

Clinical significance of *Providencia* bacteremia or bacteriuria

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The genus *Providencia* is a urease-producing gram-negative bacillus of the family Enterobacteriaceae and includes *Providencia stuartii*, *P. rettgeri*, *P. alcalifaciens*, *P. rustigianii*, and *P. heimbachae*. Among these bacteria belonging to the genus *Providencia*, *P. rettgeri* and *P. stuartii* are the most common cause of catheter-associated urinary tract infections, especially in the elderly with long-term indwelling urinary catheters. While *Providencia* species do not routinely cause urinary tract infections or bacteremia, when implicated, the overall mortality rate of bacteremia due to *Providencia* species can be high, especially in the elderly with severe underlying conditions. *P. rettgeri* and *P. stuartii* are commonly found in water, soil, and animal reservoirs, and are opportunistic pathogens in hospitalized patients and elderly residents in a nursing care facility. Most infections due to *Providencia* species are associated with long-term urinary catheter use, and interestingly, the isolated uropathogens are resistant to multiple antibiotics, and patients are more likely to have polymicrobial infections [1-3]. Therefore, a more thorough understanding of *Providencia* species is needed to prevent and/or manage the infections caused by these organisms.

Providencia species are common uropathogens in people with long-term indwelling urinary catheters who were hospitalized or resided in a nursing care facility. *P. stuartii* is a urease-positive species, and urease activity is one of several factors which contributes to the development of urolithiasis. Specifically, *P. stuartii* and *Proteus mirabilis* co-infection contribute to the increased incidence of urolithiasis and bacteremia through synergistic induction of urease activity during co-infection [1]. In addition, bacterial urease from *Proteus*, *Providencia*, and *Morganella* species, three closely related genera, catalyzes the hydrolysis of urea that results in the formation of carbon dioxide and ammonia. Thus, *Providencia* species are a gram-negative bacilli that produce bacterial urease, an important virulence factor associated with the formation of urinary tract stones, the obstruction of long-term urinary catheters, or the development of acute pyelonephritis [4]. *P. stuartii* with type 3 fimbriae adheres to urinary catheters, and *P. stuartii* colonization of indwelling urinary catheters can lead to urinary tract infections, as well as the malfunction of urinary catheters [5].

P. stuartii and *P. rettgeri* are also etiologic isolates of purple urine bag syndrome, characterized by the purple color of the indwelling urinary cath-

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eter [6,7]. *Providencia* species can deaminate aromatic amino acids including tryptophan and phenylalanine, and can influence the formation of indole and indoxyl sulphate, which are metabolites of tryptophan. Bacteria with indoxyl sulphatase activity or indoxyl phosphatase activity, such as *P. stuartii*, *P. rettgeri*, *P. mirabilis*, *Morganella morganii*, *Klebsiella pneumoniae*, and *Escherichia coli*, produce indoxyl sulphatase or indoxyl phosphatase, and these enzymes lead to the conversion of indoxyl sulphate into indigo and indirubin in the urine. In patients with purple urine bag syndrome, indigo and indirubin are known to cause the alkaline urine to become purple. Although purple urine bag syndrome is a rare condition, most patients with this syndrome are asymptomatic, when it occurs, physicians should consider the possibility of the presence of bacteria with indoxyl sulphatase or phosphatase, such as *P. stuartii* or *P. rettgeri* [7]. Urinary tract infections or an obstruction due to the persistent colonization of *Providencia* species are important problems that need to be solved to manage the care of patients with long-term indwelling urinary catheters.

Providencia species isolated from catheter-associated urinary tract infections usually exhibit resistance to multiple antibiotics, which contributes to the high mortality of patients with *Providencia* bacteremia [1,8]. Infections due to extended spectrum β -lactamase (ESBL)-producing *P. stuartii* are emerging as a significant problem in a university hospital setting [9]. *P. stuartii* is an opportunistic pathogen, and is isolated more frequently from patients with a long-term-catheterized urinary tract due to the increased number of patients residing in nursing homes. In a hospital setting or nursing care facility, *P. stuartii* has frequently exhibited resistance to multiple antibiotics, and on occasion, has resulted in bacteremia or systemic illness [3,9]. An *in vitro* study assessing the antimicrobial susceptibility of 116 ESBL-producing multidrug-resistant *P. stuartii* isolates demonstrated that gentamicin or piperacillin/tazobactam can be used as an effective alternative to carbapenem, because piperacillin/tazobactam and gentamicin are capable of killing 100% and 88%, respectively, of the *P. stuartii* strains tested [9]. Therefore, it may be difficult to manage polymicrobial catheter-associated urinary tract infections or other infectious diseases due to the presence of multidrug-resistant

Providencia species or other microorganisms. One study reported the isolation of carbapenem-resistant New Delhi metallo- β -lactamase-1 (NDM-1)-producing *P. rettgeri* clinical isolates from patients with urinary tract infections in the intensive care unit [10]. The NDM-1 gene facilitates the production of an enzyme called carbapenemase by *Providencia* species, which makes the bacteria resistant to carbapenem and nearly all other antibiotics. Therefore, physicians should try to prevent the spread of NDM-1-positive *Providencia* species and other bacteria through the use of surveillance, isolation of patients with NDM-1-positive bacteria, hand-hygiene, and disinfection of hospital equipment.

In a recent issue of *The Korean Journal of Internal Medicine*, Choi and colleagues [11] reported the results of a retrospective, cross-sectional study of the clinical and microbiological features of *Providencia* bacteremia in a tertiary care hospital by analyzing 14 patients with *Providencia* bacteremia. During the 13-year study period from May 2001 to April 2013, the incidence rate was 0.41 per 10,000 hospital admissions with an overall in-hospital mortality rate of 28.6% (4/14). This study determined that the antimicrobial susceptibility of *Providencia* isolates to cefepime, isepamicin, imipenem, piperacillin/tazobactam, and amikacin was 100%, 90%, 86%, 86%, and 86%, respectively. In addition, the antimicrobial susceptibility of *Providencia* isolates to trimethoprim/sulfamethoxazole, ciprofloxacin, ceftaxime, ceftazidime, cefoperazone/sulbactam, and gentamicin was 43%, 50%, 50%, 64%, 70%, and 71%, respectively. In this study, *Providencia* bacteremia was a nosocomial infection occurring in elderly patients with neurological or cerebrovascular disorders, which was frequently associated with long-term indwelling urinary catheters and urinary tract infections, was more fatal in cases with severe underlying diseases, and was frequently associated with polymicrobial infections.

The present study had some limitations. First, the impact of the presence of a co-pathogen on clinical characteristics and outcomes cannot be excluded, as more than half of the cases had polymicrobial bacteremia. Second, the study included a small number of patients, all of whom were from a single hospital. However, valuable information was still provided about the clinical characteristics and outcomes of patients with *Providencia* bacteremia, as well as the antibiotic suscep-

tibility of *Providencia* species.

Although the incidence rate of *Providencia* bacteremia is low in the general population, it can be increased in patient groups with long-term indwelling urinary catheters, especially in elderly patients who are hospitalized or reside in a nursing care facility. The increased number of elderly patients in nursing care facilities and/or hospitals can boost the incidence rate of *Providencia* bacteremia, leading to high rates of antibiotic resistance and mortality in the future. This is particularly problematic for elderly patients with long-term indwelling urinary catheters in conjunction with a synergic induction of urease activity in catheter-associated urinary tract infections by polymicrobial uropathogens that can promote urolithiasis and bacteremia [1]. Therefore, additional studies and analyses about the pathogenesis of *Providencia* infection are necessary for managing *Providencia* bacteremia and preventing the progression to more serious conditions.

In conclusion, *Providencia* species, which are ubiquitous in the environment, should be reviewed and reassessed as important opportunistic pathogens in patients with chronic medical illnesses requiring long-term indwelling urinary catheters. Moreover, it should be noted that *Providencia* species can cause urolithiasis and bacteremia by co-colonizing urinary catheters and inducing synergic urease activity in conjunction with other urease-positive species such as *P. mirabilis*. It is important to prevent the spread of multidrug-resistant *Providencia* species through the use of infection control practices, as choosing an empiric antimicrobial agent is very difficult.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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