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Intervention of Bacterial Lysate in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract: To study the performance of bacterial lysates in the treatment of acute exacerbation of chronic obstructive pulmonary disease(COPD). 60 patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) admitted in our hospital from November 2020 to June 2021 were prospectively studied. Divide them into two groups at random and received conventional treatment (conventional treatment group, n=30) and conventional treatment combined with bacterial lysate (bacterial lysate group, n=30) respectively. The treatment effect was assessed by the days of hospitalization, symptom scores, lung function, and the number of acute exacerbation readmissions within 6 months. The days of hospitalization was 6.77 (6,7) in the bacterial lysate group and 9.47 (8,10) in the control group, which was significantly lower in the bacterial lysate group than in the conventional treatment group (P=0.000). After treatment during hospitalization, procalcitonin decreased more significantly in the bacterial lysate group than in the conventional treatment group (P=0.024). After six months of treatment, the number of acute exacerbations was 0.90 (0,1) times in bacterial lysate group and 1.57 (1,2) times in conventional treatment group. During hospitalization, there was significant difference in 1-second forced expiratory volume (FEV1) and forced vital capacity (FVC) between the two groups and after 6-month follow-up (P=0.048, P=0.045). After 3 and 6 months of treatment, the scores of symptoms and signs in the bacterial lysate group were lower than those in the conventional treatment group. In the acute exacerbation of COPD, oral administration of bacterial lysates can reduce the number of exacerbations of COPD. shorten the days of hospitalization, improve the quality of life of patients, and delay the decline of lung function.

The COPD is characterized by persistent symptoms and impaired lung function caused by small airway obstruction and alveolar destruction, and is associated with chronic lung inflammation[1]. Acute exacerbation is the main reason for hospitalization in COPD patients, and is also a key risk factor for the progression of COPD disease. It is often manifested as worsening airflow restriction,

further deterioration of lung function, and respiratory failure when severe, which is also an important cause of death in COPD patients, so the prevention of acute exacerbation of COPD is particularly important [2]. Bacterial infection is an important factor causing acute exacerbation of COPD. The disorder of immune response in the course of COPD will increase the risk of bacterial infection, and the over-activation of inflammation after bacterial infection will increase the incidence of multiple organ dysfunction. In recent years, more studies have focused on the relationship between acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and disorders of immune system regulation. Bacterial lysate is an immunomodulator, which is composed of freeze-dried bacterial lysates of eight major respiratory tract infection strains (Klebsiella pneumoniae, Klebsiella ozaenae, Moraxella catarrhalis, Streptococcus viridans Haemophilus influenzae, Streptococcus pyogenes, Streptococcus pneumoniae, and Staphylococcus aureus). There is abundant evidence that bacterial lysates are safe and effective in preventing recurrent respiratory tract infections [3]. Studies have shown that the use of bacterial lysates in stable COPD patients significantly reduces the number of acute exacerbations of COPD [4]. Moreover, bacterial lysates can be used in the adjuvant treatment of acute respiratory tract infection, and whether the application of bacterial lysates in AECOPD patients is beneficial to control the progression of COPD is worth further discussion. In our study, we explored the clinical effects of bacterial lysates on the days of hospitalization, quality of life and times of acute exacerbations of COPD patients, which providing clinical evidence for the treatment of AECOPD patients.

1. Subjects and Methods

1.1. Subjects

From October 2020 to June 2021, There were 60 patients with acute exacerbation of COPD, 50 males and 10 females respectively. The patients were randomly divided into conventional treatment combined with bacterial lysate group (bacterial lysate group) and conventional treatment group (control group) according to computer number. COPD inclusion criteria using the Global Strategy for diagnosis, Treatment, and Prevention of COPD (Revised 2019) [1]. The inclusion criteria of all patients were: (1) patients who met the diagnostic criteria of COPD, (2) patients in group A or group B were selected according to the patient's symptom level and the history of moderate / severe acute exacerbation in the past year, (3) At the same time, patients who meet the diagnostic criteria of acute exacerbation (for example, in addition to routine changes, respiratory symptoms suddenly worsen, the main symptoms are dyspnea, chest tightness, cough, increased sputum volume, sputum color or viscosity changes and fever), and need to be hospitalized for treatment. Exclusion criteria :(1) patients with severe liver and kidney insufficiency, diabetes, bronchial asthma, tuberculosis, malignant tumor and rheumatic immune diseases; (2) Use of immune booster or vaccination within six months; (3) Allergic to the dissolved products of bacteria and other drugs involved in this study or have suspected allergic symptoms; (4) a history of alcohol and drug abuse; (5) The investigator judged that the patient's compliance was poor, and the completion of study treatment and follow-up could not be guaranteed. This study obtained informed consent from patients and was reviewed and approved by the Ethics Committee of Panyu Central Hospital. All subjects signed informed consent.

1.2. Methods

1.2.1. Study Design

General information of patients in each group was collected within 2 hours after admission. Sputum samples of all patients were collected before treatment, and blood routine and other blood tests were carried out, C-reactive protein (CRP) and Procalcitonin (PCT) were completed. Patients in each group received routine antibiotics, bronchodilators, cough suppressant and expectorant drugs. After treatment, infection indicators (total number of white blood cells, neutrophil count, CRP and PCT) were reviewed. The days of discharge were recorded when patients discharged. In the bacterial lysate group, 7mg/d bacterial lysate was added to the conventional treatment, which was continued for 10 days every month and then stopped for 20 days. The course of treatment was 3 months. The control group received routine treatment, and patients in both groups were followed up for 6 months. Patients were followed up at 3 and 6 months of treatment and scored again for symptoms and signs. During the period of acute exacerbation of patients according to the need for the use of antibiotics, glucocorticoids, bronchodilators and other symptomatic treatment.

1.2.2. Observation Index

Table 1: Scoring criteria for patient symptoms and signs

symptoms	Score 0	Score 1	Score 2	Score 3
cough	no cough	occasional cough	Moderate cough	Severe persistent cough
sputum	no sputum	small amount (10~15ml/d)	medium amount (15~50ml/d)	large amount (more than 50ml/d)
dyspnea	no dyspnea	The amount of exercise is equivalent to the breathing state after climbing two floors at medium speed	The amount of exercise is equivalent to the breathing state after walking 100 meters on flat ground	dyspnea after even slight physical movement
pulmonary rales	no rale	Only after coughing and deep breathing can you hear a small amount of rales	dispersed, moderate rales	frequent, massive rales

(1) Days of hospitalization in the acute phase of patients in the two groups. (2) comparison of infection indicators in acute and remission phases. (3) Number of acute exacerbations within 6 months: The acute exacerbation of COPD was judged according to the 2019 Global Strategy for diagnosis, treatment and prevention of COPD standards, and COPD symptoms including exacerbation of shortness of breath, increased cough, increased sputum volume, or combined with fever were recorded using diary cards, and acute exacerbation was judged based on the diagnosis and treatment records. (4) Comparison of lung function during hospitalization and after 6 months of follow-up. The pulmonary function test was conducted by The German Jaeger pulmonary function instrument, and the quality control reached the standards of the American Thoracic Society (ATS). Skilled technicians with unified training were used for the test, using the same observation indicators. Including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1%pred and FEV1/FVC ratio. (5) Evaluation of symptoms and signs: The patients' symptoms and signs were evaluated according to the medication for 3 months at admission and the follow-up for 6 months. The specific scores were shown in Table 1.

1.3. Statistical Analysis

SPSS 24.0 statistical software was used for data analysis. The measured data of normal distribution is expressed as $\bar{x} \pm s$, and compare the two groups of subjects with independent sample

t-test. If the measured data do not conform to the normal distribution, it is expressed as the median (quartile), and the Mann-Whitney U test is used for the comparison between groups. The statistical data are expressed by constituent ratio, and the comparison between groups is adopted $\chi 2$ inspection. $P < 0.05$ was considered statistically significant.

2. Results

2.1. Baseline Clinical Data of Patients in the Two Groups

There were 60 patients who reached the standard, including 30 in the bacterial lysate group and 30 in the control group.The mean age of patients in the bacterial lysate group was (71.6±9.6) years old, and there were 25 males (83.3%), 13 patients in group A and 17 patients in group B. The above indexes in the control group were (73.8±9.5) years old, 25 males (83.3%). There were 12 cases in group A and 18 cases in group B. There were no significant differences in age, sex, COPD group, lung function indicators (FEV1, FVC, FEV1/FVC, FEV1%) and infection indicators (white blood cells, neutrophils, CRP and PCT) between the two groups (Table 2, P>0.05).

Table 2: Comparison of baseline characteristics between the two groups

	bacterial lysate group	control group
n	30	30
Sex (Male:Female)	25:5	25:5
Age (years)	71.6±9.6	73.8±9.5
COPD group		
group A	13	12
group B	17	18
FVC (L)	1.83±0.68	1.84±0.46
FEV1 (L)	0.82±0.24	0.84±0.23
FEV1%	38.97±11.52	43.45±11.30
FEV1/FVC	47.93±11.95	47.53±12.47
White blood cells (10^9/L)	11.74 (7.97,13.64)	11.69 (7.34,14.32)
Neutrophils (10^9/L)	9.69 (5.37,12.87)	9.75 (5.21,13.23)
C-reaction protein(mg/L)	82.23 (11.32,117.43)	87.85 (12.57,138.54)
Procalcitonin (ng/ml)	0.77 (0.05,1.04)	0.94 (0.08,1.92)

Data are presented as mean±SEM or median (quartile); FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

2.2. Comparison of Hospitalization Days of Acute Exacerbation and the Number of Acute Exacerbations within Six Months between the Two Groups During Follow-up

Our results showed that the length of hospital stay in the bacterial lysate group was significantly lower than that in the control group. In half a year, the number of acute exacerbations in the bacterial lysate group and the control group were 27 and 47, respectively. During the six-month

follow-up period, the number of acute exacerbations in the bacterial lysate group was significantly lower than that in the control group [median (quartile): 0.90 (0,1) and 1.57 (1,2)), with a statistically significant difference (Table 3).

Table 3: Comparison of the number of days in hospital and the number of acute exacerbations within six months between the two groups

Group	Days of acute exacerbation in hospital	Number of acute exacerbations within 6 months
bacterial lysate group	6.77 (6, 7)	0.90 (0, 1)
control group	9.47 (8, 10)	1.57 (1, 2)
P value	0.000*	0.002*

Data are presented as median (quartile). *:The differences in these variables were statistically significant.

2.3. Comparison of Infection Indexes in Acute Phase and Remission Phase between the Two Groups During Hospitalization

After treatment, infection indexes in both groups decreased compared with before treatment. There was no statistical significance in the total number of white blood cells, neutrophils and CRP of patients in the acute stage and remission stage, but PCT of bacterial lysate group Becreased significantly compared with control group. (Table 4, P=0.024)

Table 4: Comparison of infection indexes between two groups before and after treatment during hospitalization

Group	White blood cells	Neutrophils	CRP	PCT
bacterial lysate group	8.43 (5.53,11.07)	6.02 (3.70,8.38)	17.86 (6,89,26.75)	0.15 (0.05,0.05)
control group	8.89 (6.36,12.56)	8.29 (5.53,11.07)	35.50 (4.23,54.82)	0.41 (0.05,0.1)
P value	0.229	0.129	0.291	0.024*

Data are presented as median (quartile). *:The differences in these variables were statistically significant.

2.4. Comparison of Lung Function between the Two Groups

There was no significant difference in lung function (FEV1, FVC, FEV1/FVC, FEV1%) between the two groups (P>0.05). After six months of follow-up, it was found that lung function in both groups had a downward trend, but the decline trend of lung function in the bacterial lysate group was more gentle than that in the control group. The lung function (FEV1 and FVC) in the control group Becreased more obviously, and the difference was statistically significant. (Table 5)

Table 5: Comparison of lung function between the two groups after 6-month follow-up

Group	FEV1	FEV1%	FVC	FEV1 / FVC
bacterial lysate group	0.74±0.20	38.51±10.32	1.79±0.68	44.79±11.53
control group	0.70±0.15	33.59±8.40	1.69±0.41	42.14±0.10.44
P value	0.048*	0.125	0.045*	0.326

Data are presented as mean±SEM. *: The differences in these variables were statistically significant.

2.5. Clinical Symptom and Signs of the Two Groups

All patients were evaluated by symptom score and lung rale score before treatment and 3 and 6 months after treatment. The results showed that there was no significant difference in the scores of symptoms and signs between the two experimental data before treatment, but there was significant difference in the scores of symptoms and signs such as cough and expectoration. After 3 months of treatment and 6 months of follow-up, dyspnea and pulmonary rales occurred in both groups. (Table 4).

Table 6: Comparison of symptom and sign scores between the two groups

Group	n	cough			sputum			dyspnea			pulmonary rales		
		Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment	Before treatment	3 months after treatment	6 months after treatment
bacterial lysates group	30	1.97± 0.41	1.13± 0.51	1.10± 0.40	1.76± 0.57	1.13± 0.50	1.20± 0.41	2.70± 0.47	1.66± 0.48	1.63± 0.49	2.40± 0.56	0.80± 0.48	0.70± 0.47
control group	30	2.10± 0.40	1.57± 0.50	1.50± 0.51	1.83± 0.53	1.56± 0.50	1.36± 0.49	2.73± 0.45	1.96± 0.49	1.93± 0.45	2.37± 0.61	1.26± 0.64	1.07± 0.45
t value		1.265	3.319	3.378	0.470	3.319	1.433	0.282	2.397	2.470	-0.219	3.186	3.101
P value		0.60	0.037 *	0.000 *	0.419	0.037 *	0.006 *	0.575	0.025 *	0.004 *	0.626	0.049 *	0.028 *

Data are presented as mean±SEM. *:The differences in these variables were statistically significant.

3. Discussion

COPD is a common disease of chronic inflammation of the respiratory system, characterized by chronic inflammation of the airway, with high morbidity and mortality [5]. Studies showed that COPD patients had humoral immunity and cellular immunity dysfunction, which led to low immune function in COPD patients, and bacterial, viral and other infections form a vicious cycle, causing repeated exacerbations. Acute exacerbation usually leads to rapid decline of pulmonary function, poor prognosis, impaired quality of life and increased socio-economic costs in patients with COPD. Many studies have shown that preventing acute exacerbation can slow down the progress of COPD [6]. The results showed that when COPD patients were acutely aggravated, Compared with the control group, the hospital stay after oral bacterial lysate was significantly shorter, and the number of acute exacerbations within half a year was reduced, also the symptom scores were improved compared with the control group. Therefore, oral bacterial lysates in patients with acute COPD could effectively prevent acute exacerbation of COPD. This might be related to the fact that bacterial lysates could stimulate or activate specific somatic cells of the immune system,

induce human cell and humoral immunity, enhance the number and activity of immune cells in the body, improve the content of immunoglobulin IgA, and then enhance human immunity, prevent respiratory tract acute infection, so as to reduce COPD acute exacerbations.

In the study, we found that oral bacterial lysates during acute exacerbations of COPD could shorten the length of hospitalization, help control infection, and improve the prognosis of COPD patients, which was consistent with previous findings [7]. In addition, we found that the number of acute exacerbations in the bacterial lysate group was significantly less than that in the control group within six months, indicating that the bacterial lysate has a good auxiliary effect on the treatment of COPD, which may be related to the immune enhancement effect of bacterial lysate. After oral administration of bacterial lysates, the resulting antigen is taken up by M cells in the intestinal tract through endocytosis and interacts with Toll-like receptors on the surface of dormant monocytes in the intestinal tract to stimulate the differentiation of monocytes into mature dendritic cells. The presentation of bacterial antigens by dendritic cells leads to activation of T and B cells, which differentiate into various mature T cells, including Th17, which mediates inflammatory response, and Treg, which mediates immune tolerance. At the same time, B cells differentiate into mature plasma cells, which convert active IgM positive B cells into IgA positive B cells and increase IgA secretion. Thus, it plays an important role in anti-respiratory tract infection [4, 8, 9]. Studies had shown increased serum and secretory IgA levels, which coincided with the treatment cycle of bacterial lysates, and this increased pattern suggested that the risk of virus and bacterial infection of COPD was reduced due to the local mucosal immune response caused by bacterial lysates treatment [10]. At the same time, Mauel et al. found that bacterial lysates could increase the production of superoxide and nitrite anions in alveolar macrophages and enhance the microbicidal and cytolytic activities [11].

The symptoms of dyspnea in patients with acute exacerbation of COPD worsen, resulting in rapid decline of pulmonary function and even respiratory failure [12]. Due to poor tolerance of hypoxia in COPD patients, improving lung function plays a key role in the prognosis of COPD patients. We found that the decline trend of lung function in the bacterial lysate group was delayed compared with the control group, indicating that bacterial dissolution products could help improve lung function and prognosis of COPD patients. This is completely consistent with the result of Jing Li et al [13].

At the same time, it was also found in our study that infection indexes of patients in both groups decreased significantly after remission during hospitalization. However, compared with the control group, white blood cells, neutrophils and CRP of patients in the bacterial lysate group showed no significant difference, while PCT decreased significantly. Although white blood cells, neutrophils and CRP all reflected the level of acute inflammation in COPD patients, there were many factors affecting CRP, white blood cells and neutrophils. The results showed that there was no significant difference in CRP concentration in patients with COPD. These results indicated that CRP concentration in blood of patients in acute exacerbation phase did not increase significantly with the progression of the disease, nor was related to the frequency of acute exacerbation [14]. Specificity of PCT for predicting bacterial infection in AECOPD was 71%, while the specificity of CRP was 62% [15, 16]. Therefore, PCT shows high diagnostic value in the diagnosis and identification of bacterial respiratory infection in patients with AECOPD [17]. Due to the limited number of cases in our study, we could not exclude the influence of other factors or the insufficient number of cases.

In conclusion, through clinical observation of two groups of acute exacerbation COPD patients, it can be learned that oral bacterial lysates in acute exacerbation COPD patients can shorten the days of hospitalization, and reduce the number of acute exacerbations within half a year, improve

COPD patients' symptoms and signs score, and have a certain effect on slowing the progression of the disease. At the same time, this study had certain limitations. This is a limited number of clinical cases. The observation time was short, and there were only two groups of experimental subjects. In the future, further studies will expand the study cases and extend the observation period to observe the long-term efficacy.

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References

[1] Singh, D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J, 2019. 53(5).

[2] Lorenz J, Bals R, Dreher M, et al. Exacerbation of COPD. Pneumologie, 2017. 71(5): p. 269-289.

[3] Troiano, G., G. Messina, and N. Nante. Bacterial lysates (OM-85 BV): a cost-effective proposal in order to contrast antibiotic resistance. J Prev Med Hyg, 2021. 62(2): p. E564-E573.

[4] Ricci, R., Palmero C, Bazurro G, et al. The administration of a polyvalent mechanical bacterial lysate in elderly patients with COPD results in serological signs of an efficient immune response associated with a reduced number of acute episodes. Pulm Pharmacol Ther, 2014. 27(1): p. 109-13.

[5] Rabin AS, Keyes CM, Oberg CL, et al. Emerging Interventional Pulmonary Therapies for Chronic Obstructive Pulmonary Disease. J Thorac Imaging, 2019. 34(4): p. 248-257.

[6] Wilkinson TM, Donaldson GC, Hurst JR, et al. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2004. 169(12): p. 1298-303.

[7] Avdeev, S.N., Nuralieva GS, Gainitdinova VV, et al. Clinical efficacy of mechanical bacterial lysate in the prevention of infectious exacerbations of chronic obstructive pulmonary disease. Ter Arkh, 2020. 92(4): p. 57-63.

[8] Lusuardi, M., Challenging mucosal immunity with bacterial extracts to prevent respiratory infections: an old therapy revisited. Monaldi Arch Chest Dis, 2004. 61(1): p. 4-5.

[9] Lusuardi M, Capelli A, Carli S, et al. Local airways immune modifications induced by oral bacterial extracts in chronic bronchitis. Chest, 1993. 103(6): p. 1783-91.

[10] Koatz AM, Coe NA, Cicerán A, et al. Clinical and Immunological Benefits of OM-85 Bacterial Lysate in Patients with Allergic Rhinitis, Asthma, and COPD and Recurrent Respiratory Infections. Lung, 2016. 194(4): p. 687-97.

[11] Mauel J, Van Pham T, Kreis B, et al. Stimulation by a bacterial extract (Broncho-Vaxom) of the metabolic and functional activities of murine macrophages. Int J Immunopharmacol, 1989. 11(6): p. 637-45.

[12] Ritchie, A.I. and J.A. Wedzicha, Definition, Causes, Pathogenesis, and Consequences of Chronic Obstructive Pulmonary Disease Exacerbations. Clin Chest Med, 2020. 41(3): p. 421-438.

[13] Jing Li, Jinping Zheng, Jinping Yuan, et al. Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive

pulmonary disease. Chinese Medical Journal,2004(06):28-34.
[14] Pinto-Plata VM, Müllerova H, Toso JF, et al. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax, 2006. 61(1): p. 23-8.
[15] Ni W, Bao J, Yang D, et al. Potential of serum procalcitonin in predicting bacterial exacerbation and guiding antibiotic administration in severe COPD exacerbations: a systematic review and meta-analysis. Infect Dis. 2019. 51(9): p. 639-650.
[16] Pázmány P, Soós A, Hegyi P, et al. Inflammatory biomarkers are inaccurate indicators of bacterial infection on admission in patients with acute exacerbation of chronic obstructive pulmonary disease-a systematic review and diagnostic accuracy network meta-analysis. Front Med (Lausanne), 2021. 8: p. 639794.
[17] Tanrıverdi H, Örnek T, Erboy F, et al. Comparison of diagnostic values of procalcitonin, C-reactive protein and blood neutrophil/lymphocyte ratio levels in predicting bacterial infection in hospitalized patients with acute exacerbations of COPD. Wien Klin Wochenschr, 2015. 127(19-20): p. 756-63.