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Increase in the Occurrence of Carbapenem-Resistant Enterobacterales in United States Hospitals from 2019 to 2021 and Activity of Novel β-Lactam/β-Lactamase Inhibitor Combinations Against These Isolates

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CONCLUSIONS

An increase in CRE isolates was noted in US hospitals in 2021, mainly driven by a rise in MBL-producing strains.
- This trend is worrisome since there are limited therapeutic options against MBL producers.

Ceftazidime-avibactam was the most active BL/BLI tested against CREs, but the increase in MBLs should be closely monitored.
- New therapies against these isolates are urgently needed.

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INTRODUCTION

- Carbapenem-resistant Enterobacterales (CRE) isolates are a threat to human health.
- Treatment options for CRE were limited until new β-lactam/β-lactamase inhibitor combinations (BL/BLIs), such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, were introduced in clinical practice after 2015.
  - These agents now are recommended by the Infectious Diseases Society of America (IDSA) for the treatment of serious infections caused by CRE isolates.
- Despite being active against isolates producing KPC enzymes and other class A carbapenemases, these agents displayed variations in their activity against isolates producing class D oxacillinases and limited activity against class B metallo-β-lactamases (MBLs).
- In this study, we evaluated the activity of these new BL/BLIs and comparator agents against CRE isolates collected in United States hospitals during a 3-year period.

MATERIALS AND METHODS

- A total of 19,157 Enterobacterales isolates were collected in 73 US hospitals.
  - Isolates were identified as the cause of infection.
  - Isolates were limited to 1 per patient.
- Isolates were susceptibility tested against meropenem-vaborbactam, ceftazidime-avibactam, and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) and M100 (2022) documents.
  - Avibactam and relebactam were tested at a fixed concentration of 4 mg/L.
  - Vaborbactam was tested at a fixed concentration of 8 mg/L.
- Quality control (QC) was performed according to the CLSI M100 (2022) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents followed CLSI M100 (2022) or the US Food and Drug Administration (FDA) website criteria.
- CRE isolates displayed elevated MIC values to imipenem or meropenem and were submitted to whole genome sequencing (WGS) and data analysis for the detection of β-lactamases.
- WGS was performed on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage.
  - Sequences were *de novo* assembled.
  - Analysis of β-lactam resistance mechanisms was performed *in silico*.
  - Genes encoding resistance were searched using a curated library and a criterion of >94% sequencing identity and 40% minimum length coverage was applied.

Figure 1. CRE rates by infection type and year

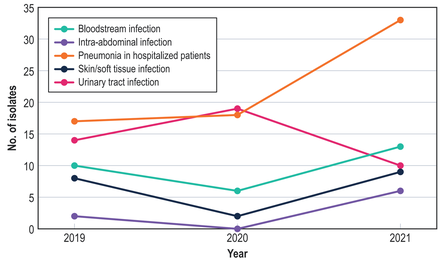
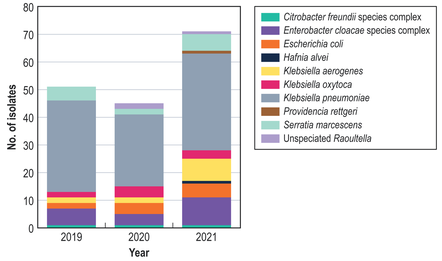


Figure 2. CRE species by year



RESULTS

- Among 19,157 Enterobacterales, 167 (0.9%) isolates were CRE.
- CREs increased to 1.1% in 2021 from 0.8% in 2019 and 0.7% in 2020.
- The CRE increase was pronounced among isolates collected from patients hospitalized with pneumonia, as this isolate population increased from 17 (1.7%) and 18 (1.8%) isolates in 2019 and 2020, respectively, to 33 (3.4%) isolates in 2021 (Figure 1).
- *K. pneumoniae* (94/167 isolates) was the predominant species among CRE in all years; however, an increase in *E. cloacae* (10 in 2021 and 6 in 2019) and *K. aerogenes* (8 in 2021 and 2 in 2019) was observed (Figure 2).
- Most CRE isolates produced KPC enzymes, mainly KPC-2 and KPC-3 (Figure 3).
- A decline of KPC-producing isolates was noted over time: 70.6% of CRE in 2019 were KPC producers but only 62.0% of CRE carried bla_{KPC} in 2021.
- MBL-producing isolates increased from 1 (2.0% of CRE) isolate in 2019 to 9 (12.7% of CRE) isolates in 2021.
  - Eight isolates carried bla_{NDM-1}, including 1 with $bla_{OXA-181}$, 4 with bla_{NDM-5}, and 2 harboring the gene encoding IMP-4.
- OXA-48–like enzymes without NDM were detected among 6 isolates (Figure 3).
- CRE isolates that did not produce carbapenemases were noted in all years; similar rates of approximately 19% were observed in 2019 and 2021.
- Ceftazidime-avibactam inhibited 91.0% of CRE isolates from all years combined.
- When comparing the activity of 3 new BL/BLIs tested against 71 CRE isolates from 2021, ceftazidime-avibactam was active against 85.9% of the CRE isolates whereas meropenem-vaborbactam inhibited 84.5% and imipenem-relebactam inhibited 80.0% of these isolates (Figure 4).
- Ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam inhibited all 44 serine-carbapenemase producing isolates from 2021 (Figure 4).

Figure 3. Carbapenemase genes detected among CRE isolates from US hospitals by year

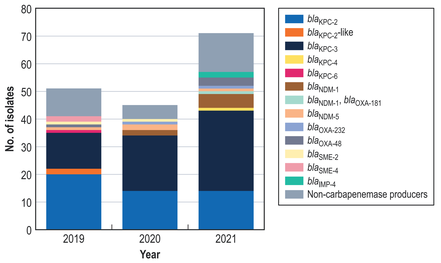
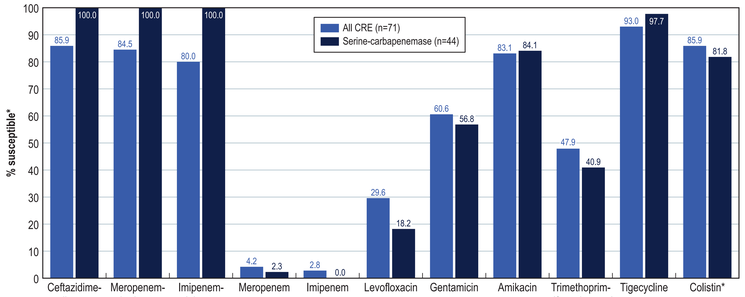


Figure 4. Activity of BL/BLI and other agents against CRE isolates from 2021



*Applying CLSI breakpoints (% intermediate for colistin/US FDA breakpoints applied for tigecycline)