

Research Progress on Drug-Resistant Bacteria

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Abstract: More and more microorganisms have developed drug resistance with the use of antibiotics, and some microorganisms have multi-drug resistance. Therefore, bacterial resistant antibiotic is a serious problem to treating infectious diseases in recent years all over the world. This paper briefly reviews the research progress of bacterial resistance mechanisms all over the world, and provides theoretical basis for exploring effective prevention measures and rational use antibiotics in clinical.

Keywords: Drug-Resistant Bacteria, Antibiotics, Drug Resistance Mechanism, Multi-Drug Resistance

1 Background

The bacterial resistance, also known as drug resistance, Refers to the bacteria resistant one or more antibiotics (antibiotics or disinfectants). Studies have shown that there are two ways to produce bacterial resistance, one is gene mutation, and the other is the acquisition of drug resistance genes. Now, we think antibiotic abuse is the main cause of bacterial resistance and continuous to evolution. Studies have shown that at the present stage, during the use of antibiotics, the bacterial shows the trend that faster and higher degree of resistance, a higher level of strains and multi-drug resistance. Bacterial resistance has become a global public health crisis.

Multi-drug resistant bacteria (MDRO) ^[1] has become an important pathogen of nosocomial infections. Multi-drug resistance (MDR) refers to resistance to three or more antibiotics, following five classes of antibiotics, which include cephalosporins, carbapenems, and β -lactamase inhibition complexes, fluoroquinolones and aminoglycosides. Pan-drug resistance (PDR) refers to resistance to all antibiotics or resistance to the above five classes of antibiotics.

The increase in bacterial resistance has led to a series of problems, such as treatment failure, increased medical expenses and rising mortality. Therefore, studying the drug resistance mechanism of drug-resistant bacteria is conducive to the rational use of antibiotics in clinical treatment, and helps to develop new antimicrobial drugs and reduce the spread of drug-resistant bacteria.

2 origin and development

2.1 The origin of bacterial resistance

In 1928, British bacteriologist Alexander Fleming discovered penicillin. In the following decades, hundreds of antibiotics were introduced, which were widely used in the treatment of various bacterial diseases in the clinic and achieved good therapeutic

effects, saved the countless of lives with infectious diseases. In fact, the problem of drug resistance occurred as early as penicillinase was found in penicillin applications ^[2]. With the widespread use of antibiotics in clinical practice, bacterial resistance has escalated, more and more bacteria have developed resistance or even multi-drug resistance, and human safety has been seriously threatened. The World Health Organization and national health departments have begun to pay attention to the problem of the drug resistance. The definition of bacterial resistance in modern medicine emphasizes that acquired resistance is the result of repeated contact between antibiotics and bacteria ^[3]. In addition, there is natural resistance bacteria. Kalan et al. found a variety of antibiotic resistance genes in soil bacterial DNA which is isolated from permafrost in the Yukon region of Canada 30,000 years ago, such as macrolide target ribosomal methylase (Erm), aminoglycoside Modified enzymes (AA enzymes), β -lactamases (TEM enzymes), tetracycline target ribosome protective proteins, and glycopeptide antibiotic-encoding genes ^[4]. Wright et al. have taken off bacteria from the surface of the Lechuguilla cave in New Mexico, more than 4 million years ago. These bacteria have never been contact with humans or their diseases and antibiotics, but several of them have multi-drug resistance. Some bacteria are even resistant to the 14 common antibiotics on the market ^[5], which indicates that bacterial resistance can also exist in non-human active environments. On the one hand, the discovery of this kind of natural resistance makes us further realize the complexity of bacterial resistance, and on the other hand, it provides a broader idea for our research on bacterial resistance. Simply using a combination of drugs or changing the use of antibiotics does not solve the problems we face at this stage. Studying bacterial resistance mechanisms at the genetic level may be an important way to find the cause of resistance.



2.2 Development of bacterial resistance

Although there are naturally resistant bacteria, this does not mean that human activities have no effect on bacterial resistance. From the half of the 1940s, since the first time that the antibiotics have been used in clinical practice, sensitive bacteria have indeed well controlled, but the insensitive bacteria that survived have also been greatly improved in just 70 years. For survive, these bacteria are constantly to self-modifying, which makes the bacterial resistance constantly in the process of evolution. The abuse of antibiotics has also played an important role in the occurrence and evolution of bacterial resistance. Zhao Shaohua et al. retrospectively analyzed the drug resistance changes of *Escherichia coli* isolated from humans and food animals in the United States from 1950 to 2002. A total of 1729 cases were isolated from humans, cattle, chickens and pigs, which were sensitive to 15 common antibiotics in clinical. Through observation, it was found that with the application of antibiotics, the resistance of these bacteria has changed significantly, especially for ampicillin, sulfonamides and tetracyclines^[6]. The proportion of multi-drug resistant bacteria in *Escherichia coli* increased from 7.2% in 1950 to 63.6% in 2002. In addition, Bush K's research found that the current clinically common bacteria to producing extended-spectrum β -lactamases (ESBLs), such as TEM and SHV ESBLs, their were closely related to the widespread use of broad-spectrum cephalosporins after the 1980s^[7].

3 present situation

3.1 multi-drug resistant bacteria

Multi-drug resistant bacteria are those parallel microbes (including bacteria, fungi, and viruses) to tolerate many different antimicrobial drugs. They mainly refer to antibiotics, also include anti-fungal drugs, anti-viral drugs, anti-parasitic drugs, and with different structures and functions compounds which can eliminate pathogenic microorganisms^[8]. In 2011, the Center for Disease Control and Prevention in European and USA, formed an international team of experts, to create a set of internationally standardized terms for describing all clinical infections and susceptibility to multi-drug resistant bacteria^[9].

Infection with multi-drug resistant bacteria often jeopardizes hospitalization for surgery, transplantation, cancer chemotherapy, intensive care, and human immunodeficiency virus (HIV) infection, as the lack of effective antibacterial to treat, brings a serious challenge to the control to clinical and nosocomial infections^[10]. The pathogens of infection are usually gram-negative bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, etc. Gram-positive bacteria include *Staphylococcus aureus*, *Enterococcus*, etc. These pathogens are mostly multi-drug resistant bacteria. To prevent and control the spread of these pathogens in hospital, multi-drug resistant bacteria must be tested [11], and infected patients should be

detected early, so that effective measures can be taken to prevent the spread of multi-drug resistant bacteria.

3.2 several common multi-drug resistant bacteria

3.2.1 methicillin-resistant *Staphylococcus* (MRS)

Methicillin-resistant *Staphylococcus* (MRS) includes methicillin-resistant *Staphylococcus aureus* (MRAS) and methicillin-resistant coagulase-negative staphylococci (MRSCN), which is due to its gene encoding the chromosome *mecA*, product a variant of a low-affinity penicillin-binding variant Protein 2a (PBP2a), causing the staphylococci to be resistant to all available β -lactam antibiotics.

In 1961, Jevons first discovered MRSA in the UK. In the mid-1960s, it expanded to many European countries and Canada. In the late 1970s, MRSA increased dramatically and spread all over the world. In the late 1980s, MRSA became a global pathogen. In 2006-2007, Mohnarin monitoring results showed that^[12], the detection rate of MRSA was 61.6%, and the average detection rate of MRSA in CHINET in 2008 was 55.9% (14.8%-77.55%)^[13]. Before 1980, MRSA accounted for only 5% of all *Staphylococcus aureus* in Shanghai, China, but it rose to 24% between 1985 to 1986, and rose to 50%-70% after 1992. The detection rates among different hospitals are quite different. The data detected by 12 hospitals in 2007 showed that the detection rate of MRSA was 58.3% on average, and the hospital with the highest detection rate reached 80.4%^[14]. With the increasing scope of MRSA resistance, the degree of drug resistance is increasing, it become the most important type of drug-resistant bacteria in clinical practice.

MRSA is resistant to methicillin/oxacillin, and is resistant to all β -lactam antibiotics, including penicillins, cephalosporins, and compound preparation containing enzyme inhibitor, the carbapenems and the monoamide antibacterial drugs regardless of the in vitro susceptibility results are sensitive or not. Even if the results in vitro are sensitive, will rapidly show the drug resistance after application, resulting in poor therapeutic effect. The drug of choice for the treatment of MRSA infection is glycopeptides, such as vancomycin or teiconin, but due to the significant increase in the use of vancomycin, vancomycin-resistant MRSA appeared in the late 1990s and began to act as a Moderate Vancomycin-resistant *Staphylococcus aureus* (VISA), the United States, Germany, Italy, South Korea and other countries have reported to detection the VISA^[15]. The US Centers for Disease Control and Prevention (CDC) officially announced the first true vancomycin-resistant *Staphylococcus aureus* (VRSA) in July 2002^[16]. In 2004, the United States reported the third strain of VRSA, which was confirmed by the US Centers for Disease Control, which caused great concern and panic in the medical community^[17]. Therefore, careful use of vancomycin is an important measure to prevent the emergence and spread of VRSA.

Coagulase-negative staphylococci (CNS) are widely found in nature and belong to one of the normal flora in humans. Staphylococcal infection accounts for a very important position in hospitals with severe infections. In recent years, coagulase-negative staphylococci and *Staphylococcus aureus* account for 14%-30% of pathogens in patients with acquired bleeding infect in hospitals; in surgical wound infections and septic arthritis, these bacteria account for 11%-50%; with the extensive use of high-efficiency broad-spectrum antibiotics and increasing interventional procedures, the detection rate and infection rate of MRCNS and multi-drug resistance is also increasing year by year, becoming one of the main pathogens of nosocomial infections and difficult to control. MRCNS is a pathogenic bacteria with low toxicity. The symptoms after infection are atypical and exhibit multi-drug resistance, which brings certain difficulties to clinical diagnosis and treatment. Therefore, designing efficient diagnostic methods has become an inevitable requirement.

3.2.2 vancomycin-resistant enterococci (VRE)

Enterococcus is a conditional pathogen that is more resistant than other Gram-positive bacteria and is more susceptible to develop new resistance. Vancomycin-resistant enterococci (VRE), a bacterium belonging to the genus *Enterococcus*, has resistance to vancomycin. Nowadays, VRE has become an important pathogen of nosocomial infections. It can cause infection of various organs in the human body. It can not only cause urinary tract infections, skin and soft tissue infections, but also cause abdominal infections, sepsis, endocarditis and meninges, which have the danger of the life, the mortality rate is 21%-27.5%.

In 1986, for the first time, Uttley et al. reported that vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* were isolated in the UK. After that, VRE spread to a global scale at an alarming rate. In 1987, it was separated in Missouri, USA. In 1990, VRE was isolated in European countries such as France, Germany, Spain and Yugoslavia. According to the National Infection Detection System (NNISS), from 1989 to 1997, the proportion of VRE in intensive care units in the United States increased from 0.3% to 15.4%, a 58-fold increase; the proportion of non-intensive care units VRE was increased from 0.3% to 15.4%, about 51 times. The resistance test of 670 hospitals in the United States in 2004 showed that VRE is the second drug-resistant bacteria in hospitals^[18]. In 2006 and 2007, the resistance rates of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* reported by Mohnarin were 1.2% and 3.2%. The resistance rates of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* reported by CHINET in 2008 were 0.4% and 3.2%. The results showed that the resistance rate of *Enterococcus faecium* in VRE was much higher than that of *Enterococcus faecalis*.

It has been confirmed that the resistance of *Enterococcus* to antibacterial drugs can be transmitted to *Staphylococcus* and *Streptococcus* through the binding of plasmids, and the drug resistance can be heterogeneously expressed and transferred between Gram-positive cocci. Once VRE transfers the anti-vancomycin gene to MRSA and PRSP, common postoperative infections, soft tissue infections, sepsis, endocardium and pneumonia are no drug is available. Therefore, we must use existing antibiotics with caution. Glycopeptide antibiotics are now an important method for the treatment of multi-drug resistant *Streptococcus*, *Enterococcus* and *Staphylococcus* and other Gram-positive bacteria.

3.2.3 Enterobacteriaceae (ESBLs) producing extended-spectrum β -lactamase

ESBLs are mainly produced by bacteria of *Klebsiella*, *Escherichia coli* and *Proteus mirabilis*, and are resistant to most penicillins and cephalosporins. After evolution, it was extended to hydrolyze third- and fourth-generation cephalosporins and monoamide antibiotics, plasmid-mediated β -lactamase, hydrolyzing activity can be inhibited by β -lactamase inhibitors. Because of its plasmid-mediated resistance, drug resistance can be transmitted in the same or different species of bacteria by conjugation, transformation, and transduction.

Since the discovery of ESBLs in *Klebsiella typhimurium* for the first time since 1983, more than 200 ESBLs have been discovered, initially with the most common TEM and SHV types, followed by non-TEM and non-SHV types, such as CTX series, PER-1 and OXA series of enzymes^[19]. According to the genotype, it can be divided into SHV, TEM, CIX-M, OXA and other types. ESBLs bacteria are widespread in the world, but the genotypes are different in different regions. The United States mainly has three genotypes, TEM-2, TEM-10 and TEM-26. France is mainly TEM-24, TEM-3 and SHV-4 genotypes, Japan is mainly *toho-2* genotype, South Korea is mainly SHV-12, SHV-2a and TEM-52 genotypes, China is mainly CTX-M genotype, but different regions show the different subtypes of enzymes, such as Beijing and Shanghai, mainly CTX-M-3 genotypes, and Guangdong, CTX-M-9, 13, and 14 genotypes.

The detection rate of ESBLs varies greatly depending on the country, region, hospital size and ward. The detection rate of ESBLs in USA *Enterobacteriaceae* is 0%-25%, and the detection rate in European countries is different. The detection rate of *Escherichia coli* and *Klebsiella pneumoniae* ESBLs in Northern Europe region (such as Germany) from 1% to 5% and in Eastern Europe countries (such as Russia) from 39% to 47%; in 2007, China test data shows that 55% of *Escherichia coli* and 44.9% of *Klebsiella* produce ESBLs^[20]. The detection rate of ESBLs increased year by year. According to the literature, the detection rates of *Escherichia coli* and *Klebsiella pneumoniae* were

32.8% and 23.5% on average in 1998-2006, but the detection rate of ESBLs was from 1998 to 2006, *Escherichia coli* increased from 4.1% to 52.1%, and *Klebsiella pneumoniae* increased from 12.9% to 36%^[21].

If the ESBLs-producing strain is diagnosed, regardless of the results of the in vitro susceptibility test, it is showed to be resistant to all penicillins, cephalosporins and aztreonam^[22]. According to clinical observations, Enterobacteriaceae bacteria are resistant to β -lactam drugs (including cephalosporins, penicillins and aztreonam), but are sensitive to cephalosporins and carbapenems. It is also sensitive to enzyme inhibitors. This limits the range of clinically selected antimicrobials.

3.2.4 Pan-resistant *Acinetobacter baumannii* (PDRAB)

Acinetobacter baumannii is a non-fermenting gram-negative bacillus and is an important pathogen of nosocomial infections. It mainly causes respiratory infections, and can also cause sepsis, urinary tract infections, secondary meningitis, and the hospital-acquired pneumonia is the main infection^[23]. *Acinetobacter baumannii* is widely distributed in the hospital environment and can survive for a long time. It is a great threat to critically ill patients and patients in CCU and ICU. Therefore, such infection is also called ICU acquired infection. Nowadays, the carbapenem-resistant *Acinetobacter baumannii* has developed rapidly, and even appeared the "total resistance" of *Acinetobacter baumannii*^[24] has brought great difficulties to clinical treatment.

The resistance mechanism of *Acinetobacter baumannii* is complex, including the production of multiple β -lactamases, expression of the outer membrane active efflux system, decreased outer membrane permeability, topoisomerase gene mutation, and production of aminoglycoside inactivating enzyme, bacterial biofilm formation, and the bacteria are highly susceptible to get the drug resistance by plasmid ligation^[25].

3.2.5 Pan-resistant *Pseudomonas aeruginosa* (PDRPA)

Pseudomonas aeruginosa is widely found in nature, hospital environments, and human skin, and is a conditional pathogen. In addition to causing wound infection, abscess, bacteremia, urinary tract infection, post-burn infection, the bacteria can also cause nosocomial infections in hospital patients, especially in intensive care units, and become the main nosocomial infection pathogen. According to a survey conducted by the National Drug Resistance Monitoring Network in 2004, the isolation rate of *Pseudomonas aeruginosa* was 10.3%, which was second, only lower than *Escherichia coli*.

The mechanism of *P. aeruginosa* resistance is very complex, including β -lactamase production, decreased

outer membrane permeability, aminoglycoside inactivating enzymes, active efflux pump overexpression and changes in target sites. To form drug resistance, the bacteria can develop resistance to various antibacterial drugs through different mechanisms, leading to clinical treatment failure. Among them, the production of β -lactamase is one of the main reasons for the resistance of *Pseudomonas aeruginosa*. At present, the total number of β -lactamase genes found in China is: TEM, OXA-2 group, OXA-10 group, SHV, CARB. , PER, VEB, GES, VIM, IMP, DHA, etc.^[26].

4 Prevention and treatment of drug-resistant bacteria,

4.1 Strengthen detection and reporting of resistant bacteria

Hospital infection caused by multi-drug resistance is an important hygienic indicator for evaluating hospital preventive measures and rational application of antibiotics^[27]. Therefore, strengthen the management of hospital infections of multi-drug resistant bacteria, effectively prevent and control the spread of multi-drug resistant bacteria in hospitals, is an important measure.

4.2 Rational use of antibiotics

The abuse or improper use of antibiotics accelerates the occurrence of drug resistance. Rational use of antibiotics is the fundamental and most important method for the prevention and treatment of drug-resistant bacteria. It is necessary to implement targeted treatment as soon as possible, as well as correctly interpret the results of clinical microbial examinations and conduct standardized medications.

4.3 Prevention and control of multi-drug resistant bacteria

(1) Separation of the same room or the same pathogen; (2) Prevention according to standards; (3) Reasonable disinfection of the environment and equipment; (4) Specialization of medical supplies; (5) Standardization of medical wastes and supplies; (6) Extend medical knowledge to patients and supervise and guide the accompanying staff.

4.4 Relevant departments strengthen the management of drugs

Multiple departments work together, to prevent and control multi-drug resistant bacteria from all aspects. The hospital should establish a management system specifically for multi-drug resistant bacteria, educate and train medical personnel on the rational application of antibiotics, and conduct regular assessments to urge medical personnel to rationally use antibiotics.

4.5 Reduce the use of antimicrobials in food and livestock farming

Drug-resistant bacteria formed in foods and animals can affect the health of humans and animals after entering the food chain. Therefore, relevant animal medication guidelines should be developed to reduce

the misuse and abuse of antibiotics in food animals.

4.6 Development of new antibacterial drugs

For example, human anti-infective antibacterial peptides, defensins, squalamine, and the squalamine. Research on bacterial resistance inhibition inhibitors at the genetic level. Looking for treatments that do not use antibiotics to treat bacterial infections. Destroy the bacterial resistance gene, in order to restore the sensitivity of the bacteria to antibiotics.

4.7 Promote the development of new specific and potent vaccines ^[28]

Prevent the occurrence of diseases and reduce the use of antibiotics.

5 Conclusion

In summary, bacterial resistance and resistance mechanisms are a very complex problem, both for pathogenic biology and for human social and behavioral reasons. Bacterial resistance is a global problem encountered during the use of antibiotics, which not only seriously affects the clinical antibacterial treatment effect, but also poses a great hazard to human health. Inappropriate treatment in the clinic and the abuse of antibiotics have made the problem of bacterial resistance increasingly serious. The WHO issued a warning: "Abuse of antibiotics has brought humans back to the era of antibiotics." It is also worth noting that bacterial resistance cannot be completely avoided. Therefore, it is necessary to rationally regulate the use of antibiotics to minimize the generation and spread of drug resistance in hospitals. This requires the full cooperation of the medical and health departments and patients. It is also a major issue that requires the attention of the whole society and efforts to solve.

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