Frequency and Antimicrobial Susceptibility of Bacteria Isolated from Patients Hospitalized with Pneumonia in US Medical Centers During 2018

Helio S. Sader, Michael D. Huband, Cecilia G. Carvalhaes, Mariana Castanheira

JMI Laboratories, North Liberty, Iowa, USA

IDWeek 2019
Poster #2217

Helio S. Sader, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

INTRODUCTION

- Rapidly introducing appropriate antimicrobial therapy is crucial to reduce morbidity and mortality of patients hospitalized with pneumonia (PHP)
- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and by the European Medicines Agency (EMA) to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia
- Ceftazidime-avibactam is also approved to treat complicated intra-abdominal infections (cIAIs) in combination with metronidazole, as well as complicated urinary tract infections, including pyelonephritis
- We evaluated the frequency and antimicrobial susceptibility of bacteria isolated from patients hospitalized with pneumonia in US medical centers and assessed the activity and spectrum of 2 recently approved β-lactamase inhibitor combinations, ceftazidime-avibactam and ceftolozane-tazobactam, and many other antimicrobial agents currently used to treat pneumonia

MATERIALS AND METHODS

Bacterial isolates

- A total of 3,860 bacterial isolates were consecutively collected (1/infection episode) from 66 US medical centers in 2018
- Among those, 1,404 *Enterobacterales* and 878 *Pseudomonas aeruginosa* isolates were tested for susceptibility as part of the International Network for Optimal Resistance Monitoring (INFORM) Surveillance program
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program

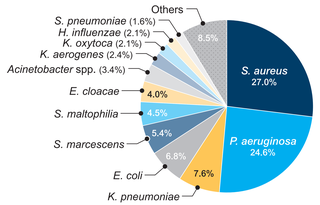
Resistant subsets and screening for β-lactamase-encoding genes

- Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 mg/L (CLSI, 2019)
  - Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* and *P. aeruginosa* strains were classified as MDR and XDR according to recommended guidelines (Magiorakos et al., 2012)
  - MDR: nonsusceptible (NS; CLSI breakpoints) to at least 1 drug in 3 classes
  - XDR: susceptible (S) to 2 or fewer antimicrobial classes
- *Enterobacterales* isolates displaying MIC values ≥2 mg/L for at least 2 β-lactams (ie, ceftazidime, ceftriaxone, aztreonam, or cefepime) and all CRE isolates were tested for β-lactamase-encoding genes using next-generation sequencing

Susceptibility testing

- Broth microdilution test method was conducted according to CLSI
- Avibactam was provided by Allergan (Irvine, California, USA) and combined with ceftazidime (avibactam at fixed concentration of 4 mg/L) for susceptibility testing
- Ceftolozane stock solution was obtained from ThermoFisher Scientific (Cleveland, Ohio, USA) and combined with tazobactam (acquired from United States Pharmacopeia [USP]) at fixed concentration of 4 mg/L for susceptibility testing
- All other compounds were obtained from USP or Sigma-Aldrich (St. Louis, Missouri, USA)

Figure 1. Frequency of organisms isolated from patients hospitalized with pneumonia in US medical centers (INFORM program, 2018)



RESULTS

- The most common organisms isolated from patients hospitalized with pneumonia were *Staphylococcus aureus* (27.0%), *P. aeruginosa* (24.6%), *Klebsiella pneumoniae* (7.6%), *Escherichia coli* (6.8%), *Serratia marcescens* (5.4%), and *Stenotrophomonas maltophilia* (4.5%); overall, 70.3% of the organisms were gram-negative and 29.7% were gram-positive organisms (Figure 1)
- Ceftazidime-avibactam ($MIC_{50/90}$, 2/8 mg/L; 95.7% susceptible [%S]), ceftolozane-tazobactam ($MIC_{50/90}$, 1/4 mg/L; 94.9%S), and colistin ($MIC_{50/90}$, 0.5/1 mg/L; 99.7% inhibited at ≤2 mg/L) were the most active compounds against *P. aeruginosa* (Table 1 and Figure 2)
- Ceftazidime-avibactam ($MIC_{50/90}$, 8/32 mg/L; 74.3%S) and ceftolozane-tazobactam ($MIC_{50/90}$, 4/>32 mg/L; 71.7%S) retained activity against *P. aeruginosa* isolates not susceptible to piperacillin-tazobactam, meropenem, and cefepime (Tables 1 and 2)
- High rates of cross-resistance were observed between meropenem, cefepime, and piperacillin-tazobactam when testing *P. aeruginosa* isolates; in contrast, ceftazidime-avibactam and ceftolozane-tazobactam retained good activity against *P. aeruginosa* isolates not susceptible to any of these β-lactams (Table 2)
- Ceftazidime-avibactam and ceftolozane-tazobactam exhibited comparable activities against *P. aeruginosa* isolates, including against resistant subsets (Tables 1 and 2 and Figure 2)
- Ceftazidime-avibactam remained active against 39.5% of *P. aeruginosa* isolates not susceptible to ceftolozane-tazobactam, and ceftolozane-tazobactam remained active against 31.6% of isolates not susceptible to ceftazidime-avibactam (Table 2)

Table 1. Antimicrobial activity of ceftazidime-avibactam and comparator agents tested against *P. aeruginosa* and *Enterobacterales* isolated from patients hospitalized with pneumonia in US medical centers (2018)

Organism/organism group (no. of isolates) Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	 %R
Pseudomonas aeruginosa (878)				
Ceftazidime-avibactam	2	8	95.7	4.3
Ceftolozane-tazobactam	1	4	94.9	3.5
Piperacillin-tazobactam	8	128	75.3	14.2
Ceftazidime	2	32	79.6	15.3
Cefepime	4	16	78.8	8.2
Meropenem	0.5	16	74.7	18.7
Levofloxacin	1	16	60.5	26.7
Amikacin	4	16	92.3	4.7
Tobramycin	0.5	4	91.6	5.8
Colistin	0.5	1	99.7	0.3
Isolates not susceptible to meropenem, cefepime, and piperacillin-tazobactam (113)				
Ceftazidime-avibactam	8	32	74.3	25.7
Ceftolozane-tazobactam	4	>16	71.7	23.0
Ceftazidime	32	>32	13.3	76.1
Tobramycin	1	>16	65.5	24.8
Amikacin	8	>32	71.7	20.4
Levofloxacin	8	>32	15.0	72.6
Colistin	0.5	1	99.1	0.9
Enterobacterales (1,404)				
Ceftazidime-avibactam	0.12	0.5	99.9	0.1
Ceftolozane-tazobactam	0.5	4	89.8	7.7
Piperacillin-tazobactam	2	64	87.3	7.3
Ceftazidime	0.25	32	83.0	15.3
Ceftriaxone	0.12	>8	78.2	20.4
Cefepime	0.06	8	87.9	8.9
Meropenem	0.03	0.06	97.6	1.9
Levofloxacin	0.06	8	82.0	15.2
Gentamicin	0.5	2	92.5	6.7
Amikacin	2	4	98.8	0.3
Tigecycline[b]	0.5	2	95.2[b]	0.4
Colistin[c]	0.12	>8	74.7[c]	
ESBL-producing isolates (117)[d]				
Ceftazidime-avibactam	0.25	0.5	100.0	0.0
Ceftolozane-tazobactam	1	8	82.4	13.0
Piperacillin-tazobactam	8	128	74.4	12.0
Meropenem	0.03	0.06	98.3	0.9
Levofloxacin	8	32	25.0	68.1
Gentamicin	1	>16	56.4	42.7
Amikacin	4	16	94.9	0.9
Tigecycline[b]	0.5	2	95.7 [b]	0.0
Colistin[c]	0.12	0.25	97.2 [c]	

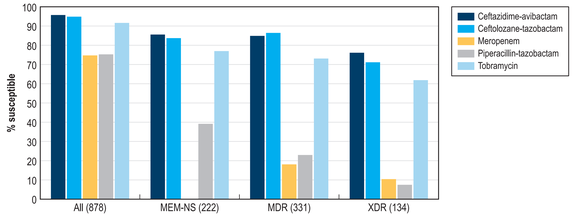
ESBL, extended-spectrum β-lactamase
[a] Criteria as published by CLSI 2019.
[b] FDA breakpoints accessed February 2019.
[c] Percentage of wild type based on epidemiologic cutoff value. CLSI M100 (2019).
[d] Excluding carbapenemase co-producers.

- Ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L; 99.9%S), amikacin ($MIC_{50/90}$, 2/4 mg/L; 98.8%S), and meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 97.6%S) were the most active compounds against *Enterobacterales* (Table 1 and Figures 3 and 4)
- Ceftazidime-avibactam ($MIC_{50/90}$, 1/2 mg/L) and tigecycline ($MIC_{50/90}$, 1/2 mg/L) were the only compounds with good activity against CRE (n=29), both with 96.6%S (Figure 4)
- Among *Enterobacterales*, the most common extended-spectrum β-lactamase (ESBL) and carbapenemase were CTX-M-15 (73%) and KPC-2/3 (76%), respectively (data not shown)
- Ceftazidime-avibactam was active against all ESBL producers (n=117; $MIC_{50/90}$, 0.12/0.5 mg/L; 100.0%S), whereas the susceptibility rate to ceftolozane-tazobactam ($MIC_{50/90}$, 1/8 mg/L) was 82.4% when carbapenemase-producing strains were excluded (Table 1 and Figures 3 and 4)
- The most active compounds against MDR (n=177) and XDR (n=31) *Enterobacterales* were ceftazidime-avibactam (98.9%S and 100.0%S, respectively) and amikacin (91.5%S and 71.0%S, respectively; Figure 4)

CONCLUSIONS

- Ceftazidime-avibactam demonstrated potent activity against a large US collection (n=2,282) of contemporary *Enterobacterales* and *P. aeruginosa* isolates from patients hospitalized with pneumonia, including organisms resistant to most currently available agents, such as CRE and meropenem-nonsusceptible *P. aeruginosa*
- Ceftazidime-avibactam and ceftolozane-tazobactam showed similar coverage (%S) against *P. aeruginosa* (95.7%S vs. 94.9%S), including against all resistant subsets, such as meropenem-nonsusceptible (85.6%S vs. 83.7%S), MDR (82.5%S vs. 80.8%S), and XDR (76.1%S vs. 71.2%S) isolates
- Although ceftazidime-avibactam and ceftolozane-tazobactam showed similar *P. aeruginosa* coverage, approximately 30-40% of isolates resistant to 1 compound were susceptible to the other
- Ceftolozane-tazobactam was less active than ceftazidime-avibactam against *Enterobacterales* in general and exhibited limited activity against resistant subsets
- Ceftazidime-avibactam represents a valuable option for treating patients hospitalized with pneumonia in US medical centers

Figure 2. Antimicrobial susceptibility of *P. aeruginosa* isolated from patients hospitalized with pneumonia in US medical centers (INFORM program, 2018)



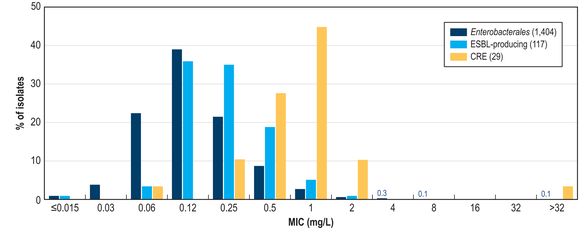
Abbreviations: MEM-NS, meropenem-nonsusceptible; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Table 2. Cross-resistance among β-lactam compounds when testing *P. aeruginosa* isolates from patients hospitalized with pneumonia

Organism subset (n)	Meropenem	Cefepime	Piperacillin-tazobactam	Ceftolozane-tazobactam	Ceftazidime-avibactam
Meropenem-NS (222)	—	42.3	39.2	83.7	85.6
Cefepime-NS (186)	31.2	—	17.7	77.8	80.6
Piperacillin-tazobactam-NS (217)	37.8	29.5	—	81.4	83.4
Meropenem-, cefepime-, and piperacillin-tazobactam-NS (113)	—	—	—	71.7	74.3
Ceftolozane-tazobactam-NS (43)	16.3	4.7	7.0	—	39.5
Ceftazidime-avibactam-NS (38)	15.8	5.3	5.3	31.6	—

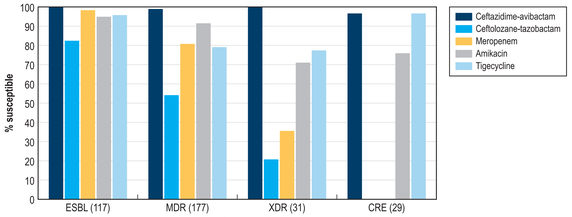
Abbreviations: NS, nonsusceptible.

Figure 3. Ceftazidime-avibactam activity (MIC distributions) against *Enterobacterales* and resistant subsets isolated from patients hospitalized with pneumonia in US medical centers (INFORM program, 2018)



ESBL, extended-spectrum β-lactamase; CRE, carbapenem-resistant *Enterobacterales*.

Figure 4. Antimicrobial susceptibility of *Enterobacterales*-resistant subsets isolated from patients hospitalized with pneumonia in US medical centers (INFORM program, 2018)



Abbreviations: ESBL, extended-spectrum β-lactamases (excluding carbapenemase-producing strains); MDR, multidrug-resistant; XDR, extensively drug-resistant, CRE, carbapenem-resistant *Enterobacterales*.

ACKNOWLEDGEMENTS

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 Allergan. Allergan was involved in the design and decision to present these results, and JMI Laboratories received compensation for services related to preparing this poster. Allergan had no involvement in the collection, analysis, or interpretation of data.

REFERENCES

1. AVYCAZ® (2016). AVYCAZ® (ceftazidime-avibactam). Allergan USA, Inc. Available at https://www.allergan.com/assets/pdf/avycaz_pi. Accessed January 2017.
2. Castanheira M, Mendes RE, Jones RN, Sader HS (2016). Changes in the frequencies of beta-lactamase genes among *Enterobacteriaceae* isolates in U.S. Hospitals, 2012 to 2014: Activity of ceftazidime-avibactam tested against beta-lactamase-producing isolates. *Antimicrob Agents Chemother* 60: 4770-4777.
3. Clinical and Laboratory Standards Institute (2019). *M100Ed29E. Performance standards for antimicrobial susceptibility testing: 29th informational supplement*. Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition*. Wayne, PA: CLSI.
5. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268–281.
6. Sader HS, Castanheira M, Mendes RE, Flamm RK (2018). Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015–17). *J Antimicrob Chemother* [in press]

Visit www.allergancongressposters.com/836655

Allergan