

ORIGINAL ARTICLE

Retrospective study for risk factors for febrile UTI in spinal cord injury patients with routine concomitant intermittent catheterization in outpatient settings

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Study design: Retrospective study.

Objectives: The objective of this study was to investigate the clinical risk factors for febrile urinary tract infection (UTI) in spinal cord injury-associated neurogenic bladder (NB) patients who perform routine clean intermittent catheterization (CIC).

Setting: Rehabilitation Hospital, Kobe, Japan.

Methods: Over a 3-year period, we retrospectively assessed the clinical risk factors for febrile UTI in 259 spinal cord injury patients diagnosed as NB and performing routine CIC with regard to the factors such as gender, the presence of pyuria and bacteriuria, and the categories of the American Spinal Injury Association (ASIA) impairment scale.

Results: A total of 67 patients had febrile UTI in the follow-up period, with 57 cases of pyelonephritis, 11 cases of epididymitis and 2 cases of prostatitis, including the patients with plural infectious diseases. The causative bacteria were ranked as follows: *Escherichia coli* (74 cases), *Pseudomonas aeruginosa* (17 cases), *Enterococcus faecalis* (14 cases) and *Klebsiella pneumoniae* (12 cases). Antibiotic-resistant *E. coli* were seen, with 10.5% instances of extended-spectrum β -lactamase (ESBL) production and 23.8% of fluoroquinolone resistance. Multivariate analyses of clinical risk factors for febrile UTI showed that gender (male, $P=0.0431$), and ASIA impairment scale C or more severe ($P=0.0266$) were significantly associated with febrile UTI occurrence in NB patients with routine CIC.

Conclusion: Our data demonstrated gender (male) and ASIA impairment scale C or more severe were significantly associated with febrile UTI occurrence in NB patients using routine CIC. Further prospective studies are necessary to define the full spectrum of possible risk factors for febrile UTI in these patients.

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INTRODUCTION

Neurogenic bladder (NB) is a voiding disturbance caused by neurogenic diseases. Cerebrovascular disease and spinal cord dysfunction, due to, for instance, spinal cord injury, and neurodegenerative disease are representative causes of NB. The main symptoms are voiding and storage disturbance, and urinary tract stones and urinary tract infection (UTI) are often involved. One of main therapeutic strategies is urinary tract catheterization, but long duration of urethral catheter storage can cause complications such as urogenital infection, bladder stone, urethral injury or urinary tract fistula.¹ Substituting intermittent catheterization may decrease such complications.

Clean intermittent catheterization (CIC) is considered as the first choice for the patients whose inability to void effectively causes overextension of the bladder wall and increase of intravesical pressure leading to the risk of UTI, vesicoureteral reflux (VUR) and upper urinary tract dysfunction. CIC is recommended for patients with lower urinary tract symptoms (LUTS) and uncontrollable autonomic hyperreflexia. The 2005 'Clinical Practice Guideline For Lower Urinary Tract Dysfunction In Patients With Chronic Spinal Cord Injury' from the Japanese Continence Society recommends CIC for the patients

who have more than 100 ml of residual urine, findings of bladder deformation or VUR on voiding cystography, or detrusor-sphincter dyssynergia (DSD), or bladder compliance <20 ml per H₂O.²

CIC tends to cause fewer urinary tract complications compared with urethral indwelling catheterizations, and the rate of febrile UTI occurrence with indwelling catheters has been reported as once/3.9 years,³ whereas patients on CIC of three times or more per day reportedly had febrile UTI of once/10 years.⁴

There are several reports regarding the risk factors for febrile UTI in NB patients, especially focusing on spinal cord injury. A study of 140 spinal cord injury patients excluding indwelled urethral catheter patients found that 75% of quadriplegic patients and 92% of patients with complete injury had hydronephrosis, and 86% of quadriplegic patients and 100% of the patients with complete injury had VUR.⁵ Quadriplegia and paralysis are considered as greater risk factors for upper urinary tract dysfunction compared with paraplegia and paresis.

Neurological examination of the sacral region related to urinary tract dysfunction appears in the first category of the American Spinal Injury Association (ASIA) evaluation sheet.⁶ The preservation of sensory function in S4–S5 and the ability to voluntarily contract the

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levator ani muscle are important for discriminating complete and incomplete injury. Complete versus incomplete injury and the ability to contract the levator ani muscle are related to DSD⁷ and therefore the severity of spinal cord diseases is considered to correlate with the risk of febrile UTI. As UTI remains one of the main complications in these patients, we investigated the clinical risk factors for febrile UTI in NB patients using CIC.

MATERIALS AND METHODS

Patients

The data were gathered from 259 spinal cord injury-related NB patients in outpatient settings without any ambulatory patients, and trauma was the main cause (Table 1) who required CIC from June 2011 to June 2014 in the Department of Urology of Hyogo Prefectural Rehabilitation Central Hospital. This retrospective study was follow patients up 3 years. All patients consented to the study in writing. The diagnosis of NB was based on voiding disturbances caused by an underlying disease such as spinal cord diseases with abnormal findings on urodynamic study (UDS), such as detrusor overactivity, DSD, low-compliance bladder in cervical or thoracic spinal cord diseases patients and overextended bladder or low detrusor activity. The study was performed in accordance with the principles of the Declaration of Helsinki.

Antibiotic susceptibilities

Susceptibility testing was performed according to the Clinical and Laboratory Standards Institute criteria. Extended-spectrum β -lactamase (ESBL) production tests were performed as in our previous study.⁸ Resistant strains in this study category were defined as ESBL-producing bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa*

Table 1 Patient demographics

<i>n</i>	259
Male	220 (84.9%)
Female	39 (15.1%)
Age (years): median (range)	47 (12–90)
<i>Level of spinal cord injury</i>	
Cervical	86 (33.2%)
Upper thoracic	50 (19.3%)
Lower thoracic	88 (34.0%)
Lumbar	34 (13.1%)
Sacral	1 (0.4%)
<i>Underlying diseases</i>	
Traumatic	
Trauma	207 (79.9%)
Nontraumatic	
Spinal infarction	10 (3.9%)
Cerebral A–V malformation	8 (3.1%)
Spinal tumor	6 (2.3%)
Myelitis	4 (1.5%)
Acute disseminated encephalomyelitis	4 (1.5%)
Epidural hematoma	3 (1.2%)
Lumbar spinal canal stenosis	3 (1.2%)
Cervical spondylosis	2 (0.8%)
Pyogenic spondylitis	2 (0.8%)
Others	10 (3.9%)
Use of continuous catheterization at night	113 (43.6%)
Number of times of CIC per day: median (range)	7 (1–20)
Anticholinergics	193 (74.5%)
Anticholinergics+ β -3 adrenergic agonist	10 (3.9%)
Other bladder pressure decreasing treatment	None

Abbreviation: CIC, clean intermittent catheterization.

(MDRP) defined as resistant to imipenem, ciprofloxacin and amikacin, or pre-MDRP was defined as resistant to two of them.

Indication for CIC and diagnosis of febrile UTI

The indications for CIC were as follows: (1) urinary retention, (2) repeated febrile UTI and (3) hydronephrosis due to bladder overflow. The diagnosis of febrile UTI was fever of 38 °C or more, and urine white blood cell of 10 or more per high power field (hpf) with no other symptoms causing such a high fever. The patients were required to visit outpatients ward or emergency rooms in case of UTI or suspected UTI in addition to scheduled follow-up, and the diagnosis of UTI was performed at those visits. We included urogenital infection such as prostatitis and epididymitis in febrile UTI.^{9,10}

Investigated factors

We tested the following potential risk factors for febrile UTI: (1) gender, (2) severity of spinal cord injury by ASIA impairment scale, (3) the duration of spinal cord injury or diseases, (4) pyuria (with 10 or more white blood cell: white blood cell counts per hpf) and bacteriuria: they were regarded as positive if they were seen in 50% or more frequency over all their office visits in 3 years study periods (We tested these urine tests every time of office visits.), (5) the number of CIC performance per day and (6) uses of anticholinergics and β -3 agonists.

Statistical analyses

Univariate and multivariate tests were performed using StatView 5.0 software (Abacus Concepts Inc., Berkeley, CA, USA). Forward stepwise logistic regression analysis was conducted to determine the association between the various parameters mentioned above and febrile UTI. Statistical significance was established at the 0.05 level.

Igawa *et al.*¹ recommended CIC of four to six times a day, and therefore we analyzed the number of CIC per day with four and six times as cutoff value and excluded the cases with nocturnal catheterization.

RESULTS

Patient demographics and ASIA impairment scale

The patient demographics are shown in Table 1. The ASIA impairment scale categorized 166 patients as A, 32 patients as B, 30 patients as C, 26 patients as D and 5 patients as E (Table 1).

Febrile UTI

A total of 67 (25.8%) patients had febrile UTI in the follow-up periods, with 57 cases of pyelonephritis, 11 cases of epididymitis and 2 cases of prostatitis, including the patients with plural infectious diseases. As to infectious events, 129 events of febrile UTI were observed, including 114 cases of pyelonephritis, 13 cases of epididymitis and 2 cases of prostatitis.

Urine cultures

A total of 88 UTI patients (including repeated UTIs) submitted urine samples. A total of 147 samples were submitted, of which 127 were bacterial-positive. A total of 181 bacteria were isolated. The causative bacteria were ranked as shown in the table, representatively, *Escherichia coli* (74 cases). In addition, antibiotic-resistant strains were seen in 29 (16.0%) isolates, including ESBL producers: 21 (11.6%). In addition, the rate of ESBL producers in all *E. coli* isolates was 28.4% and this accounted for 90.4% (19/21 strains) of all ESBL-producing isolates (Table 2).

Pyuria and bacteriuria

Pyuria was seen in 43.4% of all tested samples and 60.9% of the patients had bacteriuria. In terms of the association of pyuria and bacteriuria with the presence or absence of febrile UTI, for pyuria,

43.3% had febrile UTI and 43.9% did not ($P=0.895$); for bacteriuria, 60.4% had febrile UTI and 62.1% did not ($P=0.837$).

The number of CIC per day

We found that the median value of the number of CIC per day was seven times but there were no significant relationship between four times or less and six times or less of the number of CIC per day and the occurrence of UTI (Tables 1 and 3).

Risk factors for febrile UTI

Our clinical risk factors for febrile UTI based on multivariate analyses were shown in Table 3. Briefly, gender (male, $P=0.0431$) and ASIA impairment scale C or more severe ($P=0.0266$) were significantly associated with febrile UTI occurrence in NB patients using routine CIC (Table 3).

DISCUSSION

Regarding UTI in NB patients caused by spinal cord injury or dysfunction, symptomatic UTI reportedly occurs in 22–45%,¹¹

comparable with our data of 25.8%. As mentioned above, the rate of febrile UTI in patients on CIC performance of three or more times a day is reportedly once per 10 years,⁴ whereas our patients averaged once per 6.6 years. This difference may be because our cases tended to use broad-spectrum antibiotics for longer periods of UTI treatments regardless of guideline recommendation.¹² We have given broad-spectrum antibiotics in our follow-up periods: for instance, fluoroquinolones: 49.4% and third-generation cephalosporines: 22.8% (data not shown). This factor should be reconsidered and unnecessary broad-spectrum antibiotics need to be prevented.

In our urine culture data, the most often isolated febrile UTI-causative bacteria were *E. coli*: 40.9% followed by *P. aeruginosa*: 9.4% and *Enterococcus* spp.: 7.7%. Nicolle *et al.*¹³ found that in their CIC patients the most often isolated febrile UTI-causative bacteria were *E. coli* (35%), followed by *K. pneumonia* (26%), *P. aeruginosa* (23%) and *Proteus mirabilis* (16%). The major difference is the rate of *K. pneumonia* isolation and there is a different trend of the rate of ESBL production: for instance, ESBL-producing bacteria are reported in Japan at a rate of 1.3–6.7%, similar to our data (0%),^{14,15} but a much higher rate in the United States (34%)¹⁶ and Turkey (33%).¹⁷ Regarding antibiotic-resistant bacteria, Chong *et al.*¹⁸ found that 14.3% of all *E. coli* isolates in UTI were ESBL producers, whereas other studies reported 21.0% in CAUTI and found indwelling urethral catheterization was a risk factor for ESBL production.¹⁷ Our data showed a higher rate of ESBL production in *E. coli* (28.4%). This difference in ESBL production rate is partly because of our frequent use of broad-spectrum antibiotics such as third-generation cephalosporines or fluoroquinolones as mentioned above. Then, other reports suggest restricting the use of third-generation cephalosporines may inhibit ESBL production or contamination,^{19,20} and then anti-microbial stewardship need to be performed because our uses of antibiotics were in most cases decided by each physicians and some cases cannot be explained as to the reason of the selection of those antibiotics from retrospective chart review as mentioned above.

Table 2 Causative bacteria

<i>Escherichia coli</i>	74 (40.9%)
<i>Pseudomonas aeruginosa</i>	17 (9.4%)
<i>Enterococcus faecalis</i>	14 (7.7%)
<i>Klebsiella pneumoniae</i>	12 (6.6%)
<i>Citrobacter freundii</i>	8 (4.4%)
<i>Klebsiella oxytoca</i>	7 (3.9%)
<i>Serratia marcescens</i>	7 (3.9%)
<i>Citrobacter koseri</i>	6 (3.3%)
ESBL-producing bacteria	21 (11.6%)
<i>Escherichia coli</i>	19 (10.5%)
MRSA	7 (3.9%)
Pre-MDRP	1 (0.6%)

Abbreviations: ESBL, extended-spectrum β -lactamase; MDRP, multidrug-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; pre-MDRP, resistance to two of imipenem, ciprofloxacin and amikacin.

Table 3 Risk factors for febrile UTI

Factors	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender (male)	3.669	1.235–10.744	0.0177	3.078	1.035–9.154	0.0431
Age	1.008	0.989–1.027	0.418			
Urological surgery	0.74	0.200–2.735	0.6512			
Pyuria	0.863	0.293–2.546	0.7894			
Bacteriuria	1.037	0.590–1.823	0.8994			
Nitrite	1.339	0.725–2.698	0.3169			
Antibiotic-resistant bacteria	0.838	0.469–1.498	0.5507			
Trauma	1.451	0.698–3.015	0.3186			
Immune compromise	1.537	0.587–4.028	0.3817			
Injury of cervical or upper thoracic	1.263	0.544–2.932	0.5867			
ASIA classification C	0.997	0.994–0.999	0.0117	0.997	0.994–1.000	0.0266
Duration after trauma	1.001	0.999–1.004	0.3314			
Nocturnal catheterization	1.734	0.996–3.022	0.0519			
Anticholinergics	1.278	0.689–2.368	0.4362			
β -3 Adrenergic agonist	0.53	0.145–1.938	0.337			
Number of CIC per day (four times or more)	1.343	0.893–1.391	0.9741			
Number of CIC per day (six times or more)	1.317	0.472–3.676	0.5933			

Abbreviations: ASIA, American Spinal Injury Association; 95% CI, 95% confident interval; HR, hazard ratio. Bold represents statistical significance.

CIC or urinary tract catheterized patients often had pyuria or bacteriuria. The standard for bacteriuria in CIC patients is 10^2 or more colony-forming unit (CFU) per ml but that of pyuria in CIC patients is controversial and shows variation (urine white blood cell of 5 or more or of 10 or more per hpf).^{11,21} The relationship between urine findings and symptomatic UTI in spinal cord injury or dysfunction patients with CIC showing cloudy urine had the highest accuracy (83.1%) and the second highest positive predictive value (61.3%) and sensitivity (65.5%),²² suggesting it is realistic to initiate antibiotic treatments in cases with both pyuria- and UTI-related symptoms.

Our data showed a higher rate of febrile UTI in males compared with females. Males tend to have bladder neck occlusion anatomically with a concomitant risk of increased intravesical pressure. The further involvement of NB is considered to increase those risks. As to bladder motor function, ASIA impairment scale A, B and C classes include dysfunctions or malfunctions that tend to produce excessive high intravesical pressure or urinary incontinence. As to bladder sensory function, class A involves complete disability creating a situation where the patients do not notice excessive urine storage or urinary incontinence. Even though there are very few studies in this area, Jayawardena *et al.*²³ reported class A is at risk for positive urine culture and bacteriuria. Our data showed ASIA class C or more severe significantly related with UTI occurrence and it can be interpreted as that class is more injured as to motor (muscle) function than class D so that it may lead to low bladder compliance and possibility of VUR.

One important mechanism causing UTI is high intravesical pressures resulting from distention of the bladder wall and to prevent this, Igawa *et al.*¹ recommended CIC of four to six times a day as mentioned above.¹ However, CIC can be inconvenient in daily life and proper CIC schedules may not be followed by all patients. Our data did not show any significant factors for UTI as to the number of CIC per day and could not suggest the proper number of CIC per day as to the prevention of UTIs; however, we had the nocturnal catheterized patients in a definitive percentage of patient population and it needs caution to direct comparison. Therefore, educating CIC patients on how best to decrease their risk of UTI is important and should be an ongoing mission,²⁴ in that, for instance, many times of CIC with keeping clean technique leading to low rate of frequency of UTI occurrence.^{4,25,26}

We did not show significant relationship between anticholinergics or other bladder pressure-decreasing-treatments and UTI occurrence, and it is considered the double treatments for low-compliance bladder by CIC and those drugs mutually operated and make analysis more complicated.

We would like to emphasize the limitations of this study. First, this study is retrospective in nature and our antibiotic use included preventive ones without any evidence so that we could not include them in our investigation. Second, the standards for febrile UTI are not generally well documented in this patient population. Third, we have no available data of risk evaluation for febrile UTI by UDS. Further prospective studies need to be performed for definitive conclusions.

In conclusion, our data demonstrated that male gender, and ASIA impairment scale C or more severe were significant risk factors for febrile UTI in spinal cord injury patients. Further prospective studies are necessary to define the full spectrum of possible risk factors for febrile UTI in these patients.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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