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Longitudinal Study of the Impact of Changing Trends in Genotypes and Phenotypes of Carbapenem-Resistant *Klebsiella pneumoniae* Infection in a Tertiary Teaching Hospital in Malaysia

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Introduction

In the past few years, the recovery of carbapenem-resistant *K. pneumoniae* (CRKP) strains from clinical specimens has soared at an alarming rate (Carter et al., 2008; Hawkey and Jones, 2009; Marchaim et al., 2011; Patel et al., 2008). The development of carbapenem resistance in *Klebsiella* species involves several mechanisms. These include acquisition of carbapenemase genes (Queenan et al., 2007) that encode for the Ambler class A, B, and D β -lactamases. Carbapenem resistance may also be mediated by efflux systems and altered penicillin-binding proteins. (Bradford et al., 2004). In addition, rare chromosome-encoded cephalosporinases (Ambler class C) produced by Enterobacteriaceae may have - extended activity toward carbapenems (Queenan et al., 2007). These findings are worrying given that Carbapenems such as imipenem and meropenem which are the - first-line therapy for severe infections caused by Enterobacteriaceae producing extended spectrum β lactamases (ESBLs) will no longer be effective. (Gasink et al., 2009; Nordmann et al. 2009; Srinivasan and Patel, 2008).

Among the important carbapenemase genes, the detection of OXA-48 carbapenemases is challenging as strains harboring these genes are sensitive to broad-spectrum cephalosporins if they do not co-produce an ESBL or AmpC beta-lactamase genes (Poirel et al., 2012). Currently, the most commonly used phenotypic tests available for the detection of carbapenemase producing Enterobacteriaceae is the Modified Hodge Test (MHT). However, this method is not sensitive in detecting NDM producers (Girlich et al., 2012). As an alternative, PCR which produces results within 4–6 hours with excellent sensitivity and specificity have been widely used to overcome the limitation of phenotypic tests (Miriagou et al., 2010; Nordmann et al., 2011). Sequencing of PCR products is of particular interest for epidemiologic purposes which permits the confirmation of the type of carbapenemase gene detected.

This study aimed to establish a database of patients with CRKP infection from 2013–2015. The isolated strains were genotyped and the presence of carbapenemase genes was determined.

Materials and Methods

The medical ethics to conduct research in clinical isolates and to access the clinical/patients' data has been approved by the UMMC Medical Ethics Committee in 2013 (MEC:1059.15) and 2015 (MEC: 20154-1249). Clinical isolates of CRKP isolated from April 2013 to December 2015 identified by the hospital's Medical Microbiology Diagnostic Laboratory (MMDL) were included. Patient's details as well as the sensitivity profile of isolates were recorded.

The carbapenemase-producing isolates were genotyped by pulsed field gel electrophoresis

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(PFGE) using the standard pulsenet protocol and sequence types of the isolates were confirmed by multilocus sequencing typing (MLST). PCR targeting the carbapenemase-encoding genes (blaKPC, blaNDM, blaIMP, blaVIM and blaOXA) was also performed using specific primers.

Results

The strains used in this study were collected within a 3-year period in Universiti Malaya Medical Center (UMMC) and were the first isolate per patient. The data for the 2013 isolates has been published in a peer-reviewed journal early this year (Low et al., 2017). In 2013 and 2014, less than 20 CRKP were isolated. However, the number of CRKP increased steeply in 2015. The 2015 isolates showed high level resistance to cephalosporins and colistin resistant strains were detected. Carbapenemase genes were detected in majority of the CRKP isolates. Overall, PFGE and MLST showed great genetic diversity among the strains collected from 2013 to 2015.

Conclusion

CRE is increasing in our hospital and high diversity of the CRKP strains indicate that the genetic events may have contributed to clone emergence and adaptation to the hospital environment. Hence, it is important to monitor the changing trends and the emergence of new clonal strains so that rational treatment and pathogenic control strategies can be designed..

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