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A proposed scheme to cope with comorbidities in asthma

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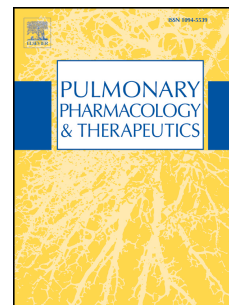
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Title

"A proposed scheme to cope with comorbidities in asthma."

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Abstract

The prevalence of non-communicable chronic diseases has been on the rise and the co-occurrence of morbidities is becoming more common. Multimorbidities are found more frequently among women, those with a history of mental disorders, lower level of schooling, and unfavorable socioeconomic condition. Physical inactivity, smoking and obesity are also associated with multimorbidities. Its occurrence is directly related to the age, affecting the majority of the individuals with more than 50 years. It is important to consider the possibility of comorbid conditions that aggravate, complicate or simulate the symptoms of the disease in the face of a patient with asthma and poor response to treatment. Among subjects with asthma, some conditions stand out as the most frequent: chronic rhinitis or rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome, obesity, and cardiovascular disorders. Comorbidities reduce the chances of optimal asthma control. It is essential to assess and manage properly these complex situations, choosing wisely preventive strategies and treatment options to avoid adverse events and optimize outcomes. Medications for asthma have the potential to worsen cardiovascular conditions, while beta-adrenergic receptor blockers and angiotensin conversion enzyme inhibitors used for cardiovascular conditions, can worsen asthma. Handling properly these cases will save lives and resources. However, there are multiple gaps in knowledge requiring investigation in this field to inform integrated care pathways and policies. It is likely information may be obtained from real life studies and electronic medical databases. Communications between the providers and patients may be facilitated by electronic technology, opening a large window for guided self-management.

Keywords

Asthma, comorbidities, multimorbidities, chronic diseases, polypharmacy, management

Abbreviations

Angiotensin conversion enzyme inhibitors (ACE inhibitors)

Cardiovascular diseases (CVD)

Chronic diseases (CD)

Chronic rhinitis (CRS)

Chronic respiratory diseases (CRD)

Diabetes mellitus (DM)

Dysfunctional breathing (DB)

Gastroesophageal reflux disease (GERD)

Ischemic heart disease (IHD)

Low-grade systemic inflammation (LGSI)

Obstructive sleep apnea syndrome (OSAS)

Vocal cord dysfunction (VCD)

Introduction

“People are living longer, but with more disease” [1]

The health profile of the population has changed globally, as better living conditions are achieved. Although changes have occurred unevenly, maternal-fetal, nutritional, and communicable disease mortality rates have been steadily declining in the vast majority of countries, leading to increased life expectancy. As a consequence of this phenomenon, the occurrence of non-communicable chronic diseases has been growing and as they are diseases of slow progression and long duration they have been changing the health scenario worldwide [2]. It is estimated that by the year 2025, 75 to 80% of the population over 60 will present at least one chronic disease. Therefore, the proportion of patients with multiple morbidities, complex therapeutic regimens, inadequate control of symptoms and higher chances of complications will continue on rising [2,3]. According to data from the World Health Organization and the Global Burden of Disease Study, neoplasms, cardiovascular diseases (CVD), chronic respiratory diseases (CRD) and diabetes mellitus (DM) currently represent the main causes of morbidity, disability and death around the world [2,4,5]. Chronic respiratory diseases occupy the third position in this ranking, accounting for 3.54 million deaths/year [4], with asthma being the third most prevalent disease in the group and responsible for a high burden and impact on people's lives: there are more than 13 million years of productive life lost as a result of disability linked to asthma [5].

Asthma burden is a result of increased severity, lack of disease control, poorer quality of life, and greater need for

health services. This happens, among other things, because some patients, even receiving the best possible treatment, do not achieve control of the disease. In general, they are patients with difficult-to-treat asthma and the poor response to treatment may be related to the presence of aggravating factors such as lack of access to medications or poor adherence to treatment, inadequate technique of inhalation, persistent environmental exposure to aeroallergens and/or airway irritants, psychosocial factors, and the presence of coexisting morbidities [6]. The identification and management of these factors are part of the recommendations for the adequate management of asthma, as they are associated to the improvement of disease outcomes [7]. Those who do not show improvement of control after this approach, while using a high dose of inhaled corticosteroids combined with other controller medication are considered ~~to present~~ treatment-resistant severe asthma patients [8], for whom new treatment alternatives may be employed according to their phenotype [9].

Thus, the aim of this article is to discuss the most relevant aspects of comorbidities in asthma and present a suggestion of an approach for more complex cases due to the association with other chronic diseases.

Chronic diseases, comorbidities and multimorbidities

In the last ten years, there has been an expressive increase in the number of publications on coexistent morbidities, reporting relevant information but indicating major gaps in knowledge [10]. One of them is the lack of a clear and comprehensive definition for chronic diseases that allows identifying the entities of greater clinical relevance from the point of view of multimorbidities [11]. The terms comorbidity and multimorbidity have been also aim of discussion. They have been frequently used as synonyms although

there is not a consensus. The distinct meaning of the terms comorbidity and multimorbidity is a relevant issue because there are some clinical, statistical and epidemiological implications when one nosological entity emerges along the clinical course of another [10]. Besides, standardizing definitions reduces the heterogeneity and allow comparability between the populations and outcomes assessed in clinical research [11]. From the health care perspective, it reflects the type of care best suited to each situation. When considering an index disease, the care for the patient with comorbidities happens predominantly in a more specialized context (secondary level or tertiary hierarchy of health services), while multimorbidities would be dealt initially in primary health care, which shall offer comprehensive and assessable patient care [12]. Anyway, to the clinical practice, the distinction between terms may be less relevant, since both comorbidities and multimorbidities are complex situations that require a broader approach to minimize the burden of all concomitant diseases. So, in order to contribute to the discussion and make the ideas clear and understandable, the terms used in the present article are employed according definitions in the table 1.

Recent studies show that multimorbidities are found more frequently among women, among those with a personal history of negative events, mental disorders, lower level of schooling, and unfavorable socioeconomic conditions [13]. Physical inactivity, smoking, and overweight/obesity are also associated with multimorbidities [14]. Its occurrence is directly related to the age [15,16], but children, adolescents, and young adults, although presenting a different disease profile, are also likely to present one or more diseases (chronic or not) [16-18]. Several biological aspects and risk factors are associated with the development of multiples diseases in susceptible individuals. Diseases that share pathophysiological processes or risk factors tend to occur concomitantly or sequentially [19]. Organs and systems become more

vulnerable to dysfunction over time, which explains the increased susceptibility to diseases with senescence [11], when the frequency of associations and the number of additional conditions also tend to increase. In addition, two or more diseases may coexist by chance and this possibility increases with increasing disease frequency in the population, further contributing to the complexity of the situation and to the burden resulting from it [20,21].

Asthma and comorbidities

Understanding comorbidities in asthma

Comorbidities/multimorbidities are a burden to the individual and to the health sector that goes beyond what would be expected by the sum of individual disease's burden [12]. The management of concomitant diseases requires novel strategies for clinical practice and research. In epidemiological research, for instance, it may interfere in the quality of collected data and confound the results of studies, if a tailored statistical analysis strategy is not adopted. The presence of comorbidities/multimorbidities can alter the clinical course of the diseases by influencing the time of diagnosis, interfering in the choice of treatment, by worsening prognosis and precipitating outcomes [10,12].

In asthma, a more difficult control of symptoms may be related to the presence of comorbidities and not necessarily to a biologically more serious condition [7]. Comorbidities may mimic or mask the diagnosis of asthma, may add more symptoms, limitations and risks to the patient, leading to a unnecessary step up in therapy, thus increasing the costs and risks of adverse effects [22].

Some diseases occur more frequently among asthmatics than in non-asthmatics. They can coexist with asthma alone or in combinations (clusters) and influence outcomes. The presence of comorbidities is independently associated with a higher frequency of exacerbations, worse asthma control and quality of life [23].

Sumino et al., investigating the contribution of 17 diseases in the morbidity and mortality indicators in patients with asthma, have confirmed some comorbidities are associated with worse outcomes in asthmatic adults and this effect depends on age. They also showed that mental disorders were associated with increased morbidity and mortality risk at all ages, except for depression that was associated with an increased risk of asthma-related events only among those younger than 64 years [24].

Why asthma and other diseases coexist?

In general, asthma is an inflammatory condition. Cellular infiltration, edema, mucus hypersecretion, epithelial desquamation, bronchial smooth muscle hypertrophy/hyperplasia, and airway remodeling result from local inflammation that is responsible for the clinical manifestations of the disease [25]. However, studies show that local allergic inflammation (for instance, in the airways) is accompanied by a systemic component that, in addition to maintaining local symptoms, may lead to inflammation in other organs [26]. Several studies have shown that the spread of inflammation occurs and is a phenomenon that can be observed in several allergic diseases, both in the lower and upper airways (including the paranasal sinuses), skin and digestive tract, with possible participation of the circulatory [27] and nervous systems [28].

Braunstahl et al. showed that bronchial provocation with allergens can induce an inflammatory infiltrate in the nasal

mucosa, confirming that local inflammation can become systemic and induce inflammation in distant organs [29]. Later, these same authors showed the presence of eosinophils and increased expression of adhesion molecules in the bronchial mucosa 24 hours after nasal provocation, proving that the "systemic spread of local inflammation" may also occur [30].

More recently, a study has shown that asthma, allergic rhinitis and atopic dermatitis often associate in a cluster, not only because they are diseases related to the immune system, but because they have the same mechanism of disease. They share increased expression of certain proteins (IL4, IL13, IL1RL1, IL18R1 and TSLP) and activation of specific cell pathways (mainly the IL2 signaling pathway, the IL4 signaling pathway, and GATA3, that participate in the activation of Th2 cytokine gene expression), suggesting the existence of a network of interrelated cellular mechanisms [31]. Burte et al. also showed that individuals with asthma and associated allergic rhinitis present more often polysensitization, more eosinophilia and greater intensity of nasal symptoms than individuals with asthma or allergic rhinitis alone, suggesting that it is a particular phenotype [32].

However, asthma can be associated with several diseases other than those with which it shares pathophysiological aspects (Table 2). As compared to what has been described with other CD(cardiovascular diseases, diabetes mellitus, obesity), asthma has a more nonspecific and systemic inflammatory profile, known as Low-grade systemic inflammation (LGSi). LGSi can be identified by elevated serum levels of acute-phase proteins such as C-reactive protein, the production of inflammatory cytokines (TNF, IL-1 β , IL-6 and IL-17)[33] and increased numbers of macrophages in peripheral tissues, but no proven tissue damage resulting from this infiltration [34]. Although LGSi is not directly linked to

organ damage, its presence is associated with an increased risk of developing some cardiovascular and metabolic diseases (obesity, insulin resistance, dyslipidemia, atherosclerotic disease, type 2 diabetes mellitus, and systemic arterial hypertension)[34].

One of the most studied LGSI biomarkers at the present time is C-reactive protein. Several studies have shown the presence of elevated serum levels of ultra-sensitive C-reactive protein (usPCR) in asthma, both in adults [35] and children [36,37], which correlates with a high number of eosinophils in the sputum and reduced pulmonary function [38]. In order to study the relationship between serum usPCR, inflammation, airway obstruction and hyperresponsiveness, Shimoda and colleagues studied patients with mild asthma between the ages of 20 and 60 years and verified increased serum levels of usPCR that correlated with eosinophilic and neutrophilic inflammation. Patients with asthma also had increased production of proinflammatory cytokines ($\text{TNF } \alpha$, $\text{IL-1 } \beta$, IL-6) and $\text{TGF- } \beta$ [39], which has also been reported in severe asthma [40].

To date, there is evidence that various diseases such as chronic rhinitis or rhinosinusitis, gastroesophageal reflux disease (GERD), psychiatric disorders (depression and anxiety), obesity, *diabetes mellitus*, dyslipidemia, osteoporosis/osteoarthritis and cardiovascular diseases (CVD) often coexist with asthma. However, studies to date have shown that the association between asthma and each of these chronic diseases is quite variable and, although it is hypothesized that they may influence each other, it is not yet known exactly how it happens [19,41,42].

Asthma and extrapulmonary illnesses

Chronic rhinitis or rhinossinusitis (CRS), gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome (OSAS), vocal cord dysfunction (VCD) and dysfunctional breathing (DB) have often been described as comorbidities of asthma. They are non-allergic extra-pulmonary conditions, mostly non-inflammatory (except for CRS) that may affect the risk of asthma exacerbations, symptom control and asthma-related quality of life [23].

CRS consists of inflammation of the nose and paranasal sinuses characterized by the presence of nasal obstruction or nasal discharge (anterior or posterior), pain or facial pressure and alteration of smell associated with objective signs in nasal endoscopy or CT scan [43]. CRS is an inflammatory disease whose pathophysiology involves complex inflammatory mechanisms, involving the innate immune response due to activation of epithelial cells and subsequent local damage, and the activation of mechanisms of the adaptive immune response (TH lymphocytes 1, 2 and 17; B cells), activation of end effector cells (eosinophils and basophils) and decreased immunoregulatory mechanisms [43]. CRS is frequently associated with asthma, increasing up to 4 times the risk of exacerbations observed in individuals with asthma without CRS [23]. Nasal polyposis and acetylsalicylic acid intolerance are often associated with CRS. Over 70% of patients with asthma have symptoms of CRS, and the upper airway disease is more frequent and severe in those with severe asthma. Treatment of asthma-associated CRS can positively affect asthma outcomes[41].

Gastroesophageal reflux disease (GERD) comprises a spectrum of disorders related to the return of gastric contents to the esophagus. It is described as one of the main morbidities associated with asthma (1.6 times more frequent among asthmatics than non-asthmatics)[44], with a frequency range between 43,6% to

66,8% among subjects with asthma difficult to treat [45,46]. Asthmatic patients with GERD present more symptoms and more severe disease, which are believed to be due to increased vagal response, bronchoconstriction and bronchial hyperresponsiveness related to direct or indirect acid stimulation [47]. In its turn, increased intrathoracic pressure in asthma and the action of some medications on the lower esophageal sphincter may predispose to or aggravate reflux. However, the response to specific GERD treatment is variable, and the improvement in asthma is mostly observed among patients with nocturnal symptoms. It is advisable to investigate other possible conditions when the use of proton pump inhibitors is ineffective in relieving the supposed GERD symptoms [48].

Vocal cord dysfunction (VCD) may mimic or coexist with asthma. CVD is defined as involuntary adduction of the vocal cords during inspiration. It is more prevalent among asthmatics (19%) than non-asthmatics (5%) and approximately 50% of CVD patients have asthma [49]. The most common symptoms are dyspnoea, wheezing, stridor and cough, but patients may also experience hoarseness and discomfort in the oropharynx. Patients may experience hypoxemia during attacks that are often precipitated by physical exercise, airway irritation, and emotional stress. The treatment is based on exercises guided by the professional in phonoaudiology and or physiotherapy, as well as psychological support [50].

Obstructive sleep apnea syndrome (SAOS) is characterized by repeated episodes of upper airway obstruction during sleep leading to short periods of no breathing (apnea) or significant reduction of airflow (hypopnea), leading to alteration of alveolar ventilation, hypoxemia and increase of PaCO_2 [51]. A recent systematic review found variable prevalence of co-occurrence of asthma and SAOS among the studies (8 to 52.8% and a study that

found no association between the two conditions). However, when the association was estimated among patients with severe asthma, the observed prevalence was much higher (50 to 95%)[52]. Wang and colleagues showed that SAOS was more frequently observed among asthmatics (19%) than among non-asthmatics (9.6%) and that asthmatic patients with SAOS were significantly more likely to exacerbate [53]. These patients are more likely to present severe nocturnal hypoxemia, develop other diseases and death. Treatment options are based on symptoms, on the severity of the problem and include educational interventions on risk factor prevention, oropharyngeal rehabilitation through exercises, tongue retention devices, positive airway pressure, pharmacotherapy, and surgical interventions [54].

Dysfunctional breathing (DB) is characterized by chronic or recurrent changes in the respiratory pattern, not attributable to another diagnosis, presenting dyspnea, chest tightness, wheezing, chest pain, hyperventilation, and yawning, which are accompanied by anxiety, dizziness, and fatigue. Pulmonary function is normal and there is no gold standard for its diagnosis [55,56]. It is a poorly understood disorder, which appears to be related to changes in respiratory mechanics, frequency or depth of breathing, and may coexist with asthma and VCD. The prevalence of RD varies from 6 to 10% in the general population, being more frequently observed among asthmatics (29%) than among non-asthmatics (8%). These patients tend to have less controlled asthma, more exacerbations, more labile asthma, and a rapid decline in lung function [55]. The treatment involves respiratory retraining with techniques of relaxation and cost-diaphragmatic breathing [56].

Asthma and systemic diseases

Several chronic diseases involving different organs and systems have been recognized as comorbidities of asthma. Hypertension, depression, chronic pain and dyspepsia were the diseases most frequently associated with asthma in a study conducted with secondary data in the Scottish population [18].

Data from the GEDA study (2009 and 2010) were analyzed for information on comorbidities related to asthma in the German population. The authors found a physician-diagnosed frequency of asthma in 5.3% of the 43,312 individuals interviewed. Asthma was independently associated with 8 diseases in particular - chronic heart failure, coronary heart disease, stroke, arterial hypertension, depression, *diabetes mellitus*, osteoarthritis and cancer, with 60% of patients with asthma having at least one other morbidity and 18% with 3 or more, which were significantly associated with poorer asthma control, more emergency visits and more need for hospital admission [57].

The possible mechanisms involved in the association between asthma and chronic diseases are still not well known, but some hypotheses have been discussed. The LGSI, the different medications used to treat each morbidity and its interactions, as well as the effects of chronic and transient hypoxia (pulmonary hypertension) stand out as possible pathophysiological explanations. The occurrence of coronary artery disease/angina, stroke and atherosclerotic disease were observed more frequently in women with late-onset asthma, suggesting the participation of female sex hormones. A recent study discusses the role of sex hormones in asthma and suggests that among other actions, estrogen may be associated with increased airway inflammation in asthma, macrophage function, and IL-17A production [58]. On the other hand, other authors have suggested that estrogen might be associated with anti-inflammatory effects due to decreased production of TNF- α , IFN- γ and NK cell activity, and may explain

the fluctuations of asthma symptoms in some women in the perimenstrual period and during menopause [59,60].

Shared risk factors, such as obesity and smoking may also explain the co-occurrence of asthma and other chronic diseases [57]. Although current and past observations warrant further investigations, LGSII may be the link between asthma and increased risk of chronic systemic diseases, especially cardiovascular and metabolic diseases.

Hypertension, Ischemic Heart Disease, and Stroke

Asthma has been particularly associated with cardiovascular disease. Some studies have found an association between asthma and CVD, especially ischemic heart disease (IHD) among women with severe asthma and late onset [61,62]. A recently published meta-analysis study of cohort studies has shown that individuals with asthma are at increased risk for incident CVD (1.42 more chances than the population without asthma) and this risk is still higher among women [63]. The risk of stroke also appears to be increased in patients with asthma [64] and atherosclerotic disease was also more frequently observed among women with severe asthma from onset in adulthood [65]. In relation to systemic arterial hypertension (SAH), Fergusson et al. found it in 24% of adults with asthma, especially among those with lower FEV₁ values and those with SAOS. When evaluating the effect of asthma treatment, the authors observed lower odds of presenting hypertension among patients using inhaled corticosteroids at lower doses, suggesting an influence of the control medication [66]. Cazzola et al. also found a slightly higher occurrence of SAH among asthmatics (28.3%) than in the general population (25.7%). The authors also reported the association of asthma with dyslipidemia, *diabetes mellitus* and GERD, and discuss the influence of obesity in these cases [42]. Although the association between asthma and arterial

hypertension is variable between different studies, it deserves attention. A recent study found a greater occurrence of left ventricular hypertrophy, identified by left ventricular mass index (LVMI), in adult asthmatics, especially among those with hypertension or associated pre-hypertension, indicating that these patients may be at greater risk of unfavorable cardiovascular outcomes and death [67]. Some medications commonly used in the treatment of arterial hypertension may affect asthma. Beta-blockers and ACE inhibitors may induce bronchoconstriction and dry cough, respectively, and should be prescribed with caution, especially for patients with severe asthma. Calcium channel blockers comprise a class of drugs with little disease-drug interaction and thus are safer [68].

Congestive heart failure

The concomitant presentation of asthma and congestive heart failure (CHF) represents a special situation, since the two entities share many symptoms, which can lead to diagnostic difficulties. Left ventricular failure presents with orthopnea and paroxysmal nocturnal dyspnea, mimicking an exacerbation of asthma. The improvement of dyspnea due to pulmonary edema with the use of fast-acting bronchodilators may make differential diagnosis even more difficult [69]. Moreover, specific medications of one disease can influence the course of the other. β -blockers, especially non-cardioselective drugs, may worsen or exacerbate asthma and even β -1 (cardioselective) blockers should not be used by patients with severe asthma. On the other hand, β -adrenergic agonists (short- and long-acting) cause hypokalemia and increase in heart rate due to their positive inotropic effects, which may increase the risk of arrhythmias (atrial fibrillation) and cardiovascular events in asthmatic patients with HF or coronary disease [69].

Depression and other psychiatric disorders

Depression has been frequently observed among patients with asthma. Cazzola and colleagues found a high frequency of depression and other non-psychotic mental disorders in this group (37.8% among asthmatics versus 28.7% in the general population)[42]. A study with data from the National Health Insurance Program of Taiwan evaluated patients with asthma, allergic rhinitis and atopic dermatitis and the risk of developing some psychiatric disorder. The authors found higher risk of dementia, depression, anxiety disorders, eating, sleep, bipolar disorder and psychosis in patients with asthma [70].

Another study conducted in patients with asthma and COPD in Puerto Rico found a greater frequency of psychosocial stress in this group of patients, and exposure to violence and history of at least one suicide attempt in life were significantly associated with asthma [OR 1.14, 95 % (1.07 - 1.21)] and [OR 3.01, 95% CI (1.80 to 5.01)], respectively [71].

Diabetes mellitus and metabolic syndrome

Metabolic syndrome is a clinical entity characterized by dyslipidemia, insulin resistance and obesity or hypertension, which is related to the development of other diseases such as atherosclerosis, *diabetes mellitus* and ischemic heart disease. De Sanctis et al. investigated the prevalence of respiratory symptoms in individuals with *diabetes mellitus*, and reported these patients had more respiratory symptoms (dyspnea, cough and sputum) than the general population but did not present asthma. In this same study, the authors observed more frequent reports of dyspnea among patients with DM and associated obesity [72]. Conversely, Cazzola et al. showed a higher occurrence of *diabetes mellitus* among asthmatics than in the general population [42].

Obesity

Obesity is among the major health conditions associated with asthma. Several studies show that obesity occurs in 18% to 22% of patients with asthma and is even higher among those with severe asthma (39%)[7,45]. Data from a recently published study evaluating 925 patients with severe asthma found obesity in 299 (32%), the proportion of overweight individuals was 66.8%. The authors showed that these patients were mostly women and had fewer peripheral blood eosinophils, less atopy identified through the positivity of the skin prick test. Most subjects had difficulty to control asthma and, as they presented less control of the symptoms and used higher doses of ICS [73]. Other authors found an association between asthma and obesity, but also with dyslipidemia, GERD and DM Type 2 [43]. The treatment of obesity, both pharmacological and surgical, is associated with improvement of symptoms and control of asthma [74].

Osteoarthritis and osteoporosis

Osteoporosis was found in 10.3% of asthmatics, mainly among women and some authors suggest that it is underdiagnosed in men. It may be associated with the use of systemic and inhaled corticosteroids [42].

Patients with osteoarticular problems comprise a group of individuals at greater risk of developing asthma exacerbations due to the use of non-steroidal anti-inflammatory drugs. They may also be more likely to have adverse effects associated with the use of systemic corticosteroids [68].

Polypharmacy or multiple medication treatment

The term polypharmacy was recently created by the need to discuss issues related to multiple drug regimens commonly prescribed for patients with multimorbidities. However, there is still no consensus as to its definition and therefore the term has been used in varied contexts. A recently published review study on the subject discusses the divergences of meanings attributed to the term and highlights some aspects of relevance to clinical practice. The authors show that the number of medications considered in the definition of polypharmacy varies widely between studies (from 2 or more up to 11 or more), as well as the time of use (90 days to 240 days), adequacy and rationality of combinations (appropriate and inappropriate polypharmacy) and some use descriptive criteria (minor, moderate, major, excessive)[75].

Considering that each morbidity has its own therapeutic regimen, the presence of multimorbidities implies in the prescription of a greater variety and, in principle, greater consumption of medicines [76], greater possibilities of interaction between the various drugs and the occurrence of adverse effects. Furthermore, the number of multimorbidities tends to grow as the age advances, increasing also the possibility of more numerous therapeutic schemes and the complexity of the patient's health situation. The prescription of a greater number of medicines leads to an increase in individual expenses with the disease, without necessarily implying better disease control. A case-control study conducted to evaluate the long-term benefits of treatment of patients ≥ 50 years with comorbidities showed the deterioration of physical and mental health conditions after 3 years of follow-up, which the authors attributed to the multiple drug regimen [77]. A cross-sectional study conducted to evaluate the issue of polypharmacy in elderly

asthmatics found 88% of the patients evaluated used 5 or more drugs to treat different diseases and approximately one third of these patients used drugs that could potentially interfere with asthma (β -blockers, ACE inhibitors and AAS) [78]. Multiple drug regimens are more associated with poor adherence, inadequate prescriptions (when potential risks outweigh the potential benefits), increased risk of falls, side effects, increased morbidity and mortality [79].

Approach to the patient with asthma and comorbidities

In the era of network medicine and according to the concept of interactoma, molecular derangements connect in a complex way leading to interacting dysfunctions, explaining the concomitant or sequential emergence of diseases (diseasoma)[80,81]. In this context, many comorbidities would not simply coincide, but would be linked through common biomolecular processes, which would further justify the need for a comprehensive and interdisciplinary approach of patients, considering all clinical and therapeutic aspects related to the different additional diseases. At the same time, the advancement of knowledge about the different biomolecular processes (endotypes) has contributed to the increasing differentiation of one patient from another with the same disease (phenotypes) and this has driven clinical practice toward precision medicine [82].

The care of a patient with comorbidities, due to the presence of a disease index, is often the responsibility of the specialist [12]. This practice is based on the fact that the biological characteristics of the disease in question often require more elaborate care and procedures that are the specialist's responsibility and often require the technology and resources available only in secondary and/or tertiary services health care. However, at a time when medical practice is no longer faced with a

chronic disease but many coexisting chronic diseases, it is crucial discussing the importance of an integral approach also at all levels of care for patients who will live more and more, aiming for better quality of life and lower costs [18,83]. Thus, the initiative to include in guidelines recommendations for multimorbidities is fundamental to adjust decisions to the current reality of complex patients. It is also important to consider the elaboration of guidelines specially designed for the management of clusters of diseases [82], similar to some documents aimed at approaching patients with multimorbidities in the context of Primary Health Care and Geriatrics [84]. Studies have shown that asthma is one of the chronic diseases that most associate with other diseases [85] and that some combinations are observed more often than others, suggesting the presence of interrelated underlying processes [84,86]. In addition, the disease-disease interaction and the interaction among the different drugs used in the specific treatment of each disease add peculiarities that must be addressed in a particular way.

It is always important to consider the possibility of comorbid conditions that aggravate, complicate or simulate the symptoms of the disease in the face of a patient with asthma and poor response to treatment [22]. Thus, it is always advisable to confirm the diagnosis of asthma and to achieve the differential diagnosis through a meticulous clinical history (including questioning about possible risk factors) and a detailed physical examination, in search of extrapulmonary or systemic diseases that may mimic asthma. Once the diagnosis of asthma has been confirmed and the presence of one or more extra morbidities has been identified, treatment should be planned, starting with the optimization of asthma treatment and treatment of the multiple morbidities, considering the patient as a whole. Because these are slowly progressive diseases, the therapeutic plan should provide for the continued and longitudinal care of the patient, together with the

specialist responsible for monitoring additional morbidity when necessary. However, the asthma specialist should be aware of the complexity of the cases and be prepared to recognize and provide for particular situations.

A suggestion for approaching comorbidities in patients with difficult-to-treat asthma is given in the flow chart of Figure 1. Table 3 presents some options of instruments for identifying and managing comorbidities most frequently associated with asthma.

Conclusions

Patients with comorbidities/multimorbidities are becoming a common situation in the current health scenario. As the complexity of health care progresses due to the coexistence of multiple morbidities, important health outcomes such as mortality, disability, functional decline, quality of life and use of health resources worsen or increase resulting in higher costs. This has generated new health needs that ranges from the creation of policies aimed at this public and adaptations of health services to provide higher quality health care to new strategies of individual approach to these cases of greater clinical complexity. It requires that health care providers and patients adapt themselves to an integrated approach to optimize the efficiency of prevention and management interventions for more than one concomitant chronic disease, which will demand synergistic team work in a context of better communications, and education of the patients to a more active role in the continuity of care. Handling properly these cases of greater complexity will lead to better disease outcomes and less health resource use. However, there are multiple gaps in knowledge requiring investigation in this field to inform care pathways and policies. It is likely a lot of precious information may be obtained from real life studies and electronic medical records databases, and the communications between the provider team

and patients will be facilitated by electronic technology and guided self-management.

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Table 1: Definitions adopted in this paper.

Chronic disease	"Disease that had a prolonged duration and either (a) left residual disability or worsening quality of life or (b) required a long period of care, treatment, or rehabilitation" [11]
Comorbidities	"Any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" [12]
Multimorbidities	"the co-occurrence of multiple chronic or acute diseases and medical conditions within one person"[13]

Table 2 – Comorbidities most often associated with asthma.

Allergic diseases	Non-allergic extrapulmonary diseases	Systemic diseases
Allergic rhinitis	Chronic rhinosinusitis	Depression and other mental disorders
Atopic dermatitis (eczema)	Gastroesophageal reflux disease (GERD)	Systemic arterial hypertension
Food allergy	Obstructive sleep apnea syndrome (OSAS)	Ischemic heart disease
"Allergy" to aspirin and other NSAID	Vocal cord dysfunction (VCD)	Stroke
	Respiração disfuncional (DB)	Obesity
		<i>Diabetes mellitus</i> (DM)
		Osteoporosis

Table 3: Practical approach to coping with the most relevant asthma comorbidities.

Disease	Identification	Initial procedures
Allergic diseases	Most common among children and young adults	
Allergic Rhinitis	• Sneezing, pruritus, rhinorrhea, congestion • Skin prick test • Specific serum IgE	• Environmental control • Oral or local anti-histamines • Intranasal corticosteroids • Leukotriene receptor antagonists(LRA) • Allergen specific immunotherapy
Atopic dermatitis (eczema)	• Typical symptoms and signs	• Skin protection and care • Oral antihistamines • Topical steroids • Topical calcineurin inhibitors (TCIs) • Management of infectious triggers • Others: phototherapy, immunosuppressive medications, biological therapy
Non-allergic extrapulmonary diseases	Mainly among adults	
Chronic rhinosinusitis (eventually with polyposis)	• Nasal obstruction, sinus headache, anterior rhinorrhea and/or post nasal drip • Sinus CT scan/ radiography • Nasal endoscopy	• Nasal irrigations (saline 0,9% or 3%) • Intranasal corticosteroids • Leukotriene receptor antagonists • Antibiotics • Oral corticosteroids
Gastroesophageal reflux disease (DRGE)	• Heart burn, chest pain, regurgitation • Proton pump inhibitor therapeutic trial • Gastrointestinal endoscopy	• Lifestyle and diet changes • Proton pump inhibitors • H₂-antihistamine blockers • Surgical intervention

	• Imaging exams • 24h pH monitoring	
Obstructive sleep apnea syndrome	• Diurnal somnolence, snoring • Epworth sleepiness scale • Polisomnography	• Lifestyle changes and weight reduction • Avoidance of alcohol and sedatives • Tongue retention devices • Continuous positive airway pressure • Surgical interventions
Vocal cord dysfunction(VCD)	• Dyspnea associated with inspiratory laryngeal stridor • Pittsburgh vocal cord dysfunction questionnaire • Spirometry flow-volume inspiratory loop • Laryngoscopy	• Oropharynx rehabilitation (exercises oriented by speech therapist or physiotherapist) • Emotional support
Dysfunctional breathing (DB)	• Typical pattern of symptoms and absence of signs of other disease	• Breathing retraining (speech therapist or physiotherapist) • Emotional support (psychotherapy)
Systemic diseases	Most common in the elderly	
Systemic arterial hypertension	• Blood pressure measurements • Electrocardiogram • Chest X-ray	• Diuretics • Angiotensin-converting enzyme inhibitors • Angiotensin II receptor antagonists • Calcium channel blockers • β-adrenergic blockers (only selective β_1 and with caution)
<i>Diabetes mellitus</i> (DM)	• Typical symptoms and signs • Fasting blood glucose (FBG) • Glucose tolerance test	• Nutritional guidance • Physical activity • Antidiabetic drugs

	(GTT) • Glycated hemoglobin	
Obesity	• Anthropometric measurements	• Nutritional guidance • Physical activity • Pharmacotherapy • Psychotherapy • Surgical intervention
Ischemic heart disease (IHD)	• Chest pain • Electrocardiogram • Treadmill test • Cardiac scintigraphy • Heart magnetic resonance imaging • Heart catheterization	• Rehabilitation • Nutritional guidance • Arterial vasodilators • Revascularization procedures
Stroke	• Typical symptoms and signs • Cranial CT scan	• Control of risk factors • Pharmacotherapy • Neuromuscular rehabilitation
Depression/anxiety/psychiatric disorders	• Typical symptoms and signs • Psychological evaluation	• Emotional support (psychotherapy) • Pharmacotherapy (antidepressants, anxiolytics, etc)
Osteoporosis	• Bone densitometry	• Nutritional guidance and controlled exposure to the sun • Physical activity • Control for risk factors • Calcium supplements • Vitamin D • Bisphosphonate (with caution as it may worsen GERD)

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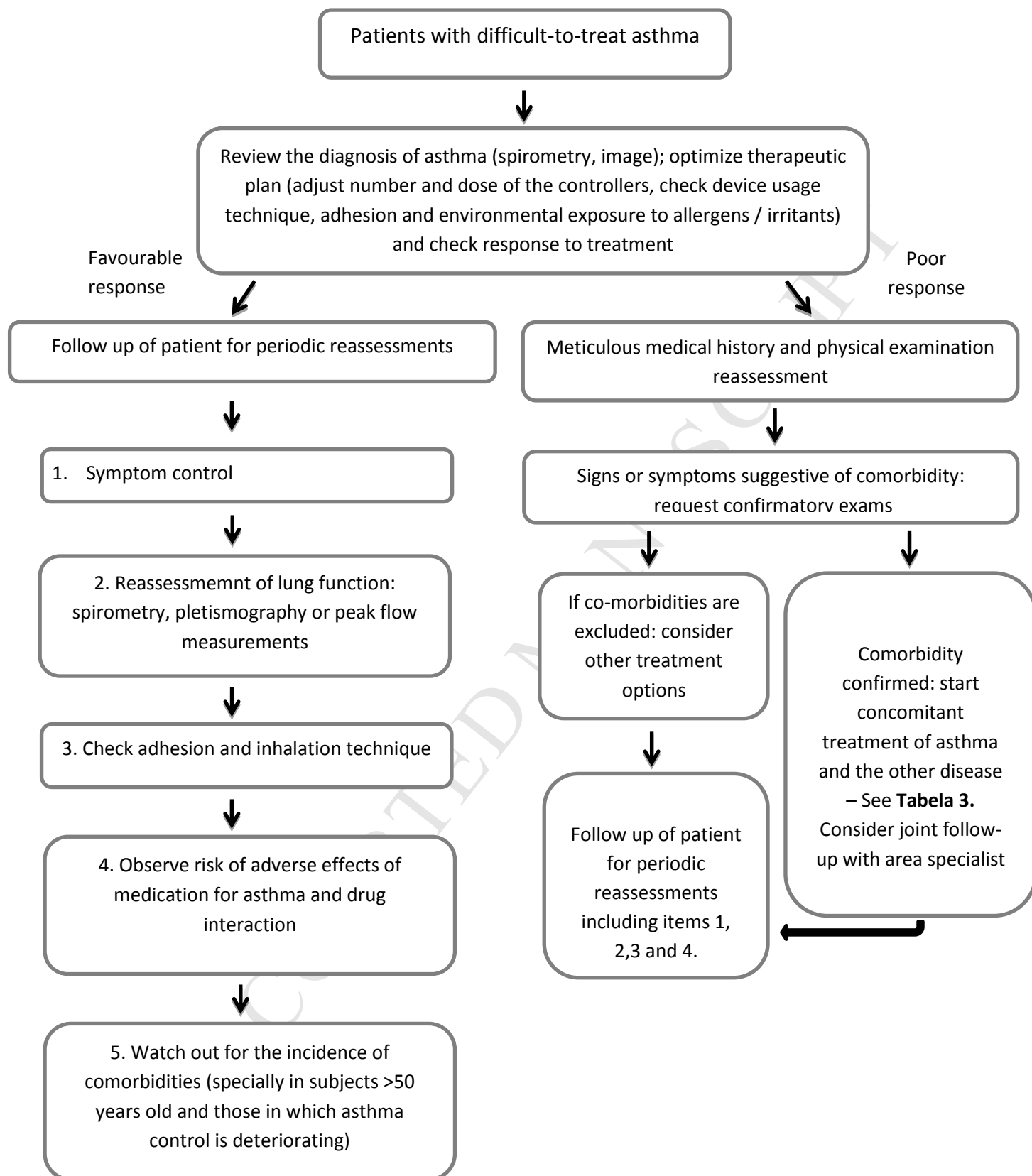


Figura 1: Suggested algorithmic approach to subjects with difficult-to-treat asthma.