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Research on the treatment of *Pseudomonas aeruginosa* pneumonia in children by macrolide antibiotics

Abstract: To observe a therapeutic effect of macrolide antibiotics in children with *Pseudomonas aeruginosa* pneumonia. Fifty-four cases of children with *Pseudomonas aeruginosa* pneumonia were randomly divided into an observation group (n=30) and a control group (n=24). The observation group was treated with macrolide antibiotics and cefoperazone/sulbactam. The control group was treated with cefoperazone/ sulbactam during a course of 10-14 days. The total effective rate was 93.3% in the observation group, and 58.3% in the control group, and results in the observation group were superior to the control group notably (P>0.05). There were no significant differences in bacterial clearance rate, adverse reaction rate between two groups (P>0.05). The combined application of cefoperazone/sulbactam with macrolide antibiotics to treat *Pseudomonas aeruginosa* pneumonia in children would be a more effective clinical method.

1 Introduction

Pseudomonas aeruginosa (*P. Aeruginosa*, PA) pneumonia caused by gram-negative bacteria *Pseudomonas aeruginosa*, is a very serious lung infection with high mortality in children. In recent years, due to a wide use of antibiotics, corticosteroids and immunosuppressive agents, as well as the promotion of mechanical ventilation therapy with artificial airway and the prolongation of critical patients hospitalization and survival duration, the incidence of *Pseudomonas aeruginosa* pneumonia has increased significantly. In order to observe a potential therapeutic effect of macrolide antibiotics in the treatment of *Pseudomonas aeruginosa* pneumonia in children and to seek the effective treatment, we analyzed 27 cases of children with *Pseudomonas aeruginosa* pneumonia diagnosed by bacteriology. We herein report the results of these studies.

2 Materials and methods

2.1 Case selection

A total of 54 cases of children with *Pseudomonas aeruginosa* pneumonia attended the respiratory ward of our hospital between August 2011 and February 2014. They were confirmed with the diagnostic criteria of *Pseudomonas aeruginosa* pneumonia [1].

A case for inclusion criteria: (1) Age (2 months to 3 years old), hospitalized patients with *Pseudomonas aeruginosa* pneumonia diagnosed by the clinic and bacteriology. (2) The clinical manifestations were as follows: body temperature > 37%, cough, sputum, rapid breathing, lung rales, abnormal white blood cell count, and an X-ray showed invasive lesions in lung caused by infection. (3) In more than three times of consecutive sputum culture, all showed *Pseudomonas aeruginosa* sensitive to cefoperazone/sulbactam by susceptibility testing. (4) The patients had not used other antibacterial drugs before the test, or had used different antibacterial drugs that have been proven to be ineffective before the test.

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Table 1: Comparison of general information of the two groups.

Group	Case No.	Age[(χ±S), month]	Gender [No. (%)] Male Female	Duration[(χ±S), d]	Whether or not used antibiotics before admission [No. (%)] yes no
Observation	30	11.13±9.89	16 (60) 12 (40)	12.60±4.24	11 (73) 4 (27)
control	24	10.17±9.57	14 (58) 10 (42)	13.17±3.90	9 (75) 3 (25)

The included cases were divided into two groups according to the treatment method: the observation group (n=15) and the control group (n=24), with a total of 54 cases. A general information and comparison between the two groups are reported in Table 1. Through the t test: the age and duration of the two groups had no statistically significant difference (P > 0.05); through the $\chi 2$ test: the gender composition and drug used before the test of the two groups had no significant differences (P >0.05) and were comparable.

Exclusion criteria: Children with any of the following criteria were excluded: (1) Allergic to penicillins, cefoperazone, sulbactam; (2) Having the history of tuberculosis, lung cancer, bronchial asthma and other abnormal reaction. (3) Having severe liver, kidney, heart failure, diabetes, immune deficiency and hematopoietic system disorders; (4) Receiving cancer chemotherapy and immunosuppressive agents; (5) With septic shock and sepsis; (6) Known to carry pathogens which are resistant to this test.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

2.2 Treatment regimen

Children were randomized into two groups. The observation group: cefoperazone/ sulbactam (produced by Pfizer Pharmaceutical Co., commodity name SULPERAZON code number approved by SFDA H10960113), 40mg/kg per time, intravenous drip, once every 12 hours for 10 to 14 days, plus one type of macrolide antibiotic such as azithromycin: 10mg/kg per time, once a day for 5 days, interval of 5 days, with 2 to 3 times; or clarithromycin: 7.5mg/kg per time, twice a day for 2 to 3 weeks.

The control group: cefoperazone/sulbactam, 40mg/kg, intravenous drip, once every 12 hours for 10 to 14 days.

2.3 Observation Project

Clinical observation: Daily record of temperature, cough, sputum, respiratory rate cases, pulmonary rales and adverse reactions.

Laboratory examination: (1) Check of white blood cell count and classification before, during and at the end of the treatment. (2) Perform sputum culture and sensitivity test before and at the end of the treatment. (3) Check liver and kidney function before and at the end of the treatment.

Radiological examination: Perform chest X-ray examination before and at the end of the treatment.

2.4 Efficacy criteria

Clinical efficacy criteria: Assessed according to the standard of "antibacterial drug clinical research guidelines" issued by the Ministry of Health. (A) Recovered: symptoms, signs, laboratory examination and etiology returned normal, if there was no etiology, the above three returned normal. (2) Markedly effective: clinical symptoms significantly reduced and signs disappeared, laboratory examination returned to normal. (3) Effective: clinical symptoms alleviated and signs disappeared, laboratory examination returned to normal. (4) Invalid: clinical symptoms, signs and laboratory examination at 72h after the treatment had no significant difference. Calculate the total number by adding the number of recovered and markedly effective patients.

Bacteriological evaluation criteria Clear: at the end of the treatment, the culture still showed negative. Not clear: at the end of the treatment, the culture showed still positive. Part clear: among more than two kinds of bacteria, one kind of bacteria was cleared. Replace: at the end of the treatment, the original pathogen disappeared, but a new pathogen was cultivated.

Table 2: Comparison of results in the two groups.

group	No. of cases	recovered	Markedly effective	effective	invalid	total efficiency [%, (cases)]	Invalid rate [%, (cases)]	bacterial clearance rate [%, (cases)]	Incidence of adverse reactions [%, (cases)]
observation	30	16	12	2	0	93.3 (14)	0	60.0 (9)	20 (3)
control	24	8	6	6	4	58.3 (7)	16.7 (2)	41.7 (5)	16.7 (2)

2.5 Statistical analysis methods

Use $\chi 2$ test to analyze whether the two groups were significantly different, and use SPSS software to perform data processing and statistical analysis.

3 Results

Clinical efficacy, bacterial clearance rate and incidence of adverse reactions of the two groups are shown in Table 2. Through the $\chi 2$ test the total efficiency of the two groups was significantly different (P <0.05), while the bacterial clearance rate and incidence of adverse reactions had no significant difference (P > 0.05).

4 Discussion

Pseudomonas aeruginosa (PA) is a kind of gram-negative bacilli being the most common non-fermenting bacteria in a clinic and widely distributed in nature. In recent years, the epidemiological features of PA infection have prominently shown in two aspects. Firstly, a nosocomial infection, particularly as incidence of lung infections is continuously increasing. There are number of large-scale epidemiological surveys, the most representative of which is the "Chinese CHINET Surveillance of bacterial resistance" showing the seriousness of PA infection in China. Statistics have shown that in 2012, the PA isolation rate in the comprehensive teaching hospitals accounted for the first five among all isolation rates [2]. The result of the Chinese hospital-acquired bacterial resistance analysis (CARES), for which 13 teaching hospitals have participated, has shown that in 2009 and 2011, PA also ranked No. 4 among all isolated bacteria [3]. The national nosocomial infection research data of the United States Centers for Disease Control and Prevention (CDC) has shown that the incidence of PA pneumonia has been increasing year by year [4]. Secondly, the high resistance rate of PA remains. Global antimicrobial resistance monitoring data (SENTRY) has ranked PA in the top of few among the hospital-

acquired pneumonia (HAP) pathogens, while resistance rates to commonly used antimicrobial drugs has been increasing year by year [5]. PA is one of the most common multidrug-resistant (MDR) and potentially drug-resistant (PDR) pathogens, of which the resistance mechanism involves many aspects [6]: (1) producing inactivated enzyme (2) membrane permeability decreasing (3) target changing (4) bacterial biofilm formation and (5) other resistance mechanisms. In a clinic, a treatment of PA lower respiratory tract infection is facing more and more difficulties, especially in children. The results of this study has shown that when macrolide antibiotic were used in a combination with cefoperazone/sulbactam in the treatment of children with *Pseudomonas aeruginosa* pneumonia, clinical efficiency was significantly higher than that of the control group with statistical significance. There are only limited reports in literature showing the use of macrolide antibiotic in a treatment of children with *Pseudomonas aeruginosa* pneumonia. Another clinical study of treatment of extensive burns with PDRPA infections has displayed that [7] macrolide antibiotics combined with β-lactamase inhibitor antibiotics can effectively control this infection. An application of macrolide antibiotics in the treatment of *Pseudomonas aeruginosa* pneumonia in children can be considered as a potential therapeutic method for the resistance mechanisms of PA. Bacterium attaches to an inert surface, then reproduces and secretes polysaccharide matrix and fiber protein complexes, which adhere and wrap the bacteria to form the membrane-like material that refers to the biofilm. Bacteria can survive through the form of biofilms to evade cytotoxicity of immune and antimicrobial drugs. Currently, what is more recognized is that 14-membered and 15-membered ring macrolide antibiotics (although have no antagonism against PA) can inhibit a formation of biofilm, while regulate immunity and enhance phagocytes. Among these macrolide antibiotics, the red ADM, clarithromycin, azithromycin and roxithromycin can effectively inhibit the formation of biofilm, which can be used together with the anti-PA drug to treat the PA biofilm-related infections. The 16-membered ring macrolide antibiotics such as midecamycin, josamycin, acetyl spiramycin are invalid

for the biofilm formation. In addition to 14-membered and 15-membered ring macrolide antibiotics, quinolones also play a certain role in inhibiting bacterial biofilm formation, however, due to the fact that fluoroquinolones may affect cartilage development, they have only little clinical use in children [8]. The results of this study showed that, although bacterial clearance rate of the observation group was higher than that of the control group, it was not statistically significant. This may suggest, that *P. aeruginosa* could not be cleared easily. Moreover our results suggest that a goal of clinical treatment should be to improve clinical performance and should not take the PA's clearance as a sign to discontinue antimicrobial agents. In addition, there are reports in a literature [9] showing that macrolide antibiotics were used in patients with chronic lung disease, such as bronchiectasis, congenital bronchial lung cysts, chronic obstructive pulmonary disease and diffuse pan-bronchiolitis.. The clinical efficacy of long course of Pseudomonas aeruginosa for the treatment of lower respiratory tract infections was satisfactory and bacterial clearance rate was high, of which the efficacy and bacterial eradication rate of six months were higher. As for pediatric clinics, long course of Pseudomonas aeruginosa for the treatment of lower respiratory tract infections needs to be further explored. The results of this study showed that adverse reaction rate of the observation group was slightly higher than that of the control group, but it was not statistically significant. The adverse reactions of the observation group were mainly gastrointestinal symptoms, which may be related to the gastrointestinal reactions of macrolide antibiotics in children. The adverse reactions disappeared with an increase of adjuvant treatment. In summary, these studies suggest that, a combination of macrolide antibiotics with cefoperazone/sulbactam in the treatment of *Pseudomonas aeruginosa* pneumonia in children can be an effective and safe clinical method.

5 Conclusions

The combined application with macrolide antibiotics to treat *Pseudomonas aeruginosa* pneumonia in children can be considered as a more effective clinical method.

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