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Erasmus University Rotterdam
Making Minds Matter

AI-driven CT quantification of mucus plugs to evaluate the effect of inhaled hypertonic saline in children aged 3–6 years with cystic fibrosis: a randomised controlled trial

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To the Editor:

Impaired mucociliary clearance is a hallmark feature of cystic fibrosis (CF) lung disease, contributing to airway inflammation, infection and progressive structural damage [1]. In young children with CF, early intervention targeting mucus clearance is critical for preservation of lung health [2]. The Saline Hypertonic in Preschoolers (SHIP-CT) study, which ran between 2016 and 2019, evaluated the effects of inhaled hypertonic saline *versus* isotonic saline on lung structure in children with CF aged 3–6 years [3]. After 48 weeks, imaging assessments using visual PRAGMA-CF scoring analysis demonstrated fewer bronchial abnormalities in the hypertonic saline group compared to the isotonic saline group, as assessed by %Disease, which was defined as the sum of % Bronchiectasis, %Mucus plugging, and %Bronchial wall thickening [3]. Similarly, bronchial wall thickening was reduced in the hypertonic saline group relative to the isotonic saline group, as measured by an automatic bronchus–artery analysis [4]. A limitation of the study was that the effect of hypertonic saline on mucus plugs could not be reliably assessed using the PRAGMA-CF hierarchical scoring system, along with the fact that there were a relatively low number of patients with visible mucus plugging. Recent advances in artificial intelligence (AI) have enabled automatic quantification of mucus plugging on chest CT scans [5]. This mucus plug analysis has been successfully validated and applied in various diseases [5–7]. In COPD, a study involving 9399 patients demonstrated an association between the number of segments containing one or more mucus plugs and increased mortality [7]. In bronchiectasis patients from the EMBARC registry, a higher mucus plug count was observed in older age, longer disease duration, *Pseudomonas aeruginosa* infection, and in patients with primary ciliary dyskinesia as underlying aetiology. Furthermore, the number of mucus plugs was associated with the number of exacerbations [8]. In CF, treatment with elexacaftor/tezacaftor/ivacaftor (ETI) leads to clinically significant reductions in both the number and volume of mucus plugs [6, 9]. The mucus plug analysis offers the opportunity to assess the effect of hypertonic saline on mucus plugging in participants included in the SHIP-CT study. Using this AI-based approach, we hypothesised that children treated with hypertonic saline would demonstrate a reduction in mucus plugging compared to those receiving isotonic saline.

A *post hoc* automatic mucus plug analysis was performed of all SHIP-CT computed tomography (CT) images using LungQ (Thirona, Nijmegen). Detailed CT acquisition and reconstruction parameters can be found in previous publications [3]. The requirements for the automatic mucus plug analysis were as follows: 1) correct digital format (correct DICOM headers); 2) sufficient inspiratory lung volume as defined by a round shape of the trachea and presence of lung parenchyma between the heart and sternum; 3) complete display of the lungs; 4) no artefacts, or artefacts with minimal effect on the visualisation of the lungs and airways; 5) no missing slices or irregular spacing between slices; and 6) slice thickness of 1.5 mm or below. The mucus plug algorithm segments the bronchial tree and identifies each bronchopulmonary segment. It detects bronchi and counts mucus plugs that completely obstruct a bronchus with a visible proximal lumen, segmenting it throughout its length or until the first bifurcation of the plugged bronchus, whichever comes first. Trained on expert annotations, the algorithm identifies on a chest CT such obstructions throughout the bronchial tree and provides their location, total mucus plug count and volume. The mucus plug analysis adds relevant information to bronchus–artery analysis, which assesses bronchial and arterial ratios to objectively evaluate bronchial dilatation and wall thickening, but is limited to airways with an open lumen.

Shareable abstract (@ERSpublications)
Inhaled hypertonic saline reduces mucus plugging and airway abnormalities in young children with CF. Combining bronchus–artery and mucus plugging analyses enables a comprehensive evaluation of treatment response and disease progression. https://bit.ly/4ooGFZa

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The primary outcome of this SHIP-CT analysis was the difference in mucus plug count between the hypertonic saline and isotonic saline groups as measured by chest CT at 48 weeks, adjusted for baseline mucus plug count and baseline age. This was investigated using a multiple linear regression model. We used mucus plug count at 48 weeks as the outcome and included treatment group, baseline mucus plug count and baseline age as the covariates in the model. Statistical significance was accepted for p-values less than 0.05. Statistical analyses were carried out with R version 4.4.2.

A total of 220 CT scans from 116 participants were collected from the SHIP-CT dataset. Five CT scans were excluded due to inconsistent slice spacing (n=4) or poor image quality (n=1). The mucus plug analysis included 113 baseline and 102 48-week CT scans from 115 participants. Of these, 60 received isotonic saline and 55 participants received hypertonic saline. Mucus plugs were detected in 24 (41%) baseline and 20 (37%) 48-week CT images in the isotonic saline group and 17 (33%) baseline and six (12%) 48-week CT images in the hypertonic saline group. For the statistical analysis, all analysed CT images were included. Among CT scans with detectable mucus plugging, the median (interquartile range) mucus plug counts in the isotonic saline group were 1 (1–2.5) at baseline and 4 (1–8) at 48 weeks. In the hypertonic saline group, the counts were 2 (1.25–7.75) at baseline and 1.5 (1–28.2) at 48 weeks. The median mucus plug volume in the isotonic saline group was 0.04 (0.01–0.11) mL at baseline and 0.07 (0.02–0.50) mL at 48 weeks. In the hypertonic saline group, the volume was 0.08 (0.03–0.33) mL at baseline and 0.05 (0.02–2.08) mL at 48 weeks. The change in mucus plug count from baseline to 48 weeks by treatment groups is shown in figure 1. At 48 weeks, the isotonic saline group had a significantly higher mucus plug count than the hypertonic saline group (mean difference 0.75, 95% CI 0.36–1.15; p=0.0005). Two examples of bronchial trees with labelled mucus plugging from participants in the hypertonic saline (figure 1b) and isotonic saline (figure 1d) groups are shown.

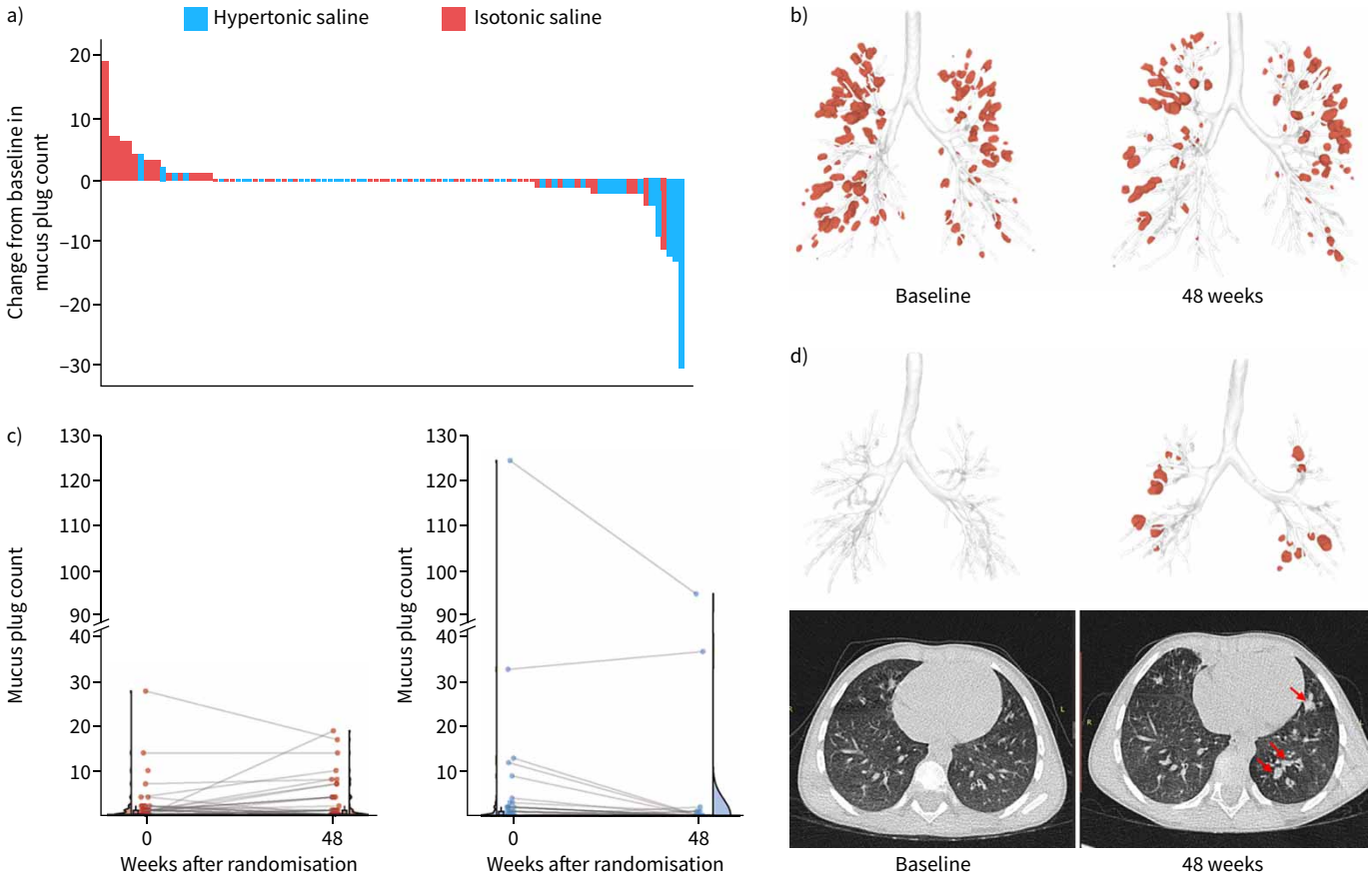

FIGURE 1 Effect of hypertonic saline on mucus plug count. a) Change in mucus plug count from baseline to 48 weeks by treatment group. Among participants with mucus plugs, plug counts increased in 15 receiving isotonic saline (red bars) *versus* three receiving hypertonic saline (blue). b) Bronchial tree of a participant treated with hypertonic saline, showing 125 plugs at baseline (left) and 95 mucus plugs after 48 weeks (right). c) Distribution of mucus plug counts from baseline to 48 weeks by treatment groups as indicated by raincloud plot. d) Participant treated with isotonic saline, with no plugs at baseline (left) and 19 plugs after 48 weeks (right). The two axial computed tomography (CT) slices are of this participant, the baseline CT is on the left and the 48-week CT on the right. The arrow heads indicate mucus plugs.

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The mucus plug analysis demonstrated that hypertonic saline prevents worsening of mucus plugging through, presumably, more effective clearance of mucus plugs from the airways. This finding underscores the therapeutic potential of hypertonic saline in reducing airway obstruction, particularly in the early stages of CF lung disease, where mucus accumulation may precede irreversible structural damage [10, 11]. This conceptually aligns with the findings of Graeber *et al*. [12], who reported that preventive treatment with 7% hypertonic saline reduced mucus obstruction to near-normal levels in the proximal airways of a CF mouse model. In children with CF, early intervention is critical toward preserving lung function and delaying disease progression. Notably, the results of the mucus plug analysis in SHIP-CT align with previous findings from the bronchus–artery analysis, demonstrating a reduction of bronchial wall thickening with hypertonic saline treatment [4]. Mucus plug analysis of the SHIP-CT images was able to detect mucus plugs that completely blocked bronchi up to the 7th segmental generation, where the segmental generation is defined as segmental generation 0 [13]. The mucus plug analysis provides a valuable additional image analysis tool for assessing the effectiveness of mucolytic therapy in structural lung disease. The mucus plug analysis adds relevant information to the bronchus–artery analysis, which assesses bronchial and arterial ratios to objectively evaluate bronchial dilatation and wall thickening, but is limited to airways with an open lumen. Together, these complementary approaches enable clinicians and researchers to better monitor disease progression and the impact of therapy, ultimately supporting earlier and more targeted intervention strategies in children with CF.

Whether hypertonic saline remains beneficial in preschool children receiving the cystic fibrosis transmembrane conductance regulator modulator therapy ETI is currently unclear. Studies in school-aged children and adults have shown that ETI does not fully eliminate infection or inflammation, nor completely reverse established structural lung disease. The recent MODUL study demonstrated that, in 188 school-aged children, ETI therapy dramatically reduced the number of mucus plugs, whereas bronchial dilatation and wall thickening did not normalise in most children [6]. In current clinical practice, it seems reasonable to reserve hypertonic saline therapy for children receiving ETI who show progressive structural lung damage on chest CT or who continue to have clinical symptoms, suggesting insufficient disease control. The effectiveness of this intervention can then be monitored using lung function tests and follow-up chest CT. Further research is needed to determine whether imaging-based stratification can identify those preschool children most likely to benefit from adjunctive hypertonic saline treatment.

This study has the following limitation. The mucus plug algorithm detects only mucus plugs that fully occlude the bronchus of bronchi that are detectable on chest CT and therefore does not include mucus plugs in non-detectable small airways. For a comprehensive evaluation of mucus-related bronchial changes, the mucus plug analysis should be combined with the automated bronchus–artery analysis to assess bronchial wall thickening.

In conclusion, inhaled hypertonic saline significantly reduced mucus plugging over 48 weeks in children with CF aged 3–6 years compared to isotonic saline, supporting previous findings that showed improvements in structural airway abnormalities in the hypertonic saline-treated group. These results further support maintenance treatment with inhaled hypertonic saline as an effective early intervention to reduce mucus obstruction and mitigate disease progression. The combined use of bronchus–artery and mucus plug analyses allows for a more comprehensive evaluation of treatment response and structural outcomes in young children with CF.

Yuxin Chen [1,2], Rudolfs Latisenko[3], Stephanie D. Davis[4], Margaret Rosenfeld[5], Felix Ratjen [6], Karen D. Hinckley Stukovsky[7], Stephen Stick[8] and Harm A.W.M. Tiddens [2,3] on behalf the SHIP-CT study group

[1]Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China. [2]Department of Paediatric, Division of Respiratory Medicine and Allergology, Sophia Children's Hospital, Erasmus MC, Rotterdam, The Netherlands. [3]Thirona, Nijmegen, The Netherlands. [4]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [5]Seattle Children's Research Institute, Seattle, WA, USA. [6]Division of Respiratory Medicine, Translational Medicine, Research Institute, Hospital for Sick Children, Toronto, ON, Canada. [7]Collaborative Health Studies Coordinating Center, The University of Washington, Seattle, WA, USA. [8]Wal-yan Respiratory Research Centre, Telethon Kids Institute, Perth, Australia.

Corresponding author: Yuxin Chen (y.chen.1@erasmusmc.nl)

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Data availability: De-identified individual participant data that underlie the results reported in this article will be immediately available after publication (note: chest CT images can only be accessed on site in the Erasmus MC). The study protocol will be available online. The data will be shared with researchers who provide a methodologically sound proposal to achieve the aims in the approved proposal. Proposals should be directed to h.tiddens@erasmusmc.nl to gain access; data requestors will need to sign a data access agreement.

This trial was prospectively registered at ClinicalTrials.gov with identifier NCT02950883.

Ethics statement: The institutional review boards and human research ethics committees at each participating centre approved the trial and written informed consent was obtained.

Conflict of interest: Y. Chen reports no conflict of interest. R. Latisenko is employed by Thirona. S.D. Davis reports grants from the Cystic Fibrosis Foundation. M. Rosenfeld reports grants from the Cystic Fibrosis Foundation. F. Ratjen reports consultancy fees from Vertex, Bayer, Roche, Genentech and Proteostasis, and is a member of the *European Respiratory Journal's* editorial board. K.D. Hinckley Stukovsky reports grants from the Cystic Fibrosis Foundation. S. Stick reports grants from the Cystic Fibrosis Foundation and the National Health and Medical Research Foundation. H.A.W.M. Tiddens reports grants from the Cystic Fibrosis Foundation and Health Holland, is a shareholder of Thirona, and was the founder, director and later deputy director of the Erasmus MC lung analysis laboratory that acts as the ECFS-CTN CT expert centre. Erasmus MC and the Telethon Kids Institute have licensed the use of PRAGMA-CF to Thirona and Resonance Health.

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