Original Article

Species distribution and antibiotic resistance in Shandong, China: 2010–2016

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Background: Infectious diseases are most commonly found in the intensive care units (ICUs). With the widespread use of broad-spectrum antibiotics, the antibiotic susceptibilities and resistance patterns of infectious diseases might be changed accordingly. We established a database of the species distributions and antibiotic resistance of infectious diseases in 34 ICUs in Shandong, China from 2010 to 2016.

Methods: Data collected from 34 ICUs were recorded by WHONET 5.6 software. The susceptibilities were determined by the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute guidelines. Chi-square tests were performed to examine the statistical differences of the proportions of different isolates in difference specimens. The trend Chi-square tests were performed for the changes of antibiotic resistance rates through the seven years.

Results: Out of 61,564 samples, 61,901 clinical isolates of pathogens were recovered from 21,412 patients. The isolated pathogens included Gram-negative bacteria (80.1%, n=49,583), Gram-positive bacteria (13.4%, n=8,289), and fungi (6.5%, n=4,029). The most common five bacteria were *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli* and *S. aureus*. For the most common and concerning multiple-drug-resistant bacteria, extended-spectrum β-lactamase-producing *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, Imipenem-resistant *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, and Imipenem-resistant *Acinetobacter baumannii* and Imipenem-resistant *Pseudomonas aeruginosa increased* (P<0.001). extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, Methicillin-resistant *Staphylococcus aureus* decreased (P<0.001).

Conclusions: The surveillance showed that Gram-negative bacteria, especially non-fermentative Gram-negative strains, are the most commonly isolated in the ICUs in Shandong, China. extended-spectrum β-lactamase-producing *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, Imipenem-resistant *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, and Imipenem-resistant *Acinetobacter baumannii* and Imipenem-resistant *Pseudomonas aeruginosa* increased in our region.

Keywords: Antimicrobial; drug resistance; antimicrobials susceptibility test; critical care medicine

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Introduction

Infectious diseases are most commonly found in the intensive care units (ICUs). Drug-resistant bacterial infections are the most challenging of these (1). With the widespread use of broad-spectrum antibiotics, the antibiotic susceptibilities and resistance patterns of infectious diseases might be changed accordingly (2). Optimal antibiotic use is crucial in septic patients (3). Unfortunately, 30% to 60% of the antibiotics used in the ICU were suboptimal, inappropriate and unnecessary (4-7). Continued monitoring of local epidemiological data is crucial to reflect current trends and appropriately guide disease management. The CHINET surveillance system has done lots of meaningful work to collect and report the changes and trends in antimicrobial resistance across China (8,9). However, data about the species distributions and antibiotic resistance of infections in local ICUs in East China are limited (10). Therefore, we aimed to establish a database of the species distributions and antibiotic resistance of infectious diseases in our local ICUs. We present this article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-121) (11).

Methods

Bacterial isolates and ethics

Clinical isolates from 34 ICUs participating in the Shandong Provincial antimicrobial resistance surveillance network were collected during 2010–2016. All of the pathogens isolated were included in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards of Qianfoshan Hospital, Shandong University (ethics approval number: 2009-S068). The institutional review board specifically approved the informed consent waiver because of the anonymous and purely observational nature of this study.

Antimicrobial susceptibility testing

The susceptibilities were determined by the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute guidelines (12,13).

Data acquisition

Data collected from 34 ICUs were recorded by WHONET 5.6 software (14,15) (http://www.whonet.org). A database was established in WHONET 5.6 for samples from the same hospital with all of the antibiotics used in the antimicrobial susceptibility test selected from the list of antibiotics. Patient information, the sample category, and the pathogen index according to the rule of WHONET were stored while documenting the pathogen information. Double entry and validation were performed. Any missing data were retrieved from the hospital medical system. At each participating hospital, databases were updated quarterly, and data from all 34 hospitals were compiled annually.

Analysis

ICUs participating in the Shandong Provincial antimicrobial resistance surveillance network held an annual meeting. The ICU department of Qianfoshan Hospital collected the WHONET databases from the 34 hospitals, which were shared and discussed during the annual meeting. Figure S1 shows the location of the 34 ICUs in Shandong Province.

Statistics

Numbers and percentages were used to report the distributions of specimens. Chi-square tests were performed to examine the statistical differences of the proportions of different isolates in difference specimens. The trend Chi-square tests were performed for the changes of antibiotic resistance rates through the seven years. The statistical tests

were performed using SAS 9.4.

Results

Distribution of isolates

A total of 61,901 clinical isolates of pathogens, from 61,564 samples, were collected, including sputum samples (76.8%, n=47,281), blood cultures (11.3%, n=6,956), urine samples (7.5%, n=4,617), pyogenic fluids (1.6%, n=985), venous catheter (1.5%, n=923) and cerebrospinal fluids (1.0%, n=615). The ratio of samples had no significant variation during 2010–2016. The 61,901 pathogens included Gram-negative bacteria (80.1%, n=49,583), Gram-positive bacteria (13.4%, n=8,289) and fungi (6.5%, n=4,029).

The most common isolations in different specimens were reported in *Table 1*. The isolation distributions in each kind of specimen were significantly different (P<0.001).

The 49,583 Gram-negative bacteria included *Acinetobacter baumannii* (32.3%, n=15,991), *Pseudomonas aeruginosa* (25.9%, n=12,824), *Klebsiella pneumoniae* (17.0%, n=8,447), *Escherichia coli* (12.6%, n=6,233), *Stenotrophomonas maltophilia* (4.9%, n=2,431), *Enterobacter cloacae* (2.9%, n=1,433), *Proteus mirabilis* (2.2%, n=1,066), *Burkholderia mirabilis* (1.1%, n=563) and others (1.1%, n=595).

The 8,289 Gram-positive bacteria included *Staphylococcus aureus* (60.1%, n=4,984), *Enterococcus aureus* (20.2%, n=1,673), *Staphylococcus epidermidis* (11.3%, n=936), *Staphylococcus haemolyticus* (6.0%, n=500) and others (2.4%, n=196). The 2033 *Enterococcus aureus* bacteria included *Enterococcus faecium* (71.1%, n=1,190) and *Enterococcus faecalis* (28.9%, n=483).

The 4,029 fungi included *Aspergillus* species (0.5%, n=20) and *Candida* species (99.5%, n=4,009). The 4,009 *Candida* species included *Candida albicans* (49.9%, n=1,999) and non-*albicans* (50.1%, n=2,010). The 2010 *non-albicans Candida* species included *Candida tropicalis* (48.9%, n=982), *Candida glabrata* (34.6%, n=697), *Candida parapsilosis* (11.2%, n=225) and *Candida krusei* (5.3%, n=106).

Antimicrobial susceptibility testing

In *Enterobacteriaceae* bacteria, the resistance of *Klebsiella pneumoniae* to Imipenem and Cefoperazone/sulbactam increased (P<0.001) to Piperacillin/tazobactam, Amikacin, Ciprofloxacin, Levofloxacin, Ceftazidime, Cefepime and Ceftriaxone decreased (P<0.001). The resistance of *Escherichia coli* to Imipenem, Meropenem, Cefoperazone/sulbactam, Amikacin, Ceftazidime, Cefepime, Levofloxacin, Ciprofloxacin and Ceftriaxone increased (P<0.001); to Piperacillin/tazobactam decreased (P<0.001). The resistance of *Proteus mirabilis* to Cefoperazone/sulbactam increased; to Meropenem, Piperacillin/tazobactam, Amikacin, Ceftazidime, Cefepime (P<0.001), Levofloxacin, Ciprofloxacin and Ceftriaxone (0.42, 0.44, 0.33, respectively) decreased. The resistance of Enterobacter cloacae to Meropenem, Piperacillin/tazobactam, Cefoperazone/sulbactam, Ciprofloxacin increased (P<0.05); to Amikacin, Cefepime, Levofloxacin, Ceftazidime and Ceftriaxone (P<0.001) decreased. The Enterobacteriaceae bacteria kept a high level of sensitivity to Carbapenems, Piperacillin-tazobactam, Cefoperazone-sulbactam and Amikacin (*Figure 1* and *Table 2*).

In non-fermentative Gram-negative bacteria, the resistance of *Acinetobacter baumannii* to Minocycline, Cefoperazone/sulbactam, Meropenem, Imipenem, Piperacillin/tazobactam, Cefepime, Ceftazidime, Levofloxacin and Ciprofloxacin increased (P<0.001); to Amikacin and Levofloxacin decreased (P<0.001). The resistance of *Stenotrophomonas maltophilia* to Minocycline increased (P<0.001); to Levofloxacin, Cefoperazone/sulbactam decreased (P<0.001, p=0.0015, respectively). There were no trend identified of *Pseudomonas aeruginosa* and *Burkholderia cepacia* (*Figure 2* and *Table 2*).

In Gram-positive bacteria, the resistance of *Staphylococcus aureus* to Rifampicin, Ciprofloxacin, Levofloxacin, Oxacillin, Erythromycin (P<0.001) decreased. The resistance of *Staphylococcus epidermidis* to Rifampicin, Oxacillin and Gentamicin (P<0.001) increased; to Ciprofloxacin, Levofloxacin and Erythromycin (P<0.001) decreased. The resistance of *Enterococcus faecium* to Vancomycin, Rifampicin (P<0.001) increased; to Teicoplanin, Gentamicin, Oxacillin, Erythromycin, Levofloxacin and Ciprofloxacin (P<0.05) decreased. The resistance of *Enterococcus faecalis* to Teicoplanin, Rifampicin (P<0.001) increased; to Linezolid, Vancomycin and Erythromycin (P<0.05) decreased (*Figure 3* and *Table 2*).

For the most common and concerning multiple-drug-resistant bacteria, extended-spectrum β-lactamase-producing *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, Imipenem-resistant *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, and Imipenem-resistant *Acinetobacter baumannii* and Imipenem-resistant *Pseudomonas aeruginosa* (P<0.001) increased. Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, Methicillin-resistant *Staphylococcus aureus* (P<0.001) decreased (*Figure 4*

Table 1 The pathogen distributions from different specimen

Bacteria	Bloodstream		Sputum		Urine		Venous catheter		Others		Total		P
	N	%	N	%	N	%	N	%	N	%	N	%	
Gram-negative bacteria	3,413	6.9	42,646	86	1,723	3.5	382	0.8	1,419	2.9	49,583	100	<0.001
Acinetobacter baumannii	698	4.4	14,258	89.2	543	3.4	63	0.4	429	2.7	15,991	100	
Klebsiella pneumoniae	784	9.3	7,257	85.9	119	1.4	71	0.8	216	2.6	8,447	100	
Escherichia coli	876	14.1	5,031	80.7	104	1.7	65	1	157	2.5	6,233	100	
Pseudomonas aeruginosa	493	3.8	11,503	89.7	492	3.8	72	0.6	264	2.1	12,824	100	
Burkholderia cepacia	61	10.8	364	64.7	45	8	13	2.3	80	14.2	563	100	
Stenotrophomonas maltophilia	217	8.9	1,995	82.1	75	3.1	26	1.1	118	4.9	2,431	100	
Enterobacter cloacae	139	9.7	1,159	80.9	41	2.9	25	1.7	69	4.8	1,433	100	
Proteus mirabilis	98	9.2	697	65.4	201	18.9	23	2.2	47	4.4	1,066	100	
Other Gram-negative bacteria	47	7.9	382	64.2	103	17.3	24	4	39	6.6	595	100	
Gram-positive bacteria	3,155	38.1	2,833	34.2	1,300	15.7	445	5.4	556	6.7	8,289	100	<0.001
Staphylococcus aureus	1,811	36.3	2,663	53.4	225	4.5	161	3.2	124	2.5	4,984	100	
Staphylococcus epidermidis	601	64.2	27	2.9	4	0.4	132	14.1	172	18.4	936	100	
Staphylococcus haemolyticus	313	62.6	12	2.4	6	1.2	41	8.2	128	25.6	500	100	
Enterococcus faecium	316	26.6	16	1.3	712	59.8	81	6.8	65	5.5	1,190	100	
Enterococcus faecalis	98	20.3	23	4.8	312	64.6	24	5	26	5.4	483	100	
Other Gram-positive bacteria	16	8.2	92	46.9	41	20.9	6	3.1	41	20.9	196	100	
fungi	388	9.6	1,802	44.7	1,594	39.6	96	2.4	149	3.7	4,029	100	<0.001
Candida albicans	207	10.4	984	49.2	687	34.4	35	1.8	86	4.3	1,999	100	
Candida tropicalis	81	8.2	673	68.5	166	16.9	41	4.2	21	2.1	982	100	
Candida parapsilosis	52	23.1	66	29.3	88	39.1	14	6.2	5	2.2	225	100	
Candida krusei	9	8.5	41	38.7	34	32.1	1	0.9	21	19.8	106	100	
Candida glabrata	34	4.9	27	3.9	619	88.8	3	0.4	14	2	697	100	
Other fungi	5	25	11	55	0	0	2	10	2	10	20	100	
Total	6,956	11.2	47,281	76.4	4,617	7.5	923	1.5	2,124	3.4	61,901	100	<0.001

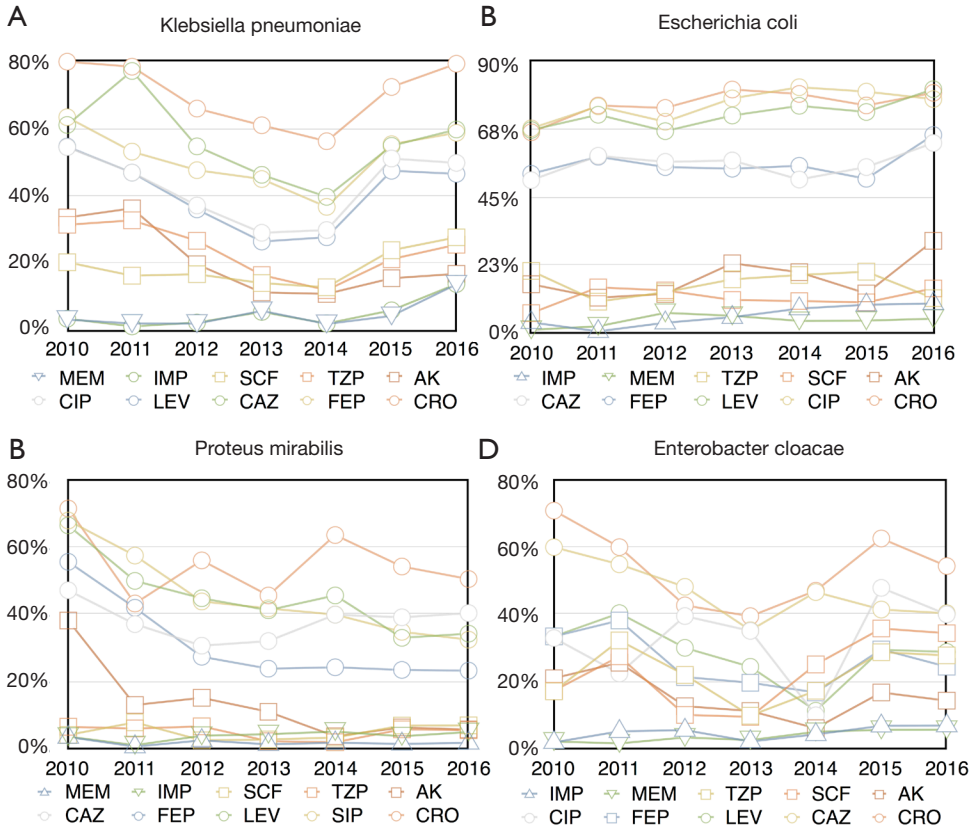

Figure 1 The trends of the resistance rates to the main agents of the mainly isolated *enterobacteriaceae* bacteria including *Klebsiella pneumoniae* (A), *Escherichia coli* (B), *Proteus mirabilis* (C) and *Enterobacter cloacae* (D) during 2010–2016. The horizontal axis represents the year. The vertical axis represents the resistance rate. Each polygonal line represents one antimicrobial agent. MEM, meropenem; IMP, imipenem; SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; AK, amikacin; CIP, ciprofloxacin; LEV, Levofloxacin; CAZ, ceftazidime; FEP, cefepime; CRO, ceftriaxone.

and *Table 2*).

Discussion

Our research indicated that non-fermentative bacteria are the most commonly isolated pathogens in our ICUs, representing more than 60% of the overall isolates, in comparison with 33% in ICUs in Taiwan (16). The high proportion of non-fermentative bacteria isolated might be related to the following causes. First, we conducted frequent routine bacterial cultures. The isolated non-fermentative bacteria were, to some extent, colonization rather than pathogenic bacteria, which might limit the meaning of their prevalence. Also, it should be noted that frequent cultures from the same patients might lead to the same isolates being included in the data collection over and over again. Second, we might have a suboptimal level of infection control. Since non-fermentative bacteria widely exist in the environment, suboptimal hand hygiene might result in the transmission of this type of bacteria (17,18). Our results prompted us to improve the hand hygiene and project-related infection control schemes in our ICUs.

From these data, the overall level of resistance to Carbapenems was on the rise. Notably, the resistance of *Acinetobacter baumannii* increased tremendously and rapidly. We noticed that the carbapenems resistance Klebsiella pneumoniae decreased in the first several years and then gradually increased in recent years. We compared our results with the CHINET surveillance (www.chinets.com). The fluctuations of the carbapenems resistant Klebsiella pneumonia rates through the seven years were similar with our results in Beijing. However, the specific rates differed

Table 2 Trend Chi-square tests for antibiotics resistance to bacteria

Antibiotic	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	2016 (%)	P value
Pseudomonas aeruginosa								
SCF	38.60	30.30	33.20	31.80	47.10	37.00	40.70	0.1693
AK	39.90	34.90	28.40	28.20	19.70	21.10	23.20	0.1717
FEP	44.20	38.80	35.70	32.70	35.50	31.80	30.20	0.5812
CAZ	46.50	43.00	41.90	39.80	51.30	43.30	44.20	0.1593
TZP	48.00	46.10	43.00	33.00	32.70	34.00	33.00	0.3539
CIP	49.70	48.50	43.00	35.40	39.10	40.50	39.80	0.9452
IMP	50.80	46.10	46.20	49.10	45.10	55.90	54.80	0.5689
MEM	50.90	45.80	47.00	43.60	36.10	41.50	41.20	0.2064
LEV	56.20	54.00	38.10	40.40	19.70	44.50	43.40	0.2424
Acinetobacter baumannii								
MH	29.60	40.30	43.00	47.20	38.60	44.20	45.10	<0.001*
SCF	30.30	32.00	42.80	42.40	46.50	53.00	53.20	<0.001*
AK	71.90	74.10	72.70	67.80	64.00	72.50	70.00	<0.001*
MEM	78.70	81.90	83.40	87.20	90.80	87.00	89.90	<0.001*
IMP	80.00	81.30	84.90	81.10	91.20	91.50	90.10	<0.001*
TZP	82.40	82.20	84.90	81.80	87.20	92.00	89.10	<0.001*
FEP	83.50	84.60	86.60	85.50	93.30	94.10	91.00	<0.001*
CAZ	85.20	88.10	91.40	86.40	92.10	95.20	93.10	<0.001*
LEV	86.30	84.30	84.40	82.10	86.10	82.80	80.20	<0.001*
CIP	86.80	86.10	83.40	86.30	94.40	95.60	93.10	<0.001*
Stenotrophomonas maltophilia								
MH	2.70	3.70	1.60	8.60	8.30	3.90	3.00	<0.001*
LEV	10.90	16.10	20.20	10.50	6.90	7.10	6.40	<0.001*
SCF	27.20	24.20	22.00	15.60	13.50	10.50	10.30	0.0015*
CIP	47.00	44.30	51.60	31.10	68.50	54.40	56.70	0.8113
TZP	54.90	52.70	55.40	53.90	57.70	56.40	57.30	0.2537
FEP	66.20	58.70	61.90	68.70	75.90	64.60	62.30	0.1253
AK	75.50	65.80	65.80	62.90	78.30	77.80	76.20	0.3038
CRO	86.90	65.30	67.70	72.10	81.10	72.20	71.30	0.7139
Burkholderia cepacia								
TZP	18.20	30.00	31.20	8.70	11.50	14.50	13.60	0.7083
FEP	20.30	20.30	28.60	22.70	37.50	39.50	39.20	0.4457
SCF	20.50	11.80	14.10	7.90	9.50	10.70	11.00	0.4947
MEM	28.60	15.00	13.00	22.20	26.10	20.30	20.80	0.2093

Table 2 (*continued*)

Table 2 (*continued*)

Antibiotic	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	2016 (%)	P value
CAZ	31.50	16.80	20.30	20.80	15.00	24.70	21.10	0.3461
CIP	37.30	58.10	60.90	64.10	72.00	67.60	59.20	0.9259
IMP	41.30	56.80	57.10	65.70	79.20	69.40	70.10	0.1719
LEV	46.20	27.20	30.80	26.90	18.00	28.90	21.10	0.411
CRO	58.10	52.50	58.70	52.20	41.70	45.40	42.30	0.1306
AK	78.70	73.00	74.40	77.50	81.00	78.20	79.80	0.6808
Klebsiella pneumoniae								
MEM	3.10	2.00	1.90	5.70	1.80	4.20	13.60	0.6808
IMP	3.40	1.10	2.30	5.40	2.00	5.90	13.70	<0.001*
SCF	20.20	16.20	16.60	14.00	12.80	23.80	27.60	<0.001*
TZP	31.40	32.70	26.60	16.40	11.90	21.10	25.40	<0.001*
AK	33.50	36.30	19.60	11.20	10.80	15.40	16.80	<0.001*
CIP	54.50	46.90	37.10	29.00	29.80	51.10	49.80	<0.001*
LEV	54.70	46.90	36.00	26.40	27.60	47.50	46.50	<0.001*
CAZ	61.10	77.20	54.70	46.30	39.70	54.90	59.70	<0.001*
FEP	63.40	53.20	47.60	45.00	36.70	55.40	58.70	<0.001*
CRO	79.90	78.40	66.00	61.00	56.20	72.40	79.30	<0.001*
Escherichia coli								
IMP	3.50	0.50	3.40	5.20	8.10	9.40	9.80	<0.001*
MEM	1.00	2.20	6.70	5.70	4.00	4.10	4.70	<0.001*
TZP	20.60	10.40	13.50	17.80	19.20	20.30	11.50	<0.001*
SCF	6.60	15.10	14.10	10.90	10.60	10.10	14.80	<0.001*
AK	16.10	11.70	12.90	23.10	20.10	13.10	30.50	<0.001*
CAZ	50.70	58.70	56.70	57.20	50.90	55.00	63.00	<0.001*
FEP	52.80	58.40	55.00	54.50	55.40	51.10	65.60	<0.001*
LEV	67.30	72.30	66.90	72.10	75.30	73.30	80.80	<0.001*
CIP	67.80	75.10	70.00	77.80	81.50	80.00	77.50	<0.001*
CRO	66.50	75.40	74.60	80.70	79.20	75.40	79.60	<0.001*
Proteus mirabilis								
MEM	3.40	0.50	2.40	1.20	1.70	1.30	1.70	<0.001*
IMP	3.50	1.00	3.80	4.20	5.00	3.60	4.90	<0.001*
SCF	4.00	7.70	2.40	2.60	3.20	6.80	6.90	<0.001*
TZP	6.40	5.90	6.60	2.10	1.80	5.60	5.40	<0.001*
AK	38.00	12.90	15.00	10.90	3.60	6.20	5.60	<0.001*
CAZ	47.00	36.90	30.50	31.90	39.70	39.00	40.20	<0.001*

Table 2 (*continued*)

Table 2 (*continued*)

Antibiotic	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	2016 (%)	P value
FEP	55.40	41.80	27.20	23.70	24.10	23.30	23.10	<0.001*
LEV	66.30	49.80	44.60	41.10	45.50	32.90	34.10	0.4205
CIP	67.70	57.30	43.70	41.60	39.80	34.70	32.30	0.4401
CRO	71.30	43.10	55.90	45.40	63.40	54.10	50.30	0.3288
Enterobacter cloacae								
IMP	1.90	5.10	5.50	2.10	4.20	6.80	6.90	0.366
MEM	2.10	1.60	3.30	2.50	5.00	5.60	5.60	0.0004*
TZP	17.00	32.10	21.90	9.80	17.20	28.60	27.70	0.003*
SCF	17.20	27.40	10.00	9.40	25.00	35.70	34.30	<0.001*
AK	20.90	25.50	12.60	11.20	6.10	16.70	14.20	<0.001*
CIP	32.80	22.30	39.40	35.00	9.90	47.70	39.90	<0.001*
FEP	33.30	38.10	21.30	19.60	16.70	29.50	24.30	0.0007*
LEV	33.30	40.20	29.90	24.30	11.20	29.40	28.70	<0.001*
CAZ	59.80	54.70	48.00	35.20	46.50	41.30	40.20	<0.001*
CRO	70.70	59.80	42.50	39.30	46.90	62.40	54.20	<0.001*
Staphylococcus aureus								
VA	0.00	0.00	0.00	0.00	0.30	0.00	0.00	<0.001*
LZD	0.10	0.00	0.00	0.00	0.80	0.00	0.00	<0.001*
TEC	0.60	0.00	0.00	0.00	0.00	0.00	0.00	<0.001*
RFP	71.50	63.80	65.30	56.30	46.10	52.20	50.50	<0.001*
CIP	81.20	82.60	71.40	67.10	65.40	60.90	63.40	<0.001*
LEV	83.90	74.60	74.80	68.70	68.50	62.10	62.30	<0.001*
OX	88.20	81.40	70.80	66.90	63.80	60.60	59.80	<0.001*
E	88.80	85.20	79.60	78.10	77.90	74.10	73.20	<0.001*
GEN	88.80	79.10	77.00	63.90	64.90	59.10	53.20	0.1238
Staphylococcus epidermidis								
VA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	<0.001*
LZD	0.00	1.00	0.00	0.00	0.00	0.00	0.00	<0.001*
TEC	1.60	0.90	0.00	0.00	0.00	0.00	0.00	<0.001*
RFP	24.40	20.70	7.60	16.30	18.30	26.10	25.30	<0.001*
CIP	48.60	64.30	48.00	44.90	42.50	40.70	42.30	<0.001*
LEV	49.10	60.60	52.70	46.40	44.30	54.60	46.80	<0.001*
OX	54.80	58.60	68.90	55.70	72.00	74.20	73.20	<0.001*
E	75.40	84.40	69.50	78.20	86.80	78.60	69.40	<0.001*
GEN	84.10	76.80	81.70	82.40	93.30	93.50	87.30	<0.001*

Table 2 (*continued*)

Table 2 (*continued*)

Antibiotic	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	2016 (%)	P value
Enterococcus faecium								
LZD	0.00	0.50	2.40	0.00	0.00	0.00	0.00	0.5689
VA	2.20	3.80	6.30	0.90	9.50	4.20	3.70	<0.001*
TEC	5.20	4.00	4.80	0.00	3.30	1.80	2.00	0.0218*
RFP	73.30	75.50	64.30	66.10	81.70	75.70	76.80	0.0008*
GEN	79.20	81.50	78.30	77.50	71.00	81.20	78.30	<0.001*
OX	90.00	77.70	90.30	82.50	87.50	89.70	83.20	0.0081*
E	91.40	93.80	91.80	88.50	92.30	87.80	86.70	<0.001*
LEV	92.60	88.20	88.10	81.00	84.50	88.60	82.10	<0.001*
CIP	97.60	90.90	89.40	90.90	88.40	90.90	89.20	<0.001*
Enterococcus faecalis								
LZD	2.10	1.60	1.90	0.00	2.30	1.20	0.00	<0.001*
TEC	2.30	1.20	1.20	0.00	6.30	4.10	2.40	<0.001*
VA	4.10	3.10	1.20	0.00	8.30	6.20	2.20	<0.001*
RFP	50.00	48.80	50.60	31.30	73.10	66.70	54.40	<0.001*
LEV	66.00	63.50	52.50	31.90	37.50	49.00	45.30	0.905
GEN	66.00	72.70	68.70	56.20	73.20	67.90	56.80	0.814
CIP	71.10	68.30	48.10	34.40	54.20	67.30	72.30	0.7721
E	87.20	71.20	77.10	75.10	65.10	83.30	67.10	0.0113*
OX	92.30	88.90	71.10	81.40	84.70	86.70	82.60	0.4055
Multiple resistant bacteria								
ESBL-Ecoli	50.70	58.70	56.70	57.20	50.90	55.00	63.00	0.0006*
ESBL-Kpn	61.10	77.20	54.70	46.30	39.70	54.90	59.70	<0.001*
MRSA	88.20	81.40	70.80	66.90	63.80	60.60	59.80	<0.001*
IMP-R Ecoli	3.50	0.50	3.40	5.20	8.10	9.40	9.80	<0.001*
IMP-R Kpn	3.40	1.10	2.30	5.40	2.00	5.90	13.70	<0.001*
IMP-R Aba	80.00	81.30	84.90	81.10	91.20	91.50	90.10	<0.001*
IMP-R Pae	50.80	46.10	46.20	49.10	45.10	55.90	54.80	<0.001*

*, P<0.05. MEM, meropenem; IMP, imipenem; SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; AK, amikacin; CIP, ciprofloxacin; LEV, Levofloxacin; CAZ, ceftazidime; FEP, cefepime; CRO, ceftriaxone; MH, minocycline; VA, vancomycin; LZD, linezolid; TEC, teicoplanin; RFP rifampicin; OX, oxacillin; E, erythromycin; GEN, gentamicin; MRSA, methicillin-resistant Staphylococcus aureus; ESBL-Ecoli, extended-spectrum β-lactamase-producing Escherichia coli; ESBL-Kpn, extended-spectrum β-lactamase-producing Klebsiella pneumoniae; IMP-R Kpn, imipenem-resistant Klebsiella pneumoniae; IMP-R Ecoli, imipenem-resistant Escherichia coli; IMP-R, Aba Acinetobacter baumannii; IMP-R, Pae Pseudomonas aeruginosa.

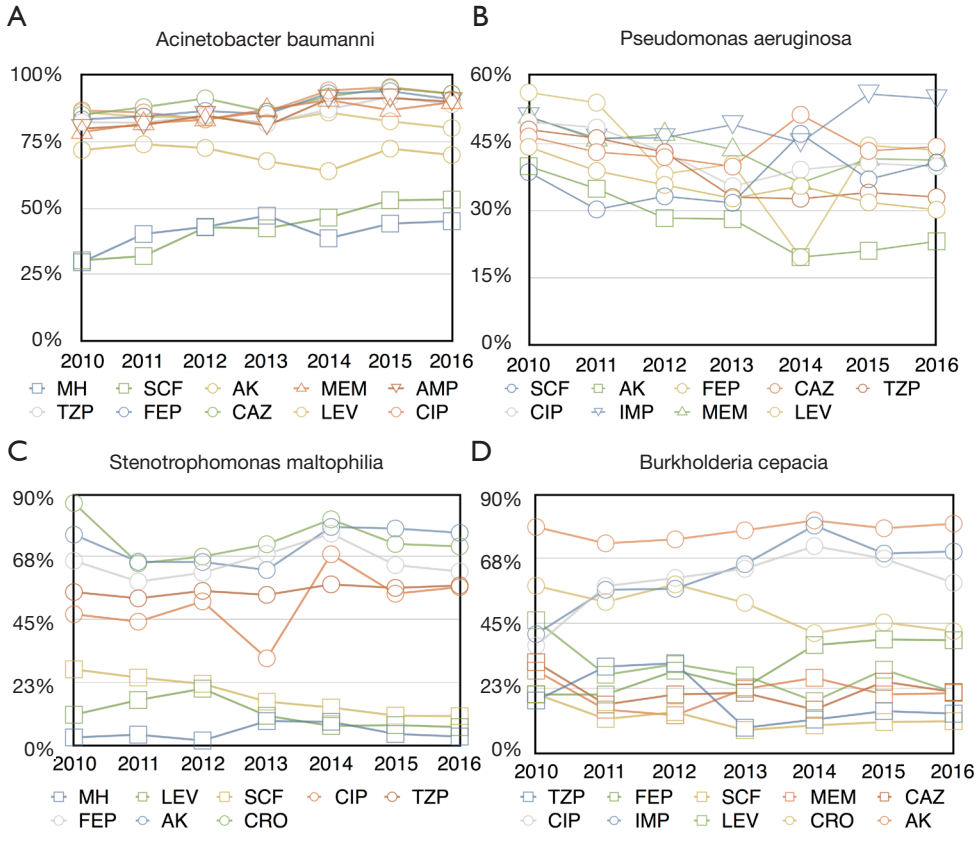

Figure 2 The trends of the resistance rates to the main agents of the mainly isolated Non-fermentative gram, including *Acinetobacter baumannii* (A), *Pseudomonas aeruginosa* (B), *Stenotrophomonas maltophilia* (C) and *Burkholderia cepacia* (D) during 2010–2016. The horizontal axis represents the year. The vertical axis represents the resistance rate. Each polygonal line represents one antimicrobial agent. MEM, meropenem; IMP, imipenem; SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; AK, amikacin; CIP, ciprofloxacin; LEV, Levofloxacin; CAZ, ceftazidime; FEP, cefepime; CRO, ceftriaxone; MH, minocycline.

tremendously from regions across China. Carbapenem resistance is a tough problem worldwide (19-21). There is a lack of potent and effective antimicrobials to Carbapenem-resistant Gram-negative bacterial infections since such strains are usually extensively drug resistant (22). As novel potent antibiotics could not be counted on, the prevention of clonal dissemination and the avoidance of Carbapenem overuse are vital to preventing the spread of these bacteria (23). Surveillance of bacteria distribution and drug resistance is also important (24).

There are strengths in our study. We conducted a continued, long-period surveillance in our local ICUs and included almost all of the major cities in Shandong Province. The data should be more related to our local clinical conditions in comparison with the surveillances of various medical departments and areas across China. To sum up, we shared the data and held a meeting annually between all member ICUs. Therefore, we kept adequate communication and made efforts to reduce the variations in bacterial cultures, data processing and also infection controls. There are several limitations to our study. First and foremost, this study did not make a distinction between pathogenic and colonized bacteria. For the vast majority of candida in sputum, the isolates had no much clinical meaning. Besides, we did not further classify the sources of specific sputum. We reported the isolates; yet, the relations between the isolates and infections were not analyzed in this study. Moreover, the clinical severity data of these bacteria were not recorded; thus the associations between bacteria and clinical severity were uncertain. Second, there was no controlled design in this study, so the relations between the variations of bacterial resistance and clinical outcomes were

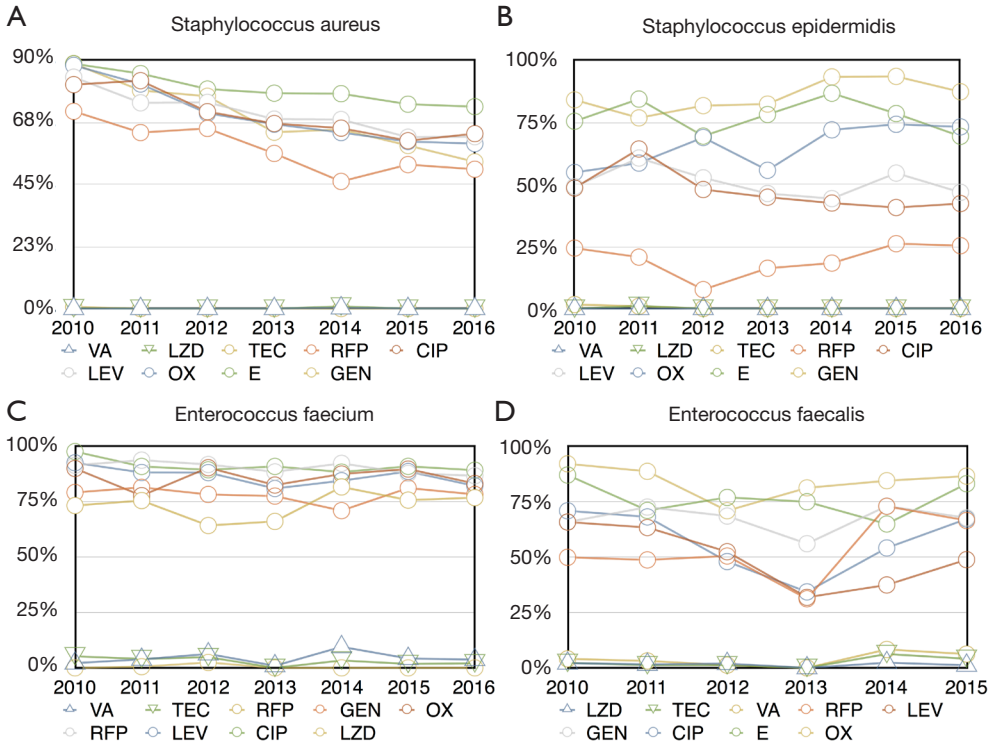

Figure 3 The trends of the resistance rates to the main agents of the mainly isolated Gram-positive bacteria, including *Staphylococcus aureus* (A), *Staphylococcus epidermidis* (B), *Enterococcus faecium* (C) and *Enterococcus faecalis* (D) during 2010–2016. The horizontal axis represents the year. The vertical axis represents the resistance rate. Each polygonal line represents one antimicrobial agent. VA, vancomycin; LZD, linezolid; TEC, teicoplanin; RFP, rifampicin; CIP, ciprofloxacin; LEV, Levofloxacin; OX, oxacillin; E, erythromycin; GEN, gentamicin.

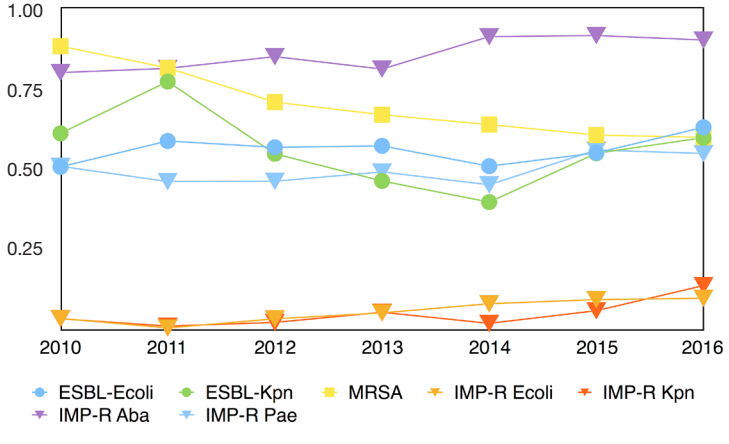

Figure 4 Rates of methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, imipenem-resistant *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* during 2010–2016. ESBL, extended-spectrum β-lactamase-producing; MRSA, methicillin-resistant *Staphylococcus aureus*; IMP-R, imipenem-resistant; Ecoli, *Escherichia coli*; Kpn, *Klebsiella pneumoniae*; Aba, *Acinetobacter baumannii*; Pae, *Pseudomonas aeruginosa*.

unclear. And without clinical interventions recorded, we could not analyze the associations of resistance changes and clinical practice. Third, the data were recorded according to the reports from the microbiology laboratories and no further genetic testing were conducted. The further identification of resistant strains was therefore limited. Fourth, we described the distribution and resistance patterns of pathogens in ICUs in our region. However, resistance patterns vary in different regions. The meaning for other regions is limited.

Conclusions

The surveillance showed that Gram-negative bacteria, especially non-fermentative Gram-negative strains, are the most commonly isolated in the ICUs in Shandong, China. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are the most commonly isolated bacteria. Non-fermentative Gram-negative bacteria had the highest antimicrobial resistance rates. *Acinetobacter baumannii* had a significantly higher level of resistance to antimicrobial agents than *Pseudomonas aeruginosa*. *Escherichia coli* showed higher antimicrobial resistance than *Klebsiella pneumoniae*. *Enterococcus faecium* showed more resistance toward all antibiotics than *Enterococcus faecalis*. extended-spectrum β-lactamase-producing *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, Imipenem-resistant *Escherichia coli*, Imipenem-resistant *Klebsiella pneumoniae*, and Imipenem-resistant *Acinetobacter baumannii* and Imipenem-resistant *Pseudomonas aeruginosa* increased in our region.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/jeccm-20-121). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards of Qianfoshan Hospital, Shandong University (ethics approval number: 2009-S068). The institutional review board specifically approved the informed consent waiver because of the anonymous and purely observational nature of this study.

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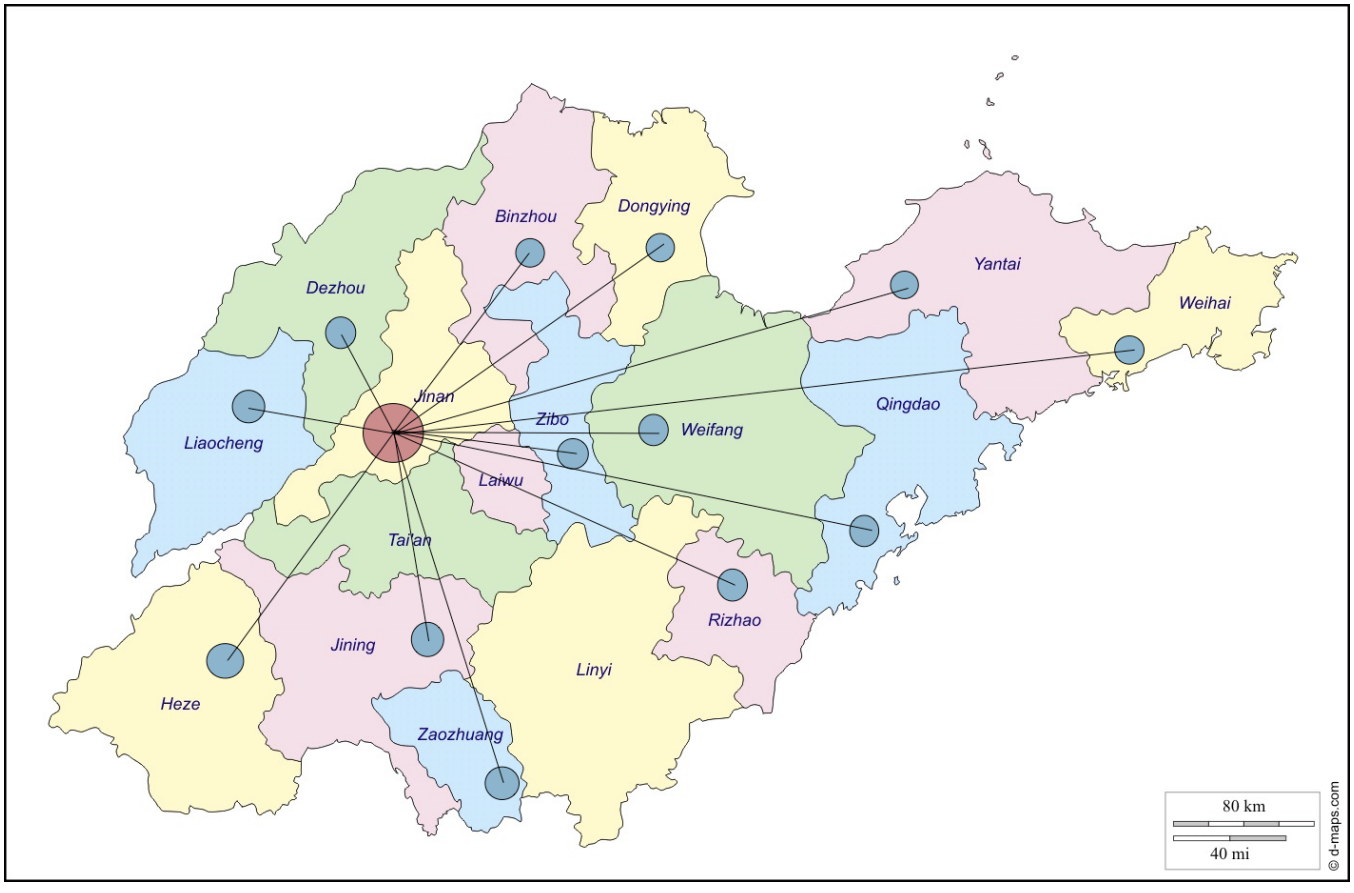
Supplementary



Jinan City: Shandong Qianfoshan Hospital; Qilu Hospital of Shandong University; General Hospital of Jinan Command; The Second Affiliated Hospital of Shandong University; Shandong Chest Hospital; East District of Shandong Provincial Hospital of Traditional Chinese Medicine; West District of Shandong Provincial Hospital of Traditional Chinese Medicine; Jinan City Central Hospital;The Forth Jinan Municipal Hospital
Weifang City: Affiliated Hospital of Weifang Medical College; Weifang People's Hospital
Binzhou City: Affiliated Hospital of Binzhou Medical College; Binzhou People's Hospital
Dezhou City: Dezhou People's Hospital
Dongying City: General Hospital of Shengli Oil Field in Dongying; Dongying People's Hospital
Heze City: Heze Municiple Hospital
Jining City: Jining First People's Hospital; Affiliated Hospital of Jining Medical College
Qingdao City: Qingdao Navy 401 Hospital;Affiliated Hospital of Qiingdao University Medical College; East District of Affiliated Hospital of Qiingdao University Medical College; East District of Oingdao Municipal Hospital;Qingdao Haici Hospital
Yenta City: Yuhuangding Hospital;Yantaishan Mountain Hospital
Liaocheng City: Liaocheng People's Hospital
Rizhao City: Rizhao People's Hospital
Tai'an City: Affiliated Hospital of Taishan Medical College; Taian City Central Hospital
Zaozhuang City: Tengzhou Central People's Hospital
Weihai City: Weihai Municipal Hospital; Wendeng Central Hospital
Zibo City: Zibo Central Hospital

Figure S1 The map of the 34 ICUs from 15 cities in Shandong Province.

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