**Steady-State Intrapulmonary Concentrations of Moxifloxacin, Levofloxacin, and Azithromycin in Older Adults**

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**Study objective:** To determine the steady-state, extracellular, and intracellular pulmonary disposition of moxifloxacin (MXF), levofloxacin (LEVO), and azithromycin (AZI) relative to that of the plasma over a 24-h dosing interval.

**Design:** Randomized, multicenter, open-label investigation.

**Patients:** Forty-seven older adults (mean ± SD age, 62 ± 13 years) undergoing diagnostic bronchoscopy.

**Interventions:** Oral administration of MXF, 400 mg, LEVO, 500 mg daily for five doses, or AZI, 500 mg for one dose, then 250 mg daily for four doses. BAL and venipuncture were completed at 4, 8, 12, or 24 h following the administration of the last dose.

**Measurements and results:** Steady-state MXF, LEVO, and AZI concentrations were determined in the plasma, epithelial lining fluid (ELF), and alveolar macrophages (AMs). The concentrations of all three agents were greatest in the AMs followed by the ELF compared to the plasma. Plasma concentrations were similar to those previously reported with these agents. The mean ELF concentrations at 4, 8, 12, and 24 h were as follows: MXF, 11.7 ± 11.9, 7.8 ± 5.1, 10.5 ± 3.7, and 5.7 ± 6.3 µg/mL, respectively; LEVO, 15.2 ± 4.5, 10.2 ± 6.7, 6.9 ± 4.4, and 2.9 ± 1.7 µg/mL, respectively; and AZI, 0.6 ± 0.4, 0.7 ± 0.4, 0.9 ± 0.5, and 0.9 ± 0.7 µg/mL, respectively. The AM concentrations at 4, 8, 12, and 24 h were as follows: MXF, 47.7 ± 47.6, 123.3 ± 126.4, 26.2 ± 19.4, and 32.8 ± 16.5 µg/mL, respectively; LEVO, 28.5 ± 30.2, 26.1 ± 15.7, 28.3 ± 12.6, and 8.2 ± 6.1 µg/mL, respectively; and AZI, 71.8 ± 50.1, 73.8 ± 75.3, 155.9 ± 81.3, and 205.2 ± 256.3 µg/mL, respectively.

**Conclusions:** The intrapulmonary concentrations of MXF, LEV, and AZI were superior to those obtained in the plasma. The AM concentrations of all agents studied were more than adequate relative to the minimum concentration required to inhibit 90% of the organism population (MIC_{90}) of the common intracellular pathogens (< 1 µg/mL). These data indicate that attainable extracellular concentrations of AZI are insufficient to reliably eradicate Streptococcus pneumoniae, based on the agent’s current minimum inhibitory concentration profile, whereas the mean concentrations of MXF and LEVO in the ELF exceed the MIC_{90} of the S pneumoniae population. Moreover, MXF concentrations exceeded the S pneumoniae susceptibility breakpoint (1.0 µg/mL) at all time points, while 2 of 15 concentrations (13%) failed to maintain LEVO concentrations above the breakpoint (2.0 µg/mL) throughout the dosing interval.

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**Key words:** azithromycin; fluoroquinolones; levofloxacin; moxifloxacin; penetration; pharmacokinetics; pulmonary

**Abbreviations:** AM = alveolar macrophage; AUC = area under the concentration-time curve; AZI = azithromycin; CARTI = community-acquired respiratory tract infection; %CV = percentage coefficient of variation; ELF = epithelial lining fluid; HPLC = high performance liquid chromatography; LEVO = levofloxacin; MIC = minimum inhibitory concentration; MIC_{90} = minimum concentration required to inhibit 90% of the organism population; MXF = moxifloxacin

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The optimal management of infection requires adequate concentrations of an antimicrobial agent at the site of infection in order to maximize the interaction between the agent and the microorganism. When considering lower respiratory tract infections, the epithelial lining fluid (ELF) and alveolar macrophage (AM) are accepted as the intrapulmonary sites that best depict the extracellular and intracellular exposure of the antimicrobial agents.
intracellular “drug-bug” interaction, respectively.\textsuperscript{1–6} \textit{Streptococcus pneumoniae}, \textit{Moraxella catarrhalis}, and \textit{Haemophilus influenzae} are the predominant extracellular pathogens, and \textit{Mycoplasma pneumoniae}, \textit{Chlamydia pneumoniae}, and \textit{Legionella pneumophila} are the predominant intracellular pathogens associated with community-acquired lower respiratory tract infections. Therefore, maximum therapeutic effectiveness against these pathogens requires that the concentration of the chosen agent be maintained in concentrations that well exceed the minimum inhibitory concentration (MIC) of the respective pathogen at the appropriate extracellular or intracellular site.

The intrapulmonary penetration of levofloxacin (LEVO), a fluoroquinolone, and azithromycin (AZI), a macrolide, has been established in previous studies, mainly involving healthy volunteers. Both of these agents have been utilized extensively for the management of community-acquired respiratory tract infections (CARTIs), and have been proven to achieve superior concentrations in the ELF and AM compared to plasma.\textsuperscript{2–7}

Moxifloxacin (MXF)\textsuperscript{3} is an 8-methoxy fluoroquinolone that is also indicated for the treatment of CARTIs. A previous study\textsuperscript{8} revealed the extensive penetration of MXF in the respiratory tract, however, these data were collected after a single dose and do not adequately characterize the intrapulmonary pharmacokinetic profile of this agent when a multiple-day regimen is utilized. Therefore, the objective of this study was to define the pulmonary disposition of MXF at steady state against that of LEVO and AZI, in older adults undergoing diagnostic bronchoscopy.

**Materials and Methods**

**Study Design and Setting**

This was a randomized, prospective, open-label investigation conducted at three centers, including Hartford Hospital (Hartford, CT), the Veterans Affairs Medical Center (Providence, RI), and Rhode Island Hospital (Providence, RI). The study protocol and informed consents were reviewed and approved by the investigational review board of each study site.

**Study Subjects**

Outpatients scheduled to undergo diagnostic bronchoscopy were considered for enrollment. The subjects were required to provide written informed consent, to be at least 18 years of age, and to be capable of self-administering medications. A prestudy evaluation, including a complete medical history, physical examination, and baseline laboratory testing, was performed in all subjects. The laboratory tests consisted of a CBC count with differential cell count, a platelet count, urinalysis, and measurement of BUN, serum creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels. Serum pregnancy tests were performed for female patients of child-bearing potential. Exclusion criteria consisted of the following: an allergy to fluoroquinolone or macrolide agents; a surgical or medical condition that would potentially interfere with GI absorption, motility, or pH; the receipt of concomitant therapy with medications known to induce the cytochrome P-450 enzyme system; concomitant therapy with medications that prolong the QTc interval; a congenital history of QT interval prolongation; the receipt of an antimicrobial agent within 7 days; clinically significant abnormal laboratory values, as assessed by the study investigators; chronic suppressive or diffuse inflammatory lung disease; and pregnancy or lactation among women.

Once enrolled, subjects were randomized to receive one of the following: MXF, 400 mg once daily for five doses; LEVO, 500 mg once daily for five doses; or AZI, 500 mg orally for one dose, followed by 250 mg daily for four doses. The last dose of each antibiotic was administered at 4, 8, 12, or 24 h prior to the scheduled bronchoscopy procedure. All doses were taken according to verbal and written instructions, and dose administration was documented in a subject diary. Study medication compliance and adverse events were assessed through daily phone interviews of subjects by study personnel. The findings of the completed poststudy physical examination and laboratory tests were identical to those performed on enrollment.

**Bronchoscopy and BAL**

The study subjects underwent a standard diagnostic bronchoscopy, as part of their routine medical care, during which a BAL and venipuncture were performed for the purpose of this study. Following a fasting period of at least 6 h, the subjects were prepared for bronchoscopy with lidocaine administered by aerosolized nebulization, sprayed into the nares and oropharynx, and with the application of 2% lidocaine jelly into the nasal passage-way. The subjects underwent conscious sedation with IV injection of diazepam, 5 to 7 mg, or midazolam, 2 mg, as needed. The BP, pulse, respiratory rate, and oxygen saturation were monitored throughout the procedure. A 10-mL blood sample was collected immediately prior to the start of the bronchoscopy procedure for the purpose of drug assay.

A fiberoptic bronchoscope was inserted via an anterior nare into a middle segment of the right middle lobe of the lung. A total of four 30-mL aliquots of normal saline solution were instilled separately and were immediately aspirated into a trap. The first aspirate was discarded, the second through fourth aspirates were pooled (BAL fluid), and the total volume was recorded.

**Specimen Processing**

Approximately 4 mL pooled BAL fluid was divided into two independent samples and was sent to the clinical laboratory for
the determination of total leukocyte count and differential cell count. The average of these two determinations was used in all subsequent calculations. The remainder of the pooled BAL fluid sample was placed on ice until centrifugation at 400g for 10 min. The supernatant was separated from the cell pellet, and both were stored at −80°C for future in drug assays and urea level determination. The blood sample was placed on ice and subsequently was centrifuged at 1,000g for 10 min, and the resultant plasma was stored at −80°C for use in future drug and urea assays.

**Antimicrobial and Urea Concentration Determinations**

Plasma and BAL fluid samples were assayed for MFX, LEVO, and AZI concentrations using validated high-performance liquid chromatography (HPLC) techniques.3 The BAL fluid and plasma samples were extracted directly, while the cell pellet was resuspended to a total volume of 5% of the recovered BAL fluid volumes with a sodium phosphate buffer (pH 8). All cell samples were placed through three freeze-thaw cycles and were vortexed prior to the extraction to ensure the full release of their intracellular contents.

For the MXF assay, a pump (model 515; Waters Associates; Milford, MA) was equipped with a C18 column (10 μm 4.6 × 250 mm, 10 μm) [Nucleosil 100; Alltech Associates; Deerfield, IL] and a Bondapak C8 precolumn (Guard-pak; Waters Associates). A programmable fluorescence detector (model 980; Applied Biosystems; Foster City, CA) was used to detect the analytes (emission, 418 nm; excitation, 295 nm; range, 0.1 absorbance units full scale). The mobile phase consisted of a mixture of 0.01 M ammonium hydrogen sulfate and acetonitrile (80:20) filtered through a 0.22-mm filter. The flow rate was 1.3 mL/min. A 150-μL aliquot of standard, quality control, or unknown sample and a 50-μL aliquot of a 2.0 μg/mL gatifloxacin internal standard were placed in a labeled tube. A 600-μL volume of acetonitrile was added to each tube and was vortexed for 30 s. The supernatants were transferred to a clean tube and dried under a stream of nitrogen at 40°C. The residuals were reconstituted in a 200-μL 0.01N solution of HCL. The solution was vortexed and transferred to vials for injection into a autosampler (model 717 Plus; Waters Associates). A chromatography data system (EZChrom Elite; Scientific Software; San Ramon, CA) was used for data acquisition. The MXF HPLC assay was linear (r = 0.999) over a concentration range of 0.05 to 6 μg/mL. The intraday quality control samples (10 samples) of 0.1 and 4 μg/mL had a percentage coefficient of variation (%CV) of 2.5%CV and 0.4%CV for the plasma, 3.3%CV and 2.3%CV for the cell pellet, and 1.3%CV and 1.3%CV for the BAL fluid. The interday quality control samples of 0.1 and 4 μg/mL had a %CV of 1.5%CV and 3.1%CV for the plasma (9 samples), 1.9%CV and 2.2%CV for the cell pellet (10 samples), and 1.3%CV and 2.8%CV for the BAL fluid (10 samples).

LEVO plasma, cell, and BAL concentrations were assayed using a validated HPLC procedure.3 The assay was linear (r = 0.999) over the concentration range of 0.05 to 5 μg/mL. The intraday quality control samples (10 samples) of 0.2 and 4 μg/mL had a %CV of 2.0%CV and 1.2%CV for the plasma, 1.0%CV and 1.6%CV for the cell pellet, and 1.9%CV and 1.8%CV for the BAL fluid. The interday quality control samples of 0.2 and 4 μg/mL had a %CV of 2.6%CV and 1.1%CV for the plasma (six samples), 2.1%CV and 1.3%CV for the cell pellet (five samples), and 2.1%CV and 1.4%CV for the BAL fluid (seven samples).

The AZI plasma, cell, and BAL fluid concentrations were assayed using a validated HPLC procedure by electrochemical detection, as previously reported.2 The assay was linear (r = 0.999) over the concentration range of 0.01 to 0.5 μg/mL.
RESULTS

A total of 53 subjects were enrolled, and 47 (mean age, 62 ± 13 years) completed the study (Table 1). No statistically significant differences existed among the MXF, LEVO, and AZI groups with regard to subject demographics. The subject population consisted mainly of older men who were undergoing diagnostic bronchoscopy. The purpose of the bronchoscopy in the majority of patients was to obtain a biopsy to test for lung malignancy due to the presence of an abnormal chest radiograph, the detection of a lung mass by CT scanning, and/or the occurrence of chronic hemoptysis. Fourteen patients had a medical history that included COPD, and 8 patients had a history of lung cancer. All patients randomized to receive LEVO received the 500-mg once-daily regimen, as their estimated creatinine clearance rate did not mandate a dosage adjustment, as previously defined by the protocol.

Six subjects were discontinued from the study for the following reasons: intolerance of the bronchoscopy procedure (two patients); cerebral vascular accident unrelated to the study (one patient); cancelled bronchoscopy procedure (one patient); discontinuation of study drug due to the initiation of an alternate antibiotic (one patient); and discontinuation of the study drug due to a mild rash that developed after a single dose of LEVO (one patient). Compliance with the study medication schedule was confirmed for all subjects via a dosing diary, which was completed by the patient and collected prior to the bronchoscopy.

The MXF, LEVO, and AZI were well-tolerated, with no serious adverse effects reported. Overall, there were seven reports of mild adverse reactions. One subject was discontinued from the study due to the development of a mild rash after the first dose of LEVO.

The plasma concentrations of each agent were at a maximum 4 h following the administration of the last dose and declined in a fairly predictable manner, falling to a minimum at 24 h. The mean AZI plasma concentrations were significantly lower than the mean MOXI and LEVO concentrations at all sampling time points (p ≤ 0.034). No significant difference was found between the MOXI and LEVO mean plasma concentrations, except at the 8-h time point, at which time LEVO was significantly higher (p = 0.034). The average steady-state plasma concentrations for the MXF, LEVO, and AZI groups are represented in Table 2, and a composite of individual values are represented in Figure 1.

The calculated volumes of ELF (mean ± SD) recovered in the BAL aspirate were 0.99 ± 0.62 mL for the MXF group, 1.13 ± 0.42 mL for the LEVO group, and 1.15 ± 0.9 mL for the AZI group. No significant differences were found between groups. Steady-state ELF concentrations were greater than those of the plasma for all agents studied. The MXF and LEVO mean ELF concentrations were measured at a maximum or a peak at 4 h; however, AZI concentrations lagged behind the plasma concentrations, reaching a peak at 24 h following the administration of the last dose. Overall, the mean ELF concentrations of MXF and LEVO were consistently and significantly higher compared to the AZI concentrations at all sampling time points. No significant differences were detected between the MXF and LEVO mean ELF concentrations. The average ELF/plasma concentration ratio was 5.2 for MXF, 3.0 for LEVO, and 15.8 for AZI over the four time points studied. MXF and LEVO reached the peak mean ELF values of 11.66 ± 11.86 μg/mL and 15.23 ± 4.53 μg/mL, respectively, compared to AZI at 0.94 ± 0.68 μg/mL. The average steady-state ELF concentrations for the MXF, LEVO, and AZI groups are represented in Table 2. A composite of individual values is represented in Figure 2.

The number of leukocytes recovered from the BAL aspirates in subjects receiving MXF, LEVO, and AZI was 1.18 × 10^7 ± 1.03 × 10^7, 2.32 × 10^7 ± 1.67 × 10^7, and 1.62 × 10^7 ± 1.82 × 10^7 cells/L, respectively. The mean percentage of macrophages identified among the leukocytes recovered was 60% for the MXF, 82% for the LEVO, and 76% for the AZI group. A significantly lower percentage of macrophages was identified in the MXF group com-

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Table 1—Demographics of Study Population*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Total No.</th>
<th>Age*, yr</th>
<th>Men, No.</th>
<th>Women, No.</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>ClCr, mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>MXF</td>
<td>16</td>
<td>67 ± 10</td>
<td>13</td>
<td>3</td>
<td>172 ± 11</td>
<td>81 ± 15</td>
<td>88 ± 31†</td>
</tr>
<tr>
<td>LEVO</td>
<td>15</td>
<td>59 ± 18</td>
<td>10</td>
<td>5</td>
<td>160 ± 46</td>
<td>83 ± 19</td>
<td>95 ± 26</td>
</tr>
<tr>
<td>AZI</td>
<td>16</td>
<td>61 ± 12</td>
<td>10</td>
<td>6</td>
<td>169 ± 7</td>
<td>80 ± 14</td>
<td>104 ± 40</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated. ClCr = estimated creatinine clearance.
†Male estimated ClCr = (140 - age) body weight (kg)/72 × serum creatinine; female ClCr = estimated ClCr male × 0.85.
†n = 15.
pared to that for the LEVO group \( (p = 0.004) \), however, no other significant differences were noted between the groups.

The intracellular penetration of each agent was superior compared to both the plasma and ELF. The MXF mean peak AM concentration was measured at the 8-h sampling time point compared to the 4-h time point for LEVO and the 24-h time point for the AZI. The AM concentrations, however, were quite variable among individual subjects for each agent studied. Similar to the ELF concentrations, the AM did not suggest a linear decline over sampling time points and exceeded peak plasma concentrations at 24 h following the administration of the last dose. Overall, AZI attained the highest mean AM concentrations with significant differences compared to MXF at 24 h \((p = 0.02)\) and LEVO at 12 h \((p = 0.04)\) and 24 h \((p = 0.02)\) following the administration of the last dose. A significant difference also was found between the MXF and LEVO AM concentrations at 24 h \((p = 0.04)\) where MXF was higher. The average AM/plasma concentration ratio was 32 for MXF, 5.8 for LEVO, and 2,483 for AZI over the four time points studied. The mean maximum AM concentrations were 123.25 ± 126.36 \(\mu\)g/mL for MXF, 28.50 ± 30.02 \(\mu\)g/mL for LEVO, and 205.21 ± 256.26 \(\mu\)g/mL for AZI. The average steady-state AM concentrations for the MXF, LEVO, and AZI groups are represented in Table 2. A composite of individual values is represented in Figure 3.

The area under the curve (AUC) for plasma or ELF for each agent was calculated to assess the drug exposure for the population (Fig 4). It must be stressed that this calculation is only a rough estimate as it is derived from the composite data of 16 patients vs serial concentrations obtained in 1 patient over time. In addition, the AUC for plasma in each agent is a conservative estimate, since the time to peak plasma concentration is generally 1 to 2 h, and our plasma sampling did not occur until 4 h postdose. However, this is not the case for the AUC for ELF concentration as the peak concentrations at this site have been noted to occur at approximately 4 h postdose. Moreover, we also calculated the \( S\) pneumoniae \( \text{AUC/MIC} \) for both the plasma and ELF compartments (Table 3). These data reveal that MXF provides the highest antimicrobial exposure at both sites relative to the current susceptibility profile of \( S\) pneumoniae for the agents studied.

### Table 2—Steady-State MXF, LEVO, and AZI Concentrations in the Plasma, ELF, and AMS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sample Collection Time After Last Dose, h</th>
<th>Subjects, No.</th>
<th>Plasma Concentrations, (\mu)g/mL</th>
<th>ELF Concentrations, (\mu)g/mL</th>
<th>AM Concentrations, (\mu)g/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MXF</td>
<td>4</td>
<td>4</td>
<td>3.23 ± 0.88</td>
<td>11.66 ± 11.86</td>
<td>47.67 ± 47.56</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>2.21 ± 0.59</td>
<td>7.80 ± 5.08</td>
<td>123.25 ± 126.36</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>1.68 ± 0.53</td>
<td>10.52 ± 3.66</td>
<td>26.21 ± 19.42</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4</td>
<td>0.78 ± 0.39</td>
<td>5.71 ± 6.28</td>
<td>32.76 ± 16.48</td>
</tr>
<tr>
<td>LEVO</td>
<td>4</td>
<td>4</td>
<td>5.08 ± 2.31</td>
<td>15.23 ± 4.53</td>
<td>28.50 ± 30.02</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3</td>
<td>4.37 ± 0.71</td>
<td>10.18 ± 6.74</td>
<td>26.14 ± 15.73</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>4.60 ± 4.58</td>
<td>6.85 ± 4.36</td>
<td>28.25 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4</td>
<td>1.52 ± 1.42</td>
<td>2.94 ± 1.74</td>
<td>8.17 ± 6.10</td>
</tr>
<tr>
<td>AZI</td>
<td>4</td>
<td>4</td>
<td>0.10 ± 0.02</td>
<td>0.63 ± 0.35</td>
<td>71.8 ± 50.07</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>0.05 ± 0.02</td>
<td>0.66 ± 0.42</td>
<td>73.83 ± 73.31</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>0.17 ± 0.86</td>
<td>0.85 ± 0.46</td>
<td>155.94 ± 51.26</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4</td>
<td>0.03 ± 0.02</td>
<td>0.94 ± 0.68</td>
<td>205.24 ± 256.26</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated.
†Three subjects. One subject was excluded due to insufficient data on the cell differential.

Discussion

This was the first investigation to assess the steady-state intrapulmonary concentrations of these agents in an older patient population with probable underlying pulmonary pathology, as previous studies had been performed either in healthy volunteers or following a single dose.\(^2\)\(^–\)\(^6\)\(^,\)\(^8\) This study offers insight into the pharmacokinetic disposition of the study agents in a patient population that is more closely representative of the demographic profile of those receiving treatment for CARTIs.

Plasma concentrations achieved with these agents were generally consistent with those seen in other previously published studies; however, elevated concentrations of LEVO were noted at 24 h postdose. The trough concentrations were 2.5 times higher than those observed with the 500-mg dose in a similar study of LEVO in healthy volunteers by Gottfried et al.\(^6\) This is to be expected since LEVO is mainly eliminated via the renal route, and our older patient population would be expected to have remitted.
duced renal clearance. Moreover, our results are consistent with those of previous studies in that all three agents displayed a substantial degree of penetration into the extracellular and intracellular compartments of the lung relative to that achieved in plasma. As a result of increasing S pneumoniae resistance to commonly utilized agents and the overall incidence of this pathogen as an etiologic agent in CARTIs, this organism is the primary extracellular pathogen of concern when considering antimicrobial therapy. Our data reveal that attainable AZI con-
centrations are inadequate in ELF to reliably eradicate *S. pneumoniae* based on the current AZI MIC profile. However, the mean concentrations of MXF and LEVO in the ELF exceed the MIC required to inhibit 90% of the organism (ie, *S pneumoniae*) population ([MIC <sub>90</sub>] MXF, 0.25 μg/mL; LEVO, 1.0 μg/mL) (Fig 1, 2). Moreover, MXF concentrations exceeded the *S pneumoniae* susceptibility breakpoint<sup>16</sup> (1.0 μg/mL) at all time points, while 2 of 15 patients (13%) failed to maintain LEVO concentrations above the breakpoint (2.0 μg/mL) at 24 h.

As mentioned, the attainment of sufficiently high intrapulmonary concentrations is imperative for maximum effectiveness in treating CARTIs. The predicted efficacy of each agent may be interpreted by the relationship between drug concentrations at the site of infection and the MIC of the particular pathogen. The AUC/MIC ratio is the pharmacodynamic parameter that is most predictive of efficacy with regard to fluoroquinolone agents as well as AZI. An AUC/MIC ratio in plasma of at least 25 for AZI and 30 to 40 for the fluoroquinolone agents is necessary to produce the maximal killing of *S pneumoniae* and is correlated with a high probability of *in vivo* bacterial eradication.<sup>17–20</sup>

Our estimated MXF plasma AUC (41.5 μg/h/mL) is consistent with the range of AUC values previously reported with this agent (31 to 48 μg/h/mL).<sup>12</sup> The plasma LEVO AUC value of 86.7 μg/h/mL is higher than that found in young (ie, mean age, 28 ± 9 years) healthy volunteers (48 μg/h/mL) and is more consistent with that reported in patients undergoing treatment in clinical trials (73 μg/h/mL) and critically ill population (60 μg/h/mL).<sup>21,22</sup> This may be explained by the fact that our older patient population experienced decreased renal clearance of the drug. As mentioned, LEVO is mainly eliminated renally, while MXF is eliminated by both renal and hepatic routes.<sup>12</sup> The estimated AZI plasma AUC value (1.5

![Figure 3. Composite of individual steady-state AM concentrations of MXF, LEVO, and AZI at 4, 8, 12, and 24 h after the administration of the last dose.](image_url)

![Figure 4. Comparative drug exposure of MXF, LEVO, and AZI in plasma and ELF.](image_url)
MIC90 values of noninvasive sampling of this site, this profile may not have utilized plasma pharmacokinetics because of the drug exposure in the lung. AUC values as a valid estimation of total extracellular composite data. Nevertheless, since the plasma AUC estimation of plasma and ELF AUC values based on these compounds. Certainly, limitations exist in the pulmonary disposition of pulmonary inflammation, which also may contribute to modifications in the pulmonary disposition of these compounds. Certainly, limitations exist in the estimation of plasma and ELF AUC values based on composite data. Nevertheless, since the plasma AUC values obtained in the same manner were consistent with those previously reported, we propose the ELF AUC values as a valid estimation of total extracellular drug exposure in the lung.

While the majority of pharmacodynamic profiling has utilized plasma pharmacokinetics because of the noninvasive sampling of this site, this profile may not always fully explain attributable clinical success or failure in the management of CARTIs. As such, many investigators have begun to examine the drug concentrations at the site of infection, much as we have undertaken to do in this study, where achievable ELF concentrations provide a surrogate for the concentrations in the lower respiratory tract. When one evaluates drug exposure at the site of infection (eg, AUC for ELF/MIC) for MXF and LEVO (Table 3), exposures are estimated at five times and two times that of the plasma pharmacodynamic profile for the agents, respectively. As a result of high achievable concentrations at the site of infection, each agent would be expected to produce a substantial bacterial kill. In comparison, despite the use of the AUC for ELF/MIC ratio for AZI, adequate exposures were still not obtained for this agent. While the full impact of accessing drug exposure at the site of infection (eg, AUC for ELF/MIC) is not completely understood due the scarcity of data, this approach may not only assist with the observations of the in vitro paradigm, as noted by Bishai, but also may assist in the selection of agents that not only result in clinical efficacy, but provide high exposures that minimize the development of resistance to the agent being used. This latter issue is of increasing importance for the fluoroquinolones (ie, LEVO, gatifloxacin, and MXF) that are used in the management of CARTIs. While the continued efficacy of the fluoroquinolones hinges on several key factors, including their appropriate utilization, once the initiation of therapy is deemed medically sound, in vivo potency, as designated by the agent’s pharmacodynamic profile, is an important consideration for ensuring both clinical efficacy and minimizing further resistance.

CONCLUSION

The intrapulmonary concentrations of MXF, LEV, and AZI were superior to those obtained in the plasma. These data indicate that attainable AZI concentrations are insufficient to reliably eradicate S pneumoniae based on the current AZI MIC profile, whereas, the mean concentrations of MXF and LEVO in the ELF exceed the MIC90 of the S pneumoniae population. The AM concentrations of all agents studied were more than adequate relative to the MIC90 of the common intracellular pathogens (< 1 μg/mL).

Table 3—Pharmacodynamic Profile (AUC/MIC) of S pneumoniae for MXF, LEVO, and AZI in Plasma and ELF

<table>
<thead>
<tr>
<th>Matrix</th>
<th>MXF</th>
<th>LEVO</th>
<th>AZI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>166</td>
<td>87</td>
<td>0.2</td>
</tr>
<tr>
<td>ELF</td>
<td>831</td>
<td>180</td>
<td>2.5</td>
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</tbody>
</table>

*MIC90 values of S pneumoniae for each agent were obtained from US surveillance studies: MXF, 0.25 μg/mL; LEVO, 1 μg/mL; AZI, 8 μg/mL.

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