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Systematic Review

The scourge of carbapenem resistant *Enterobacteriaceae*: how to fight back

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ABSTRACT

The *Enterobacteriaceae* species cause both community acquired and health care associated infections like bloodstream infections, ventilator-associated pneumonia, intra-abdominal infections and urinary tract infections. Carbapenem-resistant *Enterobacteriaceae* (CRE) have been included in the list of global priority pathogens (GPP) declared by WHO in 2017. These infections pose a serious threat due to the associated significant morbidity and mortality. The mechanisms of antimicrobial resistance in these organisms are numerous; however, β-lactamase genes carried on mobile genetic elements are a key mechanism for the rapid spread of these antibiotic-resistant strains on a global scale. The carbapenem resistance (CR) in *Enterobacteriaceae* has been recognized for the past two decades, but the carbapenemase-producing *Enterobacteriaceae* (CPE) has been a more recent issue and is spreading at an alarming pace worldwide. In this article, we conducted a systematic literature search of the PubMed, Embase, Web of Science and Cochrane Library databases to identify relevant studies that reported the epidemiology and the outcomes for hospitalised patients with confirmed infections due to CRE and carbapenem-susceptible *Enterobacteriaceae* (CSE) published between 1 January 2010 and 30 August 2023.The results emphasize that patients with CRE infection still face a greater risk of mortality and need an urgent need for newer antibiotics and appropriate treatment regimens to reduce the risk of morbidity and mortality.

Keywords: Gram-negative bacteria, *Enterobacteriaceae* infections, Carbapenemases, Drug resistance, Carbapenem-resistant, Ceftazidime-avibactam

INTRODUCTION

Due to the limited availability of effective antibiotics and high mortality rates, multidrug-resistant (MDR) and extensively drug-resistant (XDR), gram-negative bacteria (GNB) infections have become a major challenge. These pathogens include CRE, which harbour KPC, NDM, and OXA-48-like genes; MDR/XDR *Pseudomonas aeruginosa*, which produces VIM, IMP, or NDM carbapenemases combined with porin alteration; and *Acinetobacter baumannii* complex, which produces OXA-23 and OXA-58 carbapenemases.[1]

The emergence of antimicrobial resistance (AMR) has led to a decline in the effectiveness of first-line antibiotics. Consequently, patients in developing countries may not have access to or cannot afford more advanced therapies, worsening their prognosis situation.[2]

Moreover, illnesses due to bacteria that produce carbapenemases or resistant to carbapenemases show high mortality rates.[3]

When treating these resistant infections, parenteral polymyxins have shown to have poor pharmacokinetic profile. When combined with aztreonam, ceftazidime-avibactam is active against metallo beta lactamases and it is regarded as a last-resort for Ambler class A/C/D enzyme-producers. The medical community must strictly execute the antibiotic stewardship programs in order to mitigate the escalating resistance patterns.[1]

This review is centered on Indian and global trends with regards to economic impacts, management strategies and resistance mechanisms for these CR and CP GNB.

This systematic review conducted following guidelines of Cochrane guidance and the preferred reporting items for systematic reviews and meta-analyses. We conducted a literature search of databases of PubMed, Embase, web of science and the Cochrane Library for relevant studies published between 1 January 2010 and 30 August 2023. The search strategy was designed by combining the terms for 'Gram negative bacteria', 'CR', '*Enterobacteriaceae*', 'carbapenem non-susceptible' and 'CP'.

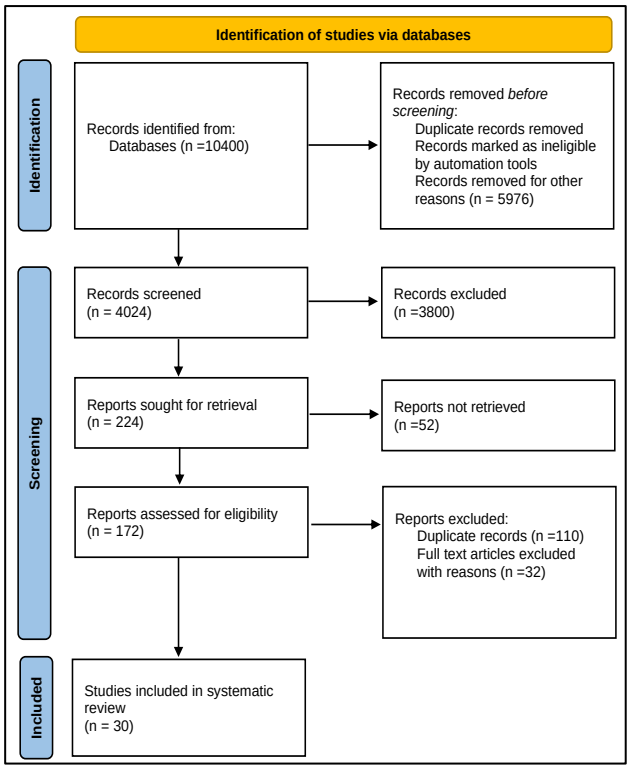

Figure 1: The study selection procedure.

METHODS

Inclusion criteria

Case-control study, cohort studies, review articles, meta-analysis, studies published between 1 January 2010 and 30 August 2023 and studies that assessed the mortality of inpatients with confirmed infections due to CRE and CSE were included.

Exclusion criteria

Studies not providing mortality data with CRE infection, studies that focused on other antibiotics resistance and publications like editorials and letters were excluded.

RESULTS

After conducting a literature search, 10400 studies were found, out of which, 30 studies were chosen for final review.

There were two studies from Africa while majority of the research (n=12) were carried out in Asia, the America (n=10) and Europe (n=6) including multicentre studies.

Bloodstream infections were the most commonly found followed by urinary tract infections and pneumonia.

One popular area of discussion is the mortality due to CRE infections with eleven studies reported mortality outcomes regardless of the specific species while four studies reported outcomes due to *E. coli* and 15 studies due to *K. pneumoniae*.

Mortality measures commonly reported were in-hospital mortality, 28-day, 30-day, infection-related, 14-day and ICU mortality. Despite the fact that there was a lot of variation in these findings, CR was linked to a higher risk of overall death.

Some studies have discussed heterogeneity and identified some confounding factors related to patients, infections, organisms and therapies. ICU mortality had the lowest pooled heterogeneity among 14-day mortality, 7-day mortality and mortality in the ICU. Compared to 14-day mortality, the pooled RR for 6- or 7-day was higher. However, in studies that focused on patients infected with *E. coli* pathogens (p=0.214; p=0.115) or oxacillinase (OXA)-producing *Enterobacteriaceae* (p=0.247; p=0.110), there was no significant difference in terms of either relative or absolute in-hospital mortality between CRE infection and CSE infection.

Furthermore, the variations in geographic location and economic condition have not been taken into account in these previous evaluations. The patients in the developing nations might not be able to access the costlier second- and third-line antibiotics or they would not be economical, having a negative impact on their prognosis.

CRE strains with varying carbapenemase types are prevalent in different parts of the world, thus impacting on the mortality patterns with two studies showing different mortality rates as per the geographic location.

The results for Zhou et al meta-analysis suggested that research published between 2017 and 2020 found a greater RR for 28-day or 30-day mortality for CRE infections versus CSE (p=0.006) than earlier studies.[17]

Regarding infection-related mortality, none of the studies like the European study or another study on patients infected with OXA-producing *Enterobacteriaceae* discovered a statistically significant difference in the mortality for CRE and CSE infections.

Regarding RR, the meta-regression for in-hospital mortality revealed that CR had a significantly higher impact on in-hospital mortality in research published between 2017 and 2020 compared to research published between 2011 and 2013 (p=0.027) and 2014 to 2016 (p=0.061). Furthermore, there appears to be a positive correlation between the year of publication and the impact of CR on 28 or 30-day mortality (p=0.006).

This effect can be explained with the smaller number of effective antibiotics due to development of resistance against molecules like colistin causing difficulty for management.

Twenty studies were reviewed for determining the risk factors for mortality in infections with *Enterobacteriaceae* with three studies reporting no relation of CR and increased risk of mortality after adjusting for patient-related factors such as age, sex, the severity of underlying illness and comorbidities.

This review also includes several papers that indicate the effect of CR on mortality was likely due to inappropriate initial antibiotic with 11 studies validating this finding while nine studies refuting it.

An array of seven studies have shown higher mortality in patients with CRE infections treated with monotherapy as compared to combination therapy. Other treatments such as adjuvant therapy, use of tigecycline and aminoglycosides may be associated with increased mortality in Klebsiella pneumoniae infections as well as isolation of KPC as an independent predictor of mortality regardless of initial treatment and patient characteristics.

The unweighted mean of in-hospital mortality as well as 28- and 30-day mortality among CSE patients in studies done from 2017 to 2020 is 11.69% and 13.43%, respectively, a decline in recent years due to evolution of medical science and therapy.

Additionally, a significant difference between infection types was found for mortality attributable to infection (p=0.075). Specifically, patients with neurosurgical infections had a significantly higher mortality, possibly as a result of the difficulty in treating CRE meningitis or encephalitis during neurosurgery.

Table 1: Ambler classification of beta lactamases.

Ambler class	Enzymes	Mechanism	Resistance to carbapenems	Resistance to aztreonam	Newer antibiotics which are active
A	KPC IMI SME	Serine based	High	Resistant	Ceftazidime avibactam, aztreonam avibactam, imipenem relebactam, meropenem vaborbactam, cefiderocol, Eravacycline, plazomicin
D	OXA	Serine based	Medium	Susceptible	Ceftazidime avibactam, aztreonam avibactam, cefiderocol, eravacycline, Plazomicin
B	VIM IMP NDM	Zinc based	Variable	Susceptible	Aztreonam avibactam, cefiderocol, eravacycline, plazomicin

The 76.5% studies described KPC, NDM and OXA as commonly detected carbapenemases with some studies describing porin mutations as an added mechanism of resistance and ICU stay having the highest reported odds ratio followed by exposure to antibiotics, medical equipment and invasive procedures.

Various interventions for the infection control were described like the use of barrier and/or contact precautions followed by patient cohorting, active surveillance, control of antibiotic use, restricted or the no admission to the affected wards, the use of chlorhexidine for the patient disinfection.

DISCUSSION

Microbiology

Among the enterobacterales, the most frequent mechanism of resistance is the production of beta lactamases hydrolysing penicillin, cephalosporins, carbapenems and monobactams. Furthermore, there are other mechanisms

which make these strains resistant to a wide range of antibiotics, including aminoglycosides, fluoroquinolones and the trimethoprim sulfamethoxazole.

β lactamases are classified into the main groups as follows (Table 1).[4]

Based on their tertiary chemical structures, classes A, C and D enzymes have a nucleophilic serine residue while class B enzymes (metallo-β-lactamases, MBL) require Zn^{2+} for their activity.

CR may also be caused by the decreased permeability due to the porin modifications. The most frequent mechanisms of CR in *Pseudomonas aeruginosa* is the loss or reduced copy numbers of OprD as well as the overproduction of active efflux pumps, the AmpC-lactamase and ESBLs, an increasing prevalence of carbapenemases [Verona integron-encoded metallo-lactamase (VIM) and the New Delhi metallo--lactamase (NDM)]. Resistance of *Acinetobacter baumannii* to carbapenems may be encoded by chromosomes as well as carry plasmid-mediated carbapenemases.[5]

Global trends of CR

Carbapenem-resistant gram-negative organisms including CRE, CR *Pseudomonas aeruginosa* (CRPA) and CR *Acinetobacter baumannii* (CRAB) pose a major global threat.[6]

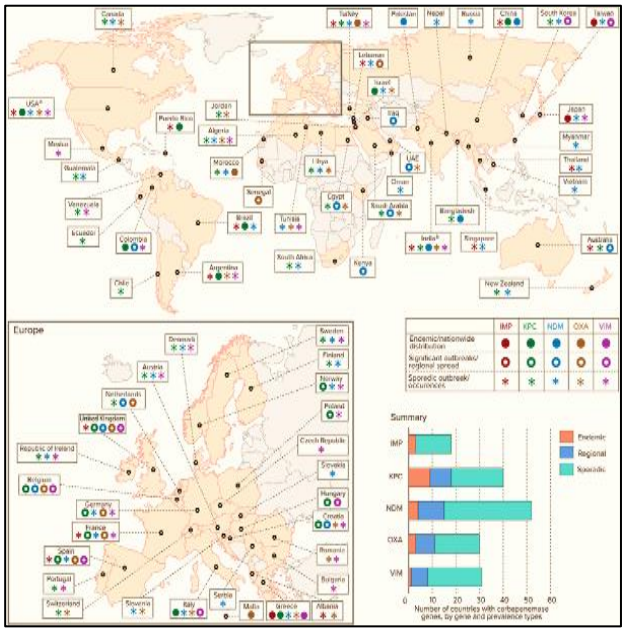

Figure 2: Global distribution of beta lactamases in *Enterobacteriaceae*, region wise.[7]

a. KPCs, b. OXA mainly refers to OXA-48, except in India, where it refers to OXA-181. Abbreviations: IMP, active on imipenem metallo-β-lactamase; KPC, Klebsiella pneumonia carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase-type carbapenem-hydrolysing β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

In Aldali et al study approximately 150 different isolates of KPC-producing *Klebsiella pneumonia* spp. have shown resistance to carbapenems and ciprofloxacin but susceptible to colistin and tigecycline. All the KPC-producing *E. coli* were susceptible to colistin, tigecycline, gentamicin and amikacin. The percentage of NDM carrying CRE was less than 1% for both CRKP and CRE *E. coli*. The MBL producing CRKP showed a high resistance against meropenem, ceftazidime, cefotaxime, aztreonam, ciprofloxacin and gentamicin with susceptibility to colistin and tigecycline. The second most commonly found carbapenemase between CRE *E. coli* and CRKP is the OXA 48 carbapenemase with OXA 48 producing CRKP resistant to meropenem, ceftazidime, aztreonam, cefotaxime, gentamicin and ciprofloxacin.[8]

A 2021 Hovan et al study on 155 patients with CRE BSI reported that KPC as the predominant carbapenemase in the CP-CRE group (92%).[9]

Falagas et al meta-analysis showed that the mortality attributed to CRE infection varied from 26 to 44% while the Zarkotou study showed the mortality rate to be 34% with older age, APACHE II score at infection onset and inappropriate antibiotic treatment as risk factors.[10,11]

Indian epidemiology studies

CRE have emerged as a public health problem in India with their intestinal colonisation considered as a risk factor for development of systemic infections.[12]

It is important to know that not all CPE are CRE. CPE includes *Enterobacterales* with low carbapenem minimum inhibitory concentrations (MIC) which are carbapenem susceptible phenotypically.[13]

In India, the prevalence of CRE varies from a range of 1.6% (Pune) to that of 38.4% (PGIMER Chandigarh).[14,15]

The ATLAS analysis (2018-19) has demonstrated that among *K. pneumoniae* isolates, OXA-48 producers were 52% and co-production of NDM with OXA-48 was found in 27% while NDM was predominantly identified in 68% followed by OXA-48 in 24% isolates among *E. coli* isolates with CR found in 51% of *K. pneumoniae* and 24% of *E. coli*.[16]

Previous hospitalisation and cumulative antibiotic exposure history with previous use of beta-lactams and carbapenems were identified as significant risk factors associated with CRE infection.[18]

The 28 patients who were being treated with beta-lactams during the current admission developed resistant infections in Sharma et al study ($p<0.05$).[19] The association between CRE colonisation and medical device use (urethral catheterisation, central lines and mechanical ventilation) has been recognised as risk factors for CRE colonisation.[15,20]

The length of stay [LOS] in the hospitals increased the risk of CRE colonisation. For CRE colonised patients, 17 days versus 9 days for non-colonised patients ($p<0.001$).[19]

Rectal colonisation with CRE has been identified as an important risk factor for the development of subsequent CRE infection.[18]

The majority of organisms from the human gut flora are from *Enterobactericeae* family. Furthermore, CPE are spread rapidly due to the horizontal transmission of plasmid encoding genes responsible for carbapenemase production occurring mainly by faeco-oral route in community-acquired infections as well as in hospitalized patients.[21]

The poor compliance by the health care individuals and the patients for hand hygiene have contributed to the high prevalence of CRE infections in surgical patients.[22]

Patients with CRE-colonisation had a 10.8-fold higher risk of CRE infection than in non-colonised patients.[18] Similarly, the Sharma et al study reported that 89.2% of CRE colonised patients developed CRE infection during the hospital stay.[19]

In the study by Pawar et al 82% of the CRE isolates belonged to Klebsiella pneumoniae (63%) and *E. coli* (19%) with similar finding observed in northern India (Chatterjee et al) where 66% of total CRE isolates were *K. pneumoniae* and *E. coli*.[23,24]

In a similar study by Lorenzoni et al, 95.7% *K. pneumonia* strains were responsible for carbapenemase production with the major gene in these organisms being blaNDM1.[24,25]

The mortality rate was found to be higher in CRE colonized patients (27.0%) compared with non-colonised patients (20.0%) ($p>0.05$) and mortality rates of 40-50% due to invasive CRE infections.[18,19]

The Kang et al study showed 33% mortality in CRE colonised patients as compared to 9.9% mortality in non-colonised patients ($p=0.004$).[26]

CRE in pediatrics

As seen in adults, there has been a progressive increase in the prevalence of MDR infections in the paediatric age group with studies reporting CR in the United States of 0% in 1999 -2000 to 0.47% in 2010- 2011 among *Enterobacterales*, 9.4% in 1999 to 20% in 2012 among *P. aeruginosa* and 0.6% in 1999 to 6.1% in 2012 among *A. baumannii* isolates.[4,27-29]

The prevalence studies from Europe report that CR among *Klebsiella pneumoniae* strains in adults was higher than that seen in children (13.5% versus 6.5%), whereas CR in *P. aeruginosa* isolates was more frequently found in children (30.7% versus 23% in adults).[30]

A report from Greece on the central line-associated BSIs (CLABSIs) in children including NICUs, PICUs and oncology wards described a prevalence of CR as 45% among *Klebsiella spp*., 36% among *Enterobacter* spp., and 38% among *P. aeruginosa* strains.[31]

Europe reported the highest burden of attributable deaths and disability-adjusted life years caused by infections with antibiotic-resistant bacteria with carbapenem resistant or colistin-resistant *Escherichia coli*, *K. pneumoniae*, *Acinetobacter* spp., and *P. aeruginosa* strains as a group as the third most significant cause of attributable deaths and disability-adjusted life years within this age group.[4]

A study of neonatal sepsis from three NICUs in India showed alarming CR rates of 78% in *Acinetobacter* spp, 31% in *Pseudomonas* spp., 35% among *Klebsiella* spp., 20% among *Enterobacter* spp. and 15% among *E. coli* spp. with notable implications since the empirical treatment proposed by the various guidelines would not be adequate in these settings.[32] Similarly, the suboptimal infection control programs have been one of the most important factors proposed in relation to the high burden of CRE found in NICUs and PICUs in some hospitals compared to that found in adult units from the same hospital.[33]

CRO (carbapenem resistant organisms) infections in the paediatric population have been shown to increase the risk of mortality 6- to 11-fold compared to that in children with non-CRO infections.[4]

One study on 50 health care-acquired CRE BSIs in children in India, mostly due to NDM-producing *K. pneumoniae*, found PICU admission, intubation, inotropic support, respiratory source, and failure to clear bacteraemia as risk factors for motality.[34]

Specific recommendations for antibiotic therapy for CRE infections in paediatric patients are based on studies including only adults.[4]

Furthermore, the FDA and EMA approvals of antibiotics in patients under 18 years old makes the treatment regimens for CRO infections more complicated in children. Antimicrobial treatment needs to be individualized according to the severity and the source of infection and the susceptibility profile of the isolated bacteria. In children, when a CRO is isolated, expert consultation is always warranted with the need for a rationalized antimicrobial treatment approach.[4,35]

Therapeutic options for CRE

Due to recent resistance patterns, clinicians have been forced to re-examine therapies for CRE which have been rarely used because of their side effects or effectiveness.[36]

Zhang et al study emphasized about the combination therapy of carbapenems plus metronidazole for the favourable therapy in *K. pneumoniae*-induced liver abscess.[37]

Polymyxins remain the cornerstone therapy for empirical therapy for the treatment of CRE infections with preference given to combination therapy in patients with high mortality risk score such as increment-CPE score (ICS) or worsening SOFA scores (>2) in the settings of NDM- strains in Indian population.

Tigecycline and fosfomycin have shown considerable potential when used in combination regimes.[38]

β-Lactam ring BLIs (clavulanic acid, sulbactam, tazobactam) are the older molecules with their activities limited to class A ß lactamases, ESBLs, some class C and D β-lactamases (AmpC and OXA-1).

New to the BLI space are avibactam and relebactam and molecules with enhanced chemistries targeting PBPs (penicillin binding proteins) like durlobactam, zidebactam, and nacubactam. In addition, some older combinations are revamped where the beta lactam has been replaced (ceftolozane-tazobactam, cefepime-tazobactam and ceftibuten-clavulanic acid).[39]

The Yang et al meta-analysis including eleven studies with 1111 patients showed that the use of ceftazidime avibactam demonstrated a lower 30-day mortality ($p<0.0001$), higher clinical success ($p<0.0001$) and lower nephrotoxicity ($p<0.05$) with respect to efficacy and safety compared with polymyxins in CRE infections.[40,41]

These novel agents like ceftazidime + avibactam or meropenem + vaborbactam do not cover the NDM which limits their use in Indian setting.[38]

Ceftolozane-tazobactam with a potent activity against P. aeruginosa including MDR strains is a potential treatment regimen against ESBL-producing *Enterobacteriaceae*.

Meropenem-vaborbactam, approved by the FDA for treatment of cUTI including pyelonephritis in adults, can be useful against many class A and C enzymes including KPC with no activity against *P. aeruginosa in vitro.*

Imipenem-cilastatin-relebactam, approved for the treatment of cUTIs and cIAIs in adults with limited or no alternative therapies available, is being further evaluated in trials for HABP and VABP. However, loss of activity is reported in *Enterobacteriaceae* due to lack of expression of porins.

Newer BL-BLI combinations are in various stages of clinical development. (cefepime-enmetazobactam, cefepime-tazobactam, aztreonam avibactam, sulbactam-durlobactam, cefepime-zidebactam, meropenem-nacubactam, cefpodoxime proxetil, cefepime-taniborbactam).

Durlobactam, zidebactam, nacubactam have a dual PBP and β-lactamase inhibitor activity (β-lactam 'enhancers) as they not only inhibit the β-lactamases, but also target PBPs.

The combination of aztreonam-avibactam will be entering phase 3 trials for the treatment of serious bacterial infections due to MBLs. Similarly, there is a pioneer in the development of antimicrobial niche therapy with sulbactam-durlobactam to target MDR Acinetobacter spp. in HABP, VABP, and bacteremia.[39]

CONCLUSION

Problems with CRE is delay in its confirmation in average laboratory set up. Though molecular methods are gold standard, they have their own limitations in the form of time consumption and cost effectiveness. For prevention of CRE infections, various other control measures have been proposed such as infection control measures in the form of contact precaution, hand hygiene, proper medical waste disposal, restricted use of invasive devices, epidemiological screening of rectal and perirectal swabs and antibiotic stewardship. There are discussions from the growing burden of CRE in Indian tertiary healthcare setting, the need for identification of resistance mechanisms and the growing utility of combination therapies in treating this subset of critical patients. Further research with high-quality clinical studies, case series, and meta-analyses to address this menace is a pressing priority.

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