Infection and Drug Resistance

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ORIGINAL RESEARCH

Retrospective Analysis of Sensitivity Characteristics of *Enterobacteriaceae*: A Study Based on Specimen Types, Sex, and Age Bracket of Patients

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Objective: *Enterobacteriaceae* have displayed widespread trends of antimicrobial resistance in recent years. Therefore, we aimed to analyse the antimicrobial susceptibility of common bacteria and explore the significance in treatment and research of infections induced by *Enterobacteriaceae*.

Methods: We retrospectively analysed 10,775 antimicrobial susceptibility test results acquired over a 6-year period in the affiliated hospital of Chengde Medical University. We divided the data based on specimen type (blood, sputum, pus, or urine), and population characteristics (age bracket and sex) for analysis. We mainly analysed the antimicrobial susceptibility of *Escherichia coli* (Eco), *Klebsiella pneumoniae* (Kpn), and *Enterobacter cloacae* (Ecl).

Results: In our study, it was found that the resistance rates of Eco, Kpn, and Ecl to most antimicrobial agents were significantly different ($P < 0.05$) on specimen type and age bracket. The Eco from sputum had the highest resistance rates except ciprofloxacin (CIP), levofloxacin (LVX), and gentamicin (GEN); the Kpn from urine had the highest resistance rates to all antimicrobial agents; the Ecl from urine had the highest resistance rates to most antimicrobial agents. The Eco from geriatric patients had the highest resistance rates except GEN and SXT; the Kpn from adult patients had the lowest resistance rates to most antimicrobial agents except LVX. The Eco isolated from males had higher resistance rates to most antimicrobial agents except CIP, LVX, and NIT than those isolated from females; the Kpn showed significant differences in antimicrobial susceptibility to only 5 out of 22 antimicrobial agents ($P < 0.05$); the Ecl showed significant differences in susceptibility only to two antimicrobial agents, LVX and TOB ($P < 0.01$).

Conclusion: The antimicrobial susceptibility of *Enterobacteriaceae* was significantly different among specimen type, age bracket and sex of patients, which is of great significance for the treatment and research of infection.

Keywords: *Enterobacteriaceae*, antimicrobial sensitivity, drug resistance, specimen type, infection

Introduction

Enterobacteriaceae consists of a large group of Gram-negative bacilli with similar morphology and biological characteristics, which widely exist in the environment. They are also part of the normal intestinal flora of humans and animals. *Enterobacteriaceae* are common bacteria that cause community and healthcare-related infections and are particularly important in the context of antimicrobial resistance.[1] With time and the widespread use of antimicrobial, *Enterobacteriaceae* have evolved to develop resistance to antimicrobial.[2] According to the Center for Disease Control's (CDC) description of the antimicrobial-resistant pathogens, *Klebsiella* species, *E. coli*, and *Enterobacter* species are the most crucial emerging resistance threats worldwide, especially their carbapenem-resistant strains.[3]

Carbapenem-resistant strains were initially reported in the 1980s and rapidly spread worldwide.[4] According to epidemiological data, different carbapenemase-producing *Enterobacteriaceae* are becoming more prevalent in different parts of the world. Bacterial infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), which are resistant to all classes of current antimicrobial agents, have become a serious challenge in the fight against bacterial infections in public health.[5–7] In the past 20 years, CRE has spread rapidly worldwide, leading to the rise of antimicrobial resistance. It

Received: 13 December 2022
Accepted: 16 March 2023
Published: 27 March 2023

is not clear whether the CRE was primitive or evolved to be resistant against antimicrobial. Based on the theory of biological evolution, the application of antimicrobial is an important factor in the formation of CRE. As a result, infections caused by CRE would spread, hospital admissions would become longer, thereby increasing economic and social expenses, and mortality would rise.[8] A study in the United States (US) from 2011 to 2014 found that 10% of *Klebsiella pneumoniae* are resistant to carbapenems, and 16–36% of *E. coli* are resistant to third-generation cephalosporins.[9] A European study found that, in clinical cases, the percentage of *K. pneumoniae* resistant to third-generation cephalosporins was 31%, and that of *E. coli* resistant to carbapenems and third-generation cephalosporins was 8% and 12%, respectively.[10] The Greek System for Antibiotic Resistant Research showed that the carbapenem resistance rate was 1% in 2001; however, by 2008 this rate increased to 30% in hospital wards and 60% in intensive care units.[11] According to the China Bacterial antimicrobial resistance Monitoring Network (CHINET), in 2005 the isolation rate of CRE was only 2.1%; however, it increased to 11.4% in 2019. The resistance rates of *K. pneumoniae* to imipenem (IPM) and meropenem (MEM) increased from 3.0% and 2.9% in 2005 to 25.3% and 26.8% in 2019, respectively.[12] This indicated that the antimicrobial resistance rate of *K. pneumoniae* increased with the increase in number of isolated antimicrobial-resistant strains.

To survive the action of antimicrobial, bacteria constantly search for new strategies, called "resistance mechanisms". Bacteria evolve to produce specific proteins that determine their resistance mechanisms. Over time, bacterial resistance mechanisms may change, leading to more resistant infections, and antibiotic-resistant bacteria can share their resistance genes with other bacteria that have not been exposed to antimicrobial. *Enterobacteriaceae* can often develop one or more resistance genes against effective antimicrobial. The main mechanisms of antimicrobial resistance in *Enterobacteriaceae* include the synthesis of carbapenemase enzymes, extended-spectrum beta-lactamases (ESBLs), AmpC enzymes, and porin loss, which reduces drug permeability.[13] Common enzymes in resistant strains are *K. pneumoniae* carbapenemase, imipenem's metallo-beta-lactamase, New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded metallo-beta-lactamase, which are among the most important acquired resistances.[14] This means that once bacteria carry multiple resistance genes, treating infections and developing antimicrobial are a huge challenge.

With the increased detection rate of CRE, carbapenem antimicrobial are not the most effective barrier to infection. Therefore, in addition to developing novel antimicrobial agents, healthcare workers should strengthen their awareness of monitoring and analysing bacterial resistance, use infection control and antimicrobial management strategies, and stop chains of transmission. This should be part of a proactive approach to tackling antimicrobial resistance at the regional, national, and international levels.[15]

Methods

Test Methods and Data Collection

A retrospective analysis was performed between July 2016 and December 2021 on clinical specimens from patients treated at the Affiliated Hospital of Chengde Medical University, a 2500-bed tertiary-care hospital in China. We collected patients' clinical data using the hospital's laboratory information system. Specimens from patients suspected of having an infection were collected in accordance with the hospital's specimen collection manual. Positive blood cultures and other samples were plated on blood agar, eosin methylene blue, and chocolate agar (Biokont, Wenzhou, China), and incubated at 35°C with 5% CO_2 for 18–24 h. Pure colonies on solid media were identified using matrix-assisted laser desorption/ionisation time of flight mass spectrometry (bioMérieux, Paris, France) according to the manufacturer's instructions. During the study period, antimicrobial susceptibility testing was performed for all isolates from each specimen using VITEK 2 automated systems (bioMérieux, Paris, France) AST-GN09 cards and E-test strips according to the Clinical and Laboratory Standards Institute guideline breakpoints.[16] The types of antimicrobial agents include ampicillin, piperacillin, amoxicillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin, tobramycin, cefazolin, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, cefepime, cefoxitin, nitrofurantoin, sulfamethoxazole-trimethoprim. *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *K. pneumoniae* ATCC BAA-1705 (American Type Culture Collection) were used as the quality control strains to ensure the quality of the procedure.

Statistical Analysis

The trend tests were performed by linear-by-linear combinations using SPSS (version 19.0). Trend bar charts were made using Origin (version 8.5). The differences in specimen type, and age bracket and sex of patients among *Enterobacteriaceae*, including *E. coli, K. pneumoniae*, and *E. cloacae*, were analysed using R × C chi-square test.

Results

A total of 10,755 strains of clinical *Enterobacteriaceae* were isolated, including *E. coli* (5,08 strains, 50.28%), *K. pneumoniae* (3034 strains, 28.21%), *E. cloacae* (711 strains, 6.61%), *Proteus mirabilis* (483 strains, 4.49%), *Klebsiella oxytoca* (312 strains, 2.9%), *Serratia marcescens* (205 strains, 1.91%), and others (602 strains, 5.6%).

In our study, we analysed data on susceptibility of *Enterobacteriaceae* to common antimicrobial agents from 2016 to 2021. We found that the antimicrobial agents against which *Enterobacteriaceae* demonstrated decreased resistance rates included ampicillin (AMP: 88.73%~82.21%), amoxicillin-clavulanic acid (AMC: 31.21%~13.62%), cefazolin (CZO:64.19%~53.62%), cefuroxime (CXM: 55.93%~50.55%), and ceftriaxone (CRO: 50.19%~45.66%), and those against which an increased antimicrobial resistance rate was observed included imipenem (IPM:2.41%~6.07%), meropenem (MEM: 2.22%~5.75%) (Figure 1). Furthermore, we analysed the trend of antimicrobial resistance rate from 2016 to 2021 and found that although the antimicrobial resistance rate of some antimicrobial increased or decreased, only the trend change of IPM and MEM showed a significant difference (Table 1).

We compared our antimicrobial resistance data of the top three bacteria among *Enterobacteriaceae* with that from the CHINET. The antimicrobial resistance rates was different from those reported by CHINET (2016–2020); However, the trend of antimicrobial resistance were similar. We emphatically analysed the antimicrobial resistance trends of top three bacteria, which had obvious differences in antimicrobial agent sensitivity. However, the trend of resistance against cefepime (FEP), a fourth-generation cephalosporin, was significantly different and the antimicrobial resistance rate decreased every year. These findings indicated that carbapenem-resistant *E. coli* was not prevalent in China or in

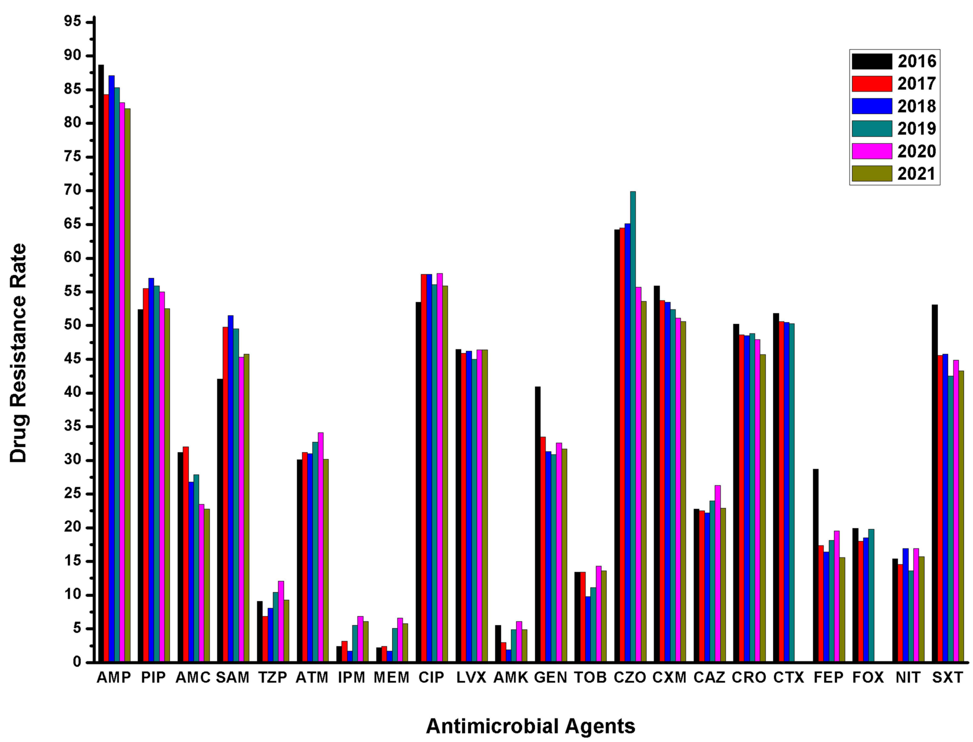

Figure 1 Changes in resistance rates of *Enterobacteriaceae* to common antimicrobial agents from 2016 to 2021.

Abbreviations: AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

Table 1 Trends in Antimicrobial Resistance Rates of *Enterobacteriaceae* from 2016 to 2021

Antimicrobial Agents	2016 (N-DR/ DR)DRR	2017 (N-DR/ DR)DRR	2018 (N-DR/ DR)DRR	2019 (N-DR/ DR)DRR	2020 (N-DR/ DR)DRR	2021 (N-DR/ DR)DRR	z	P values
AMP	(177/1393)88.73	(230/1238)84.33	(246/1664)87.12	(145/842)85.31	(168/827)83.12	(204/943)82.21	1.790	0.181
PIP	(179/197)52.39	(659/822)55.50	(822/1090)57.01	(486/617)55.94	(784/959)55.02	(930/1026)52.45	0.009	0.924
AMC	(1067/484)31.21	(983/463)32.02	(1389/509)26.82	(563/218)27.91	(1230/377)23.46	(787/233)22.84	3.128	0.077
SAM	(907/659)42.08	(737/731)49.80	(926/984)51.52	(710/696)49.50	(856/710)45.34	(954/805)45.76	0.005	0.943
TZP	(1432/144)9.14	(1383/102)6.87	(1759/154)8.05	(988/115)10.43	(1535/212)12.14	(1778/182)9.29	0.495	0.482
ATM	(225/97)30.12	(944/427)31.15	(1272/572)31.02	(955/463)32.65	(1155/597)34.08	(1370/592)30.17	0.080	0.777
IPM	(1539/38)2.41	(1438/47)3.16	(1842/31)1.66	(1330/78)5.54	(1597/118)6.88	(1812/117)6.07	4.459	0.035*
MEM	(1542/35)2.22	(1450/35)2.36	(1881/32)1.67	(1387/74)5.07	(1636/116)6.62	(1851/113)5.75	5.363	0.021*
CIP	(734/843)53.46	(630/856)57.60	(811/1100)57.56	(484/619)56.12	(740/1010)57.71	(864/1095)55.90	0.098	0.754
LVX	(843/734)46.54	(804/682)45.90	(1029/882)46.15	(803/657)45.00	(938/811)46.37	(1052/910)46.38	0.021	0.886
AMK	(1491/86)5.45	(1441/45)3.03	(1877/36)1.88	(1049/54)4.90	(1646/106)6.05	(1868/96)4.89	0.495	0.482
GEN	(932/645)40.90	(988/498)33.51	(1314/598)31.28	(763/341)30.89	(1174/568)32.61	(1336/621)31.73	1.471	0.225
TOB	(277/43)13.44	(1188/183)13.35	(1663/180)9.77	(942/118)11.13	(1502/250)14.27	(1694/267)13.62	0.106	0.745
CZO	(564/1011)64.19	(490/890)64.49	(641/1194)65.07	(219/508)69.88	(613/771)55.71	(717/829)53.62	1.766	0.184
CXM	(695/882)55.93	(687/796)53.67	(887/1022)53.54	(389/428)52.39	(835/871)51.06	(949/970)50.55	0.742	0.389
CAZ	(1216/360)22.84	(1151/334)22.49	(1487/424)22.19	(1111/350)23.96	(1292/460)26.26	(1513/450)22.92	0.156	0.693
CRO	(785/791)50.19	(764/722)48.59	(985/927)48.48	(418/399)48.84	(909/837)47.94	(1064/894)45.66	0.276	0.599
CTX	(685/735)51.76	(683/700)50.61	(935/954)50.50	(403/408)50.31	–	–	0.072	0.789
FEP	(1125/452)28.66	(1228/258)17.36	(1598/314)16.42	(1188/263)18.13	(1411/341)19.46	(1657/306)15.59	2.991	0.084
FOX	(1258/313)19.92	(1162/255)18.00	(1330/302)18.50	(190/47)19.83	–	–	0.003	0.955
NIT	(126/23)15.44	(458/78)14.55	(802/163)16.89	(247/39)13.64	(454/92)16.85	(536/100)15.72	0.069	0.793
SXT	(729/826)53.12	(808/678)45.63	(1036/876)45.82	(634/468)42.47	(964/785)44.88	(1112/850)43.32	1.866	0.172

Notes: "–"Represents the bacteria was intrinsic resistance to antimicrobial. N-DR as non-resistant strains, DR as resistant strains and DRR as antimicrobial resistance rate. (linear by linear association, *P<0.05).

Abbreviations: AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

a hospital. For *K. pneumoniae*, we found that the resistance to IPM and MEM increased significantly, which has the same trend as in the national antimicrobial resistance data. These findings indicated that carbapenem-resistant *K. pneumoniae* has increased in recent years, and aminoglycoside-resistant strains have also increased. We found that the sensitivity of *E. cloacae* to IPM and MEM also increased significantly, which has the same trend as in the national antimicrobial resistance data. Therefore, through the analysis of antimicrobial resistance of the above three kinds of bacteria and comparison with the national antimicrobial resistance data, we found that the detection rate of CRE is increasing every year; however, there are great differences between different bacterial species.(Figure 2, data are shown in Supplementary Table).

To further explore the factors influencing *Enterobacteriaceae* susceptibility to antimicrobial agents, we analysed the susceptibility of all *Enterobacteriaceae* to antimicrobial agents from 2016 to 2021, based on various dimensions, such as specimen type, and age bracket and sex of the patients.

For the specimen type, we found that *Enterobacteriaceae* isolated from blood, sputum, pus, and urine showed significant differences in response to all antimicrobial agents (Table 2). We retrospectively analysed the differences in antimicrobial susceptibility of *E. coli, K. pneumoniae*, and *E. cloacae* from different specimen types. *E. coli* showed significant differences in susceptibility to all antimicrobial agents (P < 0.01) except gentamicin (GEN). *E. coli* from sputum had the highest resistance rates to most antimicrobial agents except ciprofloxacin (CIP), levofloxacin (LVX), and GEN, whereas those from pus had the lowest resistance rates to most antimicrobial agents except CIP, LVX, and GEN. *K. pneumoniae* showed significant differences in the susceptibility to all antimicrobial agents (P < 0.01). After comparing the antimicrobial resistance rates of *K. pneumoniae* isolated from different specimens, we found *K. pneumoniae* from urine had the highest resistance rates to all antimicrobial agents, whereas those from pus had the lowest resistance rates. *Enterobacter cloacae* showed significant differences in the susceptibility to most antimicrobial agents (P < 0.01) except AMK and NIT. We found that the *E. cloacae* from urine had the highest resistance rates to most antimicrobial agents,

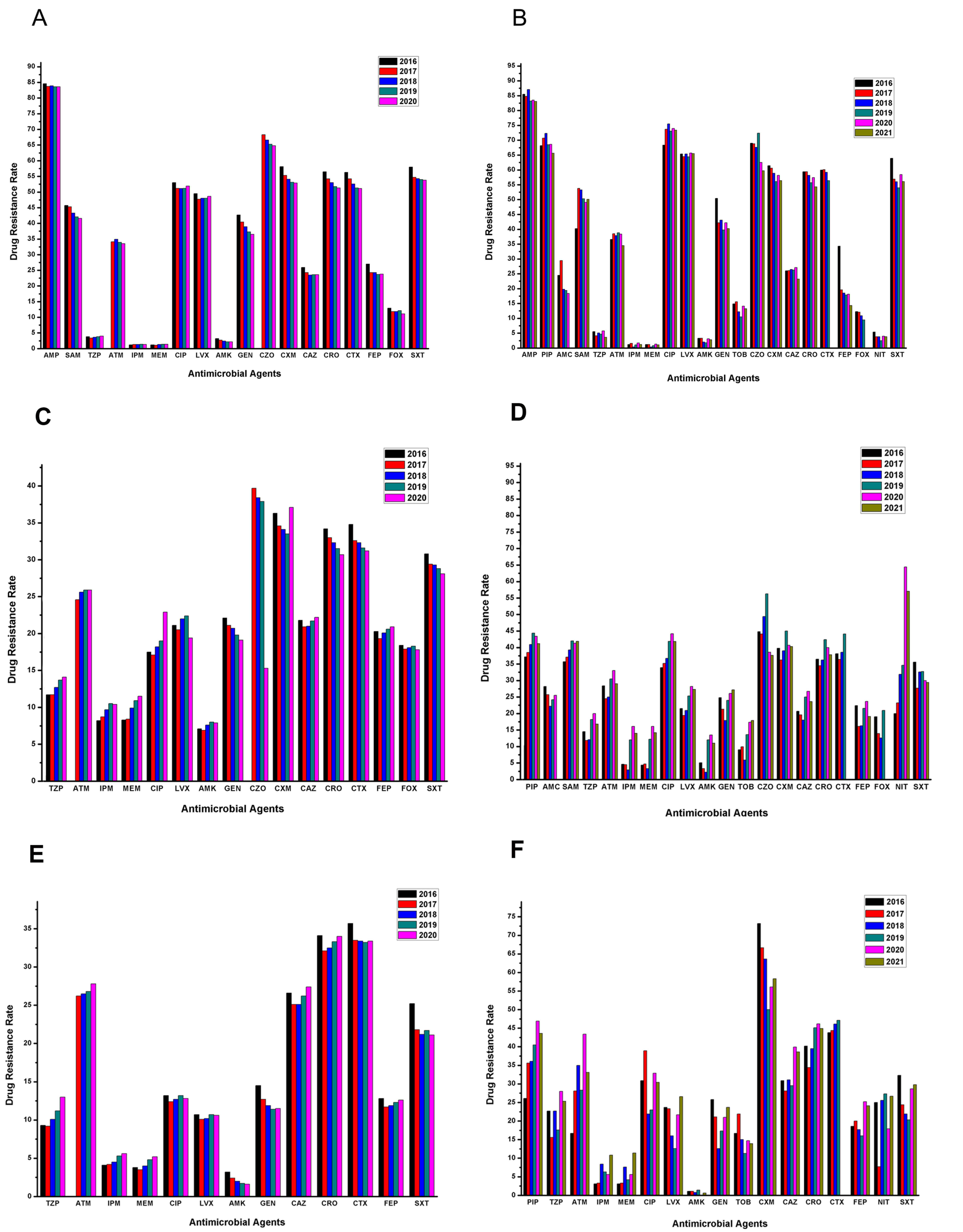

Figure 2 Changes in resistance rates of *E.coli, K. pneumoniae* and *E.cloacae* to common antimicrobial agents from 2016 to 2021. (**A** and **B**) Resistance rates of *E.coli*, (**C** and **D**) Resistance rates of *K.pneumoniae*, (**E** and **F**) Resistance rates of *E.cloacae*. (**A, C** and **E**) Resistance rates from CHINET, (**B, D** and **F**) Resistance rates from Affiliated Hospital of Chengde Medical University.

Abbreviations: AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

Table 2 Differences in Antimicrobial Susceptibility of *Enterobacteriaceae, E.coli, K.pneumoniae* and *E.cloacae* Isolated from Different Specimens

Antimicrobial Agent	Blood (N-DR/DR) DRR				Sputum (N-DR/DR) DRR				Pus (N-DR/DR) DRR
	Enterobacteriaceae	*E.coli*	*K.pneumoniae*	*E. cloacae*	*Enterobacteriaceae*	*E.coli*	*K.pneumoniae*	*E. cloacae*	*Enterobacteriaceae*
AMP	(142/895) 86.31	(116/664) 85.13	–	–	(206/1776) 89.61	(44/518) 92.17	–	–	(414/2049) 83.19
PIP	(446/596) 57.20	(204/457) 69.14	(162/84) 34.15	(42/25) 37.31	(1217/1180) 49.23	(84/401) 82.68	(793/580) 42.24	(120/110) 47.83	(1288/1557) 54.73
AMC	(757/268) 26.15	(537/148) 21.61	(188/50) 21.01	–	(1592/779) 32.86	(326/164) 33.47	(1055/343) 24.54	–	(1818/525) 22.41
SAM	(619/571) 47.98	(397/406) 50.56	(186/92) 33.09	–	(1420/1311) 48.00	(214/364) 62.98	(993/660) 39.93	–	(1669/1358) 44.86
TZP	(1093/108) 8.99	(735/46) 5.89	(234/37) 13.65	(55/16) 22.54	(2415/384) 13.72	(504/58) 10.32	(1342/241) 15.22	(209/65) 23.72	(2817/192) 6.38
ATM	(681/360) 34.58	(395/269) 40.51	(189/58) 23.48	(39/22) 36.07	(1634/781) 32.34	(225/267) 54.27	(1017/403) 28.38	(107/80) 42.78	(2121/861) 28.87
IPM	(1176/51) 4.16	(788/15) 1.87	(251/27) 9.71	(69/6) 8.00	(2666/191) 6.69	(563/16) 2.76	(1508/149) 8.99	(262/16) 5.76	(3017/105) 3.36
MEM	(1190/46) 3.72	(792/11) 1.37	(252/26) 9.35	(70/5) 6.67	(2721/189) 6.49	(565/15) 2.59	(1507/150) 9.05	(261/17) 6.12	(3097/100) 3.13
CIP	(510/691) 57.54	(226/556) 71.10	(179/91) 33.70	(56/15) 21.13	(1561/1244) 44.35	(146/417) 74.07	(977/607) 38.32	(171/103) 37.59	(1190/1819) 60.45
LVX	(634/602) 48.71	(293/510) 63.51	(219/59) 21.22	(65/10) 13.33	(2015/894) 30.73	(200/379) 65.46	(1301/356) 21.48	(206/72) 25.9	(1564/1632) 51.06
AMK	(1159/43) 3.58	(763/19) 2.43	(249/22) 8.12	(70/1) 1.41	(2621/184) 6.56	(534/29) 5.15	(1472/112) 7.07	(263/11) 4.01	(2901/111) 3.69
GEN	(785/417) 34.69	(439/343) 43.86	(216/55) 20.30	(64/7) 9.86	(2044/750) 26.84	(326/235) 41.89	(1236/345) 21.82	(189/84) 30.77	(1951/1056) 35.12
TOB	(875/132) 13.11	(547/96) 14.93	(213/27) 11.25	(53/4) 7.02	(2009/299) 12.95	(383/91) 19.20	(1196/149) 11.08	(142/42) 22.83	(2465/330) 11.81
CZO	(410/625) 60.39	(242/457) 65.38	(153/81) 34.62	–	(935/1418) 60.26	(76/416) 84.55	(767/601) 43.93	–	(1078/1538) 58.79
CXM	(534/612) 53.40	(308/443) 58.99	(172/88) 33.85	(31/39) 55.71	(1258/1406) 52.78	(117/430) 78.61	(912/621) 40.51	(84/179) 68.06	(1468/1416) 49.10
CAZ	(937/299) 24.19	(590/213) 26.53	(225/53) 19.06	(51/24) 32.00	(2224/685) 23.55	(382/198) 34.14	(1299/357) 21.56	(170/108) 38.85	(2534/660) 20.66
CRO	(585/567) 49.22	(316/435) 57.92	(179/81) 31.15	(43/28) 39.44	(1448/1256) 46.45	(121/427) 77.92	(946/586) 38.25	(136/129) 48.68	(1585/1314) 45.33
CTX	(333/369) 52.56	(190/287) 60.17	(96/56) 36.84	(22/12) 35.29	(827/787) 48.76	(73/271) 78.78	(549/349) 38.86	(79/79) 50.00	(541/395) 42.20
FEP	(1008/228) 18.45	(636/167) 20.80	(236/42) 15.11	(64/11) 14.67	(2274/628) 21.64	(392/184) 31.94	(1322/332) 20.07	(200/77) 27.80	(2728/468) 14.64
FOX	(527/91) 14.72	(386/37) 8.75	(119/15) 11.19	–	(1083/366) 25.26	(266/59) 18.15	(662/128) 16.20	–	(663/123) 15.65
NIT	(106/13) 10.92	(77/3) 3.75	(21/7) 25.00	(4/1) 20.00	(208/82) 28.28	(51/1) 1.92	(127/56) 30.60	(22/2) 8.33	(1149/199) 14.76
SXT	(629/569) 47.50	(327/397) 57.97	(191/186) 29.52	(62/0) 12.68	(1739/1053) 37.71	(210/214) 62.57	(1091/993) 30.86	(182/0) 33.33	(1534/1477) 49.05

Notes: "–"Represents the bacteria was intrinsic resistance to antimicrobial. N-DR denotes non-resistant strains, DR denotes resistant strains, and DRR denotes antimicrobial resistance rate (linear by linear association,*$P < 0.05$, **$P < 0.01$).

Abbreviations: AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

except AMK, GEN, TOB, and NIT, whereas the *E. cloacae* from pus had the lowest resistance rates to most antimicrobial agents, except NIT and sulfamethoxazole-trimethoprim (SXT).

Regarding the age bracket, we found that *Enterobacteriaceae* isolated from paediatric, adult, and geriatric patients showed significant differences in response to most antimicrobial agents except NIT and SXT. Simultaneously, we retrospectively analysed the differences in antimicrobial susceptibility of *E. coli, K. pneumoniae*, and *E. cloacae. E. coli* showed significant differences in the susceptibility to the following antimicrobial agents ($P < 0.05$): AMC, SAM, piperacillin-tazobactam (TZP), ATM, CIP, LVX, AMK, CXM, ceftazidime (CAZ), CRO, CTX, FEP, cefoxitin (FOX), and SXT. *E. coli* from geriatric patients had the highest resistance rates to most antimicrobial agents except GEN and SXT, whereas those from paediatric patients had the lowest resistance rates to most antimicrobial agents except PIP, AMC, GEN, CZO, and SXT. *K. pneumoniae* showed significant differences in the susceptibility to all antimicrobial agents ($P < 0.01$). *K. pneumoniae* from adult patients had the lowest resistance rates to most antimicrobial agents except LVX, whereas those from paediatric and geriatric patients almost had the highest resistance rates to all antimicrobial agents. *E. cloacae* showed significant differences in the susceptibility to most antimicrobial agents ($P < 0.05$) except

			Urine (N-DR/DR) DRR				Chi-square Value				*P*-values			
E.coli	***K.pneu moniae***	***E. cloacae***	***Enter obacteriaceae***	***E.coli***	***K.pneu moniae***	***E. cloacae***	***Enter obacteriaceae***	***E.coli***	***K.pneu moniae***	***E. cloacae***	***Enter obacteriaceae***	***E.coli***	***K.pneu moniae***	***E. cloacae***
(163/899) 84.65	–	–	(259/1516) 85.41	(373/1922) 83.75	–	–	37.961	25.737	–	–	0.000**	0.000**	–	–
(330/624) 65.41	(251/99) 28.29	(103/21) 16.94	(457/938) 67.24	(618/1370) 68.91	(156/208) 57.14	(37/62) 62.63	117.951	47.743	67.584	53.104	0.000**	0.000**	0.000**	0.000**
(752/177) 19.05	(278/52) 15.76	–	(1258/490) 28.03	(1610/425) 20.88	(208/140) 40.23	–	65.71	43.669	59.725	–	0.000**	0.000**	0.000**	–
(613/484) 44.12	(295/111) 27.34	–	(852/921) 51.95	(1202/1176) 49.45	(179/240) 57.28	–	22.717	54.479	84.752	–	0.000**	0.000**	0.000**	–
(1031/31) 2.92	(355/34) 8.74	(118/14) 10.61	(1645/134) 7.53	(2207/90) 3.92	(301/100) 24.94	(72/41) 36.28	101.845	51.79	41.445	22.761	0.000**	0.000**	0.000**	0.000**
(692/276) 28.51	(304/57) 15.79	(91/19) 17.27	(862/486) 36.05	(1283/765) 37.35	(210/165) 44.00	(52/40) 43.48	26.907	94.517	76.013	22.761	0.000**	0.000**	0.000**	0.000**
(1091/7) 0.64	(387/22) 5.38	(134/3) 2.19	(1719/41) 2.33	(2365/17) 0.71	(359/61) 14.52	(100/16) 13.79	62.431	23.794	21.124	14.26	0.000**	0.000**	0.000**	0.001**
(1091/7) 0.64	(386/23) 5.62	(135/2) 1.46	(1742/36) 2.02	(2367/14) 0.59	(354/66) 15.71	(100/16) 13.79	70.565	22.063	26.167	16.098	0.000**	0.000**	0.000**	0.001**
(331/731) 68.83	(282/106) 27.32	(113/19) 14.39	(479/1300) 73.07	(497/1799) 78.35	(169/232) 57.86	(66/47) 41.59	385.751	40.703	85.47	31.632	0.000**	0.000**	0.000**	0.000**
(462/636) 57.92	(338/70) 17.16	(123/14) 10.22	(605/1174) 65.99	(661/1721) 72.25	(240/180) 42.86	(78/38) 32.76	588.94	75.254	99.079	24.557	0.000**	0.000**	0.000**	0.000**
(1038/24) 2.26	(367/23) 5.90	(131/1) 0.76	(1728/51) 2.87	(2240/57) 2.48	(349/52) 12.97	(112/1) 0.88	46.412	14.046	17.82	6.412	0.000**	0.003**	0.000**	0.093
(582/480) 45.20	(315/74) 19.02	(123/9) 6.82	(1034/745) 41.88	(1322/974) 42.42	(251/150) 37.41	(82/30) 26.79	115.074	2.825	51.3	37.421	0.000**	0.419	0.000**	0.000**
(831/101) 10.84	(309/32) 9.38	(100/5) 4.76	(1148/201) 14.90	(1702/261) 13.30	(269/87) 24.44	(69/20) 22.47	7.821	19.694	50.396	22.051	0.050*	0.000**	0.000**	0.000**
(360/559) 60.83	(238/112) 32.00	–	(499/1115) 69.08	(743/1384) 65.07	(129/234) 64.46	–	49.363	87.553	90.181	–	0.000**	0.000**	0.000**	–
(489/548) 52.84	(286/93) 24.54	(75/46) 38.02	(711/1066) 59.99	(959/1296) 57.47	(167/226) 57.51	(28/83) 74.77	52.559	105.463	92.139	42.178	0.000**	0.000**	0.000**	0.000**
(899/198) 18.05	(363/46) 11.25	(112/24) 17.65	(1279/499) 28.07	(1737/644) 27.05	(257/163) 38.81	(62/54) 46.55	35.231	57.677	96.776	26.994	0.000**	0.000**	0.000**	0.000**
(499/538) 51.88	(295/84) 22.16	(99/21) 17.50	(755/1023) 57.54	(987/1269) 56.25	(176/218) 55.33	(47/65) 58.04	74.373	108.102	95.947	46.069	0.000**	0.000**	0.000**	0.000**
(287/315) 52.33	(163/52) 24.19	(42/10) 19.23	(698/1004) 58.99	(546/783) 58.92	(84/116) 58.00	(17/38) 69.09	75.789	66.038	50.426	29.321	0.000**	0.000**	0.000**	0.000**
(958/140) 12.75	(369/40) 9.78	(123/14) 10.22	(1344/432) 24.32	(1881/497) 20.90	(285/135) 32.14	(81/35) 30.17	84.142	87.437	69.85	22.753	0.000**	0.000**	0.000**	0.000**
(456/48) 9.52	(162/20) 10.99	–	(1272/238) 15.76	(1041/136) 11.55	(135/40) 22.86	–	60.684	19.184	11.92	–	0.000**	0.000**	0.008**	–
(115/1) 0.86	(32/8) 20.00	(9/3) 25.00	(1098/183) 14.29	(1808/74) 3.93	(177/165) 48.25	(65/21) 24.42	39.533	–	25.75	3.539	0.000**	–	0.000**	0.316
(414/613) 61.02	(297/295) 23.85	(115/0) 12.88	(798/972) 54.92	(1011/1202) 55.81	(229/179) 42.89	(64/0) 43.36	145.381	13.23	35.49	40.152	0.000**	0.004**	0.000**	0.000**

IPM, AMK, and CXM. In contrast to the antimicrobial resistance rates of *E. cloacae*, those of *E. coli* and *K. pneumoniae* were not visibly related to the age bracket of the patients (Table 3).

Regarding the sex, we found significant differences between *Enterobacteriaceae* isolated from males and females in response to almost antimicrobial agents except CRO ($P < 0.05$). We retrospectively analysed the differences in antimicrobial susceptibility of *E. coli, K. pneumoniae*, and *E. cloacae. E. coli* showed significant differences in susceptibility to most antimicrobial agents ($P < 0.01$). In the comparison of the antimicrobial resistance rates of *E. coli* isolated from males and females, the *E. coli* isolated from males had higher resistance rates to most antimicrobial agents except CIP, LVX, and NIT than those isolated from females. *K. pneumoniae* showed significant differences in antimicrobial susceptibility to only 5 out of 22 antimicrobial agents ($P < 0.05$). Although there were no significant differences in susceptibility to most antimicrobial based on the sex of the patients, the resistance rates to all antimicrobial were slightly higher in strains isolated from males than in those from females. *E. cloacae* showed significant differences in susceptibility only to two antimicrobial agents, LVX and TOB ($P < 0.01$). In the comparison with the antimicrobial resistance rates of *E. cloacae*, we did not find differences in antimicrobial resistance rates (Table 4).

Table 3 Differences in Antimicrobial Susceptibility of *Enterobacteriaceae, E.coli, K.pneumoniae* and *E.cloacae* Isolated from Patients of

Antimicrobial Agent	Paediatric (N-DR/DR) DRR				Adult (N-DR/DR) DRR			
	Enterobacteriaceae	*E.coli*	*K.pneumoniae*	*E.cloacae*	*Enterobacteriaceae*	*E.coli*	*K.pneumoniae*	*E.cloacae*
AMP	(90/588) 86.73	(42/221) 84.03	–	–	(6,17/3426) 84.74	(422/2259) 84.26	–	–
PIP	(281/413) 59.51	(74/173) 70.04	(76/90) 54.22	(90/145) 61.70	(2100/2227) 51.47	(761/1569) 67.34	(848/456) 34.97	(176/98) 35.77
AMC	(466/201) 30.13	(180/46) 20.35	(114/52) 31.33	–	(3166/1011) 24.20	(1892/469) 19.86	(1016/253) 19.94	–
SAM	(396/350) 46.92	(155/109) 41.29	(97/88) 47.57	–	(2715/2139) 44.07	(1445/1326) 47.85	(1002/515) 33.95	–
TZP	(715/56) 7.26	(255/8) 3.04	(159/26) 14.05	(250/21) 7.75	(4517/388) 7.91	(2571/112) 4.17	(1261/186) 12.85	(239/65) 21.38
ATM	(445/204) 31.43	(165/73) 30.67	(106/52) 32.91	(135/73) 35.10	(3170/1244) 28.18	(1571/811) 34.05	(1033/323) 23.82	(168/74) 30.58
IPM	(742/28) 3.64	(262/2) 0.76	(167/18) 9.73	(264/8) 2.94	(4827/193) 3.84	(2747/28) 1.01	(1396/128) 8.40	(297/20) 6.31
MEM	(747/26) 3.36	(263/1) 0.38	(167/18) 9.73	(265/7) 2.57	(4929/178) 3.49	(2750/25) 0.90	(1399/125) 8.20	(300/17) 5.36
CIP	(414/357) 46.30	(109/154) 58.56	(112/73) 39.46	(146/125) 46.13	(2287/2620) 53.39	(763/1920) 71.56	(972/472) 32.69	(229/75) 24.67
LVX	(540/233) 30.14	(144/120) 45.45	(162/23) 12.43	(185/87) 31.99	(2869/2233) 43.77	(1013/1762) 63.5	(1213/307) 20.20	(265/52) 16.40
AMK	(755/16) 2.08	(262/1) 0.38	(173/12) 6.49	(268/3) 1.11	(4722/191) 3.89	(2607/76) 2.83	(1359/90) 6.21	(299/5) 1.64
GEN	(503/267) 34.68	(137/126) 47.91	(140/45) 24.32	(177/94) 34.69	(3350/1553) 31.67	(1514/1168) 43.55	(1178/269) 18.59	(259/44) 14.52
TOB	(583/62) 9.61	(216/21) 8.86	(134/22) 14.10	(189/18) 8.70	(3743/477) 11.30	(1984/307) 13.40	(1149/131) 10.23	(205/24) 10.48
CZO	(225/488) 68.44	(84/161) 65.71	(73/107) 59.44	–	(1765/2407) 57.69	(850/1540) 64.44	(782/462) 37.14	–
CXM	(325/409) 55.72	(118/134) 53.17	(86/91) 51.41	(90/168) 65.12	(2400/2308) 49.02	(1134/1484) 56.68	(943/458) 32.69	(123/165) 57.29
CAZ	(596/177) 22.90	(205/59) 22.35	(138/47) 25.41	(203/69) 25.37	(4061/1043) 20.43	(2134/640) 23.07	(1246/277) 18.19	(220/96) 30.38
CRO	(362/377) 51.01	(120/132) 52.38	(90/87) 49.15	(108/152) 58.46	(26,57/2107) 44.23	(1174/1447) 55.21	(975/427) 30.46	(180/110) 37.93
CTX	(216/251) 53.75	(61/78) 56.12	(56/59) 51.30	(72/107) 59.78	(1462/1302) 47.11	(694/898) 56.41	(548/258) 32.01	(83/54) 39.42
FEP	(645/126) 16.34	(221/43) 16.29	(145/40) 21.62	(227/43) 15.93	(4282/821) 16.09	(2285/488) 17.60	(1273/249) 16.36	(268/49) 15.46
FOX	(338/93) 21.58	(125/5) 3.85	(81/20) 19.80	–	(1979/409) 17.13	(1225/147) 10.71	(596/94) 13.62	–
NIT	(80/14) 14.89	(28/1) 3.45	(11/12) 52.17	(40/1) 2.44	(1291/219) 14.50	(1030/39) 3.65	(199/106) 34.75	(37/6) 13.95
SXT	(396/375) 48.64	(97/166) 63.12	(128/57) 30.81	(125/146) 53.87	(2701/2202) 44.91	(1094/1584) 59.15	(1075/372) 25.71	(236/67) 22.11

Notes: "–"Represents the bacteria was intrinsic resistance to antimicrobial. N-DR denotes non-resistant strains, DR denotes resistant strains, and DRR denotes antimicrobial resistance rate (linear by linear association, **P* < 0.05, ***P* < 0.01). Paediatric (2 months-14 years), Adult (15–65 years), Geriatric (over 66 years).
Abbreviations; AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

Discussion

In this study, we analysed the antimicrobial susceptibility data of *Enterobacteriaceae*-related infections from 2016 to 2021 that expounded its antimicrobial susceptibility trends in recent years in Affiliated Hospital of Chengde Medical University, which were different from those reported in national data.[12,17–20] The antimicrobial susceptibility trends of *Enterobacteriaceae* observed in our study is generally consistent with those in China, which indicates that the results truly reflect the epidemic status of *Enterobacteriaceae* in recent years. However, the results indicate a challenge for medical workers working on infection-related issues. According to the US CDC report on antibiotic resistance, 131,900 cases infected by ESBL-producing *Enterobacteriaceae* were estimated in 2013, whereas 197,400 cases were estimated in 2019. In 2013, 118,00 cases infected by CRE were estimated, whereas 13,100 cases were estimated in 2019.[3] *K. pneumoniae* and *E. cloacae* showed increasing resistance to carbapenems and β-lactam antimicrobial such as IPM, MEM, SAM, TZP, and ATM every year. This indicates that the carbapenem-resistant strains have caused an increase in

Different Age Brackets

Geriatric (N-DR/DR) DRR				Chi-Square Value				*P*-values			
Enterobacteriaceae	*E.coli*	*K. pneumoniae*	*E.cloacae*	*Enterobacteriaceae*	*E.coli*	*K. pneumoniae*	*E. cloacae*	*Enterobacteriaceae*	*E.coli*	*K.pneumoniae*	*E.cloacae*
(463/2904) 86.25	(314/1782) 85.02	–	–	4.234	0.58	–	–	0.012*	0.748	–	–
(1479/2072) 58.35	(529/1280) 70.76	(575/514) 47.20	(143/134) 48.38	43.61	5.712	48.556	34.123	0.000**	0.058	0.000**	0.000**
(2393/1078) 31.06	(1386/450) 24.51	(763/335) 30.51	–	47.064	13.365	38.304	–	0.000**	0.001**	0.000**	–
(1984/2102) 51.44	(1030/11,41) 52.56	(725/599) 45.24	–	48.501	18.243	42.721	–	0.000**	0.000**	0.000**	–
(3651/466) 11.32	(1975/122) 5.82	(1027/240) 18.94	(236/79) 25.08	34.941	8.833	19.381	31.44	0.000**	0.012*	0.000**	0.000**
(2306/1301) 36.07	(1067/789) 42.51	(745/378) 33.66	(141/99) 41.25	57.028	36.754	30.716	6.022	0.000**	0.000**	0.000**	0.049*
(3998/208) 4.95	(2147/27) 1.24	(1190/136) 10.26	(298/24) 7.45	7.622	0.902	2.947	5.904	0.022*	0.637	0.229	0.052
(4079/202) 4.72	(2150/24) 1.10	(1183/143) 10.78	(297/25) 7.76	10.103	1.774	5.561	7.805	0.006**	0.412	0.062	0.020*
(1563/2555) 62.04	(453/1644) 78.4	(680/587) 46.33	(195/120) 38.10	103.38	61.363	52.769	29.609	0.000**	0.000**	0.000**	0.000**
(2062/2218) 51.82	(611/1562) 71.88	(928/398) 30.02	(227/95) 29.50	146.784	99.011	51.897	22.421	0.000**	0.000**	0.000**	0.000**
(3902/218) 5.29	(2035/64) 3.05	(1140/127) 10.02	(306/9) 2.86	20.95	6.158	14.051	2.555	0.000**	0.046*	0.001**	0.279
(2656/1459) 35.46	(1219/878) 41.87	(895/370) 29.25	(225/90) 28.57	14.876	3.995	42.571	32.692	0.001**	0.136	0.000**	0.000**
(2941/502) 14.58	(1528/250) 14.06	(892/171) 16.09	(186/48) 20.51	24.009	4.868	17.816	15.798	0.000**	0.088	0.000**	0.000**
(1256/2317) 64.85	(617/1277) 67.42	(554/551) 49.86	–	56.963	4.19	56.457	–	0.000**	0.123	0.000**	–
(1719/2261) 56.81	(796/1252) 61.13	(659/571) 46.42	(103/202) 66.23	55.133	12.292	61.976	5.871	0.000**	0.002**	0.000**	0.053
(3120/1160) 27.10	(1529/645) 29.67	(972/354) 26.70	(196/126) 39.13	57.82	29.439	30.638	13.408	0.000**	0.000**	0.000**	0.001**
(1908/2094) 52.32	(820/1228) 59.96	(686/545) 44.27	(161/147) 47.73	59.712	12.953	63.856	23.165	0.000**	0.002**	0.000**	0.000**
(1030/1253) 54.88	(451/745) 62.29	(381/310) 44.86	(78/87) 52.73	31.936	10.193	33.881	13.018	0.000**	0.006**	0.000**	0.001**
(3287/989) 23.13	(1644/526) 24.24	(1011/314) 23.7	(227/95) 29.50	78.745	35.995	24.311	24.36	0.000**	0.000**	0.000**	0.000**
(1630/418) 20.41	(932/147) 13.62	(515/105) 16.94	–	9.958	12.995	4.253	–	0.007**	0.002**	0.119	–
(1252/262) 17.31	(993/41) 3.97	(167/123) 42.41	(63/23) 26.74	4.514	0.154	5.41	14.403	0.105	0.926	0.067	0.001**
(2188/1913) 46.65	(960/1128) 54.02	(787/476) 37.69	(207/108) 34.29	5.175	36.525	45.058	63.259	0.075	0.000**	0.000**	0.000**

infections in recent years, which is a major challenge to fight. One relatively good news is that the susceptibility of *E. coli* to most antimicrobial agents has remained stable in recent years.

In the retrospective study, although the trend of antimicrobial resistance was similar in different regions of China, the resistance rate of bacteria belonging to the same genus varied greatly between different hospitals and regions. We speculate that the difference in bacterial resistance rate between hospitals may be related to differences in the administration of antimicrobial and endemic strains in the area. Nevertheless, there is no denying that the increase in infections caused by resistant strains is a serious issue.

In our further analysis, we found an interesting phenomenon of obvious differences in the susceptibility of bacteria to antimicrobial agents depending on specimen type, and age bracket and sex of the patients, which has rarely been reported in literature.

Further analysis found that *Enterobacteriaceae* showed significant differences in antimicrobial resistance based on specimen type. In general, the spectrum of bacterial infections in one hospital or region should be similar; however, the

Table 4 Differences in Antimicrobial Susceptibility of *Enterobacteriaceae, E.coli, K.pneumoniae* and *E.cloacae* Isolated from Patients of Different Sex

Antimicrobial Agent	Male (N-DR/DR) DRR				Female (N-DR/DR) DRR				Chi-Square Value				*P*-values			
	Enterobacteriaceae	*E.coli*	*K. pneumoniae*	*E.cloacae*	*Enterobacteriaceae*	*E.coli*	*K. pneumoniae*	*E. cloacae*	*Enterobacteriaceae*	*E.coli*	*K. pneumoniae*	*E. cloacae*	*Enterobacteriaceae*	*E.coli*	*K. pneumoniae*	*E. cloacae*
AMP	(501/3589) 87.75	(283/1908) 87.08	–	–	(669/3329) 83.27	(520/2529) 82.95	–	–	32.852	16.826	–	–	0.000**	0.000**	–	–
PIP	(2122/2476) 53.85	(506/1393) 73.35	(984/731) 42.62	(247/168) 40.48	(1738/2236) 56.27	(902/1760) 66.12	(515/329) 38.98	(118/78) 39.80	5.028	27.214	3.094	0.026	0.025*	0.000**	0.079	0.872
AMC	(3025/,413) 31.84	(1420/520) 26.80	(1261/451) 26.34	–	(3000/877) 22.62	(2175/491) 18.42	(632/189) 23.02	–	88.112	46.105	3.244	–	0.000**	0.000**	0.072	–
SAM	(2616/2543) 49.29	(1043/1236) 54.23	(1220/829) 40.46	–	(2479/2048) 45.24	(1684/ 14,43) 46.15	(604/373) 38.18	–	15.885	34.495	1.437	–	0.000**	0.000**	0.231	–
TZP	(4634/629) 11.95	(2043/150) 6.84	(1624/331) 16.93	(366/105) 22.29	(4249/281) 6.20	(2949/101) 3.31	(823/121) 12.82	(168/51) 23.29	95.438	34.845	8.184	0.085	0.000**	0.000**	0.004**	0.771
ATM	(3117/1536) 33.01	(1116/825) 42.50	(1249/527) 29.67	(232/126) 35.2	(2804/1213) 30.20	(1788/914) 33.83	(635/226) 26.25	(111/54) 32.73	7.885	36.304	3.334	0.305	0.005**	0.000**	0.068	0.581
IPM	(5070/311) 5.78	(2238/42) 1.84	(1845/211) 10.26	(454/31) 6.39	(4497/118) 2.56	(3113/20) 0.64	(908/71) 7.25	(210/16) 7.08	62.816	16.888	7.131	0.118	0.000**	0.000**	0.008**	0.731
MEM	(5189/295) 5.38	(2248/33) 1.45	(1841/215) 10.46	(454/31) 6.39	(4566/111) 2.37	(3111/21) 0.67	(908/71) 7.25	(212/14) 6.19	59.459	8.052	7.981	0.01	0.000**	0.005**	0.005**	0.92
CIP	(2525/2740) 52.04	(612/1583) 72.12	(1179/773) 39.60	(321/150) 31.85	(1739/2792) 61.62	(797/2251) 73.85	(585/359) 38.03	(165/54) 24.66	90.888	1.951	0.659	3.711	0.000**	0.063	0.417	0.054
LVX	(3206/2274) 41.5	(815/1465) 64.25	(1545/508) 24.74	(368/117) 24.12	(2265/2410) 51.55	(1068/ 2064) 65.90	(758/220) 22.49	(194/32) 14.16	102.63	1.576	1.837	9.241	0.000**	0.209	0.175	0.002**
AMK	(5004/266) 5.05	(2131/64) 2.92	(1791/166) 8.48	(460/11) 2.34	(4375/159) 3.51	(2970/80) 2.62	(881/63) 6.67	(216/3) 1.37	13.949	0.41	2.865	0.3	0.000**	0.522	0.091	0.584
GEN	(3576/1684) 32.02	(1215/979) 44.62	(1491/462) 23.66	(369/101) 21.49	(2933/1595) 35.23	(1767/ 1281) 42.03	(722/222) 23.52	(180/39) 17.81	11.255	3.5	0.007	1.25	0.001**	0.061	0.934	0.236
TOB	(3842/596) 13.43	(1579/277) 14.92	(1449/225) 13.44	(285/60) 17.39	(3425/445) 11.50	(2299/318) 12.15	(726/99) 12.00	(145/13) 8.23	7.031	7.242	1.017	7.335	0.008**	0.007**	0.313	0.007**
CZO	(1644/2843) 63.36	(546/1399) 71.93	(952/768) 44.65	–	(1602/2369) 59.66	(1053/ 1722) 62.05	(457/352) 43.51	–	12.217	49.77	0.29	–	0.000**	0.000**	0.59	–
CXM	(2290/2751) 54.57	(753/1376) 64.63	(1115/780) 41.16	(175/276) 61.20	(2154/2227) 50.83	(1355/ 1627) 54.56	(573/340) 37.24	(81/126) 60.87	13.152	51.984	3.951	0.006	0.000**	0.000**	0.047*	0.936
CAZ	(4111/1370) 25.00	(1599/681) 29.87	(1578/477) 23.21	(321/163) 33.68	(3666/1010) 21.60	(2417/715) 22.83	(778/201) 20.53	(150/76) 33.63	16.218	34.161	2.746	0	0.000**	0.000**	0.098	0.99
CRO	(2602/2491) 48.91	(780/1349) 63.36	(1162/735) 38.75	(262/191) 42.16	(2325/2087) 47.30	(1395/ 1590) 53.27	(589/324) 35.49	(126/86) 40.57	2.447	51.83	2.786	0.152	0.118	0.000**	0.095	0.697
CTX	(1410/1539) 52.19	(462/860) 65.05	(642/425) 39.83	(128/106) 45.30	(1298/1267) 49.40	(786/955) 54.85	(343/202) 37.06	(63/48) 43.24	4.277	32.377	1.162	0.129	0.039*	0.000**	0.281	0.72
FEP	(4332/1145) 20.91	(1731/547) 24.01	(1627/426) 20.75	(376/108) 22.31	(3882/791) 16.93	(2578/550) 17.58	(802/177) 18.08	(187/39) 17.26	25.858	33.684	3.967	2.4	0.000**	0.000**	0.085	0.121
FOX	(2010/580) 22.39	(994/165) 14.24	(786/153) 16.29	–	(1937/340) 14.93	(1403/152) 9.77	(406/66) 13.98	–	44.012	12.813	1.279	–	0.000**	0.000**	0.258	–
NIT	(889/279) 23.89	(577/21) 3.51	(213/147) 40.83	(68/20) 22.73	(1734/216) 11.08	(1511/61) 3.88	(164/94) 36.43	(35/9) 20.45	89.754	0.162	1.223	0.088	0.000**	0.687	0.269	0.766
SXT	(2965/2289) 43.57	(923/1266) 57.83	(1314/638) 32.68	(339/131) 27.87	(2320/2201) 48.68	(1290/ 1750) 57.57	(676/267) 28.31	(167/52) 23.74	25.621	0.038	5.652	1.305	0.000**	0.846	0.017*	0.253

Notes: "–"Represents the bacteria was intrinsic resistance to antimicrobial. N-DR denotes non-resistant strains, DR denotes resistant strains, and DRR denotes antimicrobial resistance rate (linear by linear association, $^{*}P < 0.05$, $^{**}P < 0.01$).

Abbreviations: AMP, ampicillin; PIP, piperacillin; AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; ATM, aztreonam; IPM, imipenem; MEM, meropenem; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CZO, cefazolin; CXM, cefuroxime; CAZ, ceftazidime; CRO, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; NIT, nitrofurantoin; SXT, sulfamethoxazole-trimethoprim.

antimicrobial susceptibility of bacteria causing infections in different sites vary greatly. A study in Taiwan[21] found that the rates of isolated ESBL-producing *E. coli* and *K. pneumoniae* from sputum and urine were higher than those from blood. This indicates that *Enterobacteriaceae* isolated from urine and sputum specimens have higher antimicrobial resistance. This is consistent with a part of our findings, because only *K. pneumoniae* isolated from urine specimens had a high antimicrobial resistance rate in our study. However, the antimicrobial resistance rate of *E. coli* isolated from sputum was higher than that of the above research. We did not analyse the resistance genes of antimicrobial-resistant strains, and ESBL is only a part of the resistance mechanism. However, we hypothesised that this might be related to the infection of specific sites caused by bacteria with certain antimicrobial-resistance genes and the distribution and accumulation concentration of antimicrobial agents in the body.

It is well known that the human body has differences in immunity at different age brackets, and it can rely on its own immune system to resist bacterial infections. Antimicrobial are external interventions provided to fight infections when the immune capacity of the body is insufficient. We found that *Enterobacteriaceae* showed great differences in antimicrobial susceptibility based on the age bracket of the patients from whom they are isolated. However, a similar significant difference in resistance rates was not observed for *E. cloacae*. In a previous study,[22] older women (aged > 65 years) were reported to have *E. coli* with higher resistance rates to AMP, CIP, and co-trimoxazole. The increasing resistance of *Enterobacteriaceae* is often associated with the higher use of antimicrobial.[23,24] Although we did not analyse medication management of infections caused by *Enterobacteriaceae*, our results show that paediatric patients have strains with the highest rates of resistance to certain antimicrobial agents, suggesting that antimicrobial resistance is not only related to the amount of drug used. In our findings, *E. coli* and *K. pneumoniae* isolated from adults had the lowest antimicrobial resistance to most antimicrobial agents. Another study showed that adding pentoxifylline to antimicrobial in murine neonatal sepsis promoted an anti-inflammatory milieu through the inhibition of plasma tumour necrosis factor and the enhancement of interleukin 10 production in the plasma and organs without increasing bacterial growth.[25] This is more likely to be related to the immune system.

We initially predicted that there might be differences in antimicrobial susceptibility based on the dimension of sex of the patients, which was confirmed by our results. However, the differences in antimicrobial susceptibility based on sex of the patients is more obvious in *E. coli*; the antimicrobial resistance rates of strains isolated from males was significantly higher than those of strains isolated from females. A study of antimicrobial susceptibility based on sex of the patients from whom the specimen was isolated showed that the susceptibility to most antimicrobial agents of strains isolated from males was significantly higher than those of strains isolated from females. Further, *E. coli* showed sensitivity differences to most antimicrobial agents based on sex of the patients.[26] Another study showed that *E. coli* strains isolated from male patients were more resistant to antimicrobial agents.[27] Currently, there is no study regarding the mechanism of this aspect; however, we speculate that there must be internal and external factors influencing this difference. On the one hand, the difference in hormones between males and females leads to differences in their antimicrobial environment; on the other hand, it may be related to the individual differences in the use of antimicrobial agents.

In conclusion, the antimicrobial susceptibility of *Enterobacteriaceae* was significantly different among specimen type, age bracket and sex of patients. The antimicrobial susceptibility observed in our study is in line with the current infection situation. However, the antimicrobial resistance rate of one hospital or region should be the guidance for the rational use of drugs. Furthermore, the difference in bacterial susceptibility to antimicrobial means that it provides data basis for clinical rational drug use and further research on bacterial drug resistance.

Data Sharing Statement

All relevant data are within the manuscript. The data underlying the findings of this study, except the data on China's bacterial antimicrobial resistance, are retained at the Affiliated Hospital of Chengde Medical University and will not be made openly accessible because of ethical and privacy concerns.

Ethical Approval Statement

Ethical approval from the Institutional Review Board of the Affiliated Hospital of Chengde Medical University. All the clinical samples were part of the routine hospital laboratory procedure and there was no additional burden on patients. We declare that our study complies with the Declaration of Helsinki.

Acknowledgments

This study was supported by the Natural Science Foundation of Chengde Medical University (grant nos. 201627).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests in this work.

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