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REVIEW

Bacterial extracts for the prevention of acute exacerbations in chronic obstructive pulmonary disease: A point of view

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Summary

Given the high prevalence of chronic obstructive pulmonary disease (COPD), the impact of exacerbations on quality of life, and the costs incurred, effective ways for the prevention of exacerbations, and for reductions in the severity and duration of COPD symptoms are needed. Bacterial immunostimulation has been advocated as a management strategy in COPD for the purposes of preventing acute exacerbations. In particular, it suggests that the use of oral multicomponent vaccines may reduce the severity and duration of acute episodes. The way in which bacterial extracts may exert their effects is not fully understood although a number of possible specific mechanisms have been suggested. Given the high prevalence of COPD worldwide and the high cost of acute exacerbations, some cost-effectiveness analyses suggest that bacterial immunostimulants may become a key element in the improved control of this condition. Nonetheless, larger and longer clinical trials are needed to investigate efficacy before oral vaccination could be recommended as part of the routine clinical management of COPD, mainly in advanced COPD. It remains also to be investigated whether this protective effect may be additive to the other treatments. In any case, it is well known that for *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae* and *Moraxella catarrhalis*, recurrent infections occur because of strain heterogeneity. Therefore, a single or even multiple strain vaccine with a killed whole cell formulation is possibly not the ideal vaccine. Moreover, the method of inactivation can affect the immunogenicity of essential antigens through denaturation. For this reason, the efficacy of bacterial immunostimulants should not only be assessed but also compared.

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Strategies to prevent exacerbations

It is now recognized that exacerbation frequency is an important outcome in chronic obstructive pulmonary disease (COPD) as patients prone to frequent exacerbations have impaired health status, reduced physical activity, increased lower airway bacterial colonization and a faster decline in lung function.¹ The frequency of exacerbations increases with the severity of COPD, but the mechanisms modulating exacerbation frequency in patients with COPD are largely unknown.

Although infection clearly has the ability to induce airway inflammation, the role that bacteria play in COPD exacerbations remains controversial.² Nonetheless, COPD exacerbation could be precipitated by an increase in bacterial number, change in the airway compartment in which bacteria are located, or acquisition of new, more virulent, and/or more proinflammatory bacterial species or strain.³ Several recent studies have shown a clear association between the isolation of bacterial species such as *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* and acute exacerbation.⁴ The underlying aetiology of the exacerbation may affect FEV₁ decline. For example, Wilkinson et al.⁵ described the greatest reduction in FEV₁ (56 ml in 1 year) in patients with a higher airway bacterial load, and this decline was greater still in patients with a change in bacteria as opposed to a single colonizing species.

Given the high prevalence of COPD, the impact of exacerbations on quality of life, and the costs incurred, effective ways for the prevention of exacerbations, and for reductions in the severity and duration of COPD symptoms are needed.⁶

Smoking cessation, vaccination against influenza and pneumococcal pneumonia, antibiotic therapy, and a short course of systemic corticosteroids are the most important strategies to prevent and control exacerbations.⁷ The Global Initiative for Chronic Obstructive Lung Disease (GOLD)⁸ also recommended long-term therapy with inhaled corticosteroids for patients with moderate-to-severe COPD who were experiencing recurring exacerbations but more recent evidence from trials combining inhaled corticosteroids and long-acting inhaled β_2 -agonists shows a significant additional effect on pulmonary function and a reduction in symptoms in those receiving combination therapy compared with its components.⁹ Potentially interesting alternative strategies for an improved control of symptoms and exacerbations in COPD include the use of mucolytic, antioxidant, and immunomodulator agents, defined as medications that

produce an enhancement of non-specific immunity and an increased infection resistance.

Bacterial immunostimulation has been advocated as a management strategy in COPD for the purposes of preventing acute exacerbations. Some previous data¹⁰ showed some interesting synergic effects of bacterial extracts in extending the immunological response to influenza vaccine in COPD patients. Thinking of influenza as one of most important risk factor in COPD exacerbations, this could be an interesting clinical outcome. It is not surprising, therefore, that use of bacterial immunostimulants is an option included in the management recommendation of some guidelines.¹¹ Inactivated microorganisms offer certain advantages as a potential vaccine for mucosal immunization. They are naturally occurring microparticles, which possess multiple antigens and are relatively inexpensive to produce. These immunomodulatory bacterial extracts are commonly administered by the oral route.

Mechanisms of action of bacterial immunostimulants

The way in which bacterial extracts may exert their effects is not fully understood. It has been suggested that bacterial immunostimulants, either killed whole cell formulations or agents containing antigens derived from several strains of bacteria, may increase resistance to infection by these organisms. They might exert their effects on lung defences by specific cell trafficking through the common mucosal immune system.¹² In animal models, recognition of the orally administered bacteria by gut-associated lymphoid tissue (the Peyer's patches in particular) is followed by trafficking of intestinally derived B- and T-cells to bronchus-associated lymphoid tissue, and this might lead to an immune response against these pathogens in the respiratory tract.¹³

A number of possible specific mechanisms have been suggested. *In vivo* and *in vitro* studies in animals and humans have shown that the action of these extracts is based on the modulation of the host immune response, and it has been found to upregulate interferon γ (IFN- γ) and interleukin (IL)-2, IL-6, and IL-8. IFN- γ plays a pivotal role in the body defence under circumstances of respiratory exposure to microorganism. CD4T cells cooperate with phagocytic cells to increase their antimicrobial effector capabilities via the secretion of IFN- γ .¹⁴ CD8 T-cells also use IFN- γ as an antiviral effector moiety.¹⁵⁻¹⁷ It has been documented that

percentage of T-cells secreting IFN- γ is reduced in both CD4 and CD8 subsets in COPD patients, compared to non-smoker and ex-smoker healthy control subjects.¹⁸

In vitro bacterial extracts exert immunomodulatory action via modulation of the signal transducer gp130 and gp130 binding cytokines, including IL-6 and IL-11.¹⁹ The increase of IL-6, which plays a protective role in attenuating acute inflammatory responses, and IL-11, which together with IL-6 protects animals from mortality in a bacterial-induced toxic shock model,²⁰ may explain enhanced T- and B-cell activity, immunoglobulin synthesis, and IgM to IgG switch.¹⁹

Other studies in experimental models have confirmed that bacterial extracts elicit long-lasting specific serum immunoglobulin (Ig) G antibody response.²¹ This is an important finding because adults with recurrent respiratory infections frequently have some variant of IgG deficiency, often associated with a functional impairment of specific antibody response.²² Assessment of IgG subclasses has shown a balanced pattern of IgG1–IgG2a responses, which indicates more balanced Th1–Th2 environment within the lungs.²¹

In addition, bacterial extracts also elicit the production of specific anti-bacterial secretory IgA (sIgA) in BAL.²¹ Interestingly, a major role of local sIgA in mucosal defence against invading pathogens has long been clearly demonstrated.²³ These antibodies have special features in the salivary fluid: for example, they have the capacity of opsonizing bacterial bodies, thus allowing their phagocytosis and subsequent killing.¹³ IgA are thus the main antibody isotype of mucosal secretions: they account for the first defence line against both bacterial and viral infections because of their activity against antigens recognized with high specificity and other antigens recognized with low specificity.²⁴

It seems to be intriguing that bacterial extracts have 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.²⁵ Moreover, they also activate bacterial killing by polymorphonuclear cells in mice and rabbits, thus enhancing the clearance of bacteria from the blood.²⁶ It has also been documented that an immunostimulating agent that includes material from eight different species of bacteria (*S. pneumoniae*, *H. influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans* and *M. catarrhalis*) that are frequently present in the lower respiratory tract, induces upregulation of adhesion molecule expression at the surface of phagocytes through CD14-independent pathways.²⁷

An analysis of pre- and post-therapeutic bronchoalveolar lavage (BAL) fluid of 28 adult patients with non-obstructive chronic bronchitis revealed that this immunostimulating agent increased the CD4+/CD8+ lymphocyte ratio and IFN- γ levels. Furthermore, the alveolar macrophage activity was normalized and the BAL IgA was moderately increased.

Contrasting conclusions on the effect of bacterial immunostimulants on exacerbations

Unfortunately, the evidence in favour of the use of bacterial immunostimulants is available only from a limited body of

data. An earlier meta-analysis suggested that these drugs may have an effect on exacerbations, but the trial quality is poor.⁶ A latest systematic review of OM-85 BV (Bronchovaxom®) to evaluate its efficacy and safety in COPD and chronic bronchitis has confirmed that consistent evidence across multiple important outcomes does not exist to clearly demonstrate clinical benefit of this agent.²⁸ Thirteen trials involving 2066 individuals were examined. Utilizing quantitative pooled analysis in these studies, with one or more acute exacerbations as the endpoint, the authors have found a non-statistically significant trend in favour of OM-85 BV [relative risk 0.83, 95% confidence interval 0.65–1.05]. Ten trials enrolled a heterogeneous population with chronic bronchitis. In these trials, exacerbation rates were less with OM-85 BV in four of the nine trials reporting this outcome. Varied results in the outcomes of hospitalization, symptom scores, and antibiotic or steroid use were found across studies. Withdrawals and adverse events were similar between OM-85 BV and placebo.

Nonetheless, a placebo-controlled study,²⁹ which investigated 350 nursing home residents aged ≥ 65 years with chronic bronchitis, found a significant reduction of acute bronchitis in patients in whom a mixed bacterial extract had been used (28% reduction in the number of lower respiratory tract infections, 40% reduction in the number of episodes of acute bronchitis, and 28% reduction in the number of antibiotic prescriptions). On the contrary, the Canadian study of Collet et al.,³⁰ a double-blind placebo-controlled randomized clinical trial that has recruited 381 patients ($n = 190$ in OM-85 BV versus $n = 191$ in placebo) and followed them up for 6 months, found no differences regarding the frequency of acute exacerbations, but it documented a significant reduction in the total number of days hospitalized (OM-85 BV for 287 days versus placebo for 642 days).

A more recent trial,³¹ which has been performed in China and has enrolled 90 patients with chronic bronchitis complicated with COPD, has documented 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 the group of patients that has been treated with 7 mg OM-85 BV daily for the first 10 days of each month for 3 consecutive months, as compared to the group that has received placebo. Symptom scores for cough, sputum, dyspnoea, as well as symptoms observed upon auscultation of the chest also improved significantly in group OM-85 BV as compared to group placebo. The bacterial clearance rate in sputum cultures from patients who received no antibiotics for the first 3 months was also significantly higher in group OM-85 BV compared to group placebo.

A short time ago, Solèr et al.³² have published a double-blind multi-centre Swiss–German study that aimed to demonstrate the protective effect of OM-85 against recurrent bronchitic exacerbations in patients with chronic bronchitis or mild COPD. They enrolled adult outpatients > 40 years old of both sexes. The treatment consisted of one capsule of OM-85 BV or placebo per day for 30 days, followed by three 10-day courses for months 3, 4 and 5, with a 6-month study duration and monthly control visits. One hundred and forty-two patients were treated with OM-85 BV

and 131 received placebo. By the end of the treatment period, the mean number of acute exacerbations in the OM-85 BV group was 0.61 per patient versus 0.86 per patient in the placebo group (−29%). The difference between treatments was most notable in patients with a history of current or past smoking (−40%). No serious adverse events were attributed to the medication and no significant laboratory changes were reported.

The economic impact of bacterial immunostimulants in the prevention of exacerbations

Although all the experimental and clinical findings suggest the possibility of treating a patient suffering from COPD with bacterial extracts in order to prevent exacerbations, the recent guidelines of European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases do not recommend the use of bacterial extracts in patients with chronic bronchitis or COPD.³³ This thought fits with the Cochrane review of Arandjuz et al.,³⁴ which has concluded that the evidence on the use of bacterial extracts to prevent exacerbations is inconclusive, although it suggests that the use of oral multicomponent vaccines may reduce the severity and duration of acute episodes.

This last point raises the question on the convenience of using bacterial immunostimulants. A cost-effectiveness analysis has been carried out in Canada to assess the economic impact of using OM-85 BV to prevent severe acute exacerbations in patients with COPD.³⁵ The median cost to prevent 1 day of hospitalization for a respiratory condition was CDN\$45, with a 95% CI of CDN\$18–210. Bootstrap of the study population and sensitivity analyses showed that the results were robust and not likely due to random fluctuation; 98.8% of the cost effectiveness and 96.8% of the cost–benefit ratios favoured the use of OM-85 BV. Indirect costs, defined as a need for help, were reduced by 36% in the group treated with OM-85 BV: 779 h of help compared with 1212 h in the placebo group. This trend, while not significant, is consistent with other results and suggests a decrease in the severity of exacerbations in the OM-85 BV-treated group. Also an Italian cost-effectiveness analysis of the use of OM-85 BV in chronic bronchitic patients showed favourable economic impact of this treatment.³⁶ Although the treatment caused only a mean value of 0.6 which prevented acute exacerbations per 6 months per patient, and a reduction of 9 days in antibiotic treatment per 6 months per patient, and this could be considered a critical parameter, these reductions involved a reduction in cost of 86,075 Lira. Considering that at the time of the study the additional costs for the preventive treatment with OM-85 BV, based on prices for Italy, were 34,980 Lira per patient per 6 months, the effective cost savings per patient per 6 months were 51,095 Lira. Even assuming 0.3 prevented exacerbations per 6 months per patient, the preventive treatment still proved to be cost effective.

Although not focussed on cost-effectiveness analysis, the Solè et al.'s trial³² has documented that the reduction in bronchitic exacerbations led to a reduction in the number of consultations of 2.2 per 10 patients and 6 months, with the corresponding diagnostic workup and treatment costs.

Bacterial immunostimulants apart from OM-85 BV

Ismigen[®] is a polyvalent mechanical bacterial lysate (PMBL) prepared by bacteria (*S. aureus*, *S. pyogenes*, *S. viridans*, *K. ozaenae*, *H. influenzae* serotype B, *M. catarrhalis*, and *S. pneumoniae*) obtained by mechanical lysis. The mechanical method is particularly efficient in that it achieves lysis of 80–100% of the bacteria. What is even more interesting, compared with other methods of lysis (such as alkaline lysis which brings about fragmentation significant enough to cause loss of immunogenicity), mechanical lysis does not alter the structure of the antigens: this ensures a preparation having excellent antigenic properties. The lysate thus induces a specific immuno-stimulation against the seven bacterial strains composing it, selected from among those most often responsible for respiratory infections. According to extensive and well-established literature, PMBL treatment seems to yield various beneficial effects, including a significant increase in antibody titre even after just one treatment cycle, in terms of IgM, IgG, and IgA.³⁷ This has a positive therapeutic effect on the amplitude of the spectrum of immunological production and on the production of opsonizing antigens.³⁸ In particular, it has been suggested that this PMBL exerts a therapeutic and preventing effect in acute and recurrent infections because it induces the activation and enhancement of both IgM memory B lymphocytes (CD24+/CD27+ cells) and IL-2 receptor-expressing lymphocytes (CD25+ cells) involved either in humoral or cellular immunity.³⁹ Moreover, it is able to induce a specific immune response in the salivary fluid of healthy subjects.²⁴ It is important to highlight that sublingual administration guarantees effective protection of the respiratory mucosae, which represent the first barrier to infection, making it possible to bypass the gastroenteric tract. This avoids denaturing the antigens and puts them directly in contact with the cells that best carry out the task of antigen-presenting cells, namely the Langherans cells.³⁷ In an Italian study conducted on 57 patients aged over 75 suffering from chronic obstructive bronchitis and affected by at least one exacerbation over the past 12 months, Ismigen[®] significantly reduced the absolute number of exacerbations, their length and seriousness, as well as the need to use antibiotic treatments, and the overall cost of the treatment of these patients during the period of treatment compared to the same period for the previous year, during which time no antibacterial prophylaxis had been administered.⁴⁰ It should be noted that the mean cost of the antibiotic therapy during the period from September to February of the year before the use of Ismigen[®] was €3459.60, while during the period from September to February of the year of the trial it was only €1499.40 (−57%). Adding the latter amount to the cost of the prophylactic therapy with Ismigen[®], equal to €1295.04, the total cost of €2794.44 was in any case significantly lower (−20%) than the cost for the same period of the previous year (an extremely important saving for the health structure management). In another multicentre study, 178 patients were randomized into two different groups: one group was treated with Ismigen[®] (first 10 days of each month for 3 consecutive months) and the other with placebo.⁴¹ The trial was double blind. At the end of treatment, patients were

followed for a further 9 months. Selected clinical endpoints were seen to be significantly lower in the group treated with the lysate than in the placebo group. Ismigen[®] treatment led to a highly significant reduction in the frequency (215 versus 248 cases) and duration (10.6 days versus 15.8 days) of exacerbations, as well as a decrease in antibiotic consumption (−270 doses) and hospitalization time (275 days versus 590 days).

Luivac[®] (LW-50020) is another standardized mixture of bacterial strains lysates (*S. aureus*, *S. pneumoniae*, *S. pyogenes*, *K. pneumoniae*, *M. catarrhalis*, *H. influenzae*) that has been evaluated in the treatment of chronic bronchitis and COPD.^{42,43} Apparently, it is efficacious in treating patients with recurrent respiratory tract infections.

Biostim[®] is composed of *K. pneumoniae* glycoprotein extract that, apparently, may impact not only the innate immune responses but potentially enhance adaptive immune responses by upregulating expression of molecules involved in antigen presentation on antigen-presenting cells.⁴⁴ In a trial that enrolled 40 patients with chronic bronchitis, it reduced the number and the duration of infectious exacerbations of chronic bronchitis with respect to those observed in the corresponding period of the previous year.⁴⁵

Ribomunyl[®] contains ribosomal RNA from bacteria causing recurrent respiratory tract infections together with the glycoprotein from *K. pneumoniae*. It seems able to change the proportions of inflammatory cells present in bronchoalveolar lavage of patients with chronic bronchitis.⁴⁶

It has been documented that in COPD patients, AM3, a commercially available immunomodulator with a low toxicity profile (its active ingredient is a polysaccharide/protein compound purified from *Candida utilis*), is able to normalize deficient effector functions in natural killer and phagocytic cells, which are involved in the innate immune response.⁴⁷

What must be done for defining the real importance bacterial immunostimulants in the prevention of exacerbations?

Given the high prevalence of COPD worldwide and the high cost of acute exacerbations, the mentioned cost-effectiveness analyses suggest that bacterial immunostimulants may become a key element in the improved control of this condition. Nonetheless, larger clinical trials are needed to investigate efficacy before oral vaccination could be recommended as part of the routine clinical management of COPD,^{34,48} mainly in advanced COPD patients, those with severely impaired lung function and, consequently, at high risk, and in selected patients with frequent exacerbations. It remains also to be investigated whether this protective effect may be additive to the other treatments. As correctly highlighted by Solèr,⁴⁹ considering that the mechanism of action of bacterial immunostimulants is distinctly different from that of the inhaled “standard treatments” for COPD, the question comes up, if the combined use of an effective inhaled anti-inflammatory regimen and/or bronchodilator regimen and the immunomodulating oral bacterial immunostimulants might lead to an additive or even better protection from COPD exacerbations. To give an answer to this question, more controlled clinical trials with bacterial

immunostimulants in well defined patients with advanced COPD are needed, where preventing an exacerbation can be expected to result in the most prominent cost savings and improvements in quality of life.

It must be highlighted that in most trials, the observation periods were 6 months and this must be considered a true bias. As recently stated by the ERS/ATS Task Force on outcomes in COPD clinical trials,⁵⁰ trials must last at least 12 months in order to understand the real impact of investigational treatment. Obviously, each exacerbation should be classified according to a severity scale.⁵⁰ In effect, it must also be stressed that the trials examined in the systematic review on oral purified extracts in chronic bronchitis and COPD published by Steurer-Stey et al.⁶ reported on a large variety of different end points. It was impossible to combine outcome data from more than five trials. The main end point, prevention of exacerbation, was reported in three trials only, and one of those trials was of limited size and quality. Further relevant end points that should be examined in future trial are hospital admission, duration of disease-free intervals, saved days of absence of work, and the need for concomitant medications, especially antibiotics and systemic corticosteroids, as all these factors contribute to cost.⁶

In any case, it is well known that for *S. pneumoniae*, nontypable *H. influenzae* and *M. catarrhalis*, recurrent infections occur because of strain heterogeneity. Therefore, a single or even multiple strain vaccine with a killed whole cell formulation is possibly not the ideal vaccine. Moreover, the method of inactivation can affect the immunogenicity of essential antigens through denaturation. For example, administration of PMBL (Ismigen[®]), i.e. products based on surface bacterial antigens, whose structure is not denatured by the use of chemicals, but obtained by simple mechanical crushing of the pathogens, can lead to a more specific antibody response to the surface structure of pathogen bacteria. For this reason, the efficacy of bacterial immunostimulants should not only be assessed but also compared.

Conflict of interest statement

Prof. Cazzola is a member of an Advisory board of Altana-Nycomed that sells Broncho-vaxom[®] and of a Scientific board of Pirri that sells Ismigen[®].

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