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ORIGINAL ARTICLE

Distribution and Carbapenem Susceptibility of Gram-Negative ESKAPE Pathogens in Hospitalized Patients from Three General Hospitals

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SUMMARY

Background: **Gram-negative ESKAPE pathogens (*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Escherichia coli*) are responsible for the increase of antibiotic-resistant infections across the globe.**
Methods: **We retrospectively evaluated the patients infected with Gram-negative ESKAPE pathogens in three tertiary general hospitals (Hospital A, Hospital B, and Hospital C) in Guilin, for the period between January 2014 and December 2018. The data were collected and summarized from the Laboratory Information System (LIS) of the hospital. Antimicrobial susceptibility testing was carried out according to a unified protocol using Vitek 2 compact system.**
Results: **We collected a total of 16,121 patients with Gram-negative ESKAPE pathogen infections in three hospitals (*E. coli*, n = 7,142; *K. pneumoniae*, n = 3,850; *P. aeruginosa*, n = 2,711; *A. baumannii*; n = 2,418). Of the Gram-negative ESKAPE pathogens, > 50% of E. coli came from females compared with others. Patients aged above 60 years represented the highest proportion of patients. As observed for E. coli and K. pneumoniae, the sensitivity rates of imipenem and meropenem exceeded 85% in three hospitals, while there was high resistance to imipenem and meropenem for *A. baumannii* (Hospital A, 51.3%; Hospital B, 56.9%; Hospital C, 43.6%). Especially for Hospital A, rates of extended-spectrum β-lactamase (ESBL) production among *E. coli* isolates were stable, between 51.2 to 51.5%. On the contrary, the resistance rate of *A. baumannii* strains to carbapenems increased from 54.8% in 2014 to 60.0% in 2017, but it decreased to 50.4% in 2018.**
Conclusions: **Enhanced surveillance of Gram-negative ESKAPE pathogens is critical for selection of appropriate antimicrobial therapy and reducing the incidence of hospital-acquired infections (HAI).**
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KEY WORDS

gram-negative ESKAPE pathogens, distribution, carbapenem susceptibility, hospital-acquired infections

INTRODUCTION

The emergence and development of antimicrobials play an important role in overcoming infectious diseases [1]. However, persistent use of antibiotics, self-medication, and exposure to infections in hospitals have provoked the emergence of multidrug-resistant (MDR) bacteria [2]. The ESKAPE group of bacterial pathogens (*Entero-*

coccus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) is responsible for a majority of hospital-acquired infections (HAI), with the Gram-negative members of this group (*Escherichia coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*) posing a particular threat owing to their unique structure that prevents many antimicrobials from accessing their targets [3-5]. In addition, there is growing anxiety that multidrug-resistant Gram-negative ESKAPE pathogens will successfully spread to community settings given the increasing numbers of immunosuppressed and critically ill patients initially seeking treatment in hospitals who return to the community once treated or stable [6]. It is, therefore, imperative to find new antimicrobial agents to treat infections especially those caused by ESKAPE pathogens.

The availability of current resistance data, generated through ongoing antimicrobial susceptibility surveillance, is important for the clinic, drug developers, and governmental policymakers, among others. In the present study, we retrospectively evaluated the prevalence, distribution, and carbapenem susceptibility of Gram-negative ESKAPE pathogens in hospitalized patients for a 5-year period, to gain an overview of the situation in three tertiary general hospitals in China.

MATERIALS AND METHODS

Study design and sample

This retrospective study was collected in three tertiary general hospitals (Affiliated Hospital of Guilin Medical University (Hospital A), The Second Affiliated Hospital of Guilin Medical University (Hospital B), Guilin Hospital of Traditional Chinese Medicine (Hospital C)) in Guilin, China, from January 2014 to December 2018. Initially, we included all inpatients with a confirmed diagnosis of bacterial infection. The diagnosis of HAI was made based on the Hospital Infection Diagnosis Standard issued by the National Health and Family Planning Commission of the People's Republic of China (NHFPC) in 2001. Susceptibility to antibiotics of bacterial isolates was determined with antimicrobial susceptibility testing (AST). Clinical and demographic data of patients were obtained from the Laboratory Information System (LIS) of the hospital and included age, gender, specimens, microbiology results, and antibiotic resistance patterns of isolates.

Bacterial isolates

Gram-negative ESKAPE pathogens (*E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*) were collected from different sources, including blood, sputum, secretions, urine, or any other site that was clinically suspected for infection based on the technical guidelines for the prevention and control of nosocomial infections of the People's Republic of China. The isolates were cultured on agar plates containing 5% sheep blood (90 mm, Autobio Diagnostics Co., China) for 24 hours at 37°C. Species identification of the isolates was performed by standard biochemical methods, API 20E system, or Vitek 2 compact system (BioMérieux SA, France).

Antimicrobial susceptibility testing

The antibiotic susceptibilities of clinical isolates were determined using Vitek 2 compact system (BioMérieux SA, France) following the instrument specifications, and the results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria (29th edition) [7].

Reference strains

Staphylococcus aureus ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were included to ensure reproducibility of the antibiotic susceptibility testing procedure.

Statistical analysis

An electronic form was prepared to collect demographic, epidemiological, clinical, and microbiological variables. Absolute and relative (percentages) frequencies and means and standard deviations (SD) were used to summarize qualitative and normally-distributed quantitative variables, respectively.

RESULTS

Age and gender distribution of patients infected with Gram-negative ESKAPE pathogens

The distribution of patients with Gram-negative ESKAPE pathogens infections in three hospitals (*E. coli*, n = 7,142; *K. pneumoniae*, n = 3,850; *P. aeruginosa*, n = 2,711; *A. baumannii*, n = 2,418) according to gender and age groups is shown in Table 1. Of the Gram-negative ESKAPE pathogens, > 50% (Hospital A, 2,457/4,130, 59.5%; Hospital B, 932/1,852, 50.3%; Hospital C, 698/1,160, 60.2%) of the *E.coli* isolates were from females compared with others. According to the data, in the 51 - 60, 61 - 70, 71 - 80 age groups, the proportion of each type of bacterial infection in each hospital was more than 10%. In addition, unlike other hospitals, Hospital B had the highest rate of bacterial infection in the age group (≤ 10 years; *E. coli*, 260/1,852, 14.0%; *K. pneumoniae*, 258/1,611, 16.0%; *P. aeruginosa*, 119/1,206, 9.8%; *A. baumannii*; 126/900, 14.0%). In general, in Hospital C the elderly represented the highest proportion of patients with Gram-negative ESKAPE pathogen infections (> 80 years; *E. coli*, 260/1,160, 22.5%; *K. pneumoniae*, 102/353, 28.9%; *P. aeruginosa*, 105/386, 27.2%; *A. baumannii*; 91/220, 41.4%) compared with others.

Table 1. Age and gender distribution of patients with Gram-negative ESKAPE pathogens.

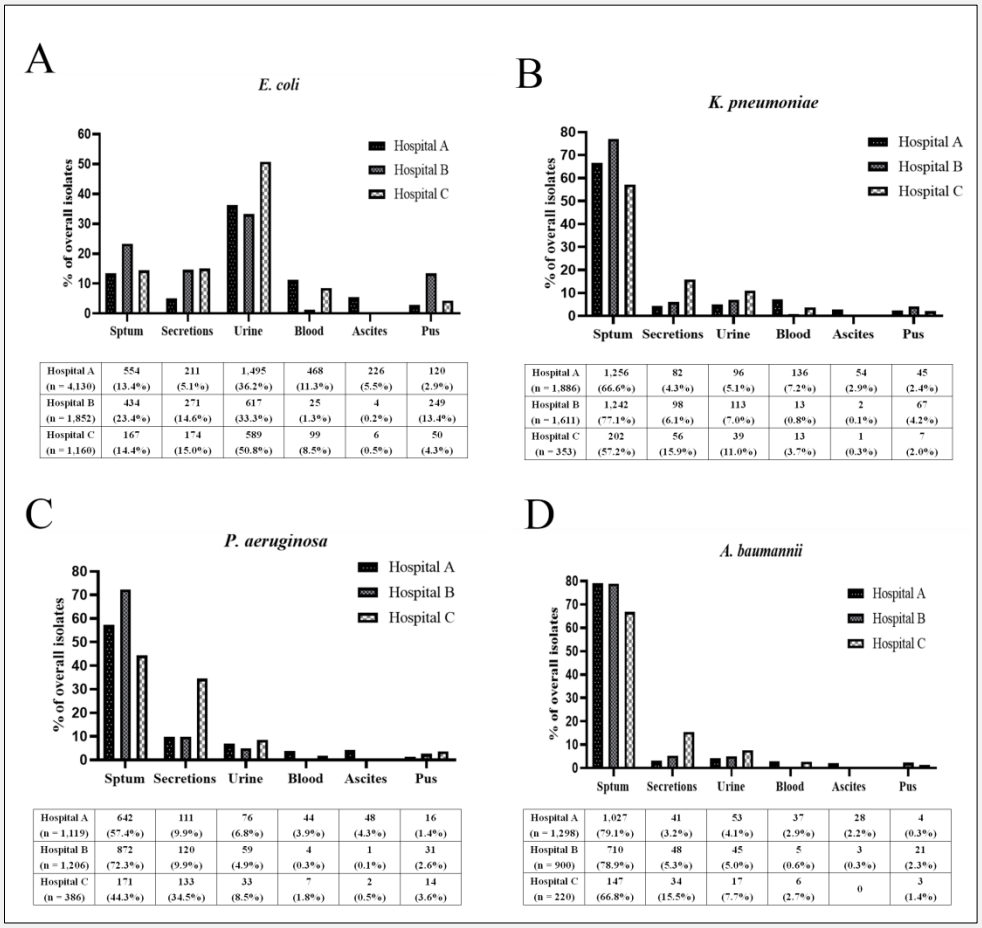
n (%)		*E. coli*			*K. pneumoniae*			*P. aeruginosa*			*A. baumannii*		
		Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C
		n = 4,130	n = 1,852	n = 1,160)	n = 1,886	n = 1,611	n = 353	n = 1,119	n = 1,206	n = 386	n = 1,298	n = 900	n = 220
Gender	Male	1,673 (40.5%)	920 (49.7%)	462 (39.8%)	1,288 (68.3%)	1,185 (73.6%)	214 (60.6%)	769 (68.7%)	821 (68.1%)	272 (70.5%)	918 (70.7%)	636 (70.7%)	153 (69.5%)
	Female	2,457 (59.5%)	932 50.3%)	698 (60.2%)	598 (31.7%)	426 (26.4%)	139 (39.4%)	350 (31.3%)	385 (31.9%)	114 (29.5%)	380 (29.3%)	264 (29.3%)	67 (30.5%)
Age (years)	≤ 10	175 (4.2%)	260 (14.0%)	47 (4.1%)	62 (3.3%)	258 (16.0%)	17 (4.8%)	33 (2.9%)	119 (9.8%)	4 (1.0%)	46 (3.5%)	126 (14.0%)	4 (1.8%)
	11 - 20	81 (2.0%)	36 (1.9%)	9 (0.8%)	33 (1.7%)	8 (0.5%)	2 (0.6%)	20 (1.8%)	30 (2.5%)	3 (0.8%)	26 (2.0%)	24 (2.7%)	0
	21 - 30	383 (9.3%)	109 (5.9%)	43 (3.7%)	63 (3.3%)	42 (2.6%)	3 (0.8%)	29 (2.6%)	34 (2.8%)	7 (1.8%)	40 (3.1%)	35 (3.9%)	4 (1.8%)
	31 - 40	388 (9.4%)	145 7.8%)	64 (5.5%)	101 (5.4%)	75 (4.7%)	15 (4.2%)	45 4.0%)	64 (5.3%)	21 (5.4%)	62 (4.8%)	68 (7.6%)	3 (1.4%)
	41 - 50	593 (14.4%)	271 (14.6%)	104 (9.0%)	260 (13.8%)	198 (12.3%)	18 (5.1%)	142 (12.7%)	135 (11.2%)	38 (9.8%)	137 (10.6%)	123 (13.7%)	3 (1.4%)
	51 - 60	759 (18.4%)	325 (17.6%)	155 (13.4%)	407 (21.6%)	315 (19.6%)	38 (10.8%)	241 (21.5%)	235 (19.5%)	53 (13.7%)	238 (18.3%)	131 (14.6%)	25 (11.4%)
	61 - 70	866 (21.0%)	372 (20.1%)	230 (19.8%)	477 (25.3%)	379 (23.5%)	71 (20.1%)	282(25.2%)	318 (26.3%)	84 (21.8%)	317 (24.4%)	179 (19.9%)	38 (17.3%)
	71 - 80	611 (14.8%)	243 (13.1%)	248 (21.4%)	309 (16.4%)	223 (13.8%)	87 (24.6%)	196 (17.5%)	195 (16.2%)	71 (18.4%)	275 (21.1%)	129 (14.3%)	52 (23.6%)
	81 - 90	244 (5.9%)	87 (4.7%)	228 (19.7%)	154 (8.2%)	105 (6.5%)	98 (27.8%)	116 (10.4%)	67 (5.6%)	94 (24.4%)	137 (10.6%)	81 (9.0%)	75 (34.1%)
	≥ 91	30 (0.7%)	3 (0.2%)	32 (2.8%)	20 (1.1%)	8 (0.5%)	4 (1.1%)	15 (1.3%)	10 (0.8%)	11 (2.8%)	20 (1.5%)	4 (0.4%)	16 (7.3%)

[*] **- Represents the percentage of Gram-negative ESKAPE pathogens in a particular group of the total number of Gram-negative ESKAPE pathogens in each of three hospitals.**

Table 2. Distribution of Gram-negative ESKAPE pathogens across major hospital departments.

Department	*E. coli*			*K. pneumoniae*			*P. aeruginosa*			*A. baumannii*		
	Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C	Hospital A	Hospital B	Hospital C
n (%)	n = 4,130	n = 1,852	n = 1,160	n = 1,886	n = 1,611	n = 353	n = 1,119	n = 1,206	n = 386	n = 1,298	n = 900	n = 220
ICU	228 (5.5%)	91 (4.9%)	29 (2.5%)	241 (12.8%)	193 (12.0%)	9 (2.5%)	143 (12.8%)	303 (25.1%)	21 (5.4%)	420 (32.4%)	462 (51.3%)	17 (7.7%)
Neuro-surgery [1]	94 (2.3%)	63 (3.4%)	82 (7.1%)	181 (9.6%)	130 (8.1%)	48 (13.6%)	73 (6.5%)	72 (6.0%)	50 (13.0%)	169 (13.0%)	50 (5.6%)	41 (18.6%)
Neurology [1]	95 (2.3%)	85 (4.6%)		83 (4.4%)	199 (12.3%)		49 (4.4%)	103 (8.5%)		82 (6.3%)	71 (7.9%)	
Cardio-thoracic surgery [2]	53 (1.3%)	46 (2.5%)	120 (10.3%)	267 (14.2%)	122 (7.6%)	82 (23.2%)	60 (5.4%)	36 (3.0%)	57 (14.8%)	107 (8.2%)	35 (3.9%)	72 (32.7%)
Respiratory [2]	53 (1.3%)	67 (3.6%)		194 (10.3%)	253 (15.7%)		100 (8.9%)	267 (22.2%)		120 (9.2%)	45 (5.0%)	
Gastro-enterology [3]	77 (1.9%)	330 (17.8%)	61 (5.3%)	81 (4.3%)	83 (5.2%)	13 (3.7%)	52 (4.6%)	55 (4.6%)	6 (1.6%)	44 (3.4%)	19 (2.1%)	3 (1.4%)
Orthopedics	76 (1.8%)	83 (4.5%)	60 (5.2%)	26 (1.4%)	42 (2.6%)	7 (2.0%)	42 (3.8%)	73 (6.1%)	12 (3.1%)	20 (1.5%)	30 (3.3%)	2 (0.9%)
Endocri-nology	188 (4.6%)	215 (11.6%)	90 (7.8%)	84 (4.5%)	114 (7.1%)	27 (7.6%)	54 (4.8%)	32 (2.7%)	36 (9.3%)	19 (1.5%)	18 (2.0%)	1 6(7.3%)
Gynecology & Obstetrics	748 (18.1%)	152 (8.2%)	70 (6.0%)	46 (2.4%)	139 (8.6%)	14 (4.0%)	9 (0.8%)	5 (0.4%)	1 (0.3%)	5 (0.4%)	4 (0.4%)	2 (0.9%)
Emergency	46 (1.1%)	3 (0.2%)	22 (1.9%)	23 (1.2%)	7 (0.4%)	7 (2.0%)	30 (2.7%)	8 (0.7%)	5 (1.3%)	18 (1.4%)	3 (0.3%)	5 (2.3%)
Nephrology	985 (23.8%)	322 (17.4%)	191 (16.5%)	99 (5.2%)	74 (4.6%)	18 (5.1%)	81 (7.2%)	44 (3.7%)	13 (3.4%)	66 (5.1%)	23 (2.6%)	4 (1.8%)
Oncology	35 (0.8%)	26 (1.4%)	47 (4.1%)	19 (1.0%)	29 (1.8%)	14 (4.0%)	13 (1.2%)	11 (0.9%)	8 (2.1%)	6 (0.5%)	6 (0.7%)	2 (0.9%)

[*] - Represents the percentage of Gram-negative ESKAPE pathogens in a particular group of the total number of Gram-negative ESKAPE pathogens in each of three hospitals, [1] - Neurosurgery department and Neurology department are collectively named as the Encephalopathy department in Hospital C (the traditional Chinese medicine system), [2] - Cardiothoracic surgery department and Respiratory department are collectively named as the Cardiopulmonary department in Hospital C (the traditional Chinese medicine system), [3] - Gastroenterology department is named as the department of Spleen and Stomach diseases in Hospital C (the traditional Chinese medicine system).



	Sptum	Secretions	Urine	Blood	Ascites	Pus
Hospital A (n = 4,130)	554 (13.4%)	211 (5.1%)	1,495 (36.2%)	468 (11.3%)	226 (5.5%)	120 (2.9%)
Hospital B (n = 1,852)	434 (23.4%)	271 (14.6%)	617 (33.3%)	25 (1.3%)	4 (0.2%)	249 (13.4%)
Hospital C (n = 1,160)	167 (14.4%)	174 (15.0%)	589 (50.8%)	99 (8.5%)	6 (0.5%)	50 (4.3%)

	Sptum	Secretions	Urine	Blood	Ascites	Pus
Hospital A (n = 1,886)	1,256 (66.6%)	82 (4.3%)	96 (5.1%)	136 (7.2%)	54 (2.9%)	45 (2.4%)
Hospital B (n = 1,611)	1,242 (77.1%)	98 (6.1%)	113 (7.0%)	13 (0.8%)	2 (0.1%)	67 (4.2%)
Hospital C (n = 353)	202 (57.2%)	56 (15.9%)	39 (11.0%)	13 (3.7%)	1 (0.3%)	7 (2.0%)

	Sptum	Secretions	Urine	Blood	Ascites	Pus
Hospital A (n = 1,119)	642 (57.4%)	111 (9.9%)	76 (6.8%)	44 (3.9%)	48 (4.3%)	16 (1.4%)
Hospital B (n = 1,206)	872 (72.3%)	120 (9.9%)	59 (4.9%)	4 (0.3%)	1 (0.1%)	31 (2.6%)
Hospital C (n = 386)	171 (44.3%)	133 (34.5%)	33 (8.5%)	7 (1.8%)	2 (0.5%)	14 (3.6%)

	Sptum	Secretions	Urine	Blood	Ascites	Pus
Hospital A (n = 1,298)	1,027 (79.1%)	41 (3.2%)	53 (4.1%)	37 (2.9%)	28 (2.2%)	4 (0.3%)
Hospital B (n = 900)	710 (78.9%)	48 (5.3%)	45 (5.0%)	5 (0.6%)	3 (0.3%)	21 (2.3%)
Hospital C (n = 220)	147 (66.8%)	34 (15.5%)	17 (7.7%)	6 (2.7%)	0	3 (1.4%)

Figure 1. Sources and proportions of Gram-negative ESKAPE pathogens in hospitalized patients from three tertiary general hospitals. Data are shown for (A) *E. coli*, (B) *K. pneumoniae*, (C) *P. aeruginosa*, (D) *A. baumannii*.

Distribution of Gram-negative ESKAPE pathogens across hospital departments

Patients with Gram-negative ESKAPE pathogen infections were distributed across various hospital departments (Table 2). For isolates of *E. coli*, the proportion of patients was the highest in the department of nephrology in Hospital A and Hospital C (Hospital A, 985/4,130, 23.8%; Hospital C, 191/1,160, 16.5%). Except for isolates of *E.coli*, Hospital C showed a higher proportion of infected patients in the cardiothoracic surgery department and respiratory department (these two departments are collectively named the cardiopulmonary department in the traditional Chinese medicine system) than in other departments (*K. pneumoniae*, 82/353, 23.2%; *P. aeruginosa*, 57/386, 14.8%; *A. baumannii*, 72/220, 32.7%). *P. aeruginosa* and *A. baumannii* were most commonly isolated from patients in ICU between Hospital A and Hospital B (*P. aeruginosa*: Hospital A, 143/1,119, 12.8%; Hospital B, 303/1,206, 25.1%. *A. baumannii*: Hospital A, 420/1,298, 32.4%; Hospital B, 462/900, 51.3%).

Main sources of Gram-negative ESKAPE pathogen bacteria

According to Figure 1, the proportion of main specimen type in the group of isolates positive for *E.coli* was as follows: the highest, urine (Hospital A, 1,495/4,130, 36.2%; Hospital B, 617/1,582, 33.7%; Hospital C, 589/1,160, 50.8%), followed by sputum (Hospital A, 554/4,130, 13.4%; Hospital B, 434/1,582, 23.7%; Hospital C, 167/1,160, 14.4%). Meanwhile, It was not difficult to find that sputum was the main source of *K. pneumoniae* (Hospital A, 1256/1,886, 66.6%; Hospital B, 1,242/1,611, 77.1%; Hospital C, 202/353, 57.2%), *P. aeruginosa* (Hospital A, 642/1,119, 57.4%; Hospital B, 872/1,206, 72.3%; Hospital C, 171/386, 44.3%) and *A.*

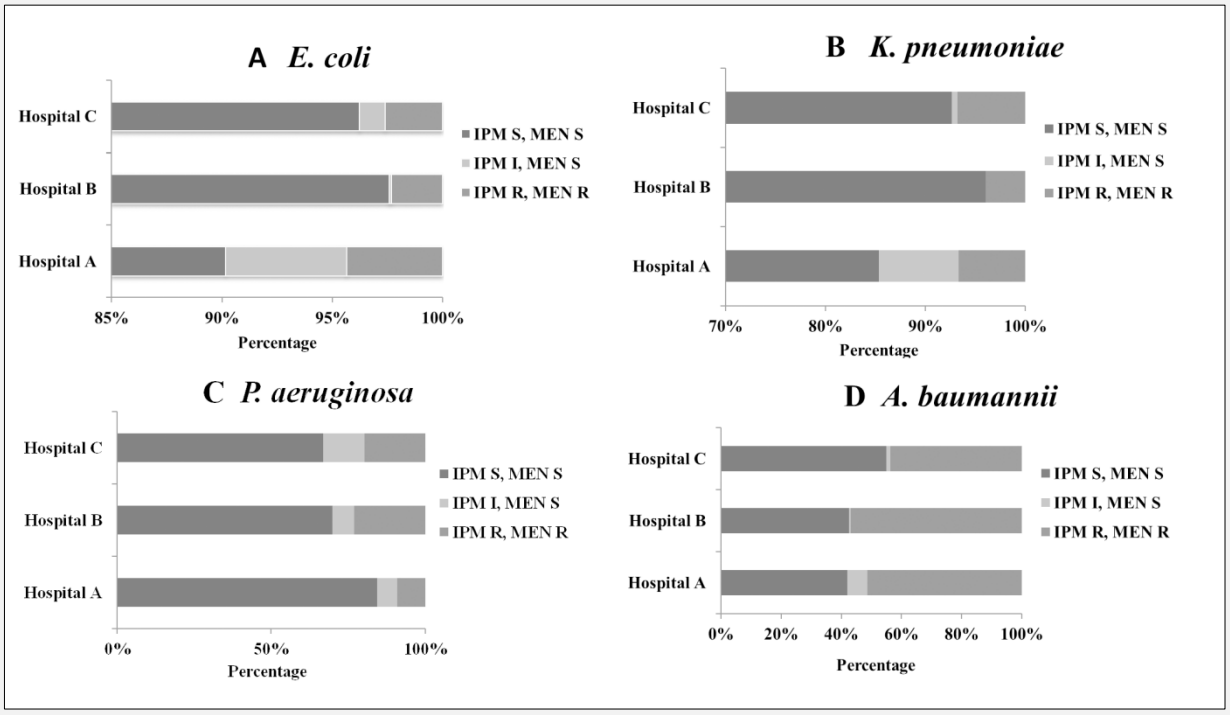


Figure 2. Carbapenem susceptibility of Gram-negative ESKAPE pathogens in hospitalized patients from three tertiary general hospitals.

A - For *E. coli*, the sensitivity rates of imipenem and meropenem exceeded 85% in each of three hospitals, B - For *K. pneumoniae*, the sensitivity rates of imipenem and meropenem exceeded 85% in each of three hospitals, C - The susceptibility rates of *P. aeruginosa* to imipenem and meropenem were above 65% (Hospital A, 84.5%; Hospital B, 69.9%; Hospital C, 66.8%), D - High resistance to imipenem and meropenem for *A. baumannii* was observed in every hospital (Hospital A - 51.3%, Hospital B - 56.9%, Hospital C - 43.6%).

baumannii (Hospital A, 1,027/1,298, 79.1%; Hospital B, 710/900, 78.9%; Hospital C, 147/220, 66.8%). However, for patients with bloodstream infection, Hospital A showed a higher infection rate (*E. coli*, 468/4,130, 11.3%; *K. pneumoniae*, 132/1,886, 7.2%; *P. aeruginosa*, 44/1,119, 3.9%; *A. baumannii*; 37/1,298, 2.9%).

Carbapenem susceptibility of Gram-negative ESKAPE pathogens

As observed for *E. coli* and *K. pneumoniae*, in general, the sensitivity rates of imipenem and meropenem exceeded 85% in each of three hospitals (Figure 2A - B). In addition, the susceptibility rates of *P. aeruginosa* to imipenem and meropenem were above 65% (Hospital A, 84.5%; Hospital B, 69.9%; Hospital C, 66.8%). However, the resistance rates of imipenem and meropenem were more than 20% for isolates of *P. aeruginosa* in Hospital B (Figure 2C). Even worse, Figure 2D showed high resistance to imipenem and meropenem for *A. baumannii* in every hospital (Hospital A, 51.3%; Hospital B, 56.9%; Hospital C, 43.6%).

Distinctions in carbapenem susceptibility and ESBL rates in different periods of Hospital A

As a large general hospital, Hospital A has more medical resources compared with the other two hospitals. Therefore, we listed it separately and counted the sensitivity of Gram-negative ESKAPE pathogens. For Figure 3A, it showed that the rate of ESBL-positive *E. coli* was stable, from 51.2% in 2014 to 51.5% in 2018. It was gratifying that the rate of ESBL-positive *K. pneumoniae* decreased from 35.0% to 24.8%. For *P. aeruginosa*, a marked resistance decrease was seen for imipenem and meropenem from 18.3% in 2014 to 7.0% in 2018 (Figure 3B). However, for *A. baumannii*, it was just the opposite of *P. aeruginosa*. A marked resistance increase was seen for imipenem and meropenem from 54.8% in 2014 to 60.0% in 2017, but it decreased to 50.4% in 2018 (Figure 3C).

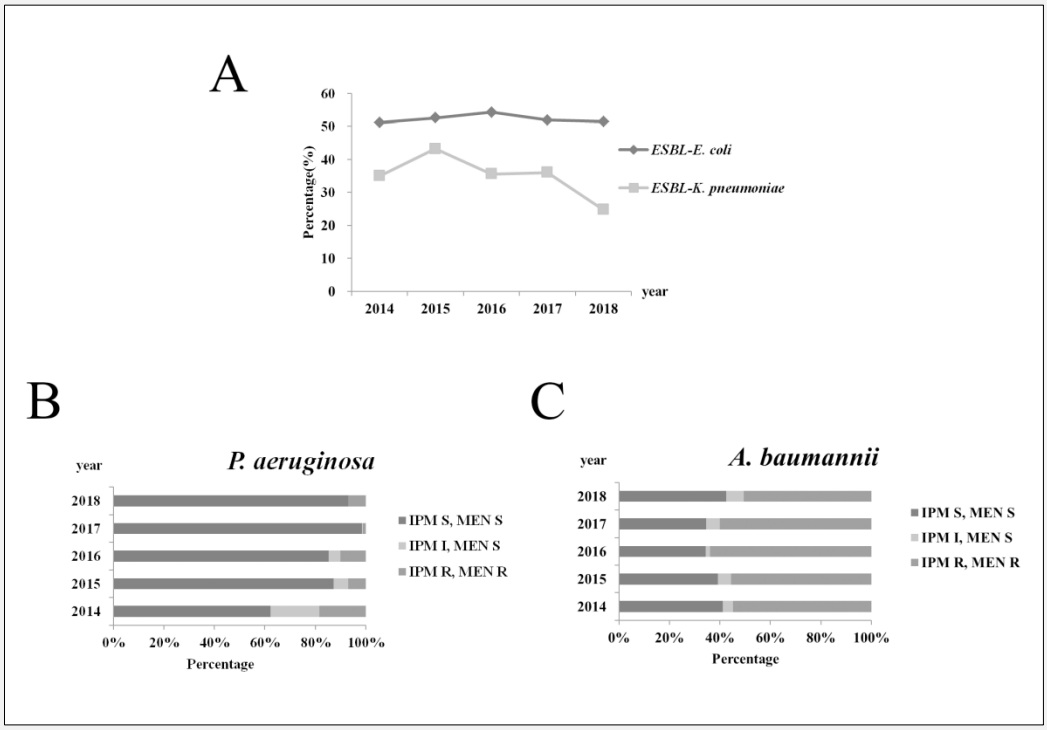


Figure 3. Distinctions in carbapenem susceptibility and ESBL rates in different periods of Hospital A.

A - the rate of ESBL-positive *E. coli* was stable from 51.2% in 2014 to 51.5% in 2018, but the rate of ESBL-positive *K. pneumoniae* decreased from 35.0% to 24.8%, B - For *P. aeruginosa*, a marked resistance decrease was seen for imipenem and meropenem from 18.3% in 2014 to 7.0% in 2018, C - For *A. baumannii*, a marked resistance increase was seen for imipenem and meropenem from 54.8% in 2014 to 60.0% in 2017, but it decreased to 50.4% in 2018.

DISCUSSION

In the past decades, the increasing frequency of antimicrobial resistance has become one of the most challenging problems in the healthcare system [5]. The spread of antimicrobial resistant pathogens has a significant impact on mortality and morbidity thereby resulting in increased health care costs [8]. ESKAPE pathogens are responsible for the majority of nosocomial infections and pose a serious therapeutic challenge due to their capacity of "escaping" the biocidal action of antimicrobial agents [9,10]. However, with every passing year, the overall number of antibiotics effective against ESKAPE is declining, which highlights the urgent need for new approaches [11]. Therefore, it is important to understand the distribution of Gram-negative ESKAPE pathogens, especially in hospitals, for the control of infection and the rational use of antibiotics.

According to our study, in gender distribution, more women were infected with *E. coli* than men. We consider that *E. coli* is the main common bacteria in urinary tract infection, and women dominated. In our study, patients aged above 60 years represented the highest proportion of patients with Gram-negative ESKAPE pathogen infections, especially in Hospital C (more than 20% of patients were over 80 years old). Elderly patients are usually considered to be high-risk groups of nosocomial infection, and Hospital C is a traditional Chinese medicine hospital, mainly recuperation, favored by the elderly. At the same time, higher disease prevalence in this population, including neurological disorders, diabetes, and respiratory diseases [12-14].

The highest number of E.*coli* positive cases were from patient specimens in the department of nephrology in Hospital A and Hospital C (Hospital A, 985/4,130, 23.8%; Hospital C, 191/1,160, 16.5%). As mentioned above, the main pathogen of urinary tract infection is *E. coli*. In addition, indwelling catheters lead to the destruction of the skin mucosal barrier, conditional pathogens (e.g., *E. coli*) easily attach to the surface of the catheter, resulting in infection. The risk of infections with Gram-negative ESKAPE pathogens is high for patients admitted to the ICU, especially *P. aeruginosa* and *A. baumannii*. It is related to the critical primary dis-

ease, impaired function of multiple organs, long hospital stay, extensive antibiotic use, various invasive procedures (e.g., mechanical ventilation, central venous catheters, and tracheotomy) [15-18]. Therefore, we should focus on strengthening the monitoring of these high-risk departments and pay attention to the epidemic or spread of Gram-negative ESKAPE pathogens in these departments [19].

According to the data, it was not difficult to find that the highest percentage of *E. coli* was obtained from urine specimens in three tertiary general hospitals, showing that the urinary system was the most frequent site of infection. Except for *E. coli*, sputum was the main source of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*. The prevalence of smoking is higher in males than in females, which makes them more prone to respiratory tract diseases, including infections. In addition, the incidence of bloodstream infection has been on the rise in the past few years. We need to combine the variety of hospital antibiotics, the concentration of drugs in the blood, and the PK/PD of antibiotics to further select appropriate antibiotics [20].

The results of the present study showed that the carbapenem resistance rates among *P. aeruginosa* and *A. baumannii* were higher in comparison with antibiotic resistance in *E. coli* and *K. pneumoniae* (Figure 2). Zavascki AP et al. [21] previously reported that it may be the existence of carbapenem enzyme with stronger hydrolysis ability or other drug resistance mechanisms. Consequently, for infections caused by carbapenem-resistant *P. aeruginosa* or *A. baumannii*, the therapeutic effect of carbapenem is limited, but if carbapenem is combined with polymyxin or aminoglycosides, it still has a synergistic bactericidal effect and can delay the emergence of drug-resistant strains [22].

Compared with the other two hospitals, Hospital A, as the largest general hospital in Guilin, has high-quality medical resources and equipment. Therefore, we analyzed the drug resistance of Gram-negative ESKAPE pathogens from 2014 to 2018 in Hospital A. As we know, most of the ESBL-producing strains are Gram-negative bacilli, among which *E. coli* and *K. pneumoniae* are more common in clinical isolates. Our data showed the rate of ESBL-positive *E. coli* was stable from 51.2% in 2014 to 51.5% in 2018, while the rate of ESBL-positive *K. pneumoniae* decreased from 35.0% to 24.8%. In an earlier study, Müller A et al. [23] reported the third-generation cephalosporins have been recognized as the main factor leading to the emergence and spread of ESBL-producing strains. Hence, reducing the use of third-generation cephalosporins can reduce the production of ESBLs positive strains in Enterobacteriaceae.

In Hospital A from 2014 to 2018, the carbapenem resistance of *P. aeruginosa* was optimistic, but that of *A. baumannii* became very serious. In the current study, the rates of susceptibility to the carbapenem tested against *A. baumannii* were < 45%. Clearly, novel agents are urgently needed to treat *A. baumannii* infections. However, it is gratifying that the resistance rates of imipenem and meropenem for *A. baumannii* has decreased from 60.0% in 2017 to 50.4% in 2018 due to strict control and strengthening of nosocomial infections. Therefore, further studies should focus on the rational use of available antibiotics and implementation of strict infection control measures to avoid the rapid spread or clonal dissemination of Gram-negative ESKAPE pathogens in healthcare institutions [24].

Limitations of the current study include that our data may not be representative of other populations because it is a regional study, and the classification of isolates by patient location in Hospital A may be imperfect as patients may move between departments during a single admission. In addition, our study was retrospective, and under-reporting might have occurred in some cases. Even with all these caveats, we provided a helpful overview of general antimicrobial resistance patterns among pathogens causing human infections.

In summary, we conclude that patients infected with Gram-negative ESKAPE pathogens were widely distributed in three tertiary general hospitals. Meanwhile, the bacterial infection was more likely to occur among elderly and ICU patients. Therefore, efforts need to focus on strategies for preventing initial development of infection and to reduce delays in the use of antimicrobials for inpatients, while at the same time attempting to limit the use of unnecessary broad-spectrum antimicrobials.

Data Availability:

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval:

Approval from the ethical committees was not necessary.

Declaration of Interest:

The authors declare that they have no competing interests.

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