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ARTICLE

# Antimicrobial activity of prulifloxacin in comparison with other fluoroquinolones against community-acquired urinary and respiratory pathogens isolated in Greece

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**Abstract** Prulifloxacin, the prodrug of ulifloxacin, is a broad-spectrum fluoroquinolone rather recently introduced in certain European countries. We compared the antimicrobial potency of ulifloxacin with that of other fluoroquinolones against common urinary and respiratory bacterial pathogens. The microbial isolates were prospectively collected between January 2007 and May 2008 from patients with community-acquired infections in Greece. Minimum inhibitory concentrations (MICs) were determined for ciprofloxacin, levofloxacin, moxifloxacin (for respiratory isolates only), and ulifloxacin using the E-test method. The binary logarithms of the MICs [$\log_2$(MICs)] were compared by using the Wilcoxon signed-ranks test. A total of 409 isolates were studied. Ulifloxacin had the lowest geometric mean MIC for the 161 *Escherichia coli*, 59 *Proteus mirabilis*, and 22 *Staphylococcus saprophyticus* urinary isolates, the second lowest geometric mean MIC for the 38 *Streptococcus pyogenes* respiratory isolates (after moxifloxacin), and the third lowest geometric mean MIC for the 114 *Haemophilus influenzae* and the 15 *Moraxella catarrhalis* respiratory isolates (after ciprofloxacin and moxifloxacin). Compared with levofloxacin, ulifloxacin had lower $\log_2$(MICs) against *E. coli* ($p<0.001$), *P. mirabilis* ($p<0.001$), *S. saprophyticus* ($p<0.001$), and *S. pyogenes* ($p<0.001$). Compared with ciprofloxacin, ulifloxacin had lower $\log_2$(MICs) against *P. mirabilis* ($p<0.001$), *S. saprophyticus* ($p=0.008$), and *S. pyogenes* ($p<0.001$), but higher $\log_2$(MICs) against *H. influenzae* ($p<0.001$) and *M. catarrhalis* ($p=0.001$). In comparison with other clinically relevant fluoroquinolones, ulifloxacin had the most potent antimicrobial activity against the community-acquired urinary isolates studied and very good activity against the respiratory isolates.

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## Introduction

The quinolones represent one of the few synthetic classes of antimicrobial agents. Nalidixic acid, the first member of this class, is primarily active against Gram-negative pathogens, but members of subsequent fluoroquinolone generations show improved activity against Gram-positive cocci [1, 2]. Over the years, several analogs of the fluoroquinolone class of antibiotics have entered into different stages of clinical development. Relatively few, however, have made an important difference in terms of a broader spectrum of antimicrobial activity or of a better safety and clinical effectiveness

profile and have remained available in the market for clinical use [2].

Prulifloxacin is a fluoroquinolone with a broad spectrum of antimicrobial activity, which covers both Gram-negative and Gram-positive pathogens. It has lipophilic properties that facilitate the absorption from the gastrointestinal tract. It is metabolized by liver esterases to ulifloxacin, which is the active drug [3, 4]. Prulifloxacin has been approved for the treatment of complicated and uncomplicated lower urinary tract infections, acute exacerbation of chronic bronchitis, and acute bacterial rhinosinusitis [5]. Moreover, prulifloxacin has been used with good results in terms of quality of life in the treatment of chronic prostatitis due to common and atypical bacterial pathogens [6].

We sought to compare the potency of the antimicrobial activity of ulifloxacin with that of other clinically relevant fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, against common urinary and respiratory tract clinical bacterial isolates in Greece.

## Methods

We prospectively evaluated the antimicrobial activity of different fluoroquinolones against bacterial strains isolated from urinary and respiratory tract specimens collected from adult outpatients, between January 2007 and May 2008, at the University Hospital of Heraklion (Heraklion, Crete), and at the Iatropolis Diagnostic Center (Halandri, Athens), Greece. The urinary pathogens studied were *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*, while the respiratory pathogens studied were *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The examined specimens were: sputum from patients with acute exacerbation of chronic bronchitis, pharyngeal swabs from patients with acute tonsillopharyngitis, sinus exudates from patients with acute rhinosinusitis, ear exudates from patients with acute otitis media, and urine from patients with either complicated and uncomplicated urinary tract infections. Only one isolate per patient was allowed. No other inclusion or exclusion criteria were set. The data were collected prospectively and recorded in electronic databases. The study was approved by the Ethics Committee of the Alfa Institute of Biomedical Sciences (AIBS).

Quantitative urine cultures were performed on Columbia blood and MacConkey agar plates (bioMérieux SA, Marcy l'Etoile, France). Plates were incubated at 36 °C for 18–24 h. The culture media for the respiratory tract specimens included sheep blood agar, chocolate agar, and MacConkey agar (bioMérieux SA). Culture plates were incubated at 36 °C in 3–5 % $CO_2$ for 48 h. Species identification was done using conventional biochemical methods, the API system (bioMérieux SA), or the Vitek 2 automated system (bioMérieux SA).

Stock bacterial cultures were prepared by using an absorbent bead system (Pro-Lab Diagnostics, Austin, TX, USA), and microorganisms were stored at −80 °C. Subcultures were performed before testing. Ciprofloxacin, levofloxacin, and ulifloxacin were tested against all isolates, whereas moxifloxacin was tested only against the respiratory tract isolates. The E-test method was used to assay the antibiotic susceptibility, according to the manufacturer's guidelines (AB Biodisk, Solna, Sweden). *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 were used as quality control strains.

The 2009 Clinical and Laboratory Standards Institute (CLSI) criteria were used for the interpretation of the antimicrobial susceptibility of the studied isolates [7]. Regarding *M. catarrhalis*, the CLSI has published criteria only for ciprofloxacin, thus, the criteria referring to *H. influenzae* were used for the interpretation of the susceptibility of the *M. catarrhalis* isolates to both levofloxacin and moxifloxacin [8]. The CLSI has not published breakpoints for ulifloxacin; susceptibility to this agent was tentatively defined by a minimum inhibitory concentration (MIC) equal to or less than 1 mg/L [9]. The antimicrobial potency of the tested fluoroquinolones was assessed first by comparing their geometric mean MIC, the $MIC_{90}$, and the $MIC_{50}$. In addition, the MICs of the tested antibiotics were transformed to their binary logarithms and the $\log_2$(MICs) of ulifloxacin were compared against those of the comparator fluoroquinolones, using the Wilcoxon signed-ranks test [10]. This comparison was the primary criterion for the antimicrobial potency in our study. A $p$-value <0.05 was considered to denote statistical significance. The statistical analysis was performed with SPSS Statistics v.17.0 (SPSS Inc., Chicago, IL, USA).

## Results

A total of 409 bacterial isolates, including 242 (59.2 %) isolates form urinary tract specimens and 167 (40.8 %) isolates from respiratory tract specimens, were included in this study. The 242 urinary tract isolates were 161 *E. coli* (66.5 %), 59 *P. mirabilis* (24.4 %), and 22 *S. saprophyticus* (9.1 %) isolates. The 167 respiratory tract isolates were 114 *H. influenzae* (68.3 %), 38 *S. pyogenes* (22.8 %), and 15 *M. catarrhalis* (9.0 %) isolates. The 167 respiratory specimens consisted of 63 (37.7 %) sputum specimens, 51 (30.5 %) pharyngeal swabs, 22 (13.2 %) sinus exudates, and 16 (9.6 %) ear exudates. The type of culture specimen was not specifically recorded for the remaining 15 (9.0 %) respiratory isolates.

Table 1 presents both the distribution of the MICs (rounded to the upper two-fold dilution, for the purpose of this table) against the isolates and their cumulative percentage of

**Table 1** Distribution of minimum inhibitory concentrations[a] of ulifloxacin and other fluoroquinolones against community-acquired urinary and respiratory tract pathogens and cumulative percentage inhibition at different concentrations

| **Pathogens (number of isolates)/** Fluoroquinolones | **Minimum inhibitory concentration (mg/l)[a]** Number of isolates Cumulative percent of isolates inhibited | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **0.002** | **0.004** | **0.008** | **0.016** | **0.032** | **0.064** | **0.125** | **0.25** | **0.5** | **1** | **2** | **4** | **8** | **16** | **32** | **>32** |
| ***Escherichia coli* (n=161)** | | | | | | | | | | | | | | | | |
| Ciprofloxacin | | 2 | 63 | 71 | 6 | | 4 | 3 | 1 | | | 2 | | | 1 | 8 |
| | | 1.2% | 40.4% | 84.5% | 88.2% | | 90.7% | 92.5% | 93.2% | | | 94.4% | | | 95.0% | 100% |
| Levofloxacin | | | | 6 | 50 | 79 | 7 | 1 | 6 | 1 | | | | 2 | 3 | 6 |
| | | | | 3.7% | 34.8% | 83.9% | 88.2% | 88.8% | 92.5% | 93.2% | | | | 94.4% | 96.3% | 100% |
| Ulifloxacin | | 1 | 47 | 89 | 5 | 3 | 4 | | 1 | 1 | 2 | | 1 | 4 | | 3 |
| | | 0.6% | 29.8% | 85.1% | 88.2% | 90.1% | 92.5% | | 93.2% | 93.8% | 95% | | 95.7% | 98.1% | | 100% |
| ***Proteus mirabilis (n=59)*** | | | | | | | | | | | | | | | | |
| Ciprofloxacin[b] | | | | 32 | 12 | | | | 8 | 3 | | | | 1 | | 1 |
| | | | | 56.1% | 77.2% | | | | 91.2% | 96.5% | | | | 98.2% | | 100% |
| Levofloxacin | | | | | | 41 | 3 | | | 11 | 1 | 1 | | 1 | | 1 |
| | | | | | | 69.5% | 74.6% | | | 93.2% | 94.9% | 96.6% | | 98.3% | | 100% |
| Ulifloxacin | | | 3 | 39 | 4 | | | 1 | 10 | | | 1 | | | | 1 |
| | | | 5.1% | 71.2% | 78.0% | | | 79.7% | 96.6% | | | 98.3% | | | | 100% |
| ***Staphylococcus saprophyticus (n=22)*** | | | | | | | | | | | | | | | | |
| Ciprofloxacin | | | | | | | 1 | 21 | | | | | | | | |
| | | | | | | | 4.5% | 100% | | | | | | | | |
| Levofloxacin | | | | | | | | 2 | 20 | | | | | | | |
| | | | | | | | | 9.1% | 100% | | | | | | | |
| Ulifloxacin | | | | | | | 1 | 21 | | | | | | | | |
| | | | | | | | 4.5% | 100% | | | | | | | | |
| ***Haemophilus influenzae (n=114)*** | | | | | | | | | | | | | | | | |
| Ciprofloxacin | 1 | | 21 | 79 | 7 | 1 | 2 | 2 | | 2 | | | | | | |
| | 0.9% | | 18.4% | 87.7% | 93.9% | 94.7% | 96.5% | 98.2% | | 100% | | | | | | |
| Levofloxacin | 1 | | 1 | 35 | 62 | 7 | 4 | | 3 | 1 | | | | | | |
| | 0.9% | | 1.8% | 32.5% | 86.8% | 93.0% | 96.5% | | 99.1% | 100% | | | | | | |
| Moxifloxacin | 1 | | 2 | 40 | 52 | 13 | 4 | 2 | | | | | | | | |
| | 0.9% | | 2.6% | 37.7% | 83.3% | 94.7% | 98.2% | 100% | | | | | | | | |
| Ulifloxacin | 1 | | 3 | 45 | 41 | 17 | 2 | 1 | 4 | | | | | | | |
| | 0.9% | | 3.5% | 43% | 78.9% | 93.9% | 95.6% | 96.5% | 100% | | | | | | | |
| ***Streptococcus pyogenes (n=38)*** | | | | | | | | | | | | | | | | |
| Ciprofloxacin[c] | | | | | | | 5 | 29 | 4 | | | | | | | |
| | | | | | | | 13.2% | 89.5% | 100% | | | | | | | |
| Levofloxacin | | | | | | | | 7 | 31 | | | | | | | |
| | | | | | | | | 18.4% | 100% | | | | | | | |
| Moxifloxacin[d] | | | | | | 6 | 25 | 7 | | | | | | | | |
| | | | | | | 15.8% | 81.6% | 100% | | | | | | | | |
| Ulifloxacin | | | | | | 2 | 29 | 7 | | | | | | | | |
| | | | | | | 5.3% | 81.6% | 100% | | | | | | | | |
| ***Moraxella catarrhalis (n=15)*** | | | | | | | | | | | | | | | | |
| | **0.002** | **0.004** | **0.008** | **0.016** | **0.032** | **0.064** | **0.125** | **0.25** | **0.5** | **1** | **2** | **4** | **8** | **16** | **32** | **>32** |
| Ciprofloxacin | | | | 2 | 12 | | | 1 | | | | | | | | |
| | | | | 13.3% | 93.3% | | | 100% | | | | | | | | |
| Levofloxacin | | | | | 2 | 12 | | 1 | | | | | | | | |
| | | | | | 13.3% | 93.3% | | 100% | | | | | | | | |
| Moxifloxacin | | | | | 7 | 8 | | | | | | | | | | |
| | | | | | 46.7% | 100% | | | | | | | | | | |
| Ulifloxacin | | | | | 4 | 10 | | 1 | | | | | | | | |
| | | | | | 26.7% | 93.3% | | 100% | | | | | | | | |

[a] For the purpose of summarizing the data for this Table, the E-test readings were rounded to the upper two-fold dilution

[b] The dotted vertical cell lines represent the minimum inhibitory concentration breakpoints of susceptibility (see text)

[c] Data for ciprofloxacin were available for 57 of the 59 *P. mirabilis* isolates

[d] The Clinical and Laboratory Standards Institute had not issued interpretative breakpoints for the susceptibility of *S. pyogenes* to ciprofloxacin and moxifloxacin

inhibition with increasing MICs. Eleven (6.8 %) of the 161 *E. coli* isolates were resistant to both ciprofloxacin and levofloxacin. One of these isolates, with a ciprofloxacin MIC of 3 mg/L and a levofloxacin MIC of 12 mg/L, remained susceptible to ulifloxacin (MIC of 1 mg/L). The remaining ten ciprofloxacin- and levofloxacin-resistant *E. coli* isolates were also non-susceptible to ulifloxacin. Cross-resistance for all of the above three fluoroquinolones was also observed for the two ciprofloxacin-resistant *P. mirabilis* isolates.

Table 2 presents the modal MIC, $MIC_{50}$, $MIC_{90}$, and the geometric mean MIC of the tested antibiotics against all the isolates.

**Table 2** Summary data regarding the antimicrobial potency of ulifloxacin and other fluoroquinolones against community-acquired urinary and respiratory pathogens

| Pathogens (number of isolates)/ fluoroquinolones | Modal MIC | $MIC_{50}$ | $MIC_{90}$ | Geometric mean MIC | *p*-Value for the difference in $log_2$(MICs) (versus ulifloxacin) |
|---|---|---|---|---|---|
| *Escherichia coli* (*n*=161) | | | | | |
| Ciprofloxacin | 0.008 | 0.012 | 0.125 | 0.020 | 0.79 |
| Levofloxacin | 0.047 | 0.047 | 0.380 | 0.072 | <0.001 |
| Ulifloxacin | 0.012 | 0.012 | 0.064 | 0.020 | NA |
| *Proteus mirabilis* (*n*=59) | | | | | |
| Ciprofloxacin[a] | 0.016 | 0.016 | 0.500 | 0.045 | <0.001 |
| Levofloxacin | 0.047 | 0.640 | 1.000 | 0.127 | <0.001 |
| Ulifloxacin | 0.016 | 0.016 | 0.380 | 0.035 | NA |
| *Staphylococcus saprophyticus* (*n*=22) | | | | | |
| Ciprofloxacin | 0.250 | 0.250 | 0.250 | 0.236 | 0.008 |
| Levofloxacin | 0.500 | 0.500 | 0.500 | 0.447 | <0.001 |
| Ulifloxacin | 0.250 | 0.250 | 0.250 | 0.217 | NA |
| All urinary isolates (*n*=242) | | | | | |
| Ciprofloxacin | 0.016 | 0.016 | 0.380 | 0.031 | 0.13 |
| Levofloxacin | 0.047 | 0.047 | 0.750 | 0.098 | <0.001 |
| Ulifloxacin | 0.016 | 0.016 | 0.250 | 0.028 | NA |
| *Haemophilus influenzae* (*n*=114) | | | | | |
| Ciprofloxacin | 0.012 | 0.012 | 0.023 | 0.015 | <0.001 |
| Levofloxacin | 0.023 | 0.023 | 0.047 | 0.026 | 0.75 |
| Moxifloxacin | 0.023 | 0.023 | 0.064 | 0.024 | 0.41 |
| Ulifloxacin | 0.016 | 0.023 | 0.047 | 0.025 | NA |
| *Streptococcus pyogenes* (*n*=38) | | | | | |
| Ciprofloxacin | 0.250 | 0.250 | 0.380 | 0.223 | <0.001 |
| Levofloxacin | 0.380 | 0.380 | 0.500 | 0.378 | <0.001 |
| Moxifloxacin | 0.125 | 0.125 | 0.190 | 0.113 | 0.17 |
| Ulifloxacin | 0.125 | 0.125 | 0.190 | 0.120 | NA |
| *Moraxella catarrhalis* (*n*=15) | | | | | |
| Ciprofloxacin | 0.023 | 0.023 | 0.032 | 0.026 | 0.001 |
| Levofloxacin | 0.047 | 0.047 | 0.047 | 0.049 | 0.458 |
| Moxifloxacin | 0.032 | 0.047 | 0.064 | 0.043 | 0.547 |
| Ulifloxacin | 0.047 | 0.047 | 0.064 | 0.046 | NA |
| All respiratory isolates (*n*=167) | | | | | |
| Ciprofloxacin | 0.012 | 0.016 | 0.250 | 0.029 | <0.001 |
| Levofloxacin | 0.023 | 0.032 | 0.380 | 0.050 | <0.001 |
| Moxifloxacin | 0.032 | 0.032 | 0.125 | 0.036 | 0.21 |
| Ulifloxacin | 0.016 | 0.032 | 0.125 | 0.038 | NA |
| All isolates (*n*=409) | | | | | |
| Ciprofloxacin | 0.016 | 0.016 | 0.250 | 0.030 | 0.002 |
| Levofloxacin | 0.047 | 0.047 | 0.500 | 0.074 | <0.001 |
| Moxifloxacin[b] | 0.032 | 0.032 | 0.125 | 0.036 | 0.21 |
| Ulifloxacin | 0.016 | 0.016 | 0.190 | 0.032 | NA |

*MIC* minimum inhibitory concentration, *NA* not applicable

[a]Data for ciprofloxacin were available for 57 of the 59 *P. mirabilis* isolates

[b]Moxifloxacin was tested only against the 167 respiratory tract isolates

From the obtained results, ulifloxacin had the lowest geometric mean MIC against the *P. mirabilis* and *S. saprophyticus* urinary isolates, compared with ciprofloxacin and levofloxacin, and a low geometric mean MIC equal to that of ciprofloxacin against the *E. coli* urinary isolates. Ciprofloxacin had the lowest geometric mean MIC against the *H. influenzae* and *M. catarrhalis* respiratory isolates, while moxifloxacin had the lowest geometric mean MIC against the *S. pyogenes* respiratory isolates.

Ulifloxacin had lower $\log_2$(MICs) than levofloxacin against all isolates, except for *H. influenzae* and *M. catarrhalis*, and lower $\log_2$(MICs) than ciprofloxacin against *P. mirabilis*, *S. saprophyticus*, and *S. pyogenes*. On the contrary, ciprofloxacin had lower $\log_2$(MICs) than ulifloxacin against *H. influenzae* and *M. catarrhalis*. No difference was observed in the $\log_2$(MICs) between ulifloxacin and moxifloxacin for any of the three respiratory pathogens studied.

## Discussion

In our study, ulifloxacin, the active drug for prulifloxacin, showed potent in vitro antimicrobial activity against common, community-acquired, urinary, and respiratory isolates in Greece. Fluoroquinolone resistance was rare among the studied isolates and cross-resistance was observed for all of the 13 ciprofloxacin-resistant isolates, except for one *E. coli* that remained susceptible to prulifloxacin. The mutational resistance to fluoroquinolones, which relates to modifications in the DNA gyrase or topoisomerase IV genes, affects all members of this class. This might not be the rule for other, plasmid-mediated mechanisms of fluoroquinolone resistance, such as the expulsion of these drugs out of the cell through multidrug efflux pumps or their inactivation by the AAC(6′)-Ib-cr enzyme [2]. The availability of different fluoroquinolone compounds for clinical use could, therefore, be clinically important.

Among the fluoroquinolones, prulifloxacin and levofloxacin have a very broad spectrum of antimicrobial activity, which covers both Gram-negative and Gram-positive aerobes, including *P. aeruginosa* and *S. pneumoniae*. Prior studies have shown that ulifloxacin has very potent in vitro antimicrobial activity against Gram-negative pathogens [11]. The ulifloxacin MICs and minimum bactericidal concentrations tend to be equal or even lower compared with ciprofloxacin, while they are generally lower compared with levofloxacin, for most Gram-negative pathogens, including *P. aeruginosa* [12–14]. The mutant prevention concentration of ulifloxacin has also been shown to be lower in comparison with other relevant fluoroquinolones for both *E. coli* and *P. aeruginosa* [12, 15].

Other studies have reported that the in vitro activity of ulifloxacin, in terms of MICs, is generally similar or weaker compared with levofloxacin against Gram-positive pathogens [12–14]. Notably, one study has found relatively elevated ulifloxacin MICs against penicillin-intermediate and penicillin-resistant *S. pneumoniae* isolates from Spain [14]. However, a similar study in Thailand showed different results [16]. In the latter study and in two additional studies that evaluated *S. pneumoniae* isolates from Italy, including penicillin-non-susceptible ones, the ulifloxacin $MIC_{90}$ values were 2, 1, and 0.75 mg/L, respectively [13, 16, 17]. The antimicrobial activity of ulifloxacin against *S. pneumoniae* could be affected by the presence of efflux pumps [18]. Interestingly, it has been shown that prulifloxacin can decrease the IL-8 level in patients affected by chronic prostatitis due to *Chlamydia trachomatis* infection, demonstrating anti-inflammatory properties [6].

We were able to detect small differences in the antimicrobial potency of the tested fluoroquinolones using statistical methodology. However, such small differences might not necessarily translate into clinical effectiveness and the selection of the most appropriate treatment cannot solely rely on antimicrobial potency data. Other pharmacokinetic and pharmacodynamic properties of the antimicrobial agents should also be considered in this regard. The comparative clinical data between prulifloxacin and levofloxacin are rather limited and no significant differences in the primary endpoints were observed for the treatment of chronic bacterial prostatitis in a randomized clinical trial involving 96 patients [19].

In conclusion, ulifloxacin showed potent antimicrobial activity, in terms of log-transformed MICs, compared with other fluoroquinolones against common respiratory tract pathogens and, particularly, urinary tract pathogens isolated from outpatients in Greece. Regarding specifically the urinary tract pathogens studied, ulifloxacin had more potent activity than levofloxacin against all of these pathogens and more potent activity than ciprofloxacin against *P. mirabilis* and *S. saprophyticus*. Regarding the respiratory tract pathogens studied, ulifloxacin did not have a difference in potency compared with moxifloxacin, while it had more potent activity against *S. pyogenes* than both levofloxacin and ciprofloxacin; ciprofloxacin had the most potent activity against *H. influenzae* and *M. catarrhalis*. Thus, prulifloxacin, the prodrug of ulifloxacin, appears to be a useful addition in the antimicrobial armamentarium for community-acquired respiratory tract infections and, particularly, urinary tract infections. With its comparatively broad spectrum of antimicrobial activity, prulifloxacin could also be useful for the empirical treatment of various infectious syndromes in the community.

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