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REVIEW ARTICLE

Four Decades of β-Lactam Antibiotic Pharmacokinetics in Cystic Fibrosis

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Abstract The pharmacokinetics (PK) of β-lactam antibiotics in cystic fibrosis (CF) patients has been compared with that in healthy volunteers for over four decades; however, no quantitative models exist that explain the PK differences between CF patients and healthy volunteers in older and newer studies. Our aims were to critically evaluate these studies and explain the PK differences between CF patients and healthy volunteers. We reviewed all 16 studies that compared the PK of β-lactams between CF patients and healthy volunteers within the same study. Analysis of covariance (ANCOVA) models were developed. In four early studies that compared adolescent, lean CF patients with adult healthy volunteers, clearance (CL) in CF divided by that in healthy volunteers was 1.72 ± 0.90 (average ± standard deviation); in four additional studies comparing age-matched (primarily adult) CF patients with healthy volunteers, this ratio was 1.46 ± 0.16. The CL ratio was 1.15 ± 0.11 in all eight studies that compared CF patients and healthy volunteers who were matched in age, body size and body composition, or that employed allometric scaling by lean body mass (LBM). Volume of distribution was similar between subject groups after scaling by body size. For highly protein-bound β-lactams, the unbound fraction was up to 2.07-fold higher in older studies that compared presumably sicker CF patients with healthy volunteers. These protein-binding differences explained over half of the variance for the CL ratio ($p < 0.0001$, ANCOVA). Body size, body composition and lower protein binding in presumably sicker CF patients explained the PK alterations in this population. Dosing CF patients according to LBM seems suitable to achieve antibiotic target exposures.

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Key Points

The pharmacokinetics of β-lactam antibiotics in cystic fibrosis (CF) patients is comparable with that in healthy volunteers after accounting for body size, body composition and potentially altered protein binding.

For highly protein-bound β-lactams, early studies in presumably sicker patients reported a considerably lower protein binding in adolescent CF patients compared with that in adult healthy volunteers.

Dosing of β-lactam antibiotics in CF patients based on allometric scaling according to LBM is useful to achieve antibiotic target exposures.

1 Introduction

The pharmacokinetics (PK) of β-lactam antibiotics in cystic fibrosis (CF) patients has been evaluated for over four decades. During this time, extensive advances in the overall care of CF patients have substantially improved their life expectancy and quality of life. However, there is considerable discordance in the PK of β-lactam antibiotics in CF patients between older and newer studies.

Studies published before 1985 found substantially higher clearances (CL) and volumes of distribution at steady state (V_{ss}) for CF patients compared with those in healthy volunteers [1, 2]. These studies reported CL and V_{ss} per kilogram total body weight (WT), and therefore linearly scaled these PK parameters by WT; however, this approach does not account for the leaner body composition of CF patients compared with that of healthy volunteers.

More recent studies found smaller differences in CL and V_{ss} of β-lactam antibiotics between CF patients and healthy volunteers [1, 2]; these differences could be well explained by body size and body composition. Several of the more recent studies used allometric scaling by body size [3] to compare CF patients and healthy volunteers. This approach scales V_{ss} linearly, whereas CL increases less than linearly with body size. Consequently, allometric scaling predicts the elimination half-life to be shorter in smaller patients (Fig. 1) [3, 4]. Several of these more recent studies applied population PK modelling to additionally estimate the between-subject variability. To translate these PK insights into optimal dosage regimens, it is important to consider the bacterial pathogen(s) that cause serious infections in CF patients.

Pseudomonas aeruginosa is among the most critical Gram-negative bacterial pathogens in CF patients. This 'superbug' causes substantial clinical challenges and can become resistant during treatment with any antibiotic in monotherapy [5–7]. Chronic lung infections by *P. aeruginosa* in CF patients are extremely difficult to eradicate [8–10]; therefore, achieving the targeted antibiotic exposure in CF patients is paramount to cure *Pseudomonas* infections.

Rationally optimized monotherapies, and especially combination therapies with available antibiotics, present a tangible and promising approach to combat *P. aeruginosa* infections [11–19]. To optimize these antibiotic dosage regimens, PK/pharmacodynamic (PK/PD) relationships have been established using both in vitro and animal infection models. These non-clinical models have been employed for over half a century [20–25] and their insights underpin our current approaches of how to optimally treat bacterial infections. To leverage these insights, it is important to know and understand potential PK alterations in a target population such as CF patients.

This review aimed to compare the PK of β-lactam antibiotics in CF patients with that in healthy volunteers, and to explain the observed differences between both subject groups. These PK insights allow us to design dosage regimens that more precisely achieve the targeted exposure of β-lactam antibiotics in CF patients. We discuss these PK considerations in the context of *P. aeruginosa* infections and their mechanisms of resistance to β-lactam antibiotics. Moreover, this review provides a future

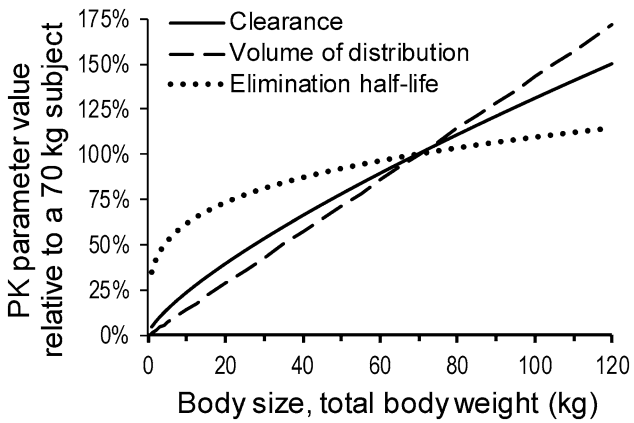

Fig. 1 Comparison of linear scaling for volume of distribution and allometric scaling for clearance in subjects of different body size. Volume of distribution is predicted to be 50% lower in a 35 kg patient compared with a 70 kg patient; however, clearance is only approximately 41% lower in a 35 kg patient. Therefore, allometric scaling predicts a slightly shorter elimination half-life in smaller patients. For this illustration, body size is represented as total body weight. To account for body composition in addition to body size, other body size descriptors such as lean body mass have been used for cystic fibrosis patients

perspective on recent approaches to rationally optimize antibiotic monotherapies and combination therapies that may benefit CF patients.

2 Review of Pharmacokinetic (PK) Data

2.1 PK of β-Lactam Antibiotics in Cystic Fibrosis Patients

We reviewed the literature for studies that compared the PK of β-lactam antibiotics in CF patients with that in healthy volunteers within the same study. For intravenously administered β-lactams, we compared total CL; renal CL was compared for orally administered β-lactams (such as dicloxacillin). In contrast to the apparent total CL after oral dosing, renal CL is not affected by potential differences in oral bioavailability between CF patients and healthy volunteers. Our search included not only MEDLINE but also studies cited in prior reviews [1, 2, 26, 27], using the keywords 'cystic fibrosis', 'pharmacokinetic*', and (clearance OR half-life OR volume of distribution).

2.2 Comparison of Clearance and Volume of Distribution

To compare volume of distribution between both subject groups, we divided the average V_{ss} in CF patients by V_{ss} in healthy volunteers after accounting for body size. The latter was achieved via scaling V_{ss} linearly by WT or lean body mass (LBM). This V_{ss} ratio was used for statistical analysis. As the unbound fraction (fu) differed between both subject groups, we additionally calculated V_{ss} based on unbound drug ($V_{ss,u} = V_{ss}/fu$) [28]. The resulting ratio of $V_{ss,u}$ in both subject groups ($V_{ss,u,CF}/V_{ss,u,HV}$) was calculated by dividing the $V_{ss,CF}/V_{ss,HV}$ for total drug by the ratio of unbound fractions (fu_{CF}/fu_{HV}).

Similarly, we divided the average CL in CF patients by that in healthy volunteers. This CL ratio based on total drug concentrations (i.e. CL_{CF}/CL_{HV}) is useful for β-lactams with low protein binding; however, it is affected by differences in protein binding between CF patients and healthy volunteers. We therefore utilized two methods to account for protein binding. The first approach calculated CL of unbound drug (CL_u) by dividing CL for total drug by fu in the respective subject group (i.e. $CL_u = CL/fu$). This approach is applicable for β-lactams with low or intermediate plasma protein binding and a total CL of less than approximately 30% of renal blood flow (i.e. for β-lactams with a low renal extraction ratio) [29].

The second approach is most suitable for β-lactams with high protein binding and high CL (i.e. dicloxacillin, cloxacillin and methicillin), and assumed a well-stirred elimination model [29–31]. For these drugs, extensive renal tubular secretion contributes substantially to total CL. In the well-stirred model, the intrinsic CL (CL_{int}) represents a transporter-mediated secretion process and can be very large. However, the observed overall secretion CL (CL_{sec}) is limited by renal blood flow (Q), since $CL_{sec} = (Q \cdot CL_{int} \cdot fu)/(Q + CL_{int} \cdot fu)$ [29–31]. Prior studies showed that Q is similar in CF patients and healthy volunteers [32]; we set Q to 63.9 L/h for subjects with 1.73 m^2 body surface area (BSA).

The glomerular filtration rate (GFR) was set to 7.0 L/h (equivalent to 11% of renal blood flow). Glomerular filtration CL was calculated as fu·GFR and was subtracted from the observed total CL; the remainder was attributed to CL_{sec}. Rearranging for CL_{sec} yields $CL_{int} = (Q \cdot CL_{sec})/[fu \cdot (Q - CL_{sec})]$. For three β-lactams (i.e. dicloxacillin, cloxacillin and methicillin), we reported the ratio of CL_{int} between CF patients and healthy volunteers ($CL_{int\ CF}/CL_{int\ HV}$) and used it for statistical analyses. This second approach considers that protein binding affects the glomerular filtration CL, but not renal tubular secretion.

2.3 Analysis of Covariance Statistics

We performed an analysis of covariance (ANCOVA) on log-scale to identify factors that influenced the ratio of CL and V_{ss} between CF patients and healthy volunteers, using the XLSTAT software (version 19.02). The ratio of the unbound fractions (fu_{CF}/fu_{HV}) in both subject groups was included as a potential predictor for the CL and V_{ss} ratios. Supported by the results for cefsulodin and ceftazidime (Table 2), we assumed that protein binding in CF patients and healthy volunteers did not differ (i.e. $fu_{CF}/fu_{HV} = 1$) for β-lactams with low protein binding (fu ≥ 70%, i.e. cefepime, meropenem, piperacillin, carumonam and cefpirome) (Table 1).

For β-lactams with intermediate protein binding (i.e. methicillin, and ticarcillin), we either assumed the same protein binding in both subject groups or used a nearest-neighbour imputation algorithm (as implemented in XLSTAT) for missing data during ANCOVA. As both approaches yielded near-identical or identical results, results for the latter approach are not shown. The second study on dicloxacillin [33] was not included in the ANCOVA since it did not report protein binding and its PK results differed substantially from those of an earlier study that reported protein binding in CF patients and healthy volunteers for dicloxacillin [34].

The demographic differences between the studied subject groups was included as an additional categorical predictor in the ANCOVA model (Table 2). We categorized the PK studies into three groups. The first group included studies that compared the PK in primarily adolescent CF patients with that in adult healthy volunteers. On average,

CF patients were more than 35% younger than their healthy volunteer control groups, and, as expected, WT, LBM and BSA differed substantially between subject groups in these four studies (Table 2, Fig. 2) [34–37].

Study group 2 primarily compared adult CF patients with adult healthy volunteers [33, 38, 39], or used age-matched subjects of various ages [40]. In this group, while mean age differed by 12% or less, WT and LBM were 24–28% and 23% smaller, respectively, in CF patients compared with healthy volunteers (Table 2, Fig. 2). These studies scaled CL and V linearly by either BSA or WT, and thus did not account for differences in body composition.

The third group included eight PK studies [41–48] where CF patients and healthy volunteers were matched in body size (LBM within ± 10%), or allometric scaling by LBM was employed in a population PK modelling analysis (Table 2, Fig. 2). This modelling approach accounted for both body size and body composition when comparing the PK in CF patients with that in healthy volunteers. Population modelling is particularly suitable to account for differences in body size and body composition while considering between-subject variability [49].

3 Comparison of Pharmacokinetic Properties between both Subject Groups

3.1 Lower Protein Binding in CF Patients

For highly protein-bound β-lactams such as dicloxacillin, considerably higher (2.07-fold) unbound fractions (i.e. lower protein binding) were reported in CF patients compared with healthy volunteers [34] (Table 1). The fu_{CF}/fu_{HV} ratio was 1.37-fold for cloxacillin and 1.19-fold in a more recent study on aztreonam [37, 44]. In contrast, protein binding was well comparable for less protein-bound β-lactams such as cefsulodin and ceftazidime.

3.2 PK Comparison for Studies Not Matched in Body Size and Body Composition

A comparison of the demographic properties of subjects in the three groups of PK studies revealed important differences (Fig. 2). The first group was comprised of presumably sicker CF patients who were studied in the 1970s and early 1980s. These CF patients were substantially younger and leaner than their healthy volunteer control groups (Table 2). In these four studies, CL of total drug (reported in L/h/1.73 m^2) in CF patients, divided by CL in healthy volunteers, was 1.72 ± 0.90 (Table 3). After accounting for the reported differences in protein binding, this ratio had a mean of 1.42 ± 0.34. For V_{ss}, this ratio was 1.13 ± 0.42, expressed as L/kg, and 1.01 ± 0.35 after accounting for protein binding. Of note, the studies in group 1 contained highly protein-bound β-lactams (i.e. dicloxacillin and cloxacillin), which are active against *Staphylococcus aureus* but not *P. aeruginosa*.

The CF patients in the second group had either similar mean age compared with their healthy volunteer control groups, or were age-matched (Table 2, Fig. 2); however, CF patients had a 24–28% lower WT compared with their healthy volunteer control groups. In these four studies, the CL ratio in CF patients compared with healthy volunteers was 1.46 ± 0.16 based on total drug, and 1.29 ± 0.48 after accounting for protein binding. CL was linearly scaled by WT or BSA, and thus the CL comparison did not account

Table 1 Comparison of fraction of drug bound in plasma

Antibiotic	Fraction bound in plasma		Fraction unbound (fu) in plasma		Ratio
	CF patients	HVs	CF patients	HVs	fu_{CF}/fu_{HV}
Dicloxacillin [34]	88.4 ± 7.7%	94.4 ± 1.9%	11.6 ± 7.7%	5.6 ± 1.9%	2.07
Methicillin [93]		49.3%		50.7%	
Cefsulodin [36]	17%	15%	83%	85%	0.98
Cloxacillin [37]	94.8 ± 5.1%	96.2 ± 2.1%	5.2 ± 5.1%	3.8 ± 2.1%	1.37
Ceftazidime [38]	3.1 ± 6.1%	2.0 ± 5.6%	96.9 ± 6.1%	98.0 ± 5.6%	0.99
Ticarcillin [39, 94, 95]		45 to 65%		35–55%	
Cefepime [96]		10%		90%	
Meropenem [56, 97]		< 2%		> 98%	
Aztreonam [44]	42.1 ± 2.7%	51.5 ± 3.1%	57.9 ± 2.7%	48.5 ± 3.1%	1.19
Piperacillin [45, 98]		30%		70%	
Carumonam [46, 99]		23%		77%	
Cefpirome [48, 100]		10%		90%	

Empty cells indicate no data

CF cystic fibrosis, *HVs* healthy volunteers, fu_{CF} fraction of drug unbound in plasma in CF patients, fu_{HV} fraction of drug unbound in plasma in HVs

Table 2 Demographic characteristics of CF patients and HVs

Study, year	Antibiotic	Age (years)			Total body weight (kg)			LBM (kg)			Body surface area (m^2)		
		CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs
Group 1													
Jusko et al. [34], 1975	Dicloxacillin	14.2 ± 4.9	26 ± 4	0.55	39.0 ± 14.9	68.7 ± 9.2	0.57						
Yaffe et al. [35], 1977	Methicillin	16.4 ± 3.9	25.7 ± 2.8	0.64							1.53 ± 0.18	1.83 ± 0.18	0.84
Arvidsson et al. [36], 1983	Cefsulodin	16.2 ± 5.3	33.8 ± 13.2	0.48							1.37 ± 0.24	1.81 ± 0.12	0.76
Spino et al. [37], 1984	Cloxacillin	14.2 ± 3.3	22.2 ± 1.0	0.64	40.8 ± 9.2	67.3 ± 13.0	0.61	34.4	51.5	0.67	1.33 ± 0.16	1.78 ± 0.21	0.75
Group 2													
Leeder et al. [38], 1984	Ceftazidime	20.8 ± 4.8	21.6 ± 1.9	0.96	55.2 ± 9.1	77.0 ± 14.8	0.72	45.6 ± 7.4	59.4 ± 12.2	0.77	1.63 ± 0.16	1.95 ± 0.26	0.84
De Groot et al. [39], 1990	Ticarcillin	20.8 ± 5.2	23.7 ± 5.7	0.88	52.5 ± 9.5	72.6 ± 14.7	0.72				1.55 ± 0.19	1.89 ± 0.24	0.82
Huls et al. [40], 1993	Cefepime	Mean: 15.3[a] Range 7–25	Mean: 16.2[a] Range 8–27	0.94	37[b]	49[b]	0.76						
Beringer et al. [33], 2008	Dicloxacillin	27 [23–38]	25 [23–28]	1.08	54.5 [49.5–59]	72.0 [56.4–90.5]	0.76	44[c]	57[c]	0.77			
Group 3													
Hedman et al. [41], 1990	Cefsulodin	19.2 ± 3.3	21.8 ± 4.6	0.88	55.4 ± 10.5	60.0 ± 9.9	0.92	46.9 ± 8.0	46.0 ± 10.0	1.02	1.64 ± 0.17	1.66 ± 0.17	0.99
Hamelin et al. [42], 1993	Cefepime	24 ± 5	25 ± 4	0.96	54.8 ± 7.3	58.1 ± 8.7	0.94	45.9 ± 7.6	47.9 ± 8.9	0.96	1.6 ± 0.1	1.7 ± 0.2	0.94
Christensson, et al. [43], 1998	Meropenem	24 ± 4	25 ± 5	0.96	62 ± 8.0	65 ± 6.0	0.95				1.72 ± 0.15	1.80 ± 0.10	0.96
Bulitta et al. [45], 2007	Piperacillin	21 ± 4	25 ± 4	0.84	43.1 ± 7.8	71.1 ± 11.8	0.61	37.2 ± 6.9	56.4 ± 7.2	0.66	1.38 ± 0.18	1.85 ± 0.18	0.75
Vinks et al. [44], 2007	Aztreonam	29.8 ± 3.2	26.6 ± 4.0	1.15	54.9 ± 6.6	58.8 ± 6.9	0.93	43.9 ± 5.7	45.6 ± 4.9	0.96	1.62 ± 0.12	1.66 ± 0.10	0.98
Bulitta et al. [46], 2009	Carumonam	21 [19–25]	25 [21–37]	0.84	54 [47–61]	61 [50–107]	0.89	47.9 [41.9–52.9]	49.7 [40.0–82.2]	0.96	1.64 [1.48–1.76]	1.73 [1.53–2.46]	0.95
Bulitta et al. [47], 2010	Ceftazidime	20 [10–45]	22 [19–33]	0.91	37.9 [14.2–73.5]	67 [56–71]	0.57	34.7 [13.3–58.6]	54.5 [46.7–60.5]	0.64			

Table 2 continued

Study, year	Antibiotic	Age (years)			Total body weight (kg)			LBM (kg)			Body surface area (m^2)		
		CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs	CF patients	HVs	Ratio CF/HVs
Bulitta et al. [48], 2011	Cefpirome	22.5 [18–34]	29 [20–35]	0.78	53.3 [31.5–66.5]	63.6 [53.0–85.0]	0.84	45.7 [26.2–55.9]	50.0 [41.8–62.7]	0.91			

Data are expressed as mean ± standard deviation or median [range]

Empty cells indicate mean data not reported

Study group 1: Primarily juvenile or adolescent CF patients vs. adult HVs

Study group 2: Primarily adult CF patients vs. adult HVs with linear scaling by total body weight

Study group 3: CF patients and HVs matched within < 10% in LBM (or total body weight) or allometric scaling by LBM

CF cystic fibrosis, *HVs* healthy volunteers, *LBM* lean body mass

[a]Each CF patient was age-matched (within 2 years) with a non-CF patient

[b]Calculated from the mean clearances reported in mL/min and mL/min/kg

[c]Calculated as weighted average over both sexes based on the reported median total body weight and body mass index data

for body composition. Interestingly, the dicloxacillin study in group 2 only found a 27% higher CL in CF patients compared with healthy volunteers. The ratio for V_{ss} (reported as L/kg) was 1.27 ± 0.12 based on total drug, and 1.11 ± 0.35 for unbound drug (Table 3).

3.3 PK Comparison While Accounting for Body Size and Composition

All eight studies in group 3 accounted for body size and body composition, and primarily compared adult CF patients with healthy volunteers. Subject groups were matched within 8% of LBM or WT, or body size and body composition were accounted for via allometric scaling by LBM within a population PK modelling analysis. The CL ratio based on total drug was within 1.00 and 1.31 for all eight studies, with an average ± standard deviation of 1.15 ± 0.11. After accounting for protein binding, this value was 1.13 ± 0.10 (range 1.00–1.27) (Table 3). The CF patients in group 3 had similar V_{ss} compared with the healthy volunteers (V_{ss} ratio: 1.00 ± 0.10).

The ANCOVA showed that differences in fu (i.e. fu_{CF}/fu_{HV}) and the study group were significant predictors ($p \leq 0.004$) for the CL and V_{ss} ratios, based on total drug concentrations (Table 4). These two factors explained 89% of the total variance for the CL ratio and 70% for the V_{ss} ratio (Fig. 3).

4 Clinical Implications and Future Perspectives

4.1 Greatly Improved Life Expectancy of CF Patients

The life expectancy of CF patients increased from a few months in the 1930s to 14 years in 1969 [1]. In the US, life expectancy was 31.3 years in 1996 [50] and 49.7 years in 2012 [51], while in Denmark, CF patients had a probability of living to at least 40 years that was as high as 83.3% in 1995 [52]. These improvements reflect impressive advances in the overall management and treatment of CF. In turn, this entails that CF patients in the earlier studies in the 1970s and early 1980s were, on average, sicker and leaner than CF patients studied in the 1990s and later (Fig. 2).

4.2 First Quantitative Model to Explain PK Alterations of β-Lactams in CF Patients

This review is the first to develop a quantitative model that compares the PK of β-lactams in CF patients with that in healthy volunteers from older and newer studies, accounting for differences in protein binding and demographic characteristics. We focused on the 16 studies that

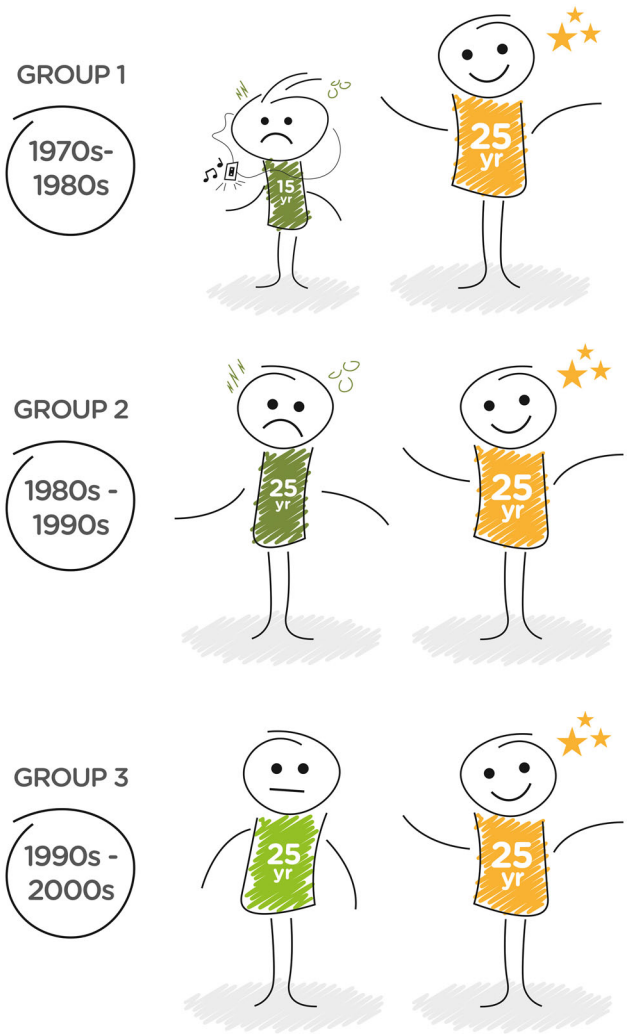

Fig. 2 Comparison of CF patients (left) and HVs (right) from the three groups of PK studies. In group 1, CF patients were considerably younger and leaner compared with HVs, while CF patients in the 1970s and 1980s were likely, on average, to be sicker. CF patients in group 2 were age-matched to HVs, but were smaller and leaner than their control groups. CF patients in group 3 were matched in age, body size and body composition, or allometric scaling based on LBM was used to account for differences in body size and body composition. These CF patients were, on average, healthier due to the improvement of CF care. *CF* cystic fibrosis, *HVs* healthy volunteers, *PK* pharmacokinetic, *LBM* lean body mass

compared the PK between CF patients and healthy volunteers within the same trial; these studies assessed 12 β-lactams, including at least one member of each β-lactam class (Table 1). This supported a within-study PK comparison based on the same clinical and bioanalytical procedures for each drug.

Highly protein-bound β-lactams (i.e. dicloxacillin and cloxacillin) were found to have a considerably higher fu in CF patients compared with that in healthy volunteers (Table 1) [34, 37]. Even if CL_u was identical between both subject groups, a higher fu will entail a higher CL of total drug. This is highlighted by the highest reported CL ratio of 2.97 for dicloxacillin (Table 3) in a study from 1975 in presumably rather sick CF patients [34]. After accounting for the 2.07-fold higher fu in CF patients (Table 2), the CL_{int} ratio between CF patients and healthy volunteers was 1.79, based on a well-stirred elimination model. For cloxacillin, the CL ratio for total drug was 1.78 (Table 3) and the CL_{int} ratio was 1.49 after accounting for the difference in protein binding (Table 2) [37].

In 2008, Beringer et al. [33] reported a CL ratio of 1.27 for total drug of dicloxacillin, which was substantially lower than the CL ratio of 2.97 reported for dicloxacillin in 1975 [34]. Presumably, CF patients in the older study were, on average, sicker and may have had more hepatic impairment. Hypoalbuminaemia is well-documented in CF patients and can be caused by extensive liver cirrhosis [53] and an enlarged plasma volume that dilutes albumin during pulmonary hypertension [54, 55].

The less-effective nutrition of CF patients in older studies may have led to lower albumin concentrations and thus less protein binding of β-lactams in CF patients compared with those in healthy volunteers in older studies (Table 1). These protein-binding results arise from the same CF patients and healthy volunteers as those included in the respective PK study. Some of these studies used ultrafiltration [36, 44], whereas others employed equilibrium dialysis [37, 38], to measure protein binding; dicloxacillin was evaluated by both methods [34]. While different methods may have affected the protein binding comparison between various β-lactams, CF patients and healthy volunteers were compared using the same method for the respective drug.

More recently, a 19% higher fu in CF patients (57.9%) compared with that in healthy volunteers (48.5%) has been reported for aztreonam (Table 2) [44]. While the CL ratio based on total drug was 1.31, after accounting for protein binding the ratio of unbound CL was 1.10 (Table 3). This suggests that unbound CL of aztreonam was comparable in these presumably healthier CF patients who were matched in body size, body composition and age with their healthy volunteer control group.

4.3 Impact of Body Size, Body Composition and Severity of Disease

The demographic characteristics differed between study groups (Fig. 2). Studies in group 1 were found to have the highest CL ratios, most likely since rather sick, adolescent CF patients were compared with adult healthy volunteers. The CL ratios were especially high when based on total drug concentrations, but were also elevated after accounting for protein binding, suggesting that more severe disease may have caused elevated CLs. While the studies in group

Table 3 Pharmacokinetic comparison of β-lactam antibiotics between CF patients and HVs. Studies were separated into three groups according to the demographic properties and body size models employed

Study	Antibiotic	CL (L/h/1.73 m^2)		CL ratio (CF/HVs) for:		V_{ss} (L/kg)		V_{ss} ratio (CF/HVs) for:		Data analysis
		CF patients	HVs	Total drug	Unbound drug	CF patients	HVs	Total drug	Unbound drug	
Group 1										
Jusko et al. [34], 1975	Dicloxacillin	16.9 ± 8.10[a]	5.70 ± 1.68[a]	2.97	1.79[b] (1.43[c])					NCA
Yaffe et al. [35], 1977	Methicillin	30.7 ± 3.7	25.4 ± 5.4	1.21	1.42[b] (1.21[c])	41.1 ± 17.4 L/1.73 m^2	30.3 ± 7.2 L/h/1.73 m^2	1.36	1.36	NCA
Arvidsson et al. [36], 1983	Cefsulodin	10.7 ± 4.9	11.3 ± 2.6	0.94	0.96	16 ± 13 L/1.73 m^2	25 ± 5 L/1.73 m^2	0.64	0.66	NCA
Spino et al. [37], 1984	Cloxacillin	15.7 ± 6.2	8.82 ± 1.8	1.78	1.49[b] (1.30[c])	0.137 ± 0.053	0.0990 ± 0.017	1.38	1.01	NCA
			Average ± SD	*1.72 ± 0.90*	*1.42 ± 0.34*			*1.13 ± 0.42*	*1.01 ± 0.35*	
Group 2										
Leeder et al. [38], 1984	Ceftazidime	0.147 ± 0.020 L/h/kg	0.089 ± 0.012 L/h/kg	1.65	1.67	0.237 ± 0.033	0.197 ± 0.033	1.20	1.22	NCA
De Groot et al. [39], 1990	Ticarcillin	9.33 ± 2.20	6.18 ± 0.98	1.51	1.51	7.24 ± 1.75 L/m^2	6.22 ± 1.25 L/m^2	1.16	1.16	NCA
Huls et al. [40], 1993	Cefepime	0.208 ± 0.080 L/h/kg	0.150 ± 0.091 L/h/kg	1.39	1.39	0.36 ± 0.09	0.25 ± 0.08	1.44	1.44	NCA
Beringer et al. [33], 2008	Dicloxacillin	7.5 [5.3–10.4][a]	5.9 [4.4–7.1][a]	1.27	0.60[b,d] (0.61[c])	27.4 [23.2–39.5][e] L/1.73 m^2	21.8 [15.6–25.3][e] L/1.73 m^2	1.26	0.61[d]	NCA
			Average ± SD	*1.46 ± 0.16*	*1.29 ± 0.48*			*1.27 ± 0.12*	*1.11 ± 0.35*	
Group 3										
Hedman et al. [41], 1990	Cefsulodin	7.76 ± 1.29 L/h	6.25 ± 0.84 L/h	1.24	1.27					NCA
Hamelin et al. [42],1993	Cefepime	7.18 ± 1.21 L/h	6.21 ± 1.19 L/h	1.16	1.16	0.27 ± 0.04	0.25 ± 0.04	1.08	1.08	NCA
Christensson et al. [43], 1998	Meropenem	13.4 ± 3.50	11.1 ± 3.01	1.21	1.21	11.0 ± 2.6 L	12.9 ± 2.3 L	0.85	0.85	NCA
Bulitta et al. [45], 2007	Piperacillin	11.3 ± 1.1 L/h[f]	11.3 ± 1.1 L/h[f]	1.00	1.00	9.61 ± 2.1 L[f]	10.4 ± 2.3 L[f]	0.92	0.92	PopPK
Vinks et al. [44], 2007	Aztreonam	6.01 ± 1.03 L/h	4.57 ± 0.44 L/h	1.31	1.10	0.199 ± 0.023	0.175 ± 0.037	1.14	0.95	PopPK
Bulitta et al. [46], 2009	Carumonam	6.33 ± 0.9 L/h[f]	6.25 ± 0.9 L/h[f]	1.01	1.01	13.2 ± 2.9 L[f]	12.7 ± 2.8 L[f]	1.04	1.04	PopPK
Bulitta et al. [47], 2010	Ceftazidime	7.82 ± 2.2 L/h[f]	6.68 ± 1.9 L/h[f]	1.17	1.18	12.8 ± 3.3 L[f]	12.7 ± 3.2 L[f]	1.01	1.02	PopPK
Bulitta et al. [48], 2011	Cefpirome	7.55 ± 1.0 L/h[f]	6.95 ± 0.9 L/h[f]	1.09	1.09	14.4 ± 4.8 L[f]	14.7 ± 5.0 L[f]	0.98	0.98	PopPK

Table 3 continued

Study	Antibiotic	CL (L/h/1.73 m^2)		CL ratio (CF/HVs) for:		V_{ss} (L/kg)		V_{ss} ratio (CF/HVs) for:		Data analysis
		CF patients	HVs	Total drug	Unbound drug	CF patients	HVs	Total drug	Unbound drug	
		Average ± SD		*1.15 ± 0.11*	*1.13 ± 0.10*			*1.00 ± 0.10*	*0.98 ± 0.08*	

CF cystic fibrosis, *HVs* healthy volunteers, *CL* total clearance, V_{ss} volume of distribution at steady state, *NCA* noncompartmental analysis, *PopPK* population pharmacokinetic modelling, fu_{CF} fraction of drug unbound in plasma in CF patients, fu_{HV} fraction of drug unbound in plasma in HVs, *SD* standard deviation

[a]Estimate represents renal clearance that was compared since renal clearance is not affected by the oral bioavailability. In contrast, a comparison of the apparent total clearance may be biased for orally administered drugs since the bioavailability might differ between both subject groups

[b]For dicloxacillin, methicillin and cloxacillin, protein binding was high or intermediate, and renal tubular secretion considerably contributed to renal clearance. We therefore calculated and reported the ratio of intrinsic clearance based on the well-stirred model

[c]The number in parentheses represents the clearance ratio based on total drug concentrations divided by the ratio of unbound fractions (fu_{CF}/ fu_{HV}). This simple correction for unbound clearance is provided for comparison, but was not used for drugs with extensive renal tubular secretion and intermediate or high protein binding

[d]The estimate assumes an unbound fraction ratio of 2.07, which was reported for dicloxacillin in 1975 [34]. It is possible that the unbound fraction ratio was closer to 1.0 in the 2008 study [33] since CF patients were likely, on average, to be healthier than those reported on in 1975

[e]Apparent volume of distribution

[f]Estimates refer to subjects with a mean lean body mass of 53 kg based on a body size model with allometric scaling. The allometric exponent was 0.75 for clearance and 1.0 for volume of distribution

2 matched age between both subject groups, they matched neither body size nor body composition (Table 2) and scaled CL and V_{ss} linearly by WT. This likely contributed to CL ratios above 1.0 for the studies in group 2. The ANCOVA showed that protein-binding differences and study group explained 89% of the total variance for the CL ratio and 70% for the V_{ss} ratio when these PK parameters were calculated based on total drug (Table 4, Fig. 3).

In group 3, CL and V_{ss} were comparable between CF patients and healthy volunteers (Table 3, Fig. 2) after matching or accounting for body size and body composition via allometric scaling by LBM [45–48]. Two β-lactams in group 3—piperacillin and meropenem—are subject to considerable tubular secretion. While meropenem follows linear PK [43, 56], several studies reported saturable elimination of piperacillin [57–59]. Saturation of renal CL at high piperacillin doses may have affected the PK comparison between CF patients and healthy volunteers [60], although the plasma PK of piperacillin in CF patients was adequately described by a linear population PK model [45]. Overall, the eight studies in group 3 demonstrated that CL in CF patients is predictable based on LBM, and suggests that LBM can be used for dose selection to achieve the target drug exposure in CF patients.

4.4 PK Considerations for Dosing of CF Patients

To achieve similar average unbound concentrations at steady state, CF patients in the 1970s would have, on average, required approximately 42% higher doses compared with those in healthy volunteers (Table 3). Nowadays, CF patients are healthier and thus may have less pronounced differences in protein binding (Table 2). Moreover, all β-lactams with clinically useful activity against *P. aeruginosa* have a rather low protein binding (i.e. $\leq$ 30%; 50% for aztreonam). Thus, protein binding differences unlikely play a major role in β-lactam dose selection against *P. aeruginosa.*

The eight studies in group 3 suggested that only 13% higher doses (range 0–27%) are required in CF patients, compared with those in healthy volunteers, to achieve similar average unbound drug concentrations at steady state (Table 3). This may not be clinically significant for less-severe infections; however, these differences may require slightly shorter dosing intervals or slightly longer durations of infusion for β-lactams in CF patients to achieve similar times of the unbound drug concentration above the minimal inhibitory concentration [44–48].

4.5 Pharmacodynamic Rationale to Treat Severe Infections

From a PD perspective, higher doses are likely required to treat more severe and chronic lung infections by *P.*

Table 4 Summary of ANCOVA results for factors influencing the natural logarithm of the ratio of clearance and volume of distribution at steady state when based on total drug concentrations

Factor	Clearance ratio (CL_{CF}/CL_{HV})	Volume of distribution ratio (V_{CF}/V_{HV})
Protein binding difference between CF patients and HVs; ln(fu_{CF}/fu_{HV})	$p < 0.0001$	$p = 0.001$
Study group	$p = 0.004$	$p = 0.004$
r^2	0.89	0.70

CL_{CF} and CL_{HV} clearance (calculated based on total drug concentrations) in CF patients and HVs, respectively, *V_{CF} and V_{HV}* volume of distribution (calculated based on total drug concentrations) in CF patients and HVs, respectively, *fu_{CF}* fraction of drug unbound in plasma in CF patients, *fu_{HV}* fraction of drug unbound in plasma in HVs, *CF* cystic fibrosis, *HV* health volunteers, *ANCOVA* analysis of covariance

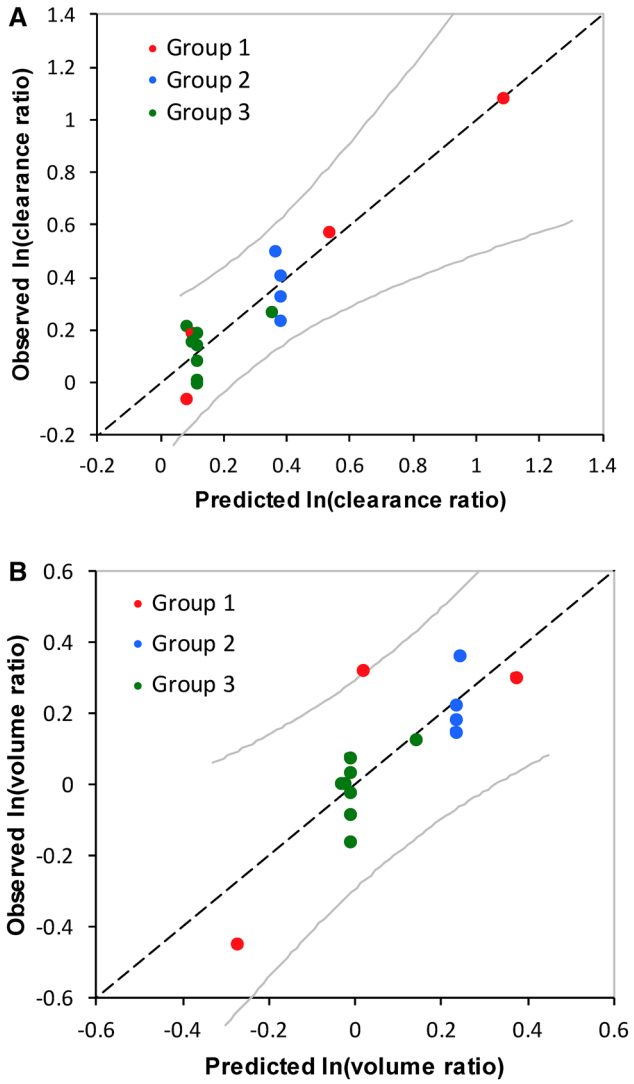

Fig. 3 Observed vs. ANCOVA-predicted ratios of **a** clearance and **b** volume of distribution between cystic fibrosis patients and healthy volunteers. *ANCOVA* analysis of covariance

aeruginosa [52]. Lung infections with a high bacterial burden are common in CF patients and likely harbour pre-existing resistant bacterial mutants. Similarly, these infections carry a higher risk for the emergence of high-level resistance during therapy as bacteria have more time to develop resistance [10].

Pseudomonas aeruginosa isolates from CF patients often have a substantially (> 100-fold) higher mutation rate due to an impairment in the DNA replication proof-reading machinery [61]. Infections by such hypermutators likely benefit from combination antibiotic therapy [15, 62, 63]. Furthermore, the phenotype of *P. aeruginosa* substantially differs in biofilm infections compared with planktonic growth. While outside the scope of this review, phenotypic changes of bacteria growing in biofilm mode often occur during chronic lung infections by *P. aeruginosa* in CF patients and should be considered for optimal antibiotic dosage regimens [64–66].

4.6 Innovative, Front-Loaded Dosage Regimens to Minimize Resistance Emergence

Increasing the dose of an antibiotic in monotherapy would seem the simplest option, however this is often not viable since antibiotic doses that can suppress resistance would lead to dose-limiting, antibiotic-related toxicity, not only for polymyxins but also aminoglycosides [67–69]. Front-loaded dosage regimens have been evaluated in non-clinical models and clinical trials [70–76]. These regimens utilize a higher dose during the first day(s) of therapy to maximize bacterial killing, kill resistant mutants, or suppress their growth. Front-loaded regimens also provide more time for the immune system to eradicate the bacteria that survive initial high-dose therapy. Thereafter, lower maintenance doses are used to optimize safety.

The emergence of *P. aeruginosa* resistance typically occurs at different times, depending on the mechanism. For polymyxins, resistance can emerge rapidly (within 1 day, or even more rapidly) [77, 78]. Efflux pumps and hypermutation can be upregulated within 1 h in vivo [19, 61]; subsequently, the most efficient pump gets selected over 1–2 days. Adaptive efflux-related resistance to

aminoglycosides can occur within 2 h, and continues to rise thereafter [62, 79–83]. Overall, this time-course of resistance favours front-loaded and once-daily aminoglycoside dosage regimens [79].

While resistant mutants with a modified outer membrane are often present in the initial inoculum, such mutations can also occur during the first day in in vitro models [77, 84, 85]. Similarly, *P. aeruginosa* can lose the outer membrane porin OprD that confers resistance to carbapenems (especially imipenem); OprD loss is a common and clinically relevant resistance mechanism and often occurs after approximately 1–5 days of therapy [86–88]. Given the time course of these resistance mechanisms, it is imperative to 'hit' *P. aeruginosa* infections hard at initiation of antibiotic therapy.

4.7 Synergy Mechanisms for Rationally Optimized Combination Dosing Strategies

Rationally optimized combination therapy is likely most beneficial for the treatment of severe infections [10]. Targeting the outer bacterial membrane, which presents a formidable penetration barrier in *P. aeruginosa* [89], offers the opportunity to achieve synergistic bacterial killing. If one antibiotic (e.g. an aminoglycoside or a polymyxin) disrupts and permeabilizes the outer membrane, the target site concentrations of a second antibiotic (e.g. a β-lactam) can be enhanced. We recently showed this synergy mechanism for aminoglycoside plus carbapenem combinations [15–17, 63, 90].

A second approach is to use one antibiotic to kill the bacterial population resistant to the other antibiotic, and vice versa [10, 12]. This subpopulation synergy strategy works best if two antibiotics with different resistance mechanisms are combined. Third, one drug (e.g. a β-lactamase inhibitor) can directly inhibit a resistance mechanism to the other antibiotic (e.g. a β-lactam). Finally, an antibiotic that inhibits protein synthesis (such as an aminoglycoside) can minimize the expression of β-lactamase enzymes and thereby decrease inactivation of the β-lactam antibiotic used in combination [10, 11, 91, 92]. Overall, rationally optimized combination dosing strategies hold great promise to target severe *P. aeruginosa* infections.

5 Conclusions

This review presents the first quantitative model that explains the observed PK differences of β-lactam antibiotics between CF patients and healthy volunteers from 16 studies over the last four decades. All eight studies that compared the PK of β-lactam antibiotics in CF patients who were matched in body size, body composition and age to their healthy volunteer control groups consistently showed only slightly higher (average 13%) CLs in CF, as well as similar volumes of distribution in both subject groups. These results support dosing of CF patients based on LBM. To achieve the same average unbound concentrations at steady state, approximately 13% higher doses are required in CF patients from a PK perspective. Alternatively, slightly shorter dosing intervals, or slightly longer durations of infusion, may be used to achieve similar times of unbound β-lactam concentrations above the minimal inhibitory concentration. However, for severe or chronic lung infections by *P. aeruginosa*, considerably higher doses and rationally optimized dosing strategies are likely required. Future studies are warranted to investigate these dosage regimens.

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Compliance with ethical standards

Conflict of interest Jürgen B. Bulitta, Yuanyuan Jiao, Stefanie K. Drescher, Antonio Oliver, Arnold Louie, Bartolome Moya, Xun Tao, Mathias Wittau, Brian T. Tsuji, Alexandre P. Zavascki, Beom Soo Shin, George L. Drusano, Fritz Sörgel, and Cornelia B. Landersdorfer declare no conflicts of interest relevant to the contents of this review.

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