

# Targeted treatment in COPD: a multi-system approach for a multi-system disease

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**Abstract:** Chronic obstructive pulmonary disease is a varied condition when examined from a number of different perspectives including factors which influence disease development, pathological process and clinical features. There may be a complex interaction between the degree by which each of these processes influences the development of COPD and the subsequent clinical phenotype with which the patient presents. The varied host response and subsequent clinical phenotype has generated much interest in recent years. It is possible that failure of treatment to impact on mortality and reverse the disease process is because of the heterogeneous nature of the condition. Identification and targeted treatment of clinical and pathological phenotypes within the broad spectrum of COPD may therefore improve outcome. This article will review previous work which has attempted to phenotype COPD and identify if specific treatment for these phenotypes has been shown to be of benefit. It will examine the work on pathological processes and clinical manifestations, both pulmonary and systemic, and will focus on pharmacological therapies.

**Keywords:** COPD, clinical phenotypes, pathological phenotypes

## Introduction

Chronic obstructive pulmonary disease (COPD), as defined in recent guidelines, is “a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.”<sup>1</sup>

The relationship between smoking and COPD is not absolute. COPD can occur in lifelong non-smokers;<sup>2</sup> indeed more than 15% of subjects worldwide who die from COPD are non-smokers. Moreover, only approximately 30% of subjects who have a significant smoking history go on to develop clinically significant COPD.<sup>3</sup>

The host response to inhaled gases and particles appears to play an important role in development of COPD, and several factors have been identified which influence this process. Genetics,<sup>4</sup> health in early life,<sup>5–7</sup> nutrition,<sup>8</sup> gender<sup>9</sup> and socioeconomic status<sup>10</sup> have all been shown to influence the development of COPD.

With so many factors influencing COPD it is unsurprising that it is a heterogeneous condition. Indeed the term Chronic Obstructive Pulmonary Disease was coined in the 1970s to encompass what was previously recognized as three separate smoking-related lung diseases, chronic bronchitis, emphysema and chronic bronchiolitis. Each of these conditions is present to variable extents in individual patients. The systemic effects of COPD including skeletal muscle dysfunction,<sup>11</sup> osteoporosis,<sup>12</sup> cardiovascular disease,<sup>13</sup>

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weight loss<sup>14</sup> and depression<sup>15</sup> also vary within populations of COPD patients.

Our understanding of the pathogenesis of COPD has increased over the last 25 years. It is now apparent that a variety of pathological processes are involved in the development of COPD. Chronic inhalation of cigarette smoke presents a significant oxidant burden for the lungs. It has been suggested that the ability of the lungs to cope with this oxidant burden has an important role in the pathogenesis of COPD.<sup>16</sup> Influx and activation of inflammatory leukocytes in the lungs is also a part of the inflammatory responses in the lungs in COPD. Increased numbers of neutrophils,<sup>17</sup> macrophages,<sup>18</sup> eosinophils<sup>19</sup> and t-cell lymphocytes<sup>20</sup> have all been implicated in the pathogenesis of COPD. The increased activity of inflammatory cells results in the release of an excess of proteolytic enzymes, such as neutrophil elastase (NE), in excess of antiproteases, such as  $\alpha$ -1 antitrypsin (AAT). This protease/antiprotease imbalance may result in lung tissue damage and subsequent development of COPD.<sup>21</sup>

In addition to imbalances between proteases/antiproteases and oxidants/antioxidants, mechanisms related to enhanced inflammatory responses include enhanced epigenetic mechanisms and autoimmunity.<sup>22,23</sup>

In parallel with an improved understanding of the pathogenesis of COPD, treatment for COPD has significantly advanced in the last 25 years. Short-acting bronchodilators can improve health status and symptomatic control but not mortality.<sup>24–27</sup> Long acting bronchodilators have also been shown to improve symptoms, exercise capacity and exacerbation rates.<sup>28,29</sup> Tiotropium, a long-acting anticholinergic, has been shown to reduce exacerbation rates, improve quality of life and increase forced expiratory volume in one second (FEV<sub>1</sub>) in stable COPD.<sup>30</sup> There is no published data as yet supporting a long-term survival benefit from tiotropium. A recent publication suggests that treatment with inhaled corticosteroid and long-acting  $\beta$  agonist therapy has survival benefit compared to tiotropium alone.<sup>31</sup>

Inhaled corticosteroids (ICS) also have a role in COPD and can improve health status and reduce exacerbation rates.<sup>32,33</sup> Inhaled corticosteroid therapy in combination with long-acting  $\beta$  agonist (LABA) have been shown to be of greater benefit than ICS alone.<sup>34,35</sup> Treatment with ICS is currently recommended for subjects with an FEV<sub>1</sub> less than 50% who have more than one exacerbation per year,<sup>36</sup> but this guideline may have to be revised in the light of recent large clinical trials showing the benefit of combinations of ICS and long-acting  $\beta$  agonists on symptom control, exacerbation rates and the rate of decline in airways obstruction.<sup>37,38</sup>

However, with the exception of one randomized controlled trial of ICS/LABA,<sup>37</sup> none of these treatments are able to improve life expectancy or reverse the COPD process. Furthermore none of these therapeutic trials take into account the heterogeneous nature of the condition.

Long term oxygen therapy in subjects with significant respiratory failure and can improve mortality and morbidity.<sup>39,40</sup> There is also evidence that pulmonary rehabilitation improves mortality and morbidity in selected patients with COPD.<sup>41</sup>

As described above, Chronic Obstructive Pulmonary Disease is a varied condition when examined from a number of different perspectives including factors which influence disease development, pathological process and clinical features. There may be a complex interaction between the degree by which each of these processes influence the development of COPD and the subsequent clinical phenotype with which the patient presents. The varied host response and subsequent clinical phenotype has generated much interest in recent years. It is possible that failure of treatment to impact on mortality and reverse the disease process is because of the heterogeneous nature of the condition. Identification and targeted treatment of clinical and pathological phenotypes within the broad spectrum of COPD may therefore improve outcome.

This article will review previous work which has attempted to phenotype COPD and identify if specific treatment for these phenotypes has been shown to be of benefit. It will examine the work on pathological processes and clinical manifestations, both pulmonary and systemic and will focus on pharmacological therapies.

## Oxidative stress in COPD

Oxidative stress results from an imbalance between oxidants and antioxidants in favor of oxidants.<sup>42</sup> This can occur from either an increase in oxidant burden or a decrease in antioxidant or both. An increase in oxidant burden in the lungs can result from inhalation of oxidants, such as those derived from cigarette smoke or air pollution, or as a result of the influx of inflammatory leukocytes which are activated to release reactive oxygen species. Inhalation of toxic particles and gases in cigarette smoke and the subsequent oxidative stress can cause direct damage to lipids and proteins in the lungs.<sup>43,44</sup> Molecular pathways and signalling mechanisms are stimulated by oxidative stress<sup>45</sup> resulting in increased gene expression, production of pro-inflammatory cytokines,<sup>46,47</sup> influx of inflammatory leukocytes and subsequent enhanced inflammation in the lung.<sup>48</sup>

Most of the antioxidant capacity of the lung is extra-cellular, present in the airspace epithelial lining fluid (ELF).<sup>49</sup> The most important antioxidant in the epithelial lining fluid is glutathione. This compound has poor bioavailability when given by mouth limiting its use as a disease modifying agent. N-acetylcysteine (NAC), a precursor of glutathione, is biochemically active in humans. In vitro NAC treatment of fetal membranes results in a reduction in production of pro-inflammatory cytokines.<sup>50</sup> In animal models, oral NAC inhibits lung inflammation<sup>51</sup> and attenuates elastase induced emphysema.<sup>52</sup>

## Treating oxidative stress

NAC has been shown to increase glutathione levels in human populations, both healthy subjects<sup>53</sup> and those with COPD.<sup>54</sup> Oral NAC results in increased plasma glutathione in COPD, but does not appear to influence bronchoalveolar lavage (BAL) levels of glutathione in patients with COPD.<sup>54</sup> However the proportion of lymphocytes in BAL decreased to levels comparable to non smoking controls after treatment with oral NAC.<sup>55</sup>

Low dose NAC (600 mg od) in patients with COPD over a 12-month placebo controlled trial reduced levels of hydrogen peroxide in exhaled breath condensate after 9 and 12 months, but not after 6 months of treatment.<sup>56</sup> Gerrits et al performed a retrospective analysis studying the impact of the introduction of NAC at high doses at the first hospital presentation with an exacerbation of COPD. This analysis suggested that NAC reduced the risk of readmission by 33% after adjustment for disease severity.<sup>57</sup> However, a further retrospective analysis suggested that oral NAC does not appear to impact on time to recover from an exacerbation.<sup>58</sup>

A Cochrane database review of randomized, double blind, placebo controlled studies with a variety of oral mucolytics, including n acetyl cysteine, was performed in subjects with chronic bronchitis (21 studies) or COPD (2 studies). Trials included in the review were to be of at least two months duration. This demonstrated a reduction in exacerbations of COPD compared with placebo. Six trial subjects required treatment with an oral mucolytic to prevent one exacerbation in the study period (range 2 months to 24 months) compared with placebo.<sup>59</sup> A quantitative systematic literature review of the use of NAC specifically has also been carried out. This review identified 11 randomized placebo controlled trials of NAC, daily doses between 400 mg and 600 mg, in treatment of chronic bronchitis over periods between 12 and

24 months. Nine of the 11 papers used exacerbation rate as an end point. Overall a reduction in exacerbations was identified in NAC versus placebo (30%–60% vs 40%–81%), with 5.8 patients requiring treatment for trial duration to prevent one exacerbation. An improvement in symptoms of breathlessness was also noted in the 5 trials which used this as an endpoint, 61.4% demonstrating an improvement in breathlessness in NAC versus 34.6% in placebo.<sup>60</sup>

The majority of studies discussed above were retrospective. A recent large scale prospective multicenter, double blind placebo control study, the Bronchus trial, of 600 mg OD of NAC over 3 years versus placebo was performed in 523 patients. No effect was noted on exacerbation rates or rate of decline in FEV<sub>1</sub>. Subgroup analysis of steroid naïve patients demonstrated a relative risk reduction for exacerbation of 0.79; however no effect was demonstrated on spirometry in this group.<sup>61</sup>

In conclusion oral NAC appears to play a role in the management of subjects with chronic bronchitis. This is most likely due to increasing intracellular glutathione although the chemical itself may also have direct antioxidant effect along with mucolytic properties. Alternatively the mucolytic property of NAC may be more likely to be of benefit in subjects with mucus hypersecretion. However, when this treatment is extended to the whole spectrum of COPD the results are less encouraging, possibly because oxidative stress is less important in development of other phenotypes. Targeting NAC treatment in subjects with the chronic bronchitis phenotype of COPD may help to reduce exacerbations.

## Lung inflammation in COPD

Oxidative stress in the lungs results in increased gene expression and production of pro-inflammatory cytokines.<sup>62</sup> This in turn causes both influx and activation of inflammatory leukocytes. Increased numbers of neutrophils, macrophages, eosinophils and T lymphocytes have all been associated with the development of COPD. Induced sputum neutrophil differentials are higher in smokers with airflow limitation, when compared with smokers with normal lung function.<sup>17,63,64</sup> There is also evidence that the percentage of neutrophils in induced sputum correlates with the rate of decline of FEV<sub>1</sub> in COPD.<sup>65</sup> Higher levels of neutrophils are also seen in the small airways and lung parenchyma in COPD, although this is not as marked as in the larger airways.<sup>66</sup> Neutrophils are thought to play an important role in the pathogenesis of COPD releasing elastase, metalloproteases and free radicals.<sup>67</sup>

The pro-inflammatory cytokine interleukin 8 (IL-8) is a potent chemotaxin for neutrophils and plays a role in recruitment and activation of neutrophil and alveolar macrophages.<sup>68</sup> Neutrophil cellular influx may result in endothelial injury which increases neutrophil- endothelial cell adhesion.<sup>69</sup>

Although the association between neutrophils and the pathogenesis of COPD is the most frequently studied, other inflammatory cell types have been implicated in the development of COPD. Patients with COPD appear to have higher levels of macrophages; a twenty five fold increase in macrophage numbers is seen in resected lung from COPD patients compared with normal smokers.<sup>18,70</sup> Furthermore, alveolar macrophages in patients with COPD are more active, secreting higher numbers of inflammatory proteins and demonstrating higher elastolytic activity compared with normal smokers.<sup>71</sup> There is also an association between macrophage numbers and COPD severity.<sup>64</sup> Macrophages in COPD patients have greater elastolytic activity. The major elastolytic enzyme secreted by AM in patients with COPD is matrix metalloproteinase 9 (MMP-9), whose activity is regulated by the transcription factor Nuclear Factor  $\kappa$ B (NF  $\kappa$ B), whose activation is associated with the development of COPD.<sup>72,73</sup>

Together with neutrophils and macrophages, both eosinophils and t-cell lymphocytes have been shown to be associated with the development of COPD. Eosinophils are elevated in airway wall biopsies of patients with COPD.<sup>20</sup> There is also increased production of eosinophilic cationic proteins in BAL of patients with COPD.<sup>74</sup> Increased t-cell lymphocytes have also been demonstrated in airways and lung tissue of patients with COPD. These T-cells are predominantly CD8 positive, which may contribute to parenchymal destruction.<sup>75</sup>

Eosinophilic bronchitis, defined as greater than 3% eosinophils in sputum, is predominately associated with asthma. Subjects with eosinophilic bronchitis may go on to develop chronic airflow obstruction without a significant smoking history.<sup>76</sup> It is not uncommon to find subjects with COPD with high levels of eosinophils in their sputum.<sup>77</sup> Rutgers et al found higher levels of eosinophils in the induced sputum and BAL fluid of non smoking COPD subjects compared to non smoking controls.<sup>78</sup> Furthermore, Lams et al found increased levels of activated eosinophils in the submucosa of resected lungs in smokers with COPD and current smokers compared to non smoking controls.<sup>79</sup>

Brightling et al gave 2 weeks of prednisolone (30 mg/day) or placebo to 67 patients with COPD in a double blind control

trial. They found that prednisolone significantly reduced the levels of eosinophils in induced sputum. Those subjects with high levels of eosinophils ( $>4.5\%$ ) demonstrated significant improvement in exercise capacity and FEV<sub>1</sub>.<sup>80</sup> Smokers with any form of airways disease, including COPD, and eosinophilic bronchitis have increased levels of reversibility compared to subjects with lower levels of eosinophils in sputum.<sup>81</sup> These data suggest that identification and treatment of eosinophilic bronchitis in COPD may be of benefit in a selected patient group.

## Anti-inflammatory therapy in COPD

Despite increasing evidence that pulmonary inflammation is a major factor in development of COPD, there is little evidence as yet that treatment of this inflammation, other than with inhaled corticosteroids, is of benefit.

Tumour necrosis factor alpha is a pro-inflammatory cytokine associated with inflammatory cell recruitment in the lung and the subsequent development of COPD.<sup>82</sup> TNF- $\alpha$  has been shown to stimulate inducible nitric oxide synthase in human vascular endothelium resulting in increased nitrosative stress.<sup>83</sup> Hypoxic alveolar macrophages have been shown to release TNF $\alpha$  which in turn results in oxidative stress by activating NF  $\kappa$ B,<sup>84</sup> furthermore transactivation of NF- $\kappa$ B by reactive oxygen species in cell models is synergized by TNF $\alpha$ .<sup>85,86</sup> TNF- $\alpha$  is also a neutrophil chemotactic agent<sup>82</sup> and elevated in sputum supernatant in COPD.<sup>87</sup>

Plasma levels of TNF $\alpha$  are elevated in COPD subjects with a low body mass index (BMI) compared with those with a normal BMI and also healthy controls.<sup>88</sup>

TNF- $\alpha$  blockade has been developed as a therapy for connective tissue diseases such as rheumatoid arthritis. A double blind placebo controlled study of TNF- $\alpha$  blockade in COPD, using the drug infliximab, has recently been published. Two hundred and thirty-four patients with moderate to severe COPD were given either infliximab, at either 3 mg/kg or 5 mg/kg or placebo. This study failed to demonstrate any impact on health status, FEV<sub>1</sub>, 6 minute walk distance or exacerbation rate. Furthermore, a non statistically significant increase in frequency of malignancy in treatment group was seen.<sup>89</sup> It may be that a specific phenotype of the COPD population may respond to TNF- $\alpha$  blockade.

A study of 30 patients with severe COPD divided into emphysematous and chronic bronchitis clinical phenotypes found that subjects with clinical emphysema had higher levels of TNF- $\alpha$  in serum and lower fat free mass.<sup>90</sup> COPD patients with evidence of low muscle mass, as measured by BMI and creatinine height index, had higher levels of TNF- $\alpha$  in serum



compared to COPD patients with normal muscle mass.<sup>91</sup> Selection of subjects with evidence of elevated TNF- $\alpha$  levels may therefore demonstrate benefit.

A further potential anti-inflammatory therapy is phosphodiesterase 4 (PDE4) inhibitors, which result in an increase in intracellular cyclic adenosine monophosphate. This action has anti-inflammatory properties including reduced production of pro-inflammatory cytokines<sup>92</sup> and recruitment of inflammatory leukocytes.<sup>93</sup> Phosphodiesterase 4 inhibition has also been shown to decrease TNF- $\alpha$  levels in bronchial epithelial cells<sup>94</sup> and reduce matrix metalloproteinase-9, a proteolytic enzyme, activity.<sup>95</sup>

Clinical studies of the efficacy of clioquinol and roflumilast, two selective phosphodiesterase-4 inhibitors, in COPD have been published. A Cochrane database review of clioquinol in COPD (4 trials) demonstrated small increases in FEV<sub>1</sub> and reduced exacerbation rates when compared to placebo.<sup>96</sup> Rabe et al showed that roflumilast treatment for 24 weeks in 1411 patients increased FEV<sub>1</sub> compared to placebo and reduced exacerbation rate from 1.13/per year in the placebo group to 1.03/year at low dose (250  $\mu$ g) and 0.75 per year at high dose (500  $\mu$ g).<sup>97</sup> A statistically significant improvement on FEV<sub>1</sub>, but not exacerbation rate, was sustained after 1 year of treatment.<sup>98</sup> These studies did not specifically target COPD patients with evidence of high levels of pulmonary inflammation. Several side effects are however associated with PDE4 inhibitors, including nausea and vomiting which affect the tolerability of these drugs. However the newer generation drugs of this class appear to be better tolerated.

Other potential anti-inflammatory therapies are as yet unproven. Previous studies of inhibition of IL-8 using a monoclonal antibody were of limited benefit, with improved dyspnea scores but no impact on FEV<sub>1</sub>, health status or 6 minute walk<sup>99</sup> and further development seems unlikely.<sup>100</sup> Reduction of inflammation by granulocyte macrophage colony stimulating factor may potentially be of benefit but there are as yet no clinical studies.<sup>101</sup>

## Protease antiprotease imbalance

Chronic increased levels of pro-inflammatory cytokines and inflammatory leukocytes have been associated with the development of COPD. Inflammatory leukocytes release proteolytic enzymes such as neutrophil elastase (NE), in excess of antiproteases, such as AAT. Other proteolytic imbalance may also occur between matrix metalloproteinases and their inhibitors. This protease/antiprotease imbalance results in lung tissue damage and subsequent development of COPD.<sup>71</sup>

Excess production of neutrophil elastase results in degradation of elastin, proteolysis and glycoproteins along with abnormalities in surfactant production.<sup>21</sup> NE also induces expression of the cytokine IL-8 in airway epithelial cells.<sup>102</sup> Tracheal instillation of NE in guinea pigs induces emphysema.<sup>103</sup> Furthermore NE inhibition reduces cigarette smoke induced emphysema in guinea pigs.<sup>104</sup> Other proteases are also involved. MMP-9 is the predominant elastolytic enzyme released by macrophages in COPD and is regulated by the NF $\kappa$ B pathway.<sup>73</sup> Other molecules with proteolytic activity include cathepsin G and proteinase 3. The lysosomal cysteine proteases may also play a role in COPD.<sup>105</sup>

In parallel with an excess of proteases, development of COPD is associated with inactivation or insufficiency of antiproteases. AAT is the main antiprotease in lung parenchyma. Subjects with AAT deficiency develop emphysema early.<sup>106</sup> Alpha-1 antitrypsin (ATT) deficiency is probably the best characterized phenotype of COPD. Impaired production of this proteinase results in early development of emphysema in smokers. There is a genetic association with ATT, the genotype protease inhibitor (PI) ZZ being most commonly associated with disease. The incidence of this genotype was 1 in 6000 in a Swedish study of 200 000 newborns.<sup>107</sup> The PIZZ genotype is seen in between 1 and 4.5% of subjects with COPD.<sup>108</sup> There are several other genotypes associated with ATT deficiency including MZ, MS, SS and SZ.<sup>109</sup>

Together with absolute or relative deficiency, inactivation of AAT has been identified in COPD. Oxidative stress through cigarette smoke, peroxynitrite and chemically generated oxidants have been shown to inactivate antiproteases *in vitro*.<sup>110,111</sup> Other antiproteases, such as secretory leukoprotease-1 (SLP-1), are present in the airways and may also be inactivated by oxidative stress.<sup>112</sup>

## Treating protease/antiprotease imbalance

Treating the excessive protease activity in COPD may improve outcome, specifically in patients where this plays a significant pathogenic role. Protease/antiprotease imbalance is the major defect in ATT deficiency therefore antiprotease therapy is most commonly studied in this phenotype of COPD although there are some studies of this treatment in the emphysematous phenotype.

Prolastin is an antiprotease which can be purified from the plasma of healthy donors and then administered intravenously to subjects with ATT deficiency. Augmentation therapy has been shown to increase the levels of ATT in plasma<sup>113</sup> and epithelial lining fluid<sup>114</sup> along with reducing

bronchial inflammation.<sup>115</sup> There is limited evidence for the benefit of this therapy with no randomized control trial data,<sup>116</sup> however the treatment appears to be well tolerated.<sup>117</sup> The current American Thoracic Society/European Respiratory Society guidelines for management of AAT deficiency suggest consideration in those subjects with FEV<sub>1</sub> between 35% and 65% predicted.<sup>108</sup>

Another potential therapy targeted at repairing the emphysematous COPD phenotype is all-trans-retinoic acid which has been shown to reverse emphysema in rats,<sup>118</sup> although not in adult mice.<sup>119</sup> This has led to a number of trials of the role of all-trans-retinoic acid in AAT deficiency. An initial study of 20 patients showed that this therapy was well tolerated, but there was no change in lung function or CT appearance after 3 months,<sup>120</sup> larger and longer term studies are awaited. A recent publication, the FORTE study, studied the role of retinoids in emphysema not associated with AAT deficiency. One hundred and forty-eight subjects with COPD who had impaired diffusion capacity and low CT density were treated with all-trans-retinoic acid for 6 months in a double-blind placebo-controlled trial with either 1 mg/kg/day or 2 mg/kg/day of retinoic acid.<sup>121</sup> Overall, results were disappointing with no impact on CT appearance or lung function. Post hoc analysis did suggest that those subjects in the group receiving the higher dose who were able to achieve high plasma levels had some improvement in emphysema as assessed by CT scanning, health status and gas transfer for carbon monoxide.<sup>121</sup>

Another potential treatment targeted at the proposed protease/antiprotease imbalance in COPD is the drug hyaluronan, which has been shown to prevent elastic fibre elastolysis, resulting from the effects of neutrophil elastase and human metalloproteinases.<sup>122</sup> Hyaluronan may also improve hydration of elastic fibres, preventing elastic tissue damage.<sup>123</sup> There are ongoing clinical trials of this therapy, but as yet there is no evidence of benefit.<sup>124</sup>

## Pathological phenotypes in COPD

The FORTE study, mentioned above, is an example of patient selection for treatment within the COPD population based on clinical phenotype. There have been several recent publications on clinical phenotypes in COPD. A recent study by Patel et al<sup>125</sup> suggested that there were significant differences in the processes involved in the development of parenchymal and airways disease in COPD. Development of emphysema appeared to have stronger genetic links, with siblings of subjects with emphysema more likely to have emphysema themselves without a strong relationship between

levels of emphysema and smoking pack years. A stronger relationship was noted between FEV<sub>1</sub> and pack years in non emphysematous COPD, compared to emphysematous COPD subjects.<sup>125</sup> Subjects with severe emphysema on CT scan are more likely to have lower BMI and worse health status compared to subjects with mild or no emphysema independent of FEV<sub>1</sub>.<sup>126</sup> A study by Fujimoto et al divided 172 patients with COPD into three groups on the basis of the presence or absence of emphysema and bronchial wall thickening. Those with emphysema but no bronchial wall thickening had lower BMI, lower gas transfer and reduced reversibility compared to those with bronchial wall thickening, but no emphysema.<sup>127</sup> A smaller study, of 24 patients, demonstrated increased inflammatory leukocytes in the sputum of subjects with evidence of emphysema on CT scan compared to those without emphysema.<sup>128</sup>

Two major smoking related forms of emphysema are recognized, centriacinar and panacinar. Centriacinar, also known as centrilobular, relates to damage of alveoli around the respiratory bronchioles and the central portions of the acinus. Centriacinar damage is usually most marked in the upper lobes. Panacinar emphysema, associated with uniform damage of airspaces distal to the terminal bronchioles, is linked with  $\alpha 1$  antitrypsin deficiency and predominately affects the lower lobes.<sup>19</sup> There is some speculation in the literature that these two processes have different pathological origins, with centriacinar related to airways damage and inflammation and panacinar a result of impaired anti-inflammatory response to inhaled insults such as cigarette smoke.<sup>129,130</sup> Previous work in this field has been based on pathological specimens. Improved lung imaging techniques allow less invasive differentiation of the emphysematous phenotype.<sup>131</sup> This may facilitate increased research of the underlying pathological process involved.

As described above there is increasing evidence that different inflammatory pathways involved in COPD pathogenesis may affect the clinical phenotype of COPD which develops. There is, as yet, limited proof that pharmacological targeting of pathways specific to the individual will have any impact on morbidity and mortality.

## Targeting pathological phenotypes in COPD

The National Emphysema Treatment Trial (NETT) is a good example of targeted therapy in COPD. Lung volume reduction surgery (LVRS) for treatment of emphysema having previously been described in the 1950s was reintroduced

in 1990s. Initial reports were encouraging from specialist centers with improved FEV<sub>1</sub> and PaO<sub>2</sub>.<sup>132</sup> However as LVRS became more widely used clinical improvements were less apparent and 90 day mortality was higher than in the initial publications.<sup>133</sup> This led to the development of the National Emphysema Treatment Trial. In this study over 1200 patients were randomized to either medical therapy or lung volume reduction surgery and followed up over a five year period. Exacerbation rates were reduced in the surgical arm by 30% compared to medical therapy and time to first exacerbation was also reduced.<sup>134</sup> However, there was no impact on morbidity and health status. Post hoc analysis of the NETT trial has identified a specific cohort who derives most benefit from this treatment. Subjects with low exercise capacity and predominant upper lobe emphysema have significant improvement in quality of life.<sup>135</sup> Furthermore, LVRS in these individuals may impact on survival.<sup>136</sup> This study suggests that rigorous patient selection, matching the treatment to the individual may help improve outcomes in COPD.

## Pulmonary and systemic manifestations of COPD

The second part of this review will describe some pulmonary and systemic manifestations of COPD and discuss if identification and treatment of these conditions may improve outcome.

## Pulmonary artery hypertension in COPD

Pulmonary artery hypertension (PAH) is associated with COPD. The incidence of significant PAH in COPD is estimated at around 1 to 2/1000.<sup>137</sup> This increases in severe disease. Right heart catheterization data from the National Emphysema Treatment Trial showed that out of 120 subjects with severe emphysema the mean pulmonary artery pressure (PAP) was 26 mmHg with approximately 25% having a resting PAP greater than 30 mmHg. Furthermore, in a study of 131 COPD subjects who had normal resting PAP, 76 demonstrated evidence of exercise induced PAH. Thirty-three of the 131 went on to demonstrate resting PAH after between 5 and 6 years follow up.<sup>138</sup> Raised PAP in COPD has a negative impact on survival<sup>139</sup> and is associated with poor response to long-term oxygen therapy (LTOT).<sup>140</sup>

Whilst PAH in COPD is thought mainly to be due to hypoxia, pulmonary vascular remodelling has been shown to affect all layers of the pulmonary vessel walls

in COPD.<sup>141</sup> As such reversal of hypoxia alone will not result in improvement in pulmonary hypertension,<sup>142</sup> which was confirmed in the Nocturnal Oxygen Treatment Trial.<sup>39</sup> Other factors which may influence the development of PAH in COPD include cigarette smoking, which may have an impact on pulmonary vessels,<sup>143</sup> and pulmonary inflammation.<sup>144</sup>

Over the last 10 years new therapies, such as endothelin receptor antagonists<sup>145</sup> and phosphodiesterase inhibitors,<sup>146</sup> have become available for idiopathic PAH (iPAH). These treatments are more easily administered and better tolerated than previous therapies, such as intravenous prostacyclin, and have been shown to improve exercise capacity, quality of life and survival in iPAH. However as yet there is little published data of the effect of these new agents in PAH associated with COPD. The incidence of significant PAH in COPD is estimated to be 100 fold that of iPAH therefore investigated and treating this condition would have significant cost implications.<sup>147</sup>

## Recurrent exacerbations of COPD

Bacterial colonization in COPD is associated with declining FEV<sub>1</sub>. Increased bacterial load is associated with increased rate of decline in FEV<sub>1</sub>.<sup>148</sup> Subjects with severe COPD have increased frequency of exacerbations of COPD compared with milder forms of the disease.<sup>149</sup> Banerjee et al studied 67 subjects with stable COPD for evidence of potentially pathogenic organisms (PPO) in induced sputum. Those subjects with PPO have higher levels of airways inflammation and worse health status, compared to those without pathogenic organisms independent of FEV<sub>1</sub>, age and BMI.<sup>150</sup> A similar study using bronchoalveolar lavage (BAL) demonstrated that in COPD subjects bacterial colonization is associated with higher levels of inflammation in BAL.<sup>151</sup>

COPD subjects who experience frequent exacerbations are more likely to have bacterial colonization, compared with infrequent exacerbators.<sup>152</sup>

Eradication of bacterial pathogens after an exacerbation of COPD is associated with reduced levels of bacterial colonization and bronchial inflammation.<sup>153</sup> There is however no study demonstrating the long-term impact of eradication of potential pathogenic organisms from the bronchial tract. There is evidence that chronic use of Azithromycin, a macrolide antibiotic, in cystic fibrosis improves FEV<sub>1</sub> and may also reduce exacerbations and improve quality of life<sup>154</sup> and there is an ongoing study of its impact in COPD.

Identification and treatment of bacterial colonization and pulmonary hypertension may be of benefit in COPD,

although there is limited evidence for this as yet. In a similar way, identifying and managing the systemic effects of COPD may improve outcomes and is discussed below.

## Systemic inflammation in COPD

COPD is associated with high levels of systemic inflammation, probably secondary to pulmonary inflammation.<sup>155</sup> This systemic inflammation has been shown to affect the cardiovascular system, muscle mass and bone metabolism. All of these factors are discussed below, as well as the affect of COPD on mental health.

Man et al published a study of 4803 patients with mild to moderate COPD. This demonstrated that high levels of systemic inflammation, as measured by serum C reactive protein (CRP), were associated with increased all cause mortality, cancer and cardiovascular death.<sup>155</sup>

## Cardiovascular risk in COPD

There is increasing evidence that COPD is associated with cardiovascular risk. Zureik et al studied 194 subjects with COPD and measured arterial stiffness as an assessment of cardiovascular disease. They found that as FEV<sub>1</sub> fell there was an increase in the degree of arterial wall stiffness, indicating that airflow obstruction may be an independent risk factor for cardiovascular disease.<sup>156</sup> Sin and Man demonstrated that subjects with severe airflow obstruction are more likely to have electrocardiogram evidence of ischemic heart disease compared to subjects with no airflow obstruction. One possible explanation for this is that systemic inflammation as a result of COPD results in systemic vascular endothelial damage. In support of this hypothesis, higher levels of systemic inflammation were found in those COPD subjects with evidence of ischemic heart disease.<sup>157</sup>

There is evidence of benefit in treating cardiovascular disease in COPD, both in terms of cardiovascular and respiratory outcomes. Soyseth et al performed a retrospective analysis on 854 subjects admitted to hospital with an exacerbation of COPD. They found that subjects treated with statins had a hazard ratio for death of 0.57 compared to subjects not taking this treatment. Survival was further improved in the group taking inhaled corticosteroid with a statin with a hazard ratio of 0.39 compared to the cohort not on either an inhaled corticosteroid or a statin.<sup>158</sup>

A further retrospective analysis of almost 6000 patients with COPD by Mancini et al found that use of a statin in combination with either an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker had

a significant impact on both cardiovascular and respiratory disease.<sup>159</sup> These therapies were associated with reduced frequency of hospital admission from exacerbation of COPD, reduced incidence of myocardial infarction and reduced overall mortality.

Identification and treatment of cardiovascular disease in COPD, possibly as a result of systemic inflammation, may improve mortality and morbidity in this population. However there has not as yet been any double-blind placebo-controlled trial to support this hypothesis. Furthermore a recent logistical regression analysis of cardiovascular risk in relation to lung function suggested that the increased cardiovascular disease in COPD may relate to traditional risk factors. This study found that after correcting for age, sex, smoking history, hypertension, cholesterol and diabetes, the risk of cardiac disease associated with airflow obstruction was significantly reduced.<sup>160</sup>

## Nutrition in COPD

A further aspect of the systemic effects of COPD is adverse nutritional effects and low body mass. Several studies have demonstrated an association between poor nutrition and COPD. Low fresh fruit intake is associated with lower FEV<sub>1</sub><sup>8</sup> and development of airflow limitation is associated with reduced dietary vitamin C intake<sup>161,162</sup> whilst high intake of fruit and whole grains appears to protect against declining lung function.<sup>8</sup> Weight loss or a low BMI is associated with increased COPD mortality, this relationship being strongest in severe COPD.<sup>14,163,164</sup> Therefore targeting COPD patients with low BMI and offering nutritional support may improve outcomes. However studies to date have not been encouraging.

A meta-analysis published in 2000 identified 9 randomized controlled trials of nutritional supplementation in COPD. These studies did not demonstrate any significant impact from supplementation with no improvement in lung function or exercise capacity,<sup>165</sup> although this may in part relate to the severity population studied.<sup>166</sup> Creatinine supplementation in a randomized control trial (RCT) of 38 patients improved health status and fat free mass but not exercise capacity.<sup>167</sup>

A more recent RCT trial showed that nutritional supplementation resulted in improved exercise capacity in well nourished, but not undernourished, patients.<sup>168</sup> One possible explanation for the rather poor results in this trial is that the subgroup of patients who have relative anorexia and high levels of inflammation are least likely to respond to nutritional supplementation.<sup>169</sup> Treating the inflammation



which causes low BMI in these subjects may be more important than treating the outcome. However this hypothesis requires testing.

A specific aspect of COPD associated with poor nutrition is muscle wasting. Schols et al reported in 1993 that 49% of patients attending for pulmonary rehabilitation had evidence of reduced muscle mass.<sup>170</sup> Subjects with reduced muscle mass have reduced exercise capacity and poorer health-related quality of life.<sup>171</sup>

Several factors present in COPD impact on the loss of skeletal muscle including hypoxia,<sup>172</sup> the use of oral and inhaled glucocorticoids,<sup>173</sup> systemic inflammation<sup>174</sup> and oxidative stress.<sup>175</sup> Local inflammation may be reduced in the muscles of subjects with COPD compared to controls although the implication of this finding is not yet fully understood.<sup>176</sup>

Pulmonary rehabilitation has been shown to improve exercise capacity and health status in COPD.<sup>177</sup> Creatine supplementation in subjects undertaking pulmonary rehabilitation programmes has been shown to further improve quality of life, but not exercise capacity.<sup>167</sup> As yet there are no studies which demonstrate improved mortality associated with increasing muscle mass in COPD and there appears to be limited evidence of the benefit of nutritional supplementation alone in patients with reduced skeletal muscle mass.

## Osteoporosis in COPD

A further disease associated with the systemic effects of COPD is osteoporosis.<sup>178</sup> Cigarette smoking is an independent risk factor for osteoporosis in healthy subjects.<sup>179</sup> McEvoy et al demonstrated in 1998 a high incidence of vertebral fractures in subjects with COPD (50%) compared to controls. Furthermore, COPD subjects on regular glucocorticoid had increased risk of vertebral fracture compared to steroid naïve subjects with an odds ratio of 1.38 for ICS and 2.16 for oral.<sup>180</sup>

Together with increased glucocorticoid use, several other factors have been identified which influence osteoporosis development. A recent study of osteoporosis in COPD demonstrated high incidence of low bone density, with a significant relationship between bone mineral density and disease severity as assessed by GOLD stage. Subjects from GOLD stage IV had a 7.6-fold increase risk of low bone mineral density compared to GOLD stage II. Low BMI was also a predictor of low bone mineral density.<sup>181</sup>

The reduced mobility and muscle strength associated with COPD is also a risk for development of osteoporosis.<sup>12</sup> Subjects with COPD have lower levels of vitamin D,

crucial for bone development.<sup>182</sup> The increased systemic inflammation in some subjects with COPD may also play a role.<sup>178</sup> Along with the direct impact of osteoporosis on morbidity and mortality, the kyphosis associated with vertebral fracture can have a negative impact on lung function.<sup>183</sup> These studies would suggest that subjects with high corticosteroid use, low BMI and high levels of inflammation are at risk of osteoporosis and targeted intervention may be of benefit.

A recent review by Gluck and Colice<sup>184</sup> recommended assessment for osteoporosis in both males and females with COPD aged greater than 60 with a significant smoking history. However to date there is limited information about the benefits of intervention specifically in COPD. Risedronate has been shown to both reduce the risk of vertebral fracture in glucocorticoid induced osteoporosis<sup>185</sup> and maintain bone mineral density (BMD) with steroid treatment.<sup>186</sup> Alendronate also prevents glucocorticoid induced osteoporosis.<sup>187</sup> These studies included all disease processes requiring steroid. In respiratory medicine there is evidence that biphosphonates maintain BMD in asthmatics on high dose inhaled treatment,<sup>188</sup> however there are no published data on the effectiveness of pharmacological treatment on COPD alone.

Non pharmacological interventions are also available. There is evidence that increasing skeletal muscle with pulmonary rehabilitation improves BMD compared to control, as does smoking cessation.<sup>189</sup>

Systemic inflammation in COPD results in several conditions which have an impact on health as described above. Low mood is a further consequence of COPD, although this is unlikely to be due to inflammation. The benefits of identification and management of mental health associated with COPD is discussed below.

## Depression and anxiety in COPD

There is an increased incidence of anxiety in COPD, a diagnosis of generalized anxiety disorder is seen in between 10% and 16% of subjects with compared to 4%–5% in the general population.<sup>190</sup> Generalized anxiety disorder in COPD is associated with impaired quality of life.<sup>191</sup> Despite evidence of a high prevalence of anxiety in COPD, there is limited evidence of benefit from therapy.<sup>190</sup> A case report of 7 patients reported improved anxiety and dyspnea after management with the antidepressant setraline<sup>192</sup> but there does not appear to be any large studies of treatment for this condition. Along with anxiety there appears to be a high incidence of depression in COPD.

Kunik et al screened 204 patients with COPD using a well established tool for evaluation of mental disorders. Thirty-nine percent were diagnosed with depression and 26% with both depression and an anxiety disorder. Only 31% of those subjects diagnosed with either depression or anxiety were receiving treatment.<sup>193</sup> As with anxiety there are little significant study data on the impact of treatment of depression in COPD.<sup>15</sup>

## Conclusion

Identifying the phenotype of COPD has become a hot topic in recent literature.<sup>194–197</sup> The purpose of this review has been to discuss treatment of various aspects of COPD, including the pathological processes involved, clinical phenotypes and systemic manifestations. It is apparent that there is significant variation in many of these aspects in the COPD population. Furthermore, many of these have significant impact on morbidity and mortality. Targeting COPD treatment to the individual and actively identifying and managing the inflammatory process involved along with pulmonary and systemic manifestations present in that patient may help to reduce this impact. However, as yet, there is limited evidence for benefit in this approach and further study of targeting phenotypes is required.

## Disclosures

The authors disclose no conflicts of interest.

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