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# Protective effect of a bacterial extract against acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease

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**Background** Immunostimulating agents made from bacterial extracts represent a class of medications that contains antigens derived from several bacterial strains and their potential ability to prevent bacterial infections results from the stimulation of the nonspecific component of the immune system. The present study investigated the effect of the oral immunostimulant Broncho-Vaxom, which includes material from eight different species of bacteria that are frequently present in the lower respiratory tract, on the frequency and severity of acute exacerbation in patients with chronic bronchitis accompanied by chronic obstructive pulmonary disease (COPD).

**Methods** Ninety patients with chronic bronchitis complicated with COPD were randomly divided into groups A and B. Forty-nine subjects in group A received oral capsules containing 7mg Broncho-Vaxom, while 41 patients in group B received similar placebo capsules. Both groups took one capsule daily for the first 10 days of each month for 3 consecutive months. The frequency of acute exacerbation, symptom scores, and lung function were recorded for the following one year period.

**Results** There was a significant decrease in the incidence, duration, and severity of acute exacerbation, as well as a reduction in the course of antibiotics administered and in the dosage of bronchodilator and mucolytic agent in group A, as compared to group B ($P<0.05$, respectively). Symptom scores for cough, sputum, dyspnea, as well as symptoms observed upon auscultation of the chest also improved significantly in group A as compared to group B ($P<0.05$, respectively). The bacterial clearance rate in sputum cultures from patients who received no antibiotics for the first 3 months was also significantly higher in group A compared to group B ($P<0.01$).

**Conclusions** Orally administered Broncho-Vaxom is associated with a decrease in the incidence of acute exacerbation and a decrease in the need for antibiotics and symptomatic relief medications in patients with chronic bronchitis accompanied by COPD. Broncho-Vaxom is also associated with a decrease in symptom scores. Without causing any apparent adverse effects, this drug may also help to eradicate pathogenic bacteria in the airways.

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Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases.[1] In most cases, COPD develops from chronic bronchitis (CB), in which respiratory tract infections (RTIs) are the most frequent factors contributing to acute exacerbations. ibiotics are considered to be effective in the agement of these infections. However, repeated and/ has led to the development of genetic mutations in pathogens, resulting in some common bacteria becoming insensitive or resistant to antibiotics. In 1994, European countries were found to

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have a 64% prevalence of penicillin-resistant *Pneumococci*, up from 13% in 1988. Of these *Pneumococci*, 64.5% had gained resistance to multiple antibiotics.[2] One recent epidemiological study on the prevalence of drug-resistant *Streptococcus pneumoniae* in Chinese children from four different cities[3] showed that penicillin-resistant *Streptococcus pneumoniae* had an average prevalence of 41% (25.9% - 60.8%) in the period 2000 to 2001. Li et al[4] analyzed 36 179 hospitalized patients between 1999 and 2000 and found that 169 (0.47%) were infected with *Klebsiella pneumoniae*. Of the 169 isolates, 166 (98.2%) were resistant to at least one antimicrobial agent and 91.1% to two or more antibiotics, with 98% of cases found to be ampicillin-tolerant. On the other hand, antibiotics are effective only on acute infections, and not protective against relapses. It is, therefore, important to improve immune function in CB patients in order to prevent acute RTIs.

Broncho-Vaxom (OM-85 BV, OM Pharma, Switzerland) is a lyophilized extract from 8 bacterial species frequently responsible for lower RTIs: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Streptococcus viridans*, and *Moraxella catarrhalis*. The main ingredients of OM-85 include lipoproteins, glycoproteins, and ribonucleic acids (data from OM Pharma, Switzerland). As an oral immunostimulant, OM-85 BV enhances cellular immunity, increases the level of cytokines and secretory IgA, and activates the airway macrophages by stimulating mucosa-associated lymphoid tissue.[5,6]

Although trials using OM-85 BV involving basic and animal research as well as clinical studies started as early as in 1980,[5,7-9] most of these studies focused on the treatment efficacy of OM-BV for CB, while little effort has been exerted to observe its protective effect against acute exacerbation in COPD patients.[9] To our knowledge, there have been no clinical studies, in particular, no randomized and double-blinded trials, of OM-85 reported in China. Therefore, we conducted a randomized, double-blinded, placebo-controlled multicenter study to investigate the benefits of OM-85 BV in the prophylaxis of acute exacerbation in CB patients accompanied by COPD.

## METHODS

### Patients

Ninety patients from the Guangzhou Institute of Respiratory Disease and the First People's Municipal Hospital of Guangzhou, aged 55 - 82 years, consisting of 49 males and 41 females, were included in this study. All of them fulfilled the case definition and diagnostic criteria of CB and COPD defined by the Fifth National Symposium of the Chinese Respirology Society. The patients were randomly chosen to receive Broncho-Vaxom [group A, n = 49, 27 males and 22 females, aged (67 ± 4) years] or a placebo [group B, n = 41, 22 males and 19 females, aged (65 ± 5) years]. All patients had a history of cigarette smoking and had suffered acute exacerbations of COPD requiring hospitalization and repeated antibiotic therapy during the year prior to our trial, but were free of acute episodes or lower RTIs during the 4 weeks before the trial. In all patients enrolled in our study, none had received immunostimulants during the previous 3 months, none had used systemic corticosteroids during the previous 4 weeks, and none suffered from complications of serious cardiopulmonary, hepatic, or renal diseases or from respiratory failure. The two experimental groups were comparable to each other in their clinical profiles, as determined statistically (Table 1).

**Table 1.** Clinical profiles of the two groups (mean ± SD)

| | Group A | Group B | *P* value |
|---|---|---|---|
| Cases | 49 | 41 | >0.05 |
| Gender (Male/Female) | 27/22 | 22/19 | >0.05 |
| Age (years) | 67 ± 4 | 65 ± 5 | >0.05 |
| Cigarette smoking (packs per year) | 22.7 ± 3.5 | 21.3 ± 2.4 | >0.05 |
| Percent of patients who still smoke (%) | 38.6 ± 3.7 | 41.8 ± 4.6 | >0.05 |
| History of chronic bronchitis (years) | 15.3 ± 5.9 | 16.4 ± 6.3 | >0.05 |
| History of dyspnea (years) | 6.8 ± 2.0 | 6.3 ± 2.7 | >0.05 |
| FVC (L) | 1.68 ± 0.37 | 1.70 ± 0.62 | >0.05 |
| Pred (%) | 70.6 ± 24.3 | 73.3 ± 21.5 | >0.05 |
| $FEV_1$ (L) | 1.04 ± 0.51 | 1.03 ± 0.65 | >0.05 |
| Pred (%) | 50.9 ± 21.0 | 53.2 ± 19.7 | >0.05 |
| $FEV_1$/FVC (%) | 69.5 ± 19.8 | 67.2 ± 17.4 | >0.05 |

Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos. FVC: forced vital capacity, $FEV_1$: forced expiratory volume in one second.

### Methods

The patients were clinically stable when enrolled in the trial. When first enrolled, their medical history was recorded, and data from a physical check-up, chest X-ray, pulmonary ventilation function examination, sputum culture, routine blood test, and tests of liver and renal functions were collected for future use. Using random and double-blind method, patients were assigned either to group A, which received daily 7 mg capsules of Bronch-Vaxom, or to group B, which received daily placebo capsules (OM Pharma, Switzerland). All medications were taken in the morning during the first 10 days of each month for three consecutive months. During the one-year follow-up, both groups were additionally treated with oral theophylline sustained-release tablets 400 mg (Protheo®, Schering-Plough, China), beclomethasone dipropionate

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600 μg (Becotide® MDI, GlaxoSmithKline, China), administered using a metered-dose inhaler, and ipatropin/salbutamol (50/120 μg per puff, Combivent® MDI, Boehringer Ingelheim Shanghai Pharm. Co., China) as needed when in dyspnea. Each patient was instructed by senior physicians for proper usage of the metered-dose inhalers. During each episode of acute RTI, second-generation cephalosporins, macrolides, or fluoquinolones were administered, and the dosage of Combivent® MDI was increased, or was combined with the ingestion of myrtol capsules (Gelomyrtol Forte®, Pohl-Boskamp GmbH & Co., Hong Kong, China). Each patient kept a morning diary card recording his/her daily medication and symptom scores of cough, sputum, and dyspnea. Each patient paid an office visit monthly or whenever suffering from acute exacerbation, defined as worsened dyspnea, deteriorated cough, presence of purulent secretions, or fever.[10] Upon each visit, the patient was examined and his/her pulmonary rales were recorded. The symptoms were scored daily as follows. Cough: 0, no cough; 1, occasional cough, which does not interfere with daily activities; 2, moderate cough, with a tickling sensation in the throat, but which does not interfere with daily activities; and 3, severe persistent cough, which interferes with daily activities and disturbs sleep at night. Sputum: 0, no sputum; 1, small amount (10 – 15 ml) expectorated per day; 2, medium amount (15 – 50 ml) expectorated per day; and 3, large amount (more than 50 ml) expectorated per day. Dyspnea: 0, no dyspnea; 1, dyspnea following an amount of exercise equivalent to going up two floors at medium pace; 2, dyspnea following an amount of exercise equivalent to walking 100 meters on a flat surface; and 3, dyspnea after even slight physical movement. Finally, pulmonary rales were rated as: 0, no rale; 1, few and occasional rales, or rales heard only after coughing and deep breathing; 2, dispersed, moderate rales; and 3, frequent, massive rales.

All patients were evaluated before treatment and at 3, 6, and 12 months after treatment for symptom scores, pulmonary rale ratings, incidences of acute exacerbation (number of episodes, duration, and severity), use of antibiotics, need for Combivent® and mucolytic agents, forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$), bacterial clearance rate in the first morning sputum after mouth-rinsing in patients free of antibiotics throughout months 1 to 3, and any possible adverse effects. The severity of acute exacerbation was rated as: ① mild, with the sum of cough + sputum + dyspnea + rale scores ranging from 1 to 4; ② moderate, with the sum of scores ranging form 5 to 8; and ③ ranging from 9 to 12. All data for evaluation were collected in the morning before twelve o' clock.

### Statistical analysis

The results were expressed as mean ± standard deviation (SD) and analyzed with SPSS 10.0 using the self-paired and between-group $t$ test and the chi-square test. Statistical significance was set at $P < 0.05$.

## RESULTS

### Acute exacerbations and the use of antibiotics

After one year of follow-up, patients in group A experienced fewer episodes of acute exacerbation, which also tended to be shorter in duration and less severe, as compared to their condition during the year before the study as well as compared to group B patients, who showed no improvements ($P < 0.01$, respectively). A decrease in the need for antibiotics was also observed in group A ($P < 0.01$, Fig. 1).

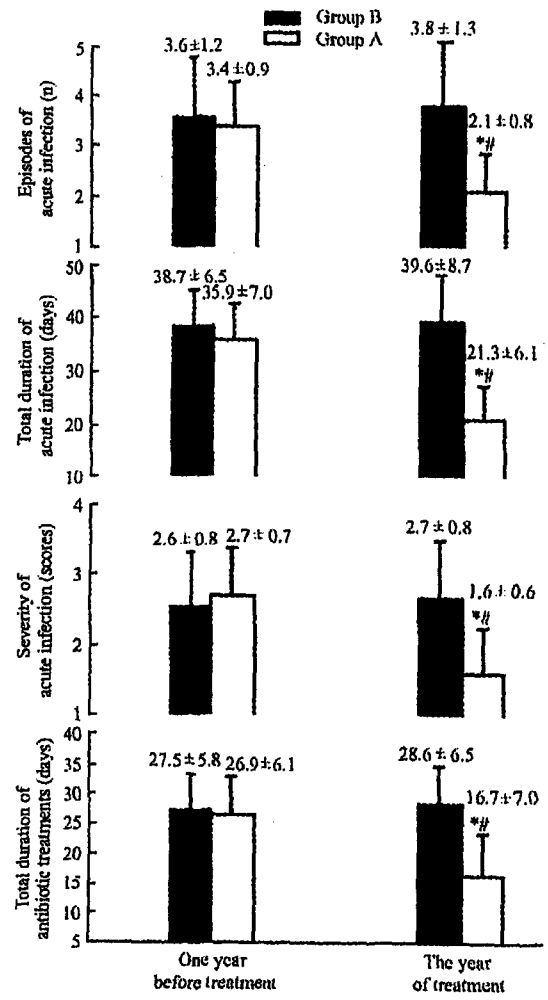


**Fig. 1.** Number of episodes, duration, severity of acute infections, and total days of antibiotic treatment in both groups. Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos. # $P < 0.01$ vs before treatment; * $P < 0.01$ vs group B.

**Table 2.** Use of symptom reduction medications in the two groups (mean ± SD)

| | Before | | Month 3 | | Month 6 | | Month 12 | |
|---|---|---|---|---|---|---|---|---|
| | Group A | Group B | Group A | Group B | Group A | Group B | Group A | Group B |
| [1]Protheo (mg/d) | 400 ± 0 | 400 ± 0 | 400 ± 0 | 400 ± 0 | 400 ± 0 | 400 ± 0 | 400 ± 0 | 400 ± 0 |
| [2]Becotide (μg/d) | 600 ± 0 | 600 ± 0 | 600 ± 0 | 600 ± 0 | 600 ± 0 | 600 ± 0 | 600 ± 0 | 600 ± 0 |
| [3]Combivent(puff/d) | 10.1 ± 2.4 | 9.8 ± 1.7 | 7.1 ± 3.4* | 8.9 ± 2.6 | 7.0 ± 2.6* | 8.3 ± 2.5 | 7.6 ± 2.2* | 9.0 ± 2.3 |
| [4]Gelomyrtol Forte (g/d) | 0.81 ± 0.4 | 0.85 ± 0.2 | 0.43 ± 0.2** | 0.89 ± 0.4 | 0.45 ± 0.1* | 0.87 ± 0.3 | 0.62 ± 0.2 | 0.7 ± 0.1 |

[1] Theophylline sustained-release tablets; [2] beclomethasone dipropionate, administered by metered-dose inhaler; [3] ipatropin/salbutamol, administered by metered-dose inhaler; [4] myrtol capsules. Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos. $*P<0.05$, $**P<0.01$ compared with group B.

### Clinical symptoms and signs

As compared to group B, the group receiving Broncho-Vaxom showed significant improvements in symptoms of sputum expectoration, assessed 3, 6, and 12 months post-treatment ($P < 0.01$, respectively); cough and pulmonary rales, assessed in months 3 and 12 ($P < 0.05$, respectively); and dyspnea, assessed in month 12 ($P<0.05$, Fig. 2).

### Use of symptom reduction medications

The total use of Combivent® MDI and Gelomyrtol Forte® was less in group A than that in group B at 3, 6, and 12 months post-treatment ($P<0.05$, respectively, Table 2).

### Pulmonary ventilation function

There was no improvement in patients from either group with regard to pulmonary ventilation function both and at 3, 6, and 12 months after treatment ($P > 0.05$, respectively, Table 3).

### Results of sputum culture

The positive rate of sputum bacterial culture in group A was 37.3%, as compared to 36.8% in group B, with no significant difference between the two values. In month 3, 18 patients (36.7%) from group A and 5 patients (12.2%) from group B were free of antibiotic therapy ($P < 0.05$). The results of sputum bacterial cultures both before treatment and 3 months after treatment among these antibiotic-free patients are presented in Table 4. Sixteen of the 18 patients in group A had positive sputum cultures before treatment, and 15 of them had fewer bacterial colonies or became germ-negative after the 3-month treatment with Broncho-Vaxom. On the contrary, the 5 patients in group B with positive bacterial cultures before the trial showed no improvement over the same period of time ($P<0.05$).

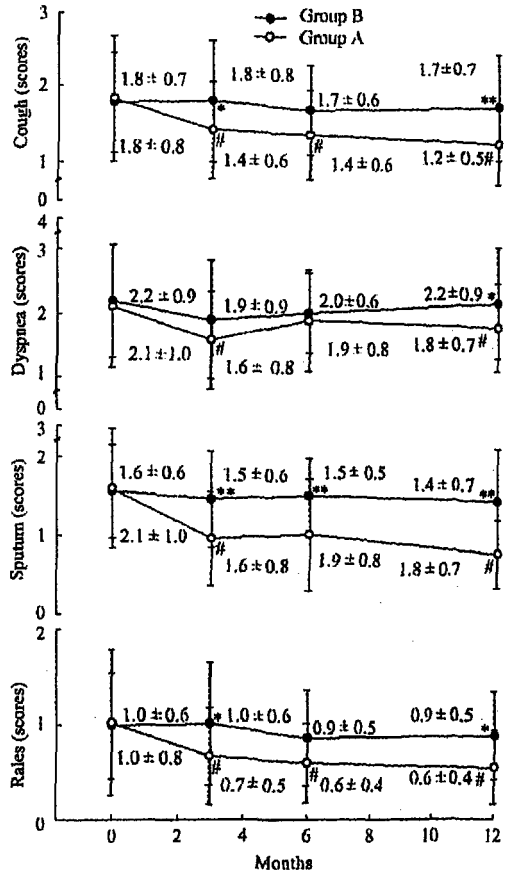


**Fig. 2.** Cough, dyspnea, sputum, and pulmonary rale scores in both groups before and after treatment. Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos. $\#P<0.01$ vs after treatment; $*P<0.05$, $**P<0.01$ vs group A.

**Table 3.** Pulmonary function in both groups before and after treatment (mean ± SD)

| | Before | | Month 3 | | Month 6 | | Month 12 | |
|---|---|---|---|---|---|---|---|---|
| | Group A | Group B | Group A | Group B | Group A | Group B | Group A | Group B |
| FVC (L) | 1.68 ± 0.37 | 1.70 ± 0.62 | 1.73 ± 0.42 | 1.71 ± 0.70 | 1.69 ± 0.41 | 1.70 ± 0.59 | 1.70 ± 0.44 | 1.69 ± 0.65 |
| $FEV_1$ (L) | 1.04 ± 0.51 | 1.03 ± 0.65 | 1.11 ± 0.63 | 1.08 ± 0.71 | 1.05 ± 0.46 | 1.06 ± 0.57 | 1.06 ± 0.54 | 1.04 ± 0.59 |
| $FEV_1$/FVC (%) | 69.5 ± 19.8 | 67.2 ± 17.4 | 68.4 ± 20.7 | 67.6 ± 19.2 | 65.7 ± 17.5 | 67.3 ± 18.8 | 68.3 ± 19.4 | 67.6 ± 19.7 |

Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos. FVC: forced vital capacity, $FEV_1$: forced expiratory volume in one second. The $P$ value for all parameters in the table is greater than 0.05 when group A is compared with group B.

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**Table 4.** Bacterial colonies observed in sputum cultures from antibiotic-free patients of both groups before and three months after treatment with Broncho-Vaxom

| ID | Group A | | | | ID | Group B | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | | Month 3 | | | Before | | Month 3 | |
| | strain | colonies | strain | colonies | | strain | colonies | strain | colonies |
| 14 | *P. Aeruginosa* | $10^5$ | *P. Aeruginosa* | $10^2$ | 29 | *Str mitis* | $10^8$ | *Str viridans* | $10^8$ |
| 16 | *A. lwoffi* | $10^8$ | *negative* | | 56 | *N. subflava* | $10^7$ | *N. subflava* | $10^8$ |
| 19 | *Str viridans* | $10^8$ | *negative* | | 68 | *P. Aeruginosa* | $10^7$ | *P. Aeruginosa* | $>10^8$ |
| 26 | *S. marcescens* | $>10^8$ | *negative* | | 72 | *H. influenzae* | $>10^8$ | *H. influenzae* | $10^7$ |
| 30 | *P. mendocina* | $>10^8$ | *negative* | | 84 | *H. influenzae* | $10^7$ | *H. parainfluenzae* | $10^8$ |
| 39 | *P. maltophilia* | $>10^8$ | *P. maltophilia* | $10^5$ | | | | | |
| 43 | *Sta. auricularis* | $10^5$ | *negative* | | | | | | |
| 53 | *N. flava* | $10^8$ | *negative* | | | | | | |
| 59 | *E. cloacae* | $10^7$ | *P. maltophilia* | $>10^8$ | | | | | |
| | *A. pydrophila* | $10^5$ | | | | | | | |
| 65 | *H. influenzae* | $10^8$ | *negative* | | | | | | |
| 67 | *H. parainfluenzae* | $>10^8$ | *negative* | | | | | | |
| 71 | *K. pneumoniae* | $10^7$ | *negative* | | | | | | |
| 73 | *E. coli* | $10^6$ | *negative* | | | | | | |
| 78 | *M. catarrhalis* | $10^7$ | *H. parainfluenzae* | $10^3$ | | | | | |
| 81 | *K. pneumoniae* | $10^7$ | *negative* | | | | | | |
| 86 | *Str Epidermis* | $10^7$ | *Sta. auricularis* | $10^2$ | | | | | |

Group A: treated with Bronch-Vaxom capsules; group B: treated with placebos.

### Adverse effects

In group A, two patients suffered from mild dyspepsia between days 30 – 60, and one patient suffered from skin pruritus, which lasted for one week between days 0 – 30. None of these three subjects quit the trial. The remaining patients in both groups did not complain of any discomfort. The two groups were not statistically different in profiles of adverse effects. Liver and renal functions were normal in patients taking Broncho-Vaxom.

## DISCUSSION

Acute exacerbation in patients with CB has been attributed to about 50% of bronchial bacterial infections and 25% – 50% of viral infections.[10] However, viruses have also been sometimes isolated from COPD patients who were clinically stable.[11] Attempts have already been made to control or reduce the frequency of acute exacerbations in COPD by using antiviral therapy and vaccinations, but the outcomes have not been promising.[12] On the other hand, antibiotic therapy for patients with acute infections has shown to be effective.[11] Research also indicates that bacterial vaccines in susceptible patients are effective in preventing acute infections by improving patient immune response.[10] OM-85 BV, an immunomodulating preparation containing antigens derived from 8 bacterial species, has been shown to upregulate the activity, phagocytosis, and antigen-presentation of macrophages, and to increase the capacity of the body to eliminate the invading pathogens.[13] Animal experiments have indicated that OM-85 BV can stimulate the formation of serum IgA, IgG, IgM, and secretory IgA in the gut and lungs of mice and rats.[14] Moreover, OM-85 BV also activates bacterial killing by polymorphonuclear cells in mice and rabbits, thus enhancing the clearance of bacteria from the blood.[8]

OM-85 BV has been applied clinically for more than 20 years and has a good safety record. Its present uses include preventing recurring upper and lower RTIs in children[15-17] and adults.[7,18,19] In recent years, there have been many clinical trials worldwide involving OM-85 BV for the prevention of acute exacerbation of CB. A double-blind placebo-controlled multicenter study of 104 patients with CB by Cvoriscec and his colleagues[19] has shown that during a 6-month period of observation, patients on OM-85 BV experience less frequent acute exacerbations, fewer days with fevers, and diminished antibiotic usage as compared to patients taking placebos. Orcel[7] studied 290 patients with CB aged over 65 years and found that patients in the OM-85 BV group (n = 147) suffered 28% fewer episodes of lower RTIs than patients in the placebo group (n = 143), an effect that can be ascribed to evidenced reduction in episodes of acute bronchitis, other than those involving pneumonia.

Broncho-Vaxom has been used in China for years. The study presented in this paper is the first double-blind, placebo-controlled, multicenter clinical trial in China investigating the preventive efficacy of OM-85 BV for

acute exacerbation of COPD. Our results show that Bronch-Vaxom can reduce the incidence rate of acute exacerbation of CB complicated by COPD (45% lower in OM-85 BV patients than in patients treated with placebos), the severity of attack (lowered 41%), the duration of episodes (lowered 46%), and the use of antibiotics (lowered 42%). These are comparable to those reported elsewhere. Meanwhile, cough, expectoration, dyspnea, and pulmonary rales in OM-85 BV patients became markedly less severe as early as month 3, with less need for Combivent® and Gelomyrtol Forte® for symptom relief, probably as a result of an enhanced immune response leading to controlled bacterial infection and reduction of airway secretions. The patients recruited in our trial had had a many year history of cigarette smoking, with moderate to severe airflow limitation as indicated by pulmonary function tests. These symptoms were not improved after a one-year period of treatment. This might be due to the irreversibility of the patients' airway obstruction or the short course of our trial.

Although the significance of sputum bacterial cultures in reflecting the pathogens of the lower respiratory tract remains controversial, the results of bacterial cultures in our study were indicative of microbial conditions in the patients' bronchi and lower respiratory tract, because all our patients were trained to rinse their mouths and collect sputum in a proper way. The sputum specimens were then strictly screened for use by our technicians. As revealed by the bacterial cultures from the first morning sputum, taken after rinsing of the mouth, the overall positive rate of bacterial presence in the patients' sputum was 37.0% when they were clinically stable. By the end of month 3, 40% of patients in the OM-85 BV group were free of antibiotic usage, compared to only 12% in the placebo group. In the OM-85 BV group, 88.9% of these patients were pathogen positive in initial sputum cultures and became pathogen free or had improved sputum microbiology after treatment with OM-85 BV. By contrast, there was no significant change in the patients in the placebo group. Therefore, it appears that in cases of COPD, airway pathogens are detectable even when the patients are stable clinically, and that these pathogens may lead to acute RTIs in time of lowered immune activity. OM-85 BV may improve the clearance of bacteria from the airway by stimulating secretory IgA formation, thus reducing the episodes of acute exacerbations and antibiotic usage. Emmerich et al[20] studied 28 patients with non-obstructive CB and found that 8 of 19 patients who had positive bacterial cultures taken by means of bronchoalveolar lavage became negative or dramatically improved when evaluated 3 months after treatment with OM-85 BV alone.

Over the past two decades, OM-85 BV has been widely accepted as an effective immunostimulant, with a good safety record, and has became the unique medicine mentioned under the category of immunostimulant in the GOLD and Swiss published guidelines. Our study shows that there are no major adverse effects when using OM-85 BV, although mild dyspepsia and skin pruritus were detected in 3 patients.

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