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A review on *Acinetobacter baumannii*

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ABSTRACT

Acinetobacter baumannii is a major cause of nosocomial infections worldwide. By summarizing the epidemiology, molecular and drug resistance mechanisms, diagnosis and treatment strategies of Acinetobacter baumannii, the clinical outcome is finally improved.

1. Introduction

A. baumannii is a kind of lactose-non-fermenting, gram-negative coccobacillus, which is widely exist in in natural environment and hospital due to its slight demand for living conditions. Besides, *A. baumannii* has strong environmental adaptability and drug resistance, and it is one of the important pathogens of infection. In recent years, it has been found clinically that the infection rate of *A. baumannii* has increased year by year, and according to the data of Chinese bacterial resistance monitoring results in 2012, the detection rate of *Acinetobacter* has exceeded that of *Pseudomonas aeruginosa*, ranked the first place among non-fermenting bacteria[1].

Moreover, *A. baumannii* is also known for its ability to develop resistance to multiple classes of antibiotics, which has been an important factor in the increased recognition of the clinical significance of this organism. The resistance rate of *Acinetobacter* (89.6% of *A. baumannii*) to meropenem and imipenem were 61.0% and 57.0%, respectively. At present, the emergence of multi-drug resistant *A. baumannii*, pan-resistant *A. baumannii* or even fully resistant *A. baumannii* have become a difficult problem in clinical anti-infective treatment[2].

In the previous decade, the infection rates of *Acinetobacter pittii* and *Acinetobacter nonsocomials* have gradually increased in the environment of medical institutions, and the infection caused by *A. baumannii* has a correlation with clinical outcomes. *A. baumannii* has strong resistance to hot and humid ultraviolet rays and chemical disinfectants, and it can survive for more than 25 d on the surface of dry objects. It is the most commonly isolated gram-negative bacilli in medical personnel, medical equipment and surface of objects, which often shows the characteristics of multi-drug resistance, extensive drug resistance and pan-drug resistance.

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2. Epidemiology

Guo N *et al* conducted a review study of 87 patients with multidrug-resistant *A. baumannii* caused by bloodstream infection during 2012-2015. The study found that the multidrug-resistant *A. baumannii* in northern China caused risk factors and clinical outcomes of bloodstream infection, including the elderly, pneumonia, the use of drainage catheters, and hospitalization time in the intensive care unit (ICU). Multivariate analysis indicated that mechanical ventilation and multidrug resistance were independent risk factors for predicting 30-day mortality of *A. baumannii* bloodstream infection. Multidrug-resistant *A. baumannii* caused a bloodstream infection mortality rate up to 59.4%[1]. At present, the most urgent task is to spread the knowledge of risk factors for multi-drug resistant bacteria among medical staff and to avoid the spread of multi-drug resistant bacteria in hospitals.

Researches on the clinical epidemiology and drug resistance mechanism of meropenem-resistant *A. baumannii* showed we were facing a severe situation regarding to the treatment of the drug-resistant *A. baumannii*. All non-duplicate *A. baumannii* isolates from 2008 to 2014 were tested for antibiotic susceptibility by disk diffusion, multilocus sequence typing, pulsedfield gel electrophoresis and characterisation of carbapenemase-encoding genes were performed on carbapenem-resistant *A. baumannii* (CRAB)[2]. Among the 441 *A. baumannii* isolates, most were detected from ICU (30.8%) and general wards (21.8%). In the ICU, strains were mainly isolated from the respiratory tract (44.1%) and bloodstream (14.0%), while in general wards, they were mainly from wound/drainage (36.5%) and bloodstream (25.0%). An outbreak of OXA-23-producing CRAB infection occurred in a 13-bed ICU in 2010. CRAB strains were more co-resistant to other antimicrobials compared with non-CRAB. Molecular genetics analysis revealed five sequence types: ST78, ST107 and ST642 and two new STs (ST830 and ST831). By analyzing bacterial multi-site sequence typing, it was found that meropenem-resistant *A. baumannii* is more susceptible to cross-infection in ICU which is the most dangerous medical site for the emergence of OXA-23-induced drug-resistant *A. baumannii*.

A. baumannii accounts for a small proportion of Gram-negative bacilli isolated from abdominal infections and urinary tract infections, but it is always multi-drug resistant which is a therapeutic challenge. A total of 2 337 specimens of *A. baumannii* collected from 453 hospitals in 48 countries were used for drug sensitivity and multidrug resistance tests, and the result showed that the proportion of multi-drug resistant bacteria was the lowest in North America (47%), the highest in Europe and the Middle East (greater than 93%), and the proportion of multi-drug resistant bacteria found in ICUs was higher than in non-ICU wards for most of these regions. The isolated multi-drug-resistant *A. baumannii* reached 70%, and the strain sensitive to imipenem was the highest in North America (64%), the lowest in Europe and the Middle East (less than 11%)[3]. The multi-drug resistance rate in the Middle East has shown an upward trend in 2011-2014, and the sensitivity of single drugs in Africa, Europe and Middle East has been declining year by year. Understanding the characteristics of resistant bacteria in different regions can help to select antibiotic and control infection.

Bowman combining with *Acinetobacter aceti*, especially *Acinetobacter pittii*, *Acinetobacter nonsocomials* are the main pathogens of nosocomial infection. The studies on the epidemiological, clinical features and prognosis of the above pathogens are limited. From 2009 to 2013, 47 cases of *Acinetobacter* from the Japanese Defense Medical University were infected through bloodstream, and the nucleotide sequence of the RNA polymerase b-subunit was analyzed. To determine the *Acinetobacter* genotype, sequence analysis found that 49% of cases were *A. baumannii*, 33.3% were *Acinetobacter pittii*, and 9.8% were *Acinetobacter nonsocomials*. The 30-day mortality rate of *A. baumannii* was 8.5%, and there was no statistically significant difference in the mortality of *Acinetobacter* species, but the clinical features were significant different[4]. *A. baumannii* is less sensitive to amikacin and levofloxacin. Due to the resistance of A. baumannii, early identification of Acinetobacter gene species is important for selection of antibiotics.

3. Molecular mechanism and drug resistance mechanism

Polymyxin is a lipopeptide antibiotic isolated from *Bacillus*, including polymyxin A, polymyxin B, polymyxin C, polymyxin D, polymyxin E. Polymyxin is a cationic antibiotic, so it is mainly used to treat against Gram-negative bacteria. It acts on cell membrane of bacteria causing leakage of important substances in the cells which is the antibacterial mechanism. More specifically, the polycation ring in the polymyxin molecule interacts with the lipid A of the lipopolysaccharide in the cell membrane, and the phospholipid embedded in the cell membrane increases the permeability of the bacterial cell membrane, finally, the leakage of the intracellular component leads to the bacteria death. Although polymyxin resistance is rare, it has begun to appear in Gram-negative bacteria such as *A. baumannii*.

Studies have shown that *A. baumannii* resistance to polymyxins includes complete loss of lipopolysaccharide (LPS) and mutation of gene pmrlocus. The complete loss of lipopolysaccharide can be finished through the lipid A biosynthesis genes *IpxA*, *IpxC*, *IpxD*. The PMR locus is an auto-regulated two-component signal transduction system, which in addition to a sensor-kinase and response-regulator, also includes an ethanolamine transferase. Phosphoethanolamine transferase helps polymyxin to reduce the negative charge resistive membrane of bacteria by adding an ethanolamine group to the lipid A component of LPS. Polymyxins have a positively charged peptide chain and are originally negatively charged. There is no electrostatic reaction between lipopolysaccharides, and then drug resistance occurs[5].

Due to the multi-drug resistance, the incidence of *A. baumannii* has increased year by year. In the United States and China, *A. baumannii* ST208 genome sequence is the main sequence produced by the

carbapenem-resistant mechanism. It is well known that the complete ST208 genomic sequence has not yet been reported. Fang Y *et al* integrates a 4 087 kb chromosome and a 112 kb plasmid of *A. baumannii* XH386 from a children's hospital in China. XH386 includes 3 986 protein codes and 94 individual RNA-encoded genes, and XH386 was found to be multi-drug resistant by genetic testing and minimal inhibitory concentration assays, showing resistance to most antibiotics, except for tigecycline[6].

Polymyxin is often the last line of defense against infections caused by multidrug-resistant *A. baumannii*. The polymyxin resistance mechanism is studied by genomic and transcriptome analysis, and four different clinical treatment doses are simulated using an *in vitro* dynamic model. It is pointed out that it is necessary to study effective combined antibiotic treatment programs[7]. Lee HY *et al* pointed out that IRAB ST455(B)/ST2(P) is the main gene sequence leading to the hospital-resistant *A. baumannii*, resulting in a high mortality among ICU patients[8]. The correlation between multidrug resistance and gene sequence of 21 cases of *A. baumannii* isolated from Los Angeles Hospital was studied. The cloned correlation analysis was performed by pulsed electric field gel electrophoresis and bacterial multi-site sequence typing. It is pointed out that drug resistance genotyping helps to better understand the spread of multi-drug resistant strains[9].

4. Detection progress

Bacteremia is a disease with high morbidity and mortality in both adult and child. There are 20 million bacteremia patients worldwide each year. Due to the inability to identify pathogens, the mortality caused by the use of broad-spectrum antibiotics or inappropriate antibiotics is very high. The overall mortality rate of bloodstream infections in the United States can be as high as 14%-63%. But after the pathogens are identified, targeted treatment can reduce the mortality rate to 5%-17%, so timely and rapid diagnosis of pathogenic bacteria is of great significance for rational use of antibiotics and shortening of treatment course.

Quick and accurate identification whether bacteria is capable of producing carbapenemase is very important for rational use of antibiotics in clinical work and for controlling the spread of *A. baumannii* infection. Hrabák J *et al* used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to detect carbapenems, meropenem and its degradation products. The enzymes of *Enterobacteriaceae* and *Pseudomonas* bacteria were verified respectively. The results showed that the sensitivity of MALDI-TOF MS for identifying whether the strain produced carbapenemase was 96.67% and the specificity was 97.87%[10]. Lasserre C *et al* found that identifying the presence of carbapenemase-free enzyme activity was a major challenge in the laboratory. The clinical treatment of infection control was delayed in time. The detection of 30 out of the 223 samples found 15 samples contained carbon penicillinase while the other 15 samples did not, and the detection coefficient was found to be very reproducible according to correlation analysis of coefficients within the group. MALDI-TOF MS is convenient, time-saving, accurate but inexpensive and can be widely used in ordinary laboratories[11]. Well hair red and other specific primers for the ITS gene of *A. baumannii* were designed to construct a melting curve analysis method, and the content of *A. baumannii* in blood and puncture drainage liquid was determined by absolute quantitative method. Real-time quantitative PCR was used to quantitatively analyze *A. baumannii* in clinical specimens. This method has good specificity, sensitivity and stability[12]. According to McConnell MJ *et al*, quantitative real-time PCR detection of *A. baumannii* colonization of in hospital environment showed detection rate of 100% within 4 h[13].

Quantitative PCR method for rapid detection of *A. baumannii*, the target gene is a biofilm-associated protein gene, encoding a cell surface protein that plays an important role in biofilm formation[14]. The DNA in the whole blood sample is extracted for rapid detection purposes.

5. Progress in treatment

Gram-negative bacilli, which is closely related to clinical outcomes, is the main pathogen causing nosocomial infections, especially in ICU. It exhibits multi-drug resistance and extensive resistance including resistance to carbapenems. Multidrug-resistant infections caused by *A. baumannii* increase hospital stay length, mortality rate and treatment costs[15]. *Acinetobacter* has long existed in the hospital environment, especially when the body's immunity is reduced or immune function is impaired in patients with pneumonia, urinary tract infection, skin and soft tissue infection, secondary meningitis, especially ventilator-associated pneumonia, *Measles pneumonia*, *etc*. *A. baumannii* has strong resistance to damp heat ultraviolet rays and chemical disinfectants, and can survive on the surface of dry objects for more than 25 d. Some studies emphasize the necessity of controlling environmental cleansing in *A. baumannii* cross infection[16].

In 2013, the European Center for Disease Control and Prevention pointed out that *A. baumannii* resistance to carbapenems was as high as 25% in seven European countries[17]. *A. baumannii* carbapenem resistant was up to 32.6% in the United States in 2005 and 2011. Other studies found that polymyxin E had the highest sensitivity. A multi-center study in Spain found that the resistance rate of polymyxin increased from 0% in 2000 to 3% in 2010.

In some European and Asian countries, polymyxin resistance is higher, with up to 28% in Korea. The difference in resistance rates is due to differences in detection methodology.

Antibiotic resistance is a ubiquitous, cruel clinical problem, often accompanied by a lack of new and effective antibiotics. The continuous development of new antibiotics in the pharmaceutical industry has exacerbated widespread antibiotic resistance, thus the renewal and innovation of non-antibiotic treatments are needed. Combined antibiotic and non-antibiotic treatment strategies enhance

antibiotic susceptibility to multi-drug resistant bacteria.

Some studies have focused on intervening the immune system to regulate immune cell recruitment, such as the application of lysophosphatidylcholine, a major component of eukaryotic phospholipids. In a study, LPS pre-treated rat peritonitis and pneumonia models were established, and the study found that it can enhance the clearance of spleen and lung bacteria, reduce bacteremia and rat mortality, and the possible mechanism: the reduction of pro-inflammatory cytokines[18].

Polypeptides or molecules with immunomodulation, such as ApoE23, Esculentin-2Cha, exhibit antibacterial activity and immunomodulatory ability in in vitro experiments. Enhancing the recruitment of neutrophils and cyclic guanosine monophosphate can protect the nasal cavity from *A. baumannii* infection. Neutrophils play an important role in host resistance to *A. baumannii* infection. LpxC-1 can prevent LPS biosynthesis, enhance phagocytosis, reduce inflammation, and ultimately protect rats from lethal infections[19].

Polymyxin is widely used in the increase of resistance to meropenem, although some studies have found that early doses tend to be low before the blood concentration of polymyxin reaches steady state, suggesting the beneficial effect of starting treatment with loading dose. Imipenem combining with sulbactam or polymyxin has been successfully used in the treatment of ventilator-associated pneumonia caused by *A. baumannii*[20].

Recently, the FDA has reported the use of tigecycline to increase the mortality rate of nosocomial infections, mainly related to the treatment of nosocomial pneumonia and severe drug-resistant infections with tigecycline alone. A retrospective study of patients with lung-infected Gram-negative bacterial infections in 27 medical centers in 2014. Colistin-based combination therapy resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates, and lower in-hospital mortality compared to colistin monotherapy. colistin-carbapenem, colistin-sulbactam, and colistin with other agent combinations for XDR-ABSI did not reveal significant differences with respect to 14-day survival and clinical or microbiological outcome before and after propensity score matching[21].

In 2015, a study showed tigecycline combining with cefoperazone sulbactam was effective on patients with mechanically ventilated pan-resistant *A. baumannii* infection. For example, sputum were changed from purulent to thin, chest radiographs showed apparent absorption, body temperature, white blood cell counts and APACHE II scores were improved significantly too. Compared with the pre-treatment statistical significance, the microbiological eradication rate was 80.00% and the curative rate was 66.67%[22]. In a multicenter prospective observational study in 2015, patients with multidrug-resistant *A. baumannii* bloodstream infection were treated with tigecycline plus polymyxin, with 14-day mortality as the main research focus. The 14-day mortality rate was 34.5% in 29 control patients, while the 14-day mortality rate was 15.4% in patients treated with carbapenem combining with polymyxin thought there was no significant difference between the two groups[23].

When severe infections caused by multi-drug/pan-resistant bacteria and nosocomial pneumonia/ventilator-associated pneumonia, bloodstream infections, and urinary tract infections, tigecycline combination therapy is recommended.

In summary, *A. baumannii* is one of the main pathogens of nosocomial infection and clinical opportunity infection, and it is also the most important strain causing outbreak of *Acinetobacter* in hospital environment. With the extensive application of broad-spectrum antibacterial drugs and the popularization of interventional procedures, *A. baumannii* is resistant to a variety of antibiotics, and gradually develops into multi-drug resistance and even total drug resistance. Inactivation enzymes, membrane pore protein changes and active efflux mechanisms are the main causes of multidrug resistance. Through the rapid and effective detection of drug resistance genes, the research on drug resistance monitoring and drug resistance mechanism of *A. baumannii* can be strengthened, thereby guiding the rational use of antibiotics in clinical practice, and adopting effective measures such as strictly implementing the disinfection and isolation system of medical supplies in hospitals. We need to pay attention to the hand hygiene of the staff in order to reduce the emergence of drug resistance and the spread of drug-resistant strains, and to cut off the spread of *A. baumannii* in the hospital environment.

Conflict of interest statement

The authors report no conflict of interest.

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