# A pilot study of inhaled dry-powder mannitol during cystic fibrosis-related pulmonary exacerbation

*To the Editor:*

Pulmonary exacerbation treatment aims to eradicate increased respiratory symptoms and recover acute loss in lung function. Current treatment strategies remain suboptimal, with conventional intravenous antibiotics and intensive physiotherapy failing to achieve this in 25% of patients [1]. Despite this worrying statistic, optimising recovery from acute pulmonary exacerbations has not been a focus of recent cystic fibrosis (CF) research efforts. There is a lack of adjunct evidence-based therapies for use in this setting [2] and strategies to optimise airway clearance with physiotherapy have been largely overlooked, despite common use in the outpatient setting [3, 4]. Inhaled dry-powder mannitol (IDPM), a mucoactive agent, improves mucociliary clearance [5], mucus rheology, and hydration and surface properties of mucus [6]. In the CF outpatient setting, IDPM treatment improves lung function, both in the short (>2 weeks) and long (>12 months) term [3, 7]. Its utility in in-patient pulmonary exacerbation care is unclear. In this pilot study, we investigated feasibility and safety of IDPM as an adjunct therapy to standard in-patient hospital care for children with pulmonary exacerbation. Efficacy was also explored using both conventional respiratory function outcomes and additional sensitive measures of peripheral airway function.

A double-blind, randomised, placebo-controlled pilot study was conducted of twice daily IDPM (10×40 mg) or very low dose IDPM (10×5 mg nonrespirable mannitol, termed "control" hereafter) administered for 12 consecutive days. Eligibility criteria for recruitment were age ⩾6 years, admission to hospital for an infective pulmonary exacerbation (defined using Fuchs' criteria 4) and baseline forced expiratory volume in 1 s ($FEV_1$) ⩾40% predicted (Global Lungs Initiative reference equations). Exclusion criteria included concurrent haemoptysis, hypertension, supplemental oxygen, oral corticosteroids, surgery or recent commencement of a mucolytic agent (within 3 months of admission). During hospital admission, subjects received combination *i.v.* antibiotic therapy (typically an aminoglycoside plus a β-lactam), daily airway clearance sessions and CF multidisciplinary team input, as clinically indicated.

Outcome parameters were assessed at admission, on day 7, on day 14 (discharge) and 1 month after discharge. Clinical status outcomes were the Cystic Fibrosis Clinical Score [8] and Revised CF Questionnaire quality of life [9]. Lung function outcomes were performed in the following order, in the morning, prior to inhalation of the study drug and airway clearance: multiple-breath nitrogen washout, using the VIASYS Vmax system (Sensormedics Corp., Yorba Linda, CA, USA) as previously described [10]; the forced oscillation technique (FOT), using custom-built equipment as previously described [11], reporting mean respiratory system resistance and reactance at 6 Hz, processed using breath-by-breath analysis [11]; spirometry and plethysmography, using the VIASYS Vmax system according to American Thoracic Society/European Respiratory Society standards [12]; and cardiopulmonary exercise testing (CPET) using the VIASYS Vmax system and a Bruce treadmill protocol as previously described [10], and reporting peak oxygen consumption ($V'_{O_2}$) and measures of ventilation efficiency at peak exercise (minute ventilation ($V'_E$)/$V'_{O_2}$ and $V'_E$/carbon dioxide production ($V'_{CO_2}$)).

Blinded randomisation was performed (ratio1/1, random number generation without stratification) to IDPM or control (both manufactured by Pharmaxis Ltd, Frenchs Forest, Australia). A study-drug tolerance test (SDTT) was deemed acceptable if baseline $FEV_1$ decreased by <50% immediately or <20% 15 min after the test dose, or if oxygen saturation remained >89%. The study drug was administered twice daily, immediately prior to individually tailored airway clearance sessions supervised by a physiotherapist. Mean treatment difference between groups, with 95% confidence intervals, was computed by linear regression using the group unstandardised beta coefficient after adjusting for baseline value (SPSS version 19.0; IBM, Armonk, NY, USA). This study was approved by the local Ethics Committee (EC no. 130; Children's Hospital at Westmead, Westmead, Australia) and registered with the Australian and New Zealand Clinical Trials Network (ACTRN 12612001167853). Written, informed consent was obtained from all participants.

23 subjects were recruited. One control-group subject failed the SDTT due to vomiting, and 22 (96%, 11 each in the IDPM and control groups) completed the study. The study drug was well tolerated. Two adverse events occurred in the IDPM group (vomiting and dizziness/headache) *versus* three in the control group (vomiting, minor haemoptysis and blurred vision). Baseline characteristics were well matched apart from baseline $FEV_1$: mean±SD 58.0±13.0% *versus* 73.1±15.6% predicted in control and IDPM groups,

respectively ($p \leq 0.05$). Dornase alfa and hypertonic saline were used regularly in 59% and 14% of the whole cohort, respectively.

Changes in outcome measures are summarised in table 1. No significant difference in improvement of conventional lung function outcomes or clinical status occurred between groups. A significant difference was detected in the magnitude of improvement in $V'_E/V'_{CO_2}$: mean (95% CI) difference −4.5 (−7.9– −1.0) (p=0.02), a decrease of 11% *versus* 3% from baseline in the IDPM *versus* control groups. The treatment effect for lung clearance index (LCI) was −1.1 (−2.2–0.1) lung turnovers (p=0.06), an improvement of 26% *versus* 13% from baseline, respectively. Improvements in other peripheral airway function measures were detected but not statistically significant (residual volume/total lung capacity ratio, p=0.08; forced expiratory flow at 25–75% of forced vital capacity, p=0.11). At 1 month post-discharge, previous described benefits were no longer present.

In this pilot study, improvements in outcomes reflecting peripheral airway function were observed with adjunctive IDPM treatment during a hospital admission for pulmonary exacerbation. Improvements were, however, temporary, suggesting no ongoing benefit once treatment was ceased. IDPM was well tolerated over 12 days with no serious adverse events and few non-serious adverse events.

This study incorporated additional sensitive outcome measures (CPET, LCI and FOT) reflecting peripheral airway function, which are feasible in this setting [10] and able to detect treatment effects despite small subject numbers (≥12 subjects per group) [14]. A significant treatment effect in $V'_E/V'_{CO_2}$, and a trend towards significance in LCI (p=0.06) was detected, despite small study numbers. Comparable changes in $V'_E/V'_{CO_2}$, to gas-mixing efficiency measures such as LCI, are not surprising given that $V'_E/V'_{CO_2}$ reflects functional clearance of carbon dioxide during exercise. The results highlight the complementary information gained from incorporation of these novel tests, in addition to conventional lung function tests. Based on the findings in this study, we speculate that IDPM, used in conjunction with airway clearance techniques, is able to improve mucus clearance in peripheral airways, augmenting recovery of peripheral airway function. Previous work in bronchiectasis subjects using radioisotope scanning also demonstrated greatest benefit of IDPM in peripheral lung regions [15].

TABLE 1 Relative change in clinical status and cardiopulmonary function in the inhaled dry-powder mannitol (IDPM) and control groups at discharge (day 14) and 1 month after discharge (follow-up), compared with admission values

| | Baseline | | Discharge | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | IDPM | Control | IDPM | Mean difference (95% CI) | p-value | Control | IDPM | Mean difference (95% CI) | p-value |
| **Clinical status** | | | | | | | | | | |
| CFCS total score | 26.4±2.6 | 26.7±4.2 | 17.4±1.8 | 18.6±2.5 | 1.1 (−0.5–2.8) | 0.17 | 19.6±3.8 | 20.7±3.1 | −1.0 (−4.1–2.1) | 0.5 |
| CFQ-R respiratory domain | 63.6±19.9 | 55.6±22.4 | 75.6±14.6 | 73.5±15.6 | 1.3 (−10.5–13.0) | 0.83 | 75.0±20.4 | 68.9±11.4 | 3.5 (−10.7–17.7) | 0.61 |
| **Spirometry** | | | | | | | | | | |
| $FEV_1$ % pred | 58.0±13.0 | 73.1±15.6 | 71.4±11.2 | 88.8±17.4 | 4.6 (−3.8–13.0) | 0.26 | 70.8±9.8 | 80.2±20.7 | 5.4 (−2.8–13.5) | 0.18 |
| $FEF_{25-75\%}$ % pred | 33.3±15.9 | 48.9±21.1 | 50.1±17.6 | 82.9±36.9 | 12.8 (−3.3–28.9) | 0.11 | 47.7±16.3 | 60.6±31.2 | 3.9 (−10.7–18.5) | 0.58 |
| FVC % pred | 75.0±13.0 | 87.1±16.5 | 83.9±12.3 | 95.4±12.4 | 2.8 (−3.5–9.2) | 0.36 | 84.2±10.2 | 92.2±15.6 | 1.7 (−4.1–7.5) | 0.55 |
| **Plethysmography** | | | | | | | | | | |
| RV/TLC | 36.4±7.2 | 31.5±6.6 | 33.9±7.0 | 25.9±5.5 | −4.8 (−10.3–0.7) | 0.08 | 31.3±6.8 | 29.8±7.5 | −2.1 (−8.4–4.3) | 0.49 |
| **MBNW** | | | | | | | | | | |
| LCI lung turnovers | 9.2±1.6 | 9.5±1.7 | 8.1±1.4 | 7.0±1.4 | −1.1 (−2.2–0.1) | 0.06 | 8.2±1.5 | 7.8±1.9 | 0.2 (−1.6–2.0) | 0.84 |
| **FOT** | | | | | | | | | | |
| $R_{rs_6}$ $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$ | 6.1±1.5 | 5.3±1.2 | 5.6±1.1 | 4.5±1.4 | −0.6 (−1.9–0.7) | 0.37 | 5.9±1.2 | 5.1±1.8 | 0.3 (−1.5–2.1) | 0.72 |
| $X_{rs_6}$ $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$ | −2.8±1.2 | −2.3±1.0 | −2.1±0.8 | −1.6±0.7 | 0.2 (−0.5–0.8) | 0.54 | −2.1±0.9 | −2.1±1.3 | 0.2 (−1.0–1.3) | 0.78 |
| **CPET** | | | | | | | | | | |
| $V'_{O_2}$ $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ | 1.5±0.2 | 1.4±0.4 | 1.6±0.2 | 1.6±0.7 | 0.1 (−0.2–0.4) | 0.41 | 1.5±0.3 | 1.7±0.7 | −0.2 (−0.5–0.0) | 0.06 |
| $V'_E/V'_{CO_2}$ | 30.4±2.8 | 31.1±4.7 | 31.1±3.1 | 26.7±3.4 | −4.5 (−7.9– −1.0)* | 0.02 | 31.5±2.3 | 30.3±2.4 | 1.4 (−1.0–3.8) | 0.23 |
| $V'_E/V'_{O_2}$ | 33.4±2.4 | 32.3±6.5 | 34.6±7.0 | 29.8±5.0 | −5.2 (−12.2–1.8) | 0.14 | 35.8±4.8 | 32.5±2.4 | 2.5 (−1.7–6.6) | 0.23 |

Data are presented as mean±SD, unless otherwise stated. Mean difference for IDPM minus control group at follow-up adjusted for baseline measure. All age reference equations used to calculate spirometric % predicted values have been shown to be applicable to Australian cohorts [13]. Complete lung clearance index (LCI), forced oscillation technique (FOT) and cardiopulmonary exercise testing (CPET) data were collected from 17 (77%) out of 22 subjects, and 15 (68%) out of 22 for plethysmography. CFCS: Cystic Fibrosis Clinical Score; CFQ-R: Revised CF Questionnaire; $FEV_1$: forced expiratory volume in 1 s; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; MBNW: multiple-breath nitrogen washout; $R_{rs_6}$: resistance of the respiratory system at 6 Hz; $X_{rs_6}$: reactance of the respiratory system at 6 Hz; $V'_{O_2}$: oxygen consumption; $V'_E$: minute ventilation; $V'_{CO_2}$: carbon dioxide production. *: p<0.05.

The limitations of our study included the relatively small sample size, preventing strong conclusions about clinical utility in this setting. Recruitment was challenged by current clinical practice of regular planned *i.v.* "tune-ups" limiting those fulfilling stringent criteria for pulmonary exacerbation at a single institution [4], and the commencement of a "hospital in the home" programme. Use of these criteria also accounts for the larger magnitude of improvement in the control group compared with a previous observational study at our institution [10]. Inability to show a significant change in more central airway measures, such as FEV1, despite benefits described in larger outpatient-based studies over a similar time period [7], may be explained by inadequate power to detect differences, non-matched FEV1 on admission across the two groups and, finally, the different phase of disease studied (*i.e.* pulmonary exacerbation *versus* outpatient setting during a period of stability). Attempts to match FEV1 on admission may affect matching of other, more sensitive outcome measures used (*e.g.* $V'E/V'CO_2$ or LCI), which, importantly, were comparable between the groups on admission. The effect of concurrent regular dornase alfa and hypertonic saline on the observed effect of adjunct IDPM also could not be examined within a cohort of this size.

In summary, IDPM is both safe and feasible as an adjunctive treatment in this setting, and offers potential to improve clinical outcomes from pulmonary exacerbation. The findings of our study support a larger, multicentre study examining the potential beneficial effect on clinical and lung function outcomes. Strategies to accelerate and maximise recovery from pulmonary exacerbations are highly desirable, given the occurrence and treatment of pulmonary exacerbations in CF are costly from the perspective of both healthcare provider and patient.

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**Mannitol is a safe feasible treatment adjunct in cystic fibrosis acute exacerbation and may improve clinical outcomes** http://ow.ly/CrU1X

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## References

1 Sanders DB, Bittner RC, Rosenfeld M, *et al.* Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010; 182: 627–632.
2 Stenbit AE, Flume PA. Pulmonary exacerbations in cystic fibrosis. *Curr Op Pulm Med* 2011; 17: 442–447.
3 Aitken ML, Bellon G, De Boeck K, *et al.* Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. *Am J Respir Crit Care Med* 2012; 185: 645–652.
4 Fuchs HJ, Borowitz DS, Christiansen DH, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994; 331: 637–642.
5 Daviskas E, Anderson SD, Brannan JD, *et al.* Inhalation of dry-powder mannitol increases mucociliary clearance. *Eur Respir J* 1997; 10: 2449–2454.
6 Daviskas E, Anderson SD, Jaques A, *et al.* Inhaled mannitol improves the hydration and surface properties of sputum in patients with cystic fibrosis. *Chest* 2010; 137: 861–868.
7 Jaques A, Daviskas E, Turton JA, *et al.* Inhaled mannitol improves lung function in cystic fibrosis. *Chest* 2008; 133: 1388–1396.
8 Kanga J, Kuhn R, Craigmyle L, *et al.* Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation. *Clin Ther* 1999; 21: 1343–1356.
9 Quittner AL, Modi AC, Wainwright C, *et al.* Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest* 2009; 135: 1610–1618.
10 Robinson PD, Cooper P, Van Asperen P, *et al.* Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis. *Pediatr Pulmonol* 2009; 44: 733–742.

11 Robinson PD, Turner M, Brown NJ, *et al.* Procedures to improve the repeatability of forced oscillation measurements in school-aged children. *Respir Physiol Neurobiol* 2011; 177: 199–206.
12 American Thoracic Society, European Respiratory SocietyATS/ERS statement: raised volume forced expirations in infants: guidelines for current practice. *Am J Respir Crit Care Med* 2005; 172: 1463–1471.
13 Hall GL, Stanojevic S, Beasley R, *et al.* Revised historical spirometry reference ranges are reflective of contemporary healthy spirometry values. *Eur Respir J* 2008; 32 Suppl. 52:382s–383s.
14 Subbarao P, Stanojevic S, Brown M, *et al.* Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis: a pilot study using inhaled hypertonic saline. *Am J Respir Crit Care Med* 2013; 188: 456–460.
15 Daviskas E, Anderson SD, Eberl S, *et al.* The 24-h effect of mannitol on the clearance of mucus in patients with bronchiectasis. *Chest* 2001; 119: 414–421.

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# Estimation of post-operative forced expiratory volume by functional respiratory imaging

*To the Editor:*

Surgical resection is a potential curative therapy for patients with early-stage non-small cell lung cancer (NSCLC). Comorbid chronic obstructive pulmonary disease (COPD) is frequently present in these patients [1], stressing the importance of an accurate estimation of post-operative (po) forced expiratory volume in 1 s ($FEV_1$) [2]. A predicted $poFEV_1$ ($PpoFEV_1$) must be calculated whenever the pre-operative $FEV_1$ or diffusing capacity for carbon monoxide is <80% predicted [3]. The anatomic segment method (ASM) and perfusion scintigraphy (QS) are often used for this prediction [4, 5]. Both are known to underestimate the $poFEV_1$ in a substantial fraction of patients, resulting in the possible exclusion from resection of a borderline operable patient [6, 7]. This stresses the need for a more precise tool to estimate $poFEV_1$.

Current imaging techniques (computed tomography (CT), magnetic resonance imaging and four-dimensional CT) allow a patient-specific description of spatial differences in lung mechanics and this information might lead to a better prediction of $poFEV_1$ [8]. Functional respiratory imaging (FRI) has added functionality to CT data by means of computational fluid dynamics (CFD) airflow calculations [9, 10]. FRI has been used in different settings and populations [11–13]. This study investigated whether FRI can be used to predict $poFEV_1$, using data at baseline and after virtual resection, and compared the predictive accuracy of FRI with those of ASM and QS.

This single-centre, prospective pilot study enrolled consecutive patients with early-stage NSCLC that was considered resectable and scheduled for lobectomy/pneumonectomy. Eligible subjects performed spirometric manoeuvres according to the American Thoracic Society/European Respiratory Society standards [14] before and after resection. $PpoFEV_1$ using ASM and QS were calculated according to previous reports [4–7]. Before surgery, all patients also underwent breath-hold spirometry and low-dose chest CT scans at two different lung levels, *i.e.* total lung capacity (TLC) and residual volume (RV). Institutional review board approval was obtained and a written informed consent was provided by all patients.

From both RV and TLC scans, a reconstruction was made of different lung lobes to assess the changes in lobar volume from RV to TLC (lobar expansion (EXP)). From the TLC scan, the airway tree was segmented up to the point where the CT image quality no longer allowed for distinction of bronchi. CFD calculations provided flow properties within the reconstructed airway trees. Image processing and steady CFD calculations (assuming 25-$L \cdot min^{-1}$ tracheal flow with flow split ratios according to the relative lobar EXP) on a noncompliant airway model were performed according to the reports by De Backer and co-workers [9, 10] to estimate pre-operative airway resistance. Virtual resection was performed by the removal of the airways leading to the lung/lobes targeted for lung resection. Again, steady CFD calculations (flow split ratios according to the relative lobar EXP of the nonresected parts) were carried out to estimate post-operative airway resistance.