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New from the Cochrane Library Systematic Reviews on Cystic Fibrosis

Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease
Norita Hussein, Stephen F Weng, Joe Kai, Jos Kleijnen, Nadeem Qureshi
Published Online: 12 AUG 2015;
Assessed as up-to-date: 25 JUN 2015
Background: Globally, about five per cent of children are born with congenital or genetic disorders. The most common autosomal recessive conditions are thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease, with higher carrier rates in specific patient populations. Identifying and counselling couples at genetic risk of the conditions before pregnancy enables them to make fully informed reproductive decisions, with some of these choices not being available if genetic counselling is only offered in an antenatal setting.

Vaccines for preventing infection with Pseudomonas aeruginosa in cystic fibrosis
Helle Krogh Johansen, Peter C Gøtzsche
Published Online: 23 AUG 2015;
Assessed as up-to-date: 17 AUG 2015
Background: Chronic pulmonary infection in cystic fibrosis results in progressive lung damage. Once colonisation of the lungs with Pseudomonas aeruginosa occurs, it is almost impossible to eradicate. Vaccines, aimed at reducing infection with Pseudomonas aeruginosa, have been developed. This is an update of a previously published review.

Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults
Khin Hnin, Chau Nguyen, Kristin V Carson, David J Evans, Michael Greenstone, Brian J Smith
Published Online: 13 AUG 2015;
Assessed as up-to-date: 21 FEB 2014
Background: The vicious cycle hypothesis for bronchiectasis predicts that bacterial colonisation of the respiratory tract perpetuates inflammatory change. This damages the mucociliary escalator, preventing bacterial clearance and allowing persistence of pro-inflammatory mediators. Conventional treatment with physiotherapy and intermittent antibiotics is believed to improve the condition of people with bronchiectasis, although no conclusive data show that these interventions influence the natural history of the condition. Various strategies have been tried to interrupt this cycle of infection and inflammation, including prolonging antibiotic treatment with the goal of allowing the airway mucosa to heal.
## New from NICE

**Block scoping reports**

<table>
<thead>
<tr>
<th>Provisional Title</th>
<th>Colistimethate sodium powder for inhaler device for the treatment of pseudomonas aeruginosa lung infection in cystic fibrosis.</th>
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### Draft remit

To appraise the clinical and cost effectiveness of colistimethate sodium powder for inhaler device within its licensed indication for the treatment of pseudomonas aeruginosa lung infection in cystic fibrosis.

### Main points from consultation

Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of colistimethate sodium powder for inhalation for the treatment of pseudomonas aeruginosa lung infection in cystic fibrosis is appropriate. The Institute recommends that tobramycin powder for inhalation is appraised alongside colistimethate sodium powder for inhalation.

During the consultation exercise and the scoping workshop, consultees highlighted that other pseudomonal antibiotics are in development for use in cystic fibrosis. Consultees considered that the MTA process would be more appropriate if the timings of the marketing authorisations for dry powder tobramycin and colistimethate sodium allowed.
To appraise the clinical and cost effectiveness of colistimethate sodium powder and tobramycin powder for inhalation within their licensed indications for the treatment of pseudomonas lung infection in cystic fibrosis.

The original cost estimate was uncertain due to the price of the drug being unknown, but estimated to be in the region of £7 million. The addition of a second therapy may not affect costs if it is for use in the same patient population and at a similar cost. However, the cost of both products are still unknown.

As this has been requested to be an MTA, producing timely guidance will not be possible.
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- Geriatrics
- Haematology
- Hospital Medicine
- Infectious diseases
- Nephrology and hypertension
- Neurology
- Obstetrics and gynaecology
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- Paediatrics
- Primary care internal medicine
- Psychiatry
- Pulmonary, critical care and sleep medicine
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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
- 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: Age- and Sex-Dependent Distribution of OGTT-Related Variables in a Population of Cystic Fibrosis Patients.

Citation: The Journal of clinical endocrinology and metabolism, Aug 2015, vol. 100, no. 8, p. 2963-2971 (August 2015)

Author(s): Battezzati, Alberto, Bedogni, Giorgio, Zazzeron, Laura, Mari, Andrea, Battezzati, Pier Maria, Alicandro, Gianfranco, Bertoli, Simona, Colombo, Carla

Abstract: Cystic fibrosis (CF) causes an exceptionally high prevalence of diabetes that increases with age, especially in females. The glucose tolerance defect is progressive, but a cystic fibrosis transmembrane conductance regulator-dependent insulin secretory defect cannot be excluded. The age and sex dependence of the secretory defect is unclear. The objective of the study was to analyze the age and sex dependency of insulin secretory and sensitivity parameters in CF. This was a cross-sectional analysis in an observational ongoing cohort (mean follow-up duration 7.5 y). The study was conducted at the CF Center of Milan. The study included 187 patients aged 8-30 years. Interventions included 3-hour oral glucose tolerance tests (n = 478) with 30-minute insulin and c-peptide sampling. Model-derived insulin secretory and sensitivity parameters were measured. Age was associated with a progressive decrement in insulinemia (at 30 min) and a subsequent increment in glycemia (at 60-90 min), returning at or below baseline (at 180 min). These changes are explained by a progressive reduction in β-cell sensitivity to glucose and a progressive increment in insulin clearance. Fasting and postprandial insulin sensitivity do not seem to be involved. Compared with males, females display higher glucose, insulin, and c-peptide responses with greater insulin secretion, β-cell sensitivity to glucose, insulin clearance, and equal insulin sensitivity. A defect in β-cell sensitivity to glucose progressively develops with age, but it is not sex specific and does not explain the worse glucose tolerance reported in females. In contrast, insulin clearance increases with age, especially in females, contributing to the deterioration in glucose tolerance. The effects of age and sex should be considered when evaluating oral glucose tolerance test results in CF patients.
**Title:** Utility of a very high IRT/No mutation referral category in cystic fibrosis newborn screening.

**Citation:** Pediatric pulmonology, Aug 2015, vol. 50, no. 8, p. 771-780 (August 2015)

**Author(s):** Kay, Denise M, Langfelder-Schwind, Elinor, DeCelie-Germana, Joan, Sharp, Jack K, Maloney, Breanne, Tavakoli, Norma P, Saavedra-Matiz, Carlos A, Krein, Lea M, Caggana, Michele, Kier, Catherine, New York State Cystic Fibrosis Newborn Screening Consortium

**Abstract:** Newborn screening for Cystic Fibrosis (CF) began in New York in October, 2002 using immunoreactive trypsinogen (IRT)/DNA methodology. Infants with at least one CFTR mutation or very high IRT and no mutations (VHIRT) are referred for sweat testing. In a preliminary analysis, we noted a very low positive predictive value (PPV) and preponderance of Hispanic infants in the group of infants with CF referred for VHIRT, which led to a decision to revise, but not eliminate, the VHIRT category. Automatic referral for specimens with VHIRT collected on the day of birth was eliminated, and the VHIRT threshold was raised from 0.2% to 0.1%. In this report, we describe outcomes from VHIRT referrals among 2.4 million infants screened between March 2003 and February 2013. Following the algorithm change, referrals decreased by 37.8% overall (annual mean 1,485 vs. 923), and the VHIRT PPV improved (0.6-1.0%). The number of infants diagnosed has remained consistent at 1 in 4,400 births. The proportion of Black/Hispanic/Asian/Other infants with confirmed CF, CFTR-related metabolic syndrome (CRMS), or possible CF/CRMS was 21.3% in infants with 1-2 mutations, but 75.8% in the VHIRT group. In conclusion, although the PPV among VHIRT referrals remains low, had this category never been implemented, 24 infants with confirmed CF, and 9 infants with CRMS or possible CF/CRMS, most of whom were Hispanic, would have been missed over the 10 years. Information from this study may be helpful in assessing the need for the VHIRT category and algorithm changes in other screening programs. Pediatr Pulmonol. 2015; 50:771-780. © 2015 Wiley Periodicals, Inc. © 2015 Wiley Periodicals, Inc.

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**Title:** Advances in the detection and management of cystic fibrosis related diabetes.

**Citation:** Current opinion in pediatrics, Aug 2015, vol. 26, no. 4, p. 525-533 (August 2015)

**Author(s):** Hameed, Shihab, Jaffé, Adam, Verge, Charles F

**Abstract:** This review will outline the screening, diagnosis and management of cystic fibrosis related diabetes (CFRD). It will also discuss advances in the detection of early glucose abnormalities, their clinical significance and the emerging role for early insulin therapy. Before the onset of diabetes (as currently defined), patients with cystic fibrosis (CF) display glucose abnormalities, detectable either by 30-minutely sampled oral glucose tolerance testing (OGTT), or by continuous ambulatory interstitial glucose monitoring (CGM). These early glucose abnormalities are associated with the presence of glucose in airway fluid, potentially promoting the growth of airway pathogens and contributing to the progression of respiratory disease. Progressive insulin deficiency underlies these glucose abnormalities, and insulin deficiency also causes catabolism. Pilot studies of once-daily insulin therapy in the early stages of insulin deficiency show improved lung function and weight gain (important predictors of survival in CF). Early stages of insulin deficiency may be contributing to catabolism and deteriorating lung function in CF. It is plausible that early insulin therapy may prevent this deterioration, a view supported by pilot studies.
Randomized controlled trials of early insulin therapy will now determine whether insulin therapy should be commenced earlier than current practice in CF.

**Title:** Early Childhood Risk Factors for Decreased FEV1 at Age Six to Seven Years in Young Children with Cystic Fibrosis.

**Citation:** Annals of the American Thoracic Society, Aug 2015, vol. 12, no. 8, p. 1170-1176

**Author(s):** Sanders, Don B, Emerson, Julia, Ren, Clement L, Schechter, Michael S, Gibson, Ronald L, Morgan, Wayne, Rosenfeld, Margaret, EPIC Study Group

**Abstract:** There are limited objective measures of the severity of lung disease before children are able to routinely perform spirometry, generally at age 6 years. Identifying risk factors for reduced lung function at age 6 provides opportunities to intervene and slow the progression of cystic fibrosis (CF) lung disease. To evaluate early childhood predictors of lung function at age 6-7 in a large U.S. CF cohort in the current era of widespread early eradication therapy for Pseudomonas aeruginosa (P. aeruginosa). Participants were children with CF enrolled before age 4 in the Early Pseudomonas Infection Control (EPIC) Observational Study, a multicenter, longitudinal study that enrolled P. aeruginosa-negative children not exceeding 12 years of age. Linear regression was used to estimate the association between potential early childhood risk factors and the best FEV1% predicted at age 6-7 years. Four hundred and eighty-four children (of 1,797 enrolled in the EPIC Observational Study) met the eligibility criteria for this analysis. Mean (SD) age at enrollment was 2.0 (1.3) years. In a multivariable model adjusted for age at enrollment, the following risk factors were significantly associated with lower mean (95% confidence interval) FEV1% predicted at age 6-7: weight percentile less than 10% during the year of enrollment (-5.3 [-9.1, -1.5]), P. aeruginosa positive during the year of enrollment (-2.8 [-5.7, 0.0]), crackles or wheeze during the year of enrollment (-5.7 [-9.4, -1.9]), mother’s education of high school or less (-4.2 [-7.3, -1.2]), and mother smoked during pregnancy (-4.4 [-8.8, 0.1]). In this large U.S. cohort, we identified several early childhood risk factors for lower FEV1 at age 6-7 years, most of which are modifiable. Clinical trial registered with www.clinicaltrials.gov (NCT00097773).

**Title:** Rate of Uptake of Ivacaftor Use after U.S. Food and Drug Administration Approval among Patients Enrolled in the U.S. Cystic Fibrosis Foundation Patient Registry.

**Citation:** Annals of the American Thoracic Society, Aug 2015, vol. 12, no. 8, p. 1146-1152

**Author(s):** Sawicki, Gregory S, Dasenbrook, Elliott, Fink, Aliza K, Schechter, Michael S

**Abstract:** Chronic cystic fibrosis (CF) therapies have variable rates of prescribed use, and therapies are rarely prescribed to more than 80% of eligible patients. Ivacaftor was approved in the United States in January 2012 for patients ages 6 years and older with a G551D mutation in their CF gene. To examine the rate of uptake and patterns of documented ivacaftor use among U.S. patients with CF during the first year after approval, to compare eligible patients with and without reported use, and to describe characteristics of early adopters of ivacaftor use. A cross-sectional study of patients in the U.S. Cystic Fibrosis Foundation Patient Registry in 2012 with at least one encounter in which ivacaftor use was documented. Ivacaftor-eligible patients were defined as any individual 6 years of age or older with a G551D mutation. We performed bivariate and multivariate regression
analyses, stratified by age group, to compare clinical and demographic characteristics of (1) eligible patients with and without documented ivacaftor use in 2012 and (2) early (February-June) versus late (July-December) adopters in 2012. A total of 1,087 patients with CF with G551D mutations were in the U.S. Cystic Fibrosis Foundation Patient Registry in 2012. By June 2012, 64% of eligible patients had documented ivacaftor use, which increased to 81% by the end of 2012. Among eligible patients younger than 18 years of age, 85% were prescribed ivacaftor, with significantly lower odds among those with higher BMI percentile, fewer clinical encounters in 2011, and later age at diagnosis. Among eligible patients age 18 years or older, 79% were prescribed ivacaftor, with significantly lower odds in nonwhite patients and those with later age at diagnosis. Documented prescriptions of ivacaftor also varied by state of residence, with a range of 42-100% of eligible patients across states. The only association with early adoption of ivacaftor in 2012 was a decreased likelihood in adults with fewer than four encounters in 2011. Uptake of ivacaftor use among eligible patients in the United States was rapid, with the majority of use initiated within 4 months of regulatory approval. Differences in ivacaftor prescriptions appear to be related to patient age, older age at diagnosis, and less frequent clinical encounters. Nutritional status also appears to play a role in children, and race seems to have an association in adults.

Title: Screening of glucose metabolism derangements in pediatric cystic fibrosis patients: how, when, why.
Citation: Acta diabetologica, Aug 2015, vol. 52, no. 4, p. 633-638 (August 2015)
Author(s): Franzese, Adriana, Mozzillo, E, Fattorusso, V, Raia, V, Valerio, G
Abstract: Diabetes mellitus is the most common comorbidity in cystic fibrosis (CF), occurring in a variable number of children and adolescents. Glucose metabolism derangements (GMDs) are responsible for a negative impact on the general health status of CF patients. Screening of GMDs is important since the youngest age and should be performed by means of OGTT, including its intermediate times, that could detect other non-traditional GMDs. Insulin treatment, administered before overt diabetes, could be beneficial in reducing the number of pulmonary infections, in improving both pulmonary function and nutritional status. Early screening of GMDs in pediatric age can exert an important preventing role regarding all aspects of health status of patients with CF.

Title: Takayasu's arteritis as the aetiology of unresolved fever in an adult patient with cystic fibrosis.
Citation: Acta clinica Belgica, Aug 2015, vol. 70, no. 4, p. 295-298, 1784-3286 (August 2015)
Author(s): Er, B, Koksal, D, Kalyoncu, U, Ozmen, O, Emiralioglu, N, Yalcin, E Gunes, Ergun, E, Emri, S
Abstract: Vasculitis is an unusual complication of cystic fibrosis (CF), normally affecting patients with more severe lung disease. Typical presentation is with skin disease but other organ involvement has been reported. Systemic response to bacterial colonisation and immune complex deposition secondary to chronic airway inflammation is thought to be underlying mechanism of the disease. The authors describe a 28-year-old female Turkish patient with CF presented with fever and artralgias. The patient was known to have chronic
Pseudomonas infection; therefore, a respiratory tract infection was assumed and the patient was treated with imipenem and amikacin for 14 days. Following through investigations of fever of unknown origin, Takayasu's arteritis was identified and the patient responded well to immunosuppression with corticosteroid.

Title: Physical Characterization of Tobramycin Inhalation Powder: I. Rational Design of a Stable Engineered-Particle Formulation for Delivery to the Lungs.

Citation: Molecular pharmaceutics, Aug 2015, vol. 12, no. 8, p. 2582-2593 (August 3, 2015)

Author(s): Miller, Danforth P, Tan, Trixie, Tarara, Thomas E, Nakamura, John, Malcolmson, Richard J, Weers, Jeffry G

Abstract: A spray-dried engineered particle formulation, Tobramycin Inhalation Powder (TIP), was designed through rational selection of formulation composition and process parameters. This PulmoSphere powder comprises small, porous particles with a high drug load. As a drug/device combination, TOBI Podhaler enables delivery of high doses of drug per inhalation, a feature critical for dry powder delivery of anti-infectives for treatment of cystic fibrosis. The objective of this work was to characterize TIP on both the particle and molecular levels using multiple orthogonal physical characterization techniques. Differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), electron spectroscopy for chemical analysis (ESCA), and Raman measurements show that a TIP particle consists of two phases: amorphous, glassy tobramycin sulfate with a glass transition temperature of about 100 °C and a gel-phase phospholipid (DSPC) with a gel-to-liquid-crystal transition temperature of about 80 °C. This was by design and constituted a rational formulation approach to provide Tg and Tm values that are well above the temperatures used for long-term storage of TIP. Raman and ESCA data provide support for a core/shell particle architecture of TIP. Particle surfaces are enriched with a porous, hydrophobic coating that reduces cohesive forces, improving powder fluidization and dispersibility. The excellent aerosol dispersibility of TIP enables highly efficient delivery of fine particles to the respiratory tract. Collectively, particle engineering has enabled development of TOBI Podhaler, an approved inhaled drug product that meaningfully reduces the treatment burden to cystic fibrosis patients worldwide.

Title: Enhancement of premature stop codon readthrough in the CFTR gene by Ataluren (PTC124) derivatives.

Citation: European journal of medicinal chemistry, Aug 2015, vol. 101, p. 236-244

Author(s): Pibiri, Ivana, Lentini, Laura, Melfi, Raffaella, Gallucci, Giulia, Pace, Andrea, Spinello, Angelo, Barone, Giampaolo, Di Leonardo, Aldo

Abstract: Premature stop codons are the result of nonsense mutations occurring within the coding sequence of a gene. These mutations lead to the synthesis of a truncated protein and are responsible for several genetic diseases. A potential pharmacological approach to treat these diseases is to promote the translational readthrough of premature stop codons by small molecules aiming to restore the full-length protein. The compound PTC124 (Ataluren) was reported to promote the readthrough of the premature UGA stop codon, although its activity was questioned. The potential interaction of PTC124 with mutated mRNA was recently suggested by molecular dynamics (MD) studies highlighting the importance of H-
bonding and stacking π-π interactions. To improve the readthrough activity we changed the fluorine number and position in the PTC124 fluoroaryl moiety. The readthrough ability of these PTC124 derivatives was tested in human cells harboring reporter plasmids with premature stop codons in H2BGFP and FLuc genes as well as in cystic fibrosis (CF) IB3.1 cells with a nonsense mutation. Maintaining low toxicity, three of these molecules showed higher efficacy than PTC124 in the readthrough of the UGA premature stop codon and in recovering the expression of the CFTR protein in IB3.1 cells from cystic fibrosis patient. Molecular dynamics simulations performed with mutated CFTR mRNA fragments and active or inactive derivatives are in agreement with the suggested interaction of PTC124 with mRNA. Copyright © 2015 Elsevier Masson SAS. All rights reserved.

**Title:** Antiinflammatory and Antimicrobial Effects of Thiocyanate in a Cystic Fibrosis Mouse Model.

**Citation:** American journal of respiratory cell and molecular biology, Aug 2015, vol. 53, no. 2, p. 193-205 (August 2015)

**Author(s):** Chandler, Joshua D, Min, Elysia, Huang, Jie, McElroy, Cameron S, Dickerhof, Nina, Mocatta, Tessa, Fletcher, Ashley A, Evans, Christopher M, Liang, Liping, Patel, Manisha, Kettle, Anthony J, Nichols, David P, Day, Brian J

**Abstract:** Thiocyanate (SCN) is used by the innate immune system, but less is known about its impact on inflammation and oxidative stress. Granulocytes oxidize SCN to evolve the bactericidal hypothiocyanous acid, which we previously demonstrated is metabolized by mammalian, but not bacterial, thioredoxin reductase (TrxR). There is also evidence that SCN is dysregulated in cystic fibrosis (CF), a disease marked by chronic infection and airway inflammation. To investigate antiinflammatory effects of SCN, we administered nebulized SCN or saline to β epithelial sodium channel (βENaC) mice, a phenotypic CF model. SCN significantly decreased airway neutrophil infiltrate and restored the redox ratio of glutathione in lung tissue and airway epithelial lining fluid to levels comparable to wild type. Furthermore, in Pseudomonas aeruginosa-infected βENaC and wild-type mice, SCN decreased inflammation, proinflammatory cytokines, and bacterial load. SCN also decreased airway neutrophil chemokine keratinocyte chemoattractant (also known as C-X-C motif chemokine ligand 1) and glutathione sulfonamide, a biomarker of granulocyte oxidative activity, in uninfected βENaC mice. Lung tissue TrxR activity and expression increased in inflamed lung tissue, providing in vivo evidence for the link between hypothiocyanous acid metabolism by TrxR and the promotion of selective biocide of pathogens. SCN treatment both suppressed inflammation and improved host defense, suggesting that nebulized SCN may have important therapeutic utility in diseases of both chronic airway inflammation and persistent bacterial infection, such as CF.

**Title:** Cathepsin S: therapeutic, diagnostic, and prognostic potential.

**Citation:** Biological chemistry, Aug 2015, vol. 396, no. 8, p. 867-882 (August 2015)

**Author(s):** Wilkinson, Richard D A, Williams, Rich, Scott, Christopher J, Burden, Roberta E

**Abstract:** Cathepsin S is a member of the cysteine cathepsin protease family. It is a lysosomal protease which can promote degradation of damaged or unwanted proteins in the endo-lysosomal pathway. Additionally, it has more specific roles such as MHC class II
antigen presentation, where it is important in the degradation of the invariant chain. Unsurprisingly, mis-regulation has implicated cathepsin S in a variety of pathological processes including arthritis, cancer, and cardiovascular disease, where it becomes secreted and can act on extracellular substrates. In comparison to many other cysteine cathepsin family members, cathepsin S has uniquely restricted tissue expression and is more stable at a neutral pH, which supports its involvement and importance in localised disease microenvironments. In this review, we examine the known involvement of cathepsin S in disease, particularly with respect to recent work indicating its role in mediating pain, diabetes, and cystic fibrosis. We provide an overview of current literature with regards cathepsin S as a therapeutic target, as well as its role and potential as a predictive diagnostic and/or prognostic marker in these diseases.

Title: Metabolomic Evaluation of Neutrophilic Airway Inflammation in Cystic Fibrosis.
Citation: Chest, Aug 2015, vol. 148, no. 2, p. 507-515 (August 1, 2015)
Author(s): Esther, Charles R, Coakley, Raymond D, Henderson, Ashley G, Zhou, Yi-Hui, Wright, Fred A, Boucher, Richard C
Abstract: Metabolomic evaluation of cystic fibrosis (CF) airway secretions could identify metabolites and metabolic pathways involved in neutrophilic airway inflammation that could serve as biomarkers and therapeutic targets. Mass spectrometry (MS)-based metabolomics was performed on a discovery set of BAL fluid samples from 25 children with CF, and targeted MS methods were used to identify and quantify metabolites related to neutrophilic inflammation. A biomarker panel of these metabolites was then compared with neutrophil counts and clinical markers in independent validation sets of lavage from children with CF and adults with COPD compared with control subjects. Of the 7,791 individual peaks detected by positive-mode MS metabolomics discovery profiling, 338 were associated with neutrophilic inflammation. Targeted MS determined that many of these peaks were generated by metabolites from pathways related to the metabolism of purines, polyamines, proteins, and nicotinamide. Analysis of the independent validation sets verified that, in subjects with CF or COPD, several metabolites, particularly those from purine metabolism and protein catabolism pathways, were strongly correlated with neutrophil counts and were related to clinical markers, including airway infection and lung function. MS metabolomics identified multiple metabolic pathways associated with neutrophilic airway inflammation. These findings provide insight into disease pathophysiology and can serve as the basis for developing disease biomarkers and therapeutic interventions for airways diseases.

Title: The Evolution of Cystic Fibrosis Care.
Citation: Chest, Aug 2015, vol. 148, no. 2, p. 533-542 (August 1, 2015)
Author(s): Pittman, Jessica E, Ferkol, Thomas W
Abstract: Cystic fibrosis (CF) is the most common life-limiting inherited illness of whites. Most of the morbidity and mortality in CF stems from impaired mucociliary clearance leading to chronic, progressive airways obstruction and damage. Significant progress has been made in the care of patients with CF, with advances focused on improving mucociliary clearance, minimizing inflammatory damage, and managing infections; these advances
include new antimicrobial therapies, mucolytic and osmotic agents, and antiinflammatory treatments. More recently, researchers have targeted disease-causing mutations using therapies to promote gene transcription and improve channel function, which has led to impressive physiologic changes in some patients. As we develop more advanced, allele-directed therapies for the management of CF, it will become increasingly important to understand the specific genetic and environmental interactions that cause the significant heterogeneity of lung disease seen in the CF population. This understanding of CF endotypes will allow for more targeted, personalized therapies for future patients. This article reviews the genetic and molecular basis of CF lung disease, the treatments currently available, and novel therapies that are in development.

Title: Clinical evaluation of the Nanoduct sweat test system in the diagnosis of cystic fibrosis after newborn screening.

Citation: European journal of pediatrics, Aug 2015, vol. 174, no. 8, p. 1025-1034

Author(s): Langen, Annette Vernooij-van, Dompeling, Edward, Yntema, Jan-Bart, Arets, Bert, Tiddens, Harm, Loeber, Gerard, Dankert-Roelse, Jeannette

Abstract: After a positive newborn screening test for cystic fibrosis (CF), a sweat test is performed to confirm the diagnosis. The success rate of the generally acknowledged methods (Macroduct/Gibson and Cooke) in newborns varies between 73 and 99%. The Nanoduct sweat test system is easier to perform and less sweat is needed. The main aim of this study was to measure the success rate of the Nanoduct compared to current approved sweat test methods in a newborn population. After informed consent of the parents, newborns with a positive screening test for CF were included. The Macroduct or Gibson and Cooke and Nanoduct were performed in all infants, during the same appointment. The chloride concentration was determined by standard coulorimetry; conductivity was measured directly and converted to a NaCl molarity. One hundred eight newborns were included: 17 with CF, 7 with cystic fibrosis transmembrane regulator (CFTR)-related metabolic syndrome (CRMS), and 84 healthy children. The success rate of the Nanoduct was 93% and for the Macroduct/Gibson and Cooke 79% (McNemar, p = 0.002). The Nanoduct detected the same CF patients as the Macroduct/Gibson and Cooke; one CF patient had an equivocal result for both tests, and no patients were missed. The area under the receiver operating characteristic curve for detection of CF with the Nanoduct was 0.999, with ideal cutoff levels of 91 and 66 mmol/l, comparable to former studies. The success rate of the Nanoduct to collect sufficient sweat in infants was higher compared to the Macroduct and Gibson and Cooke. • The internationally accepted methods for collecting and determining NaCl values in sweat, the Gibson and Cooke method and Macroduct, are difficult to perform and require well-trained and experienced personnel. The test often fails in newborns. As yet there is insufficient evidence to recommend the use of the Nanoduct which fails less often, requires less sweat, and is much easier to perform. What is new: • This study provides further evidence that the Nanoduct fails less often in newborns than the Gibson and Cooke/Macroduct and can be used to exclude or confirm the diagnosis CF in infants with a positive newborn screening test for CF.
Title: Aspects of pulmonary drug delivery strategies for infections in cystic fibrosis - where do we stand?

Citation: Expert opinion on drug delivery, Aug 2015, vol. 12, no. 8, p. 1351-1374

Author(s): Klinger-Strobel, Mareike, Lautenschläger, Christian, Fischer, Dagmar, Mainz, Jochen G, Bruns, Tony, Tuchscherr, Lorena, Pletz, Mathias W, Makarewicz, Oliwia

Abstract: Cystic fibrosis (CF) is the most common life-shortening hereditary disease among Caucasians and is associated with severe pulmonary damage because of decreased mucociliary clearance and subsequent chronic bacterial infections. Approximately 90% of CF patients die from lung destruction, promoted by pathogens such as Pseudomonas aeruginosa. Consequently, antibiotic treatment is a cornerstone of CF therapy, preventing chronic infection and reducing bacterial load, exacerbation rates and loss of pulmonary function. Many drugs are administered by inhalation to achieve high pulmonary concentration and to lower systemic side effects. However, pulmonary deposition of inhaled drugs is substantially limited by bronchial obstruction with viscous mucus and restrained by intrapulmonary bacterial biofilms. This review describes challenges in the therapy of CF-associated infections by inhaled antibiotics and summarizes the current state of microtechnology and nanotechnology-based pulmonary antibiotic delivery strategies. Recent and ongoing clinical trials as well as experimental approaches for microparticle/nanoparticle-based antibiotics are presented and their advantages and disadvantages are discussed. Rapidly increasing antimicrobial resistance accompanied by the lack of novel antibiotics force targeted and more efficient use of the available drugs. Encapsulation of antimicrobials in nanoparticles or microparticles of organic polymers may have great potential for use in CF therapy.

Title: Changing the Paradigm - Treating the Basic Defect in Cystic Fibrosis.

Citation: Indian journal of pediatrics, Aug 2015, vol. 82, no. 8, p. 727-736

Author(s): Guglani, Lokesh

Abstract: Since the first description of Cystic fibrosis (CF) more than 75 y ago, significant advances have been made in understanding its pathogenesis and in developing specific therapies. The pace of these developments was further accelerated after the discovery of CF gene in 1989 and since then, CF has been transformed from being a pediatric illness into a chronic life-limiting genetic disorder with survival up to the fourth decade. The development of mutation-specific therapies in the first decade of the 21st century has the potential to change the natural history of CF and has now ushered in the era of 'Precision Medicine'. The ability to revert the basic defect in CF by using Personalized Medicine approach based on each individual's genetic profile will serve as a model for other chronic disorders as well. This review highlights the recent advances in the field of CF research that have led to a paradigm shift in its management and outcomes

Title: Colistin and neurotoxicity: recommendations for optimal use in cystic fibrosis patients.

Citation: International journal of clinical pharmacy, Aug 2015, vol. 37, no. 4, p. 555-558
**Author(s):** Claus, Barbara O M, Snaquaert, Sylvia, Haerynck, Filomeen, Van Daele, Sabine, De Baets, Frans, Schelstraete, Petra

**Abstract:** Case description The use of i.v. colistin reappeared recently for the treatment of multidrug-resistant Gram negative organisms in the intensive care and cystic fibrosis (CF) setting. According to the latest pharmacokinetic data, a loading dose and high antibiotic doses are given. Two cases of adverse events (paraesthesias, bad taste) were observed immediately after the start of infusion of a high dose of i.v. colistin in adult CF patients at the Ghent University Hospital. Conclusion Recommendations for optimal administration of i.v. colistin in adult CF patients are scarce. This article highlights the importance of mode of administration to avoid toxicity and relates it to recent pharmacokinetic/dynamic literature.

**Title:** Lund-Mackay and modified Lund-Mackay score for sinus surgery in children with cystic fibrosis.

**Citation:** International journal of pediatric otorhinolaryngology, Aug 2015, vol. 79, no. 8, p. 1341-1345 (August 2015)

**Author(s):** Do, Bao Anh, Lands, Larry C, Mascarella, Marco A, Fanous, Amanda, Saint-Martin, Christine, Manoukian, John J, Nguyen, Lily H P

**Abstract:** Patients with cystic fibrosis (CF) frequently present with severe sinonasal disease often requiring radiologic imaging and surgical intervention. Few studies have focused on the relationship between radiologic scoring systems and the need for sinus surgery in this population. The objective of this study is to evaluate the Lund-Mackay (LM) and modified Lund-Mackay (m-LM) scoring systems in predicting the need for sinus surgery or revision surgery in patients with CF. We performed a retrospective chart review of CF patients undergoing computed tomography (CT) sinus imaging at a tertiary care pediatric hospital from 1995 to 2008. Patient scans were scored using both the LM and m-LM systems and compared to the rate of sinus surgery or revision surgery. Receiver-operator characteristics curves (ROC) were used to analyze the radiological scoring systems. A total of 41 children with CF were included in the study. The mean LM score for patients undergoing surgery was 17.3 (±3.1) compared to 11.5 (±6.2) for those treated medically (p<0.01). For the m-LM, the mean score of patients undergoing surgery was 20.3 (±3.5) and 13.5 (±7.3) for those medically treated (p<0.01). Using a ROC curve with a threshold score of 13 for the LM, the sensitivity was 89.3% (95% CI of 72-98) and specificity of 69.2% (95% CI of 39-91). At an optimal score of 19, the m-LM system produced a sensitivity of 67.7% (95% CI of 48-84) and specificity of 84.6% (95% CI of 55-98). The modified Lund-Mackay score provides a high specificity while the Lund-Mackay score a high sensitivity for CF patients who required sinus surgery. The combination of both radiologic scoring systems can potentially predict the need for surgery in this population. Copyright © 2015 Elsevier Ireland Ltd. All rights reserved.
Microbiological

Title: Matrix metalloproteinase activation by free neutrophil elastase contributes to bronchiectasis progression in early cystic fibrosis.

Citation: The European respiratory journal, Aug 2015, vol. 46, no. 2, p. 384-394

Author(s): Garratt, Luke W, Sutanto, Erika N, Ling, Kak-Ming, Looi, Kevin, Iosifidis, Thomas, Martinovich, Kelly M, Shaw, Nicole C, Kicic-Starcevich, Elizabeth, Knight, Darryl A, Ranganathan, Sarath, Stick, Stephen M, Kicic, Anthony, Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF)

Abstract: Neutrophil elastase is the most significant predictor of bronchiectasis in early-life cystic fibrosis; however, the causal link between neutrophil elastase and airway damage is not well understood. Matrix metalloproteinases (MMPs) play a crucial role in extracellular matrix modelling and are activated by neutrophil elastase. The aim of this study was to assess if MMP activation positively correlates with neutrophil elastase activity, disease severity and bronchiectasis in young children with cystic fibrosis. Total MMP-1, MMP-2, MMP-7, MMP-9, tissue inhibitor of metalloproteinase (TIMP)-2 and TIMP-1 levels were measured in bronchoalveolar lavage fluid collected from young children with cystic fibrosis during annual clinical assessment. Active/pro-enzyme ratio of MMP-9 was determined by gelatin zymography. Annual chest computed tomography imaging was scored for bronchiectasis. A higher MMP-9/TIMP-1 ratio was associated with free neutrophil elastase activity. In contrast, MMP-2/TIMP-2 ratio decreased and MMP-1 and MMP-7 were not detected in the majority of samples. Ratio of active/pro-enzyme MMP-9 was also higher in the presence of free neutrophil elastase activity, but not infection. Across the study cohort, both MMP-9/TIMP-1 and active MMP-9 were associated with progression of bronchiectasis. Both MMP-9/TIMP-1 and active MMP-9 increased with free neutrophil elastase and were associated with bronchiectasis, further demonstrating that free neutrophil elastase activity should be considered an important precursor to cystic fibrosis structural disease. Copyright ©ERS 2015.

Title: Increased efficacy of VX-809 in different cellular systems results from an early stabilization effect of F508del-CFTR.

Citation: Pharmacology research & perspectives, Aug 2015, vol. 3, no. 4, p. e00152.

Author(s): Farinha, Carlos M, Sousa, Marisa, Canato, Sara, Schmidt, André, Uliyakina, Inna, Amaral, Margarida D

Abstract: Cystic fibrosis (CF), the most common recessive autosomal disease among Caucasians, is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. The most common mutation, F508del, leads to CFTR impaired plasma membrane trafficking. Therapies modulating CFTR basic defect are emerging, such as VX-809, a corrector of F508del-CFTR traffic which just succeeded in a Phase III clinical trial. We recently showed that VX-809 is additive to two other correctors (VRTX-325 and compound 4a). Here, we aimed to determine whether the differential rescuing by these compounds results from cell-specific factors or rather from distinct effects at the early biogenesis and/or processing. The rescuing efficiencies of the above three correctors were first compared in different cellular models (primary respiratory cells, cystic
fibrosis bronchial epithelial and baby hamster kidney [BHK] cell lines) by functional approaches: micro-Ussing chamber and iodide efflux. Next, biochemical methods (metabolic labeling, pulse-chase and immunoprecipitation) were used to determine their impact on CFTR biogenesis / processing. Functional analyses revealed that VX-809 has the greatest rescuing efficacy and that the relative efficiencies of the three compounds are essentially maintained in all three cellular models tested. Nevertheless, biochemical data show that VX-809 significantly stabilizes F508del-CFTR immature form, an effect that is not observed for C3 nor C4. VX-809 and C3 also significantly increase accumulation of immature CFTR. Our data suggest that VX-809 increases the stability of F508del-CFTR immature form at an early phase of its biogenesis, thus explaining its increased efficacy when inducing its rescue.

Title: The cystic fibrosis transmembrane conductance regulator is an extracellular chloride sensor.

Citation: Pflügers Archiv : European journal of physiology, Aug 2015, vol. 467, no. 8, p. 1783-1794

Author(s): Broadbent, Steven D, Ramjeesingh, Mohabir, Bear, Christine E, Argent, Barry E, Linsdell, Paul, Gray, Michael A

Abstract: The cystic fibrosis transmembrane conductance regulator (CFTR) is a Cl(−) channel that governs the quantity and composition of epithelial secretions. CFTR function is normally tightly controlled as dysregulation can lead to life-threatening diseases such as secretory diarrhoea and cystic fibrosis. CFTR activity is regulated by phosphorylation of its cytosolic regulatory (R) domain, and ATP binding and hydrolysis at two nucleotide-binding domains (NBDs). Here, we report that CFTR activity is also controlled by extracellular Cl(−) concentration ([Cl(−)]o). Patch clamp current recordings show that a rise in [Cl(−)]o stimulates CFTR channel activity, an effect conferred by a single arginine residue, R899, in extracellular loop 4 of the protein. Using NBD mutants and ATP dose response studies in WT channels, we determined that [Cl(−)]o sensing was linked to changes in ATP binding energy at NBD1, which likely impacts NBD dimer stability. Biochemical measurements showed that increasing [Cl(−)]o decreased the intrinsic ATPase activity of CFTR mainly through a reduction in maximal ATP turnover. Our studies indicate that sensing [Cl(−)]o is a novel mechanism for regulating CFTR activity and suggest that the luminal ionic environment is an important physiological arbiter of CFTR function, which has significant implications for salt and fluid homeostasis in epithelial tissues.

Title: High variability in quorum quenching and growth inhibition by furanone C-30 in Pseudomonas aeruginosa clinical isolates from cystic fibrosis patients.

Citation: Pathogens and disease, Aug 2015, vol. 73, no. 6, p. ftv040. (August 2015)

Author(s): García-Contreras, Rodolfo, Peréz-Eretza, Berenice, Jasso-Chávez, Ricardo, Lira-Silva, Elizabeth, Roldán-Sánchez, Jesús Alberto, González-Valdez, Abigail, Soberón-Chávez, Gloria, Coria-Jiménez, Rafael, Martínez-Vázquez, Mariano, Alcaraz, Luis David, Maeda, Toshinari, Wood, Thomas K

Abstract: Pseudomonas aeruginosa colonizes the lungs of cystic fibrosis patients causing severe damage. This bacterium is intrinsically resistant to antibiotics and shows resistance
against new antimicrobials and its virulence is controlled by the quorum-sensing response. Thus, attenuating its virulence by quorum quenching instead of inhibiting its growth has been proposed to minimize resistance; however, resistance against the canonical quorum quencher furanone C-30 can be achieved by mutations leading to increased efflux. In the present work, the effect of C-30 in the attenuation of the QS-controlled virulence factors elastase and pyocyanin was investigated in 50 isolates from cystic fibrosis patients. The results demonstrate that there is a high variability in the expression of both elastase and pyocyanin and that there are many naturally resistant C-30 strains. We report that the main mechanism of C-30 resistance in these strains was not due to enhanced efflux but a lack of permeability. Moreover, C-30 strongly inhibited the growth of several of the isolates studied, thus imposing high selective pressure for the generation of resistance. © FEMS 2015. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Title: Cystic fibrosis transmembrane conductance regulator is involved in polyphenol-induced swelling of the endothelial glycocalyx.

Citation: Nanomedicine : nanotechnology, biology, and medicine, Aug 2015, vol. 11, no. 6, p. 1521-1530 (August 2015)

Author(s): Peters, Wladimir, Kutsche-Vihrog, Kristina, Oberleithner, Hans, Schillers, Hermann

Abstract: Previous studies show that polyphenol-rich compounds can induce a swelling of the endothelial glycocalyx (eGC). Our goal was to reveal the mechanism behind the eGC-swelling. As polyphenols are potent modulators of fibrosis transmembrane conductance regulator (CFTR) Cl(·) channel, the hypothesis was tested whether polyphenol-induced increase in CFTR activity is responsible for the eGC-swelling. The impact of the polyphenols resveratrol, (-)-epicatechin, and quercetin on nanomechanics of living endothelial GM7373 cells was monitored by AFM-nanoindentation. The tested polyphenols lead to eGC-swelling with a simultaneous decrease in cortical stiffness. EGC-swelling, but not the change in cortical stiffness, was prevented by the inhibition of CFTR. Polyphenol-induced eGC-swelling could be mimicked by cytochalasin D, an actin-depolymerizing agent. Thus, in the vascular endothelium, polyphenols induce eGC-swelling by softening cortical actin and activating CFTR. Our findings imply that CFTR plays an important role in the maintenance of vascular homeostasis and may explain the vasoprotective properties of polyphenols. Many vascular problems clinically can be attributed to a dysregulation of endothelial glycocalyx (eGC). The underlying mechanism however remains unclear. In this article, the authors used nanoindentation and showed that polyphenols could swell the endothelial glycocalyx and alter its function. This investigative method can lead to further mechanistic studies of other molecular pathways. Copyright © 2015 The Authors. Published by Elsevier Inc. All rights reserved.

Title: First recovery of Rasamsonia argillacea species complex isolated in adolescent patient with cystic fibrosis in Slovenia - case report and review of literature.

Citation: Mycoses, Aug 2015, vol. 58, no. 8, p. 506-510 (August 2015)

Author(s): Matos, Tadeja, Cerar, Tjaša, Praprotnik, Marina, Krivec, Uroš, Pirš, Mateja
**Abstract:** We report the isolation of the emerging fungal pathogen Rasamsonia aegroticola, which belongs Rasamsonia argillacea species complex, from a respiratory sample of a patient with cystic fibrosis. This filamentous fungus, resembling members of a Penicillium and Paecilomyces spp., was identified by morphology and confirmed by DNA sequence analysis. Susceptibility pattern showed high minimal inhibitory concentration of voriconazole and amphotericin B but low minimal inhibitory concentration of caspofungin, micafungin and itraconazole. © 2015 Blackwell Verlag GmbH.

**Title:** Metabolism and Pathogenicity of Pseudomonas aeruginosa Infections in the Lungs of Individuals with Cystic Fibrosis.

**Citation:** Microbiology spectrum, Aug 2015, vol. 3, no. 4 (August 2015)

**Author(s):** Palmer, Gregory C, Whiteley, Marvin

**Abstract:** Individuals with the genetic disease cystic fibrosis (CF) accumulate mucus or sputum in their lungs. This sputum is a potent growth substrate for a range of potential pathogens, and the opportunistic bacterium Pseudomonas aeruginosa is generally most difficult of these to eradicate. As a result, P. aeruginosa infections are frequently maintained in the CF lung throughout life, and are the leading cause of death for these individuals. While great effort has been expended to better understand and treat these devastating infections, only recently have researchers begun to rigorously examine the roles played by specific nutrients in CF sputum to cue P. aeruginosa pathogenicity. This chapter summarizes the current state of knowledge regarding how P. aeruginosa metabolism in CF sputum affects initiation and maintenance of these infections. It contains an overview of CF lung disease and the mechanisms of P. aeruginosa pathogenicity. Several model systems used to study these infections are described with emphasis on the challenge of replicating the chronic infections observed in humans with CF. Nutrients present in CF sputum are surveyed, and the impacts of these nutrients on the infection are discussed. The chapter concludes by addressing the future of this line of research including the use of next-generation technologies and the potential for metabolism-based therapeutics.

**Title:** Characterization of Staphylococcus aureus Strains Isolated from Czech Cystic Fibrosis Patients: High Rate of Ribosomal Mutation Conferring Resistance to MLSB Antibiotics as a Result of Long-Term and Low-Dose Azithromycin Treatment.

**Citation:** Microbial drug resistance (Larchmont, N.Y.), Aug 2015, vol. 21, no. 4, p. 416-423

**Author(s):** Tkadlec, Jan, Vařeková, Eva, Pantůček, Roman, Doškař, Jiří, Růžičková, Vladislava, Botka, Tibor, Fila, Libor, Melter, Oto

**Abstract:** Staphylococcus aureus is one of the most frequent pathogens infecting the respiratory tract of patients with cystic fibrosis (CF). This study was the first to examine S. aureus isolates from CF patients in the Czech Republic. Among 100 S. aureus isolates from 92 of 107 observed patients, we found a high prevalence of resistance to macrolide-lincosamide-streptogramin B (MLSB) antibiotics (56%). More than half of the resistant strains (29 of 56) carried a mutation in the MLSB target site. The emergence of MLSB resistance and mutations conferring resistance to MLSB antibiotics was associated with azithromycin treatment (p=0.000000184 and p=0.000681, respectively). Methicillin
resistance was only detected in 3% of isolates and the rate of resistance to other antibiotics did not exceed 12%. The prevalence of small-colony variant (SCV) strains was relatively low (9%) and eight of nine isolates with the SCV phenotype were thymidine dependent. The study population of S. aureus was heterogeneous in structure and both the most prevalent community-associated and hospital-acquired clonal lineages were represented. Of the virulence genes, enterotoxin genes seg (n=52), sei (n=49), and sec (n=16) were the most frequently detected among the isolates. The PVL genes (lukS-PV and lukF-PV) have not been revealed in any of the isolates.

Title: In vitro activity of colistin against biofilm by Pseudomonas aeruginosa is significantly improved under "cystic fibrosis-like" physicochemical conditions.

Citation: Diagnostic microbiology and infectious disease, Aug 2015, vol. 82, no. 4, p. 318-325

Author(s): Pompilio, Arianna, Crocetta, Valentina, Pomponio, Stefano, Fiscarelli, Ersilia, Di Bonaventura, Giovanni

Abstract: The impact of physicochemical conditions observed in cystic fibrosis (CF) lung on colistin activity against both planktonic and biofilm P. aeruginosa cells was evaluated. MIC, minimum bactericidal concentration (MBC), and minimum biofilm eradication concentration (MBEC) values were assessed against 12 CF strains both under "CF-like" (anaerobiosis, pH6.4) and "standard" (aerobiosis, pH7.4) conditions. The activity of colistin was significantly higher under "CF-like" conditions compared to "standard" ones, both against planktonic (MIC90: 1 and 4 μg/mL, respectively) and biofilm (MBEC90: 512 and 1.024 μg/mL, respectively) cells, as confirmed by scanning electron microscopy. Improved activity was not related to biofilm matrix amount. It may be necessary to adequately "rethink" the protocols used for in vitro assessment of colistin activity, by considering physicochemical and microbiological features in the CF lung at the site of infection. This could provide a more favorable therapeutic index, rationale for administration of lower doses, probably resulting in reduced toxicity and emergence of resistant clones. Copyright © 2015 Elsevier Inc. All rights reserved.

Title: Microbiome in cystic fibrosis: Shaping polymicrobial interactions for advances in antibiotic therapy.

Citation: Critical reviews in microbiology, Aug 2015, vol. 41, no. 3, p. 353-365

Author(s): Lopes, Susana P, Azevedo, Nuno F, Pereira, Maria O

Abstract: Recent molecular methodologies have demonstrated a complex microbial ecosystem in cystic fibrosis (CF) airways, with a wide array of uncommon microorganisms co-existing with the traditional pathogens. Although there are lines of evidence supporting the contribution of some of those emergent species for lung disease chronicity, clinical significance remains uncertain for most cases. A possible contribution for disease is likely to be related with the dynamic interactions established between microorganisms within the microbial community and with the host. If this is the case, management of CF will only be successful upon suitable and exhaustive modulation of such mixed ecological processes, which will also be useful to predict the effects of new therapeutic interventions.
Title: G551D-CFTR needs more bound actin than wild-type CFTR to maintain its presence in plasma membranes.

Citation: Cell biology international, Aug 2015, vol. 39, no. 8, p. 978-985

Author(s): Trouvé, Pascal, Kerbiriou, Mathieu, Teng, Ling, Benz, Nathalie, Taiya, Mehdi, Le Hir, Sophie, Férec, Claude

Abstract: Cystic Fibrosis is due to mutations in the CFTR gene. The missense mutation G551D (approx. 5% of cases) encodes a CFTR chloride channel with normal cell surface expression but with an altered chloride channel activity, leading to a severe phenotype. Our aim was to identify specific interacting proteins of G551D-CFTR which could explain the channel defect. Wild-type CFTR (Wt-CFTR) was co-immunoprecipitated from stably transfected HeLa cells and resolved by 2D gel electrophoresis. Among the detected spots, one was expressed at a high level. Mass Spectrometry revealed that it corresponded to actin which is known to be involved in the CFTR's channel function. To assess whether actin could be involved in the altered G551D-CFTR function, its basal expression was studied. Because actin expression was the same in wt- and in G551D-CFTR expressing cells, its interaction with both wt- and G551D-CFTR was studied by co-immunoprecipitation, and we found that a higher amount of actin was bound onto G551D-CFTR than onto Wt-CFTR. The role of actin upon wt- and G551D-CFTR function was further studied by patch-clamp experiments after cytochalasin D treatment of the cells. We found a decrease of the very weak currents in G551D-CFTR expressing cells. Because a higher amount of actin is bound onto G551D-CFTR than onto Wt-CFTR, it is likely to be not involved in the mutated CFTR's defect. Nevertheless, because actin is necessary to maintain the very weak global currents observed in G551D-CFTR expressing HeLa cells, we conclude that more actin is necessary to maintain G551D-CFTR in the plasma membrane than for Wt-CFTR.

Title: In Vivo Efficacy of Antimicrobials against Biofilm-Producing Pseudomonas aeruginosa.

Citation: Antimicrobial agents and chemotherapy, Aug 2015, vol. 59, no. 8, p. 4974-4981

Author(s): Pawar, Vinay, Komor, Uliana, Kasnitz, Nadine, Bielecki, Piotr, Pils, Marina C, Gocht, Benjamin, Moter, Annette, Rohde, Manfred, Weiss, Siegfried, Häussler, Susanne

Abstract: Patients suffering from cystic fibrosis (CF) are commonly affected by chronic Pseudomonas aeruginosa biofilm infections. This is the main cause for the high disease severity. In this study, we demonstrate that P. aeruginosa is able to efficiently colonize murine solid tumors after intravenous injection and to form biofilms in this tissue. Biofilm formation was evident by electron microscopy. Such structures could not be observed with transposon mutants, which were defective in biofilm formation. Comparative transcriptional profiling of P. aeruginosa indicated physiological similarity of the bacteria in the murine tumor model and the CF lung. The efficacy of currently available antibiotics for treatment of P. aeruginosa-infected CF lungs, such as ciprofloxacin, colistin, and tobramycin, could be tested in the tumor model. We found that clinically recommended doses of these antibiotics were unable to eliminate wild-type P. aeruginosa PA14 while being effective against biofilm-defective mutants. However, colistin-tobramycin combination therapy significantly reduced the number of P. aeruginosa PA14 cells in tumors at lower concentrations. Hence, we present a versatile experimental system that is providing a platform to test approved and newly developed antibiofilm compounds.
**Title:** Gallium Compounds Exhibit Potential as New Therapeutic Agents against Mycobacterium abscessus.

**Citation:** Antimicrobial agents and chemotherapy, Aug 2015, vol. 59, no. 8, p. 4826-4834

**Author(s):** Abdalla, Maher Y, Switzer, Barbara L, Goss, Christopher H, Aitken, Moira L, Singh, Pradeep K, Britigan, Bradley E

**Abstract:** The rapidly growing nontuberculous mycobacterial species Mycobacterium abscessus has recently emerged as an important pathogen in patients with cystic fibrosis (CF). Treatment options are limited because of the organism’s innate resistance to standard antituberculous antibiotics, as well as other currently available antibiotics. New antibiotic approaches to the treatment of M. abscessus are urgently needed. The goal of the present study was to assess the growth-inhibitory activity of different Ga compounds against an American Type Culture Collection (ATCC) strain and clinical isolates of M. abscessus obtained from CF and other patients. In our results, using Ga(NO₃)₃ and all of the other Ga compounds tested inhibited the growth of ATCC 19977 and clinical isolates of M. abscessus. Inhibition was mediated by disrupting iron uptake, as the addition of exogenous iron (Fe) restored basal growth. There were modest differences in inhibition among the isolates for the same Ga chelates, and for most Ga chelates there was only a slight difference in potency from Ga(NO₃)₃. In contrast, Ga-protoporphyrin completely and significantly inhibited the ATCC strain and clinical isolates of M. abscessus at much lower concentrations than Ga(NO₃)₃. In in vitro broth culture, Ga-protoporphyrin was more potent than Ga(NO₃)₃. When M. abscessus growth inside the human macrophage THP-1 cell line was assessed, Ga-protoporphyrin was >20 times more active than Ga(NO₃)₃. The present work suggests that Ga exhibits potent growth-inhibitory capacity against the ATCC strain, as well as against antibiotic-resistant clinical isolates of M. abscessus, including the highly antibiotic-resistant strain MC2638. Ga-based therapy offers the potential for further development as a novel therapy against M. abscessus.

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**Title:** EG-VEGF, BV8, and their receptor expression in human bronchi and their modification in cystic fibrosis: Impact of CFTR mutation (delF508).

**Citation:** American journal of physiology. Lung cellular and molecular physiology, Aug 2015, vol. 309, no. 3, p. L314. (August 1, 2015)

**Author(s):** Chauvet, Sylvain, Traboulsi, Wael, Thevenon, Laura, Kouadri, Amal, Feige, Jean-Jacques, Camara, Boubou, Alfaidy, Nadia, Benharouga, Mohamed

**Abstract:** Enhanced lung angiogenesis has been reported in cystic fibrosis (CF). Recently, two highly homologous ligands, endocrine gland vascular endothelial growth factor (EG-VEGF) and mammalian BV8, have been described as new angiogenic factors. Both ligands bind and activate two closely related G protein-coupled receptors, the prokineticin receptor (PROKR) 1 and 2. Yet, the expression, regulation, and potential role of EG-VEGF, BV8, and their receptors in normal and CF lung are still unknown. The expression of the receptors and their ligands was examined using molecular, biochemical, and immunocytochemistry analyses in lungs obtained from CF patients vs. control and in normal and CF bronchial epithelial cells. Cystic fibrosis transmembrane conductance regulator (CFTR) activity was evaluated in relation to both ligands, and concentrations of EG-VEGF were measured by
ELISA. At the mRNA level, EG-VEGF, BV8, and PROKR2 gene expression was, respectively, approximately five, four, and two times higher in CF lungs compared with the controls. At the cellular level, both the ligands and their receptors showed elevated expressions in the CF condition. Similar results were observed at the protein level. The EG-VEGF secretion was apical and was approximately two times higher in CF compared with the normal epithelial cells. This secretion was increased following the inhibition of CFTR chloride channel activity. More importantly, EG-VEGF and BV8 increased the intracellular concentration of Ca(2+) and cAMP and stimulated CFTR-chloride channel activity. Altogether, these data suggest local roles for epithelial BV8 and EG-VEGF in the CF airway peribronchial vascular remodeling and highlighted the role of CFTR activity in both ligand biosynthesis and secretion. Copyright © 2015 the American Physiological Society.

Title: Activation of Human Toll-like Receptor 4 (TLR4)-Myeloid Differentiation Factor 2 (MD-2) by Hypoacylated Lipopolysaccharide from a Clinical Isolate of Burkholderia cenocepacia.

Citation: The Journal of biological chemistry, Aug 2015, vol. 290, no. 35, p. 21305-21319 (August 28, 2015)

Author(s): Di Lorenzo, Flaviana, Kubik, Łukasz, Oblak, Alja, Lorè, Nicola Ivan, Cigana, Cristina, Lanzetta, Rosa, Parrilli, Michelangelo, Hamad, Mohamad A, De Soyza, Anthony, Silipo, Alba, Jerala, Roman, Bragonzi, Alessandra, Valvano, Miguel A, Martín-Santamaría, Sonsoles, Molinaro, Antonio

Abstract: Lung infection by Burkholderia species, in particular Burkholderia cenocepacia, accelerates tissue damage and increases post-lung transplant mortality in cystic fibrosis patients. Host-microbe interplay largely depends on interactions between pathogen-specific molecules and innate immune receptors such as Toll-like receptor 4 (TLR4), which recognizes the lipid A moiety of the bacterial lipopolysaccharide (LPS). The human TLR4-myeloid differentiation factor 2 (MD-2) LPS receptor complex is strongly activated by hexa-acylated lipid A and poorly activated by underacylated lipid A. Here, we report that B. cenocepacia LPS strongly activates human TLR4-MD-2 despite its lipid A having only five acyl chains. Furthermore, we show that aminoarabinose residues in lipid A contribute to TLR4-lipid A interactions, and experiments in a mouse model of LPS-induced endotoxic shock confirmed the proinflammatory potential of B. cenocepacia penta-acylated lipid A. Molecular modeling combined with mutagenesis of TLR4-MD-2 interactive surfaces suggests that longer acyl chains and the aminoarabinose residues in the B. cenocepacia lipid A allow exposure of the fifth acyl chain on the surface of MD-2 enabling interactions with TLR4 and its dimerization. Our results provide a molecular model for activation of the human TLR4-MD-2 complex by penta-acylated lipid A explaining the ability of hypoacylated B. cenocepacia LPS to promote proinflammatory responses associated with the severe pathogenicity of this opportunistic bacterium. © 2015 by The American Society for Biochemistry and Molecular Biology, Inc.

Title: Discovery of Novel CXCR2 Inhibitors Using Ligand-Based Pharmacophore Models.

Citation: Journal of chemical information and modeling, Aug 2015, vol. 55, no. 8, p. 1720-1738 (August 24, 2015)
Author(s): Ha, Helen, Debnath, Bikash, Odde, Srinivas, Bensman, Tim, Ho, Henry, Beringer, Paul M, Neamatli, Nouri

Abstract: The chemokine receptor CXCR2 is expressed on various immune cells and is essential for neutrophil recruitment and angiogenesis at sites of acute and chronic inflammation caused by tissue injury or infection. CXCR2 and its ligand, CXCL8, are implicated in a number of inflammation-mediated diseases such as chronic obstructive pulmonary disease, cystic fibrosis, and cancer. Though the development of CXCR2-specific small-molecule inhibitors as anti-inflammatory agents has been pursued by pharmaceutical companies within the past decade, there are currently no clinically approved CXCR2 inhibitors. A pharmacophore model based on previously reported CXCR2 antagonists was developed to screen a database of commercially available compounds. Small-molecule compounds identified from the pharmacophore screening were selected for in vitro screening in a cell-based CXCR2-mediated β-arrestin-2 recruitment assay and further characterized in several cell-based assays and lipopolysaccharide (LPS)-induced lung inflammation studies in mice. CX compounds identified from pharmacophore modeling inhibited cell migration, lung and colon cancer cell proliferation, and colony formation. Mechanistic studies of CX4152 showed that this compound inhibits CXCR2 signaling through downregulation of surface CXCR2. Additionally, CX4152 significantly inhibits CXCL8-mediated neutrophil migration and LPS-induced lung inflammation in mice. Using a CXCR2-inhibitor-based pharmacophore model, we identified a novel set of sulfonamides from a diverse library of small molecules. These compounds inhibit CXCR2/β-arrestin-2 association, cell migration and proliferation, and acute inflammation in mouse models. CX compounds identified from our pharmacophore models are potential leads for further optimization and development as anti-inflammatory and anticancer agents.

Title: Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function.

Citation: World journal of critical care medicine, Aug 2015, vol. 4, no. 3, p. 179-191

Author(s): Reeves, Emer P, McCarthy, Cormac, McElvaney, Oliver J, Vijayan, Maya Sakthi N, White, Michelle M, Dunlea, Danielle M, Pohl, Kerstin, Lacey, Noreen, McElvaney, Noel G

Abstract: Cystic fibrosis (CF) is a multisystem disorder with significantly shortened life expectancy. The major cause of mortality and morbidity is lung disease with increasing pulmonary exacerbations and decline in lung function predicting significantly poorer outcomes. The pathogenesis of lung disease in CF is characterised in part by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. This leads to accumulation of viscous mucus in the CF airway, providing an ideal environment for bacterial pathogens to grow and colonise, propagating airway inflammation in CF. The use of nebulised hypertonic saline (HTS) treatments has been shown to improve mucus clearance in CF and impact positively upon exacerbations, quality of life, and lung function. Several mechanisms of HTS likely improve outcome, resulting in clinically relevant enhancement in disease parameters related to increase in mucociliary clearance. There is increasing evidence to suggest that HTS is also beneficial through its anti-inflammatory properties and its ability to reduce bacterial activity and biofilm formation. This review will first describe the use of HTS in treatment of CF focusing on its efficacy and tolerability. The emphasis will then change to the potential benefits of aerosolized HTS for the attenuation
of receptor mediated neutrophil functions, including down-regulation of oxidative burst activity, adhesion molecule expression, and the suppression of neutrophil degranulation of proteolytic enzymes.

**Title:** HLA-DQ allele-restricted activation of nitroso sulfamethoxazole-specific CD4-positive T lymphocytes from patients with cystic fibrosis.

**Citation:** Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, Aug 2015, vol. 45, no. 8, p. 1305-1316 (August 2015)


**Abstract:** For certain HLA allele-associated drug hypersensitivity reactions, the parent drug has been shown to associate directly with the risk allele. In other forms of hypersensitivity, HLA risk alleles have not been identified and T cells are activated in an allele unrestricted manner. Chemically reactive drug metabolites bind to multiple proteins; thus, it is assumed that the derived peptide antigens interact with a number of HLA molecules to activate T cells; however, HLA restriction of the drug metabolite-specific T-cell response has not been studied. To utilize T cells from sulfamethoxazole (SMX) hypersensitive patients with cystic fibrosis to examine the HLA molecules that interact with nitroso SMX (SMX-NO)-derived antigens. T-cell clones were generated from 4 hypersensitive patients. Drug-specific proliferative responses and cytokine secretion were measured. Anti-human class I and class II antibodies were used to analyse HLA restriction. Antigen-presenting cells expressing different HLA molecules were used to determine the alleles involved in the presentation of SMX-NO-derived antigens to T cells. A total of 976 clones were tested for SMX-NO reactivity. Thirty-nine CD4+ clones were activated with SMX-NO and found to proliferate and secrete cytokines. The SMX-NO-specific response was blocked with an antibody against HLA-DQ. SMX-NO-specific responses were detected with antigen-presenting cells expressing HLA-DQB1*05:01 (patient 1) and HLA-DQB1*02:01 (patient 2), but not other HLA-DQB1 alleles. HLA-DQ plays an important role in the activation of SMX-NO-specific CD4+ T cells. Detection of HLA-DQ allele-restricted responses suggests that T cells are activated by a limited repertoire of SMX-NO-modified peptides. © 2015 John Wiley & Sons Ltd.

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**Title:** Incidence of Burkholderia contaminans at a cystic fibrosis centre with an unusually high representation of Burkholderia cepacia during 15 years of epidemiological surveillance.

**Citation:** Journal of medical microbiology, Aug 2015, vol. 64, no. 8, p. 927-935 (August 2015)

**Author(s):** Coutinho, Carla P, Barreto, Celeste, Pereira, Luísa, Lito, Luís, Melo Cristino, José, Sá-Correia, Isabel

**Abstract:** The Burkholderia cepacia complex (Bcc) is a heterogeneous group of bacteria comprising around 20 related species. These bacteria are important opportunistic pathogens, especially in cystic fibrosis (CF) patients, and are associated with a worse prognosis and decreased life expectancy. The taxonomic position of 20 Bcc isolates retrieved from CF patients receiving care at Hospital Santa Maria (HSM), in Lisbon, from 1995 to 2006, was re-examined in the present work. These isolates, formerly classified as Burkholderia cepacia (taxon K), are here reclassified as Burkholderia contaminans, including the former B.
cepacia IST408, which was the focus of previous studies regarding the biosynthesis of the exopolysaccharide ‘cepacian’. The CF population examined has been previously described as having an exceptionally high representation of B. cepacia, presumably due to a contamination arising from saline solutions for nasal application. Twenty-one additional isolates, obtained from a chronically infected patient, from 2006 to 2010, were also identified as B. contaminans. This study also provides insight into the potential clinical impact of B. contaminans, a species that is rarely associated with CF infections. Isolates belonging to this species were shown to be involved in chronic and transient respiratory infections, and were associated with severe lung function deterioration and with a case of death with cepacia syndrome. However, since the patients were co-infected with Burkholderia cenocepacia and other non-Burkholderia bacteria, the role played by B. contaminans is unclear. Nevertheless, B. contaminans isolates were found to prevail over B. cenocepacia isolates during co-infection of at least one chronically infected patient.

Title: Comparison of Airway and Systemic Malondialdehyde Levels for Assessment of Oxidative Stress in Cystic Fibrosis.

Citation: Lung, Aug 2015, vol. 193, no. 4, p. 597-604 (August 2015)

Author(s): Antus, Balazs, Drozdovszky, Orsolya, Barta, Imre, Kelemen, Krisztina

Abstract: Oxidative stress plays a pivotal role in the pathogenesis of cystic fibrosis (CF). In this study, airway and systemic oxidative stress was investigated in CF using malondialdehyde (MDA), an established by-product of polyunsaturated fatty acid peroxidation. Exhaled breath condensate (EBC), sputum, and plasma were collected from 40 stable CF patients during routine clinical visits and from 25 healthy controls. MDA was measured by high-performance liquid chromatography. MDA levels in sputum (279.8 ± 14.7 vs. 92.7 ± 9.2 nmol/L, p < 0.0001), EBC (139.9 ± 6.7 vs. 71.5 ± 4.3 nmol/L, p < 0.0001), and plasma (176.1 ± 15.9 vs. 129.6 ± 12.9 nmol/L, p < 0.05) were increased in patients with CF compared to healthy controls. MDA measurement in sputum [area under receiver operating characteristic curve (AUC): 0.977, p < 0.0001] or EBC (AUC: 0.94, p < 0.0001) discriminated between patients and controls with greater accuracy than in plasma (AUC: 0.677, p < 0.05). Sputum and EBC MDA levels were elevated in patients with severe pulmonary dysfunction [forced expiratory volume in 1 s (FEV1) <50 % predicted] compared to those with mild-to-moderate functional impairment (FEV1 ≥50 % predicted) (p < 0.05). MDA concentrations in CF patients colonized either with Pseudomonas aeruginosa or with other bacteria were similar (p = NS). The intra- and inter-assay repeatabilities of MDA measurements was similar in all the three types of samples, while the between-visit variability was higher in plasma. MDA is a potential new airway marker of oxidative stress in patients with CF. Sputum MDA differentiates best between patients and healthy subjects.

Title: CXCR4+ granulocytes reflect fungal cystic fibrosis lung disease.

Citation: The European respiratory journal, Aug 2015, vol. 46, no. 2, p. 395-404

Author(s): Carevic, Melanie, Singh, Anurag, Rieber, Nikolaus, Eickmeier, Olaf, Griese, Matthias, Hector, Andreas, Hartl, Dominik
Abstract: Cystic fibrosis airways are frequently colonised with fungi. However, the interaction of these fungi with immune cells and the clinical relevance in cystic fibrosis lung disease are incompletely understood. We characterised granulocytes in airway fluids and peripheral blood from cystic fibrosis patients with and without fungal colonisation, non-cystic fibrosis disease controls and healthy control subjects cross-sectionally and longitudinally and correlated these findings with lung function parameters. Cystic fibrosis patients with chronic fungal colonisation by Aspergillus fumigatus were characterised by an accumulation of a distinct granulocyte subset, expressing the HIV coreceptor CXCR4. Percentages of airway CXCR4(+) granulocytes correlated with lung disease severity in patients with cystic fibrosis. These studies demonstrate that chronic fungal colonisation with A. fumigatus in cystic fibrosis patients is associated with CXCR4(+) airway granulocytes, which may serve as a potential biomarker and therapeutic target in fungal cystic fibrosis lung disease. Copyright ©ERS 2015.

Nutrition

Title: Standardization of Research-Quality Anthropometric Measurement of Infants and Implementation in a Multicenter Study.

Citation: Clinical and translational science, Aug 2015, vol. 8, no. 4, p. 330-333 (August 2015)

Author(s): Coburn-Miller, Christine, Casey, Susan, Luong, Quynh, Cameron, Natalia, Hocevar-Trnka, Jasna, Leung, Daniel H, Gelfond, Daniel, Heubi, James E, Ramsey, Bonnie, Borowitz, Drucy

Abstract: Malnutrition is one of the earliest clinical manifestations of cystic fibrosis (CF) and is associated with poorer pulmonary and cognitive outcomes and survival later in life. Infant growth can be a responsive measure for clinical research in this age group if obtained and characterized accurately. We report here the methods to standardize and implement research-quality anthropometric measurement of infants with cystic fibrosis in the Baby Observational Nutrition Study multicenter trial. © 2015 Wiley Periodicals, Inc.

Title: Carbohydrate intake and insulin requirement in children, adolescents and young adults with cystic fibrosis-related diabetes: A multicenter comparison to type 1 diabetes.

Citation: Clinical nutrition (Edinburgh, Scotland), Aug 2015, vol. 34, no. 4, p. 732-738 (August 2015)

Author(s): Scheuing, Nicole, Thon, Angelika, Konrad, Katja, Bauer, Maria, Karsten, Claudia, Meissner, Thomas, Seufert, Jochen, Schönau, Eckhard, Schöfl, Christof, Woelfle, Joachim, Holl, Reinhard W, German/Austrian Diabetes Prospective Documentation Initiative and the BMBF Competence Network Diabetes Mellitus

Abstract: In cystic fibrosis-related diabetes (CFRD), energy needs differ from type 1 (T1D) or type 2 diabetes, and endogenous insulin secretion is not totally absent. We analyzed whether daily carbohydrate intake, its diurnal distribution and insulin requirement per 11 g of carbohydrate differ between CFRD and T1D. Anonymized data of 223 CFRD and 36,780 T1D patients aged from 10 to <30 years from the multicenter diabetes registry DPV were studied. Carbohydrate intake and insulin requirement were analyzed using multivariable
regression modeling with adjustment for age and sex. Moreover, carbohydrate intake was compared to the respective recommendations (CFRD: energy intake 130% of general population with 45% carbohydrates; T1D: carbohydrate intake 50% of total energy). After demographic adjustment, carbohydrate intake (238 ± 4 vs. 191 ± 1 g/d, p < 0.001) and meal-related insulin (0.52 ± 0.02 vs. 0.47 ± 0.004 IU/kg*d, p = 0.001) were higher in CFRD, whereas basal insulin (0.27 ± 0.01 vs. 0.38 ± 0.004 IU/kg*d, p < 0.001) and total insulin requirement per 11 g of carbohydrate (1.15 ± 0.06 vs. 1.70 ± 0.01 IU/d, p < 0.001) were lower compared to T1D. CFRD patients achieved 62% [Q1;Q3: 47; 77] of recommended carbohydrate intake and T1D patients 60% [51; 71] of age- and gender-specific recommended intake (p < 0.001). CFRD and T1D patients had a carbohydrate intake below healthy peers (79% [58; 100] and 62% [52; 74], p < 0.001). The circadian rhythm of insulin sensitivity persisted in CFRD and the diurnal distribution of carbohydrates was comparable between groups. In pediatric and young adult patients, carbohydrate intake and insulin requirement differ clearly between CFRD and T1D. However, both CFRD and T1D patients seem to restrict carbohydrates. Copyright © 2014 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

**Title:** Nutrition Management of Cystic Fibrosis in the 21st Century.

**Citation:** Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, Aug 2015, vol. 30, no. 4, p. 488-500 (August 2015)

**Author(s):** Schindler, Teresa, Michel, Suzanne, Wilson, Alexandra W M

**Abstract:** Despite significant advancements made in life expectancy over the past century, cystic fibrosis remains a life-threatening genetic disease that affects the gastrointestinal tract, and it has significant impact on the nutrition status of those with the disease. Nutrition management includes a high-calorie/high-fat diet, pancreatic enzyme replacement therapy, vitamin and mineral replacement, and enteral support as needed. As patients are living longer, clinicians may encounter patients with cystic fibrosis in obstetrician offices, endocrine clinics, or hospital settings, owing to lung transplantation or for treatment for distal intestinal obstruction syndrome. © 2015 American Society for Parenteral and Enteral Nutrition.

**Title:** Difficulty Achieving Vitamin D Sufficiency With High-Dose Oral Repletion Therapy in Infants With Cholestasis.

**Citation:** Journal of pediatric gastroenterology and nutrition, Aug 2015, vol. 61, no. 2, p. 187-189 (August 2015)

**Author(s):** Jensen, Melissa, Abu-El-Haija, Maisam, Bishop, Warren, Rahhal, Riad M

**Abstract:** Oral high-dose repletion vitamin D therapy, also known as stoss therapy, can be effective in the treatment of nutritional vitamin D deficiency rickets in infants and young children without liver disease and in patients with cystic fibrosis. There is no literature about this approach in infants with new-onset cholestasis. This was a retrospective chart review of infants with cholestasis from March 2010 to March 2012 at a pediatric tertiary care center. Four cases satisfied the inclusion criteria, and were described in detail. All of the patients received oral high-dose repletion therapy with ergocalciferol (vitamin D2) 300,000 IU daily
for 2 to 3 days. Follow-up vitamin D levels approximately 4 weeks later showed failure to achieve sufficiency levels (>20 ng/dL) in any patient. Unlike infants without liver disease, use of oral high-dose repletion therapy may not be adequate as treatment of vitamin D deficiency in the setting of cholestasis.

**Other**

**Title:** The social network of cystic fibrosis centre care and shared Pseudomonas aeruginosa strain infection: a cross-sectional analysis.

**Citation:** The Lancet. Respiratory medicine, Aug 2015, vol. 3, no. 8, p. 640-650 (August 2015)

**Author(s):** Kidd, Timothy J, Magalhães, Ricardo J Soares, Paynter, Stuart, Bell, Scott C, ACPinCF Investigator Group

**Title:** Mortality Risk and Pulmonary Function in Adults With Cystic Fibrosis at Time of Wait Listing for Lung Transplantation.

**Citation:** The Annals of thoracic surgery, Aug 2015, vol. 100, no. 2, p. 474-479 (August 2015)

**Author(s):** Hayes, Don, Kirkby, Stephen, Whitson, Bryan A, Black, Sylvestre M, Sheikh, Shahid I, Tobias, Joseph D, Mansour, Heidi M, Kopp, Benjamin T

**Title:** Moderate intensity exercise mediates comparable increases in exhaled chloride as albuterol in individuals with cystic fibrosis.

**Citation:** Respiratory medicine, Aug 2015, vol. 109, no. 8, p. 1001-1011 (August 2015)

**Author(s):** Wheatley, Courtney M, Baker, Sarah E, Morgan, Mary A, Martinez, Marina G, Liu, Bo, Rowe, Steven M, Morgan, Wayne J, Wong, Eric C, Karpen, Stephen R, Snyder, Eric M

**Title:** Risk factors for lung function decline in a large cohort of young cystic fibrosis patients.

**Citation:** Pediatric pulmonology, Aug 2015, vol. 50, no. 8, p. 763-770 (August 2015)

**Title:** Malabsorption blood test: Assessing fat absorption in patients with cystic fibrosis and pancreatic insufficiency.

**Citation:** Journal of clinical pharmacology, Aug 2015, vol. 55, no. 8, p. 854-865 (August 2015)

**Author(s):** Mascarenhas, Maria R, Mondick, John, Barrett, Jeffrey S, Wilson, Martha, Stallings, Virginia A, Schall, Joan I

**Title:** Geographic variations in cystic fibrosis: An analysis of the U.S. CF Foundation Registry.

**Citation:** Pediatric pulmonology, Aug 2015, vol. 50, no. 8, p. 754-762 (August 2015)

**Author(s):** Kopp, Benjamin T, Nicholson, Lisa, Paul, Grace, Tobias, Joseph, Ramanathan, Chandar, Hayes, Don
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