Risk Factors of Infectious Complications after Flexible Uretero-renoscopy with Laser Lithotripsy

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Purpose: To determine the perioperative risk factors for postoperative infections among patients undergoing flexible uretero-renoscopy with laser lithotripsy (FURSLL). In addition, the resistance patterns of pathogens isolated from positive preoperative urine cultures were investigated.

Materials and Methods: We retrospectively reviewed data from 492 consecutive patients who had undergone FURSLL for stone disease in our department. Postoperative infection was defined as fever (≥ 38°C) with pyuria (≥ 10 white blood cells per high power field), or systemic inflammatory response syndrome, or sepsis. Pre-operative and intra-operative characteristics between patients with and without postoperative infectious complications were compared using univariate analyses. Significant variables on univariate analyses were included in a multivariate logistic regression analysis to evaluate risk factors associated with postoperative infection following FURSLL.

Results: 42 (8.5%) of 492 patients had postoperative infectious complications after FURSLL. 59 (12%) of 492 patients had a positive preoperative urine culture. 19 (32.2% of 59) patients had multidrug resistance (MDR) isolates recovered from positive preoperative urine cultures. 75% (9/12 cultures) of the positive preoperative urine cultures of patients in whom a postoperative infectious complication developed consisted of gram-negative pathogens. On multivariate analysis positive preoperative MDR urine culture (OR:4.75;95%CI:1.55-14.56; *P* = .006) was found to be significant with the dependent variable as the postoperative infectious complications despite appropriate preoperative antibiotic therapy.

Conclusion: We found that positive preoperative MDR urine culture is a significant risk factor for infectious complications after FURSLL. Our findings point to the need for further research on assessment of risk factors for MDR infections to reduce the rate of postoperative infectious complications.

Keywords: nephrolithiasis; ureteroscopy, laser lithotripsy; urinary tract infections; multi-drug resistance.

INTRODUCTION

With the improvement in technology, minimally invasive flexible uretero-renoscopy with laser lithotripsy (FURSLL) has been recently touted as a tool to improve the outcomes of uretero-renal stone surgery. FURSLL has become an increasingly favorable option even for patients with renal and proximal ureteral stones less than 20mm.[1,2,3] For these stones, the stone-free rates of FURSLL are up to 94.1% with 28% overall risk of perioperative complications.[4,5,6]
As experience with FURSLL has grown, one of interesting topic is the increasing rate of infectious complications associated with FURSLL. Infectious complications rates including fever and sepsis in patients undergoing FURSLL have been reported to vary from 2% to 28% and from 3% to %5, respectively.[4] However, risk factors of infection after FURSLL have been investigated by limited number of studies and warrant further investigation.[7,8,9] We, therefore, aimed to identify possible risk factors for postoperative infection after FURSLL in this study. We also aimed to evaluate the prevalence and resistance patterns of pathogens isolated from preoperative urine cultures and appropriate empiric therapy for postoperative infections of patients undergoing FURSLL.

MATERIALS AND METHODS

Study Design and Population

After institutional review board approval, we retrospectively analyzed the collected data from 506 consecutive patients treated with FURSLL for either intrarenal or proximal ureteral stones between January 2010 and October 2014 at the Urology Department of Ankara Kecioren Training and Research Hospital. Patients with missing data for the clinical baseline records, or without a preoperative urine sample sent for culture, or with postoperative fever due to other potential source of infection were excluded from the study. Kidney-ure-

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Received May 2017 & Accepted September 2017

Table 1. Perioperative characteristics of total cohort and by postoperative infectious complications

Variable	Total cohort (n = 492)	Cases (n = 42, 8.5%)	Controls (n = 450, 91.5%)	*P*
Age in years, median (IQR)	42 (32-54)	39.5 (25-58)	42 (32-54)	0.333
Gender, female, %	43.7	54.7	42.6	0.131
Body-mass index, kg/m^2 (IQR)	26.4 (24.4-28.2)	26.3 (24-29.5)	26.4 (24.5-28.1)	0.943
Diabetes mellitus, %	11.8	21.4	10.9	0.043
Stone size, mm, median (IQR)	13 (10-16)	15 (12-21)	12 (10-15)	< 0.001
Stone number, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.536
Stone location, %				0.656
Upper ureteral	18.0	12.0	18.6	
Renal pelvis	39.2	40.5	39.1	
Inferior calyx	26.0	26.2	26.0	
Upper/Mid calyx	16.6	21.4	16.2	
History of previous stone treatment, %				0.392
None	49.4	64.2	48.0	
Extracorporeal shock wave lithotripsy	35.5	28.5	36.2	
Ureterorenoscopy	4.7	2.3	4.9	
Percutaneous nephrolithotomy	1.4	-	1.5	
Open surgery	2.5	-	2.7	
Multiple modalities	6.5	4.7	6.7	
Renal anatomical anomaly, %	4.7	7.1	4.4	0.428
Hydronephrosis, %				0.600
None or mild	70.7	64.3	71.3	
Moderate or severe	29.3	35.7	28.7	
Preoperative double-j stent, %	22.3	21.4	22.4	0.880
Positive preoperative non-MDR urine culture, %	8.1	16.7	7.3	0.034
Positive preoperative MDR urine culture, %	3.9	12.0	3.1	0.005
Operation time, minutes, median (IQR)	57 (46-70.5)	65 (55-95)	56 (46-70)	0.001
Use of ureteral access sheath, %				0.422
None	6.9	9.5	6.6	
9.5/11.5F	66.4	71.4	66.0	
12/14F	26.6	19.0	27.3	
Postoperative double-j stent, %	74.8	76.2	74.7	0.828
Hospitalization time, days, median (IQR)	1 (1-2)	5 (4-7)	1 (1-2)	< 0.001
Presence of residual fragments, %	18.7	19.0	18.7	0.952

Abbreviations: IQR, interquartile range; MDR, multidrug resistant.

ter-bladder radiography with or without the use of a contrast medium and ultrasonography/noncontrast-enhanced computed tomography was used for preoperative imaging variables. Four urological surgeons experienced with FURSLL performed the procedures with modifications according to each surgeon's preferences and experience. A 7.5 F Storz Flex-X2 was used for flexible URS. A hydrophilic coated ureteral access sheath (9.5/11.5F or 12/14F) was placed under fluoroscopic guidance to maintain low intrarenal pressure and to facilitate extraction of stone fragments. A manual irrigation pump was used to improve visualization during surgery. Postoperatively, a double-j stent was placed based at the surgeon's discretion and removed within two to three weeks. Midstream clean catch urine specimens were obtained for each patient. Preoperatively, a 7-day appropriate course of antibiotic therapy based on the culture sensitivity was given to the patients with positive preoperative urine culture, and FURSLL procedures were performed only after achieving a negative urine culture just prior to the procedure. As for intraoperative antibiotic prophylaxis to minimize the potential infectious complications following FURSLL, a single dose of first generation parenteral cephalosporin antibiotic (cefazolin) was given to the patients with negative preoperative urine cultures during anesthetic induction, while among those with positive preoperative urine cultures, a dose of antibiotic was given intraoperatively based on preoperative antimicrobial susceptibilities. Postoperative urine analysis and culture within 30 days following surgery was collected in the presence of fever (≥ 38 °C) or SIRS. Chest radiography, blood tests and physical examination were performed postoperatively on patients with fever to help rule-out other possible causes of infection.

Outcome assessment

A positive preoperative urine culture was defined as ≥ 50,000 CFU/ml of a pathogenic organism within 30 days before index procedure. The preoperative urine specimen was assumed to be contaminated where there was a mixed culture (growth of more than one isolate), and then a repeat culture was obtained. Multidrug resist-

Table 2. Distribution of pathogens with and without multidrug resistance (MDR) isolated from 59 positive preoperative urine culturesa

Isolated pathogens	All isolates n=59	MDR isolates n=19	Non-MDR isolates n=40	*P*
Gram-negative, %				
Escherichia coli	50.8	42.0	55.0	0.355
Klebsiella pneumoniae	15.2	22.2	12.5	0.580
Pseudomonas aeruginosa	8.5	10.5	7.5	0.697
Proteus mirabilis	3.4	5.5	2.5	0.823
Gram-positive, %				
Enterococcus species	17.0	21.0	15.0	0.563
Staphylococcus species	5.0	0.0	7.5	0.472

Table 3. Antibiotic resistance rates among gram-negative and gram-positive pathogens with and without multidrug resistance (MDR) isolated from 59 positive preoperative urine cultures

Antibiotic resistance rates among gram-negative pathogens				
Antibiotics	**All isolates n = 46**	**MDR isolates n = 15**	**non-MDR isolates n = 31**	***P***
Amoxicillin-clavulanate	39.1%	80.0%	19.3%	< 0.001
Ceftriaxone	21.7%	60.0%	3.2%	< 0.001
Meropenem	0.0%	0.0%	0.0%	-
Levofloxacin	24.0%	53.3%	9.7%	0.001
Amikacin 2.2%	6.7%	0.0%	0.146	
Gentamicin	28.3%	66.7%	9.7%	< 0.001
Trimethoprim-sulfamethoxazole	47.8%	86.7%	29.0%	< 0.001
Nitrofurantoin	15.2%	33.3%	6.4%	0.017
Antibiotic resistance rates among gram positive pathogens				
Antibiotics	**All isolates n = 13**	**MDR isolates n = 4**	**non-MDR isolates n = 9**	***P***
Ampicillin	38.4%	100.0%	11.1%	0.002
Gentamicin	46.1%	100.0%	22.2%	0.009
Levofloxacin	38.4 %	100.0%	11.1%	0.002
Vancomycin	0.0%	0.0%	0.0%	-

ance (MDR) gram-negative pathogens in urine cultures were defined as resistance to at least one antibiotic in at least three of the following antibiotic categories (antibiotics used in the analysis given in parenthesis): cephalosporins (ceftriaxone), fluoroquinolones (levofloxacin), penicillins with beta-lactamase inhibitors (amoxicillin/clavulanate), aminoglycosides (gentamicin or amikacin), carbapenems (meropenem), trimethoprim-sulfamethoxazole, and nitrofurantoin.[10] MDR analysis of gram-positive pathogens with the same criteria was performed for four antibiotic categories: aminoglycosides (gentamycin), fluoroquinolones (levofloxacin), penicillins (ampicillin), glycopeptides (vancomycin). Positive MDR culture was defined as any evidence of MDR pathogens in positive urine cultures. Positive urine cultures that did not meet the criteria were considered to be positive non-MDR cultures. Stone size was determined by measuring the longest diameter on preoperative radiologic investigation; in cases of multiple calculi, stone size was defined as the sum of the longest diameter of each stone. Hydronephrosis was graded as either none/mild or moderate/severe using the Society of Fetal Urology grading system.[11] The operative time was calculated from the time of ureteroscope insertion to the end of placing a double-j stent. SIRS was defined as the occurrence of at least two of the following criteria: fever ≥ 38 °C or hypothermia ≤ 36.0°C, tachycardia > 90 beats/minute, tachypnea > 20 breaths/minute, leucocytosis > 12,000/µL or leucopoenia < 4,000 µL and sepsis was defined as culture-proven postoperative urinary tract infection together with SIRS.[12] In the present study, we used kidney-ureter-bladder radiography and ultrasonography that was performed on the second postoperative day for the assessment of residual fragments (3 mm <).

The main outcome of the present study was postoperative infectious complication and was defined as fever (≥ 38 °C) with pyuria (≥ 10 white blood cells per high power field), or SIRS, or sepsis. Results of concern included the prevalence and resistance patterns of pathogens in urine cultures of patients undergoing FURSLL and risk factors for postoperative infectious complications.

Statistical Analysis

Perioperative characteristics between patients with and without postoperative infectious complications were compared using univariate Mann-Whitney test, Chi-square or Fisher's Exact test. All significant factors associated with postoperative infectious complications following FURSLL on univariate analyses (variables with $P < .05$) were then included in a multivariate logistic regression analysis with a backward stepwise approach to select the significant ones. STATA version 11.0 (StataCorp, USA) was used for analysis with a two-sided alpha level of < 0.05 being considered statistically significant.

RESULTS

The collected data included patient, stone, and treatment parameters. Data also included bacterial species and bacterial resistance to antibiotics used to treat preoperative urine cultures. 4 patients were excluded from the study due to having postoperative fever because of chest infection (n = 2) and tonsillitis (n = 2). We also excluded patients due to missing data on preoperative urine culture (n = 7) and body-mass index (BMI, n = 3). After these exclusions, we obtained 492 patients with complete data to identify predictors of postoperative infectious complications following FURSLL. Of the included 492 patients, 42 patients had the postoperative infectious complications (case group) and other 450 patients did not develop postoperative infection (control group). Cohort characteristics of patients with vs. without postoperative infectious complications are shown in **Table 1**. Patients in the case group had larger median stone size compared to patients in the control group, though this difference was small and median stone size for both groups was 13mm ($P < .001$). Preoperative double-j stents (n = 110, 22.3% of 492) were inserted in 2 patients with evidence of pyonephrosis, in 3 patients with severe hydronephrosis, and were inserted in the remaining majority (n = 105) to allow for passive ureteral dilation to facilitate the passage of the ureteral access sheath. Postoperative double-j stents were inserted for the purpose of facilitating passage of stone fragments in 307 cases (62.4% of 492), while double-j stents were required in all cases with intraoperative complications (n = 61, 12.4% of 492) including mucosal injury of ureter (n = 26, 5.28%), ureteral perforation (n = 4, 0.81%), and mucosal bleeding (n = 31, 6.3%). Patients in the case group were more likely to be having a positive preoperative non-MDR urine culture (16.7 vs. 7.3%, $P = .034$) and MDR urine culture (12 vs. 3.1%, $P = .005$).
Overall, 42 (8.5%) patients had postoperative infectious complications after FURSLL. Of the 42 patients with an infectious complication, 14 (33.3%) had fever with pyuria, 23 (54.8%) had SIRS, and 5 (11.9%) had sep-

Table 4. Multivariate logistic regression analysis of variables associated with postoperative infectious complications after flexible uretero-renoscopy with laser lithotripsy

	OR	95% CI	*P*
Multivariate Analysis			
Diabetes mellitus	1.99	0.85-4.64	0.110
Stone size	1.03	0.96-1.10	0.331
Operation time	1.01	0.99-1.03	0.094
Positive preoperative non-MDR urine culture	2.27	0.88-5.86	0.088
Positive preoperative MDR urine culture	4.75	1.55-14.56	0.006

Abbreviations: MDR, multidrug resistant; OR, odds ratio; CI, confidence interval.

sis. 59 (12%) of 492 patients had a positive preoperative urine culture. 19 (32.2% of 59) patients had MDR isolates recovered from positive preoperative urine cultures. The distribution of the pathogens in patients with and without MDR preoperative urine cultures is shown in Table 2. We did not identify any fungal isolates from preoperative urine cultures. Gram-negative pathogens were isolated more often than gram-positive ones in the preoperative urine cultures and the majority of pathogens were Escherichia coli and Enterococcus species. Antibiotic resistance rates among gram-negative pathogens with MDR from positive preoperative urine cultures were significantly greater than those with non-MDR, while all of the isolates were carbapenems susceptible and 97.8% of the isolates were susceptible to amikacin (**Table 3**).

Postoperative infectious complications after FURSLL were seen in 30 of 433 (6.9%) patients with negative preoperative urine cultures, 7 of 40 (17.5%) patients with preoperative non-MDR urine cultures, and 5of 19 (26%) patients with preoperative MDR urine cultures. Specifically, 75% (9/12 cultures) of the positive preoperative urine cultures of patients in whom a postoperative infectious complication developed consisted of gram-negative pathogens. Of the 42 patients with an infectious complication, 12 (28.6%) had a positive postoperative urine culture. In the 12 patients with a positive postoperative urine culture, 7 patients had a positive preoperative urine culture while 3 of 7 were positive for different pathogens. 5 patients experienced sepsis. Patients with sepsis were treated on an intensive care unit in collaboration with the infectious diseases specialists.

On multivariate analysis positive preoperative MDR urine culture (OR: 4.75, 95% CI: 1.55-14.56; P=.006) was found to be significant with the dependent variable as the postoperative infectious complications after controlling for diabetes mellitus, stone size, operative time and positive preoperative non-MDR urine culture (**Table 4**).

DISCUSSION

We examined a single-institution contemporary series of patients undergoing FURSLL for the management of intrarenal and upper ureteral calculi. Infectious complications rate after FURSLL in the current study was 8.5%, which is in line with the previously reported rates ranging from 2% to 28%.[4] The prevalence of overall MDR pathogens in positive urine cultures prior to FURSLL was 32.2%. High rates of MDR pathogens in patients with urinary tract infections have also been reported in numerous studies worldwide.[13] Unsuitable use of broad-spectrum antibiotics and unnecessary prescription of antibiotics may be responsible for these high rates.

In univariate analyses, positive preoperative non-MDR and MDR urine cultures were both associated with higher risk of postoperative infectious complications. After adjusting for clinical and intraoperative significant variables based on multivariate analysis, there was a statistically non-significant but strong trend for association of positive preoperative non-MDR urine cultures with higher risk of postoperative infectious complications. One might think that it would be easy to be accepted that positive preoperative urine cultures itself is a risk factor of postoperative infection after FURSLL whether the bacteria are MDR or non-MDR. In accordance with this point, very recent published studies demonstrated that a positive preoperative urine culture was the most powerful predictor of postoperative infection in patients undergoing FURSLL.[8,9]) Furthermore, we identified positive preoperative MDR urine culture as independent risk factor associated with a 4.75-fold increased risk of postoperative infectious complication after FURSLL in patients suffering from stone disease despite receiving appropriate preoperative antibiotic therapy. Another article highlighting the importance of positive preoperative MDR urine culture in a subset of patients with infectious complications after endoscopic surgery for renal stone disease, PCNL, was recently published by Patel et al.[14] Their finding that a positive preoperative MDR culture before PCNL increases the risk of development a postoperative infectious complication by 4.89-fold therefore has strong clinical importance and warrants extra caution to postoperative care by urologists. These relevant findings are particularly important because infections caused by MDR pathogens require timely and appropriate treatments including both empirical and definitive antibiotic therapy to reduce postoperative morbidity and costs outcomes.

We found that 12 patients with positive preoperative urine cultures still developed postoperative infection complications despite receiving appropriate preoperative antibiotic therapy. We also demonstrated that out of 12 patients with postoperative infectious complications, 3 patients had discordant culture results between positive preoperative and positive postoperative urine cultures. These findings correspond with those of Margel et al.[15] who found that 19 of 75 (25%) PCNL-treated patients with a positive stone culture had sterile urine, and the sensitivity of urine culture to predict stone colonization was only 30%. Furthermore, antibiotic prophylaxis used in this study failed to eliminate the risk of infection after FURSLL in 30 of 433 (6.9%) patients with negative preoperative urine cultures. Indeed, Martov et al.[16] showed in the Clinical Research Office of the Endourological Society (CROES) ureteroscopy (URS) Global Study that in patients with a negative baseline urine culture undergoing URS for ureteral stones (n = 1141) or renal stones (n = 184), rates of postoperative

urinary tract infection and fever were not reduced by preoperative antibiotic prophylaxis. Possible explanations for these findings might be that cultures obtained from bladder may not accurately reflect the pathogens responsible for the infection found in upper urinary tract urine or in infected stones and antibiotics may not be able to penetrate properly into the infected stone.(17)
We found that gram-negative pathogens were isolated more often than gram-positive pathogens among preoperative urine cultures of patients with postoperative infectious complications. Similar results in preoperative urine cultures were found by Gutierrez et al.,[(18)] examining 5,354 patients undergoing PCNL. They demonstrated that the prevalence of fever among PCNL-treated patients with a positive preoperative urine culture varied markedly depending on which pathogens were found in their urine cultures. These findings suggest that the risk of infection depends on the predominant pathogens identified in urine cultures of patients undergoing endourological procedures for the treatment of nephrolithiasis including FURSLL and PCNL.
One of the significant findings of our study is the importance of identifying patients with risk factors for infection after FURSLL in order to select empirical antibiotic therapy. We found that both cephalosporins and fluoroquinolones, types of antibiotics that are commonly used for treating urinary tract infections, cannot be recommended for the empirical treatment of postoperative infections after FURSLL based on the findings from our local resistance data given the high overall resistance rates among gram-negative pathogens (nearly 25%). Furthermore, all tested antibiotics in this study, except carbapenems and amikacin, were not suitable for empiric treatment among patients with a postoperative infectious complication, given that in our study we observed a nearly 5 times risk of postoperative infection in patients with a positive preoperative MDR urine culture and 79% of positive preoperative MDR urine culture consisted of gram-negative pathogens. It is well established that carbapenems has a favorable and acceptable safety profile.[(19)] Amikacin use, however, has been limited due to concerns regarding its toxicity including ototoxicity and nephrotoxicity.[(20)] Our data suggest that choices for empiric antibiotic treatment in patients with postoperative infectious complications should be based on prompt evaluation of common uropathogens relevant to the disease and on local resistance data, given that susceptibility results will take at least 48 hours after a urine culture is reported as positive. Although the choice of empiric initial antibiotic therapy for patients with infectious complication will be very much dependent on preoperative cultures and on local resistance data, carbapenems may be appropriate empiric therapy while awaiting the urine culture result in the treatment of postoperative infectious complications for FURSLL-treated patients.

Limitations

Our study has some built-in limitations. First, this is a retrospective observational study in a subset of patients who received FURSLL. Second, our recommendation for empiric antibiotic treatment (carbapenems) in patients with infectious complications after FURSLL is based on local resistance patterns using our institutional antibiogram that may not be generalizable to other centers where antibiotic resistance patterns may differ. Third, no complete data on stone composition, stone culture and upper urinary tract urine culture were available. Lastly, we did not consider the possible effect of intraoperative irrigation pressure on postoperative infectious complications, although we observed no difference between patients with and without postoperative infectious complications in ureteral access sheath use which may be helpful for maintaining low intrarenal pressure.

CONCLUSIONS

We found that positive preoperative MDR urine culture is a significant risk factor for infectious complications after FURSLL. Our findings point to the need for further research on assessment of risk factors for MDR infections to reduce the rate of postoperative infectious complications. The necessity for well-designed prospective studies is therefore urgent to answer clinical questions of how to treat and for how long to mitigate the infectious complications in the setting of positive preoperative MDR urine culture, such as dosing and duration of antibiotic therapy and the possible benefit of antibiotic combinations versus monotherapy.

CONFLICT OF INTEREST

The authors have no conflict of interest or financial disclosures to declare.

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