

# Correlations of Antibiotic Use and Carbapenem Resistance in *Enterobacteriaceae*

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**Epidemiological studies have shown a link between carbapenem use and resistance; however, the clinical relationship between antibiotic consumption and the epidemiology of carbapenem-intermediate or -resistant *Enterobacteriaceae* (CIRE) remains unclear. This study sought to analyze temporal antibiotic consumption trends for relationships with incident CIRE. In total, 310,892 days of therapy and 55 deduplicated CIRE were analyzed. When conservative corrections were applied for multiple comparisons, carbapenem class use and piperacillin-tazobactam use retained significant positive and negative relationships with the incidence of CIRE, respectively.**

Carbapenem-intermediate or -resistant *Enterobacteriaceae* (CIRE) are of increasing concern and have rapidly spread globally (1–3) and in the United States (4–6). The midwestern United States has not been spared from the emergence of CIRE. The first reported isolates of CIRE were *Klebsiella pneumoniae* strains, and mobile genetic plasmids have subsequently spread to other Gram-negative rods (7). While epidemiological studies have shown a link between carbapenems and resistance in nonfermentative Gram-negative organisms (8–12), the contribution of antibiotic consumption to CIRE incidence remains unclear. As CIRE are incident in the midwestern United States, we used this optimal opportunity to analyze temporal antibiotic consumption trends for relationships with incident CIRE.

This study was performed at Northwestern Memorial Hospital (NMH), an 897-bed, tertiary-care academic medical center located in Chicago, IL. Broad-spectrum Gram-negative antibiotics with a potential for influencing CIRE and in use at NMH were included in the analysis. Consumption was measured as numbers of days of therapy (DOT) per 1,000 patient days (13). DOT were aggregated quarterly from 1 January 2006 through 31 December 2010. Quarterly compilation allowed capture of immediate and time-delayed effects of antimicrobial use on resistance (14, 15). These antibiotics included  $\beta$ -lactams (aztreonam, cefepime, ceftazidime, ertapenem, imipenem-cilastatin, meropenem, piperacillin-tazobactam), fluoroquinolones (ciprofloxacin, moxifloxacin), glycolcyclines (tigecycline), and polymyxins (colistin methanesulfonate). Only antibiotics achieving relevant systemic concentrations were captured; any antibiotic prescribed as an ophthalmic solution, ointment, or enema was excluded from the study. Antibiotics with formulary status throughout the time period were analyzed individually. Since the preferred carbapenem(s) changed at our institution during the study period, carbapenems were analyzed as a combinatorial class.

All isolates were obtained from clinical cultures from 1 January 2006 through 31 December 2010. Only the first isolate per patient per quarter was included in the study, and incidence rate was calculated by standardizing the at-risk population to 1,000 patient hospitalization days. Susceptibility testing for all isolates was performed with the Vitek 2 system using the AST-GN25 (22230) card by following the manufacturer's instructions (bioMérieux, St. Louis, MO). CIRE were defined as isolates for which the carbapenem MIC was  $\geq 2$  mg/liter.

Antibiotic use and CIRE incidence were assessed for trends by utilizing the chi-square test for trend with Epi Info version 3.5.3 (Centers for Disease Control and Prevention, Atlanta, GA). Correlations between CIRE incidence and antibiotic consumption were assessed with Spearman's correlations using Intercooled Stata version 11.1 (StataCorp, College Station, TX). Bonferroni corrections were applied to correct for multiple comparisons, with a  $P$  of  $< 0.0056$  (i.e.,  $P = 0.05$ , with 9 comparisons) being considered significant. Significant relationships were further assessed using the Marquardt-Levenberg algorithm (SigmaPlot 12; Systat Software Inc., San Jose, CA).

During the study period, a total of 310,892 DOT and 6,753 DOT/1,000 patient days were analyzed. Antibiotic use showed increasing trends during the analysis period for the carbapenem class ( $P < 0.001$ ). Aztreonam ( $P < 0.001$ ), cefepime ( $P = 0.003$ ), ceftazidime ( $P < 0.001$ ), moxifloxacin ( $P < 0.001$ ), and piperacillin-tazobactam ( $P < 0.001$ ) had decreasing trends over the study analysis period. Ciprofloxacin, colistin, and tigecycline usage were found to be consistent throughout the study period ( $P > 0.05$  for all).

A total of 27,818 isolates were identified as *Enterobacteriaceae*, out of which there were 55 deduplicated CIRE. The following organism types were identified as CIRE: *Klebsiella pneumoniae* ( $n = 47$  [85.5%]), *Escherichia coli* ( $n = 4$  [7.3%]), *Enterobacter cloacae* ( $n = 2$  [3.6%]), *Enterobacter aerogenes* ( $n = 1$  [1.8%]), and *Klebsiella oxytoca* ( $n = 1$  [1.8%]). The number of CIRE isolates/1,000 patient days increased significantly as a function of time ( $P < 0.001$ ) per the chi-square test for trend.

There was a positive correlation between CIRE incidence and the carbapenem class ( $r = 0.62$ ,  $P = 0.004$ ) (Fig. 1); the association remained significant when the analysis was corrected for multiple comparisons (i.e., significance at the level of  $\leq 0.0056$ ). The num-

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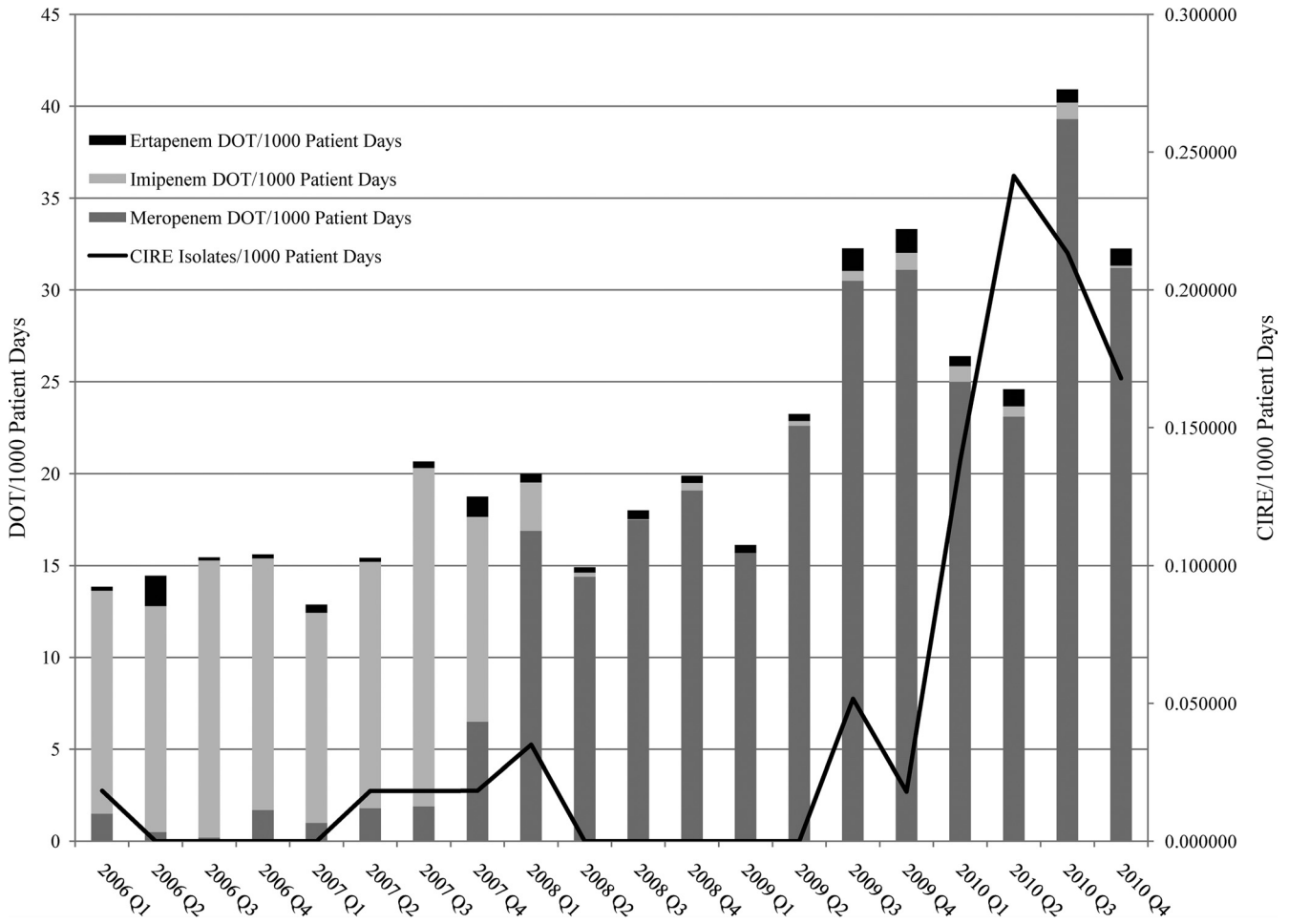


FIG 1 All days of carbapenem therapy/1,000 patient days and numbers of CIRE/1,000 patient days. DOT, days of therapy; CIRE, carbapenem-intermediate or -resistant *Enterobacteriaceae*; Q1 to -4, first to fourth quarters.

ber of CIRE isolates/1,000 patient days increased as a mathematical function of all days of carbapenem therapy/1,000 patient days ( $y = 0.0077 + 0.1307 / \{1 + \exp[-(x - 23.6967) / 0.0109]\}$ ;  $r^2 = 0.64$ ) (Fig. 2). This equation identified a sharp increase in the

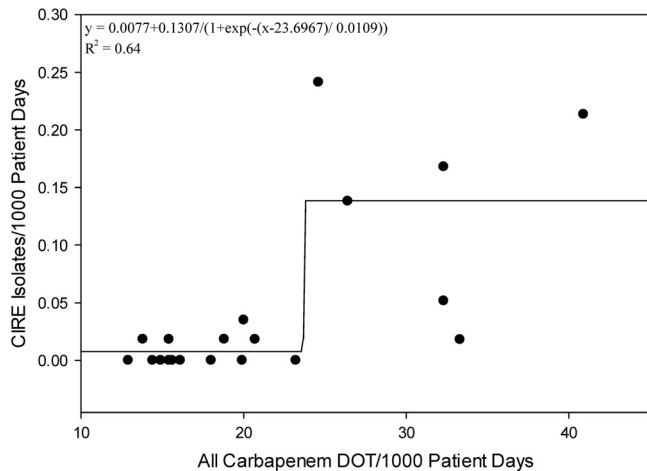


FIG 2 Numbers of CIRE isolates/1,000 patient days versus all days of carbapenem therapy/1,000 patient days.

number of CIRE/1,000 patient days after the number of days of carbapenem therapy exceeded 22/1,000 patient days.

There was a negative correlation with ceftazidime ( $r = -0.52$ ,  $P = 0.018$ ), piperacillin-tazobactam ( $r = -0.64$ ,  $P = 0.0021$ ), and moxifloxacin ( $r = -0.51$ ,  $P = 0.022$ ) usage. When the analysis was corrected for multiple comparisons among these negative correlations (i.e., significance at the level of  $\leq 0.0056$ ), only the correlation with piperacillin-tazobactam remained significant.

We found that increasing carbapenem use was correlated with increasing resistance in *Enterobacteriaceae*. Previous epidemiological studies with select Gram-negative organisms support our findings. One study analyzed carbapenem use and found that carbapenem use and carbapenem-resistant *A. baumannii* increased simultaneously (12). The correlation of carbapenem exposure and antimicrobial resistance has also been reported in case-control studies (16, 17). These analyses found that progression to CIRE is likely the result of a multifactorial process with respect to antibiotic exposure; our study corroborates these results and may indicate that replacing several antibiotics with the class of carbapenems is potentially problematic.

Limitations to our study should be noted. First, we excluded organisms tested only by disk diffusion because MICs were not available for analysis. Thus, these numbers may slightly underre-

port CIRE incidence. Second, these data are epidemiologic in nature and cannot confirm or disprove causality. However, the statistical power gained with epidemiologic analyses allowed us to stratify and analyze individual antibiotic associations. Third, carbapenems were analyzed as a class due to a change in formulary from imipenem-cilastatin to meropenem in mid-2007, though CIRE incidence occurred largely in the presence of meropenem use. This modification should improve validity, since the use of each individual carbapenem varied depending on formulary status. Fourth, our institution actively screens for nosocomial organism outbreaks. There was one outbreak of carbapenem-resistant *Enterobacteriaceae* involving three patients; however, this represented a very small portion (5.5%) of isolates studied. Thus, our results are unlikely biased by horizontal organism transfer. Lastly, this study was conducted at a single large institution in Chicago, IL. Results may not apply to areas where different pathogens predominate ecologically.

The incidence of CIRE is increasing at our institution and was associated with increasing carbapenem class use and decreasing piperacillin-tazobactam use. Further research is needed to elucidate whether knowledge of associations between antibiotic consumption and CIRE may be used to design interventions that slow CIRE spread.

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