

Analysis of Susceptibilities of Carbapenem Resistant Enterobacterales to Colistin in Intra-Abdominal, Respiratory and Urinary Tract Infections from 2015 to 2017

This article was published in the following Dove Press journal:
Infection and Drug Resistance

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Purpose: To evaluate the susceptibility rates of carbapenem-resistant (CR)-Enterobacterales strains from Chinese intra-abdominal infections (IAI), respiratory tract infections (RTI) and urinary tract infections (UTI) between 2015 and 2017 to colistin.

Methods: In total, 7138 Enterobacterales including 1074 CR-Enterobacterales strains were isolated from IAI+UTI+RTI samples and collected in 21 hospitals across 7 regions of China. Antimicrobial susceptibilities were determined at a central laboratory using CLSI broth microdilution and interpretive standards.

Results: From 2015 to 2017, *E. coli* (51.4%) and *K. pneumoniae* (30.0%) accounted for the majority of Enterobacterales isolated from IAIs, UTIs and RTIs. The percentage of CR strains within the species was highest for *S. marcescens* (27.9%), followed by *K. pneumoniae* (24.8%), *P. mirabilis* (22.6%), *K. oxytoca* (19.5%), *E. cloacae* (17.7%), *C. freundii* (12.5%), *K. aerogenes* (11.0%) and lowest for *E. coli* (6.9%). Colistin susceptibilities were generally higher in CS than in CR isolates and were 83.5% for CR-*E. coli*, 88.6% for CR-*K. pneumoniae*, 79.2% for CR-*E. cloacae* and 87.5% for CR-*K. aerogenes*. For IAI and UTI isolates in particular, CR-*E. coli* and CR-*K. pneumoniae* showed a trend of decreasing susceptibility, which was especially noted for CR-*E. coli* in UTI isolates, and for both organisms in IAI isolates susceptibility dropped markedly in 2017.

Conclusion: Colistin was a last resort antibiotics for empirical CR-Enterobacterales treatments, since especially the percentage of CR-*K. pneumoniae* was 30.0% of all IAI, UTI and RTI isolates, with an incidence of 24.8% CR strains, of which 88.6% were susceptible to colistin. Also other analyzed CR-Enterobacterales showed colistin susceptibilities of ≥80.0%. However, resistance rates of IAI derived CR-*K. pneumoniae* and CR-*E. coli*, and CR-*K. pneumoniae* UTI isolates to colistin increased between 2015 and 2017, which should further be closely monitored.

Keywords: Enterobacterales, carbapenem, colistin, intra-abdominal infection, respiratory tract infection, urinary tract infection

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Introduction

Multi-drug resistance (MDR) has become a significant problem worldwide¹ with carbapenems being commonly used for the treatment of MDR bacterial infections. However, carbapenem-resistant (CR)-Enterobacterales induce infections that have high mortality rates and limited treatment options.² The mechanisms of carbapenem resistance in Enterobacterales include AmpC expression in combination with the

loss of porin due to alterations of Omp genes, and the production of acquired carbapenemases.^{3,4} In China, the incidence of CR-Enterobacterales infections has been steadily increasing,⁵ with resistance rates to *E. coli* and *K. pneumoniae* of 0% and 0.7% in 2004⁶ raised to 1.0% and 13.4% in 2014, respectively.⁷ Therefore, we investigated the susceptibility rates of major Enterobacterales strains isolated from hospitalized patients with intra-abdominal infections (IAIs), urinary tract infections (UTIs) and respiratory tract infections (RTI) between 2015 and 2017. Isolates were collected for the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program, which was established in China in 2002 for IAIs and in 2012 for UTIs to monitor in vitro antimicrobial susceptibility profiles of clinical isolates collected from Chinese patients with IAIs and UTIs.⁸

Polymyxins are one of the last-line antibiotic choices for such infections. The World Health Organization (WHO) has designated polymyxin as the “highest priority critically important antimicrobial for human medicine”⁹ as it is often one of the only therapies available for treating serious bacterial infections in critically ill patients. However, polymyxin resistance rates of 36.1% and 15.9% have been reported in some parts of the world and were found to be independently associated with mortality.^{10,11} Emergence of resistance towards antibiotics of last-resort has also been reported in China,¹² but while colistin has been in clinical use for about five years, the sensitivities of CR-Enterobacterales to this drug remain unclear. In the present study, we analyzed the prevalence of CR-Enterobacterales isolates from Chinese IAIs, RTIs and UTIs between 2015 and 2017 focusing on the incidence of colistin resistance.

Methods

Isolates from IAI, UTI and RTI Infections

The Human Research Ethics Committee of our hospital approved the study protocols (Et. Number: S-K238). Since some Enterobacterales members have an acquired resistance against colistin but others including *Proteus* spp., *Providencia* spp., *Serratia* spp., and *Morganella* spp. have an intrinsic resistance,¹³ we focused on Enterobacterales isolates, which are known not to be naturally resistant to colistin.

In total, 7113 Enterobacterales (2015, n = 2203; 2016, n = 2375; 2017, n = 2535) and 1070 CR-Enterobacterales (2015, n = 259; 2016, n = 371; 2017, n = 440) isolates

were detected in IAI+UTI+RTI samples from 2015 to 2017 obtained from 21 centers in 7 regions of China (northeast, north, central south, southwest, east Jiangzhe and east non-Jiangzhe areas), with a range of 77 to 250 samples per year per hospital, which were consecutively collected. The majority of the IAI specimens were taken from the appendix, gall bladder, small intestine, colon, rectum, pancreas, stomach, liver and peritoneal fluid or from abscesses. The majority of the UTI specimens were sampled from urine and the urethra. The majority of the RTI specimens were taken from bronchial brushings, bronchoalveolar lavage, sputum and thoracentesis. Isolates were identified using local hospital procedures and then sent for analysis to the clinical microbiology laboratory of Peking Union Medical College Hospital for re-identification using MALDI-TOF MS (Vitek MS, BioMérieux, France). All duplicate isolates (the same genus and species from the same patient) were excluded.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed at the Peking Union Medical College Hospital center laboratory using a customized MicroScan broth microdilution techniques in 2014, with the aid of a Trek Diagnostic System (Thermo Fisher Scientific, Cleveland, US) between 2015 and 2017, with susceptibility interpretations based on the European Committee on Antimicrobial Susceptibility Testing clinical breakpoints.¹⁴ The antibiotics colistin, imipenem, ertapenem, amikacin, ceftazidime and cefoxitin were tested following the recommendations of the Surgical Infection Society and the Infectious Diseases Society of America in their guidelines for the diagnosis and management of complicated IAIs, UTIs and RTIs.¹⁵ For each MIC test batch, reference strains of *Escherichia coli* (*E. coli*) American Type Culture Collection (ATCC) ATCC 27853 and *Klebsiella pneumoniae* (*K. pneumoniae*) (ATCC 700603) were used as quality control strains. The results were analyzed only when the quality control test results fell within acceptable ranges. In the present study, a CR-strain was defined as an organism resistant to any drug in the carbapenem class. A carbapenem sensitive (CS) strain was defined as an organism susceptible to all of the tested carbapenems.

Statistical Analysis

The susceptibility rates of all the Enterobacterales, CR-Enterobacterales and CS-Enterobacterales isolates were determined using appropriate breakpoints for each species.

The trend of each year was analyzed with a chi-squared trend test for distribution and susceptibility rates. A P -value <0.05 was considered to be a statistically significant difference.

Results

General Distribution of Enterobacterales and CR-Enterobacterales from 2015 to 2017

A total of 7113 strains of Enterobacterales were collected from 2015 to 2017, and the yearly number of strains showed an increasing trend. *E. coli* (3657, 51.4%) accounted for more than half of the strains in the three years of study, followed by *K. pneumoniae* (2150, 30.2%). Other strains with more than 1% occurrence accounted for $<10\%$ of bacteria, being *Enterobacter cloacae* (*E. cloacae*) (407, 5.7%), *Proteus mirabilis* (*P. mirabilis*) (186, 2.6%), *Klebsiella aerogenes* (*K. aerogenes*) (146, 2.1%), *Serratia marcescens* (*S. marcescens*) (140, 2.0%), *Klebsiella oxytoca* (*K. oxytoca*) (123, 1.7%) and *Citrobacter freundii* (*C. freundii*) (96, 1.3%). The complete list of all Enterobacterales is provided in [Supplementary Table 1](#). A total of 1070 CR-Enterobacterales strains were collected from 2015 to 2017, and the number of strains increased year by year. The percentage of CR strains within species was highest for *S. marcescens* (27.9%), followed by *K. pneumoniae* (24.8%), *P. mirabilis* (22.6%), *K. oxytoca* (19.5%), *E. cloacae* (17.7%), *C. freundii* (12.5%), *K. aerogenes* (11.0%) and lowest for *E. coli* (6.9%) ([Table 1](#)).

Susceptibility Analysis of Colistin to All Enterobacterales from 2015 to 2017

We found that colistin was less effective against CR-Enterobacterales (76.3%) than against CS-Enterobacterales (92.9%) ([Table 2](#)). This pattern was similar for *E. coli* (CR, 83.5%; CS, 95.9%), *K. pneumoniae* (CR, 88.6%; CS, 95.8%) and *K. aerogenes* (CR, 87.5%; CS, 91.9%). ([Table 2](#)). The complete list of MIC 90 value for all Enterobacterales is provided in [Supplementary Table 1](#). These findings indicated that CR-Enterobacterales had a lower colistin susceptibility compared with CS-Enterobacterales.

MIC Distribution of Colistin to Enterobacterales in IAI, UTI and RTI

For Enterobacterales, *E. coli*, and *K. pneumoniae* there was a general trend that isolates from IAIs, UTIs and RTIs which were CS included a higher percentage with MIC values ≤ 1 and a lower percentage with MIC values >4 compared to CR

isolates. However, this was valid for *E. cloacae* only in IAIs, whereas the percentages of CR-*E. cloacae* in the MIC values ≤ 1 groups were higher in UTIs and the same in RTIs compared to CS-*E. cloacae* ([Table 3](#)).

Susceptibility Changes of Enterobacterales to Colistin in IAI, UTI and RTI Isolates from 2015 to 2017

In IAI and UTI isolates, all Enterobacterales, and particularly CR-*E. coli* and CR-*K. pneumoniae*, showed a trend of decreasing susceptibility. Especially for CR-*K. pneumoniae* in IAIs and for both in UTIs, the susceptibility decreased markedly in 2017. In RTI isolates, unlike UTI and IAI isolates, all Enterobacterales and CR-Enterobacterales showed trends of increasing or fairly constant susceptibilities. However, the vast majority of isolates from RTIs exhibited sensitivities of $\geq 80.0\%$ ([Figure 1](#)).

Susceptibility Changes of CR-Enterobacterales to Colistin in Different Regions of China in IAI, UTI and RTI Isolates from 2015 to 2017

In south and central areas, the susceptibility rates of CR-Enterobacterales to colistin decreased yearly becoming $<80.0\%$ (64.5% and 72.5%, respectively). The susceptibility of CR-Enterobacterales to colistin increased from 2016 to 2017 in the north, east (Jiangzhe) and southwest areas. In IAI isolates, the susceptibility rates to colistin in the northeast and east (non-Jiangzhe) areas increased year by year. In UTI isolates, the susceptibility rates to colistin increased in the northeast, north, central, east (non-Jiangzhe) and east (Jiangzhe) areas from 2016 to 2017. In RTI, the susceptibility rates to colistin in the northeast and central areas decreased year by year ([Figure 2](#)). The susceptibility of CR-*E. coli* to colistin increased in the east (Jiangzhe) and east (non-Jiangzhe) areas, and decreased in the central and south areas. In 2017 the susceptibility rate to colistin in the central area was only 50.0%. The susceptibility of CR-*K. pneumoniae* to colistin increased in the northeast, south and southwest areas, and exhibited a downward trend in the north, central, east (non-Jiangzhe) and east (Jiangzhe) regions from 2016 to 2017 ([Figure 2](#)). MIC 90 values and the susceptibilities to colistin of CR-Enterobacterales, CR-*E. coli* and CR-*K. pneumoniae* isolated from IAIs, UTIs and RTIs in different Chinese regions between 2015 and 2017 are

Table 1 Distribution of Enterobacteriales, CR-Enterobacteriales and CS-Enterobacteriales from 2015 to 2017 in IALs, UTIs and RTIs (N, %)

	2015					2016					2017					Total
	IAL	UTI	RTI	Subtotal	IAI	UTI	RTI	Subtotal	RTI	Subtotal	IAI	UTI	RTI	Subtotal	Subtotal	
Enterobacteriales																
CR-Enterobacteriales	1216	742	245	2203	1136	741	498	2375	498	2375	899	1000	636	2535	7113	
CS-Enterobacteriales	148 (12.2)	59 (8.0)	52 (21.2)	259 (11.8)	159 (14.0)	76 (10.3)	136 (27.3)	371 (15.6)	136 (27.3)	371 (15.6)	155 (17.2)	113 (11.3)	172 (27.0)	440 (17.4)	1070 (15.0)	
CI-Enterobacteriales	970 (79.8)	613 (82.6)	176 (71.8)	1759 (79.8)	899 (79.1)	608 (82.1)	325 (65.3)	1832 (77.1)	325 (65.3)	1832 (77.1)	679 (75.5)	830 (83.0)	424 (66.7)	1933 (76.3)	5524 (77.7)	
	98 (8.1)	70 (9.4)	17 (6.9)	185 (8.4)	78 (6.9)	57 (7.7)	37 (7.4)	172 (7.2)	37 (7.4)	172 (7.2)	65 (7.2)	57 (5.7)	40 (6.3)	162 (6.4)	519 (7.3)	
Escherichia coli																
CR- <i>Escherichia coli</i>	648	531	38	1217	618	519	72	1209	72	1209	456	692	83	1231	3657	
CS- <i>Escherichia coli</i>	47 (7.3)	18 (3.4)	5 (1.3)	70 (5.8)	52 (8.4)	35 (6.7)	10 (1.3)	97 (8.0)	10 (1.3)	97 (8.0)	39 (8.6)	36 (5.2)	12 (1.4)	87 (7.1)	254 (6.9)	
CI- <i>Escherichia coli</i>	573 (88.4)	486 (91.5)	33 (86.8)	1092 (89.7)	543 (87.9)	463 (89.2)	61 (84.7)	1067 (88.3)	61 (84.7)	1067 (88.3)	408 (89.5)	637 (92.1)	69 (83.1)	1114 (90.5)	3273 (89.5)	
	28 (4.3)	27 (5.1)	0 (0.0)	55 (4.5)	23 (3.7)	21 (4.0)	1 (1.4)	45 (3.7)	1 (1.4)	45 (3.7)	9 (2.0)	19 (2.7)	2 (2.4)	30 (2.4)	130 (3.6)	
Klebsiella pneumoniae																
CR- <i>Klebsiella pneumoniae</i>	331	114	150	595	330	137	289	756	289	756	223	179	397	799	2150	
CS- <i>Klebsiella pneumoniae</i>	55 (16.6)	22 (19.3)	36 (24.0)	113 (19.0)	69 (20.9)	28 (20.4)	87 (30.1)	184 (24.3)	87 (30.1)	184 (24.3)	69 (30.9)	45 (25.1)	123 (31.0)	237 (29.7)	534 (24.8)	
CI- <i>Klebsiella pneumoniae</i>	264 (79.8)	81 (71.1)	112 (74.7)	457 (76.8)	249 (75.5)	97 (70.8)	187 (64.7)	533 (70.5)	187 (64.7)	533 (70.5)	144 (64.6)	129 (72.1)	266 (67.0)	539 (67.5)	1529 (71.1)	
	12 (3.6)	11 (9.6)	2 (1.3)	25 (4.2)	12 (3.6)	12 (8.8)	15 (5.2)	39 (5.2)	15 (5.2)	39 (5.2)	10 (4.5)	5 (2.8)	8 (2.0)	23 (2.9)	87 (4.0)	
Enterobacter cloacae																
CR- <i>Enterobacter cloacae</i>	100	16	19	135	60	22	39	121	39	121	83	31	37	151	407	
CS- <i>Enterobacter cloacae</i>	15 (15.0)	5 (31.3)	3 (15.8)	23 (17.0)	11 (18.3)	3 (13.6)	9 (23.1)	23 (19.0)	9 (23.1)	23 (19.0)	11 (13.3)	9 (29.0)	6 (16.2)	26 (17.2)	72 (17.7)	
CI- <i>Enterobacter cloacae</i>	62 (62.0)	8 (50.0)	13 (68.4)	83 (61.5)	39 (65.0)	12 (54.5)	26 (66.7)	77 (63.6)	26 (66.7)	77 (63.6)	61 (73.5)	20 (64.5)	27 (73.0)	108 (71.5)	268 (65.8)	
	23 (23.0)	3 (18.8)	3 (15.8)	29 (21.5)	10 (16.7)	7 (31.8)	4 (10.3)	21 (17.4)	4 (10.3)	21 (17.4)	11 (13.3)	2 (6.5)	4 (10.8)	17 (11.3)	67 (16.5)	
Proteus mirabilis																
CR- <i>Proteus mirabilis</i>	29	26	7	62	20	18	11	49	11	49	24	38	13	75	186	
CS- <i>Proteus mirabilis</i>	9 (31.0)	5 (19.2)	1 (14.3)	15 (24.2)	2 (10.0)	4 (22.2)	3 (27.3)	9 (18.4)	3 (27.3)	9 (18.4)	7 (29.2)	9 (23.7)	2 (15.4)	18 (24.0)	42 (22.6)	
CI- <i>Proteus mirabilis</i>	8 (27.6)	5 (19.2)	0 (0.0)	13 (21.0)	8 (40.0)	6 (33.3)	6 (54.5)	20 (40.8)	6 (54.5)	20 (40.8)	2 (8.3)	9 (23.7)	2 (15.4)	13 (17.3)	46 (24.7)	
	12 (41.4)	16 (61.5)	6 (85.7)	34 (54.8)	10 (50.0)	8 (44.4)	2 (18.2)	20 (40.8)	2 (18.2)	20 (40.8)	15 (62.5)	20 (52.6)	9 (69.2)	44 (58.7)	98 (52.7)	
Klebsiella aerogenes																
CR- <i>Klebsiella aerogenes</i>	27	9	2	38	23	9	17	49	17	49	30	12	17	59	146	
CS- <i>Klebsiella aerogenes</i>	4 (14.8)	0 (0.0)	1 (50.0)	5 (13.2)	5 (21.7)	1 (11.1)	1 (5.9)	7 (14.3)	1 (5.9)	7 (14.3)	2 (6.7)	1 (8.3)	1 (5.9)	4 (6.8)	16 (11.0)	
CI- <i>Klebsiella aerogenes</i>	13 (48.1)	7 (77.8)	1 (50.0)	21 (55.3)	8 (34.8)	4 (44.4)	10 (58.8)	22 (44.9)	10 (58.8)	22 (44.9)	22 (73.3)	7 (58.3)	14 (82.4)	43 (72.9)	86 (58.9)	
	10 (37.0)	2 (22.2)	0 (0.0)	12 (31.6)	10 (43.5)	4 (44.4)	6 (35.3)	20 (40.8)	6 (35.3)	20 (40.8)	6 (20.0)	4 (33.3)	2 (11.8)	12 (20.3)	44 (30.1)	
Serratia marcescens																
CR- <i>Serratia marcescens</i>	9	4	10	23	10	15	35	60	35	60	15	5	37	57	140	
CS- <i>Serratia marcescens</i>	2 (22.2)	1 (25.0)	0 (0.0)	3 (13.0)	3 (30.0)	1 (6.7)	12 (34.3)	16 (26.7)	12 (34.3)	16 (26.7)	9 (60.0)	0 (0.0)	11 (29.7)	20 (35.1)	39 (27.9)	
CI- <i>Serratia marcescens</i>	5 (55.6)	1 (25.0)	6 (60.0)	12 (52.2)	6 (60.0)	11 (73.3)	16 (45.7)	33 (55.0)	16 (45.7)	33 (55.0)	2 (13.3)	2 (40.0)	16 (43.2)	20 (35.1)	65 (46.4)	
	2 (22.2)	2 (50.0)	4 (40.0)	8 (34.8)	1 (10.0)	3 (20.0)	7 (20.0)	11 (18.3)	7 (20.0)	11 (18.3)	4 (26.7)	3 (60.0)	10 (27.0)	17 (29.8)	36 (25.7)	

<i>Klebsiella oxytoca</i>	17	5	3	25	21	7	22	50	16	5	27	48	123
CR- <i>Klebsiella oxytoca</i>	1 (5.9)	1 (20.0)	1 (33.3)	3 (12.0)	3 (14.3)	0 (0.0)	7 (31.8)	10 (20.0)	3 (18.8)	1 (20.0)	7 (25.9)	11 (22.9)	24 (19.5)
CS- <i>Klebsiella oxytoca</i>	15 (88.2)	4 (80.0)	2 (66.7)	21 (84.0)	16 (76.2)	7 (100.0)	13 (59.1)	36 (72.0)	13 (81.3)	4 (80.0)	18 (66.7)	35 (72.9)	92 (74.8)
CI- <i>Klebsiella oxytoca</i>	1 (5.9)	0 (0.0)	0 (0.0)	1 (4.0)	2 (9.5)	0 (0.0)	2 (9.1)	4 (8.0)	0 (0.0)	0 (0.0)	2 (7.4)	2 (4.2)	7 (5.7)
<i>Citrobacter freundii</i>	19	18	5	42	17	5	2	24	15	12	3	30	96
CR- <i>Citrobacter freundii</i>	1 (5.3)	1 (5.6)	0 (0.0)	2 (4.8)	2 (11.8)	0 (0.0)	1 (50.0)	3 (12.5)	3 (20.0)	3 (25.0)	1 (33.3)	7 (23.3)	12 (12.5)
CS- <i>Citrobacter freundii</i>	15 (78.9)	13 (72.2)	5 (100.0)	33 (78.6)	12 (70.6)	5 (100.0)	1 (50.0)	18 (75.0)	11 (73.3)	9 (75.0)	1 (33.3)	21 (70.0)	72 (75.0)
CI- <i>Citrobacter freundii</i>	3 (15.8)	4 (22.2)	0 (0.0)	7 (16.7)	3 (17.6)	0 (0.0)	0 (0.0)	3 (12.5)	1 (6.7)	0 (0.0)	1 (33.3)	2 (6.7)	12 (12.5)
Others	36 (3.0%)	19 (2.6%)	12 (4.9%)	66 (3.0%)	37 (3.3%)	9 (1.2%)	11 (2.2%)	57 (2.4%)	37 (4.1%)	26 (2.6%)	22 (3.5%)	85 (3.4%)	208 (2.9%)

Note: Other refers to isolates <1% of the total.

Abbreviations: IAI, intra-abdominal infection; UTI, urinary tract infection RTI respiratory tract infection; CS, carbapenem sensitive; CR, carbapenem-resistant; CI, carbapenem-intermediate.

shown in [Supplementary Figure 1](#) and in [Supplementary Table 2](#).

Discussion

According to the Centre for Disease Dynamics, Economics and Policy (CDDEP), 80% of Indian *K. pneumoniae* isolates were up to 60% resistant to carbapenems. In Italy the prevalence of CR-*K. pneumoniae* isolates, which did not exist in 2008, had risen to 60% by 2013 (CDDEP: <https://cddep.org/>). This rapid rise in carbapenem resistance reflects a worrisome trend. In the present study, we observed that CR-Enterobacterales comprised 15% of all Enterobacterales collected in IAI, UTI and RTI isolates from 2015 to 2017. In particular, the proportion of CR-*K. pneumoniae* in all *K. pneumoniae* IAI, UTI and RTI isolates increased from 19% in 2015 to 24.3% and 24.8%, respectively in 2017.

Polymyxins, introduced in the 1950s to treat infections caused by Gram-negative bacteria, exert bactericidal activity by displacing membrane-stabilizing calcium and magnesium ions and targets the polyanionic lipopolysaccharide components.^{16,17} Despite their toxicity, they are considered to be one of the treatments of last resort for CR-Enterobacterales infections.¹⁸

Several studies investigated resistance to colistin between 2005 and 2010 and reported resistance rates of 6.8% for *K. pneumoniae* in South Korea,¹⁹ 0.09% for *E. coli*, 1.2% for *K. pneumoniae* and 1.5% for *E. cloacae* in Tunisia.²⁰ A global survey reported colistin susceptibility rates of 97–99% for *K. pneumoniae* and *E. coli* isolates, respectively in North America, Europe, Latin America and Asia Pacific.²¹ Available data from China collected in 2009 are 7.5% resistance of CR-Enterobacterales to colistin.²²

Later studies, however, revealed a rise of colistin resistant rates particularly for CR-*K. pneumoniae* strains in countries such as Greece (20.8% in 2010),²³ Spain (31.70% in 2012)²⁴ and Italy (36.1% in 2011 and 43% in 2013–2014).^{10,25} The overall susceptibility rates of *E. coli* and *K. pneumoniae* to colistin were ≥80% throughout the years 2015 to 2017 in the present study, but particularly for CR-*K. pneumoniae* strains from IAI isolates, and CR-*K. pneumoniae* and CR-*E. coli* isolates from UTIs, the colistin susceptibilities decreased in 2017. This decrease might be attributed to the increased treatment of infections caused by CR-Enterobacterales with colistin, which has been used in humans in China since 2015. In addition, the local distribution of CR-*E. coli* and CR-*K. pneumoniae* in 7 regions of China showed that in the east Jiangzhe area, susceptibility of CR-*E. coli* to colistin was >80.0%

Table 2 Ranges of MIC50, MIC90 and Susceptible (%), Intermediate (%) and Resistant (%) Rates of Enterobacterales to Carbapenems and Colistin Between 2015 and 2017

	N	Range	MIC50 (mg/L)	MIC90 (mg/L)	S%	I%	R%
All Enterobacterales							
Colistin	7113	≤ 1 to > 8	≤ 1	> 4	87.7	0.0	12.3
Ertapenem	7113	≤ 0.03 to > 4	≤ 0.06	> 4	83.6	3.0	13.4
Imipenem	7113	≤ 0.5 to > 32	≤ 0.5	8	83.2	5.1	11.7
Meropenem	4910	≤ 0.12 to > 16	≤ 0.12	16	88.0	0.4	11.6
CR-Enterobacterales							
Colistin	1070	≤ 1 to > 8	≤ 1	> 4	76.3	0.0	23.7
Ertapenem	1070	≤ 0.03 to > 4	> 4	> 4	10.7	0.5	88.9
Imipenem	1070	≤ 0.5 to > 32	32	> 32	18.4	3.6	78.0
Meropenem	811	≤ 0.12 to > 16	> 16	> 16	27.9	2.2	69.9
CS-Enterobacterales							
Colistin	5524	≤ 1 to > 8	≤ 1	≤ 1	92.9	0.0	7.1
Ertapenem	5524	≤ 0.03 to 0.5	≤ 0.06	0.25	100.0	0.0	0.0
Imipenem	5524	≤ 0.5 to 1	≤ 0.5	1	100.0	0.0	0.0
Meropenem	3765	≤ 0.12 to 1	≤ 0.12	≤ 0.12	100.0	0.0	0.0
<i>Escherichia coli</i>							
Colistin	3657	≤ 1 to > 8	≤ 1	≤ 1	94.6	0.0	5.4
Ertapenem	3657	≤ 0.03 to > 4	≤ 0.06	0.5	90.6	2.7	6.7
Imipenem	3657	≤ 0.5 to > 32	≤ 0.5	1	94.8	1.4	3.9
Meropenem	2440	≤ 0.12 to > 16	≤ 0.12	≤ 0.12	95.8	0.3	3.9
CR-<i>Escherichia coli</i>							
Colistin	254	≤ 1 to > 8	≤ 1	> 4	83.5	0.0	16.5
Ertapenem	254	≤ 0.03 to > 4	> 4	> 4	3.5	0.4	96.1
Imipenem	254	≤ 0.5 to > 32	4	> 32	38.6	5.9	55.5
Meropenem	184	≤ 0.12 to > 16	4	> 16	44.6	3.3	52.2
CS-<i>Escherichia coli</i>							
Colistin	3273	≤ 1 to > 8	≤ 1	≤ 1	95.9	0.0	4.1
Ertapenem	3273	≤ 0.03 to 0.5	≤ 0.06	0.25	100.0	0.0	0.0
Imipenem	3273	≤ 0.5 to 1	≤ 0.5	≤ 0.5	100.0	0.0	0.0
Meropenem	2181	≤ 0.12 to 0.5	≤ 0.12	≤ 0.12	100.0	0.0	0.0
<i>Klebsiella pneumoniae</i>							
Colistin	2150	≤ 1 to > 8	≤ 1	2	93.4	0.0	6.6
Ertapenem	2150	≤ 0.03 to > 4	≤ 0.06	> 4	73.4	2.3	24.3
Imipenem	2150	≤ 0.5 to > 32	≤ 0.5	> 32	75.6	2.7	21.7
Meropenem	1555	≤ 0.12 to > 16	≤ 0.12	> 16	75.9	0.6	23.5
CR-<i>Klebsiella pneumoniae</i>							
Colistin	534	≤ 1 to > 8	≤ 1	4	88.6	0.0	11.4
Ertapenem	534	≤ 0.06 to > 4	> 4	> 4	1.9	0.4	97.8
Imipenem	534	≤ 0.5 to > 32	> 32	> 32	9.9	2.6	87.5
Meropenem	421	≤ 0.12 to > 16	> 16	> 16	11.2	2.1	86.7
CS-<i>Klebsiella pneumoniae</i>							
Colistin	1529	≤ 1 to > 8	≤ 1	≤ 1	95.8	0.0	4.3
Ertapenem	1529	≤ 0.03 to 0.5	≤ 0.06	0.25	100.0	0.0	0.0
Imipenem	1529	≤ 0.5 to 1	≤ 0.5	1	100.0	0.0	0.0
Meropenem	1072	≤ 0.12 to 1	≤ 0.12	≤ 0.12	100.0	0.0	0.0

(Continued)

Table 2 (Continued).

	N	Range	MIC50 (mg/L)	MIC90 (mg/L)	S%	I%	R%
<i>Enterobacter cloacae</i>							
Colistin	407	≤ 1 to > 8	≤ 1	> 4	73.5	0.0	26.5
Ertapenem	407	≤ 0.03 to > 4	0.12	> 4	71.5	12.0	16.5
Imipenem	407	≤ 0.5 to > 32	≤ 0.5	8	82.6	6.6	10.8
Meropenem	272	≤ 0.12 to > 16	≤ 0.12	16	88.2	0.0	11.8
CR-<i>Enterobacter cloacae</i>							
Colistin	72	≤ 1 to > 8	≤ 1	> 4	79.2	0.0	20.8
Ertapenem	72	≤ 0.06 to > 4	> 4	> 4	6.9	0.0	93.1
Imipenem	72	≤ 0.5 to > 32	16	> 32	31.9	6.9	61.1
Meropenem	49	≤ 0.12 to > 16	16	> 16	34.7	0.0	65.3
CS-<i>Enterobacter cloacae</i>							
Colistin	268	≤ 1 to > 8	≤ 1	> 4	74.6	0.0	25.4
Ertapenem	268	≤ 0.03 to 0.5	≤ 0.06	0.5	100.0	0.0	0.0
Imipenem	268	≤ 0.5 to 1	≤ 0.5	1	100.0	0.0	0.0
Meropenem	185	≤ 0.12 to 0.25	≤ 0.12	≤ 0.12	100.0	0.0	0.0
<i>Klebsiella aerogenes</i>							
Colistin	146	≤ 1 to > 8	≤ 1	≤ 1	92.5	0.0	7.5
Ertapenem	146	≤ 0.03 to > 4	0.25	2	87.0	2.1	11.0
Imipenem	146	≤ 0.5 to > 32	1	2	65.1	28.1	6.9
Meropenem	108	≤ 0.12 to > 16	≤ 0.12	0.25	94.4	0.0	5.6
CR-<i>Klebsiella aerogenes</i>							
Colistin	16	≤ 1 to > 8	≤ 1	> 8	87.5	0.0	12.5
Ertapenem	16	2 to > 4	> 4	> 4	0.0	0.0	100.0
Imipenem	16	≤ 0.5 to > 32	4	> 32	37.5	0.0	62.5
Meropenem	11	≤ 0.12 to > 16	4	> 16	45.5	0.0	54.6
CS-<i>Klebsiella aerogenes</i>							
Colistin	86	≤ 1 to > 8	≤ 1	2	91.9	0.0	8.1
Ertapenem	86	≤ 0.03 to 0.5	0.25	0.5	100.0	0.0	0.0
Imipenem	86	≤ 0.5 to 1	1	1	100.0	0.0	0.0
Meropenem	65	≤ 0.12 to 0.25	≤ 0.12	0.25	100.0	0.0	0.0

Abbreviations: CS, carbapenem sensitive; CR, carbapenem-resistant; MIC, minimum inhibitory concentration; S, susceptibility; I, intermediate; R, resistance.

throughout the study years, but it is noteworthy that CR-*K. pneumoniae* susceptibility decreased in 2017 compared to previous years to <80%, which might indicate enhanced colistin usage in this region where the 2013 incidence of CR-*K. pneumoniae* was the highest in China.²⁶ On the other hand, it should be considered that other studies have suggested that the cause of colistin resistance is excessive veterinary usage.^{22,27–29} In addition, previous studies about PK/PD parameters of colistin indicated that sub-optimal doses of colistin might have increased the resistance rates to colistin with persistent levels being organ specific. There were high levels in muscle, kidney and liver, but poor distribution to the cerebrospinal fluid, bones, lung parenchyma and pleural cavity, which might

lead to organ specific susceptibility differences,³⁰ though in the present study RTI isolates showed consistent susceptibility rates of ≥80.0% throughout the years.

Limitations of the present study are that the paper only provides details about phenotypical testing and completely omits strain typing, such as MLST, detection of resistance genes and others.

Conclusions

Colistin is a last resort antibiotic for empirical CR-Enterobacterales therapy. *E. coli* (51.4%) and *K. pneumoniae* (30.0%) with percentages of CR-*K. pneumoniae* and CR-*E. coli* strains of 24.8% and 6.9%, accounted for the majority of Enterobacterales isolated from IAIs, UTIs and RTIs in

Table 3 MIC Distribution of Colistin Between 2015 and 2017 in IAI, RTI and UTI Isolates

Isolates (n, %)																
	IAI				UTI				RTI							
	Total	MIC (mg/L)			Total	MIC (mg/L)			Total	MIC (mg/L)						
		≤1*	2-4*	>4*		≤1*	2-4*	>4*		≤1*	2-4*	>4*				
All Enterobacteriales	3251 (100.0)	2795 (86.0)	121 (3.7)	335 (10.3)	2483 (100.0)	2154 (86.7)	100 (4.0)	229 (9.2)	1379 (100.0)	1108 (80.3)	85 (6.2)	186 (13.5)				
	462 (100.0)	320 (69.3)	28 (6.1)	114 (24.7)	248 (100.0)	163 (65.7)	20 (8.1)	65 (26.2)	360 (100.0)	286 (79.4)	20 (5.6)	54 (15.0)				
	2548 (100.0)	2335 (91.6)	83 (3.3)	130 (5.1)	2051 (100.0)	1893 (92.3)	74 (3.6)	84 (4.1)	925 (100.0)	783 (84.6)	61 (6.6)	81 (8.8)				
Escherichia coli	1722 (100.0)	1605 (93.2)	59 (3.4)	58 (3.4)	1742 (100.0)	1619 (92.9)	64 (3.7)	59 (3.4)	193 (100.0)	171 (88.6)	19 (9.8)	3 (1.6)				
	138 (100.0)	112 (81.2)	6 (4.3)	20 (14.5)	89 (100.0)	64 (71.9)	8 (9.0)	17 (19.1)	27 (100.0)	24 (88.9)	2 (7.4)	1 (3.7)				
	1524 (100.0)	1442 (94.6)	49 (3.2)	33 (2.2)	1586 (100.0)	1502 (94.7)	53 (3.3)	31 (2.0)	163 (100.0)	144 (88.3)	17 (10.4)	2 (1.2)				
Klebsiella pneumoniae	884 (100.0)	802 (90.7)	39 (4.4)	43 (4.9)	430 (100.0)	374 (87.0)	28 (6.5)	28 (6.5)	836 (100.0)	746 (89.2)	48 (5.7)	42 (5.0)				
	193 (100.0)	160 (82.9)	13 (6.7)	20 (10.4)	95 (100.0)	73 (76.8)	9 (9.5)	13 (13.7)	246 (100.0)	218 (88.6)	11 (4.5)	17 (6.9)				
	657 (100.0)	617 (93.9)	22 (3.3)	18 (2.7)	307 (100.0)	276 (89.9)	17 (5.5)	14 (4.6)	565 (100.0)	512 (90.6)	35 (6.2)	18 (3.2)				
Enterobacter cloacae	243 (100.0)	165 (67.9)	10 (4.1)	68 (28.0)	69 (100.0)	55 (79.7)	5 (7.2)	9 (13.0)	95 (100.0)	68 (71.6)	8 (8.4)	19 (20.0)				
	37 (100.0)	22 (59.5)	4 (10.8)	11 (29.7)	17 (100.0)	16 (94.1)	1 (5.9)	0 (0.0)	18 (100.0)	13 (72.2)	4 (22.2)	1 (5.6)				
	162 (100.0)	117 (72.2)	4 (2.5)	41 (25.3)	40 (100.0)	33 (82.5)	3 (7.5)	4 (10.0)	66 (100.0)	48 (72.7)	3 (4.5)	15 (22.7)				
Klebsiella aerogenes	80 (100.0)	74 (92.5)	1 (1.3)	5 (6.3)	30 (100.0)	26 (86.7)	1 (3.3)	3 (10.0)	36 (100.0)	33 (91.7)	3 (8.3)	0 (0.0)				
	11 (100.0)	9 (81.8)	0 (0.0)	2 (18.2)	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)	3 (100.0)	0 (0.0)	0 (0.0)				
	43 (100.0)	39 (90.7)	1 (2.3)	3 (7.0)	18 (100.0)	16 (88.9)	1 (5.6)	1 (5.6)	25 (100.0)	22 (88.0)	3 (12.0)	0 (0.0)				

Notes: The data are expressed as n (%). *MIC breakpoint (mg/L) of colistin to Enterobacteriales for sensitivity is ≤2; resistance is >2 according to European Committee on Antimicrobial Susceptibility Testing Breakpoint tables for interpretation of MICs and zone diameters Version 7.1, valid from 2017-03-10.

Abbreviations: MIC, minimum inhibitory concentration; IAI, intra-abdominal infection; UTI, urinary tract infection; RTI, respiratory tract infection; CS, carbapenem sensitive; CR, carbapenem-resistant.

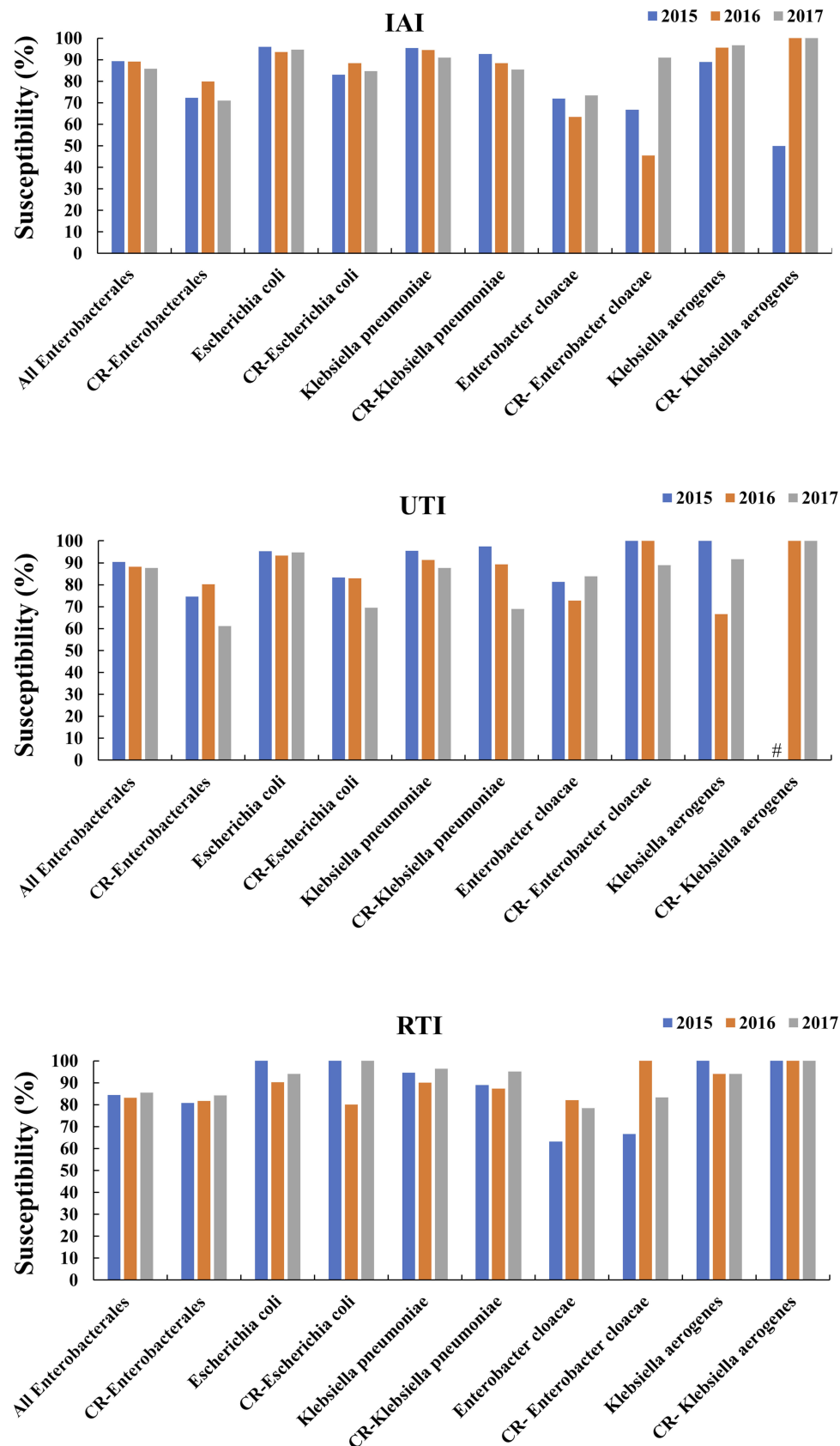


Figure 1 Changes in the of indicated Enterobacteriales sensitivity to colistin over time for the indicated infection types.

Note: # means that the susceptibility of CR-*K. aerogenes* in 2015 was not available.

Abbreviations: IAI, intra-abdominal infections; UTI, urinary tract infections; RTI, respiratory tract infections; CR, carbapenem-resistant.

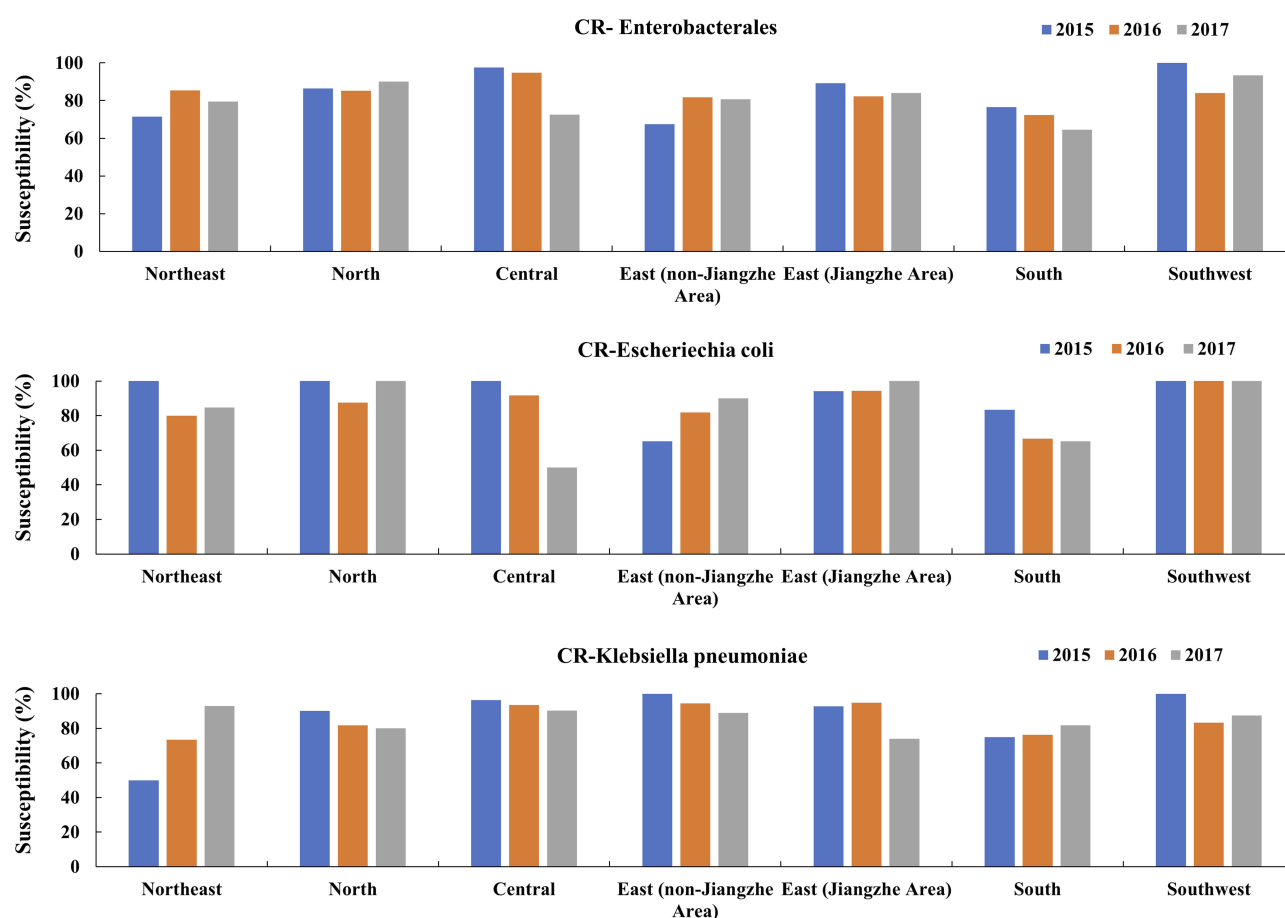


Figure 2 Changes in the susceptibility of CR-Enterobacterales, CR-*E. coli* and CR-*K. pneumoniae* to colistin over time in different regions of China.
Abbreviation: CR, carbapenem-resistant.

2015–2017. Colistin susceptibilities were generally higher in CS than in CR isolates and were 83.5% for CR-*E. coli* and 88.6% for CR-*K. pneumoniae*, respectively. However, the resistance rates of IAI derived CR-*K. pneumoniae* as well as CR-*E. coli* and CR-*K. pneumoniae* UTI isolates to colistin increased between 2015 and 2017, which should further be closely monitored.

Data Sharing Statement

The SMART database is not public and is only accessible for SMART investigators, but the data that support the findings of this study are directly available from MSD China or from the authors upon reasonable request and with permission of MSD China.

Ethics Approval and Consent to Participate

The protocol has been reviewed by the human research ethics committee of the Institutional Review Board (IRB) of the Peking Union Medical College Hospital and since the project falls under the category observational study and all bacterial strains were from residual samples used in clinical diagnosis or were strains from their subcultures, it has been determined they meet the criteria for exemption. This project does not involve any patient information nor does it affect the normal diagnosis and treatment of patients, and after consultation with the IRB, formal ethical approval was reviewed and waived and written patient consent was not required (Ethics Approval Number: S-K238).

Acknowledgments

Medical writing and editorial assistance was provided by Shanghai BIOMED Science Technology (Shanghai, China) through funding provided by MSD China. The authors were solely responsible for the conception and implementation of this study and for writing the manuscript.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Funding

This study was supported by funding from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Further support was provided by the National Key Research and Development Program of China (2018YFC1200100, 2018YFC1200105), the Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine (Grant No. 2016-I2M-3-014), the CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant No. 2016-I2M-1-014) and the Outstanding Talents Training Funding Project of Dongcheng District, Beijing (2017).

Disclosure

Yue Kang is an employee of MSD China. The authors report no other conflicts of interest in this work.

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