Recent Resistance Surveillance Results from 12 Medical Centres Across China (2011)

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Abstract

Background: Antimicrobial resistance (R) surveillance across Asia and especially in China has documented unique patterns and mechanisms. This 2011 study reports results for 2,278 infection isolates from 12 hospitals in China (94-216 strains/site); most from bacteremias (20.4%), pneumonias (29.1%) or skin infections (20.9%).

Methods: Samples were tested by CLSI broth microdilution, interpreted by CLSI and EUCAST susceptible (S) breakpoints. The most common species were: *S. aureus* (SA; 343, 45.8% MRSA), *E. coli* (EC; 288), *P. aeruginosa* (PSA; 221), *Klebsiella* spp. (KSP; 208), *Acinetobacters* (ACB; 178), Enterobacters (155), *S. pneumoniae* (SPN; 154, 46.8% PEN-S) and enterococci (137). Beta-haemolytic (BHS) and viridans gr. (VGS) streptococci were also tested.

Results: Among 849 Gram-positive cocci (GPC; **Table 1**), linezolid, tigecycline (TIG), daptomycin and vancomycin provided best coverage (≥99.7% S). R patterns of concern were: 0.3% VISA, 15.4% teicoplanin non-S coagulase-negative staphylococci, 1.5% VRE (all *E. faecium*), 1.9% levofloxacin-R BHS, and 35.1 and 12.7% ceftriaxone-non-S SPN and VGS, respectively. For Gram-negative bacilli, R in Enterobacteriaceae was highest against β-lactams (ESBL [+] strains at 73.6 and 42.8% in EC and KSP, respectively; carbapenem-R was only 2.1-4.3% with KPC-2 and IMP-26 in KSP from two Shanghai sites) and widest spectrum agents were: cefoperazone/sulbactam (79.5-86.1%), piperacillin/tazobactam (88.9-92.0%), TIG (98.6-100%), amikacin (AMK; 91.8-93.7%) and meropenem (95.7-97.1%). Best S rates against PSA were AMK (90.5%) and colistin (COL; 99.5%), with cefepime (67.9%) best among β-lactams. Only COL (100% S) and TIG (MIC_{90}, 2 mg/L) significantly inhibited ACB.

Conclusions: R among pathogens from 12 Chinese hospitals illustrates several agents active against GPC, but more serious R mechanisms among Enterobacteriaceae, PSA and ACB. Combination treatments for the latter multidrug-R strains appears necessary, guided by local antibiograms and surveillance results.

Introduction

The importance of emerging antimicrobial resistance in the recent decade indicates the need for new agents and the study of resistance profiles/epidemiology worldwide. The People's Republic of China represents approximately 20% of the world's population (1.3 billion people); and therefore, a significant portion of the infectious disease burden. Patterns of resistance have been monitored in this Chinese population since the late 1990s, noting resistance rates and mechanisms that have varied across the nation and differed from other nations in the East Asian region.

We present the results from a systematic sampling of 12 medical centers in China (eight cities) that focused on emerging resistance patterns among key Gram-positive (**Table 1**) and -negative (**Table 2**) pathogens. A wide diversity of agents were tested in a central laboratory study design applying reference broth microdilution methods (CLSI) for the sampling year of 2011.

Methods

A total 2,278 organisms were collected in prevalence study design mainly from bacteremias (20.4%), respiratory tract infections in hospitalized patients (29.1%) and skin/skin structure infections (20.9%). Twelve hospitals contributed organisms ranging from 94 to 219 strains per site. The six most commonly isolated species among Gram-positive pathogens (**Table 1**) were: *S. aureus* (343); *S. pneumoniae* (154); enterococci (137); viridans group streptococci (79; 13 species); β-haemolytic streptococci (71; 49 serogroup A and B); and coagulase-negative staphylococci (65; eight species from bloodstream infections). The most common Gram-negative organisms isolated were (**Table 2**): *E. coli* (288; 73.6% ESBL-screen phenotype-positive); *P. aeruginosa* (221); *Klebsiella* spp. (208; 45.2% ESBL-screen phenotype-positive); *Acinetobacter* spp. (178); *Enterobacter* spp. (155; 34.2% ceftazidime-resistant); and *Haemophilus* spp. (91, 68 *H. influenzae*).

Susceptibility to more than 30 antimicrobial agents was determined by reference broth microdilution methods as described by the Clinical and Laboratory Standards Institute (CLSI 2013). Quality control strains (*S. aureus* ATCC 25923 and 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25922 and 35218, and *P. aeruginosa* ATCC 27853) were tested concurrently and all QC values were observed within CLSI control ranges. Screening tests for ESBLs were determined using CLSI-recommended breakpoints of ≥2 mg/L for ceftriaxone or ceftazidime or aztreonam. Carbapenem-non-susceptible concentrations were ≥2 mg/L for doripenem or imipenem or meropenem when testing Enterobacteriaceae (CRE); and ≥4 mg/L for doripenem or imipenem or meropenem when *P. aeruginosa* strains were processed. Organisms meeting these criteria were further tested by the Check-MDR CT101 kit (Wageningen, The Netherlands) microarray method to determine β-lactamase genes and selected isolates had gene sequencing performed. At least three ESBL phenotype/CRE strains were tested by molecular methods from each institution; each isolate representative of dominant resistance profile of ESBL and CRE observed for the 2011 study year.

Table 3. Patterns of β-lactamase genes present among 65 molecularly characterized Enterobacteriaceae from all 12 Chinese medical centers, each having an ESBL phenotype.

No. of enzymes	(no. occurrences)	CTX-M-Group 1[b]	CTX-M-Group 9[c]	CMY	DHA	SHV	Carbapenemases IMP	Carbapenemases KPC	Species[d] EC/KSP/PM
One	(7)	x							6 / 1 / 0
	(27)		x						19 / 4 / 4
	(1)				x				0 / 1 / 0
	(1)					x			0 / 1 / 0
	(1)						x		0 / 1 / 0
	(1)							x	0 / 1 / 0
Two	(6)	x	x						6 / 0 / 0
	(2)		x		x				0 / 2 / 0
	(2)		x			x			0 / 2 / 0
	(2)					x		x	0 / 2 / 0
	(1)	x		x					1 / 0 / 0
	(1)	x			x				0 / 1 / 0
	(1)		x					x	0 / 1 / 0
	(1)		x				x		0 / 1 / 0
	(1)			x				x	1 / 0 / 0
	(1)				x		x		0 / 1 / 0
	(1)						x	x	0 / 1 / 0
Three	(1)	x	x				x		1 / 0 / 0
	(1)	x	x					x	1 / 0 / 0
	(1)	x	x		x				0 / 1 / 0
	(1)	x		x				x	1 / 0 / 0
	(1)		x		x	x			0 / 1 / 0
	(1)		x		x		x		0 / 1 / 0
Four	(1)	x	x		x	x			0 / 1 / 0
	(1)	x	x			x		x	0 / 1 / 0

a. ESBL, serine carbapenamase and metallo-β-lactamase groups.
b. CTX-M group includes six or more plasmidic enzymes (CTX-M-1, -3, -10, -12, -15 and FEC-1). (Bonnet, 2004).
c. CTX-M group 9 includes nine or more plasmidic enzymes (CTX-M-9, -13, -14, -16, -17, -19, -21, -27 and Toho-2) (Bonnet, 2004).
d. EC=*E. coli* (36), KSP=*Klebsiella* spp. (25), and PM=*P. mirabilis* (4).

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Results

- Among 839 Gram-positive isolates (**Table 1**), the widest spectrum agents (≥99.7% susceptible) were linezolid, tigecycline, daptomycin (not tested vs. *S. pneumoniae*), and vancomycin. Resistance patterns (CLSI criteria) of greatest concern were:
  - MRSA at 45.8%
  - VISA at 0.3 (15.4% teicoplanin-non-susceptible CoNS by EUCAST criteria)
  - Vancomycin-resistant *E. faecium* (1.5%)
  - Levofloxacin-non-susceptible β-haemolytic streptococci (15.5%)
  - Penicillin-non-susceptible *S. pneumoniae* (53.2; 35.1% ceftriaxone-non-susceptible)
  - Penicillin-non-susceptible viridans group streptococci (39.2%)
- A total sample of 868 Enterobacteriaceae were tested (**Table 2**) with the following notable resistance patterns:
  - ESBL/CRE resistance phenotypes of 73.6/2.1% and 45.2/4.3% for *E. coli* and *Klebsiella* spp., respectively.
  - Widest spectrum agents identified for these two species were amikacin (91.8-93.7% susceptible), cefoperazone/sulbactam (79.5-86.1%), meropenem (95.7-97.1), piperacillin/tazobactam (88.9-92.0%) and tigecycline (98.6-100.0%).
  - Carbapenem-resistant isolates were rare (two strains) among Enterobacters, indole-positive or -negative *Proteae*, *S. marcescens* or Citrobacters.
- *P. aeruginosa* (221 strains) and *Acinetobacter* spp. (178 strains) results are found in **Table 2**.
  - Only amikacin and the polymyxins showed >90.0% susceptibility rates versus *P. aeruginosa*.
  - β-lactam coverage of *P. aeruginosa* ranged from 55.2% (piperacillin/tazobactam) to 67.9% (cefepime).
  - Acinetobacters (178) were quite resistant to tested agents (≤40.4% susceptible using CLSI breakpoints) except for polymyxins (100.0% susceptible) and tigecycline (MIC_{90}, 2 mg/L).
- Molecular characterization of ESBL and CRE phenotype strains (65 among *E. coli* and *Klebsiella* spp.) are listed in **Table 3**.
  - One to four enzymes were noted in each strain with the most prevalent β-lactamases being CTX-M-groups 1 (21 strains) and 9 (46 strains), usually in *E. coli*.
  - Single enzyme patterns were most likely in *E. coli* and multiple enzymes were noted in *K. pneumoniae.*
  - Carbapenemases IMP (IMP-26 by sequencing) and/or KPC (usually KPC-2) were detected in 14 samples, one *K. pneumoniae* strain possessing both enzymes (**Table 3**).

Conclusions

- China patterns of antimicrobial resistance among Gram-positive pathogens does not greatly differ from those reported in other countries/continents. Only VRE seems unusually uncommon compared to the United States and some developed nations in Europe and Latin America.
- Gram-negative resistance profiles in China show remarkably elevated ESBL and CRE rates in *E. coli* and *Klebsiella* spp., highest for *E. coli* (usually multiple enzymes with CTX-M-types predominating).
- Metallo-β-lactamases and KPC-type serine carbapenemase enzymes were endemic across the sampled cities.
- Continued surveillance appears warranted to direct antimicrobial stewardship and infection control interventions.

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Table 1. Activity of antimicrobial agents when tested against Gram-positive isolates from China (2011).

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus					
MSSA (186)					
Ceftriaxone	4	4	1 – >8	99.5 / 0.0	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	67.7 / 32.3	67.7 / 32.3
Daptomycin	0.25	0.5	0.12 – 0.5	100.0 / -	100.0 / 0.0
Doxycycline	0.12	1	≤0.06 – >8	97.3 / 0.5	90.9 / 3.8
Erythromycin	>16	>16	≤0.12 – >16	40.9 / 57.5	41.4 / 58.6
Gentamicin	≤1	>8	≤1 – >8	80.6 / 18.3	79.6 / 20.4
Levofloxacin	0.25	0.5	≤0.12 – >4	91.4 / 8.1	91.4 / 8.1
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Meropenem	0.12	0.12	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Penicillin	8	>8	≤0.06 – >8	8.6 / 91.4	8.6 / 91.4
Piperacillin/tazobactam	2	2	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.06	0.12	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >4	94.6 / 5.4	94.6 / 5.4
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (157)					
Clindamycin	>2	>2	≤0.25 – >2	18.5 / 81.5	18.5 / 81.5
Daptomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Doxycycline	8	8	≤0.06 – >8	28.0 / 6.4	17.8 / 82.2
Erythromycin	>16	>16	0.25 – >16	7.6 / 89.2	8.3 / 91.1
Gentamicin	>8	>8	≤1 – >8	19.1 / 80.3	18.5 / 81.5
Levofloxacin	>4	>4	≤0.12 – >4	8.3 / 91.1	8.3 / 91.1
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	92.4 / 7.6
Tigecycline[b]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >4	90.4 / 9.6	90.4 / 8.9
Vancomycin	1	2	0.5 – 4	99.4 / 0.0	99.4 / 0.6
Coagulase-negative staphylococci (65)					
Clindamycin	≤0.25	>2	≤0.25 – >2	56.9 / 40.0	56.9 / 43.1
Daptomycin	0.5	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Doxycycline	0.5	4	≤0.06 – >8	93.8 / 4.6	80.0 / 12.3
Erythromycin	>16	>16	≤0.12 – >16	23.1 / 76.9	23.1 / 76.9
Gentamicin	8	>8	≤1 – >8	44.6 / 41.5	36.9 / 63.1
Levofloxacin	4	>4	≤0.12 – >4	24.6 / 67.7	24.6 / 67.7
Linezolid	0.5	1	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	2	>8	≤0.06 – >8	4.6 / 95.4	4.6 / 95.4
Penicillin	8	>8	≤0.06 – >8	3.1 / 96.9	3.1 / 96.9
Teicoplanin	≤2	8	≤2 – 16	96.9 / 0.0	84.6 / 15.4
Tigecycline[b]	0.12	0.12	≤0.03 – 0.25	- / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	1	>4	≤0.5 – >4	61.5 / 38.5	61.5 / 30.8
Vancomycin	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Enterococcus faecalis (60)					
Ampicillin	1	4	0.5 – 8	100.0 / 0.0	90.0 / 0.0
Daptomycin	1	1	0.5 – 4	100.0 / -	- / -
Imipenem	1	4	≤0.12 – 8	90.0 / -	90.0 / 0.0
Levofloxacin	1	>4	≤0.12 – >4	65.0 / 30.0	- / -
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.06	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Vancomycin	1	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Enterococcus faecium (67)					
Daptomycin	2	2	0.5 – 4	100.0 / -	- / -
Levofloxacin	>4	>4	1 – >4	6.0 / 88.1	- / -
Linezolid	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – >16	98.5 / 1.5	98.5 / 1.5
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – >16	98.5 / 1.5	98.5 / 1.5
S. pneumoniae					
Penicillin-susceptible (72)					
Amoxicillin/clavulanate	≤1	≤1	≤1 – >8	97.2 / 1.4	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 2	98.6 / 0.0	98.6 / 0.0
Clindamycin	>2	>2	≤0.25 – >2	13.9 / 83.3	16.7 / 83.3
Erythromycin	>16	>16	≤0.12 – >16	11.1 / 88.9	11.1 / 88.9
Levofloxacin	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Penicillin[c]	≤0.06	≤0.06	≤0.06	100.0 / 0.0	- / -
Tetracycline	>8	>8	≤0.25 – >8	11.1 / 86.1	8.3 / 88.9
Tigecycline[b]	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / -	- / -
Trimethoprim/sulfamethoxazole	4	>4	≤0.5 – >4	34.7 / 56.9	40.3 / 56.9
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-intermediate (7)					
Amoxicillin/clavulanate	≤1	-	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	0.5	-	≤0.06 – 1	100.0 / 0.0	71.4 / 0.0
Clindamycin	>2	-	≤0.25 – >2	14.3 / 85.7	14.3 / 85.7
Erythromycin	>16	-	≤0.12 – >16	14.3 / 85.7	14.3 / 85.7
Levofloxacin	1	-	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	0.5	-	0.25 – 1	100.0 / -	100.0 / 0.0
Meropenem	0.12	-	≤0.06 – 0.5	85.7 / 0.0	100.0 / 0.0
Penicillin[c]	0.5	-	0.12 – 1	100.0 / 0.0	- / -
Tetracycline	>8	-	≤0.25 – >8	14.3 / 85.7	14.3 / 85.7
Tigecycline[b]	≤0.03	-	≤0.03 – 0.06	100.0 / -	- / -
Trimethoprim/sulfamethoxazole	4	-	≤0.5 – >4	42.9 / 57.1	42.9 / 57.1
Vancomycin	0.25	-	0.25 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-resistant (75)					
Amoxicillin/clavulanate	8	>8	≤1 – >8	25.3 / 64.0	- / -
Ceftriaxone	2	8	0.5 – >8	29.3 / 36.0	4.0 / 36.0
Clindamycin	>2	>2	≤0.25 – >2	1.3 / 98.7	1.3 / 98.7
Erythromycin	>16	>16	16 – >16	0.0 / 100.0	0.0 / 100.0
Levofloxacin	1	1	0.5 – >4	96.0 / 4.0	96.0 / 4.0
Linezolid	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Meropenem	1	1	0.25 – 4	2.7 / 66.7	98.7 / 1.3
Penicillin[c]	4	8	2 – 8	20.0 / 13.3	- / -
Tetracycline	>8	>8	≤0.25 – >8	1.3 / 97.3	1.3 / 98.7
Tigecycline[b]	≤0.03	≤0.03	≤0.03	100.0 / -	- / -
Trimethoprim/sulfamethoxazole	>4	>4	≤0.5 – >4	2.7 / 92.0	5.3 / 92.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (71)					
Ceftriaxone	≤0.06	0.12	≤0.06 – 1	98.6 / -	100.0 / 0.0
Clindamycin	>2	>2	≤0.25 – >2	36.6 / 59.2	40.8 / 59.2
Daptomycin	0.12	0.25	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Erythromycin	8	>16	≤0.12 – >16	23.9 / 76.1	23.9 / 76.1
Levofloxacin	0.5	>4	0.25 – >4	84.5 / 15.5	78.9 / 15.5
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	- / -
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	9.9 / 90.1	9.9 / 90.1
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	- / -	98.6 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Viridans group streptococci (79)					
Ceftriaxone	0.25	2	≤0.06 – >8	87.3 / 6.3	82.3 / 17.7
Clindamycin	>2	>2	≤0.25 – >2	25.3 / 73.4	26.6 / 73.4
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	- / -
Erythromycin	>16	>16	≤0.12 – >16	17.7 / 82.3	- / -
Levofloxacin	1	>4	≤0.12 – >4	77.2 / 21.5	- / -
Linezolid	0.5	1	≤0.12 – 1	100.0 / -	- / -
Meropenem	≤0.06	0.5	≤0.06 – 4	92.4 / -	98.7 / 1.3
Penicillin	≤0.06	2	≤0.06 – 8	60.8 / 6.3	75.9 / 6.3
Tetracycline	>8	>8	≤0.25 – >8	21.5 / 74.7	- / -
Tigecycline[b]	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2013] and EUCAST [2013], β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
c. Criteria as published by the CLSI [2013] for 'Penicillin parenteral (non-meningitis)'.

Table 2. Activity of antimicrobial agents when tested against Gram-negative isolates for China (2011).

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Escherichia coli (288)					
Amikacin	4	8	1 – >32	93.7 / 4.5	91.3 / 6.3
Ampicillin	>8	>8	2 – >8	9.7 / 90.3	9.7 / 90.3
Ampicillin/sulbactam	32	>32	2 – >32	16.0 / 61.5	16.0 / 84.0
Cefepime	16	>16	≤0.5 – >16	43.8 / 48.3	27.4 / 63.2
Cefoperazone	>32	>32	≤0.25 – >32	26.1 / 72.8	- / -
Cefoperazone/sulbactam[b]	8	32	≤0.25 – >32	79.5 / 4.9	- / -
Ceftazidime	2	>32	0.03 – >32	62.8 / 29.9	41.3 / 37.2
Ceftriaxone	>8	>8	≤0.06 – >8	26.4 / 73.6	26.4 / 73.6
Colistin	≤0.25	0.5	≤0.25 – 4	- / -	98.6 / 1.4
Doxycycline	8	>8	0.5 – >8	33.0 / 49.3	- / -
Levofloxacin	>4	>4	≤0.12 – >4	31.3 / 63.2	29.9 / 68.8
Meropenem	≤0.06	≤0.06	≤0.06 – >8	97.9 / 1.7	98.3 / 1.0
Piperacillin/tazobactam	4	16	≤0.5 – >64	92.0 / 5.2	88.5 / 8.0
Tigecycline[c]	0.12	0.25	≤0.03 – 2	100.0 / 0.0	99.7 / 0.0
Trimethoprim/sulfamethoxazole	>4	>4	≤0.5 – >4	29.9 / 70.1	29.9 / 69.4
ESBL-phenotype (212)					
Amikacin	4	16	1 – >32	91.5 / 6.1	88.2 / 8.5
Cefepime	>16	>16	≤0.5 – >16	23.6 / 65.6	1.9 / 85.8
Cefoperazone/sulbactam[b]	16	32	1 – >32	72.2 / 6.6	- / -
Ceftazidime	8	>32	0.25 – >32	49.5 / 40.6	20.3 / 50.5
Ceftriaxone	>8	>8	4 – >8	0.0 / 100.0	0.0 / 100.0
Colistin	≤0.25	0.5	≤0.25 – 4	- / -	98.1 / 1.9
Levofloxacin	>4	>4	≤0.12 – >4	19.8 / 75.9	18.4 / 80.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	97.2 / 2.4	97.6 / 1.4
Piperacillin/tazobactam	4	32	1 – >64	89.6 / 6.6	84.9 / 10.4
Tigecycline[c]	0.12	0.25	≤0.03 – 2	100.0 / 0.0	99.5 / 0.0
Non-ESBL-phenotype (76)					
Amikacin	4	4	1 – 8	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	98.7 / 0.0
Cefoperazone	1	4	≤0.25 – >32	96.0 / 1.3	- / -
Cefoperazone/sulbactam[b]	1	2	≤0.25 – 16	100.0 / 0.0	- / -
Ceftazidime	0.12	0.25	0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Colistin	≤0.25	0.5	≤0.25 – 0.5	- / -	100.0 / 0.0
Levofloxacin	0.5	>4	≤0.12 – >4	63.2 / 27.6	61.8 / 36.8
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	≤0.5 – >64	98.7 / 1.3	98.7 / 1.3
Tigecycline[c]	0.12	0.25	0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Klebsiella spp. (208)					
Amikacin	1	8	≤0.25 – >32	91.8 / 8.2	91.8 / 8.2
Ampicillin/sulbactam	16	>32	1 – >32	45.2 / 36.1	45.2 / 54.8
Cefepime	≤0.5	>16	≤0.5 – >16	79.8 / 15.4	63.0 / 26.0
Cefoperazone	2	>32	≤0.25 – >32	57.7 / 38.0	- / -
Cefoperazone/sulbactam[b]	2	32	≤0.25 – >32	86.1 / 5.8	- / -
Ceftazidime	0.25	>32	0.03 – >32	72.6 / 22.1	67.3 / 27.4
Ceftriaxone	0.12	>8	≤0.06 – >8	55.3 / 42.8	55.3 / 42.8
Colistin	0.5	0.5	≤0.25 – 2	- / -	100.0 / 0.0
Doxycycline	2	>8	0.12 – >8	61.1 / 35.1	- / -
Levofloxacin	0.25	>4	≤0.12 – >4	78.8 / 19.2	76.4 / 21.2
Meropenem	≤0.06	≤0.06	≤0.06 – >8	95.7 / 4.3	95.7 / 3.4
Piperacillin/tazobactam	4	32	≤0.5 – >64	88.9 / 7.7	83.2 / 11.1
Tigecycline[c]	0.25	1	0.06 – >4	98.6 / 0.5	95.7 / 1.4
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	63.0 / 37.0	63.0 / 37.0
ESBL-phenotype (94)					
Amikacin	1	>32	0.5 – >32	83.0 / 17.0	83.0 / 17.0
Cefepime	8	>16	≤0.5 – >16	55.3 / 34.0	18.1 / 57.4
Cefoperazone/sulbactam[b]	8	>32	0.5 – >32	70.2 / 12.8	- / -
Ceftazidime	8	>32	0.12 – >32	39.4 / 48.9	27.7 / 60.6
Ceftriaxone	>8	>8	1 – >8	1.1 / 94.7	1.1 / 94.7
Colistin	0.5	0.5	≤0.25 – 2	- / -	100.0 / 0.0
Levofloxacin	1	>4	≤0.12 – >4	60.6 / 35.1	58.5 / 39.4
Meropenem	≤0.06	1	≤0.06 – >8	90.4 / 9.6	90.4 / 7.4
Piperacillin/tazobactam	8	>64	≤0.5 – >64	75.5 / 17.0	67.0 / 24.5
Tigecycline[c]	0.25	1	0.06 – >4	96.8 / 1.1	94.7 / 3.2
Non-ESBL-phenotype (114)					
Amikacin	1	2	≤0.25 – >32	99.1 / 0.9	99.1 / 0.9
Cefepime	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Cefoperazone	≤0.25	2	≤0.25 – 32	99.1 / 0.0	- / -
Cefoperazone/sulbactam[b]	≤0.25	2	≤0.25 – 32	99.1 / 0.0	- / -
Ceftazidime	0.12	0.5	0.03 – 1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Colistin	0.5	0.5	≤0.25 – 2	- / -	100.0 / 0.0
Levofloxacin	≤0.12	1	≤0.12 – >4	93.9 / 6.1	91.2 / 6.1
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	8	1 – 16	100.0 / 0.0	96.5 / 0.0
Tigecycline[c]	0.25	0.5	0.06 – 2	100.0 / 0.0	96.5 / 0.0

Organism (no. tested)/ antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterobacter spp.(155)					
Amikacin	2	4	0.5 – >32	96.8 / 2.6	96.1 / 3.2
Cefepime	≤0.5	>16	≤0.5 – >16	84.5 / 11.0	71.0 / 18.7
Cefoperazone/sulbactam[b]	2	32	≤0.25 – >32	87.7 / 7.1	- / -
Ceftazidime	0.5	>32	0.03 – >32	65.8 / 32.9	58.1 / 34.2
Ceftriaxone	0.5	>8	≤0.06 – >8	52.3 / 43.9	52.3 / 43.9
Colistin	0.5	>4	≤0.25 – >4	- / -	81.3 / 18.7
Doxycycline	2	>8	1 – >8	68.4 / 24.5	- / -
Levofloxacin	≤0.12	>4	≤0.12 – >4	81.9 / 15.5	77.4 / 18.1
Meropenem	≤0.06	0.12	≤0.06 – >8	98.7 / 1.3	98.7 / 0.6
Piperacillin/tazobactam	4	>64	≤0.5 – >64	77.4 / 12.3	67.1 / 22.6
Tigecycline[c]	0.25	1	0.12 – 4	98.7 / 0.0	94.2 / 1.3
Indole-positive *Proteus* spp. (69)					
Amikacin	2	4	≤0.25 – 8	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.5	1	≤0.5 – >16	97.1 / 2.9	95.7 / 2.9
Cefoperazone/sulbactam[b]	2	4	≤0.25 – >32	97.1 / 1.4	- / -
Ceftazidime	0.12	4	0.03 – 32	91.3 / 4.3	85.5 / 8.7
Ceftriaxone	≤0.06	4	≤0.06 – >8	84.1 / 10.1	84.1 / 10.1
Levofloxacin	1	>4	≤0.12 – >4	76.8 / 11.6	66.7 / 23.2
Meropenem	≤0.06	0.12	≤0.06 – 2	98.6 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	4	≤0.5 – >64	98.6 / 1.4	95.7 / 1.4
Tigecycline[c]	0.5	2	0.25 – 4	97.1 / 0.0	85.5 / 2.9
Serratia marcescens (67)					
Amikacin	2	>32	1 – >32	89.6 / 10.4	88.1 / 10.4
Cefepime	≤0.5	16	≤0.5 – >16	88.1 / 9.0	83.6 / 14.9
Cefoperazone/sulbactam[b]	1	32	0.5 – >32	89.6 / 3.0	- / -
Ceftazidime	0.25	4	0.06 – 32	92.5 / 4.5	85.1 / 7.5
Ceftriaxone	0.25	>8	0.12 – >8	85.1 / 14.9	85.1 / 14.9
Levofloxacin	≤0.12	1	≤0.12 – >4	97.0 / 1.5	92.5 / 3.0
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	1 – 64	95.5 / 0.0	94.0 / 4.5
Tigecycline[c]	0.5	1	0.25 – 4	98.5 / 0.0	97.0 / 1.5
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >4	91.0 / 9.0	91.0 / 7.5
Citrobacter spp. (53)					
Amikacin	2	8	0.5 – >32	92.5 / 7.5	92.5 / 7.5
Cefepime	≤0.5	16	≤0.5 – >16	84.9 / 9.4	62.3 / 20.8
Cefoperazone/sulbactam[b]	4	32	≤0.25 – >32	86.8 / 1.9	- / -
Ceftazidime	2	>32	0.12 – >32	54.7 / 39.6	47.2 / 45.3
Ceftriaxone	>8	>8	≤0.06 – >8	45.3 / 52.8	45.3 / 52.8
Colistin	0.5	0.5	≤0.25 – 1	- / -	100.0 / 0.0
Doxycycline	2	>8	0.5 – >8	64.2 / 28.3	- / -
Levofloxacin	0.25	>4	≤0.12 – >4	75.5 / 18.9	66.0 / 24.5
Meropenem	≤0.06	≤0.06	≤0.06 – 4	98.1 / 1.9	98.1 / 0.0
Piperacillin/tazobactam	4	>64	1 – >64	69.8 / 11.3	64.2 / 30.2
Tigecycline[c]	0.12	0.5	0.06 – 4	98.1 / 0.0	98.1 / 1.9
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5 – >4	66.0 / 34.0	66.0 / 34.0
Proteus mirabilis (28)					
Amikacin	2	8	1 – 8	100.0 / 0.0	100.0 / 0.0
Ampicillin	>8	>8	0.5 – >8	39.3 / 60.7	39.3 / 60.7
Ampicillin/sulbactam	4	32	0.5 – 32	67.9 / 21.4	67.9 / 32.1
Cefepime	≤0.5	>16	≤0.5 – >16	89.3 / 10.7	78.6 / 14.3
Cefoperazone/sulbactam[b]	1	4	≤0.25 – 4	100.0 / 0.0	- / -
Ceftazidime	0.06	0.12	0.03 – 2	100.0 / 0.0	96.4 / 0.0
Ceftriaxone	≤0.06	>8	≤0.06 – >8	78.6 / 21.4	78.6 / 21.4
Levofloxacin	1	>4	≤0.12 – >4	71.4 / 28.6	60.7 / 28.6
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	2	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Tigecycline[c]	1	4	0.25 – 4	89.3 / 0.0	64.3 / 10.7
Trimethoprim/sulfamethoxazole	>4	>4	≤0.5 – >4	46.4 / 53.6	46.4 / 53.6
Pseudomonas aeruginosa (221)					
Amikacin	4	16	0.5 – >32	90.5 / 9.1	86.0 / 9.5
Cefepime	8	>16	≤0.5 – >16	67.9 / 16.7	67.9 / 32.1
Cefoperazone/sulbactam[b]	16	>32	1 – >32	58.4 / 17.6	- / -
Ceftazidime	4	>32	0.25 – >32	67.9 / 26.2	67.9 / 32.1
Colistin	1	2	≤0.25 – 4	99.5 / 0.0	99.5 / 0.5
Levofloxacin	1	>4	≤0.12 – >4	68.3 / 22.6	52.5 / 31.7
Meropenem	1	>8	≤0.06 – >8	67.4 / 26.7	67.4 / 15.4
Piperacillin/tazobactam	16	>64	≤0.5 – >64	55.2 / 27.6	55.2 / 44.8
Acinetobacter spp.(178)					
Amikacin	>32	>32	0.5 – >32	26.4 / 73.0	25.8 / 73.6
Cefepime	>16	>16	≤0.5 – >16	14.0 / 80.3	- / -
Cefoperazone/sulbactam[b]	32	>32	0.5 – >32	31.5 / 29.2	- / -
Ceftazidime	>32	>32	1 – >32	16.9 / 83.1	- / -
Colistin	1	1	≤0.25 – 2	100.0 / 0.0	100.0 / 0.0
Doxycycline	>8	>8	≤0.06 – >8	40.4 / 57.3	- / -
Levofloxacin	>4	>4	≤0.12 – >4	20.8 / 62.9	19.1 / 79.2
Meropenem	>8	>8	0.12 – >8	22.5 / 77.5	20.2 / 77.5
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	19.1 / 80.9	- / -
Tigecycline	1	2	0.06 – >4	- / -	- / -

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. Criteria as published by the CLSI [2013] for Cefoperazone used for Cefoperazone/sulbactam.
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].