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Current Awareness Bulletin
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**Familial Chronic Thromboembolic Pulmonary Hypertension in a Pair of Japanese Brothers**
Masaharu Kataoka, MD, PhD, Yuichi Momose, MD, Yuki Aimi, MHS, Keiichi Fukuda, MD, PhD, Shinobu Gamou, PhD and Toru Satoh, MD, PhD
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**Unheated or No Humidification Bubble for Long-Term Nasal Low-Flow Oxygen: A Matter of Nasal Mucosa Response or Disease Progression**
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Selected Reports
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Pulmonary, Critical Care, and Sleep Pearls

A 34-Year-Old Pregnant Woman With Cough, Chest Pain, and a Left Upper Lobe Mass

ONLINE EXCLUSIVES

Phase III cystic fibrosis study of VX-661 in combination with ivacaftor to be terminated
16 August 2016 - Publisher: Biospace Inc.
The company (Vertex Pharmaceuticals) plans to cease the trial of VX-661 in combination with ivacaftor in people with one copy of the F508del mutation and one copy of a mutation that results in minimal CFTR protein function as the results did not warrant further study.
Read Summary

FDA grants Orphan Drug Designation to PUR1900 (inhaled itraconazole) for treatment of pulmonary fungal infections in cystic fibrosis patients
18 August 2016 - Publisher: Biospace Inc.
PUR1900 combines itraconazole with the dry powder iSPERSE technology, enabling patients to easily inhale the drug deep into their lungs, which should reduce the risk of side effects and drug interactions associated with oral itraconazole.
Read Summary

Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation - guidance (TA398)
Evidence-based recommendations on lumacaftor–ivacaftor (Orkambi) for treating cystic fibrosis in people 12 years and older who are homozygous for the F508del mutation
Read Summary

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

Cystic fibrosis: Nutritional issues
Authors: Robert D Baker, MD, PhD, Chris Coburn-Miller, MSRD, CSP, Susan S Baker, MD, PhD
Literature review current through: Aug 2016. | This topic last updated: May 27, 2016.
INTRODUCTION — Children and adolescents with cystic fibrosis (CF) frequently have growth
failure caused by the combination of malabsorption, increased energy needs, and reduced appetite. Nutrient delivery and correction of maldigestion and malabsorption are essential to achieve normal growth to support optimal pulmonary function and to prolong life.

The CF Foundation (CFF) patient registry has documented substantial improvement in life expectancy of patients with CF (figure 1) [1]. To a large degree, the longer life achieved by patients with CF can be ascribed to improved treatment of lung disease, pulmonary toilet, potent and tailored antibiotics, dornase alfa (DNase), and lung transplantation. However, greater emphasis on CF nutrition is considered important to improve longevity and quality of life. As a result, the CFF created a consensus report on practical aspects of nutrition in pediatric CF [2], and a more theoretic report on gastrointestinal outcomes and confounders in CF [3].

The evaluation, monitoring, and treatment of nutritional problems will be addressed here. The diagnosis and management of CF-related pancreatic insufficiency, and screening for CF-related comorbidities that affect nutritional status will also be discussed briefly here and in detail in separate topic reviews:

- (See “Cystic fibrosis: Assessment and management of pancreatic insufficiency”.)
- (See “Cystic fibrosis: Overview of gastrointestinal disease”.)
- (See “Cystic fibrosis-related diabetes mellitus”.)

Cystic fibrosis: Clinical manifestations and diagnosis

Author: Julie P Katkin, MD

Literature review current through: Aug 2016. | This topic last updated: Jun 08, 2016.

INTRODUCTION — Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among Caucasian populations, with a frequency of 1 in 2000 to 3000 live births. The median predicted survival for CF patients in the United States was 39.3 years (95% CI, 37.3-41.4) according to the Cystic Fibrosis Foundation 2014 Registry Report [1]. The usual presenting symptoms and signs include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels. However, many patients demonstrate mild or atypical symptoms, and clinicians should remain alert to the possibility of CF even when only a few of the usual features are present [2].

An overview of the clinical manifestations and diagnosis of CF will be presented here. The genetics, pathogenesis, and treatment of CF are reviewed separately. (See "Cystic fibrosis: Genetics and pathogenesis" and "Cystic fibrosis: Overview of the treatment of lung disease" and "Cystic fibrosis: Antibiotic therapy for lung disease" and "Cystic fibrosis: Overview of gastrointestinal disease".)
includes airway clearance techniques, pancreatic enzymes and other medications. Previous studies have found that compliance with this intensive treatment is poor, especially among adolescents. Because of both the nature and consequences of the illness and the relentless demands of the treatment, many individuals with cystic fibrosis have a poor quality of life. Anecdotal reports suggest that singing may provide both appropriate exercise for the whole respiratory system and a means of emotional expression which may enhance quality of life. This is an update of a previously published review.

**Objectives:** To evaluate the effects of singing as an adjunct therapy to standard treatment on the quality of life, morbidity, respiratory muscle strength and pulmonary function of children and adults with cystic fibrosis.

**Duration of intravenous antibiotic therapy in people with cystic fibrosis**

Amanda Plummer, Martin Wildman, Tim Gleeson  
**Online Publication Date:** September 2016  
**Background:** Respiratory disease is the major cause of mortality and morbidity in cystic fibrosis. Life expectancy of people with cystic fibrosis has increased dramatically in the last 40 years. One of the major reasons for this increase is the mounting use of antibiotics to treat chest exacerbations caused by bacterial infections. The optimal duration of intravenous antibiotic therapy is not clearly defined. Individuals usually receive intravenous antibiotics for 14 days, but treatment may range from 10 to 21 days. A shorter duration of antibiotic treatment risks inadequate clearance of infection which could lead to further lung damage. Prolonged courses of intravenous antibiotics are expensive and inconvenient and the incidence of allergic reactions to antibiotics also increases with prolonged courses. The use of aminoglycosides requires frequent monitoring to avoid some of their side effects. However, some organisms which infect people with cystic fibrosis are known to be multi-resistant to antibiotics, and may require a longer course of treatment. This is an update of previously published reviews.  
**Objectives:** To assess the optimal duration of intravenous antibiotic therapy for treating chest exacerbations in people with cystic fibrosis.

**Inhaled corticosteroids for cystic fibrosis**

Ian M Balfour-Lynn, Karen Welch  
**Online Publication Date:** August 2016  
**Background:** Reduction of lung inflammation is one of the goals of cystic fibrosis therapy. Inhaled corticosteroids are often used to treat children and adults with cystic fibrosis. The rationale for this is their potential to reduce lung damage arising from inflammation, as well as their effect on symptomatic wheezing. It is important to establish the current level of evidence for the risks and benefits of inhaled corticosteroids, especially in the light of their known adverse effects on growth. This is an update of a previously published review.  
**Objectives:** To assess the effectiveness of taking regular inhaled corticosteroids, compared to not taking them, in children and adults with cystic fibrosis.

**Drug therapies for reducing gastric acidity in people with cystic fibrosis**

Sze May Ng and Helen S Moore  
**Online Publication Date:** August 2016  
**Background:** Malabsorption of fat and protein contributes to poor nutritional status in people with cystic fibrosis. Impaired pancreatic function may also result in increased gastric
acidity, leading in turn to heartburn, peptic ulcers and the impairment of oral pancreatic enzyme replacement therapy. The administration of gastric acid-reducing agents has been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and gastrointestinal symptoms in people with cystic fibrosis. It is important to establish the evidence regarding potential benefits of drugs that reduce gastric acidity in people with cystic fibrosis. This is an update of a previously published review.

Objectives: To assess the effect of drug therapies for reducing gastric acidity for: nutritional status; symptoms associated with increased gastric acidity; fat absorption; lung function; quality of life and survival; and to determine if any adverse effects are associated with their use.

Latest 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: Bone health and disease in cystic fibrosis.

Citation: Paediatric respiratory reviews, Aug 2016, vol. 20 Suppl, p. 2-5

Author(s): Marquette, Malcolm, Haworth, Charles S

Abstract: Low bone mineral density is common in children and adults with CF. It has a multifactorial aetiology that includes direct effects of CFTR dysfunction on bone cell activity, as well as the secondary effects of CFTR dysfunction including pancreatic insufficiency (leading to malnutrition/malabsorption of fat soluble vitamins) and pulmonary infection (leading to systemic inflammation and increased bone resorption). Strategies to improve bone health in CF include optimising general CF nutritional and pulmonary care and the judicious use of bisphosphonates in selected patients. CFTR correctors/potentiators may
have positive impact on bone metabolism in people with CF. Crown Copyright © 2016. Published by Elsevier Ltd. All rights reserved

Title: An Open-Label Investigation of the Pharmacokinetics and Tolerability of Oral Cysteamine in Adults with Cystic Fibrosis

Citation: Clinical Drug Investigation, August 2016, vol./is. 36/8(605-612)

Author(s): Devereux G., Steele S., Griffiths K., Devlin E., Fraser-Pitt D., Cotton S., Norrie J., Chrystyn H., O’Neil D.

Abstract: Background and Objective: Cysteamine is licensed for use in nephropathic cystinosis but preclinical data suggest a role in managing cystic fibrosis (CF). This study aimed to determine whether oral cysteamine is absorbed in adult CF patients and enters the bronchial secretions. Tolerability outcomes were also explored. Methods: Patients >18 years of age, weighing >50 kg with stable CF lung disease were commenced on oral cysteamine bitartrate (Cystagon<sup>®</sup>) 450 mg once daily, increased weekly to 450 mg four times daily. Serial plasma cysteamine concentrations were measured for 24 h after the first dose. Participants were reviewed every week for 6 weeks, except at 4 weeks. Plasma cysteamine concentrations were measured 8 h after dosing when reviewed at 1, 2 and 3 weeks and 6 h after dosing when reviewed at 5 weeks. Sputum cysteamine concentration was also quantified at the 5-week assessment. Results: Seven of the ten participants reported adverse reactions typical of cysteamine, two participants discontinued intervention. Following the first 450-mg dose, mean (SD) maximum concentration (C<sub>max</sub>) was 2.86 (1.96) mg/l, the time corresponding to C<sub>max</sub> (T<sub>max</sub>) was 1.2 (0.7) h, the half-life (t<sub>1/2</sub>) was 3.7 (1.7) h, clearance (CL/F) 89.9 (30.5) L/h and volume of distribution (V<sub>d</sub>/F) 427 (129) L. Cysteamine appeared to accumulate in sputum with a median (interquartile range) sputum:plasma cysteamine concentration ratio of 4.2 (0.98-8.84). Conclusion: Oral cysteamine is absorbed and enters the bronchial secretions in patients with CF. Although adverse reactions were common, the majority of patients continued with cysteamine. Further trials are required to establish the risk benefit ratio of cysteamine therapy in CF.

Title: A novel treatment of cystic fibrosis acting on-target: Cysteamine plus epigallocatechin gallate for the autophagy-dependent rescue of class II-mutated CFTR

Citation: Cell Death and Differentiation, August 2016, vol./is. 23/8(1380-1393)


Abstract: We previously reported that the combination of two safe proteostasis regulators, cysteamine and epigallocatechin gallate (EGCG), can be used to improve deficient expression of the cystic fibrosis transmembrane conductance regulator (CFTR) in patients homozygous for the CFTR Phe508del mutation. Here we provide the proof-of-concept that this combination treatment restored CFTR function and reduced lung inflammation
provided that such mice were autophagy-competent. Primary nasal cells from patients bearing different class II CFTR mutations, either in homozygous or compound heterozygous form, responded to the treatment in vitro. We assessed individual responses to cysteamine plus EGCG in a single-centre, open-label phase-2 trial. The combination treatment decreased sweat chloride from baseline, increased both CFTR protein and function in nasal cells, restored autophagy in such cells, decreased CXCL8 and TNF-alpha in the sputum, and tended to improve respiratory function. These positive effects were particularly strong in patients carrying Phe508del CFTR mutations in homozygosity or heterozygosity. However, a fraction of patients bearing other CFTR mutations failed to respond to therapy. Importantly, the same patients whose primary nasal brushed cells did not respond to cysteamine plus EGCG in vitro also exhibited deficient therapeutic responses in vivo. Altogether, these results suggest that the combination treatment of cysteamine plus EGCG acts 'on-target' because it can only rescue CFTR function when autophagy is functional (in mice) and improves CFTR function when a rescuable protein is expressed (in mice and men). These results should spur the further clinical development of the combination treatment.

Title: Lumacaftor/Ivacaftor: A Review in Cystic Fibrosis.

Citation: Drugs, Aug 2016, vol. 76, no. 12, p. 1191-1201

Author(s): Deeks, Emma D

Abstract: Lumacaftor/ivacaftor (Orkambi™) is a fixed-dose tablet containing a corrector (lumacaftor) and potentiator (ivacaftor) of the cystic fibrosis transmembrane conductance regulator (CFTR) and is the first therapy approved to treat the underlying cause of cystic fibrosis in patients (aged ≥12 years) homozygous for the most common CFTR mutation, F508del. Lumacaftor improves the processing of F508del CFTR and its transport to the cell surface, while ivacaftor increases the channel’s open probability and transport of chloride. In two 24-week trials in the approved patient population (TRAFFIC and TRANSPORT), lumacaftor 400 mg plus ivacaftor 250 mg, administered every 12 h in combination with standard therapy, was associated with an ≈3 % statistically significant improvement in lung function relative to placebo (as measured by the percent predicted forced expiratory volume in 1 s). Lumacaftor plus ivacaftor did not significantly improve respiratory symptoms, although reduced pulmonary exacerbations to a clinically meaningful extent and, in one trial (TRANSPORT), significantly improved body mass index (BMI). In an ongoing extension of these studies (PROGRESS), lumacaftor plus ivacaftor provided clinical benefit over a further 72 weeks of treatment. Lumacaftor plus ivacaftor had an acceptable tolerability profile, with the most common adverse events being respiratory or gastrointestinal in nature. Thus, lumacaftor/ivacaftor expands the treatment options available for patients with cystic fibrosis homozygous for the F508del-CFTR mutation, although its precise place in clinical practice remains to be determined.

Title: Features of Severe Liver Disease With Portal Hypertension in Patients With Cystic Fibrosis.

Citation: Clinical gastroenterology and hepatology : the official clinical practice journal of
Liver disease is the third leading cause of death in patients with cystic fibrosis (CF), but features of patients with CF, severe liver disease, and portal hypertension have not been characterized fully. We performed a retrospective analysis of data from 561 patients with CF (63% male, 99% with pancreatic insufficiency), liver disease (hepatic parenchymal abnormalities consistent with cirrhosis, confirmed by imaging), and portal hypertension (esophageal varices, portosystemic collaterals, or splenomegaly), with no alternate causes of liver disease. All patients were enrolled in the Genetic Modifier Study of Severe CF Liver Disease at 76 international centers, from January 1999 through July 2013. Male patients were diagnosed with liver disease at a younger age than female patients (10 vs 11 y; P = .01). Splenomegaly was observed in 99% of patients and varices in 71%. Levels of liver enzymes were near normal in most patients. Thrombocytopenia affected 70% of patients and was more severe in patients with varices (88 × 10(9)/L vs 145 × 10(9)/L; P < .0001). Ninety-one patients received liver transplants (16%), at a median age of 13.9 years. Compared with patients who did not receive liver transplants, patients who received liver transplants had lower platelet counts (78 × 10(9)/L vs 113 × 10(9)/L; P < .0001), higher international normalized ratios (P < .0001), and lower levels of albumin (P = .0002). The aminotransferase to platelet ratio index (APRI) and fibrosis index based on 4 factor (FIB-4) values were higher than the diagnostic thresholds for CF liver disease in 96% and in 90% of patients, respectively. Patients who received liver transplants or who had varices had higher APRI and FIB-4 values than patients who did not. In patients with CF, severe liver disease develops early in childhood (approximately 10 years of age), and is more common in boys than in girls. Patients with varices and those who receive liver transplants have more abnormal platelet counts and APRI and FIB-4 scores. Copyright © 2016. Published by Elsevier Inc.

Title: Trabecular and cortical bone deficits are present in children and adolescents with cystic fibrosis

Citation: Bone, September 2016, vol./is. 90/(7-14)

Author(s): Kelly A., Schall J., Stallings V.A., Zemel B.S.

Abstract: Osteopenia and increased fracture rates are well-recognized in adults with CF, but neither the specific contributions of cortical and trabecular bone deficits to bone fragility nor their presence in youth with CF are well-characterized. This study sought to characterize cortical and trabecular volumetric bone mineral density (vBMD), geometry, and biomechanical competence in children with CF and determine their relationship to growth, body composition, and disease severity. Peripheral quantitative computerized tomography (pQCT) measures of total, cortical, and trabecular vBMD, cortical, muscle, and fat cross-sectional areas (CSA), periosteal and endosteal circumferences, and the polar unweighted section modulus (Zp) of the tibia were converted to age- and tibial length-adjusted Z-scores in 97 CF and 199 healthy children (aged 8-21 y). Effects of body composition and pulmonary
function (forced expiratory volume in 1 s, FEV1) upon pQCT outcomes were determined using linear regression. Children with CF (FEV1%-predicted: 84.4 + 19.7) had lower weight, height, BMI, and whole body lean mass (LBM)-Z and tibial length. Females with CF had lower (p < 0.01) total and trabecular vBMD; cortical, muscle, and fat CSA; Zp and periosteal circumference than females in the healthy reference group. These bone differences persisted after adjustment for BMI-Z and to a great extent following adjustment for muscle CSA. Males with CF had lower (p < 0.01) cortical, muscle, and fat CSA and their trabecular vBMD deficit approached significance (p = 0.069). Deficits were attenuated by adjustment for BMI-Z and to a greater extent adjustment for muscle CSA-Z. The relationship between FEV1%-predicted and pQCT outcomes persisted only in males following adjustment for age and BMI-Z. The CF cohort had lower tibial muscle CSA than expected for their LBM. In this relatively healthy, young CF cohort, deficits in trabecular and multiple cortical bone parameters were present. In females, deficits were greater at older ages and were not fully explained by alterations in body composition. In males worsening pulmonary function was associated with greater deficits that was not explained by increasing age or compromised nutritional status. The occurrence of these differences in CF youth highlights the importance of instituting measures to optimize peak bone mass early in the course of CF.

Title: Diagnosis and early life risk factors for bronchiectasis in cystic fibrosis: a review.

Citation: Expert review of respiratory medicine, Sep 2016, vol. 10, no. 9, p. 1003-1010

Author(s): Sly, Peter D, Wainwright, Claire E

Abstract: Lung disease in cystic fibrosis begins in early life with neutrophil-dominated inflammation and infection, is progressive and results in structural lung damage characterised by bronchial dilation and bronchiectasis. Preventative strategies must be employed in early life but require a better understanding of how bronchiectasis develops. In this review we have addressed the diagnosis and early life risk factors for bronchiectasis in young children with cystic fibrosis. A systematic review was not performed and the literature reviewed was known to the authors. Expert commentary: Bronchiectasis represents a process of progressive dilatation and damage of airway walls and is traditionally considered to be irreversible. Diagnosis is primarily by detecting a bronchial:arterial ratio of >1 on chest CT scan. Lung volume has a greater influence on airway diameter than on arterial making control of lung volume during scanning critical. Early life risk factors for the onset and progression bronchiectasis include: severe cystic fibrosis genotype; neutrophilic inflammation with free neutrophil elastase activity in the lung; and pulmonary infection. Bronchiectasis develops in the majority of children before they reach school age despite the best current therapy. To prevent bronchiectasis novel therapies are going to have to be given to infants.

Title: Healthcare resource utilization associated with ivacaftor use in patients with cystic fibrosis.

Citation: Journal of medical economics, Sep 2016, vol. 19, no. 9, p. 845-851
**Author(s):** Suthoff, Ellison D, Bonafede, Mac, Limone, Brendan, O'Callaghan, Lasair, Sawicki, Gregory S, Wagener, Jeffrey S

**Abstract:** Ivacaftor was approved in 2012 to treat patients with cystic fibrosis (CF) with specific CFTR gene mutations. The objective of this analysis was to analyze the impact of ivacaftor on health resource utilization through analysis of claims data. Patients diagnosed with CF aged ≥6 years prescribed ivacaftor between January 1, 2012 and July 31, 2014 with ≥12 months of continuous insurance coverage prior to and following the prescription were identified. All-cause and CF-specific healthcare resource utilization during the pre- and post-prescription periods and ivacaftor adherence levels were studied. The 79 identified patients had a mean age of 20.8 years, and 54% were female. The proportion of patients with inpatient admissions (all-cause and CF-related) was significantly higher in the pre index compared to post index period (p ≤ 0.05). Mean ivacaftor medication possession ratio was 0.8 (SD = 0.3), and 73% of patients had a medication possession ratio >0.80. Only a small number of patients met the inclusion criteria. Additionally, claims data may contain errors or inconsistencies and cannot be used to determine if medications were taken as prescribed. Ivacaftor therapy was associated with significant reductions in hospitalizations along with high rates of adherence to treatment over 12 months.

**Title:** SELF-ADMINISTRATION OF IN-PATIENT MEDICATIONS: A PILOT STUDY IN CHILDREN WITH CYSTIC FIBROSIS.

**Citation:** Archives of disease in childhood, Sep 2016, vol. 101, no. 9, p. e2.

**Author(s):** Khan, Khola, Harrington, Aoife, Pannu, Rupinder, Bentley, Sian, Makhecha, Sukeshi, Pentayya, Nimla, Pheasant, Clare

**Abstract:** Children with Cystic Fibrosis (CF) have complex medication regimens, where responsibility for administration usually lies with the parent/carer until the child is older and able to take over this role.1 On admission to hospital this role is usually undertaken by nurses, leaving patients/parents/carers feeling disempowered, and unprepared for discharge. All CF admissions to be offered the Self-Administration Of Medicines Scheme (SAM).> Empower patients/parents/carers with responsibility of administering their own medications> Reduce nursing time> Educate patients/parents/carers about their medications> Cost-saving by utilising Patients Own Medicines (PODs). A policy and training programme was developed and approved by the Trust’s Medicines Management Board. This provided a framework for staff to use so that they may:> Obtain consent> Evaluate and re-use PODs> Safely store and obtain supplies> Continuously negotiate accountability for administration with patient/parent/carer. The study was conducted over a 10 month period, where all families with CF admitted, were assessed for participation in SAM. The nursing teams acted as the primary assessors for SAM and any concerns were referred to the paediatric CF multidisciplinary team. To evaluate the pilot, families were given questionnaires to establish their views about the scheme. Nurses were asked to feedback if SAM decreased time for medication administration. To evaluate the associated cost-saving, data on PODs suitable for re-use was collected. 159 children with CF were admitted to the ward, 95 (60%) were assessed to participate in the scheme and 64 (40%) of these did not
join. Reasons for not joining included 32 (50%) short admissions, 13 (20%) refused, 5 (8%) patients were seriously ill and 14 (22%) had 'other' reasons. Those who joined the scheme received questionnaires and 31 (33%) of these were completed. All welcomed the scheme and stated that they would take part again with the main benefits cited as not needing to wait for nurses to administer medications, greater independence and the ability to maintain the same routine as home. When asked what participants would change, 16 (52%) stated nothing, 10 (32%) wanted the assessment process to allow for faster progression through the levels of SAM, 4 (13%) asked for larger medication lockers and 1 (3%) wanted better communication about new medications. 30 nursing questionnaires were completed and highlighted that nursing staff spent less time on administering medicines. Nurses also stated that medication administration was less pressurised as double-checking of doses could be performed with the participant, rather than another nurse. Their main concern was the extra documentation required for SAM. Where PODs were used for patients, the average cost saving per patient over a 3 month period was £1023. The pilot scheme has been well received by staff and patients/parents/carers, allowing greater engagement in the administration of medicines and cost-savings. As a result of this, the SAM scheme will be extended to the remaining patients on the ward. Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://www.bmj.com/company/products-services/rights-and-licensing/

Title: Reduced bone volumetric density and weak correlation between infection and bone markers in cystic fibrosis adult patients

Citation: Osteoporosis International, September 2016, vol./is. 27/9(2803-2813)

Author(s): Gensburger D., Boutroy S., Chapurlat R., Nove-Josserand R., Roche S., Rabilloud M., Durieu I.

Abstract: Summary: In our current adult CF population, low BMD prevalence was only 20 %, lower than that historically described. We found a mild increase of serum RANK-L levels, independent from the bone resorption level. The increased fracture risk in CF may be explained by a lower tibial cortical thickness and total vBMD. Introduction: Bone disease is now well described in cystic fibrosis (CF) adult patients. CF bone disease is multifactorial but many studies suggested the crucial role of inflammation. The objectives of this study were, in a current adult CF population, to assess the prevalence of bone disease, to examine its relationship with infections and inflammation, and to characterize the bone microarchitecture using high resolution peripheral scanner (HR-pQCT). Methods: Fifty-six patients (52 % men, 26 +/- 7 years) were assessed in clinically stable period, during a respiratory infection, and finally 14 days after the end of antibiotic therapy. At each time points, we performed a clinical evaluation, lung function tests, and biochemical tests. Absorptiometry and dorso-lumbar radiographs were also performed. A subgroup of 40 CF patients (63 % men, 29 +/- 6 years) underwent bone microarchitecture assessment and was age- and gender-matched with 80 healthy controls. Results: Among the 56 CF patients, the prevalence of low areal BMD (T-score < -2 at any site), was 20 % (95 % CI: [10.2 %; 32.4 %]). After infections, serum RANK-L (+24 %, p = 0.08) and OPG (+13 %, p = 0.04) were increased with a stable ratio. Microarchitectural differences were mostly observed at the distal tibia, with lower total and cortical vBMD and trabecular thickness (respectively -9.9, -3.0, and -5
% p < 0.05) in CF patients compared to controls, after adjustment for age, gender, weight, and height. Conclusions: In this study, bone disease among adult CF patients was less severe than that previously described with only 20% of CF patients with low BMD. We found a mild increase of biological marker levels and an impaired volumetric density of the tibia that may explain the increased fracture risk in CF population.

Title: Heart involvement in cystic fibrosis: A specific cystic fibrosis-related myocardial changes?

Citation: Respiratory Medicine, September 2016, vol./is. 118/(31-38)

Author(s): Labombarda F., Saloux E., Brouard J., Bergot E., Milliez P.

Abstract: Cystic fibrosis is a complex multi-systemic chronic disease characterized by progressive organ dysfunction with development of fibrosis, possibly affecting the heart. Over the last four decades pathological, experimental, and clinical evidence points towards the existence of a specific myocardial involvement in cystic fibrosis. Multi-modality cardiac imaging, especially recent echocardiographic techniques, evidenced diastolic and/or systolic ventricular dysfunction in cystic fibrosis leading to the concept of a cystic fibrosis-related cardiomyopathy. Hypoxemia and inflammation are among the most important factors for heart involvement in cystic fibrosis. Cystic Fibrosis Transmembrane Regulator was found to be involved in the regulation of cardiomyocyte contraction and may also account for cystic fibrosis-related myocardial dysfunction. This review, mainly focused on echocardiographic studies, seeks to synthesize the existing literature for and against the existence of heart involvement in cystic fibrosis, its mechanisms and prognostic implications. Careful investigation of the heart function may be helpful for risk stratification and therapeutic decisions in patients with cystic fibrosis.

Title: Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis

Citation: Expert Opinion on Orphan Drugs, August 2016, vol./is. 4/8(875-884)

Author(s): De Soyza A., Aksamit T.

Abstract: Introduction: Non-cystic fibrosis bronchiectasis (NCFB) is an increasingly prevalent chronic respiratory disease, characterized by a cycle of infection and inflammation. It is progressive and associated with poor quality of life, increasing healthcare costs and mortality. Inhaled antibiotics offer the potential to decrease long-term bacterial burden and reduce or delay exacerbations which are a key driver of disease progression and healthcare costs. Currently however, no inhaled treatments are approved for the prevention of exacerbations in patients with NCFB. Areas covered: We consider current evidence for inhaled treatment in NCFB and discuss ciprofloxacin dry powder for inhalation (DPI), a novel treatment using PulmoSphereTM technology, delivered via a pocket-sized, breath-actuated inhaler. We also detail the unique features of the ongoing Phase 3 RESPIRE trials for ciprofloxacin DPI. Expert opinion: The simplicity of use and short administration time could make ciprofloxacin DPI an attractive treatment option with potential to reduce the number of exacerbations in patients with NCFB. The RESPIRE studies are the largest carried out in
NCFB to date and will provide a benchmark for future trial design. If approved, following successful Phase 3 data, ciprofloxacin DPI has potential for significant use in NCFB due to its good tolerability and low treatment burden.

**Title:** Bone health and disease in cystic fibrosis.

**Citation:** Paediatric respiratory reviews, Aug 2016, vol. 20 Suppl, p. 2-5

**Author(s):** Marquette, Malcolm, Haworth, Charles S

**Abstract:** Low bone mineral density is common in children and adults with CF. It has a multifactorial aetiology that includes direct effects of CFTR dysfunction on bone cell activity, as well as the secondary effects of CFTR dysfunction including pancreatic insufficiency (leading to malnutrition/malabsorption of fat soluble vitamins) and pulmonary infection (leading to systemic inflammation and increased bone resorption). Strategies to improve bone health in CF include optimising general CF nutritional and pulmonary care and the judicious use of bisphosphonates in selected patients. CFTR correctors/potentiators may have positive impact on bone metabolism in people with CF. Crown Copyright © 2016. Published by Elsevier Ltd. All rights reserved.

**Title:** Long-term effects of azithromycin in patients with cystic fibrosis

**Citation:** Respiratory Medicine, August 2016, vol./is. 117/(1-6)

**Author(s):** Samson C., Tamalet A., Thien H.V., Taytard J., Perisson C., Nathan N., Clement A., Boelle P.-Y., Corvol H.

**Abstract:** Background Low-dose azithromycin has beneficial effects on severity of the lung disease in cystic fibrosis (CF) patients for a period of 6-12 months after initiation of the treatment. Although its impact in the longer term is uncertain, this treatment is frequently used chronically. The aim of this retrospective study was to investigate the effects of low-dose azithromycin treatment on the progression of CF lung disease in patients treated for more than 12 months. Methods All of the CF patients followed in our pediatric center and who had been on low-dose azithromycin for more than 12 sequential months were included. The clinical data were collected for one year before and three years after the initiation of the azithromycin treatment. These data comprised lung function analyses, rates of exacerbations and of antibiotic courses, and changes in the airways' bacterial colonization. Results A total of 68 patients were included (mean age: 9.95 yrs (3.61)). After 12 months, significant reductions in the numbers of pulmonary exacerbations and antibiotic courses were present. However, this effect was not maintained in the subsequent periods, during which increased rates of both pulmonary exacerbations and antibiotic courses were observed. The lung function decline was not modified during the treatment, and a decreasing time-dependent trend typical of CF was observed for the various parameters. No differences in the airway colonization by pathogens such as Pseudomonas aeruginosa and methicillin-sensitive and/or -resistant Staphylococcus aureus were observed during the treatment. However, isolated Staphylococcus aureus strains became resistant to macrolides after 6 months of azithromycin and remained resistant thereafter. Conclusions No clinical
The benefits of low-doses azithromycin were present after one year of treatment in young CF patients. Selection for macrolide-resistant strains of bacteria occurred, which should lead to a reconsideration of the duration of azithromycin treatment in CF.

**Title:** Anti-coagulant therapy with dabigatran for cystic fibrosis patients.

**Citation:** Pediatric Pulmonology, Aug 2016, vol. 51, no. 8, p. E29., 1099-0496 (August 2016)

**Author(s):** Bansal, Manvi, Ren, Clement L

**Abstract:** Patients with cystic fibrosis (CF) are at increased risk of venous thromboembolism, especially in association with central venous catheter use. Coumarin drugs and low molecular weight heparin are frequently used for anti-coagulant therapy, but are more challenging to administer in CF patients. Dabigatran, an oral thrombin antagonist, is an alternative anti-coagulant medication, but its use in CF has not been reported. We describe our experience in successfully using dabigatran for long-term anti-coagulation therapy in two CF patients. Our experience suggests that dabigatran can serve as an option for anticoagulation therapy in CF. Pediatr Pulmonol. 2016;51:E29-E30. © 2016 Wiley Periodicals, Inc. © 2016 Wiley Periodicals, Inc.

## Microbiological

**Title:** Increased prevalence of Pneumocystis jirovecii colonisation in acute pulmonary exacerbations of cystic fibrosis

**Citation:** Journal of Infection, July 2016, vol./is. 73/1(1-7)

**Author(s):** Green H.D., Bright-Thomas R.J., Mutton K.J., Guiver M., Jones A.M.

**Abstract:** Objectives: This study examined the prevalence of Pneumocystis jirovecii in the sputum of adults with cystic fibrosis during clinical stability and acute pulmonary exacerbation. Methods: This was a prospective, longitudinal observational study of patients attending the Manchester Adult Cystic Fibrosis Centre. Sputum samples were analysed for P. jirovecii DNA using PCR at enrolment and up to 5 follow-up visits. Patients were classified as stable or exacerbating using a modified Fuch's pulmonary exacerbation score. Results: 226 samples were tested from 111 patients. P. jirovecii was more likely to be detected in samples at acute pulmonary exacerbation (7/76 (9.2%)) compared with stable visits (3/150 (2%)), p = 0.03. P. jirovecii was detected less frequently if patients had received co-trimoxazole within 3 months of sample collection (0% versus 29.7%, p = 0.03). Conclusions: Prevalence of P. jirovecii in stable patients is low, but P. jirovecii is detected in approximately 1 in 10 patients experiencing an acute pulmonary exacerbation.

**Title:** Gaseous nitric oxide to treat antibiotic resistant bacterial and fungal lung infections in patients with cystic fibrosis: a phase I clinical study
Title: Does beta-cell autoimmunity play a role in cystic fibrosis-related diabetes? Analysis based on the German/Austrian Diabetes patienten verlaufsdokumentation registry

Citation: Diabetes Care, August 2016, vol./is. 39/8(1338-1344)

Author(s): Konrad K., Kapellen T., Lilienthal E., Prinz N., Bauer M., Thon A., Rietschel E., Wiemann D., Holl R.W.

Abstract: OBJECTIVE: Research on beta-cell autoimmunity in cystic fibrosis (CF)-related diabetes (CFRD) is still rare. We aimed to analyze the frequency of beta-cell autoimmunity and the influence on age at diabetes onset, insulin requirement, type of insulin therapy, and hypoglycemic or ketoacidotic events in patients with CFRD compared with antibody-negative patients with CFRD in the Diabetes Patienten Verlaufsdokumentation (DPV) registry. RESEARCH DESIGN AND METHODS: We analyzed data of 837 patients with CFRD in the German/Austrian DPV database by multivariable mixed-regression modeling. RESULTS: In our cohort, 8.5% of patients with CFRD (n = 72) were found to be beta-cell antibody positive. There was a female preponderance in this patient group: 65.3 vs. 57.6%. Diabetes onset (median [interquartile range]) was earlier (14.00 [10.15-15.90] vs. 16.10 [13.50-21.20] years; P < 0.005), and insulin dose/kg body weight was higher (0.95 [0.61-1.15] vs. 0.67 [0.33-1.04] IU/kg; P < 0.05). There were also differences in the type of insulin treatment. Insulin pump therapy was used significantly more often in patients with CFRD with beta-cell autoimmunity (18.2 vs. 6.4%; P <0.05). The differences for multiple daily injections (ICT) and conventional therapy (CT) were not significant (ICT: 67.7 vs. 79.0%; CT: 15.2 vs. 14.6). Oral antidiabetic agents were rarely used in both groups. Rate of severe hypoglycemia with coma and rate of ketoacidosis were higher in antibody-positive patients (hypoglycemia with coma: 8.0 vs. 1.4, P < 0.05; ketoacidosis: 9.3 vs. 0.9, P < 0.05). CONCLUSIONS: Presence of beta-cell
autoantibodies in our cohort of patients with CFRD (8.5%) appeared to be greater than in the general population and was associated with female sex, earlier onset of diabetes, and higher insulin requirement. Insulin pump therapy was used significantly more often in patients with beta-cell antibodies. Severe hypoglycemia and ketoacidosis were significantly more frequent in CFRD with beta-cell autoimmunity compared with beta-cell antibody-negative patients with CFRD.

Title: Young adults with cystic fibrosis have altered trabecular microstructure by ITS-based morphological analysis.

Citation: Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, Aug 2016, vol. 27, no. 8, p. 2497-2505


Abstract: Young adults with cystic fibrosis have compromised plate-like trabecular microstructure, altered axial alignment of trabeculae, and reduced connectivity between trabeculae that may contribute to the reduced bone strength and increased fracture risk observed in this patient population. The risk of fracture is increased in patients with cystic fibrosis (CF). Individual trabecular segmentation (ITS)-based morphological analysis of high-resolution peripheral quantitative computed tomography (HR-pQCT) images segments trabecular bone into individual plates and rods of different alignment and connectivity, which are important determinants of trabecular bone strength. We sought to determine whether alterations in ITS variables are present in patients with CF and may help explain their increased fracture risk. Thirty patients with CF ages 18-40 years underwent DXA scans of the hip and spine and HR-pQCT scans of the radius and tibia with further assessment of trabecular microstructure by ITS. These CF patients were compared with 60 healthy controls matched for age (±2 years), race, and gender. Plate volume fraction, thickness, and density as well as plate-plate and plate-rod connectivity were reduced, and axial alignment of trabeculae was lower in subjects with CF at both the radius and the tibia (p < 0.05 for all). At the radius, adjustment for BMI eliminated most of these differences. At the tibia, however, reductions in plate volume fraction and number, axially aligned trabeculae, and plate-plate connectivity remained significant after adjustment for BMI alone and for BMI and aBMD (p < 0.05 for all). Young adults with CF have compromised plate-like and axially aligned trabecular morphology and reduced connectivity between trabeculae. ITS analysis provides unique information about bone integrity, and these trabecular deficits may help explain the increased fracture risk in adults with CF not accounted for by BMD and/or traditional bone microarchitecture measurements.

Title: Is genotyping of single isolates sufficient for population structure analysis of Pseudomonas aeruginosa in cystic fibrosis airways?

Citation: BMC Genomics, August 2016, vol./is. 17/1(no pagination)

Abstract: Background: The primary cause of morbidity and mortality in cystic fibrosis (CF) patients is lung infection by Pseudomonas aeruginosa. Therefore much work has been done to understand the adaptation and evolution of P. aeruginosa in the CF lung. However, many of these studies have focused on longitudinally collected single isolates, and only few have included cross-sectional analyses of entire P. aeruginosa populations in sputum samples. To date only few studies have used the approach of metagenomic analysis for the purpose of investigating P. aeruginosa populations in CF airways. Results: We analysed five metagenomes together with longitudinally collected single isolates from four recently chronically infected CF patients. With this approach we were able to link the clone type and the majority of SNP profiles of the single isolates to that of the metagenome(s) for each individual patient. Conclusion: Based on our analysis we find that when having access to comprehensive collections of longitudinal single isolates it is possible to rediscover the genotypes of the single isolates in the metagenomic samples. This suggests that information gained from genome sequencing of comprehensive collections of single isolates is satisfactory for many investigations of adaptation and evolution of P. aeruginosa to the CF airways.

Title: Impact of gene editing on the study of cystic fibrosis.

Citation: Human genetics, Sep 2016, vol. 135, no. 9, p. 983-992

Author(s): Harrison, Patrick T, Sanz, David J, Hollywood, Jennifer A

Abstract: Cystic fibrosis (CF) is a chronic and progressive autosomal recessive disorder of secretory epithelial cells, which causes obstructions in the lung airways and pancreatic ducts of 70,000 people worldwide (for recent review see Cutting Nat Rev Genet 16(1):45-56, 2015). The finding that mutations in the CFTR gene cause CF (Kerem et al. Science 245(4922):1073-1080, 1989; Riordan et al. Science 245(4922):1066-1073, 1989; Rommens et al. Science 245(4922):1059-1065, 1989), was hailed as the very happy middle of a story whose end is a cure for a fatal disease (Koshland Science 245(4922):1029, 1989). However, despite two licensed drugs (Randall et al. N Engl J Med 365(18):1663-1672, 2011; Wainwright et al. N Engl J Med 373(3):220-231, 2015), and a formal demonstration that repeated administration of CFTR cDNA to patients is safe and effects a modest but significant stabilisation of disease (Alton et al. Lancet Respir Med 3(9):684-691, 2015), we are still a long way from a cure, with many patients taking over 100 tablets per day, and a mean age at death of 28 years. The aim of this review is to discuss the impact on the study of CF of gene-editing techniques as they have developed over the last 30 years, up to and including the possibility of editing as a therapeutic approach.

Title: The success of the different eradication therapy regimens for Pseudomonas aeruginosa in cystic fibrosis

Citation: Journal of Clinical Pharmacy and Therapeutics, August 2016, vol./is. 41/4(419-423)

Author(s): Emiralioglu N., Yalcin E., Meral A., Sener B., Dogru D., Ozcelik U., Kiper N.
Abstract: What is known and objective: Antibiotic therapy aimed at eradicating Pseudomonas aeruginosa (Pa), and improved regimens to treat chronic Pa infection have played a major role in increasing the median survival of patients with cystic fibrosis (CF). However, different clinical centres use varying eradication regimens. The aim of this study was to evaluate the efficacy of multiple eradication treatments against initial Pa infection and to determine the factors affecting the treatment success. Methods: This study was conducted at the Hacettepe University Department of Pediatric Pulmonology. We examined the demographic, clinical and microbiological data of 146 CF patients with first Pa isolation in sputum culture from all 630 patients with CF studied. We aimed to identify the factors that affected the eradication of Pa infection and assessed the success rates of the different eradication protocols used. Results and discussion: The mean age of the patients was 71.5 months (2 months-29 years) when Pa was first isolated; the mean duration from CF diagnosis to first Pa isolation was 40 months. The most common treatment choices consisted of 2 weeks of intravenous ceftazidim-amikacin for severe exacerbation or 3 months of inhaled gentamycin combined with 3 weeks of oral ciprofloxacin for mild exacerbation in asymptomatic patients. With these treatment regimens, eradication was observed in 47 patients (32%), intermittent colonization in 42 patients (28%) and chronic colonization in 57 patients (40%). Forced expiratory volume in 1 s decline was statistically significant in patients with chronic colonization (P = 0.006). Being older than 2 years of age or having symptoms at the first Pa isolation was negatively associated with the treatment success. What is new and conclusion: Early antibiotic treatment for Pa can eradicate the bacteria, prevent or delay the development of chronic colonization and improve the general health status. The acquisition of Pa at an older age and having symptoms at first isolation negatively affected the success of eradication. The use of intravenous antibiotics may increase the efficacy of therapy. Inhaled tobramycin for Pa eradication was approved for reimbursement in Turkey from August 2014. The relatively low eradication rate may be explained by a lack of reimbursement for inhaled tobramycin and colistin in our country during the study period.

Psychology

Title: Attitudes and decision making related to pregnancy among young women with cystic fibrosis.

Citation: Maternal and Child Health Journal, Aug 2016, (Aug 16, 2016)

Author(s): Kazmerski, Traci M., Gmelin, Theresa, Slocum, Breonna, Borrero, Sonya, Miller, Elizabeth

Abstract: Introduction The number of female patients with CF able to consider pregnancy has increased with improved therapies. This study explored attitudes and decision making regarding pregnancy among young women with CF. Methods Twenty-two women with CF ages 18–30 years completed semi-structured, in-person interviews exploring experiences with preconception counseling and reproductive care in the CF setting. Interviews were audio-recorded, transcribed, and coded using a thematic analysis approach. Results
Participants indicated CF is a major factor in pregnancy decision making. Although women acknowledged that CF influences attitudes toward pregnancy, many expressed confusion about how CF can affect fertility/pregnancy. Many perceived disapproval from CF providers regarding pregnancy and were dissatisfied with reproductive care in the CF setting. Discussion Young female patients with CF reported poor understanding of the effect of CF on fertility and pregnancy and limited preconception counseling in CF care. Improvements in female sexual and reproductive health care in CF are warranted. (PsycINFO Database Record (c) 2016 APA, all rights reserved)(journal abstract)

Nutrition

Title: Dietary intake and nutritional status of micronutrients in adults with cystic fibrosis in relation to current recommendations

Citation: Clinical Nutrition, August 2016, vol./is. 35/4(775-782)

Author(s): Li L., Somerset S.

Abstract: An increased prevalence of cystic fibrosis (CF) related complications such as impaired bone health and diabetes has accompanied increased survival of patients with CF. This review was conducted to determine the extent to which adults with CF are meeting current nutrition recommendations for micronutrients in association with CF-related complications management. Although dietary intake and nutritional status in CF has improved significantly in recent decades, micronutrient status seems to have diverged. While vitamin A and E intakes appear adequate, frequent vitamin D and K deficiency/insufficiency and compromised bone health in CF, occurs despite supplementation. Although deficiency of water-soluble vitamins and minerals is uncommon, ongoing surveillance will enhance overall health outcomes, particularly in cases of CF-related liver disease and deteriorated lung function and bone health. Salt and fluid status in CF may also need attention due to diminished thirst sensation and voluntary rehydration. Further investigation in micronutrient status optimisation in CF will inform the development of more effective and targeted nutrition therapies to enable integration of more refined recommendations for micronutrient intakes in CF based on individual needs and disease progression.

Other

Title: Cystic Fibrosis Papers of the Year 2015.

Citation: Paediatric respiratory reviews, Aug 2016, vol. 20 Suppl, p. 18-20

Author(s): Doull, Iolo

Abstract: Studies published in the last year have expanded our knowledge of potential
disease modifying agents in the treatment of class II, III and IV CFTR mutations, and included the first report of an efficacious gene therapy for CF. There is also an important message on increasing use of conventional chronic therapies even in milder disease, and the pernicious effect of chronic infection on pulmonary function. Copyright © 2016 Elsevier Ltd. All rights reserved.

**Title:** Progress in therapies for cystic fibrosis.

**Citation:** The Lancet. Respiratory medicine, Aug 2016, vol. 4, no. 8, p. 662-674

**Author(s):** De Boeck, Kris, Amaral, Margarida D

**Abstract:** Standard follow-up and symptomatic treatment have allowed most patients with cystic fibrosis to live to young adulthood. However, many patients still die prematurely from respiratory insufficiency. Hence, further investigations to improve these therapies are important and might have relevance for other diseases - eg, exploring how to increase airway hydration, how to safely downscale the increased inflammatory response in the lung, and how to better combat lung infections associated with cystic fibrosis. In parallel, development of modulators that target the underlying dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) is fast moving forward. Existing treatments are specific to certain mutations, or mutation class, in CFTR. An effective, although not yet entirely corrective, treatment is available for patients with class III mutations, and a treatment with modest effectiveness is available for patients who are homozygous for Phe508del, albeit at a very high cost. Corrective treatments that are non-specific to mutation class and thus applicable to all patients - eg, gene therapy, cell-based therapies, and activation of alternative ion channels that bypass CFTR - are being explored, but they are still in early stages of development. In view of the large number of patients with very rare mutations, a plan to advance personalised biomarkers to predict treatment effect is also being investigated and validated. Copyright © 2016 Elsevier Ltd. All rights reserved.

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**Title:** Pneumothorax in cystic fibrosis: beyond the guidelines.

**Citation:** Paediatric respiratory reviews, Aug 2016, vol. 20 Suppl, p. 30-33

**Author(s):** Lord, Robert W, Jones, Andrew M, Webb, A Kevin, Barry, Peter J

**Abstract:** Pneumothorax is a serious but common complication in patients with cystic fibrosis (CF). It has adverse prognostic implications as well as associations with subsequent reduction in lung function and significant risk of recurrence. Management dilemmas frequently occur that are beyond current guidelines. We review the evidence and highlight management difficulties in pneumothoraces in CF. Copyright © 2016 Elsevier Ltd. All rights reserved.

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**Title:** Socioeconomic status and health outcomes: cystic fibrosis as a model.

**Citation:** Expert review of respiratory medicine, Sep 2016, vol. 10, no. 9, p. 967-977
Author(s): Oates, Gabriela R, Schechter, Michael S

Abstract: Socioeconomic status (SES), which indicates one's access to financial, educational, and social resources, is a powerful determinant of health outcomes in multiple chronic diseases. Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in a single gene. Although life expectancy and quality of life for patients with CF have improved exponentially, disease severity varies substantially, even among individuals with identical genotypes. CF disease progression and outcomes are influenced by a number of nongenetic factors, such as material well-being, educational attainment, living and working conditions, physical environment and exposures, family environment, social support, health behaviors, and health care. This review discusses pathways by which financial, educational, and social resources are translated into health advantages in CF. Expert commentary: To achieve equitable CF outcomes, the contribution of nongenetic factors must be emphasized, highlighting the mechanisms through which the social and physical environments influence disease variability.

Title: Short-Term Effect of Different Physical Exercises and Physiotherapy Combinations on Sputum Expectoration, Oxygen Saturation, and Lung Function in Young Patients with Cystic Fibrosis

Citation: Lung, August 2016, vol./is. 194/4(659-664)

Author(s): Kriemler S., Radtke T., Christen G., Kerstan-Huber M., Hebestreit H.

Abstract: Purpose: Exercise and chest physiotherapy are integral components of cystic fibrosis (CF) care. We aimed to determine short-term effects of a combined exercise-physiotherapy intervention, using either trampoline or cycle exercises compared to billiard (sham training) on sputum production, oxygen saturation (SaO<sub>2</sub>) and short-term lung function in participants with CF. Methods: Twelve 16- to 29-year-old individuals with CF were randomly allocated to all 3 interventions on non-consecutive days of a week with exercise and physiotherapy parts lasting 30 min and breaks of 30 min after each procedure. Sputum weight (g) and lung function were measured before and after the exercise + rest and physiotherapy + rest interventions and SaO<sub>2</sub> was measured before and after the combined interventions. Differences in outcome measures between the different exercises and combined exercise/physiotherapy regimens were analyzed by univariate multilevel linear regression. Results: Sputum expectoration during and after trampoline exercise was significantly higher than with and after billiard (P = 0.021), and tended to be higher than with and after cycling of similar cardiovascular intensity (P = 0.074). Sputum weights during and after physiotherapy were comparable among sessions, irrespective of the prior exercise or sham procedure. The increase in SaO<sub>2</sub> was significantly higher after the combined trampoline/physiotherapy (1.7 +/- 0.9%) and cycling/physiotherapy (1.8 +/- 0.8%) sessions compared to billiard/physiotherapy (0.5 +/- 1.8%, P = 0.011 and P = 0.007). No effects were observed on lung function. Conclusions: Exercise followed by physiotherapy has an additive effect on sputum production in participants with CF and leads to improved oxygen saturation. Exercises with increased ventilation combined with mechanical vibration seem to be most efficient.
Title: Is deafness mutation screening required in cystic fibrosis patients?

Citation: Paediatric respiratory reviews, Aug 2016, vol. 20 Suppl, p. 24-26

Author(s): Abusamra, Rania, McShane, Donna

Abstract: Aminoglycosides are widely used in cystic fibrosis management. The m.1555A>G mutation predisposes to aminoglycoside ototoxicity. It may cause later onset hearing loss in the absence of aminoglycosides use and gradual hearing loss may be an inevitable consequence of the mutation. Given that aminoglycoside therapy forms the backbone of IV protocols in CF, this article recommends screening for this mutation to allow informed decision-making prior to aminoglycoside administration, to avoid preventable deafness. Crown Copyright © 2016. Published by Elsevier Ltd. All rights reserved.

Title: Progress in therapies for cystic fibrosis.

Citation: The Lancet. Respiratory medicine, Aug 2016, vol. 4, no. 8, p. 662-674

Author(s): De Boeck, Kris, Amaral, Margarida D

Abstract: Standard follow-up and symptomatic treatment have allowed most patients with cystic fibrosis to live to young adulthood. However, many patients still die prematurely from respiratory insufficiency. Hence, further investigations to improve these therapies are important and might have relevance for other diseases—eg, exploring how to increase airway hydration, how to safely downscale the increased inflammatory response in the lung, and how to better combat lung infections associated with cystic fibrosis. In parallel, development of modulators that target the underlying dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) is fast moving forward. Existing treatments are specific to certain mutations, or mutation class, in CFTR. An effective, although not yet entirely corrective, treatment is available for patients with class III mutations, and a treatment with modest effectiveness is available for patients who are homozygous for Phe508del, albeit at a very high cost. Corrective treatments that are non-specific to mutation class and thus applicable to all patients—eg, gene therapy, cell-based therapies, and activation of alternative ion channels that bypass CFTR—are being explored, but they are still in early stages of development. In view of the large number of patients with very rare mutations, a plan to advance personalised biomarkers to predict treatment effect is also being investigated and validated. Copyright © 2016 Elsevier Ltd. All rights reserved.
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