

## Pharmacokinetics and Pharmacodynamic Targets of Levofloxacin in Intensive Care Patients with Community-Acquired Pneumonia

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### Abstract

**Background:** In intensive care unit (ICU), patients present hemodynamic and metabolic changes, so pharmacokinetics parameters of the antibiotics are modified. These changes will result in a high inter-individual variability for most antibiotics.

**Objective:** The primary objective is to check whether the indices of Pharmacokinetics/Pharmacodynamics of efficiency are achieved at a levofloxacin therapy in critically ill patients suffering from community-acquired pneumonia. The secondary objective is to characterize the covariates influencing these parameters.

**Material and Method:** This prospective, open, phase IV study included 64 patients between March 2012 and March 2015 receiving 500 mg/12 hours of levofloxacin. Eight blood assays were performed after 48 hours of treatment by the method of high performance liquid chromatography (HPLC). Pharmacodynamic and pharmacokinetic analysis was conducted, therapeutic goals were set for AUIC > 125h and IQ > 12.

**Results:** For pneumococcal infections, AUIC > 125h associated with an IQ > 12 are in 11.5% of cases; to infections with other pathogens, there are in 65% of cases. A CKD-EPI  $\leq 96.23$  ml/min/1.73 m<sup>2</sup> and a SOFA > 11 factors promote the obtaining of therapeutic goals of levofloxacin.

**Conclusion:** Our study confirmed that the efficiency targets are achieved in just a little over 60% of ICU patients to a dose of 500 mg/12h and even less for pneumococcal disease. The SOFA score and CKD-EPI clearance are factors influencing the pharmacodynamics of levofloxacin.

**Keywords:** Levofloxacin; Intensive Care Patients' Pharmacokinetics; Pharmacodynamics; Community-Acquired Pneumonia

### Abbreviations

APACHE II (score): Acute Physiology and Chronic Health Evaluation II (Score); AUC: Area Under the Curve; AUIC (AUC/CMI): Area Under the Inhibitory Curve; CKD-EPI: Chronic Kidney Disease Epidemiology collaboration (Levey, 2009); CL: Clearance; Cl noncomp Levo: Non Compartmental Clearance of Levofloxacin; Cmax: Maximum Concentration; Cmax/MIC: Inhibition Ratio; Cmin: Minimum Concentration; CPM: Concentration Preventing the Mutations; CVVHDF: Continuous Venovenous Hemodiafiltration; ECMO: Extra-corporeal Membrane Oxygenation; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HPLC: High Performance Liquid Chromatography;

IGS II: Indice de Gravité Simplifié II; ICU: Intensive Care Unit; MBP: Mean Blood Pressure; MIC: Minimum Inhibitory Concentration; MSW: Mutant Selection Window; PK/PD: Pharmacokinetic/Pharmacodynamic; ROC: Receiver Operating Characteristic; SOFA (score): Sequential Organ Failure Assessment Score;  $t_{1/2}$ : Half Time; tSMW: Time in Selection Mutant Window; VD: Volume of Distribution

## Introduction

Severe community acquired pneumonia is hard to contain and responsible for many hospitalization in intensive care unit. Recommendations encourage on a probabilistic approach, to extend the spectrum, a combination of antibiotics, among which can be chosen a macrolide, or fluoroquinolone such as levofloxacin [1-3]. Its efficiency is real, most particularly in terms bacterial eradication [4,5]. Moreover, levofloxacin ensures an accurate diffusion in pulmonary parenchyma [6]. However, its use has widely decreased after the HAS (Health High Authority) recommendations, because of the risk of resistance.

Proposed dosages were established on the basis of studies conducted in healthy volunteers [7-10].

Yet, many studies involving betalactam, aminoglycosides, or quinolones, showed the risk of underdosing of these antibiotics within particular patients populations [11-14]. In intensive care unit (ICU), patients present special characteristics such as a decreasing creatinine clearance, even increasing one, organs disorders, a systemic inflammatory response syndrome (SIRS), mechanical ventilation having a role on the increase of volume distribution.

So, pharmacokinetics parameters of the antibiotics are modified: volume distribution, metabolism, phasing out [15]. These changes will result in a high inter-individual variability for most antibiotics, including quinolones [16]. This can result in a decrease of peak serum concentration, with the result of a decrease of the antibiotics efficiency. Simultaneously, renal clearance may be modified, showing a decrease (renal insufficiency) or an increase (hyper filtering patients), having an impact on the half-life of the antibiotic.

A dose adjustment seems necessary [17], especially when the over dosage is likely to be responsible for toxicity [18], the likelihood of under-dosing of the antibiotic is responsible for the emergence of resistance [19] or treatment failure.

Levofloxacin is a concentration-dependent antibiotic. Thus, therapeutic objectives predicting a successful treatment were established for the  $C_{max}/MIC$  ratios (maximum concentration/Minimum Inhibitory Concentration) and  $AUC_{24h}/MIC$  (Area under the 24 hours curve/Minimum Inhibitory Concentration) [20-22]. Only few studies addressed the pharmacokinetics of levofloxacin for critically ill patients, limited by a reduced number of patients [11,23].

## Objective of the Study

- The primary objective of this study is to verify if the efficiency of Pharmacokinetics/Pharmacodynamic (PK/PD) are reached during a treatment with levofloxacin for critically ill patients with community acquired pneumonia with a dosage of 500 mg in 60 minutes perfusions twice a day.
- The secondary objective is to characterize the covariables influencing these parameters.

## Materials and Methods

### Patients

We carried out a prospective, open, phase IV clinical trial, between March 2012 and March 2015, in the Intensive Care Unit of the University Hospital Center of Rangueil (Toulouse, France). The trial received a favorable opinion from the Persons Protection Committee of the South West and Over-Seas II on the 1st of September 2011 (2-11-23/View n°1).

Adult patients, hospitalized in this unit, with a Simplified II Severity Index (IGS II) above 20, and presenting a community acquired pneumonia for which a treatment by levofloxacin was set up were included.

A written consent was collected from the patient, or failing that, from someone close to the patient (reliable person, relative).

Patients with a contraindication for levofloxacin, such as allergy, a resistant identified germ, or a discontinuous renal dialysis were excluded [24]. Pregnant women as well as adult patients under legal protection were also excluded.

### **Dosage**

Concerned patients received 2 injections of 500mg of levofloxacin every 12 hours, over a duration of 60 minutes.

The half-life of levofloxacin is estimated between 6 and 8 hours. Steady-state is reached from 5 half-lives. From the fifth injection, that is at the 48<sup>th</sup> hour, 8 blood samples were collected on arterial catheter: to H0, H+0,5, H+1, H+2, H+4, H+6, H+8, H+12. These samples were sent to the Laboratory of Pharmacokinetics and Clinical Toxicology.

The serum dosage of levofloxacin was made by High Performance Liquid Chromatography (HPLC) [25].

### **Data collection**

The information collected for each patient were their characteristics, such as in particular, their age, weight, gender, the reason for hospital admission, IGS II, the SOFA Score, relevant biological data such as serum creatinine and its clearance (Cockcroft et Gault), the glomerular filtration flow calculated by the CKD-EPI formula, intubation. Some medical care elements such as continuous ultra-filtration and circulatory assistance (ECMO) were also recorded.

Data linked to the trial were: scheme of administration, hours of blood sampling and levofloxacin concentrations. A case report form allowed the collection of clinical and biological data, hours of administration and dosage of levofloxacin, duration of mechanical ventilation and hospitalization, mortality, side effects as well as bacteriological data with, more specifically, the germ's MIC when identified.

### **Pharmacokinetics analysis**

A "non compartmental" descriptive analysis of pharmacokinetics was completed.

From the evolution of plasma concentrations on a 12 hours interval (between the 48<sup>th</sup> and the 60<sup>th</sup> hours) the area under the curve was calculated on MedCalc® using the trapezoidal rule, allowing the determination of plasma exposure of the body to levofloxacin.

Clearance was then calculated with the equation: Clearance = Dosis/AUC and the distribution volume with the equation  $VD = CL \text{ (clearance)}/kel$  (kel being the terminal slope of the exponential decrease line of concentrations).

The half-life was calculated with the equation:  $t_{1/2} = Ln2 \times VD/CL$ .

### **Pharmacodynamics analysis**

#### **Predictive efficacy criteria**

Fluoroquinolones bactericidal is concentration-dependent and its efficiency is linked to the relation between 24H-AUC and MIC or the maximum concentration (Cmax) and the MIC. For severe community acquired lung infections with *S. pneumoniae* or Gram negative bacilli, the therapeutic efficacy seems to be at its best for peak plasma concentrations > 12 times the MIC.

Taking into account these data but also the severity of the concerned patients, we selected the following goals: an AUIC > 125 threshold and a Cmax/MIC > 12, distinguishing pneumococcus with a critical concentration below 2 mg/L and other sensitive germs for which it reaches 1mg/L.

### Predictive criteria for the prevention of resistance

The inhibition ratio and the AUIC are also risks indicators for the selection of resistant mutants. It is necessary to underline the importance of the CPM also known as the concentration preventing the mutations defined as the concentration of antibiotics for which no mutant appears for a given strain in the presence of a high bacterial inoculum ( $> 10^{10}$  bacteria). The maximum risk of resistant mutant selection is located in the window of concentrations between the MIC and the CPM which, in theory, should not exceed 20% of the time interval between two injections (the levofloxacin CPM is 8mg/l for *Pneumococcus* and seems lower for Gram negative germs such as *P. aeruginosa*).

These notions brought to us to consider in our descriptive analysis other prevention predictive parameters of the resistances such as:

- The tsmw (t Mutant Selection Window) or time spent in the selection window (between 1 or 2 mg/L and 8 mg/L).
- The percentage of patients with a concentration located in the mutant selection window below 20% of the time interval between two injections.

### Statistics analysis

The descriptive statistics analysis allowed to describe the bio-clinical data, pharmacokinetics and pharmacodynamics parameters as well as the distribution of all these variables assessed by a Kolmogorov -Smirnov test and by the Kurtosis and Skewness Ratios.

The results are expressed in median and in confidence interval of 95% (CI 95%) for quantitative variables and in percentage for qualitative variables.

The relations between the various continuous variables were analyzed with a correlation table (Spearman ranking matrix).

The studied population was separated into two groups according to the observation or non-observation of the efficiency goals and of the bacterial resistance prevention goals, that is to say an AUIC  $> 125h$  and an IQ  $> 12$ .

The patient's characteristics were compared for both groups using:

- For the continuous variables, non-parametric tests (Mann-Whitney);
- For the qualitative variables, a Fisher exact test.

The discriminating threshold of significant continuous variables according to the "AUIC  $> 125h$  and QI  $> 12$ " criteria was estimated by the study of the ROC (Receiver Operating Characteristic) curves and their associated under the curve areas. The choice for the most discriminative thresholds was made according to the best Youden index coupled with the calculation of predictive positive and negative values, sensitivity and specificity. For each threshold, a "gray zone" or uncertainty zone was established, using a two steps procedure defined by Cansesson. These ROC curves were then compared to eliminate the less discriminating covariates.

In a last step of a multivariate analysis, we evaluated the association between the various covariates and the explained variable (PK/PD goals achieved) through the measurement of odds-ratio, by running a logistic regression. We used a backward elimination procedure which consists in including all the chosen variables and to progressively retain the non-significant ones. The suitability Hosmer and Lemeshow test ( $\chi^2$  goodness of fit) allowed retaining the model proposing the best adjustment.

The trial was lead on the MedCalc® statistical software version 15 (Mariakerke, Belgium). A  $p < 0.05$  was considered statistically significant.

Results

Population

64 Patients were included (Figure 1); 56 with the characteristics presented in table 1 were analyzed.

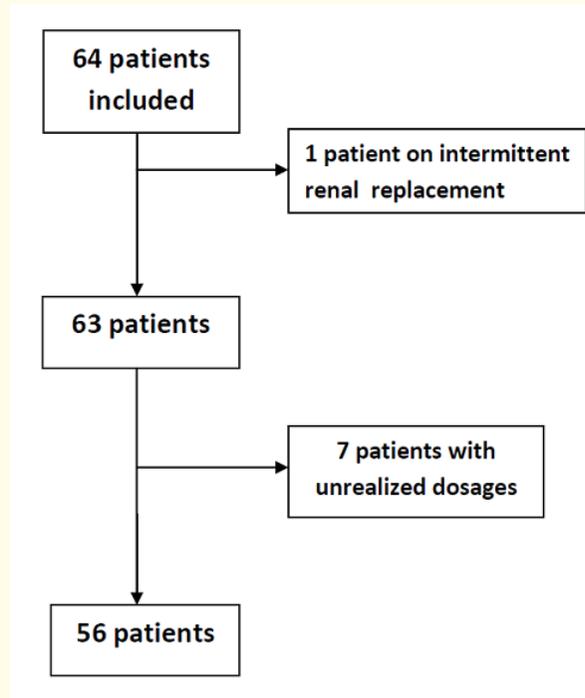


Figure 1: Flow chart.

	Median	Confidence interval 95%
Age (years)	60.4	57.3 - 63.6
Gender (M/F)	35/21	-
BMI (kg/m <sup>2</sup> )	25.6	23.9 - 29
Total Bilirubin (µmol/L)	13	10 - 16
Direct Bilirubin (µmol/L)	19	13.8 - 60.9
CKD-EPI (mL/min/1.73m <sup>2</sup> )	74.4	56.7 - 88
Cockroft clearance (mL/min/1.73m <sup>2</sup> )	75.1	59.7 - 97.7
Hb (g/dL)	10.6	9.8 - 11.6
MBP at inclusion (mmHg)	75.5	72 - 80
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	134.5	113- 157
Serum protides (g/L)	55	54 - 57
TGO (UI/L)	65	43 - 106
TGP (UI/L)	42	35 - 64
Mechanical ventilation yes/no	50/6	-
CVVHDF yes/no	6/50	-
ECMO yes/no	10/46	-
IGS II Score at the time of admission	56	51 - 61
SOFA Score	11	10 - 12
Cl noncomp levo L/h (Dosis /AUC)	4	2.9 - 5.5

Table 1: Demographic and biological characteristics for the patients included.

BMI: Body Mass Index; CKD-EPI: Chronic Kidney Disease Epidemiology collaboration (Levey, 2009); Hb: Hemoglobin; MBP: Mean Blood Pressure; CVVHDF: Continuous Veino-Veinous Hemodiafiltration; ECMO: Extracorporeal Membrane Oxygenation; Cl Non Comp Levo: Non Compartmental Clearance of Levofloxacin.

**Dosages and pharmacokinetics**

All in all, 381 samples were analyzed. The concentrations’ median is 11.1 mg/l (IC95% = 9.89 - 12.01). The lowest measured value is 0.75 mg/l and the highest is 37.45 mg/l. The distribution is skewed with a positive Skewness coefficient of 0.602 (P < 0.0001) and does not follow the normal pattern with a Kolmogorov-Smirnov test at D = 0.074 (P < 0.0001).

For the critical concentrations, that is 1 mg/l for the Gram negative bacillus and 2 mg/l for *Pneumococcus*, the average percentage of time spent in the selection window between 1 and 8 mg/L is 37.1% (IC 95%= 24.9 - 49); and between 2 and 8 mg/L, 34.7% (IC95% = 23.3 - 46). For 54.2% of the patients, the time spent in the selection window is higher than 20%.

For *Pneumococcus* infections, an AUC > 125 is observed for 50% of the cases, an IQ > 12 for 12.9%; and an AUC > 125 and an IQ > 12 for the same patient for 11.5% of the cases. For other germs infections, the AUC > 125 is also found for 84% of the cases, an IQ > 12 for 64.8%, and an AUC > 125 and an IQ > 12 at the same time for 65% of the cases.

**Factors affecting PK/PD**

A correlation continuous values table was carried out between the demographic and biological data, and the pharmacokinetics parameters. Values presenting a relation with the AUC and the Cmax, have been compared to meet therapeutic targets: AUC > 125 associated to an IQ > 12; results are shown in table 3. The 6 patients with an established extra-renal dialysis were found in the group with an AUC > 125 and an IQ > 12.

	Median	95% CI	Minimum	Maximum
AUC <sub>24h</sub> (h)	248.24	181 - 341	53.5	612.6
AUC levo <i>pneumococcus</i>	124.12	90.6 - 170.5	26.7	306.3
AUC levo other germs	248.24	181 - 341	53.5	612.7
% time C <sup>tions</sup> >CMI=1 mg/L	100	100 - 100	99.8	100
% time C <sup>tions</sup> >CMI=2 mg/L	97.6	100 - 100	41.1	100
% time C <sup>tions</sup> >CPM	95.45	33.57 - 100	0	100
C <sub>max</sub> /CPM	1.95	1.6 - 2.4	0.7	4.7
tMSW <sub>between 1 and 8 mg/L</sub>	4.55	0 - 66.4	0	100
tMSW <sub>between 2 and 8 mg/L</sub>	4.55	0 - 63.9	0	100
C <sub>max</sub> /MIC <sub>levo pneumococcus</sub>	7.8	6.28 - 9.76	2.82	18.72
C <sub>max</sub> /MIC <sub>levo other Germs</sub>	15.6	12.57 - 19.53	5.64	37.45
CL <sub>tot levo</sub> (mL/min)	67.27	48.88 - 92.09	27.2	311.74
VD <sub>Levo</sub> (L/kg)	0.85	0.76 - 1.04	0.37	3.65
Half life (h)	13.67	10.46 - 15.94	4.1	63.9

**Table 2:** PK/PD levofloxacin parameters.

AUC: Area Under the Curve; AUC: Area Under the Curve/CMI; CL<sub>tot levo</sub>: Total Clearance of levofloxacin; VD: Volume of Distribution; tMSW: Time in Mutant Selection Window

n= 56	AUC > 125 et IQ > 12	AUC < 125 et IQ < 12	p
Age (years)	60.4 [57 - 66]	55 [44 - 65]	0.073
Gender (M/F)	F= 38.9%	F= 38.2%	0.999
CKD - EPI (mL/min/1.73m <sup>2</sup> )	56.8 [44.6 - 76.5]	104.3 [86.7 - 118.2]	0.0001
Urea (mmol/L)	12.34 [9.2 - 13.6]	5.9 [4.5 - 9.6]	0.005
TGO (UI/L)	100 [42 - 218]	44 [27 - 77]	0.055
GammaGT (UI/L)	97.5 [33 - 223]	60 [30 - 108]	0.289
IGS II	59 [52 - 69]	49 [39 - 57]	0.088
SOFA	12 [10 - 14]	9.5 [7 - 10.6]	0.006
MBP <sub>inclusion</sub> (mmHg)	73 [69 - 76]	80 [74 - 89]	0.036
Mechanical ventilation	91%	83%	0.405
CVVHDF	17.6%	0%	0.081
ECMO	26.5%	5.6%	0.136

**Table 3:** Parameters comparison for patients with an AUC >125 and a IQ >12.

MBP: Mean Blood Pressure; CVVHDF: Continuous Veino - Veinous Hémodiafiltration; ECMO: Extracorporeal Membrane Oxygenation.

The continuous variables discriminating patients with an AUIC > 125 and a Cmax/MIC > 12 are specified in table 4.

	AUC	IC 95%	Threshold	Gray zone	Se. %	Sp. %	PPV %	NPV %
CKD-EPI (mL/min/1,73m <sup>2</sup> )	0.83	0.7 - 0.92	≤ 96.2	49.1 - 97	91.2	66.7	83.8	80.0
Urea (mmol/)	0.74	0.6 - 0.85	>10.1	3.2 - 13.8	58.8	88.9	90.9	53.3
SOFA	0.73	0.59 - 0.85	> 11	6 - 11	58.8	88.9	90.9	53.3
PAM <sub>inclusion</sub> (mmHg)	0.68	0.53 - 0.8	≤ 78	63 - 86	73.5	66.7	80.6	57.1

**Table 4:** Precision of Continuous clinical and biological variables discriminating patients with an AUIC > 125 and a Cmax/MIC > 12.

Se: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative predictive Value.

For a multivariate analysis, after eliminating the covariables presenting a strong connection, step by step deletion of various imperfectly fitted models (estimated values not fitted to the observed values), a CKD-EPI ≤ 96.23 ml/min/1.73 m<sup>2</sup> and a SOFA > 11 seem to be the only factors of variation reporting the findings of a AUIC > 125 associated with a IQ > 12 (Table 5).

	p	OR [IC 95%]
CKD-EPI ≤ 96.23 mL/min/1.73m <sup>2</sup>	0.0066*	27.1 [2.5 - 291]
Urea > 10.1 mmol/L	0.53	1.9 [0.26 - 13.6]
SOFA > 11	0.0146*	20.1 [1.8 - 224.3]

**Table 5:** Multivariate analysis for the factors characterizing an AUIC > 125 associated with a C<sub>max</sub>/MIC > 12.

With this pattern, the adjustment test is satisfactory (Hosmer Lemeshov at 0.96) and the percentage of patients within the targets of AUIC and Cmax/MIC correctly classified is 83%. This pattern is sufficiently discriminative since its AUC equals 0.9 [IC95= 0.78 - 0.97].

With the re-sampling technique (Bootstrap), we conducted a simulation on the basis of 1000 simulations per combination of the n variables for nn combinations whether 22. Through this process, we validated this pattern by Monte Carlo simulation over 4000 patients. The results show a significance in bilateral for these 4000 patients with a p respectively at 0.003 for a CKD-EPI ≤ 96.23 and 0.004 for a SOFA > 11.

**Discussion**

The ICU population is a particular population, subject to physiopathological changes which might affect the pharmacokinetics of various treatments, in particular antibiotics. Thus, Rebeck showed significant differences for the levofloxacin pharmacokinetics between critically ill population and healthy population with an increase of the half-life, of the Cmax, Cmin and AUC higher for the first ones [26]. On the other hand, Pea showed an AUC over 12h 30 to 40% lower and a higher urinary excretion of the levofloxacin for 10 patients in ICU [23]. The pharmacokinetics and pharmacodynamics knowledge of levofloxacin on healthy patients should not apply to critically ill population.

The Cmax/MIC and AUC/CMI ratios seem to be better factors evaluating the efficiency of levofloxacin to obtain a bactericidal activity and a prevention of optimized resistances [21,27]. The targets chosen for our study are Cmax/MIC >12 [21] and AUC/MIC >125 h [20,22,28,29]. Thus, our work targets an AUC median of 248.24 mg\*h/l over 24 hours (IC95% = 181 - 341), and so an AUIC with critical concentration for pneumococcus of 124.12h and an AUIC for the other germs of 248.24h. The median of the inhibitor ratio (Cmax/MIC) is respectively of 7.8 for pneumococcus and 15.6 for the other germs.

The association of an AUC > 125 h and C<sub>max</sub>/MIC > 12 is observed in only 11.5% of the cases for pneumonia with pneumococcus and in 65% of the cases for the other germs. In our study, the theoretic therapeutic targets are not reached for a large amount of patients. The half-life found is 13.67 hours long (IC<sub>95%</sub> = 10.46 - 15.94).

The comparison with other studies is difficult because few were realized for levofloxacin in ICU with a dosage of 500 mg/12h and concern few patients.

Boselli studied 12 patients taking 500 mg of levofloxacin twice a day. The AUC over 24h was estimated at 416 mg\*h/l, half-life at 17 hours, C<sub>max</sub> at 19.7 mg/L and clearance at 40 mL/min. C<sub>max</sub>/MIC had been calculated with patients presenting an identified pathogen and which could vary from 37 to 82 for pneumococcus and from 74 to 1710 for the other germs. The MIC for pneumococcus was measured between 0.25 and 1 mg/L and for the other germs between 0.0125 and 0.25 mg/L. The creatinine clearance was assessed at 67 mL/min [11]. However, this pioneering work included only 12 patients and only 8 germs were identified. Pea showed different results, in a study including only 10 patients in ICU with a saved renal function treated for an early pneumonia with mechanical ventilation. The AUC over 12h was assessed at 33.9 mg\*h/L, the clearance at 3.4 mL/kg/min, a half-life of 5.2 hours. The C<sub>max</sub>/MIC was realized with the identification of the germ and a 102 median was obtained. The AUC/MIC over 24h were evaluated at 930 [23].

These results substantially differ from ours because the MIC used in these studies are real and measured by samples. In both reviews, they are particularly low, and if they represent reality at a given point in time, these MIC evolve over time. In our work, we chose to use critical MIC established by the EUCAST (European committee on antimicrobial susceptibility testing), whether 2 mg/L for pneumococcus infections and 1 mg/L for other germs.

Our study also allowed to describe the pharmacokinetics for levofloxacin for a 500 mg/12h dosage for critically ill patients treated for severe community acquired pneumonia as well as factors influencing this pharmacokinetic.

Two factors could be identified: the clearance calculated with the CKD-EPI formula and the SOFA score.

The role of the renal function in the pharmacokinetics is obvious since the elimination of levofloxacin is done from 60 to 80% by urinary tract [4]. This is confirmed by our study, since the clearance median of levofloxacin was calculated at 67 mL/min, or 90% of the CKD-EPI formula estimated clearance. That conclusion was also reached by Rebeck and Boselli with the demonstration of a correlation between the clearance of the creatinine and the clearance of the levofloxacin [11,26]. In our study, all patients with a continuous extra renal dialysis reached the therapeutic goals. The total clearance of levofloxacin under these circumstances is evaluated close to 50 ml/min [30-33]. It is interesting to note that in Pea's work, which includes patients with a preserved renal function, the targets seem to be reached only thanks to CMI. On the opposite, the AUC, directly linked to the elimination of the clearance is quite low [23]. In our work, it is more difficult to reach the pharmacodynamics targets when the renal function is preserved. This is even more worrying for patients with high filtering whose clearance is increased, exposed to a treatment failure, with a selection of resisting germs.

The SOFA score affects the pharmacokinetics of levofloxacin: most of the time, patients with a high mortality rate reach the pharmacodynamics targets. This seems to reach towards the Rebeck study which showed a higher AUC for resuscitation patients than for the healthy population [26]. There is therefore a risk of under dosage for patients with less severe conditions. Thus, Shorr could not prove any significant difference of the clinical success for several criteria linked to severity: APACHE II score, the use of vasopressors, the presence of a bacteremia [34]. When less severe patients are expected to get better faster, the lack of success of therapeutic objectives might explain the non-correlation between severity and clinical success. We consider it important to obtain the levofloxacin MIC compared to the germs to be treated, in particular pneumococcus, to provide a dosage adaptation for each patient.

Our survey is the first one to study pharmacokinetics over a consequent number of critically ill patients with a 500 mg/12h dosage. We showed that therapeutic objectives are seldom reached for pneumococcus, and with a less frequency for other germs. For more than half the population, the time spent in the selection window is > 20%, presenting thus a high risk of resistance selection.

### Conclusion

Our study confirmed that the efficiency targets are hardly met for little more than 60% of patients with a 500 mg/12h dosage. They are even harder to reach for a pneumococcus infection, which is an additional argument for the precautions recommended by the HAS, because of the risk of resistances selection. It is necessary to insist on the obtaining of the MIC for the documented treatments. This work also showed, within our particular population, the factors influencing the kinetics of this molecule. However, assessment is difficult because the objectives seem better met for severe patients as well as those with a deficient renal function.

A better knowledge of pharmacokinetics parameters of levofloxacin and influencing factors might allow a better adaptation of the dosage to optimize their efficiency and limit the risk of appearance of resistance strains.

### Take-Home Message

The large variability of drug pharmacokinetic disposition is already described in ICU patients leading to important variations in drugs concentrations. The usual recommended dosages of levofloxacin are not adapted to all ICU situations and levofloxacin sometimes should be monitored closely.

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### Conflicts of Interest

None.

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