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Occurrence of β-Lactamases among *Enterobacterales* Isolated from United States Hospitals: Results of the INFORM Surveillance Program for Ceftazidime-Avibactam

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CONCLUSIONS

- Ceftazidime-avibactam was very active against ESBL-producing isolates, regardless of the type of enzyme produced.
  - This agent was also active against isolates carrying transferable AmpC genes.
- Among isolates producing serine-carbapenemases, ceftazidime-avibactam inhibited 70 of 77 at the susceptibility breakpoint.
  - Ceftazidime-avibactam included metallo-β-lactamase producers and 2 isolates with a KPC-Ω loop alteration.
- Ceftazidime-avibactam displayed potent activity against contemporary isolates producing β-lactamase collected in US hospitals.

RESULTS

- A total of 723 of 1,209 (59.8%) screened isolates harbored ESBL genes without carrying carbapenemases.
- Among ESBL-producing isolates, 675 (65.6% overall) were positive for one or more CTX-M-encoding genes.
  - 516 (42.3% overall) isolates carried $bla_{\text{CTX-M}}$ group 1.
  - 153 (12.7%) isolates carried $bla_{\text{CTX-M}}$ group 9.
  - 3 (0.2%) isolates carried $bla_{\text{CTX-M}}$ group 2.
  - $bla_{\text{CTX-M}}$ group 8+25 were detected among *E. coli* and *K. pneumoniae* only.
- The most common CTX-M-encoding genes were $bla_{\text{CTX-M-15}}$ (n=478), followed by $bla_{\text{CTX-M-27}}$ (n=113).
- Most of the ESBL-carrying isolates were *E. coli* (253/111 for $bla_{\text{CTX-M-15}}$/$bla_{\text{CTX-M-27}}$), but 211 *K. pneumoniae* harbored $bla_{\text{CTX-M-15}}$.
- A total of 162 *E. coli*, 136 *K. pneumoniae*, 12 *E. cloacae*, and 4 *Citrobacter* spp. isolates harbored the OXA-1-encoding gene.
- SHV-encoding genes with ESBL spectrum were mostly observed among *K. pneumoniae* and *E. cloacae* (39 and 17 isolates, respectively).
- Transferable cephalosporinase genes were detected among 70 isolates, including 55 *E. coli*, 8 *K. pneumoniae*, 5 *Citrobacter* spp., and 2 *E. cloacae.*
  - CMY-2 was the most common gene, detected among 45 isolates.
- Ceftazidime-avibactam inhibited all 53 isolates carrying transferable AmpC genes that did not co-produce an ESBL or a carbapenemase.
- Carbapenemase genes were noted among 77 isolates, including 65 bla_{KPC}, 3 bla_{SME}, 6 $bla_{\text{OXA-48}}$-like, and 3 bla_{NDM}.
- Ceftazidime-avibactam was the only agent active against all ESBL-producers that did not carry carbapenemases.
  - Piperacillin-tazobactam and ceftolozane-tazobactam inhibited 79.8% and 89.1% of the ESBL-carrying isolates.
- Carbapenemase-producing isolates displayed low susceptibility rates against many β-lactams.
- Ceftazidime-avibactam was active against 90.9% of the isolates producing carbapenemases.
- Seven isolates were resistant to ceftazidime-avibactam.
  - 3 isolates were NDM-producers, 1 harbored $bla_{\text{KPC-31}}$, 1 harbored $bla_{\text{KPC-3}}$, 1 carried $bla_{\text{KPC-2}}$-like, and 1 carried $bla_{\text{OXA-181}}$.

Figure 1 Distribution of acquired broad spectrum β-lactamase-encoding genes among *E. coli* and *K. pneumoniae* isolates that did not carry carbapenemases

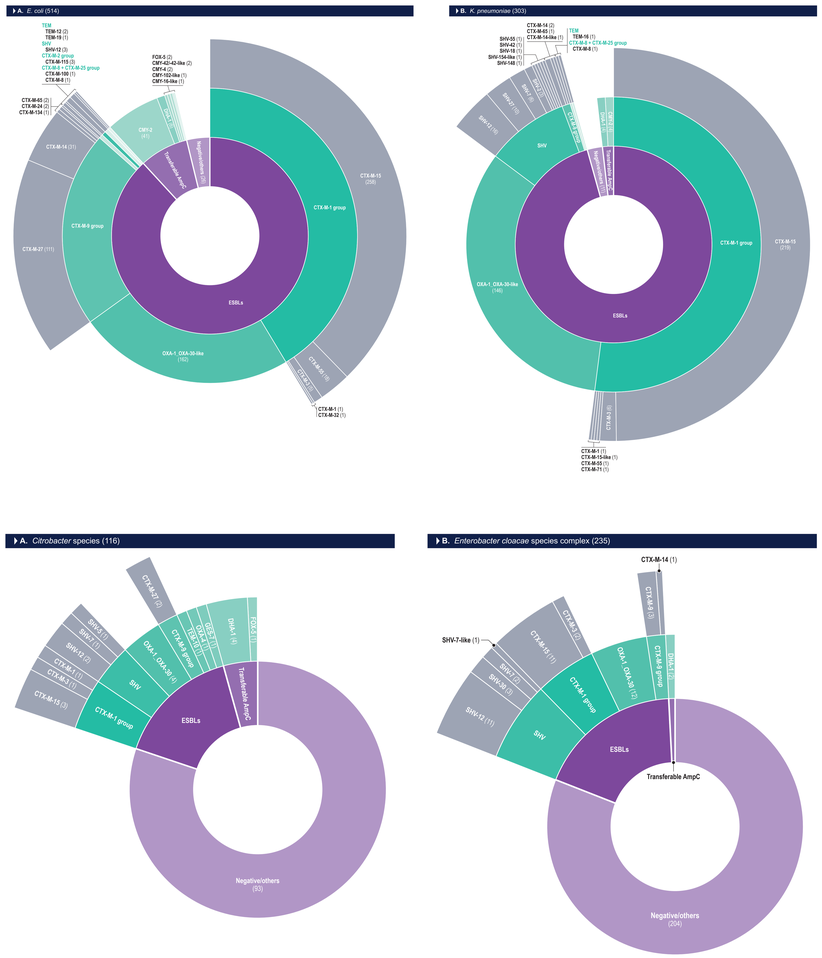


Figure 2 Distribution of acquired broad spectrum β-lactamase-encoding genes among *Citrobacter* spp. and *E. cloacae* isolates that did not carry carbapenemases

Figure 3 Distribution of acquired carbapenemases among *Enterobacterales* isolates

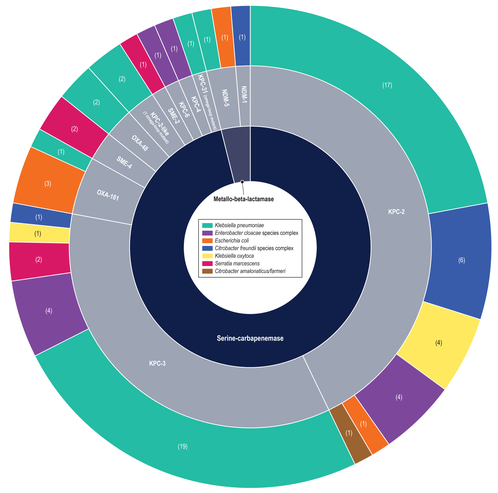
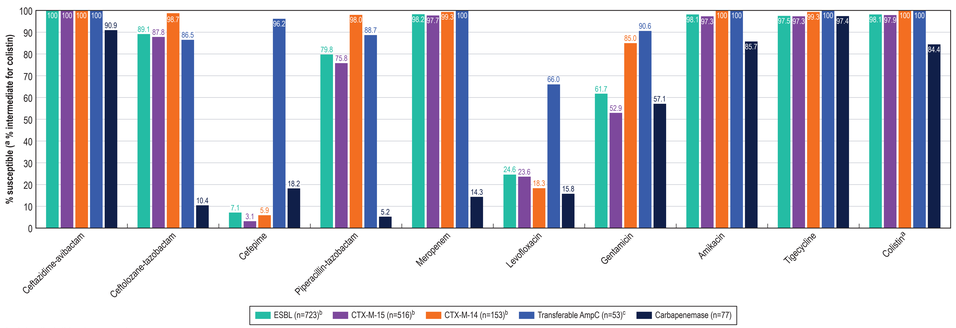


Figure 4 Activity of antimicrobial agents tested against β-lactamase-producing isolates from US hospitals



[b] Isolates that did not carry carbapenemases.
[c] Isolates that did not carry ESBL or carbapenemases.

INTRODUCTION

- Carbapenems are broadly used to treat ESBL-producing *Enterobacterales* isolates.
  - The use of these agents led to increased carbapenem resistance among *Enterobacterales*.
- The incidence of infections from ESBL-producing *E. coli* and *Klebsiella* spp. in the US increased from 1997 to 2011.
- Monitoring isolates that carry β-lactamases is important to understand their prevalence and susceptibility to clinically available antimicrobial agents.
- We evaluated the prevalence of β-lactamases and the activity of antimicrobial agents against 1,209 isolates collected in 69 US hospitals.
  - Due to elevated MIC values against broad spectrum cephalosporins, aztreonam, and the carbapenems, these isolates were submitted to whole genome sequencing and analysis.

METHODS

- A total of 9,686 *Enterobacterales* isolates were collected in US hospitals during 2019.
  - Isolates were identified as the cause of infection.
  - Isolates were limited to 1 per patient.
- Isolates were susceptibility tested using the reference broth microdilution method described by the Clinical and Laboratory Standards Institute (CLSI).
  - Categorical interpretations for all comparator agents were published by CLSI or the US FDA.
- Quality control (QC) was performed according to CLSI M07 (2018) guidelines.
- Isolates meeting the following criteria were submitted to whole genome sequencing and analysis:
  - *Escherichia coli* and *Klebsiella pneumoniae* displaying MIC values ≥2 mg/L for at least 2 of the following β-lactams: ceftazidime, ceftriaxone, aztreonam, or cefepime.

METHODS

  - *Enterobacter cloacae* and *Citrobacter* spp. displaying MIC values ≥16 mg/L for ceftazidime and/or ≥2 mg/L for cefepime.
  - *Enterobacterales* displaying elevated carbapenem (meropenem and/or imipenem) MIC results at >1 mg/L.
- 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.
  - A criterion of >94% sequencing identity and 40% minimum length coverage was applied.

DISCLOSURES

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