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Cystic fibrosis lung disease and bronchiectasis: the Lancet CF commission

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In this issue of the Lancet Respiratory Medicine, experts in cystic fibrosis from 17 countries with diverse expertise present a Lancet commission on the future of care for CF.[1] The commission is a landmark at a point in time where CF demography and management are changing rapidly. The commission comprehensively addresses the future uncertainties and challenges, including those for the management of lung disease.[1]

The improvements in survival for cystic fibrosis over the past 50 years have been remarkable.[2] As highlighted in the commission it is unclear if, or at what stage, survival improvements for CF will plateau or whether CF patients will ultimately achieve a life expectancy equivalent to the general population. The European CF patient registry forecast that the adult population would increase by 75% between 2010 and 2025. This forecast is likely to underestimate population growth as it did not account for new advances in corrector and potentiator therapy.[2] Much of the commission therefore rightly focusses on the need to develop structures of care that can cope with a growing and aging adult population.[1]

Nevertheless, respiratory disease and bronchiectasis remain the leading causes of morbidity and mortality in cystic fibrosis and will remain so for the foreseeable future. To date there is limited evidence that CFTR modulator therapy will have a major impact in regressing bronchiectasis or correcting chronic infection with organisms such as *Pseudomonas aeruginosa.* CFTR modulators therapies might have been expected to produce substantial reductions in airway bacterial burden and inflammation through improved mucociliary clearance.[3-5] Several studies have, however, found no immediate influence of ivacaftor treatment on bacterial pathogens or inflammation.[3,4] Hisbert and colleagues, in contrast, found rapid reductions in airway *P. aeruginosa* burden within 48 hours of starting treatment with ivacaftor with continued declines in the first year of treatment. In the second year, however, *P. aeruginosa* burden increased again.[5] The mechanism for this effect is not known nevertheless the message is clear that highly effective CFTR modulator therapy will not resolve all aspects of an established vicious cycle.

Emerging threats including multidrug resistance, fungi and non-tuberculous Mycobacteria are increasing in importance and the potential for patient to patient transmission or pandemic spread of Mycobacterium abscessus in particular is a cause for significant concern.[6]

There is a need, therefore, to develop new therapies for CF beyond CFTR modulation including new inhaled antibiotics to treat both Gram-negative infections such as *P. aeruginosa* but also increasingly prevalent challenges such as methicillin resistant Staphylococcus aureus and NTM infections. Anti-inflammatory therapies including those that target the neutrophil, with the exception of ibuprofen, have been largely unsuccessful to date but remain an area of intense study. A key challenge is how the pipeline of new therapeutics to treat bronchiectasis in CF can be maintained against a "moving target" of changing background therapies, CFTR modulation and evolving demography. Endpoints such as forced expiratory volume in 1 second which were used for regulatory approvals of drugs such as inhaled tobramycin in the past cease to have relevance in populations that have largely preserved lung function, while there is evidence that these endpoints are less responsive in adult compared to a paediatric CF population.[7] Pulmonary exacerbations remain a key driver of morbidity and mortality in cystic fibrosis but widespread recognition of this has led to advances in care to prevent exacerbations that mean the average exacerbation rate in CF populations is at a historically low level and projected to fall further as CFTR modulators also reduce exacerbations.[8] There is hope, as improved physiological measures such as LCI and imaging modalities (CT/MRI) allow us to characterise bronchiectasis as never before, but these remain surrogates that do not answer the crucial regulatory question of "does the medication change how a patient feels, functions or survives"?

How to develop feasible trials that can be adequately powered during an era of profound change requires careful consideration. Trial programmes are planned years in advance and uncertainty about future patient populations and endpoints can act as a disincentive to drug developers to invest in CF. This issue was the topic of a Food and Drug Administration workshop in 2018.[7]

Large parts of the world will remain unable to access CFTR modulator therapies due to cost and other considerations and randomized trials are increasingly looking to such countries to enrol patients for clinical trials. This presents significant ethical concerns, since trial participants may not be able to ultimately access the trial medications, but also raises the question of how such data can be extrapolated to the new reality in countries such as the UK and US. Inequality in disease outcomes globally is already a reality but has the potential to increase dramatically in the coming years.[9]

The centre of gravity of CF care is shifting from the treatment of established bronchiectasis in young people and adults to the prevention of bronchiectasis and delaying the onset of CF lung disease. The introduction of CFTR-directed therapies has the potential to prevent or at least significantly delay the development of bronchiectasis such that in future patients may be developing disease in their 3rd, 4th or 5th decade of life or even later, ages more associated with the onset of "non-CF bronchiectasis". Indeed advances in CFTR genetics and functional assessment is expanding the spectrum of CF into patients previous regarded as "non-CF bronchiectasis". The group of patient with clinical features of CF, such as diffuse bronchiectasis, with CFTR variants that do not meet the criteria for CF with intermediate sweat chloride measurements (referred to as CFTR-related disorder) are increasingly recognised. It remains to be seen what percentage of the "non-CF bronchiectasis" population are ultimately found to have some degree of CFTR dysfunction and undiagnosed CFTR-RD.[10] The lines between these conditions are becoming increasingly blurred.

The future of CF care promises a future of longer, healthier lives thanks to decades of exemplary clinical and translational research that many other fields would like to emulate. The Lancet CF commission provides an opportunity to reflect on past successes while preparing for the many future challenges.

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