

REVIEW SERIES

Chronic obstructive pulmonary disease • 6: The aetiology of exacerbations of chronic obstructive pulmonary disease

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Exacerbations of COPD are thought to be caused by interactions between host factors, bacteria, viruses, and changes in air quality to produce increased inflammation in the lower airway. The evidence for this and the potential mechanisms by which they result in the characteristic symptoms of exacerbations is reviewed. A better understanding of the causes and processes is needed for the appropriate use of existing treatments and the development of new ones. Future studies need to define populations clearly, stratify for known confounding factors, and should aim to identify clinical correlates so that clinical practice can be modified appropriately.

The natural history of chronic obstructive pulmonary disease (COPD) is one of a progressive decline in ventilatory function, exercise capacity, and health status that is punctuated with varying frequency by exacerbations of symptoms.¹ Patients often consult their primary care physician at the time of exacerbation,² providing a contact early in the course of their disease, and as ventilatory function declines exacerbations lead to an increasing need for medical care and hospitalisation.^{1,3} Patients who suffer the most exacerbations have significantly lower health status⁴ and there is also evidence that exacerbation frequency predicts accelerated decline in lung function,^{5,6} although this remains controversial.^{1,7}

The heterogeneity of COPD is being appreciated increasingly,^{8,9} although this is rarely taken into account in studies of exacerbations which are heterogeneous in their own right. For this and other reasons, conclusions regarding the aetiology, as well as the inflammatory processes involved and their effects, remain unresolved.

DEFINITIONS

It is perhaps surprising that there is no consistently used definition of acute exacerbation of COPD (AECOPD), either in clinical practice or in research. In 1968 Fisher wrote “the value of future work on these lines would be increased if agreement could be reached on the definition of an exacerbation”¹⁰ but, unfortunately, inconsistencies continue. Although there have been attempts to gain consensus,^{11,12} these have been imprecise and have not resulted in universal

adoption in research or clinical practice. However, recently a consensus statement defined exacerbation as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day to day variations that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD”.¹³ It is likely that this definition will become generally accepted in the future.

FACTORS DETERMINING SUSCEPTIBILITY TO EXACERBATIONS

Predictors for frequent exacerbations include various clinical factors such as daily cough, wheeze, and sputum production as well as frequency of exacerbations in the previous year.⁴ A prospective study of 5887 patients published recently showed that COPD smokers with chronic bronchitis had exacerbations 1.6–1.9 times more frequently than those without.⁶ This suggests that factors predisposing to chronic bronchitis also predispose to exacerbation, possibly due to reduced mucociliary clearance¹⁴ that facilitates bacterial invasion of mucosa.¹⁵ Indeed, excess production of mucus, which characterises chronic bronchitis, has been shown to provide a site for bacterial adherence¹⁶ and is associated with increased mortality from bacterial infection.¹⁷

Secretory leukoprotease inhibitor (SLPI) is the main proteinase inhibitor found in the larger airways and submucosal glands¹⁸ and also has antiviral and antibacterial properties.¹⁹ During the stable clinical state the level of SLPI in the sputum has been found to be significantly lower in patients with frequent exacerbations (three or more exacerbations in the preceding 12 months) than in those with infrequent exacerbations.²⁰ In addition, saliva and serum levels of lysozyme (a cationic protein with antibacterial properties with an important role in the first line of host defences) have been studied in patients with chronic bronchitis. Patients with two or more exacerbations over 12 months had significantly lower serum levels of lysozyme, lysozyme activity, and ability of saliva to aggregate non-typeable *Haemophilus influenzae* than those with less than two exacerbations.²¹ Although deficiencies in other host defence mechanisms may also predispose to infection, their role in COPD is yet to be determined.

The role of inflammatory mediators is less clear. Bhowmik *et al* found a relationship between stable state interleukin (IL)-8 and IL-6 concentrations in induced sputum samples and exacerbation frequency.²² However, there was no stratification for the presence or absence of confounding

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factors known to influence one or both of these including spontaneous sputum production, bacterial colonisation,²³ severity of airflow obstruction,²⁴ smoking status,^{25, 26} bronchiectasis,²⁷ or treatment with inhaled steroids, all of which may influence the inflammatory status. On the other hand, Gompertz *et al* found no association between IL-8 levels and exacerbation frequency when all these factors were taken into account,²⁰ which suggests that the high IL-8 concentrations observed by Bhowmik *et al*²² were reflecting another risk factor for exacerbations. However, the observation that plasma fibrinogen levels are also associated with increased rates of hospital admission with exacerbation, as well as with reduced lung function and risk of COPD,²⁸ may support a role for IL-6 which is the primary cytokine regulating fibrinogen expression.

CHARACTERISATION OF COPD EXACERBATIONS

The most widely quoted clinical criteria used in the characterisation of AECOPD are those described by Anthonisen *et al* in what remains the best placebo controlled trial of antibiotics for such episodes.²⁹ In that study exacerbations were divided into three groups: type 1 exacerbations were characterised by increased breathlessness, increased sputum volume, and new or increased sputum purulence; type 2 included any two of these symptoms; and type 3 consisted of any one of the symptoms together with at least one additional feature, including sore throat or nasal discharge within the last five days; unexplained fever; increased wheeze; increased cough; or a 20% increase in respiratory or heart rate compared with baseline. These criteria have been used as a benchmark ever since, and all proposed aetiologies of exacerbation need to establish their relationship to these key features.

PATHOPHYSIOLOGY OF EXACERBATIONS OF COPD

The stable clinical state is characterised by varying degrees of inflammation affecting the large and small airways as well as the alveoli, resulting in mucus hypersecretion, airway narrowing and alveolar destruction, respectively. The main mediators directly responsible for this damage are proteinases released by inflammatory cells, particularly neutrophils, that are found in abundance in the bronchial secretions of patients with COPD, especially as the forced expiratory volume in 1 second (FEV₁) declines.^{24, 26, 30, 31} The neutrophils are recruited from the circulation in response to chemoattractants, particularly IL-8 and LTB₄ via adhesion molecules (such as E selectin and ICAM-1) expressed on the vascular endothelium. These receptors are thought to be upregulated in COPD³⁰ and bind to their counterparts on the neutrophil (such as MAC-1) that are also upregulated.³² The activated neutrophils degranulate releasing neutrophil elastase and other proteinases (cathepsin G, proteinase 3, and matrix metalloproteinases) that are thought to be responsible for various aspects of tissue damage, as well as myeloperoxidase.¹⁸ This latter protein has a green colouration that is useful for monitoring neutrophil influx clinically (see below).³³ A proportion of patients also have increased numbers of bronchial eosinophils which may contribute to inflammation.³⁴⁻³⁶

With this background of mild inflammation there is a general belief that exacerbations are episodes where the inflammatory process is enhanced, although the processes involved and their effects are poorly understood. However, over the past two years in particular there has been an increased interest in the mechanisms involved in exacerbations of COPD,^{2, 20, 22, 37-44} although interpretation and comparison between studies has been hampered by loose definitions, differences in methodology, study populations, and patient characterisation.

Understanding the aetiology of exacerbations requires that potential mechanisms of these episodes are related to the key

Box 1 Relationship of exacerbation symptoms to potential underlying mechanisms

(1) Increased breathlessness

- Increased metabolic/catabolic state
- Airway narrowing
 - Mucosal damage, increased irritability/bronchospasm
 - Inflammatory cell infiltration into airway tissues
 - Airway oedema
 - Increased airway secretion and viscosity/mucus plugging
- Increased ventilation/perfusion (V/Q) mismatch

(2) Increased sputum production

- Mucous gland hypertrophy
- Goblet cell hyperplasia
- Goblet cell degranulation

(3) New or increased sputum purulence

- Eosinophil recruitment
- Neutrophil recruitment

symptoms outlined by Anthonisen *et al*.²⁹ The three main symptoms and how they might arise are outlined in box 1. The evidence for the relevant processes occurring during exacerbations is reviewed.

Increased metabolic/catabolic state

A systemic inflammatory response is capable of causing increased breathlessness without changes in respiratory tract pathology. The increased metabolic state associated with pyrexia increases oxygen demand and may increase hydrogen ion concentrations stimulating the respiratory centre to increase tidal volume and respiratory rate.⁴⁵ In those with normal lungs this effect may go unnoticed, but in patients with COPD the increase in ventilatory drive may lead to an increased sensation of breathlessness. Undoubtedly, a systemic effect is present during exacerbations as indicated by the rise in C reactive protein (CRP)² and IL-6.²² Whether treatment to reduce the metabolic drive (such as antipyretics) improves the sensation of dyspnoea during these episodes has yet to be proved.

Airway narrowing

Several potential mechanisms of exacerbations may exert their influence by reducing the calibre of the airways. Such a process would limit airflow further, result in increased residual volume, and hence increase the work of breathing.

In a longitudinal study of patients with moderate to severe COPD, patients recorded symptoms and peak expiratory flow rates (PEFR) in a daily diary and some also measured FEV₁ and forced vital capacity (FVC) using a handheld spirometer.⁴⁶ Significant falls in PEFR, FEV₁, and FVC were observed during the exacerbations. The recovery time was related to the magnitude of the fall, and the reduction in PEFR was greater in patients with increased dyspnoea. These findings are supported by intervention studies that have used FEV₁ as an outcome measure and demonstrated significant increases in PEFR and/or FEV₁ on recovery from exacerbation,⁴⁷⁻⁴⁹ and bronchodilator treatment has been shown to speed the resolution of airflow obstruction.⁵⁰⁻⁵⁴

One potential mechanism for this change in airflow would be bronchospasm which could be mediated by endothelin-1. In addition to promoting bronchial hyperresponsiveness, endothelin-1 may stimulate mucus secretion, promote airway oedema and smooth muscle proliferation, as well as upregulate production of cytokines. The concentration of this peptide, which is produced by the bronchial epithelium, alveolar macrophages and pulmonary endothelium, is increased in sputum

in stable COPD⁵⁵ and a recent study has shown that concentrations of endothelin-1 are increased in induced sputum during AECOPD, suggesting it may play an important role.⁴¹

Infiltration of the airway wall with inflammatory cells could also contribute to airflow limitation. This has been described extensively in stable COPD where increased numbers of CD8+ lymphocytes^{56, 57} and neutrophils²⁴ are found. During exacerbation, biopsy studies have shown that the inflammation becomes more marked with recruitment of eosinophils (see below) and an increase in the population of CD4+ lymphocytes.⁴⁴ Furthermore, sputum studies have shown increased neutrophil content and increased protein leakage from serum to sputum which also occurs during mucoid exacerbations that may lead to oedema of the airway wall.³⁹

An increase in mucus production would lead to an increase in sputum production that characterises many AECOPD. The presence of sputum in the airways would be expected to reduce the airway calibre and this effect would be enhanced if the viscosity of the sputum also increased. Such secretions would be harder to clear and result in plugging of smaller airways and hence increased breathlessness. There are numerous potential mechanisms which could cause increased sputum production and these are outlined below. Support for this feature comes from studies of mucolytic drugs that have been shown to reduce exacerbation frequency by 29%⁵⁸ and speed up resolution of symptoms when associated with bacteria.⁵⁹

Changes in ventilation/perfusion (V/Q) matching

The relationship of ventilation to perfusion has been studied in patients admitted to hospital with AECOPD using a multiple inert gas elimination technique.^{60, 61} Gas exchange deteriorates during exacerbations through worsening V/Q matching. Proportionately more blood perfuses poorly ventilated lung units than in the stable clinical state, and the resulting reduction in arterial oxygen tension is compounded by increased oxygen consumption. The relationship of these changes to airway wall oedema and mucus plugging has yet to be determined.

Eosinophilic inflammation

A potential mechanism which may explain many of the features of AECOPD is eosinophil recruitment. Biopsy studies have shown 30 fold higher numbers of eosinophils in bronchial mucosa during exacerbations⁶² and serum levels of eosinophilic cationic protein are higher in patients with exacerbations than in those with stable COPD.⁶³ Although this suggests an "asthmatic profile", the observed eosinophils are not degranulated (as they would be in asthma) and are not associated with increased IL-5 expression.⁶⁴ A recent study suggests that the chemokine associated with the influx of eosinophils is RANTES, which is secreted by both epithelial cells and the subepithelial lymphocytes.⁴⁴ The mechanism may be indirect and relate to increased TNF- α positive cells⁶² and sputum concentrations^{37, 42} during exacerbations. TNF- α increases the expression of RANTES, providing a potential mechanism for eosinophil recruitment.⁴⁴ The results suggest that at least a subset of patients experience eosinophilic exacerbations of bronchitis. The relative importance of the eosinophilia remains to be determined, but several eosinophil products may cause inflammatory damage to the airway (eosinophil peroxidase, major basic protein, eosinophil cationic protein, metalloproteinases, platelet activating factor, and cysteinyl leukotrienes)⁶⁵ and, together with histamine, can also cause bronchospasm. The presence of eosinophils in airway secretions can contribute to sputum purulence which is a feature of some exacerbations.

In stable COPD bronchial eosinophilia has been shown to be a marker for steroid responsiveness.^{66, 67} Thus, the eosinophilia associated with some exacerbations may explain the effects of

long term inhaled steroids on reducing exacerbations in COPD⁶⁸ and the beneficial effect of steroids seen in some exacerbations.^{47, 49}

Neutrophilic inflammation

A major finding in airway secretions during exacerbations is an increase in neutrophils⁶⁹ that is also associated with the presence or change in sputum purulence.³³ Neutrophil degranulation results in release of elastase and other proteinases which may cause epithelial damage, reduce ciliary beat frequency,⁷⁰ stimulate mucus secretion by goblet cells,⁷¹ and increase the permeability of the bronchial mucosa resulting in airway oedema and protein exudation into the airway.³⁹ These changes, especially in the small airways, may adversely affect airflow leading to increased breathlessness, as well as the mucus secretion and purulence characteristic of some exacerbations. The cytokine most associated with the neutrophilic inflammatory changes seen at exacerbation is LTB₄³⁹ which increases, whereas IL-8 (the other cytokine regularly associated with chronic bronchitis) is unchanged^{22, 39} except in the most severe episodes.³⁸

The increase in TNF- α in the sputum during exacerbations^{37, 42} may increase expression of endothelial adhesion molecules facilitating cell migration as well as activating neutrophils directly.²⁶ Furthermore, granulocyte/macrophage colony stimulating factor (GM-CSF) is increased in bronchoalveolar lavage fluid during exacerbations.⁶⁹ This cytokine stimulates differentiation of granulocytes and macrophages and can activate them directly,⁶⁹ providing another mechanism whereby neutrophils—as well as eosinophils and macrophages—can contribute to inflammatory changes within the airways. Studies of bronchial neutrophilic inflammation during exacerbations show resolution usually within 5 days following treatment, and this parallels clinical recovery.³⁹ Figure 1 outlines the changes which occur in neutrophilic inflammation during AECOPD.

ROLE OF BACTERIA IN EXACERBATIONS OF COPD

The association of bacteria with COPD has been appreciated for many years.⁷² Bacteria are frequently isolated from the sputum of patients when stable, and recent studies using the protected brush to obtain lower airway samples have shown that approximately one third of patients are colonised at any one time.^{73–76} *Haemophilus influenzae* and *Streptococcus pneumoniae* represent the majority of the organisms, although *Moraxella catarrhalis*, *H parainfluenzae*, Gram negative enteric bacilli, and *Pseudomonas* spp also account for a proportion. The role of bacteria in disease progression has been investigated extensively but remains relatively unclear.

There are a number of potential mechanisms by which bacteria may affect symptoms in COPD. Strains of *H influenzae*, *P aeruginosa*, and *S pneumoniae* have been shown to stimulate mucus hypersecretion in vitro,⁷⁷ and the first two organisms have been shown to inhibit ciliary beat frequency.⁷⁸ Furthermore, *H influenzae* can cause direct epithelial damage⁷⁹ and its endotoxin has been shown to increase epithelial expression of the pro-inflammatory cytokines IL-6, IL-8, and TNF- α in vitro,⁸⁰ providing potential mechanisms to upregulate inflammation. In support of this concept, patients with chronic bronchitis and COPD with a positive bacterial culture of *H influenzae* have higher concentrations of TNF- α in their sputum.²³ In a study of patients with stable chronic bronchitis, airway bacterial load has been shown to correlate directly with markers of neutrophilic inflammation, irrespective of the pathogen isolated.⁸¹ Similarly, the presence of potentially pathogenic microbes isolated from bronchoalveolar lavage fluid is strongly associated with increased neutrophils and concentrations of TNF- α .⁷⁶ Eradication or reduction of bacteria is associated with resolution of inflammation.

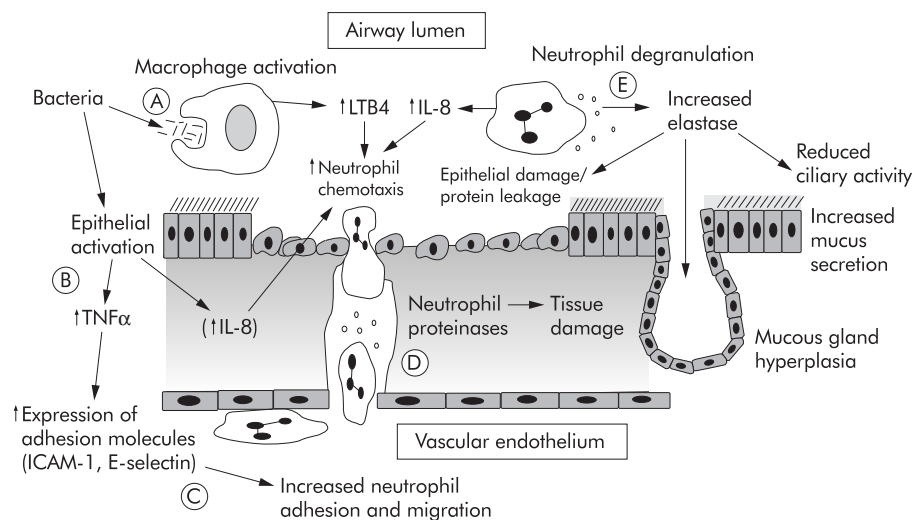


Figure 1 Neutrophilic inflammation during exacerbations of COPD. (A) Phagocytosis/macrophage activation (release of LTB₄ and TNF α). (B) Epithelial activation (in response to TNF α and bacterial products, release of TNF α and IL-8). (C) Activation of endothelium (due to TNF α , increase in adhesion molecules). (D) Neutrophil migration (follows from binding to adhesion molecules and IL-8/LTB₄ chemotactic gradient, elastase release and tissue damage). (E) Neutrophil elastase release in airway (epithelial damage and protein leakage; increased mucus secretion; reduced mucociliary clearance; associated release of IL-8 and LTB₄ resulting in amplification of chemotactic signal). LTB₄=leukotriene B₄; IL-8=interleukin 8; TNF α =tumour necrosis factor α ; ICAM-1=intercellular adhesion molecule 1.

The background of colonisation and inflammation in the stable state has led to uncertainty concerning the role of bacteria during exacerbations. Some authors suggest that there is no compelling evidence that bacteria play a role in acute exacerbations.⁸² The majority of microbiological studies aimed at establishing the role of bacteria have used cultures of spontaneously produced sputum and compared the exacerbation with the stable clinical state. Because the same organisms are frequently found both during an exacerbation and in the stable clinical state in the same patients, interpretation of their role can be difficult. Nevertheless, the proportion of patients with positive bacterial cultures and a high bacterial load increases during exacerbations in most,^{2 10 83} although not in all studies.⁸⁴ Newer molecular techniques have recently shown that colonisation is not stable and there is frequent turnover of discrete strains of *H influenzae* that elicit specific host responses to outer membrane proteins.⁸⁵ It is therefore likely that a change in the strain but not the organism may be responsible for the symptoms of an exacerbation, and studies which have failed to discriminate between different bacterial strains³⁷ may miss evidence of a new infection.

To refine our understanding, several studies have used the protected specimen brush method to derive more information about the bacteriology of the lower airways during exacerbations. Monso *et al* compared patients with an exacerbation to matched patients in the stable clinical state and showed marked differences, both in pathogen recovery (52% *v* 25% in the stable group) and bacterial load (24% of those with an exacerbation having a concentration of bacteria in excess of 10 000 cfu/ml *v* 5% of the stable group).⁷⁴ Other bronchoscopic studies have found a similar proportion of exacerbations to be associated with bacteria.^{86 87} The most common organisms isolated are *H influenzae*, *S pneumoniae*, and *M catarrhalis*.⁷⁴ However, studies have shown that exacerbations in more severe patients are more likely to be associated with recovery of Gram negative enterobacteriae and *Pseudomonas* spp.⁸⁷⁻⁸⁹ Although these data suggest a relationship with decline in lung function, the prior use of antibiotics may have influenced some of the results.

Further evidence to support the role of bacteria in AECOPD relate to studies of the immune response. Strain specific antibodies to surface outer membrane proteins of *H influenzae* have been shown to develop in relation to exacerbations.⁹⁰ Similarly, patients who experience an exacerbation of COPD with a

positive sputum culture for *M catarrhalis* have been shown to mount an antibody response to the homologous strain,⁹¹ and this has also recently been shown for *H parainfluenzae*.⁹² This, together with sputum and protected brush studies, provides compelling evidence that bacteria cause a proportion of exacerbations of COPD.

The inconclusive results of placebo controlled trials of antibiotics for exacerbations raises some further concerns about the importance of bacteria. Some studies have failed to show a significant difference in the outcome of patients treated with or without antibiotics.^{93 94} However, when Anthonisen and co-workers studied a larger numbers of patients characterised by specific symptoms it was possible to identify a subgroup of patients who benefited from antibiotics—namely, those with all three symptoms (see above).²⁹ Furthermore, meta-analysis indicates that antibiotics have a positive effect.⁹⁵ Because bacterial infections are mucosal and some are likely to resolve spontaneously, the difference between antibiotic and placebo treatment may be difficult to detect, particularly in exacerbations that have not been characterised and when a proportion will not be bacterial in origin. When relapse rate was used as an outcome measure, a recent retrospective study indicated that patients treated with antibiotics had significantly lower rates of relapse than those not receiving them,⁹⁶ again supporting a role for bacteria in at least some episodes.

As already emphasised, exacerbations are not a single entity and recent data indicate that use of a simple sputum colour chart to divide episodes into those with mucoid or purulent sputum identifies a major difference in bacterial isolation from spontaneous sputum samples.² A positive culture was obtained from 84% of sputum samples from patients with a purulent exacerbation compared with 38% from mucoid exacerbations. In the stable clinical state the proportion of patients with a positive culture was similar in the two groups (approximately 35%). The presence of green sputum was 94.4% sensitive and 77% specific for the yield of a high bacterial load, identifying a distinct subset of patients in whom bacteria are strongly associated with the exacerbation. Resolution of sputum purulence was shown to relate to resolution of symptoms.⁹⁷ Conversely, there was little evidence of a bacterial aetiology for exacerbations associated with mucoid sputum and these patients improved without antibiotics. The mixed nature of exacerbations would therefore minimise the benefit of antibiotics unless stratification is undertaken.

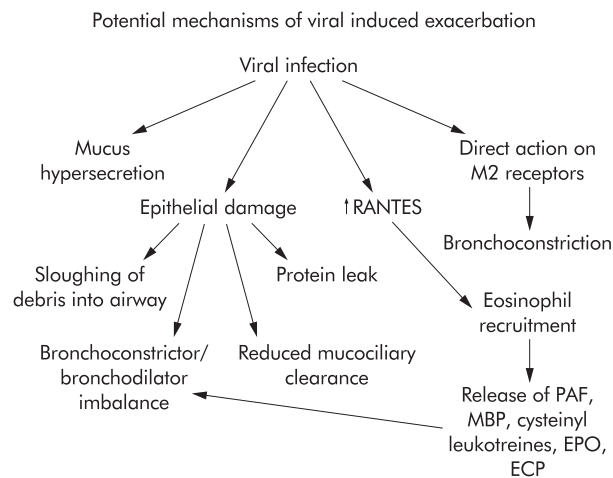


Figure 2 Potential mechanisms of viral induced exacerbations of COPD. M2=type 2 muscarinic receptors; RANTES=regulated on activation, normal T cell expressed and secreted; PAF=platelet activating factor; MBP=major basic protein; EPO=eosinophil peroxidase; ECP=eosinophil cationic protein.

ROLE OF VIRUSES IN EXACERBATIONS OF COPD

Lower respiratory tract viral infections in patients with COPD may also cause direct damage to the airway epithelium resulting in loss of ciliated epithelium, increased mucus production, sloughing of necrotic cells into the airway lumen, together with increased plasma exudation.⁹⁸ In addition to causing airway narrowing,⁴⁸ the altered environment may promote secondary bacterial infection with the further potential to promote inflammatory changes as outlined above. Viral infections have been shown to increase airway responsiveness and this may be due to a change in the balance of bronchoconstricting and bronchodilating substances in the airway.^{98, 99} Indeed, viral infections have been shown to increase levels of endothelin-1, precipitating acute episodes of asthma, and endothelin-1 also increases during exacerbations of COPD.⁴¹ Furthermore, viruses can also increase release of acetylcholine by direct and indirect effects upon M2 muscarinic receptors leading to increased bronchoconstriction.¹⁰⁰ Thus, there are several mechanisms by which viruses can cause AECOPD and these are outlined in fig 2.

Several pathological findings in COPD provide indirect evidence for the role of viruses in AECOPD. Eosinophilia has been an important feature in biopsies and it has been suggested that this may be via the increased expression of RANTES,⁴⁴ which might be a direct effect of the virus on the epithelial cell. All of the inflammatory processes, together with the systemic inflammatory response associated with viral infections, would be expected to increase the symptoms of breathlessness in COPD.

Direct evidence of viral infection is, however, necessary to establish the contribution of viruses to exacerbations. Table 1 summarises some of the more important studies of the viral aetiology of exacerbations of COPD. Most of the evidence is indirect and depends on serological assessment.^{84, 101-105} Seroconversion to specific viruses is not consistently associated with clinical deterioration and therefore seroconversion at the time of an exacerbation does not provide incontrovertible evidence of aetiology. Studies conducted over short periods can be influenced by the effect of epidemics and probably account for the variation in some of the viruses implicated.

Culture of rhinovirus has been undertaken in several studies with varying results. The largest was a longitudinal study of 150 patients over 8 years and positive culture of rhinovirus was associated with 4.8% of 1030 exacerbation episodes compared with 0.5% during illness free periods.¹⁰⁴ This finding has been supported by other shorter studies,¹⁰¹ although isolation of the virus has been achieved in up to 23% of episodes using induced sputum and nasal/throat samples assessed by polymerase chain reaction (PCR) which increases the sensitivity of rhinovirus detection.¹⁰⁶

As suggested previously, viral infection may have a role in predisposing to secondary bacterial infection in patients susceptible because of their underlying lung disease. One study specifically examined the relationship between viral infection and bacteria in COPD; viral infections were found to be associated with increased isolation of *H influenzae* and *S pneumoniae* from sputum cultures.¹⁰⁷ Furthermore, there was a higher incidence of *H influenzae* antibody seroconversion in the virus infected group, suggesting that this is a potential sequence of events.

Despite the research that has been published, the contribution of viruses to AECOPD remains to be determined and probably varies considerably with epidemics and immunisation policy. Undoubtedly, there is evidence that a proportion of episodes are associated with viral infection, particularly influenza viruses, as vaccination has shown benefit.¹⁰⁸ However, viral infections of the respiratory tract are a common cause of morbidity in otherwise healthy individuals, and whether or not patients with COPD are more susceptible to viral infections remains controversial. Some studies have shown significantly more viral infections in patients with COPD,^{102, 109} while others have found no difference from healthy subjects.^{104, 110}

ROLE OF ATYPICAL ORGANISMS IN EXACERBATIONS OF COPD

Mycoplasma pneumoniae and *Chlamydia* spp are intracellular bacteria that share some of the characteristics of viruses. The mechanism by which they cause exacerbations is likely to be similar to viral infections and, likewise, the investigations into the role of these organisms have depended largely on serological diagnosis.^{101, 104, 111-113} Mycoplasma infections predominantly affect young adults and immunity is achieved by

Table 1 Summary of main findings from viral studies

	No of exacerbations	Rhinovirus		Influenza virus		Parainfluenza virus		RSV		Adenovirus	
		Ex* (%)	Stable† (%)	Ex (%)	Stable (%)	Ex (%)	Stable (%)	Ex (%)	Stable (%)	Ex (%)	Stable (%)
Smith ¹⁰⁴	1030	4.8	0.5	4.9	0.2	2.8	0.7	0.8	0.6	0.7	0.5
Seemungal ¹⁰⁶	43	23.3	0								
Buscho ¹⁰⁶	166	2.7	0.55	10.2	6.4	6	7	0	0.7	1.2	0.7
Lamy ¹⁰³	49			28.6	1	24.5	0.5	6	1	0	0.75
Greenberg ¹¹⁰	323	4.9		2.5		6.2		2.5		0.3	
Stenhouse ¹⁰⁵	64			9.4	1.5	0	0	3.1	0		
Gump ⁸⁴	116			12.9	0.2	7.8	0.2	4.3	0.05	2.6	0

*Viral infection determined from seroconversion PCR or viral isolation in the exacerbated state.

†Viral infection determined from seroconversion PCR or viral isolation in the stable clinical state.

The figures in the table indicate the proportion of patients in the stable and exacerbated state from which each type of virus was detected or seroconversion occurred.

the time most individuals reach the age where AECOPD becomes a clinical problem. It is therefore not surprising that most studies have found that few exacerbations are associated with evidence implicating this organism,^{101–104} although a recent study implicated *M pneumoniae* in as many as 14% of exacerbations.¹¹⁴ There has, however, been more debate regarding the role of *Chlamydia pneumoniae*. Two studies of acute exacerbations (one in hospitalised patients and one in outpatients) found *C pneumoniae* in approximately 5% of episodes, and serological evidence suggesting previous infection in approximately three quarters of patients (similar to a matched population).^{111–113} However, two other recent studies have found *C pneumoniae* to be associated with 24% and 34% of exacerbations.^{112–115} The implications of these findings remain uncertain and further studies are required to resolve these issues.

AIR POLLUTION

It has been suggested that AECOPD could be induced by increases in air pollution. The effects of diesel particulates, sulphur dioxide (SO₂), ozone (O₃), and nitrogen dioxide (NO₂) have been studied and potential mechanisms by which airway inflammation is enhanced have been proposed. Recent bronchoscopic studies have shown that exposure of healthy volunteers to diesel exhaust results in increases in neutrophils^{116–117} and methylnhistamine.¹¹⁶ In vitro studies have shown that diesel exhaust particles simulated production of pro-inflammatory cytokines such as GM-CSF and IL-8, both of which may explain the enhanced neutrophilic inflammation.¹¹⁸ Ozone exposure has been shown to be associated with markers of nasal eosinophil inflammation in non-atopic children,¹¹⁹ and SO₂ and NO₂ have been shown to enhance the airway response to inhaled allergens.¹²⁰ Thus, potential mechanisms exist whereby changes in air pollution can cause exacerbations of respiratory symptoms in COPD.

Evidence to support a role for air pollution has been based on epidemiological studies that have implicated increases of SO₂, NO₂, PM₁₀, and black smoke particulate matter in changes in chronic respiratory symptoms and increased respiratory mortality in patients with COPD.^{121–126} These city based studies have investigated excess hospital admissions at times of increased atmospheric pollution and concluded that this may account for approximately 6–9% of admissions, depending on the time of year.¹²⁵ Patients with COPD have also been shown to be at increased risk of death associated with urban particle air pollution, although much of this may be cardiovascular rather than respiratory.¹²⁶

CONCLUSIONS

The evidence suggests that bacteria, viruses, and changes in air quality interact with host factors and with each other to produce increased inflammation in the lower airway. This leads to the development of the characteristic symptoms associated with exacerbations of COPD. The appreciation that exacerbations have several causes has not resulted in a change of clinical practice^{127–128} and, in particular, antibiotics remain overused, contributing to global antibiotic resistance. Patients are usually treated empirically with increased β₂ agonists, anticholinergic agents, oral steroids, and antibiotics. The appropriate use of these treatments and the development of new ones can only be established once a better understanding of the nature and causes of exacerbations has been achieved. Future studies need to define populations clearly, stratify for known confounding factors, and should aim to identify clinical correlates so that clinical practice can be modified appropriately.

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