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ORIGINAL ARTICLE

Resistance Trends Among 1,294 Nosocomial *Acinetobacter baumannii* Strains from a Tertiary General Hospital in China, 2014 - 2017

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SUMMARY

Background: **To analyze the difference of the antibiotic resistance of *Acinetobacter baumannii* (*A. baumannii*) isolated from our hospital between 2014 and 2017.**
Methods: **We retrospectively evaluated the patients with a confirmed diagnosis of *A. baumannii* infection at a tertiary general hospital in Guilin during the period between January 2014 and December 2017. The following clinical and demographic data were collected: age, gender, specimens, microbiology results, and antibiotic resistance patterns of isolates. Bacterial identification and susceptibility testing were performed using MALDI-TOF MS and VITEK 2 COMPACT systems. The results were analyzed according to the Clinical and Laboratory Standards Institute (CLSI) 2018 definitions.**
Results: **From 2014 to 2017, 1,294 strains of *A. baumannii* were detected, 41.5% of which came from ICU. The sputum separation rate from ICU was significantly higher than those from non-ICU ($p < 0.05$). Except for amikacin, levofloxacin, and compound sulfamethoxazole, the resistant rates of the others increased year by year. Meanwhile, the resistance rate of carbapenem-resistant *A. baumannii* in our hospital showed a significant upward trend and exceeded the average of the national level in 2016 - 2017.**
Conclusions: **The drug resistance of *A. baumannii* has generally increased, and active measures have been taken to develop the combined application of antibiotics. Further studies should focus on the judicious use of available antibiotics and implementation of strict infection control measures to avoid the rapid spread or clonal dissemination of *A. baumannii* in healthcare facilities.**
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Acinetobacter baumannii, drug resistance rate, nosocomial infection

INTRODUCTION

Acinetobacter baumannii (*A. baumannii*) is an important Gram negative opportunistic nosocomial bacteria that has emerged in recent years as a major cause of healthcare-associated infections and hospital outbreaks [1,2]. In 2017, *A. baumannii* was also classified in the highest level of "critical" by WHO because it is resistant to a large number of antibiotics, including carbapenems [3,4]. Therefore, *A. baumannii* isolates responsible for epidemics are frequently multidrug resistant

(MDR) or extensively drug-resistant (XDR). In the current review, we comprehensively analyzed the efficacy and safety in treatment of *A. baumannii* infection in our hospital from January 2014 to December 2017.

MATERIALS AND METHODS

Strains collection

This retrospective study was conducted at the Affiliated Hospital of Guilin Medical University, China, during the period between January 2014 and December 2017. Bacterial isolates were collected from different sources, including blood, sputum, secretions, urine, etc. A total of 1,294 clinical isolates of non-repetitive *A. baumannii* were collected from uploaded clinical data in the China Antimicrobial Resistance Surveillance System (CARSS). The isolates were cultured on agar plates containing 5% sheep blood (90 mm, Autobio Diagnostics Co., China) for 24 hours at 37°C. Matrix assisted laser desorption ionization - time of flight mass spectrometry (MALDI-TOF MS, BioMérieux SA, France) was used for identification of isolates using protein spectra of the strains. Escherichia coli ATCC8739 were used as a control strain.

Antimicrobial susceptibility testing

Clinical isolates of *A. baumannii* were obtained from the Microbiology Research Laboratory at the Affiliated Hospital of Guilin Medical University. Antimicrobial susceptibility testing was carried out according to a unified protocol using the Vitek 2 automated system (BioMérieux SA, France) with standardized inoculum. Results were analyzed according to CLSI criteria (28th edition). The following quality control (QC) strains were included: Staphylococcus aureus ATCC25923, Escherichia coli ATCC25922, and Pseudomonas aeruginosa ATCC27853.

Statistical analysis

Clinical and demographic data of patients were extracted from the Laboratory Information System (LIS) of the hospital and converted into a standard format using WHONET 5.6 software (WHO Collaborating Centre for Surveillance of Antimicrobial Resistance). We used descriptive statistics for data processing and reporting. Enumeration data were carried out using the χ^2 test for statistical analysis. $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Distribution of *A. baumannii* across hospital departments

Patients with *A. baumannii* infections were distributed across different hospital departments, especially in ICU (537/1,294, 41.5%). There was no statistically significant difference in age and gender distribution of patients between ICU and non-ICU ($\chi^2 = 2.520$, $p > 0.05$). However, the sputum separation rate from ICU was significantly higher than those from non-ICU ($\chi^2 = 30.620$, $p < 0.05$).

Sources of *A. baumannii*

From 2014 to 2017, the specimens of *A. baumannii* infection were diverse, and the main sources were sputum specimens, all of which were above 60%. The proportion of each specimen type in the group of isolates positive for *A. baumannii* was as follows: sputum (952/1,294, 73.6%), secretions (46/1,294, 3.6%), abdominal fluid (36/1,294, 2.8%), urine (69/1,294, 5.3%), blood (52/1,294, 4.0%), and other specimens (139/1,294, 10.7%). In addition, *A. baumannii* isolated from the sputum specimens in 2017 showed a significant downward trend ($\chi^2 = 49.925$, $p < 0.05$) (Table 1).

Antimicrobial susceptibility of *A. baumannii*

Between 2014 and 2017, the resistance rate of *A. baumannii* to imipenem increased from 53.7 to 64.1%. Resistance of *A. baumannii* against piperacillin/tazobactam increased with time (from 48.1 to 61.2%). The cephalosporin drugs showed an increasing trend year by year. On the contrary, amikacin, levofloxacin, and sulfamethoxazole/trimethoprim resistance levels decreased from 24.8 to 23.3%, from 39.6 to 33.8%, from 53.0 to 31.2%, respectively (Table 2).

Resistance trend of Carbapenem-resistant *A. baumannii* (CRAB)

Comparing the resistance rates of *A. baumannii* to carbapenems in Guangxi and China in CARSS from 2014 to 2017 [5-8], it demonstrated that the resistance rate of CRAB in our hospital increased simultaneously, and showed a significant increasing trend in 2016 - 2017, even exceeding the national average level of drug resistance (Figure 1).

DISCUSSION

A. baumannii, which is a pathogen frequently identified as an etiologic agent in catheter-related bacteremia, ventilator-associated pneumonia (VAP), urinary tract infections, and other types of wound infections, has become an important pathogen with the ability of causing nosocomial infections [9]. With the increasingly wide spread use of antimicrobial agents, *A. baumannii* has developed resistance to several drugs, with the emergence of multi-drug resistant strains [10].

Retrospective analysis of age and gender distribution of patients infected with *A. baumannii* from 2014 to 2017 showed that the age and gender composition of ICU and non-ICU departments were mainly elderly and male ($p > 0.05$). Elderly patients are generally considered to be at high risk of nosocomial infections due to a higher disease prevalence in this population, including neurological disorders, diabetes, and cardiovascular diseases

Table 1. Sources of *A. baumannii*.

Year	Specimen					
	Sputum	Secretions	Abdominal fluid	Urine	Blood	Others
	n (%) *	n (%) *	n (%) *	n (%) *	n (%) *	n (%) *
2014 (n = 270)	213 (78.9)	10 (3.7)	11 (4.1)	7 (2.6)	8 (3.0)	21 (7.8)
2015 (n = 335)	247 (73.7)	9 (2.7)	9 (2.7)	15 (4.5)	12 (3.6)	43 (12.8)
2016 (n = 283)	240 (84.8)	6 (2.1)	7 (2.5)	13 (4.6)	6 (2.1)	11 (3.9)
2017 (n = 406)	252 (62.1)	21 (5.2)	9 (2.2)	34 (8.4)	26 (6.4)	64 (15.8)
Percentage of total *A. baumannii* (n = 1,294)	952 (73.6)	46 (3.6)	36 (2.8)	69 (5.3)	52 (4.0)	139 (10.7)

* **- Represents the percentage of the total number of *A. baumannii* for a given specimen type per year.**

Table 2. Resistance rates (%) of *A. baumannii* to antimicrobial agents.

Antimicrobial agent	2014 (n = 270)	2015 (n = 335)	2016 (n = 283)	2017 (n = 406)
Ampicillin	73.0	75.5	75.6	82.4
Ampicillin/sulbactam	58.5	61.5	64.3	72.4
Piperacillin/tazobactam	48.1	49.9	59.4	61.2
Cefazolin	98.9	99.1	99.6	99.8
Ceftazidime	59.6	60.6	64.3	71.5
Ceftriaxone	63.6	63.3	65.4	70.8
Cefepime	58.5	60.9	63.6	70.8
Cefotetan	90.7	90.4	95.8	99.8
Aztreonam	73.2	76.1	78.7	85.4
Imipenem	53.7	53.7	62.9	64.1
Amikacin	24.8	26.0	22.6	23.3
Gentamicin	49.6	58.5	60.4	68.4
Tobramycin	50.7	58.2	61.5	67.7
Ciprofloxacin	59.3	62.7	65.0	70.8
Levofloxacin	39.6	38.5	32.9	33.8
Sulfamethoxazole/trimethoprim	53.0	34.6	19.4	31.2
Nitrofurantoin	94.1	96.7	97.2	99.8

[11,12]. Meanwhile, these results suggest that ICU admission is an important risk factor for *A. baumannii* infection, similar to the results of Manisha Jain, etc. [13]. Most patients admitted to ICU are mainly unconscious, have low autoimmunity and excessive frequency. Excessive use of the ventilator causes the patient's swallow, cough, and other physiological reflexes to weaken or even disappear, so that the sputum accumulates in the lower respiratory tract, causing the patient's primary or secondary respiratory infection, which is the ventilator-associated *A. baumannii* infectious pneumonia [14]. In this study, the specimens of A. baumannii infection were diverse between 2014 and 2017. It was known that the top ones were still sputum, secretions, abdominal fluid, urine, and blood samples, and sputum specimens were much higher than other specimens (the separation rate can be as high as 60%). The results of the present study show that *A. baumannii* infection is mainly in the upper respiratory tract, and sputum specimens are easily obtained, but attention should be paid to the eligibility

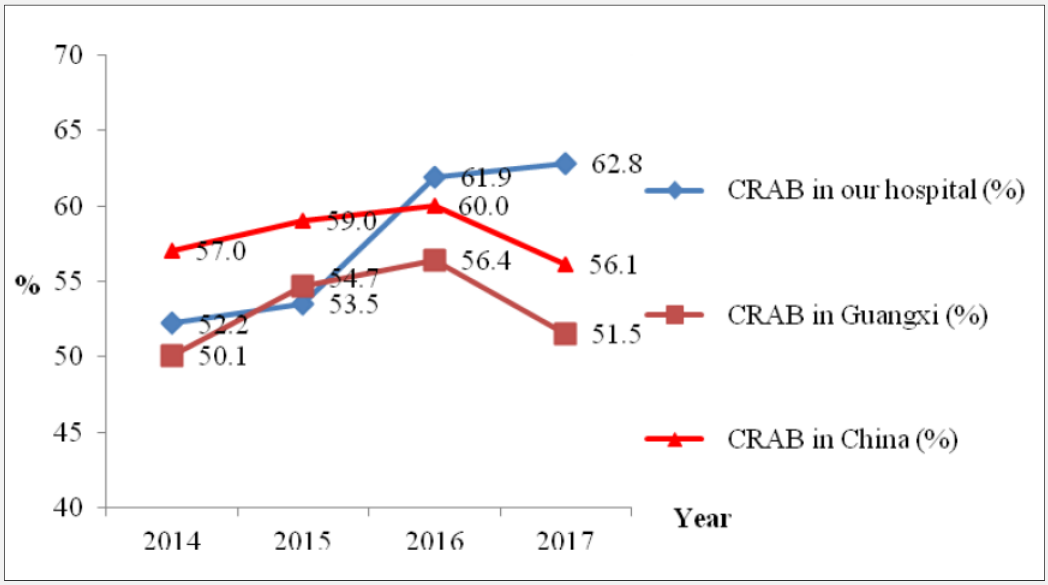

Figure 1. The tendency of carbapenem-resistant *Acinetobacter baumannii*.

of the specimens. Meanwhile, the infection and colonization of *A. baumannii* should be analyzed in combination with clinical identification [15]. In addition, we can find that the detection rate of sputum specimens showed a significant downward trend in 2017 (Figure 1). The main reason is that the microbiology research laboratory of our hospital has strengthened the control of the eligibility of sputum specimens, and actively trained the clinical staff in real time, thereby we could improve the positive rates.

Carbapenems are the most potent and reliable β-lactam antibiotics that are widely regarded by clinicians as "last-line" antibiotics, particularly for the management of critically ill patients and/or those with antimicrobial-resistant Gram-negative infections, such as multidrug-resistant *A. baumannii* [16,17]. However, the present study showed the resistance rate of *A. baumannii* to carbapenems had increased year by year, and the resistance rate of our hospital in 2016 - 2017 had exceeded Guangxi, even higher than the national average level. Because treatment options for these infections are limited, few clinical data are available on which to base antibiotic recommendations. Moreover, the use of inappropriate empirical antibiotic therapy or delayed appropriate antibiotic therapy can lead to worse outcomes. Although *A. baumannii* is intrinsically resistant to many antibiotics and readily acquires resistance to others, the resistance rate to amikacin, levofloxacin, and sulfamethoxazole/trimethoprim showed a decreasing trend. Analysis of the reasons may be related to clinical over-pursuit of high-end drugs, and some cheap drugs are relegated to the second line due to factors such as cost or toxic side effects [18].

CONCLUSION

In summary, this study demonstrated that CRAB has been emerging and increasing in our hospital. This may be related to our hospital belonging to the tertiary general hospital in North Guangxi. The patients admitted to the hospital are relatively serious and need long-term antibiotic treatment. The development of new antibacterial drugs currently used to treat these infections caused by CRAB is relatively rare (such as polymyxin and tigecycline), and these drugs are limited to clinic due to expensive cost or toxic side effects [19]. In view of the mouse pneumonia model established in the previous study [20], we have found that minocycline in combination with either rifampicin or amikacin was more effective against multi-drug resistant *A. baumannii* than tigecycline or polymyxin B alone in an *in vitro* susceptibility test. Therefore, further research should focus on how to develop antibacterial activity of antimicrobial agents in combination. At the same time, we need to strengthen the health of clinical staff, regulate the use and management of antibiotics, and avoid the rapid spread or clonal dissemination of CRAB in healthcare facilities.

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Authors' Contributions:
Li Zhao and Zhu Hong collected this data about *A. baumannii*. Zheng Li and Meilian Quan analyzed and interpreted this data. Songzhe He and Qiu Yang were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Declaration of Interest:
The authors declare that they have no competing interests.

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