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

**INTRODUCTION**

Carbapenems are currently recommended as a first-line therapy for severe infections caused by Enterobacteriaceae-producing extended spectrum beta-lactamases (ESBLs). 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.

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. Groups 1–3 represent cephalosporinases, serine beta-lactamases and metallo-beta-lactamases (MBLs), respectively. In the Ambler classification, 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. 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*. 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. 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 Enterobacteriaceae in the United Kingdom, accounting for 44% of carbapenemase producers in 2009, just one year after it was first isolated. 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. 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 Enterobacteriaceae 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. 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.

We describe the first local mortality associated with complications following an infection by NDM-1-positive
The isolates were identified by the Vitek 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, interpreted 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.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Tigecycline (mg/l)</td>
<td>≤ 0.5</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Amicillin (mg/l)</td>
<td>≥ 32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftriaxone†</td>
<td></td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime (mg/l)</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Imipenem* (mg/l)</td>
<td>&gt;32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem* (mg/l)</td>
<td>24</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin (mg/l)</td>
<td>≥ 16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amikacin (mg/l)</td>
<td>≥ 64</td>
<td>Resistant</td>
</tr>
<tr>
<td>Polymyxin B (mg/l)</td>
<td>0.5</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Ciprofloxacin (mg/l)</td>
<td>≥ 4</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cotrimoxazole (mg/l)</td>
<td>≥ 320</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ertapenem (mg/l)</td>
<td>≥ 8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Fosfomycin (mg/l)</td>
<td>0.380</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>

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

† Inferred from cefotaxime MIC.

Polymerase chain reaction detection performed on the carbapenem-resistant cultures was positive for the blaNDM-1 gene using the primers NDM1 FOR (5’-CAACTGGATCAAGCGAGA-3’) and NDM1 REV (5’-TCGATCCCAACGGGTATT-3’). The primers were designed according to the sequence of the blaNDM-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 bacteremia 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 bacteremia 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. The management of febrile neutropenia caused by carbapenem-resistant Gram-negative bacteria is a
NDM-1. We opted instead for strict infection control we did not perform any active surveillance cultures for warded in a single room from the time of admission, infections reported in Singapore and our patient had been As there have only been sporadic cases of NDM-1 setting.(16) However, the role of surveillance cultures resistant Gram-negative organisms in an outbreak (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.\(^{18}\) 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.\(^{14}\)

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

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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.
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.