MINI REVIEW

First literature review of carbapenem-resistant *Providencia*

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Abstract

Providencia species are Gram-negative bacteria that belong to the *Enterobacteriaceae* family. They have intrinsic resistance to colistin and tigecycline, which makes treatment of the multidrug-resistant strains of *Providencia* challenging. Carbapenem-resistant *Providencia* species are increasingly reported. In this review, patients' characteristics, resistance mechanisms, treatment and infection control measures of carbapenem-resistant *Providencia* species in the literature are described.

Keywords: Carbapenem, carbapenem-resistant, *Providencia*, *rettgeri*, *stuartii*
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Introduction

Species of *Providencia* are Gram-negative bacteria that belong to the *Enterobacteriaceae* family. Unlike many other bacteria of this family, species of *Providencia* are an infrequent cause of nosocomial infections. Among species of *Providencia, stuartii* and *rettgeri* are the most common causes of infections in hospitalized patients, mainly urinary tract infections. In addition to urinary tract infections, *P. stuartii* and *P. rettgeri* can cause pneumonia, meningitis, endocarditis, wound and bloodstream infections [1–3]. Infections with species of *Providencia* have significant impact on patients' morbidity, mortality and treatment [4,5].

In 1904, the first species of *Providencia* was isolated by Rettger [1]. At first the bacterium was noticed in chickens; it was believed to be an epidemic of fowl cholera. The bacterium was characterized in 1918, when it was named *Bacterium rettgerii* by Hadley *et al.* [6]. In 1951, Kauffmann and Edwards [7] first suggested the genus name *Providencia,* which included a cluster of microorganisms studied by Stuart and colleagues at Brown University in Providence, Rhode Island, USA. By 1983, *P. rettgeri, P. stuartii, P. alcalifaciens* and *P. rustigianii* were fully differentiated with urea hydrolyzation and DNA hybridization [8]. In 1986, *P. heimbachae* was the fifth species discovered in the genus *Providencia* [9].

Species of *Providencia* are non–lactose fermenting, methyl red and phenylpyruvic acid positive bacilli. Species of *Providencia* are positive for the phenylalanine deaminase test but negative for lysine decarboxylase, ornithine decarboxylase and arginine dihydrolase tests [1]. Generally, they can be recognized by their fruity smell. Species of *Providencia* are commonly susceptible to carbapenems, amikacin, aztreonam, and second and third-generation cephalosporins including cefaclor, cefuroxime, cefetamet, cefpodoxime, ceftazidime, ceftriaxone and cefotaxime [1]. Alternative choices for antimicrobial therapy include ciprofloxacin and cotrimoxazole [1]. Species of *Providencia* are generally resistant to gentamicin, tobramycin, aminopenicillins and first-generation cephalosporins [1]. *P. stuartii* and *P. rettgeri* can produce inducible AmpC β-lactamases [10]. Moreover, plasmid-mediated resistance mechanisms such as extended-spectrum β-lactamases and metallo-β-lactamases have also been recovered from species of *Providencia* causing nosocomial infections [11,12]. Unlike other Gram-negative bacteria (e.g. *Acinetobacter baumannii, Klebsiella pneumonia*), species of *Providencia* have intrinsic resistance to colistin and tigecycline, which makes treatment of the multidrug-resistant (MDR) strains of this pathogen challenging. Resistance can be transmissible from

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MDR *Providencia* species to other bacterial pathogens like susceptible strains of *Escherichia coli* and *vice versa* by transformation and conjugation [11,13]. Carbapenem-resistant *Providencia* species are increasingly reported.

In this review, patients' characteristics, resistance mechanisms, treatment and infection control measures of carbapenem-resistant *Providencia* species in the literature are described.

Methods

We performed a nonsystematic narrative review about carbapenem-resistant *Providencia* species described in the literature. PubMed was searched using the following terms: (carbapenem) AND (resistant) AND (*Providencia*). The search returned 52 articles; all were screened for relevance to the subject of this review. Publications in languages other than English were excluded. Additional articles of interest were identified from the references listings of reviewed articles. Species of *Providencia* were included in this review if the isolate test revealed resistance to any of the carbapenem agents (doripenem, ertapenem, imipenem, or meropenem) or if testing demonstrated carbapenemase production through a phenotypic or molecular assay. Twenty-nine publications met our search criteria and are the subject of this review.

Patient characteristics

Eighty cases of carbapenem-resistant *Providencia* were described in 29 reports (Table 1). All studies were descriptive. There were no reports that included a case–control component. The first case of carbapenem-resistant *Providencia* was reported from Japan in 2003 [14]. Carbapenem-resistant *Providencia* was detected in other countries: Afghanistan, Algeria, Argentina, Brazil, Bulgaria, Canada, China, Ecuador, Greece, India, Israel, Italy, Mexico, Nepal, Pakistan, Portugal, South Africa, South Korea, United Kingdom and United States. Carbapenem resistance was discovered in only two *Providencia* species: *P. stuartii* (39 cases were described in 11 reports) and *P. rettgeri* (41 cases were described in 18 reports). Carbapenem-resistant *Providencia* species usually infect adult immunocompromised patients; they were not reported in paediatric patients. The mean age ± SD of the patients was 50.90 ± 18.63 years. Twenty-eight subjects were male, 20 female and gender not specified in 32. Carbapenem-resistant *Providencia* species were isolated from urine (n = 32 cases), bloodstream (n = 20), respiratory tract sites (n = 7), catheter tip (n = 3), soft tissue (n = 3), pus (n = 2), stool (n = 2) and bone (n = 1). Carbapenem-resistant *Providencia* was recovered from rectal swab in one case report [15]. The site of isolation of carbapenem-resistant *Providencia* was not mentioned in nine instances. Four outbreaks of carbapenem-resistant *Providencia* were reported in the literature [5,11,16,17]; three were caused by carbapenem-resistant *P. stuartii* (CRPS) and one was linked to carbapenem-resistant *P. rettgeri* (CRPR). All the outbreaks occurred in intensive care units (ICUs).

Nine of 29 reports mentioned whether or not the patients received prior antimicrobial therapy [5,11,13,15,18–21]; all patients in the nine reports received antibiotics before detection of carbapenem-resistant *Providencia* species except one. In one outbreak of CRPS [5], the elevated polymyxin B consumption in that ICU, because of high rates of *Pseudomonas aeruginosa* and *A. baumannii,* might be the cause of the emergence of CRPS. One patient with CRPS in this outbreak had received prior therapy with polymyxin before CRPS detection. Four patients with CRPS received colistin before the isolation of CRPS in two reports [20,21]. Six critically ill patients were infected with a CRPS isolate in one outbreak in Greece [11], and three received prior therapy with colistin. Three patients received prior tigecycline therapy before the isolation of CRPS [11,13,20].

Length of hospitalization before isolation of carbapenem-resistant *Providencia* was rarely reported. However, prolonged hospitalization before isolation of carbapenem-resistant *Providencia* was mentioned in four reports [11,17,22,23]. Prolonged hospitalization ranging from 24 to 106 days before isolation of CRPS was present in one outbreak [11]. In another report [17], the median length of ICU stay was 39, days while acquisition of CRPS occurred in a median of 16 days after ICU admission.

Regarding CRPR, the average time to positive urine cultures for CRPR was 29 days (range, 12–68 days) in one report [22]. In another report [23], the length of hospital stay was 68 days while acquisition of CRPR occurred 52 days after ICU admission. Common equipment such as dialysis machines might facilitate the spread of carbapenem-resistant *Providencia.* In one outbreak of CRPR in South Africa [16], all patients with CRPR were on dialysis; dialysis machines could be the source of CRPR in this outbreak. Three patients were HIV positive, which indicates that immunocompromised patients are more susceptible to CRPR infections. It is worth mentioning that many patients with carbapenem-resistant *Providencia* had urinary catheters [13,15–17,24].

Mechanisms of carbapenem resistance

New Delhi metallo-β-lactamase 1 (NDM-1) is the most common resistance mechanism to carbapenems in *Providencia*

TABLE 1. Clinical and demographic characteristics of cases of infection or colonization with carbapenem-resistant *Providencia*

Case no.	Reference	Location	Species	Year of isolation	Sex	Age (years)	Comorbidities	Site of isolation	Antimicrobial therapy	Prior antimicrobial therapy	Mechanism of carbapenem resistance	Outcome
1	5	Brazil	*P. stuartii*	2008	M	41	NR	Urine	None	Ceftriaxone, ciprofloxacin, gentamicin	Derepression of chromosomally encoded AmpC and ESBL production	Died
2					F	54	NR	Blood	Piperacillin/tazobactam plus meropenem	Cefepime, imipenem, polymyxin B		Discharged
3					M	14	NR	Surgical wound	Imipenem plus amikacin	Imipenem		Discharged
4					F	52	NR	Central venous catheter	None for carbapenem-resistant *Providencia stuartii*	Cefepime, imipenem		Died
5					F	46	NR	Tracheal aspirate	Levofloxacin	None		Discharged
6	11	Greece	*P. stuartii*	December 2012 - March 2013	F	NR	NR	Urine	NR	All the patients received several antimicrobial agents (β-lactams, quinolones and aminoglycosides) before isolation of *P. stuartii*, three received colistin and received tigecycline	VIM-1	Discharged
7					F	NR	NR	Urine	NR			Discharged
8					M	54	NR	Catheter tip	Meropenem			Died
9					M	27	NR	Blood	Meropenem			Died
10					F	73	NR	Blood	Meropenem			Died
11					M	NR	NR	Blood	NR			Discharged
12	13	Canada	*P. stuartii*	NR	M	65	Infected sacral ulcer	Urine	Did not receive antimicrobial therapy; it was considered colonization	Cefazolin, metronidazole, tigecycline	NDM-1	Discharged
13	15	Israel	*P. rettgeri*	2011	M	74	Diabetes, HTN	Rectal swab	NR	NR	NDM-1	NR
14	16	South Africa	*P. rettgeri*	November 2014 - January 2015.	F	26	RI on dialysis, respiratory Infection, HIV	Urine	NR	NR	NR	Transferred to high-care unit
15					F	32	RI on dialysis, HIV	Urine	NR	NR	NR	Discharged
16					M	40	RI on dialysis	Urine	NR	NR	NR	Transferred to renal unit
17					F	33	RI on dialysis, polytrauma, HIV	Tissue	NR	NR	NR	Died
18	17	Greece	*P. stuartii*	2011	M	74	Mediastinal tumour	Blood	Piperacillin/tazobactam plus amikacin	NR	VIM-1	Died
19					M	66	CABG, AVR, stroke	Urine		NR		Survived
20					M	75	Pancreatitis	Blood		NR		Died
21					F	34	Multiple trauma	Blood		NR		Survived
22					F	67	ALS, septic shock	Blood		NR		Died
23					F	63	Malignancy, sepsis	Blood		NR		Died
24					F	47	Cardiac arrest, pneumonia	Urine		NR		Survived
25					M	53	Stroke	Blood		NR		Died
26					F	54	Brain haemorrhage	Blood		NR		Survived
27					M	60	Stroke	Urine		NR		Survived
28					M	84	AAA repair	Urine		NR		Died
29					M	25	Multiple trauma	Blood		NR		Survived
30					F	75	Osteomyelitis, MOF	Blood		NR		Died
31					M	56	TTP	Blood		NR		Survived
32					M	20	Multiple trauma	Urine		NR		Survived
33	25	Afghanistan	*P. stuartii*	2011	NR	NR	Severe burns, inhalational injury	Blood	Levofloxacin plus piperacillin/ tazobactam	Patient received broad-spectrum antibiotics but were not reported	NDM-1	Died

34	26	Portugal	*P. stuartii*	NR	M	88	Enterocutaneous fistula	Urine	NR	NR	NDM-1	NR
35	27	Argentina	*P. rettgeri*	2013	M	54	Vascular disease	Catheter	Did not receive antimicrobial therapy; it was considered colonization	NR	NDM-1	Discharged
36					M	56	Terminal prostate cancer	Urine	Amikacin	NR		Died
37	28	Italy	*P. stuartii*	Between May 2011 and April 2014	NR	NR	NR	NR	NR	NR	NDM	NR
38	18	Brazil	*P. rettgeri*	2015	M	55	Diabetes, HTN, osteomyelitis	Bone	Ceftriaxone plus clindamycin	Ciprofloxacin, clindamycin, ceftriaxone	NDM	Discharged
39	22	Mexico	*P. rettgeri*	2012	M	22	NR	Urine	NR	NR	NDM-1	NR
40					M	16	NR	Urine	NR	NR		NR
41					F	50	NR	Urine	NR	NR		NR
42					F	53	NR	Urine	NR	NR		NR
43	29	Israel	*P. rettgeri*	2011	NR	NR	NR	Blood	NR	NR	NDM-1	NR
44				2011	NR	NR	NR	Blood	NR	NR		NR
45				2011	NR	NR	NR	Blood	NR	NR		NR
46				2008	NR	NR	NR	Pus	NR	NR		NR
47				2011	NR	NR	NR	Blood	NR	NR		NR
48	30	Mexico	*P. rettgeri*	2015	NR	NR	NR	NR	NR	NR	NDM-1, IMP	NR
49	24	USA	*P. rettgeri*	Between 2011 and 2013	NR	NR	History of ankle fracture	Urine	NR	NR	NDM-1	NR
50	19	Brazil	*P. rettgeri*	2013	M	NR	Diabetes, PVD	Tissue	NR	Ciprofloxacin, amoxicillin/ clavulanate	NDM-1	Discharged
51	31	India	*P. rettgeri*	2014	NR	NR	NR	NR	NR	NR	NDM	NR
52	32	China	*P. rettgeri*	2012	NR	NR	NR	Urine	NR	NR	NDM-1	NR
53	33	Nepal	*P. rettgeri*	2012	NR	NR	SSI	Pus	NR	NR	NDM-1	NR
54					NR	NR	NLRTI	Sputum	NR	NR	NDM-1	NR
55					NR	NR	NLRTI	Sputum	NR	NR	OXA-72	NR
56					NR	NR	NLRTI	Sputum	NR	NR	NDM-1	NR
57	34	Canada	*P. rettgeri*	2010	F	NR	NR	Urine	NR	NR	NDM-1	NR
58	20	Greece	*P. stuartii*	2011	F	45	SAH	Bronchial secretions	Meropenem plus ciprofloxacin	Meropenem, colistin	VIM-1	NR
59					M	72	Severe diffuse cerebral ischaemia	Urine	It was considered colonization	Colistin		NR
60					M	42	Burn injuries	Bronchial secretions	It was considered colonization	Colistin, tigecycline		Survived
61	37	Algeria	*P. stuartii*	2008	F	NR	PE	Urine	Cefotaxime	NR	VIM-19	Died
62	21	Brazil	*P. stuartii*	2011	M	52	Chronic RI, respiratory failure	Urine	None	Imipenem, polymyxin	KPC-2	Discharged
63	38	Brazil	*P. stuartii*	Between 2009 and 2011	NR	NR	NR	NR	NR	NR	KPC-2	NR
64					NR	NR	NR	NR	NR	NR		NR
65					NR	NR	NR	NR	NR	NR		NR
66					NR	NR	NR	NR	NR	NR		NR
67	39	Japan	*P. rettgeri*	2002	NR	NR	NR	Urine	NR	NR	IMP-1	NR
68					NR	NR	NR	Urine	NR	NR		NR
69					NR	NR	NR	Urine	NR	NR		NR
70					NR	NR	NR	Urine	NR	NR		NR
71					NR	NR	NR	Urine	NR	NR		NR
72					NR	NR	NR	Urine	NR	NR		NR
73					NR	NR	NR	Sputum	NR	NR		NR
74					NR	NR	NR	Blood	NR	NR		NR
75	14	Japan	*P. rettgeri*	Between January 2001 and December 2002	NR	NR	NR	NR	NR	NR	IMP-1	NR
76					NR	NR	NR	NR	NR	NR		NR
77	35	Pakistan	*P. rettgeri*	Between 16 August and 29 September 2010	NR	NR	NR	Stool	NR	NR	NDM-1	NR
78					NR	NR	NR	Stool	NR	NR		NR

Continued

TABLE 1. Continued

Case no.	Reference	Location	Species	Year of isolation	Sex	Age (years)	Comorbidities	Site of isolation	Antimicrobial therapy	Prior antimicrobial therapy	Mechanism of carbapenem resistance	Outcome
79	36	Bulgaria	*P. rettgeri*	Between October 2013 and November 2014	NR	NR	NR	Urine	NR	NR	NDM-1	NR
80	23	Ecuador	*P. rettgeri*	December 2014	M	49	MI	Urine	Meropenem plus vancomycin plus tigecycline	Ciprofloxacin, fluconazole	NDM-1	Discharged

AAA, abdominal aortic aneurysm; ALS, amyotrophic lateral sclerosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; HTN, hypertension; ICU, intensive care unit; MI, myocardial infarction; MOF, multiple organ failure; NLRTI, nosocomial lower respiratory tract infection; NR, not reported; PE, pulmonary embolism; PVD, peripheral vascular disease; RI, renal impairment; SAH, subarachnoid haemorrhage; SSI, surgical site infection; TTP, thrombotic thrombocytopenic purpura.

species; it has been increasingly detected among CRPS and CRPR in several countries [13,15,18,19,22–36]. Production of VIM-1 metallo-β-lactamase was responsible for carbapenem resistance in *P. stuartii* in two cases and one outbreak [11,17,20]. VIM-19 β-lactamase was detected in one case of CRPS associated urinary tract infection [37]. KPC-2 was recovered from CRPS isolates in Brazil [21,38]. OXA-72 carbapenemase was isolated from *P. rettgeri* in Nepal [33]. While metallo-β-lactamase IMP-1 was detected in CRPR isolates in Japan [14,39] and one isolate of CRPR was found to produce NDM-1 as well [30], to our knowledge, this is the only reported *Providencia* isolate to date that produced two carbapenemases. Two reports described carbapenemase production in *Providencia,* but they did not mention the species [12,40]; one report described VIM-2 production in three isolates of *Providencia* in South Korea [12], while the second report described NDM production in three isolates of *Providencia* in the United Kingdom [40].

In one outbreak of CRPS [5], the carbapenem-resistant phenotype was explained by AmpC hyperproduction and extended-spectrum β-lactamase production (CTX-M-2); hyperproduction of AmpC was due to derepressed chromosomally encoded AmpC. Carbapenem resistance in this outbreak probably occurred by of the following mechanisms: modification of the penicillin-binding proteins, conformational change in outer membrane protein or efflux-pump expression. These were not analyzed in this report. This is the first report of the emergence of carbapenem resistance in *Providencia* species due to noncarbapenemase mechanism.

Treatment

Like other bacterial infections, treatment of carbapenem-resistant *Providencia* should depend on the susceptibility of isolates to antibiotics. In addition, the duration of treatment will be dependent on the daily clinical assessment of the treating physician and the microbiologic response to antimicrobial agents. Treatment of carbapenem-resistant *Providencia* was described in nine reports [5,11,17,18,20,23,25,27,37]. Because extended infusion of high-dose meropenem (2 g every 8 hours provided via intravenous infusion over 3 hours) is an effective strategy for treating carbapenemase-producing *Enterobacteriaceae* [41], it was part of the antibiotic regimens of many cases of infection with carbapenem-resistant *Providencia* described in the literature. Zavascki *et al.* [5] described the treatment of three of five patients who were infected with CRPS in one outbreak; one patient with bloodstream infection was treated with a combination regimen of high-dose piperacillin/tazobactam (4.5 g every 6 hours) and high-dose extended-infusion

meropenem (2 g every 8 hours in a 3-hour infusion); a second patient was treated with amikacin 1 g every 24 hours in combination with imipenem 500 mg every 6 hours for a relatively mild surgical wound infection; and a third patient received levofloxacin (the dose was not reported). The three patients had good outcomes and were discharged from the hospital.

Tshisevhe *et al.* [16] described the treatment of four patients who had urinary tract infections resulting from CRPR. The four patients received carbapenem therapy (drug and dose were not mentioned). Three patients survived and were transferred to home, a high-care unit or a renal unit. Only one patient died; the cause of death was not described in this outbreak. Oikonomou *et al.* [11] reported the treatment of a CRPS isolate that caused infection in six critically ill patients; the *P. stuartii* isolates retained some susceptibility to doripenem and meropenem. Three of six patients (the three had bloodstream infection) were treated with meropenem by prolonged infusion in this outbreak; these three patients died.

Antibiotic synergy tests were proven to be effective in achieving microbiologic eradication in patients infected with CRPS [17]. Douka *et al.* [17] reported one outbreak of CRPS; all isolates had identical susceptibility, patterns with MICs $\geq$ 16 g/mL to meropenem and imipenem. An antibiotic synergy test was carried out by Etest according to the Clinical and Laboratory Standards Institute guidelines. The most effective combination *in vitro* was piperacillin/tazobactam with amikacin for all the *P. stuartii* isolates. All patients were treated with piperacillin/tazobactam (4.5 g every 8 hours) plus amikacin (1 g every 24 hours) according to the *in vitro* synergy, resulting in microbiologic eradication in all patients involved. However, seven patients died during their hospitalization. Third-generation cephalosporins were used to treat two cases of CRPS [20,37]. One case of CRPS, in a patient with severe burns and inhalational injury, was treated with levofloxacin and piperacillin/tazobactam; the patient died from complications of severe injuries and central nervous system infection 12 days after injury [25].

Infection control measures

Stringent infection control practices are important in preventing the spread of carbapenem-resistant *Providencia* species [5,16,17,20,29]. Any new cases of carbapenem-resistant *Providencia* species in a healthcare facility should promptly draw the attention of the infection control teams. Isolation of patients infected or colonized with carbapenem-resistant *Providencia* species is indispensable. All patients should be under contact precautions. Exclusive medical and nursing equipment for each patient is recommended as well. Thorough sterilization and cleaning of medical equipment like dialysis machines is of paramount importance in the prevention of bacterial contamination and infection [16]. Education of healthcare personnel plays a pivotal role in controlling carbapenem-resistant *Providencia* species–related outbreaks. Hand hygiene practice must be repeated to healthcare personnel, as proper hygienic practice is important in the prevention of bacterial infections in any healthcare facility [16,17]. One report described four CRPR clinical isolates [22]; a possible epidemiologic link between the patients was a surgical resident involved in the care of the four patients.

Zavascki *et al.* [5] described the infection control measures that were applied to an outbreak of CRPS; private rooms were used to isolate all patients with CRPS. All patients were under contact precautions, including the use of gloves and gowns by any healthcare professional involved in patient treatment. Medical and nursing equipment were restricted for each patient. A strict environmental cleaning policy for rooms and objects that might have contacted colonized patients was applied. The outbreak was terminated after a 40-month period; no additional CRPS cases were detected. If isolating the patients with MDR microorganisms is not feasible, placing the patients in one area of any unit can prevent the further spread of highly MDR Gram-negative bacteria [42]. Identifying and eradicating the outbreak source is essential. In the CRPR outbreak that was described earlier [16], dialysis machines might have been the source. Healthcare providers should thus pay attention when using common equipment. A point prevalence surveillance of colonization must be performed on a regular basis for early identification of equipment and environmental contamination.

Conclusion

Infections with carbapenem-resistant *Providencia* species greatly affect patient morbidity, mortality and treatment. To our knowledge, this is the first review of the literature about carbapenem-resistant *Providencia* species. Usually carbapenem-resistant *Providencia* species are recovered from adult, critically ill and/or immunocompromised patients. Carbapenemase production is the main mechanism of carbapenem resistance in *Providencia* species; the most common isolated carbapenemase is NDM-1. Treatment of carbapenem-resistant *Providencia* should depend on the susceptibility of isolates to antibiotics. Extended infusion of high-dose meropenem is usually part of the antibiotic regimen. Finally, stringent infection control practices are important in preventing the spread of carbapenem-resistant *Providencia* species.

Conflict of interest

None declared.

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