

Levofloxacin for the Treatment of Urosepsis

From left to right

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Urosepsis accounts for approximately 20–30% of all patients with sepsis and frequently arises from complicated urinary tract infections (UTIs). The bacterial spectrum in urosepsis is above all represented by Gram-negative rods, such as *Escherichia coli* (50%), *Proteus* spp. (15%), *Enterobacter* and *Klebsiella* spp. (15%), and *Pseudomonas aeruginosa* (5%), although Gram-positive organisms can also be involved, but less frequently (15%). The distribution of antibiotic resistance rates has not been specifically described for urosepsis but only for UTIs in general, and it is reasonable to believe that the pathogens and related resistance patterns are similar. One of the most important questions about community-acquired uropathogens, particularly *E. coli*, is the increasing level of co-trimoxazole (CTX) resistance. While the resistance of *E. coli* and other Gram-negative pathogens to CTX has risen markedly over the past decade, quinolones have continued to exhibit good activity against these organisms, even although there have also been recent reports about increasing levels of resistance to these drugs.

Injectable antibiotics, such as fluoroquinolones and piperacillin/tazobactam, are recommended in the treatment of urosepsis (26). Levofloxacin has double the renal excretion rate of ciprofloxacin and this make it an ideal agent for UTIs together with the advantage that it can be administered as sequential therapy, being available in an intravenous and oral form. Despite these characteristics, few clinical trials have been performed to define its role in urosepsis.

Introduction

Urinary tract infections (UTIs) can manifest themselves in a wide range of clinical forms, ranging from bacteriuria, with or without limited clinical signs and symptoms, to severe disorders such as sepsis or septic shock.

Urosepsis accounts for approximately 20–30% of all patients with sepsis and frequently arises from complicated UTIs, such as urothelial infections associated with an obstruction to the urine flow (i.e., urethral stones, anatomical anomalies, stenosis or tumor) or metabolic disorders (i.e., diabetes, azotemia) and/or immune deficiencies (i.e., neutropenia, transplant recipient) (1).

UTIs account for about 40% of nosocomial infections (NI) (2, 3) and are, therefore, the most common, followed by pneumonitis or wound in-

fections depending on the type of hospital ward.

Richards et al (4) have described the epidemiology of NI in combined medical-surgical intensive care units (ICUs) and found that, between 1992–1998, 23% of all NI were UTIs and they occurred more frequently in catheterized patients (97%). Considering the aetiology of these infections, 45% of reported isolates were Gram-negative bacilli and 31% were fungal, with fungi being more commonly responsible for catheter-associated infections. Similarly, Vincent et al (5) reported a 17.6% incidence of nosocomial UTIs in European ICUs, after pneumonia (46.9%) and ahead of bloodstream infections (12%).

In 2000, the ESGNI-004 (6), a pan-European study, reported an incidence of nosocomial-acquired UTIs (NAUTIs) of 3.55 /1,000 patient-days and 51.5% of all patients were febrile, 31.9%

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went on to develop plain sepsis, 2% severe sepsis, 0.3% septic shock and 1.7% multiorgan failure.

During the period 2003–2004, two other point-prevalence studies about NAUTIs in urology departments were carried out, the first one the Pan European Prevalence (PEP) study and the second one the Pan EuroAsian Prevalence (PEAP) study. The prevalence of NAUTIs in the PEP study was 10% and 14% in the PEAP, with a prevalence of 11% in the combined analysis; the majority of NAUTIs involved asymptomatic bacteriuria (29%) and urosepsis accounted for 12% of all episodes (3).

The bacterial spectrum in urosepsis is above all represented by Gram-negative rods, such as *Escherichia coli* (50%), *Proteus* spp. (15%), *Enterobacter* and *Klebsiella* spp. (15%), and *Pseudomonas aeruginosa* (5%), while Gram-positive organisms can also be involved, but less frequently (15%) (1). The ESGNI-004 reported that Gram-positive organisms represented 21.2% of all NAUTIs isolates, whereas Gram-negative organisms accounted for 65.9% and yeasts 12.9%; the five most commonly isolated pathogens were *E. coli* (25%), *Enterococcus* spp. (13.2%), *Candida* spp. (16.4%), *Klebsiella* spp. (10%), and *P. aeruginosa* spp. (10.5%). Furthermore, the ESGNI-004 data compared the pathogens of catheterized patients with non-catheterized ones when it was found that in the first group *Candida* spp. (12.9% vs. 6.6%) and *P. aeruginosa* (8.2% vs. 4.1%) were more common, with *E. coli* being the first isolated bacterium in both groups (30.6% in catheterized patients and 40.5% in non-catheterized patients) (6).

Data from the PEP and PEAP studies reported a microbiologically proven infection in 74% of patients (urine culture 91%, blood culture 7%, other source 2%). The most common pathogen was *E. coli* (31%), followed by *Pseudomonas* spp. (13%), *Enterococcus* spp. (10%), *Klebsiella* spp. (10%), *Enterobacter* (6%), *Proteus* spp. (6%) and *Candida* spp. (4%). *Candida* spp. and *Pseudomonas* spp. occurred significantly more frequently as a causative agent in patients with urosepsis (13% and 23% respectively) than in those with other types of infection (7).

The distribution of antibiotic resistance rates has not been specifically described for urosepsis but for UTIs in general, and it is reasonable to believe that the pathogens and related resistance patterns are similar.

One of the most important questions about community-acquired uropathogens, particularly *E. coli*, is the increasing level of co-trimoxazole (CTX) resistance. Over the past 20 years, CTX has been the basis of UTIs therapy, because of its effectiveness against the most-common Gram-negative uropathogens, but a lot of recent reports

describe the increasing levels of resistance to this drug around the world, particularly in the case of *E. coli*.

The SENTRY Antimicrobial Surveillance Program for 1997–1999 showed that urinary isolates of *E. coli* from hospitalized patients were CTX-resistant in 25% of cases (8–10), and discouraging results have been also obtained in a surveillance study of over 1,200 isolates from outpatients and hospitalized patients with UTIs in the UK during 1999–2000, with a 40% incidence of CTX-resistance.

While the resistance of *E. coli* and other Gram-negative pathogens to CTX has risen markedly over the recent decades, quinolones have continued to exhibit good activity against these organisms, even although there have been recent reports about increasing levels of resistance to these drugs as well. A surveillance study by Karlowsky et al reported the antimicrobial resistance among UTIs isolates of *E. coli* from female outpatients in the United States from 1995 to 2001; ciprofloxacin was the only agent studied that demonstrated a consistent increase in resistance during the study period, from 0.7% in 1995 to 2.5% in 2001 (> 3-fold increase) (11).

A gradual reduction in the susceptibility of *E. coli* to fluoroquinolones in the United States has also been reported by the SENTRY surveillance program (approximately 1% per annum) (9, 11, 12), and outside the United States (11–15) by PEP and PEAP studies in which *E. coli* was susceptible to CTX in only 48% of isolates and to ciprofloxacin in 59% (7).

Currently first-line empiric antimicrobial therapy for uncomplicated bacterial cystitis in healthy adults and in settings where the prevalence of resistance to this antibiotic is < 10–20%, is CTX (16). If the resistance rates are higher than 10–20%, fluoroquinolones should be considered as an alternative, with a 3-day course for uncomplicated UTIs and a 7–10 day course for complicated ones.

Urosepsis represents the most severe clinical manifestation of UTIs and its treatment differs from that of simple UTIs because, together with the antibacterial therapy, there is a need for adjunct measures, such as volaemic expansion, steroids and blood glucose control, as well as control of the source of infection (i.e., drainage of any obstruction and/or removal of foreign bodies within the urinary tract). All these three strategies need to be started within a few hours in order to significantly improve the patient's outcome (1).

Adequate initial empirical antibiotic therapy is fundamental to achieve this target; it is usually based upon the expected pathogen and its antibi-

otic susceptibility, so it should offer a broad antibacterial coverage and should later be modified on the basis of microbiological results.

In any infection of the kidney or bladder, a significant part of the bacteria is found in the bladder lumen and, therefore, high urinary excretion of the antibacterial is needed together with an appropriate spectrum of antibacterial activity. If the infection involves renal tissues or the patient has urosepsis, high serum concentrations are also necessary to produce adequate tissue penetration and this requires the administration of high-dose intravenous antibacterials.

Another element that influences the treatment of UTIs is the ability of most uropathogens to produce a biofilm, not only on the surface of the catheter but also on foreign bodies, such as stones. Bacteria inside a biofilm are several-fold less susceptible to antibiotics than planktonic ones and only high-dose drugs can achieve penetration (17, 18).

Fluoroquinolones are widely used for the treatment of uncomplicated and complicated UTIs because of their broad antibacterial spectrum and ability to achieve high urinary concentrations.

Moreover, fluoroquinolones appear to be effective in eradicating biofilm-catheter infections, as described by Goto et al (18), although concentrations 32- to 64-fold the minimum bactericidal concentration (MBC) are needed. In another trial, Drago et al (19) reported the inhibition of bacterial adherence to uroepithelial cells using both ciprofloxacin and levofloxacin at sub-inhibitory concentrations (Table 1).

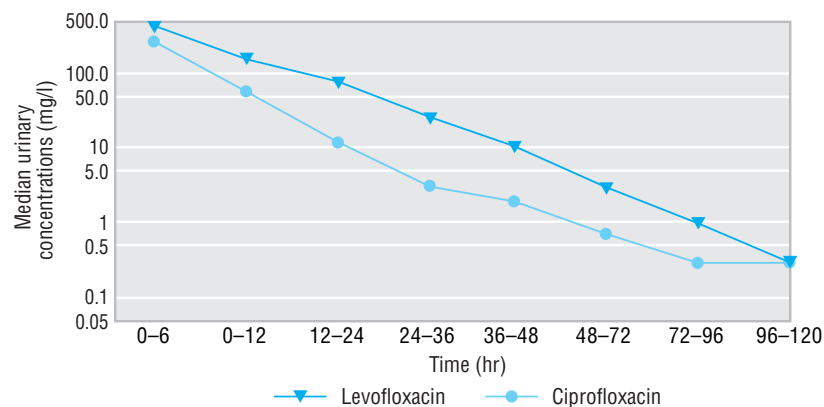
Among recently developed fluoroquinolones, levofloxacin is widely used in clinical practice (19–21) and is less likely to select resistant strains compared with older members of this group (22, 23).

Naber et al (24) reported that, in healthy volunteers, after an oral administration of 500 mg ciprofloxacin or 500 mg levofloxacin, the urinary concentrations of the latter were higher and were maintained for longer (Figure 1). Furthermore they showed that, despite the lower minimum in-

hibitory concentration (MIC) of ciprofloxacin compared with levofloxacin against Gram-negative uropathogens, the urinary bactericidal titres of levofloxacin were significantly higher and were maintained for longer than those of ciprofloxacin. The authors concluded that, *in vitro*: 1) for Gram-negative uropathogens a dosage of 500 mg twice daily of ciprofloxacin was comparable with that of 500 mg levofloxacin once daily; 2) for the treatment of UTIs caused by Gram-positive bacteria, low-dose levofloxacin (500 mg QD) was superior to ciprofloxacin even when a higher posology of the latter was used (500 mg bid). Comparing this result with the antibacterial activity, pharmacokinetic (PK) and pharmacodynamic (PD) properties as well as the results of the few published clinical trials, a dosage of 500 mg ciprofloxacin bid could be equivalent to levofloxacin 500 mg QD for the treatment of severe complicated UTIs. However, they also suggested the use of higher dosages in case of less susceptible pathogens, such as *P. aeruginosa*.

In another study by Pea et al (25), because levofloxacin is renally excreted mainly as unchanged drug (< 75%), it appeared that the high dose regimen of 500 mg bid IV levofloxacin ensures and maintains very high urinary concentrations, with mean values at least 50-fold higher

Figure 1. Median urinary concentrations in healthy volunteers (n = 14) after a single oral dose of 500 mg ciprofloxacin or 500 mg levofloxacin



Adapted from reference (24).

Table 1. Effect of sub-inhibitory concentrations of levofloxacin and ciprofloxacin on bacterial adherence to uroepithelial cells

	Control (bacteria/cell)	0.25 x MIC		IA (%)		0.125 x MIC		IA(%)	
		LVFX	CPFV	LVFX	CPFV	LVFX	CPFV	LVFX	CPFV
<i>S. aureus</i>	81 ± 12	51 ± 4.6 ^a	47 ± 16 ^a	37 ± 11	43 ± 11	60 ± 26.6	73 ± 16	27 ± 21	10 ± 6.1
<i>E. coli</i>	76 ± 11	43 ± 17 ^a	46 ± 10 ^a	43 ± 20	38 ± 15	57 ± 7.2	61 ± 12	24 ± 8.7	19 ± 14

^a *p* < 0.05 versus control

Abbreviations: MIC = minimum inhibitory concentration, IA = inhibition of adherence, LVFX = levofloxacin, CPFV = ciprofloxacin, *S. aureus* = *Staphylococcus aureus*, *E. coli* = *Escherichia coli*.

Adapted from reference (19).

than the MIC₉₀ of most susceptible uropathogens. Moreover, considering that an optimal PK/PD relationship may be obtained for pathogens presenting with a MIC \leq 16 mg/L, a value much higher than the MIC₉₀ of levofloxacin for most urinary pathogens, high doses of this antibiotic may be helpful for the treatment of UTIs not only when caused by susceptible micro-organisms, but probably also for bacteria that are resistant or exhibit intermediate susceptibility to this antibiotic. The authors emphasize that this would be theoretically acceptable for UTIs but not for systemic or renal infections since, in pyelonephritis, bacteria could also be localized in the parenchyma of the organ and, in this situation, it is mandatory to achieve adequate serum drug concentrations.

Injectable antibiotics, such as fluoroquinolones and piperacillin/tazobactam, are recommended for the treatment of urosepsis (26). Levofloxacin exhibits double the renal excretion rate of ciprofloxacin and this make it an ideal drug for UTIs together with the advantage that it can be administered as sequential therapy, being available in an intravenous and oral form. Despite these characteristics, few clinical trials have been performed to define its role in urosepsis, even although Geddes et al (27) showed that there were no clinically significant differences in treating hospitalized patients with suspected bacteraemia/sepsis with levofloxacin 500 mg twice daily or imipenem/cilastatin 1 gm three times daily.

We have performed a clinical trial to compare levofloxacin urosepsis therapy with standard treatment.

Patients

This was a multicenter, randomized, open-label, pilot trial approved by the Ethical Committee of each of the 7 participating hospitals. Patients over 18 years of age with sepsis of a suspected urinary source (both uncomplicated and complicated UTIs) were included in the study after obtaining their written informed consent. The diagnosis of sepsis was made according to the ACCP/SCCM Consensus Conference criteria (28). Major exclusion criteria included pregnancy, hospitalization in an ICU, severe renal impairment (creatinine clearance $<$ 10 ml/min), previous antibacterial therapy and suspected pathogens not included in the spectrum of the study drugs.

Methods

During visit 1 the patients were randomized to receive levofloxacin 500 mg bid intravenously (IV) or piperacillin/tazobactam 4 g/0.5 g three times

a day IV, both in combination with amikacin 7.5 mg/kg twice a day, for a maximum of 14 days.

In both groups, between day 3–7 of treatment in the presence of clinical improvement of the patient and in the absence of isolation of *P. aeruginosa* or *Acinetobacter baumannii*, amikacin could be suspended. In the levofloxacin group, intravenous levofloxacin could be stopped and continued orally after at least 3 days of treatment in the case of resolution of at least one of the clinical symptoms, body temperature \leq 37°C on two consecutive measurements, clinically stable patient with normal central nervous system and no gastrointestinal disorders.

The primary endpoint of the trial was clinical success in the two groups at visit 4 (1–5 days after the end of treatment), defined as the resolution/improvement of the clinical situation. Bacterial eradication was the secondary endpoint.

Results

Overall, 47 patients were enrolled in the study (23 in the levofloxacin group and 24 in the piperacillin/tazobactam group). After randomization, the two groups were homogeneous in terms of demographic data, localization of infection and systemic inflammatory response syndrome criteria.

In the levofloxacin group, pyuria and bacteriuria were positive in 16 (76.2%) and 16 (69.6%) patients, respectively, and in the piperacillin/tazobactam group the corresponding figures were 16 (80%) and 12 (52.2%). In only 15 cases there was a positive blood culture.

The bacteria isolated were *E. coli* (24), *Kluyvera* spp. (2), *Klebsiella* spp. (1) and *P. aeruginosa* (1).

Clinical outcomes are described in Table 2. Clinical success in the intent-to-treat (ITT) population at visit 4 (1–5 days after the end of treatment) was 65.2% (15/23) in the levofloxacin group and 70.8% (17/24) in the piperacillin/tazobactam group. However, if we consider the per-protocol (PP) population, the clinical success at visit 4 was 100% in both groups. The results change at visit 5, because the clinical success in the levofloxacin group was 86.7% and 76.5% in the other group, although the difference was not statistically significant.

In the ITT population, clinical stabilization after 72hr was obtained in 90.5% of patients in the levofloxacin group compared with 72.7% of patients in the other group.

Bacterial eradication was obtained in 100% of bacteriologically evaluable patients in the levofloxacin group and in 91.7% of the piperacillin/tazobactam group. In the levofloxacin group, all of the eradicated pathogens were *E. coli* with *in vitro* sensitivity both to levofloxacin and piperacil-

Table 2. Clinical outcomes in the different study populations

Parameters	Levofloxacin group	Piperacillin/tazobactam group
Age in years \pm SD	49.0 \pm 22.4	59.0 \pm 19.4
ITT analysis – clinical success (n of pts) at visit 4 ^a (%)	65.2 (15/23)	70.8 (17/24)
PP analysis – clinical success (n of pts) at visit 4 ^a (%)	100 (15/15)	100 (17/17)
PP analysis – clinical success (n of pts) at visit 5 ^a (%)	86.7 (13/15)	76.5 (13/17)
PP analysis – bacterial eradication (n of pts) at visit 4 ^a (%)	100 (11/11)	91.7 (11/12)
ITT analysis – pts with clinical stabilization after 72hr ^a (%)	90.5	72.7
– body temperature \geq 36°C or \leq 38°C	95.2	86.4
– heart rate \leq 90/min	95.2	90.5
– respiratory rate \leq 20/min or PaCO ₂ \geq 32 mmHg	88.9	84.2
– white cell count 4000 \geq or \leq 12000 mm ³	76.2	57.1
Mean time to clinical stability (days)	3.9	4.9
ITT analysis – combination therapy with amikacin		
– withdrawn (%)	91.3	75.0
– mean duration of combination (days)	4.1 \pm 1.5	4.6 \pm 1.1
Mean duration of antibiotic treatment (days)	12.5 \pm 3.8	11.8 \pm 3.6
ITT analysis – mean duration of hospitalization (days)	10.9 \pm 7.7	17.2 \pm 11.2

^a Not statistically significant

Abbreviations: SD = standard deviation, ITT = intent-to-treat, pts = patients, PP = per-protocol.

lin/tazobactam.

Combination treatment with amikacin was more frequently stopped in the levofloxacin group and also earlier compared with patients in the piperacillin/tazobactam group (4.1 days \pm 1.5 vs. 4.6 days \pm 1.1); in the levofloxacin group, sequential therapy was performed in most patients (19/23, 82.6%), after 4.8 \pm 1.7 days of intravenous administration.

The mean duration of antibiotic treatment was longer in the levofloxacin group (12.5 days \pm 3.8 vs. 11.8 days \pm 3.6), but in the same group the mean duration of hospitalization was significantly shorter (10.9 days \pm 7.7 vs. 17.2 days \pm 11.2).

Overall, the frequency of adverse events was 27.6% and the most frequently reported events involved the gastrointestinal tract; in the piperacillin/tazobactam group there were 2 patients with serious side effects and one of these died.

Discussion

The decision to compare levofloxacin with piperacillin/tazobactam both in association with amikacin arose from the recommendations for severe UTIs management including urosepsis (26), in the absence of clinical trials that considered the equivalence of these two drugs for such types of disease, and it was supported by Geddes et al (27) who demonstrated the non-inferiority of levofloxacin 500 mg bid compared with imipenem-cilastatin 1 g tid in patients with suspected bacteraemia/sepsis.

In our study there was no real advantage or disadvantage associated with levofloxacin or piper-

acillin/tazobactam as shown by the lack of statistical significance in the clinical success rate in both the ITT and PP populations, although the main issue of the trial is its low power. In actual fact, in this study the number of patients enrolled was lower than planned (47 vs. 64) because of the poor recruitment rate in some centers, despite prolongation of the study.

The real difference between the two randomized groups was that in our trial, with a similar mean duration of antibiotic treatment in both groups, the levofloxacin treatment duration was longer than the hospitalization, due to the possibility of switching from intravenous to oral administration. In fact levofloxacin patients could be discharged from hospital as soon as their clinical condition improved, continuing *per os* treatment with the same antibiotic at the same dosage as outpatients. This permits a reduction in the hospital stay (in our trial 6.3 days in the ITT population), compared with piperacillin/tazobactam, which is an advantage in terms of cost.

In conclusion, the use of effective antimicrobial therapy is essential for the management of serious infections, including urosepsis, although it remains challenging. The use of sequential therapy in the levofloxacin group allowed the early hospital discharge of patients with urosepsis, offering a substantial cost saving for the hospital(s) involved.

Acknowledgements

We would like to thank Dr. Federico Marchetti for his help in revising the manuscript.

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