Predictive factors of postoperative septic complications after flexible ureteroscopy for urinary stones.

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Facteurs prédictifs de complications postopératoires infectieuses après urétéroscopie souple pour calculs urinaires

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Words count

Abstract: 233 words
Manuscript: 2140 words
3 tables
25 references

Key words

Ureteroscopic surgeries, stone disease, sepsis

Abstract:

Background: Flexible ureteroscopy (fURS) is one of the recommended treatments for urinary stones. Urosepsis is one of the most frequent complications of fURS however its predictive factors remain uncertain. Our objective was to assess the septic complications rates of fURS and to determinate predictive factors of these complications in patients undergoing fURS.

Methods: Our retrospective analysis included all patients admitted for any fURS for stone disease in our center from December 2009 to April 2013. Patients' medical history, urine culture, stone composition, surgical and anesthetic characteristics were collected. The primary endpoint was

defined by the presence of any septic complication (i.e. postoperative fever, urosepsis, septic shock or death). We used multivariate logistic regression to assess predictive factors of septic complication related to fURS.

Results: 282 patients were included in this study. Urosepsis rate was 9.8% while 18.9% developed postoperative hyperthermia (>37.5°C). In multivariate analysis, the predictive risk factors of septic complication were: a neurologic disorder (OR=6.1; CI95%: 2.9-17.1), a history of urinary tract infection (UTI) (OR=19.6; CI95%: 7.3-52.1), exposure to per operative nitrous oxide (OR=3.2; CI95%: 1.5-6.8) and intraoperative use of a laser (OR=8.0; CI95%: 13.0-30.3).

Conclusion: The use of fURS is associated with relatively frequent septic complications. Patients with neurologic disorders or a history of UTI carry an increased risk of postoperative complications. Limitations should be drawn with the use of per operative nitrous oxide. These results should be further validated.

Introduction

Stone disease is a widespread pathology affecting 5% to 10% of the French population and other developed countries [1–3] . 75-90% of patients will expulse spontaneous their stones but others will require an intervention [4,5]. Treatment modalities include extracorporeal shockwave lithotripsy (SWL), ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL) (6). Compared to SWL or PCNL, the use of URS has increased from 30 to 70% over the past 20 years, mainly due to concomitant Holmium:Yttrium-Aluminium-Garnet (Ho:YAG) laser development worldwide [7,8].

A large range of septic complication is reported in the available data to our knowledge with incidence rates ranging from 7 to 30%, the most common of which is postoperative fever (1 to 23%), followed by sepsis (2 to 8%) [6,9–11].

An in-depth analysis of urological and anesthetic factors has not yet been investigated together.

In addition, many URS are currently performed as an outpatient procedure. However, some patients may develop septic complications at home. Moreover, an enhanced assessment of patient risk for septic complications may help clinicians to identify patients eligible for outpatient management safely. We aimed to describe the septic complications rates of fURS. The secondary objective was to analyze predictive factors of septic complications for patients with urinary stones.

Methods

Study population:

In this single-center retrospective study, all patients admitted to our institution for fURS between December 2009 and April 2013 were included. Exclusion criteria were the indication of fURS other than stone disease. Preoperative culture was mandatory. The Ethic Committee of the Association Française d'Urologie (CERU_2020/019) approved the study.

Data collection and definitions:

We recorded demographic characteristics, underlying diseases, prior urological diseases or procedures and history. Data regarding surgical management (URS indication, stone characteristics, laser utilization, surgical complications, presence of ureteral stent), peri operative (ASA score, anesthetic drugs), and infectious intervention care (history of UTI related to this stone disease episode, urinary analysis, antibiotherapy) were collected. Data collected from recovery room (length of stay, temperature, hematuria, septic complications, pain) and hospital stays (length of stay, hospitalization in a conventional unit or intensive care) were recorded as well.

Outcomes assessment:

The primary outcome was in-patient septic complications rate. Any septic event was measured: i) the presence of fever (body temperature above to 37.5°C). ii) sepsis (defined by the presence of fever and one hemodynamic parameter failure). iii) septic shock (defined by sepsis with no initial response to IV fluids) or iv) sepsis-related death.

All patients underwent a careful clinical examination to rule out any possibility of a non-urinary septic complication

Statistical analysis:

We performed descriptive analyses to compare and summarize the data. Qualitative variables were compared using nonparametric tests. Chi-square or Fisher exact tests (when Chi- square was not applicable) were used. Quantitative variables were compared by analysis of variance on ranks and median comparison (Wilcoxon test). Quantitative variables are expressed using median associated with the inter-quartile interval in each group. Mean ± standard deviation (mean ± SD) is given in the total population.

Predictive factors of infectious complications were analyzed with a multivariate logistic regression. Final variables included in the model were selected using a stepwise method. The latter was performed on the significant variables in the bivariate analysis with p-value below 0.20. Differences between groups were considered significant if p-value was < 0.05. All statistical analyses were performed using SAS Software, V9.2 (SAS Institute Inc., Cary, NC, USA).

Results:

During the study period, 352 patients underwent fURS +/- laser Ho:YAG and were admitted in our institution. Gender ratio was 1. Of all procedures, 80% (n=282) of patients underwent fURS for stone disease. 7% (n=25) a diagnostic URS and 5% (n=17) for endoscopic management of upper tract tumors. The main characteristics of patients are summarized in table 1.

The main complication post fURS was sepsis with 27 cases (9.8%). During our study period 2 septic shocks (0.7%) occurred, with one resulting in death (0.4%). Postoperative fever rate was 18.9% (n=52) (table 2).

In our cohort, 49% had a past medical history of urinary tract infection (UTI) related to their stone history prior fURS. Moreover 22% of them suffered from upper tract abnormalities (horseshoe or pelvic kidney) and 11% presented with neurological disorder (spina bifida, paraplegia or tetraplegia).

The most common type of stone was I and II from classification of Michel Daudon [12] (oxalocalcium, 63.5%), followed by type III (urate, 20.5%) and type V (cystine, 13.5%).

Regarding to past medical history of septic complications, 11% (n=32) of the stone disease population had a history of postoperative URS complications.

After chart review, only 56% (n=154) of the patients had an available preoperative culture and 48 of them had a positive culture. The preoperative antibiotherapy was adapted according to the urine culture. The mean time for antibiotherapy initiation was 7 days prior surgery. To be noted 5% of patients with negative urine culture (n=14) had antibiotic prophylaxis started 48 hours before the fURS related to a history of severe septic episode based on their previous urinary bacterial ecology.

Patients without a preoperative urine culture are systematically cancelled and re-scheduled. 83% of patients (n=231) received an antibiotic prophylaxis by Cefazoline or Cefamandole (Gentamycine in case of allergy).

Concerning anesthetic procedures, we performed 99.7% of fURS under general anesthesia (1 under spinal anesthesia). For general anesthesia cases, 272 were done with orotracheal intubation and 9 with laryngeal masks. Nitrous oxide was used in 46% cases.

Characteristics of patient with or without septic complications are summarized in table 2. Out of the 282 patients, 7 were excluded from the multivariate analysis due to missing values from postoperative data. The rate of septic complication was higher for female (69% vs 45%. p=0.013), patient with neurological disorders (28% vs 6%. p<0.0001), history of UTI (88% vs 38%. p<0.0001), an abnormal urinary tract (43% vs 17%. p<0.0001). Hypertension (HTN) was less frequent in the non-septic group. Preoperative ureteral stenting was used in 50% and 59%, postoperative stenting in 92.2% and 94.8% of patients without and with septic complications respectively (p>0.05). Ureteral access sheath (UAS) was used in 83% of cases for both groups (p>0.05). We performed 80% cases of fURS with Ho:YAG laser.

A preoperative positive urine culture was more frequent in the septic group than the non-septic group 46.5% and 19.9% respectively (p=0.0028). Antibioprophylaxis in the operative room was administrated 15 minutes (+/-28.3) in the non-septic group vs 18.6 minutes (+/- 33.6) before the beginning of the fURS (p=0.429).

Regarding the anesthetic method, the absence of per operative warming and the use of nitrous oxide were more frequent in the septic group (27% vs 48%. p=0.004 and 59% vs 46%. p=0.04. respectively) as reported in table 2. Non-steroidal anti-inflammatory drug was administrated in peroperative with no difference between two groups (20% vs 11%. p=0.11).

Concerning fURS, renal stones >20mm (19% vs 5%. p=0.0065), residual stones (55% vs 34%, p=0.004) and the use of laser (90% vs 76%, p=0.03) are also more frequent in patients with septic complications as summarized in the table 2. We used irrigation with an automated pressure system measured at 103.9 +/- 19.7 cmH2O for the non-septic group and 100.7 +/- 10.2 for the other one (p=0.27). The duration of surgery was similar for both (56.1 vs 62.3 minutes, p=0.18).

Hospital lengths of stay were longer for patients with a past medical history of UTI: 4 +/- 2 days versus 2.4 +/-1 (p=0.0001).

The germs most incriminated in preoperative culture were Escherichia Coli (42%), followed by Enterococcus faecalis (29%) (Table 3). To be noted, 75% patients with a positive preoperative culture for Candida Albicans had a septic complication after the intervention.

In the multivariate analysis, the presence of a neurologic disorder, a history of UTI, the use of laser and nitrous oxide were predictive factors of postoperative septic complications (respectively OR=6.124, CI95%: 2.91-17.115; OR=19.549, CI95%: 7.334-52.109; OR=7.971, CI95%: 2.905-30.329 and OR=3.205, CI95%:1.502-6.84).

Discussion

Our study revealed that urosepsis following fURS is common and may occurred in up to 10% in patients with stone disease. The predictive factors of septic complications are a medical history of neurological disorder, a history of UTI related to the lithiasic episode and the peroperative use of laser or nitrous oxide.

Stauffer et al. in a retrospective study identified the presence of a neurological disorder as predictive factor for post-operative sepsis, they included 467 ureteroscopies (9% vs 1.4% p=0.1) [13]. For Hanau et al., neurological comorbidities are also a predictive factor of prolonged length of stay (OR=4.39) in retrospective study of a 272 ureteroscopies [14]. Besides, for Baboudjian et al., a UTI within the last 6 months was associated with postoperative UTI (OR=1.02, p=0.02) in a retrospective study including 600 patients undergoing a fURS for nephrolithiasis [15].

Regarding to the anesthesiologist management, the use of nitrous oxide appeared to be a risk factor for septic complication. To our knowledge, it is the first time that the use of nitrous oxide was analyzed for ureteroscopies. Literature provided proofs of its implications in surgical site infection due to in vitro evidence of its depression of monocytes' chemotactic migration and its leukocytes DNA damage [16–19]. The ENIGMA trial, a randomized controlled trial including 2,050 patients who underwent non cardiac surgeries, suggested that avoidance of nitrous oxide and the concomitant increase in inspired oxygen concentration decreases the incidence of complications after major surgery [19]. More recently ENIGMA-II, an international randomized single-blind trial with more than 7,000 patients, designed to assess cardiovascular complications, has suggested contrasting results with the previous trial and their findings support the safety profile of nitrous oxide use [18]. The two ENIGMA trials included patients who underwent non cardiac surgeries therefore the influence of nitrous oxide administration on surgical site infection post fURS remains unanswered and our results are not in favor of its use for fURS.

Although not significant in the multivariate analysis, we also observed that perioperative warming leads to fewer septic complications even for relatively short procedures such as fURS. Per operative warming was also shown to be a useful measure against postoperative sepsis in a double-blind, randomized, multicenter trial where infection rate were reduced from 19% to 6% (p=0.01) on 200 patients undergoing colon surgery [20].

In our results, the use of a laser was an independent factor of septic complications. This use is most likely related to the release of bacteria during stone fragmentation. According to literature, bacteria can be easily isolated from stones in approximately 15% to 70% of cases [21] . This notion is well established for struvite stones [22] and calcium stones [21]. The proposed underlying mechanism is a release of aggregated crystals and bacteria when the laser hits the stone.

Furthermore, our study did not show any benefit associated with the use of preoperative antibiotic prophylaxis. Martov et al. had also demonstrated in a prospective, observational, multicenter study over 1,400 patients with a negative preoperative urine culture undergoing fURS for stone that the rates of postoperative fever were not reduced by the use of such therapy [23].

Our study contains several limitations. Besides the single center retrospective design, we observed a high rate of septic complications. The meta-analysis from Nutall et al. [24], with 45 studies, reported a sepsis rate of 2% post fURS. The EULIS [9] review reported a urosepsis rate of 0.17.4% and a 1-23% fever rate. Different factors can explain our larger septic complications rates.

We used a temperature cutoff (≥37.5°C) value to define hyperthermia is lower than the one used in most studies. This choice was made due to paracetamol's systematic use, allowing increasing the sensibility for septic complication detection. Many patients referred to our tertiary care center have complex urolithiasis and medical history resulting in a selection bias. In our population 21% and 13% of patients had uric acid and cystine stones respectively but the stone subtype of classification according to Daudon [12] is not specified for all the series. Roger et al. reported in a retrospective study [9], investigating the composition of urinary stones with more than 5000 patients, a rate of

67% oxalo-calcic stones, 13% of uric acid and 0.7% of cystin. Although patients with neurologic bladder traditionally have stones composed primarily of struvite and carbonate apatite [25], we were unable to identify this stone subtype in our series, neither the frequency of urine derivation. Moreover, the pressure irrigation could have influenced the septic findings although there is no significant difference between groups.

This study's originality resides in the fact that we are one of the first to combine urologic and anesthetic factors to assess the risk of septic complications post fURS. These conclusions reinforce the need for collaboration between anesthesiologists and urologists especially for frail patients undergoing fURS.

Conclusion

In conclusion fURS carries an inherent risk of septic complications especially with stone fragmentation procedures. Patients with neurologic disorders or a history of UTI drive an increased risk of postoperative complications. Limitations should be drawn with the use of peroperative nitrous oxide. These results should be further validated.

Acknowledgments

Funding: None

Footnote

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

	N=352	%
Female	176	50
Male	176	50
Age (years)	52.1 +/-14.8	
IMC>30	90	26.5
ASA score		
ASA 1	105	29.6
ASA 2	165	47
ASA 3	82	23.4
Indication of fURS		
Urinary stones	282	80.1
Oxalo-calcium (type I and II)	99	63.5
Uric acid (type III)	32	20.5
Cystine (type V)	21	13.5
others	4	2.5
Diagnostic URS	25	7.1
Upper tract tumor	17	4.8
Pyelo-ureteral junction diseases	16	4.5
Other	12	3.5
Duration of surgery (min)	56.7 +/- 29.7	
Per operative complications	77	22
Ureteral obstruction	17	4.9
Haematuria	17	4.9
Postoperative complications		
Septic complications	66	19.2
Fever	61	17.7
Sepsis	29	8.4
Septic shock	3	0.9
Death	1	0.3
Length of stay (days)	2.86 +/- 1.56	

Table 1: Overall cohort demographics, pre-, per-and postoperative characteristics.

	Patients with no septic complications (n=217)	Patients with septic complications (n=58)	Total (n=275)	
	N (%)	N (%)	N (%)	p
Comorbidities				
Female	98 (45.2)	40 (69)	138 (50.2)	**0.0013**
Obesity	87 (40.5)	19 (33.3)	106 (38.5)	0.33
Diabetes	40 (18.4)	7 (12.1)	47 (17.1)	0.25
Chronic renal failure	16 (7.4)	6 (10.3)	22 (8)	0.42
Hypertension	74 (34.1)	12 (20.7)	86 (31.3)	0.05
Neurologic disorder	13 (6)	16 (27.6)	29 (10.5)	**<0.0001**
History of urinary tract infection	82 (38)	50 (87.7)	132 (48)	**<0.0001**
Urinary tract malformation	36 (16.6)	25 (43.1)	61 (22.2)	**<0.0001**
Score ASA	1.9 +/- 0.7	1.8 +/- 0.7		0.13
Age	49.8 +/- 13.4	50 +/- 13.2		0.92
BMI	28 +/- 6.7	26.7 +/- 7.3		0.22
Creatinine (mg/L)	10.6 +/- 3.4	10.2 +/- 4.3		0.58
Intra-operative anesthetic characteristics				
Propofol use	211 (97.2)	54 (94.7)	265 (96.4)	0.35
Neuromuscular blocking agent	81 (37.3)	15 (26.3)	96 (34.9)	0.12
Nitrous oxide	93 (43.3)	33 (58.9)	126 (45.8)	**0.04**
Per operative warming	103 (48.1)	15 (26.8)	118 (42.9)	**0.0041**
Hemodynamic stability	156 (71.9)	37 (64.9)	193 (70.2)	0.30
Non steroidal anti-inflammatory drug	43 (19.9)	6 (10.7)	49 (17.8)	0.11
Peri operative fluid (mL)	852.3 +/- 300.6	854.6 +/- 307.8		0.88
Ephedric use (mL)	13 +/- 7.3	11 +/- 9.1		0.34
Urological characteristics				
Intra renal stone	165 (82.1)	43 (76.8)	208 (75.6)	0.37
Pyelo-ureteral stone	21 (10.5)	4 (7.3)	25 (9)	0.48
Proximal ureter	23 (11.5)	4 (7.1)	27 (9.8)	0.35
Distal ureter	27 (13.5)	6 (19.7)	33 (12)	0.58
Single stone	85 (41.9)	21 (37.5)	106 (38.5)	0.55
Stone >20mm	8 (4.9)	8 (18.6)	16 (5.8)	**0.0065**
Bilateral	39 (18.5)	11 (19.3)	50 (18.1)	0.89
Use of laser	161 (76.3)	51 (89.5)	212 (77.1)	**0.03**
Residual stone	72 (34.4)	32 (55.2)	104 (37.8)	**0.004**
Preoperative ureteral stent	107 (50)	34 (58.6)	141 (51.3)	0.24
Postoperative ureteral stent	200 (92.2)	55 (94.8)	255 (92.7)	0.49
Ureteral Acces Sheath	180 (83)	48 (82.7)	228 (82.9)	0.6
Irrigation pressure (cmH20)	103.9 +/- 19.7	100.7+/- 20.2		0.27
Duration (minutes)	56.1 +/- 31.3	62.3 +/- 28.8		0.18

Table 2: Comorbidities, anesthetic and urological characteristics in stone patients with or without septic complications

	All fURS N=352	fURS for stone disease N=282
	N (%)	N (%)
Preoperative positive culture	72 (20)	59 (21)
Incriminated germs		
Gram Negative Bacilli	57 (79.2)	37 (62.7)
E. Coli	40 (55.6)	25 (42.4)
Klebsiella Pneumoniae	7 (9.7)	3 (5.1)
Enterobacter	4 (5.6)	4 (6.8)
Proteus Mirabillis	2 (2.8)	0 (0)
Pseudomonas aeruginosa	2 (2.8)	3 (5.1)
Morganelle morganii	2 (2.8)	2 (3.4)
Gram Positive Cocci	28 (38.9)	19 (32.2)
Enterococcus faecalis	17 (23.6)	17 (28.8)
Streptococcus B	9 (12.5)	2 (3.4)
Staphylococcus	2 (2.8)	0 (0)
Other	19 (26.4)	9 (15.3)
Candida Albicans	7 (9.7)	3 (5.1)
Polymicrobial	12 (16.7)	6 (10.2)

Table 3: Microbiological data.

	N=352	%
Female	176	50
Male	176	50
Age (years)	52.1 +/-14.8	
IMC>30	90	26.5
ASA score		
ASA 1	105	29.6
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ASA 3	82	23.4
Indication of fURS		
Lithiasis	282	80.1
Oxalo-calcium	99	63.5
Uric acid	32	20.5
Cystine	21	13.5
others	4	2.5
Diagnostic URS	25	7.1
Upper tract tumor	17	4.8
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Ephedric use (mL)	13 +/- 7.3	11 +/- 9.1		0.34
Urological characteristics				
Intra renal stone	165 (82.1)	43 (76.8)	208 (75.6)	0.37
Pyelo-ureteral stone	21 (10.5)	4 (7.3)	25 (9)	0.48
Proximal ureter	23 (11.5)	4 (7.1)	27 (9.8)	0.35
Distal ureter	27 (13.5)	6 (19.7)	33 (12)	0.58
Single stone	85 (41.9)	21 (37.5)	106 (38.5)	0.55
Stone >20mm	8 (4.9)	8 (18.6)	16 (5.8)	**0.0065**
Bilateral	39 (18.5)	11 (19.3)	50 (18.1)	0.89
Use of laser	161 (76.3)	51 (89.5)	212 (77.1)	**0.03**
Residual stone	72 (34.4)	32 (55.2)	104 (37.8)	**0.004**
Preoperative ureteral stent	107 (50)	34 (58.6)	141 (51.3)	0.24
Postoperative ureteral stent	200 (92.2)	55 (94.8)	255 (92.7)	0.49
Ureteral Acces Sheath	180 (83)	48 (82.7)	228 (82.9)	0.6
Irrigation pressure (cmH20)	103.9 +/- 19.7	100.7+/- 20.2		0.27
Duration (minutes)	56.1 +/- 31.3	62.3 +/- 28.8		0.18

Table 2: Comorbidities, anesthetic and urological characteristics in stone patients with or without septic complications

	All fURS N=352	fURS for lithiasis N=282
	N (%)	N (%)
Preoperative positive culture	72 (100)	59 (100)
Incriminated germs		
Gram Negative Bacilli	57 (79.2)	37 (62.7)
E. Coli	40 (55.6)	25 (42.4)
Klebsiella Pneumoniae	7 (9.7)	3 (5.1)
Enterobacter	4 (5.6)	4 (6.8)
Proteus Mirabillis	2 (2.8)	0 (0)
Pseudomonas aeruginosa	2 (2.8)	3 (5.1)
Morganelle morganii	2 (2.8)	2 (3.4)
Gram Positive Cocci	28 (38.9)	19 (32.2)
Enterococcus faecalis	17 (23.6)	17 (28.8)
Streptococcus B	9 (12.5)	2 (3.4)
Staphylococcus	2 (2.8)	0 (0)
Other	19 (26.4)	9 (15.3)
Candida Albicans	7 (9.7)	3 (5.1)
Polymicrobial	12 (16.7)	6 (10.2)

Table 3: Microbiological data.