Cystic Fibrosis

Current Awareness Newsletter

August 2015
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**Lunchtime Drop-in Sessions**

**Literature Searching**
An in-depth guide on how to search the evidence base, including an introduction to UpToDate and Anatomy.tv.

Useful for anybody who wants to find the best and quickest way to source articles.

**How to understand an article**
How to assess the strengths and weaknesses of published articles.

Examining bias and validity.

**Medical Statistics**
A basic introduction to the key statistics in medical articles.

Giving an overview of statistics that compare risk, test confidence, analyse clinical investigations, and test difference.

**August** (12pm)
- Fri 14th Literature Searching
- Tues 18th Understanding articles
- Weds 26th Statistics

**September** (1pm)
- Thurs 3rd Literature Searching
- Fri 11th Understanding articles
- Mon 14th Statistics
- Tues 22nd Literature Searching
- Weds 30th Understanding articles

**October** (12pm)
- Thurs 8th Statistics
- Fri 16th Literature Searching
- Mon 19th Understanding articles
- Tues 27th Statistics

**November** (1pm)
- Weds 4th Literature Searching
- Thurs 12th Understanding articles
- Fri 20th Statistics
- Mon 23rd Literature Searching

**December** (12pm)
- Tues 1st Understanding articles
- Weds 9th Statistics
- Thurs 17th Literature Searching
New Cochrane Library Systematic Reviews on Cystic Fibrosis

Intravenous antibiotics for pulmonary exacerbations in people with cystic fibrosis

Matthew N Hurley, Andrew P Prayle and Patrick Flume

Online Publication Date: July 2015

Background

Cystic fibrosis is a multi-system disease characterised by the production of thick secretions causing recurrent pulmonary infection, often with unusual bacteria. Intravenous antibiotics are commonly used in the treatment of acute deteriorations in symptoms (pulmonary exacerbations); however, recently the assumption that exacerbations are due to increases in bacterial burden has been questioned.

Objectives

To establish if intravenous antibiotics for the treatment of pulmonary exacerbations in people with cystic fibrosis improve short- and long-term clinical outcomes.

New from NICE

Proposed technology appraisals

...vein occlusion) – aflibercept Cystic fibrosis – lumacaftor and ivacaftor Melanoma (advanced, unresectable...matrix PDF 40 kB Back to top Cystic fibrosis – lumacaftor and ivacaftor Suggested...marketing authorisation for treatingcystic fibrosis in people who are homozygous...

Published July 2015

http://www.nice.org.uk/search?am=([{%22drm%22:}%22%20last%203%20months%20%22]})&q=cystic%20fibrosis&s=date
To access electronic resources you need an NHS Athens username and password.

To register, click on the link: https://openathens.nice.org.uk/

You need to register using an NHS PC and an NHS email address.

Registration is a quick, simple process, and will give you access to a huge range of online subscription resources, including:

- UpToDate
- Dynamed
- NHS Evidence
- Anatomy.tv
- E-journals
- E-books

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Current Awareness Database Articles on Cystic Fibrosis

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

- Medical
- Microbiological
- Psychological
- 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

Title: Novel inhaled combined antibiotic formulations in the treatment of Pseudomonas aeruginosa airways infections in cystic fibrosis

Citation: Expert Review of Anti-Infective Therapy, July 2015, vol./is. 13/7(897-905)

Author(s): Antoniu S.

Abstract: In cystic fibrosis, chronic airways infection caused by Pseudomonas aeruginosa can be treated with inhaled antibiotics such as inhaled tobramycin, aztreonam or colistin. However, biofilm formation induced by this bacterium can reduce the effectiveness of such therapies and can contribute to antibiotic resistance. Inhaled antibiotic combination might represent an optimal antibiofilm strategy in this setting. This review discusses the rationale for combining the antibiotics as well as some emerging or existing combinations. Most of the combinations except for fosfomycin/tobramycin are at an early stage of development. The latter combination was found to be effective in Phase II clinical studies and is planned to be tested in Phase III trials. The clinical data on long-term efficacy are currently missing, but the existing evidence as well as the unmet therapeutic need can prompt the further evaluation of such compounds.

Title: National healthcare delivery systems influence lung transplant outcomes for cystic fibrosis

Citation: American Journal of Transplantation, July 2015, vol./is. 15/7(1948-1957)

Author(s): Merlo C.A., Clark S.C., Arnaoutakis G.J., Yonan N., Thomas D.,

Abstract: Successful lung transplantation (LTx) depends on multiple components of healthcare delivery and performance. Therefore, we conducted an international registry analysis to compare post-LTx outcomes for cystic fibrosis (CF) patients using the UNOS registry in the United States and
the National Health Service (NHS) Transplant Registry in the United Kingdom. Patients with CF who underwent lung or heart-lung transplantation in the United States or United Kingdom between January 1, 2000 and December 31, 2011 were included. The primary outcome was all-cause mortality. Kaplan-Meier analysis and Cox proportional hazards regression evaluated the effect of healthcare system and insurance on mortality after LTx. 2,307 US LTx recipients and 451 individuals in the United Kingdom were included. 894 (38.8%) US LTx recipients had publically funded Medicare/Medicaid insurance. US private insurance and UK patients had improved median predicted survival compared with US Medicare/Medicaid recipients (p<0.001). In multivariable Cox regression, US Medicare/Medicaid insurance was associated with worse survival after LTx (US private: HR0.78, 0.68-0.90, p=-0.001 and UK: HR0.63, 0.41-0.97, p=-0.03). This study in CF patients is the largest comparison of LTx in two unique health systems. Both the United States and United Kingdom have similar early survival outcomes, suggesting important dissemination of best practices internationally. However, the performance of US public insurance is significantly worse and may put patients at risk. In this multicenter study from the United States and United Kingdom, the authors examine differences in lung transplant outcomes for cystic fibrosis patients undergoing transplantation across two different healthcare systems.

Title: Patients’ experience of portacaths in cystic fibrosis: Questionnaire-based study

Citation: Archives of Disease in Childhood, July 2015, vol./is. 100/7(659-661)

Author(s): McIntosh L.A., Walker G.M.

Abstract: Backgrounds and aims: Portacaths are regularly used in children with cystic fibrosis (CF). We aimed to assess patient satisfaction with lateral chest wall portacaths in children with CF. Methods: All children in a geographical region with CF and portacath in situ were identified. Site of chest wall placement was identified on X-ray; only children with lateral chest wall portacaths were sent questionnaires. Data collected included preoperative information, cosmesis and interference with activities. Results: Of the 46 patients identified, 42 had lateral chest wall ports. 25 of this 42(60%) submitted their questionnaires. 22(88%) were happy with preoperative information although only 8(32%) recall being offered choice of position. 23(92%) were satisfied with cosmesis. 2 patients reported problems with physiotherapy only with indwelling needles. 6(24%) patients had problems with clothing, 7(32%) with sports and 3(12%) with seatbelts. Conclusions: Lateral chest wall portacaths are cosmetically acceptable. Impact on daily activities is less common than that reported with anterior chest wall placement.

Title: Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy

Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(419-430)

Author(s): Cantin A.M., Hartl D., Konstan M.W., Chmiel J.F.

Abstract: Lung disease is the major cause of morbidity and mortality in patients with cystic fibrosis (CF). Although CF lung disease is primarily an infectious disorder, the associated inflammation is both intense and ineffective at clearing pathogens. Persistent high-intensity inflammation leads to permanent structural damage of the CF airways and impaired lung function that eventually results in respiratory failure and death. Several defective inflammatory responses have been linked to cystic fibrosis transmembrane conductance regulator (CFTR) deficiency including innate and acquired immunity dysregulation, cell membrane lipid abnormalities, various transcription factor signaling defects, as well as altered kinase and toll-like receptor responses. The inflammation of the CF lung is dominated by neutrophils that release oxidants and proteases, particularly elastase. Neutrophil
elastase in the CF airway secretions precedes the appearance of bronchiectasis, and correlates with lung function deterioration and respiratory exacerbations. Anti-inflammatory therapies are therefore of particular interest for CF lung disease but must be carefully studied to avoid suppressing critical elements of the inflammatory response and thus worsening infection. This review examines the role of inflammation in the pathogenesis of CF lung disease, summarizes the results of past clinical trials and explores promising new anti-inflammatory options.

Title: A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients

Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(507-514)

Author(s): Stuart Elborn J., Geller D.E., Conrad D., Aaron S.D., Smyth A.R., Fischer R., Kerem E.,

Abstract: Background: Inhaled antibiotics are standard of care for persons with cystic fibrosis (CF) and chronic Pseudomonas aeruginosa airway infection. APT-1026 (levofloxacin inhalation solution, LIS) is fluoroquinolone in development. We compared the safety and efficacy of LIS to tobramycin inhalation solution (TIS) in persons > 12 years old with CF and chronic P. aeruginosa infection. Methods: This multinational, randomized (2:1), non-inferiority study compared LIS and TIS over three 28-day on/off cycles. Day 28 FEV<sub>1</sub> % predicted relative change was the primary endpoint. Time to exacerbation and patient-reported quality of life were among secondary endpoints. Results: Baseline demographics for 282 subjects were comparable. Non-inferiority was demonstrated (1.86% predicted mean FEV<sub>1</sub> difference [95% CI -0.66 to 4.39%]). LIS was well-tolerated, with dysgeusia (taste distortion) as the most frequent adverse event. Conclusions: LIS is a safe and effective therapy for the management of CF patients with chronic P. aeruginosa infection.

Title: Intraductal papillary mucinous neoplasm of the pancreas in an adult patient with cystic fibrosis after double-lung transplantation

Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(523-525)

Author(s): Eigner W., Mesteri I., Tribl B., Ba-Ssalamah A., Friedl J., Trauner M., Kazemi-Shirazi L.

Abstract: We report on an adult patient with cystic fibrosis after double-lung transplantation under triple immunosuppression with non-specific abdominal symptoms and a pancreatic cystic tumor, resulting in the diagnosis of an intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Pancreatic cysts in adult patients with cystic fibrosis, especially after transplantation, merit close attention and thorough investigation.

Title: Cystic fibrosis - From basic science to clinical benefit: A review series

Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(415-416)

Author(s): Hartl D., Amaral M.

Title: UNDERSTANDING AND MANAGING CYSTIC FIBROSIS.

Citation: Primary Health Care, 01 July 2015, vol./is. 25/6(18-24), 02645033
**Author(s):** Dack, Kamilla, Peres, Alan, Thrift, Linda, Talbot, Susan, Madge, Susan

**Abstract:** Cystic fibrosis (CF) is one of the most common inherited diseases in the UK. It is a multi-system disease, mainly affecting the lungs and gastrointestinal tract, but also the liver, pancreas, joints, sinuses and male reproductive system. Diagnosis is commonly through screening newborns, although older children and adults are also diagnosed with CF. Treatment is daily, complex and time-consuming and, although most of it is conducted at home, there is an increasing need for hospital admission as individuals age and the disease progresses. CF is life-limiting, with no cure. However, life expectancy throughout Europe is improving thanks to early and aggressive treatment, specialist centre care and novel therapies. Of the 32,248 patients registered in Europe with CF, 49.3% are more than 18 years old, although the median age of death across Europe is 28 years (European Cystic Fibrosis Society 2014) based on the latest available figures. Children born with CF today are expected to live into their fifties and sixties.

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**Title:** Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial.

**Citation:** Journal of Physiotherapy (Elsevier), 01 July 2015, vol./is. 61/3(142-147)

**Author(s):** Dwyer, Tiffany J, Robbins, Lisel, Kelly, Patrick, Piper, Amanda J, Bell, Scott C, Bye, Peter T P

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**Title:** New and Emerging Treatments for Cystic Fibrosis.

**Citation:** Drugs, Jul 2015, vol. 75, no. 11, p. 1165-1175

**Author(s):** Barry, Peter J, Jones, Andrew M

**Abstract:** Recently, a significant number of additional key medications have become licensed in Europe for the treatment of patients with cystic fibrosis (CF), including a number of inhaled antibiotics, such as nebulised aztreonam and dry powder versions of colistin and tobramycin for inhalation; dry powder inhaled mannitol, an agent to improve airway hydration and aid airway clearance; and ivacaftor, an oral therapy that directly acts on dysfunctional CFTR to correct the basic defect encountered in CF patients with the G551D CF gene mutation. The marked success of ivacaftor both in clinical trials and in post-licensing evaluation studies in treating patients with G551D and other gating mutations has greatly encouraged the ongoing development of similar therapies that can directly target the underlying cause of CF. Other therapies, including a number of anti-infectives, anti-inflammatory and replacement pancreatic enzymes, are currently undergoing clinical studies. This article reviews those treatments that have been recently licensed for CF and highlights some of the exciting emerging therapies presently under evaluation in clinical trials. In addition, it discusses some of the potential challenges being encountered by research and clinical teams in developing and delivering treatments for this condition.

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**Title:** Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR.

**Citation:** The New England journal of medicine, Jul 2015, vol. 373, no. 3, p. 220-231 (July 16, 2015)

**Author(s):** Wainwright, Claire E, Elborn, J Stuart, Ramsey, Bonnie W, Marigowda, Gautham,
**Abstract:** Cystic fibrosis is a life-limiting disease that is caused by defective or deficient cystic fibrosis transmembrane conductance regulator (CFTR) protein activity. Phe508del is the most common CFTR mutation. We conducted two phase 3, randomized, double-blind, placebo-controlled studies that were designed to assess the effects of lumacaftor (VX-809), a CFTR corrector, in combination with ivacaftor (VX-770), a CFTR potentiator, in patients 12 years of age or older who had cystic fibrosis and were homozygous for the Phe508del CFTR mutation. In both studies, patients were randomly assigned to receive either lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or matched placebo for 24 weeks. The primary end point was the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (FEV1) at week 24. A total of 1108 patients underwent randomization and received study drug. The mean baseline FEV1 was 61% of the predicted value. In both studies, there were significant improvements in the primary end point in both lumacaftor-ivacaftor dose groups; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV1 ranged from 2.6 to 4.0 percentage points (P<0.001), which corresponded to a mean relative treatment difference of 4.3 to 6.7% (P<0.001). Pooled analyses showed that the rate of pulmonary exacerbations was 30 to 39% lower in the lumacaftor-ivacaftor groups than in the placebo group; the rate of events leading to hospitalization or the use of intravenous antibiotics was lower in the lumacaftor-ivacaftor groups as well. The incidence of adverse events was generally similar in the lumacaftor-ivacaftor and placebo groups. The rate of discontinuation due to an adverse event was 4.2% among patients who received lumacaftor-ivacaftor versus 1.6% among those who received placebo. These data show that lumacaftor in combination with ivacaftor provided a benefit for patients with cystic fibrosis homozygous for the Phe508del CFTR mutation. (Funded by Vertex Pharmaceuticals and others; TRAFFIC and TRANSPORT ClinicalTrials.gov numbers, NCT01807923 and NCT01807949.).

**Title:** Inhaled Aztreonam Lysine versus Inhaled Tobramycin in Cystic Fibrosis. An Economic Evaluation.

**Citation:** Annals of the American Thoracic Society, Jul 2015, vol. 12, no. 7, p. 1030-1038 (July 2015)

**Author(s):** Schechter, Michael S, Trueman, David, Farquharson, Rachel, Higuchi, Keiko, Daines, Cori L

**Abstract:** Pseudomonas aeruginosa infection is a significant cause of morbidity and mortality in patients with cystic fibrosis and is associated with a high economic burden. A recently published comparator trial demonstrated that outcomes in patients with cystic fibrosis with chronic P. aeruginosa infections switched from tobramycin solution for inhalation to aztreonam lysine for inhalation were better than those of patients who continued on tobramycin. To compare overall costs of treatment of chronic inhaled tobramycin and aztreonam lysine in patient with cystic fibrosis who have chronic Pseudomonas infection, taking differences in outcomes into account. A cost-effectiveness analysis with a 3-year time horizon was performed to simulate the economic consequences of either treatment from the perspective of a third party payer in the United States. We extrapolated results from the comparator trial and used data regarding clinical outcomes, quality of life, and costs from published literature and proprietary databases. A Markov structure was used to consider transitions between health states, defined principally by levels of percent predicted of FEV1. Extensive scenario and probabilistic sensitivity analyses were performed. Use of aztreonam lysine for inhalation was associated with an average cost saving of $41,947 per patient over 3 years, as well as greater quality-adjusted life-years and total life-years. Scenario analyses demonstrated that these findings were robust to changes in key assumptions. It appears, with high likelihood, that the use of aztreonam solution for inhalation is associated with cost savings, an increase in quality-
adjusted life-years, and improved clinical outcomes among patients with extensive prior use of tobramycin solution for inhalation who are naive to inhaled aztreonam lysine.

Title: Clinical relevance of *Pseudomonas aeruginosa* hypermutation in cystic fibrosis chronic respiratory infection.

Citation: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, Jul 2015, vol. 14, no. 4, p. e1.

Author(s): Oliver, Antonio

Title: Clinical relevance of *Pseudomonas aeruginosa* hypermutation in cystic fibrosis chronic respiratory infection: Response to Dr. Oliver.

Citation: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, Jul 2015, vol. 14, no. 4, p. e3.

Author(s): Bar-Meir, Maskit

Title: Ivacaftor as salvage therapy in a patient with cystic fibrosis genotype F508del/R117H/IVS8-5T.

Citation: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, Jul 2015, vol. 14, no. 4, p. e4.

Author(s): Carter, S, Kelly, S, Caples, E, Grogan, B, Doyle, J, Gallagher, C G, McKone, E F

Abstract: Ivacaftor is a novel CFTR potentiator that increases CFTR activity and improves clinical outcomes in cystic fibrosis (CF) patients with at least one copy of CFTR-G551D. Clinical trials have shown an improvement in lung function, weight and CF pulmonary exacerbation in adults with CFTR-G551D leading to the approval of ivacaftor as a novel CF therapy [1]. In vitro studies of ivacaftor have also shown significant improvements in CFTR chloride channel opening time in other non-G551D CFTR mutations suggesting that ivacaftor may be of benefit to patients with mutations other than gating mutations [2]. R117H-CFTR is a relatively common CFTR mutation that demonstrates an in-vitro response to ivacaftor [2,3]. A clinical trial has suggested that there may be a role for ivacaftor in older patients with R117H-CFTR although this trial did not include patients with very severe CF lung disease [4]. In 2014, ivacaftor was approved in the United States as a treatment for CF subjects aged greater than 6 years old with a copy of R117H-CFTR. We present a case demonstrating a substantial therapeutic effect of ivacaftor in a CF patient with genotype F508del/R117H and advanced lung disease. Copyright © 2015 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Title: Prevalence and Severity of Dysphonia in Patients with Cystic Fibrosis: A Pilot Study.


Author(s): Willis, John, Michael, Deirdre D, Boyer, Holly, Misono, Stephanie
Abstract: To assess the prevalence and severity of dysphonia in patients with cystic fibrosis sinusitis. We hypothesized that patients with CF sinusitis, compared with 2 control groups, would have higher self-reported prevalence of dysphonia and greater severity of dysphonia, according to patient-reported outcome measures as well as auditory-perceptual evaluation by expert listeners. Cross-sectional comparative pilot study. Academic tertiary care clinic. Analysis included 37 study participants: 17 patients with CF sinusitis, 10 healthy individuals, and 10 patients with non-CF sinusitis. All participants completed the 10-item Voice Handicap Index (VHI-10) questionnaire and provided voice samples. On all samples, 6 blinded speech-language pathologists independently performed auditory-perceptual evaluation, using Consensus Auditory-Perceptual Evaluation of Voice. To assess severity of sinonasal symptoms, we used the 20-item Sinonasal Outcome Test (SNOT-20). Standard parametric and nonparametric statistical analysis was performed. The differences between the 3 groups in prevalence of abnormal VHI-10 scores were not statistically significant. SNOT-20 scores were similar in the 2 sinusitis patient groups. VHI-10 scores were highest in patients with CF sinusitis, intermediate in patients with non-CF sinusitis, and lowest in healthy individuals (P = .005). Auditory-perceptual evaluation demonstrated greater overall severity of dysphonia in patients with CF sinusitis compared with the 2 control groups (P = .0005). Cystic fibrosis sinusitis appeared to be associated with worse vocal function as measured by patient self-report as well as auditory-perceptual evaluation of voice compared with patients with non-CF sinusitis and healthy controls. Further investigation in this area is warranted. © American Academy of Otolaryngology—Head and Neck Surgery Foundation 2015.

Title: Oxygen uptake kinetics and exercise capacity in children with cystic fibrosis.

Citation: Pediatric pulmonology, Jul 2015, vol. 50, no. 7, p. 647-654

Author(s): Fielding, Jeremy, Brantley, Lucy, Seigler, Nichole, McKie, Katie T, Davison, Gareth W, Harris, Ryan A

Abstract: Exercise capacity, an objective measure of exercise intolerance, is known to predict quality of life and mortality in cystic fibrosis (CF). The mechanisms for exercise intolerance in patients with cystic fibrosis (CF), however, have yet to be fully elucidated. Accordingly, this study sought to investigate oxygen uptake kinetics and the impact of fat-free mass (FFM) on exercise capacity in young patients with CF. 16 young patients with CF (age 13 ± 4 years; 10 female) and 15 matched controls (age 14 ± 3 years; nine female) participated. Pulmonary function and a maximal exercise test on a cycle ergometer using the Godfrey protocol were performed. Exercise capacity (VO2 peak), VO2 response time (VO2 RT), and functional VO2 gain (ΔVO2 /ΔWR) were all determined. Lung function was the only demographic parameter significantly lower (P < 0.05) in CF compared to controls. Exercise capacity was lower in CF (P < 0.014) only when VO2 peak was normalized for FFM (43.5 ± 7.7 vs. 50.6 ± 7.4 ml/kg-FFM/min) or expressed as % predicted (70.1 ± 14.3 vs. 85.4 ± 16.0%). The VO2 RT was slower (36.1 ± 15.1 vs. 25.0 ± 12.4 sec; P = 0.03) and the ΔVO2 /ΔWR slope was lower (8.4 ± 3 ml/min/watt vs. 10.1 ± 1.4 ml/min/watt; P = 0.02) in patients compared to controls, respectively. In conclusion, a delayed VO2 response time coupled with the lower functional VO2 gain (ΔVO2 /ΔWR) suggest that young patients with CF have impairment in oxygen transport and oxygen utilization by the muscles. These data in addition to differences in VO2 peak normalized for FFM provide some insight that muscle mass and muscle metabolism contribute to exercise intolerance in CF. Pediatr Pulmonol. 2015; 50:647-654. © 2015 Wiley Periodicals, Inc. © 2015 Wiley Periodicals, Inc.

Title: Five years of experience with biochemical cystic fibrosis newborn screening based on IRT/PAP in Germany.
Evidence from recent studies suggests that IRT/PAP protocols may be successfully used as a purely biochemical newborn screening (NBS) for cystic fibrosis (CF) that does not require genetic screening. However, the experience with the performance of different IRT/PAP protocols remains limited. In this study, we evaluated the performance of IRT/PAP-based CF-NBS used in two German regions between 2008 and 2013 in a large cohort. In both regions slightly different IRT/PAP protocols were used to screen newborns for CF. In contrast to the original IRT/PAP protocol published by Sarles et al., both German protocols contained an IRT-dependent safety net strategy (CF-NBS positive, if IRT ≥ 99.9th percentile). Positive rating of the screening result led to confirmatory diagnostics using sweat chloride testing and clinical assessment. A total of 328,181 newborns were tested with IRT/PAP in Germany within 5 years. 639 of these newborns (0.19%) were tested positive, and 60 infants were diagnosed with CF leading to a sensitivity of 0.968 and a PPV (positive predictive value) of 0.097. Compared to IRT/DNA protocols, the PPV of IRT/PAP is lower, but PAP used as second tier test has the advantage of a lower detection rate of healthy carriers and CF patients with equivocal results. Our results obtained in a large cohort of ~330,000 newborns support the use of a purely biochemical IRT/PAP protocol as an acceptable alternative when genetic CF-NBS has to be avoided. Pediatr Pulmonol. 2015; 50:655-664. © 2015 Wiley Periodicals, Inc. © 2015 Wiley Periodicals, Inc.

Title: Cystic fibrosis, ivacaftor, and the Arg117His-CFTR mutation.

Citation: The Lancet. Respiratory medicine, Jul 2015, vol. 3, no. 7, p. 498-499

Author(s): Accurso, Frank J

Title: Gene therapy in cystic fibrosis: from lab benches to lungs.

Citation: The Lancet. Respiratory medicine, Jul 2015, vol. 3, no. 7, p. 521-522

Author(s): Arthur, Greer

Title: Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial.

Citation: The Lancet. Respiratory medicine, Jul 2015, vol. 3, no. 7, p. 524-533


Abstract: Ivacaftor has been previously assessed in patients with cystic fibrosis with Gly551Asp-CFTR or other gating mutations. We assessed ivacaftor in patients with Arg117His-CFTR, a residual function mutation. We did a 24-week, placebo-controlled, double-blind, randomised clinical trial, which enrolled 69 patients with cystic fibrosis aged 6 years and older with Arg117His-CFTR and percentage of predicted forced expiratory volume in 1 s (% predicted FEV1) of at least 40. We randomly assigned eligible patients (1:1) to receive placebo or ivacaftor 150 mg every 12 h for 24 weeks. Randomisation was stratified by age (6-11, 12-17, and ≥18 years) and % predicted FEV1 (<70, ≥70 to ≤90, and >90). The primary outcome was the absolute change from baseline in % predicted FEV1 through week 24. Secondary outcomes included safety and changes in sweat chloride
concentrations and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain scores. An open-label extension enrolled 65 of the patients after washout; after 12 weeks, we did an interim analysis. After 24 weeks, the treatment difference in mean absolute change in % predicted FEV1 between ivacaftor (n=34) and placebo (n=35) was 2.1 percentage points (95% CI -1.13 to 5.35; p=0.20). Ivacaftor treatment resulted in significant treatment differences in sweat chloride (-24.0 mmol/L, 95% CI -28.01 to -19.93; p=0.0001) and CFQ-R respiratory domain (8.4, 2.17 to 14.61; p=0.009). In prespecified subgroup analyses, % predicted FEV1 significantly improved with ivacaftor in patients aged 18 years or older (treatment difference vs placebo: 5.0 percentage points, 95% CI 1.15 to 8.78; p=0.01), but not in patients aged 6-11 years (-6.3 percentage points, -11.96 to -0.71; p=0.03). In the extension study, both placebo-to-ivacaftor and ivacaftor-to-ivacaftor groups showed % predicted FEV1 improvement (absolute change from post-washout baseline at week 12: placebo-to-ivacaftor, 5.0 percentage points [p=0.0005]; ivacaftor-to-ivacaftor, 6.0 percentage points [p=0.006]). We did not identify any new safety concerns. The studies are registered with ClinicalTrials.gov (the randomised, placebo-controlled study, number NCT01614457; the open-label extension study, number NCT01707290). Although this study did not show a significant improvement in % predicted FEV1, ivacaftor did significantly improve sweat chloride and CFQ-R respiratory domain scores and lung function in adult patients with Arg117His-CFTR, indicating that ivacaftor might benefit patients with Arg117His-CFTR who have established disease. Vertex Pharmaceuticals Incorporated. Copyright © 2015 Elsevier Ltd. All rights reserved.

Title: Treatment of the Adult Patient with Cystic Fibrosis.

Citation: AARC Times, 01 July 2015, vol./is. 39/7(8-10)

Author(s): Weagraff, Chad

Microbiological

Title: Sputum induction improves detection of pathogens in children with cystic fibrosis.

Citation: Pediatric pulmonology, Jul 2015, vol. 50, no. 7, p. 638-646

Author(s): Hoppe, Jordana E, Towler, Elinor, Wagner, Brandie D, Accurso, Frank J, Sagel, Scott D, Zemanick, Edith T

Abstract: Sputum induction is a safe, well tolerated means of obtaining lower airway secretions from children with cystic fibrosis (CF), particularly for assessment of airway inflammation but the clinical value in diagnosing outpatient infections has not been extensively studied. Investigate the success rate and microbiologic yield of induced sputum (IS) compared to oropharyngeal swabs (OP) and expectorated sputum (ES) samples in children with CF, and determine if IS culture results impact treatment. Two cohorts were included in this prospective, longitudinal comparative study. In one cohort, simultaneously collected OP, ES, and IS specimens were obtained from 17 CF children at three visits over 1 year. In the second group, sputum induction was performed in 35 CF subjects at four annual visits, and culture results were compared to their nearest respiratory culture within 4 months. Antimicrobial treatment regimens were captured retrospectively. Sputum induction was successful in 149 of 158 (94%) visit encounters. Polymicrobial infection (combined P = 0.005) and gram negative organisms (combined P = 0.003) were detected more frequently in IS samples compared to OP, as were the individual pathogens Pseudomonas aeruginosa (combined P = 0.04)
and Stenotrophomonas maltophilia (combined P = 0.05). The microbiologic yield of serial IS samples collected over 1 year was stable. IS culture results led to antibiotic changes in 6% of visit encounters. However, based on current practice 13% of visits could have resulted in treatment changes. Sputum induction is feasible in the outpatient setting and appears to improve pathogen detection in children with CF. Pediatr Pulmonol. 2015; 50:638-646. © 2015 Wiley Periodicals, Inc. © 2015 Wiley Periodicals, Inc.

Title: Ion chromatography for the precise analysis of chloride and sodium in sweat for the diagnosis of cystic fibrosis

Citation: Annals of Clinical Biochemistry, July 2015, vol./is. 52/4(421-427)


Abstract: Measurement of chloride in sweat is an essential part of the diagnostic algorithm for cystic fibrosis. The lack in sensitivity and reproducibility of current methods led us to develop an ion chromatography/high-performance liquid chromatography (IC/HPLC) method, suitable for the analysis of both chloride and sodium in small volumes of sweat. Methods Precision, linearity and limit of detection of an in-house developed IC/HPLC method were established. Method comparison between the newly developed IC/HPLC method and the traditional Chlorocounter was performed, and trueness was determined using Passing Bablok method comparison with external quality assurance material (Royal College of Pathologists of Australasia). Results Precision and linearity fulfill criteria as established by UK guidelines are comparable with inductively coupled plasma-mass spectrometry methods. Passing Bablok analysis demonstrated excellent correlation between IC/HPLC measurements and external quality assessment target values, for both chloride and sodium. With a limit of quantitation of 0.95 mmol/L, our method is suitable for the analysis of small amounts of sweat and can thus be used in combination with the Macroduct collection system. Conclusions Although a chromatographic application results in a somewhat more expensive test compared to a Chlorocounter test, more accurate measurements are achieved. In addition, simultaneous measurements of sodium concentrations will result in better detection of false positives, less test repeating and thus faster and more accurate and effective diagnosis. The described IC/HPLC method, therefore, provides a precise, relatively cheap and easy-to-handle application for the analysis of both chloride and sodium in sweat.

Title: Candida albicans chronic colonisation in cystic fibrosis may be associated with inhaled antibiotics

Citation: Mycoses, July 2015, vol./is. 58/7(416-421), 0933-7407:1439-0507

Author(s): Noni M., Katelari A., Kaditis A., Theochari I., Lympari I., Alexandrou-Athanassoulis H.

Abstract: Candida albicans is increasingly recognised as a coloniser of the respiratory tract in cystic fibrosis (CF) patients. Yet, the potential role, if any, of the micro-organism in the progress of the disease remains unclear. In this study, we investigated the association between inhaled antibiotics and C. albicans chronic colonisation in patients with CF. A cohort of 121 CF patients born from 1988 to 1996 was, respectively, studied. The medical records of each patient were reviewed from the first time they attended the CF Centre until the occurrence of C. albicans chronic colonisation or their last visit for the year 2010. Chronic colonisation was defined as the presence of C. albicans in more than 50% of cultures in a given year. A number of possible confounders were included in the multivariate...
logistic regression analysis to identify an independent association between inhaled antibiotics and C. albicans chronic colonisation. Fifty-four (44.6%) of the 121 patients enrolled in the study developed chronic colonisation by the micro-organism. Multivariate logistic regression analysis determined the independent effect of inhaled antibiotic treatment on the odds of chronic colonisation (OR 1.112, 95% CI [1.007-1.229], P = 0.036). Candida albicans chronic colonisation may be associated with the duration of inhaled antibiotic treatment.

Title: Rapid detection of emerging pathogens and loss of microbial diversity associated with severe lung disease in cystic fibrosis

Citation: Journal of Clinical Microbiology, July 2015, vol./is. 53/7(2022-2029)

Author(s): Flight W.G., Smith A., Paisey C., Marchesi J.R., Bull M.J., Norville P.J., Mutton K.J.,

Abstract: Respiratory infection in cystic fibrosis (CF) is polymicrobial, but standard sputum microbiology does not account for the lung microbiome or detect changes in microbial diversity associated with disease. As a clinically applicable CF microbe surveillance scheme, total sputum nucleic acids isolated by a standard high-throughput robotic method for accredited viral diagnosis were profiled for bacterial diversity using ribosomal intergenic spacer analysis (RISA) PCR. Conventional culture and RISA were performed on 200 paired sputum samples from 93 CF adults; pyrosequencing of the 16S rRNA gene was applied to 59 patients to systematically determine bacterial diversity. Compared to the microbiology data, RISA profiles clustered into two groups: the emerging nonfermenting Gram-negative organisms (eNFGN) and Pseudomonas groups. Patients who were culture positive for Burkholderia, Achromobacter, Stenotrophomonas, and Ralstonia clustered within the eNFGN group. Pseudomonas group RISA profiles were associated with Pseudomonas aeruginosa culture-positive patients. Sequence analysis confirmed the abundance of eNFGN genera and Pseudomonas within these respective groups. Low bacterial diversity was associated with severe lung disease (P < 0.001) and the presence of Burkholderia (P < 0.001). An absence of Streptococcus (P < 0.05) occurred in individuals with lung function in the lowest quartile. In summary, nucleic acids isolated from CF sputum can serve as a single template for both molecular virology and bacteriology, with a RISA PCR rapidly detecting the presence of dominant eNFGN pathogens or P. aeruginosa missed by culture (11% of cases). We provide guidance for how this straightforward CF microbiota profiling scheme may be adopted by clinical laboratories.

Title: Molecular epidemiology of Aspergillus collected from cystic fibrosis patients

Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(474-481)

Author(s): Sabino R., Ferreira J.A.G., Moss R.B., Valente J., Verissimo C., Carolino E., Clemons K.V.,

Abstract: Background: Aspergillus respiratory infection is a common complication in cystic fibrosis (CF) and is associated with loss of pulmonary function and allergic disease. Methods: Fifty-three Aspergillus isolates recovered from CF patients were identified to species by Internal Transcribed Spacer Region (ITS), beta-tubulin, and calmodulin sequencing. Results: Three species complexes (Terrei, Nigri, and Fumigati) were found. Identification to species level gave a single Aspergillus terreus sensu stricto, one Aspergillus niger sensu stricto and 51 Aspergillus fumigatus sensu stricto isolates. No cryptic species were found. Conclusions: To our knowledge, this is the first prospective study of Aspergillus species in CF using molecular methods. The paucity of non-A. fumigatus and of cryptic species of A. fumigatus suggests a special association of A. fumigatus sensu stricto with CF airways, indicating it likely displays unique characteristics making it suitable for chronic residence in
that milieu. These findings could refine an epidemiologic and therapeutic approach geared to this pathogen.

**Title:** Trends in bone mineral density in young adults with cystic fibrosis over a 15 year period.

**Citation:** Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, Jul 2015, vol. 14, no. 4, p. 526-532

**Author(s):** Putman, Melissa S, Baker, Joshua F, Uluer, Ahmet, Herlyn, Karen, Lapey, Allen, Sicilian,

**Abstract:** Improvements in clinical care have led to increased life expectancy in patients with cystic fibrosis (CF) over the past several decades. Whether these improvements have had significant effects on bone health in patients with CF is unclear. This is a cross-sectional study comparing clinical characteristics and bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) in adults with CF evaluated in 1995-1999 to age-, race-, and gender-matched patients with CF evaluated in 2011-2013 at the same center on calibrated DXA machines. The cohorts were similar in terms of age, BMI, pancreatic insufficiency, presence of F508del mutation, and reproductive history. In the most recent cohort, pulmonary function was superior, and fewer patients had vitamin D deficiency or secondary hyperparathyroidism. Areal BMD measures of the PA spine, lateral spine, and distal radius were similarly low in the two cohorts. Although pulmonary function and vitamin D status were better in patients in the present-day cohort, areal BMD of the spine was reduced in a significant number of patients and was no different in patients with CF today than in the late 1990s. Further attention to optimizing bone health may be necessary to prevent CF-related bone disease.

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**Title:** Host-pathogen interplay in the respiratory environment of cystic fibrosis

**Citation:** Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(431-439)

**Author(s):** Yonker L.M., Cigana C., Hurley B.P., Bragonzi A.

**Abstract:** Significant advances have been made in the understanding of disease progression in cystic fibrosis (CF), revealing a complex interplay between host and pathogenic organisms. The diverse CF microbiota within the airway activates an aberrant immune response that is ineffective in clearing infection. An appreciation of how the CF host immune system interacts with these organisms is crucial to understanding the pathogenesis of CF pulmonary disease. Here we discuss the microbial complexity present in the lungs of individuals with CF, review emerging concepts of innate and adaptive immune responses to pathogens that chronically inhabit the CF lung, and discuss therapies that target the aberrant inflammatory response that characterizes CF. A greater understanding of the underlying mechanisms will shed light on pathogenesis and guide more targeted therapies in the future that serve to reduce infection, minimize lung pathology, and improve the quality of life for patients with CF.

**Title:** Osteopontin is increased in cystic fibrosis and can skew the functional balance between ELR-positive and ELR-negative CXC-chemokines

**Citation:** Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(453-463)

**Author(s):** Jovic S., Shikhagaie M., Morgelin M., Erjefalt J.S., Kjellstrom S., Egesten A.
**Abstract:** Background: The glycoprotein osteopontin plays important roles in several states of disease associated with inflammation, for example by recruiting neutrophils but its expression and possible roles in cystic fibrosis (CF) have not been investigated. Methods: Immunohistochemistry and ELISA were used to detect osteopontin in clinical samples. In addition, osteopontin-binding and functional interference with antibacterial (ELR-negative) and neutrophil-recruiting (ELR-positive) CXC-chemokines were investigated using in vitro assays. Results: Increased osteopontin-expression was found in the airways of CF patients compared with controls. Interestingly, osteopontin bound to ELR-negative CXC-chemokines, reducing their antibacterial and receptor-activating properties while no binding or interference with the function of ELR-positive chemokines was found. Conclusions: High expression of osteopontin is likely part of the dysregulated inflammation seen in CF, impairing the activities of ELR-negative chemokines that both serve as innate antibiotics and recruit NK and cytotoxic T cells, instead promoting an excessive influx of neutrophils, and may thus contribute to disease progress.

**Title:** Increase of Serum γ-Glutamyltransferase Associated With Development of Cirrhotic Cystic Fibrosis Liver Disease.

**Citation:** Journal of pediatric gastroenterology and nutrition, Jul 2015, vol. 61, no. 1, p. 113-118

**Author(s):** Bodewes, Frank A J A, van der Doef, Hubert P J, Houwen, Roderick H J, Verkade, Henkjan J

**Abstract:** Identification of patients at risk for developing cirrhotic cystic fibrosis liver disease (CCFLD) is essential for targeting potentially preventive treatment. We studied the evolution of serum liver enzymes and thrombocyte counts as predictors of CCFLD development. For this study, we defined the diagnosis of CCFLD as the combination of splenomegaly (on either physical examination or ultrasound scan) and macronodularity of the liver on ultrasound scan. We reviewed the medical records of 277 pediatric patients with CF for the diagnosis of CCFLD. In each patient with CCFLD, we reviewed serum liver enzymes and thrombocyte counts in the 2-year period preceding the diagnosis of CCFLD. We compared these results with a non-CCFLD control group (patients with CF older than 15 years with no reported signs or symptoms of CCFLD). In the 2 years preceding the diagnosis, the γ-glutamyltransferase (GGT) levels of patients with CCFLD were significantly higher compared to non-CCFLD controls (42 ± 5 vs 17 ± 2 U/L, respectively; P < 0.001). Corresponding aspartate aminotransferase and alanine aminotransferase levels did not significantly differ between patients with CCFLD and controls. The thrombocyte counts in patients with CCFLD were significantly lower than those in controls (252 ± 108 vs 320 ± 94 × 10^9 /L, respectively; P < 0.05). The predictive value for CCFLD of a single GGT measurement was low; however, for patients with CF with a mean GGT > 35 U/L, based on repeated measurements, the odds ratio for developing CCFLD was 39 (95% confidence interval 9-175, specificity was 95%, sensitivity was 64%, positive predictive value was 50%). For the thrombocytes, however, no reliable cutoff value could be identified. In pediatric patients with CF, a persistently high-normal GGT is strongly associated with the diagnosis of CCFLD within 2 years. The prognostic value of a single GGT measurement is limited, but repeated GGT measurements may allow the identification of groups of patients at increased risk for CCFLD.

**Title:** Iron-Mediated Control of Pseudomonas aeruginosa-Staphylococcus aureus Interactions in the Cystic Fibrosis Lung.

**Citation:** Journal of bacteriology, Jul 2015, vol. 197, no. 14, p. 2250-2251

**Author(s):** Barnabie, Patricia M, Whiteley, Marvin
Abstract: Communication is an important factor for bacterial survival, growth, and persistence. Much work has examined both inter- and intraspecies interactions and their effects on virulence. Now, researchers have begun to explore the ways in which host-modulated factors can impact bacterial interactions and subsequently affect patient outcomes. In this issue, two papers discuss how the host environment alters interactions between the pathogens Pseudomonas aeruginosa and Staphylococcus aureus, largely in the context of cystic fibrosis. Copyright © 2015, American Society for Microbiology. All Rights Reserved.

Title: Coculture of Staphylococcus aureus with Pseudomonas aeruginosa Drives S. aureus towards Fermentative Metabolism and Reduced Viability in a Cystic Fibrosis Model.

Citation: Journal of bacteriology, Jul 2015, vol. 197, no. 14, p. 2252-2264

Author(s): Filkins, Laura M, Graber, Jyoti A, Olson, Daniel G, Dolben, Emily L, Lynd, Lee R,

Abstract: The airways of patients with cystic fibrosis are colonized with diverse bacterial communities that change dynamically during pediatric years and early adulthood. Staphylococcus aureus is the most prevalent pathogen during early childhood, but during late teens and early adulthood, a shift in microbial composition occurs leading to Pseudomonas aeruginosa community predominance in ~50% of adults. We developed a robust dual-bacterial in vitro coculture system of P. aeruginosa and S. aureus on monolayers of human bronchial epithelial cells homozygous for the ΔF508 cystic fibrosis transmembrane conductance regulator (CFTR) mutation to better model the mechanisms of this interaction. We show that P. aeruginosa drives the S. aureus expression profile from that of aerobic respiration to fermentation. This shift is dependent on the production of both 2-heptyl-4-hydroxyquinoline N-oxide (HQNO) and siderophores by P. aeruginosa. Furthermore, S. aureus-produced lactate is a carbon source that P. aeruginosa preferentially consumes over medium-supplied glucose. We find that initially S. aureus and P. aeruginosa coexist; however, over extended coculture P. aeruginosa reduces S. aureus viability, also in an HQNO- and P. aeruginosa siderophore-dependent manner. Interestingly, S. aureus small-colony-variant (SCV) genetic mutant strains, which have defects in their electron transport chain, experience reduced killing by P. aeruginosa compared to their wild-type parent strains; thus, SCVs may provide a mechanism for persistence of S. aureus in the presence of P. aeruginosa. We propose that the mechanism of P. aeruginosa-mediated killing of S. aureus is multifactorial, requiring HQNO and P. aeruginosa siderophores as well as additional genetic, environmental, and nutritional factors. In individuals with cystic fibrosis, Staphylococcus aureus is the primary respiratory pathogen during childhood. During adulthood, Pseudomonas aeruginosa predominates and correlates with worse patient outcome. The mechanism(s) by which P. aeruginosa outcompetes or kills S. aureus is not well understood. We describe an in vitro dual-bacterial species coculture system on cystic fibrosis-derived airway cells, which models interactions relevant to patients with cystic fibrosis. Further, we show that molecules produced by P. aeruginosa additively induce a transition of S. aureus metabolism from aerobic respiration to fermentation and eventually lead to loss of S. aureus viability. Elucidating the molecular mechanisms of P. aeruginosa community predominance can provide new therapeutic targets and approaches to impede this microbial community transition and subsequent patient worsening. Copyright © 2015, American Society for Microbiology. All Rights Reserved.

Title: Quantitative Proteomics Reveals an Altered Cystic Fibrosis In Vitro Bronchial Epithelial Secretome.

Citation: American journal of respiratory cell and molecular biology, Jul 2015, vol. 53, no. 1, p. 22-32

Author(s): Peters-Hall, Jennifer R, Brown, Kristy J, Pillai, Dinesh K, Tomney, Amarel, Garvin,
Abstract: Alterations in epithelial secretions and mucociliary clearance contribute to chronic bacterial infection in cystic fibrosis (CF) lung disease, but whether CF lungs are unchanged in the absence of infection remains controversial. A proteomic comparison of airway secretions from subjects with CF and control subjects shows alterations in key biological processes, including immune response and proteolytic activity, but it is unclear if these are due to mutant CF transmembrane conductance regulator (CFTR) and/or chronic infection. We hypothesized that the CF lung apical secretome is altered under constitutive conditions in the absence of inflammatory cells and pathogens. To test this, we performed quantitative proteomics of in vitro apical secretions from air-liquid interface cultures of three life-extended CF (ΔF508/ΔF508) and three non-CF human bronchial epithelial cells after labeling of CF cells by stable isotope labeling with amino acids in cell culture. Mass spectrometry analysis identified and quantitated 666 proteins across samples, of which 70 exhibited differential enrichment or depletion in CF secretions (±1.5-fold change; P < 0.05). The key molecular functions were innate immunity (24%), cytoskeleton/extracellular matrix organization (24%), and protease/antiprotease activity (17%). Oxidative proteins and classical complement pathway proteins that are altered in CF secretions in vivo were not altered in vitro. Specific differentially increased proteins—MUC5AC and MUC5B mucins, fibronectin, and matrix metalloproteinase-9—were validated by antibody-based assays. Overall, the in vitro CF secretome data are indicative of a constitutive airway epithelium with altered innate immunity, suggesting that downstream consequences of mutant CFTR set the stage for chronic inflammation and infection in CF airways.

Title: Regulation of β2-adrenergic receptor cell surface expression by interaction with cystic fibrosis transmembrane conductance regulator-associated ligand (CAL).

Citation: Amino acids, Jul 2015, vol. 47, no. 7, p. 1455-1464

Author(s): Yang, Longyan, Zheng, Junfang, Xiong, Ying, Meng, Ran, Ma, Qian, Liu, Hua, Shen,

Abstract: The beta-2 adrenergic receptor (β2AR), a member of GPCR, can activate multiple signaling pathways and is an important treatment target for cardiac failure. However, the molecular mechanism about β2AR signaling regulation is not fully understood. In this study, we found that cystic fibrosis transmembrane conductance regulator-associated ligand (CAL) overexpression reduced β2AR-mediated extracellular signal-regulated kinase-1/2 (ERK1/2) activation. Further study identified CAL as a novel binding partner of β2AR. CAL is associated with β2AR mainly via the third intracellular loop (ICL3) of receptor and the coiled-coil domains of CAL, which is distinct from CAL/β1AR interaction mediated by the carboxyl terminal (CT) of β1AR and PDZ domain of CAL. CAL overexpression retarded β2AR expression in Golgi apparatus and reduced the receptor expression in plasma membrane.

Title: The activin A antagonist follistatin inhibits cystic fibrosis-like lung inflammation and pathology.

Citation: Immunology and cell biology, Jul 2015, vol. 93, no. 6, p. 567-574 (July 2015)

Author(s): Hardy, Charles L, King, Susannah J, Mifsud, Nicole A, Hedger, Mark P, Phillips, David J, Mackay, Fabienne, de Kretser, David M, Wilson, John W, Rolland, Jennifer M, O’Hehir, Robyn E

Abstract: Cystic fibrosis (CF) is the most common life-limiting genetically acquired respiratory disorder. Patients with CF have thick mucus obstructing the airways leading to recurrent infections, bronchiectasis and neutrophilic airway inflammation culminating in deteriorating lung function.
Current management targets airway infection and mucus clearance, but despite recent advances in care, life expectancy is still only 40 years. We investigated whether activin A is elevated in CF lung disease and whether inhibiting activin A with its natural antagonist follistatin retards lung disease progression. We measured serum activin A levels, lung function and nutritional status in CF patients. We studied the effect of activin A on CF lung pathogenesis by treating newborn CF transgenic mice (β-ENaC) intranasally with the natural activin A antagonist follistatin. Activin A levels were elevated in the serum of adult CF patients, and correlated inversely with lung function and body mass index. Follistatin treatment of newborn β-ENaC mice, noted for respiratory pathology mimicking human CF, decreased the airway activin A levels and key features of CF lung disease including mucus hypersecretion, airway neutrophilia and levels of mediators that regulate inflammation and chemotaxis. Follistatin treatment also increased body weight and survival of β-ENaC mice, with no evidence of local or systemic toxicity. Our findings demonstrate that activin A levels are elevated in CF and provide proof-of-concept for the use of the activin A antagonist, follistatin, as a therapeutic in the long-term management of lung disease in CF patients.

Title: Assessing Airway Microbiota in Cystic Fibrosis: What More Should Be Done?

Citation: Journal of clinical microbiology, Jul 2015, vol. 53, no. 7, p. 2006-2007 (July 2015)

Author(s): LiPuma, John J


Title: Harnessing the Early-Life Microbiota to Protect Children with Cystic Fibrosis.

Citation: The Journal of pediatrics, Jul 2015, vol. 167, no. 1, p. 16 (July 2015)

Author(s): Segal, Leopoldo N, Blaser, Martin J

Title: Associations between Gut Microbial Colonization in Early Life and Respiratory Outcomes in Cystic Fibrosis.

Citation: The Journal of pediatrics, Jul 2015, vol. 167, no. 1, p. 138

Author(s): Hoen, Anne G, Li, Jing, Moulton, Lisa A, O’Toole, George A, Housman, Molly L

Abstract: To examine patterns of microbial colonization of the respiratory and intestinal tracts in early life in infants with cystic fibrosis (CF) and their associations with breastfeeding and clinical outcomes. A comprehensive, prospective longitudinal analysis of the upper respiratory and intestinal microbiota in a cohort of infants and young children with CF followed from birth was performed. Genus-level microbial community composition was characterized using 16S-targeted pyrosequencing, and relationships with exposures and outcomes were assessed using linear mixed-
effects models, time-to-event analysis, and principal components analysis. Sequencing of 120 samples from 13 subjects collected from birth to 34 months revealed relationships between breastfeeding, microbial diversity in the respiratory and intestinal tracts, and the timing of onset of respiratory complications, including exacerbations and colonization with Pseudomonas aeruginosa. Fluctuations in the abundance of specific bacterial taxa preceded clinical outcomes, including a significant decrease in bacteria of the genus Parabacteroides within the intestinal tract prior to the onset of chronic P aeruginosa colonization. Specific assemblages of bacteria in intestinal samples, but not respiratory samples, were associated with CF exacerbation in early life, indicating that the intestinal microbiome may play a role in lung health. Our findings relating breastfeeding to respiratory outcomes, gut diversity to prolonged periods of health, and specific bacterial communities in the gut prior to respiratory complications in CF highlight a connection between the intestinal microbiome and health and point to potential opportunities for antibiotic or probiotic interventions. Further studies in larger cohorts validating these findings are needed. Copyright © 2015 Elsevier Inc. All rights reserved.

Title: Increased Prevalence and Resistance of Important Pathogens Recovered from Respiratory Specimens of Cystic Fibrosis Patients During a Decade.

Citation: The Pediatric infectious disease journal, Jul 2015, vol. 34, no. 7, p. 700-705 (July 2015)

Author(s): Raidt, Lena, Idelevich, Evgeny A, Dübbers, Angelika, Küster, Peter, Drevinek, Pavel, Peters, Georg, Kahl, Barbara C

Abstract: The study objective was to identify changes of prevalence and resistance of important pathogens in specimens of cystic fibrosis (CF) patients within a decade. Samples of 94 patients, who attended 2 CF centers from 2001 to 2011 were retrospectively analyzed. Staphylococcus aureus was the most prevalent organism (74.5% in 2011) with an increase of methicillin-resistant S. aureus in patients (0% vs. 9.6%, n = 9). Resistance of S. aureus to gentamicin decreased (41.8% vs. 21%; P < 0.001), whereas resistance to rifampicin and trimethoprim/sulfamethoxazole (P < 0.05) increased significantly with a trend to increased resistance to clindamycin and erythromycin (P = 0.063). Methicillin-resistant S. aureus isolates belonged to 6 spa types (t003, t008, t011, t034, t045, t548). There was a significant increase of Pseudomonas aeruginosa prevalence (63.8% in 2011 vs. 46.8% in 2001, P = 0.019). Resistance of P. aeruginosa increased significantly to imipenem, gentamicin, amikacin, tobramycin, ciprofloxacin and fosfomycin, whereas resistance to piperacillin-tazobactam, meropenem and aztreonam decreased. Significantly fewer Stenotrophomonas maltophilia isolates were susceptible to all the analyzed antibiotics (trimethoprim/sulfamethoxazole, ciprofloxacin and colistin) in 2011 compared with 2001 (13.5% vs. 42.1%; P = 0.023), whereas the resistance to colistin increased significantly (11.1% vs. 62.2%; P < 0.001). Burkholderia cepacia complex and nontuberculous mycobacteria were not detected in 2001 but in 2011 in 7.4% (n = 9) and 7.4% (n = 9) of patients, respectively. B. cepacia complex isolates belonged to 8 multilocus sequence types. Our retrospective analysis revealed an increase of important CF-related pathogens, the emergence of new pathogens and a substantial increase of multidrug-resistant CF-specific isolates. Our findings are of importance to clinicians for the alertness of local epidemiology, which may be useful for prevention and treatment strategies.

Title: Bacteriophage-based therapy in cystic fibrosis-associated Pseudomonas aeruginosa infections: Rationale and current status

Citation: Drug Design, Development and Therapy, July 2015, vol./is. 9/(3653-3663)

Author(s): Hraiech S., Bregeon F., Rolain J.-M.
Abstract: Pulmonary infections involving Pseudomonas aeruginosa are among the leading causes of the deterioration of the respiratory status of cystic fibrosis (CF) patients. The emergence of multidrug-resistant strains in such populations, favored by iterative antibiotic cures, has led to the urgent need for new therapies. Among them, bacteriophage-based therapies deserve a focus. One century of empiric use in the ex-USSR countries suggests that bacteriophages may have beneficial effects against a large range of bacterial infections. Interest in bacteriophages has recently renewed in Western countries, and the in vitro data available suggest that bacteriophage-based therapy may be of significant interest for the treatment of pulmonary infections in CF patients. Although the clinical data concerning this specific population are relatively scarce, the beginning of the first large randomized study evaluating bacteriophage-based therapy in burn infections suggests that the time has come to assess the effectiveness of this new therapy in CF P. aeruginosa pneumonia. Consequently, the aim of this review is, after a brief history, to summarize the evidence concerning bacteriophage efficacy against P. aeruginosa and, more specifically, the in vitro studies, animal models, and clinical trials targeting CF.

Psychological

Title: Breaking bad news, the diagnosis of cystic fibrosis in childhood
Citation: Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(540-546),
Author(s): Havermans T., Tack J., Vertommen A., Proesmans M., de Boeck K.

Abstract: Background: The day parents are told their child has cystic fibrosis (CF) is imprinted in their memory. Parents often show strong emotions (e.g. shock, anxiety); they need to cope with bad news and restructure their lives taking into account CF. Aims: The aims of this study are (1) to explore how parents recall circumstances of the CF diagnosis and the information they received and (2) to investigate their current coping styles. Methods: Parents (n = 38) of 20 children (diagnosed during the past 5 years) were interviewed using a semi-structured interview. Coping was assessed using the Utrecht Coping List. The association between coping and time since diagnosis/severity of illness was investigated. Results: Fifteen parents first heard the term 'CF' from their local pediatrician or GP. All were informed in detail by the CF specialist. All parents recalled specifics about the information, the attitude of the doctor, their thoughts and emotions. Most parents were satisfied with the content and manner in which they had received information. Nineteen appreciated the doctor showing some emotions during the talks. One couple criticized the doctor for not showing emotions. Parents reported higher use (than normative scores) of the active coping style ‘social support seeking’ and the accommodative coping styles ‘palliative reaction pattern’ and ‘comforting cognitions’. Perception of severity of illness was associated with higher scores on palliative coping. Conclusions: This study shows the importance of physicians and CF teams to tailor the way of providing bad news to parents’ needs and preferences. It is important to help and encourage parents to use active or accommodative coping strategies. The diagnosis is the starting point of a long-term relationship. ‘Doing things well from the start’ helps families to learn to live with CF and treatment.

Title: Protocol for a study of the psychosocial determinants of health in early childhood among children with cystic fibrosis.

Citation: Journal of advanced nursing, Jul 2015, vol. 71, no. 7, p. 1704-1716
Author(s): Douglas, Tonia, Jordan, Brigid, Priddis, Lynn, Anderson, Vicki, Sheehan, Jane, Kane,

Abstract: To investigate the causal associations between family relationships, family functioning, social circumstances and health outcomes in young children with cystic fibrosis. The anticipated health gains for patients with cystic fibrosis, promised by early diagnosis through newborn screening, have yet to be fully realized, despite advances in cystic fibrosis health care with aggressive management in multidisciplinary clinics and the development of specific medications. Adverse psychosocial functioning may underpin the current lack of progress as it is well recognized that compromised early parent-child attachment relationship experiences and adverse social circumstances have negative impacts on lifelong health status and health resource use, even in healthy children. A cross-sectional (initial) and longitudinal (progressive), multicentre study of children aged 3 months-6 years with cystic fibrosis, who have been diagnosed by newborn screening. Questionnaire and observational measures of parent psychosocial functioning, parenting and parent-child attachment and social markers; and including clinical outcomes of regular health surveillance with clinical, lung imaging (computerized tomography) and bronchoalveolar lavage for airway microbiology and inflammation. This will be the first study to investigate the causal effect of psychosocial functioning, parenting and attachment on physical health outcome measures in children with cystic fibrosis. © 2015 John Wiley & Sons Ltd.

Title: Cystic Fibrosis Foundation and European Cystic Fibrosis Society Survey of cystic fibrosis mental health care delivery.

Citation: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, Jul 2015, vol. 14, no. 4, p. 533-539 (July 2015)

Author(s): Abbott, J, Elborn, J S, Georgiopoulos, A M, Goldbeck, L, Marshall, B C, Sabadosa,

Abstract: Psychological morbidity in individuals with cystic fibrosis (CF) and their caregivers is common. The Cystic Fibrosis Foundation (CFF) and European Cystic Fibrosis Society (ECFS) Guidelines Committee on Mental Health sought the views of CF health care professionals concerning mental health care delivery. An online survey which focused on the current provision and barriers to mental health care was distributed to CF health care professionals. Of the 1454 respondents, many did not have a colleague trained in mental health issues and 20% had no one on their team whose primary role was focused on assessing or treating these issues. Insufficient resources and a lack of competency were reported in relation to mental health referrals. Seventy-three percent of respondents had no experience with mental health screening. Of those who did, they utilized 48 different, validated scales. These data have informed the decision-making, dissemination and implementation strategies of the Mental Health Guidelines Committee sponsored by the CFF and ECFS. Copyright © 2014 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Title: Prevalence of Symptoms of Depression and Anxiety in Adults With Cystic Fibrosis Based on the PHQ-9 and GAD-7 Screening Questionnaires.

Citation: Psychosomatics, Jul 2015, vol. 56, no. 4, p. 345-353

Author(s): Quon, Bradley S, Bentham, Wayne D, Unutzer, Jurgen, Chan, Ya-Fen, Goss, Christopher H, Aitken, Moira L

Abstract: To examine the prevalence of symptoms of depression and anxiety among patients with cystic fibrosis (CF) who were followed up at the University of Washington Adult CF clinic and to
identify sociodemographic and clinical factors associated with symptoms. A total of 178 adults with CF were asked to complete the Patient Health Questionnaire-9 for depression and General Anxiety Disorder-7 for anxiety when clinically stable. Clinically significant symptoms of depression and anxiety were defined in the following 2 ways: (1) symptom definition—presence of moderate-to-severe symptoms based on the questionnaires and (2) composite definition—symptom definition or the use of psychiatric medications to manage symptoms. Associations between Patient Health Questionnaire-9 and General Anxiety Disorder-7 scores with sociodemographic (gender, age, age of CF diagnosis, vocation, and spousal status) and clinical factors (forced expiratory volume in 1 second, body mass index, and CF-related diabetes on insulin) were examined. Of 178 patients, 153 (85%) completed the screening questionnaires. Based on the symptom definition, 7% of patients had symptoms of depression and 5% had symptoms of anxiety. Using the composite definition, 22% of patients had symptoms of depression and 10% had symptoms of anxiety. Based on the Patient Health Questionnaire-9, 5% of patients reported suicidal thoughts. In multiple linear regression analysis, only forced expiratory volume in 1 second % predicted was independently associated with Patient Health Questionnaire-9 depression scores, and no sociodemographic or clinical factors were associated with General Anxiety Disorder-7 anxiety scores. We conclude that all adults with CF should be screened for symptoms of depression and anxiety given the difficulty in identifying strong clinical risk factors and the unexpected high rates of suicidal ideation. Copyright © 2015 The Academy of Psychosomatic Medicine. Published by Elsevier Inc. All rights reserved.

**Nutrition**

**Title:** Supplementation with Red Palm Oil Increases Beta-Carotene and Vitamin A Blood Levels in Patients with Cystic Fibrosis

**Citation:** Mediators of Inflammation, 2015, vol./is. 2015/, 0962-9351;1466-1861 (2015)

**Author(s):** Sommerburg O., De Spirt S., Mattern A., Joachim C., Langhans C.-D., Nesaretnam K.

**Abstract:** Patients with cystic fibrosis (CF) show decreased plasma concentrations of antioxidants due to malabsorption of lipid soluble vitamins and consumption by chronic pulmonary inflammation. Beta-Carotene is a major source of retinol and therefore is of particular significance in CF. The aim of this study was to investigate the effect of daily intake of red palm oil (RPO) containing high amounts of beta-carotene on the antioxidant levels in CF patients. Sixteen subjects were recruited and instructed to enrich their food with 2 to 3 tablespoons of RPO (~1.5 mg of beta-carotene) daily over 8 weeks. Carotenoids, retinol, and alpha-tocopherol were measured in plasma at baseline and after intervention. In addition beta-carotene, lycopene, alpha-tocopherol, and vitamin C were measured in buccal mucosa cells (BMC) to determine the influence of RPO on antioxidant tissue levels. Eleven subjects completed the study properly. Plasma beta-carotene, retinol, and alpha-carotene of these patients increased, but plasma concentrations of other carotenoids and alpha-tocopherol as well as concentrations of beta-carotene, lycopene, alpha-tocopherol, and vitamin C in BMC remained unchanged. Since RPO on a daily basis did not show negative side effects the data suggest that RPO may be used to elevate plasma beta-carotene in CF.

**Title:** Vitamin D deficiency is associated with pulmonary dysfunction in cystic fibrosis
**Citation:** Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(497-506)

**Author(s):** Sexauer W.P., Hadeh A., Ohman-Strickland P.A., Zanni R.L., Varlotta L., Holsclaw D.

**Abstract:** Background: Vitamin D deficiency is common in CF. Whether vitamin D affects pulmonary function in CF is unknown. Methods: Data were abstracted from clinically stable CF patients who had pulmonary function studies and serum 25-hydroxyvitamin D [25(OH)D, ng/ml] levels drawn within 2 months of each other. Findings were adjusted for multiple variables known to affect pulmonary function in CF. Results: Enrollees totaled 597. Overall mean 25(OH)D level was 29.6+/−12.8ng/ml (SD). Serum 25(OH)D levels showed a significant correlation with forced expiratory volume in 1s (FEV<inf>1</inf>) % predicted (r=0.20, p<0.0001) and forced vital capacity % predicted (r=0.13, p=0.0019). Multivariate analysis revealed that serum 25(OH)D remained an independent predictor of FEV<inf>1</inf> % predicted even after controlling for multiple other factors known to affect CF lung function. Conclusions: Serum 25(OH)D levels are significantly associated with pulmonary function in CF. Further study is required to determine whether this association is causa

**Title:** Differences in Immunoreactive Trypsin Values Between Type of Feeding and Ethnicity in Neonatal Cystic Fibrosis Screening: A Cross-Sectional Study.

**Citation:** Neonatal Intensive Care, 01 July 2015, vol./is. 28/3(46-50)

**Author(s):** Cortés, Ernesto, Roldán, Ana María, Palazón-Bru, Antonio, Rizo-Baeza, Maria Mercedes, Manero, Herminia, Gil-Guillén, Vicente Francisco

**Other**

**Title:** Experience of care from the perspective of individuals with cystic fibrosis and families: Results from 70 CF Foundation accredited programs in the USA

**Citation:** Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(515-522)

**Author(s):** Homa K., Sabadosa K.A., Marrow L.C., Marshall B.C.

**Title:** Year in review 2014: Interstitial lung disease, physiology, sleep and ventilation, acute respiratory distress syndrome, cystic fibrosis, bronchiectasis and rare lung disease

**Citation:** Respirology, July 2015, vol./is. 20/5(834-845)

**Author(s):** Maher T.M., Piper A., Song Y., Restrepo M.I., Eves N.D.

**Title:** An unusual cause of growth failure in cystic fibrosis: A salutary reminder of the interaction between glucocorticoids and cytochrome P450 inhibiting medication

**Citation:** Journal of Cystic Fibrosis, July 2015, vol./is. 14/4(e9-e11)
Author(s): Albert B.B., Jaksic M., Ramirez J., Bors J., Carter P., Cutfield W.S., Hofman P.L.

Title: Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis, Cytisine versus Nicotine for Smoking Cessation, and FACED Score for Non-Cystic Fibrosis Bronchiectasis.

Citation: American journal of respiratory and critical care medicine, Jul 2015, vol. 192, no. 2, p. 249-251
Author(s): Mulhall, Aaron, Cole, Adam, Patel, Sanjeevkumar

Title: Cystic fibrosis in Europe: patients live longer but are we ready?

Citation: The European respiratory journal, Jul 2015, vol. 46, no. 1, p. 11-12 (July 2015)
Author(s): Schwarz, Carsten, Hartl, Dominik

Title: A new chapter in therapy for cystic fibrosis.

Author(s): Bilton, Diana

Title: Another Beginning for Cystic Fibrosis Therapy.

Citation: The New England journal of medicine, Jul 2015, vol. 373, no. 3, p. 274-276 (July 16, 2015)
Author(s): Davis, Pamela B

Title: TOBI Podhaler for cystic fibrosis patients with Pseudomonas aeruginosa.

Citation: The Nurse practitioner, Jul 2015, vol. 40, no. 7, p. 16-17 (July 15, 2015)
Author(s): Farinde, Abimbola

Title: Pulmonary function, functional capacity and quality of life in adults with cystic fibrosis.

Citation: Revista portuguesa de pneumologia, Jul 2015, vol. 21, no. 4, p. 198-202 (2015 Jul-Aug)
Author(s): Ribeiro Moço, V J, Lopes, A J, Dos Santos Vigário, P, de Almeida, V P, de Menezes, S L S

Title: Future trends in cystic fibrosis demography in 34 European countries.

Citation: The European respiratory journal, Jul 2015, vol. 46, no. 1, p. 133-141 (July 2015)
Author(s): Burgel, Pierre-Régis, Bellis, Gil, Olesen, Hanne V, Viviani, Laura, Zolin, Anna

Title: Global Lung Function Initiative equations improve interpretation of FEV1 decline among patients with cystic fibrosis.

Citation: The European respiratory journal, Jul 2015, vol. 46, no. 1, p. 262-264
Author(s): Stanojevic, Sanja, Bilton, Diana, McDonald, Alexandra, Stocks, Janet, Aurora, Paul,

Title: Public awareness on cystic fibrosis: results from a national pragmatic survey.

Citation: The European respiratory journal, Jul 2015, vol. 46, no. 1, p. 264-267

Author(s): Braido, Fulvio, Baiardini, Ilaria, Sumberesi, Massimo, Canonica, Giorgio Walter,
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Journal of Cystic Fibrosis
Vol. 14, iss. 4, July 2015

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