## Contents

Your Friendly Local Librarian... .............................................................................................................................................. 2

New Cochrane Library Systematic Reviews on Cystic Fibrosis................................................................................................ 3

New from NICE ............................................................................................................................................................................ 3

New from Public Health England ................................................................................................................................................ 3

New Activity in UptoDate and DynaMed .................................................................................................................................. 3

Current Awareness Database Articles on Cystic Fibrosis ........................................................................................................... 4

Medical ......................................................................................................................................................................................... 4

Microbiological ............................................................................................................................................................................ 12

Psychological .............................................................................................................................................................................. 23

Other ................................................................................................................................................................................................ 25

Journal Tables of Contents .......................................................................................................................................................... 26

Journal of Cystic Fibrosis ............................................................................................................................................................. 26

American Journal of Respiratory and Critical Care Medicine ................................................................................................... 27

Thorax ................................................................................................................................................................................................ 27

Chest ................................................................................................................................................................................................ 30

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### Your Friendly Local Librarian...

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New Cochrane Library Systematic Reviews on Cystic Fibrosis

Vitamin K supplementation for cystic fibrosis

Vanitha A Jagannath, Zbys Fedorowicz, Vidhu Thaker, Anne B Chang

Published 18\textsuperscript{th} Jan 2015

Cystic fibrosis is a genetic disorder which can lead to multiorgan dysfunction. Malabsorption of fat and fat-soluble vitamins (A, D, E, K) may occur and can cause subclinical deficiencies of some of these vitamins. Vitamin K is known to play an important role in both blood coagulation and bone formation. Supplementation with vitamin K appears to be one way of addressing the deficiency, but there is very limited agreement on the appropriate dose and frequency of use of these supplements. **Objectives:** To assess the effects of vitamin K supplementation in people with cystic fibrosis and to determine the optimal dose and route of administration of vitamin K for both routine and therapeutic use.


New from NICE

Cystic fibrosis: long-term azithromycin (NICE Advice)

New from Public Health England

Newborn babies screened for more rare conditions

New Activity in UptoDate and DynaMed

vitamin K supplementation has insufficient evidence to evaluate benefits and adverse effects in patients with CF
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: Medical and obstetric complications among pregnant women with cystic fibrosis

Citation: American Journal of Obstetrics and Gynecology, January 2015, vol./is. 212/1(98e1-98e9), 0002-9378;1097-6868 (01 Jan 2015)

Author(s): Patel E.M., Swamy G.K., Heine R.P., Kuller J.A., James A.H., Grotegut C.A.

Abstract: Objective The objective of this study was to estimate the nationwide prevalence of cystic fibrosis (CF) in pregnancy and determine what medical complications exist at delivery among pregnant women with CF. Study Design The Nationwide Inpatient Sample (NIS) was queried for all delivery-related discharges. Women with CF were identified by International Classification of Diseases, 9th revision, Clinical Modifications codes and compared with women without CF. The prevalence of selected severe medical complications was compared between the 2 groups (NIS years 2008-2010) using multivariable logistic regression and the linear change in prevalence of CF at delivery determined (NIS years 2000-2010). Results From 2000 to 2010, there was a significant linear increase in the prevalence of CF at delivery from 3.0 to 9.8 per 100,000 deliveries, in 2000 and 2010, respectively (R<sup>2</sup> = 0.92, P <.0001). From 2008-2010, there were 1119 deliveries to women with CF and 12,627,627 to women without CF. Women with CF were more likely to be white (P <.0001) and have diabetes (odds ratio [OR], 14.0; 95% confidence interval [CI], 11.8-16.7) or asthma (OR, 5.1; 95% CI, 4.3-6.1). Multivariable logistic regression demonstrated that women with CF were more likely to die (adjusted OR [aOR], 76.0; 95% CI, 31.6-183), require mechanical ventilation (aOR, 18.3; 95% CI, 10.8-31.2), or have pneumonia (aOR, 56.5; 95% CI, 43.2-74.1), acute renal failure (aOR, 17.3; 95% CI, 9.1-32.6), preterm labor (aOR, 2.2; 95% CI, 1.9-2.6), or an adverse composite CF outcome (aOR, 28.1; 95% CI, 21.8-36.3). Conclusion Pregnant women with CF are more likely to die, require mechanical ventilation, and have infectious complications compared with women without CF, although the absolute risks are low and these events are relatively rare.
Title: Survival benefit of induction immunosuppression in cystic fibrosis lung transplant recipients

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(104-110), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Kirkby S., Whitson B.A., Wehr A.M., Lehman A.M., Higgins R.S., Hayes D.

Abstract: Background: Despite resistant microbes, induction immunosuppression is used in patients with cystic fibrosis (CF) undergoing lung transplantation (LTx). Methods: To evaluate the effect of induction immunosuppression on survival, the United Network for Organ Sharing (UNOS) was queried restricting analysis to transplant patients 6-55 years old from 2001 to 2012, who received induction agents (INDUCED) or did not (NONE). Results: A total of 1721 CF patients who underwent LTx were included in the analysis; of these 791 (46%) were INDUCED. Of the INDUCED patients, 65% received basiliximab, 10% alemtuzumab, and 25% thymoglobulin/anti-thymocyte globulin. Mean age was 28.0 years (SD. = 9.7) and 28.5 (SD. = 9.5) for the INDUCED and NONE groups, respectively. The median survival in the INDUCED group was 93.8 months (95% CI: 73.8, --) compared to 61.8 months (95% CI: 55.8-73.8) for the NONE group (log rank p-value <. 0.001). Conclusions: Antibody-based induction immunosuppression had a survival benefit in CF patients undergoing LTx.

Title: Determinants of respiratory pump function in patients with cystic fibrosis

Citation: Paediatric Respiratory Reviews, January 2015, vol./is. 16/1(75-79), 1526-0542;1526-0550 (01 Jan 2015)

Author(s): Dassios T.

Abstract: Respiratory failure constitutes the major cause of morbidity and mortality in patients with Cystic Fibrosis (CF). Respiratory failure could either be due to lung parenchyma damage or to insufficiency of the respiratory pump which consists of the respiratory muscles, the rib cage and the neuromuscular transmission pathways. Airway obstruction, hyperinflation and malnutrition have been historically recognised as the major determinants of respiratory pump dysfunction in CF. Recent research has identified chronic infection, genetic predisposition, dietary and pharmaceutical interventions as possible additional determinants of this impairment. Furthermore, new methodological approaches in assessing respiratory pump function have led to a better understanding of the pathogenesis of respiratory pump failure in CF. Finally, respiratory muscle function could be partially preserved in CF patients with structured interventions such as aerobic exercise, inspiratory muscle training and non-invasive ventilation and CF patients could consequently be relatively protected from respiratory fatigue and respiratory failure.

Title: Outcome in patients with cystic fibrosis liver disease
**Citation:** Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(120-126), 1569-1993;1873-5010 (01 Jan 2015)

**Author(s):** Rowland M., Gallagher C., Gallagher C.G., Laoide R.T., Canny G., Broderick A.M., Drummond J., Greally P., Slattery D., Daly L., McElvaney N.G., Bourke B.

**Abstract:** Background: Liver disease is an important complication in CF. Aims: To determine if CFLD is a risk factor for mortality in CF, and which baseline characteristics predict all-cause mortality.

Methods: Irish children with CFLD, and their age and gender matched controls were enrolled at baseline and reviewed after 10. years to determine which characteristics predict mortality. Results: 72/84 (85.71%) participants were followed, (mean age Cases 21.71 yrs SD 6.5, CF controls 23.62 SD 5.6, 22 (61%) males), with no difference in duration of follow-up. Nineteen participants (26.4%) died, 38.9% (14/36) with CFLD and 13.89% (5/36) CF controls (Odds Ratio (OR) 3.94 95% CI:1.23-12.56 p. = 0.005). In logistic regression, liver disease (OR 4.28 95% CI 1.07-17.16) female gender (OR 12.25 95% CI 2.37-63.24), reduced pulmonary function, (OR 5.11 95% CI 1.09-23.81) were each independent risk factors for mortality in CF. Conclusions: Liver disease is an independent risk factor for mortality in CF.

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**Title:** Influence of macrolides, nutritional support and respiratory therapies in diabetes and normal glucose tolerance in cystic fibrosis. A retrospective analysis of a cohort of adult and younger patients

**Citation:** Diabetes and Metabolic Syndrome: Clinical Research and Reviews, January 2015, vol./is. 9/1(1-6), 1871-4021;1878-0334 (01 Jan 2015)

**Author(s):** Megias M.C., Albarran O.G., Vasco P.G., Ferreiro A.L., Carro L.M.

**Abstract:** Aim The development of cystic fibrosis related diabetes is associated with increased morbidity and mortality, worse nutritional status and lung function decline. It is known that patients with cystic fibrosis have a chronic inflammation status and that beta pancreatic cells are very sensitive to oxidative stress. So these inflammatory mediators could contribute to the onset of progressive pancreatic fibrosis and, hence, to impair glucose metabolism. So, it could be hypothesized that the treatment with macrolides would protect and preserve beta-cell function by decreasing pro-inflammatory cytokines and free oxidative radicals. Methods We retrospectively analyzed a cohort of 64 patients affected of cystic fibrosis, older than 14 years, by using the first pathological 2-h oral glucose tolerance test; peripheral insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA - IR) and pancreatic beta-cell function was estimated according to Wareham. The influence of macrolides, microbiological colonization, nutritional support and related clinical parameters were analyzed. Results Comparing CFRD without FPG and NGT, and after adjustment for microbial colonization, the significance of the use of macrolides was lost (p = 0.1), as a risk or protective factor for any of the studied groups. Non-significative associations were found in the use of macrolides, inhaled corticosteroids and nutritional support therapies within the different disorders of carbohydrate metabolism. Conclusions The anti-inflammatory and immunomodulating effect of macrolides did not seem to affect the beta cell function or insulin resistance in patients with cystic fibrosis. The use of inhaled corticosteroids or
nutritional supplements have not any influence in the carbohydrate metabolism. Further prospective studies are needed to analyze a potential protective role of macrolides in the development of carbohydrate metabolism alterations in cystic fibrosis.

Title: Quantitative Bone Ultrasound at the Distal Radius in Adults with Cystic Fibrosis

Citation: Ultrasound in Medicine and Biology, January 2015, vol./is. 41/1(334-338), 0301-5629;1879-291X (01 Jan 2015)


Abstract: It is of clinical importance to identify bone disease related to cystic fibrosis (CF) early in its course to allow therapeutic interventions that optimize bone health. To test the technical (precision) and clinical (percentage of abnormal results, correlation with clinical parameters) performance of a commercial quantitative ultrasound apparatus for radial measurements, speed of sound (SOS) was measured at the distal third of the left radius with the Omnisense 7000p apparatus (Sunlight Medical, Tel-Aviv, Israel) in a group of young adult CF patients with regular follow-up at the Brussels and Ghent University Hospital. Sixty-three (37 males) CF patients at a median (range) age of 23.5y (18.1-39.9) were included. SOS, SOS z-score and SOS t-score were respectively 4017+/-97 m/s, -0.31+/-0.74 and -0.60+/-0.78 in males and 4086+/-97 m/s, -0.19+/-0.75 and -0.51+/-0.95 in females. Mean SOS t-score was significantly lower compared with the manufacturer’s reference data for males (p<0.0001) and females (p=0.01). SOS z- and t-scores correlated with weight z-score and body mass index z-score in females. No significant correlation was found between SOS and forced expiratory volume in 1s (%). Neither diabetes mellitus nor liver disease was found to influence SOS. Radial quantitative ultrasound has a precision of 0.55%. The SOS is in the low normal range in 14% of CF patients and is influenced by weight in female patients, but not by the severity of the lung disease.

Title: Several siblings with Cystic Fibrosis as a risk factor for poor outcome

Citation: Respiratory Medicine, January 2015, vol./is. 109/1(74-78), 0954-6111;1532-3064 (01 Jan 2015)

Author(s): Lavie M., Shemer O., Sarouk I., El Bar Aluma B., Dagan A., Efrati O., Vilozni D.

Abstract: Background Occurrence of Cystic Fibrosis (CF) in more than one member in a family is not uncommon. The aim of our study was to assess the influence of multiple siblings with CF on disease expression and outcome. Methods Study group consisted of 2-siblings (2-sibs, n = 42) or 3/4 siblings (3/4-sibs, n = 22) with CF in one family. Each sibling was matched by age, mutation, and gender to a single CF patient. Results 3/4-sibs subgroup compared to singles showed a lower mean FEV1 with a faster decline rate (58.4 +/- 25.4 and -5 +/- 6.4 vs. -1.7 +/- 2.8 %predicted decline/year respectively, p <.05), more airway colonization by Pseudomonas aeruginosa and Mycobacterium abscessus (15 (68%) vs. 8 (36%) and 7 (32%) vs. 4 (18%), respectively, p <.05) and
more lung transplants (5 (23%) vs. 2 (9%), respectively, p <.02). Last mean FEV1 within 3/4-sibs was significantly lower for the youngest sib (p <.05).

Conclusions Three or more CF patients in one family may be a risk factor for more severe disease and poor prognosis. In our view this reflects the burden of disease on the patients and families.

Title: Central venous thrombosis and thrombophilia in cystic fibrosis: A prospective study

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(97-103), 1569-1993;1873-5010 (01 Jan 2015)


Abstract: Background and Aims: Catheter venous thrombosis may result in life-threatening embolic complications. Recently, a thrombophilic tendency was described in cystic fibrosis (CF), the significance of which remains unclear. The aims of this study were to (1) document the frequency of catheter venous thrombosis detected by colour-Doppler-ultrasound (Doppler-US), (2) assess genetic and acquired thrombophilia risk factors for catheter venous thrombosis and hypercoagulability status and (3) provide recommendations on laboratory screening when considering insertion of a totally implantable vascular access device (TIVAD) in CF patients. Methods: We designed a multicentre prospective study in patients selected at the time of catheter insertion. Doppler-US was scheduled at 1 and 6 months after insertion and before insertion in case of a previous central line. Blood samplings were drawn at insertion and at 1 and 6 months later. Results: One-hundred patients received a TIVAD and 90 completed the 6-month study. Prevalence of thrombophilia abnormalities and hypercoagulability was found in 50% of the cohorts. Conversely, catheter venous thrombosis frequency was low (6.6%). Conclusion: Our data do not support biological screening at the time of a TIVAD insertion. We emphasise the contribution of a medical history of venous thromboembolism and prospective Doppler-US for identifying asymptomatic catheter venous thrombosis to select patients who may benefit from biological screening and possible anticoagulant therapy.

Title: Indicators of pulmonary exacerbation in cystic fibrosis: A Delphi survey of patients and health professionals

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(90-96), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): McCourt F., O'Neill B., Logan I., Abbott J., Plant B., McCrum-Gardner E., McKeown S., Stuart Elborn J., Bradley J.M.
Abstract: Background: There is uncertainty about the most important indicators of pulmonary exacerbations in CF. Methods: Two parallel Delphi surveys in 13 CF centres (UK and Ireland). Delphi 1: 31 adults with CF, > one exacerbation over 12 months. Delphi 2: 38 CF health professionals. Rounds 1 and 2 participants rated their level of agreement with statements relating to indicators of exacerbation; Round 3 participants rated the importance of statements which were subsequently placed in rank order. Results: Objective measurements were of higher importance to health professionals. Feelings of increased debility were rated most important by adults with CF. Conclusions: There were clear differences in perspectives between the two groups as to the most important indicators of an exacerbation. This highlights that CF health professionals should take more cognisance of specific signs and symptoms reported by adults with CF, especially since these may be a precursor to an exacerbation.

Title: Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(111-119), 1569-1993;1873-5010 (01 Jan 2015)


Abstract: Background: Consensus guidelines recommend early treatment to eradicate newly acquired Pseudomonas aeruginosa (Pa) infection in cystic fibrosis (CF) patients although there is no single preferred regimen. Aztreonam for inhalation solution (AZLI) significantly reduces sputum Pa density in CF patients with chronic Pa infection and has been well tolerated in the pediatric population. This single-arm, open-label Aztreonam Lysine for Pseudomonas Infection Eradication (ALPINE) study was conducted to evaluate the safety and efficacy of a 28-day treatment course of AZLI to eradicate newly acquired Pa infection in pediatric CF patients. Methods: CF patients (3 months to < 18 years) with new onset Pa infection were treated with AZLI 75 mg 3 times daily for 28 days. New onset Pa infection was defined as first lifetime Pa-positive respiratory tract culture (throat swab, sputum) or Pa-positive culture after a > 2-year history of Pa-negative cultures (> 2 cultures/year). Sputum or throat swab cultures were collected at study entry (baseline) and at weeks 4 (end of treatment), 8, 16, and 28. Primary endpoint was the percentage of patients with cultures negative for Pa at all post-treatment time points. Results: A total of 105 pediatric CF patients enrolled (3 months to < 2 years, n = 24; 2 to < 6 years, n = 25; 6 to < 18 years, n = 56). Of the 101 patients who completed treatment, 89.1% (n = 90) were free of Pa at the end of treatment and 75.2% (n = 76) were free of Pa 4 weeks after the end of treatment. Of the 79 patients evaluable for the primary endpoint, 58.2% were free of Pa at all post-treatment time points. Conclusions: AZLI was effective and well tolerated in eradicating Pa from newly infected pediatric patients with CF. These eradication rates are consistent with success rates reported in the literature for various antibiotic regimens, including other inhaled antibiotics studied for eradication.ClinicalTrials.gov: NCT01375049.

Title: Cystic fibrosis-related bone disease explored using a four step algorithm
Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(127-134), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Brookes D.S.K., Briody J.N., Munns C.F., Davies P.S.W., Hill R.J.

Abstract: Background: A suboptimal bone accrual in young individuals with cystic fibrosis (CF) may be related to the development of a premature CF-related bone disease. Dual energy X-ray absorptiometry (DXA) is the mainstream measure of bone health; however, the influence of body size and lean tissue mass (LTM) on bone data is poorly interpreted. Methods: Total body dual-energy X-ray absorptiometry (DXA) measurements of bone mineral content (BMC) and LTM in 53 individuals with CF (7.00-17.99 years) were compared to 53 sex-matched controls. BMC, height, and LTM in relation to height and BMC Z-scores were calculated and used in a 4-step algorithm. Results: Pubertal females with CF had less total body BMC for age (p. = 0.02); pre-pubertal males (p. = 0.05) and pubertal females with CF (p. = 0.03) were shorter; and pubertal females with CF showed less total body BMC for LTM (p. = 0.01). Conclusions: The algorithm showed the following: (1) prior to puberty lowered total body BMC was primarily due to short stature, (2) LTM was appropriate for body size, and (3) pubertal females with CF had significantly less total body BMC for their LTM. Longer controlled trials are needed to clinically interpret CF-related bone disease using DXA derived data that considers patient size and body composition.

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Title: Disposition index identifies defective beta-cell function in cystic fibrosis subjects with normal glucose tolerance

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(135-141), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Merjaneh L., He Q., Long Q., Phillips L.S., Stecenko A.A.

Abstract: Background: In non-cystic fibrosis (CF) subjects, the disposition index (DI) is a strong predictor of the development of type 2 diabetes. CF subjects are at high risk of diabetes. We hypothesized that DI would be reduced in CF patients with normal glucose tolerance (NGT), indicating beta-cell dysfunction, and DI would worsen with progression from CF with NGT to CF-related diabetes (CFRD). Methods: This was a cross-sectional study in 39 CF patients and 21 healthy controls (Con) who underwent oral glucose tolerance test (OGTT). Insulin sensitivity was estimated as (1/fasting insulin) and insulin secretion as (DELTAINSULIN 0-30. min/DELTAGlucose 0-30. min). DI was calculated as (insulin sensitivity). x. (insulin secretion). Results: Among CF subjects, 14 had NGT, 20 had prediabetes and 5 had CFRD. Among the controls, 14 had NGT and 7 had prediabetes. DI was significantly lower in CF-NGT compared to Con-NGT (p = 0.0035). DI was also lower in CFRD compared to CF-NGT (p = 0.025). There were no significant relationships in the CF groups between DI and age, BMI, percent body fat or FEV1. Conclusion: beta-Cell function as measured by DI is reduced in CF patients compared to non-CF controls—even in CF-NGT—and is decreased further in CF patients with diabetes. If DI proves to be a predictor of the development of CFRD in larger studies, then it could be used to identify CF patients who are at particularly high risk, allowing early interventions aimed to delay or prevent CFRD.
Title: Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(84-89), 1569-1993;1873-5010 (01 Jan 2015)


Abstract: Background: Ivacaftor corrects the cystic fibrosis transmembrane conductance regulator (CFTR) gating defect associated with G551D mutation and is quickly becoming an important treatment in patients with cystic fibrosis (CF) due to this genetic mutation. Methods: A single-center study was performed in CF patients receiving ivacaftor to evaluate the usefulness of high resolution computed tomography (HRCT) of the chest as a way to gauge response to ivacaftor therapy. Results: Ten patients with CF were enrolled for at least one year before and after starting ivacaftor. At time of enrollment, mean age was 20.9 +/- 10.8 (range 10-44) years. There were significant improvements from baseline to 6. months in mean %FVC (93. +/- 16 to 99. +/- 16) and %FEV1 (79. +/- 26 to 87. +/- 28) but reverted to baseline at one year. Mean sweat chloride levels decreased significantly from baseline to one year. Mean weight and BMI improved at 6. months. Weight continued to improve with stabilization of BMI at one year. Chest HRCT showed significant improvement at one year in mean modified Brody scores for bronchiectasis, mucus plugging, airway wall thickness, and total Brody scores. Elevated bronchiectasis and airway wall thickness scores correlated significantly with lower %FEV1, while higher airway wall thickness and mucus plugging scores correlated with more pulmonary exacerbations requiring IV and oral antibiotics respectively. Conclusions: Based on our findings, HRCT imaging is a useful tool in monitoring response to ivacaftor therapy that corrects the gating defect associated with the G551D-CFTR mutation.

Title: Putting lung function and physiology into perspective: Cystic fibrosis in adults

Citation: Respirology, January 2015, vol./is. 20/1(33-45), 1323-7799;1440-1843 (01 Jan 2015)

Author(s): Horsley A., Siddiqui S.

Abstract: Adult cystic fibrosis (CF) is notable for the wide heterogeneity in severity of disease expression, both between patients and within the lungs of individuals. Although CF airways disease appears to start in the small airways, in adults there is typically widespread bronchiectasis, increased airway secretions, and extensive obstruction and inflammation of the small airways. The complexity and heterogeneity of airways disease in CF means that although there are many different methods of assessing and describing lung 'function', none of these single-dimensional tests is able to provide a comprehensive assessment of lung physiology across the spectrum seen in adult CF. The most widely described measure, the forced expiratory volume in 1-s, remains a useful and simple clinical tool, but is insensitive to early changes and may be dissociated from other more detailed assessments of disease severity such as computed tomography. In this review, we also discuss the use of more sensitive novel assessments such as multiple breath washout tests and impulse oscillometry, as well as the role of cardiopulmonary exercise testing. In the future, hyperpolarized gas magnetic resonance imaging techniques that combine regional structural and functional
information may help us to better understand these measures, their applications and limitations. See case report in Respirology Case Reports http://dx.doi.org/10.1002/rcr2.69 Watch the Video introducing the Review Series on lung function testing

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**Title:** Association between serum YKL-40 level and dysglycemia in cystic fibrosis

**Citation:** Cytokine, February 2015, vol./is. 71/2(296-301), 1043-4666;1096-0023 (February 01, 2015)

**Author(s):** Bouvet G.F., Maignan M., Arslanian E., Coriati A., Rabasa-Lhoret R., Berthiaume Y.

**Abstract:**

Background: YKL-40, a chitinase-like protein, is a biomarker for type 1 and type 2 diabetes prognosis. We hypothesized that YKL-40 protein levels are elevated in CF patients with dysglycemia. Methods: Seventeen healthy control subjects and 66 CF patients were prospectively recruited and subjected to an oral glucose tolerance test. In all participants, fasting serum YKL-40 was compared between control and CF patients and between normal glucose-tolerant patients (NG-CF) and CF patients with dysglycemia (DG-CF). A Botnia clamp procedure was performed on a subset of patients for each group to determine the impact of acute increases of either glucose or insulin on YKL-40 concentration. Results: CF patients had higher serum YKL-40 values than the controls (113 [49;288] vs. 38 [30;50] ng/ml, p<.001). YKL-40 concentrations in CF patients were mainly increased in the DG-CF group, who had significantly higher values: 213 [93;383] vs. 67 [27;97] ng/ml in the NG-CF group, p<.001). No significant modulation of YKL-40 concentration was observed in serum of CF (NG or DG-CF) or non-CF patients, after acute exposure to glucose or insulin. Conclusions: Higher serum YKL-40 levels in CF patients are significantly associated with dysglycemia. The increase in YKL-40 is potentially associated with an inflammatory response resulting from chronic glucose intolerance or CF disease evolution.

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**Microbiological**

**Title:** Ibuprofen rescues mutant cystic fibrosis transmembrane conductance regulator trafficking

**Citation:** Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(16-25), 1569-1993;1873-5010 (01 Jan 2015)

**Author(s):** Carlile G.W., Robert R., Goepp J., Matthes E., Kus B., Macknight S.D., Rotin D., Hanrahan J.W., Thomas D.Y.

**Abstract:**

Background: Small molecules as shown by VX809 can rescue the mislocalization of F508del-CFTR. The aim of this study was to identify correctors with a clinical history and their targets of action. Methods: CFTR correctors were screened using two F508del-CFTR expressing cell based HTS assays. Electrophysiological studies using CFBE41o<sup>-</sup> and HBE cells and in-vivo mouse assays confirmed CFTR rescue. The target of action was attained using pharmacological inhibitors and siRNA to specific genes. Results: Ibuprofen was identified as a CFTR corrector. Ibuprofen treatment of polarized CFBE41o<sup>-</sup> monolayers increased the short-circuit current (I<sub>sc</sub>) response to stimulation. In vivo CF mice treatment with ibuprofen restored
the CFTR trafficking. SiRNA knock down of cyclooxygenase expression caused partial F508del-CFTR correction. Conclusion: These studies show that ibuprofen is a CFTR corrector and that it causes correction by COX-1 inhibition. Hence ibuprofen may be suitable to be part of a future CF combination therapy.

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

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(6-15), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Rivas Caldas R., Boisrame S.

Abstract: Background: Cystic Fibrosis (CF) is a severe genetic disorder that is common among the Caucasian population. Bacterial respiratory infections are the main cause of morbidity and mortality in CF patients. Pseudomonas aeruginosa is the main pathogen of lower airways (LAW) decline. Method: To understand chronic broncho-pulmonary colonization, a systematic review is conducted. The aim of our article is to identify the pathways of contamination in the upper aero-digestive tract. Results: A large number of articles report that P. aeruginosa is established first at nasopharyngeal sites. The vast majority of authors agree that the upper aero-digestive tract is the first location of colonization by P. aeruginosa and its presence appears to be predictive of subsequent broncho-pulmonary colonization. Conclusion: This review supports the possible involvement of the nasal and paranasal sinuses and oral cavity as means of contamination.

Title: Increasing nontuberculous mycobacteria infection in cystic fibrosis

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(53-62), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Bar-On O., Mussaffi H., Mei-Zahav M., Prais D., Steuer G., Stafler P., Hananya S., Blau H.

Abstract: Background: Nontuberculous mycobacteria (NTM) are emerging infections in the CF population. Aims: To assess NTM infection prevalence and associated features in our CF clinic population. Methods: Patient records, 2002-2011, were reviewed for NTM infection. FEV₁, pancreatic function, sputum microbiology, and serum cytokines were compared in patients with and without NTM infection. Results: Incidence rate of NTM infection increased from 0 in 2002 to 8.7% in 2011 (p. < .0001). NTM infection prevalence increased 3-fold from 5% (4/79) in 2003 to 14.5% (16/110) in 2011 (p. = 0.05). Prevalence of chronic NTM lung disease has decreased somewhat since a peak in 2009, with institution of aggressive triple therapy. Of NTM-infected compared to uninfected patients, 88.2% vs. 60.3% had a known ‘severe’ CFTR genotype (p. = 0.04), 88.2% vs. 58.9% were pancreatic insufficient (p. = 0.02); 70.6% vs. 43.8% had chronic Pseudomonas aeruginosa (p. = 0.06); 75% vs. 32% had Aspergillus infection (p. = 0.007) and 23.5% vs 2.7% had allergic bronchopulmonary aspergillosis (p. = 0.01). Patients infected with Mycobacterium abscessus had increased TGF-beta, TNF-alpha, IL-1beta, IL-2, IL-4 and IL-5 levels (p. < .05). There was no
difference in cytokine levels for all NTM infected compared to uninfected patients. M. abscessus comprised 46% of all NTM infections. Comparing M. abscessus versus other NTM, duration was 10.5 (1-118) months versus 1 (1-70) month, median (range) (p. = 0.004); lung disease occurred in 69% versus 17% (p. = 0.0004), with sputum conversion in 4/11 versus 5/6, respectively (NS). Conclusions: NTM incidence and prevalence have increased dramatically in our CF clinic, associated with a severe CF genotype and phenotype. M. abscessus, the most prevalent NTM, caused prolonged infection despite therapy. There has been some decrease in the prevalence of NTM lung disease since 2009.

Title: Transcriptional adaptations during long-term persistence of Staphylococcus aureus in the airways of a cystic fibrosis patient

Citation: International Journal of Medical Microbiology, January 2015, vol./is. 305/1(38-46), 1438-4221;1618-0607 (01 Jan 2015)

Author(s): Windmuller N., Witten A., Block D., Bunk B., Sproer C., Kahl B.C., Mellmann A.

Abstract: The lungs of Cystic fibrosis (CF) patients are often colonized and/or infected by Staphylococcus aureus for years, mostly by one predominant clone. For long-term survival in this environment, S. aureus needs to adapt during its interactions with host factors, antibiotics, and other pathogens. Here, we study long-term transcriptional as well as genomic adaptations of an isogenic pair of S. aureus isolates from a single patient using RNA sequencing (RNA-Seq) and whole genome sequencing (WGS). Mimicking in vivo conditions, we cultivated the S. aureus isolates using artificial sputum medium before harvesting RNA for subsequent analysis. We confirmed our RNA-Seq data using quantitative real-time (qRT)-PCR and additionally investigated intermediate isolates from the same patient representing in total 13.2 years of persistence in the CF airways. Comparative RNA-Seq analysis of the first and the last ("late") isolate revealed significant differences in the late isolate after 13.2 years of persistence. Of the 2545 genes expressed in both isolates that were cultivated aerobically, 256 genes were up- and 161 were down-regulated with a minimum 2-fold change (2f). Focusing on 25 highly (>8f) up- (. n= 9) or down- (. n= 16) regulated genes, we identified several genes encoding for virulence factors involved in immune evasion, bacterial spread or secretion (e.g. spa, sak, and esxA). Moreover, these genes displayed similar expression trends under aerobic, microaerophilic and anaerobic conditions. Further qRT-PCR-experiments of highly up- or down-regulated genes within intermediate S. aureus isolates resulted in different gene expression patterns over the years. Using sequencing analysis of the differently expressed genes and their upstream regions in the late S. aureus isolate resulted in only few genomic alterations. Comparative transcriptomic analysis revealed adaptive changes affecting mainly genes involved in host-pathogen interaction. Although the underlying mechanisms were not known, our results suggest adaptive processes beyond genomic mutations triggered by local factors rather than by activation of global regulators.

Title: Denitrification by cystic fibrosis pathogens - Stenotrophomonas maltophilia is dormant in sputum
**Abstract:** Objective: Chronic Pseudomonas aeruginosa lung infection is the most severe complication for cystic fibrosis (CF) patients. Infected endobronchial mucus of CF patients contains anaerobic zones mainly due to the respiratory burst of polymorphonuclear leukocytes. We have recently demonstrated ongoing denitrification in sputum from patients infected with P. aeruginosa. Therefore we aimed to investigate, whether the pathogenicity of several known CF pathogens is correlated to their ability to perform denitrification. Methods: We measured denitrification with N\textsubscript{2}O microsensors in concert with anaerobic growth measurements by absorbance changes and colony counting in isolates from 32 CF patients chronically infected with the highly pathogenic bacteria P. aeruginosa, Achromobacter xylosoxidans, Burkholderia multivorans or the less pathogenic bacterium Stenotrophomonas maltophilia. Consumption of NO\textsubscript{3}\textsuperscript{-} and NO\textsubscript{2}\textsuperscript{-} was estimated by the Griess Assay. All isolates were assayed during 2 days of incubation in anaerobic LB broth with NO\textsubscript{3}\textsuperscript{-} or NO\textsubscript{2}\textsuperscript{-}. PNA FISH staining of 16S rRNA was used to estimate the amount of ribosomes per bacterial cells and thereby the in situ growth rate of S. maltophilia in sputum. Results: Supplemental NO\textsubscript{3}\textsuperscript{-} caused increased production of N\textsubscript{2}O by P. aeruginosa, A. xylosoxidans and B. multivorans and increased growth for all pathogens. Growth was, however, lowest for S. maltophilia. NO\textsubscript{3}\textsuperscript{-} was metabolized by all pathogens, but only P. aeruginosa was able to remove NO\textsubscript{2}\textsuperscript{-}. S. maltophilia had limited growth in sputum as seen by the weak PNA FISH staining. Conclusions: All four pathogens were able to grow anaerobically by NO\textsubscript{3}\textsuperscript{-} reduction. Denitrification as demonstrated by N\textsubscript{2}O production was, however, not found in S. maltophilia isolates. The ability to perform denitrification may contribute to the pathogenicity of the infectious isolates since complete denitrification promotes faster anaerobic growth. The inability of S. maltophilia to proliferate by denitrification and therefore grow in the anaerobic CF sputum may explain its low pathogenicity in CF patients.

**Title:** Purification and characterization of a mycelial catalase from Scedosporium boydii, a useful tool for specific antibody detection in patients with cystic fibrosis

**Citation:** Clinical and Vaccine Immunology, January 2015, vol./is. 22/1(37-45), 1556-6811;1556-679X (01 Jan 2015)

**Author(s):** Mina S., Marot-Leblond A., Cimon B., Fleury M.J.J., Larcher G., Bouchara J.-P., Robert R.

**Abstract:** Scedosporium boydii is an opportunistic filamentous fungus which may be responsible for a wide variety of infections in immunocompetent and immunocompromised individuals. This fungus belongs to the Scedosporium apiospermum species complex, which usually ranks second among the filamentous fungi colonizing the airways of patients with cystic fibrosis (CF) and may lead to allergic bronchopulmonary mycoses, sensitization, or respiratory infections. Upon microbial infection, host
phagocytic cells release reactive oxygen species (ROS), such as hydrogen peroxide, as part of the antimicrobial response. Catalases are known to protect pathogens against ROS by detoxification of the hydrogen peroxide. Here, we investigated the catalase equipment of Scedosporium boydii, one of the major pathogenic species in the S. apiospermum species complex. Three catalases were identified, and the mycelial catalase A1 was purified to homogeneity by a three-step chromatographic process. This enzyme is a monofunctional tetrameric protein of 460 kDa, consisting of four 82-kDa glycosylated subunits. The potential usefulness of this enzyme in serodiagnosis of S. apiospermum infections was then investigated by an enzyme-linked immunosorbent assay (ELISA), using 64 serum samples from CF patients. Whatever the species involved in the S. apiospermum complex, sera from infected patients were clearly differentiated from sera from patients with an Aspergillus fumigatus infection or those from CF patients without clinical and biological signs of a fungal infection and without any fungus recovered from sputum samples. These results suggest that catalase A1 is a good candidate for the development of an immunoassay for serodiagnosis of infections caused by the S. apiospermum complex in patients with CF.

Title: Transcription factors and miRNAs that regulate fetal to adult CFTR expression change are new targets for cystic fibrosis

Citation: European Respiratory Journal, January 2015, vol./is. 45/1(116-128), 0903-1936;1399-3003 (01 Jan 2015)

Author(s): Viart V., Bergougnoux A., Bonini J., Varilh J., Chiron R., Tabary O., Molinari N., Claustres M., Taulan-Cadars M.

Abstract: The CFTR gene displays a tightly regulated tissue-specific and temporal expression. Mutations in this gene cause cystic fibrosis (CF). In this study we wanted to identify trans-regulatory elements responsible for CFTR differential expression in fetal and adult lung, and to determine the importance of inhibitory motifs in the CFTR-3’ UTR with the aim of developing new tools for the correction of disease-causing mutations within CFTR. We show that lung development-specific transcription factors (FOXA, C/EBP) and microRNAs (miR-101, miR-145, miR-384) regulate the switch from strong fetal to very low CFTR expression after birth. By using miRNome profiling and gene reporter assays, we found that miR-101 and miR-145 are specifically upregulated in adult lung and that miR-101 directly acts on its cognate site in the CFTR-3’ UTR in combination with an overlapping AU-rich element. We then designed miRNA-binding blocker oligonucleotides (MBBOS) to prevent binding of several miRNAs to the CFTR-3’ UTR and tested them in primary human nasal epithelial cells from healthy individuals and CF patients carrying the p.Phe508del CFTR mutation. These MBBOS rescued CFTR channel activity by increasing CFTR mRNA and protein levels. Our data offer new understanding of the control of the CFTR gene regulation and new putative correctors for cystic fibrosis.

Title: Analysis of changes in diversity and abundance of the microbial community in a cystic fibrosis patient over a multiyear period
**Citation:** Journal of Clinical Microbiology, January 2015, vol./is. 53/1(237-247), 0095-1137;1098-660X (01 Jan 2015)

**Author(s):** Stokell J.R., Gharaibeh R.Z., Hamp T.J., Zapata M.J., Fodor A.A., Steck T.R.

**Abstract:** The evolution of pulmonary disease in cystic fibrosis (CF) usually begins when bacteria get trapped in mucus in the lungs and become established as a chronic infection. While most CF patients experience periods of stability, pulmonary exacerbations (PEs) can occur multiple times per year and result in permanent damage to the lungs. Little is known of the shift from a period of stability to a PE, but this shift is likely to be attributed to changes in the bacterial community. Here, we identified changes in the lung microbiota to determine if they reflect patient health, indicate the onset of exacerbations, or are related to antibiotic treatment. In contrast to most bacterial studies on CF, we collected weekly samples from an adult CF patient over a period of 3 years and performed quantitative PCR (qPCR) and Illumina sequencing on those samples. While many DNA-based studies have shown the CF microbiota to be relatively stable, we observed an increase in the total bacterial abundance over time (P < 0.001), while the number of different taxa (bacterial richness) and the number of different taxa and their abundances (diversity) significantly decreased over time (P < 0.03), which was likely due to repeated antibiotic exposure. Using genus-specific primers with qPCR, we observed an increase in the abundance of Burkholderia multivorans, a CF-associated pathogen, prior to the occurrence of a PE (P = 0.006). Combining these DNA-based techniques with frequent sampling identified a potential initiator for exacerbations and described a response of the CF microbiota to time and antibiotic treatment not observed in previous CF microbiota studies.

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**Title:** In vitro efficacy of high-dose tobramycin against Burkholderia cepacia complex and Stenotrophomonas maltophilia isolates from cystic fibrosis patients

**Citation:** Antimicrobial Agents and Chemotherapy, January 2015, vol./is. 59/1(711-713), 0066-4804;1098-6596 (01 Jan 2015)

**Author(s):** Ratjen A., Yau Y., Wettlaufer J., Matukas L., Zlosnik J.E.A., Speert D.P., LiPuma J.J., Tullis E., Waters V.

**Abstract:** Burkholderia cepacia complex and Stenotrophomonas maltophilia infections are associated with poor clinical outcomes in persons with cystic fibrosis (CF). The MIC<sub>50</sub> based on planktonic growth and the biofilm concentration at which 50% of the isolates tested are inhibited (BIC<sub>50</sub>) of tobramycin were measured for 180 B. cepacia complex and 101 S. maltophilia CF isolates and were 100 μg/ml for both species. New inhalation devices that deliver high tobramycin levels to the lung may be able to exceed these MICs.

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**Title:** Comparison of Cf-252 thin-film sources prepared by evaporation or self-transfer

**Citation:** Applied Radiation and Isotopes, February 2015, vol./is. 96/(135-138), 0969-8043;1872-9800 (February 01, 2015)

**Author(s):** Algutifan N.J., Sherman S.R., Alexander C.W.
**Abstract:** Thin-film sources containing Cf-252 were prepared by two techniques—evaporation and self-transfer—to determine whether sources prepared by simple evaporation work as well as sources prepared by self-transfer for alpha particle studies. The sources were analyzed by alpha and gamma spectroscopy. Results indicate that self-transfer sources exhibit less alpha energy straggling and alpha energy loss than evaporative sources. Fission fragments may also self-transfer, and sources made by self-transfer may need time to decay before reaching radioactive equilibrium.

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**Title:** CT Density Distribution Analysis in Patients with Cystic Fibrosis: Correlation with Pulmonary Function and Radiologic Scores

**Citation:** Academic Radiology, February 2015, vol./is. 22/2(179-185), 1076-6332;1878-4046 (01 Feb 2015)

**Author(s):** de Lavernhe I., Le Blanche A., Degrugilliers L., Carette M.-F., Bayat S.

**Abstract:** Rationale and Objectives: The progressive changes in lung morphology observed in cystic fibrosis (CF) can potentially affect the statistical distribution of computed tomography (CT) density values. This study aimed to characterize the lung CT density distributions by quantifying indices of the kurtosis and skewness of the lung density distribution and to compare these indices to radiologic scores and lung function parameters in children and young adults with CF. Materials and Methods: CT scans and lung function of 26 patients with CF were retrospectively examined. The Bhalla radiologic scoring was performed separately, in random order, by two expert radiologists, blinded to the patient’s identity, age, clinical status, results of lung function tests, and the other paired observer’s score. Results: Positive relations were evidenced between the log indices of lung density distribution kurtosis (iKurtosis) and the overall radiologic scores (RS) of both observers (R=0.58; P<.001 vs RS1 and R=0.71; P<.001 vs RS2). A similar relationship was evidenced with the log index of the degree of distribution asymmetry (iSkewness; R=0.62; P<.001 vs RS1 and R=0.62; P<.001 vs RS2). Log-iKurtosis and log-iSkewness were related to FEV1 (R=-0.56; P<10<sup>-5</sup> and R=-0.55; P<10<sup>-5</sup>) and to residual volume (R=0.40; P<.001 and R=0.45; P<.001, respectively). Both radiologic scores showed significant relation with lung function. The correlation between RS1 and RS2 was excellent (R=0.93), with a Cohen weighted kappa of 0.43. Conclusions: Characteristic indices of lung CT density distribution are correlated to lung function and radiologic scores in patients with CF and merit further evaluation as part of more comprehensive automated methods for quantifying CF lung CT data.

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**Title:** Cystic fibrosis airway epithelium remodelling: Involvement of inflammation

**Citation:** Journal of Pathology, February 2015, vol./is. 235/3(408-419), 0022-3417;1096-9896 (01 Feb 2015)

**Author(s):** Adam D., Roux-Delrieu J., Luczka E., Bonnomet A., Lesage J., Merol J.-C., Polette M., Abely M., Coraux C.
Abstract: Chronic inflammation is a hallmark of cystic fibrosis (CF) lung disease and airway epithelium damage and remodelling are important components of lung pathology progression in CF. Whether this remodelling is secondary to deleterious infectious and inflammatory mediators, or to alterations of CF human airway epithelial (HAE) cells, such as their hyper inflammatory phenotype or their basic cystic fibrosis transmembrane conductance regulator (CFTR) default, remains debated. In this study, we evaluated the involvement of alterations of CF HAE cells in airway epithelium remodelling. HAE cells from non-CF and CF patients were cultured in an air-liquid interface, with and without inflammatory stimulation, along the regeneration process, and the remodelling of the reconstituted epithelium was analysed. We confirmed that CF HAE cells showed a hyperinflammatory phenotype which was lost with time. In comparison to non-CF epithelium, CF epithelium regeneration in the absence of exogenous inflammation was higher and exhibited basal cell hyperplasia. This remodelling was mimicked by inflammatory stimulation of non-CF cells and was absent when CF HAE cells were no longer hyperinflamed. Moreover, the number of goblet cells was similar in non-CF and CF cultures and increased equally under inflammatory stimulation. Finally, whatever the inflammatory environment, CF cultures showed a delay in ciliated cell differentiation. In conclusion, alterations of CF HAE cells partly regulate airway epithelium remodelling following injury and regeneration. This remodelling, together with goblet cell hyperplasia induced by exogenous inflammation and alteration of ciliated cell differentiation, may worsen mucociliary clearance impairment, leading to injury.

Title: Characterization by phenotypic and genotypic methods of metallo-beta-lactamase-producing Pseudomonas aeruginosa isolated from patients with cystic fibrosis

Citation: Molecular Medicine Reports, January 2014, vol./is. 11/1(494-498), 1791-2997;1791-3004 (01 Jan 2015)

Author(s): Li Y., Zhang X., Wang C., Hu Y., Niu X., Pei D., He Z., Bi Y.

Abstract: Pseudomonas aeruginosa continues to be a predominant cause of infections with high intrinsic resistance to antibiotics, resulting in treatment failure. P. aeruginosa is the leading cause of respiratory infections among cystic fibrosis (CF) patients. Resistance to carbapenem antibiotics among P. aeruginosa has been reported. Thus, this study was undertaken to characterize the metallo-beta-lactamase (MBL) production of P. aeruginosa by phenotypic and genotypic methods. A total of 572 sputum samples were collected from cystic fibrosis patients along with the patient demographic details in a questionnaire. In total, 217 P. aeruginosa isolates were collected and an antibiogram revealed that 159 (73.3%) and 141 (64.9%) of these colonies exhibited resistance to imipenem and meropenem, respectively. Ceftazidime and tobramycin resistance were both identified in 112 (51.6%) isolates, and resistance to piperacillin.tazobactam, gatifloxacin and netilmicin was detected in 96 (44.2%) respective samples. A total of 62 (28.6%) respective samples were resistant to cefoperazone, cefepime and ceftriaxone. The least antibiotic resistance was shown to amikacin and ceftizoxime with 51 (23.5%) and 32 (14.7%) respective colonies resistant to the antibiotics. The minimum inhibitory concentration (MIC) for imipenem revealed a reduction in the MIC values. MBL screening by the zone enhancement method using ceftazidime plus EDTA discs demonstrated that 63 (56.25%) of the colonies were positive for MBL. A total of 53 (84.1%) samples expressed blaVIM and 48 (76.1%) expressed blaIMP genes, as detected by duplex polymerase chain
reaction. In conclusion, carbapenem resistance is of great clinical concern in cystic fibrosis patients with P. aeruginosa infection. Therefore, mandatory regular screening and monitoring the resistance in P. aeruginosa among CF patients is required.

Title: Anti-ETAR and anti-AT1R autoantibodies are elevated in patients with endstage cystic fibrosis

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(42-45), 1569-1993;1873-5010 (01 Jan 2015)


Abstract: Autoantibodies against endothelin-1 type A receptor (ET<sub>A</sub>R) are present in systemic sclerosis complicated by lung fibrosis and pulmonary hypertension. As increased serum levels and local overproduction of endothelin-1 in the airways are reported in cystic fibrosis (CF) patients, we reasoned that anti-ET<sub>A</sub>R antibodies could be prevalent in endstage CF patients prior to lung transplantation (LTx). Also, ET<sub>A</sub>R autoantibodies are frequently associated with autoantibodies against the angiotensin II type 1 receptor (AT<sub>1</sub>R). We analyzed the presence of anti-ET<sub>A</sub>R and anti-AT<sub>1</sub>R autoantibodies in 43 LTx patients (chronic obstructive pulmonary disease (COPD), n=20; CF, n=13; interstitial lung disease (ILD), n=1). We observed overall higher anti-ET<sub>A</sub>R and anti-AT<sub>1</sub>R autoantibody titers in sera taken prior to LTx in the CF patient group as compared to COPD. No difference was found in autoantibody levels between patients with CF versus ILD. In sera taken post-LTx we found the same difference in anti-ET<sub>A</sub>R and anti-AT<sub>1</sub>R autoantibody titers between patients with CF versus COPD. No difference was found in antibody titers between sera taken prior to or 6 months after LTx. There was no association between autoantibody levels and other relevant demographic parameters, and we found no association between autoantibody titers and the development of the bronchiolitis obliterans syndrome. Both autoantibody titers were strongly correlated. We hypothesize that due to prolonged exposure to bacterial infection, increased levels of AT<sub>1</sub>R and ET<sub>A</sub>R result in a deregulated immune response causing autoantibody formation. Further research is expedient to elucidate the occurrence of autoantibodies against ET<sub>A</sub>R and AT<sub>1</sub>R and their role in disease progression.

Title: Mannose-binding lectin gene as a modifier of the cystic fibrosis phenotype in Argentinean pediatric patients

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(78-83), 1569-1993;1873-5010 (01 Jan 2015)

Author(s): Gravina L.P., Crespo C., Giugno H., Sen L., Chertkoff L., Mangano A., Castanos C.
**Abstract:** Background: There is a considerable variation in the phenotype and course of the disease in cystic fibrosis (CF) even in patients with the same CFTR genotype, suggesting that other factors are important for prognosis. Mannose-binding lectin (MBL) has been proposed as one of these factors. We therefore investigated the influence of MBL2 gene variants on disease severity, age at acquisition of Pseudomonas aeruginosa, and survival in CF patients. Methods: MBL2 variants were studied in 106 Argentinean pediatric CF patients carrying two severe CFTR mutations. Clinical phenotype was defined according to the Shwachman score and lung function tests. Age at infection with P. aeruginosa and age at death were also recorded. Results: MBL insufficiency was associated with a 3.5-fold risk of having a severe phenotype (CI 95%: 1.2-10.3, p=0.03). It was also associated with an earlier onset of infection with P. aeruginosa (p=0.035). No statistically significant differences were found in FEV$_1$ and survival. Conclusions: MBL insufficiency was associated with detrimental progression of the disease. These results together with previous findings suggest that the effect of MBL2 expression may be a major determinant of the severity of the clinical phenotype in patients with CF.

**Title:** Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia

**Citation:** Journal of Cystic Fibrosis, January 2015, vol/is. 14/1(46-52), 1569-1993;1873-5010 (01 Jan 2015)


**Abstract:** Background: Nontuberculous mycobacteria (NTM) are an emerging threat to cystic fibrosis (CF) patients but their epidemiology is not well described. Methods: In this retrospective observational study we identified all Scandinavian CF patients with a positive NTM culture from airway secretions from 2000 to the end of 2012 and used national CF databases to describe microbiological and clinical characteristics. Results: During the 13-year period 157 (11%) CF patients were culture positive for NTM at least once. Mycobacterium abscessus complex (MABSC) (45%) and Mycobacterium avium complex (MAC) (32%) were the predominant species with geographical differences in distribution. Younger patients were more prone to MABSC (p<. 0.01). Despite treatment, less than one-third of MABSC patients with repeated positive cultures cleared their infection and a quarter had a lung transplant or died. Conclusion: NTM are significant CF pathogens and are becoming more prevalent in Scandinavia. MABSC and MAC appear to target distinct patient groups. Having multiple positive cultures despite treatment conveys a poor outcome.

**Title:** Comparing Mycobacterium massiliense and Mycobacterium abscessus lung infections in cystic fibrosis patients
**Citation:** Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(63-69), 1569-1993;1873-5010 (01 Jan 2015)


**Abstract:** Background: Mycobacterium massiliense is closely related to Mycobacterium abscessus and is also a frequent cause of mycobacterial lung disease in patients with cystic fibrosis (CF). There has been no previous investigation of possible differences between M. massiliense and M. abscessus infections in the setting of CF. Methods: We studied a prospective cohort of 16 M. massiliense and 27 M. abscessus lung infection cases with CF, with a mean follow-up of 6. years. Results: M. massiliense cases were younger than M. abscessus cases (mean age: 12.8 vs 17.1 years; p=0.02) at the time of the first mycobacterial isolation and also had lower body mass index values (mean: 16.4 vs 19.3 kg/m<sup>2</sup>, p=0.002). All M. massiliense cases, except one, had negative BMI Z-score values at the time of the first mycobacterial isolation (11/12 vs 16/23 M. abscessus cases, p=0.04). Clarithromycin-based combination therapies led to mycobacterial eradication in 100% of M. massiliense cases but only in 27% of M. abscessus cases (p=0.009). Conclusion: Our data show a particular link between M. massiliense and malnutrition specifically in CF patients. Unlike M. abscessus, the bacteriological response of M. massiliense to combination antibiotic therapies containing clarithromycin was excellent. Distinguishing between M. massiliense and M. abscessus has major clinical implications for CF patients.

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**Title:** Antimicrobial efficacy of tobramycin polymeric nanoparticles for Pseudomonas aeruginosa infections in cystic fibrosis: Formulation, characterisation and functionalisation with dornase alfa (DNase)

**Citation:** Journal of Controlled Release, January 2015, vol./is. 198/(55-61), 0168-3659;1873-4995 (28 Jan 2015)

**Author(s):** Deacon J., Abdelghany S.M., Quinn D.J., Schmid D., Megaw J., Donnelly R.F., Jones D.S., Kissenpfennig A., Elborn J.S., Gilmore B.F., Taggart C.C., Scott C.J.

**Abstract:** Inhaled antibiotics, such as tobramycin, for the treatment of Pseudomonas aeruginosa pulmonary infections are associated with the increase in life expectancy seen in cystic fibrosis (CF) patients over recent years. However, the effectiveness of this aminoglycoside is still limited by its inability to penetrate the thick DNA-rich mucus in the lungs of these patients, leading to low antibiotic exposure to resident bacteria. In this study, we created novel polymeric nanoparticle (NP) delivery vehicles for tobramycin. Using isothermal titration calorimetry, we showed that tobramycin binds with alginate polymer and, by exploiting this interaction, optimised the production of tobramycin alginate/chitosan NPs. It was established that NP antimicrobial activity against P. aeruginosa PA01 was equivalent to unencapsulated tobramycin (minimum inhibitory concentration 0.625 mg/L). Galleria mellonella was employed as an in vivo model for P. aeruginosa infection. Survival rates of 90% were observed following injection of NPs, inferring low NP toxicity. After infection with P. aeruginosa, we showed that a lethal inoculum was effectively cleared by
tobramycin NPs in a dose dependent manner. Crucially, a treatment with NPs prior to infection provided a longer window of antibiotic protection, doubling survival rates from 40% with free tobramycin to 80% with NP treatment. Tobramycin NPs were then functionalised with dornase alfa (recombinant human deoxyribonuclease I, DNase), demonstrating DNA degradation and improved NP penetration of CF sputum. Following incubation with CF sputum, tobramycin NPs both with and without DNase functionalisation, exhibited anti-pseudomonal effects. Overall, this work demonstrates the production of effective antimicrobial NPs, which may have clinical utility as mucus-penetrating tobramycin delivery vehicles, combining two widely used CF therapeutics into a single NP formulation. This nano-antibiotic represents a strategy to overcome the mucus barrier, increase local drug concentrations, avoid systemic adverse effects and improve outcomes for pulmonary infections in CF.

Title: New pharmacological approaches for cystic fibrosis: Promises, progress, pitfalls

Citation: Pharmacology and Therapeutics, January 2015, vol./is. 145/(19-34), 0163-7258;1879-016X (January 2015)

Author(s): Bell S.C., De Boeck K., Amaral M.D.

Abstract: With the discovery of the CFTR gene in 1989, the search for therapies to improve the basic defects of cystic fibrosis (CF) commenced. Pharmacological manipulation provides the opportunity to enhance CF transmembrane conductance regulator (CFTR) protein synthesis and/or function. CFTR modulators include potentiators to improve channel gating (class III mutations), correctors to improve abnormal CFTR protein folding and trafficking (class II mutations) and stop codon mutation read-through drugs relevant for patients with premature stop codons (most class I mutations). After several successful clinical trials the potentiator, ivacaftor, is now licenced for use in adults and children (>six years), with CF bearing the class III G551D mutation and FDA licence was recently expanded to include 8 additional class III mutations. Alternative approaches for class I and class II mutations are currently being studied. Combination drug treatment with correctors and potentiators appears to be required to restore CFTR function of F508del, the most common CFTR mutation. Alternative therapies such as gene therapy and pharmacological modulation of other ion channels may be advantageous because they are mutation-class independent, however progress is less well advanced. Clinical trials for CFTR modulators have been enthusiastically embraced by patients with CF and health care providers. Whilst novel trial end-points are being evaluated allowing CFTR modulators to be efficiently tested, many challenges related to the complexity of CFTR and the biology of the epithelium still need to be overcome.

Psychological

Title: Cystic fibrosis (CF) care through the patients’ eyes - A nationwide survey on experience and satisfaction with services using a disease-specific questionnaire
Citation: Respiratory Medicine, January 2015, vol./is. 109/1(79-87), 0954-6111;1532-3064 (01 Jan 2015)

Author(s): Steinkamp G., Stahl K., Ellemunter H., Heuer E., Van Koningsbruggen-Rietschel S., Busche M., Bremer W., Schwarz C.

Abstract: The patients' perspective is an important aspect of quality management. A newly developed disease-specific questionnaire was used to assess the patients' experiences with care provided in specialised cystic fibrosis (CF) care centres. Methods 90 CF centres in Germany were invited to participate. Centre staff collected patient consent forms and sent the patients' addresses to the study centre. The questionnaires for adults and parents had 100 and 104 items respectively, with 3-6 response categories each. Items were dichotomised into "problem scores" (PS), indicating the presence or absence (PS 0%) of a reported problem. Results 56 CF centres took part in the survey and recruited 1642 adults with CF and 1205 parents. The response rates were 74% in each group, with 1221 completed questionnaires from adults and 891 from parents. Participants reported good experiences with care. Factor analysis revealed 10 factors covering 70 items. Participants reported the best results for the factors "Physiotherapists" (PS 6%) and "Physician-Patient Relationship" (PS 9%). Factors with the highest problem scores were inpatient and outpatient "Facilities, Hygiene and Services". CF centres received reports of their own results and mean problem scores of all participating institutions. The problem scores differed considerably between CF centres. Conclusions The nation-wide CF-specific patient experience survey identified specific shortcomings which were mainly related to communication, centre organisation, and facilities. Centre staff can use the results to improve the quality of care. We suggest that patients' views should become an integral component of efforts to promote patient-centred care.

Title: Primary care providers' experiences notifying parents of cystic fibrosis newborn screening results

Citation: Clinical Pediatrics, January 2015, vol./is. 54/1(67-75), 0009-9228;1938-2707 (10 Jan 2015)

Author(s): Finan C., Nasr S.Z., Rothwell E., Tarini B.A.

Abstract: This study examines primary care provider (PCP) experiences with the initial parental disclosure of cystic fibrosis (CF) newborn screening (NBS) results in order to identify methods to improve parent-provider communication during the CF NBS process. PCPs of infants who received positive CF NBS results participated in semistructured phone interviews. Interviews were analyzed using a qualitative content analysis. PCPs acknowledged the difficulty of "breaking bad news" to parents, and emphasized minimizing parental anxiety and maximizing parental understanding. PCPs used a variety of methods to notify parents, and shared varying information about the significance of the results. Variation in the method of parental notification, information discussed, and attention to parents' emotional needs may limit successful follow-up of children with positive CF NBS results. A multifaceted intervention to improve PCP knowledge, management, and communication could improve provider confidence, optimize information transfer, and minimize parental distress during the initial disclosure of CF NBS results.
Title: Sexual and reproductive health in cystic fibrosis: A life-course perspective

Citation: The Lancet Respiratory Medicine, January 2015, vol./is. 3/1(70-86), 2213-2600;2213-2619 (01 Jan 2015)

Author(s): Frayman K.B., Sawyer S.M.

Abstract: Adolescents and adults with cystic fibrosis now approach developmental milestones, including sexual and reproductive ones, at a similar time to their healthy peers. Yet, their sexual and reproductive health (SRH) is profoundly affected by their disease, and their SRH decisions can substantially affect their health. Navigation of SRH milestones in the context of cystic fibrosis needs education, guidance, and access to SRH services. In this Review, we discuss scientific knowledge of SRH in patients with cystic fibrosis across the life course and clinical practices for SRH within cystic fibrosis care. We identify crucial gaps in SRH education of patients and their access to resources and then present a model of care for provision of developmentally appropriate SRH education and care within cystic fibrosis services across the life course. This model emphasises the central importance of the cystic fibrosis team and service links to primary and specialist SRH care.

Title: Opportunities for cystic fibrosis care teams to support treatment adherence

Citation: Journal of Cystic Fibrosis, January 2015, vol./is. 14/1(142-148), 1569-1993;1873-5010 (01 Jan 2015)


Abstract: Background: The purpose of this study was to identify the extent to which pediatric and adult cystic fibrosis (CF) care teams implement best practices in adherence assessment and counseling. Methods: All US CF Foundation accredited programs were invited to participate in a web-based survey; 80% (92/115) of pediatric and 40% (38/95) of adult centers participated. Health care providers reported on current approaches and barriers to implementing adherence promotion practices. Results: 64% discussed adherence at every clinic visit while only 8% used an objective assessment of adherence. Most centers reported frequent use of strategies to increase knowledge behavioral and support strategies were used less regularly. Several barriers to adherence promotion were reported. Conclusions: Many opportunities exist for care teams to improve consistency in adherence practices and integrate a greater repertoire of effective counseling strategies into clinic visits. Adherence promotion practices should be considered for quality improvement (QI) projects.

Title: Origins of cystic fibrosis lung disease

Citation: New England Journal of Medicine, January 2015, vol./is. 372/4(351-62), 0028-4793;1533-4406 (2015 Jan 22)

Author(s): Stoltz DA, Meyerholz DK, Welsh MJ
Journal Tables of Contents

The most recent issues of the following journals:

- Journal of Cystic Fibrosis
- American Journal of Respiratory and Critical Care Medicine
- Thorax
- Chest

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Journal of Cystic Fibrosis
Vol. 14, iss. 1, January 2015

The growing threat of nontuberculous mycobacteria in CF

News

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

Ibuprofen rescues mutant cystic fibrosis transmembrane conductance regulator trafficking

Stimulation of $\beta_2$-adrenergic receptor increases CFTR function and decreases ATP levels in murine hematopoietic stem/progenitor cells

Function, pharmacological correction and maturation of new Indian CFTR gene mutations

Anti-ET$_A$R and anti-AT$_1$R autoantibodies are elevated in patients with endstage cystic fibrosis

Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia

Increasing nontuberculous mycobacteria infection in cystic fibrosis

Comparing Mycobacterium massiliense and Mycobacterium abscessus lung infections in cystic fibrosis patients

Impact of alginate-producing Pseudomonas aeruginosa on alveolar macrophage apoptotic cell clearance

Mannose-binding lectin gene as a modifier of the cystic fibrosis phenotype in Argentinean pediatric patients

Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation
Indicators of pulmonary exacerbation in cystic fibrosis: A Delphi survey of patients and health professionals

Central venous thrombosis and thrombophilia in cystic fibrosis: A prospective study

Survival benefit of induction immunosuppression in cystic fibrosis lung transplant recipients

Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study

Outcome in patients with cystic fibrosis liver disease

Cystic fibrosis-related bone disease explored using a four step algorithm

Disposition index identifies defective beta-cell function in cystic fibrosis subjects with normal glucose tolerance

Opportunities for cystic fibrosis care teams to support treatment adherence

Book review

Raw meat contaminated with epidemic clones of Burkholderia multivorans found in cystic fibrosis patients

Pancreatic enzymes and Fibrosing Colonopathy

Use of neutrophil gelatinase-associated lipocalin (NGAL) in CF

What is hepcidin telling us about the natural history of cystic fibrosis?

Regarding the article entitled “Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis”

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

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American Journal of Respiratory and Critical Care Medicine
Vol. 191, iss. 3, 1st February 2015

The growing threat of nontuberculous mycobacteria in CF

News

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

Ibuprofen rescues mutant cystic fibrosis transmembrane conductance regulator trafficking
Stimulation of $\beta_2$-adrenergic receptor increases CFTR function and decreases ATP levels in murine hematopoietic stem/progenitor cells

Function, pharmacological correction and maturation of new Indian CFTR gene mutations

Anti-ET$_A$R and anti-AT$_1$R autoantibodies are elevated in patients with endstage cystic fibrosis

Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia

Increasing nontuberculous mycobacteria infection in cystic fibrosis

Comparing Mycobacterium massiliense and Mycobacterium abscessus lung infections in cystic fibrosis patients

Impact of alginate-producing Pseudomonas aeruginosa on alveolar macrophage apoptotic cell clearance

Mannose-binding lectin gene as a modifier of the cystic fibrosis phenotype in Argentinean pediatric patients

Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation

Indicators of pulmonary exacerbation in cystic fibrosis: A Delphi survey of patients and health professionals

Central venous thrombosis and thrombophilia in cystic fibrosis: A prospective study

Survival benefit of induction immunosuppression in cystic fibrosis lung transplant recipients

Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study

Outcome in patients with cystic fibrosis liver disease

Cystic fibrosis-related bone disease explored using a four step algorithm

Disposition index identifies defective beta-cell function in cystic fibrosis subjects with normal glucose tolerance

Opportunities for cystic fibrosis care teams to support treatment adherence

Book review

Raw meat contaminated with epidemic clones of Burkholderia multivorans found in cystic fibrosis patients

Pancreatic enzymes and Fibrosing Colonopathy

Use of neutrophil gelatinase-associated lipocalin (NGAL) in CF

What is hepcidin telling us about the natural history of cystic fibrosis?
Regarding the article entitled “Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis”

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

Thorax
Vol. 70, iss. 2, February 2015

What's hot that the other lot got

Highlights from this issue

Growing old(er) with postinfectious bronchiolitis obliterans

Asthma biomarkers: what constitutes a 'gold standard'?

Deprivation, distance and death in lung cancer

PRO: confronting resistance to rule-based medicine is essential to improving outcomes

CON: encouraging resistance to rule-based medicine is essential to improving outcomes

External validation of blood eosinophils, FENO and serum periostin as surrogates for sputum eosinophils in asthma

Mortality trends in women and men with COPD in Ontario, Canada, 1996-2012

Thoracentesis outcomes: a 12-year experience

The effect of oxidative stress polymorphisms on the association between long-term black carbon exposure and lung function among elderly men

The role of receipt and timeliness of treatment in socioeconomic inequalities in lung cancer survival: population-based, data-linkage study

The impact of the 'hub and spoke' model of care for lung cancer and equitable access to surgery

Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: a data linkage study

What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK?

Pulmonary function of a paediatric cohort of patients with postinfectious bronchiolitis obliterans. A long term follow-up
Linear endobronchial ultrasonography: a novelty turned necessity for mediastinal nodal assessment

Markers of inflammation: data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA

UK trainee experience in interstitial lung disease: results from a British Thoracic Society survey

Response to: What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK?

Author’s response: What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK?

A new instrument to assess physician skill at chest tube insertion: the TUBE-iCOMPT

Pleural procedures and patient safety: a national BTS audit of practice

Role of CT in assessing pleural malignancy prior to thoracoscopy

Mediastinal mass in a healthy adolescent at The Children’s Hospital at Westmead, Australia

Pneumococcal vaccination for welders

Stomach versus lungs: the case of a giant hiatal hernia

Chest
Vol. 147, iss. 2, February 2015

The Complexities of ICU Discharge

Is a Raised Eucapnic Blood Bicarbonate Value a Bellwether of Preclinical Obesity Hypoventilation Syndrome? Bicarbonate Values and Obesity Hypoventilation Syndrome

“All That Wheezes Is Not Asthma” (or COPD)! Spirometry and COPD

POINT: Should Lung Cancer Screening by Chest CT Scan Be a Covered Benefit? Yes Cover Lung Cancer Screening? Yes

COUNTERPOINT: Should Lung Cancer Screening by Chest CT Scan Be a Covered Benefit? No Cover Lung Cancer Screening? No

Rebuttal From Dr Yankelevitz
Rebuttal From Dr Yankelevitz

Rebuttal From Drs Courtright and Manaker
Rebuttal From Drs Courtright and Manaker

Components Necessary for High-Quality Lung Cancer Screening

Supplemental materials
Natural Disasters and Nontuberculous Mycobacteria: A Recipe for Increased Disease?

The Future of Lung Transplantation

A Scoping Review of Patient Discharge From Intensive Care: Opportunities and Tools to Improve Care

Preintubation Application of Oral Chlorhexidine Does Not Provide Additional Benefit in Prevention of Early-Onset Ventilator-Associated Pneumonia

Single-Dose Etomidate Does Not Increase Mortality in Patients With Sepsis: A Systematic Review and Meta-analysis of Randomized Controlled Trials and Observational Studies

Impact of Diagnostic Criteria on the Incidence of Ventilator-Associated Pneumonia

Noninvasive Positive Pressure Ventilation Following Esophagectomy: Anastomosis Pressure Tolerance: Safety Demonstrated in a Pig Model

Is a Raised Bicarbonate, Without Hypercapnia, Part of the Physiologic Spectrum of Obesity-Related Hypoventilation? Bicarbonate and Obesity Hypoventilation

Factors Predictive of Airflow Obstruction Among Veterans With Presumed Empirical Diagnosis and Treatment of COPD

Quality of Well-being Outcomes in the National Emphysema Treatment Trial

What Is the Role of Tiotropium in Asthma? Tiotropium for Asthma: A Systematic Review With Meta-analysis

The Effect of Omega-3 Fatty Acids on Bronchial Hyperresponsiveness, Sputum Eosinophilia, and Mast Cell Mediators in Asthma

Improved Management of Acute Asthma Among Pregnant Women Presenting to the ED

The Clinical Course of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Palliative Care and Location of Death in Decedents With Idiopathic Pulmonary Fibrosis

Validation of the GAP Score in Korean Patients With Idiopathic Pulmonary Fibrosis

Racial Difference in Sarcoidosis Mortality in the United States
**CT Scan Findings of Probable Usual Interstitial Pneumonitis Have a High Predictive Value for Histologic Usual Interstitial Pneumonitis**

*Usual Interstitial Pneumonitis on Chest CT Scan*

**The MUC5B Promoter Polymorphism Is Associated With Idiopathic Pulmonary Fibrosis in a Mexican Cohort but Is Rare Among Asian Ancestries**

*Polymorphism in Idiopathic Pulmonary Fibrosis*

**Association Between Occupational Dust Exposure and Prognosis of Idiopathic Pulmonary Fibrosis**

*Occupation and Idiopathic Pulmonary Fibrosis: A Korean National Survey*

**Direct Oral Anticoagulants in Patients With VTE and Cancer**

*Direct Oral Anticoagulants in Patients With Cancer: A Systematic Review and Meta-analysis*

**Hospitalization and Survival in Patients Using Epoprostenol for Injection in the PROSPECT Observational Study**

*Epoprostenol Hospitalization and Survival*

**Pulmonary Arterial Hypertension in the Southern Hemisphere**

*Pulmonary Arterial Hypertension in Brazil: Results From a Registry of Incident Brazilian Cases*

**Accuracy of Fluorodeoxyglucose-PET Imaging for Differentiating Benign From Malignant Pleural Effusions**

*Labeled PET Imaging For Pleural Effusion Diagnosis: A Meta-analysis*

**Derivation and Validation of a CT Scan Scoring System for Discriminating Malignant From Benign Pleural Effusions**

*CT Scan Scoring System for Pleural Effusions*

**Optimal Duration of Anti-TB Treatment in Patients With Diabetes**

*Anti-TB Treatment in Patients With Diabetes Mellitus: Nine or Six Months?*

**New Molecular Targets of Pulmonary Vascular Remodeling in Pulmonary Arterial Hypertension**

*Molecular Targets: Importance of Endothelial Communication*

**Comprehensive CT Cardiothoracic Imaging**

*Comprehensive CT Cardiothoracic Imaging: A New Challenge for Chest Imaging*

**The Value of Respiratory Muscle Testing in Children With Neuromuscular Disease**

*Muscle Tests in Neuromuscular Disease*

**Integration of Palliative Care in the Context of Rapid Response**

*Rapid Response Palliative Care: A Report From The Improving Palliative Care in the ICU Advisory Board*

**Sleep-Disordered Breathing in Down Syndrome**

*Sleep Apnea and Down Syndrome*

**First Rights: Letter to Dr. Kreitman**

**My Father Walks Five Blocks in Winter**

**Two Possibilities**

**Miracle Baby**
Therapeutic Hypothermia After Cardiac Arrest in a Patient With Systemic Sclerosis and Raynaud Phenomenon

Bronchiolitis Obliterans Organizing Pneumonia Following a Jalapeño Grease Fire Lung Injury Following Jalapeño Grease Fire

A Middle-Aged Man With Hypoxia After Cranial Metastasectomy

An Unusual Case of Postpartum Dyspnea

A 41-Year-Old Woman With Shortness of Breath and History of Rash and Recurrent Laryngeal Edema Woman With Dyspnea, Rash, and Laryngeal Edema

A 60-Year-Old Asymptomatic Woman With Pulmonary Lesions and Cervical Lymphadenopathy

An 81-Year-Old Man With an Abnormal Right-Sided Heart Shadow on Chest Radiograph

Critical Care Use in Patients With Lung Cancer

MRI in Allergic Bronchopulmonary Aspergillosis: A New Paradigm in Imaging Evaluation of Allergic Bronchopulmonary Aspergillosis?

How Japanese Medical Journals Manage Conflicts of Interest

National Trends in Benign Pulmonary Resections

Brain Natriuretic Peptide and Fluid Restrictive Approaches to Prevent Ventilator-Associated Pneumonia

Mortality vs Case Fatality in the Assessment of Sarcoidosis Lethality

ABO Blood Type and ARDS

Brain Death and the Moral Code of Islam

Dabigatran and Myocardial Infarction
Bronchial Thermoplasty: Ready for Prime Time - The Evidence Is There!

Response

Response

Response

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