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High prevalence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in community-onset bloodstream infections in China

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Objectives: Community-onset bloodstream infections (COBSIs) caused by ESBL-producing *Escherichia coli* (ESBL-EC) and ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) are increasing globally. This study aimed to investigate the epidemiology and risk factors of ESBL-EC and ESBL-KP in COBSIs in China.

Methods: A prospective, multicentre study was performed in 28 tertiary hospitals from September 2013 to November 2014. All isolates and ESBLs were microbiologically characterized. A statistical analysis of risk factors was performed using binary logistic regression. The trial was registered with ClinicalTrials.gov (NCT01961206).

Results: A total of 919 consecutive episodes of COBSIs were reported and 640 *E. coli* and 279 *K. pneumoniae* isolates (non-duplicate) were collected. According to the criteria, 662 (72.0%) cases were classified as having community-acquired bloodstream infections, while the remaining 257 (28.0%) were classified as having healthcare-associated bloodstream infections. The proportions of ESBL producers were 55.5% (355/640) among *E. coli* isolates and 16.5% (46/279) among *K. pneumoniae* isolates, respectively. Healthcare-associated infections, obstructive urinary tract disease, previous surgical history and use of a cephalosporin antibiotic within 3 months were independent predictors of COBSIs caused by ESBL-EC. Heart failure was the only independent risk factor for COBSIs due to ESBL-KP. Age was not independently associated with infections caused by ESBL producers. CTX-M-14 was the most common ESBL genotype and was widespread throughout the country.

Conclusions: ESBL producers are highly prevalent in COBSIs in China, especially among cases caused by *E. coli*. For these resistant pathogens, clinicians should consider adequate empirical therapy, and different risk factors for prediction should be used in this country.

Introduction

Bloodstream infections (BSIs) are major causes of infectious disease worldwide and are associated with high morbidity and mortality.[1,2] Enterobacteriaceae, particularly *Escherichia coli* and *Klebsiella pneumoniae*, have been shown to be the predominant Gram-negative pathogens in community-onset BSIs (COBSIs).[1] BSIs caused by ESBL-producing *E. coli* (ESBL-EC) and ESBL-producing *K. pneumoniae* (ESBL-KP) are usually severe and have been associated with increased rates of treatment failure, high mortality and high hospitalization costs.[3] COBSIs caused by ESBL-EC and ESBL-KP have already raised public-health concerns and are gradually becoming a clinical challenge.[4]

In recent years, several studies have reported on the incidence of ESBL-positive bacteria in COBSIs: the incidence of ESBL-EC was 7.4% in Spain,[4] 9.5% in North Korea[5] and 21.4% in Israel.[6] In China, there has not thus far been a nationwide study about COBSIs caused by *E. coli* or *K. pneumoniae*. However, a high prevalence of ESBL-producing Enterobacteriaceae in faecal samples from healthy individuals from different provinces of China has recently been reported, with incidences ranging from 42.0% to 82.6%.[7–9] Recognizing the prevalence and risk factors of ESBL-associated infections in the community will help clinicians to judge whether or not the patients might be infected with ESBL-producing pathogens and to initiate appropriate therapies.[10,11]

Therefore, this study aimed to investigate the prevalence and genotype of ESBL-EC and ESBL-KP in COBSIs in China, as well as to evaluate the relevant risk factors.

Patients and methods

Study design and participants

This was a prospective, observational, multicentre study performed from September 2013 to November 2014. It included 28 tertiary hospitals of 22 provinces and municipalities located in seven geographical regions of China (Figure 1), which overall accounted for a population of about one billion. Given the lack of health insurance cover and the underdevelopment of Chinese primary medical care, patients usually prefer to attend tertiary teaching hospitals rather than community centres even for minor problems such as upper respiratory infections.[12] Thus, the vast majority of patients with BSIs would attend tertiary hospitals and then be enrolled in our study. The trial was registered with ClinicalTrials.gov (NCT01961206).

Only non-duplicate isolates of *E. coli* or *K. pneumoniae* from adult (aged ≥18 years) BSI outpatients or patients within the first 48 h following hospital admission were included.[4,5,13] Isolates were identified and stored by bacteriologists, while clinical data were collected by infectious disease clinicians; clinical data included age, sex, admission time, specimen collection time, causative microorganisms and risk factors, e.g. underlying diseases, previous surgical history, hospitalization within 3 months, antibiotic use within 3 months and indwelling catheter within 3 months. All the clinical data were collected by face-to-face interviews, using a questionnaire designed previously. Isolates and clinical data were all sent to the study's central laboratory (Sir Run Run Shaw Hospital) to be tested and analysed. The risk factors for COBSIs caused by ESBL-EC and ESBL-KP were studied using a case-control design. Only those cases with complete clinical data and confirmed isolates were included in the analysis.

Ethics

This study was approved by the local ethics committees of the participating hospitals (20130910-13) with a waiver of informed consent.

Definitions

COBSIs were further classified as community-acquired BSIs (CABSIs) or healthcare-associated BSIs (HCABSIs). The former was defined as a positive blood culture obtained within the first 48 h of hospitalization, with the following exclusion criteria: >48 h of hospital admission within 3 months, invasive catheters (including urinary catheter, peritoneal drainage tube, mechanical ventilation, etc.) within 3 months, receipt of haemodialysis or peritoneal dialysis, receipt of intravenous medication in the previous 30 days, and residence in a nursing home or long-term care facility. The other cases that occurred in the community were considered to be healthcare associated.[5]

Microbiological methods

Isolates were identified using the automated Vitek 2 system (bioMérieux, France). The ESBL phenotypic confirmation test was performed using the double-disc dilution method in accordance with CLSI performance standards.[14] The ESBL-encoding genes were identified by PCR (using primers shown in Table S1, available as Supplementary data at *JAC* Online).[15] PCR products were validated by DNA sequencing (Biosune, Shanghai).

ESBL-producing isolates were also analysed by MLST. Databases were available at http://mlst.warwick.ac.uk/mlst/dbs/Ecoli and http://bigsdb.web.pasteur.fr/klebsiella.

Antibiotic susceptibility testing (AST)

AST was performed using the MIC-based methods according to CLSI guidelines.[14] The same AST protocol was performed for all the isolates in the central laboratory (Sir Run Run Shaw Hospital). The MIC breakpoint of cefoperazone for Enterobacteriaceae was used to determine cefoperazone/sulbactam susceptibility according to Jones *et al.*[16] Standard strains *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as quality controls.

Statistical analysis

Descriptive data were reported as the mean ± SD, median (IQR) or number and percentage. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the independent sample *t*-test for normally distributed data. Multivariate analysis was performed using binary logistic regression. Variables introduced into the multivariate analysis included those with a crude *P* value of <0.1. ORs and the associated 95% CIs were calculated. All *P* values were two-tailed and a *P* value of <0.05 was considered statistically significant. All data were analysed using SPSS v. 21.0 software (IBM Corporation).

Results

During the study period, 1023 consecutive, non-duplicate episodes of community-onset bacteraemia caused by *E. coli* (721) or *K. pneumoniae* (302) occurred. The overall proportions of ESBL-producing *E. coli* and *K. pneumoniae* were 56.7% (409/721) and 16.2% (49/302), respectively. One hundred and four cases were excluded because of incomplete clinical data; thus, 919 cases (640 caused by *E. coli* and 279 caused by *K. pneumoniae*) were included in this study, with the prevalence of ESBL-EC and ESBL-KP being 55.5% (355/640) and 16.7% (46/279), respectively.

Clinical features and risk factors

According to the criteria mentioned previously, 662 (72.0%) cases were classified as having CABSIs (463 cases caused by *E. coli* and 199 cases caused by *K. pneumoniae*), while the remaining 257 (28.0%) were classified as having HCABSIs. The mean age of the 919 patients was 60 ± 16 years with a range of 18–96 years and 51.6% (474/919) of the patients were males. A total of 87.3% (802/919) of the patients had one or more underlying diseases or comorbidities, among which diabetes mellitus was most common. Furthermore, 94 (10.2%) patients had previously undergone surgery. Almost one-third (276/919) of the patients had a history of antibiotic use within the last 3 months. Among patients with HCABSIs, 197 (76.7%) had undergone hospitalization for 2 or more days once during the previous 3 months, while 39 (15.2%) patients had undergone hospitalization two or more times. There were also 80 (31.1%) patients who had received indwelling catheters (Table 1).

The overall proportion of ESBL-producing strains was 55.5% (355/640) among the 640 patients with community-onset *E. coli* bacteraemia. Of the 463 patients with community-acquired infections caused by *E. coli*, 236 (51.0%) were infected with ESBL producers, while 119 (67.2%) of the 177 patients with healthcare-associated infection were infected with ESBL producers ($P < 0.001$). Univariate analyses of risk factors for COBSIs caused by ESBL-EC identified significant association with age,

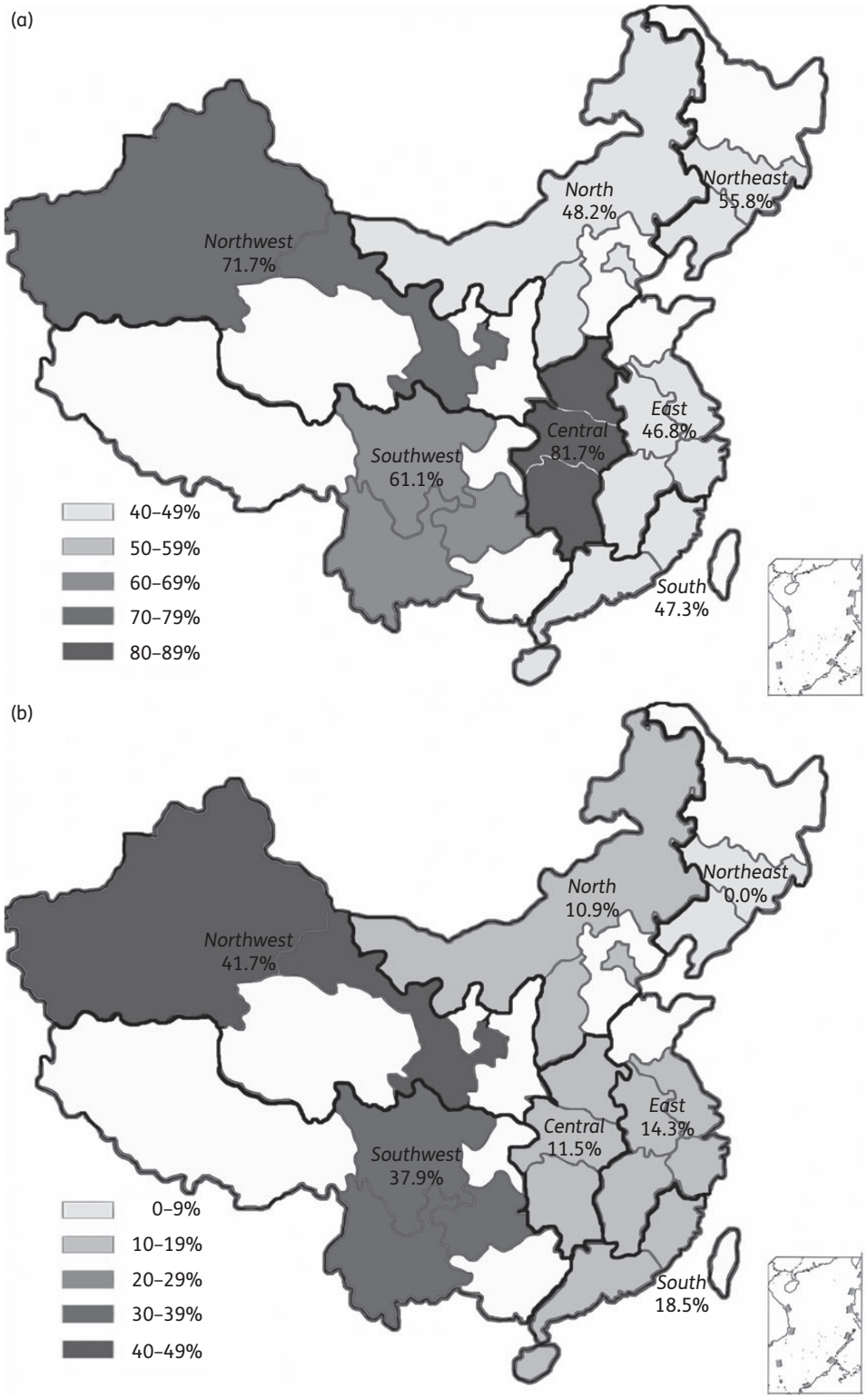

Figure 1. Percentage of ESBL-EC (a) and ESBL-KP (b) causing COBSIs in seven geographical regions of China. The blank spaces indicate that no isolate was collected in the study.

healthcare-associated infections, obstructive urinary tract disease, malignancy, previous surgical history and use of cephalosporins in the preceding 3 months (Table 1). In the multivariate analysis, healthcare-associated infections (OR=1.572, 95% CI=1.062–2.326, P=0.024), obstructive urinary tract disease (OR=1.874, 95% CI=1.126–3.118, P=0.016), previous surgical

Table 1. Univariate analyses of risk factors for ESBL-EC and ESBL-KP causing COBSIs

Risk factor	ESBL-EC, $n=355$	non-ESBL-EC, $n=285$	OR (95% CI)	P	ESBL-KP, $n=46$	non-ESBL-KP, $n=233$	OR (95% CI)	P
Age (years), mean ± SD	59.31 ± 17.11	61.66 ± 16.16	0.992 (0.982–1.001)	0.078	59.63 ± 14.86	60.59 ± 15.84	0.996 (0.976–1.016)	0.703
18–44	70 (19.7)	46 (16.1)			8 (17.4)	32 (13.7)		
45–64	142 (40.0)	98 (34.4)	1.500 (0.968–2.327)	0.070	21 (45.7)	109 (46.8)	1.353 (0.533–3.435)	0.525
≥65	143 (40.3)	141 (49.5)	1.429 (1.010–2.021)	0.044	17 (37.0)	92 (39.5)	1.043 (0.519–2.093)	0.907
Male	172 (48.5)	124 (43.5)	1.22 (0.892–1.669)	0.213	26 (56.5)	152 (65.2)	0.693 (0.364–1.317)	0.261
Healthcare-associated infections	119 (33.5)	58 (20.4)	1.973 (1.373–2.837)	<0.001	22 (47.8)	58 (24.9)	2.766 (1.443–5.299)	0.002
Community-acquired infections	236 (66.5)	227 (79.6)	0.507 (0.352–0.728)	<0.001	24 (52.2)	175 (75.1)	0.362 (0.189–0.693)	0.002
Underlying diseases or comorbidity conditions	310 (87.3)	244 (85.6)			42 (91.3)	206 (88.4)		
diabetes mellitus	104 (29.3)	74 (26.0)	1.181 (0.833–1.676)	0.350	17 (37.0)	92 (39.5)	0.898 (0.467–1.727)	0.748
autoimmune disease	27 (7.6)	10 (3.5)	2.264 (1.077–4.759)	0.027	4 (8.7)	7 (3.0)	3.075 (0.862–10.969)	0.070
benign prostatic hyperplasia	20 (5.6)	15 (5.3)	1.075 (0.540–2.139)	0.838	4 (8.7)	10 (4.3)	2.124 (0.636–7.090)	0.211
obstructive urinary tract disease	56 (15.8)	26 (9.1)	1.866 (1.138–3.058)	0.012	4 (8.7)	14 (6.0)	1.490 (0.467–4.749)	0.498
obstructive biliary tract disease	69 (19.4)	62 (21.8)	0.868 (0.590–1.275)	0.470	11 (23.9)	58 (24.9)	0.948 (0.453–1.987)	0.888
liver cirrhosis	15 (4.2)	16 (5.6)	0.742 (0.360–1.527)	0.416	2 (4.3)	17 (7.3)	0.578 (0.129–2.590)	0.468
COPD	32 (9.0)	22 (7.7)	1.184 (0.672–2.087)	0.558	6 (13.0)	10 (4.3)	3.345 (1.151–9.719)	0.020
chronic renal failure	33 (9.3)	18 (6.3)	1.52 (0.837–2.761)	0.166	2 (4.3)	16 (6.9)	0.616 (0.137–2.777)	0.525
heart failure	16 (4.5)	10 (3.5)	1.298 (0.580–2.906)	0.525	6 (13.0)	6 (2.6)	5.675 (1.743–18.477)	0.001
malignancy	48 (13.5)	24 (8.4)	1.700 (1.014–2.852)	0.042	7 (15.2)	21 (9.0)	1.812 (0.721–4.552)	0.201
surgery	53 (14.9)	22 (7.7)	2.098 (1.243–3.542)	0.005	3 (6.5)	16 (6.9)	0.946 (0.264–3.389)	0.932
Prior antibiotic use within 3 months	137 (38.6)	64 (22.5)			20 (43.5)	55 (23.6)		
penicillin	14 (3.9)	8 (2.8)	1.422 (0.588–3.438)	0.433	0 (0.0)	10 (4.3)		0.152
cephalosporin	52 (14.6)	12 (4.2)	3.904 (2.041–7.469)	<0.001	9 (19.6)	27 (11.6)	1.856 (0.808–4.263)	0.140
fluoroquinolone	17 (4.8)	11 (3.9)	1.253 (0.577–2.719)	0.568	5 (10.9)	6 (2.6)	4.614 (1.345–15.825)	0.008
macrolide	5 (1.4)	1 (0.4)	4.057 (0.471–34.925)	0.168	1 (2.2)	4 (1.7)	1.272 (0.139–11.649)	0.831
aminoglycoside	4 (1.1)	3 (1.1)	1.071 (0.238–4.826)	0.929	2 (4.3)	1 (0.4)	10.545 (0.936–118.829)	0.019
carbapenem	2 (0.6)	4 (1.4)	0.398 (0.072–2.189)	0.273	3 (6.5)	3 (1.3)	5.349 (1.045–27.385)	0.025
other antibiotics[a]	7 (2.0)	7 (2.5)			5 (10.9)	8 (3.4)		
not clear[b]	63 (17.7)	32 (11.2)			8 (17.4)	15 (6.4)		

[a]Aztreonam, ornidazole, metronidazole, voriconazole, clindamycin, moxalactam, teicoplanin, tinidazole, vancomycin, etc.
[b]Those who had used antibiotics, but could not report which ones.

Table 2. Multivariate analyses of risk factors for ESBL-EC and ESBL-KP causing COBSIs

Risk factor	OR	95% CI lower	95% CI upper	*P*
E. coli				
age (years)				
18–44				0.08
45–64	1.555	0.987	2.452	0.057
≥65	1.392	0.97	1.998	0.072
healthcare-associated infections	1.572	1.062	2.326	0.024
underlying diseases or comorbidity conditions				
obstructive urinary tract disease	1.874	1.126	3.118	0.016
malignancy	1.366	0.776	2.406	0.280
surgery	1.776	1.012	3.117	0.045
prior antibiotic use within 3 months				
cephalosporin	3.223	1.629	6.376	0.001
K. pneumoniae				
healthcare-associated infections	1.832	0.881	3.81	0.105
underlying diseases or comorbidity conditions				
autoimmune diseases	1.664	0.379	7.306	0.500
COPD	1.684	0.491	5.774	0.407
heart failure	4.076	1.077	15.43	0.039
prior antibiotic use within 3 months				
fluoroquinolone	2.374	0.548	10.29	0.248
aminoglycoside	2.842	0.076	106.864	0.572
carbapenem	1.53	0.119	19.685	0.744

history (OR=1.776, 95% CI=1.012–3.117, *P*=0.045) and use of a cephalosporin antibiotic within 3 months (OR=3.223, 95% CI=1.629–6.376, *P*=0.001) were independent predictors of COBSIs caused by ESBL-EC (Table 2).

Among the 279 patients with community-onset *K. pneumoniae* bacteraemia, the overall number of ESBL-producing strains was only 46 (16.5%). Of the 199 patients with community-acquired infection caused by *K. pneumoniae*, 24 (12.1%) were infected with ESBL producers, while 22 (27.5%) of the 80 patients with healthcare-associated infection were infected with ESBL producers (*P*<0.001). The following risk factors for COBSIs caused by ESBL-KP were detected by univariate analysis: healthcare-associated infections, autoimmune diseases, chronic obstructive pulmonary disease, heart failure and use of a fluoroquinolone or aminoglycoside or carbapenem antibiotic within the preceding 3 months (Table 1). In the multivariate analysis, heart failure (OR=4.076, 95% CI=1.077–15.43, *P*=0.039) was the only independent risk factor of COBSIs caused by ESBL-KP (Table 2).

The prevalence of ESBLs varied dramatically between different geographical regions, ranging from 81.7% in central China to 46.8% in east China (Figure 1a) for *E. coli* and from 47.1% in northwest China to 0% in northeast China for *K. pneumoniae* (Figure 1b).

Microbiological characteristics

CTX-M alleles accounted for 98.8% (396/401) of ESBL-producing isolates, with the CTX-M-9 being the most predominant cluster (Table S2). Twenty-eight ESBL-EC produced two CTX-M alleles and five isolates were confirmed to have novel CTX-M alleles (Table S3). Thirteen ESBL-KP isolates produced two EBSLs and one isolate produced three ESBLs (SHV plus two CTX-M alleles).

The ESBL gene distributions varied among the seven regions of China. CTX-M-14 and CTX-M-15 were predominant in most regions, while in east China and northeast China, the prevalence of CTX-M-55 exceeded that of CTX-M-15. CTX-M-27 was commonly encountered in southwest China and east China, but was absent in other regions (Figure 2).

MLST analyses revealed significant genetic diversity among ESBL-EC and ESBL-KP. All the ESBL-EC could be grouped in 80 different STs, 17 of which represented new types. The most prevalent ST was ST131 (20.8%, 74/355), followed by ST38 (11.8%, 42/355) and ST1193 (5.1%, 18/355) (Figure S1a). Similarly, the 46 ESBL-KP could be grouped in 32 different STs; one ESBL-KP isolate was untyped since the *infB* allele could not be amplified (Figure S1b).

AST

A high incidence of resistance was observed in ESBL-EC isolates against the antimicrobials ceftazidime (63.7%), cefotaxime (96.9%), cefepime (92.7%), cefoxitin (23.9%), levofloxacin (69.6%), ciprofloxacin (68.1%) and trimethoprim/sulfamethoxazole (67.9%) (Table S4). ESBL-KP isolates showed similar resistance rates against ceftazidime (58.7%), cefotaxime (93.5%), cefepime (87%) and trimethoprim/sulfamethoxazole (69.6%), but were less frequently resistant to levofloxacin (34.8%) and ciprofloxacin (39.1%). ESBL-KP isolates were significantly more frequently resistant than ESBL-EC isolates to nitrofurantoin (39.1% versus 1.7%).

As expected, the most active antimicrobials against both ESBL-EC and ESBL-KP were the carbapenems. Only one ESBL-EC isolate was resistant to imipenem and meropenem, while two ESBL-EC isolates and one ESBL-KP isolate were resistant to ertapenem. For piperacillin/tazobactam and cefoperazone/sulbactam, the incidence of resistance appeared to be low, with 71.7%–93.5% of the isolates susceptible. In addition, several other antibiotic agents, namely moxalactam, amikacin and fosfomycin, also showed good *in vitro* activity (>90% susceptibility) against both ESBL-EC and ESBL-KP isolates.

Discussion

In this study, the overall proportion of ESBL-producing isolates among cases of community-onset *E. coli* and *K. pneumoniae* bacteraemia in China was significantly higher than previous studies reported for any other countries, notably Spain, South Korea, Israel and some African countries (with reported percentages ranging from 1.3% to 21.4%).[4–6,17] For community-acquired infections caused by *E. coli*, the proportion of ESBL producers was still >50%, suggesting that ESBL producers have disseminated throughout China.

Recently, a study revealed that the widespread prevalence of ESBL-producing bacterial isolates among outpatient community-onset infections had reached a high level (46.5%, 256/550) in county hospitals in China.[18] Coincidentally, the faecal carriage rates of ESBL-producing Enterobacteriaceae in healthy persons are also extremely high in China. For instance, data from 18 villages in three counties of Shandong province revealed a high faecal

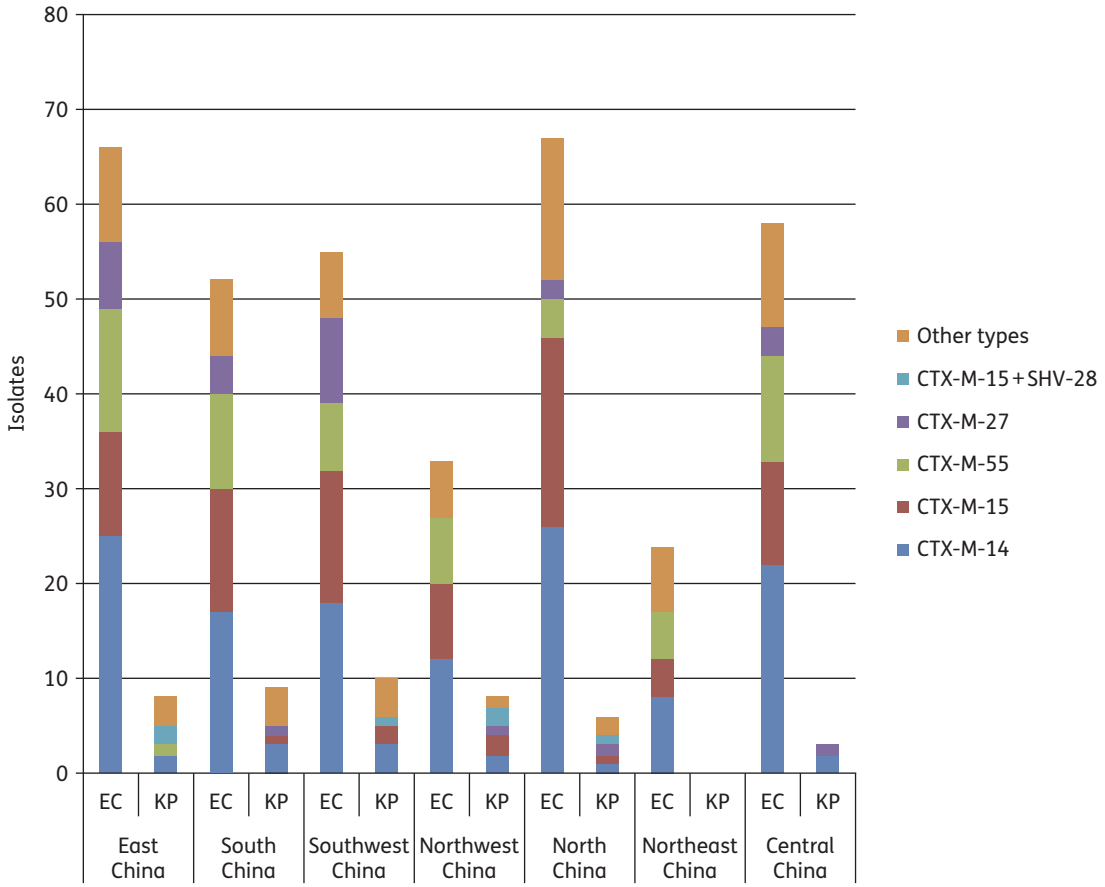

Figure 2. Distribution of ESBL genotypes in seven geographical regions of China.

carriage rate of ESBL-producing *E. coli* in rural areas (41.8%, 418/1000) in 2014.[7] Another study showed that the faeces of 51.0% (287/563) of healthy individuals contained ESBL-producing *E. coli* in Hunan province.[8] A surprisingly high faecal carriage rate of ESBL-producing *E. coli* of 82.6% (512/620) was also recently reported in Taian, a large city in Shandong province.[9] These high ESBL carriage rates are thought to contribute to the high prevalence of community-onset infections caused by ESBL-producing Enterobacteriaceae.[19]

There are two possible explanations for this considerably high prevalence of ESBL-producing bacteria in Chinese communities. In contrast to developed countries where policies are implemented to restrict antibiotic use, antibiotic overuse or misuse is still universal in China, particularly in rural areas. The use of antibiotics is higher in China than in developed countries such as the USA and Sweden.[20] Our results also displayed higher proportions of ESBL-EC in southwest, northwest and central China, which are all relatively underdeveloped areas. One possible explanation for this is that the inappropriate use of antimicrobials is more serious in the less developed regions of China, since people living in impoverished regions have a stronger need for antimicrobial therapy and poverty can encourage shorter courses of treatment, or use of lower quality drugs.[21–23] On the other hand, awareness of the problems related to antibiotic resistance is low among the general public. Before 2011, antibiotics were considered as 'magic drugs' and freely available in China, either over the counter or online, leading to the habit of self-medication.[22] Although the situation appears to have improved after 2011, drug overprescription is still higher in China and antibiotic-resistant bacteria are still circulating at high levels.[24]

Another explanation for the high incidence of ESBL-producing bacteria in Chinese communities is that the incidence of these bacteria is also high in animals, including pets and livestock, ranging from 27.4% to 50.2%.[25–28] The use of antimicrobial agents for growth promotion, disease prevention and therapeutic purposes in animal husbandry may lead to the emergence of antimicrobial-resistant bacteria through natural selection.[29] Resistant bacteria of animal origin can be transmitted to humans through the environment, food products or by direct contact with livestock.[23,29]

Given the high prevalence of ESBL-producing bacteria among COBSIs and the increased mortality associated with infection by ESBL-producing bacteria, it is important to identify the relevant risk factors to help guide appropriate initial therapies.[30] Our study found, similar to prior studies,[4,5,31] that the independent risk factors for ESBL-EC were the presence of an obstructive urinary tract disease, surgical history and use of a cephalosporin antibiotic within the preceding 3 months. In contrast, for ESBL-KP-associated COBSIs, the only independent risk factor identified in our study was underlying heart failure, which may be associated with repeated hospital exposure and poor health status of patients.[32,33] Intriguingly, our study showed that the incidence of ESBL-

producing Enterobacteriaceae is similar between different age groups, ~50% for *E. coli* and ~15% for *K. pneumoniae* in all the included age groups. Old age is considered to be closely associated with ESBL-producing bacterial infection in Western countries.[30,34,35] However, age is not independently associated with bacteraemia caused by ESBL producers in China, which may be due to high prevalence of ESBLs in healthy persons and livestock there. Therefore, we conclude that the risk factors of ESBL-producing Enterobacteriaceae infection in Western countries are not applicable to China.

Our study also demonstrated that CTX-M was the most prevalent ESBL genotype in China, with a positive rate of 98.8%. Among CTX-M-type ESBLs, CTX-M-14 was the most common type. This type was found to be widespread throughout the country and accounted for 42.4% of all isolates. We also found that CTX-M-27, a member of the CTX-M-9 cluster, was spreading in east and southwest China. A recent study reported that CTX-M-27 accounted for 26.8% (11/41) of 41 ESBL-producing strains isolated from diseased farm pigeons in Guangzhou.[36] Similar results were found for ducks in south China[26] and in birds in Guangdong province.[27] These data indicated that birds may have been a source of CTX-M-27, contributing to the prevalence of this ESBL gene. Among ESBL-EC, ST131 was the most common sequence type, and this is now the predominant *E. coli* lineage among extra-intestinal pathogenic *E. coli* isolates worldwide. The success of this clone can be attributed to its virulence and adaptation to humans, leading to a worldwide increase in ESBL-producing *E. coli* isolates in both in the community and in healthcare facilities.[37]

As expected, third/fourth-generation cephalosporins, fluoroquinolones and trimethoprim/sulfamethoxazole showed poor activities against the ESBL-producing isolates in our study, indicating that these antibiotics are not ideal choices for empirical therapy against COBSIs in China.[38] Meanwhile, moxalactam, amikacin and fosfomycin retained high *in vitro* activity against both ESBL-EC and ESBL-KP, which could be considered as alternatives for the treatment of COBSIs caused by ESBL producers.

Our study also has some limitations. Although this study was performed nationwide, some provinces or municipalities were not included. Furthermore, as we aimed to delineate the prevalence, risk factors, and molecular epidemiology of community-onset *E. coli* and *K. pneumoniae* bacteraemia due to ESBL producers, no investigation of the treatment, outcomes and source of BSIs was conducted in this study. Finally, there were no available data on the nationwide epidemiology of ESBL carriage in healthy people and animals, which we are planning to investigate in further studies.

Conclusions

ESBLs are highly prevalent in COBSIs in China, particularly ESBL-producing *E. coli*. If we do not address these issues, during the next decade the medical community may be forced, as predicted, to use carbapenems as the first choice for the empirical treatment of serious infections that originate in the community.[11] Our study also implies a strong need for a 'One Health' approach requiring research, surveillance and interventions across human, animals and livestock to fight the spread of these resistant pathogens.

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Transparency declarations

None to declare.

Supplementary data

Tables S1–S4 and Figure S1 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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