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Review Article

Antibiotic Resistance in *Providencia* spp. in Iran: A Comprehensive Review of Patterns, Mechanisms, and Public Health Implications

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Abstract

Background: The genus *Providencia*, a member of the *Enterobacteriaceae* family, has emerged as a significant pathogen in human infections, particularly in immunocompromised individuals and hospital settings. With increasing global reports of antimicrobial resistance in *Providencia* species, understanding the resistance patterns and mechanisms in specific geographic regions is critical. This review evaluated the antibiotic resistance status of *Providencia* spp. in Iran, summarizing findings from existing literature to identify trends, gaps, and implications for public health and clinical practice.

Methods: For this purpose, Google, PubMed, and Scopus databases were searched, along with conducting a systematic review of peer-reviewed articles, clinical case reports, and surveillance studies to assess the antibiotic resistance profiles of *Providencia* in Iran. Studies published from 2000 to 2024 were included in this review, with a focus on *Providencia* resistance to critical antibiotics such as carbapenems, cephalosporins, fluoroquinolones, and the like, which are multidrug resistant (MDR) or pandrug resistance (PDR) *Providencia* based on CLSI performance guidelines for antimicrobial susceptibility testing. The data were analyzed to identify prevalent resistance genes, mechanisms, and regional variations.

Results: The findings revealed a concerning rise in MDR among *Providencia* isolates in Iran, with resistance to carbapenems, fluoroquinolones, aminoglycosides, and extended-spectrum beta-lactams frequently reported. Regional studies highlight variability in resistance rates, likely reflecting differences in antimicrobial stewardship and healthcare practices. Emergency PDR *Providencia* is a serious health threat due to its intrinsic resistance to some antibiotics, such as colistin, and tigecycline, which are used for other MDR *Enterobacteriaceae* species. Accordingly, understanding regional resistance patterns is helpful in choosing the appropriate treatment option.

Conclusion: Given the high rate of carbapenem resistance, this is likely substantiated by other studies conducted in Asia that have identified various carbapenemases, including VIM, IMP, NDM-1 MBL, OXA-48, and KPC, which underscores the urgent need for effective antimicrobial stewardship and surveillance strategies to combat the spread of these resistant pathogens.

Keywords: *Providencia*, Antibiotic resistance, Iran, Multidrug resistance, Extended-spectrum beta-lactamase, Carbapenemase, Antimicrobial stewardship

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Introduction

The genus *Providencia*, a group of Gram-negative bacilli within the *Enterobacteriaceae* family, was first discovered by Rettger in 1904 and later formally named by Kauffmann in 1951. The species *P. stuartii* naturally inhabits environments such as soil, water, and sewage (1,2). The *Providencia* genus includes five distinct species, namely, *P. stuartii*, *P. rettgeri*, *P. alcalifaciens*, *P. heimbachae*, and *P. rustigianii*. These bacteria are typically found in human secretions, including urine, sputum, blood, stool, and wounds. *P. rettgeri* and *P. stuartii* are particularly significant as they are associated with infections such as urinary tract infections and can lead to bacteremia in immunocompromised individuals; they are infrequent opportunistic pathogens within the *Enterobacteriaceae* family (3). Their impact on human and animal health is noteworthy, often resulting in outbreaks of hospital-acquired infections. The rising prevalence of multidrug resistant (MDR) strains of *P. rettgeri* poses a considerable global public health threat. Although carbapenems have been extensively used for treating

MDR bacterial infections, certain isolates of *P. rettgeri* have developed resistance to these critical antibiotics (4). The first case of carbapenem-resistant *Providencia* was reported in Japan in 2000. Since then, similar cases have emerged in various countries, including Nepal, Pakistan, Portugal, South Africa, South Korea, the United Kingdom, Afghanistan, Algeria, Argentina, Brazil, Bulgaria, Canada, China, Ecuador, Greece, India, Israel, Italy, Mexico, and the United States (5). This highlights the urgent need for ongoing monitoring of β-lactamase- and carbapenemase-producing strains of *P. rettgeri* in clinical settings.

In Iran, numerous studies have examined the resistance patterns of *Enterobacteriaceae* from a variety of samples. However, there is limited information regarding antimicrobial resistance specifically in *Providencia*. Two particular studies conducted in Tehran and Ardabil have provided partial insights into the antibiotic resistance patterns of *Providencia* within *Enterobacteriaceae* samples.

Methods

To achieve the study's objectives, several databases, including Google, PubMed, and Scopus, were searched, in addition to performing a systematic review of clinical case reports, peer-reviewed articles, and surveillance studies to evaluate the antibiotic resistance profiles of *Providencia* in Iran. Different published studies (2000–2024) were included in this investigation, focusing on *Providencia* resistance to critical antibiotics, such as cephalosporins, carbapenems, fluoroquinolones, and the like. These antibiotics are MDR or pandrug resistance (PDR) *Providencia* based on CLSI performance guidelines for antimicrobial susceptibility testing. The obtained data were analyzed to determine prevalent resistance genes, mechanisms, and regional variations.

Discussion

The high prevalence of MDR *Providencia* in Iran underscores the need for immediate interventions, including stricter antimicrobial stewardship, enhanced surveillance systems, and molecular epidemiological studies to track resistance dynamics.

Providencia stuartii, first isolated by Rettger (1904) and formally named by Kauffmann (1951), is typically found in natural environments such as water, soil, and sewage (6). Its presence as a rare opportunistic pathogen within the *Enterobacteriaceae* family can lead to significant outbreaks of hospital-acquired infections. Despite extensive research on resistance patterns among *Enterobacteriaceae* in various Iranian medical centers, *Providencia*, being less common, has only been identified in two specific locations focused on *Enterobacteriaceae*. The first report of carbapenem-resistant *Providencia* emerged in Japan in 2000, with subsequent detections reported in other countries, including Nepal, Pakistan, Portugal, South Africa, South Korea, the United Kingdom, Afghanistan, Algeria, Argentina, Brazil, Bulgaria, Canada, China, Ecuador, Greece, India, Israel, Italy, Mexico, and the United States (5,7). The initial clinical isolates of *P. rettgeri* producing the IMP-1 metallo-β-lactamase (MBL) were documented in laboratory-based surveillance in western Japan during the same year (8). In 2008, Algeria reported the first clinical isolate of *P. stuartii* that produced the VIM-19 MBL (9). Evidence indicates that IMP-type MBL-producing isolates have been identified in Japan, South Korea, and the United States, while NDM-type MBL-producing isolates have emerged globally. Conversely, the majority of carbapenem-resistant *P. stuartii* isolates predominantly produce VIM-type MBLs, which are especially prevalent in Algeria and Greece (10). Notably, an NDM-type MBL-producing isolate of *P. stuartii* has been documented in Afghanistan (11, 12). In recent years, there has been a concerning increase in reports of carbapenem-resistant *P. stuartii* and *P. rettgeri* isolates harboring the *blaNDM* gene. For instance, one report identified five clinical isolates of carbapenem-resistant *P. rettgeri*- and *P. stuartii*-producing IMP-type MBLs across three distinct hospitals in Japan. In Switzerland, *P. stuartii* isolates containing chromosomally encoded *blaNDM*-1 and *blaOXA-48* carbapenemase genes were identified in wound samples from a patient transferred from Macedonia. Additionally, various isolates with carbapenemases, including KPC and VIM, have been documented in Greece, Argentina, Brazil, and Saudi Arabia (13-16). In Iran, while numerous studies have focused on the resistance patterns of *Enterobacteriaceae* from diverse samples, limited information exists regarding the antimicrobial resistance specific to *Providencia*. However, two studies—one in Tehran and the other in Ardabil—have provided insights into the resistance patterns of *Providencia*. In the study conducted in Ardabil, investigating antibiotic resistance patterns among enteric organisms in children, 305 fecal samples were collected between April and August 2017. Among them, three *Providencia* cases were identified, with 70% exhibiting MDR, and their resistance mechanisms did not involve AMPC/ESBL (17). Another

Table 1. Susceptibility of *Providencia* spp. (*P. stuartii* and *P. rettgeri*) of Various Studies in Iran and Other Countries in Asia Based on CLSI Performance Guidelines for Antimicrobial Susceptibility Testing

Year(s) of Isolation	Country of Isolation (City)	Resistance Pattern	Reference
2022, 2024	Iran (Tehran)	MDR (OXA and MBL types) and MDR	19, 20
2017	Iran (Tehran)	MDR	18
2021, 2024	Iran (Ardabil)	MDR (non-AMPC/non-ESBL) Susceptible OR MDR (OXA 48, MBL)	17
2011	Afghanistan	MBL (NDM 1)	5
2014	India	MBL (NDM 1)	5
2012	China	MBL (NDM 1)	5
2001-2002, 2020	Japan	MBL (IMP)	5, 8
2010	Pakistan	MBL (NDM 1)	5

Note. MDR: Multidrug resistance; CLSI: Clinical and Laboratory Standards Institute.

study from Tehran University examined 11 157 urine samples, discovering that 9171 belonged to gram-negative bacteria, including six cases of *Providencia*, where 50% were found to be MDR. Table 1 provides details regarding the specific resistance profiles of these six isolates. Given the high rate of carbapenem resistance, this is likely substantiated by other studies conducted in Asia that have identified various carbapenemases, including VIM, IMP, NDM-1 MBL, OXA-48, and KPC, which underscores the urgent need for effective antimicrobial stewardship and surveillance strategies to combat the spread of these resistant pathogens. The increasing issues surrounding resistance in *Providencia* species, particularly *P. stuartii*, are drawing global attention. The emergence of carbapenem resistance and the production of MBLs have been reported worldwide. Various MBL variants (e.g., IMP-type and NDM-type) have surfaced in different regions, indicating a troubling trend in the evolution of resistance mechanisms and underscoring the need for continuous monitoring and targeted research (18).

Results

Although *Providencia* is a rare opportunistic pathogen among the *Enterobacteriaceae* and is infrequently isolated from human secretion samples, our findings demonstrated a concerning rise in antimicrobial resistance among *Providencia* isolates in Iran, with resistance to carbapenems and extended-spectrum beta-lactams frequently reported. Moreover, it was found that its antibiotic resistance patterns can complicate treatment. Emergency PDR *Providencia* is a critical health threat since it is intrinsically resistant to various commonly used antibiotics, including colistin, and tigecycline, which is utilized for some other MDR *Enterobacteriaceae* spp. Studies conducted in Iran indicate that between 50% and 70% of *Providencia* cases exhibit MDR or PDR with resistance mechanisms; this resistance is not solely attributable to extended-spectrum beta-lactamases (ESBLs) or AmpC beta-lactamases; given the high rate of carbapenem resistance observed, it is likely corroborated by other studies in Asia that have identified carbapenemases such as VIM, IMP, NDM-1 metallo-beta-lactamase (MBL), OXA-48, and KPC.

Regional studies highlight variability in resistance rates, probably reflecting variations in healthcare practices and antimicrobial stewardship.

Conclusion

The findings of this study are significant for guiding the appropriate prescription of antibiotics for infections caused by *Providencia* species.

The escalating antibiotic resistance in *Providencia* spp. within Iran presents a substantial challenge to public health due to their intrinsic resistance to some used antibiotics, such as colistin, and tigecycline, utilized for several other MDR *Enterobacteriaceae* spp., considering the possibility of the carbapenem resistance pattern, as in other studies in Asia, including carbapenemases (e.g., VIM, IMP, NDM-1 MBL, OXA 48, and KPC). Therefore, antibiotics such as aztreonam and ceftazidime-avibactam should be considered for MBL-type carbapenem-resistant *Providencia* species and OXA48 carbapenemase *Providencia* species, respectively.

Comprehensive strategies encompassing improved genetic and molecular studies of resistance patterns, diagnostics, rational antibiotic use, and robust monitoring are imperative to curb the spread of resistant strains.

Future research should prioritize the characterization of resistance determinants and the development of targeted therapeutic approaches.

Authors' Contribution

Conceptualization: Shiva Shabani.
Data curation: Shiva Shabani.
Formal analysis: Shiva Shabani.
Funding acquisition: Shiva Shabani.
Investigation: Shiva Shabani.
Methodology: Shiva Shabani.
Project administration: Shiva Shabani.
Resources: Shiva Shabani.
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Supervision: Shiva Shabani.
Validation: Shiva Shabani.
Visualization: Shiva Shabani.

Competing Interests

None.

Ethical Approval

Not applicable.

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