What is COPD?

The vicious circle of COPD

Chronic obstructive pulmonary disease, or COPD, is defined as: “A common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients” (1) (Figure 1).

The major risk factor for COPD is long-term cigarette smoke (up to 90% of cases of COPD are linked to smoking), but also outdoor and indoor air pollution (fumes) and occupational exposure to noxious particles [e.g. mines], all growing factors in developing countries where COPD is on the rise. Lung infections are other important factors. Other non environmental factors [genetic] are also certainly involved in the onset of the condition.

The natural history of the disease is characterized by episodes of acute exacerbations which are often triggered by lung infections. After each acute exacerbation episode the patient lung function declines (2) (Figure 2). It is estimated that patients with moderate to severe COPD experiment between 1.5-3 exacerbations/year.

Exacerbations are predominantly due to lung infections. Until recently, bacterial infections were essentially linked with exacerbations (3,4), but the use of more sensitive detection methods (PCR) has recently shown that the role of viral infections had been underestimated. The presence of newly emerging viruses has recently been shown, and, since they are not routinely detected they could account for a number of exacerbations which are not visibly linked to any infection (5,6). A 2006 study reports that combined bacterial and viral infection could be identified in 25% of exacerbations and these dual infections are often more severe (7). Figure 3 represents the main pathogens implicated.

Acute exacerbations strongly affect the patient’s quality of life and represent important health expenses (hospitalization, treatments, indirect costs...). Moreover, exacerbations are a factor of disease progression. If lung dysfunction cannot be reversed...
in COPD patients, the objective of the clinician is to prevent acute exacerbations in order to break the disease vicious circle and slow down its progression.

**A major healthcare burden worldwide: prevalence**

Today, COPD represents a major healthcare burden: it affects over 210 million people worldwide and is the fourth leading cause of death worldwide. In 2005, over 3 million people died of COPD in the world, representing 5% of the deaths worldwide.

COPD median prevalence worldwide in adult population is estimated between 9-10% with important variations according to the survey methods [8]. Thus, in order to better analyze the prevalence of COPD, it is preferable to perform regional analysis. The BOLD study estimated a median population prevalence of 10.1% with a slightly higher prevalence in women than in men (8.5% vs. 7.8%), but the difference was not significant. The BOLD study also documented a more severe stage of COPD than previously found and even in non smokers the prevalence varied from 3-11% depending on the regions [1]. Moreover, the environment appears to have a great impact on COPD prevalence, for example, the BOLD study estimated that in Iceland as much as 18% of the adult population was in GOLD stage I and 9% in Gold stage II.

**In Europe**, the prevalence in adult population has been estimated between 4-10% [9].

In **South and Latin America**, the PLATINO study estimated the prevalence of COPD in adult population in five different cities of five different countries: São Paulo, Ciudad de Mexico, Montevideo, Santiago de Chile, and Caracas. The prevalence ranged from 7.8% in Mexico to 19.7% in Montevideo. In each country it has been noticed that COPD prevalence increased with age and the highest prevalence was found among those over 60 years [1, 10]. It has to be highlighted as well that COPD is often underdiagnosed in 89% of cases and misdiagnosed in 63% of cases. According to this study, only a quarter of COPD patients received treatment [11].

**In India**, a large multicentric study was conducted in 2006 that estimated the prevalence in adult population at around 4.1%, with more men (5%) affected than women (3.2%). The male:female ratio was 1.56:1. [12]

COPD remains today the only major cause of death that is still rising, especially in developing countries as air pollution and cigarette smoke are growing issues. WHO has predicted that COPD will be the third leading cause of death worldwide by 2020.

**Financially**, COPD represents a tremendous burden, due to both direct healthcare costs (antibiotherapy, inhaled corticosteroids, long acting beta-agonists, hospitalizations, oxygen therapy...), and indirect costs, the latter representing by far the major financial burden of COPD. Indeed, among all respiratory diseases, COPD represents the first cause of work absenteeism. For example, in Europe, the number of work days lost due to the condition is estimated at 41,300 days / 100,000 inhabitants, and productivity losses total €78.5 billion/year. Outpatients care represents a further €4.7 billion expenses, inpatients care another €2.9 billion, and pharmaceuticals costs represent €2.9 billion [9].

**Symptoms and Diagnostic**

The primary symptom experienced by the patient is shortness of breath, or dyspnea. Other common signs include chronic cough, sputum production, and the presence of risks factor, in particular a history of heavy smoking. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined criteria to assess the severity of COPD and stage of the disease based on spirometry (FEV₁, measurement): COPD is diagnosed when FEV₁/FVC < 0.70. Table 1 summarizes the correspondence between FEV₁ and COPD severity [1].

<table>
<thead>
<tr>
<th>In patients with FEV₁/FVC &lt;0.70:</th>
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<tbody>
<tr>
<td>GOLD 1: Mild</td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td>GOLD 2: Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>GOLD 3: Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>GOLD 4: Very severe</td>
<td>FEV₁ &lt; 30% predicted</td>
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</table>

Table 1: Classification of severity of airflow limitation in COPD based on post-bronchodilator FEV₁ (updated GOLD guidelines 2011).
There is no cure for COPD, and the keyword is prevention. COPD management strategy is based on a set of occasional symptomatic treatments and long-term preventive measures to reduce the number of exacerbations (13):

First of all, elimination of risks/aggravating factors is recommended, in particular smoking. Vaccination represents an effective strategy to prevent acute exacerbations since those are often triggered by infections: influenza and pneumococcal immunization should be systematically offered to COPD patients.

Finally, the use of oral vaccines, or immunostimulants, in the form of bacterial lysates which target a range of common respiratory pathogens, is increasingly advocated as a complementary measure to reduce both the occurrence and severity of acute exacerbations and to reduce the associated costs.

Table 2 gives an overview of the main pharmacological measures. To these we should add non pharmacological approaches to COPD management: pulmonary rehabilitation, oxygen therapy and eventually surgery.

<table>
<thead>
<tr>
<th>Pharmacological approach</th>
<th>Benefits</th>
<th>Limitation</th>
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<tbody>
<tr>
<td>Bronchodilators</td>
<td>• Effective both as regular or as needed treatments.</td>
<td>Symptomatic management of COPD (long acting BD are expensive).</td>
</tr>
<tr>
<td>Inhaled glucocorticosteroids</td>
<td>• Reduces the frequency of exacerbations and health status. • Symptomatic treatment effective for patients with FEV₁ &lt;50% predicted.</td>
<td>Dos not prevent long-term decline of FEV₁.</td>
</tr>
<tr>
<td>Antioxydant agents (N-acetylcysteine)</td>
<td>• Could reduce the frequency of exacerbations. • Could play a role in treatment of patients with recurrent exacerbations.</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>• Only recommended to treat infectious exacerbations.</td>
<td>Emergence of antibioresistance.</td>
</tr>
<tr>
<td>Vaccination</td>
<td>• Preventive approach. • Triggers specific immune response. • Prevents exacerbations, • Reduces mortality.</td>
<td>Limited number of pathogens can be addressed this way.</td>
</tr>
<tr>
<td>Polyvalent bacterial lysates</td>
<td>• Preventive approach. • Address the main pathogens at once. • Triggers adaptive and innate immune response. • Reduces both frequency and duration of exacerbations.</td>
<td></td>
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</tbody>
</table>

Table 2: Review of COPD pharmacological treatments (from Braido et al., 2007).
How Bacterial lysates can help?

**Bacterial lysates** are mixtures of bacterial antigens derived from different inactivated pathogenic bacteria. The principle of bacterial lysates is to trigger immune surveillance and to up-regulate immune defences to prevent and help fight infections. Bacterial lysates are sometimes referred to as ‘oral vaccines’.

**Polyvalent bacterial lysates** are prepared from different species of bacteria, typically the most commonly occurring pathogens of the upper and lower respiratory tract. Each bacterial strain is grown independently, harvested, inactivated and lysed using either mechanical or chemical lysis in order to obtain the antigens.

Based on the method used for cellular lysis, two distinct types of bacterial lysates are defined: chemical (PCBL, for polyvalent chemical bacterial lysates) and mechanical (PMBL for polyvalent mechanical bacterial lysates).

While PCBL is obtained by the action of chemical alkaline substances that may denature proteins, PMBL* is obtained by increased pressure which preserves the particulate antigens. It has recently been shown that mechanical lysates, thanks to their conserved antigenic structures are 10-100 times more effective to trigger an immune response than chemical lysates (14). (Figure 4). Moreover, PMBL contains the major bacterial pathogens associated with COPD exacerbations: S. pneumoniae, H. influenzae, M. catarralis, K. pneumoniae, S. aureus, S. viridans, K. ozaenae, S. pyogenes.

The advantage of PMBL also resides in its mode of administration. PMBL is formulated in **sublingual** tablets. Lately, the sublingual route of administration of bacterial lysates has been proposed as a safer and effective immunotherapy to stimulate strong and long-lasting systemic and mucosal antigen-specific humoral and cell-mediated immunity. It has recently been shown that sublingual immunization was more effective to enhance anti-microbial defences as compared to other routes of immunization, via the generation of antigen specific memory CD4+ T (15).

The presence of high number of dendritic cells in the sublingual mucosa could provide an explanation for the high T cell response observed after oral immunization (16). Moreover, it is well known that a satisfactory antibody barrier of mucosal IgA is of fundamental importance in preventing infections as it allows to act as first line of defense. Several studies have shown that sublingual immunization induced a significant increase in salivary specific IgA, triggering an efficient immune response which is reflected in a positive clinical outcome in patients (17, 18).

PMBL represents a good **complementary tool in COPD management strategy**, both for the prevention of bacterial infections that can lead to acute exacerbations (19, 20), but also as an adjuvant to conventional treatment of acute exacerbations (21).

*Ismigen, Immubron, Respibron, Provax, PIR-05*
**PMBL in COPD: the clinical evidences**

Bacterial lysates have been developed in the 1970s and PMBL has been marketed for over 15 years: a large number of prospective studies and randomized clinical trials have been published that validate their efficacy in the prevention and treatment of chronic respiratory tract infections and diseases in adults and children.

Concerning PMBL clinical efficacy in COPD patients, three randomized studies showed its efficacy to reduce acute exacerbation occurrences in patients [19, 20, 21], resulting in reduced hospitalizations and antibiotherapy (Figure 5).

Interestingly, PMBL was effective in combination with salmeterol/fluticasone treatment, reducing even further the number and severity of exacerbations. This synergy was explained by the fact that the mechanism of action of bacterial immunostimulants is different from that of the inhaled standard treatments [20].

Recently, two meta-analysis were conducted based on these trials [22, 23]. A statistically significant trend in favor of the treatment with PMBL in the prevention of exacerbations in patients with COPD or bronchitis was reported (RR, 0.83; 95% CI, 0.77–0.89) (Figure 6). We detail below the main outcome of two of these studies.

### STUDY 1
**REDUCTION OF INFECTIONAL EXACERBATION IN MODERATE TO VERY SEVERE COPD**

(Cazzola, 2006)

#### STUDY DESIGN
- Placebo controlled randomized trial.
- Study duration: 12 months.
- 178 patients, randomized in 2 groups.
- Moderate- very severe COPD.
- Treatment regimen: daily administration of Ismigen for 10 consecutive days X 3 months.
- 9 months follow-up.

#### RESULTS
- Significant reduction of the frequency of acute exacerbation: 215 vs. 248 cases.
- Significant reduction of the duration of exacerbation s (10.6 vs. 15.8 days).
- Significant reduction of antibiotherapy (1 270 doses used with COPD).
- 50% reduction of total hospitalization time: lower hospitalization rate (31 vs. 56 cases) and shorter hospitalization duration (8.9 vs. 10.5 days, P<0.05).
- No adverse effect reported.

#### CONCLUSION
- “On the basis of the important clinical results of this trial, i.e., lower incidence of exacerbations and greater efficacy of antibiotic treatment in patients immunized with bacterial lysates, it is possible to state that this therapeutic approach should always be considered in patients suffering from moderate to very severe COPD.”

### STUDY 2
**ADJUVANT THERAPY TO REGULAR COPD TREATMENT (SALMETEROL/FLUTICASONE)**

(Cazzola, 2009)

#### STUDY DESIGN
- Study duration: 12 months.
- 63 patients, randomized in 2 groups [A and B].
- All treated with Salmeterol/Fluticasone + 33 received PMBL (group B).
- Treatment regimen: daily administration of Ismigen for 10 consecutive days X 3 months.
- Reduction of the total number of exacerbations.
- Reduction of the rate of exacerbations/ patient/year (0.54 vs. 0.67).
- Reduction of the number of exacerbations that needed treatment with oral corticosteroids (43% vs. 52%).
- Reduction of hospitalizations rate (0.09 vs. 0.13).
- Decreased antibiotic consumption.

#### CONCLUSION
- “The results of the study suggest that PMBL is effective in advanced COPD patients, those with severely impaired lung function and, consequently, at high risk (the usual population that is treated with a combination of long-acting ß2-agonist plus an inhaled corticosteroid) and its protective effect may be additive to the other treatments.”
The expert’s opinion

Questions to Prof. M. Cazzola, Associate Professor of Respiratory Medicine at the University of Rome ‘Tor Vergata’ Rome, Italy.

1. When do you recommend PMBL for COPD patients?

I recommend PMBL when COPD patients suffer from acute exacerbations (AECOPD). It is known that AECOPD are associated with more rapid decline in lung function, that leads to reduced physical activity, quality of life, and increase mortality risk. This is the reason why preventing these episodes of acute exacerbations, reducing their severity and duration is important in the management of COPD. It has to be noted as well that infections account for up to 80% of AECOPD episodes, hence preventing these infections could be a good option for the management of acute exacerbations. PMBL has shown interesting results by reducing the number of episodes of AECOPD, their duration and severity, and by reducing the associated costs, such as hospitalizations, use of antibiotics, inhaled corticosteroids, long-acting beta2-agonists or tiotorpium.

2. What course of treatment do you recommend?

My recommendation is to take 2 courses of PMBL to prevent AECOPD. The first course (1 tablet per day during 10 days/month for 3 months) shall be taken from October to December to prevent the winter infections, while a second course can be taken during the spring to ensure a complete protection all year long. Of course PMBL can be taken along with inhaled corticosteroids, long-acting bronchodilators, antibiotics, or mucolytic agents.

3. Is there any seasonality as regards to acute exacerbations in COPD?

Of course during the winter period, the number of respiratory infections is increasing, so the number of AECOPD is increasing accordingly. A recent publication in Chest (2012) by G.C Donaldson demonstrated that exacerbations are also more severe between November and February. Nevertheless the environment plays an important role too on acute exacerbations and air pollution is another important factor. It has been estimated that up to 9% of admissions with AECOPD may be due to atmospheric pollution during the summer months. A study carried out in Hong Kong has also noticed two peaks of viral infections in AECOPD patient: during spring and summer. In conclusion even if AECOPD is more frequent and severe during winter time, it can also happen during summer.

4. Is this why you recommend two courses of PMBL per year?

Yes, as I have highlighted in point 2, and based on the possible occurrence of AECOPD during summer, it is preferable to recommend two courses of PMBL to offer a complete protection to patients all year long. In any case, I must admit that I have some patients suffering from COPD and bronchiectasis who are using PMBL every day of the year, and others with previous frequent COPD exacerbations who are using PMBL every day for a month continuously each second or third month. In both conditions PMBL is effective.

5. Do PMBL work for all patients or do you see some success factors for the treatment?

Obviously, patients who are prone to frequent exacerbations might better benefit from PMBL, while non-frequent exacerbators remain relatively protected regardless of the prevention treatment. Apparently, patients with chronic bronchitis experience exacerbations more frequently.

6. Do you see good treatment compliance?

Treatment compliance is always a matter of explaining the treatment and its benefit. What is important in AECOPD is to explain to the patient that if he/she is able to decrease the occurrence of exacerbations, this will prevent the development of the vicious circle that causes a drop of his/her lung function. Patients must be also aware that PMBL can lead to an extra cost at the beginning of the treatment, but the reduction of the number of episodes of acute exacerbation and their relative costs (hospitalizations, absenteeism, antibiotics, ICS, LABA, mucolytic...) will compensate this extra cost later on. It is an investment in their health and quality of life. In that way the patient’s acceptance and feed-back is often positive.
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**STUDY 1**

**REDUCTION OF INFECTIOUS EXACERBATION IN MODERATE TO VERY SEVERE COPD**

(Cazzola, 2006)

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Study 2: Adjuvant Therapy to Regular COPD Treatment (Salmeterol/Fluticasone) (Cazzola, 2009)

**Study Design**
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- 63 patients, randomized in 2 groups (A and B).
- All treated with Salmeterol/fluticasone + 33 received PMBL (group B).
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**Results**
- Reduction of the total number of exacerbations.
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