University Hospitals Bristol NHS
NHS Foundation Trust

Cystic Fibrosis

Evidence Update

August 2017

(Bimonthly)

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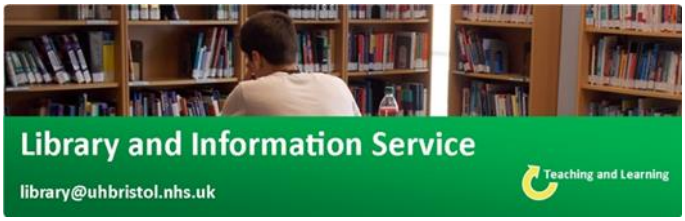

Training Sessions 2017

All sessions are one hour

August (12.00-13.00)

15th (Tues)	Interpreting Statistics
24th (Thurs)	Critical Appraisal

September (13.00-14.00)

Fri 1st	Literature Searching
Mon 4th	Critical Appraisal
Tue 12th	Interpreting Statistics
Wed 20th	Literature Searching
Thu 28th	Critical Appraisal

Your Outreach Librarian: Jo Hooper

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Contents

NICE National Institute for Health and Care Excellence

Fluconazole 2 mg/ml solution for infusion - Summary of Product Characteristics (SPC) - (eMC)

Source: electronic Medicines Compendium - eMC - 26 July 2017

This is just the first eMC Summary of Product Characteristics. See all

Safety in Lactation: Mucolytics and other drugs for cystic fibrosis

Source: Specialist Pharmacy Service - 04 June 2017

Additional information relating to breastfeeding Read Summary

Kalydeco 150 mg film-coated tablets - Summary of Product Characteristics (SPC) - (eMC) ▼

Source: electronic Medicines Compendium - eMC - 02 June 2017

This is just the first eMC Summary of Product Characteristics from your search. See all

UKMi comment

Colistimethate sodium 1 MIU and 2 MIU powder for solution for injection - PL 34328/0013-4;UK/H/6255/001-002/DC [PDF]

Source: Medicines and Healthcare products Regulatory Agency - MHRA - 12 July 2017

BNF for children **Mucolytics for cystic fibrosis | Treatment summary**

Source: British National Formulary for Children - BNFc - 14 July 2017

BNF **Mucolytics for cystic fibrosis | Treatment summary**

Source: British National Formulary - BNF - 14 July 2017

Cochrane Library

Combination antimicrobial susceptibility testing for acute exacerbations in chronic infection of Pseudomonas aeruginosa in cystic fibrosis

Valerie Waters, Felix Ratjen **Online Publication Date: June 2017**

Continuous versus intermittent antibiotics for non-cystic fibrosis bronchiectasis

Tim Donovan , Lambert M Felix , James D Chalmers , Stephen J Milan , Alexander G Mathioudakis and Sally Spencer **Online Publication Date: July 2017**

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Cystic fibrosis: Treatment of acute pulmonary exacerbations

- Incidence and consequences
- Definition
- Summary and recommendations
-

Cystic fibrosis: Carrier screening

- CF mutations
- Noninvasive prenatal diagnosis
- Summary and recommendations

Cystic fibrosis: Nutritional issues

- Cystic fibrosis-related liver disease
- Summary and recommendations

Cystic fibrosis: Antibiotic therapy for chronic pulmonary infection

- Consequences of cystic fibrosis lung infection
- Summary and recommendations

Cystic fibrosis: Genetics and pathogenesis

- Genetics
- Class I mutations: Defective protein production
- Summary

Cystic Fibrosis Trust **@cftrust · Twitter**

Community unites to call for #OrkambiNow!

The cystic fibrosis (CF) community joined together at protests across the UK and online yesterday to call for access to Orkambi for those who...

27/06/2017

Great strides gets greater!

11-year-old takes it in her stride as hundreds come together for endurance challenge

14/06/2017

Transplant campaign victory for CF community

Urgent National Lung Allocation System to bring fairer access to life-saving transplants in the UK.

06/06/2017

KnowledgeShare

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Collaboration and knowledge sharing

As more library and knowledge services join KnowledgeShare it becomes more powerful for sharing evidence and generating communities of practice.

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Journal Tables of Contents

The most recent issues of the following journals:

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

Click on the links for abstracts. If you would like any of these papers in full text then get in touch: library@uhbristol.nhs.uk

Journal of Cystic Fibrosis

July 2017, Volume 16, Issue 4

http://www.cysticfibrosisjournal.com/current

American Journal of Respiratory and Critical Care Medicine

July 15 2017, Volume 196, Issue 2

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

Thorax

August 2017, Volume 72, Issue 8

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

Chest

July 2017, Volume 152, Issue 1

http://journal.chestnet.org/current

Database Articles on Cystic Fibrosis

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

- **Medical**
- **Microbiological**
- **Psychological**
- **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

Adult-onset cystic fibrosis liver disease: Diagnosis and characterization of an underappreciated entity

Author(s): Koh C.; Sakiani S.; Surana P.; Eccleston J.; Liang T.J.; Hoofnagle J.H.; Heller T.; Zhao X.

Source: Hepatology; Aug 2017; vol. 66 (no. 2); p. 591-601

Publication Type(s): Article

Abstract: Cystic fibrosis (CF) liver disease (CFLD), a leading cause of death in CF, is mostly described in pediatric populations. Adult-onset CFLD lacks sufficient characterization and diagnostic tools. A cohort of CF patients without CFLD during childhood were followed for up to 38 years with serologic testing, imaging, and noninvasive fibrosis markers. Historical CFLD diagnostic criteria were compared with newly proposed CFLD criteria. Thirty-six CF patients were followed for a median of 24.5 years (interquartile range 15.6-32.9). By the last follow-up, 11 (31%) had died. With conventional criteria, 8 (22%) patients had CFLD; and by the new criteria, 17 (47%) had CFLD at a median age of 36.6 years (interquartile range 26.5-43.2). By the new criteria, those with CFLD had higher median alanine aminotransferase (42 versus 27, P = 0.005), aspartate aminotransferase (AST; 26 versus 21, P = 0.01), direct bilirubin (0.13 versus 0.1, P = 0.01), prothrombin time (14.4 versus 12.4, P = 0.002), and AST-to-platelet ratio index (0.31 versus 0.23, P = 0.003) over the last 2 years of follow-up. Subjects with a FibroScan >6.8 kPa had higher alanine aminotransferase (42 versus 28U/L, P = 0.02), AST (35 versus 25U/L, P = 0.02), AST-to-platelet ratio index (0.77 versus 0.25, P = 0.0004), and Fibrosis-4 index (2.14 versus 0.74, P = 0.0003) and lower platelet counts (205 versus 293, P = 0.02). One CFLD patient had nodular regenerative hyperplasia. Longitudinally, mean platelet counts significantly declined in the CFLD group (from 310 to 230 U/L, P = 0.0005). Deceased CFLD patients had lower platelet counts than those alive with CFLD (143 versus 258 U/L, P = 0.004) or those deceased with no CFLD (143 versus 327U/L, P = 0.006). Conclusion: Adult-onset CFLD may be more prevalent than previously described, which suggests a later wave of CFLD that impacts morbidity; routine liver tests, radiologic imaging, noninvasive fibrosis markers, and FibroScan can be used algorithmically to identify adult CFLD; and further evaluation in other CF cohorts should be performed for validation. (Hepatology

2017;66:591-601).

Immunosuppression Drug Therapy in Lung Transplantation for Cystic Fibrosis

Author(s): Burcham P.; Sarzynski L.; Khalfoun S.; Tumin D.; Hayes D.; Novak K.J.; Miller J.C.

Source: Pediatric Drugs; Aug 2017; vol. 19 (no. 4); p. 339-346

Publication Type(s): Review

Abstract: Cystic fibrosis (CF) is a common indication for lung transplantation (LTx) in children and adults with severe and irreversible lung disease. In the setting of LTx in the CF population, immunosuppressive medications are used to prevent allograft rejection despite the majority of these patients being chronically infected with numerous, and often antibiotic-resistant, pathogens. There is limited evidence for the optimal post-LTx immunosuppression regimen in patients with CF, particularly in children. This article provides a review of immunosuppression regimens in the pediatric and adult CF post-LTx population, investigating drug dosing and monitoring, and medication combinations. Currently used immunosuppressive medications and related systemic adverse effects are reviewed. With limitations of data in the pediatric population, future research should address immunosuppression in these children to help guide pediatric drug management as a means to optimize clinical outcomes after LTx.

Effect of allergic bronchopulmonary aspergillosis on FEV 1 in children and adolescents with cystic fibrosis: A European Cystic Fibrosis Society Patient Registry analysis

Author(s): Kaditis A.G.; Miligkos M.; Bossi A.; Zolin A.; Colombo C.; Hatziagorou E.; Kashirskaya N.

Source: Archives of Disease in Childhood; Aug 2017; vol. 102 (no. 8); p. 742-747

Publication Type(s): Article

Available in full text at Archives of disease in childhood - from Highwire Press

Abstract: Objective To evaluate the effect of allergic bronchopulmonary aspergillosis (ABPA) on FEV 1 percent predicted in children and adolescents with cystic fibrosis. Design Longitudinal data analysis (2008-2010). Setting Patients participating in the European Cystic Fibrosis Society Patient Registry. Participants 3350 patients aged 6-17 years. Main outcome measure FEV 1 percent predicted was the main outcome measure (one measurement per year per child). To describe the effect of ABPA (main explanatory variable) on FEV 1 while controlling for other prognostic factors, a linear mixed effects regression model was applied. Results In 2008, the mean (+/-SD) FEV 1 percent predicted was 78.6 (+/-20.6) in patients with ABPA (n=346) and 88 (+/-19.8) in those without ABPA (n=2806). After considering other variables, FEV 1 in subjects with ABPA on entry to the study was 1.47 percentage points lower than FEV 1 in patients of similar age without ABPA (p=0.003). There was no FEV 1 decline associated with ABPA over the subsequent study years as the interaction of ABPA with age was not significant (p>0.05). For patients aged 11.82 years (population mean age), poor body mass index had the greatest impact on FEV 1 in 2008, followed by high-risk genotype (two severe mutations), female gender, diabetes mellitus, chronic Pseudomonas aeruginosa infection and ABPA in descending order of effect size. Conclusions In contrast to the common clinical belief of ABPA having a serious impact on lung function, the difference in FEV 1 between young patients with and without the complication was found to be modest when the effect of other prognostic factors was considered.

Economic Evaluation of Tobramycin Inhalation Powder for the Treatment of Chronic Pulmonary Pseudomonas aeruginosa Infection in Patients with Cystic Fibrosis

Author(s): Panguluri S.; Gunda P.; Debonnett L.; Hamed K.

Source: Clinical Drug Investigation; Aug 2017; vol. 37 (no. 8); p. 795-805

Publication Type(s): Article

Abstract:Background: Chronic lung infection with Pseudomonas aeruginosa occurs in approximately 50% of patients with cystic fibrosis (CF). This infection further compromises lung function, and significantly contributes to the increased healthcare costs. Objectives: Inhaled tobramycin, used to manage P. aeruginosa infection in CF patients, is available as powder (tobramycin inhalation powder, TIP) and solution (tobramycin inhalation solution, TIS). Evidence suggests increased adherence with the use of TIP over TIS. Hence, this analysis aimed to evaluate the potential pharmacoeconomic benefit of increased adherence with TIP over TIS in the US setting. Methods: A patient-level simulation model was developed to compare TIP with TIS. Both costs and benefits were predicted over a 10-year time horizon from a payer's perspective, and were discounted annually at 3%. All costs were presented in 2016 US dollars. Results: TIP was associated with greater quality-adjusted life-years (by 0.27) and lower total costs (by US$36,168) as compared with TIS over a 10-year time horizon. TIP-treated patients experienced a decreased mean number of exacerbations than TIS-treated patients (39.24 vs 50.20). Furthermore, administration of TIP via the T-326 Inhaler was associated with significant cost savings per patient, because of the nebulizer required for administering TIS (by US$1596) and exacerbation costs (by US$76,531). Probabilistic sensitivity analysis showed that TIP was dominant over TIS in 100% of the simulations. Conclusion: TIP is likely to be a more cost-effective treatment than TIS, and therefore may reduce the economic burden of CF.

Impact of pharmacy services on cystic fibrosis medication adherence

Author(s): Zobell J.T.; Asfour F.; Schwab E.; Collingridge D.S.; Ball C.; Nohavec R.

Source: Pediatric Pulmonology; Aug 2017; vol. 52 (no. 8); p. 1006-1012

Publication Type(s): Article

Abstract: Objectives: The purpose of this study is to characterize the impact of pharmacy services on medication adherence and hospitalizations for pediatric cystic fibrosis (CF) patients. Methods: A retrospective health insurance claims analysis and patient medical charts review from January 1, 2014 to December 31, 2016 of patients from the Pediatric Intermountain CF Center was performed. Adherence to dornase alfa and hospital admissions for pulmonary exacerbations pre and post the implementation of an integrated pharmacy team were reviewed. Dornase alfa adherence was measured by the medication possession ratio (MPR) both monthly and yearly. Results: Fifty-four patients met inclusion criteria. The mean dornase alfa yearly MPR improved from 0.75 (2014) to 0.92 (2016). Patients were 2.8 times more likely to be adherent to dornase alfa when followed by integrated pharmacy team model (P

Comparison of FEV₁ reference equations for evaluating a cystic fibrosis therapeutic intervention

Author(s): Konstan M.W.; VanDevanter D.R.; Wagener J.S.; Pasta D.J.; Millar S.J.; Morgan W.J.

Source: Pediatric Pulmonology; Aug 2017; vol. 52 (no. 8); p. 1013-1019

Publication Type(s): Article

Abstract: Objectives: The Global Lung Function Initiative (GLI, 2012) developed reference equations for forced expiratory volume in 1 s (FEV1). Previous equations were developed by groups led by Knudson (1983), Wang (1993), Hankinson (1999), and Stanojevic (2008).1,2,4,6 We assessed how different prediction equations affect the conclusions from a therapeutic intervention study that evaluated the rate of percent predicted FEV1 (ppFEV1) decline. Methodology: Using data from the Epidemiologic Study of cystic fibrosis (CF), we re-analyzed our previous study evaluating the relationship of dornase alfa (DA) use with ppFEV1 using the Knudson, Wang & Hankinson, Stanojevic, and GLI equations. The change in intercept and change in slope of ppFEV1 from a 2-year pre-index period and 2-year post-index period were compared between the treated (N = 2483) and comparator groups (N = 6992, from 4110 unique patients). Results: Change in intercept for the comparator group was similar across equations except that Wang & Hankinson values were more negative. The difference in change in intercept between the DA and comparator groups ranged from 3.38 to 4.02% predicted. The change in slope for the comparator group ranged from -0.58 to +0.30 ppFEV1/year, but the difference in change in slope between the DA and comparator groups was in a narrower range from +0.53 to +0.89 ppFEV1/year. Conclusions: Although individual patient results are impacted by the choice of reference equations, the study conclusions from this evaluation of a therapeutic intervention were minimally affected. GLI equations are recommended for future studies, but prior results based on other equations should be accepted as reliable.

Outcomes Following Bronchial Artery Embolisation for Haemoptysis in Cystic Fibrosis

Author(s): Flight W.G.; Barry P.J.; Bright-Thomas R.J.; Butterfield S.; Ashleigh R.; Jones A.M.

Source: CardioVascular and Interventional Radiology; Aug 2017; vol. 40 (no. 8); p. 1164-1168

Publication Type(s): Article

Abstract: Background: Bronchial artery embolisation (BAE) is recommended for the treatment of massive haemoptysis in cystic fibrosis (CF), but there are no randomised controlled trials of this therapy and its role in sub-massive haemoptysis is unclear. This study aimed to determine the outcomes and safety of BAE in adults with CF. Materials and Methods: All patients with CF undergoing BAE at our centre between March 2011 and January 2015 were identified at the time of the procedure. Patient records were reviewed at hospital discharge, death or one month post-procedure (whichever was soonest). Follow-up continued to January 2016. Severity of haemoptysis was classified as: massive (>240 ml/24 h or >100 ml/day for >=2 days), moderate-severe (>20 ml/24 h) or mild

Non-invasive Ventilation as Airway Clearance Technique in Cystic Fibrosis.

Author(s): Rodriguez Hortal, Maria Cecilia; Nygren-Bonnier, Malin; Hjelte, Lena

Source: Physiotherapy Research International; Jul 2017; vol. 22 (no. 3)

Publication Type(s): Academic Journal

Abstract: Background and Purpose For patients with cystic fibrosis, chest physiotherapy is crucial for evacuating airway secretions. Because chest physiotherapy increases energy expenditure, fatigue and dyspnoea, non-invasive ventilation (NIV) could be beneficial for severely ill patients during airway clearance. The aim of the study is to evaluate and compare the effects between NIV and positive expiratory pressure (PEP) on airway clearance. Methods Prospective, randomized trial compares PEP to NIV. Thirty-two subjects, mean age 31 years, mean forced expiratory volume in 1

second 47% (±14) and mean forced vital capacity 69% (±13), completed a 3-month randomized trial comparing NIV with standard PEP treatment as airway clearance technique. Lung functions testing, 6-minute walk test, blood gases, sputum culture and inflammatory parameters were measured before and after the treatment period. Results There was a significant reduction in lung clearance index (LCI) following NIV compared with PEP (p = 0.01). LCI is performed within the lung function testing. Discussion Non-invasive ventilation was shown to be a good alternative to PEP in chest physiotherapy for patients with cystic fibrosis who are severely ill.

Objective Measurement of Adherence to Out-Patient Airway Clearance Therapy by High-Frequency Chest Wall Compression in Cystic Fibrosis.

Author(s): Mikesell, Christina L.; Kempainen, Robert R.; Laguna, Theresa A.; Menk, Jeremiah S.

Source: Respiratory Care; Jul 2017; vol. 62 (no. 7); p. 920-927

Publication Type(s): Academic Journal

Available in full text at Respiratory Care - from Highwire Press

Abstract:BACKGROUND: Objective measures of adherence to high-frequency chest wall compression (HFCWC), a form of airway clearance therapy for patients with cystic fibrosis, are lacking. We used a novel electronic monitoring device integrated into an HFCWC vest to measure adherence compared with self-reported adherence. We determined factors that influenced adherence and how adherence correlated with baseline pulmonary function and pulmonary exacerbations. METHODS: Data were collected by direct measurement of date, time of day, and duration of HFCWC use to determine the number of daily treatments and daily duration of treatments. Chart review provided prescribed airway clearance therapy treatment and demographic and clinical information. Subject and caregiver report of the daily number of airway clearance therapy treatments was obtained by telephone interviews. Analysis used 2-sample and paired t test, analysis of variance, and linear regression. RESULTS: Average adherence was 69%. Adherence was highest in children (82%, P = .02) and those receiving assistance with treatment (82%, P < .001). Subjects overestimated therapy duration from a mean ± SD of 127 ± 169% by adults to 19.2 ± 26.3% by parents or guardians of children. Average adherence decreased with increasing prescribed therapy time (P = .02). Average daily therapy time and adherence had significant positive associations with baseline FEV1 percent of predicted (P = .02 and P = .02, respectively) and negative associations with pulmonary exacerbations during the pre-study period and at baseline (P = .044 and P = .02, respectively). CONCLUSIONS: Greater adherence to HFCWC measured directly by a novel recorder was associated with better baseline pulmonary function and fewer exacerbations in the pre-study and baseline period. Adherence decreased with age and prescribed therapy time and increased with therapy assistance. Self-report overestimation is large and thus not an accurate measure of adherence.

Overcoming an Extremely Drug Resistant (XDR) Pathogen: Avibactam Restores Susceptibility to Ceftazidime for Burkholderia cepacia Complex Isolates from Cystic Fibrosis Patients

Author(s): Papp-Wallace K.M.; Becka S.A.; Zeiser E.T.; Mojica M.F.; Gatta J.A.; Winkler M.L.;

Source: ACS Infectious Diseases; Jul 2017; vol. 3 (no. 7); p. 502-511

Publication Type(s): Article

Abstract: Burkholderia multivorans is a significant health threat to persons with cystic fibrosis (CF). Infections are difficult to treat as this pathogen is inherently resistant to multiple antibiotics. Susceptibility testing of isolates obtained from CF respiratory cultures revealed that single agents selected from different antibiotic classes were unable to inhibit growth. However, all isolates were found to be susceptible to ceftazidime when combined with the novel non-beta-lactam beta-

lactamase inhibitor, avibactam (all minimum inhibitor concentrations (MICs) were 2/K of (2 +/- 1) x 106 muM-1 s-1 and a slow koff of (2 +/- 1) x 10-3 s-1. Mass spectrometry revealed that avibactam formed a stable complex with PenA for up to 24 h and that avibactam recyclized off of PenA, re-forming the active compound. Crystallographic analysis of PenA-avibactam revealed several interactions that stabilized the acyl-enzyme complex. The deacylation water molecule possessed decreased nucleophilicity, preventing decarbamylation. In addition, the hydrogen-bonding interactions with Lys-73 were suggestive of a protonated state. Thus, Lys-73 was unlikely to abstract a proton from Ser-130 to initiate recyclization. Using Galleria mellonella larvae as a model for infection, ceftazidime-avibactam was shown to significantly (p

Pilot trial of tobramycin inhalation powder in cystic fibrosis patients with chronic Burkholderia cepacia complex infection

Author(s): Waters V.; Beaudoin T.; Wettlaufer J.; Tom S.K.; Yau Y.; McDonald N.; Klingel M.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 492-495

Publication Type(s): Article

Abstract: There is no effective chronic suppressive therapy Burkholderia cepacia complex infection in cystic fibrosis (CF) patients. This was a pilot, open-label clinical trial of tobramycin inhalation powder (TIP) delivered via Podhaler twice daily for 28 days in adults and children with CF and chronic B. cepacia complex infection in Toronto, Canada. A total of 10 subjects (4 pediatric, 6 adult patients) were treated. There was a mean drop of 1.4 log (CFU/ml) in sputum bacterial density (p = 0.01) and sputum IL-8 levels decreased significantly after 28 days of TIP (p = 0.04). The mean relative change in FEV1 (L) from Day 0 to Day 28 of TIP administration was a 4.6% increase but this was not statistically significant. The majority of patients (70%) had no or mild adverse events.

Technological advances shed light on left ventricular cardiac disturbances in cystic fibrosis

Author(s): Sayyid Z.N.; Sellers Z.M.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 454-464

Publication Type(s): Review

Abstract: Cystic fibrosis (CF), the most common autosomal recessive lethal disease in Caucasians, causes chronic pulmonary disease and can lead to cor pulmonale with right ventricular dysfunction. The presence of the cystic fibrosis transmembrane conductance regulator (CFTR) in cardiac myocardia has prompted debate regarding possible defective ion channel-induced cardiomyopathy. Clinical heart disease in CF is considered rare and is restricted to case reports. It has been unclear if this is due to the lack of physiological importance of CFTR in the heart, the relatively short lifespan of those with CF, or a technical inability to detect subclinical disease. Extensive echocardiographic investigations have yielded contradictory results, leading to the dogma that left ventricular defects in CF occur secondary to lung disease. In this review, we consider why studies examining heart function in CF have not provided clarity on this topic. We then focus on data from new echocardiographic and magnetic resonance imaging technology, which are providing greater insight into cardiac function in CF and demonstrating that, in addition to secondary effects from pulmonary disease, there may be an intrinsic primary defect in the CF heart. With advancing lifespans and activity levels, understanding the risk of cardiac disease is vital to minimizing morbidity in adults with CF.

Multisystem imaging findings of cystic fibrosis in adults: Recognizing typical and atypical patterns of disease

Author(s): Averill S.; Lubner M.G.; Kennedy T.A.; Pickhardt P.J.; Menias C.O.; Bhalla S.; Mellnick V.M.

Source: American Journal of Roentgenology; Jul 2017; vol. 209 (no. 1); p. 3-18

Publication Type(s): Review

Abstract:OBJECTIVE. There is an expanding and increasingly heterogeneous population of adult patients with cystic fibrosis (CF). Although CF is usually diagnosed in children with progressive multisystem involvement, up to 7% of CF cases are currently diagnosed de novo in adults with subtle manifestations distinct from the typical features of classic CF. The purpose of this article is to present the wide spectrum of CF in adults, including both classic and nonclassic variants, with an emphasis on the nonclassic imaging findings. CONCLUSION. Recurrent pancreatitis, chronic sinusitis, and congenital bilateral absence of the vas deferens (CBAVD) are several of the ways in which CF is identified in adult patients with relatively rare mutations and with overall milder manifestations. It is important for radiologists to recognize the wide spectrum of CF to optimally monitor disease progression and response to therapeutic interventions in distinct adult patient populations.

Ease of use of tobramycin inhalation powder compared with nebulized tobramycin and colistimethate sodium: A crossover study in cystic fibrosis patients with pulmonary Pseudomonas aeruginosa infection

Author(s): Cao W.; Mastoridis P.; Debonnett L.; Hamed K.; Greenwood J.; Schwarz C.

Source: Therapeutic Advances in Respiratory Disease; Jul 2017; vol. 11 (no. 7); p. 249-260

Publication Type(s): Article

Abstract: Background: This study assessed the ease of use of tobramycin inhalation powder (TIP) administered via T-326 inhaler versus tobramycin inhalation solution (TIS) and colistimethate sodium (COLI), both administered via nebulizers, for the treatment of chronic pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis (CF). Methods: A real-world, open-label, crossover, interventional phase IV study was conducted in CF patients aged >=6 years with forced expiratory volume in 1 second (FEV1) >=25% to

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

Author(s): Zobell J.T.; Epps K.L.; Young D.C.

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

Publication Type(s): Letter

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.

Source: Medical Hypotheses; Jul 2017; vol. 104 ; p. 86-88

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.

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

Author(s): Villate-Beitia I.; Zarate J.; Puras G.; Pedraz J.L.

Source: Drug Development and Industrial Pharmacy; Jul 2017; vol. 43 (no. 7); p. 1071-1081

Publication Type(s): Review

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.

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.

Prevalence of hearing and vestibular loss in cystic fibrosis patients exposed to aminoglycosides.

Author(s): Handelsman, Jaynee A; Nasr, Samya Z; Pitts, Crystal; King, William M

Source: Pediatric pulmonology; Jul 2017

Publication Type(s): Journal Article

Abstract:AIMCystic Fibrosis (CF) patients frequently use aminoglycosides (AGS) to treat CF exacerbation due to colonization with Pseudomonas aeruginosa. Although AGS can cause vestibular and auditory sensory losses that can negatively impact quality of life, little is known about the prevalence of vestibular loss in this population. The aim of this study was to determine the prevalence of hearing loss and/or vestibular dysfunction in CF patients treated with AGS.METHODSThe relationship between hearing status and vestibular status was also investigated. Hearing was determined to be normal or abnormal based on pure tone air and bone conduction thresholds. Vestibular outcome was divided into four categories; normal, non-lateralized vestibular dysfunction, unilateral loss, and bilateral loss based on results of post head shaking testing, positional and positioning testing, bithermal calorics, sinusoidal, and rotational step testing.RESULTSOf our cohort of 71 patients, 56 (79%) patients have vestibular system dysfunction while only 15 (21%) have normal vestibular system function. Overall, 16 patients (23%) have hearing loss. In considering the relationship between auditory and vestibular function, 12 (17%) demonstrated both normal hearing and normal vestibular function and 13 (18%) have both hearing loss and abnormal vestibular function. Of the 55 (78%) patients with normal hearing, 43 (61%) have vestibular dysfunction, while 3 (4%) of patients with normal vestibular function have hearing loss.CONCLUSIONThese results suggest that monitoring hearing alone is insufficient to detect ototoxicity in CF patients being treated with systemic AGS.

Endocrine aspects in cystic fibrosis.

Author(s): Kiess, Wieland; Penke, Melanie; Kobelt, Louise; Lipek, Tobias; Henn, Constance; Gausche, Ruth; Vogel, Mandy; Prenzel, Freerk

Source: Journal of pediatric endocrinology & metabolism : JPEM; Jul 2017

Publication Type(s): Editorial

Sensitivity and specificity of cystic fibrosis-related diabetes screening methods: which test should be the reference method?

Author(s): Boudreau, Valérie; Lehoux Dubois, Catherine; Desjardins, Katherine; Mailhot, Marjolaine; Tremblay, François; Rabasa-Lhoret, Rémi

Source: Journal of pediatric endocrinology & metabolism : JPEM; Jul 2017

Publication Type(s): Letter

Ataluren in cystic fibrosis: development, clinical studies and where are we now?

Author(s): Zainal Abidin, Noreen; Haq, Iram J; Gardner, Aaron I; Brodlie, Malcolm

Source: Expert opinion on pharmacotherapy; Jul 2017

Publication Type(s): Journal Article

Abstract:INTRODUCTIONCystic fibrosis (CF) is one of the most common genetically-acquired life-limiting conditions worldwide. The underlying defect is dysfunction of the cystic fibrosis transmembrane-conductance regulator (CFTR) which leads to progressive lung disease and other multi-system effects. Around 10% of people with CF have a class I nonsense mutation that leads to production of shortened CFTR due to a premature termination codon (PTC). Areas covered: We discuss the discovery of the small-molecule drug ataluren, which in vitro has been shown to allow read-through of PTCs and facilitate synthesis of full-length protein. We review clinical studies that have been performed involving ataluren in CF. Early-phase short-term cross-over studies showed improvement in nasal potential difference. A follow-up phase III randomised controlled trial did not show a significant difference for the primary outcome of lung function, however a post-hoc analysis suggested possible benefit in patients not receiving tobramycin. A further randomised controlled trial in patients not receiving tobramycin has been reported as showing no benefit but has not yet been published in full peer-reviewed form. Expert opinion: A small-molecule approach to facilitate read-through of PTCs in nonsense mutations makes intuitive sense. However, at present there is no high-quality evidence of clinical efficacy for ataluren in people with CF.

Immunomodulatory Cell Therapy to Target Cystic Fibrosis Inflammation.

Author(s): Khoury, Oula; Barrios, Christopher; Ortega, Victor; Atala, Anthony; Murphy, Sean V

Source: American journal of respiratory cell and molecular biology; Jul 2017

Publication Type(s): Journal Article

Abstract: Cystic fibrosis (CF) is associated with exaggerated and prolonged inflammation in the lungs, which contributes to lung injury, airway mucus obstruction, bronchiectasis and loss of lung function. This hyper-inflammatory phenotype appears to be caused by an imbalance between the pro- and anti-inflammatory regulatory pathways, with heightened pro-inflammatory stimuli, a decreased counter-regulatory response, and reduced effectiveness of immune cell function and inflammatory resolution. Thus, therapies that can target this inflammatory environment would have a major impact in preventing the progression of lung disease. Due to the complex phenotype of CF inflammation, current anti-inflammatory regimens have proven to be inadequate for the targeting of these multiple dysregulated pathways and effects. Several approaches utilizing cell therapies have shown potential therapeutic benefit for the treatment of CF inflammation. This review provides an overview of the immune dysfunctions in CF and current therapeutic regimens and explores the field of cell therapy as a treatment for CF inflammation, and focuses on the various cell types utilized, their immunomodulatory functions, and the current approaches to mitigate the inflammatory response and reduce the long-term damage for CF patients.

Epithelial Na+ channel inhibitors for the treatment of cystic fibrosis.

Author(s): Smith, Nichola J; Solovay, Catherine F

Source: Pharmaceutical patent analyst; Jul 2017

Publication Type(s): Journal Article

Abstract: The epithelial Na+ channel (ENaC) is a key regulator of the volume of airway surface liquid (ASL) and is found in the human airway epithelium. In cystic fibrosis (CF), Na+ hyperabsorption

through ENaC, in the absence of cystic fibrosis transmembrane conductance regulator mediated anion secretion, results in the dehydration of respiratory secretions and the impairment of mucociliary clearance. The hypothesis of utilizing an ENaC blocking molecule to facilitate restoration of the airway surface liquid volume sufficiently to allow normal mucociliary clearance is of interest in the management of lung disease in CF patients. This review summarizes the published patent applications from 2014 to the end of 2016 that claim approaches to inhibit the function of ENaC for the treatment of CF.

Adeno-Associated Virus (AAV) gene therapy for cystic fibrosis: current barriers and recent developments.

Author(s): Guggino, William B; Cebotaru, Liudmila

Source: Expert opinion on biological therapy; Jul 2017 ; p. 1-9

Publication Type(s): Journal Article

Abstract:INTRODUCTIONSince the cystic fibrosis (CF) gene was discovered in 1989, researchers have worked to develop a gene therapy. One of the most promising and enduring vectors is the AAV, which has been shown to be safe. In particular, several clinical trials have been conducted with AAV serotype 2. All of them detected viral genomes, but identification of mRNA transduction was not consistent; clinical outcomes in Phase II studies were also inconsistent. The lack of a positive

outcome has been attributed to a less-than-efficient viral infection by AAV2, a weak transgene promoter and the host immune response to the vector. Areas covered: Herein, the authors focus on AAV gene therapy for CF, evaluating past experience with this approach and identifying ways forward, based on the progress that has already been made in identifying and overcoming the limitations of AAV gene therapy. Expert opinion: Such progress makes it clear that this is an opportune time to push forward toward the development of a gene therapy for CF. Drugs to treat the basic defect in CF represent a remarkable advance but cannot treat a significant cohort of patients with rare mutations. Thus, there is a critical need to develop a gene therapy for those individuals.

Microbiological

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.; O'Connell, N H

Source: Journal of Hospital Infection; Aug 2017; vol. 96 (no. 4); p. 397-398

Publication Type(s): Academic Journal

Increasing Total Serum IgE, Allergic Bronchopulmonary Aspergillosis, and Lung Function in Cystic Fibrosis

Author(s): Gothe F.; Kappler M.; Griese M.

Source: Journal of Allergy and Clinical Immunology: In Practice; Aug 2017

Abstract: Background: Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder contributing to lung disease in cystic fibrosis (CF) and challenging to diagnose. Objective: This study

analyzed the predictive value of increasing total IgE (t-IgE) levels in a CF cohort alongside with clinical and serologic data. Methods: A total of 387 children and young adults were followed from 2000 to 2006 and retrospectively classified into 6 groups. Patients with t-IgE levels 1) declines (r = -0.21, P 1 preservation effect was only detectable if t-IgE levels at least doubled within 3 months and exceeded the 95th age-specific percentile (P

Dry powders for the inhalation of ciprofloxacin or levofloxacin combined with a mucolytic agent for cystic fibrosis patients

Author(s): Akdag Cayli Y.; Sahin S.; Vural I.; Oner L.; Buttini F.; Balducci A.G.; Montanari S.

Source: Drug Development and Industrial Pharmacy; Aug 2017; vol. 43 (no. 8); p. 1378-1389

Publication Type(s): Article

Abstract: Objective: This study aimed to design and characterize an inhalable dry powder of ciprofloxacin or levofloxacin combined with the mucolytics acetylcysteine and dornase alfa for the management of pulmonary infections in patients with cystic fibrosis. Methods: Ball milling, homogenization in isopropyl alcohol and spray drying processes were used to prepare dry powders for inhalation. Physico-chemical characteristics of the dry powders were assessed via thermogravimetric analysis, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), X-ray diffractometry and scanning electron microscopy. The particle size distribution, dissolution rate and permeability across Calu-3 cell monolayers were analyzed. The aerodynamic parameters of dry powders were determined using the Andersen cascade impactor (ACI). Results: After the micronization process, the particle sizes of the raw materials significantly decreased. X-ray and DSC results indicated that although ciprofloxacin showed no changes in its crystal structure, the structure of levofloxacin became amorphous after the micronization process. FT-IR spectra exhibited the characteristic peaks for ciprofloxacin and levofloxacin in all formulations. The dissolution rates of micro-homogenized and spray-dried ciprofloxacin were higher than that of untreated ciprofloxacin. ACI results showed that all formulations had a mass median aerodynamic diameter less than 5 mum; however, levofloxacin microparticles showed higher respirability than ciprofloxacin powders did. The permeability of levofloxacin was higher than those of the ciprofloxacin formulations. Conclusion: Together, our study showed that these methods could suitably characterize antibiotic and mucolytic-containing dry powder inhalers.

Clinically Promising Biomarkers in Cystic Fibrosis Pulmonary Exacerbations

Author(s): Scott L.K.; Toner R.

Source: Lung; Aug 2017; vol. 195 (no. 4); p. 397-401

Publication Type(s): Review

Abstract: Cystic fibrosis is a complex genetic disease hallmarked by repetitive infectious exacerbations that leads to destruction of airway architecture, acute on chronic inflammatory changes, and deterioration in lung function. Predicting an exacerbation may help preempt some of these changes by the initiation of swift antibiotic and anti-inflammatory therapy. A search for biomarkers that could predict exacerbations or help guide duration of antibiotic therapy is being aggressively sought. In this review, we discuss the most recent and promising biomarkers that hopefully will assist in the future management of the CF patient.

Bronchocele density in cystic fibrosis as an indicator of allergic broncho-pulmonary aspergillosis: A preliminary study

Author(s): Occelli A.; Ranc C.; Leloutre B.; Boyer C.; Baque-Juston M.; Soize S.; Giovannini-Chami L.

Source: European Journal of Radiology; Aug 2017; vol. 93 ; p. 195-199

Publication Type(s): Article

Abstract: Objective Allergic broncho-pulmonary aspergillosis (ABPA) is a severe and under-diagnosed complication of cystic fibrosis (CF). The aim of the study was to determine whether the mucus content of bronchoceles in cystic fibrosis complicated with ABPA reveals a higher density than the mucus content of non-ABPA cystic fibrosis. Materials and methods We studied retrospectively 43 computed tomography scans (CT scans) of a pediatric population of cystic fibrosis patients. We measured the mucus attenuation in Hounsfield Units (HU) of all bronchoceles >5 mm in diameter. Results We found bronchoceles >5 mm in 13/43 patients. 5/13 patients had a positive diagnosis of ABPA. The median HU value of bronchoceles was higher in patients with than without ABPA [98 HU (26-135) vs 28 HU (10-36); P = 0,02]. Moreover, all patients with a bronchocele density >36HU were ABPA positive. Conclusions CF complicated with ABPA shows higher attenuation bronchoceles on CT scans of the chest. Systematic density measurements of bronchoceles could help to raise the difficult diagnosis of ABPA in patients suffering from cystic fibrosis. Larger series could confirm a threshold in HU which could become a new imaging criterion for the diagnosis of ABPA.

Ciprofloxacin-loaded PLGA nanoparticles against cystic fibrosis P. aeruginosa lung infections

Author(s): Gunday Tureli N.; Tureli A.E.; Torge A.; Lehr C.-M.; Schneider M.; Juntke J.; Schneider-Daum N.; Schwarz B.C.

Source: European Journal of Pharmaceutics and Biopharmaceutics; Aug 2017; vol. 117 ; p. 363-371

Publication Type(s): Article

Abstract: Current pulmonary treatments against Pseudomonas aeruginosa infections in cystic fibrosis (CF) lung suffer from deactivation of the drug and immobilization in thick and viscous biofilm/mucus blend, along with the general antibiotic resistance. Administration of nanoparticles (NPs) with high antibiotic load capable of penetrating the tight mesh of biofilm/mucus can be an advent to overcome the treatment bottlenecks. Biodegradable and biocompatible polymer nanoparticles efficiently loaded with ciprofloxacin complex offer a solution for emerging treatment strategies. NPs were prepared under controlled conditions by utilizing MicroJet Reactor (MJR) to yield a particle size of 190.4 +/- 28.6 nm with 0.089 PDI. Encapsulation efficiency of the drug was 79% resulting in a loading of 14%. Release was determined to be controlled and medium-independent in PBS, PBS + 0.2% Tween 80 and simulated lung fluid. Cytotoxicity assays with Calu-3 cells and CF bronchial epithelial cells (CFBE41o-) indicated that complex-loaded PLGA NPs were non-toxic at concentrations >> MICcipro against lab strains of the bacteria. Antibacterial activity tests revealed enhanced activity when applied as nanoparticles. NPs' colloidal stability in mucus was proven. Notably, a decrease in mucus turbidity was observed upon incubation with NPs. Herewith, ciprofloxacin complex-loaded PLGA NPs are introduced as promising pulmonary nano drug delivery systems against P. aeruginosa infections in CF lung.

High incidence of non-tuberculous mycobacteria-positive cultures among adolescent with cystic fibrosis

Author(s): Cavalli Z.; Reynaud Q.; Bricca R.; Nove-Josserand R.; Durupt S.; Perceval M.; Durieu I.

Source: Journal of Cystic Fibrosis; Aug 2017

Publication Type(s): Article In Press

Abstract: Background: We evaluated the prevalence of non-tuberculous mycobacteria (NTM)-positive cultures among our cystic fibrosis (CF) center patients, reviewed risk factors for NTM positivity, and determined its impact on lung function evolution. Methods: From 2009 to 2014, CF adults and children attending the CF center of Lyon (France) and having at least one positive NTM isolate were included. Each case was matched by age and gender with two CF patients with no NTM isolate (controls). Results: 48 CF patients with NTM-positive isolates were matched to 96 controls. The age group for whom incident NTM was higher was young adolescents aged 13 to 17. A significant association for NTM positivity was found with Staphylococcus aureus in multivariate analysis and with allergic bronchopulmonary aspergillosis, corticosteroid and itraconazole in univariate analysis. Mean annual FEV1 decline was faster for NTM-positive patients compared to controls. Conclusion: These data highlight the high incidence of NTM-positive cultures among young adolescents with CF.

Pleural effusions in non-transplanted cystic fibrosis patients

Author(s): Belanger A.R.; Nguyen K.; Akulian J.A.; Osman U.; Gilbert C.R.; Allen K.; Al Rais A.F.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 499-502

Publication Type(s): Article

Abstract: Background Pleural effusions are considered rare in cystic fibrosis (CF) patients. There is a paucity of available information in the literature concerning the nature and significance of pleural effusions in non-transplanted CF patients. Methods We conducted a multicenter retrospective evaluation of non-transplanted adult CF patients. Given the small sample size, only descriptive statistics were performed. Results A total of 17 CF patients with pleural effusion were identified, of whom 9 patients underwent thoracentesis. The crude incidence of pleural effusion was 43 per 10,000 person-years in hospitalized CF patients at large CF centers. All sampled effusions were inflammatory in nature. All samples submitted for culture grew at least one organism. Conclusion Pleural effusions are rare in adult non-transplanted CF patients. These fluid collections appear to be quite inflammatory with a higher rate of empyema than in the general population.

Outcomes associated with antibiotic regimens for treatment of Mycobacterium abscessus in cystic fibrosis patients

Author(s): DaCosta A.; Jordan C.L.; Giddings O.; Esther C.R.; Lin F.-C.; Gilligan P.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 483-487

Publication Type(s): Article

Abstract: Background Mycobacterium abscessus infection is associated with declining lung function in cystic fibrosis (CF), but there is little evidence on clinical efficacy to guide treatment. Methods Retrospective review of 37 CF patients treated for M. abscessus respiratory infection at a single center from 2006 to 2014. Outcomes included change in FEV1 at 30, 60, 90, 180, and 365 days after treatment and clearance of M. abscessus from sputum cultures. Results Lung function was

significantly improved after 30 and 60 days of treatment, but not at later time points. Gains were inversely related to starting lung function. Antibiotic choices did not influence outcomes except for greater clearance with clarithromycin. Conclusions Treatment of M. abscessus resulted in short term improvement in lung function that is inversely related to pre-treatment FEV1.

Prevalence and outcomes of achromobacter species infections in adults with cystic fibrosis: A North American cohort study

Author(s): Edwards B.D.; Somayaji R.; Rabin H.R.; Greysson-Wong J.; Waddell B.; Storey D.G.

Source: Journal of Clinical Microbiology; Jul 2017; vol. 55 (no. 7); p. 2074-2085

Publication Type(s): Article

Available in full text at Journal of Clinical Microbiology - from National Library of Medicine

Abstract: Achromobacter species are increasingly being detected in cystic fibrosis (CF) patients, with an unclear epidemiology and impact. We studied a cohort of patients attending a Canadian adult CF clinic who had positive sputum cultures for Achromobacter species in the period from 1984 to 2013. Infection was categorized as transient or persistent (-50% positive cultures for 1 year). Those with persistent infection were matched 2:1 with age-, sex-, and time-matched controls without a history of Achromobacter infection, and mixed-effects models were used to assess pulmonary exacerbation (PEx) frequency and lung function decline. Isolates from a biobank were retrospectively assessed, identified to the species level by nrdA sequencing, and genotyped using pulsed-field gel electrophoresis (PFGE). Thirty-four patients (11% of those in our clinic), with a median age of 24 years (interquartile range [IQR], 20.3 to 29.8 years), developed Achromobacter infection. Ten patients (29%) developed persistent infection. Persistence did not denote permanence, as most patients ultimately cleared infection, often after years. Patients were more likely to experience PEx at incident isolation than at prior or subsequent visits (odds ratio [OR], 2.7 [95% confidence interval {CI}, 1.2 to 6.7]; P

Pseudomonas aeruginosa Alters Staphylococcus aureus Sensitivity to Vancomycin in a Biofilm Model of Cystic Fibrosis Infection.

Author(s): Orazi, Giulia; O'Toole, George A

Source: mBio; Jul 2017; vol. 8 (no. 4)

Publication Type(s): Journal Article

Available in full text at mBio - from Highwire Press

Abstract: The airways of cystic fibrosis (CF) patients have thick mucus, which fosters chronic, polymicrobial infections. Pseudomonas aeruginosa and Staphylococcus aureus are two of the most prevalent respiratory pathogens in CF patients. In this study, we tested whether P. aeruginosa influences the susceptibility of S. aureus to frontline antibiotics used to treat CF lung infections. Using our in vitro coculture model, we observed that addition of P. aeruginosa supernatants to S. aureus biofilms grown either on epithelial cells or on plastic significantly decreased the susceptibility of S. aureus to vancomycin. Mutant analyses showed that 2-n-heptyl-4-hydroxyquinoline N-oxide (HQNO), a component of the P. aeruginosa Pseudomonas quinolone signal (PQS) system, protects S. aureus from the antimicrobial activity of vancomycin. Similarly, the siderophores pyoverdine and pyochelin also contribute to the ability of P. aeruginosa to protect S. aureus from vancomycin, as did growth under anoxia. Under our experimental conditions, HQNO, P. aeruginosa supernatant, and growth under anoxia decreased S. aureus growth, likely explaining

why this cell wall-targeting antibiotic is less effective. P. aeruginosa supernatant did not confer additional protection to slow-growing S. aureus small colony variants. Importantly, P. aeruginosa supernatant protects S. aureus from other inhibitors of cell wall synthesis as well as protein synthesis-targeting antibiotics in an HQNO- and siderophore-dependent manner. We propose a model whereby P. aeruginosa causes S. aureus to shift to fermentative growth when these organisms are grown in coculture, leading to reduction in S. aureus growth and decreased susceptibility to antibiotics targeting cell wall and protein synthesis.IMPORTANCE Cystic fibrosis (CF) lung infections are chronic and difficult to eradicate. Pseudomonas aeruginosa and Staphylococcus aureus are two of the most prevalent respiratory pathogens in CF patients and are associated with poor patient outcomes. Both organisms adopt a biofilm mode of growth, which contributes to high tolerance to antibiotic treatment and the recalcitrant nature of these infections. Here, we show that P. aeruginosa exoproducts decrease the sensitivity of S. aureus biofilm and planktonic populations to vancomycin, a frontline antibiotic used to treat methicillin-resistant S. aureus in CF patients. P. aeruginosa also protects S. aureus from other cell wall-active antibiotics as well as various classes of protein synthesis inhibitors. Thus, interspecies interactions can have dramatic and unexpected consequences on antibiotic sensitivity. This study underscores the potential impact of interspecies interactions on antibiotic efficacy in the context of complex, polymicrobial infections.

Psychological

Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis.

Author(s): Talwalkar, Jaideep S; Koff, Jonathan L; Lee, Hochang B; Britto, Clemente J;

Source: Psychosomatics; 2017; vol. 58 (no. 4); p. 343-354

Publication Type(s): Journal Article Review

Abstract:BACKGROUNDIndividuals with cystic fibrosis (CF) are at high risk for depression and anxiety, which are associated with worse medical outcomes. Novel therapies for CF hold great promise for improving physical health, but the effects of these therapies on mental health remain poorly understood.OBJECTIVEThis review aims to familiarize psychiatrists with the potential effect of novel CF therapies on depression and anxiety.METHODSWe discuss novel therapies that directly target the mutant CF protein, the CF transmembrane regulator (CFTR), which are called CFTR modulators. We summarize depression and anxiety screening and treatment guidelines under implementation in accredited CF centers. Case vignettes highlight the complexities of caring for individuals with CF with comorbid depression and anxiety, including patients experiencing worsening depression and anxiety proximate to initiation of CFTR modulator therapy, and management of drug-drug interactions.CONCLUSIONSAlthough CFTR modulator therapies provide hope for improving clinical outcomes, worsening depression and anxiety occurs in some patients when starting these novel agents. This phenomenon may be multifactorial, with hypothesized contributions from CFTR modulator-psychotropic medication interactions, direct effects of CFTR modulators on central nervous system function, the psychologic effect of starting a potentially life-altering drug, and typical triggers of depression and anxiety such as stress, pain, and inflammation. The medical and psychiatric complexity of many individuals with CF warrants more direct involvement of mental health specialists on the multidisciplinary CF team. Inclusion of mental health variables in patients with CF registries will facilitate further examination at an epidemiologic level.

Communication, Comfort, and Closure for the Patient With Cystic Fibrosis at the End of Life: The Role of the Bedside Nurse.

Author(s): Price, Deborah M.; Knotts, Sharon E.

Source: Journal of Hospice & Palliative Nursing; Aug 2017; vol. 19 (no. 4); p. 298-304

Publication Type(s): Academic Journal

Abstract: Cystic fibrosis is a life-threatening genetic disease that causes persistent lung infections and progressively limits the ability to breathe. The median predicted survival age of the patient with cystic fibrosis is 40 years. In the terminal care of the patient with cystic fibrosis, the role of the bedside nurse is critical in providing seamless, interdisciplinary care in order to promote a ''good death'' and ensure that the patient's and family's wishes are respected at the end of life (EOL). Key components of the bedside nurse's role in EOL care for the cystic fibrosis patient include the facilitation of interdisciplinary patient/family--centered communication, the provision of comfort to ease suffering from breathlessness and pain, and the promotion of patient and family closure within the family and among caregivers. This case study depicts the critical role of the bedside nurse in a young female patient with cystic fibrosis at the EOL to honor patient and family wishes and promote a peaceful, dignified death.

‘I’ve got to prioritise’: being a parent with cystic fibrosis.

Author(s): Barker, Hazel; Moses, Jennifer; O’Leary, Catherine

Source: Psychology, Health & Medicine; Jul 2017; vol. 22 (no. 6); p. 744-752

Publication Type(s): Academic Journal

Abstract: Due to advances in earlier diagnosis and treatment, the life expectancy of a person born with cystic fibrosis (CF) has increased. Therefore, more people with CF are becoming parents but the psychological understanding of CF has lagged behind advances in medical treatment; there is very limited applied psychological research on which parents and professionals can draw when considering issues of parenting in this context. This qualitative research explored how mothers and fathers with CF experience and manage the dual roles of being a parent and living with CF. The aim was to facilitate development of an understanding of experience rather than test existing theory. A qualitative methodology was chosen as it allowed participants to reflect openly on their individual experiences. Nine participants completed semi-structured interviews either in their own homes or a clinic base which examined parenting, CF and the interaction between the two roles. Four participants were male and five were female with an age range of 21–50. Interpretive Phenomenological Analysis was used to interpret the participants’ accounts and generate super-ordinate and master themes. ‘Being a parent on compressed time’ was the super-ordinate theme which reflected the challenge of parenting within both a limited life trajectory and a complex treatment regime with daily adherence and time pressures. The findings have implications for parents with CF, those considering parenting and for health professionals working in CF services whose guidance needs to be grounded in an evidence-base. Further research is needed to explore the experiences of parents within different family structures, parents who have had a transplant and the perspectives of others in the wider system in which parents with CF are located.

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

Author(s): McKinzie C.J.; Goralski J.L.; Noah T.L.; Retsch-Bogart G.Z.; Prieur M.B.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 525-527

Publication Type(s): 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.

Nutritional

Associations between micronutrient intakes and gut microbiota in a group of adults with cystic fibrosis.

Author(s): Li, Li; Krause, Lutz; Somerset, Shawn

Source: Clinical Nutrition; Aug 2017; vol. 36 (no. 4); p. 1097-1104

Publication Type(s): Academic Journal

Abstract: Summary Background Cystic fibrosis (CF) involves chronic inflammation and oxidative stress affecting mainly the respiratory and digestive systems. Survival rates for CF have improved with advances in treatment including nutritional interventions such as micronutrient supplementation. Diet can modulate gut microbiota in the general population with consequences on local and systemic immunity, and inflammation. The gut microbiota appears disrupted and may associate with pulmonary status in CF. This study investigated associations between micronutrient intakes and gut microbiota variations in a group of adults with CF. Methods Faecal microbiota of sixteen free-living adults with CF was profiled by 16ss rDNA sequencing on the GS-FLX platform. Associations were tested between UniFrac distances of faecal microbiota and time-corresponding micronutrient intakes. Associations between relative abundances of bacterial taxa and micronutrient intakes (those showing significant associations with UniFrac distances) were examined by Spearman correlation. Results Unweighted UniFrac distances were associated with intakes of potassium and antioxidant vitamins C, E and beta-carotene equivalents, whereas weighted UniFrac distances were associated with antioxidant vitamins riboflavin, niacin equivalents, beta-carotene equivalents and vitamin A equivalents. Intakes of beta-carotene equivalents, vitamin C, vitamin E, niacin equivalents and riboflavin correlated negatively with Bacteroides and/or its corresponding higher level taxa. Intakes of beta-carotene equivalents and vitamin E also positively correlated with Firmicutes and specific taxa belonging to Firmicutes . Conclusion Some micronutrients, particularly antioxidant vitamins, correlated with gut microbiota variations in the studied cohort. Further research is required to clarify whether antioxidant vitamin intakes can influence CF gut microbiota and potential clinical/therapeutic implications in CF.

Increased Fat Absorption from Enteral Formula Through an In-line Digestive Cartridge in Patients with Cystic Fibrosis

Author(s): Freedman S.; Orenstein D.; Black P.; Brown P.; McCoy K.; Stevens J.; Grujic D.; Clayton R.

Source: Journal of Pediatric Gastroenterology and Nutrition; Jul 2017; vol. 65 (no. 1); p. 97-101

Publication Type(s): Article

Abstract: Objectives: Supplemental enteral nutrition (EN) is used by approximately 12% of people with cystic fibrosis (CF). The objective of this study was to evaluate the safety, tolerability, and fat

absorption of a new in-line digestive cartridge (Relizorb) that hydrolyzes fat in enteral formula provided to patients with CF. Methods: Patients with CF receiving EN participated in a multicenter, randomized, double-blind, crossover trial with an open-label safety evaluation period. Plasma omega-3 fatty acid (FA) concentrations were measured and used as markers of fat absorption. Gastrointestinal symptoms were recorded to evaluate safety and tolerability. Information regarding the effect of EN on appetite and breakfast consumption was also collected. Results: Before study entry, participants had received EN for a mean of 6.6 years at a mean volume of approximately 800mL, yet had a mean body mass index of only 17.5kg/m 2 and omega-3 FA plasma concentrations were only 60% of levels found in normal healthy subjects. Compared with placebo, cartridge use resulted in a statistically significant 2.8-fold increase in plasma omega-3 FA concentrations. There were no adverse experiences associated with cartridge use, and a decrease in the frequency and severity of most symptoms of malabsorption was observed with cartridge use. Participants reported increased preservation of appetite and breakfast consumption with cartridge use compared with their pre-study regimen. Conclusions: Use of this in-line digestive cartridge was safe and well tolerated, and resulted in significantly increased levels of plasma omega-3 FA used with enteral formula, suggesting an overall increased fat absorption.

Survival of Patients with Cystic Fibrosis Depending on Mutation Type and Nutritional Status.

Author(s): Szwed, A; John, A; Goździk-Spychalska, J; Czaiński, W; Czerniak, W; Ratajczak, J; Batura-Gabryel, H

Source: Advances in experimental medicine and biology; Jul 2017

Publication Type(s): Journal Article

Abstract: The purpose of the study was to evaluate the influence of nutrition and of the severity of mutation type on survival rate in cystic fibrosis (CF) patients. Data were longitudinally collected from 60 hospitalized adult CF patients, aged 18-50. The variables consisted of body mass index (BMI) ratio, Cole's BMI cut-off points, severity of mutation type, and survival rate of CF patients. We found that the mean BMI was strongly associated with the severity of mutation type and was significantly lower in patients with severe mutations of grade I and II. The mutation type significantly affected the patients' survival rate; survival was greater in patients with mild and undefined mutation types. The BMI and Cole's cut-off points also had a significant influence on survival rate. CF patients, who suffered from malnutrition and emaciation, had a shorter survival rate than those with proper nutritional status. In conclusion, the study findings confirmed a significant effect of nutritional status and of mutation type on survival rate of CF patients.

The changing face of nutrition in cystic fibrosis

Author(s): Wolfe S.P.; Collins C.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 436-438

Publication Type(s): Editorial

Other

Hearing thresholds at high frequency in patients with cystic fibrosis: a systematic review.

Author(s): Caumo, Debora T M; Geyer, Lúcia B; Teixeira, Adriana R; Barreto, Sérgio S M

Source: Brazilian journal of otorhinolaryngology; 2017; vol. 83 (no. 4); p. 464-474

Publication Type(s): Journal Article

Abstract:INTRODUCTIONHigh-frequency audiometry may contribute to the early detection of hearing loss caused by ototoxic medications. Many ototoxic drugs are widely used in the treatment of patients with cystic fibrosis. Early detection of hearing loss should allow known harmful drugs to be identified before the damage affects speech frequencies. The damage caused by ototoxicity is irreversible, resulting in important social and psychological consequences. In children, hearing loss, even when restricted to high frequencies, can affect the development of language.OBJECTIVETo investigate the efficacy and effectiveness of hearing monitoring through high-frequency audiometry in pediatric patients with cystic fibrosis.

Scoring and validation of the cystic fibrosis disclosure questionnaire

Author(s): Borschuk, Adrienne Paige

Source: Dissertation Abstracts International: Section B: The Sciences and Engineering; 2017; vol. 77 (no. 12)

Publication Type(s): Dissertation Abstract Dissertation

Abstract: As more patients with cystic fibrosis (CF) are living into adulthood, patients may need to disclose their CF status to others, such as in romantic or professional settings. Patients who choose not to disclose their CF status may be limited in their closeness with others, which may negatively affect their psychological functioning and health-related quality of life. Few studies, however, have examined disclosure in CF, and currently no validated measures of CF disclosure exist. The purpose of this study was to explore CF disclosure in adults and validate a new assessment of CF disclosure, the Cystic Fibrosis Disclosure Scale (CFDS).

Disclosures of Cystic Fibrosis-Related Information to Romantic Partners

Author(s): Broekema, Katie; Weber, Kirsten M

Source: Qualitative Health Research; Aug 2017; vol. 27 (no. 10); p. 1575

Publication Type(s): Journal Article

Abstract: In this article, we offer insights into how individuals with cystic fibrosis (CF) share information about their disease with a romantic partner. Using communication privacy management as a sensitizing theoretical construct, four themes emerged following 13 qualitative interviews with persons with CF.

The role of social media in the relationship between social support and adherence in children with cystic fibrosis

Author(s): Babyar, Heather Michelle

Source: Dissertation Abstracts International: Section B: The Sciences and Engineering; 2017; vol. 78 (no. 2)

Publication Type(s): Dissertation Abstract Dissertation

Abstract: Although person-to-person contact between CF patients is discouraged, the World Wide Web represents a relatively new source of health information and support available online. With this increased access to social networking sites, it is possible for young people with CF to seek out social support online as person-to-person contact is discouraged. The present study aims to examine the social network use of adolescent and young adults with CF regarding social support and explore how social network experiences/exposure affects health related behaviors.

Pregnancy among cystic fibrosis women in the era of CFTR modulators

Author(s): Heltshe S.L.; Godfrey E.M.; Josephy T.; Aitken M.L.; Taylor-Cousar J.L.

Source: Journal of Cystic Fibrosis; Aug 2017

Publication Type(s): Article In Press

Abstract: Background: Little is known about how new therapies that partially correct the basic cystic fibrosis (CF) defect (ivacaftor and lumacaftor) might alter hormonal contraceptive effectiveness, impact pregnancy outcomes, or affect pregnancy timing. Examination of pregnancy rates among CF women during periods of CFTR modulator therapy initiation will provide foundation for further research in this area.

Innovating cystic fibrosis clinical trial designs in an era of successful standard of care therapies

Author(s): VanDevanter D.R.; Mayer-Hamblett N.

Source: Current Opinion in Pulmonary Medicine; Jul 2017

Publication Type(s): Article In Press

Abstract:PURPOSE OF REVIEW: Evolving cystic fibrosis 'standards of care' have influenced recent cystic fibrosis clinical trial designs for new therapies; care additions/improvements will require innovative trial designs to maximize feasibility and efficacy detection.

Estimating Direct Cost of Cystic Fibrosis Care Using Irish Registry Healthcare Resource Utilisation Data, 2008-2012

Author(s): Jackson A.D.; Fletcher G.; Harrington M.; Zhou S.; Jackson A.L.; Doyle G.; Cullinane F.

Source: PharmacoEconomics; Jul 2017 ; p. 1-15

Publication Type(s): Article In Press

Abstract: Background: Understanding the determinants of cost of cystic fibrosis (CF) care and health outcomes may be useful for financial planning for the delivery of CF services. Registries contain information otherwise unavailable to healthcare activity/cost monitoring systems. We estimated the direct medical cost of CF care using registry data and examined how cost was affected by patient characteristics and CF gene (CF Transmembrane Conductance Regulator [CFTR]) mutation.

Ethnicity impacts the cystic fibrosis diagnosis: A note of caution

Author(s): Bosch B.; Cuppens H.; De Boeck K.; Bilton D.; Sosnay P.; Raraigh K.S.; Mak D.Y.F.

Source: Journal of Cystic Fibrosis; Jul 2017; vol. 16 (no. 4); p. 488-491

Publication Type(s): Article

Abstract: Background The diagnosis of Cystic Fibrosis (CF) is by consensus based on the same parameters in all patients, yet the influence of ethnicity has only scarcely been studied. We aimed at elucidating the impact of Asian descent on the diagnosis of CF.

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; Jul 2017; vol. 12 (no. 3); p. 180-190

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.

Highlights from the 2016 North American Cystic Fibrosis Conference

Author(s): Zemanick E.T.; Daines C.L.; Dellon E.P.; Esther C.R.; Muhlebach M.S.; Kinghorn B.; Ong T.

Source: Pediatric Pulmonology; Aug 2017; vol. 52 (no. 8); p. 1103-1110

Publication Type(s): Review

Abstract: The 30th annual North American Cystic Fibrosis Conference (NACFC) was held in Orlando, FL, on October 27-29, 2016. Abstracts were published in a supplement to Pediatric Pulmonology. This review summarizes several major topic areas addressed at the conference: the pathophysiology of cystic fibrosis (CF) lung disease, clinical trials, clinical management issues, and quality improvement. We sought to provide an overview of emerging concepts in several areas of CF research and care, rather than a comprehensive review of the conference. Citations from the conference are by first author and abstract number or symposium number, as designated in the supplement.

Exercise: Confounding Bias in Research Methodology

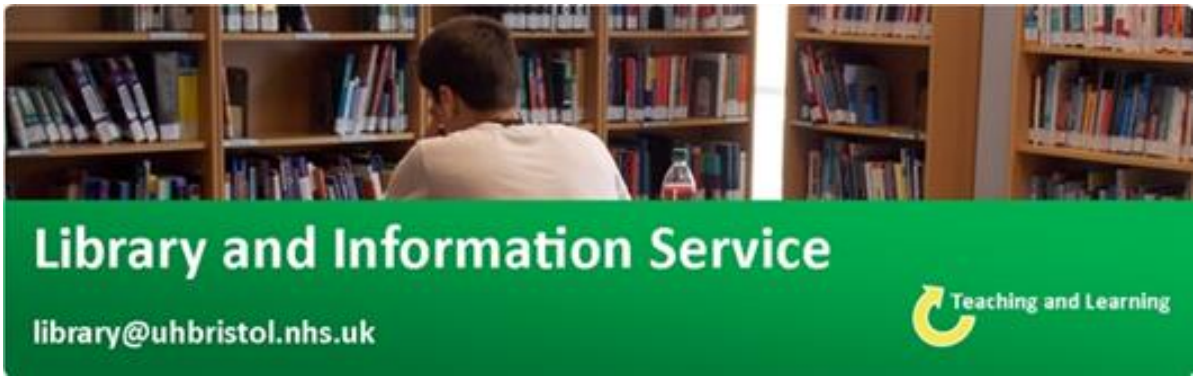
A confounder is a factor that is:

- *Linked to the outcome of interest, independent of the exposure*
- *Linked to the exposure but not the consequence of the exposure*

What is the confounding factor in the following relationships:

- People who carry matches are more likely to develop lung cancer
- People who eat ice-cream are more likely to drown
- Training in anaesthesia is more likely to make doctors commit suicide

*To find out more about bias in research methodology, sign up for one of our **Critical Appraisal training sessions**. For more details, email library@uhbristol.nhs.uk.*



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