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The Risk Factors of Febrile Urinary Tract Infection After Ureterorenoscopic Lithotripsy

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We aimed to evaluate the risk factors for febrile urinary tract infection (fUTI) following ureterorenoscopic lithotripsy (URSL) for upper urinary tract stones. We retrospectively reviewed the data of 109 patients with upper urinary tract stones who underwent URSL at our hospital from October 2016 to March 2019. We divided the patients into two groups: those who developed fUTI after URSL (fUTI group) and those who did not (non-fUTI group). The retrospectively collected data, including age, sex, body mass index (BMI), mobility, diabetes mellitus, operative duration, preoperative ureteral stent placement, number of stones, stone diameter, CT value of stone, stone location, preoperative UTI, preoperative urine culture, preoperative pyelonephritis, and stone-free status were compared between the two groups. Postoperative fUTI occurred in three of the 109 patients (2.8%). Comparing the two groups, a significant risk factor for developing fUTI after URSL was a low BMI. However, in our study, only three cases developed fUTI after URSL; thus, a multivariate analysis could not be performed. One of the three cases in which fUTI occurred was accompanied by anorexia nervosa and an extremely low BMI of 11 kg/m^2. In summary, even though we had only 3 fUTI patients and did not perform multivariate analysis, our data suggested a significant risk factor for developing fUTI was a low BMI. Increasing the sample size, and further study seem desirable.

INTRODUCTION

Ureterorenoscopic lithotripsy (URSL) has become a more common treatment for upper urinary tract stones because of the reduction in ureteroscope diameter and other device improvements. However, URSL may indicate postoperative febrile urinary tract infection (fUTI) with serious complications. Sugihara et al. reported that 2.39% of 12372 patients who underwent URSL had serious complications, such as septic shock (1). Postoperative fUTI measures are crucial when performing URSL for upper urinary tract stones more safely. In this study, we investigated the incidence of fUTI after URSL in our hospital and examined the risk factors for fUTI.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the data of 109 patients with upper urinary tract stones who underwent URSL at our hospital from October 2016 to March 2019. Patient data included age, sex, body mass index (BMI), mobility, preoperative ureteral stent placement, stone diameter, CT value, number of stones, stone location, preoperative pyuria, positive for preoperative urine culture, and preoperative pyelonephritis. All patients underwent a urine culture if a UTI was found in the preoperative urinalysis. Preoperative urinalysis indicated a UTI in 54 patients and 23 patients of them were positive for urine culture. Twenty-three patients with positive preoperative urine culture showed no evidence of systemic inflammation, and antibiotics were used during surgery according to the antimicrobial susceptibilities of the urine culture. Preoperative ureteral stent placement was performed in 62 patients (56.9%) before surgery. Thirty-two patients (29.4%) had a history of preoperative pyelonephritis, they underwent URSL after their inflammatory findings had improved enough (Table I).

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Procedures

Preoperative ureteral stent placement was performed 1-2 weeks before surgery, and the ureteral stent was removed at the start of surgery. At our facility, URSL was performed in pairs and under the supervision of a senior physician. We used a 5.3/8.4 Fr. flexible ureterorenoscope (OLYMPUS, URF-P5, Tokyo, Japan), 9.9 Fr. flexible ureterorenoscope (Richard Wolf Medical Instruments Cooperation, Cobra-M, Knittlingen, Germany), or 8.0/9.0 Fr. rigid ureterorenoscope (Richard Wolf Medical Instruments Cooperation, Knittlingen, Germany). We used a ureteral access sheath with an 11/13-12/14 Fr. Stones were fragmented using a holmium:YAG laser (Lumenis, VersaPulse Select 80W, Yokneam, Israel) and a 200 μm laser fiber with an energy of 0.5-1.5 J and a rate of 5-20 Hz. We picked out fragments using a nitinol stone retrieval basket (Zero Tip, Boston Scientific, Natick, MA, USA). A 6 Fr. ureteral stent and 14 Fr. urethral catheter was placed at the end of the operations in all cases. The ureteral stent was removed 1-2 weeks after the URSL procedure.

Antibiotics

Usually, cefazolin (CEZ) 1 g was infused before the start of the operation and in the evening of the operation day. When a preoperative urine culture was positive, antibiotics were selected in consideration of the antimicrobial susceptibilities.

Definition

UTI was defined as ≥5 white blood cells/high power field in urinary sediment findings (2). Significant bacteriuria was defined as $\geq 10^5$ colony-forming units (CFU)/ml of ≥1 bacterial species in a urine specimen. fUTI was defined as the need to prolong antibiotic treatment or change drugs based on clinical symptoms, laboratory findings, imaging findings, etc. Naturally, relieving fever was not included in the fUTI. A diagnosis of SIRS was made based on two or more of the following four criteria: white blood cell count >12,000 or <4000/ mm^3; temperature <36°C or >38 °C; heart rate >90/min; respiratory rate >12/min; or PaCO2 <32 mmHg (3). Success of the procedure was evaluated using a kidney–ureter–bladder (KUB) radiogram. At follow-up, stone-free status was reevaluated with abdominal CT between 1 and 3 months postoperatively. Stone-free status was defined as a case where the fragment was 4 mm or less.

Statistical analysis

Medians (interquartile ranges [IQRs]) are used to describe continuous variables, while categorical variables are reported as numbers (percentages). Groups were compared using Wilcoxon’s rank sum test for continuous variables and Fisher's exact test for categorical variables. All P-values were two-tailed, and P-values <0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table I. Patients' backgrounds

Number		109
Age: median (IQR)		64 (54, 74)
Sex (male/female)		62/47
BMI: median (IQR)		23 (21, 26)
Mobility	independent	101
	walking with cane	1
	wheelchair	6
	immobile	1
Preoperative ureteral stent placement		62
Stone diameter (longest, mm): median (IQR)		9 (7, 13)
CT value (HU): median (IQR)		946 (681, 1172)
Number of stones	1	59
	2	29
	3	9
	4	8
	≧5	4
Stone location	R2	18
	R3	17
	U1	47
	U2	8
	U3	12
	bil. ureter	7
Preoperative UTI		54
Positive for preoperative urine culture		23
Preoperative pyelonephritis		32

IQR: interquartile range**,** BMI: body mass index (kg/m^2), HU: Hounsfield units

RESULTS

The median operative duration was 77 minutes. The types of surgery included rigid transurethral ureteroscopic lithotripsy (rURSL) in 32 cases, fURSL in 50, and rURSL + fURSL in 22; in five cases, the procedure was completed only with ureteral stent placement due to ureteral stenosis. In all cases, ureteral stents were placed at the end of surgery and removed 1-2 weeks later. The overall stone-free rate (SFR) was 78.0%. SFR by stone location was 55.6%, 58.8%, 85.1%, 87.5%, 100%, and 85.7% for R2, R3, U1, U2, U3, and bilateral ureter, respectively (Table II).

Complications included postoperative fUTI in three cases, intraoperative ureteral injury in one case, and postoperative ureteral stenosis in one case. Preoperative UTI was observed in all three cases with postoperative fUTI, but only one case had the same bacterial type in the preoperative and postoperative urine culture results. Two of the three cases met the diagnostic criteria for SIRS. Two of the three cases had fUTI on the day of surgery. Cefazolin (CEZ) was used as the antibiotic during surgery in all three cases. Antibiotics after the onset of fUTI were determined by considering the results of preoperative urine cultures and the results of post-onset urine and blood cultures. Case No. 3 was also negative in urine culture after onset of UTI, but because *Streptococcus sanguinis* was found in blood culture after onset of UTI, the antibiotic was changed to ABPC (ampicillin sodium) according to antimicrobial susceptibilities. In all three cases antimicrobial susceptibilities of the causative organism were susceptible. There were no cases of shock and none required the use of catecholamines. All three patients with fUTI recovered and were discharged with antibiotic treatment (Table III).

Table II. Results of operation

Operative duration (min.): median (IQR)		77 (55, 99)
Type of operation	rURSL	32
	fURSL	50
	rURSL + fURSL	22
	ureteral stent placement	5
SFR (%)	overall	78.0
SFR by stone location (%)	R2	55.6
	R3	58.8
	U1	85.1
	U2	87.5
	U3	100
	bilateral ureter	85.7

rURSL: rigid transurethral ureteroscopic lithotripsy, fURSL: flexible transurethral ureteroscopic lithotripsy, SFR: stone free rate,

Table III. patients' backgrounds of positive for postoperative fUTI

Case No.	Age	Sex	BMI	Mobility	DM	Operative duration (min.)	Preoperative ureteral stent placement
1	82	F	20.7	wheelchair	+	66	+
2	47	F	11.1	independent	-	129	+
3	82	M	20.9	independent	-	65	-

Case No.	Number of stones	Stone diameter (mm)	CT value (Hounsfield Unit)	Stone location	Preoperative UTI
1	1	8	1275	U1	+
2	6	12	1172	U1	+
3	1	8.1	482	U1	+

Case No.	Preoperative pyelonephritis	Preoperative urine culture	Postoperative urine culture	SIRS
1	+	*Staphylococcus haemolyticus (MRS)*	*Pseudomonas aeruginosa*	+
2	-	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	+
3	-	negative	negative	-

Case No.	Onset	Antibiotics used during surgery	Antibiotics used after fUTI onset	Antimicrobial susceptibilities of causative bacteria	Discharge
1	POD4	CEZ	CAZ	Susceptible	POD17
2	POD0	CEZ	MEPM	Susceptible	POD8
3	POD0	CEZ	CEZ→ABPC	Susceptible	POD16

POD: postoperative day, CEZ: cefazolin, CAZ: ceftazidime, MEPM: meropenem, ABPC: ampicillin sodium

We divided the patients into two groups: those who developed fUTI after URSL (fUTI group) and those who did not (non-fUTI group). The retrospectively collected data, including age, sex, BMI, mobility, diabetes mellitus, operative duration, preoperative ureteral stent placement, number of stones, stone diameter, CT value of stone, stone location, preoperative UTI, preoperative urine culture, preoperative pyelonephritis, and stone-free status were compared between the two groups. Comparing the two groups, a significant risk factor for developing fUTI after URSL was a low BMI. (Table IV).

Table IV. Patients' data and univariate analysis of risk factors for fUTI

	Groups		p value
	fUTI group	non-fUTI group	
Number	3	106	
Age (years): median (IQR)	82 (47, 82)	64 (54, 73)	0.364
<80	1	92	0.056
80<=	2	14	
Sex (male/female)	1/2	61/45	0.577
BMI: median (IQR)	21 (11, 21)	23 (21, 27)	0.029
Mobility			
Independent	2	99	0.206
Walking with cane	0	1	
Wheelchair	1	5	
Immobile	0	1	
Diabetes mellitus	1	33	1.000
Operative duration (min.): median (IQR)	66 (65, 129)	77 (54, 99)	0.839
<90	2	69	1.000
90<=	1	37	
Preoperative ureteral stent placement	2	60	1.000
Number of stones			
1	2	57	1.000
multiple	1	49	
Stone diameter (longest, mm): median (IQR)	8 (8, 12)	9 (7, 13)	0.985
CT value of stone: median (IQR)	1172 (482, 1275)	945 (683, 1166)	0.727
Stone location			
R2	0	18	0.820
R3	0	17	
U1	3	44	
U2	0	8	
U3	0	12	
Bil. Ureter	0	7	
Preoperative UTI	3	51	0.118
Preoperative urine culture			
Positive	2	21	0.193
Negative	1	57	
Preoperative pyelonephritis	1	31	1.000
Stone-free	2	83	0.530

DISCUSSION

We analyzed data from 109 patients who underwent their first URSL for upper urinary tract stones and examined the risk factors for postoperative fUTI development. Three patients (2.8%) developed fUTI after URSL. In our study, a significant risk factor for developing fUTI after URSL was a low BMI. However, only three cases developed fUTI after URSL; thus, a multivariate analysis could not be performed. One of the three patients who developed fUTI was accompanied by anorexia nervosa and had an extremely low BMI of 11 kg/m^2. Given these facts, the low incidence of fUTI after URSL and the small sample size may be a limitation of this study. Increasing the sample size, and further study seems desirable.

Sugihara et al. reported that 2.39% of 12,372 URSL cases in Japan had serious complications, including fUTI (1). Geavlete et al. reported that in 2735 semirigid ureterorenoscopy (URS), 1.13% had postoperative fever or sepsis (4). There have been many reports regarding the risk factors for fUTI development after URS or URSL, and the results of multivariate analysis have reported longer operative duration (1, 5-7), female sex (1, 8, 9), positive for preoperative urine culture (6, 9, 10), infectious stones (6, 8, 11), and preoperative pyelonephritis (5, 9) as risk factors. In addition, Berardinelli et al. reported that in 403 patients undergoing URSL, seven (1.7%) experienced SIRS and three (0.7%) experienced sepsis after surgery, and infectious complications after URSL were investigated. Multivariate analysis did not identify significant factors. They reported that this was due to the low rate of inflammatory complications (12). In our study, three patients (2.8%) developed fUTI after URSL surgery, and a small number of events may make data analysis difficult. In addition, all three patients who had postoperative fUTI had some of the risk factors reported by various authors. Reducing any of these risk factors may reduce the incidence of fUTI.

In our study, one of the three patients who developed fUTI after URSL had a match between preoperative and postoperative urine cultures. Mariappan et al. reported that urine and stone or renal pelvic urine culture results are unlikely to match and urine culture results are not predictive of infected stones or renal pelvic urine infection (13). Yoshida et al. reported a 64.5% agreement between preoperative urine culture results and intraoperative renal pelvic urine culture results (8).

We performed preoperative ureteral stent placement. However, preoperative ureteral stent placement is reported to be a risk factor for fUTI (5). We also placed ureteral stents at the end of URSL in all cases. The EAU guidelines state that postoperative ureteral stent placement must not be detained in URSL that is completed without any problems (14). It has also been reported that early removal of the stent is desirable even when the stent is placed (15). We may have performed unnecessary stenting.

In summary, even though we had only 3 fUTI patients and did not perform multivariate analysis, our data suggested a significant risk factor for developing fUTI was a low BMI. In the future, we think it is important to consider further increase the number of cases being evaluated. In our study, all three patients who had postoperative fUTI had some of the risk factors reported by various authors. Reducing any of these risk factors may reduce the incidence of fUTI. It may also be useful to consider the risk factors on a case by case basis.

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REFERENCES

1. **Sugihara, T., Yasunaga, H., Horiguchi, H., Nishimatsu, H., Kume, H., et al.** 2013. A nomogram predicting severe adverse events after ureteroscopic lithotripsy: 12372 patients in a Japanese national series. BJU Int **111**: 459-66.
2. **Mitsuzuka, K., Nakano, O., Takahashi, N., and Satoh, M.** 2016. Identification of factors associated with postoperative febrile urinary tract infection after ureteroscopy for urinary stones. Urolithiasis **44**: 257-62.
3. **Bone, R.C., Balk, R.A., Cerra, F.B., Dellinger, R.P., Fein, A.M., et al.** 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest **101**: 1644-55.
4. **Geavlete, P., Georgescu, D., Niţă, G., Mirciulescu, V., and Cauni, V.** 2006. Complications of 2735 retrograde semirigid ureteroscopy procedures: a single-center experience. J Endourol **20**: 179-85.
5. **Omori, C., Hori, S., Otsuka, K., Iida, K., Morizawa, Y., et al.** 2018. The risk factors and chemoprevention of febrile urinary tract infection after transurethral ureterolithotripsy. Nihon Hinyokika Gakkai Zasshi **109**: 74-84 (in Japanese)
6. **Fan, S., Gong, B., Hao, Z., Zhang, L., Zhou, J., et al.** 2015. Risk factors of infectious complications following flexible ureteroscope with a holmium laser: a retrospective study. Int J Clin Exp Med **8**: 11252-9.

7. **Ozgor, F., Sahan, M., Cubuk, A., Ortac, M., Ayranci, A., and Sarilar, O.** 2019. Factors affecting infectious complications following flexible ureterorenoscopy. Urolithiasis **47**: 481-6
8. **Yoshida, S., Takazawa, R., Uchida, Y., Kohno, Y., Waseda, Y., and Tsujii, T.** 2019. The significance of intraoperative renal pelvic urine and stone cultures for patients at a high risk of post-ureteroscopy systemic inflammatory response syndrome. Urolithiasis **47**: 533-40.
9. **Uchida, Y., Takazawa, R., Kitayama, S., and Tsujii, T.** 2018. Predictive risk factors for systemic inflammatory response syndrome following ureteroscopic laser lithotripsy. Urolithiasis **46**: 375-81.
10. **Blackmur, J.P., Maitra, N.U., Marri, R.R., Housami, F., Malki, M., and McIlhenny, C.** 2016. Analysis of Factors' Association with Risk of Postoperative Urosepsis in Patients Undergoing Ureteroscopy for Treatment of Stone Disease. J Endourol 30: 963-9.
11. **Zhong, W., Leto, G., Wang, L., and Zeng, G.** 2015. Systemic inflammatory response syndrome after flexible ureteroscopic lithotripsy: a study of risk factors. J Endourol **29**: 25-8.
12. **Berardinelli, F., De Francesco, P., Marchioni, M., Cera, N., Proietti, S., et al.** 2016. Infective complications after retrograde intrarenal surgery: a new standardized classification system. Int Urol Nephrol **48**: 1757-62.
13. **Mariappan, P., and Loong, C.W.** 2004. Midstream urine culture and sensitivity test is a poor predictor of infected urine proximal to the obstructing ureteral stone or infected stones: a prospective clinical study. J Urol **171**: 2142-5.
14. EAU Guidelines: Urolithiasis. 2020 https://uroweb.org/guideline/urolithiasis/#3
15. **Toprak, T., Şahin, A., Kutluhan, M.A., Akgul, K., Danacıoğlu, Y.O., et al.** 2020. Does duration of stenting increase the risk of clinical infection? Arch Ital Urol Androl **91**: 237-40.