Frequency and Antimicrobial Susceptibility of Bacteria Isolated from Patients Hospitalized with Pneumonia in United States Medical Centers (2017–2018)

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INTRODUCTION

- The initial antimicrobial management of patients with pneumonia is determined mostly by the understanding of causative pathogens, and there is very little current information regarding the frequency and antimicrobial susceptibility of organisms causing healthcare-associated pneumonia
- Although *Staphylococcus aureus* is a significant cause of pneumonia in hospitalized patients, the importance of gram-negative organisms such as *Pseudomonas aeruginosa* and *Enterobacterales* species, mainly *Klebsiella pneumoniae*, *Enterobacter* spp., and *Escherichia coli*, has increased substantially in recent years
- 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 (HABP), including ventilator-associated bacterial pneumonia (VABP)
- 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 gram-negative 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 7,787 clinical isolates were consecutively collected from patients hospitalized with pneumonia (1/patient) in 66 US medical centers in 2017–2018
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program

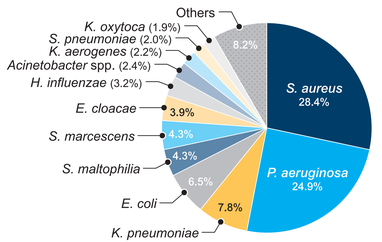
Resistant subsets

- 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 the intrinsically elevated MIC values
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* and *P. aeruginosa* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows:
  - MDR = nonsusceptible (NS; CLSI breakpoints) to at least 3 antimicrobial classes
  - XDR = susceptible (S) to 2 or fewer antimicrobial classes

Susceptibility testing

- The 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 (2017–2018)



Screening for β-lactamase-encoding genes

- *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
- Libraries were normalized using the bead-based normalization procedure (Illumina) and sequenced on MiSeq
- FASTQ files were assembled using SPAdes Assembler and subjected to a proprietary software (JMI Laboratories) for screening of β-lactamase genes

RESULTS

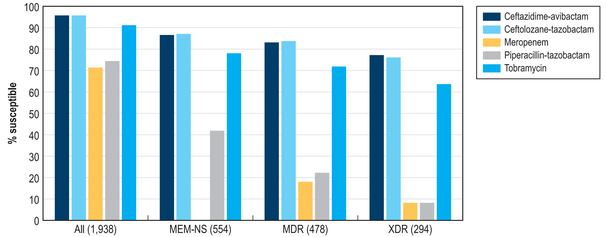
- The most common organisms were *S. aureus* (28.4%), *P. aeruginosa* (24.9%), *K. pneumoniae* (7.8%), *E. coli* (6.5%), *Stenotrophomonas maltophilia* (4.3%), *Serratia marcescens* (4.3%), and *Enterobacter cloacae* (3.9%); overall, 68.1% of the organisms were gram-negative and 31.9% were gram-positive (Figure 1)
- All *S. aureus* isolates were susceptible (S) to dalbavancin (MIC_{90}, 0.06 mg/L), linezolid, teicoplanin, and vancomycin; 99.9%S to tigecycline; 95.8%S to ceftaroline; and 55.9%S to oxacillin (Table 1)
- Ceftazidime-avibactam and ceftolozane-tazobactam were very active against *P. aeruginosa* isolates and exhibited identical coverage against these organisms (95.7%S; Table 2)
- Ceftazidime-avibactam retained activity against *P. aeruginosa* isolates nonsusceptible to meropenem (86.6%S), MDR (83.1%S), XDR (77.2%S), and nonsusceptible to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam (68.4%S; Table 2 and Figure 2)
- Ceftazidime-avibactam exhibited potent activity against *Enterobacterales* ($MIC_{50/90}$, 0.12/0.5 mg/L; 99.9%S), including extended-spectrum β-lactamase (ESBL)-producing strains ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0%S), CRE ($MIC_{50/90}$, 1/2 mg/L; 96.3%S), MDR ($MIC_{50/90}$, 0.25/1 mg/L; 99.3%S), and XDR isolates ($MIC_{50/90}$, 1/2 mg/L; 96.1%S; Table 3 and Figure 3)

Table 1 Antimicrobial susceptibility of *S. aureus* isolates (n=2,080) from patients hospitalized with pneumonia in US medical centers

Antimicrobial	MIC_{50}[a]	MIC_{90}[a]	%S[b]	%R[b]
Dalbavancin	0.03	0.06	100.0	
Ceftaroline	0.25	1	95.8	0.0
Clindamycin	0.06	>2	80.6	19.2
Levofloxacin	0.25	>4	62.2	37.7
Linezolid	1	2	100.0	0.0
Oxacillin	1	>2	55.9	44.1
Teicoplanin	0.5	0.5	100.0	0.0
Tigecycline	0.12	0.12	99.9[b]	
TMP-SMX	≤0.5	≤0.5	98.5	1.5
Vancomycin	1	1	100.0	0.0

TMP-SMX, trimethoprim-sulfamethoxazole.
[a] MIC_{50} and MIC_{90} values in mg/L; criteria as published by CLSI (2019).
[b] US FDA breakpoints were applied.

Figure 2 Antimicrobial susceptibility of *P. aeruginosa* isolated from patients hospitalized with pneumonia in US medical centers (INFORM Program, 2017–2018)



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

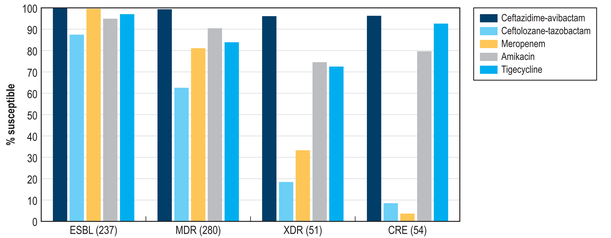
- The most active agents against *Enterobacterales* were ceftazidime-avibactam (99.9%S), amikacin (98.7%S), meropenem (97.7%S), and tigecycline (94.8%S), but only ceftazidime-avibactam and tigecycline retained good activity (≥90%S) against CRE (96.3% and 92.6%S, respectively; Figure 3)
- The most active agents against MDR *Enterobacterales* were ceftazidime-avibactam (99.3%S) and amikacin (90.4%S), whereas ceftolozane-tazobactam and meropenem were active against only 62.6% and 81.1% of these organisms, respectively (Figure 3)
- Only 2 *Enterobacterales* isolates (0.1%) were ceftazidime-avibactam resistant; 2 *S. marcescens* isolates from New York, NY, 1 with KPC-3, OXA-10, OXA-9, SRT-like, TEM-1, and alterations in *ompC* and *ompF* isolated in 2017 and 1 with NDM-1 and alterations in *ompC* isolated in 2018
- Among ESBL-producing *Enterobacterales* (excluding carbapenemase-producing) isolates, susceptibility to ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem was 100.0%, 85.5%, and 99.6%, respectively (Table 3 and Figure 3)
- The most common ESBLs found among *Enterobacterales* isolates were CTX-M-15 (62.0% of ESBL), OXA-1/OXA-30 (37.6%), CTX-M-27 (11.4%), and SHV-12 (8.9%); 49 of 51 (96.1%) carbapenemase-producing *Enterobacterales* displayed a KPC-2 and/or a KPC3 (data not shown)

Table 2 Antimicrobial susceptibility of *P. aeruginosa* isolates from patients hospitalized with pneumonia in US medical centers

Antimicrobial	MIC_{50}[a]	MIC_{90}[a]	%S[a]	%R[a]
P. aeruginosa (1,938)				
Ceftazidime-avibactam	2	8	95.7	4.3
Ceftolozane-tazobactam	1	2	95.7	2.8
Piperacillin-tazobactam	8	128	74.4	14.1
Meropenem	0.5	16	71.3	20.7
Ceftazidime	2	32	79.2	15.7
Cefepime	4	16	78.8	9.1
Levofloxacin	1	16	70.4	20.1
Gentamicin	2	16	78.7	11.4
Amikacin	4	16	92.5	4.1
Colistin	0.5	1	99.9	0.1
β-lactam-nonsusceptible *P. aeruginosa* (212)[b]				
Ceftazidime-avibactam	8	32	68.4	31.6
Ceftolozane-tazobactam	4	>32	70.3	20.9
Colistin	0.5	1	99.5	0.5
Levofloxacin	8	>16	27.0	60.7
Amikacin	8	>32	74.1	18.4
Tobramycin	2	>16	67.9	25.0

[a] MIC_{50} and MIC_{90} values in mg/L; criteria as published by CLSI (2019).
[b] β-lactam-nonsusceptible defined as nonsusceptible to ceftazidime, cefepime, meropenem, and piperacillin-tazobactam.

Figure 3 Antimicrobial susceptibility of *Enterobacterales* isolated from patients hospitalized with pneumonia in US medical centers (INFORM Program, 2017–2018)



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

Table 3 Antimicrobial susceptibility of *Enterobacterales* isolates from patients hospitalized with pneumonia in US medical centers

Antimicrobial	MIC_{50}[a]	MIC_{90}[a]	%S[a]	%R[a]
Enterobacterales (2,370)				
Ceftazidime-avibactam	0.12	0.5	99.9	0.1
Ceftolozane-tazobactam	0.25	2	91.0	6.8
Piperacillin-tazobactam	2	64	87.0	7.0
Meropenem	0.03	0.06	97.7	2.0
Ceftriaxone	0.12	>8	76.4	21.6
Ceftazidime	0.25	32	82.0	16.3
Cefepime	≤0.12	8	86.9	9.3
Levofloxacin	0.06	16	79.5	17.6
Tigecycline	0.5	2	94.8[b]	0.6[b]
Gentamicin	0.5	2	91.7	7.4
Amikacin	2	4	98.7	0.2
Colistin	0.12	>8		
ESBL-producing *Enterobacterales* (excluding carbapenemases; 237)				
Ceftazidime-avibactam	0.25	0.5	100.0	0.0
Ceftolozane-tazobactam	0.5	8	85.5	12.3
Piperacillin-tazobactam	8	64	80.6	9.3
Meropenem	0.03	0.06	99.6	0.4
Ceftriaxone	>8	>8	1.3	96.6
Ceftazidime	32	>32	17.3	73.0
Cefepime	>16	>16	10.5	70.0
Levofloxacin	8	>16	24.5	67.9
Tigecycline	0.25	1	97.0[b]	0.0[b]
Gentamicin	1	>16	59.5	37.6
Amikacin	2	8	94.9	0.4
Colistin	0.12	0.25	98.2[b]	

ESBL, extended-spectrum β-lactamase.
[a] MIC_{50} and MIC_{90} values in mg/L; criteria as published by CLSI (2019).
[b] US FDA breakpoints were applied.
[c] Percentage of wild type based on ECV (CLSI M100, 2019).

CONCLUSIONS

- Ceftazidime-avibactam demonstrated potent activity against a large US collection of contemporary *Enterobacterales* (n=2,370) and *P. aeruginosa* (n=1,938) isolates from patients 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), including against MDR (83.1%S vs. 83.7%S) and XDR (77.2%S vs. 76.1%S) isolates, respectively
- 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 caused by gram-negative organisms in US medical centers

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