

Hong Kong experiences the 'Ultimate superbug': NDM-1 *Enterobacteriaceae*

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We report the second imported case of New Delhi metallo-beta-lactamase (NDM-1) *Enterobacteriaceae* encountered in Hong Kong soon after the patient's arrival in the territory for medical care. As NDM-1 is spreading throughout the world via international travel, being an international city, Hong Kong was always expected to encounter the same public health threat. This case also illustrates the importance of active surveillance of at-risk patients in preventing the spread of this 'superbug'.

Case report

A 54-year-old Indian woman suffering from a subdural haematoma underwent repeated neurosurgical interventions in May 2010 in the province of Punjab, India. She had been hospitalised there for more than 3 months and received several courses of antibiotics including carbapenems for treatment of postoperative infections. As her family members stayed in Hong Kong, she was transferred here for further medical care.

Soon after arrival on 17 December 2010, she was admitted to our hospital for fever and shortness of breath. Owing to her unstable condition, she was transferred to the intensive care unit for ventilation and inotropic support. Septic workup grew carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species from endotracheal aspirate and right thigh wound swab specimens, respectively. Carbapenem-resistant *Acinetobacter* species, *Enterococcus faecalis*, coagulase-negative staphylococci and *Bacillus* species were also isolated from the blood culture. Colistin was prescribed according to the susceptibility results, and the patient responded well with defervescence of fever.

In view of the concerns about the spread of carbapenem-resistant *Enterobacteriaceae* (CRE) worldwide, Hong Kong set up an enhanced surveillance system for detection of such extensively resistant organisms. All newly admitted patients with potential risk factors (eg overseas hospitalisation in the past 6 months) are actively screened for colonisation by rectal swab/stool sample culture. Such screening for this patient was done on the third admission day; the rectal swab specimen was inoculated into 5-mL trypticase soy broth with a 10- μ g ertapenem disc. The broth was then incubated overnight at 35°C in ambient air. An aliquot of 100 μ L of broth fluid was vortexed and inoculated onto Uriselect 4 chromogenic agar with a 10- μ g ertapenem disk placed on the agar surface, and then incubated overnight at 35°C in ambient air.¹ On day 3, pink colonies (suggestive of *Escherichia coli*) were seen growing around the ertapenem disk. The isolate was subjected to further biochemical identification by the Vitek GNI identification system and ertapenem, imipenem and meropenem susceptibility testing by disc diffusion test according to the Clinical Laboratory Standards Institute guideline.² After the isolate was confirmed to be carbapenem-resistant *E coli*, it was subjected to a modified Hodge test and combined-disk test with boronic acid and EDTA,³ and found to test positive (Fig 1). The zone diameter of carbapenem-EDTA combined disks showed >5 mm increase when compared with carbapenem disks alone (Fig 2). The harbouring of a metallo-beta-lactamase (MBL)-carrying strain was suspected and single room isolation of the patient was instituted. Polymerase chain reaction and further nucleotide sequencing by the Public Health Laboratory Centre confirmed the presence of New Delhi metallo-beta-lactamase 1 (*NDM-1*) gene in the isolate. The isolate was found to be resistant to most antimicrobial agents except colistin (minimum inhibitory concentration [MIC] 0.5 μ g/mL, Etest) and tigecycline (MIC 0.25 μ g/mL, Etest). As regards the two *Acinetobacter* isolates detected in blood cultures, they were resistant to most tested antibiotics except colistin. Only meropenem (first isolate) and ertapenem (second isolate) showed positive synergy tests with EDTA. Subsequently, molecular testing for the presence of the respective gene (*NDM-1*) by polymerase chain reaction on these non-fermenter isolates was negative. In this patient, so far we have not identified transfer of the *NDM-1* gene from *E coli* to *Acinetobacter* species.

Key words

Anti-bacterial agents; beta-Lactamases;
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「終極超級細菌」NDM-1腸道菌感染症 登陸香港

本文報告香港第二宗從外地引入的新德里金屬-β-內酰胺酶1（簡稱NDM-1）的病例。病人抵港後不久隨即接受治療。近年由於國際交流頻繁，NDM-1的散播也相當迅速。而香港作為一個國際城市，自然有機會面對相同的公共衛生威脅。本病例亦顯示了主動監測高危病人有助防止這種「超級細菌」的蔓延。

Active screening was also performed for patients residing in the same cubicle as the index patient, none of whom were found to be colonised with the same strain of *E coli*. Proper infection control measures have been advised for her family and sequential rectal swab surveillance has been arranged to monitor their carriage status for carbapenemase-producing *E coli*.

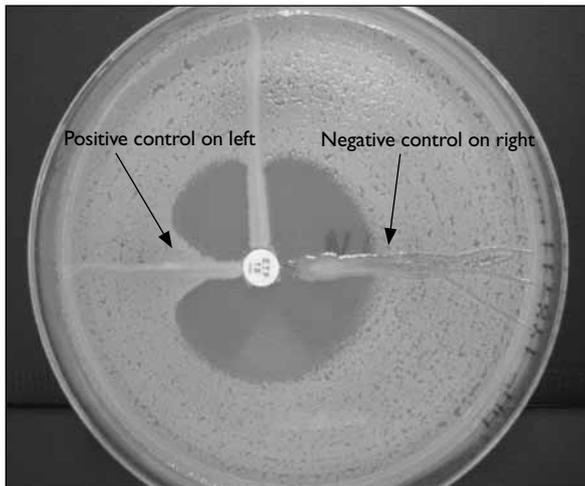


FIG 1. Modified Hodge test

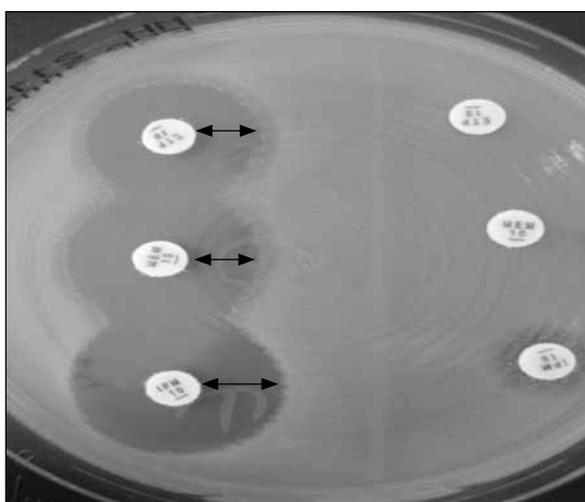


FIG 2. Carbapenem-EDTA combined disk test
The patient's isolate shows >5 mm increase in zone size as indicated by the double headed arrows

Discussion

The increase in carbapenem resistance among Gram-negative bacteria has challenged both clinicians and researchers worldwide. The most common mechanism of resistance is the production of carbapenemases, including enzymes of Ambler class A, B, and D. An important feature of these enzymes is that they are mostly associated with mobile genetic elements that may be transferable to other bacterial strains.^{4,5} Examples of class A carbapenemases include KPC (*Klebsiella pneumoniae* carbapenemase) and IMI (imipenem-hydrolysing beta-lactamase). Class B carbapenemases are also called MBLs. The production of MBLs, mainly VIM and IMP types, has been largely associated with *P aeruginosa*, *Acinetobacter* species and, more recently, *Enterobacteriaceae*. Class D carbapenemases found in *Enterobacteriaceae* were mainly OXA-48.^{6,7}

New Delhi MBL-1 is a novel MBL first reported in Sweden in a *K pneumoniae* strain (05-506) isolated from the urine culture of a patient after treatment in a hospital in New Delhi, India.⁸ Such an NDM-1 gene was also carried by an *E coli* strain in the gut of the same patient. With the co-existence of extended-spectrum or AmpC beta-lactamases and 16S rRNA methylases, NDM-1 harbouring pathogens render most antibiotics ineffective with few exceptions, such as colistin or tigecycline.⁸ As of 18 June 2012, a total of 306 cases were reported worldwide with 12 deaths.⁹ Cases of NDM-1 were mostly reported from India, Pakistan, Canada, and United Kingdom.⁹ Sporadic cases have also been reported from the Asia Pacific region, including Australia, Singapore, Taiwan, Oman, Japan, and Malaysia.⁹ Over 70% of patients in the European series had reported a travel history, and 65% had surgical intervention in hospital settings.¹⁰ In Hong Kong, an NDM-1-positive *E coli* strain was first identified by retrospective testing of an *E coli* strain with reduced susceptibility to imipenem that was isolated from a urine specimen in October 2009 (HK-01). The patient had spent 3 weeks in India before the onset of urinary tract infection.¹¹ By the time of writing of this article, the third imported NDM-1 case (*Citrobacter freundii*) was detected in a 60-year-old Chinese man who suffered from terminal lung cancer with bone metastasis. He had had repeated episodes of hospitalisation in mainland China for left-sided weakness and back pain over the past 3 months. He denied having received any antibiotics or surgical interventions while in mainland China. Notably, he also denied past travel to endemic areas such as India or Pakistan.

The extensive resistance profile, coupled with widespread clonal dissemination and horizontal plasmid mediated transfer of the NDM-1 gene among Gram-negative organisms, poses an imminent public health threat both in community and hospital

settings.¹² More NDM-1 β -lactamase-producing bacteria, including *Shigella boydii* and *Vibrio cholerae*, have recently been found in environmental samples including drinking tap water and seepage in New Delhi.¹³ This prevalence survey signifies that NDM-1-positive bacterial species are currently 'circulating' in communities residing in the Indian subcontinent and possibly further afield. This survey also suggests a possible significant impact not only on the management of *E coli*, *K pneumoniae*, *Enterobacter cloacae*, *C freundii*, but in the near future also on a lot of other infections. Thus, apart from the *Enterobacteriaceae* family (including *E coli*, *Klebsiella oxytoca*, *E cloacae*, *Proteus* spp, *C freundii*, *Morganella morganii*, and *Providencia* spp, etc), NDM-1 has also recently been found in *Acinetobacter* species in India, China, and Egypt.¹⁴⁻¹⁶ The NDM gene reported in Egypt was found to have an amino acid substitution and that variant was designated as NDM-2.¹⁶ Since *Acinetobacter* species have the ability to survive in human reservoirs and remain viable for months in dry environmental conditions, the presence of the NDM-1 gene in *Acinetobacter* species in human reservoirs or merely in hospital environments could well lead to significant therapeutic and infection control challenges.

To date, very little is known about the potential risk of acquiring NDM-1 and the determining factors for persistent rectal carriage. Asymptomatic NDM-1 carriers may act as reservoirs for infections within the community or as sources of in-hospital transmissions. Thus, early identification and physical isolation of NDM-1 carriers appear to be the key components of an effective infection control strategy in health care settings. As *Enterobacteriaceae* positive for NDM-1 are still not endemic in Hong Kong, it may be cost-effective to adopt a 'proactive approach' to halt their spread before they become established. Our patient had persistent carriage of the organism for more than 3 months after stopping colistin, whereas the third imported case became free from carriage within 10 days of admission without receiving any colistin treatment. Both cases illustrate the importance of heightened awareness among frontline health care colleagues and the effectiveness of our CRE screening programme targeting high-risk groups.

All in all, our newly enhanced territory-wide surveillance programme not only provides timely identification of patients colonised with CRE, but also allows us to adopt appropriate infection control practices to prevent the spread of this 'ultimate superbug' in hospital settings.

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