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LETTER TO THE EDITOR

Authors' Reply to De Sutter, De Waele, and Vermeulen: "Penetration of Antibacterial Agents into Pulmonary Epithelial Lining Fluid: An Update"

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Dear Editor,

We thank De Sutter, De Waele, and Vermeulen for their comments and interest regarding our publication on the penetration of antibacterial agents into pulmonary epithelial lining fluid (ELF) [1, 2]. We agree that a timely review of this highly relevant topic was needed as a significant number of published studies occurred during the past decade and new antibacterial drug development programs are incorporating these clinical observations [2–4]. As we outlined, most of the intrapulmonary penetration studies have been conducted in healthy adult subjects using bronchoalveolar lavage to determine whether an antibacterial agent penetrated into ELF and in what amount [2, 5, 6]. Currently, there are a limited number of bronchoalveolar lavage studies measuring ELF concentrations in critically ill patients secondary to the practical and ethical issues associated with such research [2, 5].

We appreciate and applaud the authors' interest in physiologically based pharmacokinetic (PBPK) models and non-invasive sampling techniques for studying intrapulmonary concentrations in critically ill patients. The application of PBPK modeling has advanced over the last two decades and serves as another option for modeling and simulating concentration–time data using physiological and mechanistic approaches, in vitro information, and in silico methods [7]. This sophisticated and potentially complex analysis is being employed by academic, regulatory, and industry investigators to address drug selection and system-specific development issues (e.g., study design, first-in-human dosing, various dosage formulations, drug–drug interactions, and pharmacokinetic variability) in different patient populations even when drug exposure data may be difficult to determine [7, 8]. Several recently published manuscripts have documented the usefulness of PBPK modeling to predict systemic and pulmonary ELF exposure of antibacterial agents, including drugs being repurposed for COVID-19 [9–12].

When we first started conducting intrapulmonary penetration studies almost 30 years ago, lung tissue homogenates and comparison with concomitant plasma concentrations were still being advocated [13, 14]. Since that time, the paradigm has shifted to measuring specific sites of where bacterial lung infections occur (i.e., extracellular and intracellular drug concentrations), assessing in vivo pharmacodynamics of antibacterial agents in animal infection models, and applying population pharmacokinetic-pharmacodynamic modeling and simulation for developing dosage regimens applicable to both research studies and/or clinical practice [2, 4, 5]. We acknowledge that measuring ELF concentrations and population-pharmacokinetic modeling are not a panacea for understanding intrapulmonary penetration of antibacterial agents and ensuring clinical success for the treatment of bacterial pneumonia. However, this current approach has advanced the importance of drug exposure in the lung and assisted in the dose selection of new (and old) antibacterial agents.

There is little doubt that the collection of site concentrations in critically ill patients is challenging and one of the major limitations of why there is limited ELF concentration–time data during drug development programs. Non-invasive techniques would surely improve the opportunities to collect lung concentrations to assist in the optimal design of dosage regimens for the treatment of critically ill

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patients with hospital-acquired and ventilator-associated bacterial pneumonia. The use of exhaled breath condensate has already been used for non-invasive evaluation of lung diseases [15]. The combination of exhaled breath condensate samples with nanobiosensor sensitive analytical techniques and/or endogenous dilution markers (i.e., urea) should improve quantification issues of antibacterial concentrations [16–18]. However, further validation of these techniques will be needed and comparison to other sample collection methods of assessing intrapulmonary drug concentrations should be considered. Using real-world exhaled breath condensate concentrations and clinical information to perform PBPK modeling will however be challenging, appealing for critically ill patients during (and after) the drug development program for antibacterial agents. We encourage these types of investigations for measuring intrapulmonary concentrations of anti-infective agents and pharmacokinetic-pharmacodynamic modeling options to improve the care of patients with lower respiratory tract infections.

Declarations

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Conflict of Interests/Competing Interests Emily Drwiega has no conflicts of interest that are directly relevant to the content of this letter. Keith Rodvold has conducted research and/or served as a consultant for intrapulmonary studies discussed in this letter for Cempra Pharmaceuticals, Cubist Pharmaceuticals, Durata Therapeutics, Entasis Therapeutics, GlaxoSmithKline, Ortho-McNeil Pharmaceutical, Paretek Pharmaceuticals, Shionogi & Co., The Medicine Company/Rempex, and Wockhardt Ltd. Keith Rodvold has served on advisory boards, speaking bureaus, or as a consultant for Merck Inc., Shionogi & Co., Sinovent, Spero Therapeutics, The Medicine Company/Qpex Biopharma, and Venatorx Pharmaceuticals.

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Consent to Participate Not applicable.

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