NDM-1 imported from India – first reported case in South Africa

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Carbapenem-resistant *Enterobacteriaceae* have been increasingly reported throughout the world. The first South African report of a New Delhi metallo-beta-lactamase was from Gauteng in August 2011. Despite maintaining a high degree of vigilance, the first such case was seen in KwaZulu-Natal almost a year later. Other cases have been unable to confirm a definite link to any other affected areas; this is the first case in South Africa showing this direct epidemiological link.

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Carbapenems have long been a reliable last line of defence in the treatment of infections caused by antimicrobial-resistant *Enterobacteriaceae*. However, the emergence of resistance in *Enterobacteriaceae* mediated via carbapenemases is a major public health concern as these isolates show resistance to antibiotics commonly used to treat Gram-negative infections.[1] Furthermore, these highly resistant strains have been shown to have the propensity to spread rapidly.[2] A large variety of carbapenemases belonging to 3 classes of β-lactamases have been identified in *Enterobacteriaceae*: the Ambler class A, B and D β-lactamases. Carbapenem resistance as a result of *Klebsiella pneumoniae* carbapenemase (KPC; Class A), New Delhi metallo-beta-lactamase-1 (NDM-1; Class B) and OXA-subtypes (Class D) are thought to occur at low levels in Africa.[1]

The first case of NDM-1 carbapenem resistance in South Africa (SA) occurred in August 2011[3] and was reported from a hospital in Johannesburg. The first documented case of NDM-1-producing *Enterobacteriaecae* in KwaZulu-Natal (KZN), SA, is reported here and documents a direct epidemiological link to the Indian subcontinent.

Method and results

Case report

A 61-year-old woman presented to her general practitioner on 2 November 2012 for removal of a urinary catheter. She had been hospitalised in India from 21 to 24 October for management of a fractured femur. Antibiotics administered intra-operatively included cephalosporins and amikacin. Of note, urine submitted on admission to the hospital in India revealed no abnormalities. She was discharged on cefuroxime axetil 500 mg twice daily for 1 week. She returned to South Africa on 1 November 2012 with a urinary catheter *in situ* (for ease of travel on the flight). On removal of the catheter the following day, her urine was noted to be turbid. She was, nevertheless, apyrexial and otherwise asymptomatic. There were no associated comorbid conditions. Urine dipstix revealed leucocyte esterase, prompting treatment with 3 doses of 3 g fosfomycin administered 2 days apart. A midstream urine specimen was sent to the laboratory.

Laboratory investigations

Urine microscopy revealed 10 red blood cells and 9 leucocytes/high-power field. Culture revealed *Enterobacter cloacae* with the susceptibility pattern outlined in Table 1. Identification was confirmed using the automated Vitek 2 system (Biomerieux, Johannesburg, SA). Susceptibility testing was performed using the Kirby Bauer method and the Vitek 2 system. All susceptibility test results were interpreted using Clinical and Laboratory Standards Institute (CLSI) 2012 guidelines,[4] except for tigecycline and colistin for which the 2012 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used.[5] Carbapenem and tigecycline minimum inhibitory concentrations (MICs) were determined by using E-tests (Biomerieux, South Africa) on Mueller-Hinton agar. Carbapenemase activity was suggested by the Vitek 2 expert system and confirmed by a positive modified Hodge test (CLSI guidelines 2012). A validated commercially available real-time PCR assay (Shanghai ZJ Bio-Tech) was used for the detection of New Delhi metallo-beta-lactamase 1 (NDM-1). DNA was extracted from culture, amplified and detected using a labelled primer/probe set. Inhibition was monitored by the use of an internal control. The isolate was confirmed NDM-1 positive. This result was verified by the National Institute for Communicable Diseases by multiplex real-time PCR using the LightCycler 480 Probes Master kit (Roche Diagnostics, USA). Repeat urine on 15 November 2012 showed no abnormalities and a negative culture.

Discussion

NDM-1 was first detected in an isolate of *Klebsiella pneumoniae* from a Swedish patient of Indian origin in 2008.[6] It was subsequently detected in *Enterobacteriaceae* in India, Pakistan, the UK, USA, Canada, Japan, Brazil and Africa.[7,8,10] The first documented report of NDM-1 in *Enterobacteriacae* in SA was from Gauteng in August 2011.[3] The case presented here is the first documented case in KwaZulu-Natal, SA.

With increasing resistance among the *Enterobacteriaceae* to various classes of antimicrobial agents, carbapenems have formed

Table 1. Antimicrobial susceptibility test results: *Enterobacter cloacae* NDM-1 positive

	Susceptibility test results			
	Vitek 2	Interpretation	E-test	Interpretation
Antimicrobial agents	MIC (μg/ml)	S/I/R	MIC (μg/ml)	S/I/R
Ampicillin	≥32	R	NT	
Amoxycillin-clavulanic acid	≥32	R	NT	
Piperacillin-tazobactam	≥128	R	NT	
Cefepime	≥64	R	NT	
Ceftriaxone	≥64	R	NT	
Cefoxitin	≥64	R	NT	
Cefuroxime	≥64	R	NT	
Ceftazidime	≥64	R	NT	
Doripenem	NT		16	R
Ertapenem	≥8	R	NT	
Imipenem	≥16	R	12	R
Meropenem	≥16	R	24	R
Gentamicin	≥16	R	NT	
Amikacin	≥32	R	NT	
Tigecycline*	NT		0.5	S
Ciprofloxacin	≥4	R	NT	
Cotrimoxazole	≥320	R	NT	
Fosfomycin†	NT		NT	
Colistin*	≤2	S	NT	

S = susceptible; I = intermediate; R = resistant; NT = not tested; MIC = minimum inhibitory concentration.
*EUCAST 2012 interpretive criteria.
†Susceptible by CLSI zone diameter interpretive criteria for *E. coli*.

the backbone of treatment. The emergence of novel β-lactamases with direct carbapenem-hydrolysing activity has contributed to an increased prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE). These are usually accompanied by resistance mechanisms to other classes of antibiotics, thereby posing an additional therapeutic challenge.[8] CREs are a significant threat for a number of reasons: the frequency with which they cause infections, the high mortality with which they are associated[9] and the potential for their widespread transmission via mobile genetic elements.[8] The NDM-1 gene found on a plasmid is highly transmissible to other bacteria. NDM-1-positive bacteria are capable of colonising the gastro-intestinal tract of humans for prolonged periods and are spread through contamination of water and environmental surfaces.[6] The ease and frequency of international travel has contributed additionally to rapid global dissemination.

Current data suggest that recent hospitalisation in, and perhaps even travel to, the Indian subcontinent be identified as a risk factor for colonisation with the NDM-1-producing strain,[8,11] recognising that medical care is often sought by individuals visiting relatives in India and Pakistan. A recent case of NDM-1-producing *Providencia rettgeri* in an Australian who received elective plastic surgery in India illustrates this phenomenon.[10] Despite these factors, there are very few cases with a confirmed epidemiological link.[11] In the editorial by Coetzee *et al*., on the emergence of CREs in SA, the origin of the NDM-1s was not determined.[12] In the light of the KZN case, strong consideration should be given to screening patients (testing of rectal swabs for detection of NDM-1 carriage) with a history of recent hospitalisation in the Indian subcontinent who present for medical care. Given that NDM-1 is a globally emerging phenomenon, a case might be made for routine screening for CRE colonisation in patients after recent hospitalisation overseas and in those recently admitted to hospitals in Gauteng and Cape Town, since, following the first reported case in Gauteng, that outbreak has been ongoing.

It is also important to note that other molecular mechanisms of carbapenem resistance have been reported in SA, *viz*. OXA-48, KPC, VIM and GESs.[13] Early recognition and reporting provides an opportunity to establish national measures to prevent such isolates becoming endemic in healthcare settings. Owing to the limited therapeutic options available, early identification of CREs and timely isolation and infection control measures are key to curtailing the spread of these organisms. Concerns about carbapenemases justify a high index of suspicion in diagnostic laboratories and the routine screening of all clinically significant *Enterobacteriaceae* for susceptibility to carbapenem agents. Rapid detection is essential for patient management and prevention of further transmission, with the aim of limiting the public health impact of these extremely drug-resistant strains.

Conclusion

To our knowledge, this is the first documented case of an NDM-1 *Enterobacteriacea* in KZN and the first case in SA where a direct epidemiological link to the Indian subcontinent has been established. Since the detection of this isolate, other cases in several hospitals have been identified. Ongoing vigilance and strict infection control measures need to be maintained.

References

1. Chen LF, Anderson DJ, Paterson DL. Overview of the epidemiology and the threat of *Klebsiella pneumonia* carbapenemases (KPC) resistance. Infect Drug Resist 2012;5:133-141. [http://dx.doi.org/10.2147/IDR.S26613]
2. Kumarasamy K, Thirunarayan MA, Krishnan P. Coexistence of blaOXA-23 with blaNDM-1 and armA in clinical isolates of *Acinetobacter baumanii* from India. J Antimicrob Chemother 2010;65:2253-2254. [http://dx.doi.org/10.1093/jac/dkq273]
3. W Lowman, C Sriruttan, T Nana, et al. NDM-1 has arrived: First report of a carbapenem resistance mechanism in South Africa. S Afr Med J 2011;101(12):873-875.
4. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-second informational supplement. CLSI document M100-S22. Wayne, PA, USA: CLSI, 2012.
5. European Committee on Antimicrobial Susceptibility Testing (Eucast) documents. Document version 2.0 2012-01-01; 2012. http://www.eucast.org/clinical_breakpoints/ (accessed 14 November 2012).
6. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla (NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrob Agents Chemother 2009;53:5046-5054. [http://dx.doi.org/10.1128/AAC.00774-09]
7. Poirel L, Revathi G, Bernabeu S, Nordmann P. Detection of NDM-1-producing *Klebsiella pneumoniae* in Kenya. Antimicrob Agents Chemother 2011;55:934-936. [http://dx.doi.org/10.1128/AAC.01247-10]
8. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10:597-602. [http://dx.doi.org/10.1016/S1473-3099(10)70143-2]
9. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 2008;52:1028-1033. [http://dx.doi.org/10.1128/AAC.01020-07]
10. Walsh T. New Delhi metallo-β-lactamase-1: Detection and prevention. CMAJ 2011;183(11):1240-1241. [http://dx.doi.org/10.1503/cmaj.111100]
11. Borgia S, Lastovetska O, Richardson D, et al. Outbreak of carbapenem-resistant *Enterobacteriacae*- containing blaNDM-1, Ontario, Canada. Clin Infect Dis 2012;55:e109-117. [http://dx.doi.org/10.1093/cid/cis737]
12. Coetzee J, Brink A. The emergence of carbapenem resistance in *Enterobacteriaceae* in South Africa. S Afr J Epidemiol Infect 2011;26(4):239-240.
13. Brink A, Coetzee J. The spread of carbapenem-resistant *Enterobacteriacea* in South Africa: Risk factors for acquisition and prevention. S Afr Med J 2012;102(7):599-601.

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