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Original article

Emergence of antimicrobial-resistant uropathogens isolated from pediatric patients with cystitis on daily clean intermittent catheterization

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ABSTRACT

One of the major complications of clean intermittent catheterization (CIC) is urinary tract infection (UTI). Recent reports showed that community-acquired UTIs caused by antimicrobial-resistant pathogens were gradually presenting in adults. However, there have been few reports about UTIs caused by antimicrobial-resistant bacteria in pediatric patients. Therefore, we retrospectively reviewed the medical charts of 45 children with CIC due to neurogenic bladder dysfunction from January 2010 to March 2013.

Sixty-two episodes of cystitis occurred in 27 patients. Seventy bacterial strains were isolated from urine samples. The rate of Gram-negative bacteria was 84.3%. Six extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) strains were isolated from 4 patients. An ESBL-producing *Proteus mirabilis* strain and a methicillin-resistant *Staphylococcus aureus* strain were isolated from one patient each.

Most of the pathogens of cystitis in the pediatric patients with CIC were Gram-negative bacilli, especially *E. coli*. We should be aware that ESBL producing *E. coli* as potential pathogens cause cystitis and regularly survey antimicrobial susceptibility to understand the resistant strains that develop.

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1. Introduction

There is a high possibility that children with spina bifida or spinal injury will develop neurogenic bladder dysfunction. They often require regular management by clean intermittent catheterization (CIC) for preventing future renal damage due to voiding dysfunction with high intravesical pressure. Although this management is certainly proper for them, urinary tract infections (UTIs) often occur as one of the major complications. Children with acute cystitis are not seriously ill; however, they have to be properly treated by antimicrobial agents because febrile UTI can develop without appropriate treatment. They are usually treated in the outpatient clinic without hospitalization.

In general, the major pathogens that cause UTIs are mostly Gram-negative bacilli [1]. While those pathogens are likely to be antimicrobial-resistant in the hospital setting, pathogens that cause community-acquired UTIs have favorable antimicrobial susceptibility to most antimicrobial agents. However, a recent report [2] suggests that antimicrobial-resistant pathogens, including extended-spectrum β-lactamase-producing *Escherichia coli* (*E. coli*), can cause community-onset UTIs. When those drug-resistant pathogens are isolated from patients with community-acquired UTIs, we should choose appropriate and limited antimicrobials and treat them carefully. Although the optimal antimicrobial chemotherapy should be carefully considered, the frequencies of the pathogens isolated and the clinical backgrounds of children with acute complicated cystitis mostly remain unclear. Therefore, we retrospectively analyzed the clinical features and bacteriological characteristics of such pediatric patients.

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2. Patients and methods

We retrospectively reviewed the medical charts of 45 children with CIC due to neurogenic bladder dysfunction treated in the Department of Pediatric Urology of the Hokkaido Medical Center for Child Health and Rehabilitation from January 2010 to March 2013.

In our department, CIC is generally used for children with neurogenic bladder dysfunction according to the potential risk of future renal dysfunction. The risk factors in this study include detrusor leak point pressure of more than 40 cmH_2O, low bladder compliance of less than 10 ml/cmH_2O on cystometrography, post-void residual urine of 50% or more of estimated bladder capacity, and/or detrusor overactivity [3].

Abdominal ultrasound examination was done once every 4 months for 0- to 2-year-old children, once every six months for 2- to 5-year olds, once every 9 months for 5- to 9-year olds, and once a year for those aged 10 or more years. Voiding cystourethrography was done once every 8 months for 0 to 2-year-old children, once a year for those 2–5 years old, once every 18 months for 5- to 9-year olds, and once 2 years for those 10 or more years old. To lower high intravesical pressure, the anticholinergic agent oxybutynin was administered to the children at a dose of 0.1 mg/kg to 0.2 mg/kg two or three times a day. In addition, amoxicillin (AMPC: 12.5 mg/kg once daily) was administered to all of the children who were diagnosed with neurogenic bladder dysfunction until the age of 10 months and sulfamethoxazole-trimethoprim (SMX-TMP) (TMP; 2 mg/kg once daily) was given to those aged 11 months to 2 years as antimicrobial prophylaxis against febrile UTI.

The children were diagnosed with acute complicated cystitis when they had specific symptoms, including lower abdominal pain and/or frequency of incontinence, bacteriuria of 10^4 colony-forming units (CFU)/mL or more and were afebrile. When cystitis was suspected, culture of urine obtained by urethral catheterization was conducted before the administration of antimicrobial agents. The minimum inhibitory concentration (MIC) was measured using a WalkAway® system (SIEMENS Japan, Tokyo, Japan). Antimicrobial susceptibility was interpreted according to the report from the Clinical and Laboratory Standards Institute (CLSI) (M100-S19) [4]. For other antimicrobial agents without a definition of the MIC by the CLSI, breakpoints were set based on antimicrobial agents of similar systems. The MIC breakpoints of cefpirome (CPR), cefcapene pivoxil (CFPN-PI), and fosfomycin (FOM) were defined as 8, 1, 4 μg/mL, respectively. Because pyuria generally exists in the urine of patients with CIC, clinical cure was defined as the resolution all symptoms. We did not examine the elimination of pathogens in order to limit the patients' discomfort caused by catheterization because this was a retrospective study. When the patients were diagnosed as having acute complicated cystitis, instructive advice was given to them and their parents, including information about the need for catheterization two or more times, clean manipulation, and perfect handwashing.

3. Results

Sixty-two events of acute complicated cystitis occurred in 27 patients (60%) (Table 1). Fourteen events developed in 9 patients with antimicrobial prophylaxis. Eighteen patients had no cystitis (Table 1). Table 1 shows the ages of the patients without cystitis as of March 2013. Of the patients without cystitis, 11 were 2-year olds who were administered antimicrobial prophylaxis. Seven of those with cystitis had vesicoureteral reflux (VUR), as did 5 of those without cystitis. Three patients with VUR of grade IV or V had only febrile urinary tract infection.

Table 1
Backgrounds of the 45 patients.

Items		Patients with cystitis $N = 27$		Patients without cystitis $N = 18$
Median age (range)		5 years (9 months–17 years)		2 years (5 months–16 years)
Sex (male:female)		14:13		6:12
Underlying congenital disorders	Spina bifida	16		13
	Tethered cord	4		1
	Others	7		3
Grade of vesicoureteral reflux (right and left)	III and II	1	II and II	1
	II and III	1	II and none	1
	II and II	2	IV and V	1
	None and II	2	None and IV	1
	II and none	1	IV and IV	1

As empiric therapy, CFPN-PI was administered for 46 events (74.2%), AMPC for 4 (6.5%), SMX-TMP for 4 (6.5%), FOM for 2 (3.2%), levofloxacin (LVFX) for 2 (3.2%), ampicillin (ABPC) for 2 (3.2%), cefditoren pivoxil (CDTR-PI) for 1 (1.6%), and cefdinir (CFDN) for 1 (1.6%).

Totally, 70 strains were isolated from the urine of the patients with acute complicated cystitis (Table 2). Four patients, 6 phenomena had several pathogens (2 phenomena had 3 pathogens). *Klebsiella pneumoniae* (*K. pneumoniae*), *Streptococcus* species and *Staphylococcus epidermidis* were isolated from urine culture on one phenomenon. *E. coli* and *Enterococcus faecalis* (*E. faecalis*) were done another phenomenon. *E. coli* and *Staphylococcus hominis* were done, *Acinetobacter baumannii* (*A. baumannii*) and *Morganella morganii* (*M. morganii*) were done, *A. baumannii* and *M. morganii* and extended-spectrum β-lactamase (ESBL)-producing *Proteus mirabilis* (*P. mirabilis*) were done, *K. pneumoniae* and *Streptococcus anginosus* were done, respectively. Of those strains, Gram-negative bacterial strains accounted for 84.3%. The most predominant isolated bacteria were *E. coli* strains and their frequency was 52.9%. The susceptibilities to ABPC, CFPN-PI and SMX-TMP were 62.1%, 75.6% and 64.8%, respectively. Fluoroquinolone-resistant *E. coli* strains accounted for 19% of all *E. coli*. *E. coli* strains were commonly susceptible to imipenem/cilastatin (IPM/CS) and gentamicin (GM) (Table 3).

Six ESBL-producing *E. coli* strains were isolated from 4 patients (Table 4). One ESBL-producing *P. mirabilis* strain was isolated from one patient and one methicillin-resistant *Staphylococcus aureus* (MRSA) strain was isolated from another patient. Two cases, C and D in Table 4, had past histories of grade II VUR; therefore they

Table 2
Numbers of strains isolated from urine in cases with cystitis.

Gram negative bacterium	No. of strains (%)	Gram positive bacterium	No. of strains (%)
Escherichia coli	37 (52.9)	*Enterococcus faecalis*	2 (2.9)
Klebsiella pneumoniae	6 (8.6)	*Staphylococcus saprophyticus*	2 (2.9)
Morganella morganii	4 (5.7)	*Staphylococcus epidermidis*	1 (1.4)
Acinetobacter baumanii	3 (4.3)	*Staphylococcus aureus*	1 (1.4)
Citrobacter freundii	3 (4.3)	*Staphylococcus anginosus*	1 (1.4)
Klebsiella oxytoca	2 (2.9)	*Staphylococcus hominis*	1 (1.4)
Proteus mirabilis	2 (2.9)	*Streptococcus sanguis*	1 (1.4)
Enterobacter gergoviae	1 (1.4)	*Streptococcus* species	2 (2.9)
Proteus vulgaris	1 (1.4)		
Total	59 (84.3%)		11 (15.7)

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