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Occurrence of β-lactamases among Enterobacterales isolates from United States Hospitals in a 10-year period: Report from the International Network for Optimal Resistance Monitoring (INFORM) Program

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CONCLUSIONS

An overall decrease in β-lactamase-producing isolates has been observed in 2022 when compared to prior years but these isolates are still prevalent in US hospitals.

Ceftazidime-avibactam and the carbapenems were the most active agents in all study years against β-lactamase-producing isolates, but the carbapenems had limited activity against CREs.

Recent changes in the prevalence of β-lactamase-producing isolates demonstrate the importance of monitoring these isolates and their susceptibility profiles at a local and global level since the presence of these enzymes impacts patient treatment.

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INTRODUCTION

- β-lactams are the most broadly used class of antimicrobials; however, β-lactamase-production can limit the use of these agents.
- Among Enterobacterales, ESBLs and carbapenemases hydrolyze third and fourth generation cephalosporins and/or carbapenems that are important therapeutic options to treat serious infections caused by these organisms.
- Longitudinal surveillance of β-lactamases on a large scale is scarce. The INFORM program surveys β-lactamases and monitors the activity of ceftazidime-avibactam and comparator agents in US hospitals since 2012.
- In this study, we analyzed 10 years (2013–2022) of data from the INFORM Program to report trends in β-lactamase-production and susceptibility profiles of the isolates carrying these enzymes.

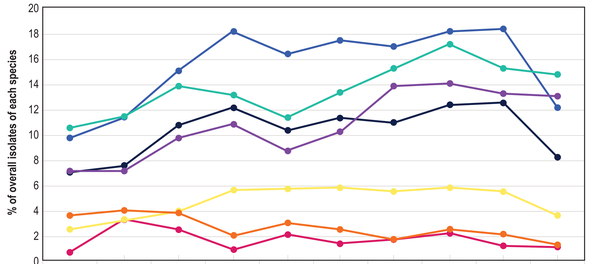
MATERIALS AND METHODS

- A total of 36,534 Enterobacterales isolates were consecutively collected in 22 US hospitals participating in the INFORM program during 2013 to 2022.
  - 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 as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2024) and M100 (2024) documents.
- Quality control (QC) was performed according to the CLSI M100 (2024) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents followed CLSI M100 (2024) or the US Food and Drug Administration (FDA) website criteria.
- *Escherichia coli* and *Klebsiella pneumoniae* displaying MICs ≥2 mg/L for two of: ceftriaxone, ceftazidime, cefepime, or aztreonam; or carbapenem-resistant Enterobacterales (CRE; resistant to meropenem or imipenem) were submitted to analysis for the detection of β-lactamases using Microarray/PCR (2013–2015) and whole genome sequencing (WGS; 2016–2022).
  - Check-MDR CT101 kit (Check-points, Wageningen, Netherlands) microarray was performed according to the manufacturer's instructions and results confirmed by PCR.
  - WGS was performed on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage.
    - Analysis of β-lactam resistance mechanisms was performed *in silico*.

RESULTS

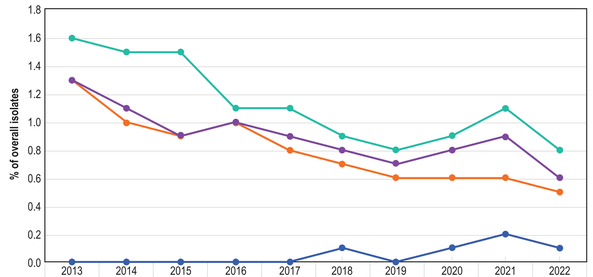
- Overall, ESBLs were detected among 2,334 out of 2,691 screened (15.6% of 14,969 overall non-CRE isolates) *E. coli* and 964 of the screened 1,051 (13.8% of 6,988) *K. pneumoniae.*
- The most common ESBL detected among *E. coli* and *K. pneumoniae* was CTX-M-15-like.
  - This enzyme was detected among 10.5/58.3% of the *E. coli* overall/screened and 11.0/73.4% of the *K. pneumoniae.*
- The incidence of *E. coli* isolates displaying an ESBL genotype, producing CTX-M-15-like or CTX-M-9/14/27 increased until 2021, but a decline in these rates was noted in 2022 when compared to the two previous years (Figure 1).
- SHV ESBLs among *K. pneumoniae* (3.9% to 1.4%; Figure 1) had a steady decline since 2015.
- Transferable AmpC enzymes among *E. coli* increased in 2014 and 2015 but slightly declined since.
- CRE isolates declined steadily from 1.6% in 2013 to 0.8% in 2022 (Figure 2).
- Carbapenemase-positive isolates also declined from 1.3% to 0.6%, with a decline in KPC producers but an increase in isolates producing NDM that were initially detected in 2015 and range from 10–16 isolates in the last 3 study years.
- Ceftazidime-avibactam and the carbapenems are the most active agents against isolates producing ESBLs inhibiting >99.0% and 84.4% to 99.9% of the isolates, respectively (Figure 3).
- Against CREs, ceftazidime-avibactam (93.4% susceptible) followed by tigecycline (96.8% susceptible) were the most active agents against CREs.
  - 82.0% of the isolates were intermediate to colistin applying the CLSI breakpoints.

Figure 1. Rates of ESBLs and transferable AmpC among *Escherichia coli* and *Klebsiella pneumoniae* over 10 years



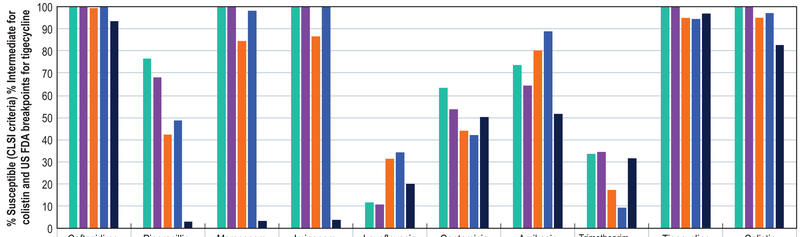
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
KPN ESBL	10.6	11.5	13.9	13.2	11.4	13.4	15.3	17.2	15.3	14.8
KPN CTX-M-15-like	7.2	7.2	9.8	10.9	8.8	10.3	13.9	14.1	13.3	13.1
KPN SHV ESBL	3.7	4.1	3.9	2.1	3.1	2.6	1.8	2.6	2.2	1.4
EC ESBL	9.8	11.4	15.1	18.2	16.4	17.5	17.0	18.2	18.4	12.2
EC CTX-M-15-like	7.1	7.6	10.8	12.2	10.4	11.4	11.0	12.4	12.6	8.3
EC CTX-M-9/14/27	2.6	3.3	4.0	5.7	5.8	5.9	5.6	5.9	5.6	3.7
EC Transferable AMPC	0.8	3.4	2.6	1.0	2.2	1.5	1.8	2.3	1.3	1.2

Figure 2. Rates of CRE among Enterobacterales over 10 years



	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
CRE	1.6	1.5	1.5	1.1	1.1	0.9	0.8	0.9	1.1	0.8
Carbapenemase positive	1.3	1.1	0.9	1.0	0.9	0.8	0.7	0.8	0.9	0.6
KPC	1.3	1.0	0.9	1.0	0.8	0.7	0.6	0.6	0.6	0.5
NDM	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.2	0.1

Figure 3. Activity of ceftazidime-avibactam and comparator agents tested against β-lactamase-producing isolates from US hospitals



	Ceftazidime-avibactam	Piperacillin-tazobactam	Meropenem	Imipenem	Levofloxacin	Gentamicin	Amikacin	Trimethoprim-sulfamethoxazole	Tigecycline	Colistin
EC ESBL (n=2,334)	99.9	76.5	99.9	99.8	11.5	63.3	73.6	33.4	99.9	99.5
EC CTX-M-15-like (n=1,568)	99.9	68	99.9	99.8	10.5	53.6	64.3	34.3	99.9	99.6
KPN ESBL (n=1,125)	99.3	42.1	84.4	86.5	31.2	43.9	80.2	17.1	94.9	94.2
KPN CTX-M-15-like (n=771)	100	48.5	98.1	99.9	34.1	41.9	88.8	9.1	94.4	96.3
CRE (n=1,020)	93.4	2.8	31.1	3.6	19.9	50.1	51.5	31.4	96.8	82