Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

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Carbapenem-resistant strains have emerged among species belonging to the *Enterobacteriaceae* family. Carbapenemases are a class of enzymes that can confer resistance to carbapenems and other Beta-lactam antibiotic drugs, but not all carbapenemase-producing isolates are carbapenem-resistant. Among the known carbapenemases are *Klebsiella pneumoniae* carbapenemase, or KPC, and Verona integrin–encoded metallo-Beta-lactamase, or VIM. Several outbreaks caused by carbapenem-resistant *Enterobacteriaceae*, or CRE, have been recorded in health care facilities around the world, and in some places, CRE have become endemic. Serious concurrent conditions and prior use of fluoroquinolones, carbapenems, or broad-spectrum cephalosporins have been independently associated with acquisition of infections caused by CRE.

Several studies have provided data regarding clinical outcomes for CRE infections. However, controversy remains concerning the number of deaths among persons infected with CRE compared with the number among persons infected with carbapenem-susceptible *Enterobacteriaceae,* or CSE. In this context, the goal of our study was to evaluate the number of deaths attributable to CRE infections by conducting a systematic review and metaanalysis of the available data.

The main finding of this metaanalysis is that the rate of CRE-attributable deaths ranged from 26 percent to 44 percent in 7 studies and was −3 percent and −4 percent, respectively, in 2 studies. Furthermore, CRE-infected patients had an unadjusted number of deaths 2-fold higher than that for CSE-infected patients.

Six of the included studies showed significantly more deaths among CRE-infected than CSE-infected patients. In the 3 remaining studies, the lack of a significant difference in death rates for the CRE-infected and CSE-infected patients could be explained by the similarity of underlying disease characteristics for the 2 groups of patients. On the contrary, in the 3 studies that provided relevant data, concurrent condition scores or severity of illness scores were higher in CRE-infected than CSE-infected patients. In 2 studies, the Acute Physiology and Chronic Health Evaluation II score was independently associated with death.

A critical finding of our metaanalysis is that the number of deaths was 2-fold higher among patients with bacteremia caused by CRE than among patients with bacteremia caused by CSE.

However, a significant difference in death rates was not detected between the 2 compared groups in studies reporting on patients with undetermined infections, patients with infections other than bacteremia, or patients among whom the percentage of bacteremia cases was low. Therefore, it could be suggested that the higher rate of death among patients with CRE infections, compared with CSE infections, is due to the higher rate of death among patients with bacteremia caused by CRE. The smaller number of patients included in this subgroup analysis, or 267 patients, compared with the number in the group who had bacteremia as the only infection, which was

718 patients, along with the considerable heterogeneity among the included studies, but not among the type of infection, may justify the absence of statistical significance. Apart from the sample size, other variables that have not been analyzed might have affected the strength of the death, or outcomes, analysis. Additional and larger studies reporting on infections other than bacteremia could elucidate this issue.

Many factors other than underlying concurrent condition or severity of illness at the initial medical visit could be responsible for the higher rate of death among patients with infections caused by CRE. A key relevant factor could be the higher frequency of inappropriate empirical treatments among the CRE patients. Only 2 of the included studies provided comparative data for patients who received appropriate empirical antibiotic treatment. Those studies showed that patients with infections caused by CRE were significantly more likely than those infected by CSE to receive inappropriate antibiotic treatment. In addition, another study showed that inappropriate empirical antibiotic treatment was independently associated with death in patients infected with KPC-producing *Klebsiella pneumoniae.* Apart from empirical treatment, the antibiotics used for treatment might be less effective against carbapenem-resistant infections as well. There are few published clinical data available on the effectiveness of colistin, tigecycline, fosfomycin, and gentamicin (which are likely to be active in vitro against CRE) for the treatment of CSE infections. From a pharmacokinetic–pharmacodynamic perspective, these agents might be suboptimal for the treatment of serious CRE infections, particularly bloodstream infections.

Five studies showed that carbapenem resistance or KPC production were independent predictors of death after adjustment for concurrent condition or severity of illness. KPC ST258, a widely distributed clone of KPC-producing *Klebsiella pneumoniae*, is considered a successful pathogen because of its ability to persist and spread, causing nosocomial outbreaks.

Data regarding the association between carbapenem resistance and virulence are scarce. In vivo and in vitro findings from1 study argued that carbapenem-resistant *Klebsiella pneumoniae* isolates are less virulent and fit than carbapenem-susceptible isolates in an antibiotic-free environment. This reduction in virulence and fitness was due to the loss of the major porins OmpK35 and 36 (through which Beta -lactams penetrate into *Klebsiella pneumoniae* isolates) and the presence and expression of OmpK26 in the resistant isolates.

In addition, the number of deaths attributable to CRE infections varied between studies; the susceptibility profile of the microbes in the control groups could have an influence on this outcome. Metaanalyses have shown that death rates are higher among patients with infections caused by extended-spectrum Beta -lactamase–producing or multidrug-resistant *Enterobacteriaceae* isolates than among patients with infections caused by non–extended-spectrum Beta -lactamase or non–multidrug-resistant isolates. However, the type of infection, concurrent conditions, prior antibiotic use, and the length of preinfection hospital stay could also have played a role in the observed differences in attributable death in our metaanalysis. Also, the virulence characteristics of the carbapenem-resistant isolates may differ among isolates with different types of carbapenemases or among strains that belong to different clones. This is important because some of the studies might have only included clonal isolates (for example, KPC isolates in an endemic setting), and others might have included isolates from different clones (for example, VIM producers that are typically polyclonal).

It should be emphasized that the findings of this systematic review and metaanalysis may not apply to the current Clinical and Laboratory Standards Institute breakpoints for carbapenem susceptibility.

Our study findings should be interpreted in light of certain other limitations. The effect of the possible confounding factors (for example, concurrent condition, severity of illness) on death could not be detected in the pooled analysis because only unadjusted data were entered. Furthermore, 8 of the 9 included studies had a retrospective study design. Data from such studies may be suboptimal compared with data from prospective studies, but this could not be tested due to the lack of prospective studies.

In conclusion, our findings suggest that the number of deaths attributable to carbapenem resistance is considerably high among persons with *Enterobacteriaceae* infections. Further original studies are needed to determine the reason or reasons for the increased risk for death from carbapenem-resistant isolates versus carbapenem-susceptible isolates. Our findings imply a need for strict infection control measures and a need for new antibiotics to protect against CRE infections.

I'm Dr. Mike Miller, for *Emerging Infectious Diseases*, and I've been reading an abridged version of the article Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections.You can read the entire article online and in the July 2014 issue of Emerging Infectious Diseases at cdc.gov/eid.

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