Int J Clin Exp Med 2019;12(10):12322-12330
www.ijcem.com /ISSN:1940-5901/IJCEM0097664

*Original Article*

# Clinical distribution, drug resistance and risk factor analysis of *Pseudomonas aeruginosa* infections

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Received May 28, 2019; Accepted September 2, 2019; Epub October 15, 2019; Published October 30, 2019

**Abstract:** To investigate the clinical features of *Pseudomonas aeruginosa* (PA) infections and provide a reference for clinical treatment and prevention. The clinical data of 668 patients with PA infection who were hospitalized in Qilu Hospital of Shandong University from July 2013 to July 2017 were retrospectively analyzed. The distribution of PA was mainly found in the intensive care unit (ICU), respiratory department, and geriatrics department. PA was mainly derived from sputum, skin and soft tissue secretion, and urine. The resistance rate of PA to aminoglycosides, levofloxacin and ciprofloxacin showed a downward trend, and the resistance rate to carbapenems and ceftazidime increased. Staying in the ICU for 90 days (P=0.006), invasive ventilation (P=0.022), arterial or central venous catheterization (P<0.001), nasogastric or nasojejunal catheterization (P=0.031), and diabetes (P=0.011) were the main risk factors for CRPA infection. Diabetes (P=0.028, OR=2.096, 95% CI: 1.082~4.06) was an independent risk factor for CRPA infection. We should strictly control nosocomial infections in ICU, respiratory department, and geriatrics department. The resistance of PA to carbapenem antibiotics is severe, and empirical anti-infective treatments could warrant the use of aminoglycosides, quinolones, piperacillin/tazobactam or cefoperazone/sulbactam. Application of invasive ventilation, arterial or central venous catheterization, nasogastric or nasojejunal catheterization, and diabetes may increase the risk of CRPA infections.

**Keywords:** Pseudomonas aeruginosa, clinical distribution, drug resistance, risk factors

## Introduction

*Pseudomonas aeruginosa* (PA) is a common non-fermentative gram-negative bacillus commonly found in hospitals. It is also widely found in nature and is easy to grow in humid environments; it is more robst than other Gram-negative bacteria and can be a normal flora which easily settles in the respiratory tract, skin, digestive tract or external auditory canal of the human body [1, 2], and it has natural resistance to a variety of chemical disinfectants and antibiotics. Opportunistic PA infection is the result of decreased immunity, imbalance or translocation of normal microbiota; which can cause respiratory infection, urinary tract infection, central nervous system infection, septicemia and so on.

The prevalence and drug resistance of PA has been a huge concern to many clinicians around the world. The 2016 European bacterial resistance surveillance data showed that the resistance rate of PA to piperacillin/tazobactam was 16.3%, followed by fluoroquinolones (15.0%), carbapenems (15.0%) and ceftazidime (13.0%) [3]. The United States 2015 bacterial resistance surveillance report revealed that the detection rate of carbapenem-resistant PA (CRPA) was higher than that of carbapenem-resistant Enterobacteriaceae and carbapenem-resistant Acinetobacter [4]. The 2016 CHINET data displayed the resistance rates to carbapenems in different regions of China ranging from 9.8% to 31.6%. From 2011 to 2016, the detection rate of imipenem-resistant PA has been relatively stable [5].

The incidence of nosocomial infection of CRPA and multi-drug resistant PA is increasing worldwide and has been reported to lead to higher mortality rates [6]. Improper initial antimicrobi-

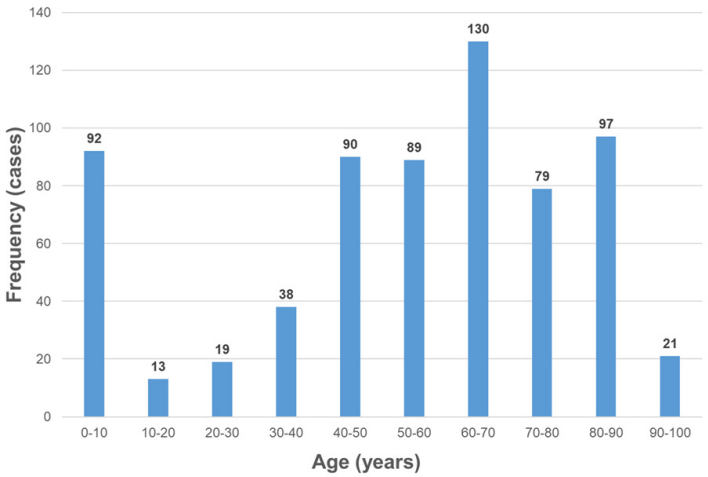


**Figure 1.** Age frequency of patients infected with PA.

**Table 1.** Distribution of strains in different wards

| Wards | Total | CRPA | CRPA Detection Rate |
|---|---|---|---|
| ICU[1] | 251 | 141 | 56.20% |
| Respiratory Medicine | 86 | 38 | 44.20% |
| Geriatrics department | 79 | 32 | 40.50% |
| Neonatal department | 50 | 43 | 86.00% |
| Surgery department[2] | 45 | 12 | 26.70% |
| Pediatric department[3] | 40 | 7 | 17.50% |
| Emergency surgery | 29 | 10 | 34.50% |
| Neurosurgery department | 23 | 8 | 34.80% |
| Neurology department | 15 | 3 | 20.00% |
| Hematology department | 11 | 2 | 18.20% |
| Others[4] | 39 | 13 | 33.30% |
| Total | 668 | 309 | 46.30% |

[1]ICU includes the Department of Critical Care Medicine, Extracardiac ICU, Respiratory ICU, Emergency ICU, and Department of Critical Care Medicine in the Eastern Hospital of Qilu Hospital; [2]Surgery department includes thoracic surgery, hand and foot surgery, kidney transplantation, burn and plastic surgery, general surgery, urology, orthopedic surgery, liver transplantation, and hepatobiliary surgery; [3]Pediatric department includes pediatric medicine and pediatric surgery; [4]Others include Department of Traditional Chinese Medicine, Cardiology, Gastroenterology, Dermatology, Endocrinology, Urology, Rehabilitation, Infection, Hepatology, Rheumatology, Otolaryngology, and Comprehensive internal medicine of Eastern part of Qilu Hospital.

al therapy for highly drug-resistant PA infections may lead to adverse clinical outcomes [7-9]. Therefore, it is important to explore the clinical distribution characteristics of PA infection cases, the prevalence of different drug-resistant phenotypes of PA, and the risk factors of CRPA infection for early selection of appropriate antimicrobial agents and the implementation of appropriate infection prevention and control measures [10]. PA has obvious spatio-temporal difference in popularity.

## Materials and methods

### *Subjects*

From July 2013 to July 2017, 668 inpatients with PA infection in the Qilu Hospital of Shandong University and from this population 668 isolated strains of PA (only the first isolated strain was taken when the same bacteria were repeatedly isolated from the same specimens of the same patient) were selected for retrospective statistical analysis.

Inclusion criteria: there are corresponding symptoms, signs, laboratory tests and imaging examinations of the infection. PA was considered as the pathogenic bacteria of this infection.

Exclusion criteria: combined with other clinical manifestations, auxiliary examinations and risk factors, PA was considered as contaminated or colonized bacteria after comprehensive judgment. More than one pathogen including PA were cultured simultaneously [11].

### *Strain identification and drug susceptibility*

Bacterium appraisal and drug sensitivity test adopted French VITEK-2 fully automatic expression. Drug sensitivity results were determined in accordance with the national clinical laboratory standards of the United States. If necessary, the K-B method or the E test was used for review.

### *Research methods and statistics*

Cross-sectional and case-control studies were used in this investigation. The distribution of gender, age, medical departments and specimens were analyzed by descriptive statistics. Chi-square test was used to compare the drug resistance rates and mortality, and for single factor analysis. Multivariate analysis employed unconditioned logistic regression analysis. All the above were run on SPSS 24 statistical soft-

**Table 2.** Specimen distribution of PA isolates

| Specimen | Total | CRPA | CRPA Detection Rate |
|---|---|---|---|
| Sputum | 500 | 251 | 50.20% |
| Secretion (skin, soft tissue) | 50 | 12 | 24.00% |
| Urine | 40 | 7 | 17.50% |
| Secretion or drainage (digestive or abdominal) | 23 | 11 | 47.80% |
| Blood | 17 | 5 | 29.40% |
| Alveolar lavage fluid | 14 | 7 | 50.00% |
| Catheter tip | 11 | 11 | 100.00% |
| Pleural effusion | 4 | 2 | 50.00% |
| Cerebrospinal fluid | 3 | 1 | 33.30% |
| Others* | 6 | 2 | 33.30% |
| Total | 668 | 309 | 46.30% |

*Others include secretions (ears), lung abscess drainage, oral throat swabs, brain abscess drainage, and osteomyelitis tissue.

**Table 3.** Annual detection rates of different resistant PA phenotypes

| Detection rate \ Years | 2013-2014 | 2014-2015 | 2015-2016 | 2016-2017 | Total |
|---|---|---|---|---|---|
| MDR-PA | 27.02% | 24.63% | 30.00% | 30.10% | 28.29% |
| pXDR-PA | 9.46% | 4.48% | 10.00% | 7.65% | 8.08% |
| CRPA | 43.20% | 38.80% | 45.30% | 54.60% | 46.30% |

Abbreviations: MDR-PA, multidrug-resistant pseudomonas aeruginosa; pXDR-PA, possible extensively drug-resistant pseudomonas aeruginosa.

**Table 4.** Comparison of multi-drug resistance of different PA colony forms

| Colony forms | Mucoid PA | non-mucoid PA | P |
|---|---|---|---|
| MDR-PA | 10 | 233 | - |
| MDR-PA% | 21.70% | 37.50% | 0.032 |

ware, and the significance level was set at $P<0.05$.

## Results

*Clinical characteristics and strains distribution*

In total there were 461 (69%) males and 207 (31%) females. Their distribution of age, department and tissue specimen had respective regularities (**Figure 1**; **Tables 1**, **2**). We also calculated the annual detection rate of PA with different drug resistance phenotypes, and compared the multi-drug resistance of PA with different colony forms (**Tables 3**, **4**).

*Drug resistance analysis*

The drug resistance rate of the 668 strains to aminoglycosides and quinolones decreased slightly in four years. The resistance rate of ceftazidine, carbapenems and piperacillin increased distinctly, and that of cefepime, piperacillin/tazobatan and cefoperazone/sulbactam fluctuated between 30% and 40% (**Figure 2**; **Table 5**). This research contrasts the resistance of CRPA with carbapenem-susceptible Pseudomonas aeruginosa (CSPA) to various antibiotics in different years (**Figure 3**; **Table 6**).

*Risk factors analysis*

We randomly selected 305 cases and divided them into CRPA group and CSPA group. Univariate analyses revealed that CRPA infection was associated with being in the intensive care unit (ICU) for 90 days ($P=0.006$), invasive ventilation ($P=0.022$), arterial or central venous catheterization ($P<0.001$), nasogastric or nasojejunal catheterization ($P=0.031$) and diabetes mellitus ($P=0.011$) (**Table 7**). Diabetes mellitus ($P=0.028$, OR=2.096, 95% CI: 1.082~4.06) was an independent risk factor for CRPA infection.

*Clinical outcomes*

Among the 305 patients, a total of 250 patients (81.97%) improved, 28 patients (9.18%) were

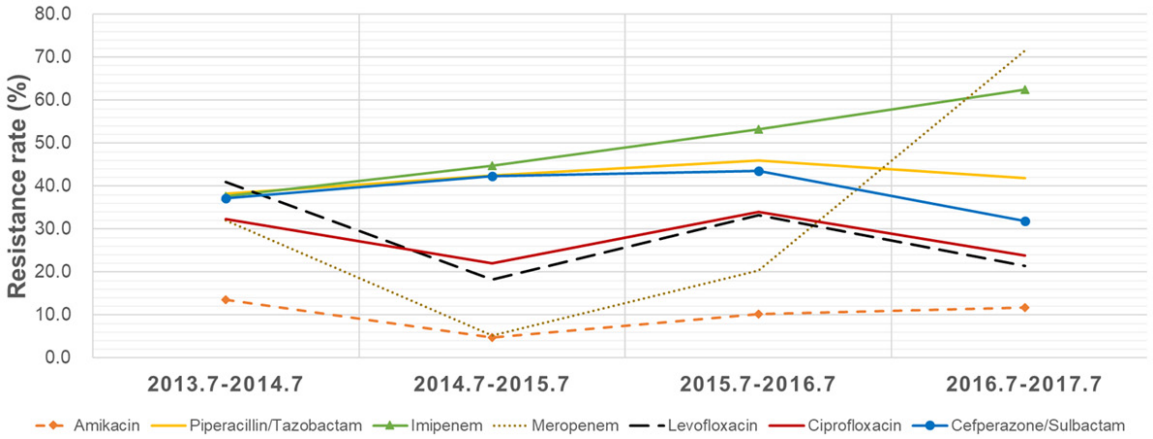


**Figure 2.** PA resistance change.

**Table 5.** Pseudomonas aeruginosa resistance change

| | 2013-2014 | | | 2014-2015 | | | 2015-2016 | | | 2016-2017 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R (%) | I (%) | S (%) | R (%) | I (%) | S (%) | R (%) | I (%) | S (%) | R (%) | I (%) | S (%) |
| Amikacin | 13.5 | 0 | 86.5 | 3.9 | 0.8 | 95.3 | 8.6 | 1.6 | 90.2 | 6.6 | 5.1 | 88.3 |
| Gentamicin | 21.2 | 3.4 | 75.3 | 4.8 | 8.0 | 87.2 | 15.1 | 4.9 | 80.0 | 9.7 | 6.6 | 83.7 |
| Tobramycin | 18.6 | 1.7 | 79.7 | 4.8 | 0.8 | 94.4 | 13.7 | 3.8 | 82.4 | 7.4 | 1.6 | 91.0 |
| Ceftazidime | 25.9 | 4.9 | 69.2 | 27.9 | 5.4 | 66.7 | 28.6 | 10.6 | 60.8 | 24.1 | 19.0 | 56.9 |
| Cefepime | 23.4 | 7.1 | 69.5 | 14.3 | 18.3 | 67.5 | 18.5 | 17.4 | 65.2 | 20.1 | 7.2 | 72.7 |
| Piperacillin/Tazobactam | 21.1 | 17.2 | 61.7 | 20.8 | 21.6 | 57.6 | 21.6 | 24.3 | 54.1 | 12.0 | 29.8 | 58.1 |
| Imipenem | 34.9 | 2.7 | 62.3 | 38.4 | 6.4 | 55.2 | 46.7 | 6.6 | 46.7 | 48.7 | 13.8 | 37.4 |
| Meropenem | 28.8 | 3.2 | 68.0 | 5.2 | 0 | 94.8 | 19.0 | 1.3 | 79.7 | 38.5 | 33.0 | 28.5 |
| Levofloxacin | 32.8 | 8.2 | 59.0 | 12.9 | 5.3 | 81.8 | 27.0 | 6.3 | 66.7 | 14.3 | 7.1 | 78.6 |
| Ciprofloxacin | 27.0 | 5.4 | 67.6 | 11.8 | 10.2 | 78.0 | 29.2 | 4.8 | 65.9 | 18.6 | 5.3 | 76.1 |
| Aztreon | 44.0 | 18.7 | 37.3 | - | - | - | - | - | - | - | - | - |
| Polymyxin B | 0 | 0 | 100 | - | - | - | - | - | - | - | - | - |
| Piperacillin | 26.9 | 13.4 | 59.7 | 5.1 | 28.2 | 66.7 | 16.7 | 50.0 | 33.3 | 23.4 | 38.7 | 37.8 |
| Cefperazone/Sulbactam | 15.1 | 22.1 | 62.8 | 20.3 | 22.0 | 57.6 | 20.1 | 23.5 | 56.4 | 18.4 | 13.5 | 68.1 |

discharged automatically, and 27 patients (8.85%) died. The mortality was higher in CRPA group than in CSPA group (P=0.045).

## Discussion

PA, with its low outer membrane permeability and strong adaptive mechanism, is prone to multiple drug resistance in clinical practice and is listed as a "superbug" [12-14].

In this study, we found the following clinical features of patients infected with PA. First, patients were middle aged, or older male patients, and also low-weight premature infants who suffered from bronchopulmonary dysplasia and neonatal respiratory distress syndrome were more susceptible to PA. Some domestic studies believe that preterm infants with PA infection have a variety of clinical manifestations. Therefore preterm infants with severe underlying diseases, low body weight, mechanically assisted ventilation, or long hospitalization duration should be watched for PA infection [15, 16]. Secondly, the incidence of PA infection, especially CRPA infection, was higher in the ICU, respiratory department, geriatrics department and neonatal department. Thus clinicians should be vigilant in the monitoring of bacterial resistance and infection control in these departments. Moreover, PA infections mainly occur in the respiratory tract, skin and soft tissue, urinary tract and digestive tract.

Our data revealed that the CRPA detection rate rises year after year. Many studies have shown

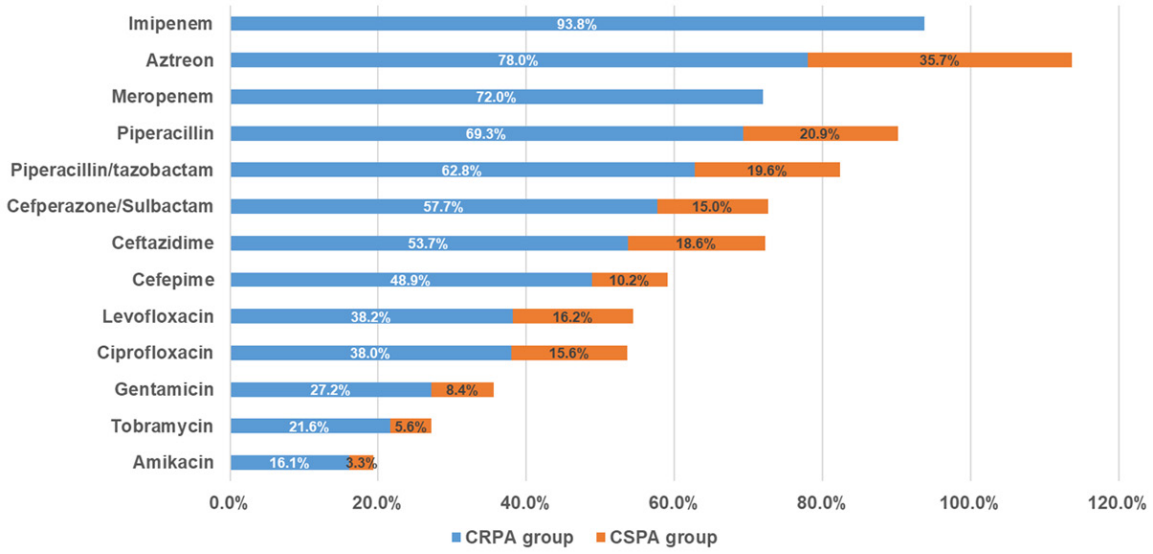


**Figure 3.** Comparison of resistance rates between CRPA and CSPA.

**Table 6.** Comparison of resistance rates between CRPA and CSPA

| | 2013-2014 | | P | 2014-2015 | | P | 2015-2016 | | P | 2016-2017 | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CRPA | CSPA | | CRPA | CSPA | | CRPA | CSPA | | CRPA | CSPA | |
| Amikacin | 21.9% | 7.1% | 0.009 | 12.2% | 0 | 0.006 | 18.8% | 2.0% | <0.001 | 15.3% | 3.0% | 0.007 |
| Gentamicin | 36.5% | 15.7% | 0.004 | 25.5% | 5.1% | 0.001 | 31.4% | 10.1% | <0.001 | 21.5% | 6.0% | 0.006 |
| Tobramycin | 26.7% | 16.7% | 0.586 | 12.5% | 1.3% | 0.023 | 29.8% | 7.1% | <0.001 | 12.2% | 3.1% | 0.038 |
| Ceftazidime | 46.7% | 19.3% | <0.001 | 58.3% | 18.5% | <0.001 | 56.5% | 25.0% | <0.001 | 55.3% | 18.5% | <0.001 |
| Cefepime | 53.3% | 13.6% | <0.001 | 59.2% | 15.6% | <0.001 | 57.0% | 15.3% | <0.001 | 39.0% | 4.5% | <0.001 |
| Piperacillin/tazobactam | 61.1% | 21.6% | <0.001 | 75.6% | 23.8% | <0.001 | 72.3% | 24.5% | <0.001 | 56.0% | 15.2% | <0.001 |
| Imipenem | 87.3% | 0 | <0.001 | 100.0% | 0 | <0.001 | 97.0% | 0 | <0.001 | 94.6% | 0 | <0.001 |
| Meropenem | 88.9% | 0 | <0.001 | 57.1% | 0 | <0.001 | 61.5% | 0 | <0.001 | 71.8% | 0 | <0.001 |
| Levofloxacin | 62.7% | 25.4% | <0.001 | 32.0% | 9.8% | 0.001 | 47.0% | 18.0% | <0.001 | 26.0% | 12.3% | 0.028 |
| Ciprofloxacin | 42.9% | 26.1% | 0.135 | 38.0% | 11.5% | <0.001 | 47.5% | 18,4% | <0.001 | 31.2% | 9.5% | 0.001 |
| Aztreon | 88.9% | 38.5% | <0.001 | - | - | - | - | - | - | - | - | - |
| Piperacillin | 60.6% | 20.6% | 0.001 | 71.4% | 12.0% | <0.001 | 75.0% | 50.0% | 1.000 | 72.6% | 29.6% | <0.001 |
| Cefperazone/Sulbactam | 61.0% | 15.6% | <0.001 | 89.5% | 20.0% | <0.001 | 67.7% | 15.7% | <0.001 | 43.7% | 11.7% | <0.001 |

that the occurrence of CRPA strains in clinical practice is significantly positively correlated with the use of carbapenems and the intervention of medical devices [17, 18]. The reason for the increase in prevalence needs to be further explored, in combination with the use of antibiotics in hospitals and environmental sanitation of medical institutions. In terms of mechanism, PA can produce resistance to carbapenems through encoding carbapenems hydrolytic enzyme by turning on drug resistance genes (IMP, VIM, ndm-1, gim-1, etc.), increasing the exocrine pump (MexAB-OprM and MexXY-OprM) expression levels, and reduction of outer membrane protein OprD [19-22]. In addition, it is worth noting that in our hospital the average detection rate of multi-drug resistance PA was 36.4% in recent years, which is higher than the reporting results of many other hospitals at home and in other countries. This result reflects the significant regional differences in PA resistance.

Pseudomonas aeruginosa can form five kinds of colonies in culture on a blood plate and McConkay Agar plate. Among them, mucoid PA easily absorbs into the mucosa or on the surface of medical devices to form a biofilm, thus avoiding the reach of antibacterial drugs and the body's defense mechanisms, leading to

**Table 7.** Univariate analysis of risk factors for CRPA infection

| Factor | CRPA group (n=194) | CSPA group (n=111) | P |
|---|---|---|---|
| Gender (male) | 126 (64.95%) | 73 (65.77%) | 0.885 |
| Hospitalization history within 90 days (excluding this hospitalization) | 152 (78.35%) | 92 (82.89%) | 0.884 |
| Intensive care unit within 90 days (including this hospitalization) | 105 (54.12%) | 42 (37.84%) | 0.006 |
| History of trauma within 30 days | 24 (12.37%) | 16 (14.41%) | 0.611 |
| History of surgery within 30 days (except for tracheotomy) | 58 (29.90%) | 37 (33.33%) | 0.533 |
| Invasive ventilation | 98 (50.52%) | 41 (36.94%) | 0.022 |
| Arterial or central venous catheter | 82 (42.27) | 21 (18.92%) | 0.000 |
| Bronchoscopy | 9 (4.64%) | 3 (2.70%) | 0.596 |
| Urine tube | 102 (52.58%) | 53 (47.75%) | 0.417 |
| nasogastric or nasojejunal catheterization | 119 (61.34%) | 54 (48.65%) | 0.031 |
| Abdominal drainage tube | 10 (5.15%) | 8 (7.21%) | 0.464 |
| Gastroscopy | 4 (2.06%) | 1 (0.90%) | 0.764 |
| PPI | 68 (35.05%) | 43 (38.74%) | 0.520 |
| Immune inhibitor | 3 (1.55%) | 2 (1.80%) | 1.000 |
| Glucocorticoid | 32 (16.50%) | 16 (14.41%) | 0.631 |
| Radiotherapy | 4 (2.06%) | 0 (0) | 0.317 |
| Chemotherapy | 4 (2.06%) | 6 (5.41%) | 0.208 |
| Hypoalbuminemia | 103 (53.10%) | 46 (41.44%) | 0.050 |
| Chronic obstructive pulmonary disease | 17 (8.76%) | 4 (3.60%) | 0.087 |

colonization, chronic or repeated infection and the failure of anti-infection treatment; and its pathogenicity is also stronger than non-mucoid PA [23]. From this study it is suggested that the detection rate of mucoid PA was lower (6.89%), and its multiple drug resistance rate (21.70%) was also lower than that of non-mucoid PA. Thus, it can be inferred that the sensitivity of mucoid PA to antimicrobial drugs *in vitro* is higher than that of non-mucoid PA, which is consistent with the results of many studies [24, 25]. However, drug susceptibility test *in vitro* cannot accurately reflect the bacteria's sensitivity to drugs in the whole body environment. As such clinicians need to be aware of isolated mucoid PA, and consider the combination of anti-biofilm drugs such as azithromycin and N-acetylcysteine in the process of anti-infection treatments [26].

Our research showed that the resistance rate of PA to antibiotics other than aminoglycosides, piperacillin/tazobatan, levofloxacin and polymyxin was higher than the average level in Europe and China during the same period [5]. It is critical to prevent and control the spread and diffusion of drug-resistant bacteria. The statistical results of drug resistance rates in this paper are enlightening the fact that experimental anti-PA infection treatment could give priority to cefoperazone/sulbactam, cefepime, aminoglycosides and quinolones according to the individual situation.

We observed that CRPA is often resistant to many antibiotics other than carbapenems. Multiple experiments have confirmed that PA can generate cross-resistance between different types of drugs through a common resistance mechanism [27-29]. Therefore, for the treatment of CRPA, we have fewer antibacterial options, and it is particularly important to conduct timely pathogenic examinations and drug sensitivity tests to select the antibiotic therapy with weak induction resistance. At the same time, we should fully understand the types of drugs with anti-PA activity and pharmacokinetic/pharmacokinetic characteristics at present, so as to formulate a variety of effective treatment schemes and facilitate the implementation of prevention and control strategies for the rotation of antimicrobial agents. In addition to the drugs in the susceptibility test, antibacterial agents for the treatment of PA infection include: ticarcillin, carbenicillin, mezlocillin, azlocillin, ticarcillin/clavulanic acid, panipenem, biapenem, isepamicin, netilmicin, etimicin, polymyxin

E, and fosfomycin. Furthermore, the use of some aerosolized inhalants can be regarded as a supplement to intravenous treatment of lower respiratory tract PA infections, such as aminoglycosides [11].

Risk factor analysis revealed that diabetes was an independent risk factor for CRPA infection. Diabetic patients, with impaired immune function, are prone to a variety of opportunistic infections, and infections are prone to repeated, prolonged hospital stay and antibiotic exposure time. A systematic review and meta-analysis concluded that the use of carbapenems and medical devices are major risk factors for carbapenem resistance [18]. One study confirmed that PA exposure to different concentrations of antibacterial agents produced different selection pressures. Lower concentrations of imipenem could induce PA resistance to carbapenems by strongly inducing high production of AmpC enzymes [30]. The risk factors derived from our study were not the same as other similar reports. Combined with the previous reports, we can summarize that long-term or repeated hospitalization, the use of antibiotics especially carbapenems, invasive medical device operations, and chronic underlying diseases may increase the risk of CRPA infection to varying degrees, leading to its production and spread. Therefore, comprehensive measures should be taken to prevent and control the spread of CRPA and multi-drug resistant PA; such as shortened antibacterial course, rationally select sensitive antibiotics, actively treat the basic diseases, improve the general physiological condition of the patients, monitor drug resistance, strict disinfection and isolation, medical invasive operation strictly follow the principle of aseptic principle, keep medical equipment clean, and minimize the time of invasive ventilation and catheter placement.

CRPA infection increases the risk of death in patients with PA infection. Several studies found that factors affecting the mortality rate of PA infection include ineffective empiric therapy, admission to the ICU, and higher APACHE II scores [31, 32].

Our current study did have some limitations. First, this study was a single-center retrospective study. Second, the drug resistance analysis lacked sensitivity assessment of aztreonam, polymyxin and fosfomycin. Third, we did not know the history of antibiotic treatment before admission, therefore, it was not included into the risk factor analysis, which would cause deviation in our final conclusion. We are collecting multi-center clinical data and samples for more representative results, in order to present the PA resistant phenotypes and the drug resistance genotypes.

In conclusion, this study presents a comprehensive and accurate review of the PA epidemic situation, clinical distribution and drug resistance analysis in a large hospital in Shandong province in recent years. Our results also provide a sufficient basis for clinical rational anti-infective treatment and infection prevention, indicating a development direction of new anti-PA drugs.

## Disclosure of conflict of interest

None.

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