The Antimicrobial Therapy Puzzle: Could Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients?

Federico Pea and Pierluigi Viale

1Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, and 2Clinic of Infectious Diseases, Department of Medical and Morphological Research, Medical School, University of Udine, Udine, Italy

Until recently, the in vitro susceptibility of microorganisms was considered the only fundamental aspect for antibiotic efficacy in treating pneumonia. However, the relevance of pharmacokinetic-pharmacodynamic relationships in optimizing drug exposure has been progressively highlighted. Antimicrobial agents were divided into concentration-dependent or time-dependent groups, with the most consistently relevant pharmacodynamic parameters for efficacy being either the ratio of the plasma peak concentration to the minimum inhibitory concentration or the time the plasma concentration persists above the minimum inhibitory concentration of the etiological agent, respectively. For the adequate treatment of pneumonia, optimal pharmacodynamic exposure should be ensured also at the infection site. To investigate this, a methodologically correct approach may be to detect drug concentration levels in the epithelial lining fluid and in the alveolar macrophages for extracellular and intracellular pathogens, respectively. From this perspective, the pharmacokinetic factors—only in some instances—support the achievement of optimal exposure during the treatment of pneumonia with fixed standard dosing regimens of antimicrobials; conversely, in other instances, the pharmacokinetic factors suggest the need for an implemented dosage regimen or even the choice of a different drug.

Careful and detailed policies for wise antibiotic use should be accurately implemented hospital-wide, with the double intent of maximizing clinical outcome in a single patient and preventing the environmental spread of resistance [1]. Inappropriate empirical therapy in patients with severe infections was significantly associated with increased mortality rate, regardless of the either the site of infection or the bacterial pathogens involved [2, 3]. These findings seem to support the primary role of a patient's status as a major factor influencing clinical outcome. Exemplary is the work of Lodise et al. [4], a retrospective cohort analysis of 167 episodes of Staphylococcus aureus bloodstream infection that showed that delayed antimicrobial therapy significantly increased the risk of infection-related mortality only in critically ill patients with APACHE II severity scores of $\geq 15.5$.

As far as pneumonia is concerned, the major role of severity scores and functional status of the patient as predictors of mortality were recently confirmed in patients with community-acquired pneumonia [5]. Additionally, the pivotal role of appropriate antimicrobial coverage has been well recognized. Hanes et al. [6] showed that inadequate empirical antimicrobial therapy was significantly associated with reduced survival rate ($P = .02$) in patients with severe Stenotrophomonas maltophilia–related ventilator-associated pneumonia (VAP). Even the number of episodes of illness with inappropriate treatment was recently found to significantly affect the mortality rate for VAP [7]. Conversely, the influence of timing of antibiotic administration on clinical success rates in community-acquired pneumonia is still debated, the delay of the administration of the first in-hospital antibiotic dose being either associated [8, 9] or not associated [5, 10] with an increased mortality rate.
The full meaning of “appropriate antimicrobial therapy” should be better defined. In the literature, most of the evidence-based studies consider appropriateness mainly in terms of antimicrobial coverage. Of note, most of these fixed dosing regimens were administered regardless of the infection site and patients’ pathophysiological conditions (apart from the empyema functions). Additionally, very few studies, if any, tried to correlate the clinical outcome to antimicrobial exposure at the infection site. Therefore, it may be reasonably supposed that some of the unsuccessful treatments might have occurred because of underexposure. Rello et al. [11] retrospectively showed that, despite appropriate therapy with glycopeptides, an increased attributable mortality occurred in patients with VAP due to oxacillin-resistant S. aureus (VAP-ORSA), compared with matched intubated control subjects without VAP-ORSA. The poor pulmonary penetration of glycopeptides was supposed to be responsible for this disappointing result, but, interestingly, the mortality risk in the VAP-ORSA patients receiving vancomycin by means of continuous infusion was not increased. This highlights the relevant importance of maximizing exposure at the infection site [12].

Indeed, antimicrobial therapy in critically ill patients may seem like a puzzle composed of several different pieces that must merge together to ensure both clinical cure and prevention of resistance spread (figure 1). In the recent past, the in vitro antimicrobial susceptibility patterns of the microorganisms assessed by means of the interaction between the bacterial pathogen in standard growth cultural conditions and the antimicrobial agent at the MIC was the only major factor guiding the antimicrobial choice. Although fundamental, this might not suffice for optimal cure, because 2 other pieces may be at least of similar importance. These effective concentrations should also be ensured at the infection site, and in critically ill patients, this may be a very difficult goal to achieve, considering that several pathophysiological conditions that alter drug disposition may often require higher dosages than what is currently recommended [13].

The starting point for appropriate exposure to antimicrobials must be considered to be the administration schedule that is consistent with the drugs’ intrinsic pharmacodynamic characteristics. Better understanding of pharmacokinetic-pharmacodynamic relationships and the pattern of bactericidal activity enable the defining of the best dosing regimen for each of the different classes of antimicrobial agents. β-Lactams, glycopeptides, and oxazolidinones exhibit time-dependent activity, so the time that the plasma concentration (t) persists above the MIC of the etiological agent (t>MIC) is considered the major determinant for efficacy. Although t>MIC should be 50%–60% of the dosing interval for standard efficacy [14], it should increase to 100% in immunocompromised patients, efficacy improving only slightly with concentrations 4–5-fold the MIC [15]. Because of the poor postantibiotic effect against gram-negative microorganisms (except for carbapenems) [16], very low trough levels dropping to less than the MIC should be avoided, with the intent of preventing bacterial regrowth and breakthrough resistance. Accordingly, we believe that the maintenance of plasma trough level (C_{min}) above the MIC (C_{min}>MIC) should be considered the optimal goal for time-dependent agents. The shorter the drug elimination half-life, the more frequent the dose fractioning must be. Additionally, the application of intravenous continuous infusion, which ensures the highest steady-state concentration under the same total daily dosage, may be the most effective way of maximizing pharmacodynamic exposure with time-dependent agents [17].

On the other hand, fluoroquinolones and aminoglycosides are concentration-dependent agents whose efficacy is mainly related to the plasma peak concentration (C_{peak}) to MIC ratio (C_{peak}/MIC) and to the area under the plasma concentration versus time curve (AUC) to MIC ratio (AUC/MIC). Whereas the AUC/MIC threshold for maximal efficacy should be 100–125 against gram-negative bacteria [18], a value of 30–40 might suffice against gram-positive bacteria [19]. Importantly, a C_{peak}/MIC ratio of 10–12 was shown to ensure clinical cure and prevent resistance to these agents [20]. Unlike time-dependent agents, sub-MIC trough levels at the end of the dosing interval may be allowed, considering that most aminoglycosides and fluoroquinolones exhibit valid postantibiotic effects against both gram-positive and gram-negative bacteria [21]. Because of this, once-daily dosing with concentration-dependent antibiotics should be preferred whenever possible, with the intent of achieving the highest peak plasma level.
The correct application of pharmacokinetic-pharmacodynamic principles may surely improve appropriate antimicrobial use, but this might not suffice for optimal cure of pneumonia, if appropriate exposure is not also ensured at the infection site as well as in plasma.

A shared, methodologically correct approach to the investigation of drug exposure in the lungs of humans after systemic administration of antimicrobials is the detection of drug levels in the epithelial lining fluid (ELF) for the extracellular respiratory pathogens (the most frequent bacterial etiological agents of pneumonia) or in the alveolar macrophages for the intracellular respiratory pathogens (Legionella pneumophila or Chlamidia pneumoniae) by means of bronchoalveolar lavage.

Although most of the pharmacokinetic-pharmacodynamic studies of antibiotics in pneumonia are currently based on serum concentrations, it could be argued that achievement of optimal pharmacodynamic exposure in ELF and/or in alveolar macrophages (i.e., $C_{\min}/MIC$ for time-dependent agents and $C_{\max}/MIC > 10$ for concentration-dependent agents) could be useful predictor for appropriate pneumonia treatment.

Interestingly, antimicrobials may exhibit significantly different pharmacokinetic behavior in the lung compartments consistent with their physicochemical properties (figure 2). Hydrophilic agents, such as β-lactams, glycopeptides, and aminoglycosides, are unable to passively diffuse through the plasmatic membrane of the eukaryotic cells so that, from a pharmacodynamic point of view, they are inactive against the intracellular pathogens, and from a pharmacokinetic point of view, they exhibit extracellular limited distribution and major renal elimination as unmodified drugs. Conversely, lipophilic agents—namely, macrolides, most fluoroquinolones, tetracyclines, chloramphenicol, rifampicin, and oxazolidinones—by freely crossing the membranes, are characterized from a pharmacodynamic point of view by their activity against the intracellular pathogens and from a pharmacokinetic point of view by wide distribution with intracellular accumulation. Additionally, they have often to undergo metabolism through different pathways, mainly in the liver, to become more easily eliminable from the body.

As a general rule, lipophilic compounds may achieve higher levels in ELF, compared with hydrophilic compounds, and are the only compounds able to significantly accumulate in alveolar macrophages (table 1). Here, we report some examples analyzing the clinical implications these differences in pulmonary disposition might have.

After a single 1-g intravenous dose, meropenem concentrations in the ELF of healthy volunteers were lower than the corresponding plasma levels, with mean values (mean concentration, 0.59 mg/L) dropping significantly below the MIC$_{90}$ for both $Pseudomonas aeruginosa$ and $Streptococcus pneumoniae$ just 6 h after administration [23]. In our opinion, these findings support the opportunity of administering a dose every 6 h rather than every 8 h to ensure better pharmacodynamic exposure with meropenem during pneumonia.

Boselli et al. [22] simultaneously assessed plasma and ELF exposure to ceftazidime in patients receiving 4 g per day intravenously by continuous infusion for the treatment of severe nosocomial pneumonia. Interestingly, although this dosing regimen enabled maximized pharmacodynamic exposure in plasma by ensuring steady-state concentrations 4–5-fold the MIC breakpoint for $P. aeruginosa$ (32–40 mg/L), this was not the case in ELF, for which concentrations $\leq$ 8 mg/L were observed in 8 (53%) of 15 patients. These findings suggest that this hydrophilic antipseudomonal compound, despite its very
### Table 1. Pulmonary disposition of some antimicrobial agents.

<table>
<thead>
<tr>
<th>Antimicrobial agent (dosage)</th>
<th>Concentration levels at different time points, h</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ELF, mg/L</td>
<td>ELF-to-plasma ratio</td>
</tr>
<tr>
<td></td>
<td>0.5 1 2 4 6 8 12 24 48</td>
<td>0.5 1 2 4 6 8 12 24 48</td>
</tr>
</tbody>
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#### Hydrophilic agents
- **Ceftazidime (4g/day CI)**
  - Concentration: 8.2, 8.2, 8.2, 8.2, 8.2, 8.2, 8.2, 8.2, 8.2
  - ELF-to-plasma ratio: 0.21, 0.21, 0.21, 0.21, 0.21, 0.21, 0.21, 0.21, 0.21
  - Reference: [22]

- **Meropenem (1g)**
  - Concentration: 5.04, 7.07, 3.86, 2.20, 0.59
  - ELF-to-plasma ratio: 0.19, 0.51, 0.33, 1.04, 0.82
  - Reference: [23]

- **Vancomycin (15 mg/kg)**
  - Concentration: 4.5, 4.5, 4.5, 4.5, 4.5, 4.5, 4.5, 4.5, 4.5
  - ELF-to-plasma ratio: 0.19, 0.19, 0.19, 0.19, 0.19, 0.19, 0.19, 0.19, 0.19
  - Reference: [24]

#### Lipophilic agents
- **Linezolid (600mg every 12 h)**
  - Concentration: 64.3, 31.4, 24.3, 7.60, 0.7
  - ELF-to-plasma ratio: 4.15, 3.53, 2.38, 4.22, 3.5
  - Reference: [25]

- **Linezolid (600 mg every 12 h)**
  - Concentration: 14.4
  - ELF-to-plasma ratio: 1.05, 1.04
  - Reference: [26]

- **Levofloxacin (500 mg every 24 h)**
  - Concentration: 17.8, 11.9
  - ELF-to-plasma ratio: 1.27, 1.31
  - Reference: [27]

- **Azithromycin (500 mg LD, 250 mg every 24 h)**
  - Concentration: 1.01, 2.18
  - ELF-to-plasma ratio: 12.62, 24.22
  - Reference: [28]

- **Clarithromycin (500 mg every 12 h)**
  - Concentration: 34.5, 26.1, 15.1, 4.60
  - ELF-to-plasma ratio: 17.25, 16.84
  - Reference: [29]

**NOTE**
- AM, alveolar macrophages; CI, continuous infusion; ELF, epithelial lining fluid; LD, loading dose.
- Steady-state.
- Dosage adjusted by means of therapeutic drug monitoring.
- Median concentration level.
low plasma protein binding, may only partially diffuse in ELF (mean ELF-to-plasma ratio, 0.21), so that in the empirical treatment of patients at very high risk for \textit{P. aeruginosa}–related pneumonia, higher dosages (6 g per day intravenously by continuous infusion) should be administered with the intent of maximizing efficacy.

The assessment of the relationship between ELF and plasma concentrations of vancomycin after systemic administration in 14 critically ill patients with VAP highlighted that mean ELF penetration was $\sim 20\%$, with ELF and plasma levels averaging 4.5 mg/L and 24.0 mg/L, respectively [24]. Accordingly, it may be speculated that in the presence of vancomycin trough plasma concentrations in the currently recommended therapeutic window (10–15 mg/L), optimal pharmacodynamic exposure in ELF may be expected only against fully susceptible bacterial strains with MIC values $\leq 1–2$ mg/L. Conversely, in the presence of pathogens with MICs near the susceptibility breakpoint (4–8 mg/L), plasma trough concentrations much higher than what is currently advised (30–35 mg/L) should be maintained, with the intent of maximizing exposure in ELF. Interestingly, a clear relationship between the MICs of clinical methicillin-resistant \textit{S. aureus} (MRSA) isolates and the efficacy of vancomycin for the treatment of MRSA-related bacteremia was recently highlighted [30]. Particularly, whereas the successful rate against MRSA isolates with an MIC $<0.5$ mg/L was 55%, it decreased to 9.5% in the presence of bacterial strains with MICs of 1–2 mg/L, suggesting that standard vancomycin dosages might be clinically unsuccessful for the treatment of infections due to intermediate susceptible MRSA.

On the contrary, linezolid, a moderately lipophilic compound, was shown to achieve much higher levels in the ELF of both healthy volunteers and patients. Conte et al. [25] demonstrated in healthy volunteers that the steady-state pharmacokinetic behavior of linezolid in ELF was similar to that observed in plasma. ELF-to-plasma ratios at different time intervals after administration always averaged $>2$, and the mean ELF trough value at the end of the 12-h dosing interval (24.3 mg/L) was 6-fold higher than the MIC$_{90}$ for MRSA. The optimal pharmacodynamic exposure to linezolid was very recently shown in 16 patients with VAP treated with 600 mg intravenously every 12 h [26]. Steady-state peak and trough ELF-to-plasma ratios, averaging 1.05 and 1.04 respectively, confirmed that, even in patients with VAP, this antimicrobial agent may achieve similar levels simultaneously in plasma and in ELF. The achieved mean ELF trough value (2.6 mg/L) might predict effective pharmacodynamic exposure against most of the susceptible pathogens.

Indeed, a frequently unanswered question in the treatment of MRSA-related VAP is when is it better to use linezolid: as a rescue therapy after failure with glycopeptides or as a first-
line option? The very favorable pulmonary pharmacokinetic characteristics surely would support the latter hypothesis. Additionally, this would be consistent with the data of Wunderink et al. [31], who retrospectively analyzed the results of 2 prospective, randomized, double-blind studies comparing linezolid and vancomycin in the treatment of VAP. They showed that, in patients with MRSA-related pneumonia, the former was associated with significantly better clinical cure rates (62.2% vs. 21.2%; P < .001). Indeed, 2 methodological limitations might have affected the relevance of the conclusions of this study: (1) the retrospective nature of the study design that analyzed 2 noninferiority trials, and (2) the choice of an administration schedule for vancomycin (every 12 h), which likely may be suboptimal for pneumonia treatment [12]. Conversely, these results should stimulate a discussion about the opportunity of redefining the pattern of clinical efficacy of vancomycin at standard dosages against MRSA-related pneumonia. In fact, with the current in vitro microbiological breakpoint of susceptibility, it is likely that the poor disposition of vancomycin in ELF may cause a situation of clinical resistance even in the presence of S. aureus strains microbiologically labeled as susceptible. Therefore, while waiting for the result of a superiority trial, the role of linezolid in the treatment of MRSA-related pneumonia still remains to be defined, considering that wise use of oxazolidinones is recommended with the intent of preventing the spread of resistance.

We would like to propose the weighted algorithm that we usually apply at our university hospital as a suitable option for treating MRSA-related pneumonia (figure 3). In this algorithm, vancomycin is suggested for treatment when fully susceptible pathogens are involved (MIC, ≤0.5 mg/L). Conversely, linezolid is used against MRSA strains when the MIC values for vancomycin is ≥1 mg/L, considering that, despite theoretical in vitro susceptibility, these levels may be very difficult to consistently achieve in ELF using vancomycin with the currently recommended plasma levels.

Similarly, in critically ill patients with severe community-acquired pneumonia, levofloxacin—another moderately lipophilic drug—showed high penetration rates in ELF; the steady-state ELF-to-plasma ratios 1 h after intravenous administration of a 500-mg dose every 24 h and every 12 h were always >1 [27]. Considering that 1 mg/L is the MIC<sub>90</sub> against S. pneumoniae and the MIC<sub>90</sub> against P. aeruginosa, levofloxacin C<sub>max</sub> in ELF should be at least 10 mg/L to ensure and ELF C<sub>max</sub>/MIC ratio ≥10. Interestingly, the mean C<sub>max</sub> in ELF was 11.9 mg/L with the 24-h dosing schedule and 17.8 mg/L with the 12 h dosing schedule, whereas the threshold of 10 mg/L was always exceeded with the 12-h dosing schedule. Conversely, this did not happen with the 24-h dosing schedule. This suggests that, in critically ill patients with severe pneumonia, the 12-h dosage regimen might ensure more appropriate exposure.

Overall, the lower ELF concentrations and ELF-to-plasma ratios exhibited by the hydrophilic antimicrobials seem to support the hypothesis that dosages higher than what is needed for the treatment of bacteremia could be advisable when treating pneumonia with these agents to ensure optimal pharmacodynamic exposure at the infection site.

Conversely, extremely high concentrations in alveolar macrophages are always achieved by fluoroquinolones and macrolides after systemic administration, thanks to their lipophil-
icity. Interestingly, their intracellular accumulation may ensure levels several tens of times higher than the MIC90 of the involved pathogens (table 1). Consistent with this, high cure rates are usually observed when treating pneumonia due to intracellular pathogens with these drugs, especially fluoroquinolones, which are true concentration-dependent agents. An exhaustive comparative study between fluoroquinolones and macrolides in the treatment of legionnaires disease was recently performed, where, in a contest of excellent efficacy, time to apirexia was significantly shorter in the fluoroquinolone group (77.1 h vs. 48 h in the macrolide group; \( P = .000 \)) [32]. Additionally, drug underexposure in the ELF of critically ill patients during pneumonia treatment might sometimes be related to peculiar pathophysiological conditions (the last piece of the antimicrobial therapy puzzle) if these conditions are not appropriately taken into account. Variations in the extracellular fluid content and/or in renal function are the most relevant and frequent pathophysiological mechanisms possibly affecting drug disposition in critically ill patients [13]. In contrast with healthy volunteers or non–critically ill patients, by altering distribution and/or elimination processes, some of these situations may promote significant changes of drug disposition, even in the brief period of hours. Of note, hydrophilic antibiotics (e.g., \( \beta \)-lactams, aminoglycosides, and glycopeptides) and renally excreted, moderately lipophilic antibiotics (e.g., ciprofloxacin, gatifloxacin, and levofloxacin) have to be considered as having a much higher risk of exhibiting substantial daily fluctuations of plasma concentrations that may require repeated subsequent dosage adjustments in a single patient [13]. An algorithm of the possible causes affecting the pharmacokinetic behavior of antibiotics in critically ill patients is depicted in figure 4.

As an example, we report 2 of our recent experiences concerning levofloxacin in the treatment of lower respiratory tract infection [33, 34]. Of note, to ensure comparable total daily plasma exposure to levofloxacin in terms of AUCs in intensive care unit patients with early-onset VAP (67.80 mg \( \times \) h per L) versus elderly stable patients with lower respiratory tract infection (74.97 mg \( \times \) h per L) a double daily dose had to be administered (500 mg every 12 h instead of every 24 h). This was related to an almost doubled renal clearance in intensive care unit patients (3.40 vs. 1.87 mL/min per kg) due to an enhanced renal blood flow caused by hyperdynamic sepsis and/or cotreatment with hemodynamically active drugs [35]. This is consistent with renal clearance being shown as the major responsible factor for the pharmacokinetic variability of levofloxacin [20].

Finally, it is worth noting that even incongruous prescribing habits of physicians might promote the failure of antimicrobial treatment and the spread of resistance. An interesting example was recently reported in the literature. It is well known that the optimal oral bioavailability of fluoroquinolones may be significantly decreased by 50%–90% as a consequence of improper coadministration with divalent or trivalent cation–containing drugs. Barton et al. [36] retrospectively assessed the coadministration rate of divalent or trivalent cation–containing drugs among patients receiving oral levofloxacin during a 2-year period in a 625-bed university hospital. They observed that 3227 levofloxacin doses in 997 patients were complicated by at least 1 coadministration. Additionally, limiting the analysis to those patients receiving at least 5 different divalent or trivalent cation–containing drugs in the same day of treatment, they observed that 386 courses of levofloxacin in 397 patients were complicated by at least 1 true coadministration and assumed that this extremely common prescribing error might cause both clinical failure and resistance to fluoroquinolones. When the authors subsequently analyzed the same cohort for a nested case-control study assessing fluoroquinolone breakthrough resistance, they found a significant relationship between the appearance of fluoroquinolone-resistant isolates and the number of days with levofloxacin diveral or trivalent cation–containing coadministrations, thus confirming the negative impact this improper practice may have on resistance spread in the clinical setting [37].

In conclusion, it is indubitable that the choice of the antimicrobial agent for treating pneumonia should be based on several clinical aspects (e.g., risk factors and severity of disease), epidemiological aspects (e.g., selective pressure), and drug-related aspects (e.g., pharmacokinetic drug-drug interactions and acquisition costs), but in any instance, the application of the most appropriate dosage according to pharmacokinetic-pharmacodynamic principles, the infection site and the patient’s pathophysiological status may be of paramount importance for achieving clinical cure and containing the spread of resistance.

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