Does a single *Pseudomonas aeruginosa* isolation predict COPD mortality?

To the Editor:

Patients with chronic obstructive pulmonary disease (COPD) often suffer from acute exacerbations (AECOPD) of their disease, which have a significant impact on their health status [1]. Evidence suggests that ~50% of these exacerbations are attributable to bacteria [2]. *Pseudomonas aeruginosa* can cause AECOPD and is associated with reduced survival in cystic fibrosis (CF) and bronchiectasis [3, 4]. Some studies have found that the presence of *P. aeruginosa* is also associated with mortality in COPD, but these findings have been based on patients hospitalised with exacerbations [5, 6] or those hospitalised with multidrug-resistant organisms [7].

The impact of *P. aeruginosa* identified in sputum from COPD outpatients is less clear but is an important issue for determining how aggressive strategies to attempt eradication should be. Therefore, we conducted a nested case–control study to investigate whether the isolation of *P. aeruginosa* in the sputum of a general COPD population was associated with long-term mortality.

We first identified all sputum specimen results from Royal Brompton Hospital (London, UK) microbiology records between 2000 and 2012. These were cross-correlated with patients listed on our COPD research audit database. The reason for obtaining a sputum culture was not recorded systematically, but included repeated exacerbations and deterioration in symptom severity and/or clinical status, as well as opportunistic collection from patients with chronic sputum production. The laboratory threshold for a culture to be considered *P. aeruginosa* positive was 200 CFU·mL⁻¹ (a semi-quantitative method). For patients with repeated positive sputum cultures the date of the first culture was recorded. Demographic variables, lung function measurements, gas transfer data, arterial blood gases and exacerbation frequency during the year prior to entering the study were recorded for all patients.

All analyses were performed using the Predictive Analytics Software (version 18; SPSS Inc., Chicago, IL, USA). Group comparisons were conducted utilising a t-test or the Chi-squared test as appropriate. Proportional Cox hazard analysis was utilised to assess: 1) the impact of parameters that differed between *P. aeruginosa* culture-positive and culture-negative groups and 2) the impact of antibiotic treatment on mortality. The proportionality hazard assumption was tested using partial residual plots (Schoenberg
residuals proportionality hazard test). The Kaplan–Meier survival curve with the Log rank comparison was used to assess the impact of *P. aeruginosa* isolation on mortality and estimate the median survival of the *P. aeruginosa* culture-positive and culture-negative groups. A p-value < 0.05 was considered significant.

The initial cohort consisted of 380 subjects (247 male and 133 female), with a mean ± SD age of 66.3 ± 10.3 years and a forced expiratory volume in 1 s (FEV1) of 36.7 ± 13.6 % predicted. 95 (25%) patients from the initial population had at least one positive sputum culture for *P. aeruginosa*, while the rest had either negative cultures or cultured bacteria other than *P. aeruginosa*. 66 *P. aeruginosa* culture-positive patients from the initial cohort were matched to another 66 *P. aeruginosa* culture-negative patients for sex, age and FEV1 % predicted.

Differences in demographics and clinical characteristics between the initial COPD cohort and the study population, and *P. aeruginosa* culture-positive and culture-negative patients are presented in table 1. Although the initial matching was done according to three baseline variables, the two final groups were found to be similar in all recorded parameters of lung function (forced vital capacity, FEV1/forced vital capacity, diffusing capacity of the lung for carbon monoxide, total lung capacity, residual volume and residual volume/total lung capacity), as well as body mass index and arterial oxygen tension. Arterial carbon dioxide tension (p = 0.018) and exacerbation rate (p = 0.008) were higher in the *P. aeruginosa* culture-positive patients compared to the *P. aeruginosa* culture-negative patients (table 1). However, proportional Cox hazard analysis, which was conducted separately for each group, indicated that exacerbation rate had no impact on mortality (*P. aeruginosa* culture-positive: hazard ratio 1.334 (95% CI 0.351–5.067), p = 0.672; *P. aeruginosa* culture-negative: hazard ratio 2.161 (95% CI 0.576–8.112), p = 0.253). The results were similar for arterial carbon dioxide tension (*P. aeruginosa* culture-positive: hazard ratio 1.134 (95% CI 0.758–1.697), p = 0.539; *P. aeruginosa* culture-negative: hazard ratio 1.074 (95% CI 0.842–1.369), p = 0.572), indicating that it was not associated with survival.

Median (range) survival for the study population (n = 132) was 81.2 (50.8–109.5) months. During this period 51 (38.6%) patients died, of these 52.9% (n = 27) were *P. aeruginosa* culture-positive and 47.1% (n = 24) were *P. aeruginosa* culture-negative. The Kaplan–Meier survival curve, using the Log rank comparison, indicated that *P. aeruginosa* positive sputum culture was not associated with mortality in this population. Median (range) survival for *P. aeruginosa* culture-positive patients was 80.1 (40.1–120.1) months compared to 88.6 (52–125.3) months in the *P. aeruginosa* culture-negative patients (p = 0.49) (fig. 1). Furthermore, no differences in survival as a function of the presence of *Pseudomonas* would have been identified if the entire population of 380 had been analysed (data not shown).
A secondary analysis was also undertaken to identify whether *Pseudomonas* eradication treatment among *P. aeruginosa* culture-positive patients had any impact on survival. Sputum samples were ordered on a clinical basis and the decision of whether to attempt to eradicate *Pseudomonas* was at the discretion of the treating physician. Out of 66 *P. aeruginosa* culture-positive patients, 34 (25.8%) did not receive any treatment while 32 (24.2%) were treated either with oral ciprofloxacin or appropriate intravenous antibiotics, depending on resistance pattern. These two patient subgroups were similar regarding age, sex, body mass index, pulmonary function testing variables and exacerbation rate (data not shown). Cox proportional hazard analysis indicated that *P. aeruginosa* treatment was not associated with mortality (hazard ratio 1.452 (95% CI 0.666–3.163), *p* = 0.348) among *P. aeruginosa* culture-positive patients.

This study indicates that a single isolate of *P. aeruginosa* in sputum from a general COPD population is not associated with worse survival. Recently, three different patterns of *P. aeruginosa* infection in COPD patients have been described: 1) short carriage and clearance of a *P. aeruginosa* strain; 2) acquisition of a new strain associated with an AECOPD; and 3) persistence of *P. aeruginosa* colonisation with unknown clinical significance [8]. Although the specific pattern of *P. aeruginosa* infection was not investigated in the current study, our results indicate that even though a single positive *P. aeruginosa* sputum culture was correlated with a higher exacerbation frequency, it was not associated with a worse long-term outcome in COPD outpatients.

The results of our study may, to some extent, be limited by its retrospective design and by the relatively small number of patients included, although a formal power estimation was not conducted. However, most of the published studies in the field have used similar sample sizes to investigate the potential impact of *P. aeruginosa* infection on COPD survival [2, 6, 9]. Another limitation is the lack of baseline data on exercise capacity, dyspnoea severity and frequency of previous hospitalisations, all of which could have affected mortality. Moreover, high-resolution computed tomography of the chest was not systematically conducted in all patients so the prevalence of bronchiectasis, a factor which could have favoured *P. aeruginosa* infection, could not be estimated; although it should be noted that our institution runs separate clinics for patients known to have either CF or non-CF bronchiectasis. However, several of these prognostic factors [6, 7] and imaging data [6, 7, 9] are also lacking in previously published studies that investigated the effect of *P. aeruginosa* on COPD mortality. Furthermore, careful patient matching has controlled for most of the lung function parameters that could affect mortality [10], so these negative results could not be attributed to a selected patient subgroup.

In conclusion, this study indicated that a single *P. aeruginosa* sputum isolation is not a predictor of long-term mortality in a general COPD outpatient population. Current clinical practice usually targets *P. aeruginosa* eradication using radical treatment, after its isolation in the sputum of a COPD patient with clinical deterioration or frequent exacerbations. Although eradicating *Pseudomonas* may be justified to improve health status, patients and clinicians can, to an extent, be reassured by these data that if this is not possible the impact on survival of a single *P. aeruginosa* isolation is not as significant as it is in CF [3] or bronchiectasis [4]. Future prospective, case–control studies are needed in order to define exact criteria for chronic *P. aeruginosa* infection in COPD patients and the best stratification criteria for a clinical trial of *P. aeruginosa* eradication in COPD.
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A single positive *Pseudomonas aeruginosa* sputum culture is not associated with increased long-term mortality in COPD http://ow.ly/x5wvD

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### Does traffic noise influence respiratory mortality?

*To the Editor:*

Over the last decade, several studies have investigated the association between noise levels, primarily due to road traffic in large cities, and pathologies not related to either traditional hearing impairments or sleep disorders. These pathologies are mainly hypertension and cardiovascular, connective system and respiratory diseases [1]. Their impact on public health has been assessed in time series studies, indicating a traffic noise effect on both cardiovascular and respiratory hospital admissions rates similar to that attributed to air pollutants [2]. In addition, a recent study has shown an association of noise levels with cardiovascular mortality [3]. The description of the physiopathological mechanisms involved in this association reveal an actual impact of current road traffic noise levels on health [1]. Others question this because of the high correlation between traffic noise and air pollution [4], although a previous study in our setting showed an independent association between noise and cardiovascular mortality from the effect of the primary chemical air pollutants [5]. However, the effect of noise on respiratory mortality has not yet been investigated.

In this study, we examined the association between daily mortality due to respiratory causes (International Classification of Diseases, 9th revision, codes 460–519) and daytime noise levels in the city of Madrid.