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Reviewed work(s):

Source: *Infection Control and Hospital Epidemiology*, Vol. 33, No. 6 (June 2012), pp. 627-630

Published by: [The University of Chicago Press](http://www.press.uchicago.edu) on behalf of [The Society for Healthcare Epidemiology of America](http://www.shea-online.org)

Stable URL: <http://www.jstor.org/stable/10.1086/665730>

Accessed: 14/05/2012 14:47

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CONCISE COMMUNICATION

Outbreak of Carbapenem-Resistant *Providencia stuartii* in an Intensive Care Unit

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Outbreaks by carbapenem-resistant *Providencia stuartii* (CRPS) are rarely described. Clinical characteristics of patients with CRPS in an intensive care unit and resistance mechanisms were investigated. Carbapenemase production and/or outer membrane alterations were not detected; only CTX-M-2 and AmpC hyperproduction were noted. The outbreak was ultimately controlled in a 3-month period.

Infect Control Hosp Epidemiol 2012;33(6):627-630

Providencia species are members of the *Enterobacteriaceae*, which, unlike many other bacteria of this family, are an uncommon cause of infections. Among the *Providencia* species, *P. stuartii* and *P. rettgeri* are the most common causes of infections, especially urinary tract infections in hospitalized patients, although other infections can occur.¹

Virtually all *Providencia* species can produce inducible AmpC β -lactamases, and many isolates may also produce extended-spectrum β -lactamases (ESBLs) in nosocomial settings.¹ Nonetheless, carbapenem-resistant *Providencia* species are still rarely reported. In the few descriptions of carbapenem resistance in *Providencia* species, this phenotype was mediated by metallo- β -lactamase (MBL) production.¹⁻³ Carbapenem resistance in *Providencia* species is of particular concern because these bacteria are intrinsically resistant to polymyxins and tigecycline. In this study, we report an outbreak of carbapenem-resistant *P. stuartii* (CRPS) that occurred in an intensive care unit (ICU).

METHODS

All patients were admitted to Hospital São Lucas, a Brazilian teaching hospital; those who had a CRPS isolate recovered from April 2008 (index case) to June 2008 were included. The presence of infection was determined according to the Centers for Disease Control and Prevention (CDC) criteria.⁴ Medical records were reviewed to retrieve clinical information.

All isolates of each patient were analyzed, except the isolate of the index case, which was not viable for culturing. Isolates were identified using the Vitek system (bioMérieux). Susceptibility testing was determined by disk diffusion and interpreted by the Clinical and Laboratory Standards Institute criteria.⁵ Minimal inhibitory concentrations (MICs) were determined by E-test (bioMérieux). *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were tested as quality control strains. Phenotypic assay for detection of ESBL and AmpC production were conducted as described elsewhere.^{5,6} The genetic relatedness of the CRPS isolates was performed by pulsed-field gel electrophoresis (PFGE) and interpreted according to Tenover criteria.⁷

Isoelectric focusing analysis was performed as screening to identify the β -lactamase production using crude β -lactamase extracts on ampholine polyacrylamide gel (pH 3.5–9.5; GE Healthcare), as described elsewhere.⁸ For detection of carbapenemase production among the CRPS, a hydrolysis test of imipenem was assessed by ultraviolet spectrophotometry assays, as described elsewhere.⁹ Specific primers were used under standard polymerase chain reaction (PCR) conditions to detect ESBL- and carbapenemase-encoding genes, namely, *bla*_{TEM}, *bla*_{SHV}, *bla*_{CTX-M}, *bla*_{GES}, *bla*_{KPC}, *bla*_{OXA-48}, *bla*_{IMP}, *bla*_{VIM}, *bla*_{SPM-1}, *bla*_{GIM-1}, and *bla*_{NDM-1}.⁹ The detection of plasmid-mediated AmpC (pAmpC) encoding genes was carried out by a multiplex PCR, as described elsewhere.¹⁰ Amplicon sequencing was performed for identification of the CTX-M encoding gene.

Outer membrane protein (OMP) analysis of the CRPS was performed by SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis).¹¹ The OMP of the *P. rettgeri* ATCC 29944 and *P. stuartii* IAL 11 were also analyzed for comparison purposes.

RESULTS

In total, 11 isolates from 5 patients were recovered during the study period. Clinical characteristics of the 5 patients with CRPS are presented in Table 1. All but 1 patient received at least 1 β -lactam antibiotic, including cefepime, ceftriaxone, or imipenem, at the time of or right before the isolation of CRPS. Only 2 patients received appropriate therapy with piperacillin-tazobactam (4.5 g every 6 hours) and amikacin (1 g every 24 hours), in combination with carbapenems, meropenem (2 g every 8 hours in a 3-hour infusion), and imipenem (500 mg every 6 hours), respectively.

All patients with CRPS were isolated in private rooms under contact precautions by the use of gown and gloves by any healthcare professional involved in the assistance of these patients. Exclusive medical and nursing equipment for each patient was used, as well as a strict environmental cleaning policy for rooms and for any object that might have come

TABLE 1. Clinical and Demographic Characteristics of the 5 Patients with Carbapenem-Resistant *Providencia stuartii* (CRPS)

Pt	Sex	Age, years	Date of isolation	Site of isolation	Antimicrobial therapy in previous month	Treatment	Outcome (no. of days from recovery of first isolate to outcome)
1	M	41	April	Urine	Ceftriaxone, ciprofloxacin, and gentamicin	None	Death (1); attributable to a <i>Staphylococcus aureus</i> bloodstream infection
2	F	54	May	Blood ^a	Cefepime, imipenem, and polymyxin B	Piperacillin-tazobactam plus meropenem	Hospital discharge (62)
3	M	14	May	Surgical wound ^b	Imipenem	Imipenem plus amikacin	Hospital discharge (34)
4	F	52	May	Central venous catheter ^c	Cefepime and imipenem	None for CRSP ^d	Death (6); possibly related to CRPS infection
5 ^e	F	46	June	Tracheal aspirate	None	Levofloxacin	Hospital discharge (22)

NOTE. All isolations took place in 2008. F, female; M, male; Pt, patient.

^a Another CRPS was recovered from an ulcer secretion 19 days after its first isolation. We could not precisely define it as an infection or colonization.

^b One isolate was recovered from the same body site 4 days later, and 3 other CRPS isolates were recovered from urine after 12, 15, and 16 days after of its first isolation. This patient also fulfilled the CDC criteria for urinary tract infection.⁸

^c Another CRPS was recovered from tracheal aspirate 3 days after its first isolation. This patient also fulfilled the CDC criteria for ventilator-associated pneumonia.⁸

^d Coinfection with methicillin-resistant *S. aureus* treated with linezolid.

^e Classified as a colonizer.

into contact with colonized patients. No other measure, including restriction in carbapenem use, was adopted. The outbreak was ultimately interrupted after the recovery of CRPS from patient 5. No CRPS case was detected in a 40-month period after the recovery of the last isolate.

The cephalosporin and carbapenem MIC results are shown in Table 2. ESBL phenotypic assay was positive for all isolates, and AmpC production was detected as well. No imipenem hydrolysis was observed. The presence of *bla*_{CTX-M-2} was detected in all isolates. No carbapenemase or pAmpC encoding genes were detected in any CRPS. The isoelectric focusing of crude β -lactamase extracts from these strains supported our findings, showing β -lactamases at estimated pIs of 5.4, 7.9, and 8.8 compatible with a class A non-ESBL TEM-1, CTX-M-2 (an ESBL), and de-repressed chromosomally encoded AmpC, respectively. The OMP profile of the CRPS showed 2 bands corresponding to the 2 major porins of 37 and 40 kDa, as described elsewhere.¹² All CRPS showed a single PFGE pattern belonging to a unique clone.

DISCUSSION

CRPS isolates represent a serious clinical threat because these organisms are intrinsically resistant to last-resort agents such as polymyxins and tigecycline. Carbapenem resistance in *Enterobacteriaceae* at this institution has been rare, so the finding of a CRPS, followed by a second case within a few days, has promptly drawn the attention of an infection control team. The high polymyxin B consumption in our ICU, owing to elevated rates of *P. aeruginosa* and *Acinetobacter baumannii*, might have played a role in the emergence of CRPS, although only a single patient has received such antibiotics prior to

CRPS recovery, and this patient was not the index case. Fortunately, the outbreak was small, had a short duration, and was interrupted <3 months after the index case identification only with the adoption of contact precaution measures.

The resistance mechanism to carbapenems could not be precisely defined, but it was not mediated by carbapenemase production such as *Klebsiella pneumoniae* carbapenemase or metallo- β -lactamases. To our knowledge, this is the first description of the emergence of carbapenem resistance due to noncarbapenemase production mechanism among *P. stuartii*. The role of AmpC production in conferring carbapenem resistance is supported by the fact that the index case patient had received a third-generation cephalosporin just before the CRPS isolation, which is known as a strong chromosomal AmpC inducer, and its use might have favored the AmpC de-repression. In addition, the other 2 patients were receiving imipenem, which is also a potent chromosomal AmpC inducer, when the CRPS isolates were recovered. The OMP profile of the CRPS showed 2 bands probably corresponding to Omp A and OmpPst1 of 40 and 37 kDa, respectively, as described elsewhere.¹² The presence of this protein on the SDS gel suggests that it was expressed, but we cannot rule out a potential conformational modification in these OMPs that could affect carbapenem permeability. Thus, the carbapenem-resistant phenotype was due to de-repression of chromosomally encoded AmpC and ESBL production, probably coupled with one of the following mechanisms: conformational OMP alteration, modification of the penicillin-binding proteins, or efflux-pump expression, which were not investigated in this study.

Regarding antimicrobial therapy, 1 patient with blood-

TABLE 2. Susceptibility Profile of the 10 *Providencia stuartii* Clinical Isolates against Selected Antimicrobial Agents by E-test

Pt ^a	Strain	MIC in µg/mL (category of susceptibility)										AmpC phenotypic test	ESBL	
		AMK	PTZ	POB	CTX	CAZ	FEP	IMP	MEM	ERT	DOR			
2	P8	2 (S)	16 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
2	P7	2 (S)	8 (S)	>32 (R)	>256 (R)	4 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
3	P3	2 (S)	8 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
3	P4	2 (S)	8 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
3	P8	2 (S)	8 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
3	P9	2 (S)	16 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
3	P10	2 (S)	16 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
4	P5	2 (S)	16 (S)	>32 (R)	>256 (R)	3 (S)	256 (R)	>32 (R)	>32 (R)	>32 (R)	>32 (R)	>32 (R)	POS	CTX-M2
4	P6	2 (S)	8 (S)	>32 (R)	>256 (R)	4 (S)	>256 (R)	>32 (R)	POS	CTX-M2				
5	P11	4 (S)	16 (S)	>32 (R)	>256 (R)	2 (S)	>256 (R)	>32 (R)	POS	CTX-M2				

NOTE. Category of susceptibility determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines. AMK, amikacin; CAZ, ceftazidime; CTX, cefotaxime; DOR, doripenem; ERT, ertapenem; FEP, cefepime; IMP, imipenem; MEM, meropenem; MIC, minimum inhibitory concentration; POB, polymyxin B; POS, positive; Pt, patient; PTZ, piperacillin/tazobactam; R, resistant; S, susceptible.

^a The isolate from patient 1 was not recovered for analysis.

stream infection was treated with a combination regimen of high-dose piperacillin-tazobactam and high-dose extended-infusion meropenem. These measures might have overcome the effect of de-repressed AmpC coupled with ESBL production. The other patient was treated with aminoglycoside in combination with imipenem for a relatively mild surgical wound infection.

In summary, we described a small outbreak caused by rarely described CRPS isolates. Carbapenem resistance could not be attributed to carbapenemase production. De-repression of chromosomally encoded AmpC coupled with ESBL production certainly contributed for this phenotype, but it was probably associated with other adjuvant mechanisms that require further investigation.

ACKNOWLEDGMENTS

We thank Dr Luis Martínez-Martínez from the University Hospital Marqués de Valdecilla, Santander, Spain, for helping with the OMP evaluation. We also thank the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil, for providing researcher grants to A.P.Z. (process number: 301829/2008-0) and A.C.G. (process number: 307816/2009-5).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Received October 26, 2011; accepted January 6, 2012; electronically published April 24, 2012.

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