REVIEW ARTICLE

A Current Review on Prevalence and Molecular Charaterisation of Carbapenem Resistant *Klebsiella Pneumoniae* in Malaysia

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ABSTRACT

Klebsiella pneumoniae resistant to carbapenems is becoming a major global public health crisis. Due to the ability of *Klebsiella pneumoniae* to spread easily in hospitals and the environment, preventing it's spread is thus a major public health challenge. Several pathways are involved in the emergence of carbapenem resistance in *Klebsiella* species. Carbapenem-resistant *Klebsiella pneumoniae* has been molecularly characterised in some studies from different regions of Malaysia. The most commonly found carbapenemase genes were blaNDM and blaOXA-48. The prevalence of carbapenem-resistant *Klebsiella pneumoniae* in Malaysian hospitals was quite low, even though it is increasing. Thus, making it critical to have a surveillance system for monitoring trends and emergence of new resistant genes. This will aid in the development of an effective infection control strategy and antibiotic stewardship to prevent further spread. The aim of this review was to highlight the prevalence, epidemiology, and molecular charaterisation of carbapenem-resistant *Klebsiella pneumoniae* in Malaysia.

Keywords: Carbapenem-Resistant, *Klebsiella pneumoniae*, Carbapenemase, *ß*-lactamase, Malaysia

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INTRODUCTION

Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) (1) is rapidly becoming an increasingly serious health threat among community (2), and these multidrug-resistant *Klebsiella pneumoniae* strains that are now spreading globally have built resistance to the common *ß*eta-lactams antibiotics for example carbapenems (3). Carbapenems (i.e doripenem, ertapenem, imipenem, and meropenem) (4) have traditionally been utilised as the last line therapy for infections due to multidrug-resistant bacteria or in specific, Enterobacteriaceae resistance (5). These antibiotics can be inactivated by enzymes (carbapenemases) in CR-KP which leads to resistance (4). Ambler class A *ß*-lactamases (e.g. *Klebsiella pneumoniae* carbapenemases (KPC)), class B Metallo-lactamases (MBLs) (e.g.Verona integrin-encoded Metallo-lactamases (VIM), New Delhi Metallo-lactamases (NDM)), and Class D enzymes of the Oxacillinase (OXA) are some examples of carbapenemases (6). Infection with CR-KP greatly modifies patients' treatment of whom are at higher risk of being compromised or colonised with the microorganisms (7).

The most suitable treatment for CR-KP infections continues being a challenge notwithstanding the immense threat posed by its increasing burden (8). Most clinicians have recommended use of combination therapy in treating CR-KP-infected patients, largely due to the potential toxicity and ineffectiveness of alternative treatments (9). This was supported by a previous study proving that combination therapy is better than monotherapy in saving the lives of infected patients (10). Polymyxins and colistin are antibiotics currently used as therapeutic choices (11). The alarming increase in resistance to these last resource agents, on the other hand, is a significant public health concern (12). Increased antibiotic use and abuse, global travel, and inefficient infection control practices in clinical and

community settings are some of the possible reasons for increased global resistance (13). These factors lead to the emergence and spread of multidrug-resistant bacterial infections (14) in the population through increasing and widespread genetic mutations (13).

Malaysia, like other Asian nations, is dealing with the spread of CR-KP (15). The prevalence rate of CR-KP shows a variation depending on geographical region. Carbapenem resistance is linked to limited therapeutic options, longer hospital stay, increased healthcare costs, and higher morbidity and mortality in Malaysia (16). Molecular characterisation of CR-KP isolates provides data on carbapenem resistance and identification of risk factors associated with colonisation and infection of patients which are very critical in the reduction of infection rates in Malaysian hospitals (17). This review sought to collate data on the prevalence, epidemiology and molecular charaterisation of carbapenem-resistant *Klebsiella pneumoniae* detected in some hospitals across Malaysia.

MATERIALS AND METHODS

Search Strategy

A PubMed, Web of Science and Scopus database search of the literature from February to June 2021 was conducted using the terms: '*Klebsiella*', *'pneumoniae*' 'Malaysia', 'Carbapenem', '*ß*-lactamase', and 'Resistant' as keywords. Peer-reviewed journals reporting data on CR-KP in Malaysia were searched for published articles. In addition, articles published in international journals describing CR-KP infections from Malaysia were also included. Only full text research articles published in English from 2015 to 2021 reporting the prevalence of CR-KP isolated from patients in hospital environment in Malaysia, studies detailing *Klebsiella pneumoniae* phenotypic and genotypic methods used to detect CR-KP, and studies describing CR-KP isolated from humans only were the studies included in this review. The studies conducted outside of Malaysia, reviews, editorials, and studies that did not provide details on the carbapenem-resistant isolates' resistance mechanisms were excluded. Figure 1 shows the search strategy flow chart of this review referring to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (18).

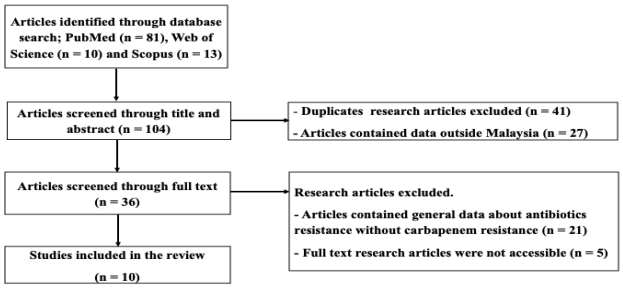

Figure 1: Flowchart of search strategy based on the PRISMA guidelines.

RESULTS AND DISCUSSION

Prevalence and epidemiology of carbapenem- resistant *Klebsiella pneumoniae*

Antimicrobial resistance surveillance systems have been established and introduced in Malaysia in the year 2000 (19). According to Hsu et al, Malaysia has been able to publish National Surveillance of Antimicrobial Resistance (NSAR) reports dating back to 2003 since 2006 (20). Data is acquired from the Malaysian hospital microbiology laboratories and compiled at the Institute for Medical Research. Based on the NSAR reports, carbapenem resistance among *Klebsiella pneumoniae* isolates increased from 0.5% (n=11,935) to 1.6% (n=27,911) between 2010 to 2014, respectively. In the report, a total of 31143 cases of CR-KP was reported which equals to 974.7 per 100,000 population (21). The first CR-KP was discovered in Malaysia in June 2004, and it was mostly resistant to imipenem. More cases of CR-KP in Malaysia appeared within the next few years. The majority of infection cases were carbapenemase-producing *Klebsiella pneumoniae* carrying carbapenemase genes such as NDM-1 (22), IMP-4 (16), OXA-48 (23) and KPC-1 (22). The Malaysian Ministry of Health is especially worried about the dissemination of carbapenem-resistant genes and the elevated risk of resistant *Klebsiella pneumoniae* associated infections (19). Based on literature search, majority of the CR-KP studies were done in Kuala Lumpur. In comparison, there are only a few studies that describe molecular charaterisation as well as the resistance pattern of *Klebsiella pneumoniae* to carbapenems from other parts of Malaysia. A recent study by Lau and colleagues (17) characterised the resistant genes from 63 patients infected with CR-KP at the University Malaya Medical Centre in Kuala Lumpur and found that all isolates were resistant to ertapenem and imipenem. NDM-1, OXA-21, and OXA-48 seem to be the most prevalent carbapenemases in Malaysian *Klebsiella pneumoniae* (24). OXA-181 and IMP-4 were detected very rarely in isolates of *Klebsiella pneumoniae* clinical specimens from a university hospital in Kelantan (16). Other studies were published from Pahang, Kelantan, and Selangor, in addition to Kuala Lumpur's findings (16,23,25). These included studies on antibiotic resistance trends (26,27) and CR-KP molecular characterisation (13,28). There were reports of a high faecal carriage of CR-KP in a university hospital (16). Table I summarises the findings on CR-KP in terms of prevalence and molecular characterisation of CR-KP isolates among Malaysian studies.

Mechanisms of resistance in carbapenem-resistant *Klebsiella pneumoniae*

The inhibition of carbapenems by carbapenemases, which are primarily encoded on plasmids, is the main mechanism of carbapenem resistance, as previously stated (29). Considering that *Klebsiella pneumoniae* is one of the major culprits responsible for infections

Table I: Prevalence and Molecular Charaterisation of Carbapenem Resistant *Klebsiella pneumoniae* in Malaysia from 2015-2021

Author	Type of Publication	Source of Isolates	No. of CR-KP positive isolates	Methods for Carbapenamase detection	Carbapenamase genes detected	Prevalence of carbapenamase among *Klebsiella pneumoniae* isolates
1. Zainol et al., 2015 (26)	Research article	Various clinical specimens	16	AST + PCR	blaNDM-1 positive	The prevalence of NDM-1 gene among *Klebsiella pneumoniae* isolates was 0.14%.
2. Zaidah et al., 2017 (16)	Research article	Rectal swab, urine, blood, tracheal aspirate, swab, sputum	388	AST + MHT + PCR	blaNDM-1 and blaIMP-4	The prevalence of CR-KP among Enterobacteriaceae was 5.0%
3. Low et al., 2017 (13)	Research article	Rectal swab, Urine, blood, tracheal aspirate, swab, sputum, drainage fluid, tissue	17	AST + MHT + PCR + PFGE + MLST	blaOXA-48, detected in 12 strains others were blaKPC-2, blaIMP-8, blaNMC-A, and blaNDM-1.	The prevalence of CR-KP among Enterobacteriaceae was 5.0%.
4. Hamzan et al., 2017 (22)	Research article	Rectal swab, Urine, blood, tracheal aspirate, swab, sputum	13	AST + MHT + CDT + PCR	blaNDM-1 and blaKPC	The prevalence of Carbapenamase genes among 321 *Klebsiella. pneumoniae* isolates was 4.05%
5. Mohamed et al., 2018 (23)	Research article	Blood, urine tracheal aspirate, pus aspirate	18	AST + PCR	blaOXA-48 and NDM co-producer amongst CRE isolates.	Prevalence of carbapenamase genes (NDM-1 and OXA48, KPC) among isolates *Klebsiella pneumoniae* was 0.60%
6. Mohsen et al., 2018 (25)	Research article	Blood, urine, and swabs,	4	AST + MHT + PCR	blaNDM	Prevalence of NDM-producing *Klebsiella pneumoniae* in the hospital was 1.15%
7. Ming et al., 2019 (28)	Research article	Not stated	8	AST + WGS	blaNDM (1/5) and blaKPC (2/6)	All 8 isolates were carbapenem resistant 100%
8. Heng et al., 2019 (27)	Research article	Blood, urine, pus [including from catheter tip], tissue, swab, bile, tracheal aspirate, and sputum	7	AST + MHT + PCR	blaOXA-48 and OXA-181	The prevalence of OXA-48 and OXA-181 is 0.069% and 0.008%, respectively.
9. Lau et al., 2021 (17)	Research article	Clinical isolates	63	AST + PCR + PFGE	blaOXA-48 and blaNDM	From 55 isolates of CR-KP blaOXA-48 was 63.5% and blaNDM 36.5%

Note: AST=Antibiotic susceptibility testing, PCR=Polymerase Chain Reaction, MHT=Modified Hodge's test, CDT=Combined disc test, PFGE=Pulsed gel electrophoresis, MLST=Multilocus sequence typing, WGS=Whole genome sequencing

in hospital setting (30), this bacteria is of particular interest when it comes to the issue of carbapenem resistance (31). Depending on their specific enzymatic range and substrate affinity, the Ambler classification scheme divides β-lactamases into four classes (32) where carbapenemases can be found in classes A, B, and D; however class C enzymes mainly hydrolyse cephalosporins (33). Metallo-β-lactamases (MBLs) have zinc in the active site while serine is found in the active catalytic site of enzymes in groups A, C, and D (34). Class A carbapenemases do not show inherent carbapenemase activity, although this category of enzymes includes the commonly occurring KPC (*Klebsiella pneumoniae* carbapenemase) (4). In Class B , carbapenemase activity is present in all MBLs which is found in many Enterobacteriaceae and examples include the acquired NDM, IMP, and VIM enzymes (31). Class C enzymes include AmpC β-lactamase which may play a significant

role in carbapenem resistance in the case of permeability mutation, although they are not carbapenemases in and of themselves because their catalytic action towards carbapenems is rather poor or absent (35). Class D carbapenemases (Oxacillin carbapenemase) are a varied group of lactamases with carbapenemase activity, the most common of which are OXA-48–type and OXA-23 (36). The expression of efflux pump genes (such as, MexCD-OprJ MexAB-OprM or MexXY-OprM) (37), loss of porin-encoding genes expression, and encoded porin genes becoming mutated are some of the other non-enzymatic carbapenem resistance mechanisms (38). Many reports from Malaysia have identified CR-KP producing NDM enzyme is encoded by the blaNDM gene (13,16,23). In Malaysia, the first study on CR-KP was conducted in 2004 where an imipenem-resistant strain was isolated from a 42-year-old woman's blood culture (13). NDM-1, OXA-48, OXA-23, OXA-181, blaKPC-1-6 and IMP-4 are some of the carbapenemases found in *Klebsiella pneumoniae* isolated in Malaysia so far (39,40).

Types of carbapenemase detection methods

In the included studies, in addition to antibiotic sensitivity testing, Polymerase Chain Reaction (PCR) was carried out to confirm carbapenemase genes present. Six of the studies in addition to antibiotic sensitivity testing and PCR, carried out Modified Hodge test (MHT) for carbapenemase detection (13,21,22,26,28). Only one study conducted in Kelantan combined two phenotypic methods (combined disc test and MHT) for the detection of carbapenemase out of five studies that performed phenotypic detection of carbapenemase (22).

Molecular characterisation of *Klebsiella pneumoniae*

Only a few studies (13,17,23) have investigated the probable carbapenem resistance mechanisms in *Klebsiella pneumoniae* isolates from Malaysia. As of the time of writing this review, the major carbapenemases causing resistance in CR-KP recorded from Malaysia are blaNDM and blaOXA-48 enzymes. This is not surprising given that these enzymes are the most common causes of CR-KP infections and the most common carbapenemases globally (41). Other carbapenemases and isolates possessing *Klebsiella pneumoniae* carbapenemase (IMP and KPC), were rare in Malaysia (19). A study in a university hospital molecularly characterised 13 CR-KP isolates of which seven isolates were blaNDM-1 and six were blaIMP-4 even though other resistant genes (blaKPC, blaOXA, blaVIM) were not detectable (16). In another study (13), however, the authors reported that out of the 17 CR-KP isolates screened, 12 harboured the blaOXA-48 gene (70.6%) and the predominant sequence type was ST101. Interestingly, other carbapenemases which are not commonly detected in Malaysia (blaKPC-2 and blaIMP-8) were also reported (16,22). A study from Universiti Kebangsaan Malaysia Medical Centre showed the prevalence of the blaNDM-1 gene was 89.0% from 16 CR-KP isolates (26). This study however did not include NDM variants or other carbapenemase genes. Similarly, another study between 2015 and 2016 from Universiti Sains Islam Malaysia reported that *Klebsiella pneumoniae* that co-produced NDM-1 and OXA-48 genes were the most encountered (41%), followed by OXA-48 (35%), NDM-1 (12%), and KPC (6%) (23). Furthermore, a similar study at the Hospital Tengku Ampuan Afzan showed that three out of four CR-KP isolates were blaNDM positive. However, all NDM positive isolates were also positive for at least one other β-lactamase (CTX, SHM, and TEM) (23). It has been reported that out of the 87 non-repetitive isolates of CR-KP studied in a healthcare institution in Malaysia, nine (10.3%) were positive for OXA-48 of which seven were *Klebsiella pneumoniae*. This is the first study to ascertain the prevalence of OXA-48- and OXA-181 producing Enterobacteriaceae (26). Between 2016 and 2017, carbapenemase genes were found in 55 out of 63 CR-KP isolated strains from a tertiary teaching hospital, with the most common carbapenemase gene being blaOXA-48 (63.5%) (42). In a recent study by Ming and colleagues (28), whole-genome sequencing of eight CR-KP strains harbouring blaNDM and blaKPC from a hospital was done. It was the first study to report the first blaKPC-6 harbouring plasmid contig assembled for *Klebsiella pneumonia*e.

Risk factors of carbapenem-resistant *Klebsiella pneumoniae*

The emergence of CR-KP infections in Malaysia has been linked to several risk factors such as indiscriminate use of antibiotics and co-morbidities (43). The widespread use of carbapenems as first-line treatment (44) for invasive infections caused by carbapenemase-producing *Klebsiella pneumoniae* is also believed to be an important risk factor for its emergence (4). Antibiotic misuse and abuse, an absence of effective antibiotic resistant surveillance programs, and the large surge of different populations, especially from other Asian countries such as India, Pakistan and Bangladesh are all considered huge risk factors (19). Tourism and international travel of people carrying resistant *Klebsiella pneumoniae* strains are very well known risk factors that lead to extensive spread of multidrug-resistant *Klebsiella pneumoniae* (45). Specific risk factors, such as co-morbidities, previous carbapenem use, hospitalisation duration, and invasive procedures, were significantly associated with CR-KP infections in Malaysia.

CONCLUSION

In Malaysia, there are a few studies on molecular characterisation of CR-KP have been conducted. In this review, we examined the trends of carbapenem resistance in *Klebsiella pneumoniae* isolated from various hospitals in Malaysia. The most commonly encountered carbapenemase genes were blaNDM and blaOXA based on the findings from the various hospitals in different regions. According to the national

antimicrobial surveillance report, carbapenem resistance rate for *Klebsiella pneumoniae* for 2019 was below 5%. Antimicrobial resistance in *Klebsiella pneumoniae* is a serious problem that requires constant monitoring to be overcome. It is important to design a prevention and control strategy to address this public health hazard. This can be accomplished by establishing a signaling system at the hospital through active surveillance to collect epidemiological data, the establishment of a ward for CR-KP positive patients, and the formulation of regulations for new antibiotics.

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