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Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalized with bloodstream infections in United States medical centers (2015–2017)☆

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ABSTRACT

The frequency and antimicrobial susceptibility of organisms causing bloodstream infections in the United States were evaluated by consecutively collecting (1/patient) 9210 bacterial isolates from 33 US medical centers in 2015–2017. Isolates were susceptibility tested by reference broth microdilution methods. Whole genome sequencing was performed on carbapenem-resistant Enterobacteriaceae (CRE). The most common organisms were *Staphylococcus aureus* (24.3%), *Escherichia coli* (20.8%), and *Klebsiella pneumoniae* (9.1%). Overall, 50.0% of isolates were gram-negative bacilli and 41.4% were Enterobacteriaceae. The most active agents against Enterobacteriaceae were ceftazidime–avibactam (99.9% susceptible), amikacin (99.7% susceptible), and the carbapenems meropenem and doripenem (99.1% susceptible). Among 28 CRE isolates (0.7% of Enterobacteriaceae), 21 produced a KPC-like carbapenemase, 2 an NMD-like, and 1 a KPC-17 and an NDM-1. Colistin (100.0% susceptible), ceftolozane–tazobactam (98.7% susceptible), ceftazidime–avibactam (98.2% susceptible), amikacin (97.9% susceptible), and tobramycin (95.6% susceptible) were very active against *Pseudomonas aeruginosa*. Among *S. aureus* isolates, 57.8% were oxacillin-susceptible.

1. Introduction

The etiology of bloodstream infections (BSIs) has changed substantially in the last 2 decades. Initially, we observed an increase of gram-negative bacteria and fungal pathogens, especially *Candida* spp., over gram-positive organisms. In the last few years, however, the most significant changes in the etiology of BSIs have been the antimicrobial resistance patterns, especially among gram-negative organisms (Lake et al., 2018; Timsit et al., 2014; Weiner et al., 2016). Moreover, the etiology of BSIs may vary significantly according to the type of patient and source of infection, and studies evaluating large series of BSIs with non-selected types of patients or specific pathogens are scarce.

The emergence and spreading of multidrug-resistant (MDR) gram-negative bacilli, mainly carbapenem-resistant Enterobacteriaceae (CRE), triggered the development of a series of drugs to address these problems. A few of these drugs have been approved for clinical use in the last few years, including 3 β-lactamase inhibitor combinations, e.g., ceftazidime–avibactam, ceftolozane–tazobactam, and meropenem–vaborbactam, and the novel aminoglycoside plazomicin (Carvalhaes et al., 2018; Castanheira et al., 2017, 2018; Sader et al., 2018a, 2018b). In this investigation, we evaluated the frequency and antimicrobial susceptibility of organisms isolated from patients with BSIs 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 BSIs.

2. Materials and methods

2.1. Bacterial isolates

A total of 9210 bacterial isolates were collected from patients with BSIs in 33 US medical centers in 23 states from all 9 US census divisions from January 2015 through December 2017. Most participating centers were represented by tertiary medical centers. Each participating center was asked to collect 100 consecutive isolates (1/patient) per year. Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program. Species identification was confirmed at JMI Laboratories by standard biochemical tests and using the matrix-assisted laser desorption ionization–time of flight mass spectrometer Biotyper (Bruker Daltonics, Billerica, MA, USA) according to the manufacturer instructions, when necessary. Carbapenem-resistant Enterobacteriaceae (CRE) was defined as resistant (MIC, ≥4 mg/L [CLSI]) to imipenem (imipenem was **not** applied to

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Proteus mirabilis or to indole-positive Proteeae), meropenem, or doripenem (CLSI, 2018b).

2.2. Susceptibility testing

Antimicrobial susceptibility was evaluated by reference broth microdilution methods conducted according to Clinical and Laboratory Standard Institute (CLSI) procedures (CLSI, 2018a). Avibactam was provided by Allergan (Irvine, CA, 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, OH, USA) and combined with tazobactam (acquired from United States Pharmacopeia [USP]) at fixed concentration of 4 mg/L for susceptibility testing. Ceftolozane–tazobactam was only tested against isolates collected in 2017, whereas all other compounds were tested against isolates from 2015 to 2017. All other compounds were obtained from USP or Sigma-Aldrich (St. Louis, MO, USA). Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures. QC strains included *Escherichia coli* ATCC 25922 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA 1705, and *P. aeruginosa* ATCC 27853. CLSI (CLSI, 2018b) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2018) susceptibility interpretive criteria were used to determine susceptibility/resistance rates for comparator agents.

2.3. Screening for carbapenemase-encoding genes

Enterobacteriaceae isolates displaying MIC values ≥2 mg/L for at least 2 β-lactams (i.e., ceftazidime, ceftriaxone, aztreonam, or cefepime) and all CRE isolates were tested for carbapenemase-encoding genes using next-generation sequencing (NGS). Total genomic DNA was extracted using the fully automated ThermoScientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, OH, USA). To perform NGS, DNA extracts were quantified using the Qubit™ High Sensitivity DS-DNA assay (Invitrogen, ThermoFisher Inc.) and normalized to 0.2 ng/μL. A total of 1 ng high-quality genomic DNA was used as input material for library construction using the Nextera XT™ DNA library preparation kit (Illumina, San Diego, CA, USA). 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 annotation of β-lactamase genes.

3. Results

The most common organisms isolated from patients with BSIs were *Staphylococcus aureus* (24.3%), *E. coli* (20.8%), *K. pneumoniae* (9.1%), coagulase-negative staphylococci (CoNS) (7.3%), *Enterococcus faecalis* (5.5%), *P. aeruginosa* (4.7%), β-hemolytic streptococci (BHS) (4.6%), *Enterobacter cloacae* (3.3%), and *E. faecium* (3.1%; Fig. 1). Overall, 50.0% of isolates were gram-negative bacilli and 41.4% were Enterobacteriaceae (Fig. 1). Overall, 80.0% of isolates were from adults (≥18 years old), 17.6% from children (≤17 years old), and 2.6% from patients whose age was not provided.

The most active agent (highest susceptibility rate per CLSI) against Enterobacteriaceae was ceftazidime–avibactam ($MIC_{50/90}$, 0.12/0.25 mg/L; 99.9% susceptible), followed by amikacin ($MIC_{50/90}$, 2/4 mg/L; 99.7%/98.8% susceptible per CLSI/EUCAST) and the carbapenems meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 99.1%/99.3% susceptible per CLSI/EUCAST) and doripenem ($MIC_{50/90}$, ≤0.06/0.12 mg/L; 99.1%/99.1% susceptible per CLSI/EUCAST; Table 1). Antimicrobial activity of ceftazidime–avibactam tested against the main organisms and resistant subsets is displayed in Supplemental Table S1. Overall 99.8% of Enterobacteriaceae, including 100.0% of extended-spectrum β-lactamase (ESBL)–producing isolates, were inhibited at a ceftazidime–avibactam MIC of ≤2 mg/L. Moreover, only 3 Enterobacteriaceae isolates (0.1%)

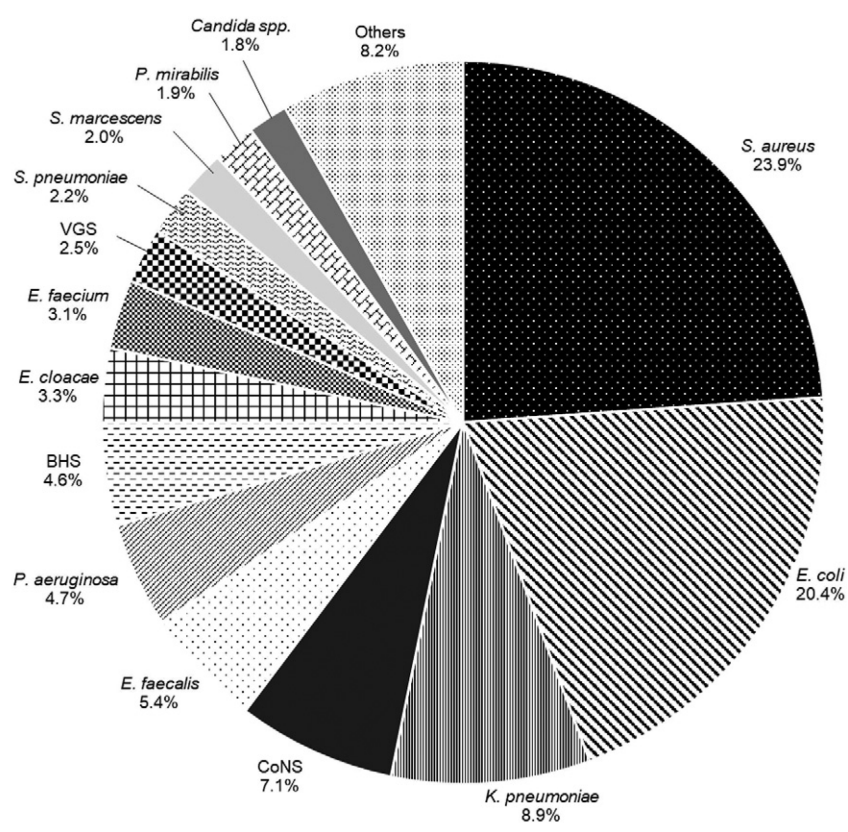

Fig. 1. Frequency of organisms isolated from patients with bloodstream infections from US medical centers (INFORM program, 2015–2017). Abbreviations: CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.

Table 1
Antimicrobial activity of ceftazidime–avibactam, ceftolozane–tazobactam, and comparator agents tested against Enterobacteriaceae and *P. aeruginosa* isolated from patients with bloodstream infections (INFORM program; 2015–2017).

Organism/antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]		EUCAST	
	(mg/L)	(mg/L)	%S	%R	%S	%R
Enterobacteriaceae (3746)						
Ceftazidime–avibactam	0.12	0.25	99.9	0.1	99.9	0.1
Ceftolozane–tazobactam[b]	0.25	0.5	96.9	2.5	95.7	4.3
Ceftriaxone	≤0.06	≫8	83.8	15.6	83.8	15.6
Ceftazidime	0.25	16	87.1	11.6	84.5	12.9
Cefepime	≤0.12	8	88.8	9.3	87.4	10.4
Piperacillin–tazobactam	2	8	93.4	3.3	90.3	6.6
Meropenem	0.03	0.06	99.1	0.7	99.3	0.4
Doripenem	≤0.06	0.12	99.1	0.7	99.1	0.7
Levofloxacin	0.06	≫4	78.9	19.5	76.0	22.0
Gentamicin	0.5	8	89.6	9.8	89.2	10.4
Amikacin	2	4	99.7	0.1	98.8	0.3
Tigecycline	0.25	1	97.3 [c]	0.3 [c]	93.8	2.7
Colistin	0.12	≫8			86.2	13.8
ESBL-producing Enterobacteriaceae (391)[d]						
Ceftazidime–avibactam	0.12	0.5	100.0	0.0	100.0	0.0
Ceftolozane–tazobactam[b]	0.5	4	88.8	9.1	83.2	16.8
Piperacillin–tazobactam	4	64	81.6	8.7	69.3	18.4
Meropenem	0.03	0.06	99.0	0.8	99.2	0.0
Doripenem	≤0.06	0.12	99.0	0.8	99.0	0.8
Levofloxacin	≫4	≫4	22.8	73.1	14.6	79.3
Gentamicin	2	≫8	51.9	45.8	50.9	48.1
Amikacin	4	8	98.7	0.3	93.9	1.3
Tigecycline	0.25	1	98.0 [c]	0.0 [c]	93.4	2.0
Colistin	0.12	0.25			96.9	3.1
Carbapenem-resistant Enterobacteriaceae (28)[e]						
Ceftazidime–avibactam	1	≫32	89.3	10.7	89.3	10.7
Ceftolozane–tazobactam[b]	≫16		0.0	83.3	0.0	100.0
Piperacillin–tazobactam	≫64	≫64	0.0	89.3	0.0	100.0
Meropenem	8	≫32	0.0	92.9	7.1	50.0
Doripenem	8	≫8	0.0	92.9	0.0	92.9
Levofloxacin	≫4	≫4	14.3	82.1	3.6	89.3
Gentamicin	2	≫8	53.6	39.3	50.0	46.4
Amikacin	8	≫32	78.6	10.7	67.9	21.4
Tigecycline	0.5	2	96.4 [c]	0.0 [c]	75.0	3.6
Colistin	0.12	≫8			85.2	14.8
Pseudomonas aeruginosa (433)						
Ceftazidime–avibactam	2	4	98.2	1.8	98.2	1.8
Ceftolozane–tazobactam[b]	0.5	1	98.7	0.7	98.7	1.3
Ceftazidime	2	16	87.8	9.5	87.8	12.2
Cefepime	2	16	87.8	4.2	87.8	12.2
Piperacillin–tazobactam	4	64	85.5	7.2	85.5	14.5
Meropenem	0.5	8	80.1	12.9	80.1	8.1
Doripenem	0.5	8	84.0	10.2	76.5	16.0
Levofloxacin	0.5	≫4	78.5	16.6	70.2	29.8
Gentamicin	2	8	88.7	5.8	88.7	11.3
Amikacin	4	8	97.9	1.4	93.3	2.1
Tobramycin	0.5	2	95.6	4.1	95.6	4.4
Colistin	1	1	100.0	0.0	100.0	0.0

[a] Criteria as published by CLSI (CLSI, 2018b).
[b] Tested only in 2017 against 1311 Enterobacteriaceae, including 131 ESBL-producing and 6 carbapenemase-resistant isolates and 149 *P. aeruginosa* isolates.
[c] FDA breakpoints (US FDA, 2019).
[d] Organisms include *Enterobacter aerogenes* (1), *E. cloacae* species complex (15), *Escherichia coli* (277), *Klebsiella oxytoca* (4), *K. pneumoniae* (90), and *Proteus mirabilis* (4).
[e] Organisms include *Enterobacter cloacae* species complex (3), *Escherichia coli* (5), *Klebsiella oxytoca* (2), *K. pneumoniae* (16), and *Serratia marcescens* (2). See Table 2 for a list of carbapenemases produced by these isolates.

Table 2
Carbapenemases produced by carbapenem-resistant Enterobacteriaceae isolates.

Organism/carbapenemase	No. of isolates
K. pneumoniae	**16**
KPC-2	6
KPC-3	5
KPC-17	1
KPC-17 plus NDM-1	1
Negative[a]	3
E. coli	**5**
KPC-2	2
NDM-1	1
NDM-9	1
Negative[a]	1
E. cloacae	**3**
KPC-3	3
K. oxytoca	**2**
KPC-2	2
S. marcescens	**2**
KPC-2	1
KPC-3	1
Total	**28**

[a] No carbapenemase gene found.

were ceftazidime–avibactam resistant, 2 *E. coli* and 1 *K. pneumoniae*: all 3 were NDM-like producers (2 NDM-1 and 1 NDM-9) from a single hospital in Texas (Table 2 and Supplemental Table S1).

Antimicrobial susceptibility of the 5 most common Enterobacteriaceae species is displayed in Supplemental Table S2. Ceftazidime–avibactam demonstrated potent activity against ESBL producers ($n = 391$; $MIC_{50/90}$, 0.12/0.5 mg/L; 100.0% susceptible). Meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 99.0%/99.2% susceptible per CLSI/EUCAST), doripenem ($MIC_{50/90}$, ≤0.06/0.12 mg/L; 99.0% susceptible), amikacin ($MIC_{50/90}$, 4/8 mg/L; 98.7%/93.9% susceptible per CLSI/EUCAST), and tigecycline ($MIC_{50/90}$, 0.25/1 mg/L; 98.0%/93.4% susceptible per US FDA/EUAST) were also very active against ESBL-producing isolates (Table 1). Ceftolozane–tazobactam (tested in 2017 only) was active against 96.9%/95.7% of Enterobacteriaceae overall and 88.8%/83.2% of ESBL-producing (excluding carbapenemase) isolates per CLSI/EUCAST criteria (Table 1).

CRE represented only 0.7% of Enterobacteriaceae isolates ($n = 28$) and were observed in 12 of 33 (36.4%) medical centers surveyed. Among 28 CRE, 21 produced a KPC, 1 an NDM-1, 1 an NDM-9, and 1 a KPC-17 and an NDM-1 (Table 2). The most active agents against CRE isolates were ceftazidime–avibactam ($MIC_{50/90}$, 1/≫32 mg/L; 89.3% susceptible) and tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 96.4%/75.0% susceptible per CLSI/EUCAST; Table 1).

Against *P. aeruginosa*, colistin (100.0% susceptible), ceftolozane–tazobactam (98.7% susceptible), ceftazidime–avibactam (98.2% susceptible), amikacin (97.9%/93.3% susceptible per CLSI/EUCAST), and tobramycin (95.6% susceptible) were the most active agents (Table 1). Furthermore, ceftazidime–avibactam and ceftolozane–tazobactam retained good activity against *P. aeruginosa* isolates nonsusceptible to meropenem (93.0% and 95.0% susceptible, respectively), piperacillin-tazobactam (88.9% and 91.3% susceptible), and/or ceftazidime (86.8% and 88.2% susceptible; data not shown).

All *S. aureus* isolates were susceptible to dalbavancin (MIC_{50} and MIC_{90}, 0.03 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L), teicoplanin ($MIC_{50/90}$, ≤0.5/≤0.5 mg/L), telavancin ($MIC_{50/90}$, 0.03/0.06 mg/L), tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L). Moreover, susceptibility rates for daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L), and oxacillin ($MIC_{50/90}$, 0.5/≫2 mg/L) were ≫99.9%, 97.6%, and 57.8%, respectively (Table S3). Although the overall oxacillin resistance rate was relatively high among *S. aureus* (42.2%), it decreased significantly during the study period from 45.4% in 2015 to 39.5% in 2017 ($P \ll 0.05$). Among CoNS, all isolates were susceptible to daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and vancomycin ($MIC_{50/90}$, 1/2 mg/L), 33.1% were susceptible to oxacillin, and the highest MIC values for dalbavancin and ceftaroline were 0.25 mg/L and 4 mg/L, respectively (Table S3).

All *E. faecalis* isolates were susceptible to ampicillin (MIC_{50} and MIC_{90}, 1 mg/L), daptomycin ($MIC_{50/90}$, 0.5/1 mg/L [CLSI only]), and linezolid ($MIC_{50/90}$, 1/2 mg/L), and susceptibility rates per CLSI were 96.4% for dalbavancin, 99.8% for tigecycline, and 96.0% for vancomycin, whereas only daptomycin ($MIC_{50/90}$, 1/2 mg/L; 98.6% susceptible) and linezolid ($MIC_{50/90}$, 1/2 mg/L; 99.0% susceptible) exhibited good activity against *E. faecium* (Table S3). All BHS were susceptible to ceftaroline ($MIC_{50/90}$, ≤0.008/0.015 mg/L), ceftriaxone ($MIC_{50/90}$, ≤0.03/0.06 mg/L), dalbavancin ($MIC_{50/90}$, 0.015/0.03 mg/L), daptomycin ($MIC_{50/90}$, 0.12/0.25 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), penicillin ($MIC_{50/90}$, ≤0.03/0.06 mg/L), tigecycline (MIC_{50} and MIC_{90}, 0.06 mg/L), and vancomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; Table S3).

4. Discussion

Nearly 2 million episodes and 250,000 deaths from BSI are estimated to occur annually in the United States and Europe combined (Goto and Al-Hasan, 2013). Early adequate treatment of BSI is critical and should be based on knowledge, guidelines, rapid microbiological identification, and administering proper antimicrobial treatment (Lopez-Cortes et al., 2017; Retamar, et al., 2012; Timbrook et al., 2017). Clinicians selecting appropriate antimicrobials should consider local microbial epidemiology, patient risk factors for multidrug-resistant organisms, and patient-specific characteristics that may influence treatment options. Although microbial epidemiology and resistance rates may vary substantially from hospital to hospital, results from a large, well-monitored surveillance program, such as those presented here, can provide useful information by detecting signs of emerging pathogen populations/resistance patterns, as well as trends of antimicrobial resistance mechanisms.

The etiology of BSI is poorly studied and publications on the frequency of occurrence and antimicrobial susceptibility of organisms isolated from patients with BSIs are very scarce. We evaluated ≫9000 isolates consecutively collected from 33 medical centers over 3 years, and we observed that approximately two-thirds of the cases (65.7%) were caused by *S. aureus* (24.3%) or Enterobacteriaceae species (41.4%). Several antimicrobial agents exhibited complete or almost complete activity (≥99.9% susceptibility) against *S. aureus*, including dalbavancin, daptomycin, linezolid, teicoplanin, and telavancin. Furthermore, tigecycline, vancomycin, and ceftaroline were active against 97.6% of isolates, and MRSA rates decreased significantly during the study period.

Enterobacteriaceae isolates represented an important proportion of BSI isolates and exhibited ≫99% susceptibility to ceftazidime–avibactam (99.9%), doripenem (99.1%), meropenem (99.1%), and amikacin (99.7%). Furthermore, slight increases in susceptibility rates were observed for a few antimicrobial agents, including the carbapenems doripenem and meropenem (from 98.4–98.5% in 2015 to 99.5% in 2017), ceftriaxone (from 77.2% in 2015 to 84.1% in 2017), and levofloxacin (from 77.2% in 2015 to 79.8% in 2017). *P. aeruginosa* also showed improved susceptibility to some agents during the study period (from 2015 to 2017), including ceftazidime–avibactam (from 95.7% to 99.3%), ceftazidime (from 84.9% to 88.0%), and meropenem (from 75.5% to 86.0%), but susceptibility to piperacillin-tazobactam decreased slightly from 84.9% to 84.0%.

Ceftazidime–avibactam demonstrated potent activity against a large US collection of contemporary Enterobacteriaceae and *P. aeruginosa* isolates from patients with BSIs, including organisms resistant to most currently available agents, such as CRE and meropenem-nonsusceptible *P. aeruginosa.* Ceftolozane–tazobactam exhibited similar activity against *P. aeruginosa* but more limited activity against Enterobacteriaceae, especially MDR, ESBL-producing, and CRE isolates, when compared to ceftazidime–avibactam. Ceftazidime–avibactam is approved by the United States Food and Drug Administration (US FDA) and by the European Medicines Agency to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia; complicated intra-abdominal infections in combination with metronidazole; and complicated urinary tract infections, including pyelonephritis (AVYCAZ®, 2018). Ceftazidime–avibactam is not licensed for treating BSIs but is potentially important in treating infections due to highly resistant Enterobacteriaceae and *P. aeruginosa.*

The main limitation of this investigation is that the criterion used to categorize a bacterial isolate as “clinically significant” was not defined in the study protocol and was based on local algorithms, which may vary among participating medical centers. Another limitation of the study was not differentiating primary from secondary BSI (CDC, 2019). However, these limitations are very unlikely to have introduced significant bias to the study. In summary, this investigation provided a valuable assessment of the frequency and antimicrobial susceptibility of organisms causing BSIs in US medical centers and emphasized the importance of comprehensive antimicrobial resistance surveillance programs.

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Conflict of interest

There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2019.06.002.

References

AVYCAZ® (ceftazidime–avibactam). 2018 Available at https://www.allergan.com/assets/pdf/avycaz_pi February 2018

Carvalhaes CG, Castanheira M, Sader HS, Flamm RK, Shortridge D. Antimicrobial activity of ceftolozane–tazobactam tested against gram-negative contemporary (2015–2017) isolates from hospitalized patients with pneumonia in US medical centers. Diagn Microbiol 2019;94:93–102. *[Infect Dis]*.

Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem–vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 2017;61, e00567.

Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. *In vitro* activity of plazomicin against Gram-negative and Gram-positive isolates collected from U.S. hospitals and comparative activities of aminoglycosides against carbapenem-resistant *Enterobacteriaceae* and isolates carrying carbapenemase genes. Antimicrob Agents Chemother 2018;62, e00313.

Centers for Disease Control & Prevention (CDC). 2019. Bloodstream infection event (central line-associated bloodstream infection and non-central line associated bloodstream infection). Available at https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf. Accessed December 18, 2018.

Clinical and Laboratory Standards Institute (CLSI). M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. eleventh ed. PA: Clinical and Laboratory Standards Institute, Wayne; 2018a.

Clinical and Laboratory Standards Institute (CLSI). M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement. Clinical and: Laboratory Standards Institute, Wayne, PA; 2018b.

EUCAST. Breakpoint tables for interpretation of MIC's and zone diameters. Version 80 2018(January 2018). Available at http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf.

Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect 2013;19:501–9.

Lake JG, Weiner LM, Milstone AM, Saiman L, Magill SS, See I. Pathogen distribution and antimicrobial resistance among pediatric healthcare-associated infections reported to the National Healthcare Safety Network, 2011-2014. Infect Control Hosp Epidemiol 2018;39:1–11.

Lopez-Cortes LE, Cueto M, Rodriguez-Bano J. How should we best treat patients with bloodstream infections? Future Microbiol 2017;12:927–30.

Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother 2012;56:472–8.

Sader HS, Castanheira M, Mendes RE, Flamm RK. 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 2018a;73:3053–9.

Sader HS, Flamm RK, Carvalhaes CG, Castanheira M. Antimicrobial susceptibility of *Pseudomonas aeruginosa* to ceftazidime–avibactam, ceftolozane–tazobactam, piperacillin–tazobactam, and meropenem stratified by U.S. census divisions: results from the 2017 INFORM program. Antimicrob Agents Chemother 2018b;62, e01587-18.

Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis 2017;64:15–23.

Timsit JF, Soubirou JF, Voiriot G, Chemam S, Neuville M, Mourvillier B, et al. Treatment of bloodstream infections in ICUs. BMC Infect Dis 2014;14:489.

US FDA. 2019. Antibacterial susceptibility test interpretive criteria. Available at https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed 05 May 2019.

Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 2016;37:1288–301.