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Factors predicting postoperative febrile urinary tract infection following percutaneous nephrolithotomy in prepubertal children

Onur Kaygısız [a], Nihat Satar [b], Ali Güneş [c], Hasan Serkan Doğan [d], Ahmet Erözenci [e], Ender Özden [f], Mehmet Mesut Pişkin [g], Deniz Demirci [h], Serdar Toksöz [i], Tufan Çiçek [j], Serhat Gürocak [k], Hakan Kılıçarslan [a], Oktay Nazlı [l], Aykut Kefi [m], Volkan İzol [b], Ali Beytur [c], Şaban Sarıkaya [f], Serdar Tekgül [d], Bülent Önal [e]

[a]Department of Urology, Uludağ University Faculty of Medicine, Bursa, Turkey

[b]Department of Urology, Cukurova University Faculty of Medicine, Adana, Turkey

[c]Department of Urology, İnönü University Faculty of Medicine, Malatya, Turkey

[d]Department of Urology, Hacettepe University Faculty of Medicine, Ankara, Turkey

[e]Department of Urology, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey

[f]Department of Urology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

[g]Department of Urology, Necmetin Erbakan University, Meram Faculty of Medicine, Konya, Turkey

[h]Department of Urology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[i]Department of Urology, Baskent University Faculty of Medicine, Ankara, Turkey

[j]Department of Urology, Baskent University Faculty of Medicine, Konya, Turkey

[k]Department of Urology, Gazi University Faculty of Medicine, Ankara, Turkey

[l]Department of Urology, Ege University Faculty of Medicine, İzmir, Turkey

[m]Department of Urology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Correspondence to: O. Kaygısız, Department of Urology, Faculty of Medicine, Uludağ University, 16059 Görükle, Bursa, Turkey

onurkygsz@yahoo.com (O. Kaygısız)

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Summary

Background
Predictive tables and scoring systems can predict stone clearance. However, there is a paucity of evidence regarding the prediction of complications during percutaneous nephrolithotomy (PCNL), particularly in children, which remains under-researched. To our knowledge, no studies have evaluated the risk factors for febrile urinary tract infection (FUTI) after pediatric PCNL.

Objectives
To assess the predictive factors of FUTI in prepubertal children after PCNL and determine whether any prophylactic cephalosporins are superior for decreasing the FUTI rate.

Study design
Data from 1157 children who underwent PCNL between 1991 and 2012 were retrieved from the multicenter database of the Turkish Pediatric Urology Society. Children $>$12 years of age were excluded, leaving 830 children (364 girls, 466 boys). Data were analyzed according to the presence of FUTI and compared between the FUTI and non-FUTI groups.

Results
Mean age was 6.46 $\pm$ 3.38 years. Twenty-nine (3.5%) children had FUTI which was confirmed by urine culture. FUTI occurred more frequently in young children (5.5%) than school-age children (2.4%). In univariate analysis, there were significant differences between the FUTI and non-FUTI groups regarding age, cephalosporin subgroup (first, second and third generation cephalosporin), side of PCNL, staghorn stones, tract size, operative time, postoperative ureteral catheter usage, perioperative complications (SATAVA), and blood transfusion. Multivariate analysis revealed that age, side of PCNL, staghorn stones, tract size, operative time, and blood transfusion were independent predictors of FUTI.

Discussion
The smaller tract size could cause FUTI with poor fluid drainage that may lead to elevate renal pelvic pressure and trigger bacteremia-causing pyelovenous backflow. Filling the calyx and renal pelvis by a staghorn stone and the resulting obstruction of fluid drainage may elevate intrarenal pelvis pressure. Longer operative time is likely to increase renal pelvic pressure over longer periods, which may account for FUTI after pediatric PCNL.

Conclusions
Younger age, right-sided PCNL, staghorn stones, mini-PCNL, longer operative time, and blood transfusion are risk factors for FUTI. First-, second-, and third-generation cephalosporins are equally effective for prophylaxis in prepubertal children undergoing PCNL.

Table Predictive factors for FUTI.

		Multivariate Analysis		
		p-value	OR	95% CI
Age categories	School-aged (ref)	0.025	2.760	1.138–6.696
	Young children			
Side	Left (ref)			
	Right	0.004	4.374	1609–11,890
Staghorn stone	None (ref)			
	Yes	0.006	3.902	1.488–10.231
Tract size	$>$20 Fr (ref)			
	$\leq$20 Fr	0.011	3.148	1.307–7.580
Operative time		0.043	1.008	1.001–1.016
Blood transfusion	None (ref)			
	Yes	0.011	5.898	1.509–23.050

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Introduction

Percutaneous nephrolithotomy (PCNL) is the first-choice treatment for large and complex stones with a high stone-free rate and morbidity improvements [1]. The post-operative complication rate for PCNL varies according to the complexity of urolithiasis and patient and procedure-related factors. The reported post-pediatric PCNL complication rates are 20–39% [2–4]. Postoperative fever is common and occurs in <15% of pediatric PCNL procedures [1]. While it is often transient after PCNL, febrile urinary tract infection (FUTI) is less frequent. Urosepsis occurs in 0.9–4.7% of PCNL procedures [5] and is related to increased hospitalization and potential life-threatening complications. Fever requiring antibiotic therapy after pediatric PCNL occurs in 6% of patients [2–4].

FUTI occurs for several reasons: bacteria released via the fragmentation of calculi colonizing the stone or gaining access to the body during percutaneous tract insertion. Antibiotic prophylaxis in patients undergoing PCNL is associated with a significant reduction in postoperative fever risk [6]. Therefore, antibiotic prophylaxis is mostly used prior to PCNL and cephalosporins are the preferred perioperative antibiotics for children [2]. It is still unclear whether the type of cephalosporin used for prophylaxis affects postoperative FUTI. Elevated intrapelvic pressure caused by smaller tract size may also contribute to postoperative fever [7]. Additionally, staghorn stones, infection-related stones, blood transfusion, stone size, prolonged operative time, tract number, recurrent urinary tract infection, and positive preoperative urine and stone cultures could cause FUTI or systemic inflammatory response syndrome (SIRS) [8–12].

Predictive tables and scoring systems can predict stone clearance but the available evidence about the prediction of complications during PCNL is limited, especially in children [2,13]. To our knowledge, no studies have evaluated the risk factors for FUTI after pediatric PCNL. The research regarding postoperative fever includes patients with transient fever or only assessed SIRS or FUTI in adults [8–12]. Thus, in this study, the main aim is to assess the predictive factors for FUTI in prepubertal children. This study also sets out to determine whether any categories of cephalosporin prophylaxis are superior for decreasing the FUTI rate after PCNL.

Materials and methods

Data for 1157 children (1205 renal units [RUs]) who underwent PCNL between 1991 and 2012 were retrieved from the Turkish Pediatric Urology Society's pediatric database. Children >12 years of age were excluded: 830 (364 girls and 466 boys) remained. Of these, eight had undergone bilateral PCNL.

Data for the following variables were available: patient age, gender, preoperative factors (ipsilateral renal surgery history, preoperative urine culture findings history, previous kidney surgery history, renal anomalies, stone opacity, stone size, stone location), operative factors (perioperative prophylactic antibiotic usage, operative time, tract dilatation type, tract number, tract size, blood transfusion, intraoperative complications), and postoperative factors (length of hospitalization, stone status 1 month after PCNL, postoperative complications, postoperative FUTI confirmed with urine culture, additional therapy).

A staghorn stone was defined as a branched stone that filled the renal pelvis and branched into two or more major calyces [14]. Percutaneous nephrolithotomy was defined as a mini-PCNL procedure when the sheath caliber was $\leq$20 Fr.

All children underwent PCNL in prone position. Nephrostomy tubes were clamped directly 2 days after surgery or after an uneventful antegrade pyelogram and were removed if symptoms were absent. Postoperative stone status was determined by plain X-ray of the kidneys, ureter, and bladder and with excretory urography or ultrasonography in all patients at 1 month postoperatively and at the conclusion of additional therapy. Patients were designated either as stone-free or as having residual stones (any evidence of persistent stone fragments, irrespective of size). Stone analysis was performed using the X-ray diffraction method. Intraoperative complications were recorded according to the SATAVA classification system [15].

Transient fever was defined as increased temperature with negative urine culture occurring only on the first night after the operation and was not considered as FUTI. A postoperative fever of >38.5 °C, secondary to a urinary tract infection and confirmed with urine culture, was defined as FUTI. The children with FUTI underwent ultrasonic examination.

Twenty children did not take prophylactic antibiotics, 318 children took first-generation cephalosporin (cefazolin), 76 children took second-generation cephalosporin (cefuroxime), and 416 children took third-generation cephalosporin (ceftriaxone). The first dose of prophylactic antibiotics was administered at anesthesia induction and continued until the time of nephrostomy removal. Children with positive cultures prior to PCNL were treated with appropriate antibiotics based on a culture sensitivity profile for at least 7 d prior to surgical intervention. The same antibiotic was continued until nephrostomy removal.

Prepubertal children were divided into two age categories according to WHO classification criteria. Infants, toddlers, and preschool-age children (0–4 years) were classified as young children and those aged 5–12 years were classified as school-age children.

All data (demographic variables and perioperative parameters) were compared between the FUTI and non-FUTI groups.

Statistical analysis

Statistical analysis was performed with SPSS version 23 (SPSS Inc., Chicago, IL). The Shapiro–Wilk test was used to assess the normality of continuous variables. All continuous variables were not normally distributed. Continuous variables were compared with the Mann–Whitney *U*-test and presented as medians (minimum–maximum). Nominal data are presented as frequencies and percentages. Between-group differences were assessed by chi square and Fisher's exact tests. Factors with a significant association with FUTI were included in the binary multivariate logistic regression analysis. A p-value <0.05 was considered statistically significant.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Complete data were available for 838 RUs from 830 prepubertal children. The mean age was 6.4 ± 3.38 years. Fever occurred in 75 (9%) children: 29 (3.5%) had FUTI confirmed with urine culture, whereas others had transient fever. FUTI occurred in 5.5% of young children and 2.4% of school-age children ($p = 0.028$).

There were no significant differences between the FUTI and non-FUTI groups with respect to age, gender, renal anomaly, preoperative urine culture, previous kidney surgery history, stone area, solitary renal unit, tract number, and type of instrument used for stone fragmentation (Tables 1 and 2). However, no children who did not require stone fragmentation during the procedure developed FUTI.

Twenty patients did not take prophylactic antibiotics. Of these, two developed FUTI. No patients who received second-generation cephalosporin developed FUTI. According to the FUTI rate, there were 3.3% and 10% in the groups that received prophylactic antibiotics and did not receive prophylactic antibiotics, respectively ($p = 0.153$). However, there was a significant difference between the different cephalosporin groups in univariate analysis ($p = 0.033$) (Table 1).

Only 289 children underwent stone analysis: 44 (15.2%) stones were infection-related (struvite, carbonate apatite)

Table 1 Clinical characteristics and preoperative parameters of children undergoing PCNL.

		Group		p-value
		Non-FUTI (801)	FUTI (29)	
Age		7 (1/12)	4 (1/12)	0.083
		6.50 ± 3.37	5.40 ± 3.46	
Age categories	Young children (291)	275	16	0.028
		94.5%	5.5%	
	School-age children (539)	526	13	
		97.6%	2.4%	
Gender	Girl (364)	95.9%	4.1%	0.448
	Boy (466)	97.0%	3.0%	
Renal anomaly	None (822)	96.5%	3.5%	N/A
	Yes (8)	100%	0%	
Preoperative urine culture	Negative (714)	96.6%	3.4%	0.394
	Positive (102)	95.1%	4.9%	
Antibiotic therapy	None	18 (90%)	2 (10%)	0.152
	Yes	783 (96.7%)	27 (3.3%)	
Antibiotic therapy (cephalosporin)	1st	301 (94.7%)	17 (5.3%)	0.033
	2nd	76 (100%)	0 (0%)	
	3rd	406 (97.6%)	10 (2.4%)	
Previous kidney surgery	No (698)	96.1%	3.9%	0.455
	Yes (132)	97.7%	2.3%	
Side				0.030
• Right (439)		95.2%	4.8%	
• Left (383)		97.9%	2.1%	
• Bilateral (8)		100%	0%	
Stone area (cm^2)		2.5 (0.12–36)	2.86 (0.5–20)	0.531
		3.75 ± 3.61	4.25 ± 4.19	
Stone composition	Non-infection stones (245)	95.5%	4.5%	0.455
	Infection stones (44)	93.2%	6.8%	
No. of stones	Solitary (561)	97.3%	2.7%	0.007
	Multiple (168)	97.0%	3.0%	
	Staghorn (101)	91.1%	8.9%	
Staghorn stone	None (729)	97.3%	2.7%	0.005
	Yes (101)	91.1%	8.9%	
Preoperative creatinine		0.5 (0.1–8.8)	0.50 (0.2–1.1)	0.509
		0.57 ± 0.50	0.51 ± 0.20	

FUTI = febrile urinary tract infection; PCNL = percutaneous nephrolithotomy.

Table 2 Comparison of perioperative and postoperative characteristics of children undergoing PCNL between FUTI and non-FUTI groups.

		Group		p-value
		Non-FUTI (801)	FUTI (29)	
Tract location	Upper (69)	95.7%	4.3%	0.306
	Mid (228)	98.2%	1.8%	
	Lower (398)	95.7%	4.3%	
	Multiple (85)	95.3%	4.7%	
Tract number	1 (743)	96.5%	3.5%	0.394
	2 (77)	98.7%	1.3%	
	≥3 (10)	80.0%	20.0%	
Tract number	1–2 (820)	96.7%	3.3%	0.045
	≥3 (10)	80%	20%	
Tract size	≤20 Fr (276)	93.9%	6.2%	0.005
	>20 Fr (554)	97.8%	2.2%	
Tract dilatation	Balloon (85)	98.8%	1.2%	0.349
	Amplatz (745)	96.2%	3.8%	
Instrument used for stone fragmentation	None (95)	100%	0%	0.618
	Ultrasonic (43)	93.0%	7.0%	
	Laser (78)	91.0%	9.0%	
	Pneumatic (595)	96.9%	3.1%	
Operative time (min)		75 (20–500)	95 (35–220)	0.002
		85.1 ± 47.1	110.2 ± 46.4	
Ureteral catheter usage	No (639)	95.8%	4.2%	0.041
	Yes (188)	98.9%	1.1%	
Blood transfusion	No (747)	97.3%	2.7%	0.001
	Yes (83)	89.2%	10.8%	
SATAVA	0 (740)	97.0%	3.0%	0.030
	1 (90)	92.2%	7.8%	
Hospitalization day		4 (1–25)	5 (2–14)	0.007
		4.87 ± 3.2	6.79 ± 3.76	
SF rate		81.8%	75.9%	0.462

FUTI = febrile urinary tract infection; PCNL = percutaneous nephrolithotomy; SF = stone-free.

stones and the rates of positive urine culture before surgery were 22.7% and 10.2% in infection-related stones and non-infection-related stones, respectively ($p = 0.041$). There were no differences in infection-related stones and non-infection-related stones between FUTI and non-FUTI groups (Table 1). No children who underwent bilateral PCNL developed FUTI, and the FUTI rates were 4.8% and 2.1% for the right and left sides, respectively ($p = 0.03$) (Table 1).

The FUTI rates were 6.2% in mini-PCNL and 2.2% in standard PCNL ($p = 0.005$). Postoperative ureter catheter usage decreased the FUTI rate from 4.2% to 1.1% ($p = 0.041$). Staghorn stones were associated with FUTI more frequently than multiple or solitary stones (Table 1). Perioperative complications classified by SATAVA were related to FUTI in univariate analyses ($p = 0.03$). Blood transfusion was related to FUTI; FUTI rates were 10.8% in children who received transfusions and 2.7% in children who did not.

In univariate analysis, age, cephalosporin subgroup, side of PCNL, staghorn stones, tract size, operative time, post-operative ureteral catheter usage, perioperative complications (SATAVA), and blood transfusion were significant predictors of FUTI. In multivariate analysis, however, only age, side of PCNL, staghorn stones, tract size, operative time, and blood transfusion were significant independent predictors of FUTI (Table 3).

Discussion

In this study, younger age was an independent predictor of FUTI. In contrast, Guven et al. studied fever in 107 children and found no differences between preschool (0–4 years) and school-age (5–14 years) children [16]. Dogan et al. examined 45 children (51 RUs) and compared success and complication rates between preschool (≤5 years) and older children (5 years), finding no differences in terms of fever [17]. However, both previous studies investigated transient fever and FUTI together in a smaller number of patients than in this study, which could explain the inconsistent results.

FUTI could be associated with bacteria released from surgical manipulation or the fragmentation of calculi. Koras et al. showed that infection-related stones were independent predictors for the development of SIRS and sepsis [9]. In the present study, stone composition was not a predictor for FUTI in the 34.8% of stones analyzed. Forty-four (15.2%)

Table 3 Predictive factors for FUTI.

		Multivariate analysis		
		p-value	OR	95% Cl
Age categories	School-aged (ref)			
	Young children	0.025	2.760	1.138–6.696
Cephalosporin subgroup		0.191		
Side	Left (ref)			
	Right	0.004	4.374	1609–11,890
Staghorn stone	None (ref)			
	Yes	0.006	3.902	1.488–10.231
Tract size	>20 Fr (ref)			
	≤20 Fr	0.011	3.148	1.307–7.580
Tract number	1–2 (ref)	0.773		
Operative time		0.043	1.008	1.001–1.016
Ureteral catheter usage	Yes	0.337		
Perioperative complication	SATAVA 0 (ref)	0.286		
Blood transfusion	None (ref)			
	Yes	0.011	5.898	1.509–23.050

Ref = reference value; FUTI = febrile urinary tract infection.

stones were related to infection (struvite or carbonate apatite) and treated with appropriate antibiotics because 10 of them had positive urine culture before surgery. One explanation for this is that 22.7% of children with infection-related stones received an appropriate antibiotic before surgery.

While perioperative antibiotic prophylaxis is recommended for all patients undergoing PCNL in the European Association of Urology (EAU) stone guidelines [18], there is no such recommendation in EAU pediatric urology stone guidelines [1]. Gravas et al. reported that antibiotic prophylaxis decreased postoperative fever and complications after adult PCNL [6]. In their study, antibiotic prophylaxis decreased fever rates from 7.4% to 2.5% [6]. In the present study, most (97.5%) children undergoing PCNL received antibiotic prophylaxis, although 20 children did not (two of these developed FUTI). The FUTI rate was higher in children who did not receive antibiotic prophylaxis than in those who did, consistent with guidelines and current literature [6,18]. This difference was not statistically significant, this could be because of the low number of patients who did not receive antibiotic. However, in contrast to previous studies, children with positive urine cultures prior to the PCNL had similar FUTI rates compared with children with negative urine cultures in this study [19], possibly because of preoperative treatment with appropriate antibiotics in children with positive urine cultures.

Cephalosporins are the preferred antibiotics for pediatric surgical prophylaxis [20], although it is unclear which type of cephalosporin is superior prior to pediatric PCNL. Few studies have examined which antibiotic is superior in adult PCNL [21]. In two prospective studies of adult patients, second-generation cephalosporin (cefuroxime) was compared with ampicillin/sulbactam, while third-generation cephalosporin (ceftriaxone) was compared with ciprofloxacin. No relationship was found between these antibiotics and the development of SIRS [22,23]. No study has compared all generations of cephalosporins in terms of FUTI prevention after PCNL. No FUTI was observed in children who received cefuroxime and the FUTI rate was lower in children who received ceftriaxone (2.4%) rather than cefazolin (5.3%). Although cefuroxime and ceftriaxone seemed to decrease the FUTI rate (compared with first-generation cephalosporin), no differences were observed in multivariate analysis.

Tract size could lead to FUTI. Smaller tract size causes poor fluid drainage that could result in elevated renal pelvic pressure [7] and trigger bacteremia-causing pyelovenous backflow. Renal pelvic pressure >30 mmHg is not itself associated with postoperative fever [7,24], but over time can cause postoperative fever. Renal pelvic pressure ≥30 mmHg for >50 s may contribute to postoperative fever [7]. In the present study, FUTI rates were higher in mini-PCNL than those in standard PCNL. Moreover, as in previous studies, longer operative time was an independent predictor of FUTI [10,25], possibly because of increased renal pelvic pressure over longer periods.

Rivera et al. reported that the occurrence of staghorn stones was significantly associated with fever/SIRS/sepsis after adult PCNL in multivariate analysis [8]. In the present study, staghorn stones were an independent predictor of FUTI. It seems that filling of the calyx and renal pelvis by a staghorn stone and the resulting obstruction of fluid drainage leads to elevated intrarenal pelvis pressure.

Blood transfusion was an independent predictor of FUTI in this study, in accordance with the findings of Chen et al. in SIRS [11]. Blood transfusions are often required to resolve excessive bleeding caused by cutting calyx necks' vessels. Bacteria released from the fragmented calculi can easily enter the parenchyma and venous system.

The presence of two tracts decreases renal pelvic pressure [7]. The lowest FUTI rate was observed in cases involving two tracts in this study. Moreover, three or more tracts were associated with a 20% occurrence of FUTI. Significant differences in FUTI rate were found between cases involving two or fewer tracts and three or more tracts. However, there were no significant differences in multivariate analysis. As more bleeding and the occurrence of staghorn stones were independent predictors of FUTI, the reason for higher FUTI rates in cases of three or more tracts in univariate analysis could be related to more bleeding and multiple calyx-involved stones. In the present study, the right side was also an independent predictor of FUTI. The underlying reason for this difference is not clear and more research is warranted.

The number of hospitalization days was greater in cases of FUTI because of the need for treatment. Thus, the number of hospitalization days does not cause FUTI but is a result of it. Therefore, we did not consider hospitalization days in the multivariate analysis model for risk factors of FUTI.

This study was limited in a few ways. First, the study was retrospective in design. Retrospective data were included from 14 centers covered a 20-year period. To minimize the scope for potential bias because of the large number of centers, a standard data sheet was used for data extraction. However, many studies in adults and a few in children support the results of the present study. Furthermore, despite this limitation, the present results serve as a guideline for clinicians aiming to significantly reduce the rate of febrile urinary tract infections in their clinical practice.

Conclusions

Young age (0–4 years), right-sided PCNL, staghorn stones, mini-PCNL, long operative time, and blood transfusion are independent risk factors for FUTI after PCNL. First-, second-, and third-generation cephalosporins are equally effective for prophylaxis in pediatric patients undergoing PCNL and none is better for preventing FUTI. Clinicians should consider these findings when performing PCNL in prepubertal children.

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Conflict of interest

None.

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