REVIEW ARTICLE

Penetration of Antibacterial Agents into Pulmonary Epithelial Lining Fluid: An Update

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Abstract

A comprehensive review of drug penetration into pulmonary epithelial lining fluid (ELF) was previously published in 2011. Since then, an extensive number of studies comparing plasma and ELF concentrations of antibacterial agents have been published and are summarized in this review. The majority of the studies included in this review determined ELF concentrations of antibacterial agents using bronchoscopy and bronchoalveolar lavage, and this review focuses on intrapulmonary penetration ratios determined with area under the concentration-time curve from healthy human adult studies or pharmacokinetic modeling of various antibacterial agents. If available, pharmacokinetic/pharmacodynamic parameters determined from preclinical murine infection models that evaluated ELF concentrations are also provided. There are also a limited number of recently published investigations of intrapulmonary penetration in critically ill patients with lower respiratory tract infections, where greater variability in ELF concentrations may exist. The significance of these changes may impact the intrapulmonary penetration in the setting of infection, and further studies relating ELF concentrations to clinical response are needed. Phase I drug development programs now include assessment of initial pharmacodynamic target values for pertinent organisms in animal models, followed by evaluation of antibacterial penetration into the human lung to assist in dosage selection for clinical trials in infected patients. The recent focus has been on β-lactam agents, including those in combination with β-lactamase inhibitors, particularly due to the rise of multidrug-resistant infections. This manifests as a large portion of the review focusing on cephalosporins and carbapenems, with or without β-lactamase inhibitors, in both healthy adult subjects and critically ill patients with lower respiratory tract infections. Further studies are warranted in critically ill patients with lower respiratory tract infections to evaluate the relationship between intrapulmonary penetration and clinical and microbiological outcomes. Our clinical research experience with these studies, along with this literature review, has allowed us to outline key steps in developing and evaluating dosage regimens to treat extracellular bacteria in lower respiratory tract infections.

1 Introduction

In 2011, two reviews were published in this journal regarding the penetration of anti-infective agents into pulmonary epithelial lining fluid (ELF) [1, 2]. A significant number of studies have arisen during the past decade since the determination of ELF concentrations of new antibiotics has become an integral part of phase I drug development programs.

Consequently, intrapulmonary penetration studies are often conducted once single and multiple ascending dose studies are completed. This, in combination with initial pharmacodynamic (PD) target values determined from animal models, assists in providing a basis for dosage selection in the treatment of bacterial pneumonia (Fig. 1) [3, 4]. The aims of these studies in healthy adult subjects are to characterize the antibiotic penetration to pulmonary effect sites and provide support for dose selection of future clinical trials in patients with community- or hospital-acquired bacterial pneumonia.

Historically, investigator-initiated studies evaluating intrapulmonary penetration in infected patients frequently involved antibacterial agents that had regulatory approval, been marketed for over a decade, and commonly used in the intensive care unit [3–5]. More recently, manufacturer-initiated intrapulmonary pharmacokinetic (PK) studies are being conducted in critically ill patients as part of phase III

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Key Points

Intrapulmonary penetration studies in healthy adult subjects are commonly conducted as a phase I clinical trial to assess plasma and epithelial lining fluid concentrations of new antibacterial drug candidates.

In recent years, a significant number of intrapulmonary penetration studies have been conducted with β-lactam agents, with or without β-lactamase inhibitors.

The number of intrapulmonary penetration studies of newer agents in critically ill patients are limited, however they have demonstrated greater variability in extent and consistency in epithelial lining fluid penetration compared with healthy subjects.

Pharmacokinetic/pharmacodynamic analysis of plasma and intrapulmonary concentration-time data from preclinical animal models, healthy subjects, and critically ill patients has provided support for evaluating optimal dosing of antibacterial agents for the treatment of pneumonia.

drug development programs [6–8]. These studies are allowing assessment of the wide variability observed in plasma and ELF concentrations in critically ill patients. Such PK studies are likely to have an impact on dose selection, target PD parameters, and susceptibility breakpoints.

Bronchoscopy and bronchoalveolar lavage (BAL) are commonly used methodologies for determining concentrations of antibacterial agents in ELF. These methods have been previously described [1]. In the previous 2011 reviews, ELF to plasma penetration ratio was frequently reported for each sampling time. However, to account for hysteresis and to minimize the issues with single sampling time, changes in penetration ratio over time should be considered [3]. In more recent studies, the ELF to plasma penetration ratio is determined by the ratio of the area under the concentration-time curve (AUC) values, often determined from the mean site concentration for each sampling time or by population PK analysis of all available plasma and ELF concentrations. In addition, the penetration ratios were calculated assuming no protein binding in ELF (i.e., unbound ELF) and either unbound or total plasma (i.e., dependent on whether plasma protein binding was determined or assumed from previous studies). This methodology does inherently have limitations, including small sample of studies, sampling location with respect to infection site, and determining an AUC based on sampling from different patients. These limitations have been previously described [1, 3]. This review presents intrapulmonary penetration ratios in this way except where specified.

The aim of this review was to provide a comprehensive update of the previous assessment of the concentrations of antibacterial agents in ELF and the extent of their intrapulmonary penetration [1]. Literature for this review was obtained through a comprehensive search of MEDLINE from 2011 to 2021 for the drugs included in this review. Product packaging information was also used. Our focus is on human studies that compared ELF with plasma concentrations and determined intrapulmonary penetration ratios from AUC or PK modeling methods. A brief commentary is provided if murine or other animal infection models have quantified ELF concentrations and assisted in determining best PK/PD parameters. A discussion is also included regarding recent investigations assessing the penetration of selected antibacterial agents into ELF of critically ill patients with lower respiratory tract infections.

Fig. 1 Preclinical and human pharmacokinetic/pharmacodynamic methods to support dosage selection of antibacterial agents for the treatment of pneumonia. Reprinted with permission from Rizk et al. [4]. *PK* pharmacokinetic, *PD* pharmacodynamic, *ELF* epithelial lining fluid
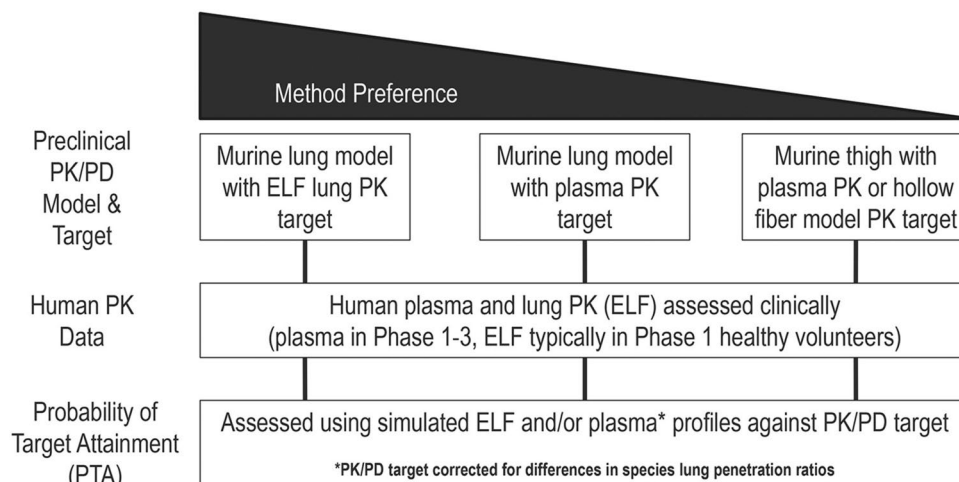
2 β-Lactam Agents With and Without β-Lactamase Inhibitors

In the past 10 years, a significant number of intrapulmonary penetration studies have been conducted with β-lactam agents. Antibiotic development programs during this time focused on cephalosporins and carbapenems, including combinations with β-lactamase inhibitors, for the treatment of multidrug-resistant infections. The following sections will review the ELF penetration studies involving β-lactam agents and the β-lactamase inhibitor component. The discussion has been separated into investigations involving healthy adult subjects and those evaluating critically ill patients with lower respiratory tract infections. Monte Carlo simulations were also included when population PK analysis and target indexes (e.g., time of unbound drug concentrations are above the minimum inhibitory concentration [fT>MIC] in plasma and ELF for β-lactams and the duration of time for a fixed concentration for β-lactamase inhibitors) were incorporated.

2.1 Healthy Subjects

Plasma and ELF concentrations in healthy adult subjects for β-lactams and β-lactam/β-lactamase inhibitor combinations are displayed in Tables 1 and 2, respectively. Penetration ratios were based on values for AUC in ELF (assuming no protein binding) and plasma (accounting for the percentage of plasma protein binding when available).

2.1.1 Ceftaroline

Ceftaroline is a broad-spectrum cephalosporin with *in vitro* activity against both Gram-positive and Gram-negative organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) [9]. Ceftaroline fosamil is the prodrug that is converted to the active form, ceftaroline, and is approved in the US for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia [10]. A study comparing ELF and plasma concentrations of ceftaroline was conducted in 50 healthy adult subjects [11]. Ceftaroline fosamil 600 mg was administered as a 1-h intravenous infusion. Half of the subjects were dosed every 12 h for seven total doses and the other half of the subjects were dosed every 8 h for 10 total doses. The penetration ratios of ELF to unbound plasma based on ceftaroline AUC were 0.23 and 0.24 in the 12-h and 8-h dosing groups, respectively, accounting for 20% protein binding of ceftaroline in plasma (Table 1). In both groups, ceftaroline concentrations in ELF were observed to exceed 1 μg/mL (e.g., US FDA-approved MIC breakpoint of ceftaroline for *S. aureus*) only 1 and 2 h after the infusion.

PK data from these 50 subjects were included in a population PK analysis, and the penetration ratio of ELF to unbound plasma concentrations was reported as 0.25. Simulations were used to assess the achievement of fT>MIC in plasma and ELF. At an MIC of 1 μg/mL for *S. aureus*, approximately 14% and 53% of patients receiving ceftaroline fosamil 600 mg every 12 h and every 8 h, respectively, were predicted to achieve 42% fT>MIC in ELF. The PK/PD targets used in this target attainment analysis of ceftaroline were derived in a neutropenic murine lung infection model [12]. The required fT>MIC target to produce stasis and a 1-log reduction in colony forming units were 16% and 41%, respectively, for *S. aureus* isolates with MIC values ranging from 0.5 to 4 μg/mL. Ceftaroline concentrations in serum and ELF were similar in magnitude at each sampling time, and no differences in these concentrations were observed in infected and uninfected mice.

2.1.2 Cefiderocol

Cefiderocol is a novel siderophore cephalosporin available as an intravenous formulation and is approved in the US for the treatment of adult patients with complicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia [13, 14]. A study has assessed plasma and ELF concentrations in 20 healthy adult males after receiving a single dose of cefiderocol 2000 mg as a 1-h intravenous infusion [15]. Samples of BAL were collected at 1, 2, 4, and 6 h after the start of the infusion (Table 1). The concentration-time profile of ELF and plasma concentrations of cefiderocol tended to decrease in a parallel pattern. The intrapulmonary penetration ratio of ELF to total cefiderocol plasma based on AUC_6 was 0.101. When accounting for plasma protein binding of 57.8%, the penetration ratio was 0.24. The cefiderocol AUC ratios of alveolar macrophage (AM) to plasma were 0.02 and 0.04 based on total drug in plasma and unbound drug in plasma, respectively. These findings lend further support for the continued evaluation of cefiderocol for the treatment of lower respiratory tract infections.

2.1.3 Doripenem

Doripenem is a carbapenem available for intravenous administration and is approved by the FDA for the treatment of complicated intra-abdominal infections and complicated urinary tract infections [16, 17]. A study has assessed plasma and intrapulmonary concentrations in 40 healthy adults after receiving doripenem 500 or 1000 mg every 8 h as a 4-h intravenous infusion for a total of three doses [18]. Samples of BAL were collected at 3, 4.5, 6, or 8 h. Mean ELF to total

Table 1 Plasma and epithelial lining fluid concentrations of β-lactam agents in healthy subjects

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Ceftaroline	600 mg IV q12h × 7 doses	5	1	0.23[c]	18.73 (14.8, 25.7)[d]	3.38 (2.08, 7.63)	[11]
		5	2		8.47 (5.49, 11.4)[d]	1.60 (1.08, 3.45)	
		5	4		3.27 (2.2, 4.9)[d]	0.54 (0.36, 1.26)	
		5	8		0.90 (0.4, 1.2)[d]	0.18 (0.00, 0.22)[e]	
		5	12		0.27 (0.11, 0.43)[d]	0.00 (0.00, 0.00)[f]	
	600 mg IV q8h × 10 doses	5	1	0.24[g]	21.31 (16.7, 28.9)[d]	3.56 (2.69, 5.07)	
		5	2		9.46 (7.85, 12.0)[d]	2.57 (0.61, 3.2)	
		5	4		3.56 (2.85, 5.49)[d]	0.58 (0.39, 0.98)	
		5	6		1.74 (1.28, 3.29)[d]	0.27 (0.17, 0.52)	
		5	8		0.99 (0.20, 1.74)[d]	0.26 (0.00, 0.7)[e]	
Cefiderocol	2000 mg IV × 1 dose	5	1	0.24[h]	NR	13.8 (26.9)[i]	[15]
		5	2			6.69 (23.1)[i]	
		5	4			2.78 (37.2)[i]	
		5	6			1.38 (11.8)[i]	
Doripenem	500 mg IV q8h over 4 h × 3 doses	5	3	0.30[j]	7.14 ± 0.53	2.14 ± 0.51	[18]
		5	4.5		4.89 ± 1.51	1.67 ± 0.55	
		5	6		1.63 ± 0.38	0.93 ± 0.36	
		5	8		0.49 ± 0.24	0.32 ± 0.18[k]	
	1000 mg IV q8h over 4 h × 3 doses	5	3	0.28[j]	13.85 ± 1.26	3.80 ± 0.66	
		5	4.5		10.92 ± 1.81	3.50 ± 0.78	
		5	6		3.57 ± 0.31	1.73 ± 0.51	
		5	8		1.06 ± 0.26	0.53 ± 0.38	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *IV* intravenously, *NR* not reported, *qxh* every *x* hours, *SD* standard deviation, *CV%* percentage coefficient of variation

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations expressed as mean ± SD or median (minimum, maximum)

[c]Based on the ratio of AUC_{12} in ELF to AUC_{12} in unbound plasma, assuming 20% protein binding in plasma

[d]Median value based on 25 total plasma samples at each sampling time

[e]Four of five subjects had measurable ceftaroline concentrations at the 8-h sampling time

[f]No subjects (*n* = 5) had measurable ceftaroline concentrations at the 12-h sampling time

[g]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 20% protein binding in plasma

[h]Based on the ratio of AUC_6 in ELF to AUC_6 in unbound plasma, assuming 57.8% protein binding in plasma

[i]Values expressed as geometric mean (CV% geometric mean)

[j]Based on the ratio of AUC_8 in ELF to AUC_8 in total plasma

[k]Four of five subjects had measurable doripenem concentrations at the 8-h sampling time

plasma ratios ranged from 0.30 to 0.62 and 0.28 to 0.53 for patients receiving 500 and 1000 mg doses, respectively (Table 1). The penetration ratio of ELF to total doripenem based on AUC_8 were similar (0.30 and 0.28, respectively) for each dosing level. Intrapulmonary penetration into ELF with doripenem is similar to previously reported intrapulmonary penetration with other carbapenem antibiotics [1]. Doripenem concentrations in AM were reported below the quantitative limit of detection.

2.1.4 Piperacillin/Tazobactam

Plasma and ELF concentrations of piperacillin/tazobactam and ceftolozane/tazobactam were compared in healthy adult subjects [19]. Twenty-five subjects were assigned to receive three doses of piperacillin/tazobactam 4.5 g every 6 h as a 2-h intravenous infusion. The ELF to total plasma ratio based on AUC_6 for piperacillin and tazobactam was 0.26 and 0.54, respectively (Table 2). After accounting for plasma

protein binding of 30% for piperacillin, the ELF to unbound plasma penetration ratio was 0.38. These results were subsequently added to a population PK model and compared with critically ill patients receiving piperacillin/tazobactam, further described below.

2.1.5 Ceftolozane/Tazobactam

Ceftolozane is a parenteral cephalosporin with *in vitro* activity against many Gram-negative organisms, including multidrug-resistant *Pseudomonas aeruginosa* [20]. The addition of tazobactam improves the antibacterial coverage of ceftolozane against selected Enterobacterales in the presence of selected extended-spectrum β-lactamases (e.g., TEM-, SHV- and CTX-M-type extended-spectrum β-lactamases). Ceftolozane/tazobactam has three FDA-approved indications, including complicated urinary tract infections and complicated intra-abdominal infections, at a recommended dosage of 1.5 g every 8 h as a 1-h intravenous infusion, and, more recently, for the treatment of

Table 2 Plasma and epithelial lining fluid concentrations of β-lactam/β-lactamase inhibitor combination products in healthy subjects

Antibacterial agent	Dosage regimen	Subjects [*n*]	Sampling time [h][a]	Ratio of ELF to plasma based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Piperacillin/ tazobactam	Piperacillin 4 g IV q6h × 3 doses	5	0.5	0.26[c]	263 ± 45	58.8 ± 12.5	[19]
		5	1		152 ± 24	31.0 ± 10.9	
		5	2		69.5 ± 19.8	19.7 ± 9.5	
		5	4		14.8 ± 6.0	6.4 ± 4.5	
		5	6		3.4 ± 1.1	3.0 ± 1.0	
	Tazobactam 0.5 g IV q6h × 3 doses	5	0.5	0.54[c]	29.9 ± 6.1	15.3 ± 7.8	
		5	1		19.0 ± 2.6	7.2 ± 2.8	
		5	2		9.6 ± 2.4	5.2 ± 3.2	
		5	4		1.9 ± 2.4	1.8 ± 1.2	
		5	6		0.7 ± 0.2	1.0 ± 1.0	
Ceftolozane/ tazobactam	Ceftolozane 1 g IV q8h × 3 doses	5	1	0.48[d]	58.5 ± 7.8	21.8 ± 6.4	
		5	2		34.0 ± 3.8	14.9 ± 3.0	
		5	4		14.3 ± 2.4	9.3 ± 6.0	
		5	6		5.5 ± 1.6	4.9 ± 2.4	
		5	8		3.9 ± 1.4	4.2 ± 2.5	
	Tazobactam 0.5 g IV q8h × 3 doses	5	1	0.44[d]	15.2 ± 1.9	4.5 ± 1.1	
		5	2		3.9 ± 0.7	1.7 ± 0.6	
		5	4		0.7 ± 0.1	0.5 ± 0.2	
		5	6		0.2 ± 0[e]	0.2 ± 0.1[f]	
		5	8		BQL[g]	0.3 ± 0.1[e]	
Ceftazidime/ avibactam	Ceftazidime 2000 mg IV q8h × 9 doses	22	2	0.31[d]	NR	NR	[24]
			4				
			6				
			8				
	Ceftazidime 3000 mg IV q8h × 9 doses	21	2	0.32[d]	NR	NR	
			4				
			6				
			8				
	Avibactam 500 mg IV q8h × 9 doses	22	2	0.35[d]	NR	NR	
			4				
			6				
			8				
	Avibactam 1000 mg IV q8h × 9 doses	21	2	0.32[d]	NR	NR	
			4				
			6				
			8				

Table 2 (continued)

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	Ratio of ELF to plasma based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Cefepime/ zidebactam	Cefepime 2 g IV q8h × 7 doses	6	0.5	0.39[d]	84.06 ± 17.94	26.31 ± 9.89	[30]
		5	1.25		107.0 ± 11.03	35.24 ± 3.89	
		6	3		45.97 ± 6.16	19.77 ± 3.71	
		6	6		14.43 ± 4.76	7.62 ± 4.56	
		6	8		8.50 ± 4.34	4.62 ± 1.63	
		6	10		3.73 ± 2.24	2.18 ± 0.84	
	Zidebactam 1 g IV q8h × 7 doses	6	0.5	0.38[d]	36.03 ± 6.94	11.41 ± 4.46	
		5	1.25		45.80 ± 3.29	14.61 ± 1.87	
		6	3		19.65 ± 3.22	7.59 ± 1.77	
		6	6		5.89 ± 1.89	2.77 ± 1.54	
		6	8		3.30 ± 1.65	2.80 ± 3.27	
		6	10		1.55 ± 0.90	0.74 ± 0.33	
Cefepime/ enmetazobactam	Cefepime 2 g IV over 2 h q8h × 9 doses	19	2	0.61[h]	NR	NR	[35]
			4				
			6				
			8				
	Enmetazobactam 1 g IV over 2 h q8h × 9 doses	19	2	0.53[h]	NR	NR	
			4				
			6				
			8				
Meropenem/ vaborbactam	Meropenem 2 g IV q8h × 3 doses	5	1.5	0.63[d]/0.65[i]	41.2 ± 5.02	21.4 ± 3.96	[39]
		5	3.25		47.7 ± 7.28	28.3 ± 6.69	
		5	4		23.8 ± 4.30	16.1 ± 4.77	
		5	6		7.24 ± 2.79	7.51 ± 5.29	
		5	8		1.36 ± 0.51	2.51 ± 1.13	
	Vaborbactam 2 g IV q8h × 3 doses	5	1.5	0.53[d]/0.79[j]	42.1 ± 5.00	18.6 ± 3.76	
		5	3.25		51.1 ± 6.78	26.1 ± 7.12	
		5	4		28.2 ± 5.32	15.7 ± 3.36	
		5	6		10.8 ± 2.82	8.04 ± 5.81	
		5	8		2.74 ± 1.12	2.61 ± 1.35	
Imipenem/ relebactam	Imipenem 500 mg IV q6h × 5 doses	4	0.5	0.44[k]/0.55[l]	NR	32.09 (21.26, 48.44)[m]	[40]
		4	1.0			20.27 (13.43, 30.59)[m]	
		4	1.5			16.47 (10.92, 24.87)[m]	
		4	3.0			5.99 (3.97, 9.04)[m]	
	Relebactam 250 mg IV q6h × 5 doses	4	0.5	0.43[k]/0.54[l]	NR	14.93 (9.89, 22.53)[m]	
		4	1.0			10.93 (7.24, 16.50)[m]	
		4	1.5			9.49 (6.29, 14.32)[m]	
		4	3.0			4.27 (2.83, 6.45)[m]	

Table 2 (continued)

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	Ratio of ELF to plasma based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Sulbactam/ durlobactam	Sulbactam 1 g IV q6h × 3 doses	6	1	0.50[c]/0.81[n]	17.28 ± 2.97	9.22 ± 2.25	[46]
		6	2.5		21.42 ± 3.31	10.25 ± 2.29	
		6	3.25		12.03 ± 2.66	5.67 ± 1.74	
		6	4		8.58 ± 1.90	4.64 ± 1.56	
		6	6		2.24 ± 1.01	1.27 ± 0.49	
	Durlobactam 1 g IV q6h × 3 doses	6	1	0.37[c]/0.41[o]	24.33 ± 3.35	9.14 ± 1.51	
		6	2.5		31.23 ± 3.80	10.47 ± 1.70	
		6	3.25		20.78 ± 4.54	7.14 ± 1.66	
		6	4		15.10 ± 2.68	6.03 ± 1.88	
		6	6		5.33 ± 1.80	2.15 ± 0.78	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *IV* intravenously, *BQL* below quantitative limit of detection, *NR* not reported, *SD* standard deviation, *qxh* every *x* hours

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations reported as mean ± SD

[c]Based on the ratio of AUC_6 in ELF to AUC_6 in total plasma

[d]Based on the ratio of AUC_8 in ELF to AUC_8 in total plasma

[e]Two of five subjects had concentrations equal to or above the quantitative limit of detection of 0.1 μg/mL

[f]Five of five subjects had concentrations BQL of 0.1 μg/mL

[g]Three of five subjects had concentrations equal to or above the quantitative limit of detection of 1.0 ng/mL

[h]Based on the ratio of AUC_{24} in ELF to AUC_{24} in total plasma (calculated from Bayesian posterior estimates)

[i]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 2% protein binding in plasma

[j]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 33% protein binding in plasma

[k]Based on the ratio of AUC_∞ in ELF to AUC_∞ in total plasma

[l]Based on the ratio of AUC_∞ in ELF to AUC_∞ in unbound plasma, assuming 20% protein binding in plasma

[m]Geometric mean (95% confidence interval) reported in units of μM

[n]Based on the ratio of AUC_6 in ELF to AUC_6 in unbound plasma, assuming 38% protein binding in plasma

[o]Based on the ratio of AUC_6 in ELF to AUC_6 in unbound plasma, assuming 10% protein binding in plasma

hospital-acquired and ventilator-associated bacterial pneumonia at an intravenous dosage of 3.0 g every 8 h infused over 1 h. Intrapulmonary penetration of ceftolozane/tazobactam was evaluated in mice [21]. Following an 8 mg/kg dose of ceftolozane and tazobactam, the ELF to total plasma ratio based on AUC was 0.32 for ceftolozane and 0.45 for tazobactam. In mice, there were no significant differences between ceftolozane and tazobactam PK alone compared with combined administration.

Plasma and ELF concentrations of ceftolozane and tazobactam have been reported for 25 healthy adult subjects assigned to receive three doses of ceftolozane/tazobactam 1.5 g every 8 h as a 1-h intravenous infusion [19]. The ELF to total plasma ratio based on AUC_8 for ceftolozane and tazobactam was 0.48 and 0.44, respectively (Table 2). After accounting for a plasma protein binding of 20% for ceftolozane, the ELF to unbound plasma ratio was 0.59. The

observed difference in tazobactam concentrations between piperacillin/tazobactam and ceftolozane/tazobactam was most likely due to differences in measurable concentrations and dosing frequency (i.e., every 6 h vs. every 8 h).

Xiao and colleagues developed a population PK model using this same plasma and ELF data of ceftolozane and tazobactam [22]. The calculated penetration ratios, based on parametric intracompartment clearance parameters, were 52% for ceftolozane and 46% for tazobactam. Monte Carlo simulated concentration-time profiles and the probability of target attainment were determined in plasma and ELF for dosage regimens of 1.5 and 3 g administered as a 1-h intravenous infusion every 8 h. For Enterobacterales and *P. aeruginosa* with MIC values of up to 8 μg/mL, the probability of achieving a target attainment of 40% fT>MIC in ELF was 75% for the 1.5 g dose and 95.6% for the 3 g dose. These consistent and higher probability of target attainment of the

3 g dose lend support for the dose that was evaluated in the pivotal phase III clinical trial and ultimately recommended for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia in adult patients with a creatinine clearance > 50 mL/min.

2.1.6 Ceftazidime/Avibactam

Ceftazidime/avibactam is the combination of ceftazidime, a third-generation, antipseudomonal cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor. Multidrug-resistant Enterobacterales are an important cause of nosocomial pneumonia. Avibactam restores ceftazidime activity to bacteria producing Ambler class A and C β-lactamases, including extended-spectrum β-lactamases, and carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPCs) [23]. In a study assessing the interaction between pulmonary surfactant and ceftazidime/avibactam, pulmonary surfactant did not inhibit the *in vitro* activity of ceftazidime, with or without avibactam, supporting continued investigation for ceftazidime/avibactam for the treatment of pneumonia [23]. A PK study evaluating the penetration of two different doses of ceftazidime/avibactam into ELF was conducted in 42 healthy adults [24]. Subjects received either ceftazidime 2000 mg with avibactam 500 mg or ceftazidime 3000 mg with avibactam 1000 mg administered every 8 h as a 2-h intravenous infusion for nine doses. In both plasma and ELF, the mean AUC of ceftazidime was approximately 1.5-fold greater in the higher dosing regimen. The intrapulmonary penetration ratio of ceftazidime based on noncompartmental AUC_8 calculations for the two doses were similar at 0.31 and 0.32 (Table 2). The mean AUC_8 values of avibactam in plasma and ELF, respectively, were 1.98 and 1.81 times higher with the 1000 mg dose compared with the 500 mg dose. The ELF to plasma ratio based on similar AUC calculations for avibactam 500 mg and 1000 mg were 0.35 and 0.32, respectively. The ratio of ELF to plasma in human subjects was higher than in the murine infection model (i.e., the mean intrapulmonary penetration based on AUC for ceftazidime and avibactam was 0.24 and 0.22, respectively) [25]. Ceftazidime/avibactam has been approved for hospital-acquired and ventilator-associated bacterial pneumonia for the ceftazidime 2000 mg with avibactam 500 mg dose [26]. The higher dosing regimen of ceftazidime 3000 mg with avibactam 1000 mg was not pursued for approval of use in patients with lower respiratory tract infections.

Subsequently, Dimelow and colleagues used the healthy subject data for ceftazidime and avibactam to develop several population PK models to evaluate non-linear relationships between plasma and ELF concentrations [27]. Different direct response models were used to evaluate ELF penetration, including an effect site equilibration method and a plasma–ELF link function that incorporated proportional, power, or saturable models. Concentration-time profiles were simulated for 1000 subjects receiving ceftazidime 2000 mg and avibactam 500 mg administered every 8 h as a 2-h intravenous infusion. A saturable Michaelis–Menten model provided the best description of the non-linear plasma–ELF relationship for ceftazidime (i.e., ELF penetration was higher at low plasma concentrations, but saturable at plasma concentrations > 250 μg/mL), whereas avibactam was best described with a power model (i.e., lesser degree of a non-linear plasma–ELF relationship). Overall, the ELF penetration ratio was 0.52 at clinically relevant ELF and plasma concentrations of 8 μg/mL and 15.2 μg/mL, respectively. For avibactam, the penetration ratio was 0.47 at ELF and plasma concentrations of 1 μg/mL and 2.4 μg/mL, respectively. The ELF concentration-time simulations supported plasma PK/PD targets of 8 μg/mL and 1 μg/mL for ceftazidime and avibactam, respectively, and the median simulated ELF concentrations were 14.7 μg/mL and 1.4 μg/mL.

2.1.7 Cefepime/Zidebactam

WCK 5222 is a combination of a cephalosporin, cefepime, and β-lactam enhancer, zidebactam (formerly known as WCK 5107). Zidebactam is a novel non-β-lactam bicyclo-acyl hydrazide that inhibits penicillin-binding protein 2 and β-lactamases. Cefepime/zidebactam is being studied for the treatment of multidrug resistant Gram-negative infections [28, 29]. Plasma and ELF concentrations of cefepime and zidebactam were compared in adult subjects who received seven doses of WCK 5222 (cefepime 2 g and zidebactam 1 g) every 8 h as an intravenous infusion over 1 h [30]. Table 2 displays the plasma and ELF concentrations for both components. The ratio of ELF to total plasma based on AUC_8 values calculated from the mean concentration of cefepime at each BAL sampling time was 0.39. A similar ratio value (0.38) was observed for zidebactam. Cefepime ELF penetration ratios have previously been reported as ranging from 0.99 to 1.12, however this was in critically ill patients with nosocomial pneumonia receiving continuous infusion cefepime [31]. Concentrations of cefepime and zidebactam in AM were also evaluated. The ratios of AM to total plasma based on AUC_8 values for cefepime and zidebactam were 0.27 and 0.10, respectively. The ratio of ELF to total plasma in human subjects was lower than concentrations in a neutropenic murine lung infection model (i.e., the mean intrapulmonary penetration for cefepime and zidebactam was 0.50 and 0.70, respectively) [32]. The respective target %fT>MIC for cefepime when co-administered with zidebactam was 18%, and 31% for stasis and 1-$\log_{10}$ bactericidal activity against metallo-β-lactamase producing Enterobacterales. A second study using a similar murine lung infection model demonstrated 1-$\log_{10}$ to 2-$\log_{10}$ bactericidal activity against multidrug resistant *P. aeruginosa* with an MIC ≤16 μg/mL,

when ELF concentrations were matched to those observed in healthy subjects [33]. These data support further evaluations of WCK 5999 for the treatment of nosocomial pneumonia caused by multidrug resistant Gram-negative microorganisms.

2.1.8 Cefepime/Enmetazobactam

Cefepime/enmetazobactam is a β-lactam/β-lactamase inhibitor combination undergoing clinical investigation for a variety of infections, including nosocomial pneumonia [34]. Enmetazobactam (formerly known as AAI101) is a novel β-lactamase inhibitor, restoring activity of cefepime against Enterobacterales expressing extended-spectrum β-lactamases, OXA-48, and AmpC enzymes. While intrapulmonary penetration of cefepime has been previously described, this study represented the first evaluation of enmetazobactam concentrations in ELF from 19 healthy adult subjects [35]. Participants received cefepime 2 g and enmetazobactam 1 g simultaneously, every 8 h, as an intravenous infusion over 2 h for nine doses. A three-compartment population PK model was developed, and Bayesian posterior parameter estimates of each subject were used to determine steady-state AUC_{24} values. The mean ratios of ELF to total plasma based on these AUC_{24} values were 0.61 and 0.53 for cefepime and enmetazobactam, respectively (Table 2). A strong correlation ($r = 0.916$, $p < 0.001$) was observed between cefepime and enmetazobactam AUC values in ELF. A slightly higher ratio (i.e., AUC_8 ELF to AUC_8 total plasma of 0.734 and 0.615 for cefepime and enmetazobactam, respectively) was observed in a neutropenic murine lung infection model using population PK modeling [36]. Additionally, PD targets in ELF were identified and associated with a $\geq$ 2-$\log_{10}$ decline in bacterial burden when fT>MIC for cefepime and fT>2 µg/mL for enmetazobactam were 20%. Monte Carlo simulations for 1000 subjects, using a dosage regimen of cefepime 2 g and enmetazobactam 1 g every 8 h and the dual PD targets in ELF, were found to have a 94.4% and 78.1% probability of target attainment at MIC values of 8 µg/mL and 16 µg/mL, respectively. These results support further development of the combination of cefepime and enmetazobactam for the treatment of nosocomial pneumonia.

2.1.9 Meropenem/Vaborbactam

Meropenem is a carbapenem antibiotic with activity against a broad spectrum of aerobic and anaerobic Gram-positive and Gram-negative organisms and is used for a wide variety of severe infections. Vaborbactam (formerly known as RPX7009) is a non-β-lactam, cyclic boronic acid-based β-lactamase inhibitor, currently approved in the US as a fixed-dose combination with meropenem for the treatment

of complicated urinary tract infections. Vaborbactam has inhibitory activity against serine β-lactamases belonging to Amber classes A and C, including KPC-producing Enterobacterales [37]. The *in vitro* antibacterial potency of meropenem and meropenem/vaborbactam was not affected by bovine pulmonary surfactant [38].

Wenzler and colleagues compared the plasma, ELF, and AM concentrations of the combination product meropenem/vaborbactam [39]. Healthy adults received three doses of meropenem 2 g in fixed-dose combination with vaborbactam 2 g every 8 h as a 3-h intravenous infusion. Plasma and ELF concentrations of meropenem and vaborbactam are reported in Table 2. The AUC_8 (based on mean concentrations at the BAL sampling times) of meropenem in ELF was 111.7 µg·h/mL and the AUC_8 ratio of ELF to total plasma was 0.63. The mean ratios of ELF to unbound plasma concentrations at the BAL sampling times of meropenem ranged from 0.525 to 2.13. The AUC_8 of vaborbactam in ELF was 105.1 µg·h/mL, and the AUC_8 ratio of ELF to total plasma for vaborbactam was 0.53. When accounting for 33% protein binding, this ratio increased to 0.79. The range for mean ratios of vaborbactam ELF concentrations to unbound plasma concentrations at the BAL sampling times was 0.45–1.01.

The AM concentrations of meropenem and vaborbactam were also evaluated in this study [39]. The median AM concentrations of vaborbactam at BAL sampling times ranged from 2.28 to 6.94 µg/mL, while the mean ratios of vaborbactam AM to plasma concentrations ranged from 0.06 to 2.58. However, the AM concentrations for meropenem were below the lower limit of quantification at all sampling times. Given that meropenem AM concentrations were unable to be detected, the clinical significance of the AM concentrations of the β-lactamase inhibitor vaborbactam are unknown.

2.1.10 Imipenem/Relebactam

Imipenem is a carbapenem antibiotic co-formulated at a 1:1 ratio with cilastatin, an inhibitor of renal dipeptidase. Imipenem has broad spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria and is used for serious hospital-acquired infections. Relebactam (formerly known as MK-7655) is a non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor and exhibits activity against Ambler Class A and C β-lactamase enzymes produced by Gram-negative bacilli [37]. Imipenem/cilastatin/relebactam has three FDA-approved indications, including treatment of complicated urinary tract infections, complicated intra-abdominal infections, and hospital-acquired and ventilator-associated bacterial pneumonia. The recommended dosage is 1.25 g (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) every 6 h as a 30-min intravenous infusion.

Plasma and ELF concentrations for imipenem and relebactam were evaluated in a phase I study of 16 healthy adult subjects receiving imipenem/cilastatin (500 mg of each component) in combination with relebactam 250 mg every 6 h as an intravenous infusion over 30 min [40]. Participants received five doses and BAL collection period was limited to 3 h after the last dose (Table 2). Like other carbapenems, imipenem concentrations in ELF were lower than concurrent plasma concentrations at each sampling time. The imipenem and relebactam penetration ratios for ELF to unbound plasma based on AUC_∞ were 0.55 and 0.54, respectively. In addition, a population PK model using unbound plasma concentrations and a time-invariant partition coefficient value of 0.55 best fit the ELF data, consistent with penetration ratios. Van Hasselt and colleagues have previously reported a pooled population PK model to quantify total plasma concentrations and ELF penetration of imipenem [41]. Penetration of imipenem and relebactam into AM was lower than observed for ELF. Most of the AM concentrations for imipenem were below the lower limit of detection and were therefore not reported. Geometric mean ratios for AM to plasma concentrations of relebactam ranged from 0.14 to 0.51 and increased over the sampling times of 0.5–3 h. The relebactam penetration ratio of AM to unbound plasma based on AUC_∞ was 0.36. These data provided support for the dosage regimens of imipenem/cilastatin/relebactam using the phase III clinical trial for the treatment of bacterial pneumonia [42, 43].

2.1.11 Sulbactam/Durlobactam (Formerly ETX2514SUL)

Sulbactam is a β-lactamase inhibitor with intrinsic activity against *Acinetobacter baumannii*, and has been approved for use in the US as a combination product with ampicillin. Durlobactam (formerly known as ETX2514) is a novel β-lactamase inhibitor with broad spectrum *in vitro* activity against Ambler class A, C, and D β-lactamase enzymes [44]. β-lactamase inhibition accomplished by durlobactam restores sulbactam activity against carbapenem-resistant *A. baumannii* [45]. Intrapulmonary concentrations of sulbactam and durlobactam were compared in 30 adult healthy subjects who received three doses of concurrent administration of sulbactam 1 g and durlobactam 1 g every 6 h as a 3-h intravenous infusion [46]. Plasma (total) and ELF concentrations for both components are shown in Table 2. The AUC_6 values of plasma and ELF based on mean sulbactam concentrations at the BAL sampling times were 67.89 μg·h/mL and 34.7 μg·h/mL, respectively. The penetration ratio for ELF to total plasma based on these AUC_6 values was 0.5. This ratio increases to 0.81 when unbound plasma concentrations of sulbactam are used. For durlobactam, AUC_6 values of total plasma and ELF concentrations were 109.05 μg·h/mL and 40.1 μg·h/mL, respectively. The ratio of ELF

to total plasma based on AUC_6 values was 0.37. Durlobactam is not significantly protein bound (approximately 10%), therefore the ratio of ELF to unbound durlobactam in plasma increased to 0.41. These findings support the further exploration of sulbactam/durlobactam for the treatment of lower respiratory tract infections caused by β-lactamase-producing *A. baumannii.* While AM concentrations were evaluated in this study for both sulbactam and durlobactam, the AUC ratios were not presented as concentrations were low and were generally consistent across the 6-h interval.

2.2 Critically Ill Patients

Concerns continue to exist on whether intrapulmonary penetration studies in healthy subjects are reflective of the time course, pattern, and/or magnitude of ELF concentrations in serious ill patients with lower respiratory tract infections [3]. During the past 10 years, several PK studies and data analyses have attempted to provide further insight into the differences in ELF concentration-time profiles between healthy subjects and critically ill patients with pulmonary infections. This section reviews the plasma and ELF concentrations in critically ill patients for the most commonly studied antibiotics, β-lactams, and β-lactam β-lactamase inhibitor combinations.

2.2.1 Piperacillin/Tazobactam

Steady-state plasma and ELF concentrations of piperacillin and tazobactam in critically ill patients with nosocomial pneumonia have previously been reviewed [1]. Since then, Felton and colleagues assessed steady-state piperacillin/tazobactam PK in 17 critically ill patients [47]. Intubated patients with pneumonia received piperacillin 4 g combined with tazobactam 0.5 g every 8 or 12 h based on renal function. A population PK analysis was conducted based on 128 plasma and 31 ELF samples. Bayesian posterior parameter estimates were used to determine AUC in plasma and ELF for each patient. The median penetration ratios ($AUC_{ELF}/AUC_{unbound\ plasma}$) for piperacillin and tazobactam were 0.49 (range 0.02–5.16) and 1.21 (range 0.11–3.91), respectively (Table 3). The observed high variability could not be explained by relationships of pulmonary permeability and antibiotic concentrations in plasma or ELF. The probability of achieving PD targets to treat an organism with an MIC of 1 μg/mL and 16 μg/mL were estimated using a 5000-subject Monte Carlo simulation. For empirical administration of a piperacillin dosage regimen of 4 g every 8 h infused intravenously over 30 min, both unbound plasma and ELF concentrations would achieve 50% and 100% T>MIC in an estimated 96% and 77% of patients, respectively. However, suppression of the emergence of resistance (based on C_{min}/MIC >3.4, where C_{min} is the minimum concentration)

occurred in only 38–41% of patients. The probability of achieving 50% and 100% T>MIC, when the MIC is 16 µg/mL, was 54% and 20%, respectively. C_{min}/MIC >3.4 only occurred in 6% of patients. Individualization of dosage regimens for piperacillin/tazobactam may be required in order to optimize plasma and ELF concentrations in critically ill patients.

A population PK analysis was conducted using previously published serum and ELF concentrations of piperacillin to determine and compare intrapulmonary penetration of 25 healthy adult subjects and 53 critically ill patients [48]. The piperacillin dose studied in healthy subjects was 4 g every 6 h for three doses, whereas critically ill patients received 4 g every 8 h as a 5- or 30-min infusion, or 12–16 g/day as a continuous intravenous infusion. Although all participants had received the combination product piperacillin/tazobactam, only data for piperacillin were included in this analysis. The critically ill patients had higher median serum (304.2 vs. 238.4 µg•h/mL) and ELF (173.5 vs. 78.8 µg•h/mL) AUC values than the healthy subjects, with the respective interquartile ranges (IQR) being six times (331.7 µg•h/mL vs. 48.3 µg•h/mL) and four times (218.7 µg•h/mL vs. 51.3 µg•h/mL) greater in patients. When a 5000-subject Monte Carlo simulation was conducted based on the PK data, the median (IQR) intrapulmonary penetration ratios based on AUC from 18 to 24 h ($AUC_{18–24}$) were 0.33 (0.18) and 0.54 (0.51) for healthy subjects and critically ill patients, respectively. Assessment of target attainment for a dosage regimen of 4 g of piperacillin every 8 h as a 30-min intravenous infusion predicted > 95% of healthy subjects and patients had adequate exposure in both serum and ELF to treat organisms with an MIC of 1 µg/mL. Approximately 50% of critically ill patients had appropriate serum and ELF concentrations of piperacillin to treat an organism with a MIC value of 16 µg/mL. However, predicted piperacillin concentrations in healthy subjects would result in an inadequate exposure at this MIC value. While the median penetration ratio in critically ill patients was considerably greater than in healthy subjects, the marked variability of serum and lung concentrations in critically ill patients must be considered when designing dosage regimens based on PK and penetration data from healthy subjects.

2.2.2 Ceftazidime

The intrapulmonary penetration and ELF concentrations of ceftazidime in critically ill patients have been previously reviewed [1, 49]. Prior studies administered ceftazidime as either a single intramuscular injection or by continuous intravenous infusion. Cousson and colleagues compared plasma and ELF concentrations of ceftazidime in 34 mechanically ventilated patients with pneumonia [50]. Patients were randomized to receive ceftazidime as either a

20 mg/kg intravenous bolus over 30 min followed by a continuous intravenous infusion of 60 mg/kg/day or intermittent intravenous infusions of 20 mg/kg over 30 min every 8 h. Serial plasma concentrations of ceftazidime were collected over the first 48 h of therapy and a single BAL was performed at 44 h after the start of ceftazidime administration. The median AUC_{48} for total plasma was 1348 µg·h/mL and 1361 µg·h/mL in the continuous infusion and intermittent infusion groups, respectively. The respective median ELF concentration and ELF to total plasma penetration ratio were 12 µg/mL and 0.42 in the continuous infusion group and 6 µg/mL and 0.44 in the intermittent infusion group (Table 3). These results suggest higher intrapulmonary exposure when ceftazidime is administered by continuous infusion. In addition, the dosage regimen evaluated in this study resulted in higher intrapulmonary ceftazidime exposures than previously reported (e.g., mean ELF concentration of 8.2 µg/mL and intrapulmonary penetration of 0.206) in critically ill adult patients receiving ceftazidime 4 g/day for the treatment of severe bacterial pneumonia [51].

2.2.3 Cefiderocol

The ELF penetration of cefiderocol was evaluated in seven mechanically ventilated patients with pneumonia. Adult patients were administered cefiderocol 2 g (or 1.5 g if renally impaired) every 8 h as a 3-h intravenous infusion (or every 6 h if the patient had augmented renal function [estimated creatinine clearance > 120 mL/min]) [52]. Total plasma and ELF concentrations of cefiderocol after the start of the infusion are reported in Table 3. The geometric mean (range) for ELF to unbound plasma concentration ratios at 3 h (n = 4) and 5 h (n = 3) were 0.211 (0.090–0.422) and 0.547 (0.443–0.822). These ratios were approximately two- to fourfold higher than observed in healthy subjects receiving a single 2 g dose of cefiderocol infused intravenously over 1 h [15]. These results suggest higher ELF exposures of cefiderocol in patients with pneumonia compared with healthy subjects.

2.2.4 Ceftolozane/Tazobactam

Plasma and ELF penetration was evaluated in 26 ventilated critically ill patients receiving ceftolozane/tazobactam [53]. Participants received four to six doses of ceftolozane/tazobactam 3 g every 8 h administered as a 1-h intravenous infusion. A reduced dose was administered in patients with creatinine clearance < 50 mL/min or < 30 mL/min, respectively (Table 3). The penetration ratios for ELF to unbound plasma (i.e., 21% and 30% plasma protein binding assumed for ceftolozane and tazobactam, respectively) were 0.50 for ceftolozane and 0.62 for tazobactam, based on AUC_8 values calculated from the geometric means of ELF concentrations

Table 3 Plasma and epithelial lining fluid concentrations of β-lactams in critically ill patients

Antibacterial agent	Dosage regimen	Patients [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Piperacillin/ tazobactam	Piperacillin 4 g IV over 30 min q8h (q12h if CL_{CR} < 20 mL/min)	16	Between 7.88 and 148.33[c]	0.49[d]	Range: 5.26– 241.62	Range: 0.14– 295.43	[47]
	Tazobactam 0.5 g IV over 30 min q8h (q12h if CL_{CR} < 20 mL/ min)	16	Between 7.88 and 148.33[c]	1.21[d]	Range: 3.24– 33.90	Range: 0.62– 62.48	
Ceftazidime	Intermittent infusion: 20 mg/kg IV over 30 min q8h	17	44[e]	ND	95 and 6[f]	6.0	[50]
	CI: 20 mg/kg IV over 30 min loading dose, followed by 60 mg/kg/day IV CI	17	44[e]	ND	27.0	12.0	
Cefiderocol	2 g IV (1.5 g if renally impaired) over 3 h q8h (q6h if CL_{CR} >120 mL/ min) for 6–9 doses	7	1	ND	60.3[g]	NC	[52]
		7	3		80.8[g]	7.63[g,h]	
		7	5		56.3[g]	10.4[g,i]	
		7	7		44.6[g]	NC	
Ceftolozane/ tazobactam	Ceftolozane 2 g IV over 1 h q8h if CL_{CR} >50 mL/min (1 g IV over 1 h q8h if CL_{CR} 30–50 mL/min; 500 mg IV over 1 h q8h if CL_{CR} 15–29 mL/min) for 4–6 doses	5	1	0.50[j]	NR	NR	[53]
		5	2		NR	NR	
		5	4		NR	NR	
		4	6		NR	NR	
		3	8		NR	NR	
	Tazobactam 1 g IV over 1 h q8h if CL_{CR} >50 mL/min (500 mg IV over 1 h q8h if CL_{CR} 30–50 mL/min; 250 mg IV over 1 h q8h if CL_{CR} 15–29 mL/min) for 4–6 doses	5	1	0.62[k]	NR	NR	
		5	2		NR	NR	
		5	4		NR	NR	
		4	6		NR	NR	
		3	8		NR	NR	
Meropenem	2 g or 500 mg IV over 3-h infusion q8h or 1 g IV over 30 min q8h	17	NR	0.25[l]	NR	NR	[55]

Table 3 (continued)

Antibacterial agent	Dosage regimen	Patients [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Meropenem	1 g IV over 30 min q8h	5	0	0.20[m]	NR	NR	[56]
		5	0.5		NR	NR	
		5	1		NR	NR	
		5	3		NR	NR	
		5	4		NR	NR	
		5	6		NR	NR	
	1 g IV over 3 h q8h	5	0	0.29[m]	NR	NR	
		5	1		NR	NR	
		5	3		NR	NR	
		5	4		NR	NR	
		5	6		NR	NR	
Meropenem	Loading dose of 2 g IV over 15 min followed by 3 g/day CI	15	0	0.32[m]	12.9	NC	[57]
		15	1.5		13.4	NC	
		15	3		13.3	NC	
		15	6		11.7	3.9	
		15	8		12.3	NC	
	Loading dose of 2 g IV over 15 min followed by 6 g/day IV CI	15	0	0.36[m]	23.0	NC	
		15	1.5		23.9	NC	
		15	3		21.4	NC	
		15	6		22.4	6.6	
		15	8		18.9	NC	
Doripenem	500 mg IV over 1 h	2	0	0.29	NR	NR	[58]
		2	2		NR	NR	
		2	4		NR	NR	
		2	6		NR	NR	
	500 mg IV over 4 h	2	0	0.21	NR	NR	
		2	2		NR	NR	
		2	4		NR	NR	
		2	6		NR	NR	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *IV* intravenously, CL_{CR} creatinine clearance, *CI* continuous intravenous infusion, *ND* not determined, *NC* no samples collected at this time, *NR* not reported, *qxh* every *x* hours

[a]Sampling time after the last dose

[b]Values expressed as median

[c]Sample collection occurred throughout therapy

[d]Median value for the ratio of AUC in ELF to AUC in unbound plasma, assuming 30% protein binding in plasma

[e]Sampling time was at steady-state (44 h after starting therapy)

[f]Maximum and minimum ceftazidime concentration, respectively

[g]Values expressed as geometric mean

[h]Four patients had an ELF concentration at 3 h

[i]Three patients had an ELF concentration at 5 h

[j]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 21% protein binding in plasma

[k]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 30% protein binding in plasma

[l]Median value for the ratio of AUC in ELF to AUC in total plasma

[m]Based on the ratio of AUC_{24} in ELF to AUC_{24} in total plasma

[n]Calculated from the reported values of AUC_8 in ELF and total plasma

at each BAL sampling time. These findings were comparable with previously reported intrapulmonary penetration ratios in healthy adult subjects [19]. However, the plasma and ELF concentration-time profiles in critically ill patients had higher interpatient variability and a delay in the time to maximum ELF concentration (i.e., geometric mean of 6 h for ceftolozane and 2 h for tazobactam). These observations were further explored and confirmed by Zhang and colleagues, who developed a population PK model that incorporated 16 clinical trials, including the intrapulmonary penetration studies of healthy subjects and critically ill patients and the plasma concentrations obtained in the pivotal phase III study in patients with hospital-acquired and ventilator-associated bacterial pneumonia [54]. By using a hypothetical link compartment model, the respective disposition rate constants to describe ceftolozane and tazobactam distribution between plasma and ELF and ELF elimination were shown to be 97% and 52% lower in patients with pneumonia compared with healthy subjects. These results provide further elaboration on the delayed distribution, large interindividual variability, and sustained ELF exposure of ceftolozane and tazobactam in critically ill patients.

2.2.5 Meropenem

In addition to the previously reported intrapulmonary penetration of meropenem in healthy subjects, multiple studies have evaluated the ELF concentrations of meropenem in patients with nosocomial pneumonia. Lodise and colleagues described the plasma and ELF PK of meropenem in 39 intubated patients with hospital-acquired pneumonia [55]. Population PK modeling was conducted from a total of 269 plasma concentrations and 17 ELF concentrations. The derived pulmonary penetration ratios based on AUC values in ELF and total plasma included 0.30 when calculated from the mean parameter vector of the population model, a median value of 0.264 when determined with Bayesian parameter estimates for the 17 patients with an ELF sample, and a median value of 0.254 when estimated from a 9999-subject Monte Carlo simulation. However, the mean ($\pm$ standard deviation [SD]) penetration ratio in the Monte Carlo simulation was 0.816 ($\pm$ 2.542), with the 10th and 90th percentiles being 0.037 and 1.78, respectively. This study confirms that ELF penetration of meropenem has a wide range of variability in critically ill patients with hospital-acquired pneumonia.

In a study evaluating 55 adult patients with severe nosocomial pneumonia, meropenem 1 g every 8 h was administered as an intravenous infusion, either over 30 min or 3 h (Table 3) [56]. Noncompartmental PK estimates based on mean values of plasma and ELF concentrations at each sampling time demonstrated a higher AUC_{24} in plasma (502 μg•h/mL vs. 422 μg•h/mL, $p = 0.082$) and ELF (150 μg•h/mL vs. 80.3 μg•h/mL, $p = 0.010$) for the 3-h versus 30-min infusion groups.

The penetration ratio of meropenem ELF to plasma based on AUC_{24} was 0.20 for the 30-min infusion group and 0.29 for the 3-h extended infusion group. Population PK modeling and Monte Carlo simulations were used to provided support of an empiric dose of meropenem for the treatment of severe nosocomial pneumonia. The dosage regimen of 2 g every 8 h as a 3-h extended intravenous infusion was predicted to achieve PD target values of 40–100% fT>MIC for susceptibility breakpoint ranges of 2–8 μg/mL in plasma and 0.06–1.0 μg/mL in ELF.

A PK study comparing two dosage regimens of meropenem administered by continuous infusion was conducted in 31 intensive care unit patients with nosocomial pneumonia [57]. Participants received a 2 g loading dose of meropenem administered as a 15 min IV infusion and were randomly assigned to receive either a 3 g/day or 6 g/day continuous intravenous infusion of meropenem. Population PK modeling was conducted from a total of 151 plasma concentrations and 30 ELF concentrations, and Bayesian posterior parameter estimates were used to calculate AUC in plasma and ELF for each patient. The respective median (IQR) AUC from 48 to 72 h ($AUC_{48–72}$) for the 3 g/day and 6 g/day regimens was 322.7 (225.6) μg·h/mL and 492.3 (354.1) μg·h/mL in plasma, and 101.5 (78.5) μg·h/mL and 175.9 (258.7) μg·h/mL in ELF. The median (IQR) penetration ratios (AUC_{ELF}/AUC_{plasma}) were 0.32 (0.34) and 0.36 (0.44) for the 3 g/day and 6 g/day groups, respectively (Table 3). Monte Carlo simulations were performed to estimate the probability of achieving a target of 50% fT>MIC in ELF for three dosage regimens of meropenem. Target attainment in ELF could be achieved with a 2 g loading dose followed by 3 g/day and 6 g/day continuous infusion dosing strategies when MIC values were < 2 μg/mL and < 4 μg/mL, respectively. These target attainment goals were supported by outcome observations among 12 patients, where clinical cures occurred in all patients achieving >50% fT>MIC in ELF and treatment failures when fT>MIC was 33% [57].

2.2.6 Doripenem

Plasma and ELF concentrations were compared in 16 mechanically ventilated, intensive care patients receiving doripenem for the treatment of pneumonia [58]. Patients received multiple intravenous doses (i.e., 3–24) of doripenem 500 mg every 8 h and divided into two groups based on whether administration was a 1-h or 4-h intravenous infusion. Each patient had a serial collection of plasma samples at steady-state, along with a single BAL sample either before or at 2, 4, or 6 h after the start of the infusion (Table 3). The mean total plasma AUC_8 of doripenem was 52.98 μg·h/mL in patients receiving the 1-h infusion and 70.64 μg·h/mL in patients receiving the 4-h infusion. The doripenem AUC_8 based on the mean of two ELF concentrations at each BAL sampling time were 15.3 μg·h/mL and 14.8 μg·h/mL

for patients receiving the 1-h and 4-h infusions, respectively. Neither of the infusion methods for administering a 500 mg dose were able to sustain ELF concentrations of doripenem above 1 µg/mL over the 8-h dosing interval. These lower and more variable ELF concentrations above the MIC may lend support to the observed lower clinical cure rate and increased risk of death for a 7-day course of doripenem when compared with a 10-day course of imipenem-cilastatin in a randomized clinical trial of patients with ventilator-associated pneumonia [59].

2.2.7 Ertapenem

Single-dose plasma and intrapulmonary concentrations of ertapenem in patients with early-onset ventilator-associated pneumonia or undergoing thoracotomy have been previously reviewed [1]. Bader and colleagues have subsequently re-evaluated the PK/PD profile of plasma and ELF concentrations of ertapenem obtained from patients with ventilator-associated pneumonia [60, 61]. A population PK model was developed to account for ELF penetration and non-linear plasma protein binding of ertapenem. Monte Carlo simulations were used to calculate the percentage probabilities of target attainment for unbound plasma and ELF at T>MIC target values of 35%, 40%, and 45%. Five intermittent dosing strategies of ertapenem were assessed, including 1 g and 2 g every 24 h infused intravenously over 30 min or 3 h, and 1 g every 12 h infused intravenously over 30 min. The penetration ratio was 0.34 based on the estimated median AUC_{24} values of 68.2 µg·h/mL and 200 µg·h/mL for ELF and unbound plasma, respectively. The probabilities of achieving a target attainment of 35% T>MIC in ELF was >90% for MIC values ranging between 0.008 and 0.12 µg/mL for all five dosage regimens. Ertapenem regimens that included 2 g/day dosing or a 3-h infusion were able to extend the range of MIC coverage to 0.25 µg/mL and 0.5 µg/mL. Similar results were observed at the higher target values in ELF. The probabilities of target attainment of specific Gram-negative pathogens (at MIC_{90} values) ranged from 99.8 to 100%, 97.9% to 100%, 10.6% to 74.1%, and 0 to 1.5% for *Escherichia coli* (0.06 µg/mL), *Serratia marcescens* (0.12 µg/mL), *Enterobacter* spp. (1 µg/mL), and *K. pneumoniae* (> 2 µg/mL), respectively. These results provide support for dosing options of ertapenem to be combined with other antibacterial agents for the treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia.

3 Macrolides and Ketolides

Intrapulmonary penetration for many macrolides, azalide, and ketolides has previously been reported [1]. The majority of these studies included clarithromycin, azithromycin, and telithromycin, and demonstrated markedly higher ELF and AM concentrations compared with plasma concentrations. Two novel agents from the ketolide class have subsequently been evaluated.

3.1 Solithromycin

Solithromycin is a fluoroketolide antibiotic that has been in clinical development for the treatment of bacterial infections. Solithromycin has demonstrated in vitro activity against organisms that commonly cause community-acquired pneumonia, including *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, and atypical respiratory pathogens. Plasma, ELF, and AM concentrations were compared in 30 healthy adult subjects to determine intrapulmonary penetration following the oral administration of solithromycin 400 mg once daily for 5 days [62]. Compared with the simultaneously collected solithromycin plasma concentrations, ELF concentrations were 2.4 to 28.6 times greater during the 24-h sampling period. The respective AUC_{24} values for ELF were 80.3 µg·h/mL and 63.2 µg·h/mL based on the mean and median concentrations in ELF at each sampling time. The ELF to plasma concentration ratios were 10.3 and 10.0 based on these AUC_{24} values, respectively (Table 4). In comparison, steady-state AUC_{24} of telithromycin in ELF was previously reported as 58.3 µg·h/mL, and the mean ELF to plasma telithromycin ratio based on AUC_{24} was 8.05 [63].

The 30 ELF concentrations were combined with 1966 plasma concentrations to simulate population concentration-time data of solithromycin in ELF and plasma using a physiologically based PK model [64]. The modeling supported a high AUC/MIC target attainment following administration of the oral dosing regimen of solithromycin 800 mg on day 1 and 400 mg once daily on days 2–5. Okusanya and colleagues performed a PK/PD analysis of solithromycin in a neutropenic murine lung infection model [65]. The observed solithromycin total drug ELF to unbound drug plasma AUC_{24} ratio in mice was 2.7, which was considerably lower than solithromycin penetration in human lung ELF.

Compared with plasma, AM concentrations of solithromycin were simultaneously 44 to 515 times greater during the 24-h time period after the final solithromycin dose [62]. The ratios of AM to plasma based on mean and median AUC_{24} values were 193 and 202, respectively. Given that total plasma drug concentrations were evaluated in this study and used for determining ELF and AM ratios, intrapulmonary penetration ratios would be greater when using unbound plasma concentrations. Only the oral formulation of solithromycin has been evaluated in humans.

Table 4 Plasma and epithelial lining fluid concentrations of ketolides

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Solithromycin	400 mg PO q24h × 5 days	6	3	10.3[c]	0.730 ± 0.692	7.58 ± 6.69	[62]
		6	6		0.595 ± 0.325	6.50 ± 2.73	
		6	9		0.301 ± 0.185	3.78 ± 4.32	
		6	12		0.300 ± 0.171	2.54 ± 2.55	
		6	24		0.086 ± 0.070	1.02 ± 0.83	
Nafithromycin	800 mg PO q24h × 3 doses	6	3	13.8[c]	1.105 ± 0.140	18.48 ± 12.31	[66]
		6	6		0.966 ± 0.439	15.29 ± 14.53	
		6	9		0.922 ± 0.286	8.37 ± 4.38	
		5	12		0.817 ± 0.261	9.67 ± 6.20	
		6	24		0.239 ± 0.055	4.13 ± 1.38	
		6	48		0.060 ± 0.029	1.62 ± 0.86	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *PO* by mouth, *qxh* every *x* hours, *SD* standard deviation

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations expressed as mean ± SD

[c]Based on the ratio of AUC_{24} in ELF to AUC_{24} in total plasma

3.2 Nafithromycin

Nafithromycin is an oral ketolide being evaluated for the treatment of community-acquired bacterial pneumonia. Compared with the other macrolides and ketolides, higher plasma and ELF concentrations are achieved. Plasma, ELF, and AM concentrations of nafithromycin were evaluated in healthy adult subjects following 800 mg once-daily oral dosing for 3 days [66]. Nafithromycin concentrations in ELF were 2.5 to 36.3 times higher than plasma concentrations during the 48-h sampling period. The AUC_{24} value based on the mean concentrations in ELF at each sampling time was 224.1 μg·h/mL, which resulted in a penetration ratio of ELF to total plasma of 13.8 (Table 4). The AUC_{24} of nafithromycin in AM was 8538 μg·h/mL, with a penetration ratio of 527 based on AUC_{24} values in AM and plasma. These ratios were based on total plasma drug concentrations as opposed to unbound plasma concentrations. Compared with the other macrolides and ketolides, the AUC values of nafithromycin in both plasma and ELF were substantially higher. Specifically, the mean nafithromycin AUC_{24} is about three times greater than observed with solithromycin, which could be advantageous for nafithromycin in the treatment of bacterial pneumonia, although the MIC_{90} is higher for solithromycin [65, 67]. The pattern of intrapulmonary penetration of the AUC values of ELF and AM being circa 10-fold and 100-fold higher, respectively, than total plasma concentrations for these two novel agents are consistent with previously reported findings for azithromycin, clarithromycin, and telithromycin.

4 Fluoroquinolones

Fluoroquinolones are used for a wide variety of infectious syndromes, given their antibacterial activity against a broad spectrum of microorganisms. Levofloxacin and moxifloxacin are recommended treatment choices for community-acquired pneumonia, and levofloxacin and ciprofloxacin are treatment options for hospital- and ventilator-acquired pneumonia [68, 69]. Intrapulmonary penetration for moxifloxacin, ciprofloxacin, and levofloxacin has previously been reported and supports the use of these agents for lower respiratory tract infections [1].

4.1 Levofloxacin

A wide range of levofloxacin dosages have been evaluated following both oral and intravenous administration. Older studies report ELF to plasma concentration ratios ranging from 1.59 to 2.69 based on AUC [1]. Since then, two studies comparing intrapulmonary concentrations of levofloxacin have been published, one study evaluating patients with idiopathic pulmonary fibrosis and one study evaluating patients with acute exacerbation of chronic bronchitis [70, 71]. Huang and colleagues compared plasma and ELF concentrations of 10 patients with idiopathic pulmonary fibrosis with 10 patients in a control group following a single oral dose of levofloxacin 500 mg [70]. The mean ELF concentration was 10.17 μg/mL in the idiopathic pulmonary fibrosis group and 27.81 μg/mL in the control group. While ELF concentrations were significantly different between groups, the findings are consistent with previously published studies

on intrapulmonary penetration in both healthy subjects and those who may have impaired pulmonary diffusion. The second study serving as an addition to the levofloxacin intrapulmonary penetration literature is a PK evaluation of levofloxacin 750 mg orally once daily in adults undergoing treatment for acute exacerbation of chronic bronchitis [71]. This study observed an ELF to plasma penetration ratio of 1.13, comparable with previous studies with similar patient populations. The observed AUC to MIC ratios were considered adequate for the treatment of common causative organisms of chronic bronchitis, including *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

A subsequent retrospective analysis used population PK modeling and Monte Carlo simulation to compare the ELF penetration of these 18 infected patients with acute exacerbations of chronic bronchitis and 15 uninfected patients undergoing diagnostic bronchoscopy [72]. The infected patients demonstrated a lower median penetration ratio (1.29 vs. 3.39) compared with uninfected patients based on AUC values of levofloxacin in ELF and unbound plasma. The simulated 24-h AUC values in total plasma of levofloxacin were similar among infected and uninfected patients (mean $\pm$ SD: 140.5 $\pm$ 5.48 µg•h/mL vs. 133.7 $\pm$ 61.6 µg•h/mL), whereas the AUC in ELF values in infected patients were significantly lower than uninfected patients (mean $\pm$ SD: 189.1 $\pm$ 210.5 µg•h/mL vs. 461.0 $\pm$ 558.7 µg•h/mL). These results suggest a higher oral dosing regimen (e.g., 750 mg every 24 h) may be necessary in infected patients in order provide adequate ELF exposures.

4.2 Alalevonadifloxacin

Several new fluoroquinolones are undergoing clinical investigation for their potential use in the treatment of lower respiratory tract bacterial infections. Alalevonadifloxacin is an oral prodrug of levonadifloxacin under investigation as a novel benzoquinolizine quinolone with *in vitro* activity against other fluoroquinolone-resistant organisms, including MRSA [73]. Plasma, ELF, and AM levonadifloxacin concentrations were compared in 30 healthy adults following oral administration of alalevonadifloxacin 1000 mg administered every 12 h for nine doses [74]. Levonadifloxacin total drug concentrations in plasma and ELF were similar, with a penetration ratio close to 1 (Table 5). Compared with other fluoroquinolones, levonadifloxacin is highly protein bound (85%). The total drug in ELF to unbound drug in plasma penetration ratios were 7.66 and 7.58 based on the mean and median AUC_{12} values, respectively. AM concentrations of levonadifloxacin in the 12 h following alalevonadifloxacin administration were lower than total drug plasma and ELF concentrations at all time points evaluated. The penetration ratios of AM to unbound plasma concentrations of levonadifloxacin based on the respective mean and median AUC_{12} values were 1.58 and 1.44.

4.3 Sitafloxacin

Sitafloxacin is a desfluoroquinolone antibiotic currently available in Thailand and Japan and has a broad spectrum in vitro activity against quinolone-resistant Gram-positive and Gram-negative organisms [75]. No studies have evaluated the intrapulmonary PK of sitafloxacin in healthy subjects; however, Paiboonvong and colleagues evaluated sitafloxacin ELF penetration in 12 critically ill patients with pneumonia (Table 5) [76]. The mean sitafloxacin AUC_8 for plasma and ELF were 5.58 µg·h/mL and 4.77 µg·h/mL, respectively. The resultant ELF to unbound plasma AUC_8 penetration ratio was 0.85, substantially lower than many other fluoroquinolones evaluated in healthy subjects. However, this study had several limitations, including a limited BAL sampling period, technique errors in BAL collection procedures, small sample size, and large variability in the observed ELF concentrations. There are currently no studies evaluating sitafloxacin intrapulmonary penetration after multiple doses or at steady state.

4.4 Avarofloxacin

Avarofloxacin (formerly known as JNJ-Q2) is a broad-spectrum fluoroquinolone being clinically evaluated for the treatment of community-acquired bacterial infections, including pneumonia. Intrapulmonary penetration was studied in eight healthy subjects following oral administration of avarofloxacin 250 mg every 12 h for seven doses [77]. The ELF to unbound plasma penetration ratios ranged from approximately 17 to 64 over the 6-h sampling time (Table 5). The AM to plasma penetration ratios for this same time period ranged from approximately 74 to 157. AUC values for plasma or intrapulmonary concentrations were not reported for this limited dataset since the sponsor discontinued the study after enrollment of only 10 subjects (8 receiving avarofloxacin). Intrapulmonary concentrations following intravenous dosing of avarofloxacin were not evaluated.

4.5 Lascufloxacin

Lascufloxacin is a fluoroquinolone in clinical development for the treatment of community-acquired pneumonia and other respiratory tract infections [78]. Plasma, ELF, and AM concentrations were compared in 30 healthy, male adults following a single oral dose of lascufloxacin 75 mg [79]. Plasma and ELF concentrations are shown in Table 5. After accounting for an estimated 26% plasma protein binding, the total drug ELF to unbound plasma penetration ratio based on lascufloxacin AUC_{24} was 61.7. Ohya and colleagues

Table 5 Plasma and epithelial lining fluid concentrations of fluoroquinolones

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	ELF to plasma based on AUC	Plasma concentration [µg/mL][b]	ELF concentration [µg/mL][b]	References
Alalevonadifloxacin[c]	1000 mg PO q12h × 9 doses	6	2	1.15[d]	20.5 ± 6.3	26.0 ± 15.9	[74]
		6	4		17.6 ± 6.1	19.7 ± 7.2	
		6	6		16.4 ± 4.7	19.9 ± 11.1	
		6	8		9.49 ± 4.25	10.6 ± 6.0	
		6	12		4.88 ± 1.09	4.28 ± 1.40	
Sitafloxacin	200 mg PO × 1 dose	12	0.5–2	0.85[e]	0.60 ± 0.46	0.19 ± 0.20	[76]
		12	3-4		1.37 ± 0.51	0.48 ± 0.29	
		12	5-6		1.99 ± 2.34	1.07 ± 0.93	
		12	7-9		0.85 ± 0.77	0.61 ± 0.77	
JNJ-Q2	250 mg PO q12h × 7 doses	2	1	NR	0.65 (26.7)[f]	39.8 (35.4, 44.2)	[77]
		2	2		0.78 (20.2)[f]	34.5 (31.8, 37.2)	
		2	4		0.71 (11.3)[f]	11.4 (10.5, 12.3)	
		2	6		0.64 (8.9)[f]	35.0 (34.9, 35.1)	
Lascufloxacin	75 mg PO × 1 dose	6	1	61.7[g]	0.576 ± 0.145	12.3 ± 3.74	[79]
		6	2		0.501 ± 0.0876	9.22 ± 3.45	
		6	4		0.443 ± 0.0419	7.15 ± 3.21	
		6	6		0.387 ± 0.0119	5.84 ± 1.72	
		6	24		0.176 ± 0.0545	2.65 ± 0.88	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *PO* by mouth, *NR* not reported, *qxh* every *x* hours, *SD* standard deviation

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations expressed as mean ± SD or median (minimum, maximum)

[c]Measured concentrations are levonadifloxacin, the active drug from the alalevonadifloxacin prodrug

[d]Based on the ratio of AUC_{12} in ELF to AUC_{12} in total plasma

[e]Based on the ratio of AUC_8 in ELF to AUC_8 in unbound plasma, assuming 63% protein binding in plasma

[f]Values expressed as mean (percent coefficient of variation), assuming 65% protein binding in plasma

[g]Based on the ratio of AUC_{24} in ELF to AUC_{24} in unbound plasma, assuming 74% protein binding in plasma

explored the in vitro mechanism by which lascufloxacin distributes into the ELF, given the higher penetration ratios observed in the intrapulmonary penetration study [80]. Compared with other fluoroquinolones and phospholipids, lascufloxacin demonstrated greater binding to phosphatidylserine in pulmonary surfactant, indicating a likely mechanism for higher distribution of lascufloxacin into ELF. AM concentrations were also evaluated. The mean AUC_{24} of lascufloxacin in AM was 325 µg·h/L and the mean total drug AM concentration to unbound serum concentration penetration ratio based on AUC_{24} was 163. The MIC_{90} values for common extra- and intracellular respiratory pathogens were well exceeded by the ELF and AM concentrations of lascufloxacin, respectively [79]. No studies evaluating steady-state intrapulmonary concentrations of lascufloxacin have been reported.

5 Other Antibacterial Agents with Gram-Positive Activity

5.1 Vancomycin

MRSA is an important cause of nosocomial pneumonia. It is imperative that antibiotics with activity against MRSA have reliable lung penetration for the treatment of lower respiratory tract infections. We have previously reviewed the intrapulmonary penetration and ELF concentrations of vancomycin observed in both healthy subjects and critically ill patients [1]. Subsequently, an abstract by Drusano and colleagues describing a population PK modeling study and vancomycin penetration into ELF fluid has been published [81].

Ten healthy adult subjects received vancomycin 1000 mg intravenously every 12 h and had BAL sampling at 4 and 12 h after the ninth dose [81]. ELF to plasma penetration ratios, based on individual AUC estimates, ranged from

0.24 to 4.77. However, if excluding the outlier of 4.77, the mean penetration ratio for the remaining nine subjects was 0.41, similar to the noncompartmental analysis of the same data [82]. A 9999-subject Monte Carlo simulation resulted in mean and median AUC_{ELF}/AUC_{plasma} penetration ratios of 0.675 and 0.474, respectively.

5.2 Linezolid

Linezolid is an oxazolidinone antibiotic available for both intravenous and oral administration. Linezolid is approved for the treatment of lower respiratory tract infections caused by *S. pneumoniae* or *S. aureus*, including both methicillin-susceptible and methicillin-resistant strains. As previously described, the ELF to plasma concentration ratios of linezolid ranged from 2.3 to 4.2 for 48 h after the fifth 600 mg oral dose in healthy adults, and approximately 1.04 at 2 and 12 h after the fourth 600 mg intravenous dose in critically ill patients with ventilator-associated pneumonia [1, 83, 84].

Boselli and colleagues also conducted an analysis of intrapulmonary penetration of linezolid when administered as a continuous intravenous infusion in patients with ventilatory-associated pneumonia [85]. Twelve critically ill patients received linezolid 600 mg as a 1 h intravenous infusion loading dose followed by a 1200 mg/day continuous intravenous infusion for 2 days. The median linezolid ELF AUC_{24} was 164 μg·h/mL and the median ELF to serum penetration ratio was 0.97. Despite using two different intravenous dosing strategies, the intrapulmonary penetration ratio of linezolid was similar for every 12-h intermittent intravenous infusions compared with continuous intravenous infusion [84, 85].

Intrapulmonary and plasma concentrations of linezolid were also compared when linezolid was administered by intermittent and continuous intravenous infusion to 22 critically ill obese patients with ventilator-associated pneumonia [86]. In this analysis, patients were randomized to receive either linezolid as an intermittent intravenous infusion of 600 mg over 60 min every 12 h or a loading dose of 600 mg intravenously over 60 min followed by 1200 mg/day administered as a continuous intravenous infusion. Linezolid concentrations were collected after 2 days of linezolid therapy, with ELF concentrations determined in 14 patients (e.g., 7 patients in each drug administration group). The median linezolid ELF to plasma ratio was 0.80 for the intermittent intravenous infusion group and 1.06 for the continuous intravenous infusion group ($p = 0.46$). When a 1000-subject Monte Carlo simulation was conducted, a significant difference in the penetration ratio (0.871 vs. 0.988, $p < 0.001$) was observed between the two dosing regimens. It is unclear if the reduced penetration in the intermittent infusion group can be attributed to PK differences in the obese patient population.

5.3 Tedizolid

Tedizolid is also a member of the oxazolidinone class with activity against Gram-positive organisms, including *S. pneumoniae* and MRSA. The MIC values for these two organisms are approximately eightfold lower for tedizolid compared with linezolid. Tedizolid has high plasma protein binding (89.44%) and is available as an oral and intravenous formulation. Intrapulmonary penetration was evaluated in 20 healthy adult subjects following three oral doses of tedizolid 200 mg administered every 24 h [87]. Plasma and ELF concentrations of tedizolid are shown in Table 6. The mean unbound plasma and total ELF AUC_{24} estimated by noncompartmental analysis were 2.65 μg·h/mL and 109.3 μg·h/mL, respectively. The ELF to unbound plasma ratio based on these AUC_{24} values was 40. Population PK modeling and Monte Carlo simulation resulted in similar estimates of penetration ratio (39.7 and 36.3) based on respective mean and median values of AUC_{24} in unbound plasma (2.67 μg·h/mL and 2.59 μg·h/mL) and ELF (106.0 μg·h/mL and 93.9 μg·h/mL) The antibacterial efficacies of tedizolid, linezolid, and vancomycin were compared in an MRSA murine pneumonia model using ELF exposure similar to those observed in humans (i.e., 109 μg·h/mL, 960 μg·h/mL, and 92 μg·h/mL, respectively) [88]. The median MICs for the three stains of MRSA strains used were 0.5 μg/mL, 4 μg/mL, and 1 μg/mL for tedizolid, linezolid, and vancomycin, respectively. Tedizolid and linezolid demonstrated similar efficacy and resulted in higher reduction in bacterial counts and lower mortality compared with vancomycin. These findings lend support to the further exploration of tedizolid for the treatment of lower respiratory tract infections.

5.4 Dalbavancin

Dalbavancin is a lipoglycopeptide antibiotic available for intravenous administration in the treatment of acute bacterial skin and skin structure infection. Dalbavancin has a prolonged half-life (i.e., 14.4 days), allowing for either a single- or two-dose dosing regimen [89, 90]. A study comparing the ELF and plasma concentrations of dalbavancin was conducted in 35 healthy adults using a bronchial microsampling technique (i.e., catheter sponge probes) since dalbavancin is not soluble in the normal saline commonly used with BAL procedures [91]. Subjects received a single dose of dalbavancin 1500 mg administered as an intravenous infusion over 30 min. The total plasma and ELF concentrations collected over a 7-day period are shown in Table 6. The mean plasma AUC_{24} and AUC_{168} were 5255 μg·h/mL and 21,087 μg·h/mL, respectively. The median ELF AUC_{168} was 527 μg·h/mL. The ratio of ELF to unbound plasma based on AUC_{168} values was 0.36, since plasma protein binding of dalbavancin is 93%. Dalbavancin concentrations in ELF

Table 6 Plasma and epithelial lining fluid concentrations of tedizolid and dalbavancin

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Tedizolid	300 mg PO q24h × 3 doses	5	2	40[c]	2.01 ± 0.55	9.05 ± 3.83	[87]
		5	6		1.51 ± 0.33	4.45 ± 2.18	
		5	12		0.946 ± 0.31	5.62 ± 1.99	
		5	24		0.398 ± 0.17	1.33 ± 0.59	
Dalbavancin	1500 mg IV infused over 30 min × 1 dose	5	4	0.36[d]	279 ± 32[e]	1.9 ± 1.0	[91]
		5	8		222 ± 27[e]	3.1 ± 1.9	
		5	12		194 ± 24[e]	3.6 ± 2.1	
		5	24		169 ± 20[e]	2.7 ± 0.5	
		5	72		120 ± 14[e]	7.3 ± 8.2	
		5	120		94 ± 11[e]	11.9 ± 20.1	
		5	168		79 ± 9[e]	2.0 ± 0.6	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *PO* by mouth, *IV* intravenously, *q24h* every 24 h, *SD* standard deviation

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations expressed as mean ± SD

[c]Based on the ratio of AUC_{24} in ELF to AUC_{24} in unbound plasma, calculated using each participant's derived unbound fraction

[d]Based on the ratio of AUC_{168} in ELF to AUC_{168} in unbound plasma, assuming 93% protein binding in plasma

[e]Thirty-seven plasma concentrations were reported at each sampling time; values expressed as median ± SD

were observed to exceed the MIC_{90} values for *S. aureus* and *S. pneumoniae* for up to 7 days after administration. The estimated $fAUC_{24}/MIC_{90}$ values in ELF for these pathogens were greater than plasma $fAUC_{24}/MIC_{90}$ values needed to achieve stasis, 1-log, and 2-log bactericidal activity in murine infection models. These findings support the further exploration of dalbavancin as a single 1500 mg dosing regimen for the treatment of pneumonia caused by these susceptible Gram-positive organisms.

6 Tetracyclines

Tetracycline antibiotics have antibacterial activity against a broad spectrum of microorganisms. Newer analogs have improved potency and retained activity against mechanisms of older tetracycline resistance, including tetracycline efflux pumps and ribosomal protection proteins. Parenteral tigecycline steady-state serum and intrapulmonary concentrations in healthy adults have previously been reported [1]. Tigecycline was found to have mean total serum concentrations ranging from 0.10 to 0.19 μg/mL over a 12-h interval [92]. Given that tigecycline is highly protein bound, unbound concentrations are likely much lower. ELF concentrations ranged from 0.06 to 0.37 μg/mL and the AUC_{12} was 2.28 μg·h/mL. Population PK modeling found a median ELF AUC_{24} of 9.03 μg·h/mL and a median penetration ratio of 1.15 for tigecycline [93].

6.1 Omadacycline and Tigecycline

Omadacycline is an aminomethylcycline antibiotic and a semisynthetic derivative of minocycline available for both intravenous and oral administration [94]. A study comparing the intrapulmonary penetration of tigecycline and omadacycline was conducted in 50 healthy adults [94]. Subjects received either omadacycline 100 mg intravenously every 12 h for two doses followed by 100 mg every 24 h for three doses, or tigecycline 100 mg intravenously for one dose followed by 50 mg every 12 h for six doses. Plasma and ELF concentrations are shown in Table 7. Tigecycline concentrations in both serum and ELF were higher than those previously reported [92, 94]. In comparison, omadacycline concentrations were higher in serum and ELF than tigecycline. The total drug ELF to total drug serum penetration ratios based on AUC values were similar for both agents [94]. Once protein binding estimates were accounted for (approximately 21% and approximately 80% for omadacycline and tigecycline, respectively), the total drug ELF to unbound serum penetration ratios were 1.84 for omadacycline and 6.59 for tigecycline [94]. Lakota and colleagues conducted a population PK analysis for omadacycline using the same omadacycline ELF data and plasma concentration-time data from phase I and III clinical research studies [95]. The total drug ELF to unbound plasma penetration ratio based on AUC_{24} values at day 4 of therapy was calculated to be 2.06. The ratio of ELF to total or unbound plasma AUC values

reported in human subjects has tended to be higher than in a murine lung infection model (range 0.72–1.02) since omadacycline concentrations in plasma and ELF are nearly identical and protein binding is slightly lower (approximately 15%) in mice [96].

Tigecycline and omadacycline have indications for community-acquired bacterial pneumonia, necessitating utility of these agents against intracellular and atypical pathogens such as *Chlamydophila pneumoniae, Legionella pneumophila,* and *Mycoplasma pneumoniae*. For this reason, AM concentrations were evaluated. AM concentrations for both tigecycline and omadacycline were greater than plasma or ELF concentrations at any given time evaluated in this study [94]. The ratio of AM to total plasma concentration based on the mean AUC was 20.8 and 302.46 for tigecycline over 12 h and omadacycline over 24 h, respectively. These findings provide support for the use of omadacycline in the treatment of community-acquired bacterial pneumonia caused by susceptible organisms. No intrapulmonary studies have been conducted for omadacycline following oral administration.

Plasma and ELF concentrations of tigecycline were evaluated in 32 non-obese critically ill patients receiving a high-dose regimen of a 200 mg intravenous loading dose followed by 100 mg every 12 h infused intravenously over 30 min [97]. Nineteen patients had a single mini-BAL (i.e., 40 mL of 0.9% saline solution) collection on day 4 of therapy and the mean ($\pm$ standard error [SE]) concentration in ELF at 1 h and 12 h was 0.78 ± 0.2 μg/mL ($n = 12$) and 0.36 ± 0.1 μg/mL ($n = 7$), respectively. The mean ($\pm$ SE) ratio of ELF to total plasma concentrations at these respective sampling times were 2.81 ± 1.08 and 2.98 ± 0.61. The higher dosage regimen of tigecycline in critically ill patients was associated with similar ELF to total plasma penetration ratios at both the peak and trough sampling times and were higher than observed in healthy adult subjects.

6.2 Eravacycline

Eravacycline is a fluorocycline antibiotic that was developed by a synthetic methodology to permit chemical modifications of the tetracycline core D-ring. Eravacycline is currently available only as an intravenous formulation and is indicated for the treatment of adult patients with complicated intra-abdominal infections [98, 99]. A study has assessed plasma and intrapulmonary concentrations in 20 healthy adults after receiving eravacycline 1 mg/kg intravenously every 12 h for a total of seven doses [100]. Samples were collected at 2, 4, 6, or 12 h (Table 7). Protein binding (mean $\pm$ SD: $82.5\% \pm 1.7\%$) was accounted for and unbound drug plasma concentrations were calculated. The AUC_{12} of eravacycline in the ELF was more than sixfold greater than the AUC_{12} of unbound drug concentrations in plasma. This is similar to the protein-adjusted ELF penetration ratio

previously estimated for tigecycline [94]. These findings lend support to the further exploration of eravacycline for the treatment of lower respiratory tract infections.

6.3 Doxycycline and Minocycline

No human studies currently exist for doxycycline or minocycline, however findings from limited animal studies are worth noting. The minocycline intrapulmonary penetration ratio, based on the ratio of the AUC of ELF to serum, was estimated in mice and ranged from 2.5 to 2.8 [101]. Doxycycline intrapulmonary concentrations have also been evaluated in foals and horses [102, 103]. The ratio of the AUC of ELF to plasma in horses was 0.87 [102]. These findings have not yet been validated in human studies.

7 Miscellaneous Antibacterial Agents

7.1 Hydroxychloroquine

Hydroxychloroquine has recently been repurposed for the management of patients with coronavirus disease 2019 (COVID-19) for its proposed antiviral activity. A retrospective, observational study of 22 critically ill patients with COVID-19 measured 28 plasma and ELF concentrations of hydroxychloroquine [104]. All patients were intubated and received oral hydroxychloroquine as crushed tablets administered by nasogastric tube at a dose of 400 mg once daily or 200 mg three times daily. Plasma and ELF concentrations were measured 7–12 days after the start of hydroxychloroquine therapy (Table 8). The respective median ratios of ELF to total plasma concentrations of hydroxychloroquine were 39.96 (range 2.1–290.4) and 21.22 (range 13.4–168) for dosage regimens of 400 mg once daily and 200 mg three times daily. Concentrations of hydroxychloroquine in ELF were considerably greater than those in plasma and exhibited wide interpatient variability. Plasma concentrations of hydroxychloroquine were not reflective of ELF concentrations and may not be useful in determining the amount of drug in the ELF of COVID-19 patients.

7.2 Ivermectin

Similar to hydroxychloroquine, ivermectin's antiviral properties were being explored for use in the management of COVID-19. Jermain and colleagues developed a minimal physiologically based PK model simulating oral administration of ivermectin and resulting lung penetration following 12, 30, and 120 mg oral doses [105]. Even at a dose of 120 mg, the simulated peak lung concentration of 772 ng/mL is much lower than the previously reported in vitro IC_{50} (or half the maximal inhibitory concentration) against severe

Table 7 Plasma and epithelial lining fluid concentrations of tetracyclines

Antibacterial agent	Dosage regimen	Subjects [n]	Sampling time [h][a]	ELF to plasma ratio based on AUC	Plasma concentration [µg/mL][b]	ELF concentration [µg/mL][b]	References
Tigecycline	100 mg IV 0.5 h infusion × 1 dose, then 50 mg IV 0.5 h infusion q12h × 6 doses	4	2	1.71[c]	0.217 ± 0.051	0.553 ± 0.497	[94]
		5	4		0.159 ± 0.026	0.233 ± 0.070	
		4	6		0.157 ± 0.036	0.268 ± 0.097	
		4	12		0.121 ± 0.036[d]	0.149 ± 0.028[e]	
Omadacycline	100 mg IV 0.5 h infusion q12h × 2 doses, then 100 mg IV 0.5 h infusion q24h × 3 doses	6	0.5	1.47[f]	1.80 ± 0.13	1.73 ± 1.01	[94]
		6	1		0.89 ± 0.19	2.25 ± 0.72	
		5	2		0.93 ± 0.33	1.51 ± 0.94	
		6	4		0.54 ± 0.12	0.95 ± 0.33	
		6	8		0.56 ± 0.12	0.58 ± 0.19	
		6	12		0.42 ± 0.07	0.61 ± 0.29	
		6	24		0.27 ± 0.05	0.41 ± 0.13	
Eravacycline	1 mg/kg (maximum 100 mg) IV 1 h infusion q12h × 7 doses	5	2	6.44[g]	0.083 ± 0.012[h]	0.70 ± 0.30	[100]
		5	4		0.065 ± 0.011[h]	0.57 ± 0.20	
		5	6		0.054 ± 0.009[h]	0.34 ± 0.16[i]	
		5	12		0.037 ± 0.009[h]	0.25 ± 0.13[j]	

ELF epithelial lining fluid, *AUC* area under the concentration-time curve, *IV* intravenously, *BLQ* below the lower limit of quantification, *qxh* every *x* hours, *SD* standard deviation

[a]Sampling time after the last dose

[b]Total plasma and ELF concentrations expressed as mean ± SD

[c]Based on the ratio of AUC_{12} in ELF to AUC_{12} in total plasma

[d]Three concentrations were available at this sampling time

[e]Two of the four subjects had ELF concentrations BLQ (< 1 ng/mL)

[f]Based on the ratio of AUC_{24} in ELF to AUC_{24} in total plasma

[g]Based on the ratio of AUC_{12} in ELF to AUC_{12} in unbound plasma, assuming protein binding between 79.3 and 87.1% in plasma

[h]Twenty concentrations were available at each sampling time

[i]Two of the five subjects had ELF concentrations BLQ (< 0.5 µg/mL)

[j]Three of the five subjects had ELF concentrations BLQ (< 0.5 µg/mL)

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of 1750 ng/mL [106].

7.3 Colistin

Colistin methanesulfonate (CMS) is a prodrug of colistin and is approved for the treatment of multidrug-resistant Gram-negative infections, including those caused by *P. aeruginosa*. Twelve critically ill adults with ventilator-associated pneumonia received CMS 2 million international units (MIU) by nebulization followed by CMS 2 MIU every 8 h by intravenous infusion over 1 h [107]. Plasma and BAL samples were collected at steady-state (i.e., after 7–12 doses). Plasma concentrations of the active compound, colistin, ranged from 0.15 µg/mL to 4.7 µg/mL, and ELF concentrations ranged from 1.48 µg/mL to 28.9 µg/mL. It is possible that ELF concentrations were overestimated due to remaining intrapulmonary colistin following the initial aerosolized loading dose where the observed ELF concentrations (range

9.53–1137 µg/mL) were significantly higher than in plasma (range 0.15–0.73 µg/mL). Population PK/PD modeling and simulations supported the initial addition of aerosol CMS because of the higher antimicrobial activity, lower systemic exposure to CMS (9% of the dose), and because a lower proportion (1.4%) of CMS was presystemically converted to colistin.

7.4 Amikacin

Amikacin is an aminoglycoside often used in combination therapy in the setting of resistant Gram-negative nosocomial infections [108]. Intrapulmonary penetration of amikacin in healthy adults has not been evaluated, however ELF concentrations of amikacin have been studied in eight critically ill patients with ventilator-associated pneumonia [109]. Each patient was administered a single dose of amikacin 20 mg/kg as an intravenous 30-min infusion. Plasma and ELF concentrations are reported in Table 8. The mean and median

Table 8 Plasma and epithelial lining fluid concentrations of antibacterial agents

Antibacterial agent	Dosage regimen	Subjects (n)	Sampling time (h)[a]	ELF to plasma based on AUC	Plasma concentration (μg/mL)[b]	ELF concentration (μg/mL)[b]	References
Hydroxychloroquine	400 mg PO once daily	22	7–12 days	ND	0.09 (0.03, 0.19)[c,d]	3.74 (0.13, 36.75)[c,d]	[104]
	200 mg PO three time daily	22	7–12 days	ND	0.07 (0.03, 0.09)[c,d]	1.81 (0.34, 10.08)[c,d]	
Amikacin	20 mg/kg IV × 1 dose	8	1	NR	59.6 ± 23	ND	[109]
		8	2		34.3 ± 18	7 ± 6.3	
		8	4		27.4 ± 21.2	ND	
		8	6		19.4 ± 10	ND	
Plazomicin	15 mg/kg IV × 1 dose	4	2	0.13	NR	NR	[112]
		4	4				
		4	6				
		4	8				
		4	10				
GSK2251052	1500 mg IV × 1 dose	5	2	0.54[f]	NR	3.30 (31.5)[e]	[120]
		5	6			1.05 (40.2)[e]	
		5	12			0.635 (12.9)[e]	
	1500 mg IV q12h × 5 doses	5	2	0.53[f]	NR	5.01 (25.1)[e]	
		5	6			2.17 (55.8)[e]	
		5	12			1.16 (16.5)[e]	
GSK1322322	1500 mg IV q12h × 7 doses	6	2	1.2[f]	13.2 ± 3.80[g]	18.2 ± 7.55	[123]
		5	6		3.19 ± 1.40[g]	6.26 ± 6.12	
		6	12		0.406 ± 0.178[g]	0.703 ± 0.301	

ELF epithelial lining fluid; *AUC* area under the concentration-time curve; *IV* intravenously; *ND* not determined; *NR* not reported, *PO* by mouth, *qxh* every x hours, *SD* standard deviation

[a]Sampling time after the last dose

[b]Values expressed as mean ± SD

[c]Values expressed as median (range)

[d]A total of 28 plasma and ELF concentrations from 22 patients

[e]Values expressed as mean (percent coefficient of variation)

[f]Based on the ratio of AUC_{12} in ELF to AUC_{12} in total plasma

[g]There were 17 concentrations in plasma at each sampling time

concentrations of amikacin in ELF at 2 h after the start of infusion were 7 μg/mL and 3.6 μg/mL, respectively. The mean (± SD) penetration ratio of ELF to plasma concentrations of amikacin was 0.18 ± 0.17. These results are comparable with the mean ELF to plasma ratio of tobramycin in critically ill patients previously reported [1, 110].

Concentrations of amikacin in ELF have also been evaluated in 17 mechanically ventilated neonates [111]. Dosage regimens for amikacin were administered as 20-min intravenous infusions and were based on guidelines according to postmenstrual age (range 25.1–41 weeks). The median peak (i.e., 1-h after the start of the infusion) and trough plasma concentrations of amikacin were 39.1 μg/mL (range 24.1–73.2 μg/mL) and 2.1 μg/mL (range 1–7.1 μg/mL). The median concentration of amikacin in ELF was 6.5 μg/mL (range 1.5–23 μg/mL), however these observations were

obtained over a 24-h time period. The highest concentrations of amikacin in ELF were reported between 6 and 14.5 h after amikacin administration.

7.5 Plazomicin

Plazomicin is a newly FDA-approved aminoglycoside with an indication for complicated urinary tract infection. Plasma and intrapulmonary concentrations were compared in 20 healthy adult subjects after a single dose of plazomicin 15 mg/kg as a single dose infused over 10 min [112]. These investigators used a bronchoscopic microsampling technique, which involves a polyester fiber rod probe to obtain serial ELF concentrations from each subject at the surface of a bronchus (termed 'bronchial ELF'), compared with a single BAL sample obtained from the alveolar space of each

subject. The respective mean AUC_{10} values in plasma and ELF were 286 µg·h/mL and 28.8 µg·h/mL. The ratio of ELF to plasma based on mean AUC_{10} was 0.13. Although this study was performed in healthy adult subjects, the intrapulmonary penetration ratio is similar to what has been previously described for tobramycin and amikacin in critically ill patients [1, 109, 110].

7.6 Arbekacin

Arbekacin is an investigational aminoglycoside being evaluated as a potential treatment for pneumonia given its activity against Gram-negative pathogens and MRSA. The PK of arbekacin in serum and ELF were evaluated in six healthy adults using the bronchial microsampling technique [113]. Each subject received a single dose of arbekacin 200 mg administered as an intravenous infusion over 1 h. Serial serum and BAL samples were collected over 6 h after the start of arbekacin infusion. Mean ($\pm$ SD) AUC_{∞} values for plasma and ELF were 51.2 $\pm$ 6.9 µg·h/mL and 34.6 $\pm$ 15.2 µg·h/mL, respectively. The penetration ratio of ELF to serum was 0.67. In addition, the mean ($\pm$ SD) maximum concentration (C_{max}) in ELF was 10.4 $\pm$ 1.9 µg/mL, and occurred at 1.7 $\pm$ 0.3 h. While MIC breakpoints for arbekacin have not yet been described, the mean C_{max} and AUC_{∞} values identified in this study suggest that PD targets (e.g., C_{max}/MIC and/or AUC/MIC) could be attained for organisms with an MIC of 1 µg/mL. Further studies are needed to determine the safety and efficacy of arbekacin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia.

7.7 Lefamulin

Lefamulin (formerly known as BC 3781) is a novel semi-synthetic pleuomutilin antibiotic and the first drug of its class available for systemic use in humans. Lefamulin has both an intravenous and oral formulation and is FDA-approved for the treatment of community-acquired bacterial pneumonia [114, 115]. Pulmonary surfactant has been shown not to inhibit the *in vitro* activity of lefamulin [116]. Plasma and ELF concentrations have been assessed in 12 healthy adults after receiving a single dose of lefamulin 150 mg intravenously infused over 1 h [117]. The median AUC_{8} of lefamulin in total plasma and ELF was 4.99 µg·h/mL and 3.87 µg·h/mL, with a calculated intrapulmonary penetration ratio of 0.75. Assuming a plasma protein binding of 87%, ELF concentrations were approximately 5.7-fold greater than unbound plasma concentrations of lefamulin. In comparison, mice treated with subcutaneous lefamulin doses of 35 mg/kg or 70 mg/kg were observed to have higher pulmonary penetration ratios based on AUC (i.e., ELF to total plasma approximately twofold, and ELF to unbound plasma approximately tenfold) [116].

Population PK modeling and Monte Carlo simulations were performed using the data from the previously described 12 subjects, as well as plasma concentrations from 20 subjects receiving either lefamulin 150 mg intravenously or 600 mg orally under both fed and fasted conditions [118]. The median ELF to unbound plasma ratio based on AUC_{24} was approximately 5, regardless of intravenous or oral administration of lefamulin. PK/PD targets for AUC/MIC ratios were established for ELF and unbound plasma concentration in a neutropenic murine pneumonia model [117]. Both formulations of lefamulin were shown to have >92% probability of achieving target attainment associated with a 1-$\log_{10}$ reduction in colony-forming units from baseline for *S. pneumoniae* and *S. aureus* for MIC_{90} values of 0.12 µg/mL [119]. These PK/PD target attainment analyses of ELF and unbound plasma concentrations provided support for the dose selection decisions of lefamulin during the clinical drug development program.

7.8 GSK2251052

GSK2251052 is a boron-containing leucyl-tRNA synthetase inhibitor that prevents protein synthesis of Gram-negative bacteria. Plasma and intrapulmonary concentrations were compared in 30 healthy adults [120]. Fifteen subjects were evaluated following a single intravenous dose of GSK2251052 1500 mg and another 15 subjects were assessed after five doses of GSK2251052 1500 mg every 12 h intravenously infused over 1 h. Sampling times and mean concentrations of GSK2251052 in plasma and ELF are listed in Table 8. The respective AUC_{12} values in plasma and ELF after a single dose were 30.0 µg·h/mL and 16.1 µg·h/mL, whereas AUC_{12} values after multiple doses were 55.1 µg·h/mL and 29.4 µg·h/mL. The AUC_{12} ratios of ELF to total plasma were similar after single and multiple doses (0.54 and 0.53, respectively). Exposure of GSK2251052 in ELF was slightly higher in healthy humans than in a murine infection model (0.54 vs. 0.34) [121].

AM concentrations were also evaluated and AUC_{12} ratios of AM to total plasma were 6.21 and 4.98 after single and multiple doses, respectively. Therefore, respective concentrations in ELF and AM were approximately 50% and 500% of those in plasma. Unfortunately, further investigations of GSK2251052 were discontinued after bacterial resistance rapidly developed in patients being treated for complicated urinary tract infection during a phase II clinical trial [122].

7.9 GSK1322322

GSK1322322 is a potent inhibitor of peptide deformylase and novel hydrazinopyrimidine with in vitro antibacterial activity against common skin and respiratory tract pathogens. An evaluation of the intrapulmonary penetration

of GSK1322322 into ELF and AM was performed in 17 healthy adults [123]. Subjects received GSK1322322 1500 mg every 12 h intravenously infused over 1 h for seven doses. Plasma and ELF concentrations at the three sampling times are listed in Table 8. The mean AUC_{12} values in total plasma, unbound plasma (assuming protein binding of 66%), and ELF were 66.7 µg·h/mL, 22.7 µg·h/mL, and 78.9 µg·h/mL, respectively. The calculated AUC_{12} ratios of ELF to total plasma and ELF to unbound plasma were 1.2 and 3.5, respectively. In comparison, the AUC_{12} ratios of AM to total plasma and AM to unbound plasma were 2.5 and 7.4, respectively. Further investigations for the clinical development of GSK1322322 have been discontinued.

7.10 Fosfomycin

Fosfomycin is currently FDA-approved as a single-dose oral antibiotic for the treatment of uncomplicated acute cystitis in women. Outside of the US, intravenous fosfomycin is commercially available and is used for a wide variety of infectious syndromes, including systemic multidrug-resistant infections. Although no studies evaluating ELF concentrations of fosfomycin in humans have been published, measurement of interstitial concentrations of fosfomycin from healthy and infected lung tissue of seven patients with sepsis has been described [124]. The mean ($\pm$ SD) lung to plasma penetration ratio using AUC_{∞} values was 0.63 $\pm$ 0.31 and 0.53 $\pm$ 0.31 for healthy and infected lung tissues, respectively. A study evaluating ELF concentrations of fosfomycin was performed in six piglets receiving a single intramuscular dose of fosfomycin 15 mg/kg [125]. The mean fosfomycin AUC_8 for plasma and ELF was 98.70 µg·h/mL and 12.37 µg·h/mL, respectively. The mean ratio of ELF to plasma concentrations was 0.12. Additional studies are needed to evaluate ELF concentrations of fosfomycin in humans and to hopefully resolve the observed differences in penetration ratios of various lung matrices.

8 Conclusions

The penetration of antibacterial agents into the ELF has continued to be extensively evaluated during the past 10 years. This review provides information since our previous review in 2011 and includes the ELF concentrations and intrapulmonary penetration ratios from more than 40 studies [1]. The antibiotic class with the largest contribution to this review are β-lactam agents, with or without β-lactamase inhibitors. This matches the current focus of antibacterial drug development programs seeking regulatory approval of new agents for the treatment of serious infections caused by multidrug-resistant Gram-negative bacteria.

The majority of intrapulmonary penetration studies have been conducted in healthy adult subjects using BAL as a reliable method for measuring antibiotic concentrations in the lungs. Penetration ratios have mainly been determined from AUC values during a single dosing interval following the administration of multiple doses (e.g., steady-state). Protein binding of plasma concentrations has been commonly accounted for so that ratios can represent unbound drugs in the ELF and plasma. These studies in healthy subjects answer the initial question on whether the antibacterial agent can penetrate into the ELF. If penetration does occur, the next questions center on achieving sufficient ELF concentrations with a dosage regimen that is considered to be well-tolerated and effective against extracellular bacteria associated with pneumonia.

The past decade has also witnessed an increased number of preclinical studies in the neutropenic murine lung infection model where both plasma and ELF concentrations of antibacterial agents were measured. This model, as well as murine thigh and hollow fiber models, have been useful in identifying which PK/PD parameter(s) best correlates with antibacterial activity and defining drug exposure targets associated with various bacterial reduction endpoints in plasma and ELF [126]. Combining the animal PD target values with human plasma and ELF data from healthy subjects has proven useful as a pharmacological rationale in the dosage selection to treat bacterial pneumonia (Fig. 1) [4].

The number of intrapulmonary penetration studies in critically ill patients remain limited. The observations thus far have suggested noteworthy differences in the time course, magnitude, and variability of ELF concentrations compared with healthy adult subjects [3, 5]. These alterations can be important considerations for optimizing dosage regimens of antibacterial agents in clinical situations, such as ventilator-associated bacterial pneumonia, where pathogens may have elevated MIC values. Additional studies are merited in this patient population to further understand the potential impact on concentrations at the sites of pulmonary infection.

This review of the literature and our clinical research experience with these studies has allowed us to further consider the role of intrapulmonary studies during the antibacterial drug development process. We believe the following issues are key steps in developing and evaluating dosage regimens to treat extracellular bacteria in lower respiratory tract infections: (1) assess ELF concentrations in murine infection models to assess both drug penetration and PK/PD target exposures associated with each organism likely to be treated with the agent; (2) conduct an intrapulmonary penetration study in healthy adult subjects to determine that the agent penetrates into the lung, and document the concentration-time profile in ELF and unbound plasma; (3) consider and incorporate the wide variability and differences in ELF concentrations that may occur in critically ill patients

as part of the dosage regimen design; (4) use all available PK studies in humans and PD targets from animal and/or *in vitro* models to conduct population PK modeling, simulations, and probability of target attainment assessment to select an optimal dosage regimen for clinical trials [4, 127, 128]; (5) collect plasma and ELF concentrations in patients being treated for hospital-acquired and/or ventilator-associated bacterial pneumonia, including adequate number of samples and sampling times to understand the concentration-time profiles in critically ill patients; and (6) use plasma and ELF data from clinical studies of both healthy subjects and infected patients to develop validated population PK models with covariate effects, and conduct simulations to support target attainment of dosage recommendations in patients with normal and impaired excretion [42, 54, 129].

Penetration ratios determined from AUC values of each matrix remains the most accurate method to describe drug distribution between plasma and the potential site of infection (i.e., ELF). However, absolute drug concentrations in ELF and PK/PD target values are most useful to predict the potential efficacy of antibacterial agents against extracellular pathogens in the lung. A more robust procedure in understanding the therapeutic importance of these concentrations has occurred by linking preclinical PD exposure targets with human population PK analysis and Monte Carlo simulation. These techniques permit co-modeling of both plasma and ELF concentrations from healthy subjects and critically ill patients, and prediction of dose selection of antibacterial agents to treat pneumonia. While these methodologies are currently available, further studies are desperately needed to assess the significance of ELF concentrations in critically ill patients with pulmonary infections and to document what relationships exist between PK/PD parameters and clinical outcomes.

Declarations

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