

Review

Prevention of Exacerbations in Chronic Obstructive Pulmonary Disease: Knowns and Unknowns

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Abstract

The 2011 recommendations of the Global initiative for chronic Obstructive Lung Disease (GOLD) constituted a major paradigm shift in COPD management since they set 2 major goals for the assessment and management of patients: (1) the reduction of their current level of symptoms (i.e., treat the patient *today*); and (2) the reduction of their risk of exacerbations (i.e., prevent them *tomorrow*). Exacerbations are not only an important clinical endpoint in patients with COPD, but they are also a risk factor themselves for additional adverse outcomes since they have been shown to increase the risk for mortality, to accelerate the decline in pulmonary function, and to decrease health status and quality of life. Despite their importance, many unanswered questions related to exacerbations remain. The purpose of this review is to discuss: (1) *knowns* and *unknowns* in our current understanding of exacerbations, (2) what known factors increase their risk, and (3) how to best prevent them.

Abbreviations: computed tomography, **CT**; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, **ECLIPSE**; Body mass index-airway Obstruction-Dyspnea-Exercise capacity index, **BODE**; COPD Assessment Test, **CAT**; the EXAcerbation of Chronic Pulmonary Disease Tool, **EXACT**; hazard ratio, **HR**; confidence interval, **CI**; long-acting muscarinic antagonist, **LAMA**; long-acting β_2 -agonist, **LABA**; inhaled corticosteroids, **ICS**; TOWards a Revolution in COPD Health, **TORCH**; Prevention Of Exacerbations with Tiotropium in COPD, **POET-COPD**; obstructive sleep apnea, **OSA**; forced expiratory flow between 25% and 75% of forced vital capacity, **FEF₂₅₋₇₅**; forced expiratory volume in 1 second, **FEV₁**; interleukin, **IL**; St. George's Respiratory Questionnaire, **SGRQ**; tumor necrosis factor, **TNF**; white blood cell, **WBC**;

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Introduction

The 2011 recommendations of the Global initiative for chronic Obstructive Lung Disease (GOLD) propose that the assessment and treatment of COPD patients should be structured around 2 major goals: the reduction of the current level of symptoms (i.e., treat the patient *today*); and, the reduction of the risk of future exacerbations of the disease (COPD exacerbations) (i.e., prevent them *tomorrow*).¹ The latter is a major step forward for COPD, in many ways similar to that achieved by cardiologists decades ago when they realized that they should treat not only symptoms (dyspnea) or acute events (angina), but also to reduce the risk of future events by decreasing arterial blood pressure and/or cholesterol levels. Further, COPD exacerbations are not only important clinical endpoints in themselves,²⁻⁵ but also increase the risk for mortality^{6,7} accelerate the decline in pulmonary function,⁸⁻¹¹ worsen cardiovascular comorbidities,^{12,13} decrease health status,^{14,15} and impair activities of daily living.¹⁶⁻¹⁸

Despite their importance, many questions related to COPD exacerbations remain unanswered. The purpose of this paper is to review the current state of the art with respect to prevention of COPD exacerbations. Specifically, it discusses: (1) *knowns* and *unknowns* in our current understanding of COPD exacerbations, (2) factors that increase their risk, and (3) how to prevent them. It does not discuss the adequacy of the treatment of these episodes^{1,19} which has been the subject of recent research.^{20,21} It is important to note, however, that this is not a systematic review of the literature and basically reflects the opinions of the authors.

COPD Exacerbations: Knowns and Unknowns

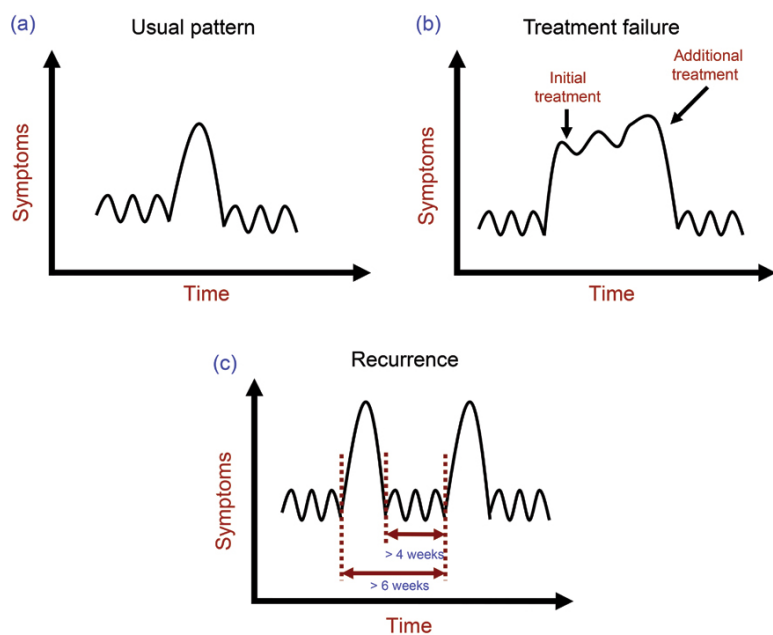
According to GOLD “an exacerbation of COPD is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.”¹ This definition is straightforward, yet it has several caveats that deserve discussion. First, it is entirely based on the perception by the patient of an increase in symptoms, which is known to vary significantly among individuals. It is entirely possible, therefore, that different patients may have different perception thresholds. This has been well established in patients with asthma,^{22,23} but has been much less investigated

in COPD. In support of this possibility is the fact that the use of diary cards to monitor COPD patients at home has shown that they may experience increases in symptoms that are indistinguishable from those occurring during exacerbations that receive treatment but are not reported/treated; so-called *unreported exacerbations*.^{14,24} Alternatively, poor family and social support may result in some patients reporting more episodes of symptom deterioration than they would have otherwise. These 2 examples illustrate the poor specificity and the unknown reproducibility of the currently accepted definition of an exacerbation of COPD. Given that this definition is used in many clinical trials, it is likely that exacerbation rates in trials are generally under-reported. It is fair to acknowledge that our current understanding of this topic is limited and that identification and proper validation of a diagnostic biomarker(s) for exacerbation is urgently needed. Using again the cardiology analogy, this would be equivalent to diagnosing or missing an acute myocardial infarction based on symptoms alone (without the aid of electrocardiography and biochemical changes). We used to do this once upon a time, but fortunately for patients with acute coronary artery disease, things have changed.

Second, some, but not all, patients appear to be particularly prone to suffer repeated exacerbations, the so-called *frequent exacerbators*.^{8,14} Whether this represents true recurrence of exacerbations or, at least in some cases, treatment failure is difficult to dissect (Figure 1)²⁵ since exacerbations cluster and frequent exacerbators are more likely to have recurrent exacerbations.²⁶ Likewise, how much time must elapse between events to consider them as independent episodes is still debated^{25,26} since it is necessary to know when the event starts and stops before a new event can be identified. It is plausible that different individual thresholds and/or degrees of social support (as discussed above) confound the rate of exacerbations reported by any single patient. Similarly, adherence to therapy is also likely to influence the frequency or persistence of exacerbations in COPD patients.

Third, exacerbations are heterogeneous. Traditionally, they have been related to viral and/or bacterial respiratory infection.^{27,28} In support of this possibility, Papi et al showed that bacteria and/or viruses could be detected in 78% of 64 patients hospitalized for exacerbations.²⁹ To explore the role of infection in the pathobiology of exacerbations further, Mallia et al³⁰

Figure 1.



Proposed time-course patterns of COPD exacerbations: (a) *usual pattern*, (b) *treatment failure* (c) *recurrence*. For further explanations, see text. Reproduced with permission from Informa Healthcare, copyright ©2010, Informa Healthcare.²⁵

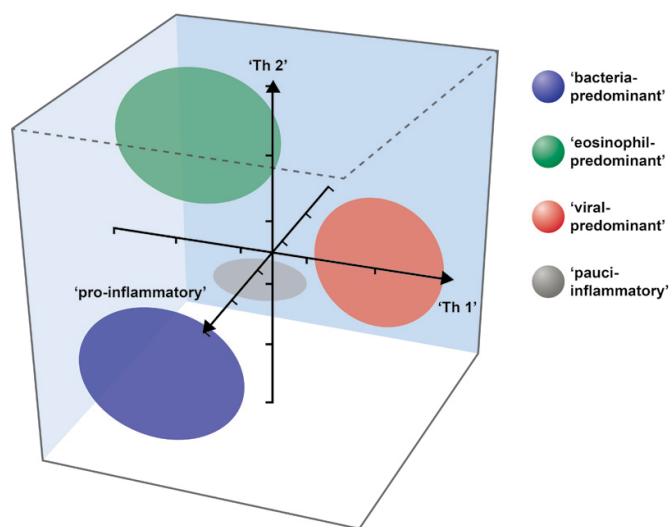
exacerbation. Other symptoms, such as cough, have been poorly studied during exacerbations and systemic features, such as lethargy and fatigue, are not routinely assessed.

Finally, cardiovascular diseases are highly prevalent among patients with COPD.³³ Recent research has begun to explore the possibility that occult cardiac disease may also play a role in the pathogenesis of COPD exacerbations. For instance, cardiac troponin has been shown to be frequently elevated in COPD exacerbations and is correlated with mortality among hospitalized patients.³⁴ In this context, it is worth noting that Garcia-Aymerich et al³⁵ used cluster analysis in a cohort of 342 patients hospitalized for the first time because of a COPD exacerbation and identified 3 groups of patients with different clinical, functional, imaging, and, more importantly, outcomes during a 4-year follow-up: Group 1 (n=126, 37%) was labeled as *severe respiratory COPD* because they were characterized by severe airflow limitation (mean FEV₁ 38% predicted) and extensive emphysema on computed tomography (CT). Group 2 (n=125, 37%) was labeled as *moderate respiratory COPD* because they showed

investigated the effects of experimental rhinovirus infection in 13 COPD patients and in 13 smokers with normal spirometry. They found that following rhinovirus infection, COPD patients developed more lower respiratory symptoms, more airflow limitation, and more systemic and airway inflammation than controls, thus providing circumstantial support for respiratory infections as a driver of exacerbations in COPD. Yet, recent research has also shown that not all exacerbations can be related to an infectious agent. Bafadhel et al³¹ studied 182 exacerbations in 145 patients and reported that bacteria and viruses could be isolated in 55% and 29%, respectively of all exacerbations but, importantly, not in all of them. These authors proposed that exacerbations may be subdivided into 4 distinct clusters: bacterial, viral, eosinophilic, and pauci-inflammatory (Figure 2) and suggested that sputum interleukin (IL)-1 β , serum CXCL10, and peripheral eosinophils could serve as diagnostic biomarkers for bacteria-, virus-, or eosinophil-associated exacerbations, respectively.³¹

Fourth, the symptoms of exacerbations include increased breathlessness, sputum volume, and sputum purulence as key features,³² but they do not always occur together and may develop at different times during the

Figure 2.



Three-dimensional, proportional ellipsoids representation of 4 clusters identified in patients with COPD exacerbations. For further explanations, see text. Reproduced from *American Journal of Respiratory and Critical Care Medicine* with permission.³¹

milder airflow limitation (mean FEV₁ 63% predicted), but had similar emphysema characteristics compared to Group 1. Group 3 (n=91, 27%) was labeled *systemic*

COPD because they combined a milder airflow limitation (FEV₁ 58% predicted) with a high proportion of obesity, cardiovascular disorders, diabetes, and systemic inflammation, but no emphysema on CT. Importantly, during follow-up, Group 1 had more frequent hospitalizations due to COPD (hazard ratio [HR]=3.28, $p<0.001$) and higher all cause mortality (HR=2.36, $p=0.018$) than the other 2 groups, whereas Group 3 had more admissions due to cardiovascular disease (HR=2.87, $p=0.014$) (Figure 3).

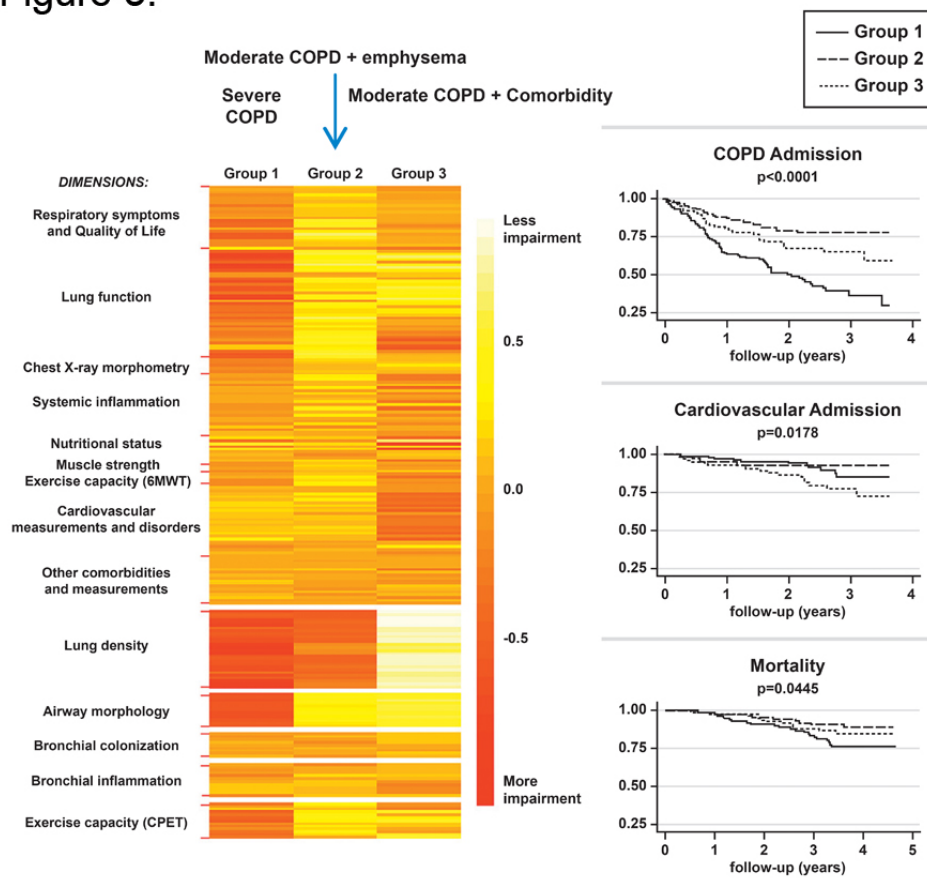
The results of this important study raise several important questions. First, how can it be that patients in Group 1 (with severe respiratory COPD) had not required hospitalization earlier during the course of their disease? Was it because they were poor perceivers, as discussed above, or just had no prior severe episodes? Second, these data provide clear evidence of heterogeneity among episodes of exacerbation and/or among individual patients suffering an exacerbation of COPD, as mentioned by the authors. Third, some exacerbations of COPD may actually represent exacerbation

of symptoms in patients with COPD due to worsening of other less apparent, but frequent, comorbid diseases, such as heart failure.³⁶ These questions deserve specific research if we are to understand, prevent, and treat these important events better and in a more effective manner.

Known Risk Factors for Future Exacerbations

The risk of exacerbations varies greatly among patients. For instance, results from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study showed that of the 2138 patients studied, 24% did not experience exacerbations during the 3 years of follow-up, 47% experienced ≥ 1 exacerbation per year, and 29% experienced ≥ 2 exacerbations.⁸ However, these figures cannot be used as standards since there are several aspects that might

Figure 3.



Panel A: Heat-map of the different COPD dimensions that characterize the 3 groups identified in the analysis. Group 1 was characterized by severe airflow limitation and worse performance in most of the respiratory domains of the disease. Group 2 combined milder airflow limitation with emphysema. Group 3 showed milder airflow limitation and a high proportion of obesity, cardiovascular disorders, diabetes and systemic inflammation; Panel B: Longitudinal clinical outcomes of these 3 groups of patients with COPD. For further explanations, see text. Reproduced from *Thorax* with permission from EMJ Publishing Group, Ltd.³⁵

have influenced them significantly. First, exacerbations were defined by a health care utilization definition and some may have been missed. Second, a period of stability was needed to be included in ECLIPSE and this may have reduced the number of frequent exacerbators recruited. Third, all patients included in ECLIPSE were treated by their local physician and this could have reduced the reported exacerbation frequency.

Table 1 summarizes the evidence supporting a number of identified risk factors for exacerbations. These include: older age,³⁷ presence of stable state symptoms (cough, sputum, and dyspnea),^{14,37-40} poor health status,^{14,40,41} severe airflow limitation,^{8,37,42} worse BMI-airway Obstruction-Dyspnea-Exercise capacity (BODE) Index score,⁴³⁻⁴⁵ presence of medical and psychiatric comorbidities,^{37,46-50} persistent pulmonary,⁵¹ and systemic inflammation,⁵² bacterial

Table 1. Risk Factors for COPD Exacerbations

Risk Factor	Details of Relationship	Reference
Previous Exacerbations	Results from ECLIPSE indicated that the major determinant of frequent exacerbations in all GOLD stages of COPD severity was a history of exacerbations.	8
Older Age	Age >65 years was a significant risk factor for exacerbations ($p=0.012$ versus individuals ≤ 65 years old) in a cohort of 551 patients with COPD.	37
Severity of Airflow Limitation	Exacerbation rate increased with COPD severity in ECLIPSE. In the first year of follow-up, it was 0.85 for patients with GOLD stage II COPD, 1.34 for patients with stage III COPD, and 2.00 for patients with stage IV disease. Overall, 22% of patients with stage II disease, 33% with stage III disease, and 47% with stage IV COPD had frequent exacerbations (≥ 2 in the first year of follow-up).	8
	Combined analysis of results from 37 studies indicated that event-based exacerbation frequencies per GOLD stage were 0.82 for mild, 1.17 for moderate, 1.61 for severe, and 2.10 for very severe COPD. Annual symptom-based frequencies were 1.15, 1.44, 1.76, and 2.09, respectively. For severe exacerbations (requiring hospital admission) annual frequencies were 0.11, 0.16, 0.22, and 0.28, respectively.	42
	Lower FEV ₁ % predicted was associated with increased risk for an exacerbation in a study of 1829 patients with moderate-to-severe COPD ($p<0.001$).	37
High BODE Index	Results from a cohort of 120 patients with mild-to-very severe COPD indicated that the relationship between the risk for moderate or severe exacerbations and BODE index score was an odds ratio of 2.08 over 1 year of follow-up.	43
	A 1-year retrospective study of 76 patients with a total of 178 exacerbations showed that exacerbation frequency was significantly correlated with BODE index score ($p=0.002$).	44
	An 8-year follow-up of 275 COPD patients indicated that the mean times to a first exacerbation and a first COPD-related emergency department visit were each inversely related to worsening BODE score (based on quartiles).	45
Chronic Bronchitis	A study of 70 patients who were followed for 1 year showed that daily cough ($p=0.018$) and daily cough and sputum ($p=0.009$) were each associated with increased exacerbation frequency.	14
	A study of 1829 patients with moderate-to-severe COPD indicated that productive cough was associated with increased risk for an exacerbation ($p=0.003$).	37
	A cross-sectional study of 433 patients with COPD indicated that those with chronic cough and sputum production had significantly increased risk for total, moderate, and severe exacerbations ($p<0.0001$).	38
	A study that included 759 patients with COPD indicated that those with chronic bronchitis had more frequent exacerbations than those without such symptoms.	39
	A case-control study of 192 patients with GOLD stage III or IV COPD who were frequent exacerbators (≥ 2 moderate-to-severe exacerbations per year) versus 153 non-exacerbators indicated the modified Medical Research Council dyspnea score and FEF ₂₅₋₇₅ % predicted were significant predictors of frequent exacerbator status ($p<0.05$).	40
Poor Health-Status	A study of 70 patients with COPD indicated that total score and each of the scales from the SGRQ were significantly correlated with risk for exacerbations (all $p<0.05$)	14
	Results from 121 patients with moderate-to-severe COPD indicated that each unit increase in the total SGRQ score was associated with a 3% higher risk of being a frequent exacerbator ($p=0.047$).	130
	Results from a study of 161 patients indicated that frequent exacerbators had significantly higher baseline CAT scores than infrequent exacerbators ($p=0.025$). ^a	41

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	Comorbid cardiovascular disease was a significant predictor of hospitalization for an exacerbation in a cohort of 1829 patients with moderate-to-severe COPD who were followed for 6 months ($p < 0.001$).	37
	Assessment of 106 patients with COPD (29 with metabolic syndrome and 77 without this condition) followed for 12 months indicated that the mean exacerbation frequency was 2.4 in those with metabolic syndrome versus 0.68 for those without this condition ($p < 0.001$).	46
Presence of Systemic Disease/Comorbidities	Results from a prospective cohort study in 491 patients with stable COPD indicated that probable depression was associated with an increased risk of symptom-based exacerbations, event-based exacerbations, and hospitalization due to exacerbations versus no depression.	47
	A study of 110 patients with stable COPD indicated that those with psychiatric disorders had significantly increased risk for exacerbations ($p = 0.003$).	48
	A study of 169 patients indicated that frequent exacerbators had a significantly higher median baseline depression score than infrequent exacerbators ($p = 0.03$).	49
	A study of 1755 COPD patients, 297 smokers with normal spirometry, and 202 non-smoker controls that were followed-up for 3 years indicated that evidence of systemic inflammation (elevated peripheral WBC count, CRP, IL-6, IL-8, fibrinogen and TNF- α) was associated with increased exacerbation frequency ($p < 0.001$).	52
	Results from 29 patients with COPD indicated that lower airway colonization (most common pathogens were <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>H parainfluenzae</i> , <i>Moraxella catarrhalis</i> , and <i>Pseudomonas aeruginosa</i>) was associated with increased exacerbation frequency ($p = 0.023$).	53
Bacterial Colonization of Lower Airways		
Bronchial Wall Thickness	A study of 1002 patients with COPD indicated that each 1 mm increase in bronchial wall thickness measured from CT scans was associated with a 1.84-fold increase in annual exacerbation rate ($p = 0.004$).	54
Emphysema	For patients with 35% or greater total emphysema, each 5% increase in emphysema was associated with a 1.18-fold increase in this rate ($p = 0.047$).	54
Gastroesophageal Reflux	Results from ECLIPSE indicated that more frequent exacerbations were associated with a history of gastroesophageal reflux disease.	8
Increased Pulmonary Artery Diameter	Pulmonary artery enlargement (a PA:A ratio of > 1), as detected by CT, was associated with severe exacerbations of COPD.	55

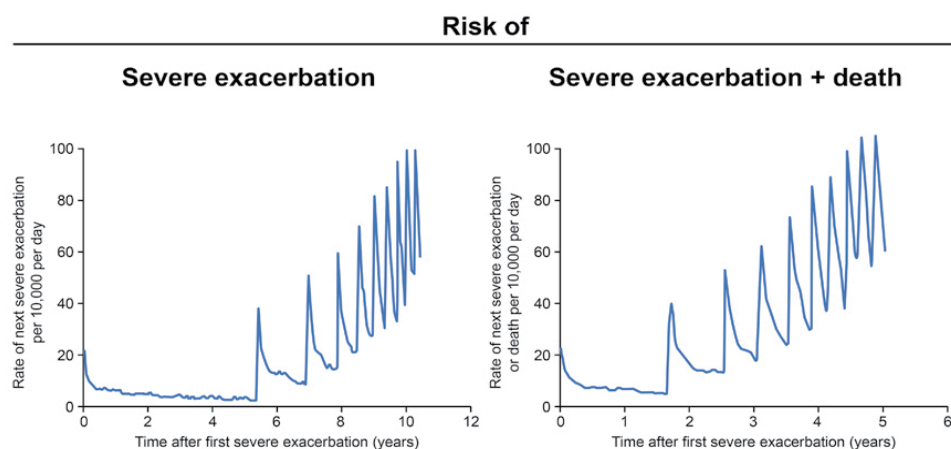
BODE = Body mass index-airflow Obstruction -Dyspnea-Exercise capacity, CRP = C-reactive protein, ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, FEF₂₅₋₇₅ = Forced Expiratory Flow Between 25% and 75% of Forced Vital Capacity, FEV₁ = forced expiratory volume in 1 second, IL = interleukin, SGRQ = St George's Respiratory Questionnaire, TNF = tumor necrosis factor, WBC = white blood cell; CAT=COPD Assessment Test

^aResults from clinical studies have shown that the minimum clinically important difference for CAT score ranges from -1.6 to -2.0.^{41,82,131} Changes of -1.3 and -3.8 were reported by patients who indicated that they felt a little better or much better, respectively, after pulmonary rehabilitation.¹³¹ Exacerbations increase the CAT score by +5.2.⁴¹

airway colonization,⁵³ airway wall thickening demonstrated by computed tomography (CT),⁵⁴ gastroesophageal reflux⁸ and pulmonary artery enlargement detected by CT.⁵⁵ Finally, female gender has been noted to be associated with increased risk of exacerbations in several recent large clinical trials^{56,57} although it is unclear whether this represents a difference in reporting or disease biology.

Furthermore, it has been suggested that exacerbations beget exacerbations. A large study carried out by Suissa et al using a Canadian Pharmacy database that included 73,106 patients hospitalized for the first time for COPD and followed for up to 17 years showed that the risk of a subsequent severe exacerbation increased 3-fold after the second exacerbation requiring hospitalization, and 24-fold after the 10th exacerbation as compared to after the first hospitalization for an exacerbation (Figure 4).

Figure 4.



Hazard function of successive hospitalized COPD exacerbations (per 10,000 per day) from the time of their first ever hospitalization for a COPD exacerbation over the follow-up period. For further explanations, see text. Reproduced from *Thorax* with permission from BMJ Publishing Group, Ltd.⁵⁸

From these observations, Suissa et al suggested that the course of COPD has 2 phases after the first hospitalized exacerbation. The first is a less than 2-year period of stable risk until the second hospitalized exacerbation or death. After the second hospitalized exacerbation, severe exacerbations recur progressively sooner after each subsequent severe exacerbation and the mortality rate rises with every new exacerbation. Thus, there is a window of opportunity during the stable phase after the first hospitalization to intervene and potentially prevent a subsequent severe exacerbation.⁵⁸ In keeping with this view, it is now recognized that COPD exacerbations cluster and that having an event makes a patient more susceptible to another event within an 8-week period.²⁶

Patients who are frequent exacerbators are also more likely to have a history of recurrent events.²⁶ However, when the gap between episodes is long, the progression of COPD itself may sensitize the patient to episodes that would have appeared minor earlier in the disease. In any case, recurrent hospitalization for exacerbations is a common and serious problem in COPD^{59,60} and reducing the risk for exacerbation-associated rehospitalization is thus an important treatment goal.

Reducing the Risk of Future Exacerbations

Decreasing or, ideally, abolishing exacerbations is an important goal in COPD.⁶¹ Over the past 2 decades, several new approaches to exacerbation risk reduction have emerged. Table 2 summarizes the efficacy of different therapeutic options in decreasing COPD exacerbations and the following sections discuss these options in detail. However, 3 notes of caution are worth emphasizing in order to interpret published findings.

First, when considering the clinical trials and meta-analyses described in the following sections, it is important to emphasize that a number of factors can influence results reported, including definition and recording of exacerbations, the baseline exacerbation rate for the patient, and study duration. Thus, while comparisons of different interventions within a given well-controlled trial provide useful

information about relative efficacy of treatments, use of results from different studies to compare treatments should be viewed with caution.

Second, multiple approaches have been employed to capture exacerbations in clinical trials. These include the occurrence of “harder” events, such as requirement for specific changes in medication (e.g, administration of systemic corticosteroids and/or antibiotics) and hospitalization⁶²; use of symptom diary cards,^{14,63} and specific questionnaires, such as the COPD Assessment Test (CAT)⁴¹ and the Exacerbations of Chronic Pulmonary Disease Tool (EXACT).⁶⁴ It has been noted that the use of different methods to define and analyze exacerbations can result in biased estimates of

Table 2. Efficacy of Different Approaches to Decreasing Risk for Exacerbations

	Efficacy	Support	References
Non-pharmacologic Interventions			
Smoking Cessation	Supported	Large-scale observational study	66
Pulmonary Rehabilitation	Supported	Small-scale clinical studies	68, 69
Vaccination Against Pneumococcal and Influenza Virus Infection	Very strongly supported	Multiple clinical trials and meta-analyses	70-74
Pharmacotherapy			
LABA	Very strongly supported	Meta-analyses and multiple clinical trials	13, 76
LAMA	Very strongly supported	Meta-analyses and multiple clinical trials	57, 79, 80, 82, 83
LABA + LAMA vs. Monotherapy	Supported for LABA + LAMA vs LAMA monotherapy	Clinical trial	132
ICS Monotherapy	Supported	Meta-analysis, benefit limited to patients with FEV ₁ <50%	91
ICS + LABA vs ICS or LABA monotherapy	Very strongly supported	Multiple clinical trials	56, 94
Triple Combination Therapy vs. Components	Variable results	Small-scale clinical trials provide conflicting results; meta-analysis indicates no significant benefit; large-scale observational study supports	102-105, 133
Systemic Treatments			
Roflumilast	Very strongly supported as add-on treatment to bronchodilators	Multiple large-scale clinical trials and meta-analysis	106-109
Macrolides/Quinolones	Strongly supported	Supported by large-scale clinical trials	116, 117
Statins	Supported	Supported by multiple observational studies, but no controlled trials to date	121, 122

ICS = inhaled corticosteroid, LABA = long-acting β 2-agonist LAMA = long-acting muscarinic antagonist

treatment effects, so it has been suggested that trials should report time-weighted intention-to-treat analyses with adjustments for between-participant variation in COPD exacerbations.⁶⁵

Third and finally, it is also of note that none of the therapeutic interventions discussed below fully prevents exacerbations. On average, most reduce their incidence by 15%-30%, so a large number of exacerbations are not prevented by current therapies. Again, however, some words of caution are necessary. First, the above caveats about the definition of exacerbations and differentiation from worsening of the same episode or recurrent episodes (Figure 1) apply here. Second, data are average results observed in large cohorts. Whether or not this occurs in an individual patient remains a different issue. In fact, Hurst et al showed that, in ECLIPSE, a significant number of individual patients switch from suffering frequent exacerbations (≥ 2 /year) to 1 or less (and vice versa).⁸ Further, the extent to which the reduction of exacerbation rates observed in clinical trials can be directly extrapolated to the real world, where compliance with treatment is likely lower,

is unclear. Finally, until we have a comprehensive understanding of the pathobiology of exacerbations (infection, spontaneous burst of inflammation, bronchospasm, others) it will be difficult to define a therapeutic strategy, including the effective treatment of all the trigger factors, that achieves an exacerbation-free COPD goal.⁶¹

Non-pharmacologic Interventions

Smoking Cessation

Stopping smoking decreases the risk for exacerbations. In a cohort of 23,971 United States military veterans, being an ex-smoker rather than a current smoker significantly reduced the risk of COPD exacerbations even after adjustment for age, comorbidity, markers of COPD severity and socioeconomic status (adjusted HR =0.78, 95% confidence interval (CI)=0.75-0.87).⁶⁶ The exact mechanism is unknown although it should be noted that nicotine is a

growth factor for non-typeable *Haemophilus influenzae*, which is thought to be a major bacterial pathogen in at least some exacerbations.⁶⁷

Pulmonary Rehabilitation

Meta-analysis of results from 9 relatively small trials that included 432 patients indicated that pulmonary rehabilitation significantly decreased future hospital admissions ($p < 0.05$).⁶⁸ Results from an additional controlled trial of 60 patients admitted to the hospital for an exacerbation also indicated that post-discharge pulmonary rehabilitation significantly decreased the risk for subsequent exacerbations ($p = 0.02$).⁶⁹ These benefits may reflect a resetting of the symptom threshold and/or the improvement of the general physical condition of the patient.

Vaccination

Results from several studies and meta-analyses have demonstrated that vaccination against influenza virus (and possibly pneumococcus) decreases the risk for

exacerbation in patients with COPD.⁷⁰⁻⁷⁴ presumably by enhancing the immunity against such organisms.

Bronchodilator Treatment

Long-acting bronchodilator treatment is the cornerstone for treatment of stable COPD⁷⁵ and it significantly decreases the risk for exacerbations.⁷⁶⁻⁷⁸ A meta-analysis of results from 9 clinical trials that compared tiotropium (a long-acting muscarinic antagonist [LAMA]) with placebo, ipratropium, or salmeterol (a long-acting β 2-agonist [LABA]) showed that tiotropium reduced the number of exacerbations per patient-year by 0.31 (95% CI=0.46-0.17) compared to placebo, and by 0.23 (95% CI=0.31-0.15) compared to ipratropium. The number of hospitalizations was reduced by 0.04 (95% CI=0.08-0.01) per patient-year compared to placebo and by 0.06 (95% CI= -0.09 to -0.03) per patient-year compared to ipratropium.⁷⁹ A significant difference in exacerbation frequency between tiotropium and salmeterol also was reported (-0.16, 95% CI= -0.29 to -0.03) based on the results from a single study included in the analysis.⁷⁹ Results from another meta-analysis of 9 studies compared salmeterol with placebo/usual care⁷⁶ and indicated that salmeterol significantly decreased the risk for moderate (requiring the use of additional oral corticosteroids and/or antibiotics) or severe (requiring hospitalization) exacerbations by 22% over 12 months ($p<0.0001$). The benefit of salmeterol was maintained regardless of the severity of airflow limitation, smoking history, or current therapy.⁷⁶

A 1-year head-to-head comparison of tiotropium and salmeterol in 7376 patients with COPD showed significant superiority of tiotropium over salmeterol in decreasing risk for exacerbations.⁸⁰ This occurred whether the effect was defined as an increase in, or new onset of, more than 1 symptom of COPD, with at least 1 symptom lasting 3 days or more ($p<0.001$), increased time to first exacerbation requiring hospitalization ($p<0.001$), or reduced frequency of annual exacerbations leading the patient's attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both ($p=0.002$), or exacerbations requiring hospitalization ($p<0.001$). Results from a 26-week comparison of tiotropium with indacaterol (a more recently developed LABA) indicated no significant difference between treatments in decreasing risk for exacerbations, defined as onset or worsening of one or more respiratory symptoms for 3 or more consecutive days, plus new treatment (e.g., systemic

steroids, antibiotics, oxygen) and/or hospitalization or an emergency department visit.¹³ Furthermore, a recent comparison of these 2 agents indicated that indacaterol was comparable to tiotropium in terms of annualized exacerbation rates (0.79 versus 0.61; ratio 1.29, one-sided 97.5% CI upper limit 1.44). In this study, an exacerbation was defined as worsening for ≥ 2 consecutive days for ≥ 2 of the major symptoms (dyspnea, sputum volume, or sputum purulence) or worsening of any 1 major symptom together with any 1 minor symptom (sore throat, colds, fever without other cause, increased cough, or increased wheeze).⁸¹

Finally, 2 more recently developed LAMAs, aclidinium and glycopyrronium bromide, have also been shown to significantly decrease the frequency of exacerbations (defined as worsening of 2 or more major symptoms for at least 2 consecutive days or worsening of any 1 major symptom together with any minor symptom for at least 2 consecutive days) in patients with COPD versus placebo.^{82,83}

In summary, available evidence clearly indicates that long-acting bronchodilators significantly reduce the occurrence of exacerbations in patients with COPD. This may represent the improvements in baseline lung function thereby resetting the symptom threshold or the prevention of episodes in which acute bronchoconstriction plays a role. An important question that remains to be definitively answered is whether the combination of a LABA and a LAMA is significantly superior to monotherapy in decreasing exacerbations. Recent results have indeed indicated that a LABA-LAMA combination was significantly superior to LAMA alone in decreasing the rate of moderate to severe exacerbations.⁸⁴ However, it should be noted that results reflect group data and it remains unclear whether the effects of LABA plus LAMA are additive in a given patient or reflect benefit to different individuals or even episodes with different characteristics.

Finally, the effects of methylxanthines in preventing exacerbations are unclear, since according to the GOLD recommendations, treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable.¹ Yet, there is some evidence that these agents may enhance the anti-inflammatory effects of steroid treatment during exacerbations.⁸⁵ Their potential role when combined with inhaled steroid treatment in preventing COPD exacerbations merits further research.

Inhaled Corticosteroids

Since an enhanced and persistent inflammatory response to inhaled gases and particles is believed to be a key pathogenic mechanism of COPD,¹ and COPD exacerbations appear to be often characterized by an inflammatory burst, the use of anti-inflammatory therapy to prevent (and treat) exacerbations is a rational treatment option.^{1,75}

Many different studies have explored the efficacy (and safety) of inhaled corticosteroids (ICS) to reduce exacerbations in patients with COPD, either alone or in combination with LABA or LABA plus LAMA (so-called, triple therapy), and these are reviewed below. It should be noted, however, that the use of ICS in COPD is controversial. *In vitro*, ICS has limited efficacy in suppressing inflammation in cells harvested from COPD patients, an effect that seems to be related to a marked reduction in histone deacetylase-2, the nuclear enzyme required by corticosteroids to de-activate inflammatory genes.⁸⁶⁻⁸⁸ In addition, high doses of ICS may have deleterious effects on bone metabolism and also appear to increase the risk of pneumonia in COPD.^{89,90}

Inhaled Corticosteroid Monotherapy

A meta-analysis of 11 studies that included 8164 patients showed that ICS alone significantly decreased the risk for exacerbations versus placebo (relative risk =0.82, $p < 0.05$ based on 95% CI).⁹¹ However because the use of bronchodilator therapy is mandatory in COPD, (at variance with patients with asthma) ICS as monotherapy is not recommended in COPD.⁹²

Inhaled Corticosteroids Plus Long-acting β -2 Agonist

There is clear evidence that the combination of LABA with ICS is superior to LABA alone in decreasing exacerbations. The Towards a Revolution in COPD Health (TORCH) study was a randomized, double-blind trial that compared salmeterol (50 μ g) plus fluticasone propionate (500 μ g) versus placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years in 6112 patients with COPD and FEV₁ <60% predicted. Study results showed that the combination regimen was significantly superior to placebo ($p < 0.001$), fluticasone ($p = 0.02$), and salmeterol ($p = 0.002$) for decreasing the rate of exacerbations requiring treatment with antibiotics, systemic corticosteroids, or a combination of these interventions ($p < 0.001$, $p = 0.02$, and $p < 0.001$, respectively). Of interest, combination therapy was significantly superior to placebo and ICS alone, but not

to salmeterol, for decreasing the rate of exacerbations requiring hospitalization.⁵⁶ Recent data have confirmed that exacerbation prevention is enhanced by adding ICS to a LABA even when these drugs are given once daily and in the absence of any apparent effect on lung function, at least in one of the trials reported.⁹³ However, patients receiving fluticasone (alone or in combination with salmeterol) had an increased risk of pneumonia.

The efficacy of another ICS/LABA combination, budesonide/formoterol, was compared with placebo, budesonide, and formoterol in 812 patients with moderate-to-severe COPD (mean FEV₁ 36% predicted) in a 12-month, randomized, double-blind, placebo-controlled, parallel-group study. Patients received 2 inhalations twice daily of budesonide/formoterol (160/4.5mg), budesonide (200mg), formoterol (4.5mg), or placebo. The combination of budesonide/formoterol significantly decreased exacerbations compared to placebo ($p = 0.035$) and formoterol alone ($p = 0.043$).⁹⁴ These results were reproduced by Calverley et al.⁹⁵ Again the added benefit of ICS may reflect prevention of a different exacerbation variant, perhaps those associated with eosinophilic inflammation.^{96,97} Some studies suggest that the risk of pneumonia is lower in patients treated with budesonide than with fluticasone.^{98,99}

Inhaled Corticosteroids Plus Long-acting Muscarinic Antagonists

The effects of ICS plus a LAMA (tiotropium) have been evaluated for outcomes, including pulmonary function, symptoms, and health-related quality of life,^{100, 101} but there is no published information regarding the benefit of this combination versus LAMA monotherapy for decreasing exacerbations. However, the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) study showed that once-daily treatment with tiotropium was more effective than twice-daily salmeterol (with or without ICS) in preventing exacerbations⁸⁰ suggesting ICS may provide little additional benefit to LAMA.

Triple Therapy

Studies that have assessed the effects of LABA plus ICS plus tiotropium on the risk of future exacerbations have produced mixed results. Those showing evidence in favor of the use of triple therapy include the following: (1) A study of 126 patients showed that the combination of tiotropium plus salmeterol/fluticasone resulted in significantly fewer exacerbations than either tiotropium

or salmeterol/fluticasone over 12 months of follow-up ($p < 0.01$).¹⁰² (2) A 12-week, randomized, double-blind, parallel-group, multicenter study that included 660 patients who received tiotropium plus either budesonide/formoterol or placebo twice daily, showed that triple therapy significantly decreased the risk for severe exacerbations ($p < 0.001$) and the frequency of hospitalizations and emergency department visits ($p = 0.011$) versus tiotropium alone.¹⁰³ This latter study, however, lasted only 12 weeks, so results should be viewed with caution since it has been recommended that studies investigating COPD exacerbations should have a duration of at least 12 months because of seasonal variation in exacerbation frequency.⁶³ (3) A recent observational study that included results from 3333 Medicare enrollees also showed that triple therapy with fluticasone, tiotropium, and salmeterol was significantly superior to tiotropium alone in reducing the risk for moderate exacerbations (HR=0.772, 95% CI=0.641-0.930) and any exacerbation (HR=0.763, 95% CI=0.646-0.949). However it should be noted that all of these studies assume that double combination is superior to monotherapy.

The ideal study should be triple therapy versus each component of the combination and an arm comprised of ICS/LABA and this has been approximated by several trials. (1) A Canadian study of 449 patients with moderate or severe COPD reported that the addition of either salmeterol, or salmeterol plus fluticasone to tiotropium did not significantly decrease the frequency of exacerbations versus tiotropium alone, although it did significantly decrease the risk for exacerbations requiring hospitalization (incidence rate ratio=0.53, $p < 0.05$ based on 95% CI).¹⁰⁴ However, this study had an excess of dropouts and was not adequately powered for exacerbations. (2) Results from a meta-analysis of 20 trials (including 6803 patients) that compared tiotropium alone versus tiotropium plus a LABA or tiotropium plus a LABA and ICS, showed no additional benefit of any of the combinations in decreasing exacerbations compared to tiotropium monotherapy.¹⁰⁵

Roflumilast

Roflumilast, a phosphodiesterase 4 inhibitor, is a novel non-steroidal anti-inflammatory drug that is administered orally for the treatment of COPD. Several studies have evaluated the additive effects of roflumilast on the frequency of exacerbations in patients with COPD. Two identical 12-month studies compared roflumilast

($n = 1537$) versus placebo ($n = 1554$) (on top of usual care) in patients with severe COPD, chronic bronchitis, and a history of at least one exacerbation in the previous year. Results showed that the rate of moderate-to-severe exacerbations was significantly reduced by 17% with roflumilast ($p < 0.0003$).¹⁰⁶ The greatest effect (22% reduction in moderate to severe exacerbations; $p = 0.0017$) was seen in patients with a history of frequent exacerbations (≥ 2 per year).¹⁰⁷ In addition, a pre-specified pooled subgroup analysis showed that roflumilast reduced moderate-to-severe exacerbations when added to LABA by 21% ($p = 0.0011$).¹⁰⁷ Addition of roflumilast to salmeterol in 933 patients with COPD for 24 weeks significantly increased time to first exacerbation ($p = 0.0067$) and decreased the proportion of patients with an exacerbation ($p = 0.0419$) versus addition of placebo.¹⁰⁸ Addition of roflumilast to tiotropium in 743 patients also significantly increased the time to first exacerbation ($p = 0.0264$) and decreased the proportion of patients with an exacerbation ($p = 0.0169$) versus addition of placebo.¹⁰⁸

Several post-hoc analyses provided further relevant clinical information: (1) The effect of roflumilast persisted even in the presence of concomitant treatment with ICS.¹⁰⁹ (2) As reported in abstract form, roflumilast significantly decreased hospitalization due to severe exacerbations¹¹⁰ and that of moderate-to-severe exacerbations when added to tiotropium in highly symptomatic patients (modified MRC scale score ≥ 2 at baseline).¹¹¹ (3) Among frequent exacerbators treated with roflumilast, 32.0% still had frequent exacerbations after 1 year of treatment, as compared to 40.8% of placebo-treated patients ($p = 0.0148$).¹¹² Conversely, 17.5% of infrequent exacerbators treated with roflumilast became frequent exacerbators at year 1, versus 22.9% of those taking placebo ($p = 0.0018$).¹¹² The beneficial effects of roflumilast were seen most clearly in COPD patients with the chronic bronchitis phenotype, suggesting that this is an important clinical biomarker for a responder group. Of note, a proportion of patients had to discontinue roflumilast mostly because of adverse gastrointestinal effects.

Prophylactic Antibiotic Treatment

Since bacterial airway colonization with potentially pathogenic organisms can occur in COPD,¹¹³ and this seems to relate to exacerbation risk,^{53,114} several studies have explored whether chronic antibiotic treatment can decrease exacerbation frequency.

Macrolides

A study in 109 COPD outpatients showed that administration of erythromycin 250mg twice daily significantly decreased the frequency and duration of exacerbations over 1 year ($p=0.003$).¹¹⁵ Similarly, a 1-year study of 1142 COPD patients who received azithromycin at a dose of 250mg/day or placebo indicated that active treatment significantly decreased exacerbation frequency ($p=0.01$).¹¹⁶ It remains uncertain whether the benefit reflects the antimicrobial or anti-inflammatory properties of macrolides. Further, development of antibiotic resistance is also a potential complication of long-term macrolide treatment. In the study carried out by Albert et al,¹¹⁶ cultures for susceptibility testing were available from 68% of the participants in the azithromycin group and 70% in the placebo group who were not colonized with selected respiratory pathogens at the time of enrollment but who became colonized during the course of the study ($p=0.76$). In these patients, the incidences of resistance to macrolides were 81% and 41%, respectively ($p<0.001$). Finally, this study also showed that audiogram-confirmed hearing deficits occurred significantly more often with azithromycin than placebo in these patients ($p=0.04$)¹¹⁶ suggesting such an approach should be considered with caution.

Quinolones

A study of 1157 COPD patients who received moxifloxacin or placebo once daily for 5 days, every 8 weeks, for a total of 6 cycles showed that antibiotic administration significantly decreased exacerbations in the per-protocol population ($p=0.046$), but not in the intent-to-treat population ($p=0.059$).¹¹⁷ Furthermore, administration of a single course of moxifloxacin treatment aimed at eradication of bronchial colonization did not significantly decrease exacerbations in a cohort of 119 stable patients with COPD.¹¹⁸ Thus, benefits of quinolones have not been proven although this may reflect failure to enrich the study population for patients colonized with bacteria and exacerbations thought to be of bacterial origin.

Statins

Statins inhibit the enzyme HMG-CoA reductase and are used in clinical practice to treat hypercholesterolemia. Statins also have significant anti-inflammatory effects, and epidemiologic studies have shown that

administration of statins is associated with significantly decreased all-cause mortality in COPD patients.^{119,120} A retrospective study of 185 patients indicated those receiving statins had a significantly lower frequency of exacerbations than those who did not ($p<0.0001$),¹²¹ but such effects have not been evaluated in a prospective controlled trial. Likewise, a study that used the Taiwan National Health Insurance database and included 6252 patients with COPD also indicated that statin use significantly decreased the risk for exacerbations requiring hospitalization.¹²² However, it remains unknown whether these episodes reflect reduction in exacerbations of a cardiac nature.

β -Blockers

It is unclear if treatment with β -blockers decreases mortality in patients with exacerbations. On the one hand, results from 825 COPD patients admitted to the hospital with an exacerbation indicated that β -blocker use was associated with reduced mortality (OR=0.39, 95% CI=0.14-0.99).¹²³ On the other, however, a prospective national study of 2249 patients starting long-term oxygen therapy for COPD in Sweden indicated increased mortality for those receiving β -blockers (HR=1.19, 95% CI=1.04-1.37, $p=0.010$).¹²⁴ Thus, the benefits/harm may be patient phenotype dependent.

Antioxidants

Since COPD is associated with significant oxidative stress, the use of antioxidant agents have also been tested in these patients.¹²⁵ Results, however, have been negative¹²⁶ or arguably reflect a number of methodological flaws¹²⁷ at prevention of exacerbations in patients with COPD.

Targets for Future Research

The studies reviewed above reveal a number of important *knowns* and *unknowns* related to COPD exacerbations. Given the importance of exacerbations in the natural history of the disease, the episodes are clear targets for future research. Among current *knowns* we would include: (1)the realization of the important impact that exacerbations have upon the natural course of the disease and the prognosis and well-being of COPD patients, (2)that multiple risk factors for exacerbations have been established; and (3)that results

from multiple clinical trials have shown that currently available treatments for COPD can decrease, but not abolish exacerbations.

On the other hand, among current *unknowns* we would highlight as particularly relevant are the following: (1) Since COPD exacerbations are heterogeneous^{24,31} there is much more to be learned about the nature of these events and how they differ across the spectrum of patients with this disease (e.g., those with mild versus more severe COPD and those with different comorbidities). Objective outcome measures for detection and assessing severity of exacerbations are required, especially for clinical trials. EXACT is a novel instrument for the study of exacerbations. Available data suggests that when EXACT is used for detection of exacerbations, the relationship between these events and standard health care utilization is not very strong. However, EXACT is a good tool for the assessment of exacerbation severity and recovery.¹²⁸ (2) We need to identify and validate reliable biomarker(s), both biochemical, clinical and physiological, to diagnose exacerbations precisely, differentiate among different types of exacerbations, guide preventive therapy, and establish the prognosis. (3) We need a defined approach for targeting therapies to prevent exacerbations based on their characteristics in a given patient and in different subgroups (i.e., phenotypes) of COPD, since effects of medication on exacerbation rate in different phenotypes have so far been disappointing. For instance, it was not possible to show that roflumilast had a greater effect on exacerbation rate in frequent exacerbators¹¹² suggesting similar variability of episodes in both frequent and infrequent exacerbators. Similarly, the effects of salmeterol/fluticasone or tiotropium on exacerbation rates were similar in GOLD stages II, III and IV. (4) We need to understand the influence of comorbidities on the risk for and nature of exacerbations since improved management of these conditions decrease exacerbation risk. For instance, results from 1 study showed that in patients with both obstructive sleep apnea (OSA) and COPD (termed an *overlap*

syndrome), treatment with continuous positive airway pressure (a standard therapy for OSA) decreased the risk for exacerbations requiring hospitalization.¹²⁹ Much more research is therefore needed to determine whether better management of common COPD comorbidities, such as cardiovascular disease, can decrease the risk for exacerbations. (5) We need to understand whether persistent systemic inflammation is a cause or effect of increasing exacerbation risk.⁵² The effects of available anti-inflammatory therapies (ICS, roflumilast, statins, other) in this particular subgroup of patients deserve further study. (6) We need to understand why we are not able to completely prevent exacerbations, even when all available drugs are used in combination. This suggests that we are not targeting some unknown but important mechanism(s). (7) In addition to treatments designed to prevent exacerbations, the management of the acute episodes clearly needs improvement, since a significant proportion of patients require early hospital readmission and post exacerbation mortality is high.

Building on the current *knowns* will certainly allow the academic community to reduce the number of current *unknowns* and, with that, improve the treatment of patients suffering from COPD, not only because symptoms will be alleviated and their health-status improved today but, importantly, we will reduce the risk of undesired events *tomorrow*.

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