Antibiotic de-escalation principle in elderly patients with chronic obstructive pulmonary disease complicated with severe pneumonia

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Abstract. The present study investigated the clinical effect of antibiotic de-escalation therapy in elderly patients with chronic obstructive pulmonary disease (COPD) complicated with severe pneumonia. According to the parity method of hospitalization number, 86 cases were selected and divided into the observation and control group with 43 cases each. Based on empirical antibiotic application, levofloxacin and cephalosporin antibiotics were used in the control group. After treatment for 3 days, the regimen was adjusted to antibiotics active against Gram-positive (G+) and Gram-negative (G-) bacteria such as the third or fourth generation cephalosporin antibiotics, combined with aminoglycoside, or macrolide antibiotics according to their effects. The treatment effects were re-evaluated after 3-7 days. Finally, broad-spectrum antibiotics such as imipenem were chosen or adjusted by bacterial cultures and drug sensitivity results in the control group. Patients in the observation group were treated according to the principle of antibiotic de-escalation therapy. Antibiotics active against G+ and G- bacteria were chosen as the first round of medication. After 3 days, broad-spectrum antibiotics such as imipenem were added to the treatment regimen. After 7 days, the treatment was changed to narrow spectrum antibiotic administration if the disease was in remission, and the antibiotic regimen was adjusted based on bacterial culture and drug sensitivity results. The treatment results were compared. The mechanical ventilation rate, antibiotic courses, number of antibiotics used, and mortality of the observation group were significantly lower than those in the control group ($P<0.05$). After treatment, lung function improved, partial pressure of oxygen and blood oxygen saturation increased, and partial pressure of carbon dioxide decreased in both groups. The improvement of all of the above parameters were more significant in the observation group ($P<0.05$). After treatment, the ratio of neutrophils over white blood cells and C-reactive protein levels of the two groups decreased, respiratory failure index (RFI) increased, and the changes were significantly more pronounced in the observation group ($P<0.05$). In conclusion, following the antibiotic de-escalation principle to treat older patients with COPD complicated with severe pneumonia can reduce the number of antibiotics required, improve lung function and clinical effects, and is safe and effective.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease. The incidence of the disease is on the increase annually. The disease is characterized by limitations in airflow, incomplete reversibility, and is rapidly progressive. It is the leading cause of respiratory failure. COPD is caused and aggravated by bacterial pneumonia, especially severe pneumonia (1). With the increasing age of the population in China, COPD with severe pneumonia has become an important cause of mortality (2). The associated clinical symptoms include septic shock and multiple organ dysfunction.

The rational use of antibiotics is key to treatment, and is important for inhibiting bacterial reproduction and controlling progression of the disease. However, antibiotics are also the main cause of bacterial resistance and corresponding decrease in effectiveness of treatment (3). Mutations in bacterial genes are an important cause of bacterial resistance (4). According to statistics (5) on COPD with pneumonia, after 10-14 days of antibiotics application, the rate of relief of clinical symptoms was 50-75%, and the rate of bacterial resistance was 5-10%. Although antimicrobial susceptibility tests can help select sensitive antibiotics, long training cycles and hysteresis of clinical application limit the application value. Based on this, the antibiotic de-escalation principle emphasizes early coverage of the bacterial spectrum, adequate sterilization, timely sensitivity enhancement, and reduction in resistance, which significantly improves the treatment efficiency and shortens the treatment course (6,7).

The present study followed the antibiotic de-escalation principle to treat elderly patients with COPD complicated with

severe pneumonia, to provide a reference for the rational use of antibiotics in clinic.

Patients and methods

Patients. A total of 86 elderly patients who were hospitalized and diagnosed with COPD combined with severe pneumonia from January, 2015 to January, 2016 were consecutively selected. The inclusion criteria were: i) Conforming to the diagnostic criteria of COPD and severe pneumonia, ii) able to provide samples of sputum and blood for bacterial culture, iii) sensitive to currently available antibiotics, and iv) achieved effective clinical treatment. The exclusion criteria included: i) Respiratory failure, consciousness disorder, severe disease condition, and expected survival time of <1 month, ii) combined with other lung diseases, such as bronchiectasis, lung cancer, and tuberculosis, iii) underlying diseases such as heart, brain, liver, kidney, and other organ dysfunctions and iv) allergic to antibiotics.

The present study obtained approval of the Ethics Committee of The Affiliated Hospital of Qingdao University (Shandong, China) and informed consent of patients and their families. According to the parity method of hospitalization number, patients were divided into control and observation groups, with 43 cases each. Baseline parameters of patients in the two groups were comparable (Table I).

Research methods. Patients in the two groups underwent routine examinations, including liver and renal functional tests, routine blood tests, blood gas analysis, and antibiotic sensitivity tests. The medical history and history of use of antibiotics were noted and the conditions of patients were comprehensively assessed. The patients received targeted treatment according to the results of assessment. Based on empirical application of antibiotics, patients in the control group were treated with levofloxacin and cephalosporin. Patients in this group received 200 mg levofloxacin two times per day, and 2 g cefoperazone sulbactam three times per day. Three days later, if treatment was effective, the treatment regimen continued. If the effect was poor, the regimen was adjusted and the next round of medication was chosen. Antibiotics active against Gram-positive (G+) and Gram-negative (G-) bacteria, such as third or fourth generation cephalosporin antibiotics combined with aminoglycoside, or macrolide antibiotics were chosen. After 3-7 days the effect of treatment was re-evaluated. If effective, the original regimen was continued, and if the effect was poor, the regimen was adjusted. Broad-spectrum antibiotics such as imipenem were chosen, or bacterial cultures and drug sensitivity tests were performed to adjust the treatment regimen.

Patients in the observation group were treated according to the principle of antibiotic de-escalation therapy. Antibiotics active against G+ and G- bacteria such as piperacillin, ceftriaxone sodium, and ciprofloxacin were chosen as the first round of medication. For inefficient cases, 3 days later, broad-spectrum antibiotics, such as imipenem, were administrated as supplement. After remission of symptoms for 7 days, the treatment was changed to narrow spectrum antibiotics, and bacterial cultures and drug sensitivity results were combined to adjust the antibiotic regimen. The patients were given symptomatic treatment, such as combined mechanical ventilation,

Table I. Baseline parameters of patients in the two groups.

Group	No. of cases	M/F	Age, years	Course of disease, year	Smoking	Hypertension	Diabetes	Mild COPD	Moderate	Severe	PRSP	*Klebsiella pneumoniae*	*Staphylococcus*	Other
Control	43	23/20	72.6±10.3	5.2±2.4	10 (23.3)	12 (27.9)	8 (18.6)	8 (18.6)	29 (67.4)	6 (14.0)	20 (46.5)	10 (23.3)	10 (23.3)	3 (7.0)
Observation	43	24/19	73.2±14.5	5.3±2.3	12 (27.9)	11 (25.6)	9 (20.9)	6 (14.0)	30 (69.8)	7 (16.3)	18 (41.9)	12 (27.9)	11 (25.6)	2 (4.7)
t/χ^2		0.047	0.126	0.251	0.244	0.059	0.073		0.380			0.536		
P-value		0.829	0.724	0.628	0.621	0.808	0.787		0.827			0.911		

M, male; F, female; COPD, chronic obstructive pulmonary disease.

Table II. Comparison of mechanical ventilation usage, course of antibiotic treatment, number of antibiotics used, and mortality rate.

Group	No. of case	Mechanical ventilation usage [case (%)]	Course of antibiotic treatment (days)	No. of antibiotics	Mortality rate [case (%)]
Control	43	26 (60.5)	16.2±3.4	5.6±0.8	13 (30.2)
Observation	43	16 (37.2)	10.6±2.3	3.4±0.6	5 (11.6)
t/χ^2		4.654	5.245	5.728	4.497
P-value		0.031	0.026	0.023	0.034

Table III. Comparison of pulmonary function improvement.

	FEV1 (%)		FEV1/FVC (%)		FVC (l)		PEER (l/sec)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	52.6±7.2	63.8±6.5	62.3±8.3	70.5±10.2	1.2±0.5	1.7±0.7	2.0±0.6	3.3±0.8
Observation	50.8±7.3	71.8±7.4	63.4±9.0	77.2±11.5	1.1±0.6	2.3±0.8	2.1±0.8	3.9±0.7
t-test	0.123	5.293	0.326	5.627	0.162	5.168	0.324	5.524
P-value	0.864	0.030	0.724	0.023	0.827	0.032	0.627	0.028

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; PEER, maximum expiratory flow rate.

Table IV. Comparison of blood gas index improvement.

	PaO_2 (mmHg)		$PaCO_2$ (mmHg)		SpO_2 (%)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	56.2±6.8	76.6±8.6	69.8±7.8	55.7±9.3	86.9±5.3	92.7±4.6
Observation	54.8±6.6	82.3±7.3	70.2±7.9	42.3±8.6	84.7±5.5	96.4±6.5
t-test	0.524	5.632	0.426	6.328	0.965	6.258
P-value	0.632	0.025	0.721	0.013	0.214	0.015

PaO_2, partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; SpO_2, blood oxygen saturation.

rehydration, nutritional support, and airway management. Adverse reactions, such as allergies, liver and kidney functional damage, and ototoxicity were monitored during the treatment.

Observational indicators and evaluation criteria. The rate of mechanical ventilation, course of antibiotics, number of antibiotics used, and mortality of the two groups were compared. Improvements of lung function, including forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), FEV1/FVC, and maximum expiratory flow rate (PEER) were compared. Improvements in blood gas indexes, including arterial partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), and blood oxygen saturation (SpO_2) were compared. Curative effects, including the ratio of peripheral blood neutrophils and white blood cells (N/WBC), the ratio of respiratory failure index (RFI) (PaO_2) and FiO_2 (inspired oxygen concentration) (PaO_2/FiO_2 = RFI) were compared as well as C-reactive protein (CRP) levels.

Statistical analysis. SPSS 19.0 (IBM SPSS, Armonk, NY, USA) software was used for statistical analysis. The measurement data are presented as mean ± standard deviation. Comparisons between and within groups were all conducted by t-test. Countable data are presented as rate and tested by χ^2; ranked data comparisons were tested by sum of ranks. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of mechanical ventilation usage, course of antibiotic treatment, number of antibiotics used, and death rate. Mechanical ventilation usage, course of antibiotic treatment, the number of antibiotics used, and death rate of the observation group were lower than those of the control group, and the differences were statistically significant ($P<0.05$) (Table II).

Table V. Comparison of clinical curative effect.

	N/WBC (%)		RFI (mmHg)		C-reactive protein (mg/l)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	82.3±10.6	72.5±9.6	326.5±24.6	432.5±63.8	13.6±5.4	8.2±1.2
Observation	84.6±13.4	64.2±8.5	316.4±30.5	465.9±56.6	14.3±5.7	6.3±1.4
t-test	0.562	6.207	0.562	6.259	0.148	6.532
P-value	0.648	0.022	0.428	0.020	0.629	0.010

N/WBC, neutrophils and white blood cells; RFI, respiratory failure index.

Comparison of pulmonary function improvement. Comparing the FEV1, FVC, FEV1/FVC, and PEER between the two groups before treatment, the differences were not statistically significant (P>0.05). The above parameters of the two groups were significantly increased after treatment. Furthermore, the improvements in these parameters in the observation group were more pronounced, and the differences were statistically significant (P<0.05) (Table III).

Comparison of blood gas index improvement. Comparing PaO_2, $PaCO_2$ and SpO_2 between the two groups before treatment, the differences were not statistically significant (P>0.05). PaO_2 and SpO_2 of the two groups increased after treatment, while $PaCO_2$ decreased. Furthermore, the improvements were more pronounced in the observation group, and the differences were statistically significant (P<0.05) (Table IV).

Comparison of clinical curative effect. Comparing N/WBC, RFI, and CRP between the two groups before treatment, the differences were not statistically significant (P>0.05). N/WBC and CRP of the two groups significantly decreased after treatment, while RFI increased. Furthermore, the observation group had more pronounced improvements, and the differences were statistically significant (P<0.05) (Table V).

Discussion

The current status of COPD in elderly patients. COPD is primarily caused by type B *Haemophilus* influenza, *Streptococcus pneumonia* and *Staphylococcus aureus*. COPD is characterized by apoptosis of alveolar epithelial cells, vascular remodeling, structural damage, complications of airway infection, and severe pneumonia (8). The incidence of COPD is relatively higher in the older population. The course of disease is long, which causes weakness, respiratory failure, decline of immune function, and decrease of tolerance to various drugs. COPD combined with nosocomial pneumonia is very common, and is difficult to treat effectively.

Application of antibiotics. COPD complicated with severe pneumonia is usually treated with broad-spectrum antibiotics, such as the third generation of cephalosporins, and levofloxacin. Antibiotics are widely used, and their use is abused. Approximately 30% of patients worldwide have succumbed because of drug resistance caused by irrational drug use (9). The rate of use of antibiotics in China is significantly higher than the recommended rate used internationally. The overuse of antibiotics is one of the most serious public health problems in China. The abuse of antibiotics has resulted in the appearance and spread of multidrug resistant and pandrug resistant strains of bacteria (10). Although empirical antibiotic application effectively controlled COPD in the short-term, with the recurrent attacks of the disease, increased frequency of use of antibiotics, and prolonged medication time, a large number of sensitive strains could not be selectively killed. Simultaneously, drug-resistant strains appear and reproduce to replace sensitive strains, which increases the incidence of drug resistance, adverse reactions, and complications. Consequently, pulmonary infection is difficult to control effectively, the course of disease will be delayed, and may even lead to mortality (11).

The importance of the de-escalation principle. The disease conditions of patients with COPD complicated with severe pneumonia progress rapidly. If no antibiotics are effective in the early treatment period, there will be a delay in recovery. Antibiotic resistance was associated with β-lactamase, which negated its effects (12). In the stage of early delay, rapid disease progression can change the target proteins on cell membranes, and reduce the affinity between the antibiotic and its binding site, so that antibiotics cannot bind. The following antibiotic failure and double infection make the conditions of the patients improve slowly (13). Therefore, in clinical practice, if the infection persists, the condition becomes worse after the improvement, which proves to be the improper choice of antibiotics. The de-escalation principle emphasizes early and comprehensive coverage of possible pathogens, uses one-step principle of the broad-spectrum antibiotics to inhibit G+ and G- pathogens, and combines sensitive antibiotics to adjust the regimen after control of the disease (14,15). The de-escalation principle not only avoids bacterial resistance, reduces the production of resistant strains and microflora disorders, but also reduces the incidence of adverse reactions in patients, shortens the time of treatment, and achieve favorable prognosis (16).

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