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New Cochrane Library Systematic Reviews on Cystic Fibrosis

Ursodeoxycholic acid for cystic fibrosis-related liver disease

Katharine Cheng; Deborah Ashby; Rosalind L Smyth

Published 15th Dec 2014

Abnormal biliary secretion leads to the thickening of bile and the formation of plugs within the bile ducts; the consequent obstruction and abnormal bile flow ultimately results in the development of cystic fibrosis-related liver disease. This condition peaks in adolescence with up to 20% of adolescents with cystic fibrosis developing chronic liver disease. Early changes in the liver may ultimately result in end-stage liver disease with people needing transplantation. One therapeutic option currently used is ursodeoxycholic acid. **Objectives:** To analyse evidence that ursodeoxycholic acid improves indices of liver function, reduces the risk of developing chronic liver disease and improves outcomes in general in cystic fibrosis.


Vitamin E supplementation in people with cystic fibrosis

Peter O Okebukola; Sonal Kansra; Joanne Barrett

Published 9th Dec 2014

People with cystic fibrosis are at an increased risk of fat-soluble vitamin deficiency including vitamin E. Vitamin E deficiency can cause a host of conditions such as haemolytic anaemia, cerebellar ataxia and cognitive difficulties. Vitamin E supplementation is widely recommended in cystic fibrosis and aims to ameliorate this deficiency. **Objectives:** To determine the effects of any level of vitamin E supplementation on the frequency of vitamin E deficiency disorders in people with cystic fibrosis.


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

Valerie Waters; Felix Ratjen

Published 3rd Dec 2014

Nontuberculous mycobacteria are mycobacteria, other than those in the *Mycobacterium tuberculosis* complex, and are commonly found in the environment. Nontuberculous mycobacteria species (most commonly *Mycobacterium avium* complex and *Mycobacterium abscessus*) are isolated from the respiratory tract of approximately 5% to 20% of individuals with cystic fibrosis; they can
cause lung disease in people with cystic fibrosis leading to more a rapid decline in lung function and even death in certain circumstances. Although there are guidelines for the antimicrobial treatment of nontuberculous mycobacteria lung disease, these recommendations are not specific for people with cystic fibrosis and it is not clear which antibiotic regimen may be the most effective in the treatment of these patients. **Objectives:** The objective of our review was to compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, for nontuberculous mycobacteria lung infections in people with cystic fibrosis. The primary objective was to assess the effect of treatment on lung function and pulmonary exacerbations and to quantify adverse events. The secondary objectives were to assess treatment effects on the amount of bacteria in the sputum, quality of life, mortality, nutritional parameters, hospitalizations and use of oral antibiotics.


**New Activity in UptoDate and DynaMed**

*Continuous oral antistaphylococcal antibiotic prophylaxis may not be more effective than treatment as needed for improving lung function, reducing hospital admissions, or other outcomes in infants and children with CF (Cochrane Database Syst Rev 2014 Nov 24)*

*Ursodiol has limited evidence for CF-related liver disease (Cochrane Database Syst Rev 2014 Dec 15)*

*Pulmonary hypertension associated with increased mortality in patients with CF (Am J Respir Crit Care Med 2014 Oct 15)*

*Vitamin E supplementation may increase serum vitamin E levels in patients with CF (Cochrane Database Syst Rev 2014 Dec 9)*
Recent Literature Searches on Cystic Fibrosis

Below is a sample of literature searches carried out by librarians for UH Bristol members of staff on the subject of Cystic Fibrosis. For further details get in touch: bennet.jones@uhbristol.nhs.uk

- CF and hyperventilation / dysfunctional breathing
- CF and dynamic hyperinflation
- CF and exercise prescription
- CF and exercise testing

Current Awareness Database Articles on Cystic Fibrosis

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

- Medical
- Microbiological
- Psychological
- 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: bennet.jones@uhbristol.nhs.uk

Medical

Title: Early respiratory infection is associated with reduced spirometry in children with cystic fibrosis.

Citation: American Journal of Respiratory & Critical Care Medicine, 15 November 2014, vol./is. 190/10(1111-1116), 1073449X


Abstract: RATIONALE: Pulmonary inflammation, infection, and structural lung disease occur early in life in children with cystic fibrosis. OBJECTIVES: We hypothesized that the presence of these markers of cystic fibrosis lung disease in the first 2 years of life would be associated with reduced lung
function in childhood. **METHODS:** Lung function (forced expiratory volume in the first three-quarters of a second [FEV0.75], FVC) was assessed in individuals with cystic fibrosis diagnosed after newborn screening and healthy subjects during infancy (0-2 yr) and again at early school age (4-8 yr). Individuals with cystic fibrosis underwent annual bronchoalveolar lavage fluid examination, and chest computed tomography. We examined which clinical outcomes (pulmonary inflammation, infection, structural lung disease, respiratory hospitalizations, antibiotic prophylaxis) measured in the first 2 years of life were associated with reduced lung function in infants and young children with cystic fibrosis, using a mixed effects model. **MEASUREMENTS AND MAIN RESULTS:** Children with cystic fibrosis (n = 56) had 8.3% (95% confidence interval [CI], -15.9 to -6.6; P = 0.04) lower FEV0.75 compared with healthy subjects (n = 18). Detection of proinflammatory bacterial pathogens (Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Aspergillus species, Streptococcus pneumoniae) in bronchoalveolar lavage fluid was associated with clinically significant reductions in FEV0.75 (ranging between 11.3 and 15.6%). **CONCLUSIONS:** The onset of lung disease in infancy, specifically the occurrence of lower respiratory tract infection, is associated with low lung function in young children with cystic fibrosis. Deficits in lung function measured in infancy persist into childhood, emphasizing the need for targeted therapeutic interventions in infancy to maximize functional outcomes later in life.

**Title:** Dry powder inhalers in cystic fibrosis: same old drugs but different benefits?

**Citation:** Current Opinion in Pulmonary Medicine, 01 November 2014, vol./is. 20/6(607-612), 10705287

**Author(s):** Uttley, Lesley, Tappenden, Paul

**Abstract:** PURPOSE OF REVIEW: Newer 'innovative' formulations of antibiotics for Pseudomonas aeruginosa lung infection in patients with cystic fibrosis include colistimethate sodium and tobramycin in the form of dry powders for inhalation (DPIs). Whilst these DPIs are anticipated to improve patient adherence because of increased convenience and ease of administration, questions remain concerning whether they are as clinically effective, safe and cost-effective as nebulized antibiotics. **RECENT FINDINGS:** This review describes the recent findings of a health technology assessment of the clinical effectiveness and cost-effectiveness of colistimethate sodium and tobramycin DPIs with regard to how innovative treatments may be judged to be incrementally better than existing treatments. The original assessment was undertaken to inform the National Institute for Health and Care Excellence’s Technology Appraisal Programme to inform national clinical guidance on the use of these new treatments in the National Health Service. **SUMMARY:** Three trials were included in the systematic review. Issues surrounding the clinical effectiveness and cost-effectiveness of colistimethate sodium DPI and tobramycin DPI are discussed in light of the considerable uncertainties associated with the available evidence.

**Title:** What is the role of noninvasive ventilation in cystic fibrosis?

**Citation:** Current Opinion in Pulmonary Medicine, 01 November 2014, vol./is. 20/6(618-622), 10705287
**Author(s):** Bright-Thomas, Rowland J, Johnson, Susan C

**Abstract:** PURPOSE OF REVIEW: The use of noninvasive ventilatory support in patients with cystic fibrosis (CF) has increased exponentially over the past 2 decades. This review examines the current knowledge and considers potential future directions for use of noninvasive ventilation in CF patients. RECENT FINDINGS: Noninvasive ventilation was originally reported as a bridge to transplantation in CF patients with severe respiratory failure but is now used as a long-term treatment modality for patients with respiratory failure independent of transplant status. In 2013 to 2014, over 400 publications on noninvasive ventilation demonstrate its increasing clinical application, however only seven reference CF. Recent technological advances and potential benefits to CF patients are considered. SUMMARY: The role of noninvasive ventilation in CF patients in chronic respiratory failure is established, but future prospective studies are needed to determine further indications and optimal timing of this intervention. Developments in both ventilator and interface design may enhance the efficacy of ventilation in CF patients but require careful individualized assessment and regular review. The implications on treatment burden and quality of life in CF also need to be studied.

**Title:** Management of the upper airway in cystic fibrosis.

**Citation:** Current Opinion in Pulmonary Medicine, 01 November 2014, vol./is. 20/6(623-631), 10705287

**Author(s):** Illing, Elisa A, Woodworth, Bradford A

**Abstract:** PURPOSE OF REVIEW: Upper airway disease engenders significant morbidity for patients with cystic fibrosis and is increasingly recognized as having a much greater role in pulmonary outcomes and quality of life than originally believed. Widespread disparate therapeutic strategies for cystic fibrosis chronic rhinosinusitis underscore the absence of a standardized treatment paradigm. This review outlines the most recent evidence-based trends in the management of upper airway disease in cystic fibrosis. RECENT FINDINGS: The unified airway theory proposes that the sinuses are a focus of initial bacterial colonization which seeds the lower airway and may play a large role in maintaining lung infections. Mounting evidence suggests more aggressive treatment of the sinuses may confer significant improvement in pulmonary disease and quality of life outcomes in cystic fibrosis patients. However, there is a lack of high-level evidence regarding medical and surgical management of cystic fibrosis chronic rhinosinusitis that makes generalizations difficult. SUMMARY: Well designed clinical trials with long-term follow-up concerning medical and surgical interventions for cystic fibrosis sinus disease are required to establish standardized treatment protocols, but increased interest in the sinuses as a bacterial reservoir for pulmonary infections has generated considerable attention.

**Title:** Aspergillus and cystic fibrosis: old disease - new classifications.

**Citation:** Current Opinion in Pulmonary Medicine, 01 November 2014, vol./is. 20/6(632-638), 10705287
Author(s): Felton, Imogen C, Simmonds, Nicholas J

Abstract: PURPOSE OF REVIEW: Aspergillus pulmonary infection has traditionally been recognized as a clinical spectrum of increasing pathogenicity, encompassing saprophytic airways colonization historically regarded of doubtful clinical significance, to allergic bronchopulmonary aspergillosis, chronic cavitatory and life-threatening invasive disease in the immunocompromised host. Whilst the latter two categories are rarely encountered in cystic fibrosis (CF), there is recognition of an extending spectrum of disease yet to be reflected in consensus management guidelines. The purpose of this review is to provide an up-to-date overview of this extending spectrum, with a focus on disease categories and their clinical significance. RECENT FINDINGS: Conflicting evidence regarding the clinical significance of Aspergillus colonization and sensitization in CF, alongside the emergence of a novel disease category 'Aspergillus bronchitis', has led to proposals for the reclassification of Aspergillus disease. In addition, lack of standardization and poor sensitivity of culture-dependent mycology techniques renders clinical and epidemiological interpretation of these isolates challenging. SUMMARY: The role of Aspergillus in the absence of established CF-allergic bronchopulmonary aspergillosis remains unclear. The following review discusses new approaches proposed to categorise the extended spectrum of CF Aspergillus disease, highlighting the need for enhanced microbiological investigation and serological monitoring of patients in light of evidence which differentiates colonization from categories of greater pathogenic potential.

Title: Prediction of Mortality in Adolescents with Cystic Fibrosis.

Citation: Medicine & Science in Sports & Exercise, 01 November 2014, vol./is. 46/11(2047-2052), 01959131

Author(s): Hulzebos, Erik H. J., Bomhof-Roordink, Hanna, Van De Weert-Van Leeuwen, Pauline B., Twisk, Jos W. R., Arets, H. G. M., Van Der Ent, Cornelis K., Takken, Tim

Abstract: Introduction: Lung function, nutritional status, and parameters of exercise capacity are known predictors of mortality in patients with cystic fibrosis (CF). The aim of the current study was to use these important parameters to develop a multivariate model to predict mortality in adolescent patients with CF. Methods: A total of 127 adolescents with CF (57 girls) with a mean age of 12.7 ± 0.9 yr and a mean percentage of predicted forced expired volume in 1 s (FEV<sub>1%predicted</sub>) of 77.7% ± 15.6% were included. Cardiopulmonary exercise testing-derived parameters, nutritional status, and resting lung functions were dichotomized according to the criterion value determined using receiver operating characteristic curves. Body mass index (BMI), FEV<sub>1%predicted</sub>, predicted peak oxygen uptake corrected for body weight (VO<sub>2peak/kg%predicted</sub>), peak minute ventilation (VE<sub>peak</sub>), peak VE/VO<sub>2</sub>, peak VE/VCO<sub>2</sub>, and breathing reserve were included in a multivariate model. The Cox proportional hazards model was used to determine the combination of parameters that best predicted mortality and/or lung transplantation. Results: The mean duration of follow-up was 7.5 ± 2.7 yr, during which, nine of the 127 patients (7.1%) died and six (4.7%) underwent lung transplantation. Mortality in this population was best predicted by the model that included FEV<sub>1%predicted</sub> (hazard ratio, 17.13; 95% confidence interval (CI), 3.76-78.06), peak VE/VO<sub>2</sub> (hazard ratio, 5.92; 95% CI, 1.27—27.63), and BMI (hazard ratio,
Conclusions: The currently developed model consisting of BMI, FEV<sub>1</sub>%predicted, and VE/VO<sub>2</sub> is a strong predictor of mortality rate in adolescents with CF. This prediction equation may be useful in clinical practice to detect patients with a high risk of mortality and to provide them with additional therapy earlier.

Title: The Effect of Ivacaftor in Adolescents With Cystic Fibrosis (G551D Mutation): An Exercise Physiology Perspective.

Citation: Pediatric Physical Therapy, 01 November 2014, vol./is. 26/4(454-461), 08985669

Author(s): Saynor, Zoe Louise, Barker, Alan Robert, Oades, Patrick John, Williams, Craig Anthony

Abstract: Purpose: The purpose of this report was to evaluate the influence of 12 weeks of ivacaftor treatment on the aerobic function of 2 teenage patients with cystic fibrosis (CF; ΔF508/G551D) using a maximal cardiopulmonary exercise test. Summary of Key Points: One patient, with relatively mild disease, demonstrated no clinically meaningful changes in maximal oxygen uptake (Vo<sub>2max</sub>). However, in the second case, with more established lung disease on imaging, Vo<sub>2max</sub> improved by approximately 30%, an improvement out of proportion with early lung function changes. This improvement resulted from increased muscle oxygen delivery and extraction. Statement of Conclusions: Cardiopulmonary exercise testing can monitor the extent and cause(s) of change following interventions such as ivacaftor, with the potential to identify functional changes independent from spirometry indices. Recommendations for Clinical Practice: Cardiopulmonary exercise testing represents an important and comprehensive clinical assessment tool, and its use as an outcome measure in the functional assessment of patients with CF is encouraged.

Title: Quality improvement initiative to reduce deep vein thrombosis associated with peripherally inserted central catheters in adults with cystic fibrosis

Citation: Annals of the American Thoracic Society, November 2014, vol./is. 11/9(1404-1410), 2325-6621 (01 Nov 2014)

Author(s): Mermis J.D., Strom J.C., Greenwood J.P., Low D.M., He J., Stites S.W., Simpson S.Q.

Abstract: Rationale: Peripherally inserted central catheters (PICCs) are common in the treatment of patients with cystic fibrosis (CF). Previous reports suggest that patients with CF are at increased risk for PICC-associated deep vein thrombosis (DVT). Objectives: We assessed potential risk factors for symptomatic PICC-associated DVT with subsequent implementation of a quality improvement (QI) initiative to reduce PICC-associated DVT in patients with CF. Methods: This was a 5-year retrospective cohort study with subsequent 21-month prospective observation following implementation of a QI intervention in adults (aged 18 yr or older) with CF. All patients with a PICC inserted from July 2006 to March 2013 at our CF Foundation-accredited center were included. Symptomatic DVT was diagnosed by Doppler ultrasound. PICC insertions were analyzed, and nine risk factors for DVT were analyzed to formulate a QI initiative to reduce risk of PICC-associated DVT. The QI program focused
on staff education and included modification to PICC order entry with a 4 French (F) single-lumen (SL) catheter as standard for all patients with CF. Measurements and Main Results: A total of 369 PICCs were analyzed in 117 unique patients for a total of 5,437 PICC-days of placement. Symptomatic DVT was diagnosed in 28 (7.6%) of the 369 PICCs analyzed. Using regression analysis, the strongest predictors for DVT occurrence were warfarin use (odds ratio [OR] = 9.2, P = 0.006) and history of PICC-associated DVT (OR = 2.97, P = 0.08). Insertion of a 4F SL PICC resulted in zero symptomatic DVT. Zero episodes of DVT associated with 4F PICC insertion prevented use of PICC size in regression analysis. However, univariate analysis revealed that insertion of a 4F SL PICC instead of either 5F double lumen or 6F triple lumen was associated with a reduction in PICC-associated DVT (P = 0.001). After the QI intervention, 4F SL catheter insertion substantially increased to 65.8% of all PICCs inserted, whereas 6F triple-lumen catheter insertion declined to 6.8% of PICCs inserted. The QI initiative resulted in an absolute risk reduction in DVT per PICC placed of 6.1% (P = 0.055).

Conclusions: To reduce risk of PICC-associated DVT in patients with CF, QI strategies should focus on insertion of smaller diameter 4F PICCs and reduction in PICC use in high-risk patients when possible.

Title: What did we learn from two decades of chest computed tomography in cystic fibrosis?

Citation: Pediatric Radiology, November 2014, vol./is. 44/12(1490-1495), 0301-0449;1432-1998 (19 Nov 2014)

Author(s): Tiddens H.A.W.M., Rosenow T.

Abstract: Despite our current treatment, many cystic fibrosis (CF) patients still show progressive bronchiectasis and small airways disease. Adequate detection and monitoring of progression of these structural abnormalities is needed to personalize treatment to the severity of CF lung disease of the patient. Chest computed tomography (CT) is the gold standard to diagnose and monitor bronchiectasis. Many studies have been done to validate the role of chest CT in CF and to improve the protocols. From these studies it became clear that for correct interpretation of the severity of bronchiectasis and small airways disease standardization of lung volume for the inspiratory and expiratory CT scan acquisition is needed. The risk related to the radiation exposure of a chest CT scan every second year is considered low. Automated and quantitative image analysis systems are developed to improve the reliability and sensitivity of assessments of structural lung changes in CF, particularly in early life. In this paper an overview is given of the lessons learned from two decades of monitoring CF lung disease using chest CT.

Title: Inflammation, oxidative stress, and cardiovascular disease risk factors in adults with cystic fibrosis

Citation: Free Radical Biology and Medicine, November 2014, vol./is. 76/(261-277), 0891-5849;1873-4596 (November 2014)

Author(s): Reverri E.J., Morrissey B.M., Cross C.E., Steinberg F.M.
Abstract: Cystic fibrosis (CF) represents one of a number of localized lung and non-lung diseases with an intense chronic inflammatory component associated with evidence of systemic oxidative stress. Many of these chronic inflammatory diseases are accompanied by an array of atherosclerotic processes and cardiovascular disease (CVD), another condition strongly related to inflammation and oxidative stress. As a consequence of a dramatic increase in long-lived patients with CF in recent decades, the specter of CVD must be considered in these patients who are now reaching middle age and beyond. Buttressed by recent data documenting that CF patients exhibit evidence of endothelial dysfunction, a recognized precursor of atherosclerosis and CVD, the spectrum of risk factors for CVD in CF is reviewed here. Epidemiological data further characterizing the presence and extent of atherogenic processes in CF patients would seem important to obtain. Such studies should further inform and offer mechanistic insights into how other chronic inflammatory diseases potentiate the processes leading to CVDs.

Title: Recent advances in the management of cystic fibrosis.

Citation: Archives of Disease in Childhood, November 2014, vol./is. 99/11(1033-6), 0003-9888;1468-2044 (2014 Nov)

Author(s): Davies JC, Ebdon AM, Orchard C

Abstract: Cystic fibrosis is a disease that still causes a reduced life expectancy. The treatment burden remains high for affected individuals with often a combination of multiple oral and inhaled medications, as well as physiotherapy, required on a daily basis. In this article, we look at an overview of the pathogenesis, how this might lead to treatment options and look at some of the available new therapies, all in the aim of increasing life expectancy and reducing treatment burden. Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions.

Microbiological

Title: The effect of the decoy molecule PA401 on CXCL8 levels in bronchoalveolar lavage fluid of patients with cystic fibrosis

Citation: Molecular Immunology, February 2015, vol./is. 63/2(550-558), 0161-5890;1872-9142 (February 01, 2015)


Abstract: Background: The chemokine interleukin-8 (CXCL8) is a key mediator of inflammation in airways of patients with cystic fibrosis (CF). Glycosaminoglycans (GAGs) possess the ability to influence the chemokine profile of the CF lung by binding CXCL8 and protecting it from proteolytic degradation. CXCL8 is maintained in an active state by this glycan interaction thus increasing infiltration of immune cells such as neutrophils into the lungs. As the CXCL8-based decoy PA401
displays no chemotactic activity, yet demonstrates glycan binding affinity, the aim of this study was to investigate the anti-inflammatory effect of PA401 on CXCL8 levels, and activity, in CF airway samples in vitro. Methods: Bronchoalveolar lavage fluid (BALF) was collected from patients with CF homozygous for the F508 mutation (n= 13). CXCL8 in CF BALF pre and post exposure to PA401 was quantified by ELISA. Western blot analysis was used to determine PA401 degradation in CF BALF. The ex vivo chemotactic activity of purified neutrophils in response to CF airway secretions was evaluated post exposure to PA401 by use of a Boyden chamber-based motility assay. Results: Exposure of CF BALF to increasing concentrations of PA401 (50-1000 pg/ml) over a time course of 2-12 h in vitro, significantly reduced the level of detectable CXCL8 (P<. 0.05). Interestingly, PA401 engendered release of CXCL8 from GAGs exposing the chemokine susceptible to proteolysis. Subsequently, a loss of PA401 was observed (P<. 0.05) due to proteolytic degradation by elastase like proteases. A 25% decrease in neutrophil chemotactic efficiency towards CF BALF samples incubated with PA401 was also observed (P<. 0.05). Conclusion: PA401 can disrupt CXCL8:GAG complexes, rendering the chemokine susceptible to proteolytic degradation. Clinical application of a CXCL8 decoy, such as PA401, may serve to decrease the inflammatory burden in the CF lung in vivo.

Title: Decreased expression of HLA-DQ and HLA-DR on cells of the monocytic lineage in cystic fibrosis

Citation: Journal of Molecular Medicine, November 2014, vol./is. 92/12(1293-1304), 0946-2716;1432-1440 (29 Nov 2014)


Abstract: Key message: * CF patients show a reduced expression of MHCII molecules in monocytes and macrophages. * HLA-DQ and HLA-DR transcript levels are also reduced in CF patients. * CF patient C-reactive protein levels correlate with low HLA-DQ expression. * Reduced expression of MHC class II molecules appears to be linked to inflammation. * CF patients exhibit an impaired response to IFNgamma.Abstract: We studied HLA class II molecules on blood monocyte subsets, blood dendritic cells, sputum macrophages, and monocyte-derived macrophages at the protein (flow cytometry) and mRNA level (RT-PCR) in adult patients with cystic fibrosis (CF) and healthy control subjects as putative contributors to the CF phenotype. In healthy donors, we found a high average HLA-DQ expression of 4.35 mean specific fluorescence intensity units (MnI) on classical blood monocytes. In F508del homozygous CF patients, the average MnI was low (1.80). Patients were divided into two groups, in which 14 of these patients had HLA-DQ expression above 2 MnI (average 3.25 MnI, CF-DQ<sup>group1</sup>) and 36 below (average 1.24 MnI, CF-DQ<sup>group2</sup>). Also, the CD16-positive monocyte subset and blood dendritic cells showed much lower levels of HLA-DQ for the CF-DQ<sup>group2</sup> patients compared with healthy controls. In macrophages from sputum and derived from monocytes, in vitro HLA-DQ expression was dramatically decreased to background levels in CF-DQ<sup>group2</sup>. MHC class II transcripts were reduced in CF with a sevenfold decrease in HLA-DQbeta1 for CF-DQ<sup>group2</sup> patients. Higher levels of the inflammation marker CRP were associated with low HLA-DQ protein expression, and in vitro treatment with the inflammatory molecule lipopolysaccharide reduced HLA-DQ expression. Interferon (IFN) could overcome this effect in healthy donor cells while, in CF, the IFN-induced
activation was impaired. Our data demonstrate a pronounced reduction of HLA-DQ expression in CF, which is associated with inflammation and a reduced response to IFN.

Title: Expression of MIG/CXCL9 in cystic fibrosis and modulation of its activities by elastase of Pseudomonas aeruginosa

Citation: Journal of Innate Immunity, November 2014, vol./is. 6/6(846-859), 1662-811X;1662-8128 (07 Nov 2014)

Author(s): Jovic S., Shikhagaie M., Morgelin M., Kjellstrom S., Erjefalt J., Olin A.I., Frick I.-M., Egesten A.

Abstract: In cystic fibrosis (CF), colonization of the airways with Pseudomonas aeruginosa is associated with disease deterioration. The mechanism behind the disease progression is not fully understood. The present work shows that the antibacterial chemokine MIG/CXCL9 is present in the airways and in sputum of CF patients. MIG/CXCL9 showed high bactericidal activity against P. aeruginosa, including some strains from the airways of CF patients. Full-length MIG/CXCL9 was detected in sputum from healthy controls and CF patients colonized with P. aeruginosa. However, degraded MIG/CXCL9 was only found in CF sputum. In vitro, elastase of P. aeruginosa cleaved off a fragment of similar size and two additional fragments from MIG/CXCL9. The fragments showed less bactericidal activity against P. aeruginosa compared with the full-length protein. The fragments did not activate the MIG/CXCL9 receptor CXCR3 (expressed e.g. by NK cells, mast cells, and activated T cells) but instead displayed noncompetitive inhibition. In vitro, a decrease in CXCR3-bearing cells was found within and in the proximity of the bronchial epithelium of CF lung tissue compared with controls. Taken together, both bactericidal and cell-recruiting activities of MIG/CXCL9 are corrupted by P. aeruginosa through release of elastase, and this may contribute to impaired airway host defense in CF.

Title: Cystic fibrosis sputum DNA has NETosis characteristics and neutrophil extracellular trap release is regulated by macrophage migration-inhibitory factor

Citation: Journal of Innate Immunity, November 2014, vol./is. 6/6(765-779), 1662-811X;1662-8128 (07 Nov 2014)

Author(s): Dwyer M., Shan Q., D’Ortona S., Maurer R., Mitchell R., Olesen H., Thiel S., Huebner J., Gadjeva M.

Abstract: Neutrophils are the main proinflammatory cell type in chronically infected lungs of cystic fibrosis (CF) patients; however, they fail to effectively clear the colonizing pathogens. Here, we investigated the molecular composition of non-mucoid and mucoid Pseudomonas aeruginosa-induced neutrophil extracellular traps (NETs) in vitro and compared them to the DNA-protein complexes present in the CF sputum. The protein composition of P. aeruginosa-induced NET fragments revealed that irrespective of the inducing stimuli, NET fragments were decorated with a conserved set of proteins. The DNA-protein complexes derived from CF sputum were consistent with
NETosis and shared a similar protein signature, suggesting that the majority of the extracellular DNA was NET derived. The ability of polymorphonuclear leukocytes to produce NETs in response to P. aeruginosa was driven by macrophage migration-inhibitory factor (MIF) by promoting mitogen-activated protein kinase. Analysis of 132 CF patient samples revealed that elevated MIF protein levels correlated with poorer lung function. We suggest that targeting MIF by small molecular inhibitors might reduce the presence of extracellular DNA and serve as an adjunct to the use of antimicrobial drugs that could ultimately reduce bacterial fitness in the lungs during the later stages of CF disease.

Title: Cystic fibrosis transmembrane conductance regulator protein (CFTR) expression in the developing human brain: comparative immunohistochemical study between patients with normal and mutated CFTR.

Citation: Journal of Histochemistry & Cytochemistry, November 2014, vol./is. 62/11(791-801), 0022-1554;1551-5044 (2014 Nov)

Author(s): Marcorelles P, Friocourt G, Uguen A, Lede F, Ferec C, Laquerriere A

Abstract: Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein has recently been shown to be expressed in the human adult central nervous system (CNS). As CFTR expression has also been documented during embryonic development in several organs, such as the respiratory tract, the intestine and the male reproductive system, suggesting a possible role during development we decided to investigate the expression of CFTR in the human developing CNS. In addition, as some, although rare, neurological symptoms have been reported in patients with CF, we compared the expression of normal and mutated CFTR at several fetal stages. Immunohistochemistry was performed on brain and spinal cord samples of foetuses between 13 and 40 weeks of gestation and compared with five patients with cystic fibrosis (CF) of similar ages. We showed in this study that CFTR is only expressed in neurons and has an early and widespread distribution during development. Although we did not observe any cerebral abnormality in patients with CF, we observed a slight delay in the maturation of several brain structures. We also observed different expression and localization of CFTR depending on the brain structure or the cell maturation stage. Our findings, along with a literature review on the neurological phenotypes of patients with CF, suggest that this gene may play previously unsuspected roles in neuronal maturation or function. The Author(s) 2014.

Title: Localization of Burkholderia cepacia complex bacteria in cystic fibrosis lungs and interactions with Pseudomonas aeruginosa in hypoxic mucus.

Citation: Infection & Immunity, November 2014, vol./is. 82/11(4729-45), 0019-9567;1098-5522 (2014 Nov)

Author(s): Schwab U, Abdullah LH, Perlmitt OS, Albert D, Davis CW, Arnold RR, Yankaskas JR, Gilligan P, Neubauer H, Randell SH, Boucher RC
Abstract: The localization of Burkholderia cepacia complex (Bcc) bacteria in cystic fibrosis (CF) lungs, alone or during coinfection with Pseudomonas aeruginosa, is poorly understood. We performed immunohistochemistry for Bcc and P. aeruginosa bacteria on 21 coinfected or singly infected CF lungs obtained at transplantation or autopsy. Parallel in vitro experiments examined the growth of two Bcc species, Burkholderia cenocepacia and Burkholderia multivorans, in environments similar to those occupied by P. aeruginosa in the CF lung. Bcc bacteria were predominantly identified in the CF lung as single cells or small clusters within phagocytes and mucus but not as "biofilm-like structures." In contrast, P. aeruginosa was identified in biofilm-like masses, but densities appeared to be reduced during coinfection with Bcc bacteria. Based on chemical analyses of CF and non-CF respiratory secretions, a test medium was defined to study Bcc growth and interactions with P. aeruginosa in an environment mimicking the CF lung. When test medium was supplemented with alternative electron acceptors under anaerobic conditions, B. cenocepacia and B. multivorans used fermentation rather than anaerobic respiration to gain energy, consistent with the identification of fermentation products by high-performance liquid chromatography (HPLC). Both Bcc species also expressed mucinases that produced carbon sources from mucins for growth. In the presence of P. aeruginosa in vitro, both Bcc species grew anaerobically but not aerobically. We propose that Bcc bacteria (i) invade a P. aeruginosa-infected CF lung when the airway lumen is anaerobic, (ii) inhibit P. aeruginosa biofilm-like growth, and (iii) expand the host bacterial niche from mucus to also include...

Title: Polymorphonuclear leukocytes restrict growth of Pseudomonas aeruginosa in the lungs of cystic fibrosis patients.

Citation: Infection & Immunity, November 2014, vol./is. 82/11(4477-86), 0019-9567;1098-5522 (2014 Nov)


Abstract: Cystic fibrosis (CF) patients have increased susceptibility to chronic lung infections by Pseudomonas aeruginosa, but the ecophysiology within the CF lung during infections is poorly understood. The aim of this study was to elucidate the in vivo growth physiology of P. aeruginosa within lungs of chronically infected CF patients. A novel, quantitative peptide nucleic acid (PNA) fluorescence in situ hybridization (PNA-FISH)-based method was used to estimate the in vivo growth rates of P. aeruginosa directly in lung tissue samples from CF patients and the growth rates of P. aeruginosa in infected lungs in a mouse model. The growth rate of P. aeruginosa within CF lungs did not correlate with the dimensions of bacterial aggregates but showed an inverse correlation to the concentration of polymorphonuclear leukocytes (PMNs) surrounding the bacteria. A growth-limiting effect on P. aeruginosa by PMNs was also observed in vitro, where this limitation was alleviated in the presence of the alternative electron acceptor nitrate. The finding that P. aeruginosa growth patterns correlate with the number of surrounding PMNs points to a bacteriostatic effect by PMNs via their strong O2 consumption, which slows the growth of P. aeruginosa in infected CF lungs. In support of this, the growth of P. aeruginosa was significantly higher in the respiratory airways than in the conducting airways of mice. These results indicate a complex host-pathogen interaction in chronic P. aeruginosa infection of the CF lung whereby PMNs slow the growth of the bacteria and...
render them less susceptible to antibiotic treatment while enabling them to persist by anaerobic respiration. Copyright 2014, American Society for Microbiology. All Rights Reserved.

**Psychological**

**Title:** Client Views and Attitudes to Non-Invasive Prenatal Diagnosis for Sickle Cell Disease, Thalassaemia and Cystic Fibrosis.

**Citation:** Journal of Genetic Counseling, 01 December 2014, vol./is. 23/6(1012-1021), 10597700

**Author(s):** Hill, Melissa, Compton, Cecilia, Karunaratna, Madhavi, Lewis, Celine, Chitty, Lyn

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**Title:** Depression, illness severity, and healthcare utilization in cystic fibrosis

**Citation:** Pediatric Pulmonology, December 2014, vol./is. 49/12(1177-1181), 8755-6863;1099-0496 (01 Dec 2014)

**Author(s):** Snell C., Fernandes S., Bujoreanu I.S., Garcia G.

**Abstract:** Cystic fibrosis (CF) is an illness associated with high healthcare utilization and healthcare costs, even when compared to other chronic illnesses. In a variety of medical populations, depression has been found to be associated with lower adherence and poorer medical outcomes. The current study is a retrospective chart review of a matched set of 40 patients with CF, half with and half without a depressive disorder diagnosis. Participants were matched on the basis of their age, gender and lung function, and compared in terms of their illness severity (lung function and weight), medical adherence, and healthcare utilization during the year prior to and following diagnosis of depression and a comparable time period for the non-depressed group. Results show an association between depression and BMI, with only the depressed group showing significant decreases in the year following their depressive disorder diagnosis (from a mean BMI z-score of -0.48 to -1.04). Depression was also strongly associated with greater healthcare utilization and healthcare costs relative to those of comparably medically ill controls, in that depressed youth were hospitalized at over three times the rate of non-depressed youth, and their healthcare costs were more than four times higher (mean number of admissions per year for the depressed group of 4.00 vs. 1.20 for the non-depressed group; mean annual costs of $280,000 for the depressed vs. $60,116 for the non-depressed). These findings highlight the importance of addressing the mental health needs of chronically ill patients as a path to better health outcomes and decreasing need for medical services.

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**Other**

**Title:** Physiotherapy and cystic fibrosis: what is the evidence base?
Citation: Current Opinion in Pulmonary Medicine, 01 November 2014, vol./is. 20/6(613-617), 10705287

Author(s): McIlwaine, Maggie Patricia, Lee Son, Nicole Marie, Richmond, Melissa Lynn

Abstract: PURPOSE OF REVIEW: To provide a comprehensive overview and evidence to support the role of physiotherapy in the management of individuals with cystic fibrosis (CF) including airway clearance, exercise, and musculoskeletal concerns which can affect activities of daily living and respiratory health. RECENT FINDINGS: Several long-term studies have looked at the efficacy of airway clearance techniques, including active cycle of breathing techniques, autogenic drainage, high frequency chest wall oscillation, postural drainage, positive expiratory pressure (PEP), and oscillating PEP. Each of these studies reported some efficacy of airway clearance in maintaining health with no one technique being superior to another. However, one study suggested that high frequency chest wall oscillation was not as effective as PEP in maintaining health in CF patients. Individual preference needs to be considered when selecting a technique. Recent studies have found exercise to increase mucociliary clearance peripherally. Musculoskeletal issues, including posture, bone density, urinary incontinence, and pain should be assessed and managed in individuals to improve the mechanics of breathing and overall well-being. SUMMARY: The role of physiotherapy in CF is complex and includes airway clearance, exercise, and management of the long-term sequelae of musculoskeletal issues. More rigorous physiotherapy studies are required to assist with evidence based practice.

Title: Adherence of Subjects With Cystic Fibrosis to Their Home Program: A Systematic Review.

Citation: Respiratory Care, 01 November 2014, vol./is. 59/11(1731-1746), 00201324

Author(s): O’Donohoe, Ruairi, Fullen, Brona M.

Abstract: BACKGROUND: The management of cystic fibrosis (CF) includes adherence to a home management program (airway clearance, medication, nutritional advice, and exercise). This has led to an increase in life expectancy, although the benefits depend greatly on a patient’s level of adherence to daily treatments at home. To date, no systematic review has established adherence rates to all World Health Organization guidelines in the home setting; hence, this review was undertaken. METHODS: The review comprised 3 phases. A methodological assessment of databases (Embase, CINAHL, PsyhiINFO, PEDro, PubMed, Cochrane Central Register of Controlled Trials) identified potentially relevant papers. These papers were screened for inclusion criteria by 2 independent reviewers, data were extracted, and the internal validity was rated using a valid and reliable scale. Results were categorized into 4 themes: medication, nutrition, airway clearance techniques, and exercise. RESULTS: The search generated a total of 26 papers, 24 of which were rated as being poor quality. Adherence to a treatment program for CF patients is generally low (from 22% for nutritional guidelines to 130% for oral antibiotics), and it varies greatly depending on the type of treatment and the method of assessment employed (objective tool vs self-reported questionnaires). CONCLUSIONS: Consensus on how to measure adherence is lacking, and the quality of studies addressing adherence in this population is generally poor. Overall, studies using self-reported measures yielded higher adherence scores than those that used objective measures,
suggesting that current efforts to improve methods of adherence are appropriate. The prevalence of non-adherence remains unclear due to these limitations.

Title: Gender differences in outcomes of patients with cystic fibrosis

Citation: Journal of Women's Health, December 2014, vol./is. 23/12(1012-1020), 1540-9996;1931-843X (01 Dec 2014)

Author(s): Harness-Brumley C.L., Elliott A.C., Rosenbluth D.B., Raghavan D., Jain R.

Abstract: Background: Cystic fibrosis (CF) is a common life-shortening genetic disease in which women have been described to have worse outcomes than males, particularly in response to respiratory infections with Pseudomonas aeruginosa. However, as advancements in therapies have improved life expectancy, this gender disparity has been challenged. The objective of this study is to examine whether a gender-based survival difference still exists in this population and determine the impact of common CF respiratory infections on outcomes in males versus females with CF.

Methods: We conducted a retrospective cohort analysis of 32,766 patients from the United States Cystic Fibrosis Foundation Patient Registry over a 13-year period. Kaplan-Meier and Cox proportional hazards models were used to compare overall mortality and pathogen based survival rates in males and females.

Results: Females demonstrated a decreased median life expectancy (36.0 years; 95% confidence interval [CI] 35.0-37.3) compared with men (38.7 years; 95% CI 37.8-39.6; p<0.001). Female gender proved to be a significant risk factor for death (hazard ratio 2.22, 95% CI 1.79-2.77), despite accounting for variables known to influence CF mortality. Women were also found to become colonized earlier with several bacteria and to have worse outcomes with common CF pathogens.

Conclusions: CF women continue to have a shortened life expectancy relative to men despite accounting for key CF-related comorbidities. Women also become colonized with certain common CF pathogens earlier than men and show a decreased life expectancy in the setting of respiratory infections. Explanations for this gender disparity are only beginning to be unraveled and further investigation into mechanisms is needed to help develop therapies that may narrow this gender gap.
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Journal of Cystic Fibrosis
Vol. 14, iss. 1, January 2015

The growing threat of nontuberculous mycobacteria in CF

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Upper aero-digestive contamination by *Pseudomonas aeruginosa* and implications in Cystic Fibrosis

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Corrigendum to “Prescribing practices for intravenous aminoglycosides in UK Cystic Fibrosis clinics: A questionnaire survey” [J Cyst Fibros (2013) 424-427]

American Journal of Respiratory and Critical Care Medicine
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