ORIGINAL ARTICLE

Impact of Prolonged Exacerbation Recovery in Chronic Obstructive Pulmonary Disease

Gavin C. Donaldson[1], Martin Law[2], Beverly Kowlessar[1], Richa Singh[1], Simon E. Brill[1], James P. Allinson[1], and Jadwiga A. Wedzicha[1]

[1]Airways Disease Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom; and [2]MRC Biostatistics Unit, Cambridge Institute of Public Health, Forvie Site, Robinson Way, Cambridge Biomedical Campus, Cambridge, United Kingdom

ORCID ID: 0000-0002-5538-4190 (G.C.D.).

Abstract

Rationale: Exacerbations are important and heterogeneous events in the natural history of chronic obstructive pulmonary disease (COPD).

Objectives: To examine the consequences of prolonged exacerbation recovery in patients with COPD.

Methods: A cohort of 384 patients with COPD (FEV_1 % predicted 45.8 [SD, 16.6] and a median exacerbation rate of 2.13 per year [interquartile range, 1.0–3.2]) were followed for 1,039 days (interquartile range, 660–1,814) between October 1995 and January 2013. Patients recorded daily worsening of respiratory symptoms and peak expiratory flow (PEF), and when stable underwent spirometry every 3 months, and completed the St. George's Respiratory Questionnaire annually. Exacerbations were diagnosed as 2 consecutive days with one major symptom plus another respiratory symptom. Exacerbation duration was defined as the time from onset to the day preceding 2 consecutive symptom-free days and recovery in PEF as return to preexacerbation levels.

Measurements and Main Results: A total of 351 patients had one or more exacerbations. Patients with a longer symptom duration (mean, 14.5 d) had a worse St. George's Respiratory Questionnaire total score (0.2 units per 1 day; $P = 0.040$). A longer symptomatic duration was associated with a shorter interval between exacerbation recovery and onset of the next exacerbation (hazard ratio, 1.004; $P = 0.013$). For 257 (7.3%) exacerbations, PEF did not recover within 99 days. These exacerbations were associated with symptoms of a viral infection (cold and sore throat). Patients with these nonrecovered exacerbations showed a 10.8 ml/yr ($P < 0.001$) faster decline in FEV_1.

Conclusions: Prolonged exacerbation symptomatic duration is associated with poorer health status and a greater risk of a new event. Exacerbations where lung function does not recover are associated with symptoms of viral infections and accelerated decline in FEV_1.

Keywords: COPD; exacerbations; recovery; risk interval; nonrecovery

Exacerbations are important events in the natural history of chronic obstructive pulmonary disease (COPD). Frequent exacerbations are associated with a faster decline in lung function (1), poorer quality of life (2), reduced exercise capacity (3), and increased airway and systemic inflammation (4). Most exacerbations are triggered by infection mainly with a respiratory virus (5) or pathogenic bacteria (6).

Treatment of COPD exacerbations typically involves prescription of antibiotics and/or oral corticosteroids, to decrease

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Correspondence and requests for reprints should be addressed to Gavin C. Donaldson, Ph.D., Airways Disease Section, National Heart and Lung Institute, Imperial College London, Guy Scadding Building, Dovehouse Street, London SW3 6LY, UK. E-mail: gavin.donaldson@imperial.ac.uk

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At a Glance Commentary

Scientific Knowledge on the Subject: We have previously reported that chronic obstructive pulmonary disease exacerbations persist symptomatically for a median of 7–8 days and that in a small percentage of exacerbations, PEF does not return to preexacerbation levels. The consequences of these prolonged or nonrecovered exacerbations on health status and subsequent events are unknown.

What This Study Adds to the Field: Prolonged chronic obstructive pulmonary disease exacerbations are associated with worse health status and the exacerbation that follows occurs sooner. A failure of airway function to return to preexacerbation levels is associated with symptoms of cold and sore throat (viral infections), and patients who have these events have a faster decline in FEV_1.

respiratory symptom intensity and shorten the duration of the exacerbation. There is evidence that treatment of a COPD exacerbation with oral antibiotics influences future events (7–9) and treatment of exacerbations with oral prednisolone shows similar effects on future events with reduced relapse rates within 30 days (10, 11). However, no study has yet investigated whether the symptomatic duration of an exacerbation is associated with the time to the occurrence of the next exacerbation event.

Patients do not always fully recover from exacerbations. Suissa and colleagues (12) reported an increasing risk of death with each successive exacerbation that was independent of age. We have previously observed that airway function (peak expiratory flow [PEF]) did not return to preexacerbation levels within 91 days in 7% of exacerbations (13).

We have now collected daily respiratory symptom and PEF data over an 18-year period, enabling us to uniquely examine whether nonrecovery in PEF is associated with any specific symptoms or exacerbation triggers, and whether patients who experienced these exacerbations have a faster decline in lung function. We have investigated whether health-related quality of life (health status) is better in patients with shorter exacerbations. We have also examined whether a proportion of exacerbations take longer to recover than predicted by chance because it would suggest a defect in the recovery process that can be potentially targeted for intervention. Some of the results of this study have been previously reported in abstract form (14, 15).

Methods

Research Subjects and Recruitment

This study consists of data collected from the London COPD cohort between October 1, 1995 and January 31, 2013. The cohort was initially recruited from patients consecutively attending an out-patient clinic. Patients who withdrew or died were replaced to maintain a cohort of up to 200 patients. At recruitment, a full medical history was taken and spirometry recorded. Thereafter, every 3 months, if stable (without exacerbation), further measurements were made of FEV_1 and FVC with either a rolling seal (Sensor Medic Corp, Yorba Linda, CA) or a Vitalograph Gold Standard (Vitalograph Ltd, Maids Moreton, UK) spirometer.

COPD was defined as an FEV_1 less than 70% predicted for age, height, and sex and a FEV_1/FVC ratio less than 0.7. Patients unable to complete daily diary cards or with any other significant respiratory diseases were not enrolled. As in many of our previous studies, to ensure an accurate estimation of exacerbation frequency, the analysis was performed on patients who had recorded daily diary card data for at least 365 days.

Ethics approval was granted from the London-Hampstead ethics committees (REC reference 09/H0720/8). All patients provided written informed consent.

Monitoring and Definition of Exacerbation

All patients completed daily diary cards (*see* Appendix E1 in the online supplement), recording any worsening in respiratory symptoms, change in medication, and the best of three PEF measurements made with a mini-Wright peak flow meter (Clement-Clarke International Ltd, Harlow, UK). Respiratory symptoms were classified as major (dyspnea, sputum purulence, or sputum volume) or minor (colds [nasal discharge/congestion], wheeze, sore throat, or cough).

Exacerbation onset was defined as the first of 2 or more days in which the patient recorded two or more new or worsening symptoms, one of which must be a major symptom (1, 13, 16, 17). Some patients recorded that they were continually breathless or producing sputum, and these continuously recorded symptoms were disregarded when diagnosing an exacerbation. Patients were asked at all study visits if they had experienced recent exacerbations, hospitalization, or health care use, and this allowed for identification of some exacerbations where no symptoms had been recorded on the diary cards. Treatment of the exacerbations was at the discretion of the attending physician and followed current guidelines.

Exacerbation Recovery

Exacerbation duration (recovery time) was defined as the number of days from exacerbation onset that increased respiratory symptoms were still being recorded. The first of 2 consecutive symptom-free days marked when the exacerbation had recovered. Thus, if a single symptom-free day was bracketed by days with increased symptoms, then the exacerbation was considered to be continuing over that period.

Recovery of PEF was determined as the number of days postexacerbation onset that PEF remained below a baseline determined as the average PEF on Days -14 to -8 before the onset of each exacerbation. An exacerbation was deemed to be nonrecovered if PEF remained below baseline over the 99 days postexacerbation onset. Recovery could not be determined if fewer data than 25 out 99 days postexacerbation were available or if another exacerbation occurred before the threshold for recovery was reached or if the baseline data were missing.

Quality-of-Life Measures

Health status was measured with the St. Georges Respiratory Questionnaire (SGRQ) (18). The questionnaires were completed at recruitment and annually thereafter. Patients may perceive their health status differently during an acute exacerbation, and to examine the persistent effects of prolonged exacerbations on health status,

we excluded questionnaires completed between 2 weeks preceding or 6 weeks following an exacerbation.

Statistical Analysis

The average total SGRQ score for all the questionnaires completed by a patient was related by multiple linear regression to the average symptom recovery time for all the exacerbations experienced by the patient. A mean recovery time was used because this would give a better measure of the total number of days a patient spent with an exacerbation than a median value, because this might not take into account the small number of very prolonged exacerbations. The regression model included as covariates age, sex, exacerbation frequency, and FEV_1 as % predicted. A piecewise regression was also used to fit the model with two slopes above and below 7 days with a common intercept. Durations longer than 7 days receive the maximum score for that question in the SGRQ. This analysis was repeated with the total symptom recovery time expressed as a percentage of the total observation time.

Normally distributed data are presented as mean and SD, skewed data as median and interquartile range (IQR), and binary distributed data as percentages. *P* less than or equal to 0.05 was considered statistically significant. Comparisons among groups were made using Student *t* tests, Wilcoxon rank sum tests, and chi-square tests as appropriate. Data were analyzed using Stata 8.2 and 12 (Stata Corporation, College Station, TX).

Decline in FEV_1 was estimated using random-effect linear regression models command xtreg in Stata. An initial model estimated the effect on FEV_1 of time elapsed from recruitment, smoking, and over the same period of observation whether the patients had experienced one or more nonrecovered exacerbation or not, and the interaction of smoking status and also nonrecovered exacerbation status with time. A second model was also constructed that allowed for the effects of frequent exacerbations on FEV_1 decline with inclusion of a variable for whether the patient had frequent exacerbations or not, defined as greater than or equal to group median annual exacerbation rate and its interaction with time. The annual exacerbation rate was calculated for each individual patient by dividing the number of their exacerbations during the entire follow-up period by the number of years of diary card data.

Risk-free interval. Treatment of exacerbations as point events that occur on a single day ignores the fact that exacerbations take time to recover and during that time the patient is not at risk of being diagnosed with a new exacerbation (19). This time-dependent bias is common in the medical literature (20). We separately assessed the effect of recovery duration on the time from when the exacerbation recovered to onset of the next event. The analysis was performed with conditional risk set model (in which the time to each event is measured from entry) that used the Cox proportional hazards model command (stcox) in Stata with stratification for the order of events (21).

Rootogram. The distribution of symptom recovery times was graphically analyzed with a suspended rootogram (22). This graphic technique compares the empirical distribution with a theoretical log-normal distribution. A plot shows the distribution of the square root of the frequencies of the variable under investigation because this facilitates comparisons between interval bins with large or small counts. Differences from the expected distribution are shown as deviations from a horizontal line ($y = 0$) rather than deviations from the fitted curve (the density function) to facilitate identification of patterns of the deviations. Confidence intervals (CIs) for each bin can be calculated assuming the number of observations in a bin follows a multinomial distribution with Goodman approximation of the 95% CI (23).

Results

Patient Characteristics

The characteristics of the 384 patients are reported in Table 1. The patient cohort had a mean FEV_1 of 45.7% predicted (SD, 16.6) and FEV_1/FVC of 0.459 (SD, 0.12). They completed a total of 512,600 days of follow-up with each patient contributing a median of 1,039 days (IQR, 660–1,814).

Exacerbations

The numbers of patients and exacerbations included in the analysis are summarized in Figure 1. Of the 384 patients, 33 patients (8.6%) did not experience any exacerbations. These 33

Table 1. Characteristics of the 384 Patients with COPD

	All COPD Patients (*n = 384*)	
	Mean	**SD**
Age, yr	68.6	8.4
FEV_1, L	1.15	0.47
FEV_1, % predicted	45.7	16.6
FVC, L	2.55	0.84
FEV_1/ FVC	0.459	0.122
Smoking, pack-years	51.9	38.4
	Median	IQR
Exacerbations per year*	2.13	1.0–3.2
Number of days with diary card data	1,039	660–1,814
Days with diary card data per a year of follow-up	348	318–360
	n	%
Male	246	64.1
Current smokers†	122	32.1
Sputum producer‡	199	52.0

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IQR = interquartile range.
*Calculated as the number of exacerbations divided by the number of days of diary card data and multiplied by 365.25.
†Missing smoking data on four patients.
‡Missing sputum data on one patient.

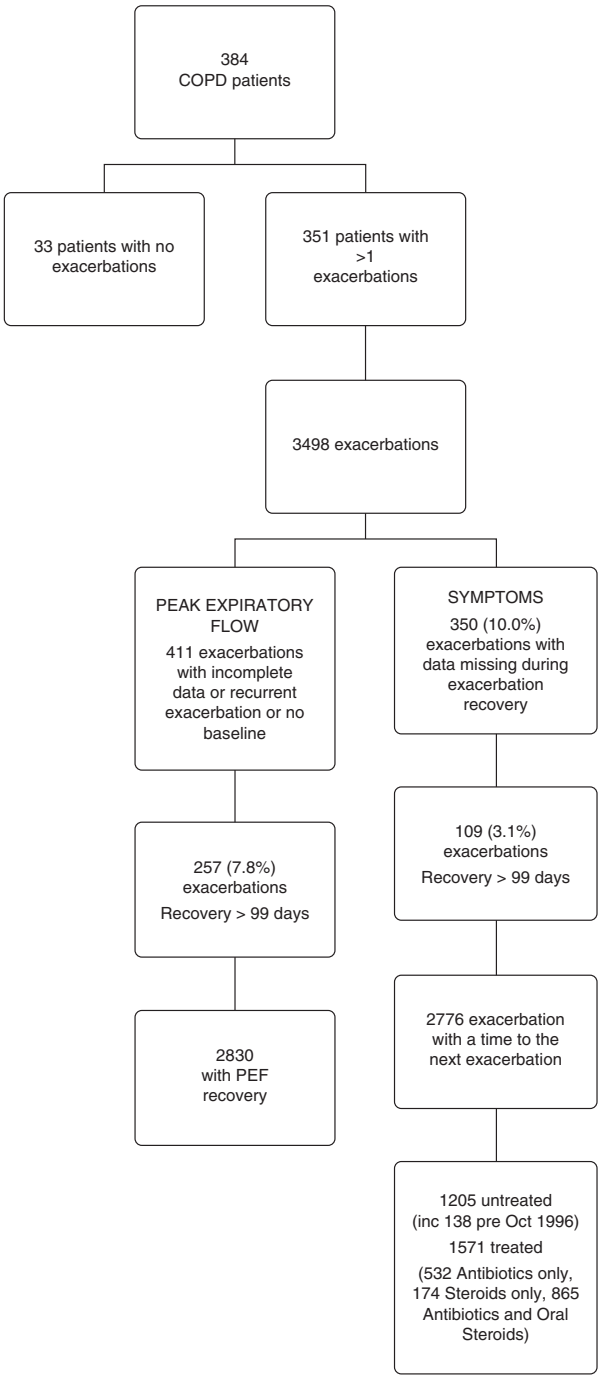

Figure 1. Consolidated Standards of Reporting Trials diagram illustrating the number of patients with chronic obstructive pulmonary disease (COPD) and exacerbations for analysis. PEF = peak expiratory flow.

patients were under observation for a significantly shorter period of 595 days (IQR, 488–925; $P < 0.001$). The remaining 351 patients experienced 3,498 exacerbations with a median of seven exacerbations (IQR, 3–13) per patient over a median of 1,096 days (IQR, 684–1,903).

Exacerbation Recovery and SGRQ

The symptom duration of the exacerbations could only be calculated for 3,039 of the 3,498 exacerbations (86.9%). The duration was not determined for 109 exacerbations (3.1%) when symptoms persisted for more than 99 days and for a further 350 exacerbations (10.0%) where symptom data were not recorded on diary cards for 2 or more days. The median duration for these 3,039 exacerbations was 10 days (IQR, 6–18) and the mean duration was 14.7 days (SD, 14.2).

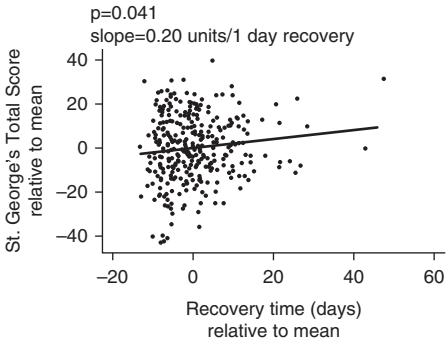

Figure 2. Partial residual plot of the average St. George's Respiratory Questionnaire total score against the patient with chronic obstructive pulmonary disease average symptom recovery time. Data are plotted on a relative scale related to the mean score and recovery time after removing the linear effect of the other independent variables.

Of the 351 patients with an exacerbation, SGRQ data were available for 334 patients (95.2%). For these 334 patients, the average of each patient's mean total score was 53.1 (SD, 16.2) and mean symptom duration of the average for each individual was 14.5 days (SD, 8.4). Figure 2 shows a partial regression plot of the relationship between mean total score and mean exacerbation duration after allowance for age, sex, exacerbation frequency, and FEV_1 % predicted. The SGRQ total score increased if the patient experienced longer exacerbations, by 0.20 units per 1 day longer recovery (95% CI, 0.009–0.394; $P = 0.040$). The findings were unchanged if the durations were logarithmically transformed. Because an average duration may be unduly influenced by very prolonged exacerbations, we also examined the total time spent with exacerbation as a percentage of the observation period. The patient average was 9.0% (SD, 7.4). The SGRQ score increased by 0.57 units (95% CI, 0.34–0.78; $P < 0.001$) per 1% increase in time with exacerbation, after allowance for age, sex, and FEV_1 % predicted, and by 0.40 units per 1% (95% CI, 0.07–0.72; $P = 0.017$) if exacerbation rate was then added to the model.

If the regression line was fitted to two different portions of the relationship, for

average exacerbations greater than or equal to 7 days in duration and for those less than 7 days, the former had a slope of 0.20 per 1-day recovery ($P = 0.041$) and the latter a slope of 0.14 per day recovery ($P = 0.713$).

Exacerbation Recovery and Time to the Next Exacerbation

Of the 3,039 exacerbations with a symptom recovery time, time to the next exacerbation onset could be calculated for 2,776 exacerbations. Of these, 1,571 (56.6%) had been treated with antibiotics and/or oral corticosteroids. The median symptomatic duration of treated exacerbations was 11 days (IQR, 7–20) compared with the duration of untreated exacerbations, median 8 days (IQR, 4–16; $P < 0.001$).

The hazard ratio for the effect of exacerbation duration on the time interval from when an exacerbation resolved to onset of the next exacerbation, therefore excluding the time when the patient was not at risk, was 1.004 per day (95% CI, 1.0008–1.007; $P = 0.013$). This indicated that shorter duration exacerbations were associated with a longer time to the onset of the next event. The effect was present in treated exacerbations (hazard ratio, 1.005 per d [95% CI, 1.0005–1.009]; $P = 0.026$) but not untreated exacerbations (hazard ratio,1.003 per d [95% CI, 0.998–1.007]; $P = 0.181$).

Distribution of Exacerbation Recovery Time

Figure 3 shows the suspended rootogram of the symptom recovery times. Binned into 10-day intervals, there were significantly more exacerbations with duration of between 52 and 72 days than the expected log normal distribution, because the 95% CIs did not cross the horizontal line, which designates that the actual and theoretical distributions matched.

Exacerbation Nonrecovery in PEF

For all 3,498 exacerbations, there were 411 exacerbations for which nonrecovery in PEF could not be determined because there were 25 or fewer days of data postexacerbation PEF data (n = 178) or because another exacerbation occurred before PEF recovery was achieved (n = 94) or because a preexacerbation baseline could not be calculated (n = 139). Of the remaining 3,087 exacerbations, there were 257 (7.3%) during which PEF did not return to baseline values within 99 days. A higher percentage of nonrecovered exacerbations, (9.4%; 148 of 1,569) had been treated with antibiotics and/or oral corticosteroids than were untreated (7.2%; 109 of 1,518; $P = 0.024$).

The median time for the PEF to return to preexacerbation level in the 2,830 with an evaluable exacerbation was 5 days (IQR, 0–14) and the mean duration was 10.3 days (SD, 15.0). There were 2,740 exacerbations with both a PEF and symptom recovery. Recovery in PEF was significantly earlier than symptom recovery by 3.6 days ($P < 0.0001$) but there was also a weak correlation between the two recovery parameters (Spearman $\rho = 0.084$; $P < 0.001$).

The annual rate of nonrecovered exacerbations was positively correlated with the overall exacerbation rate (Spearman $\rho = 0.033$; $P < 0.001$). Independently of exacerbation frequency, age, and sex, the annual rate of nonrecovered exacerbations was higher in more severe patients by 0.0018 events per year per 1% lower FEV_1 % predicted (95% CI, 0.004–0.0001; $P = 0.048$). A total of 230 (59.9%) of the 384 patients never experienced a nonrecovered exacerbation.

Figure 4 shows the PEF time-course of the 3,034 PEF-recovered exacerbations and the 257 non–PEF-recovered exacerbations. Nonrecovered exacerbations were more likely than recovered exacerbations to be associated with symptoms of upper airway colds (37.7% vs. 29.8%; $P = 0.008$) and sore throat (17.5% vs. 12.0%; $P = 0.010$) on the day of exacerbation onset (Day 0).

PEF Nonrecovery and FEV_1 Decline

Figure 5 illustrates the FEV_1 decline in four COPD patient groups: 153 nonsmokers and 75 smokers (sum = 228) who never experienced an exacerbation during which PEF failed to return to preexacerbation levels, and 105 nonsmokers and 47 smokers (sum = 152) who had one or more nonrecovered exacerbations. Smoking status was not recorded on four patients at recruitment. For all these 380 patients, there were 6,066 stable FEV_1 readings over a maximum 16.6 years. The percentage of the 380 patients with one or more nonrecovered exacerbations was 40% (152 of 380). Table E1 in the online supplement compares the characteristics of the two groups.

In the 228 patients with no nonrecovered exacerbations, FEV_1 declined by −22.8 ml/yr (−28.2 to −17.4; $P < 0.001$) but in the 152 patients who had one or more nonrecovered exacerbations, there was an additional −10.8 ml/yr FEV_1 decline (−16.9 to −4.7; $P < 0.001$) or in total, 33.6 ml/yr. The decline associated with active smoking just failed to reach significance (−5.6 ml/yr; −11.4 to 0.0002; $P = 0.061$). Patients at time of recruitment who were still smoking had a slightly higher FEV_1 of 66.5 ml (−28.8 to 162 ml; $P = 0.172$) and those with a nonrecovered exacerbation, a very slightly lower FEV_1 of 39.3 ml (−130 to 51 ml; $P = 0.395$).

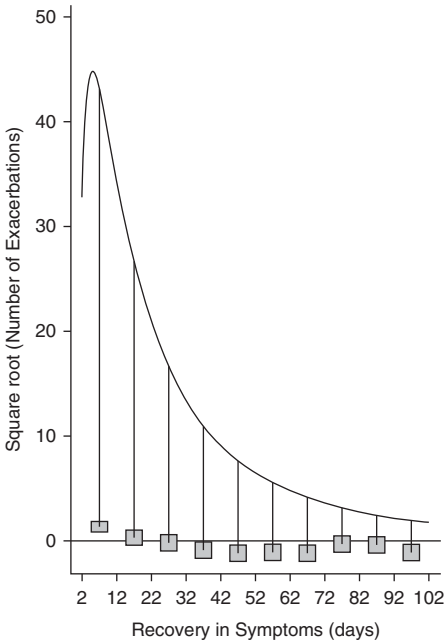

Figure 3. Rootogram showing deviations in the number of exacerbations with symptom recovery grouped into 10-day-wide bins and a theoretical log-normal distribution. The *squares* indicate the 95% confidence intervals for the actual data relative to the expected as gauged by the *horizontal line*.

Results of the second model showed that the FEV_1 decline in the 152 patients with one or more nonrecovered exacerbations was −15.9 ml/yr (−22.3 to −9.4; $P < 0.001$) faster than in the 228 patients with zero nonrecovered exacerbations who declined by −28.0 (−33.9 to −22.2 ml/yr; $P < 0.001$) after allowance for smoking and whether patients were frequent exacerbators (>2.13 per yr) or not. At the start of observation, patients who had frequent exacerbations had a lower FEV_1 of −129 ml (−220 to −37; $P < 0.001$) and smokers had a higher FEV_1 of 72.3 ml (−22.6 to 16.7; $P = 0.135$).

Discussion

There are several important novel findings in this study involving prolonged

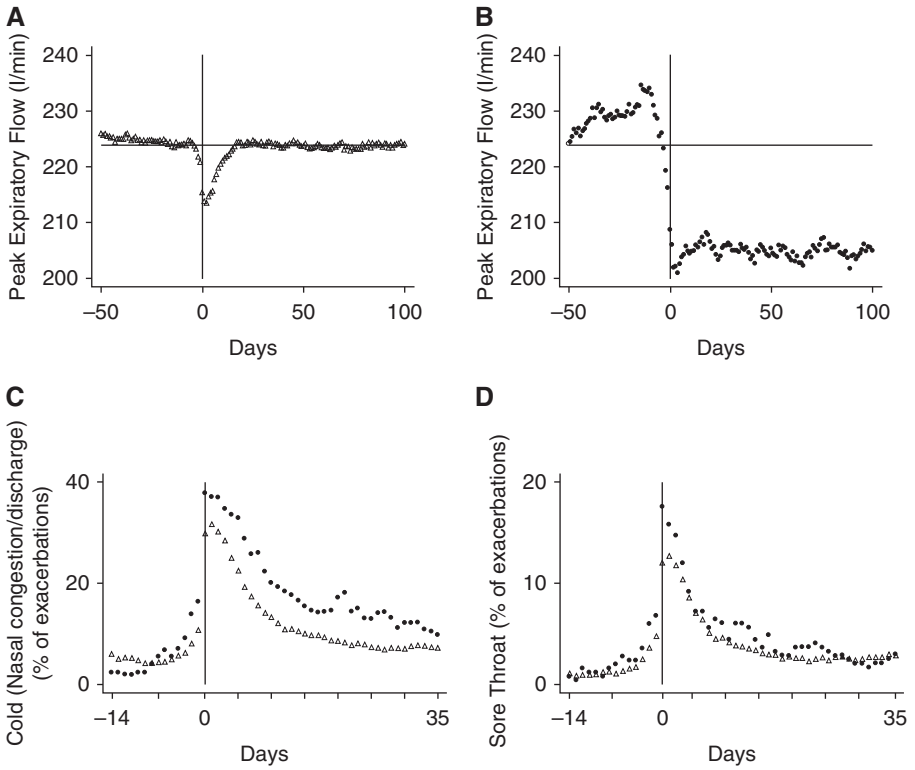

Figure 4. (*A*) Time course of peak expiratory flow (PEF) during recovered chronic obstructive pulmonary disease exacerbations (n = 3,034). (*B*) Time course of PEF during nonrecovered exacerbations (n = 257). (*C*) Time course of cold symptoms in recovered (*triangles*) and nonrecovered (*circles*) exacerbations. (*D*) Time course of sore throat symptoms in recovered (*triangles*) and nonrecovered (*circles*) exacerbations.

exacerbation duration in patients with COPD with respect to increased risk of the next event, worse health status, and the abnormal duration of some exacerbations.

We have previously reported that PEF does not always recover to preexacerbation levels (13). We can now show that these exacerbations are associated with symptoms of upper airway colds and sore throat. We have also shown for the first time that patients who experience these nonrecovered exacerbations have a faster decline in lung function. These important questions could only be addressed by the prospective and consistent daily monitoring of respiratory symptoms and PEF during nearly 3,500 exacerbations in a large number of patients with COPD over an 18-year period.

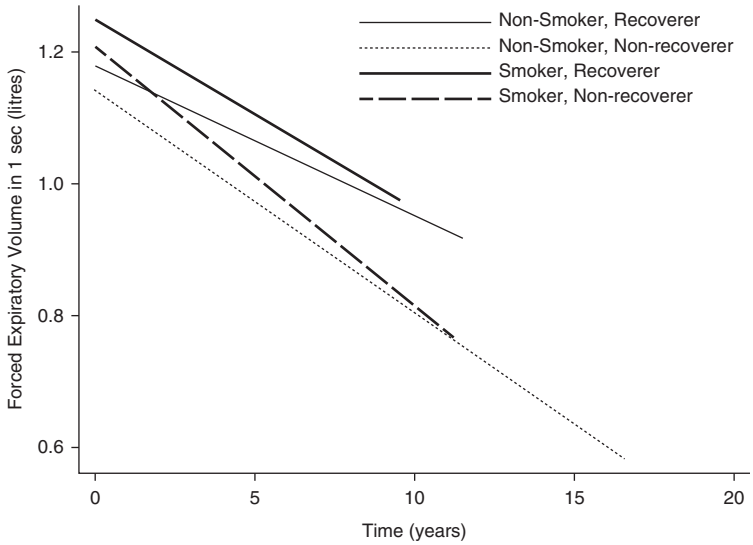

Figure 5. FEV_1 decline in four groups of patients with chronic obstructive pulmonary disease (smokers and nonsmokers) and those with and without exacerbations where peak expiratory flow never returned to preexacerbation levels.

We found that longer exacerbations were associated with an increased risk of a new event (hazard ratio, 1.004; $P = 0.013$). This small effect was stronger in treated exacerbations that met the health care use definition of an exacerbation. We have previously shown that treated exacerbations are associated with higher EXACT symptom scores at presentation and thus are likely to be more severe (24). The biologic mechanism may be that prolonged exacerbations are associated with a greater inflammatory burden that makes the next event more likely. We have previously reported that increased systemic inflammation (C-reactive protein) at Day 14 postexacerbation onset predicts a shorter time to the next event in COPD (25).

In this analysis, we used the true "time at risk," which excluded the period when the patient had an exacerbation and could not therefore be diagnosed with a new exacerbation. Specifying the "time at risk" is not a problem in mortality studies or where the event is short-lived (e.g., myocardial infarction), but is necessary in hospital readmission studies (e.g., where a patient cannot be admitted while in hospital and therefore the period at risk starts at discharge). Allowance for the true "time at risk" has implications for clinical trials that use exacerbation frequency as an outcome measure. Without any allowance, patients whose exacerbations recover quickly are at risk of another event for a longer period than patients whose exacerbations are prolonged. Because of this, exacerbation rates could be higher in the former than the latter assuming an identical duration of follow-up, but more work is needed to model and quantify this effect.

Stable patients who experience shorter exacerbations had a better health-related quality of life, which to our knowledge has not been previously reported. The finding was independent of several important covariates including exacerbation frequency

(2). This finding was not unexpected because the SGRQ questionnaire asks about "how long the worse attack of chest trouble lasted," with the minimal reply being "less than a day" and the maximal response "a week or more." However, the total SGRQ score increased further in patients whose exacerbations were on average longer than 7 days and who would have received the maximal score on this question. It suggests that this finding is not just caused by the properties of the questionnaire and that any reduction in exacerbation duration even if they still last longer than 7 days will benefit the patient.

The rootogram analysis presented shows that exacerbation duration has a distribution that generally matches that of a log-normal distribution, but also that there were more prolonged exacerbations around the 52- to 72-day duration period than expected. This is unlikely to be caused by poor clinical follow-up because patients in the London cohort are seen early at exacerbation and on several occasions in the subsequent 6 weeks, during which patients are retreated if necessary. It is now known that a respiratory viral infection can cause a secondary bacterial infection postexacerbation (26, 27) and without treatment this bacterial infection may take a few weeks to naturally resolve, thus extending the duration of the exacerbation. Other mechanisms that may contribute to these moderately prolonged exacerbations include defective phagocytosis of bacteria, such as *Haemophilus influenza*e (28, 29), and impairment of repair evidenced by the presence of apoptotic cells in the lungs of patients with COPD (30).

We observed a faster decline in FEV_1 in patients who had experienced one or more exacerbations, with impaired recovery in PEF compared with those who had recovered exacerbations. The annual rate of nonrecovered exacerbations was positively correlated with the overall exacerbation rate, so this finding would partially explain why patients with frequent exacerbations have an accelerated decline in lung function (1, 31). This finding questions the previous work of Fletcher and colleagues (32) about the understanding of lung function decline in COPD, with all patients exhibiting an accelerated but variable decline. However, our data suggest that in 40% of patients, some exacerbations also cause a greater decrement in airway function. There was a higher prevalence of symptoms of cold or sore throat at the onset of exacerbations that did not recover in PEF.

We have previously reported that patients who report symptoms of a cold (nasal congestion or discharge) are 3.55 times more likely, and with symptoms of a sore throat 2.27 times more likely, to have a respiratory virus detected in their nasal aspirates (5) and human rhinovirus load are higher with these symptoms (27). We have also shown that exacerbations associated with viral infection and cold symptoms have more prolonged symptoms (4, 5, 33). In addition, larger rises in sputum IL-6 and IL-8 between baseline and Day 7 of the exacerbation are associated with longer symptomatic recoveries (25). Increased sputum IL-8 and neutrophils has been reported during experimental rhinovirus infection (34) and sputum eosinophils and sputum IL-6 in naturally occurring exacerbations (25, 35). To date, the findings of symptoms of a cold or sore throat in this study are the only clinical indicators of a COPD exacerbation from which lung function may not recover. The clinical implications of these findings are that patients who present with these symptoms should be specifically targeted for follow-up postexacerbation.

One of the major strengths of this study is the very long period of observation and the capture of a large number of exacerbations from which FEV_1 decline and the rate of nonrecovered exacerbation could be examined against each other. Another strength is the collection of PEF daily, which could be used to make an objective determination of nonrecovery because patients might alter the perception of the intensity of their respiratory symptom over time. PEF is not normally considered a useful clinical outcome measure in COPD because it changes little at exacerbation (13). Instead, we used PEF to assess whether airway function remained below preexacerbation levels for 99 consecutive days. In this study, we used a symptomatic definition of an exacerbation that captured both treated and untreated events, thus our median exacerbation rate of 2.13 per year is higher than rates observed in recent prospective trials that used a healthcare utilization definition. The importance of untreated exacerbations is not fully understood because they are associated with poor health status (36) but do not add to the financial burden on health services.

There are also several limitations of this study. The suggestion that nonrecovered exacerbations are associated with respiratory viral infection is only based on the greater prevalence of cold and sore throat symptoms. Molecular detection techniques are required to provide stronger evidence as to the greater prevalence of respiratory viruses in sputum or nasal washes collected during exacerbations that do not recover. Another limitation of our study is that we cannot distinguish between whether prolonged exacerbations worsen disease severity or that more severe patients experience longer exacerbations because the two occur at the same time. The symptomatic duration of some exacerbations may have been underestimated if another exacerbation occurred while the patient was recovering and still reporting minor symptoms.

In summary, prolonged symptomatic COPD exacerbations increase the risk of future events and worsen health status. Exacerbations associated with symptoms of cold and sore throat are more likely to cause accelerated decline in lung function and thus eventually to contribute to disease progression in COPD. This study highlights the need for better therapies to prevent viral infections and treatments for acute exacerbations across COPD severities that reduce the duration of exacerbations, because persistent exacerbations worsen quality of life and increase the likelihood of another event. Clinical follow-up of exacerbations with incident symptoms suggestive of a respiratory viral infection needs to be encouraged because these exacerbations are more likely to be associated with a persistent reduction in lung function and thus heightened disability. ■

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