



<b>Title</b>	<b>Emergence of Klebsiella pneumoniae ST258 with KPC-2 in Hong Kong</b>
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1 Emergence of *Klebsiella pneumoniae* ST258 with KPC-2 in Hong Kong

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13 Sir,

14           The emergence of carbapenemase-mediated resistance to all the  $\beta$ -lactam, including  
15 the carbapenem is a major public health threat. In *Enterobacteriaceae*, one of the most  
16 frequent carbapenemases is the *Klebsiella pneumoniae* carbapenemase (KPC) enzymes [1-3].  
17 Since the first KPC-producing isolate was identified from North Carolina, United States in  
18 1996, occurrence of KPC-producing bacteria have been reported in other parts of the United  
19 States, Europe, South America, the Middle East and Asia [1,2]. In September 2010, Hong  
20 Kong set up an enhanced surveillance system for detection of carbapenem-resistant  
21 *Enterobacteriaceae*; following recent concerns that the transmission of these extensively  
22 resistant organisms may be associated with medical tourism or surgery abroad in areas where  
23 they are endemic [1-3]. In all the public hospitals, all newly admitted patients with potential  
24 risk factors for carbapenem-resistant *Enterobacteriaceae* (e.g. overseas hospitalization) will  
25 be actively screened for colonization. In clinical microbiology laboratories, all carbapenem-  
26 resistant *Enterobacteriaceae* isolates will be assessed for carbapenemase activity using  
27 inhibition tests with boronic acid and ethylene diamine tetra-acetic acid (EDTA) [1]. Isolates  
28 with positive carbapenemase screen test will be sent to the public health laboratory for  
29 molecular characterization. Additionally, strains of carbapenem-resistant *Enterobacteriaceae*  
30 previously stored in MicroBank (Pro-Lab Diagnostics Inc., Canada) at -80 °C in a regional  
31 hospital in Hong Kong were retrieved for testing. This lead to the retrospective identification  
32 of the first case of KPC-producing *K. pneumoniae* in Hong Kong and the findings were  
33 reported here.

34           In August 2006, a multidrug-resistant *Klebsiella pneumoniae* isolate was recovered from  
35 the mid-stream urine sample of a 75 year old lady who attended an outpatient clinic for  
36 follow-up. She has history of diabetes mellitus, hypertension and atrial fibrillation. Patient  
37 travelled to the United States frequently and sometimes had medical follow up there. Past

38 health was relevant for a history of cholecystectomy in New York, United States in July 2005.  
39 She was totally asymptomatic with no fever or any urinary symptom. Her WBC count was  
40 normal. No antibiotic was given. Personal hygiene was advised. The isolate was identified as  
41 *K. pneumoniae* using a Vitek system (GNI, bioMerieux, Hazelwood, USA). Disc diffusion  
42 test showed that the isolate was resistant to cephalosporins (ceftriaxone, ceftazidime,  
43 cefepime), beta-lactam- $\beta$ -lactamase inhibitor combinations (amoxicillin-calvulanate,  
44 piperacillin-tazobactam), imipenem, ciprofloxacin, chloramphenicol, aminoglycosides  
45 (amikacin, gentamicin, and netilmicin), nitrofurantoin, and cotrimoxazole at the CLSI  
46 breakpoints [4]. For these drugs, there was no inhibition zone or very small inhibition zone  
47 around the discs. The MIC for the following drugs was determined by Etest (AB Biodisk,  
48 Solna, Sweden): meropenem (32  $\mu$ g/ml, resistant), imipenem (32  $\mu$ g/ml, resistant),  
49 fosfomycin (24  $\mu$ g/ml, sensitive) and colistin (0.38  $\mu$ g/ml, sensitive).

50 The isolate was retrieved and tested for primers specific for the KPC genes. A positive  
51 PCR result was obtained. Subsequent sequencing showed that a KPC-2 gene was carried by  
52 the isolate. In order to identify the genetic background of this strain, the organism was  
53 characterized by multilocus sequencing (MLST) [2,3]. This strain has an allelic profile 3-3-1-  
54 1-1-1-79 (gapA-infB-mdh-pgi-phoE-rpoB-tonB), corresponding to ST258. In the United  
55 States, this clone has disseminated widely and accounted for 70% of the national collection  
56 from 1996 to 2008 [2]. In contrast, the dominant KPC clone in mainland China is an ST11  
57 variant with the allelic profile 3-3-1-1-1-4 [3]. The finding suggests that our patient has  
58 likely acquired the organism from the United States during her previous travel visits.

59 This case raises several important issues. Firstly, the importation of multidrug-resistant  
60 bacteria, such as carbapenem-resistant Enterobacteriaceae among patients with history of  
61 medical treatment abroad may be underestimated. Kennedy et al reported that colonization  
62 with *E. coli* resistant to gentamicin, ciprofloxacin and/or third generation cephalosporins

63 increased from 7.8% at baseline to 49% after international travel [5]. In 18% of the  
64 individuals, prolonged colonization for over 6 months occurred [5]. These individuals may  
65 act as reservoirs for infection within the community or sources of outbreak when they are  
66 hospitalized [2,3,5]. In many countries, there are no national guidelines for admission  
67 screening of individuals who have history of medical treatment abroad. Secondly, the optimal  
68 treatment for invasive carbapenem-resistant Enterobacteriaceae infections is uncertain and is  
69 complicated by the frequent occurrence of co-resistance to many other antibiotics. The agents  
70 that are potentially active against carbapenem-resistant Enterobacteriaceae are colistin,  
71 tigecycline, fosfomycin and isepamicin. In solid organ and bone marrow transplant recipient,  
72 infections by these organisms represent tremendous threat. In response to these challenges,  
73 hospitals in Hong Kong have recently introduced active screening for carbapenem-resistant  
74 Enterobacteriaceae carriage at hospital admission. Under the arrangement, all newly admitted  
75 patients with history of hospitalization, surgery or dialysis in an overseas institution in the  
76 previous 12 months would be screened.

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79 **Declarations**

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83 **Competing Interests:** All authors have nothing to declare

84 **Ethical Approval:** Not required

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88 **References**

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