B (NF-κB) and inhibitors of p38 mitogen-activated protein-kinase, although none of these have reached clinical trials.

Drug Delivery

Current inhaler devices have been developed to deliver drugs to the conducting airways in patients with asthma. However, COPD predominantly affects peripheral airways and lung parenchyma, which may not be optimally targeted by current inhalers. It is likely that new inhaler devices delivering aerosols of smaller particle size or systemic drugs are more likely to be useful in COPD. In the future, targeted delivery to specific cells, such as macrophages, might be possible, particularly if new treatments have systemic toxicity. There is also a rationale for giving systemic therapies to reach the lung periphery and to treat systemic features of the disease.

See also: **Bronchodilators**: Anticholinergic Agents; Beta Agonists. **Chronic Obstructive Pulmonary Disease**: Emphysema, Alpha-1-Antitrypsin Deficiency; Emphysema, General. **Corticosteroids**: Therapy. **Leukocytes**: Pulmonary Macrophages. **Oxygen Therapy**.

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Acute Exacerbations

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Abstract

Chronic obstructive pulmonary disease (COPD) is a condition characterized by lower respiratory tract symptoms, airflow obstruction, and airway inflammation. The natural history of COPD is punctuated by episodes of acute deterioration in respiratory health termed exacerbations. Exacerbations are responsible for much of the morbidity, mortality, and healthcare costs associated with COPD, and also affect the rate of decline in lung function. Most exacerbations are caused by episodes of tracheobronchial infection. The clinical features comprise a worsening in symptoms beyond usual day-to-day variation. Examination may reveal tachypnea and signs of respiratory failure. Pathologically, exacerbations are associated with an increase in airway and systemic inflammation which, at least in more severe disease, is predominantly neutrophilic. Simple investigations are indicated to exclude differential diagnoses and assess exacerbation severity. Treatment aims to support respiratory function whilst drugs aimed at the underlying cause are able to act. The cornerstone of therapy is inhaled bronchodilators, with oral corticosteroids in all but the mildest exacerbations. Antibiotics are indicated if there has been a change in the character of the sputum. Some patients with respiratory failure will require supplemental oxygen or assisted ventilation. Strategies to prevent exacerbations include inhaled corticosteroids, long acting bronchodilators, and influenza vaccination.

Introduction

It would be difficult to exaggerate the importance of chronic obstructive pulmonary disease (COPD) as a global health problem for the twenty-first century. COPD is the fifth commonest cause of death in the world and, unlike other prevalent diseases, death rates from COPD continue to rise. Much of this mortality is related to episodes of acute deterioration in respiratory health termed exacerbations.

COPD is defined by the presence of lower respiratory tract symptoms, poorly reversible airflow obstruction, and inflammation of the lung. The natural history of COPD comprises progression of this airflow obstruction, associated with worsening symptoms and increasing limitation to daily activities. However, patients are also prone to periodic

deteriorations in respiratory health termed exacerbations. Exacerbations are important events that cause much of the morbidity, mortality, hospital admissions, and therefore healthcare costs associated with this disease. In the UK, around 10% of acute medical admissions to hospital may be attributed to exacerbations of COPD, the in-hospital mortality is 10%, and exacerbations account for 70% of the direct medical costs attributable to COPD.

Exacerbations become more frequent and more severe as the severity of the underlying disease increases. In patients with moderately severe COPD, the median annual exacerbation frequency is between two and three events per year. However, this masks important differences between individual patients, some of whom are more susceptible to exacerbation than others. The factors determining a greater susceptibility to exacerbation are poorly understood but are thought to include the presence of daily bronchitic symptoms, greater severity of underlying disease, greater lower airway inflammation, and the presence of lower airway bacteria in the stable state.

Exacerbations are extremely heterogeneous events responsible, at one extreme, for life-threatening episodes of respiratory failure in patients with severe COPD, but to no more than a troublesome and transient increase in symptoms in patients with milder disease. This heterogeneity has caused debate about exactly how an exacerbation should be defined, but for practical purposes an exacerbation is a sustained episode of increased symptoms, acute in onset, that is beyond the patient's usual day-to-day variation. This may or may not necessitate a change in therapy.

In addition to direct effects on morbidity and mortality, exacerbation frequency also affects the natural history of disease. Patients susceptible to frequent exacerbations experience an accelerated decline in forced expiratory volume in 1 s (FEV_1), and have a poorer quality of life.

The importance of exacerbations are summarized in Figure 1.

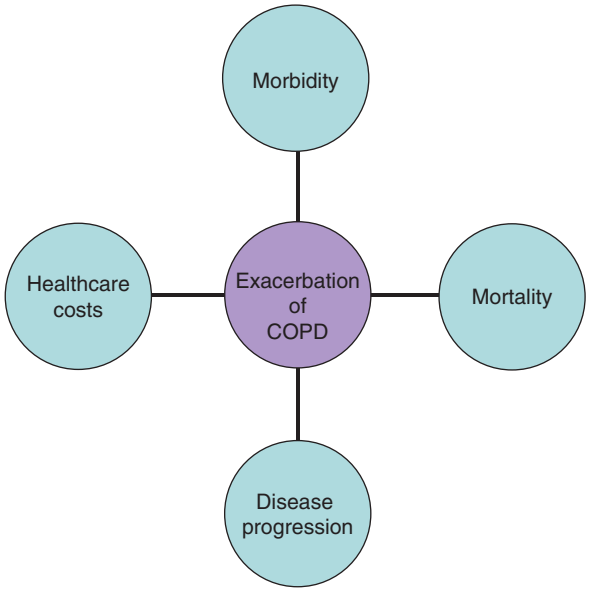

Figure 1 The importance of exacerbations in COPD.

Table 1 The most important bacterial and viral pathogens isolated from lower airway samples in patients with exacerbations of COPD

Bacteria	*Viruses*
Haemophilus influenzae	**Rhinovirus**
Moraxella catarrhalis	Coronavirus
Streptococcus pneumoniae	Influenza
Pseudomonas aeruginosa	Parainfluenza
	Adenovirus
	Respiratory syncytial virus

Bold type indicates the most common isolates.

Etiology

It is generally accepted that exacerbations are caused by episodes of tracheobronchial infection, and perhaps pollution. Evidence for the former is derived from reports demonstrating a higher prevalence of pathogens in samples taken from the lower airways at the time of exacerbation than in the stable state. Evidence that pollution causes exacerbations arises from relationships between the degree of air pollution and hospital admissions for COPD. PM_{10} (particulate matter up to 10 μm in size), largely produced by diesel exhaust, appear particularly important. In a proportion of exacerbations, the cause remains obscure.

A number of studies have investigated the isolation frequency of individual pathogens at exacerbation of COPD. The relative prevalence of specific agents varies by the methodology of the study, and the severity of both the patient and exacerbation. In patients with moderate to severe underlying disease, bacterial and viral pathogens may each be isolated from lower airway samples in approximately 50% of exacerbations. The most important bacterial and viral pathogens are listed in Table 1.

The identification of organisms in lower airway samples at the time of exacerbation has been taken to imply causation, but the issue is complex because pathogenic microorganisms may also be found in the lower airways of patients with stable COPD. This is especially true for bacteria where up to 50% of patients with severe disease have the same bacterial species present in the stable state, a phenomenon

termed lower airway bacterial colonization. More recently, it has been suggested that a change in the colonizing strain may result in exacerbation, and further evidence that bacteria do indeed cause exacerbations may be drawn from the clinical benefit observed in trials of antibiotics during such events. There is ongoing controversy regarding the role of atypical organisms such as Chlamydia and Mycoplasma in the etiology of exacerbations.

The most important viral pathogen is rhinovirus. Exacerbations in which a virus is isolated, or those associated with coryzal symptoms, are more severe as assessed by changes in symptoms and lung function. Reflecting the circulation of respiratory viruses, exacerbations are more common in the winter than the summer months.

Pathology

COPD is defined as a disease state characterized by lower respiratory tract symptoms and airflow obstruction in association with an abnormal inflammatory response within the lung. A number of studies using endobronchial biopsy, bronchoalveolar lavage, sputum, and exhaled markers have demonstrated that airway inflammation is increased at exacerbation compared to the baseline state. In studies examining endobronchial biopsies, exacerbations in mild COPD were associated with an infiltration of eosinophils, whilst in more severe disease the infiltrate was characterized by neutrophils. Regarding soluble mediators, increased concentrations of various neutrophilic indices have been reported including interleukin-8, leukotriene-B_4, myeloperoxidase, and elastase.

Clinical Features

Exacerbations are defined as an increase in respiratory symptoms, acute in onset, that is beyond the patient's usual day-to-day variation. These symptoms typically include increased dyspnea, sputum volume and sputum purulence, with or without increased cough, wheeze, chest tightness, coryzal symptoms, fatigue, edema, and confusion. Findings on examination are non-specific, but may include tachypnea and use of the accessory muscles of respiration, pursed-lip breathing, polyphonic expiratory wheeze, and, in severe exacerbations, signs of CO_2 retention such as flap and bounding pulse.

Pathogenesis

It is generally assumed (based on observations that pathogens are more frequently isolated at the time of exacerbation and that airway inflammatory markers are increased at exacerbation) that exacerbations result from increased airway inflammation following acquisition of a new pathogen. However, a direct relationship between the clinical severity of exacerbation and degree of airway inflammation has never been demonstrated, and the mechanisms by which airway inflammation results in worsening symptoms and lung function remain largely obscure.

It has also been reported that systemic inflammatory markers such as interleukin-6, fibrinogen, and C-reactive protein are higher at exacerbation than in stable COPD. This is important because of the association between systemic inflammatory markers and cardiovascular events, cardiovascular disease being a common cause of death in COPD. The origin of the systemic inflammatory response is unclear, though a 'spillover' effect from the lung is thought most likely.

Animal Models

There is no animal model of exacerbation of COPD.

Management and Current Therapy

A summary of the clinical management of an exacerbation of COPD is presented in Table 2.

Initial management is directed at excluding differential diagnoses and assessing exacerbation severity. The diagnosis of exacerbation is symptomatic, there is no confirmatory test, and follows exclusion of differential diagnoses such as pneumonia, pneumothorax, pleural effusion, lung carcinoma, pulmonary embolus, or cardiac disease which may also occur in a patient with COPD and mimic the presence of exacerbation. Such diagnoses may generally be excluded on the basis of a clinical history, examination, and simple investigations such as the chest radiograph and electrocardiogram.

Assessment of severity is important for guiding decisions on initial treatment strategy and the need for hospital admission. However, there is no widely accepted severity scoring system. pH, more useful than $PaCO_2$ as a marker of acute changes in alveolar ventilation, and PaO_2 are important indicators. A pH <7.30 suggests a severe exacerbation. It should be remarked that measuring lung function is usually unhelpful as changes at exacerbation may be small, absolute values may be misleading in the absence of a baseline, and the tests may be difficult to perform in patients who are acutely unwell.

The principles of treatment are to support respiratory function whilst therapies directed against the underlying pathophysiology, such as antimicrobial and anti-inflammatory agents, are able to act.

Table 2 A summary of the management of an acute exacerbation of COPD in the hospital setting

Principle	*Details*
Assess severity	Clinical findings and pH/arterial blood gas tensions
Give oxygen	Controlled therapy, aiming for arterial saturations 90–92%. Reassess blood gas tensions after 30 min
Give bronchodilators	Increased dose or frequency of β_2-agonists and/or anticholinergics. Nebulised or inhaled via spacer
Give corticosteroids	Oral, or with initial intravenous dose
Give antibiotics	When there has been a change in the character of sputum. Usually oral
Consider need for ventilatory support	In respiratory failure not responding to controlled oxygen therapy
Also consider	Fluid balance, anticoagulation, comorbidities, and need for additional therapies, e.g., intravenous theophylline

The cornerstone of therapy, all that may be required in the most mild exacerbations, is an increase in the dose or frequency of inhaled bronchodilators. Although the airflow obstruction in COPD is, by definition, largely irreversible, there may be additional bronchoconstriction at exacerbation and these drugs can achieve a dramatic symptomatic response through effects on dynamic hyperinflation. Short-acting β_2-adrenoceptor agonists such as salbutamol have a more rapid onset of action and are preferred to anticholinergics such as ipratropium. Combinations of β_2-agonists and anticholinergics are often recommended in exacerbations not responding to β_2-agonists alone. Inhaled therapy via a large volume spacer is as effective as wet nebulization.

Exacerbations not responding to an increase in bronchodilators alone should be treated with systemic corticosteroids. The rationale is that these drugs may act on the increased inflammation observed at exacerbation, though specific evidence for this is lacking. Systemic corticosteroids result in a more rapid improvement in FEV_1, though at the expense of more frequent adverse events, particularly hyperglycemia. A dose of 30–40 mg prednisolone equivalent for 10–14 days is appropriate. Longer courses have no additional effect and there is no benefit from dose tapering. Nebulized budesonide is an alternative.

The evidence of benefit from antibiotics is restricted to those exacerbations characterized by a change in the character of sputum. Sputum purulence is a reliable predictor of the presence of bacteria. Parenteral antibiotics are rarely required and given that coverage of *Haemophilus influenza*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* is required, an oral aminopenicillin, macrolide, or tetracycline agent is most commonly used first line.

Severe exacerbations, or exacerbations in patients with more severe underlying disease, may result in arterial hypoxemia, primarily through ventilation–perfusion imbalance. Oxygen should be administered to correct this respiratory failure. The risk of hypercapnia in a proportion of patients with COPD necessitates that oxygen be administered in a controlled manner. There is little risk of hypercapnia if oxygen is titrated to achieve saturations between 90% and 92%. Achieving adequate oxygenation only at the expense of rising $PaCO_2$ or decreasing pH suggests the need for noninasive ventilation (NIV). NIV is clearly superior to respiratory stimulant drugs such as doxapram in the management of acute hypercapnic respiratory failure, with improvements in mortality, length of hospital stay, and the need for tracheal intubation. NIV is most commonly administered as pressure-cycled bi-level positive airway pressure (BiPAP), and is thought to be effective by off-loading fatigued respiratory muscles.

Patients failing to improve on NIV, or those with a particularly severe exacerbation, may require endotracheal intubation and a period of mechanical ventilation. The decision to institute such therapy in COPD is complex and should consider the wishes and prior functional status of the patient, comorbidities, and the degree of reversibility. However, mortality in the intensive-care unit for patients with COPD, around 20%, is not greater than that seen in respiratory failure from other causes.

Regarding other therapies, there is no evidence that the routine use of theophyllines, heliox, antitussives, mucolytics, or respiratory physiotherapy is beneficial. Other supportive measures such as fluid balance should be attended to, and comorbidities managed. Patients failing maximal therapy or in whom escalation of therapy is inappropriate should be considered for a range of palliative drugs.

Given the importance of exacerbations, considerable benefit may be anticipated from therapies which prevent these events. Large trials have demonstrated evidence for benefit of high-dose inhaled corticosteroids (fluticasone $1000\,\mu g\,day^{-1}$) in patients with moderate to severe underlying disease ($FEV_1 < 50\%$ predicted). Long-acting bronchodilators, both β_2-agonists and anticholinergics, have also been associated with decreased exacerbation frequency, as has

influenza vaccination. Initial trials of antibiotic prophylaxis were carried out many years ago, often in patients with simple chronic bronchitis, and current interest in this area, with more modern drugs, is high. Mucolytics may reduce exacerbation frequency in patients with milder disease. Finally, appropriate use of long-term oxygen therapy and domiciliary NIV in patients with respiratory failure is associated with reduced hospitalization, though a specific effect on exacerbations has not been demonstrated.

See also: **Bronchoalveolar Lavage**. **Chronic Obstructive Pulmonary Disease**: Overview. **Interleukins**: IL-6. **Viruses of the Lung**.

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Relevant Website

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Emphysema, Alpha-1-Antitrypsin Deficiency

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Abstract

Serum α_1-antitrypsin (AAT) deficiency is the most common genetic condition recognized in a Caucasian population of Northern European origin. It predisposes to several clinical entities, although the susceptibility to the development of emphysema predominates. The classical clinical presentation (although not universal) is of early onset basal panacinar emphysema associated with neutrophilic inflammation in the lower airways. Proteinases released from these neutrophils remain active in the lung due to the deficiency of AAT and damage many of the structural proteins (particularly elastin), leading to alveolar destruction and coalescence. The progression is generally more rapid than in nondeficient subjects, leading to respiratory failure and cor pulmonale. Therapy is predominantly along conventional lines for chronic obstructive pulmonary disease, although AAT-deficient patients are more likely to be accepted as potential lung transplant recipients because of their younger age and general lack of comorbidity. Augmentation therapy is available in some countries, and circumstantial evidence suggests that it is effective in disease modification. However, no suitably powered controlled clinical trial has been undertaken to prove this hypothesis.

Serum deficiency of α_1-antitrypsin (AAT) was first noted and described by Laurell and Eriksson in 1963. The authors identified five serum samples with an absence of a protein band in the α_1 region on paper electrophoresis. Review of the patients indicated that three had emphysema at an early age (younger than 45 years old) and a fourth individual had a family history of emphysema. In subsequent studies, it became apparent that all individuals possessed two genes for AAT that were expressed in a codominant manner. However, some genes led to decreased serum levels, and whereas heterozygotes did not appear to be excessively at risk for developing emphysema, homozygotes did show such a risk. This led to the apparent autosomal recessive nature of inheritance of the disease trait (**Figure 1**).