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REVIEW

Influence of comorbid conditions on asthma

L-P. Boulet

ABSTRACT: Various conditions such as rhinosinusitis, gastro-oesophageal reflux disease, psychological disturbances, chronic infections and obstructive sleep apnoea are often observed in asthmatic patients and may affect asthma control and outcomes. These comorbidities may change the asthma phenotype, be part of the same pathophysiological process, act as confounding factors in the diagnosis or assessment of control of asthma, and/or result from specific environmental exposures. The influences of these conditions on asthma are variable and for many of them still uncertain; nevertheless, they may alter asthma responses to current therapy. A systematic evaluation and an appropriate treatment of asthma-associated comorbid conditions should be part of asthma management, particularly for severe disease. With regard to clinical research, associated conditions may influence the results of trials and should be taken into account in the subjects' inclusion criteria and analysis of data.

KEYWORDS: Asthma comorbidities, gastro-oesophageal reflux disease, glottic dysfunction, obesity, obstructive sleep apnoea, rhinitis/sinusitis

Bronchial asthma is currently defined as ''a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment'' [1]. Asthma is most frequently mild to moderate but a significant proportion of patients have severe asthma [2, 3].

Although it still cannot be cured, control of asthma (usually defined as minimal or no symptoms, normal activities and sleep, and optimal pulmonary function) may be achieved in the majority of patients with appropriate education, environmental control, avoidance of triggers and inducers, and individualised pharmacotherapy [1, 4, 5]. Lack of control of asthma may be due to any one of the following: 1) an incorrect diagnosis (*e.g.* chronic obstructive pulmonary disease (COPD), vocal cord dysfunction, congestive heart failure or lung neoplasm); 2) undertreatment, due to either underassessment of the patient's asthma medication needs or poor patient compliance with therapy; 3) ongoing exposure to sensitising agents, such as common allergens or various occupational substances, or to high levels of irritants, particularly tobacco smoke; or 4) severe asthma, often associated with a marked or unresponsive underlying inflammatory process [2, 3, 6, 7]. Finally, various comorbid conditions are increasingly recognised as frequent contributors to uncontrolled asthma, although their role in the clinical expression of asthma has not been fully elucidated. The identification of comorbidities is now recognised as an integral part of the core management of asthma [1–3]. In the present article, the main comorbid conditions associated with asthma are reviewed and their effects on asthma control discussed. Their relationships with severe asthma are also examined.

WHAT ARE THE MAIN COMORBID CONDITIONS ASSOCIATED WITH ASTHMA?

Among the most frequently encountered comorbid conditions associated to asthma are rhinosinusitis, gastro-oesophageal reflux disease (GERD), psychological disturbances, chronic infections and obstructive sleep apnoea (OSA). Various other conditions and contributing factors that may influence asthma control are shown on figure 1.

CORRESPONDENCE
L-P. Boulet
Institut Universitaire de Cardiologie et de Pneumologie
Université Laval
2725 Chemin Sainte-Foy
Québec
QC
Canada G1V 4G5
Fax: 1 4186564762
E-mail: lpboulet@med.ulaval.ca

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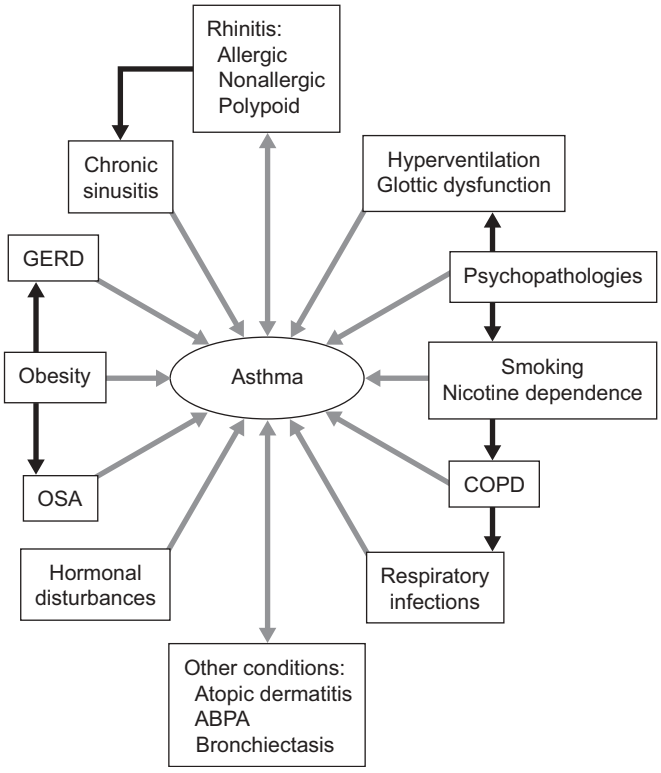

FIGURE 1. Asthma-related comorbidities. GERD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea; ABPA: allergic bronchopulmonary aspergillosis; COPD: chronic obstructive pulmonary disease.

The prevalence of comorbidities seems to be particularly high in severe asthma, and may be particularly detrimental to asthma control in such individuals [2, 3, 8–11]. In the National Heart, Lung, and Blood Institute cohort, severe asthma presented an increase in aspirin intolerance, in GERD (41% *versus* 12–16%), and in history of sinusitis (54% *versus* 33–37%) or pneumonia (63% *versus* 35–36%) compared with nonsevere asthma [8]. In the European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) cohort, severe asthma was associated with obesity, aspirin sensitivity and sinusitis in females, and inversely associated with atopy [9]. TEN BRINKE *et al.* [10] reported that severe nasal sinus disease (adjusted odds ratio (OR) 3.7), GERD (OR 4.9), recurrent respiratory infections (OR 6.9), psychological dysfunction (OR 10.8) and OSA (OR 3.4) were associated with frequent asthma exacerbations in severe asthma. Multivariate analyses indicated that severe chronic sinus disease and psychological dysfunction were the only factors independently associated with frequent exacerbations. However, this last analysis had some methodological limitations, as multiple regression analyses took into account 13 different co-factors for a limited sample size, with the quoted ORs applying to independent factors corrected for age and asthma duration, but not the other factors.

UPPER AIRWAYS DISEASES

Allergic rhinitis is associated with an increased risk of asthma [12–14]. Upper airways conditions, such as allergic or nonallergic rhinitis and sinusitis, are commonly associated with asthma and influence asthma outcomes, although there is still controversy regarding the magnitude of this effect [15–18]. The ''united airways'' concept suggests that upper and lower airways inflammatory processes such as asthma and rhinitis are of a similar type [19, 20]. Rhinitis may influence asthma through various mechanisms, including: 1) the release of mediators into the airways or peripheral circulation; 2) neural reflexes; 3) increased production of bone marrow progenitors of inflammatory cells; 4) increased lower airway exposure to airborne contaminants from mouth breathing; and 5) increased need for conditioning the inspired air.

BRAUNSTAHL and co-workers [21, 22] have reported that segmental bronchial allergen provocation in nonasthmatic allergic rhinitis patients resulted in peripheral blood eosinophilia and induction of allergic inflammation in the nose, while nasal allergen provocation in patients with allergic rhinitis resulted in generalised airway inflammation through upregulation of adhesion molecules. This suggests that nasal and bronchial inflammation affect each other, possibly through a systemic effect [23, 24].

Most allergic asthmatic patients also suffer from rhinitis, with the proportion being as high as 95% in some studies [12, 15, 25]. Rhinitis is also common in nonallergic asthma [14] and it is actually underdiagnosed, particularly in primary care [26]. Overall, the literature suggests both children and adults with comorbid rhinitis and asthma have more frequent physician's visits, emergency room visits and hospital admissions for asthma, and higher asthma-related drug expenses [12, 15, 17, 18, 27].

Agents acting on both the upper and lower airways, such as anti-immunoglobulin E and leukotriene receptor antagonists, may lead to a concomitant improvement of these conditions, and a positive response of one of these diseases usually predicts a response to the other [28, 29]. However, it was surprising to note an increase in symptoms of rhinitis in a large population of severe allergic asthmatics treated with omalizumab compared with placebo [29]. Although there is still some controversy about the benefits of adequately treating rhinitis for asthma outcomes, there is evidence that this does improve asthma patients' disease control and quality of life [17, 30–34]. In asthmatic patients with allergic rhinitis, PRICE *et al.* [35] suggested that combined treatment with montelukast and budesonide provided significantly greater efficacy in reducing airflow obstruction compared with doubling the dose of budesonide, possibly through an effect of the former on both the nose and lower airways.

With regard to the prevention of asthma in patients with allergic rhinitis, it has been suggested that specific immunotherapy may prevent the development of asthma in children with allergic rhinitis [36, 37]. A 3-yr course of specific immunotherapy with standardised allergen extracts in children with rhinoconjunctivitis reduced the development of asthma at 10-yr follow-up, as evaluated by clinical symptoms up to 7 yrs after treatment [36]. A similar protective effect was suggested in another study of adult rhinitic patients [37]. Furthermore, one trial has reported that the use of cetirizine in children aged <2 yrs of age with atopic dermatitis and at least one parent or sibling with a history of asthma or allergy delayed or, in some cases, prevented the development of

asthma in a subgroup sensitised to grass pollen and, to a lesser extent, house dust mite [38].

It remains unknown whether the above observations are the result either of an effect of upper airway inflammation on lower airways or *vice versa*, or of a common global airway inflammatory process, but it is nonetheless possible that these processes influence bone marrow or activation of systemic inflammation [20, 23].

With respect to chronic sinusitis, it has been reported that ~90% of patients with mild to moderate asthma, and almost 100% of those with severe asthma, have radiological abnormalities of the sinuses [39]. Chronic rhinosinusitis has been associated with both more severe and more difficult to control asthma. TEN BRINKE *et al.* [40] found extensive sinus disease in 24% of patients with severe asthma, with these patients having increased exhaled nitric oxide, blood eosinophils and induced sputum eosinophils.

The form of chronic rhinosinusitis associated with nasal polyposis and aspirin intolerance is reported in ~5% of patients with asthma. For example, LAMBLIN *et al.* [41] reported increased lower eosinophilic airway inflammation in patients with asthma and nasal polyps. Nasal polyps are associated with an increased production of cytokines (as well as of growth and chemotactic factors, such as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-5, eosinophil cationic protein and eotaxin) contributing to eosinophil chemotaxis, migration, activation and prolonged survival [42]. Furthermore, nasal polyposis is often associated with aspirin intolerance and a more severe asthma phenotype [43]. In comorbid nasal polyposis and asthma, increased numbers of bronchoalveolar lavage eosinophils and eosinophil peroxidase-staining cells has been reported in subjects with airway hyperresponsiveness, compared with those without such hyperresponsiveness, along with an increased expression of IL-5 and eotaxin [43]. Involvement of IL-9 has also been suggested [44]. Similarly, the current author's group has recently reported a more marked lower airway inflammation in patients with nasal polyps and asthma that required inhaled corticosteroids, compared with those either without asthma, or with asthma but without nasal polyps [45].

GERD

The majority of patients with asthma report symptoms related to GERD and/or have an abnormal 24-h oesophageal pH test [46–48]. However, the effect of GERD on asthma is still debated because improvement in asthma following GERD treatment is variable [48–51]. Asthma may promote GERD through changes in intrathoracic pressure or medications acting on the gastro-oesophageal sphincter; as a corollary, reflux may promote bronchoconstriction through various mechanisms, such as vagally mediated reflexes, increased airway responsiveness, chronic microaspiration of gastric fluid into the airways, or through airway neurogenic inflammatory responses.

HARDING [46] reported that 82% of people with asthma have an abnormal 24-h oesophageal pH test, although asthma symptoms improved in 69% of patients after treatment of GERD. Moreover, in a recent systematic review of the association between GERD and asthma, HAVEMANN *et al.* [47] concluded that there is a significant association between GERD and asthma, but found a paucity of data on the direction of causality; in the analysis, the average prevalence of abnormal oesophageal pH, oesophagitis and hiatal hernia in asthmatic subjects was 50.9%, 37.3% and 51.2%, respectively, while the mean prevalence of asthma in individuals with GERD was 4.6% (3.9% in controls). FIELD *et al.* [48] previously reported that anti-reflux surgery could help asthma symptoms without changing pulmonary function. Another study found that in adult patients with moderate to severe persistent asthma and symptoms of acid reflux, treatment with lansoprazole for 24 weeks improved asthma-related quality of life and reduced exacerbations, particularly in those patients receiving more than one asthma control medication [50]. However, it did not improve asthma control, as assessed by symptoms, pulmonary function or rescue medication use. The effects of GERD on asthma, therefore, are different from one patient to another, and a medication trial may be the best way in which to assess the influence of GERD on asthma [51].

OSA

OSA is a common problem that may be associated with asthma and obesity, but the relationships between these conditions are still to be well defined [52, 53]. Weight loss usually improves both conditions, although it is unclear whether improvement of OSA is part of the improvement in asthma that follows weight loss. YIGLA *et al.* [52] conducted a prospective cohort study in 20 patients with severe unstable asthma and found an unexpectedly high prevalence of OSA among those receiving long-term chronic or frequent bursts of oral corticosteroid therapy [52]. The authors suggested that the latter phenomenon could be due to increased airway collapsibility.

OSA is associated with both upper and systemic airway inflammation [54, 55]. Pharyngeal inflammation in OSA may promote upper airway collapse, while systemic inflammation may increase cardiovascular morbidity. DEVAOUASSOUX *et al.* [56] reported bronchial neutrophilia and a high IL-8 concentration on sputum analysis in patients with untreated OSA compared with controls. IL-8 in sputum supernatant was correlated with apnoea/hypopnoea index.

Furthermore, it has been suggested that mechanical changes from treatment with continuous positive airway pressure for OSA could influence airway responsiveness, but LAFOND *et al.* [57] reported no significant changes in airway responsiveness from baseline after 6 weeks of nocturnal continuous positive airway pressure treatment, although the subjects' asthma-related quality of life improved.

PSYCHOPATHOLOGIES

Psychological dysfunction has been observed in asthma, with problems such as anxiety, depression and panic disorders being more frequent than in the general population [58–62]. Patients with severe asthma who frequently use healthcare facilities show more psychological abnormalities, particularly anxiety, depression, and lack of trust towards healthcare providers [59, 62]. Psychological factors may trigger asthma symptoms and affect patients' asthma symptom perception, but also may influence medication compliance and, thus, should be detected and treated promptly and appropriately [62–66]. These conditions are associated with an increased use of urgent care and hospital admissions [67, 68].

Depression and anxiety disorders are common in severe asthma and may be either a consequence of, or a contributor to, this condition [63]. NOWOBILSKI *et al.* [65] reported that dyspnoea correlated with anxiety trait and anxiety state, neuroticism, and depression in asthmatic males but not in females. Furthermore, KATON *et al.* [66] observed that youths with asthma have an almost two-fold higher prevalence of comorbid anxiety and depressive disorders compared with controls. Finally, in a prospective community-based cohort study of asthmatic subjects aged 19 and 40 yrs, asthma was associated with anxiety and panic disorder, while after adjusting for potentially confounding variables, active asthma also predicted subsequent panic disorder [69].

Although studies have indicated that treatment of panic disorders can improve asthma outcomes, the authors of a Cochrane meta-analysis on the role of psychological interventions for children with asthma were unable to draw firm conclusions about the efficacy of this approach [70–73]. Studies reporting positive effects were usually conducted by specialists treating well-defined psychopathological comorbidities, whereas studies of psychoeducational interventions carried out by nonspecialists seemed less effective. Finally, more extreme forms of psychopathology, such as bipolar disorder, personality disorders and schizophrenia, have not been identified as occurring more commonly in severe asthma [3, 61, 74].

RESPIRATORY INFECTIONS

The role of respiratory infections in asthma exacerbations has been recognised for a long time and viruses, *e.g.* rhinovirus, have particularly been associated with increased asthma hospitalisations in children and adults [75, 76]. Respiratory viruses can act synergistically with other factors, such as allergen or pollutants exposures, to cause asthma exacerbations. How respiratory infections may aggravate asthma is now better known and it has been shown that in asthmatic patients, both innate and adaptive antiviral immunity may be impaired, resulting in the release of inflammatory mediators and cell death, which, associated with the increased viral load, may result in uncontrolled airway inflammation and exacerbation [77].

Agents such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been implicated in asthma exacerbations and also in long-term decrease in lung function, although their contribution to asthma-related morbidity remains undocumented [78]. Virally induced exacerbations are relatively refractory to corticosteroids. There is evidence that in asthma, impaired interferon response following a rhinovirus infection allows the virus to continue to replicate and then to damage the airway epithelium [79]. Furthermore, DENNING *et al.* [80] have suggested that a phenotype of severe asthma could be associated with sensitisation to fungal allergens that is sometimes, but not always, associated with allergic bronchopulmonary aspergillosis [80]. The possible role of a colonisation with an enhanced response of the airways to fungi has to be explored.

HYPERVENTILATION SYNDROME AND GLOTTIC DYSFUNCTION

There are several conditions that may mimic asthma, such as hyperventilation syndrome or various types of glottic dysfunction, and they usually present as a paradoxical adduction of the vocal cords during inspiration [81–83]. These conditions are also often associated with anxiety or other psychological disturbances. NEWMAN *et al.* [83] reported that 56% of 95 patients fulfilling the criteria of paradoxical vocal cord motion disorder, proven with laryngoscopy, had a concomitant asthma. HUSSEIN *et al.* [84] reported that paradoxical vocal cord dysfunction is more common among females and older individuals, and can be a comorbidity associated with asthma, GERD and previous abuse. Psychotherapy and/or speech therapy may address the problem in such cases. It is unknown whether comorbid asthma and hyperventilation syndrome or glottic dysfunction alters the long-term clinical expression of asthma.

HORMONAL DISORDERS

Asthma may worsen during the pre-menstrual period in up to 40% of females, possibly due to a reduced response to corticosteroids and bronchodilators [85]. However, this rarely causes severe exacerbations. The higher prevalence of adult-onset asthma and severe asthma in females than in males suggests a possible hormonal influence [86]. In pregnancy, however, asthma usually improves rather than worsens [87–89]. Furthermore, asthma is more often related to obesity in females than in males, a factor that is probably involved in difficult-to-control asthma among females [90].

OBESITY

Worldwide, obesity is at epidemic levels, and there is significant morbidity associated with it [90, 91]. Obesity is associated with an increased prevalence of asthma, particularly among the morbidly obese and females, and a causal relationship between obesity and asthma has been suggested by recent animal and human studies [92, 93]. Furthermore, all studies evaluating the effects of weight loss in the obese have shown an improvement in asthma symptoms, control and medication needs [94–96]. Mechanical, inflammatory and genetic/developmental factors and a higher prevalence of comorbidities have been implicated in the development of asthma in obese individuals [93].

Obesity has a major role in the development of OSA and GERD, and may theoretically act on asthma through these associated conditions. MOSEN *et al.* [97] have suggested, however, that even after adjusting for demographics, smoking status, oral corticosteroid use and evidence of GERD, obese adults were more likely than those with a normal body mass index (BMI) to report poor asthma-specific quality of life, poor asthma control and a history of asthma-related hospitalisations. There has been a parallel increase in prevalence of obesity, OSA and asthma in the past years. The possible causal association of asthma and OSA has not, however, been systematically studied [98].

Asthma in the obese patient appears to be a specific phenotype associated with pulmonary function changes caused by breathing at low lung volumes, a systemic inflammatory process that may possibly influence airways and a reduced response to asthma medications [93, 99–101]. Thus, all of these factors combined probably explain why asthma is difficult to control in these individuals.

With regard to asthma medication responses, the current author's group has previously shown [101], as was suggested

in an analysis by PETERS-GOLDEN *et al.* [102], that obese asthmatic patients had a reduced response to inhaled corticosteroids. Furthermore, SUTHERLAND *et al.* [103] recently evaluated the relationship between BMI and glucocorticoid response in subjects with and without asthma, and also found that an elevated BMI was associated with blunted *in vitro* response to dexamethasone in overweight and obese patients with asthma. The mechanisms by which obesity could impair asthma medication responses are yet to be determined, but may involve mechanical factors or an underlying change in the type of inflammation, making it less responsive to current asthma medications. In this regard, a systemic inflammatory state may be observed in obesity, with increased circulating leukocytes and an increase of various cytokines [93]. Other mechanisms leading to a reduced response to corticosteroids, such as the presence of oxidative stress or a defect of the glucocorticoid receptor remain possible.

Furthermore, ENELI *et al.* [104] performed a systematic review of studies looking at the effects of weight loss and asthma outcomes. Of the 15 relevant studies evaluated, regardless of the type of intervention (surgical *versus* medical), all noted an improvement in at least one asthma outcome after weight loss, in patients of various ages and countries of origin, or of either sex.

COPD AND SMOKING

Smoking may lead to COPD, but may also affect asthma in the absence of an obvious COPD component [105–107]. Asthma and COPD are common conditions that should be distinguished in order to offer optimal treatment, even though they co-exist in many individuals [108–110]. COPD may develop in patients with pre-existing asthma who smoke, and can influence the underlying phenotype and treatment response [105, 110]. Compared with asthma, in general, a COPD diagnosis is suggested by a later age of presentation, a smoking history of >10 pack-yrs, less reversible airflow limitation, reduced elastic recoil, hyperinflation at rest and impaired diffusing capacity; a history of atopy favours a diagnosis of asthma, as does increased eosinophil count on induced sputum analysis.

The evidence is now irrefutable that active smoking is a major factor in modifying the phenotype of asthma and influencing both treatment response and outcomes. In this regard, we may not consider smoking as a disease, although nicotine dependence may be considered so. There is an association between nicotine dependence and psychopathology with high prevalence rates of these last being reported for smokers [111]. It is possible that, at least in some subjects, smoking requires an additional comorbid condition to influence asthma development or clinical expression, as recently suggested in a study showing that subjects with allergic rhinitis who smoke are at higher risk of developing asthma [112].

The current author's group has previously reported that young people with asthma and who smoke have early COPD-like features, such as more severe airway obstruction, lower carbon monoxide diffusion capacity and increased prevalence of chest tomodensitometry abnormalities [105]. LANGE *et al.* [106] also have demonstrated an accelerated decline in pulmonary function in people with asthma, which is even more marked in those who smoke. Furthermore, smoking is associated with neutrophilic airway inflammation, more difficult-to-control asthma and a reduced response to inhaled corticosteroids [105, 107, 113–115].

The mechanism by which corticosteroid response is reduced in asthmatic smokers is still uncertain but may be due to neutrophilic airway inflammatory phenotype, changes in glucocorticoid receptor α/β ratio, and/or reduced histone deacetylase activity [114].

Therefore, asthma in smokers seems to represent a separate phenotype, and more research should be done on new therapeutic strategies that have been proposed for these patients in order to determine the optimal management approach [115].

Finally, the importance of smoking cessation in improving asthma outcomes, in addition to preventing other morbidities, should be stressed [116].

ATOPIC DERMATITIS

There is epidemiological evidence that asthma and atopic dermatitis often overlap early in life, with the latter also being a risk factor for asthma and being associated with severe forms of this disease [117, 118].

OTHER CONDITIONS

Allergic bronchopulmonary aspergillosis is occasionally observed in asthmatic patients and may lead to the development of central bronchiectasis. It is associated with high blood eosinophil and immunoglobulin E levels, positive skin tests and precipitins to Aspergillus, and it has been sometimes associated with severe asthma [119].

HOW DO COMORBIDITIES INFLUENCE THE SEVERITY OF ASTHMA?

The conditions described above may modulate asthma severity in various ways. They may: 1) be responsible for the development, or an evolution towards, a different asthma phenotype (as is probably the case with obesity, smoking, aspirin intolerance and allergic bronchopulmonary aspergillosis); 2) be part of the same pathophysiological process (*e.g.* rhinitis and asthma, as per the united airways hypothesis); 3) act as confounding factors in the diagnosis or assessment of control (*e.g.* obesity and OSA); and/or 4) be associated with a specific exposure or condition that can modulate the clinical expression of asthma or affect the efficacy of or compliance to treatment (*e.g.* GERD, respiratory infections, smoking and psychological disturbances).

As stressed in current guidelines, identification of comorbidities should be part of the core management of all types of asthma, particularly in severe or refractory asthma [1–3, 120]. It has also been shown that more than one comorbidity may affect asthma in a given individual [10].

Among the mechanisms by which comorbid conditions such as obesity, smoking, infections and, possibly, OSA could influence asthma is the development of systemic inflammation. In this regard, SUTHERLAND *et al.* [121] looked at possible interactions between systemic and local inflammation in obese subjects with asthma; markers of systemic inflammation were increased with obesity, and T-helper type 2 cytokines were

increased with asthma, but no important interactions were identified. SUTHERLAND *et al.* [121] concluded that the link between obesity and asthma was unlikely to be explained by enhancement of the ''classical'' forms of airway inflammation resulting from the systemic inflammatory effects of obesity itself. However, other mechanisms may prevail, such as oxidative stress, although this remains to be studied.

INVESTIGATION OF COMORBIDITIES IN ASTHMA PATIENTS

The identification of comorbidities it is now recognised as an integral part of the core management of asthma, particularly in more severe forms of the disease. Algorithm-based approaches incorporating key steps assessing underlying factors for severe asthma may be of assistance in detecting one or more potential causes for poor control and in establishing a diagnosis [2, 3, 120]. The investigations to be considered according to the suspected comorbid conditions are shown in table 1.

IMPLICATIONS OF THE PRESENCE OF ASTHMA COMORBIDITIES FOR CLINICAL CARE AND RESEARCH

With regard to clinical care, the presence of comorbidities has significant implications in terms of the evaluation and assessment of asthma control, and medication needs. It has been shown that many of these conditions may worsen asthma severity or render asthma control more difficult to achieve, in addition to altering the response to current asthma medications. This may result from a change in asthma phenotype, an increased or less responsive airway inflammation (*e.g.* polypoid rhinitis and smoking), or mechanical changes (*e.g.* obesity). Furthermore, assessment of asthma control criteria may be affected by sysmptoms (*e.g.* cough) that may be attributed to asthma but may be due to an associated rhinitis or GERD. This could lead to an inappropriate increase in asthma medication while it would be better to control the comorbidities. A systematic evaluation, not only of the presence of comorbid conditions, is necessary, but we have to ensure that these are also adequately treated/controlled, so that their effect on asthma is minimised.

TABLE 1 Techniques to be considered for investigation of asthma-related comorbidities

Allergy skin testing
Rhinoscopy
Sinus radiography/computed tomography
Sputum bacteriological testing
Therapeutic trial of GERD with proton pump inhibitor or pH probe
Sleep studies
Precipitins for Aspergillus
Pulmonary function tests (including lung volume and $D_{L,CO}$)
Chest radiography/computed tomography
Bronchoscopy with or without bronchoalveolar lavage
Laryngoscopy
Psychological evaluation
Induced sputum cell counts

Additional tests may be required. GERD: gastro-oesophageal reflux disease; $D_{L,CO}$: diffusion capacity of the lung for carbon monoxide.

With regard to research, the same principles apply. Furthermore, in randomised clinical trials, assessment of treatment responses may be affected by the presence of confounding factors. For example, if a subgroup includes more obese patients or some with a more marked smoking history, the effects of the therapy may differ.

REMAINING QUESTIONS

Much remains to be known about the contribution of comorbid conditions to the clinical manifestations of asthma, particularly persistent or severe asthma. We need to determine what the best therapeutic approaches are, as well as the optimal and most efficient ways to identify these conditions. Among the most pressing questions are the following. 1) What is the specific contribution of various comorbidities to the severity of asthma, and by which mechanisms are they influencing asthma? 2) What is the impact of treatment of comorbidities on asthma severity and long-term clinical outcomes? 3) Does severe asthma ever exist without comorbidities? Answers to these questions should lead to an improvement in control of the disease, and possibly a reduction in its severity. Furthermore, much remains to be known regarding how comorbidities influence clinical trials with respect to the choice of asthma outcomes, study design and sample size calculations.

CONCLUSIONS

Numerous comorbidities are frequently associated with asthma and may influence the clinical expression and severity of asthma. They should be investigated and treated appropriately in order to determine their respective influence on asthma and improve asthma control. More research is needed to shed further light on the relationships between the various common comorbidities associated with asthma and the clinical features and outcomes of those suffering from asthma.

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