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New Cochrane Library Systematic Reviews on Cystic Fibrosis

**Standard versus biofilm antimicrobial susceptibility testing to guide antibiotic therapy in cystic fibrosis**

Valerie Waters, Felix Ratjen

Published: 5 March 2015

The antibiotics used to treat pulmonary infections in people with cystic fibrosis are typically chosen based on the results of antimicrobial susceptibility testing performed on bacteria traditionally grown in a planktonic mode (grown in a liquid). However, there is considerable evidence to suggest that *Pseudomonas aeruginosa* actually grows in a biofilm (or slime layer) in the airways of people with cystic fibrosis with chronic pulmonary infections. Therefore, choosing antibiotics based on biofilm rather than conventional antimicrobial susceptibility testing could potentially improve response to treatment of *Pseudomonas aeruginosa* in people with cystic fibrosis. This is an update of a previously published Cochrane Review.

**Objectives:** To compare biofilm antimicrobial susceptibility testing-driven therapy to conventional antimicrobial susceptibility testing-driven therapy in the treatment of *Pseudomonas aeruginosa* infection in people with cystic fibrosis.

**Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis**

David KH Lo, Matthew N Hurley, Marianne S Muhlebach, Alan R Smyth

Published: 18 February 2015

Cystic fibrosis is an inherited recessive disorder of chloride transport that is characterised by recurrent and persistent pulmonary infections from resistant organisms that result in lung function deterioration and early mortality in sufferers.

Meticillin-resistant *Staphylococcus aureus* (MRSA) has emerged as, not only an important infection in long-term hospitalised patients, but also as a potentially harmful pathogen in cystic fibrosis, and has been increasing steadily in prevalence internationally. Chronic pulmonary infection with MRSA is thought to confer cystic fibrosis patients with a worse overall clinical outcome and, in particular, result in an increased rate of decline in lung function. Clear guidance for the eradication of MRSA in cystic fibrosis, supported by robust evidence from good quality trials, is urgently needed.

**Objectives:** To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for people with cystic fibrosis.
New from NICE

IN DEVELOPMENT: Cystic fibrosis: diagnosis and management of cystic fibrosis

NICE Guideline. Anticipated publication date Feb 2017

New Activity in UptoDate and DynaMed

vitamin K supplementation has insufficient evidence to evaluate benefits and adverse effects in patients with CF

Current Awareness Database Articles on Cystic Fibrosis

Below is a selection of articles on cystic fibrosis recently added to the healthcare databases, grouped in the following categories:

- Medical
- Microbiological
- Psychological
- Other

If you would like any of the following articles in full text, or if you would like a more focused search on your own topic, then get in touch: bennet.jones@uhbristol.nhs.uk

Medical

Title: Cystic fibrosis newborn screening: A model for neuromuscular disease screening?

Citation: Annals of Neurology, February 2015, vol./is. 77/2(189-197), 0364-5134;1531-8249 (01 Feb 2015)

Author(s): Scully M.A., Farrell P.M., Ciafaloni E., Griggs R.C., Kwon J.M.

Abstract: Congenital neuromuscular disorders, such as Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), and Pompe disease (acid maltase deficiency [AMD]), are candidates for universal newborn screening (NBS). In this article, we discuss the future path of NBS for these
disorders with particular emphasis on DMD NBS, because of the likely approval of new gene-modifying treatments, the possible benefits of earlier treatment with corticosteroids, and the recently demonstrated feasibility of a 2-tiered approach to NBS with screening by creatine kinase (CK) levels in dried blood spots followed by mutation detection in those with elevated CK. The cystic fibrosis (CF) NBS program is a successful model for NBS. CF outcomes have consistently improved into adulthood following introduction of CF NBS because considerable resources have been devoted to practices that include: attention to improving laboratory screening, consistent confirmatory testing and immediate referral of all newly diagnosed infants to designated CF care centers that follow established practice guidelines, and ongoing evaluation of CF care centers via a centralized clinical database. Like CF, DMD, SMA, and infantile AMD are inexorably debilitating and require lifetime multidisciplinary clinical management. NBS would address the delays in diagnosis that prevent patients from receiving timely treatments. Standardized care following early diagnosis would reduce disparities in clinical care and outcomes. NBS in these neuromuscular disorders should be implemented, utilizing lessons learned from the past 20 years of CF NBS: standardized protocols for all patients identified by DMD NBS, longitudinal follow-up in multidisciplinary clinics, and coordinated oversight of these clinics.

Title: Medical reversal of chronic sinusitis in a cystic fibrosis patient with ivacaftor

Citation: International Forum of Allergy and Rhinology, February 2015, vol./is. 5/2(178-181), 2042-6976;2042-6984 (01 Feb 2015)


Abstract: Background: Chronic sinusitis is universal in cystic fibrosis (CF) and our current treatments are ineffective in reversing sinus disease. The objective of this work was to determine if increasing CF transmembrane conductance regulator (CFTR) activity by ivacaftor could treat CF sinus disease and assess its effect on primary sinus epithelial cultures. Methods: Case report of 1 patient with long-standing chronic sinus disease and a new diagnosis of CF with a mild mutation (P205S) and a severe mutation (G551D). We discuss clinical changes in symptoms, radiographic findings, nasal potential difference testing, and nasal pH values before and after treatment with ivacaftor. We then developed primary sinonasal epithelial cell cultures from a biopsy of the patient to determine changes in airway surface liquid (ASL) pH and ASL viscosity after ivacaftor treatment. Results: Ivacaftor treatment reversed CT findings of CF sinus disease, increased nasal voltage and pH, and resolved sinus symptoms after 10 months of therapy. Ivacaftor significantly increased ASL pH and decreased ASL viscosity in primary airway cultures. Conclusion: This report documents the reversal of CF sinus disease. Based on our in vivo and in vitro results, we speculate that ivacaftor may reverse CF sinusitis by increasing ASL pH and decreasing ASL viscosity. These studies suggest that CFTR modulation may be effective in treating CF and perhaps non-CF sinusitis.

Title: A one-year retrospective review of vitamin D level, bone profile, liver function tests and body mass index in children with cystic fibrosis in a Children’s University Hospital
Abstract: Vitamin D deficiency is common in young cystic fibrosis (CF), and is due to the impaired absorption of fat-soluble vitamins, decreased sun exposure, and suboptimal intake of vitamins-containing foods and/or supplements. Given that childhood is a critical period for the accrual of bone mass, with 90% peak bone mass laid in the first two decades of life, it is essential that optimal vitamin D levels are achieved in this time frame. Methods: We conducted a retrospective review from January 1, 2012 to January 1, 2013, through which we reviewed levels of vitamin D and correlated with bone profile, liver function tests, lung function, genotype, age, dual-energy X-ray absorptiometry scan and body mass index z score. Results: Of the 95 children with CF, 6 were excluded due to incomplete data, bringing our study population to a total of 89 children. Results showed 77.5% vitamin D deficiency (mean 59.42 nmol/L). No significant statistical correlation was found between vitamin D and the parameters described. Protocol supplementation did not raise vitamin D to therapeutic level in 63.2% of the study population. Those with genotype delta 508 (homozygous/heterozygous) had 92% vitamin D deficiency. Conclusion: We attribute the non-responder group to vitamin D to poor compliance. Compliance level could not be addressed because our study is a retrospective review. Thus, further research is needed to define implications of pulmonary exacerbations on vitamin D and vice versa. Doing so can help assess the implication of genotype influence on vitamin D.

Title: Why is insulin pump treatment rarely used in adolescents and young adults with cystic fibrosis-related diabetes?

Abstract: Background: In type 1 diabetes (T1D), the use of continuous subcutaneous insulin infusion (CSII) has increased steadily in the last years. Compared with conventional insulin injection regimes, major advantages might be a nearly physiological insulin secretion, lower rates of hypoglycemia, higher flexibility in daily life, and increased quality of life. Data on CSII in cystic fibrosis-related diabetes (CFRD) are scarce. Objective: To analyze current use of insulin pumps in CFRD and compare demographics of pump-treated patients between CFRD and T1D. Methods: Data from the prospective German/Austrian diabetes patient registry on insulin-treated patients with either CFRD (n = 515) or T1D (n = 43 165) aged >10 yr at manifestation of diabetes were analyzed. Results: A total of 4.1% (n = 21) of CFRD and 17.7% (n = 7647) of T1D patients received insulin pump treatment within the recent year of care (p < 0.001). Pump-treated patients with CFRD had a significantly shorter duration of diabetes [median (Q<sub>1</sub>; Q<sub>3</sub>): 5.8 (2.9; 9.5) vs. 7.8 (4.3; 20.4) yr, p = 0.026] and tended to be younger [22.0 (18.2; 30.1) vs. 24.9 (17.3; 45.9) yr] than pump-treated T1D patients. Age at initiation of CSII seemed to be lower in CFRD [19.2 (16.5; 29.2) vs. 23.3...
(14.8; 43.5 yr). Insulin pump therapy was used slightly more often in male CFRD patients than females (4.7 vs. 3.6%), whereas in T1D the opposite was observed (14.9 vs. 21.2%, p < 0.001). Discontinuation rate of CSII was higher in CFRD than T1D (30.0 vs. 12.7%, p = 0.005). Conclusions: Despite potential advantages, insulin pump therapy was rarely used among adolescent and young adult CFRD patients.

Title: Cystic fibrosis airway epithelium remodelling: Involvement of inflammation

Citation: Journal of Pathology, February 2015, vol./is. 235/3(408-419), 0022-3417;1096-9896 (01 Feb 2015)

Author(s): Adam D., Roux-Delrieu J., Luczka E., Bonnomet A., Lesage J., Merol J.-C., Polette M., Abely M., Coraux C.

Abstract: Chronic inflammation is a hallmark of cystic fibrosis (CF) lung disease and airway epithelium damage and remodelling are important components of lung pathology progression in CF. Whether this remodelling is secondary to deleterious infectious and inflammatory mediators, or to alterations of CF human airway epithelial (HAE) cells, such as their hyper inflammatory phenotype or their basic cystic fibrosis transmembrane conductance regulator (CFTR) default, remains debated. In this study, we evaluated the involvement of alterations of CF HAE cells in airway epithelium remodelling. HAE cells from non-CF and CF patients were cultured in an air-liquid interface, with and without inflammatory stimulation, along the regeneration process, and the remodelling of the reconstituted epithelium was analysed. We confirmed that CF HAE cells showed a hyperinflammatory phenotype which was lost with time. In comparison to non-CF epithelium, CF epithelium regeneration in the absence of exogenous inflammation was higher and exhibited basal cell hyperplasia. This remodelling was mimicked by inflammatory stimulation of non-CF cells and was absent when CF HAE cells were no longer hyperinflamed. Moreover, the number of goblet cells was similar in non-CF and CF cultures and increased equally under inflammatory stimulation. Finally, whatever the inflammatory environment, CF cultures showed a delay in ciliated cell differentiation. In conclusion, alterations of CF HAE cells partly regulate airway epithelium remodelling following injury and regeneration. This remodelling, together with goblet cell hyperplasia induced by exogenous inflammation and alteration of ciliated cell differentiation, may worsen mucociliary clearance impairment, leading to injury.

Title: Evidence for the efficacy of aztreonam for inhalation solution in the management of Pseudomonas aeruginosa in patients with cystic fibrosis

Citation: Therapeutic Advances in Respiratory Disease, February 2015, vol./is. 9/1(16-21), 1753-4658;1753-4666 (05 Feb 2015)

Author(s): Hansen C., Skov M.

Abstract: Chronic airway infection in cystic fibrosis (CF) is a main cause of the increased morbidity and mortality found with this disease. The most common cause of Gram-negative infection is
Pseudomonas aeruginosa. The introduction of inhaled antibiotics has changed the lives of affected patients and the clinical outcome of this infection; this article focuses on the use of inhaled antibiotics in chronic P. aeruginosa infection in CF, and specifically on studies including the use of inhaled aztreonam lysine in P. aeruginosa infection. Studies were identified using PubMed and ClinicalTrials.gov, searching for 'inhaled aztreonam' and 'cystic fibrosis'. Inhaled aztreonam is an important new treatment option for chronic P. aeruginosa infection in CF. Long-term studies have shown that the drug is safe and superior to inhaled tobramycin in these specific infections.

Title: Prevalence of inadequate vitamin D status and associated factors in children with cystic fibrosis

Citation: Nutrition in Clinical Practice, February 2015, vol./is. 30/1(111-116), 0884-5336;1941-2452 (22 Feb 2015)

Author(s): Norton L., Page S., Sheehan M., Mazurak V., Brunet-Wood K., Larsen B.

Abstract: Background: This study aimed to determine the prevalence of inadequate serum 25-hydroxyvitamin D (25(OH)D) levels in a pediatric Canadian cystic fibrosis (CF) population and to assess the effectiveness of a vitamin D supplementation protocol on improving vitamin D status. A secondary objective was to analyze factors that may be associated with inadequate 25(OH)D levels.

Methods: Vitamin D supplementation, 25(OH)D levels, and factors hypothesized to be associated with 25(OH)D levels were collected through a retrospective chart review (2010 and 2011) of 96 patients (1-18 years) at one CF clinic in Canada. Adequacy of 25(OH)D was set at >75 nmol/L. Patients with inadequate 25(OH)D levels in 2010 were prescribed an additional 1000 IU/d for levels <60 nmol/L or 400 IU/d for levels 60-75 nmol/L. Results: Inadequate 25(OH)D levels were observed in 26% of patients in 2010 and 23% in 2011. After supplementation was increased for those with inadequate 25(OH)D levels in 2010 (n = 20), a significant increase in 25(OH)D levels was observed in 2011 (P =.03). Adequate status was achieved in 50% of these patients (n = 10). Age was significantly negatively associated with 25(OH)D levels in both years (P =.002). Percentage of forced expiratory volume in 1 second was significantly positively associated with 25(OH)D levels in 2011 (P =.03).

Conclusion: While vitamin D supplementation was effective at increasing serum 25(OH)D, this protocol did not achieve optimal serum 25(OH)D levels in 25% of the population. Increasing age had the strongest association with 25(OH)D. Current supplementation protocols may require reevaluation based on emerging evidence and revised Cystic Fibrosis Foundation guidelines.

Title: Nutrition and pancreatic enzyme intake in patients with cystic fibrosis with distal intestinal obstruction syndrome

Citation: Nutrition in Clinical Practice, February 2015, vol./is. 30/1(134-137), 0884-5336;1941-2452 (22 Feb 2015)

Author(s): Declercq D., Van Biervliet S., Robberecht E.
**Abstract:** Background: The etiology of distal intestinal obstruction syndrome (DIOS) remains unclear. Food intake and pancreatic enzyme replacement therapy (PERT) are often blamed for its occurrence. This study evaluates the nutrition intake and PERT of patients with cystic fibrosis (CF) at a first episode of DIOS. Methods: All patients with CF perform annually a 3-day intake diary to evaluate their caloric, protein, fat, dietary fiber, liquid, and PERT intake. Patients diagnosed with a first episode of DIOS (n = 12) retrospectively completed an intake diary of the 3 days preceding the DIOS episode supervised by an expert dietitian. Results were compared with those of 1 year before and also with 36 CF controls matched for age, sex, genotype, and disease severity. All were pancreatic insufficient. Results: A first DIOS episode was diagnosed in 12 patients with CF. Only the absolute median fat intake (P = .015) and pancreatic enzyme intake (P = .035) were higher at the time of the DIOS attack in comparison to the preceding year. This could result from the difference in data collection or from the recommendations to increase fat intake and concomitant enzyme intake, since this trend was also found in the control group. The significant difference disappears when enzyme intake is expressed as units of lipase/g of fat. No other significant dietary differences were found. Conclusions: This study provides no indications for a potential role of nutrition factors or pancreatic enzymes in the first occurrence of DIOS.

**Title:** Levofloxacin inhalation solution for the treatment of chronic Pseudomonas aeruginosa infection among patients with cystic fibrosis

**Citation:** Expert Review of Respiratory Medicine, February 2015, vol./is. 9/1(13-22), 1747-6348;1747-6356 (01 Feb 2015)

**Author(s):** Stockmann C., Hillyard B., Ampofo K., Spigarelli M.G., Sherwin C.M.

**Abstract:** Chronic pulmonary infections are common among patients with cystic fibrosis. By 10 years of age, Pseudomonas aeruginosa is the predominant pathogen. Inhaled levofloxacin solution (MP-376) is a promising new therapy that exhibits rapid antibacterial activity and excellent biofilm penetration against P. aeruginosa. In the largest trial to date, 151 patients were randomized to receive MP-376 or placebo. At the end of the 28-day treatment period, patients who received MP-376 had decreased P. aeruginosa density in sputum, improved lung function parameters and improved respiratory symptoms. MP-376 also appeared to be safe and well tolerated. The results of two recently completed Phase III trials have not yet been released; however, these data will be critical in determining whether MP-376 is a safe and effective maintenance therapy for chronic pulmonary P. aeruginosa infections among patients with cystic fibrosis.

**Title:** The problems of antibiotic resistance in cystic fibrosis and solutions

**Citation:** Expert Review of Respiratory Medicine, February 2015, vol./is. 9/1(73-88), 1747-6348;1747-6356 (01 Feb 2015)

**Author(s):** Lopez-Causape C., Rojo-Molinero E., Macla M.D., Oliver A.
Abstract: Chronic respiratory infection is the main cause of morbidity and mortality in cystic fibrosis (CF) patients. One of the hallmarks of these infections, led by the opportunistic pathogen Pseudomonas aeruginosa, is their long-term (lifelong) persistence despite intensive antimicrobial therapy. Antimicrobial resistance in CF is indeed a multifactorial problem, which includes physiological changes, represented by the transition from the planktonic to the biofilm mode of growth and the acquisition of multiple (antibiotic resistance) adaptive mutations catalyzed by frequent mutator phenotypes. Emerging multidrug-resistant CF pathogens, transmissible epidemic strains and transferable genetic elements (such as those encoding class B carbapenemases) also significantly contribute to this concerning scenario. Strategies directed to combat biofilm growth, prevent the emergence of mutational resistance, promote the development of novel antimicrobial agents against multidrug-resistant strains and implement strict infection control measures are thus needed.

Title: Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis

Citation: Gastroenterology, February 2015, vol./is. 148/2(427-439), 0016-5085;1528-0012 (01 Feb 2015)


Abstract: Background & Aims Excessive consumption of ethanol is one of the most common causes of acute and chronic pancreatitis. Alterations to the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) also cause pancreatitis. However, little is known about the role of CFTR in the pathogenesis of alcohol-induced pancreatitis. Methods We measured CFTR activity based on chloride concentrations in sweat from patients with cystic fibrosis, patients admitted to the emergency department because of excessive alcohol consumption, and healthy volunteers. We measured CFTR levels and localization in pancreatic tissues and in patients with acute or chronic pancreatitis induced by alcohol. We studied the effects of ethanol, fatty acids, and fatty acid ethyl esters on secretion of pancreatic fluid and HCO$_3^-$, levels and function of CFTR, and exchange of Cl$^-$ for HCO$_3^-$ in pancreatic cell lines as well as in tissues from guinea pigs and CFTR knockout mice after administration of alcohol. Results Chloride concentrations increased in sweat samples from patients who acutely abused alcohol but not in samples from healthy volunteers, indicating that alcohol affects CFTR function. Pancreatic tissues from patients with acute or chronic pancreatitis had lower levels of CFTR than tissues from healthy volunteers. Alcohol and fatty acids inhibited secretion of fluid and HCO$_3^-$, as well as CFTR activity, in pancreatic ductal epithelial cells. These effects were mediated by sustained increases in concentrations of intracellular calcium and adenosine 3',5'-cyclic monophosphate, depletion of adenosine triphosphate, and depolarization of mitochondrial membranes. In pancreatic cell lines and pancreatic tissues of mice and guinea pigs, administration of ethanol reduced expression of CFTR messenger RNA, reduced the stability of CFTR at the cell surface, and disrupted folding of CFTR at the endoplasmic reticulum. CFTR knockout mice
given ethanol or fatty acids developed more severe pancreatitis than mice not given ethanol or fatty acids. Conclusions Based on studies of human, mouse, and guinea pig pancreata, alcohol disrupts expression and localization of the CFTR. This appears to contribute to development of pancreatitis. Strategies to increase CFTR levels or function might be used to treat alcohol-associated pancreatitis.

Title: Ivacaftor improves appearance of sinus disease on computerised tomography in cystic fibrosis patients with G551D mutation

Citation: Clinical Otolaryngology, February 2015, vol./is. 40/1(16-21), 1749-4478;1749-4486 (01 Feb 2015)


Abstract: Background: Most patients with Cystic fibrosis (CF) have chronic sinus disease which may require multiple sinus surgeries and antibiotic courses. Ivacaftor can improve lung function, lower sweat chloride levels and improve weight by targeting the primary defect, a faulty gene and its protein product, cystic fibrosis transmembrane conductance regulator (CFTR) in patients with the G551D mutation. Its role in improving sinus disease has not been evaluated. Objective: The objective of this study was to evaluate efficacy of ivacaftor in improving CF related sinus disease. Design: Observational study. Participants: Twelve patients with cystic fibrosis and a G551D-CFTR mutation. Methods: Twelve patients with a G551D-CFTR mutation were monitored for at least one year before and after starting ivacaftor. Outcome Measures: Sinus disease progression was monitored by comparing computed tomography (CT) of sinuses before and at one year on therapy. Hospital admissions, pulmonary exacerbations, weight, BMI and lung function were also compared. Results: Median age was 17 years (range 10-44). Weight, BMI, FEV1 significantly increased and sweat chloride significantly decreased by six months on ivacaftor therapy. CT of the sinuses in all patients improved. Seven patients had severe sinus disease, improved to moderate in three and mild in remaining four. Four patients had moderate disease which improved to mild in all. One patient had normal sinus CT before and after the therapy. Conclusions: Patients with CF and G551D mutation, within 6 months of starting ivacaftor had significant improvements in weight, BMI and mean % FEV1. Significant lessening of underlying sinus disease measured by CT scan was noted, suggesting a disease modifying effect.

Title: CT Density Distribution Analysis in Patients with Cystic Fibrosis: Correlation with Pulmonary Function and Radiologic Scores

Citation: Academic Radiology, February 2015, vol./is. 22/2(179-185), 1076-6332;1878-4046 (01 Feb 2015)

Author(s): de Lavernhe I., Le Blanche A., Degrugilliers L., Carette M.-F., Bayat S.

Abstract: Rationale and Objectives: The progressive changes in lung morphology observed in cystic fibrosis (CF) can potentially affect the statistical distribution of computed tomography (CT) density values. This study aimed to characterize the lung CT density distributions by quantifying indices of
the kurtosis and skewness of the lung density distribution and to compare these indices to radiologic scores and lung function parameters in children and young adults with CF. Materials and Methods: CT scans and lung function of 26 patients with CF were retrospectively examined. The Bhalla radiologic scoring was performed separately, in random order, by two expert radiologists, blinded to the patient's identity, age, clinical status, results of lung function tests, and the other paired observer's score. Results: Positive relations were evidenced between the log indices of lung density distribution kurtosis (iKurtosis) and the overall radiologic scores (RS) of both observers (R=0.58; P<.001 vs RS1 and R=0.71; P<.001 vs RS2). A similar relationship was evidenced with the log index of the degree of distribution asymmetry (iSkewness; R=0.62; P<.001 vs RS1 and R=0.62; P<.001 vs RS2). Log-iKurtosis and log-iSkewness were related to FEV1 (R=-0.56; P<10^-5 and R=-0.55; P<10^-5) and to residual volume (R=0.40; P<.001 and R=0.45; P<.001, respectively). Both radiologic scores showed significant relation with lung function. The correlation between RS1 and RS2 was excellent (R=0.93), with a Cohen weighted kappa of 0.43. Conclusions: Characteristic indices of lung CT density distribution are correlated to lung function and radiologic scores in patients with CF and merit further evaluation as part of more comprehensive automated methods for quantifying CF lung CT data.

Title: Association between serum YKL-40 level and dysglycemia in cystic fibrosis

Citation: Cytokine, February 2015, vol./is. 71/2(296-301), 1043-4666;1096-0023 (February 01, 2015)

Author(s): Bouvet G.F., Maignan M., Arslanian E., Coriati A., Rabasa-Lhoret R., Berthiaume Y.

Abstract: Background: YKL-40, a chitinase-like protein, is a biomarker for type 1 and type 2 diabetes prognosis. We hypothesized that YKL-40 protein levels are elevated in CF patients with dysglycemia. Methods: Seventeen healthy control subjects and 66 CF patients were prospectively recruited and subjected to an oral glucose tolerance test. In all participants, fasting serum YKL-40 was compared between control and CF patients and between normal glucose-tolerant patients (NG-CF) and CF patients with dysglycemia (DG-CF). A Botnia clamp procedure was performed on a subset of patients for each group to determine the impact of acute increases of either glucose or insulin on YKL-40 concentration. Results: CF patients had higher serum YKL-40 values than the controls (113 [49;288] vs. 38 [30;50] ng/ml, p<. 0.001). YKL-40 concentrations in CF patients were mainly increased in the DG-CF group, who had significantly higher values: 213 [93;383] vs. 67 [27;97] ng/ml in the NG-CF group, p<. 0.001). No significant modulation of YKL-40 concentration was observed in serum of CF (NG or DG-CF) or non-CF patients, after acute exposure to glucose or insulin. Conclusions: Higher serum YKL-40 levels in CF patients are significantly associated with dysglycemia. The increase in YKL-40 is potentially associated with an inflammatory response resulting from chronic glucose intolerance or CF disease evolution.

Microbiological

Title: Proteomics of hosts and pathogens in cystic fibrosis
Citation: Proteomics - Clinical Applications, February 2015, vol./is. 9/1-2(134-146), 1862-8346;1862-8354 (01 Feb 2015)

Author(s): Kamath K.S., Kumar S.S., Kaur J., Venkatakrishnan V., Paulsen I.T., Nevalainen H., Molloy M.P.

Abstract: Cystic fibrosis (CF) is a congenital disease that results in great morbidity and mortality mainly in the Caucasian population. Although CF is a monogenic disease caused by mutation in the CF conductance transmembrane regulator (CFTR) gene, most of the related mortality can be attributed to infection mediated by opportunistic bacterial and fungal pathogens. Over the past decade, advancements in the field of proteomics have helped to gain insight into the repertoire of host and pathogen proteins involved in CF pathophysiology. This review provides an overview of the contributions of proteomic studies in advancing our knowledge of the biology of CF and disease progression associated with pathogen infection and host defense responses.

Title: Intestinal lesions are associated with altered intestinal microbiome and are more frequent in children and young adults with cystic fibrosis and cirrhosis

Citation: PLoS ONE, February 2015, vol./is. 10/2, 1932-6203 (06 Feb 2015)

Author(s): Flass T., Tong S., Frank D.N., Wagner B.D., Robertson C.E., Kotter C.V., Sokol R.J., Zemanick E., Accurso F., Hoffenberg E.J., Narkewicz M.R.

Abstract: Background and Aims: Cirrhosis (CIR) occurs in 5-7% of cystic fibrosis (CF) patients. We hypothesized that alterations in intestinal function in CF contribute to the development of CIR. Aims: Determine the frequency of macroscopic intestinal lesions, intestinal inflammation, intestinal permeability and characterize fecal microbiome in CF CIR subjects and CF subjects with no liver disease (CFnoLIV). Methods: 11 subjects with CFCIR (6 M, 12.8 yrs +/- 3.8) and 19 matched with CFnoLIV (10 M, 12.6 yrs +/- 3.4) underwent small bowel capsule endoscopy, intestinal permeability testing by urinary lactulose: mannitol excretion ratio, fecal calprotectin determination and fecal microbiome characterization. Results: CFCIR and CFnoLIV did not differ in key demographics or CF complications. CFCIR had higher GGT (59+/-51 U/L vs 17+/-4 p = 0.02) and lower platelet count (187+/-126 vs 283+/-60 p = 0.04) and weight (-0.86 +/- 1.0 vs 0.30 +/- 0.9 p = 0.002) z scores. CFCIR had more severe intestinal mucosal lesions on capsule endoscopy (score >4, 4/11 vs 0/19 p = 0.01). Fecal calprotectin was similar between CFCIR and CFnoLIV (166 mug/g +/- 175 vs 136 +/- 193 p = 0.58, nl <120). Lactulose:mannitol ratio was elevated in 27/28 subjects and was slightly lower in CFCIR vs CFnoLIV (0.08 +/-0.02 vs 0.11 +/-0.05, p = 0.04, nl <0.03). Small bowel transit time was longer in CFCIR vs CFnoLIV (195 +/-42 min vs 167 +/-68 p<0.001, nl 274 +/- 41). Bacteroides were decreased in relative abundance in CFCIR and were associated with lower capsule endoscopy score whereas Clostridium were more abundant in CFCIR and associated with higher capsule endoscopy score. Conclusions: CFCIR is associated with increased intestinal mucosal lesions, slower small bowel transit time and alterations in fecal microbiome. Abnormal intestinal permeability and elevated fecal calprotectin are common in all CF subjects. Disturbances in intestinal function in CF combined with changes in the microbiome may contribute to the development of hepatic fibrosis and intestinal lesions.
Title: Preimplantation genetic diagnosis for cystic fibrosis: The Montpellier center’s 10-year experience

Citation: Clinical Genetics, February 2015, vol./is. 87/2(124-132), 0009-9163;1399-0004 (01 Feb 2015)

Author(s): Girardet A., Ishmukhametova A., Willems M., Coubes C., Hamamah S., Anahory T., Des Georges M., Claustres M.

Abstract: This study provides an overview of 10 years of experience of preimplantation genetic diagnosis (PGD) for cystic fibrosis (CF) in our center. Owing to the high allelic heterogeneity of CF transmembrane conductance regulator (CFTR) mutations in south of France, we have set up a powerful universal test based on haplotyping eight short tandem repeats (STR) markers together with the major mutation p.Phe508del. Of 142 couples requesting PGD for CF, 76 have been so far enrolled in the genetic work-up, and 53 had 114 PGD cycles performed. Twenty-nine cycles were canceled upon in vitro fertilization (IVF) treatment because of hyper- or hypostimulation. Of the remaining 85 cycles, a total of 493 embryos were biopsied and a genetic diagnosis was obtained in 463 (93.9%), of which 262 (without or with a single CF-causing mutation) were transferable. Twenty-eight clinical pregnancies were established, yielding a pregnancy rate per transfer of 30.8% in the group of seven couples with one member affected with CF, and 38.3% in the group of couples whose both members are carriers of a CF-causing mutation [including six couples with congenital bilateral absence of the vas deferens (CBAVD)]. So far, 25 children were born free of CF and no misdiagnosis was recorded. Our test is applicable to 98% of couples at risk of transmitting CF.

Title: Comprehensive CFTR gene analysis of the French cystic fibrosis screened newborn cohort: Implications for diagnosis, genetic counseling, and mutation-specific therapy

Citation: Genetics in Medicine, February 2015, vol./is. 17/2(108-116), 1098-3600;1530-0366 (05 Feb 2015)

Author(s): Audrezet M.P., Munck A., Scotet V., Claustres M., Roussey M., Delmas D., Ferec C., Desgeorges M.

Abstract: Purpose: Newborn screening (NBS) for cystic fibrosis (CF) was implemented throughout France in 2002. It involves a four-tiered procedure: immunoreactive trypsin (IRT)/DNA/IRT/sweat test was implemented throughout France in 2002. The aim of this study was to assess the performance of molecular CFTR gene analysis from the French NBS cohort, to evaluate CF incidence, mutation detection rate, and allelic heterogeneity. Methods: During the 8-year period, 5,947,148 newborns were screened for cystic fibrosis. The data were collected by the Association Francaise pour le Depistage et la Prevention des Handicaps de l'Enfant. The mutations identified were classified into four groups based on their potential for causing disease, and a diagnostic algorithm was proposed. Results: Combining the genetic and sweat test results, 1,160 neonates were diagnosed as having cystic fibrosis. The corresponding incidence, including both the meconium ileus (MI) and false-negative cases, was calculated at 1 in 4,726 live births. The CF30 kit, completed with a
comprehensive CFTR gene analysis, provides an excellent detection rate of 99.77% for the mutated alleles, enabling the identification of a complete genotype in 99.55% of affected neonates. With more than 200 different mutations characterized, we confirmed the French allelic heterogeneity. Conclusion: The very good sensitivity, specificity, and positive predictive value obtained suggest that the four-tiered IRT/DNA/IRT/sweat test procedure may provide an effective strategy for newborn screening for cystic fibrosis. Genet Med 17 2, 108-116.

Title: Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells

Citation: European Respiratory Journal, February 2015, vol./is. 45/2(428-439), 0903-1936;1399-3003 (01 Feb 2015)


Abstract: Virus-associated pulmonary exacerbations, often associated with rhinoviruses (RVs), contribute to cystic fibrosis (CF) morbidity. Currently, there are only a few therapeutic options to treat virus-induced CF pulmonary exacerbations. The macrolide antibiotic azithromycin has antiviral properties in human bronchial epithelial cells. We investigated the potential of azithromycin to induce antiviral mechanisms in CF bronchial epithelial cells. Primary bronchial epithelial cells from CF and control children were infected with RV after azithromycin pre-treatment. Viral RNA, interferon (IFN), IFN-stimulated gene and pattern recognition receptor expression were measured by real-time quantitative PCR. Live virus shedding was assessed by assaying the 50% tissue culture infective dose. Pro-inflammatory cytokine and IFN-beta production were evaluated by ELISA. Cell death was investigated by flow cytometry. RV replication was increased in CF compared with control cells. Azithromycin reduced RV replication seven-fold in CF cells without inducing cell death. Furthermore, azithromycin increased RV-induced pattern recognition receptor, IFN and IFN-stimulated gene mRNA levels. While stimulating antiviral responses, azithromycin did not prevent virus-induced pro-inflammatory responses. Azithromycin pre-treatment reduces RV replication in CF bronchial epithelial cells, possibly through the amplification of the antiviral response mediated by the IFN pathway. Clinical studies are needed to elucidate the potential of azithromycin in the management and prevention of RV-induced CF pulmonary exacerbations.

Title: The metabolomics of airway diseases, including COPD, asthma and cystic fibrosis

Citation: Biomarkers, February 2015, vol./is. 20/1(5-16), 1354-750X;1366-5804 (01 Feb 2015)

Author(s): Nobakht M Gh B.F., Aliannejad R., Rezaei-Tavirani M., Taheri S., Oskouie A.A.

Abstract: Chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis (CF) are characterized by airway obstruction and an inflammatory process. Reaching early diagnosis and discrimination of subtypes of these respiratory diseases are quite a challenging task than other chronic illnesses. Metabolomics is the study of metabolic pathways and the measurement of unique biochemical molecules generated in a living system. In the last decade, metabolomics has already
proved to be useful for the characterization of several pathological conditions and offers promises as a clinical tool. In this article, we review the current state of the metabolomics of COPD, asthma and CF with a focus on the different methods and instrumentation being used for the discovery of biomarkers in research and translation into clinic as diagnostic aids for the choice of patient-specific therapies.

Title: Characterization of gene mutations and phenotypes of cystic fibrosis in Chinese patients

Citation: Respirology, February 2015, vol./is. 20/2(312-318), 1323-7799;1440-1843 (01 Feb 2015)

Author(s): Liu Y., Wang L., Tian X., Xu K.-F., Xu W., Li X., Yue C., Zhang P., Xiao Y., Zhang X.

Abstract: Background and objective Cystic fibrosis (CF) is a relatively common autosomal recessive disorder in Caucasians. CF is considered a very rare disease in Asians, and fewer than 30 Chinese CF patients are reported in the literature. We enrolled seven patients of Chinese Han origin diagnosed with CF at the Peking Union Medical College Hospital, to characterize gene mutations and phenotypes of CF in Chinese patients. Methods We analysed the clinical presentation and screened the coding region of the CFTR gene for each patient. Results Patients were 0-6 years old at onset of symptoms and were 10-28 years old at the time of diagnosis with CF. None of the seven patients had a family history of CF, and only one patient had parents who were consanguineous. Two patients had gastrointestinal symptoms but stool Sudan III results were normal. Four of the seven CF patients also had allergic bronchopulmonary aspergillosis. The concentration of chloride in patients' sweat ranged from 66 mmol/l to 154 mmol/l. In total, we identified 11 different mutations in seven CF patients, including one novel mutation (deltaE7-E11). Only one of these mutations (R553X) is present in the Caucasian CFTR common mutation-screening panel; and none of the 11 mutations are common in Caucasian CF patients. Conclusions CF in China is difficult to diagnose because of a combination of low awareness, atypical clinical symptoms, and a lack of sweat and genetic testing facilities in most hospitals. The mutations identified in Chinese CF patients are different from the common Caucasian gene mutations. We conducted research on seven Chinese cystic fibrosis patients. Their CFTR mutations are uncommon compared with those commonly found in Caucasians. Therefore, physicians in both China and western countries should pay more attention to atypically affected CF-like patients, especially those who are of Chinese origin.

Title: Identification of new bacterial and fungal pathogens on surveillance bronchoscopy prior to sinus surgery in patients with cystic fibrosis

Citation: Pediatric Pulmonology, February 2015, vol./is. 50/2(137-143), 8755-6863;1099-0496 (01 Feb 2015)

Author(s): Kirkby S., Hayes D., Ginn-Pease M., Gatz J., Wisely C.E., Lind M., Elmaraghy C., Ryan-Wenger N., Sheikh S.I.

Abstract: Background: Flexible fiberoptic bronchoscopy was performed prior to functional endoscopic sinus surgery (FESS) while under general anesthesia to collect bronchoalveolar lavage
fluid (BALF) for lower respiratory tract cultures in patients with cystic fibrosis (CF). Methods: A retrospective chart review was performed on all CF patients who underwent combined FESS and bronchoscopy between January 2009 and October 2010. Along with demographic data, bacterial, fungal, and acid fast bacillus culture data from BALF was collected and compared to oropharyngeal swab and sputum cultures obtained over the year prior to FESS and bronchoscopy. Results: A total of 77 patients were enrolled with mean age 12.5 +/- SD 6.5 (range 2-29) years. Mean FEV1 was 86% +/- 18.4 (range 33-128) % of predicted. Patients averaged 6.5 (range 1-13) sputum or OP cultures in the year prior to FESS. BALF cultures identified a new bacterial pathogen in 19% (n = 15) of patients, which altered antibiotic regimen immediately in two patients and sub-acutely in five patients. BALF cultures identified a new fungal pathogen in 42% (n = 32) of patients, which resulted in the addition of antifungal therapy in eight patients. BALF cultures did not identify previously undetected AFB culture positive patients. No significant differences were found between patients with and without new discoveries of bacterial or fungal pathogens with regards to key clinical demographic data, lung function parameters, healthcare utilization, or need for antibiotics over the year prior to FESS. There was no relationship between the total number of respiratory cultures obtained in the year prior to bronchoscopy and the identification of new bacterial or fungal pathogens. Conclusions: Surveillance BALF cultures obtained prior to FESS identified bacterial and fungal pathogens not previously detected by sputum or OP swab cultures in a cohort of CF patients with chronic sinus disease. Moreover, the identification of these new pathogens altered clinical management in a small number of patients.

Title: Persistent cystic fibrosis isolate Pseudomonas aeruginosa strain RP73 exhibits an underacylated LPS structure responsible of its low inflammatory activity

Citation: Molecular Immunology, February 2015, vol./is. 63/2(166-175), 0161-5890;1872-9142 (February 01, 2015)

Author(s): Di Lorenzo F., Silipo A., Bianconi I., Lore' N.I., Scamporrino A., Sturiale L., Garozzo D., Lanzetta R., Parrilli M., Bragonzi A., Molinaro A.

Abstract: Pseudomonas aeruginosa, the major pathogen involved in lethal infections in cystic fibrosis (CF) population, is able to cause permanent chronic infections that can persist over the years. This ability to chronic colonize CF airways is related to a series of adaptive bacterial changes involving the immunostimulant lipopolysaccharide (LPS) molecule. The structure of LPSs isolated from several P. aeruginosa strains showed conserved features that can undergo chemical changes during the establishment of the chronic infection. In the present paper, we report the elucidation of the structure and the biological activity of the R-LPS (lipooligosaccharide, LOS) isolated from the persistent CF isolate P. aeruginosa strain RP73, in order to give further insights in the adaptation mechanism of the pathogen in the CF environment. The complete structural analysis of P. aeruginosa RP73 LOS was achieved by chemical analyses, NMR spectroscopy and MALDI MS spectrometry, while the assessment of the biological activity was attained testing the in vivo pro-inflammatory capacity of the isolated LOS molecule. While a typical CF LPS is able to trigger a high immune response and production of pro-inflammatory molecules, this P. aeruginosa RP73 LOS showed to possess a low pro-inflammatory capacity. This was possible due to a singular chemical
structure possessing an under-acylated lipid A very similar to the LPS of P. aeruginosa found in chronic lung diseases such as bronchiectasis.

Title: The effect of the decoy molecule PA401 on CXCL8 levels in bronchoalveolar lavage fluid of patients with cystic fibrosis

Citation: Molecular Immunology, February 2015, vol./is. 63/2(550-558), 0161-5890;1872-9142 (February 01, 2015)


Abstract: Background: The chemokine interleukin-8 (CXCL8) is a key mediator of inflammation in airways of patients with cystic fibrosis (CF). Glycosaminoglycans (GAGs) possess the ability to influence the chemokine profile of the CF lung by binding CXCL8 and protecting it from proteolytic degradation. CXCL8 is maintained in an active state by this glycan interaction thus increasing infiltration of immune cells such as neutrophils into the lungs. As the CXCL8-based decoy PA401 displays no chemotactic activity, yet demonstrates glycan binding affinity, the aim of this study was to investigate the anti-inflammatory effect of PA401 on CXCL8 levels, and activity, in CF airway samples in vitro. Methods: Bronchoalveolar lavage fluid (BALF) was collected from patients with CF homozygous for the deltaF508 mutation (n=13). CXCL8 in CF BALF pre and post exposure to PA401 was quantified by ELISA. Western blot analysis was used to determine PA401 degradation in CF BALF. The ex vivo chemotactic activity of purified neutrophils in response to CF airway secretions was evaluated post exposure to PA401 by use of a Boyden chamber-based motility assay. Results: Exposure of CF BALF to increasing concentrations of PA401 (50-1000 pg/ml) over a time course of 2-12 h in vitro, significantly reduced the level of detectable CXCL8 (P<0.05). Interestingly, PA401 engendered release of CXCL8 from GAGs exposing the chemokine susceptible to proteolysis. Subsequently, a loss of PA401 was observed (P<0.05) due to proteolytic degradation by elastase like proteases. A 25% decrease in neutrophil chemotactic efficiency towards CF BALF samples incubated with PA401 was also observed (P<0.05). Conclusion: PA401 can disrupt CXCL8:GAG complexes, rendering the chemokine susceptible to proteolytic degradation. Clinical application of a CXCL8 decoy, such as PA401, may serve to decrease the inflammatory burden in the CF lung in vivo.

Psychological

Title: Motivating adherence among adolescents with cystic fibrosis: Youth and parent perspectives

Citation: Pediatric Pulmonology, February 2015, vol./is. 50/2(127-136), 8755-6863;1099-0496 (01 Feb 2015)

Author(s): Sawicki G.S., Heller K.S., Demars N., Robinson W.M.

Abstract: As advances in the care of individuals with cystic fibrosis (CF) have resulted in improved survival, therapeutic regimens for treatment of CF have become increasingly complex. This high
treatment burden poses challenges to chronic disease self-management, particularly amongst adolescents. The aim of this qualitative study was to understand the barriers and facilitators of adherence to chronic CF therapies as perceived by adolescents with CF and their parents. In a series of structured interviews with 18 youth and their parents, we explored issues related to daily routines, youth and parental roles regarding chronic therapy, and motivators for adherence. All interviews were audio-recorded and coded for themes and patterns. Reported barriers to adherence included time pressures, competing priorities, heightened awareness of disease trajectory, privacy concerns, and lack of perceived consequences from non-adherence. Identified facilitators for adherence included recognizing the importance of therapies, developing strong relationships with care teams, establishing structured routines, and focusing on shifting responsibilities from a parent to their adolescent child. The themes uncovered by these interviews identify areas for intervention and support by clinical programs seeking to improve adherence and self-management strategies for adolescents with CF.

Title: An exploration of how young people and parents use online support in the context of living with cystic fibrosis.

Citation: Health Expectations: An International Journal of Public Participation in Health Care & Health Policy, February 2015(No Pagination Specified), 1369-6513;1369-7625 (Feb 17, 2015)

Author(s): Kirk, Susan, Milnes, Linda

Abstract: Abstract Background There is increasing recognition of the Internet's potential role in providing information and support for people living with long-term conditions. However, how young people and parents use online forms of self-care support in the context of living with childhood chronic illness has been under-researched. Objective To explore how online peer support is used by young people and parents to support self-care in relation to cystic fibrosis (CF). Setting and participants Online forum for young people and parents based on a CF charity website. A total of 279 individuals participated in the forum during the study. Design An online ethnographical approach, involving observing, downloading and analysing discussion group postings. All postings made over a random 4-month period were included (151 discussion threads). Results The online setting enabled a physically disconnected group to connect and create a safe space to collectively share experiences and receive support to manage and live with cystic fibrosis. Participants exchanged experientially derived advice and views on how to manage treatments, emotions, relationships, identity and support from services. While parents sought information and support on managing specific therapies/services and ways of maintaining their child's health, the information and support young people desired appeared to be more directed at how to 'fit' CF into their everyday lives. Discussion and conclusions Online support groups appear to supplement professional support in relation to self-management. They enable young people and parents to share experiences, feelings and strategies for living with long-term conditions with peers and develop the expertise to empower them in interactions with health-care professionals. (PsycINFO Database Record (c) 2015 APA, all rights reserved) (journal abstract)
Title: Glucose tolerance affects pubertal growth and final height of children with cystic fibrosis

Citation: Pediatric Pulmonology, February 2015, vol./is. 50/2(144-149), 8755-6863;1099-0496 (01 Feb 2015)

Author(s): Bizzarri C., Montemitro E., Pedicelli S., Ciccone S., Majo F., Cappa M., Lucidi V.

Abstract: There are few data about the impact of cystic fibrosis-related diabetes (CFRD) on growth. We analyzed 17 children with cystic fibrosis (CF) presenting with newly diagnosed CFRD during puberty, in comparison with a matched control group of 52 CF children with normal glucose tolerance (NGT). Anthropometric evaluation showed that body mass index at CFRD diagnosis was significantly reduced in children with CFRD, in comparison with children with NGT (CFRD: -0.48 +/- 1.08 vs. NGT: 0.2 +/- 0.99; P = 0.01), and the same difference remained evident at the end of follow-up (CFRD: -0.49 +/- 0.95 vs. NGT: 0.13 +/- 0.89; P = 0.04). Height standard deviation score (SDS) at baseline was slightly but not significantly lower in CFRD children (CFRD: -0.71 +/- 0.83 vs. NGT: -0.25 +/- 1.08; P = 0.08), while final height SDS was significantly reduced (CFRD: -1.61 +/- 1.12 vs. NGT: -0.61 +/- 1.15; P = 0.003). Mean final height SDS of the whole group was lower than mean target height SDS (final height SDS: -0.86 +/- 1.2 vs. target height SDS: -0.3 +/- 0.85; P < 0.001). Target adjusted final height was lower in CFRD children, although the difference between CFRD and NGT children did not reach statistical significance (CFRD: -0.8 +/- 1.03 vs. NGT: -0.47 +/- 0.9; P = 0.09). Pubertal growth and final height are negatively affected by CFRD. Intensive insulin treatment does not appear to be effective in normalizing growth, even when treatment is started early in the course of the disease, before the onset of clinical deterioration.

Title: Novel personalized therapies for cystic fibrosis: Treating the basic defect in all patients

Citation: Journal of Internal Medicine, February 2015, vol./is. 277/2(155-166), 0954-6820;1365-2796 (01 Feb 2015)

Author(s): Amaral M.D.

Abstract: Cystic fibrosis (CF) is the most common genetic life-shortening condition in Caucasians. Despite being a multi-organ disease, CF is classically diagnosed by symptoms of acute/chronic respiratory disease, with persistent pulmonary infections and mucus plugging of the airways and failure to thrive. These multiple symptoms originate from dysfunction of the CF transmembrane conductance regulator (CFTR) protein, a channel that mediates anion transport across epithelia. Indeed, establishment of a definite CF diagnosis requires proof of CFTR dysfunction, commonly through the so-called sweat Cl<sup>-</sup> test. Many drug therapies, including mucolytics and antibiotics, aim to alleviate the symptoms of CF lung disease. However, new therapies to modulate defective CFTR, the basic defect underlying CF, have started to reach the clinic, and several others are in development or in clinical trials. The novelty of these therapies is that, besides targeting the basic defect underlying CF, they are mutation specific. Indeed, even this monogenic disease is influenced by a large number of different genes and biological pathways as well as by environmental
factors that are difficult to assess. Accordingly, every person with CF is unique and so functional assessment of patients' tissues ex vivo is key for diagnosing and predicting the severity of this disease. Of note, such assessment will also be crucial to assess drug responses, in order to effectively treat all CF patients. It is not because it is a monogenic disorder that personalized treatment for CF is much easier than for complex disorders.

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