Levofloxacin: Is It Still Suitable as an Empirically used Antibiotic During the Perioperative Period of Flexible Ureteroscopic Lithotripsy? A Single-center Experience with 754 Patients

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Keywords: flexible ureteroscopic lithotripsy, levofloxacin, urine culture

ABSTRACT

Purpose: To determine the empirical usage of antibiotics and analyze the pathogen spectrum during the perioperative period of flexible ureteroscopic lithotripsy (FURSL) with a focus on levofloxacin.

Materials and Methods: This retrospective analysis included 754 patients who underwent FURSL successfully in our hospital from January 2015 to July 2019. All patients were indicated urine cultures and prescribed antibiotics during the perioperative period. Patients with negative preoperative urine cultures were divided into levofloxacin (LVXG) and non-levofloxacin groups (NLVXG) based on the empirical use of antibiotics. Operative time, the length of postoperative hospital stays and total hospital stays, total hospitalization costs, postoperative fever rate and removal rate of stones were compared. Patients with positive urine cultures were analyzed for pathogen distribution and antibiotic resistance.

Results: In the empirical use of antibiotics among 541 cases with negative urine cultures, the prescription rate of levofloxacin was 68.95%. Compared to that in NLVXG, LVXG had a lower cost of antibiotics but higher postoperative fever rate and longer hospital stay. There were no significant differences in operative time, the total hospitalization costs and the removal rate of stones between the two groups. The top two common pathogens were Escherichia coli (36.11%) and Enterococcus faecalis (24.07%), with resistance rates of 74.36% and 71.15% to levofloxacin, respectively.

Conclusion: Levofloxacin might be no longer suitable as the first-line choice of clinical experience when performing FURSL in our center.

INTRODUCTION

Flexible ureteroscopic lithotripsy (FURSL) has been widely performed for the removal of kidney stones in several Chinese regional hospitals in recent years. The prevalence of kidney stones is about 5.88% in China and is higher in the South.[1] However, increasing cases of perioperative urinary tract infection (UTI) and even sepsis have been reported.[2,3] Asian urologists tend to prescribe antibiotics to reduce the risk of UTI during ureteroscopic lithotripsy, even in patients with negative preoperative urine cultures.[4] The appropriate use of antibiotics is a common concern of doctors and patients. Levofloxacin is a quinolone antibiotic commonly used in urology owing to its efficacy and low price. Recently, we observed that sometimes the anti- infective effect of levofloxacin was not satisfactory. Studies have demonstrated typical pathogens with increased resistance to levofloxacin.[5-8] To date, there are few studies regarding the use of levofloxacin in the perioperative period of FURSL and the use of empirical antibiotics in ureteroscopic lithotripsy.[9] In this study, we aimed to evaluate whether levofloxacin is still suitable as an empirically used antibiotic during the perioperative period of FURSL. We conducted a case-control study to evaluate the pathogenic distribution in urine culture and analyze antibiotic resistance, which provided a reference for the rational usage of antibiotics.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board (No. WK2017F01), we conducted a retrospective study on patients with a high incidence of stones who underwent FURSL successfully between January 2015 and July 2019, at the urology department of the First Affiliated Hospital of Wannan Medical College in Southern China. In all patients, the diagnosis of upper urinary calculi was confirmed using ultrasound, plain radiography, a computed tomography scan, and intravenous pyelography. Surgical indications for FURSL were determined by analyzing the imaging data and clinical conditions, and a preoperative double-J stent was indwelt for 1- 4 weeks.

In all patients, a routine preoperative urinalysis and urine culture were performed the morning before surgery, and re-examined based on the clinical condition after surgery. Patients with negative urine cultures were empirically treated using antibiotics during the perioperative period of FURSL to prevent UTI. Empirical antibiotics, which we refer to the antibiotics chosen by surgeons based on clinical experience when the pathogen test results were unknown or negative, were prescribed with a course of intravenous treatment that lasted 30-60 minutes preoperatively to 24-48 hours postoperatively in patients without risk factors for infection. Correspondingly, the course of antibiotics in patients with risk factors for infection (long history of lithiasis, severe hydronephrosis, chronic kidney disease, and diabetes mellitus) was prolonged from 24-48 hours preoperatively to 48-72 hours postoperatively. Based on the antibiotic regimen used, patients were divided into two groups, namely: levofloxacin group (LVXG) and non-levofloxacin group (NLVXG). Levofloxacin hydrochloride injection (Yangtze River Pharmaceutical Group, China) was usually used in LVXG at a dosage of 0.2 g twice daily. Perioperative characteristics and postoperative clinical outcomes, including patient gender, age, the side, location, size, and history of urinary stones were recorded. Additionally, conditions such as severe hydronephrosis, chronic kidney disease, diabetes mellitus, operative time, postoperative and total hospital stay, the total cost of hospitalization, postoperative fever rate and removal rate of stones were recorded for each group. Operative time was defined as the time from ureteroscopy insertion to the placement of the ureteral stent. Axillary temperature above 38℃ was considered as postoperative fever, which indicated the diagnostic criteria of systemic inflammatory response syndrome. The definition of complete removal of stones by surgery was when no residual stones were observed in the kidney or if stone fragments less than 4mm were revealed upon imaging studies one month later.

The clinical outcomes of FURSL were compared between the two groups to evaluate the intervention effect of empirically used antibiotics focusing on levofloxacin.

Pathogen distribution and their antibiotic sensitivities were obtained in patients with positive urine cultures. Urine samples from those patients were tested again after they were administered anti-infective treatment using sensitive antibiotics; FURSL was carried out when a negative culture report was obtained or when the leukocytes in their urine decreased. Endoscopic surgery apparatus and accessory tools such as modular flexible ureteroscope (PolyDiagnost, Germany), fiberoptic flexible ureteroscope (Storz, Germany), digital flexible ureteroscope (Olympus, Japan), rigid ureteroscope (Wolf, Germany), holmium laser (Lumenis, USA), ureteral access sheath (Cook, USA) and nitinol stone baskets (Cook, USA) were used when required. In most cases, the procedure of FURSL was as follows: patients were general anesthesia in the lithotomy position. The double-J stent, placed preoperatively, was removed using ureteroscopy (8/9.8F), and the ureteroscope was drawn out leaving a retrograde safety guidewire. Subsequently, a flexible ureteroscope was inserted after the ureteral access sheath (12/14F) had been placed under the guidance of wire. While locating the kidney stones, a 200-μm holmium laser fiber was prepared for fragmenting calculi using appropriate parameters (1.0J, 20Hz). Larger fragments were taken out using a nitinol stone basket and subjected to analysis using infrared spectroscopy to evaluate the calculi composition. Lastly, 5F double-J stent and 16F catheter were retained.

Statistical Package for Social Sciences for Windows version 22.0 was used for comparing the perioperative characteristics and postoperative clinical outcomes between the two groups using the independent sample t-test and Chi-squared test with two-sided $p < 0.05$ being regarded as statistically significant.

Multivariate logistic regression analysis was performed to confirm the role of risk factors of postoperative fever in patients with negative preoperative urine cultures. Furthermore, the pathogen spectrum determined from positive urine cultures and resistance rates of antibiotics were listed and analyzed.

RESULTS

During the perioperative period of FURSL, 541 patients with negative urine cultures were prescribed antibiotics, including quinolones, β-lactams and lincosamides which concerned mainly with the use of levofloxacin and cephalosporins. The empirical utilization rate of levofloxacin was as high as 68.95% (373/541) (Table 1). The preoperative characteristics of all patients with negative urine cultures are described in Table 2. No significant differences about the characteristics between the characteristics of LVXG and NLVXG are seen, which indicates good comparability. Table 3 demonstrates that NLVXG has similar postoperative clinical outcomes compared to that of LVXG in terms of operative time, the total cost of hospitalization, and the removal rate of stones, On the other hand, LVXG has a lower cost of antibiotics (53.83±10.17 *vs* 68.28±13.81 USD, p=0.000) but higher postoperative fever rate (9.4% *vs* 4.2%, p=0.036), longer postoperative hospital stay (2.74±1.36 *vs* 2.38±1.62, p=0.007) and total hospital stay (8.51±3.25 *vs* 7.83±2.68, p=0.011) compared to that in NLVXG.

Perioperative urine culture was positive in 213 patients, including 80 males (37.56%) and 133 females (62.44%). A total of 216 positive isolates were detected, which comprised 115 types of Gram-negative bacteria, 82 types of Gram-positive bacteria, and 19 variants of fungi. The most common pathogen isolated was Escherichia coli (36.11%) followed by Enterococcus faecalis (24.07%) (Table 4). After investigating the drug sensitivity test reports of pathogens to antibiotics, it was found that the common Gram-negative bacteria that are sensitive to cefoperazone sulbactam, piperacillin tazobactam, cefotetan, amikacin, imipenem etc., had high resistance to ampicillin, cefazolin, ceftriaxone, levofloxacin and aztreonam (Table 5). Similarly, the typical Gram-positive bacteria, that are sensitive to vancomycin, linezolid, furantoin etc., had high resistance to tetracycline, clindamycin, erythromycin, gentamycin and levofloxacin (Table 6). Remarkably, our study showed high resistance rate for levofloxacin for *E. coli*, Proteus mirabilis and Klebsiella pneumoniae with values of 74.36%, 61.11% and 66.67% respectively, while the corresponding values were determined to be 71.15%, 83.33%, and 66.67% for *E. faecalis*, Staphylococcus epidermidis and Streptococcus agalactiae.

In the multivariate logistic regression analysis, the use of levofloxacin, moderate to severe hydronephrosis, and history of diabetes were independent risk factors for postoperative fever in preoperative urine culture-negative patients ($P < 0.05$) (Table 7).

DISCUSSION

It is well known that the treatment of large upper urinary tract stones, especially kidney stones, relied on open surgery in the past. Currently, minimally invasive percutaneous nephrolithotripsy (PCNL) and FURSL are the primary choices.[10,11] Clinical studies have confirmed that FURSL is effective in treating renal calculi that are around 2 cm in size.[12-15] In such cases, FURSL is more popular than PCNL as the former involves less trauma, is a safer procedure and associated with faster patient recovery[16]. However, there are still some serious complications in the perioperative period of FURSL, such as postoperative UTI, urosepsis and even septic shock. These could be caused by factors such as preoperative UTI, obstruction due to renal calculi, high intrarenal pressure, kidney injury, pathogens invading the blood after lithotripsy, and prolonged surgical duration.[8,17,18]Despite generally attaching importance to the FURSL procedure, knowledge regarding the prevention of infection and selection of antibiotics during the perioperative period of FURSL is limited.

Routine urine cultures during the perioperative period are of great value to prevent UTI and help select suitable antibiotics.[19] In our institution, urine culture and drug susceptibility testing should be performed at least once before FURSL. Surgery can only be carried out if the urine culture is negative. Studies have shown that positive urine cultures, hydronephrosis, large stones, infectious stones, high renal pressure and diabetes are risk factors for postoperative infection of upper urinary tract in patients who have undergone endoscopy.[20,21] However, preoperative urine cultures may not accurately reflect the infection status of patients with renal obstruction and those in whom the Double-J stent is not appropriately placed in the renal pelvis.[21] In such patients, pyelouria or core fragments of the stone can be used for culture and antibiotic susceptibility tests. Furthermore, a postoperative urine culture should also be repeated to prevent changes in pathogens.

Calculi generally obstruct the urinary tract, which may result in bacteriuria or infection following lithotripsy. Studies have shown that the prophylactic antibiotics can reduce the incidence of bacteriuria after ureteroscopic lithotripsy, but can not reduce the risk of postoperative UTI.[22-24] A reduction in the incidence of bacteriuria should reduce the risk of infection; however, the actual situation may be complicated and depend on several factors, including damage to the ureteral wall during the procedure, location of the stone, and pressure of the irrigation fluid, which may increase the chances of postoperative infection in the urinary tract. Of late, most urologists recommend the use of prophylactic antibiotics prior to ureteroscopic lithotripsy.[24] The use of the ureteroscope, especially during lithotripsy, causes varying degrees of ureteral-wall injury. The extent of damage depends on the clinical experience of the surgeon. Generally, complicated renal calculi treated using ureteroscopic lithotripsy pose higher risks of infection. Therefore, even if urine cultures are negative in patients who have been indicated lithotripsy, empirical antibiotic treatment is still necessary.(25) In this study, 541 patients with negative urine cultures were empirically prescribed antibiotics to prevent UTI. The commonly prescribed antibiotics in our department are levofloxacin and cephalosporins. Compared to NLVXG, patients in LVXG had similar clinical outcomes, such as operative time, the total cost of hospitalization and complete stone removal rate, but lower total cost of antibiotics, higher postoperative fever rate, and longer hospitalization. Although levofloxacin is inexpensive and a frequently prescribed drug in China, our study shows that levofloxacin use did not significantly reduce the total cost incurred by patients, but rather increased postoperative fever rate and prolonged the hospital stay, leading to increased costs. This may be related to the false-negative results of urine cultures and levofloxacin resistance, both of which resulted in an unsatisfactory anti-infective effect. To a certain extent, our study reveals that there is no obvious value or advantage in prescribing levofloxacin empirically during the perioperative period of FURSL.

After analyzing the pathogen spectrum and drug-susceptibility results from positive cultures, we found that *E. coli* (36.11%) and *E. faecalis* (24.07%) were the top two bacteria that were highly resistant to levofloxacin.(7,8,26) The most accepted method to determine an antibiotic regimen is to select appropriate and sensitive anti-infective agents based on culture results. However, since laboratory reports are obtained

relatively late, the norm is to first prescribe antibiotics empirically and then titrate the regimen based on laboratory findings and patient condition. Prolonged delays and waiting for culture results may adversely affect the efficacy of drug therapy, especially in patients with high-risk of UTIs; therefore, it is particularly essential to choose suitable antibiotics during the perioperative period. The rate of levofloxacin resistance in bacteria was more than 60% and as high as 74.36% in the case of *E. coli* in our investigation, which suggested that this antibiotic was not efficacious and, therefore, unsuitable for empirical use. Our clinical study reveals the experiential rate of levofloxacin to be 68.95%, which is inappropriate. On the other hand, if high-grade antibiotics such as ceftriaxone, imipenem, and vancomycin are used directly to achieve anti-infective effect when culture studies are not indicated, patients are treated by supposed safe medication with the suspicion of abusing antibiotics which may lead to more resistant pathogens and even super-bacteria in the long run. The increasing insensitivity of ceftriaxone to pathogens for UTI treatment is
a problem that has been faced in recent years.[27,28]

Based on the data from our study, we believe that the empirical utilization of levofloxacin should be reduced in the perioperative period of FURSL. In line with our analysis, antibiotics, such as cefotetan, piperacillin-tazobactam and amikacin, or similar drugs (cefoxitin, piperacillin sulbactam, etimicin,etc.) , with low resistance to common bacteria may be used instead of levofloxacin. Eventually, these antibiotics can be adjusted based on the results of drug-susceptibility tests. In addition, easy-to-use tools, for instance, "Excel" spreadsheets for monitoring and standardizing the management of antibiotics and, summarizing the pathogens spectra and antibiotic sensitivity, thereby reducing the irrational use of antibiotics in clinical work.[29] In the long run, such measures may not only improve the safety and effectiveness of the procedure, but also accelerate the postoperative rehabilitation of patients Therefore, this would be in accordance with the concept of enhanced recovery after surgery.[30]

Our study had some limitations. In addition to the limitations of the retrospective study itself, several surgeons were involved in performing FURSL. At times, the choice of antibiotic inevitably depended on the surgeon's preference or the clinical knowledge of antibiotic-resistance profiles of microorganisms, which may have resulted in in different surgical outcomes. In this single-center investigation, FURSL procedures were performed by qualified senior endoscopic specialists of our department, and we believe that this difference may have had minimal impact on standardized FURSL. Owing to the increase in surgical steps and associated costs, we did not consider urine from the renal pelvis or the core part of the stone for pathogen cultures. However, it has been reported that the discordance between the results of urine and stone cultures carries a high risk of postoperative systemic inflammatory response syndrome.[21,31] Therefore, this study needs further improvement and our future work will be directed toward a multicenter prospective cohort study to obtain more convincing data that could serve as a powerful reference for the rational use of antibiotics during the perioperative period of FURSL.

CONCLUSIONS

This study determined that levofloxacin, which is familiar to surgeons, was used empirically in the perioperative period of FURSL and often used excessively. Despite it being inexpensive, levofloxacin was found to be unsatisfactory in clinical practice and displayed an inordinate resistance rate. When FURSL is performed in areas with a high incidence of urinary calculi, levofloxacin might no longer be suitable as an empirically used antibiotic in our center; therefore, a decrease in the use of levofloxacin and using alternative sensitive antibiotics based on the findings from urine culture is recommended.

COMPLIANCE WITH ETHICAL STANDARDS

The research was approved by the Research Ethics Committee of The First Affiliated Hospital of Wannan Medical College. Informed consents were obtained from the participants. The leader of The First Affiliated Hospital of Wannan Medical College and the ethics committees made an agreement on this research and approved this consent procedure.

ACKNOWLEDGEMENTS

To The First Affiliated Hospital of Wannan Medical College, the Department of Urology for their assistance in the writing of our report.

CONFLICT OF INTEREST

None declared.

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TABLES:

Table 1. Empirical Use of Antibiotics with Negative Urine Cultures during Perioperative Period

Antibiotics	*Cases (n)*	*Prescription rate (%)*
Levofloxacin	373	68.95
Cefoxitin sodium	79	14.60
Cefotaxime sodium	27	5.00
Piperacillin-sulbactam	19	3.51
Cefotaxime	22	4.07
Sulbacillin sodium	6	1.11
Clindamycin	3	0.55
Piperacillin-tazobactam	6	1.11
Ceftriaxone sodium	3	0.55

Etimicin sulfate	3	0.55
Total	541	100.00

Table 2. Preoperative Characteristics of Patients with Negative Urine Cultures

Parameters	***Total***	***LVXG***	***NLVXG***	***P***
Patients, *n*	541	373	168	
Gender, *n*(%)				0.297
Male	371(68.6)	261(70.0)	110(65.5)	
Female	170(31.4)	112(30.0)	58(34.5)	
Age in years, mean ± SD	49.57±11.27	49.01±10.68	50.82±12.41	0.085
Stone side, *n*(%)				0.687
Left	256(47.3)	181(48.5)	75(44.6)	
Right	256(47.3)	173(46.4)	83(49.4)	
Bilateral	29(5.4)	19(5.1)	10(6.0)	
Stone location, *n*(%)				0.211
Kidey	477(88.2)	335(89.8)	142(84.5)	

Upper ureteral	25(4.6)	15(4.0)	10(6.0)	
Kidney and upper ureteral	39(7.2)	23(6.2)	16(9.5)	
Stone size, mm, mean ± SD	18.87±3.74	18.94±3.79	18.69±3.64	0.467
History of urinary stone, *n*(%)				0.493
Positive	208(38.4)	147(39.4)	61(36.3)	
Negative	333(61.6)	226(60.6)	107(63.7)	
Severe hydronephrosis, *n*(%)				0.832
Positive	18(3.3)	12(3.2)	6(3.6)	
Negative	523(96.7)	361(96.8)	162(96.4)	
Chronic kidney disease, *n*(%)				0.494
Positive	30(5.5)	19(5.1)	11(6.5)	
Negative	511(94.5)	354(94.9)	157(93.5)	
Diabetes mellitus, *n*(%)				0.894
Positive	47(8.7)	32(8.6)	15(8.9)	
Negative	494(91.3)	341(91.4)	153(91.1)	

LVXG = levofloxacin group; NLVXG = non-levofloxacin group; *n* = number of patients; SD = standard deviation.

Table 3. Postoperative Clinical Outcomes in LVXG Versus NLVXG

Parameters	***Total***	***LVXG***	***NLVXG***	***P***
Patients, *n*	541	373	168	
Operative time, min, mean ± SD	90.49±37.66	89.42±36.23	92.85±40.68	0.328
Postoperative hospital stay, d, mean ± SD	2.63±1.45	2.74±1.36	2.38±1.62	0.007
Total hospital stay, d, mean ± SD	8.30±3.01	8.51±3.25	7.83±2.68	0.011
Total cost of antibiotics, USD, mean ± SD	58.32±13.23	53.83±10.17	68.28±13.81	0.000
Total cost of hospitalization, USD, mean ± SD	2704±522.3	2692±508.5	2731±552.1	0.415
Postoperative fever, *n*(%)				0.036
Positive	42(7.8)	35(9.4)	7(4.2)	
Negative	499(92.2)	338(90.6)	161(95.8)	
Stone removal, *n*(%)				0.521
Complete	412(76.2)	287(76.9)	125(74.4)	

Incomplete	129(23.8)	86(23.1)	43(25.6)

LVXG = levofloxacin group; NLVXG = non-levofloxacin group; *n* = number of patients; SD = standard deviation; USD = United States dollar (Converted from CNY at the exchange rate on October 22, 2019).

Table 4. Distribution and Constituent Ratio of Pathogens in Urine Cultures during Perioperative Period

Isolated pathogens	*Isolates (n)*	*Constituent Ratio (%)*
Gram-negative	115	53.24
Escherichia coli	78	36.11
Proteus mirabilis	18	8.33
Klebsiella pneumoniae	9	4.17
Pseudomonas aeruginosa	3	1.39
Acinetobacter junii	3	1.39
Serratia marcescens	2	0.93
Aeromonas hydrophila	2	0.93
Gram-positive	82	37.96
Enterococcus faecalis	52	24.07

Staphylococcus epidermidis	12	5.56
Streptococcus agalactiae	9	4.17
Staphylococcus haemolyticus	6	2.78
Staphylococcus saprophyticus	1	0.46
Staphylococcus aureus	2	0.93
Fungus	19	8.80
Candida albicans	11	5.09
Candida glabrata	8	3.70

Table 5. Resistance Rates of Common Gram-negative Pathogens to Antibiotics

Antibiotics	***Escherichia coli* (n = 78)**		***Proteus mirabilis* (n = 18)**		***Klebsiella pneumoniae* (n = 9)**	
	Isolates (n)	***Resistance Rate (%)***	***Isolates (n)***	***Resistance Rate (%)***	***Isolates (n)***	***Resistance Rate (%)***
Ampicillin	66	84.62	13	72.22	9	100.00
Ampicillin-sulbactam	55	70.51	7	38.89	7	77.78
Cefoperazone-sulbactam	0	0.00	0	0.00	0	0.00
Piperacillin-tazobactam	6	7.69	0	0.00	0	0.00
Ciprofloxacin	61	78.21	7	38.89	7	77.78
Levofloxacin	58	74.36	11	61.11	6	66.67
Cefazolin	66	84.62	7	38.89	4	44.44
Cefotaxime	6	7.69	0	0.00	0	0.00

Ceftazidime	49	62.82	4	22.22	4	44.44
Cefatriaxone	64	82.05	3	16.67	3	33.33
Cefepime	52	66.67	3	16.67	0	0.00
Compound sulfamethoxazole	38	48.72	13	72.22	7	77.78
Tobramycin	26	33.33	4	22.22	0	0.00
Aztreonam	55	70.51	4	22.22	0	0.00
Gentamicin	32	41.03	10	55.56	0	0.00
Amikacin	14	17.95	0	0.00	0	0.00
Nitrofurantoin	6	7.69	17	94.44	4	44.44
Imipenem	3	3.85	3	16.67	0	0.00

Table 6. Resistance Rates of Common Gram-positive Pathogens to Antibiotics

Antibiotics	***Enterococcus faecalis (n = 52)***		***Staphylococcus epidermidis (n = 12)***		***Streptococcus agalactiae (n = 9)***	
	Isolates (n)	***Resistance Rate (%)***	***Isolates (n)***	***Resistance Rate (%)***	***Isolates (n)***	***Resistance Rate (%)***
Ampicillin	3	5.77	10	83.33	0	0.00
Clindamycin	35	67.31	11	91.67	8	88.89
Ciprofloxacin	12	23.08	11	91.67	6	66.67
Erythromycin	29	55.77	11	91.67	7	77.78
Gentamicin	23	44.23	1	8.33	6	66.67
Tetracycline	38	73.08	5	41.67	5	55.56
Vancomycin	0	0.00	0	0.00	0	0.00
Levofloxacin	37	71.15	10	83.33	6	66.67
Penicillin	6	11.54	11	91.67	1	11.11
Linezolid	0	0.00	0	0.00	0	0.00
Moxifloxacin	12	23.08	10	83.33	5	55.56
Nitrofurantoin	0	0.00	0	0.00	0	0.00
Tegafycline	0	0.00	0	0.00	0	55.56

Table 7 Multivariate analysis of fever after FURSL in patients with preoperative urine culture Negative Cases

	P value	*OR*	95%*CI*
Use of levofloxacin	<0.001	8.901	2.633～30.095
Moderate to severe hydronephrosis	0.001	7.381	2.305～23.632
Operative time（≥60min）	0.342	0.561	0.170～1.851
history of diabetes（yes）	0.015	4.437	1.338～14.714