

Microbial colonization and ureteral stent-associated storage lower urinary tract symptoms: the forgotten piece of the puzzle?

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Abstract

Purpose Ureteral stents are frequently associated with side effects. Most patients suffer from storage lower urinary tract symptoms (LUTS). Storage LUTS are commonly attributed to the irritation of the trigone, smooth muscle spasm or a combination of factors. The relationship between microbial ureteral stent colonization (MUSC) and de novo or worsening storage LUTS has not been investigated yet.

Methods Five hundred ninety-one polyurethane ureteral stents from 275 male and 153 female patients were

prospectively evaluated. The removed stents were sonicated to dislodge adherent microorganisms. Urine flow cytometry was performed to detect pyuria. A standardized urinary symptom questionnaire was given to all patients.

Results Thirty-five per cent of male and 28% of female cases showed de novo or worsened storage LUTS. MUSC was more common in patients with storage LUTS compared to patients without storage LUTS (men: 26 vs. 13%, respectively, $P < 0.05$; women: 63 vs. 48%, respectively, $P = 0.13$). Pyuria was significantly more common in patients with storage LUTS compared to patients without storage LUTS (men: 55 vs. 40%, respectively, $P < 0.05$; women: 70 vs. 45%, respectively, $P < 0.05$). No significant correlation was observed between the detected genera of microorganisms and storage LUTS.

Conclusions Our data show a significant association between MUSC- and stent-related de novo experienced or worsened storage LUTS in men. The incidence of MUSC is most common in both female and male patients with storage LUTS and accompanying pyuria. In these patients, a combination of antibiotics and anti-inflammatory drugs may be regarded as treatment option.

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Introduction

Ureteral stents are widely used to maintain upper urinary tract function. However, many patients experience unpleasant urinary symptoms, flank pain and haematuria. The most commonly reported stent-associated symptoms include frequency, nocturia, urgency and urgency urinary

incontinence [1–3], summarized as ‘storage lower urinary tract symptoms’ (storage LUTS). The pathophysiology of stent-related storage LUTS is poorly understood. Multiple theories have been suggested including mechanical irritation of the bladder, exacerbation of pre-existing detrusor overactivity and smooth muscle spasms of the distal ureter. Similar to other medical implants, ureteral stents bear an intrinsic risk of microbial colonization and consecutive biofilm formation. The relationship between microbial ureteral stent colonization (MUSC) and storage LUTS has not yet been investigated. We have recently shown that sonication of ureteral stents is a valuable means for the detection of MUSC [4, 5] and, therefore, allows for the study of its effects on patients. We report here the results of a prospective clinical trial using sonication in the detection of MUSC. Data on clinical signs and symptoms as well as laboratory urine analyses were evaluated in an attempt to correlate these results with MUSC.

Methods

Study population

All patients who had their stent(s) removed during the study period (March 2008–July 2010) for any clinical reason were eligible for the study. After providing informed consent, patients were followed using a standardized case report form. The study was approved by the local ethics committee. Exclusion criteria included renal transplant ($n = 93$), refusal of consent ($n = 5$), bilateral stents ($n = 30$), missing questionnaire ($n = 1$), stent migration into the bladder ($n = 1$), missing urine or urine flow cytometry results ($n = 12$) and urine sampling via an ileal conduit or an indwelling transurethral catheter ($n = 11$).

Patient questionnaire

All patients were asked to fill in a standardized questionnaire (‘Appendix in Electronic supplementary material’) at the time of their stent removal. The formally non-validated questionnaire was designed with the objective to assess the prevalence of de novo experienced or worsened storage LUTS (Urinary frequency, urgency, nocturia and urgency urinary incontinence) and pain (suprapubic pain, flank pain and flank pain during voiding) in the period of stenting. It consists of eight questions. The alternatives of the questions were dichotomous, having only the options yes or no. If one or more of the questions a–d was answered with ‘yes’, the patient was allocated to the storage LUTS group. Patients were interviewed, when they were unable to fill in the form or answers were unclear. Data were transferred to a spread sheet (Microsoft Office Excel 2010) and cross-

checked before being exporting to statistical analysis software.

Urine analysis

Urine samples were obtained prior to device removal and analysed by conventional culture methods and the Sysmex UF1000i (TOA Medical Electronics, Kobe, Japan). This device is a fully automated fluorescence flow cytometer able to classify and count cells and formed particles in native uncentrifuged urine samples [8].

Ureteral stent sonication

Ureteral stents were removed under aseptic conditions, divided into small parts, placed in sterile tubes and processed by the microbiology laboratory within 6 h. Stent colonization was detected by sonication as described previously [4]. Microorganisms were enumerated and classified by routine microbiologic techniques.

Statistical analysis

Analyses were performed using SPSS version 17 software (SPSS, Inc., Chicago, IL). McNemar’s test was applied as appropriate. A P value of <0.05 was considered to indicate statistical significance. All tests were two-sided.

Definitions

Microbial ureteral stent colonization (MUSC)

Growth of $\geq 10^2$ CFU/mL in sonicate-fluid culture (SFC). Because no validated cut-off value for MUSC diagnosed by sonication exists, a threshold of $\geq 10^2$ CFU/mL was chosen according to recommendations for intravascular catheters [6].

Ureteral stent contamination

Growth of $<10^2$ CFU/mL and mixed gram-positive flora in SFC.

Positive urine culture (PUC) and urine contamination

Urine sample collection, quantitation (CFU/mL) and organism isolation and enumeration were performed as described by Wilson et al. [7].

Pyuria

Presence of ≥ 40 leucocytes per microlitre of urine detected by the urine flow cytometer Sysmex UF1000i [8].

Storage lower urinary tract symptoms (LUTS)

Urinary frequency, urgency, nocturia and urge incontinence [9].

Unique ureteral stent insertion

Stents obtained from patients undergoing singular stenting or the first stent removed from patients with continuous stenting.

Continuous ureteral stenting

Stents obtained from patients with continuous stenting with the exception of the first-placed stent.

Results

Five hundred ninety-one (591) polyurethane stents from 275 male and 153 female patients were removed during the study period. One hundred fifty-three (153) devices were excluded based on the outlined exclusion criteria. Complete data for 438 stents from 197 male and 118 female patients were analysed (Table 1).

Sonicate-fluid culture

Sonicate-fluid culture (SFC) detected MUSC in 31%. Fifty-three discordant observational pairs were positive with sonication only, compared to 13 positives with urine culture only. All negative controls ($n = 8$) were negative in SFC. Stents obtained from female patients showed significantly higher proportion of MUSC (52%) than stents obtained from men (18%, $P < 0.05$).

Urine culture

The relationship between positive urine culture, SFC and pyuria and the association with de novo or worsened storage LUTS are demonstrated in Table 2. In addition, we observed a significantly higher proportion of asymptomatic bacteriuria (ASB) in female compared with male cases (20 vs. 6%, $P < 0.05$).

Male patients

On the day of stent removal, 35% of male cases showed de novo or worsened storage LUTS. MUSC was more common in patients with storage LUTS (26%) than in patients without storage LUTS (13%, $P < 0.05$). Furthermore, pyuria was significantly more common in patients with storage LUTS (55%) than in patients without storage LUTS (40%,

Table 1 Study population

Variables	<i>N</i>	Storage LUTS	No storage LUTS
Study group	438 (100%)	142 (32%)	296 (68%)
Unique ureteral stent insertion	303 (69%)	96 (32%)	207 (68%)
Continuous stent insertion	135 (31%)	46 (34%)	89 (66%)
Sex			
Male	274 (63%)	96 (35%)	178 (65%)
Female	164 (37%)	46 (28%)	118 (72%)
Age			
Up to 50 years	168 (39%)	54 (32%)	114 (68%)
>50 years	270 (61%)	88 (33%)	182 (67%)
Indwelling time			
<30 days	202 (46%)	64 (32%)	138 (68%)
≥30 days	236 (54%)	78 (33%)	158 (67%)
Sonication			
MUSC	135 (31%)	54 (40%)	81 (60%)
No MUSC	303 (69%)	88 (29%)	215 (71%)
Urine culture			
Positive	68 (16%)	33 (49%)	35 (51%)
Negative	370 (84%)	109 (29%)	261 (71%)
Urine flow cytometry			
Pyuria	209 (48%)	85 (41%)	124 (59%)
No Pyuria	229 (52%)	57 (25%)	172 (75%)
Indication			
Ureterorenoscopy	162 (37%)	58 (36%)	104 (64%)
Obstructive uropathy	141 (32%)	48 (34%)	93 (66%)
Malignancy	27 (6%)	8 (30%)	19 (70%)
Other	108 (25%)	28 (26%)	80 (64%)

MUSC microbial ureteral stent colonization; LUTS lower urinary tract symptoms

Table 2 Relationship between positive urine culture sonicated fluid culture, pyuria and de novo experienced or worsened storage LUTS

	Storage LUTS			No storage LUTS		
	MUSC (%)	PUC (%)	<i>P</i> value	MUSC (%)	PUC (%)	<i>P</i> value
Men						
Pyuria	36	23	<0.05	20	11	<0.05
No pyuria	14	7	0.2482	9	3	<0.05
Women						
Pyuria	69	47	<0.05	58	36	<0.05
No pyuria	50	21	0.1336	40	8	<0.05

MUSC microbial ureteral stent colonization; PUC positive urine culture; LUTS lower urinary tract symptoms

$P < 0.05$). Patients with storage LUTS and accompanying pyuria showed significantly more MUSC (36%) than patients with storage LUTS without pyuria (14%, $P < 0.05$). Patients

Table 3 Microorganisms detected by sonication in male cases

Male cases	<i>N</i>	Storage LUTS	No storage LUTS
No. of microorganisms	64 (100%)	36 (51%)	28 (49%)
<i>CoNS</i> ^a	21 (33%)	12 (57%)	9 (43%)
<i>Enterococcus</i> spp.	11 (17%)	4 (36%)	7 (64%)
<i>Enterobacteriaceae</i> ^b	10 (16%)	7 (70%)	3 (30%)
<i>Candida</i> spp.	9 (14%)	6 (67%)	3 (33%)
<i>Streptococcus</i> spp.	4 (6%)	3 (75%)	1 (25%)
<i>Corynebacterium</i> spp.	3 (5%)	1 (33%)	2 (67%)
Other ^c	6 (9%)	3 (50%)	3 (50%)

LUTS lower urinary tract symptoms

^a Coagulase-negative staphylococci spp

^b *Escherichia coli* (*n* = 6), *Serratia marcescens* (*n* = 2), *Proteus* spp. (*n* = 1), *Klebsiella pneumoniae* (*n* = 1)

^c *Kocuria kristinae* (*n* = 1), *Staphylococcus aureus* (*n* = 2), *Pseudomonas aeruginosa* (*n* = 2), *Moraxella catarrhalis* (*n* = 1)

without storage LUTS and accompanying pyuria showed more MUSC (20%) than patients without storage LUTS and missing pyuria (9%, *P* = 0.08).

Female patients

On the day of stent removal, 28% of female cases showed de novo or worsened storage LUTS. No statistical significance in the incidence of MUSC could be detected when comparing female patients with storage LUTS (63%) and without storage LUTS (48%, *P* = 0.13). Pyuria was significantly more frequent in patients presenting with storage LUTS (70%) than in patients without storage LUTS (45%, *P* < 0.05). Patients with storage LUTS and accompanying pyuria showed more MUSC (69%) than patients with storage LUTS and no pyuria (50%, *P* = 0.38). Similarly, patients without storage LUTS and accompanying pyuria showed more MUSC (58%) than patients without storage LUTS and no pyuria (40%, *P* = 0.07).

Microorganisms detected by sonication

Details of the detected microorganisms and their association with de novo or worsened storage LUTS are shown in Tables 3 and 4. No significant correlations between the detected genera of microorganisms and storage LUTS were observed.

Discussion

Indwelling ureteral stents frequently result in major patient morbidity. Studies examining stent composition, size, length, design and position with the objective to improve

Table 4 Microorganisms detected by sonication in female cases

Female cases	<i>N</i>	Storage LUTS	No storage LUTS
No. of microorganisms	136 (100%)	50 (37%)	86 (63%)
<i>CoNS</i> ^a	13 (10%)	4 (31%)	9 (69%)
<i>Enterococcus</i> spp.	23 (17%)	9 (39%)	14 (61%)
<i>Enterobacteriaceae</i> ^b	27 (20%)	14 (52%)	13 (48%)
<i>Candida</i> spp.	17 (13%)	7 (41%)	10 (59%)
<i>Streptococcus</i> spp.	9 (7%)	0 (0%)	9 (100%)
<i>Corynebacterium</i> spp.	13 (10%)	3 (23%)	10 (77%)
<i>Lactobacillus</i> spp.	17 (13%)	8 (47%)	9 (53%)
<i>Gardnerella vaginalis</i>	5 (4%)	2 (40%)	3 (60%)
Other ^c	12 (12%)	3 (25%)	9 (75%)

LUTS lower urinary tract symptoms

^a Coagulase-negative staphylococci spp

^b *Escherichia coli* (*n* = 22), *Proteus* spp. (*n* = 3), *Klebsiella pneumoniae* (*n* = 1), *Citrobacter freundii* (*n* = 1)

^c *Kocuria rosea* (*n* = 5), *Kocuria kristinae* (*n* = 2), *Staphylococcus aureus* (*n* = 1), *Pseudomonas aeruginosa* (*n* = 1), *Erysipelothrix rhusiopathiae* (*n* = 1), *Demacoccus nishinomiyaensis* (*n* = 1), *Aerococcus urinae* (*n* = 1)

patient quality of life are contradictory [10–13]. Patients most commonly report symptoms of overactive bladder including urinary frequency, urgency, nocturia and urgency urinary incontinence [1–3]. These symptoms are commonly referred to as storage LUTS [9]. Storage LUTS are generally attributed to smooth muscle spasm and local irritation of the trigone by the distal coil of the stent [3, 14–17].

The role of MUSC in the pathogenesis of stent-related storage LUTS has not yet been studied. MUSC and consecutive biofilm development is a multistep process [18, 19] starting with the formation of a conditioning film consisting of host proteins, electrolytes and other substances [20]. The final biofilm is formed by materials offered by the environment and extracellular polymeric substances produced by pathogens. After a biofilm is formed, microorganisms detach as a result of cell growth and division or the removal of biofilm aggregates which contain masses of cells. Urothelial cells sense biofilm pathogens by diverse receptors and react by producing substances (e.g. nitric oxide, cathelicidin and β -defensin-2) toxic to invaders [21–23]. In addition, they produce a number of chemokines and proinflammatory cytokines. Cytokine-mediated upregulation of adhesion molecules and cytokine receptors facilitate the process of immune cell migration. Leucocytes accumulate in the urine and urothelium to eliminate bacteria. However, their released toxic contents damage not only pathogens, but also the surrounding tissue. Local inflammation leads to stimulation and activation of afferent nerves, resulting in storage LUTS. In addition, bacterial toxins (e.g., LPS) were recognized by the immune system and initiate local

and systemic responses. The question of why some patients with MUSC suffer from storage LUTS, while others remain asymptomatic could be answered by differences in both antibacterial protection mechanisms and pathogen virulence. In addition, it has to be kept in mind that urinary tract infection (UTI) and even asymptomatic bacteriuria (ASB) are more common in women than in men. Consequently, the rate of MUSC is higher in stents removed from women compared with those from men [4]. Indeed, our study population showed both a significant higher rate of MUSC and ASB in female compared with male cases. It seems to be obvious that in accordance with the higher rate of ASB, a major female subgroup is able to tolerate the presence of MUSC without suffering from storage LUTS. This observation might serve as an explanation for the insignificant association of MUSC and stent-related storage LUTS in women. However, our results showed a clear trend for such an association. In addition, the female study population might be underpowered.

In contrast to the inconsistent relationship between MUSC and storage LUTS, pyuria was found to be significantly more common both in female and male patients with storage LUTS than patients without storage LUTS. This observation serves as a link to neurogenic inflammation (NI), another potential aetiological factor of stent-related storage LUTS. Pathophysiological, initial ureteral stent activation of sensory nerves ($A\delta$ or C-fibres) located in the bladder wall leads to transmission of signals to the central nervous system [24]. These neurons express among others, members of the transient receptor potential (TRP) family of ion channels, which are frequently involved in idiopathic and neurogenic detrusor overactivity [25, 26]. Initial receptor activation is followed by NI, which consists of a series of vascular and non-vascular inflammatory responses. NI is mediated by the release of proinflammatory neuropeptides including substance P (SP), neurokinin A, and calcitonin gene-related peptide (CGRP) in the periphery. These peptides lead to oedema, leucocyte accumulation, formation of radical oxygen species and promote smooth muscle contraction of the ureter, bladder wall and urethra [27].

The identification of MUSC and NI as potential aetiological factors of stent-related storage LUTS offers an explanation for the insufficient pharmaceutical treatment of stent-related morbidity. Although recent studies showed an improvement of a subset of urinary symptoms by oral administration of alpha blockers [28], the medical therapy for the majority of patients with stent-associated storage LUTS remains unsatisfactory. In this context, MUSC and NI should be taken into account when developing a multimodal treatment approach for stent-associated storage LUTS. Especially in patients with de novo or worsened storage LUTS and accompanying pyuria, the combination of antibiotics targeting most commonly isolated microorganisms with anti-inflammatory drugs

should be regarded as a treatment option. Furthermore, our data might be useful to estimate the risk of MUSC prior to stent manipulation which bears the risk of severe infectious complications [29, 30].

The limitations of this study include (1) the lack of a gold-standard definition of ureteral stent-related infection and (2) the fact that the ureteral symptom questionnaire used has not been formally validated.

Conclusions

This study demonstrates a significant correlation between MUSC and stent-related de novo or worsened storage LUTS in men. The incidence of MUSC is most common in male as well as in female patients with storage LUTS and pyuria. In these patients, the combination of antibiotics and anti-inflammatory drugs should be regarded as a treatment option. In addition, the estimation of MUSC based on the presence of storage LUTS and pyuria prior to stent manipulation might be helpful to minimize the risk of severe post-operative infectious complications.

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