

# Considerations for Effect Site Pharmacokinetics to Estimate Drug Exposure: Concentrations of Antibiotics in the Lung

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**ABSTRACT**

Bronchoalveolar lavage (BAL) and microdialysis have become the most reliable and relevant methods for measuring lung concentrations of antibiotics, with the majority of BAL studies involving either healthy adult subjects or patients undergoing diagnostic bronchoscopy. Emphasis on the amount of drug that reaches the site of infection is increasingly recognized as necessary to determine whether a dose selection will translate to good clinical outcomes in the treatment of patients with pneumonia. Observed concentrations and/or parameters of exposure (e.g., area-under-the-curve) need to be incorporated with pharmacokinetic-pharmacodynamic indices so that rational dose selection can be identified for specific pathogens and types of pneumonic infection (community-acquired versus hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia). While having measured plasma or lung concentration-time data from critically ill patients to incorporate into pharmacokinetic-pharmacodynamic models is very unlikely during drug development, it is essential that altered distribution, augmented renal clearance, and renal or hepatic dysfunction should be considered. Notably, the number of published studies involving microdialysis and intrapulmonary penetration of antibiotics has been limited and mainly involve beta-lactam agents, levofloxacin, and fosfomycin. Opportunities to measure in high-resolution effect site spatial pharmacokinetics (e.g. with MALDI-MSI or PET imaging) and in vivo continuous drug concentrations (e.g. with aptamer-based probes) now exist. Going forward these studies could be incorporated into antibiotic development programs for pneumonia in order to further increase the probability of candidate success.

## INTRODUCTION

An adequate drug concentration at the site of an infection continues to have an important role in our ability to understand the pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics [1]. During the past 50 years, numerous studies have been conducted to measure tissue, cell or fluid concentrations of antibiotics in the lung [2,3,4••,5,6••,7•, 8••]. Various methods and sampling sites have been used. Nevertheless, no clear consensus exists on the optimal approach for measuring the concentrations of antibiotics in the lung [3, 4••,5,6••,7•,9]. Methods that involve measuring the concentrations of antibiotics within specific subcompartments of the lung provide important insights into antimicrobial efficacy. Bronchoalveolar lavage (BAL) and microdialysis are currently the most reliable and relevant methods for measuring lung concentrations of antibiotics [4••,5,7•,8••]. This review will focus on human studies that have used these two techniques to measure intrapulmonary concentrations of antibiotics.

## INTRAPULMONARY PENETRATION

A variety of methodologies have been used for measuring concentrations of antibiotics and determining their distribution patterns in the lungs [6••,8••]. Each has its advantages, potential limitations, and methodological issues. Historically, anti-infective drug concentrations were measured by obtaining lung tissue during a surgical procedure. Although this is one of the oldest methods for measuring drug concentrations in the lung, whole-tissue concentrations may be difficult to interpret [9]. The major drawback of drug concentrations reported from whole lung tissue, bronchial tissues and/or secretions is the assumption that antibiotics are uniformly distributed within all lung compartments (e.g. extracellular, intracellular, interstitium). The measured drug concentration will therefore represent a mixture from all compartments instead of the drug concentration at the clinically relevant site of infection. Currently, the two preferred methods for measuring antibiotic concentrations in the lung are

BAL and microdialysis. Bronchoscopy with BAL can determine concentrations in both the epithelial lining fluid (ELF) and alveolar macrophages (AM), whereas microdialysis measures concentrations in the interstitial fluid of the lung [4••,8••]. The ELF is the relevant site for the extracellular respiratory pathogens that are causative in acute bacterial pneumonia and infective exacerbation of chronic bronchitis. These lower respiratory tract infections may progress to involve the interstitial fluid of the lung. In contrast, infections caused by intracellular pathogens such *Legionella pneumophila* and *Chlamydomphila pneumoniae* exist within AM.

### **Assessment of Antimicrobial Drug Concentrations in Lungs**

Most studies that measure drug concentrations at an infection site often place too much emphasis on the value of the penetration ratio. Unfortunately, ratios are used to claim that specific antibiotics may be better for treating pneumonia. The ratio of site-to-plasma concentrations provides an important pharmacological characteristic. However, in isolation it is not adequate to determine whether an agent will be effective at treating pulmonary infection and also does not identify how much drug needs to be administered.

Penetration ratios change as a function of time because concentrations in plasma and at the site of infection demonstrate system hysteresis (e.g., increases and decreases at different rates from each other). Such time-dependency limits the interpretability of measures from a single sampling time and the true penetration of a drug into the lung. To overcome this limitation, samples should be collected from a population of patients throughout the dosing interval (even though an individual patient only contributes a single lung concentration). In addition, an overall measure of drug exposure (i.e. the area-under-the-curve [AUC]) in each compartment should be calculated and used to determine the penetration ratio.

The amount of drug that reaches the site of infection is an important determinant of dose selection. Observed concentrations and/or measures of drug exposure (e.g., area-under-the-curve, AUC) are fundamental to rational dose selection for specific pathogens and pneumonic diseases (e.g. community-acquired [CABP] versus hospital-acquired [HABP] bacterial pneumonia, including ventilator-associated bacterial pneumonia [VABP]).

The following aspects in study design are critical for a precise estimate of drug exposure and to support clinical dose and candidate regimen selection for new agents: (i) investigating regimens that are most likely to be progressed to subsequent clinical trials; (ii) ensuring serial sampling from plasma throughout the dosing interval in individual patients; (iii) sampling from the lung that covers the dosing interval at a population level (because each patient can only contribute a single lung concentration); (iv) determining concentration ratios from robust estimates of AUC in plasma and the relevant pulmonary subcompartment; (v) considering plasma protein binding with both unbound and total drug concentrations in plasma and using these data to better understand penetration characteristics; (vi) using analytical procedures that are both sensitive and specific for plasma and effect site concentrations; (vii) correcting for dilution from sampling (i.e. BAL) with urea estimation being the most commonly used procedure; (viii) translating effect site exposures using non-clinical PK-PD targets, for example relating human ELF exposure to ELF PK-PD targets from highly predictive murine models of pneumonia; and (ix) performing PK-PD modelling and simulation to assess and predict the performance of various candidate regimens.

### **Bronchoalveolar Lavage (BAL) Studies**

Bronchoscopy with BAL has become a reliable technique for measuring concentrations of antibiotics in ELF. During the past two decades, several groups of investigators have used this method to determine drug penetration into ELF and to compare plasma and ELF concentrations of antibiotics [4••, 10]. Using

BAL studies to assess ELF concentrations has become an important component of antibacterial drug development programs since the majority of pneumonic infections are caused by extracellular pathogens [11••,12]. Table 1 provides an update on published studies evaluating plasma and ELF exposures of antibiotics that have recently been approved or are currently in development [13-25]. We direct the reader to our previous review publications regarding data for other anti-infective agents as well as a detailed description of using bronchoscopy and BAL for measuring ELF drug concentrations and determining intrapulmonary penetration [4••,5].

**Healthy Subjects.** The majority of BAL studies have involved either healthy adult subjects or patients undergoing diagnostic bronchoscopy (Table 1) [4••, 13-25]. A few studies have targeted older outpatients or patients with a clinical diagnosis of mild to moderate chronic bronchitis, chronic obstructive pulmonary disease, or community-acquired bacterial pneumonia [4••]. A comparison of these patients with mild to moderate respiratory tract infections and/or inflammatory processes has suggested that ELF concentrations were similar in magnitude and time course to those observed in healthy subjects. Thus, antibacterial concentrations in ELF from healthy subjects tend to serve as an estimate of the average drug exposure at extracellular sites of lung infection.

Pharmacokinetics and pharmacodynamics are increasingly recognized to be essential tools in the development of new antibiotics in order to maximize the probability that the right dose for infected patients will be studied first time [1,11••]. An intrapulmonary penetration study in healthy subjects can assist a drug development program by determining whether or not an antibiotic penetrates into lung, and if it does, whether concentrations of the antibiotic can be adequately achieved to treat the target pathogens. These two assessments are extremely valuable for making earlier and better “go/no go” decisions, and to establish whether a candidate regimen is suitable for further clinical study or requires adaptation prior to progression.

Designing an appropriate dosage regimen to treat patients with CABP or HABP has increasingly involved the incorporation of preclinical exposure-response relationships, phase 1 clinical pharmacology dose ranging studies, and ELF concentration-time data from healthy subjects [12]. Computer simulations using population PK modeling can be performed to estimate the proportion of patients likely to reach the probability of target attainment for the PK-PD indices established from dynamic *in vitro* (e.g., hollow fiber model) and/or *in vivo* animal model(s). This supports optimal dose selection by translating relevant non-clinical effect site exposures that are associated with efficacy to clinical data. For example, ELF PK-PD targets from murine lung infection models can be assessed to determine if these targets can consistently be achieved given human ELF exposures for a particular agent. Various different dosing regimens for that agent can be generated and compared in order to make a final dose selection based on the probability that the majority of patients (e.g.,  $\geq 90\%$ ) achieve the desired PK-PD target attainment. Conducting an intrapulmonary penetration study in healthy subjects during a phase 1 program can accelerate drug development and minimize the risk associated with dose selection for clinical trials of antibiotics for pneumonia. Delaying an intrapulmonary pharmacology study until late phase 2 or during phase 3 pivotal pneumonia studies is now strongly discouraged to prevent inadequate dose selection for respiratory tract infections [12].

Ambrose and colleagues have elegantly reviewed the pharmacokinetic-pharmacodynamic considerations for HABP and VABP studies [11••]. At least two published studies have illustrated the difficulties in achieving drug exposures and target attainment in VABP patients relative to HABP patients during drug development programs [11••,12,26,27]. To overcome these issues during drug development, dose and dosing regimens should be established with Monte Carlo simulations and target attainment studies that incorporate as much specific information as possible for critically ill patients with HABP and VABP. Ideally, this information would include a wide range of demographic characteristics and laboratory data that reflects the target population of patients with pneumonia, lung

penetration and pharmacodynamics at the infected site, and MIC distribution data of recent bacterial isolates obtained from hospitalized patients with pneumonia. MIC distributions for Enterobacteriaceae commonly implicated in HABP and VABP can differ significantly [11••]. Therefore, a broad range of microbiological data encompassing both clinical entities should be considered when assessing effect site exposures that are important for nosocomial pneumonia. While having measured plasma or lung concentration-time data from critically ill patients to incorporate into pharmacokinetic-pharmacodynamic models is very unlikely, considerations of altered distribution, augmented renal clearance, and renal or hepatic dysfunction should be considered [28,29]. Differing values of mean or median population pharmacokinetic parameters as well as the high variability associated with each parameter should also be considered for subgroups of patients with HABP and VABP. This approach to dosage design should lower the risk of treatment failures during a clinical trial program of seriously ill patients treated for VABP and/or HABP. Prospectively collected pharmacokinetic-pharmacodynamic data during pivotal clinical trials can confirm and re-evaluate the adequacy of the selected dosing regimen to achieve desired efficacy and safety margins.

***Critically Ill Patients.*** There are only a limited number of BAL studies in patients who were in an intensive care unit, receiving mechanical ventilation, and/or being treated for severe pneumonia (Table 2) [30-48]. All of the studies published to date were conducted with antibiotics that had already received regulatory approval and had been used in clinical practice for several years. Jamal and colleagues have used these data to provide clinical dosing strategies for various antibiotic drug classes based on physiochemical characteristics, pharmacodynamics properties, and relative degree of ELF penetration (Figure 1) [10].

One of the most recent concerns in drug development programs has been whether healthy subjects adequately reflect the intrapulmonary concentrations observed in critically ill patients. It is well known



that a wide range of inter- and intra-patient variability is observed in plasma drug concentrations and pharmacokinetic parameters of critically ill patients [49,50,51]. Many of these patients have additional variables (e.g., augmented renal function, obesity, and hepatic or renal dysfunction) along with their potentially life-threatening pneumonic infection that may substantially affect the disposition of antibiotics. Furthermore, critically ill patients often receive various treatments (e.g., intravenous fluid resuscitation, drug therapy, and continuous renal replacement therapy) that can alter apparent volume of distribution and/or clearance of antibiotics. Alterations in pulmonary permeability, dilution of intrapulmonary concentrations due to an increased volume, and/or disruption in transport systems in the lungs because of injury or infection have been suggested as physiological explanations for lower intrapulmonary concentrations in the critically ill patient [37••]. Regimens based on studies from healthy subjects or non-critically ill patients may lead to suboptimal antibiotic exposure in plasma and/or lung.

Methodological issues differ between studies conducted in critically ill patients and healthy subjects. In critically ill patients, the BAL procedure often involves microlavage or minilavage (e.g. 20 mL of 0.9% normal saline solution instilled as one or two aliquots per sampling time) [52]. The number of patients studied (n = 8 to 12 patients) is about one-third of the typical number studied in healthy human subjects. Sampling schemes are usually limited to either a set of peak and trough concentrations during an intermittent dosing interval, or a single sampling time during intermittent or continuous infusion. Rarely are samples collected over an entire dosing interval because studies occur in an uncontrolled environment. Despite differences in study procedures for critically ill patients, the reported mean or median penetration ratios of ELF-to-plasma for most antibiotics tend to be similar (e.g., aminoglycosides, linezolid) or higher (e.g., beta-lactams) than those observed in healthy subjects and outpatients. However, antibiotic concentrations demonstrate a substantial amount of variability in critical illness, which can result in a lower drug exposure in plasma and subsequently at the site of

infection (e.g., lung). For example, the average ratio of ELF-to-unbound plasma concentrations for piperacillin and tazobactam in healthy subjects has been reported as 38% and 77%, respectively (Table 1) [17]. In seventeen critically ill patients, the respective median ratios for these two drugs were reported as 49% (range: 2% to 516%) and 121% (11% to 381%) during intermittent dosing and 63% (29% to 117%) and 138% (57% to 326%) for continuous infusion, respectively (Table 2) [36,37••]. The wide ranges around these median values illustrates marked pharmacokinetic variability, which is commonly observed in critically ill patients.

An intrapulmonary pharmacokinetic study conducted in critically ill patients during the development program for a new antibiotic is highly desirable. However, it is both practically and ethically challenging because of the need to obtain informed consent from individual patients. A pragmatic approach could include an optional BAL collection designed as part of the research protocol for patients enrolled into these safety and efficacy clinical trials. However, data from phase 1 ELF studies carried out in healthy volunteers will allow for dose and regimen selection to be completed as optimally as possible prior to these phase 3 studies. Appropriate timing of dose administration and sample collection (e.g., both plasma and BAL fluid) by experienced investigators is still required to provide robust and reliable pharmacokinetic data. Additional studies with consideration of these issues are desperately warranted to determine which underlying physiological and pathological processes in patients with HABP and VABP have the greatest impact on plasma and lung concentrations. In addition, defining relationships between pharmacokinetic-pharmacodynamic parameters, clinical or microbiological outcomes, and resistance suppression are likely to be associated with a higher probability of favorable therapeutic response in these seriously ill patients.

### **Microdialysis**

Microdialysis is an additional technique for estimating intrapulmonary drug concentrations [7•, 8••]. This technique allows direct measurement of unbound drug concentrations in the interstitial fluid compartment of the lung. In addition to measuring unbound, pharmacologically active drug concentrations in the interstitium, microdialysis allows for continuous sampling of drug concentrations in both the lung and plasma of the same patients. However, the placement of microdialysis catheters into the lung has practical difficulties and this has limited its use to patients undergoing elective thoracic surgery.

The number of published studies involving microdialysis and intrapulmonary penetration of antibiotics has been limited and includes beta-lactam agents, levofloxacin, and fosfomycin (Table 3) [53-60]. Antibiotic penetration into interstitial fluid tends to be lower in patients with infection as compared to healthy subjects. These differences may be related to the clinical condition and treatment of intensive care patients with septic shock. Similar to bronchoalveolar lavage studies in critically ill patients, microdialysis studies have been limited to antibiotics currently approved for clinical use and not as part of an antibacterial drug development program.

### **Future technologies for assessing lung penetration**

Opportunities to measure in high-resolution effect site spatial pharmacokinetics (e.g. with MALDI-MSI or PET imaging) now exist [61-63]. These tools may be explored to further understand antibiotic exposure-response relationships within the lungs of highly predictive animal models of pneumonia. Data generated may then be usefully applied to help predict candidate success and facilitate more-informed “go/no-go” decisions when deciding whether to progress a new drug from the preclinical to the clinical arena. Furthermore, tools have been developed to measure continuous *in vivo* drug concentrations with aptamer-based probes, allowing for real-time measurement of small molecules in animal and human studies [64-65]. These tools hold the potential to allow for better translation from animal to human

studies and to facilitate detailed analyses of patient specific pharmacokinetic variation in clinical settings. Going forward these new technologies could also be incorporated into antibiotic development programs for pneumonia to further increase the probability of candidate success.

## **SUMMARY**

Rational dose selection of antibiotics for the treatment of bacterial pneumonia continues to be a challenge. Measurement of antibiotic concentrations by techniques such as BAL and microdialysis have become reliable and consistent in describing the amount of drug exposure at sites of lung infection. Effect site exposure remains essential to incorporate into the evaluation of specific dosing regimens designed to be efficacious against potential bacterial pathogens in pneumonia. Further studies are warranted in critically ill patients with pulmonary infections to explore important differences in the pattern, time course and magnitude of intrapulmonary concentrations compared to healthy subjects. In addition, potential links between pharmacokinetic-pharmacodynamic indices based on plasma exposures and clinical or bacterial outcomes in pneumonia would be valuable. These data could be used to optimize regimens for new antibiotics in clinical trials for efficacy, or for the clinical care of seriously ill patients with drugs that are currently available.

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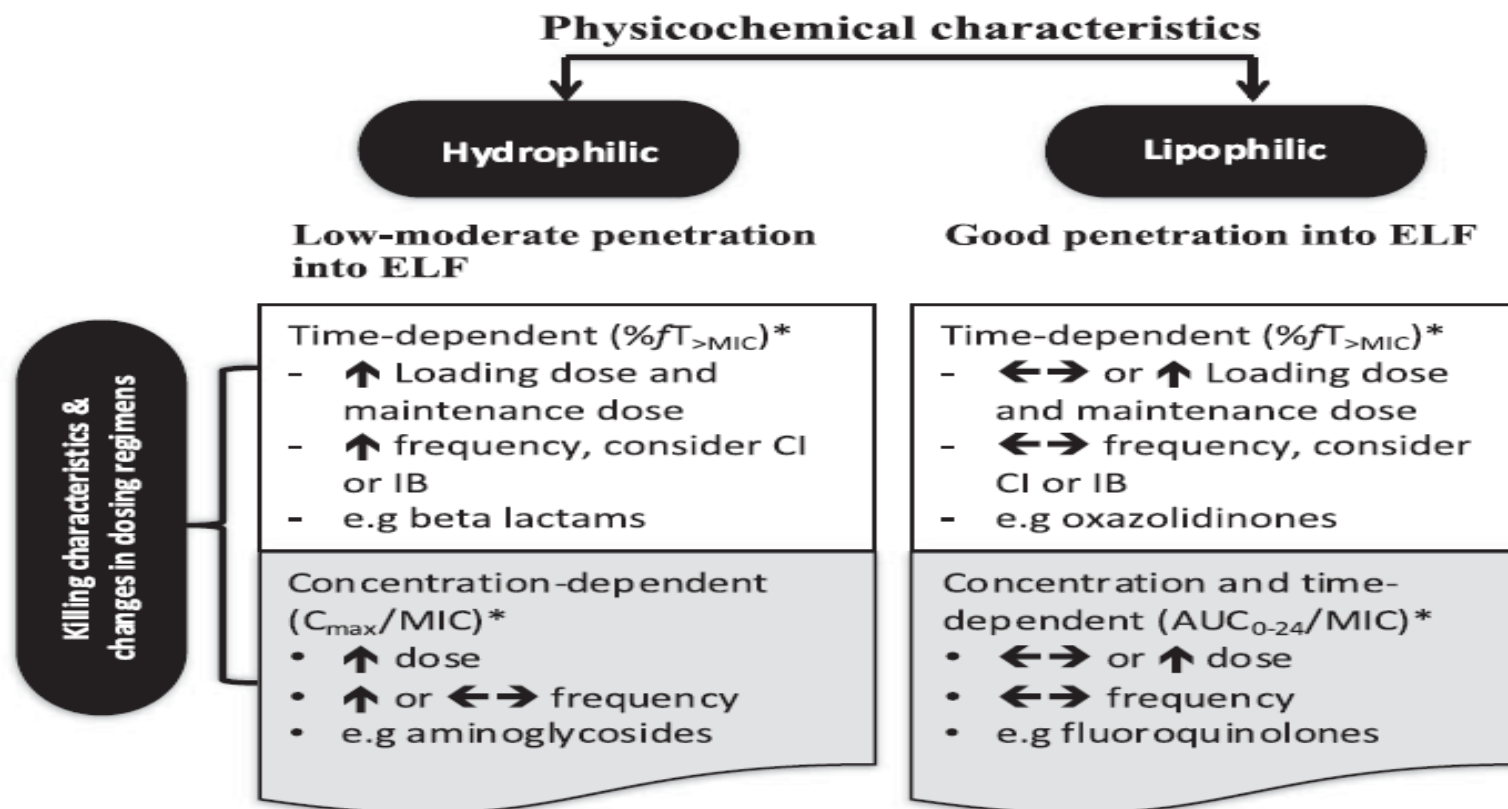
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**FIGURE 1** Strategies for defining dosing of antibiotics for infections in the lung [10]



**Table 1 Published studies on epithelial lining fluid concentrations of selected antibiotics in healthy adult subjects**

Antibiotic	Dose	Penetration Ratio (ELF-to-Total Plasma)	Penetration Ratio (ELF-to-Unbound Plasma)	AUC <sub>ELF</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	AUC <sub>total-plasma</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )
Ceftaroline [13]	600 mg q12h	18.0%	22.5%	8.09	45.0 $\pm$ 7.32
	600 mg q8h	17.7%	23.6%	9.36	53.0 $\pm$ 7.16
Imipenem [14]	250-500 mg q6h	44%	55%	N.R.	N.R.
Meropenem- Vaborbactam [15]	2.0 g q8h	63%	65%	111.7	186 $\pm$ 33.6
	2.0 g q8h	53%	79%	105.1	204 $\pm$ 34.6
Ceftazidime- Avibactam [16]	2.0 g q8h	31.3%	N.R.	92.3	295
	0.5 g q8h	34.9%	N.R.	13.7	39.2
	3.0 g q8h	32.4%	N.R.	147	454
	1.0 g q8h	32.0%	N.R.	24.8	77.6
Ceftolozane- Tazobactam [17]	1.0 g q8h	48%	59%	75.1	158.5 $\pm$ 24.1
	0.5 g q8h	44%	N.R.	8.5	19.3 $\pm$ 2.9
Piperacillin- Tazobactam [17]	4.0 g q6h	26%	38%	94.5	357.3 $\pm$ 65.9
	0.5 g q6h	54%	N.R.	24.7	46.1 $\pm$ 8.7
Eravacycline [18]	1 mg/kg q12h	132%	644%	4.93	4.56 $\pm$ 0.94
Omadacycline [19]	100 mg q12h x 3, then 100 mg q24h	147%	184%	17.23	12.14 $\pm$ 3.22
Tigecycline [19]	100 mg x 1, then 50 mg q12h	171%	659%	3.16	2.20 $\pm$ 0.42
Tedizolid [20]	200 mg Q24h	433%	4120%	109.3	25.13 $\pm$ 5.78
Nafithromycin [21]	800 mg q24h	1380%	N.R.	224.1	16.2
Solithromycin [22]	400 mg q24h	1030%	N.R.	80.3	7.92 $\pm$ 4.39
Lafamulin [23]	150 mg x 1	75%	570%	3871	4985
GSK1322322 [24]	1.5 g 12h	120%	350%	78.9	66.7
GSK2251052 [25]	1.5 g 12h	53.4%	59.3%	29.4	55.1

Data presented as mean or mean  $\pm$  SD; N.R., not reported  
Penetration ratio was determined in all studies by the ratio of AUC<sub>ELF</sub>/AUC<sub>plasma</sub>

**Table 2 Reported penetration of selected antibiotics into epithelial lining fluid of critically ill patients**

Antibiotic Class	Antibiotic	Dosing	Mean Penetration Ratio	Interpretation, Comments
Aminoglycoside	Tobramycin [30]	7-10 mg/kg IV once daily	~12% (range: 0.8%-12.8%)	Single sampling time at 30 minutes after end of 30-minute infusion
	Tobramycin [31]	Concentration-adjusted dosing	0.5-hour: 30 ± 3 % 2.0-hour: 42 ± 16 % 4.0-hour: 64 ± 37 % 8.0-hour: 153 ± 76 %	
	Tobramycin [32]	150 mg IM single dose 300 mg IM once daily x 4 days	140 ± 80 % 160 ± 60 %	Single sampling time at 6 hours after end of 30-minute infusion
	Gentamicin [33]	240 mg IV once daily	1.0-hour: 30 ± 5 % 2.0-hour: 85 ± 10 % 4.0-hour: 114 ± 26 % 6.0-hour: 74 ± 18 %	
	Netilmicin [34]	450 mg IV single dose	1.0-hour: 35% 2.0-hour: 78% 3.0-hour: 177% 4.0-hour: 145%	
Beta-lactam beta-lactamase inhibitor combination product	Piperacillin-tazobactam [35]	4.5 g IV q8h	P: 56.8 ± 33.6 % T: 91.3 ± 27.7 %	Penetration ratio (ELF/Plasma <sub>total</sub> ) determined at single sampling time
	Piperacillin-tazobactam [36]	<u>No/Mild Renal Failure:</u> 13.5 g/24 hours IV continuous infusion	Median P: 46% (IQR: 29%-62%) Median T: 85% (IQR: 68%-132%)	Penetration ratio (ELF/Plasma <sub>total</sub> ) determined at single sampling time
		18 g/24 hours IV continuous infusion	Median P: 43% (IQR: 30%-65%) Median T: 84% (IQR: 50%-105%)	
		<u>Moderate/Advanced Renal Failure:</u> 13.5 g/24 hours IV continuous infusion	Median P: 39% (IQR: 31%-48%) Median T: 49% (IQR: 39%-69%)	
	18 g/24 hours IV	Median P: 85% (IQR: 60%-96%)		

	Piperacillin-tazobactam [37••]	continuous infusion 4.5 g IV q8h or q12h	Median T: 65% (IQR: 63%-80%) Median P: 49.3% (range: 2.0%-515.9%) Median T: 121.2% (range: 11.0%-391.3%)	Penetration ratio determined as $AUC_{ELF}/AUC_{unbound=plasma}$
Carbapenem	Meropenem [38]	2 g or 500 mg IV as a 3-h infusion q8h or 1 g IV as a 0.5-h infusion q8h	81.6% ± 223 % Median: 25.42%	Penetration ratio determined as $AUC_{ELF}/AUC_{total-plasma}$
	Meropenem [39•]	1 g IV as a 0.5-h infusion q8h	20%	Penetration ratio determined as $AUC_{ELF}/AUC_{total-plasma}$
		1 g IV as a 3-h infusion q8h	29%	
	Ertapenem [40]	1 g IV as a 1-h infusion once daily	Median 32% (IQR: 28-46%)	Penetration determined by $ELF/C_{unbound-plasma}$ where C is either at 1-, 12- or 24-h after the end of infusion
	Ertapenem [41]	1 g IV as a 1-h infusion once daily	1.0-hour: 6.19% ± 11.0% 3.0-hour: 6.85% ± 6.45% 5.0-hour: 9.40% ± 10.7%	Penetration determined by $ELF/C_{total-plasma}$ where C is either at 1-, 3- or 5-h after the end of infusion
Cephalosporin	Cefepime [42]	2 g as a 0.5-h infusion followed by 4 g/24 hours IV continuous infusion	104% ± 8.9 %	Penetration determined by $ELF/C_{total-plasma}$ where C is either at 8:00am, 12:00pm or 6:00pm after 2 days of IV continuous infusion
	Ceftazidime [43]	2 g as a 0.5-h infusion followed by 4 g/24 hours IV continuous infusion	20.6% ± 8.9 %	Penetration determined by $ELF/C_{total-plasma}$ where C is either at 8:00am, 12:00pm or 6:00pm after 2 days of IV continuous infusion
Fluoroquinolone	Levofloxacin [44]	500 mg IV q24h	Peak: 131% ± 31 % Trough: 118% ± 36 %	Each patient had two standardized bronchoalveolar microlavage procedures
		500 mg IV q12h	Peak: 127% ± 46 % Trough: 112% ± 40 %	
Glycopeptide	Vancomycin [45]	Dose-adjusted (plasma trough concentration of	24.6% (range: 19.2% - 42.6%) 14% (range: 2.3% - 28.5%)	Vancomycin penetration higher in patients when ELF albumin values $\geq 3.4$ mg/mL

		15-20 mg/L)		than with normal values <3.4 mg/mL ( $p < 0.02$ )
Oxazolidinone	Linezolid [46]	600 mg IV q12h	Peak: 105% ± 34 % Trough: 104% ± 28 %	Each patient had two standardized bronchoalveolar microlavage procedures
	Linezolid [47]	1200 mg/24 hours (50mg/h) IV continuous infusion	Median 97% (IQR: 80-108%)	Penetration determined by ELF/serum C <sub>ss</sub> or AUC ratios
	Linezolid [48]	600 mg IV q12h (II Group)  1200 mg/24 hours (50mg/h) by IV continuous infusion (CI Group)	II Group: Median 80% (IQR: 56.6-130.5%)  CI Group: Median 106% (IQR: 71.6-116%)	Critically ill obese (BMI ≥ 30 kg/m <sup>2</sup> ) adults; Penetration ratios based on Monte Carlo simulation for II group had a median of 87.1% (IQR: 78.7-95.4%) compared to CI group had a median of 98.8% (IQR: 93.8-104.3%)

**Table 3 Published studies on microdialysis and lung penetration of selected antibiotics in patients**

Antibiotic	Dose	Penetration Ratio	AUC <sub>lung</sub> (µg·h/mL)	AUC <sub>plasma</sub> (µg·h/mL)
Cefpirome [53]	2 g	Mean: 67%	Mean ± SEM: 261 ± 24	Mean ± SEM: 174 ± 15
Cefpirome [54]	30 mg/kg	Median: 46% (range: 32-98) * Median: 63% (range: 19-155) #	Median: 206 (range: 49-379) * Median: 182 (range: 80-382) #	Median: 291 (range: 133-713)
Piperacillin-Tazobactam [55]	4.5 g	Piperacillin: Mean ± SD: 63% ± 29% Tazobactam: Mean ± SD: 193% ± 156%	Piperacillin: Mean ± SD: 288.0 ± 167.0 Tazobactam: Mean ± SD: 45.7 ± 44.8	Piperacillin: Mean ± SD: 470.0 ± 142.0 Tazobactam: Mean ± SD: 36.2 ± 26.0
Meropenem [56]	1 g	Mean ± SD: 41% ± 21%	Mean ± SD: 36.2 ± 17.9	Mean ± SD: 95.4 ± 46.6
Levofloxacin [57]	500 mg	Median: 60% (range: 40-90)	Median: 18.6 (range: 10.1-33.6)	Median: 32.6 (range: 24.3-44.2)
Levofloxacin [58]	500 mg	Mean: 67%	Median: 37.8 (range: 33.0-39.3)	Median: 56.3 (range: 41.8-89.6)
Levofloxacin [59]	500 mg	Median: 30% (range: 10-70) ‡ Median: 70% (range: 40-80) †	Median: 15.7 (range: 2.7-24.3) ‡ Median: 72.2 (range: 22.2-95.8) †	Median: 77.2 (range: 53.5-95.2) ‡ Median: 82.5 (range: 66.3-106.7) †
Fosfomycin [60]	4 g	Mean ± SD: 53% ± 31%* Mean ± SD: 63% ± 31%#	Mean ± SD: 315.1 ± 151.2* Mean ± SD: 367.6 ± 111.9#	Mean ± SD: 665.9 ± 179.5

Penetration ratio was determined in all studies by the ratio of  $AUC_{\text{interstitial fluid}}/AUC_{\text{plasma}}$

\* infected lung

# uninfected lung

‡ patients undergoing coronary artery bypass with cardiopulmonary bypass

† patients operated with the off-pump coronary artery bypass grafting technique.