Klebsiella pneumoniae Antimicrobial Drug Resistance, United States, 1998–2010

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We studied antimicrobial-resistant Klebsiella pneumoniae for 1998–2010 by using data from The Surveillance Network. Susceptibility results (n = 3,132,354) demonstrated significant increases in resistance to all antimicrobial drugs studied, except tetracycline. Cross-resistance among carbapenem-resistant K. pneumoniae was lower for tetracycline and amikacin.

K. pneumoniae antimicrobial susceptibility results were stratified by specimen source (blood, sputum, urine, and wounds). Imipenem-resistant K. pneumoniae isolates from 2010 were examined for cross-resistance to other antimicrobial agents and prevalence in ICU versus non-ICU settings. We used \( \chi^2 \) testing to determine whether changes in K. pneumoniae antimicrobial drug resistance were statistically significant from 2000 to 2010 and whether 2010 antimicrobial drug resistance differed by specimen source. The \( \alpha \) level was set at 0.05. Analyses were performed by using R version 2.11.0 (www.r-project.org).

We analyzed a total of 3,132,354 K. pneumoniae antimicrobial susceptibility results for 1998–2010 (Table 1). Statistically significant increases in antimicrobial drug resistance to all agents (p<0.0001) except tetracycline (p = 0.0745) (Figure 1) were observed. Resistance to imipenem first appeared in TSN Database-USA in 2004 and rose gradually to 4.3% by the end of our study period. In 2010, K. pneumoniae resistance to tigecycline was 2.6% (data not shown). The largest increases in antimicrobial drug resistance from 1998 to 2010 were observed for aztreonam (7.7% to 22.2%), ceftazidime (5.5% to 17.2%), and ciprofloxacin (5.5% to 16.8%). Changes in resistance were smaller for tetracycline (14.2% to 16.7%) and amikacin (0.7% to 4.5%).

In 2010, isolates from the lower respiratory tract showed higher levels of resistance than did isolates from urine for all antimicrobial agents (p<0.0001) except tetracycline (p = 0.54) (Table 2). CRKP was more prevalent in ICU settings than in non-ICU settings (6.3% vs. 3.8%, respectively) (online Technical Appendix, www.cdc.gov/EID/pdfs/12-0310-Techapp.pdf).
Imipenem-resistant isolates of *K. pneumoniae* showed the lowest resistance to tetracycline (19.9%) and amikacin (36.8%). High prevalence of cross-resistance was observed for ciprofloxacin (96.4%) (Figure 2).

Conclusions

In our study, the proportion of *K. pneumoniae* isolates resistant to carbapenems was lower than those previously reported (7,8). In 2010, we observed a resistance rate of 4.3% for imipenem. The Centers for Disease Control and Prevention (CDC) reported that, among health care–associated infections, 8% of *Klebsiella* spp. isolates were carbapenem resistant in 2007 compared with <1% in 2000 (9). Most studies of *K. pneumoniae* antimicrobial drug resistance have focused on patient populations with higher exposures to antimicrobial agents, such as those in critical care and academic hospital settings. In contrast, the lower prevalence of CRKP in our study might have resulted from a wider variety of institution types and inclusion of isolates from hospital patients outside of the critical care setting. Furthermore, within our study, a high percentage of isolates were from urine and showed lower levels of resistance than did isolates from respiratory samples. Interpretive breakpoint criteria for the antimicrobial agents included did not change during the study period.

The low cross-resistance to tetracycline among CRKP and stable resistance rate of *K. pneumoniae* to this agent during the study period are noteworthy. In our analysis of cross-resistance among imipenem-resistant *K. pneumoniae*, tetracycline had the greatest antimicrobial activity against CRKP. Although resistance of *K. pneumoniae* increased for all antimicrobial agents studied, resistance to tetracycline increased only slightly from 1998 to 2010. Later-generation tetracyclines may prove useful in the treatment of CRKP-related infections because of their improved tissue penetration, antimicrobial activity, and decreased propensity to develop antimicrobial drug resistance compared with their older counterparts (10). Tigecycline, a glycylyclcline antimicrobial agent that is structurally similar to tetracycline, has been used to treat CRKP-related infections and is often active against carbapenemase–producing *K. pneumoniae* (11,12). Data for tigecycline that used FDA interpretive breakpoints showed *K. pneumoniae* antimicrobial drug resistance was 2.6% in 2010. Tigecycline data were included only for 2010 because the drug was not FDA approved until 2005 and an insufficient number of results were available before 2010.

The widespread transmission of carbapenemase–producing *K. pneumoniae* has become the most common cause of carbapenem resistance among *Enterobacteriaceae* in the United States (13) and probably accounts for most of the imipenem resistance shown in this study. The spread of carbapenemase–producing organisms threatens to extend carbapenem resistance to the community (14).
increasing antimicrobial drug resistance to *K. pneumoniae* in our study, a concurrent lack of novel antimicrobial agent development (15), and limited therapeutic options available for treating CRKP-related infections add further urgency to improve prevention efforts and treatment strategies.

Our study data have strengths and limitations. The strengths are the wide variety of antimicrobial agents included, the number of laboratories reporting data, the nationally representative geographic distribution of these institutions, and the large number of isolates. Geography is a critical consideration with surveillance of this organism because distribution of *K. pneumoniae* antimicrobial drug resistance varies within the United States (13). The limitations of these data include a lack of central laboratory testing and the variety of test methods used. Because of a lack of Clinical Laboratory Standards Institute or FDA interpretive breakpoints for *K. pneumoniae* and colistin or fosfomycin, these data were not collected by TSN Database-USA and were not included in this study. Resistance to carbapenems might have been underreported at the beginning of our study period because of a lower frequency of susceptibility testing of these agents and the inability of antimicrobial susceptibility test methods to detect low-level carbapenem resistance.

Our study shows that *K. pneumoniae* antimicrobial drug resistance increased for every antimicrobial class studied except tetracyclines. Cross-resistance among imipenem-resistant *K. pneumoniae* was high for ciprofloxacin but lower for tetracycline and amikacin. This emerging problem presents a major threat to public health and warrants due diligence in future surveillance efforts.

**Acknowledgements**

We thank Eurofins-Medinet for providing the data and recognize Alexis M. Baird and Jacqueline N. Wilkins for their contributions in editing and formatting this work.

No authors received financial support for doing this research, nor do they have any conflicts of interest to disclose. No organizations have a financial interest in the completion of this work.

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**References**


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**Technical Appendix**


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*ICU, intensive care unit.*