

Time to Awaken a Forgotten Antibacterial Agent: A 10-year Nationwide Surveillance of Latamoxef Resistance in China Based on 46,716 Isolates and Establishment of Tentative Epidemiological Cut-Off Values

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Purpose: Latamoxef has been used to treat various bacterial infections. To provide data supporting the rational clinical use of latamoxef, bacterial resistance over 10 years was analyzed at multiple centers throughout China. The results were used to develop tentative epidemiological cut-off values (TECOFFs) for latamoxef.

Methods: A total of 46,716 strains of common *Enterobacteriaceae* were collected from patients with bloodstream infections at 72 hospitals in 21 provinces of China between 2014 and 2023. The in vitro antimicrobial activities of latamoxef were compared with those of other commonly used cephalosporin and carbapenem. The distribution of minimum inhibitory concentrations was subjected to cumulative log-normal fitting to obtain the TECOFFs of latamoxef for common *Enterobacteriaceae*.

Results: The sensitivities of *Escherichia coli* (*E. coli*), *Salmonella* species, *Serratia marcescens* (*S. marcescens*) and *Proteus mirabilis* (*P. mirabilis*) to latamoxef ranged from 94.37% to 98.08%. *Klebsiella oxytoca* (*K. oxytoca*) and *Enterobacter aerogenes* (*E. aerogenes*) had sensitivities of 89.91% and 87.21%, respectively, whereas *Klebsiella pneumoniae* (*K. pneumoniae*) and *Enterobacter cloacae* (*E. cloacae*) had lower sensitivities. The in vitro activity of latamoxef against these bacteria, especially extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae*, was similar to the activities of ertapenem and meropenem and significantly higher than the activities of ceftriaxone, ceftazidime, and cefepime. The sensitivities of ESBL (+) *E. coli* and ESBL (+) *P. mirabilis* to latamoxef were similar to their sensitivities to ertapenem and meropenem. ESBL (+) *K. pneumoniae* and ESBL (+) *K. oxytoca* exhibited comparable but lower rates of sensitization to latamoxef, ertapenem, and meropenem. Latamoxef had TECOFFs of 2 μ g/mL for *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *E. aerogenes*, *Salmonella*, and *S. marcescens*, and 4 μ g/mL for *E. cloacae*.

Conclusion: Latamoxef has good and stable in vitro antimicrobial activity against *Enterobacteriaceae*, including ESBL-producing *Enterobacteriaceae*. The calculated TECOFFs of latamoxef provide an important reference for subsequent use of this antibiotic against *Enterobacteriaceae*.

Keywords: latamoxef, moxalactam, antimicrobial resistance, surveillance, epidemiological cut-off values

Introduction

Antimicrobial resistance (AMR) is a major global public health problem. It has been estimated that more than 1 million people worldwide died of AMR annually between 1990 and 2021, with AMR-related deaths being the third leading cause of death worldwide after ischemic heart disease and stroke.¹ The development of new antimicrobial agents effective against AMR has lagged, however, with the rate of approval of new antibiotics being 90% lower after than before 1970.² The World Health Organization (WHO) published a *Bacterial Priority Pathogens List* in 2017 to increase funding for antibiotic development.³ However, strains of *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* have been found to be resistant to 13 antibiotics introduced after 2017 or are currently in development, indicating the rapid development of bacterial resistance in antibiotic-exposed environments.⁴ At present, the creation of a more viable ecosystem for the judicious use of currently available antibiotics may be more feasible and effective than the development of additional novel antibiotics. For example, repurposing forgotten antibiotics may be effective and worthwhile in alleviating the healthcare pressures of AMR.

Flomoxef produced clinical cure and satisfactory microbiological responses in 85.7% and 100% of patients, respectively. These results were similar to those obtained with latamoxef (87% and 100%, respectively).⁵

Latamoxef (moxalactam) is a semi-synthetic, broad-spectrum, oxazolidinone- β -lactam antibiotic that exhibits broad-spectrum activity against both Gram-positive and Gram-negative bacteria. Latamoxef also exhibits antibacterial activity against anaerobic bacteria, such as *Bacteroides fragilis*, *Fusobacterium nucleatum*, and *Clostridium perfringens*, with minimum inhibitory concentrations (MIC) typically ranging from 2 to 16 $\mu\text{g/mL}$.^{6,7} Latamoxef is effective in the treatment of a wide range of infections, including urinary tract infections, pneumonia, gynecologic and obstetric infections, skin and soft-tissue infections, osteomyelitis, bacteremia, peritonitis, and many others.⁷ For critically ill patients admitted to the intensive care unit with infections, latamoxef achieves an 80% clinical cure rate.⁸ Among neonates, 96.77% (30/31) showed improvement following latamoxef therapy, and all renal, liver, and coagulation tests showed normal results.⁹

Like other β -lactam antibiotics, latamoxef binds to transpeptidase and D-alanine carboxypeptidase, inhibiting the cross-linking process in cell wall peptidoglycan biosynthesis.⁷ Structurally, the sulfur atom at the 1 position of the cephem nucleus is replaced in latamoxef by an oxygen atom. Moreover, the α -carboxyl group of its phenyl malonyl side chain and its 7- α -methoxy group have been found to contribute to the resistance of latamoxef to hydrolysis by β -lactamases and carbapenemases, respectively.^{10,11}

The primary reasons limiting the clinical use of latamoxef are its potential to induce coagulation disorders and bleeding risks.^{12–14} Furthermore, the lack of clinical studies and breakpoint assessments also contributes to the fact that latamoxef has not yet been approved for clinical use in the United States and some European countries. By contrast, latamoxef is still utilized to treat patients in Korea, Japan, and numerous developing countries in the Western Pacific region, including China.^{13,15,16} Currently, the main international organizations that develop breakpoints for antibiotics are the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI), whose breakpoints are widely used around the world to guide clinical therapy. To date, however, EUCAST has not proposed breakpoints for latamoxef. Although the CLSI has reported that *Enterobacteriaceae* have resistance breakpoints of ≥ 64 and susceptibility breakpoints of ≤ 8 for latamoxef, these breakpoints have not been evaluated by the CLSI for a long period of time because of the difficulty of obtaining latamoxef in many countries. In addition, the CLSI suggests the need for extended-spectrum β -lactamase (ESBL) testing if latamoxef is being considered for treatment of patients infected with *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca* (*K. oxytoca*), or *Proteus spp.*, with isolates that test as ESBL positive be reported as resistant. These guidelines, however, do not fully align with the established antimicrobial activity of latamoxef.

Enterobacteriaceae are the most common pathogens in clinical infections and are under tremendous selective environmental antibiotic pressure. Currently, many facilities report that 45% and 35% of patients infected with *K. pneumoniae* and *E. coli*, respectively, are ESBL (+).¹⁷ ESBL-producing *Enterobacteriaceae* have been identified by the WHO as a critical group of antibiotic-resistant bacteria that need to be prioritized for resolution. A multicenter study on *Enterobacteriaceae* from 2013 to 2014 reported that the susceptibility rates to latamoxef of ESBL-producing *E. coli*,

K. pneumoniae, and *Proteus mirabilis* (*P. mirabilis*) were 98.0%, 90.0%, and 94.1%, respectively.⁶ Latamoxef has definite antimicrobial activity against ESBL-producing bacteria and is used in Asian countries for the treatment of serious infections caused by multidrug-resistant *Enterobacteriaceae*,¹⁸ and as an alternative drug for the clinical treatment of *Enterobacteriaceae*. Therefore, it is inaccurate to report that all ESBL (+) *Enterobacteriaceae* strains are resistant to latamoxef.

The ambiguity surrounding the breakpoints of latamoxef affects the assessment and monitoring of latamoxef resistance. This ambiguity also affects the ability of clinicians to accurately gauge pathogen susceptibility to latamoxef, which may result in inappropriate dosing, poor therapeutic efficacy, or antibiotic abuse. Breakpoints are used to define the susceptibility and resistance of a strain to an antibiotic. Application of the recommended dose to the site of infection can yield an antibiotic concentration that inhibits susceptible strains. Because wild-type isolates of a species show a range of values in MIC assays, EUCAST proposed that ECOFF be defined as the highest MIC (X mg/L) of an antimicrobial agent for microbial species devoid of phenotypically detectable acquired resistance mechanisms. Therefore, ECOFF can be considered the most sensitive phenotypic measure for ruling out drug resistance and is the basis for the laboratory detection of acquired resistance and monitoring of resistance development. ECOFF distinguishes between wild-type and non-wild-type strains of a bacterial population and is important for establishing clinical breakpoints and monitoring stable bacterial resistance.¹⁹

Bloodstream infections are a leading cause of AMR-related deaths worldwide, second only to lower respiratory tract and chest infections.¹ To determine variations in latamoxef resistance and appropriate breakpoints, a multicenter epidemiological survey covering 72 hospitals in 21 provinces in China was performed. This survey enabled determination of the distribution of *Enterobacteriaceae* resistant to latamoxef and its trends, as well as the development of tentative epidemiological cut-off values (TECOFF) of latamoxef against *Enterobacteriaceae*. These results provide an important reference for formulating or updating or latamoxef breakpoints.

Materials and Methods

Collection of Strains

A total of 46,716 strains of common *Enterobacteriaceae*, including *E. coli* (n=28130), *K. pneumoniae* (n=13570), *Enterobacter cloacae* (*E. cloacae*) (n=1895), *Salmonella* (n=782), *Serratia marcescens* (*S. marcescens*) (n=693), *Enterobacter aerogenes* (*E. aerogenes*) (n=563), *P. mirabilis* (n=548), and *K. oxytoca* (n=535), were collected from patients with bloodstream infections (BSI) at 72 hospitals in 21 provinces of China from January 2014 to December 2023. The vast majority of patients are adults, with a small number being children. This study collected strains isolated from the first blood samples of patients after admission. If the patient was readmitted after discharge and strains were cultured from their blood, the strains isolated at the time of the subsequent admission were also included in the study. The strains were identified by MALDI-TOF MS.²⁰

Antibiotic Susceptibility Testing

The MIC of these 46,716 strains against latamoxef, ceftriaxone, ceftazidime, cefepime, ertapenem, and meropenem were determined by the agar dilution method, as recommended by the CLSI.²¹ The agar dilution method uses Mueller–Hinton agar. Read results after 16–20 hours of incubation in a 37°C incubator. When interpreting endpoints, place plates on a non-reflective surface and record the MIC that completely inhibits bacterial growth. *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains in all experiments. Antibiotic susceptibility testing is conducted annually on strains collected during the previous year.

ESBL Testing

ESBL tests of *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *K. oxytoca* strains were performed using the disk diffusion method, as recommended by the CLSI.²¹ ESBL tests utilise four types of disk: ceftazidime (30µg), ceftazidime-clavulanate (30µg/10µg), cefotaxime (30µg) and cefotaxime-clavulanate (30µg/10µg). The disk diffusion method uses Mueller–Hinton agar. After incubation at 37°C for 16–20 hours, the results are read. If the diameter of the inhibition zone

for either ceftazidime or cefotaxime increases by ≥ 5 mm after adding clavulanate compared to the inhibition zone without clavulanate, the strain is classified as an ESBL-producing strain. *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as quality control strains in all experiments.

Data Analysis

Bacterial susceptibility was analyzed in accordance with CLSI guidelines.²¹ A strain was judged to be a carbapenem-resistant *Enterobacteriaceae* (CRE) if it was resistant to ertapenem and/or meropenem. The susceptibility profiles of all strains, including ESBL (+) and CRE strains, to the antibiotics tested were analyzed, whereas the susceptibility profiles of ESBL (+) strains to these antibiotics tested included only ESBL (+), while excluding CRE strains.

The susceptibility rates of eight *Enterobacteriaceae* species, ESBL (+) *Enterobacteriaceae* and ESBL (-) *Enterobacteriaceae* to latamoxef over a 10-year period were analyzed for trends using Spearman's rank correlation, a non-parametric method that evaluates whether there was a significant trend in the susceptibility rates over time. The Spearman correlation coefficient (ρ) was then computed, with a two-tailed P-value less than 0.05 considered statistically significant. The trends in the proportion of eight *Enterobacteriaceae* species, ESBL (+) *Enterobacteriaceae*, and ESBL (-) *Enterobacteriaceae* within the total population over time were also analyzed using the aforementioned method.

Differences in susceptibility rates between ESBL-positive and ESBL-negative isolates were compared using the chi-square test (χ^2 -test). A two-tailed P value < 0.05 was considered statistically significant.

Graphs and data analysis were performed using GraphPad Prism 9.0 (<https://www.graphpad.com/>)²² and R 4.4.3 (<https://www.R-project.org/>).²³

ECOFF Determination

The ECOFFs of latamoxef against *Enterobacteriaceae*, including ESBL (+) and CRE strains, were determined using ECOFFinder 2.1¹⁹ (<https://clsi.org/resources/ECOFFinder/>). The MIC distribution data and the number of strains of each bacterial species were entered into the software, with the actual MIC distribution data fit to a cumulative log-normal distribution using an iterative statistical curve-fitting method based on the cumulative log-normal distribution. The ECOFF was determined by the best fit of the cumulative log-normal curve. ECOFFs were also set using two complementary approaches, statistical and visual ECOFFs. Visual ECOFFs were determined by observing the upper limit of the MIC distribution of the wild-type strain. When the statistical and visual approaches agreed, the ECOFF was considered to be set. If the discrepancy between the visual and statistical approaches was greater than one two-fold dilution, an ECOFF was not set, with additional MIC distributions required to strengthen the dataset.²⁴

Results

Types and Distribution of Strains

Of the 46,716 strains of eight common *Enterobacteriaceae* identified in blood culture-positive samples from 72 hospitals in 21 provinces of China between 2014 and 2023, *E. coli* was the most common (28130/46,716, 60.21%), followed by *K. pneumoniae* (13570/46,716, 29.05%), *E. cloacae* (1895/46,716, 4.06%), *Salmonella* (782/46,716, 1.67%), *S. marcescens* (693/46,716, 1.48%), *E. aerogenes* (563/46,716, 1.21%), *P. mirabilis* (548/46,716, 1.17%), and *K. oxytoca* (535/46,716, 1.15%). *E. coli* was the most common *Enterobacteriaceae* isolated from BSI in 20 provinces (Figure 1), whereas *K. pneumoniae* (40.07%) was more common than *E. coli* (36.82%) in Liaoning province.

During the 10-year study period, *E. coli* and *K. pneumoniae* had the highest isolation rates, ranging from 58.26% to 65.55% and from 21.31% to 32.44%, respectively. The annual isolation rate of *E. cloacae* generally ranged from 3.15% to 6.09% but was significantly lower in 2018 (0.60%). The annual isolation rates of *Salmonella*, *S. marcescens*, *E. aerogenes*, *P. mirabilis*, and *K. oxytoca* generally ranged from 0.50% to 2.00% (Figure 2). A significant positive correlation was observed for *K. pneumoniae* ($\rho = 0.76$, $P < 0.05$), indicating an increasing trend over time. Moreover, the isolation rates of *E. coli* ($\rho = -0.68$, $P < 0.05$) and *Salmonella* ($\rho = -0.75$, $P < 0.05$) showed a statistically significant negative correlation with time (Table S1).

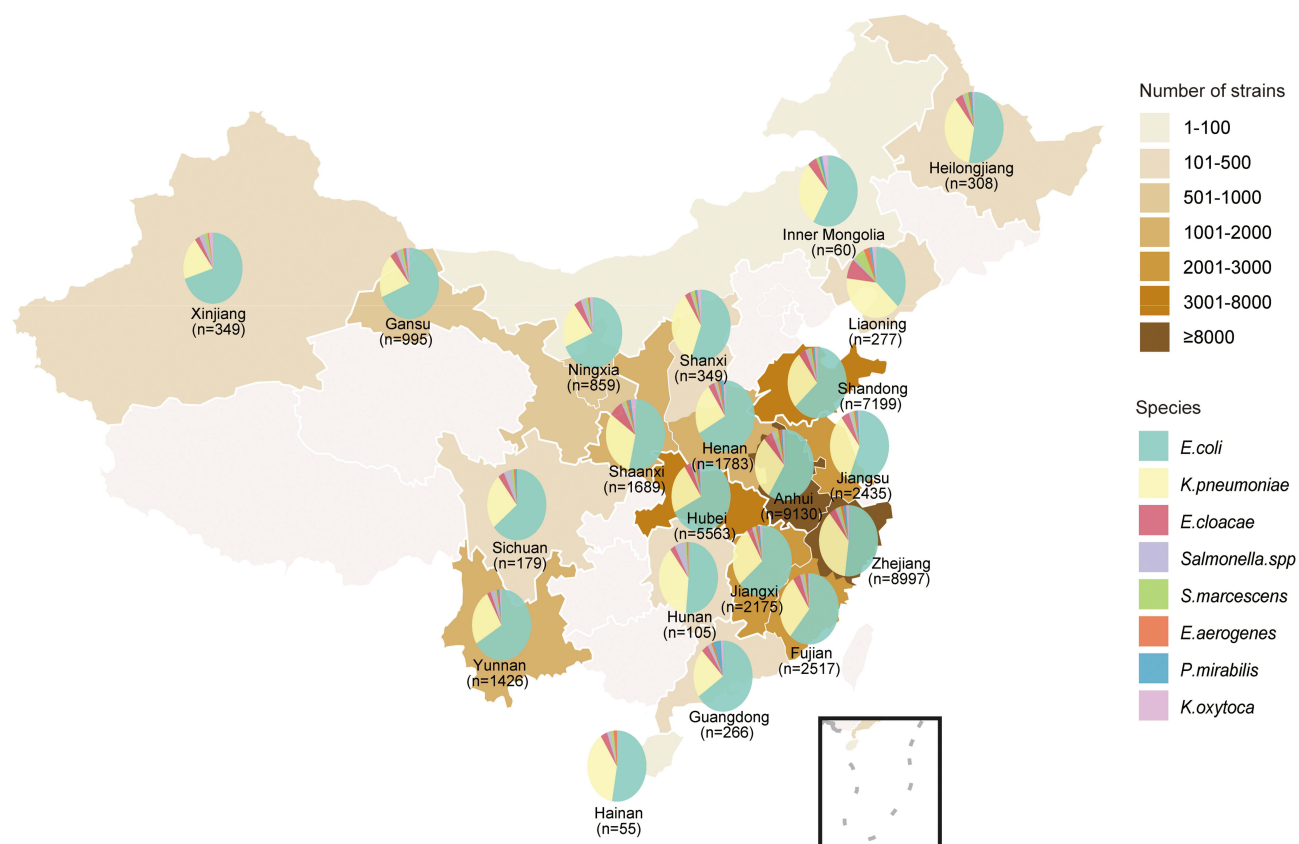


Figure 1 Rates of isolation of the eight most common *Enterobacteriaceae* from BSI and their geographical distributions in China, 2014–2023. The legend “Number of strains” indicates the quantity of strains collected from each province involved in this study, with colors ranging from light to dark representing increasing strain numbers. The total number of strains collected from each province is labeled beneath the province name. Pie charts within each province indicate the proportional distribution of the eight most frequently isolated species, and the color-species combinations in the “Species” legend correspond to those in the pie charts.

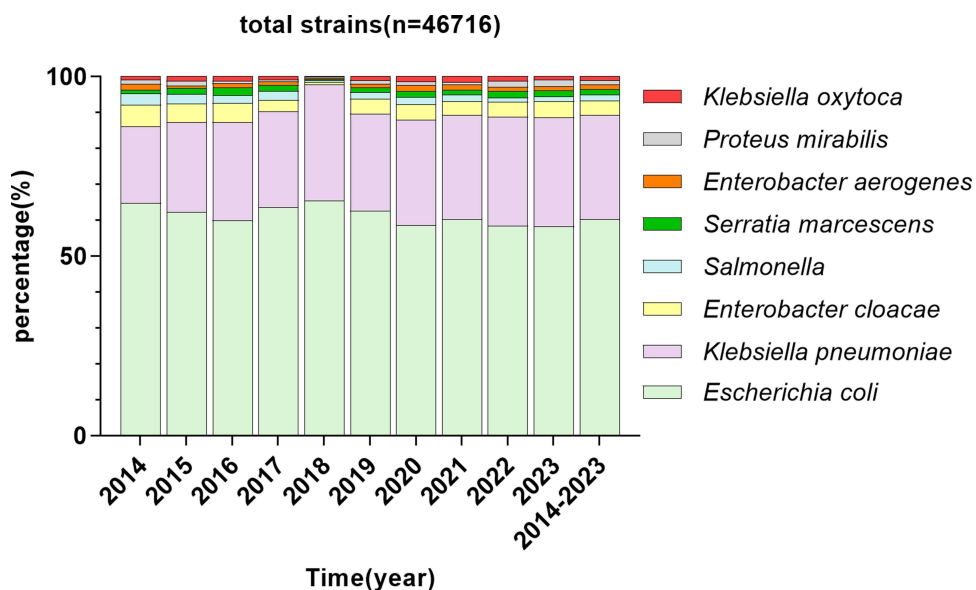


Figure 2 Yearly rates of isolation of the eight most common *Enterobacteriaceae* from BSI in China, 2014–2023.

Enterobacteriaceae Demonstrate a Favorable Response to Latamoxef

The in vitro antimicrobial activity of latamoxef against all 46,716 strains of bacteria was compared with the activities of clinically available cephalosporin (ceftriaxone, ceftazidime, and cefepime) and carbapenem (ertapenem and meropenem). *Enterobacteriaceae* exhibited comparable susceptibilities to latamoxef, ertapenem, and meropenem but were significantly less susceptible to ceftriaxone, ceftazidime, and cefepime (Table 1).

Over 96% of *E. coli* strains and over 98% of *Salmonella* and *P. mirabilis* strains were sensitive to latamoxef. Except for *S. marcescens*, which had an MIC₅₀ to latamoxef of 0.5 µg/mL, all other *Enterobacteriaceae* species tested had an MIC₅₀ of 0.25 µg/mL. *E. coli*, *Salmonella*, *S. marcescens*, and *P. mirabilis* had MIC₉₀ values to latamoxef ranging from 0.25 µg/mL to 2 µg/mL, all of which were less than the sensitive breakpoints defined by the CLSI.

The rates of susceptibility of *E. coli* strains to latamoxef, ertapenem, and meropenem were 96.48%, 97.82%, and 98.58%, respectively, higher than their rates of susceptibility to cefepime, ceftriaxone, and ceftazidime (59.22%, 63.56%, and 47.58%, respectively). The rates of resistance of *E. coli* strains to latamoxef, ertapenem, and meropenem were 2.11%, 1.49%, and 1.21%, respectively, whereas 52.55%, 28.05%, and 20.78% of these strains were resistant to ceftriaxone, ceftazidime, and cefepime, respectively.

The rates of susceptibility of *P. mirabilis* and *Salmonella* strains to latamoxef (98.00% and 98.08%, respectively) were similar to their rates of susceptibility to ertapenem (99.12% and 99.87%, respectively) and meropenem (98.36% and 98.20%, respectively) but higher than their rates of susceptibility to ceftriaxone (60.95% and 87.72%, respectively), ceftazidime (90.69% and 90.42%, respectively), and cefepime (77.74% and 90.24%, respectively). The in vitro activities of latamoxef (94.37%), ceftazidime (91.91%), ertapenem (93.91%), and meropenem (94.95%) against *S. marcescens* were similar but significantly higher than the activities of ceftriaxone (78.36%) and cefepime (86.00%).

Strains of *E. cloacae* and *E. aerogenes* were less susceptible to latamoxef (83.21% and 87.21%, respectively) than to ertapenem (89.43% and 94.56%, respectively) and meropenem (92.15% and 95.38%, respectively). Rates of susceptibility to latamoxef were similar to rates of susceptibility to cefepime (79.84% and 87.74%, respectively), but higher than rates of susceptibility to ceftriaxone (61.90% and 69.45%, respectively) and ceftazidime (62.34% and 66.43%, respectively).

The rates of susceptibility of *K. pneumoniae* strains to latamoxef (82.91%), ertapenem (82.19%), and meropenem (84.40%) were similar, but lower than those of the other *Enterobacteriaceae* tested. These rates, however, were higher than their rates of susceptibility to ceftriaxone (63.72%), ceftazidime (67.58%), and cefepime (66.94%).

Over time, most of the bacteria showed relatively stable susceptibility to latamoxef from 2014 to 2023 (Figure 3). The sensitivity rate of *E. coli* ($\rho = 0.89$, $P < 0.05$) to latamoxef increased over time, demonstrating statistical significance (Table S2). Although the susceptibility rates of the remaining bacterial species to latamoxef fluctuated, they remained relatively stable, with no significant upward or downward trends.

Latamoxef Has High Antibacterial Activity Against ESBL-Producing Enterobacteriaceae

In accordance with CLSI recommendations, supplemental ESBL testing was performed on four *Enterobacteriaceae*: *E. coli* (n=13930), *K. pneumoniae* (n=3264), *P. mirabilis* (n=205), and *K. oxytoca* (n=67). ESBL-producing *E. coli* and *P. mirabilis* strains were highly prevalent during the 10-year period from 2014 to 2023, with isolation rates of 49.52% and 37.41%, respectively (Table 2). Over the past decade, the proportion of ESBL (+) *E. coli* ($\rho = -0.95$, $P < 0.05$) and ESBL (+) *K. pneumoniae* ($\rho = -0.76$, $P < 0.05$) among ESBL (+) Enterobacteriaceae has shown a decreasing trend over time (Table S3).

The rates of susceptibility of ESBL (+) *E. coli* and ESBL (+) *P. mirabilis* to latamoxef, ertapenem, and meropenem, were generally higher than 97.50%, except for ESBL (+) *E. coli*, which showed 95.99% susceptibility to latamoxef (Figure 4).

The prevalence rates of ESBL (+) *K. pneumoniae* (24.05%) and ESBL (+) *K. oxytoca* (12.52%) were lower than those of ESBL (+) *K. pneumoniae* to latamoxef, ertapenem, and meropenem were 79.44%, 79.06%, and 84.19%, respectively, which were marginally lower than the rates of sensitivity of ESBL (+) *K. oxytoca* to these three antibiotics (80.60%, 87.63%, and 89.47%, respectively).

Table 1 Characterization of Susceptibility of Enterobacteriaceae to Six Antibiotics and Their TECOFFs to Latamoxef, 2014–2023

	MIC ₅₀ (μg/mL)						MIC ₉₀ (μg/mL)						S (%)						R (%)						TECOFF (μg/mL)	
	MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM	99.00%	Visual
Breakpoint																										
<i>E. coli</i> (n=28130)	0.25	16	1	1	0.016	0.03	2	64	64	32	0.125	0.06	96.48	47.58	63.56	59.22	97.82	98.58	2.11	52.55	28.05	20.78	1.49	1.21	2	2
<i>K. pneumoniae</i> (n=13570)	0.25	0.125	0.5	0.06	0.016	0.03	128	64	64	64	32	32	82.91	63.72	67.58	66.94	82.19	84.40	15.19	36.47	29.23	26.59	15.54	15.06	2	2
<i>K. oxytoca</i> (n=5335)	0.25	0.125	0.25	0.06	0.016	0.03	16	64	64	16	0.5	0.5	89.91	71.59	81.87	82.40	90.86	92.15	9.72	26.36	16.45	12.36	7.98	6.36	2	1
<i>P. mirabilis</i> (n=548)	0.25	0.25	0.125	0.125	0.016	0.03	0.25	16	4	8	0.03	0.125	98.00	60.95	90.69	77.74	99.12	98.36	1.64	35.22	7.85	7.30	0.88	1.46	1	2
<i>E. cloacae</i> (n=1895)	0.25	0.5	0.5	0.06	0.016	0.03	32	64	64	16	1	0.125	83.22	61.90	69.45	79.84	89.43	94.56	8.87	35.30	28.39	12.66	7.39	3.80	4	2
<i>E. aerogenes</i> (n=563)	0.25	0.25	0.5	0.06	0.03	0.03	16	64	64	8	0.5	0.125	87.21	62.34	66.43	87.74	92.15	95.38	6.04	36.23	29.66	8.35	4.98	3.91	2	2
<i>Salmonella</i> (n=782)	0.25	0.125	0.25	0.06	0.008	0.03	1	32	4	2	0.016	0.06	98.08	87.72	90.24	90.24	99.87	98.20	0.38	12.15	8.86	6.80	0.13	1.80	2	2
<i>S. marcescens</i> (n=693)	0.5	0.125	0.25	0.06	0.016	0.06	2	64	4	8	0.125	0.125	94.37	78.36	91.91	86.00	93.91	94.95	3.61	20.78	6.65	8.37	5.45	3.61	2	1

Abbreviations: MOX, latamoxef; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; ETP, ertapenem; MEM, meropenem.

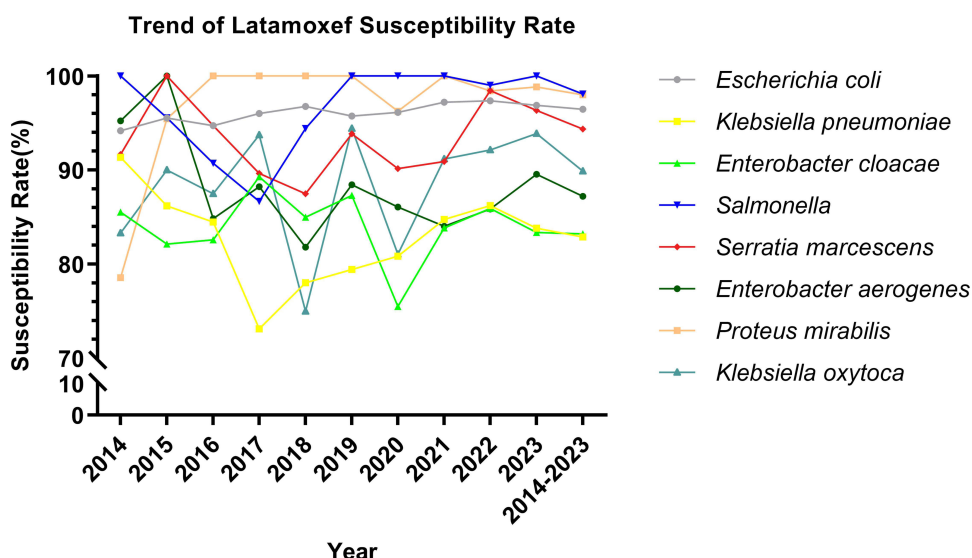


Figure 3 Rates of susceptibility of *Enterobacteriaceae* strains to latamoxef over time from 2014–2023.

Latamoxef exhibits excellent in vitro activity against ESBL (-) strains. Except for *P. mirabilis* ($\chi^2 = 0.63$, $P > 0.1$), ESBL-positive strains of *E. coli* ($\chi^2 = 35.61$, $P < 0.0001$), *K. pneumoniae* ($\chi^2 = 396.7$, $P < 0.0001$), and *K. oxytoca* ($\chi^2 = 46.46$, $P < 0.0001$) exhibited significantly higher resistance rates to latamoxef compared to ESBL-negative strains (Figure S1 and Table S4).

The susceptibility of ESBL (+) *Enterobacteriaceae* to latamoxef did not show a significant increase or decrease over time. In contrast, the susceptibility of ESBL (-) *E. coli* ($\rho = 0.83$, $P < 0.05$) and ESBL (-) *K. pneumoniae* ($\rho = 0.72$, $P < 0.05$) to latamoxef exhibited a statistically significant positive correlation with time (Figure S1 and Table S5).

Calculation of TECOFFs for Latamoxef of Common Enterobacteriaceae

Based on the distribution of MICs of bacterial strains to latamoxef, TECOFFs were calculated using ECOFFinder (Figure 5 and Table 1). Because the measured MICs were not normally distributed normally, the MIC distribution curves that were fitted by nonlinear regression did not fully overlap with the actual MIC distribution curves.

Except for *S. marcescens*, where the MICs of most of the strains were distributed at 0.25 µg/mL and 0.5 µg/mL, most of the MICs of the other species were distributed at 0.25 µg/mL. The MIC distributions of *E. cloacae*, *Salmonella*, and *E. aerogenes* were bimodal.

The 99.00% TECOFFs of *E. coli*, *K. pneumoniae*, *Salmonella*, and *K. oxytoca* were all 2 µg/mL for latamoxef, whereas the 99.00% TECOFFs for latamoxef were 4 µg/mL for *E. cloacae* and 1 µg/mL for *P. mirabilis*. All visual estimates of TECOFF and 99.00% TECOFFs calculated using ECOFFinder were identical or within two-fold dilution of each other. From this, the TECOFFs for *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *E. aerogenes*, *Salmonella*, and *S. marcescens* were all 2 µg/mL for latamoxef and 4 µg/mL for *E. cloacae*.

Discussion

Because latamoxef has good antimicrobial activity and is more affordable than newer antibiotics, it is commonly used to treat patients in Korea, Japan, and many developing countries. Latamoxef has been found to be effective in the treatment of a wide range of infections with varying degrees of severity, ranging from mild skin and soft tissue infections to bacteremia.⁷ Latamoxef has been shown to produce clinical cure and satisfactory microbiological response in 87% and 100% of patients hospitalized with sepsis and Gram-negative bacteremia, respectively.⁵ Furthermore, latamoxef has shown good central nervous system penetration,²⁵ with cerebrospinal fluid (CSF) levels > 30-fold higher than the MICs of pathogenic bacteria in patients with meningitis.²⁶ Latamoxef has also been found to effectively penetrate the CSF of pediatric patients diagnosed with bacterial meningitis, exhibiting a cure rate of 96.67% (29/30),²⁷ suggesting its potential

Table 2 Characterization of the Susceptibility of ESBL (+) Enterobacteriaceae to Six Antibiotics, 2014–2023

	Percentage (%)	MIC ₅₀ (µg/mL)						MIC ₉₀ (µg/mL)						S (%)						R (%)					
		MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM	MOX	CRO	CAZ	FEP	ETP	MEM
Breakpoint																									
<i>E. coli</i> (n=13930)	49.52	0.5	64	16	8	0.016	0.016	2	64	64	64	0.25	0.06	95.99	1.72	33.91	22.38	97.77	99.16	1.79	98.07	50.83	38.46	0.88	0.69
<i>K. pneumoniae</i> (n=3264)	24.05	1	64	32	16	0.06	0.03	128	64	64	64	16	32	79.44	3.89	21.94	16.76	79.06	84.19	16.21	95.37	67.25	59.04	16.23	15.13
<i>K. oxytoca</i> (n=67)	12.52	0.5	64	16	8	0.03	0.03	128	64	128	64	2	2	80.60	1.50	33.08	31.58	87.63	89.47	19.40	96.99	57.89	39.85	10.31	6.02
<i>P. mirabilis</i> (n=205)	37.41	0.25	8	0.25	2	0.008	0.03	0.25	32	64	16	0.016	0.125	98.54	16.59	81.46	51.22	99.47	99.02	0.98	77.56	16.10	15.12	0.53	0.49

Abbreviations: MOX, latamoxef; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; ETP, ertapenem; MEM, meropenem.

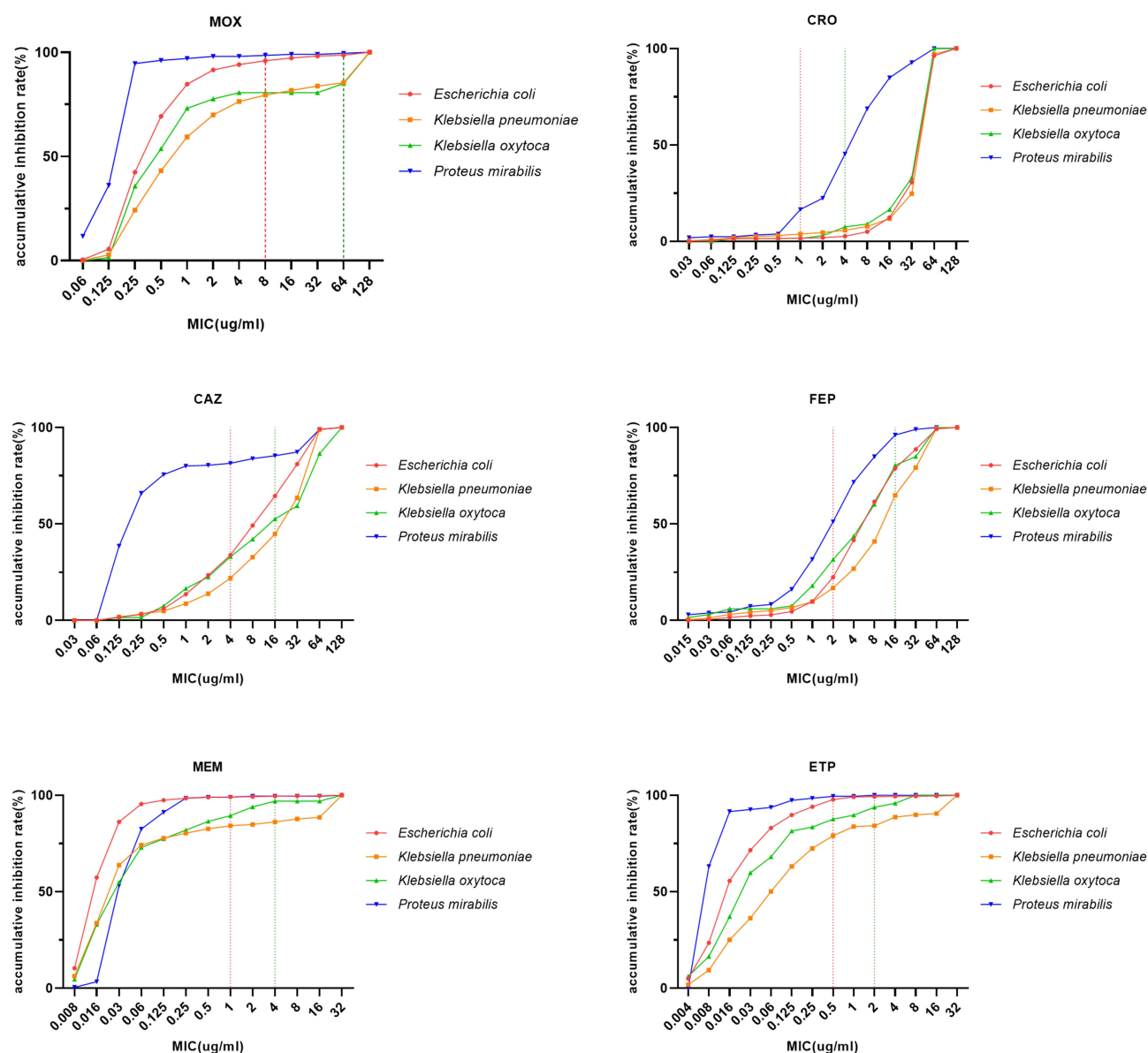


Figure 4 Cumulative inhibition profiles of latamoxef and other antibiotics against ESBL (+) *Enterobacteriaceae*, 2014–2023. The red dashed lines indicate the sensitivity breakpoints and the green dashed lines indicate the resistance breakpoints. Sub-figures A–F represent antibiotics MOX, CRO, CAZ, FEP, MEM, and ETP, respectively. **Abbreviations:** MOX, latamoxef; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; MEM, meropenem; ETP, Ertapenem.

efficacy in the postoperative prophylaxis of patients who have undergone neurosurgical procedures.^{28,29} Therefore, latamoxef may have considerable potential in the management of patients infected with *Enterobacteriaceae*.

In this study, 46,716 BSI strains of bloodstream *Enterobacteriaceae* infections were obtained from patients in 21 provinces of China between 2014 and 2023. Latamoxef was found to have better in vitro activity against *Enterobacteriaceae* than three other clinically used cephalosporins, ceftriaxone, ceftazidime, and cefepime. Over 94.00% of the *E. coli*, *Salmonella*, *S. marcescens*, and *P. mirabilis* strains tested were susceptible to latamoxef (89.91% of the *K. oxytoca* and 87.21%, the *E. aerogenes* strains). The susceptibility rates of the *K. pneumoniae* and *E. cloacae* strains to latamoxef were somewhat lower, although these rates exceeded 80.00%. In contrast, the susceptibility rates of *Enterobacteriaceae* to ceftazidime (63.56%–91.91%), cefepime (59.22%–90.24%), and ceftriaxone (47.58%–87.72%) were much lower. Moreover, latamoxef has been reported to have greater activity against Gram-negative bacteria than cephalothin, cefazolin, cefamandole, cefoxitin, and tobramycin.³⁰ The in vitro bactericidal activity of latamoxef against *E. coli*, *K. pneumoniae*, *Salmonella*, *S. marcescens*, *P. mirabilis*, and *K. oxytoca* was similar to the

activities of other clinically used carbapenem (ertapenem and meropenem). In addition, the rates of susceptibility to latamoxef in the bacteria collected in this study exhibited relative stability or minimal fluctuations between 2014 and 2023, with no indications of increased resistance over time.

The in vitro bactericidal activities of latamoxef and cefepime against *E. cloacae* and *E. aerogenes* were similar. Although they were slightly lower than those of ertapenem and meropenem, they showed higher in vitro bactericidal activity against ceftriaxone and ceftazidime. Inducible expression of chromosomal *AmpC* by third-generation cephalosporins and acquisition of transferable *AmpC* by plasmids and transposons can lead to overproduction of AmpC β -lactamases, a frequent cause of resistance in *E. cloacae* and *E. aerogenes* to third-generation cephalosporins. *E. aerogenes* has a high horizontal gene exchange capacity facilitated by its flagellar system and efficient integration of exogenous genes, suggesting its high potential for development into a multidrug-resistant pathogen.³¹ The rapid dissemination of ESBL and carbapenemases in *E. cloacae*, coupled with their frequent occurrence as endogenous intestinal bacteria, has led *E. cloacae* to become the third most prevalent species of *Enterobacteriaceae* that contributes to nosocomial infections, following *E. coli* and *K. pneumoniae*. Further research is needed on the spread of *E. cloacae* and *E. aerogenes* in susceptible populations, as well as on trends in antibiotic resistance.

Because the breakpoints of latamoxef have not been evaluated to date, the CLSI recommends that ESBL tests be performed if latamoxef is considered for the treatment of infections caused by *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *K. oxytoca*. Although the CLSI recommends that ESBL-positive isolates should be resistant to latamoxef, the present study found that latamoxef had good in vitro activity against ESBL (+) *Enterobacteriaceae*.

Latamoxef was found to have significantly higher in vitro activity than ceftriaxone, ceftazidime, and cefepime against ESBL (+) *Enterobacteriaceae* and similar or higher in vitro activity than the carbapenems ertapenem and meropenem. The susceptibility rates of ESBL (+) *E. coli* and ESBL (+) *P. mirabilis* to latamoxef were 95.99% and 98.54%, respectively, which were similar to their susceptibility rates to ertapenem (97.77% and 99.47%, respectively) and meropenem (99.16% and 99.02%, respectively). The rates of susceptibility of ESBL (+) *Klebsiella* spp. to the six

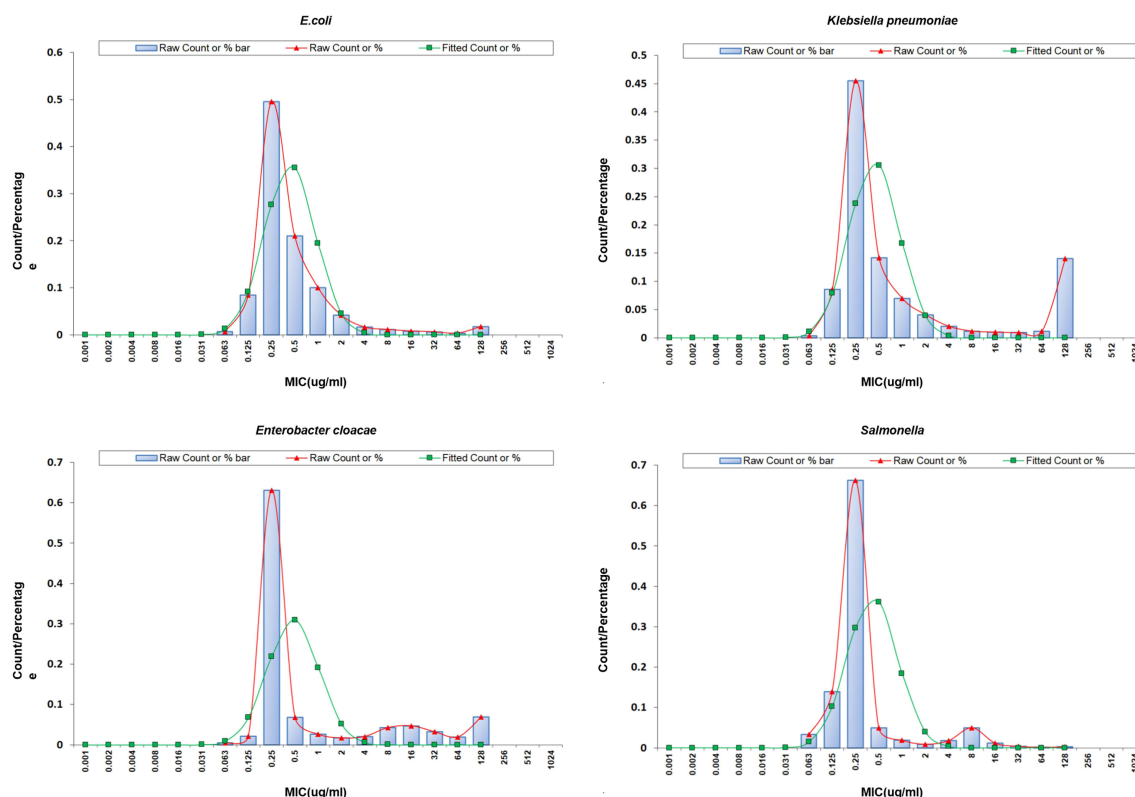


Figure 5 Continued.

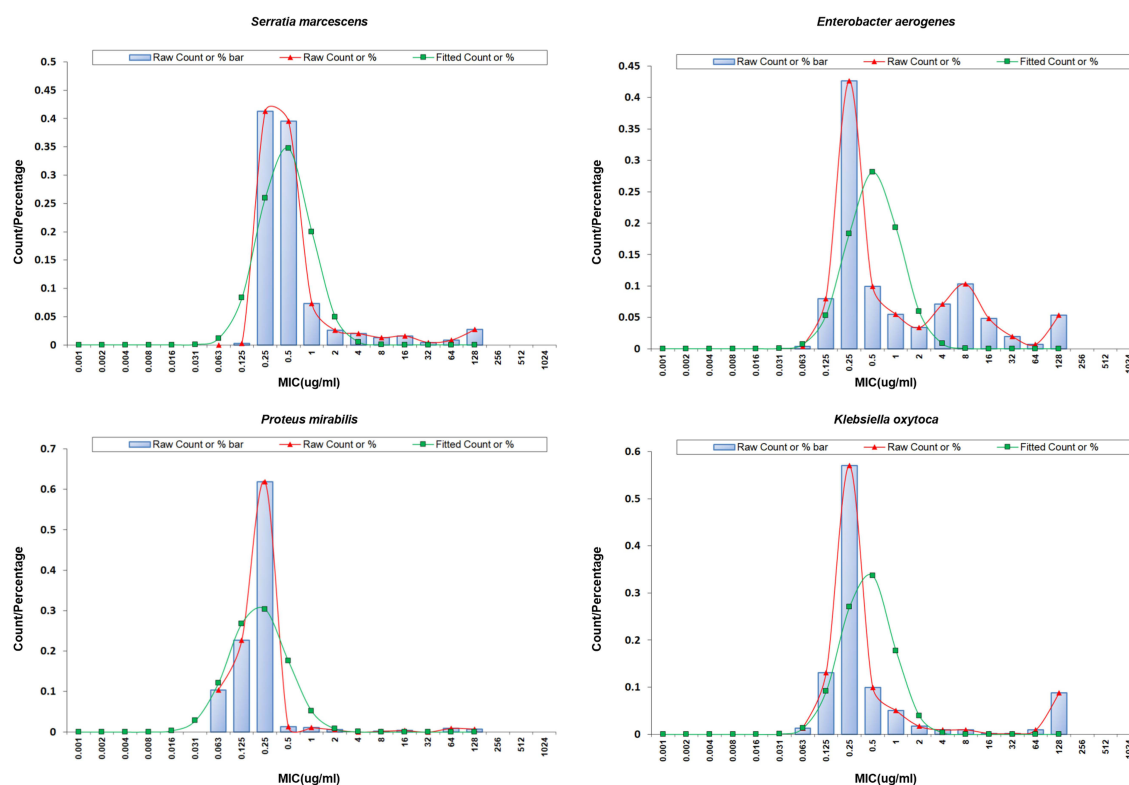


Figure 5 Nonlinear regression fitting MIC distribution of TECOFF for *Enterobacteriaceae*. Sub-figures A-H sequentially depict the MIC distributions and TECOFF fitting curves for *E. coli*, *K. pneumoniae*, *E. cloacae*, *Salmonella*, *S. marcescens*, *E. aerogenes*, *P. mirabilis*, and *K. oxytoca*, respectively. Blue bars: raw count or %; red curves: raw count or % for measured MICs; green curves: fitted count or % for simulated MIC data.

antibiotics tested in this study were relatively low, with ESBL (+) *K. pneumoniae* and ESBL (+) *K. oxytoca* showing similar and significantly higher sensitivity rates to latamoxef, ertapenem, and meropenem than to ceftriaxone, ceftazidime, and cefepime.

Latamoxef has been reported to exhibit strong antimicrobial activity against various genera of *Enterobacteriaceae*, including ESBL-producing *E. coli*, *K. pneumoniae*, and *P. mirabilis*, with susceptibility rates of >90%.⁶ The overall efficacy rate of latamoxef (96.0%) in treating children with pneumonia infected with ESBL-producing *E. coli* was significantly higher than that of sulbactam/cefoperazone (84.0%).³²

Latamoxef can form a transiently stable covalent complex with hydrolytic enzymes to inhibit their enzymatic activity, with its unique side-chain carboxyl group and 7 alpha-methoxy group being necessary to stabilize the complexes.³³ Latamoxef was not degraded by any of the beta-lactamases tested, including TEM-type beta-lactamases, the cephalosporinases (class I), and chromosomal broad-spectrum beta-lactamases (class IV).³⁴ The in vitro 50% inhibitory concentrations of latamoxef against plasmid-mediated extended-spectrum beta-lactamases (TEM-3, TEM-5 and TEM-10) were below 0.2 mg/L.³⁵ None of the ESBL (+) *E. coli* and ESBL (+) *K. pneumoniae* strains from nine hospitals in Zhejiang, China, all carrying CTX-M and SHV genes, were resistant to latamoxef.³⁶ Another study found that the sensitivity of ESBL-producing *E. coli* and *K. pneumoniae* to latamoxef was 97.44%.³⁷ SHV, TEM, and both β -lactamase genes were carried by 41.66%, 8.33%, and 50%, respectively, of the ESBL (+) *K. pneumoniae* strains and by 96.3%, 0%, and 3.7%, respectively, of the ESBL (+) *E. coli* strains.³⁷ Similarly, the dominant type of ESBL (+) *E. coli* in Japan shifted from CTX-M-14 to CTX-M-15 and/or CTX-M-27 between 2006 and 2010, but most isolates remained sensitive to latamoxef.³⁸ MOX-1 is a plasmid-mediated class C β -lactamase that confers resistance to latamoxef.^{39,40} In addition, TEM-52 is associated with a reduced susceptibility of *K. pneumoniae* to latamoxef.⁴¹ Therefore, latamoxef has good inhibitory activity against more common ESBLs (eg, CTX-M, SHV, and TEM).

Although carbapenems are the antibiotics of choice for treating ESBL (+) bacterial infections, carbapenem-resistant strains are becoming more prevalent. CRE was relatively uncommon before 2000, but its prevalence has increased two-

fold over a 10-year period.⁴² The prevalence of CRE infection has been reported to be as high as 43.06%,⁴³ with a mortality rate of up to 50%.⁴⁴ Both CRE and ESBL-producing *Enterobacteriaceae* are listed as priority pathogens by the WHO.⁴⁵ Therefore, rational treatment of CRE and ESBL-producing *Enterobacteriaceae* infections is needed to control AMR, particularly that of *K. pneumoniae*.

The present study found that the in vitro antibacterial activity of latamoxef against ESBL (+) *Enterobacteriaceae* was significantly higher than that of other cephalosporins and similar to that of carbapenems. Monitoring *Enterobacteriaceae* resistance in patients hospitalized at 19 tertiary care hospitals in China between 2004 and 2014 also revealed that the effectiveness of latamoxef against *Enterobacteriaceae* isolates was second only to that of carbapenems.⁴⁶ These findings suggest that latamoxef is one of the most important antibiotics for treating *Enterobacteriaceae* infections, especially infections caused by ESBL-producing bacteria. In the future, latamoxef may be considered an alternative to carbapenems for treating ESBL-producing bacterial infections and may slow the development of carbapenem resistance in *Enterobacteriaceae*.

In this study, the MICs to latamoxef of 46,716 strains of common *Enterobacteriaceae*, assorted into eight species, were monitored over a 10-year period. Seven of these species (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *Salmonella*, *P. mirabilis*, *E. aerogenes*, and *S. marcescens*) had TECOFFs of 2 µg/mL for latamoxef, whereas the eighth species (*E. cloacae*) had an TECOFF of 4 µg/mL.

Inadequate assessment and monitoring of latamoxef has resulted in its limited clinical use. In contrast to EUCAST, which has not reported the breakpoints for latamoxef, the CLSI continues to report its microbiological breakpoints, although these breakpoints have not been assessed recently. This may lead to inappropriate clinical use of latamoxef. MIC breakpoints may be determined by comparing tentative breakpoints with defined wild-type MIC distributions, thereby ensuring that the breakpoints do not delineate the MIC distribution of the target microorganism.⁴⁷ In addition to monitoring resistance and guiding clinical therapy, determining ECOFFs of latamoxef for *Enterobacteriaceae* may provide epidemiological data that informs the development or updating of resistance breakpoints. Furthermore, ECOFFs can determine whether an isolate is wild type for the drug and excluded from resistance, which helps adjust therapeutic doses. It should be noted that the MIC distribution of the strains exhibits a bimodal pattern, indicating potential overlap between wild-type and non-wild-type populations. This suggests that a small number of non-wild-type strains may exist within the wild-type population. ECOFF should be interpreted as an approximate upper limit for the wild-type population rather than a strict threshold for the wild-type group.

The increased risk of coagulation disorders and bleeding associated with latamoxef is the main reason for its reduced clinical use.^{14,48,49} Latamoxef interferes with vitamin K metabolism via its N-methylthiotetrazole side chain^{12,50} and inhibits adenosine diphosphate-induced platelet aggregation.⁵¹ Although latamoxef is associated with higher rates of decreased prothrombin and prolonged prothrombin time, no statistically significant association exists between latamoxef and bleeding event.¹⁵ A retrospective cohort study in China found that, compared with cefotaxime, latamoxef may increase the risk of coagulation disorders, but does not increase the risk of bleeding events.⁵² Furthermore, platelet dysfunction induced by latamoxef can resolve within days after discontinuation^{12,53} and vitamin K supplementation can alleviate latamoxef-related coagulation abnormalities.⁵⁴ When using latamoxef to treat bacterial infections, monitoring coagulation parameters and providing vitamin K supplementation are recommended.^{12,52,54}

The primary limitation of this study was that the antimicrobial activity of latamoxef against *Enterobacteriaceae* was monitored only in vitro. Additional clinical studies are needed to validate the therapeutic efficacy of latamoxef against *Enterobacteriaceae* infections, particularly ESBL-producing bacterial infections.

Conclusion

This study demonstrated that latamoxef exhibits favorable in vitro antimicrobial activity against prevalent clinical strains of *Enterobacteriaceae*, including ESBL-producing strains. The in vitro activity of Latamoxef has been shown to be comparable to that of Ertapenem and Meropenem, and significantly superior to Ceftriaxone, Ceftazidime, and Cefepime. As a broad-spectrum antibiotic, Latamoxef is widely used in clinical practice across numerous countries. However, a significant issue currently exists regarding the absence or lack of evaluation of breakpoints for Latamoxef. This study established TECOFFs for Latamoxef against *Enterobacteriaceae* based on multicenter surveillance data to guide clinical use and breakpoint establishment. It should be noted that variation among strains can broaden the distribution of wild-

type strains, thereby affecting the accuracy of wild-type population assessments—particularly when MIC distributions exhibit a bimodal pattern. In order to optimize clinical treatment and curb the development of AMR, further research is essential. This research should include conducting Latamoxef-related clinical research (including coagulation-related adverse reactions) and reassessing or establishing breakpoints for Latamoxef.

Ethics Approval and Consent to Participate

This study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang (approval number: 2022-106). The strains were derived from clinical examination samples of infected patients for diagnostic purposes. Since waiving the informed consent of the subjects does not have a negative impact on their rights and interests, and this study does not involve personal privacy or commercial interests, the ethics committee approved that informed consent from all participants was waived. The study was conducted by the principles of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Murray CJL, Ikuta KS, Sharara F. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655. doi:10.1016/S0140-6736(21)02724-0
2. Luepke KH, Suda KJ, Boucher H, et al. Past, present, and future of antibacterial economics: increasing bacterial resistance, limited antibiotic pipeline, and societal implications. *Pharmacotherapy*. 2017;37(1):71–84. doi:10.1002/phar.1868
3. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report: 2022 [Global report]. 2022.
4. Daruka L, Czikkely MS, Szili P, et al. ESKAPE pathogens rapidly develop resistance against antibiotics in development in vitro. *Nat Microbiol*. 2025;10(2):313–331. doi:10.1038/s41564-024-01891-8
5. Chen YC, Hung CC, Lin SF, et al. Comparison of flomoxef with latamoxef in the treatment of sepsis and/or Gram-negative bacteremia in adult patients. *Int J Antimicrob Agents*. 1996;7(1):69–74. doi:10.1016/0924-8579(96)00013-1
6. Quan JJ, Wang Y, Ji JS, et al. The activity of moxalactam against Enterobacteriaceae and anaerobias in vitro. *Zhonghua yi xue za zhi*. 2016;96(18):1459–1464. doi:10.3760/cma.j.issn.0376-2491.2016.18.015
7. Carmine AA, Brogden RN, Heel RC, et al. Moxalactam (latamoxef). A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs*. 1983;26(4):279–333. doi:10.2165/00003495-198326040-00001
8. Mouton Y, Beaucaire G, Caillaux M, et al. Use of moxalactam in intensive care units: clinical and bacteriological results related to serum and bronchial concentrations. *Pathologie-Biologie*. 1982;30(6 Pt 2):495–500.
9. de Louvois J, James J, Mulhall A. Latamoxef and the newborn. *Arch Dischildhood*. 1984;59(4):346–350. doi:10.1136/adc.59.4.346
10. Fitzpatrick BJ, Standiford HC. A comparative evaluation of moxalactam: antimicrobial activity, pharmacokinetics, adverse reactions, and clinical efficacy. *Pharmacotherapy*. 1982;2(4):197–212. doi:10.1002/j.1875-9114.1982.tb03187.x
11. Murakami K, Yoshida T. Role of the 7 alpha-methoxy and side-chain carboxyl of moxalactam in beta-lactamase stability and antibacterial activity. *Antimicrob Agents Chemother*. 1981;19(1):1–7. doi:10.1128/AAC.19.1.1
12. Zhang RY, Zhang JJ, Li JM, et al. Latamoxef-induced severe thrombocytopenia during the treatment of pulmonary infection: a case report. *World J Clin Cases*. 2022;10(22):7906–7912. doi:10.12998/wjcc.v10.i22.7906
13. Zhang A, Zuo M, Sun Y, et al. Latamoxef dosing regimen adjustments and pharmaceutical care in pediatrics. *Front Pediatrics*. 2024;12:1302087. doi:10.3389/fped.2024.1302087
14. Brown RB, Klar J, Lemeshow S, et al. Enhanced bleeding with cefoxitin or moxalactam. Statistical analysis within a defined population of 1493 patients. *Archiv Internal Med*. 1986;146(11):2159–2164. doi:10.1001/archinte.1986.00360230079013
15. Park GH, Kim S, Kim MS, et al. The association between cephalosporin and hypoprothrombinemia: a systematic review and meta-analysis. *Int J Environm Res Public Health*. 2019;16(20):3937. doi:10.3390/ijerph16203937
16. Ito A, Tatsumi Y, Wajima T, et al. Potent antibacterial activities of latamoxef (moxalactam) against ESBL producing Enterobacteriaceae analyzed by Monte Carlo simulation. *Japanese J Antibiotics*. 2014;67(2):109–122.
17. Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β -lactamase producing enterobacterales infections: an update. *Infect Dis Clin North America*. 2020;34(4):677–708. doi:10.1016/j.idc.2020.06.003
18. Srinivasan S, Francke EL, Ortiz-Neu C, et al. The use of moxalactam in the treatment of serious infections due to multi-resistant organisms. *Infection*. 1983;11(6):291–295. doi:10.1007/BF01641349
19. Kahlmeter G, Turnidge J. Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility. *Clin Microbiol Rev*. 2023;36(4):e0010022. doi:10.1128/cmr.00100-22

20. CLSI. *Methods for the Identification of Cultured Microorganisms Using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry*. 1st ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2017. CLSI guideline M58.
21. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 35th ed. 2025. CLSI supplement M100.
22. Motulsky HJ. GraphPad Statistics Guide. Available from: <http://www.graphpad.com/guides/prism/10/statistics/index.htm> Accessed 18 February 2026.
23. R Core Team. R: a language and environment for statistical computing. Austria: R Foundation for Statistical Computing V; 2020.
24. Testing ECoAS. MIC distributions and epidemiological cut-off value (ECOFF) setting, EUCAST SOP 10.2 2021. Available from: <http://www.eucast.org>. Accessed February 10, 2026.
25. Chartrand SA, Marks MI, Scribner RK, et al. Moxalactam therapy of Haemophilus influenzae type b meningitis in children. *J Pediatr*. 1984;104(3):454–459. doi:10.1016/S0022-3476(84)81116-6
26. Fisher JF, Carter MJ, Parsons J, et al. Moxalactam (LY127935) in treatment of meningitis due to gram-negative bacilli. *Antimicrob Agents Chemother*. 1981;19(2):218–221. doi:10.1128/AAC.19.2.218
27. Freedman JM, Hoffman SH, Scheld WM, et al. Moxalactam for the treatment of bacterial meningitis in children. *J Infect Dis*. 1983;148(5):886–891. doi:10.1093/infdis/148.5.886
28. Miyake S, Tanigawa M, Manabe T, et al. Clinical experience of latamoxef in the field of neurosurgery on the penetration into the cerebrospinal fluid in the patients with postoperative meningitis. *Japanese J Antibiotics*. 1985;38(12):3464–3470.
29. Modai J, Wolff M, Lebas J, et al. Moxalactam penetration into cerebrospinal fluid in patients with bacterial meningitis. *Antimicrob Agents Chemother*. 1982;21(4):551–553. doi:10.1128/AAC.21.4.551
30. Cynamon MH, Granato PA. In vitro comparative activity of moxalactam, GR 20263, and N-formimidoyl thienamycin to other beta-lactam antibiotics and tobramycin against enterobacteriaceae and staphylococci. *Chemotherapy*. 1982;28(3):204–208. doi:10.1159/000238077
31. Davin-Regli A, Pages JM. *Enterobacter aerogenes* and *Enterobacter cloacae*; versatile bacterial pathogens confronting antibiotic treatment. *Front Microbiol*. 2015;6:392. doi:10.3389/fmicb.2015.00392
32. Hongfa Dai ZH, Liao C, Peiming MI. Effect of Latamoxef in the treatment of extended-spectrum β -lactamase *Escherichia coli* pneumonia in children. *China Modern Med*. 2019;26(10):122–124.
33. Murakami K, Yoshida T. Covalent binding of moxalactam to cephalosporinase of *Citrobacter freundii*. *Antimicrob Agents Chemother*. 1985;27(5):727–732. doi:10.1128/AAC.27.5.727
34. Mouton RP, Bongaerts GP, van Gestel M, et al. Activity and specific beta-lactamase susceptibility of cefoperazone and moxalactam. Comparison with other cephalosporins. *Chemotherapy*. 1981;27(5):318–324. doi:10.1159/000237999
35. Sotto A, Brunschwig C, O'Callaghan D, et al. In-vitro evaluation of beta-lactamase inhibition by latamoxef and imipenem. *J Antimicrob Chemother*. 1996;37(4):697–701. doi:10.1093/jac/37.4.697
36. Lu T, Quan J, Wang Y, et al. Prevalence of extended-spectrum beta-lactamases-producing *Escherichia coli* and *Klebsiella pneumoniae* in community-onset bloodstream infections from county hospitals of Zhejiang Province. *Chin J Infect Dis*. 2017;35(4):198–202.
37. Guan X, Liu Y, Wang R. Resistance characterization and genotyping of clinical ESBLs-producing bacteria Chinese. *J Antibiotics*. 2001;6(26):15–19.
38. Hara T, Sato T, Horiyama T, et al. Prevalence and molecular characterization of CTX-M extended-spectrum β -lactamase-producing *Escherichia coli* from 2000 to 2010 in Japan. *Japanese J Antibiotics*. 2015;68(2):75–84.
39. Oguri T, Furuyama T, Okuno T, et al. Crystal structure of Mox-I, a unique plasmid-mediated class C β -lactamase with hydrolytic activity towards moxalactam. *Antimicrob Agents Chemother*. 2014;58(7):3914–3920. doi:10.1128/AAC.02363-13
40. Horii T, Arakawa Y, Ohta M, et al. Plasmid-mediated AmpC-type beta-lactamase isolated from *Klebsiella pneumoniae* confers resistance to broad-spectrum beta-lactams, including moxalactam. *Antimicrob Agents Chemother*. 1993;37(5):984–990. doi:10.1128/AAC.37.5.984
41. Poyart C, Mugnier P, Quesne G, et al. A novel extended-spectrum TEM-type β -Lactamase (TEM-52) associated with decreased susceptibility to moxalactam in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 1998;42(1):108–113. doi:10.1128/AAC.42.1.108
42. Gupta N, Limbago BM, Patel JB, et al. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clin Infect Dis*. 2011;53(1):60–67. doi:10.1093/cid/cir202
43. Tuhamiz B, Bazira J. Carbapenem-resistant Enterobacteriaceae in the livestock, humans and environmental samples around the globe: a systematic review and meta-analysis. *Sci Rep*. 2024;14(1):16333. doi:10.1038/s41598-024-64992-8
44. van Duin D, Kaye KS, Neuner EA, et al. Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes. *Diagn Microbiol Infect Dis*. 2013;75(2):115–120. doi:10.1016/j.diagmicrobio.2012.11.009
45. WHO bacterial priority pathogens list bpophitgr, development and strategies to prevent and control antimicrobial resistance. Geneva: World Health Organization; 2024.
46. Liu XJ, Lyu Y, Li Y, et al. Trends in antimicrobial resistance against enterobacteriaceae strains isolated from blood: a 10-year epidemiological study in Mainland China (2004–2014). *Chinese Med J*. 2017;130(17):2050–2055. doi:10.4103/0366-6999.213407
47. Turnidge J, Kahlmeter G, Kronvall G. Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values. *Clin Microbiol Infect*. 2006;12(5):418–425. doi:10.1111/j.1469-0691.2006.01377.x
48. Meisel S. Severe bleeding diathesis associated with moxalactam administration. *Drug Intell Clin Pharm*. 1984;18(9):721–722. doi:10.1177/106002808401800909
49. Al-Fallouji MA, Al-Quisi NK. Fatal retroperitoneal bleeding following Latamoxef (Moxalactam) use. *British J Clin Pract*. 1985;39(6):249.
50. MacLennan FM, Ah-See AK, Wong AE, et al. Severe depletion of vitamin-K-dependent clotting factors during postoperative latamoxef therapy. *Lancet*. 1983;1(8335):1215. doi:10.1016/S0140-6736(83)92486-8
51. Bang NU, Tessler SS, Heidenreich RO, et al. Effects of moxalactam on blood coagulation and platelet function. *Rev Infect Dis*. 1982;4 Suppl (Supplement_3):S546–54. doi:10.1093/clinids/4.Supplement_3.S546
52. Cai Y, Zhang M, Wang Y, et al. Latamoxef-induced coagulation disorders: incidence and risk factors. *J Clin Pharm Therapeutics*. 2021;46(5):1382–1386. doi:10.1111/jcpt.13435
53. Peters GR, Metzler CM. The effects of cefmetazole and latamoxef on platelet function in healthy human volunteers. *J Antimicrob Chemother*. 1989;23 Suppl D(suppl D):119–123. doi:10.1093/jac/23.suppl_D.119
54. Zhu Y, Shen J, Wu W, et al. Latamoxef induced a severe coagulation disorder in older patients in China: two case reports. *J Clin Pharm Therapeutics*. 2021;46(1):227–229. doi:10.1111/jcpt.13266

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