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News article

1. Papers just published

Rapid Improvement After Starting Elexacaftor-tezacaftor-ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease. The remarkable clinical effects of elexacaftor-tezacaftor-ivacaftor are well described in clinical trials data, but less is currently known about its impact in advanced respiratory disease. This prospective study from 47 french CF centres collected data from 245 CF patients (≥12 years, ppFEV$_1$<40) at drug initiation, 1m and 3m follow-up visits. Side effects were mild and, despite a temporary pause for 14 patients (mostly due to rash), all were able to continue treatment. From a median baseline ppFEV1 of 29, the mean absolute change in ppFEV1 was 15.1%, and in weight 4.2Kg. Approximately 50% of patients came off long-term oxygen therapy, 50% stopped enteral tube feeding and 30% had non-invasive ventilation withdrawn. 11 of the 15 patients on the transplant waiting list at study initiation were removed by the end of follow-up, and 36 of the 37 patients undergoing transplant assessment no longer met the clinical severity criteria. The authors highlight the rapid, significant clinical benefits of elexacaftor-tezacaftor-ivacaftor for patients with established severe disease, and hypothesise that the drug will come with an associated gain in life expectancy. *Am J Resp Crit Care Med*, DOI: 10.1164/rccm.202011-4153OC.

Determinants of lung disease progression measured by lung clearance index in children with cystic fibrosis. The lung clearance index (LCI) as measured by multiple breath washout is now established as a sensitive test for early structural lung disease in children with CF, though the trajectory of LCI progression through pre-school and school age is not yet established. This dual-centre study followed healthy (n=48) and CF (n=64) school aged subjects (5-10 yrs) with 3-monthly LCI over 24 months, and compared this to their previously measured pre-school values. 57.8% of children with CF had elevated pre-school and first school-age LCI. It remained stable for healthy and CF children during school-aged follow-up. First pre-school LCI, and importantly it's rate of deterioration during this period, were both predictors of school age LCI and spirometry. Growths of *S. aureus* and *A. fumigatus* were associated with higher LCI at that visit independent of concurrent exacerbation treatment. The authors conclude that these data contribute to the evidence that the pre-school years remain a critical period for intervention strategies to alter disease trajectories. *Eur Respir J*, DOI: 10.1183/13993003.03380-2020.

Polyclonality, shared strains, and convergent evolution in chronic CF S. aureus airway infection. In comparison with *P. aeruginosa*, little is known about the acquisition and genetic adaptation of *S. aureus* – now the most common respiratory pathogen in US CF patients. This study details the whole genome sequencing and analysis of 1,382 *S. aureus* longitudinal isolates from 246 children from five US CF centres over a mean 2.2 years. 46% of patients carried multiple, co-existing *S. aureus* lineages with often different antibiotic susceptibility profiles, which could include both methicillin resistant (MRSA) and sensitive strains (MSSA). Adaptation of longitudinal isolates was commonly seen in genes conferring persistence and antimicrobial resistance, some to drugs which the organism has not encountered. Shared isolates were also seen - mostly between patients with close contact - highlighting the importance of healthcare infection control methods. The accompanying editorial explores the degree of spatial separation of isolates within the CF lungs and, alongside the authors, identifies a pressing need for enhanced routine laboratory testing of isolates in order to inform treatment decisions and guide the development of new anti-microbial agents (DOI: 10.1164/rccm.202012-4533ED). *Am J Resp Crit Care Med*, DOI: 10.1164/rccm.202003-0735OC.

Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). This newly published Cochrane Review examines the existing literature for CFTR modulator therapies for people with CF. It includes evidence from eight monotherapy randomised controlled trials (RCTs, 344 participants), six dual-therapy RCTs (1840 participants) and five triple-therapy RCTs (775 participants). Participants were mostly homozygous F508del, in whom no significant efficacy was demonstrated with corrector monotherapy. Both dual therapies studied (Lum-Iva, Tez-Iva) resulted in similar improvements in QoL and respiratory function with lower pulmonary exacerbation rates, with a preferable side-effect profile with Tez-Iva. Triple-therapy combinations improved QoL scores, lung function, and increased time to the next pulmonary exacerbation. High-quality evidence led the authors to conclude that elexacaftor-tezacaftor-ivacaftor triple therapy should be the standard of care for pwCF with one or two F508del variants aged 12 years or older. DOI: 10.1002/14651858.CD010966.pub3.

2. Upcoming events

- American Thoracic Society International Conference: 14th - 19th May 2021. San Diego, California, USA. Registration open: https://conference.thoracic.org/attendees/index.php.
- 44th ECFS European CF Conference: 9th - 12th June 2021. Registration open: https://www.ecfs.eu/digital2021. Conference will be attended virtually through video streaming.
- European Respiratory Society International Congress: 4th – 8th Sept 2021. Barcelona, Spain. Registration opens spring 2021.
- 35th North American CF Conference: 30th Sept - 2nd Oct 2021. San Antonio, Texas, USA.

https://doi.org/10.1016/j.jcf.2021.03.001
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3. People

The community lost two major members of our CF family recently. Here we highlight them and their contributions to our knowledge of cystic fibrosis.

Obituary for Professor Gianni Mastella

Professor Gianni Mastella graduated as a medical doctor in 1955 and as a paediatrician in 1958. Cystic fibrosis (CF) at that time was poorly known, under-diagnosed, and treatment options very limited. In 1957 he made the first of a long series of CF diagnoses and began following an increasing number of patients. In 1967 he was appointed director of the newly established Verona CF Center. Mastella developed the Center with the intent not only for diagnosis and treatment, but also to support the patients and their families more globally, addressing the everyday challenges caused by the progressive disease. In the spirit of this vision, he engaged and inspired a multi-disciplinary team of doctors, nurses, physiotherapists, dieticians, psychologists and social workers, a model unusual in those years and only later adopted by other centers and in other chronic conditions. The Center grew, eventually following as many as 800 patients from many Italian regions. Still, Professor Mastella recognized the hardships for patients and families traveling so far, and he mentored a whole generation of health professionals who visited the Verona center to learn an approach to care they later put into practice in their own places. His efforts to build a greater CF clinical network culminated in legislation specific for CF was enacted in Italy in 1993. Mastella was instrumental in bringing about law 548, which mandated the creation of multi-professional CF Centers in every Italian region providing free access to treatment for all people with CF.

He strongly believed in early diagnosis and initiated a laboratory that anticipated newborn screening, first by measuring meconium proteins and later being one of the first CF centers to adopt immunoreactive trypsinogen in dried blood spots. In the years before 1989, the laboratory was already offering prenatal diagnosis by microvillar enzyme testing, and shortly after the CFTR gene discovery a pilot project of cascade carrier screening was started.

Mastella repeatedly served as chairman of the Italian CF Working Group, later to become the Italian CF Society. He received the Rossi Medal in 2003, now known as the ECFS award, given annually to honor a person who has made an outstanding contribution to the treatment or care of patients with CF. After his retirement, he was the catalyst for the establishment of the Italian CF Research Foundation, of which he was Scientific Director until his demise. The Foundation has been and is a major channel for CF research in Italy and has so far invested 32 million euros, supported more than 400 research projects and 200 laboratories, and contributed to identify a new CFTR corrector which should enter clinical phase in 2022.

The CF community will sorely miss this pioneer in care and research and an inspirational and charismatic leader.

Carlo Castellani

Obituary for Professor Kevin Gaskin

Professor Kevin Gaskin was a renowned paediatric gastroenterologist in the field of cystic fibrosis (CF). He retired in 2017 though continued academic work, including the supervision of a PhD achieved in 2020. Kevin was born in New Zealand, went to Otago University Medical School and did his residency in Wellington. In 1976 he commenced a fellowship at Hospital for Sick Children in Toronto followed by four years on staff as a Consultant. Kevin thrived under the leadership of Dr Dick Hamilton and the mentorship of Dr Gord Forstner, who sparked Kevin's interest in pancreatic disease, resulting in several landmark studies including the development of a pancreatic exocrine stimulation test and the subsequent discovery of co-lipase as an essential co-factor for lipase. Children with CF became an obvious clinical and research focus. Gaskin and Forstner were the first to recognise abnormal anion secretion as the basis for CF but because their studies utilised pancreatic secretions they focussed on bicarbonate rather than chloride, thus missing the chance to claim discovery of the chloride defect in this disease. Kevin and Mary Corey went on to define the different phenotypes of CF (pancreatic sufficiency v insufficiency) and this proved to be a vital step in establishing the phenotype/genotype correlations which followed the discovery of the cyCF gene by the Toronto group in 1989.

Kevin returned to Sydney in 1983, where he established diverse collaborations that led to the discovery of bile duct strictures as a contributor to CF liver disease, studies of pancreatic disease in infants uncovered by one of the first newborn screening programs in the world, detailed body composition studies in CF, and a range of other childhood disorders associated with malnutrition. He revitalised GI and nutrition in the CF clinic having a major impact on patient outcomes and contributed to academic CF research. His last paper on CF Liver Disease was published in JCF in May 2020.

Kevin supervised multiple PhD students several of whom are now full professors. Kevin was an astute and outstanding clinician and an excellent teacher who was involved in the training of over 20 fellows, local and from overseas. He was an enthusiastic tennis player, supporter of the All Blacks (New Zealand rugby team) and an oenophile. He leaves behind his beloved Christine, four children and five grandchildren.

Ted O'Loughlin and Cheryl Frazer