Analysis of Anti-infective Treatment and Monitoring of Adverse Reactions in a Case of Pulmonary Infection with Multidrug Resistant Acinetobacter Baumannii

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Abstract: Objective: To discuss the characteristics of anti-infection treatment of multidrug-resistant acinetobacter baumannii in pulmonary infection and the necessity of pharmaceutical care. **Methods:** Taking a case of pneumonia with multidrug-resistant acinetobacter baumannii indicated by pulmonary alveolar lavage fluid as an example, which was treated by clinical pharmacists in the form of consultation. And expounding the importance of rational use of antibiotics and characteristics of pharmaceutical care by referring to literature and pharmacokinetics. **Results**: Multidrug-resistant acinetobacter baumannii was found by alveolar lavage after admission, and the infection symptoms were not effectively controlled after tigecycline treatment. With the consultation assistance of clinical pharmacists, it was found that the patient had low albumin, which had a great influence on tigecycline with high protein binding rate. Later, cefoperazone sulbactam + tigecycline was used on the premise of albumin supplementation. That is recommended by clinical pharmacists. One week later, the patient's symptoms improved and were discharged. During the treatment, the clinical pharmacist took pharmaceutical care of the patient, timely solved the adverse reaction of vomiting in the early stage of medication, and solved the concerns of doctors. **Conclusions:** In the case of pulmonary infection with multidrug-resistant Acinetobacter baumannii, not only the drug sensitivity list, we should also refer to the pharmacokinetics of drugs and monitor the adverse reactions of drugs in the process of treatment, which has a certain positive significance for the scientific use of antibiotics.

Keywords: Acinetobacter baumannii; Antiinfective therapy; Clinical pharmacist; Pharmacokinetics

DOI: https://doi.org/10.12346/jnp.v2i1.6285

1. Introduction

Lung Infection is an inflammation that occurs in the terminal airway, alveoli, and interstitium of the Lung. It is caused by pathogenic microorganisms, physical and chemical factors, immune damage, allergies, and other factors.The most common clinical pulmonary infection is caused by pathogen infection, such as bacterial infection, fungal infection, viral infection, atypical pathogen infection, etc. bacterial pneumonia is the most common [1]. Acinetobacter baumannii has a strong ability to obtain drug resistance and clonal transmission. Multi drug resistance, wide drug resistance and all drug resistance Acinetobacter baumannii are prevalent all over the world. It has become one of the most important pathogens of nosocomial infection in China.The most common site of nosocomial infection of Acinetobacter baumannii is the lung [2], which is an important pathogen of hospital acquired pneumonia (HAP), especially ventilator-associated pneumonia (VAP). Because Acinetobacter baumannii is a conditional pathogen, patients often have high-risk factors such as low immunity, long-term use of antibiotics, malnutrition and so on before they are infected with Acinetobacter baumannii [3]. The prognosis of patients is often poor.

The author mainly reported the treatment process of a patient with pulmonary acinetobacter baumannii infection, combined with relevant literature guidelines and through analysis and correction of the patient's anti-infection treatment plan. To provide clinicians or pharmacists with relevant experience in the future diagnosis and treatment or consultation process

2. Summary of Medical Records

An 88-year-old male patient with a history of COPD

was hospitalized due to "cough, sputum and fever for 3 days". The patient had cough, expectoration and paroxysmal cough after catching cold 3 days ago. He coughed light yellow viscous sputum, which was not easy to cough out, accompanied by fever, up to 40.0 °C. Chest CT showed that multiple patchy increased density shadows were found in the posterior segment and lower lobe of the upper lobe of the right lung. After admission, the patient was given cefoperazone sulbactam (3G Q8H IVGTT) + moxifloxacin hydrochloride and sodium chloride injection (0.4g QD IVGTT) for infection treatment. After 3 days of improvement, he coughed and expectorated again. The heat peak reached 39 °C and coughed a small amount of white mucus. The blood routine cell count showed that the leukocyte count was normal, the neutrophil count was 7.87x109/L, and the CRP hint was 70.7mg/L^{-1}. Sputum culture and blood culture were monitored, and amikacin injection (0.4g QD IVGTT) was added for anti infection treatment. After 3 days, the patient's symptoms were still not improved, and he still had fever, cough and expectoration. Reexamination of blood routine showed that white blood cell count was 14.56*109/L and neutrophil count was 7.87x109/L. Sputum culture and blood culture were negative. Bronchoalveolar lavage fluid test was carried out with the consent of the patient and his family. The alveolar lavage fluid showed Acinetobacter baumannii, drug sensitivity showed that he was sensitive to tegacyclin, MIC = 2ug/mL, resistant to all the rest.

The patient had a history of chronic obstructive pulmonary disease for 20 years. He inhaled Salmeterol Xinafoate and Fluticasone Propionate Powder for Inhalation regularly. He had no history of hypertension and diabetes. He had 35 years of smoking history. And smoked an average of 20 per day. He had quit smoking for 10 years. He has quit smoking for 10 years and no drinking history. Denied a history of drug allergy. Body temperature at admission: 38.0 °C, low respiratory sound on both lungs, dry and wet rales on both lungs.Admission diagnosis: bacterial pneumonia.

3. Treatment Process

On the day of admission, relevant examinations were completed, and symptomatic treatment such as acetyl cysteine, ambroxol expectorant, terbutaline to reduce phlegm and ease asthma was given. Cefoperazone sulbactam (2:1) (3g q8h IVGTT day 1-6) + Moxifloxacin hydrochloride sodium chloride injection (0.4g q24h IVGTT day 1-6) was given anti-infection treatment. The patient felt that the disease symptoms were alleviated.

On the 3rd day after admission, the patient's symptoms worsened, the number of cough and expectoration increased, and the heat peak reached 39 °C. CRP prompt: 70.7mg/L^{-1}, neutrophil count: 7.87x109/L. The doctor thought that the anti infection strength was not enough. After sputum culture and blood culture, amikacin for injection (0.4g q2h IVGTT on the 3rd-6th day) was added to strengthen the anti infection strength.

On the 6th day after admission, the patient still had no improvement in symptoms, still coughed and expectorated, and the heat peak reached 39.3 °C. Blood routine showed that the leukocyte count was 14.56 * 109/L, and the neutrophil count was 7.87x109/L. Sputum culture and blood culture were negative, and Acinetobacter baumannii was indicated in the alveolar lavage fluid. According to the drug sensitivity prompt, the doctor used tegacyclin for injection (50mg q12h IVGTT days 6-18 after the load dose of 100mg on the first day)

On the 8th day after admission, the patient's symptoms and body temperature still did not improve, and the heat peak reached 39.7 °C, and the patient began to have nausea and vomiting. The vomit was the content of the stomach and vomited three times during the day. The doctor invited the clinical pharmacist for consultation. The clinical pharmacist found that the patient's albumin level was low, 25.6g/L. The clinical pharmacist suggested that the patient should be supplemented with albumin, and cefoperazone sulbactam (1:1) (3G q6h IVGTT days 8-18) should be used again for combination therapy. After pharmaceutical consultation and excluding the patient's original disease, the clinical pharmacist considered nausea and vomiting as the adverse reaction of tegacyclin, and recommended routine symptomatic treatment without stopping the drug. In the process of treatment, it is necessary to test the patient's liver and kidney function and blood routine.

On the 12th day after admission, the patient felt that the symptoms were improved, the cough and expectoration were reduced.The sputum was white and easy to cough up,the symptoms of nausea and vomiting did not appear again, the body temperature decreased, the heat peak was 37.8 °C, the blood routine showed that the leukocyte count was 9.56 * 109/L, CRP: 12.5mg/L^{-1}, and the liver and kidney function and coagulation routine of the patient were normal.

On the 18th day after admission, the patient had stable body temperature, no cough and sputum, normal blood routine, CRP: 10.0mg/L^{-1}, no nausea and vomiting, and was discharged tomorrow.

4. Discussion

4.1 Analysis of Baumannii with Lung Infection

Bacterial pneumonia is the most common cause of pneumonia and the most common type of infection in China. With the aging of the world population, pneumonia in the elderly has become a more and more important clinical problem. Pneumonia is one of the main causes of hospitalization among people over 65, and in some cases is the main cause of death in this population. Even for people over the age of 60, pneumonia is a predictor of increased mortality after the onset of a specific disease and in the years later [4,5]. Although there are cases in which mild pneumonia symptoms can be self limiting, the use of antimicrobial agents is the main means to treat pneumonia. In terms of reducing microbial burden, antimicrobial therapy can reduce the duration of disease, the risk of complications and mortality [6].

Acinetobacter baumannii is a gram-negative bacillus, which can cause serious hospital and community-acquired infection. It is a well-known conditional pathogen [3]. Due to the abuse of antibiotics, Acinetobacter baumannii has become the most common MDR bacteria in China. Acinetobacter baumannii has strong resistance and high drug resistance rate. The guidelines suggest that Acinetobacter baumannii treatment should be combined and used in sufficient dose [7]. According to Chinet, Acinetobacter baumannii in China is generally sensitive to polymyxin, cefoperazone, sulbactam and tegacyclin.

The patient with pulmonary infection in this case is an elderly male with a history of COPD. Considering that the immune defense system of the patient's lung is weak [8]. He came to our hospital for treatment because of bacterial pneumonia. Under the condition of using broad-spectrum antibiotics, only bacteria sensitive to antibiotics were removed, resulting in an increase in the breeding space of antibiotic insensitive Acinetobacter baumannii, which accelerated bacterial reproduction, In addition, due to the original disease COPD and age, the bacterial clearance is too slow, resulting in the aggravation of patients' symptoms [9]. Then, Acinetobacter baumannii was detected in the sterile alveolar lavage fluid. This culture is considered to be meaningful [10]. It needs to be actively treated according to drug sensitivity, so as to prevent the symptoms from aggravating again and even infecting the whole body, resulting in sepsis.

4.2 Analysis of Anti Infection Treatment Scheme of Patients

4.2.1 Rationality evaluation of the initial antimicrobial treatment plan before consultation

The patient was diagnosed with community-acquired pneumonia at the initial admission, however, due to the structural lung disease caused by COPD, structural lung disease is believed to aggravate the risk of Pseudomonas aeruginosa infection in patients [11]. For the initial treatment, drugs that can cover Pseudomonas aeruginosa should be selected. After the patient is admitted to the hospital, generally speaking, anti aeruginosa can be selected β Lactam drugs are used together with quinolones against Pseudomonas aeruginosa. In the initial treatment, cefoperazone sulbactam is considered to have anti aeruginosa activity, and the dosage frequency is consistent with the antibacterial PK/PD theory, but moxifloxacin is not considered to have anti Pseudomonas aeruginosa activity. Recently, it has been proposed that quinolones and fluoroquinolones may cause the risk of aortic aneurysm in the elderly. At present, there is evidence that the elderly are generally after the age of 60. The infection possibility of atypical pathogens becomes smaller, so the use of moxifloxacin does not improve the coverage. Considering the safety, the treatment scheme of moxifloxacin is inappropriate, so it should be considered to use levofloxacin lactate or cefoperazone sulbactam alone [12].

Three days later, the patient symptoms, patient temperature and inflammation index suggest infection is not well controlled, doctors choose to continue to expand the treatment, the patient after the hospital, to aggravation, according to the consensus diagnosis, the patient should consider hospital acquired pneumonia (HAP), repeated infection in the short term, considering the high risk of death, here choose the same anti-aerugin active amikacin, double gram-negative bacteria capping treatment.

4.2.2 Failure causes and adjustment scheme of tegacyclin treatment in consultation

After admission, the doctor gave cefoperazone sulbactam + moxifloxacin + amikacin with antibacterial spectrum including Pseudomonas aeruginosa and most Gram-negative bacteria. After 6 days of treatment, the infection was still poorly controlled. According to the drug sensitivity of alveolar lavage fluid, Acinetobacter baumannii was only sensitive to tegacyclin, but after the doctor started tegacyclin treatment, there was still fever Cough and other symptoms. By consulting the literature, clinical pharmacists found that the phenotypes of common Acinetobacter baumannii genotype 3 and Acinetobacter baumannii genotype 13tu are very similar in biochemistry, so the drug resistance and virulence of the four flora are very similar [13]. Acinetobacter baumannii has many drug resistance pathways, and its enzyme production and membrane protein have changed to common drug resist-

ance pathways [14]. However, according to the results of machine, the sensitivity rate of Acinetobacter baumannii to tegacyclin has always been at a high stage, but tegacyclin has a high protein binding rate. Due to the weight loss of COPD all year round, the patients have poor nutrition and low albumin, only 25g/L, Hypoproteinemia has a great impact on drugs with high protein binding rate [15].

The literature points out that the clinical significance of protein binding for drugs lies in controlling the free drug binding in the body and playing a role. When drugs with high protein binding rate are affected by hypoproteinemia, due to insufficient protein binding, the increase of free drugs will lead to the abnormal distribution, excretion and metabolism of drugs. Finally, it will cause the decrease of blood drug concentration [16]. After discovering this, the clinical pharmacist pointed it out to the doctor, gave medication education to the patient, informed the patient of the importance of albumin infusion, and the family members expressed their understanding and consent.

In addition, reactivation of cefoperazone sulbactam is also an important part of treatment. For Pan drug resistant bacteria (XDR) sensitive only to tegacyclin, multi drug combination treatment should be used as much as possible even when drug sensitivity indicates that no drugs are available. However, considering the failure of previous treatment with cefoperazone sulbactam, clinical pharmacists found that, the previous manufacturer's specification ratio was 3G per bottle of cefoperazone sulbactam (2:1), that is, only 1g of sulbactam in one dose, and only 3G per day in the case of Q8H infusion.

The guidelines suggest that the common dose of sulbactam in Acinetobacter baumannii infection is 4.0g/d [7,16]. If it is in XDR, it can even be increased to 6.0g/d. Therefore, the ratio of 1:1 is selected for the treatment of cefoperazone sulbactam. At the same time, according to the PK/PD theory, for time-dependent drugs, the time of T > MIC is prolonged, and the dose of sulbactam is also increased to 6.0g/d, The two drugs were treated for 10 days. During this process, the pharmacist communicated with doctors and nurses to prompt the monitoring of patients' coagulation function and renal function. In case of abnormalities, the treatment plan should be adjusted in time [7].

It is a pity that the patient did not receive alveolar lavage and microbiological examination at the later stage of treatment, and the patient did not have a better specific procalcitonin test. Procalcitonin can not only evaluate the curative effect, but also guide the withdrawal of antibiotics and the prognosis of the patient. It has great clinical practical value in anti infection. We need to increase the promotion of calcitonogenen examination in later cases and treatments.

4.3 Monitoring and Analysis of Adverse Reactions by Clinical Pharmacists

The patient developed nausea and vomiting when using tegacyclin on the 8th day of admission. After excluding the symptoms caused by the patient's disease (for example, some pneumonia and stress ulcer can also cause similar symptoms), the clinical pharmacist considered that the adverse reaction of the drug should be caused by tegacyclin according to the time correlation. And use the Nordic adverse reaction related scale to judge, so as to use the causality supported by objective evidence and quantitative test results, to avoid relying on personal empirical judgment [17]. According to the preliminary calculation, the score of tegacyclin is about 7 (Table 1). According to the evaluation, it is considered "likely to be relevant".

As previously mentioned, the tetracycline used in the patients was a high protein binding rate drug. The patient had hypoproteinemia, and tegecycline did not have sufficient albumin for binding, resulting in more free drugs in the blood, increasing the activity of tegecycline, but also increasing the metabolism and excretion of tegec-cycline. Generally, fat soluble compounds are filtered through the glomerulus, then reabsorbed at the renal tubular membrane. But usually the biological transformation reaction in vivo is to produce more polar, inactive metabolites excluded from the body. Tegacyclin loses its pharmacological activity while being biotransformed by the first phase due to too much free state. In addition, tetracycline and glycylcycline drugs have the characteristics of "bone reservoir" [18]. Therefore, the concentration of tegacyclin in the blood increases, but the clearance rate is higher, resulting in the results of treatment not reaching the ideal effect, and the increase of blood concentration leads to the possibility of side effects, so the patients have adverse reactions of nausea and vomiting.

According to the information consulted by the clinical pharmacist, the side effects of nausea and vomiting of tegacyclin generally occur within 1-2 days before infusion, and in view of the necessity of anti infective drugs, the treatment should be continued, and the doctor should be informed to monitor the patient's liver and kidney function and digestive system symptoms [19-20]. On the 12th day after admission, the patient's nausea and vomiting disappeared, and there were no abnormal gastrointestinal symptoms and liver function. On the 18th day, the patient's infection symptoms disappeared, and he will be discharged tomorrow. It has been 12 days since tegacyclin was used to treat HAP. It is recom-

Table 1. Nuo's evaluation results of nausea and vomiting caused by tegacyclin

Related issues	Scores			
	Yes	No	Unknown	Rating grounds
1.Whether the ADR was previously conclusive was reported ?	+1			It is suggested in the ABX guidelines that about 20 – 30% of patients may develop nausea and vomiting
2.Whether the ADR occurred after the use of a suspicious drug ?	+2			Nausea and vomiting occur after the use of tegecycline
3. Whether this ADR is relieved after withdrawal or application of an antagonist ?			0	The patient used no antagonist and was not stopped
4.Does the ADR appear after the reuse of a suspicious drug ?			0	The patient did not stop the medication after tetracycline administration
5.Whether there is any other cause of the ADR alone ?		+2		After investigation, there are no other drugs or diseases that can cause nausea or vomiting
6. Is the ADR repeated after a placebo application?			0	The patient did not use a placebo
7.Whether the drug reaches a toxic concentration in the blood or other body fluids ?	+1			The concentration of free drug increased, likely exceeding the treatment concentration
8. Does the ADR increase with an increasing dose?Dose dose reduced and remission? ?			0	The patient did not adjust for the drug dose
9.Whether the patient has been exposed to the same or similar drugs with similar reactions ?			0	The patient had no previous history of glycine ycline or tetracycline
10. Whether there was any objective evidence confirming the response ?	+1			Patient nausea and vomiting without any symptoms or cause can be regarded as objective evidence
Total score	7			

mended to stop tegacyclin.

5. Summary

To sum up, the anti-infection treatment plan of the patient was changed several times and suffered many setbacks. However, with the joint assistance of pharmacists, doctors and nurses, the patient recovered from infection and was discharged from the hospital. In this case of senile pneumonia caused by hospital acquired Acinetobacter baumannii, we deeply realize that anti infection treatment is not as simple as using correct antibiotics to cover possible pathogens and target treatment. We also need to know the PK/PD characteristics of drugs, the analysis of in-depth drug sensitivity reports, the distribution and metabolism of drugs, so that, even the same drug treatment will be very different in the treatment results. In the treatment of tegacyclin, a drug with high protein binding rate, we must pay attention to the patient's albumin value and liver function. Otherwise, in the treatment, the binding protein may be insufficient due to the low albumin, and the free tegacyclin may be metabolized, resulting in poor treatment effect. In addition, we should pay attention to the adverse reactions of tegacyclin during treatment. The most common adverse reaction is nausea and vomiting, but it usually disappears within 1-2 days. Only symptomatic treatment is needed. In the case of middle-aged and elderly patients, special attention should be paid to the liver and kidney function of patients. If there are abnormalities or adverse reactions such as pancreatitis, timely measures should be taken to avoid the aggravation of adverse reactions.

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