementary Table S1.

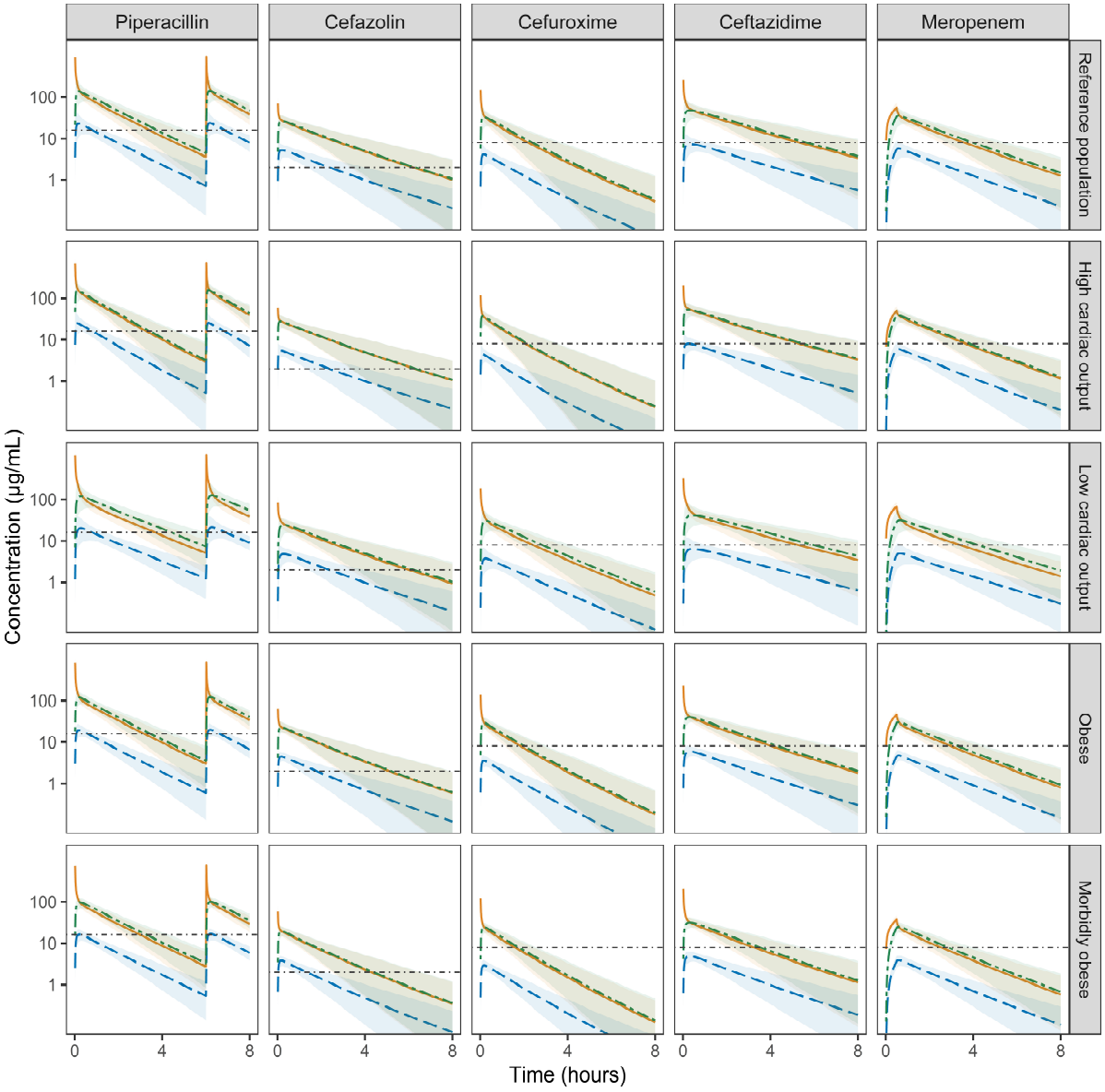

Figure S4: PBPK predicted concentrations of the five beta-lactams in plasma (unbound, orange solid line) and adipose tissue (total concentration (blue dashed line) and unbound interstitial fluid concentration (uISF, green dot-dashed line)) for different virtual populations. Standard dosage regimens as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST): piperacillin: 4g (bolus) q6h, cefazolin: 1g (bolus) q8h, cefuroxime: 0.75g (bolus) q8h, ceftazidime: 1g (bolus) q8h, meropenem: 1g (30min infusion) q8h. The shaded areas signify 5-95% percentiles around the mean predicted concentration. The grey line denotes the non-species specific resistant minimal inhibitory concentration (MIC) for each drug.

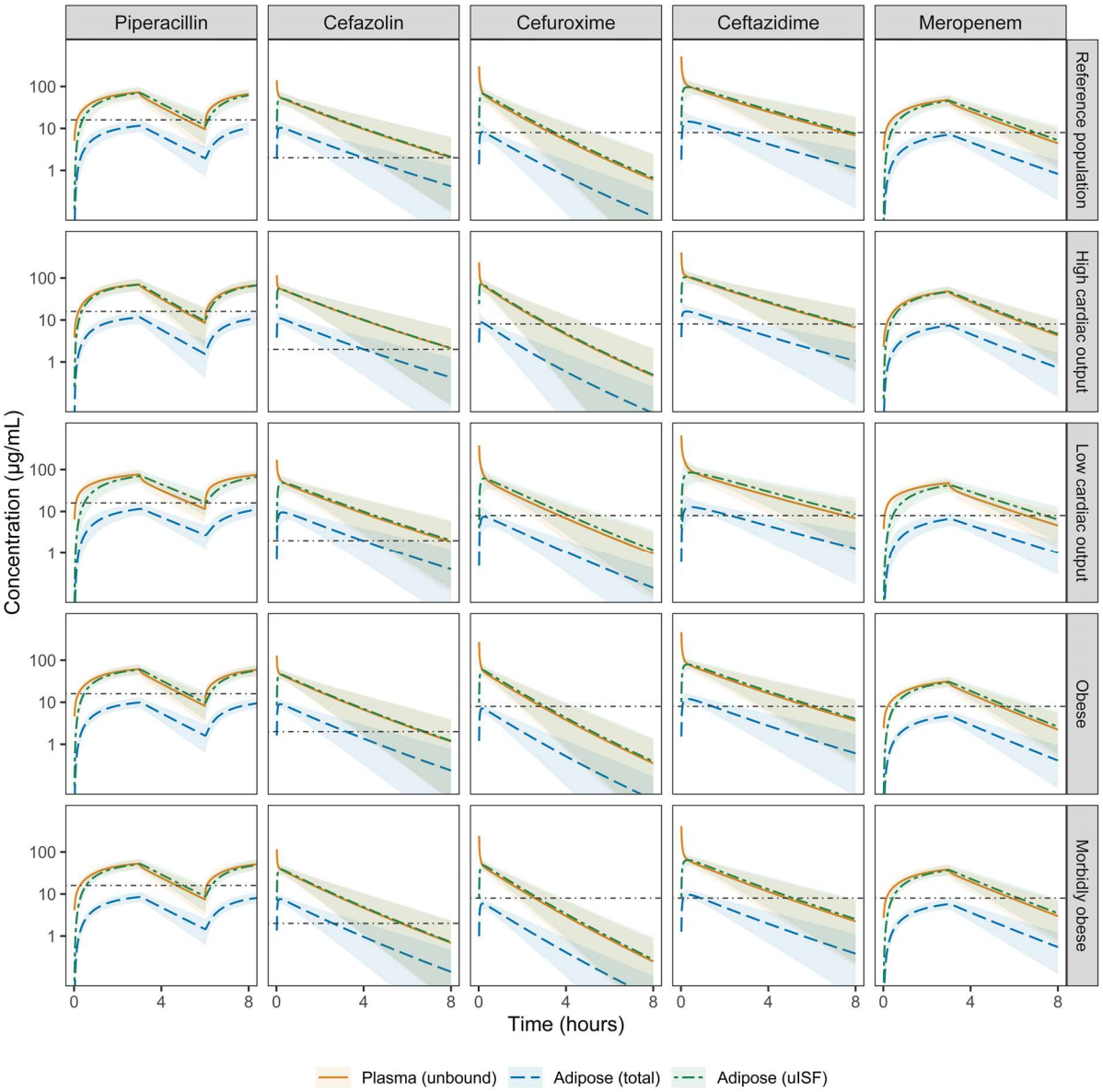

Figure S5: PBPK predicted concentrations of the five beta-lactams in plasma (unbound, orange solid line) and adipose tissue (total concentration (blue dashed line) and unbound interstitial fluid concentration (uISF, green dot-dashed line)) for different virtual populations. High dosage regimens as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST): piperacillin: 4g (3h infusion) q6h, cefazolin: 2g (bolus) q8h, cefuroxime: 1.5g (bolus) q8h, ceftazidime: 2g (bolus) q8h, meropenem: 2g (3h infusion) q8h. The shaded areas signify 5-95% percentiles around the mean predicted concentration. The grey line denotes the non-species specific resistant minimal inhibitory concentration (MIC) for each drug.

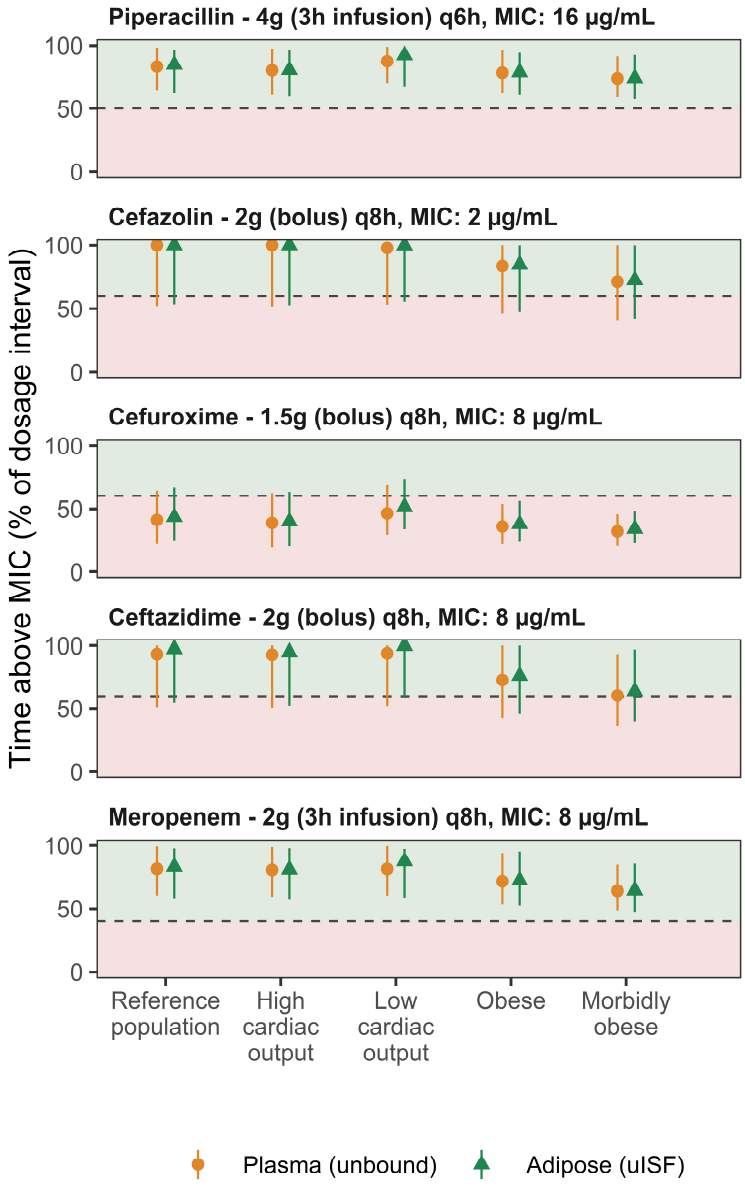

Figure S6: Target attainment using high dosages recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in five different virtual populations using different physiologically based pharmacokinetic (PBPK) predicted concentrations as input. The mean time the unbound plasma concentration (orange circles) and adipose unbound interstitial fluid (uISF) concentration (green triangles) exceed the non-species specific resistant minimal inhibitory concentration breakpoint (MIC) is given as a percentage of the dosage interval, together with 5-95% percentiles (lines). The dashed lines represent conventional antibiotic-specific goals for target attainment. See supplementary Figure S5 and Table S7 for the simulated profiles and population characteristics, respectively.

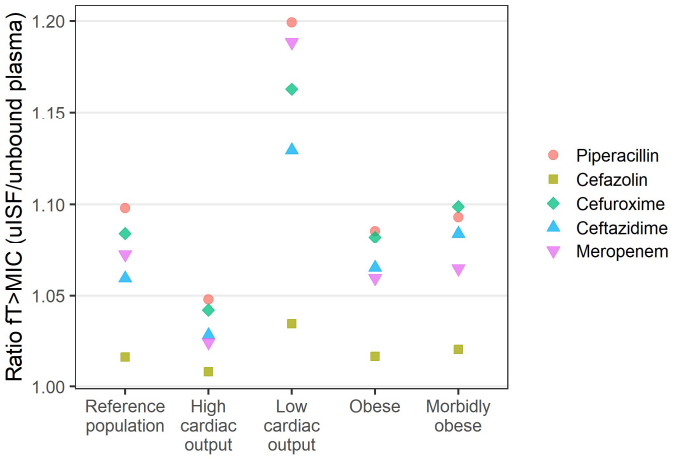

Figure S7: Relative differences in target attainment for the standard dosage resulting from using unbound interstitial fluid (uISF) or unbound plasma concentrations as driving factor, expressed as the ratio of time above the minimal inhibitory concentration (*f*T>MIC) in plasma to the *f*T>MIC in uISF.

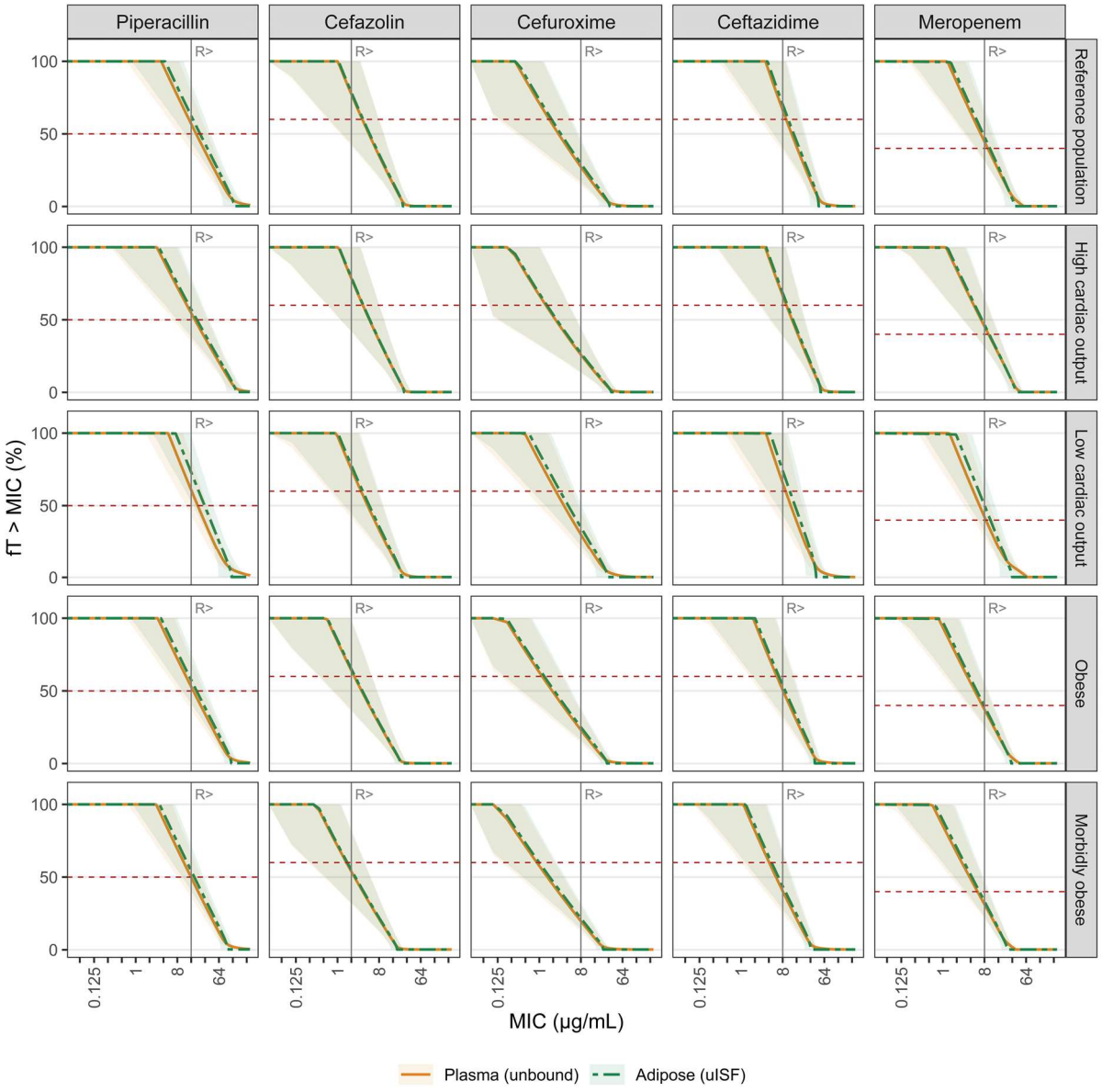

Figure S8: Target attainment in function of the minimal inhibitory concentration (MIC) using standard dosages recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in five different virtual populations. Target attainment is defined as the time the unbound concentration exceeds the MIC (fT>MIC), as percentage of the dosing interval and using the physiologically based pharmacokinetic (PBPK) predicted mean unbound concentrations in plasma (orange solid lines) and the interstitial fluid concentration in adipose tissue (uISF, green dot-dashed lines) as inputs (see supplementary Figure S4 for the corresponding concentration-time profiles). The shaded areas represent 5-95% percentiles. The horizontal dashed red lines represent the antibiotic specific targets while the vertical solid grey line represent the non-species specific resistant MIC.

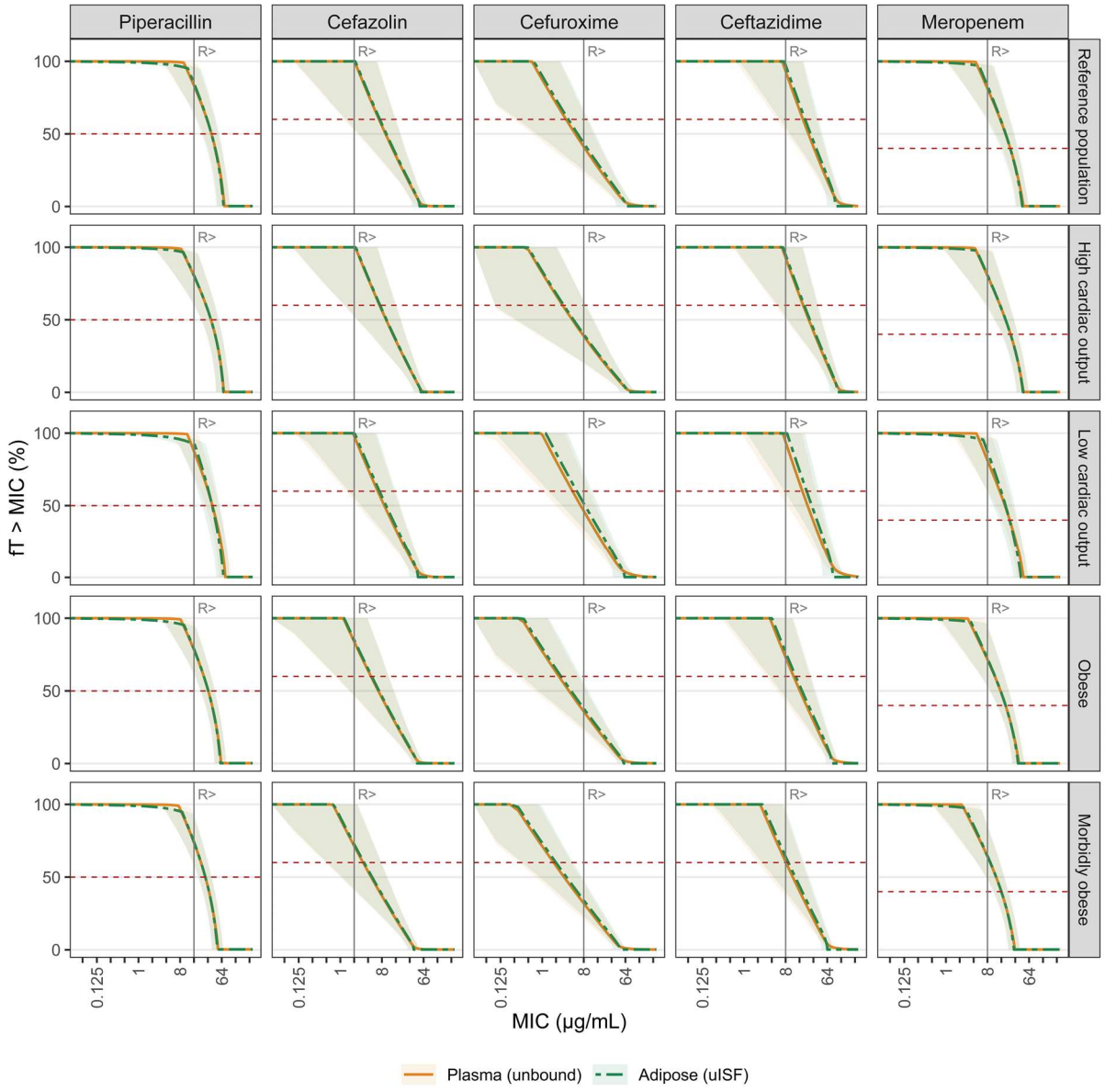

Figure S9: Target attainment in function of the minimal inhibitory concentration (MIC) using high dosages recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in five different virtual populations. Target attainment is defined as the time the unbound concentration exceeds the MIC (fT>MIC), as percentage of the dosing interval and using the physiologically based pharmacokinetic (PBPK) predicted mean unbound concentrations in plasma (orange solid lines) and the interstitial fluid concentration in adipose tissue (uISF, green dot-dashed lines) as inputs (see supplementary Figure S5 for the corresponding concentration-time profiles). The shaded areas represent 5-95% percentiles. The horizontal dashed red lines represent the antibiotic specific targets while the vertical solid grey line represent the non-species specific resistant MIC.

Supplementary Tables S1-8

Table S1: Variability in tissue-to-plasma partition coefficients (Kp)

Drug	Tissue	R&R Method	Alternative Kp method (% difference with R&R)		
			P&T +	R&R+	Schmitt
Piperacillin	adipose	0.133	0.151 (+14%)	0.131 (-2%)	0.259 (+95%)
	bone	0.207	0.610 (+195%)	0.193 (-7%)	0.411 (+99%)
	muscle	0.293	0.788 (+169%)	0.266 (-9%)	0.654 (+123%)
Cefazolin	adipose	0.064*	0.043 (-33%)	0.063 (-2%)	0.039 (-39%)
	bone	0.130*	0.289 (+122%)	0.120 (-8%)	0.111 (-15%)
	muscle	0.107*	0.495 (+363%)	0.087 (-19%)	0.175 (+64%)
Cefuroxime	adipose	0.117*	0.128 (+9%)	0.113 (-3%)	0.112 (-4%)
	bone	0.190*	0.394 (+107%)	0.153 (-19%)	0.329 (+73%)
	muscle	0.251*	0.676 (+169%)	0.179 (-29%)	0.521 (+108%)
Ceftazidime	adipose	0.136	0.172 (+26%)	0.134 (-1%)	0.144 (+6%)
	bone	0.147	0.441 (+200%)	0.126 (-14%)	0.441 (+200%)
	muscle	0.181	0.768 (+326%)	0.139 (-23%)	0.698 (+286%)
Meropenem	adipose	0.154	0.188 (+22%)	0.149 (-3%)	0.157 (+2%)
	bone	0.231	0.460 (+99%)	0.184 (-20%)	0.480 (+108%)
	muscle	0.351	0.800 (+128%)	0.259 (-26%)	0.760 (+117%)

P&T+: Poulin & Theil method (Poulin and Theil, 2002) with a Berezhovskiy correction (Berezhkovskiy, 2004), implemented as "method 1" in Simcyp V20,

R&R: Rodgers & Rowland method (Rodgers and Rowland, 2007) , implemented as "method 2" in Simcyp V20 (input values),

R&R +: Rodgers & Rowland + ionization method, implemented as "method 3" in Simcyp V20,

Schmitt: Schmitt method (Schmitt, 2008), calculated using uniform tissue composition (Utsey *et al.*, 2020),

*: input Kp value in the model is scaled by a factor 0.7 (Hsu *et al.*, 2014; Abduljalil *et al.*, 2022)

Table S2: Model verification of the piperacillin model in plasma

	Simulation parameter				Plasma profiles		Area under the plasma concentration-time curve (AUC)			
Study	**IV dose (infusion duration)**	**N**	**Age in years (min-max)**	**Females**	**AFE**	**AAFE**	**AUC interval**	**Observed (mg.min/mL)**	**Predicted (mg.min/mL)**	**FE**
(Landersdorfer *et al.*, 2012)	3g (5min) SD	10	19-29	50%	0.73	1.37	N.R.	N.R.	N.R.	N.R.
(Bulitta *et al.*, 2010)	4g (5min) SD	4	22-24	50%	1.02	1.43	N.R.	N.R.	N.R.	N.R.
(Tjandramaga *et al.*, 1978)	6g (3min) SD	5	18-29	0%	1.07	1.31	0-inf	438	436	1.00
(Batra *et al.*, 1979)	4g (30min) SD	6	18-50	0%	0.79	1.31	0-6h	371	286	0.77
(Batra *et al.*, 1979)	6g (30min) SD	6	18-50	0%	0.76	1.33	0-6h	470	429	0.91
(Occhipinti *et al.*, 1997)	3g (30 min) q6h	12	23-30	0%	1.16	1.44	48-72h	968	860	0.89
(Occhipinti *et al.*, 1997)	4g (30min) q8h	12	23-30	0%	1.05	1.36	48-72h	979	860	0.88
(Kim *et al.*, 2001)	6g (60 min) q12h	12	20-43	33%	0.48	2.10	24-36h	962	434	0.45
Overall AFE					0.85					0.84
Overall AAFE						1.44				1.19

*Abbreviations: AAFE: absolute average fold error, AFE: average fold error, FE: fold error, IV: intravenous, N: number of study subjects, simulations were done with N*10 virtual subjects, N.R.: not reported, SD: single dose*

Table S3: Study selection process

Drug – tissue pair (Study reference)	Study inclusion decision[a]
Piperacillin – adipose (total)	
(Kinzig *et al.*, 1992)	Included
(van Lindert *et al.*, 1990)	Not preferred, not newest
(Russo *et al.*, 1982)	Not preferred, not newest
Piperacillin – bone (total)	
(Al-Nawas *et al.*, 2008)	Excluded, unsuitable tissue data (sample time unclear)
(Incavo *et al.*, 1994)	Included
(Kato and Morimoto, 1984)	Not preferred, older study & full text in Japanese
Piperacillin – muscle (total)	
(Kinzig *et al.*, 1992)	Included
(Russo *et al.*, 1982)	Not preferred, older study
(Daschner *et al.*, 1982)	Excluded, unsuitable tissue data (hypothermic tissue 25-35°C)
(Daschner *et al.*, 1981)	Excluded, unsuitable tissue data (time intervals)
Piperacillin – adipose (uISF)	
(Busse *et al.*, 2021 a)	Included
(Joukhadar *et al.*, 2001)	Not preferred, already included (Piperacillin - muscle ISF)
(Brunner *et al.*, 2000)	Included, substitutes missing data in bone ISF
(Nolting *et al.*, 1996)	Not preferred, dosing mg/kg without individual bodyweight
Piperacillin – bone (uISF)	
No studies found	
Piperacillin – muscle (uISF)	
(Joukhadar *et al.*, 2001)	Included
(Brunner *et al.*, 2000)	Not preferred, already included (Piperacillin - muscle ISF)
Cefazolin – adipose (total)	
(Tchaick *et al.*, 2017)	Not preferred, population less suited (CPB)
(Kram *et al.*, 2017)	Excluded, unsuitable tissue data (obese)
(Young *et al.*, 2015)	Excluded, unsuitable tissue data (obese)
(Maggio *et al.*, 2015)	Excluded, unsuitable tissue data (obese)
(Ohge *et al.*, 1999)	Included
Cefazolin – bone (total)	
(Yamada *et al.*, 2011)	Included
(Deacon *et al.*, 1996)	Not preferred, lack of plasma data
(Friedman *et al.*, 1990)	Not preferred, older study
(Williams *et al.*, 1983)	Not preferred, older study
(Polk *et al.*, 1983)	Not preferred, older study
(Tetzlaff *et al.*, 1978)	Excluded, in children and unsuitable tissue data (infected bone)
(Cunha *et al.*, 1977)	Not preferred, older study
Cefazolin – muscle (total)	
(Dudley *et al.*, 1984)	Not preferred, population less suited (cardiac surgery)
(Polk *et al.*, 1982)	Not preferred, population less suited (cardiac surgery)
(Sinagowitz *et al.*, 1976)	Included
Cefazolin – adipose (uISF)	
(Palma *et al.*, 2018)	Excluded, unsuitable tissue data (obese)
(Himebauch *et al.*, 2016)	Excluded, study in adolescents (12-17 year)
(Roberts *et al.*, 2015)	Included, substitutes missing bone data study, population less suited (critically ill patients) but no better alternative study available
(Brill *et al.*, 2014)	Included, most suited study
(Andreas *et al.*, 2013)	Not preferred, population less suited (normothermic CPB)
(Bhalodi *et al.*, 2013)	Excluded, unsuitable tissue data (infected tissue)
(Douglas *et al.*, 2011)	Included, substitutes missing muscle data study, population less suited (cardiac surgery) but no better alternative study available
(Hutschala *et al.*, 2007)	Not preferred, population less suited (normothermic CPB)
Cefazolin – bone (uISF)	
(Andreas *et al.*, 2015)	Not preferred, unclear when second dose was administered
Cefazolin – muscle (uISF)	
No studies found	
Cefuroxime – adipose (total)	
(Lovering *et al.*, 1997)	Not preferred, lack of plasma data (only blood)
(Alfter *et al.*, 1995)	Not preferred, plasma data not suited (time intervals)

(Huizinga *et al.*, 1989)	Included
(Johnson, 1987)	Not preferred, lack of plasma data
(Adam *et al.*, 1979)	Not preferred, older study and full text unavailable
Cefuroxime – bone (total)	
(Gergs *et al.*, 2020)	Included
(Gergs *et al.*, 2014)	Not preferred, older study
(Garazzino *et al.*, 2011)	Excluded, unsuitable tissue data (septic tissue)
(Vuorisalo *et al.*, 2000)	Excluded, unsuitable tissue data (sample time unclear)
(Katzer *et al.*, 1997)	Not preferred, older study
(Kaukonen *et al.*, 1995)	Not preferred, plasma data not suited (time intervals)
(Nungu *et al.*, 1995)	Excluded, unsuitable tissue data (sample time unclear)
(Alvarez Ferrero *et al.*, 1994)	Not preferred, older study
(Rout and Frame, 1992)	Excluded, unsuitable tissue data (time intervals)
(Johnson, 1987)	Not preferred, lack of plasma data
(Davies *et al.*, 1986)	Not preferred, older study
(Hughes *et al.*, 1982)	Not preferred, older study
(Leigh *et al.*, 1982)	Not preferred, older study
(Lovering *et al.*, 1997)	Not preferred, lack of plasma data (only blood)
Cefuroxime – muscle (total)	
(Alfter *et al.*, 1995)	Not preferred, plasma data not available as with Kaukonen et al. 1995 but less datapoints
(Kaukonen *et al.*, 1995)	Included, no plasma data available but more datapoints than Alfter et al. 1995
(Connors *et al.*, 1990)	Excluded, unsuitable tissue data (sample time unclear)
Cefuroxime – adipose (uISF)	
(Hanberg *et al.*, 2021)	Included
(Hanberg *et al.*, 2020)	Not preferred, older study and lack of plasma data
(Tøttrup *et al.*, 2019)	Not preferred, older study
(Skhirtladze-Dworschak *et al.*, 2019)	Not preferred, population less suited (CPB)
(Barbour *et al.*, 2009)	Excluded, unsuitable tissue data (obese)
Cefuroxime – bone (uISF)	
(Hanberg *et al.*, 2021)	Not preferred, study already included (Cefuroxime - adipose uISF)
(Hanberg *et al.*, 2020)	Not preferred, lack of plasma data
(Tøttrup *et al.*, 2019)	Included
Cefuroxime – muscle (uISF)	
(Hanberg *et al.*, 2021)	Not preferred, (already included (Cefuroxime - adipose uISF))
(Hanberg *et al.*, 2020)	Not preferred, no plasma data
(Skhirtladze-Dworschak *et al.*, 2019)	Not preferred, population less suited (CPB)
(Schwameis *et al.*, 2017)	Included
(Barbour *et al.*, 2009)	Not preferred, population less suited (obese)
(Pojar *et al.*, 2008)	Excluded, unsuitable tissue data (time intervals)
Ceftazidime – adipose (total)	
(Raymakers *et al.*, 1998)	Excluded, unsuitable tissue data (amputated/infected limb)
(Dounis *et al.*, 1995)	Not preferred, lack of plasma data
(Papaioannou *et al.*, 1994)	Excluded, unsuitable tissue data (time-intervals)
(Frank *et al.*, 1987)	Excluded, unsuitable tissue data (time-intervals + hypothermic tissue (25-35°C))
(Loebis, 1986)	Included
(Adam *et al.*, 1983)	Not preferred, population less suited (cardiac surgery)
Ceftazidime – bone (total)	
(Lozano-Alonso *et al.*, 2016)	Excluded, unsuitable tissue data (amputated/infected limb)
(Dounis *et al.*, 1995)	Not preferred, lack of plasma data
(Papaioannou *et al.*, 1994)	Excluded, unsuitable tissue data (time intervals)
(Leigh *et al.*, 1985)	Excluded, unsuitable tissue data (time intervals)
(Adam *et al.*, 1983)	Not preferred, population less suited (cardiac surgery)
(Wittmann *et al.*, 1981)	Included
Ceftazidime – muscle (total)	
(Lozano-Alonso *et al.*, 2016)	Excluded, unsuitable tissue data (amputated/infected limb)
(Dounis *et al.*, 1995)	Not preferred, lack of plasma data
(Papaioannou *et al.*, 1994)	Excluded, unsuitable tissue data (time intervals)
(Frank *et al.*, 1987)	Excluded, unsuitable tissue data (hypothermic tissue 25-35°C)
(Loebis, 1986)	Included
(Adam *et al.*, 1983)	Not preferred, population less suited (cardiac surgery)

Ceftazidime – adipose (uISF)	
(Tůma *et al.*, 2022)	Excluded, unsuitable tissue data (diabetic/infected foot)
Ceftazidime – bone (uISF)	
No studies found	
Ceftazidime – muscle (uISF)	
No studies found	
Meropenem - adipose (total)	
No studies found	
Meropenem – bone (total)	
(Lozano-Alonso *et al.*, 2016)	Excluded, unsuitable tissue data (amputated/infected limb)
(Sano *et al.*, 1993)	Included
Meropenem – muscle (total)	
(Lozano-Alonso *et al.*, 2016)	Excluded, unsuitable tissue data (amputated/infected limb)
(Condon *et al.*, 1997)	Excluded, unsuitable tissue data (time intervals)
(Newsom *et al.*, 1995)	Included, population less suited (cardiac surgery) but no alternative study available
Meropenem – adipose (uISF)	
(Busse *et al.*, 2021 b)	Included
(Simon *et al.*, 2020)	Included, "substitutes" missing bone uISF study
(Hanberg *et al.*, 2018)	Not preferred, population less suited (CPB)
(Varghese *et al.*, 2015)	Not preferred, population less suited (hemodiafiltration)
(Wittau *et al.*, 2015)	Not preferred, population less suited (obese)
(Roberts *et al.*, 2009)	Not preferred, population less suited (septic)
Meropenem – bone (uISF)	
No studies found	
Meropenem – muscle (uISF)	
(Tomaselli *et al.*, 2004)	Included, population less suited (pneumonia) but no alternative studies available

[a]: *When multiple studies were available for a given tissue-drug pair, a single study was selected ("included") based on the predefined criteria noted in the methods section of the manuscript. Studies which were eligible for inclusion but were not selected are denoted as "not preferred".*

Abbreviations: CPB: cardio pulmonary bypass, uISF: unbound interstitial fluid.

Table S4: Demographic data of included studies

Drug - matrix pair	Population	Type and location of tissue sample	Age (years)[a]	Bodyweight (kg)[a]	Reported renal function[a]	Reference
Piperacillin						
Adipose (total)	Patients undergoing colorectal surgery for rectal-, colon- or sigmoid cancer, tubovillous adenoma or colostomy/ileostomy	Nontumorous abdominal subcutaneous fat	66.8 ± 12 (29-77)	72.3 ± 11.4 (53-93)	*"all patients were found to have normal kidney function in relation to their age"*	(Kinzig *et al.*, 1992)
Bone (total)	Patients undergoing an elective total hip replacement	Femoral cancellous bone	63.4 (44-86)	(45-102)	Excluded if CrCL <40mL/min or sCr >2.5mg/dl	(Incavo *et al.*, 1994)
Skeletal muscle (total)	Patients undergoing cholecystectomy or sphincteroplasty (biliary tract surgery)	Abdominal skeletal muscle	46 (21-74)	N.R.	CrCL: (51 - 106) mL/min	(Russo *et al.*, 1982)
Adipose (uISF)	Patients undergoing elective abdominal surgery (non-obese cohort)	Subcutaneous adipose tissue of both upper arms	>18	75 (67-84)	CrCL: (75.1 - 106)mL/min	(Busse *et al.*, 2021 a)
Adipose (uISF)	Healthy control group	Subcutaneous adipose layer of the thigh	(25-37)	81 ± 5	*"Normal kidney function tests"*	(Brunner *et al.*, 2000)
Skeletal muscle (uISF)	Healthy control group	Skeletal muscle	66 ± 3	76 ± 5	sCr: 1.06 ± 0.06 mg/dL	(Joukhadar *et al.*, 2001)
Cefazolin						
Adipose (total)	Patients undergoing pancreatic surgery	Subcutaneous abdominal adipose tissue	(52-79)	N.R., BMI: (16.8-27.5) kg/m²	CrCL ≥ 60 ml/min	(Ohge *et al.*, 1999)
Bone (total)	Patients undergoing total hip arthroplasty or total knee arthroplasty	Cancellous bone from the femur or tibia	74.8 ± 7.9	55.4 ± 8.2 (41-75)	sCr: 0.7 ± 0.2 (all < 1.5) mg/dL	(Yamada *et al.*, 2011)
Skeletal muscle (total)	Patients undergoing urological operations	Abdominal skeletal muscle which macroscopically looked well perfused	N.R.	N.R.	N.R.	(Sinagowitz *et al.*, 1976)
Adipose (uISF)	Non-obese patients undergoing Toupet fundoplication	Subcutaneous abdominal adipose tissue	52.7 ± 6.3 (42-61)	86.2 (72-109)	Excluded if eGFR < 60 mL/min	(Brill *et al.*, 2014)
Adipose (uISF)	Patients after major trauma and low to moderate illness severity	Subcutaneous tissue	37 ± 14 (19-65)	87 ± 23 (60-175)	CrCL: 163 ±44 (50-253) mL/min, sCr: 19.7 (40-145) µmol/L	(Roberts *et al.*, 2015)
Adipose (uISF)	Patients undergoing semi elective abdominal aortic aneurism open repair surgery	Subcutaneous tissue of the upper arm	70 (59-81)	88 (80-128)	CrCL: 98 (37-236) mL/min , sCr: 88 (68-137) µmol/L	(Douglas *et al.*, 2011)
Cefuroxime						
Adipose (total)	Patients undergoing elective abdominal operations	Subcutaneous adipose tissue of the abdomen	42.6 (27-66)	71.6 ± 6.8	*"All patients had normal renal function"*	(Huizinga *et al.*, 1989)

Bone (total)	Patients undergoing hip surgery	Cancellous pelvic bone	65 ± 9.1	N.R., BMI 27.7 ± 3.5 kg/m²	Excluded if sCr > 130 µmol/L	(Gergs *et al.*, 2020)
Skeletal muscle (total)	Patients with hip fracture undergoing hemiarthroplasty	Skeletal muscle of the thigh	81 (59-96)	58 (39-100)	N.R.	(Kaukonen *et al.*, 1995)
Adipose (uISF)	Patients undergoing hallux valgus or hallux rigidus surgery	Subcutaneous tissue from non-tourniquet mid-lower leg	58 (45-67)	72 (56-89)	sCr: 75 (60-90) µmol/L	(Hanberg *et al.*, 2021)
Bone (uISF)	Patients undergoing a total knee replacement	Cancellous tibia bone	68.7 (58-76)	99 (73-110)	sCr: 76 (64-99) µmol/L	(Tøttrup *et al.*, 2019)
Skeletal muscle (uISF)	Patients undergoing an elective knee arthroscopy	Skeletal muscle of the thigh	34.2 ± 13.6 (45-67)	N.R.	N.R.	(Schwameis *et al.*, 2017)
Ceftazidime						
Adipose (total)	Surgical patients (gynecological and other cases)	Fatty tissue	N.R.	(34-75)	N.R.	(Loebis, 1986)
Bone (total)	Patients undergoing a total hip arthroplasty	Bone from the femur or pelvis	58.4 ± 10.2	N.R.	*"Normal renal function"*	(Wittmann *et al.*, 1981)
Skeletal muscle (total)	Surgical patients (gynecological and other cases)	Skeletal muscle	N.R.	(34-75)	N.R.	(Loebis, 1986)
Meropenem						
Bone (total)	Patients undergoing orthopedic surgery (total hip or knee replacement, other joint surgery, laminectomy or joint aspiration)	Bone	56.3 (29-75)	N.R.	N.R.	(Sano *et al.*, 1993)
Cardiac muscle (total)	Patients undergoing cardiac valve surgery (aortic or mitral -stenosis, -incompetence or -valve incompetence)	Atrial cardiac muscle tissue	65.3 (47-75)	69.2 (45.5-91)	N.R.	(Newsom *et al.*, 1995)
Adipose (uISF)	Non-obese control subjects	Subcutaneous adipose tissue of both upper arms	50 (31-64)	65 (52-84)	CrCL: 76 (53.6-136) mL/min, sCr: 66.4 (51.8-127) µmol/L	(Busse *et al.*, 2021 b)
Adipose (uISF)	Non-obese patients undergoing elective abdominal surgery (mainly tumor resection)	Subcutaneous adipose tissue of both upper arms	49.5 ± 10	67.9 ± 8.8	sCr: 75.3 ± 18.8 µmol/L	(Simon *et al.*, 2020)
Skeletal muscle (uISF)	Patients with sepsis undergoing decortication over al lateral thoracotomy for pneumonia	Healthy pectoralis major muscle tissue	58.7 (30-70)	72.3 (68-87)	N.R.	(Tomaselli *et al.*, 2004)

[a]: data presented as mean or median ± standard deviation (min-max)

Abbreviations: BMI: body mass index, CrCL: creatinine clearance, eGFR: estimated glomerular filtration rate, N.R.: Not reported, sCr: serum creatinine, uISF: unbound interstitial fluid concentration

Table S5 Bioanalytical data of included studies

Drug-Matrix	Analysis method	LLOQ tissue samples	External calibration	Sampling interval	Reported time	Data format	Reference observed data
Piperacillin							
Adipose (total)	HPLC-UV	0.10 µg/mL	No blood contamination correction	Exact	Exact	Figure	(Kinzig *et al.*, 1992)
Bone (total)	HPLC-UV	0.157 µg/mL	No blood contamination correction	Exact	Exact	Table	(Incavo *et al.*, 1994)
Skeletal muscle (total)	Microbiologic	N.R.	Blood contamination correction (3-5%)	Exact	Exact	Table	(Russo *et al.*, 1982)
Adipose (uISF)	HPLC-UV	0.03 mg/mL	Retrodialysis calibration	30 or 60 minutes	Midpoint	Figure	(Busse *et al.*, 2021 a)
Adipose (uISF)	HPLC-UV	2 µg/mL	Retrodialysis calibration	20 minutes	Endpoint[a]	Figure	(Brunner *et al.*, 2000)
Skeletal muscle (uISF)	HPLC-UV	2 µg/mL	Retrodialysis calibration	20 minutes	Endpoint[a]	Figure	(Joukhadar *et al.*, 2001)
Cefazolin							
Adipose (total)	Microbiologic	0.063 µg/mL	N.R.	Exact	Exact	Figure	(Ohge *et al.*, 1999)
Bone (total)	HPLC-UV	N.R.	N.R.	Exact	Exact	Figure	(Yamada *et al.*, 2011)
Skeletal muscle (total)	Microbiologic	N.R.	Blood contamination correction (6.3%)	Exact	Exact	Figure	(Sinagowitz *et al.*, 1976)
Adipose (uISF)	HPLC-UV	1.0 µg/mL	Retrodialysis calibration	20 minutes	Midpoint[a]	Figure	(Brill *et al.*, 2014)
Adipose (uISF)	HPLC-MS/MS	N.R.	Retrodialysis calibration	20 or 30 minutes	Endpoint[a]	Figure	(Roberts *et al.*, 2015)
Adipose (uISF)	HPLC-MS/MS	N.R.	Retrodialysis calibration	30 minutes	Endpoint[a]	Figure	(Douglas *et al.*, 2011)
Cefuroxime							
Adipose (total)	HPLC-UV	1.0 µg/g	No blood contamination correction	Exact	Exact	Figure	(Huizinga *et al.*, 1989)
Bone (total)	HPLC-UV	0.1µg/mL	N.R.	Exact	Exact	Figure[b]	(Gergs *et al.*, 2020)
Skeletal muscle (total)	HPLC-UV	1.25 µg/mL	Blood contamination correction (<30%)	Exact	Exact	Table	(Kaukonen *et al.*, 1995)
Adipose (uISF)	HPLC-UV	0.06 µg/mL	Retrodialysis calibration	15, 30 or 60 minutes	Midpoint	Figure	(Hanberg *et al.*, 2021)
Bone (uISF)	HPLC	0.06 µg/mL	Retrodialysis calibration	30 minutes	Midpoint	Figure	(Tøttrup *et al.*, 2019)
Skeletal muscle (uISF)	HPLC-UV	0.3 µg/mL	Retrodialysis calibration	30 or 60 minutes	Endpoint	Figure	(Schwameis *et al.*, 2017)
Ceftazidime							
Adipose (total)	Microbiologic	N.R.	Blood contamination correction	Exact	Exact	Figure	(Loebis, 1986)
Bone (total)	Microbiologic	0.08 µg/mL	*"Samples contaminated with blood were excluded"*	Exact	Exact	Table[c]	(Wittmann *et al.*, 1981)
Skeletal muscle (total)	Microbiologic	N.R.	Blood contamination correction	Exact	Exact	Figure	(Loebis, 1986)
Meropenem							
Bone (total)	Microbiologic	N.R.	N.R.	Exact	Exact	Table	(Sano *et al.*, 1993)
Cardiac muscle (total)	HPLC-UV	0.01 µg/mL	No blood contamination correction	Exact	Exact	Figure	(Newsom *et al.*, 1995)
Adipose (uISF)	HPLC-UV	0.02 µg/mL	Retrodialysis calibration	30 or 60 minutes	Midpoint	Figure	(Busse *et al.*, 2021 b)
Adipose (uISF)	HPLC-UV	0.02 µg/mL	Retrodialysis calibration	30 or 60 minutes	Midpoint	Figure	(Simon *et al.*, 2020)
Skeletal muscle (uISF)	HPLC	N.R.	Retrodialysis calibration	20 minutes	Midpoint	Figure	(Tomaselli *et al.*, 2004)

Abbreviations: HPLC: high pressure liquid chromatography, LLOQ: lower limit of quantification, MS/MS tandem mass spectrometry, , N.R.: not reported, uISF: unbound interstitial fluid concentration, UV: ultraviolet spectrometry

[a]*: not explicitly mentioned but assumed based on reported methodology and results*

[b]*: plasma samples digitized up to 330 minutes (after that, limited contrast with zero on graph)*

[c]*: plasma samples after 8 and 12h excluded*

Table S6 Area under the curve (AUC) assessment for PBPK model verification

		$AUC_{Plasma,u}$			AUC_{Tissue}			$AUC_{Tissue/Plasma,u}$			
Drug - Matrix	**AUC interval**	**Observed (mg.min/mL)**	**Predicted (mg.min/mL)**	**FE**	**Observed (mg.min/mL)**	**Predicted (mg.min/mL)**	**FE**	**Observed**	**Predicted**	**FE**	**Reference observed data**
Piperacillin											
Adipose (total)	0-inf	289[a]	254	0.88	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	(Kinzig *et al.*, 1992)
Adipose (uISF)	0-4h	70	216	3.10	29	209	7.32	0.43	0.97	2.25	(Brunner *et al.*, 2000)
Muscle (uISF)	0-4h	506	237	0.47	264	232	0.88	0.55	0.98	1.78	(Joukhadar *et al.*, 2001)
Cefazolin											
Adipose (uISF)	0-4h	N.R.	108	N.R.	N.R.	106	N.R.	1.02	0.98	0.96	(Brill *et al.*, 2014)
Adipose (uISF)	0-6h	46	52	1.12	33	52	1.58	0.74	1.00	1.35	(Roberts *et al.*, 2015)
Adipose (uISF)	0-8h	78	132	1.71	66	132	2.01	0.85	1.00	1.17	(Douglas *et al.*, 2011)
Cefuroxime											
Adipose (uISF)	0-6h	92 [a]	113	1.23	142	113	0.80	1.64[a]	1.00	0.61	(Hanberg *et al.*, 2021)
Bone (uISF)	0-inf	97	110	1.14	101	110	1.09	1.03	1.00	0.97	(Tøttrup *et al.*, 2019)
Muscle (uISF)	0-8h	101	99	0.98	178	99	0.56	1.79	1.00	0.56	(Schwameis *et al.*, 2017)
Meropenem											
Adipose (uISF)	0-8h	N.R.	87	N.R.	N.R.	86	N.R.	0.31 [a]	1.00	3.23	(Busse *et al.*, 2021 b)
Adipose (uISF)	0-inf	88 [a]	94	1.07	45	94	2.12	0.49 [a]	1.00	2.04	(Simon *et al.*, 2020)
Muscle (uISF)	0-8h	93 [a]	101	1.08	44	101	2.29	0.61 [a]	1.00	1.63	(Tomaselli *et al.*, 2004)

[a]: observed unbound AUC in plasma obtained by multiplying reported total AUC in plasma value by the free fraction used in the PBPK simulation

Abbreviations: $AUC_{Plasma,u}$*: area under the curve unbound plasma,* AUC_{Tissue}*: area under the curve tissue (total or unbound interstitial fluid concentration),* $AUC_{Tissue/Plasma,u}$ *: penetration ratio (ratio* AUC_{Tissue} *to* $AUC_{Plasma,u}$ *), FE: fold error, N.R.: not reported, uISF: unbound interstitial fluid concentration.*

Table S7: Characteristics of the simulated populations

Population	Body weight (kg)	Body mass index (kg/m²)	GFR (mL/min/ 1.73m²)	Serum albumin (g/L)	Adipose blood flow (L/h)	Adipose volume (L)	Adipose perfusion[a] (h^{-1})
Reference population	77.1 (52.9-105.2)	27.2 (19.6-35.6)	110 (61-171)	44.9 (38.0-53.0)	20.3 (13.7-28.4)	26.7 (5.4-48.5)	1.06 (0.40-3.07)
High cardiac output	77.1 (52.9-105.2)	27.2 (19.6-35.6)	110 (61-171)	44.9 (38.0-53.0)	40.5 (27.4-56.7)	26.7 (5.4-48.5)	2.13 (0.80-6.15)
Low cardiac output	77.1 (52.9-105.2)	27.2 (19.6-35.6)	110 (61-171)	44.9 (38.0-53.0)	10.1 (6.9-14.2)	26.7 (5.4-48.5)	0.53 (0.20-1.54)
Obese	97.5 (78.5-118.3)	34.9 (31.7-38.4)	159 (84-247)	43.9 (36.5-52.0)	39.5 (27.9-54.0)	43.1 (25.4-58.6)	0.98 (0.60-1.51)
Morbidly obese	123.2 (100.2-155.5)	44.6 (40.8-49.0)	209 (116-316)	43.1 (35.9-51.2)	54.7 (43.9-67.3)	63.1 (43.3-83.8)	0.90 (0.63-1.24)

Data presented as mean and 90 percentiles (5-95%) of simulated population,

[a] : adipose perfusion calculated as adipose blood flow/adipose volume,

Abbreviations: GFR: glomerular filtration rate.

Table S8 Selection of EUCAST minimal inhibitory concentrations (MIC) (mg/L)

	Piperacillin	Cefazolin	Cefuroxime	Ceftazidime	Meropenem
Non-species related (PK-PD)	16	2	8	8	8
Enterobacteriaceae	8	4	8	4	8
Escherichia coli	8*	4*	8*	1*	0.06*
Pseudomonas aeruginosa	16	-	-	8*	2*
Staphyloccoccus aureus	4*	2*	4*	32*	0.5*
Streptococcus groups A,B, C and G	0.25	0.25	0.25	0.25	0.25
Streptococcus pneumoniae	1	-	-	1	2

MIC breakpoints (Resistant, R>) taken from The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022. http://www.eucast.org"

**: Epidemiological cut-off values (ECOFF), data from EUCAST MIC distribution website, last accessed 14/Dec/2022. http://www.eucast.org.*

PK-PD: pharmacokinetic-pharmacodynamic

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