

# Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease

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Asthma is a chronic inflammatory disorder of the airways which causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, symptoms which are usually associated with reversible airflow limitation.<sup>1,2</sup> This definition includes the recurrence of respiratory symptoms which might be otherwise classified as asthma exacerbations. However, the term asthma exacerbation is usually reserved for more severe and/or more persistent respiratory symptoms requiring a prolonged increase of current antiasthma medication.<sup>1,2</sup> Chronic obstructive pulmonary disease (COPD) is defined as a progressive airflow limitation, mostly irreversible.<sup>3,4</sup> The term COPD includes patients with obstructive chronic bronchitis and/or pulmonary emphysema.<sup>3,4</sup> Patients with moderate or severe persistent asthma may also have an irreversible component of airflow limitation, and thus they may also be included in the definition of COPD.<sup>3</sup> The definition of COPD does not include exacerbations,<sup>3,5</sup> even if exacerbations are the main cause of medical intervention and admission to hospital in these patients.

## Definitions of mild and severe exacerbations of asthma and COPD

Recent guidelines provide classifications of exacerbations of asthma and COPD based on clinical parameters.<sup>1–4,6</sup> Although these classifications may provide a useful tool for clinical studies, they are not standardised and they are rather cumbersome and difficult to use in clinical practice. The definitions derived from the literature are operational and vary with investigators.<sup>7–14</sup> In this article we will try to provide some definitions to be subsequently used to discuss the pathogenesis and treatment of the two diseases.

Mild exacerbations of asthma may be defined as increased intensity or frequency of symptoms and/or worsened lung function—that is, decreased forced expiratory flows or increased variability of peak expiratory flow—that force the patient either to change prescribed treatment and/or to seek medical attention.<sup>13,14</sup> The borderline between ongoing symptoms with frequent use of rescue medication and mild exacerbations may be difficult to identify in individual asthma patients as asthma may not be completely asymptomatic even after proper treatment in some subjects. Asthma exacerbations can be defined as severe if the patient has a lack of response to initial treatment, if the exacerbation has progressed quickly, or if the patient is at a high risk of asthma related death.<sup>2,15</sup> Severe asthma exacerbations usually require admission to the emer-

gency room and in some cases may be associated with acute respiratory failure.<sup>2,16–19</sup>

Mild exacerbations of COPD may be defined as increased breathlessness, possibly associated with increased cough and sputum production, that force the patient to seek medical attention outside the hospital.<sup>11</sup> COPD exacerbations may be defined as severe when they are associated with acute respiratory failure.<sup>20</sup> Severe COPD exacerbations frequently require admission to hospital.<sup>3</sup>

## Importance of exacerbations in asthma and COPD

Exacerbations represent an important feature of the clinical manifestation and natural history of asthma and COPD. They represent the main cause of visits to general practitioners, emergency departments, and hospital admissions in affluent countries.<sup>21,22</sup>

Asthma exacerbations are usually associated with increased variability of peak flow, decreased forced expiratory flows and, in more severe patients, acute respiratory failure with marked abnormalities of the ventilation/perfusion relationship and blood gas tensions.<sup>23–25</sup> Most asthma exacerbations are mild and require only a change of prescribed therapy. Few asthma exacerbations are severe enough to require aggressive treatment with high dose bronchodilators and systemic glucocorticoids, and only occasionally result in acute respiratory failure requiring intubation and mechanical ventilation.<sup>16–19</sup>

The incidence and prevalence of asthma exacerbations are not well established, particularly because the definition and assessment of severity vary greatly between studies. For example, a recent study specifically designed to assess the effect on asthma exacerbations of a low (100 µg bid) or high (400 µg bid) dose inhaled budesonide alone or in combination with inhaled formoterol (12 µg bid) showed that more than 70% of mild to moderate asthmatic subjects develop an average of 40 mild exacerbations per year, and more than 40% of the same subjects develop an average of almost two severe exacerbations per year.<sup>14</sup> By contrast, another study conducted in a similar population to compare the effect of a combination of beclomethasone and salmeterol with a higher dose of beclomethasone alone reported a much lower frequency of exacerbations,<sup>8</sup> probably because exacerbations were not specifically investigated but were detected from the adverse events, and the criteria for severe exacerbations were more stringent (for example, hospital admission). Because of the heterogeneity of definition and classification of

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exacerbations, it is difficult to estimate the real incidence of exacerbations in asthmatic subjects. In particular, it is difficult to define the border between ongoing symptoms of asthma and asthma exacerbations, and it is unclear whether all asthmatic subjects develop recurrent exacerbations or whether there is a subgroup of "exacerbators" who develop recurrent exacerbations.<sup>7 9 13 26 27</sup> It is important to define these patients to tailor a specific treatment. Unfortunately the characteristics of these patients are not clear. It has been suggested that sensitisation to some substances such as aspirin and other non-steroidal anti-inflammatory agents is associated with more severe asthma and more frequent asthma exacerbations,<sup>28</sup> but reliable data are lacking.

On average, patients with COPD experience exacerbations with a frequency of 0.1 per patient per month of observation.<sup>29 30</sup> In one recent study almost half of the patients with COPD had only one or no exacerbations per year, and only 30% had three or more exacerbations per year.<sup>31</sup> Also, in COPD few of the exacerbations are severe enough to require aggressive treatment but these exacerbations more often result in acute respiratory failure requiring mechanical ventilation (nearly half in one study<sup>20</sup>), probably because they develop in a more compromised lung. The mortality of patients admitted to hospital with COPD exacerbations is about 14%, a dramatic figure which exceeds current hospital mortality for myocardial infarction.<sup>32</sup> The mortality of patients with COPD admitted to an intensive care unit (ICU) for exacerbations is 24%, and for patients aged 65 years or older the mortality doubles in one year from 30% to 59%.<sup>33</sup>

Although symptoms of chronic bronchitis are associated with an increased risk of subsequent hospital admission because of COPD,<sup>34</sup> it is not known whether patients with COPD have more frequent acute chest illnesses than individuals of the same age without COPD.<sup>35</sup> It is more likely that there is a subgroup of COPD patients who develop recurrent exacerbations.<sup>31 36</sup> While mild COPD exacerbations are not associated with a significant change in lung function,<sup>37</sup> moderate to severe COPD exacerbations are usually associated with a transient decrease in lung function.<sup>35</sup> Interestingly, it has not yet been established whether exacerbations contribute to the excessive decline in forced expiratory volume in one second (FEV<sub>1</sub>) which occurs in patients with COPD,<sup>38</sup> or even to the shorter life expectancy of these patients.<sup>3 4</sup>

Overall asthma mortality at 5–34 years of age is approximately four deaths per million person years in the USA,<sup>39</sup> a rate that is markedly lower than the mortality of COPD. In countries where asthma death rates can be separated, COPD is clearly associated with the highest mortality—for example, in Europe the rate is 10–50/100 000 person years.<sup>4</sup>

#### **Lack of understanding of the aetiology of asthma and COPD exacerbations**

The aetiology of most asthma exacerbations is not established. Viral and, to a much lesser

extent, bacterial respiratory infections occur in conjunction with most asthma exacerbations, particularly in children<sup>40 41</sup> but also in adults.<sup>42–44</sup> The precise mechanisms by which respiratory viruses, and particularly rhinoviruses,<sup>40 42 44</sup> may induce asthma exacerbations are largely unknown.<sup>45</sup> Indeed, experimental rhinovirus infection may cause lymphocyte and eosinophil infiltration of the bronchial mucosa more persistently in asthmatic subjects, where it is accompanied by bronchial hyperreactivity.<sup>46 47</sup> On the other hand, asthma is associated with upregulation of the ICAM-1 adhesion molecule in the airway mucosa which further increases during asthma exacerbations.<sup>48</sup> ICAM-1 is the major surface receptor for rhinoviruses<sup>49</sup> and thus an asthma exacerbation may theoretically increase the risk of the patient developing rhinovirus infections. Allergens, sensitising agents, and drugs may also trigger asthma exacerbations, sometimes severe ones.<sup>28</sup> Another aspect of exacerbations that has not been explained is how it persists after a single exposure to a triggering agent—for example, how a single exposure to allergen or sensitising agent may be followed by an asthmatic response that may last for weeks.<sup>50 51</sup>

The aetiology of COPD exacerbations is even less well established. In fact, the role of bacterial infections, once believed to be the main cause of COPD exacerbations, still remains controversial<sup>52</sup> and the role of viral infections is not so well established as it is in asthma.<sup>53</sup> In addition to air pollution,<sup>54</sup> other diseases more often associated with COPD than asthma may be responsible for COPD exacerbations including pulmonary hypertension and heart failure,<sup>55</sup> airways plugging by excessive mucus,<sup>56</sup> fatigue of the respiratory muscles,<sup>57 58</sup> and thromboembolism.<sup>59 60</sup>

#### **Pathology of exacerbations of asthma and COPD**

The pathology of exacerbations of asthma and COPD has not been adequately examined, probably because of the difficulty in performing invasive manoeuvres such as brushing, lavage, or biopsies in symptomatic patients. Some recent studies have included non-invasive examination of patients with an exacerbation by collecting spontaneous or induced sputum. These studies have provided new and interesting information.

Mild asthma exacerbations induced by tapering the dose of inhaled steroids are associated with sputum eosinophilia.<sup>61</sup> By contrast, mild spontaneous asthma exacerbations are associated with eosinophilia in about half the subjects, the other half having a normal cell count.<sup>62</sup> In contrast to mild exacerbations, severe asthma exacerbations are associated with more prominent sputum neutrophilia.<sup>63</sup> Interestingly, COPD exacerbations are associated with similar changes in the cell count in the sputum. In fact, mild COPD exacerbations are associated mainly with eosinophilia in sputum and in biopsy specimens, and severe COPD exacerbations are associated with sputum neutrophilia.<sup>37 64 65</sup> Thus, in the sputum at

least the changes in inflammatory cells during exacerbations are similar in asthma and COPD.

In contrast to the few studies conducted in living patients, more studies have examined the pulmonary pathology of subjects who have died from asthma and COPD. Fatal asthma and COPD can be considered as extreme slopes of exacerbations of the diseases. Although several studies have described the pathology of fatal asthma, there is still limited information comparing the pathology of severe asthma with milder forms of the disease. As reported by Synek and co-workers,<sup>66</sup> fatal asthma is associated with a greater number of eosinophils in the large airway wall and with a relative deficiency of T lymphocytes in the epithelium of the large airways compared with mild to moderate asthma. By contrast, inflammation in the small peripheral airways is similar in fatal asthma and in mild to moderate disease. The increased number of eosinophils is more marked in the larger airways of patients with fatal asthma than in those with non-fatal asthma which suggests that, when asthma is more severe, the degree of inflammatory response is more marked in the central airways.<sup>66</sup> This is in agreement with the findings of Carroll *et al*<sup>67,68</sup> who found increased wall thickness in the large airways but not in the small airways of cases of fatal asthma compared with non-fatal asthma. This increase in thickness involved the inner wall, outer wall, smooth muscle, mucous glands, and cartilage. Sudden onset fatal asthma seems to be associated with fewer eosinophils and more neutrophils in the airway submucosa<sup>68,69</sup> and less mucus in the lumen of the airways.<sup>69,70</sup>

Curiously, studies on the pathology of COPD are very few. The largest study showed that death from COPD is associated with both emphysema and small airway inflammation.<sup>71,72</sup> When all the subjects were considered together, the most consistent relationship occurred between severe emphysema and degree of airflow obstruction, indicating that bronchiolar disease may not contribute significantly to chronic airflow obstruction. However, if only subjects with less severe emphysema were considered, several indices of bronchiolar inflammation correlated with the degree of airflow obstruction. Therefore, as pointed out by Gordon-Snyder,<sup>73</sup> the findings of Nagai and colleagues must be cautiously interpreted. Their data indicated that, when emphysema is moderate or severe, loss of elastic recoil becomes overwhelmingly important and thus it may mask the effects of bronchiolar disease on chronic airflow limitation. By contrast, when emphysema is mild, the contribution of bronchiolar abnormalities to chronic airflow limitation is evident.<sup>73</sup>

#### Treatment of exacerbations of COPD and asthma

The treatment of asthma exacerbations is reasonably standardised with inhaled  $\beta_2$  agonists and systemic glucocorticoids as the cornerstone of pharmacological treatment with oxygen when required. This approach is based

on several studies reported in the literature and recently reviewed,<sup>1,2,15,74,75</sup> and is consistently recommended by national and international guidelines.<sup>1,2,15,74</sup> By contrast, the treatment of COPD exacerbations is much less established, probably because of the limited number of properly conducted studies.<sup>3,4</sup> In fact, the treatment of asthma and COPD exacerbations is similar and is based on the administration of oxygen, short acting bronchodilators, and systemic glucocorticoids.<sup>1-4,15,74</sup>

Short acting inhaled  $\beta_2$  agonists are usually the preferred bronchodilators used in the treatment of both asthma and COPD exacerbations.<sup>2-4,15,74,75</sup> If there is no prompt response, the addition of an anticholinergic is recommended, particularly for COPD exacerbations,<sup>1-4,15,74</sup> even if supportive evidence for the effectiveness of the combination is rather controversial.<sup>76-79</sup> Despite the consolidated clinical practice, the role of aminophylline in the treatment of asthma and COPD exacerbations also remains controversial, as most of the studies have shown that aminophylline increases the toxicity but not the efficacy of  $\beta_2$  agonists, particularly in asthma.<sup>1,2,74,80,81</sup>

Even the role of systemic glucocorticoids, and particularly high dose systemic glucocorticoids, remains controversial in asthma exacerbations.<sup>82</sup> Indeed, the current guidelines, based on existing evidence, recommend that all asthma exacerbations not responding to bronchodilators should be treated with systemic glucocorticoids.<sup>1,2,15,74</sup> By contrast, although common clinical practice, there is no firm recommendation for the use of systemic glucocorticoids in the treatment of COPD exacerbations.<sup>3,4,12,83</sup> A recent study has clearly shown the effectiveness of inhaled corticosteroids (fluticasone dipropionate) in preventing the episodes of severe exacerbations in patients with COPD.<sup>84</sup>

Antibiotics are rarely used and, in any case, are not recommended in the treatment of asthma exacerbations unless there is clearcut evidence of bacterial infections.<sup>1,2,15,74</sup> In contrast, antibiotics are very often used in the treatment of COPD exacerbations with the erroneous rationale that they are due to airway infections.<sup>57</sup> A recent meta-analysis has shown a significant but marginal benefit of antibiotics<sup>85</sup> and has provided the rationale for the recommendation to consider them in the presence of some evidence of infection.<sup>3,4</sup> However, a recent negative study has further weakened even this very cautious recommendation.<sup>86</sup>

Immunostimulating agents containing different species of bacteria frequently involved in lower respiratory infections have been tested in several clinical trials which have shown the ability of these compounds to reduce the number of acute exacerbations in patients with COPD.<sup>87-89</sup> A recent study has also shown the efficacy of the immunostimulating agent OM-85 BV on both patient morbidity and consumption of health care services.<sup>29</sup> These compounds are thought to stimulate the immune system by promoting direct activation of lung macrophages with increased specific

responses of T and B lymphocytes via the enhancement of antigen presentation mechanisms.<sup>90</sup> Finally, even if long term treatment with mucocactive drugs has been successful in preventing chronic bronchitis exacerbations in patients with severe COPD,<sup>91</sup> the role of mucolytic agents remains controversial and they are not recommended by current guidelines.<sup>3,4</sup>

### Conclusion

The definition, characterisation, and management of exacerbations of asthma and COPD still rely on clinical empirism with very little scientific support. Nonetheless, the diagnosis, assessment and management of asthma exacerbations is fairly straightforward whereas much less is known on the diagnosis, assessment, and management of COPD exacerbations. Despite the fact that both exacerbations of asthma and COPD are associated with acute airway inflammation, the cornerstone of treatment for both asthma and COPD exacerbations remains short acting bronchodilators while glucocorticoids have consistently been proved to be beneficial only in asthma exacerbations.

As often happens when reviewing the literature on a clinical topic, one finds more questions than answers. Exacerbations of asthma and COPD are certainly clear events in the mind of practising physicians. However, when one tries to provide simple concepts such as definition, classification, pathogenesis, or even a summary of the epidemiological data, one realises how little we know. Happily, in the last few years some epidemiological studies have been designed to measure the incidence and prevalence of asthma and COPD exacerbations,<sup>32,92</sup> and some pharmacological multicentre studies have been organised to investigate the effect of treatment on asthma and COPD exacerbations.<sup>14,93-96</sup> Additional studies are ongoing or have been initiated on the aetiopathogenesis and pathology of exacerbations. Thus, in a few years we should be able to understand more on this issue.

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