

Epidemiology of carbapenem resistant *Enterobacteriaceae* (CRE) during 2000-2012 in Asia

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Background: Over the past decade, the worldwide emergence of carbapenem resistance in *Enterobacteriaceae* has become a severe public health issue. This meta-analysis aims to describe the epidemiology of carbapenem resistant *Enterobacteriaceae* (CRE) during the years of 2000-2012 in Asian area.

Methods: PubMed and Embase databases were searched to identify the qualified papers. Random or fixed-effect model was used to deal with the data.

Results: Over all the 49 Asian countries (or regions), only 37.5% [19] of them contributed epidemiology data of CRE, and the rest ones provided either only case reports or no information at all. In Asia, the prevalence of CRE was still low during the study period with average resistance rates of 0.6% (95% CI, 0.6-0.8%, imipenem) and 0.9% (95% CI, 0.7-1.2%, meropenem). Resistance rates to imipenem and meropenem in *Enterobacteriaceae* exhibited stably escalating trend. Similar trend can also be observed among each *Enterobacteriaceae* genus, such as *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. *Klebsiella* spp. accounted for the largest proportion among the isolates resistant to imipenem, and then followed by *E. coli* and *Serratia*. The rank order of resistance rates to imipenem among *Enterobacteriaceae* genus during the period of 2000-2012 was as follows: *Serratia* spp. (1.8%) > *Proteus* spp. (1.6%) > *Klebsiella* spp. (0.8%) = *Citrobacter* spp. (0.8%) > *Enterobacter* spp. (0.7%) > *E. coli* (0.2%).

Conclusions: Given the fact that the prevalence of CRE was increasing during the past decade, it is urgent for us to establish regional surveillance worldwide, carry out more effective antibiotic stewardship and infection control measures to prevent further spread of carbapenem resistance in *Enterobacteriaceae*.

Keywords: *Enterobacteriaceae*; carbapenem; epidemiology; Asia

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Introduction

Enterobacteriaceae family is an important cause of urinary tract infections (UTIs), bloodstream infections, hospital acquired pneumonias and various intra-abdominal infections. The prevalence of ESBLs producing *Enterobacteriaceae* made carbapenem, a broad-spectrum antimicrobial agent became a preferred drug in the treatment of multi-drug-resistant (MDR) *Enterobacteriaceae*. Because of their safety and established efficacy, carbapenems

used to serve as the ultimate last resort option for treating MDR. Over the past decade, the emergence of carbapenem resistant *Enterobacteriaceae* (CRE) has become a formidable threat to public health. The prevalence of CRE, according to some institutions in epidemic area, varies between 24.7% and 29.8% (1,2). The rapid and extensive dissemination of CRE demonstrated that we still lacked sufficient and effective measures to reverse or at least control the current situation.

The emergence of CRE is a menace to patients,

particularly to those who are debilitated, with various underlying diseases, complex infections or medical interventions (3). Moreover, pathogens resistance to carbapenems often shows high resistance to other antibiotic agents as well, such as cephalosporins, quinolones and aminoglycosides, leaving few or, in some cases, no optimal therapeutic options. What's more, some extra factors, such as delayed identification, lack of accurate judgment of pathogens, also lead to high mortality, prolonged hospital stay, and huge medical expenses in CRE infected patients (4,5).

To hinder the spread of CRE, it's important for us to know its epidemiology first. Recently, many Asian countries have reported the emergence of CRE as well as the rates of resistance (6-8). Based on the data published during 2000-2013, this article aims to give a comprehensive analysis of the prevalence of carbapenem resistance in *Enterobacteriaceae* across Asian area. Information documented in this study may offer significant help in the control and empirical antibiotic treatment of CRE.

Methods

Search strategy

A systematic literature search has been conducted of PubMed and Embase (for articles published from January 2001 to December 2013). Our search strategy uses the following terms: "carbapenem" "imipenem" "meropenem" "*Enterobacteriaceae*" "*E. coli*" "*Klebsiella*" "*Enterobacter*" "*Serratia*" "*Citrobacter*" "*Morganella*" "Asia". The search is not limited by language.

Study selection

Two authors (Yanling Xu and Bing Gu) have independently performed the literature search following such criteria: (I) basic experimental studies and reviews are not eligible for inclusion; (II) studies that only offered rates of susceptibility or focused on selected isolates with certain drug resistance pattern or genes are not included either; (III) studies on clinical or animal research were also excluded; (IV) according to our literature search, no data was reported about the prevalence of CRE in the year of 2013. Therefore we divided the previous 13 years [2000-2012] into three periods (2000-2004, 2005-2008, and 2009-2012). Studies that could not be allocated into any of the three periods will not be included. All discrepancies between the two reviewers were resolved by the consensus of all authors.

We also assess the adherence to standard of experimental procedures in each article, including details of if the susceptibility test was in accordance with guidelines established by the Clinical and Laboratory Standards Institute (CLSI); if the reports provide the exact study years and countries/regions; when data in one study was overlapped with another, the data in the more recent and larger studies was included in the analysis. Data from these smaller studies were used if additional useful information could be extracted.

Data extraction

Two reviewers independently extracted the relevant data, using a standardized collection form to extract data from the included articles. The following data gets extracted from each study: (I) years that the bacteria were isolated; (II) countries; (III) bacteria species; (IV) number of the whole tested strains; (V) carbapenems tested (only imipenem and meropenem were included in this study due to the lack of relevant data of other carbapenems); (VI) number of resistance strains or the rates of resistance to carbapenem.

If an integer is not obtained when doing multiplication between the number of whole strains and the resistance rate, the rounding method is used.

Outcomes analysis

The heterogeneity between studies is assessed by using the Q-statistic test; a P value <0.1 defines statistical significance in the analysis of heterogeneity. We present results from the fixed effects model when there is no heterogeneity between the analyzed studies (P>0.1); otherwise, we present results from the random effects model. Freeman-Tukey arcsine transformations are used to stabilize variances. We perform data manipulation and statistical analyses by statistical software package STATA 10.0 (STATA Corp, College Station, TX, USA).

Results

Result of the systematic literature search

Figure 1 shows a flow diagram describing our selection process, which is applied to identify the eligible studies. Among 1,150 articles found through electronic and reference list searches, 61 studies met the inclusion criteria and are included in this meta-analysis.

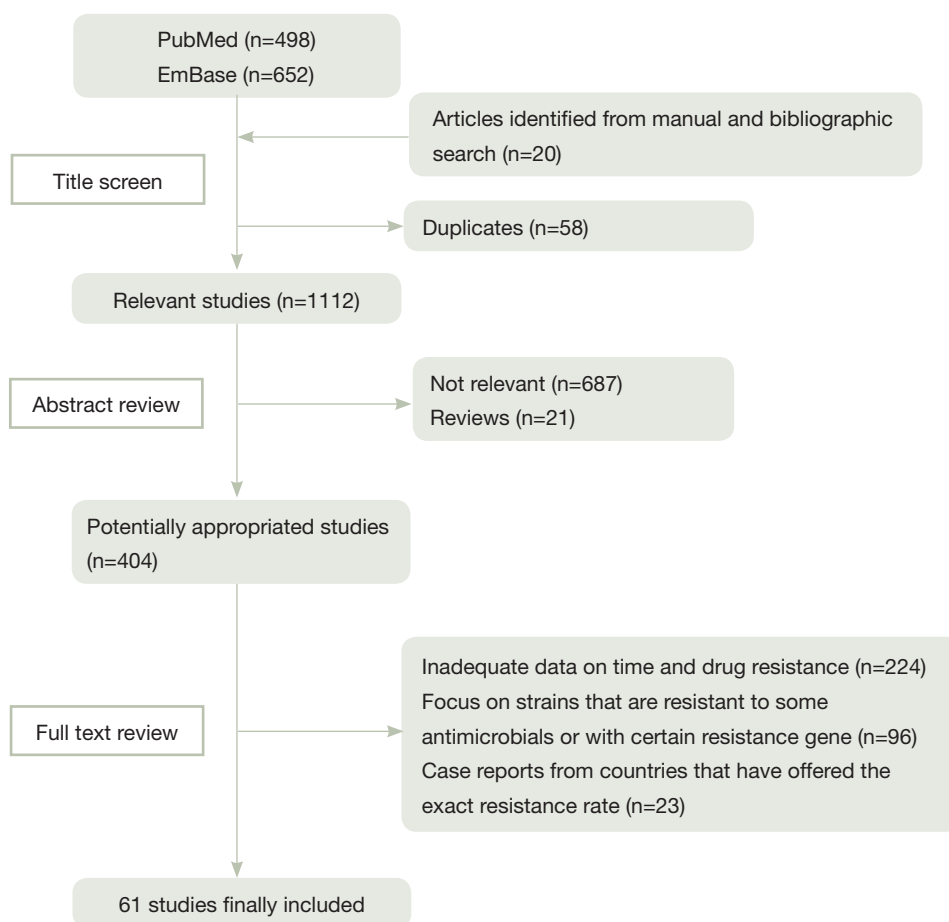


Figure 1 Flow diagram of the selection process of the included studies.

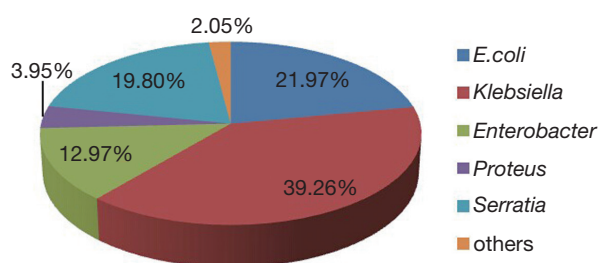


Figure 2 Pathogen distribution of CRE in Asia. CRE, carbapenem resistant *Enterobacteriaceae*.

Pathogen distribution in Asia

Among the *Enterobacteriaceae* genera, the most commonly organisms collected in this study are *E. coli*, *Klebsiella* spp., *Enterobacte* spp., *Serratia* spp., *Proteus* spp. and *Citrobacter* spp. Only case reports are obtained on the carbapenem

resistance in *Morganella* spp. and *Shigella* spp. As *Figure 2* shows, *Klebsiella* spp. and *E. coli* account for the largest proportion of CRE, namely 39.3% and 22.0%, and then followed by *Serratia* spp. (19.8%), *Enterobacter* spp. (13.0%), *Proteus* spp. (4.0%), and *Citrobacter* spp. (2.0%).

Overall carbapenem resistance in Enterobacteriaceae in Asia

During the period of 2001 to 2012, the rates of resistance to imipenem and meropenem in *Enterobacteriaceae* are 0.8% (95% CI, 0.6-0.9%) and 1.0% (95% CI, 0.8-1.3%) respectively. Though the resistant rates are still low, they keep an escalating trend from 2000 to 2012. *Figure 3* explicitly depicts the prevalence of CRE during each study period. In the first period [2000-2003], the *Enterobacteriaceae* resistance rates of imipenem and meropenem are both 0.5%, and the rates increased stably afterwards. From 2009 to

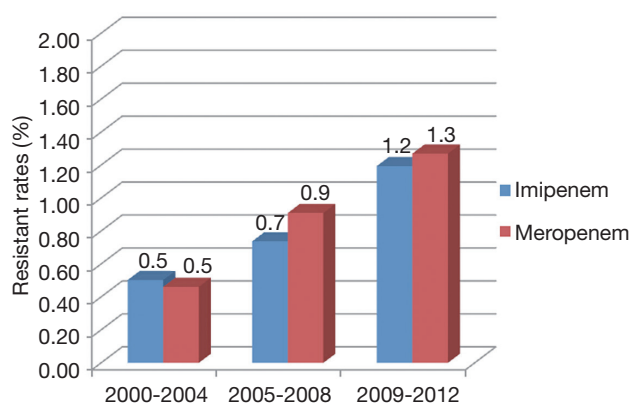


Figure 3 Resistance to imipenem and meropenem in *Enterobacteriaceae* during 2000-2012.

2012, the resistance rates rise to 1.2% (95% CI, 0.9-1.5%) and 1.3% (95% CI, 1.0-1.7%). No obvious difference is observed between the resistance rates of imipenem and meropenem.

CRE in different Asia countries

For all the 49 Asian countries (or regions), only 37.5% [19] of them contribute epidemiology data of CRE, and 18 of them provide exact resistance rates during the study years [2000-2012]. The rest ones provide either only case reports (Israel, Oman, Bangladesh and so on) (9-13) or no information at all (Figure 4).

Among all the *Enterobacteriaceae* collected, the rates of resistance to imipenem vary from 0.1% (95% CI, 0.1-1.2%) to 5.8% (95% CI, 2.2-11.0%) with different Asian countries. The top three countries with the highest resistance rates to imipenem are Indonesia (5.8%), Vietnam (3.0%) and Philippines (3.7%). Singapore (0.1%), Kuwait (0.1%) and Japan (0.2%) show the lowest resistance rates. Rate of resistance to imipenem in China is 1.4% (95% CI, 1.0-1.6%), higher than the average rate (0.7%).

As to meropenem resistance in *Enterobacteriaceae*, only six countries contribute available data. The average rate of resistance to meropenem is 0.9% (95% CI, 0.7-1.2%). Turkey (2.9%) and India (2.6%) show higher resistance rates than others. In China, the prevalence of meropenem resistance rate among *Enterobacteriaceae* is 1.4% (95% CI, 1.0-1.9%).



Figure 4 Prevalence of CRE in different Asian countries. CRE, carbapenem resistant *Enterobacteriaceae*.

CRE in different species

Table 1 demonstrates the resistance pattern of imipenem and meropenem in each genus of *Enterobacteriaceae* from 2000 to 2012. The rank order of imipenem resistance in *Enterobacteriaceae* is as follows: *Serratia* spp. > *Proteus* spp. > *Klebsiella* spp. > *Enterobacter* spp. = *Citrobacter* spp. > *E. coli*. The rates of resistance to meropenem in each genus generally follow the same order as imipenem.

Three most commonly isolated *Enterobacteriaceae* genera, *Klebsiella*, *E. coli* and *Enterobacter*, are analyzed to discover their resistance trends to carbapenems (imipenem and meropenem) during the collection years (Table 2).

Among the three most common *Enterobacteriaceae* genera, *Klebsiella* spp. has the highest resistance rates to imipenem and meropenem. In 2000-2004, its resistance rates are 0.5% (95% CI, 0.2-0.8%) and 0.3% (95% CI, 0-0.8%), and they keep stably escalating trends during the later years. In 2009-2011, they have risen to 1.9% (95% CI, 1.3-2.7%) and 2.4% (95% CI, 1.5-3.5%), over three times higher than the first period.

Similar to *Klebsiella* spp., *Enterobacter* spp. shows increasing resistance to imipenem and meropenem as well. Its rates are 0.4% (95% CI, 0.3-0.5%) and 0.2% (95% CI,

Table 1 Rates of resistance to imipenem and meropenem in each genus in *Enterobacteriaceae* from 2000 to 2012 (14-37)

| Genus | Imipenem | | Meropenem | |
|---------------------|----------------|-------------|----------------|-------------|
| | R% (95% CI) | % weight | R% (95% CI) | % weight |
| <i>E. coli</i> | 0.2 (0.1-0.3) | 32.9 | 0.2 (0.1-0.4) | 25.6 |
| <i>Klebsiella</i> | 0.8 (0.6-1.1) | 26.3 | 1.4 (0.8-2.1) | 25.5 |
| <i>Enterobacter</i> | 0.7 (0.5-0.9) | 19.2 | 0.8 (0.5-1.1) | 24.9 |
| <i>Serratia</i> | 1.8 (0.2-2.5) | 11.6 | 1.6 (0.4-3.8) | 13.4 |
| <i>Citrobacter</i> | 0.8 (0.3-1.5) | 5.7 | 1.6 (0.8-2.6) | 4.5 |
| <i>Proteus</i> | 1.6 (0.9-2.6) | 4.3 | 0.9 (0.6-1.3) | 6.2 |

0.1-0.4%) respectively. When it come to the third period, the resistance rates markedly increased to 1.4% (95% CI, 1.1-1.7%) and 1.2% (95% CI, 0.8-1.7%).

E. coli exhibits the lowest carbapenems resistance rates among all the *Enterobacteriaceae* genera, and no obvious increase is found among imipenem resistance rates calculated from three periods. The prevalence of meropenem resistance shows escalating trend and it has risen to 0.5% (95% CI, 0.2-0.9%) in the third period, compared with the rates in previous two periods (0.1%).

Discussion

Enterobacteriaceae are inhabitants of the intestinal flora and important pathogens in both nosocomial and community settings. As illustrated in this study, CRE exhibits rapid and extensive dissemination across Asian area. This may be caused by the factors listed below. Firstly, in terms of *Enterobacteriaceae*, they spread easily between humans by hand carriage as well as contaminated food and water; they also have a propensity to acquire genetic material through horizontal gene transfer, mediated mostly by plasmids and transposons (60,61). Secondly, among the main mechanisms causing carbapenem resistance in *Enterobacteriaceae*, the acquisition of specific genes encoding carbapenemases plays the most important role (62). Lots of research papers show that genes encoding carbapenemases are mostly plasmid-located and associated with various mobile genetic structures, such as transposons or integrons (63). Such a characteristic certainly accelerates inter-/intra-species dissemination of carbapenemase genes. Thirdly, the high prevalence of ESBLs and the limited therapeutic options to MDR infections increase the consumption of carbapenems. CRE are the successful products under the drug selective

pressure. Other factors, such as the international travel and medical tourism, long term hospitalization and frequent use of invasive medical devices, have also fueled the rapid rise in carbapenems resistance (64).

According to our research, seven countries, including Vietnam, Thailand, South Korea, Japan, China, India and Turkey, provide national or multi-centers surveillance data. Studies performed in other countries are mostly conducted in single institutions or a small number of tertiary care hospitals. As we all know, most countries in Asia are developing countries with poor medical and health conditions, and the prevalence of CRE in such area are not optimistic. Therefore, there's urgent need to establish more and better surveillance in Asian countries to obtain a clearer and more accurate pictures of this situation.

The present study demonstrates the increasing prevalence of CRE from a whole view of Asia, where data from each country (or regions) also shows consistent trends. In mainland China, according to the report of Mohanrin, the imipenem resistance of *E. coli* and *K. pneumoniae* in 2004-2005 is 0.0% and 0.7% (65), while the rate increases to 0.5% and 2.7% in 2010 (66). In Korea, the carbapenems resistance also follows such tendency. As the result of the KONSAR (67), *E. coli* and *K. pneumoniae* is completely sensitive to imipenem in 2000, while in 2009, the resistance rates come to 0.1% and 0.5% respectively (68).

Besides the common trend and resistance level, geographic variation also exhibits in some regions. A report in the UAE shows the rates of resistance to imipenem in *E. coli* and *Klebsiella* spp. are 35.7% and 29.8% respectively (1), much higher than the average rates. This phenomenon alarms us that it is important to assess susceptibility patterns by a specific country or region because they may provide more accurate data for treatment and control of CRE infections in local area.

Klebsiella spp. accounts for the largest proportion of carbapenem resistance in *Enterobacteriaceae*, namely 39.3%. This outcome is not surprising with the fact *Klebsiella* spp. is not only the leading cause of nosocomial infections but also a notorious "collector" of multidrug resistance plasmids. As the most important carbapenemases, KPC enzymes disseminate mainly among *Klebsiella* spp., and result in decreased susceptibility to carbapenems (69). Antibiotic treatment to carbapenem resistant *Klebsiella* spp. is limited to a few choices, typically including colistin, tigecycline, and one or more aminoglycoside. Further research is needed to investigate the best therapy to these patients.

Among all the *Enterobacteriaceae* species collected,

Table 2 Resistance to impenem and meropenem in *Enterobacteriaceae* during 2000-2012^a

| Study period | <i>Klebsiella</i> spp. | | <i>E. coli</i> | | <i>Enterobater</i> spp. | |
|--------------|------------------------|-----------------------|----------------|----------|-------------------------|----------|
| | R% (95% CI) | % weight ^b | R% (95% CI) | % weight | R% (95% CI) | % weight |
| 2000-2004 | | | | | | |
| Impenem | 0.5 (0.2-0.8) | 30.5 | 0.2 (0.1-0.3) | 46.5 | 0.4 (0.3-0.5) | 37.0 |
| Meropenem | 0.3 (0.0-0.8) | 15.5 | 0.1 (0-0.2) | 20.1 | 0.2 (0.1-0.4) | 25.6 |
| 2005-2008 | | | | | | |
| Impenem | 0.4 (0.2-0.7) | 37.1 | 0.3 (0.1-0.5) | 28.2 | 0.7 (0.4-0.1.1) | 45.9 |
| Meropenem | 0.3 (0.0-1.3) | 22.9 | 0.1 (0.0-0.5) | 31.2 | 0.9 (0.7-1.2) | 18.4 |
| 2009-2012 | | | | | | |
| Impenem | 1.9 (1.3-2.7) | 32.4 | 0.2 (0.1-0.4) | 25.3 | 1.4 (1.1-1.7) | 17.2 |
| Meropenem | 2.4 (3.5-1.5) | 61.6 | 0.5 (0.2-0.9) | 48.8 | 1.2 (0.8-1.7) | 56.1 |

^a, references (38-59); ^b, weight refers to how much each row contributes to the "2000-2012" years. CI, confidence interval.

Serratia spp. exhibits the highest carbapenems resistance rates. It is an opportunistic pathogen with ability to survive and grow under extreme conditions (70). During the past decades, *Serratia* spp. has played a more and more important role in the nosocomial infections, and has already become a great threat to patients' health with mortality rates of approximately 40-50% in *S. marcescens* bacteremia (71,72). In China, the prevalence of carbapenem resistance in *S. marcescens* has risen to 5.6% in 2008, obviously higher than other genus (73). The carbapenems resistance in *Serratia* spp. was found highly related to chromosomally encoded β -lactamases, SME (74). Three point mutant variants of SME (SME-1, SME-2 and SME-3) have been sporadically isolated throughout the world (75,76). These enzymes significantly hydrolyse penicillins, cephalosporins and carbapenems and are inhibited by clavulanic acid. All these facts above alarm us that more attention should be focused on *Serratia* spp., a potential reservoir for carbapenems resistant *Enterobacteriaceae*.

We have recognized several limitations associated with this systematic review. Firstly, systematic reports in developing countries are rare while the hygiene conditions in those countries are often worrisome. So the real situation of CRE in Asia may be underestimated. Secondly, biased sampling may not be totally excluded. For instance, some studies have been conducted in a single institution or a small number of tertiary care hospitals covering limited times. Thirdly, the method of antimicrobial susceptibility test and interpretation of the result also influence the

resistant rates. At last, the change of CLSI breakpoints in the year of 2010 may increase the carbapenems resistant rates in *Enterobacteriaceae*. Despite these limitations, this study represented a current assessment of the prevalence of carbapenems-resistant *Enterobacteriaceae* across the Asian area.

The main preventive efforts for containing the emergence and spread of carbapenem-resistant *Enterobacteriaceae* could be directed at antimicrobial stewardship and infection control. A case-case control investigation has found that antimicrobial exposure is the strongest independent predictor for CRE isolation and concluded that antimicrobial stewardship plays a pivotal role in preventing CRE isolation (77). Therefore, optimizing and limiting unnecessary antimicrobial use are great weapons for us to fight against the emergence of CRE.

Interventions such as hand hygiene, contact precautions, healthcare personnel education, minimizing device use and so on are recommended in the guidelines published in USA and Europe for interventions to control CRE transmission in health care facilities (78,79). What's more, two important approaches emphasized in the guidelines are: to recognize CRE as epidemiologically important and to understand the prevalence in their region. As illustrated in this study, it still needs lots of work to establish better surveillance programs in most Asian countries. So we advocate that surveillance programs would be set up Asia-wide and even worldwide. Only when we cooperate together to prevent the diffusion of CRE from every link, can we survive in this storm of CRE.

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