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NDM-1 Metallo-β-Lactamase and ArmA 16S rRNA methylase producing *Providencia rettgeri* clinical isolates in Nepal

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Abstract

Background: Drug-resistant *Providencia rettgeri* producing metallo-β-lactamase and 16S rRNA methylase has been reported in several countries. We analyzed *P. rettgeri* clinical isolates with resistance to carbapenems and aminoglycosides in a hospital in Nepal.

Methods: Five clinical isolates of multidrug-resistant *P. rettgeri* were obtained in a hospital in Nepal. Antimicrobial susceptibilities were determined using the microdilution method and entire genomes were sequenced to determine drug-resistant genes. Epidemiological analysis was performed by pulsed-field gel electrophoresis.

Results: Four of the 5 isolates were resistant to carbapenems (imipenem and meropenem), with MICs ≥16 mg/L, with the remaining isolate showing intermediate resistance to imipenem, with an MIC of 2 mg/L and susceptibility to meropenem with an MIC ≤1 mg/L. All 5 isolates had bla_{VEB-1}. Of the 4 carbapenem-resistant strains, 3 had bla_{NDM-1} and 1 had bla_{OXA-72}. All isolates were highly resistant to aminoglycosides (MICs ≥1,024 mg/L) and harbored *armA*. As the result of pulsed-field gel electrophoresis pattern analysis in the 5 *P. rettgeri* isolates, 4 had identical PFGE patterns and the fifth showed 95.7% similarity.

Conclusions: This is the first report describing multidrug-resistant *P. rettgeri* strains harboring bla_{NDM-1} or bla_{OXA-72} and *armA* isolated from patients in Nepal.

Keywords: NDM-1, OXA-72, 16S rRNA methylase, *Providencia rettgeri*, Molecular epidemiology

Background

Providencia rettgeri has been associated with hospital acquired infections, including catheter-related urinary tract infections, bacteremia, skin infections, diarrhea, and gastroenteritis [1,2]. To date, there have been 5 reports of *P. rettgeri* isolates harboring metallo-β-lactamase (MBL) encoding genes, including IMP-type MBL producers in Japan [3,4]; VIM-type MBL, PER-1 extended-spectrum β-lactamase (ESBL) and 16S rRNA methylase ArmA in Korea [5]; and NDM-type MBL in Israel [6] and Brazil [7].

NDM-type MBL was initially identified in *Klebsiella pneumoniae* and *Escherichia coli* in 2009 in Sweden [8]. Since then, NDM-1-producing *Enterobacteriaceae* have been isolated in various parts of the world [9,10].

Exogenously acquired 16S rRNA methylase genes responsible for very high levels of resistance to various aminoglycosides are widely distributed among *Enterobacteriaceae* and glucose-nonfermentative microbes [11]. Gram-negative pathogens producing 16S rRNA methylase ArmA have been isolated in various countries [11].

Although co-production of several resistance determinants is not rare in *Enterobacteriaceae* [12-16], it is less common in *P. rettgeri* [5]. We describe here *P. rettgeri* clinical isolates from Nepal that produce carbapenemase (NDM-1 or OXA-72) and 16S rRNA methylase (ArmA).

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Table 1 Summary of the characteristics of the 5 *P. rettegeri* strains, including antimicrobial resistance profiles and resistant genes

Strains	Tissue sources	Infection	MIC (mg/L)														Antibiotics resistant genes
			PIP	TZP	CAZ	FEP	IPM	DPM	MEM	ATM	ABK	AMK	GEN	CIP	CST	FOF	TIG	
IOMTU1	Pus	SSI	1,024	512	>1,024	64	32	16	64	1,024	>1,024	>1,024	>1,024	128	>128	512	4	bla_{NDM-1}, bla_{OXA-10}, bla_{VEB-1}, bla_{TEM-1}, bla_{ADC-67}, *armA*, *aadA1*, *aadA2*
IOMTU4	Sputum	NLRTI	1,024	128	>1,024	256	16	16	32	1,024	>1,024	>1,024	>1,024	>256	>128	512	4	bla_{OXA-72}, bla_{OXA-10}, bla_{VEB-1}, bla_{TEM-1}, bla_{ADC-67}, *armA*, *aadA1*
IOMTU91	Sputum	NLRTI	>1,024	1,024	>1,024	1,024	64	32	64	1,024	>1,024	>1,024	>1,024	256	128	128	4	bla_{NDM-1}, bla_{OXA-10}, bla_{VEB-1}, bla_{TEM-1}, bla_{ADC-67}, *armA*, *aadA1*
IOMTU94	Pus	SSI	1,024	4	>1,024	256	2	1	1	>1,024	1,024	1,024	>1,024	256	>128	1,024	4	bla_{OXA-10}, bla_{VEB-1}, bla_{TEM-1}, bla_{ADC-67}, *armA*, *aadA1*
IOMTU99	Sputum	NLRTI	>1,024	512	>1,024	128	64	32	64	1,024	>1,024	>1,024	>1,024	>256	>128	1,024	4	bla_{NDM-1}, bla_{VEB-1}, bla_{OXA-10}, bla_{TEM-1}, bla_{ADC-67}, *armA*, *aadA1*

SSI, surgical site infection; NLRTI, nosocomial lower respiratory tract infection PIP, piperacillin; TZP, piperacillin/tazobactam; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; DPM, doripenem; MEM, meropenem; ATM, aztreonam; ABK, arbekacin; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; CST, colistin; FOF, fosfomycin; TIG, tigecycline.

Methods

Bacterial strains

Five *P. rettgeri* clinical isolates were obtained from May to July 2012 from 5 patients at Tribhuvan University Teaching Hospital in Kathmandu, Nepal. Three isolates were from sputum and 2 from pus at surgical sites. Samples were obtained as part of standard patient care. Phenotypical identification [17] was confirmed by API 32GN (BioMérieux, Mercy l'Etoile, France) and 16S rRNA sequencing (1,497 bp) [18,19].

Antimicrobial susceptibilities

MICs were determined using the microdilution method, according to the guidelines of the Clinical Laboratory Standards Institute (CLSI) [20]. Breakpoints to antibiotics were determined. The modified Hodge test, the meropenem-sodium mercaptoacetic acid double-disk synergy test (Eiken Chemical, Tokyo, Japan) and E-test (imipenem/EDTA) (AB Biodisk, Solna, Sweden) were performed.

Entire genome sequencing

The entire genomes of these isolates were extracted and sequenced by MiSeq (Illumina, San Diego, CA). CLC genomics workbench version 5.5 (CLC bio, Tokyo, Japan) was used for de novo assembly of reads and to search for 923 drug-resistance genes, including genes encoding β-lactamases, 16S rRNA methylases and aminoglycoside-acethyl/adenylyltransferases; point mutations in the *gyrA*, *parC* and *pmrCAB* operons; and point mutations in the *fos* genes, including *fosA*, *fosA2*, *fosA3*, *fosC* and *fosC2*.

Pulsed-field gel electrophoresis (PFGE) and southern hybridization

PFGE analysis was performed as described [3]. An 813 bp probe for $bla_{\text{NDM-1}}$ was synthesized by PCR amplification using the primers 5′-atggaattgcccaatattatg-cac-3′ (forward) and 5′-tcagcgcagcttgtcggccatgcggg-3′ (reverse), and a 780 bp probe for $bla_{\text{OXA-72}}$ was synthesized using the primers 5′-agtttctctcagtgcatgttcatctat-3′ (forward) and 5′-agaaccagacattccttctttcatttc-3′ (reverse). Southern hybridization to detect $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-72}}$ was performed using these probes, which were detected using DIG High Prime DNA labeling and detection starter kit II (Roche Diagnostics, Mannheim, Germany).

Nucleotide sequence accession numbers

The nucleotide sequences surrounding $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-72}}$ have been deposited in GenBank with the accession number AB828598 and AB857844, respectively.

Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board of the Institute of Medicine, Tribhuvan University (ref. 6-11-E) and the Biosafety Committee, National Center for Global Health and Medicine (approval number: 23-M-49).

Results

Antimicrobial susceptibilities

Four of the 5 isolates were resistant to carbapenems (doripenem, imipenem and meropenem) and piperacillin/tazobactam, whereas the fifth was susceptible to piperacillin/tazobactam, doripenem and meropenem and showed intermediate resistance to imipenem (Table 1). All 5 isolates were highly resistant to cephalosporins (ceftazidime and cefepime), aztreonam, aminoglycosides (arbekacin, amikacin and gentamicin), ciprofloxacin, colistin and fosfomycin, and all 5 showed intermediate resistance to tigecycline. The four isolates resistant to carbapenems were negative with the modified Hodge test, but three of the four isolates were positive with the meropenem-sodium mercaptoacetic acid double-disk synergy test and E-test/EDTA.

Drug-resistant genes

All 5 isolates tested had several genes associated with β-lactam and aminoglycoside-resistance (Table 1). These isolates had $bla_{\text{VEB-1}}$, $bla_{\text{OXA-10}}$, $bla_{\text{TEM-1}}$, $bla_{\text{ADC-67}}$ (*ampC*), *armA* and *aadA1*; 3 had $bla_{\text{NDM-1}}$; and 1 had $bla_{\text{OXA-72}}$. None of these isolates had any other β-lactamase encoding genes, including the class A genes bla_{SHVs} and $bla_{\text{CTX-Ms}}$; the class B genes bla_{AIM}, bla_{DIM}, bla_{FIM}, bla_{GIM}, bla_{IMPs}, bla_{INDs}, bla_{KHM}, bla_{SIM}, bla_{SMB}, bla_{SPM}, bla_{TMBs}, and bla_{VIMs}; or the class D gene bla_{OXAs} except for $bla_{\text{OXA-10}}$ and $bla_{\text{OXA-72}}$. None had other genes encoding 16S rRNA methylases or aminoglycoside acetyl/adenylyltransferases. All 5 isolates had point mutations in the quinolone-resistance-determining regions of *gyrA* and *parC*, with amino acid substitutions of S83I and D87E in GyrA and S80I in ParC, but none had any mutations in the *pmrCAB* operon and *fos* genes. All sequences of the drug-resistant genes tested were identical to those registered in GenBank.

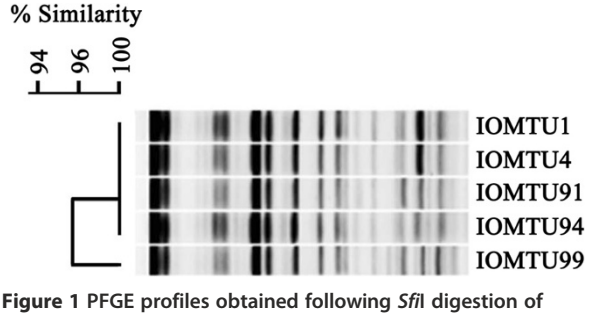

Figure 1 PFGE profiles obtained following *Sfi*I digestion of *P. rettgeri* chromosomes.

PFGE and southern hybridyzation

Of the 5 *P. rettgeri* isolates, 4 had identical PFGE patterns and the fifth showed 95.7% similarity (Figure 1). Three of these isolates had a plasmid harboring $bla_{\text{NDM-1}}$ and one had a plasmid harboring $bla_{\text{OXA-72}}$, with plasmid sizes ranging from 9.42 to 23.1 kbp (data not shown).

Genomic structures surrounding $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-72}}$

The genetic environments surrounding $bla_{\text{NDM-1}}$ (Accession no. AB828598) was $bla_{\text{NDM-1}}$-ble_{MBL}-*trpF-dsbC-cutA1*. All 3 isolates harboring $bla_{\text{NDM-1}}$ (IOMTU1, 91 and 99) had the same genetic environments. The $bla_{\text{OXA-72}}$ gene was flanked by conserved inverted repeats at the XerC/XerD binding sites [21], indicating mobilization by site-specific recombination mechanisms. The *rep1* gene was located downstream of $bla_{\text{OXA-72}}$ (Accession no. AB857844).

Discussion

The relatively high MICs to piperacillin/tazobactam and carbapenems of the five *P. rettgeri* isolates were likely due to the presence of $bla_{\text{NDM-1}}$ or $bla_{\text{OXA-72}}$. The enzymatic activities of metallo-β-lactamases, including NDM-1, were not inhibited by tazobactam [22], a β-lactamase inhibitor, in agreement with the MIC profiles of these isolates to piperacillin/tazobactam. The high MICs of all 5 isolates to ceftazidime, cefepime and aztreonam were likely due to the presence of $bla_{\text{VEB-1}}$ [23], and the presence of *armA* in these isolates was likely associated with their extremely high resistance to all aminoglycosides tested [11]. Point mutations in the quinolone-resistance-determining regions of *gyrA* and *parC* have been associated with high resistance to quinolones [24]. Point mutations in *pmrCAB* operon have been associated with the resistance of *Acinetobacter* spp. [25] and *Pseudomonas aeruginosa* [26] to polymxyin and colistin; and the presence of *fos* genes, including *fosA*, *fosA2*, *fosA3*, *fosC* and *fosC2*, has been associated with resistance to fosfomycin in Gram-negative bacteria [27-29].

Plasmids containing $bla_{\text{NDM-1}}$ or $bla_{\text{OXA-72}}$ may be disseminated among Gram-negative pathogens in Nepal. The genetic environments surrounding $bla_{\text{NDM-1}}$ in our *P. rettgeri* strains ($bla_{\text{NDM-1}}$-ble_{MBL}-*trpF-dsbC-cutA1*) were also observed in other plasmids, including *A. baumannii* plasmid pAbNDM-1 from China (Accession no. JN377410), *Citrobacter freundii* plasmid pYE315203 from China (Accession no. JX254913), *E. coli* plasmid pNDM102337 from Canada (Accession no. JF714412), *K. pneumoniae* plasmid pKP-NCGM18-1 from Nepal (Accession no. AB824738) [30], *K. pneumoniae* plasmids pKPX-1, pKPN5047 and pNDM-HN380 from China (Accession nos. AP012055, KC311431 and JX104760, respectively), and *P. rettgeri* plasmid pFR90 (Accession no. JQ362415) from China. In addition, the genetic structures of OXA-72 producing *Acinetobacter* spp [31-34] and *K. pneumoniae* (Accession no. JX268653 and AB825955 deposited in 2012 and 2013, respectively) had the same genetic structure ($bla_{\text{OXA-72}}$-*rep1*) as our strain of *P. rettgeri*.

Conclusions

To our knowledge, this is the first report describing *P. rettgeri* strains harboring $bla_{\text{NDM-1}}$ or $bla_{\text{OXA-72}}$ and *armA* isolated from patients in Nepal. These 5 strains were highly resistant to both β-lactams and aminoglycosides and expanded in a clonal manner in the hospital.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

TT: Performed PCR and sequencing, analyzed data and drafted the manuscript. TMA: Performed entire genome sequencing. RKD and MKS: Performed drug susceptibility tests. HO: Supervised this study. KS: Performed pulsed-field gel electrophoresis and its pattern analysis. TK and BMP: Designed protocols and supervised this study. All authors read and approved the final manuscript.

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