Treatment for patients with multidrug resistant *Acinetobacter baumannii* pulmonary infection

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Abstract. Bacterial infections are common but have become increasingly resistant to drugs. The aim of the present study was to examine the combined treatment of traditional Chinese and Western medicine in 30 cases of pulmonary infection with multidrug resistant *Acinetobacter baumannii*. Patients were divided into groups A and B according to drug treatments. Cefoperazone or sulbactam and tanreqing were administered in group A, and cefoperazone or sulbactam in group B. The curative effect and prognosis of the two groups were recorded and the remaining treatments were performed routinely in the clinic. For the combined therapy group, which was administered sulperazone and tanreqing, 8 patients were recovered, 6 patients had significant effects, 3 patients exhibited some improvement and 1 patient had no response. One of the patients did not survive after 28 days. By contrast, there were 4 patients that were successfully treated, 3 patients with significant effects, 2 patients with some improvement and 2 patients had no response in the sulperazone group, and 4 patients did not survive after 28 days. In conclusion, the combined therapy of cefoperazone or sulbactam supplemented with tanreqing was identified to be more effective than cefoperazone or sulbactam as monotherapy, for treating multidrug resistant *Acinetobacter baumannii*.

Introduction

The extensive use of antibiotics and the gradual increase of different types of drugs have made bacteria resistant to drugs (1,2). Appropriate selection of antibiotics for the treatment of the majority of severe microbial infections. The emerging resistance of different pathogenic microbes to drugs refers to multidrug-resistant, extensively drug-resistant or pandrug-resistant bacteria.

The drug resistance of acinetobacter is more severe due to the emergence of pan-resistant *Acinetobacter baumannii*, which is pan-resistant to antibacterial agents in current routine testing (3,4). Consequently, the treatment of pan-resistant *Acinetobacter baumannii* has become a worldwide issue. Pan-resistant, *Acinetobacter baumannii* is defined as the bacterial strain that is pan-resistant to common anti-gram-negative antibiotics such as penicillin, cephalosporin, monocyclic lactams, aminoglycosides, quinolones, carbapenems, tetracyclines and sulfonamides (5).

To circumvent infections caused by this infectious bacteria, Xiangyang Hospital has applied combined treatment of traditional Chinese and Western medicine to pan-resistant *Acinetobacter baumannii* cases in intensive care unit patients during the period January 1, 2008 to December 31, 2009, which has achieved promising effects. The present study examined the effect of the combined therapy of sulperazone supplemented with tanreqing, and sulperazone, as monotherapy.

Materials and methods

Patients. The present study included 30 patients suffering from pulmonary infection with pan-resistant *Acinetobacter baumannii* in the Xiangyang Hospital during the period January 1, 2008 to December 31, 2009.

Microbiological methods. Clinical samples were collected aseptically. The sputum specimens were taken through the artificial airway and a drug sensitivity test was performed according to the agar diffusion method to determine their sensitivity to 19 antibacterial drugs.

Clinical data. The extracted pan-resistant *Acinetobacter baumannii* was observed immediately and was divided into colonized bacteria and infectious bacteria according to the hospital infection diagnostic criteria established by the Ministry of Health. The extracted bacterium was defined as colonized bacteria if it did not qualify for the diagnostic criteria (6).

The treatment effects of groups A and B were retrospectively analyzed. The antibacterial drugs employed in group A were a combination of cefoperazone, sulbactam (Pfizer, NY, USA) and tanreqing (Kangbao, Shanxi,China). Cefoperazone

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(2 g) and sulbactam (3 g) were administered by intravenous drip every 8 h. Tanreqing (20 ml) was then added into the intravenous drip once a day. For group B, the cases were treated with only cefoperazone and sulbactam. The curative effect and prognosis of the two groups were recorded and the remaining treatments were administered as per clinical routine. The effects were evaluated based on the guiding principles of clinical research on antibacterial agents, as established released by the Ministry of Health (7). The main criteria for the clinical effects were symptom, sign and laboratory inspection. The 4 grades for assessment were: recovery, significantly improved, improved and no response. In addition, mortality within 28 days after infection was observed.

Statistical analysis. Enumeration data were carried out using the χ^2 test for statistical analysis. P<0.05 was considered to indicate a statistically significant difference.

Results

Treatment effects. Table I shows the outcomes for the two different drug treatments for *Acinetobacter baumannii*. For the sulperazone and tanreqing group, there were 8 recovered patients, 6 patients with significant effects, 3 patients with some improvement and 1 case with no response. In addition one patient succumbed after 28 days. By contrast, in the sulperazone-treated group there were 4 patients who were successfully treated, 3 patients with significant effects, 2 patients with some improvement and 2 patients with no response. Four patients succumbed after 28 days.

Comparison of the disappearing time of clinical symptoms between the two groups. After relieving the fever, the time period in which cough, phlegm, asthma, pulmonary rales and pulmonary shadow disappeared were compared between the two groups. Significant differences were identified (P<0.05, Table II).

Adverse reactions. None of the patients exhibited skin rash or other allergic reactions during treatment. Liver and renal function, a urine routine examination, and ECG showed no significant changes prior to and following treatment.

Discussion

Since the establishment of the Xiangyang Hospital in 1992, we have observed the emergence of *Acinetobacter baumannii* and currently there are infection cases of pan-resistant *Acinetobacter baumannii* (8-10). The challenge for treating pulmonary infection with pan-resistant *Acinetobacter baumannii* involves selection of medication (11). Previous findings have shown that cefoperazone sodium and sulbactam sodium, as well as minocycline and polymyxin are effective in terms of treating pan-resistant *Acinetobacter baumannii* (12-15). However, since polymyxin is no longer available, cefoperazone sodium and sulbactam sodium tanreqing were used in the present study to compare the effectiveness of the combination of the two drugs (16).

Table I. Comparison of treatment effects in the two groups.

Group	Cases	Clinical efficiency	Mortality in 28 days	P-value
Sulperazone + tanreqing	15	68.4%	6.66%	<0.05
Sulperazone	15	45.0%	26.66%	<0.05

Drug resistance arises in pan-resistant *Acinetobacter baumannii* from several mechanisms, the most important of which are the production of many types of hydrolases, changing the affinity of antibiotics and penicillin-binding protein (PBP), and decreasing the permeability of the outer membrane of bacteria or active efflux. Thus, the production of many types of hydrolases has become the main resistance mechanism.

Sulbactam inhibits many different types of β-lactamases (TEM1, TEM2 and SHV1) and most extended spectrum of β-lactamases are produced by bacteria in order to manage many bacteria resistant to hydrolase (17,18). It can have direct effects on PBP2 of bacteria and can enhance the sensitivity by 60-100%. There is also a direct correlation between its bacteriostasis and drug concentration. Cefoperazone and sulbactam have synergistic effects on 61% of the acinetobacter bacterial strain and have additive effects on 39% of acinetobacter bacterial strain, which can fully present its unique bactericidal effects on acinetobacter (19).

As an efficient, low toxicity and safe new traditional Chinese medicine, tanreqing is composed of radix scutellariae, bear bile powder, cornu gorais, honeysuckle and fructus forsythiae and has beneficial roles for clearing heat, detoxicating and resolving phlegm. The honeysuckle and fructus forsythiae in tanreqing can inhibit and disinfect many pathogenic microorganisms, as well as increase the anti-inflammatory effects of neutrophil and macrophage. This improves the content of serum lytic enzyme and enhances the immune mechanism (20-22). Furthermore, tanreqing improves Th1- and Th2-cell function and promotes the immunity of body cells and fluids. Moreover, tanreqing has significant inhibitory effects on the increase of centric fever medium prostaglandin E2 and cyclic adenosine

Table II. Comparison of the time period clinical symptoms terminated between the two groups (day, mean ± standard deviation).

Group	Patient no.	Fever relieving	Time cough, phlegm, asthma terminated	Time pulmonary rales terminated	Time shadow terminated
Sulperazone + tanreqing	15	2.42±0.87	5.47±2.17	4.37±1.53	7.22±1.56
Sulperazone	15	2.92±1.02	7.13±3.03	6.05±1.86	8.69±2.25

monophosphate and hypersensitivity process of immune cells (23,24). Tanreqing has bacteriostasis effects on 10 common bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, β-hemolytic *Streptococcus*, *Haemophilus influenza*e, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteusbacillus vulgaris*, *K. pneamoniae*, *Mycoplasma* and *mycobacterium tuberculosis*. In addition, tanreqing lowers the mortality of mice infected by *Staphylococcus aureus* and influenza virus (25).

In summary, the results have shown that sulperazone in combination with tanreqing is more effective in controlling pan-resistant *Acinetobacter baumannii*. The combined therapy of sulperazone and tanreqing has higher clinical efficiency (68.4%) compared to the monotherapy of sulperazone (45%). Additionally, the combination therapy enhances the survivability of infected patients with 6.66% of mortality rate compared to 26.6% with sulperazone alone. Thus, the combination therapy of sulperazone and tanreqing is recommended in the regulation of *Acinetobacter baumannii*-induced pan-resistance in hospitalized patients undergoing critical care.

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