The perils of medical tourism: NDM-1-positive *Escherichia coli* causing febrile neutropenia in a medical tourist

Chan H L E, Poon L M, Chan S G, Teo J W P

ABSTRACT

NDM-1 is a new metallo-beta-lactamase that readily hydrolyses carbapenems, penicillins and cephalosporins. Its rising incidence has been reported in many countries around the world, with many cases linked to a possible origin from the Indian subcontinent. Due to the lack of effective antibiotic regimes to treat these infections, the increased prevalence of NDM-1 is alarming. We describe a case of NDM-1 infection in an immunocompromised foreign patient, and discuss its implications.

Keywords: medical tourism, NDM-1

Singapore Med J 2011;52(4):299-302

INTRODUCTION

Carbapenems are currently recommended as a first-line therapy for severe infections caused by Enterobacteriaceae-producing extended spectrum beta-lactamases (ESBLs).[1] However, carbapenem resistance has been increasingly reported around the world; this is a real cause of concern, as severe infections caused by such bacteria are virtually impossible to treat with antibiotics. This problem is compounded by the slow development of new antimicrobial agents to treat these emerging resistant infections.[2]

Beta-lactamase enzymes usually exist as monomeric enzymes, although a few do exist as dimers or tetramers. They are categorised into two classification schemes, Bush-Jacob (Group 1–3) and Ambler (Class A–D). The Bush system is a functional classification that has been recently updated.[3] Groups 1–3 represent cephalosporinases, serine beta-lactamases and metallo-beta-lactamases (MBLs), respectively. In the Ambler classification,[4-6] these enzymes are classified by their protein sequence. Class A, C and D enzymes contain serine-based amino acid sequences, while Class B enzymes, the MBLs, require a bivalent metal ion, usually zinc, for activity.[7] The MBLs are subclassified as B1–B3 according to the specific active site, and they are a diverse group of enzymes with many differences among them. New Delhi MBL 1 (NDM-1) is a new subclass of B1 MBL that is commonly found within a transmissible genetic element encoding multiple resistance genes. The majority of NDM-1-positive bacteria carry this genetic element on conjugative plasmids of variable sizes. NDM-1 has been found in many different host species, although the most frequently encountered are *Escherichia (E.) coli* and *Klebsiella (K.) pneumoniae*.[8,9] NDM-1 was first described in a 59-year-old Swedish man of Indian origin who was first hospitalised in Punjab, then in New Delhi, where he was operated on for a large gluteal abscess. A carbapenem-resistant MBL-producing *K. pneumoniae* was detected from this man's urine culture on January 9, 2008.[10] Subsequent cultures from the same patient did not recover the same isolate, but researchers discovered instead an MBL-positive *E. coli* isolate NF-NDM-1.

What is particularly alarming about NDM-1 is that it appears to be highly transmissible; NDM-1-positive was recognised as the predominant carbapenemase-producing Enterobacteriaece in the United Kingdom, accounting for 44% of carbapenemase producers in 2009, just one year after it was first isolated.[8] This publication raises an alert regarding NDM-1 across Europe, and assessments of NDM-1-producing bacteria have been carried out among many European countries.[9] A total of 77 cases were reported from 13 countries between 2008 and 2010, out of which 31 cases had a history of hospitalisation in either India or Pakistan.

As of today, NDM-1-containing Enterobactericeae isolates have been reported in several countries worldwide, including Singapore, the United States, Israel, Turkey, China, India, Japan, Kenya, Australia, France and Taiwan. Many of these cases were isolated from patients who had a positive travel history to India, with or without receiving medical care.[9-11] In Singapore, at least eight patients have been colonised or infected by NDM-1-positive Enterobacteriaceae since it was first discovered here last year in September 2010; however, many of the later cases have no apparent history of travel to the Indian subcontinent.[12]

We describe the first local mortality associated with complications following an infection by NDM-1-positive

Department of Haematology-Oncology, National Univeristy Hospital, 1E Lower Kent Ridge Road, NUHS Tower Block Level 7, Singapore 119228

Chan HLE, MBBS, MRCP
Registrar

Poon LM, MBBS, MRCP
Associate Consultant

Department of Laboratory Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074

Chan SG, MBBS, MRCP, FRCP
Registrar

Teo JWP, PhD
Scientific Officer

Correspondence to:
Dr Esther HL Chan
Tel: (65) 6779 5555
Fax: (65) 6779 5678
Email: esther.
hl.chan@gmail.com

E. coli bacteraemia. This occurred in a neutropenic patient who was newly diagnosed with acute lymphoblastic leukaemia (ALL); this patient had also travelled from the Indian subcontinent to Singapore for further treatment. The implications of this case are further discussed.

CASE REPORT

A 46-year-old Bangladeshi woman was admitted to our institution on October 18, 2010. She had first been hospitalised in Dhaka from October 4–14, 2010 where she had been diagnosed with ALL following bone marrow examination (BMA) for pancytopenia associated with fever and myalgia. In Dhaka, she was initially treated with oral cephalexin for fever, but was subsequently escalated to intravenous (IV) cefepime and gentamicin in view of unremitting fever and neutropenia. All bacterial cultures (including blood and sputum cultures) done in Bangladesh tested negative. The patient subsequently arrived in Singapore for further treatment.

On admission, the patient was febrile and lethargic but not toxic. She was prescribed IV piperacillin/tazobactam as per the febrile neutropenia protocol at our institution. A repeat BMA was carried out, which confirmed a diagnosis of Common ALL antigen (CALLA)-positive B-cell ALL. Repeat cultures done on admission were negative, and the patient's temperature settled after three days of antibiotics. She was thus started on definitive chemotherapy (HYPERCVAD#1A) on the fifth day of hospitalisation. Piperacillin/tazobactam was discontinued after seven days and oralised to amoxicillin/clavulanate and levofloxacin. However, on Day 6 of her chemotherapy (Day 10 of hospitalisation), the patient developed a new spike in fever, with blood cultures positive for a Gram-positive coccus and a Gram-negative rod. Her antibiotic therapy was escalated to IV vancomycin and imipenem while waiting for the final culture and susceptibility testing results.

On Day 12 of hospitalisation, multidrug-resistant bacteria, including carbapenem-resistant *E. coli* (Table I) and *Staphylococcus (S.) haemolyticus*, were isolated from her blood cultures. Blood cultures were performed by the BacT/Alert automated system (bioMérieux Inc, Durham, NC, USA). The isolates were identified by the Vitek 2 system (bioMérieux Inc) as *S. haemolyticus* and *E. coli*. Susceptibilities by the Vitek 2, intepreted using the EUCAST guidelines 2010, showed *E. coli* to be resistant to multiple antimicrobials, including carbapenems. Imipenem and meropenem resistance was confirmed by the performance of Etests (AB bioMérieux, Askim, Sweden), which gave minimum inhibitory concentrations of > 32 mg/l and 24 mg/l, respectively.

Table I. Sensitivities of multidrug-resistant *Escherichia coli*.

Antibiotic	MIC	Sensitivity
Tigecycline (mg/l)	≤ 0.5	Sensitive
Amipicillin (mg/l)	≥ 32	Resistant
Ceftriaxone†		Resistant
Ceftazidime (mg/l)	≥ 64	Resistant
Imipenem* (mg/l)	>32	Resistant
Meropenem* (mg/l)	24	Resistant
Gentamicin (mg/l)	≥ 16	Resistant
Amikacin (mg/l)	≥ 64	Resistant
Polymyxin B (mg/l)	0.5	Sensitive
Ciprofloxacin (mg/l)	≥ 4	Resistant
Cotrimoxazole (mg/l)	≥ 320	Resistant
Ertapenem (mg/l)	≥ 8	Resistant
Fosfomycin (mg/l)	0.380	Sensitive

† Inferred from cefotaxime MIC.
* MIC results by Etest, while the rest of the MIC results by Vitek 2.
MIC: minimum inhibitory concentration

Polymerase chain reaction detection performed on the carbapenem-resistant cultures was positive for the bla$_{NDM}$-1 gene using the primers NDM1 FOR (5'-CAACTGGATCAAGCAGGAGA-3') and NDM1 REV (5'-TCGATCCCAACGGTGATATT-3'). The primers were designed according to the sequence of the bla$_{NDM}$-1 gene of the GenBank database. The patient's respiratory culture also tested positive for the same *E. coli*. High-dose IV tigecycline was prescribed and the patient's peripherally inserted central catheter was removed. However, on the same night, her condition deteriorated and she was sent to the medical intensive care unit (MICU). IV polymyxin B was additionally prescribed.

Although the bacteraemia was successfully cleared, the patient's treatment course was challenging and complicated. In addition to requiring dialysis for severe renal impairment likely secondary to polymyxin B, she had probable invasive aspergillosis and an upper airway obstruction that required a tracheostomy. She finally succumbed to sepsis from a perforated viscus four weeks after hospitalisation.

DISCUSSION

This is the first case of NDM-1-positive *E. coli* bacteraemia occurring in a patient with febrile neutropenia reported in the world, and the first local mortality resulting from complications associated with infection by such bacteria. Post-chemotherapy febrile neutropenia is a medical emergency associated with significant mortality, particularly when the causative agent is a multidrug-resistant Gram-negative bacteria.[13] The management of febrile neutropenia caused by carbapenem-resistant Gram-negative bacteria is a

formidable challenge, given the vulnerable host immune system and the lack of safe and/or effective antibiotics against such pathogens. Our patient developed acute renal impairment requiring renal replacement therapy following high-dose polymyxin B therapy, and this undoubtedly contributed to her demise.

From a more macroscopic perspective, an increasing prevalence of NDM-1-positive Enterobacteriaceae-causing febrile neutropenia would complicate the design of antibiotic regimens for the management of this condition, as most of these bacteria are also concomitantly multidrug-resistant, including to aminoglycosides. A balance between safe and generally effective antibiotics (i.e. beta-lactam antibiotics that NDM-1-positive Enterobacteriaceae are resistant to) versus antibiotics that are effective against NDM-1 (i.e. tigecycline and polymyxin B) is hard to achieve, and the impact of such combinations has not been thoroughly studied. Tigecycline is bacteriostatic, has little anti-pseudomonal activity and may not achieve significant levels for the treatment of Gram-negative bacteraemia at conventional dosing regimens.[14] Polymyxin B is relatively more toxic and may well be less effective compared to beta-lactams.[15]

The spread of such bacteria in haematology-oncology units is of particular concern, given that many patients are severely immunocompromised. Our patient was initially nursed in a ward where all the patients were either undergoing chemotherapy or stem cell transplantation. Many were also neutropenic. She was subsequently transferred to the MICU, where all the patients were critically ill and fitted with invasive devices. Fortunately, with reverse barrier nursing, full contact precautions and the use of personal protective equipment, no other cases of NDM-1 infection have been isolated from these wards after a period of two months.

Contact precautions and active surveillance cultures have been shown to reduce infections with multidrug-resistant Gram-negative organisms in an outbreak setting.[16] However, the role of surveillance cultures in a non-outbreak setting has not been shown to have a significant impact on both colonisation and infection rates.[17] There is currently insufficient data to guide infection control of these multidrug-resistant Gram-negative organisms; hence, the measures suggested vary according to the prevalence of these infections.[18]

As there have only been sporadic cases of NDM-1 infections reported in Singapore and our patient had been warded in a single room from the time of admission, we did not perform any active surveillance cultures for NDM-1. We opted instead for strict infection control

measures, including the briefing of all staff involved in the patient's care and close monitoring of any possible spread of NDM-1 infection among the high-risk patients housed in the same wards as our patient. As no other cases of NDM-1 infection in our hospital have emerged since then, this approach may be an effective infection control measure for multidrug-resistant Gram-negative organisms in a non-outbreak setting.

With increasing globalisation, travel is made more convenient with the establishment and expansion of new airline routes. Foreign countries are now easily accessible, with many being only a few hours away by flight. This has opened up a whole new industry of medical tourism. However, with medical tourism comes the risk of transmission of multi-resistant superbugs from the patient's country of origin. It may thus be advisable to screen patients from endemic countries on admission and to practise full contact precautions while awaiting the results of the screen. In our case, full contact precautions were not taken until she was confirmed to have NDM-1 *E. coli* septicaemia. This delay might have potentially resulted in an outbreak of NDM-1 in the high-risk wards where our patient was warded.

In conclusion, this case highlights the harsh realities of clinical practice; managing febrile neutropenia secondary to a new strain of multidrug-resistant Gram-negative organism, NDM-1. As the prevalence of NDM-1 is high in the Indian subcontinent, this organism is likely to have colonised the immunocompromised medical tourist when she was initially warded. It is thus important to be aware of current infection trends globally in the wake of the boom in medical tourism. Due to the potentially high mortality and morbidity associated with these multidrug-resistant organisms, the importance of effective antimicrobial therapy and infection control measures to manage these difficult cases cannot be overemphasised. As current data is still lacking, we await the result of more studies to guide future strategies in the management of these multidrug-resistant organisms.

REFERENCES

1. Nicaso AM, Kuti JL, Nicolau DP. The current state of multidrug-resistant gram-negative bacilli in North America. Pharmacotherapy 2008; 28:235-49.
2. Infectious Diseases Society of America. Bad Bugs, No Drugs as Antibiotic Discovery Stagnates … A Public Health Crisis Brews, July 2004. In: Infections Diseases Society of America (IDSA) [online]. Available at: www.idsociety.org/10x20.htm. Accessed April 15, 2011.
3. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother 2010; 54:969-76.
4. Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci 1980; 289:321-31.
5. Jaurin B, Grundstrom T. ampC cephalosporinase of Escherichia

coli K-12 has a different evolutionary origin from that of beta-lactamases of the penicillinase type. Proc Natl Acad Sci USA 1981; 78:4897-901.

6. Ouellette M, Bissonnette L, Roy PH. Precise insertion of antibiotic resistance determinants into Tn21-like transposons: nucleotide sequence of the OXA-1 beta-lactamase gene. Proc Natl Acad Sci USA 1987; 84:7378-82.

7. Bush K. Metallo-enzymes: a class apart. Clin Infect Dis 1998; 27 suppl 1:S48-S53.

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.

9. Struelens M, Monnet D, Magiorakos A, et al. New Delhi metallo-beta-lactamase 1-producing Enterobacteriaceae: emergence and response in Europe. Euro Surveill 2010; 15 pii:19716.

10. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-β-lactamase gene, blaNDM-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; 53:5046-54.

11. Centers for Disease Control and Prevention (CDC). Detection of Enterobacteriaceae isolates carrying metallobeta-lactamase - United States, 2010. MMWR Morb Mortal Wkly Rep 2010; 59:750.

12. Koh TH, Khoo CT, Wijaya L, et al. Global spread of New Delhi metallo-β-lactamase 1. Lancet Infect Dis 2010; 10:828.

13. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteraemia: impact of severe neutropenia. Antimicrob Agents Chemother 2008; 52:3188-94.

14. Bassetti M, Nicolini L, Repetto E, et al. Tigecycline use in serious nosocomial infections: a drug use evaluation. BMC Infect Dis 2010; 10:287.

15. Paul M, Bishara J, Levcovich A, et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother 2010; 65:1019-27.

16. Ben-David D, Maor Y, Keller N, et al. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant Klebsiella pneumoniae infection. Infect Control Hosp Epidemiol 2010; 31:620-6.

17. Gardam MA, Burrows LL, Kus JV, et al. Is surveillance for multidrug-resistant enterobacteriaceae an effective infection control strategy in the absence of an outbreak? J Infect Dis 2002; 186:1754-60.

18. Carmeli Y, Akova M, Cornaglia G, et al. Controlling the spread of carbapenemase-producing Gram-negatives: therapeutic approach and infection control. Clin Microbiol Infect 2010; 16:102-11.