

# *Providencia* Causing Urinary Tract Infections: Are We Reaching a Dead End?

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## ABSTRACT

**Background:** The genus *Providencia*, earlier considered a rare pathogen, is now increasingly recognized as a notorious opportunistic pathogen capable of causing serious nosocomial infections, mainly urinary tract infections (UTIs). Treating these infections is an onerous task given the resistance seen in clinical strains to many currently available antimicrobials. The objective of the present study is to provide an overall view into the prevalence of *Providencia* spp. causing UTIs, their antibiotic susceptibility pattern, and respective clinical outcomes.

**Materials and methods:** This is a retrospective observational study carried out in a tertiary care teaching referral hospital located in Jaipur, India from March 2021 to May 2021. All *Providencia* spp. strains isolated from urine samples were included in the study. Data were entered in Microsoft Office Excel worksheet. Results are presented in numbers and percentages.

**Results:** Out of 1,261 urine samples processed in the laboratory during the study period, 426 were culture positive and the majority were gram-negative isolates and included *Escherichia coli* (46.0%) and *Klebsiella* spp. (28.0%). *Providencia* spp. was the fourth most common gram-negative pathogen (6.0%). The median age of patients was 65 years. The male:female ratio was 3:2 and maximum patients belonged to the 30–60-year age-group. Diabetes was the commonest associated comorbidity. All patients had an indwelling urinary catheter. Three (20.0%) patients succumbed to infections.

**Conclusion:** *Providencia* is an opportunistic pathogen that cannot be neglected due to escalating antibiotic resistance. Effective infection control and antibiotic stewardship policies are required to prevent the development of further antibiotic resistance.

**Keywords:** Antibiotic resistance, Antibiotic susceptibility, Nosocomial infection, *Providencia*, Urinary tract infection.

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## INTRODUCTION

The genus *Providencia* constitutes natural human gastrointestinal tract flora. The most commonly encountered species include *P. alcalifaciens*, *P. rettgeri*, *P. stuartii*, *P. rustigianii*, and *P. heimbachae*. It is commonly found in soil, water, and sewage.<sup>1</sup> Human isolates of *Providencia* species have been recovered from urine, throat, perineum, axillae, stool, blood, and wound specimens. Earlier, it was considered an uncommon pathogen as its potential to cause a nosocomial infection was not much understood. It is now increasingly recognized as a notorious opportunistic pathogen capable of causing a wide variety of nosocomial infections.<sup>1,2</sup>

Commonly, *Providencia* infections include urinary tract infections (UTIs), gastroenteritis, and septicemia. It is being increasingly reported from a plethora of other conditions like burns, pneumonia, neonatal sepsis, community and hospital-acquired neuro infection, etc.<sup>2–6</sup> Their isolation from clinical milieu is strongly associated with the presence of long-term indwelling urinary catheters in critically ill patients, diabetes, and other immunocompromised states. Various contemporary studies have documented the recent rise in infections caused by *Providencia* and highlighted the need for more research in this area.<sup>1–7</sup>

Treatment of these infections is an onerous task because clinical strains are intrinsically resistant to many commonly used antibiotics including ampicillin, first-generation cephalosporins, polymyxins, and tigecycline.<sup>1</sup> Furthermore, in recent years, the increasing prevalence of antibiotic resistance has been described, making this an important emerging pathogen. Their antibiogram is fast evolving, and the emergence of extended-spectrum  $\beta$ -lactamase (ESBL)- and carbapenemase-producing *Providencia* strains has

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also been described.<sup>8–10</sup> Increasing isolation of such strains from patients' samples is a serious clinical dilemma. Recently few outbreaks have also been reported from other parts of the world.<sup>11</sup> Thorough understanding of *Providencia* species is thus needed to manage the infections caused by these organisms.

There is scarce literature available to make a firm estimate on the exact prevalence of *Providencia* spp. causing UTIs. Considering these factors, the present study was conducted to provide an

overall view into the prevalence of *Providencia* spp. causing UTIs, their antibiotic susceptibility profile, and subsequent clinical outcomes. The overall objective is to use this evidence to sensitize the clinicians to the merits of appropriate antimicrobial use.

## MATERIALS AND METHODS

### Study Area and Population

We conducted a retrospective observational study in a teaching tertiary care referral hospital located in Jaipur, the capital city of Rajasthan, from March 2021 to May 2021. This is a multispecialty 1,800 bedded hospital with 80 intensive care unit (ICU) beds and provides treatment to over 8 lakhs outpatients and 70,000 inpatients annually. This hospital caters to the needs of patients from nearby urban and rural areas and of patients referred from various districts of Rajasthan and nearby states.

### Patients and Bacterial Isolates

All urine samples received in the Department of Microbiology during the study period were processed as per the standard microbiological guidelines. Their antimicrobial susceptibility profile was determined as per Clinical and Laboratory Standards Institute guidelines.

All *Providencia* strains isolated from urine samples during the study period were included in the study. Only one isolate per patient was included. Bacterial identification and antibiotic susceptibility testing were done by VITEK-2 Compact Automated System (BioMerieux, France). Medical records of the patients were retrospectively reviewed from the hospital information management system.

Multidrug resistance (MDR) was defined as nonsusceptibility to at least one agent in more than three antimicrobial categories/groups. Extensively drug resistance was defined when the isolate was found susceptible to only one or two antimicrobial categories. Isolates resistant to all agents in all antimicrobial categories were defined as pandrug resistant (PDR).<sup>12</sup>

### Ethical Consideration

Ethical approval was obtained from our institutional ethical committee for conducting the study (approval number MGMC&H/IEC/JPR/2021/540).

## Statistical Analysis

Calculations were done using Microsoft Excel. Results were presented as frequencies and percentages, and Z-test was applied when necessary and the results were considered significant with a *p*-value  $\leq 0.05$ .

## RESULTS

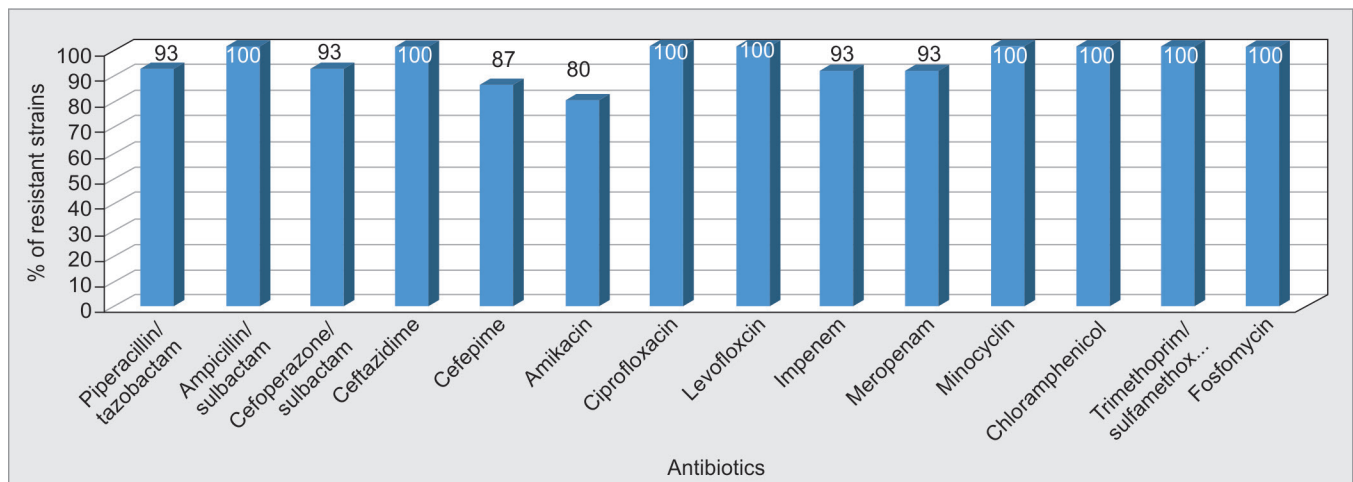
Of 1,261 urine samples received during the study period, 426 were culture positive, with the culture positivity rate being 34.0%. The majority were gram-negative isolates amounting to 56.0% and included *E. coli* (46.0%) and *Klebsiella* spp. (28.0%) most commonly. *Providencia* spp. was the fourth most common among gram-negative isolates accounting for 6.0% of UTI cases (Table 1).

The antimicrobial resistance profile of 15 clinical isolates of *Providencia* spp. is as shown in Figure 1.

The demographic and clinicoepidemiological characteristics of patients with *Providencia* infection have been summarized in Table 2. The median age of patients was 65 years, interquartile range (IQR) being 18–80 years. The male:female ratio observed in the study was 3:2 and 87.0% (13/15) of patients belonged to the age-group of 30–60 years. Among the risk factors studied, diabetes

**Table 1:** Profile of gram-negative bacteria causing UTIs during March–May 2021

Sl. No.	Name of organism	No. of isolates	Percentage
1	<i>E. coli</i>	111	46
2	<i>Klebsiella</i>	68	28
3	<i>Myroides</i>	16	7
4	<i>Providencia</i>	15	6
5	<i>Pseudomonas</i>	12	5
6	<i>Enterobacter</i>	6	2
7	<i>Acinetobacter</i>	4	2
8	<i>Proteus</i>	2	0.8
9	<i>Sphingomonas</i>	2	0.8
10	<i>Citrobacter</i>	1	0.4
11	<i>Burkholderia</i>	1	0.4
12	<i>Morganella</i>	1	0.4
Total		239	



**Fig. 1:** Antimicrobial resistance profile of 15 clinical isolates of *Providencia* spp

**Table 2:** Summary of demographic and clinicoepidemiological features of 15 patients with *Providencia* causing UTIs during March–May 2021

Variables	No. of patients (15) N (%)
Median age	65 years (IQR: 18–80 years)
Gender	
Male	9 (60)
Female	6 (40)
Location	
ICUs	15 (100)
OPD	Nil
Catheter change after culture report (ICU pts. n = 13)	
Yes	15 (100)
No	Nil
Clinical status (ICU pts. n = 13)	
Critical	12 (80)
Noncritical	3 (20)
Comorbidities (n = 15)	
Diabetes mellitus	10 (67)
Chronic respiratory condition	8 (53)
Malignancy	1 (7)
Chronic liver/kidney/heart disease	5 (33)
H/o recent surgery	5 (33)
H/o previous ICU stay (90 days)	Nil
Previous exposure to antibiotics (90 days)	5 (33)
Previous exposure to antifungals (90 days)	Nil
H/o steroid intake	Nil
Immunosuppressives/chemotherapy	1 (7)
Indwelling catheters (n = 13)	
CVP lines	8 (53)
Foley urinary catheter	15 (100)
Drains	3 (23)
Mechanical ventilation	12 (85)
COVID-19 status (n = 15)	
Positive	8 (53)
Negative	7 (47)
Median duration of hospital stay (n = 13)	17 days (IQR: 8–30 days)
Clinical outcome	
Discharged	8/13 (61)
LAMA	2/15 (13)
Expired	3/13 (20)

ICU, intensive care unit; OPD, outpatient department

was found to be the most common seen in 87.0% (10/15), followed by chronic respiratory conditions seen in 53.0% (8/15) of patients. All patients were admitted into the ICU and had an indwelling urinary catheter.

**Patient outcomes:** During the course of treatment, 3/13 patients succumbed to infection, with the mortality rate being 20.0%.

## DISCUSSION

While the healthcare infrastructure is still reeling under pressure caused by the sheer number of COVID patients requiring medical care, other issues yet unnoticed may surface with the passage of time. There has been a great deal of discussion on the possible

escalation in antimicrobial resistance due to massive empirical antibiotic usage during the current pandemic.<sup>13,14</sup> Our study highlights 15 clinical isolates of *Providencia* spp. causing UTIs in patients admitted in ICU, unresponsive to a large number of currently used drugs. The objective of the study is to determine the prevalence and risk factors associated with *Providencia* spp. causing UTIs in our setup.

Out of 426 urine samples that yielded significant growth during the study period, 15 strains of *Providencia* spp. were isolated. The clinical significance of an isolate was determined by various factors like the purity of growth, presence of significant growth, presence of concomitant significant pyuria, isolation from repeat sample and clinical improvement, and clearance of pathogen after catheter change.

There can be several factors responsible for the high prevalence observed in our study. It is noteworthy to mention that the hospital is operated as a dedicated COVID Care Center during the ongoing pandemic, and 53.0% of isolates are from COVID-positive patients. It is a common observation that infection control and hand hygiene practices have taken a hit during the pandemic. The use of the same gloves for multiple patients without following hand hygiene practices has also been noticed.<sup>13</sup>

Hayakawa et al. hypothesized that the increased use of colistin may be an important factor leading to an increase in *Providencia* infection. The overuse of colistin as the last resort antibiotic in critically ill patients selects for and promotes resistance in *Providencia* spp. infections because of its intrinsic resistance to colistin. All *Providencia* isolates in the current study are from patients admitted to ICU. The authors suggest that antibiotic selection pressure in intensive care setups should be urgently considered in order to prevent the selection of resistant isolates.<sup>15</sup>

The complex trilogy of urinary catheterization, presence of underlying comorbid conditions (diabetes being the most common), and a prolonged ICU stay predispose to infection with earlier lesser-known pathogens. All 15 patients included in the study were fitted into this clinical paradigm. There is ample literature showing that *Providencia* is isolated from the urine of catheterized patients.<sup>1,4,5</sup>

Twelve patients in our study were critically ill and required mechanical ventilation. The associated comorbidities included diabetes mellitus which was most common (10/15; 67.0%) followed by chronic respiratory illness (8/15; 53.0%) and chronic liver/kidney/heart disease (5/15; 33.0%). Five patients (33.0%) had undergone surgery in the recent past and gave a history of usage of high-end antibiotics. All the patients had an indwelling urinary catheter, and the most common presenting feature was fever and hypotension. The presence of similar risk factors has been highlighted in a multitude of studies.<sup>2–5,8,16</sup>

The urine of chronically catheterized patients is the usual reservoir of this organism.<sup>2,5</sup> The authors want to emphasize that *Providencia* once detected in urine cultures must not be ignored. The most common source of sepsis in patients requiring intensive care is via a urinary route as *Providencia* strains tend to adhere directly to the urinary catheters and uroepithelial cells. Biofilm formation coupled with urease-producing property has been described as an important mechanism of virulence for this genus. These organisms migrate from the urinary tract to other organs, causing a plethora of infections including pericarditis, endocarditis, osteomyelitis, peritonitis, and meningitis.<sup>17–19</sup> In the current study, however, we did not find any case of bacteremia secondary to a UTI.

Preventive strategies include proper handwashing and strict compliance to device-related bundle care protocols. These include the aseptic insertion technique, maintaining a closed sterile drainage system, and ensuring an unobstructed urine flow. Bacteriuria is inevitable in patients with long-term catheterization, and in most cases, treatment should be started only in the presence of symptoms.<sup>4,5</sup> Treatment of UTI in patients with urinary catheters requires replacement of the catheter and selection of antibiotics based on the results of urine culture. In the current study, urinary catheters were changed immediately on the receipt of laboratory results and treatment customized as per antibiotic sensitivity reports.

Another remarkable feature is that all the isolates in our study were *P. rettgeri* in contrast to studies from other geographical areas where both *P. rettgeri* and *P. stuartii* have been isolated. This underlines the variation seen in different geographical areas and further strengthens the case for conducting large-scale prospective studies to understand the evolving epidemiology of this organism.<sup>2,7</sup>

Antibiotic sensitivity testing of our isolates has revealed an alarming degree of resistance to most of the routinely used drugs. About 33.0 and 53.0% of isolates have been found to be extremely and PDR, respectively. Also, 80.0 and 87.0% of isolates have been found to be resistant to aminoglycosides (amikacin) and fourth-generation cephalosporin (cefepime), respectively. About 93% of isolates have been found resistant to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations (piperacillin-tazobactam and cefoperazone-sulbactam) and carbapenems (imipenem and meropenem). Complete resistance is seen for third-generation cephalosporins, fluoroquinolones, minocycline, chloramphenicol, co-trimoxazole, and fosfomycin (Fig. 1).

It is interesting to note the evolution and geographical variation in antimicrobial resistance observed in clinical *Providencia* strains on a global level. In an early study conducted between 1972 and 1979, details of 117 cases of *Providencia* spp. have been reported. The majority of isolates were from the urinary tract and high rates of sensitivity were found, all being sensitive to amikacin and cefuroxime.<sup>16</sup> In a study from Korea also, excellent sensitivity has been described to cefepime, amikacin, imipenem, and piperacillin-tazobactam in strains isolated from bacteremia.<sup>10</sup>

Lately, several studies have documented the presence of ESBL-producing *P. rettgeri* in Eastern Europe and New Delhi metallo- $\beta$ -lactamase-1-producing *P. rettgeri* isolates in South America and Asia.<sup>6</sup> About 75.0% of *Providencia* isolates were found to be MDR by Godebo et al., and Linhares et al. identified *Providencia* species as the most common cause of MDR UTI.<sup>20,21</sup>

In a survey conducted in 10 Italian laboratories, greater than 40.0% of *P. stuartii* isolates were reported to be resistant to aminoglycosides, nitrofurantoin, penicillins (amoxicillin, Augmentin, ampicillin, ampicillin-sulbactam, and ticarcillin), quinolones, trimethoprim/sulfamethoxazole, tetracycline, and chloramphenicol. Most isolates, however, remained susceptible to third-generation cephalosporins and meropenem in contrast to our findings.<sup>22</sup> Fass et al. reported a steep decline in the sensitivity of *Providencia* to ciprofloxacin (from 100.0 to 46.0%), reiterating emerging resistance in this genus and hence emphasizing the need for routine susceptibility tests.<sup>23</sup>

High levels of ciprofloxacin and cotrimoxazole resistance (60–75.0%) have been reported for *Providencia* spp., especially in hospitals where the use of these agents is unrestricted. In a study from Bosnia, UTI was found to be very common in patients with

spinal cord injuries with a chronically inserted urinary catheter. *Providencia* spp. was the most common isolate accounting for 19% of cases and MDR was seen in as many as 87.0% of isolates.<sup>13,24,25</sup>

The first case of carbapenem-resistant *Providencia* was reported from Japan in 2003. Since then, they have been detected in other countries too like Nepal, Pakistan, Portugal, South Africa, South Korea, United Kingdom, Afghanistan, Algeria, Argentina, Brazil, Bulgaria, Canada, China, Ecuador, Greece, India, Israel, Italy, Mexico, and United States. It has been documented in most studies that carbapenem-resistant *Providencia* species usually infect adult immunocompromised patients.<sup>5,8</sup> All the patients included in our study were admitted to ICU and had various comorbid illnesses, thus producing an immunocompromised state.

Very recently, in the early part of 2021, reports of genes encoding aminoglycoside-modifying enzymes, such as aminoglycoside acetyltransferases, have also come forth from Brazil. These enzymes are known to compromise the activity of fluoroquinolones too.<sup>26</sup> All *Providencia* isolates were found to be resistant to fluoroquinolones like in our study. Regarding the  $\beta$ -lactam group also, a significant proportion showed resistance to carbapenems and  $\beta$ -lactamase inhibitors (tazobactam), indicating low effectiveness of these antimicrobials. Overall, least resistance was seen for amikacin. The presence of these genes indicates that the resistance arsenal of this species is increasing, thus limiting therapeutic options.

Various types of resistance mechanisms are being reported in *Providencia* isolates on a global level. Shin et al. recently described an outbreak caused by MDR *P. rettgeri* isolates co-producing NDM-1 carbapenemase and PER-1 ESBL in Korea. All these patients were admitted to a surgical ICU and had a urinary catheter in place.<sup>11</sup>

Against this backdrop of a rapid increase in multiresistant pathogens and the resulting lack of effective antibiotic therapy, some older antibiotics have been tested for new therapeutic uses. One of these is fosfomycin, which was found to be quite promising. In the current study, however, all isolates were found to be resistant to this miracle drug. In a study conducted in the Czech Republic in 2017 also, a mere 44.0% of *Providencia* strains were found to be sensitive to fosfomycin.<sup>24</sup>

Given the inherent resistance seen in the genus *Providencia* to various key drugs especially meant for use in critically ill patients (colistin and tigecycline) and the dismal antibiotic sensitivity profile seen in study isolates, clinical management can be quite difficult. At the time of analysis, 2/15 patients had left against medical advice. Sixty-one percent (8/13) patients were discharged following clinical improvement while 20.0% (3/13) succumbed to infection. High rates of mortality have been reported by other studies as well.<sup>2,11</sup> The presence of comorbid conditions could have contributed to the high mortality seen in this group of patients. The high level of resistance may be due to the empirical use of broad-spectrum antibiotics and poor compliance with hospital antibiotic policy. A fact worth mentioning is that with our institution being a tertiary care referral institute, most patients may already have received treatment at various other centers, hence harboring the resistant organisms by the time they reach us.

The increasing prevalence and antibiotic resistance clearly indicate that this organism is expanding its boundaries in the confines of the hospital. The susceptibility of *Providencia* isolates should be closely monitored, and the treatment regimen should be guided by susceptibility results provided by the laboratory. Owing to a near-complete absence of any novel antibiotic and increasing

surge of MDR organisms, our armamentarium remains prevention of the growth of such bugs.

The authors postulate that possible lapse in infection control practices (during the corona pandemic) and empirical overuse of broad-spectrum antimicrobials coupled with comorbid illnesses leading to prolonged catheterization has probably provided a fertile ground for this originally harmless bacterium to cause severe infections. While there does not seem to be any light at the end of this tunnel, prevention seems to be the best cure in dealing with these organisms. There is an urgent need to reinforce the principles of antimicrobial stewardship and infection control. Together, these interventions only can lead to a reduction in mortality and morbidity related to such drug-resistant infections.

This study has a few limitations. It presents a retrospective analysis of complete clinical and microbiological data encompassing 15 *Providencia* isolates. There may have been poor control on a few confounding factors. The results are rather difficult to generalize considering the immense pressure faced by the healthcare system during the current COVID pandemic. Also, with ours being a tertiary care referral institute, patients may have reached after previous hospitalizations where they acquired these pathogens. Molecular mechanisms of resistance and clonal relatedness could not be ascertained because of infrastructural constraints. Nevertheless, these factors do not negate the importance of the results.

Despite these limitations, to the best of our knowledge, this is the first study that gives the prevalence and antibiotic susceptibility profile of *Providencia* spp. causing UTIs during the current pandemic, and it highlights an urgent need to improve infection control practices in hospitals and rationalize antibiotic prescriptions. Our findings are also important when defining an algorithm for empiric antimicrobial therapy in hospitalized patients with COVID-19 to achieve better therapeutic outcomes.

## CONCLUSION

*Providencia* is an emerging opportunistic pathogen. Management of infections caused by these isolates is a herculean task, especially in times of escalating antibiotic resistance. Their inherent drug resistance to several commonly used drugs leaves very few options for clinicians. We need to develop a robust system for the early detection of these pathogens. Also, effective infection control and antibiotic stewardship are emphasized to prevent the development of further antibiotic resistance in *Providencia* species.

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