Pharmacokinetic-Pharmacodynamic Considerations in the Design of Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia Studies: Look before You Leap!

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Our thesis is a simple one: although a drug can fail in an individual patient for many reasons, appropriately sized and conducted drug-development programs often fail because of insensitive, uninformative end points, and/or poor a priori regimen decisions. The difficulty in successfully developing antimicrobial agents at present is often exacerbated by company decision-makers who are either uninformed or disregard the difference between empirical-based (ie, akin to playing pin-the-tail on the donkey) and quantitative model-based development plans. Frequently, the focus is on Gantt charts (project event schedules) and the on-time submission of a New Drug Application to a regulatory body, such as the US Food and Drug Administration. Such misplaced focus has led and will continue to lead to a number of problems, including program failure or, even worse, regulatory approval of an inappropriate dosing regimen with associated negative safety and efficacy sequelae. We believe that the goal of drug development is not a New Drug Application submitted on time but, rather, an approved, differentiated, safe, and effective new medicine. Here, we focus on the pharmacokinetic-pharmacodynamic data needed to guide dosing regimen decisions for patients with hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia. Early consideration of these data in development programs will reduce risk not only to sponsors but also, most importantly, to the patients enrolled in the clinical trials.

After making the decision to transition a new molecular entity from discovery to clinical development, the selection of a dosing regimen and supporting rationale (ie, how much, how often, and for what duration an agent should be administered for the indication(s) being pursued and the basis for these decisions) are most important. Paradoxically, there is limited consideration in early development planning, insufficient time and resource allocation, and, frequently, a misconception that one dosing regimen is sufficient for all potential indications. The result is an increased risk to patients enrolled in a given clinical trial, trial failure, and an overall inability to bring a potentially meaningful drug to the therapeutic armamentarium. One way to select an effective dosing regimen and, thereby, increase the likelihood of a successful New Drug Application is through pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) systems analysis.

In the context of the development of antimicrobial agents, valuable PK-PD insights have traditionally been gained using preclinical infection models. PK-PD infection models, such as the murine-thigh or -pneumonia infection models, have been used to identify the PK-PD index (or indices) for a given antimicrobial agent most closely associated with bacterial killing and, therefore, the magnitude of the PK-PD index necessary to achieve therapeutic effects. Although PK-PD infec-

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Clinical Infectious Diseases 2010; 51(S1):S103–S110

1058-4838/2010/5103S1-0017$15.00
DOI: 10.1086/653057

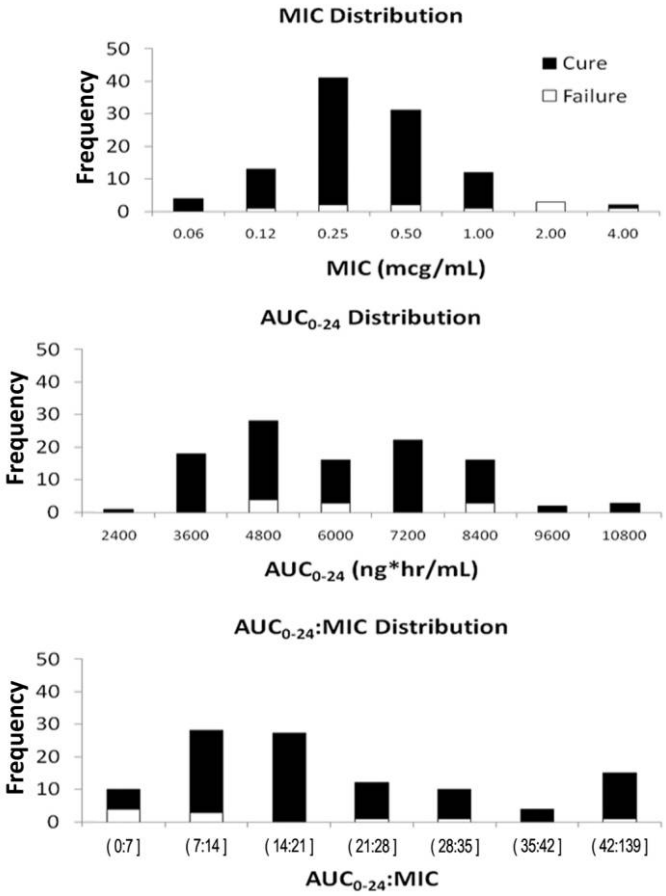

Figure 1. Bacteriologic response by the minimum inhibitory concentration (MIC) of the baseline pathogen (predominantly Enterobacteriaceae), steady-state area under the drug concentration–time curve at 0–24 h (AUC_{0-24}), and steady-state AUC_{0-24}:MIC for 106 pathogens from 71 tigecycline-treated patients with complicated intraabdominal infections who were enrolled in phase 2 and 3 clinical trials.

tion models have been successfully used in early-stage drug evaluation in recent years [1], it is critical to realize that additional data derived using PK and PK-PD systems analysis are required to consistently and robustly identify thresholds for safe and efficacious dosing regimens in various patient populations and subpopulations before the conduct of phase 2 and 3 clinical trials.

The goal of a more thorough PK or PK-PD systems analysis is to consider enough of the determinants and confounders of patient response to mitigate risk and enable appropriate identification of an effective dosing regimen for the study indication of interest. Determinants or confounders of response can be microbiologic, pharmacokinetic, or physiologic. For antimicrobial agents being developed to treat pneumonia, these considerations include the following: bridging of PK and PK-PD relationships from the murine-pneumonia model to that of the human model (confounders of response), the significance of drug penetration into pulmonary fluids (determinant of response), the variability in clearing organ function (determinant of response), and pathogen susceptibility in the overall patient population and in the subpopulations of interest (determinant of response). The acquisition of these data is usually straightforward and, thus, should be an early consideration for integration in the drug development plan.

THE PK-PD INDEX

It is important to remember that each part of a PK-PD index, such as the ratio of the area under the drug concentration–

Table 1. Tigecycline Exposure, as Measured by Steady-State Area Under the Drug Concentration–Time Curve at 0–24 h (AUC_{0-24}), in 123 Patients Stratified by Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Status.

Variable	HABP	VABP
No. of patients	78	45
Mean AUC_{0-24} (CV, %)	7.08 (47.8)	5.48 (62.5)
Median AUC_{0-24} (range)	5.98 (1.82–17.5)	4.80 (1.78–20.1)

NOTE. The median steady-state AUC_{0-24} in patients with VABP was 20% less than that in patients with HABP. CV, coefficient of variation.

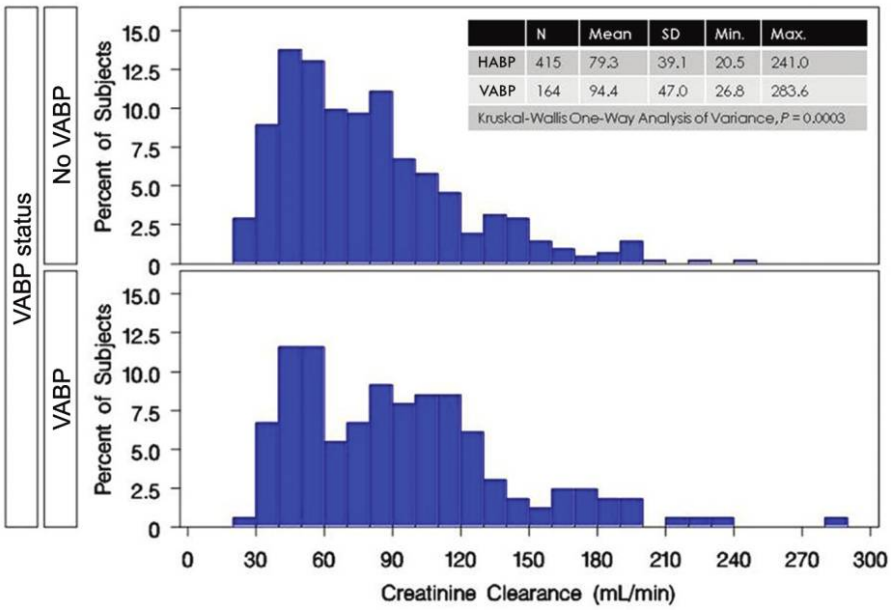

Figure 2. Histograms showing the creatinine clearance distributions and summary statistics of 579 patients with either hospital-acquired bacterial pneumonia (HABP; *top*) or ventilator-associated bacterial pneumonia (VABP; *bottom*). Data are from the Institute for Clinical Pharmacodynamics, Ordway Research Institute Demographic Database.

time curve (AUC) to the minimum inhibitory concentration (MIC) of the drug to the microorganism, has important and independent information. Figure 1 shows bacteriologic response by the MIC of the baseline pathogen (all patients were infected with at least 1 Enterobacteriaceae, which predominantly [~80%] had the highest MIC value), steady-state AUC, and AUC:MIC for 106 pathogens from 71 tigecycline-treated patients with complicated intraabdominal infections enrolled in phase 2 and 3 clinical trials [2]. Usually, in vitro activity (MIC) and drug exposure (AUC) independently do not provide enough information to explain response to therapy. When exposure is indexed to in vitro activity, as in this case with the AUC:MIC, response to therapy becomes more reliably predictable. To guide dosing regimen decisions for patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), factors that affect both components of the PK-PD index—the drug exposure and in vitro activity—must be understood.

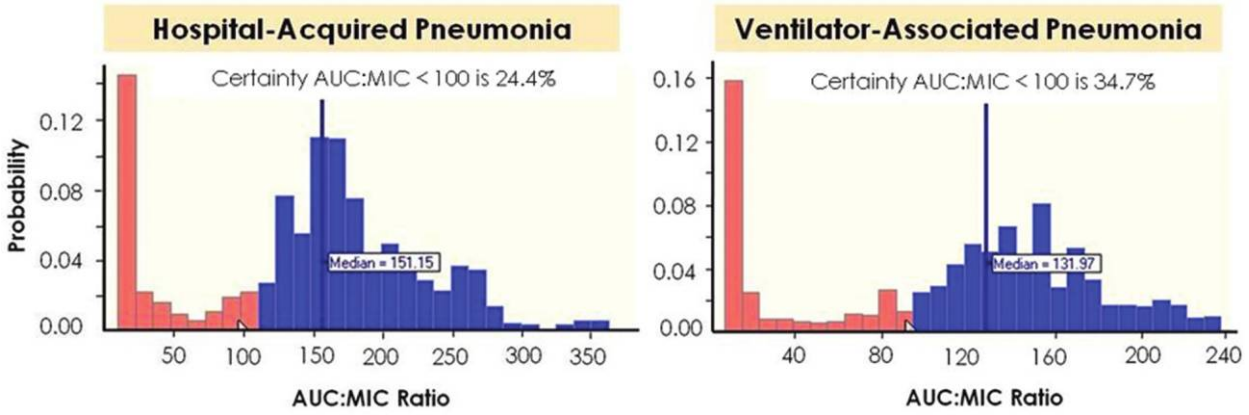

Figure 3. Monte Carlo simulation results showing the probability of attaining a levofloxacin area under the drug concentration–time curve (AUC) to minimum inhibitory concentration (MIC) ratio against *Klebsiella pneumoniae* after a 750-mg once-daily dosing regimen. Simulations were based on a population pharmacokinetic model for levofloxacin based on patients with hospital-acquired bacterial pneumonia and/or ventilator-associated bacterial pneumonia [3], hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia creatinine clearance distributions (Institute for Clinical Pharmacodynamics, Ordway Research Institute, unpublished data), and *K. pneumoniae* MIC distribution [4].

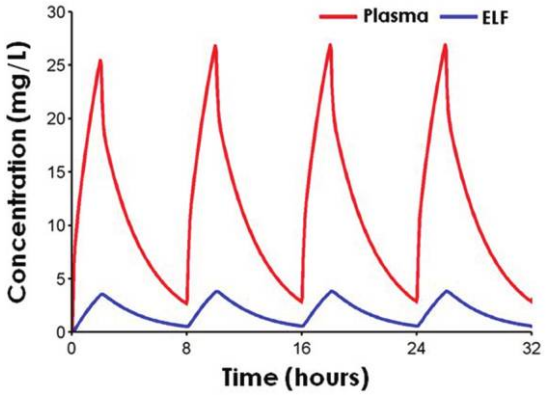

Figure 4. Median ceftobiprole concentration-time profiles in plasma and epithelial lining fluid (ELF) after intravenous administration of 500 mg every 8 h. The median area under the drug concentration–time curve $(AUC)_{ELF}$:AUC_{serum} was 0.153 (derived from [14]).

THE FIRST HALF OF THE PK-PD EQUATION: DRUG EXPOSURE

For an antibiotic to be effective, it must rapidly reach the infection site in sufficient concentrations to inhibit some necessary bacterial cell process. Factors that affect the magnitude of drug exposure include dose, clearing organ function, and penetration into the infection site. A less appreciated but critical issue involves how rapidly effective drug exposures can be achieved at the infection site. Delayed penetration into the infection site not only will have a negative impact on clinical efficacy but also will likely increase the probability of emergence of drug resistance.

Clearing organ function. Clearing organ function is often a major determinant of drug exposure. Figure 2 shows histograms of the creatinine clearance distributions and summary statistics for 579 patients with either HABP or VABP. It is important to note the differences between these creatinine clearance distributions: (1) the mean and data dispersion are statistically different between the 2 populations ($P < .001$), and (2) the HABP distribution is unimodal, whereas that for VABP is no less than bimodal. The multimodal nature of the VABP creatinine clearance distribution is likely to be a function of hyperdynamic patient subpopulations, a phenomenon well recognized by critical care specialists. The following question can then be asked: can such variations in creatinine clearance distributions make a difference?

Figure 3 shows the results of an analysis in which a population PK model for levofloxacin based on data from patients with HABP or VABP [3], the aforementioned creatinine clearance distributions, and Monte Carlo simulation were used to examine the probability of PK-PD target attainment against *Klebsiella pneumoniae* [4] after a 750-mg once-daily dosing regimen. For fluoroquinolones, an AUC:MIC of ~100 against Enterobacteraceae and *Pseudomonas aeruginosa* has been associated with efficacy in PK-PD animal infection models [5] and in patients with HABP or VABP [3,6]. Relative to patients with HABP, it is critical to note that ~50% more patients with VABP fail to attain this critical PK-PD threshold. In other words, the patients at greatest risk for mortality are those patients most likely to have a lower AUC:MIC and, thus, incomplete therapeutic effects.

Despite the fact that clearing organ function is a major determinant of drug exposure, adequate analyses that account for clearing organ function in patient populations are frequently not conducted before the selection of dosing regimens for phase 2 and 3 studies. Databases that catalogue baseline clinical trial patient demographic and laboratory data are rare, and those that exist are underutilized. Prospective use of patient population demographic and laboratory databases are a key element for improving analyses for dosing regimen decision support. In other words, look before you leap!

Infection site penetration. When treating patients with HABP or VABP, it is crucial to determine the penetration of the drug under study into epithelial lining fluid (ELF). Although some controversy exists about ELF [7], it is currently the best measure of drug penetration into the space where the target pathogens reside. The extent and rate of penetration into ELF differs significantly by and within drug class and does not correlate with the fraction of drug bound to serum proteins. Macrolide agents have the greatest penetration into ELF. For example, azithromycin has a median AUC_{ELF}:AUC_{serum} of 13.3 [8]. Very dissimilar agents, such as linezolid and levofloxacin, have relatively similar penetration (median linezolid AUC_{ELF}:AUC_{serum}, 1.99 [9]; median levofloxacin AUC_{ELF}:AUC_{serum}, 1.43 [10]). Of interest, the β-lactams have a wide range of penetration ratios documented, with no unifying principle. For instance, the median AUC_{ELF}:AUC_{serum} of ceftazidime is 0.201 [11], and that of cefepime exceeds 1.04 [12]. Ertapenem, which

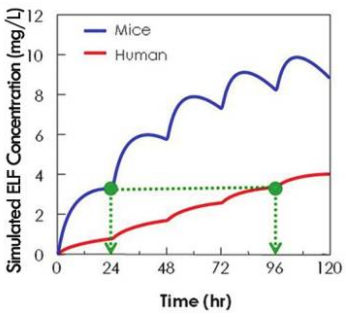

Figure 5. Simulated murine and human oritavancin epithelial lining fluid (ELF) concentration–time profiles over 120 h after drug administration. In mice, the concentrations attained at 24 h were efficacious in a *Staphylococcus aureus* neutropenic murine-pneumonia model. In humans, 96 h are required to reach these same concentrations *(green arrows).*

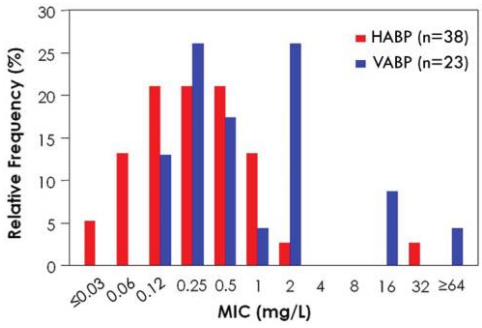

Figure 6. Minimum inhibitory concentration (MIC) distribution for 61 tigecycline-treated patients who had sufficient pharmacokinetic data for analysis and who were clinically and microbiologically evaluable, stratified by hospital-acquired bacterial pneumonia (HABP) and ventilator-assco-ciated bacterial pneumonia (VABP) status.

is ~90% protein bound to serum proteins, has a median AUC_{ELF}:AUC_{serum} of ~0.30 [13].

The importance of determining ELF penetration before the performance of phase 2 and 3 clinical trials can be shown with ceftobiprole. After the initiation of phase 3 clinical trials, ceftobiprole PK properties were studied in human plasma and ELF. The median AUC_{ELF}:AUC_{serum} was found to be 0.153 [14], which was similar to that of ceftazidime (0.201) [11] and much less than that of cefepime (1.04) [12]. In phase 3 clinical trials, ceftobiprole was compared with ceftazidime plus linezolid in patients with HABP or VABP. Because of (1) the comparable ELF penetration of ceftobiprole and ceftazidime, (2) the comparable in vitro potency against Enterobacteriaceae of ceftobiprole and ceftazidime, (3) the daily ceftazidime dose being 4-fold greater than that of ceftobiprole (6 vs 1.5 g/day), and (4) the penetration of linezolid (median AUC_{ELF}:AUC_{serum}, 1.99) [9] into ELF to a much greater extent relative to ceftobiprole, one should have correctly predicted that the dosage of ceftobiprole would be insufficient and that the drug would be outperformed by ceftazidime plus linezolid, especially in patients with VABP.

The importance of early examination of tissue penetration in humans and in relevant animal species is shown by the penetration of ceftobiprole into ELF in murine pneumonia model studies. In this model, the plasma and ELF PK-PD targets associated with efficacy were virtually identical, and the median AUC_{ELF}:AUC_{serum} in mice was 0.69 [14]. As described above and shown by the plasma and ELF concentration-time profiles in Figure 4, the median AUC_{ELF}:AUC_{serum} in humans was later found to be only 0.153 [14]. Thus, bridging from mice to humans without consideration of human ELF data has the potential to produce a critical miscalculation about the drug exposure expected at the infection site.

It is also critical to recognize that drugs take time to obtain therapeutic concentrations at an infection site. In the 1980s, Fleishaker and McNamara [15] recognized that binding to serum proteins, particularly when binding is >90%, may have an impact on the rapidity with which therapeutic concentrations are reached. This point is well shown by oritavancin, a promising agent for treatment of gram-positive infections. The binding of oritavancin to human plasma proteins was >87%, whereas oritavancin is more extensively bound to mouse plasma proteins (95%). Because *Staphylococcus aureus* pneumonia was considered to be a potential indication, both murine and healthy volunteer ELF penetration studies were undertaken.

Figure 5 shows simulated murine and human oritavancin ELF concentration-time profiles over 120 h after drug administration [16]. In the neutropenic murine-pneumonia model, the exposures at 24 h were associated with efficacy. However, it is critical to note that, in humans, it took 96 h to reach the necessary exposures associated with efficacy. These data, therefore, suggested that, in patients with pneumonia, a very large loading dose would be needed to match the early and effective exposures achieved in animals. These data were critical to halting the program for oritavancin treatment of *S. aureus* pneumonia [16].

The take-home message from the aforementioned vignettes is that ELF penetration studies should be conducted before the selection of dosing regimens for HABP or VABP studies, particularly because patients with these types of pneumonia are often moribund and mortality rates are substantial. Because rodent pneumonia models are typically used to identify PK-PD exposure targets, which guide dosing regimen selection for

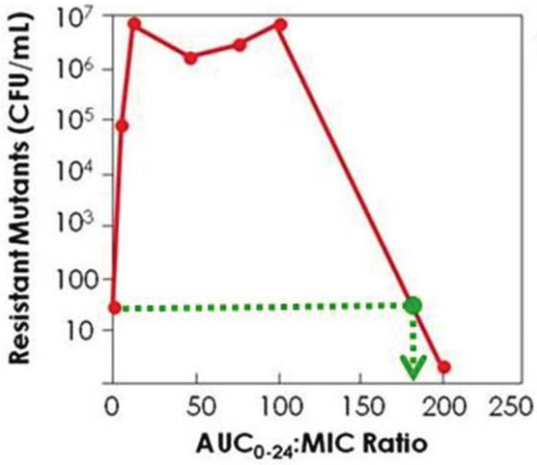

Figure 7. Data developed in the hollow fiber system, in which *Pseudomonas aeruginosa* responds to different degrees of antimicrobial pressure from a quinolone [19]. The figure shows the number of drug-resistant colonies identified after 48 h of varying magnitudes of drug exposure, mimicking that observed in humans. The green arrow indicates the area under the drug concentration–time curve at 0–24 h (AUC_{0-24}) to minimum inhibitory concentration (MIC) ratio (190) that prevents drug-resistance amplification (adapted from [19]).

Table 2. Free-Drug Area Under the Drug Concentration–Time Curve (AUC) to Minimum Inhibitory Concentration (MIC) Ratio and Clinical Response Rates, Stratified by Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Status, in 61 Tigecycline-Treated Patients with Sufficient Pharmacokinetic Data for Analysis and Who Were Clinically and Microbiologically Evaluable.

		Free-drug AUC_{0-24}:MIC			
Types of pneumonia	No. of patients	Mean ± SD	Median (range)	Proportion of patients cured (%)	Proportion of patients with treatment failure (%)
HABP	38	9.45 ± 12.0	5.69 (0.0490–54.1)	31/38 (82)	7/38 (18)
VABP	23	3.10 ± 4.03	1.14 (0.00557–16.1)	12/23 (52)	11/23 (48)

NOTE. As a result of having lower AUC_{0-24} and higher MIC values, the median AUC_{0-24}:MIC ratio for patients with VABP was 20% of that for patients with HABP, and patients with VABP had a much lower cure rate.

humans, and because the rate and extent of ELF penetration in rodents and humans can differ, an understanding of ELF penetration in animal infection models and humans is needed to make the best dosing regimen decisions. In other words, look before you leap!

THE SECOND HALF OF THE PK-PD EQUATION: THE MIC

In the article by Jones in this supplement [17], MIC statistics differ between patients with HABP and patients with VABP. Of note, *K. pneumoniae* (the third most common pathogen; causing 10% of HABP and/or VABP cases) is less susceptible across major drug classes in VABP than in HABP, *P. aeruginosa* (the second most common pathogen; 22% of cases) and *Acinetobacter* species (the fourth most common pathogen; 7% of cases) are less susceptible in VABP than in HABP, and lastly, *S. aureus* (the most common pathogen; 28% of cases), including methicillin-resistant *S. aureus,* are more susceptible in VABP than in HABP. The following question can be asked: could variations in MICs in patient subpopulations have adversely affected outcomes in recent HABP and VABP programs?

Figure 6 shows the MIC distribution for 61 tigecycline-treated patients, stratified by HABP and VABP status, who had sufficient PK data for analysis and who were clinically and microbiologically evaluable [18]. Of note, MICs of baseline pathogens in patients with VABP were systematically higher than those in patients with HABP. MICs ⩾16 mg/L were present in infections due to *P. aeruginosa,* MICs of 1 and 2 mg/L were present in pneumonia due to *K. pneumoniae* and *Acinetobacter* species.

Table 1 shows tigecycline exposure, as measured by steady-state AUC_{0-24}, in 123 patients stratified by HABP and VABP. Of note, drug exposure in patients with VABP is considerably lower than that in patients with HABP [18]. When the MICs in patients (Figure 6) are integrated with their respective steady-state free-drug AUC_{0-24} values, corrected for protein binding, it is obvious that patients with VABP had much lower steady-state AUC_{0-24}:MIC values and corresponding lower cure rates (Table 2) [18]. Nine (56%) of 16 patients with free-drug AUC:MIC values ⩽1.14 experienced therapy failure (7 of 12 patients with VABP and 2 of 4 patients with HABP), and only 9 (20%) of 45 patients with free-drug AUC:MIC values >1.14 experienced therapy failure ($P = .01$) [18].

From this vignette, it is apparent that many key pathogens tend to be less susceptible to drug in patients with VABP than in patients with HABP. This is a major contributor to lower PK-PD indices in patients with VABP, and thus, prospective consideration of patient population differences in the in vitro susceptibility distributions is required. Current surveillance databases need to be expanded to effectively capture this objective. In other words, look before you leap!

PREVENTING THE EMERGENCE OF DRUG RESISTANCE

Amplification of drug resistance has been related to exposure in the shape of an inverted U [19]. Figure 7 is derived from data developed in the hollow fiber system, in which *P. aeruginosa* responds to different degrees of antimicrobial pressure from a quinolone [20]. This figure shows the number of drug-resistant colonies identified after 48 h of varying magnitudes of drug exposure, mimicking that observed in humans. The first point, at zero AUC_{0-24}:MIC, is the number of drug-resistant colonies present at therapy initiation. Of note, as the AUC_{0-24}:MIC increases, the number of recovered drug-resistant mu-

Table 3. Penetration of Levofloxacin, Tigecycline, and Ceftobiprole into Epithelial Lining Fluid (ELF).

Drug	Study	Median AUC_{ELF}:AUC_{serum} (5th–95th percentile)
Levofloxacin	[10]	1.43 (0.14–19)
Tigecycline	[21]	1.15 (0.56–5.2)
Ceftobiprole	[14]	0.153 (0.035–78.7)

NOTE. The magnitude of ELF penetration at the lower margin (5th percentile) can be very small.

tants increases until a plateau of $1 \times 10^{6.5-7}$ is reached over an AUC_{0-24}:MIC range of 10–137. An AUC_{0-24}:MIC ≥190 results in suppression of amplification of the drug-resistant subpopulation. When variability in ELF penetration (especially that at the lower bound of the 95% confidence interval) (Table 3) and the high exposures needed to prevent drug-resistance amplification are considered, there is an inescapable conclusion. Simply put, it is impossible to prevent drug-resistance amplification with monotherapy by using safe dosing regimens in patients with HABP or VABP. Combination therapy is essential to get over the hump of the inverted U. However, it is unknown whether combination intravenous drug therapy penetration is colinear in patients. If so, combination intravenous therapy is unlikely to drastically improve the situation, and other solutions, perhaps adjunctive inhalational antimicrobial therapy, will be required.

THE PATH FORWARD

Poor decisions for selection of dosing regimens were likely to have been the major contributor to recent unsuccessful drug development programs for the indications of HABP and VABP. Clearly, the lower drug exposures, which result from lower AUC and higher MIC values in patients with VABP, compared with patients with HABP, suggest that larger doses are required. There is good news, however, in that this problem may be remedied, if we look before we leap, and inform dosing regimen decisions by prospectively considering (1) the target patient population demographic and laboratory data, (2) penetration into the infection site, (3) differences with respect to in vitro drug-susceptibility distributions in patient populations, and (4) the use of simulation to compare the PK-PD profile of the challenge regimen with that of the standard regimen.

Although not prospectively required by regulatory agencies before initiating pursuit of each indication, sponsors should raise the bar and establish an early and clear dosing regimen rationale document for each indication pursued. This document should explicitly include details of the clinical plan, targeted patients, safety, efficacy, and other relevant scientific considerations and the PK and PK-PD rationale for the proposed dosing regimens. This is a small yet reasonable effort that will greatly reduce risk to sponsors and, most importantly, to the patients enrolled in the clinical trials.

Acknowledgments

Potential conflicts of interest. P.G.A. has served as a consultant to and received grants from Cerexa, Peninsula Pharmaceuticals, and Wyeth Research and is a Special Government Employee, serving as a pharmacology consultant, with the Department of Health and Human Services, Public Health Services, and Food and Drug Administration. S.M.B. has received grants from Cerexa, Peninsula Pharmaceuticals, and Wyeth Research. E.J.E.-G. is a former employee of Wyeth/Pfizer and has served as a consultant to companies that have developed and/or are developing antibacterials for ventilator-associated bacterial pneumonia and/or hospital-acquired bacterial pneumonia. G.L.D. received an educational grant from Johnson & Johnson Research and Development for the mathematical analysis of ceftobiprole epithelial lining fluid penetration.

Supplement sponsorship. This article was published as part of a supplement entitled "Workshop on Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia," sponsored by the US Food and Drug Administration, Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and the Society of Critical Care Medicine, with financial support from the Pharmaceutical Research and Manufacturers of America, AstraZeneca Pharmaceuticals, and Forest Pharmaceuticals.

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