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Immunoactive preparations and regulatory responses in the respiratory tract: potential for clinical application in chronic inflammatory airway diseases

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Abstract:

Introduction: The prevalence of chronic inflammatory airway diseases is rising. Their treatment with corticosteroids increases infection risk, while overuse of antimicrobial agents may increase morbidity and antimicrobial resistance. Non-specific immunomodulatory compounds alter immune responses to both infectious and atopic challenges. These compounds may offer an alternative approach for symptom reduction and prophylaxis against both infections and exacerbations in chronic inflammatory airway disease.

Areas covered: We assessed the available data on the efficacy of non-specific immunomodulators including bacterial lysates, synthetic compounds, and vaccines in chronic rhinosinusitis (CRS); allergic and non-allergic rhinitis; chronic obstructive pulmonary disease (COPD), and asthma. A search of PubMed was carried out using the 'Clinical Trials' filter for each condition and immunomodulatory product detailed below, where available, data from meta-analyses were reported.

Expert opinion: Pre-clinical data has revealed a coherent mechanistic path of action for oral immunomodulators on the respiratory immune system, principally via the gut-lung immune axis. In patients with asthma, allergic rhinitis, CRS, and COPD immunomodulatory therapy reduces symptoms, exacerbations, hospitalizations, and drug consumption. However, data are heterogeneous, and study quality remains limited. A lack of high-quality recent trials remains the major unmet research need in the field.

Keywords: immunomodulation; immunostimulation; asthma; chronic obstructive pulmonary disease; chronic rhinosinusitis; allergic rhinitis; bacterial lysates; probiotics

Article highlights

- Pre-clinical data have created a detailed picture of the action of immunomodulators on the respiratory immune system principally via the gut-lung immune axis.
- In patients with asthma, allergic rhinitis, chronic rhinosinusitis, and chronic obstructive lung disease immunomodulatory therapy can reduce symptoms, exacerbations, hospitalizations, and drug consumption.
- The results of some available meta-analyses on the clinical effects of immunomodulators have not been addressed in the current guidelines.
- A lack of high-quality trials remains the major unmet research need in the field.

1.0 Introduction

1.1 Unmet needs in chronic inflammatory airway diseases

Chronic inflammatory airway diseases can be anatomically grouped into those of the upper (Chronic Rhinosinusitis [CRS], Persistent Allergic Rhinitis [AR] and Persistent Non-Allergic Rhinitis (NAR)) and lower (Chronic Obstructive Pulmonary Disease [COPD] and asthma) airways. Although in the majority of patients with chronic airway diseases symptoms can be effectively controlled by standard therapies, a significant minority remain symptomatic despite recommended pharmacological treatment [1]. Moreover, impaired quality of life, social functioning, sleep, and school/work performance are commonly reported, even by patients with relatively good symptom control [1].

Prevalence of AR and asthma are on the increase, contributing to the allergy pandemic which is, at least partially, an unwanted consequence of increased urbanization worldwide [2]. In a 2014 global survey, approximately 70% of Ear, Nose and Throat specialists stated that the prevalence of AR was 'surely increasing' in their country [3]. Global Burden of Disease Study data indicate that the prevalence of asthma increased by approximately 13% between 1990 and 2015, while the same data source showed a 44% increase in COPD prevalence over the same period [4]. In addition, an allergic phenotype of COPD characterized by increased respiratory symptoms and a higher risk of exacerbations was described during the past decade [5, 6•]. COPD is currently the 3rd leading cause of death globally and, like asthma, its prevalence is rising [7]. Importantly, patients with allergic and non-allergic asthma, as well as patients with COPD, show signs of nasal inflammation and report higher levels of nasal symptoms [8]. This reflects a phenomenon known as 'united airway disease' which is indicative of the integrated nature of the upper and lower airways. This heterogeneous condition encompasses multiple endotypes which may be both atopic and non-atopic in nature [8, 9].

Current treatment guidelines for chronic inflammatory airway diseases all rely to a greater or lesser extent on anti-inflammatory therapeutics, particularly corticosteroids, as well as infection control when necessary [10, 11, 12]. Next-generation monoclonal therapies have shown promise in COPD, asthma, CRS, and AR [13, 14, 15, 16]. However, these therapies remain expensive and beyond the reach of developing countries where the majority of the world's population reside and where the prevalence of allergic respiratory disease is likely to rise alongside increasing urbanization [2, 17].

Reliance on corticosteroid therapy, which is common in moderate-to-severe chronic inflammatory airway disease, and during exacerbations, increases the risk of upper and lower respiratory-tract infections, particularly in patients with asthma and COPD [18, 19••, 20]. As respiratory infections are a well-known risk factor for exacerbations and worsening of inflammatory airway diseases, a vicious circle may emerge with increased risk of infections due to corticosteroid therapy and further worsening of the disease triggered by infections [21, 22•]. An overuse of antimicrobial agents in patients with chronic inflammatory airway diseases is also common and may result in unnecessary or prolonged hospital stays, higher costs, and increased risk of treatment failure [23]. Furthermore, data from animal models suggest that antimicrobial-induced reductions in microbiome diversity are related

to impaired immune function and higher mortality following viral infection [24, 25••]. Emerging evidence from human population studies suggests that community structures of commensal bacterial also modulate susceptibility to infection [26].

1.2 The gut-lung immune axis: infection and inflammation

The "hygiene hypothesis" and other related concepts, including the 'old friends' and 'biodiversity' hypotheses, have become cornerstones of modern immunology. These theories are supported by two widely accepted concepts that can be briefly outlined as follows: contact with the external environment is essential for the biodiversity of the internal environment; and the biodiversity of the internal environment is essential for proper immune function [27, 28, 29].

Mucosal membranes, in particular those of the gut and respiratory system, represent the major points of contact between the immune system and the environment. A wealth of evidence, extensively reviewed elsewhere, has demonstrated that the mucosal immune system functions as an integrated unit, with substantial crosstalk allowing an integrated immune response against pathogens detected in either mucosa [2, 30, 31, 32]. This so called gut-lung axis was proposed as early as the year 2000, however, the concept that changes in the gut microbiome may impact lung immunity has gained particular traction within the scientific community during the last 5 years [1]. Reduced microbial diversity, so call dysbiosis, in the gut has been linked to lung disease in humans, and increasing evidence suggests that both microbial components (antigens) and metabolites such as short-chain fatty acids have a role in maintaining immune homeostasis [32].

Dendritic cells (DCs) function as immune sentinels within the mucosal membranes, where the detection of live bacteria, viruses, or their associated antigens by pattern recognition receptors (PRR) triggers an immune cascade. The resulting migration of innate and adaptive immune cells via the lymphatic system confers protection against infections throughout the body's mucosae. In addition, increasing evidence suggests that immune activity at one mucosal site can result in migration of regulatory cells which modulate activity at distant mucosal membranes reducing inflammation and atopic reactions [32, 33, 34, 35] (**Figure 1]**).

Non-specific immunomodulatory compounds interact with the innate and acquired immune system, modulating the immune response to various challenges including infectious, atopic, or neoplastic insults. Non-specific immunomodulators include bacterial lysates, synthetic modulators of PRR-mediated signaling, and vaccine adjuvants. Immunoactive preparations have demonstrated the ability to activate DCs in the digestive-tract mucosa resulting in a protective immune response in the lungs [33, 36]. Much of this anti-infective response depends on the creation of an immunostimulatory, proinflammatory milieu [33]. Yet, a growing body of evidence indicates that such preparations can be also effective in the chronic inflammatory airway diseases mentioned above [33]. The explanation behind this apparent mechanistic dichotomy relies on the ability of immunomodulatory compounds to

mimic the activity of naturally occurring microbiota. During infancy, and in response to allergens, atopy-related type 2 T-helper cells (Th2) responses predominate [37, 38]. Exposure to microbiota or immunomodulatory compounds can shift the balance from an atopic Th2 response to a non-atopic type 1 (Th1) response via the activation of DCs and subsequent regulatory T-cell activity [25••, 33••, 35, 39, 40, 41, 42, 43].

In this paper we will summarize the mechanistic and clinical evidence base for the activity of various immunomodulatory compounds in chronic airway diseases. Searches for the treatment and condition were carried out in PubMed using the 'Clinical Trials' filter e.g. (OM-85 [title/abstract] OR bronchovaxom [title/abstract]) AND asthma (OM-85 [title/abstract] OR bronchovaxom [title/abstract]) AND wheeze), supplemented with previous literature reviews and author expertise. Condition-specific mechanistic data will be summarized briefly and, whenever possible, high-quality data from meta-analyzes or randomized trials will be reported.

2.0 Probiotics

2.1 Asthma

The mechanistic underpinning of probiotics as an anti-asthma intervention is derived from hypotheses which link a lack of exposure to diverse microbial agents with the risk of developing atopic disease (i.e. the hygiene hypothesis). Numerous bacterial species have been investigated as probiotics, with *Bifidobacterium* and *Lactobacillus* being the major probiotic genera [44, 45, 46]. Several studies in animal models, suggest a beneficial role of probiotics in asthma prevention [47•, 48].

A recent meta-analysis that included pooled data from 910 children with mild to moderate asthma demonstrated a higher proportion of children with fewer asthma episodes following treatment with probiotics as compared to controls (risk ratio [RR]: 1.3; 95% confidence interval [CI]: 1.06, 1.59). In addition, the authors reported a probiotic-induced increase in IFN-γ and a decrease in IL-4 levels. However, the above effects were not associated with significant changes in disease severity as measured by childhood asthma control test, asthmatic symptoms during the day or night, number of symptom-free days, forced expiratory volume (expressed as the percentage of predicted), or peak expiratory flow (**Table 1**) [49]. In a large meta-analysis comprising data from 5,157 infants < 1 year old exhibiting asthma or wheezing, probiotic therapy was not found to reduce the overall risk of asthma (RR: 0.94; 95% CI: 0.82, 1.09) or wheeze (RR: 0.97; 95% CI: 0.88, 1.06) (**Table 1**) [50]. However, probiotics administration was associated with a reduction in the incidence of wheeze among infants with atopic disease (n=225; RR: 0.61; 95% CI: 0.42, 0.90) [50]. Finally, in a meta-analysis comprising 4,755 children at high risk of atopy there was no difference in the incidence of asthma and wheezing between infants who received probiotics (gestational or at < 3 months old) compared with those who did not (RR: 0.99; 95% CI: 0.77, 1.27; and RR: 1.02; 95% CI: 0.89, 1.17, respectively) (**Table 1**) [51].

Overall, these results suggest that probiotics lack consistent efficacy in asthma prevention, however, their use may be associated with a reduction in the incidence of wheeze in atopic infants, although larger trials are necessary.

2.1.1 Asthma guidelines

The sole mention of non-specific immunoactive preparations in the current Global Initiative for Asthma (GINA) report refers to the negative results of a meta-analysis on probiotics and asthma development [11]. Favorable statements in the recently published review by the European Academy of Allergy and Clinical Immunology Task Force on Anti-infectives in Asthma may represent the beginning of a shift in perception within the research community. However, the need for higher quality studies is emphasized [55].

2.2 COPD/chronic bronchitis

Few mechanistic studies on the effects of probiotics in COPD have been carried out. However, the NK-1 suppressing effect of cigarette smoke was attenuated in smokers given fermented milk containing *L. casei* [56]. Also, an *in vitro* study showed that phagocytosis of *L. rhamnosus* or *B. breve* by human macrophages was associated with the inhibition of inflammatory response to cigarette smoke [57]. The above-discussed inflammatory cross talk between gut and airways is probably one of the major mechanisms responsible for the ability of probiotics to suppress cigarette-smoke induced airway inflammation [44, 56].

We were unable to find any clinical data on the effect of probiotics on the severity of airway inflammation in patients with COPD/chronic bronchitis.

2.3 Chronic rhinosinusitis

CRS is a chronic inflammatory condition of the nose and paranasal sinuses with a multifactorial etiology and pathophysiology and two major phenotypes; CRS with and without nasal polyps (CRSwNP and CRSsNP, respectively) [58]. Genetic predisposition and environmental factors (exposure to cigarette smoke) and microbial factors (changes in microbiome diversity, biofilm formation) contribute to the onset and course of the disease, influencing epithelial barrier integrity and the adaptive immune response [59, 60, 61, 62, 63].

The conceptual basis for probiotic protection against CRS relies principally on the effects of commensal organisms directly on the mucosa of the upper airway, rather than indirectly via the shared mucosal immune axis [64]. Probiotic species may act as direct competitors to pathogens, both for nutrients and access to cell surface receptors which aid adherence [65]. In addition, production of antibacterial peptides and metabolites may create a more hostile environment for pathogens, for example lowering of pH by lactobacilli has been proposed as an inhibitor of *Pseudomonas aeruginosa,* a common pathogen in CRS [65]. Topical probiotics also have the potential to modulate the immune

system. Intranasal delivery of *Bacillus subtilis* in piglets resulted in increased expression of PRRs, increased numbers of DCs, B cells and T cells, as well as higher levels of IgA [66]. In a randomized trial of a nasal spray containing various lactobacilli and bifidobacteria there was no effect on symptom scores, microbiological flora, or inflammatory mediators. However, the study showed that the topical application was feasible and safe (**Table 2**) [67•]. Oral probiotics have also been investigated in CRS. In a randomized trial, oral *L. rhamnosus* had no effect on sinonasal quality-of-life scores (**Table 2**) [68].

2.3.1 Chronic rhinosinusitis guidelines

Probiotics are not recommended by the current European guidelines for CRS and these agents have not been mentioned in the Canadian or US guidelines [58, 72, 73]. Also, despite acknowledgement and discussion of the importance of the microbiome, a recent international consensus paper on rhinosinusitis does not refer to probiotics [74].

2.4 Allergic rhinitis

Persistent AR occurs for periods longer than four days per week during more than four consecutive weeks. Both symptoms and their impact on quality of life range from mild to severe.

Down regulation of type 2 immune response following intranasal delivery of probiotics has been demonstrated in a mouse model of AR [75, 76, 77]. Additionally, oral intake of probiotic products has been suggested to improve health status in children with AR [76, 78]. Meta-analysis data have demonstrated an effect of probiotics on the type 1:type 2 immune ratio, but no apparent effect on IgE levels [79, 80•, 81•].

In a meta-analysis comprising 2,242 children and adults with AR, probiotic therapy resulted in a significant reduction in total nasal (standardized mean [SMD] difference: −1.23; 95% CI: −1.84, −0.62) and total ocular symptoms scores (SMD: −1.84; 95% CI: −2.83, −0.84). QoL was significantly better in a sub-analysis of the Lp-33 lactobacillus strain. However, total nasal and ocular quality-of-life scores were similar to placebo (**Table 4**) [79]. Conversely, in a meta-analysis of 1,919 patients the positive effect of probiotics on Rhinitis Quality of Life (RQLQ) scores, was significant (SMD: −2.23; 95% CI: −4.07, −0.40) though there was no effect on Rhinitis Total Symptom Scores (RTSS) (SMD −0.36; (95% CI: −0.83, 0.10) (**Table 4**) [80•]. In their 2015 systematic review (N=1,527), Peng et al. reported a significant combined improvement of the quality-of-life scores and nasal symptom scores of patients with AR (mean difference: −2.97 [95% CI, −4.77, −1.16)]) (**Table 4**) [81•]. There was a high risk of bias in the majority of the studies, highlighting the need for better quality trials [79, 80•].

2.4.1 Allergic rhinitis guidelines

Currently there is no mention of probiotics in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, despite available data from meta-analyzes suggesting an impact on symptom control [86].

2.5 Non-allergic rhinitis

NAR is a heterogeneous group of conditions including rhinitis of the elderly, hormonal-induced rhinitis, gustatory rhinitis, occupational rhinitis and idiopathic rhinitis. In the small randomized study, patients received standard of care with or without an oral probiotic supplement containing *L. acidophilus NCFM, B. lactis*, and fructo-oligosaccharides. The probiotic group had a lower prevalence of symptoms and endoscopic signs, and a reduction in inflammatory cell infiltrate (**Table 4**) [82].

2.5.1 Allergic rhinitis guidelines

In line with the level of evidence, there is currently no mention of probiotics in the US or European AR guidelines [87, 88].

3.0 OM-85

3.1 Asthma

OM-85 is produced by the alkaline lysis of 21 strains of eight species of common bacterial respiratory-tract pathogens (see footnote **Table 1**). The results of studies on experimental models suggest that OM-85 remains immunologically active following ingestion [89]. The proposed mechanism of OM-85's immunomodulatory activity was recently reviewed [33••]. Briefly, a two-pronged anti-infective and anti-inflammatory mechanistic path has been proposed for OM-85 in wheezing and asthma. This includes reductions in viral infections, and associated exacerbations, likely via release of antimicrobial peptides, activation of macrophages, release of antiviral cytokines, and rapid neutrophil recruitment (**Figure 1**) [33••, 90, 91, 92, 93, 94•]. In addition, OM-85 induces a shift in balance of type 1 and type 2 immune responses reducing the likelihood of allergen-induced airway hyper-responsiveness during exacerbations [33••, 35, 91, 95]. In mouse models of asthma, OM-85-induced: down regulation of type 2 markers on gut DCs; damping of DC-responses to aeroallergens; trafficking of Treg cells to the airway; a shift towards a type 1 cytokine balance; reduced inflammatory cell infiltration; and reductions in serum IgG1 (IgG4 equivalent) and IgE (**Figure 1**). These effects were associated with suppression of mucous metaplasia and mucus hypersecretion, reduced airway hyper-responsiveness, and remodeling [33••, 35, 89, 90, 91, 92, 93, 96•, 97, 98, 99]. Shifts in the cytokine balance in favor of a type 1 rather than type 2 immune response were consistently demonstrated in children with asthma and related conditions [33••, 53••, 99, 100, 101].

A recently published meta-analysis (N=4,851) of the efficacy and safety of OM-85 in pediatric recurrent respiratory-tract infections included 8 studies (702 children) which assessed wheezing episodes. OM-85 therapy resulted in a substantial reduction in the duration of wheezing (mean difference –3.37; 95% CI: –4.25, –2.22) (**Table 1**) [52]. Another recently submitted meta-analysis

investigated the efficacy of bacterial lysates in children with preschool wheezing and asthma. Three trials assessing OM-85 were eligible for data extraction (N=88). The frequency of wheezing episodes and asthma exacerbations was reduced in patients who received OM-85 compared with placebo (**Table 1**). The quality of the trials of bacterial lysates overall was assessed as intermediate [53••].

In the 33 studies which reported adverse events (AEs) in the Yin meta-analysis, OM-85 was well tolerated with mild gastrointestinal symptoms and rash being the most common AEs. Although AEs were more common in patients treated with OM-85 they did not interfere with treatment (RR = 1.39; 95% CI: 1.02, 1.88, P = 0.04) [52]. AEs were not reported separately for OM-85 in the recently submitted meta-analysis, however, AEs for bacterial lysates overall had a similar incidence as those occurring in placebo/standard of care groups [53••].

The above analyzes acknowledged the fact that higher quality trials are required before firm conclusions could be drawn regarding the prophylactic efficacy of OM-85 in asthma/wheezing. The large scale ORal Bacterial EXtracts (ORBEX, NCT02148796; N=986) for the prevention of wheezing lower respiratory-tract illness trial, should contribute towards addressing this need [102]. The trial will address infants and young children at risk of developing chronic airway disease due to familial atopy, some of whom have experienced 1–2 wheezing episodes, and will investigate whether OM-85 prevents or delays wheezing. Results are expected in 2024.

3.1.1 Asthma guidelines

OM-85 is not currently mentioned in the GINA report [11]. As with probiotics, the European Academy of Allergy and Clinical Immunology Task Force on Anti-infectives in Asthma mentions the potential of bacterial lysates alongside the need for higher quality studies before inclusion in guidelines can be recommended [55].

3.2 COPD/chronic bronchitis

A number of studies have evaluated the potential mechanisms of OM-85 prophylaxis against COPD exacerbations. OM-85 therapy increased the CD4+:CD8+ lymphocyte ratio and IFN-γ levels, and exerted a regulatory effect on alveolar macrophage activity and IgA levels in the bronchoalveolar lavage fluid of patients with non-obstructive chronic bronchitis [103]. OM-85 was shown to play a protective role against Rhinovirus-induced cell death in isolated bronchial epithelial cells from COPD patients. Improved antiviral activity due to increased bronchial epithelial cell expression of immune proteins C1q-R and β-defensin as well as activation of Erk1/2 MAPK, an upstream regulator of macrophage activity, likely contribute to OM-85's protective effect [94•]. IL-1β is a prominent mediator of COPD which drives neutrophilic inflammation and has been implicated in the initiation, maintenance and exacerbation of airway inflammation [104]. Data indicating OM-85 may interfere with inflammasome activation and IL-1β release induced by alum suggests a potential route for the inhibition of airway inflammation in COPD, particularly during exacerbations. A similar mechanism is likely also at play during asthma exacerbations [90]. Although specific data are sparse, *in vitro* data,

including from peripheral blood mononuclear cells from patients with COPD, suggests that a dual anti-infection/anti-inflammation mechanism similar to that proposed in asthma may play a role in the reduction of exacerbation rates in COPD patients treated with OM-85 (see data below) [90, 94•].

A meta-analysis on the effects of OM-85 therapy in COPD published in 2015 included five randomized trials and 1,190 patients. The exacerbation rate was reduced by 20% (RR: 0.80; 95% CI: 0.65, 0.97) and the incidence of antibiotic use was reduced by 39% (RR: 0.61; 95% CI: 0.48, 0.77) compared with placebo. The authors did not find any change in duration of hospitalization (weighted mean difference: −7.33 days; 95% CI: −18.34, 3.67; P = 0.19), severity of acute exacerbations (weighted mean difference: 0.72 score; 95% CI: −1.55 to 0.11 score; P = 0.09), or total adverse events (RR, 0.94; 95% CI: 0.84 – 1.05; P = 0.24) (**Table 3**). The need for better quality trials was emphasized in the conclusions of this meta-analysis [105••]. In a second more recent meta-analysis (N=1,008) presented at European Academy of Allergy and Clinical Immunology 2019, a 23% reduction in COPD exacerbation rate was reported (RR: 0.77; 95% CI: 68, 0.88; P = 0.0002) (**Table 3**) [106].

Three cost-effectiveness trials of OM-85 in COPD/chronic bronchitis have been carried out. In an Italian study conducted in the 1990s, the effective cost savings per patient per 6 months were 51,095 Lira, a 60% cost saving, and these savings were found to be associated solely with OM-85's ability to prevent exacerbations [113]. A Canadian study published in 2001 analyzed data collected in 1995. The cost of preventing one day of hospitalization due to a respiratory cause was CND$45 (95% CI: 18, 210), with an average cost for one day of respiratory hospitalization at $382 leading to an 88% saving per hospitalization prevented [114]. The authors of a more recent Argentinian study reported a 21% reduction in total costs related to reinfections in a group of COPD patients who received OM-85 prophylaxis (1,356.5 vs 1,708.2 ARS). Similarly, the total cost associated with disease exacerbations was reduced by 24% (1,217.5 vs 1,599.6 ARS) [115].

3.2.1 COPD guidelines

Current GOLD Science Committee Guidelines mention two RCTs of OM-85, both of which were conducted before 2005, noting the reductions in disease severity and exacerbations achieved. The Committee recommends the need for further studies into the long term effects of 'immunoregulators' alongside current maintenance therapies [10].

3.3 Chronic rhinosinusitis

A study examining potential mechanisms for OM-85 prophylaxis in CRS has been carried out using a mouse model [116]. Administration of OM-85 alongside amoxicillin vs amoxicillin alone significantly reduced levels of suppressor of cytokine signaling 1 (SOCS1), SOCS3, TNF-α, and IFN-γ. Both SOCS1 and SOCS3 have been found to be upregulated in CRS, and both TNF-α, and IFN-γ have been shown to be drivers of SOCS1 and SOCS3 expression. The authors suggest that reduced expression of SOCS1 and SOCS3 may ameliorate CRS-related inflammation [116]. A second study showed direct application of OM-85 to the sinus increased ciliary beat frequency via a NO dependent mechanism,

which the authors contend may have protective effects in rhinosinusitis [117]. In an older trial, efficacy of OM-85 in children with CRS correlated with increased IgA levels, presenting a potential anti-infective mechanism [71].

A randomized trial was carried out in children during the acute remission phase of CRS, in which OM-85 significantly improved the visual analogue score for rhinosinusitis, nasal discharge and obstruction scores, number of days with rhinitis attacks per month, and number of days with antibiotic use per month over the following year (**Table 2**) [69]. In a randomized trial in adults with chronic prurient sinusitis, OM-85 improved the rate of infections, symptom scores, and x-ray sinus opacity (**Table 2**). Side-effects were minimal with the same number of patients reporting AEs in the placebo and OM-85 groups (n = 2) [70]. In a 6-month study conducted in 1988, incidence of cough, nasal discharge scores (up to month 5), nasal congestion, episodes of infection, and the duration of antibiotic therapy were reduced in children treated with OM-85 following an acute episode of rhinosinusitis (**Table 2**). No side effects were observed during therapy in either treatment group [71]. Finally, in a Chinese cost-effectiveness analysis of OM-85 therapy, the cost to prevent a full episode of rhinosinusitis exacerbation was RMB 1182.84, while each acute exacerbation of rhinosinusitis cost RMB 1807.21, representing a 35% cost saving [118].

3.3.1 Chronic rhinosinusitis guidelines

Bacterial lysates in general, and OM-85 in particular, are recommended for the treatment of CRS in adults by the European guideline/Consensus Paper with a very high – A grading [58]. A similar recommendation is also given in a Pan-American guideline paper [119].

3.4 Allergic rhinitis

Inflammatory cytokines, infiltration of proinflammatory cells, and increased serum IgG1 and IgE, indicative of a type 2 immune response, are inhibited by OM-85 in a mouse model of AR [33••, 120].

In a study of adult patients with AR, infections were reduced by 33%, although there was no change in the number of exacerbations (**Table 4**) [83]. In a small (N=60) randomized trial recently carried out in China, OM-85 therapy reduced medication use, nasal symptoms, and improved type 1:type 2 cytokine balance [84]. A cost-effectiveness analysis carried out in Argentina showed that total cost per patient per month caused by reinfections and exacerbations were 448.9 ARS and 269.9 ARS, respectively in patients treated with OM-85, compared with 660.40 ARS and 574.40 ARS in the year previous to treatment [115].

3.4.1 Allergic rhinitis guidelines

Currently there is no mention of OM-85 in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines or the most recent US allergic rhinitis guidelines [86, 88].

4.0 Pidotimod

4.1 Asthma

Pidotimod is a synthetic thymic dipeptide which appears to share a number of mechanistic similarities with bacterial immunomodulators [33••, 121]. Pidotimod is thought to stimulate two PRRs, toll-like receptor 2 (TLR2) and TLR4, which are expressed on DCs (**Figure 1**) [33••, 122, 123, 124, 125]. Single nucleotide polymorphisms of PRRs have a role in a number of chronic lung diseases, and reduced expression of these receptors has been found to correlate with the severity of atopic disease [126, 127]. In an *ex vivo* study examining the effects of pidotimod on peripheral blood mononuclear cells from children with atopic asthma and healthy controls, the type 2-related cell marker CD30 was down regulated in response to pidotimod in both groups [128]. CD30 has been implicated in the development of atopic asthma, and its expression appears to play a role in type 2 cytokine production by CD4+ and CD8+ human T-cell clones [128, 129, 130, 131]. However, mechanistic data are mixed. In a mouse model of asthma, proinflammatory effects of pidotimod on IgE and eosinophils were demonstrated [132].

To date, there have been no high-quality meta-analyzes on the efficacy of pidotimod in asthma. Also, there are no studies assessing the impact of pidotimod on the rate of asthma exacerbations. However, in a prospective multicenter trial, pidotimod reduced the number of respiratory infections during a three-month observation period in a mixed group of children over half of whom had atopic conditions including asthma (**Table 1**). But, there was no longer a significant difference at the 6-month follow-up [54].

4.1.1 Asthma guidelines

There is no mention of pidotimod in current GINA guidelines, however, TLR agonists are mentioned alongside other non-specific immunomodulators by the European Academy of Allergy and Clinical Immunology Task Force on Anti-infectives in Asthma, with the above-mentioned caveats [11, 55].

4.2 COPD/Chronic bronchitis

The potential efficacy of pidotimod in COPD was reviewed in 2015 [125]. Since then, we have not found any new data on the use of this molecule in COPD patients. In an early mechanistic study, pidotimod was found to increase T-cell blastogenesis in patients with COPD, highlighting a potential route for potentiation of immune response in COPD [133].

Three randomized trials of pidotimod have been conducted in Italy in patients with chronic bronchitis. Pidotimod reduced the rate of infectious relapses and improved expectoration characteristics (serous, mucous, mucopurulent, or purulent) (**Table 3**). Side effects were transient and mild in nature and occurred to a similar rate in placebo and pidotimod groups [107, 125]. Similarly, pidotimod added to amoxicillin resulted in faster symptom resolution (dyspnea, cough, sputum, and hyperpyrexia) in patients with chronic bronchitis suffering from bacterial exacerbations (**Table 3**). Six patients had

adverse reactions (nausea; rash; vomiting) at the beginning of treatment resulting in discontinuation of pidotimod, in the placebo group 3 patients withdrew treatment due to AEs [108]. In clinically stable patients with severe COPD (GOLD stage 3), those receiving pidotimod exhibited fewer infectious exacerbations, a longer time to first exacerbation, and a shorter duration of acute infectious episodes. These differences were associated with lower use of antibiotics and less interference with daily activities and work in the pidotimod group (**Table 3**). Therapy was well tolerated with AEs occurring in approximately 6% of both the pidotimod and placebo group [109, 125]. Given the lack of recent clinical trials on pidotimod in COPD, further studies would be helpful in strengthening conclusions regarding efficacy in this group.

4.2.1 COPD guidelines

There is no mention of pidotimod in the current COPD guidelines [10].

5.0 Polyvalent mechanical bacterial lysate (PMBL)

5.1 Asthma

PMBL is a sublingually delivered bacterial lysate produced using a mechanical process that preserves the structure of bacterial antigens [33••, 134]. PMBL increases the number of $CD8^+$ T cells, Treg cells and NK cells in children with uncontrolled or partially controlled asthma (**Figure 1**) [33••, 135]. Other, potentially relevant immunological effects on asthma prevention include a pro-type 1 shift in cytokine balance, as well as infection prophylaxis which may protect against exacerbations.

Two trials assessing the efficacy of PMBL in preschool wheezing and asthma (N=136) were included in the previously mentioned meta-analysis on the effect of bacterial lysates on preschool wheezing. The frequency of wheezing episodes and asthma exacerbations was reduced, although the reduction did not reach significance compared with placebo (**Table 1**). AEs were not reported separately for PMBL, however, AEs for bacterial lysates overall had a similar incidence as those occurring in placebo/standard of care groups. The overall quality of the trials of bacterial lysates was assessed as intermediate [53••].

5.1.1 Asthma guidelines

There is no mention of PMBL in current GINA guidelines, however, as mentioned above the European Academy of Allergy and Clinical Immunology Task Force on Anti-infectives in Asthma mentions the potential of bacterial lysates and the need for further research [11, 55].

5.2 COPD/Chronic bronchitis

In elderly patients with COPD receiving PMBL, peripheral blood samples were assessed to establish the phenotypes of circulating peripheral blood mononuclear cells. Changes were evident in B cell

subsets which may be indicative of PMBL-induced maturation, potentially driven by increased numbers of Th (CD3+/CD4+) cells. CD8+ and CD25+ T-cell subsets were unaffected, while the number of Treg cells was reduced and the number of circulating NK cells increased significantly. The authors suggested that these results are indicative of a broad immune response to PMBL involving polyclonal activity [136].

In a pilot study comparing patients treated with an inhaled corticosteroid (ICS) and long acting beta-agonist (LABA) combination (salmeterol/fluticasone) vs patients treated with ICS/LABA plus PMBL, the latter group were characterized by a reduced exacerbation rate, fewer hospitalizations, and a reduced need for both oral corticosteroids and antibiotics (**Table 3**) [110]. In a multicenter phase IV trial of PMBL in patients with moderate to very severe COPD, the primary outcome of a 25% reduction in exacerbation rate was not achieved. However, the number of days with fever and days in poor health were significantly fewer in patients treated with PMBL. Also, the interval between the first and second exacerbations was significantly longer (**Table 3**). Potentially treatment-related AEs were uncommon at 3% with placebo and 0% with PMBL [111•]. Finally, in a randomized trial in elderly patients with COPD, PMBL resulted in increased levels of circulating antibodies and reduced infectious episodes (**Table 3**) [112].

PMBL appears to be effective in the reducing exacerbation rates in COPD, presumably due to a reduction in infectious episodes. We note that the studies on PMBL were better designed than many others in the field (power calculations, CONSORT reporting etc.). We strongly encourage the conduct of similar high-quality studies on immunoactive preparations in order to challenge skepticism within the medical community and produce definitive results.

5.2.1 COPD guidelines

There is no mention of PMBL in the current COPD guidelines [10].

5.3 Allergic rhinitis

In a small randomized trial, 61.5% of patients with AR treated with PMBL showed a significant and clinically relevant improvement (graded by symptom scores) while the rest (38.4%) showed a stationary clinical response (**Table 4**). No cases of negative side effects were reported. The authors also evaluated immunological response, although there were no changes in IgE and IFN-γ concentrations, some patients showed a decrease in the type 2 cytokine IL-4 [85]. A recent open-label study in 38 children suffering from Seasonal Allergic Rhinitis (SAR) caused by grass pollen treated with PMBL and standard treatment during pollen season demonstrated substantial reduction of the symptoms of SAR as compared to the control group [137].

5.3.1 Allergic rhinitis guidelines

Currently there is no mention of PMBL in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines or the most recent US allergic rhinitis guidelines [86, 88].

6. Conclusion

Although research has been gathering pace in recent years, the data regarding the impact of non-specific immunomodulators on chronic respiratory diseases remain heterogeneous. Initial excitement around probiotics has been tempered by discouraging data in terms of asthma prevention although some efficacy in symptom control is apparent. Although bacterially derived immunomodulators have been used clinically for many years, the past decade has seen a substantially increased understanding of the mucosal immune-derived mechanisms underlying their clinical effects. Positive trial results must be viewed through a prism of skepticism due to the low quality of many studies and there is a tremendous need for methodologically robust, placebo-controlled studies designed according to the established principles for conducting clinical trials (CONSORT criteria). However, in cases where the data are sufficiently robust, expertly conducted meta-analyzes have shown consistent efficacy for some of the immunomodulators discussed above.

Despite this, current guideline recommendations appear to be ignorant or dismissive of the recent robust meta-analysis-derived data. Though reductions in symptoms and exacerbations may be moderate in some cases, given the good safety profile of these immunomodulatory preparations, consideration of their utility as potential complimentary therapies which may reduce reliance on corticosteroids must be given more serious consideration.

7. Expert opinion

Following an initial phase of distrust, the growing body of evidence for the efficacy of immunoactive preparations in chronic inflammatory airway diseases has attracted the attention of researchers and physicians. Data supports a cogent mechanistic pathway for oral immunomodulatory products through the activity of the gut-lung immune axis. Efficacy against both infectious and inflammatory insults via dual regulatory and non-specific immune responses also has a clear mechanistic backbone. However, further studies are required to fill in gaps in this picture and identify potential biomarkers of efficacy (see below). It is also necessary to investigate whether the persistent clinical and immunomodulatory effects of the above drugs are associated with epigenetic reprogramming of innate immune memory, so called trained immunity [155].

Despite the substantial strides forward in understanding the mechanism of action of bacterially derived immunoactive preparations, there is little understanding of how the specific composition of these preparations relates to efficacy. Comparative studies on the clinical efficacy and mechanisms of action of immunoactive drugs with different compositions and routes of administration are required (bacterial lysates vs synthetic modulators of PRR-mediated signaling, sublingual bacterial lysates vs oral bacterial lysates, bacterial lysates vs probiotics, PMBLs vs chemical bacterial lysates etc.). The logical aim of these studies is to identify the most biologically active synthetic or purified natural components of bacterial cells mimicking the main immunomodulatory effects of multicomponent

bacterial preparations; while recognizing that this multicomponent nature may, in fact, be intrinsic to their efficacy.

As inflammatory and immune reactions are deeply involved in pathogenesis of chronic obstructive airway diseases, immunoactive preparations which affect different pathways of immune and inflammatory response might favorably change the clinical course of these diseases. The data presented in this paper shows that the use of non-specific immunoactive preparations is associated with some beneficial effects in patients with asthma and COPD. Besides assessing the changes in frequency and severity of exacerbations, a potentially very important and under-researched aspect of the effectiveness of immunoactive preparations are the putative effects on the immune system during remission of chronic disease.

From a clinical point of view, the typical moderate and individually variable effect size of immunomodulator therapies indicates that subgroups of responders and non-responders may exist. Confirmation of the presence of these subgroups followed by investigations into the presence of biomarkers would be worthwhile. We need to be open to investigating immune biomarkers, infectious agents as triggers, and the role of the microbiome in order to identify patient populations who may respond best to therapy.

Another rational direction of further research in this area is comparison of the efficiency of non-specific immunoactive drugs in patients with different phenotypes and endotypes of chronic respiratory disease (allergic or non-allergic, eosinophilic or non-eosinophilic, type 2-dependent or type 2-independent, with polyps or without polyps). Randomized placebo-controlled trials stratified by endotypes/phenotypes of disease, should be a considered part of research strategies.

Conventional approaches to the treatment of asthma and COPD are increasingly being brought into question in favor of the 'treatable traits' concept. According to this approach, identification of specific disease features amenable to targeted therapy can be used to personalize and optimize management strategies. Investigating which treatable traits are most amenable to immunomodulatory therapy could be another fertile avenue of research.

There are still unmet needs in the management of chronic lung disease such as asthma and COPD, including an increasing prevalence of disease and unsatisfactory disease control in patients treated with standard drug regimens. The latter might be at least partially explained by relatively low patient compliance associated with the inhalation therapy which is a cornerstone of both asthma and COPD treatment. Existing therapeutic methods in other chronic respiratory airway diseases are outdated (steroids) or cause unacceptable collateral damage (antibiotics). Thus, other alternative and/or complimentary forms of therapy which are well tolerated and easily accepted by patients are welcome.

Therapies targeting the immune system are increasing important throughout modern medicine, and monoclonal antibody therapies targeting type 2 inflammation already have proven efficacy in both

atopic asthma and atopic dermatitis. However, the expense and burden of adverse events currently restrict these therapies to moderate-to-severe cases of disease. Cost effective therapies without an appreciable side-effect burden, such as immunoactive therapies, are likely to solidify a place in this burgeoning therapeutic landscape presuming the high-quality data necessary for wide acceptance are generated.

We hope that the current strong evidence for specific preparations in particular disease areas, alongside ongoing work, will soon be more widely reflected in recommendations issued by large international scientific societies. Continuing research will help to refine recommendations for the clinical use of non-specific immunoactive preparations in chronic airway diseases and focus the attention of practitioners on the most effective drugs with known cellular and molecular mechanisms of action.

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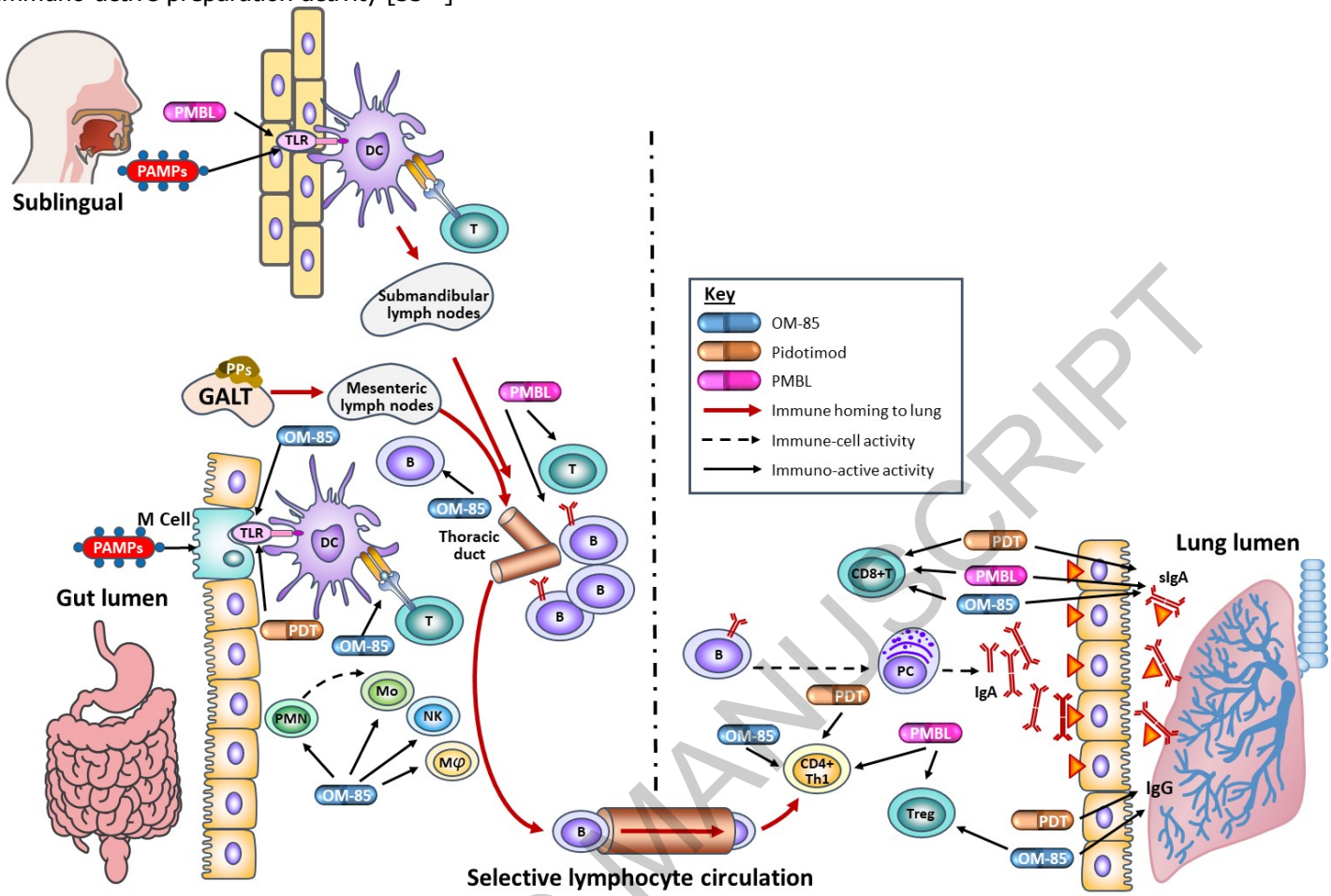
Figure 1: Illustration of immune activity in the mucosa-associated lymphoid tissue, showing detection of PAMPS at distant mucosa and homing of immune cells to the lung via the shared mucosal immune axes, as well as sites of immuno-active preparation activity [33••]



B, B cell; GALT, gut-associated immune tissue; Mφ, macrophage; Mo, monocyte; NK, natural killer cell; PAMPS, pathogen-associated molecular patterns; PC plasma cell; PMN, polymorphonuclear neutrophil; PPs, Peyer's patches; T, T-cell; Treg, regulatory T cell.

Table 1: Summary of showing improvement, worsening, or no change in clinical outcomes of immunomodulator therapy in asthma/wheezing

Intervention	Study	Design	Studies included	Species included	Population	Outcome: improvement (↑), worsening (↓), or no change (↔)
Probiotics	Lin et al. 2018 [49]	Meta-analysis	11	Mixed cultures of *Lactobacillus sp. Bifidobacterium sp.*, and less commonly, *Streptococcus sp.*; Mixed cultures of *Bifidobacterium sp.*; Single *Lactobacillus sp. cultures*[a]	Children; N=910	↑ Children with fewer episodes of asthma ↔ C-ACT ↔ Asthmatic symptoms (day or night) ↔ Symptom-free days ↔ Forced expiratory volume ↔ Peak expiratory flow
Probiotics	Wei et al. 2019 [50]	Meta-analysis	19	Single Lactobacillus sp. cultures; Single *Bifidobacterium sp.* cultures; Mixed cultures of *Lactobacillus sp.*; Mixed cultures of *Bifidobacterium sp.*; Mixed cultures of *Lactobacillus sp., Bifidobacterium sp.* and *Propionibacterium*[a]	Children; N=5,157	↔ Asthma risk ↔ Wheeze risk ↑ Wheeze incidence in infants with atopic disease
Probiotics	Zuccotti et al. 2015 [51]	Meta-analysis	17	Mixed cultures of *Lactobacillus sp. and Bifidobacterium sp.*; single *Lactobacillus sp.* cultures[a]	Children; N=4,755	↔ Asthma prevention ↔ Wheezing prevention ↓ Eczema development ↔ Rhinoconjunctivitis
OM-85	Yin et al. 2018 [52]	Meta-analysis	8 Wheezing (53 total)	See footnote[b]	Children; n=702 (N=4,851)	↑ Duration of wheezing
OM-85	De Boer et al. 2019 [53••]	Meta-analysis	3 (5 total)	See footnote[b]	Children; N=88	↑ Wheezing episodes and asthma exacerbations
Pidotimod	Namazova-Baranova et al. 2014 [54]	Prospective multicenter trial	N/A	N/A	'Frail' children including those with atopic diseases (≈55%); N=157	↑ Acute respiratory infections ↑ Antibacterial therapy ↑ Disease severity ↑ Complications
PMBL	De Boer et al. 2019 [53••]	Meta-analysis	2 (5 total)	See footnote[c]	Children; N=137	↔ Wheezing episodes and asthma exacerbations

[a]See original references for full list of specific cultures from studies included in meta-analyses; [b]*Haemophilus influenzae* (1 strain), *Streptococcus pneumoniae* (4 strains), *Klebsiella pneumoniae subsp. pneumoniae* (2 strains), *Klebsiella pneumoniae subsp. ozaenae* (1 strains), *Staphylococcus aureus* (6 strains), *Streptococcus pyogenes* (1 strains), *Streptococcus sanguinis* (3 strains), *Moraxella (Branhamella) catarrhalis* (3 strains) [90]; [c]*Staphylococcus*

aureus, S. pyogenes, Streptococcus viridans, K. ozaenae, *H. influenza serotype B, M. catarrhalis* and *S. pneumoniae* [110]. CT/C-ACT, Asthma Control Test/Childhood Asthma Control Test; SABA, short-acting β agonists.

Table 2: Summary of showing improvement, worsening, or no change in clinical outcomes of immunomodulator therapy in CRS

Intervention	Study	Design	Studies included	Species included	Population	Ou or
Probiotics	Mårtensson et al., 2017 [67•]	Randomized trial	N/A	Mixed culture of honey bee associated Lactobacillus sp. and *Bifidobacterium* sp.[a]	Adults; N=21	↔ ↔
Probiotics	Mukerji et al., 2009 [68]	Randomized trial	N/A	*Lactobacillus hamnosus R0011*	Children (> 15 years old) and adults (< 70 years old), N=77	↔ ↔
OM-85	Chen et al., 2017 [69]	Randomized trial	N/A	See footnote[b]	Children 4 to 12 years old; N=96	↑ ↑ ↑ ↑ ↑ ↑
OM-85	Heintz et al., 1989 [70]	Randomized trial	N/A	See footnote[b]	Adults ≥ 16 years old; N=284	↑ ↑ ↑ ↑ ↑ ↑
OM-85	Zagar et al., 1988 [71]	Placebo-controlled prospective trial	N/A	See footnote[b]	Children 4 to 12 years; N=55	↑ ↑ ↑ ↑ ↑ ↑

[a]See original references for full list of specific cultures; [b]*Haemophilus influenzae* (1 strain), *Streptococcus pneumoniae* (4 strains), *Klebsiella pneumoniae subsp. pneumoniae* (2 strains), *Klebsiella pneumoniae subsp. ozaenae* (1 strains), *Staphylococcus aureus* (6 strains), *Streptococcus pyogenes* (1 strains), *Streptococcus sanguinis* (3 strains), *Moraxella (Branhamella) catarrhalis* (3 strains) [90]. SNOT-22, Sino-Nasal; VAS, visual analogue scale.

Table 3: Summary of showing improvement, worsening, or no change in clinical outcomes of immunomodulator therapy in COPD

Intervention	Study	Design	Studies included	Population	Outcome: improve change (↑↔↓)
OM-85	Pan et al., 2015 [105••]	Meta-analysis	5	Adults; N=1,190	↑ Exacerbation ra ↑ Antibiotic use ↔ Hospitalizations ↔ Severity of acut ↔ Total adverse ev
OM-85	De Boer et al. 2019 [106]	Meta-analysis	4	Adults; N=1,008	↑ Exacerbations
Pidotimod	Bisetti et al. 1994 [107]	Randomized trial	N/A	Adults; N=181	↑ Infectious relaps ↑ Expectoration cl
Pidotimod	Pozzi et al. 1994 [108]	Randomized trial	N/A	Adults > 40 years old; N=137	↑ Patients with de ↑ Sputum volume ↑ Faster decrease ↑ Time to recover ↑ Immunity (skin ↑ Investigator glo
Pidotimod	Ciaccia et al., 1994 [109]	Randomized trial	N/A	Adults > 40 years old; N=580	↑ Exacerbations ↑ Time to first exa ↑ Duration of infe ↑ Number of days ↑ Days of work m ↑ Investigator glo
PMBL	Cazzola et al., 2009 [110]	Randomized trial	N/A	Adults ≥ 50 years old; N=63	↑ Exacerbations ↑ Rate of exacerb ↔ Exacerbation sy ↑ Exacerbations re ↑ Hospitalizations ↑ Duration of anti ↑ Duration of cort
PMBL	Braido et al., 2015 [111•]	Randomized trial	N/A	Adults > 40 years old; N=288	↔ 25% reduction i ↔ Time to first exa ↑ Time between f ↑ Days with fever ↑ Days in poor he ↔ All-cause hospit ↑ Hospitalization f
PMBL	Ricci et al., 2014 [112]	Randomized trial	N/A	Adults ≥ 65 years; N=28	↑ Infectious episo

Table 4: Summary of showing improvement, worsening, or no change in clinical outcomes of immunomodulator therapy in allergic and non-allergic rhinitis

Intervention	Condition	Study	Design	Studies included	Species included	Population	Outcome: improvement (↑), worsening (↓), or no change (↔)
Probiotics	Allergic Rhinitis	Güvenç et al., 2016 [79]	Meta-analysis	22	Single *Lactobacillus sp. cultures*[a]; Single *Tetragenococcus sp.* culture; Single *Bifidobacterium sp.* culture; Single *E. coli sp.* culture. Mixed culture of *Lactobacillus sp.* and live yoghurt[a]	Children and adults; N=2,242	↑ Nasal symptom score ↑ Ocular symptom score ↑ QoL (LP-33 subgroup)
Probiotics	Allergic Rhinitis	Zajac et al., 2015 [80•]	Meta-analysis	23	Sixteen studies used *Lactobacillus sp.*, six *used Bifidobacterium; E. coli (Nissle 1917), Tetragenococcus halophilus (Th221), and Bacillus clausii* were used in single studies	Adult; N=1,919	↑ Rhinitis Quality of Life scores ↔ Rhinitis Total Symptom Scores
Probiotics	Allergic Rhinitis	Peng et al., 2015 [81•]	Meta-analysis	11	Mixed cultures of *Lactobacillus sp. Bifidobacterium sp.* and, less commonly, Propionibacterium, and Streptococcus; *Single Lactobacillus sp. cultures*; Single *Bifidobacterium sp.* cultures[a]	Adults and children; N=1,527	↑ QoL and symptoms scores
Probiotics	Non-allergic rhinitis	Gelardi et al. 2017 [82]	Randomized trial	N/A	*Lactobacillus acidophilus* and *Bifidobacterium lactis*	Adults; N=93	↑ Patients with nasal obstruction ↑ Patients with rhinorrhea Patients with endoscopic signs
OM-85	Allergic Rhinitis	Koatz et al., 2016 [83]	Prospective trial	N/A	See footnote[b]	Adult; N=84 (allergic rhinitis n=29)	↔ Number of exacerbations ↑ RTIs
OM-85	Allergic Rhinitis	Meng et al. 2019 [84]	Randomized trial	N/A	See footnote[b]	Adult; N=60 (9 patients with mild asthma)	↑ Medication use ↑ Nasal symptoms scores Itching

							symptom scores ↑↑ Type 2/Type 1 cytokine balance Eosinophils
PMBL	Allergic Rhinitis	Banchereau et al. 2007 [85]	Randomized trial	N/A	See footnote[c]	Adult; N=41	↑↑ Nasal blockage and rhinorrhea ↑ Ocular symptoms Asthmatic symptoms

[a]See original references for full list of specific cultures from studies included in meta-analyses; [b]*Haemophilus influenzae* (1 strain), *Streptococcus pneumoniae* (4 strains), *Klebsiella pneumoniae subsp. pneumoniae* (2 strains), *Klebsiella pneumoniae subsp. ozaenae* (1 strains), *Staphylococcus aureus* (6 strains), *Streptococcus pyogenes* (1 strains), *Streptococcus sanguinis* (3 strains), *Moraxella (Branhamella) catarrhalis* (3 strains) [90]; [c]*Staphylococcus aureus, S. pyogenes, Streptococcus viridans*, K. ozaenae, *H. influenza serotype B, M. catarrhalis* and *S. pneumoniae* [110]. BCG-PSN, BCG polysaccharide nucleotide