Ministry of Defence

Synopsis of Causation

Chronic Obstructive Pulmonary Disease

Author: Dr Robert Whittle, Medical Author, Medical Text, Edinburgh
Validator: Dr Noel Snell, Royal Brompton Hospital, London

September 2008

Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1 Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressive disorder of the lungs characterised by an increased resistance to air flow, with related symptoms such as chronic productive cough, expectoration, breathlessness and wheeze.[1]

1.2 COPD is now the generally preferred term for the disease and has been accepted by most authorities, including the British Thoracic Society.[2]

1.3 This term supersedes a number of previously used clinical labels and acronyms, including chronic obstructive airways disease (COAD), chronic airflow limitation (CAL) and non-reversible obstructive airways disease (NROAD). The term was coined to encompass both major phenomena of the condition, i.e. the narrowing of airways and the destruction of lung tissue.

1.4 The British Thoracic Society has defined COPD as 'a chronic, slowly progressive disorder characterised by airflow obstruction … that does not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilators or other therapy.[2] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as 'a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases'.[3]

1.5 The components of COPD are chronic bronchitis and emphysema, either of which may predominate. In addition there is often a variable degree of hyper-reactivity of the airways, which may be temporarily reversible with bronchodilator treatment. In an individual patient with COPD, chronic bronchitis or emphysema may be present independently or all three components may coexist to various degrees;[1] however, some degree of irreversible airways obstruction must always be present for the diagnosis of COPD to be made.

1.6 **Chronic bronchitis** In this component of COPD there is excess secretion of mucus into the air passages. Chronic bronchitis is often defined as the presence of cough that is productive of sputum on most days for at least three months of two successive years, in a person in whom other causes of chronic cough have been excluded.

1.7 **Emphysema** This component of COPD refers to a condition of abnormal dilatation of the terminal air spaces of the lung, with destruction of their walls, and as such it is an anatomically defined condition – it is difficult to diagnose radiologically until it has become fairly severe (although newer techniques such as high-resolution computed tomography (CT) scans are diagnostic,[4] and novel techniques such as aerosol bolus dispersion for quantifying emphysema are under development). Therefore, emphysema is often made as a presumptive diagnosis on the basis of clinical findings that suggest its presence. It may be identified retrospectively, at post-mortem examination.

1.8 **Hyper-reactivity of the airways** This component is usually also present in COPD to a variable extent. It predisposes to constriction of the airways that is partly reversible by medication. It shares some of the features of incompletely reversible asthma, and indeed the distinction between the two has not yet been clarified precisely. Most patients with COPD show some temporary improvement after using bronchodilators. However, much of this improvement may be due to a reduction in lung hyperinflation rather than to a direct bronchodilator effect. The apparent overlap between COPD and asthma is reflected in outmoded terms such as chronic asthmatic bronchitis and adult wheezy bronchitis.

1.9 The importance of distinguishing between this aspect of COPD and chronic incompletely reversible asthma relates largely to the prognosis for progression and mortality, which is considerably worse in COPD. However, although it is widely presumed that the pathogenesis of asthma and COPD is entirely different, there is some evidence that asthma is in fact a risk factor for the development of COPD.[5,6]

1.10 Certainly the two conditions can co-exist, and there is evidence of a marked increase in sputum eosinophils (normally considered a marker of allergic disease) in a proportion of patients with COPD when they experience acute exacerbations of their disease.

1.11 Some patients with chronic bronchitis and/or emphysema show no signs of airways obstruction. Such patients are excluded from the diagnosis of COPD, as are those with completely reversible airways obstruction (i.e. asthma). Similarly, the term COPD does not include obstruction of the airways that is due to specific pathology such as clinically significant bronchiectasis, post-tuberculous fibrosis, pulmonary oedema and obliterative bronchiolitis, although use of high-resolution CT scanning shows that 30–40% of patients with COPD have a degree of unsuspected bronchiectasis.

1.12 COPD is a major cause of chronic morbidity and mortality and is currently the fourth leading cause of death in the world. In the UK, approximately one death in 20 is attributable to COPD. Further increases in its prevalence and mortality can be predicted in the coming decades.

2. Clinical Features

2.1. The onset of COPD is insidious. Typically, it gradually manifests itself in the fifth, sixth or seventh decades of life. On the one hand, it may present with a chronic productive cough and with recurrent, increasingly frequent bronchial infections in which the sputum becomes purulent and increased wheeze is experienced. On the other hand, the main complaint may be gradually increasing breathlessness on effort. Usually the patient reports a combination of these two types of symptom.

2.2. There is usually a gradual progression of disability over a period of years, with increasingly frequent absence from work, reduced exercise tolerance and increased restriction of activities. The sedentary patient may fail to notice breathlessness until a significant proportion of lung function has been permanently lost.

2.3. Early in the progress of the disease there may be few clinical signs and cases of mild to moderate severity are difficult to diagnose on clinical grounds alone. Even in moderately advanced COPD, routine chest X-rays often fail to show significant changes.

2.4. Tiredness is a very common feature of moderate-to-severe COPD, and other systemic manifestations (e.g. loss of weight and skeletal muscle dysfunction) may also be noted.[7] These clinical features may be medicated by cytokines (e.g. tumour necrosis factor, interleukin-6).

2.5. The most practical and accurate screening of at-risk patients is by means of spirometry, whereby a reduction in the forced expiratory volume in 1 second (FEV_1) may be identified. Spirometry yields other measurements of lung function, which can further refine diagnostic and therapeutic issues, e.g. forced vital capacity (FVC).

2.6. As a general rule, a patient's activity is significantly restricted when the FEV_1 falls to about 50% of the predicted normal for age, sex and height, while a patient in whom the FEV_1 is less than 30% of predicted normal is usually severely incapacitated.

2.7. Early diagnosis of COPD is important in order to give advice on stopping smoking and so avoid further irreversible damage to the lungs.

2.8. The FEV_1 is also a good indicator of prognosis in that it predicts all-cause mortality. However, it is not so useful in monitoring treatment, for which other measures of lung function (e.g. the residual volume, the total lung capacity, the inspiratory capacity) may be more sensitive.

2.9. Complications include acute respiratory infections, pneumothorax (particularly in older patients) and pulmonary embolism. Left ventricular heart failure may occur, possibly as a result of myocardial hypoxia, and this is particularly dangerous because maintenance of cardiac output is essential to help compensate for the low arterial oxygen caused by the COPD.

2.10. The major change encountered in the blood is a raised haematocrit (secondary polycythaemia). This increases blood viscosity and contributes to the flow resistance in the vascular bed of the lung. Some patients with severe COPD develop marked pulmonary hypertension, right ventricular dysfunction and tricuspid incompetence (a concatenation of clinical features that is sometimes referred to as **cor pulmonale** – heart disease secondary to lung disease). Indeed, right ventricular failure is a much more common complication of COPD than left ventricular failure.

3. Aetiology

3.1 **Endogenous factors** There are a number of endogenous factors associated with COPD, but none is as important as cigarette smoking in the aetiology.

3.1.1 **Genetic factors: Alpha-1 antitrypsin deficiency** Normally, the lung is protected from the damaging effect of inflammation by the naturally occurring protein, alpha-1 antitrypsin (AAT), also known as alpha-1 protease inhibitor. AAT protects the alveolar walls from destruction by leukocyte elastase, a substance released by neutrophils activated by inflammatory processes. If AAT is deficient or absent, the end result may be emphysema. Cigarette smoke may overwhelm the body's ability to produce AAT and in addition may directly inactivate it.

3.1.2 AAT deficiency can result from a rare inherited autosomal-recessive disorder that occurs in one in 3000 live births. Familial AAT deficiency accounts for less than 5% of all cases of COPD.

3.1.3 Patients with AAT deficiency are at increased risk of COPD and they are likely to develop it at an earlier age than those who develop COPD as a result of cigarette smoking.[8] People who are heterozygous for the Z mutation probably also have an increased rate of FEV_1 decline, although less severely so than homozygotes.[9]

3.1.4 **Other genetic factors** Other genetic factors, as yet undefined, probably play a role in the development of COPD.[9]

3.2 **Other endogenous factors** Certain other endogenous factors have been said to affect the risk of developing COPD:

3.2.1 **Low birth weight** Low birth weight may predispose to the later development of COPD, possibly because of a correlation between birth weight and the maximum lung function that is achieved before the natural age-related decline begins. The relevance of this factor is uncertain at present.

3.2.2 **Sex** Many population-based studies have suggested that men are at higher risk than women of developing COPD, even when differences in smoking are controlled for.[8] However this relationship is by no means certain, and in any case the incidence of COPD in women is increasing as more succumb to the effects of long-term smoking. Indeed, other studies have suggested that, for a given amount smoked, women have a higher risk of COPD than men.[10,11]

3.2.3 **Race** Some races (e.g. Chinese) seem to have a lower susceptibility to developing COPD than others, although blacks are generally more susceptible than whites.[12]

3.3 **Exogenous factors: cigarette smoking** By far the most important factor in the aetiology of COPD in the developed world is cigarette smoking,[2,13] and It has been estimated that smoking accounts for 80–90% of the risk of developing COPD.[8]

3.3.1 The link between cigarette smoking and COPD is well established. Data from many studies of various designs have consistently shown that cigarette smokers have higher rates of prevalence and incidence for all the components of COPD (emphysema, chronic bronchitis and airway hyper-responsiveness) than non-smokers. They also have a higher death rate from emphysema and chronic bronchitis.[8]

3.3.2 It has been said that there is a varying susceptibility to smoking-induced lung damage in the population and that only 15–20% of smokers will develop COPD.[8] The reasons for this are probably that COPD develops more slowly in some people than it others, perhaps as a result of differences in genetic susceptibility. A long-term study has shown that [8], if followed for long enough, 50% of smokers develop COPD,[14] and probably 100% would if they could be followed for even longer and if they did not die before showing the changes of COPD.

3.3.3 Even in healthy people there is an inevitable and progressive decrease in lung function with age. This is reflected in a decline in the FEV_1. In patients with COPD who continue to smoke this decline is accelerated. Stopping smoking slows the abnormal rate of decline significantly and may extend life-span.

3.3.4 There is some relation to the total dose of tobacco inhaled, so the age of starting smoking is significant, as is the number of cigarettes smoked over the years.[15] Conventionally this is recorded as 'pack-years' (one pack-year being equivalent to smoking 20 cigarettes a day for one year). The tar content of the cigarettes, however, does not appear to influence the condition.

3.3.5 Pipe and cigar smoking may also cause the disorder, but to a much lesser extent.[8]

3.3.6 **Passive smoking.** The role of passive smoking in the development of COPD is still unclear. It is known, for example, that children living with smoking parents (particularly a smoking mother) have a higher risk of developing respiratory symptoms and have small but measurable differences in lung function compared with other children, but the significance of this to the future development of lung disease is not known.[8,15] There is also no clear evidence to link passive smoking in adulthood with COPD.

3.4 **Other exogenous factors** Several other exogenous risk factors influence the development and course of COPD.

3.4.1 **Environmental pollution** Several studies have demonstrated that people living in urban areas have lower lung function (as measured by FEV_1) and higher levels of respiratory symptoms (cough and phlegm production) than people living in non-urban areas. Although the specific pollutants involved have not been proved, a causal relationship between air pollution and loss of pulmonary function over time seems likely.[15] There also may be an indirect causal link in that air pollution may increase the risk of childhood respiratory illness, which may increase the risk of COPD.[16] However the contribution of atmospheric pollution is small compared with the effect of smoking, although episodes of increased pollution do lead to epidemics of acute exacerbation of COPD, as occurred, for example, with the 'Great Smog' of 1952 in London.

3.4.2 **Indoor pollution** In some cultures (e.g. in Hong Kong, India, the Middle East, Nepal, New Guinea) long-term exposure to fumes from domestic cooking devices in a poorly ventilated environment may be associated with COPD.[15,17] In these populations COPD may be more common in women than in men.

3.4.3 **Occupation** Occupational exposure to dusts may increase a person's susceptibility to COPD. High-risk occupations include mining, jobs that involve contact with cadmium, construction work that involves handling cement, metal work and grain handling. Data from some studies suggests that the role of dust exposure in the development of COPD in non-smokers is not certain, and that

there may be an interaction between smoking and exposure to dust in the development of COPD.[18] In any case the effect of smoking far outweighs any influences from the work environment.

3.4.4 Occupational exposure to gases and fumes is less clearly associated with COPD, possibly exerting an effect on respiratory symptoms but not on long-term airflow obstruction.[19]

3.4.5 **Childhood respiratory infections** Repeated respiratory infections during childhood may slow growth and reduce the maximum lung function attained before the natural age-related decline begins. This may increase the likelihood of developing symptoms from COPD in later life,[20] although no definite association has been proved.[15]

3.4.6 **Adult respiratory infections** Evidence that respiratory infections during adulthood lead to COPD is lacking. Once COPD is established, however, episodes of respiratory infection, either viral or bacterial, cause exacerbations of the symptoms, which may be very troublesome.[21] Repeated episodes, which occur in many patients with COPD, may accelerate the decline in lung function.[19,22]

3.4.7 **Socioeconomic deprivation** There is evidence that COPD is more prevalent in areas of socioeconomic deprivation.[23] This may simply be due to the higher proportion of the population that smokes, or to the increased likelihood of occupational exposure.

3.4.8 **Diet** There is some evidence to suggest that increased dietary intake of omega-3 fatty acids (found in oily fish) may reduce the risk of developing COPD.[24] However, the association is far from clear.[15]

3.4.9 **Other factors** There appears to be no association between the development of COPD and pet ownership, alcohol use or regular exercise.[25] There is no evidence that adverse climatic factors have any bearing on the aetiology of COPD.

4. Prognosis

4.1 COPD is a progressive condition, and once established the gross pathological changes in the lung are irreversible with currently available therapies.

4.2 Quality of life is often severely and increasingly affected by breathlessness and other respiratory symptoms, which are often exacerbated by respiratory infections.

4.3 Cessation of smoking (in the vast majority of patients with COPD, who are smokers) usually slows the rate of decline in lung function and reduces bronchial hyper-responsiveness, although inflammatory changes may persist.[26]

4.4 Management strategies depend on the degree of disability. Bronchodilators are symptomatically helpful in the majority of patients (anticholinergics and beta-agonists being similarly effective, although individual patients may respond better to one or the other).

4.5 The role of inhaled corticosteroids is still being evaluated. They appear to give a modest improvement in FEV_1 and to reduce the incidence of acute exacerbations and the rate of decline of health-related quality of life, but they do not reduce the rate of decline in lung function.[27]

4.6 If an acute exacerbation is suspected to be infective in origin (indicated by increased cough and sputum volume and a change in sputum colour), appropriate antibiotics should be prescribed. Systemic (but not inhaled) corticosteroids have been shown to shorten the duration of hospitalisation for acute exacerbations.[28] There is some evidence that mucolytic agents may reduce the number and duration of acute exacerbations.[29]

4.7 Long-term oxygen therapy for at least 18 hours per day reduces mortality in severe COPD.

4.8 Lung reduction surgery shows some promise in patients with severe emphysema.

4.9 Prompt recognition and treatment of complications such as pneumothorax and cor pulmonale is important.

4.10 Prognosis depends to a large extent on the degree of airflow obstruction, with patients who have mild airflow obstruction having a survival rate that is only slightly worse than smokers without airflow obstruction. Once airflow obstruction is severe (indicated generally by FEV_1 somewhat 50% of the predicted normal for age, sex and height), mortality rate at 1 year is approximately 30% and at 10 years approximately 95%.[8]

4.11 Death is usually due to a medical complication of COPD, such as pneumonia, pneumothorax, overwhelming infection or cor pulmonale.

5. Summary

5.1 COPD is a progressive condition characterised by chronic airway obstruction. It has multiple components – emphysema, chronic bronchitis and hyper-reactivity of the airways. In an individual patient with COPD, chronic bronchitis or emphysema may be present independently or all three may coexist to various degrees.

5.2 The condition has an insidious onset and symptoms frequently go unrecognised by the patient until significant irreversible respiratory damage has occurred.

5.3 It is caused almost exclusively by smoking, although certain occupations may predispose to it, and urban atmospheric pollution contributes to it. Rarely, it may be caused by an inherited abnormality. It is not caused by exposure to adverse climatic conditions or by respiratory infections in adulthood.

5.4 Once established the pathological changes are irreversible and prevention of progressive disability by early diagnosis and cessation of smoking is of prime importance. Current treatments are generally symptomatic. The only interventions that have been proven to modify the course of COPD are stopping smoking and, in hypoxaemic patients, long-term oxygen therapy.

6. Related synopses

Asthma

7. Glossary

bronchiectasis	Chronic dilatation of one or more bronchi (one of the large air passages in the lung).
bronchodilator	A medication, often taken by inhalation, that dilates the airways.
cytokines	Proteins that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types, rather than specialist glands.
fibrosis	A process whereby normal tissue is replaced by scar tissue.
forced expiratory volume in 1 second (FEV_1)	The volume of air that a person can breathe out in 1 second, usually expressed in litres or as a percentage of the predicted normal for the patient's age, sex and height; measured by spirometry.
forced vital capacity (FVC)	The total maximum volume of air that a person can breathe out, from maximal inspiration to maximal expiration, usually expressed in litres or as a percentage of the predicted normal for the patient's age, sex and height; measured by spirometry.
haematocrit	The proportion of the volume of whole blood that is occupied by red blood cells (expressed usually as a percentage, sometimes as a decimal fraction); it is measured as part of a full blood count and gives a non-specific indication of the both the number and the size of the red blood cells
hypoxaemia	Inadequate oxygenation of the blood. Hence *hypoxaemic*.
hypoxia	Lack of oxygen.
inspiratory capacity	The volume of air that can be inspired from full expiration.
obliterative bronchiolitis	Concentric narrowing of the bronchioles (small air passages) caused by fibrosis.
pneumothorax	Air or gas in the pleural cavity (the space between the two layers of the pleura, which line the lungs).
polycythaemia	an increase in the total mass of cells in the blood;

	primarily used to refer to an increase in the mass of red blood cells
pulmonary oedema	Accumulation of fluid in the lungs.
residual volume	The volume of air remaining in the lung after full, forced exhalation.
spirometry	A lung function test in which the patient breathes into a volume-measuring device (a spirometer). It is used to measure, for example, the FEV_1 and the FVC, which are used in the diagnosis of various lung conditions and also to monitor the effectiveness of treatment.
total lung capacity	The volume of air that can be held within the lungs at full inspiration.
tricuspid incompetence	A condition in which the tricuspid valve of the heart (the valve between the right atrium and the right ventricle) fails to close sufficiently tightly during the cardiac cycle, allowing some of the blood in the right ventricle to flow back into the right atrium during contraction of the ventricle; also known as tricuspid regurgitation

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