Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae*: Are We at the End of the Road?

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*Klebsiella pneumoniae* strains expressing *K. pneumoniae* carbapenemase (KPC) first appeared in the United States in the late 1990s and have spread rapidly across hospitals and long-term care facilities in many countries around the world. KPC-producing *K. pneumoniae* is by far the most commonly encountered carbapenem-resistant Enterobacteriaceae (CRE) species, and its global spread has been attributed to the expansion of a specific successful clonal lineage represented by sequence type 258 (ST258) (1). KPC-producing *K. pneumoniae* is resistant to carbapenems as well as to most agents that would otherwise be active against this species. Agents of last resort include colistin, which is an antimicrobial peptide with activity against a wide range of Gram-negative bacteria, that was approved for clinical use in the 1950s (2). Colistin use was largely abandoned soon after its introduction in favor of aminoglycosides, which have a more favorable side effect profile as well as improved efficacy. However, the use of colistin has increased again in the last decade due to the emergence of carbapenem-resistant pathogens, including CRE. Colistin has become the single most important agent in the treatment of CRE infections, and it is often used in combination with one or more other agents. However, the increase in the use of colistin has been accompanied by reports of KPC-producing *K. pneumoniae* strains that are resistant to this agent (3, 4).

In this issue of the *Journal of Clinical Microbiology*, Giani and colleagues report a large and sustained outbreak of colistin-resistant KPC-producing *K. pneumoniae* that caused bloodstream infections in 93 patients over 4 years in a hospital in Italy (5). KPC-producing *K. pneumoniae* was first introduced to this hospital in 2008. Bloodstream infection from colistin-resistant KPC-producing *K. pneumoniae* was first observed there in 2010 and increased in incidence until 2012. The proportion of colistin-resistant cases among KPC-producing *K. pneumoniae* cases also increased rapidly over time, from 12% in 2011 to 65% in 2012 and 57% in 2013. These increases coincided well with a surge in the consumption of colistin at this hospital, suggesting that selective pressure from colistin use is a major factor that drives resistance to this agent, as has also been shown for colistin resistance in *Acinetobacter baumanii* (6). Of the 59 colistin-resistant isolates available for analysis, 56 produced KPC-3 and belonged to ST512, which is closely related to ST258 and known to be dominant in Italy. Intriguingly, 50 of these isolates shared the identical 11-bp deletion in the mgrB gene. mgrB encodes a transmembrane protein which negatively regulates PhoPQ, a two-component regulatory system that governs modifications of lipid A that are associated with resistance to colistin (7). Inactivation of mgrB therefore confers colistin resistance. The fact that most isolates had the identical mgrB deletion suggests that, instead of colistin resistance developing in individual patients after they acquired a colistin-susceptible isolate, the outbreak was primarily driven by a single colistin-resistant ST512 strain with this deletion that spread from patient to patient and caused bloodstream infections. This is a significant observation which suggests that colistin resistance may be imparted to KPC-producing *K. pneumoniae* with minimal impact on either its ability to spread from patient to patient or its ability to cause invasive disease.

What are the clinical implications of these findings? First, colistin resistance can emerge rather quickly once KPC-producing *K. pneumoniae* is introduced into the health care environment, and colistin is used to treat infections from this organism. Second, colistin-resistant, KPC-producing *K. pneumoniae* may directly colonize or infect patients who are not colonized with the colistin-susceptible counterparts, at least in the setting of continuous selective pressure from high-level colistin use. Two questions arise from this point. If susceptibility to colistin cannot be assumed, should clinical microbiology laboratories consider performing susceptibility testing of the isolates for colistin for all patients who receive this agent, instead of just those who are colistin experienced? Also, from an infection prevention perspective, should patients colonized or infected with colistin-resistant strains be grouped or isolated from those with colistin-susceptible strains? If the data presented here are confirmed in other settings, the an-
swers to both questions would be yes. Finally, spread of colistin-resistant strains further complicates the already-challenging treatment considerations for CRE, including KPC-producing \textit{K. pneumoniae}. Another recent cohort study from Italy reported colistin resistance as a strong independent risk factor for mortality among patients with KPC-producing \textit{K. pneumoniae} infections (8). While data, albeit observational, are accumulating on the treatment of KPC-producing \textit{K. pneumoniae} infections in general (9), there are almost no data that guide us on how to manage patients infected with colistin-resistant strains. One positive development in this regard is the recent approval of ceftazidime-avibactam for clinical use in the United States. Ceftazidime-avibactam is active against most KPC-producing \textit{K. pneumoniae} strains (10) and, while specific data are lacking at this time, it is reasonable to assume that this combination would maintain activity against colistin-resistant strains as well. Of note, avibactam does not inhibit metallo-\(\beta\)-lactamases, such as New Delhi metallo-\(\beta\)-lactamase-1 (NDM-1), whose production is an increasingly prevalent mechanism of carbapenem resistance in \textit{Enterobacteriaceae} in some countries (11). In a recent study from the United Kingdom, colistin resistance was observed in 10\% of NDM-1-producing CRE (12). In addition to ceftazidime-avibactam, several other agents with anti-CRE activity are in late clinical development and may provide in the near future additional treatment options for colistin-resistant CRE infections, except for those caused by strains producing a metallo-\(\beta\)-lactamase. They include imipenem-relebactam, meropenem-RPX7009, eravacycline, and plazomicin. However, how these new agents actually perform when used for the treatment of CRE infections remains to be seen. Furthermore, we should remain cautious as we start using these agents in clinical practice and make the greatest efforts to preserve their activity; for example, variants of KPC-2 that confer resistance to ceftazidime-avibactam have already been reported (13).

Outbreaks of colistin-resistant CRE are clearly not a welcome development and bring to us a renewed sense of urgency to develop better ways to control these challenging pathogens. Areas in acute need of further research include diagnostics that can rapidly identify colistin resistance, infection prevention interventions that reduce transmission of colistin-resistant organisms, and studies correlating treatment approaches and clinical outcomes. We have to act now if we are to prevent colistin-resistant CRE from becoming the norm in our hospitals and long-term care facilities.

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