



Weight gain during acute treatment of an initial pulmonary exacerbation is associated with a longer interval to the next exacerbation in adults with cystic fibrosis

To the Editor:

Cystic fibrosis (CF) results in a variety of clinical phenotypes, including increased susceptibility to pulmonary infections [1] and malnutrition [2]. As a consequence, one of the priorities in the clinical care for individuals with a diagnosis of CF is to treat chest infections promptly [3], with the aim of minimising the decline in lung function that occurs in individuals who experience recurrent pulmonary exacerbations [4]. Optimising nutrition is another important consideration in the care of patients with CF [3]. It is well recognised that nutritional status and lung function are correlated [5] and that individuals with lower levels of nutrition have increased mortality [6] compared to those individuals with better nutrition.

Treatment of pulmonary exacerbations represents an opportunity to intervene to improve nutrition. We hypothesised that individuals who gain more weight during treatment of a pulmonary exacerbation may subsequently have a better clinical outcome than those who did not. We used an existing dataset to test this hypothesis in a secondary analysis of a population of adult CF patients with known chronic infection with *Pseudomonas aeruginosa* who were treated for a pulmonary exacerbation.

The study population consisted of 59 adults with CF known to have chronic pulmonary infection with *P. aeruginosa*, who were recruited for a biomarker study [7] and have a pulmonary exacerbation as defined by the Rosenfeld criteria [8]. The inclusion and exclusion criteria have been reported previously [7]. Both the choice of antibiotic and the duration of treatment were chosen at the discretion of the patient's clinician, and treatment included nutritional support from a CF specialist dietician. At the start and end of treatment, patients were weighed. Pulmonary function tests were performed according to the joint European Respiratory Society/American Thoracic Society criteria [9] at the end of the exacerbation. Patients were recruited between July 28, 2009 and December 8, 2010 and were followed up until March 1, 2012. The time to next exacerbation was documented as the interval between the date of completion of antibiotics during the initial episode and the date intravenous antibiotics were commenced for the subsequent pulmonary exacerbation. The study was approved by the local ethics committee (NREC1: 09/H0407/1), and informed written consent was obtained for all participants.

Data were analysed using Cox regression with the time to next exacerbation as the dependent variable. The following co-variables were added to the univariate model of the association between change in weight and time to subsequent treatment for pulmonary exacerbation model to explore potential confounding factors: sex, age in categories, forced expiratory volume in one second (FEV₁) at discharge, height, duration of pulmonary *P. aeruginosa* infection in quintiles, long-term use of oral steroids, gastro-oesophageal reflux disease, pancreatic insufficiency and diabetes mellitus. A confounding factor was defined as one that changed the hazard ratio (HR) by 10% or more. The final model was tested to ensure that the Cox



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regression proportional hazard assumption was not violated using Schoenfeld residuals. The analysis used STATA 14 statistical software (StataCorp, College Station, TX, USA).

The clinical details of the 59 participants are summarised in table 1. The median duration of treatment with antibiotics was 14 days (interquartile range (IQR) of 14–14). The median weight gain was +1.00 kg, with an IQR of –0.10 to +2.30 kg. A total of 58 (98%) participants had a pulmonary exacerbation during the follow-up period, and the median interval to subsequent exacerbation was 2.8 months (IQR 1.3–5.4 months). Gaining weight during treatment for a pulmonary exacerbation was associated with a longer period to the subsequent next pulmonary exacerbation after the end of antibiotic treatment. A 1 kg increase in weight over the course of treatment was associated with an HR of 0.83 (95% CI 0.70–0.98). Addition of potential confounding factors did not modify this association, so they were not incorporated

TABLE 1 Baseline participant characteristics

Male	33 (56%)
Age years	28 (17–59)
Genotype	
F508del homozygous	23 (39%)
F508del heterozygous	19 (32%)
Other	6 (10%)
Unknown	11 (19%)
Comorbidities	
Pancreatic insufficiency	54 (92%)
CF-related diabetes mellitus	32 (54%)
CF-related liver disease	13 (22%)
ABPA	8 (14%)
Asthma	2 (3%)
GORD	24 (41%)
Maintenance therapies	
Nebulised colistin	37 (63%)
Nebulised tobramycin	6 (10%)
Nebulised dornase alpha	35 (59%)
Nebulised hypertonic saline	20 (34%)
Oral corticosteroids	10 (17%)
Oral azithromycin	48 (81%)
Duration of <i>Pseudomonas aeruginosa</i> infection years	7.7 (0.3–14.4)
Baseline sputum microbiology	
<i>P. aeruginosa</i>	52 (88%)
MSSA	8 (14%)
MRSA	3 (5%)
<i>Candida albicans</i>	4 (7%)
<i>Aspergillus fumigatus</i>	2 (3%)
<i>Haemophilus influenzae</i>	1 (2%)
No respiratory pathogens	3 (5%)
Intravenous antibiotic administered	
Tobramycin	31 (53%)
Ceftazidime	28 (47%)
Colomycin	24 (41%)
Meropenem	24 (41%)
Aztreonam	7 (12%)
Piptazobactam	5 (8%)
Other	5 (8%)
Spirometry	
FEV ₁ [#] L	1.70±0.71
FEV ₁ [#] % predicted	47.0±17.0
Anthropometric measures	
Height m	1.68±0.09
BMI kg·m ⁻²	21.9±3.7
Change in weight kg	+1.00 [–0.10– +2.30]

Data are presented as n (%), median [range] or mean±SD. CF: cystic fibrosis; ABPA: allergic bronchopulmonary aspergillosis; GORD: gastro-oesophageal reflux disease; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; BMI: body mass index. #: n=57.

into the final model. After adjustment for disease severity using FEV₁, the HR decreased to 0.79 (95% CI 0.67–0.94) per kg increase in weight.

This is the first study to explore the association of change in weight during a pulmonary exacerbation with the interval for subsequent pulmonary exacerbations in adults with CF. These data show that greater weight gain is associated with a longer exacerbation-free interval, even after adjustment for pulmonary disease severity as measured by lung function.

The strengths of the study include the well-characterised cohort, which is broadly representative of patients attending two UK adult CF specialist centres. The availability of weight data from patients at the beginning and end of their pulmonary exacerbation allowed confidence in the accuracy of these measurements. Lung function measurements at end of treatment permitted adjustment for disease severity, which represents an important potential confounding factor, providing confidence that these associations are reliable. The long follow-up period ensured that a high proportion of patients had an exacerbation during this interval. No patients were lost to follow-up, thus eliminating this potential cause of bias.

Several limitations in our study warrant consideration. The main concern is that this analysis represents a secondary analysis of data and hence these data should be considered hypothesis-generating rather than a definitive result. As a consequence of this, there were no data collected on nutritional interventions for individual patients. The initiation of treatment for a pulmonary exacerbation has an encounter-based component and may therefore be based on subjective assessment by either the clinician or the patient. This can range from an unexpected emergency admission to a more planned course of treatment, with differences varying between individuals that are difficult to measure. There were no standardised data on baseline weight, so acute weight loss during the acute exacerbation prior to treatment could not be assessed. As this is an observational study, we are unable to exclude residual confounding by variations in medical care.

The study of factors that prevent or delay pulmonary exacerbations is important, as these are well recognised to be associated with accelerated loss of lung function in adults [4, 10], decreases in quality of life that are independent of measures of disease severity [11] and mortality [12]. The observation that a gain in weight while receiving treatment for a pulmonary exacerbation is associated with a longer subsequent exacerbation-free interval is an important one, as weight gain is a therapeutic outcome in itself in the context of CF. It is not clear if this association is causal; *i.e.* a gain in weight protects against subsequent pulmonary exacerbations or is simply indicative of a good clinical response to the treatment of the respiratory infection that triggered the exacerbation. For example, a patient with a rapid clinical response to antibiotic treatment would be expected to mobilise sooner and have a better appetite, thus promoting more weight gain over the period of receiving treatment with *i.v.* antibiotics. Future studies in this area should consider targeting weight gain as an outcome variable and assessing the impact on subsequent disease activity, ideally in the context of a randomised clinical trial. This could represent a potential quality improvement target that could be used to compare institutional care [13, 14] and provide a better clinical outcome than lung function, where a good response after treatment for pulmonary exacerbation is not positively related with a longer time to the next exacerbation [15]. It is worth commenting on the baseline sputum microbiology, because, although all patients were selected on the basis of prior *P. aeruginosa* infection, 88% grew this microbe at entry to the study and 5% grew no respiratory pathogens at all. This correlates with clinical experience, where sputum microbiology does not always correlate with prior results or clinical status.

In summary, weight gain during treatment of a pulmonary exacerbation is associated with a longer interval until the next pulmonary exacerbation. This represents a modifiable risk factor for pulmonary exacerbations that has the potential to improve quality of life and clinical care in individuals with CF.

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