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Cystic Fibrosis

Evidence Update

June 2017

(Bimonthly)

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    8th (Thurs) Interpreting Statistics

    13th (Tues) Critical Appraisal

    29th (Thurs) Literature Searching

July (13.00-14.00)

    3rd (Mon) Interpreting Statistics

    12th (Wed) Critical Appraisal

    21st (Fri) Literature Searching

    26th (Wed) Interpreting Statistics

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NICE National Institute for Health and Care Excellence

Mucolytics for cystic fibrosis | Treatment summary

Source: British National Formulary for Children - BNFc - 20 June 2017

Mucolytics for cystic fibrosis | Treatment summary

Source: British National Formulary - BNF - 20 June 2017

FDA approves expanded use of ivacaftor to treat additional mutations of cystic fibrosis

Source: US Food and Drug Administration - FDA - 17 May 2017 - Publisher: US Food and Drug Administration

Safety in Lactation: Mucolytics and other drugs for cystic fibrosis

Source: Specialist Pharmacy Service - 04 June 2017

Read Summary

Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial

09 June 2017 - Publisher: The Lancet Respiratory Medicine

Draft clinical guideline on diagnosis and management of cystic fibrosis issued for consultation

Source: National Institute for Health and Care Excellence - NICE - 04 May 2017 - Publisher: National Institute for Health and Care Excellence

Read Summary

Adherence to tobramycin inhaled powder vs inhaled solution in patients with cystic fibrosis: analysis of US insurance claims data

Source: Medicines Management Collection - 01 May 2017 - Publisher: Patient Preference And Adherence

Read Summary

Investigating the feasibility of text message reminders to improve adherence to nebulized medication in children and adolescents with cystic fibrosis

Source: Medicines Management Collection - 01 May 2017 - Publisher: Patient Preference And Adherence

Read Summary

Cochrane Library

Prophylactic anti-staphylococcal antibiotics for cystic fibrosis

Alan R Smyth and Margaret Rosenfeld

Online Publication Date: April 2017

Interventions for fatigue and weight loss in adults with advanced progressive illness

Cathy Payne , Philip J Wiffen and Suzanne Martin

Online Publication Date: April 2017

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Cystic fibrosis: Clinical manifestations and diagnosis

- o Diagnostic criteria
- o Overview of clinical features
- o Summary and recommendations

Cystic fibrosis: Hepatobiliary disease

- o Liver transplantation
- o Summary and recommendations
- o

Cystic fibrosis: Treatment of acute pulmonary exacerbations

- o Incidence and consequences
- o Definition
- o Summary and recommendations

Cystic fibrosis: Overview of the treatment of lung disease

- o Macrolide antibiotics
- o CFTR modulators
- o Summary and recommendations

Cystic fibrosis: Overview of gastrointestinal disease

- o Cystic fibrosis-related liver disease (CFLD)

NHS Choices:Behind the Headlines

No News

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- ❖ Allergy and immunology
- ❖ Cardiovascular medicine
- ❖ Dermatology
- ❖ Drug therapy
- ❖ Endocrinology and diabetes mellitus
- ❖ Family medicine
- ❖ Gastroenterology and hepatology
- ❖ General surgery
- ❖ Geriatrics
- ❖ Haematology
- ❖ Hospital Medicine
- ❖ Infectious diseases
- ❖ Nephrology and hypertension
- ❖ Neurology
- ❖ Obstetrics and gynaecology
- ❖ Oncology
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- ❖ Primary care internal medicine
- ❖ Psychiatry
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- ❖ Rheumatology

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Current Awareness Database Articles on Cystic Fibrosis

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

- **Medical**
- **Microbiological**
- **Nutritional**
- **Other**

If you would like any of the following articles in full text, or if you would like a more focused search on your own topic, then get in touch: library@uhbristol.nhs.uk

Medical

Cystic Fibrosis Papers of the Year 2016

Author(s): Doull I.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: This is arguably the most exciting era in the treatment of Cystic Fibrosis (CF) with the emergence of potentially disease modifying therapies. The last year has seen fewer landmark papers, with the consolidation of existing knowledge and advances in the understanding of the patho-physiology and management of CF.Copyright © 2017.

Highlights from the 30th North American Cystic Fibrosis Conference, Orlando 2016

Author(s): Shawcross A.; Barry P.J.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: This is a selection of papers presented at the 30th North American Cystic Fibrosis Conference held in Orlando in October 2016. The papers discussed are thought to be of particular interest to CF caregivers in the UK. We highlight the major themes covered in the conference including novel therapies, recently published and proposed guidelines and insights from registry studies.Copyright © 2017.

Disease-modifying drug therapy in cystic fibrosis

Author(s): Harman K.; Dobra R.; Davies J.C.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: Whilst substantial progress has been made in the treatment of cystic fibrosis, the disease still carries a significant burden in terms of symptoms, requirement for treatment and early

mortality. The last decade has witnessed a new era in the development of small molecule drugs targeting the CFTR protein, which for the first time may provide a truly disease-modifying approach to treatment. This article reviews progress and highlights some of the current and future challenges in CFTR modulator therapies.Copyright © 2017.

Medical devices for cystic fibrosis care may be portable reservoirs of potential pathogens

Author(s): Linnane B.; Collins L.; Bussmann N.; O'Connell N.H.; Dunne C.P.

Source: Journal of Hospital Infection; 2017

Publication Type(s): Article In Press

Anorexia nervosa in cystic fibrosis

Author(s): Linkson L.; Macedo P.; Perrin F.M.R.; Elston C.M.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: This article explores the challenges associated with diagnosing and managing eating disorders such as anorexia nervosa amongst adolescents and adults with cystic fibrosis. It reviews the known risk factors, generic verses disease specific eating disorder risk screening tools and considers the ethical dilemmas associated with critically low body mass indices. A case review is included to illustrate the complexities of managing both conditions in the context of declining respiratory function.Copyright © 2017.

Folate Protects Hepatocytes of Hyperhomocysteinemia Mice From Apoptosis via Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)-Activated Endoplasmic Reticulum Stress

Author(s): Yang A.; Huang M.; Huang Y.; Sun Y.; Mao C.; Yang S.; Deng M.; Ding N.; Yang X.;

Source: Journal of Cellular Biochemistry; 2017

Publication Type(s): Article In Press

Abstract: Folate deficiency is a known risk factor for liver injury; however, the underlying mechanism remains unclear. In this study, we employed a high homocysteine-induced liver injury model of Apolipoprotein E-deficient (ApoE-/-) mice fed high-methionine diet and found that high homocysteine induced endoplasmic reticulum (ER) stress and liver cell apoptosis by downregulation of cystic fibrosis transmembrane conductance regulator (CFTR) expression; observations that were attenuated with supplementation of dietary folate. The regulation on CFTR expression was mediated by CFTR promoter methylation and trimethylation of lysine 27 on histone H3 (H3K27me3). Mechanistically, folate inhibited homocysteine-induced CFTR promoter methylation and H3K27me3, which resulted in upregulation of CFTR expression, and reduced ER stress and liver cell apoptosis. Further study showed that folate inhibited the expression of DNA methyltransferase 1 and enhancer of zeste homolog 2, downregulated the cellular concentrations of S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) and upregulated the SAM/SAH ratio, leading to the inhibition of Hcy-induced DNA hypermethylation and H3K27me3 in CFTR promoter. In conclusion, our results provide insight into the protective role of folate in homocysteine-induced ER stress and liver cell apoptosis through the regulation of CFTR expression.Copyright © 2017 Wiley Periodicals, Inc.

Liver disease in cystic fibrosis presents as non-cirrhotic portal hypertension

Author(s): Witters P.; Libbrecht L.; Cassiman D.; Roskams T.; De Boeck K.; Proesmans M.;

Source: Journal of Cystic Fibrosis; 2017

Publication Type(s): Article In Press

Applying recent advances in the science of CFTR-based therapeutics to improve outcomes in patients with cystic fibrosis

Author(s): Clancy J.P.; Benitez D.S.; Fajac I.; Jain M.; Rowe S.M.; Sawicki G.

Source: Journal of Cystic Fibrosis; 2017

Publication Type(s): Article In Press

Abstract: The content for this activity is based on the satellite symposium, "Applying Recent Advances in the Science of CFTR-based Therapeutics to Improve Outcomes in Patients With Cystic Fibrosis", that was presented at the 30th Annual North American Cystic Fibrosis Conference in Orlando, Florida on October 28, 2016 (Online access: http://courses.elseviercme.com/nacfc16/655e). The content highlights the latest advancements, particularly in CFTR-based therapeutics, for the treatment of patients with cystic fibrosis. Expert faculty discuss the most up-to-date analysis for clinical decision-making, including updates on assessment, monitoring, and management of patients treated with CFTR modulator therapies. The goal of this activity is to increase the knowledge and competencies of the multidisciplinary team involved in the management of patients with CF, and provide strategies for improving the lives of patients. Upon completion of this activity, healthcare providers will be better equipped with imperative information for creating more effective personalized treatment plans and improving patient outcomes.Copyright © 2017 European Cystic Fibrosis Society.

Imaging the abdominal manifestations of cystic fibrosis

Author(s): Gillespie C.D.; O'reilly M.K.; Chan V.O.; Ridge C.A.; Allen G.N.; McDermott S.

Source: International Journal of Hepatology; 2017; vol. 2017

Publication Type(s): Review

Abstract: Cystic fibrosis (CF) is a multisystem disease with a range of abdominal manifestations including those involving the liver, pancreas, and kidneys. Recent advances in management of the respiratory complications of the disease has led to a greater life expectancy in patients with CF. Subsequently, there is increasing focus on the impact of abdominal disease on quality of life and survival. Liver cirrhosis is the most important extrapulmonary cause of death in CF, yet significant challenges remain in the diagnosis of CF related liver disease. The capacity to predict those patients at risk of developing cirrhosis remains a significant challenge. We review representative abdominal imaging findings in patients with CF selected from the records of two academic health centres, with a view to increasing familiarity with the abdominal manifestations of the disease. We review their presentation and expected imaging findings, with a focus on the challenges facing diagnosis of the hepatic manifestations of the disease. An increased familiarity with these abdominal manifestations will facilitate timely diagnosis and management, which is paramount to further improving outcomes for patients with cystic fibrosis.Copyright © 2017 C. D. Gillespie et al.

Gene delivery to the lungs: pulmonary gene therapy for cystic fibrosis.

Author(s): Villate-Beitia, Ilia; Zarate, Jon; Puras, Gustavo; Pedraz, José Luis

Source: Drug development and industrial pharmacy; Jul 2017; vol. 43 (no. 7); p. 1071-1081

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) is a monogenic autosomal recessive disorder where the defective gene, the cystic fibrosis transmembrane conductance regulator (CFTR), is well identified. Moreover, the respiratory tract can be targeted through noninvasive aerosolized formulations for inhalation. Therefore, gene therapy is considered a plausible strategy to address this disease. Conventional

gene therapy strategies rely on the addition of a correct copy of the CFTR gene into affected cells in order to restore the channel activity. In recent years, genome correction strategies have emerged, such as zinc-finger nucleases, transcription activator-like effector nucleases and clustered regularly interspaced short palindromic repeats associated to Cas9 nucleases. These gene editing tools aim to repair the mutated gene at its original genomic locus with high specificity. Besides, the success of gene therapy critically depends on the nucleic acids carriers. To date, several clinical studies have been carried out to add corrected copies of the CFTR gene into target cells using viral and non-viral vectors, some of them with encouraging results. Regarding genome editing systems, preliminary in vitro studies have been performed in order to repair the CFTR gene. In this review, after briefly introducing the basis of CF, we discuss the up-to-date gene therapy strategies to address the disease. The review focuses on the main factors to take into consideration when developing gene delivery strategies, such as the design of vectors and plasmid DNA, in vitro/in vivo tests, translation to human use, administration methods, manufacturing conditions and regulatory issues.

The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis.

Author(s): Aksamit, Timothy; Bandel, Tiemo-Joerg; Criollo, Margarita; De Soyza, Anthony;

Publication Type(s): Journal Article

Abstract: The primary goals of long-term disease management in non-cystic fibrosis bronchiectasis (NCFB) are to reduce the number of exacerbations, and improve quality of life. However, currently no therapies are licensed for this. Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) has potential to be the first long-term intermittent therapy approved to reduce exacerbations in NCFB patients. The RESPIRE programme consists of two international phase III prospective, parallel-group, randomized, double-blinded, multicentre, placebo-controlled trials of the same design. Adult patients with idiopathic or post-infectious NCFB, a history of ≥2 exacerbations in the previous 12months, and positive sputum culture for one of seven pre-specified pathogens, undergo stratified randomization 2:1 to receive twice-daily Ciprofloxacin DPI 32.5mg or placebo using a pocket-sized inhaler in one of two regimens: 28days on/off treatment or 14days on/off treatment. The treatment period is 48weeks plus an 8-week follow-up after the last dose. The primary efficacy endpoints are time to first exacerbation after treatment initiation and frequency of exacerbations using a stringent definition of exacerbation. Secondary endpoints, including frequency of events using different exacerbation definitions, microbiology, quality of life and lung function will also be evaluated. The RESPIRE trials will determine the efficacy and safety of Ciprofloxacin DPI. The strict entry criteria and stratified randomization, the inclusion of two treatment regimens and a stringent definition of exacerbation should clarify the patient population best positioned to benefit from long-term inhaled antibiotic therapy. Additionally RESPIRE will increase understanding of NCFB treatment and could lead to an important new therapy for sufferers.TRIAL REGISTRATIONThe RESPIRE trials are registered in ClinicalTrials.gov, ID number NCT01764841 (RESPIRE 1; date of registration January 8, 2013) and NCT02106832 (RESPIRE 2; date of registration April 4, 2014).

Iron chelation as novel treatment for lung inflammation in cystic fibrosis

Author(s): Aali M.; Caldwell A.; House K.; Chappe V.; Lehmann C.; Zhou J.

Publication Type(s): Article

Abstract: Cystic fibrosis (CF) is an autosomal recessive genetic disorder that results in defective cystic fibrosis transmembrane conductance regulator (CFTR) protein expression and function in various tissues. The leading cause of CF mortality and morbidity is the progressive destruction of the lungs

due to recurrent infections and chronic inflammation. CFTR defect also affects immune cells, including neutrophils, resulting in ineffective, severe and persistent inflammatory response. Since unopposed recruitment of neutrophils significantly contributes to lung tissue damage through the generation of reactive oxygen species (ROS), we hypothesize that the administration of iron chelators could serve as a novel treatment to attenuate chronic inflammation in CF lungs since iron is significantly involved in ROS production by neutrophils. Ideally, the iron chelator should sequester host iron effectively, prevent bacterial access to chelator-bound iron and penetrates lung tissues efficiently, e.g. by inhalational route of administration.Copyright © 2017 Elsevier Ltd

A treatment evaluator tool to monitor the real-world effectiveness of inhaled aztreonam lysine in cystic fibrosis

Author(s): Plant B.J.; Eustace J.A.; Downey D.G.; Gunaratnam C.; Haworth C.S.; Jones A.M.;

Source: Journal of Cystic Fibrosis; Jul 2017

Publication Type(s): Article In Press

Abstract: Background: Studies are required that evaluate real-world outcomes of inhaled aztreonam lysine in patients with cystic fibrosis (CF). Methods: Our treatment-evaluator tool assessed the effectiveness of inhaled aztreonam in routine practice in 117 CF patients across four time periods (6-12 (P2) and 0-6months (P1) pre-initiation, and 0-6 (T1) and 6-12months (T2) post-initiation). Outcomes were: changes in %-predicted forced expiratory volume in 1s (FEV1), body-mass index (BMI), hospitalisation days and intravenous antibiotic usage. Results: Median FEV1% predicted for each 6-month period was 38.9%, 34.6%, 37.1% and 36.5%; median change was -2.0% between P2 and P1, increasing to +0.6% (p<0.001) between P1 and T1. Annualised hospital bed-days was reduced (p=0.05) post-initiation, as was intravenous antibiotics days (p=0.001). BMI increased over 6months post-initiation (p<=0.001). Conclusions: In patients with CF in routine practice, inhaled aztreonam lysine is associated with improved lung function and weight, and reduced hospitalisation and intravenous antibiotic use.Copyright © 2017 The Authors.

Cystic Fibrosis Pulmonary Exacerbations Attributable to Respiratory Syncytial Virus and Influenza: A Population-Based Study.

Author(s): Somayaji, Ranjani; Goss, Christopher H; Khan, Umer; Neradilek, Moni; Neuzil, Kathleen M

Source: Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; Jun 2017; vol. 64 (no. 12); p. 1760-1767

Publication Type(s): Journal Article

Abstract: Background.Characterization of the role of respiratory viral pathogens on cystic fibrosis (CF) pulmonary disease is needed. We aimed to determine the association of influenza and respiratory syncytial virus (RSV) activity with risk of pulmonary exacerbation (PEx) in persons with CF in the United States.Methods.We conducted a cohort study from January 2003 to March 2009 using the CF Foundation Patient Registry merged with Centers for Disease Control and Prevention respiratory virus surveillance data. The primary goal was to determine the association between regional influenza or RSV detections with risk of PEx requiring intravenous antibiotics or hospitalization. We analyzed outcomes by geographic region and week of event using multivariable regression models adjusted for demographic and clinical predictors of PEx stratified for children (<18 years) and adults (≥18 years) to calculate relative risks (RRs) of PEx.Results.There were 21022 individuals (52% male) in the CF patient cohort in 2003 comprised of 12702 children and 8320 adults. The overall incidence rate of PEx was 521.9 per 10000 person-months. In children, a 10% increase in the proportion of surveillance tests positive for influenza or RSV was significantly associated with increased PEx risk (RR, 1.02; 95% confidence interval [CI], 1.01-1.03) and (RR, 1.05; 95% CI, 1.02-1.07), respectively. In adults, surveillance tests positive for influenza (RR, 1.02; 95% CI, 1.01-1.02), but not RSV (RR, 0.99;

95% CI, .98-1.01), had a significant association with PEx risk.Conclusions.Our large CF population-based cohort demonstrated a significant association between PEx risk and influenza activity in children and adults and with RSV activity in children.

An Early Health Economic Analysis of the Potential Cost Effectiveness of an Adherence Intervention to Improve Outcomes for Patients with Cystic Fibrosis.

Author(s): Tappenden, Paul; Sadler, Susannah; Wildman, Martin

Source: PharmacoEconomics; Jun 2017; vol. 35 (no. 6); p. 647-659

Publication Type(s): Journal Article

Abstract:BACKGROUNDCystic fibrosis (CF) negatively impacts upon health-related quality of life and survival. Adherence to nebulised treatments is low; improving adherence is hypothesised to reduce rates of exacerbation requiring intravenous antibiotics and lung function decline.OBJECTIVEA state transition model was developed to assess the cost effectiveness of an intervention aimed at increasing patient adherence to nebulised and inhaled antibiotics compared with current CF care, in advance of the forthcoming CFHealthHub randomised controlled trial (RCT).METHODSThe model estimated the costs and health outcomes for each option from the perspective of the UK National Health Service and Personal Social Services over a lifetime horizon. Health gains were valued in terms of quality-adjusted life-years (QALYs) gained. Forced expiratory volume in 1 second (FEV1) trajectories were predicted over three lung function strata: (1) FEV1 ≥70%, (2) FEV1 40-69% and (3) FEV1 <40%. Additional states were included to represent 'post-lung transplantation' and 'dead'. The model was populated using CF Registry data, literature and expert opinion. Costs were presented at 2016 values. Uncertainty was assessed using deterministic and probabilistic sensitivity analyses.RESULTSIf effective, the adherence intervention is expected to produce an additional 0.19 QALYs and cost savings of £64,078 per patient. Across all analyses, the intervention dominated current care. Over a 5-year period, the intervention is expected to generate cost savings of £49.5 million for the estimated 2979 patients with CF with Pseudomonas aeruginosa currently aged ≥16 years in the UK. If applied to a broader population of adult patients with CF receiving any nebulised therapy, the expected savings could be considerably greater.CONCLUSIONSIf effective, the adherence intervention is expected to produce additional health gains at a lower cost than current CF care. However, the economic analysis should be revisited upon completion of the full RCT. More generally, the analysis suggests that considerable gains could be accrued through the implementation of adherence interventions that shift care from expensive hospital-based rescue to community-based prevention.

The Meanings of Helping: An Analysis of Cystic Fibrosis Patients' Reasons for Participating in Biomedical Research.

Author(s): Christofides, Emily; Stroud, Karla; Tullis, Diana Elizabeth; O'Doherty, Kieran

Source: Journal of empirical research on human research ethics : JERHRE; Jun 2017 ; p. 1556264617713098

Publication Type(s): Journal Article

Abstract: Research participants often report wanting to help as a reason for participation, but who they want to help and why is rarely explored. We examined meanings associated with helping among 21 adults with cystic fibrosis (CF)-a group with high participation in research. Meanings included helping to advance research, helping others with CF, helping as their job, helping themselves, helping because they are special, and helping to give back. While some meanings were primarily oriented toward helping others, some also involved hoping for benefits for oneself, and some included feelings of responsibility. Despite indicating that they understood that research is not

designed to help them directly, participants nevertheless hoped that it might. We discuss implications for research ethics oversight.

Complications of long and intermediate term venous catheters in cystic fibrosis patients: A multicenter study.

Author(s): May, Teresa L; Gifford, Alex H; Lahiri, Thomas; Black, Adam; Trang, Janet;

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jun 2017

Publication Type(s): Journal Article

Abstract:BACKGROUNDTotally implantable venous access devices (TIVADs) or peripherally inserted central venous catheters (PICCs) are commonly used in the care of patients with cystic fibrosis (CF), but they are associated with various complications, including thrombosis, infection, and insertion site symptoms.METHODSWe conducted a retrospective review of PICC and TIVAD use in adults and children with CF over an 8-year period at 3 accredited care centers. Patient attributes included CFTR genotype, comorbidities, lung function, body mass index, use of anticoagulation, and respiratory tract microbiology. Catheter data included line type, caliber, and lumen number. We assessed practice variation by surveying physicians.RESULTSIn a population of 592 CF patients, 851 PICC and 61 TIVADs were placed between January 1, 2003 and July 1, 2011. Larger catheter caliber and increased lumen number were risk factors for PICC complications in adults. Patient-related risk factors for PICC complications included poor nutritional status, infection with Burkholderia cepacia spp., and having ≥5 lines inserted during the study period. The probability of a PICC complication varied across centers (2.6% to 14.1%, p=0.001) and remained significant after adjustment for patient-and line-related risk factors. The median complication-free survival of TIVADs, however, did not vary significantly by center (p=0.85).CONCLUSIONSThis is the first longitudinal, multicenter assessment of complication rates for PICCs and TIVADs in a large cohort of adults and children with CF. Specific patient- and catheter-related characteristics were associated with increased risk of complications. Center effects on complication rates were observed for PICCs.

A clinical tool to calculate post-transplant survival using pre-transplant clinical characteristics in adults with cystic fibrosis.

Author(s): Stephenson, Anne L; Sykes, Jenna; Berthiaume, Yves; Singer, Lianne G; Chaparro, Cecilia;

Source: Clinical transplantation; Jun 2017; vol. 31 (no. 6)

Publication Type(s): Journal Article

Abstract:BACKGROUNDWe previously identified factors associated with a greater risk of death post-transplant. The purpose of this study was to develop a clinical tool to estimate the risk of death after transplant based on pre-transplant variables.METHODSWe utilized the Canadian CF registry to develop a nomogram that incorporates pre-transplant clinical measures to assess post-lung transplant survival. The 1-, 3-, and 5-year survival estimates were calculated using Cox proportional hazards models.RESULTSBetween 1988 and 2012, 539 adult Canadians with CF received a lung transplant with 208 deaths in the study period. Four pre-transplant factors most predictive of poor post-transplant survival were older age at transplantation, infection with B. cepacia complex, low FEV1 percent predicted, and pancreatic sufficiency. A nonlinear relationship was found between risk of death and FEV1 percent predicted, age at transplant, and BMI. We constructed a risk calculator based on our model to estimate the 1-, 3-, and 5-year probability of survival after transplant which is available online.CONCLUSIONSOur risk calculator quantifies the risk of death associated with lung transplant using pre-transplant factors. This tool could aid clinicians and patients in the decision-making process and provide information regarding the timing of lung transplantation.

Heterogeneity in Survival in Adult Patients With Cystic Fibrosis With FEV1 < 30% of Predicted in the United States.

Author(s): Ramos, Kathleen J; Quon, Bradley S; Heltshe, Sonya L; Mayer-Hamblett, Nicole; Lease, Erika D; Aitken, Moira L; Weiss, Noel S; Goss, Christopher H

Abstract:BACKGROUNDLung transplantation (LTx) is frequently considered for patients with cystic fibrosis (CF) when the FEV1 reaches 6.5 years for patients with CF and an FEV1 < 30%, exceeding prior survival estimates. There was substantial heterogeneity in survival, with some patients with CF dying soon after reaching this lung function threshold and others living for many years. For this reason, we conclude that FEV1 < 30% remains an important marker of disease severity for patients with CF. Patients with a supplemental oxygen requirement or frequent exacerbations should have prompt referral because of their increased risk of death.

Preserving Lung Function: The Holy Grail in Managing Cystic Fibrosis.

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

Available in full text at Annals of the American Thoracic Society - from EBSCOhost

Combined lung-liver-pancreas transplantation in a recipient with cystic fibrosis.

Author(s): Barbas, A S; Dib, M J; Al-Adra, D P; Goldaracena, N; Sapisochin, G; Waddell, T K; Keshavjee, S; Selzner, N; Chaparro, C; Cattral, M S

Abstract: Cystic fibrosis (CF) affects multiple organs including the lung, liver, and pancreas. Lung transplant, liver transplant, and combined lung-liver transplant have become well-established therapies for CF patients with end-stage organ failure. Thus far, however, there has been limited experience with pancreas transplantation in CF. In this report, we detail the clinical history, transplant procedure, and post-operative recovery of a patient who underwent combined lung-liver-pancreas transplant for advanced CF.

Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis: MR Imaging of Airway Mucus Contrasts as a Tool for Diagnosis.

Author(s): Dournes, Gaël; Berger, Patrick; Refait, John; Macey, Julie; Bui, Stephanie; Delhaes, Laurence; Montaudon, Michel; Corneloup, Olivier; Chateil, Jean-François; Marthan, Roger; Fayon, Michaël; Laurent, François

Abstract: Purpose To assess the diagnostic accuracy of mucus contrast characterization by using magnetic resonance (MR) imaging to discriminate allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF). Materials and Methods The study was approved by the local Ethics Committee, and all patients or their parents gave written informed consent. One hundred ten consecutive patients with CF were screened between January 2014 and July 2015. All patients underwent a non-contrast material-enhanced MR protocol that included routine T1-weighted and T2-weighted sequences. The presence of mucus with both high T1 and low T2 signal intensities and the so-called inverted mucoid impaction signal (IMIS) sign was qualitatively and quantitatively assessed by two

physicians who were blinded to all other data. The reference standard for a diagnosis of ABPA was the criteria of the Cystic Fibrosis Foundation Consensus Conference. ABPA status was followed up for 1 year. Reproducibility was assessed by using the κ test, correlation was assessed by using the Spearman coefficient, and diagnostic accuracy was assessed by calculating the sensitivity and specificity of IMIS. Results One hundred eight patients with CF were included (mean age, 20 years ± 11 [standard deviation]; range, 6-53 years): 18 patients with ABPA and 90 patients without ABPA. At the lobar level, inter- and intrareader reproducibility were very good (κ > 0.90). IMIS had 94% sensitivity (95% confidence interval [CI]: 73%, 99%) and 100% specificity (95% CI: 96%, 100%) for the diagnosis of ABPA. A complete resolution of IMIS was observed in patients with ABPA after 3 months of specific treatment that was significantly correlated with decrease in total immunoglobulin E level (ρ = 0.47; P = .04). Conclusion The IMIS sign was both specific and sensitive for the diagnosis of ABPA in CF. Allergic fungal inflammation appears to induce characteristic modifications of mucus contrasts that are assessable by using a noninvasive, contrast material-free, and radiation-free method. © RSNA, 2017 Online supplemental material is available for this article.

MRI of cystic fibrosis lung manifestations: sequence evaluation and clinical outcome analysis.

Author(s): Scholz, O; Denecke, T; Böttcher, J; Schwarz, C; Mentzel, H-J; Streitparth, F; Maurer, M H; Pfeil, A; Huppertz, A; Mehl, A; Staab, D; Hamm, B; Renz, D M

Source: Clinical radiology; May 2017

Publication Type(s): Journal Article

Abstract:AIMTo evaluate different magnetic resonance imaging (MRI) sequences for diagnosis of pulmonary manifestations of cystic fibrosis (CF) in comparison to chest computed tomography (CT), including an extended outcome analysis.MATERIALS AND METHODSTwenty-eight patients with CF (15 male, 13 female, mean age 30.5±9.4 years) underwent CT and MRI of the lung. MRI (1.5 T) included different T2- and T1-weighted sequences: breath-hold HASTE (half Fourier acquisition single shot turbo spin echo) and VIBE (volumetric interpolated breath-hold examination, before and after contrast medium administration) sequences and respiratory-triggered PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) sequences with and without fat signal suppression, and perfusion imaging. CT and MRI images were evaluated by the modified Helbich and the Eichinger scoring systems. The clinical follow-up analysis assessed pulmonary exacerbations within 24 months.RESULTSThe highest concordance to CT was achieved for the PROPELLER sequences without fat signal suppression (concordance correlation coefficient CCC of the overall modified Helbich score 0.93 and of the overall Eichinger score 0.93). The other sequences had the following concordance: PROPELLER with fat signal suppression (CCCs 0.91 and 0.92), HASTE (CCCs 0.87 and 0.89), VIBE (CCCs 0.84 and 0.85) sequences. In the outcome analysis, the combined MRI analysis of all five sequences and a specific MRI protocol (PROPELLER without fast signal suppression, VIBE sequences, perfusion imaging) reached similar correlations to the number of pulmonary exacerbations as the CT examinations.CONCLUSIONAn optimum lung MRI protocol in patients with CF consists of PROPELLER sequences without fat signal suppression, VIBE sequences, and lung perfusion analysis to enable high diagnostic efficacy and outcome prediction.

Early childhood lung function is a stronger predictor of adolescent lung function in cystic fibrosis than early Pseudomonas aeruginosa infection

Author(s): Pittman J.E.; Noah H.; Calloway H.E.; Davis S.D.; Leigh M.W.; Knowles M.R.; Drumm M.; Sagel S.D.; Accurso F.J.; Sontag M.K.

Source: PLoS ONE; May 2017; vol. 12 (no. 5)

Publication Type(s): Article

Available in full text at PLoS ONE - from EBSCOhost

Abstract: Objective: Pseudomonas aeruginosa has been suggested as a major determinant of poor pulmonary outcomes in cystic fibrosis (CF), although other factors play a role. Our objective was to investigate the association of early childhood Pseudomonas infection on differences in lung function in adolescence with CF. Methods: Two populations of subjects with CF were studied: from the Gene Modifier Study (GMS), 346 F508del homozygotes with severe vs. mild adolescent lung disease, and from the Colorado Newborn Screen Study (NBS) 172 subjects diagnosed with CF by newborn screening. Associations of Pseudomonas infection and lung function in early childhood with lung function in adolescence were investigated using multivariate linear regression analyses. Results: Among GMS subjects, those with severe adolescent lung disease had worse lung function in childhood (FEV1 25 percentage points lower) compared to subjects with mild adolescent lung disease, regardless of early childhood Pseudomonas status. Among NBS subjects, those with lowest adolescent lung function had significantly lower early childhood lung function and faster rate of decline in FEV1 than subjects with highest adolescent lung function; early Pseudomonas infection was not associated with rate of FEV1 decline. The strongest predictor of adolescent lung function was early childhood lung function. Subjects with a higher percentage of cultures positive for Pseudomonas before age 6 or a lower BMI at 2-4 years old also had lower adolescent lung function, though these associations were not as strong as with early childhood lung function. Conclusions: In separate analyses of two distinct populations of subjects with CF, we found a strong correlation between lower lung function in early childhood and adolescence, regardless of early childhood Pseudomonas status. Factors in addition to early Pseudomonas infection have a strong impact on lung function in early childhood in CF. Further exploration may identify novel underlying genetic or environmental factors that predispose children with CF to early loss of lung function.

Is there a role for sphingosine-1-phosphate pathway in cystic fibrosis bone disease?

Author(s): Jourdain M.-L.; Abdallah D.M.; Guillaume C.; Gangloff S.C.; Jacquot J.; Velard F.; Le Pimpec-Barthes F.; Sermet-Gaudelus I.

Abstract: Objectives: The increasing life expectancy of patients with cystic fibrosis (CF) has been associated with the emergence of co-morbidities such as CF-related bone disease (CFBD). F508del mutation in Cftr gene induced a deficit of osteoblastic maturation in F508del osteoblasts (Velard et al., 2014). Bone homeostasis involves cytokines and lipid mediators such as the prostaglandin E2 (PGE2) and the sphingosine 1-phosphate (S1P). We have showed that a CFTR corrector and potentiator, the C18 (Vertex) is able to restore deficient expression of COX-2/PGE2 and reduce the RANKL production in CF cells (Velard et al., 2015; Delion et al., 2016). These results have opened new domains to explore actors of bone metabolism in CF patients including the S1P/S1P1-5/COX-2/PGE2/RANKL pathway (Jacquot et al., 2016). Methods: To investigate the role of the S1P pathway in CFBD, we evaluated the involvement of defective CFTR on the mRNA expression level of SphK1, 2 and S1P1-5 receptors in primary F508del osteoblasts patients (n=4) compared to primary normal osteoblasts (n=5). The effect of the addition of the CFTR corrector C18 in F508del osteoblasts culture was also evaluated. Results: Our results showed that F508del mutation in osteoblasts significantly reduced SphK2, but not SphK1 mRNA expression. Normal and F508del osteoblasts expressed the S1P1, 2, 3, 4 but rarely the S1P5 receptor (2 of 10 samples). The S1P4 receptor mRNA expression was slightly upregulated in F508del osteoblasts compared to normal osteoblasts. Addition of C18 in F508del osteoblasts restored the SphK2 mRNA expression, increased S1P2 and S1P3 mRNA expression and reduced the S1P4 mRNA expression. Summary and Conclusion: These preliminary

data encourage us to now explore the production level of SphK1&2, S1P and receptors at protein level in F508del osteoblasts compared to normal osteoblasts in the context of CFBD.

Accrual of bone mass in children and adolescents with cystic fibrosis

Author(s): Sharma S.; Cundy T.; Jaksic M.; Byrnes C.; Fenwick S.

Source: Journal of Clinical Endocrinology and Metabolism; May 2017; vol. 102 (no. 5); p. 1734-1739

Publication Type(s): Article

Abstract: Context: Low bone density is a complication of cystic fibrosis (CF). Hypothesis: Accrual of bone mass is most impaired in the sickest children, as judged by nutritional status and pulmonary function. Design: Retrospective analysis of correlation between lumbar spine bone mineral density (BMD), body mass index (BMI), and forced expiratory volume in 1 second (FEV1) z scores in children and adolescents with CF. Setting: Pediatric hospital specialist CF service. Patients: Sixty participants aged 5.9 to 18.8 years (24 female) with confirmed CF. Interventions: Lumbar spine BMD, BMI, and FEV1 z scores measured at first BMD scan; 40 participants had sequential scans. Change in L1-L4 z scores over time was used as a measure of bone accrual, and BMI as a measure of nutritional status. Outcome Measures: Correlations between lumbar spine BMD, BMI, and FEV1 z scores. Results: Mean BMI and BMD z scores were strongly correlated at the initial scan (P Copyright © 2017 Endocrine Society.

Sibling relationships and life satisfaction from the perspective of children and adolescents with cystic fibrosis

Author(s): Renner G.; Bob K.

Source: Developmental Medicine and Child Neurology; May 2017; vol. 59 ; p. 5-6

Publication Type(s): Conference Abstract

Abstract: Introduction: Research on sibling relationships in families with chronically ill children has almost exclusively focused on wellbeing and adjustment of the healthy sibling. The present study aimed at presenting first data on the quality of sibling relationships from the perspective of children and adolescents with cystic fibrosis. Patients and method: 75 children/adolescents (aged 10-18y) with cystic fibrosis from German-speaking countries participated in an online survey and completed the 'Students Life Satisfaction Scale' (SLSS) and the 'Questions on Life Satisfaction for adolescents and adults with cystic fibrosis' (FLZM- CF). 50 participants who had one sibling were additionally given the 'Sibling Relationship Questionnaire' (SRQ-Deu) and a new questionnaire focusing on illness-related aspects of sibling relationships. Results: Compared to normative data, life satisfaction was significantly reduced (p<0.001, d=-0.52). Participants with and without siblings did not differ on SLSS and FLZM-CF. SRQ factors Warmth/Closeness (p=0.02; d=0.35) and Rivalry (p=0.02; d=0.34; indicating perceived parental partiality in favor of the sibling with CF) were significantly elevated. Warmth/Closeness correlated positively with SLSS and FLZM-CF (both r=30, p=0.04). Most participants described positive cystic fibrosis-related emotional support. Conclusion: In this study, most children and adolescents with cystic fibrosis have a positive view of their sibling relationships and experience warmth and closeness. Although having a sibling per se did not have an impact on well-being in our sample, the quality of sibling relationships may contribute to general and cystic fibrosisrelated life satisfaction.

Determinants and outcomes of upfront surgery versus medical therapy for chronic rhinosinusitis in cystic fibrosis

Author(s): Ayoub N.; Thamboo A.; Habib A.-R.; Nayak J.V.; Hwang P.H.

Source: International Forum of Allergy and Rhinology; May 2017; vol. 7 (no. 5); p. 450-458

Publication Type(s): Article

Abstract: Background: The indications for surgical management of chronic rhinosinusitis (CRS) in patients with cystic fibrosis (CF) are poorly defined. In this study we compare outcomes of medical versus surgical treatment and examine trends associated with the transition from medical to surgical therapy in CF patients. Methods: One hundred thirty-six patients with CF referred to a tertiary rhinology practice were retrospectively divided into 3 cohorts: Medical, Upfront Surgery, or Crossover, if they converted from medical to surgical management. The 22-item Sino-Nasal Outcome Test (SNOT-22) and pulmonary function test (PFT) data were assessed up to 48 months. Results: Compared to patients initially managed medically (n = 90), those who pursued upfront surgery (n = 46) had a greater incidence of nasal polyposis (p = 0.0011), prior sinus surgery (p = 0.0025), lower percent-predicted forced expiratory volume in 1 second (%FEV1) (p = 0.0063), and higher Lund-Mackay (p = 0.0025) and SNOT-22 (p = 0.0229) scores. Within the medical group, 35.5% converted to surgery after a mean of 14.3 months. Crossover (n = 32) was associated with a 6.1-point increase in SNOT-22 and a 4.5% deterioration in %FEV1. Despite worsened symptom severity, the Crossover cohort ultimately achieved similar postoperative SNOT-22 scores (p = 0.831) and %FEV1 (p = 0.114) as those who underwent upfront surgery. Although the Medical cohort had the lowest baseline SNOT-22 scores (p Copyright © 2017 ARS-AAOA, LLC

Lobar double lung transplantation in a patient with cystic fibrosis after extended ECMO-therapy

Author(s): Feth M.; Wilkens H.; Seiler F.; Kamp A.; Wehrfritz H.; Bals R.; Lepper P.M.; Trudzinski F.C.; Langer F.; Schafers H.-J.

Publication Type(s): Conference Abstract

Abstract:: Introduction: The prognosis of cystic fibrosis (CF) patients treated on extracorporeal membrane oxygenation (ECMO) is limited and often depending on timely lung transplantation (LTX). Case Report: We report the case of an 18 year old CF patient (139 cm/38 kg). He had pneumonia complicated by a tension pneumothorax and was hospitalized in an external hospital. After intubation and mechanical ventilation (MV), he progressed to severe ARDS and was put on ECMO. He was already treated on ECMO for 10 days when he was transferred to our center by our mobile ECMO team. After retrieval he was weaned from ECMO and MV and listed for LTX after a structured and critical review of all data. However, during the same hospital stay the patient deteriorated again, MV, extracorporeal carbon dioxide removal (ECCO2R) and finally ECMO with a double-lumen cannula were established. Being 139 cm tall, he required an offer of relatively small lungs. After a prolonged course of extracorporeal support without a donor organ offer, extended organ acceptance criteria without an upper total lung capacity (TLC) limit were set. An allograft with a TLC of 7 liter was accepted for transplantation after a course of 46 days on ECMO in total. According to the size mismatch an anatomic lobar reduction with transplantation of the left upper-and the right upper and middle lobe was performed. The patient could be weaned from ECMO 3 days and from MV 18 days later and was finally discharged home. Three month after LTX, he started to work again. Conclusion: The time frame for LTX in CF patients on extracorporeal support is short. Lobar transplantation is a lifesaving option for patients who cannot wait for size matched organs.

Extracorporeal membrane oxygenation as a as bridge to lung transplantation in patients with cystic fibrosis

Author(s): Feth M.; Frank A.; Seiler F.; Kamp A.; Flaig M.; Metz C.; Becker S.L.; Wilkens H.; Bals R.; Lepper P.M.; Trudzinski F.; Langer F.; Schafers H.-J.

Publication Type(s): Conference Abstract

Abstract:The prognosis of patients with cystic fibrosis (CF) requiring mechanical ventilation due to acute respiratory failure (ARF) is poor. Whether extracorporeal membrane oxygenation (ECMO) improves outcome in these patients remains controversial. Methods: Retrospective analysis of all CF patients with ARF treated with ECMO at University Hospital of Saarland from December 2012 to July 2016. Results: We identified 20 patients fulfilling the criteria above (mean age 29.1 +/- 10.6 years, 6 (30%) male). Reasons for deterioration were pulmonary exacerbations in themajority of cases. All patients were primarily treated on veno-venous ECMO. Two patients ultimately received veno-veno-arterial cannulation for severe hemodynamic impairment. 3 Patients who had previously undergone lung transplantation (LTX) suffered from chronic lung allograft dysfunction. 11 (55%) patients were enlisted to LTX on hospital admission. 6 patients (30%) received LTX evaluation and were listed on ECMO. 3 Patients were listed with high urgency status. After Lung Allocation Score (LAS) implementation in Germany (12/2011), 17 patients were listed (mean LAS 91.0 +/- 4 pts). 8/17 Patients finally (47%) underwent LTX, 3/8 (37.5%) as re-LTX. Mean time on ECMO was 30.8 +/- 13 days. 9 Patients (45%) died on the waiting list and 3 (15%) could be weaned from ECMO without direct transplantation. Conclusion: The prognosis of CF patients treated on ECMO is limited and often depending on timely LTX. Mortality on the waiting list is still an important problem despite implementation of the LAS.

Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease

Author(s): Popowicz N.; Wood J.; Tai A.; Morey S.; Mulrennan S.

Publication Type(s): Article

Abstract:Safety-data for lumacaftor/ivacaftor (LUM/IVA) combination therapy in patients with severe lung disease (percent predicted forced expiratory volume in 1 s [ppFEV1] 1: 34 [31-36]) prescribed LUM/IVA. All patients experienced a decline in ppFEV1 from baseline at 2-hours (median [IQR] relative change: - 19 [- 21 to - 11]%, p 1Copyright © 2017

Oscillating devices for airway clearance in people with cystic fibrosis

Author(s): Morrison L.; Innes S.

Publication Type(s): Review

Abstract:Background: Chest physiotherapy is widely prescribed to assist the clearance of airway secretions in people with cystic fibrosis. Oscillating devices generate intra- or extra-thoracic oscillations orally or external to the chest wall. Internally they create variable resistances within the airways, generating controlled oscillating positive pressure which mobilises mucus. Extra-thoracic oscillations are generated by forces outside the respiratory system, e.g. high frequency chest wall oscillation. This is an update of a previously published review. Objectives: To identify whether oscillatory devices, oral or chest wall, are effective for mucociliary clearance and whether they are equivalent or superior to other forms of airway clearance in the successful management of secretions in people with cystic fibrosis. Search methods: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and hand searches of relevant journals and abstract books of conference proceedings. Latest search of the Cystic Fibrosis Trials Register: 27 April 2017. In addition we searched the trials databases ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Latest search of trials databases: 26 April 2017. Selection criteria: Randomised controlled studies and controlled clinical studies of oscillating devices compared with any other form of physiotherapy in people with cystic fibrosis. Single-treatment interventions (therapy technique used

only once in the comparison) were excluded. Data collection and analysis: Two authors independently applied the inclusion criteria to publications and assessed the quality of the included studies. Main results: The searches identified 76 studies (302 references); 35 studies (total of 1138 participants) met the inclusion criteria. Studies varied in duration from up to one week to one year; 20 of the studies were cross-over in design. The studies also varied in type of intervention and the outcomes measured, data were not published in sufficient detail in most of these studies, so meta-analysis was limited. Few studies were considered to have a low risk of bias in any domain. It is not possible to blind participants and clinicians to physiotherapy interventions, but 11 studies did blind the outcome assessors. Forced expiratory volume in one second was the most frequently measured outcome. One long-term study (seven months) compared oscillatory devices with either conventional physiotherapy or breathing techniques and found statistically significant differences in some lung function parameters in favour of oscillating devices. One study identified an increase in frequency of exacerbations requiring antibiotics whilst using high frequency chest wall oscillation when compared to positive expiratory pressure. There were some small but significant changes in secondary outcome variables such as sputum volume or weight, but not wholly in favour of oscillating devices. Participant satisfaction was reported in 15 studies but this was not specifically in favour of an oscillating device, as some participants preferred breathing techniques or techniques used prior to the study interventions. The results for the remaining outcome measures were not examined or reported in sufficient detail to provide any high level evidence. Authors' conclusions: There was no clear evidence that oscillation was a more or less effective intervention overall than other forms of physiotherapy; furthermore there was no evidence that one device is superior to another. The findings from one study showing an increase in frequency of exacerbations requiring antibiotics whilst using an oscillating device compared to positive expiratory pressure may have significant resource implications. More adequately-powered long-term randomised controlled trials are necessary and outcomes measured should include frequency of exacerbations, individual preference, adherence to therapy and general satisfaction with treatment. Increased adherence to therapy may then lead to improvements in other parameters, such as exercise tolerance and respiratory function. Additional evidence is needed to evaluate whether oscillating devices combined with other forms of airway clearance is efficacious in people with cystic fibrosis.There may also be a requirement to consider the cost implication of devices over other forms of equally advantageous airway clearance techniques. Using the GRADE method to assess the quality of the evidence, we judged this to be low or very low quality, which suggests that further research is very likely to have an impact on confidence in any estimate of effect generated by future interventions.Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Risk factors for mortality before age 18 years in cystic fibrosis.

Author(s): McColley, Susanna A; Schechter, Michael S; Morgan, Wayne J; Pasta, David J; Craib, Marcia L; Konstan, Michael W

Source: Pediatric pulmonology; Jul 2017; vol. 52 (no. 7); p. 909-915

Publication Type(s): Journal Article

Abstract:BACKGROUNDUnderstanding early-life risk factors for childhood death in cystic fibrosis (CF) is important for clinical care, including the identification of effective interventions.METHODSData from the Epidemiologic Study of Cystic Fibrosis (ESCF) collected 1994-2005 were linked with the Cystic Fibrosis Foundation Patient Registry (CFFPR) demographic and mortality data from 2013. Inclusion criteria were ≥1 visit annually at age 3-5 years and ≥1 FEV1 measurement at age 6-8 years. Demographic data, nutritional parameters, pulmonary signs and symptoms, microbiology, and FEV1 were evaluated as risk factors for death before age 18 years. Multivariable Cox proportional hazards regression was used to model the simultaneous effects of risk factors associated with death before age 18 years.RESULTSAmong 5365 patients enrolled in ESCF who met inclusion criteria, 3880 (72%) were linked to the CFFPR. Among these, 191 (5.7%) died before age 18 years; median age at death

was 13.4 ± 3.1 years. Multivariable regression showed clubbing, crackles, female sex, unknown CFTR genotype, minority race or ethnicity, Medicaid insurance (a proxy of low socioeconomic status), Pseudomonas aeruginosa on 2 or more cultures, and weight-for-age <50th percentile were significant risk factors for death regardless of inclusion of FEV1 at age 6-8 years in the model.CONCLUSIONWe identified multiple risk factors for childhood death of patients with CF, all of which remained important after incorporating FEV1 at age 6-8 years. Among the factors identified were the presence of clubbing or crackles at age 3-5 years, signs which are not routinely collected in registries.

Interventions for preventing distal intestinal obstruction syndrome (DIOS) in cystic fibrosis

Author(s): Green J.; Gilchrist F.J.; Carroll W.

Source: Cochrane Database of Systematic Reviews; Apr 2017; vol. 2017 (no. 4)

Publication Type(s): Article

Abstract: This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: This review aims to evaluate the effectiveness and safety of laxative agents of differing types for preventing DIOS (complete and incomplete) in children and adults with CF. If possible, we aim to assess the optimal laxative regimen by comparing the evidence for osmotic laxatives, stimulant laxatives and mucolytic agents.Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Diagnosis of Cystic Fibrosis in Screened Populations.

Author(s): Farrell, Philip M.; White, Terry B.; Howenstine, Michelle S.; Munck, Anne; Parad, Richard B.; Rosenfeld, Margaret; Sommerburg, Olaf; Accurso, Frank J.; Davies, Jane C.; Rock, Michael J.; Sanders, Don B.; Wilschanski, Michael; Sermet-Gaudelus, Isabelle; Blau, Hannah; Gartner, Silvia; McColley, Susanna A.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Academic Journal

Abstract: Objective: Cystic fibrosis (CF) can be difficult to diagnose, even when newborn screening (NBS) tests yield positive results. This challenge is exacerbated by the multitude of NBS protocols, misunderstandings about screening vs diagnostic tests, and the lack of guidelines for presumptive diagnoses. There is also confusion regarding the designation of age at diagnosis.Study Design: To improve diagnosis and achieve standardization in definitions worldwide, the CF Foundation convened a committee of 32 experts with a mission to develop clear and actionable consensus guidelines on diagnosis of CF with an emphasis on screened populations, especially the newborn population. A comprehensive literature review was performed with emphasis on relevant articles published during the past decade.Results: After reviewing the common screening protocols and outcome scenarios, 14 of 27 consensus statements were drafted that apply to screened populations. These were approved by 80% or more of the participants.Conclusions: It is recommended that all diagnoses be established by demonstrating dysfunction of the CF transmembrane conductance regulator (CFTR) channel, initially with a sweat chloride test and, when needed, potentially with newer methods assessing membrane transport directly, such as intestinal current measurements. Even in babies with 2 CF-causing mutations detected via NBS, diagnosis must be confirmed by demonstrating CFTR dysfunction. The committee also recommends that the latest classifications identified in the Clinical and Functional Translation of CFTR project [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis. Finally, to avoid delays in treatment, we provide guidelines for presumptive diagnoses and recommend how to determine the age of diagnosis.

Cystic Fibrosis Diagnostic Challenges over 4 Decades: Historical Perspectives and Lessons Learned.

Author(s): Farrell, Philip M.; White, Terry B.; Derichs, Nico; Castellani, Carlo; Rosenstein, Beryl J.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Academic Journal

Abstract: Objective: Because cystic fibrosis (CF) can be difficult to diagnose, and because information about the genetic complexities and pathologic basis of the disease has grown so rapidly over the decades, several consensus conferences have been held by the US CF Foundation, and a variety of other efforts to improve diagnostic practices have been organized by the European CF Society. Despite these efforts, the application of diagnostic criteria has been variable and caused confusion.Study Design: To improve diagnosis and achieve standardization in terms and definitions worldwide, the CF Foundation in 2015 convened a committee of 32 experts in the diagnosis of CF from 9 countries. As part of the process, all previous consensus-seeking exercises sponsored by the CF Foundation, along with the important efforts of the European CF Society, were comprehensively and critically reviewed. The goal was to better understand why consensus conferences and their publications have not led to the desired results.Results: Lessons learned from previous diagnosis consensus processes and products were identified. It was decided that participation in developing a consensus was generally not inclusive enough for global impact. It was also found that many efforts to address sweat test issues were valuable but did not always improve clinical practices as CF diagnostic testing evolved. It also became clear from this review that premature applications of potential diagnostic tests such as nasal potential difference and intestinal current measurement should be avoided until validation and standardization occur. Finally, we have learned that due to the significant and growing number of cases that are challenging to diagnose, an associated continuing medical education program is both desirable and necessary.Conclusions: It is necessary but not sufficient to organize and publish CF diagnosis consensus processes. Follow-up implementation efforts and monitoring practices seem essential.

Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation.

Author(s): Farrell, Philip M.; White, Terry B.; Ren, Clement L.; Hempstead, Sarah E.; Accurso, Frank; Derichs, Nico; Howenstine, Michelle; McColley, Susanna A.; Rock, Michael; Rosenfeld, Margaret; Sermet-Gaudelus, Isabelle; Southern, Kevin W.; Marshall, Bruce C.; Sosnay, Patrick R.

Source: Journal of Pediatrics; Feb 2017; vol. 181

Publication Type(s): Academic Journal

Abstract: Objective: Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis criteria.Study Design: To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with CFTR mutations. An a priori threshold of ≥80% affirmative votes was required for acceptance of each recommendation statement.Results: After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and a second round of voting.Conclusions: It is recommended that diagnoses associated with CFTR mutations in all individuals, from newborn to adult, be established by evaluation of CFTR function with a sweat chloride test. The latest mutation classifications annotated in the Clinical and Functional Translation of CFTR project (http://www.cftr2.org/index.php) should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional

and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis; these terms are now merged and equivalent, and CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis may be used. International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes for use in diagnoses associated with CFTR mutations are included.

Use of FEV₁ in cystic fibrosis epidemiologic studies and clinical trials: A statistical perspective for the clinical researcher

Author(s): Szczesniak R.; Heltshe S.L.; Mayer-Hamblett N.; Stanojevic S.

Publication Type(s): Review

Abstract: Background Forced expiratory volume in 1 s (FEV1) is an established marker of cystic fibrosis (CF) disease progression that is used to capture clinical course and evaluate therapeutic efficacy. The research community has established FEV1 surveillance data through a variety of observational data sources such as patient registries, and there is a growing pipeline of new CF therapies demonstrated to be efficacious in clinical trials by establishing improvements in FEV1. Results In this review, we summarize from a statistical perspective the clinical relevance of FEV1 based on its association with morbidity and mortality in CF, its role in epidemiologic studies of disease progression and comparative effectiveness, and its utility in clinical trials. In addition, we identify opportunities to advance epidemiologic research and the clinical development pipeline through further statistical considerations. Conclusions Our understanding of CF disease course, therapeutics, and clinical care has evolved immensely in the past decades, in large part due to the thoughtful application of rigorous research methods and meaningful clinical endpoints such as FEV1. A continued commitment to conduct research that minimizes the potential for bias, maximizes the limited patient population, and harmonizes approaches to FEV1 analysis while maintaining clinical relevance, will facilitate further opportunities to advance CF care.Copyright © 2017 European Cystic Fibrosis Society

The cumulative effects of intravenous antibiotic treatments on hearing in patients with cystic fibrosis

Author(s): Garinis A.C.; Cross C.P.; Carroll K.; Feeney M.P.; Putterman D.B.; Steyger P.S.; Keefe D.H.; Hunter L.L.; Srikanth P.; Cohen D.M.; Gold J.A.

Publication Type(s): Article

Abstract: Background Aminoglycosides (AGs) and glycopeptides are antibiotics essential for treating life-threatening respiratory infections in patients with cystic fibrosis (CF). The goal of this study was to examine the effects of cumulative intravenous (IV)-AG (amikacin and/or tobramycin) and/or glycopeptide (vancomycin) dosing on hearing status in patients with CF. Methods Hearing thresholds were measured from 0.25 to 16.0 kHz, in 81 participants with CF. Participants were categorized into two groups: normal hearing in both ears (25 dB HL for any frequency band in either ear). Participants were also characterized into quartiles by their cumulative IV-AG (with or without vancomycin) exposure. Dosing was calculated using two strategies: (i) total number of lifetime doses, and (ii) total number of lifetime doses while accounting for the total doses per day. This was referred to as the "weighted" method. Results Participants in the hearing loss group were significantly older than those in the normal-hearing group. After adjusting for gender and age at the time of hearing test, participants in the two highest-quartile exposure groups were almost 5 X more likely to have permanent sensorineural hearing loss than those in the two lowest-quartile exposure groups. There was a small group of CF patients who had normal hearing despite high exposure to IV-antibiotics. Conclusions Cumulative IV-antibiotic dosing has a significant negative effect on hearing

sensitivity in patients with CF, when controlling for age and gender effects. A trend for increasing odds of hearing loss was associated with increasing cumulative IV-antibiotic dosing.Copyright © 2017 European Cystic Fibrosis Society

Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease

Author(s): Hubert D.; Honore I.; Kanaan R.; Burgel P.-R.; Chiron R.; Camara B.; Grenet D.; Prevotat A.; Bassinet L.; Dominique S.; Rault G.; Macey J.; Leroy S.; Desmazes Dufeu N.

Publication Type(s): Article

Abstract: Objective To investigate the short-term adverse events and effectiveness of lumacaftor/ivacaftor combination treatment in adults with cystic fibrosis (CF) and severe lung disease in a real life setting. Methods A multicentre observational study investigated adverse events, treatment discontinuation, FEV1 and body mass index (BMI) one month and three months after lumacaftor/ivacaftor initiation in adults with CF and FEV1 below 40% predicted. Results Respiratory adverse events (AEs) were reported by 27 of 53 subjects (51%) and 16 (30%) discontinued treatment. The mean absolute change in FEV1 was + 2.06% after one month of treatment (P = 0.086) and + 3.19% after 3 months (P = 0.009). BMI was unchanged. Conclusions Treatment with lumacaftor/ivacaftor in patients with CF and severe lung disease was discontinued more frequently than reported in clinical trials, due to respiratory AEs. Nevertheless, the patients who continued treatment had an increase in lung function comparable to what was observed in pivotal trials.Copyright © 2017 European Cystic Fibrosis Society

Physiological markers of exercise capacity and lung disease severity in cystic fibrosis

Author(s): Smith L.; Reilly C.C.; MacBean V.; Jolley C.J.; Moxham J.; Rafferty G.F.; Elston C.

Publication Type(s): Article

Abstract: Background and objective: Peak aerobic capacity (VO2peak) is an important outcome measure in cystic fibrosis (CF), but measurement is not widely available and can be influenced by patient motivation, pain and fatigue. Alternative markers of disease severity would be helpful. Neural respiratory drive, measured using parasternal intercostal muscle electromyography (EMGpara), reflects the load to capacity balance of the respiratory system and provides a composite measure of pulmonary function impairment in CF. The aim of the study was to investigate the relationship between exercise capacity, EMGpara and established measures of pulmonary function in clinically stable adult CF patients. Methods: Twenty CF patients (12 males, median (range) age: 22.3 (17.0-43.1) years) performed the 10-m incremental shuttle walk test (ISWT) maximally with contemporaneous measures of aerobic metabolism. EMGpara was recorded from second intercostal space at rest and normalized using peak electromyogram activity obtained during maximum respiratory manoeuvres and expressed as EMGpara%max (EMGpara expressed as a percentage of maximum). Results: VO2peak was strongly correlated with ISWT distance (r = 0.864, P LCO) % predicted was best correlated with VO2peak (r = 0.842, P 2peak (-0.757, P 1) % predicted and forced vital capacity (FVC) % predicted were less strong. A TLCO% predicted of 2peak LCO% predicted and EMGpara%max relate strongly to exercise performance markers in CF and may provide alternative predictors of lung disease progression.Copyright © 2016 Asian Pacific Society of Respirology

Attitudes and Decision Making Related to Pregnancy Among Young Women with Cystic Fibrosis.

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

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

Strengthening care teams to improve adherence in cystic fibrosis: A qualitative practice assessment and quality improvement initiative

Author(s): Gardner A.J.; Gray A.L.; Self S.; Wagener J.S.

Available in full text at Patient preference and adherence - from National Library of Medicine

Abstract: Background: Treatment regimens for patients with cystic fibrosis (CF) are complex, time consuming, and burdensome, and adherence to CF treatment is suboptimal. CF care teams play a critical role in supporting patients' chronic self-management skills, but there is no uniform method for assessing patients' adherence to treatment or standard interventions to help patients improve when necessary. Methods: Between May 2015 and March 2016, care team members from 10 CF centers in the USA participated in a practice assessment and quality improvement (QI) initiative. The intervention included a baseline practice assessment survey, personalized continuing medical education (CME)-certified Webconferences with expert study faculty, targeted reinforcement of key practice points, and follow-up online survey and telephone interviews to evaluate the benefits and limitations of the intervention. Results: Responses to the baseline practice assessment survey were received from 50 multidisciplinary care team members representing 10 CF centers. Primary barriers to adherence-related aspects of care in their clinics were motivating patients and caregivers to improve adherence and obtaining accurate information about adherence from patients. At the conclusion of the initiative, participants reported improvements in communication within their care team, implementation of new approaches to asking about adherence, and a renewed commitment to asking patients and caregivers about adherence at each clinic visit. Conclusion: Structured QI interventions that bring multidisciplinary care teams together to reflect on clinic processes and elicit objective insights from outside faculty have the potential to improve practice patterns related to the assessment and improvement of patient adherence in CF.Copyright © 2017 Gardner et al.

Microbiological

Ciprofloxacin-loaded lipid-core nanocapsules as mucus penetrating drug delivery system intended for the treatment of bacterial infections in cystic fibrosis.

Author(s): Torge, Afra; Wagner, Stefanie; Chaves, Paula S; Oliveira, Edilene G; Guterres, Silvia S; Pohlmann, Adriana R; Titz, Alexander; Schneider, Marc; Beck, Ruy C R

Publication Type(s): Journal Article

Abstract: Treatment of bacterial airway infections is essential for cystic fibrosis therapy. However, effectiveness of antibacterial treatment is limited as bacteria inside the mucus are protected from antibiotics and immune response. To overcome this biological barrier, ciprofloxacin was loaded into lipid-core nanocapsules (LNC) for high mucus permeability, sustained release and antibacterial activity. Ciprofloxacin-loaded LNC with a mean size of 180nm showed a by 50% increased drug permeation through mucus. In bacterial growth assays, the drug in the LNC had similar minimum inhibitory concentrations as the free drug in P. aeruginosa and S. aureus. Interestingly, formation of biofilm-like aggregates, which were observed for S. aureus treated with free ciprofloxacin, was avoided by exposure to LNC. With the combined advantages over the non-encapsulated drug, ciprofloxacin-loaded LNC represent a promising drug delivery system with the prospect of an improved antibiotic therapy in cystic fibrosis.

In vitro activity of ceftolozane-tazobactam against multidrug-resistant nonfermenting Gram-negative bacilli isolated from patients with cystic fibrosis

Author(s): Grohs P.; Taieb G.; Kaibi I.; Podglajen I.; Lavollay M.; Mainardi J.-L.; Compain F.; Morand P.

Publication Type(s): Article

Available in full text at Antimicrobial Agents and Chemotherapy - from National Library of Medicine

Abstract: Ceftolozane-tazobactam was tested against 58 multidrug-resistant nonfermenting Gram-negative bacilli (35 Pseudomonas aeruginosa, 11 Achromobacter xylosoxydans, and 12 Stenotrophomonas maltophilia isolates) isolated from cystic fibrosis patients and was compared to ceftolozane alone, ceftazidime, meropenem, and piperacillin-tazobactam. Ceftolozane-tazobactam was the most active agent against P. aeruginosa but was inactive against A. xylosoxydans and S. maltophilia. In time-kill experiments, ceftolozane-tazobactam had complete bactericidal activity against 2/6 clinical isolates (33%).Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Aspergillus fumigatus in cystic fibrosis: An update on immune interactions and molecular diagnostics in allergic bronchopulmonary aspergillosis

Author(s): Carsin A.; Dubus J.-C.; Vitte J.; Romain T.; Mege J.-L.; Ranque S.; Reynaud-Gaubert M.

Publication Type(s): Article In Press

Abstract:A wide spectrum of pathological conditions may result from the interaction of Aspergillus fumigatus and the immune system of its human host. Allergic bronchopulmonary aspergillosis is one of the most severe A. fumigatus-related diseases due to possible evolution toward pleuropulmonary fibrosis and respiratory failure. Allergic bronchopulmonary aspergillosis occurs almost exclusively in cystic fibrosis or asthmatic patients. An estimated 8%-10% of patients with cystic fibrosis experience this condition. The diagnosis of allergic bronchopulmonary aspergillosis relies on criteria first established in 1977. Progress in the understanding of host-pathogen interactions in A. fumigatus and patients with cystic fibrosis and the ongoing validation of novel laboratory tools concur to update and improve the diagnosis of allergic bronchopulmonary aspergillosis.Copyright © 2017 EAACI and John Wiley and Sons A/S.

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis

Author(s): Aslam A.; Jahnke N.; Remmington T.; Southern K.W.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Scedosporium apiospermum complex in cystic fibrosis; should we treat?

Author(s): Noni M.; Katelari A.; Kapi A.; Doudounakis S.-E.; Stathi A.; Dimopoulos G.

Source: Mycoses; 2017

Publication Type(s): Article In Press

Abstract: Species of the Scedosporium apiospermum complex are the second most frequent filamentous fungi after Aspergillus fumigatus that can be found in cystic fibrosis (CF). Mixed colonisation by S. apiospermum complex and A. fumigatus is also quite common. In this study we summarise all CF patients who were colonised by S. apiospermum complex during their childhood and we present two CF patients who were treated as fungal bronchitis due to S. apiospermum complex. The medical records of 400 CF patients were reviewed in order to identify those with positive respiratory cultures for S. apiospermum complex. Scedosporium apiospermum complex was isolated in 10 CF patients and six of them had more than two positive sputum cultures during the study period. By the time of first isolation, the median age was 14.5 years, the median BMI was 19.41 kg/m2, the median predicted FEV1% was 78.65% and six patients had a history of A. fumigatus isolation. Two patients presented symptoms of infection while they were colonised by S. apiospermum complex. A rapid remission of their symptoms was observed only when antifungal therapy was administered. Antifungal treatment should be considered in CF patients who present symptoms of infection not responding to antibacterial therapy and S. apiospermum complex is persistently growing in sputum cultures.Copyright © 2017 Blackwell Verlag GmbH.

Chest computed tomography scores in patients with cystic fibrosis colonized with methicillin-resistant Staphylococcus aureus

Author(s): Gur M.; Spinelli E.; Tridello G.; Assael B.M.; Baltieri S.; Pinali L.; Montemezzi S.; Bentur L.

Publication Date: 2017

Publication Type(s): Article In Press

Abstract: Background: Methicillin-resistant Staphylococcus aureus (MRSA) is an important pathogen in cystic fibrosis (CF), with increasing incidence in recent years. We examined the association between bacterial colonization in the sputum (MRSA with or without pseudomonas (PA)) and computed tomography (CT) scores in CF patients. Methods: MRSA patients were divided according to PA status based on at least three consecutive sputum cultures; controls were patients without MRSA (with or without PA), matched for gender and age at CT. Clinical data and CT scores were compared between groups. Results: Of 33 patients with MRSA, 14 had no PA (MRSA+PA-) and 19 had also PA (MRSA+PA+). MRSA+PA- and MRSA+PA+ patients had CT scores similar to their controls PA+ (38.25+/-20.18 vs. 32.22+/-18.74, P=.4, and 41.88+/-18.18 vs. 45.33+/-11.5, P=.4, respectively). Although MRSA+PA- had worse CT scores than their matched PA- controls, their mean FEV1 values were similar. Conclusions: Colonization with MRSA in CF is associated with structural CT changes at least similar to those in PA. A cause and effect relationship cannot be established. The current findings call for a larger study assessing longitudinally the impact of MRSA acquisition and eradication protocols.Copyright © 2016 John Wiley & Sons Ltd.

Clostridium difficile and cystic fibrosis: Management strategies and the role of faecal transplantation

Author(s): Dunwoody R.; Simmonds N.; Steel A.; Landy J.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: Clostridium difficile is a bacterial infection that colonises the gut in susceptible hosts. It is associated with exposure to healthcare settings and antibiotic use. It could be assumed that cystic fibrosis (CF) patients are a high-risk group for C.difficile. However, despite high carriage rates, CF patients have low rates of active disease.There are guidelines for the treatment of C.difficile, however little is published specific to treating C.difficile in CF. This article provides an overview of the current management strategies for C.difficile in CF, including a description of the first faecal transplantation in this patient population.Copyright © 2017 Elsevier Ltd.

Ralstonia mannitolilytica in cystic fibrosis: A new predictor of worse outcomes

Author(s): Coman I.; Lavoie A.; Carricart M.; Tremblay F.; Berthiaume Y.; Bilodeau L.; Zlosnik J.E.

Source: Respiratory Medicine Case Reports; 2017; vol. 20 ; p. 48-50

Publication Date: 2017

Publication Type(s): Article

Abstract: Background Patients with Cystic Fibrosis are subject to repeated respiratory tract infections, with recent increasing isolation of unusual pathogens. Ralstonia species have lately been isolated at our institution, an organism historically frequently misidentified as Burkholderia or Pseudomonas. The prevalence of Ralstonia spp. in cystic fibrosis populations has yet to be determined, along with its clinical implications. Case presentations Seven patients out of the 301 followed at our cystic fibrosis clinic have had Ralstonia strains identified in their respiratory tract. Most strains identified were multi-drug resistant. After aquisition of Ralstonia spp., the patients' clinical course was characterized by more frequent and more severe respiratory infections along with prolonged hospitalizations, greater decline of lung function, and greater mortality. The mortality rate in this group of patients was 86%. No other factor that could explain such a dramatic evolution was identified upon review of patient data. Some of the strains involved were recognized as clones on Pulse Field Electrophoresis Gel, raising the question of person-to-person transmission. Conclusion New pathogens are identified with the evolution of the microbiota in cystic fibrosis respiratory tracts. In our cohort of patients, acquisition of Ralstonia spp. was associated with dramatic outcomes in terms of disease acceleration and raised mortality rates. It is of critical importance to continue to better define the prevalence and clinical impact of Ralstonia in cystic fibrosis populations.Copyright © 2016 The Authors

Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: II. Cephalosporins and penicillins update.

Author(s): Zobell, Jeffery T; Epps, Kevin L; Young, David C

Source: Pediatric pulmonology; Jul 2017; vol. 52 (no. 7); p. 863-865

Publication Type(s): Letter

tomography?

Author(s): Caudri, Daan; Zitter, David; Bronsveld, Inez; Tiddens, Harm

Source: Pediatric pulmonology; Jun 2017

Publication Type(s): Journal Article

Abstract:BACKGROUNDCystic Fibrosis (CF) lung disease is characterized by a marked heterogeneity. Sweat chloride-level is a functional marker of the CF Transmembrane Regulator (CFTR) protein and could be an important predictor of later disease severity.METHODSIn this retrospective analysis

children from the Rotterdam CF clinic with available sweat chloride level at diagnosis and at least one routine spirometry-controlled volumetric chest CT scan in follow-up were included. CT scans were scored using the CF-CT scoring system (% of maximum). Associations between sweat chloride-levels and CF-CT scores were calculated using linear regression models, adjusting for age at sweat test and age at follow-up. Because structural lung damage develops over the course of many years, effect modification by the age at follow-up CT-scan was tested for by age-stratification.RESULTSIn 59 children (30 male) sweat chloride was measured at diagnosis (median age 0.5 years, range 0-13) and later chest CT performed (median age 14 years, range 6-18). Sweat chloride was associated with significantly higher CT-CT total score, bronchiectasis score, and mucus plugging score. Stratification for age at follow-up in tertiles showed this association remained only in the oldest age group (range 15-18 years). In that subgroup associations were found with all but one of the CF-CT subscores, as well as with all tested lung functions parameters.CONCLUSIONSweat chloride-level is a significant predictor of CF lung disease severity as determined by chest CT and lung function. This association could only be demonstrated in children with follow-up to age 15 years and above.

Clinical implications of Pseudomonas aeruginosa location in the lungs of patients with cystic fibrosis.

Author(s): Moore, J E; Mastoridis, P

Source: Journal of clinical pharmacy and therapeutics; Jun 2017; vol. 42 (no. 3); p. 259-267

Publication Type(s): Journal Article Review

Abstract:WHAT IS KNOWN AND OBJECTIVEPseudomonas aeruginosa is the leading cause of lung infection in patients with cystic fibrosis (CF) and is associated with significant morbidity and mortality. Antibiotics are regarded as the foundational pharmacological treatment for the suppressive management of chronic P. aeruginosa infections and to eradicate the first infection by P. aeruginosa. Inhalation remains a preferred route for drug administration, providing direct access to the site of infection while minimizing systemic side effects. Effective suppressive management of P. aeruginosa infections, however, requires an understanding of the location of the bacteria in the lungs and consideration of the factors that could limit access of the inhaled antibiotic to the infected area. This review provides a systematic assessment of the scientific literature to gain insight into the location of P. aeruginosa in the lungs of patients with CF and its clinical implications. The characteristics of antibiotic inhalation systems are also discussed in this context.METHODSWe reviewed evidence-based literature from both human and animal studies in which P. aeruginosa lung location was reported. Relevant publications were identified through a screening strategy and summarized by reported P. aeruginosa location.RESULTS AND DISCUSSIONMost areas of the conductive and respiratory zones of the lungs are susceptible to P. aeruginosa colonization. Deposition of an inhaled antibiotic is dependent on the device and formulation characteristics, as well as the ability of the patient to generate sufficient inhaled volume. As patients with CF often experience a decline in lung function, the challenge is to ensure that the inhaled antibiotic can be delivered throughout the bronchial tree.WHAT IS NEW AND CONCLUSIONAn effective drug delivery system that can target P. aeruginosa in both the respiratory and conductive zones is required. The chosen inhalation device should also offer a drug formulation that can be quickly and effectively delivered to specific lung locations, with minimal inspiratory effort from the patient

The Evolving Cystic Fibrosis Microbiome: A Comparative Cohort Study Spanning Sixteen Years.

Author(s): Acosta, Nicole; Whelan, Fiona J; Somayaji, Ranjani; Poonja, Ali; Surette, Michael G; Rabin, Harvey R; Parkins, Michael D

Source: Annals of the American Thoracic Society; May 2017

Available in full text at Annals of the American Thoracic Society - from EBSCOhost

Abstract:RATIONALEThe cystic fibrosis (CF) airways are infected with a diverse polymicrobial community.OBJECTIVESUnderstanding how changes in the CF microbiome have occurred over time, similar to the observed changes in the prevalence of cultured pathogens, is key in understanding the microbiome's role in disease.METHODSDrawing from a prospectively collected and maintained sputum biobank, we identified 45 patients with sputum samples collected between the ages of 18-21 years in three successive cohorts of adults transitioning to our CF clinic: A(1997-2000), B(2004-2007), and C(2010-2013). Patient demographics, clinical status, and medications were collected from detailed chart review. Microbial communities were assessed by Ilumina MiSeq sequencing of the variable 3 (V3) region of the 16S rDNA.RESULTSThe three cohorts were similar with respect to baseline demographics. There was a trend towards improved health and use of disease modifying therapies in each successive cohort. Shannon-diversity increased in the most recent cohort, suggesting an increase in the diversity of organisms between cohorts. Furthermore, the proportion of samples with Pseudomonas-dominated communities decreased over time, while Streptococcus increased. While beta diversity was associated with transition cohort, the greatest predictor of diversity remained lung function. Furthermore, core microbiome constituents were preserved across cohorts.CONCLUSIONSModest changes in the composition and structure of the microbiome of three successive cohorts of young adults with CF were observed, occurring in parallel with successive improvements in clinical status. Importantly, however, the core microbiome constituents were preserved across cohorts.

Impact of azithromycin on the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis

Author(s): Nichols D.P.; Happoldt C.L.; Bratcher P.E.; Taylor-Cousar J.L.; Caceres S.M.; Malcolm K.C.; Saavedra M.T.; Nick J.A.; Chmiel J.F.; Saiman L.

Abstract: Background Concomitant use of oral azithromycin and inhaled tobramycin occurs in approximately half of US cystic fibrosis (CF) patients. Recent data suggest that this combination may be antagonistic. Methods Test the hypothesis that azithromycin reduces the clinical benefits of tobramycin by analyses of clinical trial data, in vitro modeling of P. aeruginosa antibiotic killing, and regulation of the MexXY efflux pump. Results Ongoing administration of azithromycin associates with reduced ability of inhaled tobramycin, as compared with aztreonam, to improve lung function and quality of life in a completed clinical trial. In users of azithromycin FEV1 (L) increased 0.8% during a 4-week period of inhaled tobramycin and an additional 6.4% during a subsequent 4-week period of inhaled aztreonam (P Copyright © 2016 European Cystic Fibrosis Society

Staphylococcus aureus survives in cystic fibrosis macrophages, forming a reservoir for chronic pneumonia

Author(s): Li C.; Wu Y.; Riehle A.; Ma J.; Gulbins E.; Grassme H.; Kamler M.

Available in full text at Infection and Immunity - from National Library of Medicine

Abstract: Staphylococcus aureus plays an important role in sepsis, pneumonia, wound infections, and cystic fibrosis (CF), which is caused by mutations of the cystic fibrosis transmembrane conductance regulator (Cftr). Pulmonary S. aureus infections in CF often occur very early and prior to colonization with other pathogens, in particular Pseudomonas aeruginosa. Here, we demonstrate that CF mice

are highly susceptible to pulmonary infections with S. aureus and fail to clear the pathogen during infection. S. aureus is internalized by Cftr-deficient macrophages in the lung, but these macrophages are unable to kill intracellular bacteria. This failure might be caused by a defect in the fusion of phagosomes with lysosomes, while this process occurs rapidly in wild-type macrophages and serves to kill intracellular pathogens. Transplantation of infected Cftr-deficient alveolar macrophages into the lungs of noninfected CF mice is sufficient to induce pneumonia. This suggests that intracellular survival of S. aureus in macrophages may allow the pathogen to chronically infect CF lungs.Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Author(s): Langton Hewer S.C.; Smyth A.R.

Source: Cochrane Database of Systematic Reviews; Apr 2017; vol. 2017 (no. 4)

Publication Type(s): Review

Abstract: Background: Respiratory tract infection with Pseudomonas aeruginosa occurs in most people with cystic fibrosis. Once chronic infection is established, Pseudomonas aeruginosa is virtually impossible to eradicate and is associated with increased mortality and morbidity. Early infection may be easier to eradicate. This is an update of a Cochrane review first published in 2003, and previously updated in 2006, 2009 and 2014. Objectives: To determine whether antibiotic treatment of early Pseudomonas aeruginosa infection in children and adults with cystic fibrosis eradicates the organism, delays the onset of chronic infection, and results in clinical improvement. To evaluate whether there is evidence that a particular antibiotic strategy is superior to or more cost-effective than other strategies and to compare the adverse effects of different antibiotic strategies (including respiratory infection with other micro-organisms). Search methods: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Most recent search: 10 October 2016. Selection criteria: We included randomised controlled trials of people with cystic fibrosis, in whom Pseudomonas aeruginosa had recently been isolated from respiratory secretions. We compared combinations of inhaled, oral or intravenous antibiotics with placebo, usual treatment or other combinations of inhaled, oral or intravenous antibiotics. We excluded non-randomised trials, cross-over trials, and those utilising historical controls. Data collection and analysis: Both authors independently selected trials, assessed risk of bias and extracted data. Main results: The search identified 60 trials; seven trials (744 participants) with a duration between 28 days and 27 months were eligible for inclusion. Three of the trials are over 10 years old and their results may be less applicable today given the changes in standard treatment. Some of the trials had low numbers of participants and most had relatively short follow-up periods; however, there was generally a low risk of bias from missing data. In most trials it was difficult to blind participants and clinicians to treatment given the interventions and comparators used. Two trials were supported by the manufacturers of the antibiotic used. Evidence from two trials (38 participants) at the two-month time-point showed treatment of early Pseudomonas aeruginosa infection with inhaled tobramycin results in microbiological eradication of the organism from respiratory secretions more often than placebo, odds ratio 0.15 (95% confidence interval (CI) 0.03 to 0.65) and data from one of these trials, with longer follow up, suggested that this effect may persist for up to 12 months. One randomised controlled trial (26 participants) compared oral ciprofloxacin and nebulised colistin versus usual treatment. Results after two years suggested treatment of early infection results in microbiological eradication of Pseudomonas aeruginosa more often than no anti-pseudomonal treatment, odds ratio 0.12 (95% CI 0.02 to 0.79). One trial comparing 28 days to 56 days treatment with nebulised tobramycin solution for inhalation in 88 participants showed that both treatments were effective and well-tolerated, with no notable additional improvement with longer over shorter duration of therapy. However, this trial was not powered to detect non-inferiority or equivalence . A trial of oral

ciprofloxacin with inhaled colistin versus nebulised tobramycin solution for inhalation alone (223 participants) failed to show a difference between the two strategies, although it was underpowered to show this. A further trial of inhaled colistin with oral ciprofloxacin versus nebulised tobramycin solution for inhalation with oral ciprofloxacin also showed no superiority of the former, with increased isolation of Stenotrophomonas maltophilia in both groups. A recent, large trial in 306 children aged between one and 12 years compared cycled nebulised tobramycin solution for inhalation to culture-based therapy and also ciprofloxacin to placebo. The primary analysis showed no difference in time to pulmonary exacerbation or proportion of Pseudomonas aeruginosa positive cultures. An analysis performed in this review (not adjusted for age) showed fewer participants in the cycled therapy group with one or more isolates of Pseudomonas aeruginosa, odds ratio 0.51 (95% CI 0.31 to 0.28). Using GRADE, the quality of evidence for outcomes was downgraded to moderate to very low. Downgrading decisions for Pseudomonas aeruginosa eradication and lung function were based on applicability (participants mostly children) and limitations in study design, with imprecision an additional limitation for lung function, growth parameters and adverse effects. Authors' conclusions: We found that nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment for early infection with Pseudomonas aeruginosa. Eradication may be sustained for up to two years. There is insufficient evidence to determine whether antibiotic strategies for the eradication of early Pseudomonas aeruginosa decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment. Four trials comparing two active treatments have failed to show differences in rates of eradication of Pseudomonas aeruginosa. There have been no published randomised controlled trials that investigate the efficacy of intravenous antibiotics to eradicate Pseudomonas aeruginosa in cystic fibrosis. Overall, there is still insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early Pseudomonas aeruginosa infection in cystic fibrosis.Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive Diagnosis.

Author(s): Ren, Clement L.; Borowitz, Drucy S.; Gonska, Tanja; Howenstine, Michelle S.; Levy, Hara; Massie, John; Milla, Carlos; Munck, Anne; Southern, Kevin W.

Abstract: Objective: An unintended consequence of cystic fibrosis (CF) newborn screening (NBS) is the identification of infants with a positive NBS test but inconclusive diagnostic testing. These infants are classified as CF transmembrane conductance regulator-related metabolic syndrome (CRMS) in the US and CF screen positive, inconclusive diagnosis (CFSPID) in other countries. Diagnostic and management decisions of these infants are challenges for CF healthcare professionals and stressful situations for families. As CF NBS has become more widespread across the world, increased information about the epidemiology and outcomes of these infants is becoming available. These data were reviewed at the 2015 CF Foundation Diagnosis Consensus Conference, and a harmonized definition of CRMS and CFSPID was developed.Study Design: At the consensus conference, participants reviewed published and unpublished studies of CRMS/CFSPID and used a modified Delphi methodology to develop a harmonized approach to the definition of CRMS/CFSPID.Results: Several studies of CRMS/CFSPID from populations around the world have been published in the past year. Although the studies vary in the number of infants studied, study design, and outcome measures, there have been some consistent findings. CRMS/CFSPID occurs relatively frequently, with CF:CRMS that ranges from 3 to 5 cases of CF for every 1 case of CRMS/CFSPID in regions where gene sequencing is not used. The incidence varies by NBS protocol used, and in some regions more cases of CRMS/CFSPID are detected than cases of CF. The majority of individuals with CRMS/CFSPID do not

develop CF disease or progress to a diagnosis of CF. However, between 10% and 20% of asymptomatic infants can develop clinical features concerning for CF, such as a respiratory culture positive for Pseudomonas aeruginosa. Most studies have only reported short-term outcomes in the first 1-3 years of life; the long-term outcomes of CRMS/CFSPID remain unknown. The European CF Society definition of CFSPID and the CF Foundation definition of CRMS differ only slightly, and the consensus conference was able to create a unified definition of CRMS/CFSPID.Conclusions: CRMS/CFSPID is a relatively common outcome of CF NBS, and clinicians need to be prepared to counsel families whose NBS test falls into this classification. The vast majority of infants with CRMS/CFSPID will remain free from disease manifestations early in life. However, a small proportion may develop clinical features concerning for CF or demonstrate progression to a clinical phenotype compatible with a CF diagnosis, and their long-term outcomes are not known. A consistent international definition of CRMS/CFSPID will allow for better data collection for study of outcomes and result in improved patient care.

Challenges in Laboratory Detection of Fungal Pathogens in the Airways of Cystic Fibrosis Patients.

Author(s): Chen, Sharon C-A; Meyer, Wieland; Pashley, Catherine H

Source: Mycopathologia; Jun 2017

Publication Type(s): Journal Article

Abstract: Study of the clinical significance of fungal colonization/infection in the airways of cystic fibrosis (CF) patients, especially by filamentous fungi, is challenged by the absence of standardized methodology for the detection and identification of an ever-broadening range of fungal pathogens. Culture-based methods remain the cornerstone diagnostic approaches, but current methods used in many clinical laboratories are insensitive and unstandardized, rendering comparative studies unfeasible. Guidelines for standardized processing of respiratory specimens and for their culture are urgently needed and should include recommendations for specific processing procedures, inoculum density, culture media, incubation temperature and duration of culture. Molecular techniques to detect fungi directly from clinical specimens include panfungal PCR assays, multiplex or pathogen-directed assays, real-time PCR, isothermal methods and probe-based assays. In general, these are used to complement culture. Fungal identification by DNA sequencing methods is often required to identify cultured isolates, but matrix-assisted laser desorption/ionization time-of-flight mass spectrometry is increasingly used as an alternative to DNA sequencing. Genotyping of isolates is undertaken to investigate relatedness between isolates, to pinpoint the infection source and to study the population structure. Methods range from PCR fingerprinting and amplified fragment length polymorphism analysis, to short tandem repeat typing, multilocus sequencing typing (MLST) and whole genome sequencing (WGS). MLST is the current preferred method, whilst WGS offers best case resolution but currently is understudied.

Psychology

The psychometric properties of the Leicester Cough Questionnaire and Respiratory Symptoms in CF tool in cystic fibrosis: A preliminary study

Author(s): Ward N.; Rowe H.; Holland A.E.; Stiller K.

Source: Journal of Cystic Fibrosis; May 2017; vol. 16 (no. 3); p. 425-432

Publication Type(s): Article

Abstract: Background There are few tools to quantify the impact of cough in cystic fibrosis (CF). The psychometric properties of the Leicester Cough Questionnaire (LCQ) and Respiratory Symptoms in CF (ReS-CF) tool were investigated in adults with CF. Methods Validity and reliability were assessed in clinically stable participants who completed the questionnaires twice, along with the Cystic

Fibrosis Questionnaire - Revised (CFQ-R). Responsiveness was assessed by change in questionnaires following treatment for an acute respiratory exacerbation. Results Correlations between the LCQ and CFQ-R respiratory domain were moderate (n = 59, rs = 0.78, p s = - 0.50, p Copyright © 2016 European Cystic Fibrosis Society

Current characteristics, challenges and coping strategies of young people with cystic fibrosis as they transition to adulthood

Author(s): Askew K.; Bamford J.; Hudson N.; Moratelli J.; Miller R.; Anderson A.; Doe S.; Bourke S.J.

Source: Clinical Medicine, Journal of the Royal College of Physicians of London; Apr 2017; vol. 17 (no. 2); p. 121-125

Publication Date: Apr 2017

Publication Type(s): Article

Available in full text at Clinical Medicine - from EBSCOhost

Abstract: This study provides detailed data on the current characteristics, perceptions and outcomes of 45 young people with cystic fibrosis (CF) as they transition into adulthood. Although many had severe disease, they generally coped well, found attendance at a transition clinic helpful and welcomed the increased independence of an adult healthcare environment. Levels of psychological distress were low with only 15.6% having anxiety and 6.7% depression. The main psychological coping strategy used was optimistic acceptance. Overall, most remained stable after transfer but 33% had some decline in lung function and 9% in nutritional status, requiring intensification of treatment. They had high levels of satisfaction with their relationships and life situations and 76% were in employment or education. These results are encouraging and as life expectancy improves, young adults with CF are coping well with transition into adulthood.Copyright © Royal College of Physicians 2017. All rights reserved.

Evaluation of Pain, Dyspnea, and Goals of Care Among Adults With Cystic Fibrosis: A Comprehensive Palliative Care Survey

Author(s): Chen, Elaine; Killeen, Kathryn M.; Peterson, Sarah J.; Saulitis, Anna K.; Balk, Robert A.

Source: American Journal of Hospice and Palliative Medicine; May 2017; vol. 34 (no. 4); p. 347-352

Publication Type(s): Article

Abstract: Background: Palliative care is increasingly important in the care of adults with cystic fibrosis (CF). Symptoms such as pain and dyspnea are prevalent, yet severity may be underestimated. Little information is available to describe patient preferences for end-of-life care (EOLC). The objective of this study was to describe patient perceptions about pain, dyspnea, and advance care planning. Methods: We developed a survey to assess pain, dyspnea, and EOLC in adults with CF. Questions were compiled and adapted from existing tools. The survey was administered to all patients in a single adult CF care center. Descriptive data were compiled as counts (proportions) and median (25th and 75th percentile). Mann Whitney U test was used to determine differences between individuals who experienced pain and dyspnea. A P value of .05 was utilized to determine significance. Results: Thirty-seven of 43 surveys were returned. Twenty-four percent reported chronic pain. Patients who reported pain with airway clearance had lower lung function (predicted forced expiratory volume in 1 [FEV1] 42% vs 65%, P < .05) and body mass index (19.6 vs 22.3, P < .05) than patients without pain. Those reporting dyspnea at rest had lower median FEV1 (28% vs 61%, P

Worsening anxiety and depression after initiation of lumacaftor/ivacaftor combination therapy in adolescent females with cystic fibrosis.

Author(s): McKinzie, Cameron J; Goralski, Jennifer L; Noah, Terry L; Retsch-Bogart, George Z; Prieur, Mary Beth

Source: Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society; Jun 2017

Publication Type(s): Journal Article

Abstract: In both phase III studies of LUM/IVA, as well as an extension study, worsening of mental health was not reported as a common side effect. Here we describe five cases in adolescent female patients that suggest a worsening of anxiety or depression associated with its use. In these five patients, two experienced suicidal ideation and three made suicide attempts that resulted in psychiatric hospitalizations.

Nutrition

Nutritional management of cystic fibrosis an update for the 21st century

Author(s): Collins S.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: Nutritional management is an essential part of multidisciplinary care for infants, children and adults with cystic fibrosis (CF). In 2016 two updated nutritional consensus guidelines were published [1,2]. This review will explore some of the key points in the nutritional management of people with CF in the 21st Century.Copyright © 2017.

Telemedicine is the way forward for the management of Cystic Fibrosis - the case in favour. The debate: Telemedicine is the future for CF care

Author(s): Ketchell R.I.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: Despite rapid changes in Information and Communication Technology, outpatient chronic disease management has changed very little in decades. However, the introduction of Telemedicine defined here as the use of remote patient-centred clinical services including the use of video and audio connections, telemonitoring and mobile applications provides us with an ideal opportunity to revolutionise care. Its appeal in cystic fibrosis (CF) care is clear offering better access to services, the opportunity of earlier intervention and improved monitoring and self management through virtual clinics and the use of real-time applications for adherence monitoring. It has the potential to reduce costs and has been shown to be effective in other chronic disease conditions. There is a lack of good quality data in CF and studies are needed to provide supportive evidence. Nonetheless, it would seem that telemedicine is the future of CF care.Copyright © 2017.

Telemedicine is the way forward for the management of Cystic Fibrosis- The case against

Author(s): Lenney W.

Source: Paediatric Respiratory Reviews; 2017

Publication Type(s): Article In Press

Abstract: It is reasonable to suggest that Telemedicine could help in the management of chronic diseases by giving patients more flexibility to remain at home with opportunities to forward electronic data to healthcare professionals, reduce hospital emergency attendances and reduce overall costs. The reality, particularly in cystic fibrosis care, is this has not happened. There is

concern that home-generated lung function data is of poor quality and virtually no studies show improved outcomes. The UK has a poor record in developing novel IT programmes and we need many more well designed clinical studies in Telemedicine before wading in with ill-conceived expensive plans just because the idea seems interesting.Copyright © 2017.

Vitamin K status in cystic fibrosis patients with liver cirrhosis.

Author(s): Krzyżanowska, Patrycja; Drzymała-Czyż, Sławomira; Pogorzelski, Andrzej; Duś-Żuchowska, Monika; Skorupa, Wojciech; Bober, Lyudmyla; Sapiejka, Ewa; Oralewska, Beata; Rohovyk, Nataliya; Moczko, Jerzy; Nowak, Jan; Wenska-Chyży, Ewa; Rachel, Marta; Lisowska, Aleksandra; Walkowiak, Jarosław

Publication Type(s): Journal Article

Abstract: The available data on the influence of liver cirrhosis on vitamin K status in CF patients is scarce. Therefore, the aims of the present study were to assess the prevalence of vitamin K deficiency in cirrhotic CF subjects and to determine whether it correlates with liver cirrhosis. The study group comprised of 27 CF patients with and 63 without liver cirrhosis. Vitamin K status was assessed using prothrombin induced by vitamin K absence (PIVKA-II) and the percentage of undercarboxylated osteocalcin (u-OC). PIVKA-II concentrations were higher in cirrhotic than in non-cirrhotic CF patients (median [1st-3rd quartile]: 3.2ng/ml [1.0-10.0] vs. 1.3ng/ml [0.2-2.6], p=0.0029). However, the differences in u-OC percentages between the studied groups did not reach the level of significance (49.4% [7.0-73.8] vs. 8.0% [2.6-59.1], p=0.0501). Based on multiple linear regression analysis the dose of vitamin K and F508del mutation were potentially defined as determinants of vitamin K deficiency. Liver cirrhosis was not documented to be an independent risk factor. In CF patients with liver cirrhosis vitamin K deficiency is not only more frequent, but also more severe. However, not liver cirrhosis, but the presence of a F508del CFTR mutation constitutes an independent risk factor for vitamin K deficiency.

The Vitamin D for Enhancing the Immune System in Cystic Fibrosis (DISC) trial: Rationale and design of a multi-center, double-blind, placebo-controlled trial of high dose bolus administration of vitamin D3 during acute pulmonary exacerbation of cystic fibrosis.

Author(s): Tangpricha, Vin; Smith, Ellen M; Binongo, Jose; Judd, Suzanne E; Ziegler, Thomas R; Walker, Seth; Tirouvanziam, Rabindra; Zughaier, Susu M; Lee, Moon Jeong; Chesdachai, Supavit; Hermes, Wendy A; Chmiel, James F; Gaggar, Amit; Grossmann, Ruth E; Joseph, Patricia M; Alvarez, Jessica A

Publication Type(s): Journal Article

Abstract: Vitamin D deficiency is highly prevalent in children and adults with cystic fibrosis (CF). Recent studies have found an association between vitamin D status and risk of pulmonary exacerbations in children and adults with CF. The ongoing Vitamin D for enhancing the Immune System in Cystic fibrosis (DISC) study is a multi-center, double-blind, randomized, placebo-controlled trial that will test the hypothesis of whether high dose vitamin D given as a single oral bolus of 250,000 IU to adults with CF during a pulmonary exacerbation followed by a maintenance dose of vitamin D will improve time to next pulmonary exacerbation and re-hospitalization, improve survival and lung function compared to placebo and reduce the rates of pulmonary exacerbation,. Subjects will be randomized 1:1 at each clinical site to vitamin D or placebo within 72 hours of hospital admission for pulmonary exacerbation. Clinical follow-up visits will occur at 1, 2, 3, and 7 days, and 1, 3, 6 and 12 months after randomization. Blood and sputum will be collected and determination of

clinical outcomes will be assessed at each visit. The primary endpoint will be the time to next pulmonary exacerbation requiring antibiotics, re-hospitalization or death. The secondary endpoints will include lung function assessed by forced expiratory volume in 1 second (FEV1), blood markers of inflammatory cytokines, anti-microbial peptide expression by peripheral blood mononuclear cells and circulating concentrations in blood. Other exploratory endpoints will examine the phenotype of neutrophils and monocyte/macrophages in sputum. Nutritional status will be assessed by 3 day food records and food frequency questionnaire.

< .05). Patients with lower lung function are more likely to have considered end-of-life decisions (73% vs 31%, P < .05). Conclusion: Pain and dyspnea are common among adults with CF. Few had an advance directive in place, but most are open to discussing EOLC issues. Results of this single-center study may not represent the entire population, thus a multicenter investigation should be pursued. References

Oral calorie supplements for cystic fibrosis

Author(s): Smyth R.L.; Rayner O.

Source: Cochrane Database of Systematic Reviews; May 2017; vol. 2017 (no. 5)

Publication Type(s): Review

Abstract: Background: Poor nutrition occurs frequently in people with cystic fibrosis and is associated with other adverse outcomes. Oral calorie supplements are used to increase total daily calorie intake and improve weight gain. However, they are expensive and there are concerns they may reduce the amount of food eaten and not improve overall energy intake. This is an update of a previously published review. Objectives: To establish whether in people with cystic fibrosis, oral calorie supplements: increase daily calorie intake; and improve overall nutritional intake, nutritional indices, lung function, survival and quality of life. To assess adverse effects associated with using these supplements. Search methods: We searched the Cochrane Cystic Fibrosis Trials Register comprising references from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings. We contacted companies marketing oral calorie supplements. Last search: 18 October 2016. Selection criteria: Randomised or quasi-randomised controlled trials comparing use of oral calorie supplements for at least one month to increase calorie intake with no specific intervention or additional nutritional advice in people with cystic fibrosis. Data collection and analysis: We independently selected the included trials, assessed risk of bias and extracted data. We contacted the authors of included trials and obtained additional information for two trials. Main results: We identified 21 trials and included three, reporting results from 131 participants lasting between three months and one year. Two trials compared supplements to additional nutritional advice and one to no intervention. Two of the included trials recruited only children. In one trial the risk of bias was low across all domains, in a second trial the risk of bias was largely unclear and in the third mainly low. Blinding of participants was unclear in two of the trials. Also, in one trial the clinical condition of groups appeared to be unevenly balanced at baseline and in another trial there were concerns surrounding allocation concealment. There were no significant differences between people receiving supplements or dietary advice alone for change in weight, height, body mass index, z score or other indices of nutrition or growth. Changes in weight (kg) at three, six and 12 months respectively were: mean difference (MD) 0.32 (95% confidence interval (CI) -0.09 to 0.72); MD 0.47 (95% CI -0.07 to 1.02); and MD 0.16 (-0.68 to 1.00). Total calorie intake was greater in people taking supplements at 12 months, MD 265.70 (95% CI 42.94 to 488.46). There were no significant differences between the groups for anthropometric measures of body composition, lung function, gastro-intestinal adverse effects or activity levels. Moderate quality evidence exists for the outcomes of changes in weight and height and low quality evidence exists for the outcomes of change in total calories, total fat and total protein intake as results are applicable only to children between the ages of 2 and 15 years and many post-treatment diet diaries were not

returned. Evidence for the rate of adverse events in the treatment groups was extremely limited and judged to be of very low quality Authors' conclusions: Oral calorie supplements do not confer any additional benefit in the nutritional management of moderately malnourished children with cystic fibrosis over and above the use of dietary advice and monitoring alone. While nutritional supplements may be used, they should not be regarded as essential. Further randomised controlled trials are needed to establish the role of short-term oral protein energy supplements in people with cystic fibrosis and acute weight loss and also for the long-term nutritional management of adults with cystic fibrosis or advanced lung disease, or both.Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Does probiotic supplementation affect pulmonary exacerbation and intestinal inflammation in cystic fibrosis: a systematic review of randomized clinical trials

Author(s): Nikniaz Z.; Somi M.H.; Faramarzi E.; Nikniaz L.; Bilan N.

Source: World Journal of Pediatrics; Apr 2017 ; p. 1-7

Publication Type(s): Article In Press

Abstract: Background: Patients with cystic fibrosis (CF) usually have abnormal intestinal microbiota due to massive exposure to antibiotics. Probiotics could modify the gut microbiota and hence may affect CF management. So the aim of present systematic review was evaluation of the efficacy and safety of probiotic supplementation for the management of cystic fibrosis. Data sources: We searched PubMed, Science Direct, Google Scholar, Springer Cochrane Library Databases until January 2016 for randomized controlled trials (RCTs) performed in pediatric or adult populations related to the study aim. Key words were selected based on Mesh terms. Based on the Critical Appraisal Skills Programme checklist, eligibility of included articles was evaluated. Results: Five studies included in this review represent 188 participants with a follow up period ranging from 1 month to 6 months. The results of the included studies supporting the use of probiotics in management of pulmonary exacerbation and intestinal calprotectin in patients with cystic fibrosis. However the level of evidence was limited. Conclusions: The lack of high quality RCTs makes it impossible to support a general recommendation about the use of probiotics in the treatment of CF pulmonary exacerbation and intestinal inflammation.Copyright © 2017 Children's Hospital, Zhejiang University School of Medicine and Springer-Verlag Berlin Heidelberg

Other

Chest physiotherapy can affect the lung clearance index in cystic fibrosis patients

Author(s): Grosse-Onnebrink J.; Werner C.; Mellies U.; Olivier M.; Stehling F.

Source: Pediatric Pulmonology; May 2017; vol. 52 (no. 5); p. 625-631

Publication Date: May 2017

Publication Type(s): Article

Investigating self-efficacy, disease knowledge and adherence to treatment in adolescents with cystic fibrosis

Author(s): Faint N.R.; Staton J.M.; Stick S.M.; Schultz A.; Foster J.M.

Source: Journal of Paediatrics and Child Health; May 2017; vol. 53 (no. 5); p. 488-493

Publication Type(s): Article

Continuous glucose monitoring, insulin resistance, and sleep in adolescents with cystic fibrosis

Author(s): Simon S.L.; Vigers T.; Campbell K.; Pyle L.; Branscomb R.; Nadeau K.; Chan C.L.

Source: Sleep; 2017; vol. 40

Publication Type(s): Conference Abstract

Provider Attitudes and Practices toward Sexual and Reproductive Health Care for Young Women with Cystic Fibrosis

Author(s): Kazmerski T.M.; Sawicki G.S.; Borrero S.; Miller E.; Abebe K.Z.; Pilewski J.M.; Jones K.A.; Weiner D.J.; Orenstein D.M.; Tuchman L.K.

Source: Journal of Pediatric and Adolescent Gynecology; 2017

Publication Type(s): Article In Press

Investigating the feasibility of text message reminders to improve adherence to nebulized medication in children and adolescents with cystic fibrosis

Author(s): Morton R.W.; Edwards E.; Daw W.J.; West N.S.; Elphick H.E.

Source: Patient Preference and Adherence; May 2017; vol. 11 ; p. 861-869

Publication Type(s): Article

Available in full text at Patient preference and adherence - from National Library of Medicine

Impact of pharmacy services on cystic fibrosis medication adherence.

Author(s): Zobell, Jeffery T; Schwab, Elizabeth; Collingridge, Dave S; Ball, Cody; Nohavec, Robert; Asfour, Fadi

Source: Pediatric pulmonology; Jun 2017

Publication Type(s): Journal Article

Body sanctification and sleep in adolescents with cystic fibrosis: A pilot study

Author(s): Kopp, Antonia T.; Chini, Barbara A.; Dimitriou, Sophia M.; Grossoehme, Daniel H.

Source: Journal of Religion and Health; May 2017

Publication Type(s): Journal Peer Reviewed Journal

Adherence and Recursive Perception Among Young Adults with Cystic Fibrosis.

Author(s): Oddleifson, D. August; Sawicki, Gregory S.

Source: Anthropology & Medicine; Apr 2017; vol. 24 (no. 1); p. 65-80

Publication Type(s): Academic Journal

Travelling abroad with cystic fibrosis: Assessment of risks and healthcare requirements

Author(s): Miller, Rachel; Blanch, Laura; Lenaghan, Sarah; Anderson, Alan; Doe, Simon; Bourke, Stephen J

Source: Respiratory Medicine; Apr 2017; vol. 125 ; p. 92

Publication Type(s): Journal Article

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- **Thorax**
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Journal of Cystic Fibrosis
July 2017, Volume 16, Issue 4

http://www.cysticfibrosisjournal.com/current

American Journal of Respiratory and Critical Care Medicine
July 2017, Volume 196, Issue 1

http://www.atsjournals.org/toc/ajrccm/current

Thorax
July 2017, Volume 72, Issue 7

http://thorax.bmj.com/content/current

Chest
June 2017, Volume 151, Issue 6

http://journal.publications.chestnet.org/issue.aspx

Exercise: Sensitivity and Specificity

Sensitivity:

If a person has a disease, how often will the test be positive (true positive rate)?

If the test is highly sensitive and the test result is negative you can be nearly certain that they don't have disease.

Specificity:

If a person does not have the disease how often will the test be negative (true negative rate)?

If the test result for a highly specific test is positive you can be nearly certain that they actually have the disease.

Quick Quiz:

1. **A very sensitive test, when negative, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

2. **A test which is highly specific, when positive, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

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Answers: 1b; 2a

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