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Treatment of Pneumoniae: A Comparison of the Effects of Colistin and Ceftazidime-Avibactam

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Abstract:

This study compares the cure rate, risk, and benefit-risk of two drugs used to treat pneumonia by surveying statistics from five U.S. hospitals. Data from the past few years show that bacterial pneumonia is a highly contagious and pathogenic disease that is spreading worldwide. A review of the data compiled from previous studies concluded that there are two main drugs used for the treatment of pneumonia and that the two drugs use different mechanisms in the treatment of pneumonia. One is a combination of antibiotics to which bacterial resistance has been found to develop, while the other has been shown to be potentially harmful to the human renal system and nervous system. Therefore, the selection of the appropriate drug in combination with the patient's complex multispecies infection is an important future research direction.

Keywords: Pneumoniae; Colistin; Ceftazidime-avibactam; Carbapenem resistance; Resistance

1. Introduction

The lungs are important organs in the human body and are mainly responsible for respiratory functions, the inhalation of oxygen and the elimination of carbon dioxide. The lungs are located in the thoracic cavity, one on the left and one on the right, and are wrapped by the pleura. The main structures of the lungs include the bronchial tubes, lobes, and alveoli. Air first passes through the nose or mouth, through the larynx and trachea into the bronchi, and then into the lobes of the lungs. Each lobe is subdivided into many lobe segments, and within each lobe segment are many alveoli. The alveoli are the basic functional units of the lungs and are covered with a large number of capillaries, which are the main sites of gas exchange.

During respiration, the oxygen we inhale passes through the alveoli into the bloodstream, where it is carried by the red blood cells throughout the body to be supplied to the cells for use; at the same time, the waste carbon dioxide produced by the cells is transported through the bloodstream to the alveoli, where it is then exhaled by us. The lungs also have a number of other functions, such as being involved in regulating the acid-base balance of the blood and the secretion of certain hormones. In addition, the lungs have certain immune functions that prevent inhaled microorganisms and other harmful substances from causing harm to the body.

The more common approach to the pathway of pneu-

monia infection is that Airway infection occurs primarily through the aspiration of organisms colonizing the upper respiratory tract [1]. Pneumonia bacteria are spread into the air by people through sneezing, coughing, etc., and are then picked up by the next host through airborne transmission. Although people's three-tiered immune system stops most of the bacteria from harming their health, there are still some bacteria that have evolved defenses that can get into a person's block and system, causing illness. An example of this is Streptococcus pneumoniae; this bacterium is able to evade the immune action of white blood cells through the formation of pods made of polysaccharides in vitro and thus the body produces (Fig .1).

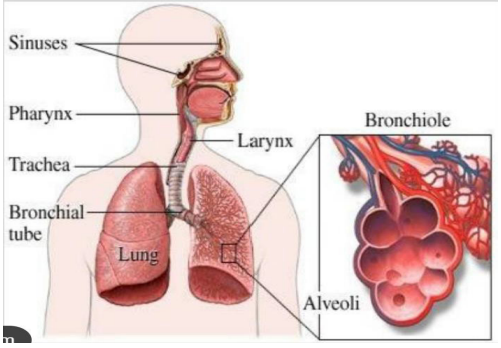

Fig.1. The structure of the human lungs and the way they are linked to the outside world

After entering the human body through the respiratory tract and other means, bacteria can attack human organs in many ways. Some of the more common ones are: 1. Bacteria damage the cell membranes of human cells by producing a variety of toxins to take their place; for example, Streptococcus pneumoniae produces pneumococcal toxins, which cause the death of normal human cells. 2. Bacterial metabolites often cause damage to human cells, and these metabolites can cause localised inflammation that can lead to illnesses such as pneumonia.3. Bacterial antigens often trigger an immune response. antigens usually trigger an immune response in the body. During this process, the immune system releases a large number of inflammatory mediators, which can cause an inflammatory response.4. Some bacteria can directly damage the structure and function of cells, leading to tissue damage. Before the discovery of antibiotic drugs, the treatment of pneumonia was mainly limited to the treatment of symptoms and some natural remedies. When people contract pneumonia, they experience high temperatures, coughing, and difficulty breathing. Doctors would give antipyretics and oxygen, or use herbs or steam inhalation to relieve symptoms. All of these measures were limited to strengthening the patient's immune system and were not effective in treating pneumonia. In the early 1900s, it was discovered that antibodies could be extracted from the blood of recovered pneumonia patients and injected into them to help them fight off the pathogen. This method was known as serotherapy and was one of the main means of fighting pneumonia at the time. However, this method of fighting bacteria by increasing autoimmunity was not effective in reducing the mortality rate of pneumonia. It wasn't until 1928 that the invention of penicillin helped people discover an effective weapon against it. At this point, people began to formally utilize the role of antibiotic drugs in fighting bacterial-based diseases.

2. Pneumonia Bacteria

2.1 Bacterial Infections of the Lungs

The lower respiratory tract is not a sterile environment and is constantly exposed to environmental pathogens. Invasion and propagation of bacteria into lung parenchyma at the alveolar level can cause bacterial pneumonia [2]. For strains of Streptococcus pneumoniae, Staphylococcus aureus, and Klebsiella; the lungs, which are interconnected with the outside air and have plenty of alveolar space, are the perfect place to multiply. Therefore, the lungs are the ideal “nesting place” for many Gram-negative bacteria. Their polysaccharide shells help them to effectively evade the immune function of macrophages, dendritic cells, and other white blood cells.

2.2 Transmissibility and Pathogenicity of Pneumonia Bacteria

Pneumoniae has demonstrated widespread and progressive drug resistance as the main prevalent type of pneumonia worldwide. According to data from three Chinese hospitals in 2022, the number of clinical pneumoniae strains in all three hospitals showed a steady increase between 2014 and 2017; from 20%, 8.7% and 6.4% to 36.3%, 61.4% and 18% (Fig.2) [1].

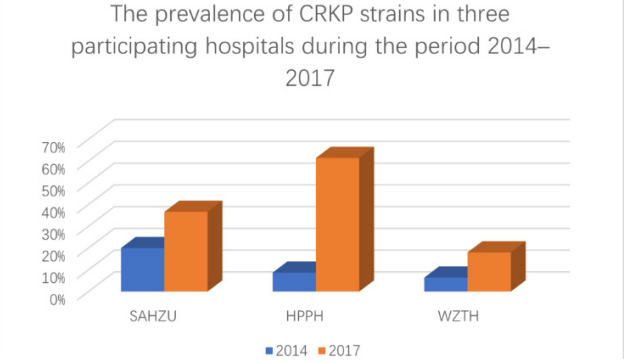

Fig.2. The prevalence of CRKP strains in the three participating hospitals during the period 2014-2017

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According to the records of a hospital in China, five patients were admitted to the intensive care unit as a result of a car accident. They were infected with different types of bacteria, even after receiving post-surgical antimicrobial treatment and mechanical ventilation, including pneumococcus. All five patients eventually died of lung infections (Fig.3). Thus, pneumonia possesses a high degree of transmissibility and mortality.

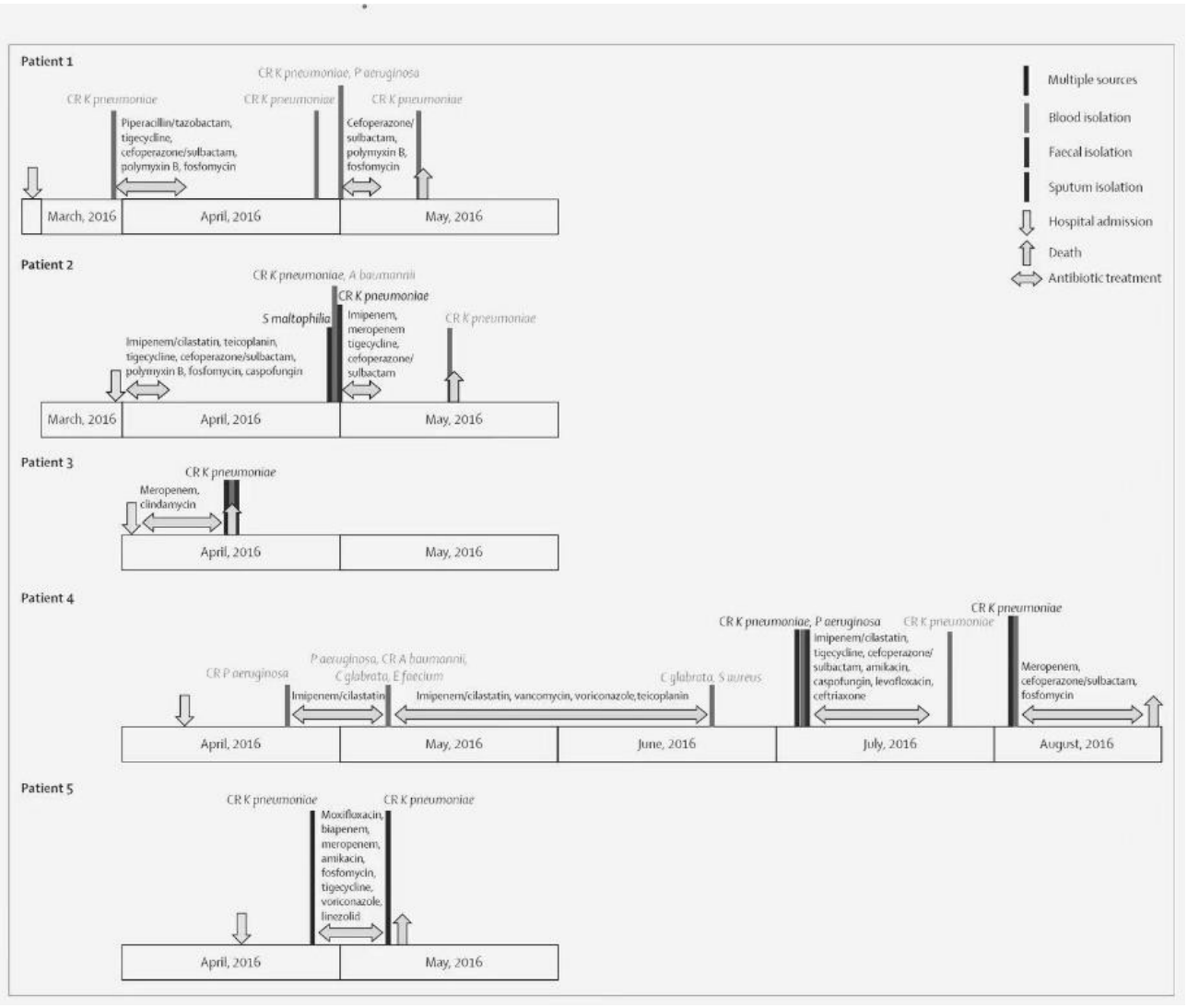

Fig.3. Epidemiology of the Klebsiella pneumoniae outbreak cases

2.3 Ceftazidime-Avibactam: Preventing Bacteria from Making Cell Walls

Ceftazidime-avibactam is an antibiotic medicine. It consists of two drugs, ceftazidime and avibactam. Ceftazidime is a cephalosporin antibiotic (Fig.4). The action of ceftazidime is mainly through its beta-lactam ring structure. This structure binds to a key enzyme in bacterial cell wall synthesis called transpeptidase, thereby preventing the normal function of this enzyme. The main role of transpeptidases is to catalyze the cross-linking reaction of peptidoglycan chains in the cell wall, which is key to bacterial cell wall stability. When ceftazidime binds to transpeptidase, it prevents this enzyme from catalysing the cross-linking reaction of the peptidoglycan chains, thereby interfering with cell wall synthesis. Without a stable cell wall, bacteria are unable to maintain their shape and structure or to grow and reproduce properly. In addition, damage to the cell wall makes the bacteria more susceptible to external environmental influences, such as changes in osmotic pressure, which can lead to bacterial death. Avibactam is a non-β-lactam inhibitor of β-lactamase, a bacterial enzyme that destroys the structure of β-lactam antibiotics (e.g., penicillin, cephalosporins, etc.), rendering these antibiotics ineffective. Avibactam inhibits the activity of β-lactamase, thereby protecting β-lactam antibiotics from

being destroyed and enhancing their antibacterial effect.

2.4 Resistance of Pneumoniae to Ceftazidime Drugs

The increasing prevalence of multidrug resistant (MDR) Gram-negative bacterial pathogens worldwide is a significant global public health concern [1–3]. Antimicrobial resistance among Gram-negative pathogens (in particular, resistance to b-lactam antimicrobials) is commonly driven by the production of b-lactamases. This article will present a comparison of the mechanism of action and effect of the two drugs [3]. Unlike the polysaccharide outer membrane of normal pneumococci, drug-resistant S. pneumoniae destroys carbapenem antibiotics by producing β-lactamases, thereby protecting the bacteria from the effects of antibiotics, leading to the destruction of the cell wall. As a result, Ceftazidime generally works in the human body as a combination antibiotic drug with Avibactam. The University of Pittsburgh, USA, conducted a study of 109 patients with CR-Kp bacteraemia who were treated with the Ceftazidime-Avibactam combination antibiotic; the study showed that the Ceftazidime-Avibactam combination antibiotic had the highest therapeutic efficacy in comparison with the other three treatments (Fig.5) [4].

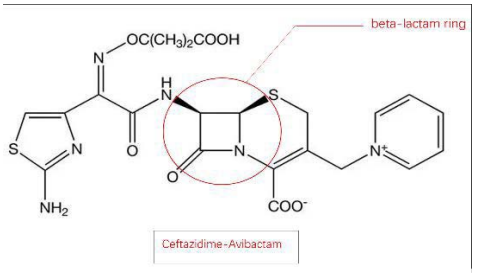

Fig.4 Chemical structure of ceftazidime-avibactam

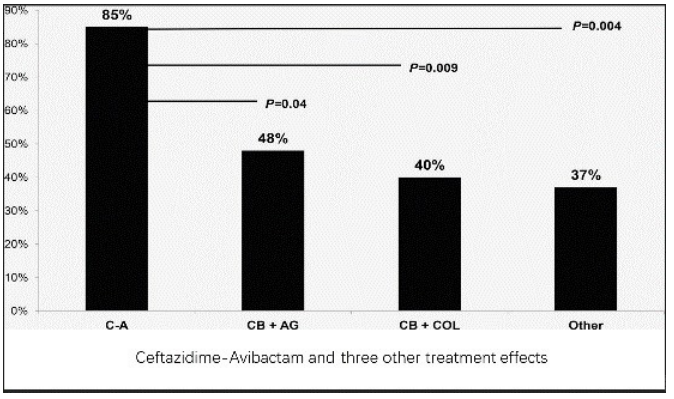

Fig. 5 Comparison of ceftazidime-avibactam efficacy with the therapeutic effects of three other drugs

2.5 Colistin: Disrupts the Cell Membrane of Bacteria

Colistin is a peptide antibiotic whose mechanism of action is to disrupt bacterial cell membranes. The colistin molecule contains a series of amino acids and fatty acids that allow it to bind to phospholipid molecules in bacterial cell membranes. In particular, colistin is able to form ionic bonds with the phosphate portion of the phospholipid molecules on the cell membrane, thereby destabilizing the cell membrane. When colistin binds to the cell membrane, it causes the structure of the cell membrane to change, forming holes. These pores allow substances (e.g., ions, proteins, etc.) from inside the cell to flow out freely while also allowing substances from outside to enter the cell. This imbalance in the exchange of substances leads to a serious disruption of the physiological processes of the cell, which ultimately leads to the death of the bacteria.

2.6 Colistin Still Has Antimicrobial Activity Against Drug-Resistant Strains of Bacteria

Colistin is a peptide antibiotic whose mechanism of action is to disrupt the integrity of the bacterial cell membrane by interacting with phospholipids on the bacterial cell membrane, resulting in bacterial death. This mechanism of action is different from that of many other antibiotics (e.g., beta-lactam antibiotics), which usually prevent bacterial growth by inhibiting a specific enzyme or protein in the bacteria.

Therefore, it is unlikely that bacteria will become resistant to Colistin even if they become resistant to other antibiotics. This is because for bacteria to become resistant to Colistin, they would need to change the phospholipid composition of their cell membranes, which is biologically very difficult. However, every coin has two sides; although colistin is not affected by bacterial resistance, its interaction with phospholipids also occurs in normal

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cells of the body. In the kidneys, colistin may disrupt the cell membranes of renal tubular cells, leading to cell death and thus affecting the normal function of the kidneys. In the nervous system, Colistin may affect the function of nerve cells. Signaling in nerve cells depends on the proper functioning of ion channels in the cell membrane. Colistin may disrupt these ion channels, affecting nerve signaling and leading to neurotoxicity.

3. Methods

3.1 Patient Data

The CRACKLE Study is a prospective observational study of statistics from 18 hospitals in 8 healthcare systems in the Great Lakes region of the United States. Data on all patients with penicillin-resistant Klebsiella pneumoniae in the CRACKLE Study from 2011 to 2015 were selected for a US study [5]. Patients who had developed bacteremia were selected and the source was not considered. Finally, a single Pitt bacteremia score was included for these patients at the time of their most recent treatment for CRE infection, and patients with a score of ≥44 were selected for consideration.

3.2 Statistical Methods

The experiment was statistically analyzed from three different perspectives: efficacy, safety, and benefit-risk. A total of 137 samples were selected for the efficacy analysis set; the safety analysis, as well as the benefit-risk set, was performed by selecting a total of 72 samples who developed renal failure at the start of treatment, as these patients with initial renal failure would not be at risk for the primary safety outcome. The analyses focused on ordinal outcomes based on benefits and harms that had a significant impact on patients over the course of their treatment (Fig. 6).

Analysis	Outcomes			
Efficacy	1. Hospital death	2. Alive in hospital or discharged not to home	3. Discharged home	
Safety	1.Hospital death	2.Not observed to die, with incident renal failure	3. Not observed to die, without incident renal failure	
Benefit-risk	1. Hospital death	2. Alive in hospital or discharged not to home, incident renal failure	3. Alive in hospital or discharged not to home, no incident renal failure	4. Discharged home

Fig.6. Statistical analysis project

4. Results

During the study period, 137 patients who met the criteria for infection were initiated on treatment with ceftazidime-avibactam or colistin, respectively. Thirty-eight of them received ceftazidime- avibactam and the rest received colistin. The vast majority of these pneumonia patients were infected with S. pneumoniae (n=133; 97%) the remaining four were infected with Streptococcus pneumoniae (n=4 3%). At the end stage of the experiment, statistics in terms of efficacy showed that there were 3 deaths out of 38 cases in the ceftazidime-avibactam group, while the number of deaths in the colistin group was 33 out of 99 cases (33%). According to the statistical analysis, patients treated with ceftazidime-avibactam had a lower mortality rate and a higher chance of being discharged to home during the first 30 days after the start of the treatment, and the probability that ceftazidime-avibactam had better therapeutic efficacy than colistin was 64%.

In terms of safety, a total of 72 samples were included in the safety/benefit-risk analysis set, of which 26 were treated with ceftazidime-avibactam, and the remaining 46 were treated with colistin. Estimates based on the three analytical perspectives of (1) in-hospital death, (2) death from unobserved renal failure, and (3) death from unobserved renal failure were 9%, 5%, and 86%, respectively, for ceftazidime-avibactam, whereas colistin was found to be safer than colistin in the study by constructing a function of (1) in-hospital death, (2) death from unobserved renal failure, and (3) death from unobserved renal failure. colistin.

In terms of benefit-risk, benefit-risk was assessed using the safety/benefit-risk analysis set (n = 72); the IPTW-adjusted estimates for ceftazidime-avibactam for (1) in-hospital deaths, (2) surviving in-hospital or being discharged without returning home with renal failure, (3) surviving in-hospital or being discharged without returning home without renal failure, and (4) being discharged to home were 9, 5, and 20%, respectively, 65%, and 20%, respectively, whereas the estimates for colistin were 25%, 11%, 56%, and 8%, respectively. Thus, ceftazidime-avibactam had a similarly higher benefit-risk index than colistin.

5. Conclusion

In the above article we introduced pneumonia and the two main therapeutic drugs and compared some of the characteristics of the two drugs. The ceftazidime-avibactam is a combination antibiotic characterized by its high curative and safety profile, while colistin is an emergency drug used as a last resort and is characterized by the fact that bacteria are not resistant to it. They play an important

role in killing Gram-negative bacteria as well as various bacteria that cause pneumonia. In everyday clinical practice, ceftazidime-avibactam is often used as a general therapeutic agent due to its high curative properties and low risk. However, certain bacteria have evolved resistance to this class of drugs. Therefore, colistin is generally used as an emergency drug and the last line of defense for such diseases. The experiments mentioned in this paper have a number of issues that need to be further considered and resolved: for example, this experiment lacks an understanding of the performance of the two drugs in the presence of a mixture of diseases in humans and the small number of samples collected in this experiment. At the same time, the continued growth of bacterial resistance to ceftazidime antibiotics in pneumonia is an area that needs to be considered in depth when treating Gram-negative bacterial infections.

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