A challenge to the seven widely believed concepts of COPD

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Abstract: This review proposes a critical reassessment (based entirely on published evidence) of the following seven common beliefs about chronic obstructive pulmonary disease (COPD): (1) COPD is one disease. (2) There is a valid definition for COPD. (The current definition includes cases of irreversible asthma and bronchiectasis, and occasionally, other obstructive lung conditions). (3) Irreversible asthma in smokers and COPD cannot be differentiated. (4) A “chronic bronchitis” form of COPD exists and is characterized by blue bloater status and normal carbon monoxide diffusion studies. (5) Phenotyping has no bearing on medication choice in COPD. (6) Computerized scoring of lung attenuation on CT scans can diagnose emphysema. (Emphysema scores overlap in irreversible asthma and COPD); however, qualitative visual changes may be useful for differentiation. (7) A definable entity called the overlap (of COPD and asthma) syndrome exists. Conflict over the abovementioned points denies patients proper phenotype-guided therapy and encourages a multidrug approach to COPD management. The recently coined term, overlap syndrome, invites a double-barreled therapy aimed at asthma and COPD, despite the absence of any agreement about how to define the syndrome and the lack of any related drug trials (in the area of inhaled corticosteroids). A diagnosis of COPD is associated with high morbidity and escalating costs, suggesting the need for a thorough new examination of the evidence.

Keywords: asthma, computerized tomography, COPD, global initiative for chronic obstructive lung disease, overlap syndrome

How is COPD currently diagnosed?

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as “the presence of post-bronchodilator FEV₁/FVC < 0.70 which confirms the presence of persistent airflow limitation and thus COPD,” if associated with symptoms and/or history of exposure to risk factors.¹ Even in nonsmokers, irreversible airway obstruction is sometimes called never-smoker COPD or NSCOPD, despite being largely attributable to asthma.² Although all guidelines accept that irreversible asthma is an important differential diagnosis for COPD, even the most recent ones conclude that in some patients, the currently available physiological and radiological testing techniques are not able to make a clear distinction between the irreversibility forms of asthma and COPD.¹

A substantial number of cases of irreversible asthma “masquerade” as COPD. Based on the clinical and physiological testing used to differentiate the two conditions, Bellia et al estimates that 20% of elderly COPD patients are suffering...
from irreversible asthma. However, this is likely to be an underestimate, and the mislabeling is not limited to the elderly. Irreversible obstruction is reported to occur in 23% of chronic asthmatics. A lengthy history of asthma and smoking is an important risk factor that increases the likelihood that asthma will become irreversible. Asthma has a prevalence of 10% to 12% in the general population, including the elderly. Therefore, it is expected that 2.5% to 3% of the general population (including smokers) suffers from irreversible asthma. Roughly translated, this indicates that one-third of all cases of COPD are actually asthmatic. This estimate is supported by two studies that utilized bronchial biopsy, computerized tomography (CT) scan, and physiological tests to differentiate irreversible asthma and COPD. The findings of these papers and the value of various techniques in differentiating irreversible asthma and COPD are discussed below.

The role of bronchial biopsy in differentiating irreversible asthma and COPD

Early studies concluded that bronchial biopsy could not differentiate asthma and COPD. However, these studies were performed on asthmatics with mild, reversible asthma. In the most important of these studies, the mean forced expiratory volume in one second (FEV1) was 94% (range: 79%–100%) in the asthmatic group versus 59% (45%–67%) in the COPD group. Fabbrì et al’s landmark work on bronchial pathology used asthma and COPD patients with the same degree of fixed (irreversible) airways and mean post bronchodilator FEV1 values of 62% and 59%, respectively. That study established the features that overlapped between the two conditions and those that were useful for differentiation. The basement membrane thicknesses were 6.6–9.7 µm in asthmatics and 4.2–6.2 µm in COPD patients. However, the other changes, such as asthmatics having higher eosinophil counts and CD4+/CD8+ lymphocyte ratios in the bronchial wall, overlapped between the two conditions and were not useful for differentiation.

Clinical significance of histological differentiation

The thickening of the reticular basement membrane in asthma results from extracellular matrix deposition, and is considered to represent an imbalance between collagen-degrading metalloproteases (originating from eosinophils) and their inhibitors. Thickening of the basement membrane has been considered “characteristic for asthma while is not found in COPD.” Even in reversible asthma (before thickness develops), the basement membrane is reported to have a different composition and staining properties from the basement membrane in COPD.

In 1996, Chanéz et al reported that 12 out of 25 (48%) COPD patients had spirometric reversibility upon receiving prednisolone, and their bronchial biopsies demonstrated uniform thickening of the basement membrane. In 2011, Al-Kassimi et al published a study where patients were divided into irreversible asthma and COPD groups on the basis of qualitative visual CT scan findings of panlobular emphysema with multiple bullas (Figure 1), the presence of hypercapnic respiratory failure with raised serum bicarbonate (never described in stable asthma), and bronchial histology. Figure 2A and B show the histological criteria used to differentiate asthma and COPD. Table 1 shows the characteristics of both groups in that study.

There is some concern about whether the abovementioned methods have been validated to delineate two different clinical syndromes. In other words, did the patients in the COPD population diagnosed as asthma by bronchial biopsy behave clinically and physiologically like asthmatics? The studies are unanimous on the presence of a strong association or total concurrence between thickness of the reticular basement membrane and the following features: hypertrophy of the nasal turbinates, normal carbon monoxide diffusion capacity (DLco), and response to oral prednisolone and inhaled corticosteroids (ICS).

The clinical differentiation of asthma and COPD is of great importance. We have encountered heavy smokers with irreversible airflow limitation who were labeled as having COPD. The diagnosis was shifted to irreversible asthma based on normal transfer coefficient (KCO) calculated as carbon monoxide diffusion capacity/ alveolar volume (DLco/VA), and bronchial histology. Dramatic improvements in FEV1 and dyspnea were produced with the anti-Ig-E therapy,omalizumab, a treatment that would not have been considered with the diagnostic label of COPD.

Why carbon monoxide diffusion studies are not performed in COPD

Numerous studies have documented that DLco remains normal in severe or irreversible asthma unless there is concomitant bronchiectasis. Although DLco and KCO were found to be reduced in emphysema, KCO correlated better with the high resolution computerized tomography (HRCT) scoring of emphysema. Several studies have documented the specificity of DLco in diagnosing
However, the test has two limitations: first, $DL_{CO}$ may be normal in early COPD, but it decreases considerably as the disease progresses; second, in emphysema induced by $\alpha_1$-antitrypsin deficiency (which is limited to the lower lobes, unlike smoker's COPD), $DL_{CO}$ may be paradoxically normal. This is referred to as discordant emphysema.

In conclusion, low $DL_{CO}$ is specific to COPD (if bronchiectasis is ruled out by CT scan), but sensitive only in advanced disease. There are no data on the level of advanced disease that lowers $DL_{CO}$. In studies on patients with $FEV_1/FVC$ < 0.70, there was concurrence between bronchial biopsy indicating COPD and low $DL_{CO}$ or $KCO$. The question is often raised as to why patients with the “chronic bronchitis form” of COPD develop low $DL_{CO}$. Should $DL_{CO}$ be used as a tool for differentiating the chronic bronchitis (blue bloater) and emphysema (pink puffer) forms of COPD?

The blue bloater and pink puffer types of COPD
The concept of “blue bloater” COPD without emphysema (and therefore with normal $DL_{CO}$) is contradicted by pathological studies and CT scans. Although blue bloaters and “pinkuffers” present clinical differences, no major
differences in the severity of emphysema are revealed by pathological studies at the time of death.\textsuperscript{23} Based on CT scans, COPD cases were divided into Phenotype A (with features of asthma and normal DL\textsubscript{CO}), Phenotype M (mixed emphysema/bronchitis), and Phenotype E (emphysema).\textsuperscript{24} Phenotypes M and E had low DL\textsubscript{CO}.\textsuperscript{24} Studies going back 30 years have used the a priori assumption that if DL\textsubscript{CO} or DL\textsubscript{CO}/VA is normal, a chronic bronchitis form of COPD is diagnosed without considering that the subjects may be suffering from irreversible asthma.\textsuperscript{25} A paper published in 1970 reported that in 45 patients with “obstructive bronchitis” and chronic purulent expectoration (characteristics of the chronic bronchitis type), the DL\textsubscript{CO} was 44.3 (±23.7)% predicted.\textsuperscript{26} The authors concluded that “DL\textsubscript{CO} is fixed at a nearly constant low level in obstructive bronchitis … We regard this as a useful test to differentiate the two diseases (chronic bronchitis and asthma).”\textsuperscript{26} This conclusion was drawn despite the low DL\textsubscript{CO} of some of the patients in the asthmatic group, which is at odds with published reports from as far back as 1970.\textsuperscript{27} This discrepancy may have resulted from the fact that in 1970, it was not appreciated that transient or persistent sputum eosinophilia also occurs in COPD and that its presence does not automatically differentiate between diseases. The asthmatic group in that study (selected on the basis of eosinophilia) may have included a number of eosinophilic COPD patients with low DL\textsubscript{CO}.

**Why is COPD treated as a second-class condition?**

The tradition of dismissing the possibility of irreversible asthma persists. In a large study published in 2007, 105 out of 307 COPD patients had no or little emphysema on HRCT scan.\textsuperscript{28} The possibility that some of these patients might have been asthmatic was dismissed by excluding subjects who were diagnosed by their physicians as having asthma and by the absence of FEV\textsubscript{1} reversibility upon inhaling 400 µg albuterol.\textsuperscript{29} Acute reversibility tests fail to differentiate between asthma and COPD;\textsuperscript{29} however, the long-term fluctuation of FEV\textsubscript{1} in response to therapy with inhaled corticosteroids shows promising results.\textsuperscript{10} GOLD has also taken the position that “the degree of reversibility has never been shown to add to the diagnosis or differential diagnosis with asthma.”\textsuperscript{31} Lung biopsy, diffusion studies and CT scans are widely advocated in cases of interstitial lung disease and have resulted in great strides in the classification and management of that condition. We would like this review to generate a discussion about why these techniques are not advocated in COPD (which we prefer to call “chronic airflow limitation” until fully investigated). Irreversible asthma is not the only concern. Bronchiectasis is sometimes a common concomitant or alternative diagnosis in COPD cases.\textsuperscript{30} The prevalence of bronchiectasis is highest in cases of moderate or severe COPD (up to 57%, but much less in most other studies) and is associated with bacterial colonization and a higher frequency of exacerbation.\textsuperscript{31} The association between the two conditions is so strong that some researchers have speculated that severe COPD is a predisposing factor for bronchiectasis.\textsuperscript{32} It is also possible that cases that are diagnosed as COPD began as bronchiectasis with irreversible airway obstruction and reduced diffusing capacity.
Phenotyping

Although phenotyping and clustering according to clinical characteristics (including airway reversibility) has clearly shown the heterogeneous nature of COPD, considerable overlap exists between these clusters. Phenotyping, both with cytology and CT scan, will be discussed.

Phenotyping with cytology

The cellular infiltrate in COPD has been studied in bronchial tissue, bronchoalveolar lavage, and sputum samples. Although discrepancies have been recorded in the percentage of cells, both techniques show similar overall cellularity trends. Eosinophil counts, in particular, show good agreement when determined using the three techniques. The cellular infiltrate in stable COPD shows increased numbers of neutrophils, macrophages, lymphocytes, and occasionally, eosinophils. However, neutrophils and eosinophils have attracted the most attention. Bronchial biopsies and induced sputum have consistently shown a correlation between the severity of airway obstruction and neutrophil count.

In normal subjects, eosinophils account for less than 3% of the cells in induced sputum (usually less than 1%). In stable COPD, 20% to 40% of patients show increased eosinophil levels in sputum. Although eosinophils surge by 0.5- to 30-fold during exacerbations, they account, on average, for less than 5% of sputum cells; in contrast, neutrophils account for more than 70% of sputum cells. This may explain why prednisolone has a modest effect on expediting recovery in acute exacerbations.

Significance of “eosinophilic COPD”

It is tempting to speculate that the 20% to 40% of stable COPD subjects with “eosinophilic bronchitis” are instead cases of irreversible asthma. Barnes and Barnes speculated that such cases represent an asthmatic component in the COPD syndrome or concomitant asthma and COPD, although other researchers have offered alternative explanations. The views of Barnes and Barnes may be supported by the response of “eosinophilic COPD” to corticosteroids. Prednisolone produced a significant increase of FEV₁ values and shuttle distance only in COPD patients who had sputum eosinophilia exceeding 3%. In another study, sputum eosinophilia was associated with higher Interleukin-5 in sputum and a positive response to oral prednisolone. Similarly, ICS produced a modest but significant increase in FEV₁ and Chronic Respiratory Questionnaire scores only in patients with sputum eosinophilia (Figure 3).

Although several studies have shown a marginal reduction of neutrophils or total cells in response to ICS, a large number of studies have found no such effect on inflammatory cells or markers. Some studies have shown that inhaled corticosteroids reduce eosinophils, while other studies have failed to produce such results. Oral prednisolone, in contrast, has been shown to generally reduce eosinophils in sputum. These findings further support the mounting evidence that COPD (apart from the eosinophilic cases) is not steroid responsive and that the delivery of inhalers to terminal bronchioles and alveoli is inadequate to suppress eosinophils in a consistent manner.

Phenotyping via CT scan

Phenotyping using CT attenuation scores

The “emphysema index” is measured as the percentage of lung area with CT attenuation (~820 to ~950 Hounsfield units = HU). This scoring method can be computerized or visual. Although quantitative computerized scoring of emphysema has greatly advanced our understanding of COPD, it has a serious drawback. It interprets any increased attenuation of the lungs (whether caused by hyperinflation as in asthma or emphysematous destruction of alveolar walls)
as emphysema. Severe asthma is a particular area of overlap. Based on computerized CT scores, the mean value of the lowest fifth percentile of CT lung density was -912 HU in nonsmoking asthmatics and -942 HU in COPD patients.

CT measurement of airway thickening
Airway thickening can be measured with CT scans. It is usually expressed as wall area percentage (WA %) and has been found to correlate with FEV$_1$ and residual volume-total lung capacity (RV/TLC), but not DL$_{CO}$. Patients with chronic bronchitis symptoms are more likely to have greater airway thickening than those who have similar airway obstruction but no symptoms. Although the bronchial changes of COPD occur predominantly in the small airways, the presence of "surrogate" changes in large airways ensures the usefulness of WA % in diagnosing bronchitis. Airway thickening is not synonymous with chronic bronchitis as a pathological diagnosis. Both irreversible asthma and COPD produce airway thickening, and no cut-off level can distinguish between them.

Visual qualitative assessment of CT scans
This is achieved by inspecting the CT scans for qualitative changes like bullas size and distribution or the degree of attenuation and branching of blood vessels. Table 2 summarizes the visual qualitative differences between asthma and COPD and explains why radiologists may report "emphysema" in asthmatics who have never smoked.

Examination of Table 2 makes it clear that panlobular emphysema is the only specific radiological sign of COPD. Widespread centrilobular emphysema or multiple bullas imply the presence of COPD, provided that the observer is aware that the same changes, if limited, can be caused by either asthma or COPD. In smoking-induced COPD, centrilobular emphysema is more common (two-thirds of patients) than panlobular emphysema (one-third of patients). Panlobular emphysema is the predominant form in α1-antitrypsin deficiency.

CT scans split "COPD" into asthma and two types of COPD proper
Data with startling practical implications have been reported. Using visual evaluation of HRCT scans, Fujimoto et al classified COPD patients into three phenotypes: absent or little emphysema (Phenotype A), emphysema with bronchial thickening (Phenotype M), and emphysema without bronchial wall thickening (Phenotype E). Phenotype A included 18% of never-smokers, and it was characterized by normal DL$_{CO}$ and significant responsiveness to β-2 agonists. Fujimoto concluded that the majority of patients with Phenotype A are asthmatic. Phenotype M was associated with a clinical picture of chronic bronchitis, low DL$_{CO}$ responsiveness to β-2 agonists, and higher rates of exacerbation and hospitalization. Phenotype E had even lower DL$_{CO}$ and no significant responsiveness of FEV$_1$.

Using visual quantitative grading of CT scans from the Boston early-onset COPD study, Hersh et al found that the group with the least emphysema (scores of 0–6 out of 24) had asthma-like features. The mean FEV$_1$ in that group was 22.4% predicted, which shows that severe obstruction can occur with irreversible asthma. In 2009, Lee et al reported that the emphysema-dominant subtype showed no improvement of FEV$_1$ or dyspnea after three months of treatment with salmeterol/fluticasone or formoterol/budesonide.

COPD is not a single disease that can be treated with the same drugs regardless of phenotype. It includes asthma, mixed bronchitis/emphysema COPD, and emphysema-dominant COPD (which Fujimoto referred to as Phenotypes A, M, and E). When phenotyping is applied (eg, bronchial histology, CT scan, sputum eosinophilia, or DL$_{CO}$), different patterns of responsiveness to corticosteroids are elicited. ICS withdrawal results in no decline of FEV$_1$ or FVC in COPD patients with panlobular emphysema, bronchial biopsy indicating COPD, or low KCO. The controversy over the role of ICS in COPD was attributed to the fact that we are attempting to treat two different conditions with the same drug regimen.

### Table 2 Qualitative CT scan changes in asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
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<tbody>
<tr>
<td>Wide branching and thinning of blood vessels</td>
<td>May be present</td>
<td>Common</td>
</tr>
<tr>
<td>Centrilobular or paraseptal emphysema</td>
<td>Occasionally described (0%–10%); usually limited</td>
<td>Common and usually diffuse</td>
</tr>
<tr>
<td>Panlobular emphysema</td>
<td>Never described</td>
<td>Common (more in 1-α1-antitrypsin deficiency than in smoker’s COPD)</td>
</tr>
<tr>
<td>Bullas</td>
<td>Rare/anecdotal reports; usually single</td>
<td>Common</td>
</tr>
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**Revolution and counterrevolution: the rise and fall of the “overlap syndrome” of COPD and asthma**

**Overview of the overlap syndrome**
Phenotyping is truly a revolution. By demonstrating that the response to inhaled corticosteroids is restricted to one
phenotype with asthmatic features, phenotyping promises targeted, and less costly treatments for COPD. This is at odds with the newly coined overlap syndrome that merges asthma into COPD, and more importantly, has prompted some authors to recommend a multidrug approach that targets both conditions. Some authors have recommended that, in addition to inhaled corticosteroids, long-acting β-2 agonists, and long-acting muscarinic antagonists, “adjunctive treatments such as leukotriene receptor antagonists, 5-lipoxygenase inhibitors, methylxanthines, or omalizumab deserve further study and should be administered by pulmonary subspecialists.”69

**Definition(s) and prevalence of the overlap syndrome**

There is no consensus on a clear definition for the overlap syndrome.69 Some authors have used patients’ reports of receiving an asthma diagnosis before the age of 40 years or without any age restriction.70 Others have used the presence of variable but incompletely reversible airflow obstruction.69,71–74 “Asthmatic symptoms” occurring with COPD, such as episodic breathlessness, wheezing, cough, or chest tightness worsening at night, were also considered diagnostic of the overlap syndrome.75,76 Sputum eosinophilia or history of atopy were also listed as criteria for diagnosis.69,74 Some of the authors who advocate the overlap syndrome have recognized the lack of specificity of criteria based on spirometry or symptoms.69 Nevertheless, other authors have concluded that the overlap syndrome has been “confirmed by objective testing.”77 The study they quote in support of their theory was highly valuable in showing the heterogeneity of obstructive lung disease, but failed to prove the overlap of asthma and COPD, as it used the same criteria that lacked specificity.77 For instance, cough and sputum production, which were used to diagnose chronic bronchitis, are more likely to be caused by asthma, especially asthma associated with rhinitis.78 Even excessive sputum production is more commonly caused by postnasal drip syndrome or asthma than by bronchitis.79 Similarly, centrilobular and paraseptal emphysema have been described in asthma.59,60 Furthermore, significant post bronchodilator response is well described in COPD, especially in the combined emphysema-bronchitis phenotype.24,80 Using these arbitrary criteria, the reported prevalence of the overlap syndrome was 13% to 21% of COPD patients.69,70 Some studies found that patients in the overlap group were the same age as those in the COPD group, but other studies reported that patients in the overlap group were younger.69,70,75 The syndrome has even been reported in patients in their thirties.69

**Drug management of the overlap syndrome**

Concerns that a multidrug approach to therapy is necessary to manage the overlap syndrome have not been proven. The only study so far (until June 2012) that has examined the therapeutic response of the overlap syndrome reported that the response to inhaled corticosteroids was significantly correlated with sputum eosinophilia and bronchial wall thickening.75 Both features are known to be associated with irreversible asthma.3,17 Back to basics: phenotyping, and not overlap syndrome, determine the response to ICS. This supports our speculation that what is referred to as overlap syndrome consists of separate cases of asthma and COPD, selected for longer illness (asthma diagnosed under the age of 40) and more labile disease (variable airflow obstruction), which explains the significant association with more frequent and severe exacerbations and worse disease-related quality of life.70,81

**Are we dealing with a “syndrome” or a “non-syndrome”?**

The tide may be turning back against the overlap syndrome. In the first half of 2012, PubMed listed only two publications on the asthma and COPD overlap syndrome. One of these is the Kitaguchi paper, which reports on the association between eosinophilia and the response to ICS.75 Compare those two results with 56 results for a search on “phenotyping and COPD.” The phenotype and overlap syndrome approaches are incompatible. One aims at splitting, while the other aims at merging the various strands of COPD. More importantly, phenotyping predicts response to ICS, while the only study that tested the overlap syndrome found that the syndrome (not surprisingly) split into steroid-responsive and unresponsive groups.75 The overlap syndrome has all the features of a non-syndrome, ie, arbitrary definitions that defy published evidence and on which there is no agreement, heterogeneous features, the inability to be defined by such objective tests as histology or CT scan, and a lack of uniform response to therapy.

**Practical diagnostic approach to irreversible airway limitation in smokers**

1. All patients should receive a full pulmonary function test. A diagnosis of COPD is made in the presence of low KCO or hypercapneic respiratory failure with raised serum bicarbonate. Attention should be paid to the fact that CO diffusion studies may be reduced in pulmonary edema, and that hypercapneic respiratory failure may be
the result of obesity hypoventilation syndrome. However, these are generally clinically overt conditions that are not easily missed.

2. If pulmonary function tests do not support a diagnosis of COPD, fiberoptic bronchial biopsy (3rd order bronchus) should be offered. Common experience and published evidence indicate the lack of mortality or serious side effects with endobronchial biopsy in patients free of respiratory failure and coagulation disorders. The average pathologist should review the recent publications on the histology of irreversible asthma and COPD before reporting the specimens.

3. CT scan of the lungs should be ordered in patients who refuse bronchoscopy. A pattern of panlobular or widespread centrilobular emphysema is diagnostic of COPD. Hyperinflation with attenuation of blood vessels is not conclusive and CO diffusion studies would favor either asthma or COPD.

4. CT scan of the lungs should be performed in any patient with moderate or severe airway obstruction if associated with abundant purulent sputum to exclude bronchiectasis.

Conclusion

What is currently defined as COPD consists of irreversible asthma and COPD proper. The COPD entity is subdivided further into mixed bronchitis/emphysema (Phenotype M) and predominantly emphysema (Phenotype E). Irreversible asthma and COPD can be differentiated by CO diffusion studies and bronchial biopsy. Additionally, a CT scan showing widespread panlobular or centrilobular emphysema (by visual qualitative inspection) is diagnostic of COPD. However, the computerized emphysema score, which reads the degree of lung attenuation, overlaps in irreversible asthma and COPD. Patients with moderate or severe airway obstruction producing copious or purulent sputum may be suffering from bronchiectasis.

Response to corticosteroids is limited to irreversible asthma and when eosinophilia is documented in the sputum. The overlap syndrome has all the features of a non-syndrome, including the absence of any agreement about how to define it and the lack of uniform response of ICS.

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References


73. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64(8):728–735.


