

First report of neonatal bacteraemia caused by *bla*_{NDM-1} *Raoultella ornithinolytica*

Yesholata Mahabeer^{ab*}, Ashika Singh-Moodley^{cd}, Harshavadan Mackanje^e, Olga Perovic^{cd} and Koleka P Mlisana^{ab} 

^aDepartment of Medical Microbiology, National Health Laboratory Services, Durban, South Africa

^bSchool of Laboratory Medicine and Medical Sciences, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

^cCentre for Opportunistic, Tropical and Hospital Infections, National Institute for Communicable Diseases, Johannesburg, South Africa

^dFaculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

^eDepartment of Paediatrics, Inkosi Albert Luthuli Central Hospital, Durban, South Africa

*Corresponding author, email: mahab@ukzn.ac.za



Raoultella ornitholytica, an environmental organism, has only recently been reported as a cause of infections in humans, and is associated mainly with bacteraemia in elderly patients. Carbapenem resistance is unusual in *Raoultella spp.* We describe the first paediatric case of *bla*_{NDM-1} *Raoultella ornitholytica* bacteraemia in a preterm neonate that developed three days after hospitalisation. This case report discusses a rare organism that had an unexpected susceptibility profile and caused bacteraemia in a neonate. Treatment options are explored.

Keywords: bacteraemia, *bla*_{NDM-1}, carbapenemase, neonate, *Raoultella ornithinolytica*

Introduction

Raoultella spp. are usually found in aquatic environments, were originally categorised within the genus *Klebsiella* and, following DNA-DNA hybridisation studies and sequence analysis of the 16S rRNA gene, *K. planticola* and *K. ornitholytica* were moved into a separate genus, *Raoultella*.¹ *R. planticola* comprised about 9% of *Klebsiella spp.* isolated from rectal and oropharyngeal swabs in a neonatal ward.² *R. ornitholytica* is an unusual human pathogen that is mainly associated with bacteraemia in adults and is a rare cause of infections in neonates.^{3–8}

We describe the first neonate with bacteraemia caused by *bla*_{NDM-1} *Raoultella ornitholytica*, which has only recently been detected in pus from adults.^{9,10} To date, carbapenem resistance has not been reported in paediatric isolates of *R. ornitholytica*.

Case report

A preterm baby born at 33 weeks via a Caesarean section was admitted three days after birth to the neonatal unit at a tertiary hospital in Durban, South Africa, for ventilation due to hyaline membrane disease. His birth weight was 1.78 kg and the Apgar scores were 7 and 8 after one and five minutes, respectively. He received penicillin and gentamicin for three days at a local hospital and, on arrival at the unit, piperacillin/tazobactam plus amikacin was commenced. The septic markers on admission were as follows: white cell count 4.82 x 10⁹ cells/L; neutrophil count 3.66 x 10⁹ cells/L; C-reactive protein 28 mg/L; and procalcitonin 9.92 µg/L. The blood culture taken on admission flagged positive on the Bactec automated blood culture system (bioMérieux SA, France). After overnight incubation, mucoid lactose-fermenting colonies resembling *Klebsiella spp.* were isolated. These were identified as *Raoultella ornitholytica* using matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (bioMérieux SA, France). The Vitek 2 AST N255 card (bioMérieux SA, France) was used for susceptibility testing of the isolate that demonstrated resistance to all beta-lactams and aminoglycosides tested (Table 1). The isolate was susceptible to ciprofloxacin, colistin and tigecycline. Ciprofloxacin was commenced two days later when the susceptibility results were available. DNA was

extracted from the phenotypically carbapenem-resistant isolate using a crude extraction method and screened for *bla*_{NDM-1}, *bla*_{KPC}, *bla*_{OXA-48} and its variants, *bla*_{GES}, *bla*_{IMP} and *bla*_{VIM} using multiplex real-time polymerase chain reaction (PCR) (LightCycler 480 II (Roche Applied Science, USA), LightCycler 480 Probes master kit (Roche Diagnostics, USA) and the individual LightMix modular kits (Roche Diagnostics, USA)) were used as per manufacturer's instructions. The PCR confirmed the presence of *bla*_{NDM-1}. The patient was extubated eight days after admission and transferred back to the base hospital on ciprofloxacin. The significance of this isolate was unclear and we were unable to find a focus for the organism. It is possible that this may have been a contaminant, but as the patient was clinically septic at the time of the culture, the organism was thought to be significant and treatment was commenced. There was no epidemiological link to other patients with infections caused by organisms harbouring *bla*_{NDM-1}.

Table 1: Antibiogram of *Raoultella ornithinolytica*

Antimicrobial agent	MIC (µg/ml)
Ampicillin	≥32
Amoxicillin/clavulanic acid	≥32
Piperacillin/tazobactam	≥128
Cefuroxime	≥64
Cefoxitin	≥64
Cefotaxime	≥64
Ceftazidime	≥64
Imipenem	≥16
Meropenem	≥16
Amikacin	≥64
Gentamicin	≥16
Ciprofloxacin	1
Tigecycline	2
Colistin	≤0.5
Trimethoprim/sulfamethoxazole	≥320

Discussion

R. ornitholytica has only recently been described as a human pathogen with most infections occurring in adults.^{3–5,9,10} The most common infection caused by *R. ornitholytica* is bacteraemia. A review of cases of bacteraemia found that most patients were elderly or had biliary tract disease.^{3–5} Apart from bacteraemia, *R. ornitholytica* has also caused urinary tract, skin and soft tissue infections, as well as pyrexia of unknown origin and enteric disease.^{8–14}

Three cases of *R. ornitholytica* infections in children, two of which occurred in neonates, have been published.^{6–8} Mau *et al.* reported that a neonate who presented with heterotaxy and asplenia had *R. ornitholytica* isolated from blood culture. The patient was commenced on meropenem and amikacin, and subsequently improved.⁶ The second neonate was a preterm baby who developed severe sepsis and purpura fulminans. *R. ornitholytica* was isolated from a blood culture and despite being treated with meropenem, the patient demised.⁷ Sener *et al.* described a 16 month old patient with fever of unknown origin in whom *R. ornitholytica* was isolated from broncho-alveolar lavage fluid. The child recovered after treatment with aminopenicillin plus clavulanate.⁸ In all these cases, skin manifestations were present which were described as skin flushing and urticarial plaques, which are thought to be due to histamine release. These findings were absent in our patient. Furthermore, all these isolates were susceptible to carbapenems while our isolate was resistant.

Raoultella spp are often susceptible to most beta-lactam agents, however isolates that produce extended-spectrum beta-lactamases and carbapenemases have emerged.^{9,10,14–17} In 2009, Castenheira *et al.* first described two cases of *R. planticola* and one case of *R. ornitholytica* containing *bla*_{KPC-2} and *bla*_{KPC-3} from a surveillance study conducted in USA.¹⁴ Khajuria *et al.* reported a case of *R. ornitholytica* which carried *bla*_{NDM-1} gene that caused a surgical site infection.⁹ The patient recovered after treatment with tigecycline. Recently, Zhou *et al.* conducted a retrospective analysis of carbapenem resistant *Enterobacteriaceae* in China and detected *bla*_{NDM-1} gene in *R. ornitholytica* isolated from an abscess.¹⁰ In both these cases of *bla*_{NDM-1} *R. ornitholytica*, the organism was isolated 48–72 h after hospitalisation, which is in keeping with our case.

The optimal treatment of carbapenemase-producing *Enterobacteriaceae* is unclear. Current recommendations include combination regimens that are either carbapenem-containing or carbapenem-sparing, based on carbapenem MICs.^{18,19} Prolonged carbapenem infusion with aminoglycosides, tigecycline or quinolones is suggested for organisms that have carbapenem MICs ≤ 8 µg/ml. If carbapenem MICs are higher, then colistin should be combined with aminoglycosides, tigecycline or quinolones based on susceptibility. Combination therapy is advised because lower mortality rates were observed compared to colistin monotherapy in small retrospective studies.^{18,19} It is postulated that colistin monotherapy results in selection for resistance and bacterial regrowth.^{18,19}

Identification of *Raoultella spp* may be problematic. They need to be differentiated from *Klebsiella spp*, especially *K. oxytoca* with which there is much similarity. Furthermore, differentiation of *R. planticola* from *R. ornitholytica* is often difficult in a routine microbiology laboratory. Conventional biochemical testing using API-20E strip (bioMérieux, France) and Vitek 2 (bioMérieux, France) has been used by authors previously.^{6,9,13} Vitek 2 correctly identified four *R. ornitholytica* isolates during an evaluation of the

Gram-negative card.²⁰ Park *et al.* found that Vitek 2 also compared well with sequence-specific primer PCR, while API-20E needed additional confirmatory testing.²¹ Walckenaer *et al.* described amplification of the *bla* gene as a reliable tool for identification of *Raoultella spp.*²² Matrix-assisted laser desorption/ionisation-time of flight mass spectrometry has been shown to differentiate *R. ornitholytica/planticola* and *K. oxytoca*,²³ which we also used to identify the isolate. A possible limitation of our report is that we did not use 16S rRNA sequencing, which is not widely available at our institution, to confirm the identification of the isolate.

We describe the first case of *bla*_{NDM-1} *Raoultella ornitholytica* in a neonate. This case highlights both an unusual organism causing neonatal bacteraemia, and an unexpected susceptibility profile of the isolate.

Note

i Presented at 6th FIDSSA congress, Drakensberg, South Africa, 5–8 November 2015.

ORCID

Koleka P Mlisana  <http://orcid.org/0000-0002-8436-3268>

References

- Drancourt M, Bollet C, Carta A, et al. Phylogenetic analyses of *Klebsiella* species delineate *Klebsiella* and *Raoultella* gen. nov., with description of *Raoultella ornitholytica* comb. nov., *Raoultella terrigena* comb. nov and *Raoultella planticola* comb. nov. *Int J Syst Evol Microbiol.* 2001;51:925–32.
- Podschun R, Acktun H, Okpara J, et al. Isolation of *Klebsiella planticola* from newborns in a neonatal ward. *J Clin Micro.* 1998;36:2331–2.
- Haruki Y, Hagiya H, Sakuma A, et al. Clinical characteristics of *Raoultella ornitholytica* bacteremia: a case series and literature review. *J Infect Chemother.* 2014;20:589–91. <https://doi.org/10.1016/j.jiac.2014.05.005>
- de Jong E, Erkens-Hulshof S, van der Velden LBJ, et al. Predominant association of *Raoultella* bacteremia with diseases of the biliary tract. *Scand J Infect Dis.* 2014;46:141–3. <https://doi.org/10.3109/00365548.2013.857044>
- Chun S, Yun JW, Huh HJ, et al. Clinical characteristics of *Raoultella ornitholytica* bacteremia. *Infection.* 2015;43:59–64. doi: 10.1007/s15010-014-0696-z.
- Mau N, Ross LA. *Raoultella ornitholytica* bacteremia in an infant with visceral heterotaxy. *Pediatr Infect Dis J.* 2010;29:477–8. <https://doi.org/10.1097/INF.0b013e3181ce9227>
- Sandal G, Ozen M. Fatal *Raoultella ornitholytica* sepsis and purpura fulminans in a preterm newborn. *Indian J Paediatr Dermatol.* 2014;15:24–6. <https://doi.org/10.4103/2319-7250.131833>
- Sener D, Cokhras H, Camcioglu Y, et al. *Raoultella* infection causing fever of unknown origin. *Pediatr Infect Dis J.* 2011;30:1122–3. <https://doi.org/10.1097/INF.0b013e31822bf4f6>
- Khajuria A, Praharaj AK, Grover N, et al. First report of *bla*(NDM-1) in *Raoultella ornitholytica*. *Antimicrob Agents Chemother.* 2013;57:1092–3. <https://doi.org/10.1128/AAC.02147-12>
- Zhou G, Guo S, Luo Y, et al. NDM-1-producing Strains, Family *Enterobacteriaceae*, in Hospital, Beijing, China. *Emerg Infect Dis.* 2014;20:340–2. <https://doi.org/10.3201/eid2002.121263>
- Garcia-Lozano T, Pascual Pla FJ, Aznar Oroval E. *Raoultella ornitholytica* in urinary tract infections. Clinical and microbiological study of a series of 4 oncologic patients. *Medic Clin.* 2013;141:138–9. <https://doi.org/10.1016/j.medcli.2012.11.021>
- Solak Y, Gul EE, Atalay H, et al. A rare human infection of *Raoultella ornitholytica* in a diabetic foot lesion. *Ann Saudi Med.* 2011;31:93–4.
- Morais VP, Daporta MT, Bao AF, et al. Enteric fever-like syndrome caused by *Raoultella ornitholytica* (*Klebsiella ornitholytica*). *J Clinical Microbiol.* 2009;47:868–9. <https://doi.org/10.1128/JCM.01709-08>
- Castanheira M, Deshpande LM, DiPersio JR, et al. First descriptions of *bla*(KPC) in *Raoultella spp.* (*R. planticola* and *R. ornitholytica*): report from the SENTRY antimicrobial surveillance program. *J Clinical Microbiol.* 2009;47:4129–30. <https://doi.org/10.1128/JCM.01502-09>

15. Osterblad M, Kirveskari J, Hakanen AJ, et al. Carbapenemase-producing Enterobacteriaceae in Finland: the first years (2008–11). *J Antimicrob Chemother.* 2012;67:2860–4. <https://doi.org/10.1093/jac/dks299>
16. Tseng S-P, Wang J-T, Liang C-Y, et al. First Report of bla(IMP-8) in *Raoultella planticola*. *Antimicrob Agents Chemother.* 2014;58:593–5. <https://doi.org/10.1128/AAC.00231-13>
17. Li J, Lan R, Xiong Y, et al. Sequential isolation in a patient of *Raoultella planticola* and *Escherichia coli* bearing a novel ISCR1 element carrying blaNDM-1. *PLoS ONE.* 2014;9:e89893. doi: 10.1371/journal.pone.0089893.
18. Hsu AJ, Tamma PD. Treatment of multidrug-resistant gram-negative infections in children. *Clin Infect Dis.* 2014;58:1439–48. doi: 10.1093/cid/ciu069.
19. Yamamoto M, Pop-Vicas AE. Treatment for infections with carbapenem-resistant Enterobacteriaceae: what options do we still have? *Crit Care.* 2014;18:229. doi: 10.1186/cc13949.
20. Renaud FNR, Bergeron E, Tigaud S, et al. Evaluation of the new Vitek 2 GN card for the identification of gram-negative bacilli frequently encountered in clinical laboratories. *Eur J Microbiol Infect Dis.* 2005;24:671–6. <https://doi.org/10.1007/s10096-005-0026-6>
21. Park JS, Hong KH, Lee HJ, et al. Evaluation of three phenotypic identification systems for clinical isolates of *Raoultella ornithinolytica*. *J Med Microbiol.* 2011;60:492–9. <https://doi.org/10.1099/jmm.0.020768-0>
22. Walckenaer E, Leflon-Guibout V, Nicolas-Chanoine M-H. How to identify *Raoultella* spp. including *R. ornithinolytica* isolates negative for ornithine decarboxylase? The reliability of the chromosomal bla gene. *J Microbiol Methods.* 2008;75:405–10. <https://doi.org/10.1016/j.mimet.2008.07.011>
23. de Jong E, de Jong AS, Smidts-van den Berg RJ, et al. Differentiation of *Raoultella ornithinolytica/planticola* and *Klebsiella oxytoca* clinical isolates by matrix-assisted laser desorption/ionization-time of flight mass spectrometry. *Diagn Microbiol Infect Dis.* 2013;75:431–3. <https://doi.org/10.1016/j.diagmicrobio.2012.12.009>

Received: 02-03-2016 Accepted: 06-07-2016