Functional consequences of COPD exacerbation: suggestions for the clinicians to get a tailored personalized approach to prevent them

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Summary

Exacerbations of COPD (E-COPD) lead to an accelerated lung functional decline and contribute to increase morbidity and mortality connected to the disease. The prevention of exacerbations is a key point in the COPD management that needs to be based not just on the number but even on the most frequent cause of exacerbations. Each prevalent type of E-COPD, in a given patient, should be appropriately prevented by specific treatments that cannot invariably be the use of high dose ICS, as presently recommended by many guidelines.

KEY WORDS: COPD, acute exacerbation, prevention of E-COPD.

Introduction

The natural history of about 1/3 of patients suffering from chronic obstructive pulmonary disease (COPD) is frequently (>1 each year) signed by episodes of so called exacerbations (E-COPD). These episodes are recognized by the patients because of deterioration of their otherwise pretty stable clinical condition occurring acutely (from hours to few days), due to the progressive increase of lung (and systemic) inflammation above the baseline lung inflammation, caused by different reasons (1).

Current definition of COPD exacerbation fails an objective and standardized diagnosis.

E-COPD still lack of a sensitive and specific biomarker (functional, biochemical, radiological, etc.) and therefore they suffer from the absence of a strict definition and diagnosis based on objective and standardized tools.

Thus, the E-COPD definition relies empirically on worsening of symptoms (chronic dyspnea and/or phlegm and cough) with or without fever and their severity is judged according to the reaction they elicit (increase of baseline treatment usually by the patients themselves, prompt change of the therapy as prescribed by the physician or need to be hospitalized because of respiratory, gas exchange or ventilatory failure).

Moreover, the E-COPD diagnosis is based on exclusion criteria, by eliminating other possibilities as responsible of acute clinical deterioration in COPD patients such as pneumonia, bronchiectasitis, pleuritis, pneumothorax, pulmonary edema of different nature, acute or acute-on-chronic heart failure, pulmonary embolism, cardiac arrhythmias (2).

Once a reliable clinical diagnosis of E-COPD is obtained in a COPD patient, the most difficult think rather than treating it, is recognizing its nature: infectious (bacterial or viral or both), eosinophilic, or pauci-inflammatory (Figure 1) (3).

In fact, pneumologists or other physicians are not used to sample any matrix (blood, sputum, urine, etc.) to seek for changes in some indicative biomarkers such as elevated eosinophils blood count, high plasma IP-10 level for rhinovirus infection, increased sputum IL-1b level for bacterial infections or even their absence during an E-COPD, especially in those COPD patients who are frequent exacerbators (4).

Frequent exacerbators often experience a sort of vicious cycle leading to a progressive reduction of time intervals between one episode and another.

This information could be useful to better focus the treatment during a single episode, but might be more relevant in order to plan the prevention of E-COPD that is by far the most important strategy to implement besides the baseline therapy in such patients (5). The reason for that is well known. The major risk to have a new exacerbation is to be a frequent exacerbator, in a sort of vicious cycle that tends to progressively reduce the time interval between one episode and another. The consequence is an accelerated functional decline, because there is not enough time to recover, with worsening of baseline airflow obstruction that in turn represents a relevant risk of frequent E-COPD (6-10).

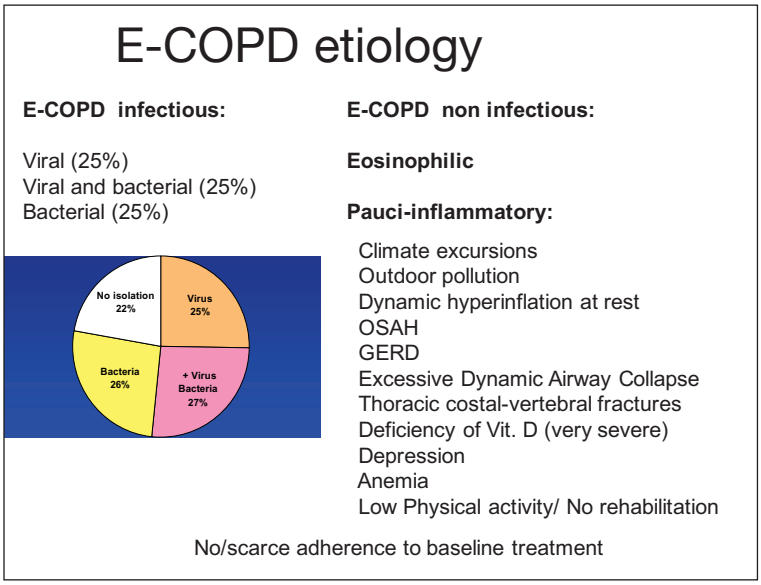

Figure 1 - The figure lists the main causes of E-COPD.

Exacerbations

Albeit their diagnosis, essentially based on worsening of chronic symptoms reported by the patients, is presently still based on the exclusion of other diseases, most of the acute and chronic biological and functional consequences and clinical characteristics of E-COPD are known (Figure 2) (11-16).

Their obvious relevance claims for a deeper knowledge of various nature of E-COPD to understand the underlying patho-physiological mechanisms that can be very different among different patients, but often similar in a given patient. Finding reliable and practical biomarkers of the E-COPD spectrum should be a crucial aim to be reached in the next future to better define the prevalent phenotype and individualize their treatment and prevention (Figures 3, 4) (4).

Finding reliable and practical biomarkers of COPD exacerbation is mandatory to better define phenotypes and individualize treatment and prevention.

The prevention of E-COPD is a point of paramount importance in the COPD management that needs a completely different approach, because it cannot be addressed simply with the baseline pharmacological treatment. Suffering from two or more E-COPD or from one severe E-COPD leading to hospitalization in the previous year is without doubt a marker of COPD severity independently from the underlying disease, degree of airflow obstruction and entity of symptoms or BODE index, even if lower FEV_1 is associated with higher risk of frequent and more severe exacerbations. Although the probability of having a new E-COPD is greater in those COPD patients who previously experienced E-COPD (so called frequent exacerbators) (17), such status, with few exceptions (18-20), should not be identified as a distinct phenotype, rather as a condition requiring more strict social and medical attention. In fact, it is quite easy to shift from a frequent exacerbator to a non-frequent exacerbator and viceversa, sometimes without an obvious reason, but often clearly because of a more adequate and comprehensive treatment and viceversa (21). Given the prognostic importance of E-COPD, however, we cannot limit our interest to count them, but we must learn how to consistently recognize the prevalent type in a single patient, if any. Such possibility is crucial to prevent more effectively the E-COPD tailoring more specific therapies.

Some plasma, blood or sputum biomarkers have been shown to be associated with high sensitivity and specificity to a prevalent clinical type of E-COPD: eosinophilic, infectious either virus or bacteria-associated, that can be distinguished from those called pauci-inflammatory, due to several possible other causes that have to be identified essentially during stable conditions (4). More interestingly, specific biomarkers tend to be detectable also in stable conditions, at least in sputum eosinophilia- and bacteria-associated exacerbations, allowing an easier identification of the most likely future pattern of E-COPD (4). Thus, when possible, each prevalent type of E-COPD in a given patient who is a frequent exacerbator, should be appropriately prevented by specific treatments that cannot invariably be the use of high dose ICS, as presently recommended (1, 22). ICS are very useful to prevent the eosinophilic exacerbations (23-25), but it is hardy to see how ICS can avoid infectious exacerbations, or even non-eosinophilic and non-infectious exacerbations (pauci-inflammatory), apart from strengthening the action of some bronchodilators such LABA in some circumstances (26).

On the other hand, long acting bronchodilators and mainly ultra-long acting bronchodilators (both beta-2 agonist and especially anti-muscarinic drugs) are able

What is known about E-COPD

About 50% of mild E-COPD (defined as a temporary increase of symptoms) are not reported
1 over 8 leads to hospitalization - They represent about 5% of all causes of hospitalization
In acute 10% mortality, up to 15% for those in ICU
They can develop acutely (neutrophils increase) or subacutely (neutrophils + eosinophils increase)
They can aggregate in cluster (higher probability of a second one up to 8 weeks)
75-80% are infectious (25% bacteria, 25% virus, 25% virus and bacteria)
20-25 % are non infectious (GERD, climate change, pollution, OSAH etc.)
Different biological phenotypes: high blood eosinophils, high sputum IL-17 e IL-5; increased plasma IP-10; pauci-inflammatory
The phenotype seems consistent
They alter respiratory mechanics and gas exchange
Airflow obstruction, dynamic hyperinflation and symptoms increase acutely during E-COPD
They increase morbidity and reduce quality of life
They may accelerate lung functional decline
They increment centrilobular emphysema
They increase mortality in a long term (in relationship to their number and mostly their severity)
They increase acutely the specific markers (local and systemic) of inflammation
They increase the plasma pro-trombotic factors
They induce inflammation of intercostal muscles
They cause weakness and decrease endurance of skeletal muscles
They reduce the physical daily activity
They worse comorbidities acutely : IMA, heart failure, stroke
They worse comorbidities chronically (+ arterial stiffness, + osteoporosis, + depression)
They increase (acutely and chronically) pulmonary arterial hypertension
They increase the direct (mostly) and indirect costs of COPD

Figure 2 - Biological, functional and clinical consequences of E-COPD are decribed.

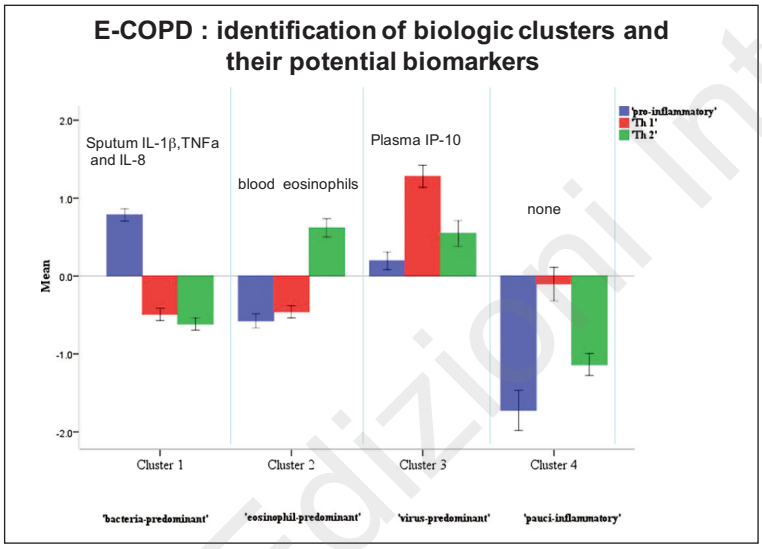

Figure 3 - The biological clusters and their most relevant acute biomarkers are illustrated according to the nature of E-COPD (*modified from Bafadhel et al.*).

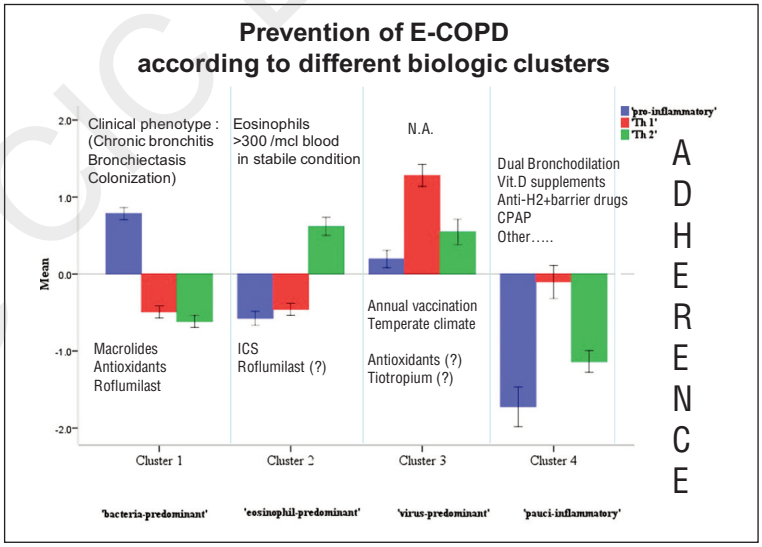

Figure 4 - The possible targeted treatments to prevent E-COPD, based on their biological clusters and the related functional and clinical predictors (*modified from Bafadhel et al.*).

There is strong evidence that macrolides may reduce significantly of exacerbations in some clinical phenotypes of COPD patients with high risk of bacterial colonization or chronic infections.

to prevent up to 30% of COPD exacerbations when given alone (26) and possibly even more when given in combination (27).

In many COPD patients with bronchiectasis and chronic bronchitis a lot of E-COPD are infectious and bacterial in nature and must be prevented with antibiotic prophylaxis, at least in the cold season. There is strong evidence that macrolides may reduce significantly E-COPD (28-30), suggesting that this kind of exacerbation can be prevented in some clinical phenotypes of COPD patients with high risk of bacterial colonization or chronic infections.

Presently, only adequate immunization against influenza virus can be offered for the prevention of viral exacerbations in COPD patients and we urgently need same effective tools for rhinovirus infection, the most common cause of virus-associated E-COPD.

All other types of E-COPD (noninfectious, non-eosinophilic) deserve accurate work-up and specific treatment should be applied to prevent them when the cause is recognized. Many of these exacerbations, in fact, can be largely avoided with targeted approaches (26, 31-33).

For instance, in the presence of COPD patients with presumable high oxidative stress (those who continue smoking, those with chronic bronchitis, and those with high exposure to environment pollution) an adequate antioxidant support might significantly reduce E-COPD in a long term (34, 35).

A strict adherence to therapy is crucial either to reduce exacerbations with their consequences and for a better control of the disease.

Finally, a strict adherence to baseline chronic therapy should be assured throughout a strong relationship between COPD patients and their physicians and care-givers, because this aspect seems crucial also to obtain a better control of E-COPD and their consequences (36).

In summary, in patients with COPD after having established the baseline treatment to control symptoms and improve both lung function and exercise tolerance and quality of life, look at the exacerbations of COPD. If they are frequent (more than one in a year) try to detect their prevalent phenotype (eosinophilic, bacterial or due to other causes) and treat to prevent them accordingly.

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