Chapter

Airway Disorders as Predictive Factors of Exacerbations in Asthma and COPD

Hiroaki Kume, Natsumi Watanabe and Yasuhito Suzuki

Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are heterogenous diseases in the respiratory system. Since wheezing, reduced FEV_1, eosinophilic airway inflammation, and airway hyperresponsiveness are observed in some patients with COPD similar to asthma, differential diagnosis is sometimes difficult in subset of these diseases. To advance the management and treatment of asthma and COPD, it is necessary to accurately classify patients with these two diseases according to distinct clinical phenotypes based on clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, and prognosis. However, since several phenotypes are present in individual patients, a search for treatable traits needs to establish precision medicine for asthma and COPD. Since these diseases worsen with each repeated exacerbation, the establishment of treatment to avoid exacerbations is the most important goal of the long-term management of these diseases. Airway physiological and pathological disorders, such as reversibility in FEV_1, airway hyperresponsiveness, airway eosinophilic inflammation, and upper respiratory infection, are probably considered as major predictors of exacerbations. This chapter states clinical phenotypes related to acute exacerbation to establish treatable traits for asthma and COPD.

Keywords: airway eosinophilia, airway hyperresponsiveness, lung function, phenotypes, treatable traits, precision medicine

1. Introduction

Not only bronchial asthma (asthma) but also chronic obstructive pulmonary disease (COPD) is generally considered as a common, preventable, and treatable disease, and these two diseases are complex and heterogeneous [1, 2]. Moreover, the differential diagnosis between elderly asthma and COPD is sometimes difficult using symptoms and lung function tests [3]. To indicate the complexity and heterogeneity concerning asthma and COPD, each patient with these two diseases should be meaningfully divided into groups according to similar clinical characteristics (clinical phenotypes). However, it has not been yet clinically established to identify and classify patients with these two diseases into defined subtypes according to distinct phenotypes. In these heterogenous diseases, individual patients can be stratified according to clinical phenotypes [4, 5]. Stratified medicine for these diseases based on

distinct phenotypes is essential to advance toward personalize (precision) medicine, which is optimal medicine for these heterogenous and incurable diseases, such as asthma and COPD [6–8].

In recent years, longitudinal cohort studies for asthma [9] and COPD [10] were conducted to recognize the heterogeneity of these diseases. These cohort studies are probably beneficial to research clinical phenotypes, which are multiple characteristics in each disease, and for the development of treatable traits based on these distinct phenotypes, leading to the establishment of precision medicine in these two diseases. Each patient with these diseases can be grouped according to phenotypes, and these groupings are proposed to determine clusters of patients with common characteristics that relate to clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, and prognosis (stratified medicine) [5, 11]. Furthermore, multifocal approaches to deal with diseases probably provide relevant information that can classify different subtypes of these diseases. Hence, these heterogeneous diseases should be assessed using multiple dimensions including clinical, physiological, imaging, and endotyping [8, 12].

Since severe exacerbations are closely related to comorbidity, prevention of acute exacerbations is a primary goal of management and therapy for asthma and COPD. Symptoms of these diseases possibly become worse based on various factors including upper airway infections, airway inflammation, comorbidities, and environmental risks [13]. In exacerbations, these two diseases have similar symptoms such as dyspnea, wheezing, chest tightness due to airway obstruction, and mucus production due to airway inflammation. Despite the present guideline-compliant therapy, acute exacerbations are not completely prevented in some cases of these diseases. Mild–moderate exacerbations require additional treatment such as rapid-acting bronchodilators, corticosteroids, and antibiotics. Repeated exacerbations result in a significant deterioration of lung function through airway remodeling [13, 14]. Accelerated loss of lung function in turn brings about increased risk of recurrent exacerbations in these patients, referred to as a vicious cycle. This phenomenon may cause the exacerbation-prone subset of asthma and COPD as novel phenotypes of these diseases [14, 15]. Functional and morphological alterations in the airways probably are associated with exacerbation triggers in these diseases.

Patients who are prone to exacerbations of asthma and COPD will deteriorate quality of life because of emergency visits and hospitalizations. Therefore, to stabilize symptoms related to these diseases in the future, it is necessary to search for distinct predictors of exacerbations. Moreover, it is desirable that suitable therapy for long-term management for these diseases should be established based on accurately predictable factors for exacerbations as treatable traits [14, 16–20]. This chapter states clinical phenotypes related to acute exacerbation to establish treatable traits for asthma and COPD.

2. Asthma

2.1 Clinical features

Although asthma is a common disease, diagnosis criteria are not clearly stated in the latest Global Initiative for Asthma (GINA) report [21]. Asthma is a heterogeneous and chronic respiratory disease, and airway inflammation and airway

hyperresponsiveness are fundamentally pathophysiological features of this disease. These characteristics are beneficial to diagnose asthma accurately but are not clinically used much because the related methods of examinations such as sputum induction and methacholine provocation test are complicated. These characteristics are usually persisted even when symptoms are absent, and lung function is within normal limit. Moreover, it is quite difficult to return airway hyperresponsiveness to normal using conventional treatment with corticosteroids. However, the latest GINA report states that these two characteristics are not necessary and sufficient for the diagnosis of asthma [21], although they are probably therapeutic targets for the cure of asthma. This disease is generally diagnosed based on the history of respiratory symptoms (wheezing, dyspnea, chest tightness, and cough) that vary in intensity over time with variable expiratory airflow limitation (a reduction in forced expiratory volume in 1 second: FEV_1). These variations are often triggered by factors such as allergen exposure, exercise, and viral airway infections. The reversibility of airflow limitation is useful for the diagnosis of this disease, but this examination is probably low diagnostic sensitivity to asthma. The reversibility of airflow limitation is sometimes undetectable because lung function remains normal in many patients with asthma during a stable period.

2.2 Clinical phenotypes

Asthma is grouped as phenotype classifications according to their relative expression of symptoms and inflammation in primary care with predominantly mild to moderate disease and in secondary care with refractory disease populations [4]. Two groups, "early onset atopic" and "obese, noneosinophilic" is common and concordant in both care populations. In contrast, marked discordance is observed in secondary-care asthma between clusters "early onset symptom predominant" and "late-onset inflammation predominant", which is specific to refractory asthma [4]. The reasons for this dissociation are unclear; however, measurement of airway inflammation in these subgroups is probably beneficial to a reduction in exacerbation frequency in the inflammation-predominant group [4]. In another trial, distinct clinical phenotypes of severe asthma are classified into five categories using unsupervised hierarchical cluster analysis [22]: (1) early onset atopic asthma with normal lung function, (2) early onset atopic asthma with preserved lung function but increased medication requirements, (3) older obese women with late-onset nonatopic asthma, and (4, 5) severe airflow obstruction (Cluster 4: %FEV1 more than and equal to 65, Cluster 5: %FEV1 less than 65) [22]. Recently, cluster analysis for patients with asthma has been carried out based on a novel multidimensional approach, such as Th2, non-Th2, and mixed inflammation in the natural history of asthma [23, 24]. The risk factors (genetic variants and environmental exposures) and the molecular mechanisms (endotypes) may interact in complex manners in each patient, and they are shared by some, but not all, patients [20]. The latest GINA report states that phenotypes of asthma similarly are identified in five clusters according to clinical and pathophysiological features, that is, (1) allergic, (2) nonallergic, (3) adult-onset, (4) persistent airflow limitation, and (5) obesity [21]. However, except in patients with severe asthma, relationships are not clearly observed between the pathological characteristics and the clinical patterns or response to treatment. More studies are needed to establish the clinical utilities of phenotype classification in asthma [21].

2.3 Exacerbations

Patients with exacerbation-prone asthma generally have reduced lung function, such as forced expiratory volume in one second (FEV_1)/forced volume capacity (FVC), percent predicted FEV_1, percent predicted FVC, compared with other patients with asthma [25]. Exacerbations are generally considered to make symptoms and lung function worse than the usual condition. Although there is no clear consensus concerning asthma exacerbations, a severe exacerbation is defined as the need for treatment with systemic corticosteroids, emergency visits, and hospital admissions [26]. Environmental (respiratory virus, allergen, etc.) and personal factors (IgE, eosinophils, etc.) are associated with worsening symptoms and lung function in asthma [27]. Exacerbations are mostly triggered by viral infections in the upper airway; and airway eosinophilic inflammation induced by Th_2 cytokines is also generally considered to enhance susceptibility to exacerbations [28]. Moreover, another report has also indicated that regulation of Th_2 cytokine acts as phenotype/endotype-specific therapeutic targets for severe asthma management [29]. However, asthma exacerbations caused by low Th_2 phenotypes are difficult to distinguish physiologically and symptomatically from those caused by high Th_2 phenotypes [30]. It needs to be further understood concerning low Th_2 phenotypes. Major predictors associated with respiratory disorders for asthma exacerbations are shown in **Figure 1**.

2.3.1 Infection

Rhinoviruses mostly cause asthma exacerbations in children and adults. Infections of upper airway epithelial cells with Rhinovirus cause the release of pro-inflammatory cytokines and chemokines and the recruitment of inflammatory cells, such as neutrophils, lymphocytes, and eosinophils. Rhinovirus types are classified into three

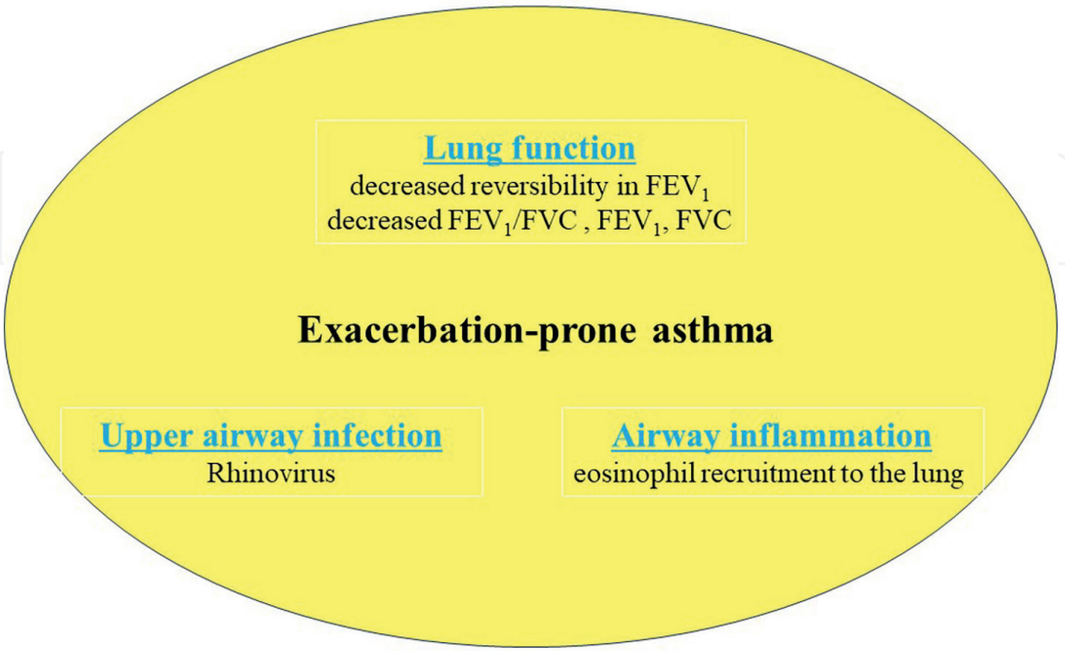

Figure 1.
Major predictors of exacerbations associated with respiratory disorders include function, infection, and inflammation in exacerbation-prone asthma. Illustrated based on Refs. [13, 25, 31, 32].

species (Rhinovirus-A, -B, and -C). Rhinovirus-A and -C are more likely to cause asthma exacerbations, and Rhinovirus-C infections in the upper airways are probably associated with severe asthma exacerbations and admission to intensive care for respiratory compromise [13]. In contrast, bacterial infections may not be so closely related to acute asthma exacerbations. However, respiratory virus infections in the upper airways may impair the antibacterial defenses, resulting in emergence of bacterial infections or changes in the microbiome.

2.3.2 Reversibility of airflow limitation

Reversibility of airway obstruction (airflow limitation) is proven by an increase of FEV_1 of more than 12% and 200 mL from baseline after inhalation of a short-acting β_2-adrenergic agonist using spirometry, and this bronchodilator reversibility is considered not only a recommended diagnostic criteria for asthma but also an indicator of stable long-term management of this disease. The maximal post-bronchodilator reversibility is associated with the frequency of asthma exacerbations [13, 25]. In contrast, other clinical reports have indicated that reversibility of airflow limitation is not always associated with asthma exacerbations [33], and that reduced bronchodilator reversibility is a risk factor against sensitivity to asthma therapy and is related to future asthma exacerbations [34]. It remains controversial whether the reversibility of airflow limitation can be a predictive factor for asthma exacerbations. A lack of reversibility in airflow limitation may be observed in a deterioration of lung function (airway remodeling) due to poor long-term management; in contrast, this phenomenon is also observed in an amelioration of lung function due to good long-term management. Therefore, the reversibility of airflow limitation may be insufficient to accurately evaluate long-term asthma management status.

2.3.3 Airway hyperresponsiveness

Airway hyperresponsiveness is a fundamental feature in the pathophysiology of asthma. This characteristic pathophysiology is represented as increased reactivity to muscarinic receptor agonists (acetylcholine and methacholine), histamine, and mannitol in the airway. The inhalation provocation test using these contractile agonists is clinically performed to examine airway hyperresponsiveness, which is diagnosed as threshold values of 8 mg/mL in these agents when the cumulative dose curve causing a 20% reduction in FEV_1 (PC_{20}) was calculated in the inhalation challenge test using these agents [35, 36]. However, the latest GINA report states that airway hyperresponsiveness is not necessary to make the diagnosis of asthma [21]. Since airway hyperresponsiveness is resistant to the currently recommended treatment using inhaled corticosteroids, it is generally considered that asthma cannot be cured. The severity of airway hyperresponsiveness may related to instability of symptoms or frequency of exacerbations. However, the relationship between asthma exacerbations and airway hyperresponsiveness still remains unclear. Although the inhalation provocation test using these contractile agents has the highest sensitivity to diagnose asthma, this provocation test to detect airway hyperresponsiveness is not always performed routinely for clinical diagnosis of asthma, probably because of its complexity. A recent clinical study has demonstrated that tezepelumab, a human anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody, may reduce airway hyperresponsiveness to mannitol in patients with refractory asthma [37]. In vitro studies have shown that hyperresponsiveness to muscarinic agonists (airway hyperresponsiveness) is inhibited through the inactivation of Rho-kinase, a target molecule of RhoA (a monomeric GTP-binding

protein) in airway smooth muscle [38, 39]. Since Rho-kinase, an inhibitor of myosin phosphatase, contributes to contraction, cell migration, cell proliferation, and reorganization of actin cytoskeleton through Ca^{2+} sensitization, this molecule is probably a therapeutic target for airflow limitation, airway hyperresponsiveness, eosinophil recruitment, and airway remodeling, which are the major features of asthma [40, 41].

2.3.4 Airway eosinophilia

Eosinophilic airway inflammation (eosinophil recruitment to the airways) is also a fundamental feature in the pathophysiology of asthma. However, the latest GINA report also states that airway eosinophilia is not necessary or sufficient to make the diagnosis of asthma [21]. Allergen challenges cause eosinophil recruitment to the airways in a sensitized mouse model of asthma, and this phenomenon is attenuated in the presence of Rho-kinase inhibitors [39]. Eosinophil recruitment to the airways is also clinically observed not only in unstable asthma [31] but also in stable asthma [42]. Eosinophilic airway inflammation is probably associated with symptoms and exacerbations in unstable periods in asthma, but little is unknown about the meaning of eosinophilic airway inflammation in stable periods in this disease. In pathological findings using bronchoscope, eosinophil infiltration to the distal airways is associated with nocturnal symptoms in patients with asthma [31]. Small airway eosinophilia may be involved in asthma exacerbations [43]. However, since clinical examination for small airways has not been established yet, details are unknown about it. Although sputum examination is a minimally invasive and accurate method to evaluate airway inflammation, the cut-off value (a criterion value for clinical diagnosis) is not established yet in quantitative analysis of sputum examination, but eosinophilic airway inflammation is generally defined as eosinophil fraction more than 3% [32]. In contrast, blood tests and fractional exhaled nitric oxide (FeNO) are clinically used widely, probably because of their convenience, but these values may be inaccurate because of indirect measurements for airway inflammation. A previous clinical trial has demonstrated that a treatment strategy due to normalization of sputum eosinophil count markedly reduces asthma exacerbations and admissions with the need for additional anti-asthma agents, compared with a standard management strategy due to guidelines [32]. Among four measures of Th_2-related inflammation (eosinophil counts in blood and sputum, FeNO, IgE), a reduction in the sputum eosinophils markedly suppresses the frequency of asthma exacerbations; in contrast, other three clinical examinations related to Th_2 inflammation are not associated with a reduction in asthma exacerbations [26]. Therefore, the number of eosinophils in the sputum examination is probably a predictor for asthma exacerbations as a future risk.

3. COPD

3.1 Clinical features

Chronic obstructive lung disease (COPD) is also generally considered a heterogenous, preventable, and treatable disease that is defined as persistent respiratory symptoms (shortness of breath, chronic cough, and sputum production) and persistent airway obstruction (airflow limitation) that will not return to the normal range [44]. The pathogenesis of COPD is brought about by chronic lung inflammation due to oxidative stress through cigarette smoke and other environmental exposures (biomass fuel, air

pollution, etc.) [45]. Responses to chronic lung inflammation caused by neutrophils and macrophages are modified in patients with COPD, leading to emphysema and small airway fibrosis (the pathological features of this disease). Since COPD is diagnosed only based on persistent airflow limitation in spirometry, but because FEV_1/FVC physiologically decreases with age, the fixed cut-off point for FEV_1/FVC ratio < 70% may be inaccurate to use for diagnosis of COPD may result in overdiagnosis of COPD in older adults. The airflow limitation is progressive, and a decline of FEV_1 varies in each patient with COPD. The loss of alveolar attachment to the small airways causes not only airflow limitation but also gas trapping, such as an increase in residual volume (RV) or a decrease in inspiratory capacity (IC), other than airflow limitation due to the loss of alveolar attachment to the small airways. Since COPD is associated with small airway and alveolar damage [46], some cases of COPD develop a low lung diffusing capacity for carbon monoxide (DL_{CO}). A reduction in FEV_1 is not always related to shortness of breath in patients with COPD; in contrast, a reduction in IC and an increase in RV cause shortness of breath through dynamic hyperinflation. Moreover, abnormities of DLco probably cause shortness of breath through hypoxemia via a reduction in diffusion capacity during exercise. It is generally considered that airflow limitation could be observed in a variety of overlapping conditions among airway inflammatory diseases in patients with COPD and asthma [47, 48]. Moreover, airway eosinophilia and airway hyperresponsiveness probably develop in a subset of COPD as clinical phenotypes similar to asthma [3].

3.2 Clinical phenotypes

As the first phenotype classification, COPD was separated into two groups, such as the "Pink Puffers" and the "Blue Bloaters" [49]. However, COPD has complexity and heterogeneity in symptoms, progression, exacerbations, functional outcomes, and response to treatment, pathogenesis, and pathology [5, 50]. Hence, it is desirable to meaningfully identify and classify groups of patients with similar clinical characteristics, referred to as clinical phenotypes. However, it has not been established to classify patients with COPD into defined subtypes according to distinct phenotypes for clinical use. Patients with this disease should be stratified according to clinical phenotypes [5, 16, 51]. Stratified medicine is needed to assess multiple dimensions that include clinical (symptoms, exacerbations, and comorbidity), physiologic (airflow limitation, impaired diffusion, airway trapping, small airway dysfunction, and airway hyperresponsiveness), imaging (emphysema and small airway narrowing), and endotyping (inflammatory profiling) dimensions [5, 8, 11, 12], resulting in classifications of patients to distinct prognostic and therapeutic subgroups for both clinical and research purposes as a heterogeneous disease in COPD. However, clinical characteristics is mixed in various proportions in individual patients with COPD. Ever since 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report states a multidimensional assessment of patients with COPD that includes two new dimensions: symptoms experienced by the patient and the risk of future exacerbations. Even though symptoms disappear through treatment for an exacerbation, the severity of COPD may not be decreased. Since COPD gradually worsens with each exacerbation, it is very important to know what characteristics patients prone to exacerbations have. A group of subjects with 2 or more exacerbations per year is considered as frequent exacerbator of COPD [14, 44]. Therefore, searches for phenotypes in COPD prone to exacerbations are beneficial to advance the management and treatment of COPD. Major predictors associated with respiratory disorders for COPD exacerbations are shown in **Figure 2**.

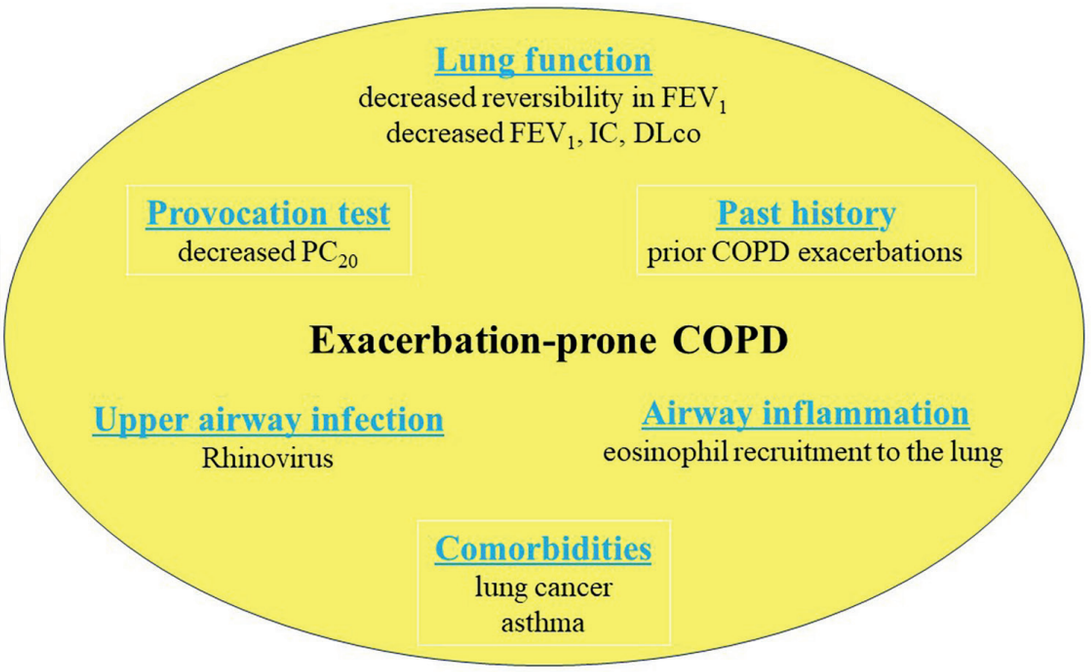

Figure 2.
In exacerbation-prone COPD, major predictors of exacerbations are associated with respiratory disorders such as function, hyperresponsiveness, infection, diseases, inflammation, and prior exacerbations. Illustrated based on Refs. [3, 14, 52–58].

3.3 Exacerbations

3.3.1 Prior exacerbations

A longitudinal trial enrolled 2138 patients with COPD has been performed to evaluate predictors of exacerbations over 3 years (the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints: ECLIPSE study) [14]. Exacerbations were defined as additional treatments by antibiotics or corticosteroids and hospitalization (severe exacerbations). This clinical study has indicated that the most reliable predictor of exacerbations is a history of prior exacerbations, referred to as a frequent exacerbation phenotype [14]. Recently, another clinical study has been performed to evaluate the history of exacerbations and other factors as predictors over 1 year (the Acute COPD Exacerbation Prediction Tool: ACCEPT) [59]. Predicted and observed exacerbation rates in this study are similar to the results shown in the ECLIPSE study [59]. A literature review has indicated that exacerbation history within the past year is also a reliable predictor of future exacerbations [52], and there is a significant relationship between exacerbation history and risk of future moderate-to-severe exacerbations [52]. The late GOLD report states that COPD is classified into four stages (Grade I–IV) based on the percentage predicted FEV_1. Modified Medical Research Council (mMRC) Dyspnea Scale and exacerbation history are each divided into two to form four groups A–D [21]. This assessment approach will guide more precise treatment toward individualized patients with COPD. However, this classification is still insufficient to express the heterogeneity of COPD accurately.

3.3.2 Comorbidities

Many previous reports have indicated that comorbidities are associated with the occurrence of moderate-to-severe exacerbations [52]. Comorbidities related to

moderate-to-severe exacerbations include various diseases (malignancy, cardiovascular, respiratory comorbidities, etc.) [52]. Among these comorbidities, cardiovascular diseases are most closely associated with COPD readmissions in the emergency room. The number of comorbidities also augments the degree of risk for both moderate and severe exacerbations. Chronic comorbidities frequently develop in COPD; 88% of patients with COPD have at least one comorbidity, such as hypertension, coronary heart disease, osteoarthritis, etc. [53]. Moreover, the comorbidities related to the great risk of frequent exacerbations are pulmonary cancer, heart failure, and asthma [53]. Since airway disorders (infection, airflow limitation, hyperresponsiveness) overlap in subset of asthma and COPD, asthma can be a predictor for COPD exacerbations.

3.3.3 Infections

When infections develop in patients with COPD, stable periods are sometimes interrupted by acute worsening of respiratory symptoms, and additional treatments are required (exacerbations). In acute COPD exacerbation periods, pathological microorganisms (bacteria, viruses) are observed in the lower airway secretions with a relatively high frequency [60]. *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common bacterial pathogens for exacerbations [61]. However, viral infections in the upper respiratory system are more closely related to COPD exacerbations. Rhinovirus is most frequently associated with exacerbations [54], whereas Coronavirus, Parainfluenza, Adenovirus, and Influenza viruses are less prevalent. In addition to these acute infections, persistent chronic systemic inflammation can be attributed to the frequency of COPD exacerbations. When patients with COPD are divided into low and high interleukin 6 (IL-6) groups, more frequent exacerbations are observed in the high IL-6 group than in the low IL-6 group. The values of IL-6 (14.03 pg./mL or more) can be a predictor for two or more COPD exacerbations in the following year [62].

3.3.4 Lung function

COPD with a normal lung function in early adulthood is related to a higher risk of mortality than that with a reduced lung function already in early adulthood; however, the clinical relevance of the attained FEV_1 trajectory to exacerbations is still unknown in this report [63]. Many clinical trials have indicated that mean increases in trough FEV_1 cause significant decreases in exacerbations and hospitalizations [64], indicating that treatment effects on FEV1 can avoid the future risk of COPD. The annual decline in FEV_1 is related to the annual exacerbation rate but not to mortality [55]. Furthermore, a literature review has demonstrated that there is a positive relationship between the risk of future COPD exacerbations and lack of bronchodilator reversibility in FEV_1 [52] and that four stages of (Grade I–IV) based on the percentage predicted FEV_1 is not related to future COPD exacerbations [52]. Measurement of DLco was not carried out in some large cohort studies, such as ECLIPSE, but a previous clinical study with a relatively small sample size has suggested that a reduction in DLco is related to the frequency of COPD exacerbations [56]. In the meta-analysis, DL_{CO} % predicted is significantly lower in the high exacerbation risk group in the GOLD report (group C/D) than in the low exacerbation risk group in the GOLD report (group A/B); and DL_{CO} % predicted is also lower in frequent exacerbators than in nonexacerbators [65]. In analysis from the Genetic Epidemiology of COPD (COPDGene) study, a reduction in DL_{CO} of 10% predicted to cause approximately

14% higher rate of hospitalization for COPD exacerbations [57]. Moreover, impairments in DLco (50% predicted or less) are independently associated with an increased rate of severe exacerbations, and combined impairments in DLco and FEV_1 (both 50% predicted or less) further increase the rate of severe exacerbations [57]. A reduction in IC due to an increase in RV causes shortness of breath through hyperinflation independent of hypoxemia. A clinical trial has indicated that the IC percentage predicted is significantly reduced in COPD with frequent exacerbations, and the Motley index (RV/total lung capacity (TLC) percentage) is also significantly increased in these patients with COPD [58]. Therefore, FEV_1, DLco, IC, and RV/TLC can be predictors for COPD exacerbations.

3.3.5 Airway hyperresponsiveness

Airway hyperresponsiveness is conventionally considered a hallmark of asthma; however, it has been recently proven that this pathophysiological feature is also observed in approximately 45% of patients with COPD [3, 66]. Airway hyperresponsiveness in COPD is not related to eosinophil recruitment to the lung and complications of asthma [3]. The methods of the inhalation provocation test and diagnosis of airway hyperresponsiveness are described in Section 2.3.3. Since FEV_1 is markedly reduced in a subset of COPD, the inhalation provocation test should be performed in the limited cases with FEV_1 70% or more of predicted values to avoid the occurrence of risk of respiratory failure and the production of false positive results [3]. A recent clinical trial has demonstrated that COPD exacerbations occur much more frequently in patients who have airway hyperresponsiveness than in patients who do not have that, and airway hyperresponsiveness is considered a predictor for COPD exacerbations and can be a treatable trait for this disease, similar to asthma [3]. Although there is currently no treatment for airway hyperresponsiveness related to COPD, tezepelumab (human anti-TSLP monoclonal antibody) and Rho-kinase inhibitors may be effective for airway hyperresponsiveness related to COPD, similar to asthma, as described in Section 2.3.3. [38, 40].

3.3.6 Airway eosinophilia

Eosinophilic airway inflammation is conventionally considered the essential pathophysiology of asthma, as described in Section 2.3.4.; however, it has been recently proven that eosinophil recruitment to the lung (3% or more of sputum eosinophil) is also recognized in approximately 35% of patients with COPD independent of asthma using sputum induction [3, 67]. Airway eosinophilia should be evaluated using sputum eosinophil counts because blood eosinophil counts cannot directly reflect airway conditions and cannot accurately evaluate eosinophilic airway inflammation. Daily administration of inhaled corticosteroids is effective for these patients with COPD who have higher values of sputum eosinophil, and few exacerbations occurred in these cases after induction of the inhaled corticosteroid therapy [3]. On the other hand, daily inhalation of corticosteroid was not administered to patients with COPD who have less than 3% of sputum eosinophil because eosinophilic airway inflammation is considered inactive. As a result, COPD exacerbation occurred more frequently in the untreated patients with lower values of sputum eosinophil counts than in the treated patients with higher values of sputum eosinophil count [3]. Although values of cutoff in sputum eosinophil counts are not established yet, less than 3% of sputum eosinophil is probably meaningful to detect airway eosinophilia.

Moreover, inhaled corticosteroids should be administered daily to patients with COPD who have qualitatively eosinophils in the sputum. Therefore, eosinophilic airway inflammation is considered a predictor for COPD exacerbations and can be a treatable trait.

4. Conclusions

Impaired physiological function and enhanced inflammation in the airways worsen symptoms (dyspnea, wheezing, and chest tightness) and require additional therapy (systemic corticosteroids and antibiotics), leading to hospitalization in some cases of asthma and COPD. Impaired lung function (decreases in FEV_1, IC, and DLco), decreased bronchodilation in response to β_2-adrenergic agonists (reversibility in FEV_1), and increased bronchoconstriction in response to muscarinic agonists (airway hyperresponsiveness) are probably predictors of acute exacerbations for these diseases. Furthermore, eosinophil recruitment to the lung (airway eosinophilia) and viral infections in the upper airways are also probably predictors of acute exacerbations for these diseases. These airway disorders can be treatable traits as clinical phenotypes for exacerbations-prone asthma and COPD. Advances in therapy for asthma and COPD need a search for distinct treatable traits for the prevention of acute exacerbations based on these predictors.

Conflict of interest

Hiroaki Kume: none.
Natsumi Watanabe: none.
Yasuhito Suzuki: none.

Author details

Hiroaki Kume*, Natsumi Watanabe and Yasuhito Suzuki
Department of Infectious Diseases and Respiratory Medicine, Fukushima Medical University Aizu Medical Center, Tanisawa, Kawahigashi, Aizuwakamatsu City, Fukushima, Japan

*Address all correspondence to: h-kume@fmu.ac.jp

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