ICAAC 2015
C-137

Trends in β-lactamase Occurrence in USA Hospitals During the 2012-2014 Period and Activity of Ceftazidime-Avibactam against a Large Collection of β-lactamase Producing Isolates

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Abstract

Background: Dissemination of β-lactamases (BLs) is a worrisome and an evolving issue that requires monitoring. We evaluated the occurrence of BLs among consecutively collected isolates in hospitals participating in three years of the INFORM survey and the activity of CAZ-AVI and comparators against this collection.

Methods: Among 15,888 clinical isolates collected in 63 USA hospitals from 2012 to 2014 and susceptibility (S) tested by reference broth microdilution methods, 2129 displayed an ESBL-phenotype (*E. coli* [EC; n=1048], *K. pneumoniae* [KPN; 843], *K. oxytoca* [135] and *P. mirabilis* [103]) and were evaluated for the presence of genes encoding ESBLs, KPC, NDM and transferable AmpC enzymes. Statistical analysis was performed by Fisher's exact test comparing 2012 and 2014 rates.

Results: ESBL rates were similar over time (13.1-13-8%); however, CRE (2.3/1.8% in 2012/2014; p=0.064) and KPN-CRE (6.7/5.0%; p=0.003) rates were lower in 2014 compared to prior years. CTX-M-15-like genes were observed among 900 isolates (including 569 EC and 298 KPN). Production of CTX-M-15-like was stable, but a decrease among EC (59.5/49.5%; p=0.005) and increase among KPN (34.0/40.8%; p=0.059) in 2014 was noted. KPC-production (304 isolates; 285 KPN) decreased over the years (17.0/10.9%; p=0.003) mainly due to the decrease in KPC-producing KPN (37.1/28.2%; p=0.003) in hospitals where these isolates were formerly highly prevalent. CMY-2- and CTX-M-14-producing isolates increased (8.4/11.8% and 9.3/12.8, respectively; p=0.04 for both), and SHV ESBL-producers decreased (25.6/12.7%; p=<0.001) over the studied years. Other enzymes were detected in smaller numbers, including four NDM-producers (2 in 2012 and 2 in 2014). Diversity of rates among USA Census regions was noted, but no significant differences over the study period were observed. CAZ-AVI was very active against the ESBL-phenotype isolates ($MIC_{50/90}$, 0.5/1 µg/ml; 99.7% S) and CRE strains ($MIC_{50/90}$, 0.5/2 µg/ml; 99.0% S). CRE displayed elevated MIC values for comparators (<65% S), except for tigecycline (98.1% S; CLSI breakpoint) and colistin (80.6% S, EUCAST breakpoint).

Conclusions: Significant changes were noted in the occurrence of BLs in USA hospitals over 3 years (2012-2014). CAZ-AVI was very active against all isolates producing serine-BL.

Introduction

The β-lactamase prevalence scenario in the US differs from other countries regarding the occurrence and distribution of β-lactamase-producing isolates and enzyme types. While in the mid-2000s CTX-M-producing isolates were considered endemic in nosocomial and community settings in countries from Europe and Asia, the first studies showing the dissemination of CTX-M-producers in the US date from 2007. After initial reports, a rapid spread of CTX-M-15- and CTX-M-14-like producing strains was observed in US hospitals and currently the rates are similar to those observed in other nations.

KPC enzymes were first described in New York City and rapidly became endemic in that area. More recently, KPC-producing strains also became very prevalent in other parts of the US, such as Texas, as well as in several other countries. However, their prevalence scenario may change with the emergence of NDM-producing isolates.

As a result, constant surveillance of the organisms producing β-lactamases seems prudent. In this study, we assessed the occurrence of β-lactamase-producing isolates collected in 63 US hospitals participating over three consecutive years of ceftazidime-avibactam activity surveillance. The activity of this compound and comparator agents was also evaluated.

Methods

Bacterial isolates. A total of 15,888 clinical isolates of *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* were collected in 63 US hospitals between 2012 and 2014 and analyzed. Only one isolate per patient infection episode was included in the study. Species identification was confirmed when necessary by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (MALDI-TOF MS) using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions.

Antimicrobial susceptibility testing. All isolates were susceptibility tested using reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Categorical interpretations for all antimicrobials were those found in CLSI M100-S25 (2015) and quality control (QC) was performed using *E. coli* ATCC 25922 and 35218, *Klebsiella pneumoniae* 700603 and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within the ranges published in CLSI documents.

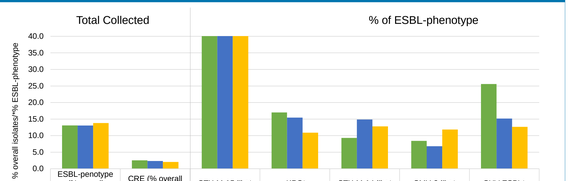
Screening for β-lactamases. A total of 2,129 isolates displayed an ESBL-phenotype (MIC >1 µg/mL for aztreonam and/or ceftazidime and/or ceftriaxone; M100-S25 2015) and were tested for β-lactamase-encoding genes using the microarray based assay Check-MDR CT101 kit (Check-points, Wageningen, Netherlands). The assay was performed according to the manufacturer's instructions. This kit has the capabilities to detect CTX-M Groups 1, 2, 8+25 and 9, TEM wild-type (WT) and ESBL, SHV WT and ESBL, ACC, ACT/MIR, CMYII, DHA, FOX, KPC and NDM-1.

Statistical analysis and definitions. Statistical analysis was performed by Fisher's exact test using EpiInfo7 (Centers for Disease Control and Prevention, Georgia, USA) comparing 2012 and 2014 rates. Carbapenem-resistant Enterobacteriaceae (CRE) were defined as isolates displaying imipenem and/or meropenem MIC values of >2 µg/mL.

Results

- Among the ESBL-phenotype isolates were 1,048 *E. coli*, 843 *K. pneumoniae*, 135 *K. oxytoca* and 103 *P. mirabilis,* and these isolates were recovered from bloodstream infections (n=340), intra-abdominal infections (n=154), pneumonia in hospitalized patients (n=556), skin/soft tissue infections (n=468), urinary tract infection (n=504) and other or unknown sites (n=107).
- ESBL rates were similar over time and were 13.1, 13.1 and 13.8% in 2012, 2013 and 2014, respectively (Figure 1). CRE rates showed a decreasing trend from 2.5% in 2012 to 2.0% in 2014 (Figure 1; *p*=0.064; OD 1.244 95% CI [0.950 – 1.632]) with the highest decrease among carbapenem-resistant *K. pneumoniae* isolates from 6.7% in 2012 and 2013 to 5.1% in 2014 (*p*=0.022; OD 1.415 95% CI [1.058 – 1.893]).
- CTX-M-15-like genes were noted among 295, 297 and 308 isolates in 2012, 2013 and 2014, respectively. Although the overall prevalence of these isolates was stable (43.6, 42.1 and 41.9% in 2012, 2013 and 2014, respectively), a decrease in CTX-M-15-like-producing *E. coli* (59.5 to 49.5%; *p*=0.005; OD 1.498 95% CI [1.109 – 2.025]) and increase in the occurrence of this enzyme among *K. pneumoniae* (34.0 to 40.8%; *p*=0.059; OD 0.744 95% CI [0.526 – 1.05]) was observed in 2014 (Figures 1 and 2).
- A decrease in KPC-production was noted in the study years: 17.0% of ESBL-phenotype isolates carried bla_{KPC} in 2012, 15.4% in 2013 and only 10.9% in 2014 (*p*=0.003; OD 1.490 95% CI [1.117 – 1.988]). KPC-producing *K. pneumoniae* had a decrease from 37.1 to 28.2% (*p*=0.003; OD 1.546 CI [1.140 – 2.096]) (Figure 2).
- CTX-M-14-producing isolates increased in the study period from 9.3% in 2012 to 14.9% in 2013 and 12.8% in 2014; and the difference from 2012 to 2014 was statistically significant (*p*=0.042; OD 0.700 95% CI [0.499 – 0.982]), although higher rates were noted in 2013 (Figure 1).
- CMY-2-producing isolates increased from 2012 (8.4 %) to 2014 (11.8%; *p*=0.042; OD 0.685 95% CI [0.482 – 0.974]), but only 6.8% of the 2013 ESBL-phenotype isolates carried the gene encoding this enzyme (Figure 1). Among the organisms carrying bla_{CMY-2}-like, *E. coli* isolates displayed a similar increase to the overall ESBL-phenotype population: 14.5, 10.1 and 17.9% in 2012, 2013 and 2014, respectively (Figure 2).
- A decrease in the occurrence of SHV ESBL-producing organisms was observed from 2012 (25.6%; Figure 1) to 2014 (12.7%; *p*=<0.001; OD 2.374 95% CI [1.798 – 3.134]) and this was caused by a decrease in SHV ESBL occurrence among *K. pneumoniae* isolates from 50.5% in 2012 to 19.2% in 2014 (Figure 2).
- Other enzymes were detected in small numbers and no trends were noted in the occurrence of these enzymes (data not shown). Only four NDM-producing isolates were detected in 2012 (two isolates in Montana, CO) and 2014 (two isolates; one from Los Angeles, CA and another from New York, NY).
- Ceftazidime-avibactam was very active against the ESBL-phenotype isolates ($MIC_{50/90}$, 0.5/1 µg/ml; 99.7% susceptible; Figure 3), including CRE strains ($MIC_{50/90}$, 0.5/2 µg/ml; 98.5% susceptible) that had elevated MIC values for comparator agents, except for tigecycline (98.9% susceptible; US-FDA breakpoint) and colistin (80.6% susceptible, EUCAST breakpoint).

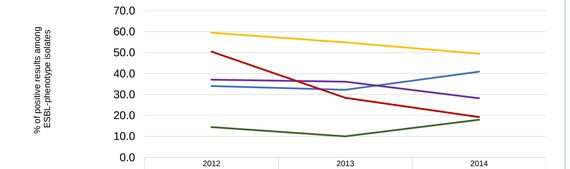
Figure 1. Overall prevalence of resistant phenotypes (ESBL and CRE) and β-lactamase genotypes among *E. coli*, *Klebsiella* spp. and *P. mirabilis* collected in 63 US hospitals during 2012 to 2014. Statistically significant changes over time (*p* values ranged from <0.001 to 0.064) were observed in the occurrence of CRE isolates in the overall Enterobacteriaceae population and production of KPC, CTX-M-14-like, CMY-2-like and SHV ESBL.



	ESBL-penotype (% overall isolates)	CRE (% overall isolates)	CTX-M-15-like*	KPC*	CTX-M-14-like*	CMY-2-like*	SHV ESBL*
2012	13.1	2.5	43.6	17.0	9.3	8.4	25.6
2013	13.1	2.4	42.1	15.4	14.9	6.8	15.2
2014	13.8	2.0	41.9	10.9	12.8	11.8	12.7

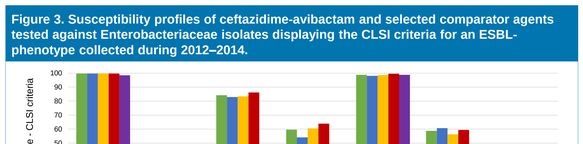
*rates among ESBL-phenotype strains.

Figure 2. Organisms and β-lactamases with statistically significant changes (*p* values ranged from <0.001 to 0.059) in the study period.



	2012	2013	2014
CTX-M-15-like E. coli	59.5	54.9	49.5
CTX-M-15-like K. pneumoniae	34.0	32.3	40.9
KPC K. pneumoniae	37.1	36.1	28.2
CMY-2-like E. coli	14.5	10.1	17.9
SHV ESBL K. pneumoniae	50.5	28.4	19.2

Figure 3. Susceptibility profiles of ceftazidime-avibactam and selected comparator agents tested against Enterobacteriaceae isolates displaying the CLSI criteria for an ESBL-phenotype collected during 2012–2014.



	Ceftazidime-avibactam	Ceftazidime	Meropenem	Piperacillin-tazobactam	Tigecycline	Gentamicin	Levofloxacin
All years	99.7	30.2	84.2	59.6	98.8	58.8	29
2012	99.7	28.6	82.9	54.1	98.1	60.7	29.4
2013	99.7	30.6	83.4	60.5	98.6	56.3	25.6
2014	99.7	31.3	86.2	63.9	99.6	59.4	31.9
CRE	98.5	0.9	0.9	0.3	98.8	48.2	13.5

Conclusions

- Important differences were noted across the three years of surveillance in US hospitals, with a decrease in CRE and KPC-production rates in 2014 when compared to 2012. This lower occurrence of KPC-producing organisms might be due to better infection control practices in a few hospitals that displayed elevated KPC rates in the earlier years.
- The most significant changes in the occurrence of β-lactamase genes were among *K. pneumoniae* isolates that displayed a higher prevalence of CTX-M-encoding genes and a considerable reduction in the prevalence of KPC and SHV ESBLs in the later years of the study.
- Ceftazidime-avibactam displayed good activity against isolates producing the commonly observed β-lactamases that are prevalent in the US, including KPC-producers.

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Acknowledgment

The authors would like to thank all participants of the International Network for Optimal Resistance Monitoring (INFORM) program for providing bacterial isolates.

This study was supported by Cerexa, Inc., an Allergan affiliate. Forest Laboratories, LLC, an Allergan affiliate provided financial support for the analysis of the data and was involved in the design and decision to present these results. Neither Cerexa, Inc. nor Forest Laboratories, LLC, had any involvement in the collection, analysis, and interpretation of data.