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Original article

Antimicrobial resistance patterns of bacterial colonization in urine of patients with spinal cord lesion admitted at Thai Red Cross Rehabilitation Center

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Background: The emergence of extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* at the stand-alone Rehabilitation Center of the Thai Red Cross Society has become a concern for treatment of patients with neurogenic bladder.
Objective: To identify commonly observed bacterial colonization in urine of patients with spinal cord lesions.
Methods: Medical records of all 135 patients with spinal cord lesions and who were admitted to the Thai Red Cross Rehabilitation Center were retrospectively reviewed for demographic data, type of neurogenic bladder and bladder management, and common bacterial colonization in urine specimens with antimicrobial susceptibility reports.
Results: Of the 135 spinal cord lesion patients, 100 were male with the median age of 47 years old: 85% of them had neurogenic bladder, 39.8% detrusor overactivity (DO), 35% DO with detrusor sphincter dyssynergia, 24.3% detrusor underactivity, and 1% mixed type. *Escherichia coli* was the most frequent isolate followed by *Klebsiella pneumoniae.* Both *E. coli* and *K. pneumoniae* were multidrug-resistant (MDR) strains: 100% resistant to penicillin, fluoroquinolones (FQ), trimethoprim/ sulfamethoxazole (TMP-SMZ), and amoxicillin-clavulanic acid (AMC); 66.7% resistant to cephalosporin; 28.6% resistant to carbapenems; and, 28.6% resistant to aminoglycosides.
Conclusion: MDR *E.coli* and *K. pneumoniae* were the most commonly observed bacterial colonizations in patients with spinal cord lesion who were admitted at our institute. *E. coli* isolates are highly resistant to almost all antimicrobials except aminoglycosides and carbapenems. *K. pneumoniae* isolates are highly resistant to all antimicrobials which were firstly found resistant to aminoglycosides and carbapenems in the 2015.

Keywords: Bacterial colonization, spinal cord lesion, neurogenic bladder, urinary tract infection, extended spectrum beta-lactamase producing Enterobacteriaceae.

The emergence of extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* at the stand-alone Rehabilitation Center of Thai Red Cross Society has become a concern for treatment of patients with neurogenic bladder due to their spinal cord lesions. [1] Patients with spinal cord lesions who have neurogenic bladder (NGB) have a tendency to develop urinary tract infections (UTI).[2-4] Urinalysis and antimicrobial susceptibility tests were frequently performed among these patients at the Rehabilitation Center of Thai Red Cross Society from 2007 to 2015 because proper antimicrobial prescription is necessary for patients diagnosed with UTI. Bacterial colonizations in urine

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and perineum area are considered the risk factors associated with UTI. [2] The present study aimed to identify commonly observed bacterial colonization in urine specimens and antimicrobial resistance patterns to implement new strategic approaches for this ESBL-producing Enterobacteriaceae.

Materials and Methods

The medical records of all 135 patients with spinal cord lesions who were admitted to the Thai Red Cross Rehabilitation Center were retrospectively reviewed for demographic data, type of neurogenic bladder and bladder management, common bacterial colonization in urine specimens with antimicrobial susceptibility reports, and episodes of UTI.

Operational definition

Patients with spinal cord lesions who were admitted to the Rehabilitation Center, the Thai Red Cross Society, were defined as patients with a length of hospital stay greater than 48 hours.Bacterial colonization was defined as bacteria present in urine specimen. Pyuria was defined as urinalysis reporting the white blood cell (WBC) counts per high power field (HPF) as being 10 WBC or more. [5] High pyuria level was defined as a WBC count greater than 50 WBC count/HPF whereas low pyuria level was defined as a WBC count range from 10 – 50 WBC count/HPF. [6]

Urinary tract infection (UTI) was defined as bacteriuria ($\geq 10^2$ colony forming units (CFU)/mL for intermittent catheter specimens; ($\geq 10^4$ CFU/mL) for condom catheter and any value from indwelling urethral and suprapubic catheter with tissue invasion and resultant tissue response with signs and/or symptoms. Significant bacteriuria was defined as bacteriuria of 10^5 CFU/mL or higher. For patients with spinal cord lesions and NGB, signs and/or symptoms sometimes differed from general patients by the following: fever, discomfort or pain over the kidney or bladder increasing in spasticity, new episodes and/or increasing in urinary incontinence and autonomic dysreflexia. [7] Asymptomatic bacteriuria represented bacterial colonization of the urinary tract without symptoms or signs. [7]

Uropathogens represented bacterial colonization of the urinary tract resulting in urinary tract infection. Nosocomial urinary tract infection (NUTI) was defined as the infection is acquired in any healthcare institution. [8] NUTI in the present study was determined by the onset greater than 3 days after admission. Reviewed antimicrobial susceptibility reports were defined as reports from urine cultures performed under the attending clinician's decision.

Study design, setting, and ethical considerations

This retrospective study was performed at the Thai Red Cross Rehabilitation Center. Data from January 2013 to May 2015 of the patients with spinal cord lesions were retrospectively reviewed. The data included in-patient records, urinalysis reports and antimicrobial susceptibility reports. The protocol for the study has been approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB. No 289/58). This study was registered in the Thai Clinical Trials Registry (TCTR20160712003).

Statistical analysis and data presentation

Data were analysed using SPSS Statistics version 22.0 (SPSS, Inc., Chicago, IL, USA). Demographic data were collected and tested for normal distribution. Normal distribution data were demonstrated as mean and percentage whereas non – normal distribution data were demonstrated as median and interquartile range; IQR1- IQR3. Resistance patterns to each antimicrobial agent of the most of most common bacterial colonizations were reported as biannual percentages.

Results

In total, there were 135 patients with spinal cord lesions (male:-female = 100:35) in the study; their median age was 47 years old; all together, there were 154 admissions. Eighty-five percent of the patients were diagnosed with NGB. The median length of hospital stay was 39 days. All other demographic data are presented in Table 1. Of the 135 patients, all urinalyses revealed pyuria (63%); 87 antimicrobial susceptibility reports were reviewed during the 30-month study period. These reports revealed asymptomatic bacteriuria (49%) and uropathogens (51%). The bacterial colonization in each biannual percentage demonstrated multiple organisms (0 – 31.6%) and single organisms (68.4 – 100%).

During the 30-month study, out of 135 patients with UTI, 36 patients were with UTI (26.7 %) and 32 patients with NUTI (23.7%). Most patients had a single episode of UTI while 7 patients had recurrent UTI. *E. coli* was the common isolate (66.7%, 33.3%,

52.9%, 36.8% and 56.5% in the first half and second half of 2013, 2014 and the first half of 2015, respectively) followed by *K. pneumoniae* (0 – 40.0 %) as shown in Table 2. Both organisms are susceptible to cephalosporin, aminoglycosides and carbapenem but demonstrated high resistance to penicillin, fluoroquinolones (FQ), trimethoprim/sulfamethoxazole (TMP-SMZ) and amoxicillin-clavulanic acid (AMC). The antibiotic susceptibility patterns of the two most common isolates are described in (Table 3).

Table 1. Demographic data.

Demographic data	Value
Male (%)	74.0
Age (years) Median, IQR ; IQR 1- IQR3	47.0; 28.0 - 67.0
Onset of spinal cord lesion (days) Median, IQR ; IQR 1- IQR3	18.0; 7.0 - 51.0
Length of hospital stay (days)	39.0; 30.0 - 58.5
Traumatic causes of spinal cord lesion (%)	51.0
Level of spinal cord lesion (%)	
Cervical	59.0
Thoracic	25.0
Lumbar	13.0
Sacrum	2.0
Cauda equina	1.0
ASIA impairment scale (%)	
A/B/C/D/E	32.0/12.0/21.0/47.0
Neurogenic bladder (%)	85.0
Detrusor overactivity	40.0
Detrusor overactivity with detrusor sphincter dyssynergia	35.0
Detrusor underactivity	24.0
Mixed type	1.0
Bladder Management	
Clean intermittent catheterization	41.0
Able to perform void	28.0
Indwelling urethra	27.0
Pampers	3.0
Condom	1.0
Accommodation before admission (%)	
Home	95.0
Hospital	2.0
Rehabilitation center	1.0
Unspecified	2.0

Table 2. The first four commonly isolated organisms.

Organisms	1st half of 2013	2nd half of 2013	1st half of 2014	2nd half of 2014	1st half of 2015
Escherichia coli	66.7	33.3	52.9	36.8	56.5
Klebsiella pneumoniae	-	40.0	11.8	10.5	4.3
Enterococcus faecalis	-	6.7	-	10.5	-
Pseudomonas aeruginosa	22.2	6.7	-	-	-

Table 3. Antimicrobial susceptibility patterns in two commonly isolated organisms.

Organism	Antimicrobials		1st half of 2013	2nd half of 2013	1st half of 2014	2nd half of 2014	1st half of 2015
E. coli	FQ	S	0% (0/6)	16.7% (1/6)	40% (4/10)	10% (1/10)	25% (5/20)
		R	100% (6/6)	83.3% (5/6)	60% (6/10)	90% (9/10)	75% (15/20)
	TMP-SMZ	S	16.7% (1/6)	16.7% (1/6)	10% (1/10)	30% (3/10)	45% (9/20)
		R	83.3% (5/6)	83.3% (5/6)	90% (9/10)	50% (5/10)	50% (10/20)
	Penicillin	S	0% (0/6)	0% (0/6)	10% (1/10)	0% (0/10)	15% (3/20)
		R	100% (6/6)	100% (6/6)	90% (9/10)	100% (6/10)	75% (15/20)
	AMC	S	50% (3/6)	16.7% (1/6)	30% (3/10)	10% (1/10)	55% (11/20)
		R	16.7% (1/6)	66.7% (4/6)	30% (3/10)	50% (5/10)	30% (6/20)
	Cephalosporin	S	66.7% (4/6)	16.7% (1/6)	70% (7/10)	50% (5/10)	70% (14/20)
		R	33.3% (2/6)	66.7% (4/6)	20% (2/10)	30% (3/10)	25% (5/20)
	Aminoglycosides	S	100% (6/6)	100% (6/6)	90% (9/10)	90% (9/10)	100% (20/20)
		R	0% (0/6)	0% (0/6)	0% (0/10)	0% (0/10)	0% (0/20)
	Carbapenems	S	100% (6/6)	100% (6/6)	100% (10/10)	100% (10/10)	100% (20/20)
		R	0% (0/6)	0% (0/6)	0% (0/10)	0% (0/10)	0% (0/20)
K. pneumoniae	FQ	S	-	66.7% (4/6)	100% (2/2)	50% (2/4)	28.6% (2/7)
		R	-	33.3% (2/6)	0% (0/2)	50% (2/4)	71.4% (5/7)
	TMP-SMZ	S	-	66.7% (4/6)	0% (0/2)	0% (0/4)	57.1% (4/7)
		R	-	33.3% (2/6)	100% (2/2)	75% (3/4)	42.9% (3/7)
	Penicillin	S	-	0% (0/6)	0% (0/2)	0% (0/4)	0% (0/7)
		R	-	66.7% (4/6)	50% (1/2)	75% (3/4)	100% (7/7)
	AMC	S	-	66.7% (4/6)	0% (0/2)	50% (2/4)	28.6%(2/7)
		R	-	16.7% (1/6)	100% (2/2)	25% (1/4)	42.9% (3/7)
	Cephalosporin	S	-	83.3% (5/6)	0% (0/2)	75% (3/4)	71.4% (5/7)
		R	-	16.7% (1/6)	0% (0/2)	25% (1/4)	28.6% (2/7)
	Aminoglycosides	S	-	100% (6/6)	50% (1/2)	75% (3/4)	71.4% (5/7)
		R	-	0% (0/6)	0% (0/2)	0% (0/4)	28.6% (2/7)
	Carbapenems	S	-	100% (6/6)	100% (2/2)	100% (4/4)	71.4% (5/7)
		R	-	0% (0/6)	0% (0/2)	0% (0/4)	28.6% (2/7)

Abbreviation: FQ; Fluoroquinolone, Trimethoprim-sulfamethoxazole; (TMP-SMZ), Penicillin; PCN, Amoxicillin + Clavulanic acid; AMC, S; Sensitive, R; Resistant

Table 4. Antimicrobial resistant patterns of isolated bacteria from 2014 to 2016.

Antimicrobials	Organisms	1st half of 2013	2nd half of 2013	1st half of 2014	2nd half of 2014	1st half of 2015
FQ	*E. coli*	100.0	83.3	60.0	90.0	75.0
	K. pneumoniae	-	33.3	-	50.0	71.4
TMP-SMZ	*E. coli*	83.3	83.3	90.0	50.0	50.0
	K. pneumoniae	-	33.3	100.0	50.0	42.9
Penicillin	*E. coli*	100.0	100.0	90.0	100.0	75.0
	K. pneumoniae	-	66.7	50.0	75.0	100.0
AMC	*E. coli*	16.7	66.7	30.0	50.0	30.0
	K. pneumoniae	-	16.7	100.0	25.0	42.9
Cephalosporin	*E. coli*	33.3	66.7	20.0	30.0	25.0
	K. pneumoniae	-	16.7	-	25.0	28.6
Carbapenems	*E. coli*	-	-	-	-	-
	K. pneumoniae	-	-	-	-	28.6
Aminoglycosides	*E. coli*	-	-	-	-	-
	K. pneumoniae	-	-	-	-	28.6

Abbreviation: FQ; Fluoroquinolone, Trimethoprim-sulfamethoxazole; (TMP-SMZ) Penicillin; PCN, Amoxicillin + Clavulanic acid; AMC

Discussion

Significant bacterial colonizations were found among all urine specimens. Multidrug-resistant (MDR) *E. coli* and *K. pneumoniae*, were commonly presented in urine specimens. These finding were similar to as previous studies which were performed at rehabilitation wards of acute hospital care. [9, 10] In the early review period at 12 months, *Pseudomonas aeruginosa* was as high as 20% in our stand-alone rehabilitation center. It then disappeared for 18 months. In comparison with our setting as a stand-alone rehabilitation center, *P. aeruginosa* was found to be significantly higher at 9.1% - 17.3% in rehabilitation wards of acute hospital care.[9 - 11]

The prevalence of UTI in the present study demonstrated lower rates than the previous study. For cephalosporin, ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae*, our findings revealed higher resistance animicrobial patterns than the previous study performed in 2007 (20% vs. 25%). [1] As for aminoglycosides, *E. coli* revealed great susceptability that was similar to previous studies, whereas *K. pneumoniae* revealed first-half resistance in 2015 with a slightly higher rate than previous studies (20% vs. 28.6%). Moreover, these causative organism were found as new infections. The present study demonstrates that antimicrobial resistance patterns of bacterial colonization in urine specimens among patients with spinal cord lesions is higher than prior studies; moreover, the resistance of *K. pneumoniae* to carbapenem and aminoglycoside was first demonstrated in the first half of 2015. [1] These findings require close monitoring together with controlling the spread of the organism.

Nitrofuratoin is recommended as the initial treatment for lower urinary tract infections with proven optimal efficacy when it is prescribed for 5 days. Short-term usage of nitrofurantoin for 14 days or lower revealed low adverse events such as pulmonay fibrosis, gastrointestinal side effect and hepatotoxicity. Moreover, acquisition of resistance to nitrofurantoin is relatively rare. [12] Frequent urine specimen screening by urine analysis and culture for all patients with spinal cord lesion is necessary to identify pyuria and ESBL-producing Enterobacteriaceae might not be a cost-effective strategy, nevertheless an optimal control strategy to restrict the spread of ESBL-producting Enterobacteriaceae seems more appropriate. [13]

The present study provides important information for our stand-alone rehabilitation center, the Thai Red Cross Society. Strategic approaches for ESBL-producing Enterobacteriaceae at our setting requires extensive changes. Firstly, managing and control of the spread of ESBL-producing Enterobacteriaceae is required. Secondly, urine specimen screening by urine analysis and urine culture among patients with spinal cord lesions should be terminated because these methods are ineffective. Routine clinical assessement proves more important and beneficial than these tests as urine analysis and culture are only indicated for clinical presentations with suspected UTI before prescribing antimicrobials to patients. Thirdly, tne initially prescribed antimicrobial for patients diagnosed with UTI should be amikacin for those with a high risk of upper tract infection and nitrofuratoin for patients with lower tract infections. Proper antimicrobial medication must then be selected according to the antisusceptility report. The appropriate duration for treating patients with NGB is recommended for at least 14 days. [14 - 15] Fourthly, cephalosporin usage as antimicrobial prophylaxis before urodynamic (UDM) assessment should be terminated in order to prevent an increasing percentage of cephalosporin resistance.

Conclusion

Extended spectrum beta-lactamase (ESBL)-producing MDR *E. coli* and *K. pneumoniae* are observed as the most common bacterial colonizations in patients with spinal cord lesions admitted at our institute. Regarding the high percentage of resistance, *E. coli* isolates had high resistance to almost all antimicrobials except aminoglycosides and carbapenems. *K. pneumoniae* isolates are highly resistant to all antimicrobials which were first found to be resistant to aminoglycosides and carbapenems in the first half of 2015.

Conflict of interest

None of the authors has any potential conflict of interest to disclose.

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