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Antimicrobial susceptibilities of aerobic and facultative gram-negative bacilli isolated from Chinese patients with urinary tract infections between 2010 and 2014

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Abstract

Background: The objective of this study was to investigate the distribution and susceptibility of aerobic and facultative Gram-negative bacilli isolated from Chinese patients with UTIs collected within 48 h (community acquired, CA) or after 48 h (hospital acquired, HA) of hospital admission.

Methods: From 2010 to 2014, the minimum inhibitory concentrations (MICs) of 12 antibiotics for 4,332 aerobic and facultative Gram-negative bacilli, sampled in 21 hospitals in 16 cities, were determined by the broth microdilution method.

Results: *Enterobacteriaceae* composed 88.5% of the total isolates, with *Escherichia coli* (*E. coli*) (63.2%) the most commonly isolated species, followed by *Klebsiella pneumoniae* (*K. pneumoniae*) (12.2%). Non-*Enterobacteriaceae* accounted for only 11.5% of all isolates and included mainly *Pseudomonas aeruginosa* (*P. aeruginosa*) (6.9%) and *Acinetobacter baumannii* (*A. baumannii*) (3.3%). Among the antimicrobial agents tested, the susceptibility rates of *E. coli* to the two carbapenems, ertapenem and imipenem as well as amikacin and piperacillin-tazobactam ranged from 92.5 to 98.7%. Against *K. pneumonia,* the most potent antibiotics were imipenem (92.6% susceptibility), amikacin (89.2% susceptibility) and ertapenem (87.9% susceptibility).

Although non-*Enterobacteriaceae* did not show high susceptibilities to the 12 common antibiotics, amikacin exhibited the highest in vitro activity against *P. aeruginosa* over the 5-year study period, followed by piperacillin-tazobactam, imipenem, ceftazidime, cefepime, ciprofloxacin, and levofloxacin. The Extended Spectrum Beta-Lactamase (ESBL) rates decreased slowly during the 5 years in *E. coli* from 68.6% in 2010 to 59.1% in 2014, in *K. pneumoniae* from 59.7 to 49.2%, and in *Proteus mirabilis* (*P. mirabilis*) from 40.0 to 26.1%. However, the ESBL rates were different in 5 regions of China (Northeast, North, East, South and Middle-China).

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Conclusion: *E. coli* and *K. pneumonia* were the major pathogens causing UTIs and carbapenems and amikacin retained the highest susceptibility rates over the 5-year study period, indicating that they are good drug choices for empirical therapies, particularly of CA UTIs in China.

Keywords: Urinary tract infections, Extended spectrum beta-lactamases (ESBLs), Carbapenems, Antimicrobial resistance

Background

Several national and international surveillance programs have been initiated for monitoring susceptibilities of clinically important pathogens in urinary tract infections (UTIs) [1–3]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a surveillance program designed to monitor globally susceptibilities of aerobic and facultative Gram-negative bacilli collected from intra-abdominal infections and UTIs (initiated in 2002) [4]. UTIs are frequently encountered in clinical practice and include uncomplicated and complicated pyelonephritis, ureteritis, cystitis and urethritis [5]. The etiologies of these infections arise from Gram-negative bacilli, especially *Enterobacteriaceae,* and some Gram-positive bacteria [6]. During the last decade, multidrug-resistant Gram-negative Enterobacteriaceae have become a challenge for physicians [7] and particularly *E. coli* and *K. pneumonia* strains isolated from UTIs have been reported to increasingly produce ESBLs in the recent years [8–10]. The choice of an empiric UTI antimicrobial therapy should be based on knowledge of the pathogen distribution and the resistance extent of common microorganisms, in addition to hospital-specific resistance patterns particularly for HA infections. This study, as part of the global SMART project, focused on ESBL-producing rates of UTI isolates from 21 centers in 16 Chinese cities between 2010 and 2014 and on UTI derived sample resistance rates against carbapenems, a combination of drugs containing penicillins with β-lactamase inhibitors, a cephamycin, an aminoglycoside, 3rd and 4th generation cephalosporins as well as 2nd generation fluoroquinolones, in order to provide guidance for antimicrobial therapies of IAIs.

Methods

Clinical isolates

During our study period (2010–2014), a total of 4,332 aerobic and facultative Gram-negative bacilli were consecutively isolated from patients with UTIs in 21 hospitals sited in 16 Chinese cities (Beijing, Shanghai, Hangzhou, Nanjing, Shenyang, Tianjin, Wuhan, Changsha, Jinan, Zhengzhou, Guangzhou, Nanchang, Haikou, Harbin, Changchun and Chongqing).

All isolates were cultured from specimens collected from patients who met both clinical and laboratory criteria of urinary tract infections (3,994 from clean catch

midstream urine, 154 from urinary bladder, 136 from ureter, 29 from kidney, 13 from urethra, 6 from prostate). Duplicate isolates (same species and genus from one patient) were excluded.

Standard methods were used by the participating clinical microbiology laboratories for initial bacteria identification, and re-identification was carried out by a central laboratory (Peking Union Medical College Hospital) using Vitek 2 Compact (2010–2011) (Biomerieux, France) and MALDI-TOF MS (2012–2014) (Vitek MS, Biomerieux, France).

Isolates were considered to be community-associated (CA) if they were recovered from a specimen taken less than 48 h after the patient was admitted to a hospital, and hospital-associated (HA) if the specimen was taken 48 or more hours after hospital admission, as previously described [11].

Antimicrobial susceptibility test method

Minimum inhibitory concentration (MIC) determinations were performed in a central lab using dehydrated MicroScan broth microdilution panels (Siemens Medical Solutions Diagnostics (West Sacramento, CA) according to Clinical and Laboratory Standards Institute (CLSI) guidelines [12] and susceptibility interpretations were based on clinical CLSI breakpoints [13]. Twelve commonly used antimicrobial agents for UTI treatments were analyzed namely, imipenem (IPM), ertapenem (EPM), ceftriaxone (CRO), cefotaxime (CTX), ceftazidime (CAZ), cefoxitin (FOX), cefepime (FEP), piperacillin-tazobactam (TZP), ampicillin-sulbactam (SAM), amikacin (AMK), ciprofloxacin (CIP) and levofloxacin (LVX). For each batch of MIC testing, the reference strains *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *K. pneumonia* ATCC 700603 were used as quality controls. Results were only included in the analysis when corresponding quality control isolate test results were in accordance with CLSI guidelines and therefore within an acceptable range.

Extended-spectrum β-lactamases (ESBLs) detection

Phenotypic identification of ESBL production in *E.coli, K. pneumonia, Klebsiella oxytoca* (*K. oxytoca*)*,* and *P. mirabilis* was carried out according to CLSI recommended methods [13]. If cefotaxime or ceftazidime MICs were ≥ 2 μg/mL, the MICs of cefotaxime + clavulanic acid (4 μg/mL) or

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ceftazidime + clavulanic acid (4 μg/mL) were comparatively determined. ESBL production was defined as a ≥ 8-fold decrease in MICs for cefotaxime or ceftazidime tested in combination with clavulanic acid, compared to their MICs without clavulanic acid.

Statistical analysis

The susceptibility of all gram-negative isolates combined was calculated using breakpoints appropriate for each species and assuming 0% susceptible for species with no breakpoints for given drug. Ninety-five percent confidence intervals were calculated using the adjusted Wald method; linear trends of ESBL rates in different years were assessed for statistical significance using the Cochran-Armitage test and comparison of ESBL rates in 6 different geographic areas were assessed using Chi-square test. *P* values < 0.05 were considered statistically significant.

Results

Distribution of organisms from urinary tract infection

A total of 4,332 isolates were collected from UTIs between 2010 and 2014. The highest distribution of bacteria was *E. coli,* which accounted for 63.2% (2,737 strains), followed by *K. pneumonia* (12.2%, 529 strains) and *P. aeruginosa* (6.9%, 297 strains) (Table 1)*.* We also investigated the distribution of strains from HA (n = 2765, 72.16%) and CA (n = 1039, 27.11%) (P < 0.0001) infections, but most of the isolates were sampled from HA infections (62.59–80.42%) (Table 1). *Enterobacteriaceae* were present in the majority of isolates and accounted for 88.5%, including mainly *E.coli* (63.2%), followed by *K. pneumonia* (12.2%), *P. mirabilis* (3.4%) and *Enterobacter cloacae* (*E. cloacae*) (3.3%), while others were present at a rate < 1.3%. Non-*Enterobacteriaceae* accounted for only 11.5% of all isolates and

included mainly *P. aeruginosa* (6.9%) and *Acinetobacter baumannii* (*A. baumannii*) (3.3%).

In vitro susceptibility of Enterobacteriaceae and non-Enterobacteriaceae during 2010–2014

Among the 12 analyzed antimicrobial agents, the susceptibility rates of ertapenem and imipenem against *E. coli* over 5 years were 96.4% (2,639/2,737) and 98.7% (2,702/2,737), with MIC$_{90}$ values of 0.25 μg/mL for both drugs. Most *E.coli* isolates remained susceptible to amikacin (92.8%) and piperacillin-tazobactam (92.51%). However, the susceptibilities to third- and fourth-generation cephalosporins were relatively low, with rates of 58.5, 38.2, 34.6 and 34.4% for ceftazidime (CAZ), cefepime (FEP), cefotaxime (CTX) and ceftriaxone (CRO), respectively. The susceptibility rates of *E. coli* to fluoroquinolones and ampicillin-sulbactam were also less than 30 and 20%, respectively (Fig. 1, Table 2).
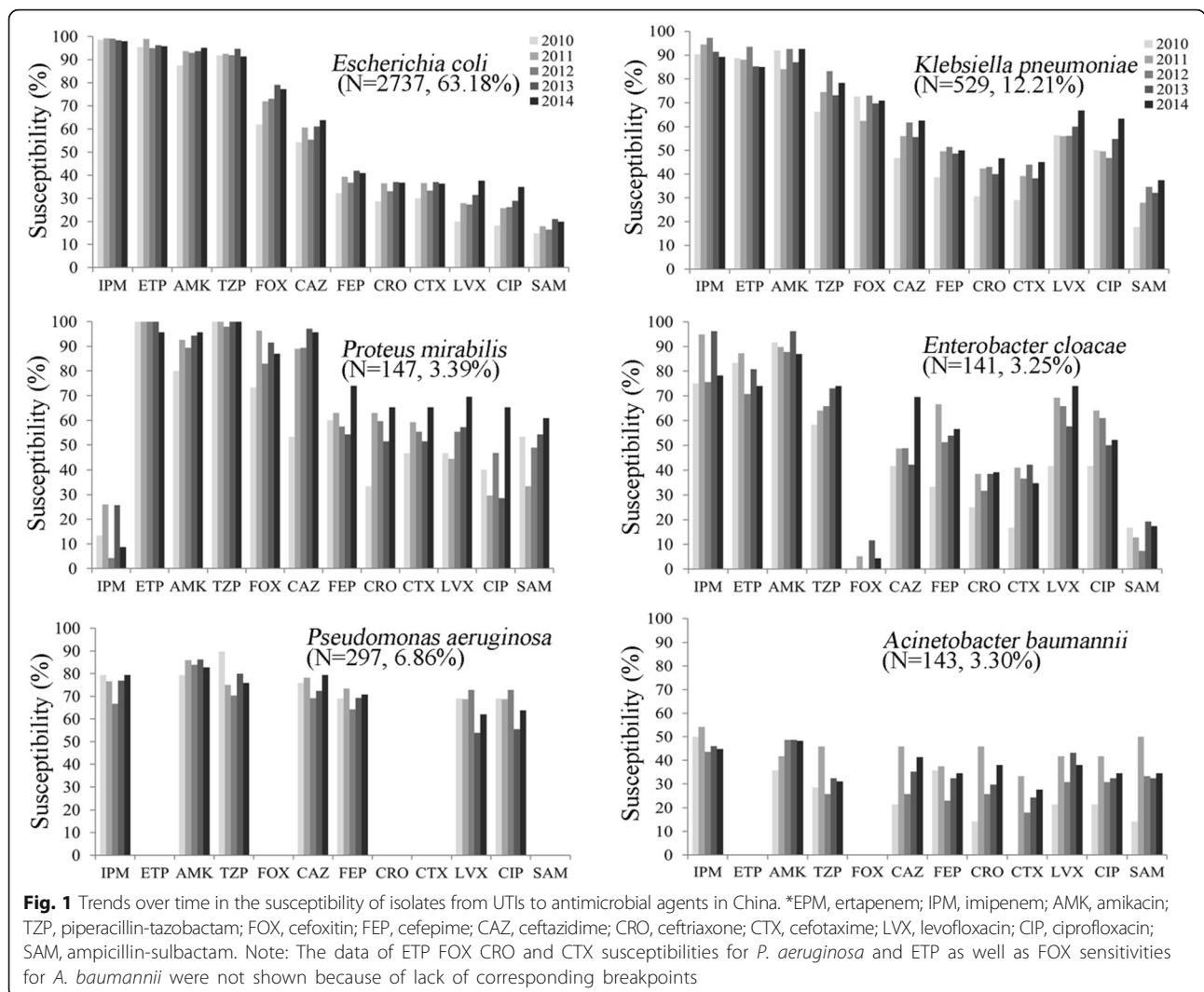
Against *K. pneumonia,* the most potent antibiotics were imipenem (92.6% susceptibility), amikacin (89.2% susceptibility) and ertapenem (87.9% susceptibility), with MIC$_{90}$ values of 1 μg/mL, > 32 μg/mL and 1 μg/mL, respectively. Piperacillin-tazobactam was the fourth most active agent, with a susceptibility of 75.8%. The susceptibility rates of other antibiotics ranged from 30.6% (ampicillin-sulbactam) to 67.5% (cefoxitin) (Fig. 1, Table 2,).

Against *P. mirabilis*, antimicrobial agents with > 90% susceptibility rates included ertapenem (99.3%), piperacillin-tazobactam (99.3%) and amikacin (91.2%), but in HA infections, a > 90% susceptibility rate was found for ceftazidime (90.2%). Cephalosporin susceptibility rates were 55.8–88.4% whereas fluoroquinolones exhibited 41.5–55.1% activity. Imipenem had poor

Table 1 Distribution of the UTI pathogens in China between 2010 and 2014

	Total	CA (n/% of total)	HA (n/% of total)	Not identified (n/% of total)	*P*-value
Enterobacteriaceae	3,832	1,039 (27.11)	2,765 (72.16)	28 (0.73)	<0.0001
Escherichia coli	2,737	739 (27.00)	1,976 (72.20)	22 (0.80)	<0.0001
Klebsiella pneumoniae	529	129 (24.39)	398 (75.24)	2 (0.38)	<0.0001
Proteus mirabilis	147	54 (36.73)	92 (62.59)	1 (0.68)	0.011
Enterobacter cloacae	141	39 (27.66)	101 (71.63)	1 (0.71)	<0.0001
Citrobacter freundii	54	11 (20.37)	43 (79.63)	0 (0.00)	0.0003
Klebsiella oxytoca	51	18 (35.29)	33 (64.71)	0 (0.00)	0.1205
other	173	49 (28.32)	122 (70.52)	2 (1.16)	<0.0001
Non-Enterobacteriaceae	500	105 (21.00)	391 (78.2)	4 (0.8)	<0.0001
Pseudomonas aeruginosa	297	65 (21.89)	231 (77.78)	1 (0.34)	<0.0001
Acinetobacter baumannii	143	26 (18.18)	115 (80.42)	2 (1.40)	<0.0001
other	60	14 (23.33)	45 (75.00)	1 (1.67)	<0.0001
All	4,332	1,144 (26.41)	3,156 (72.85)	32 (0.74)	<0.0001

Not identified: A total of 32 isolates lacked partial demographic information and could not be identified as CA or HA isolates. They were not included in further analyses

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Fig. 1 Trends over time in the susceptibility of isolates from UTIs to antimicrobial agents in China. *EPM, ertapenem; IPM, imipenem; AMK, amikacin; TZP, piperacillin-tazobactam; FOX, cefoxitin; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; LVX, levofloxacin; CIP, ciprofloxacin; SAM, ampicillin-sulbactam. Note: The data of ETP FOX CRO and CTX susceptibilities for *P. aeruginosa* and ETP as well as FOX sensitivities for *A. baumannii* were not shown because of lack of corresponding breakpoints

activity against *P. mirabilis* isolates, with a mean susceptibility rate of only 15.0% in both CA and HA derived isolates (Figs. 1 and 2, Table 2).

Antimicrobial resistance in *Enterobacter cloacae* was more pronounced than in *E. coli* and *K. pneumonia*. The antimicrobial agents with susceptibility rates of > 80% were amikacin (90.1%) and imipenem (85.1%) over the 5-year study period. Particularly in 2014, ertapenem and piperacillin-tazobactam susceptibility rates in HA infections dropped to 53.9%, whereas CA UTIs were still 100% susceptible to both antibiotics (Fig. 2). However, ertapenem was the third most active agent with susceptibilities of 78.7% in all isolates, followed by piperacillin-tazobactam (67.4%), levofloxacin (64.5%), ciprofloxacin (56.7%) and cefepime (55.3%) (Fig. 1, Table 2).

Although non-*Enterobacteriaceae* did not show high susceptibilities to the 12 common antibiotics, amikacin exhibited the highest in vitro activity against *P. aeruginosa*, with a susceptibility rate of 84.2% over the 5-year study period,

followed by piperacillin-tazobactam, imipenem, ceftazidime, cefepime, ciprofloxacin, and levofloxacin. (Figure 1, Table 2).

A. baumannii was the second most frequently isolated non-fermentative Gram-negative bacillus, comprising 3.3% (143/4,332) of all UTIs. The most active agents against *A. baumannii* were imipenem and amikacin, with susceptibility rates of 46.9 and 46.2%, respectively over the entire study period. The other analyzed agents were less effective, with susceptibility rates of < 40% (Fig. 1, Table 2).

The trend of extended spectrum beta-lactamases (ESBL) – producing bacteria occurrence in UTIs from 2010 to 2014

Figure 2a-c shows the frequency of ESBL-producing *E.coli, K. pneumonia, K. oxytoca* and *P. mirabilis* strains over the study period. The percentage of ESBL positive *E. coli* isolates decreased from 68.6% in 2010 to 59.1% in 2014, while the ESBL rate in *K. pneumonia* decreased from 59.7 to 49.2% and in *P. mirabilis* from 40.0 to 26.1% during the 5-year study period. The susceptibility

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Table 2 Susceptibilities of UTI pathogens isolated between 2010 and 2014

	Antibiotics	S%	MIC50 (μg/ml)	MIC90 (μg/ml)
Escherichia coli	IPM	98.72	0.12	0.25
	ETP	96.42	≤0.03	0.25
	AMK	92.88	≤4	16
	TZP	92.51	≤2	16
Klebsiella pneumoniae	IPM	92.63	0.25	1
	AMK	89.22	≤4	>32
	ETP	87.9	≤0.03	1
	TZP	75.8	≤2	>64
Proteus mirabilis	ETP	99.32	≤0.03	0.06
	TZP	99.32	≤2	4
	AMK	91.16	8	16
	CAZ	88.44	≤0.5	8
Enterobacter cloacae	AMK	90.07	≤4	16
	IPM	85.11	0.5	2
	ETP	78.72	0.12	4
	TZP	67.38	4	>64
Pseudomonas aeruginosa	AMK	84.18	8	>32
	TZP	76.43	4	>64
	IPM	74.75	1	>8
	CAZ	74.41	4	64
Acinetobacter baumannii	IPM	46.85	8	>8
	AMK	46.15	>32	>32
	LVX	36.36	>4	>4
	CAZ	34.27	64	>128

differences to ertapenem and imipenem between ESBL and non-ESBL producing strains were generally small, but were greater for other agents, particularly for the third- and fourth-generation cephalosporins, including ceftriaxone (1.1% against ESBL-producing isolates vs 91.0% against ESBL-non-producing isolates), ceftazidime (38.4% vs 93.5%) and cefepime (4.5% vs 96.7%) (data not shown).
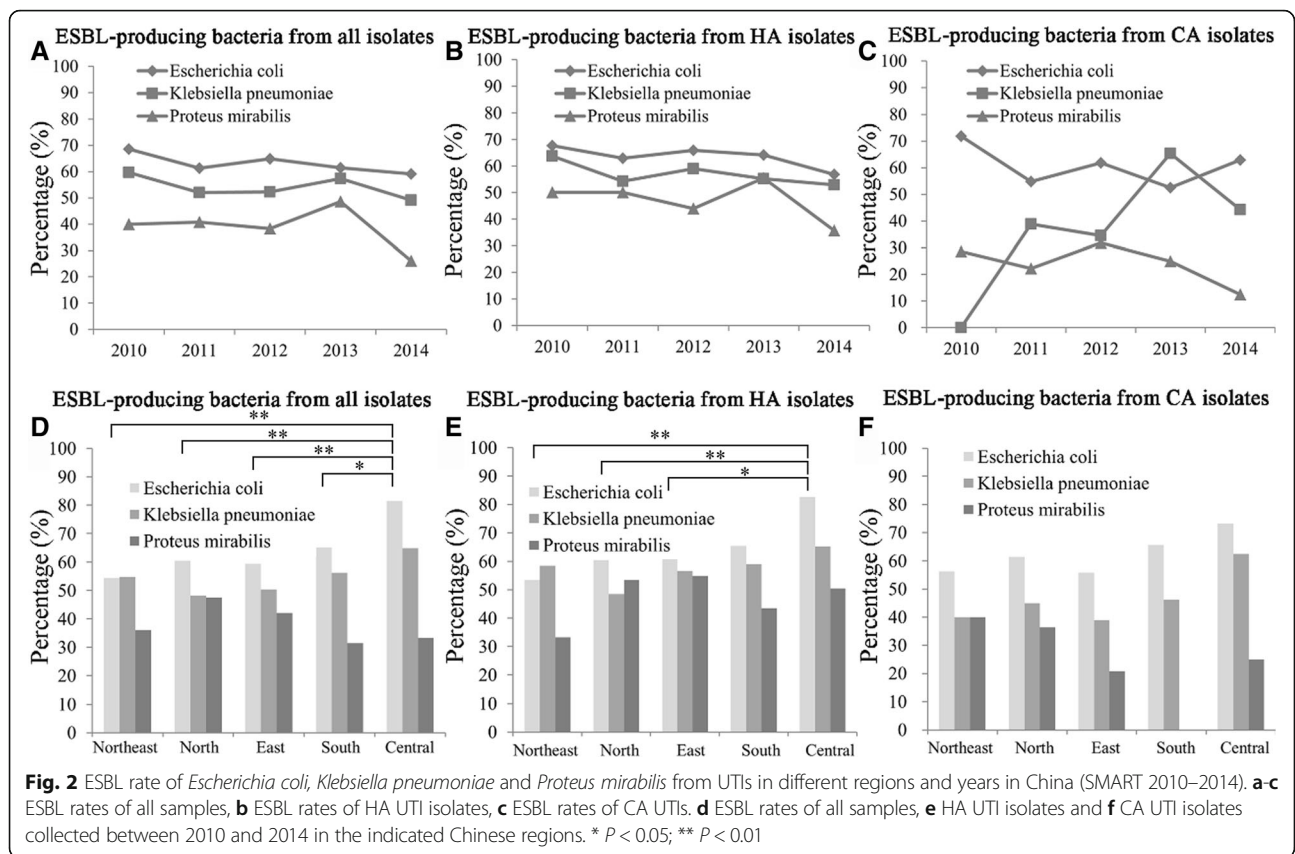
Figure 2d-e shows the ESBL rates in *E. coli, K. pneumonia, and P. mirabilis* from UTIs in different regions in China. We categorized the 21 participating sites into 5 different regions in China (Northeast (Haerbin, Changchun and Shenyang), North (Beijing and Tianjing), East (Hangzhou, Nanjing, Jinan, Nanchang and Shanghai), South (Chongqing, Guangzhou and Haikou) and Central China (Changsha, Zhengzhou and Wuhan)). The two sites in the Central China region exhibited higher ESBL rates in *E. coli* (81.5%) and *K. pneumonia* (64.9%), while other regions showed relatively lower ESBL rates in these two species (54.5–65.1% for *E. coli*, and 48.1–56.3% for *K. pneumoniae*). For *P. mirabilis*, the

ESBL rates ranged from 31.4% (South China region) to 47.5% (North China region).

Discussion

Nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, fluoroquinolones and beta-lactams are commonly recommended antimicrobial agents for urinary tract infections [14]. However, fosfomycin and nitrofurantoin are not often used in China [2]. The usage of trimethoprim-sulfamethoxazole for the treatment of UTIs in China is also limited because of a high resistance rate to this agent among *E.coli* isolates [15]. In view of this finding, we focused on the activity of beta-lactams, fluoroquinolones and aminoglycoside against uropathogens in the present study. Since *Enterobacteriaceae* accounted for the majority of aerobic and facultative anaerobic pathogens causing UTIs (88.5% of all isolates) in our study, with *E.coli, K. pneumonia, P. mirabilis* and *Enterobacter cloacae* the most frequently isolated species, knowledge of their resistance pattern is beneficial.

Cephalosporins are commonly recommended as empirical choices for UTIs, but their efficacy is greatly reduced when the pathogens produce ESBL. Over the entire study period, susceptibility rates of *Enterobacteriaceae* to third-generation and fourth-generation cephalosporins were 51.4–66.0% for ceftazidime, 29.4–46.9% for cefotaxime, 29.9–41.2% for ceftriaxone and 35.1–47.1% for cefepime, indicating that these agents might not be the optimum medications for empirical UTI therapies. In the present study, the percentage of ESBL positive *E. coli* isolates decreased from 66.9% in 2010 to 59.1% in 2014, while for *K. pneumonia* it decreased from 59.7 to 48.8% and from 40.0 to 26.1% among *P. mirabilis*. The data were well matched with the non-susceptibility rates to cephalosporins against each species, which indicated that ESBL production might be a reason for cephalosporin resistance [16]. The decrease of ESBL rates in *E. coli, K. pneumonia* and *P. mirabilis* may have been a result of China's antimicrobial stewardship policy on antimicrobial use, which has been promoted for a number of years [17–19]. Our study also highlighted the variation in ESBL rates in different regions of China, with the Central-China region having a higher ESBL prevalence in *E. coli* and *K. pneumonia*. Researchers previously reported that the ESBL genotypes in China were mainly CTX-M types [20–22], especially CTX-M-14, –15, and –55 for *E. coli* and *K. pneumonia*, and CTX-M-65 and –14 for *P. mirabilis* [22]. Plasmids encoding these CTX-M enzymes reached human opportunists, where they have proliferated in community *E. coli* and hospital *K.* species. CTX-M families are dominate in different regions: CTX-M-15 is predominant in most of Europe, North America, the Middle East, and India, but

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Fig. 2 ESBL rate of *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* from UTIs in different regions and years in China (SMART 2010–2014). **a**-**c** ESBL rates of all samples, **b** ESBL rates of HA UTI isolates, **c** ESBL rates of CA UTIs. **d** ESBL rates of all samples, **e** HA UTI isolates and **f** CA UTI isolates collected between 2010 and 2014 in the indicated Chinese regions. * *P* < 0.05; ** *P* < 0.01

CTX-M-14 is most common in China, Southeast Asia and Spain, while CTX-M-2 is predominant in Argentina, Israel, and Japan [23, 24]. Increased numbers of enzyme types and prevalence made determination of resistance profiles more complicated.

Fluoroquinolones, especially ciprofloxacin and levofloxacin, were considered to be effective antimicrobial agents against uropathogens because of high drug concentrations are reached in the urine. However, fluoroquinolone-resistant *E. coli* is also problematic in China. The susceptibility of *E. coli* to fluoroquinolones (ciprofloxacin and levofloxacin) was 26.9–28.9%, with rates of 30.2–32.1% against CA isolates and 25.7–27.8% against HA isolates. Wang et al. also previously reported about ciprofloxacin-resistant *E. coli* strains with multiple gyrA and parC gene substitutions [25]. Regarding the low effectiveness of fluoroquinolones against *Enterobacteriaceae*, ciprofloxacin and levofloxacin should not be considered as first line agents for empirical therapies of complicated UTIs. Our data also showed that susceptibilities of ESBL-producing *E. coli* and *K. pneumonia* strains to fluoroquinolones were significantly lower than that of ESBL-non-producing strains, which is in agreement with previous findings [26].

Carbapenems can still be considered to be suitable for severe infections and as alternative empiric treatment for UTIs caused by bacterial strains highly suspicious of being ESBL-producing or AmpC-derepressed *Enterobacteriaceae* [27–29]. Although carbapenems were not the first line choices for uncomplicated cystitis and pyelonephritis in women according to the IDSA guideline, they were good alternatives against multidrug resistant Gram-negative bacilli that caused UTIs. Our study showed that ertapenem and imipenem were the most effective agents against *Enterobacteriaceae* causing UTIs, with susceptibility rates of 92.5–96.5% and 89.9–95.2%, respectively (2010–2014). On the other hand, carbapenem-resistant *Enterobacteriaceae* have emerged, which has also been noted in other reports [30–33], especially KPC-producing *K. pneumonia* in the northeastern area of the United States of America [31], KPC/VIM-producing *Enterobacteriaceae* in Greece [32, 33] and KPC-producing isolates in eastern China. In our study, very few *E. coli* isolates (<4%) were non-susceptible to carbapenems, while there was a certain proportion of carbapenem-non-susceptible *K. pneumonia* isolates (13.8% to ertapenem), *P. mirabilis* (85% to imipenem) and *E. cloacae* (21.3% to ertapenem and 14.9% to imipenem), which should be noted by
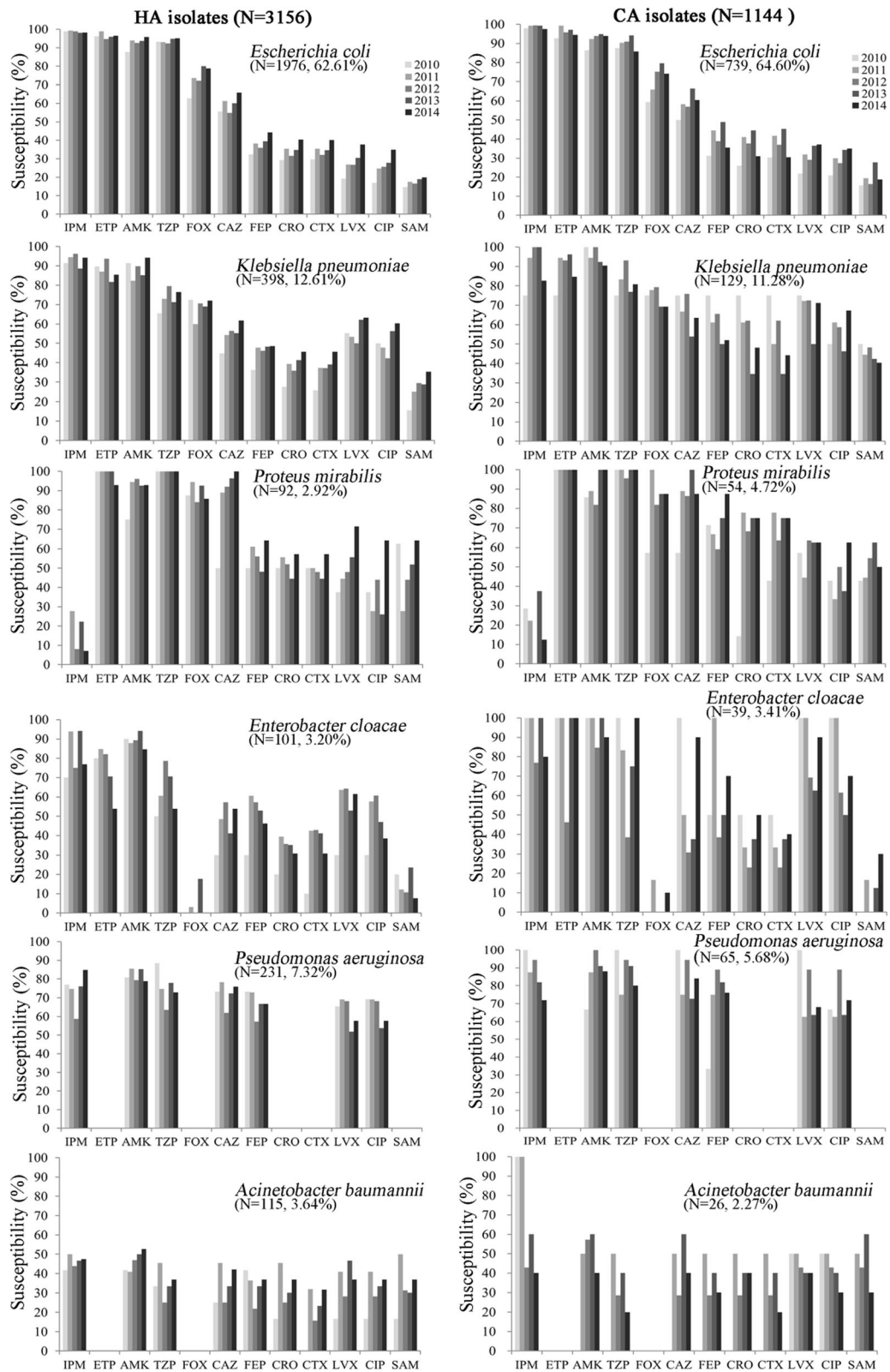
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Fig. 3 (See legend on next page.)

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clinicians. Especially for *E. cloacae* the susceptibility of HA samples to ertapenem has dropped to 53.9%, while for CA UTIs its susceptibility rate is 100%. Hospital infections caused by *E. cloacae*, which is a typical commensal under normal conditions, have been suggested to be mainly caused by endogenous translocation from the digestive tract in debilitated patients and that under antibiotic therapy, *E. cloacae* strains may selectively reproduce excessively in the gastrointestinal tract [34]. This might be the reason for the high ertapenem resistance in UTIs mainly caused by HA *E. cloacae*. The main resistance mechanism to carbapenem in *Enterobacteriaceae* was reported to be carbapenemase production and porin loss in China [35]. However, the resistance of *P. mirabilis* to imipenem was caused by a mechanism other than carbapenemase [13].

Among the tested antimicrobial agents, amikacin exhibited good activity against most of the uropathogens (80.0–96.2% susceptibility rate against *Enterobacteriaceae* and 83.6% against *P. aeruginosa*). Although the use of this aminoglycoside is limited because of its toxicity, it has also been recommended as an alternative to carbapenems against ESBL-producing isolates that cause UTIs [36].

Conclusion

Carbapenems remain the most effective antimicrobial agents against UTI Gram-negative pathogens, followed by amikacin and piperacillin-tazobactam in China between 2010 and 2014. Due to the reduced susceptibility of *Enterobacteriaceae* to cephalosporins and fluoroquinolones, we recommend that these antibiotics should not be used for empirical UTI therapies in China.

Abbreviations
AMK: Amikacin; CA: Community acquired; CAZ: Ceftazidime; CIP: Ciprofloxacin; CLSI: Clinical and Laboratory Standards Institute; CRO: Ceftriaxone; CTX: Cefotaxime; EPM: Ertapenem; ESBLs: Extended spectrum beta-lactamases; FEP: Cefepime; FOX: Cefoxitin; HA: Hospital acquired; IPM: Imipenem; LVX: Levofloxacin; MICs: Minimum inhibitory concentrations; SAM: Ampicillin-sulbactam; SMART: Study for monitoring antimicrobial resistance trends; TZP: Piperacillin-tazobactam; UTIs: Urinary tract infections

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
All participating institutions agreed to comply with Investigational Review Boards, Good Clinical Practices, and Good Laboratory Practices. The approval of each hospital Investigational Review Board (IRB) has been obtained prior to the start of the investigation, depending on the IRB policies at the institutions.

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References

1. Bi XC, Zhang B, Ye YK, He HC, Han ZD, Dai QS, et al. Pathogen incidence and antibiotic resistance patterns of catheter-associated urinary tract infection in children. J Chemother. 2009;21:661–5.
2. Qiao LD, Chen S, Yang Y, Zhang K, Zheng B, Guo HF, et al. Characteristics of urinary tract infection pathogens and their in vitro susceptibility to antimicrobial agents in China: data from a multicenter study. BMJ Open. 2013;3:e004152.
3. Hertz FB, Schonning K, Rasmussen SC, Littauer P, Knudsen JD, Lobner-Olesen A, et al. Epidemiological factors associated with ESBL- and non ESBL-producing E. coli causing urinary tract infection in general practice. Infect Dis (Lond). 2016;48:241–5.
4. Guembe M, Cercenado E, Alcala L, Marin M, Insa R, Bouza E. Evolution of antimicrobial susceptibility patterns of aerobic and facultative gram-negative bacilli causing intra-abdominal infections: results from the SMART studies 2003–2007. Rev Esp Quimioter. 2008;21:166–73.
5. Stapleton AE. Urinary tract infection pathogenesis: host factors. Infect Dis Clin North Am. 2014;28:149–59.
6. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28:1–13.
7. Wellington EM, Boxall AB, Cross P, Feil EJ, Gaze WH, Hawkey PM, et al. The role of the natural environment in the emergence of antibiotic resistance in gram-negative bacteria. Lancet Infect Dis. 2013;13:155–65.
8. Caccamo M, Perilli M, Celenza G, Bonfiglio G, Tempera G, Amicosante G. Occurrence of extended spectrum beta-lactamases among isolates of Enterobacteriaceae from urinary tract infections in southern Italy. Microb Drug Resist. 2006;12:257–64.
9. Al Yousef SA, Younis S, Farrag E, Moussa H, Bayoumi FS, Ali AM. Clinical and laboratory profile of urinary tract infections associated with extended Spectrum beta-Lactamase producing Escherichia coli and Klebsiella pneumoniae. Ann Clin Lab Sci. 2016;46:393–400.
10. Bonkat G, Muller G, Braissant O, Frei R, Tschudin-Suter S, Rieken M, et al. Increasing prevalence of ciprofloxacin resistance in extended-spectrum-beta-lactamase-producing Escherichia coli urinary isolates. World J Urol. 2013;31:1427–32.
11. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE. In vitro susceptibilities of aerobic and facultative anaerobic Gram-negative bacilli from patients with intra-abdominal infections worldwide from 2005–2007: results from the SMART study. Int J Antimicrob Agents. 2009;34:585–8.
12. Institute CaLS. Method for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. 9th ed. Wayne: PA:CLSI document M7-A9; 2012.
13. Institute CaLS. Performance standards for antimicrobial susceptibility testing. Twenty-fifth informational supplement. Wayne: PA:Document M100-S25; 2015.
14. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. 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. 2011;52:e103–20.
15. Zhao L, Chen X, Zhu X, Yang W, Dong L, Xu X, et al. Prevalence of virulence factors and antimicrobial resistance of uropathogenic Escherichia coli in Jiangsu province (China). Urology. 2009;74:702–7.
16. Hope R, Potz NA, Warner M, Fagan EJ, Arnold E, Livermore DM. Efficacy of practised screening methods for detection of cephalosporin-resistant Enterobacteriaceae. J Antimicrob Chemother. 2007;59:110–3.
17. Guo W, He Q, Wang Z, Wei M, Yang Z, Du Y, et al. Influence of antimicrobial consumption on gram-negative bacteria in inpatients receiving antimicrobial resistance therapy from 2008–2013 at a tertiary hospital in Shanghai, China. Am J Infect Control. 2015;43:358–64.
18. Ding H, Yang Y, Wei J, Fan S, Yu S, Yao K, et al. Influencing the use of antibiotics in a Chinese pediatric intensive care unit. Pharm World Sci. 2008;30:787–93.
19. Zou YM, Ma Y, Liu JH, Shi J, Fan T, Shan YY, et al. Trends and correlation of antibacterial usage and bacterial resistance: time series analysis for antibacterial stewardship in a Chinese teaching hospital (2009–2013). Eur J Clin Microbiol Infect Dis. 2015;34:795–803.
20. Chanawong A, M'Zali FH, Heritage J, Xiong JH, Hawkey PM. Three cefotaximases, CTX-M-9, CTX-M-13, and CTX-M-14, among Enterobacteriaceae in the People's Republic of China. Antimicrob Agents Chemother. 2002;46:630–7.
21. Wang H, Kelkar S, Wu W, Chen M, Quinn JP. Clinical isolates of Enterobacteriaceae producing extended-spectrum beta-lactamases: prevalence of CTX-M-3 at a hospital in China. Antimicrob Agents Chemother. 2003;47:790–3.
22. Yang Q, Zhang H, Cheng J, Xu Z, Xu Y, Cao B, et al. In vitro activity of flomoxef and comparators against Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis producing extended-spectrum beta-lactamases in China. Int J Antimicrob Agents. 2015;45:485–90.
23. Hawkey PM. Prevalence and clonality of extended-spectrum beta-lactamases in Asia. Clin Microbiol Infect. 2008;14 Suppl 1:159–65.
24. Bush K. Extended-spectrum beta-lactamases in North America, 1987–2006. Clin Microbiol Infect. 2008;14 Suppl 1:134–43.
25. Wang H, Dzink-Fox JL, Chen M, Levy SB. Genetic characterization of highly fluoroquinolone-resistant clinical Escherichia coli strains from China: role of acrR mutations. Antimicrob Agents Chemother. 2001;45:1515–21.
26. Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin Infect Dis. 2009;49:682–90.
27. Livermore DM, Oakton KJ, Carter MW, Warner M. Activity of ertapenem (MK-0826) versus Enterobacteriaceae with potent beta-lactamases. Antimicrob Agents Chemother. 2001;45:2831–7.
28. Essack SY. Treatment options for extended-spectrum beta-lactamase-producers. FEMS Microbiol Lett. 2000;190:181–4.
29. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect. 2000;6:460–3.
30. Kaczmarek FM, Dib-Hajj F, Shang W, Gootz TD. High-level carbapenem resistance in a Klebsiella pneumoniae clinical isolate is due to the combination of bla(ACT-1) beta-lactamase production, porin OmpK35/36 insertional inactivation, and down-regulation of the phosphate transport porin phoe. Antimicrob Agents Chemother. 2006;50:3396–406.
31. Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, et al. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med. 2005;165:1430–5.
32. Vatopoulos A. High rates of metallo-beta-lactamase-producing Klebsiella pneumoniae in Greece–a review of the current evidence. Euro Surveill. 2008;13.
33. Maltezou HC, Giakkoupi P, Maragos A, Bolikas M, Raftopoulos V, Papahatzaki H, et al. Outbreak of infections due to KPC-2-producing Klebsiella pneumoniae in a hospital in Crete (Greece). J Infect. 2009;58:213–9.
34. Keller R, Pedroso MZ, Ritchmann R, Silva RM. Occurrence of virulence-associated properties in Enterobacter cloacae. Infect Immun. 1998;66:645–9.
35. Yang Q, Wang H, Sun H, Chen H, Xu Y, Chen M. Phenotypic and genotypic characterization of Enterobacteriaceae with decreased susceptibility to carbapenems: results from large hospital-based surveillance studies in China. Antimicrob Agents Chemother. 2010;54:573–7.
36. Han SB, Lee SC, Lee SY, Jeong DC, Kang JH. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae. BMC Infect Dis. 2015;15:414.