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

Keith A. Rodvold1, Sara E. Boyd2,3, William W. Hope2

1 Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago, Illinois, USA and 2Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

3 Division of Infectious Diseases & Immunity, Imperial College London, London, United Kingdom

**Journal Submission:** *Current Opinion in Pharmacology*

**Running title:** Intrapulmonary concentrations of antibiotics

**Key words:** Antibiotics, epithelial lining fluid, bronchoalveolar lavage, microdialysis

**Address correspondence to:**

Keith A. Rodvold, Pharm.D. FCCP, FIDSA

University of Illinois at Chicago, College of Pharmacy

833 South Wood Street, Room 164, m/c 886

Chicago, Illinois 60612 USA

Phone: 312-996-3341

Fax: 312-413-1797

Email: kar@uic.edu

**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 *Chlamydophila 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., ≥ 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 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.

**REFERENCES and RECOMMENDED READINGS**

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Onufrak NJ, Forrest A, Gonzalez D. **Pharmacokinetic and pharmacodynamics principles of anti-infective dosing.** *Clin Ther* 2016, **38**:1930-1947.

2. Baldwin DR, Honeybourne D, Wise R. **Pulmonary disposition of antimicrobial agents: methodological considerations.** *Antimicrob Agents Chemother* 1992, **36**:1171-1175.

3. Baldwin DR, Honeybourne D, Wise R. **Pulmonary disposition of antimicrobial agents: in vivo observations and clinical relevance.** *Antimicrob Agents Chemother* 1992, **36**:1176-1180.

4. Rodvold KA, George JM, Yoo L. **Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents.** *Clin Pharmacokinet* 2011, **50**:637-664.

•• Comprehensive review of bronchoalveolar lavage studies and the data generated up to 2011 for intrapulmonary penetration of antibiotics.

5. Rodvold KA, Yoo L, George MJ. **Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antifungal, antitubercular and miscellaneous anti-infective agents.** *Clin Pharmacokinet* 2011, **50**:689-704.

6. Bamberger DM, Foxworth J, Kallenberger MA, Pepito BS, Gerding DN. **Extravascular antimicrobial distribution and the respective blood and urine concentrations in humans.** In: *Antibiotics in Laboratory Medicine*, 6th edition. Edited by Amsterdam D. Wolters Kluwer Health; 2015:678-780.

•• Comprehensive review of types of extravascular sites, methodology to study distribution of antibiotics in humans, and accurate determination and interpretation of data. Extensive use of tables to summarize and illustrate concentrations of antibiotics in a variety of tissues and fluids.

7. Zeitlinger M, Muller M, Joukhadar C. **Lung microdialysis: a powerful tool for the determination of exogenous and endogenous compounds in the lower respiratory tract (mini-review).** *AAPS J* 2005, **7**:E600-608.

• A review that highlights the differences between bronchoalveolar lavage and microdialysis studies for determining drug concentrations in the lower respiratory tract.

8. Dhanani J, Roberts JA, Chew M, Lipman J, Boots RJ, Paterson DL, Fraser JF. **Antimicrobial chemotherapy and lung microdialysis: a review.** *Int J Antimicrob Agents* 2010, **36**:491-500.

•• A review on the use of microdialysis studies to determine intrapulmonary concentrations of antibiotics studies in patients.

9. Mouton JW, Theuretzbacher U, Craig WA, Tulkens PM, Derendorf H, Cars O. **Tissue concentrations: do we ever learn?** *J Antimicrob Chemother* 2008, **61**:235-237.

10. Jamal J-A, Abdul-Aziz M-H, Lipman J, Roberts JA. **Defining antibiotic dosing in lung infections.** *Clin Pulmonary Med* 2013, **20**:121-128.

11. Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, Drusano GL. **Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap!** Clin Infect Dis 2010, **51(S1)**:S103-s110.

•• A critical evaluation for why determining intrapulmonary concentrations of antibiotics before starting clinical trials in patients with HABP and VABP.

12. Ambrose PG. **Antibacterial drug development program successes and failures: a pharmacometric explanation.** *Curr Opin Pharmacol* 2017; **36**:1-7.

13. Riccobene TA, Pushkin R, Jandourek A, Knebel W, Khariton T. **Penetration of ceftaroline into the epithelial lining fluid of healthy adult subjects.** *Antimicrob Agents Chemother* 2016, **60**:5847-5857.

14. van Hasselt JG, Rizk ML, Lala M, Chavez-Eng C, Visser SA, Kerbusch T, Danhof M, Rao G, van der Graaf PH. **Pooled population pharmacokinetic model of imipenem in plasma and the lung epithelial lining fluid.** *Br J Clin Pharmacol* 2016, **81**:1113-1123.

15. Wenzler E, Gotfried MH, Loutit JS, Durso S, Griffith DC, Dudley MN, Rodvold KA. **Meropenem-RPX7009 concentrations in plasma, epithelial lining fluid, and alveolar macrophages of healthy adult subjects.** *Antimicrob Agents Chemother* 2015, **59**:7232-7239.

16. Nicolau DP, Siew L, Armstrong J, Li J, Edeki T, Learoyd M, Das S. **Phase 1 study assessing the steady-state concentration of ceftazidime and avibactam in plasma and epithelial lining fluid following two dosing regimens.** *J Antimicrob Chemother* 2015, **70**:2862-2869.

17. Chandorkar G, Hunington JA, Gotfried MH, Rodvold KA, Umeh O. **Intrapulmonary penetration of ceftolozane/tazobactam and piperacillin/tazobactam in healthy adult subjects.** *J Antimicrob Chemother* 2012, **67**:2463-2469.

18. Connors KP, Housman ST, Pope JS, Russomanno J, Salerno E, Shore E, Redican S, Nicolau DP. **Phase 1, open-label, safety and pharmacokinetic study to assess bronchopulmonary disposition of intravenous eravacycline in healthy men and women.** *Antimicrob Agents Chemother* 2014, **58**:2113-2118.

19. Gotfried MH, Horn K, Garrity-Ryan L, Villano S, Tzanis E, Chitra S, Manley A, Tanaka SK, Rodvold KA. **Comparison of omadacycline and tigecycline pharmacokinetics in the plasma, epithelial lining fluid, and alveolar cells in healthy adult subjects.** *Antimicrob Agents Chemother* 2017, **62**:e01135-17.

20. Housman ST, Pope JS, Russomanno J, Salerno E, Shore E, Kuti JL, Nicolau DP. **Pulmonary disposition of tedizolid following administration of once-daily oral 200-milligram tedizolid phosphate in healthy adult subjects.** *Antimicrob Agents Chemother* 2012, **56**:2627-2634.

21. Rodvold KA, Gotfried MH, Chugh R, Gupta M, Friedland HD, Bhatia A. **Comparison of plasma and intrapulmonary concentrations of nafithromycin (WCK 4873) in healthy adult subjects.** *Antimicrob Agents Chemother* 2017, **62**:e01096-17.

22. Rodvold KA, Gotfried MH, Still JG, Clark K, Fermandes P. **Comparison of plasma, epithelial lining fluid, and alveolar macrophage concentrations of solithromycin (CEM-101) in healthy adult subjects.** *Antimicrob Agents Chemother* 2012, **56**:5076-5081.

23. Zeitlinger M, Schwameis R, Burian A, Burian B, Matzneller P, Muller M, Wicha WW, Strickman DB, Prince W. **Simultaneous assessment of the pharmacokinetics of a pleuromutilin, lefamulin, in plasma, soft tissues and pulmonary epithelial lining fluid.** *J Antimicrob Chemother* 2016, **71**:1022-1026.

24. Naderer OJ, Rodvold KA, Jones LS, Zhu JZ, Bowen CL, Chen L, Dumont E. **Penetration of GSK1322322 into epithelial lining fluid and alveolar macrophages as determined by bronchoalveolar lavage.** *Antimicrob Agents Chemother* 2014, **58**:419-423.

25. Tenero D, Bowers G, Rodvold KA, Patel A, Kurtinecz M, Dumont E, Tomayko J, Patel P. **Intrapulmonary pharmacokinetics of GSK2251052 in healthy volunteers.** *Antimicrob Agents Chemother* 2013, **57**:3334-3339.

26. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, Scheeren TW, Sanchez AS, Zhou X, Saulay M, Engelhardt M. **A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia.** *Clin Infect Dis* 2014, **59**:51-61.

27. Koffef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R. **A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia.** *Crit Care* 2012, **16**:R218.

28. Roberts JA, Lipman J. **Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility.** *Crit Care Med* 2013, **41**:489-495.

29. Katsube T, Wajima T, Ishibashi T, Arjona Ferreira JC, Echols R. **Pharmacokinetic/pharmacodynamics modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function.** *Antimicrob Agents Chemother* 2016, **61**:e01381-16.

30. Boselli E, Breilh D, Djabarouti S, Guillaume C, Rimmele T, Gordien J-B, Xuereb F, Saux M-C, Allaouchiche B. **Reliability of mini-bronchoalveolar lavage for the measurement of epithelial lining fluid concentrations of tobramycin in critically ill patients.** *Intensive Care Med* 2007, **33**:1519-1523.

31. Carcas AJ, Garcia-Satue JL, Zapater P, Frias-Iniesta J. **Tobramycin penetration into epithelial lining fluid of patients with pneumonia.** *Clin Pharmacol Ther* 1999, **65**:245-250.

32. Mazzei T, Noveilli A, De Lalla F, Mini E, Periti P. **Tissue penetration and pulmonary disposition of tobramycin.**  *J Chemother* 1995, **7**:363-370.

33. Panidis D, Markantonis SL, Boutzouka E, Karatzas S, Baltopoulos G. **Penetration of gentamicin into the alveolar lining fluid of critically ill patients with ventilator-associated pneumonia.** *Chest* 2005, **128**:545-552.

34. Valcke Y, Vogelaers DP, Colardyn FA, Pauwels RA. **Penetration of netilmicin into the lower respiratory tract after once-daily dosing.** *Chest* 1992, **101**:1028-1032.

35. Boselli E, Breilh D, Cannesson M, Xuereb F, Rimmele T, Chassard D, Saux M-C, Allaouchiche B. **Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia.** *Intensive Care Med* 2004, **30:**976-979.

36. Boselli E, Breilh D, Rimmele T, Guillaume C, Xuereb F, Saux M-C, Bouvet L, Chassard D, Allaouchiche B. **Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia.** *Crit Care Med* 2008, **36:**1500-1506.

37. Felton TW, McCalman K, Malagon I, Isalska B, Whalley S, Goodwin J, Bentley AM, Hope WW. **Pulmonary penetration of piperacillin and tazobactam in critically ill patients.** *Clin Pharmacol Ther* 2014, **96:**438-448.

•• Outstanding research manuscript using bronchoalveolar lavage and pharmacokinetic-pharmacodynamic modelling to determine intrapulmonary penetration of piperacillin and tazobactam in critically ill patients

38. Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. **Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia.** *Antimicrob Agents Chemother* 2011, **55:**1606-1610.

39. Frippiat F, Musuamba FT, Seidel L, Albert A, Denooz R, Charlier C, Van Bambeke F, Wallemacq P, Descy J, Lambermont B, Layios N, Damas D, Moutschen M. **Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study.** *J Antimicrob Chemother* 2015, **70:**207-216.

• Illustrates the variability in meropenem concentrations in seriously ill patients with nosocomial pneumonia and the impact of two different modes of drug administration on target attainment rates

40. Boselli E, Breilh D, Saux M-C, Gordien J-B, Allaouchiche B.  **Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia.** *Intensive Care Med* 2006, **32:**2059-2062.

41. Burkhardt O, Majcher-Peszynska J, Borner K, Mundkowski R, Drewelow B, Derendorf H, Welte T.  **Penetration of ertapenem into different pulmonary comparatments of patients undergoing lung surgery.** *J Clin Pharmacol* 2005, **45:**659-665.

42. Boselli E, Breilh D, Duflo F, Saux M-C, Debon R, Chassard D, Allaouchiche B.  **Steady-state plasma and intrapulmonary concentrations of cefepime administered in continuous infusion in critically ill patients with severe nosocomial pneumonia.** *Crit Care Med* 2003, **31:**2102-2106.

43. Boselli E, Breilh D, Rimmele T, Poupelin J-C, Saux M-C, Chassard D, Allaouchiche B.  **Plasma and lung concentrations of ceftazidime administered in continuous infusion to critically ill patients with severe nosocomial pneumonia.** *Intensive Care Med* 2004, **30:**989-991.

44. Boselli E, Breilh D, Rimmele T, Djabarouti S, Saux M-C, Chassard D, Allaouchiche B.  **Pharmacokinetics and intrapulmonary diffusion of levofloxacin in critically ill patients with community-acquired pneumonia.** *Crit Care Med* 2005, **33:**104-109.

45. Lamer C, De Beco V, Soler P, Calvat S, Fagon J-Y, Dombret M-C, Farinotti R, Chastre J, Gilbert C. **Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients.** *Antimicrob Agents Chemother* 1993, **37:**281-286.

46. Boselli E, Breilh D, Rimmele T, Djabarouti S, Toutain J, Chassard D, Saux M-C, Allaouchiche B. **Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia.** *Crit Care Med* 2005, **33:**1529-1533.

47. Boselli E, Breilh D, Caillault-Sergent A, Djabarouti S, Guillaume C, Xuereb F, Bouvet L, Rimmele T, Saux M-C, Allaouchiche B. **Alveolar diffusion and pharmacokinetics of linezolid administered in continuous infusion to critically ill patients with ventilator-associated pneumonia.** *J Antimicrob Chemother* 2012, **67:**1207-1210.

48. De Pascale G, Fortuna S, Tumbarello M, Cutuli SL, Vallecoccia M, Spanu T, Bello G, Montini L, Pennisi MA, Navarra P, Antonelli M. **Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration.** *Intensive Care Med* 2015, **41:**103-110.

49. Felton TW, Hope WW, Roberts JA. **How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it?** *Diagn Microbiol Infect Dis* 2014, **79**:41-447.

50. Asin-Prieto E, Rodriguez-Gascon A, Isla A. **Applications of the pharmacokinetic/pharmacodynamics (PK/PD) analysis of antimicrobial agents.** *J Infect Chemother* 2015, **21**:319-329.

51. Tangden T, Ramow Martin V, Felton TW, Nielsen EI, Marchand S, Bruggemann RJ, Bulitta JB, Bassetti M, Theuretzbacher U, Tsuji BT, Wareham DW, Friberg LE, De Waele JJ, Tam VH, Roberts JA. **The role of infection models and PK/PD modelling for optimizing care of critically ill patients with severe infections.** *Intensive Care Med* 2017, **43**:1021-1032.

52. Mimoz O, Dahyot-Fizelier C. **Mini-broncho-alveolar lavage: a simple and promising method for assessment of antibiotic concentration in epithelial lining fluid.** *Intensive Care Med* 2007, **33**:1495-1497.

53. Herkner H, Muller MR, Kreischitz N, Mayer BX, Frossard M, Joukhadar C, Klein N, Lackner E, and Muller M. **Close-chest microdialysis to measure antibiotic penetration into human lung tissue.** *Intensive Care Med* 2007, **33**:1519-1523.

54. Lindenmann J, Kugler SA, Matzi V, Porubsky C, Maier A, Dittrich P, Graninger W, Smolle-Juttner FM, Joukhadar C. **High extracellular levels of cefpirome in unaffected and infected lung tissues of patients.** *J Antimicrob Chemother* 2011, **66**:160-164.

55. Tomaselli F, Dittrich P, Maier A, Woltsche M, Matzi V, Pinter J, Nuhsbaumer S, Pinter H, Smolle J, Smolle-Juttner FM. **Penetration of piperacillin and tazobactam into pneumonic human lung tissue measured by *in vivo* microdialysis.** *Br J Clin Pharmacol* 2003, **55**:620-624.

56. Tomaselli F, Maier A, Matzi V, Smolle-Juttner FM, Dittrich P. **Penetration of meropenem into pneumonic human lung tissue as measured by *in vivo* microdialysis.** *Antimicrob Agents Chemother* 2004, **48**:2228-2232.

57. Hutschala D, Skhirtladze K, Zuckermann A, Wisser W, Jaksch P, Mayer-Helm BX, Burgmann H, Wolner E, Muller M, Tschernko EM. **In vivo measurement of levofloxacin penetration into lung tissue after cardiac surgery.** *Antimicrob Agents Chemother* 2005, **49**:5107-5111.

58. Hutschala D, Kinstner C, Skhirtladze K, Mayer-Helm B-X, Zeitlilnger M, Wisser W, Muller M, Tschernko E. **The impact of perioperative atelectasis on antibiotic penetration into lung tissue: an in vivo microdialysis study.** *Intensive Care Med* 2008, **34**:1827-1834.

59. Zeitlinger MA, Traunmuller F, Abrahim A, Muller MR, Erdogan Z, Muller M, Joukhadar C. **A pilot study testing whether concentrations of levofloxacin in interstitial space fluid of soft tissues may serve as a surrogate for predicting its pharmacokinetics in lung.** *Int J Antimicrob Agents* 2007, **29**:44-50.

60. Matzi V, Lindenmann J, Porubsky C, Kugler SA, Maier A, Ditrich P, Smolle-Juttner FM, Joukhadar C. **Extracellular concentrations of fosfomycin in lung tissues of septic patients.** *J Antimicrob Chemother* 2010, **65**:995-998.

61. Prideaux B, ElNaggar MS, Zimmerman M, Wideman JM, Li X, Dartois V. **Mass spectrometry imaging of levofloxacin distribution in TB-infected pulmonary lesions by MALDI-MSI and continuous liquid microjunction surface sampling.** *Int J Mass Spectrom*. 2015; 377: 699-708.

62. Zhao Y, Prideaux B, Nagasaki Y, Lee MH, Chen PY, Blanc L, Ho H, Clancy CJ, Nguyen MH, Dartois, Perlin DS. **Unravelling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-Abdominal Abscess Model.** *Antimicrob Agents Chemother.* 2017. Doi: 10.1128/AAC.01009-17. [Epub ahead of print]

63. Zhang Z, Gogarty KR, Fereidoon D, Tonge PJ. **Pharmacokinetic and Pharmacodynamics Relationships**. In: *Imaging Infections*. Edited by Jain S. Springer, Cham; 2017: 195-207.

64. Arroyo-Currás N, Somerson J, Vieira PA, Ploense KL, Kippen TE, Plaxco KW. **Real-time measurement of small molecules directly in awake, ambulatory animals.** *Proc Natl Acad Sci* U.S.A. 2017; 114(4): 645-650

65. Rawson TM, Sharma S, Georgiou P, Holmes A, Cass A, O’Hare D. **Towards a minimally invasive device for beta-lactam monitoring in humans.** *Electrochemistry communications.* 2017; 88: 1-5

**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)** | **AUCELF**  **(µg🞄h/mL)** | **AUCtotal-plasma**  **(µg🞄h/mL)** |
| Ceftaroline [13] | 600 mg q12h  600 mg q8h | 18.0%  17.7% | 22.5%  23.6% | 8.09  9.36 | 45.0 ± 7.32  53.0 ± 7.16 |
| Imipenem [14] | 250-500 mg q6h | 44% | 55% | N.R. | N.R. |
| Meropenem-  Vaborbactam [15] | 2.0 g q8h  2.0 g q8h | 63%  53% | 65%  79% | 111.7  105.1 | 186 ± 33.6  204 ± 34.6 |
| Ceftazidime-Avibactam [16] | 2.0 g q8h  0.5 g q8h  3.0 g q8h  1.0 g q8h | 31.3%  34.9%  32.4%  32.0% | N.R.  N.R.  N.R.  N.R. | 92.3  13.7  147  24.8 | 295  39.2  454  77.6 |
| Ceftolozane-  Tazobactam [17] | 1.0 g q8h  0.5 g q8h | 48%  44% | 59%  N.R. | 75.1  8.5 | 158.5 ± 24.1  19.3.± 2.9 |
| Piperacillin-Tazobactam [17] | 4.0 g q6h  0.5 g q6h | 26%  54% | 38%  N.R. | 94.5  24.7 | 357.3 ± 65.9  46.1 ± 8.7 |
| Eravacycline [18] | 1 mg/kg q12h | 132% | 644% | 4.93 | 4.56 ± 0.94 |
| Omadacycline [19] | 100 mg q12h x 3, then 100 mg q24h | 147% | 184% | 17.23 | 12.14 ± 3.22 |
| Tigecycline [19] | 100 mg x 1, then 50 mg q12h | 171% | 659% | 3.16 | 2.20 ± 0.42 |
| Tedizolid [20] | 200 mg Q24h | 433% | 4120% | 109.3 | 25.13 ± 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 ± 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 ± SD; N.R., not reported

Penetration ratio was determined in all studies by the ratio of AUCELF/AUCplasma

**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]  Tobramycin [31]  Tobramycin [32]  Gentamicin [33]  Netilmicin [34] | 7-10 mg/kg IV once daily  Concentration-adjusted dosing  150 mg IM single dose  300 mg IM once daily x 4 days  240 mg IV once daily  450 mg IV single dose | ~12% (range: 0.8%-12.8%)  0.5-hour: 30 ± 3 %  2.0-hour: 42 ± 16 %  4.0-hour: 64 ± 37 %  8.0-hour: 153 ± 76 %  140 ± 80 %  160 ± 60 %  1.0-hour: 30 ± 5 %  2.0-hour: 85 ± 10 %  4.0-hour: 114 ± 26 %  6.0-hour: 74 ± 18 %  1.0-hour: 35%  2.0-hour: 78%  3.0-hour: 177%  4.0-hour: 145% | Single sampling time at 30 minutes after end of 30-minute infusion  Single sampling time at 6 hours after end of 30-minute infusion  Penetration ratios based on reported mean concentrations in plasma and lining fluid in original report |
| Beta-lactam beta-lactamase inhibitor combination product | Piperacillin-tazobactam [35]  Piperacillin-tazobactam [36]  Piperacillin-tazobactam [37••] | 4.5 g IV q8h  No/Mild Renal Failure:  13.5 g/24 hours IV continuous infusion  18 g/24 hours IV continuous infusion  Moderate/Advanced Renal Failure:  13.5 g/24 hours IV continuous infusion  18 g/24 hours IV continuous infusion  4.5 g IV q8h or q12h | P: 56.8 ± 33.6 %  T: 91.3 ± 27.7 %  Median P: 46% (IQR: 29%-62%)  Median T: 85% (IQR: 68%-132%)  Median P: 43% (IQR: 30%-65%)  Median T: 84% (IQR: 50%-105%)  Median P: 39% (IQR: 31%-48%)  Median T: 49% (IQR: 39%-69%)  Median P: 85% (IQR: 60%-96%)  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 (ELF/Plasmatotal) determined at single sampling time  Penetration ratio (ELF/Plasmatotal) determined at single sampling time  Penetration ratio determined as AUCELF/AUCunbound=plasma |
| Carbapenem | Meropenem [38]  Meropenem [39•]  Ertapenem [40]  Ertapenem [41] | 2 g or 500 mg IV as a 3-h infusion q8h or 1 g IV as a 0.5-h infusion q8h  1 g IV as a 0.5-h infusion q8h  1 g IV as a 3-h infusion q8h  1 g IV as a 1-h infusion once daily  1 g IV as a 1-h infusion once daily | 81.6% ± 223 %  Median: 25.42%  20%  29%  Median 32% (IQR: 28-46%)  1.0-hour: 6.19% ± 11.0%  3.0-hour: 6.85% ± 6.45%  5.0-hour: 9.40% ± 10.7% | Penetration ratio determined as AUCELF/AUCtotal-plasma  Penetration ratio determined as AUCELF/AUCtotal-plasma  Penetration determined by ELF/Cunbound-plasma where C is either at 1-, 12- or 24-h after the end of infusion  Penetration determined by ELF/Ctotal-plasma where C is either at 1-, 3- or 5-h after the end of infusion |
| Cephalosporin | Cefepime [42]  Ceftazidime [43] | 2 g as a 0.5-h infusion followed by 4 g/24 hours IV continuous infusion  2 g as a 0.5-h infusion followed by 4 g/24 hours IV continuous infusion | 104% ± 8.9 %  20.6% ± 8.9 % | Penetration determined by ELF/Ctotal-plasma where C is either at 8:00am, 12:00pm or 6:00pm after 2 days of IV continuous infusion  Penetration determined by ELF/Ctotal-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  500 mg IV q12h | Peak: 131% ± 31 %  Trough: 118% ± 36 %  Peak: 127% ± 46 %  Trough: 112% ± 40 % | Each patient had two standardized bronchoalveolar microlavage procedures |
| Glycopeptide | Vancomycin [45] | Dose-adjusted (plasma trough concentration of 15-20 mg/L) | 24.6% (range: 19.2% - 42.6%)  14% (range: 2.3% - 28.5%) | Vancomycin penetration higher in patients when ELF albumin values ≥3.4 mg/mL than with normal values <3.4 mg/mL (*p* < 0.02) |
| Oxazolidinone | Linezolid [46]  Linezolid [47]  Linezolid [48] | 600 mg IV q12h  1200 mg/24 hours (50mg/h) IV continuous infusion  600 mg IV q12h (II Group)  1200 mg/24 hours (50mg/h) by IV continuous infusion (CI Group) | Peak: 105% ± 34 %  Trough: 104% ± 28 %  Median 97% (IQR: 80-108%)  II Group: Median 80% (IQR: 56.6-130.5%)  CI Group: Median 106% (IQR: 71.6-116%) | Each patient had two standardized bronchoalveolar microlavage procedures  Penetration determined by ELF/serum Css or AUC ratios  Critically ill obese (BMI ≥ 30 kg/m2) 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** | **AUClung (µg🞄h/mL)** | **AUCplasma (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 AUCinterstitial fluid/AUCplasma

\* infected lung

# uninfected lung

‡ patients undergoing coronary artery bypass with cardiopulmonary bypass

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