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Colistin and Tigecycline Resistance in Carbapenem-Resistant Enterobacteriaceae: Checkmate to Our Last Line Of Defense

To the Editor—The emergence and spread of antimicrobial drug resistance in Enterobacteriaceae is posing a serious threat to the treatment of nosocomial infections. Of particular importance are the pathogens of this family that produce metallo-β-lactamases (IMP-type carbapenemases [IMP], New Delhi metallo-β-lactamase, or Verona integron-encoded metallo-β-lactamase [VIM]), non-metallo enzymes (*Klebsiella pneumoniae* carbapenemase and Oxacillinase [OXA]-48), β-lactamases with a broad profile of substrate activity such as extended-spectrum β-lactamases, or AmpC enzyme with porin loss. Until recently, carbapenems have been successfully used for the treatment of infections caused by Enterobacteriaceae, including those producing extended-spectrum β-lactamases.[1] Antibiotic treatment options for these emerging carbapenem-resistant Enterobacteriaceae (CRE) are becoming limited.[2] Colistin and tigecycline have been reported as the remaining armamentarium against the species of Enterobacteriaceae.[3,4] In the present study, a total of 210 clinically significant Enterobacteriaceae isolates were collected from various clinical samples of admitted patients (blood, urine, wound, and burn) over a period of 2 years (2013–2015). Susceptibility testing was performed by Clinical and Laboratory Standards Institute broth microdilution method, and isolates with a meropenem or imipenem minimum inhibitory concentration (MIC) of at least 4 mg/L were categorized as CRE. *Escherichia coli* ATCC 25922 was used as the control strain. Among these 210 isolates, 31 bacteria showed resistance to both imipenem (MIC ≥32 mg/L) and meropenem (MIC 32 mg/L). By means of 16S rRNA sequence of 31 CRE isolates, the following members of the Enterobacteriaceae family were identified: *Enterobacter cloacae* (5), *Enterobacter aerogenes* (4), *Serratia marcescens* (2), *Providencia stuartii* (2), *Klebsiella pneumoniae* (6), *Citrobacter freundii* (2), *Proteus mirabilis* (4), and *E. coli* (6). CRE are increasingly prevalent in many parts of the world.[5] These CRE isolates were further screened for their resistance toward colistin (MIC 32–64 mg/L) and tigecycline (MIC 16-64 mg/L). All the strains of *S. marcescens*, *K. pneumoniae*, and *E. coli* showed resistance to both colistin and tigecycline (Figure 1). Resistance to colistin was 100% for all the strains of *E. cloacae*, *P. stuartii*, *C. freundii*, and *P. mirabilis*, whereas only 75% of strains of *E. aerogenes* were colistin resistant (Figure 1). A total of 80% of strains of *E. cloacae* and 75% of strains of *P. mirabilis* were resistant to tigecycline (Figure 1). Similarly, 50% of strains of *E. aerogenes*, *P. stuartii*, and *C. freundii* were tigecycline resistant (Figure 1). In the past few years, there have been sporadic reports of colistin-resistant CRE cases from various parts of the world, such as Greece, Israel, South Korea, United States, and Singapore,[6] and of tigecycline-resistant CRE.[7] Colistin- and tigecycline-resistant CRE cases have never been reported from India. It should be further noted that co-resistance to both colistin and tigecycline among the CRE strains was not reported before.

Thus, there is clearly a need for the development and screening of new antimicrobial agents to keep pace with the

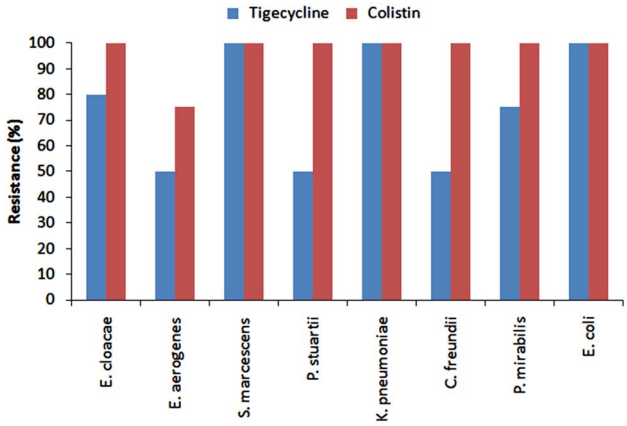

FIGURE 1. Resistance pattern of carbapenem-resistant *Enterobacteriaceae to last resort antibiotics. C. freundii, Citrobacter freundii; E. aerogenes, Enterobacter aerogenes; E. cloacae, Enterobacter cloacae; E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; P. mirabilis, Proteus mirabilis; P. stuartii, Providencia stuartii; S. marcescens, Serratia marcescens.*

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development and spread of drug resistance mechanisms in the Enterobacteriaceae family.

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