Barr, Helen L. and Cámara, Miguel and Barrett, David and Williams, Paul and Forrester, Doug and Smyth, Alan and Honeybourne, David and Whitehouse, Joanna and Nash, Edward and Dewar, Jane and Knox, Alan and Fogarty, Andrew W. (2017) 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. ERJ Open Research, 3 (3). pp. 1-4. ISSN 2312-0541

ORIGINAL RESEARCH LETTER

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-variates 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 (FEV_1) 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

@ERSpublications
Weight gain during treatment for a cystic fibrosis exacerbation http://ow.ly/f1zl30dU9AO

Cite this article as: Barr HL, Cámara M, Barrett D, *et al*. 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. *ERJ Open Res* 2017; 3: 00057-2017 [https://doi.org/10.1183/23120541.00057-2017].

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 *Pseudomonas aeruginosa* infection years	7.7 (0.3–14.4)
Baseline sputum microbiology	
P. aeruginosa	52 (88%)
MSSA	8 (14%)
MRSA	3 (5%)
Candida albicans	4 (7%)
Aspergillus fumigatus	2 (3%)
Haemophilus influenzae	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 $kg \cdot m^{-2}$	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 FEV_1, 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.

Helen L. Barr[1], Miguel Cámara[2], David Barrett[3], Paul Williams[2], Doug Forrester[1], Alan Smyth[4], David Honeybourne[5], Joanna Whitehouse[5], Edward Nash[5], Jane Dewar[6], Alan Knox[1] and Andrew W. Fogarty[7]

[1]Division of Respiratory Medicine, University of Nottingham, Nottingham, UK. [2]Centre for Biomolecular Sciences, School of Life Sciences, University of Nottingham, Nottingham, UK. [3]School of Pharmacy, University of Nottingham, Nottingham, UK. [4]Department of Child Health, University of Nottingham, Nottingham, UK. [5]West Midlands Adult CF Centre, Heart of England NHS Foundation Trust, Birmingham, UK. [6]Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK. [7]Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK.

Correspondence: Andrew W. Fogarty, Division of Epidemiology and Public Health, University of Nottingham, Medical School, Nottingham NG7 2UH, UK. E-mail: andrew.fogarty@nottingham.ac.uk

Received: April 26 2017 | Accepted after revision: July 03 2017

Support statement: This study was supported by the UK Medical Research Council. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at openres.ersjournals.com

Acknowledgements: The authors would like to thank all the participants of this study for their help and support.

Author contributions: A. Knox, A. Smyth, D. Forrester, A. Fogarty, D. Barrett, M. Camara conceived the study. H. Barr, J. Dewar, D. Honeybourne, J. Whitehead, and E. Nash collected the data. A. Fogarty carried out the analysis. All authors contributed to the study and have read and approved the final manuscript.

References

1 Ratjen F, Doring G. Cystic fibrosis. *Lancet* 2003; 361: 681–689.
2 Matel J. Nutritional management of cystic fibrosis. *J Parenter Enteral Nutr* 2012; 36: 60S–67S.
3 Smyth A, Bell S, Bojcin S, *et al.* European Cystic Fibrosis Society standards of care: best practice guidelines. *J Cystic Fibrosis* 2014; 13: S23–S42.
4 Sanders D, Bittner R, Rosenfeld M, *et al.* Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. *Pediatr Pulmonol* 2011; 46: 393–400.
5 Forrester D, Knox A, Smyth A, *et al.* Are different measures of body habitus associated with lung function in individuals with cystic fibrosis? A cross-sectional study. *J Cystic Fibrosis* 2013; 12: 284–289.
6 Fogarty A, Britton J, Clayton A, *et al.* Are measures of body habitus associated with mortality in cystic fibrosis? *Chest* 2012; 142: 712–717.
7 Barr H, Halliday N, Camara M, *et al. Pseudomonas aeruginosa* quorum sensing molecules correlate with clinical status in cystic fibrosis. *Eur Resp J* 2015; 46: 1046–1054.
8 Rosenfeld M, Emerson J, Williams-Warren J, *et al.* Defining a pulmonary exacerbation in cystic fibrosis. *J Pediatr* 2001; 139: 359–365.
9 Miller M, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
10 Amadori A, Antonelli A, Balteri I, *et al.* Recurrent exacerbations affect FEV1 decline in adult patients with cystic fibrosis. *Respir Med* 2009; 103: 407–413.
11 Britto M, Kotagal U, Hornung R, *et al.* Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002; 121: 64–72.
12 Mayer-Hamblett N, Rosenfeld M, Emerson J, *et al.* Developing cystic fibrosis lung transplant referral criteria using predictiors of 2-year mortality. *Am J Respir Crit Care Med* 2002; 166: 1550–1555.
13 Schechter M, Fink A, Homa K, *et al.* The Cystic Fibrosis Foundation Patient Registry as a tool for use in quality improvement. *BMJ Qual Saf* 2014; 23: i9–i14.
14 Godfrey M, Oliver B. Accelerating the rate of improvement in cystic fibrosis care: contributions and insights of the learning and leadership collaborative. *BMJ Qual Saf* 2014; 23: i23–i32.
15 Helshe S, Goss C, Thompson V, *et al.* Short-term and long-term response to pulmonary exacerbation in cystic fibrosis. *Thorax* 2016; 71: 223–229.