COPD Exacerbations
Causes, Prevention, and Treatment

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KEYWORDS

- Chronic obstructive pulmonary disease • Exacerbation • Respiratory viruses
- Bacteria

KEY POINTS

- Respiratory viruses (in particular rhinovirus) and bacteria both play a major role in the etiology of exacerbate COPD.
- A distinct group of patients appears susceptible to frequent exacerbations, irrespective of disease severity and this phenotype is stable over time.
- Many current therapeutic strategies help reduce exacerbation frequency.

Chronic obstructive pulmonary disease (COPD) is associated with episodes of acute deterioration in respiratory health termed "exacerbations." Exacerbations are characterized by a worsening of symptoms from the usual stable state, especially dyspnea, increased sputum volume, and purulence. When diagnosing COPD exacerbations, clinicians must also exclude other causes for respiratory deterioration, such as pneumothoraces, pulmonary emboli, and pneumonia, using clinical examination and appropriate investigations if required. Exacerbations are among the most common causes of emergency medical hospital admission in the United Kingdom[1] (and elsewhere) and the rate at which they occur seems to reflect an independent susceptibility phenotype.[2] Exacerbations are important events in the natural history of COPD that help drive lung function decline,[3,4] increase the risk of cardiovascular events,[5] and are responsible for much of the morbidity[6] and mortality[7] associated with this highly prevalent condition.

FREQUENT EXACERBATOR PHENOTYPE

Patients with a history of frequent exacerbations exhibit faster decline in lung function,[3] have worse quality of life,[6] have increased risk of hospitalization,[8] and have greater mortality (**Fig. 1**).[7] Therefore, it is important to identify patients at risk of

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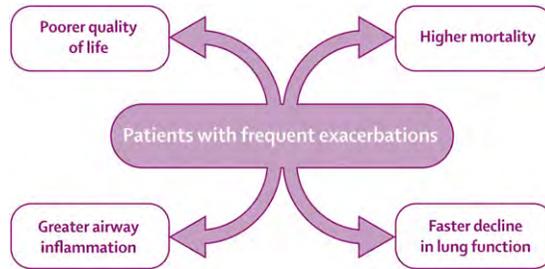
Fig. 1. Effect of COPD exacerbations in the group with frequent exacerbations. (*From* Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370(9589):786–96; with permission.)

frequent exacerbations. Exacerbations become more frequent and severe as COPD severity increases.[9] However, a distinct group of patients seems to be susceptible to exacerbations, irrespective of disease severity, and the major determinant of exacerbation frequency is a history of prior exacerbations.[2] This phenotype of susceptibility to exacerbations is stable over time and is seen across all severity of airflow obstruction,[2] suggesting that patients with the frequent exacerbator phenotype are prone to exacerbations as a result of intrinsic susceptibility, and develop exacerbations when exposed to particular triggers, such as respiratory infections.

Exacerbations are associated with increased systemic and airway inflammation and may be triggered by bacterial and respiratory viral infections. They may also be precipitated by environmental factors (**Fig. 2**).

VIRAL INFECTIONS
Rhinovirus

Rhinovirus is responsible for the common cold and initial evidence that respiratory viral infections were important triggers of COPD exacerbations came from the association of coryzal symptoms with exacerbations. Seemungal and colleagues[10] found that up to 64% of exacerbations were associated with a symptomatic cold occurring up to 18 days before exacerbation onset. Additionally, exacerbations associated with dyspnea and coryza at onset are associated with larger falls in peak flow, prolonged recovery times, and higher levels of airway inflammatory markers (interleukin [IL]-6).[11,12]

Studies using molecular biology polymerase chain reaction techniques have provided further evidence of the role of rhinovirus in the cause of COPD exacerbations. In studies from the London COPD cohort, up to 40% of exacerbations were associated with respiratory viral infections. Rhinovirus was the most common respiratory virus detected and found in 58% of viral exacerbations.[10] Rohde and colleagues[13] corroborated these findings in a separate study of hospitalized patients, detecting respiratory viruses in 56% of exacerbations. Rhinovirus was again the most prevalent virus, being detected in 36% of virus-associated exacerbations.

Experimental Rhinovirus Infection Models

Mallia and colleagues[14] have used experimental rhinovirus infection to provide evidence of a direct causal relationship between respiratory virus infection and acute exacerbations of COPD. In that study, 13 subjects with COPD and 13 control subjects with a similar smoking history but normal lung function were closely observed after infection with rhinovirus serotype 16. Daily upper and lower respiratory symptom scores were increased significantly above baseline levels and were significantly
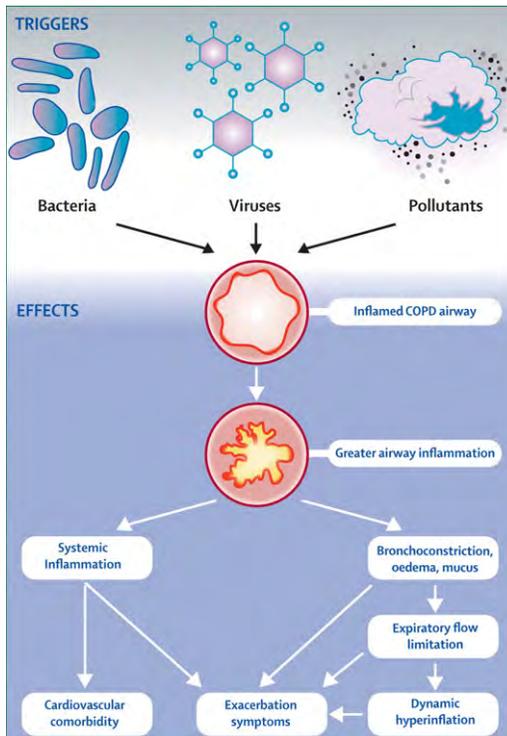
Fig. 2. Triggers of COPD exacerbations and associated pathophysiologic changes leading to increased respiratory symptoms. (*From* Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370(9589):786–96; with permission.)

greater in the COPD group compared with control subjects. Postbronchodilator peak expiratory flow fell and in blood and airway inflammatory markers increased significantly from baseline in patients with COPD but not control subjects. Nasal lavage virus load was significantly higher in the COPD group compared with control subjects and peak sputum virus load in subjects with COPD correlated positively with peak serum C-reactive protein concentration and sputum inflammatory markers (neutrophils, IL-6, IL-8, neutrophil elastase, and tumor necrosis factor-α). Furthermore, there was a temporal relationship between virus detection in the respiratory tract and the onset of symptoms and airflow obstruction, and virus clearance was followed by clinical recovery. Thus, Mallia and colleagues[14] provide direct evidence that the symptomatic and physiologic changes seen at acute exacerbations of COPD can be precipitated by rhinovirus infection.

Susceptibility to Virus-Induced Exacerbations

Defective immunity may lead to increased susceptibility to virus-induced exacerbations. Interferon-β is an essential component of antirhinoviral immunity and Mallia and colleagues[14] have reported impaired interferon-β response to rhinovirus infection in COPD. Furthermore, cells from patients with COPD manifest increased viral titer and copy numbers after rhinovirus infection compared with control subjects[15] and intercellular adhesion molecule-1, the rhinovirus major group receptor, is up-regulated on the bronchial epithelium of patients with COPD.[16]

Seasonal Environmental Variations and Viral Infection

In the Northern hemisphere, COPD exacerbations are more common in the winter months and may also be more severe, because small but significant falls in lung function in patients with COPD occur with a reduction in outdoor temperature.[17] The increase in exacerbations may be caused by the increasing prevalence of respiratory viruses in low temperature winter months or increased susceptibility to upper respiratory tract virus infections in cold weather. In children, respiratory syncytial virus (RSV) outbreaks cause a significant increase in hospital admissions during the winter season[18] and increased RSV activity has been observed when temperatures decrease.[19]

RSV

Seemungal and colleagues[10] detected RSV in nasal aspirates at exacerbation, although more patients had RSV detected in the stable state than at exacerbation (23.5% vs 14.2%). Stable patients in whom RSV has been detected have elevated inflammatory markers, more severely impaired gas exchange (higher Pa_{CO_2}) and accelerated lung function decline.[10,20] Thus, RSV may also be a cause of chronic airway infection in COPD.

Influenza Virus

Influenza has been detected relatively infrequently at COPD exacerbation,[10] though this may relate to widespread use of influenza immunization for patients with chronic lung disease. In studies of older patients with chronic lung disease, those not vaccinated with influenza had twice the hospitalization rate in the influenza season compared with the noninfluenza season.[21] This highlights the importance of influenza vaccination in patients with COPD and suggests that influenza may still be an important etiologic factor during influenza epidemics.

BACTERIAL INFECTIONS
Species

Bacteria are isolated from sputum using standard culture techniques in 40% to 60% of exacerbations.[22] The three most common species isolated in COPD exacerbations are *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. Less frequently, exacerbations may be caused by *Pseudomonas aeruginosa*, gram-negative Enterobacteriacea, *Staphylococcus aureus*, *Haemophilus parainfluenzae*, and *Haemophilus hemolyticus*.[23–25]

Sputum Characteristics

Some of the earliest evidence supporting a causative role for bacteria in COPD exacerbations came from antibiotic studies, including the seminal paper by Anthonisen and colleagues,[26] which identified exacerbation features predictive of benefit from antibiotics. Patients with increased dyspnea, sputum volume, and sputum purulence showed a significant benefit with antibiotic therapy, whereas those with only one of these three features showed none. After this paper, studies related sputum characteristics to the presence of bacteria and bacterial load. Theoretically, airway bacterial infection should be accompanied by an influx of neutrophils, resulting in a change in secretions from mucoid to purulent, because neutrophil-derived myeloperoxidase is green. Antibiotic therapy, by reducing bacterial load, should reverse this process.[27]

In studies during exacerbations of COPD, positive bacterial cultures were obtained from 84% of patients if sputum was purulent at presentation but only 38% if the sputum was mucoid (*P*<.0001). Moreover, the median bacterial load for positive

purulent culture samples was significantly higher than for mucoid samples. When the same patients were reexamined in the stable state after antibiotics, sputum color improved significantly in the group who presented with purulent sputum. In purulent exacerbations a clear relationship was demonstrated between semiquantitative neutrophil count and sputum color. The presence of green (purulent) sputum was 94.4% sensitive and 77% specific for a high bacterial load (>10^7 colony forming units per milliliter).[27]

Colonization

Darker sputum color in stable COPD may reflect bronchial bacterial colonization,[28] which has traditionally been characterized as the isolation by culture of significant numbers of bacteria in samples obtained from the lower airways of patients with COPD when clinically stable.[29] Bacteria in the lower airways have been hypothesized to disrupt host defense mechanisms leading to a vicious cycle of epithelial cell injury, defective mucociliary clearance, chronic mucous hypersecretion, and inflammatory cell infiltration, further damaging host defenses and leading to bacterial adherence and growth.[23] This mechanism may explain why colonization in the stable state has been associated with increased exacerbation frequency (**Fig. 3**).[30] However, recent technologic advances in bacterial detection have challenged conventional thinking and definitions in the field of bacterial colonization.

Molecular Analysis Techniques

Classically, it was thought the lower airways were sterile in healthy patients; however, the development of culture-independent molecular techniques using 16S-rRNA techniques has challenged this assumption. The 16S-rRNA gene is a section of prokaryotic DNA found in all bacteria. 16S-rRNA gene sequences contain hypervariable regions that can provide species-specific signature sequences useful for bacterial identification. Consequently, 16S rRNA gene sequencing provides a potentially more accurate alternative to traditional methods of bacterial identification. Hilty and colleagues[31]
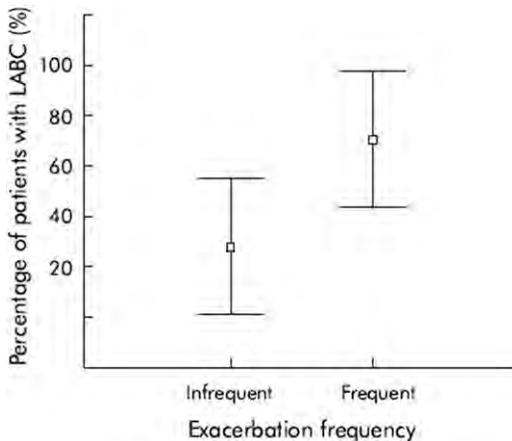
Fig. 3. Relationship between lower airway bacterial colonization (LABC) by a possible pathogen in induced sputum and frequent (>2.58 exacerbations per year; n = 14) and infrequent exacerbations (<2.58 exacerbations per year; n = 14) with 95% confidence intervals. (*From* Patel IS, Seemungal TA, Wilks M, et al. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax 2002;57(9):759–64; with permission.)

used molecular analysis of the polymorphic bacterial 16S-rRNA gene to characterize the composition of bacterial communities from the airways of patients with asthma, patients with COPD, and healthy control subjects. Over 5000 16S rRNA bacterial sequences were identified from 43 subjects and the bronchial tree of all patient groups was nonsterile. However, proteobacteria, especially *Haemophilus* sp, were much more frequently identified in the bronchi of patients with asthma and patients with COPD compared with control subjects, suggesting that the bronchial tree contains a characteristic microbial flora that differs between health and disease. Further studies using these techniques have also revealed that there are significant microanatomic differences in bacterial communities within the same lung of subjects with advanced COPD.[32] These techniques are exciting developments in the study of bacteria in patients with COPD, but should be interpreted with caution because studies using these methods have been conducted on small numbers of patients[31,32] and the clinical applicability of the results remains uncertain.

Bacterial Load

The prevalence of potentially pathogenic microorganisms and airway bacterial load in sputum have been shown to increase from stable state to exacerbation. The most frequently isolated organism is *H influenzae*, followed by *M catarrhalis* and *S pneumoniae*.[33] Studies using protected brush specimens collected in the stable state and at exacerbation have also demonstrated an increased prevalence of positive bacterial cultures at exacerbation. In the stable state, patients colonized by potentially pathogenic microorganisms on culture had greater disease severity (reduced mean forced expiratory volume in 1 second [FEV_1]% predicted) and multivariate analyses demonstrated that a high potentially pathogenic microorganism load in lower airway secretions was a major determinant of exacerbation risk and lung function impairment.[34]

Strain Changes

Strain changes may play an important role in the cause of COPD exacerbations. In a prospective study, Sethi and colleagues[25] hypothesized that acquisition of a new bacterial strain would be associated with an exacerbation of COPD and so collected sputum samples from 81 outpatients with moderate to severe COPD on a monthly basis and at exacerbation. Molecular typing of sputum showed that isolation of a new strain of a pathogen (*H influenzae*, *M catarrhalis*, and *S pneumoniae*) was associated with a significant increase in the risk of exacerbation. These findings were proposed as a mechanism to explain recurrent bacterial exacerbations of COPD, the authors speculating that after a first exacerbation, patients develop a protective immune response that is strain specific. Therefore, acquisition of a different strain from the same bacterial species may still lead to a second exacerbation. However, not all exacerbations were associated with strain change, and not all strain changes were associated with exacerbation.

Controversy exists regarding the relative contributions made by exacerbation load and strain change to the cause of COPD exacerbations. Sethi and colleagues[35] further explored this issue by examining sputum from 104 patients when stable and at exacerbation over a period of 81 months. Among preexisting strains, no differences were found between exacerbation and stable bacterial load for *H influenzae*. *M catarrhalis* was present at significantly lower concentrations during exacerbation with a similar trend observed for *S pneumoniae*. However, for *H influenzae* and *M catarrhalis* (but not *S pneumoniae*) increased load of new strains was seen during exacerbation compared with during stable visits. In the case of *H influenzae*, bacterial load increased significantly from $10^{7.28}$ to $10^{7.76}$ colony forming units per milliliter. When

the same strain was isolated during stable and exacerbation visits paired analysis also showed a significant increase in load for *H influenzae*. The observed increases of around 0.5 log in magnitude, although representing a small relative change,[35] equate to a 202% or threefold increase in absolute bacterial numbers,[36] suggesting that changes in bacterial load remain an important mechanism for some exacerbations.

Interaction of Bacteria and Viruses

Frequent exacerbators have a higher incidence of lower airway bacterial colonization[30] and bacteria may also play a role in susceptibility to viral infection in COPD. *H influenzae* increases expression of intercellular adhesion molecule-1 and Toll-like receptor-3, and augments binding of rhinovirus to cultured human airway epithelial cells.[37] Therefore, patients colonized with bacteria may be more susceptible to the development of virally triggered exacerbations.

Wilkinson and colleagues[33] demonstrated a synergistic effect of viral and bacterial infections at exacerbation in patients with COPD. Exacerbation symptoms and FEV_1 decline were more severe in the presence of bacteria and colds (as a surrogate of viral infection) than with a cold or bacterial pathogen alone, and exacerbations associated with human rhinovirus and *H influenzae* exhibited a greater bacterial load and inflammation than those without both pathogens. Patients hospitalized because of COPD exacerbations also have more marked lung function impairment and increased length of stay in the context of bacterial and viral coinfection.[38]

ENVIRONMENTAL FACTORS
Air Pollution

Epidemiologic data supports a role for air pollution in the cause of some COPD exacerbations with studies showing an increased risk of hospitalization for COPD with increased levels of pollutants.[39–41] Air pollution likely causes COPD exacerbations through modulation of airway inflammation and immunity. Diesel exhaust induces airway inflammation in healthy volunteers as characterized by an increased percentage of sputum neutrophils, IL-6, and methylhistamine.[42] Furthermore, diesel exhaust reduces T-cell activation and induces migration of alveolar macrophages into the airspaces.[43]

EXACERBATION PREVENTION

There are now a wide range of pharmacologic and nonpharmacologic interventions documented to reduce exacerbation frequency or hospitalization in COPD (**Table 1**). However, there remains a real need for further novel interventions because

Table 1	
Interventions to reduce exacerbation frequency or hospitalization in patients with COPD	
Pharmacologic	**Nonpharmacologic**
Inhaled corticosteroids	Lung volume reduction surgery
Long-acting bronchodilators	Home oxygen
Phosphodiesterase inhibitors	Ventilatory support
Theophyllines	Pulmonary rehabilitation
Long-term antibiotics	
Mucolytics	
Vaccination	

current approaches are not completely effective, even when targeted and used optimally.

PHARMACOLOGIC THERAPIES

Conceptually, some pharmacotherapy (eg, a vaccine) may be delivered once with lasting effect on reducing exacerbations, whereas other interventions need to be administered continually for that effect to be maintained.

Vaccination

The largest study of the efficacy of influenza vaccination was conducted retrospectively using data pooled from 18 cohort studies of community-dwelling elderly patients over 10 influenza seasons. In this data set composed of 713,872 person-seasons of observation, influenza vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza and a 48% reduction in the risk of death.[44] The same authors also conducted a 2-year retrospective cohort study of elderly patients with diagnosis of chronic lung disease to assess the health-economic benefits of pneumococcal vaccination.[45] Pneumococcal vaccination was associated with significantly lower risks of hospitalization for pneumonia and death. However, a randomized controlled trial of pneumococcal polysaccharide vaccine in patients with COPD demonstrated no significant reduction in rates of community-acquired pneumonia when the entire study population was analyzed.[46] Subanalyses of the data showed a reduction in the incidence of community-acquired pneumonia in those patients younger than age 65 years and those with severe airflow obstruction, although no mortality benefit was demonstrated.[46] Data also suggest an additive benefit of combined influenza and pneumococcal vaccination[45] and hence both vaccines are recommended to all patients with COPD.[47] It is important to note that these studies have not specifically addressed exacerbations of COPD.

Bacterial immunostimulation has also been advocated as a method to prevent exacerbations of COPD and reduce the severity and duration of acute episodes. OM-85 BV (Bronchovaxom) is a detoxified immunoactive bacterial extract that has been examined in multiple trials; however, assessment of its efficacy is hampered by heterogeneity of study design and conflicting results.[48–51] Furthermore, it is not known if any protective effects seen are additive to other conventional treatments and thus larger and longer trials are required before this vaccine can be recommended as part of the routine clinical management of COPD.[52]

Inhaled Corticosteroids and Long-Acting Bronchodilators

The Inhaled Steroid in Obstructive Lung Disease in Europe study was performed primarily to assess the effect of inhaled corticosteroids (ICS) on the rate of FEV_1 decline in patients with moderate-to-severe COPD. Although this primary outcome was negative, a 25% reduction in exacerbation frequency was noted in the group who received fluticasone.[53] Long-acting β-agonists (LABA) also reduce exacerbation frequency and in the Toward A Revolution in COPD Health (TORCH) study, in which 6112 patients were followed over 3 years, inhaled fluticasone and salmeterol reduced exacerbation frequency when administered separately compared with placebo.[54] In the same study, the combination of fluticasone and salmeterol (SFC) reduced exacerbation frequency further still, in addition to improving health status and lung function compared with placebo. The annual rate of moderate and severe exacerbations in the placebo group was 1.13 per year, compared with 0.97 for salmeterol, 0.93 for fluticasone, and 0.85 in patients receiving SFC. The combination of ICS and LABA also

resulted in fewer hospital admissions over the study period and trended toward a mortality benefit. Reduction in exacerbation frequency has been found for other ICS, and other LABA, singly and in combination. New drugs in development include once-daily ICS and LABA.

Long-acting antimuscarinics (LAMA) also reduce exacerbation frequency. In the Understanding Potential Long-Term Impacts on Function with Tiotropium trial 5993 patients were randomized to tiotropium or placebo over 4 years, with concomitant therapy allowed. Although the primary end point of the trial (a reduction in rate of decline in FEV_1) was negative, the group of patients randomized to tiotropium in addition to usual care had a significant reduction in exacerbation frequency, related hospitalizations, and respiratory failure.[55] Because this trial involved the addition of tiotropium to existing therapy, which could include combination preparations of ICS and LABA, many patients were in effect on triple combination of therapy.

Triple combination therapy is commonly prescribed in advanced COPD. This approach was examined in the OPTIMAL study, which examined whether combining tiotropium with salmeterol or SFC improved outcomes compared with tiotropium alone in patients with moderate to severe COPD.[56] The primary outcome was negative, because the addition of SFC to tiotropium therapy did not statistically influence rates of COPD exacerbation. However, triple combination therapy did improve lung function, quality of life, and hospitalization rates compared with tiotropium plus placebo. In keeping with the TORCH study, drop-outs in the placebo arm may have affected the study: more than 40% of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or LABA.

An important clinical question is which combination of therapies is most effective for different patients. Network analysis techniques have assessed the relative effectiveness of competing inhaled drug regimens for the prevention of COPD exacerbations.[57] Based on 35 trials, all inhaled drug regimens (LABA, LAMA, and ICS, alone and in combination) significantly reduced exacerbations but there were no significant differences between them. In subanalyses, in patients with FEV_1 less than or equal to 40% predicted, LAMA, ICS, and combination treatment reduced exacerbations significantly compared with LABA alone, but not if FEV_1 was greater than 40% predicted. This effect modification was significant for ICS and combination treatment but not for LAMA suggesting that combination treatment may be more effective than LABA alone in patients with a low FEV_1.

Phosphodiesterase Inhibitors

There is some evidence that theophyllines reduce exacerbation frequency.[58,59] However, they are nonselective phosphodiesterase inhibitors, potentially toxic with the need to monitor plasma levels, and with potential for interaction with other medication, restricting therapeutic use. This is a particularly important consideration in elderly patients because of differences in pharmacokinetics, increased prevalence of comorbidities, and concomitant medications. Therefore, theophyllines should only be used after a trial of other more effective therapies (LABA, LAMA, or ICS), or in patients unable to use inhaled therapy. If prescribed, the theophylline dose must be monitored or reduced at exacerbation when macrolide or fluoroquinolones antibiotics are used.[47]

Selective phosphodiesterase-4 inhibitors inhibit the airway inflammatory processes associated with COPD and have a considerably better side effect profile than theophylline. Evidence from a pooled analysis of two large placebo-controlled, double-blind multicentre trials revealed a significant reduction of 17% in the frequency of moderate

(glucocorticoid treated) or severe (hospitalization or death) exacerbations.[60] However, the study design of these trials limits the generalizability: patients had to have an FEV_1 less than 50% (Global Initiative for Chronic Obstructive Lung Disease stages 3 and 4); bronchitic symptoms; and a history of exacerbations. Furthermore, only LABA were allowed as maintenance therapy during the study and there are currently no comparator studies of roflumilast with ICS. Discontinuations because of adverse events were more common in the roflumilast group than in the placebo group, the most frequent adverse events leading to discontinuation (with the exception of COPD) being diarrhea, nausea, and headache. Weight loss was also noted in the roflumilast group, with a mean reduction of 2.1 kg after 1 year, which was greatest in obese patients. Concerns regarding tolerability and side effects of roflumilast therapy may have limited its clinical use.

Long-Term Antibiotics

At present there is insufficient evidence to recommend routine prophylactic antibiotic therapy in the management of stable COPD. However, recent studies have shown promise, particularly those involving macrolides, which have anti-inflammatory and antimicrobial properties. Erythromycin reduced the frequency of moderate or severe exacerbations (treated with systemic steroids or antibiotics, or hospitalized) and shortened exacerbation length when taken twice daily over 12 months by patients with moderate-to-severe COPD.[61] The macrolide azithromycin has been used as prophylaxis in patients with cystic fibrosis and is also suitable for use in patients with COPD for exacerbation prevention. A large United States trial of more than 1500 patients with COPD at high risk of exacerbations recently reported that when added to usual treatment, azithromycin taken daily for 1 year decreased the frequency of exacerbations and improved quality of life. However, patients in the azithromycin intervention group were more likely to become colonized with macrolide-resistant organisms and suffer hearing decrements.[62] Ongoing concerns regarding the development of antibiotic resistance have led to trials of alternative, pulsed antibiotic regimens. Intermittent pulsed moxifloxacin when given to stable patients significantly reduced exacerbation frequency in a per-protocol population, and in a post hoc subgroup of patients with bronchitis at baseline. However, this reduction did not meet statistical significance in the intention-to-treat analysis and further work is required in this area.[63]

Mucolytics

The routine use of these agents is not currently recommended. Some evidence exists that mucolytics, such as carbocysteine, may reduce exacerbation frequency in selected patients with viscous sputum.[64] However, it is not certain if these treatments provide additional benefit to patients already being treated with LABA or ICS.

Novel Anti-Inflammatory Drugs

COPD is an inflammatory condition associated with relative steroid resistance and approaches to restore steroid sensitivity may lead to novel future therapies.[65] Histone deacetylase-2 is reduced in airway tissue from patients with COPD compared with healthy nonsmokers and has been implicated in impaired sensitivity to corticosteroids.[66] Increasing histone deacetylase-2 expression or activation may be a potential avenue to reversing corticosteroid subsensitivity in COPD. Low doses of oral theophylline have been shown to increase histone deacetylase-2 expression in alveolar macrophages from patients with COPD[67,68] and so potentially may restore corticosteroid responsiveness in vivo.

There is evidence of significantly increased phosphoinositide-3-kinase activity in peripheral blood monocytes from patients with COPD compared with smokers and normal control subjects, a pathway that is also associated with reduced corticosteroid sensitivity.[69] The addition of a phosphoinositide-3-kinase inhibitor has been shown to restore steroid sensitivity toward normal[70] and a number of phosphoinositide-3-kinase–delta inhibitors are currently under development.

Alveolar macrophages from patients with COPD demonstrate increased p38 mitogen-activated protein kinase activity.[71] In patients with COPD, selective p38 (p38 mitogen-activated protein kinase) inhibitors reduce lipopolysaccharide-induced cytokine production in alveolar macrophages and synergistically increase the cytokine suppressive effects of dexamethasone.[72]

NONPHARMACOLOGIC THERAPIES
Lung Volume Reduction Surgery

The National Emphysema Treatment Trial reported that lung volume reduction surgery can improve morbidity and mortality in a subset of patients with COPD who have predominantly upper-lobe emphysema and low baseline exercise capacity.[73] A retrospective investigation of data from the same study also showed that lung volume reduction surgery reduces the frequency of COPD exacerbations, possibly through postoperative improvement in lung function[74] and reduction in dynamic hyperinflation. Therefore, this therapeutic option should be explored in selected eligible patients.

Home Oxygen and Ventilatory Support

Although a specific effect of oxygen on reducing exacerbations has not been demonstrated, long-term oxygen therapy has a proved mortality benefit in COPD.[75,76] Furthermore, under-prescription of long-term oxygen therapy where indicated was associated with increased hospital admissions.[77] Domiciliary noninvasive ventilation (NIV) may also improve survival for patients with COPD with hypercapneic respiratory failure[78]; however, controlled trials in this area with regard to exacerbations are also lacking.

Pulmonary Rehabilitation

There is evidence that multiprofessional exercise and education pulmonary rehabilitation programs reduce hospitalization rates in COPD, while improving health status and functional capacity.[79] Maintenance programs may be necessary to maintain these benefits.

Exacerbation therapy is administered in a step-wise model as previously mentioned (**Fig. 4**).[80] The mainstay of exacerbation therapy is an increase in the dose and frequency of short-acting bronchodilators and systemic corticosteroids. Antibiotics are reserved for exacerbations associated with increasing sputum volume or purulence.

Self Management

Patient education is vital to improved management of COPD exacerbations. Rapid recognition of exacerbation symptoms and earlier treatment improves recovery and reduces the risk of hospitalization.[81] These findings have been incorporated into many patient self-management plans and programs that are designed to enable patients to respond appropriately to the first signs of an exacerbation without leading to overtreatment of minor symptom variations. Patients at high risk of exacerbations can be provided with a course of "rescue" antibiotics and corticosteroids to keep at home for use as part of a self-management strategy and instructed to commence
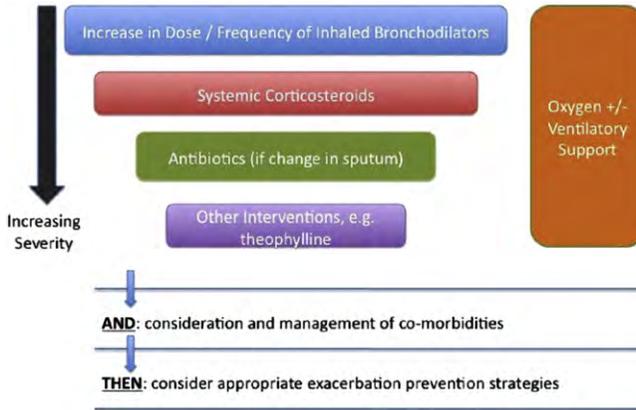
Fig. 4. General scheme for management of a chronic obstructive pulmonary disease (COPD) exacerbation. (*From* Hurst JR, Wedzicha JA. Management and prevention of chronic obstructive pulmonary disease exacerbations: a state of the art review. BMC Med 2009;7:40.)

oral corticosteroid therapy if their increased dyspnea interferes with activities of daily living, either independently or after seeking advice from a healthcare professional. Antibiotics should be started in response to increased sputum volume or purulence and bronchodilator therapy increased to control symptoms.[47] Such interventions have been shown to reduce admission rates[82,83]; however, not all patients are suitable for these strategies. Patients with COPD are frequently elderly and may have cognitive difficulties limiting their ability to self manage, particularly when acutely unwell. Further research is required in this area, with a focus on identification and management of patients at high risk of hospital admission.[84]

Inhaled or Nebulized Bronchodilators

Bronchodilators relieve dyspnea and airflow obstruction during exacerbations[85] and short-acting inhaled β_2 agonists are usually the preferred bronchodilators for the initial treatment of COPD exacerbations.[86] The addition of anticholinergics has the potential for increased therapeutic benefit; however, empiric evidence to support this combination is lacking[85] and the drugs are generally reserved for exacerbations that exhibit a suboptimal response to inhaled β_2 agonists alone.[86] Nebulizers and hand-held inhalers can be used to administer inhaled bronchodilators during exacerbations of COPD and the choice of delivery method should consider the ability of the patient to use the device and the dose of drug required.[47]

Antibiotics

There is considerable evidence to support the role of bacteria in COPD exacerbation etiology and most guidelines highlight that antibiotics are beneficial in selected patients.[86] Purulent sputum is a reasonable surrogate of bacterial infection[27] and routine antibiotic use is normally advised only in the context of exacerbations associated with an increase in sputum purulence.[86] Much of the evidence for these recommendations stems from the seminal study by Anthonisen and colleagues[26] that provided strong evidence that antibiotics had a significant effect on peak expiratory flow rate (PEFR) and led to earlier resolution of symptoms. Type 1 exacerbations (those associated with increased sputum volume, sputum purulence, and dyspnea) benefited the most with resolution of symptoms in 63% of the antibiotic-treated

exacerbations and 43% of the placebo group. However, patients with type 3 exacerbations (who met just one of the three cardinal symptoms) did not show significant benefit.

Studies have also assessed the benefits of stratifying antibiotic use according to exacerbation severity. However, the concept of exacerbation severity is difficult, reflecting the severity of the initiating insult, and that of the underlying COPD. In COPD exacerbations requiring mechanical ventilation, oral ofloxacin reduced in-hospital mortality, duration of hospital stay, length of mechanical ventilation, and the need for additional courses of antibiotics.[87] Therefore, in addition to exacerbations associated with increased sputum purulence, antibiotics are recommended in severe exacerbations requiring mechanical ventilation.[86]

The choice of antibiotics remains uncertain, predominantly because of methodologic limitations hampering comparison of studies examining different antibiotics. At present, most guidelines suggest initial empiric treatment should be in the form of an aminopenicillin, a macrolide, or a tetracycline, taking into account guidance from local microbiologists and in the light of local resistance patterns.[47] In hospitalized patients, sputum should be sent for culture at exacerbation if purulent, and the appropriateness of therapy checked against sensitivities when available. In those patients at high risk of *P aeruginosa*, fluoroquinolones should be considered.

Antiviral Agents

Viral infections (in particular rhinovirus) play a key role in exacerbation etiology and a variety of potential therapeutic agents have been trialed for the treatment of rhinoviral infections. Compounds have attempted to target cell susceptibility, viral attachment and receptor blockade, viral uncoating, viral RNA replication, and viral protein synthesis. Unfortunately, although the neuraminidase inhibitors amantadine and zanamivir are effective against influenza, antirhinoviral compounds have failed to demonstrate a clinically significant benefit in trials and are often complicated by adverse events and lack of tolerability.[88,89]

Systemic Corticosteroids

Multiple studies have found significant short-term benefits of corticosteroids in the treatment of COPD exacerbations. Corticosteroids lead to improvements in FEV_1 in the first 3 to 5 days of treatment[90–92] and Pa_{O_2} in the first 72 hours compared with placebo.[92,93] Corticosteroids have also been shown to reduce hospitalization length[90,91] and the likelihood of treatment failure.[94] However, treatment of exacerbations with corticosteroids has not been shown to improve mortality.[94]

Considerable debate exists regarding the optimal dose and duration of treatment for acute exacerbations, often because of the heterogeneity of treatment regimens in different clinical trials.[95] There is no clear benefit of intravenous therapy over oral preparations and most guidelines recommend a dose of 30 to 40 mg oral prednisone per day for duration of 7 to 14 days.[47,86] There is no advantage in prolonged courses of therapy[91] and shorter courses of therapy reduce the risk of adverse effects. Tapering of this regimen is not required for most patients.[96] The most common reported adverse effect of corticosteroid therapy is hyperglycemia, particularly in patients with preexisting diabetes mellitus,[91] although osteoporosis prophylaxis should also be considered in patients requiring frequent courses of treatment.

The addition of antibiotics to oral steroids as part of exacerbation treatment may have further benefits to regimens composed of oral corticosteroids alone. Epidemiologic research using data from historical cohorts found that adding antibiotics to oral corticosteroids as part of index exacerbation treatment was associated with an

increased time to the next exacerbation,[97] a reduced risk of future exacerbations, and reduced risk of all-cause mortality.[98]

Methylxanthines (Theophylline)

Intravenous theophyllines seem to increase respiratory drive, act as bronchodilators, and produce small improvements in acid–base balance during COPD exacerbations.[99] However, they do not improve lung function, dyspnea, or length of hospital stay when given in addition to nebulized bronchodilators and corticosteroids.[99] Given the toxicity associated with these medications, intravenous theophyllines are reserved for patients inadequately responding to standard therapy consisting of nebulized bronchodilators, oral corticosteroids, and antibiotics where indicated.

Oxygen

Oxygen is a treatment for hypoxemia, not breathlessness. However, when patients are hospitalized for exacerbations oxygen is not uncommonly administered during ambulance transportation, at assessment, and on admission. Oxygen must be prescribed with caution in this context because the respiratory drive of some patients with COPD may depend on their degree of hypoxia rather than the usual dependence on hypercapnia. Although rarely seen, overzealous and unmonitored oxygen therapy may result in suppression of a patient's respiratory drive, CO_2 narcosis, and respiratory arrest. Therefore, on arrival at the emergency room, arterial blood gases should be measured and the inspired oxygen concentration adjusted accordingly. Patients who have had a prior episode of hypercapnic respiratory failure should be issued with an oxygen alert card and a 24% or 28% Venturi mask for use during transportation.[47] For most patients with known COPD a target saturation range of 88% to 92% is recommended pending the availability of blood gas results.[100]

NIV

NIV, usually administered as pressure-cycled bi-level positive airway pressure is the treatment of choice for hypercapnic respiratory failure at acute exacerbation of COPD that persists despite optimal medical therapy including controlled oxygen therapy. NIV has been shown to improve gas exchange and acid–base disturbances. Consequently, NIV can reduce the length of hospital stay, mortality, and the need for intubation compared with usual medical care.[101] NIV should be delivered in a dedicated setting by trained, experienced staff. Before patients commence treatment, a clear management plan must be established to determine a course of action in the event of deterioration and to define the ceiling of care.[47]

Invasive Ventilation

If patients do not respond adequately or tolerate NIV (eg, because of multiorgan failure or reduced levels of consciousness), they may require endotracheal intubation and invasive ventilation. Historically, there has been a reluctance to intubate patients with COPD because of concerns about weaning and long-term outcomes. However, patients receiving mechanical ventilation because of acute decompensation of COPD have a significantly lower mortality (estimated 22%) than patients receiving mechanical ventilation for acute respiratory failure from other etiologies.[102] Thus, patients with exacerbations of COPD should be considered eligible to receive treatment on intensive care units, including invasive ventilation when necessary. Factors to be considered before admission include premorbid functional status, body mass index, the prevalence and severity of comorbidities, stable-state oxygen requirements, and

prior intensive care unit admissions, in addition to age and degree of airflow obstruction or lung function impairment.[47]

Palliative Care

Palliative care involves the active care of patients and their families by a multidisciplinary team when a patient's disease is no longer responsive to curative treatment. Palliative care focuses on symptom control and optimizing quality of life. Anxiety and depression is common in COPD and may become particularly problematic in patients with end-stage disease, and those hospitalized with exacerbations. These symptoms should be treated with conventional pharmacotherapy. Intractable dyspnea that is unresponsive to other medical therapies may be treated with opiates, benzodiazepines, and tricyclic antidepressants[47]; however, there is little evidence to support the use of oxygen to relieve dyspnea in nonhypoxemic patients.[103] Palliative care should also include consideration of admission to hospices.

SUMMARY

The mechanisms of COPD exacerbation are complex. Respiratory viruses (in particular rhinovirus) and bacteria play a major role in the causative etiology of COPD exacerbations. In some patients, noninfective environmental factors may also be important. Data recently published from a large observational study identified a phenotype of patients more susceptible to frequent exacerbations. Many current therapeutic strategies can reduce exacerbation frequency. Future studies may target the frequent exacerbator phenotype, or those patients colonized with potential bacterial pathogens, for such therapies as long-term antibiotics, thus preventing exacerbations by decreasing bacterial load or preventing new strain acquisition in the stable state. Respiratory viral infections are also an important therapeutic target for COPD. Further work is required to develop new anti-inflammatory agents for exacerbation prevention, and novel acute treatments to improve outcomes at exacerbation.

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