

Cystic Fibrosis

Evidence Update

February 2018

(Quarterly)

Respecting everyone
Embracing change
Recognising success
Working together
Our hospitals.



Training Sessions 2018

All sessions are one hour

February (12.00-13.00)

1st (Thu)	Literature Searching
9th (Fri)	Critical Appraisal
12th (Mon)	Statistics
20th (Tue)	Literature Searching
28th (Wed)	Critical Appraisal

March (13.00-14.00)

8th (Thu)	Statistics
12th (Mon)	Literature Searching
20th (Tue)	Critical Appraisal
28th (wed)	Statistics

April (12.00-13.00)

5th (Thu)	Literature Searching
9th (Mon)	Critical Appraisal
17th (Tue)	Statistics
25th (Wed)	Literature Searching




Your Outreach Librarian: Jo Hooper

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Outreach: Your Outreach Librarian can help facilitate evidence-based practice for all in the restorative dentistry team, as well as assisting with academic study and research. We can help with **literature searching, obtaining journal articles and books**. We also offer one-to-one or small group training in **literature searching, accessing electronic journals, and critical appraisal**. Get in touch: library@uhbristol.nhs.uk

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Updates

NICE National Institute for
Health and Care Excellence

[Induced sputum in children with cystic fibrosis](#) Source: [UK Clinical Trials Gateway - UKCTG](#) - 10 January 2018

[Treatment of chronic rhinosinusitis with dornase alfa in patients with cystic fibrosis: a systematic review](#) Source: [PubMed](#) - 11 January 2018 - Publisher: International Forum Of Allergy & Rhinology
[Read Summary](#)

[Symdeko \(ivacaftor and tezacaftor\) approved in US to treat selected patients with cystic fibrosis](#)
13 February 2018 - Publisher: PharmaTimes [Read Summary](#)

[Treating cough due to non-CF and CF bronchiectasis with non-pharmacological airway clearance: CHEST Expert Panel Report](#) Source: [PubMed](#) - 17 January 2018 - Publisher: Chest [Read Summary](#)

[Licence extension for Orkambi \(lumacaftor/ivacaftor\) approved in EU for treatment of children with cystic fibrosis aged 6-11 with two copies of F508del mutation](#) 10 January 2018 -
Publisher: Biospace Inc.



[Inhaled mannitol for cystic fibrosis](#): Online Publication Date: February 2018

[Physical exercise training for cystic fibrosis](#): Online Publication Date: November 2017

UpToDate[®]

OpenAthens login required. Register here: <https://openathens.nice.org.uk/>

[Cystic fibrosis: Treatment of acute pulmonary exacerbations](#)

Literature review current through: Jan 2018. | **This topic last updated:** Dec 12, 2017.

[Cystic fibrosis: Overview of the treatment of lung disease](#)

Literature review current through: Jan 2018. | **This topic last updated:** Feb 07, 2018.

[Cystic fibrosis: Overview of gastrointestinal disease](#)

Literature review current through: Jan 2018. | **This topic last updated:** Dec 04, 2017.

[Cystic fibrosis: Genetics and pathogenesis](#)

Literature review current through: Jan 2018. | **This topic last updated:** Jan 08, 2018.

**Cystic
Fibrosis Trust**

@cftrust · Twitter

[Vertex announces plans for phase III trials of triple drug combinations](#) Feature - Dr Belinda Cupid - 02/02/2018

[Survival statistics - what if I'm already 30?](#) News - 17/01/2018

Journal Tables of Contents

The most recent issues of the following journals:

- **Journal of Cystic Fibrosis**
- **American Journal of Respiratory and Critical Care Medicine**
- **Thorax**
- **Chest**

Click on the links for abstracts. If you would like any of these papers in full text then get in touch: library@uhbristol.nhs.uk

Journal of Cystic Fibrosis

January 2018, Volume 17, Issue 1

<http://www.cysticfibrosisjournal.com/current>

American Journal of Respiratory and Critical Care Medicine

February 1 2018, Volume 197, Issue 3

<http://www.atsjournals.org/toc/ajrccm/current>

Thorax

February 2018, Volume 73, Issue 2

<http://thorax.bmj.com/content/current>

Chest

February 2018, Volume 153, Issue 2

<http://journal.chestnet.org/current>

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
- Nutritional
- 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: library@uhbristol.nhs.uk

Medical

Understanding Pseudomonas status among adults with cystic fibrosis: a real-world comparison of the Leeds criteria against clinicians' decision.

Author(s): Hoo, Zhe Hui; Edenborough, Frank Peter; Curley, Rachael; Prtak, Laura; Dewar, Jane

Source: European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology; Jan 2018

Publication Type(s): Journal Article

Abstract: Pseudomonas aeruginosa status influences cystic fibrosis (CF) clinical management but no 'gold standard' definition exists. The Leeds criteria are commonly used but may lack sensitivity for chronic P. aeruginosa. We compared clinicians' decision with the Leeds criteria in three adult CF centres. Two independent prospective datasets (Sheffield dataset, n = 185 adults; ACTiF pilot dataset, n = 62 adults from two different centres) were analysed. Clinicians involved in deciding P. aeruginosa status were blinded to the study objectives. Clinicians considered more adults with CF to have chronic P. aeruginosa infection compared to the Leeds criteria. This was more so for the Sheffield dataset (106/185, 57.3% with clinicians' decision vs. 80/185, 43.2% with the Leeds criteria; kappa coefficient between these two methods 0.72) compared to the ACTiF pilot dataset (34/62, 54.8% with clinicians' decision vs. 30/62, 48.4% with the Leeds criteria; kappa coefficient between these two methods 0.82). However, clinicians across different centres were relatively consistent once age and severity of lung disease, as indicated by the type of respiratory samples provided, were taken into account. Agreement in P. aeruginosa status was similar for both datasets among adults who predominantly provided sputum samples (kappa coefficient 0.78) or adults > 25 years old (kappa coefficient 0.82). Across three different centres, clinicians did not always agree with the Leeds criteria and tended to consider the Leeds criteria to lack sensitivity. Where disagreement occurred, clinicians tended to diagnose chronic P. aeruginosa infection because other relevant information was considered. These results suggest that a better definition for chronic P. aeruginosa might be developed by using consensus methods to move beyond a definition wholly dependent on standard microbiological results.

Exploring Opportunities for Primary Outpatient Palliative Care for Adults with Cystic Fibrosis: A Mixed-Methods Study of Patients' Needs.

Author(s): Hobler, Mara R; Engelberg, Ruth A; Curtis, J Randall; Ramos, Kathleen J; Zander, Miriam I

Source: Journal of palliative medicine; Jan 2018

Publication Type(s): Journal Article

Abstract:BACKGROUND Persons with cystic fibrosis (CF) experience high morbidity and mortality, yet little is known about their palliative care needs and how clinicians may address these needs. OBJECTIVES (1) To identify palliative care and advance care planning needs of patients with CF and their families; and (2) to identify clinicians' potential roles in meeting these needs. METHODS A mixed-methods study of adult patients (age ≥ 18 years) with moderate-to-severe CF [forced expiratory volume in the first second (FEV₁) $< 65\%$ predicted] were recruited from a CF Center. Semi-structured interviews (30-60 minutes) and questionnaires were administered in person or by phone. Grounded theory was used to analyze the interviews. Questionnaires were analyzed descriptively. RESULTS Forty-nine patients (FEV₁ % range = 19%-63%) participated; the participation rate was 80% for eligible patients. Three main domains of palliative care needs were identified: (1) to be listened to, feel heard, and be "seen"; (2) understanding the context around CF and its trajectory, with the goal of preparing for the future; and (3) information about, and potential solutions to, practical and current circumstances that cause stress. In questionnaires, few patients (4.3%) reported talking with their clinician about their wishes for care if they were to become sicker, but mixed-methods data demonstrated that more than half of participants were willing to receive palliative care services provided those services were adapted to CF. CONCLUSION Patients expressed a need for and openness to palliative care services, as well as some reluctance. They appreciated clinician communication that was open, forthcoming, and attuned to individualized concerns.

RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis.

Author(s): Aksamit, Timothy; De Soyza, Anthony; Bandel, Tiemo-Joerg; Criollo, Margarita

Source: The European respiratory journal; Jan 2018; vol. 51 (no. 1)

Publication Type(s): Journal Article

Abstract:We evaluated the efficacy and safety of ciprofloxacin dry powder for inhalation (DPI) in patients with non-cystic fibrosis bronchiectasis, two or more exacerbations in the previous year and predefined sputum bacteria. Patients were randomised 2:1 to twice-daily ciprofloxacin DPI 32.5 mg or placebo in 14- or 28-day on/off treatment cycles for 48 weeks. Primary end-points were time to first exacerbation and frequency of exacerbations. Enrolling countries and α level split (0.049 and 0.001 for 14- and 28-day cycles, respectively) differed from RESPIRE 1. Patients were randomised to ciprofloxacin DPI (14 days on/off (n=176) or 28 days on/off (n=171)) or placebo (14 days on/off (n=88) or 28 days on/off (n=86)). The exacerbation rate was low across treatment arms (mean \pm sd 0.6 \pm 0.9). Active treatment showed trends to prolonged time to first exacerbation (ciprofloxacin DPI 14 days on/off: hazard ratio 0.87, 95.1% CI 0.62-1.21; p=0.3965; ciprofloxacin DPI 28 days on/off: hazard ratio 0.71, 99.9% CI 0.39-1.27; p=0.0511) and reduced frequency of exacerbations (ciprofloxacin DPI 14 days on/off: incidence rate ratio 0.83, 95.1% CI 0.59-1.17; p=0.2862; ciprofloxacin DPI 28 days on/off: incidence rate ratio 0.55, 99.9% CI 0.30-1.02; p=0.0014), although neither achieved statistical significance. Ciprofloxacin DPI was well tolerated. Trends towards clinical benefit were seen with ciprofloxacin DPI, but primary end-points were not met.

Oral glucose tolerance test and continuous glucose monitoring to assess diabetes development in cystic fibrosis patients.

Author(s): Clemente León, María; Bilbao Gassó, Laura; Moreno-Galdó, Antonio; Campos Martorell, Ariadna; Gartner Tizzano, Silvia; Yeste Fernández, Diego; Carrascosa Lezcano, Antonio

Source: Endocrinología, diabetes y nutrición; Jan 2018; vol. 65 (no. 1); p. 45-51

Publication Type(s): Journal Article

Abstract:INTRODUCTION Patients with cystic fibrosis (CF) undergo a slow and progressive process toward diabetes. Oral glucose tolerance test (OGTT) is recommended to diagnose impaired glucose

levels in these patients. Continuous glucose monitoring (CGM) measures glucose profiles under real-life conditions. OBJECTIVE To compare OGTT and CGM results in CF patients. METHODS Paired OGTT and 6-day CGM profiles (146.2±9.1h/patient) were performed in 30 CF patients aged 10-18 years. RESULTS According to OGTT, 14 patients had normal glucose tolerance (NGT), 14 abnormal glucose tolerance (AGT), and two cystic fibrosis-related diabetes (CFRD). In 27 patients (13 NGT, 13 AGT, 1 CFRD), CGM showed glucose values ranging from 140 to 200mg/dL during similar monitoring times (2%-14% with NGT, 1%-16.9% with AGT, and 3% with CFRD). Glucose peak levels ≥200mg/dL were seen in seven patients (3 NGT, 3 AGT, 1 CFRD). According to CGM, two patients had all glucose values under 140mg/dL (1 NGT, 1 AGT). Seventeen patients had glucose levels ranging from 140 to 200mg/dL (10 NGT, 6 AGT, 1 CFRD). Ten patients (3 NGT, 7 AGT) had glucose values ≥200mg/dL for ≤1% of the monitoring time and one (CFRD) for >1% of the monitoring time. CONCLUSIONS OGTT results did not agree with those of the CGM. CGM allows for diagnosis of glucose changes not detected by OGTT. Such changes may contribute to optimize pre-diabetes management in CF patients.

Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations.

Author(s): Hadjiliadis, Denis; Khoruts, Alexander; Zauber, Ann G; Hempstead, Sarah E

Source: Gastroenterology; Dec 2017

Publication Type(s): Journal Article

Abstract: BACKGROUND & AIMS Improved therapy has substantially increased survival of persons with cystic fibrosis (CF). But the risk of colorectal cancer (CRC) in adults with CF is 5-10 times greater compared to the general population, and 25-30 times greater in CF patients after an organ transplantation. To address this risk, the CF Foundation convened a multi-stakeholder task force to develop CRC screening recommendations. METHODS The 18-member task force consisted of experts including pulmonologists, gastroenterologists, a social worker, nurse coordinator, surgeon, epidemiologist, statistician, CF adult, and a parent. The committee comprised 3 workgroups: Cancer Risk, Transplant, and Procedure and Preparation. A guidelines specialist at the CF Foundation conducted an evidence synthesis February-March 2016 based on PubMed literature searches. Task force members conducted additional independent searches. A total of 1159 articles were retrieved. After initial screening, the committee read 198 articles in full and analyzed 123 articles to develop recommendation statements. An independent decision analysis evaluating the benefits of screening relative to harms and resources required was conducted by the Department of Public Health at Erasmus Medical Center, Netherlands using the Microsimulation Screening Analysis model from the Cancer Innervation and Surveillance Modeling Network. The task force included recommendation statements in the final guideline only if they reached an 80% acceptance threshold. RESULTS The task force makes 10 CRC screening recommendations that emphasize shared, individualized decision-making and familiarity with CF-specific gastrointestinal challenges. We recommend colonoscopy as the preferred screening method, initiation of screening at age 40 years, 5-year re-screening and 3-year surveillance intervals (unless shorter interval is indicated by individual findings), and a CF-specific intensive bowel preparation. Organ transplant recipients with CF should initiate CRC screening at age 30 years within 2 years of the transplantation because of the additional risk for colon cancer associated with immunosuppression. CONCLUSIONS These recommendations aim to help CF adults, families, primary care physicians, gastroenterologists, and CF and transplantation centers address the issue of CRC screening. They differ from guidelines developed for the general population with respect to the recommended age of screening initiation, screening method, preparation, and the interval for repeat screening and surveillance.

Use of ceftolozane-tazobactam in a cystic fibrosis patient with multidrug-resistant pseudomonas infection and renal insufficiency.

Author(s): Stokem, Katie; Zuckerman, Jonathan B; Nicolau, David P; Wungwattana, Minkey

Source: Respiratory medicine case reports; 2018; vol. 23 ; p. 8-9

Publication Type(s): Journal Article

Available at [Respiratory medicine case reports](#) - from Europe PubMed Central - Open Access

Abstract:We report the successful use of ceftolozane/tazobactam (C/T) to treat a pulmonary exacerbation in a 35 year old female, post lung transplant, with cystic fibrosis (CF), malnutrition, chronic kidney disease, and multi-drug resistant *Pseudomonas aeruginosa* infection (MDR PSA). Given the complexity of the clinical profile, we measured drug levels of C/T during treatment of her current exacerbation to determine pharmacokinetics. The patient achieved an estimated ceftolozane peak of 174.1 µg/mL and trough of 9.2 µg/mL. Serum half-life was found to be slightly shorter than previously reported in normal subjects, (2.3 hr. vs. 2.6 hr.) despite the presence of renal insufficiency. Treatment resulted in improvement in serum inflammatory markers and symptoms and was well-tolerated.

Revisiting sweat chloride test results based on recent guidelines for diagnosis of cystic fibrosis

Author(s): Pagaduan J.V.; Ali M.; Dowlin M.; Suo L.; Ward T.; Ruiz F.; Devaraj S.

Source: Practical Laboratory Medicine; Mar 2018; vol. 10 ; p. 34-37

Publication Type(s): Article

Available at [Practical Laboratory Medicine](#) - from nih.gov

Abstract:Objectives Recent sweat chloride guidelines published by the Cystic Fibrosis Foundation changed the intermediate sweat chloride concentration range from 40-59 mmol/L to 30-59 mmol/L for age > 6 months. We wanted to know how this new guideline would impact detection of cystic fibrosis among patients who previously had sweat tests done at Texas Children's Hospital. Methods We revisited sweat chloride test results (n = 3012) in the last 5 years at Texas Children's Hospital based on the new guidelines on diagnosis of cystic fibrosis from the Cystic Fibrosis Foundation. Results We identified 125 patients that would be reclassified in the intermediate sweat chloride value with the new guidelines that were classified as "unlikely to have CF" in the previous guidelines. 8 (32%) patients with CFTR gene testing were positive for CFTR gene mutation(s). 4 (50%) of these patients were identified to have 2 CFTR mutations. One had variant combination that was reported to cause CF but all were diagnosed with CFTR-related metabolic syndrome. Conclusion Our findings concur with the new CF diagnosis guidelines that changing the intermediate cut-off to 30-59 mmol/L sweat chloride concentration in combination with CFTR genetic analysis enhances the probability of identifying individuals that have risk of developing CF or have CF and enables for earlier therapeutic intervention. Copyright © 2018 The Authors

Cystic fibrosis liver disease in adults: Limits of noninvasive tests of fibrosis

Author(s): Hillaire S.; Cazals-Hatem D.; Erlinger S.; Paradis V.

Source: Hepatology; 2018

Publication Type(s): Article In Press

Adults with cystic fibrosis have deficits in bone structure and strength at the distal tibia despite similar size and measuring standard and relative sites

Author(s): Nishiyama K.K.; Agarwal S.; Kepley A.; Rosete F.; Shane E.; Hu Y.; Guo X.E.; Keating C.L.

Source: Bone; Feb 2018; vol. 107 ; p. 181-187

Publication Type(s): Article

Abstract: Individuals with cystic fibrosis (CF) have lower bone mineral density (BMD) by DXA and are at higher risk of fracture than healthy controls. However, the 2-dimensional measurement of areal BMD (aBMD) provided by DXA is influenced by bone size and the true extent of the bone deficit is unclear. Our objective was to use high-resolution peripheral quantitative computed tomography (HR-pQCT) and individual trabecula segmentation (ITS) analysis to compare volumetric BMD (vBMD), microarchitecture and estimated strength at the distal radius and tibia in 26 young adults with CF and 26 controls matched for age, gender, and race. To assess the effect of limb length and minimize the confounding effects of size on HR-pQCT outcomes, we scanned participants at both the standard fixed HR-pQCT measurement sites and at a subject-specific relative site that varied according to limb length. CF participants did not differ significantly in age, height, weight, or BMI from controls. Ulnar and tibial lengths were 9 mm shorter in CF patients, though differences were not significant. CF patients had significantly lower BMI-adjusted aBMD by DXA at the lumbar spine (8.9%, $p < 0.01$), total hip (11.5%, $p < 0.01$) and femoral neck (14.5%, $p < 0.01$), but not at the forearm. At the fixed radius site, thickness of trabecular plates and torsional stiffness were significantly lower in CF participants than controls. At the relative radius site, only torsional stiffness was significantly lower in CF participants. At the tibia, total, trabecular and cortical vBMD were significantly lower at both fixed and relative sites in CF participants, with fewer, more widely-spaced trabecular plates, lower trabecular connectivity, and lower axial and torsional stiffness. Our results confirm that aBMD is lower at the spine and hip in young adults with CF, independent of BMI and body size. We also conclude that vBMD and stiffness are lower at the weight-bearing tibia. The pathogenesis of these differences in bone density and strength at the tibia appear to be related to trabecular drop-out and reduced trabecular connectivity and to be independent of differences in limb length, as assessed by scanning participants at both standard and relative sites. We concluded that significant deficits in bone structure and strength persist in young adults with CF, despite advances in care that permit them to attain relatively normal height and weight. Copyright © 2017 Elsevier Inc.

New Combination Therapy for Cystic Fibrosis.

Author(s): Slomski, Anita

Source: JAMA; Jan 2018; vol. 319 (no. 4); p. 333

Publication Type(s): Journal Article

Available at [JAMA](#) - from EBSCO (MEDLINE Complete)

Timing of Spirometry May Impact Hospital Length of Stay for Cystic Fibrosis Pulmonary Exacerbation.

Author(s): Krivchenia, Katelyn; Tumin, Dmitry; Nemastil, Christopher J; Tobias, Joseph D; Hayes, Don

Source: Lung; Jan 2018

Publication Type(s): Journal Article

Abstract: **PURPOSE** The optimal timing of spirometry during hospitalization for acute pulmonary exacerbation (PEX) in patients with cystic fibrosis (CF) is unclear. We retrospectively evaluated whether measuring spirometry earlier during hospitalization was associated with a shorter length of stay (LOS). **METHODS** In this retrospective study, we analyzed data from the electronic medical record of CF patients 6 years of age and older admitted to a single center for acute PEX requiring IV antibiotic therapy between 2009 and 2016. After excluding patient encounters with missing data on covariates, random-effects linear regression was used to predict LOS as a function of days to first pulmonary function testing (PFT), which was spirometry for our study. **RESULTS** One thousand thirty-five hospitalizations of 242 patients met inclusion criteria, with 801 including complete data on covariates. Mean LOS was 10 ± 7 days, with mean time to first PFT of 4 ± 3 days after admission. In multivariable analysis, each additional day to first PFT was associated with 0.97 days longer LOS

(95% CI 0.29, 1.64; $p = 0.005$). **CONCLUSIONS** As CF researchers and clinicians work to improve management of PEx, the timing of spirometry during hospitalization remains an important question. Obtaining objective lung function data earlier during the course of therapy may provide information which can lead to reduced hospital LOS for PEx.

Cystic Fibrosis Foundation Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis.

Author(s): Ren, Clement L; Morgan, Rebecca L; Oermann, Christopher; Resnick, Helaine E;

Source: Annals of the American Thoracic Society; Jan 2018

Publication Type(s): Journal Article

Available at [Annals of the American Thoracic Society](#) - from EBSCO (MEDLINE Complete)

Abstract: **BACKGROUND** CFTR modulators are a new class of medications that target the underlying defect in cystic fibrosis (CF). Ivacaftor (IVA) and IVA combined with lumacaftor (IVA/LUM) have been approved by the FDA for use in CF patients. However, the FDA label for these medications encompasses patient groups that were not studied as part of the drug approval process. CF clinicians, patients, and their families have recognized a need for recommendations to guide the use of these medications. **METHODS** A multidisciplinary committee of CF caregivers and patient representatives was assembled. A methodologist, an epidemiologist, a medical librarian, and a biostatistician were recruited to assist with the literature search, evidence grading, and generation of recommendations. The committee developed clinical questions using the Patient-Intervention-Comparison-Outcome format. A systematic review was conducted to find relevant publications. The evidence was then evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and recommendations were made based on this analysis. **RESULTS** The systematic review yielded 6 publications applicable to our clinical questions. The certainty of the evidence ranged from very low to moderate. This resulted in primarily conditional recommendations for therapy, although there were some strong recommendations. **CONCLUSIONS** Using the GRADE approach we have made recommendations for the use of CFTR modulators in patients with CF. These recommendations will be of help to CF clinicians, patients, and their families in guiding decisions regarding use of these medications. We anticipate that these guidelines will be revised as newer data and medications become available.

Static hyperinflation is associated with ventilatory limitation and exercise tolerance in adult cystic fibrosis.

Author(s): Stevens, Daniel

Source: The clinical respiratory journal; Jan 2018

Publication Type(s): Journal Article

Abstract: **INTRODUCTION** Lung hyperinflation is a potential mechanism limiting exercise tolerance. However, available data on the impact of static hyperinflation on exercise performance in adult cystic fibrosis is lacking. Furthermore, the relative contribution of both static and dynamic hyperinflation to exercise performance is unknown. **OBJECTIVES** To determine the impact of static hyperinflation on exercise tolerance and lung dynamics in adult cystic fibrosis. **METHODS** Clinical data of 107 adult patients with cystic fibrosis, including pulmonary function, lung volumes, and cardiopulmonary exercise from the Toronto Cystic Fibrosis database were collected and analyzed. Patients were classified as having static hyperinflation with a residual volume to total lung capacity (RV/TLC) ratio of 30% or greater. **RESULTS** Patients with static hyperinflation demonstrated a significant reduction in exercise performance (peak oxygen uptake (%predicted) 70 ± 17 Vs. 80 ± 17 ; $p = .006$), and were more likely to experience ventilatory limitation when exercising (Fishers Exact test $p < .001$). Correlation analysis showed significant relationships between measures of static

hyperinflation (RV/TLC ratio (%)) and exercise performance (peak oxygen uptake (%predicted)) ($r = .38$, $p < .001$), and dynamic hyperinflation ($r = .35$, $p < .001$). Multiple linear regression showed that the contribution of static hyperinflation to exercise performance (peak oxygen uptake (%predicted)) was greater than that of airway obstruction (forced expiratory volume in one second). **CONCLUSION** Clinicians working with this patient group in a pulmonary rehabilitation or healthcare setting may wish to consider using measures of static hyperinflation as end points to determine program or treatment efficacy. This article is protected by copyright. All rights reserved.

Pharmacokinetics of high-dose extended-infusion meropenem during pulmonary exacerbation in adult cystic fibrosis patients: a case series.

Author(s): Delfino, Emanuele; Fucile, Carmen; Del Bono, Valerio; Marchese, Anna; Marini, Valeria

Source: The new microbiologica; Jan 2018; vol. 41 (no. 1)

Publication Type(s): Journal Article

Abstract: This case series explored the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of meropenem (MEM) in adult cystic fibrosis (CF) patients hospitalized for a pulmonary exacerbation. From January 2015 to June 2016, all adult patients with cystic fibrosis (CF) and chronic pulmonary infection due to meropenem (MEM)-susceptible/intermediate *Pseudomonas aeruginosa* who received at least 48 h of MEM as an extended 3-hour infusion for treating a pulmonary exacerbation were enrolled. MEM plasma concentrations were determined by high-performance liquid chromatography. Six adult CF patients with a median age of 47 years were included in the study. MEM showed a high V_d (mean 45.98 L, standard deviation [SD] ± 34.45). A minimal PK/PD target of 40% $T >$ minimum inhibitory concentration (MIC) with respect to the MEM MIC of *P. aeruginosa* strains isolated from sputum during exacerbation was achieved in 5/6 patients (83%). MEM failed to achieve this target only in one patient, whose strain showed the highest MEM MIC in our cohort (8 mg/L). In all patients, MEM was well tolerated, and no adverse events were reported. In conclusion, high-dose, extended-infusion MEM during pulmonary exacerbation showed a high V_d in six adult CF patients with high median age, and was well tolerated.

Patient-Reported Outcome Measures for Symptom Perception During a Cystic Fibrosis Exacerbation.

Author(s): Schmid-Mohler, Gabriela; Caress, Ann-Louise; Spirig, Rebecca; Benden, Christian

Source: Respiratory care; Jan 2018

Publication Type(s): Journal Article

Abstract: **BACKGROUND** Symptom burden increases during pulmonary exacerbations of cystic fibrosis (CF), and patient-reported outcome measures (PROMs) are often used to evaluate symptoms as either primary or secondary outcomes. However, there is currently no guidance on the use of PROMs to assess symptom burden during pulmonary exacerbations. **METHODS** A systematic literature search was conducted to identify PROMs measuring symptom experience, management, or influencing factors, which were developed for CF patients and had been used at least once during pulmonary exacerbations. The PROMs included were assessed for relevance and psychometrics, according to the criteria of the United States FDA guideline and the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist. **RESULTS** Five PROMs were identified, all measuring symptom perception. The CF Respiratory Symptom Diary (CFRSD) and the Symptom Scoring System were developed to assess symptom severity during pulmonary exacerbations. Of the other 3, which also included symptom scores of 2 quality of life measures, one assessed symptom severity exclusively, and 2 measured symptom severity in addition to other dimensions (such as symptom distress). All 5 instruments measured respiratory symptoms. Other relevant symptoms, such as energy and emotions, were covered by 4 instruments; pain and

gastrointestinal symptoms were covered by 2 measures. All of the instruments demonstrated good internal consistency and sensitivity to change over a period up to 4 weeks. The symptom scores of the 2 quality of life measures with longer recall periods are not suitable for measuring assessed changes in a period of < 2 weeks. Criterion validity for gastrointestinal subscores has not been established. Discriminant validity was established in all of the instruments reviewed except for the Symptom Score System. CONCLUSIONS Of the current PROMs used during CF pulmonary exacerbations, only 2 have been developed for this purpose, and only the CFRSD fulfilled all FDA guideline criteria. To date, there is no instrument that assesses exacerbation-specific symptom distress.

Quantifying fluctuation in glucose levels to identify early changes in glucose homeostasis in cystic fibrosis.

Author(s): Brugha, Rossa; Wright, Marie; Nolan, Suzie; Bridges, Nicola; Carr, Siobhán B

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018

Publication Type(s): Journal Article

Abstract: BACKGROUND Cystic fibrosis related diabetes (CFRD) is associated with increased morbidity in CF. Variability in physiological systems is associated with dysfunctional homeostasis. We examined whether fluctuation in glucose is a marker of CFRD or "pre-diabetes". METHODS Using a machine learning approach, we compared glucose IQR to current diagnostic criteria in a review of continuous glucose monitoring data. RESULTS Analysis was performed on 248 studies from 142 children. Calculated IQR (cIQR) was increased between children with CFRD, normal glucose homeostasis and indeterminate status ($p < 0.0001$) and impaired glucose tolerance ($p < 0.05$, Kruskal-Wallis test). In subjects who developed CFRD ($n = 20$), cIQR increased between baseline and diagnosis (1.4 mmol/L versus 2.4 mmol/L, $p < 0.0001$, Wilcoxon test). Area under the curve for CFRD on the basis of cIQR was 0.865 ($p < 0.0001$). Neither episodes of hypoglycaemia nor cIQR at baseline predicted CFRD. CONCLUSIONS Glucose fluctuation on CGMS can be quantified by calculating the IQR. This information may improve early recognition of abnormal glucose homeostasis.

The use of an alternate side lying positioning strategy during inhalation therapy does not prolong nebulisation time in adults with Cystic Fibrosis: a randomised crossover trial.

Author(s): Dentice, Ruth L; Elkins, Mark R; Dwyer, Genevieve M; Bye, Peter T P

Source: BMC pulmonary medicine; Jan 2018; vol. 18 (no. 1); p. 3

Publication Type(s): Journal Article

Available at [BMC pulmonary medicine](#) - from EBSCO (MEDLINE Complete)

Abstract: BACKGROUND Inhalation of nebulised medications is performed in upright sitting to maximise lung volumes. The pattern of deposition is poor for inhaled medications in people with Cystic Fibrosis. The pattern tends to be non-uniform and typically the upper lobes receive a reduced dose compared to the rest of the lung. One strategy that has been proposed as having the potential to improve homogeneity of deposition is to adopt an alternate side lying position for the inhalation procedure. This study sought to determine whether, among adults with Cystic Fibrosis, there is any disadvantage to delivery time of nebulised medications with a strategy of alternate side lying, compared to upright sitting. METHODS A randomised crossover trial with concealed allocation, intention-to-treat analysis and blinded assessors was undertaken. The participants were 24 adults with stable Cystic Fibrosis. They inhaled 4 mL of normal saline via an LC Star™ nebuliser twice within 24 h. In random order, participants sat upright throughout nebulisation, or alternated between left and right side lying at each minute during the nebulisation period. The nebuliser was stopped and weighed each minute until the residual volume was reached. The primary outcome was the time required for 3.5 mL to be delivered. The secondary outcomes were: respiratory rate; ratio of the

volume delivered on right and left sides; and calculation of how long the periods in side lying can be extended without causing greater than 20% discrepancy in dose delivered in the two positions. **RESULT** The delivery time did not significantly differ between sitting and side lying (mean difference 0.58 min, 95% confidence interval (CI) -1.40 to 0.24). There was no significant correlation between delivery time, lung function or subject height (all $R^2 < 0.4$). Increasing side lying duration from 1 to 2 min did not significantly impact the dose delivered on each side. Turning each 3 min however, significantly worsened the disparity (mean ratio 1.32, 95% CI 1.24 to 1.40). **CONCLUSION** Side lying during inhalation therapy does not prolong nebulisation time. 2-min periods should provide an equal dose in the two side lying positions. **TRIAL REGISTRATION** Prospectively registered on 4 July 2011; ACTRN12611000672954 .

Posaconazole tablets in real life lung transplantation: impact on exposure, drug-drug interactions and drug management in lung transplanted patients, including cystic fibrosis.

Author(s): Launay, Manon; Roux, Antoine; Beaumont, Laurence; Douvry, Benoit; Lecuyer, Lucien

Source: Antimicrobial agents and chemotherapy; Jan 2018

Publication Type(s): Journal Article

Abstract: Appropriate exposure to Posaconazole (PSZ) was limited since the recent approval of the delayed release oral tablet formulation. Our goal was to determine the exposure obtained by using the standard dose of 300mgx1 in lung transplant patients (LT) including cystic fibrosis (CF) background. PSZ trough concentrations (C₀) were determined using LCMS assay. Indicative thresholds of interest were <0.7mg/L (prophylaxis) and 1-3mg/L (curative). Tacrolimus (TRL) and everolimus (ERL) C₀ measured during PSZ exposure were collected. Interaction with proton-pump inhibitors (PPI) was evaluated. We recorded 21 CFLT, 11 LT-not CF (NCFLT) and 27 non LT patients (NT) addressed to Pneumology department. Respectively for NCFLT vs CFLT vs NT: demographics were 59.2±8.4 vs 48.8±8.4 vs 63.7±16.6 kg ($p=0.001^*$), and C₀ PSZ exposure was 1.9±1.5 vs 1.1±0.8 vs 2.4±1.8mg/L ($p<0.00001^*$). More than 60% of the concentrations were in the therapeutic range. In CFLT patients, 1x300mg-PSZ tablet administration quickly achieved similar exposure than with 3 or 4 times a day PSZ OSF used for several months. TRL C₀/dose ratio (TRL C₀/D) 7.4±4.4mg/L with PSZ tablets vs 4.6±0.8 with PSZ oral solution ($p=0.034^*$). ERL C₀/D was similar with both formulations. PPI had no impact on PSZ concentration (1.49±1.07mg/L without PPI, vs. 1.33±1.17mg/L with PPI, $p=0.4134^*$). Despite high exposure, PSZ remained well tolerated (one diarrhea and one fatigue). PSZ tablets administration allows satisfactory exposure, even on CFLT patients, with lower posology. This once-a-day formulation was not impacted by PPI, extensively used in CF patients.

Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data.

Author(s): Keogh, Ruth H; Szczesniak, Rhonda; Taylor-Robinson, David; Bilton, Diana

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018

Publication Type(s): Journal Article

Abstract: **BACKGROUND** Cystic fibrosis (CF) is the most common inherited disease in Caucasians, affecting around 10,000 individuals in the UK today. Prognosis has improved considerably over recent decades with ongoing improvements in treatment and care. Providing up-to-date survival predictions is important for patients, clinicians and health services planning. **METHODS** Flexible parametric survival modelling of UK CF Registry data from 2011 to 2015, capturing 602 deaths in 10,428 individuals. Survival curves were estimated from birth; conditional on reaching older ages; and projected under different assumptions concerning future mortality trends, using baseline characteristics of sex, CFTR genotype (zero, one, two copies of F508del) and age at diagnosis. **FINDINGS** Male sex was associated with better survival, as was older age at diagnosis, but

only in F508del non-homozygotes. Survival did not differ by genotype among individuals diagnosed at birth. Median survival ages at birth in F508del homozygotes were 46years (males) and 41years (females), and similar in non-homozygotes diagnosed at birth. F508del heterozygotes diagnosed aged 5 had median survival ages of 57 (males) and 51 (females). Conditional on survival to 30, median survival age rises to 52 (males) and 49 (females) in homozygotes. Mortality rates decreased annually by 2% during 2006-2015. Future improvements at this rate suggest median survival ages for F508del homozygous babies of 65 (males) and 56 (females).

INTERPRETATION Over half of babies born today, and of individuals aged 30 and above today, can expect to survive into at least their fifth decade.

RESEARCH IN CONTEXT Evidence before this study We searched PubMed with terms "(cystic fibrosis survival) and (projection OR model OR registry OR United Kingdom OR UK)" to identify relevant studies on survival estimates for individuals with cystic fibrosis (CF). We also considered the most recent annual report from the UK Cystic Fibrosis Registry (Cystic Fibrosis Trust, 2016), a review by Buzzetti and colleagues (2009), the chapter on Epidemiology of Cystic Fibrosis by MacNeill (2016), the study of MacKenzie and colleagues (2014), and references therein. There have been many studies of factors associated with survival in CF; most have focused on identifying risk factors, and only a few have presented estimated survival curves, which are the focus of this work. The most recent study of survival in the UK is by Dodge and colleagues (2007), who used data obtained from CF clinics and the national death register, and gave an estimate of survival for babies born in 2003. We found no previous studies that have obtained detailed information on survival using UK Cystic Fibrosis Registry data. Jackson and colleagues obtained survival estimates for the US and Ireland using registry data (Jackson et al., 2011). MacKenzie and colleagues used US Cystic Fibrosis Foundation Patient Registry data from 2000 to 2010 to project survival for children born and diagnosed with CF in 2010, accounting for sex, genotype and age at diagnosis (MacKenzie et al., 2014). Previous studies on estimated survival in CF have become out of date or have not accounted for the full range of patient characteristics available at birth. Few have presented conditional survival estimates (Dodge et al., 2007). Added value of this study This is the first study to yield detailed survival statistics using the UK Cystic Fibrosis Registry, which is one of the largest national CF registries outside of the US and has almost complete coverage of the UK CF population. The primary goal was to leverage the long-term follow-up of the nearly complete UK CF population available in the Registry for the purposes of producing accurate, precise predictions in the modern era of CF care. Estimates are presented from birth and conditional on survival to older ages. These are the first conditional estimates in CF to also account for genotype, sex and age at diagnosis, which were each included in the modelling using a flexible approach. Projections are also provided under different scenarios based on downward trends in mortality rates. Our use of flexible parametric survival models is novel in this field, and our approach could be used to provide modern survival statistics for other chronic diseases and disorders. Implications of all the available evidence Our estimates of future survival in CF under a range of different scenarios are based on data on nearly all individuals living with the disease in the UK in recent times, reflective of a modern era of care, and are most appropriate for the families of babies being born in the present day with CF. Conditional estimates inform patients who have already reached an older age, and their clinicians. Over half of babies born today, and of individuals aged 30years and above alive today, can expect to survive into their fifth decade. Insights based on our survival projections can be used to inform future needs in CF health care provision.

A systematic review of the prevalence and impact of urinary incontinence in cystic fibrosis.

Author(s): Frayman, Katherine B; Kazmerski, Traci M; Sawyer, Susan M

Source: Respirology (Carlton, Vic.); Jan 2018; vol. 23 (no. 1); p. 46-54

Publication Type(s): Journal Article Review

Abstract: This systematic review synthesizes published articles investigating the prevalence, severity and impact of urinary incontinence (UI), a condition associated with cystic fibrosis (CF). References

were identified through searching Medline, Embase and PubMed using the medical subject headings 'cystic fibrosis' AND 'urinary incontinence'. Articles were included if UI prevalence was investigated as an outcome. Twelve studies met selection criteria. The prevalence of UI ranged from 5% to 76%. Age and gender contributed to this variability. When assessed, UI commonly limited airway clearance, exercise and/or spirometry, and had a variable impact on patients' lives. Worry and embarrassment were features for many; others were less affected. In CF, UI is common and can interfere with respiratory care and social well-being. The prevalence, characteristics and impact are poorly understood, which is made worse by inconsistent definitions across studies. Future research is needed to improve approaches to prevention, identification, management and education.

Combined lung-liver-pancreas transplantation in a recipient with cystic fibrosis.

Author(s): Barbas, A S; Dib, M J; Al-Adra, D P; Goldaracena, N; Sapisochin, G; Waddell, T K

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. e1

Publication Type(s): Journal Article

Abstract:Cystic fibrosis (CF) affects multiple organs including the lung, liver, and pancreas. Lung transplant, liver transplant, and combined lung-liver transplant have become well-established therapies for CF patients with end-stage organ failure. Thus far, however, there has been limited experience with pancreas transplantation in CF. In this report, we detail the clinical history, transplant procedure, and post-operative recovery of a patient who underwent combined lung-liver-pancreas transplant for advanced CF.

Multiple prevalent fractures in relation to macroscopic bone architecture in patients with cystic fibrosis.

Author(s): Stahl, Mirjam; Holfelder, Christian; Kneppo, Carolin; Kieser, Meinhard; Kasperk, Christian

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 114-120

Publication Type(s): Journal Article

Abstract:BACKGROUNDThe relative risk for bone fractures in patients with cystic fibrosis (CF) and its relationship to macroscopic bone architecture assessed by pQCT and DXA are incompletely defined.METHODSIn a cross-sectional study of 43 CF patients (age, 17.8±6.2years), rate and location of fractures, bone mass, density, geometry, and strength of the radius as well as forearm muscle size were investigated.RESULTSThe fracture rate in CF was 9.2-fold higher compared to an age-matched German control population. The probability of remaining free of any fracture in CF patients at 25years was reduced to 39.8% compared to 84.6% in controls (P<0.001). Assessment of macroscopic bone architecture by DXA and pQCT allowed the differentiation of patients with multiple prevalent fractures with a high sensitivity (up to 100%) and specificity (up to 94.3%).CONCLUSIONSBone densitometry is a useful tool for noninvasive assessment of fracture risk in CF patients.

Complications of long and intermediate term venous catheters in cystic fibrosis patients: A multicenter study.

Author(s): May, Teresa L; Gifford, Alex H; Lahiri, Thomas; Black, Adam; Trang, Janet

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 96-104

Publication Type(s): Journal Article

Abstract:BACKGROUND Totally implantable venous access devices (TIVADs) or peripherally inserted central venous catheters (PICCs) are commonly used in the care of patients with cystic fibrosis (CF), but they are associated with various complications, including thrombosis, infection, and insertion site symptoms. METHODS We conducted a retrospective review of PICC and TIVAD use in adults and children with CF over an 8-year period at 3 accredited care centers. Patient attributes included CFTR genotype, comorbidities, lung function, body mass index, use of anticoagulation, and respiratory tract microbiology. Catheter data included line type, caliber, and lumen number. We assessed practice variation by surveying physicians. RESULTS In a population of 592 CF patients, 851 PICC and 61 TIVADs were placed between January 1, 2003 and July 1, 2011. Larger catheter caliber and increased lumen number were risk factors for PICC complications in adults. Patient-related risk factors for PICC complications included poor nutritional status, infection with *Burkholderia cepacia* spp., and having ≥ 5 lines inserted during the study period. The probability of a PICC complication varied across centers (2.6% to 14.1%, $p=0.001$) and remained significant after adjustment for patient- and line-related risk factors. The median complication-free survival of TIVADs, however, did not vary significantly by center ($p=0.85$). CONCLUSION This is the first longitudinal, multicenter assessment of complication rates for PICCs and TIVADs in a large cohort of adults and children with CF. Specific patient- and catheter-related characteristics were associated with increased risk of complications. Center effects on complication rates were observed for PICCs.

Is there an association between back pain and stress incontinence in adults with cystic fibrosis? A retrospective cross-sectional study.

Author(s): Ashbrook, Jane E; Shacklady, Carol; Johnson, Sue; Yeowell, Gillian; Goodwin, Peter Charles

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 78-82

Publication Type(s): Journal Article

Abstract:BACKGROUND Back pain and stress urinary incontinence (SUI) are common in adults with cystic fibrosis (CF). This study aimed to establish whether there is an association between back pain, lung function and stress urinary incontinence and its relative risk. METHOD This was a cross-sectional, retrospective analysis of the Manchester Musculoskeletal Screening Tool (MMST) data. It includes pain, (Short Form McGill Pain Questionnaire (SF-MPQ and VAS)) and International Consultation on Incontinence Short Form (ICIQ-UI-SF) measures. Associations were tested using Spearman's rank correlation coefficient. Relative risk of developing symptoms was calculated the sig level was $p=0.05$. RESULTS ICIQ-UI-SF was associated with back pain (SF-MPQ) ($Rho=0.32$, $p<0.001$) and pain (VAS) ($Rho=0.23$, $p<0.01$). RR of developing SUI with back pain was 2; RR of developing back pain with SUI was 1.3. CONCLUSION An association is indicated between back pain (SF-MPQ and VAS), and SUI in adults with CF. This information is important when developing management strategies in the CF population.

The relationship between sweat chloride levels and mortality in cystic fibrosis varies by individual genotype.

Author(s): Espel, Julia C; Palac, Hannah L; Bharat, Ankit; Cullina, Joanne; Prickett, Michelle;

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 34-42

Publication Type(s): Journal Article

Abstract:RATIONALE The association between CFTR genotype, sweat chloride and mortality has been inconsistent, but no previous analyses have examined the association stratified by individual genotypes. OBJECTIVE To evaluate the genotype-specific association between sweat chloride and mortality. METHOD The CFF Patient Registry was assessed and included all patients in the registry

between 1996 and 2012 with at least one F508del allele. We excluded patients without a documented genotype or plausible sweat chloride level. The primary outcome was time to mortality during the observation period. We examined 15 genotypes using the three most prevalent alleles in each of 5 classes. We compared subgroups of sweat chloride using Kaplan-Meier curves, log-rank tests, and multivariable Cox PH models. The overall predictive value of sweat chloride on mortality was assessed using area under the receiver operating characteristic curves. MEASUREMENTS AND MAIN RESULTS 18,893 subjects met inclusion criteria. Sweat chloride distribution was similar across genotypes in patients with class 1 mutations, but was significantly different across genotypes in mutation classes 2-5. The R117H/F508del genotype patients demonstrated an association between sweat chloride and mortality (HR: 1.32 for every 10mmol/L increase in sweat chloride [95% CI 1.12-1.54]). There were also significant associations in patients with F508del/F508del, I507del/F508del, G551D/F508del and 2789+5G→A/F508del genotypes, though the clinical relevance for these genotypes is unclear. CONCLUSION There is significant variability in sweat chloride distribution across CFTR class 2-5 genotypes. The relationship between sweat chloride and mortality varies by genotype with a relatively strong relationship in R117H/F508del patients.

Hospitalized patients with cystic fibrosis: National profile estimates and comorbidity predictors

Author(s): Rampa S.; Nalliah R.; Allareddy V.

Source: Critical Care Medicine; Jan 2018; vol. 46 ; p. 535

Publication Type(s): Conference Abstract

Available at [Critical Care Medicine](#) - from Ovid (Journals @ Ovid)

Abstract: Learning Objectives: Current national estimates of Cystic fibrosis (CF) related hospitalizations and associated comorbidity in this cohort are unclear. We sought to examine the profile of hospitalized patients with CF and assessed patient predictors of chronic co-morbid condition (CCMC) burden in this cohort. We hypothesized that a mix of patient level factors would be associated with a higher comorbid burden. Methods: We performed a retrospective analysis of the Nationwide Inpatient Sample for the years 2012 to 2014. All hospitalized patients with either a primary or secondary diagnosis of CF were selected. 29 different CCMCs were examined and comorbid burden severity score was computed by summing the occurrence of each CCMC. This was the primary outcome of interest. A mix of patient level factors were the independent variables. The association between patient level factors and comorbid burden was examined by a multivariable linear regression model. Results: During the study period, a total of 90,725 patients who were hospitalized had CF. 71.7% had pulmonary manifestations (exacerbations), 24.6% were without mention of meconium ileus, 23% had gastrointestinal manifestations, and 14.7% presented with other manifestations. 33.4% were aged < 18 yrs, 54.4% were 18 to 39yrs, 10.7% were 40 to 64yrs, and 1.5% were > 65yrs. Females accounted for 54.2%. Whites (84.8%) were the predominating race followed by Hispanics (8.1%), Blacks (4.3%), and other races (< 3%). 1220 patients (1.3%) died in hospitals. Close to 80% had at least one CCMC. The mean comorbid burden score was 1.9. The most frequently occurring conditions were Diabetes (31.1%), chronic pulmonary diseases (31%), weight loss (27.3%), fluid/electrolyte disorders (16.2%), depression (15.7%), and deficiency anemias (13.3%). CF with pulmonary manifestations (Regression Parameter Estimate [RPE]=0.1543, $p < 0.001$), increasing age (RPE=0.0418, $p < 0.001$), females (RPE=0.1251, $p < 0.0001$), those with Medicare (RPE=0.5863, $p < 0.0001$) or Medicaid (RPE=0.2677, $p < 0.0001$) insurance were associated with significantly higher comorbid burden scores (Positive PRE implies higher while negative implies lower). Hispanics had lower comorbid burden scores (RPE=-0.1328, $p = 0.007$) compared to Whites. Conclusions: In this large epidemiological study Cystic fibrosis related hospitalizations are considerable. Several patient factors associated with higher comorbid burden are identified. Nearly 16% of hospitalized CF patients had depression. Further strategies are required to optimize care in CF patients.

Is there a role for inhaled anti-inflammatory drugs in cystic fibrosis treatment?

Author(s): Sheikh Z.; Ong H.X.; Pozzoli M.; Young P.M.; Traini D.

Source: Expert Opinion on Orphan Drugs; Jan 2018; vol. 6 (no. 1); p. 69-84

Publication Type(s): Review

Abstract:Introduction: Cystic fibrosis (CF) is a congenital life-limiting, orphan disease affecting 1/2500-1/3000 people worldwide with the greatest prevalence in Europe, North America and Australia. The primary reason underpinning the cause of morbidity and mortality of CF patients is associated with recurrent pulmonary inflammation and infection that leads to chronic, progressive lung deterioration and ultimately death of CF patients. Areas covered: This review aims to explore the potential role for inhaled anti-inflammatory drugs as a more successful treatment option for CF, in comparison with current oral delivery. Specifically, the focus is on ibuprofen, the only nonsteroidal anti-inflammatory drug approved for chronic use in CF. The need for inhalation therapy has also been highlighted with an insight on the reasons and challenges associated with developing an inhalation therapy of nonsteroidal anti-inflammatory drugs (NSAIDs). Expert opinion: There is a fundamental need to direct research towards development of anti-inflammatory drugs to control inflammation rather than just targeting infection. Development of an inhalable preparation of ibuprofen alone or in combination with an antibiotic holds the potential to be the most effective treatment option among the existing array of therapies available for CF. Copyright © 2017 Informa UK Limited, trading as Taylor & Francis Group.

Use of continuous infusion ceftolozane-tazobactam with therapeutic drug monitoring in a patient with cystic fibrosis: A case report

Author(s): Davis S.E.; Ham J.; Hucks J.; Gould A.; Foster R.; Nicolau D.; Bookstaver P.B.

Source: Pharmacotherapy; 2017; vol. 37 (no. 12)

Publication Type(s): Conference Abstract

Abstract:INTRODUCTION: Modified dosing strategies are utilized to manage multi-drug resistant (R) pathogens and augmented drug clearance in cystic fibrosis (CF). We describe the use of continuous infusion (CI) ceftolozane-tazobactam (C/T) with therapeutic drug monitoring (TDM) in a CF patient with R *Pseudomonas aeruginosa* and *Escherichia coli*. CASE: A 30-year-old woman with a history of CF was admitted for pulmonary exacerbation. Past medical history revealed a mild penicillin allergy and multiple CF exacerbations in the past year with positive sputum cultures for extended-spectrum beta-lactamase (ESBL) *E. coli*, *R. P. aeruginosa*, and methicillin-susceptible *Staphylococcus aureus* (MSSA). Empiric antibiotic therapy included inhaled amikacin, IV ceftazidime-avibactam, and IV vancomycin. Sputum cultures were positive for *R. P. aeruginosa* (mucoid strain), ESBL + *E. coli* and MSSA. Susceptibility of C/T was determined by E-test (*E. coli* MIC 0.25 µg/mL; *P. aeruginosa* MIC 0.19 µg/mL). On hospital day 7, the antimicrobial stewardship team recommended discontinuation of cef-tazidime-avibactam and initiation of C/T 3 g loading dose followed by CI (6 g/500 mL over 24 h) for 10 additional days to transition to a favorable outpatient regimen. C/T serum TDM is detailed in Table 1. The patient experienced clinical resolution and improvement in pulmonary function tests. Table 1. HDLC assay Ceftolozane and Tazobactam serum concentrations: DISCUSSION: Limited guidance exists for C/T dosing in CF patients, but evolving data suggest 3 g every 8 h via intermittent infusion in deep-seated infections. The patient clinically improved on 6 g CI C/T and serum concentrations were well above the MIC, despite anticipated augmented renal clearance. CONCLUSION: These data suggest that sufficient C/T concentrations may be achieved in CF patients when delivered via CI.

Cost-Effectiveness of Screening Individuals With Cystic Fibrosis for Colorectal Cancer.

Author(s): Gini, Andrea; Zauber, Ann G; Cenin, Dayna R; Omidvari, Amir-Houshang; Hempstead, Sarah E; Fink, Aliza K; Lowenfels, Albert B; Lansdorp-Vogelaar, Iris

Source: Gastroenterology; Dec 2017

Publication Type(s): Journal Article

Abstract:BACKGROUND & AIMS Individuals with cystic fibrosis are at increased risk of colorectal cancer (CRC) compared to the general population, and risk is higher among those who received an organ transplant. We performed a cost-effectiveness analysis to determine optimal CRC screening strategies for patients with cystic fibrosis. METHODS We adjusted the existing Microsimulation Screening Analysis-Colon microsimulation model to reflect increased CRC risk and lower life expectancy in patients with cystic fibrosis. Modeling was performed separately for individuals who never received an organ transplant and patients who had received an organ transplant. We modeled 76 colonoscopy screening strategies that varied the age range and screening interval. The optimal screening strategy was determined based on a willingness to pay threshold of \$100,000 per life-year gained. Sensitivity and supplementary analyses were performed, including fecal immunochemical test (FIT) as an alternative test, earlier ages of transplantation, and increased rates of colonoscopy complications, to assess whether optimal screening strategies would change. RESULTS Colonoscopy every 5 years, starting at age 40 years, was the optimal colonoscopy strategy for patients with cystic fibrosis who never received an organ transplant; this strategy prevented 79% of deaths from CRC. Among patients with cystic fibrosis who had received an organ transplant, optimal colonoscopy screening should start at an age of 30 or 35 years, depending on the patient's age at time of transplantation. Annual FIT screening was predicted to be cost-effective for patients with cystic fibrosis. However, the level of accuracy of the FIT in population is not clear. CONCLUSIONS Using a Microsimulation Screening Analysis-Colon microsimulation model, we found screening of patients with cystic fibrosis for CRC to be cost-effective. Due to the higher risk in these patients for CRC, screening should start at an earlier age with a shorter screening interval. The findings of this study (especially those on FIT screening) may be limited by restricted evidence available for patients with cystic fibrosis.

Hypoglycaemia in cystic fibrosis: An analysis of a single centre adult cystic fibrosis clinic.

Author(s): Armaghanian, Natasha; Markovic, Tania P; Brand-Miller, Jennie C; Bye, Peter T P

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Dec 2017

Publication Type(s): Journal Article

Abstract:BACKGROUND Hypoglycaemia in cystic fibrosis (CF) is known to occur during oral glucose tolerance tests (OGTT) and continuous glucose monitoring, however demographic, clinical and mechanistic data are limited. The aims of this study were to review patient electronic medical records (EMR) in order to 1) describe patient characteristics of a university teaching hospital CF clinic, 2) determine the prevalence of hypoglycaemia on OGTT and explore associations with demographic and clinical characteristics, and 3) explore patient reported symptoms suggestive of hypoglycaemia documented in the EMR. METHODS Adults who attended the RPA CF clinic between January 2009 to April 2016 were included in the study. The prevalence of hypoglycaemia on OGTT was determined and clinical and demographic data were compared to age, sex and glucose tolerance matched controls. Reported symptoms suggestive of hypoglycaemia documented in EMR were qualitatively explored. RESULTS Hypoglycaemia on OGTT was prevalent in 25 (3 fasting and 22 reactive) of 169 patients who had an OGTT. They were heavier, less likely to have pancreatic insufficiency and had a lower insulin response at 2-h. Another 14 patients reported symptoms suggestive of hypoglycaemia in their EMR. No patient appropriately suppressed insulin at 2-h on OGTT. CONCLUSIONS This study identified two potentially different presentations of hypoglycaemia occur in different clinic sub-populations. Knowledge gaps in the aetiology and triggers of hypoglycaemia remain.

Relation of Ultrasound Findings and Abdominal Symptoms obtained with the CFAbd-Score in Cystic Fibrosis Patients.

Author(s): Tabori, Harold; Jaudszus, Anke; Arnold, Christin; Mentzel, Hans-Joachim; Lorenz, Michael

Source: Scientific reports; Dec 2017; vol. 7 (no. 1); p. 17465

Publication Type(s): Journal Article

Available at [Scientific reports](#) - from nih.gov

Abstract: Abdominal symptoms are a hallmark of Cystic fibrosis (CF). Yet, their association with morphological abnormalities of different abdominal organs is still poorly understood. Aim was therefore to relate these symptoms, assessed with a questionnaire, to findings in abdominal ultrasound (US). In 114 CF patients of all ages, findings in US considering seventeen specific parameters were related to abdominal symptoms compiled with our novel CF-specific 26-modal symptom score (CFAbd-Score). US abnormalities were detected in 95% of the patients. Most frequent findings were pancreatic lipomatosis (88%), liver steatosis (37%), hepatomegaly (31%), and thickened bowel walls (23%). Highest burden of GI-symptoms was clearly associated with pancreatic lipomatosis ($p = 0.036$). In detail, patients revealing this pathology reported higher rates of abdominal pain ($p = 0.018$), flatulence ($p = 0.006$), heartburn ($p = 0.04$), and reflux of stomach content ($p = 0.006$). Patients with pancreatic sufficiency had less US-findings ($p = 0.033$), which in turn was associated with lower rates of abdominal symptoms. The majority of them were carriers of class IV-VI or G551D mutations. Our approach gives new insights regarding the underestimated multi-organ abdominal involvement in CF. The new score can be of high interest e.g. as a complementary tool to assess the gastrointestinal effects of promising novel CF therapeutics.

Novel magnetic resonance technique for functional imaging of cystic fibrosis lung disease.

Author(s): Nyilas, Sylvia; Bauman, Grzegorz; Sommer, Gregor; Stranzinger, Enno; Pusterla, Orso

Source: The European respiratory journal; Dec 2017; vol. 50 (no. 6)

Publication Type(s): Journal Article

Abstract: Lung function tests are commonly used to monitor lung disease in cystic fibrosis (CF). While practical, they cannot locate the exact origin of functional impairment. Contemporary magnetic resonance imaging (MRI) techniques provide information on the location of disease but the need for contrast agents constrains their repeated application. We examined the correlation between functional MRI, performed without administration of contrast agent, and lung clearance index (LCI) from nitrogen multiple-breath washout (N₂-MBW). 40 children with CF (median (range) age 12.0 (6-18) years) and 12 healthy age-matched controls underwent functional and structural MRI and lung function tests on the same day. Functional MRI provided semiquantitative measures of perfusion (RQ) and ventilation (RFV) impairment as percentages of affected lung volume. Morphological MRI was evaluated using CF-specific scores. LCI measured global ventilation inhomogeneity. MRI detected functional impairment in CF: RFV 19-38% and RQ 16-35%. RFV and RQ correlated strongly with LCI ($r=0.76$, $p<0.0001$ and $r=0.85$, $p<0.0001$, respectively), as did total morphology score ($r=0.81$, $p<0.0001$). All indices differed significantly between patients with CF and healthy controls ($p<0.001$). Noninvasive functional MRI is a promising method to detect and visualise perfusion and ventilation impairment in CF without the need for contrast agents.

Bone mineral density is related to lung function outcomes in young people with cystic fibrosis-A retrospective study.

Author(s): Smith, Nathan; Lim, Angelina; Yap, Matthew; King, Louise; James, Simon; Jones, Alicia

Source: Pediatric pulmonology; Dec 2017; vol. 52 (no. 12); p. 1558-1564

Publication Type(s): Journal Article

Abstract:INTRODUCTIONImprovements in the medical management of cystic fibrosis (CF) in recent years have resulted in increased prevalence of long-term sequelae of the condition, such as low bone mineral density (BMD) and hence an increased risk of fractures in later life. Aim To explore the interaction between BMD and lung function, nutrition, and genotype.METHODSThis study was a retrospective audit of 202 children with CF from August 2000 to January 2016 to investigate associations between BMD Z-scores with clinical status, nutrition, and genetics using dual-energy absorptiometry X-ray data from the Royal Children's Hospital Melbourne, Australia.RESULTSSeverity of both lung disease ($P < 0.0001$) and nutritional status ($P < 0.05$) was found to be strongly associated with BMD Z-scores.CONCLUSIONSThis is the biggest study to date to provide further evidence that the severity of pulmonary disease is related to BMD in CF patients and therefore screening guidelines for bone health in children with CF should target individuals with the poorest clinical status.

An update on new and emerging therapies for cystic fibrosis.

Author(s): Hudock, Kristin M; Clancy, John Paul

Source: Expert opinion on emerging drugs; Dec 2017; vol. 22 (no. 4); p. 331-346

Publication Type(s): Journal Article

Abstract:INTRODUCTIONCystic fibrosis (CF) is a genetic disorder that results in a multi-organ disease with progressive respiratory decline that ultimately leads to premature death. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for the CFTR anion channel. Established CF treatments target downstream manifestations of the primary genetic defect, including pulmonary and nutritional interventions. Areas covered: CFTR modulators are novel therapies that improve the function of CFTR, and have been approved in the past five years to mitigate the effects of several CF-disease causing mutations. This review summarizes currently approved CFTR modulators and discusses emerging modulator therapies in phase II and III clinical trials described on clinical trials.gov as of April, 2017. Results of relevant trials reported in peer-reviewed journals in Pubmed, scientific conference abstracts and sponsor press releases available as of November, 2017 are included. Expert opinion: The current scope of CF therapeutic development is robust and CFTR modulators have demonstrated significant benefit to patients with specific CFTR mutations. We anticipate that in the future healthcare providers will be faced with a different treatment paradigm, initiating CFTR-directed therapies well before the onset of progressive lung disease.

A national study of non-invasive ventilation and clinical outcomes in cystic fibrosis

Author(s): Archangelidi O.; Cullinan P.; Simmonds N.J.; Carr S.B.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract:Introduction/Objectives Non-invasive ventilation (NIV) is often used as a 'bridge' to transplantation, for symptom control or as an adjunct to physiotherapy. Whether or not NIV is being appropriately used in UK patients with CF, successfully targeting those who will benefit most, is unknown; nor is there information on the life expectancy of those who start on NIV. Methods The present study is part of the CF-Epidemiological Network (CF-EpiNet project) and uses data from the UK Cystic Fibrosis Registry to describe the patterns of NIV use by patients in the UK. We examined the records of 11 120 patients and assembled a longitudinal, retrospective cohort from those seen between 2007 and 2015. We used Cox proportional hazard models to assess the survival of patients on NIV. Results 1077 patients (715 adults and 362 children<16 years) had reported use of NIV recorded at least once. Usage increased after 2012 (figure 1). At the first recorded use of NIV the

median (IQR) age was 21 years (14, 28), BMI 18.4 kg/m² (16.8, 22.7), 49.2% were male, 90.3% on PERT, 75.1% growing *Pseudomonas*, 54.6% homozygous F508del; the mean FVCpp was 64.5% and FEV1 pp 47.2%. At this time 68.8% of patients had a FEV1 pp <60%; 52% were <40%, while in adults this percentage reached 61%. In children there was a higher proportion starting treatment with better lung function ie $\geq 60\%$ (33.8%). The median survival of patients who start NIV is 3.47 years. The hazard ratio for NIV use was 3.90 (95% CI: 3.06-4.96). Conclusions Not surprisingly, patients start NIV when their lung function is significantly impaired. Yet, increased proportions of people with FEV1 pp $\geq 40\%$ on NIV were also identified. The higher lung function at the start of NIV for children may reflect that it is used for purposes other than a bridge to transplant in this group; the registry only collects a yes/no variable for NIV use and not the reason for use. Survival after initiation of NIV is poor; this is likely reflect that NIV is a marker of disease severity but further analysis will be needed to explore this.

Diabetes and pseudomonas, a terrible combination? examining the UK cystic fibrosis registry for a sex difference in outcomes (2008-2013)

Author(s): Hippolyte S.S.; Griesenbach U.; Simmonds N.J.; Bilton D.; Keogh R.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract: Introduction FEV1 and BMI are well-validated predictors of disease severity and outcome in cystic fibrosis (CF), however, the impact of sex remains debated. The UK-CF Registry features demographic and clinical information on >99% of the UK-CF population (~10 000 individuals). Data were used to investigate whether there was a sex difference in change in FEV1 and BMI between 2008-2013, and if this difference could be explained by chronic *Pseudomonas aeruginosa* (cPsA) infection or CF-related diabetes (CFRD). Methods Longitudinal analyses (2008-2013) compared male/ female age at cPsA acquisition as well as FEV1 and BMI differences between individuals with cPsA infection. Regression analysis examined for a difference in change in BMI and FEV1 between the sexes depending on CFRD and cPsA status, adjusting for age, genotype and ethnicity. A survival analysis completed the sex comparison. Results Females were significantly younger than males at the time of new cPsA infection (20.9 vs 22.4 years; $p < 0.001$) with a lower mean BMI with new cPsA (21.3 vs 22.2 years; $p < 0.001$) but no difference in FEV1 at time of new cPsA. Females had greater decline in FEV1 than males (8.2% vs 7.0% over 5 years; $p < 0.001$), this was even greater in individuals with cPsA (10.2% vs 8.2% in males: $p = 0.002$). Females had less of an increase in BMI than males (0.2 vs 0.6 in males; $p < 0.001$), this difference was only seen in individuals with cPsA. Sex differences in change in BMI were also seen in the CFRD population. Overall, median survival for females was significantly less than males (39.5 vs 44.2 years, $p < 0.001$). Females with CFRD had the worst survival overall. Males without cPsA had the greatest median survival while males with cPsA had similar survival to females irrespective of their cPsA status. Conclusions Females had earlier cPsA infection and lower BMI. cPsA was associated with greater decline in FEV1 and BMI in females than males, with worse survival in females with cPsA that was not seen in males with cPsA. CFRD was associated with less BMI increase in females, with females with CFRD having worse survival overall. These data suggest a measurable sex difference in clinically relevant CF outcomes in the UK population. (Figure Presented).

An open-label extension (EXT) study of lumacaftor/ivacaftor (LUM/IVA) therapy in patients aged 6 to 11 years with cystic fibrosis (CF) homozygous for F508del-CFTR

Author(s): Chilvers M.; Tian S.; Marigowda G.; Bsharat M.; Hug C.; Solomon M.; Black P.; Rosenfeld M.; Sawicki G.; Hoppe J.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals

Abstract: Objective Lumacaftor/Ivacaftor (LUM/IVA) was well tolerated and had beneficial effects on lung function, sweat chloride (SwCl), and body mass index (BMI) in a 24 week, open-label study (VX15-809-011B [011B]) in patients aged 6 to 11 years with cystic fibrosis (CF) homozygous for F508del. We report 36 weeks of additional safety and efficacy data in an ongoing 96 week extension (EXT) study (VX15-809-110; NCT02544451). Methods Eligible patients from 011B received LUM 200 mg/IVA 250 mg every 12 hours (q12h; 6-11 years) or LUM 400 mg/IVA 250 mg q12h (≥ 12 years). Primary endpoint was safety. Secondary endpoints included changes in SwCl and lung clearance index based on lung volume turnover required to reach 2.5% of starting N₂ concentration (LCI_{2.5}) through week 24, and BMI and percent predicted FEV₁ (ppFEV₁) through week 36. Results Of the 49 enrolled patients (mean age [SD], 9.2 [1.48] years), 47 completed 36 weeks of the EXT study. Adverse events (AEs) were reported in 91.8% of patients (34.7% mild; 49.0% moderate). Common AEs (cough, n=18; infective pulmonary exacerbation, n=18) were consistent with expected CF manifestations. Eight (16.3%) patients had serious AEs. Four (8.2%) patients had ≥ 1 respiratory AE (2 wheezing; 1 bronchial hyperreactivity; 1 dyspnea; 1 respiration abnormal). Six (12.2%) patients had elevated alanine aminotransferase or aspartate aminotransferase (≥ 3 to 5x upper limit of normal [ULN], n=3; ≥ 5 to 8xULN, n=1; $\geq 8x$ ULN, n=2). No drug discontinuations were due to AEs. Changes from 011B baseline (BL) in ppFEV₁ and SwCl were similar to those at 011B week 24 (Table). BMI continued to improve. LCI_{2.5} improvements were stable through EXT week 4 (n=18); values at EXT week 24 in a reduced sample size (n=12) were similar to those at 011B BL. Conclusion LUM/IVA was well tolerated for up to 60 weeks in patients aged 6 to 11 years, with no new safety concerns compared with previous LUM/IVA studies conducted in this patient population. LUM/IVA was associated with improved BMI and maintenance of lung function. Please refer to page A257 for declarations of interest in relation to abstract S96. (Table Presented).

Microbiological

Omaliuzumab treatment for allergic bronchopulmonary aspergillosis in young patients with cystic fibrosis.

Author(s): Perisson, Caroline; Destruys, Leila; Grenet, Dominique; Bassinet, Laurence

Source: Respiratory medicine; Dec 2017; vol. 133 ; p. 12-15

Publication Type(s): Journal Article

Abstract: BACKGROUND Allergic bronchopulmonary aspergillosis (ABPA) is a severe lung disease complication caused by an *Aspergillus fumigatus*-induced hypersensitivity that affects 2-15% of patients with cystic fibrosis (CF). The mainstay treatment consists of a combination of corticosteroids and antifungals. However, repeated or long-term corticosteroid therapies can lead to serious side effects. The monoclonal anti-IgE antibody, omalizumab, has demonstrated its efficacy in allergic asthma. As ABPA results from a hypersensitivity to a specific allergen, omalizumab might benefit CF patients with ABPA. Therefore, we conducted a retrospective study to investigate the effects of omalizumab on ABPA in CF patients. METHODS We retrospectively analyzed the clinical records of young patients with CF treated with omalizumab for an ABPA in several French CF centers. The clinical data were collected 3 months before the start of omalizumab treatment, at initiation, and every 3 months up to 12 following initiation. These data comprised clinical, biological, nutritional, and functional parameters. RESULT SEIGHTEEN patients were included (mean age: 17.1 \pm 5.2 yrs). Under omalizumab was observed a stabilization of the lung function decline associated with a significant decrease in the corticosteroid daily dose ($p = 0.0007$) and an improvement in the nutritional status ($p = 0.01$). No serious side effect of omalizumab was reported. CONCLUSION This

study suggests that omalizumab might be an interesting therapeutic strategy in ABPA, associated with less side effects compared to long-term corticosteroids. Further randomized-controlled trials are needed to ascertain the efficacy of omalizumab in CF patients with ABPA.

Clinical outcomes of aspergillus disease phenotypes in adult cystic fibrosis patients

Author(s): Collier L.J.; Bright-Thomas R.J.; Jones A.M.; Baxter C.; Richardson M.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract: Objectives Aspergillus disease in cystic fibrosis (CF) patients has been proposed to encompass 4 classes: Class 1; No disease, Class 2; Allergic Bronchopulmonary Aspergillosis (ABPA), Class 3; Aspergillus sensitised, Class 4; Aspergillus Bronchitis.¹ The clinical consequence of non-ABPA Aspergillus disease in CF is not fully understood. We evaluated the survival of patients with different classes of Aspergillus disease who were diagnosed as part of Baxter's work between 2008-2011 in order to determine the clinical consequences of the different phenotypes of disease. Methods A retrospective case note analysis was undertaken for all 129 patients from the Baxter et al. patient cohort. Survival outcomes were documented for all patients, and baseline demographics including age, gender, FEV1, BMI and co-pathogens were collected. Any patients who received double lung transplantation or who moved away from the unit during this time were identified. The best FEV1 for each year of follow up, FEV1 closest to annual consent date, and BMI were collected for each year of follow in every patient until the current day, or date of death, transplant, or move away. Data was tested for normality and between group comparisons were calculated with one-way anova. Survival was assessed with Kaplan Meier and re-analysed with Cox Regression to adjust for other prognostic factors. Results There was no statistical significance in survival rates between the 4 classes of Aspergillus disease (P value 0.521). The sole predictor of survival was baseline FEV1% predicted at time of diagnosis (P value < 0.001). Conclusions There was no statistically significant difference in survival for CF patients with Aspergillus disease over 6-8 years follow up. Further work is being undertaken to continue monitoring and reclassify disease phenotype in this patient cohort.

Activities of Dual Combinations of Antibiotics Against Multidrug-Resistant Nontuberculous Mycobacteria Recovered from Patients with Cystic Fibrosis.

Author(s): Schwartz, Matthew; Fisher, Stefanie; Story-Roller, Elizabeth; Lamichhane, Gyanu;

Source: Microbial drug resistance (Larchmont, N.Y.); Jan 2018

Publication Type(s): Journal Article

Abstract: Patients with cystic fibrosis (CF) are at risk for recurrent pulmonary infections due to increased viscosity of airway secretions, leading to persistent colonization with pathogenic bacteria, including nontuberculous mycobacteria (NTM). Extensive antibiotic use for treatment of infections has led to increasing antimicrobial resistance, which is a significant barrier to the treatment of NTMs. We examined the in vitro activity of several antibiotics against a selection of the most drug-resistant clinical isolates of *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium avium* complex recovered from CF patients at our institution, as well as paired combinations of antibiotics against a subset of *M. abscessus* strains, to determine whether they exhibit synergy in inhibiting bacterial growth. Most isolates displayed resistance to at least six of the nine antibiotics tested for which phenotypic interpretation is available, and elevated minimum inhibitory concentrations (MICs) were observed for many of the other drugs. The major exception was clofazimine, which had relatively low MICs for most isolates across all species. When synergy testing was performed by using paired combinations of drugs, clofazimine and clarithromycin exhibited 100% synergy for all combinations tested, as did amikacin, with the exception of one isolate. These results suggest that

synergistic antibiotic combinations are capable of overcoming drug resistance in vitro, and laboratories might consider implementation of synergy testing in multidrug-resistant (MDR)-NTM organisms to guide treatment decisions in the setting of extensive antimicrobial resistance.

Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR.

Author(s): Donaldson, Scott H; Pilewski, Joseph M; Griese, Matthias; Cooke, Jon

Source: American journal of respiratory and critical care medicine; Jan 2018; vol. 197 (no. 2); p. 214-224

Publication Type(s): Journal Article

Available at [American journal of respiratory and critical care medicine](#) - from EBSCO (MEDLINE Complete)

Abstract: RATIONALE Tezacaftor (formerly VX-661) is an investigational small molecule that improves processing and trafficking of the cystic fibrosis transmembrane conductance regulator (CFTR) in vitro, and improves CFTR function alone and in combination with ivacaftor. OBJECTIVE To evaluate the safety and efficacy of tezacaftor monotherapy and of tezacaftor/ivacaftor combination therapy in subjects with cystic fibrosis homozygous for F508del or compound heterozygous for F508del and G551D. METHOD This was a randomized, placebo-controlled, double-blind, multicenter, phase 2 study (NCT01531673). Subjects homozygous for F508del received tezacaftor (10 to 150 mg) every day alone or in combination with ivacaftor (150 mg every 12 h) in a dose escalation phase, as well as in a dosage regimen testing phase. Subjects compound heterozygous for F508del and G551D, taking physician-prescribed ivacaftor, received tezacaftor (100 mg every day). MEASUREMENTS AND MAIN RESULTS Primary endpoints were safety through Day 56 and change in sweat chloride from baseline through Day 28. Secondary endpoints included change in percent predicted FEV₁ (ppFEV₁) from baseline through Day 28 and pharmacokinetics. The incidence of adverse events was similar across treatment arms. Tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) resulted in a 6.04 mmol/L decrease in sweat chloride and 3.75 percentage point increase in ppFEV₁ in subjects homozygous for F508del, and a 7.02 mmol/L decrease in sweat chloride and 4.60 percentage point increase in ppFEV₁ in subjects compound heterozygous for F508del and G551D from baseline through Day 28 (P < 0.05 for all). CONCLUSION These results support continued clinical development of tezacaftor (100 mg every day) in combination with ivacaftor (150 mg every 12 h) in subjects with cystic fibrosis. Clinical trial registered with www.clinicaltrials.gov (NCT01531673).

The use of fructosamine in cystic fibrosis-related diabetes (CFRD) screening.

Author(s): Lam, Grace Y; Doll-Shankaruk, Michelle; Dayton, Jan; Rodriguez-Capote, Karina

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 121-124

Publication Type(s): Journal Article

Abstract: OBJECTIVE To determine whether serum fructosamine correlates with glycemic control and clinical outcomes in patients being screened for cystic fibrosis-related diabetes (CFRD). METHODS Fructosamine and percent predicted forced expiratory volume in 1s (FEV₁) were measured in patients undergoing a 2h oral glucose tolerance test (OGTT) for CFRD screening. Fractional serum fructosamine (FSF) was calculated as fructosamine/total protein. RESULTS FSF exhibited a positive correlation with 2h OGTT results (r²=0.3201, p=0.009), and ROC curve analysis suggested that FSF can identify patients with an abnormal OGTT (AUC=0.840, p=0.0002). FSF also exhibited a negative correlation with FEV₁ (r²=0.3732, p=0.035). Patients with FSF ≥ 3.70 μmol/g had significantly lower FEV₁ (median 47%) compared to those with FSF < 3.70 μmol/g (median 90%; p=0.015). CONCLUSIONS FSF correlated with both OGTT results and FEV₁, and reliably identified

patients with abnormal OGTT results. This simple blood test shows potential as an effective tool in CFRD screening.

Long-acting inhaled bronchodilators for cystic fibrosis.

Author(s): Smith, Sherie; Edwards, Christopher T

Source: The Cochrane database of systematic reviews; Dec 2017; vol. 12 ; p. CD012102

Publication Type(s): Journal Article Review

Available at [The Cochrane database of systematic reviews](#) - from Cochrane Collaboration (Wiley)

Abstract:BACKGROUND Cystic fibrosis is a life-limiting inherited condition which affects one in 2500 newborns in the UK and 70,000 children and adults worldwide. The condition is multifaceted and affects many systems in the body. The respiratory system is particularly affected due to a build up of thickened secretions and a predisposition to infection. Inhaled bronchodilators are prescribed for 80% of people with cystic fibrosis in order to widen the airways and alleviate symptoms. Both short- and long-acting inhaled bronchodilators are used to improve respiratory symptoms. Short-acting inhaled bronchodilators take effect in minutes and typically last for four to eight hours (muscarinic antagonists). Long-acting inhaled bronchodilators also take effect within minutes but typically last for around 12 hours and sometimes longer. This review is one of two which are replacing a previously published review of both long- and short-acting inhaled bronchodilators. OBJECTIVE This review aims to evaluate long-acting inhaled bronchodilators in children and adults with cystic fibrosis in terms of clinical outcomes and safety. If possible, we aimed to assess the optimal drug and dosage regimen. SEARCH METHODS We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. Date of last search: 10 October 2017. We also carried out a separate search of Embase and the reference lists of included trials. We searched clinical trials registries for any ongoing trials and made contact with pharmaceutical companies for any further trials. Date of Embase search: 11 October 2017. SELECTION CRITERIA Randomised or quasi-randomised parallel trials comparing long-acting inhaled bronchodilators (beta-2 agonists and muscarinic antagonists) with placebo, no treatment or a different long-acting inhaled bronchodilator in adults and children with cystic fibrosis. DATA COLLECTION AND ANALYSIS Both authors independently assessed trials for inclusion (based on title, abstract and full text). The authors independently assessed the included trials for quality and risk of bias and extracted data. Discrepancies were resolved by a third party. MAIN RESULTS The searches identified 195 unique references, of which 155 were excluded on title and abstract. We assessed the full texts of the remaining references, excluded 16 trials (28 references) and included four trials (12 references) in the review with 1082 participants. One trial (n = 16) measuring the effect of beta-2 agonists reported an improvement in forced expiratory volume at one second (FEV1) after treatment (at one month), but the trial was small with an unclear risk of bias so we judged the evidence to be very low quality. The trial did not report on participant-reported outcomes, quality of life or adverse events. Three trials (n = 1066) looked at the effects of the muscarinic antagonist tiotropium at doses of 2.5 µg and 5.0 µg in both the short term (up to 28 days) and the longer term (up to three months). Only one of the trials reported the change in FEV1 (L) after 28 days treatment and showed no significant difference between groups; with 2.5 µg tiotropium, mean difference (MD) -0.02 (95% confidence interval (CI) -0.13 to 0.09), or 5.0 µg tiotropium, MD 0.00 (95% CI -0.10 to 0.10) (moderate-quality evidence). All three trials of muscarinic antagonists provided data on adverse events which were found to differ little from placebo at doses of 2.5 µg, risk ratio (RR) 1.01 (95% CI 0.92 to 1.11) or 5.0 µg, RR 0.98 (95% CI 0.90 to 1.06). Very little participant-reported outcome data or quality of life data were available for analysis. Two of the trials were at low risk of bias overall whilst the remaining trial was at an unclear risk overall. AUTHORS' CONCLUSIONS Neither long-acting beta-2 agonists nor long-acting muscarinic antagonist bronchodilators demonstrate improvement in our primary outcome of FEV1. No difference was observed between intervention and placebo in

terms of quality of life or adverse events. The quality of evidence for the use of beta-2 agonists was very low. The use of a long-acting inhaled bronchodilator may help to reduce the burden of treatment for people with cystic fibrosis as it is taken less often than a short-acting inhaled bronchodilator, but future trials would benefit from looking at the effects on our primary outcomes (spirometric changes from baseline, quality of life and adverse effects) in the longer term.

Rate of lung function decline in patients with cystic fibrosis (CF) having a residual function gene mutation

Author(s): Sawicki G.; Konstan M.W.; McKone E.; Moss R.B.; Lubarsky B.; Suthoff E.; Millar S.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract: Objective Patients with cystic fibrosis (CF) and mutations associated with residual CFTR chloride transport have improved survival rates compared with those homozygous for the F508del-CFTR mutation. Since little is known about rate of lung function decline in patients with CF and residual function (RF) mutations, we evaluated differences in rates of percent predicted FEV1 (ppFEV1) decline between patients with an RF mutation who were heterozygous for F508del and those who were homozygous for F508del, and whether rates of ppFEV1 decline differed across age groups. Methods Patients in the US CF Foundation Patient Registry from 2006 to 2014 with an RF mutation heterozygous for F508del were compared with F508del-homozygous patients. Mutations were identified based on clinical or in vitro evidence of residual ion transport. Annual rates of ppFEV1 decline were estimated for patients 6 to 45 years of age with ≥ 3 ppFEV1 values spanning 0.5 years in a randomly chosen 2 year period that began at the first ppFEV1 measurement in the calendar year. Results A total of 1242 RF and 11,916 F508del-homozygous patients were included. At the first visit, the RF cohort was older (mean [SD], 23.0 [12.1] vs 18.0 [9.6] years) and had better nutritional status (mean [SD] BMI z score, 0.36 [1.09] vs 0.29 [1.08]). Mean (SD) ppFEV1 differed at the first visit between cohorts (80.4 [24.8] vs 73.4 [26.5]; $p < 0.001$). Annual rate of ppFEV1 decline was estimated at 0.70 (SE, 0.20) in the RF cohort compared with 1.91 (0.05) in the F508del-homozygous cohort ($p < 0.001$). After excluding patients with R117H ($n = 889$), the rate of decline was 1.05 (0.39) ppFEV1 per year ($p < 0.001$ vs F508del). The rate of decline for RF patients was most rapid in the 18 to 24-year age group, 1.38 (0.39), but was still significantly less than the 2.52 (0.09) for F508del-homozygous young adults ($p = 0.004$). Conclusion Patients with CF and an RF mutation have lower rates of lung function decline compared with F508del-homozygous patients. However, patients with an RF mutation still demonstrate progressive lung disease, particularly during young adulthood.

Genomic investigation unmask evidence of transmission across mycobacterium abscessus cystic fibrosis patients

Author(s): Alateah S.; Dhasmana D.J.; Pettigrew K.; Fallon R.; Sloan D.J.; Holden M.; Gillespie S.H.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract: Background Mycobacterium abscessus (Mabs) is a critical respiratory pathogen in Cystic Fibrosis (CF), with significant challenges in diagnosis and treatment. Recent whole genome sequencing (WGS) studies have challenged the assumption that acquisition in CF is primarily from soil and water systems.¹ We sought to investigate potential transmission of Mabs within and between CF centres through WGS analysis of CF isolates from the Scottish Mycobacteria Reference

Laboratory. Methods 64 isolates were recovered and sequenced from CF samples positive for Mabs between 2008 and 2016. Multilocus sequence typing (MLST), and phylogenetic analysis based on core genome Single Nucleotide Polymorphisms (SNPs) was used to identify dominant circulating clones. Probable transmission clusters were defined by <20 SNPs between isolates, as suggested by previous studies. This work was carried out as part of a public health investigation. Results MLST analysis of the 64 confirmed Mabs isolates demonstrated the following: 8 strain types (ST) associated with Mabs subspecies abscessus, including ST9 (n=18), ST24 (12), ST5 (7), ST26 (4), ST21 (3), and ST10 (2); 11 identified as subspecies massiliense associated with ST4 (4), ST6 (3), ST7 (2) and ST3 (2); 4 identified as subspecies bolletti. Phylogenomic analysis provided higher resolution and identified significant relatedness between and within clonal complexes. The most prevalent subspecies abscessus clone was ST9, of which 16 isolates were distinguished by <20 SNPs, 12 of which from one hospital region. Five of the ST9 isolates were indistinguishable at the SNP level, and yet originated from different Health Board regions and different hospitals. ST5, ST24 and ST26 also contained isolates distinguished by <20 SNPs and originated from several geographically distinct regions. Conclusion WGS has provided strong evidence of the circulation of dominant clones between and within CF centres across geographically diverse settings over an 8 year period. The high genomic relatedness provides strong evidence of transmission between CF patients, even though the precise mechanisms of transmission remain uncertain. Further studies are underway to understand the mechanism of transmission in this clinical context.

Tezacaftor-ivacaftor is safe and efficacious in patients with cystic fibrosis with Phe508del mutations.

Author(s): Kirby, Tony

Source: The Lancet. Respiratory medicine; Jan 2018; vol. 6 (no. 1); p. 13-14

Publication Type(s): Journal Article

Antimicrobial Activity of Ibuprofen Against Cystic Fibrosis Associated Gram-Negative Pathogens.

Author(s): Shah, Parth N; Marshall-Batty, Kimberly R; Smolen, Justin A; Tagaev, Jasur A

Source: Antimicrobial agents and chemotherapy; Jan 2018

Publication Type(s): Journal Article

Abstract: Clinical trials have demonstrated the benefits of ibuprofen therapy in cystic fibrosis (CF) patients, an effect that is currently attributed to ibuprofen's anti-inflammatory properties. Yet, a few previous reports demonstrate an antimicrobial activity of ibuprofen as well, although none investigate its direct effects on the pathogens found in the CF lung, which is the focus of this work. Determination of ibuprofen's in vitro antimicrobial activity against *Pseudomonas aeruginosa* and *Burkholderia* spp. strains through measurements of endpoint colony-forming units (CFU) and growth kinetics showed that ibuprofen reduces the growth rate and bacterial burden of tested strains in a dose-dependent fashion. In an in vitro *Pseudomonas* biofilm model, a reduction in the rate of biomass accumulation over 8-h of growth with ibuprofen treatment was observed. Next, an acute *Pseudomonas* pneumonia model was used to test this antimicrobial activity after oral delivery of ibuprofen. Following intranasal inoculation, ibuprofen-treated mice exhibited lower CFU counts and improved survival compared with control animals. Preliminary biodistribution studies performed after aerosolization of ibuprofen to mice demonstrated a rapid accumulation of ibuprofen in serum and minimum retention in lung tissue and bronchoalveolar lavage fluid. Therefore, ibuprofen-encapsulating polymeric nanoparticles (Ibu-NPs) were formulated to improve the pharmacokinetic profile. Ibu-NPs, formulated for aerosol delivery, inhibited the growth of *P. aeruginosa* in vitro and may provide a convenient dosing method. These results provide an additional explanation for the

previously observed therapeutic effects of ibuprofen in CF patients, and further strengthen the argument for its use for these patients.

Chasing Zero: Increasing Infection Control Compliance on an Inpatient Cystic Fibrosis Unit.

Author(s): Johnson, Samantha; McNeal, Mallory; Mermis, Joel; Polineni, Deepika; Burger, Stephanie

Source: Journal of nursing care quality; ; vol. 33 (no. 1); p. 67-71

Publication Type(s): Journal Article

Abstract:Patients with cystic fibrosis have increased risk of pulmonary infections, and reducing spread of microorganisms is critical. To improve hospital-staff adherence to infection control guidelines, we implemented brightly colored Safe Zone floor decals, staff compliance contracts, and an infection control in-service video. Audits of staff adherence conducted pre and postintervention demonstrated an increased and sustainable improvement among each group ($P < .05$). These effective measures may be implemented to improve infection control compliance elsewhere.

Pseudomonas aeruginosa in cystic fibrosis patients with c.1652G>A (G551D)-CFTR treated with ivacaftor-Changes in microbiological parameters

Author(s): Millar B.C.; Moore J.E.; McCaughan J.; Rendall J.C.; Downey D.G.

Source: Journal of Clinical Pharmacy and Therapeutics; 2018; vol. 43 (no. 1); p. 92-100

Publication Type(s): Article

Abstract:What is known and objective: The CFTR potentiator, ivacaftor (IVA), has been widely used in the treatment of cystic fibrosis (CF) patients with the G551D mutation. To date, there has been limited information on the microbiological status of patients on this therapy and no data on the effect (if any) on the in vivo antibiotic susceptibility of *Pseudomonas aeruginosa* isolated from patients on therapy. Although IVA intervention is not designed per se as anti-infective, the effect (if any) of this molecule to CF patients' microbiological status merits careful monitoring. Therefore, it was the aim of this observational study to examine the effect in patients, both before and after commencement of IVA therapy, on several commonly reported microbiological markers in CF patients, including (i) bacterial density, (ii) frequency (rate) of isolation of bacterial pathogens, particularly *P. aeruginosa*, and (iii) antimicrobial susceptibility of these isolates to commonly prescribed oral and iv antibiotics. In addition, we wished to examine the requirements for these antibiotics in CF patients, before and after commencement of IVA therapy. Methods: Archived data from 15 adult cystic fibrosis patients with the c.1652G>A (G551D) mutation were followed from two years pre-IVA therapy to two years after commencement of IVA therapy. The microbiological parameters examined included (i) oral antibiotic courses taken, (ii) intravenous (iv) antibiotic courses taken, (iii) rate of isolation of non-mucoid *Pseudomonas aeruginosa* (NM-PA) and mucoid *P. aeruginosa* (M-PA), (iv) density of NM-PA and M-PA and (v) antimicrobial susceptibility of NM-PA and M-PA to 11 antibiotics [aminoglycosides, beta-lactams, polymyxin and fluoroquinolone]. Results and discussion: Following commencement of IVA therapy, patients required less iv antibiotic courses but no change in number of oral antibiotics courses. There was significant reduction in both the rate of isolation and density of M-PA ($P = .02$; $P = .006$, respectively). In contrast, there was no significant reduction in both the rate of isolation and density of NM-PA ($P = .90$; $P = .07$, respectively). Antimicrobial susceptibility in NM-PA and M-PA was not significantly reduced within any of the antibiotics classes or individual antibiotics examined. Increased susceptibility was noted in the beta-lactam class for NM-PA and M-PA, in particular with ceftazidime. What is new and conclusion: Overall, (i) the requirement for less iv antibiotic therapy, (ii) a reduction in the rate and density of M-PA and (iii) no reduction in antibiotic susceptibility indicate that microbiological parameters with patients on IVA therapy were not detrimentally affected. Copyright © 2017 John Wiley & Sons Ltd

Successful eradication of newly acquired MRSA in six of seven patients with cystic fibrosis applying a short-term local and systemic antibiotic scheme.

Author(s): Kiefer, Alexander; Bogdan, Christian; Melichar, Volker O

Source: BMC pulmonary medicine; Jan 2018; vol. 18 (no. 1); p. 20

Publication Type(s): Journal Article

Available at [BMC pulmonary medicine](#) - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUND In individuals with cystic fibrosis (CF), colonization with methicillin-resistant Staphylococcus aureus (MRSA) was reported to be associated with a deterioration of pulmonary disease as reflected by an accelerated decline in lung function. Thus, an early eradication of MRSA could be beneficial in these patients. Here, we report on an intensified MRSA eradication protocol. METHODS Since 2012 a protocol for the eradication of newly acquired MRSA has been used in our CF Clinic, combining oral rifampicin and fusidic acid, inhaled vancomycin, nasal mupirocin, local antiseptic treatment and hygienic directives all of which are applied for only 7 days during an inpatient hospital stay. RESULTS Since 2012 seven patients (3 male, 4 female; age range 4 to 30 years) newly acquired MRSA. In 6 of the 7 patients (86%) successful eradication of MRSA was achieved upon first treatment using the protocol described above. In one patient a second course of treatment was performed which, however, also failed to eliminate the colonizing MRSA. CONCLUSIONS Our protocol led to an eradication rate of 86%. The impact of each individual component of the protocol remains to be determined.

Hypertonic saline has a prolonged effect on mucociliary clearance in adults with cystic fibrosis.

Author(s): Trimble, Aaron T; Whitney Brown, A; Laube, Beth L; Lechtzin, Noah; Zeman, Kirby L

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018

Publication Type(s): Journal Article

Abstract:BACKGROUND Inhaled hypertonic saline (HS) has been shown to increase mucociliary clearance (MCC) and improve clinical outcomes in adults and adolescents with cystic fibrosis (CF). However, in younger children with CF, a large study failed to demonstrate clinical benefits. This discrepancy could reflect pharmacodynamic differences in the MCC response to HS in different populations. We previously demonstrated the absence of a sustained effect of HS on MCC in healthy adults and in this study sought to characterize the durability of the MCC response to HS in adults with CF. METHODS At two study sites, MCC was measured in CF adults using gamma scintigraphy during three separate visits: at baseline, 15 min, and 4 h after a single dose of HS (7% NaCl, 4 mL). Particle clearance rates at these visits were used to assess the durability of the MCC response to HS. RESULTS The average 90-minute clearance rate measured 4 h after HS was significantly increased ($21.81\% \pm 12.8$) when compared to baseline ($13.77\% \pm 8.7$, $p = .048$) and showed no apparent slowing relative to the rate measured 15 min after HS. While not all subjects responded to HS, the acute response strongly predicted the sustained effect in these subjects ($r = 0.896$, $p < .0001$). CONCLUSIONS These results suggest that, in contrast to healthy adults, a single dose of HS has a prolonged effect on MCC in adults with CF, which lasts at least 4 h. This may explain its clinical efficacy in this population.

Volatile molecules from bronchoalveolar lavage fluid can 'rule-in' Pseudomonas aeruginosa and 'rule-out' Staphylococcus aureus infections in cystic fibrosis patients.

Author(s): Nasir, Mavra; Bean, Heather D; Smolinska, Agnieszka; Rees, Christiaan A

Source: Scientific reports; Jan 2018; vol. 8 (no. 1); p. 826

Publication Type(s): Journal Article

Available at [Scientific reports](#) - from Europe PubMed Central - Open Access

Abstract:Respiratory infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the leading cause of morbidity and mortality in cystic fibrosis (CF) patients. The authors aimed to identify volatile biomarkers from bronchoalveolar lavage (BAL) samples that can guide breath biomarker development for pathogen identification. BAL samples (n = 154) from CF patients were analyzed using two-dimensional gas chromatography time-of-flight mass spectrometry. Random Forest was used to select suites of volatiles for identifying *P. aeruginosa*-positive and *S. aureus*-positive samples using multiple infection scenarios and validated using test sets. Using nine volatile molecules, we differentiated *P. aeruginosa*-positive (n = 7) from *P. aeruginosa*-negative (n = 53) samples with an area under the receiver operating characteristic curve (AUROC) of 0.86 (95% CI 0.71-1.00) and with positive and negative predictive values of 0.67 (95% CI 0.38-0.75) and 0.92 (95% CI 0.88-1.00), respectively. We were also able to discriminate *S. aureus*-positive (n = 15) from *S. aureus*-negative (n = 45) samples with an AUROC of 0.88 (95% CI 0.79-1.00) using eight volatiles and with positive and negative predictive values of 0.86 (95% CI 0.61-0.96) and 0.70 (95% CI 0.61-0.75), respectively. Prospective validation of identified biomarkers as screening tools in patient breath may lead to clinical application.

Effects of Lumacaftor/Ivacaftor Therapy on CFTR Function in Phe508del Homozygous Patients with Cystic Fibrosis.

Author(s): Graeber, Simon Y; Dopfer, Christian; Naehrlich, Lutz; Gyulumyan, Lena

Source: American journal of respiratory and critical care medicine; Jan 2018

Publication Type(s): Journal Article

Available at [American journal of respiratory and critical care medicine](#) - from EBSCO (MEDLINE Complete)

Abstract:RATIONALEThe combination of the CFTR corrector lumacaftor with the potentiator ivacaftor has been approved for the treatment of patients with cystic fibrosis (CF) homozygous for the Phe508del CFTR mutation. The phase 3 trials examined clinical outcomes, but did not evaluate CFTR function in patients.OBJECTIVESTo examine the effect of lumacaftor-ivacaftor on biomarkers of CFTR function in Phe508del homozygous CF patients aged 12 years and older.METHODSThis prospective observational study assessed clinical outcomes including FEV1 % predicted and BMI, and CFTR biomarkers including sweat chloride concentration, nasal potential difference (NPD) and intestinal current measurement (ICM) before and 8-16 weeks after initiation of lumacaftor-ivacaftor.MEASUREMENTS AND MAIN RESULTSA total of 53 patients were enrolled in the study and 52 patients had baseline and follow up measurements. After initiation of lumacaftor-ivacaftor sweat chloride concentrations were reduced by 17.8 mmol/L (IQR -25.9 to -6.1; p<0.001), NPD showed partial rescue of CFTR function in nasal epithelia to a level of 10.2% (IQR 0.0 to 26.1; p<0.011), and ICM showed functional improvement in rectal epithelia to a level of 17.7% of normal (IQR 10.8 to 29.0; p<0.001). All patients improved in at least one CFTR biomarker, but no correlations were found between CFTR biomarker responses and clinical outcomes.CONCLUSIONS Lumacaftor-ivacaftor results in partial rescue of Phe508del CFTR function to levels comparable to the lower range of CFTR activity found in patients with residual function mutations. Functional improvement was detected even in the absence of short-term improvement of FEV1 % predicted and BMI. Clinical trial registration available at www.clinicaltrials.gov, ID NCT02807415.

One time quantitative PCR detection of *Pseudomonas aeruginosa* to discriminate intermittent from chronic infection in cystic fibrosis.

Author(s): Boutin, Sébastien; Weitnauer, Michael; Hassel, Selina; Graeber, Simon Y; Stahl, Mirjam

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018

Publication Type(s): Journal Article

Abstract:BACKGROUNDChronic airway infection with *Pseudomonas aeruginosa* is a major risk factor of progression of lung disease in patients with cystic fibrosis (CF). Chronic *P. aeruginosa* infection evolves from intermittent infection that is amenable to antibiotic eradication, whereas chronically adapted *P. aeruginosa* becomes resistant to antibiotic therapy. Discrimination of intermittent versus chronic infection is therefore of high therapeutic relevance, yet the available diagnostic methods are only partly satisfactory. The aim of the present study was, therefore, to evaluate the usage of quantitative PCR (qPCR) to measure pathogen abundance and to discriminate between intermittent and chronic *Pseudomonas* infection in patients with CF.METHODUsing an established qPCR protocol, we analyzed the abundance of *P. aeruginosa* in 141 throat swabs and 238 sputa from CF patients with intermittent or chronic infection with *P. aeruginosa*, as determined by standard culture based diagnostics.RESULTSWe observed a large increase of abundance of *P. aeruginosa* in throat swabs and sputum samples from patients with chronic compared to intermittent infections with *P. aeruginosa*. The data show that abundance of *P. aeruginosa* as measured by qPCR is a valuable tool to discriminate intermittent from chronic infection. Of note, *P. aeruginosa* burden seems more sensitive than mucoid phenotype to discriminate chronic from intermittent strains. Furthermore we observed that molecular detection in throat swabs was linked to a viable culture in the sputum when sputum was available. This result is of special interest in young patients with cystic fibrosis that often cannot expectorate sputum. We also observed that qPCR in comparison to culture detected the infection earlier.CONCLUSIONThe results suggest that qPCR detection and quantification of *P. aeruginosa* is a precious tool to be added to the diagnostic toolbox in cystic fibrosis.

Retrospective observational study of French patients with cystic fibrosis and a Gly551Asp-CFTR mutation after 1 and 2years of treatment with ivacaftor in a real-world setting.

Author(s): Hubert, Dominique; Dehillotte, Clémence; Munck, Anne; David, Valérie; Baek, Jinmi

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 89-95

Publication Type(s): Journal Article

Abstract:BACKGROUNDIvacaftor has been shown to improve lung function and body weight in patients with CF and a gating mutation. Real-world evaluation is warranted to examine its safety and effectiveness over the long term.METHODSA retrospective observational multicentre study collected clinical data in the year before and the 2years after ivacaftor initiation in patients with CF and a Gly551Asp-CFTR mutation.RESULTSFifty-seven patients were included. Mean absolute change in FEV1% predicted improved from baseline to Year 1 (8.4%; $p < 0.001$) and Year 2 (7.2%; $p = 0.006$). Statistically significant benefits were observed with increased body mass index, fewer *Pseudomonas aeruginosa* and *Staphylococcus aureus* positive cultures, and decreased IV antibiotics and maintenance treatment prescriptions (including azithromycin, Dornase alpha and nutritional supplements). No significant adverse events were reported.CONCLUSIONThe clinical benefits of ivacaftor reported in previous clinical trials were confirmed in a real-world setting two years post-initiation, also reducing treatment burden.

Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor.

Author(s): Flume, Patrick A; Wainwright, Claire E; Elizabeth Tullis, D; Rodriguez, Sally

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 83-88

Publication Type(s): Journal Article

Abstract:BACKGROUNDPulmonary exacerbations (PEX) are associated with acute loss of lung function that is often not recovered after treatment. We investigated lung function recovery

following PEx for ivacaftor- and placebo-treated subjects. **METHODS** Short- and long-term pulmonary function recovery data after PEx were summarized from a placebo-controlled trial in 161 cystic fibrosis patients ≥ 12 years old with the G551D-CFTR mutation (NCT00909532). Short-term recovery was measured 2 to 8 weeks after treatment, and long-term recovery was determined at the end-of-study, both compared with baseline measured just prior to the PEx. **RESULTS** Fewer patients receiving ivacaftor experienced a PEx than patients receiving placebo (33.7% vs. 56.4%; $P=0.004$) and had a lower adjusted incidence rate of PEx (0.589 vs. 1.382; $P<0.001$). The proportion of PEx followed by full short-term recovery of percent predicted forced expiratory volume in 1s was similar (ivacaftor vs. placebo, 57.1% vs. 53.7%), as was the proportion of patients having long-term recovery (46.4% vs. 47.7%). **CONCLUSIONS** Ivacaftor treatment reduces the frequency of PEx but does not improve on the rate of complete lung function recovery after PEx when compared with placebo.

KB001-A, a novel anti-inflammatory, found to be safe and well-tolerated in cystic fibrosis patients infected with *Pseudomonas aeruginosa*.

Author(s): Jain, R; Beckett, V V; Konstan, M W; Accurso, F J; Burns, J L; Mayer-Hamblett, N

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Dec 2017

Publication Type(s): Journal Article

Abstract: **BACKGROUND** Chronic *Pseudomonas aeruginosa* (Pa) airways infection, exuberant local inflammation, and progressive lung function loss are hallmarks of cystic fibrosis (CF). KB001-A is an anti-PcrV PEGylated monoclonal antibody fragment to the Type III secretion system of Pa. This 16-week study evaluated KB001-A associated effect on time-to-need for antibiotics for worsening respiratory signs and symptoms, as well as safety, and treatment-associated changes in symptom scores, inflammatory markers, and spirometry. **METHODS** This was a randomized, double-blind, placebo-controlled, repeat-dose study in CF subjects with Pa. Intravenous 10mg/kg KB001-A or placebo infusions were administered at baseline and weeks 2, 4, 8, and 16, with a 4-week follow-up. Sputum inflammatory markers were assessed in a sub-study. Time-to-need for antibiotics was compared between groups by Kaplan Meier analysis and Cox proportional hazards modeling adjusting for randomization strata. **RESULTS** Of 182 subjects, 169 received at least one infusion of KB001-A ($n=83$) or placebo ($n=86$). KB001-A was generally safe and well-tolerated as compared to placebo, with no significant emergent adverse effects other than one serious adverse event of elevated hepatic enzymes of unclear etiology. Time to need for antibiotics did not differ between groups (HR: 1.00; 95% CI: 0.69, 1.45, $p=0.995$). A 3.2 increase in ppFEV1 from placebo favoring KB001-A was observed at week 16 (95% CI: 1.12, 5.30, $p=0.003$). Mean changes from baseline in log₁₀ sputum neutrophil elastase (NE) had a non-significant decrease (-0.27, 95% CI: -0.58, 0.04, $p=0.084$) while IL-8 concentrations at week 16 were significantly lower (-0.27, 95% CI: -0.55, 0.00, $p=0.048$) among KB001-A subjects ($n=16$) relative to placebo ($n=13$). **CONCLUSIONS** KB001-A was safe and well-tolerated and associated with a modest FEV1 benefit and reduction in select sputum inflammatory markers (IL-8). KB001-A was not associated with an increased time to need for antibiotics. The lack of efficacy seen with KB001-A may be due, in part, to the low levels of the type III secretion proteins previously reported in sputum of CF patients chronically infected with Pa.

Vx-809/Vx-770 treatment reduces inflammatory response to *Pseudomonas aeruginosa* in primary differentiated cystic fibrosis bronchial epithelial cells.

Author(s): Ruffin, Manon; Roussel, Lucie; Maillé, Émilie; Rousseau, Simon; Brochiero, Emmanuelle

Source: American journal of physiology. Lung cellular and molecular physiology; Dec 2017

Publication Type(s): Journal Article

Abstract: Cystic fibrosis patients exhibit chronic *P. aeruginosa* respiratory infections and sustained pro-inflammatory state favoring lung tissue damage and remodeling, ultimately leading to

respiratory failure. Loss of CFTR function is associated with MAPK hyper-activation and increased cytokines expression, such as the interleukin 8 (CXCL8). Recently, new therapeutic strategies directly targeting the basic CFTR defect have been developed and ORKAMBI (Vx-809/Vx-770 combination) is the only FDA-approved treatment for CF patients homozygous for the F508del mutation. Here we aimed to determine the effect of the Vx-809/Vx-770 combination on the induction of the inflammatory response by fully-differentiated primary bronchial epithelial cell cultures from CF patients carrying F508del mutations, following exposure to *P. aeruginosa* exoproducts. Our data unveiled that CFTR functional rescue with Vx-809/Vx-770 drastically reduces CXCL8 (as well as CXCL1 and CXCL2) transcripts and p38 MAPK phosphorylation in response to *P. aeruginosa* exposure through a CFTR-dependent mechanism. These results suggest that ORKAMBI has anti-inflammatory properties that could decrease lung inflammation and contribute to the observed beneficial impact of this treatment in CF patients.

Increased platelet activation occurs in cystic fibrosis patients and correlates to clinical status.

Author(s): Lindberg, Ulrika; Svensson, Lisbeth; Hellmark, Thomas; Segelmark, Mårten;

Source: Thrombosis research; Dec 2017; vol. 162 ; p. 32-37

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) is an inflammatory lung disease. Platelets have an emerging role in inflammation, however previous studies of platelet activation in CF have generated conflicting results. In this study, we determined platelet function in CF patients and correlated platelet activation to establish clinical and laboratory parameters. Twenty-two patients, aged 20.7 to 54.4 (mean 34.0, SD 9.45) years and with a mean FEV1%pred (forced expiratory volume in one second, % of predicted) of 72 (SD 21.4, range 32-110) were recruited. A combination of platelet assays was used: platelet aggregation, platelet activation and platelet-leukocyte complex formation. Platelets from CF patients exhibited significantly increased aggregation when stimulated ex-vivo, a tendency towards increased platelet upregulation of CD62P, but no increase of GPIIb/IIIa activation (PAC-1). Platelet-monocyte complex (PMC) formation was significantly increased in CF patients compared to controls, while platelet-neutrophil complex formation was not. In the CF group, platelet aggregation correlates with levels of anti-neutrophil cytoplasmic antibodies (ANCA) with specificity for bactericidal/permeability-increasing protein (BPI), BPI-ANCA ($r=0.56$). The formation of PMCs correlates with lung function decline (1-FEV1%), CRP and BPI-ANCA ($r=0.61, 0.55, 0.5$). We therefore confirm the presence of increased platelet activation in CF patients, and determine that further evaluation of platelet activation in relation to prognostic factors in CF is warranted.

Effect of Lumacaftor/Ivacaftor on glucose metabolism and insulin secretion in Phe508del homozygous cystic fibrosis patients.

Author(s): Thomassen, Jan C; Mueller, Matthias I; Alejandro Alcazar, Miguel A; Rietschel, Ernst

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Dec 2017

Publication Type(s): Journal Article

Abstract: OBJECTIVE To investigate the effect of Lumacaftor/Ivacaftor on glucose metabolism and insulin secretion in patients with cystic fibrosis (CF) (Phe508del/Phe508del). METHODS A standard oral glucose tolerance test (OGTT) and an intravenous glucose tolerance test (IVGTT) were performed to investigate glucose metabolism and insulin secretion before and after 6-8 weeks of treatment with Lumacaftor/Ivacaftor in 5 Phe508del-homozygous CF patients. The area under the curve (AUC) for glucose and insulin levels was calculated using the trapezoidal approximation. RESULTS 5 participants were investigated. Treatment with Lumacaftor/Ivacaftor was followed by an improvement of the 2h glucose levels in 3 patients and worsening in 2 patients. Analysis of the time course of blood glucose levels during OGTT revealed an increase of the AUC in 3

of 5 patients. In response to IVGTT, acute insulin secretion improved in 2 patients and worsened in 3. **CONCLUSION** The investigation could not demonstrate that treatment with Lumacaftor/Ivacaftor had a consistent impact on glucose tolerance and insulin secretion. Further adequately-powered studies examining glucose metabolism are needed to properly evaluate drug response in the endocrine pancreas and to test whether this treatment could eventually prevent the development of cystic fibrosis-related diabetes (CFRD).

Correlation between sinus and lung cultures in lung transplant patients with cystic fibrosis.

Author(s): Choi, Kevin J; Cheng, Tracy Z; Honeybrook, Adam L; Gray, Alice L; Snyder, Laurie D

Source: International forum of allergy & rhinology; Dec 2017

Publication Type(s): Journal Article

Abstract: **BACKGROUND** Lung transplantation has revolutionized the treatment of end-stage pulmonary disease due to cystic fibrosis. However, infection of the transplanted lungs can lead to serious complications, including graft failure and death. Although many of these patients have concurrent sinusitis, it is unclear whether bacteria from the sinuses can infect the allograft. **METHODS** This is a single-institution retrospective study of all patients who underwent lung transplantation for cystic fibrosis from 2005 to 2015 at Duke University Hospital. Pre- and posttransplant nasal and pulmonary cultures obtained via nasal endoscopy and bronchoalveolar lavage (BAL), respectively, were analyzed. **RESULTS** A total of 141 patients underwent 144 lung transplants. Sinus cultures were available for 76 patients (12 pretransplant, 42 posttransplant, 22 both pre- and posttransplant). Pretransplant BAL cultures were available for 139 patients, and posttransplant BAL cultures were available for all patients. *Pseudomonas aeruginosa* (PsA) and methicillin-resistant *Staphylococcus aureus* (MRSA) were the most common organisms cultured. There was a significant correlation between pretransplant sinus and posttransplant BAL cultures for PsA ($p = 0.003$), MRSA ($p = 0.013$), and *Burkholderia cepacia* ($p = 0.001$). **CONCLUSION** There was a high correlation between pretransplant sinus cultures and posttransplant BAL cultures for PsA, MRSA, and *Burkholderia* sp. This suggests that the paranasal sinuses may act as a reservoir for allograft colonization in patients with cystic fibrosis. Further studies are needed to determine whether treatment of sinusitis affects allograft colonization and transplant outcomes.

High proportion of abnormal pap smear tests and cervical dysplasia in women with cystic fibrosis.

Author(s): Rousset-Jablonski, Christine; Reynaud, Quitterie; Nove-Josserand, Raphaëlle;

Source: European journal of obstetrics, gynecology, and reproductive biology; Dec 2017; vol. 221 ; p. 40-45

Publication Type(s): Journal Article

Abstract: **OBJECTIVES** Insufficient gynecological follow-up and cervical screening has been reported in women with cystic fibrosis (CF). Some of these patients will require a pulmonary transplantation, known to be associated with a higher risk of cervical dysplasia. The aim of this study was to explore the results of cervical screening in adult women with CF, and to report the prevalence of abnormal pap smear tests in this population. **STUDY DESIGN** We retrospectively analyzed medical records of sexually active women with CF who attended a gynecological consultation in Lyon University CF referral center between June 2014 and December 2015. The primary outcome was the result of the pap smear test. **RESULTS** Forty-seven women (32 non-transplanted and 15 transplanted) were included in the study. The median age of the patients was 28 (range 18-53). The clinical examination revealed that 20 (42.5%) women presented an abnormality (inflammatory cervix, cervical or vulvovaginal condyloma). An abnormal pap smear was found in 8/32 (25%) non-transplanted women and in 5/15 (33.3%) transplanted women, with no significant difference between the two groups ($p=0.75$): seven atypical squamous cells of undetermined significance (ASC-US), five low grade

squamous intraepithelial lesion (LSIL), one atypical glandular cells (AGC). Six (12.8%) (four non transplanted, and two transplanted) women had an histologically proven dysplasia (four Cervical Intraepithelial Neoplasia (CIN)1, one CIN2, and one endocervical adenocarcinoma in situ). Overall, ten (21.3%) women had a Human Papilloma Virus (HPV) related disease (cervical and/or vulvovaginal). CONCLUSION A high proportion of transplanted and non-transplanted women with CF had abnormal pap smear tests and cervical dysplasia. A regular gynaecological follow-up, periodic cervical screening, and routine HPV vaccination are strongly recommended in this population.

Direct detection of Exophiala and Scedosporium species in sputa of patients with cystic fibrosis.

Author(s): Chen, Min; Kondori, Nahid; Deng, Shuwen; Gerrits van den Ende, A H G; Lackner, M

Source: Medical mycology; Dec 2017

Publication Type(s): Journal Article

Abstract: Detection of species of *Exophiala* and *Scedosporium* in the respiratory tracts of cystic fibrosis (CF) patients remains controversial because of highly variable results. The results of our study suggested a significantly higher prevalence and more complex colonization than previously estimated. Approximately 17% (27/162) of clinical sputum samples were found to be positive for *Exophiala dermatitidis* and 30% (49/162) were positive for *Scedosporium apiospermum* / *S. boydii* species complex determined by reverse line blot (RLB) hybridization. In contrast, only 14.2% (23/162) and 1.2% (2/162) of clinical sputa were positive for *E. dermatitidis* and *S. apiospermum* / *S. boydii* species complex when tested by culture, respectively. Molecular detection methods, such as loop-mediated isothermal amplification (LAMP) or reverse line blot (RLB) hybridization, have the potential to become powerful alternatives to selective culture, providing a more realistic understanding on the prevalence of *E. dermatitidis* and *S. apiospermum* / *S. boydii* species complex in the respiratory tract of CF patients.

Forecasting the Long-Term Clinical and Economic Outcomes of Lumacaftor/Ivacaftor in Cystic Fibrosis Patients with Homozygous phe508del Mutation.

Author(s): Dilokthornsakul, Piyameth; Patidar, Mausam; Campbell, Jonathan D

Source: Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research; Dec 2017; vol. 20 (no. 10); p. 1329-1335

Publication Type(s): Journal Article

Abstract: OBJECTIVE To forecast lifetime outcomes and cost of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis (CF) with homozygous phe508del mutation from the US payer perspective. METHODS A lifetime Markov model was developed from a US payer perspective. The model included five health states: 1) mild lung disease (percent predicted forced expiratory volume in 1 second [FEV1] >70%), 2) moderate lung disease (40% ≤ FEV1 ≤ 70%), 3) severe lung disease (FEV1 < 40%), 4) lung transplantation, and 5) death. All inputs were derived from published literature. We estimated lumacaftor/ivacaftor's improvement in outcomes compared with a non-CF referent population as well as CF-specific mortality estimates. RESULTS Lumacaftor/ivacaftor was associated with additional 2.91 life-years (95% credible interval 2.55-3.56) and additional 2.42 quality-adjusted life-years (QALYs) (95% credible interval 2.10-2.98). Lumacaftor/ivacaftor was associated with improvements in survival and QALYs equivalent to 27.6% and 20.7%, respectively, for the survival and QALY gaps between CF usual care and their non-CF peers. The incremental lifetime cost was \$2,632,249. CONCLUSIONS Lumacaftor/ivacaftor increased life-years and QALYs in CF patients with the homozygous phe508del mutation and moved morbidity and mortality closer to that of their non-CF peers but it came with higher cost.

Patient-specific modelling of regional tobramycin concentration levels in airways of patients with cystic fibrosis: can we dose once daily?

Author(s): Bos, Aukje C; Mouton, Johan W; van Westreenen, Mireille; Andrinopoulou, Eleni-Rosalina

Source: The Journal of antimicrobial chemotherapy; Dec 2017; vol. 72 (no. 12); p. 3435-3442

Publication Type(s): Journal Article

Abstract:Background Inhaled tobramycin is important in the treatment of *Pseudomonas aeruginosa* (Pa) infections in cystic fibrosis (CF). However, despite its use it fails to attenuate the clinical progression of CF lung disease. The bactericidal efficacy of tobramycin is known to be concentration-dependent and hence changing the dosing regimen from a twice-daily (q12h) inhalation to a once-daily (q24h) inhaled double dose could improve treatment outcomes. Objectives To predict local concentrations of nebulized tobramycin in the airways of patients with CF, delivered with the small airway-targeting Akita[®] system or standard PARI-LC[®] Plus system, with different inspiratory flow profiles. Methods Computational fluid dynamic (CFD) methods were applied to patient-specific airway models reconstructed from chest CT scans. The following q12h and q24h dosing regimens were evaluated: Akita[®] (150 and 300 mg) and PARI-LC[®] Plus (300 and 600 mg). Site-specific concentrations were calculated. Results Twelve CT scans from patients aged 12-17 years (median = 15.7) were selected. Small airway concentrations were 762-2999 mg/L for the q12h dosing regimen and 1523-5997 mg/L for the q24h dosing regimen, well above the MIC for WT Pa strains. Importantly, the q24h regimen appeared to be more suitable than the q12h regimen against more resistant Pa strains and the inhibitory effects of sputum on tobramycin activity. Conclusions CFD modelling showed that high concentrations of inhaled tobramycin are indeed delivered to the airways, with the Akita[®] system being twice as efficient as the PARI-LC[®] system. Ultimately, the q24h dosing regimen appears more effective against subpopulations with high MICs (i.e. more resistant strains).

Rifampicin potentiation of aminoglycoside activity against cystic fibrosis isolates of *Pseudomonas aeruginosa*.

Author(s): Mikalauskas, Alaya; Parkins, Michael D; Poole, Keith

Source: The Journal of antimicrobial chemotherapy; Dec 2017; vol. 72 (no. 12); p. 3349-3352

Publication Type(s): Journal Article

Abstract: Objectives Rifampicin potentiates the activity of aminoglycosides (AGs) versus *Pseudomonas aeruginosa* by targeting the AmgRS two-component system. In this study we examine the impact of rifampicin on the AG susceptibility of cystic fibrosis (CF) lung isolates of *P. aeruginosa* and the contribution of AmgRS to AG resistance in these isolates. Methods amgR deletion derivatives of clinical isolates were constructed using standard gene replacement technology. Susceptibility to AGs ± rifampicin (at ½ MIC) was assessed using a serial 2-fold dilution assay. Results Rifampicin showed a variable ability to potentiate AG activity versus the CF isolates, enhancing AG susceptibility between 2- and 128-fold. Most strains showed potentiation for at least two AGs, with only a few strains showing no AG potentiation by rifampicin. Notably, loss of amgR increased AG susceptibility although rifampicin potentiation of AG activity was still observed in the ΔamgR derivatives. Conclusions AmgRS contributes to AG resistance in CF isolates of *P. aeruginosa* and rifampicin shows a variable ability to potentiate AG activity against these, highlighting the complexity of AG resistance in such isolates.

Environmental fungal sampling in a cystic fibrosis centre

Author(s): Collier L.J.; Bright-Thomas R.J.; Jones A.M.; Richardson M.

Source: Thorax; Dec 2017; vol. 72

Publication Type(s): Conference Abstract

Available at [Thorax](#) - from BMJ Journals - NHS

Abstract: Objectives Aspergillus is a ubiquitous organism and CF lungs are vulnerable to infection. Aspergillus is known to be found in high numbers in organic matter and during building works. We commenced environmental fungal air sampling prior to and during building work carried out adjacent to our CF unit to evaluate and monitor our air quality. Methods An SAS Microbial air sampler sampled 1 cubic metre of air over 5 min in assigned locations throughout our ward on a weekly basis. Outdoor samples were taken during this time for comparison. Each plate was cultured for 4 days at 30°C. Results The predominant organism was Aspergillus fumigatus, the second Penicillium Spp. Site 1, outdoor air: revealed a maximum yield of 59 colony forming units (CFU) A. fumigatus (range 0-59 CFU, median 9), and 8 CFU Penicillium (0-8, median 0). Site 2, ward corridor: 29 CFU A. fumigatus (0-29 CFU, median 2.5), 15 CFU Penicillium (0-15, median 0.5). Site 3, patient room: 12 CFU A. fumigatus (0-12 CFU, median 2), 9 CFU Penicillium (0-9, median 0). Site 4, positive pressure anteroom: 2 CFU A. fumigatus (0-2 CFU, median 0), 1 CFU Penicillium (0-1 CFU, median 0). Site 5, patient room: 58 CFU A. fumigatus (0-58 CFU, median 4.5), 5 CFU Penicillium (0-5 CFU, median 2.5). There was a clear rise in Aspergillus yield demonstrated during the summer months in all areas except our positive pressure anteroom which persistently yielded negligible fungal growth. Conclusions High levels of A. fumigatus were persistently yielded from sites 1, 2, 3 and 5, both at baseline and during building works, with peak counts being found in the summer months. Fungal ingress onto the ward was demonstrated in all sites except in our positive pressure anteroom, with ≥ 10 air changes per hour, leading to isolation rooms. This gives doubts about the efficacy of our ventilation system in the majority of locations throughout our ward and needs to be clinically correlated with patient outcomes.

Psychological

Online versus paper-based screening for depression and anxiety in adults with cystic fibrosis in Ireland: a cross-sectional exploratory study.

Author(s): Cronly, Jennifer; Duff, Alistair J; Riekert, Kristin A; Perry, Ivan J; Fitzgerald, Anthony P

Source: BMJ open; Jan 2018; vol. 8 (no. 1); p. e019305

Publication Type(s): Journal Article

Available at [BMJ open](#) - from Europe PubMed Central - Open Access

Abstract: OBJECTIVE To compare online and paper-based screening for depression and anxiety in adults with cystic fibrosis (CF). DESIGN AND SETTING Cross-sectional study in CF clinics in Ireland and through the Cystic Fibrosis Ireland online community. PARTICIPANTS 160 adult patients aged 18 or above were recruited. Of these, 147 were included in the analysis; 83 online and 64 paper-based. The remaining 13 were excluded because of incomplete data. MEASURES Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). Data on pulmonary function (forced expiratory volume in 1 s %) and body mass index were self-reported based on clinical assessments. Sociodemographic data were collected. RESULTS Compared with the paper-based participants, the online participants were more likely to be female (61.7% vs 48.4%), older (mean 32.2 vs 28.2 years) and were more likely to be married (32.5% vs 15.6%), living with their spouse or partner (42.5% vs 22.6%) and working either full time (33.7% vs 15.9%) or part time (30.1% vs 17.5%). The prevalence rates of elevated anxiety and depression were not significantly different ($P=0.71$ and $P=0.56$). HADS anxiety and depression scores were not statistically different between online ($P=0.83$) and paper-based ($P=0.92$) participants based on Mann-Whitney U test. A significant negative correlation was found between depression and pulmonary function ($r=-0.39$, $P=0.01$) and anxiety and pulmonary function ($r=-0.36$, $P=0.02$). Based on Cronbach's alpha, there were no statistically significant differences between the online and paper-based participants on the internal consistency of the HADS anxiety ($P=0.073$) and depression ($P=0.378$) scales. CONCLUSIONS Our findings suggest

that online and paper-based screening for depression and anxiety in adult patients with CF yield comparable findings on prevalence rates and scores, associations with health and internal consistency of subscales. This study highlights that online screening offers an alternative method to paper-based screening. Further research with a larger sample and assessment of measurement equivalence between online and paper based screening is needed to confirm our results.

Effect of oral glycine on the clinical, spirometric and inflammatory status in subjects with cystic fibrosis: a pilot randomized trial.

Author(s): Vargas, Mario H; Del-Razo-Rodríguez, Rosangela; López-García, Amando

Source: BMC pulmonary medicine; Dec 2017; vol. 17 (no. 1); p. 206

Publication Type(s): Journal Article

Available at [BMC pulmonary medicine](#) - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUND Patients with cystic fibrosis (CF) have airway inflammation that contributes to symptoms and to pulmonary function derangement. Current drugs used to diminish airway inflammation improve the clinical and spirometric status of patients with CF, but their use is limited due to their undesired side effects, for example, glucose intolerance, growth retardation, and cataracts with corticosteroids, gastrointestinal toxicity with ibuprofen, and macrolide resistance with azithromycin. Glycine is known to decrease activation of inflammatory cells, including alveolar macrophages and neutrophils, and is relatively inexpensive, palatable, and virtually devoid of untoward effects. These features make glycine a good candidate for antiinflammatory treatment of CF. Thus, we aimed to explore whether glycine can exert a beneficial effect in a population of patients with CF. METHOD This was a randomized, double blinded, cross-over pilot clinical trial. Subjects with CF received, in random order, oral glycine (0.5 g/kg/day, dissolved in any liquid) and placebo (glass sugar), each during 8 weeks with an intermediate 2-week wash-out period. RESULT Thirteen subjects aged 6-23 years, 8 females, completed the two arms of the study. As compared with placebo, after glycine intake patients had better symptom questionnaire scores ($p = 0.02$), mainly regarding sputum features and dyspnea. While spirometric variables tended to decline during placebo intake, they remained stable or even increased during glycine treatment ($p = 0.04$ to $p = 0.003$). In this context, FEV1 declined 8.6% after placebo and increased 9.7% at the end of the glycine period. Pulse oximetry improved after glycine intake ($p = 0.04$ vs. placebo). TNF- α in serum and IL-6 and G-CSF in sputum tended to decline at the end of the glycine period ($p = 0.061$, $p = 0.068$ and $p = 0.04$, respectively, vs placebo). Glycine was remarkably well tolerated. CONCLUSION The clinical, spirometric and inflammatory status of subjects with CF improved after just 8 weeks of glycine intake, suggesting that this amino acid might constitute a novel therapeutic tool for these patients. Thus, further studies are warranted. TRIAL REGISTRATION www.clinicaltrials.gov , registration number: NCT01417481 , date of registration: March 12, 2012.

Nutritional

The effect of enteral tube feeding in cystic fibrosis: A registry based study

Author(s): Libeert D.; Wanyama S.; Thomas M.; Declercq D.; Van daele S.; De Baets F.

Source: Journal of Cystic Fibrosis; 2018

Publication Type(s): Article In Press

Abstract:Background: Long-term effect of enteral tube feeding (ETF) in cystic fibrosis (CF) remains equivocal. Methods: A Belgian CF registry based, retrospective, longitudinal study, evaluated the pre- and post- ETF ($n = 113$) clinical evolution and compared each patient with 2 age, gender, pancreatic status and genotype class-matched controls. Results: At baseline ETF had a worse BMI z-

score ($p < 0.0001$) and FEV1% ($p < 0.0001$) compared to controls. Patients eventually receiving ETF, had already a significant worse nutritional status and pulmonary function at first entry in the registry. Both parameters displayed a significant decline before ETF-introduction. ETF had more hospitalization and intravenous antibiotic (IVAB) treatment days ($p < 0.0001$). After ETF introduction hospitalizations and IVAB decreased significantly. After ETF-introduction BMI z-score recuperated towards the original curve before the decline, but remained below the controls. Starting ETF had no effect on rate of height gain in children. The pre-index FEV1 decline ($-1.52\%/year$ ($p = 0.002$)) stabilized to $+0.39\%/year$ afterwards. Controls displayed decline of $-0.48\%/year$ ($p < 0.0001$). Conclusion: ETF introduction improved BMI z-score and stabilized FEV1, associated with less hospitalizations and IVAB treatments. Higher mortality and transplantation in the ETF cases, leading to drop-outs, made determination of the effect size difficult. Copyright © 2018 European Cystic Fibrosis Society.

Survival of Patients with Cystic Fibrosis Depending on Mutation Type and Nutritional Status.

Author(s): Szwed, A; John, A; Goździk-Spychalska, J; Czaiński, W; Czerniak, W; Ratajczak, J

Source: Advances in experimental medicine and biology; 2018; vol. 1023 ; p. 65-72

Publication Type(s): Journal Article

Abstract:The purpose of the study was to evaluate the influence of nutrition and of the severity of mutation type on survival rate in cystic fibrosis (CF) patients. Data were longitudinally collected from 60 hospitalized adult CF patients, aged 18-50. The variables consisted of body mass index (BMI) ratio, Cole's BMI cut-off points, severity of mutation type, and survival rate of CF patients. We found that the mean BMI was strongly associated with the severity of mutation type and was significantly lower in patients with severe mutations of grade I and II. The mutation type significantly affected the patients' survival rate; survival was greater in patients with mild and undefined mutation types. The BMI and Cole's cut-off points also had a significant influence on survival rate. CF patients, who suffered from malnutrition and emaciation, had a shorter survival rate than those with proper nutritional status. In conclusion, the study findings confirmed a significant effect of nutritional status and of mutation type on survival rate of CF patients.

Role of vitamin D on gut microbiota in cystic fibrosis.

Author(s): Kanhere, Mansi; Chassaing, Benoit; Gewirtz, Andrew T; Tangpricha, Vin

Source: The Journal of steroid biochemistry and molecular biology; Jan 2018; vol. 175 ; p. 82-87

Publication Type(s): Journal Article Review

Abstract:This review explores the potential for vitamin D to favorably alter the gut microbiota, given emerging evidence of the role of vitamin D in controlling mucosal inflammation in the gut. It will focus on cystic fibrosis (CF) patients, a population with both vitamin D deficiency due to gut malabsorption and an altered gut microbiota composition. Recent evidence shows that vitamin D acts to maintain the integrity of the gut mucosal barrier by enhancement of intercellular junctions that control mucosal permeability and reduction of pro-inflammatory cytokines such as IL-8. In addition, vitamin D receptor-mediated signaling has been shown to inhibit inflammation-induced apoptosis of intestinal epithelial cells. As a result of these effects on the intestinal mucosa, maintenance of sufficient vitamin D status may be essential for the development of a healthy gut microbiota, particularly in conditions defined by chronic mucosal inflammation such as CF. We hypothesize here that high dose vitamin D may be used to favorably manipulate the aberrant mucosa seen in patients with CF. This may result in improved clinical outcomes in association with a low inflammatory environment that allows beneficial bacteria to outcompete opportunistic pathogens. Current evidence is sparse but encouraging, and additional evidence is needed to establish vitamin D as a therapeutic approach for gut microbiota modification.

Vitamin D3 supplementation among adult patients with cystic fibrosis.

Author(s): Coriati, Adèle; Labrèche, Évelyne; Mailhot, Marjolaine; Mircescu, Hortensia; Berthiaume, Yves; Lavoie, Annick; Rabasa-Lhoret, Rémi

Source: Clinical nutrition (Edinburgh, Scotland); Dec 2017; vol. 36 (no. 6); p. 1580-1585

Publication Type(s): Journal Article

Abstract:BACKGROUND & AIMS Vitamin D (Vit D) deficiency in cystic fibrosis (CF) is partially secondary to exocrine pancreatic insufficiency. Our aim was to establish a Vit D3 supplementation protocol that will increase 25(OH)D to the recommended level (30 ng/mL).METHODS Retrospective study of 200 patients (≥18 years) conducted from February 2007 to June 2014 at the CF clinic of the Centre Hospitalier de l'Université de Montréal. Vit D3 supplementation protocol was 1600 IU/day or 10,000 IU/week during the summer (May 1st to October 31st) and 3200 IU/day or 20,000 IU/week during the winter (November 1st to April 30th), in addition to the 1200 IU/day included in multivitamins.RESULTS Significant increase in serum 25(OH)D levels from baseline (25.9 ± 10.3 ng/mL) to follow-up (37.0 ± 11.4 ng/mL) (P ≤ 0.001). At follow-up, increased doses during the winter improved serum 25(OH)D levels to a degree comparable to the summer.CONCLUSIONS This supplementation protocol is efficient and needs to be tested in other CF adult cohorts and correlated to potential health benefit measurements.

Other

Drugs during pregnancy and breast feeding in women diagnosed with Cystic Fibrosis - An update.

Author(s): Kroon, M A G M; Akkerman-Nijland, A M; Rottier, B L; Koppelman, G H; Akkerman, O W

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 17-25

Sexual and reproductive health care utilization and preferences reported by young women with cystic fibrosis.

Author(s): Kazmerski, Traci M; Sawicki, Gregory S; Miller, Elizabeth; Jones, Kelley A; Abebe, Kaleab Z

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 64-70

Sexual and reproductive health behaviors and experiences reported by young women with cystic fibrosis.

Author(s): Kazmerski, Traci M; Sawicki, Gregory S; Miller, Elizabeth; Jones, Kelley A; Abebe, Kaleab Z

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2018; vol. 17 (no. 1); p. 57-63

Home monitoring of cystic fibrosis

Author(s): Kwon M.; Willey D.; Patel N.; Roberson J.

Source: Journal of Clinical Outcomes Management; Jan 2018; vol. 25 (no. 1)

The experience of men and women with cystic fibrosis who have become a parent: a qualitative study.

Author(s): Jessup, Melanie; Li, Anne; Fulbrook, Paul; Bell, Scott

Source: Journal of clinical nursing; Dec 2017

Personalized Medicine in CF: From Modulator Development to Therapy for Cystic Fibrosis Patients with Rare CFTR Mutations.

Author(s): Harutyunyan, Misak; Huang, Yunjie; Mun, Kyu-Shik; Yang, Fanmuyi; Arora, Kavisha

Source: American journal of physiology. Lung cellular and molecular physiology; Dec 2017

Functional capacity, peripheral muscle strength, and quality of life following interval versus continuous rehabilitative exercise training in cystic fibrosis

Author(s): Kaltsakas G.; Koulouris N.G.; Anastasopoulos N.; Chynkiamis N.; Vogiatzis I.; Zeliou P

Source: Thorax; Dec 2017; vol. 72

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