Prevention of Exacerbations
How Are We Doing and Can We Do Better?

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Prevention of exacerbations of chronic obstructive pulmonary disease (COPD) can involve removing the cause or reducing the patient's vulnerability to the cause. This article addresses the following issues: What is the problem during an exacerbation, what are the causes of an exacerbation, what can prevent exacerbations, and who are we? The difference between a patient with COPD during an exacerbation and after recovery is small. It is unlikely that patients with early COPD experience less exposure to exacerbation causes than those with severe disease; it is just that the consequences are more severe for those with severe disease. Interventions that produce small absolute benefits can therefore have a disproportionately large effect on exacerbation reduction. Recognized causes include season, cold weather, pollution events, bacterial infection, viral infection, and treatment withdrawal. Countries with warmer climates have much larger mortality in cold weather than those with colder climates. Reducing exacerbations in more temperate climates may be altered as much by changes in clothing and bedroom heating as by changes in treatment. Taking more exercise in cold weather may be the underlying reason for the reduction of exacerbations after pulmonary rehabilitation. Influenza vaccination reduces influenza severity and reduces transmission from health care workers to patients. There are a number of pharmacologic interventions shown to reduce (the effect of) exacerbations, including inhaled corticosteroids, long-acting β-agonists, long-acting anticholinergics, mucolytics, and perhaps antibiotics that reduce *Haemophilus* carriage. The effect of the bronchodilators is additive to inhaled corticosteroids; how far the other interventions are complementary is unclear. So far, we have had a very medical response to COPD exacerbations. Altering social and behavioral aspects is likely to be complementary.

Keywords: COPD exacerbation; weather; prevention; prophylaxis

FOR A PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE, WHAT IS THE DIFFERENCE BETWEEN THE STABLE STATE AND AN EXACERBATION?

Exacerbations of chronic obstructive pulmonary disease (COPD) in essence are defined by the patient as being in a worse state than usual. Most agree that increased breathlessness is the cardinal symptom (1), and at least for exacerbations due to bacterial infection, there is usually an increase in sputum volume and purulence (2). Finding an increase in sputum allows the clinician to attribute the increased breathlessness to a COPD exacerbation, rather than other common causes, such as heart failure or pulmonary embolism, both of which are difficult to diagnose in a patient with advanced COPD. Exacerbations are a feature of moderate to severe COPD (3), and appear infrequently in the earlier stages of the disease (4, 5). Because infection is believed to be the commonest cause, it is not immediately obvious why infections should be confined to those with more advanced disease. A clue comes from studying patients prospectively and measuring lung function during a stable phase and during an exacerbation. The differences are surprisingly small. In a study of 37 exacerbations, Bhowmik and colleagues (6) found a mean decrease in FEV_1 of 80 ml during an exacerbation. Such a small change is unlikely to be noticed by a patient with early disease, but may be critical in patients with advanced disease, perhaps explaining how patient-defined exacerbations are largely confined to those with advanced disease. It might also explain why interventions that produce a small absolute improvement in lung function might result in larger reductions in exacerbations. The exacerbations in this study were defined from changes in symptoms from prospectively kept diary cards, raising the possibility that the exacerbations were too mild to warrant the label of exacerbation. A further study of this cohort showed that those whose diary cards indicated an exacerbation but who did not seek emergency medical attention had an increased risk of hospital admission and a worse quality of life than those seeking attention, supporting the significance of diary card–defined exacerbations (7).

INFECTION-INDUCED EXACERBATIONS

If more exacerbations are to be prevented, either the causes need to be reduced or the impact of those causes reduced. Viral and bacterial infections are the most frequently identified precipitants of COPD exacerbations. Exacerbations are more common in patients with COPD with regular sputum (8). This might be related to a degree of bronchiectasis that is common in this group, and raises the possibility of sputum modification as a therapeutic target. The literature on mucolytics is now confusing. There is a Cochrane analysis showing a reduction in exacerbations from 2.7 to 1.9/yr with a range of mucolytic trials (9). The large BRONCUS study (Bronchitis Randomised on N-acetylcysteine Cost-Utility Study) using acetylcysteine 600 mg/d was unable to reproduce this (10), but the dose of acetylcysteine used was relatively low. It is also possible that reducing sputum bacterial load, or eradicating *Haemophilus influenzae* carriage, prolongs the time between exacerbations (11).

BENEFITS OF VACCINATION

Vaccines that may (or may not) confer consistent benefits in reducing COPD exacerbation are those directed against influenza and *Streptococcus pneumoniae*. Although there are no randomized studies of influenza vaccinations in patients with COPD, community studies show that those vaccinated have fewer admissions (12) and that mortality is reduced, the effects being greater as age increases (13). Although it seems to be accepted widely that vaccination against influenza during the influenza season is a highly cost-effective way of reducing exacerbation frequency, convincing evidence of benefit in patients with COPD is absent. Influenza vaccination is recommended in all current treatment

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guidelines and is a routine consideration in people with a diagnosis of COPD at any stage of their disease.

Influenza can also spread from health care workers to patients; mortality in nursing home residents can be reduced by vaccinating their carers. In one study, increasing staff influenza vaccination rates from 4 to 67% reduced the numbers of hospital-acquired influenza infections significantly in a tertiary referral hospital (14). There was an inverse association between health care worker compliance with vaccination and influenza infections in patients.

Pneumococcal vaccination is generally recommended for patients with COPD, although the evidence from randomized trials is conflicting. A Cochrane review concluded that case-control studies showed a significant effect of reducing invasive pneumococcal disease in adults (odds ratio [OR], 0.47; confidence interval [CI], 0.37–0.59). The earlier randomized studies showed a greater effect than later studies; when taken together, however, neither the reduction in death (OR, 0.9; CI, 0.76–1.07) nor pneumonia (OR, 0.77; CI, 0.58–1.02) was statistically significant (15). A recent study investigated the epidemiology of pneumococcal colonization and infection in COPD, effects of pneumococcal colonization on the development of exacerbation, and the immunologic response against *S. pneumoniae* (16). Sputum was cultured from patients with stable disease and during exacerbations. Colonization with only pneumococci (monocultures) increased the risk of an exacerbation. Furthermore, pneumococcal antibody titers were significantly lower in patients with COPD than in vaccinated healthy adults, and the data indicated that pneumococcal colonization in patients with COPD is frequently caused by vaccine serotype strains. Pneumococcal colonization is a risk factor for exacerbation of COPD, even though the patients with COPD were able to mount a significant immune response to pneumococcal infection. The authors conclude that patients with COPD may benefit from pneumococcal vaccination (16). Although these observations are not from high-quality placebo-controlled randomized studies, there is sufficient evidence to recommend pneumococcal vaccination and annual influenza vaccination to patients with COPD, and to administer annual influenza vaccination to their medical (and perhaps social) carers.

SEASONAL EXACERBATIONS

In the United Kingdom, there is a consistent increase in death and hospital admissions in the winter months, which produces severe stresses on the health care system. The majority of the increase is due to respiratory and cardiovascular disease. Figure 1 shows the adjusted annual mortality for those older than 75 yr (17). The increased winter mortality is partly reduced by adjusting for influenza incidence, and is largely abolished by also adjusting for temperature.

It has been somewhat of a surprise to Britons that this increase is not seen in all countries with cold winters. In fact, the increase did not occur in the Siberian city of Yekaterinburg until the temperature fell below 0°C, and from visual inspection of Figure 2, not until −20°C (18). In Yekaterinburg, most of the population continued to go outside even in the coldest weather, but wore more clothes and seldom shivered. Hats were nearly always worn when the temperature fell below 8°C. The living room temperature was maintained around 20°C, even when the outdoor temperature fell below −25 °C. Few slept in unheated bedrooms. A study from Yakutsk in eastern Siberia, where it is even colder, showed no increase in all-cause mortality, even when the outdoor temperature fell to −48°C (19). The proportion going out during the day fell from 82% when the outdoor temperature was −20°C to 44% at −48°C. Those going out wore thick clothing rather than anoraks, mostly made from fur, preventing cold stress. (The Yekaterinburg, Yakutsk, and Eurowinter centers used the same methodology. Sampling was two-stage, primary sampling by area selected to be representative of social groups and population density from a central register. Secondary sampling was haphazard but every two addresses had to be separated by at least four others, and not more than two addresses were sampled per apartment block or street. Interviews took place after 5:00 P.M. in the living room of the sampled address. One thousand residents were sampled, equally distributed by sex and age groups [50–59 and 65–74 yr] in each area. The countries and cities were chosen because of available research teams and not by any sampling process.)

The relationship between relatively cold weather and mortality has been studied across Europe in the Eurowinter study (20). The warmer the average temperature, the greater the mortality in cold weather (Figure 3). Increased mortality per °C below 18°C fell from 2.15% in Athens to 0.27% in southern Finland. There were statistically significant associations of increased mortality, after adjusting for sex and age, with low living room temperatures (Figure 4), limited bedroom heating, low proportion of people wearing hats (Figure 5), gloves, and anoraks, and inactivity outdoors when the temperature fell to 7°C.

The epidemiologic data therefore suggest that increased winter mortality can be reduced or prevented by reducing cold stress both indoors and outdoors. There are no controlled studies showing that such a strategy works, but the data support interventions unrelated to pharmacotherapy that might have a substantial impact on COPD exacerbations. One of the features of life in the coldest environments studied has been the continuing exercise despite freezing temperatures. In more temperate environments, pulmonary rehabilitation has been shown to reduce

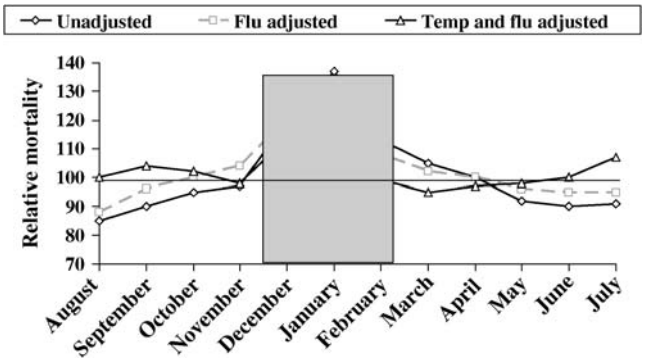

Figure 1. Seasonal mortality in individuals older than 75 yr in the United Kingdom related to influenza incidence and mean outdoor temperature. Reprinted by permission from Reference 18.

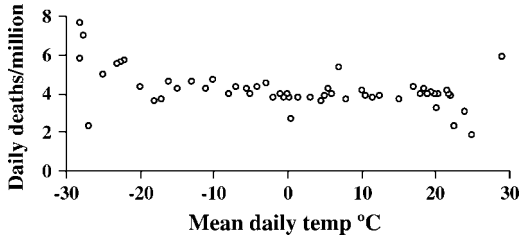

Figure 2. Deaths from respiratory disease in 50- to 74-yr-olds in Yekaterinburg, Siberia, 1990–1994, related to mean daily temperature. Redrawn from Reference 18.

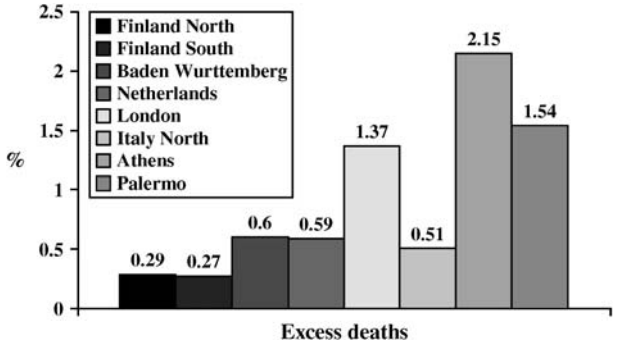

Figure 3. Relationship between increased mortality at temperatures below 18°C in the Eurowinter study. Reprinted by permission from Reference 20.

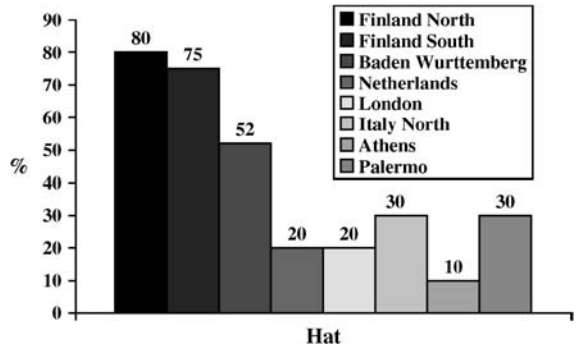

Figure 5. The proportion of the population wearing hats when the outdoor temperature falls below 7°C from the Eurowinter study. Reprinted by permission from Reference 20.

exacerbation rates and length of hospital stays (21). It seems that inactivity is bad for COPD.

PULMONARY REHABILITATION

Pulmonary rehabilitation reduces hospitalizations due to exacerbation of severe COPD (21). A recent meta-analysis of six clinical trials showed that pulmonary rehabilitation after suffering from exacerbation of COPD reduced readmissions (relative risk [RR], 0.26 [0.12–0.54]) and mortality (RR, 0.45 [0.22–0.91]). Exercise capacity was improved as expected: 6-min walking distance improved from 64 to 215 m and shuttle walking test by 81 m (22).

Boxall and coworkers reported recently that a 12-wk home-based program of pulmonary rehabilitation was effective in improving exercise tolerance, dyspnea, and quality of life for housebound patients with COPD (23). At 6 mo, those subjects undergoing pulmonary rehabilitation had a significantly shorter average length of stay at readmission to hospital with exacerbations.

PHARMACOLOGIC INTERVENTIONS

There is now consistent evidence that inhaled corticosteroids reduce the exacerbation rate in patients with COPD. A meta-analysis of some of the earlier studies is shown in Figure 6 (24). The Copenhagen City Lung Study caused heterogeneity in the results. This study was of very early COPD when exacerbations were very infrequent, and which produced no evidence for benefit for the inhaled budesonide using any outcome (5). The other studies produced homogeneous results. The benefit seems to be maintained over time as shown in the Inhaled Steroids and Obstructive Lung Disease in Europe (ISOLDE) trial (3); results for the 3 yr of the trial are shown in Figure 7. Those patients with frequent exacerbations were withdrawn from the study by design, making the results shown a likely underestimate of the true effect. Exacerbations were defined as worsening of symptoms requiring antibiotic or corticosteroid treatment in most modern studies (3, 25–28). Some patients only required the use of oral corticosteroids (29). Earlier studies before systemic corticosteroid use for exacerbations was widespread generally required a self-reported increase in respiratory symptoms alone (30). The Lung Health Study in North America did not define exacerbations but found reduced hospitalizations for respiratory conditions in the triamcinolone-treated patients, but no significant difference in emergency room visits (31).

A double-blind randomized study withdrawing fluticasone from patients maintained on 500 μg twice daily showed a reduced

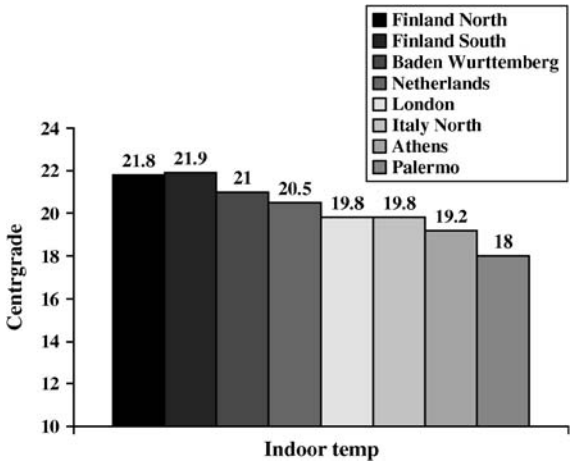

Figure 4. Relationship between measured indoor temperature and region in the Eurowinter study when the outdoor temperature was 7°C (Reference 20).

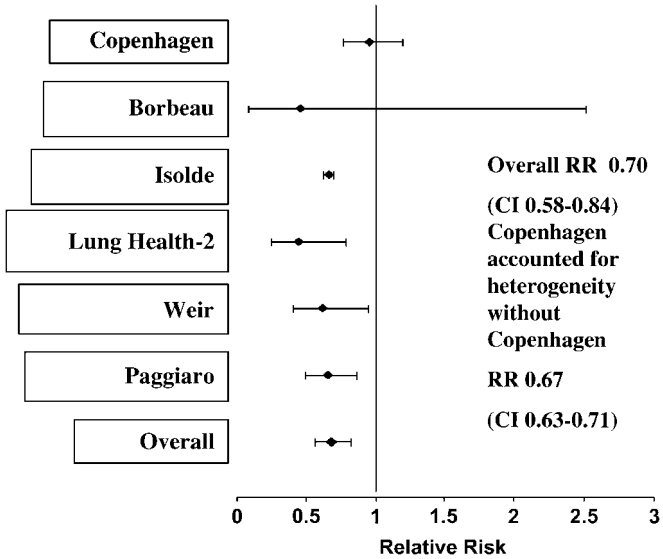

Figure 6. Meta-analysis of exacerbation rates in studies comparing inhaled corticosteroids with placebo. Reprinted by permission from Reference 24.

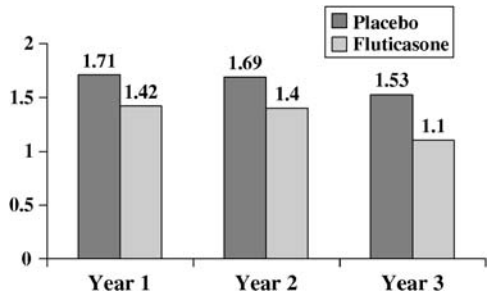

Figure 7. Exacerbations of chronic obstructive pulmonary disease/yr in the Inhaled Steroids and Obstructive Lung Disease in Europe (ISOLDE) trial, which compared fluticasone propionate 500 μg twice daily with placebo. Reprinted by permission from Reference 3.

time to the next exacerbation on those randomized to placebo compared with those remaining on fluticasone (28).

Long-acting bronchodilators also reduce exacerbation rates, although there are fewer long-term studies than those using inhaled corticosteroids alone. Two studies using formoterol 12 μg twice daily (26, 32), one using salmeterol 50 μg twice daily (27), and three studies using tiotropium 18 μg daily (33–35) showed reductions in exacerbations.

Self-management plans have not been shown to reduce exacerbations in patients with COPD, unlike the situation in asthma (36–38). The Lung Health Study on smoking cessation treatment showed no change in hospitalization rates between those in the control and intervention groups (39).

COMBINATIONS OF APPROACH

Individual interventions reviewed above have shown exacerbation reductions after exercise, immunization, mucolytics, antibiotics, bronchodilators, and inhaled corticosteroids. The mechanisms underlying some of these interventions is unclear, making it difficult to predict which can be combined with benefit. The best evidence comes from the combination of bronchodilators with inhaled corticosteroids. Two studies have shown additive effects of budesonide and fenoterol (26, 32), and one has shown additive effects of fluticasone and salmeterol (27). The benefits of the combinations were, however, similar to the benefit of fluticasone alone in the ISOLDE trail (3) (~ 30% reduction in exacerbations), suggesting that there might be a ceiling with this type of intervention. Trials of tiotropium combined with long-acting β-adrenergic agonists and inhaled corticosteroids are overdue. In one of the tiotropium studies, more than 80% of those studied were taking inhaled corticosteroids (35), making it likely that the effects of tiotropium and inhaled corticosteroids are also additive. The BRONCUS study failed to show a benefit from acetylcysteine (10), which had been demonstrated in a meta-analysis of smaller studies (9). Most of those studied in the BRONCUS study were also taking inhaled corticosteroids. In a retrospective analysis, those patients naive to inhaled corticosteroids showed a reduction of exacerbations, whereas those on inhaled corticosteroids did not, perhaps accounting for the discrepancy with the meta-analysis.

THE WAY FORWARD

From the above review, it seems that a multidisciplinary approach is needed. At present, randomized controlled trials are largely confined to pharmaceutical interventions. There are, however, persuasive epidemiologic arguments for a much more wide-ranging approach. In relatively warmer countries, indoor temperatures need to be higher in cold weather in both living rooms and bedrooms; patients with COPD need to be able to afford heating, and houses need to be designed with warmer bedrooms (a role for architects and social planners). In the United Kingdom, around 30% of patients with COPD sleep with the window open in winter, something that may be a residue of this advice in the control of tuberculosis in the past (a role for health educationists). Regular exercise outdoors seems beneficial, helped by pulmonary rehabilitation. However, cold stress is detrimental, and adequate clothing required. There is a challenge for the clothing industry to develop socially desirable warm clothing. There is a particular problem with headwear, which in some countries is often used to make social statements (a role for fashion designers and clothing manufacturers). Health care workers have often been reluctant to have regular influenza vaccinations themselves. It seems that nosocomial infection can be reduced by regular carer vaccination (a role for occupational health and infection-control professionals). The pharmaceutical industry also has work to do. One company does not have all the best drugs. Cooperation among manufacturers is required to study anticholinergic, β-agonist and inhaled corticosteroid combinations, and perhaps produce a poly-inhaler to rival the cardiologists' polypill (a role for the pharmaceutical industry). Finally, the medical professions need to have a much more positive approach to patients with COPD, who are often blamed for their disease much more than is common with cardiovascular disease (a role for primary care and respiratory specialists). Integrated long-term care combining the above approaches with patient education and support is often lacking. Monitoring annual exacerbation rates is rarely attempted, despite exacerbations being the most important determinant of reduced quality of life (40), and the most costly aspect of COPD care. "We" are therefore architects, clothing manufacturers, infection-control professionals, fashion designers, health educationists, occupational health professionals, the pharmaceutical industry, primary care physicians and nurses, respiratory specialists, and social planners, all of who should work together to reduce the impact of COPD on those suffer from it.

Conflict of Interest Statement: P.S.B. has been reimbursed by AstraZeneca for speaking at the conference on which this paper is based and occasionally at other scientific meetings. He has been an advisor to the U.K. Meteorological Office on the relationship between COPD and weather (unpaid) and has attended as a speaker meetings and courses organized and financed by other pharmaceutical companies (GlaxoSmithKline and IVAX). He has had a grant of £10,000 for studying mortality in patients with COPD from GlaxoSmithKline (2001). He has one share in GlaxoSmithKline. He has no institutional financial interest. He has developed the Oasys plotter for analyzing serial measurements of peak expiratory flow in relationship to the presence or absence of occupational asthma and currently makes this available free of charge to interested clinicians on request. He funds the Website www.occupationalasthma.com, which provides support for this and a question and answer forum. He has no income to support this. He has received research funding related to occupational lung disease from the government of Ghana, the European Chemical Industry Foundation, the U.K. Health and Safety Executive, the COLT Foundation, and the E.U. Socrates Programme. He has had grants related to COPD from the Birmingham Health Authority.

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