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Burkholderia Cepacia Causing Nosocomial Urinary Tract Infection in Children

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Purpose: *Burkholderia cepacia* is an aerobic, glucose–non-fermenting, gram-negative bacillus that mainly affects immunocompromised and hospitalized patients. *Burkholderia cepacia* has high levels of resistance to many antimicrobial agents, and therapeutic options are limited. The authors sought to analyze the incidence, clinical manifestation, risk factors, antimicrobial sensitivity and outcomes of *B. cepacia* urinary tract infection (UTI) in pediatric patients.

Methods: Pediatric patients with urine culture-proven B. cepacia UTI between January 2000 and December 2014 at Samsung Medical Center, a tertiary referral hospital in Seoul, Republic of Korea, were included in a retrospective analysis of medical records.

Results: Over 14 years, 14 patients (male-to-female ratio of 1:1) were diagnosed with *B. cepacia* UTI. Of 14 patients with UTI, 11 patients were admitted to the intensive care unit, and a bladder catheter was present in 9 patients when urine culture was positive for *B. cepacia*. Patients had multiple predisposing factors for UTI, including double-J catheter insertion (14.2%), vesico-ureteral reflux (28. 6%), congenital heart disease (28.6%), or malignancy (21.4%). *Burkholderia cepacia* isolates were sensitive to piperacillin-tazobactam and sulfamethoxazole-trimethoprim, and resistant to amikacin and colistin. Treatment with parenteral or oral antimicrobial agents including piperacillin-tazobactam, ceftazidime, meropenem, and sulfamethoxazole-trimethoprim resulted in complete recovery from UTI.

Conclusion: *Burkholderia cepacia* may be a causative pathogen for nosocomial UTI in pediatric patients with predisposing factors, and appropriate selection of antimicrobial therapy is necessary because of high levels of resistance to empirical therapy, including aminoglycosides.

Key words: *Burkholderia cepacia* , Children, Urinary tract infection

Introduction

Burkholderia cepacia is an aerobic, glucose–non-fermenting, gram-negative bacillus that mainly affects immunocompromised and hospitalized patients as well as those with chronic granulomatous disease and cystic fibrosis[1-3]. There have also been reports of *B. cepacia* causing endocarditis, infections of the central nervous system, and neonatal sepsis[2-4]. This organism is not normal human flora, and is usually found in hospital environments, such as in contaminated disinfectants, nebulizer solutions, medical devices, and on the skin of healthcare workers[3,5-7]. Recently, *B. cepacia* infections have increased because of increased use of broad-spectrum antimicrobial agents, longer duration of hospitalization and indwelling device-related infections[4,7,8]. This organism has high levels of resistance to many antimicrobial agents, and sulfamethoxazole-trimethoprim has been the drug of choice for treatment[1,4].

There have been rare reports of urinary tract infection (UTI) caused by *B. cepacia*. Hosts with predisposing factors, such as post renal transplant, vesico-ureteral reflux (VUR), neurogenic bladder, bladder irrigation, or use of contaminated medical devices, have been reported to be susceptible to *B. cepacia* UTI[9-11]. We sought to analyze the incidence, clinical manifestations, risk factors, antimicrobial sensitivity and outcomes of *B. cepacia* UTI in pediatric patients.

Methods

This retrospective study was conducted at Samsung Medical Center, a tertiary referral hospital in Seoul, Republic of Korea. Patients with urine culture-proven *B. cepacia* UTI between January 2000 and December 2014 were included in the retrospective analysis of medical records. Urinary tract infection was defined as a positive urine test plus at least one of the symptoms or signs of infection, including temperature > 38℃, dysuria, or costovertebral angle tenderness. A positive urine test was defined as a urine culture with ≥ 10^5 colony forming units (CFU)/mL of *B. cepacia* from a urine sample collected either via catheter (if during the catheterization period), or by voiding (if the age was more than 3 years) or intermittent catheterization (if the age was less than 3 years). Collected data included gender, age, primary disease, risk factors, antimicrobial sensitivity and outcomes. Antimicrobial susceptibility was determined via VITEK 2 (Bio-Merieux, Durham, NC, USA) according to Clinical and Laboratory Standards Institute guideline. Result with intermediate was considered as resistance.

Results

1. Annual incidence of *B. cepacia* UTI

During 14 years, 14 patients (male-to-female ratio of 1:1) were diagnosed with *B. cepacia* UTI. The annual incidence of *B. cepacia* UTI is shown in Fig. 1. Although *B. cepacia* UTI sporadically occurred from 2000 to 2013, 5 such patients (35.7%) were treated in the pediatric intensive care unit in 2014.

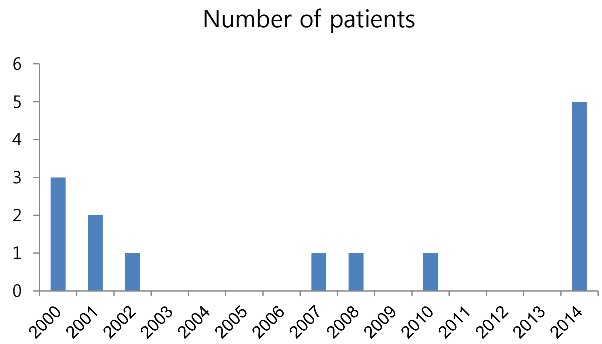

Fig. 1. Annual incidence of B. cepacia urinary tract infection in pediatric patients

2. Host factors for *B. cepacia* UTI

The characteristics of the studied patients are presented in Table 1. Of 14 patients with UTI, 11 patients were admitted to the pediatric intensive care unit. Nine of these 11 patients had a bladder catheter (Foley) in place when urine culture grew *B. cepacia*. Patients had multiple predisposing factors for UTI, including double-J catheter insertion, VUR, congenital heart disease, or malignancy.

1) Catheter-related infection

Two patients developed double-J catheter-related *B. cepacia* UTIs, and were treated with parenteral antimicrobial agents. Subsequent urine culture was negative after treatment, and they were discharged after the removal of the double-J catheter. During follow-up, they did not develop recurrent UTI.

2) Vesico-ureteral reflux-associated infection

Four patients with VUR developed *B. cepacia* UTI. A 1-month-old girl with a cloaca anomaly associated VUR developed UTI after colostomy operation. A subsequent urine culture was negative after the treatment, and she was discharged with no further antimicrobial agents. During follow-up, the patient did not develop recurrent UTI. A 2-month-old boy with bilateral VUR grade IV developed *B. cepacia* UTI in spite of chemoprophylaxis, and follow-

Table 1. Demographic characteristics and risk factors of 14 pediatric patients with Burkholderia cepacia urinary tract infection

Case no.	Sex	Age at diagnosis of UTI	Year at diagnosis of UTI	Primary disease	Etiology for admission	ICU admission	Genitourinary catheter	Antimicrobial agents	Outcomes
1	M	16 years	2000	Renal stone	Stone removal	N	Double-J stent, PCN	Piperacillin-tazobactm	Cure
2	F	13 months	2000	CHD	OHS	Y	Foley	Piperacillin-tazobactm	Cure
3	F	1 month	2000	Cloaca anomaly, VUR	Colostomy op	Y	Foley	ceftazidime	Cure
4	M	17 years	2001	UPJ obstruction	endpyelotomy	N	Double-J stent	tobramycin, flomoxef	Cure
5	M	2 months	2001	chromosome 9 deletion, VUR	No admission	N	-	Sulfamethoxazole-trimethoprim	Cure
6	M	3 months	2002	preterm	Preterm	Y	Foley	Cefdinir	Cure
7	F	12 years	2007	leukemia	BMT	Y	Foley	Imipenem	Death
8	F	3 months	2008	CHD	OHS	Y	Foley	Piperacilline-tazobactm	Death
9	M	2 years	2010	VUR, Rubinstein-Taybe syndrome	UNC	Y	PCN	Ceftazidime	Cure
10	M	1 month	2014	single kidney, VUR, CHD	OHS	Y	Foley	Levofloxacin	Cure
11	F	18 years	2014	Glioblastoma	Tumor removal	Y	Foley	Piperacillin-tazobactam	Cure
12	F	8 days	2014	Neuroblastoma	Chemotherapy	Y	-	Meropenem	Cure
13	F	1 month	2014	CHD	OHS	Y	Foley	Piperacillin-tabactam	Cure
14	M	2 momths	2014	CHD	respiratory distress	Y	Foley	Meropenem	Death

UTI Urinary tract infection, CHD Congenital heart disease, VUR Vesico-ureteral reflux, UPJ Uretero-pelvic junction, OHS Open heart surgery, BMT Bone marrow transplantation, UNC Ureteroneocystostomy, PCN Percutaneous nephrostomy

up urine culture was negative after the treatment. He suffered from recurrent UTI, and ureteroneocystostomy was performed at the age of 18 months. A 2-year-old boy with Rubinstein-Taybe syndrome and bilateral VUR developed *B. cepacia* UTI after the operation of ureteroneocystostomy under the condition of PCN. After the treatment, he was discharged after removal of PCN, and did not suffer from recurrent UTI. Finally, a 1-month-old boy with ventricular septal defect (VSD) and a single kidney associated with VUR developed *B. cepacia* UTI despite the use of a third-generation cephalosporin, and levofloxacin was given intravenously for 14 days, and the infection resolved.

3) Congenital heart disease and prolonged catheterization

Four patients with congenital heart disease were diagnosed with *B. cepacia* UTI from bladder catheter urine samples. Three patients were admitted to the pediatric intensive care unit for congenital heart disease repair, and febrile UTI developed while a bladder catheter was in place after the operation. They were treated with intravenous antimicrobial, and the subsequent urine culture showed no growth. Finally, a 2-month-old boy with total anomalous pulmonary venous return was admitted to the pediatric intensive care unit because of severe respiratory distress. While in the intensive care unit receiving mechanical ventilation, he developed fever despite use of a third-generation cephalosporin. His urine sample from a bladder catheter grew over 10^5 CFU/mL of *B. cepacia*. The patient was treated with parenteral meropenem for 14 days. The subsequent urine culture was negative, but he died of uncompensated respiratory failure.

4) Immunocompromised hosts

Three patients had malignancies including leukemia, glioblastoma, and neuroblastoma, and 2 patients with leukemia and neuroblastoma were on chemotherapy. A 12-year-old girl with acute lymphoblastic leukemia developed *B. cepacia* UTI during treatment with parenteral antimicrobial agents (cefotaxime and amikacin). She was treated

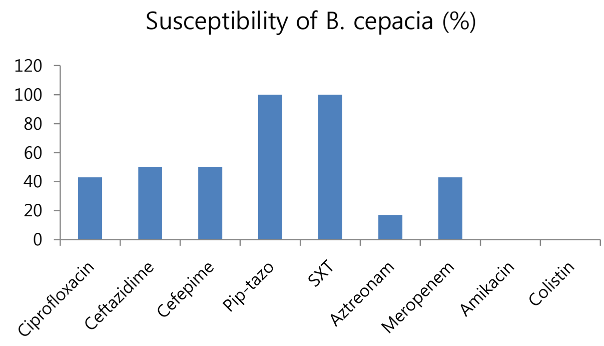

Fig. 2. Antimicrobial susceptibility of B. cepacia isolates
Abbreviations: Pip-tazo, Piperacilline-tazobactam; SXT, trimethoprim-sulfamethoxazole.

with parenteral imipenem for 14 days, and follow-up urine culture did not grow any organisms. Unfortunately, she died of uncontrolled sepsis. Next, an 18-year-old girl with glioblastoma developed *B. cepacia* UTI after tumor removal, and treated with parenteral piperacillin-tazobactam for 14 days. The subsequent urine culture was negative. An 8-day-old girl with prenatally diagnosed neuroblastoma developed *B. cepacia* UTI after the first cycle of chemotherapy during the use of empirical antimicrobial agents (cefotaxime and amikacin). The antimicrobial agents were changed to parenteral meropenem, and urine culture demonstrated clearance after treatment. Finally, a 3-month-old boy who was born at a gestational age of 25+2 weeks developed *B. cepacia* UTI during the hospitalization of neonatal intensive care unit. He was treated with oral cefdinir, and follow-up urine culture was negative. He improved clinically and was discharged without the need for further antimicrobial agents.

3. Antimicrobial susceptibility pattern of *B. cepacia*

Pediatric patients were treated with piperacillin-tazobactam, ceftazidime, meropenem, levofloxacin, sulfamethoxazole-trimethoprim, and other third-generation cephalosporins for 7 to 14 days. Most patients were treated with parenteral antimicrobial agents. Follow-up urine cultures were sterile in all patients after this treatment period. The antimicrobial sensitivity pattern of *B. cepacia* is shown in Figure 2. *B. cepacia* isolates were sensitive to piperacillin-tazobactam and sulfamethoxazole-trimethoprim, and resistant to amikacin and colistin.

Discussion

Burkholderia cepacia usually causes nosocomial infections in immunocompromised hosts, and the most common infectious focus is the respiratory tract, followed by intravascular catheters[2,3,8)]. *Burkholderia cepacia* survives in moist environments, and outbreaks of *B. cepacia* infection have been described in association with contaminated nebulizers, indigo-carmine dye, mouthwash, and moisturizing body milk[3,5-7)]. In our study, the incidence of *B. cepacia* in 2014 was relatively high, and surveillance cultures for intensive care unit environments were conducted; however, negative results were found.

There have been few reports of the characteristics of *B. cepacia* UTI. Affected patients often have predisposing factors, such as renal transplantation, prolonged bladder catheterization, or urethrocystoscopy[9-11)]. In our study, predisposing host factors such as prolonged genitourinary catheterization, VUR, congenital heart disease, and immunocompromised status were suggested. Twelve of 14 patients with *B. cepacia* UTI had genitourinary catheterization such as bladder catheter, PCN, or double-J stents. Zeeshan et al. reported that VUR in a renal transplant recipient was a risk factor for *B. cepacia* UTI [11)]. In our study, 4 patients (29%) showed VUR-related UTI in spite of prophylactic antimicrobial agents. VUR was also associated with other anomalies such as cloaca anomaly or chromosome abnormality. In cases of congenital heart disease, patients required prolonged pediatric intensive care unit stays and bladder catheterization, which increased their susceptibility to *B. cepacia* UTI. In addition, immunocompromised oncology patients have been reported to be susceptible to *B. cepacia* infection[8)].

Burkholderia cepacia is a multidrug-resistant organism, and therapeutic options are limited[1)]. Although trimethoprim-sulfamethoxazole has been the drug of choice, it is difficult to administer because of hypersensitivity, lack of availability, and resistance in some cases. Avgeri et al. reported that ceftazidime, meropenem, and piperacillin, either alone or in combination, may be used as alternative options in *B. cepacia* infections[1)]. Patra et al. reported that piperacillin-tazobactam, ciprofloxacin, and trimethoprim-sulfamethoxazole, either alone or in combination, could result in complete recovery of *B. cepacia* sepsis in neonates.

The highest susceptibility was observed with meropenem[4]. In our study, piperacillin-tazobactam, ceftazidime, trimethoprim-sulfamethoxazole, levofloxacin, and meropenem were used in the majority of cases. All patients experienced complete recovery from UTI. In our study, the highest susceptibility was observed with piperacillin-tazobactam and trimethoprim-sulfamethoxazole. Importantly, there was 100% resistance to amikacin and colistin. Even so, Li et al. reported a case of *B. cepacia* UTI after renal transplantation that required a graft nephrectomy because *B. cepacia* showed in vivo resistance to all available antimicrobial agents, and long-term use of piperacillin could not resolve the septic foci[9]. Because of such antimicrobial resistance, a combination of antimicrobial agents and surgical treatment in some cases may be required.

Burkholderia cepacia is a pathogen with intrinsic resistance to numerous antimicrobial agents that causes nosocomial UTI in pediatric patients with risk factors such as prolonged genitourinary catheterization, VUR, congenital heart disease, or malignancy. Prompt removal of catheters and appropriate antimicrobial therapy for *B. cepacia* UTI in high-risk patients can ensure complete recovery. In addition, a surveillance program for nosocomial infection in intensive care units is necessary to prevent *B. cepacia* infections.

There is no conflict of interest to declare

This study was approved by Samsung Medical Center Institutional Review Board and informed consent was not applicable because the study was designed to perform the retrospective analysis of medical records.

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