Levofloxacin in the treatment of ventilator-associated pneumonia

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ABSTRACT

The use of levofloxacin in critically ill patients has progressively increased since commercial marketing of the drug in 1999, despite the fact that few studies have been designed to assess the use of levofloxacin in this population. Pharmacological characteristics, broad spectrum of activity, and tolerability account for the high interest in the drug for the treatment of different infectious diseases, including ventilator-associated pneumonia (VAP), and the recommendation of levofloxacin in guidelines developed by a number of scientific societies. According to pharmacokinetic–pharmacodynamic data, it seems reasonable to assume that an increase in activity follows from a larger dose, so that 500 mg/12 h is adequate in patients with VAP. In critically ill patients with VAP, levofloxacin monotherapy is indicated for empirical treatment of patients with early onset pneumonia without risk factors for multiresistant pathogens, and in combination therapy for late onset VAP or for patients at risk for multiresistant pathogens. The use of levofloxacin in combination therapy is supported by multiple reasons, including: increased empirical coverage in infections with suspected intracellular pathogens; substitution for more toxic antimicrobial agents (e.g., aminoglycosides) in patients with renal dysfunction and in those at risk for renal insufficiency; and severity of systemic response to infection (septic shock) that justifies multiple treatment with better tolerated antibiotics. The availability of the oral formulation allows sequential therapy, switching from the intravenous route to the oral route. Levofloxacin is well tolerated by critically ill patients, with few adverse events of mild to moderate severity.

Keywords  Critical care, critically ill patient, levofloxacin, nosocomial pneumonia, review, ventilator-associated pneumonia

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INTRODUCTION

Treatment of pneumonia related to mechanical ventilation (ventilator-associated pneumonia, VAP), as for the treatment of most nosocomial infections diagnosed in critically ill patients admitted to the intensive care unit (ICU), should be started promptly using antimicrobial agents prescribed empirically, as soon as the infection is suspected on clinical grounds and immediately after samples from the lower respiratory tract have been collected. Different studies have highlighted the importance of the selection of empirical antibiotics [1–5]. Appropriate empirical antibiotic treatment is associated with lower morbidity and higher survival rates. In a recent set of guidelines [6], levofloxacin has been included for the first time as one of the antimicrobial agents recommended for use in monotherapy for empirical treatment of early onset pneumonia in mechanically ventilated patients without known risk factors for the selection of multiresistant pathogens. Levofloxacin has also been included in the combined antibiotic therapy for patients with late onset VAP and for patients with pneumonia in the presence of risk factors for multiresistant pathogens (Fig. 1). This antibiotic has been selected for several reasons, including pharmacological characteristics (spectrum of activity, pharmacodynamics, adverse events profile) and clinical tolerability, allowing safe administration of the drug in patients with renal failure or haemodynamic instability.

Later, when the aetiology of pneumonia has been established, and according to the clinical
response, treatment should be modified according to results of antibiotic susceptibility testing, selecting the most effective and best-tolerated drug with reduced spectrum of activity and lower effect on the endogenous anaerobic intestinal flora. In the majority of cases, directed treatment can be continued in monotherapy. Combined treatment should only be maintained in cases of polymicrobial infections, when *Pseudomonas aeruginosa* has been isolated, or in patients with a protracted clinical course. In these circumstances, levofloxacin continues to be a therapeutic option among various available quinolones.

The present review describes the criteria used for the selection of levofloxacin as one of the antimicrobial agents for treating VAP, new pharmacokinetic–pharmacodynamic concepts that justify the choice of levofloxacin, and current evidence for the use of this drug.

**Rationale for the Use of Levofloxacin in the Treatment of VAP**

Adequate broad spectrum of activity to cover causative pathogens of VAP

Microorganisms responsible for VAP vary largely in relation to the patient’s underlying disease, previous use of antimicrobials, days on mechanical ventilation before respiratory infection, and the presence of epidemics or endemics for a particular pathogen in the hospital or service where the patient is hospitalised. VAP is caused by more than one pathogen in approximately 25% of patients [7].

(a) Early onset VAP or patients without risk factors for multidrug resistant pathogens. In early onset pneumonia that develops during the first 4 days of mechanical ventilation in patients without
previous antibiotic exposure and in the absence of chronic underlying illnesses (diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis), primary endogenous flora present in the patient at the time of admission (methicillin-sensitive Staphylococcus aureus [MSSA], Haemophilus influenzae, Streptococcus pneumoniae, and enterobacteria) are predominately responsible for the respiratory infection. Early onset pneumonias in patients with altered consciousness or in the immediate postoperative period following elective surgery are typical examples of this group [8–11]. The antimicrobial activity of levofloxacin includes all microorganisms expected in this clinical scenario [12,13].

(b) Late onset VAP or patients at risk for multidrug resistant pathogens. Late onset pneumonia that develops in patients previously admitted to the hospital and previously using antibiotics for the treatment or prophylaxis of infection, and/or with chronic underlying conditions is mostly due to secondary endogenous flora (Gram-negative bacteria, especially P. aeruginosa, Acinetobacter baumannii, and Staph. aureus, often methicillin-resistant) [11,14,15]. In general, pathogens most prevalent in the area in which the patient has been admitted predominate in the secondary endogenous flora, so that knowledge of the epidemiological map of the ICU allows selection of the empirical antibiotic regimen [16].

The use of a combination of antimicrobial agents in the empirical treatment of late onset VAP, including two or more drugs active against possible causative pathogens, has not been associated with a higher survival [17]. However, although this practice has been questioned [18], it is accepted according to most therapeutic guidelines, particularly in cases in which P. aeruginosa is suspected as the responsible organism [6,19]. There are limited data regarding the efficacy of antibiotic monotherapy for the treatment of P. aeruginosa pneumonia, but it seems that this modality is associated with a lower rate of microbiological eradication and/or higher relapse [20]. For this reason, these cases are treated with antibiotic combinations, including a β-lactam with antipseudomonal activity together with aminoglycosides or quinolones. Levofloxacin is a potentially useful drug in this situation [6].

Favourable pharmacokinetic indicators

Levofloxacin is widely distributed throughout the body, and penetrates well into most body tissues and fluids. The relation of drug concentrations in lung tissue and sputum compared with those observed in plasma is greater than one [21]. After the administration of oral levofloxacin, 500 or 750 mg once daily, significantly higher steady-state concentrations were achieved in epithelial lining fluid and alveolar macrophages compared with ciprofloxacin, 500 mg twice daily [22], but lower than azithromycin after intravenous administration [23]. In a recent study, the steady-state plasma and epithelial lining fluid concentrations of intravenous levofloxacin, 500 mg, administered once or twice daily in critically ill patients with severe community-acquired pneumonia were determined [24]. The plasma and epithelial lining fluid peak concentrations of levofloxacin were 12.6 and 11.9 mg/L, respectively, in the 24 h regimen and 19.7 and 17.8 mg/L, respectively, in the 12 h regimen, showing a pulmonary percentage penetration of > 100% in both groups. In another study, pharmacokinetic disposition of intravenous and oral levofloxacin in critically ill adults was characterised [25]. Pharmacokinetic evaluations were performed in 28 patients receiving intravenous levofloxacin. Ten of these patients were subsequently switched to oral levofloxacin and underwent a second pharmacokinetic evaluation during oral therapy. Maximum and minimum serum concentrations (C max and C min) were significantly lower in the sequential treatment group than after intravenous dosing, but appeared to be adequate for most pathogens found in critically ill patients with normal renal function. On the other hand, in-vitro studies have shown that levofloxacin penetrates actively in the phagocytic cells, which may facilitate action against intracellular microorganisms as well as increase drug concentration in the infectious foci through mechanisms of phagocytic release. After exposure to 5 and 50 mg/L of levofloxacin, the mean ratios between intracellular and extracellular concentrations in neutrophils were 8.8 and 9.8, respectively [26].

Levofloxacin pharmacokinetics are described by a linear two-compartment open model with first-order elimination, with C max and the area under the concentration-time curve (AUC) both increasing linearly in a dose-proportional fashion.
Excellent tolerability in patients with renal failure or at risk for renal dysfunction

In a pharmacosurveillance study performed 3 years after commercialisation of levofloxacin in the United States, unexpected severe adverse events requiring modification of the technical form of the product were not registered [33]. However, safety and tolerability data in the special population of critically ill patients, in which failure of one or more organs is common, are lacking. Adverse events recorded in an observational study carried out in Spanish ICUs [34] in patients treated with levofloxacin at doses between 500 and 1000 mg/day were scarce, i.e., c. 12.5% and not necessarily attributed to the use of levofloxacin since all patients were given other drugs, half of which were from other antibiotic classes. No case of withdrawal or modification of the treatment regimen due to adverse events was recorded. However, the identification of heart rhythm disturbances that required medical treatment in 2% of patients should encourage close monitoring to assess the relationship with levofloxacin [34], particularly in patients treated with high doses of the drug. In a clinical trial conducted in healthy volunteers to assess the effect of increasing doses of levofloxacin on the QT and QTc interval (500, 1000, and 1500 mg), small increases in QTc were observed with the 1500 mg dose [35]. Single doses of 1000 mg of levofloxacin transiently increased heart rate without affecting the uncorrected QT interval.

Favourable pharmacodynamic parameters

In experimental models with fluoroquinolones, pharmacodynamic indicators relating microbiological and pharmacokinetic variables have shown a correlation between C<sub>max</sub>/MIC ratio and bactericidal effect, so that this class of antimicrobial agent is classified as concentration-dependent killing [36]. Pharmacodynamic studies of levofloxacin demonstrated that the clinical and microbiological outcome was predicted by the ratio of peak plasma concentration to MIC (peak/MIC ratio) [37]. Assessments of the in-vitro activity of two doses of levofloxacin (500 mg every 12 and 24 h, and 750 mg daily dose) against <i>P. aeruginosa</i> and <i>Strep. pneumoniae</i> strains showed an increase in bactericidal activity in relation to higher peak concentrations [38,39]. In patients with hospital-acquired pneumonia the factors influencing the probability of a good microbiological or clinical outcome following the administration of an infusion of levofloxacin (total dose, 750 mg) was studied [40]. For patients with <i>P. aeruginosa</i> or methicillin-resistant <i>Staph. aureus</i> (MRSA), a second drug was added. Mean C<sub>max</sub> of levofloxacin was 15.0 mg/L and AUC 147.1 mg·h/L. Multivariate logistic regression analysis demonstrated that the achievement of an AUC/MIC ratio of ≥87 had a significant effect on eradication of the pathogen [40].

The area under the inhibitory curve (AUIC) is a relatively new indicator of efficacy, mainly used in studies of fluoroquinolones. An in-vitro study examined the relationship between concentration and the bactericidal power of fluoroquinolones, as well as the impact on selection of resistance [41]. Strains of <i>P. aeruginosa</i>, Klebsiella pneumoniae, Escherichia coli, and Staph. aureus were exposed to changing drug concentrations, mimicking human two-compartment pharmacokinetics. Peak concentration to MIC ≥10 or AUIC >125 resulted in optimisation of bactericidal activity and prevention of bacterial regrowth. Based on studies in animal models, AUIC values of at least 100 should be achieved for maximum clinical and bacterio-
logical efficacy against Gram-negative and intracellular pathogens [42]. It has been shown that AUIC values > 40 are predictors of clinical and bacteriological efficacy in Gram-positive cocci [43]. Pharmacodynamic analysis of the activity of levofloxacin against Strep. pneumoniae revealed that, 99% of the time, hospitalised patients achieve an AUC/\text{MIC} > 30. This indicates that levofloxacin will be very effective in treating Strep. pneumoniae infections in the majority of patients. In the study carried out in patients admitted to the ICU with early onset VAP who were treated with levofloxacin (500 mg/12 h), it was shown that C\text{max}/\text{MIC} ratio and the AUIC were constantly above the threshold of efficacy, which indicates that this therapeutic regimen ensures an optimal exposure to prevent both clinical failure and the development of bacterial resistance. However, in three of the patients a sustained superinfection by pathogens intrinsically resistant to levofloxacin was diagnosed [31,32].

**Development of resistance during treatment**

Although therapeutic failures due to the development of bacterial resistance during treatment with levofloxacin, in particular against Strep. pneumoniae have been reported [45,46], the risk is lower than with the use of ciprofloxacin. In a dynamic in-vitro model, time-kill data for ciprofloxacin, clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, and trovafloxacin against three isolates of quinolone-susceptible Strep. pneumoniae were generated [47]. The rank order of activity, with respect to bactericidal effect, was ciprofloxacin (least active) < levofloxacin < grepafloxacin, trovafloxacin < clinafloxacin and moxifloxacin (most active), whereas the rank order with respect to the selection of resistance was ciprofloxacin (most likely) > grepafloxacin, moxifloxacin, and trovafloxacin > levofloxacin > clinafloxacin. The ongoing TRUST (Tracking Resistance in the United States Today) study, which began monitoring antimicrobial resistance among respiratory pathogens in 1996, routinely tracks resistance at national and regional levels [48]. The 1999–2000 TRUST study analysed 9499 Strep. pneumoniae, 1934 H. influenzae, and 1108 Moxarella catarrhalis isolates. Levofloxacin resistance was 0.5% nationally (regional range, 0.1–1.0%). Using data derived from mice infected with the bacterium P. aeruginosa and treated with a fluoroquinolone antibiotic, a mathematical model was developed to describe relationships between antimicrobial drug exposure and changes in drug-susceptible and -resistant bacterial subpopulations [49]. AUIC/MIC ratio of 157:1 was considered the minimum threshold to suppress emergence of resistance. Monte Carlo simulations were also performed for 750 mg of levofloxacin one daily and ciprofloxacin 400 mg IV every 8 h; the overall expected AUIC/MIC target attainment rate was calculated to be 61.2% for levofloxacin and 61.8% for ciprofloxacin. These results do not favour the use of this fluoroquinolone in monotherapy for the treatment of P. aeruginosa infection.

**EVIDENCE FROM CLINICAL USE OF LEVOFLOXACIN IN THE TREATMENT OF VAP**

Although multiple studies on the efficacy and tolerability of levofloxacin in the treatment of different infections, especially respiratory tract infections, were conducted during the preclinical phase [50–58] and with the marketed drug [59–65], few studies have been carried out in patients with VAP. Patients with VAP were only included in two studies [31,32,64], the objectives of which, however, were very different. One was a prospective, noncomparative open study [31,32] that included ten patients with early onset VAP treated with levofloxacin, 500 mg/12 h. All patients had normal renal function. The objective of this study was to assess pharmacokinetic and pharmacodynamic characteristics of levofloxacin in this patient population and the results obtained have been described already. Clinical results included in the study demonstrated the efficacy of levofloxacin in patients with early onset VAP. At the end of treatment, only eight patients treated for a median of 8 days were evaluable. The overall success rate was 75%, with eradication of the initial causative pathogen in all cases. However, in three patients selection of levofloxacin-resistant microorganisms was observed (A. baumannii in two, P. aeruginosa in one).

The goal of the second study [64] was to compare the efficacy and safety of levofloxacin 750 mg and imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia, half of whom had VAP. This was a multicentre, prospective, randomised, open-label
trial conducted in North America. Patients were randomly assigned to one of two treatment arms: levofloxacin 750 mg/24 h given intravenously initially and then orally for 7–15 days or imipenem/cilastatin 500 mg to 1 g given intravenously every 6–8 h, followed by oral ciprofloxacin 750 mg every 12 h for 7–15 days. Doses were adjusted to renal function. Adjunctive antibacterial therapy was mandatory in patients with documented or suspected \( P. \) aeruginosa, including ceftazidime 2 g/8 h (or noncaepenem \( \beta \)-lactam) in the levofloxacin arm, or amikacin 7.5 mg/kg/12 h (or an alternative aminoglycoside) in the imipenem/cilastatin arm. Vancomycin was added to any of the groups in which MRSA was suspected. The primary predefined outcome measure was the clinical response in microbiologically evaluable patients. In patients evaluable for microbiological efficacy, clinical success (cure or improvement) was achieved in 58.1% of patients who received levofloxacin, compared with 60.6% of patients who received the comparator regimen [95% confidence interval (CI) −12.0 to 17.2]. Similar clinical results were seen in patients evaluable for clinical efficacy and in the intent-to-treat population. In the 187 patients evaluable for microbiologic efficacy, eradication was achieved in 66.7% of patients receiving levofloxacin and 60.6% of patients receiving imipenem/cilastatin (95% CI, −20.3 to 8.3). In this study, levofloxacin was at least as effective and was as well tolerated as imipenem/cilastatin, followed by ciprofloxacin in adult patients with nosocomial pneumonia, as demonstrated by comparable clinical and microbiological success rates. These findings, however, do not support the use of monotherapy with levofloxacin in patients with VAP since a high percentage of patients were given combined regimens because of suspected or confirmed \( P. \) aeruginosa infection [66].

In a subanalysis of the subgroup of patients with VAP from the aforementioned multicentre, prospective, randomised trial comparing levofloxacin and imipenem/cilastatin [67], 222 patients were included in the study cohort with half \((n = 111)\) of the patients assigned to each treatment group. The patients in both groups were similar with respect to age, severity of illness (APACHE II score 14.8 vs. 15.1), and duration of mechanical ventilation before the onset of VAP (7.8 vs. 9.8 days). The distribution of other markers of severity, including use of vasopressor drugs (17.1% vs. 12.6%), pleural effusion (2.7% vs. 0%), multilobar radiologic involvement (1.8% vs. 4.5%), bacteraemia (6.3% vs. 2.7%), or serum creatinine concentration greater than 1.5 mg/dL (8.1% vs. 12.6%) was similar in both arms. The study groups were well balanced in regard to MRSA isolates (10.8% vs. 9.9%), concomitant use of vancomycin (11.7% vs. 9.9%), or administration of empirical combinations of antibiotics for the treatment of suspected \( P. \) aeruginosa pneumonia (30.6% vs. 25.2%). The main pathogens treated in the levofloxacin group were MSSA (18 cases), \( P. \) aeruginosa (16 cases), \( S. \) marcescens (13 cases), and \( H. \) influenzae (13 cases), whereas \( H. \) influenzae (21 cases), MSSA (19 cases), \( P. \) aeruginosa (18 cases), and \( E. \) cloacae (11 cases) were the pathogens isolated in the imipenem/cilastin group. In five cases in each group, MRSA was cultured. Among the intention-to-treat population, clinical success (between 3 and 15 days after the end of treatment) was achieved in 58.6% of patients receiving levofloxacin compared with 63.1% of patients receiving imipenem/cilastatin (95% CI, −8.77% to 17.79%). Similar results were obtained in patients with VAP caused by \( P. \) aeruginosa (87.5% vs. 61.1%, \( p = NS \)). Multivariate analysis demonstrated that assignment to different antibiotic treatments (i.e., levofloxacin vs. imipenem/cilastatin) was not predictive of outcomes. The overall mortality was lower than 15%. The frequency of adverse events was similar (30.6% vs. 32.4%) and for only four patients in the levofloxacin group and two patients in the imipenem group, treatment was withdrawn because of adverse events. The only difference between treatment arms identified in the study was related to the development of \( P. \) aeruginosa superinfection: ten patients in the imipenem/cilastin group, compared with three patients in the levofloxacin group (\( p = 0.045 \)). Results of this secondary analysis in a population of patients with VAP suggests that levofloxacin and imipenem/cilastin are equivalent for the treatment of one of the most frequent and serious infections in patients admitted to the ICU.
These findings are similar to those reported for ciprofloxacin in the management of nosocomial pneumonia in prospective, randomised and comparative studies [20,68–70]. Imipenem was the comparator drug in two studies [20,68], ceftazidime in one, and the comparator treatment was not standardised in another study [70]. The efficacy of quinolones and comparator antibiotics was similar in the individual studies as well as in a meta-analysis of all trials of quinolones for treatment of nosocomial pneumonia, with a pooled odds ratio for clinical cure of 1.12 (95% CI, 0.80–1.55). In the studies in which data on microbiological outcome was provided [20,64,68], there was a lower tendency towards the emergence of resistant pathogens especially {P. aeruginosa} among levofloxacin-treated patients.

Paradoxically, despite the small number of studies in critically ill patients, a progressive increase in the use of levofloxacin in ICUs throughout Spain has been observed. Levofloxacin was the 10th antimicrobial agent most frequently prescribed in 2004, the 11th among those used in patients with extra-ICU nosocomial infection, and the 13th among antibiotics used for the treatment of ICU-acquired infection (annual report ENVIN-UCI 2004, unpublished data).

In an observational study of the use of levofloxacin in critically ill patients, with the participation of 30 Spanish ICUs [34] and an analysis of 543 prescriptions of this drug, 32.2% of all indications corresponded to treatment of nosocomial infections, especially those acquired in the ICU. In a secondary analysis of data from this study, focused on the use of levofloxacin for the treatment of pneumonia [72], 39 patients with ICU-acquired pneumonia, most of them in relation to mechanical ventilation (87.2%), received levofloxacin. Combined antibiotic treatment was administered to 25 patients and the response was satisfactory in 78.3% of cases. Although the aim of this descriptive study was not to assess the effectiveness of levofloxacin in VAP, data on the use of this drug confirm that levofloxacin is an alternative in this clinical situation.

CRITERIA TO BE CONSIDERED IN CHOOSING LEVOFLOXACIN FOR DIRECTED TREATMENT OF VAP

A large number of antimicrobial agents evaluated in clinical trials have been approved by the regulatory agencies for use in the treatment of VAP. The choice of one of these drugs in daily practice depends on different factors, such as: inclusion in therapeutic guidelines recommended by prestigious scientific societies [6,19]; characteristics of the individual patients with VAP (immunosuppression, allergy to β-lactams, renal dysfunction, etc.); risk factors for multidrug resistant pathogens; possibility to switch to the oral route (sequential treatment); and cost (drug and monitoring of plasma concentrations). Levofloxacin has been approved by the US Food and Drug Administration (FDA) for use in the treatment of nosocomial pneumonia, including those caused by {P. aeruginosa} [73]. Criteria to be considered in choosing levofloxacin among other antimicrobial agents for the empirical and directed treatment of VAP are as follows:

1. **Patients with suspected or confirmed allergy to β-lactam antibiotics.** The majority of antibiotics used in the treatment of VAP, both empirical and directed, are β-lactams. Levofloxacin is a primary antibiotic of choice in this clinical situation, either as monotherapy (early onset VAP, no risk of multiresistant pathogens) or combined with aminoglycosides and/or glycopeptides (late onset VAP, risk for multiresistant pathogens). When the drug is used empirically in monotherapy, it should be remembered that in patients with successive re-admissions to hospital and previous exposure to fluoroquinolones, resistance to levofloxacin and other quinolones against {P. aeruginosa} and {Strep. pneumoniae} has been reported [74,75].

2. **Patients with impairment of renal function.** Levofloxacin is an alternative to aminoglycosides for empirical treatment with combined antibiotics in patients with renal dysfunction or at high risk of renal failure (advanced age, haemodynamic instability). Levofloxacin is the drug of choice if various nephrotoxic drugs are used simultaneously, such as vancomycin, amphotericin or cyclosporine.

3. **Need to extend antibiotic coverage to intracellular pathogens.** Patients immunocompromised because of an underlying disease or medications administered can develop VAP in which a large list of pathogens can be implicated, including *Legionella pneumophila*. Antibiotic coverage for this pathogen is particularly indicated in hospitals with *L. pneumophila* endemicity or if
**L. pneumophila** has been identified in their water systems. Levofloxacin has an adequate antibacterial activity against this microorganism [76] and has demonstrated its usefulness in circumstances of endemicity or outbreaks [77].

4 **High concentrations in lung tissue and respiratory secretions.** The penetration capacity of levofloxacin in different tissues, especially alveoli and lung tissue [21–23], is associated with high concentrations of the antibiotic in the infection site, as opposed to reduced penetration and low levels in the lung tissue as with the use of aminoglycosides [78]. Concentration of levofloxacin in the lung tissue is higher than that achieved with ciprofloxacin, given at the recommended doses according to the technical specifications of the products [79]. For this reason, although higher inhibitory concentrations for *P. aeruginosa* are required with this antibiotic, different pharmacodynamic relationships are favourable to levofloxacin at doses of 500 mg/12 h, as compared with ciprofloxacin at doses of 400 mg/12 h [79,80]. According to pharmacodynamic indicators, both antimicrobial agents are equivalent; no comparative study has been performed to assess the clinical differences between the drugs.

5 **Possibility of sequential therapy in patients with satisfactory clinical response.** The minimum criteria for the use of sequential therapy include the availability of both intravenous and oral formulations of the drug, and demonstration of sufficient bioavailability to ensure plasma equivalent concentrations. Levofloxacin is a new quinolone that meets both requirements, and multiple studies have shown the usefulness of this drug in the treatment of hospitalised patients with a low level of severity of illness [49–57,81]. In the ICU setting, it has been shown that up to one third of critically ill patients receiving levofloxacin treatment was switched to the oral route [34]. These are patients with less severe clinical conditions in whom antibiotic treatment was started as monotherapy. Cost-effectiveness studies of levofloxacin compared with ceftriaxone for the treatment of community-acquired pneumonia have shown that oral administration of the drug, when switching from the intravenous to the oral route was possible, was associated with lower resource consumption, mostly due to differences in hospitalisation costs [82,83]. This aspect, however, is less relevant in critically ill patients admitted to the ICU.

6 **Synergistic activity in combined treatment against *P. aeruginosa*.** In the treatment of infections due to *P. aeruginosa*, treatment with a combination of antibiotics is recommended in order to increase the antibacterial spectrum of empirical treatment and to enhance the bactericidal power of directed therapy [6,19], although up to the present time there is no evidence for a greater efficacy of combined antibiotic treatment vs. monotherapy with an active antimicrobial agent in the treatment of infections caused by this pathogen [84,85]. Levofloxacin has shown different rates of synergism when administered in association with cefepime, ceftazidime, imipenem, and piperacillin/tazobactam, indicating that combination with these antibiotics increases its activity against *P. aeruginosa* [80,86–88]. Although the MIC of ciprofloxacin for *P. aeruginosa* is four-fold lower than the MIC of levofloxacin (0.124 mg/L vs. 0.5 mg/L), different studies showed that the percentage of strains susceptible to both antibiotics is very similar [89–92].

7 **Lower capacity to induce *P. aeruginosa* resistance.** An in-vitro study demonstrated the lower capacity to induce resistance against *P. aeruginosa* with the association of imipenem plus levofloxacin [93,94]. Another in-vitro study with different strains of *P. aeruginosa* has shown a higher bactericidal activity of levofloxacin in comparison with ciprofloxacin [95]. These data support the results of different comparative clinical studies on the use of quinolones (ciprofloxacin or levofloxacin) in the treatment of nosocomial pneumonia, in which a lower tendency towards the selection of resistant strains was demonstrated when quinolones were administered [20,64,68].

8 **No need to monitor plasma drug concentrations to ensure effectiveness and to avoid toxicity.** According to pharmacodynamic data on levofloxacin, it is recommended to prescribe doses of 500 mg/12 h when the drug is given empirically for the treatment of nosocomial pneumonia, including the potential presence of *P. aeruginosa* [31,32], although the new formulation of 750 mg may possibly improve the pharmacodynamic parameters related to...
greater effectiveness. In contrast to aminoglycosides and vancomycin, monitoring plasma drug concentrations to reduce risks of toxicity is not necessary.

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REFERENCES


33. Khan JB. Latest industry information on the safety profile of levofloxacin in the US. *Chemotherapy* 2001; **47** (Suppl. 3): 32–37.


