Advances in Studies of Ceftazidime-Avibactam Application and Resistance Mechanism Research

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Abstract: Ceftazidime-Avibactam (CAZ-AVI) is a novel β-lactamase/β-lactamase inhibitor combination. Since put into the market, CAZ-AVI has shown high bactericidal activity when treating patients with Carbapenem-Resistant Enterobacteriaceae (CRE) infections with bacteremia, pneumonia caused by Carbapenem-Resistant Klebsiella pneumoniae (CRKP), or post-transplantation infections. However, with the widespread use of CAZ-AVI, there are more and more reports of resistance to the compound by Gram-negative bacteria isolated from clinical samples. The main mechanism of resistance to CAZ-AVI was found to be mutations in the amino acid sequences of β-lactamase, such as KPC, AmpC, and OXA-48 enzyme, and there were also a small number of reports of resistance due to altered permeability of the bacterial outer membrane, mutations in penicillin-binding proteins (PBPs), and overexpression of efflux pumps. This paper focuses on the review of the resistance mechanisms present in various types of bacteria to CAZ-AVI.

Keywords: Ceftazidime-Avibactam; β-lactamase inhibitor; mechanism resistance

1. Introduction

1.1 Mechanisms of Bacterial Drug Resistance

Antibiotics have been used effectively in the treatment of bacterial infections since their discovery in 1945. However, with the misuse of broad-spectrum antibiotics, antibiotic resistance has become a serious challenge in global public health[1]. Most bacteria resistant to carbapenem antibiotics, such as Enterobacteriaceae, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii, can gain the advantage of surviving in antibiotic environment through intrinsic resistance, mutations in resistance genes or conjugative transformation between bacteria. Bacterial drug resistance can be categorized into intrinsic resistance and acquired resistance. Intrinsic resistance is a resistance characteristic inherent in the bacterial chromosome and passed down from generation to generation, and is continuously strengthened with the selection of antibiotics; acquired resistance is a resistance characteristic in which the bacteria are exposed to antibiotics, and then, in the face of the pressure of survival, change their own metabolic pathways through the mediation of plasmids, so as to make them not to be killed by antibiotics. We focus here on the mechanism of acquired resistance in bacteria. When bacteria are exposed to antibiotics, they become resistant mainly through several mechanisms, the main resistance mechanisms include: (1) β-lactamase-producing enzymes: they can inactivate β-lactam antibiotics. β-lactamase are classified into four categories according to Amber's method: class A enzymes, such as KPC, SHV, and CTX-M; class B enzymes, such as NDM, VIM, and IMP; class C enzymes, such as AmpC; and some of the class D enzymes, such as OXA-48. (2) Alteration of the target of the action of the antibiotic. (3) Altered permeability of the bacterial outer membrane. (4) Altered efflux pumps. (5) Bacterial biofilm formation[2].

1.2 Strategies to Address Bacterial Resistance

When bacteria are resistant to a certain antibiotic, the choice of antibiotics available to them after infection becomes more and more limited, and although new antibiotics are constantly being introduced, resistant bacteria against that antibiotic will soon emerge, making the modern pharmaceutical industry largely a competition with the newborn drug-resistant bacteria. Therefore, the rational use of drugs and the control of the development of drug resistance is also a challenge for the world to solve the problem of bacterial infections. In addition to the development of new antibiotics, drug combination is one of
the strategies to address bacterial antibiotic resistance. As a result, compounded formulations of drug combinations have emerged and have achieved remarkable success in clinical treatment. Avibactam (AVI) is a new type of non-β-lactam β-lactamase inhibitor, which can inactivate β-lactamase, except class B enzymes, so that they lose their activity of hydrolyzing antibiotics. When combined with Ceftazidime (CAZ), Avibactam protects it from hydrolysis still binds to penicillin-binding proteins (PBPs), and exerts antimicrobial effects[3-4]. Meanwhile, compared with other β-lactamase inhibitors, Avibactam has the significant advantages of a long half-life, small molecular weight, and easier binding to the β-lactamase active site[5].

2. Application development of Ceftazidime-Avibactam

Ceftazidime-Avibactam (CAZ-AVI), a novel β-lactam antibiotic/β-lactamase inhibitor combination, was approved for marketing by the US FDA (the US Food and Drug Administration), the European EMA (the European Medicines Agency) in 2015 and 2016. Ceftazidime-Avibactam has shown favorable efficacy in the treatment of complicated urinary tract infections and complicated intra-abdominal infections[6]. Ceftazidime-Avibactam has shown high bactericidal activity in the treatment of Carbapenem-Resistant Enterobacteriaceae (CRE) infections with bacteremia, Carbapenem-Resistant Klebsiella pneumoniae (CRKP) pneumonia, post-liver and kidney transplantation infections with CRKP, and patients infected with CRE in intensive care units (ICU)[7-9]. Clinical studies have shown that Ceftazidime-Avibactam exhibits higher bacterial clearance and clinical success (≥28 days) relative to antibiotics such as Polymyxin and Tigecycline[10]. Ceftazidime-Avibactam marketed has undergone two phases of validation, animal experiments and clinical trials by Merdjan, Borgonovi, Cottagnoud, Crandon, et al. The results of the experiments showed that infected animal models with bacterial loads after injection of Ceftazidime-Avibactam demonstrated superior antimicrobial activity compared to the control group using other antibiotics[11,12]. Its use as a novel antibiotic combination provides an important option for the treatment of infections with clinically resistant strains of bacteria.

2.1 Animal experiments of Ceftazidime-Avibactam

By comparing the colony counts of lung tissues in three groups of mouse models of pneumonia, namely saline, Ceftazidime, and Ceftazidime-Avibactam, we can see the significant effect of the Ceftazidime-Avibactam group in reducing the bacterial load[11]. In a study against AmpC-producing, ultra broad-spectrum β-lactamase (ESBLs) Enterobacteriaceae bacteria infected nephritis mouse model, the Ceftazidime-Avibactam combination showed significant antibacterial benefits[12]. In another rabbit model of encephalitis infected by AmpC-producing and Ceftazidime-Resistant Klebsiella pneumoniae, the rabbit brain bacterial load was lower in the combination group compared to the Ceftazidime and Meropenem single-agent group, which further demonstrated the efficacy and superiority of Ceftazidime-Avibactam in the treatment of infections with resistant strains of the bacterial species[13]. Using a mouse model of Pseudomonas aeruginosa infection, the difference between the two groups in reducing bacterial load was assessed by comparing the therapeutic efficacy of the Ceftazidime-Avibactam group with that of the Ceftazidime group and the reduction in Pseudomonas aeruginosa load was more pronounced in the mice in the two-drug group compared to that in the Ceftazidime-mono group after the administration of the treatment[14]. In conclusion, Ceftazidime-Avibactam shows good efficacy and potential in the treatment of infections caused by Multi-Drug-Resistant (MDR) Gram-negative bacteria. However, further studies and validation of its safety and long-term effects are still needed.

2.2 Phase III Clinical Trial of Ceftazidime-Avibactam

Clinical data from a randomized, double-blind, prospective trial conducted to evaluate the efficacy of Ceftazidime-Avibactam versus Meropenem in the treatment of complicated abdominal infections in adults showed that the two groups of testers had similar time to clinical response endpoints and rates of adverse reactions, indicating that the two drugs have similar efficacy and safety in the treatment of complicated abdominal infections. Secondly, in evaluating the therapeutic efficacy, it was concluded that: (1) The median time to reach the clinical response endpoint was 6.0 days and 6.5 days for the two trial groups, respectively, and the percentage of reaching the clinical response endpoint was about 90% for both groups. (2) Ceftazidime-Avibactam, which may be effective against some Ceftazidime-non-susceptible pathogens, confirms that the addition of Avibactam to Ceftazidime restores activity of Gram-negative organisms resistant to Ceftazidime. (3) The probability of adverse
reactions, such as nausea, vomiting, and abdominal pain was close to that of the Meropenem group with (64.4%) and (57.8%), respectively. The results of the trial showed that Avibactam restored the antimicrobial activity of Ceftazidime, which provided more basis for clinicians in choosing treatment options[15]. The results of another randomized, double-blind, prospective trial showed that Ceftazidime-Avibactam and Imipenem-Cilastatin exhibited similar effects in the treatment of complicated urinary tract infections in adults. Specifically, Ceftazidime-Avibactam was effective in approximately 71.0% (49/69) of treatments compared to 79.4% (54/68) for Imipenem-Cilastatin, and the results showed that the difference in treatment efficacy between the two was not significant[16].

3. Study on the Resistance Mechanism of Ceftazidime-Avibactam

With the widespread use of Ceftazidime-Avibactam, the emergence of its resistant strains has become a global concern. According to statistics, the resistance rate of Gram-negative bacteria to this compound is about 3.7% in the United States[17], and about 1.1% and 1.7% in Europe and the Asia-Pacific region, while the resistance rate of Pseudomonas aeruginosa is about 8.9% and 7.4%[18-19]. According to statistics, the percentage of Ceftazidime-Avibactam resistant Klebsiella pneumoniae in China is about 12.3%[20]. This combination preparation shows a good antibacterial effect against Gram-negative bacteria with a relatively low resistance rate, but the resistance mechanism still needs to be explored in depth to slow down the progress of resistance. Currently, the known resistance mechanisms include the following[21][28][40][42], (1) producing class B β-lactamase; (2) amino acid mutations in the active site of β-lactamase: Ω-loop mutations in the class A enzyme, KPC; (3) alterations in the permeability or structure of cell membranes: mutations in the membrane pore proteins, OmpK35 and OmpK36, and penicillin-binding proteins; and (4) overexpression of exocytotic pump. Because Avibactam is ineffective against metallo-β-lactamase (MBLS), it is often not used in the treatment of bacterial infections producing this enzyme, and of the remaining resistance mechanisms, the most important was KPC amino acid mutations. The presence of these resistance mechanisms poses a challenge to the therapeutic efficacy of Ceftazidime-Avibactam. Therefore, in clinical application, it is necessary to pay close attention to the changes in bacterial resistance and select appropriate therapeutic measures according to the resistance mechanism to slow down the progression of resistance. At the same time, strengthening antimicrobial drug management to ensure rational use of drugs is also one of the important measures to reduce drug resistance[1].

3.1 Resistance Mediated by Amino Acid Mutations in the β-lactamase Active Site

Bacteria express a variety of β-lactamase and mediate resistance to antibiotics through amino acid mutations in the active site. Each of these mutations has unique characteristics (Table 1), which I will describe below in points based on the information in the referenced article.

The Ω-loop is a structural domain consisting of amino acids 164-179, which is a key active region of β-lactam antibiotics. This region is critical for antibiotic binding to bacterial targets and inhibiting bacterial growth, and when mutations occur in the Ω-loop, these mutations may lead to an increase in Ceftazidime clearance while decreasing the binding capacity of Avibactam. This change allows the bacteria to resist the combined action of Ceftazidime-Avibactam and thus develop resistance. KPC-2, CTX-M, and SHV are all different types of β-lactamase that hydrolyze β-lactam antibiotics thus helping the bacteria to resist the bactericidal effects of antibiotics. When the Ω-loop in these enzymes is mutated, it may allow the bacteria to hydrolyze Ceftazidime more efficiently or reduce the inhibitory effect of Avibactam, further promoting the development of resistance[21].

The KPC enzyme is by far the most common carbapenemase and is characterized by a high percentage of insertions and deletions compared to other β-lactamase. In particular, mutations in specific regions of the KPC enzyme have been widely reported in studies related to Ceftazidime-Avibactam resistance. KPC variants with mutations in the Ω-loop region, the loop 237-243 region, and the loop 266-275 region are strongly associated with Ceftazidime-Avibactam resistance. These mutations usually result in increased Ceftazidime clearance and decreased Avibactam binding, which triggers resistance. Multiple studies of Ceftazidime-Avibactam resistant Escherichia coli and Klebsiella pneumoniae have reported that the KPC Arg164ser, Pro169Leu, Gln169Leu, Asp179Tyr, Asp179Asn, Val240Gly, and Thr243Met single amino acid mutations, two amino acid mutations in Asp179Tyr/Thr243Met, and 165-166 Glu-Leu insertion, 167-168 Glu-Leu insertion, 182-183 Ser insertion, and 267-268 Pro-Asn-Arg-Ala insertion mutations expressed as Ceftazidime-Avibactam resistance[22-32]. There for, both specific amino acid mutations and insertion
mutations in these KPC enzymes have been shown to be closely associated with resistance to Ceftazidime-Avibactam in *Escherichia coli* and *Klebsiella pneumoniae*. These bacterial species are relatively common in clinical practice, and therefore knowledge of these resistance mechanisms is important for clinical diagnosis and treatment.

CTX-M-15 enzyme is a widely distributed β-lactamase that is associated with resistance to a variety of antibiotics in bacteria such as *Escherichia coli*. The Gly130Ser and Gln169Leu double mutations in the CTX-M-15 enzyme were found to mediate resistance to Ceftazidime-Avibactam in *Escherichia coli*. These two mutations may alter the structure or function of the enzyme, allowing it to hydrolyze Ceftazidime-Avibactam more efficiently, leading to the development of resistance. CTX-M-14 enzyme is another common β-lactamase, also widely found in bacteria such as *Escherichia coli*. It has been shown that Pro170Ser and Thr264Ile double mutations in the CTX-M-14 enzyme can significantly enhance resistance to Ceftazidime-Avibactam in *Escherichia coli*. These mutations may affect the structure and function of the enzyme in a similar manner, thereby altering its ability to hydrolyze Ceftazidime-Avibactam. The relationship between the SHV enzyme and Ceftazidime-Avibactam resistance has not been verified experimentally. However, it has been suggested that mutations in the SHV enzyme may be associated with Ceftazidime-Avibactam resistance, possibly alone or in combination with other mechanisms leading to the development of resistance. This implies that mutations in the SHV enzyme may affect bacterial susceptibility to Ceftazidime-Avibactam by altering its substrate specificity, enzyme activity, or other mechanisms.

<table>
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<tr>
<th>Enzyme</th>
<th>Position</th>
<th>Omega loop 164-179</th>
<th>Loop 237-243</th>
<th>Loop 266-275</th>
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<tr>
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<td>Val240Gly</td>
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AmpC is a β-lactamase enzyme produced by Gram-negative bacteria such as *Pseudomonas aeruginosa*. This enzyme is capable of hydrolyzing a wide range of β-lactam antibiotics, including Penicillins, Cephalosporins, and Monoamidate antimicrobials, thereby rendering these antibiotics sterile and leading to bacterial resistance to these drugs. However, the AmpC enzyme can be hydrolyzed by Avibactam, thereby restoring the antibacterial activity of Ceftazidime. It has been found that *Pseudomonas aeruginosa* reduces its ability to bind to Avibactam by altering the H-10 helical structure of its AmpC enzyme, which in turn develops resistance to Ceftazidime-Avibactam. In response to AmpC mutation-mediated resistance, several studies have been devoted to the development of new inhibitors or therapeutic strategies, and it is important to note that, although AmpC is widespread in bacteria such as *Pseudomonas aeruginosa*, not all resistance development is attributed to AmpC. Other types of β-lactamase (e.g., ESBLs and MBLs) as well as non-enzymatic resistance mechanisms (e.g., efflux pumps and altered membrane permeability) may also contribute to bacterial resistance to antibiotics. Therefore, in clinical practice, multiple factors need to be considered to develop effective treatment strategies.

OXA-48 enzyme is a class D β-lactamase (or class D carbapenemase) with the ability to hydrolyze...
Penicillin and Carbapenem antibiotics. Carbapenem antibiotics are considered to be the “last line of defense for antibiotics”, but the effectiveness of these antibiotics is greatly reduced by the action of OXA-48 enzyme. Although the wild-type OXA-48 enzyme can be hydrolyzed by Avibactam, the fact that the OXA-48 gene can be present in chromosomes and plasmids allows it to spread rapidly from one bacterium to another, creating so-called “superbugs. These OXA-48 gene-carrying bacteria are resistant to a variety of antibiotics, making clinical treatment more difficult. The OAX-48 variant with a double amino acids mutation in the OXA-48 enzyme Pro68Ala/Tyr211Ser has been reported to evade the inhibitory effect of Avibactam, leading to bacterial resistance to Ceftazidime-Avibactam\(^{[37]}\). Therefore, by enhancing its detection, inhibitor development, and mutant research, we can better meet the challenge of drug-resistant bacteria and improve the success rate of clinical treatment.

In summary, bacteria mediate their resistance to Ceftazidime-Avibactam mainly through different β-lactamase mutations. These mutations may affect bacterial susceptibility to antibiotics by altering enzyme structure, function, or substrate specificity. Therefore, understanding these mutations and their mechanisms is important for guiding clinical use and developing new therapeutic strategies and drugs.

### 3.2 Resistance Mediated by Altered Permeability of the Bacterial Outer Membrane

Bacterial cell walls and cell membranes are semi-permeable, allowing water molecules to pass through, while other substances have a selective passage effect. This selective permeability is an important mechanism for bacterial survival and adaptation to the environment. When the permeability of the bacterial outer membrane is altered, it may affect bacterial susceptibility to antimicrobial drugs. For example, bacteria can reduce the permeability of the outer membrane by altering the nature and number of channel proteins, thereby developing resistance to antimicrobial drugs. Two mutations in *Klebsiella pneumoniae*, the Arg191Leu mutation in the pore protein ompK36 and the KPC-2 enzyme mutation, have similar minimum inhibitory concentrations (MIC) to Ceftazidime-Avibactam, and both exhibit resistance\(^{[38]}\). A strain of *Klebsiella pneumoniae* resistant to Ceftazidime-Avibactam with the Thr333Asn mutation in the pore protein OmpK36 reduces the pore protein activity and affected susceptibility to Ceftazidime-Avibactam\(^{[39]}\). Whole gene analysis of *Klebsiella pneumoniae* expressing KPC variants resistant to Ceftazidime-Avibactam revealed the presence of both ompK35, a pore protein truncated at amino acid 41, and OmpK36, a pore protein with a 134-135 Gly-Asp insertion mutation in the resistant strains, and it was hypothesized that pore protein mutations may be involved in bacterial resistance in conjunction with KPC mutations\(^{[39]}\). Reduced expression of the pore protein OmpK36 or truncated OmpK35 due to an early termination code was also directly associated with Ceftazidime-Avibactam resistance\(^{[28]}\). Therefore, altered permeability of the bacterial outer membrane is important for bacterial drug resistance.

### 3.3 Penicillin-Binding Protein Mutation-Mediated rResistance

Penicillin-binding proteins (PBPs) play a crucial role in bacterial cell wall synthesis. These proteins are the main target of action of β-lactam antibiotics. When β-lactam antibiotics bind to PBPs, they irreversibly inhibit the activity of these proteins, leading to a reduction in the strength of the bacterial cell wall and eventual lysis. Insertion mutations, a specific type of mutation in which additional nucleotide sequences are inserted into a gene, resulting in a change in the protein sequence, have been reported in several studies. Insertion of four amino acids Thr-Ile-Pro-Tyr\(^{[40]}\), Tyr-Arg-Ile-Asn, or Tyr-Arg-Ile-Lys\(^{[41]}\) into specific positions of PBP3 may lead to significant structural and functional changes in PBP3, which in turn affects the ability to bind between Ceftazidime and PBP3 and manifests itself as resistance to Ceftazidime-Avibactam. As a result of these insertion mutations in PBP3, bacteria are now able to survive and multiply in the presence of Ceftazidime-Avibactam, which poses a challenge for antibiotic therapy.

### 3.4 Resistance Mediated by Altered Structure and Number of Efflux Pumps

The efflux pump plays an important role in the development of bacterial resistance. When bacteria are exposed to antibiotic pressure, the expression of the efflux pump may increase, thereby enhancing the bacterial efflux of antibiotics and decreasing the intracellular concentration of antibiotics, allowing the bacteria to survive in an environment where antibiotics are present. This mechanism can lead to bacterial cross-resistance to multiple antibiotics. The efflux pump can be classified into different types based on their substrate specificity and energy source, mainly including: the Major Facilitator Superfamily (MFS), the Resistance-Nodulation-Cell Division (RND), the Multiple Antibiotic and
Toxic Compound Extrusion (MATE), Small Multidrug Resistance (SMR)\textsuperscript{[42]}. And the efflux pumps expressed by different bacteria differ significantly. In Ceftazidime-Avibactam resistant Enterobacteriaceae, the efflux pump inhibitor phenylalanine-arginine β-naphthamide (PaaN) failed to increase bacterial susceptibility to antibiotics\textsuperscript{[43]}. In contrast, the efflux pump inhibitor carbonyl cyanide m-chlorophenylhydrazone (CCCP) significantly reduced the minimum inhibitory concentration of Ceftazidime-Avibactam in resistant Pseudomonas aeruginosa, thus suggesting that the mechanism of efflux pump overexpression in Pseudomonas aeruginosa is closely related to Ceftazidime-Avibactam resistant drug resistance\textsuperscript{[44]}. Resistance of Pseudomonas aeruginosa to Ceftazidime-Avibactam may not only be related to the efflux pump. It was noted that this resistance may also be related to the combined effect of two mechanisms, AmpC-producing as well as high expression of the MexAB-OprM gene. Which shows the complexity and diversity of drug resistance mechanisms in P. aeruginosa\textsuperscript{[45]}. In summary, overexpression of efflux pumps is one of the important factors affecting antibiotic efficacy, but different bacteria do not respond to efflux pump inhibitors in the same way. Therefore, when treating drug-resistant bacterial infections, it is necessary to comprehensively consider the resistance mechanism of bacteria and select an appropriate combination of antibiotics and efflux pump inhibitors to improve the therapeutic effect.

4. Summary and Prospects

Microbial drug resistance is one of the long-standing challenges in healthcare. With the deepening of research, the understanding of drug resistance mechanisms has gradually deepened, providing a variety of potential strategies to address the problem of drug resistance in the future. We can study the mechanism of action of drug resistance genes, protein expression and metabolic changes within drug-resistant bacteria more accurately through more diversified detection means such as gene editing technology CRISPER/Cas9, proteomics and metabolomics\textsuperscript{[46][47]}. At the same time, new antibacterial drugs with strong targeting can be designed according to the different mechanisms of drug resistance, such as inhibitors against specific drug-resistant enzymes or drug-resistant targets. Or through the combined use of different drugs, to increase the killing effect on drug-resistant bacteria and reduce the emergence of drug resistance. Since its approval, Ceftazidime-Avibactam has demonstrated a wide range of uses and precise therapeutic effects in clinical applications. However, due to its relatively short time on the market, clinical data on its efficacy assessment are still limited and its scope of application is still narrow. Many reports claim that bacteria can become resistant to the combination within a short period after exposure to Ceftazidime-Avibactam, and this rapid development of resistance limits the long-term application of the drug\textsuperscript{[42][48][49]}. Therefore, further studies and clarification of the resistance mechanism are important to slow down the progression of resistance and ensure the effective use of the drug.

The emergence of Ceftazidime-Avibactam resistance implies the need to find new therapeutic strategies or develop new antibiotics to deal with these resistant bacteria. At the same time, understanding these mechanisms helps us to better understand and address the challenge of drug resistance. Although Avibactam is effective in inhibiting β-lactamase, it is ineffective against metal-β-lactamase-producing Gram-negative bacteria. To overcome this limitation, co-administration of the monocyclic ring β-lactamase antibiotic Aztreonam (ATM), which is not hydrolyzed by metallo-β-lactamase, became a solution. Ceftazidime-Aztreonam-Avibactam, a new combination, is currently in phase III clinical trials and is therapeutically effective in several reports. It usually shows better antibacterial activity against MDR bacteria as well as Ceftazidime-Avibactam resistant bacteria. In a treatment involving 102 patients with CRE bloodstream infections (including 79 cases of NDM-producing Klebsiella pneumoniae, 3 cases of Escherichia coli, and 14 cases of VIM-producing Klebsiella pneumoniae), the efficacy of Ceftazidime-Aztreonam-Avibactam was demonstrated by a significant reduction in the 30-day mortality rate and a significant reduction in the length of hospitalization after treatment with Ceftazidime-Aztreonam-Avibactam\textsuperscript{[50]}. In conclusion, the use of Ceftazidime-Avibactam provides an effective treatment option for patients with β-lactamase-producing gram-negative bacilli infections. For ultra-broad-spectrum β-lactamase-producing bacterial infections resistant to Ceftazidime-Avibactam, the therapeutic efficacy can be further improved by co-administration of Aztreonam. At the same time, the research, prevention and control of drug resistance mechanisms is a complex and long-term process that requires interdisciplinary cooperation and technological innovation on a global scale. Through in-depth research on drug resistance mechanisms, the development of new antibacterial drugs, and the application of gene therapy and immunotherapy, we can hope to effectively deal with the problem of drug resistance and protect human health in the future.
References


