Current knowledge gaps in Cystic Fibrosis care and research: what should we focus on?

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Acknowledgement of Country

The University of Queensland (UQ) acknowledges the Traditional Owners and their custodianship of the lands on which we meet.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

We recognise their valuable contributions to Australian and global society.

The Brisbane River pattern from *A Guidance Through Time* by Casey Coolwell and Kyra Mancktelow.

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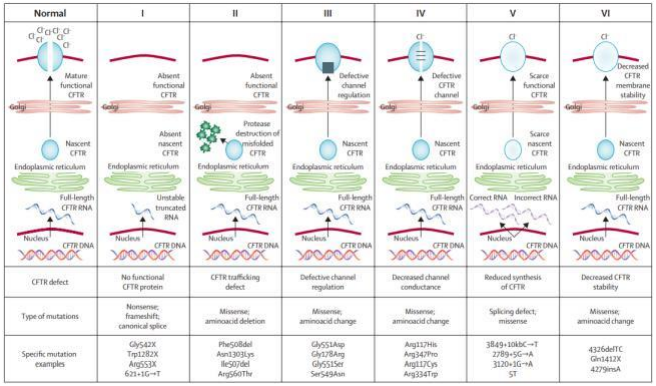
The Lancet Respiratory Medicine Commission

The future of cystic fibrosis care: a global perspective

CF overview

- 1st documented in 1938
- Autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Responsible for transport of chloride ions across epithelial cells (airway, intestine, pancreas, kidney, sweat glands and male reproductive tract)
- 6 functional class mutations -> wide spectrum of disease



CF overview

FIGURE 1.3: ACFDR 1998-2021: PAEDIATRIC VS ADULTS PROFILE OVER TIME

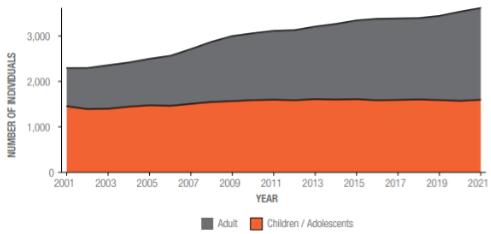
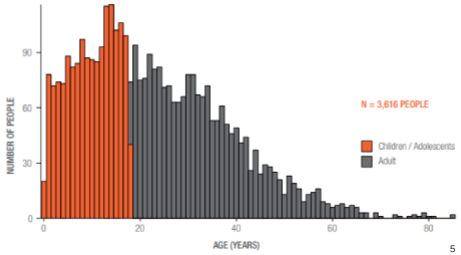


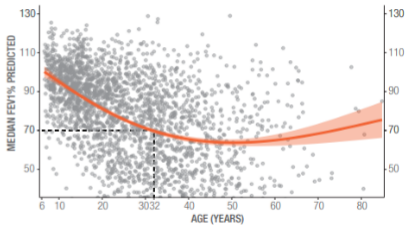
FIGURE 1.1: ACFDR 2021: PEOPLE WITH CF IN AUSTRALIA BY AGE



CF overview

- CF continues to limit survival and quality of life
  - large burden for patients and families
- Becoming more frequent in non-European populations

FIGURE 3.1: ACFDR 2021: MEDIAN FEV1 % PREDICTED BY AGE



Panel 2: Phenotypic features of cystic fibrosis

Typical features of cystic fibrosis

Respiratory
- Bronchiectasis with chronic infection
- Pneumothorax
- Haemoptysis
- Respiratory failure
- Chronic rhinosinusitis and nasal polyposis

Gastrointestinal (luminal)
- Meconium ileus
- Gastro-oesophageal reflux disease
- Distal intestinal obstruction syndrome
- Chronic constipation
- Rectal prolapse
- Intussusception
- Colorectal cancer and colonic polyposis
- Other gastrointestinal malignancies

Gastrointestinal (hepatobiliary)
- Pancreatic insufficiency
- Recurrent acute pancreatitis (in patients with pancreatic sufficiency)
- Biliary sludge or cholelithiasis
- Biliary cirrhosis

Metabolic complications
- Cystic fibrosis-related diabetes: microvascular complications (≥10 years from diagnosis)
- Cystic fibrosis-related bone disease or osteoporosis: increased fracture risk
- Ureteric calculi
- Oligomenorrhoea

Male infertility
- Congenital bilateral absence of the vas deferens

Common issues complicating cystic fibrosis and its treatment

Mental health conditions
- Depression
- Anxiety

Vascular access complications
- Thrombosis risk with vascular access devices

Drug complications
- Antibiotic hypersensivity reactions and intolerance
- Vestibulo-auditory disturbance including tinnitus
- Chronic kidney disease

Metabolic complications
- Overweight and obesity (especially in patients with residual exocrine pancreatic function)

Post-transplant complications (relevant to cystic fibrosis)
- Chronic kidney disease and renal failure (in people with or without pretransplant cystic fibrosis-related diabetes)
- Multiresistant organisms contributing to airway complications
- Cancer in long-term survivors (including gastrointestinal, skin, and urogenital cancers)

The Lancet Respiratory Medicine Commission

The future of cystic fibrosis care: a global perspective

Scott C Bell*, Marcos A Mall, Hector Gutierrez, Milan Macek, Susan Madge, Jane C Davies, Pierre-Régis Burgel, Elizabeth Tullis, Claudio Castaldo, Carlo Castellani, Catherine A Byrnes, Fiona Cathcart, Sanjay H Chotirmall, Rebecca Cosgriff, Irmgard Eichler, Isabelle Fajac, Christopher H Goss, Pavel Drevinek, Philip M Farrell, Anna M Gravelle, Trudy Havermans, Nicole Meyer-Hamblett, Nataliya Kashirskaya, Eitan Kerem, Joseph L Mathew, Edward F McKone, Lutz Naehrlich, Samya Z Nasr, Gabriela R Oates, Ciaran O'Neill, Ulrike Pypops, Karen S Raraigh, Steven M Rowe, Kevin W Southern, Sheila Sivam, Anne L Stephenson, Marco Ziampoli, Felix Ratjen*

Section 1: The changing epidemiology of cystic fibrosis
1. Newborn screening has been implemented in many parts of the world, supporting an early diagnosis of cystic fibrosis.
2. Improved molecular genetic diagnostics have allowed the identification of cystic fibrosis in non-European populations and in individuals with nonclassical presentations of cystic fibrosis and related disorders.
3. Cystic fibrosis transmembrane conductance regulator (CFTR)-related disease represents a spectrum ranging from single-organ manifestations to a multisystem disease. Defining the threshold of CFTR function associated with disease manifestations is a priority to guide disease monitoring and treatment decisions.

Section 2: Clinical care and its delivery
1. Children with cystic fibrosis are healthier than in previous decades and the vast majority are living well into adulthood in the developed world.
2. Diagnostics to allow enhanced monitoring and earlier detection of deterioration of organ function and detection of new airway infections are key priorities.
3. Models of care need to consider management approaches (including disease monitoring) to maintain health and delay lung transplantation, while minimising the burden of care for patients and their families.

Section 3: Cystic fibrosis care in developing nations
1. Information about the genetic and clinical features of cystic fibrosis in non-European populations has improved understanding of the disease in low-income and middle-income countries (LMICs).
2. Partnerships between lay organisations, governments, and the pharmaceutical industry are needed urgently to provide sustained, affordable access to cystic fibrosis therapies for people with cystic fibrosis living in LMICs.
3. Clinical registries are being developed in countries where cystic fibrosis is now recognised. Data elements in new and established cystic fibrosis registries need to be harmonised to support understanding of health-care outcomes, especially in LMICs.

Section 4: Novel therapeutics
1. CFTR modulator therapies targeting the basic molecular defect in cystic fibrosis have been developed for specific *CFTR* mutations and are associated with improved health outcomes, including improved respiratory function and nutritional status, and enhanced quality of life.
2. New CFTR modulator drugs are showing promise in up to 90% of patients, including in patients with *CFTR* mutations for which earlier modulators were ineffective. Early commencement of CFTR-directed therapies might prevent the establishment of irreversible airway complications and slow disease progression in paediatric and adult patients.
3. Drug development requires substantial investment, which contributes to the current high cost of approved CFTR modulators and, in turn, to delays in funding for such therapies in many countries. Current drug prices make them unaffordable for many LMICs, and even in some developed countries, governments have not yet funded these therapies. These problems could be addressed through increased transparency as to how prices are determined, and opportunities to revise assessments in light of new information.

Section 5: Patient experience, engagement, and involvement
1. The complexity of care has increased for people with cystic fibrosis in parallel with increased life expectancy, leading to a substantial burden of care and disease monitoring. Novel technologies have the potential to support self-monitoring and shared decision making between patients and health-care teams.
2. Mental health complications are more common in people with cystic fibrosis (and in the parents of children with cystic fibrosis) than in the general community, affecting quality of life for patients and their families. Adherence to complex therapeutic regimens is often suboptimal, which has a negative effect on clinical outcomes.
3. Patients are highly engaged in the approaches to delivery of clinical care and in providing their perspective on research priorities. Cystic fibrosis patient organisations have important roles as patient advocates for the delivery of clinical care, treatment access, and support and education for patients with cystic fibrosis and their families.

Early Life Origins of CF (ELO) Study

- Queensland Cystic Fibrosis Research Program
  - Cystic Fibrosis Foundation, Children's Health Foundation, Medical Research Future Fund, University of Queensland

- Pulmonary inflammation, infection and structural disease are present in patients without evidence of respiratory symptoms (AREST CF program)
  - BAL neutrophilic inflammation in pts 3months old
  - 80% infants with abnormal chest CTs (bronchial dilation, wall thickening and gas trapping)
  - Radiological bronchiectasis in 57% school aged children

- Lack of sensitive and/or age appropriate measures to detect and monitor early CF lung disease progression
  - Limitations with traditional 'gold standard' techniques – spirometry, MBW, CT scans

Early Life Origins of CF (ELO) Study

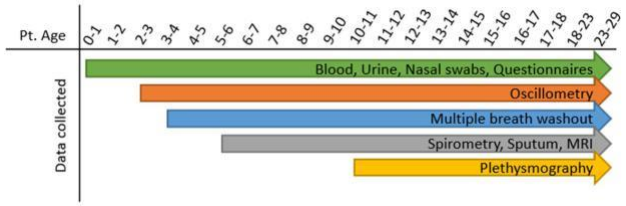
Aims

1. Improve clinical outcome measures across the lifespan and disease severity spectrum in CF
2. Develop biomarkers and clinical indicators in children and adults with CF that allow for better prediction of the onset of acute exacerbations
3. Characterize age-related changes in anxiety and resilience in children with CF and the relationships between emotional wellbeing and sensitive markers of lung disease

Early Life Origins of CF (ELO) Study

Protocol

- CF patients aged 3 months – 30 years @ QCH, TPCH and Mater
- Data collection at clinic visits, annual reviews, and exacerbation related admission



- Biomarkers of systemic inflammation
- Inflammatory and immune mechanisms
- Respiratory and gastrointestinal microbiome analysis
- Lung function measurements
- Structural and functional assessments
- Psychosocial measurements

Preliminary results

- 166 children and 12 adults recruited

Intra-breath Oscillometry (IB-OSC)

IB-OSC vs. MBW

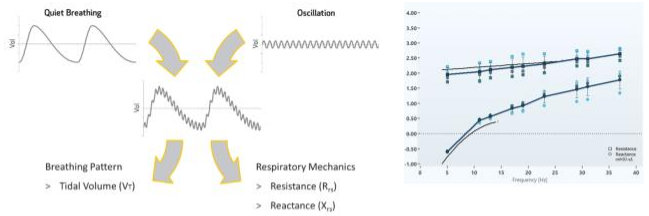
Urinary GSA

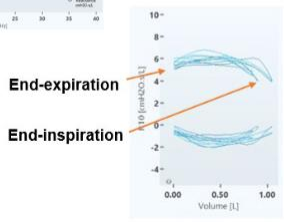
MRI

Psychosocial Questionnaires

Intra-breath oscillometry

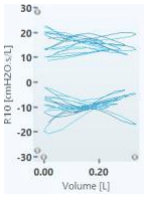
- Oscillometry measures respiratory system resistance (R) and reactance (X)



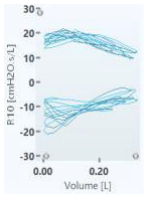


- IB-OSC uses a single 10Hz waveform, collects 10-16 samples per second = 'tracking' of changes during breathing
- In CF, distinct changes in resistance and reactance data

Case study 1
4.5yr male, history of exacerbations



Visit 1:
- Asymptomatic
- Obstruction and inhomogeneity



Visit 2:
- Mild symptoms
- Increased resistance and decreased reactance
- LCI 10.2

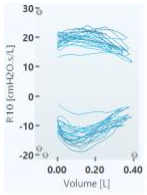
Trend graph - R variables

	Visit 1	Visit 2
ReE	15.79	21.22
Rel	13.68	14.85
ReE-el	2.34	6.25

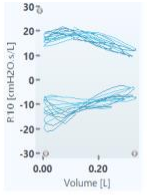
Trend graph - X variables

	Visit 1	Visit 2
XeE	-11.88	-12.47
Xel	-8.06	-7.79
XeE-el	-3.72	-4.45

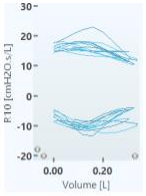
Case study 2
3yr male, asymptomatic



Visit 1:
- Asymptomatic
- Obstruction and inhomogeneity
- LCI 11.1



Visit 2:
- CT performed
- Increased resistance and decreased reactance



Visit 3:
- Pulmozyme and seretide
- Results improved
- LCI 8.9

Trend graph - R variables

	Visit 1	Visit 2	Visit 3
ReE	18.83	21.63	15.33
Rel	15.37	18.66	12.34
ReE-el	3.28	2.70	3.04

Trend graph - X variables

	Visit 1	Visit 2	Visit 3
XeE	-9.88	-13.55	-8.26
Xel	-8.26	-10.77	-5.78
XeE-el	-1.47	-2.83	-2.75

IB-OSC vs. MBW

- MBW is the gold standard for detecting early changes in peripheral airways -> feasibility in young children can be low & time consuming
- Xrs measurements include small peripheral airways = also reflect ventilation inhomogeneity

$LCI_{2.5\%}$

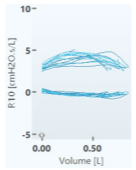
XeE
Xel
ΔX

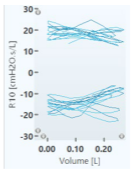
- Paired measurements on 79 children
  - 8 unable to achieved MBW, 4 unable to achieve both

IB-OSC vs. MBW

- No differences in gender, age, height or CFTR mutations btw those with normal and abnormal MBW results
- Significantly more negative (decreased) Xrs variables in pts with abnormal MBW
- 70% of patients were classified correctly by both techniques, fair concordance

Variable Median (25^{th}-75^{th}%)	Normal $LCI_{2.5\%}$ (n=45)	Abnormal $LCI_{2.5\%}$ (n=34)	p-value*
XeE	-1.08 (-1.84, -0.48)	-2.69 (-4.07, -0.85)	**0.003**
Xel	-1.10 (-1.93, -0.83)	-2.10 (-3.01, -1.53)	**0.005**
XeE-el	0.09 (-0.14, 0.36)	-0.15 (-0.96, 0.20)	**0.016**
ΔX/VT	0.18 (-0.51, 0.94)	-0.24 (-2.29, 0.33)	**0.021**





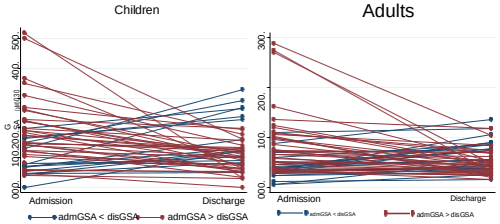
Urinary GSA

- Glutathione sulphonamide (GSA) -> irreversible by-product of glutathione oxidation
- Urine GSA correlates well with GSA levels measured in BAL and serum samples, and other markers in neutrophilic inflammation
- Potential for urinary GSA as a non-invasive biomarker of lung inflammation for CF pts

Urinary GSA

- 102 children (median age 11.5 years, 25%-75% 6.4-14.4) and 64 adults (median age 32.5 years, 25%-75% 25.0-39.0) admitted to hospital for management of an acute pulmonary exacerbation
- Urine samples collected at admission and discharge

	Admission	Discharge	p-value
Children (n=49)	0.15 µM (0.07-0.20)	0.09 µM (0.06-0.14)	**0.024**
Adults (n=60)	0.05 µM (0.03-0.09)	0.05 µM (0.03-0.07)	0.078



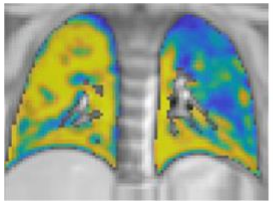
- Urinary GSA was responsive to the resolution of an acute pulmonary exacerbation
  - Correlated with subjective and objective measures of disease activity for children

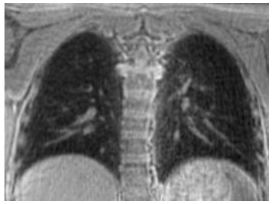
MRI

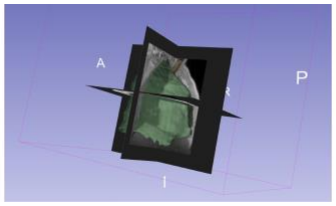
- New protocol that allows for analysis of lung structure and assessment of respiratory function
  - Breath hold = Ultrashort echo time (UTE) & spiral volumetric interpolated breath-hold examination (VIBE)
  - Free breathing = 3D UTE & spiral VIBE
  - Slow, deep breathing = 2D dynamic fast low angle shot (FLASH)

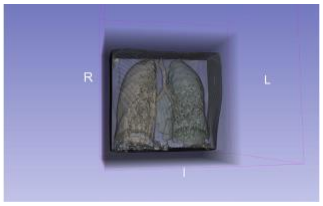
- Performed in pts >6 yrs
- Requires a matched CT scan

MRI









Psychosocial questionnaires

1. Health Related Quality of Life (CFQ-R) – CF-specific instrument designed to measure impact on overall health, daily life, perceived well-being, and symptoms
2. The Child and Youth Resilience Measure (CYRM) – A screening tool to explore the resources (individual, relational, communal, and cultural) available to individuals, that may bolster their resilience
3. The Spence Childhood Anxiety Score (SCAS) – An instrument developed to assess the severity of anxiety symptoms. The scale assesses six domains of anxiety including generalized anxiety, panic/agoraphobia, social phobia, separation anxiety, obsessive compulsive disorder and physical injury fears
4. The Family Assessment Device (FAD) – Assesses structural and organizational properties of families and the patterns of transactions among family members
5. The Cystic Fibrosis Problem Checklist (CFPC) – Developed to assess treatment adherence behaviour in relation to cystic fibrosis

Psychosocial questionnaires

- Administered/sent 287 surveys to parents = 196 returned (68%)
- Administered/sent 98 surveys to children = 35 returned (36%)

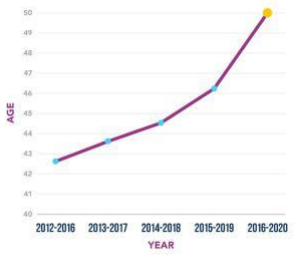
- Noting changes in anxiety and health related scores and poorer lung function outcomes
- Noting trends in adherence across all a number of CF domains and patients with worse clinical symptoms; parents still identifying that they would like more help surrounding these issues

- First surveys to be performed in very young children and to assess family dynamics and relationships

Summary

- Seeing major improvements to CF care
- New challenges will emerge
  - Early detection of lung disease progression
  - Tailoring care to individual needs and phenotypes
  - CFTR modulators
  - Adult care

- Keep doing what we're doing but embrace the new things coming!!!



Thank you!

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