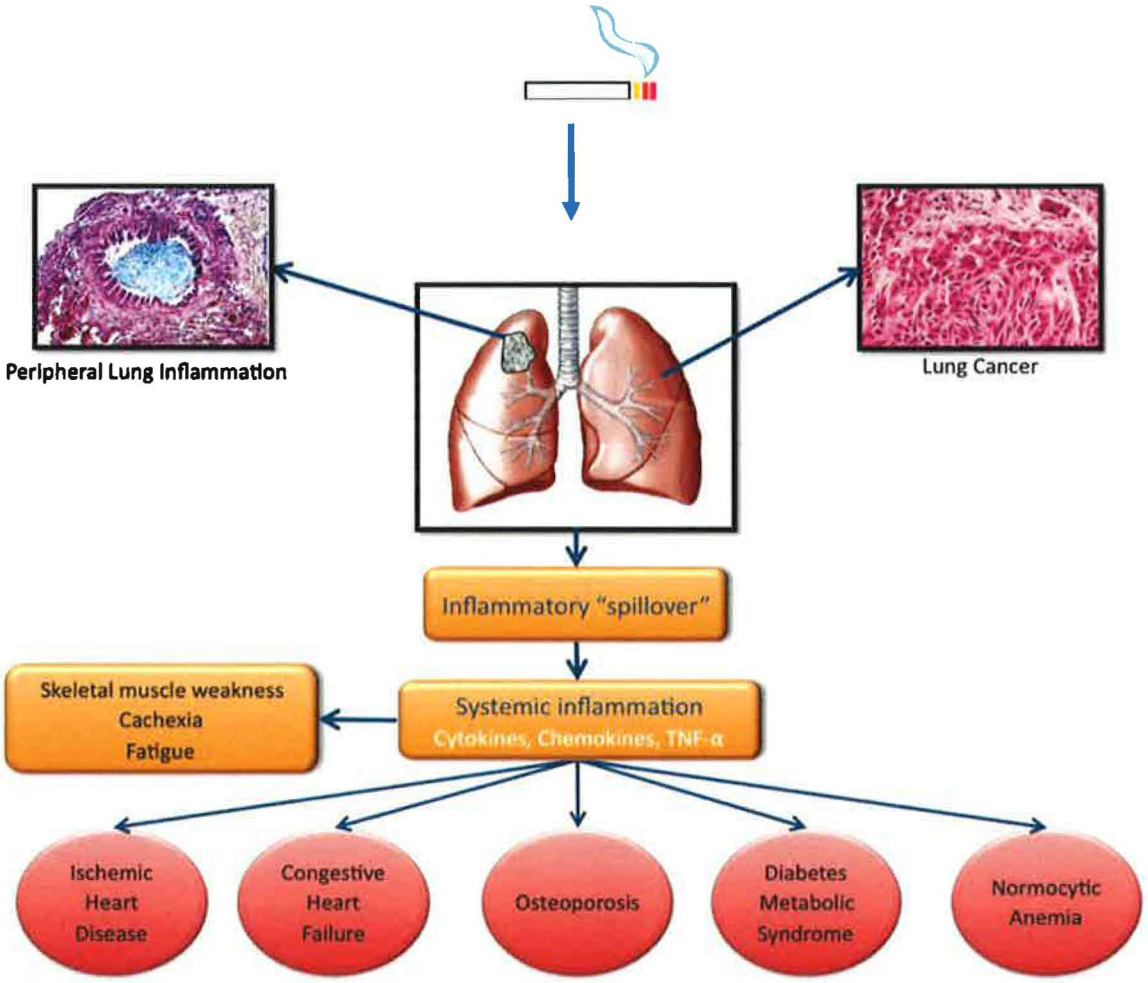
Chronic Obstructive Pulmonary Disease (COPD)
Beyond Inhalers



Adapted from Barnes PJ Eur Resp J 2009; 33:1165-1185.

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Internal Medicine Grand Rounds
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CASE STUDY: A patient with a history of moderate-severe COPD presents after hospitalization for severe COPD exacerbation.

B.M. is a 57 y/o corporate secretary and avid traveler with moderate-to-severe COPD (GOLD Stage III) and a prior history of non-small-cell lung cancer s/p RLL lobectomy in 2000. She has noted stable dyspnea on exertion and rare wheezing for the last 12 years with slight progression over the last year.

Mrs. B.M. presented to UH-SP emergency room after a family trip to Gulf Shores, Alabama. She noted the onset of a cough productive of yellow sputum, chest tightness, and increased SOB. She was admitted to the ICU after an arterial blood gas revealed a pH 7.30, pCO_2 of 52 mmHg, and pO_2 75 mmHg on 2 liters nasal cannula. She developed increased dyspnea and confusion requiring non-invasive facemask ventilation. Treatment consisted of inhaled bronchodilators, intravenous methylprednisolone, and oral antibiotics with recovery.

Two weeks post-hospitalization, B.M. presents to the Aston Center for follow-up. She is compliant with combined fluticasone/salmeterol 250/50 mcg inhaler, tiotropium inhaler, albuterol MDI p.r.n, levalbuterol nebulizer p.r.n, and fluticasone nasal inhaler. She is up-to-date with pneumococcal and influenza vaccinations. Pulmonary function tests reveal severe airflow limitation with an FEV_1 of 1.11 liters or 42% predicted, a FVC of 3.02 liters or 92% of predicted, no significant response to bronchodilators, and a severe reduction in diffusion capacity at 8.96 or 38% predicted.

Mrs. B.M. asked the following questions:

- "Why is my breathing worse despite smoking cessation 10 years ago?"
- "What caused this recent breathing attack and bronchitis?"
- "Is there anything you can prescribe besides these inhalers?"
- "What does the future hold for me?"

INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is defined by the American Thoracic Society[1], and the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[2] program as:

- *"A **preventable and treatable** disease with some **significant extrapulmonary** effects that may contribute to the severity in individual patients."*
- *"Its pulmonary component is characterized by airflow limitation that is not fully reversible."*
- *"The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.[2]"*

COPD has significant global impact with increasing morbidity, mortality, and disability[2].

Worldwide, 600 million people are affected and is estimated that 3 million people die yearly from this disease[3]. It is currently the 5th most common cause of death with an expected increase of 30% in the next 10 years. By the year 2030, it is predicted to be the 3rd leading cause of death[4-6]. The estimated world-wide prevalence of COPD ranges from 3% to 23% of the at-risk population[7]. In the United States, the NHANES III study reported a 16% prevalence in the population aged 25-75 years of age[8].

In contrast with advances in the care of other "top killers", i.e. cardiovascular disease, stroke, infectious diseases, and cancer, COPD has few available treatment options that prevent functional decline or improve survival[9]. The clinical course is characterized by progressive symptoms, recurrent exacerbations, and disability[2, 10]. This decline persists even after smoking cessation suggesting the presence of a chronic, self-perpetuating, and uncontrolled inflammatory response[4, 11]. Death is usually due to co-morbid conditions, such as lung cancer and cardiovascular disease, and less commonly due to respiratory failure[8-9].

In recent years, there has been an exponential growth in the investigation and publication of new hypotheses on the pathogenesis and therapeutic targets for COPD[9-10, 12-15]. Many of these new therapeutic interventions are already recruiting or completing Phase II or Phase III trials[9-10, 16]. As physicians, we must change our approach to COPD patients from "unjustified nihilism"[8] to actively addressing a disease characterized by a chronic and systemic inflammatory response.

The purpose of this Protocol is to discuss the current therapy available for COPD, explore new provocative hypotheses, and provide a fresh look to future therapeutics. The discussion will evolve in the following sections:

- Anatomical lesions of COPD
- Overview of the current available management guidelines
- New insights into COPD pathogenesis and potential therapeutic targets
  Is COPD a...
  - Chronic inflammatory disease?
  - Oxidant-mediated disease?
  - Systemic disease?
  - Immune disease?
  - Chronic infectious disease?

ANATOMICAL LESIONS AND SITE OF AIRFLOW OBSTRUCTION IN COPD:

An understanding of the various anatomical lesions of COPD is essential in order to comprehend its pathogenesis, manifestations, and potential therapeutic targets. Clinically, the term COPD encompasses chronic bronchitis and emphysema, which are two distinct but frequently superimposed processes[2, 4]. Most patients are unable to be classified purely into one of the two entities and in fact, the COPD guidelines avoid distinguishing between them and recommend a unified treatment algorithm[2].

Within the diagnosis of COPD, there are four different lesions involved with varying pathogenesis, intensity, and timing[9, 11, 17-19]:

1. Emphysema
2. Chronic bronchitis
3. Small airway disease and remodeling
4. Vascular and endothelial damage

Emphysema is characterized by the detachment of alveolar septae and destruction of the lung parenchyma[20]. There is dilatation of the alveoli and loss of alveolo-capillary surface area impairing oxygen transfer and leading to loss of elasticity[21]. This loss of elastic recoil likely contributes to dynamic small airway collapse[4]. Chronic bronchitis is characterized by submucosal gland hypertrophy, excessive mucus production, ciliary dysfunction, and mucostasis[4].

Interestingly, the severity of emphysema and chronic bronchitis does not clearly correlate with the FEV_1, which is the common measure of airflow obstruction. Five decades ago, a seminal publication by Hogg and colleagues demonstrated that the anatomical site for airflow limitation in COPD is in the small airways and not the large airways, as previously thought[22]. The decline in airflow correlates best with small airway inflammation, remodeling, and wall thickening[23-24]. Lastly, patients with COPD demonstrate vascular endothelial cell dysfunction with reduced alveolar-capillary bed surface area leading to impaired gas exchange[25] and decreased ventricular stroke volume[26-27].

A major pitfall in the study of COPD has been focusing new drug development to an "airway-centric" approach[17]. There is increasing evidence that the all compartments of the lung are involved and merit careful study. Furthermore, there is increasing evidence that the inflammatory process spills over to the systemic circulation leading to progressive extra-pulmonary manifestations[17, 19, 28].

CURRENT COPD THERAPY:

COPD has few interventions that impact the decline in lung function over time or improve survival[8, 29]. These are smoking cessation[30-31], chronic oxygen supplementation for hypoxemia[32-33], and management of exacerbations with non-invasive ventilation[8, 34].

The current goals of COPD therapy include improving symptoms, FEV_1, exercise tolerance, and survival, meanwhile decreasing hyperinflation, exacerbations, and hospitalizations[31]. Inhaled bronchodilators decrease hyperinflation and improve dyspnea and FEV_1[2, 8, 31, 35]. β-2 agonists and anti-cholinergic muscarinic antagonists are the most commonly prescribed inhalers and are available in short-acting and long-acting formulations[2, 8, 31, 35-36]. Combined inhaled therapy provides greater bronchodilatation than single agents[31].

The NIH/NHLBI GOLD COPD guidelines (last updated in 2010) divide patients by GOLD stages based on FEV_1 with a recommended step-wise management (see Figure 1)[37]. All patients are encouraged to stop smoking and have yearly influenza vaccination. For GOLD stage I, the use of short-acting β-2 agonist or anti-cholinergic antagonist p.r.n. is recommended. Patients who remain symptomatic despite this therapy should receive one or more long-acting bronchodilators daily as part of a maintenance schedule. The short-acting bronchodilator should then be used for "rescue" therapy as needed[2].

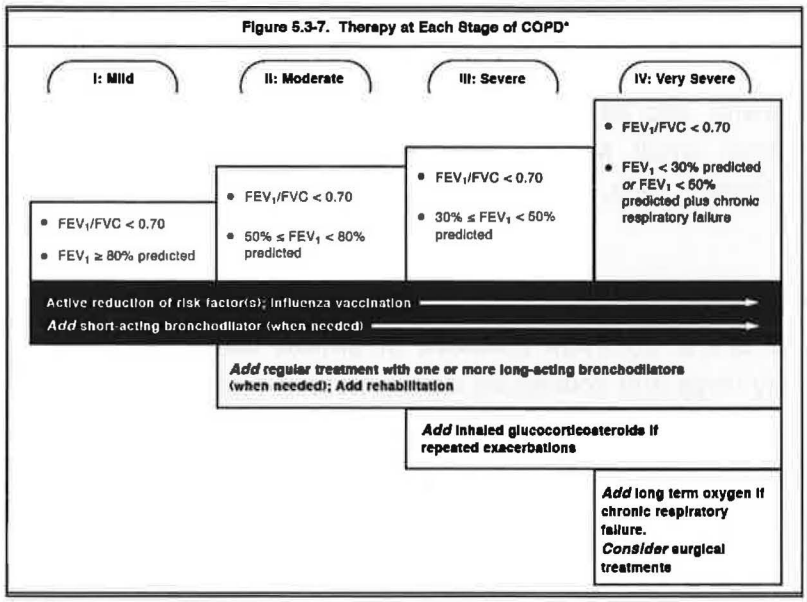

Figure 1: GOLD guidelines for the management of COPD.

The addition of inhaled steroids to the long-acting inhaled bronchodilator(s) is recommended at GOLD stage III (FEV_1 < 50%) and repeated exacerbations[2]. This recommendation is based on studies that have demonstrated that inhaled steroids decrease the rate of exacerbations and have additive effects on bronchodilatation[2, 38-39]. This is in contrast with asthma where inhaled steroids are recommended at every stage of the disease[39].

The GOLD stepwise management has not changed much in the last 6 years despite two large randomized controlled clinical trials exploring the role of long-acting bronchodilators with and without addition of inhaled corticosteroids[40]. The TORCH study published in 2007 was a 3-year multi-center, double-blind trial with 6184 COPD patients (FEV_1 < 60%) randomized to placebo vs. salmeterol vs. fluticasone vs. combination therapy [40]. The subjects treated with combined long-acting β-2 agonist (LABA) and inhaled corticosteroids (ICS) had a trend to reduced mortality (primary endpoint) with a hazard ratio 0.825 (95% CI, 0.681-1.002, P=0.052). This combination was associated with a reduction in annual rate of exacerbations and FEV_1. The decline in FEV_1 over time (secondary endpoint) was modestly decreased in patients receiving inhaled steroids (See Figure 2)[40]. Of concern, an increase in the risk for pneumonia was associated with inhaled steroid use[38, 40].

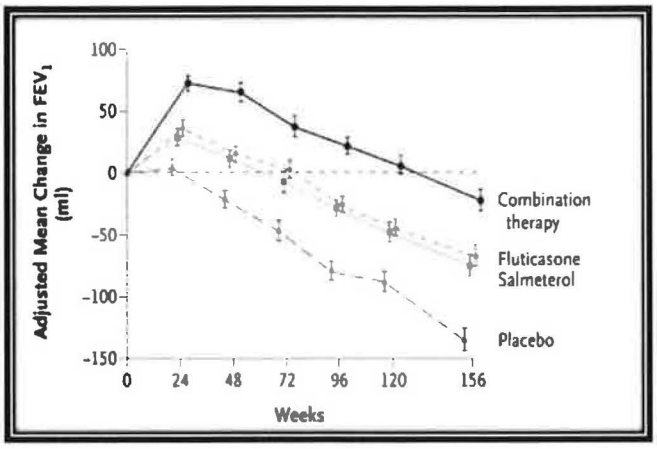

Figure 2: Inhaled steroid and LABA combination may alter FEV1 decline over time. From Calverley PMA. NEJM 2007;356:775-89.

A second large-scale study (UPLIFT) randomized 5993 COPD patients (mean FEV_1 of 48% predicted) to the inhaled long-acting anticholinergic, tiotropium vs. placebo[41]. The primary endpoint or rate of decline in the mean FEV_1 was not met (see Figure 3). One possible explanation for this lack of efficacy was attributed to the fact that a large number of patients in the placebo group were already on inhaled steroids and long-acting β-2 agonists with an annual loss of FEV_1 that was lower than expected[42]. Secondary endpoints, such as respiratory health and reduction in exacerbations, hospitalizations, and respiratory failure were achieved[41]. Post-hoc analysis revealed a decreased risk for death in the tiotropium group with a hazard ratio 0.84 (95% CI: 0.73-0.97; p=0.034) and suggested a possible cardiovascular risk protection[43].

Table 2. Annual Rates of Decline in FEV_1 and FVC before and after Bronchodilation and Scores on Health-Related Quality of Life.*

Variable	Tiotropium		Placebo		Difference between Tiotropium and Placebo (95% CI)	P Value†
	Patients	Mean Decline	Patients	Mean Decline		
	no.	*ml/yr*	*no.*	*ml/yr*		
FEV_1						
Before bronchodilation	2557	30±1	2413	30±1	0±2 (–4 to 4)	0.95
After bronchodilation	2554	40±1	2410	42±1	–2±2 (–6 to 2)	0.21

Figure 3: UPLIFT study- Tiotropium does not alter the decline in FEV_1 over time. From Tashkin DP. NEJM 2008;359:1543-54.

In summary, the current use of long-acting inhaled bronchodilators and steroids have impacted the care of COPD patients by improving symptoms, bronchodilatation, and overall quality of life with added benefit of reducing exacerbations. Analysis of secondary endpoints for TORCH and UPLIFT studies suggest, but not definitely prove, that combined salmeterol/fluticasone may alter the decline in FEV1 over time[36, 40] and that inhaled tiotropium may have a positive impact on survival[43]. Currently, significant efforts are being made to design

"super inhalers" that combine long-acting β-2 agonists with long-acting anticholinergic agents, and furthermore, triple therapy with the addition of inhaled steroids[14-15, 35].

PATHOGENESIS OF COPD: A REVIEW AND UPDATE

The most accepted and "traditional" hypothesis of COPD is the "protease-antiprotease hypothesis" proposed in 1964 after the discovery of a genetic deficiency in alpha-1 antitrypsin, an important lung anti-protease, in association with emphysema[6, 44-45]. This traditional hypothesis proposes that the inhalation of toxic gases or particles from cigarette smoke or environmental and occupational pollutants lead to an inflammatory and oxidant response within the lung causing an imbalance between proteases and anti-proteases[12, 46]. This imbalance leads to increased elastolytic activity within the lung parenchyma developing the emphysematous lesion[45-46]. This hypothesis is well-supported by animal and human clinical studies and has served as the centerpiece of COPD research (Figure 4)[12, 45].

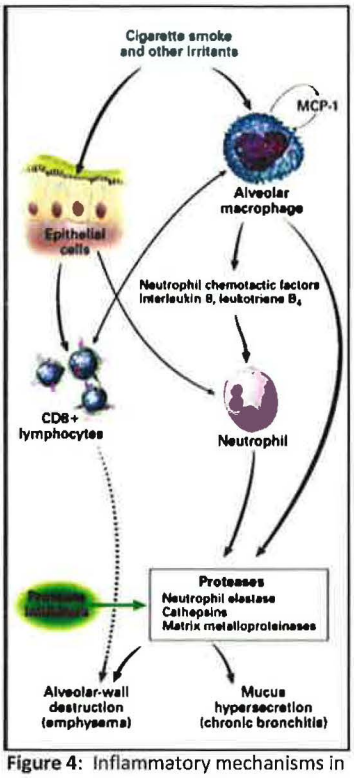

Figure 4: Inflammatory mechanisms in COPD as of the year 2000. Barnes P. NEJM 2000;343:269-80.

The most current hypothesis incorporates the fact that COPD is composed of different lesions or processes that include emphysema, chronic bronchitis, small airway fibrosis and remodeling, and vascular insufficiency. There is good evidence that each lesion may have different pathogenesis with varying severity and timing (Figure 5)[6, 11-13, 46].

Cigarette smoke and other inhaled irritants directly stimulate lung epithelial cells[47] and alveolar macrophages to produce chemokines and cytokines, such as CXCL1 and CCL2, that attract inflammatory cells into the lungs[10-11, 48]. T-helper 1 (Th1) and type 1 cytotoxic T-cells are recruited into the small airways and alveolar spaces[11]. Cytotoxic T-cells are implicated in inducing apoptosis of the alveolar epithelial cells by secretion of perforins leading to alveolar detachment and the characteristic emphysema lesion[49]. The inflammatory response is amplified by activated epithelial and inflammatory cells thus explaining the persistence of inflammation despite smoking cessation[4, 16].

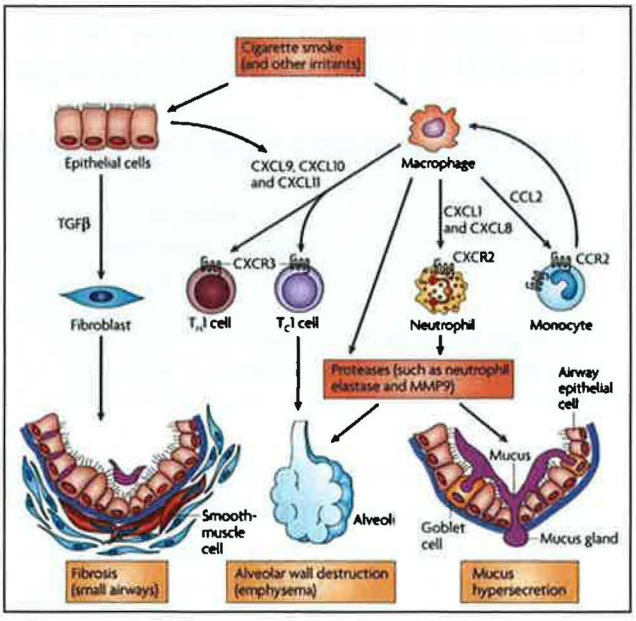

Figure 5: Inflammatory and immune cellular cascade in COPD. From Barnes PJ. Nature Reviews 2008.

The recruited and activated neutrophils and macrophages release proteases, such as neutrophil elastase and matrix metalloproteinases, that digest elastin within alveolar structures and promote mucus secretion in the airways[10-11]. The activated inflammatory and epithelial cells also produce transforming growth factor-β (TGF-β), which stimulates fibroblast proliferation with development fibrosis and narrowing of the small airways[11, 50]. Finally, the vascular compartment of the lung is directly affected by cigarette smoke with expression of vasoconstrictive and vasoproliferative mediators causing alteration of the endothelium[18].

Recent groups have proposed new paradigms for the pathogenesis of COPD stimulating further scientific research on new potential therapies. Is COPD a:

- Chronic inflammatory disease?
- An oxidant-mediated disease?
- A systemic disease?
- An immune disease?
- A chronic infectious disease?

COPD: A CHRONIC INFLAMMATORY DISEASE?

COPD is characterized by a chronic inflammatory process involving all lung compartments with epithelial and endothelial cells, inflammatory cells, chemokines, and cytokines perpetuating inflammation. If this is correct, then why is COPD resistant to systemic or inhaled steroids[51]?

- **A case for steroid resistance:**

Corticosteroids do not significantly decrease the inflammatory process or clearly modulate the progression of airflow obstruction, as demonstrated by limited effect on the decline in FEV_1 over time[16, 52].

Recent work has delineated an important pathway that could explain steroid resistance in COPD. Steroids work broadly by binding and activating the glucocorticoid (GC) receptor leading to its migration to the nucleus. Within the nucleus, the GC receptor suppresses the transcription of inflammatory genes[4, 52]. The expression of inflammatory genes is controlled by the acetylation of core histones that uncoil DNA chromatin permitting RNA polymerase to bind leading to gene transcription[53]. In order to suppress inflammatory gene transcription, steroids and the GC receptor utilize histone deacetylases (HDAC's) to reverse

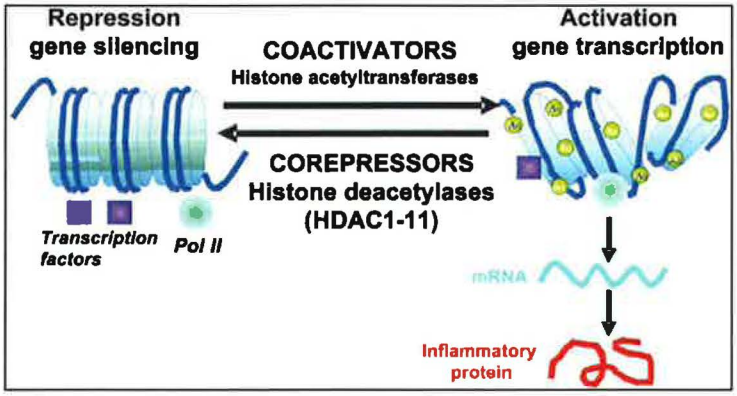

Figure 6: Gene activation and inactivation are controlled by core histone acetylation. From Barnes PJ CHEST 2006.

histone acetylation and tighten the chromatin inhibiting the transcription of inflammatory genes (Figure 6)[49, 51, 54]. Glucocorticoid resistance may be caused by oxidative stress generated from smoking and the inflammatory cascade leading to decreased expression and activity of histone deacetylases in the lung and alveolar macrophages of COPD patients[52, 55].

Theophylline is a phosphodiesterase inhibitor that has been used for at least 75 years in the treatment of COPD. It exerts weak bronchodilator effects by increasing intracellular cyclic AMP and cGMP[9, 54]. Theophylline increases HDAC activity and suppress the transcription of inflammatory genes in the presence of corticosteroids[4, 52, 54]. Low doses of theophylline (at serum concentrations of 5 mg/L) seem to enhance the anti-inflammatory effects of steroids by 100-1000 fold[54]. The combination of theophylline and an inhaled or low dose systemic steroids could overcome steroid resistance and modulate the chronic inflammation seen in COPD[54]. Its narrow therapeutic window with significant cardiovascular and GI side effects has hampered its use. This has led to the development of more specific phosphodiesterase inhibitors.

- **Selective phosphodiesterase (PDE-4) inhibitors:**

The selective inhibitors of phosphodiesterase-4 isoenzyme are the newest drugs for COPD with future potential for FDA approval. This isoenzyme is one of the 11 known phosphodiesterases and is expressed in macrophages, CD8+ lymphocytes, and neutrophils[9, 56]. Their theoretical advantage over theophylline is selective isoenzyme inhibition in inflammatory cells with a better side effect profile. In animal models of COPD, PDE4 inhibitors reduce cytokine expression and inhibit neutrophil recruitment and activation[56-58]. Its use in COPD is associated with a decline in sputum neutrophils and eosinophils[56-58]. A second generation PDE-4 inhibitor, roflumilast at 500 μg orally once daily has been studied in two different 1-year Phase III trials in patients with severe COPD ($FEV_1 \leq 50\%$) and a history of prior COPD exacerbation[57-58]. Concomitant use LABA's and rescue inhalers but not inhaled steroid or tiotropium use was allowed. Pooled results met primary endpoints with an increase in pre-bronchodilator FEV_1 of 48 ml and a 17% relative risk reduction in COPD exacerbation (Figure 7)[56]. The side effects of roflumilast include nausea, diarrhea, headaches, and mild weight loss[56-58].

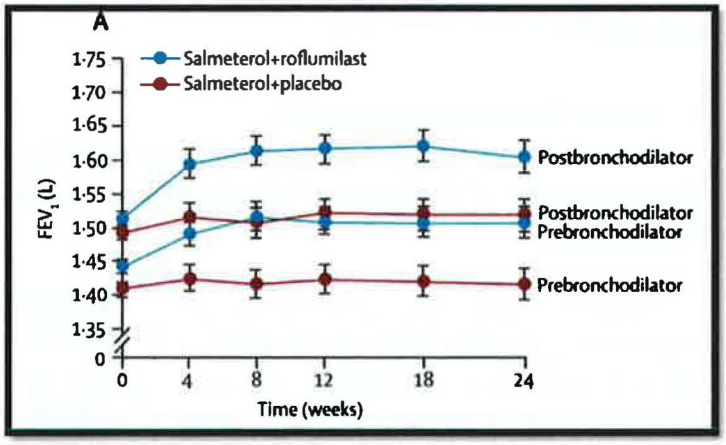

Figure 7: Oral roflumilast improves FEV_1 when added to salmeterol inhaler. From Fabbri LA. Lancet 2009.

In July 2010, the European Commission granted approval for marketing to roflumilast (Daxas™) for the treatment of COPD patients with $FEV_1 < 50\%$ and frequent exacerbations[56]. The potential benefits of roflumilast in modulating chronic inflammation and/or its potential augmentation of steroid responsiveness remain to be proven.

- **Anti-TNF therapy, an anti-inflammatory strategy:**

Tumor necrosis factor (TNF-∝) is a potent cytokine with pro-inflammatory activity via the induction of other cytokines and chemotaxis and activation of neutrophils and macrophages in the lung[9]. COPD patients have higher levels of TNF in sputum, bronchoalveolar lavage, and serum[16, 59]. Furthermore, the cachexia associated with COPD has been attributed to elevated systemic TNF concentrations[59]. Anti-TNF therapy in COPD was expected to mirror the success demonstrated in other chronic inflammatory processes, such as rheumatoid arthritis and Chron's disease[14, 59].

Various placebo-controlled clinical trials have looked unsuccessfully at the effects of TNF-blockade in COPD. A multicenter, double-blind, and placebo-controlled trial using infliximab (humanized monoclonal TNF antibody) at 3 mg/kg or 5 mg/kg for 24 weeks in moderate-to-severe COPD evaluated its effect on quality of life as primary endpoint[10, 60]. The results of the study were disappointing without achievement of primary or secondary endpoints. Subgroup analysis suggested that younger and more cachectic subjects had improved 6-minute walk testing[10]. Of concern, there were increased number of malignancies and pneumonias in the group treated with infliximab[10]. This study and others have ruled against the use of these agents in COPD. Experts propose that single cytokine inhibition is likely to be ineffective in COPD due to multiple competing and redundant inflammatory pathways[14, 59].

- **Anti-Interleukin 8 therapy:**

IL-8 or CXCL8 is a potent chemokine implicated in neutrophil and monocyte influx into the airways and lung parenchyma in COPD and cystic fibrosis[9, 28]. ABX-IL8 is a humanized monoclonal IgG2 antibody that has been evaluated in a Phase I study in COPD with good tolerance and safety[9, 61]. Three monthly intravenous ABX-IL8 administrations led to improved dyspnea, which was sustained for 3 months after discontinuation[9]. This early report suggests that direct chemokine inhibition in COPD could lead to measurable clinical effects with low toxicity. Further confirmatory studies may be limited by the cost of chronic intravenous antibody infusions and possible risk for increased infection with chronic inhibition of this important chemokine function in host defense[9-10].

- **Protein kinase inhibition:**

Recent work has demonstrated that p38 MAPK enzyme is an essential regulator of the synthesis of IL-8 (CXCL8), TNF-alpha, and matrix metalloproteinases involved in the parenchymal and airway destruction seen in COPD[10]. COPD patients have elevated expression of p38 MAPK in lung and peripheral mononuclear cells[4, 15]. Various investigators and pharmaceutical companies have synthesized selective small molecule inhibitors of p38 MAPK. GW-856553 is the most studied selective inhibitor with demonstrated suppression of IL-8 production by mononuclear cells of COPD patients[10]. A Phase II study with GW-856553 evaluating the safety and efficacy of this compound in COPD (NCT00642148) has been completed with pending results[62]. There is concern for toxicity based on p38 MAPK ubiquitous expression and role in normal cellular homeostasis[52].

COPD: AN OXIDANT MEDIATED DISEASE:

The role of oxidative stress in the pathogenesis of COPD has strong scientific support and is complementary to the protease-antiprotease and the chronic inflammatory disease hypotheses. This hypothesis proposes that oxidative stress derived from oxygen radical species recruit inflammatory cells, activate transcription factors for pro-inflammatory cytokines, inactive anti-proteases, interfere with normal injury repair, induce epithelial cell apoptosis, and promote mucus hypersecretion[12, 63-64]. Radical oxygen species (ROS) and reactive nitrogen species are generated from cigarette smoke and from activated epithelial and resident inflammatory cells[63]. Normally, this oxidative injury is balanced or quenched by potent anti-oxidant enzymes and scavengers. In COPD, an imbalance in oxidant and anti-oxidant state leads to airway and lung parenchymal injury (Figure 8)[12, 64].

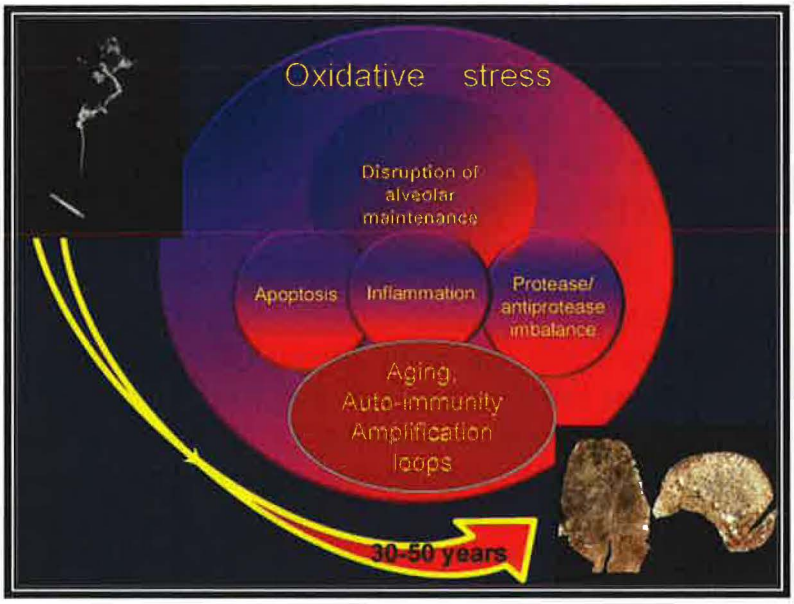

Figure 8: Hypothesis proposing the broad and instrumental role of oxidative stress in the pathogenesis of COPD. From MacNee W. Proc Am Thorac Soc 2009.

In contrast with healthy smokers, COPD patients have increased exhaled hydrogen peroxide and alveolar macrophages with increased secretion of ROS[63]. Also, anti-oxidant molecules are reduced in the lungs of COPD patients. Enhancing antioxidant activity in smokers with and without COPD could potentially alter disease progression. Oral supplementation of anti-oxidants, such as vitamin C and E and beta-carotene, have shown variable response[63].

N-acetyl cysteine (NAC) is a commercially available agent capable of replenishing glutathione stores, an important cellular and intracellular anti-oxidant[63]. Oral administration of NAC increases glutathione levels in the serum and bronchoalveolar lavage fluid and inhibits phagocyte ROS production[63]. Clinical studies have demonstrated modest effects in COPD with decreased cough and sputum production, decreased rate of hospitalizations, and bacterial colonization[63, 65]. Nevertheless, a recent randomized, controlled clinical trial in COPD (the BRONCUS trial) with NAC 600 mg/day vs. placebo for three years did not demonstrate an improvement in FEV_1 decline (Figure 9) or COPD exacerbation rates[66]. This data suggests that therapeutic strategies that affect one of the anti-oxidant pathways may be insufficient in controlling the complex oxidative cascade in COPD.

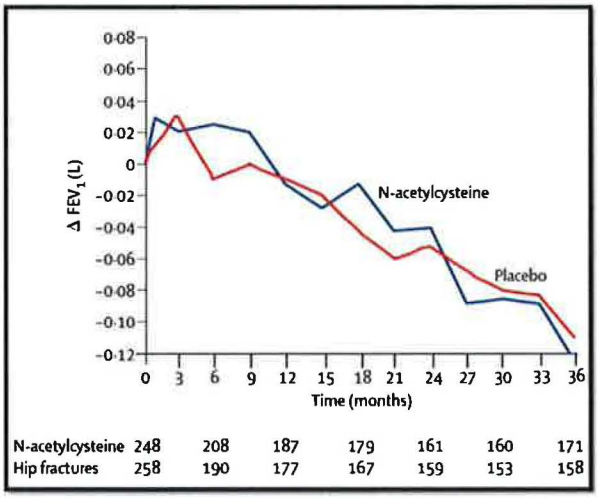

Figure 9: In patients with COPD, treatment with NAC did not significantly alter the decline in FEV1 when compared to placebo.

Recent exciting evidence for the role of oxidative stress in COPD focuses on the role of nuclear erythroid-related factor 2 (Nrf2), an important key transcription factor with broad control of the expression of multiple anti-oxidant enzymes[12]. Mice deficient in Nrf2 are more susceptible to the development of emphysema upon exposure to cigarette smoke. In animal models, small molecule activators of Nrf2 protect from development of emphysema[12]. A recent study utilizing lung biopsy specimens demonstrated low expression of antioxidants controlled by Nrf-2 correlating with severity of COPD[67]. This exciting research proposes a new therapeutic target for COPD.

COPD, A SYSTEMIC DISEASE?

Recent studies have focused on the systemic manifestations of COPD and their role in increasing morbidity and mortality. The FEV_1 is the most utilized marker of disease progression but is a poor predictor or determinant of mortality. Patients with COPD suffer from multisystem organ involvement that is not easily explained by lung-limited inflammation (see Table 1)[8, 28, 68]. The mechanisms that direct these systemic manifestations are not well known but it is suspected that COPD causes a systemic "spill-over" of inflammatory cytokines, chemokines, and cells into the peripheral circulation[28]. Therapeutic strategies that focus on these systemic manifestations could benefit quality of life, decrease exacerbations, and improve survival without having an effect on the FEV_1[8].

Table 1: Systemic Manifestations of COPD
Skeletal muscle wasting
Cachexia
Lung cancer
Pulmonary hypertension
Ischemic heart disease: endothelial dysfunction
Congestive cardiac failure
Osteoporosis
Normocytic anemia
Diabetes
Metabolic syndrome
Obstructive sleep apnea
Depression

Adapted from Barnes ERJ 2009.

A complete discussion of the systemic manifestations is beyond the scope of this protocol but the modification of cardiovascular complications with β-blockade and the possible role of statins in reducing systemic inflammation will be discussed.

- **β-Blockers for COPD? Have we lost our minds?**

COPD is a known risk factor for cardiovascular disease[69]. In COPD, a perpetuated lung inflammation caused by cigarette smoking could induce a "systemic" endothelial dysfunction increasing cardiovascular risk[68-69]. Other experts advocate a more likely explanation that COPD and cardiovascular disease are co-morbid conditions that share common risk factors, such as aging, cigarette smoking, physical inactivity, deconditioning, and obesity[19].

There is perhaps unjustified resistance to initiating β-blockers in COPD patients with cardiovascular disease because of fear of provoking acute bronchospasm[70-71]. Only one-third of patients with COPD and concomitant congestive heart failure (CHF) and/or coronary artery disease are prescribed β-blockers despite these agents being first-line therapy and known to reduce cardiovascular mortality by 30-40%[72]. The Lung Health Study demonstrated that cardiovascular disease is the leading cause of hospitalization and the second cause of death (22%) in mild-to-moderate COPD[72-73]. The increased risk of cardiovascular disease in COPD may be related to increased adrenergic activity as demonstrated by increased serum norepinephrine levels and turnover in this population when compared to matched controls[74].

The current Heart Failure Society of America (HFSA) 2010 Comprehensive Heart Failure Practice Guideline recommends the use of β-blockers in patients with heart failure with decreased left ventricular function and concomitant COPD[75]. Thus, physicians should consider the use of "cardioselective" β-blockers in COPD patients with concomitant CHF, coronary artery disease, and/or significant active cardiac risk factors. These agents have significant decreased

affinity for the β-2 airway receptors and are more selective for β-1 cardiac receptors[70]. A current review recommended the following β-blockers for patients with CHF and concomitant COPD (see Table 2)[76].

Table 2: Recommended β-beta-blockers and dosages for CHF with concomitant COPD:

Drug	β-Receptor Selectivity	Starting Dose	Target Dosage
Bisopropol (Zebeta™)	120-fold $\beta_1 > \beta_2$	2.5 mg/day	10 mg/day
Metoprolol (Lopressor™)	75-fold $\beta_1 > \beta_2$	12.5–25 mg/day	200 mg/day
Carvedilol (Coreg™)	β_1, β_2, and α_1-receptors	6.25 mg/day	50 mg/day (100 mg/day if >85 kg)

Adapted from Matera MG. Pulmonary Pharmacology & Therapeutics 2010; 23:1-8.

A group in the Netherlands recently published an observational cohort study of 2,230 COPD patients utilizing electronic medical records from general practitioners[77]. The use of a β-blocker was associated with an adjusted hazard ratio for mortality of 0.68 (95% CI, 0.56-0.83) Figure 10. COPD exacerbations were also reduced with a hazard ratio of 0.71 (95% CI, 0.60-0.83). Interestingly, these effects were seen even in COPD patients without overt cardiovascular disease.

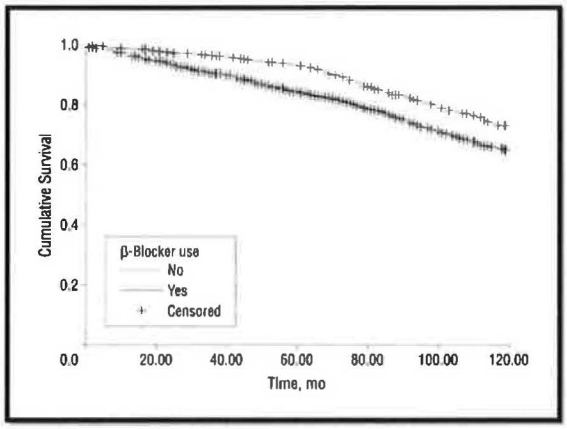

Figure 10: Cumulative survival of COPD patients treated or not with β-blockers. From Rutten FH. Arch Intern Med 2010.

Recent studies have demonstrated that the use of cardioselective β-blockers:

- Do not worsen or precipitate respiratory symptoms[70]
- Do not lower FEV_1[70]
- May lessen responsiveness to inhaled β-2 agonists[71]
- May reduce COPD exacerbation rates[77]
- May reduce mortality[77]

Cardioselective β-blockers could suppress hyperadrenergic activity associated with COPD and impact morbidity and mortality in a similar fashion as in CHF and recent myocardial infarction[74]. Furthermore, chronic β-blocker use in animal models have demonstrated upregulation in airway β-2 receptors[72] and perhaps explains recent reports of increased response to bronchodilators in COPD patients being treated with β-blockers[78].

- **Statins: Systemic therapy for a systemic disease?**

HMG-CoA reductase inhibitors (statins) have many "pleiotropic" activities, such as anti-oxidant, immunomodulatory, and anti-inflammatory properties[51, 79]. Statins mediate these

functions by inhibiting the expression of cell adhesion molecules that are essential for recruitment of inflammatory cells into the lung[51]. Statins also block cytokines and chemokines associated with the chronic inflammatory response associated with the pathogenesis of COPD[51, 79]. In a mouse model of cigarette smoke inhalation, statins prevented the development emphysema[51, 80].

Janda and colleagues performed a clinical review and analysis of nine different studies with statins in COPD demonstrating a positive impact on multiple endpoints including exacerbations, pulmonary function, and survival[68, 81-82]. The only published randomized-control clinical trial evaluated the effect of pravastatin (40 mg/day) in 125 stable COPD patients for a 6-month period[83]. This study demonstrated a 54% increase in exercise time in the pravastatin group when compared to placebo. Furthermore, a reduction in CRP levels, a marker of systemic inflammation, was noted in 79% of patients and correlated with increased exercise time (Figure 11)[83].

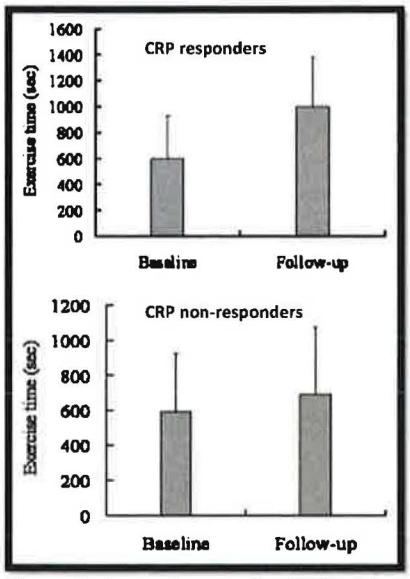

Figure 11: Statins decrease CRP levels and correlate with increased exercise time. From Lee TM. Am J Cardiol 2008.

The potential role of statins in reducing systemic and local lung inflammation remains to be proven. Based on their broad action, statins may improve survival in COPD by reducing the impact of associated systemic manifestations including cardiovascular disease, mineral bone loss, and cancer[51, 68]. If these effects are confirmed by future RCT's, statins and/or β-blocker administration could provide outcomes that are superior to inhaled bronchodilators and steroids. Currently, there are multiple studies recruiting COPD patients for determining the role of statins and β-blockers in this complex disease (www.clinicaltrials.gov).

COPD: AN IMMUNE DISEASE?

The pathogenesis of COPD depends on chronic inflammation driven by cigarette smoke that persists and progresses even after smoking cessation. Recent important work hypothesizes that COPD develops from an overwhelmed innate immune system and the subsequent activation of adaptive immunity (Figure 12)[6, 50, 84].

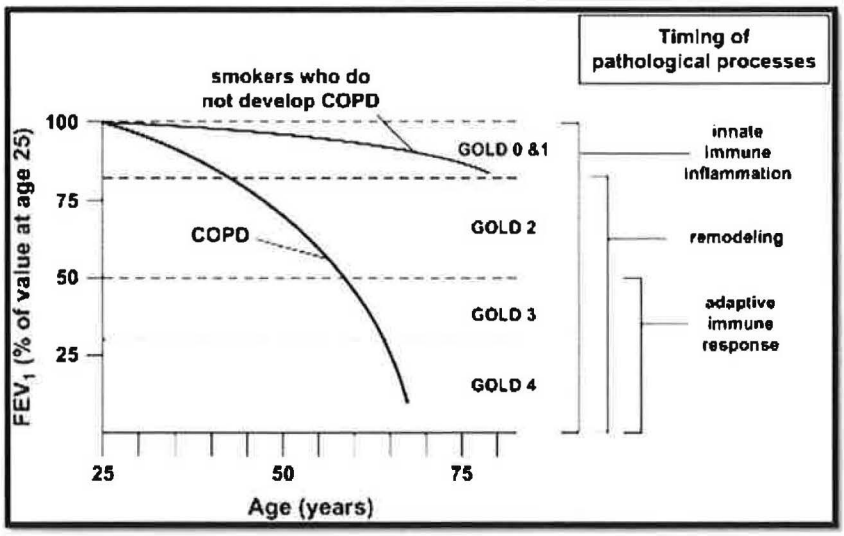

Figure 12: Timing of Immunopathogenesis of COPD by GOLD COPD stages superimposed on Fletcher's diagram. From Curtis JL. Proc Am Thorac Soc 2007.

The immune hypothesis proposes that cigarette smoke and/or infections cause epithelial cell damage and cellular stress that release important cytokines and chemokines activating the innate immune system. The innate immune defense includes the activated and recruited neutrophils and macrophages, epithelial and endothelial cell responses, mucous production, and the mucociliary system[6, 50]. These cells release metalloproteinases and oxygen radicals with damage to epithelial cells and extracellular matrix. The adaptive immune system is likely turned on by exposure of dendritic cells to this cellular and extracellular matrix debris with uptake of these auto-antigens and presentation to CD8+ lymphocytes leading to further proliferation and activation of T cells[6]. CD8+ cytotoxic T cells exert direct cellular damage on epithelial cells with cell death. CD4+ cells also accumulate in the lung likely in response to auto-antigens with release of Th1 cytokines controlling inflammatory cell chemotaxis and release of metalloproteinases perpetuating the characteristic COPD injury and repair process[6, 85].

There is evidence in COPD that as the inflammation becomes chronic and progressive, the airways develop increased number of immune cells characteristic of the adaptive immune response: B-cells and CD8+ T-cells. These cells aggregate and organize to form lymphoid follicles around the small airways[23] and suggest the presence of an active and robust adaptive immune response in the pathogenesis of COPD[50, 86]. These bronchial-associated follicles are rare in smokers without airflow obstruction or in the early stages of COPD and become more numerous at the later stages of COPD (GOLD stages III-IV) correlating with decline in FEV_1[23, 50].

Various investigational studies have demonstrated that the adaptive immune response is directed to auto-antigens released during lung digestion[85], to viral and bacterial colonization/infection[6, 13], or to products of cigarette smoke[50, 87]. Lee and colleagues recently demonstrated that peripheral CD4+ cells from patients with COPD proliferated and released interferon-γ and IL-10 in response to elastin peptide fragments. Furthermore, auto-antibodies directed to elastin were demonstrated (Figure 13)[85].

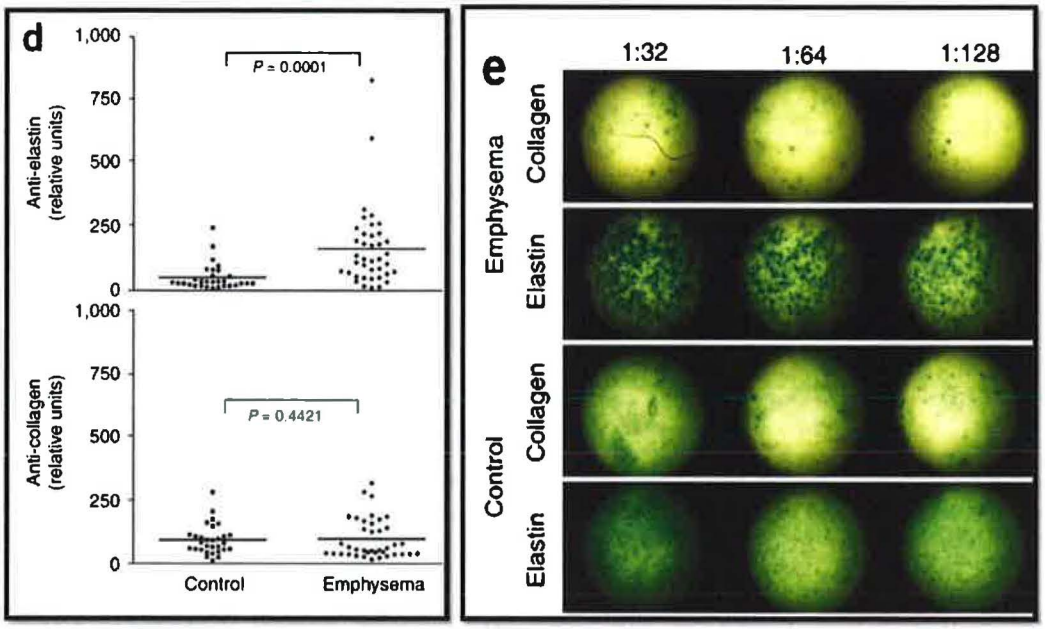

Figure 13: Panel D demonstrates the presence of anti-elastin antibodies in patients with emphysema. No anti-collagen antibodies were detected. Panel E is an ELISpot plate with serial dilutions (1:32–1:128) of single-cell suspensions from human lung tissue of a patient with emphysema and control subject. The blue spots represent individual cells secreting anti-elastin antibodies. From Lee S-H. Nature Medicine 2007.

The presence of anti-elastin antibodies has not been reproduced by other investigators raising questions whether there is a humoral autoimmune response in COPD[88-89]. Nevertheless, these reports have generated continued interest in studying therapeutic targets in COPD following a strategy similar to that used for chronic autoimmune diseases, such as rheumatoid arthritis[87]. A Phase I trial evaluating the dose, toxicity, and efficacy of inhaled cyclosporine in modulating markers of the adaptive immune system has been recently completed with pending results[90]. Early therapy suppressing a dysregulated adaptive immune system may prevent progression from cigarette smoking to advanced COPD[84, 87].

COPD: A CHRONIC INFECTIOUS DISEASE?

In the 1950-1960's, the "British hypothesis" proposed that COPD was a byproduct of recurrent viral or bacterial infections, airway pathogen colonization, and increased airway mucus secretion[91]. This hypothesis was contested by investigational work that failed to demonstrate a difference in the frequency of isolated respiratory pathogens between stable versus exacerbated COPD patients[91]. Recently, there has been a resurgence of the "British hypothesis" fueled by studies supporting the role of chronic infection in the onset of COPD exacerbations and the pathogenesis of COPD.

The normal lung is usually devoid of bacterial or viral pathogens thanks to its active epithelial cell barrier, resident cells, and robust innate immune system[91]. In contrast, 25-50% of

patients with stable COPD are colonized with respiratory tract pathogens even in the absence of exacerbation or increased respiratory symptoms[13, 91-92]. Airway bacterial pathogens are detected by bronchoalveolar lavage (BAL) in 35% of patients with stable COPD versus only 7% of non-smokers[92]. If PCR-based techniques are used to detect common respiratory pathogens, such as non-typeable *Haemophilus influenzae*, the rate of colonization is much higher in COPD patients even with negative sputum cultures[13]. Similar increased prevalence of respiratory viral pathogens, such as RSV and adenovirus, has been reported[13, 93]. These colonized patients have significantly increased BAL neutrophils and levels of IL-8, TNF-α, active metalloproteinases, and endotoxin[13, 92] correlating with the presence of mucus hypersecretion and airflow obstruction[13].

Sethi and colleagues proposed the "Vicious Circle Hypothesis" as a unifying hypothesis for the role of chronic infection in the pathogenesis of COPD[13, 91]. This hypothesis recognizes the important role of cigarette smoking and other pollutants in overwhelming the lung's innate defense system. This system consists of ciliated bronchial and alveolar epithelial cells that serve as barriers against tissue invasion and clear mucus and bacteria. Resident macrophages, neutrophils, and dendritic cells provide for non-specific pathogen scavenging and oxidant response. The epithelial and resident cells also secrete important antimicrobial peptides, mucin, IgA, and mediators of inflammation (See Figure 14)[13, 91].

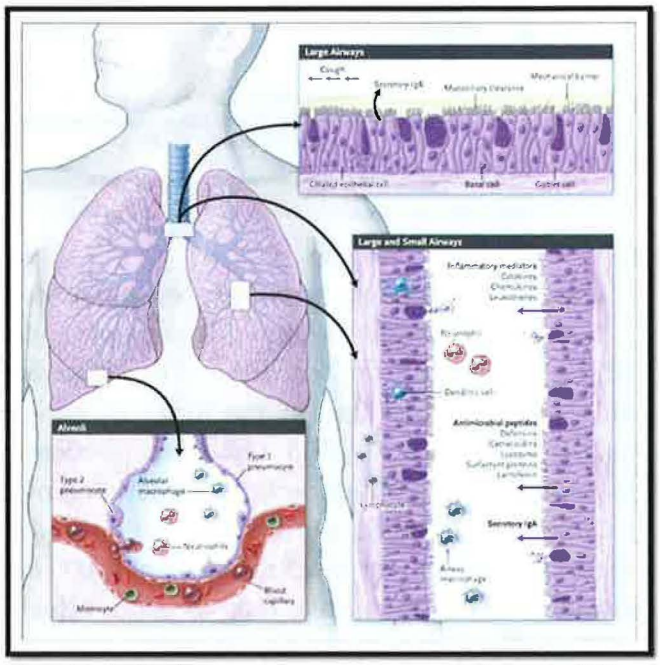

Figure 14: The lung's innate defense system. From Sethi S. NEJM 2008.

Patients with COPD have decreased ciliary function, increased mucin production, and decreased levels of bacteriostatic surfactant proteins. As the innate immune response is weakened by repetitive insults, bacterial and viral pathogens are able to colonize and/or invade the lung. Bacterial-specific molecules are recognized by pattern-recognition receptors that are expressed by host epithelial cells and resident macrophages. Some of these receptors, the "toll-like" receptors activate cellular signaling pathways promoting an inflammatory response potentially damaging the airways and lung parenchyma[91]. Furthermore, the adaptive immune response to these pathogens is perpetuated by chronic airway and parenchymal lung injury (Figure 15). Could the development of COPD in susceptible smokers be prevented by treatment strategies directed at controlling bacterial or viral colonization or enhancing the innate defense response?

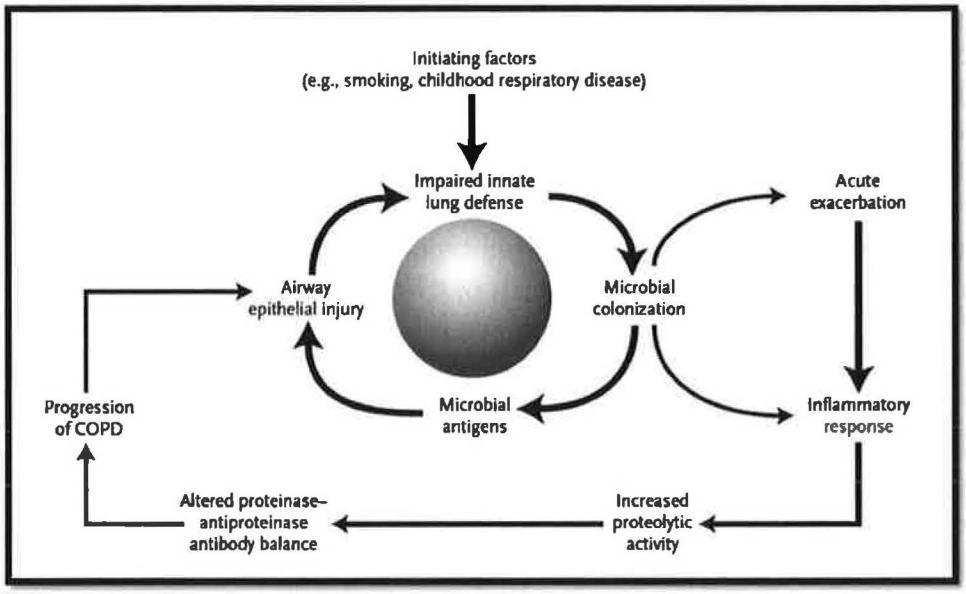

Figure 15: The Vicious-Circle hypothesis of Infection and Inflammation in the pathogenesis of COPD. From Sethi S. NEJM 2008.

- **Chronic Macrolides: Antibiotics or immunomodulators in COPD:**

If chronic bacterial or viral colonization and its associated inflammatory response leads to COPD exacerbation and contribute to its pathogenesis, then strategies directed at reducing pathogenic bacteria load in the lungs of patients with COPD could be of benefit. A meta-analysis published in 2003 reviewed publications from the 1960's to 1970's that utilized prolonged courses of antibiotics (tetracycline or penicillin for durations of 4-7 months per year) in COPD[94]. Antibiotic prophylaxis led to a modest reduction in the days of illness during exacerbations but no statistically-significant reduction in exacerbations rates. Its use was associated with increased risk of side effects and was suspected to increase antibiotic resistance[94].

Most recent attention has focused on the use of chronic macrolide therapy in COPD. Macrolides are effective antibiotics with oral bioavailability and intracellular accumulation. Some of the macrolides, rapamycin and FK-506, are immunosuppressive drugs utilized in preventing transplant allograft rejection[95]. Azithromycin, clarithromycin, and erythromycin have anti-inflammatory properties believed to be related to their intracellular accumulation with modulation of cellular and immune mechanisms and pathways[95-96]. Macrolides have potent therapeutic benefits in Diffuse Panbronchiolitis, a rare bronchiolar disease

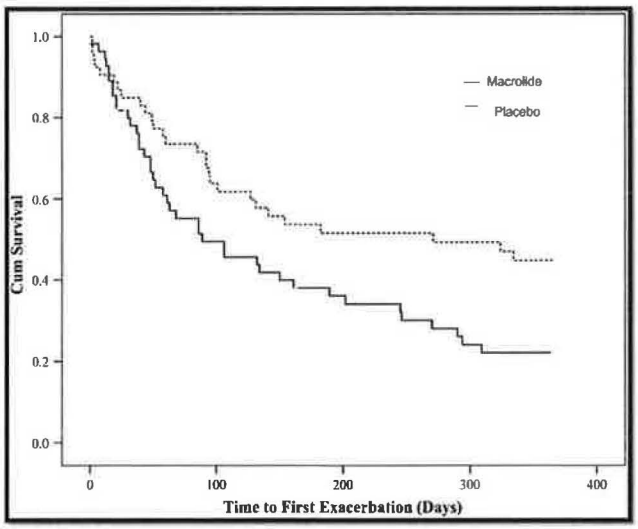

Figure 16: Kaplan-Meier curve demonstrating time to first exacerbation. Erythromycin vs placebo. p=0.02. From Seemungal TA. Am J Respir Crit Care Med 2008.

associated with bacterial colonization and chronic inflammation[97]. These agents are now being studied in other inflammatory airway diseases like cystic fibrosis, chronic bronchiectasis, and asthma[95-96].

A recent study randomized 109 stable COPD patients to one year of erythromycin 250 mg twice a day vs. placebo[98]. Most patients were already on bronchodilators and inhaled steroids. Patients treated with low dose erythromycin had a relative reduction in exacerbations rates of 0.648 (95%CI: 0.489-0.859; p=0.003) with no increase in adverse events. No improvement in FEV_1, bacterial counts, serum C-reactive protein (CRP), or inflammatory cytokines was noted (Figure 16). The NIH/NHLBI COPD Clinical Research Network has recently completed enrollment for a large multi-center RCT with the use of azithromycin 250 mg once daily in patient with moderate-to-severe COPD and history of frequent exacerbations[99].

- **Novel mucolytic strategies to reduce bacterial colonization:**

Normal airway mucus production and clearance are necessary for lung homeostasis and innate defense against inhaled particles, toxins, and pathogens. The airway mucus typically has a low viscosity allowing for rapid clearance and mobilization by ciliary action of bronchial airway cells[100]. Cigarette smokers and particularly patients with COPD have increased mucus secretion and poor mucociliary clearance. Airway mucus production and increased viscosity are due to increased goblet cell mucin production and airway dehydration[100] and are associated with bacterial colonization, FEV_1 decline, and COPD exacerbations[9, 16]. A reduction in the airway mucus production or retention could decrease the incidence of bacterial colonization[63] and/or infection thus preventing the "vicious circle" of infection and inflammation[91].

A Cochrane systematic review analyzed 28 trials and determined that mucolytics provide a modest reduction in exacerbation rates with no effect on lung function decline[100-101]. Recent novel mucolytic agents focus on the role of cilia, airway hydration, and goblet cell mucin production[9, 16, 100]. The most developed strategies utilize N-acetylcysteine (NAC) for its mucolytic and anti-oxidant properties and nebulized hypertonic saline and mannitol for their hydration of the bronchial ciliary aqueous layer[100].

The BRONCUS study was a double-blind and placebo-controlled study of 523 COPD patients treated with 600 mg/day of NAC vs. placebo for 3 years. This study did not alter the decline in FEV_1 or exacerbation rates[66]. Subgroup analysis suggested that there was a decrease in exacerbations in patients not on inhaled corticosteroids[14, 66]. A Chinese multicenter RCT of 709 COPD patients (PEACE study) randomized to high-dose oral carbocisteine vs. placebo demonstrated a reduction in exacerbations with a risk ratio of 0.75 (95% CI 0.62-0.92; P=0.004)[102]. Many experts recommend that higher doses of these well-tolerated agents (NAC 1,200-1,800 mg/day) should be considered in future investigations. Further confirmatory studies are underway.

Nebulized hypertonic saline (3%-7%) has demonstrated significant effects in patients with cystic fibrosis and bronchiectasis by decreasing the mucous viscosity through a proposed mechanism of shifting intracellular fluid to the airway ciliary layer[100]. This technique is being

evaluated in COPD despite reports of bronchospasm and hyperinflation with single doses of nebulized 3% hypertonic saline[103].

In summary, reducing bacterial or viral colonization in the lung or boosting the innate immune defense could reduce symptoms and exacerbations in COPD. Furthermore, this strategy could break the "vicious circle" of infection that may drive the cellular inflammation and tissue degradation associated with COPD.

FUTURE THERAPEUTIC TARGETS IN COPD:

As discussed in this Protocol, new hypotheses for the pathogenesis of COPD have expanded our knowledge of this complex disease and fueled research into new potential therapeutics going "beyond bronchodilators". There are currently 373 clinical therapeutic trials in COPD listed in the clinicaltrials.gov website. Table 3 summarizes potential targets and proposed therapeutic agents that may become available in the future.

Table 3: Future Therapeutic Strategies for COPD

Smoking cessation: CNS nicotine addiction center	**Phosphodiesterase inhibitors:** Theophylline PDE4 inhibitors (cilomilast, roflumilast)
Cytokine therapy: TNF-α antagonists (infliximab, etanercept) TACE inhibitors IL-8 inhibitors (ABX-IL-8) IL-10 and analogues IL-1β antagonist (ACZ-885)	**Oxidants:** Anti-oxidants (Glutathione precursors) Thiazolidine N-acetyl cysteine Nrf2 restorers (sulforaphane) Resveratrol iNOS inhibitors
Chemokine inhibition: CXCR1/2 antagonists (SCH-527123, SB-656933) CXCR3 antagonists CCR1 antagonist (AZD-4818) CCR2 antagonists Proline-glycine-proline (PGP) blockers.	**Proteinases:** Endogenous (α-1 antitrypsin, SLPI, TIMP, elafin) Neutrophil elastase inhibitors (AZD-9668, ONO-6818) MMP inhibitors (AZD-1236, AZD-3342, AZD-6067, Maristamat) Cysteine proteinase inhibitors
Kinases and transcription factors: NFκB inhibitors p38 MAPK inhibitors (SB-681323, GW-856553, PH-797804) P13Kγ inhibitors PPAR activators	**Mucus hypersecretion:** N-acetylcysteine EGF receptor inhibitors (gefitinib, BIBW 2948 BS) CACC inhibitors (niflumic acid, MSI 1956) MARCKS inhibitors Inhaled mannitol
Adhesion molecules: Antibodies to CD11/CD18, ICAM1 E-selectin inhibitors	**Lung regeneration agents:** Retinoic acid Retinoic acid receptor γ agonist (R667) Stem cell therapy
Leukotrienes: BLT_1 antagonists (LY 29311, SB 201146, BIIL284) 5-lipoxygenase inhibitors (zileuton)	

Adapted from Barnes PJ. The Lancet 2004;364:985-96 and Morjaria JB. Drug Discovery Today 2010;15:396-405.

CONCLUSION:

COPD is a complex disease with progressive airflow obstruction, gas exchange abnormalities, and disability. Its pathogenesis involves a variety of pathways with new exciting hypotheses being proposed. At the present time, smoking cessation is the most effective therapeutic strategy and remains a challenge for patients and their physicians. The current available COPD therapies, such as inhaled bronchodilators and corticosteroids, are mostly incapable of altering the decline in FEV_1 over time or improving survival.

A growing number of new agents are under investigation targeting the pathogenesis of COPD. Clinical validation of these agents will surely take time and be quite costly. A few of the anti-inflammatory agents described in this Protocol are in Phase III clinical investigation or in the process of FDA submission. These current investigations should provide patients and physicians with hope thus changing our previous "nihilistic"[8] approach to COPD.

The questions posed by Mrs. B.M. are at the center of the controversies in COPD pathogenesis and new drug development in COPD. At the present time, I would manage her COPD as follows:

- Adhere to the GOLD guidelines:
    - Full vaccination
    - Combined inhaled LABA and long-acting anticholinergic
    - Inhaled corticosteroids
    - Assess need for chronic oxygen supplementation
- Address the systemic component of COPD:
    - Osteoporosis prevention with calcium supplementation and biphosphonates
    - Nutrition assessment with maximization
    - Pulmonary rehabilitation and exercise program
    - Statins (?)
    - Cardioselective beta-blockade use (if HTN or active CAD?)
- Off-label alternatives:
    - Low-dose theophylline for its putative effect on corticosteroid resistance (?)
    - If recurrent exacerbations, chronic macrolide therapy and/or N-acetylcysteine (?)
- Strongly consider inclusion in a multicenter investigational study
- If further worsening,
    - Oxygen
    - Bronchoscopic endobronchial valve placement
    - Lung volume reduction surgery
    - Lung transplantation

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