What you don't know can hurt you; early asymptomatic lung disease in cystic fibrosis

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Clinicians caring for children with cystic fibrosis (CF) should now take note; despite your best clinical care, lung disease in CF infants develops surreptitiously and ill-defined by early symptoms. By the time lung disease has symptomatically declared itself, it's probably structurally established and too late to reverse. What you don't know can hurt you.

Hoo and colleagues in this issue provide evidence of early lung disease in patients with CF diagnosed by newborn screening.[1] At a mean 3 months of age, 34% of CF patients had abnormalities of pulmonary function (including lung clearance index (LCI) and/or forced expiratory volume in 0.5 second ($FEV_{0.5}$)) when compared with healthy controls. The presence of symptoms, sometimes aggressively treated, did not reliably identify those with abnormal pulmonary function. This study, by the London CF Collaborative, used contemporaneous healthy controls and adhered to treatment protocols from diagnosis. The research examines with great clarity the vital question of how early lung disease starts in those born with CF. The children studied were provided with every opportunity for optimal health, by the use of newborn screening, regular chest physiotherapy and prophylactic oral flucloxacillin. Disappointingly, our current best care is not good enough to prevent lung disease. Of even greater disappointment is that those with lung disease do not stand out from the crowd.

This is not isolated data. Studies over the past decade have shown that lung disease is established very early in life with bronchiectasis and ventilation inhomogeneity preceding both symptoms and a notable decline in FEV_1. Children at 12 years of age on the US CFF Registry (http://www.cff.org), maintain mean FEV_1% predicted at c95%, yet at the same age bronchiectasis will be established in 59%.[2] Bronchiectasis is present, and persists, in 33% of children between 2 and 3 years of age.[3] In 17-month-old CF toddlers, airways have thicker walls and smaller lumens when compared with healthy controls.[4] Even as young as 3 months of age, the trailblazing Australian AREST CF study of newborn-screened infants has demonstrated a degree of chest CT abnormality in 81%.[5] The physiological chronology has been demonstrated too, with more sensitive measures of lung function able to identify abnormality at younger ages. Measurement of ventilation inhomogeneity by multiple breath washout (MBW) LCI enables a sensitive assessment of pulmonary function across age ranges. MBW LCI is above the healthy control normal range in 95% of school age CF children,[6] 73% of preschool children,[7] 32% of toddlers at 18 months of age[8] and 21% of infants at 3 months of age.[1] In infants and children, such progressive anatomical and physiological change is commonly disassociated from symptoms,[1 5 8] despite the findings that LCI is more abnormal in those with evidence of lower respiratory tract infection.[6 8]

Bronchiectasis, destructive and substantially irreversible, is considered of most concern in CF, defining the final common pathway of lung destruction to respiratory failure. Limiting the development of bronchiectasis is considered key to reducing CF morbidity; prevention of bronchiectasis is the primary outcome in the current Australian study of Azithromycin in CF infants (COMBAT CF: clinical trials.gov NCT01270074). Averting bronchiectasis is understood, but what about ventilation inhomogeneity? Are early abnormalities of ventilation inhomogeneity fully reversible, or if unchecked, how do they evolve into longer-term structural change with associated symptoms?

Ventilation inhomogeneity, particularly in the young, carries a clinical sense that if only we worked harder with chest physiotherapy and mucolytics we may be able to reverse such change. Possibly. In children under 5 years treated with nebulised hypertonic saline as part of the ISIS trial, while the primary outcome for the trial was negative, measures of forced expiratory flow demonstrated significant improvement in the subset of patients tested, suggesting that more sensitive measures may be able to demonstrate effectiveness of therapies when studying younger children.[9]

The association between changes in ventilation inhomogeneity and structural change on imaging also needs more investigation. Inevitably CT Chest, readily available, will be the predominant anatomical comparator in such studies, but hyperpolarised helium MRI (HeMRI) may also offer useful insight, as it is able to provide synchronous imaging and quantifiable measure of focal ventilation inhomogeneity. In a recent interventional study of Ivacaftor, focal areas of ventilation inhomogeneity (assessed by HeMRI) were improved by therapeutic intervention, but the same areas 'relapsed' once the intervention was terminated.[10] If focal areas of ventilation inhomogeneity become chronically susceptible to injury, then early intervention trials to prevent such change may be critical to avert early CF lung disease. As a technology, HeMRI has constrained application in the clinical context, so the ability of MBW LCI to sensitively and specifically identify ventilation defects detected by HeMRI warrants further research.

To prevent early CF lung disease, bronchiectasis and ventilation inhomogeneity, as surrogate biomarkers should be made primary outcomes in clinical research studies. To become primary outcomes, surrogate biomarkers require to be approved by regulatory authorities and adopted by pharmaceutical companies for phase III clinical trials. The sensitivity of CT chest and ventilation inhomogeneity to early lung disease in CF has been recognised in recent US NHLBI workshop[11] and European Respiratory Society Research Seminar (Rotterdam, March 2012). Both Ct and MBW LCI were identified as critical areas for further development and standardisation, to enable their use as primary outcomes in multicentre interventional studies. The CF research community is growing in confidence to challenge and support both regulators and pharmaceutical companies to make more effective assessments of potential therapies using these novel surrogate biomarkers. This is particularly pressing for infants and preschool children where current regulatory requirements may be considered insufficiently demanding of patient benefit. In response, regulators will request that

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proposed novel surrogate biomarkers are exposed to appropriate levels of critical scrutiny: demonstrated to be safe, quantifiable and reproducible, sensitive to meaningful changes in patient health, and reflect relevant clinical patient benefit.

Several CF interventional clinical studies have now reported CT chest and LCI as trial endpoints, supporting the case that these novel surrogate biomarkers can be sensitive and meaningful measures of patient health. Treatment of a respiratory exacerbation in CF children at mean age of 3 years with a course of intravenous antibiotics and intensive chest physiotherapy is associated with an improvement in chest CT scores, particularly bronchial dilatation/bronchiectasis.[12] Further evidence that novel pulmonary function measures (LCI) may provide a more sensitive signal of therapeutic benefit has recently been reported in three studies where patients receiving the intervention had normal range spirometry. Statistically significant improvements in LCI over placebo was demonstrated for hypertonic saline,[13] dornase α[14] and ivacaftor in G551D patients.[15] Systematic amalgamation of current evidence, supported by unpublished standardisation data, should enable these biomarkers to enter routine use in CF clinical trials. The entrance will be timely; multiple novel agents are in Phase II and III trials, and could benefit from more sensitive markers of effect for pharmacological intervention of cystic fibrosis transmembrane regulator (CFTR) malfunction (UK CF Gene Therapy Multidose Trial, Vertex Pharmaceutical interventions for Class II and IV mutations, and Class III mutations in young children, PTC Therapeutics for Class I mutations).

Clinicians increasingly understand how much they must strive to deliver their patients to the point of future pharmacogenetic correction with no, or limited, lung damage. The report by Lum and colleagues adds clinical pressure at an earlier age. But, how can we do this, if we can't see it, can't hear it and can't routinely measure it? In this age of enlightenment to the dangers of early CF lung disease, early intervention trials with appropriately approved biomarkers hold the key.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

Thorax 2012;**67**:849–850.
doi:10.1136/thoraxjnl-2012-202465

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