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Cystic Fibrosis

Current Awareness Bulletin

Jan-Feb 2017

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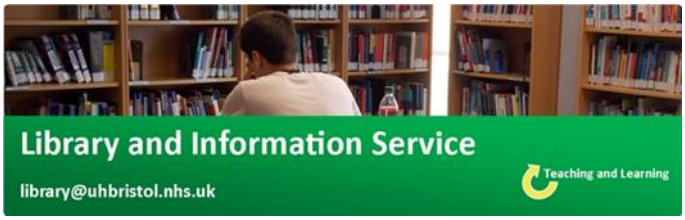

Training Sessions 2017

All sessions are 1 hour

January (13.00)	
Tues 10th	**Literature Searching**
Wed 18th	**Critical Appraisal**
Thur 26th	**Statistics**
February (12.00)	
Fri 3rd	**Literature Searching**
Mon 6th	**Critical Appraisal**
Tues 14th	**Statistics**
Wed 22nd	**Literature Searching**

Your Outreach Librarian: Jo Hooper

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Contents

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New Additions to NICE, the Cochrane Library and UptoDate

NICE National Institute for Health and Care Excellence

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cysticfibrosis
Source: Cochrane Database of Systematic Reviews - 19 January 2017
More: Systematic Reviews

High-frequency chest wall compression for cystic fibrosis
Source: Centre for Reviews and Dissemination Health Technology Assessments - CRD HTA - 05 January 2017
Read Summary
- **More:** Health Technology Assessments

Prevention of Staphylococcus aureus lung infection in cystic fibrosis
Source: British National Formulary for Children - BNFc - 18 January 2017
Read Summary
- **More:** Prescribing and Technical Information

SMI B 40: Investigation of specimens for Mycobacterium species [PDF]
Source: GOV UK - Source: Public Health England - 17 January 2017
More: Policy and Strategy

Ivacaftor and lumacaftor
Source: British National Formulary for Children - BNFc - 18 January 2017
Read Summary
- **More:** Prescribing and Technical Information

Ivacaftor and lumacaftor
Source: British National Formulary - BNF - 18 January 2017
Read Summary
- **More:** Prescribing and Technical Information

Cochrane Library

Timing of hypertonic saline inhalation for cystic fibrosis

Mark Elkins, Ruth Dentice

Online Publication Date: December 2016

Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis

Valerie Waters, Felix Ratjen

Online Publication Date: December 2016

Single versus combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis

Heather E Elphick, Alison Scott

Online Publication Date: December 2016

UpToDate®

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

Cystic fibrosis: Antibiotic therapy for lung disease

Literature review current through: Jan 2017. | **This topic last updated:** Jun 15, 2016

- Periodic hospitalization
- Early eradication of P. aeruginosa
- Nontuberculous mycobacteria
- Summary and recommendations

Cystic fibrosis: Genetics and pathogenesis

Literature review current through: Jan 2017. | **This topic last updated:** Oct 26, 2016.

- Disease pathogenesis
- Summary

Cystic fibrosis: Nutritional issues

Literature review current through: Jan 2017. | **This topic last updated:** Dec 09, 2016.

- Cystic fibrosis-related liver disease
- Summary and recommendations

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UpToDate

NHS Evidence

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Current Awareness 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**
- **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

The diagnosis and management of respiratory viral infections in cystic fibrosis.

Author(s): Flight, W G; Jones, A M

Source: Expert review of respiratory medicine; Jan 2017

Publication Type(s): Journal Article

Abstract: Introduction Respiratory viruses, such as those that cause influenza and the common cold, are a regular feature of life for the entire human population. Among people with CF, these viruses are associated with prolonged respiratory illness and show a clear association with pulmonary exacerbations which in turn are associated with lung function decline and risk of death. Human rhinovirus is the most commonly encountered respiratory viral pathogen in CF although adenovirus, bocavirus, coronavirus, influenza, parainfluenza, metapneumovirus and respiratory syncytial virus are all also responsible for infections in this population. Areas Covered This article reviews the epidemiology, clinical impact and therapeutic options for respiratory virus infection in both children and adults with CF. Expert Commentary The management of CF to date has largely focused on airway clearance strategies, nutritional support and aggressive antibacterial therapy. We highlight the significant role that respiratory viruses play in CF lung disease and argue that these pathogens represent an under-exploited target in the battle to control patients' symptoms and disease progression.

Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: Is the oral glucose tolerance test still the standard?

Author(s): Mainguy C.; Bellon G.; Delaup V.; Mazur S.; Reix P.; Ginoux T.; Kassai-Koupai B.; Rabilloud M.; Remontet L.

Source: Journal of Pediatric Endocrinology and Metabolism; Jan 2017; vol. 30 (no. 1); p. 27-35

Publication Date: Jan 2017

Publication Type(s): Journal: Article

Abstract: Cystic fibrosis-related diabetes (CFRD) is a late cystic fibrosis (CF)-associated comorbidity whose prevalence is increasing sharply lifelong. Guidelines for glucose metabolism (GM) monitoring rely on the oral glucose tolerance test (OGTT). However, this test is neither sensitive nor specific. The aim of this study was to compare sensitivity and specificity of different methods for GM monitoring

in children and adolescents with CF. Continuous glucose monitoring system (CGMS), used as the reference method, was compared with the OGTT, intravenous glucose tolerance test (IGTT), homeostasis model assessment index of insulin resistance (HOMA-IR), homeostasis model assessment index of beta-cell function (HOMA-%B) and glycated haemoglobin A1C. Patients were classified into three groups according to CGMS: normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM). Twenty-nine patients (median age: 13.1 years) were recruited. According to CGMS, 11 had DM, 12 IGT and six NGT, whereas OGTT identified three patients with DM and five with IGT. While 13 of 27 had insulin deficiency according to IGTT, there was 19 of 28 according to HOMA-%B. According to HOMA-IR, 12 of 28 had insulin resistance. HOMA-%B was the most sensitive method for CFRD screening [sensitivity 91% (95% CI), specificity 47% (95% CI) and negative predictive value 89% (95% CI)]. OGTT showed the weak capacity to diagnose DM in CF and should no longer be considered as the reference method for CFRD screening in patients with CF. In our study, HOMA-%B showed promising metrics for CFRD screening. Finally, CGMS revealed that pathological glucose excursions were frequent even early in life.

Ciprofloxacin Dry Powder for Inhalation in Patients with Non-Cystic Fibrosis Bronchiectasis or Chronic Obstructive Pulmonary Disease, and in Healthy Volunteers

Author(s): Stass H.; Nagelschmitz J.; Kappeler D.; Sommerer K.; Kietzig C.; Weimann B.

Source: Journal of Aerosol Medicine and Pulmonary Drug Delivery; Feb 2017; vol. 30 (no. 1); p. 53-63

Publication Type(s): Journal: Article

Abstract: Background: Ciprofloxacin dry powder for inhalation (Ciprofloxacin DPI) is in development as long-term intermittent therapy to reduce the frequency of acute exacerbations in non-cystic fibrosis bronchiectasis (NCFB) patients with respiratory bacterial pathogens. There is no approved therapy in this indication. Reliable, reproducible lung deposition is a prerequisite for inhaled drugs. Methods: In this phase I study, six patients with NCFB, six with chronic obstructive pulmonary disease (COPD), and 12 healthy volunteers (HVs), received one dose of 99mTc-Ciprofloxacin DPI 32.5 mg to assess pulmonary drug deposition by quantitative scintigraphy. 81mKrypton ventilation scans were performed to map lung contours. Systemic exposure as mediated by absorption in the lung was measured using the charcoal block method. HVs ingested activated charcoal orally (20 g before and 2 x 10 g after inhalation) to block gastrointestinal absorption of drug swallowed during inhalation. Indirect determination of pulmonary drug deposition was based on plasma and urine pharmacokinetic (PK) data. Results: Scintigraphic data revealed high, reproducible lung deposition in all participants (intrapulmonary deposition relative to nominal dose, mean [standard deviation; range]: NCFB, 53% [11%; 38%-64%]; COPD, 51% [10%; 34%-61%]; HVs, 51% [7%; 40%-64%] to 53% [8%; 44%-70%]). Similar ratios of central-to-peripheral airway deposition were seen across groups. Systemic exposure to ciprofloxacin was low. Relative bioavailability of Ciprofloxacin DPI was reduced by ~60% after charcoal block, suggesting that systemic exposure was mainly caused by uptake via the lung. Lung deposition of 30% was estimated from PK data, but this may be an underestimation due to drug clearance from the lung and transintestinal secretion. Adverse events were no more frequent or severe in patients with lung diseases versus HVs, and no clinically relevant influence on vital signs or lung function was observed. Conclusion: This study supports the continued development of Ciprofloxacin DPI in NCFB patients with respiratory bacterial pathogens.

A prospective pilot study of home monitoring in adults with cystic fibrosis (HOME-CF): Protocol for a randomised controlled trial

Author(s): Choyce J.; Whitehouse J.L.; Nash E.F.; Shaw K.L.; Sitch A.J.; Mistry H.

Source: BMC Pulmonary Medicine; Jan 2017; vol. 17 (no. 1)

Publication Type(s): Journal: Article

Available in full text at BMC Pulmonary Medicine - from National Library of Medicine

Abstract: Background: Home monitoring has the potential to detect early pulmonary exacerbations in people with cystic fibrosis (CF), with consequent improvements in health outcomes and healthcare associated costs. This study aims to assess the effects of home monitoring on hospital admissions, quality of life, antibiotic requirements, exacerbation frequency, lung function, nutritional outcomes, anxiety, depression, costs and health outcomes, as well as the qualitative effects on the patient experience. Methods: This randomised controlled mixed-methods trial aims to recruit 100 adults with CF cared for in one large regional CF centre. Participants are randomly allocated 1:1 to the intervention group (twice-weekly home monitoring of symptoms measured by the Cystic Fibrosis Respiratory Symptom Diary - Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) and Forced Expiratory Volume in one second (FEV1)) or a control group (routine clinical care) for the 12-month study period. Measurements are recorded at study visits at baseline, 3, 6, 9 and 12 months. Spirometry, body weight, co-morbidities, medications, hospital inpatient days, courses of antibiotics (oral and intravenous), pulmonary exacerbations (defined by the modified Fuchs criteria) are recorded at each study visit. Health status, capability and health economics are measured at each study visit by the Hospital Anxiety and Depression Scale (HADS), the ICEpop CAPability measure for Adults (ICECAP-A), EuroQol 5 dimensions (EQ-5D-5L) questionnaire and an adapted resource use questionnaire. The patient experience is assessed by semi-structured qualitative interviews at baseline and 12 months. Discussion: Results from this study will help to determine the effect of home monitoring on inpatient bed days and quality of life in adults with CF, as well as other relevant health and health economic outcomes. Trial registration: This study protocol is registered with Clinicaltrials.gov (NCT02994706), date registered 16th July 2014 Copyright © 2017 The Author(s).

Cystic Fibrosis Diagnostic Challenges over 4 Decades: Historical Perspectives and Lessons Learned

Author(s): Farrell P.M.; White T.B.; Derichs N.; Castellani C.; Rosenstein B.J.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Journal: Article

Abstract: Objective Because cystic fibrosis (CF) can be difficult to diagnose, and because information about the genetic complexities and pathologic basis of the disease has grown so rapidly over the decades, several consensus conferences have been held by the US CF Foundation, and a variety of other efforts to improve diagnostic practices have been organized by the European CF Society. Despite these efforts, the application of diagnostic criteria has been variable and caused confusion. Study design To improve diagnosis and achieve standardization in terms and definitions worldwide, the CF Foundation in 2015 convened a committee of 32 experts in the diagnosis of CF from 9 countries. As part of the process, all previous consensus-seeking exercises sponsored by the CF Foundation, along with the important efforts of the European CF Society, were comprehensively and critically reviewed. The goal was to better understand why consensus conferences and their publications have not led to the desired results. Results Lessons learned from previous diagnosis consensus processes and products were identified. It was decided that participation in developing a consensus was generally not inclusive enough for global impact. It was also found that many efforts to address sweat test issues were valuable but did not always improve clinical practices as CF diagnostic testing evolved. It also became clear from this review that premature applications of potential diagnostic tests such as nasal potential difference and intestinal current measurement

should be avoided until validation and standardization occur. Finally, we have learned that due to the significant and growing number of cases that are challenging to diagnose, an associated continuing medical education program is both desirable and necessary. Conclusions It is necessary but not sufficient to organize and publish CF diagnosis consensus processes. Follow-up implementation efforts and monitoring practices seem essential. Copyright © 2016

Bronchodilators in cystic fibrosis: a critical analysis

Author(s): Barry P.J.; Flume P.A.

Source: Expert Review of Respiratory Medicine; Jan 2017; vol. 11 (no. 1); p. 13-20

Publication Type(s): Journal: Article

Abstract: Introduction: Cystic fibrosis airways disease is characterized by chronic inflammation and infection resulting in bronchiectasis. Published guidelines recommend medications for use by CF patients to maintain lung health. There are conflicting recommendations regarding inhaled bronchodilators. This is primarily because of the interpretation of the available evidence, which suffers from studies using small numbers of subjects, varying doses and durations of treatment, and modest effects on clinically relevant endpoints. Areas covered: Herein we review the available evidence demonstrating the challenge in determining whether bronchodilators have benefit for patients. We examine the potential indications and the current guidance from clinical studies. We highlight the outstanding questions examining bronchodilator use in CF. Expert commentary: The use of bronchodilators in CF remains commonplace despite the lack of solid evidence. Further studies should define key endpoints to determine a role for bronchodilators in light of a substantial treatment burden endured by people with CF. Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group.

Early lung surveillance of cystic fibrosis: what have we learnt?

Author(s): Foong R.E.; Rosenow T.; Garratt L.W.; Hall G.L.

Source: Expert Review of Respiratory Medicine; Jan 2017; vol. 11 (no. 1); p. 1-3

Publication Type(s): Journal: Editorial

Exocrine and endocrine interactions in cystic fibrosis: A potential key to understanding insulin secretion in health and disease?

Author(s): Cobelli C.; Vella A.

Source: Diabetes; Jan 2017; vol. 66 (no. 1); p. 20-22

Publication Type(s): Journal: Note

Available in full text at Diabetes - from Highwire Press

Can Cystic Fibrosis Patients Finally Catch a Breath With Lumacaftor/Ivacaftor?

Author(s): Schneider E.K.; Reyes-Ortega F.; Li J.; Velkov T.

Source: Clinical Pharmacology and Therapeutics; Jan 2017; vol. 101 (no. 1); p. 130-141

Publication Type(s): Journal: Review

Abstract: Cystic fibrosis (CF) is a life-limiting disease caused by defective or deficient cystic fibrosis transmembrane conductance regulator (CFTR) activity. The recent US Food and Drug Administration (FDA) approval of lumacaftor combined with ivacaftor (Orkambi) targets patients with the F508del-CFTR. The question remains: Is this breakthrough combination therapy the "magic-bullet" cure for the vast majority of patients with CF? This review covers the contemporary clinical and scientific knowledge-base for lumacaftor/ivacaftor and highlights the emerging issues from recent conflicting literature reports. Copyright © 2016 American Society for Clinical Pharmacology and Therapeutics

Cystic Fibrosis is Associated with Adverse Neonatal Outcomes in Washington State, 1996-2013

Author(s): Ramos K.J.; Sack C.S.; Mitchell K.H.; Starr J.R.; Goss C.H.

Source: Journal of Pediatrics; Jan 2017; vol. 180 ; p. 206

Publication Type(s): Journal: Article

Abstract: Objective To determine whether cystic fibrosis (CF) is associated with adverse neonatal outcomes in a recent birth cohort in the US. Study design A retrospective matched cohort study of infants born in Washington State from 1996 to 2013 was identified through birth certificate data and linked to statewide hospital discharge data. Infants with CF were identified by hospitalization (through age 5 years) in which a CF-specific International Classification of Diseases, Ninth Revision code was recorded. "Unexposed" infants lacked CF-related International Classification of Diseases, Ninth Revision codes and were randomly selected among births, frequency-matched to "exposed" infants on birth year. Associations of CF with adverse neonatal outcomes (low birth weight [LBW], small for gestational age [SGA], preterm birth, and infant mortality) were estimated through Poisson regression. We performed extreme value imputation to address possible ascertainment bias. Results We identified 170 infants with CF and 3400 unexposed infants. CF was associated with increased relative risk (95% CI) of 3.5 (2.5-4.9), 1.6 (1.1-2.4), 3.0 (2.2-4.0), and 6.8 (1.7-26.5) for LBW, SGA, preterm birth, and infant death, respectively. The estimated relative risks were similar among infants born from 2006 to 2013, except SGA was no longer associated with CF diagnosis. Results were robust to extreme value imputation and exclusion of infants with meconium ileus. Conclusions Observed associations of CF with LBW, preterm birth, and infant death are unlikely to be due to ascertainment bias. Further work is needed to determine how to prevent these adverse neonatal outcomes. Copyright © 2016 Elsevier Inc.

Changes in the inner ear structures in cystic fibrosis patients

Author(s): Pauna H.F.; Monsanto R.C.; Kurata N.; Paparella M.M.; Cureoglu S.

Source: International Journal of Pediatric Otorhinolaryngology; Jan 2017; vol. 92 ; p. 108-114

Publication Type(s): Journal: Article

Abstract: Objective Although prolonged use of antibiotics is very common in cystic fibrosis (CF) patients, no studies have assessed the changes in both cochlear and peripheral vestibular systems in this population. Methods We used human temporal bones to analyze the density of vestibular dark, transitional, and hair cells in specimens from CF patients who were exposed to several types of antibiotics, as compared with specimens from an age-matched control group with no history of ear disease or antibiotic use. Additionally, we analyzed the changes in the elements of the cochlea (hair cells, spiral ganglion neurons, and the area of the stria vascularis). Data was gathered using differential interference contrast microscopy and light microscopy. Results In the CF group, 83% of patients were exposed to some ototoxic drugs, such as aminoglycosides. As compared with the control group, the density of both type I and type II vestibular hair cells was significantly lower in all structures analyzed; the number of dark cells was significantly lower in the lateral and posterior

semicircular canals. We noted a trend toward a lower number of both inner and outer cochlear hair cells at all turns of the cochlea. The number of spiral ganglion neurons in Rosenthal's canal at the apical turn of the cochlea was significantly lower; furthermore, the area of the stria vascularis at the apical turn of the cochlea was significantly smaller. Conclusions Deterioration of cochlear and vestibular structures in CF patients might be related to their exposure to ototoxic antibiotics. Well-designed case-control studies are necessary to rule out the effect of CF itself. Copyright © 2016 Elsevier Ireland Ltd

Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation

Author(s): Farrell P.M.; Rock M.; White T.B.; Hempstead S.E.; Marshall B.C.; Ren C.L.; Howenstine M.; Accurso F.; Derichs N.; McColley S.A.; Rosenfeld M.; Sermet-Gaudelus I.; Southern K.W.; Sosnay P.R.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Journal: Article

Abstract: Objective Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis criteria. Study design To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with CFTR mutations. An a priori threshold of>80% affirmative votes was required for acceptance of each recommendation statement. Results After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and a second round of voting. Conclusions It is recommended that diagnoses associated with CFTR mutations in all individuals, from newborn to adult, be established by evaluation of CFTR function with a sweat chloride test. The latest mutation classifications annotated in the Clinical and Functional Translation of CFTR project (http://www.cftr2.org/index.php) should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis; these terms are now merged and equivalent, and CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis may be used. International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes for use in diagnoses associated with CFTR mutations are included. Copyright © 2016

Glomerular and Tubular Renal Function after Repeated Once-Daily Tobramycin Courses in Cystic Fibrosis Patients

Author(s): Stehling F.; Mellies U.; Buscher R.; Hoyer P.F.; Grosse-Onnebrink J.

Source: Pulmonary Medicine; 2017; vol. 2017

Publication Type(s): Journal: Article

Abstract: Introduction. Antibiotic treatment regimens against Pseudomonas aeruginosa lung infection in cystic fibrosis (CF) patients often include aminoglycoside antibiotics that may cause chronic renal failure after repeated courses. Aminoaciduria is an early marker of acute aminoglycoside-induced renal tubular dysfunction. We hypothesized that urinary amino acid reabsorption is decreased after repeated once-daily tobramycin therapies. Methods. In this

prospective cross-sectional study creatinine clearance was estimated by the Schwartz and the Cockcroft-Gault formula. Tubular amino acid reabsorption was determined by ion exchange chromatography in 46 patients with CF who received multiple tobramycin courses (6.3+/-10.1 (1-57)) in a once-daily dosing regimen and 10 who did not. Results. Estimated creatinine clearance employing the Cockcroft-Gault was mildly reduced in 17/46 (37%) of the patients who received tobramycin and 5/10 (50%) of the patients who did not but in none using the Schwartz formula. No association with lifetime tobramycin courses was found. Tubular amino acid reabsorption was not influenced by the amount of once-daily tobramycin courses. Conclusion. Clinically not significant reduction of eCCL occurred in a minority of CF patients. However, chronic tubular dysfunction was not present in patients with CF repeatedly treated with tobramycin in the once-daily dosing scheme.

Timing of hypertonic saline and airway clearance techniques in adults with cystic fibrosis during pulmonary exacerbation: Pilot data from a randomised crossover study

Author(s): O'Neill K.; Elborn J.S.; Moran F.; Tunney M.M.; Bradbury I.; Downey D.G.; Rendall J.; Bradley J.M.

Source: BMJ Open Respiratory Research; Jan 2017; vol. 4 (no. 1)

Publication Type(s): Journal: Article

Abstract: Background: Streamlining the timing of treatments in cystic fibrosis (CF) is important to optimise adherence while ensuring efficacy. The optimal timing of treatment with hypertonic saline (HTS) and airway clearance techniques (ACT) is unknown. Objectives: This study hypothesised that HTS before ACT would be more effective than HTS during ACT as measured by Lung Clearance Index (LCI). Methods: Adults with CF providing written informed consent were randomised to a crossover trial of HTS before ACT or HTS during ACT on consecutive days. ACT treatment consisted of Acapella Duet. Patients completed LCI and spirometry at baseline and 90 min post treatment. Mean difference (MD) and 95% CIs were reported. Results: 13 subjects completed the study (mean (SD) age 33 (12) years, forced expiratory volume in 1second % (FEV1%) predicted 51% (22), LCI (no. turnovers) 14 (4)). Comparing the two treatments (HTS before ACT vs HTS during ACT), the change from baseline to 90 min post treatment in LCI (MD (95% CI) -0.02 (-0.63 to 0.59)) and FEV1% predicted (MD (95% CI) -0.25 (-2.50 to 1.99)) was not significant. There was no difference in sputum weight (MD (95% CI) -3.0 (-14.9 to 8.9)), patient perceived ease of clearance (MD (95% CI) 0.4 (-0.6 to 1.3) or satisfaction (MD (95% CI) 0.4 (-0.6 to 1.5)). The time taken for HTS during ACT was significantly shorter (MD (95% CI) 14.7 (9.8 to 19.6)). Conclusions: In this pilot study, HTS before ACT was no more effective than HTS during ACT as measured by LCI.

Reduced survival in adult cystic fibrosis despite attenuated lung function decline

Author(s): Keating C.; Poor A.D.; DiMango E.; Liu X.; Chiuzan C.; Backenroth D.; Zhang Y.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 78-84

Publication Type(s): Journal: Article

Abstract: Background There is limited data on disease progression and survival in adult diagnosis cystic fibrosis (CF). This study evaluates change of lung function over time and rates of death/lung transplant in adult diagnosis CF. Methods The CF Foundation Patient Registry was reviewed for patients diagnosed 1993-2003. Rate of FEV1 decline was calculated up to 2010 for age groups 6-11, 12-17, and 18 and above. Kaplan Meier method was used for 10 and 15 year survival rate calculations for patients diagnosed as adults. Cox Proportional hazards models using predictors

affecting disease progression and survival without transplant were run. Results Between 1993 and 2003, 11,884 patients were diagnosed with CF, of which 2848 were ages 6 and older. Annual rate of change of FEV1% predicted over 5 years differed by diagnosis age group: - 1.42% per year for ages 6-11, - 2.04% for ages 12-17 and - 1.13% for ages 18-65 (p 18 years were 76% and 65% by 10 and 15 years, respectively. Of adults with FEV1 of > 70% predicted at diagnosis, 95% were alive without transplant at 10 years, whereas of those with FEV1 < 40% predicted at diagnosis, 31% were alive without transplant at 10 years. Conclusions Lung function declines at a slower rate in adult diagnosis CF. However, particularly in those with low lung function at diagnosis, rates of death or transplant in adult diagnosis CF after 10 and 15 years is not negligible.

Adherence to infection prevention and control guidelines: A vignette-based study of decision-making and risk-taking in young adults with cystic fibrosis

Author(s): Bowmer G.; Dye L.; Lawton C.; Duff A.; Latchford G.; Lee T.; Denton M.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 146-150

Publication Date: Jan 2017

Publication Type(s): Journal: Article

Abstract: Background Balancing cystic fibrosis (CF) care with demands of normal life is associated with decreased adherence to infection prevention and control (IPC) guidelines. Methods Adults with CF, aged 18-25 years, were invited to participate via UK CF Trust social media platforms. An online survey evaluated participants' decision-making in nine clinician-rated vignettes and assessed the perceived influence of infection-related information sources. Results Participants (n = 87, mean 21.4 years [SD = 2.45]; 75% female) were less likely to engage in the high-risk scenarios, although demonstrated greater awareness of cross-infection than environmental risks. Associations between risk-perception and willingness to participate in five vignette-based hypothetical activities were significant ($p < 0.05$). Thematic analysis emphasised influences of past experience and a need to achieve good quality of life. Knowledge gaps were evident. Conclusions People with CF make decisions that discriminate between risk-levels but are not always based on robust knowledge. They also show some inclination towards engaging in risky behaviours.

The fate of inhaled antibiotics after deposition in cystic fibrosis: How to get drug to the bug?

Author(s): Bos A.C.; Passe K.M.; Janssens H.M.; Tiddens H.A.W.M.; Mouton J.W.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 13-23

Publication Type(s): Journal: Review

Abstract: Background Chronic airway infections in patients with cystic fibrosis (CF) are most often treated with inhaled antibiotics of which deposition patterns have been extensively studied. However, the journey of aerosol particles does not end after deposition within the bronchial tree. Objectives To review how local conditions affect the clinical efficacy of antibiotic aerosol particles after deposition in the airways of patients with CF. Methods Electronic databases were searched from inception to September 2015. Original studies describing the effect of CF sputum or bacterial factors on antibiotic efficacy and formulations to increase efficacy were included. Results 35 articles were included which mostly described in vitro studies and mainly investigated aminoglycosides. After deposition, diffusion through the mucus layer was reduced for aminoglycosides, beta-lactam antibiotics and fluoroquinolones. Within CF mucus, low oxygen tension adversely affected aminoglycosides, beta-lactam antibiotics, and chloramphenicol; and molecules inactivated

aminoglycosides but not beta-lactam antibiotics. Finally, the alginate layer surrounding Pseudomonas aeruginosa was an important factor in the resistance against all antibiotics. Conclusions After deposition in the airways, the local efficacy of inhaled antibiotics can be reduced by molecules within CF mucus and the alginate layer surrounding P. aeruginosa.

Airway inflammation in mild cystic fibrosis

Author(s): Eckrich J.; Zissler U.M.; Serve F.; Leutz P.; Schmitt-Grohe S.; Fussbroich D.; Schubert R.; Zielen S.; Eickmeier O.; Smaczny C.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 107-115

Publication Type(s): Journal: Article

Abstract: Background Airway infection and inflammation play major roles in the progression of cystic fibrosis (CF) lung disease. In patients with mild disease, airway inflammation is a clinically relevant and often underdiagnosed feature. Lung function, sputum cell counts, and cytokine profiles in CF with mild disease might be different in patients with and without involvement of small airway disease (SAD). Methods Patients with mild CF (n = 32) and 22 healthy controls were enrolled in this study. Patients with CF were assigned to two groups: (1) patients without SAD (n = 19, median age 12.3 years, MEF25> 50% predicted), and (2) patients with SAD (n = 13 median age, 13.2 years, MEF25< 50% predicted). Lung function parameters were measured, cells in induced sputum were counted, and cytokines/chemokines (IL-1beta, IL-6, IL-8, TNF-alpha) were analyzed by real-time quantitative PCR (qRT-PCR) and cytometric bead array (CBA). Results Patients with CF had significant elevated levels of pro-inflammatory genes in qRT-PCR and secreted gene products in CBA compared to controls. Patients with CF and SAD had significantly increased trapped air (RV/TLC) and pronounced airway inflammation compared to controls as indicated by elevated levels of sputum biomarkers like total cells, neutrophils, and IL6. Conclusions Our study demonstrated that patients with CF with mild disease defined by lung function might be further endotyped according to their involvement of SAD. In patients with CF and SAD, airway neutrophilic inflammation is more pronounced and is in part distinct from that seen in patients without SAD. Copyright © 2016 European Cystic Fibrosis Society.

Therapeutic benefit of ivacaftor in late cystic fibrosis caused by homozygous IVS8-5T CFTR polymorphism

Author(s): Magne F.; Durupt S.; Nove-Josserand R.; Durieu I.; Reynaud Q.; Bey-Omar F.; Laoust L.; Cottin V.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 89-90

Publication Type(s): Journal: Letter

The changing prevalence of pulmonary infection in adults with cystic fibrosis: A longitudinal analysis

Author(s): Ramsay K.A.; Bell S.C.; Wainwright C.E.; Sandhu H.; Geake J.B.; Ballard E.; O'Rourke P.; Reid D.W.; Kidd T.J.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 70-77

Publication Type(s): Journal: Article

Abstract: Background Increased patient longevity and aggressive antibiotic treatment are thought to impact on the microbial composition of the airways of adults with cystic fibrosis (CF). In this study, we sought to determine if a temporal change in the airway microbiology of adults with CF has occurred over time. Methods Longitudinal analysis of sputum microbiology results was undertaken on patients attending a large adult CF centre. Clinical status and health outcomes of transitioning patients were also assessed. Results A decrease in the prevalence of Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia complex and Aspergillus spp. ($p = 0.001$, $p < 0.001$, $p = 0.002$ and $p < 0.001$, respectively) occurred. Improvements in lung function among transitioning patients infected with P. aeruginosa were observed. Conclusion Overtime, a decline in the prevalence of many CF airway pathogens has occurred. Significantly, an incremental improvement in lung function was reported for transitioning patients with current P. aeruginosa infections. Copyright © 2016 European Cystic Fibrosis Society.

Cancer risk among lung transplant recipients with cystic fibrosis

Author(s): Fink A.K.; Marshall B.C.; Yanik E.L.; Safaeian M.; Engels E.A.; Wilschanski M.; Lynch C.F.; Austin A.A.; Copeland G.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 91-97

Publication Type(s): Journal: Article

Abstract: Background Previous studies demonstrated increased digestive tract cancers among individuals with cystic fibrosis (CF), particularly among lung transplant recipients. We describe cancer incidence among CF and non-CF lung recipients. Methods We used data from the US transplant registry and 16 cancer registries. Standardized incidence ratios (SIRs) compared cancer incidence to the general population, and competing risk methods were used for the cumulative incidence of colorectal cancer. Results We evaluated 10,179 lung recipients (1681 with CF). Risk was more strongly increased in CF recipients than non-CF recipients for overall cancer (SIR 9.9 vs. 2.7) and multiple cancers including colorectal cancer (24.2 vs. 1.7), esophageal cancer (56.3 vs. 1.3), and non-Hodgkin lymphoma (61.8 vs. 9.4). At five years post-transplant, colorectal cancer was diagnosed in 0.3% of CF recipients aged 50. Conclusions CF recipients have increased risk for colorectal cancer, suggesting a need for enhanced screening. Copyright © 2016 European Cystic Fibrosis Society.

Cystic fibrosis physicians' perspectives on the timing of referral for lung transplant evaluation: A survey of physicians in the United States

Author(s): Ramos K.J.; Somayaji R.; Lease E.D.; Goss C.H.; Aitken M.L.

Source: BMC Pulmonary Medicine; Jan 2017; vol. 17 (no. 1)

Publication Type(s): Journal: Article

Available in full text at BMC Pulmonary Medicine - from BioMed Central

Abstract: Background: Prior studies reveal that a significant proportion of patients with cystic fibrosis (CF) and advanced lung disease are not referred for lung transplant (LTx) evaluation. We sought to assess expert CF physician perspectives on the timing of LTx referral and investigate their LTx knowledge. Methods: We developed an online anonymous survey that was distributed by the Cystic Fibrosis Foundation (CFF) to the medical directors of all CFF-accredited care centers in the United States in 2015. The survey addressed only adult patients (>18 years old) and was sent to 119 adult CF physicians, 86 CFF-affiliated CF physicians (who see adults and children, but have smaller program sizes than adult or pediatric centers), and 127 pediatric CF physicians (who see some adults, but mostly children). The focus of the questions was on CFF-care center characteristics, physician experience and indications/contraindications to referral for LTx evaluation. Results: There were

114/332 (34%) total responses to the survey. The response rates were: 57/119 (48%) adult physicians, 12/86 (14%) affiliate physicians and 43/127 (34%) pediatric physicians; 2 physicians did not include their CFF center type. Despite the poor ability of FEV11< 30% predicted. Only 54% of respondents report that pulmonary hypertension would trigger referral. Pulmonary hypertension is an internationally recommended indication to list a patient for LTx (not just for referral for evaluation). Very few physicians (N = 17, 15%) employed components of the lung allocation score (LAS) to determine the timing of referral for LTx evaluation. Interestingly, patient preference not to undergo LTx was "often" or "always" the primary patient-related reason to defer referral for LTx evaluation for 41% (47/114) of respondents. Conclusions: Some potential barriers to timely LTx referral for patients with CF include physician knowledge regarding non-lung function-based recommendations related to timing of referral and listing for LTx, and patient preference not to undergo LTx. Further exploration of physician-level and CF patient-level barriers to timely LTx referral is warranted.

Increasing Incidence of Multidrug Resistance among Cystic Fibrosis Respiratory Bacterial Isolates

Author(s): Rutter W.C.; Burgess D.R.; Burgess D.S.

Source: Microbial Drug Resistance; Jan 2017; vol. 23 (no. 1); p. 51-55

Publication Type(s): Journal: Article

Abstract: Pseudomonas aeruginosa and Staphylococcus aureus are common pathogens in cystic fibrosis (CF) patients with increasing multidrug resistance (MDR). This study characterized antimicrobial susceptibility trends among organisms isolated from the respiratory tract of CF patients. Microbiological culture and sensitivity results for all CF patients were collected from January 2010 through December 2014. Minimum inhibitory concentrations were obtained using Phoenix and Etest methods. Clinical and Laboratory Standards Institute guidelines were used to remove duplicate isolates and develop antimicrobial susceptibility reports. MDR was defined as resistance to one agent in three or more antibiotic classes or oxacillin resistance in S. aureus. Overall, 542 bacterial isolates from 376 cultures were analyzed for trends. P. aeruginosa (41%), S. aureus (40%), and Stenotrophomonas maltophilia (8%) were the most commonly isolated organisms. Multidrug-resistant organism isolation increased from 39% to 49% (r = 0.76, p = 0.13), while representing 47.6% of all isolates. Multidrug-resistant P. aeruginosa incidence increased each year from 26% to 43% (r = 0.89, p = 0.046), while P. aeruginosa isolation decreased from 47% to 38% over the study period (r = -0.93, p = 0.02). MRSA accounted for 62.6% of all S. aureus isolated, while overall multidrug-resistant S. aureus incidence was 73.1% in all cultures. MDR among common pathogens in CF continues to increase. Empiric therapy for CF exacerbations should be targeted to previous antimicrobial susceptibility, and P. aeruginosa and S. aureus should be empirically covered.

Clinical value of pulmonary hyperinflation as a treatment outcome in cystic fibrosis

Author(s): Stevens D.

Source: Respirology; Jan 2017; vol. 22 (no. 1); p. 12-13

Publication Type(s): Journal: Editorial

Abstract: See article, page 141.

Relationship between pulmonary hyperinflation and dyspnoea severity during acute exacerbations of cystic fibrosis

Author(s): Nicholson T.T.; Barry P.J.; Waterhouse D.F.; Nolan G.M.; McKone E.F.; Gallagher C.G.

Source: Respirology; Jan 2017; vol. 22 (no. 1); p. 141-148

Abstract: Background and objective: Acute exacerbations of cystic fibrosis (CF) occur frequently throughout the course of the disease. Dyspnoea is the most common and distressing symptom experienced by patients during these episodes. We tested the hypothesis that pulmonary hyperinflation is an important determinant of dyspnoea severity during acute exacerbations. Methods: We studied patients during an acute exacerbation of CF. Lung volumes, spirometry and dyspnoea scores were measured at Day 0, Day 7, at the end of treatment (EOT) and 14 days following the EOT. Results: At the start of treatment, mean residual volume (RV)/total lung capacity (TLC) was 54.9%, which decreased significantly with treatment, as did vital capacity (VC), inspiratory capacity (IC) and dyspnoea scores. IC was the only independent predictor of dyspnoea severity. Conclusion: Our study demonstrates significant improvements in hyperinflation, spirometry and dyspnoea scores with treatment of acute exacerbations of CF. Hyperinflation, rather than airflow limitation, may contribute towards the increased dyspnoea during exacerbations. Copyright © 2016 Asian Pacific Society of Respirology

Ralstonia mannitolilytica in cystic fibrosis: A new predictor of worse outcomes

Author(s): Coman I.; Lavoie A.; Carricart M.; Tremblay F.; Berthiaume Y.; Bilodeau L.; Zlosnik J.E.

Source: Respiratory Medicine Case Reports; 2017; vol. 20 ; p. 48-50

Abstract: Background Patients with Cystic Fibrosis are subject to repeated respiratory tract infections, with recent increasing isolation of unusual pathogens. Ralstonia species have lately been isolated at our institution, an organism historically frequently misidentified as Burkholderia or Pseudomonas. The prevalence of Ralstonia spp. in cystic fibrosis populations has yet to be determined, along with its clinical implications. Case presentations Seven patients out of the 301 followed at our cystic fibrosis clinic have had Ralstonia strains identified in their respiratory tract. Most strains identified were multi-drug resistant. After aquisition of Ralstonia spp., the patients' clinical course was characterized by more frequent and more severe respiratory infections along with prolonged hospitalizations, greater decline of lung function, and greater mortality. The mortality rate in this group of patients was 86%. No other factor that could explain such a dramatic evolution was identified upon review of patient data. Some of the strains involved were recognized as clones on Pulse Field Electrophoresis Gel, raising the question of person-to-person transmission. Conclusion New pathogens are identified with the evolution of the microbiota in cystic fibrosis respiratory tracts. In our cohort of patients, acquisition of Ralstonia spp. was associated with dramatic outcomes in terms of disease acceleration and raised mortality rates. It is of critical importance to continue to better define the prevalence and clinical impact of Ralstonia in cystic fibrosis populations. Copyright © 2016 The Authors

Cystic fibrosis: a clinical view

Author(s): Castellani C.; Assael B.M.

Source: Cellular and Molecular Life Sciences; Jan 2017; vol. 74 (no. 1); p. 129-140

Publication Type(s): Journal: Review

Abstract: Cystic fibrosis (CF), a monogenic disease caused by mutations in the CFTR gene on chromosome 7, is complex and greatly variable in clinical expression. Airways, pancreas, male genital system, intestine, liver, bone, and kidney are involved. The lack of CFTR or its impaired function causes fat malabsorption and chronic pulmonary infections leading to bronchiectasis and progressive lung damage. Previously considered lethal in infancy and childhood, CF has now attained

median survivals of 50 years of age, mainly thanks to the early diagnosis through neonatal screening, recognition of mild forms, and an aggressive therapeutic attitude. Classical treatment includes pancreatic enzyme replacement, respiratory physiotherapy, mucolitics, and aggressive antibiotic therapy. A significant proportion of patients with severe symptoms still requires lung or, less frequently, liver transplantation. The great number of mutations and their diverse effects on the CFTR protein account only partially for CF clinical variability, and modifier genes have a role in modulating the clinical expression of the disease. Despite the increasing understanding of CFTR functioning, several aspects of CF need still to be clarified, e.g., the worse outcome in females, the risk of malignancies, the pathophysiology, and best treatment of comorbidities, such as CF-related diabetes or CF-related bone disorder. Research is focusing on new drugs restoring CFTR function, some already available and with good clinical impact, others showing promising preliminary results that need to be confirmed in phase III clinical trials.

Translational research and clinical applications in the management of cystic fibrosis

Author(s): Quittner, Alexandra L.; Nicolais, Christina J.; Saez-Flores, Estefany; Bernstein, Ruth

Source: Family resilience and chronic illness: Interdisciplinary and translational perspectives; 2017 ; p. 63-289

Publication Type(s): Book Edited Book Chapter

Abstract:A number of important conclusions can be drawn from this chapter. First, the needs of individuals with cystic fibrosis are constantly changing alongside systemic changes in medicine and policy. This chapter highlights literature examining the impact of cystic fibrosis on affected families and clearly shows that family functioning plays a role in adherence to treatment and health outcomes. Positive family functioning is particularly predictive of positive mental and physical health outcomes. Thus, interventions targeting family communication and problem solving are necessary for this population. This chapter makes clear the significance of the transition to independence and self-management and demonstrates the need for systemic intervention to adequately prepare families for this transition. (PsycINFO Database Record (c) 2017 APA, all rights reserved) (Source: chapter)

Bronchial tree-shaped mucous plug in cystic fibrosis: imaging-guided management.

Author(s): Salamone, Ignazio; Mondello, Baldassare; Lucanto, Maria Cristina; Cristadoro, Simona; Lombardo, Mariangela; Barone, Mario

Source: Respirology case reports; Mar 2017; vol. 5 (no. 2); p. e00214

Publication Type(s): Journal Article

Abstract: We report the case of a 17-year-old boy with cystic fibrosis (CF) who presented with persistent cough; after starting intravenous antibiotics for Pseudomonas aeruginosa he underwent a computed tomography (CT) scan of the chest. CT revealed extensive consolidation in the right lower lobe with relative bronchus obstruction; the cause of bronchial obstruction was detected in the mediastinal window, corresponding to a bronchial tree-shaped, thick, tenacious mucous plug. This was extracted 48 h after unresponsive bronchial washing and endobronchial instillation of rhDNAse, using foreign-body forceps, with subsequent resolution of cough. This case, which is the second report of plastic bronchitis in CF, was resolved by mechanical removal of the mucous plug, suggesting that a careful observation of CT imaging may guide intervention aimed at resolution of atelectasis.

Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.

Author(s): Konstan, Michael W; McKone, Edward F; Moss, Richard B; Marigowda, Gautham;

Source: The Lancet. Respiratory medicine; Feb 2017; vol. 5 (no. 2); p. 107-118

Publication Type(s): Journal Article

Abstract: The 24-week safety and efficacy of lumacaftor/ivacaftor combination therapy was shown in two randomised controlled trials (RCTs)-TRAFFIC and TRANSPORT-in patients with cystic fibrosis who were aged 12 years or older and homozygous for the F508del-CFTR mutation. We aimed to assess the long-term safety and efficacy of extended lumacaftor/ivacaftor therapy in this group of patients in PROGRESS, the long-term extension of TRAFFIC and TRANSPORT. PROGRESS was a phase 3, parallel-group, multicentre, 96-week study of patients who completed TRAFFIC or TRANSPORT in 191 sites in 15 countries. Patients were eligible if they were at least 12 years old with cystic fibrosis and homozygous for the F508del-CFTR mutation. Exclusion criteria included any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering the study drug to the participant, history of drug intolerance, and history of poor compliance with the study drug. Patients who previously received active treatment in TRANSPORT or TRAFFIC remained on the same dose in PROGRESS. Patients who had received placebo in TRANSPORT or TRAFFIC were randomly assigned (1:1) to receive lumacaftor (400 mg every 12 h)/ivacaftor (250 mg every 12 h) or lumacaftor (600 mg once daily)/ivacaftor (250 mg every 12 h). The primary outcome was to assess the long-term safety of combined therapy. The estimated annual rate of decline in percent predicted FEV1 (ppFEV1) in treated patients was compared with that of a matched registry cohort. Efficacy analyses were based on modified intention-to-treat, such that data were included for all patients who were randomly assigned and received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01931839. Between Oct 24, 2013, and April 7, 2016, 1030 patients from the TRANSPORT and TRAFFIC studies enrolled in PROGRESS, and 1029 received at least one dose of study drug. 340 patients continued treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h; 176 patients who had received placebo in the TRANSPORT or TRAFFIC studies initiated treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h, the commercially available dose, for which data are presented. The most common adverse events were infective pulmonary exacerbations, cough, increased sputum, and haemoptysis. Modest blood pressure increases seen in TRAFFIC and TRANSPORT were also observed in PROGRESS. For patients continuing treatment, the mean change from baseline in ppFEV1 was 0·5 (95% CI -0·4 to 1·5) at extension week 72 and 0·5 (-0·7 to 1·6) at extension week 96; change in BMI was 0·69 (0·56 to 0·81) at extension week 72 and 0·96 (0·81 to 1·11) at extension week 96. The annualised pulmonary exacerbation rate in patients continuing treatment through extension week 96 (0·65, 0·56 to 0·75) remained lower than the placebo rate in TRAFFIC and TRANSPORT. The annualised rate of ppFEV1 decline was reduced in lumacaftor/ivacaftor-treated patients compared with matched controls (-1·33, -1·80 to -0·85 vs -2·29, -2·56 to -2·03). The efficacy and safety profile of the lumacaftor 600 mg once daily/ivacaftor 250 mg every 12 h groups was generally similar to that of the lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h groups. The long-term safety profile of lumacaftor/ivacaftor combination therapy was consistent with previous RCTs. Benefits continued to be observed with longer-term treatment, and lumacaftor/ivacaftor was associated with a 42% slower rate of ppFEV1 decline than in matched registry controls. Vertex Pharmaceuticals Incorporated.

New horizons for cystic fibrosis treatment.

Author(s): Fajac, Isabelle; De Boeck, Kris

Source: Pharmacology & therapeutics; Feb 2017; vol. 170 ; p. 205-211

Publication Type(s): Journal Article Review

Abstract: Cystic fibrosis is an inherited multi-system disease associated with chronic lung infection, malabsorption, salt loss syndromes, male infertility and leading to numerous comorbidities. The landscape in cystic fibrosis care has changed markedly with currently more adult patients than children in many countries. Over 2000 different mutations in the CFTR gene have been reported and the majority are extremely rare. Understanding how CFTR mutations translate to disturbed synthesis or function of the CFTR protein has opened the way to 'personalized' treatments to correct the basic defect. The first 2 drugs have reached the clinic: a CFTR potentiator to augment CFTR channel function, and the combination of this potentiator with a corrector to increase CFTR expression at the cell membrane. To obtain robust correction of CFTR expression at the cell membrane, combinations of correctors with additive efficacy are under investigation. Other mutation type-specific treatments under clinical investigation are premature stop codon-read through drugs and antisense oligonucleotides that correct the basic defect at the mRNA level. Restoring the defective gene by gene editing can already be achieved ex vivo. Mutation agnostic treatments are explored as well: stabilizing CFTR expression at the cell membrane, circumventing the CFTR channel by blocking or activating other ion channels, and gene therapy. Combinations of these therapies can be anticipated. The pipeline of corrective strategies under clinical investigation is increasing continuously and a rising number of pharmaceutical companies are entering the field.

Case series of omalizumab for allergic bronchopulmonary aspergillosis in cystic fibrosis patients.

Author(s): Nové-Josserand, Raphaële; Grard, Soazic; Auzou, Lila; Reix, Philippe; Murris-Espin, Marlène; Brémont, François; Mammar, Benyebka; Mely, Laurent; Hubert, Dominique; Durieu, Isabelle; Burgel, Pierre-Régis

Source: Pediatric pulmonology; Feb 2017; vol. 52 (no. 2); p. 190-197

Publication Type(s): Journal Article

Abstract: Allergic bronchopulmonary aspergillosis (ABPA) affects up to 15% of patients with cystic fibrosis (CF). Corticosteroids are used as first-line therapy, but relapse and adverse effects commonly occur. Case reports have suggested the efficacy of the anti-IgE recombinant humanized monoclonal antibody omalizumab. A retrospective multicenter observational French study retrieved 32 CF patients (11 children and 21 adults) who have received omalizumab for more than 3 months in the context of ABPA. Clinical characteristics, concomitant medications (inhaled and oral corticosteroids, antifungal drugs), lung function, body mass index (BMI), and serum IgE were compared at the start and during the first year of omalizumab therapy. Omalizumab-related adverse effects and costs were also evaluated. No significant difference with omalizumab could be demonstrated with regard to lung function, BMI, or the number of patients receiving oral corticosteroids. At the time of initiation of omalizumab, 56% of patients were receiving oral corticosteroids. Five patients were able to discontinue corticosteroids during follow-up and nine patients were able to reduce their daily dose. A total of 78% of the patients had received antifungal therapy at the time of the initiation of omalizumab. Treatment tolerance was good (12.5% of patients experienced side effects). The median cost of omalizumab treatment was €3,620 per patient per month. Omalizumab may represent a steroid-sparing therapy in CF patients with ABPA. A randomized-controlled trial is urgently required to provide higher level of evidence regarding the efficacy and cost-effectiveness of omalizumab in CF patients with ABPA. Pediatr Pulmonol. 2017;52:190-197.

Prediction Equations Underestimate Resting Energy Expenditure in Patients With End-Stage Cystic Fibrosis.

Author(s): Hollander, Francis M; Kok, Annemieke; de Roos, Nicole M; Belle-van Meerkerk, Gerdien; van de Graaf, Ed A

Source: Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition; Feb 2017; vol. 32 (no. 1); p. 116-121

Publication Type(s): Journal Article

Abstract: Resting energy expenditure (REE) is increased in patients with cystic fibrosis (CF) with end-stage lung disease due to chronic inflammation and pulmonary infections. After lung transplantation (LTx), energy expenditure is expected to be lower because inflammation will decrease. We assessed the agreement between measured and predicted REE in pre-LTx CF and post-LTx patients with CF and differences in REE in pre-LTx CF and post-LTx patients with CF in a cross-sectional study. Included were 12 pre-LTx patients with CF (9 women; median age 31.6 years; interquartile range [IQR], 23.3-40.0) and 12 patients with CF within 2 years after LTx (6 women; median age 33.5 years; IQR, 22.3-40.3). REE was measured in a fasted state using indirect calorimetry. Values were compared with predicted REE calculated by formulas of Harris-Benedict (1919 and 1984), Schofield, and the World Health Organization (1985). A calculated REE between 90% and 110% of REE measured was considered adequate. Prediction equations underestimate REE in at least 75% of pre-LTx and 33% of post-LTx patients with CF. Mean (SD) REE measured by indirect calorimetry was 1735 (251) kcal pre-LTx and 1650 (235) kcal post-LTx (P = .40). REE expressed per kilogram of fat-free mass (FFM) was 40.5 kcal/kg in pre-LTx patients with CF, which was higher than the 34.3 kcal/kg in post-LTx patients with CF (P = .01). Prediction equations underestimate REE in patients with end-stage CF. REE per kg of FFM is lower post-LTx than pre-LTx in patients with CF. Measurement of REE is recommended for patients with CF, especially pre-LTx, to optimize energy requirements for improving nutrition status.

Importance to question sinonasal symptoms and to perform rhinoscopy and rhinomanometry in cystic fibrosis patients.

Author(s): Bock, J M; Schien, M; Fischer, C; Naehrlich, L; Kaeding, M; Guntinas-Lichius, O; Gerber, A; Arnold, C; Mainz, J G

Source: Pediatric pulmonology; Feb 2017; vol. 52 (no. 2); p. 167-174

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) patients almost regularly reveal sinonasal pathology. The purpose of this study was to assess association between objective and subjective measurements of sinonasal involvement comparing nasal airflow obtained by active anterior rhinomanometry (AAR), nasal endoscopic findings, and symptoms assessed with the Sino-Nasal Outcome Test-20 (SNOT-20). Nasal cavities were explored by anterior rigid rhinoscopy and findings were compared to inspiratory nasal airflow measured by AAR to quantify nasal patency and subjective health-related quality of life in sinonasal disease obtained with the SNOT-20 questionnaire. Relations to upper and lower airway colonization with Pseudomonas aeruginosa, medical treatment, and sinonasal surgery were analysed. A total of 124 CF patients were enrolled (mean age 19.9 ± 10.4 years, range 4-65 years). A significant association of detection of nasal polyposis (NP) in rhinoscopy was found with increased primary nasal symptoms (PNS) which include "nasal obstruction," "sneezing," "runny nose," "thick nasal discharge," and "reduced sense of smell." At the same time patients with pathologically decreased airflow neither showed elevated SNOT-20 scores nor abnormal rhinoscopic findings. Altogether, rhinomanometric and rhinoscopic findings are not significantly related. Among SNOT-20 scores the PNS subscore is related to rhinoscopically detected polyposis and sinonasal

secretion. Therefore, we recommend including short questions regarding PNS into CF-routine care. At the same time our results show that a high inspiratory airflow is not associated with a good sensation of nasal patency. Altogether, rhinomanometry is not required within routine CF-care, but it can be interesting as an outcome parameter within clinical trials. Pediatr Pulmonol. 2017;52:167-174. © 2016 Wiley Periodicals, Inc. © 2016 Wiley Periodicals, Inc.

Fatty Acid Cysteamine Conjugates as Novel and Potent Autophagy Activators That Enhance the Correction of Misfolded F508del-Cystic Fibrosis Transmembrane Conductance Regulator (CFTR).

Author(s): Vu, Chi B; Bridges, Robert J; Pena-Rasgado, Cecilia; Lacerda, Antonio E; Bordwell, Curtis; Sewell, Abby; Nichols, Andrew J; Chandran, Sachin; Lonkar, Pallavi; Picarella, Dominic; Ting, Amal; Wensley, Allison; Yeager, Maisy; Liu, Feng

Source: Journal of medicinal chemistry; Jan 2017; vol. 60 (no. 1); p. 458-473

Publication Type(s): Journal Article

Abstract:A depressed autophagy has previously been reported in cystic fibrosis patients with the common F508del-CFTR mutation. This report describes the synthesis and preliminary biological characterization of a novel series of autophagy activators involving fatty acid cysteamine conjugates. These molecular entities were synthesized by first covalently linking cysteamine to docosahexaenoic acid. The resulting conjugate 1 synergistically activated autophagy in primary homozygous F508del-CFTR human bronchial epithelial (hBE) cells at submicromolar concentrations. When conjugate 1 was used in combination with the corrector lumacaftor and the potentiator ivacaftor, it showed an additive effect, as measured by the increase in the chloride current in a functional assay. In order to obtain a more stable form for oral dosing, the sulfhydryl group in conjugate 1 was converted into a functionalized disulfide moiety. The resulting conjugate 5 is orally bioavailable in the mouse, rat, and dog and allows a sustained delivery of the biologically active conjugate 1.

Treatment decisions for MRSA in patients with cystic fibrosis (CF): when is enough, enough?

Author(s): Bell, Scott C; Flume, Patrick A

Source: Thorax; Jan 2017

Publication Type(s): Editorial

Available in full text at Thorax - from Highwire Press

Aminoglycoside resistance of Pseudomonas aeruginosa in cystic fibrosis results from convergent evolution in the mexZ gene.

Author(s): Prickett, Michelle H; Hauser, Alan R; McColley, Susanna A; Cullina, Joanne; Potter, Eileen; Powers, Cathy; Jain, Manu

Source: Thorax; Jan 2017; vol. 72 (no. 1); p. 40-47

Publication Type(s): Journal Article

Available in full text at Thorax - from Highwire Press

Abstract: Aminoglycoside (AG) resistance of Pseudomonas aeruginosa in cystic fibrosis (CF) is associated with poorer clinical outcomes and is usually due to overexpression of the efflux pump MexXY. MexXY is regulated by mexZ, one of the most commonly mutated genes in CF P. aeruginosa isolates. Little is known about the evolutionary relationship between AG resistance, MexXY expression and mexZ mutations. To test the hypothesis that AG resistance in P. aeruginosa

develops in parallel with higher MexXY expression and mexZ mutations. CF P. aeruginosa isolates were compared for chronically infected (CI) adults, CI children and children with new infection. One P. aeruginosa isolate from each patient was analysed for mexZ mutations, mexY mRNA expression and amikacin resistance. 56 patients with CF were enrolled: 21 children with new P. aeruginosa infection, 18 CI children and 17 CI adults. Amikacin resistance and mexY mRNA expression were higher in cohorts with longer P. aeruginosa infection. The prevalence of non-conservative mexZ mutations was 0%, 33% and 65% in children with new infection, CI children and CI adults, respectively. The same trend was seen in the ratio of non-conservative to non-synonymous mexZ mutations. Of isolates with non-conservative mexZ mutations, 59% were amikacin-resistant compared with 18% of isolates with non-synonymous mutations. The doubling rate of amikacin resistance and non-conservative mexZ mutations was approximately 5 years. P. aeruginosa mexZ mutations undergo positive selection resulting in increased mexY mRNA expression and amikacin resistance and likely play a role in bacterial adaption in the CF lung. Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://www.bmj.com/company/products-services/rights-and-licensing/.

Clostridium difficile infection in cystic fibrosis: an uncommon but life-threatening complication.

Author(s): Piccolo, Francesco; Tai, Anna Sze; Ee, Hooi; Mulrennan, Siobhain; Bell, Scott; Ryan, Gerard

Source: Respirology case reports; Jan 2017; vol. 5 (no. 1); p. e00204

Publication Type(s): Journal Article

Abstract: Adults with cystic fibrosis (CF) have significant rates of asymptomatic Clostridium difficile carriage and are frequently exposed to risk factors for C. difficile infection (CDI). Despite this, the rate of reported CDI in CF is low. We describe three cases of near fatal CDI in adults with CF and review the literature regarding presentation, management, and recurrence prevention. Early recognition is important as the clinical presentation may be atypical and the illness can be severe and even life-threatening. Management can be complicated by respiratory and nutritional failure. CF-related gastrointestinal dysfunction may alter the typical host-pathogen interaction between patient and C. difficile, potentially explaining the low rates of CDI and atypical presentation.

Implementing Standardized Palliative Care Education for Children and Adults with Cystic Fibrosis (S732).

Author(s): Hailey, Claire; Prieur, Mary; Helms, Sarah; Schmidt, Howard; Carney, Scott; Dellon, Elisabeth

Source: Journal of Pain & Symptom Management; Feb 2017; vol. 53 (no. 2); p. 427-427

Publication Type(s): Academic Journal

Microbiological

Ivacaftor and symptoms of extra-oesophageal reflux in patients with cystic fibrosis and G551D mutation

Author(s): Zeybel G.L.; Pearson J.P.; McDonnell M.; Zeybel M.; Brodlie M.; Ward C.; Krishnan A.; Jones R.; Bourke S.J.; Doe S.; Anderson A.; Faruqi S.; Morice A.H.; Dettmar P.W.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 124-131

Publication Type(s): Journal: Article

Abstract: Background Extra-oesophageal reflux (EOR) may lead to microaspiration in patients with cystic fibrosis (CF), a probable cause of deteriorating lung function. Successful clinical trials of ivacaftor highlight opportunities to understand EOR in a real world study. Methods Data from 12 patients with CF and the G551D mutation prescribed ivacaftor (150 mg bd) was collected at baseline, 6, 26 and 52 weeks. The changes in symptoms of EOR were assessed by questionnaire (reflux symptom index (RSI) and Hull airway reflux questionnaire (HARQ)). Results Six patients presented EOR at baseline (RSI > 13; median 13; range 2-29) and 5 presented airway reflux (HARQ > 13; median 12; range 3 to 33). Treatment with ivacaftor was associated with a significant reduction of EOR symptoms (P < 0 . 04 versus baseline) denoted by the reflux symptom index and Hull airway reflux questionnaire. Conclusion Ivacaftor treatment was beneficial for patients with symptoms of EOR, thought to be a precursor to microaspiration. Copyright © 2016 The Authors

Correlation of sweat chloride and percent predicted FEV in cystic fibrosis patients treated with ivacaftor

Author(s): Fidler M.C.; Van Goor F.; Beusmans J.; Panorchan P.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 41-44

Publication Type(s): Journal: Article

Abstract: Ivacaftor, a CFTR potentiator that enhances chloride transport by acting directly on CFTR to increase its channel gating activity, has been evaluated in patients with different CFTR mutations. Several previous analyses have reported no statistical correlation between change from baseline in ppFEV1 and reduction in sweat chloride levels for individuals treated with ivacaftor. The objective of the post hoc analysis described here was to expand upon previous analyses and evaluate the correlation between sweat chloride levels and absolute ppFEV1 changes across multiple cohorts of patients with different CF-causing mutations who were treated with ivacaftor. The goal of the analysis was to help define the potential value of sweat chloride as a pharmacodynamic biomarker for use in CFTR modulator trials. For any given study, reductions in sweat chloride levels and improvements in absolute ppFEV1 were not correlated for individual patients. However, when the data from all studies were combined, a statistically significant correlation between sweat chloride levels and ppFEV1 changes was observed (p < 0.0001). Thus, sweat chloride level changes in response to potentiation of the CFTR protein by ivacaftor appear to be a predictive pharmacodynamic biomarker of lung function changes on a population basis but are unsuitable for the prediction of treatment benefits for individuals. Copyright © 2016 The Authors

Variability of sweat chloride concentration in subjects with cystic fibrosis and G551D mutations

Author(s): Vermeulen F.; De Boeck K.; Le Camus C.; Davies J.C.; Bilton D.; Milenkovic D.

Source: Journal of Cystic Fibrosis; Jan 2017; vol. 16 (no. 1); p. 36-40

Publication Type(s): Journal: Article

Abstract: Introduction Sweat chloride concentration, a biomarker of CFTR function, is an appropriate outcome parameter in clinical trials aimed at correcting the basic CF defect. Although there is consensus on a cut-off value to diagnose CF, we have only limited information on the within subject variability of sweat chloride over time. Such information would be useful for sample size calculations in clinical trials. Therefore, we retrospectively analyzed repeated sweat chloride values obtained in patients with G551D mutation(s) assigned to placebo in an ivacaftor interventional trial. Methods In subjects with G551D at least 12 years of age, a pilocarpine sweat test using Macroduct collector was taken on both arms at 8 time points over 48 weeks. We explored 1062 pilocarpine sweat test values obtained in 78 placebo patients of the VX08-770-102 trial. Results Mean overall sweat chloride value

(all patients, all tests, n = 1062) was 100.8 mmol/L (SD 12.7 mmol/L). Using a multilevel mixed model, the between-subject standard deviation (SD) for sweat chloride was 8.9 mmol/L (95% CI 7.4-10.6) and within-subject SD was 8.1 mmol/L (95% CI 7.5-8.7). Limits of repeatability for repeat measurements were - 19.7 to + 21.6 mmol/L using values from one arm, and - 13.3 to 11.8 mmol/L using mean of values obtained at 4 test occasions. Sample size calculations showed that the minimal treatment effect on sweat chloride concentration that can be demonstrated for a group of 5 patients is around 15 mmol/L, using a cross-over design and combinations of 4 tests for each phase of the trial. Conclusion Although the sweat test is considered a robust measure, sweat chloride measurements in patients with CF and a G551D mutation had an inherent biological variability that is higher than commonly considered. Further analyses of placebo group data are crucial to learn more about the natural variability of this outcome parameter.

Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive Diagnosis

Author(s): Ren C.L.; Howenstine M.S.; Borowitz D.S.; Gonska T.; Levy H.; Massie J.; Milla C.; Munck A.; Southern K.W.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Journal: Article

Abstract: Objective An unintended consequence of cystic fibrosis (CF) newborn screening (NBS) is the identification of infants with a positive NBS test but inconclusive diagnostic testing. These infants are classified as CF transmembrane conductance regulator-related metabolic syndrome (CRMS) in the US and CF screen positive, inconclusive diagnosis (CFSPID) in other countries. Diagnostic and management decisions of these infants are challenges for CF healthcare professionals and stressful situations for families. As CF NBS has become more widespread across the world, increased information about the epidemiology and outcomes of these infants is becoming available. These data were reviewed at the 2015 CF Foundation Diagnosis Consensus Conference, and a harmonized definition of CRMS and CFSPID was developed. Study design At the consensus conference, participants reviewed published and unpublished studies of CRMS/CFSPID and used a modified Delphi methodology to develop a harmonized approach to the definition of CRMS/CFSPID. Results Several studies of CRMS/CFSPID from populations around the world have been published in the past year. Although the studies vary in the number of infants studied, study design, and outcome measures, there have been some consistent findings. CRMS/CFSPID occurs relatively frequently, with CF:CRMS that ranges from 3 to 5 cases of CF for every 1 case of CRMS/CFSPID in regions where gene sequencing is not used. The incidence varies by NBS protocol used, and in some regions more cases of CRMS/CFSPID are detected than cases of CF. The majority of individuals with CRMS/CFSPID do not develop CF disease or progress to a diagnosis of CF. However, between 10% and 20% of asymptomatic infants can develop clinical features concerning for CF, such as a respiratory culture positive for Pseudomonas aeruginosa. Most studies have only reported short-term outcomes in the first 1-3 years of life; the long-term outcomes of CRMS/CFSPID remain unknown. The European CF Society definition of CFSPID and the CF Foundation definition of CRMS differ only slightly, and the consensus conference was able to create a unified definition of CRMS/CFSPID. Conclusions CRMS/CFSPID is a relatively common outcome of CF NBS, and clinicians need to be prepared to counsel families whose NBS test falls into this classification. The vast majority of infants with CRMS/CFSPID will remain free from disease manifestations early in life. However, a small proportion may develop clinical features concerning for CF or demonstrate progression to a clinical phenotype compatible with a CF diagnosis, and their long-term outcomes are not known. A consistent international definition of CRMS/CFSPID will allow for better data collection for study of outcomes and result in improved patient care.

Microbiome in the pathogenesis of cystic fibrosis and lung transplant-related disease

Author(s): Cribbs S.K.; Beck J.M.

Source: Translational Research; Jan 2017; vol. 179 ; p. 84-96

Publication Type(s): Journal: Review

Abstract: Significant advances in culture-independent methods have expanded our knowledge about the diversity of the lung microbial environment. Complex microorganisms and microbial communities can now be identified in the distal airways in a variety of respiratory diseases, including cystic fibrosis (CF) and the posttransplantation lung. Although there are significant methodologic concerns about sampling the lung microbiome, several studies have now shown that the microbiome of the lower respiratory tract is distinct from the upper airway. CF is a disease characterized by chronic airway infections that lead to significant morbidity and mortality. Traditional culture-dependent methods have identified a select group of pathogens that cause exacerbations in CF, but studies using bacterial 16S rRNA gene-based microarrays have shown that the CF microbiome is an intricate and dynamic bacterial ecosystem, which influences both host immune health and disease pathogenesis. These microbial communities can shift with external influences, including antibiotic exposure. In addition, there have been a number of studies suggesting a link between the gut microbiome and respiratory health in CF. Compared with CF, there is significantly less knowledge about the microbiome of the transplanted lung. Risk factors for bronchiolitis obliterans syndrome, one of the leading causes of death, include microbial infections. Lung transplant patients have a unique lung microbiome that is different than the pretransplanted microbiome and changes with time. Understanding the host-pathogen interactions in these diseases may suggest targeted therapies and improve long-term survival in these patients. Copyright © 2016

Impact of high diversity of Achromobacter populations within cystic fibrosis sputum samples on antimicrobial susceptibility testing

Author(s): Dupont C.; Jumas-Bilak E.; Michon A.-L.; Marchandin H.; Chiron R.

Source: Journal of Clinical Microbiology; Jan 2017; vol. 55 (no. 1); p. 206-215

Publication Type(s): Journal: Article

Abstract: Chronic colonization by opportunistic environmental bacteria is frequent in the airways of cystic fibrosis (CF) patients. Studies of Pseudomonas aeruginosa evolution during persistence have highlighted the emergence of pathoadaptive genotypes and phenotypes, leading to complex and diversified inpatient colonizing populations also observed at the intraspecimen level. Such diversity, including heterogeneity in resistance profiles, has been considered an adaptive strategy devoted to host persistence. Longitudinal genomic diversity has been shown for the emergent opportunistic pathogen Achromobacter, but phenotypic and genomic diversity has not yet been studied within a simple CF sputum sample. Here, we studied the genomic diversity and antimicrobial resistance heterogeneity of 132 Achromobacter species strains (8 to 27 strains of identical or distinct colonial morphotypes per specimen) recovered from the sputum samples of 9 chronically colonized CF patients. We highlighted the high within-sample and within-morphotype diversity of antimicrobial resistance (disk diffusion) and genomic (pulsed-field gel electrophoresis) profiles. No sputum sample included strains with identical pulsotypes or antibiotic susceptibility patterns. Differences in clinical categorization were observed for the 9 patients and concerned 3 to 11 antibiotics, including antibiotics recommended for use against Achromobacter. Within-sample antimicrobial resistance heterogeneity, not predictable from colonial morphology, suggested that it may represent a selective advantage against antibiotics in an Achromobacter persisting population and potentially

compromise the antibiotic management of CF airway infections.

Polyanion-tobramycin nanocomplexes into functional microparticles for the treatment of Pseudomonas aeruginosa infections in cystic fibrosis

Author(s): Craparo E.F.; Porsio B.; Schillaci D.; Cusimano M.G.; Giammona G.; Cavallaro G.;

Source: Nanomedicine; Jan 2017; vol. 12 (no. 1); p. 25-42

Publication Type(s): Journal: Article

Abstract: Aim: Efficacy of antibiotics in cystic fibrosis (CF) is compromised by the poor penetration through mucus barrier. This work proposes a new 'nano-into-micro' approach, used to obtain a combinatorial effect: achieve a sustained delivery of tobramycin and overcome mucus barrier. Methods: Mannitol microparticles (MPs) were loaded with a tobramycin polymeric nanocomplex and characterized in presence of CF artificial mucus. Results & discussion: MPs are able to alter the rheological properties of CF artificial mucus, enhancing drug penetration into it and allowing a prolonged drug release. MPs resulted to be effective in Pseudomonas aeruginosa infections if compared with free tobramycin. Conclusion: MPs resulted to be a formulation of higher efficacy, with potential positive implications, as lower required dose, administration frequency, side effects and antibiotic resistance problems.

Activity of antimicrobial peptides, alone or combined with conventional antibiotics, against Staphylococcus aureus isolated from the airways of cystic fibrosis patients

Author(s): Garbacz K.; Kamysz W.; Piechowicz L.

Source: Virulence; Jan 2017; vol. 8 (no. 1); p. 94-100

Publication Type(s): Journal: Letter

Evaluation of a bovine antibody test for diagnosing Mycobacterium avium complex in patients with cystic fibrosis

Author(s): Qvist T.; Pressler T.; Katzenstein T.L.; Hoiby N.; Collins M.T.

Source: Pediatric Pulmonology; Jan 2017; vol. 52 (no. 1); p. 34-40

Publication Type(s): Journal: Article

Abstract: Introduction: The aim of this study was to test a commercial bovine enzyme-linked immunosorbent assay for investigating antibody activity against Mycobacterium avium complex. Methods: All patients at the Copenhagen Cystic Fibrosis (CF) Center who had culture for nontuberculous mycobacteria performed were included. A commercially available antibody test used in veterinary medicine, was adjusted for human use, and applied to patient sera in a cross sectional test. The test positivity threshold was determined using a receiver operating curve (ROC). A longitudinal analysis of antibody kinetics before and after culture conversion was performed in case patients. Results: Out of 286 included subjects, six had clinical M. avium complex pulmonary disease at the time of sera sampling. These patients presented with higher antibody test values (P-value <0.01). A test cut point of 0.78 was chosen, corresponding to a sensitivity of 100% (54-100), specificity of 66% (60-72), a positive predictive value of 6% (2-13), and negative predictive value of 100% (98-100). Conclusion: While not suited for direct diagnosis of M. avium complex due to a high number of false positive subjects, the assay proved useful at ruling out pulmonary disease. Screening sera from patients with CF could guide clinicians to focus attention on patients at higher risk of M.

avium complex pulmonary disease. Pediatr Pulmonol. 2017;52:34-40. © 2016 Wiley Periodicals, Inc.

Discovery of Multi-Target Agents Active as Broad-Spectrum Antivirals and Correctors of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) for Associated Pulmonary Diseases.

Author(s): Tassini, Sabrina; Sun, Liang; Lanko, Kristina; Crespan, Emmanuele; Langron, Emily; Falchi, Federico; Kissova, Miroslava; Armijos-Rivera, Jorge I; Delang, Leen; Mirabelli, Carmen; Neyts, Johan; Pieroni, Marco; Cavalli, Andrea; Costantino, Gabriele; Maga, Giovanni; Vergani, Paola; Leyssen, Pieter; Radi, Marco

Source: Journal of medicinal chemistry; Jan 2017

Publication Type(s): Journal Article

Abstract: Enteroviruses (EVs) are among the most frequent infectious agents in humans worldwide and represent the leading cause of upper respiratory tract infections. No drugs for the treatment of EV infections are currently available. Recent studies have also linked enterovirus infection with pulmonary exacerbations, especially in cystic fibrosis (CF) patients, and the importance of this link is probably underestimated. The aim of this work was to develop a new class of multi-target agents active both as broad-spectrum antivirals and as correctors of the F508del-CFTR folding defect responsible for >90% of CF cases. We report herein the discovery of the first small-molecules able to simultaneously act as correctors of the F508del-CFTR folding defect and as broad-spectrum antivirals against a panel of enteroviruses representative of all major species.

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis.

Author(s): Aslam, Aisha A; Higgins, Colin; Sinha, Ian P; Southern, Kevin W

Source: The Cochrane database of systematic reviews; Jan 2017; vol. 1 ; p. CD012040

Publication Type(s): Journal Article Review

Abstract: Cystic fibrosis is a common life-shortening genetic disorder in the Caucasian population (less common in other ethnic groups) caused by the mutation of a single gene that codes for the production of the cystic fibrosis transmembrane conductance regulator protein. This protein coordinates the transport of salt (and bicarbonate) across cell surfaces and the mutation most notably affects the airways. In the lungs of people with cystic fibrosis, defective protein results in a dehydrated surface liquid and compromised mucociliary clearance. The resulting thick mucus makes the airway prone to chronic infection and inflammation, which consequently damages the structure of the airways, eventually leading to respiratory failure. Additionally, abnormalities in the cystic fibrosis transmembrane conductance regulator protein lead to other systemic complications including malnutrition, diabetes and subfertility.Five classes of mutation have been described, depending on the impact of the mutation on the processing of the cystic fibrosis transmembrane conductance regulator protein in the cell. In class I mutations, the presence of premature termination codons prevents the production of any functional protein resulting in a severe cystic fibrosis phenotype. Advances in the understanding of the molecular genetics of cystic fibrosis has led to the development of novel mutation-specific therapies. Therapies targeting class I mutations (premature termination codons) aim to mask the abnormal gene sequence and enable the normal cellular mechanism to read through the mutation, potentially restoring the production of the cystic fibrosis transmembrane conductance regulator protein. This could in turn make salt transport in the cells function more normally and may decrease the chronic infection and inflammation that characterises lung disease in people with cystic fibrosis. To evaluate the benefits and harms of ataluren and similar compounds on clinically important outcomes in people with cystic fibrosis with class I mutations (premature termination codons). We searched the Cochrane Cystic Fibrosis

Trials Register which is compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles. Last search of Group's register: 24 October 2016.We searched clinical trial registries maintained by the European Medicines Agency, the US National Institutes of Health and the WHO. Last search of clinical trials registries: 28 November 2016. Randomised controlled trials of parallel design comparing ataluren and similar compounds (specific therapies for class I mutations) with placebo in people with cystic fibrosis who have at least one class I mutation. Cross-over trials were reviewed individually to evaluate whether data from the first treatment arm could be included. We excluded trials that combined therapies for premature termination codon class I mutations with other mutation-specific therapies. The authors independently assessed the risk of bias and extracted data from the included trial; they contacted trial authors for additional data. Our searches identified 28 references to eight trials; five trials were excluded (three were cross-over and one was not randomised and one did not have relevant outcomes), one cross-over trial is awaiting classification pending provision of data and one trial is ongoing. The included parallel randomised controlled trial compared ataluren to placebo for a duration of 48 weeks in 238 participants (age range 6 to 53 years) with cystic fibrosis who had at least one nonsense mutation (a type of class I mutation).The quality of evidence and risk of bias assessments for the trial were moderate overall. Random sequence generation, allocation concealment and blinding of trial personnel were well-documented; participant blinding was less clear. Some participant data were excluded from the analysis. The trial was assessed as high risk of bias for selective outcome reporting, especially when reporting on the trial's post hoc subgroup of participants by chronic inhaled antibiotic use.The trial was sponsored by PTC Therapeutics Incorporated with grant support by the Cystic Fibrosis Foundation, the Food and Drug Administration's Office of Orphan Products Development and the National Institutes of Health (NIH).The trial reported no significant difference between treatment groups in quality of life, assessed by the Cystic Fibrosis Questionnaire-Revised respiratory domain score and no improvement in respiratory function measures (mean difference of relative change in forced expiratory volume at one second 2.97% (95% confidence interval -0.58 to 6.52)). Ataluren was associated with a significantly higher rate of episodes of renal impairment, risk ratio 17.70 (99% confidence interval 1.28 to 244.40). The trial reported no significant treatment effect for ataluren for the review's secondary outcomes: pulmonary exacerbation; computerised tomography score; weight; body mass index; and sweat chloride. No deaths were reported in the trial.A post hoc subgroup analysis of participants not receiving chronic inhaled tobramycin (n = 146) demonstrated favourable results for ataluren (n = 72) for relative change in % predicted forced expiratory volume at one second and pulmonary exacerbation rate. Participants receiving chronic inhaled tobramycin appeared to have a reduced rate of pulmonary exacerbation compared to those not receiving chronic inhaled tobramycin. This drug interaction was not anticipated and may affect the interpretation of the trial results. There is currently insufficient evidence to determine the effect of ataluren as a therapy for people with cystic fibrosis with class I mutations. Future trials should carefully assess for adverse events, notably renal impairment and consider the possibility of drug interactions. Cross-over trials should be avoided given the potential for the treatment to change the natural history of cystic fibrosis.

In vitro activity of ceftolozane-tazobactam against multidrug-resistant non-fermenting Gram-negative bacilli isolated from patients with cystic fibrosis.

Author(s): Grohs, Patrick; Taieb, Gary; Morand, Philippe; Kaibi, Iheb; Podglajen, Isabelle; Lavollay, Marie; Mainardi, Jean-Luc; Compain, Fabrice

Source: Antimicrobial agents and chemotherapy; Jan 2017

Publication Type(s): Journal Article

Abstract: Ceftolozane-tazobactam was tested against 58 multidrug-resistant non-fermenting Gram-negative bacilli (35 Pseudomonas aeruginosa, 11 Achromobacter xylosoxydans and 12 Stenotrophomonas maltophilia) isolated from cystic fibrosis patients and compared to ceftolozane alone, ceftazidime, meropenem and piperacillin-tazobactam. Ceftolozane-tazobactam was the most active agent against P. aeruginosa but was inactive against A. xylosoxydans and S. maltophilia In time-kill experiments ceftolozane-tazobactam had complete bactericidal activity against 2/6 (33%) clinical isolates.

Mechanisms of intrinsic resistance and acquired susceptibility of Pseudomonas aeruginosa isolated from cystic fibrosis patients to temocillin, a revived antibiotic.

Author(s): Chalhoub, Hussein; Pletzer, Daniel; Weingart, Helge; Braun, Yvonne; Tunney, Michael M; Elborn, J Stuart; Rodriguez-Villalobos, Hector; Plésiat, Patrick; Kahl, Barbara C; Denis, Olivier; Winterhalter, Mathias; Tulkens, Paul M; Van Bambeke, Françoise

Source: Scientific reports; Jan 2017; vol. 7 ; p. 40208

Publication Type(s): Journal Article

Abstract: The β-lactam antibiotic temocillin (6-α-methoxy-ticarcillin) shows stability to most extended spectrum β-lactamases, but is considered inactive against Pseudomonas aeruginosa. Mutations in the MexAB-OprM efflux system, naturally occurring in cystic fibrosis (CF) isolates, have been previously shown to reverse this intrinsic resistance. In the present study, we measured temocillin activity in a large collection (n = 333) of P. aeruginosa CF isolates. 29% of the isolates had MICs ≤ 16 mg/L (proposed clinical breakpoint for temocillin). Mutations were observed in mexA or mexB in isolates for which temocillin MIC was ≤512 mg/L (nucleotide insertions or deletions, premature termination, tandem repeat, nonstop, and missense mutations). A correlation was observed between temocillin MICs and efflux rate of N-phenyl-1-naphthylamine (MexAB-OprM fluorescent substrate) and extracellular exopolysaccharide abundance (contributing to a mucoid phenotype). OpdK or OpdF anion-specific porins expression decreased temocillin MIC by ~1 two-fold dilution only. Contrarily to the common assumption that temocillin is inactive on P. aeruginosa, we show here clinically-exploitable MICs on a non-negligible proportion of CF isolates, explained by a wide diversity of mutations in mexA and/or mexB. In a broader context, this work contributes to increase our understanding of MexAB-OprM functionality and help delineating how antibiotics interact with MexA and MexB.

Alternative Indexes to Estimate the Functional Capacity From the 6-Minute Walk Test in Children and Adolescents With Cystic Fibrosis.

Author(s): Okuro, Renata Tiemi; de Oliveira Ribeiro, Maria Angela Gonçalves; Ribeiro, José Dirceu; Minsky, Rafaela Coelho; Schivinski, Camila Isabel Santos

Source: Respiratory care; Jan 2017

Publication Type(s): Journal Article

Available in full text at Respiratory Care - from Highwire Press

Abstract: Cystic fibrosis is a multi-systemic disease related to reduced functional capacity. The distance covered in the 6-min walk test (6MWT) has been known to assess functional capacity, but little is known about other indexes that can be derived. We sought to compare the performance during the 6MWT and the estimated indexes of functional capacity from the 6MWT between subjects with cystic fibrosis (CF) and healthy individuals as well as to assess the relationship among these indexes and disease severity, pulmonary function, and nutritional status in CF. This cross-sectional study was carried out at a university referral center for CF. It included a group of 55 non-

oxygen-dependent CF subjects (CF group) with no acute pulmonary exacerbations and a group of 185 healthy controls (control group). All subjects were submitted to 6MWT and anthropometrics measurements. Regarding performance during the 6MWT, the mean values of work, physiological cost index, average velocity, and 6-min walk distance (6MWD) were significantly lower in the CF group than in the control group (work: 21,690.58 ± 10,427.77 vs 26,057.51 ± 11,228.49 m × kg [P = .007]; physiological cost index: 0.31 ± 0.19 vs 0.37 ± 0.17; average velocity: 94.71 ± 12.89 vs 104.55 ± 9.13 m/min [P < .001]; and 6MWD: 568.02 ± 76.31 m versus 627.54 ± 54.81 m [P < .001]). Subjects with less severe CF had higher 6MWD, work, and average velocity during the 6MWT, compared with subjects with more severe CF (P = .008, P = .012, and P = .007, respectively). There was a correlation between 6MWD, work, average velocity, and disease severity and pulmonary function. Considering the importance of standard measure (6MWD) the in 6MWT, alternative indexes can be useful as complementary outcomes and to provide a better understanding of limiting factors of exercise response in children and adolescents with CF.

CFTR founder mutation causes protein trafficking defects in Chinese patients with cystic fibrosis.

Author(s): Leung, Gordon K C; Ying, Dingge; Mak, Christopher C Y; Chen, Xin-Ying; Xu, Weiyi; Yeung, Kit-San; Wong, Wai-Lap; Chu, Yoyo W Y; Mok, Gary T K; Chau, Christy S K; McLuskey, Jenna; Ong, Winnie P T; Leong, Huey-Yin; Chan, Kelvin Y K; Yang, Wanling; Chen, Jeng-Haur; Li, Albert M; Sham, Pak C; Lau, Yu-Lung; Chung, Brian H Y; Lee, So-Lun

Source: Molecular genetics & genomic medicine; Jan 2017; vol. 5 (no. 1); p. 40-49

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) is a rare condition in Asians. Since 1985, only about 30 Chinese patients have been reported with molecular confirmation. Using our in-house next-generation sequencing (NGS) pipeline for childhood bronchiectasis, we identified disease-causing CFTR mutations in CF patients in Hong Kong. After identifying p.I1023R in multiple patients, haplotype analysis was performed with genome-wide microarray to ascertain the likelihood of this being a founder mutation. We also assessed the processing and gating activity of the mutant protein by Western hybridization and patch-clamp test. Molecular diagnoses were confirmed in four patients, three of whom shared a missense mutation: CFTR:c.3068T>G:p.I1023R. The results suggested that p.I1023R is a founder mutation in southern Han Chinese. In addition, the processing and gating activity of the mutant protein was assessed by gel electrophoresis and a patch-clamp test. The mutant protein exhibited trafficking defects, suggesting that the dysfunction is caused by reduced cell surface expression of the fully glycosylated proteins. Together with other previously reported mutations, the specific founder mutation presented herein suggests a unique CFTR mutation spectrum in the southern Chinese populations, and this finding has vital implications for improving molecular testing and mutation-specific treatments for Chinese patients with CF.

Correlation of sweat chloride and percent predicted FEV1 in cystic fibrosis patients treated with ivacaftor.

Author(s): Fidler, Meredith C; Beusmans, Jack; Panorchan, Paul; Van Goor, Fredrick

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jan 2017; vol. 16 (no. 1); p. 41-44

Publication Type(s): Journal Article

Abstract: Ivacaftor, a CFTR potentiator that enhances chloride transport by acting directly on CFTR to increase its channel gating activity, has been evaluated in patients with different CFTR mutations. Several previous analyses have reported no statistical correlation between change from baseline in

ppFEV1 and reduction in sweat chloride levels for individuals treated with ivacaftor. The objective of the post hoc analysis described here was to expand upon previous analyses and evaluate the correlation between sweat chloride levels and absolute ppFEV1 changes across multiple cohorts of patients with different CF-causing mutations who were treated with ivacaftor. The goal of the analysis was to help define the potential value of sweat chloride as a pharmacodynamic biomarker for use in CFTR modulator trials. For any given study, reductions in sweat chloride levels and improvements in absolute ppFEV1 were not correlated for individual patients. However, when the data from all studies were combined, a statistically significant correlation between sweat chloride levels and ppFEV1 changes was observed ($p<0.0001$). Thus, sweat chloride level changes in response to potentiation of the CFTR protein by ivacaftor appear to be a predictive pharmacodynamic biomarker of lung function changes on a population basis but are unsuitable for the prediction of treatment benefits for individuals.

Psychology

A case report of the treatment of obsessive compulsive disorder in a patient with Cystic Fibrosis: Potential protective role of contamination fears

Author(s): Mac Neil B.A.; Prost E.; Leung P.; Gates J.

Source: Journal of Obsessive-Compulsive and Related Disorders; Jan 2017; vol. 12 ; p. 9-14

Publication Type(s): Journal: Article

Nutrition

A Quality Improvement Initiative to Improve Patient Adherence to Vitamin Supplementation in Cystic Fibrosis.

Author(s): Garavaglia, Lisa; Duncan, Christina; Toucheque, Malorie; Farley, Allilene; Moffett, Kathryn S

Source: Journal of pediatric gastroenterology and nutrition; Feb 2017; vol. 64 (no. 2); p. 292-295

Publication Type(s): Journal Article

Abstract: Patients with cystic fibrosis (CF) and pancreatic insufficiency are prescribed fat-soluble vitamins, although compliance remains low. Our objective was to identify patient and caregiver knowledge deficits regarding vitamin supplementation, provide targeted education, and examine serum vitamin levels pre-and posteducation. This prospective quality improvement study involved 118 patients. A vitamin knowledge survey was given to patients/caregivers during a clinic visit, education was provided targeting knowledge deficits, and the survey was re-administered at the next clinic visit. Serum vitamin levels were collected at pre- and postsurvey. Results showed significant pre-post increases for patient and caregiver knowledge scores, and significant decreases in self-reported nonadherence to vitamin use and number of reported barriers affecting adherence. A significant change in vitamin E level to therapeutic range post-education was demonstrated. Our brief, targeted educational interventions regarding vitamin supplementation showed utility in a routine clinic setting.

Clinical impact of vitamin D treatment in cystic fibrosis: a pilot randomized, controlled trial.

Author(s): Pincikova, T; Paquin-Proulx, D; Sandberg, J K; Flodström-Tullberg, M; Hjelte, L

Source: European journal of clinical nutrition; Feb 2017; vol. 71 (no. 2); p. 203-205

Publication Type(s): Journal Article

Abstract: Vitamin D insufficiency in cystic fibrosis is common. Vitamin D3 is currently preferred over D2. We aimed to study the efficacy of vitamin D2 and D3 at increasing serum 25-hydroxyvitamin D (s25OHD) concentrations and their effect on respiratory health in cystic fibrosis. Sixteen CF patients were randomized to receive vitamin D2 or D3 or to serve as controls. The starting dose of 5000 IU (<16 years old) or 7143 IU/day (⩾16 years old) was further individually adjusted. Three months of intervention were followed by two of washout (ClinicalTrials.gov NCT01321905). To increase s25OHD, the mean daily dose of vitamin D2 and D3 had to be increased up to 15650 and 8184 IU, respectively. The combined group of vitamin D2 and D3 treated patients decreased plasma IL-8 (P<0.05). Patients provided vitamin D3 improved FVC at the end of the trial (P<0.05). Change in s25OHD was positively correlated with changes in the adult Quality-of-Life respiratory score at the end of supplementation (P=0.006, r=0.90), and with changes in FEV1 (P=0.042, r=0.62) and FVC (P=0.036, r=0.63) at one month of washout. Vitamin D supplementation may contribute to reduced inflammation and improved lung function in CF.

Other

Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients.

Author(s): Grosse-Onnebrink, Joerg; Mellies, Uwe; Olivier, Margarete; Werner, Claudius; Stehling, Florian

Source: Pediatric pulmonology; Jan 2017

Publication Type(s): Journal Article

Abstract: The lung clearance index (LCI) is determined by multiple-breath washout lung function (MBW). It is increasingly used as an endpoint in clinical trials. Chest physiotherapy (CP) is part of routine cystic fibrosis (CF) care. Whether the LCI is useful in detecting short-term treatment effects of CP has not been sufficiently investigated. We assessed the short-term influence of CP with highly standardized high-frequency chest wall oscillation (HFCWO) on the LCI in CF patients. In this randomized controlled study, the LCI was obtained in 20 CF patients (7-34 years) hospitalized for infective pulmonary exacerbation prior to and immediately after a single treatment of HFCWO. Twenty-one control group CF patients (7-51 years) received no treatment. We calculated the coefficient of repeatability (CR) to estimate the clinical relevance of possible treatment effects. HFCWO improved (ie, decreased) the LCI by a median of 0.9 (range -0.45; 3.47; P = 0.002); the LCI decreased in 15 of 20 intervention group patients. In five patients the decrease in LCI exceeded the CR (2.15), indicating a clinically relevant treatment effect; in five patients the LCI increased but did not exceed the CR. The LCI did not change significantly in the control group patients. HFCWO can have a short-term decreasing effect on the LCI, but the treatment response is heterogeneous. In future trials using LCI as an endpoint, the timing of CP in relation to MBW should be considered a possible bias. © 2017 Wiley Periodicals, Inc.

Effects of treadmill exercise versus Flutter on respiratory flow and sputum properties in adults with cystic fibrosis: A randomised, controlled, cross-over trial

Author(s): Dwyer T.J.; Zainuldin R.; Alison J.A.; Daviskas E.; Bye P.T.P.

Source: BMC Pulmonary Medicine; Jan 2017; vol. 17 (no. 1)

Publication Type(s): Journal: Article

Available in full text at BMC Pulmonary Medicine - from BioMed Central

Abstract: Background: Treadmill exercise and airway clearance with the Flutter device have previously been shown to improve mucus clearance mechanisms in people with cystic fibrosis (CF) but have not been compared. It is therefore not known if treadmill exercise is an adequate form of airway clearance that could replace established airway clearance techniques, such as the Flutter. The aim of this study was to evaluate respiratory flow, sputum properties and subjective responses of treadmill exercise and Flutter therapy, compared to resting breathing (control). Methods: Twenty-four adults with mild to severe CF lung disease (FEV1 28-86% predicted) completed a three-day randomised, controlled, cross-over study. Interventions consisted of 20min of resting breathing (control), treadmill exercise at 60% of the participant's peak oxygen consumption and Flutter therapy. Respiratory flow was measured during the interventions. Sputum properties (solids content and mechanical impedance) and subjective responses (ease of expectoration and sense of chest congestion) were measured before, immediately after the interventions and after 20min of recovery. Results: Treadmill exercise and Flutter resulted in similar significant increases in peak expiratory flow, but only Flutter created an expiratory airflow bias (i.e. peak expiratory flow was at least 10% higher than peak inspiratory flow). Treadmill exercise and Flutter therapy resulted in similar significant reductions in sputum mechanical impedance, but only treadmill exercise caused a transient increase in sputum hydration. Treadmill exercise improved ease of expectoration and Flutter therapy improved subjective sense of chest congestion. Conclusions: A single bout of treadmill exercise and Flutter therapy were equally effective in augmenting mucus clearance mechanisms in adults with CF. Only longer term studies, however, will determine if exercise alone is an adequate form of airway clearance therapy that could replace other airway clearance techniques. Trial registration: Australian and New Zealand Clinical Trials Registry, Registration number num ACTRN12609000168257, Retrospectively registered (Date submitted to registry 26/2/2009, First participant enrolled 27/2/2009, Date registered 6/4/2009).

Ventilatory limitation and dynamic hyperinflation during exercise testing in Cystic Fibrosis

Author(s): Karapanagiotis S.; Gambazza S.; Brivio A.; Colombo C.; D'Abrosca F.

Source: Pediatric Pulmonology; Jan 2017; vol. 52 (no. 1); p. 29-33

Publication Type(s): Journal: Article

Abstract: Objective: To investigate the presence of dynamic hyperinflation after the Modified Shuttle Test (MST) and its relationship with lung function, exercise tolerance, and clinical symptoms in Cystic Fibrosis (CF). Methods: Retrospective observational study. Subjects in clinically stable condition with a CF diagnosis based on a positive sweat test (chloride >60 mEq/L) and/or presence of two disease causing mutations, with available data on MST, spirometry, maximal voluntary ventilation, and inspiratory capacity manoeuvres were considered for the analysis. Breathing reserve was calculated and a threshold value of 0.7 was subsequently chosen as a value of pulmonary mechanical limit. Subjects were then categorized into two groups according to the change in the inspiratory capacity from rest to peak exercise. Unconditional logistic regression was used to estimate unadjusted odds ratios, 95% confidence intervals and P-values. Results: Twenty-two subjects demonstrated evidence of dynamic hyperinflation during the MST. Thirteen out of 22 subjects were ventilatory limited during exercise including 5 of those without evidence of dynamic hyperinflation (P = 0.24). No combination of variables resulted in a parsimonious regression model. Conclusions: Dynamic hyperinflation is common in CF and it is not associated with traditionally defined ventilatory limitation parameters during the MST. Pediatr Pulmonol. 2017;52:29-33.

Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis.

Author(s): Beaudoin, Nadia; Bouvet, Guillaume F; Coriati, Adèle; Rabasa-Lhoret, Rémi; Berthiaume, Yves

Source: Medicine and science in sports and exercise; Feb 2017; vol. 49 (no. 2); p. 231-237

Publication Type(s): Journal Article

Abstract: Glucose abnormality and diabetes are the most common comorbidities in cystic fibrosis (CF). Combined (aerobic and resistance) exercise program in type 2 patients with diabetes demonstrated an improvement of glycemic control. The aim of the study was to determine whether a combined exercise program is beneficial to improve plasma glucose at 2 h of the oral glucose tolerance test in CF. Eighteen adults with CF with glucose abnormality were recruited (Clinicaltrial.gov: NTC02127957), and 17 were randomly assigned to a control or exercise group for 12 wk. V˙O2max, oral glucose tolerance test, muscular endurance and strength, and quality of life were measured pre- and postintervention. Fourteen participants completed the protocol. Patients in the exercise group improved significantly their 2-h plasma glucose values (-2.34 ± 1.26 mmol·L, P < 0.007, confidence interval = 99.22%) and presented a reduction of 17.2% (P < 0.05) in total glucose excursion. No significant change for other parameters was observed. A combined exercise program improves glycemic control in CF.

Maternal co-morbidities and neonatal outcomes associated with cystic fibrosis.

Author(s): Jelin A.C.; Sharshiner R.; Caughey A.B.

Source: Journal of Maternal-Fetal and Neonatal Medicine; Jan 2017; vol. 30 (no. 1); p. 4-7

Publication Type(s): Journal: Article

Abstract: Objective: To evaluate maternal co-morbidities and adverse perinatal outcomes associated with cystic fibrosis (CF). Methods: This is a retrospective cohort study of 2 178 954 singleton pregnancies at >20 weeks' gestation with and without CF in the state of California during the years 2005-2008. ICD-9 codes and linked hospital discharge and vital statistics data were utilized. Rates of maternal co-morbidities, fetal congenital anomalies and adverse perinatal outcomes were compared in those with CF and those without. Maternal co-morbidities included gestational hypertension, preeclampsia, gestational diabetes and primary cesarean delivery. Perinatal outcomes included neonatal demise, preterm birth, intrauterine growth restriction, macrosomia, anomaly, fetal demise, asphyxia, respiratory distress syndrome, jaundice, intraventricular hemorrhage, hypoglycemia and necrotizing enterocolitis. Results: The cohort included 2 178 954 pregnancies of which 77 mothers had CF. Mothers with CF were more likely to have pre-gestational diabetes and had higher rates of primary cesarean delivery. Neonates delivered to mothers with CF were more likely to be born preterm and have congenital anomalies but otherwise were not at increased risk for significant neonatal morbidity or mortality when adjusted for gestational age. Conclusion: Mothers with CF are more likely to have pre-gestational diabetes, deliver preterm (<37 weeks gestation) and have a primary cesarean delivery. Infants are more likely to have congenital anomalies. In addition to early diabetic screening and genetic counseling, a detailed fetal anatomy ultrasound should be performed in women with CF.

Adherence to therapies in cystic fibrosis: a targeted literature review.

Author(s): Narayanan, Siva; Mainz, Jochen G; Gala, Smeet; Tabori, Harold; Grossoehme, Daniel

Source: Expert review of respiratory medicine; Feb 2017; vol. 11 (no. 2); p. 129-145

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) is a life-shortening condition with no cure. Available therapies relieving the symptoms of CF are complex and time-consuming. A comprehensive review assessing adherence to different CF therapies, association of adherence with outcomes, and factors influencing adherence could inform optimal patient management strategies. Areas covered: A targeted literature review of studies published from 2010-2016 assessed adherence to CF therapies. Nineteen studies qualified for inclusion. Adherence to CF therapies was sub-optimal, and varied by treatment, mode of treatment administration, age, season, time and method of adherence measurement. Adherence to ivacaftor and inhaled antibiotics were reported higher than dornase alfa or hypertonic saline, oral pancreatic enzyme and vitamin supplements, and airway clearance therapy. Several patient, healthcare provider and treatment related factors influenced adherence. Sub-optimal adherence was shown to impact clinical and economic burden of the disease. Expert commentary: Higher adherence to CF therapies can lower disease burden, and improve patient outcomes. Healthcare providers and policy makers should devise patient-centered and caregiver-enabled interventions to improve adherence. Research on long-term adherence and outcomes associated with promising oral treatments such as CFTR modulators is needed. Identifying ways to overcome key barriers to adherence can positively affect outcomes associated with CF.

Growth in Prepubertal Children With Cystic Fibrosis Treated With Ivacaftor.

Author(s): Stalvey, Michael S; Pace, Jesse; Niknian, Minoo; Higgins, Mark N; Tarn, Valerie; Davis, Joy; Heltshe, Sonya L; Rowe, Steven M

Source: Pediatrics; Jan 2017

Publication Type(s): Journal Article

Available in full text at Pediatrics - from Highwire Press ; Notes: Username: library5 Password: library5

Abstract: Cystic fibrosis (CF) is known for its impact on the lung and pancreas of individuals; however, impaired growth is also a common complication. We hypothesized that targeting the biological defect in the CF transmembrane conductance regulator (CFTR) protein may affect growth outcomes. In this post hoc analysis, we assessed linear growth and weight in 83 children (aged 6-11 years) enrolled in 2 clinical trials, the longitudinal-observation GOAL study and the placebo-controlled ENVISION study, to evaluate the effects of ivacaftor, a CFTR potentiator. We calculated height and weight z scores and height and weight growth velocities (GVs). In ivacaftor-treated children in GOAL, height and weight z scores increased significantly from baseline to 6 months (increases of 0.1 [P < .05] and 0.26 [P < .0001], respectively); height GV increased significantly from 3 to 6 months (2.10-cm/year increase; P < .01). In ivacaftor-treated children in ENVISION, height and weight z scores increased significantly from baseline to 48 weeks (increases of 0.17 [P < .001] and 0.35 [P < .001], respectively). Height and weight GVs from baseline to 48 weeks were also significantly higher with ivacaftor than with placebo (differences of 1.08 cm/year [P < .05] and 3.11 kg/year [P < .001], respectively). Ivacaftor treatment in prepubescent children may help to address short stature and altered GV in children with CF; results from these analyses support the existence of an intrinsic defect in the growth of children with CF that may be ameliorated by CFTR modulation.

A Case Report of Pregnancy During Use of Targeted Therapeutics for Cystic Fibrosis.

Author(s): Ladores, Sigrid; Kazmerski, Traci M; Rowe, Steven M

Source: Journal of obstetric, gynecologic, and neonatal nursing : JOGNN; 2017; vol. 46 (no. 1); p. 72-77

Publication Type(s): Journal Article

Abstract: New therapeutics, such as ivacaftor, and the combination drug lumacaftor/ivacaftor that target the underlying genetic cause of cystic fibrosis are being hailed as game-changers in this era of personalized medicine. Although these drugs improve lung function, their effects on female fertility have not been studied. In this case report we describe one woman's experience with ivacaftor and her unanticipated pregnancy. Implications related to comprehensive sexual and reproductive health care for women with cystic fibrosis are presented.

Journal Tables of Contents

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Journal of Cystic Fibrosis

January 2017, Volume 16, Issue 1

http://www.cysticfibrosisjournal.com/current

American Journal of Respiratory and Critical Care Medicine

January 15 2017, Volume 195, Issue 2

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

Thorax

February 2017, Volume 72, Issue 2

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

Chest

January 2017, Volume 151, Issue 1

http://journal.publications.chestnet.org/issue.aspx

Exercise: Sensitivity and Specificity

Sensitivity:
If a person has a disease, how often will the test be positive (true positive rate)?

If the test is highly sensitive and the test result is negative you can be nearly certain that they don't have disease.

Specificity:
If a person does not have the disease how often will the test be negative (true negative rate)?

If the test result for a highly specific test is positive you can be nearly certain that they actually have the disease.

Quick Quiz:

1. **A very sensitive test, when negative, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

2. **A test which is highly specific, when positive, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

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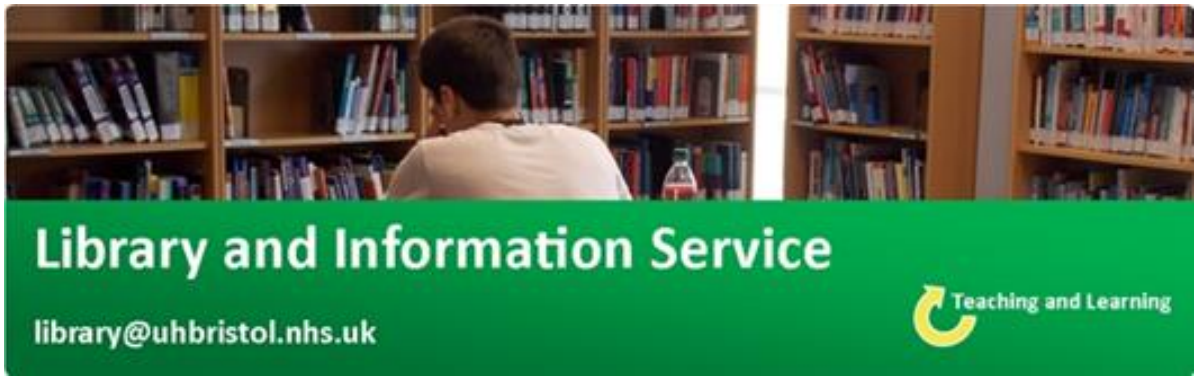
Answers: 1b; 2a



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