

Cumulative clinical experience from over a decade of use of levofloxacin in urinary tract infections: critical appraisal and role in therapy

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Abstract: The treatment of urinary tract infections (UTIs) continues to evolve as common uropathogens increasingly become resistant to previously active antimicrobial agents. In addition, bacterial isolates, which were once considered to be either colonizers or contaminants, have emerged as true pathogens, likely related to the more complex array of settings where health care is now delivered. Even though the reliability of many antimicrobial agents has become less predictable, the fluoroquinolone group of agents has remained a frequent, if not the most often prescribed, antimicrobial therapy for almost all types of UTIs. Levofloxacin has taken its position at the top of the list as one of the most regularly administered fluoroquinolone agents given to patients with a suspected or proven UTI. The authors review the clinical experience of the use of levofloxacin over the past decade and suggest that the use of levofloxacin for the treatment of UTIs, although still fairly dependable, is perhaps not the best use of this important antimicrobial agent.

Keywords: fluoroquinolone, antimicrobial agent, UTI, resistance

Introduction

More than a decade has passed since levofloxacin was introduced as one of the newer fluoroquinolone antimicrobial agents. Exhibiting greater activity against Gram-positive cocci than its predecessors in the fluoroquinolone class, levofloxacin quickly emerged as a mainstay option for the treatment of community-acquired respiratory tract infection, where *Streptococcus pneumoniae* is an important pathogen. Successful clinical trials pitting levofloxacin against already approved antimicrobial agents for the treatment of a variety of urinary tract infections (UTIs), along with the potential for shorter treatment courses with a drug administered once daily, proved to be two major factors leading to the very frequent prescribing of this medication for UTIs. As levofloxacin has not proven superior to alternative antimicrobial agents when treating UTIs caused by susceptible pathogens, the question of whether or not this is the best use for this valuable drug can be posed, particularly when less-expensive options are available. This comprehensive review of the utilization of levofloxacin for the treatment of UTIs is intended to help the prescriber make this decision.

UTIs are often classified, based on anatomic location, as either lower (cystitis) or upper (pyelonephritis, perinephric abscess), and as either complicated or uncomplicated, based on the host comorbidities as well as on neurological or structural abnormalities.¹ In general, except when encountered in a premenopausal, nonpregnant woman with no known anatomic urologic abnormality, most UTIs are felt to be complicated infections, and the etiologic microorganisms responsible for these infections are more likely to

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have resistance to at least one or more of the commonly used antimicrobial agents for treating UTIs.^{2,3} Another epidemiologic feature divides UTIs into two main groups: catheter-associated UTIs (CA-UTIs), which are almost always nosocomially related, and non-catheter-associated UTIs, which are most often community acquired.

Community-acquired UTIs account for more than 7 million office visits and 1 million hospitalizations annually in the United States (US), making them one of the most common recognized infections dealt with in clinical practice. In females, the incidence of UTIs increases with the onset of sexual activity, frequently in the adolescent years.⁴ Although UTIs are not uncommon in males during the first year of life, and are usually associated with urologic abnormalities, thereafter men under the age of 50 years rarely suffer from a UTI. The National Health and Nutrition Examination Survey, which used a survey with a self-reporting UTI history, reported the annual incidence of UTI in the US for women aged 18 years and older was 12.6%, whereas for men it was just 3%.⁵ An estimated 1 million cases of nosocomial UTI are diagnosed in the US annually, and most are related to indwelling urinary catheters. In fact, a CA-UTI is the most prevalent nosocomial infection, accounting for approximately 40% of all hospital-associated infections. However, many of these CA-UTIs are in reality nothing more than the unavoidable bacteriuria associated with having an indwelling bladder catheter, rather than real symptomatic infections.

Definitions and diagnosis of UTIs

The diagnosis of a UTI is based on a combination of clinical signs and symptoms localizing the infectious process to either the lower (dysuria, frequency, and urgency) or upper urinary tract (flank pain and fever with or without lower urinary tract symptoms), along with the finding of significant bacteriuria and pyuria (the presence of bacteria and pus in the urine, respectively). These criteria may not strictly apply to CA-UTIs, where much of the literature fails to distinguish between symptomatic and asymptomatic bacteriuria. Bacteriuria is best quantified by obtaining a urine specimen for culture from a fresh voided sample or via sterile urethral catheterization. Normally, urine in the bladder is sterile. However, urine specimens are often contaminated during the collection process. By quantitating bacteria in midstream clean-voided urine, it becomes possible to separate contamination from a true UTI. The number of bacteria isolated in these cultures defines the term “significant bacteriuria.” Voided urine usually contains 10^5 bacteria/mL in patients with infection. However, about one-third of young women with

symptomatic lower UTIs have fewer than 10^5 bacteria/mL of urine, prompting a consensus definition of cystitis as 10^3 colony-forming units (CFU)/mL or more of a uropathogen and, for pyelonephritis, 10^4 CFU/mL or more.⁶ Bacteriuria is not an uncommon finding in otherwise asymptomatic patients (particularly elderly women), and as such it has been assigned the term “asymptomatic bacteriuria.” Although the presence of bacteria in the urine increases the risk of a symptomatic UTI, with the exception of pregnant women or those about to undergo an invasive urologic procedure, it generally does not need to be looked for or treated.⁷

Additional to the entrance of bacteria into the bladder via an indwelling urinary catheter, the routes by which these microorganisms invade and spread within the urinary tract include the ascending, hematogenous, and lymphatic pathways. The ascending route of infection is the most common and more than 95% of UTIs involve a single bacterial species, the majority of which are Gram-negative aerobic bacilli. Uropathogenic *Escherichia coli*, a pathogen distinct from that which generally colonizes the gastrointestinal tract, is the predominant strain leading to 75%–95% of UTIs in otherwise healthy young women.⁸ Surface adhesins, as well as other attachment organelles unique to *E. coli* and other urinary pathogens, enable these microorganisms to adhere to epithelial cell membranes, thus promoting colonization of the perineum, vagina, and urethral area with bacteria normally found in the colon. Certain activities such as sexual intercourse are known to help these colonized bacteria ascend into the bladder, and at times into the kidney. The less common urinary pathogens include other members of the Enterobacteriaceae family, streptococci (especially group B beta-hemolytic streptococci), enterococcal species, staphylococcal species (most often *Staphylococcus saprophyticus* and *Staphylococcus aureus*) and *Candida* species. UTIs occurring in hospitals and long-term care facilities frequently involve a more varied group of organisms that may include various species of *Proteus*, *Klebsiella*, *Enterobacter*, *Providencia*, *Morganella*, *Citrobacter*, *Serratia*, and *Pseudomonas*, as well as other uncommon bacterial organisms.⁹ While, the isolation of *S. aureus* from the urine should suggest the possibility of a hematogenous derived process, it may also be related to instrumentation and indwelling urinary catheters.

Factors that need be taken into consideration when choosing an antimicrobial agent to treat a UTI include (1) the anatomic location of the infection (ie, upper versus lower urinary tract or prostate); (2) complicated versus uncomplicated infection; and (3) community versus nosocomial

acquisition of infection. In addition, local patterns of bacterial resistance, cost, patient compliance and allergy history must be taken into account.¹⁰ Table 1 provides information defining the various types of UTIs, the usual microorganisms encountered in these infections, and consensus antimicrobial agent recommendations. For over a decade of use and for every form of UTI, levofloxacin has had an important role in treating these infections.

Levofloxacin

Currently available fluoroquinolone antibiotics that are approved by the US Food and Drug Administration (FDA) for the treatment of UTIs (cystitis, prostatitis, complicated UTIs, and acute pyelonephritis) include ciprofloxacin, norfloxacin, ofloxacin, and levofloxacin. First patented in 1987 and placed into initial clinical use in Japan in 1993, levofloxacin received subsequent FDA approval in the US for the treatment of severe and life-threatening bacterial infections in 1996. Primarily considered to be an antimicrobial agent best suited for the treatment of various respiratory tract infections caused by susceptible bacterial organisms, levofloxacin has also gained approval for use in treating skin and skin-structure infections as well as for postexposure treatment of inhalation anthrax.¹¹ Moreover, based upon evidence resulting from various clinical trials, levofloxacin has proved effective for treating various forms of UTIs using different doses and durations of treatment in diverse patient populations. It is unique in that it has an approved indication for short-course regimens (5 days) for complicated UTIs and pyelonephritis, thus making it one of today's most frequently prescribed anti-infective medications for this indication. In fact, levofloxacin ranked nineteenth in world sales of prescribed drugs in the year 2007 and was the most frequently prescribed fluoroquinolone drug.

The first antimicrobial agent in the quinolone class, nalidixic acid, was derived from the antimalarial drug chloroquine.¹² The evolution of these synthetic quinolone antimicrobial agents involves side-chain substitutions and nuclear manipulations. Involving the common quinolone dual-ring structure, these modifications result in improvements in the spectrum and potency of antimicrobial activity and in superior bioavailability. The addition of a fluorine atom at position C-6 of the parent compounds (nalidixic acid and cinoxacin) gave rise to the original fluoroquinolones, commonly referred to as second-generation quinolones.¹³ As a group, these second-generation agents offer improved coverage against Gram-negative bacteria along with moderately enhanced Gram-positive antibacterial activity.

Marketed under the brand names LEVAQUIN® (Ortho-McNeil-Janssen Pharmaceuticals, Inc, Raritan, NJ) and Tavanic® (Sanofi-Aventis, Paris, France), the chemical name for levofloxacin is (–)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate. The levofloxacin compound is the L-isomer, or S-enantiomer, of the two stereoisomeric racemic drug substance ofloxacin. Being the more potent of the two ofloxacin stereoisomers, levofloxacin exhibits twice the in vitro potency of ofloxacin.¹⁴ The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair, and recombination.¹⁵ For most Gram-negative bacteria, DNA gyrase is the primary quinolone target; for many Gram-positive bacteria, topoisomerase IV is the primary target, with gyrase being the secondary target. These patterns appear to result from the relative sensitivities of these two topoisomerases to a given quinolone, with the more sensitive of the two enzymes defining the target of a particular quinolone and eventually attributing to the activity and potency of each drug against Gram-negative and/or Gram-positive bacterial microorganisms.¹⁶ In any event, the ultimate outcome of quinolone-driven rapid inhibition of bacterial DNA synthesis is rapid bacterial cell death, which takes place even among bacteria in stationary phases of growth.

Antimicrobial spectrum of activity

Levofloxacin, like all current fluoroquinolone agents, is most active against aerobic Gram-negative bacilli, particularly members of the Enterobacteriaceae family. Although ciprofloxacin remains the most potent of the available fluoroquinolones against Gram-negative bacteria, levofloxacin is the only other marketed drug belonging to this class of antimicrobial agents with sufficient activity for use against susceptible strains of *Pseudomonas aeruginosa*. A distinct advantage of levofloxacin and other advanced-generation fluoroquinolones over their predecessors is their enhanced antimicrobial activity against certain Gram-positive organisms, especially species of streptococci.¹⁷ However, in vitro susceptibility data may not translate into successful in vivo outcomes, owing to the fact that drug concentrations necessary for effective antimicrobial action at the specific site of infection may not be achievable when interpreted in relation to peak drug concentrations in serum. Nevertheless, even though activity in vitro is diminished in the presence

Table 1 Representative urinary tract infections (UTIs)

Type	Subtype	Definition	Microbiology	Therapy
Uncomplicated UTI	ASB ^a	Two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $> 10^5$ CFU/mL OR a single, clean-catch voided urine specimen with one bacterial species isolated in quantitative counts $\geq 10^5$ CFU/mL in men OR a single catheterized specimen with one bacterial specimen isolated in a quantitative count of $\geq 10^2$ CFU/mL in women or men AND No clinical signs or symptoms of infection All of the above AND A syndrome manifested as dysuria, frequency, urgency, and occasionally suprapubic tenderness	Enterobacteriaceae (<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Proteus mirabilis</i> , <i>Providencia stuartii</i> , <i>Morganella morganii</i>), coagulase-negative staphylococci, <i>Enterococcus</i> spp, <i>Gardnerella vaginalis</i>	No therapy indicated, unless the patient is pregnant or undergoing an invasive urologic procedure
	Cystitis ^b		<i>E. coli</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>Staphylococcus saprophyticus</i>	Nitrofurantoin monophosphate/macrocystals 100 mg PO bid for 5 days; TMP/SMX 160/800 mg PO bid for 3 days (avoid if resistance prevalence is $\geq 20\%$ or if used for UTI in the previous 3 months); fosfomycin trometamol 3 g PO single dose; pivmecillinam 400 mg bid for 5 days Ciprofloxacin 500 mg PO bid for 7 days if resistance in the community is $\leq 10\%$ Ciprofloxacin extended release 1 g PO daily for 7 days OR levofloxacin 750 mg PO daily for 5 days, if resistance $\leq 10\%$ If resistance in the community is $\geq 10\%$, an initial IV dose of a long-acting parenteral antibiotic such as ceftriaxone 1 g or a consolidated 24-hour dose of an aminoglycoside is recommended Removal/replacement of the catheter is recommended The therapy is usually based on microbiologic results and susceptibilities
	Pyelonephritis	Syndrome manifested as flank pain, tenderness, or both, and fever; often associated with dysuria, urgency, and frequency Associated with significant bacteriuria and acute infection in the kidney	<i>E. coli</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>S. saprophyticus</i>	
	CA-ASB/CA-UTI ^c	The urinary catheters literature generally reports on CA-ASB or catheter-associated bacteriuria (when no distinction is made between CA-ASB and CA-UTI) rather than CA-UTIs A CA-UTI is defined as the presence of either lower or upper UTI symptoms in a patient with a urinary catheter in place and significant bacteriuria	<i>Proteus</i> spp, <i>P. aeruginosa</i> , <i>Providencia</i> spp, <i>E. coli</i> , <i>K. pneumoniae</i> , <i>Serratia marcescens</i> , <i>Citrobacter freundii</i> , <i>Enterobacter cloacae</i> , <i>S. saprophyticus</i> , <i>Enterococcus</i> spp, <i>Candida</i> spp Long-term urinary catheters are usually associated with polymicrobial infections	

Complicated UTI	Complicated pyelonephritis, perinephric abscess, obstructive uropathy ^d	UTI in a host with significant comorbidities (eg, diabetes mellitus) and neurological or structural abnormalities (eg, urinary tract calculi) Suspect bacteremia if high fevers, rigors, or hypotension is evident	Enterobacteriaceae including multidrug-resistant strains MRSA	<p>Surgical evaluation and antibiotics based upon culture and susceptibility data or empirical therapy based upon the most likely etiologic pathogen(s)</p> <p>Empirical therapy recommendations in community-acquired complicated infection: consider piperacillin/tazobactam at 18 g of piperacillin/day; ampicillin/sulbactam at 12 g of ampicillin/day; third-generation cephalosporins (cefotaxime, ceftriaxone) or aztreonam 3–6 g/day; a parenteral fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycosides (gentamicin 3–5 mg/kg/day)</p> <p>Empirical therapy recommendations in hospitalized or long-term facility residents: consider an initial selection of antibiotics based on the antibiotic susceptibility patterns in the facility</p> <p>Consider ceftazidime (2–6 g/day); ceftepime (2–4 g/day); piperacillin/tazobactam at 18 g of piperacillin/day; aztreonam 3–6 g/day; imipenem 2 g/day; meropenem 1.5–3 g/day; or ertapenem 1 g/day</p> <p>All of the above in combination with aminoglycosides or parenteral fluoroquinolones</p> <p>Empirical therapy for MRSA must be considered</p>
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Abbreviations: ASB, asymptomatic bacteriuria; bid, twice daily; CA-ASB, catheter-associated asymptomatic bacteriuria; CA-UTI, catheter-associated urinary tract infection; CFU, colony-forming unit; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral administration; TMP/SMX, trimethoprim/sulfamethoxazole.

of urine (reduced by pH values below 7), except for those fluoroquinolones that are largely excreted by nonrenal mechanisms (ie, moxifloxacin), levofloxacin, as well as others, demonstrates drug concentrations in urine that are much higher than in serum. Table 2 lists the better-known Gram-negative and Gram-positive uropathogens against which levofloxacin has demonstrated sufficient antimicrobial activity in controlled clinical trials (approved indications based on in vivo data), and Table 3 lists other bacterial species against which antimicrobial activity data have been documented in studies conducted in vitro only. Although adequate in vitro activity suggests that levofloxacin may be effective against these potential UTI bacterial isolates in clinical practice, this fact has not been established in well-controlled clinical trials. Combining levofloxacin with a beta-lactam or aminoglycoside antimicrobial agent has not proven to be synergistic. When used together with one of these agents, the bactericidal activity achieved is at best additive, but generally indifferent, making such practice unwarranted when using levofloxacin to treat UTIs.¹⁷

Pharmacokinetics and pharmacodynamics

The favorable pharmacokinetic properties of the later-generation fluoroquinolones, in part, have encouraged their widespread use.¹⁸ Among these agents, levofloxacin has one of the best pharmacokinetic profiles (Table 4). Its bioavailability of 99%, rapid absorption (1–3 hours), and good tissue penetration (volume of distribution 102 L), allow for dependable treatment of UTIs and many other clinical infection syndromes with the oral administration of levofloxacin. Following the oral or intravenous administration of a 500 mg dose, a maximum concentration of 5.7 µg is reached, 60% of which is free or active owing to low serum protein binding (40%). The ingestion of food may delay the time it takes for

Table 2 Levofloxacin antimicrobial activity in vitro and in vivo for urinary pathogens (clinical studies described in manufacturer's Indications and Usage)¹²

Aerobic Gram-negative microorganisms	
<i>Enterobacter cloacae</i>	
<i>Escherichia coli</i>	
<i>Klebsiella pneumoniae</i>	
<i>Proteus mirabilis</i>	
<i>Pseudomonas aeruginosa</i>	
Aerobic Gram-positive microorganisms	
<i>Enterococcus faecalis</i> (many strains are only moderately susceptible)	
<i>Staphylococcus aureus</i> (methicillin-susceptible strains)	
<i>Staphylococcus epidermidis</i> (methicillin-susceptible strains)	
<i>Staphylococcus saprophyticus</i>	

Note: Approved indications based on in vivo data.

Table 3 Levofloxacin antimicrobial activity in vitro for urinary pathogens (clinical significance not established in adequate, well-controlled trials)

Aerobic Gram-negative microorganisms

Acinetobacter baumannii
Acinetobacter lwoffii
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Pantoea agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens

Aerobic Gram-positive microorganisms

Staphylococcus haemolyticus
Streptococcus agalactiae (beta-hemolytic group B)
Viridans streptococci

levofloxacin to attain its maximal serum concentration, but meals do not hinder the extent of levofloxacin absorption. Approximately 77% of levofloxacin is excreted as unchanged drug via renal elimination and this occurs at a clearance of 116 mL/min. Levofloxacin has an elimination half-life of 6–8 hours, allowing for once-daily dosing of this antimicrobial agent. Adjustments in levofloxacin dosing are required in the setting of renal insufficiency. It is recommended that the usual normal doses of 250–750 mg every 24 hours should be lowered to one-half this amount given every 24 hours if the glomerular filtration rate (GFR) is between 10 and 50 mL/min and extended to every 48 hours if the GFR falls below 10 mL/min.¹⁹ Neither hemo- nor peritoneal dialysis remove levofloxacin to any significant degree, eliminating the need for

Table 4 Levofloxacin pharmacokinetic/pharmacodynamic properties in serum (single oral dose)

Property	Dose (mg)		
	250	500	750
Bioavailability (%)	99	99	99
Protein binding (%)	40	40	40
T _{max} (h)	1.6	1.6	1.6
C _{max} (µg/mL)	2.8	5.1	9.3
Vd (L)	ND	102	83
Half-life (h)	7.3	6.3	7.5
AUC (µg.h/mL)	27	50	101
Renal excretion (%)	77	77	77
Renal clearance (avg mL/min)	142	103	ND

Abbreviations: AUC, area under the concentration-time curve; avg, average; C_{max}, maximum concentration; ND, not determined; T_{max}, time to maximum concentration; Vd, volume of distribution.

any further alterations in dosing in patients undergoing these procedures.²⁰ Fewer data are available on the effects of hepatic insufficiency on quinolone half-life, but in general no specific dosage adjustment is recommended when using levofloxacin in patients with Child classes A and B cirrhosis.

On the whole, interactions with other drugs are of minimal concern when using levofloxacin. However, the formation of a cation-quinolone complex is known to occur when levofloxacin is coadministered orally with antacids that contain the di- and trivalent cations aluminum, magnesium, zinc, or calcium. Absorption of these complexes is difficult, markedly reducing the bioavailability of levofloxacin as well as other orally administered fluoroquinolone agents when given together with antacids.²¹ Consequently, staggering the oral dosing of levofloxacin is suggested if given to a patient who is also receiving any product containing these cations. In general, it is recommended to administer the levofloxacin 2 hours before or 4 hours after the offending agent. Unlike some of its predecessor quinolone agents, levofloxacin has little or no effect on slowing the metabolism of the methylxanthines theophylline and caffeine, owing to its minimal inhibitory effect on the hepatic cytochrome P450 isoenzyme 1A2 (CYP1A2).²² Levofloxacin may uncommonly promote the anticoagulation effect of warfarin but has never convincingly been associated with excessive bleeding. Nonsteroidal anti-inflammatory drugs may potentiate the central nervous system stimulant effects of certain fluoroquinolones, particularly levofloxacin, and possibly lead to seizure activity, requiring a warning to patients receiving both medications.²³

Optimizing the bactericidal activity of any antimicrobial agent is critical in order to best achieve the main goal of their use – that is, to eradicate the causative organism(s) from the site of infection, thereby helping to bring about a successful clinical outcome. Ideally, the choice of antimicrobial agent would also effectively limit the development and selection of bacterial resistance to a single drug or to others within or outside the chosen antibiotic class. Therefore, using the minimal inhibitory concentration (MIC), either predicted or measured, of a bacterial isolate as the single criterion for selecting an agent fails to fully take into consideration the mechanism of antimicrobial killing for a particular drug. The pharmacodynamic parameters typically used to predict the antimicrobial efficacy of levofloxacin, as for all of the fluoroquinolones, are the ratios of the area under the concentration-time curve to the MIC (AUC/MIC) and peak concentration to the MIC (C_{max}/MIC).²⁴ Since the fluoroquinolones fall into this category of concentration-dependent killers, capitalizing

on these pharmacodynamic parameters not only improves the likelihood of bacterial eradication but also helps to prevent the development of resistance to fluoroquinolone agents, a relatively new concept known as the mutant prevention concentration effect.²⁵ Although a threshold value of AUC/MIC likely varies by disease state and target organism, when treating infectious processes involving aerobic Gram-negative bacilli, an AUC/MIC ratio greater than 125 has been associated with a superior probability of clinical and microbiologic cure.²⁶ By modeling the pharmacodynamic data from trials using levofloxacin, it has been determined that a C_{max}/MIC ratio of at least 12.2 is necessary in order to achieve favorable outcomes.²⁷ Retrospective analysis of pooled clinical trials suggested that the AUC/MIC ratio was also a relatively strong predictor of bacterial resistance, which was found to occur significantly more often when this ratio fell below 100.^{26,27}

Achieving these desired pharmacodynamic parameters is generally not an obstacle when using levofloxacin, particularly when treating UTIs, where the concentration of the drug greatly exceeds that of serum. The MICs of most Enterobacteriaceae for levofloxacin are significantly low, so that at a dose of 500 mg every 24 hours, the AUC of levofloxacin in serum (total drug) that approximates 48 mg/h/L yields an AUC/MIC ratio that is magnitudes higher than the desired target value of 125. Treating some isolates of *P. aeruginosa* with levofloxacin may prove to be more challenging, because of higher MICs against this organism. Nevertheless, the readily achievable drug levels in urine helps to overcome this problem.

Clinical efficacy

More than 600 million persons worldwide have been prescribed levofloxacin, mostly for the treatment of UTIs and respiratory tract infections.²⁸ Approval for its use in treating UTIs in the US dates back to 1998. Currently, levofloxacin is indicated for acute, mild to moderate uncomplicated UTIs (250 mg/day for 3 days), complicated UTIs or acute pyelonephritis (both 250 mg/day for 10 days and 750 mg/day for 5 days), and chronic bacterial prostatitis (500 mg/day for 28 days). The initial safety and efficacy trial comparing levofloxacin 250 mg orally once daily with ciprofloxacin 500 mg orally twice daily for 10 days was conducted in a randomized, double-blind, multicenter fashion in the US between 1993 and 1995.^{29,30} Microbiologic efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1–12 days post therapy in patients with a pathogen identified at entry. In the modified intent-to-treat (mITT) population,

which included all patients with a documented pathogen at baseline, overall bacteriologic eradication at the test-of-cure visit occurred in 83% and 84% in the levofloxacin and ciprofloxacin arms, respectively, in patients with complicated UTIs or acute pyelonephritis. In the microbiologically evaluable (ME) population (this did not include patients with missing response who were counted as failures in the mITT arm), the results were 92% for levofloxacin versus 93% for ciprofloxacin.

Levofloxacin is unique among the quinolone class of drugs in having the only indication for short-course regimens (5 days) for complicated UTIs and pyelonephritis. The observed non-inferiority of a shorter treatment course comes from a recent randomized, double-blind trial that compared levofloxacin 750 mg taken intravenously or orally once daily for 5 days with ciprofloxacin 400 mg taken intravenously or 500 mg taken orally twice daily for 10 days.³¹ Inclusion criteria consisted of the demonstration of greater than 10^5 CFUs of one or two uropathogens; two or more signs or symptoms including fever, leukocytosis, or costovertebral angle tenderness; and symptoms of a UTI. A complicated UTI was defined as having at least one complicating factor such as (1) a neurogenic bladder or urinary retention; (2) partial obstruction; or (3) intermittent catheterization. The majority of the isolated Gram-negative bacilli pathogens were *E. coli*, while enterococci accounted for about one-half of the infrequently involved Gram-positive bacterial organisms. The overall bacteriologic cure rates were 75% versus 75% for levofloxacin and ciprofloxacin, respectively, in the mITT population and 86% versus 89% for levofloxacin and ciprofloxacin, respectively, in those patients considered ME by meeting protocol-specific evaluability criteria. Bacteriologic cure rates in both populations were numerically higher in those diagnosed with acute pyelonephritis compared with complicated UTI, probably related to the lack of confounding complicating factors in the former. No significant difference was observed in relation to the specific pathogen isolated at baseline either within the levofloxacin-treated group or when compared with the ciprofloxacin arm. Not surprisingly, in the subgroup of patients who had a urinary catheter, eradication of the baseline bacteria occurred less frequently than in those who did not. However, an interesting observation was that a significantly greater proportion of patients treated with levofloxacin achieved microbiologic eradication compared with ciprofloxacin recipients with catheters. In spite of this finding, the rate of clinical success was not significantly different between levofloxacin and ciprofloxacin patients even in this group of catheterized individuals when keeping to the observed outcome in the overall population of treated patients.

Coinciding with the proliferation of trimethoprim/sulfamethoxazole (TMP/SMX)-resistant *E. coli*, fluoroquinolones were advocated for recommendation as the first-line empirical therapy of choice for acute uncomplicated cystitis,³² especially when local resistance to TMP/SMX exceeded 10%–20%. Over the years, levofloxacin has assumed the position as one of the most often, if not the most often, prescribed antimicrobial agents for this condition. However, contrary to the early 2000s, when levofloxacin was proposed for infections as simple as uncomplicated cystitis, the most recent Infectious Diseases Society of America guidelines have relegated levofloxacin, together with other fluoroquinolone agents, to alternative status, in part because of increasing fluoroquinolone local resistance of bacterial pathogens in both cystitis and acute pyelonephritis, along with the perceived need to reserve these important drugs for more serious infections such as pyelonephritis.

Chronic bacterial prostatitis, which involves the persistence of bacteria in the male lower urinary tract, is often an arduous condition to resolve. Factors that may influence the risk of antimicrobial treatment failure include suboptimal diffusion of many antimicrobial agents into the prostatic parenchyma, alterations in prostatic pH level associated with infection, and calculi that can act as foci for chronic bacterial infection. The fluoroquinolone agents are considered the preferred drugs for treatment of this condition, with cure rates of 70% or more in some series.³³ In the randomized, double-blind, multicenter trial comparing levofloxacin 500 mg with ciprofloxacin 500 mg, both once daily for a total of 28 days,³⁴ the microbiologic eradication rates at 5–18 days after completion of therapy were equivalent: 75% in the levofloxacin group and 76% in the ciprofloxacin group. Moreover, the eradication rates in both arms were similar, regardless of whether or not Gram-negative bacilli or Gram-positive pathogens were involved. Clinical success, defined as cure plus improvement with no need for further antimicrobial therapy 5–18 days after completion of treatment, and clinical long-term success (24–45 days after completion of treatment) were 75% and 66%, respectively, for levofloxacin-treated patients and 72% and 77%, respectively, for ciprofloxacin-treated patients. Although not proven in clinical trial, levofloxacin would appear to have a potential treatment advantage based upon the knowledge that in one study volunteers receiving a single dose of levofloxacin 250 mg were measured to have both plasma and prostatic fluid concentrations of drug significantly higher than those who were given a single dose of ciprofloxacin 250 mg.³⁵ Interestingly, a large, Canadian, randomized, placebo-controlled, multicenter trial

aimed at evaluating the safety and efficacy of 6 weeks of levofloxacin therapy (500 mg once daily) compared with placebo in chronic prostatitis/chronic pelvic pain syndrome resulted in symptom improvement that was not significantly different from that with placebo at the end of treatment or follow-up.³⁸ These results likely relate to the fact that only approximately 5% of men with chronic prostatitis/chronic pelvic pain syndrome have definite bacterial infection,³⁷ and therefore giving a drug aimed at the eradication of bacteria would intuitively seem to offer little, if any, advantage over other non-antimicrobial therapies.

All of the major clinical studies evaluating levofloxacin for the treatment of various UTIs used another fluoroquinolone drug as the comparator. Without exception, levofloxacin produced similar microbiologic and clinical response rates, with the major distinction being that levofloxacin performed equally well when only given for a 5-day treatment period. To date, no data are available regarding a comparison of levofloxacin with other classes of antimicrobial drugs. Nonetheless, recognizing the lack of direct comparisons, similar microbiologic success rates ranging from 71% to 91% have been reported in trials using beta-lactams, monobactams, carbapenems, and aminoglycosides.³⁸ However, a parenteral route of administration was necessary with these other agents.

Resistance

The huge expansion in the use of fluoroquinolone antimicrobial agents for a variety of infections, including conditions with proven indications as well as those lacking trial study data, has correlated with the increasing development of resistance. This disturbing phenomenon has occurred on both ecologic and individual levels.³⁹ The emergence of fluoroquinolone-resistant strains of Enterobacteriaceae among in- and outpatients in the US and around the world has outpaced that observed with Gram-positive pathogens, except in Asia, where *S. pneumoniae*-resistance rates are now greater than 13%.³⁹ Historically, resistance to fluoroquinolones has been determined to be caused by either mutation of the target enzymes or reduction of intracellular drug concentration via the action of efflux pumps or alterations in porin channels through which the drug enters the bacterial cell. Chromosomal point mutations due to amino acid substitutions in the corresponding genes in DNA gyrase and topoisomerase IV at a site corresponding to a region on the DNA-binding surface of the enzyme effect drug affinity at the DNA-enzyme complex.⁴⁰ A single mutation in one of these genes is often sufficient to significantly reduce sensitivity to

the fluoroquinolones. In a stepwise fashion, those bacteria that are able to survive the bactericidal effect of the drug accumulate additional mutations, subsequently resulting in a further increase in resistance to the drug. The primary target enzyme for a bacterial strain (eg, DNA gyrase in Gram-negative bacilli and topoisomerase IV for Gram-positive organisms) is most often the first affected by mutation.

A second mechanism of resistance involves the overexpression of efflux pumps in some bacteria. Generally, these intrinsic components of the bacterial cell membrane expel waste and other harmful substances from the organism. The efflux pump allows for survival of the bacteria in the presence of the fluoroquinolone agent by actively expelling the drug across the cell membrane, thereby diminishing the intracellular concentration of drug to sublethal levels. The action of the efflux pump is dependent on the degree to which the drug binds to the bacterial efflux protein required for exportation. Certain fluoroquinolone agents (eg, moxifloxacin) are less susceptible to this mechanism of resistance, owing to their bulky molecular side chains. Since efflux pumps tend to export a number of different classes of antimicrobial agents in addition to the fluoroquinolones, multidrug-resistant organisms may be selected out.⁴¹ In general, efflux pumps are associated with lower levels of nonsusceptibility to fluoroquinolones than target enzyme mutations.

More recently, transferable fluoroquinolone resistance has been linked to plasmid-mediated mechanisms in many clinical isolates of Enterobacteriaceae from wide geographic areas.⁴² It appears that the plasmid-encoded genes, named *qnr*, produce proteins that protect DNA gyrase and topoisomerase IV from inhibition by the fluoroquinolone drug. Although, the acquisition of these transferable genes may not be sufficient to confer clinical resistance to fluoroquinolones, they are thought to facilitate bacterial survival, and thus aid in the selection of chromosomal mutations.⁴⁰ On the whole, in regard to Gram-negative bacilli uropathogens, any organism that is found to be resistant to ciprofloxacin by the Clinical and Laboratory Standards Institute will likely demonstrate a similar or higher level of resistance to levofloxacin.

Surveillance of urinary bacterial isolates collected between 1989 and 1997 found that fluoroquinolone resistance in *E. coli* was virtually nonexistent during this period of time.⁴³ Unfortunately, extensive hospital-wide use has correlated with the rising resistance now observed, particularly among *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. In fact, in one large urban teaching hospital in South Florida, about 50% of the *E. coli* strains submitted to the microbiology laboratory for susceptibility testing

were found to be resistant to levofloxacin, according to their 2010 antibiogram (L Bush, personal communication). The newly and worrisome increment in extended-spectrum beta-lactamase-producing *E. coli* and other Gram-negative bacilli plays a significant role in resistance to fluoroquinolones. The vast majority of these strains carry with them resistant determinants to all available agents in the fluoroquinolone class of antimicrobials.⁴⁴ In a carbapenem susceptibility test information collection program performed in 15 US medical centers in 2007, resistance to fluoroquinolone agents was detected in 29%, 21%, 201%, and 20% of *E. coli*, *Klebsiella* species, *P. mirabilis*, and *P. aeruginosa*, respectively.⁴⁵ Resistance to Enterobacteriaceae as well as nonfermenting Gram-negative bacilli is not exclusive to health care-associated infections. A North American Urinary Tract Infection Collaborative Alliance multicenter surveillance study carried out in the US and Canada between 2003 and 2004 determined that resistance to levofloxacin and ciprofloxacin was about 6%.⁴⁶ Contributing factors to the expansion of fluoroquinolone resistance now recognized in the outpatient setting include, but are not limited to, (1) their frequent use in treating respiratory tract infections leading to colonization of the fecal flora with resistant *E. coli*; (2) prophylactic use in oncology patients during periods of neutropenia; and (3) the heavily criticized utilization of quinolone agents in the poultry and beef industries, resulting in the possibility of contaminating the food supply with resistant *E. coli*. Although levofloxacin has been found to present the lowest frequency of resistance mutations at normal plasma concentrations,⁴⁷ only the judicious and appropriate use of this, as well as other marketed fluoroquinolone agents, will curtail the ever-growing crisis of resistance to our limited armamentarium of effective antimicrobial agents.

Safety, tolerability, and adverse events

When considering the significant amount of doses of levofloxacin administered over more than a decade's worth of prescribing, it can be confidently stated that this antimicrobial agent has proven to be safe and well tolerated and to have no higher frequency of adverse events than the comparator fluoroquinolones used in study trials or clinical practice. Overall, several pre- and post-marketing trials with levofloxacin have identified the overall incidence of any grade adverse reaction to be from 2% to 10%.¹⁸ When reviewing a total of 7537 treated patients from 29 phase 3 clinical trials, the overall incidence and type of adverse reactions was independent of the dose of levofloxacin administered. The most frequently reported adverse reactions ($\geq 1\%$) are

listed in Table 5. In total, 4% of the enrollees discontinued levofloxacin because of an adverse drug reaction, most commonly gastrointestinal complaints or headache.

Partly as a result of many of its predecessor or contemporary fluoroquinolone agents (eg, temafloxacin, lomefloxacin, sparfloxacin, gatifloxacin, grepafloxacin, and trovafloxacin) being removed from clinical use for reasons of severe toxicity (including hepatotoxicity, hemolytic anemia, photosensitivity, dysglycemia, and increased risk of cardiac arrhythmia), levofloxacin comes with package insert warnings mentioning the rare possibility of these harmful events occurring while on medication. As with all other antimicrobials, the most frequently reported side effects attributed to levofloxacin use are gastrointestinal symptoms, including anorexia, nausea, vomiting, abdominal discomfort, and diarrhea. Specific molecular structural components on the fluoroquinolone compound, such as side-chain or ring substitutions, are known to be related to certain side effects or toxicities. However, no particular structural element has been determined to correlate with gastrointestinal toxicity.⁴⁸ Among the newer fluoroquinolone agents, levofloxacin appears to produce the lowest frequency of non-gastrointestinal side effects. Central nervous system side effects are reported to take place in anywhere from 1% to 11% of patients prescribed fluoroquinolones. Second only to gastrointestinal complaints, these events can manifest as mild to severe headache, dizziness, confusion, insomnia, and mood swings. Seizures may also occur and are hypothesized to be connected to the drug's interaction with the inhibitory neurotransmitter gamma-aminobutyric acid or its brain-tissue receptor.⁴⁹ The development of a rash while taking levofloxacin, felt to be an allergic reaction to the medication, occurs much less frequently than with beta-lactam or sulfa-based

Table 5 Levofloxacin clinical trial adverse reactions ($\geq 1\%$)

Organ system and type	% (N = 7537)
Gastrointestinal	
Nausea	7
Diarrhea	5
Constipation	3
Dyspepsia	2
Abdominal pain	2
Vomiting	2
Central nervous system	
Headache	6
Dizziness	3
Psychiatric	
Insomnia	4
Skin/tissue disorders	
Rash	2
Pruritus	1

antimicrobial agents. However, this cutaneous event must be distinguished from a phototoxicity reaction, which manifests as a severe sunburn in unprotected areas appearing within hours of exposure to ultraviolet light. Those fluoroquinolones (most have been removed from the market) that are multi-fluorinated or that possess halogen atoms at position 8, of which levofloxacin is not, are known to increase phototoxicity. Levofloxacin has rarely been associated with anaphylactoid reactions (≤ 1.2 cases per 100,000).³⁹ A history of anaphylaxis to any fluoroquinolone drug should preclude the prescribing of levofloxacin, since substantial cross-reactivity exists among these agents. Over the years, levofloxacin has infrequently been implicated as a cause of nephro- or hepatotoxicity, the latter generally presenting as mild and reversible elevations in serum transaminases and alkaline phosphatase. Crystal-luria and interstitial nephritis have been reported with the administration of levofloxacin.

Certain serious toxicities that have been reported to occur with levofloxacin use are unique to the fluoroquinolone family of antimicrobial agents. Tendinopathy, presenting as tendonitis or tendon rupture, mostly involving the Achilles tendon but also other tendons of weight-bearing joints, has been reported in association with the earliest quinolone agents. In 2008, the FDA added a “black box” warning to all fluoroquinolone agents cautioning of this risk, which appears to be increased in certain populations, such as patients over 60 years of age, those taking corticosteroid medications, and organ transplant recipients.^{50,51} Prolongation of the electrocardiogram QT interval leading to torsades de pointes and other ventricular arrhythmias is a serious toxicity that may occur while on a fluoroquinolone drug. By blocking the potassium channels, thereby delaying ventricular repolarization, these drugs may cause this potentially life-threatening event, particularly in certain patient populations at increased risk for developing cardiac arrhythmias. Persons who may be more prone to QT interval prolongation while on levofloxacin are those who have significant cardiac disease, electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), and/or are receiving other drugs likely to prolong the QT interval (eg, class Ia or III antiarrhythmic). Levofloxacin and ciprofloxacin appear to have lesser effects on QT interval prolongation than other drugs within their class.⁵² Contrary to some fluoroquinolones that have been noted to cause elevations in blood glucose levels (hyperglycemia), a slight increase in the risk for hypoglycemia has been linked to treatment with levofloxacin. The mode of action is believed to be an increase in pancreatic insulin secretion by inhibition of adenosine triphosphate-sensitive potassium channels in beta cells.⁵³

Levofloxacin, along with all other fluoroquinolone agents, has not been established as safe for use in pregnant women, and likewise should be avoided in nursing mothers. It is also not recommended for pediatric use.

The acceptance by patients of levofloxacin for treatment of UTIs and other indicated infections has been quite positive, as evidenced by the millions of prescriptions filled. However, a notable exception to this is the severe condemning statements posted by patients on websites such as WebMD (<http://www.webmd.com>) and that of the Fluoroquinolone Toxicity Research Foundation (<http://www.fqresearch.org>), the majority of which focus on tendinopathy issues and central nervous system events. Levofloxacin is also significantly more expensive than other fluoroquinolones that are now available in generic form and which have shown similar efficacy for the treatment of UTIs.

Conclusion

Since receiving FDA approval for the treatment of UTIs, levofloxacin has taken its place as a mainstay antimicrobial agent for management of this condition. Possessing exceptional pharmacokinetic and pharmacodynamic profiles, a broad spectrum of antimicrobial activity against most uropathogens, and a safety record that has withstood the test of time, levofloxacin undoubtedly has played an important role in the treatment of UTIs and has earned its status as a “standard of care” drug for these infections. However, other than having a 5-day indication for the treatment of complicated UTI and acute pyelonephritis, and more activity against common Gram-positive organisms sometimes encountered in UTIs (although this is of questionable clinical benefit), levofloxacin has not proven superior to other drugs from either the fluoroquinolone or alternative classes of antimicrobial agents. Moreover, acknowledging that adverse drug reactions and toxicities attributed to fluoroquinolone use may vary in reported incidence, and in fact may prove lower with levofloxacin, patients prescribed levofloxacin for UTIs must still be warned of these potentially serious side effects.

Worrisome levels of fluoroquinolone resistance have developed as a consequence of the heavy use of levofloxacin and other drugs from this class. As pointed out in recent UTI treatment guideline papers,³² resistance in Gram-negative uropathogens jeopardizes the continued empirical use of levofloxacin for any form of UTI. Because of these concerns, as well as the significantly higher cost of treating a UTI with this medication, perhaps, except for specific circumstances, levofloxacin should be relegated to treatment of respiratory tract infections, a role it now seems better suited to.

Disclosures

The authors report no conflicts of interest in this work.

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