Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease

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Background: Chronic obstructive pulmonary disease (COPD) is characterised by both an accelerated decline in lung function and periods of acute deterioration in symptoms termed exacerbations. The aim of this study was to investigate whether these are related.

Methods: Over 4 years, peak expiratory flow (PEF) and symptoms were measured at home daily by 109 patients with COPD (81 men; median [IQR] age 68.1 [63–74] years; arterial oxygen tension (PaO2) 9.00 [8.3–9.5] kPa, forced expiratory volume in 1 second (FEV1) 1.00 [0.7–1.3] l, forced vital capacity (FVC) 2.51 [1.9–3.0] l); of these, 32 (29 men) recorded daily FEV1. Exacerbations were identified from symptoms and the effect of frequent or infrequent exacerbations (> or < 2.92 per year) on lung function decline was examined using cross sectional, random effects models.

Results: The 109 patients experienced 757 exacerbations. Patients with frequent exacerbations had a significantly faster decline in FEV1, and peak expiratory flow (PEF) of –40.1 ml/year (n=16) and –2.9 l/min/year (n=46) than infrequent exacerbators in whom FEV1 changed by –32.1 ml/year (n=16) and PEF by –0.7 l/min/year (n=63). Frequent exacerbators also had a greater decline in FVC (PaO2) 9.00 (8.3–9.5) kPa, forced expiratory volume in 1 second (FEV1) 1.00 (0.7–1.3) l, forced vital capacity (FVC) 2.51 (1.9–3.0) l); of these, 32 (29 men) recorded daily FEV1. Exacerbations were identified from symptoms and the effect of frequent or infrequent exacerbations (> or < 2.92 per year) on lung function decline was examined using cross sectional, random effects models.

Conclusions: These results suggest that the frequency of exacerbations contributes to long term decline in lung function of patients with moderate to severe COPD.

C hronic obstructive pulmonary disease (COPD) is in the top five leading causes of deaths in the world, and is associated with a significant health and economic burden through hospital admission and absenteeism from work. The accelerated decline in forced expiratory volume in 1 second (FEV1) with age has been related to the severity of airway inflammation.

Exacerbations of COPD are an important cause of unscheduled physician visits and hospitalisation, and patients prone to frequent exacerbations have a reduced quality of life. We have recently shown that COPD exacerbations may increase airway inflammation and that a significant proportion may not show complete symptomatic or physiological resolution. Thus, it is possible that exacerbations by their incomplete recovery play a part in the decline in FEV1.

Previous studies of the relation of exacerbations and decline in lung function have been inconclusive. In 1976 Fletcher and colleagues concluded from their 10 year study that there was no relation between lung function decline and chest infections. However, their cohort had mild or no airflow obstruction, the diagnosis of exacerbation was retrospectively based on patient recollections, and the study possibly lacked the statistical power to identify any effect after adjustment for smoking, age, and body size. Kanner and colleagues reported in 1979 an association between decline in lung function and episodes of lower respiratory tract illnesses, although again the patients were relatively young and with mild airflow obstruction. More recently the Lung Health Study has reported that one lower respiratory tract illness per year, for which a physician was consulted, increased FEV1 decline by 7 ml/year in continuing smokers and intermittent smokers. A similar effect was not observed in sustained quitters and the average number of illnesses was only 0.24 per year. However, whether the decline in FEV1 is related to exacerbation frequency in patients with moderate to severe COPD is not known. Such information would be of importance as currently only smoking cessation is known to affect FEV1, decline in COPD.

In this study we have prospectively investigated a cohort of 109 patients with moderate to severe COPD over a 4 year period. Daily lung function and symptomatic data were collected to identify exacerbations and the relationship between decline in lung function and exacerbation frequency was then evaluated.

METHODS

Patients

Between November 1995 and November 1998, 161 patients with a diagnosis of COPD who attended outpatient clinics were recruited. Inclusion criteria were: FEV1 <70% predicted from age and height, β2 agonist reversibility <15% and/or 200 ml, and absence of asthma, bronchiectasis, bronchial carcinoma, or other significant respiratory disease. To investigate changes over time, the analysis was confined to 109 of these 161 patients who had recorded data on at least 365 days. The reasons for failing to record 365 days of data were: withdrawal from the study, death, or inadequate completion of diary cards combined with late enrolment. These 109 patients did not differ significantly from the 52 excluded patients in any of the characteristics reported in table 1 except in peak expiratory flow (PEF).

Baseline measurements were made of spirometric parameters and PEF by rolling seal spirometer (Sensor Medic Corporation, Yorba Linda, CA, USA) when the patients were stable—that is, with no history of an exacerbation requiring treatment during the previous 4 weeks. Measurements were also taken of reversibility to 400 μg inhaled salbutamol and arterialised ear lobe blood gas tensions (model 278 Blood Gas Analyzer; Ciba-Corning, Medfield, MA, USA), and a history was taken of smoking, chronic symptoms, and long term
inhaled and oral steroid use. The patients recorded on diary cards daily PEF (Mini-Wright, Clement Clark International Ltd, Harlow, UK) measured after medication around 10.00 hours, and increase over normal in symptoms of dyspnoea, amount and purulence of sputum, wheeze, sore throat, cough, or nasal congestion/discharge. Due to funding restrictions only 32 patients (29 men) in addition measured daily FEV1 at home using a spirometer (Micro Medical Ltd, Chatham, Kent, UK). They were similar to the other 77 patients in all characteristics listed in table 1, except they had a higher PEF (245 (IQR 180–300) l/min, p=0.003 (Wilcoxon test)).

The study was approved by the ethics committee of the East London and City Health Authority and the patients provided written informed consent.

Exacerbation identification and treatment

Every 3 months patients were reviewed in the outpatients clinic and their diary cards collected. Exacerbations were diagnosed according to previously accepted criteria if the following symptom patterns were experienced for at least two consecutive days: either two or more of three major symptoms (increase in dyspnoea, sputum purulence or sputum volume) or any one major symptom together with any one of the following minor symptoms: increase in nasal discharge, wheeze, sore throat, cough or fever. Symptoms recorded continuously in the 5 day period before exacerbation onset were discounted when deciding whether an exacerbation had occurred or not. Some exacerbations where no diary card symptoms were recorded were identified by questioning the patient about their symptoms when at the clinic visits or on admission to hospital. Patients experiencing increased symptoms were encouraged to contact the clinical team and were generally seen before treatment within 48 hours. These exacerbations were classified as “reported exacerbations” with those unseen termed “unreported exacerbations”. During the study the number of hospital admissions and length of hospital stay for acute exacerbations of COPD were noted. Records of drug treatment, dosage, and course duration at these visits were kept from November 1996 and any treatment by primary care physicians was obtained where possible.

Exacerbation frequency

The annual exacerbation rate of each patient was calculated by dividing the number of exacerbations by the number of days they participated in the study, and multiplying by 365. As the

Table 1 Characteristics of the 109 study patients with COPD measured at recruitment and of the 32 who recorded FEV1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Interquartile range</th>
<th>Median Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1 (n=109)</td>
<td>66.8 (n=32)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>1.00 (0.74–1.3)</td>
<td>1.00 (0.77–1.48)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>38.2 (27.0–50.0)</td>
<td>36.0 (24.7–50.2)</td>
</tr>
<tr>
<td>FEV1 (% reversibility)</td>
<td>5.2 (0–12.8)</td>
<td>6.9 (0–14.1)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.51 (1.86–2.94)</td>
<td>2.60 (2.00–2.90)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>42.3 (33.1–53.3)</td>
<td>45.1 (32.3–53.5)</td>
</tr>
<tr>
<td>PEF (l/min)</td>
<td>200 (150–264)</td>
<td>245 (180–300)</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>9.00 (8.27–9.51)</td>
<td>9.05 (8.31–9.92)</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>5.77 (5.40–6.36)</td>
<td>5.85 (5.49–6.46)</td>
</tr>
<tr>
<td>Smoking (years)</td>
<td>40% (n=109)</td>
<td>40% (n=32)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>74.3 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Chronic dyspnoea</td>
<td>45.0 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Chronic wheeze</td>
<td>33.0 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Chronic cough</td>
<td>49.5 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Chronic sputum production</td>
<td>56.0 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Smoking at recruitment</td>
<td>30.8 (31.2)</td>
<td></td>
</tr>
<tr>
<td>Taking inhaled steroids</td>
<td>91.7 (87.5)</td>
<td></td>
</tr>
</tbody>
</table>

FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; PEF=peak expiratory flow; PaO2; PaCO2=arterial oxygen and carbon dioxide tensions.

Table 2 Annual changes in treatment of exacerbations with oral steroids and antibiotics

<table>
<thead>
<tr>
<th>Exponentiated regression coefficient*</th>
<th>95% CI</th>
<th>p value</th>
<th>No of exacerbations</th>
<th>No of subjects†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroids (infrequent exacerbators)</td>
<td>0.89</td>
<td>0.59 to 1.35</td>
<td>0.589</td>
<td>165</td>
</tr>
<tr>
<td>Oral steroids (frequent exacerbators)</td>
<td>1.20</td>
<td>0.90 to 1.60</td>
<td>0.208</td>
<td>396</td>
</tr>
<tr>
<td>Antibiotics (infrequent exacerbators)</td>
<td>0.87</td>
<td>0.61 to 1.26</td>
<td>0.477</td>
<td>165</td>
</tr>
<tr>
<td>Antibiotics (frequent exacerbators)</td>
<td>1.106</td>
<td>0.87 to 1.41</td>
<td>0.418</td>
<td>396</td>
</tr>
</tbody>
</table>

*The regression coefficient is of the form e^b and is the odds ratio (OR) giving the relative amount by which the odds of the outcome increase (OR >1) or decrease (OR <1) when the independent variable time is increased by 1 year.
†Data were not available on all 109 patients as records of medication were only kept from November 1996 and not all patients had exacerbations.
study focused on decline in FEV₁, we calculated the median exacerbation rate in the 32 patients recording FEV₁, and divided all the patients into two groups—those experiencing less than the median rate of 2.92 exacerbations per year (“infrequent exacerbators”) and those with more than 2.92 per year (“ frequent exacerbators”). Exacerbation rates for each 12 month period for all the patients who took part in the study were also calculated from the date of their enrolment and used to assess consistency in exacerbation frequency from year to year.

Statistical analysis
Data are presented as mean (SD) or median (interquartile range; IQR) values and comparisons were performed by unpaired \( t \) test, Wilcoxon matched paired sign rank test, or \( \chi^2 \) tests as appropriate. Cross sectional random effects models were used to determine the effect of exacerbation frequency on decline in lung function, with lung function as the dependent variable and time (in years) as the independent variable. These models allow examination of the time variations independently of the cross sectional variations in panel data. The lung function data were logarithmically transformed as the work of Fletcher suggests a non-linear decline in lung function over time; the transformation also gave higher \( r^2 \) values for the regression analysis, indicating that it provided a better model. We calculated the regression coefficients for infrequent and frequent exacerbator groups separately. The coefficients were then compared using their standard errors, although not optimal, is statistically more secure as the sample size in this study is relatively small. We also repeated the analysis but stratified the patients into four groups by exacerbation frequency and whether or not the patient currently smoked. The analysis was also repeated after stratifying the patients into two groups according to whether they had more or less than 1.5 reported exacerbations per year. This was the median rate for those exacerbations seen at clinic by the clinical team. The rationale for this was that the symptoms for these exacerbations were validated. Cross sectional, random effects models were also used to examine changes in binomial data on treatment with oral steroids and antibiotics over time assuming a logit relationship. The analysis was performed using Stata 5.0 (Stata Corporation) and the cross sectional models fitted using the Xtetreg and Xgc commands.

RESULTS
Patients
The 109 patients studied had moderate to severe COPD (table 1). Of these, 100 patients took inhaled steroids daily and 12 were on prednisolone taking a mean (SD) dose of 5.91 (3.0) mg/day; 10 patients used both oral and inhaled steroids. Data on exacerbation treatment collected over the last 3 years of the study showed that 124 of 561 exacerbations (22.1%) were treated with oral steroids and 341 of 561 (60.8%) with antibiotics. Table 2 shows how the probability of treatment changed per year in the frequent and infrequent exacerbator groups, and indicates that there was no significant change over time in the likelihood of treatment with either oral steroids or antibiotics. No significant change was seen if the exacerbations were categorized according to frequency and whether or not the patient currently smoked. The analysis was also repeated after stratifying the patients into four groups by exacerbation frequency and whether or not the patient currently smoked. The analysis was also repeated after stratifying the patients into four groups by exacerbation frequency and whether or not the patient currently smoked. The analysis was also repeated after stratifying the patients into four groups by exacerbation frequency and whether or not the patient currently smoked. The analysis was also repeated after stratifying the patients into four groups by exacerbation frequency and whether or not the patient currently smoked.

Exacerbations
One hundred of the 109 patients had one or more exacerbations, with a total of 757 of which 649 (85.7%) were

![Table 3](https://example.com/table3.png)

**Table 3** Initial and annual change in lung function in patients with infrequent and frequent exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Starting value</th>
<th>Annual change</th>
<th></th>
<th>Infrequent</th>
<th>Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Exacerbations (reported and unreported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (l/min)</td>
<td>214</td>
<td>232</td>
<td>&lt;50% percentile,</td>
<td>2.92 per year,</td>
<td>&gt;50% percentile,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n=63)</td>
<td>(n=46)</td>
<td>(n=46)</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>893</td>
<td>950</td>
<td>-0.72</td>
<td>-2.94***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n=16)</td>
<td>(n=16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-32.1</td>
<td>-40.1 *</td>
<td></td>
</tr>
</tbody>
</table>

PEF=peak expiratory flow, FEV₁=forced expiratory volume in 1 second.
* \( p<0.05 \), ** \( p<0.001 \) annual rates of change between infrequent and frequent exacerbators.
identified from the symptom data recorded by the patients on their diary cards. A total of 380 (50.1%) exacerbations were reported and seen by the clinical team. There were no differences in daily symptoms recorded by the patient at exacerbation onset between those unreported and those reported to the clinic team (dyspnoea 61% and 62% respectively; sputum purulence 26% and 24%; sputum amount 44% and 39%; wheeze 33% and 31%; sore throat 13% and 11%; cough 23% and 28%) except in nasal congestion/discharge (22% and 19%; sneezing 39% and 33%; sputum purulence 26% and 24%; sputum amount 44% and 38%).

There were no differences in age, physical size, sex, lung function, blood gas tensions, and smoking habits between the infrequent and frequent exacerbators. There were also no differences in long term inhaled steroid use. However, chronic symptoms of dyspnoea and wheeze were significantly more likely in the frequent exacerbators. Similar comparisons limited to the 32 patients who recorded FEV\(_1\) showed, in addition to the chronic symptoms above, differences in age (frequent exacerbators were slightly younger than those with infrequent exacerbations (median 61.6 years (IQR 56.9–70.5) vs 71.5 years (IQR 63.7–74.0); p=0.033, Wilcoxon)) and in the chronic symptom of cough (75% vs 12.5% (p=0.001, \(\chi^2\) test).

In these 32 patients there were more current smokers among the frequent exacerbators (9 of 16) than among those

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**Table 4** Comparison between patients who experience frequent exacerbations (>2.92 per year) and those who experience infrequent exacerbations (<2.92 per year)

<table>
<thead>
<tr>
<th></th>
<th>Infrequent (n=63)</th>
<th>IQR</th>
<th>Frequent (n=46)</th>
<th>IQR</th>
<th>p value Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>69.8</td>
<td>64.4–73.9</td>
<td>65.6</td>
<td>58.8–73.5</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m(^2))</strong></td>
<td>25.2</td>
<td>23.1–28.0</td>
<td>25.2</td>
<td>21.5–29.1</td>
<td>0.813</td>
</tr>
<tr>
<td><strong>FEV(_1) (l)</strong></td>
<td>1.05</td>
<td>0.74–1.30</td>
<td>0.96</td>
<td>0.72–1.35</td>
<td>0.988</td>
</tr>
<tr>
<td><strong>FEV(_1) (% predicted)</strong></td>
<td>38.5</td>
<td>26.1–49.8</td>
<td>37.7</td>
<td>28.0–52.8</td>
<td>0.766</td>
</tr>
<tr>
<td><strong>FEV(_1) (% reversibility)</strong></td>
<td>5.4</td>
<td>0–13.6</td>
<td>3.6</td>
<td>0–12.6</td>
<td>0.497</td>
</tr>
<tr>
<td><strong>FVC (l)</strong></td>
<td>2.68</td>
<td>1.82–3.00</td>
<td>2.38</td>
<td>1.86–2.90</td>
<td>0.461</td>
</tr>
<tr>
<td><strong>FEV(_1)/FVC (%)</strong></td>
<td>41.9</td>
<td>33.1–48.9</td>
<td>46.6</td>
<td>31.8–53.8</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>PEF (l/min)</strong></td>
<td>188</td>
<td>147–250</td>
<td>210</td>
<td>160–300</td>
<td>0.129</td>
</tr>
<tr>
<td><strong>PaO(_2) (kPa)</strong></td>
<td>8.95</td>
<td>8.41–9.44</td>
<td>9.09</td>
<td>7.98–9.57</td>
<td>0.578</td>
</tr>
<tr>
<td><strong>PaCO(_2) (kPa)</strong></td>
<td>5.75</td>
<td>5.43–6.21</td>
<td>5.95</td>
<td>5.40–6.44</td>
<td>0.306</td>
</tr>
<tr>
<td><strong>Smoking (years)</strong></td>
<td>40</td>
<td>30–50</td>
<td>41.5</td>
<td>30–50</td>
<td>0.673</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>%</td>
<td>79.4</td>
<td>%</td>
<td>67.4</td>
<td>0.158</td>
</tr>
<tr>
<td><strong>Chronic dyspnoea</strong></td>
<td>30.2</td>
<td>65.2</td>
<td>%</td>
<td>65.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Chronic wheeze</strong></td>
<td>22.2</td>
<td>47.8</td>
<td>%</td>
<td>47.8</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Chronic cough</strong></td>
<td>42.9</td>
<td>58.7</td>
<td>%</td>
<td>58.7</td>
<td>0.102</td>
</tr>
<tr>
<td><strong>Chronic sputum production</strong></td>
<td>52.4</td>
<td>60.1</td>
<td>%</td>
<td>60.1</td>
<td>0.378</td>
</tr>
<tr>
<td><strong>History of smoking</strong></td>
<td>93.7</td>
<td>95.6</td>
<td>%</td>
<td>95.6</td>
<td>0.651</td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td>22.2</td>
<td>39.3</td>
<td>%</td>
<td>39.3</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Daily inhaled steroid use</strong></td>
<td>88.7</td>
<td>95.7</td>
<td>%</td>
<td>95.7</td>
<td>0.186</td>
</tr>
</tbody>
</table>

FEV\(_1\)=forced expiratory volume in 1 second; FVC=forced vital capacity; PEF=peak expiratory flow; PaO\(_2\), PaCO\(_2\)=arterial oxygen and carbon dioxide tensions.
with infrequent exacerbations (1 of 16). Analysis of the effect of smoking status at recruitment and exacerbation frequency on decline in FEV, showed that frequent exacerbations contributed 21.5 ml/year (95% CI 20.2 to 22.7) to the decline in FEV, independently of smoking which added a further 6.8 ml/year (95% CI 4.1 to 9.7); both effects were significant (p<0.001).

DISCUSSION

This study has shown for the first time that patients with moderate to severe COPD who suffered frequent exacerbations (>2.92 per year) experienced a significantly greater decline in FEV, of 40 ml/year and in PEF of 2.9 l/min/year than patients who had infrequent exacerbations (<2.92 per year) in whom FEV, declined by only 32 ml/year and PEF by 0.7 l/min/year. Similar differences in the decline in FEV, were found whether or not the patient visited a physician at exacerbation. Frequent exacerbations were also associated with a faster decline in FEV, if allowance was made for smoking status, although there was only a relatively small effect of smoking, possibly because there was only one smoker in the infrequent exacerbator group. A faster decline in the group with frequent exacerbations could be explained by less treatment of their exacerbations, but during the study we found no change over time in the probability of treatment of exacerbations with antibiotics or oral steroids in the frequent and infrequent exacerbation groups. Patients with frequent exacerbations had significantly more hospital admissions and spent a longer time in hospital. Other studies have recently shown that exacerbation frequency is an important independent risk factor for treatment failure and hospitalisation.15 16

The mean decline in FEV, of 36 ml/year for all the patients is consistent with other recent studies of patients treated with long term inhaled steroids; 92% of our patients were treated with inhaled steroids. Renkema et al18 found a median decline of 30 ml/year with budesonide, but the ISOLDE study reported a 50 ml/year decline in FEV, with fluticasone.19 Vestbo et al20 reported values of 30.0 ml/year and 45.5 ml/year respectively for male non-smokers and heavy smokers without mucus hypersecretion, which suggests a figure of around 35 ml/year in a patient group comprising 30% current smokers, although their studies did not have a diagnosis of COPD and were about 10–15 years younger than the patients in our study.

The difference in the decline in FEV, between the infrequent and frequent exacerbators was 8 ml/year, and their median exacerbation rates were 1.9 and 4.2 per year, respectively. In the Lung Health Study21 of FEV, in continuing smokers and intermittent quitters declined by 7 ml/year with each lower respiratory tract illness, with 0.15–0.25 illnesses reported per year. This suggests that exacerbations in moderate to severe COPD contribute a greater proportion to the decline in FEV, in this study the difference of 8 ml/year between the two groups represents a 23% increase in decline due to the effect of frequent exacerbations.

Patients in this study were monitored on a daily basis over a 4 year period with exacerbations identified using previously accepted criteria of respiratory symptom increase.14 About half the exacerbations identified from the patients' self-reported symptoms were confirmed by the study team at the clinic. We are therefore confident that few exacerbations were missed or misdiagnosed. The median exacerbation rate for the whole cohort of 2.53 per year was higher than that previously reported for patients with COPD of similar severity of lung function (1–2 per year15 and 0.99 per year16) This can be explained mainly by inclusion of about 50% of the exacerbations which were not seen in the clinic by the study team but which were diagnosed from diary cards. These unreported exacerbations would not have been included in the previous studies where definitions required a worsening of respiratory symptoms that involved physician intervention. However, we found no symptomatic differences between reported and unreported exacerbations except that the incidence of nasal congestion was higher with reported exacerbations.

There are a number of mechanisms that might explain the association between frequent exacerbations and decline in lung function, but it is also possible that a common mechanism leads to both. The decline may be mediated by airway inflammation which would be further increased by COPD exacerbations,7 especially if triggered by viral or bacterial infections.14 The presence of bacteria in the airways has been associated with increased airway neutrophilia and inflammatory markers,22 23 and persistent bacterial colonisation of airways is related to the severity of the underlying airflow obstruction.24 25 We have recently found that patients with frequent exacerbation are more likely to have increased bacterial colonisation.15 We have also shown that patients with frequent exacerbations have higher levels of the cytokines interleukin (IL)-6 and IL-8 in induced sputum, which suggests that frequent COPD exacerbations are associated with increased airway inflammation.1 The increased airway inflammation in patients with frequent exacerbations may therefore lead to the accelerated decline in FEV, seen in this study.

We have shown that the annual exacerbation rate remains fairly consistent within a patient from one year to the next. The consistency is important in contributing to the accelerated decline in FEV, associated with frequent exacerbations. We have previously shown that exacerbation frequency is strongly related to health status and to airway inflammatory markers. This finding confirms the basis for categorising patients into frequent and infrequent exacerbation groups, and emphasises the importance of targeting treatment at those with frequent exacerbations.

This study has shown that exacerbation frequency is an important determinant of decline in lung function in COPD. Strategies for prevention or ameliorating COPD exacerbations may have an important impact on the health burden of this common disease and thus improve the morbidity and mortality.

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References


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Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease

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rates are clearly significant, favouring varen- 
ecline over nicotine replacement therapy 
(NRT) (p = 0.04).

In addition, while Hillman et al question 
the justification of the additional cost of 
varenicline over NRT, the NICE technology 
appraisal guidance concluded that, over a 
lifetime, varenicline is more cost-effective 
than both bupropion SR and NRT.1

In conclusion, we feel that we honestly 
reported our results, not claiming any super-
iority of varenicline over NRT in the long 
term, either in the abstract or in the 
conclusion of the paper. Rather, we hoped 

to convey the message that any intervention 
shown to be at least as clinically effective as 
NRT is an important additional option for 
smokers attempting to quit.

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GlaxoSmithKline, Novartis and Pfizer. In the past 5 years JRB 
has received consultancy fees from Xenova and Novartis 
and his employing institution has received consultancy fees, 
and honoraria on his behalf from Pfizer. CO has received 
honoraria and consulting fees from Pfizer; nicotine and 
placebo products for research studies at no cost from 
GlaxoSmithKline; and honoraria from Pri-Med and CME 
ofﬁcers. CBB, JG, KEW and KRR are employees of Pfizer.

REFERENCES
comparative trial of varenicline, nicotine patch, 
nasal spray, and an inhaler. Arch Intern Med 
comparison of sustained-release bupropion 
and placebo for smoking cessation. N Engl J Med 
controlled trial of sustained-release bupropion, a 
nicotine patch, or both for smoking cessation. 
criteria in smoking cessation trials: proposal 
for a common standard. Addiction 2005;100: 
298–303.
http://www.nice.org.uk/nicemedia/pdf/
TA123Guidance.pdf (accessed 
28 March 2008).

CORRECTION
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G C Donaldson, T A R Seemungal, A Bhowmik, and J A Wedzicha. Relationship 
between exacerbation frequency and lung 
function decline in chronic obstructive 

The legend for fig 2 should read: ‘‘Change 
in FEV1, with standard errors over 4 years. 
Open circles represent frequent exacerbators; 
closed circles represent infrequent 
exacerbators.’’

Pulmonary puzzle

ANSWER
From the question on page 746

The differential diagnosis for pulmonary infiltrates in the immunocompromised host includes 
opportunistic infections, drug toxicity, alveolar haemorrhage and progression of the primary 
disease. The diagnostic yield of bronchoscopy in immunocompromised patients with lung 
infiltrates is variable with a higher yield (~81%) for infectious aetiologies. On the basis of the 
larvae in the bronchoalveolar lavage ﬂuid, our case was diagnosed as Strongyloides 
hyperinfection.

Strongyloidiasis is caused by an infection with Strongyloides stercoralis, a helminth that can 
complete its life cycle entirely within the human host.1 This autoinfection permits the organism 
to persist for decades and allows hyperinfection to occur in states of impaired cell-mediated 
immunity.2 Detection of a large number of larvae in the stool and/or bronchoalveolar lavage 
ﬂuid or sputum is a hallmark of hyperinfection. The diagnosis requires a high index of suspicion and 
patients who have peripheral eosinophilia, serpiginous rash or history of soil exposure in tropical 
and subtropical areas should be screened by stool studies before any form of immunosuppression. 
In disseminated disease or steroid exposure eosinophilia may be absent.

The respiratory symptoms in Strongyloides are caused by the migrating larvae producing 
alveolar haemorrhage, oedema or inﬂammatory changes. Adult worms are known to cause 
chronic bronchitis or asthma-like symptoms. The chest radiograph or a CT scan in those with 
clinical signs and symptoms will usually show abnormal ﬁndings including ﬁne miliary nodules 
or diffuse reticular inﬁltrates. As the infection progresses there may be bronchopneumonia with 
scattered ill-deﬁned alveolar, segmental or even lobar opacities similar to those seen in Löffler’s 
syndrome or eosinophilic pneumonitis.

The current treatment of choice for Strongyloides is ivermectin with albendazole as an 
alternative. Our patient was treated with ivermectin for 5 days. He was extubated and his 
nodular inﬁltrates cleared slowly over 6 weeks.

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REFERENCES