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Concise Communication

Characterization of resistance to newer antimicrobials among carbapenem-resistant *Klebsiella pneumoniae* in the post–acute-care setting

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Abstract

We assessed susceptibility patterns to newer antimicrobial agents among clinical carbapenem-resistant *Klebsiella pneumoniae* (CRKP) isolates from patients in long-term acute-care hospitals (LTACHs) from 2014 to 2015. Meropenem-vaborbactam and imipenem-relebactam nonsusceptibility were observed among 9.9% and 9.1% of isolates, respectively. Nonsusceptibility to ceftazidime-avibactam (1.1%) and plazomicin (0.8%) were uncommon.

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Infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) pose a major clinical and public health challenge due to their high mortality rates and limited treatment options.[1] The burden of CRKP is especially high among chronically, critically ill (CCI) patients due to their extensive healthcare and antibiotic exposures. Colonization rates among patients in long-term acute-care hospitals (LTACHs), which serve as a site of post-acute care for CCI patients, have been reported to be 8- to 9-fold higher than those of patients in short-stay acute-care hospitals.[2] Although therapies for CRKP infections now include several β-lactam/β-lactamase inhibitor combinations including ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, as well as the aminoglycoside plazomicin, resistance to these agents is poorly characterized among CRKP in the post–acute-care setting. We describe the antimicrobial resistance profiles of CRKP isolates from patients in a multistate sample of LTACHs.

Methods

Study setting

This study was conducted from August 1, 2014, through July 25, 2015, at 21 LTACHs within a national LTACH network. LTACHs were distributed across 4 US states: 12 LTACHs in southern California including 11 in Los Angeles and 1 in San Diego; 6 LTACHs in Houston, Texas; 2 LTACHs in Tampa, Florida; and 1 LTACH in Louisville, Kentucky.

CRKP collection

CRKP isolates from blood, respiratory, urine, or wound cultures were collected from patients in participating LTACHs. CRKP was identified, according to 2015 US Centers for Disease Control and Prevention (CDC) criteria, as *K. pneumoniae* with a meropenem or imipenem minimum inhibitory concentration (MIC) of ≥4 μg/mL or an ertapenem MIC of ≥2 μg/mL, according to testing performed by the clinical microbiology laboratories that service the participating LTACHs.[3] Confirmatory testing of isolates has been previously described.[4] Among patients with >1 CRKP isolate during the study period, only the first isolate was included.

Antibiotic susceptibility testing

Antimicrobial susceptibility testing for meropenem-vaborbactam, imipenem-relebactam, ceftazidime-avibactam, amikacin, plazomicin, tigecycline, and colistin were performed using a custom Sensititre colorimetric broth microdilution panel (ThermoFisher, Waltham, MA).[5,6] 2021 Clinical and Laboratory Standard Institute (CLSI) interpretative criteria were used for all agents except for tigecycline and plazomicin, for which US Food and Drug Administration (FDA) break points were used.[7,8]

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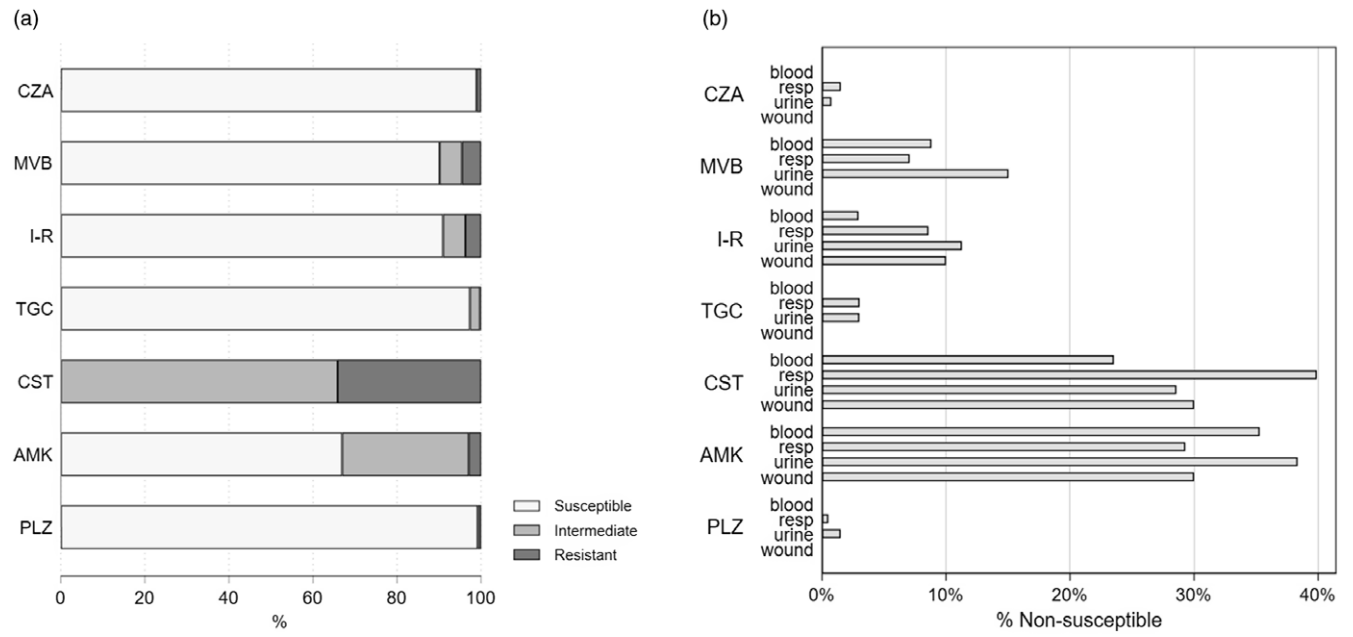

Fig. 1. (A) Overall antimicrobial susceptibility interpretations and (B) prevalence of nonsusceptibility by anatomic source among carbapenem-resistant *Klebsiella pneumoniae* isolates, August 2014 through July 2015. In panel B, isolates with colistin minimum inhibitory concentration ≥4 μg/mL are denoted as "nonsusceptible." Note. AMK, amikacin; CST, colistin; CZA, ceftazidime-avibactam; I-R, imipenem-relebactam; MVB, meropenem-vaborbactam; PLZ, plazomicin; TGC, tigecycline; resp, respiratory.

Antibiotic nonsusceptibility was defined as an MIC in the intermediate or resistant category.

Phylogenetic analysis

Whole-genome sequencing (WGS), variant calling, and phylogenetic tree reconstruction were performed as described by Han et al.[4] and Lapp et al.[9] Phylogenies were visualized in R version 4.2.0 using ggtree version 3.4.0, ggnewscale version 0.4.7, phytools version 1.0-3, and cowplot version 1.1.1 packages.[10–12] Due to the enrichment of sequence type (ST) 258 in the data set, the phylogenies of ST258 and non-ST258 isolates were visualized separately. 7 isolates were excluded from phylogenetic analysis due to low sequencing or assembly quality. Kleborate version 2.0.4 (https://github.com/katholt/Kleborate/releases) was used to identify and classify β-lactamase genes.[13]

Statistical analyses

Data were analyzed using Stata IC version 16.1 software (StataCorp, College Station, TX). Bivariate comparisons were performed using the Fisher exact test or the Pearson χ^2 test. Two-tailed *P* values are reported.

Results

In total, 375 CRKP isolates were collected: 198 (52.8%) respiratory isolates, 133 (35.5%) urine isolates, 34 (9.1%) blood isolates, and 10 (2.7%) wound isolates. Among them, 336 (89.6%) were from patients in southern California; 29 (7.7%) were from patients in Texas, 9 (2.4%) were from patients in Florida, and 1 (0.3%) was from a patient in Kentucky. Colistin resistance was observed in 128 (34.1%) isolates. Amikacin nonsusceptibility was observed in 124 isolates (33.1%; 113 [30.1%] intermediate and 11 [2.9%] resistant). Tigecycline nonsusceptibility was observed in 10 isolates (2.7%; 9 [2.4%] intermediate and 1 [0.3%] resistant).

Regarding newer agents, 37 isolates (9.9%) were nonsusceptible to meropenem-vaborbactam (20 [5.3%] intermediate and 17 [4.5%] resistant); 34 isolates (9.1%) were nonsusceptible to imipenem-relebactam (20 [5.3%] intermediate and 14 [3.7%] resistant); 4 isolates (1.1%) were resistant to ceftazidime-avibactam; and 3 isolates (0.8%) were nonsusceptible to plazomicin (2 [0.5%] intermediate and 1 [0.3%] resistant) (Fig. 1 and Supplementary Fig. 1 online). Among colistin-resistant isolates, 9 (7.0%) were nonsusceptible to meropenem-vaborbactam, 14 (10.9%) were nonsusceptible to imipenem-relebactam, 3 (2.3%) were nonsusceptible to ceftazidime-avibactam, and 2 (1.6%) were nonsusceptible to plazomicin. 18 meropenem-vaborbactam nonsusceptible isolates (48.6%) also demonstrated nonsusceptibility to imipenem-relebactam, and 4 (10.8%) also demonstrated nonsusceptibility to ceftazidime-avibactam. Among imipenem-relebactam nonsusceptible isolates, 18 (52.9%) were nonsusceptible to meropenem-vaborbactam and 4 (11.8%) were nonsusceptible to ceftazidime-avibactam (Supplementary Fig. 2 online).

The prevalences of meropenem-vaborbactam nonsusceptibility by anatomic source were as follows: 20 (15.0%) of 133 urinary isolates, 14 (7.1%) of 198 respiratory isolates, 3 (8.8%) of 34 blood isolates, and 0 (0%) of 10 wound isolates ($P = .095$). The prevalences of imipenem-relebactam nonsusceptibility by anatomic source were as follows: 15 (11.3%) of 133 urinary isolates, 17 (8.6%) of 198 respiratory isolates, 1 (2.9%) of 34 blood isolates, and 1 (10.0%) of 10 wound isolates ($P = .44$). Nonsusceptibility did not differ significantly by geographic region for either meropenem-vaborbactam ($P = .91$) or imipenem-relebactam ($P = .50$). Among isolates collected from southern California, the prevalence

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Table 1. Beta-Lactamase Genes detected Among Carbapenem-Resistant *Klebsiella pneumoniae* Clinical Isolates in Long-Term Acute-Care Hospitals (LTACHs), August 2014 through July 2015

Gene	Overall (N = 368), No. %	CZA Nonsusceptible (N = 4), No. %	MVB Nonsusceptible (N = 37), No. %	I-R Nonsusceptible (N = 33), No. %
Any CTX-M	29 (7.9)	0 (0.0)	3 (8.1)	1 (3.0)
CTX-M-14	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
CTX-M-15	24 (6.5)	0 (0.0)	3 (8.1)	1 (3.0)
Any KPC	359 (97.6)	4 (100.0)	37 (100.0)	32 (97.0)
KPC-2	129 (35.1)	0 (0.0)	24 (64.9)	18 (54.5)
KPC-3	227 (61.7)	4 (100.0)	13 (35.1)	13 (39.4)
KPC-5	3 (0.8)	0 (0.0)	0 (0.0)	1 (3.0)
LAP-2	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Any SHV	367 (99.7)	4 (100.0)	37 (100.0)	33 (100.0)
SHV-1	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
SHV-5	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
SHV-11	300 (81.5)	4 (100.0)	33 (89.2)	28 (84.8)
SHV-12	39 (10.6)	0 (0.0)	1 (2.7)	3 (9.1)
SHV-26	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
SHV-28	22 (6.0)	0 (0.0)	3 (8.1)	1 (3.0)
SHV-61	1 (0.3)	0 (0.0)	0 (0.0)	1 (3.0)
Any TEM	196 (53.3)	1 (25.0)	24 (64.9)	16 (48.5)
TEM-1	194 (52.7)	1 (25.0)	24 (64.9)	16 (48.5)
TEM-26	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
CMY-2	10 (2.7)	1 (25.0)	3 (8.1)	3 (9.1)
Any OXA	139 (37.8)	0 (0.0)	7 (18.9)	7 (21.2)
OXA-1	10 (2.7)	0 (0.0)	1 (2.7)	1 (3.0)
OXA-9	128 (34.8)	0 (0.0)	6 (16.2)	5 (15.2)
OXA-10	1 (0.3)	0 (0.0)	0 (0.0)	1 (3.0)

Note. CZA, ceftazidime-avibactam; MVB, meropenem-vaborbactam; I-R, imipenem-relebactam; CTX-M, plasmid-mediated cefotaximase; KPC, *Klebsiella pneumoniae* carbapenemase; SHV, sulfhydryl variable; TEM, temoniera; OXA, oxacillinase.

of meropenem-vaborbactam nonsusceptibility differed by facility ($P = .009$), ranging from 0% to 26.7% (Supplementary Table 1 online). In contrast, imipenem-relebactam nonsusceptibility did not significantly differ by facility ($P = .17$).

Of 368 whole-genome sequenced CRKP isolates, 335 (91.0%) were ST258 (Supplementary Fig. 3 online). All ceftazidime-avibactam nonsusceptible isolates were ST258. ST258 isolates comprised 34 (91.9%) meropenem-vaborbactam nonsusceptible isolates, with the remaining 3 belonging to ST307. Among imipenem-relebactam nonsusceptible isolates, 31 (93.9%) were ST258, 1 was ST193, and 1 was ST307. Plazomicin nonsusceptible isolates included 2 ST258 and 1 ST193. The resistance genes detected among isolates are summarized in Table 1.

Discussion

Although a high prevalence of colistin and amikacin nonsusceptibility was observed in this collection of CRKP isolates from patients in LTACHs, most were susceptible to newer antimicrobials including ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, and plazomicin. Additionally, >90% of isolates that were nonsusceptible to either of the carbapenem/β-lactamase inhibitors retained susceptibility to ceftazidime-avibactam. In contrast, a previous study reported that only 6 (60%) of 10 meropenem-vaborbactam nonsusceptible KPC-positive Enterobacterales isolates from a global repository were ceftazidime-avibactam susceptible.[14] However, we did note a high prevalence of cross resistance between meropenem-vaborbactam and imipenem-relebactam, for which mechanisms should be investigated in future studies. Notably, our CRKP isolates were collected prior to the widespread use of ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, or plazomicin. Of these, ceftazidime-avibactam was the only agent to be granted FDA approval during the study period. Because resistance patterns may have evolved since the introduction of these agents into clinical practice, this study should be repeated in a contemporary sample.

This study had some limitations. Most isolates in this study were from patients in southern California, limiting generalizability to other geographic regions. Additionally, the findings of this study may not apply to other patient populations.

In conclusion, susceptibility to the novel β-lactam/β-lactamase inhibitor combinations and plazomicin were common in this

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collection of CRKP isolates from patients in LTACHs. These findings may help inform antibiotic formulary and empiric treatment decisions for CCI patients with suspected CRKP infection in the post–acute-care setting.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.185

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Conflicts of interest. J.H.H. is an employee of, and holds shares in, the GlaxoSmithKline group of companies.

References

1. Martin A, Fahrbach K, Zhao Q, Lodise T. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to Enterobacteriaceae: results of a systematic literature review and meta-analysis. *Open Forum Infect Dis* 2018;5:ofy150.
2. Marquez P, Terashita D, Dassey D, Mascola L. Population-based incidence of carbapenem-resistant *Klebsiella pneumoniae* along the continuum of care, Los Angeles County. *Infect Control Hosp Epidemiol* 2013;34:144–150.
3. National Center for Emerging and Zoonotic Infectious Diseases. Facility guidance for control of carbapenem-resistant Enterobacteriaceae (CRE), November 2015 update—CRE toolkit. Centers for Disease Control and Prevention website. https://www.cdc.gov/hai/pdfs/cre/cre-guidance-508.pdf. Published Novemebr 2015. Accessed July 15, 2022.
4. Han JH, Lapp Z, Bushman F, *et al.* Whole-genome sequencing to identify drivers of carbapenem-resistant *Klebsiella pneumoniae* transmission within and between regional long-term acute-care hospitals. *Antimicrob Agents Chemother* 2019;63.
5. Matuschek E, Ahman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin—evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. *Clin Microbiol Infect* 2018;24:865–870.
6. Jones RN, Holliday NM, Krause KM. Validation of Sensititre dry-form broth microdilution panels for susceptibility testing of ceftazidime-avibactam, a broad-spectrum β-lactamase inhibitor combination. *Antimicrob Agents Chemother* 2015;59:5036–5039.
7. *Performance Standards for Antimicrobial Susceptibility Testing, 28th edition.* CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
8. Antibacterial susceptibility test interpretive criteria. US Food & Drug Administration website. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed January 14, 2022.
9. Lapp Z, Han JH, Wiens J, Goldstein EJC, Lautenbach E, Snitkin ES. Patient and microbial genomic factors associated with carbapenem-resistant *Klebsiella pneumoniae* extraintestinal colonization and infection. *mSystems* 2021;6:e00177–21.
10. Yu G, Smith D, Zhu H, Guan Y, TTY L. ggtree: an R package for visualization and annotation of phylogenetic trees with their covariates and other associated data. *Methods Ecol Evol* 2017;8:28–36.
11. Revell LJ. phytools: an R package for phylogenetic comparative biology (and other things). *Methods Ecol Evol* 2012;3:217–223.
12. Wilke C, Wickham H, Wilke M. Package 'cowplot.' Streamlined plot theme and plot annotations for 'ggplot2. Cowplot website. https://wilkelab.org/cowplot/. Published 2019. Accessed July 14, 2022.
13. Lam MMC, Wick RR, Watts SC, Cerdeira LT, Wyres KL, Holt KE. A genomic surveillance framework and genotyping tool for *Klebsiella pneumoniae* and its related species complex. *Nat Commun* 2021;12:4188.
14. Hackel MA, Lomovskaya O, Dudley MN, Karlowsky JA, Sahm DF. In vitro activity of meropenem-vaborbactam against clinical isolates of KPC-Positive Enterobacteriaceae. *Antimicrob Agents Chemother* 2018;62:e01904–17.