Chapter 2

Asthma and COPD – Overlapping Disorders or Distinct Processes?

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58234

1. Introduction

Historically, asthma and COPD (chronic obstructive pulmonary disease) have been considered separate and unique diseases with distinct characteristics. Classically, asthma has been characterized by reversible airways obstruction and COPD by fixed, less reversible, or irreversible airways obstruction. The definitions of asthma and COPD have undergone major revisions recently and COPD, like asthma, has now been recognized as an inflammatory disease of the airways [1, 2]. Even though asthma and COPD *can* be and are often *appropriately* separated as clinical entities, there are times when they are clinically and physiologically indistinguishable. As the American Thoracic Society guidelines for the diagnosis of COPD [3] state, "the obstruction in many patients with COPD may include a significant reversible component and that some patients with asthma may go on to develop irreversible airflow obstruction indistinguishable from COPD." This intersection of physiologic findings in asthma and COPD has led to the development of the concept of what is now known as the overlap syndrome of asthma and COPD [4]. As subcategories or phenotypes of asthma and COPD are identified, the distinction between these two disorders is less well defined. Some of the phenotypes exhibit very similar clinical, physiologic, and inflammatory profiles. The concept of asthma and COPD viewed as separate disease states has evolved as definitions and categorization of asthma and COPD change, and, as such, we are now encountering more overlap among these two disorders than was previously recognized. So we now pose the question: should asthma and COPD always be recognized and viewed as completely distinct diseases or is there enough similarity to view them equivalently at times? In essence, does an asthma-COPD overlap syndrome occur in some patients?

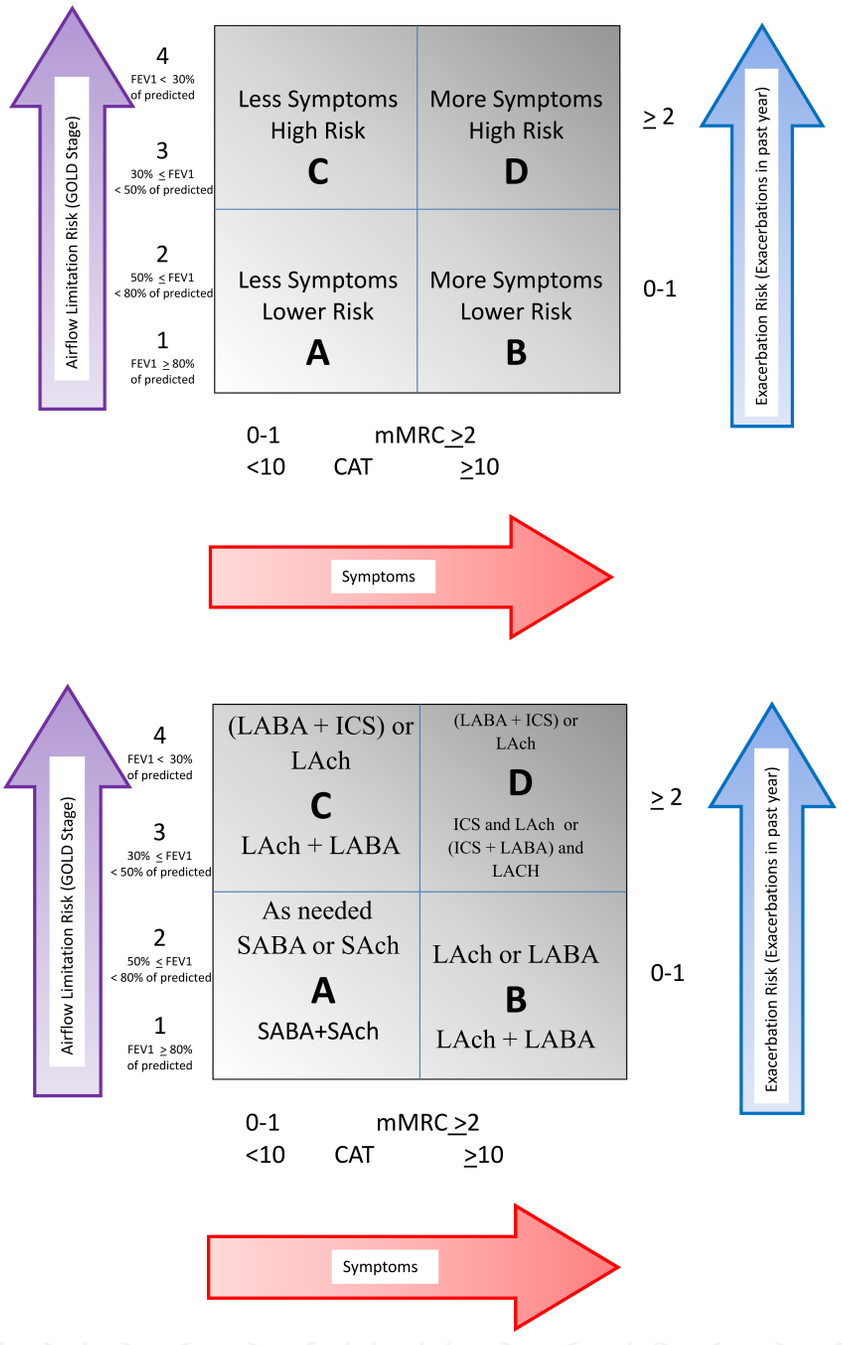
Multiple researchers have begun to view asthma as a diverse array of diseases distinguished by unique phenotypes. In other words, perhaps asthma is not one single disease entity, but a

collection of multiple subgroupings. Similarly, recent evaluations of COPD suggest that it is also composed of multiple phenotypes [5, 6]. Furthermore, some of these COPD and asthma subgroupings or phenotypes share similar clinical presentations and characteristics [7]. So, from a clinical perspective, it may be appropriate to view these diseases as overlapping. Other authors have extended these observations to speculate that asthma and COPD are part of the same disease spectrum. Some offer the hypothesis that perhaps asthma turns into COPD or perhaps asthma and COPD have similar pathogenetic origins in individuals with similar host substrates and environmental exposures. Orie and coworkers [8] initiated a unified approach over five decades ago when they postulated common processes and evolution of asthma and COPD; they adopted the term chronic non-specific lung disease to include both disorders: "asthma, chronic bronchitis and emphysema should be considered as different expressions of one disease entity, in which both endogenous (host) and exogenous (environmental) factors play a role in the pathogenesis."

In addition, the new Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria that were established in 2011 [9] began to characterize patients with COPD based not just on their physiologic features, but also considered their clinical symptoms and risk for healthcare utilization. The GOLD guidelines proposed categorization of individuals with COPD into four distinct phenotypes based upon these characteristics (see Figure 1). Further, treatment guidelines are based upon the patient's categorization and phenotype.

New insights into asthma and COPD now recognize that there is much *heterogeneity* amongst individual patients with asthma and with COPD. However, when comparing asthma and COPD phenotypes, there appears to be cross-disease *homogeneity* amongst some of these specific asthma and COPD phenotypes. Therefore, as asthma and COPD research continues, the question remains: are asthma and COPD distinct and separate disease entities or are there enough similarities between them to allow us to view them equivalently at times? In other words, are asthma and COPD different disease states or is there significant overlap at the ends of the spectrum? Furthermore, are they two distinct phenotypes of a similar disease process?

In this chapter, we will investigate the historical definitions and perspectives of these two diseases and how they have been viewed and reported as distinct entities that are quite different from each other. While explaining the historical definitions of these diseases, we will highlight the differences and similarities in clinical manifestations, physiology, and airways inflammation between COPD and asthma. We also describe asthma and COPD phenotypes and discuss how separating asthma and COPD into multiple subcategories has paved the way to recognize the heterogeneity of these processes. These phenotypes can often overlap across disease states, especially those asthmatic patients that have a less-reversible form of airways obstruction that presents like that of COPD. We will review airway remodeling and how it can lead to chronic, more fixed obstruction in asthma. The concept of airways obstruction reversibility will be reviewed and the ambiguity and confusion of this nomenclature discussed. Finally, we will discuss the overlap of treatment and therapies now used to treat both asthma and COPD and where we are beginning to see success for the use of classical asthma treatments for COPD and vice-versa.



Abbreviations:*mMRC*-Modified Medical Research Council Dyspnea Scale, *CAT*-COPD Assessment Test questionnaire, *SABA*=short acting beta-agonist, *LABA*-long acting beta-agonist, *SAch*-short acting anti-cholinergic, *LAch*-long acting anti-cholinergic (also known as LAMA or long acting muscarinic antagonist), *ICS*-inhaled corticosteroid,

Figure 1. Adapted from [9]. A. Categorization of individuals according to the GOLD Guidelines [9] utilizes physiologic impairment based upon the reduction in the FEV1, symptoms measured by either the COPD Assessment Test (CAT) or the mMRC dyspnea scale, and risk measured by the number of exacerbations in the previous year. B. Use of the four GOLD categories to define management strategies. Note the risk assessments are now made on the vertical axes with airflow limitation and prior exacerbations taken into account, and the symptoms of the patient are also accounted for on the horizontal axis. The symptoms assessments are identified and scored by patient reported items such as the mMRC and CAT.

1.1. Ambiguous nomenclature and the bronchodilator response controversy: should we stop using the term reversible?

Although the historic definitions of asthma and COPD put an emphasis on the response to a bronchodilator, there are some instances and examples where this delineation may not be as useful. Although many asthmatics have normal lung function in between exacerbations or symptoms and require bronchoprovocation testing to induce airflow limitation, the majority of asthmatics experience relief of airflow limitation (AFL) when administered a bronchodilator (BD) in a laboratory setting. Between 39 and 73% of individuals with COPD also will experience significant improvement in AFL after receiving a BD [10]. In the Pulmonary Function Laboratory, an increase of 12% and at least 200 ml in either the FEV1 or FVC is usually defined as bronchodilator responsive airflow limitation [11] that many clinicians consider "reversible." Reversibility is also frequently used in the definitions of asthma and COPD: asthma is reversible and COPD is non-reversible airflow limitation; but in these definitions, reversible does not refer to the response to a bronchodilator but to the ability of airflow to return to normal or predicted levels in asthma and the inability to return to normal or predicted levels in COPD. Thus, *reversible* refers to *two very different concepts*: response to a bronchodilator (in the PFT lab) and normalization (in the definitions of COPD and asthma). This ambiguous use of the word reversible has led many clinicians to diagnose asthma when a patient has a measured response to bronchodilators in the PFT lab even when their lung function does not achieve predicted levels. Similarly, an individual with airflow limitation that does not improve with bronchodilators is often diagnosed with COPD and not asthma. Pulmonary physiology measured in the PFT lab can *assist* with the diagnosis of COPD and asthma but is insufficient to diagnosis either COPD or asthma.

Throughout this chapter, we will distinguish between bronchodilator responsivity and normalization of spirometric lung function and clarify use of the ambiguous term, reversibility. Bronchodilator responsivity will refer to improvement in either FEV1 or FVC by 12% and 200 cc after bronchodilator administration [12] and normalization will refer to a return to normal or predicted values for the FEV1 and FVC either during intercurrent periods of pulmonary disease activity or after bronchodilator use.

Thus, an individual with COPD will have non-normalizing lung function but could still have a bronchodilator response and most individuals with asthma will have normalizing lung function during periods of disease inactivity. Asthmatics with fixed airflow limitation have lost the ability to normalize their lung function and are inseparable physiologically from individuals with COPD.

In the December 2011 revision, the GOLD Guidelines [9] list several differences between asthma and COPD and stress the importance of the concept of "reversible" (normalizing) airflow obstruction. COPD is described as having onset in mid-life, slowly progressive symptoms, and a history of tobacco smoking or exposure to other types of smoke, whereas asthma begins early in life and symptoms vary widely from day to day. The definition of COPD in the GOLD guidelines clearly "excludes asthma ('reversible (normalizing) airflow limitation')" and also states that the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent (or non-normalizing) airflow limitation and thus of COPD. Once again,

we see authors stress the importance of separating "reversible" from "non-reversible" airflow limitation as helping in defining and distinguishing asthma and COPD. However, as Pellegrino and colleagues [11] state, "The lack of a response to bronchodilator testing in a laboratory does not preclude a clinical response to bronchodilator therapy." Should we limit asthma therapy to only those patients who have normalizable AFL after BD? This decision could narrow a patient's therapeutic options and exclude potentially beneficial medications.

Certainly for the majority of patients a reasonable classification of asthma and COPD can be based on how airflow returns to predicted or normal levels after the administration of a bronchodilator. But many asthmatics can have fixed or non-normalizing airflow limitation after a bronchodilator is administered in a laboratory setting. Some asthma phenotypes have significant inflammation and airway remodeling that leads to non-normalizing AFL that does not respond to a bronchodilator. Therefore, it seems plausible that some asthma patients indeed have fixed airflow obstruction and approaching them as COPD patients may allow for more appropriate therapy. Using the normalization of AFL after BD may be useful for defining the majority of asthma and COPD patients but airway remodeling due to repetitive or persistent inflammation in asthmatics as they age and are chronically exposed to stimuli can account for the fact that some asthmatics show no significant spirometric change after BD administration in a laboratory. Patients with either asthma or COPD may respond to a BD so BD responsivity is neither sensitive nor specific in distinguishing asthma and COPD.

2. Why is overlap between asthma and COPD important?

In a 15 year longitudinal study of individuals with asthma, Lange and colleagues [13] concluded that some asthmatics progress to fixed airways obstruction suggesting that this asthmatic subgroup may exhibit non-normalizing lung function and be more similar to COPD. GOLD guidelines [9], NHLBI guidelines [14], and GINA [15] guidelines state that asthma and COPD are underdiagnosed and misdiagnosed. In addition, these guidelines attempt to distinguish asthma and COPD obviating recognition of potential overlap. Simply put, there are often times where guideline-driven therapy for COPD and asthma may preclude some patients from getting more tailored therapy. In the example of the asthma/COPD overlap patient, guideline driven care may not optimize or individualize treatment sufficiently. As listed in examples cited later in this chapter, many asthmatics with fixed or non-normalizing AFL may benefit from treatments that are traditionally only considered for patients with COPD. Thus, we feel it is imperative that a subgroup of patients with asthma and COPD may benefit by approaching them therapeutically as having an "overlap" syndrome of asthma and COPD. Furthermore, classic COPD and asthma medications may be used interchangeably and successfully for patients with overlapping phenotypes. Therefore, viewing asthma and COPD similarly for some patients can lead to more treatment options and possibly better outcomes.

3. Clinical perplexity emanating from overlapping definitions and ambiguous nomenclature

3.1. Defining these disorders has proven difficult

The recent movements to subcategorize asthma and COPD into distinctive phenotypes underscores the imprecise and evolving definitions of these disorders; neither asthma nor COPD are discrete diseases but rather syndromes that are defined or characterized by multifactorial listings of historical, physical examination, radiographic, cellular, biochemical, and physiologic features [9, 14, 15].

Historically, definitions have distinguished COPD with non-normalizing AFL in older adults from asthma with normalizing AFL in children with atopy or pulmonary inflammation. Figure 2 summarizes the features of asthma and COPD that have been used historically to distinguish these two disorders. Furthermore, as described in [4], "Asthma is recognized as an allergic disease that develops in childhood, characterised physiologically by "reversible" (normalizing) airflow obstruction, and has an episodic course with a generally favourable prognosis, responding well to anti-inflammatory treatment. In contrast, COPD is typically caused by tobacco smoking, develops in mid to later life and is characterised by incompletely"reversible" (non-normalizing) airflow limitation that results in a progressive decline in lung function leading to premature death."

Further, since these disorders are syndromes, there is not a single gold standard diagnostic test for either asthma or COPD. Bronchoprovocation testing has been advocated to complement spirometric measurement of FEV1 and FVC before and after bronchodilators for the diagnosis of asthma [14, 15]. For COPD, there is much debate over thresholds to define airflow obstruction – that is with a fixed FEV1/FVC ratio less than 0.70 or an FEV1/FVC ratio less than the lower limit of normal. Thus, it has been exceedingly difficult to define these disorders precisely based upon physiologic testing.

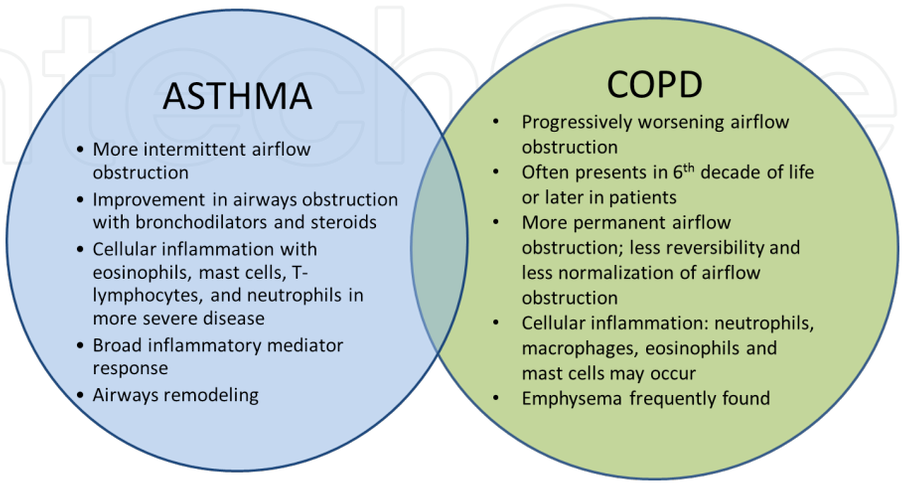


Figure 2. Historical characteristics of asthma and COPD, adapted from [16].

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3.2. Revisiting the Dutch hypothesis and overlap syndrome proposals

Scientific and clinical evidence reinforces the overlap between COPD and asthma. The clinical manifestations of these disorders, cough, breathlessness, and wheezing, may be identical. AFL is present in both processes and BD responsiveness occurs frequently in either disorder. Cellular and biochemical assessments reveal inflammation and immunological derangements. The therapeutic pharmacologic armamentarium is very similar. Consequently, some investigators have surmised that asthma and COPD may share common pathophysiologic origins. As Bleecker suggests in [16], although the concepts of the Dutch hypothesis may be controversial, they have never been disproven and approaching these two diseases in a fashion that recognizes the possibility of similarities could pave the way for new approaches for both COPD and asthma.

Figure 3 illustrates the potential theoretical overlap among the obstructive lung diseases. The need to recognize overlap amongst asthma and COPD was highlighted by Gibson and Simpson [4] as the historical definitions of asthma and COPD are "limited because they do not fully depict the spectrum of obstructive airway disease that is seen in clinical practice. In particular, now that accelerated decline in lung function is recognized to occur in asthma, especially in those with asthma who smoke and COPD is increasingly considered to be a treatment-responsive disease, there is a need to re-evaluate the concept of asthma and COPD as separate conditions, and to consider situations when they may coexist, or when one condition may evolve into the other."

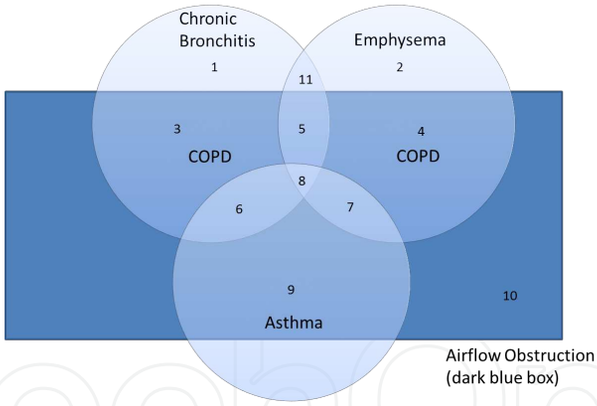

Figure 3. Overlapping of Obstructive Lung Diseases, reproduced from [3]. This non-proportional Venn diagram shows subsets of patients with chronic bronchitis, COPD, emphysema, and asthma and their intersection with airflow obstruction or airflow limitation (AFL) and each other. Patients with asthma whose airflow obstruction is reversible (normalizing) (subset 9), are not considered to have COPD. In many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis or COPD who have partially reversible (normalizing) airflow obstruction with airway hyperreactivity. Thus, some patients with unremitting asthma are classified as having COPD as shown by subsets 6, 7 and 8. Emphysema with AFL and chronic bronchitis with AFL comprise COPD patients, and are depicted in the darker circles labeled as subsets 3 and 4. Chronic bronchitis and emphysema with airflow obstruction often occur together as seen in subset 5, and some patients may have asthma associated with these two disorders as in subset 8. Individuals with asthma exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis shown in subset 6. Such patients are often referred to in the United States as having asthmatic bronchitis or the asthmatic form of COPD. Persons with chronic bronchitis or emphysema without airflow obstruction, shown by subsets 1,2,11, are not classified as having COPD.

4. Phenotypic intersection – Clinical, physiologic, and inflammatory similarities and distinctions

4.1. Clinical – Asthma phenotypes and the 5th cluster

Moore and colleagues [7] categorized a large portion of the severe asthma research program (SARP) population into 5 distinct phenotypic groups based upon cluster analysis (see Table 1). The 5th cluster had more fixed airways obstruction (non-normalizing) with little bronchodilator responsivity, similar to the physiologic profile of a more classically defined COPD patient. This type of phenotypic approach to asthma may better suit some refractory asthma patients who require more tailored and individualized therapy [17-21].

Cluster 1 – 15% of participants	Atopic, mostly younger females with onset of asthma in childhood, with normal lung function and infrequent healthcare utilization or hospitalizations
Cluster 2 – 44% of participants	Atopic, mostly females, mostly older adults, with onset of asthma in childhood, with normal lung function and more asthma medication usage than cluster 1
Cluster 3 – 8% of participants	Non-Atopic, mostly females over the age of 50 with onset of asthma in adulthood and obese with body mass index >30, some decreased lung function, abundant asthma medication usage and corticosteroid usage with the most healthcare utilization and hospitalizations that appeared to be out of proportion to the degree of decreased lung function
Cluster 4 – 17% of participants	Atopic, equal males and females with onset of asthma in childhood and the most severe decline in lung function with most meeting a severe asthma definition and with only some bronchodilator responsivity on lung function testing
Cluster 5 – 16% of participants	Less Atopic, mostly females, with onset of asthma in childhood with most meeting a severe asthma definition and with worst lung function of all clusters and little bronchodilator responsivity

Table 1. Five Asthma Phenotypes Classified Using Cluster Analysis, adapted from [7].

4.2. Clinical – COPD phenotypes and the need for GOLD criteria revision in 2011

Not all COPD patients are alike. Some require oxygen and some do not. Some require one maintenance inhaler whereas others require three. Some have 2 or more exacerbations per year and some have few or no exacerbations. How can one account for these distinct differences in patient presentation or phenotype?

Prior to 2011, the GOLD guidelines [9] categorized COPD severity based solely upon physiologic criteria, especially the reduction in the FEV1. COPD patients are not always the same and carry different risk factors for worsening lung function and exacerbations. These concepts, that physiology does not adequately define groups of patients with similar therapeutic requirements and not all COPD patients are the same, were addressed by creating new GOLD classifications. In 2011, the use of level of lung dysfunction and airways obstruction continued, but further categorization based upon clinical symptoms as well as healthcare utilization or

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risk were added to the classification scheme, as seen in Figure 1. Patients are classified into four groups, A, B, C, and D based upon these three factors. Group A patients have better lung function, fewer symptoms, and lower risk for hospitalization. Group B patients have better lung function and lower risk for hospitalization but more symptoms; Group C patients have more impaired lung function and higher risk but are less symptomatic; and Group D patients have more impaired lung function, more symptoms, and greater risk for hospitalization. By restructuring the classification system, COPD patients can now be seen as a range of potentially diverse populations, with some patients not experiencing many symptoms or risk, whereas other COPD patients have greater risk of exacerbations and symptoms and will be treated more aggressively. In summary, the phenotypic differences between more symptomatic and/or higher exacerbation risk coupled with physiologic function, are being used to not only categorize COPD patients but also guide therapeutic management.

The current GOLD classification scheme has progressed significantly beyond the historical labeling of patients with COPD as "pink puffers" or "blue bloaters." These descriptions may have addressed the physiologic differences between emphysema and chronic bronchitis patients, but these phenotypic descriptions did not translate into standardized approaches for medication usage or therapeutic management. The four phenotypes described in GOLD 2011 [9] now enable the patient's care team to choose therapeutic options based on level of pulmonary physiologic function, risk of exacerbation/healthcare utilization, and level of symptoms. Although still maintaining a stepped care approach, the use of phenotypic categories suggests therapies directed at reducing specific needs manifested by individuals within each category. The risk of exacerbations and significant lung function deterioration that can accompany them are now targeted and higher risk patients could have more access to novel therapies such as Phosphodiesterase-type 4 (PDE-4) inhibitors or chronic antibiotics like azithromycin as options to reduce their risk of COPD exacerbations [22, 23].

4.3. Airways inflammation: Often different but present in both, and sometimes similar amongst asthma & COPD

Both asthma and COPD are diseases of airway inflammation. In asthma, the inflammatory cells and cytokines include CD4+T-helper cell lymphocytes, eosinophils, and IL 4,5,10, and 13 along with GM-CSF and TNF-alpha whereas in COPD, the inflammatory profile usually consists of CD8+T-lymphocytes, neutrophils, and CD68+monocytes/macrophages [24]. Some investigators have divided asthma into eosinophilic and non-eosinophilic categories [25] emphasizing that non-eosinophilic asthma is a unique phenotype. Although there are significant differences in the inflammatory components encountered in asthma and COPD [24, 26], some asthmatics have a more neutrophil predominant inflammatory profile [27]. In contrast with these differences in the inflammatory components of asthma and COPD, there are some similar findings that occur in asthmatic and COPD patients who have fixed airways obstruction. Jeffrey [28] notes that remodeling and inflammation occur in both asthma and COPD and there are often major distinct differences in inflammation in the airways for COPD and asthma. However, these differences are most apparent when "nonsmoking patients with asthma and smokers with COPD from polar ends of the spectrum of "reversibility" (normalization) are

compared" and as "disease becomes severe and the use of corticosteroids increases, the patterns of inflammation become more similar, mainly because of increases of neutrophils in both asthma and COPD"[28]. Further similarities in inflammatory patterns between asthma and COPD include:

- Distinct subpopulations of individuals with COPD and chronic bronchitis have a thickened reticular basement membrane (RBM) and bronchoalveolar lavage (BAL) eosinophilia that are similar to what is seen in the chronic inflammatory changes of asthma [29]. The RBM is thicker than normal in this subset of COPD patients who were smokers and showed significant airflow reversibility after 14 days of oral steroid therapy [29]. RBM thickening is usually considered a hallmark of severe asthma [30].

- The structural and inflammatory profiles observed in this subset of patients with COPD and a thickened RBM and BAL eosinophilia make the distinction between asthma and COPD less clear.

- Airway smooth muscle is increased both in COPD and asthma but the location of the smooth muscle hypertrophy and enlargement may differ [31]. Airway smooth muscle enlargement is also found in COPD but usually more in the smaller airways.

- The eosinophil has been a longstanding chronic inflammatory cell in asthma, whereas eosinophils in COPD appear to be more active during acute exacerbations of COPD [24, 28]. It has been postulated that the slight increase of eosinophils encountered in stable COPD perhaps do not degranulate [32].

As stated above there are stark contrasts in airway structure and inflammation in COPD and asthma yet the question remains: why do striking similarities exist between the two as well? As mentioned, the increase in airway smooth muscle mass that is observed ubiquitously in asthmatics can be seen in COPD patients, and the eosinophil appears to be a critical inflammatory cell in both diseases, albeit in COPD, its most significant role may be during acute exacerbations. Furthermore, it is interesting to see that there are some COPD patients who appear to have an inflammatory and airway structure profile that is more consistent with the classic findings of asthma. Perhaps these findings explain why we see benefits of inhaled steroids for some COPD patients. Compared with placebo, corticosteroids improve the outcomes of COPD patients hospitalized for acute exacerbations and decrease readmission rates [33]. In addition, the TORCH investigators [34] showed that inhaled corticosteroids reduced exacerbation rates and improved the health status of COPD patients. The similarities in airways inflammation and pathobiology seen in COPD and asthma may account for the clinical improvements associated with inhaled corticosteroids in COPD patients. We now see that the mainstay of therapy for asthma, inhaled corticosteroids, may improve outcomes in COPD patients. That is, a medication historically reserved for asthmatics is now widely used for COPD patients. Later in part 6 of this chapter, we will investigate this cross-treatment of COPD and asthma further.

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5. How can an asthmatic evolve to chronic obstruction indistinguishable from COPD?

Airways remodeling in asthma can lead to more fixed, irreversible (non-normalizing) airways obstruction [13, 35]. Airways remodeling is a series of events that include structural and inflammatory changes that lead to fixed airways obstruction. Critical events in this pathway include reticular basement membrane (RBM) thickening, airway smooth muscle (ASM) hyperplasia and hyperreactivity, loss of ciliated epithelial cells, goblet cell (GC) hyperplasia and increased mucous production, as well as fibroblast and myofibroblast activation [35]. When extensive airway remodeling occurs, asthmatics can appear clinically and physiologically as if they had COPD with fixed, non-normalizing airways obstruction. Recent studies suggest that airway remodeling and airway smooth muscle (ASM) hyperplasia and hypertrophy occur at an early age, possibly even preceding the diagnosis of asthma and clinical symptoms [31, 36]. These studies suggest that reticular basement membrane thickening can occur even in childhood [37] and corroborate earlier investigations that showed that the lung function decline in some asthmatics occurred early in childhood, and not progressively throughout adulthood [38]. Thus, airway remodeling may precede both the clinical manifestations of asthma and the inflammation triggered by allergen exposure. The subsequent inflammation intensifies the remodeling process and leads to fixed airways obstruction in early adulthood. Thus, it seems plausible that the subset of asthma patients who have fixed obstruction may have defects in ASM regulatory mechanisms and that ASM hyperplasia may be an "early life event."For these individuals, the inflammation and ensuing asthma accentuates basement membrane dysregulation and ultimately leads to fixed airways obstruction in young asthma patients [31, 36-38].

6. Novel treatment paradigms: Asthma drugs treat COPD and vice-versa

According to current guidelines, inhaled corticosteroids (ICS) are the cornerstone and first line therapy of persistent asthma while long acting beta (LABA) agonists and long acting anti-muscarinic (LAMA) agents are first line therapy for COPD patients [9, 14, 15]. Despite this paradigm of "inhaled steroids first in asthma and long acting bronchodilators first in COPD", inhaled corticosteroids can be helpful for some COPD patients and long acting bronchodilators are commonly used as step up therapy in asthma when ICS therapy does not control symptoms alone. In addition, systemic corticosteroids are beneficial for the treatment of exacerbations of both diseases [9, 14, 15]. Recent investigations suggest that medications classically used for the treatment of asthma may be beneficial for COPD and pharmacologic treatments usually used for COPD may be advantageous in the management of some subpopulations of patients with asthma.

6.1. Asthma and anti-inflammatory medications used for COPD

Recent studies show that inhaled corticosteroids, the mainstay of asthma pharmacotherapy, improve multiple outcomes in individuals with COPD [9]. ICS can reduce the frequency of

acute COPD exacerbations and improve respiratory health in patients with severe COPD [9, 34]. Although combined ICS and long acting beta agonist treatment slowed the reduction of lung function in individuals with COPD in the TORCH trial, these results have not been replicated in other trials [34, 39, 40]. However, as outlined in GOLD 2011 [9], inhaled corticosteroids have a significant role in the management of COPD, particularly for those at high risk for exacerbations and who are symptomatic despite long acting bronchodilator usage (GOLD class C,D). The summary of evidence [9, 34, 39-43] supporting the role of inhaled corticosteroids in the management of COPD includes the following:

- Long term treatment with inhaled steroids is recommended for patients with severe and very severe airflow limitation and for patients with frequent exacerbations not controlled by long acting bronchodilators.
- Inhaled steroids should be considered for GOLD class C and D patients.
- Long term monotherapy with inhaled steroids is not recommended in COPD as it is less effective than a combination of LABA and ICS together.

The inflammation present in COPD, for at least some COPD patients, appears to be helped by the addition of an inhaled steroid. Thus, historically labeled "asthma treatments" such as inhaled steroids may be beneficial for patients with COPD. Additionally, anti-leukotriene medications such as montelukast have shown some promise even in COPD patients as some authors propose that the inflammation in COPD can be a target of leukotriene receptor antagonist (LTRA) therapy. LTRA usage in elderly COPD patients appears to be safe and efficacious and may improve outcomes in respiratory health in this population [44, 45].

6.2. COPD and long-acting inhaler medications used for asthma

Alternatively, treatments that were relegated historically as mainstay therapy for COPD have also been used to treat asthma. Inhaled steroids are the principal treatment for persistent asthma, but for more severe asthmatics, LABA's are added to inhaled corticosteroids, similar to adding an inhaled corticosteroid to a LABA for a more severe COPD patient. LABAs are never used as monotherapy in asthma. However, combined LABA/ICS treatment is recommended for patients with severe asthma just as this combination is suggested therapy for patients with more severe COPD.

Based upon many trials, multiple guidelines identify inhaled corticosteroids as the recommended first line treatment for asthma [14, 15, 46]. LABA inhalers are effective as step up therapy, particularly in those asthmatics not controlled with inhaled corticosteroids alone [47, 48]. LABAs are indeed used in asthma; however, due to the risk of LABA monotherapy in asthma [49], these agents are recommended only for step up therapy in those asthmatics not controlled with an inhaled corticosteroid alone [14, 15]. Thus, LABAs can be used in both COPD and asthma, although for COPD they are first line therapeutic options and for asthma they are recommended only as add-on therapy choices in addition to inhaled corticosteroids. LABAs are not first line therapy for asthma. Inhaled corticosteroid and LABA combination therapy is recommended for both asthmatics and COPD patients with more severe disease [9, 14, 15].

What about long acting muscarinic antagonist usage (LAMA) or long acting anticholinergic (LAch) therapy in asthma? Recent studies show that treatment of severe asthmatics with a LAMA can reduce exacerbations and improve airflow obstruction [50]. In patients with asthma that is inadequately controlled with ICS, addition of a LAMA improves lung function and symptoms and is equivalent to the addition of a LABA [51]. Caution, however, has been advised by some authors including Bel [52], stating that the use of LAMAs and antimuscarinic agents may best be reserved for those asthma patients who have fixed airflow obstruction as evidenced by baseline FEV1/FVC ratios of <0.70.

Table 2 describes and summarizes some of these trials which have shown cross-therapy choices for asthma and COPD.

Trial & Reference	Medications Used/Disease	Summary of Meaningful Findings
TALC [51]	LAMA (tiotropium) use in asthma	Tiotopium as effective as long acting bronchodilator for uncontrolled asthmatics
Tiotropium added to asthmatics poorly controlled on LABA/ICS [50]	LAMA (tiotropium) use in asthma	LAMA use decreased exacerbations in severe asthmatics and showed minimal improvement in FEV1
Long-term montelukast in moderate to severe COPD [44, 45]	LTRA use in COPD	LTRA use appears safe and efficacious and may improve respiratory symptom control and exacerbations, particularly for elderly moderate to severe COPD patients
Meta-Analyses for ICS usage in more severe COPD or COPD with higher risk of exacerbations [41-43]	ICS for COPD	ICS reduce the risk of exacerbations, with an emphasis placed on more severe COPD patients
TORCH [34]	ICS for COPD	ICS therapy decreases exacerbations and modestly slows the progression of respiratory symptoms in COPD; possible or minimal impact found on lung function and mortality somewhat unique to TORCH trial.
UPLIFT [53]	Triple Therapy with LAMA, LABA and ICS for COPD patients	Suggests additive benefit to triple inhaler therapy for more advanced COPD patients

Abbreviations: *LTRA*-leukotriene receptor antagonist, *LAMA*-long acting muscarinic antagonist, *LABA*-long acting beta agonist, *ICS*-inhaled corticosteroid, *FEV1*-forced expiratory volume in 1 second, *COPD*-chronic obstructive pulmonary disease

Table 2. Summary of Novel Approaches Where Cross-Disease Therapeutic Options Have Shown Benefit.

7. Conclusion

We began this chapter with the question: are asthma and COPD completely distinct diseases or is there some degree of overlap? In response, we conclude that they are separate entities that are treated and approached in unique ways for the most part; however, for subpopulations

of individuals with asthma or COPD, there is considerable clinical, physiologic, and inflammatory profile overlap. These disorders are syndromes defined by constellations of clinical, historical, physical examination, physiological, and inflammatory features. Recent investigations suggest that there are numerous subcategories of asthma and COPD and that some of these subcategories may have significant similarities.

Thus, COPD and asthma may coexist or overlap in individual patients or within specific phenotypic categories. Both diseases are characterized by airways inflammation and sometimes cannot be distinguished clinically. The physiologic differences between asthma and COPD are further confused by ambiguous use of reversibility to mean either responsiveness to bronchodilators or normalization of lung function. Historically, asthma has been associated with AFL that normalizes and returns to predicted levels with therapy whereas, in COPD, lung function progressively declines and no treatment has been shown to return it to predicted levels. However, there is a subpopulation of asthmatics that develop fixed AFL and despite treatment do not exhibit normalization of lung function.

Although the inflammatory profiles of asthma and COPD are traditionally considered to be distinct, more recent investigations and phenotypic categorizations suggest that there are populations of asthmatics with inflammatory profiles that are suggestive of COPD and some groups of patients with COPD may have inflammatory profiles that resemble those seen in asthma.

Although the principal guidelines for management of COPD and asthma are very different, considerable overlap in treatments does occur. Recent studies demonstrate that medications such as LAMAs that are traditionally used only for the treatment of COPD may be beneficial in patients with asthma and other drugs such as LTRAs that are usually only used for the treatment of asthma may be effective in patients with COPD. But, for most individuals with COPD or asthma, the initial treatment for COPD begins with maintenance long acting bronchodilators and for asthma with maintenance inhaled corticosteroids. Therefore, we feel that asthma and COPD can usually be addressed as separate entities but there are numerous times where the diseases and their treatments overlap.

In conclusion, it may be appropriate to approach some COPD patients as if they were more asthmatic, and some asthmatics as if they were more like COPD. The Dutch hypothesis suggesting that asthma and COPD may have common pathogenetic mechanisms is undergoing a resurgence as phenotypically distinct subpopulations of individuals with COPD and asthma are being identified. Although most of these subpopulations are distinct, some share similar clinical, physiologic, and inflammatory profiles. Finally, the therapeutic distinctions between asthma and COPD are blurring as medications traditionally used for one disorder are shown to be beneficial for the other. Ultimately, the goal is to develop therapeutic guidelines based upon a patient's phenotypic profile. As phenotypes become more descriptive, it may prove beneficial to categorize patients as "chronic obstructive asthma with fixed obstruction", or "COPD with asthmatic/more prominent eosinophilic airways inflammatory features", or "COPD with an allergic inflammatory component" to discern which COPD patients might benefit from inhaled corticosteroids or which asthmatics might improve with antimuscarinic bronchodilators.

http://dx.doi.org/10.5772/58234

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