AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

In Vitro Activity of Tebipenem against Various Resistant Subsets of *Escherichia coli* Causing Urinary Tract Infections in the United States (2018 to 2020)

Rodrigo E. Mendes,[a] Cory Hubler,[a] J. H. Kimbrough,[a] Valerie Kantro,[a] Ian Critchley,[b] Nicole Cotroneo,[b] Mariana Castanheira[a]

[a]JMI Laboratories, North Liberty, Iowa, USA
[b]Spero Therapeutics, Cambridge, Massachusetts, USA

ABSTRACT This study investigated the activity of an oral carbapenem, tebipenem, against various molecularly characterized subsets of *Escherichia coli*. A total of 15.0% of *E. coli* isolates (360/2,035 isolates) met the MIC criteria for screening for β-lactamases. Most of those isolates (74.7% [269/360 isolates]) carried $bla_{CTX\text{-}M}$. The CTX-M distribution varied (50% to 86%) among Census Regions, as did that of plasmid AmpC genes (up to 41% among *E. coli* isolates from the New England Region). Tebipenem and intravenous carbapenems showed uniform activity against various *E. coli* subsets.

KEYWORDS carbapenems, oral, ESBL, CTX-M, ST131, resistance, surveillance

Urinary tract infections (UTIs) remain the most common bacterial infections encountered in ambulatory care settings in the United States (1). Some cases may present with life-threatening symptoms, requiring hospitalization and the use of broad-spectrum antimicrobial agents (2). There were >600,000 hospital admissions due to complicated UTI (cUTI) in 2018, which represented approximately 2% of all annual admissions in the United States that year (3). Also, UTIs acquired in the hospital are among the most common health care-associated infections (HAIs), and approximately 75% are associated with a urinary catheter (i.e., catheter-associated UTIs [CAUTIs]) (4, 5). *Escherichia coli* is the most common pathogen implicated in community- and hospital-acquired UTIs in the United States and is the predominant pathogen recovered from all hospital-acquired infections (1, 4). In most recent years, between 13% and 25% of *E. coli* strains responsible for CAUTIs were not susceptible to extended-spectrum cephalosporins (4).

The epidemiology of *E. coli* causing community-acquired infections and HAIs is constantly evolving, affecting antimicrobial resistance patterns (4). In the past 2 decades, a shift in the epidemiology of *E. coli* occurred due to the emergence and expansion of isolates belonging to sequence type 131 (ST131) (6–8). These changes may require additional antibiotics and alternative strategies for optimizing treatment and minimizing poor outcomes. Tebipenem is an oral carbapenem in clinical development for treatment of cUTIs and pyelonephritis that has demonstrated noninferiority to intravenous ertapenem in a phase 3 clinical trial (ADAPT-PO Trial [ClinicalTrials.gov registration number NCT03788967]) (9). The present study investigated the activity of tebipenem against various genetic subsets of *E. coli* causing UTIs in patients hospitalized in the United States in 2018 to 2020.

A total of 2,395 *E. coli* isolates recovered from patients with UTIs in 58 centers in nine U.S. Census Regions in 2018 to 2020 were included in the STEWARD Surveillance Program. Participating sites followed specific instructions for selecting consecutive and unique isolates (1 per patient infection episode) deemed clinically relevant based on local criteria. Bacterial identifications were confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), and susceptibility testing was performed by using broth microdilution

Address correspondence to Rodrigo E. Mendes, rodrigo-mendes@jmilabs.com.

The authors declare a conflict of interest. This surveillance study and manuscript were conducted at JMI Laboratories and supported by Spero Therapeutics, Inc., and funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201800015C. Transparency Statement JMI Laboratories contracted to perform services in 2021 for AbbVie Inc., Affinity Biosensors, AimMax Therapeutics, Inc., Alterity Therapeutics, Amicrobe, Inc., Arietis Pharma, Armata Pharmaceuticals, Inc., Astrellas Pharma Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company (BD), bioMérieux, Inc., Boost Biomes, Brass Dome Ventures Ltd., Bravos Biosciences, Bugworks Research Inc., Centers for Disease Control and Prevention, Cerba Research, Cidara Therapeutics, Cipla Ltd., ContraFect Corp., CXC7, DiamondV, Enveda Biosciences, Fedora Pharmaceuticals, Inc., Fimbrion Therapeutics, First Light Diagnostics, Forge Therapeutics, Inc., Fox Chase Cancer Center, GlaxoSmithKline plc (GSK), Harvard University, Institute for Clinical Pharmacodynamics (ICPD), International Health Management Associates (IHMA), Inc., Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, Inc., Laboratory Specialists, Inc., (LSI), Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Menarini Group, Merck & Co., Inc., MicuRx Pharmaceuticals Inc., Mutabilis, Nabriva Therapeutics, National Institutes of Health, Novome Biotechnologies, Omnix Medical Ltd., Paratek Pharma, Pattern Bioscience, Pfizer Inc., Prokaryotics Inc., Pulmocide Ltd., QPEX Biopharma, Inc., Roche Holding AG, Roivant Sciences, SeLux Diagnostics, Inc., Shionogi Inc., Sinovent Pharmaceuticals, Inc., SNIPR Biome ApS, Spero Therapeutics, Summit Therapeutics, Inc., T2 Biosystems, TenNor Therapeutics, Thermo Fisher Scientific, University of Southern California, University of Wisconsin, USCAST, U.S. Food and Drug Administration, Venatorx Pharmaceutics, Inc., Weill Cornell Medicine, and Wockhardt Ltd. There are no speakers' bureaus or stock options to declare.

Received 12 September 2022
Accepted 14 September 2022
Published 28 September 2022

(10). Frozen-form panels were quality checked before and during use, according to CLSI guidelines (10, 11). MIC interpretations for comparator agents followed CLSI breakpoint criteria (11). Isolates with ceftazidime, ceftriaxone, and/or aztreonam MICs of $\geq$2 μg/mL were presumptively defined here as extended-spectrum β-lactamase (ESBL) producers and were sequenced for *in silico* screening of genes encoding known ESBLs, plasmid AmpC, oxacillinases, and carbapenemases (12).

A total of 15.0% of the *E. coli* isolates (360/2,035 isolates) were presumptively defined here as ESBL producers. In general, these isolates accounted for 10% to 20% of isolates from each U.S. Census Region, with fewer in the West North Central Region (7.1%) and the New England Region (8.8%) and more in the Middle Atlantic Region (47.5%) (see Table S1 in the supplemental material). Overall, most ESBL producers (74.7% [269/360 isolates]) carried $bla_{\text{CTX-M}}$, but the proportions of such isolates varied from 50% to 85.8% among regions (Table 1). The $bla_{\text{CTX-M}}$ alleles from group 1 represented the majority of β-lactamase genes with an extended-spectrum profile (59.5% [160/269 isolates]), whereas the remaining $bla_{\text{CTX-M}}$ alleles belonged to group 9 (40.9% [110/269 isolates]). One isolate (ST1722) from the South Atlantic Region carried genes associated with both group 1 and group 9 ($bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-27}}$) (data not shown). In addition, 6 U.S. Census Regions showed a greater prevalence of CTX-M alleles belonging to group 1, but the New England Region, East North Central Region, and South Atlantic Region had equal or greater proportions of group 9 genes compared to group 1 genes.

The bla_{CMY} gene (33/360 isolates [9.2%]) was the most common cephalosporinase gene, followed by bla_{DHA} (7/360 isolates [1.9%]). These cephalosporinases represented approximately 11% of the genes detected (Table 1). The proportion of plasmid AmpC genes was $<$10% in most regions, but prevalence rates of 11% to 16% were noted in the South Atlantic Region, East North Central Region, and Pacific Region, with an even higher prevalence rate (41%) in the New England Region (see Table S1). Many isolates carried multiple ESBL genes, including $bla_{\text{CTX-M}}$ and bla_{CMY} (5 isolates), $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-12}}$ (1 isolate), $bla_{\text{CTX-M-27}}$ and $bla_{\text{DHA-1}}$ (1 isolate), and $bla_{\text{CMY-2}}$ and $bla_{\text{DHA-1}}$ (1 isolate) (data not shown). One isolate each from the Middle Atlantic (New York) Region and the East South Central (Kentucky) Region carried only $bla_{\text{KPC-2}}$ or $bla_{\text{SHV-12}}$. In addition, 56 (15.6%) of the presumptive ESBL producers did not have ESBL, plasmid AmpC, or carbapenemase genes.

Tebipenem had MIC_{50} and MIC_{90} values of 0.015 μg/mL and 0.015 μg/mL, respectively, against isolates that did not meet the MIC criteria for screening of β-lactamase genes (i.e., presumptive non-ESBL-producing isolates). Other carbapenem, β-lactam, and non-β-lactam agents were active against this subset, except for amoxicillin-clavulanate (86.6% susceptible), oral cefuroxime (74.2% susceptible), levofloxacin (84.2% susceptible), and trimethoprim-sulfamethoxazole (75.1% susceptible) (Table 2). Consistent modal MIC and MIC_{50} values of 0.015 μg/mL were obtained for tebipenem against all resistant subsets described in Table 1 with $>$10 isolates, whereas ertapenem showed MIC_{50} values of $\leq$0.008 to 0.06 μg/mL (Table 1). Susceptibility results ($\leq$50.5% susceptible) for oral agents were limited against the presumptive ESBL producers, whereas carbapenem agents (93.8 to 100% susceptible) and piperacillin-tazobactam (93.8 to 93.9% susceptible) were active against these subsets (Table 2).

Tebipenem, ertapenem, meropenem, and imipenem were very potent against the *E. coli* surveillance isolates included here and their respective resistant subsets. Piperacillin-tazobactam also demonstrated *in vitro* coverage (94% susceptible) against ESBL-producing *E. coli* strains; however, a previous open-label, randomized, controlled clinical study provided evidence that this combination should be avoided for targeted therapy of concomitant bacteremia due to ESBL-producing *E. coli* (13), whereas recent studies showed that this combination was effective for UTIs (14–16). The dissemination of ESBL-producing *E. coli* strains may pose additional challenges when treating UTIs. As shown here, these isolates are resistant to fluoroquinolone (6, 17) and often coresistant to trimethoprim-sulfamethoxazole, which are among the recommended therapeutic agents (17). In summary, this study shows the increased prevalence of ESBL-producing *E. coli* strains causing UTIs in U.S. hospitals and also a possible switch to $bla_{\text{CTX-M-14}}$ from $bla_{\text{CTX-M-15}}$, the clinical significance of which remains to be elucidated. The variability of genes encoding CTX-M-15, CTX-M-14/27, and plasmid AmpC among U.S. Census Regions offers the possibility of a less predictable susceptibility

TABLE 1 *In vitro* activity of tebipenem and ertapenem against *E. coli* clinical isolates causing UTIs in U.S. hospitals

Group (no. of isolates) and agent[a]	No. (cumulative %) of isolates inhibited with MIC (μg/mL) of:											MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4		
Non-ESBL-producing (2,035)													
Tebipenem	5 (0.2)	588 (29.1)	1,351 (95.5)	72 (99.1)	14 (99.8)	4 (>99.9)	1 (100.0)					0.015	0.015
Ertapenem		1,654 (86.7)	220 (98.2)	19 (99.2)	12 (99.8)	2 (99.9)	1 (100.0)					≤0.008	0.015
ESBL-producing (360)													
Tebipenem		24 (6.7)	247 (75.3)	63 (92.8)	15 (96.9)	6 (98.6)	3 (99.4)	1 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)[b]	0.015	0.03
Ertapenem		34 (9.7)	107 (40.2)	101 (68.9)	58 (85.5)	26 (92.9)	10 (95.7)	6 (97.4)	7 (99.4)	2 (100.0)		0.03	0.12
bla_{CTX-M} (269)													
Tebipenem		20 (7.4)	195 (79.9)	40 (94.8)	9 (98.1)	4 (99.6)	1 (100.0)					0.015	0.03
Ertapenem		23 (8.8)	86 (41.6)	75 (70.2)	45 (87.4)	17 (93.9)	8 (96.9)	5 (98.9)	3 (100.0)			0.03	0.12
bla_{CTX-M} group 1[c] (159)													
Tebipenem		6 (3.8)	116 (76.7)	28 (94.3)	5 (97.5)	3 (99.4)	1 (100.0)					0.015	0.03
Ertapenem		6 (4.0)	27 (21.9)	53 (57.0)	38 (82.1)	14 (91.4)	7 (96.0)	4 (98.7)	2 (100.0)			0.03	0.12
bla_{CTX-M} group 9[d] (109)													
Tebipenem		14 (12.8)	78 (84.4)	12 (95.4)	4 (99.1)	1 (100.0)						0.015	0.03
Ertapenem		17 (15.6)	58 (68.8)	21 (88.1)	7 (94.5)	3 (97.2)	1 (98.2)	1 (99.1)	1 (100.0)			0.015	0.06
bla_{CMY}[e] (33)													
Tebipenem		1 (3.0)	16 (51.5)	13 (90.9)	1 (93.9)	1 (97.0)	0 (97.0)	1 (100.0)				0.015	0.03
Ertapenem		2 (6.2)	4 (18.8)	8 (43.8)	10 (75.0)	5 (90.6)	0 (90.6)	0 (90.6)	2 (96.9)	1 (100.0)		0.06	0.12
bla_{DHA} (7)													
Tebipenem			2 (28.6)	2 (57.1)	2 (85.7)	1 (100.0)						0.03	
Ertapenem				3 (42.9)	2 (71.4)	1 (85.7)	0 (85.7)	0 (85.7)	1 (100.0)			0.06	
Other[f] (56)													
Tebipenem		3 (5.4)	36 (69.6)	10 (87.5)	4 (94.6)	1 (96.4)	2 (100.0)					0.015	0.06
Ertapenem		8 (14.5)	19 (49.1)	15 (76.4)	2 (80.0)	5 (89.1)	2 (92.7)	1 (94.5)	3 (100.0)			0.03	0.25

[a]Non-ESBL-producing isolates are defined as isolates exhibiting MICs of <2 μg/mL for ceftazidime, aztreonam, and ceftriaxone; ESBL-producing isolates are defined as isolates that display MICs of ≥2 μg/mL for ceftazidime, aztreonam, and/or ceftriaxone and presumptively produce ESBL, AmpC, extended-spectrum oxacillinases, and/or carbapenemases. ESBL-producing isolates may contain multiple β-lactamase genes; therefore, isolates may be present in >1 subset.

[b]A single isolate carried bla_{KPC-2}; tebipenem and ertapenem MICs of 4 μg/mL and 2 μg/mL, respectively, were obtained for that isolate.

[c]Represented by $bla_{CTX-M-15}$, except for 9 isolates carrying $bla_{CTX-M-55}$ and 1 isolate with $bla_{CTX-M-32}$.

[d]Represented by $bla_{CTX-M-14}$ (21 isolates), $bla_{CTX-M-27}$ (87 isolates), and $bla_{CTX-M-65}$ (1 isolate).

[e]Includes CMY-2-, CMY-4-, CMY-42-, and CMY-102-encoding genes. Five isolates also carried bla_{CTX-M}, whereas 1 isolate had both bla_{CMY} and bla_{DHA}.

[f]Includes isolates that met the MIC criteria for screening for β-lactamases for which ESBL, plasmid AmpC, or carbapenemase genes were not detected.

TABLE 2 Antimicrobial activity of tebipenem and comparator agents against *E. coli* and resistant subsets

Group (no. of isolates) and agent[a]	MIC (μg/mL)			CLSI susceptibility result (%)[b]		
	MIC_{50}	MIC_{90}	Range	Susceptible	Intermediate	Resistant
Non-ESBL-producing (2,035)						
Tebipenem	0.015	0.015	≤0.004 to 0.25	NA	NA	NA
Ertapenem	≤0.008	0.015	≤0.008 to 0.25	100.0	0.0	0.0
Meropenem	≤0.015	0.03	≤0.015 to 0.12	100.0	0.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12 to 1	100.0	0.0	0.0
Amoxicillin-clavulanic acid	4	16	≤0.25 to >32	86.6	10.9	2.5
Aztreonam	0.12	0.25	≤0.03 to 1	100.0	0.0	0.0
Cefazolin	2	8	≤0.5 to >32	96.4[c]/96.4[d]	—	3.6/3.6
Ceftazidime	0.12	0.25	0.03 to 1	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 1	100.0	0.0	0.0
Cefuroxime	4	8	≤0.5 to 32	74.2[c]/95.3[d]	25.2/4.1	0.5/0.5
Levofloxacin	0.03	8	≤0.015 to >32	84.2	1.2	14.6
Nitrofurantoin	16	32	≤4 to >64	97.9	0.9	1.2
Piperacillin-tazobactam	2	4	≤0.06 to >128	98.9	0.3	0.8
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	75.1	—	24.9
ESBL-producing (360)						
Tebipenem	0.015	0.03	0.008 to 4	NA	NA	NA
Ertapenem	0.03	0.12	≤0.008 to 2	97.4	2.0	0.6
Meropenem	0.03	0.03	≤0.015 to 2	99.7	0.3	0.0
Imipenem	≤0.12	0.25	≤0.12 to 4	99.4	0.3	0.3
Amoxicillin-clavulanic acid	16	32	2 to >32	47.2	30.6	22.2
Aztreonam	16	>16	0.12 to >16	18.9	17.2	63.9
Cefazolin	>32	>32	8 to >32	0.6[c]/0.6[d]	—	99.4/99.4
Ceftazidime	16	>32	0.25 to >32	28.6	16.9	54.4
Ceftriaxone	>8	>8	0.12 to >8	6.4	1.4	92.2
Cefuroxime	>64	>64	8 to >64	0.0[c]/1.7[d]	4.5/2.8	95.5/95.5
Levofloxacin	8	32	≤0.015 to >32	26.1	2.5	71.4
Nitrofurantoin	16	32	≤4 to >64	90.6	3.7	5.7
Piperacillin-tazobactam	4	16	≤0.06 to >128	93.9	4.2	1.9
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	35.8	—	64.2

[a]Non-ESBL-producing isolates are defined as isolates exhibiting MICs of <2 μg/mL for ceftazidime, aztreonam, and ceftriaxone; ESBL-producing isolates are defined as isolates that display MICs of ≥2 μg/mL for ceftazidime, aztreonam, and/or ceftriaxone.
[b]Criteria as published by CLSI (11). NA, not applicable; —, not available.
[c]Using oral breakpoints.
[d]Using parenteral breakpoints.

pattern. Upon approval, an oral carbapenem, such as tebipenem, could be a useful addition to the armamentarium for treating cUTI.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

ACKNOWLEDGMENTS

We thank all participants in the SENTRY Antimicrobial Surveillance Program.

This surveillance study and manuscript preparation were conducted at JMI Laboratories, supported by Spero Therapeutics, Inc., and funded in whole or in part with federal funds from the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract HHSO100201800015C.

JMI Laboratories contracted to perform services in 2021 for AbbVie, Inc., Affinity Biosensors, AimMax Therapeutics, Inc., Alterity Therapeutics, Amicrobe, Inc., Arietis Pharma, Armata Pharmaceuticals, Inc., Astrellas Pharma, Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company, bioMérieux, Inc., Boost Biomes, Brass Dome Ventures, Ltd., Bravos Biosciences, Bugworks Research, Inc., Centers for Disease Control and Prevention, Cerba Research, Cidara Therapeutics, Cipla, Ltd., ContraFect Corp., CXC7, DiamondV, Enveda Biosciences, Fedora

Pharmaceuticals, Inc., Fimbrion Therapeutics, First Light Diagnostics, Forge Therapeutics, Inc., Fox Chase Cancer Center, GlaxoSmithKline plc, Harvard University, Institute for Clinical Pharmacodynamics, International Health Management Associates, Inc., Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, Inc., Laboratory Specialists, Inc., Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Menarini Group, Merck & Co., Inc., MicuRx Pharmaceuticals, Inc., Mutabilis, Nabriva Therapeutics, National Institutes of Health, Novome Biotechnologies, Omnix Medical, Ltd., Paratek Pharma, Pattern Bioscience, Pfizer, Inc., Prokaryotics, Inc., Pulmocide, Ltd., QPEX Biopharma, Inc., Roche Holding AG, Roivant Sciences, SeLux Diagnostics, Inc., Shionogi, Inc., Sinovent Pharmaceuticals, Inc., SNIPR Biome ApS, Spero Therapeutics, Summit Therapeutics, Inc., T2 Biosystems, TenNor Therapeutics, Thermo Fisher Scientific, University of Southern California, University of Wisconsin, USCAST, U.S. Food and Drug Administration, Venatorx Pharmaceutics, Inc., Weill Cornell Medicine, and Wockhardt Ltd. There are no speakers' bureaus or stock options to declare.

REFERENCES

1. Abbo LM, Hooton TM. 2014. Antimicrobial stewardship and urinary tract infections. Antibiotics (Basel) 3:174–192. https://doi.org/10.3390/antibiotics3020174.
2. Sabih A, Leslie SW. 2022. Complicated urinary tract infections. StatPearls, Treasure Island, FL.
3. Zilberberg MD, Nathanson BH, Sulham K, Shorr AF. 2022. Descriptive epidemiology and outcomes of hospitalizations with complicated urinary tract infections in the United States, 2018. Open Forum Infect Dis 9:ofab591. https://doi.org/10.1093/ofid/ofab591.
4. Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, Pollock D, See I, Soe MM, Walters MS, Dudeck MA. 2020. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017. Infect Control Hosp Epidemiol 41:1–18. https://doi.org/10.1017/ice.2019.296.
5. Centers for Disease Control and Prevention. 2022. Urinary tract infection (catheter-associated urinary tract infection [CAUTI] and non-catheter-associated urinary tract infection [UTI]) events. National Healthcare Safety Network, Centers for Disease Control and Prevention, Atlanta, GA. https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf.
6. Banerjee R, Johnson JR. 2014. A new clone sweeps clean: the enigmatic emergence of *Escherichia coli* sequence type 131. Antimicrob Agents Chemother 58:4997–5004. https://doi.org/10.1128/AAC.02824-14.
7. Pitout JDD, Finn TJ. 2020. The evolutionary puzzle of *Escherichia coli* ST131. Infect Genet Evol 81:104265. https://doi.org/10.1016/j.meegid.2020.104265.
8. Adams-Sapper S, Diep BA, Perdreau-Remington F, Riley LW. 2013. Clonal composition and community clustering of drug-susceptible and -resistant *Escherichia coli* isolates from bloodstream infections. Antimicrob Agents Chemother 57:490–497. https://doi.org/10.1128/AAC.01025-12.
9. Eckburg P, Muir L, Critchley I, Walpole S, Kwak H, Phelan A, Moore G, Jain A, Keutzer T, Dane A, Melnick D, Talley A. 2022. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. N Engl J Med 386:1327–1338. https://doi.org/10.1056/NEJMoa2105462.
10. Clinical and Laboratory Standards Institute. 2018. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 11th ed. M07Ed11. Clinical and Laboratory Standards Institute, Wayne, PA.
11. Clinical and Laboratory Standards Institute. 2021. Performance standards for antimicrobial susceptibility testing, 31st informational supplement. M100Ed31. Clinical and Laboratory Standards Institute, Wayne, PA.
12. Mendes RE, Jones RN, Woosley LN, Cattoir V, Castanheira M. 2019. Application of next-generation sequencing for characterization of surveillance and clinical trial isolates: analysis of the distribution of β-lactamase resistance genes and lineage background in the United States. Open Forum Infect Dis 6(Suppl 1):S69–S78. https://doi.org/10.1093/ofid/ofz004.
13. Peirano G, Pitout JDD. 2019. Extended-spectrum β-lactamase-producing Enterobacteriaceae: update on molecular epidemiology and treatment options. Drugs 79:1529–1541. https://doi.org/10.1007/s40265-019-01180-3.
14. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tamma PD. 2020. Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by extended-spectrum β-lactamase-producing organisms? Clin Infect Dis 71:e331–e337. https://doi.org/10.1093/cid/ciz1205.
15. Tullos JB, Stoudenmire LL, Pouliot JD. 2020. Piperacillin-tazobactam versus carbapenems for the treatment of nonbacteremic urinary tract infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae. Hosp Pharm 55:44–49. https://doi.org/10.1177/0018578718817933.
16. Seo YB, Lee J, Kim YK, Lee SS, Lee JA, Kim HY, Uh Y, Kim HS, Song W. 2017. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. BMC Infect Dis 17:404. https://doi.org/10.1186/s12879-017-2502-x.
17. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. 2011. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 52:e103–e120. https://doi.org/10.1093/cid/ciq257.