Review of Levofloxacin for the Treatment of Complicated Urinary Tract Infections and Acute Pyelonephritis

Levofloxacin is a fluoroquinolone antibiotic approved for the treatment of complicated urinary tract infections (cUTIs) and acute pyelonephritis (AP). A comprehensive review of the medical literature identified five publications evaluating levofloxacin for the treatment of either cUTIs or AP. All trials, although variable in their inclusion criteria and levofloxacin dosing strategies, reported microbiologic, clinical, and safety-related outcomes. High microbiologic eradication rates, ranging from 79.8% to 95.3%, were observed in the studies. Data regarding levofloxacin resistance, both at baseline and following therapy, was limited. Clinical success was observed to range from 82.6% to 93% when measured following the completion of therapy. These clinical and microbiologic results were comparable with the fluoroquinolone comparators in all trials. Levofloxacin was well tolerated in these studies, with headache, gastrointestinal effects, and dizziness the most commonly reported adverse events. The published data support the use of levofloxacin in cUTI and AP. Further trials are necessary to evaluate levofloxacin within specific patient sub-populations.

Introduction
Urinary tract infections (UTIs) are one of the most frequently occurring bacterial infections, accounting for over 7 million office visits and approximately 15% of community-prescribed antibiotics in the United States alone (1, 2). While the majority of these infections are uncomplicated, patients with complicated urinary tract infections (cUTIs) are, by definition, at greater risk of adverse outcomes. Levofloxacin, a widely-used fluoroquinolone, is approved in the U.S. for the treatment of cUTI and acute pyelonephritis (AP). This review will examine the clinical data available to evaluate the efficacy and safety of this antimicrobial for cUTI and AP.

Complicated urinary tract infections and pyelonephritis
Generally, a cUTI is considered to be an infection that occurs in the setting of any factor that predisposes to treatment failure or recurrence (3). However, no true consensus has been reached within the medical community as to what specifically defines a cUTI, and various definitions have been advanced. (4–6). Mandell’s Principles and Practice of Infectious Diseases defines cUTIs as urinary tract infections in men, pregnant women, children, hospitalized patients, and patients with functional or structural abnormalities of the urinary tract (7).

AP is commonly described as an infection of the upper urinary tract that encompasses fever and flank pain and/or tenderness that are accompanied by dysuria and urinary urgency and frequency, although it is more accurately diagnosed based on the presence of these symptoms along with bacteruria and acute renal infection (7). AP was formerly treated largely on an inpatient basis, but a recent trend towards outpatient management of this condition has been noted (8).

Methods
The PubMed search engine was used to query...
Three trials were conducted in the U.S. (11, 12, 14), two trials in the U.S. and Canada (14), and one trial was conducted in Taiwan (13). The latter was also the only single-center trial. Targeted sample size was rarely reported in these studies, with only one paper both identifying and reaching a stated goal for number of patients enrolled (11).

The definition of cUTI varied across the four trials including patients with these infections. (11–13, 15). Four trials included AP patients. In three of the trials, the definitions of AP were similar with both symptoms and abnormal laboratory results required for inclusion (11, 16). In contrast, one trial required only a clinical diagnosis of AP (13). All trials assessed the outcomes of microbiologic eradication and clinical success. These definitions were similar across all trials (Table 1).

In each of the six trials, another fluoroquinolone was selected as the comparator treatment (ciprofloxacin in three trials, lomefloxacin in two trials, and ofloxacin in one trial).

Four trials excluded patients with decreased renal function. Peng excluded patients with renal failure (and other extremely severe underlying diseases) (13). Of the two trials described in Richard et al, one excluded all patients with a creatinine clearance less than 50 ml/min and the second excluded those with a creatinine clearance less than 20 ml/min (14). In the latter trial, dosing was altered for those with a creatinine clearance between 20 and 50 ml/min. This same exclusion criterion (creatinine clearance of less than 20 ml/min) and altered dosing scheme was also applied in the study by Klimberg et al (12). In both publications, no data were provided as to the number of patients receiving altered dosing, nor were the efficacy and safety results reported within this subset of subjects. The cUTI trial by Richard et al also excluded patients with a creatinine clearance less than 50 ml/min (15).

Microbiologic response
Microbiologic eradication rates for levofloxacin were high in all trials, ranging from 79.8% to 95.3% when assessed following completion of therapy (Table 2). These rates were not statistically significantly different from that of the comparator treatments. Peng evaluated microbiologic efficacy only on day 5 of a 10-day course of levofloxacin and observed an eradication rate of 90%, which was also not significantly different from that of the comparator (13). Richard et al (15) reported relapse rates from the two trials described in that publication; at 4–6 weeks post-therapy, microbiologic relapse was observed in 13% of levofloxacin-treated subjects and in 6.5% of comparator-treated (ciprofloxacin or lomefloxacin) study subjects. The difference was not statistically significant (14).
Table 1. Overview of the study design of reviewed publications

<table>
<thead>
<tr>
<th>Population</th>
<th>Study design</th>
<th>No. subjects randomized</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Microbiologic outcome definition</th>
<th>Clinical outcome definition</th>
<th>Clinical success</th>
<th>Endpoints</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP or cUTI</td>
<td>Double-blind, multi-center RCT</td>
<td>1,093</td>
<td>Levofloxacin 750 mg IV/PO once daily for 5 days vs. Ciprofloxacin 400 mg IV/500 mg PO twice daily for 10 days</td>
<td>Eradication (&lt;10^4 cfu/ml) of uropathogen (s) identified at study entry</td>
<td>Clinical success (cure or improvement) • Cured (resolution of pretreatment clinical signs and symptoms without additional antibacterial therapy) • Improved (incomplete resolution of symptoms and no requirement for further antibiotic therapy)</td>
<td>End of blinded therapy: study day 11 ± 1</td>
<td>Post-therapy: study days 15–19</td>
<td>Post-study: study days 38–45</td>
<td>(11)</td>
</tr>
<tr>
<td>Outpatients with cUTI</td>
<td>Open-label, multi-center RCT</td>
<td>461</td>
<td>Levofloxacin 250 mg PO once daily for 7–10 days vs. Lomefloxacin 400 mg PO once daily for 14 days</td>
<td>Eradication (&lt;10^4 cfu/ml) of uropathogen (s) identified at study entry</td>
<td>Clinical success (cure or improvement) • Cured (complete resolution of the signs and symptoms associated with cUTI) • Improved (incomplete resolution of signs and symptoms and no requirement for further antibiotic therapy)</td>
<td>Post-therapy: (12) 5–9 days after completion of therapy</td>
<td>Long-term follow-up: 4–6 weeks after completion of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cUTI and AP</td>
<td>Double-blind, single-center RCT</td>
<td>46</td>
<td>Levofloxacin 100 mg PO three times daily for 10 days vs. Ofloxacin 200 mg PO three times daily for 10 days</td>
<td>Cleared or decreased bacteriuria (&lt;10^4 cfu/ml)</td>
<td>Clinical cure based on combined results on effect on pyuria, bacteriuria, and subjective symptoms</td>
<td>Endpoint evaluation: study day 5</td>
<td></td>
<td></td>
<td>(13)</td>
</tr>
<tr>
<td>Outpatients with cUTI</td>
<td>Double-blind, multi-center RCT</td>
<td>380</td>
<td>Levofloxacin 250 mg PO once a day for 10 days vs. Ciprofloxacin 500 mg PO twice daily for 10 days</td>
<td>Eradication (&lt;10^4 cfu/ml) of uropathogen (s) identified at study entry</td>
<td>Clinical Success (cured or improved) • Cured (resolution of signs and symptoms associated with active disease) • Improved (incomplete resolution of signs and symptoms but no need for additional antibiotic therapy)</td>
<td>Days 3–5 of therapy</td>
<td>Post-therapy: (14) 5–9 days after completion of therapy</td>
<td>Long-term follow-up: 4–6 weeks after therapy</td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>1. Double-blind, multi-center RCT</td>
<td>185</td>
<td>Levofloxacin 250 mg PO once a day for 10 days vs. Ciprofloxacin 500 mg PO twice daily for 10 days</td>
<td>Eradication (&lt;10^4 cfu/ml) of uropathogen (s) identified at study entry</td>
<td>Clinical cure • Complete resolution of signs and symptoms associated with active infection</td>
<td>Post-therapy: (15) 5–9 days after completion of therapy</td>
<td>Long-term follow-up: 4–6 weeks after therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Open-label, multi-center RCT</td>
<td></td>
<td>Levofloxacin 250 mg PO once daily for 7–10 days vs. Lomefloxacin 400 mg PO once daily for 14 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Publication reports the findings of two trials.

Abbreviations: AP = acute pyelonephritis, cfu = colony-forming units, cUTI: complicated urinary tract infection, RCT: randomized controlled trial, IV: intravenous, PO: oral.

Adapted from reference (9).
Adverse event rates were similar for levofloxacin and fluoroquinolone comparators in all publications. Only one publication specifically reported that no statistically significant differences in individual adverse event rates were found between treatment groups (11). The most commonly observed adverse events across all of the trials include: headache, diarrhea, dyspepsia, nausea, dyspnea, vaginitis, flatulence, and dizziness. Laboratory test abnormalities were infrequently reported.

Acute pyelonephritis versus complicated UTI

Four of the trials included in this review include patients with cUTI. However, two of these trials included patients with AP, and did not provide results stratified by infection. Of these two studies, one was primarily of AP patients (16/20 in the levofloxacin arm and 19/26 in the ofloxacin arm) (13), while Peterson et al enrolled primarily cUTI patients (391/537 in the levofloxacin arm and 391/556 in the ciprofloxacin arm) (11). The average levofloxacin efficacy rates for the two publications reporting efficacy for cUTI alone was 93.5% for microbiologic eradication and 92.6% for clinical success (12, 15). While Peterson et al did not report stratified efficacy results, a second publication by the authors (that was not included in this review due to duplication) reports the results for AP patients alone (10, 11). This publication also found levofloxacin to be equivalent to the comparator (ciprofloxacin) in both safety and efficacy (10). The average levofloxacin efficacy rates for this publication and the report by Richard et al (15) of two AP trials were 88.3% for microbiologic eradication and 88.5% for clinical success. Also noteworthy is that Peterson et al is the only trial of high-dose, short duration levofloxacin therapy (11). This trial observed efficacy rates that were 12.8% lower on average for microbiologic eradication.

In their cUTI trial, Richard et al reported a relapse rate of 9% in the levofloxacin-treated group at 4–6 weeks post-therapy, although 38% of the relapse cases were asymptomatic (15).

All publications provided information regarding the uropathogens that were most frequently isolated, and in all *Escherichia coli* (*E. coli*) was the most commonly isolated (average=61%). Among the studies that reported species-specific microbiologic eradication rates, eradication failed on average in 7% of cases caused by *E. coli* in levofloxacin-treated subjects (11, 12, 15). Peterson et al reported that levofloxacin non-susceptible bacteria were isolated from 6% of levofloxacin-treated subjects, and that no acquired resistance was observed (11). In their cUTI trial, Richard et al reported that 9.8% of isolates tested were not susceptible to levofloxacin (15). These were the only publications to provide such data.

**Clinical response**

Clinical success was observed to range from 82.6% to 93.0% when measured following the completion of therapy (Table 2). Again, Peng measured clinical efficacy mid-treatment and observed a clinical success rate of 90.0% (13). Statistical testing of the differences in clinical efficacy was only reported in three publications, and none of these reported any significant difference between the levofloxacin and comparator groups (11, 13, 15). In the remaining two publications, reported clinical efficacy rates were higher for levofloxacin than for the comparator (12, 14).

**Adverse events**

Only Peterson et al reported the occurrence of serious adverse events (17 events in levofloxacin-treated study subjects) (11). While not all events were detailed in the publication, one allergic reaction and one death were reported. The death was not reported to be treatment-related (11). Adverse event rates were similar for levofloxacin and fluoroquinolone comparators in all publications. Only one publication specifically reported that no statistically significant differences in individual adverse event rates were found between treatment groups (11). The most commonly observed adverse events across all of the trials include: headache, diarrhea, dyspepsia, nausea, dyspnea, vaginitis, flatulence, and dizziness. Laboratory test abnormalities were infrequently reported.

**Acute pyelonephritis versus complicated UTI**

Four of the trials included in this review include patients with cUTI. However, two of these trials included patients with AP, and did not provide results stratified by infection. Of these two studies, one was primarily of AP patients (16/20 in the levofloxacin arm and 19/26 in the ofloxacin arm) (13), while Peterson et al enrolled primarily cUTI patients (391/537 in the levofloxacin arm and 391/556 in the ciprofloxacin arm) (11). The average levofloxacin efficacy rates for the two publications reporting efficacy for cUTI alone was 93.5% for microbiologic eradication and 92.6% for clinical success (12, 15). While Peterson et al did not report stratified efficacy results, a second publication by the authors (that was not included in this review due to duplication) reports the results for AP patients alone (10, 11). This publication also found levofloxacin to be equivalent to the comparator (ciprofloxacin) in both safety and efficacy (10). The average levofloxacin efficacy rates for this publication and the report by Richard et al (15) of two AP trials were 88.3% for microbiologic eradication and 88.5% for clinical success. Also noteworthy is that Peterson et al is the only trial of high-dose, short duration levofloxacin therapy (11). This trial observed efficacy rates that were 12.8% lower on average for microbiologic eradication.
Levofloxacin for cUTI and AP

Discussion

The objective of this review was to identify and summarize the existing efficacy and safety data pertaining to the use of levofloxacin for the treatment of cUTI and AP. While our search of the literature revealed only five publications meeting the criteria for inclusion, all reported high microbiologic and clinical efficacy rates with minimal occurrences of serious adverse events. Despite this, the paucity of data in this area leaves several questions as to the generalizability of these trials.

Studies of cUTI included in this review generally did not present efficacy results stratified according to the specific complicating factor(s). One exception is the trial performed by Peterson et al, which reported significantly different microbiologic eradication rates among the catheterized and non-catheterized patients (11). These results suggest that the presence of catheters may influence outcomes in these studies, and future stratification of results by catheter usage is warranted.

All of the clinical studies presented compared levofloxacin with another fluoroquinolone with similar response rates noted. No data are available regarding a comparison of levofloxacin with other classes of antimicrobials. While direct comparisons are lacking, it has been noted that similar microbiologic success rates ranging from 71–91% have been reported in trials using beta-lactams and monobactams (piperacillin/tazobactam, ceftriaxone, aztreonam, ceftazidime), carbapenems (imipenem, meropenem, ertapenem) and aminoglycosides (amikacin) (17–20). It is not possible to directly compare the results of these studies with the included levofloxacin studies, but crude efficacy rates were similar.

Levofloxacin was generally well-tolerated in all of the reviewed trials; this is consistent with what has been observed in other settings at the currently approved doses (21). Additional adverse events not commonly reported in the reviewed publications, but that have been reported in association with levofloxacin, include photosensitivity, QTc prolongation, hypersensitivity, convulsions, Clostridium difficile-associated diarrhea, and tendon rupture; many of these adverse reactions are rarely reported and have been associated with other fluoroquinolones (21).

The majority of the patients included in the trials described in this review presented with infections of moderate severity, and most studies included only patients who received oral therapy on an outpatient basis. The clinical and microbiologic efficacy of levofloxacin in patients with more severe illness (including hospitalized patients) requires further study. Furthermore, larger studies are needed so that the efficacy of levofloxacin can be evaluated among patients infected with organisms other than E. coli, since the incidence of antimicrobial resistance in UTI caused by these pathogens is not well-described, and cUTI and AP are frequently caused by pathogens other than E. coli (22).

Furthermore, few studies provided meaningful information regarding the development of fluoroquinolone resistance. Although fluoroquinolone resistance in such uropathogens as E. coli remains somewhat rare in the U.S., the prevalence of such resistance is undoubtedly increasing. Peterson et al was the only publication to report on resistance that emerged during the course of therapy, although they reported zero occurrences of this event (11). New trials that examine levofloxacin in the setting of cUTI and/or AP should include data regarding the prevalence of resistance (whether it is present in the original infecting isolate or develops during fluoroquinolone therapy), as it is a mitigating factor in treatment failure.

Conclusions

Levofloxacin has demonstrated high rates of microbiologic and clinical success, with outcomes similar to those obtained by comparator fluoroquinolones in the included trials. It is difficult to assess the generalizability of studies of cUTI and/or AP because of the lack of a standardized definition of cUTI, a high degree of variability in study design, and the level of stratification with which data are reported. An important clinical outcome that was not adequately reported in the majority of these publications was the development of antimicrobial resistance while receiving therapy. This may be an important distinguishing factor among antimicrobials. Furthermore, more research is needed to determine optimal treatment durations and dosing regimens for antibiotics in the treatment of cUTI and AP. While levofloxacin has been associated with favorable outcomes in patients with AP and cUTI, further comparative trials are needed to establish the role of levofloxacin in comparison with alternative antimicrobial classes in the management of these infections.
REFERENCES