Original article

Urinary tract infections after transurethral resection of the bladder: Microbiology, antibiotic resistance, and associated risk factors

Infección de vías urinarias después de resección transuretral de vejiga: Microbiología, resistencia antibiótica y factores de riesgo asociados

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Abstract

Objective: To analyze the microbiology and incidence of antibiotic resistance in patients that underwent transurethral resection of bladder tumor (TURBT) and identify risk factors for urinary tract infection (UTI) after the procedure.
Methodological design: A retrospective, analytic, descriptive study on data from 199 patients that underwent TURBT at a tertiary care hospital in Mexico City between 2017-2019. The microbiologic characteristics of isolation frequency and drug-resistance pattern were analyzed before and after the procedure. Binary logistic regression was carried out to identify independent risk factors for UTI.
Results: Of the 199 patients evaluated, 28 (14%) had a positive urine culture (PUC) before the procedure and the most frequently isolated uropathogens were Escherichia coli (48%), Enterococcus faecalis (24%), and Proteus mirabilis (7%). UTI after TURBT was reported in the 20 patients (10%) that made up group 1. The most frequent pathogen was E. coli (45%), which was resistant to trimethoprim/sulfamethoxazole (60%) and ciprofloxacin (40%). Other isolated pathogens were E. faecalis (27%) and P. mirabilis (9%). The control group included the 179 (90%) patients that did not have a UTI. PUC was statistically significant in relation to necrosis (p=0.001) and muscle-invasive bladder cancer (p=0.03). In the multivariate analysis, PUC was associated with UTI after TURBT (OR 7.04 [95% CI 2.11-23.29]).
Limitations: A retrospective study with information limited to that in the case records.
Originality and value: There are few articles on TURBT-associated UTI in the international literature and none in Mexico, the present study being the first.
Conclusions: The prevalence of UTI after TURBT was 10%. Pre-procedure PUC was the most highly associated risk factor for UTI after TURBT. The most frequently isolated uropathogens were E. coli, E. faecalis, and P. mirabilis. E. coli was most resistant to trimethoprim/sulfamethoxazole (60%) and ciprofloxacin (40%).

Keywords:
Transurethral resection of the bladder, Urinary tract infections, Incidence, Antibiotic resistance.

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Resumen

Objetivo: Investigar la incidencia, microbiología y resistencia antibiótica en pacientes sometidos a resección transuretral de vejiga (RTUV) e identificar factores de riesgo para infección de vías urinarias (IVU) después de procedimiento.

Diseño metodológico: Estudio retrospectivo, descriptivo y analítico de 199 pacientes sometidos a RTUV en un hospital de tercer nivel en Ciudad de México entre 2017-2019. Se analizaron las características microbiológicas de frecuencia de aislamiento y patrón de resistencia antes y después del procedimiento. Se realizó regresión logística binaria para identificar factores de riesgo independientes a IVU.

Resultados: Se analizaron 199 pacientes, de estos 28 pacientes (14%) presentaron un urocultivo prequirúrgico positivo (UPP), los uropatógenos más frecuentemente aislados fueron *Escherichia coli* (48%), *Enterococcus faecalis* (24%) y *Proteus mirabilis* (7%). Se reportó IVU después de RTUV en 20 pacientes (10%) los cuales conformaron el grupo 1. El patógeno más frecuente fue *E. coli* (45%), el cual era resistente a trimetoprima/sulfametoxazol (60%) y ciprofloxacino (40%). Otros patógenos aislados fueron *E. faecalis* (27%) y *P. mirabilis* (9%). En el grupo control se incluyeron 179 (90%) pacientes ya que no presentaron IVU. Se encontró diferencia significativa en la presencia de UPP y necrosis (p=0.001), al igual que en presencia de cáncer músculo-invasor (p=0.03). En el análisis multivariado el UPP se asoció a IVU después de RTUV (OR 7.04 [95% IC 2.11-23.29]).

Limitaciones: Estudio retrospectivo limitado a información reportada en expediente.

Originalidad y valor: Existe poca literatura acerca de IVU asociadas a RTUV a nivel mundial, en México no hay información, siendo este estudio único en su campo.

Conclusiones: La prevalencia de IVU después de RTUV fue de 10%. El factor de riesgo con mayor asociación fue el UPP para IVU después de RTUV. Los uropatógenos más frecuentemente aislados fueron *E. coli*, *E. faecalis* y *P. mirabilis*. Trimetoprima/sulfametoxazol (60%) y ciprofloxacino (40%) fueron los antibióticos con mayor resistencia para *E. coli*.

Palabras clave:
Resección transuretral de vejiga, infecciones de tracto urinario, Incidencia, Resistencia antibiótica.

Introduction

Bladder cancer is the tenth most frequent cancer worldwide, with an estimated incidence of 549,393 new cases in 2018. Over the past 5 years, a prevalence of approximately 1,648,482 cases has been estimated, making bladder cancer the sixth most prevalent cancer in the world, holding thirteenth place in mortality, with approximately 200,000 deaths attributed to the disease.[1] In central Mexico, a prevalence study was conducted from 2007-2009, in which 7,838 cases of genitourinary cancer were reported, 14.4% of which corresponded to bladder cancer.[2]

Transurethral resection of bladder tumor (TURBT) is a common treatment modality in bladder cancer.[3] It is the main diagnostic and therapeutic tool because it determines stage, as well as tumor grade, as it resects or fulgurates all visible tumors.[4] Among the most frequent complications of this procedure are infection, bleeding, bladder perforation, and postoperative death.[5,6] Reports in the literature have associated urologic instrumentation with an increase in the incidence of urinary tract infection (UTI) and bacteremia.[7,8] The post-procedure infection rate usually reflects the presence of significant bacteriuria.[6] There is currently little information about infectious complications associated with TURBT.[9] The incidence of TURBT-associated UTI has been shown to vary from 18% to 75%[8] and 2% to 39%.[10]

A pre-procedure urine culture must be carried out and have negative results before the performance of any endourologic intervention.[10,11] Patients with asymptomatic bacteriuria before the procedure have an increased risk of presenting bacteremia and sepsis.[10] There is still no consensus on the use of antibiotic prophylaxis regarding TURBT, despite the fact that it is a frequent procedure.[12]

The aim of the present study was to analyze the microbiology and incidence of drug resistance in patients that underwent TURBT and to identify independent risk factors for postoperative UTI.

Materials and Methods

We conducted a descriptive and analytic retrospective study on information obtained from 199 patients that underwent TURBT between 2017-2019 at a tertiary care hospital center in Mexico City. Inclusion criteria were having undergone TURBT, age above 18 years, and preoperative urine culture. Non-inclusion criteria were incomplete case records (lack of urine culture information, no follow-up notes).

The sample was divided into 2 groups. Group 1 included the patients that presented with UTI within the first 30 days after TURBT and group 2 was made up of the patients that did not present with UTI. To determine the presence of UTI, a search of positive urine cultures (PUCs) within the first 30 days after TURBT was first carried out, after which the follow-up notes were reviewed, to confirm the diagnosis and treatment of UTI.

Demographic data (sex, age, body mass index (BMI), tobacco use, comorbidities), oncologic characteristics (histopathology report, tumor grade, necrosis, tumor quantity) and infectious characteristics (pre-procedure urine culture, isolations, and antibiotic resistance) were analyzed in the two groups.

For the statistical analysis, the IBM SPSS v24 program (BM Co., Armonk, NY, USA) was utilized to compare the two independent sam-

ples. The Student's t test was performed for the parametric variables and the Mann-Whitney U test for the nonparametric variables. Univariate and multivariate logistic regression analyses were performed to find risk factors associated with the presence of UTI. A p <0.05 was considered statistically significant.

Results

One hundred and ninety-nine case records met the inclusion criteria. Twenty patients were included in group 1 and 179 patients in group 2. The calculated incidence of UTI was 10%. Twenty-six case records were excluded due to lack of urine culture data and follow-up notes.

Baseline characteristics

The mean age in the two groups was 69 years. The sample consisted of 77% men and 23% women. The mean BMI was 26.2 kg/m^2, with a trend toward overweight in both groups. Of the patient total, 63% smoked, 26% were diagnosed with diabetes mellitus, and 48% were hypertensive. No significant difference was found between the groups regarding sex, BMI, smoking, diabetes mellitus, or hypertension. The presence of a PUC before the procedure was statistically significant (p=0.001) (Table 1).

Table 1. Baseline and oncologic characteristics between the study groups

		UTI	
Variable	*Positive*	*Negative*	*p value*
Age			
	70 (±15)	68 (±11)	0.219
Sex			
Female	8 (40%)	37 (20.7%)	0.051
Male	12 (60%)	142 (79.3%)	
BMI			
	26.7 (±4.7)	25.7 (±4.3)	0.337
Tobaco use			
Yes	11 (55%)	115 (64.2%)	0.672
No	9 (45%)	64 (35.8%)	
Diabetes mellitus			
Yes	6 (30%)	46(25.7%)	0.52
No	14 (70%)	133 (74.3%)	
Hypertension			
Yes	11 (55%)	85(47.5%)	0.301
No	9 (45%)	94 (52.5%)	
Positive urine culture before TURBT			
Yes	10 (50%)	18 (10%)	0.001
No	10 (50%)	161 (90%)	

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	UTI		
Variable	*Positive*	*Negative*	*p value*
Non-muscle-invasive bladder cancer			
	9 (45%)	105 (58.7%)	0.031
Muscle-invasive bladder cancer			
	7 (35%)	26 (14.5%)	0.031
Cystitis			
	1 (5%)	38 (21.2%)	0.11
High-grade tumor			
	14 (70%)	94(52.5%)	0.18
Presence of necrosis			
	5 (25%)	8 (4.5%)	0.001
Single tumor			
	9 (45%)	52 (49%)	0.116

Oncologic characteristics

Fifty-seven percent of the patients were reported to have non-muscle-invasive bladder cancer, 16% had muscle-invasive bladder cancer, and 19% presented with chronic cystitis. A total of 54% of the tumors were high-grade, 6% had necrosis, and 60% of the patients had a single tumor in the bladder.

Of the oncologic characteristics, the presence of necrosis (p=0.001) and muscle-invasive bladder cancer (p=0.031) were statistically significant. The presence of cystitis, high-grade tumor, and single tumor were not statistically significant (Table 1).

Univariate and multivariate analyses

Binary logistic regression was performed. In the univariate analysis, patients with a preoperative PUC (OR 8.9 [95% CI 3.28-6.71] p=0.001), the presence of muscle-invasive bladder tumor (OR 3.14 [95% CI 1.07-9.22] p=0.037), and the presence of necrosis in the histology study (OR 7.12 [95% CI 2.07-24.51] p=0.002) were statistically significant. There were no statistically significant differences in sex, age, BMI, diabetes mellitus, or the presence of cystitis and/or high-grade tumor in the histopathology report (Table 2).

Table 2. Univariate analysis of independent risk factors associated with UTI after TURBT

		UTI in the first 30 days after TURBT					
Variable	*Total No.*	*Negative*	*%*	*Positive*	*%*	*OR (95% CI)*	*p value*
Sex							
Female	45	37	82%	8	18%	2.5 (0.9-6.7)	0.056
Male	154	142	92%	12	8%		
Diabetes mellitus							
Yes	52	46	88%	6	12%	1.4 (0.49-4.03)	0.521
No	130	119	92%	11	8%		
Unknown	17	14	82%	3	18%		
Positive urine culture before TURBT							
Yes	28	18	64%	10	36%	8.9 (3.28-6.71)	0.001
No	171	161	94%	10	6%		
Non-muscle-invasive bladder cancer							
Yes	114	105	92%	9	8%	0.31 (0.10-0.93)	0.037
No	85	74	87%	11	13%		
Muscle-invasive bladder cancer							
Yes	33	26	79%	7	21%	3.14(1.07-9.22)	0.037
No	166	153	92%	13	8%		
Pathology report of cystitis							
Yes	39	38	97%	1	3%	4.64(0.59-36.13)	0.143
No	160	141	88%	19	12%		
High-grade cancer							
Yes	108	94	87%	14	13%	2.11 (0.77-5.73)	0.143
No	91	85	93%	6	7%		
Necrosis							
Yes	13	8	62%	5	38%	7.12(2.07-24.51)	0.002
No	186	171	92%	15	8%		
Mean Age, years							
		68		70		1.02(0.98-1.06)	0.321
Mean BMI, kg/m^2							
		25.7		26.7		1.05 (0.93-1.17)	0.383

In the multivariate analysis, only a preoperative PUC was statistically significant (OR 7.04 [CI 95% 2.11-23.29] p=0.001). The presence of necrosis or muscle-invasive bladder cancer in the histopathology study were not statistically significant (Table 3).

Table 3. Multivariate analysis of independent risk factors associated with UTI after TURBT

	UTI within the first 30 days after TURBT						
Variable	*Total No.*	*Negative*	*%*	*Positive*	*%*	*OR (95% CI)*	*p value*
Positive urine culture before TURBT							
Yes	28	18	64%	10	36%	7.04 (2.11-23.29)	0.001
No	171	161	94%	10	6%		
Non-muscle-invasive bladder cancer							
Yes	114	105	92%	9	8%	0.44 (0.13-1.50)	0.193
No	85	74	87%	11	13%		
Muscle-invasive bladder cancer							
Yes	33	26	79%	7	21%	2.25 (0.66-7.66)	0.193
No	166	153	92%	13	8%		
Necrosis							
Yes	13	8	62%	5	38%	4.72 (0.86-25.91)	0.074
No	186	171	92%	15	8%		

Microbiology

Twenty-eight PUCs were reported. The most frequently isolated microorganism was *E. coli* (48%), 14% of the pathogens were resistant to extended spectrum beta-lactamases (ESBLs), 71% to ciprofloxacin, and 71% to trimethoprim/sulfamethoxazole (TMP/SMX). The second most commonly isolated pathogen was *E. faecalis* (24%), and the third was *P. mirabilis* (7%).

The microorganisms isolated from the urine cultures in patients that presented with UTI after TURBT, in order of frequency, were: *E. coli* (45%), *E. faecalis* (27%), and *P. mirabilis* (9%). In the *E. coli* cultures, 10% were resistant to ESBLs, 60% to TMP/SMX, and 40% to ciprofloxacin. In the *E. faecalis* cultures, 100% were resistant to TMP/SMX (Table 4).

Table 4. Drug resistance and microbiology before and after* TURBT

	Microogranism	*n*	*ESBL*	*Nitrofurantoin*	*Gentamicin*	*Ciprofloxacin*	*Fosfomycin*	*Ampicillin*	*TMP/SMX*
Before TURBT	E. Coli	14 (48%)	2 (14%)	2 (14%)	5 (35%)	10 (71%)	7 (50%)	10 (71%)	10 (71%)
	E. Faecalis	7 (24%)	0 (0%)	2 (28%)	1 (14%)	1 (14%)	1 (14%)	0 (0%)	7 (100%)
	P. Mirabilis	2 (7%)	0 (0%)	2 (100%)	0 (0%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)
	Other	6 (21%)	3 (50%)	2 (33%)	4 (66%)	1 (16%)	6 (100%)	3 (50%)	4 (66%)
*After TURBT**	E. Coli	10 (45%)	1 (10%)	1 (10%)	1 (10%)	4 (40%)	2 (20%)	7 (70%)	6 (60%)
	E. Faecalis	6 (27%)	0 (0%)	1 (16%)	2 (32%)	2 (32%)	1 (16%)	0 (0%)	6 (100%)
	P. Mirabilis	2 (9%)	0 (0%)	2 (100%)	1 (50%)	0 (0%)	2 (100%)	1 (50%)	1 (50%)
	Other	4 (18%)	1 (33%)	1 (33%)	1 (33%)	0 (0%)	3 (100%)	3 (100%)	1 (33%)

* Drug resistance and microbiology in UTI within the first 30 days after TURBT

Discussion

Transurethral resection of the bladder is a common endourologic procedure due to its diagnostic and therapeutic utility in bladder cancer. Complications associated with TURBT, in order of frequency, are infection, bleeding, bladder perforation, and postoperative death.[5,6,13] A range of 2% to 75% in the prevalence of UTI after TURBT has been reported in the literature.[7,9,10] In Madrid, the University Hospital reported a 5.5% incidence of UTI after TURBT. *Pseudomonas aeruginosa* was isolated in 26.9% of urine cultures after the procedure, with high resistance to fluoroquinolones (43%) and third and fourth-generation cephalosporin, carbapenems, and piperacillin-tazobactam (28% each).[14] In our study, the calculated incidence of UTI was 10%, and *E. coli* was the most frequently isolated microorganism, with a high resistance to quinolones (40%) and sulfonamides (60%). Comparing the two studies, the panorama in each country is different. The pathogens isolated from the study in Madrid were from bacteria related to healthcare-associated infections, whereas the pathogens isolated in our study were from bacteria related to community-acquired infections. Those differences directly affect the therapeutic decisions made for each entity, regarding prophylaxis and antibiotic selection. Currently, there are only a limited number of studies on antibiotic prophylaxis. They were conducted years ago, and only recommend or not, the use of antibiotics.[15–17] There is one active phase 2 randomized clinical trial (NCT04209192) that is comparing fosfomycin with amikacin as prophylaxis in TURBT, and its estimated completion date is 2023.[18]

There is currently little information about preoperative risk factors associated with UTI after a TURBT. The Japanese guidelines for prevention of perioperative infections classifies the risk factors for surgical site infections as patient-related and medical care-related.[19] The ASA physical score, immunosuppression, indwelling catheter, catheterization duration after surgery, hand washing, diabetes, and smoking are possible risk factors that may contribute to infection.[14,19,20] The single most recent study

on risk factors of UTI after TURBT reported that past pelvic radiotherapy, age, preoperative hospital stay, and tumor size (>2cm) were risk factors for postoperative UTIs after TURBT. Those authors also reported their study limitations, which included a prevalence of UTI after TURBT in only 3.1% patients (n = 21) after a long observation period (11 years).[9] In the present study, we found statistically significant preoperative PUC, which can be a predisposing factor to presenting with UTI after TURBT. A total of 62.5% of resected tumors have been reported to have bacterial growth, with 91% of postoperative PUCs having the same microorganism found in the tumor.[6] The most commonly isolated microorganisms found in tumors are *E. coli*, *Klebsiella pneumoniae*, and *E. faecalis*. Junuzovic et al. demonstrated that preoperative bacteriuria was statistically significant in relation to the presentation of postoperative bacteriuria.[8] In our study, the patients with a PUC before TURBT were treated based on the antibiotic sensitivity reported in the urine culture. Those patients had no clinical symptoms or signs of UTI. However, no new urine culture was carried out to confirm the absence of bacteria in urine. The pre-procedure presence of bacteria in urine facilitates post-procedure infection, because either the tumor is colonized, or treatment is not effective in eradicating colonization. Importantly, a possible modification of the bladder defense mechanisms due to malignant processes has been suggested,[6,21] which may also be a predisposing factor to infection.

The most frequently isolated pathogen in the preoperative urine cultures of our study was *E. coli* (48%), which has the peculiarity of being able to establish a reservoir in the bladder mucosa.[22] That characteristic, plus the dysfunction of the bladder defense mechanisms, could be the reason why patients are more predisposed to a UTI after TURBT. In addition, despite giving the appropriate antibiotic therapy, *E. coli* has been reported to persist in the bladder.[22,23] That occurs because *E. coli* is able to invade the bladder epithelium, which can lead to a persistent bacterial reservoir. The bladder mucosa is a site of potential bacterial colonization after a UTI.[22] Furthermore, exfoliation of bladder epithelial cells could make lower layers of the urothelium more susceptible to infection.[23]

In our study, UTI was most frequently caused by *E. coli*, and was isolated in 45% of the postoperative urine cultures. The most common microorganisms reported to be responsible for UTI in postoperative urologic procedures are Enterobacteriaceae, *Pseudomonas aeruginosa*, enterococci, and less frequently, staphylococci.[24] The latest report from the European Center for Disease Prevention and Control (ECDC), with data from 2018, stated that *E. coli* was resistant to aminopenicillins (57.4%), fluoroquinolones (25.3%), third-generation cephalosporins (15.1%), and aminoglycosides (11.1%).[25] Studies in Mexico have reported *E. coli* resistance to fluoroquinolones, ranging from 40% to 89%, and to sulfonamides, ranging from 52% to 60%.[26–28] In our study, *E. coli* displayed similar behavior, with a reported resistance of 40% to fluoroquinolones and 60% to sulfonamides. In Mexico, compared with Europe, there is an increased resistance to fluoroquinolones, suggesting that empiric treatment for UTI in Mexico with fluoroquinolones should not be recommended, nor should those antibiotics be used as prophylactic therapy. In addition, sulfonamides are no longer recommended as treatment for UTI.

The presence of tumor necrosis is associated with poor oncologic outcomes,[29] increased

TURBT extension, solid growth, and low hemoglobin levels.[30] Necrosis has also been associated with aggressive tumor biologic features and may have an impact on oncologic outcomes.[29] Tumor necrosis was reported in 13 of our cases (6%), 38% of which presented with UTI after the procedure. That can be explained by its association with an increased extent of TURBT, resulting in long surgery duration or a more complicated procedure. Nevertheless, despite the current evidence, tumor necrosis is not yet an independent predisposing factor to infection.[12]

Limitations to our study included the fact that patients with a pre-procedure PUC were given treatment directed at antibiotic sensitivity, but no new culture was carried out before the procedure to confirm the absence of bacterial growth in urine, and so we did not know if those patients had sterile urine before the TURBT. Urine cultures for anaerobes were also not performed, which could mean that patients with tumor necrosis-associated UTIs could have been underdiagnosed. Another limitation was that not all patients had a urine culture after TURBT, so the incidence of asymptomatic bacteriuria could not be assessed.

Conclusions

The incidence of UTI after TURBT was 10%. Today, there is still a lack of information on that theme, making the use of antibiotic prophylaxis in those procedures problematic. Having the precise knowledge of the risk factors that predispose to UTI after TURBT remains a challenge. The presence of asymptomatic bacteriuria after TURBT is a common complication and its relevance is not yet known. Preoperative PUC was the strongest associated risk factor for developing UTI after the procedure. Confirming the absence of bacteria with a negative urine culture before the performance of any endourologic procedure, including TURBT, is recommended.

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